



Unraveling

BABYLONIANS THOUGHT DEMONS AFFLICTED THEM. During the Renaissance, they were touted as prophets. And even as recently as the Roaring Twenties, they were surgically prevented from having children. People with epilepsy have endured all manner of misconceptions. But today — even though we know several causes of the disease, we know its effects, and we know many ways to treat it — we still don't know how to cure it. Scientists from the University of Chicago are trying to change that. And one little girl from Sycamore, Ill., is leading them in new directions that may help.

Scientists are delving into the inner workings of this sometimes-fatal disorder

THE WORLD OF EPILEPSY

STORY BY Catherine Gianaro
PHOTOS BY Dan Dry

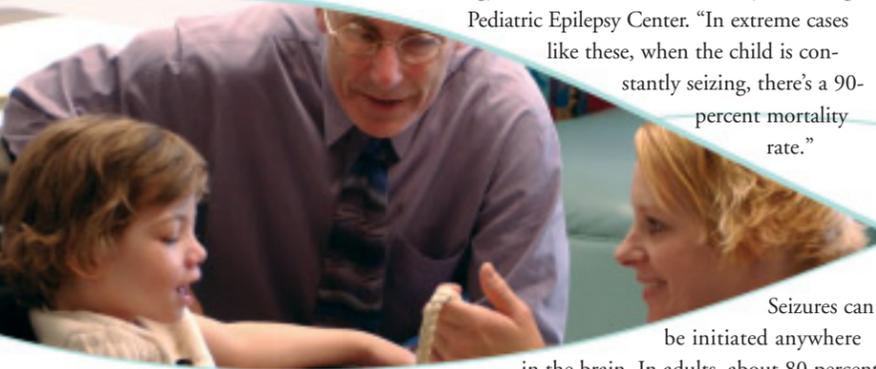


Clockwise from top: Tavian Pointer, then age 5; pediatric neurologist Charles Marcuccilli (left) and neurobiologist Nino Ramirez lead a Chicago team of researchers, including research associate Frank Elsen (far left), who slice cortical tissue of epilepsy patients to closely study the cells and to screen anticonvulsant drugs.

A LITTLE GIRL'S FATE She lived the first four years of her life in what seemed to be perfect health. But in the community pool one Saturday afternoon, Tavian Pointer suddenly stopped playing. When her mom asked what was wrong, she simply said, "I want to go home."

Within a week, Tavian was in the hospital having more than 100 epileptic seizures a day.

"She had been seizing for days when she came to us," said Kurt Hecox, MD, PhD, associate professor of pediatrics and neurology and director of the University of Chicago Pediatric Epilepsy Center. "In extreme cases like these, when the child is constantly seizing, there's a 90-percent mortality rate."



Seizures can be initiated anywhere in the brain. In adults, about 80 percent of the time they start in the temporal lobe. In children, it's much more widely distributed and, Hecox said, harder to pinpoint. Children's seizures can start almost anywhere with equal likelihood.

"The first step with cases like Tavian's is to stop the seizures," he said, "even if it's for brief periods."

Typically, medications will stop the seizures temporarily, although they also may make the child lose consciousness.

"We went through a series of medications for Tavian, but nothing worked," Hecox said. "It was clear she was going to be a very tough case."

Hecox then tried Lidocaine, which isn't used often for epilepsy in the United States, but rather for heart problems. "It stopped it cold," he said. "It didn't hold her, but she was down from continuously seizing to about a dozen a day."

That was enough time for Hecox and his team to find the source of her seizures, which they accomplished by combining routine MRIs and EEGs with non-routine mathematics to produce 3-D images of the brain. Pinpointing a source is essential if surgery is going to be an option.

In Tavian's case the cause appeared to be encephalitis in the frontal and temporal lobes. Since her epileptic foci, or "hot spots," were limited, surgery was an option after all.

Hecox turned to pediatric neurosurgeon David Frim, who implanted a grid of 144 electrodes directly onto the suspected area of Tavian's brain. For a week, the electrodes monitored brain activity and recorded her seizures. With that data, Hecox was able to map the three hot spots within 2 to 5 millimeters of an electrode. Frim and his surgical team removed the two largest ones.

