The PAIN GATE

A rare disorder brings insights into the nature of pain

By David Dobbs

For most of the 140 years since it was named, the disorder known as burning man syndrome has operated in near-total obscurity. Even today it afflicts perhaps 200 to 500 people in all of North America and a few thousand worldwide. Until about three years ago, essentially all medical knowledge about it was contained in its name, erythromelalgia, which translates as "painful red extremities." Few doctors knew of it, only a handful had seen it, and none knew what caused it or how to treat it. At any given time, the few thousand people who had it suffered its torment—searing heat in the feet and lower legs and sometimes in the hands—without understanding why. Most thought they were completely alone.

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The pain comes in a bewildering variety—shooting, burning, stabbing, electrical-like.

Pam Costa is one of only a handful of people in the U.S. with an inherited form of erythromelalgia. Gene clues from families such as hers have helped researchers pin down the mutation involved.

Pam Costa, 42, lived her first decade this way. She is one of perhaps 30 or 40 people in the U.S., and possibly 200 to 500 worldwide, known to have an inherited form of the disease.

"In the crib I would pull myself up and hang my hands over the side and just scream," Costa says. "My first word, I'm told, was 'hands,' because they were hot.

"Later, when I was in school—I grew up in southern California, and it was hot—my feet burned all the time. I frequently had to stick them in the toilet. I couldn't understand how other people could wear shoes and socks. And gym—gym was torture. I remember once we had to run track. I ran as far as I could, until the burning was shooting all up my legs, and then I fell down. They sent me to the office for trying to get out of gym.

"No one had any idea what it was. I didn't even know it had a name."

In 1976, when Costa was 10 years old, her family received a letter from a team of researchers at the University of Alabama. At the time Costa was missing most of fifth grade. Walking to and around school inflamed her legs, and her hands hurt too much to hold a pen.

The researchers' letter shed some light on this condition. The university was assembling the pedigree of an Alabama family that had several members with something called erythromelalgia, or EM, a poorly understood disorder that in this family's case seemed to be hereditary. The family tree appeared to include Costa and her mother. Did either of them ever experience burning sensations in her feet or hands?

That letter, Costa says, "was just huge. It's not like it erased the problem. But I could start to grapple with it as a thing outside of me." With help from a remarkable sixth grade teacher, Sally Jackson ("the first one," Costa says, "to notice I did 'A' work when the weather was cool"), Costa began to confront and manage her condition instead of succumbing to it. She brought ice packs to school, got released from gym to read, learned to recognize what she could and could not do, and learned she could make all A's instead of mostly D's. She went to college and then graduate school, earning a Ph.D. in psychology. She married, opened a practice, started teaching and, five years ago, adopted a daughter—all, Costa says, made possible "by Sally Jackson and by that letter 30 years ago." By naming and rationalizing her condition, the letter made it finite. And the finite, however big and ugly, could be approached.

Costa never expected another insight with that sort of power. Yet 28 years later, in September 2004, one came—this one via an e-mail from the Erythromelalgia Association, a research and support group she had joined. A team of pain researchers at the Yale University School of Medicine, building on a Beijing team's discovery of a genetic mutation underlying inherited erythromelalgia, had not only confirmed this genetic basis but had also discovered what appeared to be EM's prime physiological mechanism. A defective sodium channel in pain-sensing neurons in the legs and arms—a door, essentially, through which pain signals are sent to the brain—was too quick to open and too slow to close. When this door was open, pain rushed through like fire. But it was a door, the research suggested, that might someday be shut.

A Rootless Pain

Stephen Waxman, chair of neurology at Yale and head of the lab that published the sodium channel paper, is a man who likes a bit of history.

