IN YOUR OWN WORLD OF HURT:
An ache for you may be agony for another // An analgesic may soothe someone else's misery, but not yours // Your sensitivity to pain is as individual as your eye color.

# The Body in Pain

BY RACHAEL MOELLER GORMAN // PORTRAITS BY MICHELE ASSELIN

Nine distinct pains have plagued Terrie Cowley since the summer of 1982.

One, bone pain, "is like a glass of ice. When you pour in water, you hear that cracking. That's how my skull sometimes feels—intense, streaking pain."

Two, "chemical" headaches. "It's that horrible feeling as if you've had too much wine and you can barely pick your head up off the pillow."

Three, brush-burn pain. "If you wash your face, the slightest touch stings and burns—you feel like roadkill."

Four hits the lymph nodes, five the eyes, and six the throat. "You swallow and feel as though your eyeballs were going down your throat," Cowley says. Tooth pain, burning mouth and deep-muscle pain fill out the list.

Cowley had felt none of this before her jaw surgery, and she wondered what could have gone so terribly wrong. Immediately following the procedure to correct a clicking and popping condition in her jaw called temporomandibular joint disorder (TMJD), she asked her oral surgeon whether she had fallen off the gurney while she was unconscious. It wasn't just her head; her entire body ached and throbbed, as if she had a severe case of the flu.

Two months later, when the pain had not subsided, she asked whether he had cut her brain accidentally. Or whether she was going to die. When he told her there was nothing wrong with her, she went home and shut up because she didn't want to become grist for the rumor mill in the hospital, where her husband worked.

Cowley suffered silently for four years. But in 1986 she met a kindred spirit—a woman who experienced similar pain, though she had never had surgery. The two sponsored a meeting to see whether anyone else felt the same way. One hundred twenty people showed up. It was the beginning of a support group that now assists TMJD patients worldwide.

One in 10 Americans suffers chronic pain that lasts at least a year, a ratio that rises to six in 10 for those older than 65. Pain underlies 20% of doctor visits and 10% of all prescriptions written, even though, for many chronic-pain sufferers, drugs don't do much. Some of the most effective medicines are hardly cutting edge: Opiates, including morphine, have been in use for hundreds of years, as has the willow bark from which aspirin is derived. Newer medications such as anticonvulsants and antidepressants sometimes help, but they often leave patients feeling drugged.

"I think it is the norm, not the exception, that pain is not completely resolved," says neuroscientist Jon-Kar Zubieta of the University of Michigan in Ann Arbor. "None of the currently available drugs is very effective," says Massachusetts General Hospital neuroscientist Clifford

Woolf. "You typically need to treat four to 10 patients to get one who responds well."

But a growing understanding of the nature of pain could soon provide better options. Research into what goes on in the body during chronic pain is beginning to generate ideas for drugs and other treatments, stirred by a new focus on genetics. Gene studies reveal that everyone's experience of pain is different, and that roughly half of our sensitivity to pain is determined by our genetic makeup. Some people are much more prone than others to develop chronic pain after surgery; to suffer, without surgery, from fibromyalgia and TMJD; or to feel more pain when pricked or punched.

"We used to think reaction to pain was largely culturally determined—with stoic Northerners and hysterical Mediterraneans," says Woolf. "In fact, how one feels pain turns out to be in good part a matter of genetics. This understanding has given us a totally new perspective, and if we can target pain's underlying mechanisms, we can prevent changes that lead to chronic pain. I think we're on the cusp of a total revolution in our approach to pain."

Though doctors have hundreds of ways to catalogue pain, Woolf sticks to four categories. Nociceptive pain is the feeling that makes you pull your hand away from a hot casserole dish or sharp knife, a response essential to survival. A recent report in the journal *Nature* tells of individuals from three families in Pakistan who can't feel any type of pain at all. One, a boy well-known for his street theater—stabbing knives through his arms and walking on burning coals—jumped to his death from a roof on his 14th birthday.

Inflammatory pain is next. Think of a swollen toe that throbs at the slightest touch, the sunburn that can't stand the shower. This too is a form of protection, encouraging us to remain immobilized as we heal (though some disorders, such as rheumatoid arthritis, occur when this process continues for no healthy reason). Inflammatory pain is alleviated by drugs like aspirin, ibuprofen and acetaminophen, whereas morphine and stronger narcotics allay nociceptive pain during and after surgery.

