Analgesia: How the Body Inhibits Pain Perception

Over the past few years a great deal of evidence has indicated that the body has a built-in mechanism for killing pain. Although pain is a warning of bodily danger, the capacity to suppress awareness of it could help an animal to survive by preventing its incapacitation in life-threatening situations. Even more important to the clinician is the possibility that research into the body's intrinsic pain-killing system may aid in the development of more effective therapies for controlling pain in humans. Neurosurgeons have already begun to apply the research results to the treatment of patients suffering from debilitating and intractable pain. In addition, investigators have now suggested that acupuncture may produce analgesia by stimulating neural pathways that suppress pain.

The current idea is that certain brain centers, when appropriately activated, send nerve impulses down the spinal cord to block incoming pain signals before they reach the brain; the individual is thus prevented from perceiving the pain. In an early experiment done in 1971, David Mayer, now at the Medical College of Virginia; Huda Akil, who is currently at Stanford University Medical School; and John Liebeskind of the University of California at Los Angeles (UCLA), showed that electrical stimulation of a region (called the periaqueductal or central gray matter) in the midbrains of rats abolished the animals' responsiveness to pain. The stimulation usually produced analgesia in only one half or one quadrant of the body, and the animals responded normally to noxious stimuli in the unaffected areas. Moreover, they responded to nonpainful stimuli, such as light touch, even in the affected body parts. Similar effects were later found in cats.

Electrical stimulation of appropriate regions of the human brain also alleviates pain. In a preliminary experiment, Akil and neurosurgeon Donald Richardson of Tulane University Medical School tested the effects of stimulation for short lengths of time on patients who were undergoing another kind of brain surgery for relief of chronic pain. When the investigators placed the electrodes in the central gray matter, the patients did experience relief but it was accompanied by unacceptable side effects including nausea and dizziness. Another possible problem that must be avoided is the positioning of the electrodes in areas where stimulation may alter behavior. However, when the electrodes were implanted in a region called the periventricular gray matter, stimulation produced analgesia with only slight side effects such as a mild tingling sensation.

A number of neurosurgeons, including Richardson and John Adams of the University of California at San Francisco (UCSF), are now studying the use of permanent electrode implants in the brain for treatment of patients suffering from intractable pain that has not responded to more conventional therapies. The patients include persons with advanced cancer, amputees with "phantom-limb" pain, and individuals with chronic pain resulting from nerve or brain damage. The implants do not always work; pain resulting from brain damage is particularly difficult to control, according to Adams. But when they do the results can be dramatic and the individuals may lead much more normal lives.

Implanting Electrodes in Humans

The implant operation is done in two stages. In the first, with the patients receiving only a local anesthetic, the electrode is positioned in the brain and tested to determine whether stimulation produces analgesia without unacceptable side effects. Then, if it continues to work over a period of days or a few weeks, a second operation is performed in which the electrode wire is run under the skin to the chest where it terminates in an induction receiver about the size of a silver dollar. The patient activates the electrode by holding a stimulator that is approximately the size of a cigarette case against the receiver. Most persons can obtain several hours of pain relief by stimulating for 15 to 30 minutes.

Investigators think that stimulation of the central and periventricular gray areas produces analgesia by causing the release of endorphins (*Science*, 29 August 1975). Endorphins are substances that occur naturally in the brain and pituitary gland and mimic the effects, including analgesia, of opiates such as morphine. Morphine and the endorphins probably produce their effects by combining with specific receptors on nerve cells and altering neuronal function.

In 1971, the existence of opiate receptors and opiate-like substances in brain had not yet been established, although many investigators suspected that they were present. However, Mayer, Akil, and Liebeskind noted a number of similarities between the analgesia produced by brain stimulation and that evoked by morphine and suggested that the stimulation worked through the same neuronal pathways as the drug. One possible mechanism was that stimulation triggered the release of an endogenous opiate-like material. The discovery of the endorphins provided a prime candidate for this role.

One of the critical experiments in support of the hypothesis that electrical stimulation works through an endogenous opiate was the demonstration by Mayer, Akil, and Liebeskind that naloxone blocks—although not completely—the analgesic effects of the stimulation. Naloxone is a specific inhibitor of the action of both endogenous and exogenous opiates, and its reversal or blockage of an effect strongly indicates that the effect depends on opiate action.

