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EPILEPSY

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Cover art: Nik Spencer

Epilepsy has been documented for thousands of years and can affect anyone at any age. There are at least a dozen types of epilepsy — the exact number depends on who is being asked — that can start in and spread to different brain regions, creating a range of seizure types. The World Health Organization conservatively estimates that 50 million people worldwide have epilepsy; yet, despite its prevalence, the condition attracts relatively little research funding (page S2).

Part of the reason for the dearth of treatments is the long history of social stigma and fear that once surrounded people with the condition (page S10). Perhaps the most complex piece of the epilepsy puzzle is the fact that we still don't understand the brain itself; simply knowing some of the roles of neurotransmitters and ion channels does not explain why some people develop epilepsy (page S4). Studies have helped us understand enough of epilepsy's neurobiology to use surgery as a treatment, which is why neurologist Samuel Wiebe proposes that this tool is used more widely (page S7).

Neuroscience and genetics have exposed crucial pieces of the epilepsy process, but studies have not determined the network of genes that drive seizures (page S8). Until recently even drug-makers tackled epilepsy by trial and error, but now researchers are using new targets and drug development strategies to help create more effective medicines (page S12). A high-fat, low-carbohydrate diet can help reduce seizure frequency in young children (page S14), and in the future, sensors that can be worn to predict an oncoming seizure could have clinical and research applications (page S16).

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Mike May
Contributing Editor

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COLLECTION

THE COMPLEXITIES OF EPILEPSY

An estimated 50 million people worldwide have epilepsy. But research funding is low, treatment can fail and the mechanisms of the disease are a mystery. By **Neil Savage**.

ARCHITECTURE OF EPILEPSY

Epilepsy is one of the most common neurological disorders and is characterized by uncontrolled firing of the brain's neurons. There are more than a dozen types of epilepsy but the main ones are described below; a person can have more than one type. Precisely what happens in the brain during an epileptic seizure and the combination of brain areas involved have experts disagreeing on how to categorize the many forms of the disease. **See page S4.**

GENERALIZED EPILEPSY

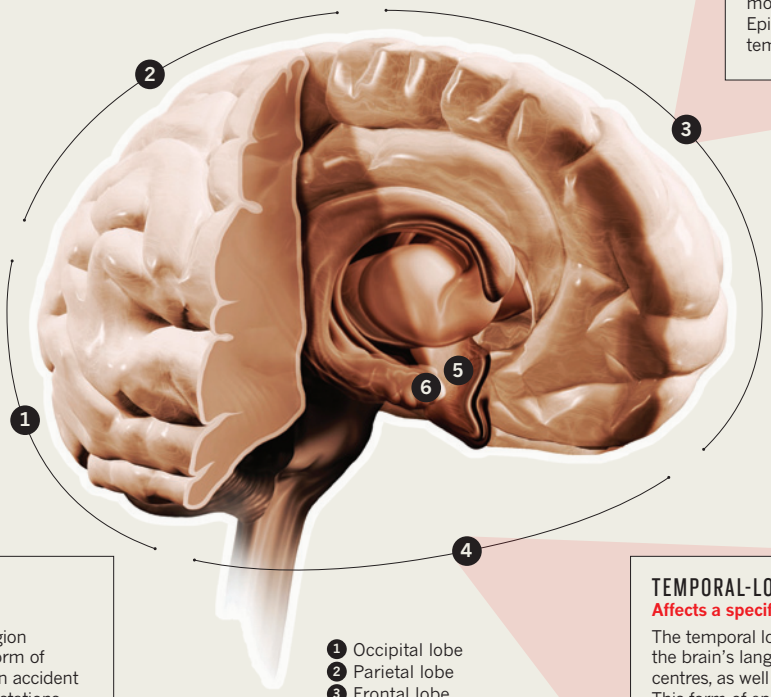
Affects most or all of the brain

Typically congenital and occurs simultaneously in both sides of the brain. The most widely recognized form is tonic–clonic, which involves a fall to the floor, jerky convulsions and unconsciousness. Absence seizures are another form of generalized epilepsy — these involve transient loss of consciousness, which may last for only a few seconds.

FRONTAL LOBE EPILEPSY

Affects a specific brain region

Seizures originating in the frontal lobe may develop into partial or generalized epilepsy. The frontal lobe brain tissues are associated with motor function and cognition. Epilepsy arising here may induce temporary alterations in personality.



of cases of epilepsy arise from unknown causes[1].

PARTIAL EPILEPSY

Affects one part of the brain

Usually limited to a specific region in one area of the brain. This form of epilepsy is often the result of an accident or neurological disease. Manifestations — such as hallucinations, twitching, smelling things or uncontrolled limb movements — can differ considerably.

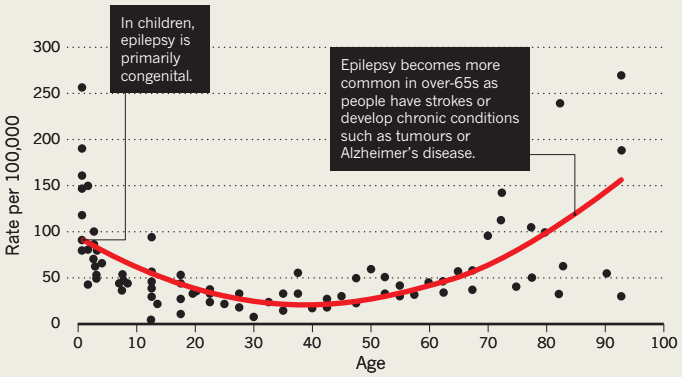
TEMPORAL-LOBE EPILEPSY

Affects a specific brain region

The temporal lobes are associated with the brain's language and auditory centres, as well as memory and emotion. This form of epilepsy varies in intensity and often arises within the hippocampus and amygdala — two structures that are deep in the brain's centre.

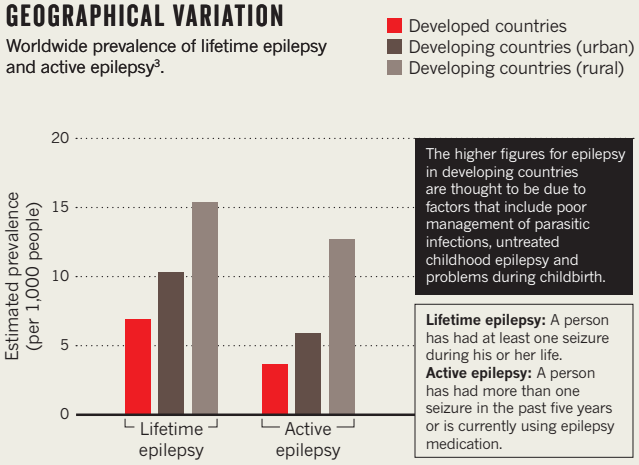
YOUNG AND OLD DANGERS

In developed countries, epilepsy is more common in children and the elderly[2].



GEOGRAPHICAL VARIATION

Worldwide prevalence of lifetime epilepsy and active epilepsy[3].

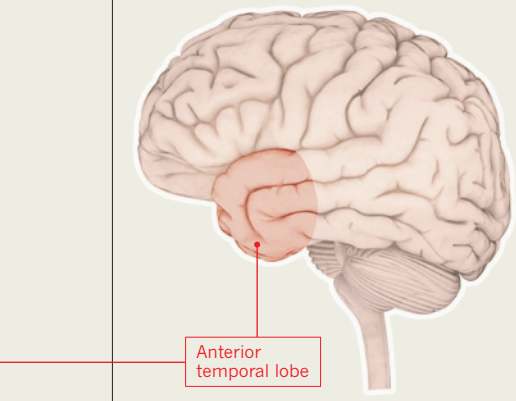


SURGICAL GAINS

Temporal lobe epilepsy is the kind most likely to be resistant to drug treatment. Fortunately, this form of epilepsy responds well to surgery. In most people suitable for surgical treatment, surgery to one side of the brain is sufficient to control seizures but sometimes the surgeon will need to operate on both sides of the brain.

How effective is surgery?

A study published in 2012 involving 38 patients reported that 11 of the 15 patients with drug-resistant mesial temporal lobe epilepsy who received surgery to alleviate seizures had two seizure-free years. None of the 23 patients who hadn't been recommended for surgery and continued with drug-only treatment had a seizure-free year[4].

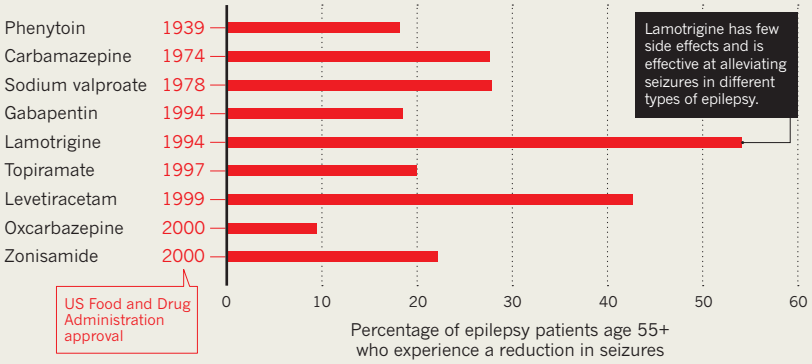


Preparation for an epilepsy operation

Data from neuroimaging techniques are used to map the brain to precisely identify regions that give rise to epileptic activity. During surgery, the aim is to remove affected tissue without damaging functionally important regions. **See page S7**.

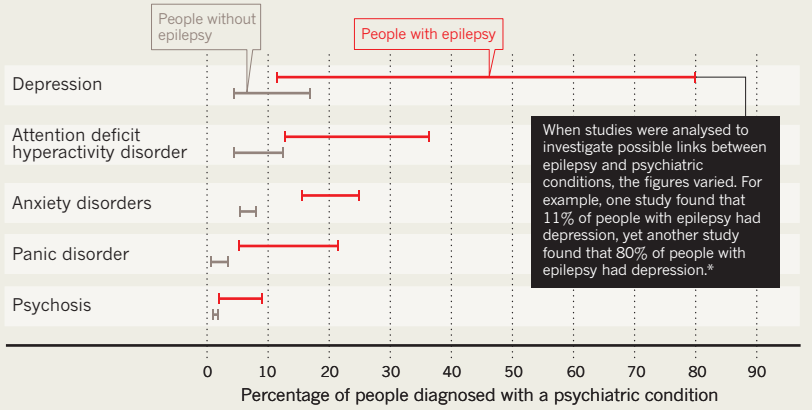
DRUGS AT WORK

Epilepsy becomes more common as people grow older (see 'Young and old dangers') but effective antiepilepsy drugs are available for patients over the age of 55 (ref. 5). **See page S12**.



