HEALTH SPECIAL

IN TESTING

Magnetic Brain
New therapy may help reset circuits that cause pain, page 68

Healing the Hurt. Finding new ways to treat pain

BY ALICE PARK

PAIN IS THE HUMAN BODYGUARD, THE COP ON the beat racing to the scene, sirens wailing, shutting down traffic. You've been cut, burned, broken: pay attention, stop the bleeding, apply heat, apply cold, do something. It's one of life's most primitive mechanisms, by which even the simplest creature, if it has anything like a central nervous system, learns to avoid danger, stay out of bad neighborhoods, hunker down to give itself time to heal. Pain is protective. Don't do that, it commands—and the command is usually a wise one. So this sensation we seek most to avoid is in fact one of the most essential ones for our survival.

But what happens when pain goes rogue, when it sends off false alarms so that all the sirens keep sounding, all the cops keep coming, all the hurts keep hurting? If even benign stimuli get distilled down to a single, primal *Ouch!*, then pain ceases to be adaptive. Rather than saving lives, it wrecks them. Rather than helping you get well or stay safe, it becomes an illness in itself. The result: persistent, unceasing torment.

That's the situation that more than 76 million Americans face. Their pain can last for days or even weeks at a time, then dissipate, only to return. The problem may be caused by something as common as arthritis, an

Photograph by Christopher Buckiow

No easy ouch
Recent revelations about chronic pain reveal that it is less like a symptom and more like a complex disease

DANZIGER PROJECTS

A HISTORY OF PAIN RELIEF
For as long as human beings have suffered pain, we've been searching for ways to overcome it. Our attempts have ranged from the peculiar to the visionary—sometimes both at once.

NEOLITHIC AGE
Trepanning—*boring a hole in the skull to relieve pressure and liberate evil spirits—was used by ancient cultures around the world.*

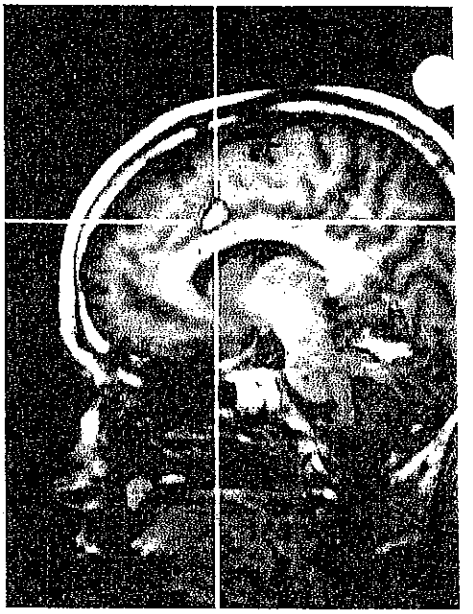
inflammation of the joints that makes them throb with discomfort. The issue could be fibromyalgia, in which a breakdown of pain signals leaves joints, muscles and tissues hypersensitive. It may be a nerve disorder known as neuropathy, triggered by diseases as diverse as cancer and diabetes. It may be that the cause is unidentifiable. Many cases of chronic pain remain unexplained, but they hurt all the same.

There's no telling who the victims of chronic pain will be, but there are ways of determining who is at highest risk. About 10% of people who have surgery, even relatively routine procedures such as knee or back operations, for example, will never be the same again, suffering a lifetime of generalized pain that may start from the incision site but is eventually diffused to other parts of the body. Around 20% of cancer patients will continue to feel pain two years after the surgery or chemotherapy that may have saved their lives. For all of them, pain is not merely a symptom but a disease in itself, one that doctors have only recently come to recognize.

But recognizing a disease is only a prelude to treating it, and doctors admit that while they're pretty good at relieving the acute pain that occurs immediately after surgery or an injury, they are usually stymied by the chronic kind. The most common complaint doctors hear from their patients is about pain that will not quit, and more than 80% of those people never receive treatment—or at least not an effective one. About a decade ago, physicians took the first step toward acknowledging the prevalence of pain and their inadequate ability to address it by including pain assessment as a vital sign along with blood pressure, respiratory rate, heart rate and temperature. "As a clinician, I'm frustrated, and I'm sure many patients are, because we do a very poor job in terms of providing relief for chronic pain," says David Borsook of the McLean Hospital and Harvard Medical School.

