

# ON THE BRAIN



## Present and Future Treatments of Pain

All of us feel pain at some time in our lives, and usually we should be grateful for it. This biological system serves to protect us against injury and disease: we need pain to survive. But pain signals can go awry, sending a useless alarm message that interferes with normal life and causes enormous suffering and disability. Fortunately, scientists have recently made great progress in understanding how pain functions and new treatments are emerging from their research.

The word “pain” is used to describe several kinds of sensations that are so unpleasant and distressing that we do our best to avoid them. Sometimes, for example, damaged tissue releases chemicals that are detected by the endings of specific nerve fibers in the skin. In other cases, special nerve endings respond to being stretched. The pain nerves send signals through the spinal cord to the brain, where certain areas produce the sensation of pain and integrate it with memory and emotion.

According to Clifford Woolf, M.D., the Richard J. Kitz Professor of Anesthesia Research at Harvard Medical School, pain sensations fall into three classes. The first kind, physiological pain, is an emergency warning device activated when the integrity of our bodies is threatened—when we touch a hot stove, for example. It tells us to withdraw as soon as possible from the source of the threat. The second kind, inflammatory pain, arises when tissue is damaged by infection, a wound, or surgery. Its function is to make the affected body part so sensitive that we leave it alone while healing and repair mechanisms go to work.

Both physiological and inflammatory pain are adaptive, but there is a third kind, neuropathic pain, which results from damage to the nervous system and has no useful function. It is truly pathological pain. Persistent neuropathic pain can overwhelm brain systems and rearrange them so that the pain becomes more severe, widespread, and chronic. The longer pain continues, the more difficult it is to relieve, so it should be treated from the moment it begins.

### Pain Relief

Different forms of pain relief work on different pain systems. We take aspirin and related drugs to decrease the effect of chemicals released from injured tissue. A dentist performing a root canal blocks pain-carrying nerves with a local anesthetic. During childbirth or surgery, doctors may inject anesthetics where pain fibers enter the spinal cord—a procedure called epidural anesthesia. In some cases of severe pain, pathways in the spinal cord and brain are interrupted surgically or by electrical stimulation.

In the treatment of moderate acute pain, the first choice is usually aspirin

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### Stress and the Brain

The tragic events of September 11 have made many individuals feel increased levels of stress. This has raised questions about what the long term effects of stress might be on the body and on the brain.

Stress is not always bad. It can provide the increased energy needed to cope with dangerous situations and can help the brain focus and retain important information. These beneficial effects occur because stress sets off a series of complicated physiological events. These include neurological changes through activation of the autonomic nervous system and hormonal changes through activation of the hypothalamic-pituitary-adrenal (HPA) system. These two systems control and stimulate the output of stress hormones (such as cortisol, noradrenaline and adrenaline) that play a key role in jump-starting the body’s defense system.

In the case of a real threat to our

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# Golf Tournament Honors David Mahoney

The First Annual David J. Mahoney Memorial Golf Tournament was held on May 17, 2001, at the Deepdale Country Club in Manhasset, Long Island, New York. It was co-chaired by Roone Arledge, Frank Gifford and Ira Harris,



Frank Gifford, Tournament Co-Chair

three of David Mahoney's close friends who conceived of the annual tournament as a way to honor David and to raise funds for the publication of the Harvard Mahoney Neuroscience Institute's newsletter, *On the Brain*.

The tournament raised \$65,000, which exceeded expectations, as contributors included not only participants in the tournament but those who were unable to attend and wanted to show their support for the Institute and its newsletter.

The golfers included co-chairs Frank Gifford and Ira Harris, Bill Bartholomay, Ken Langone, Carl Menges, Arthur Merrill, Robert Merrill, Peter Nadosy, Chuck Peebler and his son Todd, and Lew Rudin. A dinner was held following the tourna-



J. Ira Harris, Tournament Co-Chair



Roone Arledge, Tournament Co-Chair

ment, which was attended by Hillie Mahoney, Chairman, and Council Members Ed Rover and Herbert Siegel, as well as many of the wives of the golfers, including Elaine Langone, Monique Merrill, Christina Merrill, and Toni Peebler. There was much reminiscing about David and his very passionate involvement with neuroscience.

The second David J. Mahoney Memorial Golf Tournament is already in the planning phase and is scheduled to be held on May 16, 2002. □

*Stress and the Brain*  
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life, activation of these systems is both useful and protective, resulting in increased energy for running or fighting. They increase heart rate and blood pressure that protects against low blood pressure associated with blood loss and injury, and play an important role in modulating immune responses. If, however, these systems are stimulated to excess, a gradual and steady cascade of harmful physiological changes may ensue, damaging our immune and cardiovascular systems.

