
PAIN AND ITS MYSTERIES

Genetic and psychological factors help determine how well we withstand it

BY MARNI JACKSON

I was riding a bike in the Rockies, near Banff, when a bee flew into my mouth, and I felt a slim, unambiguous lance of pain, like a splinter of glass. Right away, I noticed, this sensation began to sprout a narrative. It wasn't just bad luck that the bee had stumbled into me; I saw the sting as punishment for biking "the wrong way"—distracted, churning along too fast, panting with open mouth. I had not been paying attention. Then pain had come along and rinsed the morning clear of small deceptions.

The next day, apart from having fabulous Angelina Jolie lips, I was back to normal. Unlike the chronic ache of arthritis or the lightning stab of trigeminal neuralgia, a bee sting is a wonderfully minor, finite form of pain. But the experience had nevertheless raised a swarm of questions about the mysterious nature of pain, and our relationship to it. For instance, why do we still talk about mental pain versus physical pain, when pain is always an emotional experience? How has it come about that something so universal remains so poorly understood, especially in an age of relentless self-scrutiny? And why hasn't anyone noticed the embarrassing fact that science is about to clone a human being, but it still can't cure the pain of a bad back?

The U.S. National Pain Foundation says more than four out of 10

American adults experience pain every day. The situation is likely much the same in Canada. North Americans consume four tons of ASA, a year, while chronic pain is on the rise. It's almost as if pain flourishes on our diet of analgesics. And it seems the more science learns how pain behaves (a quantum leap in the last 50 years), the less doctors want to do to treat it. To try to understand how we got ourselves in this pickle, I embarked on a four-year inquiry that zigzagged between art and science, doctor and patient. I talked to pain experts, and people who have learned to live with chronic pain. I tried to integrate the migrainish portrait of pain in Emily Dickinson's poetry or Virginia Woolf's novels with the latest MRI images of pain in the brain. I went back into the history of ideas about pain, where I encountered eccentric thinkers and unsung heroes, and forward into the genetic research into pain—where, once again, I ran into bees.

The inability to feel any pain at all is something that is inherited. Imagine: no hangovers, no sore pitching arm, no tremors in the dentist's chair. But congenital analgesia (as it's known) turns out to be both a nuisance and a life-threatening peril. Dr. Ron Melzack of McGill Univer-

sity and his British colleague, Dr. Patrick Wall—the two researchers whose "gate-control theory" revolutionized the way science now views pain—describe the consequences of a pain free life in their classic study, *The Challenge of Pain*. One girl with this condition suffered third-degree burns on her knees after climbing up on a hot radiator. And because there was no discomfort to let her know when she should shift her weight or posture, she eventually developed an inflammation in her joints and died at the age of 29.

Be glad it hurts when you stub your toe, because pain plays a vital role in our lives

Another woman with congenital analgesia felt nothing but a "funny, feathery feeling" when she delivered the first of her two children. But one of the best known examples of this rare inherited disorder was an American vaudeville performer in the 1920s, Edward H. Gibson, known as the Human Pincushion. His act involved sticking 50 to 60 pins into his body and then slowly removing them. It seems that for those born incapable of feeling pain, the career options are narrow, and life is short. Be glad it hurts when you stub your toe, because pain

plays a vital, protective role in our lives.

Congenital analgesia is at the far end of a wide spectrum of inherited pain disorders. Genetic factors are involved in 39 to 55 per cent of migraines, 55 per cent of menstrual pain, and half of the back-pain population. Gender also has an influence, which will come as a surprise to no one. Men appear to suffer less pain, but require more pain relievers. There's no proof that women tolerate pain better than men, but they are three times more likely to suffer migraines, and six times more vulnerable to fibromyalgia. In a 1999 Gallup survey, 46 per cent of American women said they felt daily pain, compared to 37 per cent of men. And whether it's gene-related or stiletto-induced, one in four women also reported that their feet hurt.

"For a long time, people have accepted that there are wide variations in the way people respond to pain or to analgesics, but no one ever seriously considered attributing it to genetics, until now."

I was talking to Jeff Mogil, the first person in the world to put together training in psychology, genetics and pain. Mogil studied under psychologist and pain science pioneer John Liebeskind in California. After post-doctoral training in genetics, he joined the faculty at the University of Illinois in 1996. In 2001, Melzack lured him up to McGill University, where Mogil has succeeded him as the E. P. Taylor professor of pain research in psychology. This suggests that the pendulum is swinging back: science has moved away from seeing pain as a slippery psychological interpretation of something that only happens to the body, to approaching it as an experience that is at once neural, emotional and deeply rooted in our cells and genes.

"Pain genetics is where all the action is now, but it was a totally empty field when I moved into it," says Mogil, who is 35. "Nobody thought that pain had anything to do

with genes. But then other people started working with knock-out mice, figuring out what happens when you remove this or that protein from a gene, and now knock-out mice are everywhere."

"Knock-out mice" always sounded to me like something you could order by the dozen at 3 a.m., from an infomercial. The sea monkeys of science. These mice are bred to lack a particular gene, and the protein it produces. "Then you look for what's wrong with the knock-out mouse when it doesn't have this or that protein any more," said Mogil. "It's the hottest technique in biology right now, and in pain research, too." It used to be that scientists didn't concern themselves with whatever strain of mouse they used in their studies, he added. But with knock-out mice "they discovered that the genetic background of the mouse was affecting their outcomes. It turned out that I was the only person paying attention to this sort of information."

