

# **What are the roots of chronic pain?**

## **New research looks within cells for answers.**

**By Felice J. Freyer**

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July 1, 2023, 2:12 p.m.

The heart monitor beeped rhythmically as Dr. Kyle Eberlin approached the operating table at Massachusetts General Hospital one morning in April. A 30-year-old Navy veteran lay unconscious, and Eberlin set to work on a frequent mission of his: to ease pain.

He slid his scalpel along the man's ankle. Fractured six years ago during a training exercise, the ankle had never stopped hurting. The skin parted easily, exposing a pearly-white cord with a bulbous end — the nerve.

Eberlin pointed to the pea-sized knob, called a neuroma. This growth, he explained, was most likely responsible for much of the veteran's pain.

A plastic surgeon specializing in extremity injuries, Eberlin has excised hundreds of neuromas over the years, and this work had raised many questions for him. Why did some neuromas cause pain and not others? What goes on inside these little blobs that causes so much misery?

He cut off a couple of inches of healthy nerve plus the neuroma. It would now head to a research laboratory, where scientists would scrutinize it for answers.

Eberlin is part of a pioneering effort to find the origins of one of humanity's most intractable afflictions: chronic pain. A team of Boston-based doctors is using novel technology that peers inside individual cells and catalogs every component, enabling the researchers to identify the features associated with pain. And while previous pain research has relied on animals, this team has found ways to study human tissue — by collecting, with patients' permission, nerve cells removed in surgeries and from autopsies.

They are undertaking an urgent task. An estimated 51.6 million US adults — just over one in five — suffer from pain that lasts three or more months. Whether it's a creaky hip, a skull-crushing migraine, or a throbbing lower back, many suffer for years.

For doctors, it's a puzzle: Pain can persist long after an injury has healed, or even arise in the absence of any apparent damage. The only way to detect it is to ask the sufferer what they're feeling. And the only way to quantify it is to ask how much it hurts.

Few find lasting relief. While opioids are effective, they pose a risk of addiction and side effects and often lose their potency over time. A key goal of the research is to find better medications, said Dr. Clifford J. Woolf, director of the F.M. Kirby Neurobiology Center at Boston Children's Hospital, a co-leader of the pain project. "We need a completely fresh approach," he said. "The way to do that is to try and understand exactly what the mechanisms are."

**The project came together** through chance encounters within the Boston medical community and what Woolf calls "an extraordinary coincidence." He met Eberlin in 2019 through a mutual acquaintance — Eberlin's squash partner, a neurobiologist — and at a most fortuitous time. A brand-new technology had recently been developed that would enable a sophisticated study of the cells in the neuromas. And, a new pot of federal grant money was becoming available.

Woolf's interest in pain was sparked when, as a medical student in South Africa, he encountered a ward full of postsurgical patients in agony. When he asked why they were in such pain, one of the senior residents replied that the patients had had surgery, so what did he expect? Woolf said he expected the patients to be more comfortable. "Well, that's your job," he was told.

And so it became his job. Woolf, who came to Boston 26 years ago, has become one of the world's leading researchers on the mechanisms that generate pain.

Pain research has always faced a troubling limitation, he said: It's mostly performed on animals, since doctors can't extract essential nerves from living humans. But the human nervous system in all its complexities is different in important ways from an animal's. And a laboratory mouse will never tell you, on a scale of one to 10, how badly it hurts.

So when Eberlin's squash partner introduced them, Woolf saw an exciting opportunity to work on this puzzle, using human tissue from Eberlin's patients.

At Woolf's suggestion, Eberlin obtained his hospital's ethics board approval to start asking patients to donate their neuromas to research, instead of having them discarded. Every one of Eberlin's neuroma patients agreed to donate nerve tissue, and he has collected about 150 samples.

He performs a procedure developed about 10 years ago for amputees suffering from phantom limb pain, a syndrome in which people feel pain where an amputated limb used to be. When limbs are severed, the sensory nerves are also cut. Left with no connection, they can become like live wires firing randomly, and twist into a neuroma.

In this surgery, Eberlin removes the neuroma and attaches the end of the remaining nerve to a motor nerve, giving it a place to discharge its energy. This does not cause twitching or affect the patient's ability to move. For many, although not all, the procedure brings relief.

Although the Navy veteran isn't an amputee, a sensory nerve in his ankle had been previously severed by another surgeon seeking to relieve the pain. After Eberlin performed an operation similar to what he does for amputees, he sent the veteran's neuroma across town in a dry-ice-filled Styrofoam cooler to the Brigham and Women's Hospital laboratory of Dr. William R. Renthal, the principal investigator of the pain research project.



Dr. William Renthal conducts neuroscience and genetics research focusing specifically on chronic pain. ERIN CLARK/GLOBE STAFF

**At 41, Renthal** sports a trim beard, blue-rimmed glasses, and the academic's button-down shirt and blazer. One wall of his office is a white board scribbled with symbols and formulas, as if in a movie about a genius. But Renthal says it's not for show; these are real notes and calculations done with his students.