Higher levels of stress can also increase alertness, which can improve

learning. This is one of the reasons we remember stressful events so clearly. Dr. Daniel Schacter, Chairman of the Psychology Department at Harvard College and author of the recent book *The Seven Sins of Memory*, says, "There are certain kinds of events that are so shocking that we record them in our brains—like a camera with a flashbulb lighting up all the details; in fact, we call them 'flashbulb memories.' We remember exactly when and where we were when this event happened." However, when stress levels are too high, memory is impaired. Moreover, when high levels of stress hormones are maintained over a long time, there can

actually be damage to brain tissue, particularly in a part of the brain that is essential for normal memory, the hippocampus.

There are marked individual differences in the way people respond to stress. Many factors are responsible for these differences including genetics, physical activity, and normality of the sleep-wake cycle. Whatever one's basic responsiveness to stress, it is important to attempt to reduce high levels of stress when they occur, in order to minimize the long term negative effects. Some may choose to talk about

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and other anti-inflammatory drugs such as ibuprofen (Motrin or Advil), or the new, more selective COX-2 inhibitors. If pain persists, physicians may prescribe narcotics, also called opiates, including codeine, Demerol, and morphine. When used properly, these drugs are not necessarily highly addicting.

## Common Pain Systems

### Back pain

One of the most common sources of recurring pain among adults is our backs, those tricky structures jury-rigged by evolution to allow us to stand upright. The spinal cord is protected by a canal made up of bones called vertebral bodies, which may deform under stress and press on nerves. Between the bones are cushions of gelatin-like material called disks that act as shock absorbers.

When the facet joints, the small joints between the bones of the spine, slip a little and cause pain, that leads to spreading muscle spasms. Sometimes, sudden pressure may push the soft material between the bones of the spine out of its bony cage and cause it to impinge on the spinal cord or the nerves connected to it—a herniated or ruptured disk.

Treatments include massage, heat, bed rest, muscle relaxants such as diazepam (Valium), and pain medications like Motrin. The best treatments are usually bed rest and traction—gentle stretching of the muscles of the neck or spine by a weighted pulley arrangement. Surgery—removing bits of disk through a small hole in the back—is needed only in cases of persistent pain and muscle weakness. Surgery should be considered only when the source of the pain is known.

If there is no clear abnormality in the spine (as shown, for example, by imaging techniques such as CT or MRI scans), surgery and other invasive procedures (stimulators or nerve blocks) may only cause new problems.

### Headache

Many everyday frustrations are called headaches, even when they don't involve pain. We talk that way because headaches are so common and have such a variety of poorly understood causes. Most headaches go away when you take an aspirin, but some are disabling, and a few are signs of serious illness.

Tension headaches, probably the most common kind, arise from the muscles at the back of the neck and scalp as a result of stress, eye-strain, poor posture, and fatigue. The pain can often be prevented by stretching the muscles involved and by changing position periodically. Treatments

include mild pain-killers like aspirin, Motrin or Tylenol. Chronic or repeated tension headaches may call for anti-anxiety and antidepressant medications or psychotherapy.

Migraine is the most common known cause of chronic, severe headache pain—a problem at some time for 6 percent of men and 20 percent of women. A classic migraine begins with a visual “aura,” such as wavy lines sweeping across the field of vision. The headache that follows is often accompanied by nausea and vomiting, and sometimes by such symptoms as weakness or numbness, vision problems, or confusion (so-called complicated migraine). The pain can be so severe that the victim

has to stop everything and lie down in the dark for hours or even days.

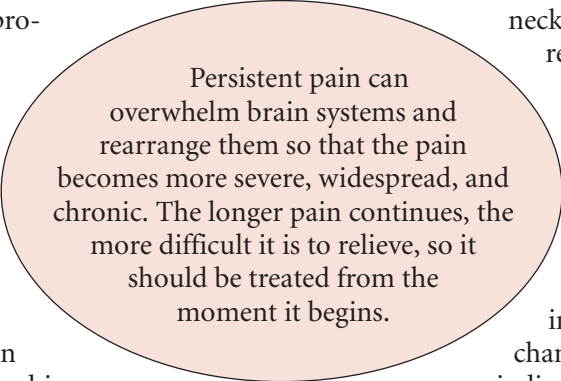
New evidence suggests that most migraine symptoms result from the irritation of blood vessels by chemicals released from abnormally functioning nerve cells. This process apparently involves the neurotransmitter (brain chemical messenger) serotonin. Migraines sometimes run in families, suggesting a genetic component, but there are also many environmental triggers, including alcohol, stress, menstruation, and certain foods. A headache diary recording times, symptoms, and circumstances helps in identifying the trigger.

To prevent migraine, patients may need to change their dietary and other habits, sometimes with the aid of psychological counseling. The attacks themselves can be treated with aspirin or with ergotamine, which narrows blood vessels and modifies the action of serotonin. The newest and possibly most effective migraine drugs act like serotonin, binding to specific receptors on blood vessels and nerve cells. Sumatriptan, the most widely used of several similar drugs, relieves the headache and associated symptoms 70 percent of the time.

