Nearly everyone has stubbed a toe or skinned a knee. The pain may be severe, but most of the time it is fleeting. In some people, however, the pain persists for months, even years, and becomes debilitating. On a balmy evening about a year ago, a woman I will call Barbara was strolling in Manhattan when her foot caught the curb as she crossed a street, and she fell face down on the pavement. A jogger helped her up, and she hobbled the few blocks to her apartment. Her left knee was bright red and extremely sore. Over the next few days, it turned black-and-blue, and the pain did not subside. Instead of the dull discomfort typical of a bruise, Barbara felt as though she had a “violent toothache” in her knee. She cut holes in her sheets to prevent them from touching the skin around the injury. Even the breeze over her knee from the air-conditioner was excruciating.

Barbara is in her early sixties, a trim, poised woman, who grew up in California riding horses and swimming in the ocean. In New York, she played tennis and worked out at the gym. But two weeks after her accident she still could not bend or straighten her left leg without intolerable pain. Unable to sleep, she spent hours each night leaning over a counter in the kitchen, shifting her weight from one foot to the other, or slumped on a sofa in the living room, gingerly holding her injured knee in front of her chest. She saw an orthopedic surgeon, who ordered an X-ray of her leg, which showed that she did not have a fracture. He told her to be patient and the wound would soon heal. A month later, she consulted a second orthopedic surgeon, an expert in sports injuries. He performed an MRI scan of the knee, which revealed no abnormalities. Nevertheless, he speculated that cartilage fragments might have broken off the kneecap and lodged in the joint. He recommended an arthroscopic lavage—a procedure in which doctors use a fibre-optic instrument to peer inside the knee and flush out debris. Barbara decided to seek another opinion. A third orthopedist told her that he could not explain her symptoms, and prescribed a potent narcotic. By this time, she had stopped going to movies and restaurants. She had a subscription to the Metropolitan Opera, but that fall she did not attend a single performance. “I couldn’t risk even letting my knee touch the seat in front of me, or having someone brush my leg while coming down the aisle,” she said. Finally, she consulted a neurologist. He gave her a different painkiller.

When I met Barbara, in January, she reached into her purse and pulled out a plastic bag full of medications: Vicodin, Darvocet, Ultracet, doxepin, naproxen, and Mobic. She said that the drugs made her feel “dopey” and “weird,” and provided only brief pain relief. But at least now Barbara had a diagnosis. Shortly before Thanksgiving, she had consulted a physical therapist she had once seen for a torn hamstring. The woman examined her knee and told her that she probably had reflex sympathetic dystrophy, or R.S.D. “I had no idea what she was talking about,” Barbara said. “I went to the Internet to see what the devil this was.”

R.S.D. patients are often dismissed as “neurotic,” a doctor said, until you meet them.
Wynne,” about the experiences of a Philadelphia Quaker during the American Revolution, published in the late eighteen-nineties.) Mitchell was renowned for his studies of the human nervous system and for his “rest cure,” a regimen involving bed rest, massage, and a high-calorie diet, which he prescribed for women suffering from nervous disorders. (His patients included Charlotte Perkins Gilman, whose short story “The Yellow Wallpaper,” about a woman’s gradual descent into madness under the oppressive ministrations of her physician husband, was inspired by his treatment.) During the Civil War, he had served as a surgeon for the Union Army and had treated soldiers wounded by bayonets, sabres, and bullets. Some continued to complain of severe pain long after their injuries—typically in an arm or a leg—had healed, and Mitchell noticed that these men had other symptoms in common: burning pain, accompanied by swelling, redness, and temperature fluctuations in the injured limb. One of his patients was a seventeen-year-old soldier named David Schiveley, who had been shot in the right shoulder at the Battle of Gettysburg and later developed pain and redness in his left hand as well. “The left hand . . . is painful on pressure or touch, especially in the palm,” Mitchell wrote. “It is difficult even to examine him properly on account of his timidity, and his whole appearance exhibits the effects of pain . . . and want of rest.”