PSYCHIATRIC CONDITIONS

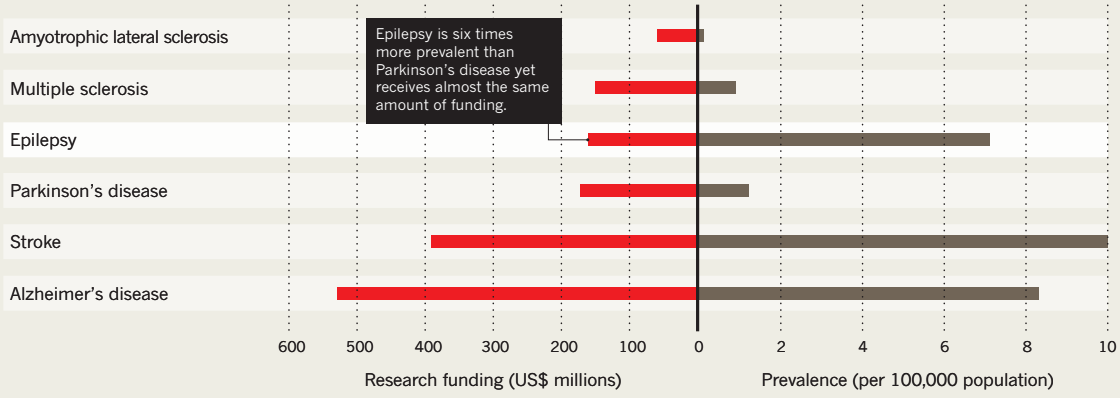
In general, people with epilepsy have more chance of developing psychiatric disorders, particularly depression, but having a psychiatric condition also raises the likelihood of developing epilepsy[6].



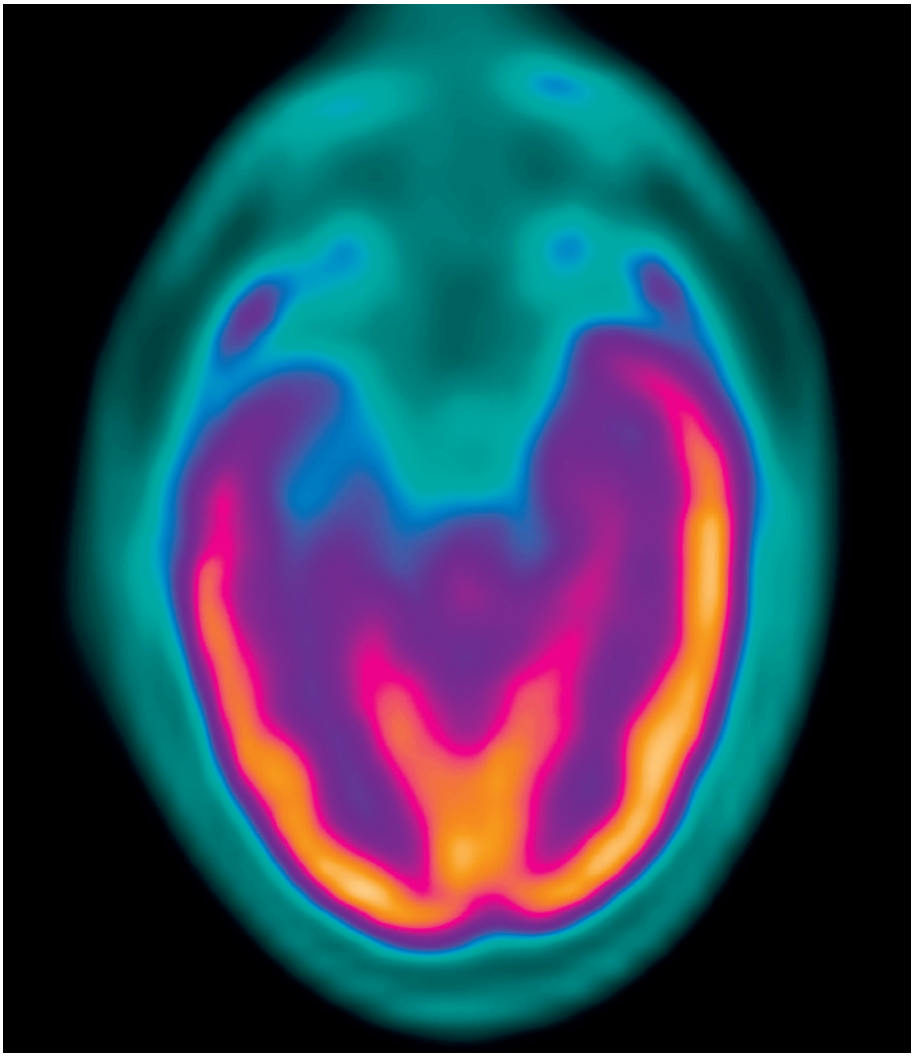
*The data used to compile the bars was extracted from studies that looked diagnosed psychiatric conditions in the general population and in people with epilepsy. The studies analysed were published between 1970 and 2002.

UNBALANCED ATTENTION

US National Institutes of Health spending on epilepsy in 2010 lagged behind less common neurological conditions. A variety of factors, from historical issues at health agencies to social stigma, may explain this discrepancy[7]. **See page S10**.



References: 1. The WHO Epilepsy Fact Sheet No. 999.; 2. Thurman, D. J. See, go.nature.com/2spiwk; 3. Ngugi, A. K. *et al*; *Epilepsia* **51,** 883–890 (2010).; 4. Engel, J. Jr. *et al. J. Am. Med. Assoc.* **307,** 922–930 (2012).; 5. Arif, H. *et al. Arch. Neurol.* **67,** 408–415 (2010).; 6. LaFrance, W. C. Jr., Kanner, A. M. & Hermann, B. *Int. Rev. Neurobiol.* **83,** 347–383 (2008).; 7. Meador, K. J. *et al. Neurology* **77,** 1305–1307 (2011).



CENTRE JEAN PERRIN, ISM/SPL

A scan showing heightened activity on the right side of the brain (bright orange) during an epileptic seizure.

NEUROBIOLOGY

Unrestrained excitement

Epilepsy arises from natural mechanisms in the brain that go awry. Researchers are trying to unravel its complexities.

BY MICHAEL EISENSTEIN

"Saying 'epilepsy' is like saying 'sneezing'," says Douglas Coulter, director of the Epilepsy Research Laboratory at the University of Pennsylvania in Philadelphia. "It's a series of disorders with a common output — seizures — but even there, you have different kinds of seizures."

During a seizure, the brain's neurons are activated in synchronized, high-frequency patterns across broad populations, starting largely without warning and ending just as abruptly. Seizures share a common feature: a breakdown in the mechanisms that normally constrain neuronal activation, or firing. Indeed, findings from one type of epilepsy can potentially inform research on other types, but it remains unclear how deep or superficial those commonalities actually are. "My view is that there are going to be common pathways," says Coulter, "but many of the mechanisms that have been described to date are quite divergent."

Reports of epileptic seizures date back thousands of years, but scientists are still grappling with the fundamental nature of the events that take place in the epileptic brain. Research continually reveals added complexity, and the blanket term 'epilepsy' has largely become anachronistic — a clinical descriptor that has limited value.

THE LIMITS OF CONTROL

At the core of epilepsy is the delicate interplay between two types of brain cell: excitatory neurons and inhibitory interneurons. Excitatory neurons release the neurotransmitter glutamate, which binds to a receptor on other neurons and promotes firing (see 'Electric ups and downs'). Inhibitory interneurons release γ-aminobutyric acid (GABA), which binds a receptor on excitatory neurons that restrains firing. Neurotransmitters typically act across synapses — the spaces between the neurons that form a neuronal circuit. However, some neurons also have receptors outside the synapse that can detect any GABA floating about, and these act as an additional failsafe when synaptic inhibition is inadequate.

Both GABA and glutamate work by modulating the amounts of positively and negatively charged ions within neurons. Normally, neurons are negatively polarized relative to their surroundings. The binding of glutamate to its receptor triggers the opening of specialized protein-based pores in the membrane known as ion channels, which allows positively charged calcium and sodium ions to flood into the responding cell. This reduces the polarization of the cell and promotes neuronal firing. GABA signalling, on the other hand, opens other channels that allow negatively charged chloride ions to enter a cell — increasing the polarization and inhibiting firing. It's therefore no wonder, says neurologist Matthew Walker of University College London (UCL) that "for epilepsies in which a mutation in a gene has been identified, the majority of the mutations affect channels and receptors".

For example, the *SCN1A* gene encodes a channel that aids excitation of a cell by allowing positively charged sodium ions to enter it. This channel is predominantly active in inhibitory interneurons; mutations that impair its function can contribute to a paediatric epileptic disorder known as Dravet syndrome as well as to certain partial epilepsies because of its effects on the release of GABA.

Fortunately, because the brain has many safeguards, even profound defects in channel and receptor function rarely establish a permanent epileptic state. Nevertheless, defects mean that under certain conditions the 'dam' that keeps uncontrolled firing at bay breaks.

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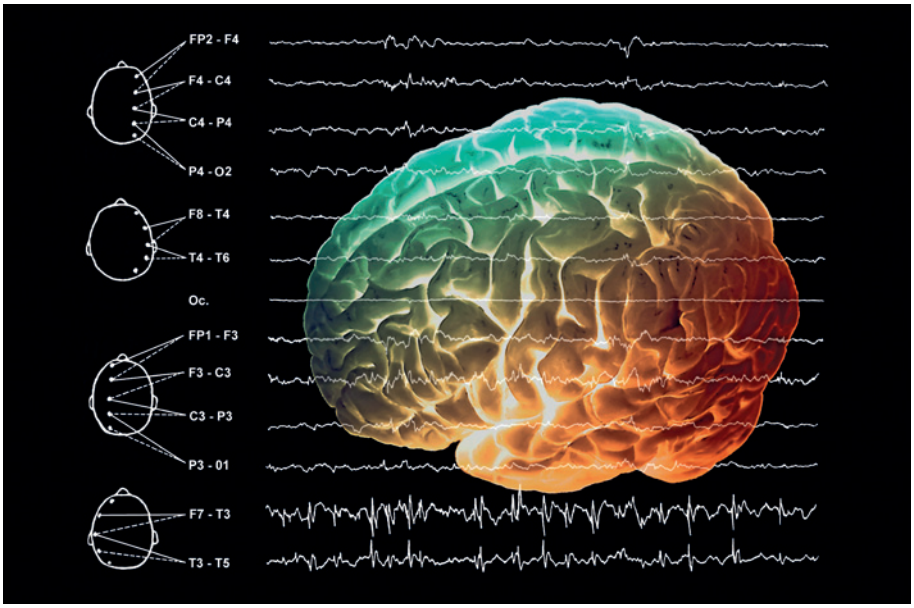


In this epileptic seizure, parts of the brain show erratic activity on an electroencephalogram (bottom traces).

"Compensatory mechanisms usually work very well until you push the system too far, and then a seizure occurs," explains Walker.

The features of various types of seizure emerge from the ordinary mechanisms of brain function. "The machinery that makes seizures happen is the same machinery that allows us to think or move," says Massimo Avoli, a neurologist at the Montreal Neurological Institute and Hospital in Canada. "It's only the balance between inhibition and excitation that is not right." Indeed, many epilepsies resemble a perverse imitation of normal activity for a given brain structure — and these lead to some of the distinctions between the pathology and activity associated with different epileptic disorders.

