



# Curing Epilepsy



The Promise of  
Research

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National Institute of  
Neurological Disorders  
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# Introduction



## Approximately

3 million Americans...

...currently live with epilepsy, a brain disorder in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally, causing seizures. Each year, another 200,000 people are diagnosed with epilepsy and an estimated 25,000 to 50,000 die of seizures and related causes. About one in every ten people in the United States will have at least one seizure during their lifetime, and epilepsy costs the United States approximately \$12.5 billion each year.

The disturbances of neuronal activity that occur during seizures may cause strange sensations, emotions, and behaviors. They also sometimes cause convulsions, muscle spasms, and loss of consciousness. During a seizure, neurons may fire as many as 500 times a second, which is much faster than normal. In some people, this happens only occasionally. Other people may

have seizures hundreds of times a day. The causes and symptoms of epilepsy vary greatly from one person to another.

About three quarters of those diagnosed with epilepsy can control their seizures with medicine or surgery. However, about 25 to 30 percent will continue to experience seizures even with the best available treatment. Doctors call this intractable (treatment-resistant) epilepsy. In some cases, people with epilepsy will develop a severe condition called status epilepticus, which is characterized by a seizure that continues for more than 5 minutes or seizures that recur without recovery of consciousness. Status epilepticus damages the brain and is life-threatening.

# 1. About Epilepsy

## Seizures

Doctors classify seizures into two groups. Focal seizures begin in one area of the brain, and may, or may not, spread to other parts. Generalized seizures are the result of abnormal neuronal activity on both sides of the brain.

About 60 percent of people with epilepsy have focal seizures. Simple focal seizures cause unusual sensations, feelings, or movements, but do not cause loss of consciousness. Complex focal seizures cause a change in or loss of consciousness and may produce a dreamlike experience or strange, repetitive behavior. Focal seizures are often described by the area of the brain in which they originate. For example, temporal lobe epilepsy, or TLE, begins in the temporal lobes located on either side of the brain. TLE is the most common type of epilepsy to feature focal seizures. Unfortunately, it is also one of the most difficult to treat.

Generalized seizures may cause loss of consciousness, falls, or massive muscle spasms. There are several different types of generalized seizures. In absence seizures, which usually begin in childhood or adolescence, an individual may appear to be staring into space or may have jerking or twitching muscles. Tonic seizures cause stiffening of muscles. Clonic seizures cause repeated jerking movements of muscles on both sides of the body. Myoclonic seizures cause jerks or twitches of the upper body, arms, or legs. Atonic seizures cause a loss of normal muscle tone, which may lead to falls or sudden drops of the head. Tonic-clonic seizures cause a mixture of symptoms, including stiffening of the body and repeated jerks of the arms or legs as well as loss of consciousness.



This EEG from a person with epilepsy shows brain wave patterns recorded from different sites in the brain. The left side shows brain waves without seizure activity. The center and right side show the steep "spike and wave" pattern associated with seizures.

Just as there are different kinds of seizures, there are different kinds of epilepsy. Doctors have identified many kinds of epilepsy syndromes, which are disorders characterized by a specific set of symptoms that include epilepsy. A minority of these syndromes appear to be hereditary. For most of the epilepsy syndromes, the cause is unknown.

## Epilepsy in Infants and Children

Many epilepsy syndromes, such as infantile spasms, Lennox-Gastaut syndrome, and Rasmussen's encephalitis, begin in childhood. Infantile spasms usually begin before the age of 6 months and may cause a baby to bend forward and stiffen. Children with Lennox-Gastaut syndrome have severe epilepsy with several different types of seizures, including atonic seizures, which cause sudden falls called drop attacks. Rasmussen's encephalitis is a rare, chronic inflammatory disease that usually affects only one hemisphere of the brain. It causes frequent and severe seizures, loss of motor skills, and can lead to severe disability.

Some childhood epilepsy syndromes, such as childhood absence epilepsy, tend to go into remission or stop entirely as a child matures. However, other syndromes such as juvenile myoclonic epilepsy and Lennox-Gastaut syndrome are usually present for life.

## Benign and Progressive Epilepsy

Epilepsy syndromes that are easily treated, that do not seem to impair cognitive functions or development, and that stop spontaneously are often described as benign. Benign epilepsy syndromes include benign infantile seizures and benign neonatal seizures. Other syndromes, such as early myoclonic encephalopathy, include neurological and developmental problems. It is often not clear whether the neurological damage in these syndromes is caused by the seizures or by underlying neurodegenerative processes.

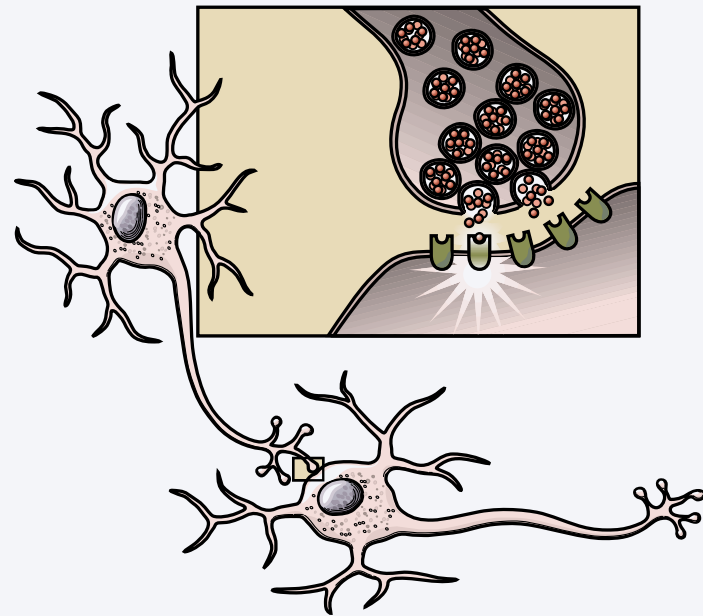
Because of the enormous economic and human costs and disability associated with epilepsy, the U.S. Federal government supports a great deal of research on this disorder. Much of this research support comes from the National Institutes of Health (NIH). The National Institute of Neurological Disorders and Stroke (NINDS) is the lead NIH institute for epilepsy research. Several other NIH institutes also fund epilepsy-related research, including the National Institute of Child Health and Human Development (NICHD), the National Human Genome Research Institute (NHGRI), the National Institute of Mental Health (NIMH), the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the John E. Fogarty International Center (FIC). Representatives from these NIH institutes and centers and from the Centers for Disease Control and Prevention (CDC) have formed an Interagency Epilepsy Working Group that aims to increase communication among institutes and agencies sponsoring epilepsy-related research and explore opportunities for increased coordination.

## April, a mother of twins...

...worries about her children's future. Seven-year-old Abigail and Amelia have tuberous sclerosis (TS), a genetic condition in which tumors grow uncontrollably throughout the body and are thought to cause epileptic seizures. These tumors can go on to affect the brain, kidneys, heart, lungs, and eyes. When Amelia was 2 weeks old she started having seizures caused by the tumors. Over the next 2 years, Amelia had many different kinds of seizures, some of them quite severe. According to her mother, this eventually affected her growth and development. Through advances in diagnostics, Amelia was found to be a good candidate for a tuber resection, which is a type of brain surgery. Due to the successful procedure and finding the right drug regimen, she has been seizure free for nearly 5 years.

Since Abigail is Amelia's identical twin, both girls have TS. However, Abigail has not had the same problem with epileptic seizures, and her last seizure was 6 years ago. Abigail did have her own brain surgery to remove a tumor that was growing and threatening her overall health. While the surgery was successful, there is always a concern that a tumor might return.

Sophisticated brain scans on the girls indicate that TS has affected as much as one half of both Amelia's and Abigail's brains. April's concern is that, due to the damage caused by her seizures, Amelia will not likely ever fully recover or live as an independent adult. Abigail, on the other hand, has not suffered as much developmentally as Amelia. Looking at them both, April admits no one knows what the future might hold but she is committed to finding a way to help others from suffering the devastation of this disease.



Neurons use electrical impulses and chemical signals to transmit information across tiny spaces called synapses. Signaling chemicals called neurotransmitters are gathered into sacs called synaptic vesicles. When the nerve receives a signal, these sacs release their neurotransmitters into the synapse. Proteins called receptors, found on the receiving neuron, bind to the neurotransmitters and trigger a new nerve impulse.

Epilepsy syndromes in which the seizures or the individual's cognitive abilities get worse over time are called progressive epilepsy.

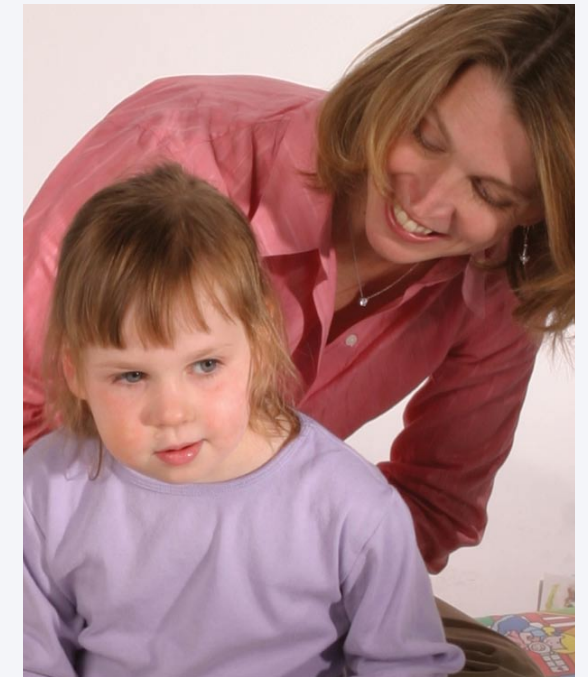
## Causes

Epilepsy has many possible causes. Almost anything that disturbs the normal pattern of neuron activity — from abnormal brain development to trauma to illness — can lead to seizures. For example, epilepsy may develop because of an abnormality in brain wiring that occurs during brain development, an imbalance of nerve-signaling chemicals called neurotransmitters, or a combination of these factors. Researchers believe that some people with epilepsy have abnormally high levels

of excitatory neurotransmitters, chemicals that increase neuronal activity. Others may have an abnormally low level of inhibitory neurotransmitters, which decrease neuronal activity in the brain. Either situation can result in too much neuronal activity and cause epilepsy. In some cases, the brain's attempts to repair itself after a head injury, stroke, or other trauma may inadvertently generate abnormal nerve connections that lead to epilepsy.

