MEDICINE

PAIN THAT WON'T QUIT

Burning. Aching. Shooting. Whatever form it takes, chronic pain can defy treatment. New insights into the causes are leading to fresh ideas for combating it

By Stephani Sutherland

IN BRIEF

Chronic pain affects more people in the U.S. and incurs greater costs than cancer, heart disease and diabetes combined.

Opiates and other existing drugs do a poor job of relieving much chronic pain and can have serious risks. **Discovery of molecular pathways** specific to pain has revealed new targets for drug development. **Substances found** in animal venom are among those being tested as next-generation painkillers.

Photograph by Gerald Slota

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MAKE SURE YOU

stop at the grocery store, not Burger King," Jama Bond instructed her husband on his cell phone as he made an ice-cube run one night in 2012. "Their ice cubes melt too fast." Bond, then 38 and nearly nine months pregnant, needed bags of ice to keep the water cold in the tub at her feet, which were red, swollen and painful. She had learned to cover them with trash bags so the ice water would not damage her skin. A few months before, Bond had been a healthy young woman with an office job at a company that installs solar panels, living a more or less normal life. Now she barely left the comfort of the water bath, except to shower, "which was torture."

Bond, who lives in Santa Rosa, Calif., was suffering from a condition called erythromelalgia (EM)—Greek for "red limb pain"—in which the hands or feet develop severe burning pain, becoming exquisitely sensitive to even mildly warm temperatures or light pressure. For most patients, like Bond, the condition arises without explanation (it has no known link to pregnancy). Although EM is rare, striking only about 13 in a million people, chronic pain in its myriad forms is astonishingly common and often has mystifying origins.

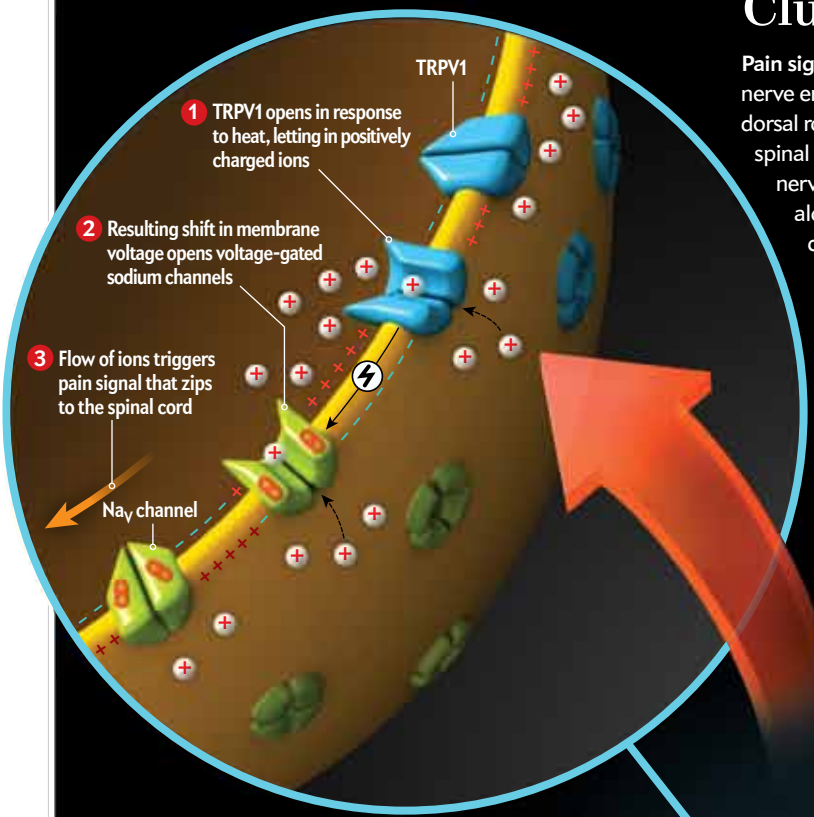
An estimated 100 million people in the U.S. struggle with it, most often in the form of back pain, headaches or arthritis. All told, chronic pain affects more Americans than diabetes, cancer and heart disease combined and costs more, too: as much as $635 billion a year in medical care and lost labor, according to a 2012 analysis. The toll in suffering is incalculable. People coping with the misery face an increased risk of disability, depression, mood and sleep disorders, drug and alcohol addiction, and suicide. Linda Porter, a pain policy adviser at the National Institute of Neurological Disorders and Stroke and director of the National Institutes of Health's Pain Policy Office in Bethesda, Md., calls chronic pain "a huge public health problem that is not adequately recognized nor addressed."