When Renthal was a college student at the University of Texas in Austin, he'd been interested in stock trading. Only after he failed to get an internship at the New York Stock Exchange and ended up at a research laboratory did he get hooked on medicine.

During his residency at the University of Texas Southwestern Medical Center, Renthal was drawn to the study of pain because it spanned both psychiatry and neurology. Here was this "weird phenomenon" that had no objective sign: A person can be in excruciating pain and yet MRIs find nothing wrong. "That disconnect to me was so fascinating," he said.

Renthal knew he wanted to work in "the world of pain," but he wasn't sure what his focus would be. And then, his daughter started having migraines at age 6. "I saw this terrible condition when I was finishing my residency," he said. The physiology of pain, he learned, is poorly understood.

Today Renthal is director of headache research at the John R. Graham Headache Center at the Brigham. He has collaborated with Woolf on chronic pain research, and became acquainted with the new technology developed at Harvard, called single-cell genomic sequencing.

And now the Navy veteran's neuroma would head to that "magical" sequencing machine.

Three researchers at the Brigham lab placed the misshapen nerve in a substance that causes it to freeze uniformly, shaved paper-thin slices from it, gently laid the translucent patches on glass slides, and stained the slides. Then, one of the slides went into a microscope and on a screen appeared a cross section of the veteran's neuroma, stained pink.

A healthy nerve consists of fibers lined up neatly in parallel; a cross section looks like uniform pebbles in a round dish.

In contrast, the cross section of the neuroma looked disorganized, a smear of dots and swirls. "We don't really know what types of cells are there," Renthal said, pointing at the screen. "We know the structures are abnormal."

Next, the neuroma will undergo much more detailed analysis. The researchers will grind up the tissue with detergent in a test tube to separate the cells, which will then be slid inside a machine the size of a toaster. This is literally a black box where, over the course of two days, what Renthal calls “the magic” occurs. Air pressure within the box pushes each cell through a channel the width of a hair, labeling each with a barcode. Then a bulky computer attached to a microscope will measure gene activity in each cell.

“We’ll be able to tell what cell types are in that sample, what genes are expressed in every one,” Renthal said, before offering this confident prediction: “We will be able to identify which of those features are associated with pain.”

And once those features are identified, they can become targets for medications.

**In addition to studying neuromas**, Renthal’s team is also studying the nerves involved in migraine, the most common, most disabling, and most mysterious headache syndrome.

That possibility came about through a chance conversation over Sunday brunch at the home of friends, all doctors. Renthal mentioned that he wished he could study the nerve cells that trigger these painful attacks in humans. His brunch companion, pathologist Jochen K. Lennerz, said, “You can!”

It turns out that whenever autopsies are performed at Mass. General, as routinely happens when doctors need to better understand why someone died, the patients’ families are asked whether they are interested in donating tissue samples for research purposes, and many agree.

Lennerz received permission from the Mass. General ethics board to collect an additional item at autopsies: the trigeminal ganglion, a clump of cells found at the base of the skull and thought to be migraine’s source.

Lennerz began removing the ganglia during autopsies about three years ago. He is collecting the nerves from people who had migraines and those who didn’t, so that Renthal’s team can try to identify the difference.

That analysis is made possible by a \$13 million grant to Mass General Brigham and Boston Children’s from the National Institutes of Health, awarded in January. The grant established the Harvard Human PRECISION Pain Center, pulling together Renthal, Woolf, Lennerz, and others with the ultimate goal of finding new treatments for chronic pain.

**Current treatments work** for only one out of three pain patients, a very poor record compared with other illnesses, said Dr. Daniel Clauw, director of the Chronic Pain and Fatigue Research Center at the University of Michigan Medical School, who is not involved with the project.

So Clauw welcomes the prospect of better medications. He cautioned, however, that looking for the biological origins of pain could lead one astray. For example, many people attribute their back pain to a bulging disk. But the majority of people with bulging disks have no pain at all.

“I’m not sure that the nerve itself is the cause of the pain,” Clauw said. “It’s the way the brain and the spinal cord and the nervous system respond to that damaged nerve.”

Pain is influenced by emotions, amplified by stress, closely linked to trauma, and affected by poverty, the environment, relationships — “the whole biopsychosocial recipe,” said Rachel Zoffness, a San Francisco pain psychologist and author of “The Pain Management Workbook.”

“The biggest mistake we’ve made in the past century in treating pain is treating it as a purely biological problem and convincing people living with pain that the solution is just a pill or procedure,” Zoffness said.

In fact, those very complexities and ambiguities are what attracted Renthal to the study of pain. Social and psychological factors clearly matter, he said — and they drive changes in nerve cells and the brain. By excavating and analyzing the culprits within cells, and finding where and how pain begins, the researchers hope to stop those nerves from firing. “We’ll be able to potentially identify new drug targets for patients with neuroma pain and migraine, and potentially other types of pain as well,” Renthal said.

As for the veteran who donated his neuroma to the project, he says he’s pleased with the results of Eberlin’s surgery, which reduced his pain by 60 to 70 percent. But he still endures pangs that stab his foot and shoot up to his back two or three times a day. Eberlin believes that problem will eventually ease. But the veteran says he’s prepared to live with it.