CHRIS COSTA

FAST FACTS

Pain That Won't Stop

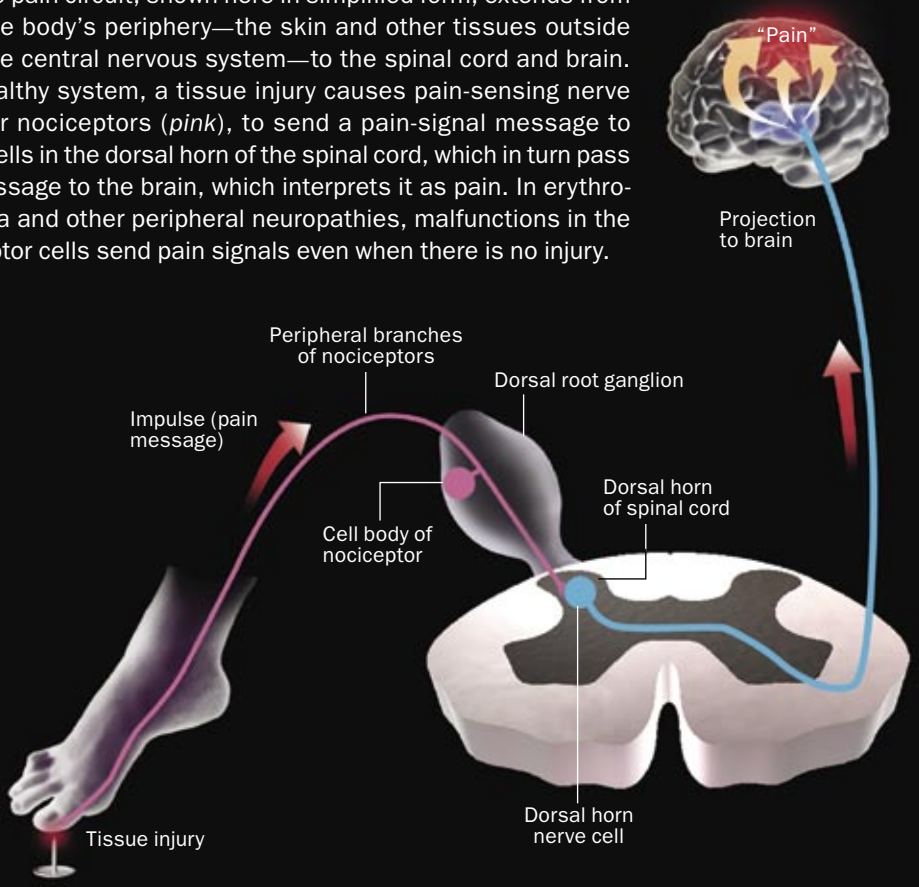
1» People who suffer from a rare disorder called burning man syndrome, or erythromelalgia, experience searing pain in the feet and lower legs and sometimes in the hands.

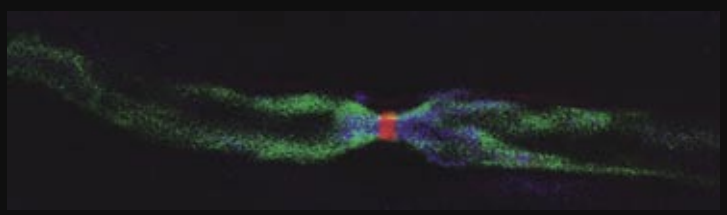
2» Investigators recently uncovered erythromelalgia's prime physiological mechanism. A defect in a sodium channel in pain-sensing neurons in the legs and arms makes the neurons overexcitable: they overreact, sending signals of blazing pain even in the absence of tissue damage.

3» Finding the flaw in this "pain gate" brings hope that researchers will learn how to shut off the searing signals.

Feeling the Pain

The pain circuit, shown here in simplified form, extends from the body's periphery—the skin and other tissues outside the central nervous system—to the spinal cord and brain. In a healthy system, a tissue injury causes pain-sensing nerve cells, or nociceptors (*pink*), to send a pain-signal message to nerve cells in the dorsal horn of the spinal cord, which in turn pass the message to the brain, which interprets it as pain. In erythromelalgia and other peripheral neuropathies, malfunctions in the nociceptor cells send pain signals even when there is no injury.





Sodium channels (*red*) are seen in a mouse nerve. In people with the chronic pain disorder erythromelalgia, similar channels in peripheral neurons are overexcitable, amplifying pain messages.

AMADEO BACHAR (*top*): FROM "INTEGRATION OF ENGRAFTED SCHWANN CELLS INTO INJURED PERIPHERAL NERVE: AXONAL ASSOCIATION AND NODAL FORMATION ON REGENERATED AXONS," BY CHRISTINE RADTKE ET AL., IN *NEUROSCIENCE LETTERS*, VOL. 387; © 2005, REPRINTED WITH PERMISSION FROM ELSEVIER (*bottom*)

When the Beijing paper drew his attention to erythromelalgia (although Waxman sees a diverse group of patients, he had never seen someone with EM) he soon took an opportunity to dig through the archives of the man who first named the disorder, Silas Weir Mitchell. It proved an illuminating dig.

