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Ideas

WHY PEOPLE ITCH AND HOW TO STOP IT

Scientists are discovering lots of little itch switches.

By Annie Lowrey

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The twinge begins in the afternoon: toes. At my desk, toes, itching. Toes, toes, toes.

I don't normally think about my toes. But as I commute home in a crowded subway car, my feet are burning, and I cannot reach them. Even if I could, what would I do with my sneakers? My ankles are itchy too. But I'm wearing jeans, which are difficult to scratch through, unless you have a fork or something similarly rigid and sharp. I contemplate getting off at the next stop, finding a spot on a bench, removing my shoes, and scratching for a while. But I need to get home. Growing desperate, I scrape at my scalp, which is not itchy. This somehow quiets things down.

I am full of these kinds of tricks. A lot of folks, if you tell them you're itchy, will recommend a specific brand of lotion. I hate these people. My husband made me a T-shirt that reads yes, I have tried lotions. They do not work. No, not that one either. Zen types will tell you to accept the itch, to meditate on it, as you might do if you were in pain. These people have no idea what they are talking about. Watching someone scratch makes you itchy; worrying about something pruritogenic, like a tick crawling on you, makes you itchy; focusing on how itchy you are when you are itchy makes you itchier. The trick, if you are itchy, is to not think about it, using those ancient psychological tricks disfavored in today's therapeutic environments: avoidance, deflection, compartmentalization, denial.

Cruelest of all are the people who tell you not to scratch. They have a point, I admit. Scratching spurs cells in your immune system to secrete the hormone histamine, which makes you itchy; in this way, scratching leads to itching just as itching leads to scratching. But if you itch like I itch, like a lot of people itch, there's no *not* scratching. It would be like telling someone to stop sneezing or not to pee. "I never tell people not to scratch," Gil Yosipovitch, a dermatologist at the University of Miami Miller School of Medicine known as "the godfather of itch," told me, something I found enormously validating.

No, the techniques that work are the techniques that work. During the day, I pace. Overnight, when the itching intensifies, I balance frozen bags of corn on my legs or dunk myself in a cold bath. I apply menthol, whose cold-tingle overrides the hot-tingle for a while. I jerk my hair or pinch myself with the edges of my nails or dig a diabetic lancet into my stomach. And I scratch.

My body bears the evidence. Right now I am not itchy—well, I am mildly itchy, because writing about being itchy makes me itchy—yet my feet and legs are covered in patches of thick, lichenified skin. This spring, I dug a bloody hole into the inside of my cheek with my teeth. I've taken out patches of my scalp, shredded the edge of my belly button, and more than once, desperate to get to an itch inside of me, abraded the walls of my vagina.

During my first pregnancy, when the itching began, it was so unrelenting and extreme that I begged for a surgeon to amputate my limbs; during the second, my doctor induced labor early to stop it. Still, I ended up hallucinating because I was so sleep-deprived. Now I have long spells when I feel normal. Until something happens; I wish I knew what. I get brain-fogged, blowing deadlines, struggling to remember to-dos, failing to understand how anyone eats dinner at 8 p.m., sleeping only to wake up tired. And I get itchy. *Maybe it will last forever*, I think. It stops. And then it starts again.

One in five people will experience chronic itch in their lifetime, often caused by cancer, a skin condition, liver or kidney disease, or a medication such as an opiate. (Mine is caused by a rare disease called primary biliary cholangitis, or PBC.) The itching is the corporeal equivalent of a car alarm, a constant, obnoxious, and shrill reminder that you are in a body: *I'm here, I'm here, I'm here*. It is associated with <u>elevated</u> levels of stress, anxiety, and depression; causes sleep deprivation; and intensifies <u>suicidal ideation</u>. In one study, the average patient with chronic itch said they would give up 13 percent of their lifespan to <u>stop it</u>.

