Pain

Hope Through Research

National Institute of Neurological Disorders and Stroke
National Institutes of Health

NINDS health-related material is provided for information purposes only and does not necessarily represent endorsement by or an official position of the National Institute of Neurological Disorders and Stroke or any other Federal agency. Advice on the treatment or care of an individual patient should be obtained through consultation with a physician who has examined that patient or is familiar with that patient's medical history.

All NINDS-prepared information is in the public domain and may be freely copied. Credit to the NINDS or the NIH is appreciated.

Table of Contents

Introduction 1

A Pain Primer: What Do We Know About Pain? ... 1

Anatomy of Pain 3

Neurochemistry of Pain 4

Genetics of Pain 8

Inflammation and Pain 8

Neural Circuits and Chronic Pain 9

How is Pain Diagnosed? 10

How is Pain Treated? 12

Gender and Pain 26

Pain in the Elderly and Children 27

What is the Future of Pain Research? 28

Hope for the Future 33

The A to Z of Pain 34

Appendix 43

- Spine Basics: The Vertebrae, Discs, and Spinal Cord 43
- The Nervous Systems 44
- Phantom Pain: How Does the Brain Feel? 45

Information Resources
(see card inside back pocket of this brochure)

Introduction

Pain in its most benign form warns us that something isn't quite right, that we should take medicine or see a doctor. At its worst, however, pain robs us of our productivity, our well-being, and, for many of us suffering from extended illness, our very lives. Pain is a complex perception that differs enormously among individual patients, even those who appear to have identical injuries or illnesses.

The burden of pain in the United States is astounding. More than 100 million Americans have pain that persists for weeks to years. The financial toll of this epidemic cost $560 billion to $635 billion per year according to *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research**, a report from the Institute of Medicine (IOM). Pain is ultimately a challenge for family, friends, and health care providers who must give support to the individual suffering from the physical as well as the emotional consequences of pain.

A Pain Primer: What Do We Know About Pain?

What is pain? The International Association for the Study of Pain (IASP) defines it as: *An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in*

---

* Committee on Advancing Pain Research, Care, and Education; Institute of Medicine of the National Academies. (2011). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research.* Washington, D.C. The National Academies Press.

terms of such damage. The IASP definition means that pain is a subjective experience; one that cannot be objectively measured and depends on the person's self-report. There can be a wide variability in how a person experiences pain to a given stimulus or injury.

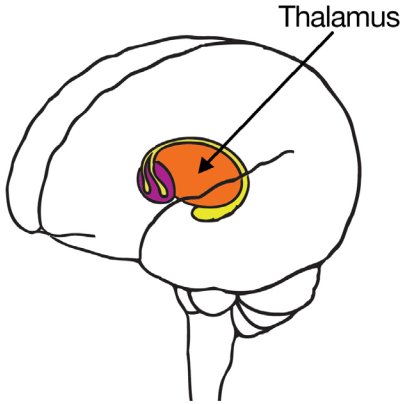
Pain can be classified as acute or chronic, and the two kinds differ greatly.

- **Acute pain**, for the most part, results from disease, inflammation, or injury to tissues. This type of pain generally comes on suddenly, for example, after trauma or surgery, and may be accompanied by anxiety or emotional distress. The cause of acute pain can usually be diagnosed and treated. The pain is self-limiting, which means it is confined to a given period of time and severity. It can become chronic.

- **Chronic pain** is now believed to be a chronic disease condition in the same manner as diabetes and asthma. Chronic pain can be made worse by environmental and psychological factors. By its nature, chronic pain persists over a long period of time and is resistant to many medical treatments. It can—and often does—cause severe problems. People with chronic pain often suffer from more than one painful condition. It is thought that there are common mechanisms that put some people at higher risk to develop multiple pain disorders. It is not known whether these disorders share a common cause.

We may experience pain as a prick, tingle, sting, burn, or ache. Normally, acute pain is a protective response to tissue damage resulting from injury,

disease, overuse, or environmental stressors. To sense pain, specialized receptors (called nociceptors) which are found throughout the body, trigger a series of events in response to a noxious (painful) stimulus. The events begin with conversion of the stimulus to an electrical impulse that travels through nerves from the site of injury or disease process to the spinal cord. These signals are transmitted to a specialized part of the spinal cord called the dorsal horn (see section on Spine Basics in the Appendix), where they can be dampened or amplified before being relayed to the brain.



The thalamus serves as a relay station that distributes signals to many other brain regions.

Anatomy of Pain

Pain signals from the head and face directly enter the brain stem where they join the pain pathways that travel from the spinal cord to the brain. One central place these signals travel to is the thalamus. The thalamus is a relay station that distributes sensory signals to many other brain regions—including the anterior cingulate cortex, somatosensory cortex, insular cortex, and prefrontal cortex. These cortical brain regions process the nociceptive (pain causing or reacting to pain) information from the body and generate the complex experience of pain. This pain experience has multiple components that include the: 1) sensory-discriminative aspect which helps us

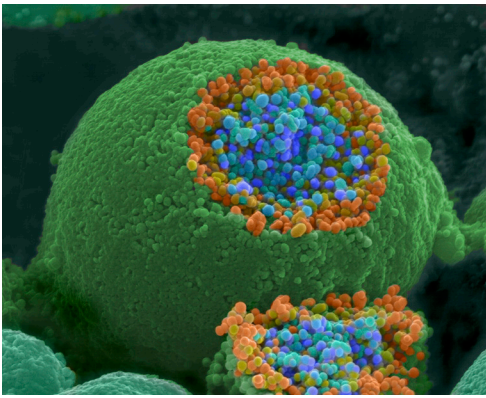
localize where on our body the injury occurs, 2) affective-motivational aspect which conveys just how unpleasant the experience is and the 3) cognitive-evaluative aspect which involves thoughtful planning on what to do to get away from the pain. Many of these characteristics of pain have been associated with specific brain systems, although much remains to be learned. Additionally, researchers have found that many of the brain systems involved with the experience of pain overlap with the experience of basic emotions. Consequently, when people experience negative emotions (e.g. fear, anxiety, anger), the same brain systems responsible for these emotions also amplify the experience of pain.

Fortunately, there are systems in the brain that help to dampen or decrease pain. Descending signals from the brain are sent back to the spinal cord and can inhibit the intensity of incoming nociceptive signals, thereby reducing the pain experience.

Neurochemistry of Pain

This complicated process by which we perceive pain involves intricate connections among multifaceted brain regions. The nervous system uses a set of chemicals, called *neurotransmitters*, to communicate between neurons within and across these stations in the pain pathway. These chemicals are released by neurons in tiny packets (vesicles) into the space between two cells. When they reach their target cell, they bind to special proteins on the

surface of the cells called *receptors*. The transmitter then activates the receptor, which functions much like a gate. The gate will either close to block (inhibitory receptor) the signal or open to send (excitatory receptor) the signal along to the next station.



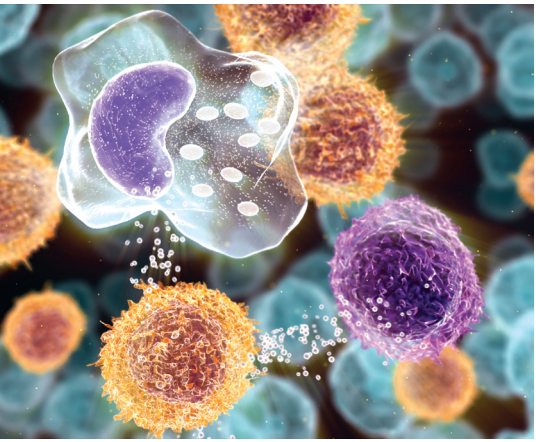
The nervous system uses chemicals called neurotransmitters to communicate between neurons within and across the pain pathway. These chemicals are released in tiny packets called vesicles into the space between two cells. The picture above shows a nerve ending that has been broken open to reveal vesicles (in orange and blue) that contain chemicals used to pass messages in the nervous system.