Mitchell, the son of a rich Philadelphia doctor, began his medical career "wanting," his own father said, "in nearly all the qualities that go to make a success in medicine." He ended it as one of the century's leading neurologists. The transformation was attributed mainly to the Civil War, during which Mitchell directed a 400-bed military hospital for nervous injuries and diseases in Philadelphia. Among the hundreds of neurological problems he saw there were three that he first described and defined. One was erythromelalgia. The other two were phantom limb, which is the sensation of retaining one's amputated appendage, and causalgia, a burning pain that sets in near a wound site after the wound is repaired and seems to have healed.

Phantom limb and causalgia result exclusively

A pain circuit in the body holds many relay switches. Where was the open one?

from trauma; erythromelalgia, not so. Yet Waxman, reading Mitchell's patient accounts and correspondence, could see why Mitchell would single out erythromelalgia as a separate but related entity. All three come from mysterious mechanisms (phantom pain is still poorly understood today). All three fall into the broad class of disorders known as peripheral neuropathies, in which numbness, poor function or pain, usually in the limbs (and thus in the "periphery"), arises not from active injury but from malfunctions in the sensory nerve fibers running from tissue to brain. Peripheral neuropathy can cause anything from numb toes to carpal tunnel syndrome to paralysis.

Often it causes pain. The pain assumes a bewildering variety of manifestations—shooting, burning, stabbing, electrical-like—and usually affects feet or hands. Some patients, like Mitchell's soldiers, develop neuropathies after experiencing injury or surgery. Many more suffer "secondary" neuropathies that accompany inflammatory or immunological disorders or diseases such as hypertension, AIDS, cancer, diabetes or multiple sclerosis. An estimated 50 million people in the U.S. alone have a form of neuropathy. Some 10 million to 20 million of them suffer pain.

Stephen Waxman, chair of neurology at Yale University, seeks to understand the roots of pain.

BILL FITZ-PATRICK

"Virtually all chronic pain is neuropathic pain," Waxman says. "My dad had severe neuropathic pain from diabetes. Toward the end only opiates would help. Awful."

Waxman and other researchers have tried for years to understand these pains, hoping to cure them and to reveal their fundamental mechanisms: if pain is a signal received, then study faulty signals. And what better signals to study than the exaggerated ones coming from neuropathies? Work as early as the 1950s showed that motor neurons damaged in trauma often emit exaggerated signals for weeks afterward. By the 1980s comparable malfunction was confirmed in sensory neurons, and this kind of sustained hyperexcitability, as if a relay switch were left on by accident, became the focal point of chronic pain research.

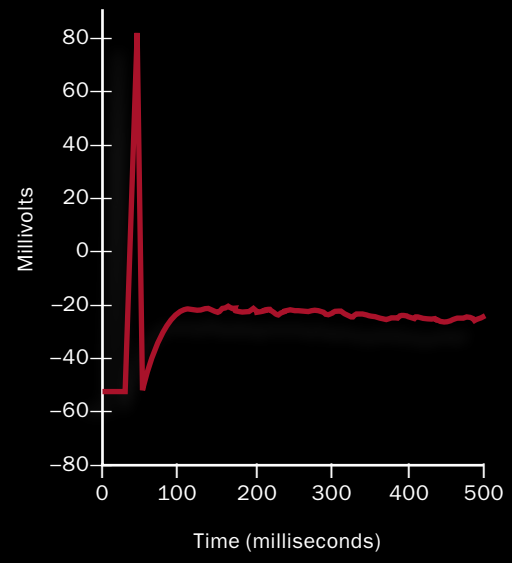
But a pain circuit holds many switches. Where was the open one? Sodium channels made the short list early. British physiologists Alan L. Hodgkin and Andrew F. Huxley established the existence and transmission role of sodium channels in 1952 by recording currents from the giant axon of an Atlantic squid. Subsequent research confirmed that sodium channels (along with calcium, potassium and other ion channels) transmit signals in many types of cells, including muscle, motor neurons and cardiac tissue. But sodium channels serve particularly vital roles in the nervous system. By releasing positively charged sodium ions through the walls of axon fibers, they create the electrical impulses—the action potentials—that start the electrochemical process by which neurons send signals.

