THE MADDENING SENSATION OF itch

How it arises is only now becoming clear

By Stephani Sutherland

IN BRIEF

Acute itch plays a role in warning us to avoid insects and poisonous plants. Chronic forms of the sensation, however, may often appear mysteriously, without any apparent cause.

Familiar causes of itch, such as an insect bite or a similar insult to the skin, provoke immune cells to produce histamine, a chemical that can spur a paroxysm of scratching.

Major gains in recent years have revealed more about molecular processes that underlie itch, raising the possibility of developing new treatments for both acute and chronic cases.

Advances stem from the identification of a range of nonhistamine pruritogens (itch-inducing substances) and a better definition of the relation between itch and pain.

Illustration by Brian Stauffer

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STARTED AS A TINY RASH ON NICOLE BURWELL'S CALF, APPEARING AT THE end of a trip to Las Vegas with her fiancé late in the summer of 2010. "I had this super, super itchy spot on my leg, but not like a mosquito bite. Not raised, not a bump. I couldn't get it to stop itching," she says. So Burwell, then 40, took the over-the-counter antihistamine Benadryl and slept the entire four-hour car ride home to Claremont, Calif. "It knocked me out," she says, but when she woke, the itch was still there. Over the next week the rash grew and with it the itch, so Burwell saw her doctor. "By then it had spread to both legs." For the next three years Burwell would battle an angry, weeping red rash that moved around her body, covering her arms and legs, hands, torso and back. But as ugly as the rash was, it did not bother Burwell nearly as much as the itch.

"I was consumed by it. I couldn't sit still; I couldn't pay attention to anything. It made me feel crazy," Burwell says. She developed a daily routine. After a day at work as a kitchen designer, she would return to her air-conditioned apartment, undress, take two Benadryls and mix herself a bourbon and Diet 7Up. "I would come home and cry because it itched so bad." Burwell kept ice packs on hand to help quiet the itch enough to fall asleep.

Burwell is not alone: an estimated one in five adults will experience itch lasting more than six weeks in their lifetime. Chronic itch can stem from any of a long list of maladies: skin diseases such as eczema or psoriasis, kidney failure, nerve damage caused by herpes or diabetes, mites burrowing in the skin, an allergic reaction to medication, even pregnancy. At its worst, itch can cause serious disability and drive people to suicide—a thought that certainly crossed Burwell's mind. Yet doctors for the most part still dismiss it as a mere nuisance. "If you don't have itch, it's not a problem, and it can be hard to relate to. We are just starting to understand that itch is really a huge problem for so many people," says Ethan Lerner, a dermatologist and itch researcher at Massachusetts General Hospital.