There are many different neurotransmitters in the human body and they play a role in normal function as well as in disease. In the case of nociception and pain, they act in various combinations at all levels of the nervous system to transmit and modify signals generated by noxious stimuli.

One excitatory neurotransmitter of special interest to pain researchers is *glutamate*, which plays a major role in nervous system function and in pain pathophysiology. The modulation of glutamate neurotransmission is complex, but it plays a key role in heightening the sensitivity to pain through increased responsiveness of excitatory receptors in the spinal cord dorsal horn and in the brain. This is part of a process called central sensitization and contributes to making pain persist. A great deal of attention has been given to developing molecules/drugs that block certain receptors for glutamate for their potential in reducing pain.

Unlike glutamate, GABA (or gamma-aminobutyric acid) is predominately an inhibitory neurotransmitter in that it generally decreases or blocks the activity of neurons. Most of what we know of its role in pain is related to its function in inhibiting spinal cord neurons from transmitting pain signals and therefore dampening pain. Chemicals that are similar to GABA have been explored as possible analgesics, but because GABA is so widespread in the nervous system it is difficult to make a GABA-like drug without affecting other nervous system functions. As we learn more about the specific roles of GABA receptors, drug development may be accelerated.

Norepinephrine and serotonin are neurotransmitters used by the descending pain pathways from the brain stem to dampen the incoming signals from painful stimuli from the site of the injury or inflammation. Drugs that modulate the activity of these transmitters, such as some antidepressants, are effective in treating some chronic pain conditions, likely by enhancing the availability of the transmitters through a recycling and reuse process. Serotonin receptors also are present on the nerves that supply the surface of the brain involved in migraines, and their modulation by a class of drugs called "triptans" is effective in acutely treating migraine.



Cytokines—a group of proteins found in the nervous system—can trigger pain by promoting inflammation, even in the absence of injury or damage. In the above photo, cytokines are shown as tiny white particles.

The opioids are another important class of neurotransmitters that are involved in pain control, as well as pleasure and addiction. Their receptors are found throughout the body and can be activated by endogenous (produced by our bodies) opioid *peptides*—short chains of amino acids that bind to opioid receptors in the brain—that are released by neurons in the brain. The enkephalins, dynorphins, and endorphins are some of the body's own natural pain killers. They may be more familiar for the role of endorphins in the feeling of well-being during exercise—the runner's high. Opioid receptors also can be activated by morphine, which mimics the effect of our endogenous opioids. Morphine is a natural product and like similar synthetic opioids, is a very potent, but potentially addictive pain killer that is used broadly for severe acute and chronic pain management. Together the opioids provide effective pain relief for many people with pain. Other peptides also transmit neuronal signals and play a role in pain responses. Scientists have shown that mice bred experimentally to lack a gene for two peptides, called *tachykinins-neurokinin A* and *substance P*, have a reduced response to severe pain. When exposed to mild pain, these mice react in the same way as mice that carry the missing gene. But when exposed to more severe pain, the mice exhibit a reduced pain response. This suggests that the two peptides are involved in the perception of pain sensations, especially moderate-to-severe pain.

Genetics of Pain

Differences in our genes highlight how different we are in respect to pain. Scientists believe that genetic variations can determine our risk for developing chronic pain, how sensitive we are to painful stimuli, whether or not certain therapies will ease our pain, and how we respond to acute or chronic pain. Many genes contribute to pain perception, and mutations in one or more pain-related genes account for some of the variability of each individual's pain experiences. Some people born genetically insensate to pain—meaning they cannot feel pain—have a mutation in part of a gene that plays a role in electrical activity of nerve cells. A different mutation in that same gene can cause a severe and disabling pain condition. Scientists have identified many genes involved in pain by screening large numbers of people with pain conditions for shared gene mutations. While genes play a role in determining our sensitivity to pain, they only account for a portion of this variability. Ultimately, our individual sensitivity to pain is governed by a complex interaction of genes, cognitions, mood, our environment and early life experiences.

Inflammation and Pain

The link between the nervous and immune systems also is important. Cytokines, a group of proteins found in the nervous system, are also part of the immune system—the body's shield for fighting off disease and responding to tissue injury. Cytokines can trigger pain by promoting inflammation, even in the absence of injury or damage. After trauma, cytokine levels rise in

the brain and spinal cord and at the site where the injury occurred. Improvements in our understanding of the precise role of cytokines in producing pain may lead to new classes of drugs that can block the action of these substances to produce analgesia.

Neural Circuits and Chronic Pain

The pain that we perceive when we have an injury or infection alerts us to the potential for tissue damage. Sometimes this protective pain persists after the healing occurs or may even appear when there was no apparent cause. This persistent pain is linked to changes in our nervous system, which responds to internal and external change by reorganizing and adapting throughout life. This phenomenon is known as neuronal plasticity, a process that allows us to learn, remember, and recover from brain injury. Following an injury or disease process, sometimes the nervous system undergoes a structural and functional reorganization that is not a healthy form of plasticity. Long-term, maladaptive changes in both the peripheral and central nervous system can make us hypersensitive to pain and can make pain persist after injuries have healed. For example, sensory neurons in the peripheral nervous system, which normally detect noxious/painful stimuli, may alter the electrical or molecular signals that they send to the spinal cord. This in turn triggers genes to alter production of receptors and chemical transmitters in spinal cord neurons setting up a chronic pain state. Scientists have methods to identify which genes' activities change with injury and chronic pain. Knowledge of the proteins that

ultimately are synthesized by these genes are providing new targets for therapy development. Increased physiological excitation of neurons in the spinal cord enhance pain signaling pathways to the brain stem and in the brain. This hypersensitivity of the central nervous system is called central sensitization. It is difficult to reverse and makes pain persist beyond its protective role.

How is Pain Diagnosed?

There is no way to tell accurately how much pain a person has. Tools to measure pain intensity, to show pain through imaging technology, to locate pain precisely, and to assess the effect of pain on someone's life, offer some insight into how much pain a person has. They do not, however, provide objective measures of pain. Sometimes, as in the case of headaches, physicians find that the best aid to diagnosis is the person's own description of the type, duration, and location of pain. Defining pain as sharp or dull, constant or intermittent, burning or aching may give the best clues to the cause of pain. These descriptions are part of what is called the pain history, taken by the physician during the preliminary examination of a person with pain. Developing a test for assessing pain would be a very useful tool in diagnosing and treating pain.

Physicians, however, do have a number of approaches and technologies they use to find the cause of pain. Primarily these include:

- A **musculoskeletal** and **neurological examination** in which the physician tests movement, reflexes, sensation, balance, and coordination.

Imaging such as MRI provides pictures of the body's structures and tissues to help locate the possible cause of pain.

- **Laboratory tests** (e.g. blood, urine, cerebrospinal fluid) can help the physician diagnose infection, cancer, nutritional problems, endocrine abnormalities and other conditions that may cause pain.