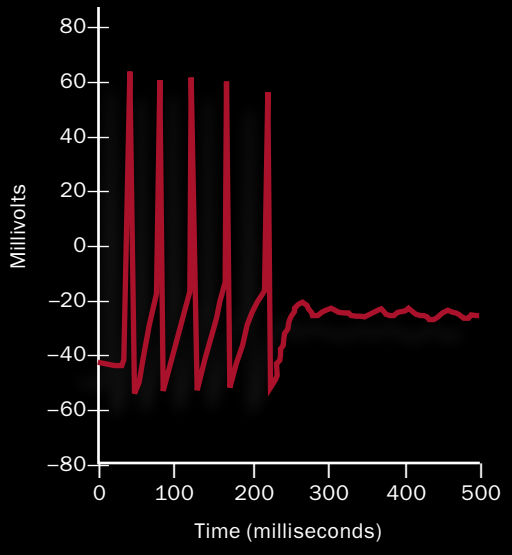
By 1990 Waxman and many other researchers had produced a pile of studies suggesting that problems associated with sodium channels, "channelopathies," might underlie neuropathic pain. But these studies, as Waxman lamented in a 1999 literature review, "did not examine the crucial question: What type(s) of sodium channels produce the … discharge associated with pain?" There were nine sodium channels altogether. Which ones were at fault?

Even as Waxman posed that question, his team was acquiring new tools of gene manipulation and observation that would help them answer it. Now they could examine an overexcited axon's various sodium channels and see which ones had genes that were behaving oddly—build-

The Gate Stays Open

Pain-sensing ends of nociceptor neurons contain ion channels called $Na_v1.7$ sodium channels—the "gateways" to nerve-cell response. A neuron with normal $Na_v1.7$ channels "fires" once in response to an electrical stimulus (*left*). In contrast, the L858H mutation results in a hyperexcitable neuron—causing sustained pain signal (*right*).





ing proteins (and thus setting off activity) when they should be dormant, for instance, or lying dormant when they should be busy. Over years of work they and others narrowed the field. To Waxman and his lab mates (as well as some researchers elsewhere), the results increasingly implicated the seventh of the nine channels, $Na_v1.7$. They call it One Seven.

They got good at creating overexcitable One Sevens. But they could not find a way to block the activity of One Seven within complete pain systems, and that meant that they could not confirm its role by absence. (The easiest way to confirm the role of a light switch is to flip it and turn off the light.) Another way to confirm its role would be to identify the particular gene underlying its odd behavior. Unfortunately, an injured neuron reacts by flipping switches on hundreds of genes, firing them up to build the proteins that send signals and repair things. They faced a needle-in-haystack situation.

"What we needed," Waxman says, "was a genetic change within the sodium channel—presumably One Seven—that we knew was isolated. In short, we needed a mutation.

"I actually said to the team, 'You know, sometimes rare genetic diseases can produce this sort of effect.' But … well, they're rare. Most neurologists go through an entire career and never see a neuropathic problem that's genetic. None of us had ever seen one. No one in this state had. But that's what we needed. We needed a family."

Haunted by Pain

While talking to Pam Costa one evening, I asked her if her condition was worsening, as EM often does. She said it was. She had roughly doubled her pain medications in the past five years or so and was now taking about eight to 10 aspirin a day, another six to eight naproxen (a pain reliever and anti-inflammatory drug) and 90 milligrams of sustained-release morphine, and she still sometimes woke in so much pain that her husband had to give her a morphine injection. And the bad stretches seemed to get longer. She had recently experienced one that lasted 17 days. "I had a friend who saw part of a shorter one," she said. "She asked me how I went 17 days. I get through it because I always tell myself that it will end. And it always does.

"I should make it clear that I consider myself extraordinarily fortunate. I have two arms and legs, and they work. This [condition] has never

(The Author)