For example, a structure deep in the brain called the hippocampus plays a key role in learning and memory. It receives incoming data from the entorhinal cortex, which relays perceptual information to a class of excitatory neurons — granule cells — in a part of the hippocampus called the dentate gyrus. However, granule cells don't get excited easily: they are influenced by a network of inhibitory interneurons and only a tiny proportion of inflowing signals register in the hippocampus. This process of 'dentate gating' is thought to be important for processes such as pattern separation, which helps the brain distinguish between relatively similar stimuli.

But dentate gating seems to break down in temporal-lobe epilepsies affecting the hippocampus, resulting in unrestrained, synchronized firing of granule cells. The onset of such seizures may begin with the perception of 'auras', characterized by unusual emotional states or a sense of déjà vu, followed by a period of confusion and memory loss. Most temporal-lobe epilepsies arise from physical trauma, either from a direct injury to the brain or through damage arising from a stroke or tumour; according to Coulter, this leads to a large loss of interneurons as well as some loss of GABA receptors on the granule cells. Once the restrictions on excitatory signalling are lost, other disruptions may follow. "We're developing a 'domino theory' of epilepsy, where a transient failure of dentate function may disrupt downstream regulatory functions and give you a secondary failure of downstream circuits," says Coulter.

The brain patterns associated with absence seizures mirror those observed in sleep.

The mechanism underlying seizures known as absence epilepsies is rather different. Absence seizures can emanate from a single site in the brain, but then give rise to a distinctive 'spike wave' electroencephalogram (EEG) pattern that is synchronized across multiple regions on both sides of the brain. This process is driven by the interplay between the brain's outer layer, the cerebral cortex, and an inner structure called the thalamus. In contrast to many of the focal epilepsies, it is the inhibitory response of interneurons that fuels absence seizures. According to neurologist John Huguenard of Stanford School of Medicine in California, incoming signals from the cortex trigger a massive wave of GABA-driven inhibition of the excitatory neurons of the thalamus, deep in the brain. However, the inhibited excitatory neurons subsequently undergo a 'rebound' response — and react with a synchronized burst of activity. That activates cells that drive another wave of inhibition.

The thalamus is involved in wakefulness and awareness, and the hallmark symptom of the absence seizure is a loss of consciousness. Intriguingly, the brain patterns associated with absence seizures — coordinated cycles of thalamic and cortical activity — closely mirror those observed in sleep, particularly during 'spindle' EEG signatures that represent the brain's efforts to keep the sleeper unconscious, but on a far grander scale.

NETWORK NEWS

For all this knowledge, homing in on the faulty wiring involved in epilepsy remains difficult, confounding efforts to achieve lasting relief through surgery to remove the areas responsible. The success rate for patients with surgically treatable focal epilepsy is initially high, with around 80% becoming seizure-free post-surgery, and many experts endorse this form of treatment (see page S7). "But when you look 5, 10 or 20 years [post-surgery], it starts to drop to about 50% seizure-free," says Walker.

Two electrophysiology researchers, Andrew Trevelyan of Newcastle University, UK, and Catherine Schevon of Columbia University Medical Center in New York, have revealed a potential reason why: conventional EEG methods can encounter difficulties in accurately pinpointing the brain regions responsible for focal epilepsies. "As the seizure wave-front propagates, you end up with recruited territories that seem to involve every neuron in the network," says Trevelyan. But this in turn triggers a massive wave of inhibitory activity among the interneurons that surround this recruited zone. After identifying this phenomenon in rodent brain slices, Trevelyan and Schevon observed this same surrounding zone of inhibition, which they term the 'ictal penumbra', in humans by performing EEG using arrays of tiny electrodes implanted in the brains of epileptic patients[1]. EEG readings from electrodes placed on the scalp will detect strong synaptic activity within the seizure zone and in the ictal penumbra, even though most of those neurons are inhibited and not participating in the seizure.

Failure to accurately pinpoint the brain regions involved in a person's seizures can lead to the misidentification of the epileptic focus and increase the likelihood of failed surgery. Electrophysiology insights could guide more sophisticated monitoring of cortical epilepsies and possibly other focal epilepsies as well.

ON AND OFF SWITCHES

The discovery of light-responsive proteins that can directly switch neurons on or off could transform efforts to tease apart and modify the function of brain circuits in epilepsy. In 'optogenetics' experiments, researchers genetically modify specific subsets of neurons in animals to express these proteins and observe the extent to which different manipulations promote or prevent seizures. For example, Walker and UCL colleagues including Stephanie Schorge and Dimitri Kullmann reprogrammed neurons to express halorhodopsin,

a light-triggered 'off' switch[2]. They found that even limited restraint of neuronal firing in a region of the motor cortex markedly reduced the number of seizure events in a rat model of cortical epilepsy. Walker notes that only a few neurons in a small area were turned off in the experiment. "This shows that treating epilepsy might not be about cutting out large areas of the brain," he says. "Modifying the right areas might be enough to stabilize the network."

Similarly, a study[3] by Huguenard's team used halorhodopsin to show that forced inactivation of thalamocortical neurons can essentially halt seizures in rats with stroke-induced cortical epilepsy. This result was striking because these neurons were situated far from the injury site, in a region typically involved with generalized absence seizures. "It was thought that the primary reorganization is among regions adjacent to the cortical stroke," says Huguenard. "We were surprised to see such a strong thalamic involvement."

Coulter sees such findings as compelling evidence that epilepsy neuroscientists need to cast a wider net. "These optogenetics studies suggest a very distributed network," he says.

FROM SUPPORTING ROLE TO STAR

The nervous system is made up of two types of cells: neurons, which transmit nerve impulses, and glial cells, which play a supporting role. Glial cells perform essential functions such as providing a myelin sheath around the neurons to enable fast transmission of nerve signals and helping to maintain the correct ion concentration. Most epilepsy research to date has focused on the role of neurons. However, the brain contains at least as many glial cells. The past two decades of research have revealed surprising ways in which these once-underappreciated cells may contribute to both the onset and progression of epilepsy.

Increased proliferation and activation of glial cells is a well-established hallmark of epilepsy. Among the glial subtypes, astrocytes are known to contribute to the epileptic state due to erosion of their role in maintaining the chemical environment of the brain. For example, elevated potassium levels render neurons hyperexcitable, and numerous studies have found impaired potassium control by astrocytes in the epileptic brain. Astrocytes also help to clean up neurotransmitter molecules in the aftermath of neuronal activity, and disruptions in the absorption and recycling of glutamate and GABA by astrocytes can similarly lead to inappropriate neuronal sensitization or inhibition in certain contexts.

More recent findings suggest that astrocytes are not merely custodians, but can themselves secrete and respond to neurotransmitters. "We know that if you stimulate astrocytes from a human biopsy, these astrocytes exhibit calcium signalling and can also release glutamate," says glia researcher Giorgio Carmignoto of the University of Padova, Italy. This glutamate can in turn contribute to the excitation of adjacent neurons, and Carmignoto describes the formation of 'tripartite synapses' in which astrocytes actively participate in conversations once thought to occur exclusively between neurons. However, activated astrocytes can also help to reduce seizure intensity: they contribute to the production of adenosine, a signalling molecule that can counter the effects of glutamate. In short, adenosine turns down the neural signals that glutamate turns up, and that could reduce seizure activity, explains Carmignoto.

Huguenard has shown that astrocytes may also contribute to seizure control within the thalamus by producing endozepines[4], which are naturally occurring molecules that resemble the sedative benzodiazepine — better known as Valium. "Astrocytes might act as sensors for seizure activity or even pre-seizure activity, and respond by enhancing the release of endozepines, thereby suppressing activity in the reticular nucleus," he says.

The injuries that trigger epilepsy are often associated with an inflammatory response in the brain, and mounting evidence suggests that astrocytes and other glial cell types are central to this process. They secrete signalling factors that normally contribute to damage control and injury repair, but they can also create a feedback loop that promotes epileptic activity. "Pathological electrical activity per se is enough to activate the glial cells," says neuropharmacologist Annamaria Vezzani of the Mario Negri Institute for Pharmacological Research in Milan, Italy. Once activated, they secrete molecules such as interleukin-1β and these initiate a signalling cascade in neurons that renders them more sensitive to glutamate-induced excitation — and therefore, seizure activity. "So on the one hand you have this neuronal effect, and on the other you have a persistence of the inflammatory milieu because these neurons are activating the glia continuously," says Vezzani. The inflammatory response also seems to disrupt the blood–brain barrier, the tight cellular seal that limits entry of materials from the bloodstream to the brain. There is evidence that penetration of this compromised barrier by molecules such as the protein albumin can exacerbate both neuronal hyperexcitability and inflammation.

What remains unclear is the extent and the timing of these various astrocyte-mediated processes, and how they trigger or suppress epilepsy in humans. The evidence, which has mostly been obtained from either isolated brain slices or animal models, is intriguing but is not conclusive enough to form a robust disease narrative. "Any time you have an increase in excitability in a neuronal network, this, for sure, will involve astrocytes," says Carmignoto. "But what comes first — the neuronal defect or the astrocyte defect — is the issue."

For now, there is not enough evidence to map the natural history of epilepsy. Better disease models and more human data are needed before these individual findings can be linked into a satisfying narrative. "Understanding epilepsy," says Carmignoto, "means understanding how the brain works. It is as complex as that." ■

Michael Eisenstein *is a freelance journalist based in Philadelphia, Pennsylvania.*

1. Schevon, C. A. *et al. Nature Commun.* **3,** 1060 (2012).
2. Wykes, R. C. *et al. Sci. Transl. Med.* **4,** 161ra152 (2012).
3. Paz, J. T. *et al. Nature Neurosci.* **16,** 64–70 (2013).
4. Christian, C. A. & Huguenard, J. R. *Proc. Natl Acad. Sci. USA* **110,** 20278–20283 (2013).

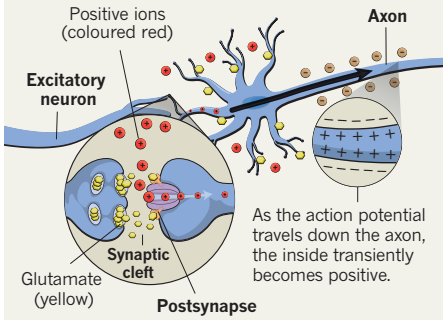
ELECTRIC UPS AND DOWNS

In a healthy brain, excitatory and inhibitory neuron dynamics are tightly balanced in a controlled way. In epilepsy, the mechanisms underlying this balance go awry, causing overly-excited neurons to fire uncontrollably.

EXCITATION

When a neuron becomes excited:
At excitatory synapses, the neurotransmitter glutamate is released. Glutamate crosses the synaptic cleft, binding to glutamate receptors at the postsynapse, initiating depolarization.

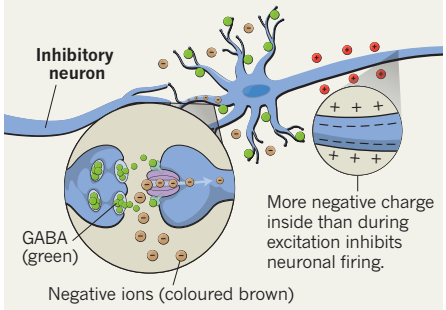
Na^+ ions enter the neuron, driving it to threshold and subsequent firing of an action potential, or nerve signal. In epilepsy, neurons are often very excitable, close to threshold and fire action potentials more readily.