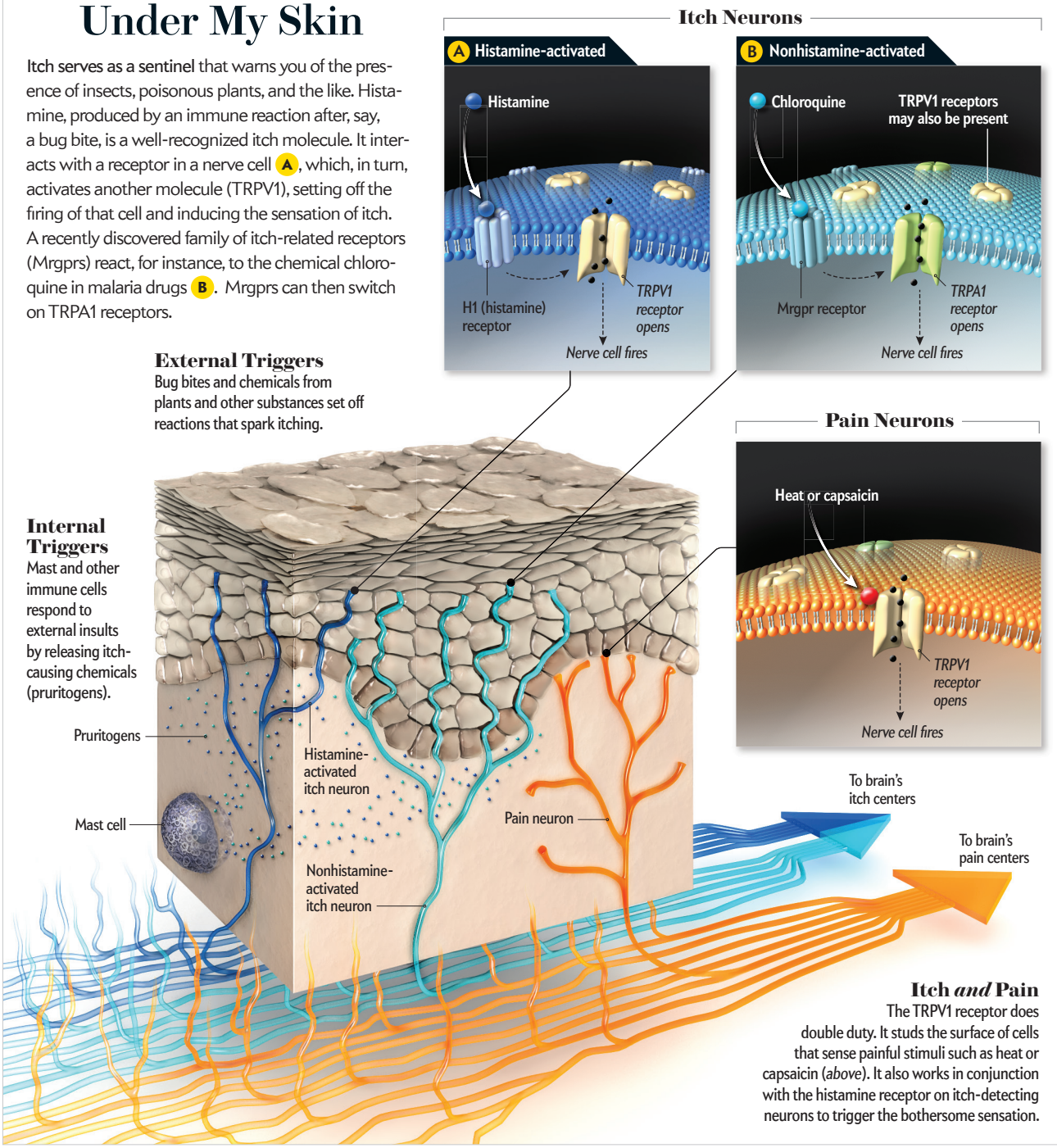
"Not all itch is equal," says Gil Yosipovitch, a researcher at Temple University. When acute, it serves an important purpose: as a sentry that protects us from the hazards of creepy-crawlies and poisonous plants [*see box on opposite page*]. But until recently, researchers had little grasp of how the vexing sensation arises from irritants in the skin. Chronic forms of itch such as Burwell's present a bigger mystery. But lately scientists have made major gains in understanding the malady, bringing them closer to developing treatments for chronic and acute itch. In particular, they have discovered new molecular receptors for pruritogens—itch-inducing substances—on nerve endings in the skin; these receptors detect the presence of the pruritogens. The new findings also reveal that part of the nervous system is specifically dedicated to itch, and it extends from the outer layer of the skin all the way to higher brain centers.

CLASSIC ITCH

THE BEST-KNOWN FORM of itch erupts when the body reacts to a simple mosquito bite. After the pest extracts its meal, it leaves behind chemicals and proteins that our immune system recognizes as foreign and so mounts a reaction at the bite site. Immune cells in the skin release cytokines, tiny chemical messengers that escalate the response. The first inkling of itch is felt on the skin—just enough to cause scratching. That, in turn, damages the protective outer layer of the epidermis. Immune cells then release a surge of histamine, a major itch-inducing chemical, along with other pruritogens. Histamine activates its receptors found on the fine endings of sensory nerves in the skin, triggering the familiar sensa-

Under My Skin

Itch serves as a sentinel that warns you of the presence of insects, poisonous plants, and the like. Histamine, produced by an immune reaction after, say, a bug bite, is a well-recognized itch molecule. It interacts with a receptor in a nerve cell (A), which, in turn, activates another molecule (TRPV1), setting off the firing of that cell and inducing the sensation of itch. A recently discovered family of itch-related receptors (Mrgprs) react, for instance, to the chemical chloroquine in malaria drugs (B). Mrgprs can then switch on TRPA1 receptors.



tion of itch. Or does it? Histamine is turning out to be less important to itch than researchers have long believed.