The other two categories, neuropathic and idiopathic pain, seem not to serve any purpose. Neuropathic pain results when a nerve is injured by surgery, trauma or a disease such as shingles or diabetes. This eventually triggers abnormal functioning of the nervous system, with neurons firing erratically and forming irregular circuits. Neuropathic pain may be spontaneous or caused by contact with something that normally wouldn't be painful. Idiopathic pain is similar to neuropathic pain but has no known trigger. It may occur all over the body—a condition known as fibromyalgia—or can be localized, such as with TMJD. Physicians treat neuropathic and idiopathic pain with the same arsenal of drugs they prescribe for nociceptive and inflammatory pain, as well as with stronger anticonvulsants and antidepressants that may provide some relief. But the pain rarely goes away.

Woolf likens the entire pain system to a fire alarm. "With nociceptive pain, there's a fire, the alarm goes off and you do something about it," he says. "With inflammatory pain, just the threat of a fire is enough to trigger the alarm while someone is healing. Neuropathic and idiopathic pain are like false alarms. The alarm goes off all the time, but there's no fire and nothing to heal. The alarm system is broken."

Unlike nociceptive and inflammatory pain, neuropathic and idiopathic pain don't happen to everyone. Around 10% to 50% of those who undergo such procedures as hernia repair and coronary bypass suffer chronic neuropathic pain, and the pain is severe for some 2% to 10%. Recent studies suggest that genetic makeup determines whether a patient will develop chronic pain, but much remains unknown.

Because the genes involved in pain sensitivity have just recently been discovered, preliminary findings have yet to be

replicated in large populations. Further complicating the search for answers is the dauntingly complex nature of pain genetics. Each type of pain—hot, cold, pinch, stab—may well be transmitted to the brain in a completely different manner, involving different genes and neurons. Yet these complexities may ultimately be a good thing, providing highly individualized targets for therapies, says Zubieta.

If that happens, it may be thanks in part to a study published in the journal *Science* in 2003 that ignited the field of pain genetics. The paper investigated whether a gene that codes for the manufacture of an enzyme called catechol-O-methyltransferase, or COMT, is involved in pain sensitivity. Researchers already had determined that COMT regulates such molecules as dopamine, epinephrine (adrenaline) and norepinephrine, all components of the endogenous opioid system—the pain-relief mechanism activated in response to a burn, stab or pinch. They also knew that a particular variant of the COMT gene, called met158, encodes a version of the COMT enzyme that works three to four times less well than the regular version in breaking down dopamine and epinephrine. (Met158 is a single nucleotide polymorphism, or SNP. Pronounced "snip," it's a small change in the DNA code that can alter a gene's function.)

Zubieta was curious to know whether people with met158 experienced pain differently than those with the regular version of the gene. So he tested the DNA of 29 subjects to determine which version of COMT they had. Then he injected hypertonic saline into their jaw muscles—causing deep, sustained muscle pain—and ran them through a PET scanner to observe their brain activity. Zubieta found that the brains of one in four subjects who had two copies of the met158 SNP—one inherited from each parent—showed less activation of the opioid system, and the subjects reported more pain.

Two years later Luda Diatchenko, a geneticist at the University of North Carolina at Chapel Hill, built on Zubieta's work. Diatchenko and William Maixner, head of the UNC Center for Neurosensory Disorders, recruited 202 healthy female volunteers for pain-sensitivity experiments. Researchers pressed the skin of their cheeks, forearms and feet with a thermal cylinder resembling a car's cigarette lighter, measuring how long it took the subjects to say the cylinder was hot. The researchers



