MEDICAL DISPATCH

THE PAIN PERPLEX

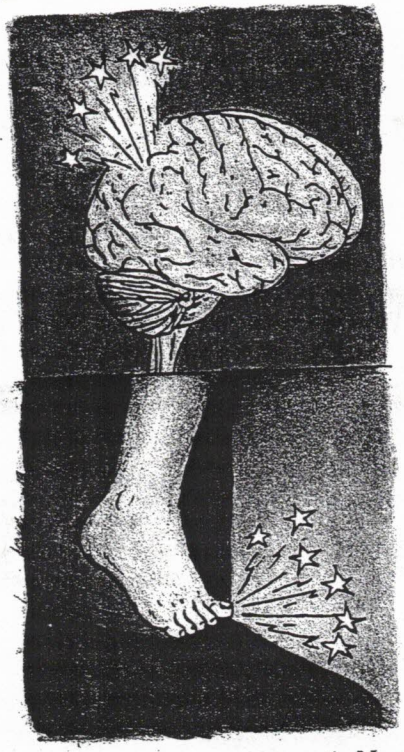
In the long search for the origin of pain, a new theory has emerged that might explain one of medicine's greatest mysteries.

BY ATUL GAWANDE

EVERY pain has a story, and the story of Rowland Scott Quinlan's goes back to an accident that happened ten years ago, when he was fifty-six. A Boston architect with a shock of white hair and a predilection for bow ties and Dutch cigarillos, Quinlan headed a thriving Beacon Street firm in his name, and had designed such buildings as the University of Massachusetts Medical School. Then, in March of 1988, he fell off a plank at the construction site of another of his commissions—a pavilion at the Franklin Park Zoo. His back was fine, but he dislocated and fractured his left shoulder, and it required several operations. In the fall, he returned to his drafting table, and there he was hit by a spasm of pain like a writhing snake in his back. The attacks recurred, and although at first he tried to ignore them, they soon became unbearable. More than once, while he was standing with a client the back pain suddenly burst forth and it was all he could do to keep from crying out while the client caught him and helped him to a seat or to the floor. Sitting in a restaurant with a colleague, he was overcome by pain so severe that he vomited right there at the table. Soon he wasn't able to work more than two or three hours a day, and he had to give up the firm to his partners.

Quinlan's orthopedist had some X-rays taken. They revealed little—perhaps a bit of arthritis, but nothing out of the ordinary. So Quinlan was sent to a pain specialist, who injected a long-needle syringe full of steroids and local anesthetic into his spine. The first few of these epidural injections worked for days, sometimes weeks, but subsequent shots provided steadily diminishing relief, until they didn't work at all.

Quinlan has been a patient at the Brigham and Women's Hospital, in Boston, where I work, and I had seen his most recent C.T. scan along with a sheaf of other tests and medical images. Nothing in them would have led me to expect the severity of his back pain: there was no fracture, no tumor, no infection, not even a sign of arthritic inflammation. The vertebrae were aligned



perfectly, like checkers in a stack. None of the soft gel-like disks that sit like cushions between the vertebrae had ruptured. In the lower back, the so-called lumbar spine, two disks bulged a bit, but that is common in men of his age, and the bulges didn't seem to be pressing against any nerves. Even a surgical resident like me could see that there was no cause for operating on this back. When doctors encounter a patient who has chronic pain without physical findings to explain it—and such patients are exceedingly common—we tend to be dismissive. It's all in the head, we're apt to conclude: not a physical pain but a different, somehow less real, "mental" pain. In fact, Quinlan's orthopedist recommended that he see a psychiatrist as well as a physical therapist.

When I visited Quinlan at his home, in the seaside village of Newburyport, Massachusetts, I found him at what turned out to be his usual perch: a worktable in the kitchen facing a wall-length window with a view of a small garden. Blueprints of unfinished projects were curled up in rolls on the table. A telephone headset lay to one side. A dozen different kinds of drawing pens, along with small rulers and a protractor, sat in a holder. He grimaced as he rose to greet me. I thought about his thorough medical workup and those clean images of his spine: Was he faking it?