Pain exists for a reason: it provides us with a built-in warning against bodily damage, compelling us to yank a hand from a hot stove before it is badly burned or to stop walking on a leg that is broken. But sometimes it persists long after the threat is gone. Although chronic pain can arise inexplicably, in general it can be divided into two categories: inflammatory—such as that caused by osteoarthritis, for example—and neuropathic, which usually stems from nerve damage caused by injury, disease or another insult.

Chronic pain is notoriously hard to treat, and the neuropathic type is particularly challenging, in part because common anti-inflammatory medications such as ibuprofen and naproxen barely touch it. Morphine and other opiates are the gold standard for severe short-term pain. But they come with side effects that range from the mundane, such as constipation and drowsiness, to a life-threatening suppression of breathing. People who use them over long periods gradually develop tolerance to these drugs and need ever higher doses, raising the risks. Addiction and abuse are also serious issues with opiates: more Americans now die from an overdose of these prescription painkillers than from overdoses of cocaine and heroin combined. Other drugs currently used to treat chronic pain include some originally prescribed to treat seizures and depression, and these, too, have limitations. Despite the possible risks to her unborn baby, Bond received a cocktail of

Clues to Dampening Pain

Pain signals generated by heat or other stimuli travel from nerve endings in the skin or other sites to structures called dorsal root ganglia, near the spinal cord, and then on to the spinal cord and brain. Genetic mutations or damage to nerves can, however, alter the behavior of key molecules along the route, including ion channels, in ways that cause pain to become chronic. Hoping to ease the suffering, researchers are now targeting those critical molecules in a variety of ways.



Hyperactive Channels

Embedded in the membranes of nerve endings that detect painful stimuli are molecules called ion channels that open and close a central pore in response to the stimuli. A channel called TRPV1, for example, detects heat. When it opens, positively charged ions (mainly sodium) rush in, boosting the membrane voltage. In response, voltage-sensitive sodium channels (Na_Vs) open and trigger a pain signal to the spinal cord. Abnormalities in NA_Vs or TRPV1 can cause excessive signaling. Agents under study may decrease channel activity and thus halt the extra signaling.

Crossed Wires

Some nerves that detect sensory inputs specialize in transmitting pain; others convey touch. Cross talk between the two pathways is regulated by cells in the spinal cord called interneurons (*blue*). This regulation is often disrupted in people with chronic pain, who then experience allodynia—pain from an innocuous stimulus such as a gentle touch. Research shows that this condition can arise after a nerve is injured, when immune cells known as microglia release chemical signals that cause spinal cord neurons to lose a molecule essential to normal signaling. Drug developers are working on ways to fix this short circuit and relieve allodynia.