## An Imperfect Arsenal //

**Analgesics for nociceptive and inflammatory pain work fairly well, but those for chronic neuropathic and idiopathic pain often fail patients. And given that side effects can be significant and that morphine has no effect on some people, treatments are sorely limited.**

| Drug Type | Pain Target | How It Works | Possible Side Effects |
|---|---|---|---|
| **OPIATES:** include morphine, codeine, oxycodone | Nociceptive, inflammatory; some neuropathic, idiopathic pain relief | Activates the mu-opioid receptor system | Drowsiness, nausea and vomiting, constipation, dependence |
| **NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS):** aspirin, ibuprofen, naproxen | Inflammatory pain | Dampens the body's inflammatory response by inhibiting COX-2 enzyme (COX-1 is inhibited as well) | Ulcers because of COX-1 inhibition, gastric hemorrhage, Reye's syndrome in children (aspirin) |
| **COX-2 INHIBITORS:** celecoxib | Inflammatory pain, especially arthritis | An NSAID; inhibits only COX-2 enzyme | With long-term use, possible increase in risk of heart attacks and stroke |
| **PARACETAMOL/ACETAMINOPHEN** | Mild acute pain | Activates cannabinoid receptors | Liver damage |
| **ANTICONVULSANTS:** carbamazepine, pregabalin, gabapentin, lamotrigine | Some neuropathic and idiopathic pain | Dampens the excitability of the central nervous system | Dizziness, drowsiness, vomiting |
| **TRICYCLIC ANTIDEPRESSANTS:** amitriptyline | Some neuropathic and idiopathic pain | Inhibits reuptake of certain neurotransmitters | Vomiting, drowsiness, anxiety, insomnia, headaches |
| **SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIS):** duloxetine | Some neuropathic and idiopathic pain | Inhibits reuptake of certain neurotransmitters | Upset stomach, nausea, dry mouth, constipation |
| **DRUG MIXTURES:** acetaminophen + oxycodone = Percocet; hydrocodone + acetaminophen = Vicodin | Moderate acute pain | Travels various pathways to attack pain | Various, depending on mixture |

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also applied pressure to different muscles, to measure the kilograms of force required for subjects to register pain. They tested how painful the hot cylinder became over time with 15 heat pulses at 53°C (127°F) to the same part of the hand. And they examined deep-muscle pain, using an arm cuff similar to those for measuring blood pressure.

After combining the subjects' responses to all these stimuli into a single pain-sensitivity measurement, the researchers sampled the subjects' DNA, testing not only for met158 (as Zubieta did) but also for five other SNPs from other parts of the COMT gene. Diatchenko found that certain groupings of these six SNPs—combinations known as haplotypes—were linked more closely to pain sensitivity than was any single gene variant. Almost four in 10 subjects had a haplotype strongly associated with low pain sensitivity (Lv), 49% had a haplotype linked to average sensitivity (Av) and 11% had the Hv haplotype, for high sensitivity. Women with the Lv haplotype also had higher levels of the COMT enzyme (encoded by the COMT gene) and were 2.3 times less likely to develop TMJD.

In a follow-up study, Diatchenko found that although people with the Lv haplotype felt less pain in general than did those with other combinations of SNPs, the difference was greatest for thermal pain. In addition, she discovered that Zubieta's met158 SNP was, by itself, strongly associated with pain that increased over time—those 15 pulses of heat became successively more painful for people with met158. (That was in line with Zubieta's findings, in which subjects with met158 felt more pain only if it was sustained for 10 to 20 minutes.)

Why do high levels of the COMT enzyme, such as those found in subjects with the Lv haplotype, dampen sensitivity to pain? In experiments with rats, Diatchenko and Andrea Nackley homed in on adrenergic receptors, proteins in neurons that bind to molecules such as adrenaline and may trigger a stress response. Previous studies had linked these receptors to pain, especially that caused by rheumatoid arthritis. When the researchers blocked beta 2- and beta 3-adrenergic receptors, COMT no longer affected pain sensitivity, suggesting a specific target for pain treatment. Zubieta found another target in 2003 when he determined that the mu-opioid pathway (the brain's internal reward system) is involved with COMT's effects, though it's not yet clear exactly how the two pathways relate.

Other studies in this young field suggest that COMT may not play a role in all types of pain. For example, a 2004 National Institute of Dental and Craniofacial Research (NIDCR) study of 500 people found no link between met158 and sensitivity to heat and cold, and the following year Spanish researchers could find no connection between met158 and sensitivity to neuropathic pain. And recently, a group from Norway determined that met158 was not associated with chronic musculoskeletal complaints or migraines. These divergent results might be

explained by differences in the duration of the pain administered, the circumstances (whether the pain was inflicted in a lab or occurred after an operation) and the types of stimuli. Larger studies, Zubieta says, should help explain these discrepancies.