INHIBITION

When a neuron becomes inhibited:
At inhibitory synapses, the neurotransmitter γ-aminobutyric acid (GABA) is released. GABA crosses the synaptic cleft, binding to GABA receptors at the postsynapse, initiating hyperpolarization.

Cl^- ions enter the neuron, driving it further from the action potential threshold, decreasing the probability that the neuron will fire. Increasing inhibition, in some cases, can assist in reducing the chance of unregulated seizure activity.



PERSPECTIVE

The surgical solution

Not enough doctors and patients opt for surgery to treat epilepsy, despite clinical evidence of the benefits, says **Samuel Wiebe**.

Sandra was 15 when she started having weekly seizures that altered her awareness and behaviour; she also started having generalized convulsions about once a year. Over the years, she has tried numerous antiepileptic drugs in various combinations. For eight years while she was in her twenties Sandra had no seizures but as she got older, new drug treatments have typically only controlled her seizures for a few months before her seizures returned with the same intensity.

The drugs made her drowsy and slowed her thinking, and the seizures caused injuries and embarrassment. Sandra's education was affected and, together with the fact that she could not find gainful employment, she became depressed and socially isolated. Finally, at the age of 54, Sandra was referred to a comprehensive epilepsy programme and was diagnosed with left-temporal-lobe epilepsy. She had brain surgery to remove part of that lobe. Now, three years later, she has no more seizures and is an advocate for early epilepsy surgery.

For many types of epilepsy, brain surgery has been shown to be safe and superior to antiepileptic drugs in all published controlled studies of drug-resistant epilepsy[1]. Among patients with specific types of focal epilepsy (seizures that start in one specific area of the brain, as opposed to multiple or bilateral brain regions), about 65% of surgically treated patients stopped having seizures, compared with 8% of those treated with antiepileptic drugs alone[2]. For every two patients given surgery, one will become seizure free. The same ratio applies for surgery performed early in the disease[3], and for the number of patients achieving clinically important improvements in quality of life[4]. By comparison, carotid surgery to prevent stroke is considered to be hugely effective but needs to treat eight to ten patients for one to benefit. Epilepsy surgery helps to prevent death from accidents, seizure-related events, suicide and sudden unexpected death in epilepsy, and also extends a patient's years of healthy life.

Evidence-based clinical practice guidelines stipulate that patients with focal epilepsy should be referred for surgical evaluation straight away, but this generally happens only after two or three decades, or not at all. Moreover, the rate of epilepsy surgery remained unchanged despite the publication in 2001 of a randomized controlled trial demonstrating the benefits of surgery[5], and the 2003 publication of evidence-based guidelines that encourage surgery[6].

WHY NOT SURGERY?

So why is this highly effective, potentially life-changing treatment used so infrequently? The clinical condition of drug-resistant epilepsy often follows a complex course marked by periods of remission, as in Sandra's case, complicating the decision to opt for surgery. Another factor is the hope that a new drug or combination of drugs will be able to control seizures.

In addition, brain surgery is a major intervention. Surgically removing part of the brain — the seat of our intelligence, emotions and sense of self — is a sobering prospect and demands meticulous evaluation of risks and benefits. Physicians need to explain to patients that in centres with experienced surgeons using modern imaging and surgical techniques, epilepsy surgery has a low complication rate of only 3–5%, and almost no mortality. Epilepsy surgery is safe.

The knowledge and attitudes of patients play a major role in the decision to explore epilepsy surgery, and some people with epilepsy come up with many reasons to avoid it. Race and socioeconomic standing also affect the decision. In the United States, for example, African-Americans, Hispanic adults and other ethnic groups or those without private insurance are less likely to consider epilepsy surgery.

The knowledge and attitudes of clinicians are equally important. International surveys show that neurologists may lack sufficient knowledge about the benefits and safety of epilepsy surgery. As well as conveying clearly and convincingly the benefits and safety of epilepsy surgery, clinicians need to be aware of the value of being completely free of seizures, and of the serious and life-threatening consequences of poorly controlled seizures. Health-care experts also need to understand that patients have a very low probability of controlling their seizures with additional medications if they fail with two appropriately chosen and adequately used antiepileptic drugs — the definition of drug-resistant epilepsy. A group of colleagues and I have created a user-friendly Internet-based tool to help clinicians identify patients who should be referred for surgical evaluation[7].

EPILEPSY SURGERY HELPS TO **PREVENT DEATH** AND ALSO HELPS EXTEND A PATIENT'S YEARS OF **HEALTHY LIFE.**

Finally, the health-care system plays a central role in providing access to specialized epilepsy centres during pre-surgical evaluation, surgery and post-operative care. Clinicians often point to limited access to these resources as one of the main barriers to epilepsy surgery. But patients need a patient-centred, well-informed clinical environment that addresses their individual concerns as they navigate the decision-making process. Neurologists and the health-care system must create that environment.

My colleagues and I need to do a better job of informing health care policy-makers and resource allocators about the high socioeconomic burden of uncontrolled epilepsy. Everyone working in health care needs to help spread awareness that epilepsy surgery is safe and cost-effective. Epilepsy patients around the world stand to gain great benefits if we succeed. ■

Samuel Wiebe *is professor of clinical neurological sciences at the University of Calgary, Canada.*

1. Schmidt, D. & Stavem, K. *Epilepsia* **50,** 1301–1309 (2009).
2. Engel, J. *et al. J. Am. Med. Assoc.* **307,** 922–930 (2012).
3. Wiebe, S. & Jette, N. *Nature Rev. Neurol.* **8,** 669–677 (2012).
4. Fiest, K. M., Sajobi, T. T. & Wiebe, S. *Epilepsia* http://dx.doi.org/10.1111/epi.12625 (2014).
5. Wiebe, S. *et al. N. Engl. J. Med.* **345,** 311–318 (2001).
6. Engel, J. Jr *et al. Neurology* **60,** 538–547 (2003).
7. Jette, N. *et al. Neurology* **79,** 1084–1093 (2012).

RUBEN SALAZAR JR

When doctors couldn't explain to Tracy Dixon-Salazar why her daughter had developed epilepsy she decided to find out for herself.

GENETICS

Complex expressions

Epilepsy is one of the most common neurological disorders to affect the human brain. Many genetic aspects of the disease have been identified, but mechanisms remains elusive.

BY CHARVY NARAIN

Some kinds of epilepsy are rooted in physical trauma — a brain injury at birth, perhaps. Others seem to show up like bolts from the blue, with no clear event to explain them. Yet one thing is clear: many cases of idiopathic epilepsy — epilepsy without an obvious physical cause — run in families, implicating heredity in their genesis. Indeed, studies[1] suggest that genetic variations in ion channels on the surface of neurons — electrically excitable cells in the nervous system — might lie at the heart of many cases of idiopathic epilepsy, and presumably cause the firing of these cells to get out of control.

But there is still much that scientists do not know about the genetics of idiopathic epilepsy. Currently, a gene variant can only be associated with 10–40% of patients, according to Holger Lerche, who researches the genetics of neurological disorders at the Centre for Integrative Neuroscience in Tübingen, Germany. "But actually, almost all idiopathic epilepsy is likely to be genetic, so this figure should be closer to 80–100%," he says. "The problem is that we haven't identified all disease-associated genes just yet — nor how they interact."

Adding to the complexity of the puzzle are the facts that two-thirds of healthy individuals carry a gene variant associated with epilepsy[2], that many genes pinpointed by genetic analyses are also implicated in other disorders, and that epilepsy often co-occurs with other diseases — 30% of children with autism also have epilepsy, for example. This makes it hard to connect a given genetic variant in a patient to one specific disease. Epilepsy is a complex genetic disorder involving interplay between many genes, often in unexpected ways.

When Tracy Dixon-Salazar's two-year-old daughter Savannah had her first seizure she thought that her child was choking. "When the paramedics told us that Savannah's symptoms sounded like a seizure, I didn't know what that was," she says. By the time she was three, Savannah had epileptic seizures every day, and by the age of five she was having hundreds. Her physical and mental development regressed dramatically, and she needed round-the-clock care. "Throughout it all," Dixon-Salazar says, "I really wanted to know why. Nobody could give us an explanation for how a child could go from being a healthy two-year-old to being completely taken over by epilepsy."

Dixon-Salazar's hunt for an explanation took her from being a stay-at-home mother, who had left full-time education after high school, to getting a PhD in neurobiology from the University of California, San Diego.

Along the way, "I fell in love with genetics," she says. As part of her postdoctoral work, she sequenced Savannah's exome — the part of the genome that encodes proteins — and finally found something approaching an explanation, hidden within an ion channel.

CHASING CHANNELS

As the name suggests, ion channels are conduits; they sit on the largely impenetrable surface of a neuron and selectively let in ions — charged particles that trigger a cascade of events that lead to the neuron producing a burst of electricity, called an action potential.

Different ion channels let in different kinds of ions, and mutations in the genes that carry instructions for making these channels have been correlated with epilepsy. These faulty channels then let in too many or too few ions, disturbing the way that the action potential is generated and how it travels down the neuron. Inheriting these faulty-channel genes leads to abnormalities in brain-cell firing.

Although Savannah Dixon-Salazar had no family history of the disease, an analysis of her genome turned up 25 ion-channel variants that mostly — based on the channels they affected, and how — would probably cause too many calcium ions to be let into the cell. And so, working with Savannah's doctors, her parents decided to try treating her with verapamil, a drug approved by the US Food and Drug Administration for treating heart arrhythmia, not epilepsy, and which disrupts the functioning of an ion channel that lets in calcium.

"The effects were startling and immediate," says Tracy Dixon-Salazar. "Within 30 days, Savannah's seizures reduced from 300 a month to around 50, and currently average around 20 to 25 a month. They now happen only at night, so she is much less likely to hurt herself." She adds that her daughter's intellectual development has come along greatly, and "she has gone from struggling to speak a word to speaking 10- to 15-word sentences easily".

Dixon-Salazar acknowledges that these results are anecdotal and that verapamil is unlikely to be a general epilepsy treatment. But it could help some. And there is a lesson there, says Ivan Soltesz, a neurobiologist and epilepsy researcher at the University of California, Irvine. "These results highlight the fact that even if you don't know exactly what is wrong, and the exact pathway involved, genetic analysis can still help with treatment," he says.

INTRICATE INTERACTIONS

DNA variants affecting the calcium ion channel seemed to lead to Savannah's epilepsy. Lerche's work has implicated a different ion channel, which he does not want to describe before publishing his research. His team has found that when two variations of the same channel gene — one known to occur in the normal population and one novel variant found only in an epilepsy patient — came together, the channel's function changed. Individually, the mutations did not alter the channel's function. "This suggests that the patient's epileptic seizures are due to the occurrence of both variants occurring simultaneously," Lerche says.