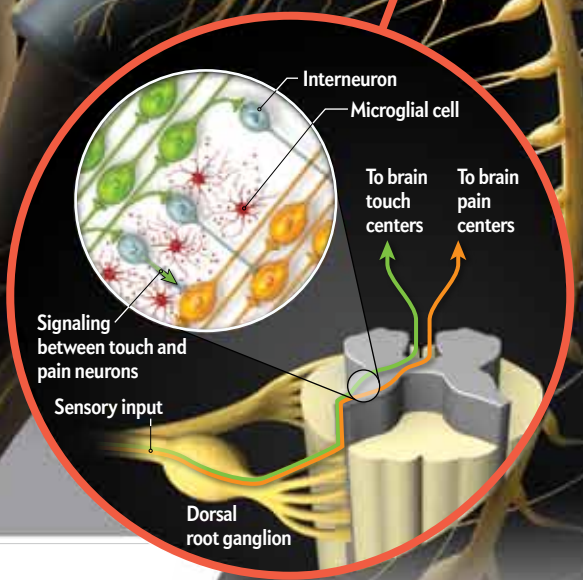


Illustration by Emily Cooper

opiates, anticonvulsants and antidepressants to help her sleep and to lower her dangerously high stress level.

Safer, more effective medications have eluded the best efforts of science, but that is beginning to change. Recent discoveries have opened several promising new avenues for drug development. "Researchers are making a lot of progress now by focusing in on pain's molecular signaling pathways," Porter says. "There is hope."

RELAY RACE

TO UNDERSTAND THESE NEW EFFORTS to control chronic pain, it is useful to know how pain arises. Pain begins as a stimulus detected by specialized nerve cells called nociceptors, which spread their feelers across the surfaces of the body, inside and out. Stimuli that could damage the body—very high or low temperature, mechanical force or a whole host of chemical threats—activate these nerve endings. Then the endings send signals zipping toward the nociceptors' cell bodies, which sit in structures known as dorsal root ganglia located just outside the spinal cord. From there the nociceptors relay the threat to neurons in the spinal cord. These, in turn, trigger the brain's extensive pain network, including areas involved in thought and emotion (which explains why placebos and distractions can sometimes ease pain).

Like all nerve signals, pain messages speed from one end of a neuron to the other via an electrical event called an action potential, created by the flow of ions—charged atoms of sodium and potassium—across a cell membrane. These ions move through tiny pores in the membrane called ion channels, made of proteins that change shape into an open or closed configuration. At nociceptors' endings, specialized ion channels detect possible threats, such as heat or chemicals spilling out from nearby damaged cells. When these channels open, positive ions flood the cell, subtly changing the balance of voltage across the membrane. This shift, in turn, triggers other ion channels that are sensitive to specific voltages. When enough of these voltage-gated ion channels open, the resulting ion flow sparks an action potential that races along the entire length of the neuron—much like a stadium crowd doing the wave. The action potential culminates in the release of a neurotransmitter in the spinal cord, a chemical message that relays information to a neighboring neuron.

Much of what has been learned about pain in the past 20 years centers on ion channels: how they detect signals such as heat and tissue damage; which of them are required for pain signaling, as opposed to playing supporting roles; and, perhaps the most pressing question, which channels could be targeted to safely silence unwanted pain signals.

Researchers and pharmaceutical companies have long understood that blocking sodium channels at nerve endings eases pain—the short-acting local anesthetics lidocaine and novocaine, for example, plug up sodium channels to numb not only pain but all sensation where they are applied. Nine voltage-gated sodium channels have been found in humans and other mammals, each opening in response to a slightly different voltage. Blocking all of them would have devastating effects because sodium channels occur in all nerve cells of the body and in other tissues, including in the brain and heart; indiscriminate blockade could interfere with the signals that give rise to heartbeat, breathing and movement. For years scientists have therefore sought a holy grail: sodium channels that are restricted to pain-sensing cells in the body.

In the late 1990s investigators got closer to this target with the discovery of three voltage-gated sodium channels that appear only in the peripheral nerve network (as opposed to in the spinal cord and brain), which is where pain signals generally begin. Designated $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$, all three are mostly relegated to nociceptors and some other neurons involved in sensation. ("Na" stands for sodium, and "$_V$" stands for voltage, with the number indicating their position in the family of nine known channels.) Once the genes encoding the channels were identified, researchers were able to manipulate the channels' activity in laboratory animals. Over the next 10 years tests confirmed that, at least in mice, quieting sensory Na_Vs could alleviate neuropathic pain.