Mayer and his colleagues in Richmond further showed that rats become tolerant to repeated or prolonged electrical stimulation in the same manner that they and other species, including humans, become tolerant to the analgesic and euphoric effects of morphine; that is, repeated stimulation or drug administration produces progressively less effect. Several investigators have evidence that the same thing happens when endorphins are administered to animals. And Adams and Akil say that patients with electrode implants in the periventricular gray matter may become tolerant, unless they are careful to restrict the stimulation to a few periods of 15 to 30 minutes per day. If stimulation does lose its effectiveness, however, it can be regained by simply not stimulating at all for a few days.

Akil and John Barchas of Stanford University Medical School have evidence that stimulating the central gray matter of rat brains increases endorphin release from the tissue. With John Hughes of the University of Aberdeen, Scotland, Akil is now attempting to determine whether the concentration of endorphins increases in the cerebrospinal fluid of humans with electrode implants.

Direct injection of morphine into an area near the central gray matter reliably produced analgesia in rats and at the same time increased neuronal firing in that part of the brain, according to Liebeskind. Injection of one of the endorphins into the same region produced anal-

gesia in eight of 19 rats tested and increased neuronal firing only in the eight with analgesia. This close association between neuronal firing and analgesia is further evidence for the importance of the central gray region in inhibiting pain perception.

However, the neurons of the central gray matter do not appear to directly connect with and inhibit the spinal nerve cells that transmit the incoming pain signals. Rather, neurons in the nucleus raphe magnus, which is located at the base of the brain, may serve as a relay station between the higher brain centers and the spinal nerve cells. Several investigators have shown that electrical stimulation of this nucleus gives rise to potent analgesic effects in animals.

The picture that has thus far developed is that stimulation of centers in the central gray area of the brain in turn stimulates nerve cells in the nucleus raphe magnus, and these ultimately inhibit the firing of nerves carrying pain signals into the spinal cord. Liebeskind and his colleagues at UCLA demonstrated that during analgesia induced by either morphine or stimulation of the central gray area, the spontaneous firing of neurons in the nucleus increased. They also measured the response of the nuclear nerve cells to painful stimuli applied to the extremities and found that during analgesia the responses were reduced. This reduction presumably reflects a decreased transmission of incoming pain signals.

There is now both functional and anatomical evidence linking the raphe nucleus with pain-transmitting neurons in the spinal cord. For example, Howard Fields and Allan Basbaum of UCSF demonstrated that electrical stimulation of the nucleus selectively inhibits the activity of pain-transmitting neurons in the spinal cords of cats. According to William Willis and his colleagues at the Marine Biomedical Institute in Galveston, stimulating the corresponding area in monkey brains inhibits the activity of several kinds of spinal neurons, although in these animals the stimulation inhibits the responses to nonpainful stimuli in addition to those to painful ones.

The evidence indicates that nerve processes from the raphe nucleus descend through the spinal cord in the dorsolateral tract. Basbaum found that cutting this portion of the cord blocks the analgesia produced by morphine injection and by stimulation of the central gray region. It also blocks the inhibitory effects of raphe nucleus stimulation on the pain-transmitting spinal neurons.

Basbaum and Fields recently demonstrated a direct anatomical connection between the nucleus and the spinal neurons. They injected the amino acid leucine bearing a radioactive label into the nucleus and showed that the radioactivity was transported down the spinal cord to the region of the incoming pain nerves through the dorsolateral tract.

Acupuncture Mechanism

The functioning of the intrinsic pain-inhibiting pathway depends on the release of endorphins that may be acting as neurotransmitters. Recent evidence indicates that the production of acupuncture analgesia also depends on release of the agents. Although the Chinese reportedly performed 400,000 operations between 1966 and 1972 on patients who had acupuncture for analgesia, the technique has been highly controversial among Western scientists. Many question not only how it works, but also whether it works. Or they think that acupuncture does not produce true analgesia in the sense of preventing the subjects from feeling pain but rather that it evokes psychological changes that make the patients more willing or able to tolerate the pain. One problem has been the lack of a generally accepted mechanism that explains how needles inserted in the body and rotated or electrically stimulated at one site could produce analgesia at a distant location. The discovery of the endorphins gave acupuncture investigators something new to look for, and evidence from studies with animals and humans indicates that acupuncture analgesia requires the release of the agents.