Mitchell called the cluster of symptoms that he observed “causalgia,” and he was evidently affected by his patients’ suffering. “Perhaps few persons who are not physicians can realize the influence which long-continued and unendurable pain may have on both body and mind,” he wrote. “Under such torments the temper changes, the most amiable grow irritable, the bravest soldier becomes a coward, and the strongest man is scarcely less nervous than the most hysterical girl.” Other physicians adopted the term causalgia to refer to a pain syndrome that occasionally developed in a limb after an injury or a medical procedure. In 1946, James Evans, a Boston physician, introduced the phrase “reflex sympathetic dystrophy” to describe a similar disorder in patients who had no discernible nerve damage, and in 1994 the International Association for the Study of Pain reclassified the disease as “complex regional pain syndrome,” or C.R.P.S., and distinguished between two types: C.R.P.S. Type 1, which occurs in the absence of a known nerve injury (what Evans called R.S.D.), and C.R.P.S. Type 2, which involves an injury to a major nerve. A 2002 World Institute of Pain report on C.R.P.S. noted that “excruciating pain is the hallmark of the disease.”

Some researchers estimate that R.S.D. occurs once for every two thousand physical traumas—the vast majority involving arms, hands, legs, or feet—and that each year as many as fifteen thousand Americans develop it. (According to the World Institute of Pain report, most R.S.D. patients—between sixty and eighty per cent—are women.) However, many doctors are unaware of the disorder, and some insist that it is primarily a psychiatric condition. Anne Louise Oaklander, an assistant professor of anesthesiology and neurology at Harvard Medical School, who studies patients with the syndrome, told me that she never learned about R.S.D. in medical school. “Patients with this were often dismissed as being ‘neurotic,’ ‘self-serving,’ or ‘somatizing,’” she said. “Then you meet them. You realize that they are reasonable people, and you see them in clinic periodically and it becomes clear that this is not a psychiatric disorder.” Oaklander believes that many cases of R.S.D. are “iatrogenic”— inadvertently caused by doctors—and arise after minor operations, such as arthroscopies of the knee, even when the procedure is performed correctly. “This is the disease that can happen to anyone,” she said. “It’s not like heart disease, where you stay slim, and you don’t smoke, and you exercise, and you can reduce the risks. There is no mammography that you can perform preventively. And sometimes it happens after the most seemingly innocent event, like slipping on the street. Virtue does not protect you.”

In order for us to feel pain, highly specialized nerves must be stimulated, and under normal conditions these are difficult to arouse. When we are exposed to intense heat, cold, irri-
tants, or pressure, nerve fibres called neurons respond by sending electrical impulses to the dorsal horn, a part of the spinal cord that acts as a relay station, transmitting the impulses to other neurons. Some neurons in the dorsal horn cause the impulses to become more powerful, or make more of them. Other neurons weaken the impulses, or reduce their number. Typically, only a small fraction of the impulses that enter the spinal cord make their way to the brain, where we experience them as pain.

Until the nineteen-eighties, scientists believed that pain impulses, whether they were triggered by a bacterial infection or a blow to the ribs, travelled along the same neural pathways to the brain. Over the past two decades, however, experiments first in rodents and then in human beings have revealed that the nervous system is much more malleable—or "plastic"—than it was previously thought to be. Clifford Woolf, a professor of anesthesia research at Harvard Medical School, who directs the Neural Plasticity Research Group at Massachusetts General Hospital, compares the nervous system to a computer. Normally, each neuron forms connections, called synapses, with thousands of other neurons, creating multiple pathways between the spinal cord and the brain. The path an impulse follows determines how we experience it—as throbbing pain or dull ache. The process, Woolf says, is like running "different software programs." When a nerve is injured, however, changes can occur in surrounding cells and synapses—in what Woolf calls the nervous system's "hardware." "The hardware change is a disease state," he says. "Pain is the disease."

Injured fibres may release small proteins that cause swelling, redness, and temperature fluctuations in surrounding tissue—symptoms that make R.S.D. easy to confuse with Lyme disease or lupus, an autoimmune disorder. In some patients, altered neurons in the spinal cord interact with nearby motor nerves, provoking muscle spasms, tremors, and dystonia, a condition characterized by involuntary muscle contractions. In the early nineteen-eighties, Woolf discovered that neurons in rats that had been repeatedly exposed to painful stimuli (such as intense heat) often began to react to innocuous stimuli (such as a light touch) as well, a phenomenon that he called "central sensitization" and which may explain the hypersensitivity to touch that frequently afflicts R.S.D. patients.