By 2000 Na_V channels were seen as promising targets for drug development, but pharmaceutical companies needed evidence beyond animal studies to justify a major investment. Those data came from four key papers tying $Na_V1.7$ to pain in people. In 2004 a group working in Beijing found mutations in the gene for $Na_V1.7$ in two Chinese families with an inherited form of erythromelalgia—the condition Bond developed spontaneously during pregnancy. In 2005 Stephen Waxman and Sulayman Dib-Hajj, both at the Yale School of Medicine and the Veterans Affairs Connecticut Healthcare System, confirmed that these mutations led to $Na_V1.7$ hyperactivity that could cause pain. Soon after, John Wood of University College London and his colleagues reported that another condition—paroxysmal extreme pain disorder, which causes pain in the rectum, eyes and jaw—also arose from an overactive mutant $Na_V1.7$ channel. Critically, Geoff Woods and James Cox, both then at the University of Cambridge, showed in 2006 that mutations in $Na_V1.7$ that wiped out its function also eliminated any sensation of pain, creating a rare and dangerous condition that often leads to death from unfelt injuries. Together these findings in unusual genetic conditions confirmed the importance of $Na_V1.7$ in human pain sensation.

"Researchers are making a lot of progress now by focusing in on pain's molecular signaling pathways," NIH's Linda Porter says. "There is hope."

Waxman explores rare genetic diseases because, he says, they can be useful as "pointers to pathological pathways that

Why Me?

A variety of factors explain why some people are more vulnerable to chronic pain than others

Take 10 people who suffer the same back injury in a car accident: three of them will have the misfortune to end up with chronic pain as a result. Or take 10 people with diabetes: about half will develop nerve damage, or neuropathy, but the injury will cause ongoing pain in only three of them. What factors make some people vulnerable and others resilient? The question has not yet been fully answered, but research points to three main influences that seem to work in concert:

Hardwiring: Genes help to determine an individual's pain sensitivity and tolerance, and some tip the scales toward unusual susceptibility to chronic pain. One of the biggest genetic factors is gender; women are far more likely than men to develop chronic pain over the course of a lifetime.

Experience: Stress, trauma and abuse—both physical and emotional—can raise the risk. Studies suggest that these experiences can cause long-term changes in gene activity, turning genes on or off in ways that affect pain pathways. In addition, the risk for chronic pain rises with age, not just because of wear and tear but probably also because the body's ability to repair injuries—including nerve damage—declines as we get older.

Personality: Certain personality traits skew risk. Pessimists, worrywarts and catastrophizers (such as *Saturday Night Live* character Debbie Downer) are more likely to suffer. Brain circuitry involved in motivation and reward also seems to influence pain vulnerability.

—*S.S.*

may be more common." In 2012, together with collaborators in the Netherlands, he made that leap to a more common condition. Small-fiber polyneuropathy is a broad label used to describe damage to pain-sensing nerves in the periphery, often the hands or feet. About half of patients diagnosed with the condition have an identifiable source of nerve damage, such as diabetes, but in the other half the cause of pain remains a mystery. Waxman and his Dutch collaborators examined DNA from patients with unexplained cases and found mutations in the genes for $Na_V1.7$ in close to 30 percent of them, mutations in $Na_V1.8$ in 9 percent and mutations in $Na_V1.9$ in another 3 percent. Waxman's group has also found that people with chronic pain from nerve injury have an increased number of $Na_V1.7$ channels in the nerves that are damaged.