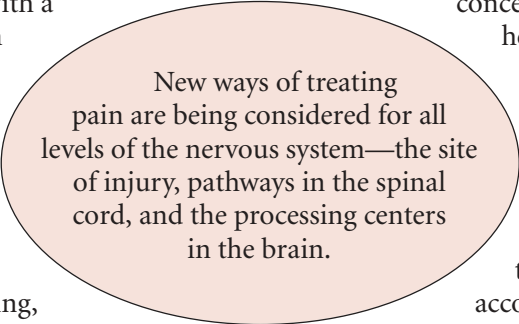
Almost any medication can cause a headache. That includes prescription, over-the-counter, and alternative preparations—even, sometimes, pain medications. Coffee and alcohol are other common culprits. If physicians find no disease, they always consider this possibility.

A very serious cause of concern is a severe headache in someone who has never had one before—especially if it awakens the patient early in the morning or is accompanied by nausea, fever, a stiff neck, or

changes in behavior and neurological functioning. The cause could be, for example, a burst blood vessel (hemorrhagic stroke) or an acute brain infec-



Persistent pain can overwhelm brain systems and rearrange them so that the pain becomes more severe, widespread, and chronic. The longer pain continues, the more difficult it is to relieve, so it should be treated from the moment it begins.



New ways of treating pain are being considered for all levels of the nervous system—the site of injury, pathways in the spinal cord, and the processing centers in the brain.

tion. A stroke can be detected with brain imaging, and a lumbar puncture (taking samples of spinal fluid) may show evidence of infection.

Many people who see a doctor for a headache secretly fear that it is a brain tumor—a concern that is justified in fewer than one out of a thousand cases. A doctor's suspicions are aroused mainly when an elderly person has a headache that is new or different from previous headaches. Brain imaging is a safe, quick, and reliable way to relieve worry about tumors.

### Alternative Approaches to Pain Management

When conventional medical and surgical procedures fail, patients may come to pain treatment centers, where teams of professionals encourage them to become more physically active and resume a normal life as much as possible. A physician prescribes pain medicines and antidepressants; a psychologist tries to change the patient's responses to pain by means of biofeedback, muscle relaxation, counseling, and other techniques. A physical therapist assigns exercises to break the vicious cycle in which pain leads to immobility and the resulting stiff joints cause more pain. Vocational counselors help the patient resume work and household activities, and a nurse specialist provides monitoring on a day-to-day basis.

### New Treatments on the Horizon

New ways of treating pain are being considered for all levels of the nervous system—the site of injury, pathways in the spinal cord, and the processing centers in the brain. Here are some examples:

A cut on your finger hurts because of chemicals released by damaged nerves. Scientists have discovered specific receptors for these chemicals on pain fibers, and they are working to develop substances that block the receptors.

Pain elicits emotional responses and memories, and the longer it continues, the stronger the associations become.

Interrupting this process may be one of the best ways to reduce the disability and suffering associated with chronic pain. Very little is known about the brain mechanisms of pain processing, but research using newer forms of imaging is expected to shed light on the mystery.

In some circumstances, we have an amazing ability to suppress and ignore pain, at least temporarily. The reason is that the brain makes its own chemicals that act like opiate drugs. They are called endorphins, and some of them

are fifty times more potent than morphine. If physicians could harness the endorphin response, pain could be turned off in advance when it is predictable, as in an operating room or dentist's office.

There are many exciting discoveries about the way genes are turned on and off to cause long-lasting changes in the brain's response to pain. Current research should lead to the development of new pain relievers without the side effects of present drugs (see Synapsot). □

## SYNAPSHOT

### Nerve Cells and Pain

Long-lasting debilitating pain develops because nerve cells (neurons) become hypersensitive—not only pain fibers near the site of an injury, but also pain transmission neurons in the spinal cord and brain. That sensitivity results from changes in the genes within nerve cells; some genes are turned off or become less active, and others are turned on or become more active.

Dr. Clifford Woolf and his colleagues at Massachusetts General Hospital recently reported research that throws new light on the process of pain sensitization. They have been studying cyclooxygenase-2 (COX-2), an enzyme needed for the production of prostaglandins, which are well known to cause pain hypersensitivity at the site of an injury during inflammation. They were especially interested in this enzyme because its activity is blocked by the most widely used class of pain relievers— aspirin, ibuprofen and other non-steroidal anti-inflammatory drugs, as well as the more selective new drugs celecoxib (Celebrex) and rofecoxib (Vioxx). Woolf has shown that COX-2 and prostaglandins not

only work at the site of an injury but also turned genes on and off within brain cells. This discovery has altered ideas about the mechanisms involved in persistent pain.