Sometimes, however, adding epilepsy-related gene variants together does the opposite of cause disease — it dampens it. In a 2007 paper[3], a group led by epilepsy researcher Jeffrey Noebels of the Baylor College of Medicine in Houston, Texas, expressed two different epilepsy-associated ion-channel gene variants in the same mouse. What they got were animals with no, or reduced, epilepsy symptoms. The mutations had opposite effects on how likely a neuron is to fire an action potential. Disruption of the *Kcna1* gene, which encodes a particular class of potassium ion channels, normally leads to large increases in neuronal electrical excitability and subsequent epilepsy; on the flip side, malfunctions in the calcium ion channel encoded by the *Cacna1a* gene result in reduced neurotransmitter release and absence seizures (when the affected individuals 'blank out'). When expressed together, the two genes seemed to compensate for each other, reducing the serious seizures and death that the *Kcna1* mutants experience and masking the absence epilepsy of animals with *Cacna1a* mutations.

RUBEN SALAZAR JR

Savannah (left) has around 20 seizures a month.

"Savannah has gone from struggling to speak a word to speaking ten-word sentences easily."

Noebels' studies also show that gene variants associated with epilepsy are common in the general population — and that the cause of the disorder is far less simple than the total number one has. In a study published in 2013, his group compared ion-channel genes between healthy people and people suffering from idiopathic epilepsy — and found that nearly 67% of the healthy group had mutations in at least one gene variant known to be linked to a familial form of epilepsy.[2] What's more, they found no gene variants that turned up only in the people with epilepsy. One of the healthy people in their study even had seven mutations in genes associated with epilepsy — just two less than the nine mutations detected in the most extreme epilepsy patient in the group. Having many gene mutations, it seems, is not a predictor of whether someone will be affected by the condition.

MODELLING MECHANISMS

Some researchers think that bioinformatics analyses — using computer simulations to look at the intricate interplay between epilepsy-associated genes — might reveal the complex genetic communication that determines who gets the disease and who doesn't. "The aim is to build a cellular map of epilepsy, including as many known epilepsy-associated genes as possible," Lerche says. "We can then use simulations to track how interactions between genes are happening."

For example, ion-channel expert Steven Petrou at the Florey Institute of Neuroscience and Mental Health in Parkville, Australia, used computational modelling to study the effect of sodium-channel mutations in a theoretical network of neurons mimicking epilepsy[4]. The results suggest that ion channel mutations may be more severe in their effects in a brain that is already abnormal. Epilepsy may initially be triggered by an external event such as a head injury or stroke — or, in a double whammy, ion-channel mutations may trigger the disease and once it is established, have an even greater effect in the altered brain than they did to begin with. It is a point not missed by Dixon-Salazar. "Savannah seized for 16 years before we found a drug that would make an impact on her seizures," she says. "The brain she had before the seizures is totally different from the one that she had afterwards. Perhaps if we had given the drug earlier, she might now be entirely seizure-free."

Noebels hopes that efforts to build computer simulations of the entire mammalian brain will help researchers to understand the complex network of interactions in the abnormal brain. "It takes a village to cause epilepsy," he says — myriad cellular factors must come together to result in disease. Eventually, the conversations between the villagers might be best tracked inside a computer. ■

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1. Lerche, H. *et al. J. Physiol.* **591,** 753–764 (2013).
2. Klassen, T. *et al. Cell* **145,** 1036–1048 (2011).
3. Glasscock, E. *et al. Nature Neurosci.* **10,** 1554–1558 (2007).
4. Thomas, E. A. *et al. Epilepsia* **51**, 136–145 (2009).

INTERFOTO/ALAMY

In centuries past, a priest would cast out the demons that were thought to cause epilepsy.

SOCIOLOGY

Shedding the shame

Plagued by a history of fear and stigma, epilepsy has languished when it comes to research funding.

BY LAUREN GRAVITZ

Throughout history, in almost every culture, epilepsy has been viewed as something to be feared, avoided and concealed. In what is thought to be the earliest written description of the condition, dating from around 1050 BC, the Babylonians referred to it as *miqtu*, or 'the falling disease', and attributed it to ghosts and demons. The ancient Greeks called it 'the sacred disease' and believed that it resulted from divine intervention. Epilepsy even makes appearances in the Bible, when Jesus heals a boy who suffers from seizures by casting out a 'demon'.

By 400 BC, Greek physician Hippocrates concluded that seizures are hereditary and originate in the brain, yet this view failed to become widely accepted for hundreds of years (see 'Epilepsy's past').

Today, at least in the developed world, the shame and suspicion surrounding epilepsy have eased, but they are far from a distant memory. In an oft-cited editorial in the *British Medical Journal*[1], neurologist Rajendra Kale wrote: "The history of epilepsy can be summarised as 4,000 years of ignorance, superstition, and stigma followed by 100 years of knowledge, superstition, and stigma."

Over the past century, researchers have made huge gains in the scientific understanding of epilepsy, thanks largely to technologies that allow for a deeper view of the brain's activity, such as the electroencephalogram (EEG) and magnetic resonance imaging (MRI).

Much of the stigma that people with epilepsy endure stems from the alarming nature of the most common type of seizure. These generalized tonic–clonic seizures begin with a loss of consciousness before the convulsions begin. Additional symptoms can include screaming, loss of bladder or bowel control and, on regaining consciousness, confusion and amnesia.

There is another reason for epilepsy's poor reputation. "Part of the mythology around epilepsy has been because it's episodic. That's what led, centuries ago, to the idea that someone was possessed: all of a sudden someone who looks perfectly fine had behaviour that was abnormal," says Gregory Bergey, director of the epilepsy centre at Johns Hopkins University in Baltimore, Maryland. "As we move into the twenty-first century, I'd like to think that this mythology about being possessed has been dispelled. But there are still misconceptions."

BREAKING DOWN BARRIERS

With misconceptions come fear and stigmatization. And the greater the stigma, the poorer the outcome: in people with epilepsy, feelings of shame have been strongly associated with inadequate seizure control, as well as with increased depression, anxiety and isolation.

Although prejudice is a known problem in almost every country, it may be greatest in developing nations, where religious and spiritual beliefs often trump medical understanding of the condition. "In Asia and Africa, families in low-income settings misinterpret what a seizure is, so you have an interpretation problem from the get-go," says Gretchen Birbeck, a neurologist and public-health researcher at the University of Rochester Medical Center in New York. "If someone develops a severe cough that doesn't go away, they recognize they need antibiotics or even a tuberculosis test. In that same family, if someone says something nonsensical, has a seizure and falls to the floor, they tend to think there's a possession or that the person's been cursed. They don't think there's a medical problem."

Misconceptions are not limited to family members. In Nigeria, for instance, at least 16% of health-care workers believe epilepsy is a mental-health disorder rather than a medical one. What's more, 6% of Nigeria's health-care workers believe it is contagious[2]. With these types of mistakes, "patients aren't going to get the right treatment", says Nathalie Jette, a neurologist at the University of Calgary in

Alberta, Canada, who is currently chairing an International League Against Epilepsy task force aimed at assessing stigma in epilepsy.

Incorrect diagnoses are one of the more obvious obstacles to appropriate care, but they are not the only one. Birbeck, who studies epilepsy and other neurological disorders in developing countries, says that even when health-care providers do recognize seizures as a medical problem, family members are often loath to seek treatment. "It casts a pall on the family: if the community realizes that someone in the family has epilepsy, the siblings won't be able to find someone to marry," she says. "So do you take someone to get care or do you hide them at home?"

Even in the developed world, through most of the twentieth century epilepsy remained an affliction that people believed was best kept out of sight. "In civil societies, including the United States, it was felt you could catch epilepsy just by looking at someone having a seizure. So people were sent off to epileptic colonies," says Steven Schachter, a neurologist at Harvard Medical School in Boston, Massachusetts, and past president of the American Epilepsy Society. The last of these colonies closed only about 50 years ago.

Yet the practice may have had some benefit. "The cultural tendency and movement to isolate people with epilepsy may have had a silver lining," Schachter says. "It provided the opportunity to conduct research and move the field forward."

FUNDING GAP

For the most part, however, epilepsy's history of stigma and superstition has done more to slow research than to further it. The disease suffers from a woeful research-funding gap. "Relative to the burden and cost-effectiveness of treatability, epilepsy is incredibly neglected," Birbeck says.

In the United States, 1% of the population has epilepsy at any given time, and 2–4% of the population will have a seizure disorder at some point during their life, making epilepsy the third most common neurological disease, after stroke and Alzheimer's disease. Yet of the six most prevalent neurological conditions, epilepsy ranks fifth in funding from the US National Institutes of Health (NIH) — that level, which equalled about 40% of the funding for stroke in 2011, is decreasing every year[3].

In low-income countries, the economic disparity is even more striking. There, the dearth of resources dedicated to treating the disease can be traced to an accident of medical evolution, Birbeck says. When the World Health Organization (WHO) was first established in 1948, it classified all neurological disorders, including epilepsy, as psychiatric disorders. As technologies such as brain scans and EEGs emerged, neurology and psychiatry began to split into separate disciplines. Yet although epilepsy was identified as a physical and potentially treatable problem in the brain, funding structures at the WHO and other global ministries of health were never rearranged to reflect that new understanding, Birbeck notes. "Global health is modelled off the WHO structure, which has no neurologic section. So, in developing countries, there are psychiatrists but no neurologists," she says.

In the developed world, the misunderstandings associated with epilepsy can also be blamed for a shortage of advocacy; the stigma of the disease has often prevented people who have the disorder and their family members from coming forward to talk about their experiences. This lack of advocacy is directly related to the lack of funding. "If you look across the board at diseases and NIH funding, you're not going to find too many in which there is huge success and great breakthroughs unless there's an advocacy group behind it and a lot of push," says Susan Axelrod, one of the founders of Citizens United for Research in Epilepsy (CURE), an advocacy organization in Chicago, Illinois, that funded about US$3.5 million of epilepsy research last year.

Despite the fact that patients with epilepsy outnumber patients with Parkinson's disease by about six to one, Parkinson's disease receives much more funding, says Axelrod. For example, the Michael J. Fox Foundation for Parkinson's Research provides about US$50 million in research funding each year.

Axelrod and others in the field say that they have met public figures who have some form of epilepsy, or who have family members with the disease, but have not gone public because of the negative images associated with it. The early onset of the disorder means that few people have the chance to become powerful advocates.

It is a difficult cycle. Stigma begets lack of advocacy, which begets lack of funding. And researchers are unlikely to choose a field in which little or no grant money is available unless they have a deeply personal reason for doing so. But it is a cycle that many are working to break. CURE, for instance, has partnered with the Howard Hughes Medical Institute to sponsor medical students' internships in epilepsy research laboratories. Also, a growing collection of molecular targets promise enhanced medications in the future (see page S12) and even watch-like devices could help (see page S16).

"We've made some strides," Axelrod says. "I'm not fatalistic. Given how few private resources there are for this disease — and how few spokespeople — I think we're making progress." ■

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1. Kale, R. *Br. Med. J.* **315,** 2–3 (1997).
2. Ekenze, O. S. & Ndukuba, A. C. *Epilepsy Behav.* **26**, 87–90 (2013).
3. Meador, K. J., French, J., Loring, D. W. & Pennell, P. B. *Neurology* **77**, 1305–1307 (2011).

EPILEPSY'S PAST

SHEILA TERRY/SPL

A brutal cure for epilepsy in the Middle Ages

c. 400 BC Ancient Greek physician Hippocrates advises treatment of epilepsy with diet and drugs.

