Deborah Reed lived in a tall historic house on a tree-lined street in tony northwest Portland, Ore. In 2003 the author and mother of two boys developed deep muscle pain and profound fatigue, seemingly out of nowhere. “I remember climbing the wood stairs to my bedroom on the third floor,” Reed recalls. “It was agonizing.” Reed would spend entire days in her bed, getting up only for trips to the bathroom. When the pain was at its worst, she once went 10 days without leaving her bedroom.

Her doctor suspected depression and explained to Reed that pain can accompany that ailment. “But I just knew that’s not what this was,” she says. “This was something else.” In addition to widespread muscle aches, Reed experienced tingling and burning sensations in her hands and feet, headaches, and painful sensitivity to temperature and light touch. Specialists tested Reed for multiple sclerosis, arthritis, cancer, lupus, Lyme disease and a catalogue of autoimmune conditions to no avail. After two years of evaluation, a rheumatologist finally gave Reed a diagnosis: fibromyalgia.

For her, like many others, the diagnosis left many questions unanswered. An estimated five million Americans are believed to have fibromyalgia, the vast majority of them women. Physicians do not call fibromyalgia a disease, however. They diagnose this syndrome when they encounter a collection of pain symptoms for which they have ruled out all other potential causes. Most often these symptoms include deep muscle pain that affects the whole body, a flulike, achy feeling and fatigue.
Physicians first identified this bundle of symptoms more than a century ago, but research languished until 1977, when scientists at the University of Toronto described the tender and aching symptoms more formally, sparking new interest. By 1990 the American College of Rheumatology had settled on the name “fibromyalgia” and developed guidelines for consistent diagnosis.

At that time rheumatologists were hunting for signs of inflammation or injury in the joints and muscles. The pain of fibromyalgia, after all, seemed to stem from these areas. Yet they came up empty time and again, and in the past 10 years scientists have instead focused largely on the brain. Now, however, some researchers are beginning to suspect that they called off the search for bodily harm too soon. New studies from neurologists working around the world suggest that these unexplained aches might arise at least in part from damaged nerves. If physicians can halt the destruction and heal those wounds, they might also stop the pain.

A Medical Mystery

For Reed, the diagnosis came as a surprise. “I had never heard of fibromyalgia,” she says. She quickly realized she was not alone—even some of her doctors were unfamiliar with the condition or doubted its existence. Despite thousands of studies spanning more than 30 years, fibromyalgia remains remarkably mysterious. The severity of symptoms seems to run the gamut: whereas some people experience only mild discomfort or fatigue, others become incapacitated.

Not all pains are equal. Typically pain is good because it alerts you that your body has sustained damage, prompting you to defend yourself against further destruction. Pain becomes chronic when a warning signal persists even after the threat is gone. Fibromyalgia is one of many recognized forms of chronic pain. Most types of long-term pain are considered either inflammatory, as in some types of arthritis, or neuropathic, which often involves nerve damage. Part of the mystery of fibromyalgia is that its symptoms come from both categories, a fact that has only served to frustrate researchers, who have failed to find consistent evidence of either inflammation or damage.

Underlying their bafflement is the conundrum of what causes fibromyalgia. One clue is that fibromyalgia appears to be partly heritable. Genes might account for up to half the risk for it. Researchers now agree that some people inherit a predisposition to chronic pain that springs from differences in genes that encode key pain-signaling molecules. Yet the genetic risk factors linked with fibromyalgia are not limited to pain-related circuitry. Some of the same quirks of the genetic code also crop up with depression and anxiety disorders.

The psychological history of fibromyalgia patients further deepens the riddle. For example, it often develops after physical or emotional trauma. Experts now suspect that fibromyalgia occurs when individuals with an inherited risk are exposed to a physiological trigger, whether from illness, injury or a psychological crisis. “One could imagine a combination of genetic predeterminants that could tip people toward pain,” says neurologist Claudia Sommer of the University of Würzburg in Germany.
“If you have a happy life, you might tolerate this well, but if catastrophes come along, they could tip you over to chronic pain.” Reed, for one, traces her symptoms to a serious head-on car collision she suffered about a year before her troubles developed.

The question of how such varied incidents trigger full-blown fibromyalgia still stumps researchers. Some physicians even suspect the syndrome is actually a collection of separate but similar ailments. Despite these unknowns, the diagnosis brings some comfort to patients like Reed, who found it tremendously helpful to name her pain, discover people with similar symptoms and be taken seriously by her doctor. “To be able to know, okay, I’m not crazy—it was such a relief,” she says.