- **Electrodiagnostic procedures** include **electromyography (EMG)**, **nerve conduction studies**, **evoked potential (EP) studies,** and **quantitative sensory testing**. These procedures measure the electrical activity of muscles and nerves. They help physicians evaluate muscle symptoms that may result from a disease or an injury to the body's nerves or muscles. **EMG** tests muscle activity. It can help physicians tell which muscles or nerves are affected by weakness or pain. **Nerve conduction studies** are usually performed along with EMG. These studies record how nerves are functioning. **EP** studies measure electrical activity in the brain in response to sight, sound, or touch stimulation. **Quantitative sensory testing** can establish thresholds for sensory perception in individuals which can then be compared to normal values. These tests are used to detect abnormalities in sensory function and nerve disorders.

- Imaging, especially **magnetic resonance imaging** or **MRI**, provides physicians with pictures of the body's structures and tissues, such as the brain and spinal cord. MRI uses magnetic fields and radio waves to differentiate between healthy and diseased tissue.

- **X-rays** produce pictures of the body's structures, such as bones and joints.

How is Pain Treated?

The goal of pain management is to improve function, enabling individuals to work, attend school, and participate in day-to-day activities. People with pain and their physicians have a number of options for treatment; some are more effective than others. Sometimes, relaxation and the use of imagery as a distraction provide relief. These methods may be powerful and effective, according to those who advocate their use. Whatever the treatment regime, it is important to remember that, while not all pain is curable, all pain is **treatable**. The following treatments are among the most common.

Treatment varies depending on the duration and type of pain. For the most part, the medications listed below have been shown in clinical studies to relieve or prevent pain associated with a specific condition(s), but none have been proven fully effective in relieving all types of pain. A health care professional should be consulted to determine which medication is effective for a given pain condition and what to expect for pain relief and side effects. Evidence for the procedures listed below is variable in its quality. In some cases, evidence suggesting that some treatments are effective is anecdotal—or based on personal experience—and in other cases it is collected from well-designed clinical studies.

Acetaminophen is the basic ingredient found in Tylenol® and its many generic equivalents. It is

sold over the counter, in a prescription-strength preparation, and in combination with codeine (also by prescription).

Acupuncture involves the application of needles to precise points on the body. It is part of a general category of healing called traditional Chinese medicine. The mechanism by which acupuncture provides pain relief remains controversial but is quite popular and may one day prove to be useful for a variety of conditions as it continues to be explored. Evidence of the effectiveness of acupuncture for pain relief is conflicting and clinical studies to investigate its benefits are ongoing.

Analgesic refers to the classes of drugs that includes most "painkillers". This includes classes of non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, and naproxen as well as acetaminophen and opioids. The word analgesic is derived from ancient Greek and means to reduce or stop pain. Nonprescription or over-the-counter pain relievers (e.g. aspirin, ibuprofen, acetaminophen) are generally used for mild to moderate pain. Prescription opioid pain relievers, sold through a pharmacy under the direction of a physician, are used for moderate to severe pain.

Anticonvulsants are used to treat seizure disorders because they dampen abnormally fast electrical impulses. They also sometimes are prescribed to treat pain. Carbamazepine in particular is used to treat

Non-prescription or over-the-counter pain relievers such as aspirin, ibuprofen, and acetaminophen often are used to relieve mild to moderate pain.

a number of painful conditions, including trigeminal neuralgia. Other antiseizure drugs, including gabapentin and pregabalin, are also used to treat some forms of pain, including neuropathic pain. Some, such as valproic acid and topiramate, are helpful in preventing migraine headaches.

Antidepressants are sometimes used to treat chronic pain and, along with neuroleptics and lithium, belong to a category of drugs called psychotropic drugs.

Anxiolytics (drugs used to inhibit anxiety) include medications in the class of benzodiazepines (which are used to decrease central nervous system activity). These drugs also act as muscle relaxants and are sometimes used for acute pain situations. Physicians usually try to treat the condition with analgesics before prescribing these drugs.

Beta-blockers are medications which inhibit one arm of the sympathetic nervous system and adrenal "fight or flight" hormones. Propranolol and timolol are used to prevent migraine headaches.

Biofeedback is used to treat many common pain problems, most notably headache and back pain. Using a special electronic machine, individuals are trained to become aware of, to follow, and to gain control over certain bodily functions, including muscle tension, heart rate, and skin temperature. The individual can then learn to change his or her responses to pain, for example, by using relaxation techniques. Eventually, these changes can be maintained without using the machine. Biofeedback is often used in combination with other treatment methods, generally without side effects. Similarly, the use of relaxation techniques to treat pain can increase a person's feeling of well-being.

Capsaicin, a chemical found in chili peppers, is a key ingredient in pain-relieving creams used to treat a number of pain conditions.

Capsaicin (pronounced cap-SAY-sin) is a chemical found in chili peppers that is also a primary ingredient in prescription or over-the-counter pain-relieving creams available as a treatment for a number of pain conditions, such as shingles. This topical cream may be particularly good for deep pain. It works by reducing the amount of substance P found in nerve endings and interferes with the transmission of pain signals to the brain. Individuals can become desensitized to the compound, however, perhaps because of long-term capsaicin-induced damage to nerve tissue. Some individuals find the burning sensation they experience when using capsaicin cream to be intolerable, especially when they are already suffering from a painful condition, such as postherpetic neuralgia (which occurs in some people after a bout of shingles). Soon, however, better treatments that relieve pain by blocking vanilloid receptors (also called capsaicin receptors) may arrive in drugstores.

Chiropractic care may ease back pain, neck pain, headaches, and musculoskeletal conditions. It involves "hands-on" therapy designed to adjust the relationship between the body's structure (mainly the spine) and its functioning. Chiropractic spinal manipulation includes the adjustment and manipulation of the joints and adjacent tissues. Such care may also involve therapeutic and rehabilitative exercises. Numerous clinical studies have been done to assess the effectiveness of spinal manipulations. A review of these trials concludes that evidence of their

benefit for acute and sub-acute low back pain is of low quality. For chronic back pain however, there is evidence for small to moderate treatment relief.

Cognitive-behavioral therapy is a well-established treatment for pain that involves helping the person improve coping skills, address negative thoughts and emotions that can amplify pain, and learn relaxation methods to help prepare for and cope with pain. It is used for chronic pain, postoperative pain, cancer pain, and the pain of childbirth. Many clinical studies provide evidence for the effectiveness of this form of treatment in pain management.

Counseling can give an individual suffering from pain much needed support, whether it comes from family, group, or individual counseling. Support groups can provide an important supplement to drug or surgical treatment. Psychological treatment can also help people learn about the physiological changes produced by pain.

Electrical stimulation, including transcutaneous electrical stimulation (TENS), implanted electric nerve stimulation, and deep brain or spinal cord stimulation, is the modern-day extension of age-old practices in which the nerves or muscles are subjected to a variety of stimuli, including heat or massage. The following techniques each require specialized equipment and personnel trained in the specific procedure being used:

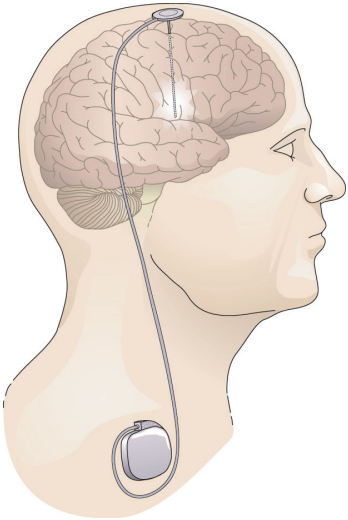
- **TENS** uses tiny electrical pulses, delivered through the skin to nerve fibers, to cause changes in muscles, such as numbness or contractions. This in turn produces temporary pain relief. There is also evidence that TENS can activate subsets of peripheral nerve fibers that can block

pain transmission at the spinal cord level, in much the same way that shaking your hand can reduce pain.