Yet itching is taken less seriously than its cousin in misery, pain. Physicians often dismiss it or ignore it entirely. Not that they could treat it effectively if they wanted to, in many cases. There are scores of FDA-approved medications for chronic pain, from ibuprofen to fentanyl. There are no medications approved for chronic itch. "Pain has so much more research, in terms of our understanding of the pathophysiology and drug development. There's so much more compassion from doctors and family members," Shawn Kwatra of the University of Maryland School of Medicine told me. Itch, he added, "is just not respected."

Perhaps doctors do not respect it because, until recently, they did not really understand it. Only in the late aughts did scientists establish that itch is a sensation distinct from pain and begin figuring out the physiology of chronic itch. And only in the past decade did researchers find drugs that

resolve it. "We're having all these breakthroughs," Kwatra said, ticking off a list of medications, pathways, proteins, and techniques. "We're in a golden age."

Once left to suffer through their commutes and to ice their shins with frozen vegetables, millions of Americans are finding relief in their medicine cabinet. For them, science is finally scratching that itch. Still, so far, none of those treatments works on me.

Itching is one of those tautological sensations, like hunger or thirst, characterized by the action that resolves it. The classic definition, the one still used in medical textbooks, comes from a 17th-century German physician: "an unpleasant sensation that provokes the desire to scratch." Physicians today classify it in a few ways. Itching can be acute, or it can be chronic, lasting for more than six weeks. It can be exogenous, caused by a bug bite or a drug, or endogenous, generated from within. It can be a problem of the skin, the brain and nervous system, the liver, the kidneys.

Most itching is acute and exogenous. This kind of itch, scientists understand pretty well. In simplified terms, poison ivy or laundry detergent irritates the skin and spurs the body's immune system to react; immune cells secrete histamine, which activates the nervous system; the brain hallucinates itch into being; the person starts to scratch. The episode ends when the offending irritant is gone and the body heals. Usually medicine can vanquish the itch by quieting a person's immune response (as steroids do) or blocking histamine from arousing the nervous system (as antihistamines do).

Yet some people itch for no clear reason, for months or even years. And many itching spells do not respond to steroids or antihistamines. This kind of itch, until recently, posed some "fundamental, basic science questions," Diana Bautista, a neuroscientist at UC Berkeley, told me. Scientists had little idea what was happening.

In the 1800s, physicians were studying the nervous system, trying to figure out how the body is capable of feeling such an astonishing panoply of sensations. Researchers found that tiny patches of skin respond to specific stimuli: You might feel a needle prick at one spot, but feel nothing a hair's breadth away. This indicated that the body has different nerve circuits for different sensations: hot, warm, cold, cool, crushing, stabbing. (Migratory birds have receptors in their eyes that detect the world's magnetic field.) The brain synthesizes signals from nerve endings and broadcasts what it senses with obscene specificity: the kiss of a raindrop, the crack of an electric shock.

In the 1920s, a German physiologist noted that when researchers poked a pain point on the skin, itch often followed ouch. This led scientists to believe that the sensations shared the same nervous-system circuits, with the brain interpreting weak messages of pain as itch. This became known as the "intensity theory"—itch is pain, below some threshold—and it became the "canonical view," Brian Kim, a dermatologist at the Icahn School of Medicine at Mount Sinai, told me.

It never <u>made much sense</u>. If you catch your finger in a door, the stinging sensation does not dissipate into itch as the swelling goes down. That the body might have different circuitries for itch and pain seemed plausible for other reasons, too. "If you take 10 patients experiencing pain and give them morphine, probably all of them will feel better. If you take 10 patients with chronic itch and you give them morphine, none of them would," Kim said. "That tells you right there." Moreover,

pain *alleviates* itch. It interrupts it. That is, in part, why you scratch: The pain creates the pleasure of relief. "The behavioral output is very different," Bautista told me. "If you encounter poison ivy or get a bug bite, you don't try to avoid the injury. You attack it. But with pain, you withdraw; you have these protective reflexes."