Brain’s Pains
To make sense of some of fibromyalgia’s brain-based symptoms—such as fatigue, memory problems and sleep disturbance—researchers have used imaging to explore whether fibromyalgia patients process pain differently than healthy people. They have found that people with this syndrome appear to have less brain volume in the cingulate cortex and the medial frontal cortex, areas thought to be critical to our overall experience of pain. Other research points to altered activity in brain areas dedicated to attention and the processing of sensory input, such as sound. Scientists hypothesize that the brain’s “volume control” for such sensations may be off-kilter, potentially magnifying pain.

These insights have helped shape the therapeutic approach to treating fibromyalgia, which has focused overwhelmingly on the brain. The only three drugs approved by the U.S. Food and Drug Administration to treat fibromyalgia are an anticonvulsant and two antidepressant medications. These serotonin and norepinephrine reuptake inhibitors, or SNRIs, are thought to dampen pain signals in the brain and spinal cord.

Yet they fail to restore most fibromyalgia patients to health. Reviews published in 2012 and 2013 concluded that the drugs provide modest pain relief for some patients but do not improve sleep or overall quality of life. Moreover, none of these findings clarified whether fibromyalgia changes the brain or whether some patients’ brains are prewired for chronic pain. Although the patterns seen in the brains of fibromyalgia patients were initially hailed as hallmarks of the syndrome, these signatures have turned out to be common across chronic pain conditions. Researchers now suspect that the experience of chronic pain actually reshapes the brain’s architecture and activity patterns, just as learning to ride a bike or speak a new language would.

Clues from the Periphery
Meanwhile nerve specialists in Germany, Boston and Spain had noticed a peculiar pattern in patients diagnosed with small-fiber polyneuropathy (SFPN), a pain condition that stems from damage to peripheral nerves. Many SFPN patients had previously received the fibromyalgia label.

One of those neurologists, Anne Louise Oaklander of Massachusetts General Hospital, began seeking collaborators to investigate the link, but she could not find a rheumatologist willing to embark on such a speculative, interdisciplinary project. Finally, Oaklander took matters into her own hands. To search for signs of nerve damage in people with fibromyalgia, her team used several tests, including a skin biopsy, in which a clinician punches out a small sample from the skin of the hand or leg and examines the tiny nerves within the sample under a microscope. “No one had really looked appropriately before at nerves,” Oaklander says.

Experts now suspect that fibromyalgia occurs when individuals with an inherited risk experience a trigger, such as an illness, injury or psychological crisis.
The team’s findings, published in 2013, revealed a troubling absence of nerve endings in 41 percent of the 27 fibromyalgia patients studied. This is identical to the damage seen in SFPN, in which injury or disease batters nerves until the endings wither away. In the same year Sommer found comparable results. The new findings were striking: together they suggested that peripheral neuropathy might contribute to fibromyalgia in some patients.

Given the heterogeneous nature of the syndrome, neither Oaklander nor Sommer would expect every patient to show consistent nerve damage. Instead the findings raise the possibility that neuropathy typifies one variant of fibromyalgia.

Comparing a skin biopsy from a healthy person (left) with one from a fibromyalgia patient (right) reveals that fibromyalgia patients have fewer nerve endings, indicated by the white arrows above.

Perhaps the battering sustained by surface-level nerves initiates fibromyalgia’s symptoms or, as Sommer suspects, indicates more extensive impairment in nerves serving muscles and tendons. In 2014 two additional reports detected peripheral nerve deterioration in fibromyalgia patients, strengthening the consensus that this damage could play an important role.

Biopsy studies confirmed the appearance of neuropathy but did not reveal how the nerves were acting. Neurologist Jordi Serra of MC Mutua and Neuroscience Technologies, both in Spain, tackled this question using a challenging technique called micro-neurography, whereby a needlelike electrode is inserted into a skin nerve to record its electrical impulses. Comparing the nerve recordings from healthy individuals with patients with either SFPN or fibromyalgia, Serra’s team found that in one third of the pain patients, pain-sensing nerves showed spontaneous, abnormal activity not seen in any control subjects.

The findings, published in 2014 in *Annals of Neurology,* suggest that nerves fire excessively in some SFPN and fibromyalgia patients. “Normally, these nerves are sitting quietly, waiting to detect a burn or pinch, for example,” Serra says. But here the pain detectors appear overactive or extra sensitized. It is possible that the same battering that knocked out nerve endings also altered nerve sensitivity. The over-activity, he says, could explain subsequent aches and distress: “Because [these nerves] are hyperexcitable, they discharge spontaneously. These signals go up to the brain, and this is the basis of ongoing pain.”