400–1400 People attribute epilepsy to demonic possession. Physicians treat epilepsy by boring holes in the skull.

c. 1800 Castration or circumcision sometimes used to treat epilepsy.

1886 English surgeon Victor Horsley performs the first epilepsy neurosurgery.

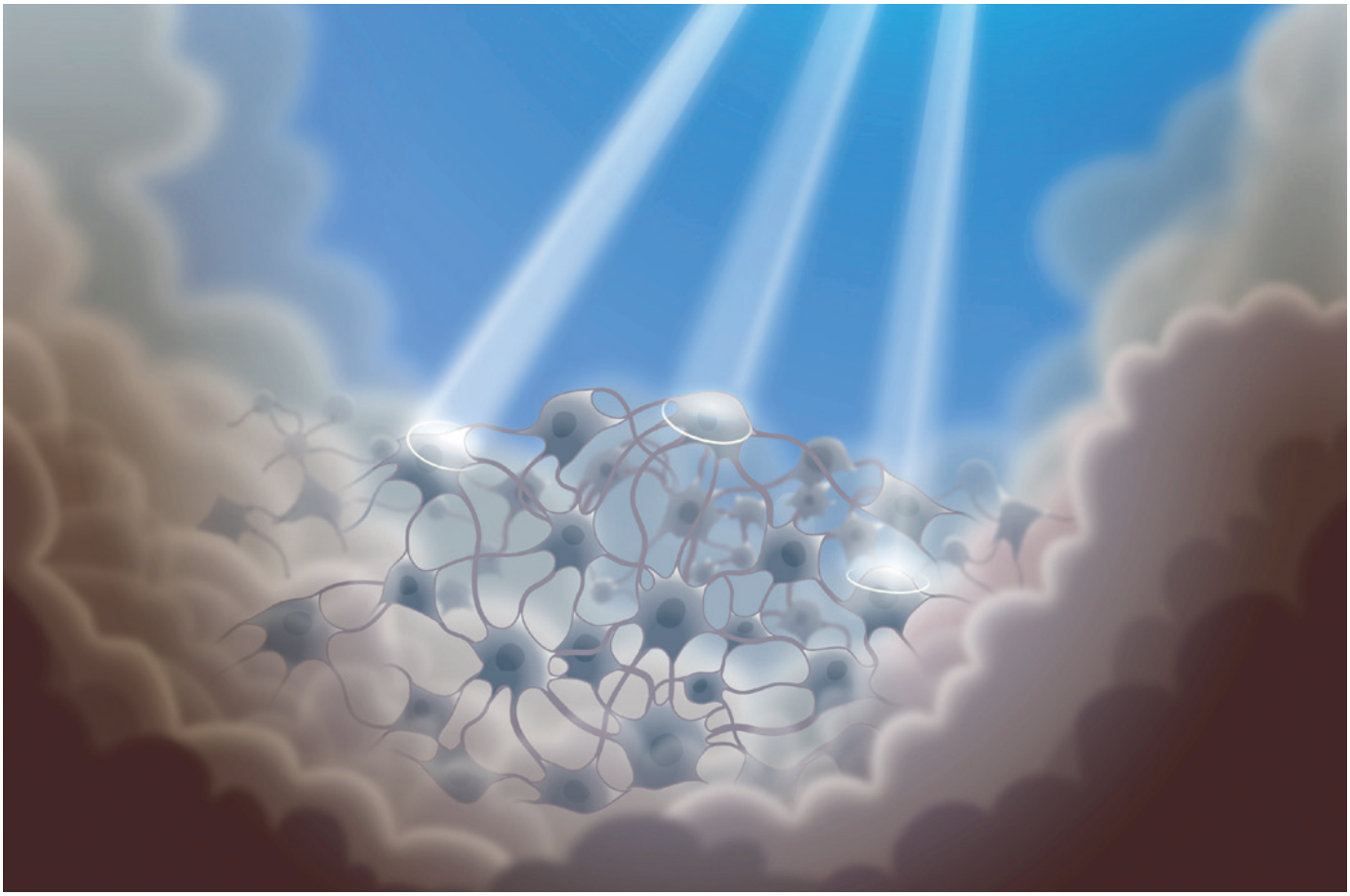
1938 Canadian neurosurgeon Kenneth McKenzie performs the first hemispherectomy for epilepsy, removing half the patient's brain.

1940 US neurosurgeons William van Wagenen and Andrew Akelaitis perform the first corpus callostomy, severing the connection between the brain halves.

1990 Lamotrigine is proved effective against epilepsy with few side effects.

2001 Canadian neurologist Samuel Wiebe publishes clinical trial results showing the benefits of surgery.

2014 Rosalind Picard and her colleagues at the Massachusetts Institute of Technology develop a wrist-worn device that detects seizures.



NIK SPENCER

DRUG DEVELOPMENT

Illuminated targets

The development of effective antiepilepsy drugs is moving on from trial-and-error approaches to sophisticated molecular solutions.

BY MEGAN CULLY

For most of the twentieth century, the development of medications to treat epilepsy relied on trial and error. "The drugs were taken through development and introduced on to the market before any molecular target or targets in the brain were identified," says Michael Rogawski, a neurologist at the University of California, Davis, adding that we still don't know the molecular target for some agents.

In the 1960s, for example, researchers in France noted that every drug they tested reduced seizures in animals. The reason, they discovered, was that they had dissolved their compounds in valproic acid, a common practice back then. It was the solvent — not the candidate drugs — that was responsible for the anticonvulsive effects. They'd accidentally uncovered the potential of a drug now known as valproate[1]. Within a year, valproate was approved and is now the most widely prescribed antiepileptic drug in the world.

Despite such successes, there is a growing realization that the old approaches are not enough. Existing medications control seizures in about 70% of people with epilepsy, but for those 30% with drug-resistant seizures, treatments remain scarce. To move forward, pharmaceutical companies and other researchers are looking to change tack. Some are shifting away from the traditional rodent model so they can ramp up their ability to screen many compounds. Others are exploring new treatments aimed at specific molecular targets.

FISH FOR SUCCESS

The traditional way of testing for antiepilepsy drugs involves the generation of epilepsy-like convulsions in rats and mice by administering electrical stimuli or chemicals such as pentylenetetrazol. A drug developer administers compounds to find ones that protect the animals from the seizures, and these then move on to human clinical trials. Nearly all of the 25 or so marketed antiepileptic drugs were identified this way, says Rogawski.

To test a wider range of targeted treatments, some researchers are turning to animals that are easier and cheaper to keep, and quicker to breed, than rodents — such as fish. Scott Baraban, a researcher at the University of California, San Francisco, has been investigating Dravet syndrome, a rare and severe form of epilepsy that affects children. It is one of the most drug-resistant types of epilepsy[2]. Around 70–80% of patients with Dravet syndrome carry a mutation in a gene called *SCN1A*, which plays a fundamental role in activating neurons; the

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To read how chemogenetics can stop seizures, see:
go.nature.com/muqfvt

mutation seems to turn them on too much and thereby causes seizures.

Baraban used a strain of zebrafish with a mutation in the *SCN1A* gene — such fish have seizure-like convulsions. He then screened for drugs that could prevent the seizures, testing more than 300 compounds from a 'repurposing' library — one containing drugs that are known to be safe for human use but for whatever reason weren't effective enough to be used today. He found that a long-forgotten antihistamine called clemizole inhibited seizures in his fish[3]. Precisely how clemizole prevents seizures is unclear, but it probably has nothing to do with histamine, the immune-modulating molecule it is known to affect. In the same way that aspirin interacts with distinct molecules in the body and so can be used for both pain relief and to reduce inflammation, clemizole possibly interacts with both histamine (or molecules controlling its release) and some element governing nerve firing — the ion channels that regulate a nerve's excitability, perhaps, or receptors that control neurotransmitter release.

The ability to breed so many zebrafish — imagine an aquarium of many, many fish versus a few rodents in a cage — allows researchers to screen numerous drugs in a short period. "We've screened over 800 drugs in about two years," says Baraban. He plans to generate mutant zebrafish for all 12 genes associated with severe forms of childhood epilepsy and use them to identify new drugs.

MOLECULAR MEDICINES

Another approach to drug development is to work out the molecular causes of seizures, then aim drugs at the targets. Researchers now have a set of promising molecules of this type, many of them identified through hereditary forms of the disorder, says Mike Ehlers, chief scientific officer for neuroscience at Pfizer in New York City. For example, pregabalin (marketed by Pfizer as Lyrica) was approved by the US Food and Drug Administration (FDA) in 2004 for nerve pain and later for seizures, and it targets a component of calcium channels, which lets calcium ions in and out of nerves and plays a role in some forms of epilepsy[4].

For a noteworthy example of developing a molecular epilepsy medicine around a known target, Ehlers points to perampanel, a drug manufactured by Tokyo-based Eisai and marketed as Fycompa, which was approved by the FDA in 2012. In the 1990s, Eisai was looking for drugs that target the AMPA receptor, a protein present on the membranes of neurons. When the neurotransmitter glutamate binds to the AMPA receptor, the neurons become excited and drive seizures in some cases. Problems with glutamate and the AMPA receptor are implicated in several neurological diseases, including epilepsy[5] — and the Eisai researchers reasoned that inhibiting the AMPA receptor could be used to treat epilepsy.

NEW TREATMENTS TRICKLING IN

Trials that are actively recruiting participants are an indication of progress in developing new medication. In epilepsy research, there are currently only five trials testing entirely new compounds.

Compound	Type of epilepsy	Phase	Target	Company
SAGE-547	Adults with super-refractory status epilepticus	I/II	$GABA_A$*	Sage Therapeutics
PRX-00023	Localization-related epilepsy	II	Serotonin receptors	US National Institute of Neurological Disorders and Stroke
YKP3089	Partial onset seizures	II	Unknown	SK Life Science
Ganaxolone	Partial onset seizures	II	$GABA_A$	Marinus Pharmaceuticals
USL261	Seizure clusters	III	$GABA_A$	Upsher-Smith Laboratories

*GABA: γ-aminobutyric acid

Some other researchers ran into trouble getting the drugs to the intended target; one drug they tested couldn't cross the blood–brain barrier. "Eisai, from the start, had strict criteria: they wanted a potent, orally active molecule with the right properties" including reaching and binding to the receptor, says Kate Carpenter, medical affairs manager at Eisai. It took more than 12 years to move a developmental compound into an approved product. Perampanel is currently approved as an add-on treatment for patients with partial-onset seizures (seizures that affect only one hemisphere of the brain).

Many of the major drug companies no longer have epilepsy programmes.

Researchers see the potential for other drugs aimed at receptors related to epilepsy. Studies have shown that a neurotransmitter called γ-aminobutyric acid (GABA) can inhibit neurons that tend to get overexcited during an epileptic seizure (see page S4). So it might be possible to design a drug that could produce this inhibition by raising the availability of GABA, as valproate does through unknown means. Or a drug might directly activate GABA receptors, with similar effects.