Many scientists preferred an alternative theory: that itch had its own dedicated "labeled line" within the body. It took until 2007 for neuroscientists to uncover an <u>itch-specific circuitry</u> that many had long suspected was there. Mice genetically engineered to lack a specific receptor, <u>scientists found</u>, felt "thermal, mechanical, inflammatory, and neuropathic pain," but not itch.

Since then, neuroscientists have refined and complicated their understanding of how things work—in particular, extending their understanding of what amplifies or overrides itch and the relationship between the pain and itch circuitries. And doctors have come to understand itch as a disease in and of itself.

And a curious disease, at that. In any given year, one epidemiological survey found, chronic itch afflicts 16 percent of the general adult population, making it half as common as chronic pain. Yet there are scores of American medical centers dedicated to treating pain and none for itch. On Facebook, I found hundreds of peer-support groups for people with chronic pain. For chronic itch, I found just one, dedicated to sufferers of the miserable dermatological condition prurigo nodularis.

Millions of us are scratching alone, a social reality with deep physiological roots. Itching is isolating. The touch of another person can be unbearable. When I get really itchy at night, I build a pillow wall between myself and my cuddle-enthusiast husband, so he does not accidentally wake me up, kickstart the itch-scratch cycle, and mechanically increase our chance of divorce. Studies also show that itch is both contagious and repellent. In the 1990s, scientists in Germany rigged up cameras in a lecture hall and filmed members of the public who came to watch a talk on pruritus. Inevitably, people in the crowd began scratching themselves. Yet people reflexively move away from others who are itching, and toward those in pain.

At best, scratching yourself is like chewing with your mouth open, <u>embarrassing</u> and undignified. At worst, it broadcasts uncleanliness, infestation, derangement, and disease, raising the specter of bedbugs, scabies, chicken pox, roseola, gonorrhea, insanity, and who knows what else. In ancient times, people believed that lice were a form of <u>godly punishment</u>: They generated spontaneously in a person's flesh, tunneled their way out, and consumed their host, thus transfiguring them into bugs. Plato is one of many historical figures <u>accused</u> by his haters of being so lousy, literally, that it killed him. And maybe it did. An extreme lice infestation can cause a person to die from a blood infection or anemia.

At least the ancients grasped how miserable being itchy can be. In 1365, a scabies-ridden Petrarch complained to Boccaccio that his hands could not hold a pen, as "they serve only to scratch and scrape." In Dante's *Inferno*, itching is meted out as a punishment to alchemists in the eighth ring of hell. Murderers in the seventh ring, including Attila the Hun, get a mere eternal dunk in a boiling river of blood.

In my experience, people do not meet an itchy person and grasp that they might be beyond the boiling river. (The physician and journalist Atul Gawande <u>wrote about</u> a patient who scratched all

the way through her skull into her brain.) The stigma and the dismissal compound the body horror. When I explain that I itch, and at some point might start itching and never stop, many people respond with a nervous giggle or incredulousness. One of my dumb lines on it involves being a distant relative of a participant—to be clear, an accuser—in the Salem witch trials. Who knew that curses work so well!

Itch is a curse, an eldritch one. At night, I sometimes feel crumbs or sand on my sheets, go to brush the grit off, and find the bed clean. One day, I was rummaging around in a basement and felt a spider drop onto my shoulder from the ceiling. I felt that same, vivid sensation a hundred times more over the next few days. The inside of my body itches, like I have bug bites on my intestines and my lungs. I swear that I can feel the floss-thin electric fibers under my skin, pinging their signals back and forth.

The worst is when I need the itch to stop and I cannot get it to stop, not by dunking myself in ice water or abrading myself with a fork or stabbing myself with a needle or taking so much Benadryl that I brown out. It generates the fight-or-flight response; it feels like being trapped. I don't know; maybe it is akin to drowning.