There is no consensus on how to treat R.S.D. Doctors currently choose from among more than twenty drugs and procedures, none of which have been approved for use with the disorder by the F.D.A. After Barbara's physical therapist told her about R.S.D., she met with Dr. Jeffrey Ngeow, an anesthesiologist and pain specialist at the Hospital for Special Surgery, in New York, who confirmed the diagnosis and proposed injecting anesthetic into the cluster of sympathetic nerves next to her spine. Such injections, commonly referred to as nerve blocks, have been administered to R.S.D. patients for decades, as a means of calming their nervous system—if only temporarily. Over the course of two weeks, Barbara received two nerve blocks in her lower back, and for a few days she felt better. Gradually, however, the anesthetic wore off and the pain returned. Discouraged, Barbara consulted an orthopedic surgeon at Ngeow's hospital, who said, "You don't have R.S.D. No more nerve blocks." He told her that she had a neuroma—a benign tumor made of nerve tissue—and persuaded Ngeow to inject anesthetic directly into her knee. The knee was numb for several hours, but soon the pain was worse than before; for several days, Barbara was unable to put any weight on her left leg. At a friend's insistence, she saw a neurologist at New York-Presbyterian Hospital, who performed a full-body CT scan and repeated the MRI scan of her knee. "He thought I had bone cancer," Barbara said. But the test showed no evidence of disease, and the neurologist told her that she probably had Lyme disease.

Barbara had been vaccinated against the disease, and told the doctor that the antibodies in her blood reflected this fact. She decided to return to Ngeow for more nerve blocks.

I met Barbara on the day that she was to receive her sixth injection. She was wearing a Lidoderm patch, which numbed the skin over her knee, and silk long johns to prevent her slacks from brushing against her leg. Over lunch, Barbara told me about a friend who she thought had probably had R.S.D. The woman had undergone numerous tests, all inconclusive, had been in constant pain, and had eventually committed suicide. Barbara began to cry. "When the pain rises up, I think it is not really worth living," she said.

Ngeow says that many of his patients who have received multiple injections are no longer in pain, but the treatment is controversial. "Nerve blocks can produce wonderful temporary relief," Oaklander told me. "And the physician has the satisfaction of knowing, as the patient walks out of the office, that he has relieved pain. But he has done no more to address the cause of the problem than if a dentist addressed an abscessed tooth only by putting in Novocain." For her R.S.D. patients, Oaklander frequently prescribes nortriptyline, an antidepressant that blocks nerve impulses. (There have been few significant clinical trials involving R.S.D. therapies, but in studies of other types of pain disorders, including shingles, nortriptyline has been shown to decrease discomfort significantly.)

Robert J. Schwartzman, a neurologist at Drexel University College of Medicine, in Philadelphia, who has treated more than five thousand people with R.S.D., is experimenting with a more radical approach to the disease. In 2001, he began collaborating with a team of anesthesiologists in Germany, whose patients included amputees suffering from phantom pain—sensations in the absent limb. The German doctors had discovered that they could reduce phantom pain by injecting the patients with ketamine, an anesthetic, and they had found that the drug was also effective for treating R.S.D. Over the past four years, Schwartzman has
sent twenty-five of his most debilitated patients—"They've tried narcotics, morphine pumps, every single pain thing we can think of," he says—to Germany, where they were injected with ketamine in doses large enough to sustain a coma for five days. The doctors hoped that the prolonged exposure to ketamine would block the receptors on neurons that transmit pain signals. "It's like rebooting the computer," Schwartzman says. "You turn off the receptors, and the system goes back to normal."

The therapy is risky. To minimize side effects, which include hallucinations, flashbacks, and memory loss, the doctors administer two other medications, clonidine and midazolam. ("Boosters" of the drugs—enough to cause sedation for several hours—are given in an outpatient setting at two weeks, one month, and three months after the initial treatment.) Of greater concern is the coma itself, which increases susceptibility to pneumonia, blood clots, and stroke; for this reason, patients are kept in an intensive-care unit throughout the procedure. According to Schwartzman, none of his patients who have received the treatment to date have suffered serious complications, and thirteen have undergone detailed cognitive assessments, which revealed no loss of brain function. Still, the therapy does not necessarily amount to a cure. "All come out of the coma with no pain," Schwartzman says. "But in fifty per cent of cases the pain comes back"—typically because the patient reinjures the limb.