"Only a minority of patients are surgical candidates," Hecox said, adding that when surgery is not an option, doctors must rely on other tools, such as medications and nerve stimulators. "And sometimes you can't solve the problem. That's why we do the science."

IT'S ALL IN THE RHYTHM A related science is being practiced just a few buildings away. In his Anatomy Building lab, Jan-Marino Ramirez spends his time listening to mice — more specifically, the respiratory cells of mice. The professor of organismal biology and anatomy studies a cluster of cells found in the brain called "pacemakers," which oscillate and set the tempo for breathing. (See "SIDS" story, page 17.)

"They're fundamental for understanding how the brain works," Ramirez said. "Their function is very defined. In fact, you can take some of them out and put them in a dish and they still generate the breathing rhythm."

He and his research team have become experts at slicing tissue from the brain stem to look more closely at the respiratory cells of mice. The team records the activity of these cells to better understand what generates these rhythms.

After Ramirez gave a campus talk about these pacemaker cells, Hecox, who sat in on the lecture, posed a challenge to him: Since he can make a slice of respiratory tissue breathe in a Petri dish, could he also make a slice of brain from an epilepsy patient mimic a seizure?

Hecox had tried this procedure before, but it had always failed. This time, however, he was recruiting an expert in using the tissue-slicing technique as well as someone who understood the fundamentals of rhythmic cells.

The combination paid off.

In November 2002, Ramirez teamed with Charles Marcuccilli, MD, PhD, a pediatric neurologist trained in electrophysiology and a researcher who specializes in biochemistry and molecular biology. They tested their first patient the following February.

The researchers are able to mimic a seizure in the Petri dish by injecting electrical current into the slice of cortical tissue. "The neurons will fire in this rhythmic activity all over the dish," Ramirez said. "It generates waves, just like in an epileptic brain."

For each slice of cells, the scientists test a different drug to see if it stops the seizure: Each drug blocks a different ion channel in the cells. "Something in these cells is wrong, and we can find out exactly what it is by blocking each of the ion channel proteins one by one [calcium, potassium, sodium, etc.] to find out which channel is not working," Ramirez said.

The researchers use the cells to screen anticonvulsant drugs, including Topamax, Lamictal, Phenytoin and Zonisamide. They plan to soon add Carbamazepine and Keppra, as well as purified forms of Zonisamide and Lamictal.

The drug screenings are just one aspect of the lab research. The scientists also compare differences between the seizure focus tissue and the surrounding silent area, or "control" tissue; they look at the mechanisms of each cell type between the focus and control; and they study the genetic characteristics of both the focus and control tissues.

Studying differences between the two tissues also will allow the researchers to see how the cells respond to certain drugs. Marcuccilli acknowledges they will never have a true control because obtaining brain tissue from a healthy person presents an ethical impasse. "The best we can do is compare least abnormal from most abnormal," he said. But that in itself is a leap forward.