Research has shown that the cell membrane surrounding a neuron plays an important role in epilepsy. Cell membranes are crucial for generating electrical impulses. For this reason, researchers are studying the membrane structure and how molecules move across, nourish, and repair membranes. A disruption in any of these processes can cause gradual changes that may eventually lead to epilepsy.

Epilepsy also may result from changes in non-neuronal brain cells called glia. These cells regulate concentrations of chemicals in the brain, which affect neuronal signaling.



In about half of all people with epilepsy, the disorder has no known cause. In other cases, the seizures are clearly linked to infection, head trauma, stroke, brain tumors, or other identifiable problems.

## Current Epilepsy Drugs

- Acetazolamide
- Carbamazepine
- Clonazepam
- Clorazepate
- Corticotropin (ACTH)
- Diazepam
- Ethosuximide
- Felbamate
- Fosphenytoin
- Gabapentin
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pregabalin
- Primidone
- Tiagabine
- Topiramate
- Valproate
- Zonisamide

## 2. Research Progress in Epilepsy



A White House-initiated international scientific conference in 2000, “Curing Epilepsy: Focus on the Future,” was a landmark event for scientists, clinicians, and patients. This conference, for the first time, focused the epilepsy research community on the concept of a cure for epilepsy, defined as “preventing epilepsy in those at risk, and no seizures, no side effects in those who develop the disorder.” The conference led to a set of Benchmarks for Epilepsy Research that serve as milestones to measure progress towards a cure (see Appendix). The NINDS, epilepsy scientists, patients, and non-governmental organizations are working together to achieve the Benchmarks and move closer to the ultimate goal of curing epilepsy.

The Benchmarks are sorted into three broad categories, meant to encourage research to:

- understand the underlying mechanisms by which epilepsy develops.

- develop new ways to prevent epilepsy in individuals at risk.
- develop better therapies to prevent seizures without side effects.

A major feature of the Benchmarks is that even though they focus on research and research outcomes, their implementation is the shared responsibility of the entire epilepsy community, including the NIH, extramural research scientists, epilepsy professional organizations, and people with epilepsy, as well as their friends and family.

While the ultimate goal of curing epilepsy has not yet been achieved, researchers have made a great deal of progress. For example, the number of studies aimed at understanding how and why epilepsy develops has increased substantially, and

researchers are banding together in collaborative efforts to overcome the limitations of individual research. Researchers also have identified a number of genes associated with epilepsy. Many technical advances, from improved brain imaging to the widespread use of microarrays, are allowing new insights. Partly as a result of these advances, a variety of new antiepileptic drugs and other treatments are now being tested in clinical studies.

Here is a look at how progress in many of these Benchmarks is being made in laboratories and clinical settings and by voluntary groups across the country.

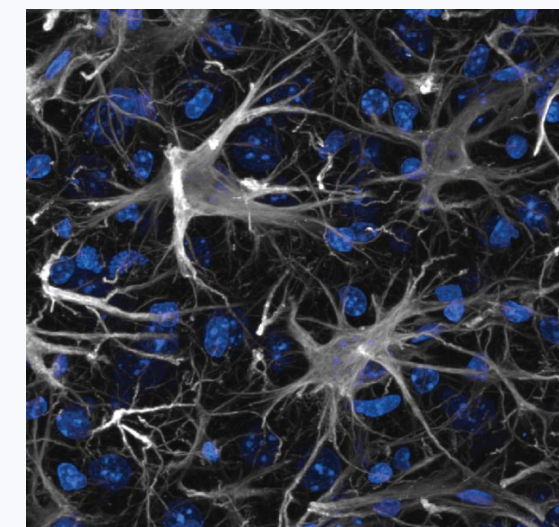
### Discovering What Happens in the Brain to Create Epileptic Seizures

To understand how to prevent, treat, and cure epilepsy, researchers first must learn how it develops. Where, how, when, and why do neurons begin to display the abnormal firing patterns that cause epileptic seizures? This process, known as epileptogenesis, is at the core of our understanding of epilepsy. Investigators are using a number of strategies to learn about epileptogenesis.

- Researchers are working to find markers that can reveal where seizures begin in the brain.
- They are working to develop a database of brain images to reveal relationships between structure and function in the brain. The image data may be correlated with demographic and historical information,

and information on seizure types, in order to reveal how different factors influence the development of epilepsy.

- Many studies have shown that having one seizure increases the risk of others. This probably results from the brain’s innate adaptability. When the brain is subjected to electrical stimuli, it tries to adapt. Unfortunately, these adaptive changes may sometimes be harmful.
- Recent studies have shown that non-neuronal cells in the brain, called astrocytes, play a central role in brain function and even produce the nerve-signaling chemical glutamate. Astrocytes also act as “housekeepers,” cleaning up pollution in the neural environment that would otherwise interfere with normal brain function. Research has shown that glutamate produced



The white, star-shaped cells in this photo are swollen astrocytes in brain tissue from a mouse model of epilepsy. This condition is called reactive gliosis. Astrocytes are the most common cells in the brain. Normally, they help the brain to function. However, they also produce the nerve-signaling chemical glutamate, which can trigger seizures. When reactive gliosis develops, astrocytes stop functioning correctly and may contribute to the development of epilepsy.



by astrocytes can trigger seizures. This suggests that factors which impair astrocyte function, ranging from genetic variations to brain damage from stroke or head injury, can cause epilepsy.

- Another study has shown that, in brain tissue from some adults with epilepsy, the usually inhibitory neurotransmitter GABA instead has excitatory effects, probably resulting from a change in the chloride concentration within cells. This change lowers the amount of stimulation needed for seizures to develop.

### The Search for Genes that Increase the Risk of Epilepsy

For centuries, people have noticed that epilepsy tends to run in families, leading scientists to propose that inherited genetic mutations contribute to the development of seizures. But this isn't the whole story. Single-gene, inherited epilepsies are rare. Current science suggests that a majority of epilepsy syndromes involve multiple genes and variable symptoms.

Most common epilepsies are probably the result of environmental factors acting in combination with genes. This would explain why there are so many epilepsy syndromes and may also explain why epilepsy is often associated with other disorders, neurological or otherwise.

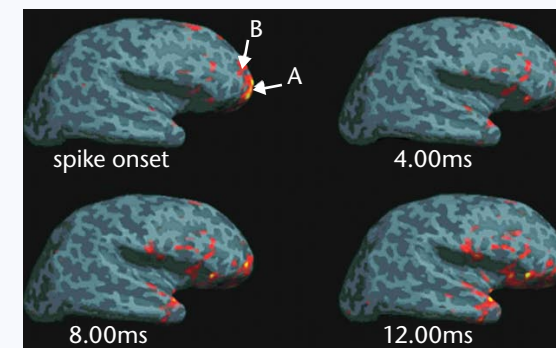
Although single-gene, inherited epilepsy syndromes are rare, studying the processes that cause seizures in these inherited forms of epilepsy can help to explain more common forms of unexplained, or idiopathic, epilepsy. These studies often yield valuable clues about how epilepsy develops and offer glimpses into how different genetic mutations and variations might work on and with each other to cause a particular syndrome. Researchers have identified specific epilepsy genes in a number of families with rare epilepsy syndromes. For example, some types of childhood absence epilepsy have been linked to a gene called *GABRG2* that codes for a type of GABA receptor, while a type of nocturnal frontal lobe epilepsy is caused by a gene called *CHRN2* that affects responses to the neurotransmitter acetylcholine. The knowledge gathered in these studies also makes genetic testing possible for single-gene forms of epilepsy and forms the basis for a definitive diagnosis.

The Epilepsy Phenome/Genome Project (EPGP) is a new initiative, supported by the NINDS and other organizations, that aims to shed new light on the relationship between genes and epilepsy. This consortium, made up of investigators from 15 U.S. medical centers, plans to collect enough data from enough patients (an expected 5,000 patients over 5 years) to allow analysis of

genes and brain abnormalities that influence epilepsy. The information will be stored in a comprehensive database that includes details about each patient's seizure types, medical and family history, seizure frequency, and other characteristics, along with an analysis of his or her genes.

### Research on New Ways to Observe Brain Chemistry and Function During Seizures

Another challenge in epilepsy research is finding ways to identify when and where seizures begin in the brain. To do this, researchers need to find characteristics, or markers, that indicate seizure activity and epileptogenesis. Markers for seizure activity could be used to identify the part of the brain to be removed during surgery or to test new treatments for epilepsy. A marker that would predict when seizures will occur could allow people to take steps to protect themselves from injury and might lead to development of treatments to stop seizures from forming. Markers could also predict disease progression in patients with epilepsy, allowing doctors to better identify people who will need surgery or other aggressive therapy.



These magnetoencephalography (MEG) images show the progression of abnormal brain activity, or "spikes," in the brain. The spikes originate in an area with abnormally formed neurons, or cortical dysplasia, in the front part of the brain (marked as "A"). They then spread across the surface of the brain.

The search for epilepsy markers is complicated because there are multiple types of epilepsy. Also, investigators have a very limited knowledge of the processes that lead to chronic epilepsy.

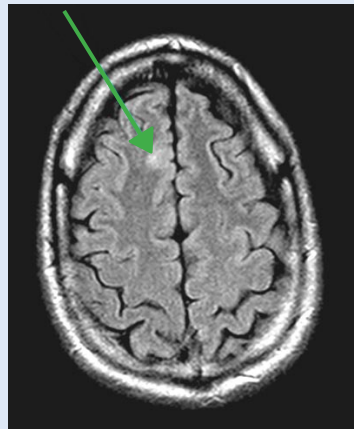
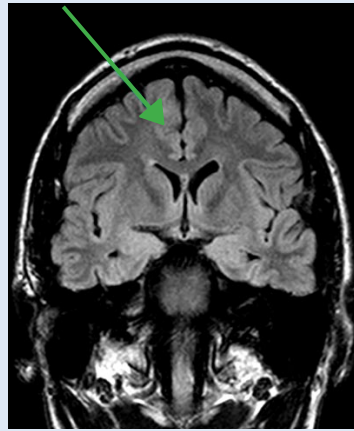
- Electroencephalograph (EEG) recordings that take place between seizures (called interictal EEG recordings) often show abnormal brainwaves, called "spikes," which are used to help diagnose epilepsy. However, these abnormal brainwaves do not occur in all people with epilepsy, and they sometimes occur in normal people. These spikes do not

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**Epilepsy is a disorder produced by malfunctions**  
in the chemical and electrical systems that control the normal activity of the brain.