My chronic itch might be a disease unto itself, but it is also a symptom. At some point in my early 30s, my immune system erred and started to destroy the cells lining the small bile ducts in my liver. This inflamed them, obstructing the flow of sticky green bile into my digestive system. The ducts are now developing lattices of scar tissue, which will spread through my liver, perhaps resulting in cirrhosis, perhaps resulting in death.

Primary biliary cholangitis is degenerative and incurable, and was until recently considered fatal. The prognosis was radically improved by the discovery that a hundred-year-old drug used to dissolve gallstones slows its progression, reducing inflammation and making bile secretion easier. But a minority of people do not respond to the medication. I am one of them.

PBC is generally slow moving. Science keeps advancing; my doctors have me on an off-label drug that seems to be working. Still, I am sick, and I always will be. I feel fine much of the time. The dissonance is weird, as is the disease. What am I supposed to do with the knowledge of my illness? Am I at the end of the healthy part of my life, at the beginning of the dying part?

I am stuck with questions I cannot answer, trying to ignore them, all the while reminded of them over and over again, itchy.

Some answers, however, are coming. Having found nerve circuits dedicated to itch, scientists also began finding receptors triggered by substances other than histamine, thus unlocking the secrets of chronic itch. "We know more about the neural circuits that allow you to experience this sensation, regardless of cause," Bautista told me. "We know more about inflammatory mediators and how they activate the circuits. We know more about triggers and priming the immune system and priming the nervous system."

I asked a number of experts to help me understand chronic itch in the same way I understood acute itch—to show me an itch map. "It's complicated," Kwatra told me. "Complicated," Kim agreed. "Complex," said Xinzhong Dong of Johns Hopkins. The issue is that there's not really a map for chronic itch. There are *multiple* itch maps, many body circuits going haywire in many ways.

Still, Dong gave me one example. The drug chloroquine "works really well to kill malaria," he explained. But chloroquine can cause extreme itchiness in people with dark skin tones. "The phenomenon is not an allergic reaction," Dong told me; and antihistamines do not ease it. In 2009, his lab <u>figured it out</u>: In highly simplified terms, melanin holds chloroquine in the skin, and chloroquine lights up an itch receptor.

Because there is no single map for chronic itch, there is no "big itch switch that you can turn off reliably with a drug," Kim told me. "I'm not so convinced that it is even doable." (Dong thought that it probably is. It just might cause debilitating side effects or even kill the itchy person in the process.) Still, there are lots of smaller itch switches, and researchers are figuring out how to flip them, one by one.

These include a pair of cytokines called interleukin 4 and interleukin 13. When a person encounters an allergen, the body secretes these chemical messengers to rev up the immune system. Yet the messengers also spur the body to produce itch-related cytokines and make the nervous system more sensitive to them. In 2017, the FDA approved a drug called Dupixent, which blocks the pair of cytokines, to treat atopic dermatitis, a form of eczema; the agency later approved it for asthma, laryngitis, and other inflammatory conditions (at a retail cost of \$59,000 a year).

Michael McDaniel found a single open blister on his bicep when he was traveling in Europe in 2013. Within a few days, he told me, a crackling, bleeding rash had engulfed his upper extremities, oozing a honey-colored liquid. His knuckles were so swollen that his hands stiffened.

Back in the United States one miserable week after his trip, he saw a dermatologist, who diagnosed him with atopic dermatitis. Nothing McDaniel tried—steroids, bathing in diluted bleach, avoiding cigarette smoke and dryer sheets, praying to any god who would listen—ended his misery. He bled through socks and shirts. He hid his hands in photographs. "I was able to get my symptoms to a manageable baseline," he told me. "It wasn't really manageable, though. I just got used to it."

McDaniel muddled through this circle of hell for seven years, until his dermatologist gave him an infusion of Dupixent. Twenty-four hours later, "my skin was the calmest it had been since my symptoms appeared," McDaniel told me. The drug was a "miracle."