Since 2002, Schwartzman has been treating patients at his clinic at Drexel with five- and ten-day courses of ketamine injections, in doses much smaller than those given in Germany. (So far, the medical-ethics committee at Drexel has not granted Schwartzman permission to treat patients to the point of coma.) In February, Barbara met Schwartzman at his office for a consultation and saw R.S.D. patients sedated in lounge chairs. Her internist had told her that if she took ketamine her brain might "never be the same," and she decided not to try a course of injections. Schwartzman has treated a hundred and thirty patients this way, and has twelve hundred more on a waiting list; it will take him four years to treat them all. Most patients report a dramatic reduction in pain for between three and eight months, he says, and for many that represents a significant respite.

One morning in March, at the Nerve Injury Unit that Oaklander runs at Massachusetts General Hospital, I met an R.S.D. patient I will call Elena. She had entered the police academy in her hometown, in western Massachusetts, at the age of forty-four, after bringing up several children, and she had been an officer on active duty for five years. During her spare time, she worked out, running and attending kickboxing classes for several hours a day, six times a week. One night in November, 2001, Elena had been patrolling bars in her town with seven other officers when a man with a history of assault-and-battery convictions punched one of her colleagues. Elena tackled the man. Then the other policemen piled on top of her, pinning her right forearm under the weight of their struggling bodies. Eventually, the suspect was subdued and handcuffed. Afterward, Elena recalled, "My arm felt heavy, as though I'd been working out at the gym with weights for hours." For several months, the discomfort persisted, and she sometimes felt a tingling sensation. In late March, 2002, she awoke from a deep sleep convinced that her house was on fire: her arm was burning. Her hand was hot, puffy, and purplish-red, and the veins had swollen so much that they looked like fingers. "I thought they were going to explode," Elena said. "I was so scared. It was as if I had the same pain as the night of the injury, and it had come back, only a hundred times worse." After a few hours, the swelling decreased and the pain began to subside. Her doctor sent her to a hand surgeon, and when she arrived for the appointment her hand was freezing. She told the surgeon that when the hand was hot and swollen the skin was too sensitive to touch. "He just said, 'R.S.D.,'" Elena said.

Oaklander gave Elena oxcarbazepine, an anti-seizure medication that decreases electrical activity in the nervous system, and calcitonin, a hormone that has been shown in clinical trials to reduce pain. But Elena experienced side effects from both drugs: the oxcarbazepine made her tired and agitated, and the calcitonin gave her nosebleeds. She then took nortriptyline for several months and is now undergoing physical therapy. She has not worked in a year and a half.

Oaklander believes that R.S.D. is caused by nerve injuries that are often...
too small to detect in standard exams, which enable doctors to measure the flow of electrical impulses along specific nerve pathways. "The conventional tests of nerve injury are usually useless," she said. However, R.S.D. can leave dramatic evidence in human tissue. In 1998, researchers in the Netherlands examined amputated legs from eight patients who suffered from severe R.S.D. The scientists found that the legs contained fewer than normal numbers of pain fibres—the neurons that fire to transmit pain signals. (The fibres degenerate when trauma damages the nerves.) Over the past several years, Oaklander has performed skin biopsies on eighteen patients with R.S.D. In all but one, she found that there were fewer pain fibres in the skin in the affected area than in skin elsewhere on the body. The difference was subtle—R.S.D. patients had an average of twenty-five per cent fewer pain fibres in the skin—but similar decreases in pain fibres have been observed in other diseases associated with chronic pain, including diabetes and shingles.

The experiment helped convince Oaklander that the distinction between the two types of C.R.P.S. is artificial. She believes that both represent a single neurological disease, in which nerve injuries may be tiny and hard to detect or large and easy to identify. When one of her R.S.D. patients fails to improve with medication, Oaklander considers two surgical options. The first, which is rarely used, involves cutting open the affected limb in order to examine the nerves and insure that no scar tissue impinges on them. The second entails implanting an electrical stimulator in the limb or near the spinal cord to send benign impulses at regular intervals along the injured nerve. Once the stimulator is implanted, the patient can turn it on or off by holding a special magnet over the skin, and some eventually find that they no longer need to turn it on. (Doctors don’t know why electrical stimulation is beneficial; the regular impulses may mimic the normal activity of the nerve, helping the brain and spinal cord to function normally.) Thousands of people have received stimulators, though complications, such as infection and electrode malfunction, are common.