Rogawski and his colleagues are working on neuroactive steroids, which target a class of GABA receptors known as $GABA_A$ receptors. Specific mutations that make this receptor insensitive can trigger epilepsy. Conversely, a drug that turns on the $GABA_A$ receptor could potentially be used to inhibit epileptic seizures.

Researchers are also attempting to develop therapies through studying the mode of action of existing antiepileptic medications. In 1999, the Belgian pharmaceutical firm UCB, in Brussels, received approval from the FDA for a drug called levetiracetam as a treatment for epilepsy. Levetiracetam binds to a protein called synaptic vesicle glycoprotein 2A (SV2A), which is found in a wide range of neuronal vesicles — spheres that contain neurotransmitters. The drug seems to inhibit the release of neurotransmitters that contribute to uncontrolled activity of the central nervous system in epilepsy[6], but it has the drawback of side effects including dizziness, drowsiness and infections such as the common cold. UCB scientists started to look for alternative compounds that bind to SV2A and found brivaracetam[7], which resembles levetiracetam in structure but binds more strongly to SV2A. It is currently in phase III trials. Higher affinity for its target should allow brivaracetam to be effective at lower doses, meaning fewer side effects[8].

LIGHT AHEAD

Despite advances in identifying molecular targets for drugs, the number of improved or new antiepilepsy medications has been slight. Consequently, many of the major pharmaceutical companies — with the notable exceptions of UCB, Eisai and Pfizer — no longer have epilepsy programmes. That leaves the bulk of the discovery and development work to academics, small biotech firms and speciality pharmaceutical companies. The result is a limited number of players in the field and some of them, such as academics, are unable to finance clinical trials, which explains the low number of trials recruiting patients to test epilepsy treatments (see 'New treatments trickling in').

Schmidt is optimistic that future research will lead to the development of drugs that will reach specific molecular targets and with fewer unwanted side effects. If we could understand how and why epilepsy develops in the first place, it might even be possible to prevent the condition in people at high risk, such as those who have had severe head trauma or stroke. ■

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1. Meunier, H. *et al. Therapie* **18,** 435 (1963).
2. Chiron, C. & Olivier, O. *Epilepsia* **52**, Supp. S2, 72–75 (2011).
3. Baraban, S. C., Dinday, M. T. & Hortopan, G. A. *Nature Commun.* **4,** 2410 (2013).
4. Davies, A. *et al. Trends Pharmacol. Sci.* **28,** 220–228 (2007).
5. Rogawski, M. *Epilepsy Curr.* **11,** 56–63 (2011).
6. Lynch, B. A. *et al. Proc. Natl Acad. Sci. USA* **101,** 9861–9866 (2004).
7. Mula, M. *Expert Rev. Neurother.* **14,** 361–365 (2014).
8. Van Paesschen, W. V. *et al. Epilespsia* **54,** 89–97 (2013).

FARLAP/ALAMY

Dairy foods such as ice cream, yoghurt and butter can help to reduce seizure frequency and intensity in children with epilepsy.

FOOD SCIENCE

Fat chance

For children with epilepsy whose condition is resistant to medication, a high-fat, low-carbohydrate diet may help bring their seizures under control.

BY RACHEL BRAZIL

My nephew, Elijah, had his first seizure when he was 18 months old. Initially, he experienced myoclonic seizures, which are brief muscle contractions that made his muscles stiffen, his arms lift up and his head jerk back. He then developed atonic seizures, in which his muscle lost tone — his muscles would go limp and he would drop to the ground. Elijah was diagnosed with Lennox–Gastaut syndrome, a difficult-to-treat epilepsy that causes multiple daily seizures and severe cognitive impairment.

Over the following 12 months, Elijah's doctors treated him with several antiepilepsy drugs to reduce or stop his seizures. Some of the prescribed medication provided short-lived relief, but there were side effects that included bloating and drowsiness. By the time he was two-and-a-half, Elijah was experiencing more than 50 seizures a day, including generalized tonic–clonic seizures in which the muscles tense and contract and cause convulsions. Falls during his atonic seizures resulted in head injuries, so he started to wear a helmet. His cognitive development stopped. He wasn't speaking or making any attempts to communicate.

At this point, Elijah's neurologist told my sister, Elijah's mother, about the ketogenic diet — low in carbohydrate and high in fat — that may help reduce or stop seizures. My sister was sceptical. A diet that would stop seizures seemed unlikely. Many neurologists were once unwilling to consider the ketogenic diet as a treatment for epilepsy because only anecdotal results were available, but trials conducted in the past decade are prompting a rethink (see 'How fats help epilepsy').

SEIZURE CONTROL

The concept of using food to help treat disease is not new. Ancient Greek texts contain references to dietary therapies for epilepsy, stemming from the observation that starvation stops seizures. Centuries later, in the 1920s and 1930s, doctors commonly prescribed the ketogenic diet for epilepsy in children. During fasting, and in people with diabetes, the liver metabolizes fatty acids into ketone bodies called β-hydroxybutyrate, acetoacetic acid and acetone that are used as an energy source when glucose levels are low. No one knows exactly why, but some evidence suggests that ketone bodies might protect against seizures[1]. A low-carbohydrate, high-fat diet creates the state of ketosis — the raised level of ketone bodies, from which the diet gets its name. The ketogenic diet fell out of favour from 1938, following the availability of a drug called phenytoin that controls the brain's electrical activity and helps to reduce the frequency of seizures. Still, about 30% of epilepsies do not respond to pharmaceuticals, which prompted the search for alternative treatments.

Russell Wilder, a metabolic-disease expert at the Mayo Clinic in Rochester, Minnesota, devised the classic ketogenic diet in 1921. It consists of a weight ratio of 3:1 or 4:1 of fat to a combination of protein and carbohydrate. This means that about 90% of daily calories come from fats, compared with the less than 35% recommended by US Department of Health and Human Services. The ratio is achieved by cutting out grains and adding cream and butter to meals. A ketogenic diet may cause short-term side effects such as constipation and nausea. Longer-term side effects include slowed growth in children and increased risks of bone fractures and kidney stones.

For my sister, the turning point came after Elijah's fourth failed drug. He started the diet in hospital and, under a nutritionist's supervision, was seizure free within six weeks.

Elijah's story is not unique. Some children

MELANIE BRAZIL

who continue to have seizures in spite of treatment with antiepileptic medication experience an improvement on a ketogenic diet. Paediatric neurologist Eric Kossoff of Johns Hopkins Hospital in Baltimore, Maryland, is a leading proponent of the diet and says that of patients who do not respond to an antiepileptic drug, 30% will respond to the next drug they try and 50% will respond to the diet. In the past decade, the short-term success of the diet has been confirmed in four randomized controlled trials[2], the largest of which enrolled 145 children at London's Great Ormond Street Hospital, and was led by childhood-epilepsy specialist Helen Cross. "About 40% got a more than 50% reduction in seizures," says Cross, and 10% became completely seizure free. Other beneficial effects of a ketogenic diet include statistically significant improvements in attention, social function and sleep patterns[3].

DIET DEVELOPMENT

The problem with a ketogenic diet is its unpalatability — such as butter in almost every meal but no bread — which is perhaps why it is used mostly for young children rather than adults. Cross says that when adults try the diet they tend to feel "persistently hungry" because eating a high ratio of fat to carbohydrate and protein leaves many unsatisfied even though they've consumed their required daily calories. Fortunately, there are three alternative diets.

In the 1960s, researchers discovered that medium-chain triglycerides (MCTs) — found in coconut oil — provide greater ketogenic effects than normal dietary fats, which are mainly long-chain triglycerides. The MCT diet, created by the late University of Chicago neurologist Peter Huttenlocher, is restrictive but incorporates more carbohydrates and protein because MCTs are absorbed more easily by the body than long-chain triglycerides. Trials[4] have found the MCT diet to be as effective as the 4:1 fat-to-carbohydrate ratio in the classic ketogenic diet.

Kossoff, for his part, designed the modified Atkins diet (MAD) in 2003. He says that the idea for the diet arose from observing similar results in people who relaxed the restrictions of the ketogenic diet[5]. In common with the Atkins weight-loss diet, MAD does not involve calorie counting, but limits carbohydrates and encourages fat consumption.

In 2005, the low-glycaemic index treatment (LGIT) came from observations that patients on a ketogenic diet had extremely stable glucose levels[6]. In addition to high fat, the LGIT includes only carbohydrates with a glycaemic index lower than 50, which means that these foods do not tend to increase blood glucose levels. The diet offers more variety — permitted low-glycaemic-index foods include whole grains, green vegetables and berries.

Despite the success of the diets, the mechanism remains largely a mystery. There is little correlation between seizure control and blood ketone body levels. What does change are the metabolic pathways used by some cells, including neurons in the brain. The processes regulating metabolism occur in mitochondria — the organelles inside cells where energy is converted from dietary fuel. This energy conversion process might link diet to reducing epileptic events.

Elijah enjoying whipped cream with blueberries.

Researchers at two institutions in Boston, Massachusetts, have studied why changing the cell metabolism reduces seizures: cell biologist Nika Danial at the Dana-Farber Cancer Institute and neurobiologist Gary Yellen at Harvard Medical School. Yellen became interested in understanding the diet through his wife, Elizabeth Thiele, a paediatric neurologist at Massachusetts General Hospital and developer of the LGIT diet. Yellen and Danial's work has identified a protein that switches a cell's fuel glucose to ketone bodies and in so doing opens a type of potassium ion channel in neurons that can dampen electrical activity[7]. "Some of the types of cells in the brain where these channels are found are well known as seizure gates that regulate whether a little bit of local excessive electrical activity gets spread to the whole brain and becomes a seizure," Yellen explains.

The success of the MCT diet suggests another pathway to seizure-protection. Neurologist Matthew Walker at University College London and molecular biologist Robin Williams at Royal Holloway, University of London, identified a number of MCTs that provide enhanced seizure control. One example is decanoic acid[8]. Simon Heales, a clinical chemist at University College London, showed that decanoic acid increases mitochondrial numbers in brain cells[9]. The mitochondria produce ATP, which helps transmit signals along the neurons, and its increased production could provide better control of potassium channels related to the seizure gates that Yellen mentions.

There is no agreement on how a ketogenic diet can help control epileptic seizures. It's likely that there isn't a single mechanism involved, and, says Cross, it may work in a different way in different children.

After four years on a ketogenic diet, Elijah has fewer seizures, but he gets hungry and is unable to take part in celebrations that involve food. And he still has severe cognitive impairments and needs assistance with daily tasks such as dressing and feeding.

But he is happy, has an increased attention span and is starting to talk. As Hippocrates, the Ancient Greek father of medicine, said: "Let food be thy medicine and medicine be thy food." ■

HOW FATS HELP EPILEPSY

Epigenetics of eating

A ketogenic diet, which is high in fatty foods such as ice cream and cheese, can reduce epileptic seizures in children. A paper published last year[10] offers some clues on the way this diet exerts its effect. The researchers looked for genetic changes between rats induced to have epilepsy that were fed a normal diet and those fed a ketogenic diet.

They found that the ketogenic diet changes the genetic pathways and could alter the expression of genes responsible for epilepsy. The mechanism is still not clear, but the team noticed that there were differences in the DNA between the two groups of rats. The rats fed a normal diet had a higher amount of methylation — the addition of a CH_3 group — in their DNA compared with the animals fed the ketogenic diet. The team suggests that these changes in methylation are linked to deactivation of the genes.