Until just a decade ago, histamine receptors remained the only known itch detectors, and so antihistamine medicines today are still the go-to treatment for itch, along with steroids to quell inflammation. But researchers have long suspected that chemicals other than histamine must trigger other kinds of itch—mainly because antihistamines do not aid many patients. Antihistamines help with some allergic reactions but not most chronic itches, Lerner says. "Doctors will escalate the dose, and it works only because it makes the person drowsy." Such was Burwell's experience: physician after physician prescribed steroids, which caused her to rapidly gain 20 pounds—and there was also a list of antihistamines that did nothing for the itch. "Only Benadryl helped—and only because it would calm me down enough to sleep," Burwell says. To find new itch receptors, scientists followed the trail of obscure substances known to trigger itch without involving histamine.

Illustration by Emily Cooper

The first discovery was cowhage, a plant used as an ingredient in itching powders sold in novelty shops. "When you put histamine in the skin, it causes a pure sensation of itch," Lerner says. "But if you talk to patients with eczema, they describe a pricking or burning sensation. That's the sensation that cowhage evokes." Back in the 1950s, the late Walter Shelley, a pioneer in itch research, speculated that cowhage's itch factor was a protein-cutting enzyme, a protease he named mucunain. In 2008 that hunch was finally confirmed when Lerner found that mucunain activates a receptor found in skin and nerve cells: protease-activated receptor 2 (PAR2). Certain proteases—including mucunain—can snip off a tiny piece of the PAR2 protein, which activates the receptor. That discovery led to a new appreciation that proteases and the peptide fragments they produce are key mediators of itch, at PAR2 and other receptors. Proteases are ubiquitous, including in insect saliva and bacterial secretions, perhaps explaining why bug bites and infections can be so itchy.

The second clue to finding new itch receptors came from chloroquine, a medicine meant to protect people from malaria. In an ironic twist, the drug prevents the disease but causes itching. The side effect, which is not alleviated by antihistamines, causes many at-risk Africans to refuse chloroquine, although it has made the drug a valuable tool for investigators to study itch. One of them was Xinzhong Dong, then working in the laboratory of David Anderson at the California Institute of Technology. In 2001 Dong discovered a family of receptors, activated by unknown chemicals, called Mrgprs (*M*as-*r*elated *G*-*p*rotein-coupled *r*eceptors). Some of the Mrgprs were found only in sensory neurons, suggesting they detected external stimuli, but what kind remained a mystery.

Dong applied chloroquine to cells containing Mrgprs to test whether the Mrgprs might qualify as undiscovered itch receptors. In research reported in 2009, Dong—now at Johns Hopkins University—and Anderson created transgenic mice that lacked one of the Mrgprs found in sensory cells, a receptor designated MrgprA3. "Normal mice showed a robust scratching response to chloroquine treatment," Dong says, but the transgenic mice lacking MrgprA3 did not. "Without MrgprA3, the animals just don't feel the itch. That was our breakthrough point," Dong says. Two other proteins in the Mrgpr family were also found to respond to pruritogens.

Thanks to the two quirky chemicals, researchers discovered some of the first new itch sensors since the histamine receptors were described in the latter half of the 20th century. "But the point was not to find the receptor for chloroquine or cowhage; the point really is to find out what activates these nonhistamine itch neurons in chronic itch conditions," says Diana Bautista, an itch researcher at the University of California, Berkeley. Researchers now want to identify those substances. "There are probably a small number of molecules in the skin that turn on Mrgprs, and finding them will lead to very good drug targets and therapies," Lerner says.