- **Peripheral nerve stimulation** uses electrodes placed surgically or percutaneously (through the skin using a needle) on a peripheral nerve. The individual is then able to deliver an electrical current as needed to the affected nerve, using a controllable electrical generator.
- **Spinal cord stimulation** uses electrodes surgically or percutaneously inserted within the epidural space of the spinal cord. The individual is able to deliver a pulse of electricity to the spinal cord using an implanted electrical pulse generator that resembles a cardiac pacemaker.

Deep brain stimulation is considered a more extreme treatment and involves surgical stimulation of the brain, usually the thalamus or motor cortex. It is used to treat chronic pain in cases that do not respond to less invasive or conservative treatments.

Exercise also may be part of the pain treatment regime for some people with pain. Because there is a known link between many types of chronic pain and tense, weak muscles, exercise—even light to moderate exercise such as walking or swimming—can contribute to an overall sense of well-being by improving blood and oxygen flow to muscles. Just as we know that stress contributes to pain, we also know that exercise, sleep, and relaxation can all help reduce stress, thereby helping to alleviate pain. Moderate exercise has been proven to help many people with low back pain. It is important, however, to work with a physician or physical therapist to create an appropriate routine.



Deep brain stimulation, or DBS, which involves surgical stimulation of the brain, is considered a more extreme pain treatment and is used for cases that do not respond to less invasive treatments.

Hypnosis was first approved for medical use by the American Medical Association in 1958. In general, hypnosis is used to control physical function or response, that is, the amount of pain an individual can withstand. How hypnosis works is not fully understood. Some believe that hypnosis delivers the person into a trance-like state, while others feel that the individual is simply better able to concentrate and relax or is more responsive to suggestion. Hypnosis may result in relief of pain by acting on chemicals in the nervous system, slowing impulses. Whether and how hypnosis works involves greater insight—and research—into the mechanisms underlying human consciousness.

Low-power lasers have been used occasionally by some physical therapists as a treatment for pain, but like many other treatments, this method is not without controversy.

Magnets are increasingly popular with athletes who are convinced of their effectiveness for the control of sports-related pain and other painful conditions. Usually worn as a collar or wristwatch, the use of magnets as a treatment dates back to the ancient Egyptians and Greeks. Although some individuals view magnet therapy with skepticism, proponents offer the theory that magnets may effect changes in cells or body chemistry, thus producing pain relief.

Marijuana or, by its Latin name, *cannabis*, continues to remain highly controversial as a pain killer. In the eyes of many individuals campaigning on its behalf, marijuana rightfully belongs with other pain remedies. Scientific studies are underway to test the safety and usefulness of cannabis for treating certain medical conditions. Currently, smoking marijuana is not recommended for the treatment of any disease or condition. In fact, federal law prohibits the use of cannabis. However, a number of states and the District of Columbia permit its use for certain medical problems.

Narcotics (see Opioids, page 22).

Nerve blocks employ the use of drugs, chemical agents, or surgical techniques to interrupt the relay of pain messages between specific areas of the body and the brain. There are many different names for the procedure, depending on the technique or agent used. Types of surgical nerve blocks include neurectomy; spinal dorsal, cranial, and trigeminal rhizotomy; and sympathectomy, also called sympathetic blockade.

Nerve blocks may involve local anesthesia, regional anesthesia or analgesia, or surgery; dentists routinely use them for traditional dental procedures. Nerve blocks can also be used to prevent or even diagnose pain and may involve injection of local anesthetics to numb the nerve and/or steroids to reduce inflammation.

In the case of a local nerve block, any one of a number of local anesthetics may be used, such as lidocaine or bupivicaine. Peripheral nerve blocks involve targeting a nerve or group of nerves that

Exercise can contribute to an overall sense of well-being by improving blood and oxygen flow to muscles.

innervate a part of the body. Nerve blocks may also take the form of what is commonly called an epidural, in which a drug is administered into the space between the spine's protective covering (the dura) and the spinal column. This procedure is most well known for its use during childbirth. However it is also used to treat acute or chronic leg or arm pain due to an irritated spinal nerve root.

- **Sympathectomy**, also called **sympathetic blockade**, typically involves injecting local anesthetic through a needle next to the sympathetic nervous system. The procedure is often performed to treat neuropathic pain of a limb (e.g. complex regional pain syndrome) as well as vascular disease pain, and other conditions. In some cases, a drug called guanethidine is administered intravenously in order to accomplish the block.
- **Neurolytic blocks** employ injection of chemical agents such as alcohol, phenol, or glycerol—or the use of radiofrequency energy—to kill nerves responsible for the transmission of nociceptive signals. Neurolytic blocks are most often used to treat cancer pain or to block pain in the cranial nerves (see The Nervous Systems).
- **Surgical blocks** are performed on cranial, peripheral, or sympathetic nerves. They are most often done to relieve the pain of cancer and

extreme facial pain, such as that experienced with trigeminal neuralgia. There are several different types of surgical nerve blocks and they are not without problems and complications. Nerve blocks can cause muscle paralysis and, in many cases, result in at least partial numbness. For that reason, the procedure should be reserved for a select group of patients and should only be performed by skilled surgeons. Types of surgical nerve blocks include:

- **Spinal dorsal rhizotomy**, in which the surgeon cuts the root or rootlets of one or more of the nerves radiating from the spinal cord. Other rhizotomy procedures include **cranial rhizotomy** and **trigeminal rhizotomy**, performed as a treatment for extreme facial pain or for the pain of cancer.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (including aspirin, ibuprofen and naproxen) are widely prescribed and sometimes called non-narcotic or non-opioid analgesics. They work by reducing inflammatory responses in tissues. Many of these drugs irritate the stomach and for that reason are usually taken with food. NSAIDS can also adversely affect the kidneys and heart and should be taken with caution by people with kidney dysfunction, heart disease, or hypertension.

- **Aspirin** may be the most widely used pain-relief agent and has been sold over-the-counter since 1905 as a treatment for fever, headache, and muscle soreness.

- **COX-2 inhibitors** may be effective for individuals with arthritis. COX-2 inhibitors

work by blocking two enzymes, cyclooxygenase-1 and cyclooxygenase-2, both of which promote production of hormones called *prostaglandins*, which in turn cause inflammation, fever, and pain. COX-2 inhibitors primarily block cyclooxygenase-2 and are less likely to have the gastrointestinal side effects sometimes produced by NSAIDs. Due to possible increased cardiovascular risk and gastrointestinal bleeding, the American Geriatic Association recommended in 2009 that NSAIDs and COX-2s be considered rarely for older people, and with extreme caution. Individuals taking any of the COX-2 inhibitors should review their drug treatment with their doctors.

- **Ibuprofen** is a member of the aspirin family of analgesics. It is sold over the counter and also comes in prescription-strength preparations.