Understanding the precise chain of events that contributes to these disruptions will help scientists develop better treatments for epilepsy and ways to prevent the development of the disorder.

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These magnetic resonance imaging (MRI) brain scans of a person with focal epilepsy show a subtle abnormality (see arrows) called cortical dysplasia. Cortical dysplasia is a common cause of epilepsy.

always originate in the brain region or regions that generate seizures, and researchers have not found any characteristics of these brainwaves that correlate with the severity of epilepsy. Therefore they are not reliable markers for epilepsy.

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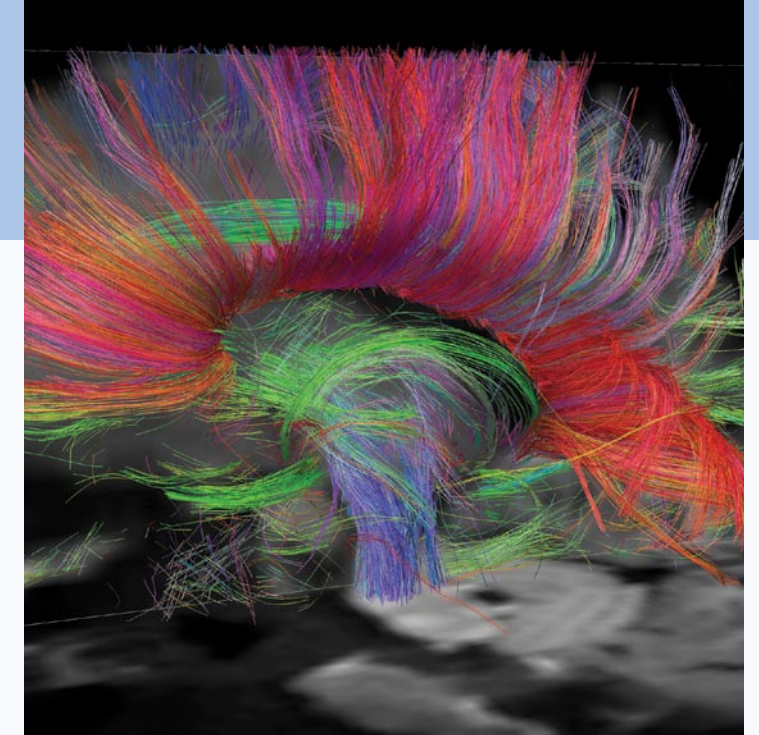
**In about 70 percent of all cases of epilepsy, the cause is unknown. It is likely that genes are involved in at least some of these cases. In fact, some genes that can lead to epilepsy have already been found. Identifying more of these genes should help scientists create new methods of treatment and prevention.**

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- A recent advance in functional MRI (fMRI) allows researchers to use magnetized nanoparticles — extremely small magnetized particles that are visible on MRI and attach to a wide variety of substances — to track changes in the brain. Imaging with these nanoparticles might allow investigators to measure regional alterations in neurotransmitter activity that reflect brain activity, cerebral metabolism, immune responses, and drug distribution. This technology may be very useful in identifying markers for seizure-generating brain regions.
- Structural MRI of rats with one type of induced status epilepticus suggests that changes in the brain cortex can predict which animals will develop epilepsy. A multi-center NINDS-supported study is now underway

to examine whether MRI changes following febrile seizures can predict which patients will ultimately develop epilepsy.

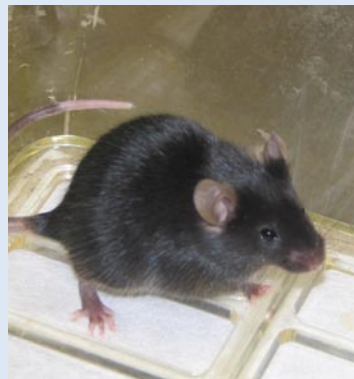
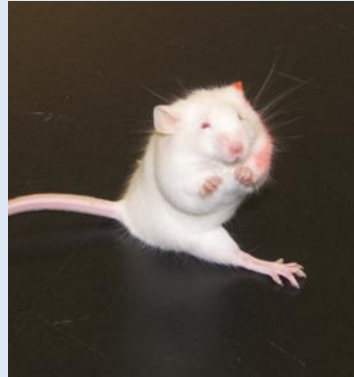
- Some studies suggest that high-frequency brainwaves (250 – 600 Hz), called “fast ripples,” may reliably show which brain areas generate seizures in people with temporal lobe epilepsy. These high-frequency brainwaves sometimes occur soon after the brain is damaged, long before seizures begin, which suggests that they could be used to identify people at high risk of developing epilepsy. If so, researchers might be able to intervene to prevent epileptogenesis. At present, high-frequency brainwaves can only be detected by direct brain recordings, which require implantation of electrodes deep in the brain. Researchers are testing whether other techniques, such as fMRI, may be able to detect the metabolic changes that result from these brainwaves.
- Researchers are studying whether the scanning technique positron emission tomography (PET) can identify seizure-generating brain tissue. One study showed that, in patients with tuberous sclerosis who have brain tubers and epileptic seizures, a substance called alpha methyl tryptophan (AMT) accumulates in seizure-generating regions of the brain and can be measured with PET. Other substances, including one that binds to a kind of serotonin receptor, also show changes in people with epilepsy and may serve as markers to identify seizure foci in the brain.
- A number of laboratories are using transcranial magnetic stimulation (TMS) as a diagnostic and therapeutic tool for epilepsy. In TMS, researchers use a powerful magnet



Scientists use diffusion spectroscopic imaging (DSI) to portray the paths that neurons use to connect to each other within the brain. In this image, DSI shows the multidirectional fiber tracks in the cortex of the developing epileptic brain, allowing scientists to examine whether altered connections lead to abnormal neuronal discharges and seizures.

held next to a person’s head to create magnetic pulses. These pulses affect neuronal activity in the brain’s cortex, and many studies have shown that TMS can be used to measure excitability in this region. In the future, TMS might be used to test the effectiveness of antiepileptic drugs.

- Other investigators are using a technique called optical intrinsic signal imaging to measure brain changes associated with neuronal activity. This type of imaging uses electrodes and a small camera placed on the surface of the brain to generate high-resolution, real-time maps of the neurons involved in seizures. Optical imaging shows a larger area of the brain at a higher resolution than EEGs and other methods. Several investigators have applied this technique to animal models of epilepsy and to patients in order to map the area of the brain to be removed during surgery.



These mice are some of the animal models used in testing potential new antiepileptic drugs. The white mouse is experiencing a seizure induced by the compound metrazol. The black mouse is displaying normal behavior, but has had encephalitis-induced seizures in the past.

### The Development of Animal Models that More Closely Resemble the Disease in Humans

One of the highlights of epilepsy research in the past decade has been the development of new animal models. These models are among the most important tools available for epilepsy research. While there is still no model that truly mimics human epilepsy, studying animal models can help to answer questions about how epilepsy develops and how repeated seizures affect brain structure and function.

Researchers use animal models to identify factors that serve as targets for antiepileptic drugs and drugs that can prevent epilepsy. The models also provide a way to test potential therapies for usefulness before they are tried in humans. Models with specific altered genes help researchers learn when biological defects arise during development, as well as which brain networks are affected by each gene. Researchers hope to use this information to learn when epilepsy might be reversible and when it could be prevented.

Most animal models for epilepsy are developed by exposing rats or other animals to toxins or electrical stimulation in order to trigger seizures. Researchers also use genetic engineering to develop animals with specific genetic abnormalities that are linked to epilepsy.

Some of the most common models of epilepsy mimic temporal lobe epilepsy. They include the “kindling model,” as well as the “post-status models” of temporal lobe epilepsy, in which epilepsy develops after status epilepticus.

Researchers also have developed a model for minimal clonic seizures. These animals display effects similar to the aura of people with partial seizures. Investigators also sometimes use a gamma-hydroxybutyrate (GHB) model of spike-wave seizures, which mimics absence seizures. These models are widely used to study how epilepsy develops and to test potential new treatments.

Several genetic models of epilepsy are also available. Studies using these models should yield important information about how drugs will work in patients with similar mutations.

Funding by the NINDS and other organizations has now led to development of several models of drug-resistant epilepsy. These models are being used with increasing frequency in the search for novel antiepileptic drugs. Researchers hope that testing drugs in these models will help to identify therapies that can help patients with drug-resistant epilepsy.

In the last decade, researchers have developed several animal models for childhood seizures and epilepsy. These include models for febrile seizures and infantile spasms.

Researchers also are working to develop new models that mimic nerve toxin exposure. Such toxins often produce highly treatment-resistant, life-threatening, status-like seizures.

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**In the search for new treatments for epilepsy, scientists usually must first conduct research on animals whose epilepsy closely resembles the disorder in humans.**

**Several models are needed to study the different types of epilepsy in people already affected as well as those at high risk for developing it.**

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These models should help researchers identify new therapies to prevent the neuropathology associated with nerve agent-induced status epilepticus. Research using these models also will increase understanding of how status epilepticus affects the brain and should ultimately lead to the development of better therapies for people affected by this condition.

A collaborative network of investigators has begun working to identify patterns of gene activity that are common to multiple animal models of epilepsy. Funds from the NIH, the American Epilepsy Society, and the University of Amsterdam are supporting a multi-laboratory study that will look at changes in gene activity in one kind of brain cell, and compare these changes in the four most often used rat models of epilepsy. The research network also has led to a collaboration between several investigators who plan to search for blood-borne markers of gene activity that can predict whether or not rats exposed to a toxin will develop epilepsy. The consortium may be able to investigate other questions about epilepsy development in the future.