Those findings were enough for drug companies to pursue the sensory-specific sodium channels in earnest. Pfizer has been developing drugs aimed at $Na_V1.7$ and $Na_V1.8$ for several years, and although it is too early to say when a new painkiller might be available, several are now being tested in patients, reports Neil Castle of Neusentis, Pfizer's pain and sensory disorders research unit in Durham, N.C. Unlike older drugs such as lidocaine, these newer molecules are not targeted to the main pore of the sodium channel, which is nearly identical from one channel subtype to the next. Instead they act on a region of the channel that senses voltage and differs from one channel to the next, giving them more specificity and, presumably, making them safer. In 2013 Castle's group reported discovery of a chemical that selectively hits the $Na_V1.7$ voltage sensor. Such molecules, Castle says, "have very high selectivity, so they do not affect heart or muscle function"—at least not in early testing.

Meanwhile a team at Duke University is also taking aim at the $Na_V1.7$ voltage sensor but is doing so with an antibody—a molecule that derives from the immune system. According to a study published in June, the antibody relieves both inflammatory and neuropathic pain in mice, and it alleviates itching, making the approach a possible three-fer in the realm of relief. Researchers exploring the ability of certain components in venoms to act on $Na_V1.7$ are having some luck as well [*see box on next page*].

HEATING UP

SODIUM CHANNELS are not the only targets painted with a bull's-eye. Another ion channel called the transient receptor potential channel V1 (TRPV1) is famously activated by hot temperatures and by capsaicin—the chemical that gives chili peppers their burn—and it is largely restricted to pain-sensing cells. Ever since David Julius and his colleagues at the University of California, San Francisco, discovered the gene for TRPV1 in 1997, scientists have been hot on the trail of molecules that could silence pain signals by closing this channel.

"TRPV1 has been such a promising and yet such an elusive target for so long," the NIH's Porter says. Early blockers that shut it down had unmanageable side effects, such as bodily overheating and insensitivity to heat that could cause burns. The channel, which also senses acid, spider toxins and substances that promote inflammation, has more recently emerged as a complex integrator of sensory signals. "The best drug would not perturb the channel's core heat-sensing ability," Julius says. It would merely calm an overactive channel.

Julius's team took a step forward in December 2013, when it published the first high-resolution pictures of the TRPV1 structure in various states. That information should help researchers to figure out a way to block the channel only when it takes on a shape that gives rise to pain.

PAIN, MISINTERPRETED

MOST PEOPLE WITH neuropathic pain experience its three hallmarks: hypersensitivity to painful stimuli; spontaneous pain that strikes out of nowhere; and allodynia, which makes a harmless touch feel painful. (Allodynia caused the pelting water of a shower to feel like torture to Bond.) Whereas research on ion channels has helped explain hypersensitivity, another line of investigation has clarified how allodynia arises. Normally pain signals and signals for nonpainful touch travel along separate pathways from nerves in the skin to the spinal cord and up to the brain, but in the case of allodynia, signals get crossed in the spinal cord: touch-sensing neurons activate the pain pathway.

How things go wrong has been worked out mainly by investigators in Japan and by two groups in Canada, one led by Yves De

Taking the Sting Out of Pain

Venom molecules could provide alternatives to addictive opiate drugs

By Mark Peplow

PAINKILLER: The Chinese red-headed centipede's toxic venom contains a component that can numb nerves without harming the rest of the body.

When Glenn King milks centipedes, he is not going after nutrition. He is milking their poison, and it is no simple task. "We tie them down with elastic bands, bring a pair of electrical forceps up to their pincers, apply a voltage, and they expel the venom," says King, a biochemist at the University of Queensland in Australia.

The microliters of fluid could hold the keys to a new set of pain-relieving drugs. Venoms are natural storehouses of nerve-numbing molecules, and with 400 different types of venom in his laboratory, King is at the forefront of efforts to identify analgesics in the stings of centipedes, spiders, snails and other poisonous beasts.