Tim Connick, a fifty-year-old warehouse worker who lives in Lynn, Massachusetts, received a stimulator four years ago. In 1996, he fell from a loading dock and broke his heel. The bone split down the middle and shattered into thirteen pieces. He had surgery at Massachusetts General Hospital and started physical therapy. But he spent most of the day with his leg suspended in a sling, immobilized by pain. “I felt like someone had taken an open pair of scissors, jabbed it into my foot, and left it there," he said. Six months after his operation, he was getting two hours of sleep a night. He returned to work, where he was reassigned to a desk job, but his constant moaning disturbed his co-workers. While driving, he wrapped strands of hair around his index finger and pulled on the hair, which helped distract him from the pain in his foot and enabled him to focus on the road.

Eventually, Connick’s surgeon referred him to the pain clinic at Massachusetts General, where nortriptyline was prescribed, and he was given a series of nerve blocks. Neither treatment helped for long. Connick next tried gabapentin, which blocks the release of pain neurotransmitters in the brain, but after several months it became clear that the medication had not reduced his pain and was making him aggressive toward his wife and children. Connick also tried phenytoin, an anti-seizure drug. His pain abated slightly, but the medicine caused ringing in his ears and double vision. Four years after his accident, Connick returned to the pain clinic and asked his doctors to cut off his foot. They suggested another course of nortriptyline. “I said, ‘Stop!’ ” Connick recalled. “You’re going in circles.” He was eventually referred to Oaklander, who told him about the surgical options, emphasizing that neither was guaranteed to permanently eliminate the pain. Connick chose to have a stimulator implanted. The operation lasted less than an hour: an electrode was placed near the nerve that runs to the heel, and attached by a wire to a generator the size of a beeper, which was implanted under the skin at the abdomen. The next day, Connick took a walk on the hospital grounds, and, for the first time in five years, felt no pain. Two years ago, he returned to his job in the warehouse, where, he says, he is “making eighteen- and twenty-year-olds look like lazy bums.”

Oaklander believes that one of the reasons doctors disagree about how to treat R.S.D. may be that they are seeing patients at different stages of the disease. She says that some may have “acute” R.S.D., which spontaneously resolves after several weeks; in such cases, reports that nerve blocks and other drugs are beneficial may be misleading. “Early on, you can tell someone that he or she is probably going to do well,” she says. “But after a year the prognosis drops off.”

The extent to which the nervous system can repair itself—how plastic its hardware is—remains a mystery, but encouraging evidence continues to accumulate. Increasing numbers of stroke patients, especially younger ones, fully
recover with the help of drugs and physical therapy, and in healthy people the acquisition of new skills has been shown to alter brain circuitry. Recent studies using sophisticated imaging techniques reveal changes in the cerebral cortex of people learning specific tactile tasks, such as how to read Braille or play the violin. One of the patients in Oaklander’s skin-biopsy study had only three per cent of the normal total of small pain fibres in the skin of her injured leg. When Oaklander repeated the biopsy almost a year later, the number of fibres in the woman’s skin had increased to near normal levels. In separate studies published in 2002 and 2003, researchers in Finland and Germany conducted brain scans of eighteen R.S.D. patients who suffered from pain symptoms in one hand. Both groups found that the region of the cortex responsible for processing sensory data from the affected hand was markedly smaller than normal. The German team noted that in some cases data from the hand were being processed by the part of the cortex normally devoted to the lips. In a follow-up study, completed last year, the brains of ten of the German R.S.D. patients were scanned again and found to be virtually normal. “Beneficial remodelling can be encouraged through deliberate practice and use,” Oaklander says. “The goal with R.S.D. is to figure out ways to remodel their spinal cord and brain back to more normal pathways of sensation.”

In March, Barbara decided to end her course of nerve blocks and stop taking medication. She forced herself to walk half an hour each day and continued to see her physical therapist. Gradually, the pain in her knee subsided. In June, however, she put on a cotton skirt, and when the material brushed her knee the pain was intolerable. That day, she wore a Lidoderm patch.

“I’ve been thrown from horses, and once fell down a set of marble stairs on my backside, and had no persistent pain,” Barbara said, still perplexed that her fall had been the source of so much agony. She confessed that over the winter, as she pondered her friend’s decision to commit suicide, she had imagined making the same choice. “I’m trying to rewire my nerves,” she said. “But sometimes the pain creeps back.”