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.
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.

“But 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.

External Triggers
Bug bites and chemicals from plants and other substances set off reactions that spark itching.

Internal Triggers
Mast and other immune cells respond to external insults by releasing itch-causing chemicals (pruritogens).

Pain Neurons
The TRPV1 receptor does double duty. It studs the surface of cells that sense painful stimuli such as heat or capsaicin (above). It also works in conjunction with the histamine receptor on itch-detecting neurons to trigger the bothersome sensation.

Itch and Pain

Physiology

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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 prickling 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 receptor A3 in skin and nerve cells; protease-activated receptor 2 (PAR2). Certain proteases—including mucunain—can snap 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, chloroquine, a medicine meant to protect people from malaria. Explaining why bug bites and infections can be so itchy.

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 Mrgrps (Mas-related G-protein-coupled receptors). Some of the Mrgrps were found only in sensory neurons, suggesting they detected external stimuli, but what kind remained a mystery.

Dong applied chloroquine to cells containing Mrgrps to test whether the Mrgrps 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 Mrgrps found in sensory cells, a receptor designated MrgrprA3. “Normal mice showed a robust scratching response to chloroquine treatment,” Dong says, but the transgenic mice lacking MrgrprA3 did not. “Without MrgrprA3, the animals just don’t feel the itch. That was our breakthrough point,” Dong says. Two other proteins in the Mrgrp 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 Mrgrps, and finding them will lead to very good drug targets and therapies,” Lerner says.

**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 Yospovitch, a researcher at Temple University.

The sensation of scratching is not particularly pleasant, and yet when it relieves an itch, it feels intensely rewarding. Yospovitch 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,” Yospovitch 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,” Yospovitch 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, Yospovitch says. —S.S.
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Bautista 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 in-
gredient that gives chili peppers their spice. The dual responsiveness suggested that nerve
cells supposedly devoted to sensing itch con-
tained 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 Califor-

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

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rons 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
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of the same sensors as pain-sensing nerves. Why? “Nature just
reused the molecules for both sensations,” Dong says.

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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 neu-
rons 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

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