Large pharmaceutical companies have been struggling to synthesize alternatives to addictive painkillers such as morphine but have had trouble making molecules that home in on the specific nerves they need to target. Venoms, however, have naturally evolved to contain molecules with this kind of specificity. In laboratory animals these molecules numb nerves without harming the rest of the body. The targets that many researchers are aiming at are called voltage-gated sodium ion channels, which are common in pain-sensing nerve cells. Plugging one particular type of channel, known as $Na_V1.7$, keeps the cell from passing a pain message to other parts of the body, as discussed in the accompanying article.

Certain venom components have just the right shape and chemical activity to latch onto a part of the channel called a voltage sensor, and that action shuts the channel. Last year King identified a venom molecule called m-SLPTX-Ssm6a that appeared to be one of the most selective inhibitors of $Na_V1.7$ ever seen. He found it in the venom of the Chinese red-headed centipede (*Scolopendra subspinipes mutilans*), which can grow up to 20 centimeters long and has a pair of vicious, pincerlike claws. "If they nail you, it'll hurt," King says. The molecule, however, had quite the opposite effect in injured mice: in experiments, it blocked pain better than morphine. But it had no unwanted effects on blood pressure, heart rate or motor function, indicating that it was not depressing the central nervous system, as an opiate such as morphine would.

King's team produced a synthetic version to see if the molecule could be manufactured as a drug. But to the researchers' dismay, this version did not work as well. King suspects that the original preparation they had made of m-SLPTX-Ssm6a actually contained traces of another active component. He is working on a further round of centipede milking to search for the mystery ingredient.

Snake venom is also a source of selective channel blockers. Anne Baron, a pharmacologist at the Institute of Molecular and Cellular Pharmacology in France, has isolated two painkilling molecules from the venom of the black mamba. "We are nearly ready for a clinical trial," Baron says. "We have done a lot of animal tests in rodents to assess toxicity." The mambalgins, as the molecules are called, plug a particular set of acid-sensing ion channels in peripheral nerve cells that, like sodium channels, help the cells send pain signals. Fortuitously, the mambalgins have no effect on most other ion channels, which may explain why mice injected with the substances had no apparent side effects.

Accurate nerve cell targeting is not the only goal of venom research, says David Craik, a biochemist at Queensland. If venom molecules are to be swallowed as pain pills, they need to resist degradation by the digestive system. In 2004 the U.S. Food and Drug Administration approved a painkilling drug called ziconotide that is based on a molecule isolated from the venomous cone snail *Conus victoriae.* But the drug could not withstand the rigors of the stomach, so it must be pump-injected slowly into patients, a cumbersome procedure. "Ziconotide hasn't been a big seller," Craik says.

Craik has started to reengineer painkillers derived from the cone snail toxins. His strategy is to turn the molecules, which are normally chains of amino acids, into rings. Circles are much more stable structures—enzymes in the body cannot snip off the ends. He spliced the ends together and gave oral doses of the rings to rats. The compound, dubbed cVc1.1, turned out to be 100 times more potent than gabapentin, a common treatment for nerve pain. And earlier this year at the American Chemical Society meeting in Dallas, Tex., he unveiled five more ring-shaped conotoxins that have also shown durability in early studies.

With tens of thousands of venomous species in the world, researchers think it is only a matter of time until they find a compound that hits the right target, is rugged and can be easily produced in quantity. "We perhaps know 1 percent of the products that are in these venoms," Baron says.

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COURTESY OF YASUNORI KOIDE

SCIENTIFIC AMERICAN ONLINE See an animation of a promising drug target for pain at ScientificAmerican.com/dec2014/pain

Koninck of the Quebec Mental Health University Institute and the other by Michael Salter of the Hospital for Sick Children in Toronto. In animal studies, they found that in response to nerve injury, microglia, the nervous system's own Pac-Man–like immune cells, release a signal that causes spinal cord neurons to reduce their complement of an ion-transporting molecule called KCC2 ("KC" stands for potassium chloride). The transporter works to maintain the delicate balance of chloride ions inside and outside cells. Under normal conditions, small nerve cells in the spinal cord called interneurons regulate communication between the pathways for painful and nonpainful sensations. They prevent ordinary touch from causing pain but allow a soothing stroke to temporarily ease it. When spinal cord neurons lose KCC2, however, this communication goes awry, and a light touch can trigger pain. Researchers theorized that if KCC2 levels could be restored, the improper signaling would stop.