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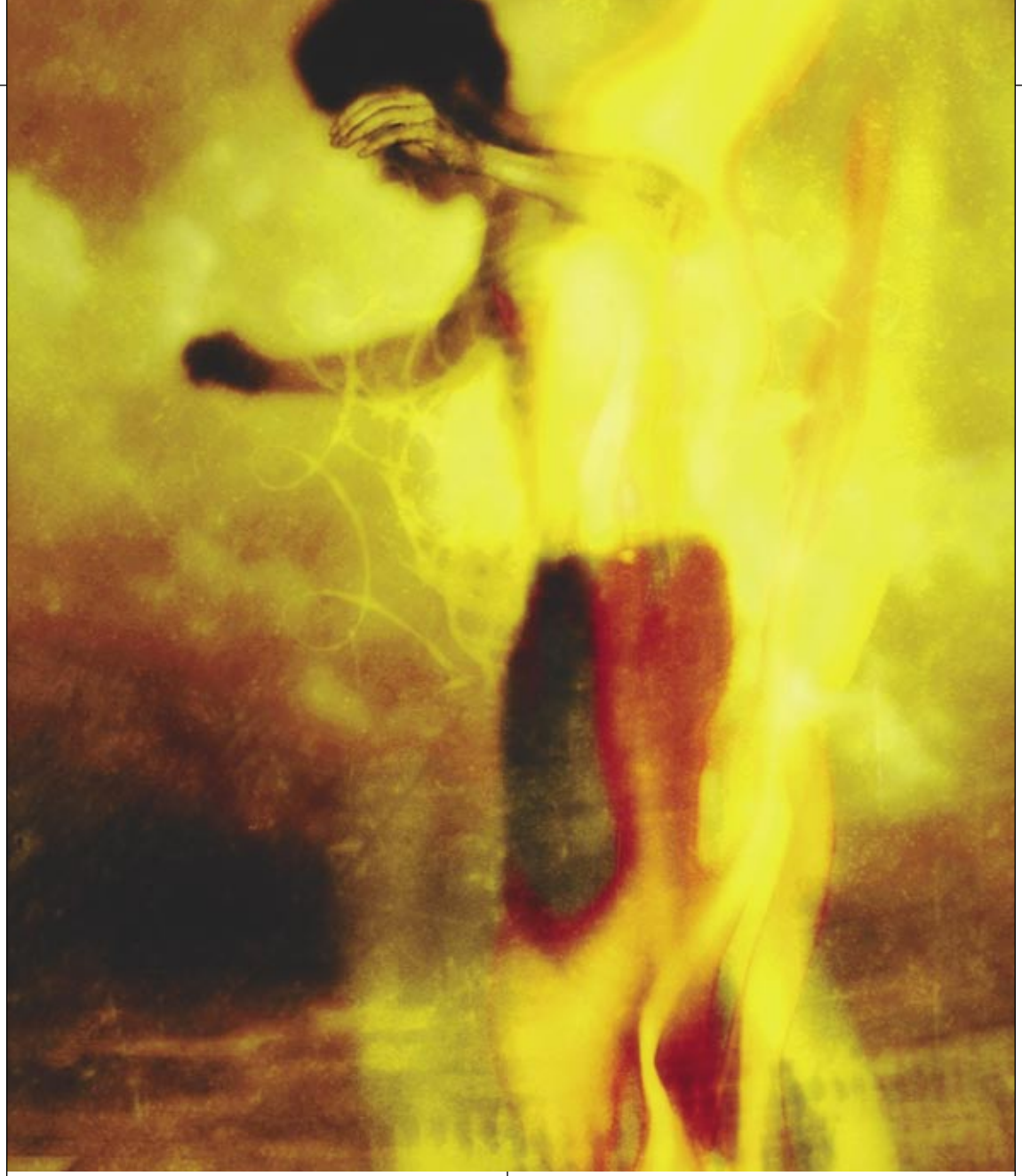
FROM "A SINGLE SODIUM CHANNEL MUTATION PRODUCES HYPER- OR HYPOEXCITABILITY IN DIFFERENT TYPES OF NEURONS," BY ANTHONY M. RUSH, SULAYMAN D. DIB-HAJJ, SHUJUN LIU, THEODORE R. CUMMINS, JOEL A. BLACK AND STEPHEN G. WAXMAN, IN *PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCE USA*, VOL. 103, NO. 2: MAY 23, 2006



KAMIL VOJNAR *Getty Images*

stopped me from pursuing my goals. I have a fabulous family. I've worked with so many people who have suffered more."

At this point she paused. Over the phone, 3,000 miles away, I could tell she was considering whether to continue.

"I have a young cousin," she said. "When Jacob [a pseudonym] was two, he was in so much pain they started giving him morphine. At first they thought he had autism, because he couldn't seem to learn anything or relate to anyone. But a rheumatologist who examined him said he was in so much pain he just couldn't take anything in. I saw Jacob a year ago, when he was three. He was not walking.

"Jacob's mother is missing, probably an opiate addict. Too much pain. His grandmother committed suicide because of the pain. Jacob is being raised by his great-grandmother, who's in her 80s."