To address that frustration, this summer, an expert panel convened by the Institute of Medicine—the independent scientific advisory arm of the National Academies—will release a report on the latest advances in understanding chronic pain and highlight the need for an all-encompassing approach that treats it as a disease of both brain and body. A strategy that lays bare the multitude of body systems involved in maintaining a world of chronic hurt also presents a multitude of treatment opportunities for science to exploit.

Brain-imaging studies and research in genetic and molecular biology, for example, suggest that a brain in chronic pain looks and acts differently from a normal brain and that the phenomenon can even run bo ways: haywire circuits cause the brain to register p sistent pain, which in turn leads to changes—perha permanent—in the way the brain and body work. A this suggests entirely new routes toward elimi pain or at least managing it better.



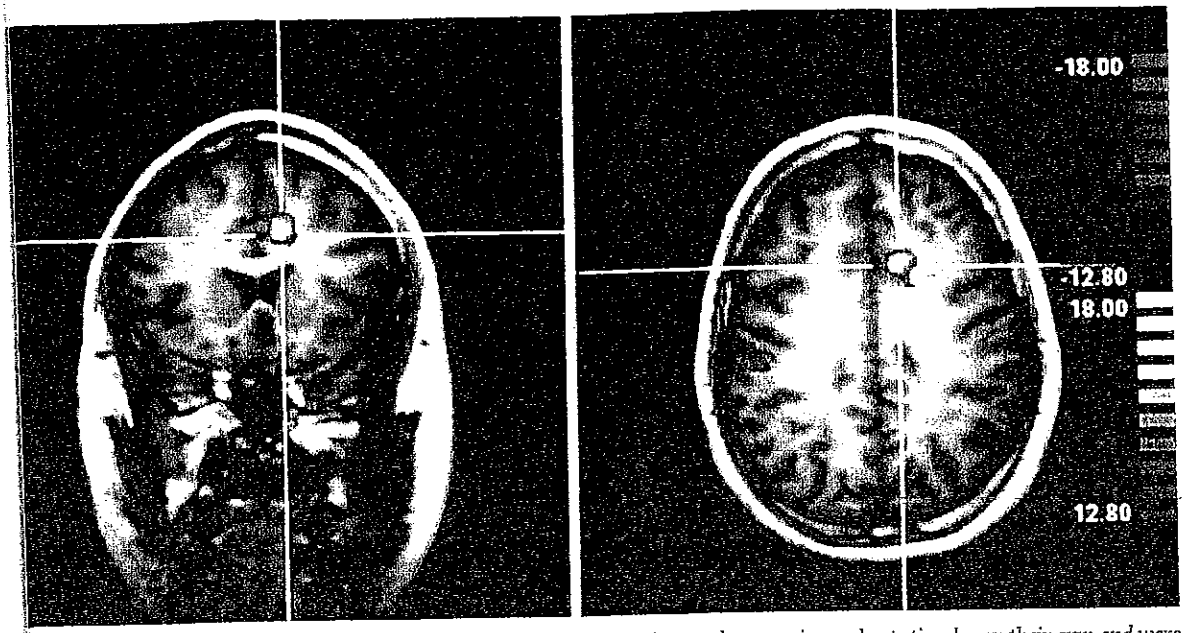
Pain is not merely a symptom but a disease in itself, one that doctors have only recently come to recognize

"There has been a shift in thinking away from pa as only a sensory experience," says Dr. Clifford Woolf neurologist at Children's Hospital Boston. "Rather tha targeting the suppression of pain as a symptom, t best treatment now has to be targeted at preventi pain as a disease. That insight really changes the w we understand pain."