## Sherry

was 8 months pregnant with her second child...

*...when her first born, Michael, who was nearly 2 years old at the time, started having seizures. Now Michael is 12, but his seizures prevented cognitive development beyond that of a 2 year old. Right after his first seizure, he started losing skills and was unable to learn new ones. Eventually, for no apparent reason, the seizures became more frequent until he started having them every day — all day.*

*Michael has shown great resilience in taking a multitude of medications and undergoing therapies in the hope that something will give him steady, continuous relief. He also underwent surgery to implant a vagus nerve stimulator, a device which is sometimes referred to as a pacemaker for the brain. While the device moderates the seizures, Michael continues to experience about three per week. He is not a candidate for other surgeries, but he and his parents continue to look for answers.*

*Meanwhile, Michael goes to a school for children with disabilities, and Sherry has found a support group that sponsors a variety of events for children with health needs and raises money for research.*

*Sherry is proud of Michael because despite all that he has been through, he is well behaved and she says he is the kind of child who is loved by people as soon as they meet him. And she is proud of her two younger sons for loving and caring for their brother despite the demands that he makes on the entire family.*

*While Sherry worries about Michael's future and what it will mean when he reaches adulthood, she is determined to share her experiences to educate others on the need for better epilepsy research, better treatments, and a cure.*

## Developing New Ways to Prevent Epilepsy

Until recently, doctors have focused almost exclusively on treating the symptoms of epilepsy after it has developed. While advances in treating epilepsy are badly needed, the ultimate goal of research is to prevent the disorder.

Measures that lessen the risk of head injury and trauma — such as improving automobile safety and wearing seatbelts and bicycle helmets — can prevent many cases of epilepsy. Good prenatal care, including treatment of high blood pressure and infections during pregnancy, can prevent brain damage in developing babies that may lead to epilepsy and other neurological problems later in life. Treating cardiovascular disease, high blood pressure, infections, and other disorders that affect the brain during adulthood and aging also may prevent many cases of epilepsy.

While preventing accidents and disease can prevent brain damage from occurring in the first place, there is currently no way to prevent epilepsy from developing after trauma or other types of brain damage. None of the available drugs has been shown to modify or prevent the development of epilepsy in humans. Researchers are working to change this.

- A series of randomized double-blind clinical trials, sponsored by the NINDS, tested whether phenytoin, valproate, or magnesium sulfate could prevent epilepsy after traumatic brain injury. Unfortunately, none of these drugs worked. Non-blinded or non-randomized studies performed with other antiepileptic drugs also failed to reduce the number of people who developed epilepsy.

- Two new clinical studies are now investigating possible ways to prevent epilepsy after traumatic brain injury. One is studying the use of levetiracetam after mild to moderate traumatic brain injury. The other is studying whether topiramate can prevent epilepsy after moderate to severe brain injury.
- Researchers are investigating possible ways to prevent epilepsy after strokes, brain tumors, and febrile seizures.
- Investigators are starting to explore whether epilepsy can be prevented in people who are at risk because of genetic or developmental problems, such as tuberous sclerosis and cortical dysplasia. If people at risk of these forms of epilepsy could be identified before seizures develop, doctors might be able to prescribe treatments that would block or overcome the problems that cause epileptogenesis.
- Identifying the genes for many neurological disorders can provide opportunities for genetic screening and prenatal diagnosis that may ultimately prevent many cases of epilepsy. In the future, genetic testing and markers for epileptogenesis may be used to identify people who are at higher than average risk of developing epilepsy after brain injury, stroke, or other problems, so that preventive treatments can be prescribed.



These are some of the new anticonvulsant drugs being tested in animal models at the NINDS-funded Anticonvulsant Screening Program at the University of Utah.

## Epilepsy has many causes.

Sometimes it occurs as a result of developmental problems before birth. Other cases are caused by infection, tumors, stroke, or injury that damages the brain. Months, even years, can pass between the time of an injury and the development of epilepsy.



**Current treatment for most people with epilepsy primarily consists of long-term use of antiepileptic drugs. If drug therapy is not successful in controlling seizures, surgery, dietary changes, or use of an electronic implant may be tried. At least one million Americans of all ages continue to have seizures despite treatment or are affected by unpleasant side effects of current therapies.**

## Developing New Treatments that Eliminate Seizures Without Side Effects

People with epilepsy have more and better treatment options than ever before. There are now 21 antiepileptic drugs approved for use in the United States, and many more are in development. The use of surgery has been greatly refined, and new surgical techniques have been developed. People also may be treated with vagus nerve stimulation or the ketogenic diet in some cases.

Individuals with seizures that are not controlled by drugs or surgery, however, make up approximately 25 to 30 percent of the epilepsy patient population. Even when seizures are controlled, the quality of life for some people with epilepsy is severely affected by the long- and short-term side effects of medication or surgery.

Fortunately, the improved understanding of epilepsy resulting from research on epileptogenesis has led to many potential new treatments. Some of these treatments are now in clinical trials, while others are still in early development. If these treatments work as anticipated, they should greatly improve the care of people with epilepsy.

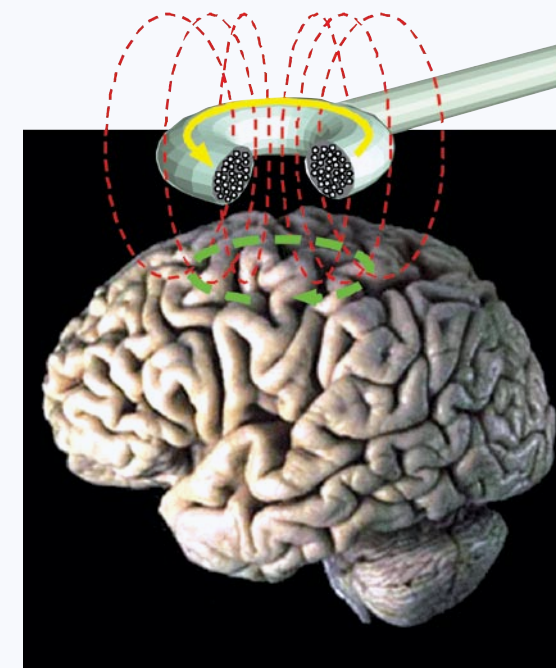
### Antiepileptic Drugs

The large amount of research on epilepsy in recent decades has led to the development of many potential antiepileptic drugs. Some are similar to drugs already in use.

- Brivaracetam and seletacetam are two new drugs that are chemically related to

levetiracetam. Because of the way these drugs work, researchers believe they may be more potent than levetiracetam. Both drugs are now being tested in large clinical trials. Another drug, eslicarbazepine, is similar to oxcarbazepine, and the new drugs fluorofelbamate and RWJ-333369 are similar to felbamate. Several other drugs — isovaleramide, valroceamide, and DP-VPA — are chemically similar to valproate.

- Some new drugs appear to work in completely new ways. These include retigabine, rufinamide, and lacosamide. Retigabine affects potassium channels in the cell membrane and may also affect the response to GABA. Rufinamide appears to affect sodium channels, and early clinical trials have shown that it can reduce treatment-resistant partial seizures and the seizures associated with Lennox-Gastaut syndrome. Both retigabine and rufinamide are now in clinical trials. Studies suggest that lacosamide works in part by altering the activity of specific sodium channels and inhibiting a protein called collapsin-response mediator protein 2 (CRMP-2) that affects axon growth. Clinical studies have shown that it can help prevent partial seizures.
- Other new drugs include talampanel, ganaxolone, and safinamide. Talampanel works by blocking one kind of glutamate receptor. Ganaxolone is a steroid that interacts with GABA receptors. Researchers do not yet know how safinamide works.
- A study in newborn rats showed that seizures could be blocked by bumetanide, a commonly used diuretic (urine-increasing) compound that blocks the effects of GABA release. While these results are preliminary, they suggest that bumetanide or related drugs might be a new way of treating seizures in young children.



This picture shows transcranial magnetic stimulation (TMS). In TMS, researchers use a powerful magnet held next to a person's head to create magnetic pulses that affect neuronal activity in the brain's cortex. Many studies have shown that TMS can be used to measure excitability in this region. In the future, TMS might be used to test the effectiveness of antiepileptic drugs.

### Surgery

Researchers have greatly refined surgical treatment of epilepsy in the past decade. Many investigators now consider surgery the most suitable option for many people with epilepsy that is not well controlled by drug therapy. Surgery is currently the only treatment that can truly cure epilepsy, at least in some people.

When seizures are caused by a brain tumor, hydrocephalus, or other conditions that can be treated with surgery, doctors may operate to treat these underlying conditions. In many cases, once the underlying condition is successfully treated, a person's seizures will disappear as well.

Doctors currently use several surgical techniques to treat epilepsy. The most common type of surgery for epilepsy is removal of a seizure focus, or small area of the brain where seizures

# Anticonvulsant Screening Program

Record numbers of researchers, supported by the NIH as well as nonprofit organizations and industry, are continuing to search for new compounds that might be used to treat epilepsy. One of the largest drug screening programs is the NINDS Anticonvulsant Screening Program (ASP). The major goals of this program are to find safer, more effective antiepileptic compounds, to discover effective treatments for patients with drug-resistant epilepsy, and to one day develop ways of stopping disease progression.

The ASP screens an average of 700 new chemicals each year, using both animal and laboratory tests. A variety of models are employed to assess candidate molecules and to compare them to standard antiepileptic drugs and similar drugs that have already been tested. ASP evaluations focus efforts on the most novel and promising drugs. These efforts provide needed incentive and resources for researchers, saving investigators years in development time. The ASP played an important role in the identification and development of the drugs felbamate and topiramate. Currently there are eight new compounds that the ASP screened and helped bring to human testing. One of these molecules, called lacosamide, has recently finished clinical testing and will soon be reviewed by the FDA for marketing.

The ASP maintains a database of approximately 27,000 compounds — the most varied collection tested for anticonvulsant activity and toxicity in the world of compounds. All of the data have been generated by a single facility with consistent methodologies to help ensure that the results are reproducible. The database has become a most critical and valuable tool, allowing NINDS staff to compare large numbers of biological and structural data to help assure that only the very best molecules are brought forward.