A LINK TO PAIN?

ANOTHER WAY INVESTIGATORS are trying to gain a fuller understanding of itch is by looking at the way the nervous system is wired to respond to it—and that inevitably leads to an examination of what causes pain. Since as early as the 1960s, scientists have understood that diverse pain-sensing neurons, which detect potentially harmful stimuli, are distinct from other sensory neurons. Some are specialized to detect heat, others cold, and still others mechanical pressure. But what about itch? Do pain-sensing neurons also sense itch, or are there specialized itch-sensing neurons—and if so, are there more than one kind?

"There is an intimate relation between itch and pain," Bautista says. As the pain of a healing wound subsides, it leaves an itch in its wake, as do some pain-relieving medications. And the pain of scratching can dissolve itch. That overlap in the senses led some researchers to lump pain and itch together. "There was an idea that a lesser stimulus—like an itchy wool sweater—would activate the same receptors and the same cells

MECHANISMS

Why Scratch?

You feel an itch, and there is no other option: you have to scratch. Ah, sweet relief. The itch subsides—at least momentarily. Why does scratching make us feel better? Relief comes from activity in the central nervous system. Scratching spurs nerve endings in the spinal cord to release the body's own painkilling molecules—endogenous opioids—which are now understood to dampen itch as well. From the spinal cord, neurons send signals to inhibit a brain region called the anterior cingulate cortex, which is strongly activated by itch; when this region quiets down, so does the feeling. "Itch and scratch are uniquely intertwined," says Gil Yosipovitch, a researcher at Temple University.

The sensation of scratching is not particularly pleasant, and yet when it relieves an itch, it feels intensely rewarding. Yosipovitch uncovered the reason in a 2013 study that imaged the brains of subjects while they scratched an acute itch and found that it activated the brain's reward system, which also lights up when, among other things, ingesting drugs of abuse.

In particular, regions linked to pleasure, craving and motivation switched on, including the striatum and the prefrontal cortex. Scratching activated the reward system more strongly in people who suffered from chronic itch than in healthy subjects, indicating that over time the reward of scratching can become amplified. That finding hinted at the addictive nature of scratching and why we are so powerless to resist when itch arises. Chronic itch sets up "a vicious cycle of itching and scratching, with no off switch," Yosipovitch says. The bottom line for doctors: "Don't tell patients not to scratch. It's so powerful, and they can't stop it."

Why does an itch compel us so strongly to rake the affected area? Consider the evolutionary purpose of scratching: itch sends a warning signal, and scratching dislodges interlopers and alerts the immune system. "Our ancestors lived in a very pruritogenic world," Yosipovitch says, one full of itchy plants and bugs that posed a real threat. That threat explains the contagious nature of itching. "When we see the signal of someone scratching, we start scratching, too," as a kind of preemptive strike, Yosipovitch says. —*S.S.*

that transmit pain," Bautista says. The idea was that mild activation evoked itch, whereas stronger stimuli produced pain.

And yet histamine—or cowhage or chloroquine—applied to the skin does not cause pain. Conversely, for the most part, painful stimuli produce only gradations of pain but not itch. And pain-sensing neurons go much deeper than the skin—the only place where itch is felt. In recent years the intensity theory faded away, and most researchers were of the mind that itch was transmitted by nerves and receptors dedicated to the sensation. Moreover, they postulated that there were multiple types of itch-sensing neurons, each detecting different itchy stimuli. "The real question that cowhage addressed was, Is there more than one kind of itch, like there is more than one kind of pain?" Lerner says. "And the answer is yes."

In 2003, however, German and Swedish researchers cast doubt on the existence of specialized itch-sensing nerves when they found that individual human nerve cells that fired in response to histamine were also activated by painful heat and capsaicin, the ingredient that gives chili peppers their spice. The dual responsiveness suggested that nerve cells supposedly devoted to sensing itch contained the receptor for capsaicin, a hallmark of pain-sensing neurons called transient receptor potential vanilloid type 1 (TRPV1). If itch neurons contained the pain-sensing TRPV1, how could they be specific for itch?