Bruce Pomeranz and his colleagues at the University of Toronto measured the responses of single neurons in the spinal cords of cats to noxious stimuli while performing acupuncture on the anesthetized animals. The needles, which were electrically stimulated, were inserted at what Pomeranz thinks are the feline equivalents of the futu and Yang Ling sites of the human. These sites are used to achieve analgesia in the feet, and the noxious stimuli were applied to the hind paws of the cats.

The spinal nerves studied by Pomeranz, which are located in the same region of the cord as the pain-transmitting neurons whose responses were inhibited by morphine and electrical stimulation of the raphe nucleus, give distinguishable responses to light touch and to painful stimuli. After 20 to 30 minutes of acupuncture the responses to light touch did not change but those to painful stimuli decreased markedly. The pain responses were suppressed for an hour or more after the acupuncture was stopped but gradually returned. Sham acupuncture performed with needles at locations away from classical acupuncture points produced no changes in the neuronal firing patterns. Acupuncture produced by electrical stimulation also raised the pain threshold of awake mice.

Several lines of evidence implicate endorphins in these effects, according to Pomeranz. Most important is the complete reversal of the analgesia by naloxone. In addition, the slow time course for development of the analgesia and recovery from it are consistent with a mechanism that depends on the release of a chemical agent.

The pituitary gland may be the source of the endorphins involved in acupuncture analgesia. Pomeranz found that removing the gland, which produces large quantities of the agents, prevents the decreased pain responses of the spinal neurons. So does cutting the spinal cord. Pomeranz thinks that nerve stimulation resulting from acupuncture triggers the release of endorphins from the pituitary gland and that cutting the spinal cord may prevent those nerve impulses from reaching the gland. Another possibility is that severing the cord blocks pain-inhibiting impulses coming down from brain centers such as the central gray area.

Acupuncture analgesia in humans, which also requires 20 to 30 minutes to develop, is similarly reversed by naloxone, according to Mayer and C. Richard Chapman of the University of Washington. Mayer found that acupuncture with manually rotated needles inserted in the hoku point at the base of the thumb raised by about 30 percent the threshold for perception of pain caused by electrical stimulation of the tooth-pulp cavity. The effect, although not large, was significant, and it was abolished completely by the opiate antagonist.

Chapman says that the technique that he uses enables the investigator to determine how much of the effect is physiological analgesia and how much is psychological. He finds that when pain caused by stimulation of the tooth pulp is relieved by acupuncture needles in the hoku point, the resulting analgesia, although equivalent to that of 33 percent nitrous oxide (a standard dental anesthetic), is largely psychological; that is, the patients still perceive the pain but it does not particularly bother them. When the needles are inserted in the cheek, which is not a traditional point, the analgesia is deeper and physiological. Naloxone only partly prevents the effects of the cheek acupuncture.

Chapman suggests that more than one mechanism is involved in achieving the analgesic effect and that one of them involves endorphins and the other does not. Other investigators have suggested

that more than one pain-inhibiting pathway may exist. Mayer, Akil, and Liebeskind found that naloxone blockage of analgesia produced by stimulation in the central gray matter was incomplete. Mayer and R. L. Hayes, who is now at the National Institute for Dental Research, showed that exposing rats to stressful stimuli produces analgesia that is not abolished by naloxone.

The pain response they studied was a spinal reflex that does not require the transmission of the pain signals to the brain. However, cutting the spinal cord prevented the reduction of the response that resulted from stress-induced analgesia. This indicates that the analgesia depends on the integrity of nerves coming down from the brain although apparently not those in the dorsolateral tract. Just cutting the fibers in this tract has the expected effect of diminishing the analgesia evoked by morphine but has no effect on that caused by stress. Finally, Akil and her colleagues have noted that stress evokes an analgesia that is incompletely blocked by the opiate antagonist. The idea of an opiate-independent path is intriguing because it raises the possibility of designing nonaddictive drugs that produce pain relief by activating this pathway.