Unpacking the Hurt

WHAT IS PAIN? DEFINING SOMETHING AS VARIED AN complex as pain continues to be a challenge for docto even as they try to improve their ability to treat it. Whi most experts agree it is a phenomenon of the nervo system, only in recent years have they accepted that pa isn't always traceable to a physical source. Patients wi amputated limbs who still feel discomfort in the missi appendage are still hurting, for example, since their bra is registering signals, however distorted, of the sensatio The subjective experience of pain is also nearly unlimit in its variety. Pain can come and go, a bothersome remin er of a past injury; it can be dull and achy or sharp a shooting; it can be concentrated in one joint or muscle seem to radiate throughout the body. With chronic pai the problem is compounded, since in most cases there's proximate cause or injury to treat. What do you do abo a surgical site that healed long ago yet still causes agon What do you do about whole-body pain that has nev stopped since a round of chemo far in the past?

Part of the answer may lie in the chemical ... bathe the brain and promote communication amor



Training the brain to ignore pain *Subjects in a study were given a heat stimulus on their arm and were allowed to see how their brain responded. After being taught to ignore pain signals by thinking pleasant thoughts, they succeeded in activating and exerting some control over the region shown in yellow*

nerve cells. Most studies of chronic pain involve people with fibromyalgia, a condition involving abnormal pain responses that generally affects women. Chronic fatigue syndrome and back disorders can also cause constant pain, and studies of patients with all these conditions have found these individuals have more-active nerve responses, which amplify pain receptors throughout the body. This can set off the pain cascade with hair-trigger sensitivity.

Fibromyalgia patients are a case in point. They often report deep aches as well as shooting discomfort from their joints, even if they don't show signs of inflammation there. What they frequently do have, however, are lower levels of endorphins compared with those who don't suffer from the condition. This may make them more sensitive to pain. Endorphins are the body's natural morphine, and they dull pain by binding to nerve-cell receptors reserved for opiates. Also linked to mood, endorphins can contribute to feelings of euphoria and satisfaction, another mechanism by which they may divert the brain from pain.

And it's not just chemical compounds but neural circuits that may be altered in chronic-pain sufferers. For example, an adaptive mechanism in which severe pain in one area of the body inhibits pain in another is impaired among women with fibromyalgia. Normally, this system works as a check on the amount of pain the brain can handle; if your arm is sore and someone steps hard on your toe, your arm will temporarily feel better as all of your brain's pain attention is focused on the new insult. In chronic-pain patients, this mechanism is faulty or nonexistent.

Genes, too, almost certainly play a role in the response to pain. Inherited differences in the number, density and type of receptors that detect pain, as well as in the body's ability to control it, could help explain why some people feel pain more acutely than others do, as well as why one patient recovers from a knee operation without lasting effects while another never does.

But unraveling the DNA-based component of pain takes more than simply comparing the genomes of chronic-pain sufferers with those of other people and isolating the differences in their genes. That would yield an overwhelming number of potential leads mixed with a good dose of genetic red herrings. So Woolf, for one, has started small, isolating some intriguing possibilities in a species that's easier to study: the fruit fly. He has already found some pain-regulating genes in that simple model, and if they work the same way in humans, those genes could be manipulated with new drugs to tackle pain in a personalized, targeted way.

Such strategies may be novel and in many cases purely theoretical, but they build on a very basic understanding of human anatomy and function. The body's natural painkilling system—the opioids and analgesics we all produce—are the basis for our most powerful painkillers, including nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and naproxen. All of them, natural and synthetic, work by stopping pain signals from speeding along neural highways into the spinal cord and brain. But there may be a more direct way to exploit this pain-dampening system than with drugs that diffuse throughout the entire body.

That's what Dr. David Fink, director of neurology at the University of Michigan, is hoping to show with a gene-therapy study, in which he will inject chronic-pain sufferers with genes coding for natural painkillers, hoping to boost their bodies' levels of those analgesic chemicals. Enkephalins are a type of opiate that the body produces to dull pain sensations, but in cases of chronic pain, these agents appear not to flow in sufficient quantities. So in the first study of its kind, Fink's team is testing

NEOLITHIC AGE *Pieces of polished or flat stone were used to prick strategic parts of the body in China—perhaps the earliest recorded use of* **acupuncture.** *By the 2nd century B.C., the stone needles were being replaced by metal.*

whether using a viral vector to inject cancer patients with the gene associated with enkephalins can boost levels of the opiate and address the subjects' pain. "If we could deliver the gene that makes enkephalins," he says, "they could be released from cells directly into the nervous system and potentially reduce pain in a more targeted fashion." As appealing and potent as that strategy is, tapping into the opiate system is also fraught with danger. The analgesic circuits are intricately intertwined with the body's reward-and-reinforcement network, meaning that activating it could lead to addictive behaviors. That's what makes prescription opioids and other painkillers so habit-forming.