When I asked him, he smiled wanly, and told me he sometimes wondered that himself. "I've got it pretty cushy here," he said. Quinlan has handicap license plates, financial security, and none of the pressures of running a business, and if he doesn't want to do something he merely has to say his back is killing him. But, despite a patch on his arm that infuses high doses of the narcotic fentanyl through his skin twenty-four hours a day, he can't do even the simplest thing—stand in a line, walk up stairs, or even sleep more than four hours at a stretch—without the acute sensation that, as he puts it, "someone is wringing out a muscle in my back."

I asked his wife, Sue, who is a tall woman several years younger than he is, and has fine features and sad eyes, if she ever thought he fakes the pain. She told me that day in and day out for a decade now she has seen the pain and lived with the increasing limits it places on his life and hers. She has seen the pain defeat him in ways that she knows he is too proud to fake. He'll try to carry the groceries, and then, shamefaced, have to hand them back a few moments later. Though he loves movies, they have not been to the cinema in years. There have been times when the pain of movement has been so severe that he has soiled his pants rather than make his way to the bathroom.

Yet there are aspects of the pain that puzzle her, and make her wonder whether it is in some respects "in the head." She notices that when he is anxious or irritable, the pain is worse, and that when he is in a good mood or is simply distracted the pain can disap-

JONATHON ROSEN

pear. He has bouts of depression which seem to bring on terrible spasms almost regardless of what he is doing physically. Like his physicians, she wonders how a pain can be so incapacitating yet arise from no identifiable physical abnormality. And what about the circumstances that tend to bring on an attack—a mood, a thought, sometimes nothing at all? These traits strike her as unusual, as needing explanation. But the disturbing truth is that Scott Quinlan isn't unusual. Among chronic pain sufferers, his case is altogether typical.

DR. EDGAR ROSS, a forty-four-year-old anesthesiologist, is the director of the chronic-pain treatment center at my hospital, where Quinlan is seen. Patients come to Dr. Ross with every imaginable kind of pain: back pain, neck pain, arthritic pain, total-body pain, neuropathic pain, AIDS-related pain, pelvic pain, chronic headaches, cancer pain, phantom-limb pain. Often, they have already seen numerous doctors and tried multiple therapies, including surgery, to no avail.

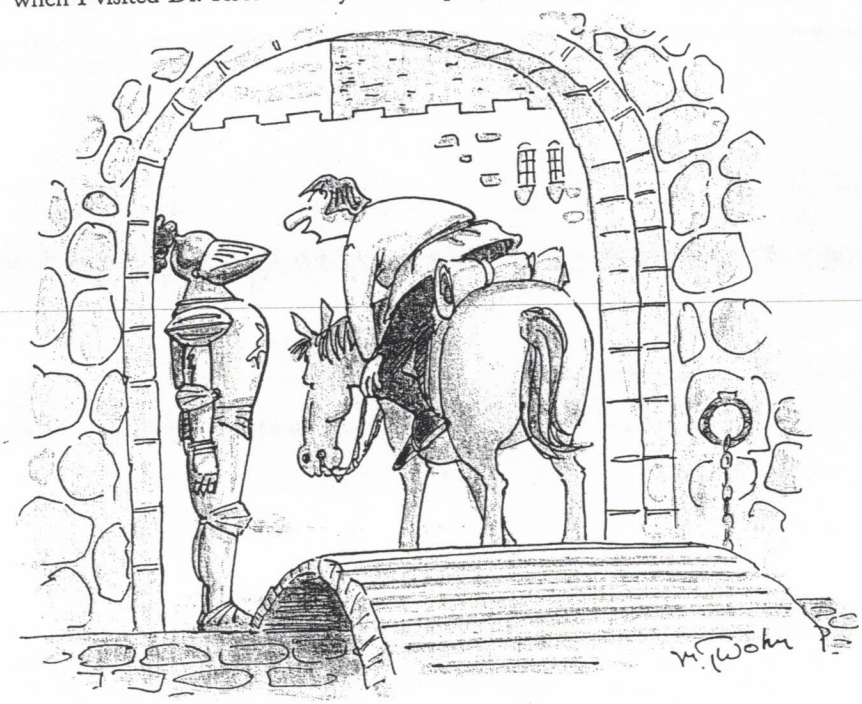
The center's waiting room looks like any other doctor's office. It has the flat blue carpet, the dated magazines, the row of expressionless patients sitting silently against the wall. A glass case displays recent thank-you letters. But when I visited Dr. Ross recently I noticed that the letters were not quite the typical testimonials that doctors like to put up. These patients did not thank the doctors for a cure. They thanked the doctors merely for taking their pain seriously—for believing in it. The truth is that doctors like me are grateful to the pain specialists, too. Though we want to be neutral in our feelings toward patients, we'll admit among ourselves that chronic-pain patients are a source of frustration and annoyance: presenting a malady we can neither explain nor alleviate, they shake our claims to competence and authority. We're all too happy to have someone like Dr. Ross to take these patients off our hands.

