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.
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 sitting for days when she came to us,” said Kurt Hecox, MD, PhD, associate professor of pediatrics and neurologist and director of the University of Chicago Pediatric Epilepsy Center. “In extreme cases like these, when the child is constantly seizing, there’s a 50-70 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,” Hecox said. “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 mathematicians 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 focus, 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.

“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 Topiramax, 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 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.

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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 pipette — an odd mixture of ultra-modern methodology, manual dexterity and dumb luck.

“When you touch a nerve cell, the resistance increases. When you get really close, you actually hear the changes 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 pipette 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.

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 team removed the two largest ones.

“Only a tiny fraction of patients are surgical candidates,” Hecox said, adding that 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 in the brain called “pacemakers,” which oscillate and fire in rhythmic activity all day.

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The scientists also compare differences between the seizure 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 tissue from most abnormal,” he said. But that in itself is a leap forward.

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When a cell is stimulated into firing, it will have one of three basic firing patterns: regular-firing, which is characteristic of motor cells; fast-spiking, which is inhibitory; and “burster” cells, which exhibit paroxysmal, quinckeoid epochs of high-frequency firing. These different firing patterns can indicate different things about a cell.

One day, as researchers were studying the cells in Tavian’s brain tissue, they noticed a particular cell firing at a high frequency. This cell was identified as a “burster” cell, which is known for its ability to initiate electrical activity and start a seizure. The researchers were able to stimulate this cell with a magnetic wand, and it began to fire at an even higher frequency, indicating that it was a “hot spot” for seizures.

The researchers were excited by this discovery, as it suggested that by targeting these “hot spots” during surgery, they might be able to control Tavian’s seizures. They continued to study the cell, and eventually they were able to identify six such cells in Tavian’s brain tissue. These cells were eventually localized to the left side of Tavian’s neck, which was the area of the brain that was responsible for his seizures.

The researchers were able to develop a technology that allowed them to stimulate the cells in Tavian’s brain tissue from the outside. They were able to do this by using a magnetic wand, and they were able to turn off Tavian’s seizures by stimulating the cells in the left side of his neck.

This approach has the potential to help thousands of people with epilepsy, as it allows for the targeted treatment of seizures. The researchers are now working on developing a device that can be used in the clinic to stimulate these cells in patients who have seizures.

The center’s lead researcher, Wim van Drooge, MD, PhD, was the first to use a clinical technique called “beam-forming,” which has previously been used only in the military. Van Drooge and his colleagues at Argonne are using this technology to stimulate the cells in Tavian’s brain tissue, and they are able to control his seizures with it.

This technology is still in its early stages, and more research is needed to determine its effectiveness. However, the researchers are hopeful that it will be a valuable tool for the treatment of epilepsy in the future.