So identifying other genes—those that regulate the addiction circuits—and finding ways to bypass them could be another avenue to treating chronic pain more effectively with existing opiates. At Stanford University Medical Center, researchers led by Martin Angst, a professor of anesthesia, are studying sets of twins in which one displays a stronger liking for painkilling drugs than the other but both experience the analgesic benefits. The idea is to try to isolate the protein markers, perhaps in the blood, produced by the genes that help one twin resist the habit-forming nature of the drugs. Spotting the protein could help doctors identify those more vulnerable to addiction. "As much as we agree that we need to look for novel pain treatments, we understand narcotics pretty well," Angst says. "And if we had a genetic thumbprint for how likely you are to suffer from drug abuse, how convenient that would be."

3300 B.C. *People may have applied* **tattoos** *to parts of the body prone to pain, like joints, as shown by those found on a mummy discovered near the Austria-Italy border. The body had markings on the spine, knee and ankle.*

Training the Brain

STILL, EVEN IF SUCH APPROACHES PRODUCE NEW SCREENS for identifying the best responders to painkillers, they won't likely be enough to address the universe of chronic pain with its widely diverse causes. To achieve that, say some researchers, we need to do more than simply muffle the nervous system's false alarms so the brain and body don't hear them. Instead, we have to retrain the brain and find a way to shut that alarm down.

That's where brain imaging—the powerful technology that allows researchers to view the brain at work, nearly in real time—becomes indispensable. What if, for example, pictures of the brain could be used to help people "think" themselves out of pain?

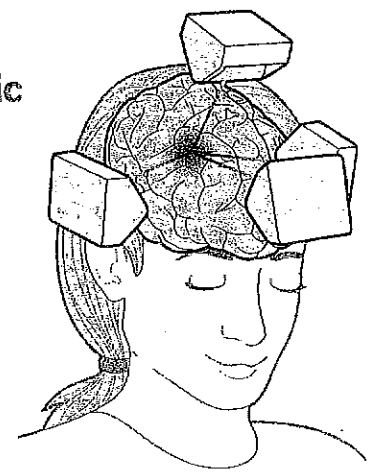
The idea borrows heavily from biofeedback, in which patients use computer screens or other instruments to monitor bodily functions like heart rate or respiration, then dial those functions up or down with just the power of their mind. For pain patients, Dr. Sean Mackey, a professor of anesthesia and pain management at Stanford, has been studying ways to do the same thing with the aid of functional magnetic resonance images (fMRI), which document active regions of the brain at work. "We want to turn the tool that we use to open windows into people's brains and instead use it as a tool to allow people to control their brains," he says.

In Mackey's study, healthy subjects in an fMRI machine were given live access to an image of their brain's activity in a region known as the anterior cingulate cortex—a key regulator of pain signals. Using a heat probe on the arm to cause pain, Mackey and his team asked the volunteers to dial down their level of discomfort when the temperature reached unbearable levels and to dial up their pain sensations when the probe wasn't generating enough heat. They did this not by actually changing the temperature of the probe—that was under the control of the researchers. Rather, they actively refocused their brains either away from or to painful thoughts, depending on the effect they were trying to achieve. To decrease their painful feelings, for example, the subjects were told to distract themselves with thoughts of more-pleasant experiences or events.

Surprisingly, it worked. After the training, the subjects improved their ability to control pain intensity by 23%. And in the ultimate test, when Mackey retrained patients with chronic pain, they reported a 64% reduction in their sensation of pain.

If the results hold, ultimately, Mackey says, retraining the brain to control the activation of pain pathways may become a powerful way of controlling pain without the dangers of addiction. "The idea is that we can specifically target particular brain regions and processes," he says. "The problem with pain pills is that they go through the entire body and manipulate regions of the brain that we don't want to manipulate."