The ASP is also in the process of developing a new web-based search tool to provide access to years of nonproprietary data about antiepileptic drugs in development. This database, called PANACHE (Public Access to Neuroactive & Anticonvulsant CHEMical Evaluations), will help investigators predict a drug's side effects based on previous data.

originate. In another surgical procedure, called multiple subpial transection, surgeons make cuts that are designed to prevent seizures from spreading into other parts of the brain while leaving the person's normal abilities intact. Doctors also may use surgical procedures called corpus callosotomy (severing of the nerve fibers that connect the two sides of the brain) and hemispherectomy (removal of half of the brain) in some cases.

A number of clinics now offer gamma knife surgery for some kinds of epilepsy, and researchers are working to improve this type of procedure. Gamma knife surgery, which was first developed in the 1960s, uses finely focused radiation beams that intersect at a specific region of the brain to alter the cells in that region. In many cases, this can stop the abnormal electrical activity that causes the seizures. A study of gamma knife surgery in patients with temporal lobe epilepsy, reported in 2006, found that 67 percent of the treated patients were seizure-free 2 years after surgery. Several ongoing clinical trials are now testing gamma knife surgery for temporal lobe epilepsy. Another study published in 2006 looked at the use of gamma knife surgery to perform callosotomy in patients with severe generalized epilepsy with drop attacks and found that the results were comparable to traditional callosotomy.

Researchers are continuing to test gamma knife surgery to learn what types of epilepsy can be effectively treated, what radiation frequencies are best, what type of presurgical testing is necessary, and what benefits and side effects are possible with this type of surgery.

Surgery can substantially improve quality of life by reducing the frequency of seizures or preventing particularly damaging seizures such



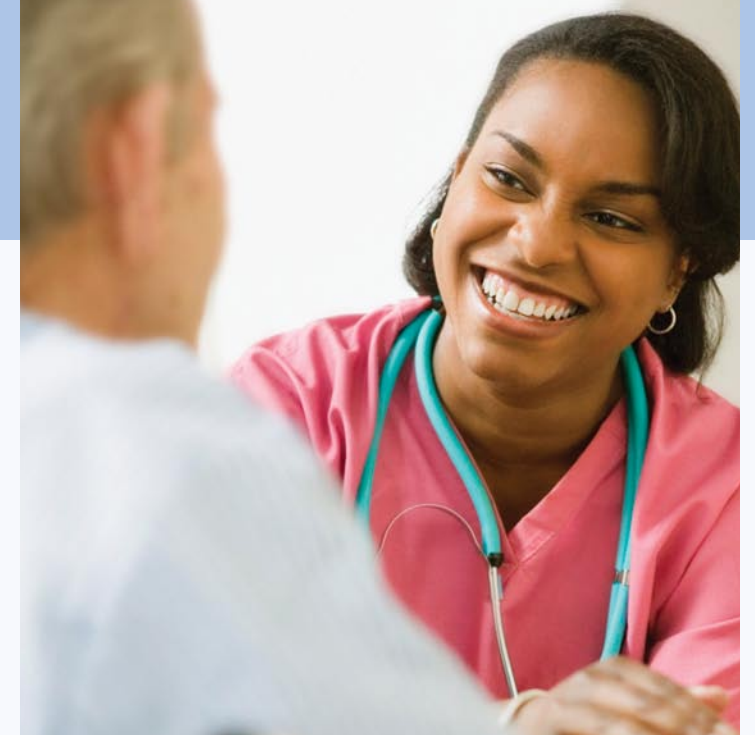
as drop attacks. However, surgery can also lead to cognitive and neurological problems. For example, surgery for temporal lobe epilepsy, which is the most common type of surgery for drug-resistant epilepsy, can sometimes cause a loss of verbal memory. Improved ways of identifying the seizure focus should reduce this risk.

Technological improvements in imaging techniques are some of the most important factors for increasing the success of epilepsy surgery. Improvements in hardware, software, and data acquisition and storage have also increased the usefulness of surgery.

- New developments in neuroimaging have made it possible to identify the brain regions where seizures begin in many people who were not formerly considered good candidates for surgery. The risks associated with epilepsy surgery are relatively low — a 4 percent risk of complications in one study — but they vary with seizure type and other factors.

- Most current NIH-funded clinical epilepsy studies are focused on finding ways to more accurately select patients by developing improved methods to identify the epileptogenic region of the brain. These include studies testing optical imaging, MRI and fMRI, PET, proton magnetic resonance spectroscopy, and improved EEG recording and data analysis. Laboratories also are testing a technique called diffusion tensor imaging. This type of analysis has been found to produce accurate information on the region and extent of the seizure-generating network in epilepsy.

- One study showed that using magnetic resonance spectroscopy to identify specific chemical abnormalities in the brain can predict the success of surgery in temporal lobe epilepsy but not neocortical epilepsy. Researchers are also testing magnetoencephalography (MEG) as a tool for detecting seizure-generating brain tissue. Investigators have shown that MEG can be as accurate as invasive video EEG at locating epileptogenic regions.



for epilepsy was the vagus nerve stimulator. In vagus nerve stimulation, an implanted device sends signals to the brain by way of the vagus nerve in the neck. Several other types of brain stimulation are now being tested for epilepsy. These include chronic deep brain stimulation, trigeminal nerve stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation.

- Researchers are conducting a multicenter clinical trial of continuous deep brain stimulation of the thalamus to treat epilepsy. The treatment is similar to the deep brain stimulation used for Parkinson's disease, dystonia, and other conditions. Previous studies have suggested that stimulating the thalamus can reduce the frequency of seizures in people with partial and generalized seizures. Some researchers also are testing stimulation of the subthalamus and other deep brain regions. For example, several studies have tested whether stimulation of the brain's thalamus can help people with treatment-resistant multifocal epilepsy. One study of this treatment showed little benefit, but another showed encouraging results.

Researchers are trying to learn exactly how the ketogenic diet prevents seizures. They hope to find ways to chemically mimic its seizure-blocking effects without the dietary restrictions.

- Several studies have suggested that substances called beta-hydroxybutyrate (BHB) and acetoacetate, which increase in people who follow the ketogenic diet, play a role in blocking seizures.
- Researchers used a chemical called 2-deoxy-D-glucose (2DG) to block carbohydrate breakdown in a rat model of epilepsy. This chemical reduced the expression of genes involved in epilepsy and reduced the number and severity of seizures in the rats. If this substance works in people, it might be the basis for a new class of antiepileptic drugs.
- Studies are examining which types of seizures and epilepsy syndromes respond best to the ketogenic diet. Studies have shown particularly good results with infantile spasms, pyruvate dehydrogenase deficiency, and glucose transporter protein deficiency. The diet is also useful for some people with other forms of epilepsy.
- Several clinical studies are now testing whether the high-protein Atkins diet and other diets that are less extreme than the ketogenic diet may help to reduce seizures.

### Brain Stimulation

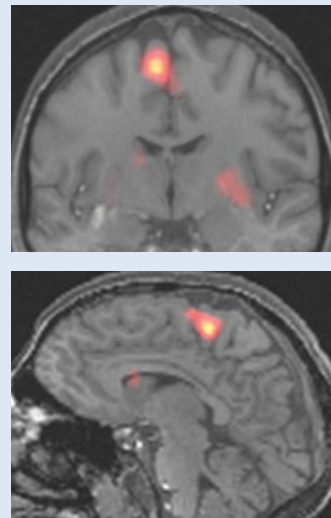
Many studies have shown that brain stimulation can reduce seizures in some people with epilepsy. The first approved brain stimulation technique

the regions where they begin often cannot be identified by current methods. Research suggests that surgery may be very effective in this patient population if doctors can determine where the seizures begin.

- Researchers are now using functional imaging, electrophysiological tests, and modeling studies in patients with multifocal epilepsy in order to better understand how multifocal seizures spread. For example, they are studying people with cortical dysplasia, tuberous sclerosis, lissencephaly, and other disorders that commonly include multifocal or symptomatic generalized epilepsy. They also are working to develop new imaging tools that can allow noninvasive, real-time imaging of seizures as they begin and spread. These studies may help identify central regions that can be activated to suppress multifocal and treatment-resistant seizures.
- Several studies have now shown that focal surgery in properly selected patients with tuberous sclerosis can have excellent results if the seizure focus is carefully located by electrophysiology. Locating seizure-generating regions with intracranial electrodes can improve the outcome of surgery. Developing less invasive ways to identify seizure-generating regions of the brain offers the opportunity to further improve treatment.

### Diet

The ketogenic diet, which includes high amounts of fat and very low amounts of carbohydrates, is an age-old treatment for epilepsy that has been revived in recent years. The diet effectively reduces seizures for some people, especially children, but it is difficult to maintain.



These images show areas of unusual brain activity during a seizure. They were generated by adding a single photon emission computed tomogram (SPECT) image to a magnetic resonance imaging (MRI) image. The image allowed doctors to identify and remove the brain area that generated the seizures.

- Another study found that single photon emission computed tomography (SPECT) was superior to PET in the imaging of receptors for the neurotransmitter acetylcholine, which made it better for identifying where seizures begin.
- Other researchers are studying whether cognitive studies can help to identify seizure-generating brain regions and predict cognitive problems following epilepsy surgery.

Researchers are also working to develop better ways of predicting the success of surgery. This information can guide the selection of patients for surgery and medical treatment after surgery.

Another challenge in epilepsy research is how to effectively treat multifocal epilepsy, in which seizures originate in more than one area of the brain. In multifocal epilepsy, which is common in people with tuberous sclerosis and several other disorders, seizures spread so rapidly that



- A study published in 2006 tested stimulation of the trigeminal nerve, which carries sensory information from the face to the brainstem, in nine people with complex partial and generalized tonic-clonic seizures. The researchers found that the stimulation was well-tolerated and reduced seizure frequency in most of the subjects. The researchers hope to test this therapy in a larger group of patients.
- Transcranial magnetic stimulation (TMS), a noninvasive type of brain stimulation that uses a powerful magnet outside of the skull to deliver magnetic pulses, is another potential treatment for epilepsy. TMS changes electrical activity in targeted regions of the brain. It has been used to study epilepsy for many years, and investigators have now begun testing whether it can be used to suppress seizures. Although some studies have shown that repeated TMS can slightly reduce seizures in some people, the benefits were short-lasting.