Ross led me into his office. Softspoken and unhurried, he has a soothing demeanor that fits perfectly with his line of work. Quinlan's kind of problem, he told me, is the one he sees most frequently. Chronic back pain is now second only to the common cold as a cause of lost work time, and it accounts for some forty per cent of workers'-compensation payments. In fact, there is a veritable epidemic of back pain in this country today, and nobody can explain why. By convention, we think of it as a mechanical problem, the result of misplaced stress on the spine. We therefore have had some sixty years of workplace programs, and now there are even "back schools," which teach the "correct way to lift." Despite the fact that the number of people who engage in manual labor has steadily declined, however, more people have chronic back pain than have ever had it before.

The mechanical explanation is almost certainly wrong, Ross noted. It's true that lifting something the wrong way can cause a muscle pull or a slipped disk. But that sort of strain occurs in almost everyone at some time, and in most people it never becomes a persistent problem. Studies have looked for physical factors that can predict which acute back injuries will evolve into chronic back pain, but they haven't found any. For instance, doctors used to assume that damaged disks were associated with pain, but recent findings have not borne this out. Spinal M.R.I. scans show that most people *without* back pain have disk bulges. Conversely, a large percentage of patients with chronic back pain, like Quinlan, are found to have no structural lesion. And even among those with abnormalities there is no relation between the severity of the pain and the severity of the abnormalities.

If the condition of your back doesn't predict whether you'll get chronic back pain, what does? Well, it's the mundane stuff that neither doctors nor patients much like to consider. Studies point to such "inorganic" factors as loneliness, involvement in litigation, receipt of workers' compensation, and job dissatisfaction. Consider the epidemic of back pain in the medical profession itself. Disability insurers once saw doctors as ideal customers. Nothing stopped doctors from working—not years of stooping over operating tables, not arthritis, not even old age. Insurers used to try to outbid one another with cheap rates and generous benefits to attract their business. In the last few years, however, the number of doctors with disabling back or neck pain has risen dramatically. Needless to say, doctors aren't suddenly being required to carry heavy packages around. But one known risk factor has been identified: with the growing role of managed care, job satisfaction in the medical profession has plunged.

THE explanation of pain which has dominated much of medical history originated with René Descartes, more than three centuries ago. Descartes proposed that pain is a purely



"A large Coke and an order of fries."

physical phenomenon—that tissue injury stimulates specific nerves that transmit an impulse to the brain, causing the mind to perceive pain. The phenomenon, he said, is like pulling on a rope to ring a bell in the brain. It is hard to overstate how ingrained this account has become. Twentieth-century research on pain has been devoted largely to the search for and discovery of pain-specific nerve fibres (now named A-delta and C fibres) and pathways. In everyday medicine, doctors see pain in Cartesian terms—as a physical process, a sign of tissue injury. We look for a ruptured disk, a fracture, an infection, or a tumor, and we try to fix what's wrong.