The future of medicine, most researchers believe, is personalized. For chronic pain, that future is only just coming into view. Treatment at even the best centers tends to rely largely on trial and error.

In November 2013 De Koninck and his colleagues reported discovery of a compound that bolsters chloride transport through KCC2. The drug restored the balance of chloride ions and electrical function in neurons of the spinal cord. Moreover, it alleviated signs of neuropathic pain in rats. The KCC2 enhancer was safe and free of side effects in the animals, even at high doses.

Although the work so far has been conducted only in animals, certain aspects of the KCC2 transporter make it an exceptionally good target for human therapies. Unlike other drugs that inhibit ion channels wholesale, this transport-enhancing agent would, for instance, affect only cells with the defect, De Koninck says. Cells with functional KCC2 would keep working as usual, and the drug would not overly boost their activity. Experiments indicate that rather than changing how KCC2 behaves, the drug shepherds more of the transporters to the cell's surface. A fuller understanding of how that traffic control works will be crucial to developing safe, effective painkillers.

PERSONALIZED PAIN TREATMENT

THE FUTURE OF MEDICINE, most researchers believe, is personalized, meaning that an individual's genes and specific drug sensitivities will determine the best course of treatment and the surest way to prevent disease. In the field of chronic pain management, that future is only just coming into view. "We would love to be able to tell what, specifically, has gone wrong in each patient. Then we could say, 'Oh, you get this drug, whereas you get that other drug,'" says David Bennett, a neurologist at the University of Oxford. But treatment at even the best comprehensive pain-management centers tends to rely largely on trial and error.

Now, however, patients with rare genetic mutations affecting the Na_V channels are helping to show the way to personalized pain therapy. For example, most people who suffer the burning limb pain of erythromelalgia because of an inherited $Na_V1.7$ mutation are not helped by carbamazepine, an antiseizure drug sometimes used to treat pain. One family with the condition, though, has a particular mutation (there are many types) that results in a good response to the drug. By studying the molecular structure and function of the family's mutated channel, Waxman and Dib-Hajj were able to see how carbamazepine calmed the channel's hyperactivity and then were able to accurately predict that it would also be effective with a somewhat different mutation. These findings are exciting, Waxman says, because they suggest that basing therapy on a person's genetic makeup "is not unrealistic" for patients with inherited erythromelalgia and those who are suffering from more common pain conditions.

As for Jama Bond, her symptoms abruptly halted just before she delivered a healthy baby boy a few weeks early. Unexpectedly, steroid injections meant to help the infant's lungs mature worked like a charm for his mother. "I woke up in the middle of the night," she recalls, "and my feet did not hurt—which had not happened in over six months." No one could explain why. The symptoms did return but never with the same severity she had endured during pregnancy. "If I am on my feet for a long time, it has a direct result: I will be in pain," Bond says. "I am managing it, and I am drug-free, so that's amazing. I would love to be cured." And pain researchers would love to bring relief to Bond and the many millions like her. SA

MORE TO EXPLORE

Black Mamba Venom Peptides Target Acid-Sensing Ion Channels to Abolish Pain. Sylvie Diochot et al. in *Nature*, Vol. 490, pages 552–555; October 25, 2012.

Discovery of a Selective $Na_V1.7$ Inhibitor from Centipede Venom with Analgesic Efficacy Exceeding Morphine in Rodent Pain Models. Shilong Yang in *Proceedings of the National Academy of Sciences USA*, Vol. 110, No. 43, pages 17,534–17,539; October 22, 2013.

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FROM OUR ARCHIVES

Toward Better Pain Control. Allan I. Basbaum and David Julius; June 2006.