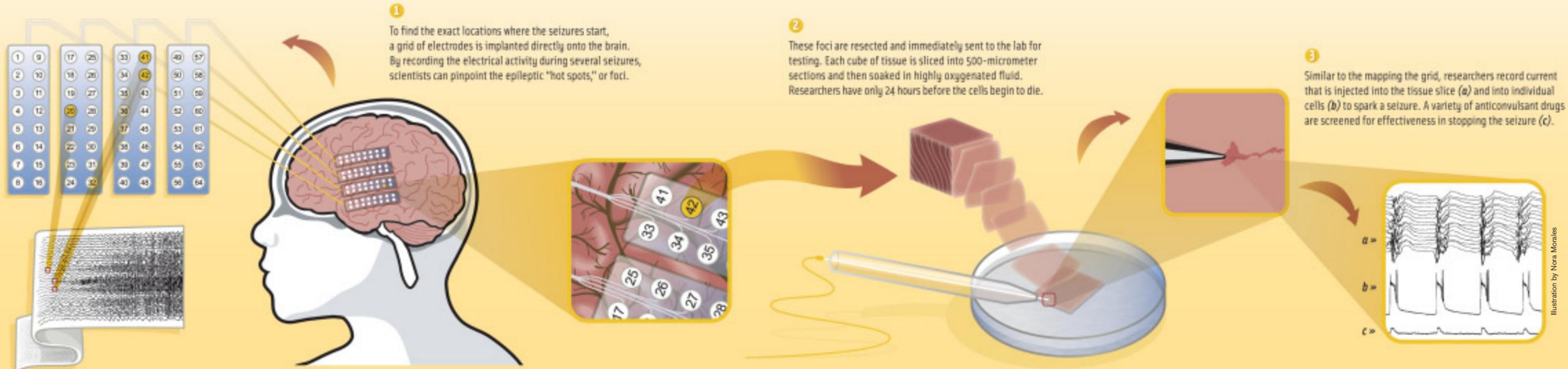
The researchers can measure the electrical activity of a cell by opening its membrane. To do this, they "patch" onto it using an electrode encased in a glass pipe — an odd mixture of ultra-modern technology, manual dexterity and dumb luck.

"When you touch a nerve cell, the resistance increases. When you get really close, you actually *hear* the change in resistance. It's like a voltage tap. We have the amplifiers to record it," Ramirez said. "It's easier to hear when we touch a cell versus seeing it. But you have to have a very good ear to know exactly when you touch it."

More precision is needed to suck open the cell. Once the pipe's head is sealed on the cell's membrane, the scientist uses a plastic tube attached to a mouthpiece to gently suck open the cell. If there's too much suction, the cell gets sucked in. If there's too little, it doesn't open. Ramirez said scientists who are new to the field might need a year before they're able to open some really sensitive pacemaker neuron cells.

Neurologist Kurt Hecox watches interaction between epilepsy patient Tavian Pointer (left) and her mother, Jennifer Embry, during a check-up nearly a year after Tavian's surgery. After enduring nonstop seizures for weeks, Tavian has had to relearn speech, motor and other developmental skills.

AGAINST THE CLOCK



SEIZURES, SLEEP & SONG INSPIRE SCIENTISTS

By Lucy Biederman

Thanks to a kumquat-sized songbird who needs a good night's sleep to learn a new song, two scientists discover more about how sleep-depriving seizures can impair language in humans.

WHEN KURT HECOX, MD, PhD, chief of pediatric neurology at the University of Chicago Children's Hospital, received a 6-year-old patient whose symptoms had stumped numerous doctors, he diagnosed her as epileptic and determined that she experienced continuous seizures during sleep.

Across campus in the Anatomy Building, Daniel Margoliash, PhD, and his research team were investigating the role of sleep in the zebra finch's ability to learn songs. It was dawning on Margoliash, a professor of organismal biology and anatomy, that songbirds undergo specific neural processes during sleep that help them learn to sing.

Familiar with Margoliash's work, Hecox began to wonder if his epilepsy patient lacked normal linguistic aptitude because of her interrupted sleep. Did she, like Margoliash's zebra finch, need sleep to learn communication skills?

Now, nearly a year later, Hecox and Margoliash are knee-deep in a series of interdisciplinary experiments looking for those answers about how epilepsy hinders language development.

"To study this in a controlled way," Hecox said, "we need animal models."

As yet, their work, funded in part by a gift from the Palmer Family Foundation, remains highly experimental. They don't know whether their collaboration will yield direct clinical application for epileptic patients. "But we'll never know if we don't try," Margoliash said. "And this is as good a synergy between science and medicine as one could hope for. We're quite enthusiastic about it."

The goal, Hecox said, is to "produce an animal model of the loss of human communication skills." And neither of the researchers would mind if, in the process, they helped solve any of epilepsy's many mysteries.

"At the moment the scientific community is really pretty blind," Margoliash said. "We have very little objective knowledge or objective evidence as to what the relationship is between seizing and language development."

