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LAST RESORTS

Doctors Put Hope in Thin Wires for a Life in Epilepsy's Clutches

By DENISE GRADY

"Squeeze my hand, Stephen," the surgeon called. "Wiggle your feet."

In an operating room at New York Weill Cornell Medical Center, doctors watched intently as Stephen R. Neiley III, roused from general anesthesia, gave a squeeze and a wiggle and went back to sleep. Reassured that the electrodes they had just implanted in his brain had done no harm, they went back to work.

The next step was to tunnel wires from the electrodes through Mr. Neiley's scalp and neck to a pacemaker-like gadget that would be implanted in his chest.

The operation was an experiment, with a goal that Mr. Neiley, 51, has been pursuing for 10 years: to stop or at least diminish the epileptic seizures that have played havoc with his life. Electrically stimulating the brain, in a region called the anterior nucleus of the thalamus, has helped prevent seizures in animals and people, in preliminary studies.

Devices like the one being tested in Mr. Neiley and other people with epilepsy are already in use to treat Parkinson's disease and other types of tremors and movement disorders. Though they are called deep brain stimulators, the devices actually work by inhibiting nerve impulses in parts of the brain that are too active.

Such stimulators, sometimes described as pacemakers for the brain, are at the forefront of research by neuroscientists seeking to treat a variety of difficult conditions that may eventually include depression, obsessive compulsive disorder and Tourette's syndrome.

"I think this certainly has a reasonable chance of working," said Dr. Gregory L. Barkley, chairman of the epilepsy program at the Henry Ford Hospital in Detroit and chairman of the professional advisory board of the Epilepsy Foundation.

New treatments that venture deep into the brain are driven by technology that lets researchers map brain activity and zero in on minute anatomical targets, and by patients' eagerness to volunteer for experiments, even ones that involve surgery and risks like bleeding, infection and stroke.

Around the country, according to the Food and Drug Administration, more than 25,000 clinical trials - medical experiments on people - are under way for conditions as varied as baldness and cancer. Advances in genetics, pharmacology and computing have yielded an abundance of new drugs and devices, and a constant demand for patients willing to test them.

Mr. Neiley is part of a trial of deep brain stimulators being conducted at a dozen medical centers in the United States on patients who have intractable epilepsy that neither drugs

nor surgery can control. The trial is sponsored by Medtronic, which adapted cardiac pacemakers to treat brain disorders. The results will probably not be in for several years.

Another trial sponsored by a different company, Neuropace, is testing a different stimulator.

Despite daily doses of several medicines, Mr. Neiley, like a third of the 2.3 million Americans with epilepsy, still has seizures. Small ones, which jolt his body briefly, can strike 20 to 30 times a day. Twice a week or so, without warning, he collapses into full-fledged, grand mal convulsions that can last several minutes and leave him confused, dead tired and frightened.

Mr. Neiley is 6-foot-3 and rangy, with close-cropped salt and pepper hair, a tawny brush of a mustache, the year-round tan of an outdoorsman and, behind his glasses, direct gray-blue eyes. He speaks softly, smiles easily and jokes with doctors and nurses.

But behind the cheer is a life dismantled by illness. Ten years ago he was a successful building contractor in Southern California, married, with three sons. Then one night in a restaurant, he opened his mouth to speak and what came out was gibberish. It was his first seizure. That moment marked the end of one life and the beginning of another.

"Epilepsy is the most elusive and most treacherous of neurological diseases, because of its intermittency, and also the cruelest, because you never know when it is going to strike next," said Dr. Ivan Osorio, a neurologist at the University of Kansas and a researcher in the Medtronic trial. He likened a seizure to a fire spreading through the brain.

Doctors could not say why Mr. Neiley had suddenly become epileptic. His case was unusual. When people begin having seizures as adults, the cause is usually brain damage from a stroke, a tumor, an infection or a previous head injury. Mr. Neiley had none of those. Tests did show scarring in his brain, but could not explain how it got there.

When epilepsy arises from one hyperactive region in the brain, the best solution is often just to slice it out. Mr. Neiley's doctors tried that. It seemed to help, but only for a year. And he found that the operation impaired his memory.

Next, he had a device implanted in his neck to stimulate the vagus nerve, which enters the lower brain. Such stimulators, approved for epilepsy in 1997, can reduce seizures or make them less severe in some people. Worldwide, about 30,000 people have the devices. Mr. Neiley said the stimulator seemed to diminish only the small seizures.

Doctors urged him to give up his business, saying that stress might bring on seizures. He took their advice. But the seizures went on. His marriage ended.

Today, he lives on a farm in northwestern Pennsylvania with his parents. He takes care of the property, hunts and works on remodeling on the house, but does not have a job.

He has contemplated getting a "seizure-alert dog" trained to watch over people having seizures and to bring them medicine or a telephone. Some research suggests that the dogs can even alert their owners when they are about to have a seizure, perhaps by detecting a change in body odor.

A few months ago, Mr. Neiley gave up the vagus device to try the Medtronic one, which stimulates the brain directly, even though that would require another brain operation. "I

hope to get out of it that we learn something, that maybe this works, that I don't have so many seizures, maybe two a month, maybe none," he said.

If it does not help him, he said, he will volunteer for still more surgery, to try the Neuropace stimulator. And if that does not work, he said, he will look for something else.

"It shows how devastating this illness is, that people are so desperate they're willing to go under the knife," said his neurologist, Dr. Douglas R. Labar, director of the epilepsy center at New York Weill Cornell Medical Center in Manhattan.

Dr. Labar said he thought there was a good chance that the stimulators would help people like Mr. Neiley. He said studies have hinted that the stimulators may have a lasting benefit, even after they are turned off. "They might modulate the central nervous system in a permanent way," he said.

Dr. Labar likened a seizure to fans doing the wave in a stadium. "Many more nerve cells than normal are firing off synchronously in an abnormally repetitive, fast way that is excessively simple," he said.

In contrast to the heart, where muscle cells must work together to pump, the job of the brain is not "to squeeze out one thought at a time," said Dr. Robert S. Fisher, director of the Stanford epilepsy center and a researcher in the trial.

"Much of the business of active brain processing involves the cells all doing individual types of work," Dr. Fisher said. "A seizure has them all doing the same thing, and many of the brain cells cannot be doing what they ought to be doing."

As to why a stimulator would prevent seizures, Dr. Fisher said: "The simple and short answer is, we don't know. Electrical stimulation breaks up synchronous firings of networks of neurons. There's a reasonable chance that's the mechanism."

Although deep brain stimulators are often compared to pacemakers, there is a striking difference. While a cardiac pacemaker emits about 70 signals a minute, a brain stimulator can send out 180 a second - much faster than the too-synchronous brain cells, which fire a few times a second during a seizure.

"When brain cells are bombarded by higher frequency activity, it disrupts the slower waves of synchrony," Dr. Fisher said.

It is possible that just implanting the electrodes, even without electrical stimulation, may affect seizures, since the surgery itself disturbs brain tissue. A placebo effect is also possible, in which patients would have fewer seizures simply because they believe the device is working. To control for those possibilities, patients will begin the study with the device switched either on or off, and neither they nor their doctors will know which it is. Eventually, all the devices will be turned on.

May 13 was Mr. Neiley's day to go through the ritual of having his stimulator activated - or not. While two nurses conferred over an electronic programming device, he smiled engagingly at a third, a young woman with high-heeled sandals and rings on her toes, and asked her softly whether he was being switched on or not. She grinned and refused to tell. He gave a good-natured shrug.

"This is going to work," he said.