The limitations of this mechanistic explanation, however, have been apparent for some time. During the Second World War, for example, Lieutenant Colonel Henry K. Beecher conducted a classic study of men with serious battlefield injuries. In the Cartesian view, the degree of injury ought to determine the degree of pain, rather like a dial controlling volume. Yet fifty-eight per cent of the men—men with compound fractures, gunshot wounds, torn limbs—reported only slight pain or no pain at all. Just twenty-seven per cent of the men felt enough pain to request pain medication, although such wounds routinely require narcotics in civilians. Clearly, something that was going on in their minds—Beecher thought they were overjoyed to have escaped alive from the battlefield—counteracted the signals sent by their injuries. Pain was far more complex than a one-way transmission from injury to "ouch."

In 1965, the Canadian psychologist Ronald Melzack and the British physiologist Patrick Wall proposed that the Cartesian model be replaced with what they called the gate-control theory of pain. Melzack and Wall argued that before pain signals reach the brain they must first go through a gating mechanism in the spinal cord which could ratchet them up or down. In some cases, this hypothetical gate could simply stop pain impulses from getting to the brain. In fact, researchers soon identified a gate for pain in a portion of the spinal cord called the dorsal horn. The theory explained such ordinary puzzles as why rubbing a painful foot makes it feel better. (The rubbing sends signals to the dorsal horn which close the gate to nearby pain impulses.)

Melzack and Wall's most startling suggestion was that what controlled the gate was not just signals from sensory nerves but also emotions and other "output" from the brain. They were saying that pulling on the rope need not make the bell ring. The bell itself—the mind—could stop it. Their theory prompted a great deal of research into how factors such as mood, gender, and beliefs influence the experience of pain. In one study, for example, researchers measured pain threshold and tolerance levels in fifty-two dancers from a British ballet company and fifty-three university students using a standard method called the cold-pressor test. The test is ingeniously simple. (I tried it at home myself.) After immersing your hand in body-temperature water for two minutes, to establish a baseline condition, you dunk your hand in a bowl of ice

ISLAND IN THE CHARLES

By being scholar first of that new night.
—Richard Crashaw

Taking the well-worn path in the mind though dusk encroaches
upon the mind, taking back alleys careful step by step
past parked cars and trash containers, three blocks to the concrete ramp
of the footbridge spanning the highway with its rivering, four-lane
unstaunchable traffic, treading on shadow and slant broken light,

my mother finds her way. By beer bottles, over smeared
Trojans, across leaf muck, she follows the track, clutching her
jacket close. The footbridge lofts her over the flashing cars
and sets her down, gently, among trees, where she is a child
in the weave of boughs, and leaf shapes plait the breeze.

She fingers silver-green blades of the crack willow, she tests dark grooves
of crack-willow bark. The tree has a secret. Its branches pour
themselves back toward earth, and my mother pauses, dredging a breath
up out of her sluggish lungs. The blade leaves scratch
her fingertips, the corrugated bark

releases a privacy darker than cataract veils.
But slashed and ribboned, glimpsed through fronds,
the river hauls its cargo of argent light
and she advances, past basswood and crab-apple clumps
along the tarmac where cyclists, joggers, rollerbladers

entranced in their varying orbits swoop
around her progress. With method, she reaches her bench,
she stations there. She sits columnular, fastened
to her difficult breath, and faces the river in late afternoon.
Behind her, voices. Before her, the current casts its glimmering

seine to a shore so distant no boundary scars
her retina, and only occasional sculls or sailboats flick
across her vision as quickened, condensing light.
There she sits, poised, while the fluent transitive Charles
draws off to the harbor and, farther, to the unseen sea

until evening settles, and takes her in its arms.

—ROSANNA WARREN

water and start a clock running. You mark the time when it begins to hurt: that is your pain threshold. Then you mark the time when it hurts too much to keep your hand in the water: that is your pain tolerance. The test is always stopped at a hundred and twenty seconds, to prevent injury.