- Another noninvasive brain stimulation technique, transcranial direct current stimulation (tDCS), uses electrodes on the head to deliver weak electrical currents that can change neuronal excitability. Researchers at the NINDS are conducting a clinical trial to determine if repeated tDCS can change seizure frequency in people with drug-resistant temporal lobe epilepsy.

### Gene Therapy

The discovery of gene mutations that cause specific epilepsy syndromes has led to the possibility of using gene therapy to counter the effects of these mutations. In gene therapy, researchers typically use viral vectors to introduce new genes into brain cells. Viruses can also be used to introduce genes for proteins such as GABA into non-neuronal cells. These cells are then transplanted into the brain to act as “factories” to produce potentially therapeutic proteins.

One advantage of gene therapy is that it can alter the cells in just one part of the brain. Researchers can control the activity of the introduced genes by using a genetic “switch” that responds to antibiotics or other chemicals. This allows doctors to turn the gene therapy off if it causes intolerable side effects or other problems. Theoretically, this type of therapy should last longer and cause fewer side effects than medication.

- A number of studies have tested gene therapy in animal models of epilepsy. In one study, researchers transferred a gene called NPY into the hippocampus of a rat model of epilepsy using an adeno-associated virus (AAV) vector. The study found that the transferred gene was widely expressed in the brain, that seizures induced by a toxin were markedly delayed, and that status epilepticus was eliminated. These results suggest that a similar approach might be useful in humans.
- A second study tested gene therapy using AAV to deliver the gene for the neuropeptide galanin, which acts as an anticonvulsant, into the brains of rats that had been exposed to a toxin or electrical stimulation to induce seizures. The treated rats had fewer seizures than those that received a control treatment.
- A third study tested transplanted myoblasts (stem cells from muscle) that were genetically engineered to release adenosine. These cells were placed inside capsules and transplanted into the brain ventricles of epileptic rats. The treatment suppressed seizures for at least 3 weeks in half of the treated rats.



### Cell Transplantation

Another emerging approach for treating epilepsy is cell transplantation. Researchers can transplant either mature cells or stem cells derived from fetal tissue. Cells used for transplant are sometimes genetically engineered to produce substances to reduce seizures or protect neurons from damage. Cell transplantation therapies for epilepsy are still in preliminary stages of development. However, the encouraging results of animal studies suggest that this type of therapy may eventually be used to treat drug-resistant human epilepsy.

- One study tested whether transplanting GABA-producing cells into the brains of rats could suppress seizures. The cells raised GABA levels in the brain tissue, raised the seizure threshold, shortened the duration of brain discharges after seizures, and slowed the development of seizures.

## Denise,

a financial administrator with the City of New York...

...suffered a head injury that dramatically changed her life. Twelve years ago, Denise was in a cab when it was involved in an accident. She hit her head and suffered a severe trauma. Not knowing the extent of the damage, Denise, who was a senior bank regulator, was gradually losing her ability to read, write, and speak. But she was unaware of the cause and of the fact that she was actually having minor seizures. Over a year and a half later, after a long international trip in which she didn't get much sleep, Denise had a tonic-clonic seizure and was finally accurately diagnosed.

She then began a 5-year odyssey of finding the right treatment. While Denise was on disability leave from work she spent a lot of time going to specialists, trying different medicines, and getting speech and physical therapy. She says her efforts paid off. She found a drug that she takes three times a day and another she takes when she feels a seizure coming on. With her seizures under control, she's back on the job doing what she loves.

Denise does a lot of public speaking about epilepsy and the need to get properly diagnosed and treated. She says that there are many more treatment options available now than there were 20 years ago. She says that without them, she wouldn't be here right now. Additionally, while she is always looking for opportunities to fight the stigma of epilepsy, she believes the public still has much to learn about the disease and the challenge of having it.

- Another study tested the effect of neural stem cell transplantation in rats with status epilepticus induced by a toxin. The neural stem cells differentiated into inhibitory interneurons and decreased neuronal excitability.
- A third study used adenosine-releasing embryonic stem cells encapsulated into polymer membranes and grafted into the brain ventricles of a rat model of epilepsy. Researchers found that the treated animals had short-term protection from convulsive seizures.
- Yet another study found that grafting specific types of fetal hippocampal cells into the brains of adult rats with toxin-induced brain lesions reduced the amount of abnormal nerve fiber growth in the brain. The grafted cells also developed connections with another region of the brain, suggesting that they may be able to form functional brain circuits.

### Vaccines

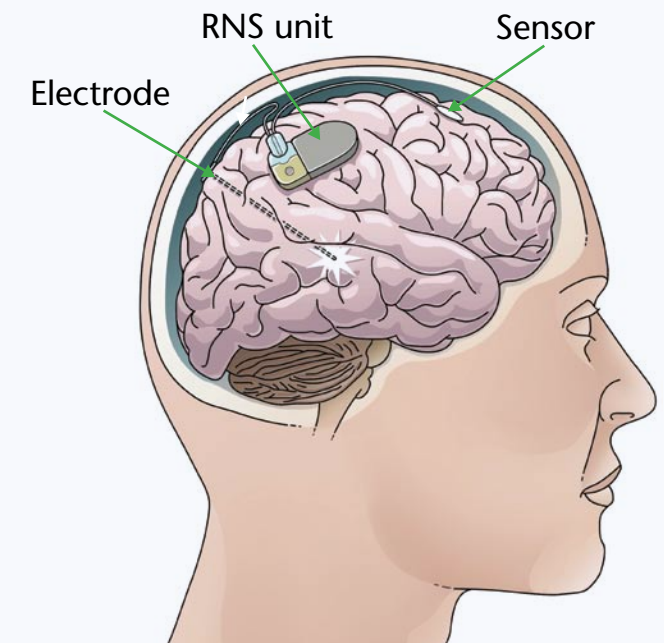
In recent years, researchers have begun to develop immune-modulating therapies, or vaccines, to treat neurological disorders. This type of therapy employs the immune system to disable proteins contributing to disease. Investigators are now beginning to test immune therapies specifically for epilepsy. For example, in one study of an experimental vaccine for epilepsy, researchers used an AAV-associated vaccine to generate antibodies that blocked a subunit of the NMDA receptor. NMDA receptors are one kind of receptor for the excitatory neurotransmitter glutamate; previous studies

have shown that they contribute to the neuronal injury associated with epilepsy. The vaccine in this study helped to prevent seizures in a rat model of temporal lobe epilepsy.

### Therapies to Predict or Interrupt Seizures

A major new area in epilepsy investigation is developing systems that anticipate epileptic seizures and then deliver a therapy to stop them. For example, researchers might be able to use electrical stimulation, a local drug infusion, or cooling of one part of the brain to arrest seizures. This type of therapy could be very useful for people who don't respond well to standard epilepsy treatments and who are not good candidates for surgery. However, the success of seizure-interrupting treatment depends upon the development of methods to detect patterns of brain activity that predict seizures.

- A number of studies have shown that high-frequency brainwaves indicate the beginning of a seizure. Studies also have shown evidence of a "pre-seizure" period in temporal lobe epilepsy. For example, EEGs of some people with temporal lobe epilepsy show prolonged bursts of complex neuronal activity hours before seizures begin and subclinical seizure-like activity up to 2 hours before onset. Some research suggests that similar pre-seizure changes may occur in other kinds of epilepsy.
- Investigators are working to develop a high-quality, complete archive of intracranial EEG data, symptoms, brain images, and other information to help researchers understand how to predict and interrupt seizures. They also are developing improved batteries, electrode arrays, and brain-computer



The responsive neurostimulator (RNS) system, which is being tested in clinical trials, monitors the brain's electrical activity using implanted electrodes. When the system detects the onset of a seizure, it uses a pacemaker-like device implanted in the brain to deliver a small amount of electricity in order to interrupt seizures before symptoms appear.

interfaces. In the future, treatments such as cooling or infusing drugs into specific brain areas might be used in place of electrical stimulation to interrupt seizures.

- One seizure-interrupting device, called a responsive neurostimulator system, is now being tested in a multicenter clinical trial of patients with temporal lobe epilepsy, bi-temporal epilepsy, and neocortical epilepsy. This therapy uses a pacemaker-like device implanted in the brain to deliver a small amount of electricity when it detects the onset of a seizure.



## Personalized Therapies

Because both the efficiency and side effects associated with specific epilepsy medications vary greatly from person to person, one way to improve epilepsy treatment is to develop ways to predict individual responses to medications. As investigators gain knowledge about genes, environmental factors, and other characteristics that influence epilepsy treatment, they believe it will eventually become possible to tailor therapies to individual patients, taking into account their age, gender, genetic variations, and other factors. This personalized treatment would give individuals better symptom relief and fewer side effects.

Recent studies have significantly improved our understanding of how age and gender affect the response to epilepsy therapy. For example, researchers now know that GABA may act as an excitatory neurotransmitter very early in life, and they are beginning to develop therapies that take this into account. Studies also have shown that gender influences the function of GABA receptors.

Much of the individual variation in how people respond to medications is due to genetic differences. For example, single-letter variations, called SNPs, in genes that regulate or produce drug-metabolizing enzymes can alter the way anticonvulsant drugs are metabolized. These variations may cause drugs to build up to unexpectedly high levels in the bloodstream, leading to serious side effects. Other gene variations can alter anticonvulsants' ability to enter or remain inside cells. These variations increase resistance to treatment.

- Investigators are working to identify more gene variations and to understand how they influence individual responses to treatment. Eventually, it may become possible to test for these genetic variations and to use the information to prescribe more effective treatments. Researchers also may be able to develop ways of overcoming genetic resistance to treatment.



- The NINDS is funding a large clinical trial in 439 patients at 32 centers to identify how genetic variations affect side effects and responses to anticonvulsants in children with childhood absence epilepsy. The investigators also are looking at the relationship between anticonvulsant effectiveness and variations in three different calcium channel genes.
- The Epilepsy Foundation has funded a study examining how variations in carbamazepine and valproic acid drug-metabolizing enzymes affect drug metabolism and side effects.
- Another project, funded by the NINDS, uses microarrays to investigate patterns of gene expression that influence the effectiveness of valproic acid and carbamazepine efficacy in children.