Remapping with Magnets. Magnetic waves can reset neural circuits involved in pain



Something borrowed Deep-brain transmagnetic stimulation (TMS) is being used to reroute nerve connections and relieve symptoms of bipolar disorder. A similar reorganization may alleviate pain

3-D target Just like gamma-knife therapy, which aims radiation at brain tumors from multiple angles, TMS directs magnetic energy toward the anterior cingulate cortex, the brain's pain center

Quieted brain The magnetic fields should reset constantly activated pain nerves and make them less sensitive to stimuli. The first studies involve giving subjects heat stimuli before and after TMS to observe any differences in sensation caused by the treatment

Retraining the brain has the added advantage of exploiting a part of the pain pathway that so far hasn't been targeted much by drugmakers: its inhibitory arm. While painkilling drugs attempt to dampen already activated pain signals, says Mackey, retraining the brain involves "trying to beef up the muscles that turn down the overall pain experience."

That idea speaks to the brain's plasticity—the way it changes and adapts to new situations. A boxer doesn't come into the world unable to feel the pain of a punch in the nose; indeed, he feels it as acutely as anyone else. Over time, however, his pain threshold adjusts so that a punch simply hurts less. Such changes may become self-perpetuating, both for better and for worse.

This kind of resculpting of the brain is leading scientists to explore other ways to rewire the connections that lead to chronic misfiring. David Yeomans, director of pain research at Stanford, was inspired by a psychiatric treatment for bipolar disorder in which magnetic stimulation shuffles nerve networks back to a near normal state. He wondered if the same technique could be applied to pain. And indeed, in early studies, he found that concentrating magnetic fields to target deep-seated pain centers can also relieve symptoms in patients who do not respond to any other therapy.

That's important, since chronic pain may be self-perpetuating, and the sooner pain can be addressed, the less likely it will be to cause persistent and relentless discomfort. "There is intriguing evidence suggesting that chronic pain in osteoarthritis, for example, itself may be causing enhanced damage to joints," says Mackey. "The altered brain is causing changes in the spinal cord that are having an effect on the joints and accelerating damage." The more pain the brain feels, the more damage that does to the body, giving it a physical reason to feel still more.

The Talking Cure

A FINAL, WONDERFULLY LOW-TECH PIECE OF THE PAIN puzzle involves the psychological, social and behavioral factors at play. Whether or not postsurgical pain becomes chronic certainly has a lot to do with a person's genetic sensitivity to activating pain pathways, but it may also depend in part on temperament and mental state. Because brain chemicals that regulate mood and emotion, such as serotonin and norepinephrine, are closely linked to those that govern crisis response—including pain—it makes intuitive sense that their functions would be intertwined, and doctors see evidence of that all the time.

"Chronic pain really is a disease of the central nervous system," says Borsook. "As such, it is a disease that affects the sensory, emotional, motivational, cognitive and modulatory pathways. And the more we understand in particular the emotional pathways, the more we begin to understand that the traditional way we approach patients in pain may need to be revised."

Borsook is convinced that psychiatrists, who have a good understanding of the brain changes caused by mental illness, can provide insights into how best to exploit them. Patients with depression or anxiety, for example, often report a higher incidence of chronic pain, and their discomfort rises as their depression worsens. In addition, the opioid-based response to pain loops in the same reward and motivational systems that reinforce behaviors like addiction. Treat the depression and you may break the entire pathological cycle.

New research into mental illness, genetics and molecular biology is giving researchers and patients new hope that pain may not have to remain so intractable and untreatable. And rethinking chronic pain as a disease, as a normally adaptive process gone awry instead of as a symptom, may be the key to finding safer and more effective ways of interrupting the hurt. ■

'Chronic pain really is a disease of the central nervous system. It affects the sensory, emotional, motivational and cognitive pathways.'
—DR. DAVID BORSOOK, HARVARD

2750 B.C.
The ancient Egyptians used ***electric eels*** *from the Nile to produce pain-relieving shocks, a precursor to modern transcutaneous electrical nerve stimulation.*