Physicians often have trouble knowing epilepsy when they see it, especially in cases like the 6-year-old, whose most obvious symptoms occurred while she slept.

"Dr. Hecox is able to treat and show improvement in many symptoms, but he's not able to address the restoration of language development," Margoliash said. "If we had some method of screening patients that was easy to distribute and accessible to doctors, the number of patients who were diagnosed at an early age would shoot up."

While preparing their first manuscript based on the collaboration, the pair is conducting experiments in which they stimulate the brains of sleeping songbirds to create a seizure-like effect. This way the researchers can control the time and place in the brain where seizures occur, target specific brain structures associated with singing activity, and get a sense of what happens at the neurological level when seizures disrupt epileptic patients' sleep and language skills.

Through the collaboration, Margoliash said they hope to "gain some scientific perspective on how aberrant brain activity leads to epilepsy."

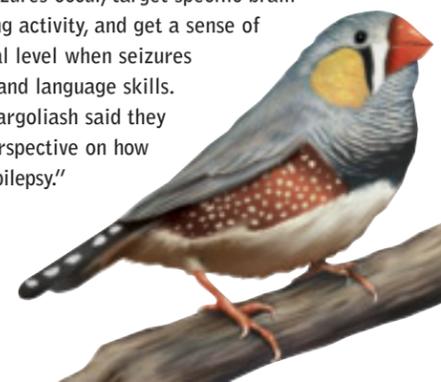


Illustration by Nora Morales

The center's lead researcher, Wim van Drongelen, PhD, was the first to use in a clinical context "beam-forming," a technology that previously had been used only by the military to detect enemy aircraft. Combining conventional diagnostic tools with this novel technique, van Drongelen and his colleagues at Chicago are able to locate elusive sources of seizures for some children — usually hidden deep within the hemispheres of the brain. Locating the source could enable surgeons to remove the hot spot, which often leaves the child seizure-free.

Van Drongelen said he hopes to produce a computer model of a network of a million neurons. With the data obtained from the team's research and some mathematical

manipulation, such a model could help scientists predict seizure behavior.

Van Drongelen's team already has done this on a much smaller scale. They've been working with computer scientists at Argonne National Laboratory, which is equipped with the hundreds of parallel computers needed to process the data and mimic an epileptic seizure. They analyze brain impulses so complex that it takes 24 hours of computer time to work through 10 seconds of brain activity. Creating a network of a million neurons will be a challenge even for Argonne's supercomputers.

Marcuccilli and Ramirez have more plans for the slices as well. They are investigating why some drugs stop working after a while. To do that, they need to find a way to keep the cells alive longer.

Ramirez also is looking more closely at burster cells. All bursters are controlled by brain chemicals called neuromodulators. These little amino-acid-like compounds in the brain control rhythmic activity. Ramirez is investigating this natural system that controls the bursting in epileptic cells and wants to learn how to manipulate it.

"My hope is that we find the neuromodulators that can turn this bursting into normal activity. Instead of going for the channel, we're going for the natural neuromodulator that controls it," he said.

"We're a long way away, but we'll have a completely new strategy to treat these children," Ramirez said. "We do all the testing, not only in case the child will need a drug to combat any recurring seizures, but also for the basic science of it. We're collecting more data and studying more tissue to learn more about this disease.

"I was happy with how we helped Tavian," he said, "but we want to develop a completely new cure that would help hundreds of other kids. What has been done for one little girl is an amazing encouragement to provide help for many more children. Tavian has shown us that this is possible."

keeping cells alive, he and his colleagues had roughly 24 hours to test Tavian's tissue. Immense amounts of data processing and mathematical manipulation happened in the weeks to follow.

The team worked nonstop gleaming as much information as they could from the precious neurons. Working at eight separate stations spread out on two different floors, researchers would induce seizures within a network of cells and individual cells to test a variety of drugs.

"The first six or seven hours are always exciting, but also often the most frustrating," Ramirez said. "Then in the eighth hour you find a drug that just stops a seizure in its tracks, which turns the entire lab into complete excitement."