Investigators are now working to develop a consortium of epilepsy researchers with an interest in pharmacogenetics (the study of how gene variations affect drug responses) to conduct coordinated studies that combine drug response information with analysis of gene variations. They also hope to develop standard approaches for analyzing and interpreting genetic data. Eventually, researchers may be able to develop microarrays or other methods that can rapidly analyze genetic variations in people with epilepsy.

## 3. Reducing the Day-to-Day Impact of Epilepsy



While research to understand, prevent, and treat epilepsy continues at a rapid pace, experts increasingly recognize the impact of epilepsy on quality of life. A number of efforts are underway to reduce this impact.

The Centers for Disease Control and Prevention sponsored two conferences on “Living Well with Epilepsy” in 1997 and 2003 to focus attention on issues of concern. These include the need for early detection and diagnosis; improved access to epilepsy specialists and comprehensive care; criteria for quality care of epilepsy and comorbid conditions; and improved understanding of epilepsy’s effects on cognition, mental health, and other aspects of life. They also include the need to foster empowerment and independence for people with epilepsy and the need for public education to overcome stigma and to improve seizure recognition and first aid. A number of initiatives have resulted from these conferences.

### Quality of Life

Many people know little about epilepsy, and are fearful of or don’t know how to respond to people who have seizures. This stigma, coupled with the restrictions commonly experienced by people with epilepsy, have harmful effects on psychological health and quality of life. Several epilepsy organizations are working to increase public knowledge about epilepsy and reduce the stigma associated with it. The Epilepsy Foundation also has developed training materials designed to help police, emergency medical technicians, and other “first responders” understand epilepsy and effectively treat seizures.

People with epilepsy may find it difficult to obtain employment because of potential employers’ fears and misconceptions about the disorder. They also may face other barriers to employment, including transportation issues and cognitive effects of medication. Public education and improved treatments for epilepsy can reduce

these problems. Epilepsy organizations are increasing public education efforts and research on how epilepsy affects cognition and mood in order to reduce barriers to employment and good quality of life.

Another quality of life issue is that people with severe, treatment-resistant seizures have, on average, an increased risk of cognitive impairment and a shorter life expectancy, particularly if seizures begin in early childhood. The cognitive impairments may result from the underlying conditions that cause epilepsy or from epilepsy treatment.

### SUDEP

People with epilepsy have an increased risk of dying suddenly. This condition is called sudden unexplained death in epilepsy (SUDEP). Research is ongoing to determine risk factors for SUDEP. It is not clear whether the use of multiple drugs causes the sudden death, or whether people who use multiple anticonvulsants have a greater risk of death because they have more severe types of epilepsy. People with tonic-clonic seizures, uncontrolled seizures, or epilepsy combined with other neurological disorders also have a greater risk of SUDEP than others.

### Reproductive Issues

Women with epilepsy are often concerned about their fertility and their ability to carry and deliver a healthy child. A recent study found that women with epilepsy are more likely than other women to develop premature ovarian failure, although the reasons are still unknown. However,

most women with epilepsy can become pregnant. The risk of birth defects in children of women with epilepsy is about 4 to 6 percent, only slightly higher than the 3 to 4 percent risk in the general population. This risk can be reduced if women and their doctors work together to minimize the risks associated with antiepileptic drugs.

A recent study has shown that children exposed to valproic acid during pregnancy have a greater risk of major birth defects and fetal death and significantly lower verbal intelligence at age 2 than children whose mothers took carbamazepine, lamotrigine, or phenytoin. However, the researchers do not yet know whether the effects on verbal intelligence are permanent or whether other antiepileptic drugs have similar effects.

### Comorbid Disorders

Expanding research on disorders that are commonly associated with epilepsy (comorbid disorders) is another important way to address quality of life issues. Epilepsy is often associated with other disorders, such as autism, Rett syndrome, cerebral palsy, tuberous sclerosis, pyruvate deficiency, neurofibromatosis, or Alzheimer’s disease. In most of these cases, the associated disorders may be caused by the same brain abnormalities or metabolic defects that caused the epilepsy.

People with epilepsy have an increased risk for depression and anxiety. These problems may sometimes be a reaction to the social problems and stress of living with epilepsy. However, several studies suggest that depression may





## Epilepsy in Children

Compared to adults, infants and children have a relatively high risk of developing epilepsy. Seizures in children may interfere with brain development by changing brain connections and response to neurotransmitters. The type and severity of the developmental effects depends on the type of seizures, their underlying cause, and the stage of brain development when seizures began. Some children will end up with long-term cognitive or neurological problems. It is often unclear whether these problems begin before the onset of seizures or whether they are actually caused by the seizures, by antiseizure medication, or by the psychological consequences of a diagnosis of epilepsy.

One study examined the use of special education services before onset of seizures and during the first 5 years after the diagnosis of epilepsy in children. The results of the study showed that, in children with epilepsy who were otherwise neurologically normal, approximately 15 percent received special educational services before the onset of their seizures. These results suggest that, at least in some cases, developmental problems began before the onset of seizures and were not directly caused by epilepsy or anticonvulsant medication.

It is not uncommon for children and others with epilepsy to develop social, behavioral, and emotional problems. Sometimes these problems are caused by embarrassment or frustration because of their disorder. Additional problems may result from teasing and other social issues in school and other social settings. The Epilepsy Foundation has developed educational materials and a campaign to increase knowledge of epilepsy among young people and reduce

precede epilepsy, and that it may be linked to the same neurotransmitter abnormalities and brain regions that are associated with epilepsy. In addition, some antiepileptic drugs, like carbamazepine and lamotrigine, affect the neurotransmitter serotonin, which is often disrupted in people with depression.

For reasons that are still unclear, people with epilepsy also have a higher prevalence of many chronic disorders, such as ulcers, migraines, chronic fatigue, and bowel disorders.

Comorbid disorders complicate epilepsy treatment and worsen quality of life. Understanding why these disorders often overlap with epilepsy and how they affect treatment and self-management is critical for improving medical care.



the stigma. The Epilepsy Foundation and the National Association of School Nurses also have developed seizure management information for school nurses.

For children who are good candidates for epilepsy surgery, studies have shown that the long-term effects are usually better if the surgery is performed as soon as possible. Because children's brains are more adaptable than those of adults, children often recover from brain surgery and seizures more easily than adults. Early surgery, if effective, also can prevent some of the problems with cognitive, social, and physical development that can be associated with repeated seizures or long-term use of anticonvulsant medication.

## Epilepsy in Older Adults

Elderly adults have a higher risk of developing epilepsy than young adults. Stroke, Alzheimer's disease, hypothyroidism, pneumonia, and other

illnesses common in the elderly sometimes cause epilepsy, and some antidepressants and other drugs commonly prescribed for elderly people may provoke seizures.

One study found that about 32 percent of all cases of newly developed epilepsy in elderly people resulted from cerebrovascular disease, which reduces the supply of oxygen to brain cells and can cause stroke or transient ischemic attacks. In addition, many elderly people take medications that may interact with antiepileptic drugs.

Studies suggest that aging also changes receptors and cell metabolism in ways that alter sensitivity to medication, and that people's resistance to developing seizures diminishes with age. Seizures in older people also are more likely to be severe than those in young adults.

## 4. Furthering Epilepsy Research — In Person



There are several ways in which individuals with epilepsy and their families can push epilepsy research forward.

People with epilepsy can help researchers test new medications, surgical techniques, and other treatments by enrolling in clinical trials. Information on clinical trials can be found at the government-sponsored website [clinicaltrials.gov](http://clinicaltrials.gov) ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) as well as at many private pharmaceutical and biotech companies, universities, and other organizations. A person who wishes to participate in a clinical trial must ask his or her regular physician to work with the doctor in charge of that trial and to forward all necessary medical records.

Patients and researchers also can learn about clinical research opportunities in epilepsy through the NINDS Clinical Research

Collaboration (CRC) ([www.nindsrcc.org](http://www.nindsrcc.org)), a service designed to help people join research studies so that new and better treatments can be developed as quickly as possible. Interested people who register as participants in the CRC will receive disease information and results from research studies.

Pregnant women with epilepsy who are taking antiepileptic drugs can help researchers learn how these drugs affect unborn children by participating in the Antiepileptic Drug Pregnancy Registry. This registry is maintained by the Genetics and Teratology Unit of Massachusetts General Hospital. For more information, call 1-888-233-2334 or visit the website at [www.massgeneral.org/aed](http://www.massgeneral.org/aed).

People with epilepsy also can help epilepsy research by donating their brains to brain banks after death. Brain banks supply

researchers with tissue they can use to study epilepsy and other disorders. Below are some brain banks that accept tissue from patients with epilepsy:

### **Brain and Tissue Bank for Developmental Disorders**

University of Maryland Department of Pediatrics  
655 West Baltimore Street, 10-035 BRB  
Baltimore, MD 21201-1559  
Tel: 800-847-1539  
Fax: 410-706-0020  
Email: [btbumab@umaryland.edu](mailto:btbumab@umaryland.edu)  
[www.btbank.org](http://www.btbank.org)

### **Brain and Tissue Bank for Developmental Disorders**

University of Miami Department of Pathology (R-5)  
1550 NW 10th Avenue  
Papanicolaou Building, Room 410  
Miami, FL 33136  
Tel: 800-59BRAIN (592-7246)  
Fax: 305-243-6970  
Email: [btb@med.miami.edu](mailto:btb@med.miami.edu)  
[www.braindonation.org](http://www.braindonation.org)

### **UM/NPF Brain Endowment Bank**

University of Miami Department of Neurology  
1501 NW 9th Avenue, Room 4013 (D 4-5)  
Miami, FL 33136  
Tel: 305-243-6219 or 800-UM-BRAIN (862-7246)  
Fax: 305-243-3649  
[www.brainbank.med.miami.edu](http://www.brainbank.med.miami.edu)



### **National Disease Research Interchange**

1628 JFK Boulevard  
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# Appendix: Benchmarks for Epilepsy Research 2000

## Basic Disease Mechanisms

*Understand the biological factors that might contribute to the development of epilepsy.*

*Discover what happens in the brain to create seizures, including changes in individual brain cells and the molecules they contain; identify other signs in the brain that predict who is at risk of developing epilepsy.*

**Background:** Epilepsy is a disorder produced by malfunctions in the chemical and electrical systems that control the normal activity of the brain. Understanding the precise chain of events that contribute to these disruptions will help scientists develop better treatments for epilepsy and ways to prevent the development of the disorder.