When it comes to pain, he found, there is no such thing as a "universal rat." Pain sensitivity varies widely from strain to strain of rats and mice. Mogil also discovered that some mice are born either "doubly unlucky"—both over-sensitive to pain and under-responsive to analgesics—or vice versa, the lucky ones who feel less pain and require less painkiller.

"What the study of knock-out mice means for humans," Mogil said, "is that it helps explain individual sensitivities to pain and to drugs, as well as the fact that while most people will recover from an injury, some five per cent won't. They'll go on to develop chronic pain. Obviously, the factors that determine this are both environmental and genetic, and it's very tricky to sort these out. But if we know that some people have a propensity to chronic pain, then we might be able to find ways to keep it from developing in the first place. And as we learn more about pharmacogenetics, we can target their treatment with more precision. It also means that people who com-

plain more about pain aren't necessarily whiners—they may actually feel more than other people. If humans really are like mice, then roughly half of that variability in pain response is due to their inherited genes."

Mogil has also studied the variety of ways people respond to painkillers. Indeed, the world seems to be divided into "responders" and "non-responders," since morphine is only successful with about 65 per cent of the population. This explains why pain doctors have to fiddle with a variety of pain medications before they get it right. Among Caucasians, about seven to 10 per cent are known as "poor metabolizers" who won't respond to codeine. They end up getting all the side effects, but none of the pain relief.

I asked Mogil whether this news would encourage more magic-bullet thinking—the notion that we can simply zero in on these "pain genes," knock them out, and throw away the Tylenol.

Genes don't work like that, he replied. "Just as there is no pain centre, there is no single pain gene that controls it. But it doesn't look like there's a hundred of them either. We're looking for a particular type of gene that exists in different forms that can be inherited—and of those genes, there are five to 10, maybe 20 tops."

But people are so eager to blame their genes for everything now, I said. Doesn't this new focus on the genetic aspect downplay the way cultural, political and social forces shape our perception of pain?

"But that's the thing about pain—the cortical stuff is really, really important," he said. Mogil automatically translates the word "culture" as "cortical activity," but I got his drift. He was referring to the emotions, ideas and attitudes that are the result of our memory, learning, and experience. And in Melzack and Wall's gate-control theory of pain, it is the "cortical stuff" that descends to the spinal cord, amplifying or muting the pain signals coming in from the periphery of the body. In

other words sensory data travels up; “culture” moves down. And for both Mogil and Melzack, “everything is equally biological.”

Melding neuroscience and psychology, Mogil (like Melzack before him) seems to be describing culture not as something “out there” but embodied in the way the brain shapes our experience of pain. It’s interesting, I said to Mogil, that he and Melzack are both psychologists, sometimes seen as low men on the totem pole when the hard-science boys get together.

“Pain is psychological,” Mogil emphasized. “There’s all this neural activity going on, but it can always be trumped by culture, attitudes and behaviour. Being a psychologist lets me do work with a high level of variability in my tests. Most scientists don’t want to see variability in their results. They’re looking for consistency. But I get happy when I see messy data.”

Then the bee came back into the picture. It turns out that pain researchers will sometimes use bee venom to induce what Ron Melzack calls a “good, classic pain, the type we can learn a lot from.” Although bee venom has a long list of active ingredients, the main toxin is a peptide called melittin. This can produce chemicals known as cytokines that play an important role in painkilling.

(Tests on beekeepers who have been stung repeatedly have revealed elevated levels of cytokines.) In fact, bee venom has been popular in treating the pain of arthritis for centuries, especially in Europe. Now it’s also being touted as helpful therapy for autoimmune conditions like multiple sclerosis, and a protective agent against X-irradiation in cancer patients. The alternative-network literature for BVT (bee venom therapy) is vast, and that’s only one aspect of apitherapy, which uses everything from bee pollen, royal jelly and honey to the wax and venom to treat an array of disorders.

So my original suspicion that a bee sting is a complicated thing was not entirely off-base. It turns out that everything involved in the orchestration of the event we call pain—the swelling, inflammation, redness, heat and stinging sensation—may, under different, controlled circumstances, also offer pain relief. In other words, better pain treatment may not lie in our efforts to suppress it or surgically excise it, but in a deeper understanding of how the body can use aspects of the pain process to promote healing and recovery. The answer to pain may lie inside pain itself.

As science looks beyond the role of pain as symptom, its hidden narrative will continue to unfold. If Jeff

Mogil is right, 50 years from now we will look at pain quite differently. Tylenol tablets will seem as quaint to us as sarsaparilla tonic. Instead, we’ll take our ID bracelet to the local pharmacologist to order some bespoke analgesics, tailored to gender and genotype. Some of us may rise at 4 a.m. to meditate, and feel the struggle against pain lighten. We’ll carry geno-cards that list our inherited predispositions: photosensitivity, osteoporosis and poor response to codeine.

Addiction might be redefined not as a character flaw but as “biochemical deficit management.” Medical schools will actually teach doctors about the way pain behaves, and how to treat it. Our emotional habits will become an accepted factor of good health, and we’ll know whether we’re at risk for depression or rheumatoid arthritis in the same way we know that we’re Scottish, or hazel-eyed. How we live with this new information, of course, will still be our choice. But we will understand that pain is sometimes history, in the body.

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