The results were striking. On the average, female students reported pain at sixteen seconds and pulled their hands out of the ice water at thirty-seven seconds. Female dancers went almost three times as long on both counts. Men in both groups had a higher threshold and tolerance for pain—as expected, since studies show women to be more sensitive than men to pain, except during the last few weeks of pregnancy—but the difference between male dancers and male nondancers was nearly as large. What explains the difference? Probably it has something to do with the psychology of ballet dancers—a group distinguished by self-discipline, physical fitness, and competitiveness, as well as by a high rate of chronic injury. Their driven personalities and competitive culture evidently inure them to pain: that's why they are able to perform through sprains and stress fractures, and why half of all dancers develop long-term injuries. (Similar to other nondancing males, I started to feel pain at around twenty-five seconds; but I had no trouble keeping my hand in for the whole hundred and twenty seconds. I will let others speculate on what this says about the submissiveness inculcated in surgical residents.)

Other studies along these lines have shown that extroverts have greater pain tolerance than introverts, that drug abusers have low pain tolerance and thresholds, and that, with training, one can diminish one's sensitivity to pain. There is also striking evidence that very simple kinds of mental suggestion can have powerful effects on pain. In one study of five hundred patients undergoing dental procedures, those who were given a placebo injection and reassured that it would relieve their pain had the least discomfort—not only less than the patients who got a placebo and were told nothing but also less than the patients who got a real anesthetic without any reassuring comment that it would work. Today, it is abundantly evident that the brain is actively involved in the experience of pain, and is no mere bell on a string. Today, every medical textbook teaches the gate-control theory as fact. There's a problem with it, though. It doesn't explain people like Scott Quinlan.

Gate-control theory accepts Descartes's view that what you feel as pain is a signal from tissue injury transmitted by nerves to the brain, and it adds the notion that the brain controls a gateway for such an injury signal. But in the case of Quinlan's chronic back pain where is the injury? Or take something like phantom-limb pain. After amputation of a limb, most people suffer a period of constant, intractable burning or cramping that feels exactly as if the limb were still there. Without a limb, however, there are no nerve impulses for the gate to control. So where does the pain come from? The rope and the clapper are gone, but the bell can still ring.

ONE spring day in 1994, Dr. Frederick Lenz, a neurosurgeon at the Johns Hopkins Hospital, brought to his operating table a patient suffering from severe hand tremors. The patient, whom I'll call Mark Taylor, was only thirty-six, but over the years his hands had come to shake so violently that the simplest of tasks—writing, buttoning his shirt, drinking from a glass, or typing on his keyboard at his job as a purchasing agent—grew absurdly difficult. Medications failed, and he lost jobs more than once because of his difficulties. Desperate for a return to a normal life, he agreed to a delicate procedure: brain surgery that would destroy cells in a small structure called the thalamus, which was already known to contribute to such excessive stimulation of the hands.

Taylor had another big problem, though: for seventeen years, he had struggled with a panic disorder. At least once a week, while he was working at his terminal or at home in the kitchen feeding a child, he would suddenly be overcome by severe chest pains, as if he were having a heart attack. His heart would pound, his ears would ring; he would grow short of breath and would have an overwhelming urge to escape. Nevertheless, a psychologist whom Lenz consulted assured him that the disorder was unlikely to hinder the operation.

Initially, Lenz says, everything went as he had expected. He injected a local anesthetic—the operation is done with the patient awake—and burred a small opening in the top of Taylor's skull. Then he cautiously inserted a long, thin electrical probe deep inside, right down into the thalamus. Lenz talked to Taylor the whole time, asking him to stick out his tongue, to move a hand, to do any of a dozen other tasks that showed he was all right. The danger in this type of surgery is that it might destroy the wrong cells: the thalamic cells involved in tremor lay just fractions of a millimetre away from cells that are essential for sensation and motor activity. So before cauterizing with a second, larger probe, the surgeon had to find the right cells by stimulating them with a gentle electric pulse. The probe was in a portion of Taylor's thalamus which Lenz labelled Site 19, and he zapped it with low voltage. He had been here a thousand times before, and typically, he told me, the site produces a prickle in the forearm. Sure enough, this is what Taylor felt. Lenz then zapped an adjacent area he labelled Site 23, where stimulation generally produces a rather ordinary sensation in the chest, usually a mild tingling. But this time Taylor cried out. It was, he said, his all too familiar chest pain, and with it came a mounting sense of suffocation and fear—all the symptoms of his panic attacks. Lenz stopped the stimulation. The pain disappeared, and Taylor immediately calmed down. Lenz zapped Site 23 again, producing exactly the same effect. He apologized for the discomfort and moved on until he found the cells controlling Taylor's tremor and cauterized them: the operation was, in fact, a success.