### ■ Benchmark

For at least one form of epilepsy, develop a way of observing brain chemistry and function in real time (i.e., as a seizure is occurring), so that it is possible to identify areas likely to produce seizures.

### ■ Benchmark

Improve the technology that allows scientists to obtain detailed images of the brain by:

- Creating a large collection of detailed MRI images of the brains of people with epilepsy. The collection would be designed so that it could be analyzed in many different ways and its images could be compared with images and information developed by researchers worldwide.
- Use part of this collection of brain images, together with information from a variety of other tests that record how the brain works, to understand the link between brain structure and brain function.

### ■ Benchmark

Establish a network of scientists who will work together to compare the results of gene-chip studies from several animal models that are used to help understand how epilepsy develops. Gene chips are research tools that allow scientists to easily measure the activity of large numbers of genes at the same time.

*Find more of the genes that make people likely to develop epilepsy.*

**Background:** In about 70 percent of all cases of epilepsy, the cause is unknown. It is likely that genes are involved in at least some of them. In fact, some genes that can lead to epilepsy have already been found. Identifying more of these genes should help scientists create new methods of treatment and prevention.

### ■ Benchmark

Increase communication and cooperation among physicians, experts in human genetics, and families with epilepsy to make it easier to study genes involved in epilepsy.

### ■ Benchmark

Organize a national group of scientists to work together in search of genes that might contribute to epilepsy by doing a large screening project that links people with epilepsy to particular gene patterns. This process should begin with a conference of leading experts to agree on which types of epilepsy should be looked at first, how the screening project will take place, and what the end results should be.

*Determine how closely the various animal models for epilepsy resemble human disease, and use the appropriate models to discover and test new kinds of treatment.*

**Background:** In the search for new treatments for epilepsy, scientists usually must first conduct research on animals whose epilepsy closely resembles the disorder in humans. Several different models are needed to study the different types of epilepsy in people already affected as well as those at high risk for developing it.

### ■ Benchmark

Develop a plan to determine how well existing animal models for epilepsy resemble what happens in human epilepsy and use the appropriate models to search for new treatments for human patients.

### ■ Benchmark

Describe and develop new animal models to study how seizures and epilepsy begin early in life and test therapies for types of epilepsy that currently cannot be successfully treated.

### ■ Benchmark

Discover and describe biological markers for epilepsy — changes in cells, tissues, or organs that occur when epilepsy is developing or has developed in the brain. Use these markers in animal models to test substances with the potential to prevent epilepsy.

## Prevention

*Create new treatments for preventing epilepsy in people who are thought to be at high risk of developing the disorder.*

**Background:** Epilepsy has many causes. Sometimes it occurs as a result of developmental problems before birth. Other cases are caused by infection, tumors, stroke, or injury that damages the brain. Months, even years, can pass between the time of an injury and the development of epilepsy. With more knowledge of how epilepsy develops before birth or following injury, it may be possible to develop treatments that will stop the process and prevent epilepsy.

### ■ Benchmark

Identify an area of the brain where seizures may begin and that has the potential to respond to preventive treatment.

### ■ Benchmark

Design clinical trials to test preventive therapies in people at highest risk for developing epilepsy. Begin planning now, so that trials can begin as soon as scientists identify potential interventions. Complete at least two major, multi-center trials.

## Treatment

*Create new medications or other treatments that will stop seizures in people with epilepsy without causing any side effects.*

**Background:** Current treatment for most people with epilepsy consists of long-term use of anti-epileptic drugs. If drug therapy is not successful in controlling seizures, surgery, dietary changes, or use of an electronic implant may be tried. At least one million Americans of all ages continue to have seizures despite treatment or are affected by unpleasant side effects of current therapies.

### ■ Benchmark

Assess how well preventive treatments work in individual patients by looking for biological markers (i.e., changes in cells, tissues, or organs that occur when epilepsy is developing or has developed in the brain) that become apparent as epilepsy develops and that can be monitored during drug treatment. Develop new treatments that are tailor-made for individuals based on their age (infants, children, adults), and on the presence of other factors that influence seizures, such as stress or hormonal cycles (in women).

### ■ Benchmark

Develop genetic tests that will help physicians identify people who may respond to a specific treatment, people who might not respond, and risk factors that may cause treatment side effects.

### ■ Benchmark

When certain natural processes in the human brain that prevent seizures don't function properly, seizures might develop. Identify and understand these processes, and use them to stop seizures or make them less severe.

### ■ Benchmark

Cure a genetic type of epilepsy by developing a therapy based on understanding the effects of a flawed or damaged gene.

### ■ Benchmark

Successfully use a device (e.g., a very small detector and/or drug pump that can be placed in the brain) that, in at least one type of epilepsy, will detect an oncoming seizure and apply treatment to stop the seizure before it begins.

### ■ Benchmark

Expand the use of surgery for epilepsy, including trying it earlier in the course of treatment. Develop new surgical treatments for epilepsy and improve existing techniques.

### ■ Benchmark

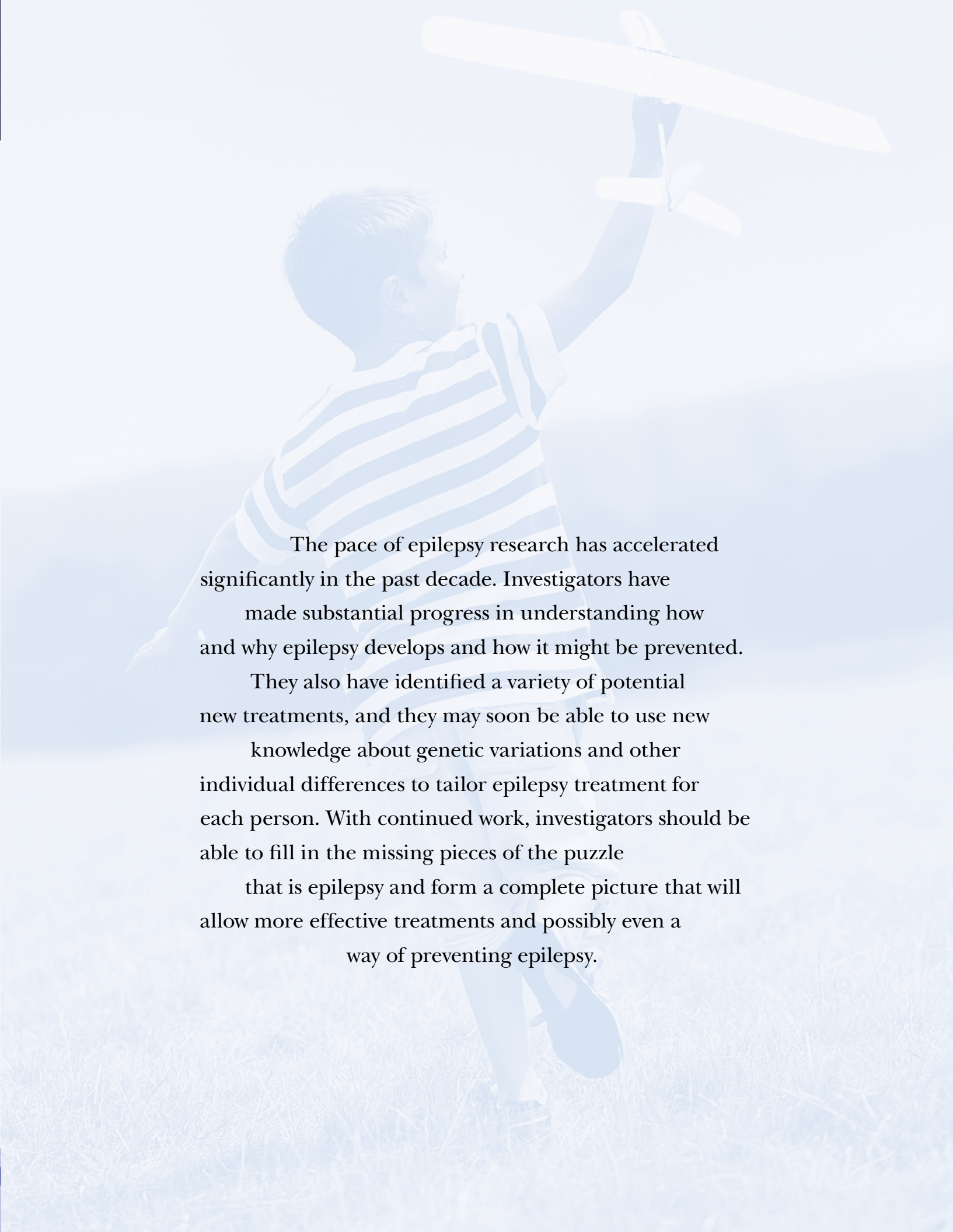
Significantly reduce seizures in at least one form of epilepsy by using a completely new type of treatment, such as cell transplantation or vaccination.

These Benchmarks for Epilepsy Research are just one part of epilepsy research efforts considered necessary to better understand and treat the disorder. They form an agenda for epilepsy research that guides the research community towards a cure. In March 2007, the NINDS sponsored a second international scientific conference, "Curing Epilepsy: Translating Discoveries into Cures." This conference will lead to a revised set of Benchmarks for Epilepsy Research that will soon be available to the scientific community. These new Benchmarks will be posted on the NINDS Epilepsy Research Web section of the NINDS website [www.ninds.nih.gov/epilepsybenchmarks](http://www.ninds.nih.gov/epilepsybenchmarks).

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The pace of epilepsy research has accelerated significantly in the past decade. Investigators have made substantial progress in understanding how and why epilepsy develops and how it might be prevented. They also have identified a variety of potential new treatments, and they may soon be able to use new knowledge about genetic variations and other individual differences to tailor epilepsy treatment for each person. With continued work, investigators should be able to fill in the missing pieces of the puzzle that is epilepsy and form a complete picture that will allow more effective treatments and possibly even a way of preventing epilepsy.



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