The experiments with stress bear on a major unanswered question regarding the identity of the normal signals for activating the pain-inhibiting systems. One theory holds that these systems may be turned on only in life-threatening situations. Another is that the systems perform at a low level all the time and are more active in times of stress or danger. If this were the case, naloxone, by blocking at least the opiate-sensitive path, should make the animal more sensitive to pain. The results of experiments designed to test this hypothesis have been mixed. Some investigators have found that the antagonist does make animals hyperreactive whereas others have found no effect. In view of the importance of the clinical goal of designing more effective but nonaddictive analgesic drugs and of the general interest in research on pain inhibition, this question and others regarding the body's built-in system for pain relief will continue to attract much attention.—JEAN L. MARX

Superheavy Elements: Confirmation Fails to Materialize

Few nuclear scientists now believe that the x-ray spectra reported last summer by a team of investigators from the Oak Ridge National Laboratory (ORNL), the University of California at Davis (UCD), and Florida State University (FSU) constitute evidence for the existence of superheavy elements with atomic numbers near 126. A principal stumbling block to acceptance has been the failure of numerous and widely varied experimental attempts to come up with any confirmatory evidence. Moreover, even without this accumulation of negative results, many scientists feel that the discovery by FSU scientists of an alternative explanation for the x-ray peak regarded as the most convincing indication of superheavy elements made the original interpretation untenable.

Thus, as the magnetic monopole episode of less than a year earlier taught only too well, in the absence of reproducible data, scientists simply will not accept evidence of a new discovery, no matter how well it fits the data, when a more conventional explanation is even remotely possible.

No one is accusing the seven-man team led by Robert Gentry (Columbia Union College and ORNL), Thomas Cahill (UCD), and Neil Fletcher (FSU) of hastily or prematurely publishing their data. Says D. Allan Bromley of Yale University, "If one believes that the function of *Physical Review Letters* (the journal in which the investigators published their data) is to include stimulating discussion of new developments, then the investigators acted responsibly by not sitting on their results until every detail was checked out." And, unlike the monopole, some (but not all) of the samples remained intact to be run again and again, if need be.

The evidence presented last July certainly seemed solid enough to merit publishing (*Science*, 16 July 1976, p. 219). Using a technique known as particle-induced x-ray emission (PIXE), the team of investigators focused a beam of protons from a Van de Graaff accelerator at FSU onto tiny monazite [(Ce, La, Th)PO_4] crystals. The x-ray spectra produced were best interpreted (best statistical fit) as being due to elements with atomic numbers 126, 124, and (possibly) 127. Because x-ray peaks ascribed to element 126 were found in five of the six monazite crystals examined, evidence for its existence was thought strongest.

The work of theorists in the middle 1960's had indicated the possibility of relatively stable elements with atomic numbers near 110 to 114, although elements with atomic numbers greater than 100 generally become progressively less stable and shorter lived. These predictions stimulated numerous searches for such superheavy elements in nature, but all failed to turn up any evidence for them. Recent attempts to produce them in accelerators at the Lawrence Berkeley Laboratory and at the Joint Institute for Nuclear Research, Dubna, U.S.S.R., which are capable of bombarding targets containing heavy elements, such as curium, with medium weight ions, such as calcium, in the hope they would fuse together to make a superheavy element, have also been unsuccessful.

Thus, the announcement of x-ray evidence for superheavy elements caused quite a stir among physicists. The excitement was compounded by two findings: The elements appeared to have higher atomic numbers than expected (atomic weights were not known), and the monazite crystals in which they resided were present in mineral formations that have been shown by dating techniques to be about 1 billion years old. Both aspects raised serious questions for theorists, answers to which would have required some revision of existing theories of nuclear structure and nucleosynthesis. Recent theoretical attempts to recalculate half-lives or otherwise assess the stability of these elements have been inconclusively divided pro and con.

In addition to its intrinsic interest, the evidence for superheavies, if it had been confirmed, would have provided a much needed shot in the arm to nuclear physics, which some have described as being in the doldrums in recent years. And it would have shown that fundamental discoveries can still come from outside the "big science" laboratories.

The most serious damage to the superheavy element evidence was that caused by the discovery by John Fox and his collaborators at FSU of a gamma ray with the same energy as the x-ray peak for element 126. The gamma ray is emitted when an excited praseodymium nucleus relaxes after being created from cerium (a principal constituent of monazite) during bombardment by protons. Not previously known to exist, the gamma ray provided a natural explanation of what had been thought an x-ray peak from an unusual element.