Researchers have known about COMT for a few years, but the pain gene Woolf and his colleagues reported in November 2006 came as a surprise. Because Woolf is interested in neuropathic pain, he injured the sciatic nerve of a rat, then looked for genes activated in response. He found 1,500—far too many to study—so he examined only those that stayed turned on six weeks after the injury (and thus seemed to be involved in chronic pain). He further narrowed the study by limiting it to genes linked in some way, assuming that there were major pathways with multiple genes that perpetuated chronic pain. There were three, one of which was GTP cyclohydrolase (GCH1). GCH1 raises levels of tetrahydrobiopterin (BH4), a molecule that helps enzymes make important neurotransmitters such as serotonin and dopamine, and Woolf found that the gene also strongly modulates pain sensitivity. "If we blocked synthesis of BH4, you got pain reduction, and if we added BH4, it produced pain," Woolf says. BH4 turned out to be implicated in inflammatory pain as well.

Turning back to humans, Woolf enlisted neurologist Mitchell Max at the NIDCR. Max screened the blood of 168 back-surgery patients for the three pain genes Woolf had investigated in rats to see whether haplotypes of those genes were associated with more or less chronic pain following surgery. He found that one GCH1 haplotype was highly associated with lower levels of persistent leg pain. Then Max and Roger Fillingim at the University of Florida tested a set of healthy people for the pain-protective GCH1 haplotype and discovered that those with two copies (one from each parent) were less than normally sensitive to thermal, mechanical and deep-muscle pain.

Armed with new knowledge about the workings of COMT and GCH1, researchers have begun to develop drugs to treat pain. Woolf has filed for a patent on his work on GCH1 and is working with a Boston startup called Solace Pharmaceuticals (Woolf is a stakeholder in the company) to find ways to manipulate levels of BH4 in the body to reduce neuropathic and perhaps inflammatory pain. But he'll have to find a drug that modulates BH4 without destroying its beneficial effects, including regulating dopamine and serotonin, which affect mood and movement, among other things.

Another potential use of the work on pain genes would be to screen patients about to go under the knife for genes that may predispose them to greater neuropathic pain. That would alert anesthesiologists and surgeons to take extra care to avoid nerves and provide adequate medication. In that way, Woolf thinks, neuropathic pain might someday be avoided completely. "We'll identify who's at risk and treat them very aggressively when they have surgery or get an attack of shingles," he says.

Meanwhile, Diatchenko's discovery that COMT works via the beta 2- and beta 3-adrenergic receptors has led her to consider drugs already on the market that block beta adrenergic receptors. Some have been used successfully to treat migraines and fibromyalgia, but have many side effects, such as depression and asthma. Medications that target just the beta 2 and beta 3 receptors might avoid some of those problems.

Much more research is needed before better pain drugs come on the market or before everyone can be tested for genetic sensitivity to pain. Diatchenko is doing some of that work, sharing a $19 million National Institutes of Health grant with researchers at four sites to follow 3,200 people for seven years to see which ones develop TMJD. The researchers will then assess the subjects' genes and other risk factors to try to determine why this condition struck them.

Such work, Woolf thinks, will ultimately lead to the creation of different drugs for people who have different types of pain, and that should have a profound effect on the lives of the millions like Terrie Cowley, who now, all too often, are told their trouble is all in their heads. "Instead of blaming people for their pain, we'll be able to say, 'You do feel more pain,'" notes Woolf. "And we'll be able to do something about it." ■



## DOSSIER


1. **"COMT val158met Genotype Affects mu-Opioid Neurotransmitter Responses to a Pain Stressor," by Jon-Kar Zubieta et al., *Science*, Feb. 21, 2003.** In one of the first papers linking human pain to a particular gene, Zubieta details his elegant experiment and uncovers a possible target for future pain medications.
2. **"Feeling Pain? Who's Your Daddy...," by Gavril W. Pasternak and Charles E. Inturrisi, *Nature Medicine*, November 2006.** A commentary on Clifford Woolf's pivotal finding that pain is partly in your genes, this paper provides an excellent description of neuropathic pain and how Woolf's discovery may be a major step toward preventing such pain.
3. **"One Size Does Not Fit All," by Ruth Landau, *Anesthesiology*, August 2006.** An editorial that discusses the genetic reasons why certain painkillers don't work very well in some of us.