That's what happened when they tested Tavian's tissue. They found her

seizures were due to malfunctions in her cells' sodium ion channels. Their diagnosis was confirmed when they tested Lamictal on the epileptic cells and the seizing stopped immediately.

Tavian was seizure-free after the operation, but in just two weeks, she started to seize again: 10 to 15 a day. Marcuccilli told Tavian's mom that, although he had hoped it wouldn't be necessary, there was still a treatment method to try: They had found a drug that stopped her daughter's seizures.

A daily dose of Lamictal had decreased the number of Tavian's seizures to one or two a week. To control those remaining seizures, surgeons implanted a vagus nerve stimulator — a pacemaker-like device that stimulates a nerve in the left side of the neck to reduce seizure activity. A VNS typically is implanted on the chest or, as with Tavian, underneath the skin of the back. Her mother activates the device by swiping a magnetic wand when a seizure starts.

"This approach has the potential to help thousands of people whose seizures are unmanageable," Hecox said. "Its success is the culmination of thousands of hours of testing, analysis, planning, discussion and meticulous surgical skill — a perfect example of cross-disciplinary science and medicine working together."

TACKLING NEW STRATEGIES Epilepsy affects more than 50 million people worldwide. In the United States, 181,000 people are diagnosed each year with epilepsy; one-third of those are children. More than 20 percent of all children with seizures have intractable epilepsy — seizures that cannot be controlled with medication alone. Because the physicians at Chicago mostly handle complex cases, many of their patients are in this category.

In 1999, the University of Chicago opened the Falk Center for Advanced Study and Care of Pediatric Epilepsy — the research arm of the Pediatric Epilepsy Center. The program is one of the largest U.S. research centers of its kind for children, like Tavian, who have intractable epilepsy.

When a cell is stimulated into firing, it will have one of three basic firing patterns: regular-firing, which is characteristic of most cells; fast-spiking, which is inhibitory; and "intrinsic bursters," which have pacemaking capabilities — the capacity to initiate electrical activity and start a seizure.

Although bursters are found easily in rodents, until recently they eluded detection in humans. Since starting their project a little more than three years ago, the Chicago researchers may have found six intrinsic burster cells.

Why are they so hard to find? According to Marcuccilli, they may not exist normally in humans at all; the six they found were in the epileptic focus, therefore the tissue may have been distorted.

Or their discoveries may be credited to more sophisticated techniques that weren't employed until the Chicago scientists began to collaborate so closely and so quickly.

"A lot of groups that do this work are not on the same campus as the hospital," Marcuccilli said, drawing a distinction between Chicago and other research institutions. "I have a five-minute walk from the OR to the lab. Some groups have an 80-kilometer drive."

That close collaboration means the scientists in Ramirez's lab can make tissue slices much sooner, which sustains the health of the cells and improves analysis.

Tissue slicing and testing has been done since the 1970s, but is rarely successful. According to Hecox, a major source of frustration in the field of epilepsy is that the slice studies had always failed.

"How could you not find bad cells? The EEG shows you there are bad spots. You put a grid right on the brain, and you can see them. Then you take them into the laboratory to study, and you can't find them," he said.

Hecox credits the success of Chicago's program on its advanced technology and the meticulousness of the entire team, especially the resections by Frim. When you take out thousands of cells comprised in a piece of brain tissue, and you're only going to test about 20 cells from it, precision is an understatement, Hecox said.

A RACE TO THE DEATH To secure what Hecox's team determined as Tavian's hot spots, Frim made his surgical resections with painstaking measures to keep the tissue oriented so the researchers could track which cells they studied. When Frim handed over the tissue to the researchers, it was a race against the clock to do as much testing as possible while the cells were still alive.

Brain cells, if carefully nourished, can live outside the body for little more than a day. Although Ramirez is an expert at

Below: Frank Elsen, a neurobiologist in Ramirez's lab, has mastered the science and fastidious art of "patching" onto a neuron; at right: stained "hot spot" from epileptic tissue cell at right.

Cell photo courtesy of Charles Marcuccilli



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