Numerous drugs similar to Dupixent have been found over the past seven years to work on chronic itch, and physicians are refining techniques such as nerve blocks and <u>ketamine infusions</u>. But finding treatments for itching that is not related to an immune response has proved harder. Progress is throttled by the relatively small number of researchers working on itch, and the limited sums Big Pharma is willing to pump into drug development and trials. Plus, treatment options do not readily translate into treatment; a lot of folks are still being told to try Benadryl, even if all it does is make them groggy.

When I saw my hepatologist in August, that's exactly what he suggested. The drug would help to quell the itching caused by my scratching, at a minimum, and help me sleep.

"I hate Benadryl," I snapped. (Maybe I need a new T-shirt.) He suggested Zyrtec or Claritin.

As I continued to press for more options, he reviewed my bloodwork. My liver enzymes were still high. He suggested more tests, a biopsy. And he said we could start trialing drugs to manage my

symptoms better. SSRIs, used to treat depression, sometimes ease itch in patients with PBC. Opioid antagonists, used to treat heroin overdoses, sometimes do the same. Cholestyramine, which soaks up bile acid (a known pruritogen), could work. Maybe UVB phototherapy. Maybe a cream charged with fatty acids that <u>activate the endocannabinoid system</u>. Maybe rifampin, an antibiotic.

These ragtag off-label treatment options reflect the fact that physicians have not yet figured out PBC's itch map. Some patients just itch and itch and it never ends. I once asked my old hepatologist what she would do if that happened to me. "Transplant your liver," she told me, not even looking up from her computer.

This was not a comforting answer. Organ transplantation is a lifesaving miracle, but a saved life is not an easy one. Recovery from a liver transplant takes at least a year. Grafts <u>die</u>, not infrequently. Many patients never heal fully. The five-year survival rate is 14 percentage points lower for PBC patients with liver transplants than it is for PBC patients who respond to the standard treatment and do not need one.

When I shared this prognosis with my mother, she responded, "You better start being nice to your siblings!" (I would rather die.) When I broke it to my husband, he paused a beat before saying he might go call his therapist.

Would I rather just live with the itch? How would I do it? I could not find a support group for the chronically itchy. But I did find two people with PBC who were willing to share their experiences with me. Carol Davis is a retired kindergarten teacher. More than a decade ago, she started itching "like crazy," she told me. "It would wake me up in the night." A doctor diagnosed her with PBC; like me, she itches on and off, and doctors have never found a set of drugs to quell her itch without causing miserable side effects.

I asked her how she has dealt with it, not in terms of doctors and drugs and lotions but in a more cosmic sense. "When you're at the end of your lifespan, you just have the mindset: These things are going to happen," Davis told me. "If I had been younger, like you, it might have been more scary." Then she ticked off a list of things she looks forward to: games of Farkle, Bible study, going to the gym, seeing her friends from her sorority, spending time with her husband of 54 years. She got out of her head, she meant. And when she found herself back there, itching or afraid or in pain, she told me, "I don't dwell on myself. I don't ask the Lord to make me well. I dwell on Him!"

Gail Fisher is 84 "and a half," she told me, and a harpist, gardener, and motor-home enthusiast. She lives alone in rural Effingham County, Illinois. Her PBC has developed into cirrhosis, and she also has arthritis and thyroid disease. The itching drives her nuts sometimes too, she told me. But she does not dwell on it either. "Gosh, don't worry about it," she said. "You don't know what tomorrow is going to bring anyway!"

When the itch is at its worst—not a bodily sensation but an existential blight, not a force begging for resignation but one driving a person to madness—that's easier said than done. Still, I knew that following Davis's and Fisher's advice would do me more good than lotion or Benadryl ever has.

I'm here, my body tells me. I'm here. I'm alive. I'm dying. I'm here.

I know, I respond. Enough. I know.

About the Author



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