Hidden in Plain Sight

One of the many oddities of this story is that although Stephen Waxman knew about erythromelalgia and even knew it had an inherited form, he did not know of the University of Alabama study and so knew nothing of Pam Costa's family. Nor did anyone in his laboratory, nor did the many colleagues with whom he inquired about familial neuropathies. This may seem a bit strange—and it is. It reflects the weird obscurity that erythromelalgia retained until 2004. Despite 25 years of increasing recognition that most chronic pain arises from neuropathy, this singu-

larly mysterious neuropathy never crossed the path of the pain research community.

"These people got sent everywhere else," Waxman says. "They got referred to dermatologists, vascular specialists, hematologists, cardiologists, rheumatologists—everybody but neurologists."

This disconnect ended in March 2004, when Waxman spotted in the *Journal of Medical Genetics* a paper titled "Mutations in SCN9A, Encoding a Sodium Channel Alpha Subunit, in Patients with Primary Erythermalgia." The authors, a team of dermatologists and geneticists in Beijing, had analyzed the genetic profiles of two relatives with inherited EM and ferreted out the faulty gene.

That was sharp work. But because the Chinese authors were dermatologists and geneticists, Waxman notes, "They did not know an important thing"—specifically, that the sodium channel encoded by the mutation they had discovered operates almost exclusively in peripheral pain-sensing neurons. Dermatologists unaware of that would naturally try to find the channel doing its work in skin. But they would not find it. It was a neuron-specific channel.

The channel in question was $Na_v1.7$. Waxman's lab certainly knew where to look for it.

"In neuroscience," Waxman explains, "it's standard fare if you find a mutation in an ion channel to clone it into some fresh cells and see what effect the mutation has. Normally it would take a year of tough work to clone a channel like that. But as it happened, we had the construct right here on the shelf. It took us two months.

"It was as we expected. The mutations lowered One Seven's activation threshold. They created overactive channels that amplify and sustain. When they're supposed to be quiet, they talk. When they're supposed to whisper, they scream."

Since Waxman's lab published the results in September 2004, it and others have confirmed and elaborated on the fact that certain mutations at SCN9A (they have identified seven so far) create a malfunction at $Na_v1.7$ that causes erythromelalgia. In December 2006 a University of Cambridge team reported an SCN9A mutation that created a complete *lack* of pain sensation. They found the mutation in the family of a 10-year-old street entertainer in Pakistan who wowed crowds by walking on hot coals and stabbing himself through the arm. He later died falling off a roof.

Waxman now knows scores of people with EM, including Costa, who provided a blood sample, complete with a mutation at SCN9A, for one of his studies. More families have emerged. A couple of times a month he gets an e-mail from a patient he did not know about. Most are wrenching. "Keeps us going," Waxman says, "when the experiments don't work."

"A lot of them ask," Waxman tells me toward the end of our visit, " 'When might you have a cure?' I don't mean to say they're impatient. They're not. They're remarkably generous-minded. But everyone needs to understand we're really still discerning fundamental biology here. And these things take a lot of time. If Merck or Abbott found on its shelves *today* a drug that quieted One Seven in a lab assay, it could still take 10 years. And this is pretty challenging biology."

> "I get through it because I always tell myself that it will end. And it always does."

On the plus side, notes Sulayman Dib-Hajj, Waxman's genetics specialist, $Na_v1.7$ makes a pretty good drug target. It appears to do little besides sending pain, so dampening it may cause few side effects. And "it expresses beautifully," generally responding to experimental manipulation in unambiguous ways, Dib-Hajj says.

"In the meantime," Dib-Hajj observes, "I like to think that patients find it helpful to know a bit more about what they have. I mean, sometimes pain is in your head. But here it's not. It's in your sodium channels."

When I tell Pam Costa about this, she laughs. "It's true!" she says. "I've *always* found it helps to think some particular physiological process was causing this. Now I have the process. I can visualize those sodium channels overacting, all those ions flowing through, and I think very hard about slowing them down." M

(Further Reading)

- **Mutations in SCN9A, Encoding a Sodium Channel Alpha Subunit, in Patients with Primary Erythermalgia.** Y. Yang, Y. Wang, S. Li, Z. Xu, H. Li, L. Ma, J. Fan, D. Bu, B. Liu, Z. Fan, G. Wu, J. Jin, B. Ding, X. Zhu and Y. Shen in *Journal of Medical Genetics*, Vol. 41, No. 3, pages 171–174; March 2004.
- The Erythromelalgia Association provides more research information at **www.erythromelalgia.org**