Yet, even as Lenz completed the procedure, his mind was racing. Only once before had he seen anything like this effect. It was in a sixty-nine-year-old diabetic woman, with a long history of anginal pain that came on with exertion. While Lenz was performing a similar operation on her, he found that stimulating much the same microscopic section of her brain brought on her familiar chest pain, just as it did with Tay-

lor: this was a sensation she described as "deep, frightful, squeezing." The implications might have easily been lost, but Lenz was known for his research on pain and realized that he had witnessed an astonishing effect. As he later noted in the journal *Nature Medicine*, the response in these two patients was wildly out of proportion to the stimulus. What in most people produces no more than a tingle was torture to them. Lenz saw that areas of the brain governing ordinary sensations could become abnormally sensitized—set to fire in response to perfectly harmless stimuli. In the woman's case, it seemed that the nerve input from her diseased heart had done it to her. In Taylor's case, by contrast, the pain was associated not with any bodily damage but with his panic disorder, his abnormal psychology. Lenz's findings suggest that *all* pain is "in the head"—and that sometimes, as in the cases of Scott Quinlan and Mark Taylor, a physical injury isn't needed to make a pain system go haywire.

"Please listen carefully to the available options."

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This is the newest theory of pain. Its leading proponent is, once again, Melzack, who abandoned gate-control theory in the late nineteen-eighties and began telling incredulous audiences to revise their understanding of pain once again. Given the evidence, he now says, we should stop thinking that pain or any other sensation is a signal passively "felt" in the brain. Yes, injury produces nerve signals that travel through a spinal-cord gate, but it is the brain that generates the pain experience, and it can do so even in the absence of external stimuli. If a mad scientist reduced you to nothing but a brain in a jar, Melzack says, you could still feel pain—indeed, you'd have the full range of sensory experience.

According to the new theory, pain and other sensations are conceived as "neuromodules" in the brain—something akin to individual computer programs on a hard drive, or to tracks on a compact disk. When you feel pain, it's your brain running a neuromodule that produces the pain experience, as if someone pressed the "play" button on a CD player. And a great many things can press the button. The way Melzack explains it, a pain neuromodule is not a discrete anatomical entity but a network, linking components from virtually every region of the brain. Input is gathered from sensory nerves, memory, mood, and other centers, like members of some committee in charge of whether the music will play. If the signals reach a certain threshold, they trigger the neuromodule. And then what plays is no one-note melody. Pain is a symphony—a complex response that includes not just a distinct sensation but also motor activity, a change in emotion, a focussing of attention, a brand-new memory.

Suddenly, a simple toe-stubbing no longer seems so simple. In this view, the signal from the toe still has to make it through the spinal-cord gate, but thereafter it joins a lot of other signals in the brain—distractions, memories, anticipation, mood. They generally combine to activate a toe-pain neuromodule. In some people, however, the physical stimulus is cancelled out, and the stubbed toe is hardly noticed. There's nothing surprising here so far. But now we can imagine—and this is the most radical implication of Melzack's ideas—that the same neuromodule can go off, generating genuine toe pain, without a toe's having been stubbed. The neuromodule could—like Site 23 in Mark Taylor's brain—become primed like a hair trigger. Then virtually anything could set it off: a mere touch, fear, frustration, or simply a memory.

"Inorganic" factors don't dictate inorganic solutions, to be sure, and the new theories have helped give direction to the pharmacology of pain. For pharmacologists, the Holy Grail of chronic-pain treatment is a pill that would be more effective than morphine but lack its side effects, such as dependence, sedation, and motor impairment. If an overactive neuronal system is the problem, then what one needs is a drug that will damp it down. That's why, in what a decade ago might have seemed a strange development, pain specialists increasingly prescribe anti-epileptic drugs,