Researchers know that SFPN can be caused by injury, diabetes, genetic mutation or an immune system attack. They therefore hypothesize that similar processes might underlie the nerve loss seen in some fibromyalgia cases. The persistent pain signal would then rewire the nervous system gradually, priming the body for pain. The resemblance to SFPN presents the enticing possibility that by treating the underlying condition, such as an autoimmune disorder, doctors could alleviate or even cure some cases of fibromyalgia.

**With the Rain Came Pain**

In Portland, where rain drips from the big-leaf maples most months of the year, Reed had noticed that her aches would mostly abate during the warm Oregon summers. But when the temperature dropped below about 55 degrees Fahrenheit and the rain inevitably returned in the fall, so would her discomfort. “That sort of weather change was the most reliable trigger of pain,” she remembers.

She and her family would take trips to Mexico every winter to afford her some relief. “As soon as I stepped off the plane into the sun and heat, I could literally feel my body healing. And the opposite happened when I would return to Portland.” Eventually Reed moved south to sunny Los Angeles, where she has found her affliction is much more manageable.

Reed’s sensitivity to weather and temperature, a feature common to many cases of fibromyalgia, could also relate to nerve anomalies. In 2013 neuroscientist Frank Rice, then at Albany Medical College, and his colleagues described the nerves that end at tiny blood vessels in the hands, called arterio-venule shunts, in fibromyalgia patients. These shunts, found near the surface of the palms, increase and decrease blood flow to regulate bodily temperature. They also regulate blood flow to deeper tissues, allowing muscles and organs to function during exercise. Rice found that compared with healthy control subjects, people with the syndrome...
Sensitivity to weather and temperature, a feature common to many patients who have fibromyalgia, could relate to nerve anomalies.

had significantly more nerve endings at the shunts dedicated to opening blood vessels.

Rice postulates that the disparity in nerve endings might cause shunts to open and close inappropriately, hindering normal heat exchange. Malfunctioning shunts could rob deep muscles and organs of proper blood flow. Muscles deprived of energizing oxygen-rich blood might also contribute to fibromyalgia’s hallmark fatigue. For the moment, Rice concedes that we do not know what role shunts play in fibromyalgia, but the anomaly warrants further investigation.

The evidence from Rice and others strongly suggests that fibromyalgia includes components of physical damage or nerve irregularities in a substantial subset of patients. None of the new studies’ authors would challenge the idea that fibromyalgia involves real changes in the central nervous system (CNS). Instead they believe that researchers will have the best shot at understanding the condition overall—and at guiding successful future treatments—by studying both its central and peripheral elements.

**Cause or Consequence?**

Not all scientists agree on the true meaning of the findings about peripheral nerves. Some, such as rheumatologist Daniel Clauw of the University of Michigan, feel strongly that the newly described nerve abnormalities are merely a by-product of an overactive nervous system. “In pain states, we know there is remodeling of the CNS,” Clauw says, alluding to the ways that pain, like learning, causes changes in the brain’s architecture. “So why wouldn’t that likewise occur in the peripheral nervous system?”

Other physicians and researchers, however, see a ray of hope in the new findings. The most effective management strategy, says Roland Staud, who studies and treats fibromyalgia at the University of Florida, addresses both body and mind. Staud recommends exercise, improved sleep habits and cognitive-behavior therapy, which teaches patients mental strategies to cope with their pain. Reed has developed her own routines, which include a healthy diet, yoga and gentle exercise, such as walking and swimming in her L.A. apartment’s outdoor pool. And Reed constantly works to minimize stress—another major pain trigger.

Staud is optimistic that for patients who have detectable damage, healing nerves could alleviate the broader symptoms of fibromyalgia. In other neuropathic pain conditions, researchers have found experimentally that blocking an aberrant nerve’s overactive signaling with anesthetics can abate even those symptoms rooted in the CNS. In addition, treating possible sources of nerve injury, such as diabetes or immune disorders, helps SFPN patients. Similar approaches might also work for fibromyalgia patients.

Ultimately, our experience of pain culminates in the brain, but it can originate anywhere, from the skin on a big toe to the cortex. The chance to quiet pain signals at any point along the way could alleviate them, so researchers need to consider all possible targets. “I don’t pretend that we have solved the mystery of fibromyalgia,” Oaklander says. Cracking that case may require teasing apart the many different kinds of patients gathered under the syndrome’s label. Yet the clues emerging from patients’ nerves might finally allow researchers to start unraveling fibromyalgia’s tangle of symptoms and bring relief to millions of patients.

**FURTHER READING**


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