The gene that contains the code for producing COX-2 is only one of many involved in pain regulation.

Recently Dr. Woolf and his colleagues have been exploring the changes that genes undergo during the experience of various kinds of pain. They work with new technology that has allowed them to identify fifteen hundred genes that can change their activity when the body becomes hypersensitive to pain. This research holds great promise for treatment. An ideal pain reliever would affect only the specific nerve circuits that are abnormally sensitive in each case. The genes that Woolf and others are studying may be targets in the search for pain relievers that have fewer side effects than currently available drugs. Some day we could have many different drugs for many distinct kinds of pain and even for genetically different individuals. □



# New Approaches to Pain Management

**D**r. Clifford Woolf, the Richard J. Kitz Professor of Anesthesia Research at Harvard Medical School, heads a large research program on pain at Massachusetts General Hospital. We spoke with him about new approaches to pain management.

**Question:** We used to think that it was best to wait as long as possible before treating pain, is this still the current thinking?

**CW:** No, quite the contrary. We have learned that different mechanisms are responsible for the production of pain and that over time one mechanism may lead to the another. It is essential therefore, to try to stop the development of chronic pain by actively treating acute pain when it first starts. We need to break the pain cycle. In addition, it is clear that a lower dose of analgesic is required if we treat pain early than if we wait. Using a lower dose also minimizes possible side effects, such as sleepiness and nausea. Now we even start treating pain before it occurs, for example, right after surgery when we know that pain will develop in a short while.

**Question:** Are there any simple guidelines for when to start treating pain?

**CW:** The earlier the better! In general terms—not all pains are similar—

each case needs to be decided on its own merits, balancing the possible effectiveness of treatment with any potential side effects or complications of the treatment.



Clifford J. Woolf, M.D.

**Question:** What is the role of pain treatment centers in pain management?

**CW:** There are really two roles. When someone is in the hospital, pain teams handle post-operative pain, or pain associated with an injury, or pain of labor. There are also special teams of individuals that handle patients with persistent pain—pain that cannot be easily controlled. In many of these cases the original disease has disappeared and pain is the major problem. Pain centers

also work with patients who have become dependent on their medication.

**Question:** Are pain treatment centers available in most major medical centers or only in a relative few?

**CW:** The number of pain centers and pain physicians has increased dramatically over the past ten years. Most large hospitals have them but the standard of care varies enormously. Patients with neuropathic pain—pain associated with damage to their nervous system—are the ones who can really benefit from such a clinic or patients where pain is destroying the quality of their life.

**Question:** What does the future hold for pain sufferers?

**CW:** We're in the middle of a revolution in our approach to management of pain. Until very recently, we had very little idea of the actual mechanisms that were responsible for our experience of pain, and treatment was often by trial and error. In the last ten years, however, we have begun to understand precisely what mechanisms produce the different types of pain, and we are beginning to target specific pain mechanisms with specific treatment. We're not there yet, but it's a beginning, and I think it makes both the study of pain and the management of pain extremely exciting. □

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their feelings, other may choose to do something they feel will make a difference by, for example, donating time or money to help others. Both approaches are likely to reduce levels of stress hormones in the brain and are therefore protective in the long run.

Some people who feel overwhelmed by a stressful experience develop a syn-

drome known as Post-Traumatic Stress Disorder (PTSD). Individuals with this syndrome experience fatigue, impaired sleep, altered pain perception, and psychological distress. "If such symptoms are present for a month or longer, it is important to seek professional help promptly," says Dr. Gail Adler from Brigham & Women's Hospital. Researchers are currently seeking treatments that might reduce the chances of getting PTSD. For example,

Dr. Roger Pitman and his colleagues at Massachusetts General Hospital are trying to develop an "anti-adrenaline drug" that might be administered right after someone has experienced a traumatic event. Currently, however, the two best treatments for PTSD are prescription medications such as Zoloft, Prozac, Paxil and Luvox and/or cognitive therapy. □

## ON THE BRAIN

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HARVARD MAHONEY  
NEUROSCIENCE INSTITUTE

*Council Members:*

Hildegarde E. Mahoney, Chairman

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Caroline Kennedy Schlossberg

Joseph B. Martin, MD, PhD

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Carla J. Shatz, PhD

Herbert J. Siegel

Daniel C. Tosteson, MD

*Writers, Editorial Advisors*

James Bakalar, Diana Griffith, PhD

Harvard Mahoney Neuroscience Institute

MGH East (149-9124)

149 13<sup>th</sup> Street, Charlestown, MA 02129

---

Internet address:

[www.hms.harvard.edu/hmni](http://www.hms.harvard.edu/hmni)

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*Correspondence/Circulation:*

MGH East (149-9124), 149 13<sup>th</sup> Street  
Charlestown, MA 02129

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