Opioids are derived from the poppy plant and are among the oldest drugs known to humankind. They include codeine and perhaps the most well-known opioid of all, **morphine**. Morphine can be administered in a variety of forms, including a pump for self-administration. Opioids are extremely effective in treating acute pain. Opioids have a narcotic effect, that is, they induce sedation as well as pain relief. In addition to drowsiness, other common side effects include constipation, nausea, and vomiting. Opioids are addictive, with severely unpleasant and potentially dangerous withdrawal symptoms occurring when drugs are stopped. Chronic opioid use is a major health problem, stimulating research to develop a less addictive alternative for severe pain. For these reasons,

people given opioids should be monitored carefully. Research is still needed to determine which patients will most benefit from opioids and which patients are most vulnerable to their addicting properties.

Rest, Ice, Compression, and Elevation—are four components prescribed by many orthopedists, coaches, trainers, nurses, and other professionals for temporary muscle or joint injuries, such as sprains or strains.

Physical therapy and rehabilitation date back to the ancient practice of using physical techniques and methods, such as heat, cold, exercise, massage, and manipulation, in the treatment of certain conditions. These may be applied to increase function, control pain, and gain full recovery.

Placebo is not a treatment for pain but is an effect generally used in clinical studies as a control factor to help determine the effectiveness of an active treatment. Placebos are inactive substances, such as sugar pills, or harmless procedures, such as saline injections or sham surgeries. Placebos offer some individuals pain relief although how they have an effect is mysterious and somewhat controversial. Although placebos have no direct effect on the underlying causes of pain, evidence from clinical studies suggests that many pain conditions such as migraine headache, back pain, post-surgical pain, rheumatoid arthritis, angina, and depression sometimes respond well to them. This positive response is known as the placebo response, which is defined as the observable or measurable change that can occur in people after administration of a placebo. One large component responsible for the

effect of placebo is the degree to which people expect the treatment to work. Placebos work, in part, by stimulating the brain's own analgesics.

R.I.C.E.—**R**est, **I**ce, **C**ompression, and **E**levation—are four components prescribed by many orthopedists, coaches, trainers, nurses, and other professionals for temporary muscle or joint injuries, such as sprains or strains. Ice is used to reduce the inflammation associated with painful and acute injuries. Ice or heat may be recommended to relieve subacute and chronic pain, allowing for reduced inflammation and increased mobility. While many common orthopedic problems can be controlled with these four simple steps, especially when combined with over-the-counter pain relievers, more serious conditions may require surgery or physical therapy, including exercise, joint movement or manipulation, and stimulation of muscles.

Serotonergic agonists—the triptans (including sumatriptan, naratriptan, and zolmitriptan)—are used specifically for acute migraine headaches. They can have serious side effects in some people and therefore, as with all prescription medicines, should be used only under a doctor's care.

Surgery, although not always an option, may be required to relieve pain, especially pain caused by back problems or serious musculoskeletal injuries. Surgery may take the form of a nerve block or it may involve an operation to relieve pain from a ruptured disc. Surgical procedures for pain due to a vertebral disc pressing on a nerve root or spinal

cord include **discectomy** or, when microsurgical techniques are used, **microdiscectomy**, in which the part of or the entire disc is removed; **laminectomy**, a procedure in which a surgeon opens up the arched portion of a vertebra, thereby allowing the nerve root to exit more freely; and **spinal fusion**, in which two or more vertebral segments are fused together. Although the operation can cause the spine to stiffen, resulting in lost flexibility, the procedure serves one critical purpose: protection of the spinal cord. Other operations for pain include **rhizotomy**, in which a nerve close to the spinal cord are burned or cut, and **cordotomy**, where bundles of nerves within the spinal cord are severed. Cordotomy is generally used only for the pain of terminal cancer that does not respond to other therapies. Another operation for pain is the **dorsal root entry zone operation**, or DREZ, in which spinal neurons corresponding to the individual's pain are destroyed surgically. **Microvascular decompression**, in which tiny blood vessels are surgically separated from surrounding nerves, is helpful for some individuals suffering from trigeminal neuralgia who are not responsive to drug treatment. Because surgery can result in scar tissue formation that may cause additional problems, people are well advised to seek a second opinion before proceeding.

Surgical procedures are not always successful. The related risks associated and other treatment options should be explored and considered. There is little measurable evidence to show which procedures work best for their particular indications.

Gender and Pain

Pain affects men and women differently. According to a recent IOM report, women are at a greater risk for many pain conditions and are likely to experience more pain from certain diseases, like cancer, than men.

It is widely believed that pain affects men and women differently. In fact, according to the Institute of Medicine's 2011 report: *Relieving Pain in America*, women often report a higher prevalence of chronic pain than men and are at a greater risk for many pain conditions. Women are likely to have more pain from certain diseases, such as cancer. Also, a number of chronic pain disorders occur only in women and others occur predominantly in women. These include chronic fatigue syndrome, endometriosis, fibromyalgia, interstitial cystitis, vulvodynia, and tempromandibular disorders.

The IOM report mentions at least three theories that may explain the differences in pain experience by gender:

- A gender-role theory that assumes it is more socially acceptable for women to report pain;
- An exposure theory that suggests women are exposed to more pain risk factors; and
- A vulnerability theory proposing that women are more vulnerable to developing certain types of pain, such as musculoskeletal pain.

Of these, the vulnerability theory is best supported by scientific evidence.

A greater understanding of gender differences in pain may lead to better avenues of pain management.

Pain in the Elderly and Children

Pain is the number one complaint of older Americans, and one in five older Americans takes a painkiller regularly. Pain management in older people differs from than in younger people. For example, older persons are much more likely to experience medication-related side effects than younger ones. In 1998, the American Geriatrics Society (AGS) issued guidelines* for improving the management of pain and quality of life in older people. The guidelines contained several non-drug approaches to treatment, including exercise, and recommended that, whenever possible, people use alternatives to aspirin, ibuprofen, and other NSAIDs because of the drugs' side effects, including stomach irritation and gastrointestinal bleeding.

The guidelines were updated in 2002 and again in 2009. In the updated guidelines, the AGS recommends that NSAIDs and COX-2s be considered rarely, and with extreme caution, in highly selected individuals due to possible increased cardiovascular risk and gastrointestinal bleeding.

---

*Journal of the American Geriatrics Society (2009; 57:1331-1346).

The primary aims of pain research include preventing chronic pain and developing better treatments for pain.

For older adults, acetaminophen is the first-line treatment for mild to moderate pain, according to the guidelines.

Pain in children also requires special attention, particularly because young children are not always able to describe the degree of pain they are experiencing. Although treating pain in children poses a special challenge to physicians and parents alike, children should never be undertreated. Special tools for measuring pain in children have been developed that, when combined with cues used by parents, help physicians select the most effective treatments.

Nonsteroidal agents, and especially acetaminophen, are most often prescribed for control of pain in children. In the case of severe pain or pain following surgery, acetaminophen may be combined with codeine.

What is the Future of Pain Research?

In the forefront of pain research are scientists supported by the National Institutes of Health (NIH), including the National Institute of Neurological Disorders and Stroke (NINDS), which is the primary federal supporter of research on the brain and nervous system. Twenty institutes and centers at NIH support pain research and as members of the NIH Pain Consortium, participate in many activities

that support and promote excellence in pain research. Preventing chronic pain and developing better pain treatments are the primary goals of pain research being conducted by these institutes and centers.

An increased understanding of the basic mechanisms of pain will have profound implications for the development of future medicines. The following areas of research are bringing us closer to an ideal pain drug. One objective is to formulate compounds that will prevent pain signals from being amplified by the nervous system or to block certain steps in the pain pathway, especially in conditions when there is no injury or trauma. Many of these agents are still in the early phase of development and not ready for widespread clinical use. However, they do appear promising in many early-phase studies.