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1. McNally, M. A. & Hartman, A. L. *J. Neurochem.* **121,** 28–35 (2012).
2. Levy, R. G., Cooper, P. N., Giri, P. & Pulman, J. *Cochrane Database Syst. Rev.* CD001903 (2012).
3. Hallböök, T., Ji, S., Maudsley, S. & Martin, B. *Epilepsy Res.* **100,** 304–309 (2012).
4. Kossoff, E. H. *et al. Epilepsia* **50,** 304–317 (2009).
5. Kossoff, E. H., Krauss, G. L., McGrogan, J. R. & Freeman, J. M. *Neurology* **61,** 1789–1791 (2003).
6. Muzykewicz, D. A. *et al. Epilepsia* **50,** 1118–1126 (2009).
7. Giménez-Cassina, A. *et al. Neuron* **74,** 719–730 (2012).
8. Chang, P. *et al. Neuropharmacology* **69,** 105–114 (2013).
9. Hughes, S. D. *et al. J. Neurochem.* **129,** 426–433 (2014).
10. Kobow, K. *et al. Acta Neuropath.* **126,** 741–756 (2013)

ICTALCARE

Portable devices could help the wearer prepare for a seizure by taking rescue medication or lying down.

TECHNOLOGY

Dressed to detect

Wearable devices that monitor seizures promise improvements in epilepsy treatments and research.

BY ELIE DOLGIN

It looks like a new-age fashion accessory, but the black, chunky bracelet on Rosalind Picard's wrist is actually the latest technology for monitoring seizures. Similar to wearable devices for tracking fitness, this experimental wristband comes packed with sensors that measure heart rate, skin temperature and movement patterns. But unlike other fitness monitors, Picard's biometric bracelet also gauges changes in electrodermal activity, or skin conductance — an indicator of the abnormalities in the nervous system that are triggered during many epileptic seizures.

Picard, an electrical engineer at the Massachusetts Institute of Technology (MIT) Media Lab in Cambridge, developed the idea for her 'Embrace' device with her former PhD student, Ming-Zher Poh. The researchers initially created a prototype bracelet called Q Sensor that tracked only electrodermal activity and movement. Two years ago, they showed that this device could accurately detect 94% of large convulsive seizures experienced by children with epilepsy[1]. What's more, the Q Sensor produced few incorrect signals — less than one false alarm per day on average — and most of these were triggered by forceful, rhythmic motion, such as shaking dice or vigorously playing with a Nintendo Wii.

NATURE.COM
How mathematical models can predict seizures:
go.nature.com/m8sfh9

About one-third of people with epilepsy continue to experience seizures despite an increasing number of available drug treatments and considerable progress in surgery (see page S12 and page S7). A portable device that warns of an impending attack could help people prepare for a seizure by lying down, say, or taking a rescue medication. Existing devices can only record epileptic events that are already occurring — a major limitation for now. Researchers therefore hope to find measurable biomarkers that would warn the wearer of a seizure before it strikes.

Nonetheless, even a device that falls short of that goal could dramatically alleviate the burden of disease. It could provide real-time information on how well a medication is working, or it could help people determine whether they need to seek medical attention. In one of Picard and Poh's studies, for example, they showed[2] that surges in electro-dermal activity detected by their device correlated with a measure of brain activity thought to be linked to the risk of sudden unexpected death in epilepsy, a mysterious complication of the disease that is the most common cause of epilepsy-related deaths. "This autonomic information tells you something that turns out to be really important in terms of what's going on inside the brain," says Picard. "That was a surprise to us, but it's a pretty cool surprise, and that is where we think the potential is: for alerting people with epilepsy to something that is life-threatening."

So far, tests of the Q Sensor prototype have taken place in hospital. Picard now hopes that the second-generation Embrace device can be used to detect seizures in the home. To achieve this, she has joined forces with Empatica, a company based in Milan, Italy, that already sells a tool for mobile stress monitoring. According to Matteo Lai, Empatica's chief executive, clinical trials involving Embrace are planned for early 2015.

SENSING SEIZURES

Most commercially available systems for 24-hour seizure monitoring currently rely on motion detection. One such system is manufactured by Smart Monitor, based in San Jose, California, which sells a device called the SmartWatch that uses three-dimensional accelerometers to detect the excessive and repetitive shaking movements that occur during a large seizure. Within seconds, the wristwatch issues alerts by text message or phone call to designated family members, who can then summon help in case of serious injury or loss of consciousness.

ICTALCARE

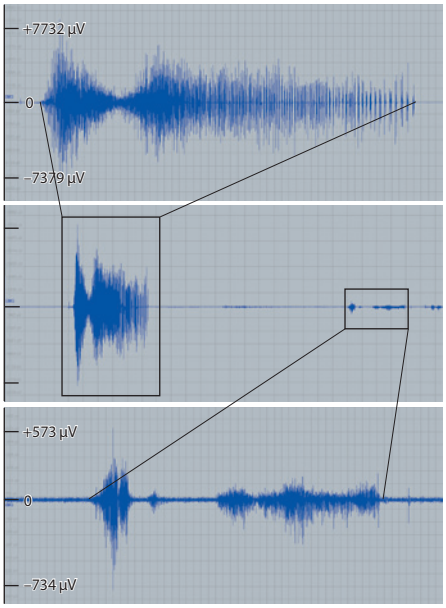
SmartWatch and other movement-based detectors have a sensitivity of around 90% for identifying generalized tonic–clonic seizures — big, whole-body convulsions — compared with video electroencephalography (EEG), a diagnostic technique that uses video equipment and electrodes on the scalp to record brain waves and behaviour at the same time. Video EEG is the gold standard but is only available in a hospital setting. Some portable EEG systems have been developed for everyday use, but they are uncomfortable and unsightly — most people with epilepsy say they would not wear scalp electrodes in public to obtain seizure warnings, nor do they want implantable alternatives. To increase the sensitivity while providing a device that is comfortable and stigma-free, some researchers are investigating physiological metrics beyond movement patterns. One such trait is electrodermal activity. Another is electromyography, the electrical activity produced by muscles.

Brain Sentinel, a start-up company in San Antonio, Texas, is developing a prototype device that is about the size of a bar of soap and can be worn around the upper arm to detect the electromyography patterns typical of generalized tonic–clonic seizures. Like the SmartWatch, Brain Sentinel's sensor can alert caregivers that a seizure is occurring. At the 2013 American Epilepsy Society's annual meeting in Washington DC, researchers from the South Texas Comprehensive Epilepsy Center in San Antonio reported that the Brain Sentinel device detected 95% of generalized tonic–clonic seizures. The device had been worn by 33 participants, each of whom wore the sensor for an average of two days, and only one false alarm was reported. A larger clinical trial, involving at least 100 participants at 11 medical centres across the United States, is ongoing.

"We're on the edge of a huge advance in epilepsy science."

Compared with detectors that rely on movement patterns, "the much lower false-positive rate [of the electromyography-based device] is definitely an advantage", says Michael Girouard, president of Brain Sentinel. "A high number of false detections can lead to alarm fatigue," he explains, as people start ignoring the warnings or stop wearing the device. But with the Brain Sentinel detector, "when the system's alert goes off, you're pretty certain somebody's having a seizure".

IctalCare, based in Hørsholm, Denmark, already sells an electromyography-based device, although it is only available in Denmark. According to Isa Conradsen, the company's clinical research manager, another benefit of using electromyography is that it can detect changes during the tonic phase of a generalized tonic–clonic seizure, when the muscles initially stiffen and people often lose consciousness, whereas accelerometers generally have to wait until the clonic phase, when the muscles begin to spasm and jerk. "Looking at surface electromyography," Conradsen says, "you can get the alarm much earlier."



Surface EMG trace (centre) on a bicep showing five minutes of a seizure and 'normal' activity with enlargements of (top) 60 seconds of seizure and (bottom) 60 seconds of 'normal' activity.

There's more to epilepsy than just generalized tonic–clonic seizures, however. "The problem is that people may die of seizures when there are no convulsions," says John Duncan, a neurologist at University College London and clinical director of the National Hospital for Neurology and Neurosurgery in London.

In these cases, measuring electrodermal activity could prove particularly helpful. In one study[2] using the Q Sensor, Picard and Poh, working with a team that included paediatric neurologist Tobias Loddenkemper of Boston Children's Hospital in Massachusetts, found that skin conductance rose significantly in 86% of complex partial seizures, a type of epileptic attack in which people often stare blankly into space but do not exhibit large convulsions. "The clinical presentation of seizures can vary," says Loddenkemper, who is now running a larger trial involving the same prototype device. "You need the right sensor for the right epilepsy type."

Other researchers are working on devices that monitor different physiological changes that occur during seizures. At the Holst Centre in Eindhoven, the Netherlands, for example, scientists are developing a wearable electrocardiogram detector to track different kinds of seizure based on variations in heart rhythm. And at RTI International, a nonprofit organization based in Research Triangle Park, North Carolina, researchers are developing a thin harness that straps around a child's chest and incorporates sensors that measure respiratory function, heart rate and body orientation to detect all generalized seizures and some types of partial seizure.

Eventually, all these signals will probably be combined into a single device. Although writing the algorithm for such a multimodal system might prove tricky, as Jacqueline French, a neurologist at New York University's Comprehensive Epilepsy Center, points out. "The more things you measure that you know change in some people's seizures, the more you're likely to see a characteristic pattern for every person."

BETTER TRIALS

Wearable seizure monitors are mostly being developed with the patient in mind. But when they have been clinically validated, these platforms should also prove useful for the biomedical research community. "It could change the way we do epilepsy trials," says Loddenkemper.

Epilepsy trials today that involve drugs, diets or other treatment interventions typically ask participants at home to keep track of their own seizure experiences in a notebook or electronic diary. But this method depends on people accurately recognizing and documenting their seizures, which is a problem because patients tend to be unaware of about half of all seizures recorded during video-EEG monitoring.

By taking direct physiological measurements instead, wearable sensors could dramatically improve diagnostic accuracy in such studies. "We would get a more objective evaluation of the seizure frequency," says Sándor Beniczky, a neurophysiologist at the Danish Epilepsy Centre in Dianalund. To test this idea, Brain Sentinel, Empatica, Smart Monitor and others are now running or planning trials designed, at least in part, to compare the accuracy of their devices with the self-reporting of seizures by patients.

Standalone systems for detecting seizures could become obsolete if multinationals such as Apple and Samsung were to roll out smart watches with clinical-grade capabilities such as electrodermal activity or electromyography. At that point, says Lunal Khuon, a biomedical engineer at Villanova University in Pennsylvania, "there will be less hardware development and more software development to use the sensors that are already available".

"We're on the edge of a huge advance in epilepsy science with better recording of seizures," says French. "It's fundamental that we understand the symptoms before initiating treatment — and it's something that we're not very good at." ■

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1. Poh, M.-Z. *et al. Epilepsia* **53,** e93–e97 (2012).
2. Poh, M.-Z. *et al. Neurology* **78,** 1868–1876 (2012).