Allan Basbaum, a pain researcher at the University of California, San Francisco, found that despite TRPV1's reputation as a pain receptor, it was also required for histamine-evoked itch, demonstrating that TRP receptors were not limited to detecting painful stimuli. The histamine receptor appears to work in conjunction with TRPV1 to help neurons transmit an electrical nerve impulse known as an action potential. But other, nonhistamine itch agents complicated the picture because they did not work through TRPV1.

Meanwhile Bautista, who has spent her career studying TRP receptors, was looking for the molecules that transmit nonhistamine itch signals. Basbaum's finding that TRPV1 was involved in triggering histamine's itch gave Bautista a clue: perhaps other related TRP receptors were involved in other types of itch. She focused on another pain-sensing receptor, TRPA1, which detects inflammatory chemicals and mustard oil, and found it was required for chloroquine-mediated itch. Within an hour after presenting that finding at a meeting in 2009, Bautista received a call from Dong, and the two immediately decided to collaborate. Dong and Bautista went on to show that TRPA1 and MrgprA3 worked together to make neurons fire in response to chloroquine. "That finding strengthened the case for separate populations of neurons that mediate different types of itch," Bautista says. And it opened a new avenue for potential anti-itch treatments. "TRPA1 is such an attractive target because it is important for so many types of inflammatory conditions, including itch. If we could somehow inhibit TRPA1 [in people], that could be very useful therapeutically."

At this point, the myriad studies sufficed to demonstrate that pain-sensing receptors also participated in detecting itch. But the nagging question persisted of whether individual sensory cells specialized in transmitting itch or whether pain-sensing cells could somehow transmit both types of stimuli. Dong tackled that mystery in a 2013 study. His team created transgenic mice in which they selectively killed off the putative itch-specific neurons: the ones containing the newly described itch receptor, MrgprA3. With the loss of those cells, mice lost the ability to sense itch, whereas pain sensation remained intact.

But Dong still had to prove that the itch sensors were truly reserved for itch and did not sense pain. With an elegant use of mouse genetics, Dong created mice lacking TRPV1 from all neurons except the proposed itch neurons. When the researchers activated TRPV1 with capsaicin—a normally painful stimulus—the mice displayed only itch, not pain. That cemented the case for itch-specific neurons and showed that those cells use some of the same sensors as pain-sensing nerves. Why? "Nature just reused the molecules for both sensations," Dong says.

The link between itch and pain turns out to be far more complex than it was once thought to be.

All these advances have come from studies of sensory neurons that innervate the skin. In fact, the latest research indicates that skin cells themselves also participate in generating itch by releasing pruritogens that activate itch-sensing nerves. The complex circuitry of itch also extends to the spinal cord, where researchers have recently found neurons and signaling molecules dedicated solely to itch. And scientists are using brain imaging to better understand how neural activity produces the unique—and oh so irritating—sensation of itch.

As for Burwell, she was finally freed of her chronic itch in late 2013, when she saw a 10th doctor—a prominent dermatologist who sees patients with intractable, unexplained itch. He performed an extensive allergy patch test on her back, which showed that Burwell was allergic to a preservative found in body care and cleaning products. "It was in everything I used," she says. Once she got rid of them and started using products from an approved list, the rash—and the itch—disappeared.

Burwell's case illustrates how misunderstood itch is by medical professionals: a straightforward test revealed an easy solution but only after three years of agony. It also underscores the importance of finding underlying causes—and reveals why the molecular complexities of this simple sensation continue to yield new puzzles. SA

MORE TO EXPLORE

Living with Itch: A Patient's Guide. Gil Yosipovitch and Shawn G. Kwatra. Johns Hopkins University Press, 2013.

Why We Scratch an Itch: The Molecules, Cells and Circuits of Itch. Diana M. Bautista, Sarah R. Wilson and Mark A. Hoon in *Nature Neuroscience*, Vol. 17, No. 2, pages 175–182; February 2014.

FROM OUR ARCHIVES

Pain That Won't Quit. Stephani Sutherland; December 2014.