Receptors: The idea of using receptors as gateways for pain drugs is a novel approach, supported by experiments involving substance P. Investigators isolated a tiny population of neurons, located in the spinal cord, which contribute to the pathway responsible for carrying pain signals to the brain. This group of cells is killed when animals are given injections of a neurotoxic cocktail of substance P linked to the chemical toxin saporin. Within days of the injections, the targeted neurons, located in the outer layer of the spinal cord, absorbed the compound and were destroyed. The animals no longer exhibited signs of persistent pain following injury, nor had an exaggerated pain response. The animals still detected noxious stimuli however, which allowed them to protect their bodies from potential injury.

There are other receptor targets being used as entry portals to selectively destroy nerves that transmit pain signals. Resinoferatoxin is a plant-derived chemical that uses a vanilloid receptor called TRPV1. (TRPV1 senses heat from hot chili peppers.) Research using this toxin has advanced to the clinic, where it is being tested on people with cancer who have uncontrolled pain. Capsaicin also uses this receptor to reach pain-sensing nerves and is delivered through the skin as an ointment or patch to deliver local pain relief.

Channels: The frontier in the search for new drug targets is represented by ion channels. Ion channels are gate-like passages found along the membranes of cells that allow electrically charged chemical particles called ions, like sodium, chloride, calcium, and potassium, to pass into the cells. Ion channels are important for transmitting signals through the nerve's membrane. The possibility now exists for developing new classes of drugs, including pain cocktails that would act at the site of channel activity. There is particular interest in developing drugs that modify channels that are only associated with the processing of signals responsible for pain. Currently, drugs that act on channels tend to be broad in the systems they act on, yielding not only pain relief but also many unpleasant side effects.

Trophic factors: A class of "rescuer" or "restorer" drugs may emerge from our growing knowledge of trophic factors, natural chemical substances found in the human body that affect the survival and function of cells. Trophic factors also prevent cell death and promote outgrowth of cell processes and

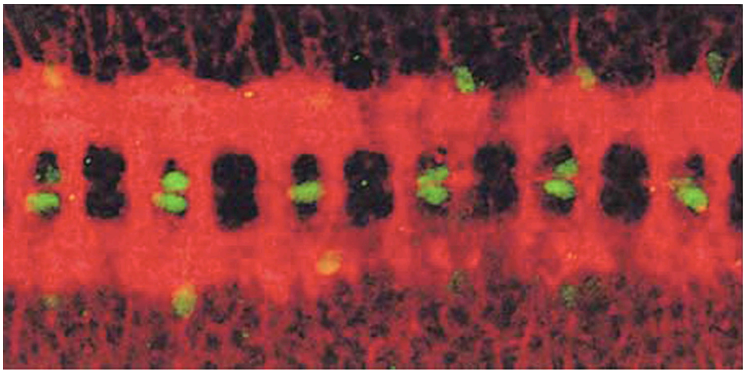
new connections between nerve cells. Investigators have observed that an over-accumulation of certain trophic factors in the nerve cells of animals results in heightened pain sensitivity, and that some receptors found on cells respond to trophic factors and interact with each other. These receptors may provide targets for new pain therapies.

Trophic factors also prevent cell death and promote outgrowth of cell processes and new connections between nerve cells.

Gene transfer: The body's natural or endogenous pain killers can be activated to fight pain through a powerful new tool that delivers genes instead of drugs to the body. Nerves that carry pain signals again may be the selected target, but in this case a gene is delivered to the nerve fiber. Genes also may be delivered to the spinal cord sites of pain-signaling neurons. The carrier for the gene is most often an inactive virus that is taken up by the nerves, like the herpes virus which causes cold sores, and transferred by them to the spinal cord. When the gene reaches its target, it produces the neurotransmitter for which it is programmed. After many years of preclinical studies, the first human trial to test this system has been completed. The researchers used a modified virus to carry the gene for enkephalin—an endogenous opioid peptide—to the spinal cord. The increased production of enkephalin was effective in ameliorating pain. Researchers have been able to transfer many different genes that target the pain-signaling pathway and are continuously improving the methods.

Imaging: Mapping pain to precise areas of the brain is becoming possible in patients. Positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and other imaging technologies offer pictures of what happens in the brain as it processes pain. Using imaging, investigators have identified key brain areas activated in response to pain. When they applied the technology to people with persistent pain, they discovered structural and functional differences compared to the brains of healthy people. Now, technical advances in imaging give us a view of how functional connections between areas of the brain change in chronic pain states compared to resting or non-pain states. This tool looks promising as a marker for chronic pain and as a means to determine whether analgesics or non-pharmacological pain therapies can reverse the functional changes in the brain associated with chronic pain.

Plasticity: Nervous system sensitization underscores the notion that chronic pain should be considered a disease of the nervous system, not simply a symptom of a chronic injury. Scientists hope that therapies directed at preventing the long-term changes that occur at all levels in the pain-signaling pathways in the nervous system will prevent the development of chronic pain conditions. Many steps in the pathway are targets for development of novel pain analgesics. Non-neuronal glial cells are recognized as playing an important role in the maladaptive plasticity associated with persistent pain, through their interaction with pain-related neurons, and are recognized as potential targets for drug therapy to treat pain. Glial cells are far more numerous than neurons in the brain and spinal cord. Their role in modulating neuronal communication and



Glial cells are potential targets for drug therapy to treat pain. The picture above shows glial cells (stained green) in a fruit fly embryo, located along a signaling pathway initiated by neighboring nerve cells (stained red).

in the immune response to injury and neural inflammation contributes to nervous system sensitization. Inhibition of glial activity reduces symptoms of neuropathic pain in animal models. As our knowledge of glial modulators expands, the opportunities to use them to alter glial activity and, thus, prevent or reverse chronic pain grow. Animal and a small number of human studies show that molecules that alter glial activity reduce chronic pain symptoms, enhance morphine analgesia, and reduce morphine tolerance. Glial cell modulation offers an exciting new area for both preventing and treating chronic pain.

Hope for the Future

Thousands of years ago, ancient peoples attributed pain to spirits and treated it with mysticism and incantations, which may very well have helped by engaging the placebo response. Over the centuries, science has provided us with a remarkable ability

to understand and control pain. Today, scientists understand a great deal about the causes and mechanisms of pain, and research has produced dramatic improvements in the diagnosis and treatment of a number of painful disorders. For people who fight every day against the limitations imposed by pain, the work of NINDS-supported scientists holds the promise of an even greater understanding of pain in the coming years. Their research offers a powerful weapon in the battle to prolong and improve the lives of people with pain: *hope*.

The A to Z of Pain

Hundreds of pain syndromes or disorders make up the spectrum of pain. There are the most benign, fleeting sensations of pain, such as a pin prick. There is the pain of childbirth, the pain of a heart attack, and the pain that sometimes follows amputation of a limb. There is also pain accompanying cancer and the pain that follows severe trauma, such as that associated with head and spinal cord injuries. A sampling of common pain syndromes follows, listed alphabetically.

Arachnoiditis is a condition in which one of the three membranes covering the brain and spinal cord, called the arachnoid membrane, becomes inflamed. A number of causes, including infection, chemical irritation, or trauma, can result in inflammation of this membrane. Arachnoiditis can produce disabling, progressive, and even permanent pain.

Arthritis, characterized by joint pain in the extremities, is one of many disorders in the spectrum of pain.

Arthritis. Millions of Americans suffer from arthritic conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and gout. These disorders are characterized by joint pain in the extremities. Many other inflammatory diseases affect the body's soft tissues, including tendonitis and bursitis.

Back pain has become the high price paid by our modern lifestyle and is a startlingly common cause of disability for many Americans, including both active and inactive people. Back pain that spreads to the leg is called sciatica and is a very common condition (see Sciatica, page 40). Another common type of back pain is associated with the discs of the spine, the soft, spongy padding between the vertebrae (bones) that form the spine. Discs protect the spine by absorbing shock, but they tend to degenerate over time and may sometimes rupture. Of note, as people age, discs tend to normally lose elasticity and degenerate. This process, by itself, is not necessarily associated with pain. **Spondylolisthesis** occurs when one vertebra extends over another and may result in pressure on nerve roots and therefore pain. It also may cause damage to nerve roots (see Spine Basics in the Appendix) so called **radiculopathy**, which can be extremely painful and can be associated with weakness or numbness due to nerve compression. Treatment for a damaged disc includes drugs such as painkillers, muscle relaxants, and steroids

(administered orally or via epidural); exercise or rest, depending on the patient's condition; adequate support, such as a brace or better mattress; and physical therapy. In some cases, surgery may be required to remove the damaged portion of the disc, especially when it is pressing a nerve root. However, surgery cannot return the disc to its original condition, it can only relieve the pressure on the nerve root. Surgical procedures include discectomy, laminectomy, or spinal fusion (see section on Surgery in How is Pain Treated? for more information on these treatments).

Burn pain (pain that is caused by burns) can be profound and poses an extreme challenge to the medical community. Depending on the injury, pain accompanying burns can be excruciating, and even after the wound has healed people may have chronic pain at the burn site.

Cancer pain can accompany the growth of a tumor, the treatment of cancer, or chronic problems related to cancer's permanent effects on the body. Fortunately, most cancer pain can be treated to help reduce discomfort and stress.

Central pain syndrome affects some individuals who have had an injury to the spinal cord and experience intense pain ranging from tingling to burning and, commonly, both. Such persons are sensitive to hot and cold temperatures and touch. For these individuals, a touch can be perceived as intense burning, indicating abnormal signals relayed to and from the brain. This condition is called **central pain syndrome** or, if the damage is in the thalamus (the brain's center for processing bodily sensations), **thalamic pain syndrome**.

Central pain syndromes affect as many as 100,000 Americans with disorders such as multiple sclerosis, Parkinson's disease, amputated limbs, spinal cord injuries, and stroke. Their pain may be severe and is extremely difficult to treat effectively. A variety of medications, including analgesics, antidepressants, anticonvulsants, and electrical stimulation, are options available to people with central pain.

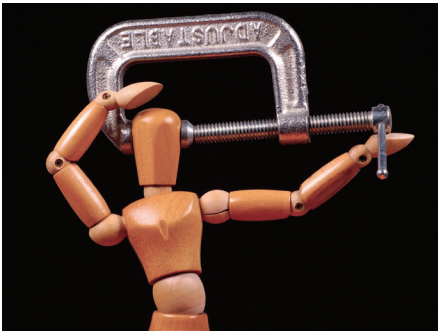
Complex regional pain syndrome (CRPS) is accompanied by burning pain and hypersensitivity to temperature. Often triggered by trauma or nerve damage, CRPS causes the skin of the affected area to become characteristically shiny and the limb swollen. In the past, CRPS was often called **reflex sympathetic dystrophy syndrome** or **causalgia**.

Fibromyalgia affects millions of Americans, more often women than men. It is a disorder characterized by fatigue, sleep disturbances, stiffness, tender points, joint tenderness, and widespread muscle pain.

Headaches affect millions of Americans. The three most common types of chronic headache are migraines, cluster headaches, and tension headaches. Each comes with its own telltale brand of pain.

- **Migraines** are characterized by throbbing head pain, sensitivity to light and sound, and sometimes by other symptoms, such as nausea, dizziness, and visual disturbances that begin before the headache. Migraines are more frequent in women than men. Stress can trigger a migraine headache, and migraines only very rarely put the sufferer at risk for stroke.

- **Cluster** headaches are characterized by excruciating, piercing pain on one side of the head and eye; they occur more frequently in men than women.
- **Tension headaches** are often described as a tight band around the head.



Tension headaches are one of the most common types of headache and are often described as having a band or "vice" being tightened around the head.

Head and facial pain can be agonizing, whether it results from dental problems or from disorders such as cranial neuralgia, in which one of the nerves in the face, head, or neck is inflamed. Another condition, **trigeminal neuralgia** (also called tic douloureux), affects the largest of the cranial nerves (see The Nervous Systems in the Appendix) and is characterized by a stabbing, shooting pain.

Muscle pain can range from an aching muscle, spasm, or strain, to the severe spasticity that accompanies paralysis. **Polymyositis**, **dermatomyositis**, and **inclusion body myositis** are painful disorders characterized by muscle inflammation. They may be caused by infection or autoimmune dysfunction and are sometimes associated with connective tissue disorders, such as lupus and rheumatoid arthritis.

Myofascial pain syndromes affect sensitive areas known as trigger points, located within the body's muscles.

Neuropathic pain is a type of pain that can result from injury to nerves, either in the peripheral or central nervous system (see The Nervous Systems in the Appendix). Neuropathic pain can occur in any part of the body and is frequently described as a hot, burning sensation, which can be devastating to the affected individual. It can result from diseases that affect nerves (such as diabetes) or from trauma, or, because chemotherapy drugs can affect nerves, it can be a consequence of cancer treatment. Among the many neuropathic pain conditions are **diabetic neuropathy** (which results from nerve damage secondary to vascular problems that occur with diabetes); **complex regional pain syndrome**, which can follow injury; **phantom limb** and **post-amputation pain** (see Phantom Pain in the Appendix), which can result from the surgical removal of a limb; **postherpetic neuralgia**, which can occur after an outbreak of shingles; and **central pain syndrome**, which can result from trauma, stroke, or injury to the brain or spinal cord.

Repetitive stress injuries are muscular conditions that result from repeated motions performed in the course of normal work or other daily activities. They include:

- writer's cramp, which affects musicians and writers and others,
- compression or entrapment neuropathies, including carpal tunnel syndrome, and
- tendonitis or tenosynovitis, affecting one or more tendons.

Sciatica is a generic term representing pain in the buttocks that continues down into the thighs, legs, ankles, and feet . Sciatica can be caused by a number of factors, including an injury or irritation to the nerve roots exiting the spinal cord that make up the sciatic nerve (e.g. herniated disc), or to the sciatic nerve directly.

Shingles and other painful disorders affect the skin and nerves. Pain is a common symptom of many skin disorders, even the most common rashes. One of the most distressing neurological disorders is shingles or herpes zoster, an infection that often causes agonizing pain resistant to treatment. Prompt treatment with antiviral agents is important to stop the infection and prevent an associated condition known as **postherpetic neuralgia**. Since postherpetic neuralgia is more common in the elderly, a vaccine is often recommended for persons over age 60 as part of one's proactive health care. Other painful disorders affecting the skin include:

- **vasculitis**, or inflammation of blood vessels;
- other infections, including **herpes simplex**;
- skin **tumors** and **cysts**, and
- tumors associated with **neurofibromatosis**, a neurogenetic disorder.

Injury and pain are common words in the language of sports. Sports-related injuries can be costly and painful, causing suffering and disability.

Sports injuries are common. Sprains, strains, bruises, dislocations, and fractures are all well-known words in the language

of sports. Pain is another. In extreme cases, sports injuries can take the form of costly and painful spinal cord and head injuries, which cause severe suffering and disability.

Spinal stenosis refers to a narrowing of the canal surrounding the spinal cord. The condition occurs naturally with aging. Spinal stenosis causes weakness in the legs and leg pain usually felt while the person is standing up and often relieved by sitting down.

Surgical pain may require regional or general anesthesia during the procedure and medications to control discomfort following the operation. Control of pain associated with surgery includes presurgical preparation and careful monitoring during and after the procedure.

Temporomandibular disorders are conditions in which the temporomandibular joint (the jaw) is damaged and/or the muscles used for chewing and talking become stressed, causing pain. The condition may result from a number of factors, such as an injury to the jaw or joint misalignment. It may give rise to a variety of symptoms, most commonly pain in the jaw, face, and/or neck muscles. Physicians reach a diagnosis by listening to the individual's description of the symptoms and by performing a simple examination of the facial muscles and the temporomandibular joint.

Trauma can occur after injuries in the home, at the workplace, during sports activities, or on the road. Any of these injuries can result in severe disability and pain.

Vascular disease or injury—such as vasculitis or inflammation of blood vessels, coronary artery disease, and circulatory problems—all have the potential to cause pain. Vascular pain affects millions of Americans and occurs when communication between blood vessels and nerves is interrupted. Ruptures, spasms, constriction, or obstruction of blood vessels, as well as a condition called ischemia in which blood supply to organs, tissues, or limbs is cut off, can also result in pain.

Appendix

Spine Basics: The Vertebrae, Discs, and Spinal Cord

Stacked on top of one another in the spine are more than 30 bones, the vertebrae, which together form the spine. They are divided into four regions:

- the seven cervical or neck vertebrae (labeled C1-C7),
- the 12 thoracic or upper back vertebrae (labeled T1-T12),
- the five lumbar vertebrae (labeled L1-L5), which we know as the lower back, and
- the sacrum and coccyx, a group of bones fused together at the base of the spine.

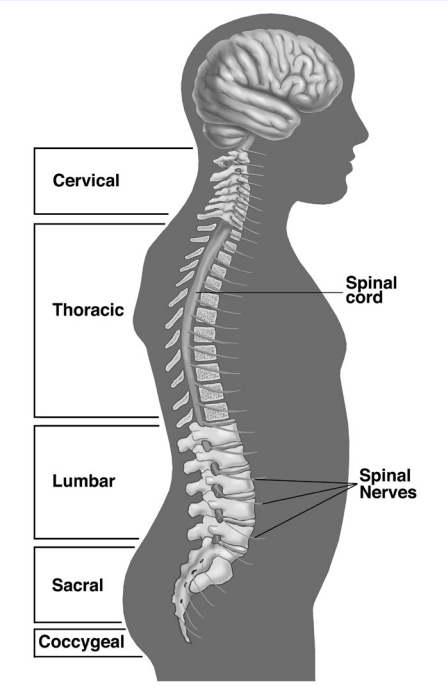
The vertebrae are linked by ligaments, tendons, and muscles. Back pain can occur when, for example, someone lifts something too heavy, causing a sprain, pull, strain, or spasm in one of these muscles or ligaments in the back.

Between the vertebrae are round, spongy pads of cartilage called *discs* that act much like shock absorbers. In many cases, degeneration or pressure from overexertion can cause a disc to shift or protrude and bulge, causing pressure on a nerve and resultant pain. When this happens, the condition is called a slipped, bulging, herniated, or ruptured disc, and it sometimes results in permanent nerve damage.

The column-like spinal cord is divided into segments similar to the corresponding vertebrae: cervical, thoracic, lumbar, sacral, and coccygeal. The cord also has nerve roots and rootlets which form branch-like appendages leading from its ventral side (that is, the front of the body) and from its dorsal side (that is, the back of the body). Along the dorsal root are the cells of the dorsal root ganglia, which are critical in the transmission of "pain" messages from the cord to the brain. It is here where injury, damage, and trauma become pain.

The Nervous Systems

The central nervous system (CNS) refers to the brain and spinal cord together. The peripheral nervous system refers to the cervical, thoracic, lumbar, and sacral nerve trunks leading away from the spine to the limbs. Messages related to function (such as movement) or dysfunction (such as pain) travel from the brain to the spinal cord and from there to other regions in the body and back to the brain. The autonomic nervous system controls involuntary functions in the body, like perspiration, blood pressure, heart rate, or heart beat. It is divided into the sympathetic and parasympathetic nervous



This diagram of the spine shows the regions of vertebrae. The spinal cord is divided into segments similar to the corresponding vertebrae.

systems. The sympathetic and parasympathetic nervous systems have links to important organs and systems in the body; for example, the sympathetic nervous system controls the heart, blood vessels, and respiratory system, while the parasympathetic nervous system controls our ability to sleep, eat, and digest food.

The peripheral nervous system also includes 12 pairs of cranial nerves located on the underside of the brain. Most relay messages of a sensory nature. They include the olfactory (I), optic (II), oculomotor (III), trochlear (IV), trigeminal (V), abducens (VI), facial (VII), vestibulocochlear (VIII), glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII) nerves. Neuralgia, as in trigeminal neuralgia, is a term that refers to pain that arises from abnormal activity of a nerve trunk or its branches. The type and severity of pain associated with neuralgia vary widely.

Phantom Pain: How Does the Brain Feel?

Sometimes, when a limb is removed during an amputation, an individual will continue to have an internal sense of the lost limb. This phenomenon is known as phantom limb and accounts describing it date back to the 1800s. Similarly, many amputees are frequently aware of severe pain in the absent limb. Their pain is real and is often accompanied by other health problems, such as depression, anxiety, sleep disorders, and a general decrease in quality of life.

What causes this phenomenon? Scientists believe that following amputation, nerve cells “rewire” themselves and continue to receive messages,

resulting in a remapping of the brain's circuitry. The brain's ability to restructure itself, to change and adapt following injury, is called plasticity (see section on Plasticity).

Our understanding of phantom pain has improved tremendously in recent years. Investigators previously believed that brain cells affected by amputation simply died off. They attributed sensations of pain at the site of the amputation to irritation of nerves located near the limb stump. Now, using imaging techniques such as positron emission tomography (PET) and magnetic resonance imaging (MRI), scientists can actually visualize increased activity in the brain's cortex when an individual feels phantom pain. When study participants move the stump of an amputated limb, neurons in the brain remain dynamic and excitable. Surprisingly, the brain's cells can be stimulated by other body parts, often those located closest to the missing limb.

Treatments for phantom pain may include analgesics, anticonvulsants, and other types of drugs; nerve blocks; electrical stimulation; psychological counseling, biofeedback, hypnosis, and acupuncture; and, in rare instances, surgery.

Credits

Illustrations and photos:

Tina Carvalho, University of Hawaii at Manoa—page 5

Courtesy of Roche—page 6

John Crawford, MedArts, NIH—page 11

Bill Branson, NIH, for NCI—page 20

NINDS DIR, NIH—page 28

Andreas Bergmann and Hermann Steller, Rockefeller University—page 33

National Institute of
Neurological Disorders
and Stroke

NIH . . . Turning Discovery Into Health

Prepared by:

Office of Communications and Public Liaison
National Institute of Neurological Disorders and Stroke
National Institutes of Health
Bethesda, Maryland 20892

NIH Publication No. 14-2406
January 2014