THE GREAT PAIN PLAN

Medical researchers are out to understand what pain is, how it's processed in brain and body and, most crucially, how it can be controlled

BY JOAN AREHART-TREICHEL

An operation is performed by bush doctors in East Africa that fascinates many of their more technologically sophisticated counterparts in the United States. Called trephination, the operation is performed on patients with incurable headaches. The bush doctor first prays for the success of the operation, then exposes the patient's skull and starts scraping away at it with a large, crude knife. Blood gushes from the skull, but the patient gives no evidence of feeling pain.

How can East African patients be so blasé about an operation that would likely be quite painful in our culture? Pain researchers aren't sure, but they are gaining insights as they study the phenomenon of pain, attempt to better understand how existing pain treatments work and devise new treatments. The study of pain, in fact, is one of the busiest and most provocative areas of biomedical research today, as a recent international symposium on pain suggests. The symposium was held at the Johns Hopkins Medical Institutions in Baltimore and was sponsored by Miles Laboratories.

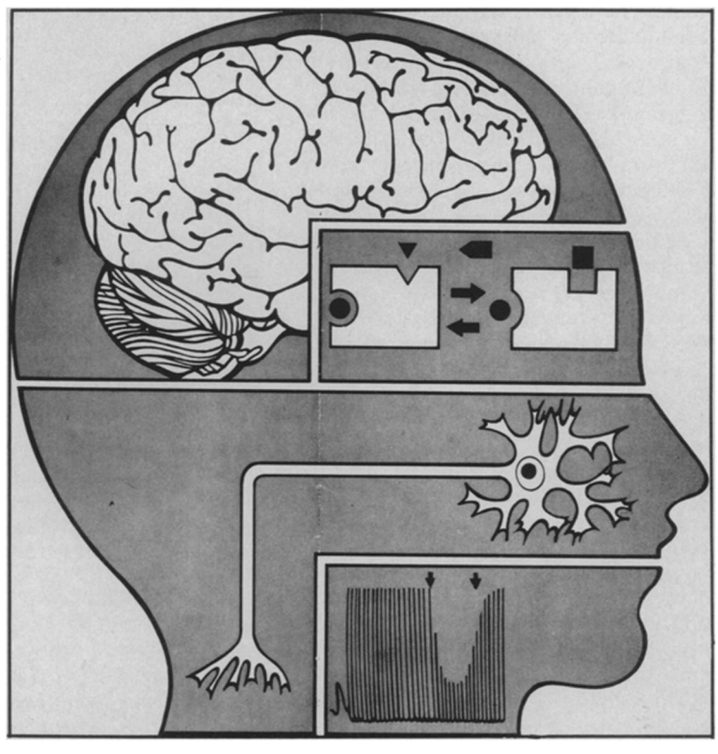
First, what is pain? Obviously something that hurts. But pain researchers are careful to point out that a physical pain stimulus is not the same as a person's perception of that stimulus. Nonetheless, the routes by which a noxious physical stimulus produces pain are being mapped with increasing precision.

A painful stimulus, say heat, strikes a nerve near the surface of the body. The nerve releases both the inflammatory substance histamine and local cellular messengers called prostaglandins, which sensitize the nerve to the painful stimulus. The nerve then passes the pain message on to the central nervous system in the spinal cord where it is coded in a region known as the dorsal horn. From there the message ascends along nerves through the brainstem to the thalamus, which appears to be a pain signal terminal.

Pain processing, however, is proving to be infinitely more complex than the schema outlined above. As both David J. Mayer of Virginia Commonwealth University in Richmond and Ronald Dubner of the National Institutes of Health in Bethesda, Md., point out, only certain sensory nerves in the peripheral and central nervous system process pain messages. What's more, nerves that transfer certain kinds of painful stimuli do not pass along other kinds of painful stimuli. William D. Willis of the University of Texas at Galveston is currently mapping which nerve cells in the dorsal horn and thalamus of the monkey transmit painful stimuli.

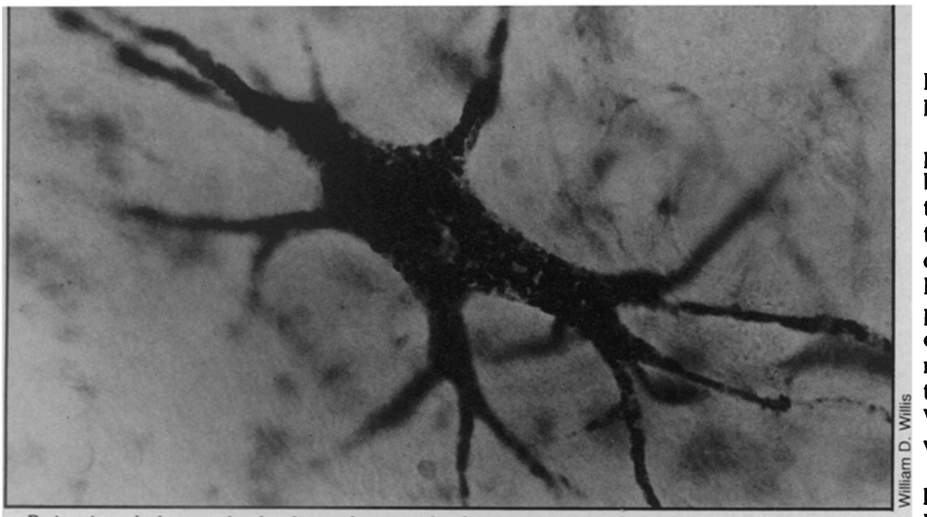
The processing of pain by nerves in the spinal cord also appears to depend on the amount of enkephalins in the spinal fluid, reports John C. Liebeskind of the University of California at Los Angeles. Enkephalins are proteins believed to be the brain's own natural pain-relieving molecules. In other words, chronic pain patients have fewer enkephalins in their spinal fluid than do pain-free persons, suggesting that an abundance of enkephalins in the spinal fluid wards off pain messages and that a paucity lets pain messages through. But how do the enkephalins interact with nerves conducting pain messages to the brain? Pain researchers aren't sure. But as the discoverers of the enkephalins — John Hughes of the Imperial College of Science and Technology in London and Hans W. Kosterlitz of the University of Aberdeen in Scotland — point out, there is increasing evidence to support their initial hypothesis that the enkephalins act as neurotransmitters. Whether the enkephalins help nerves transmit pain messages up the spinal cord, however, is doubtful, because the enkephalins are known to counter pain, not to cause it. So it's more likely that the enkephalins service nerves descending the spinal cord, which are known to counter ascending pain signals.

In addition to sensory nerves and the enkephalins, pain processing probably depends on other factors. For instance, as Federigo Sicuteri of the University of Florence, Italy, explains, there is increasing evidence that migraine headaches may be due to a deficiency of the neurotransmitter serotonin in the brainstem. This nerve-transmitting chemical, like the enkephalins, may help descending nerves counter pain messages ascending the spinal cord. Leif Olgart of the Karolinska Institute in Stockholm reports that tooth pain triggered by cold air or mechanical probing is due to these stimuli first moving fluid in the dentin (mineralized tissue) of teeth. This fluid may then interact with sensory nerves innervating the dentin and triggering pain messages to the brainstem.



What dark recesses of the human brain, what nerves and chemicals, are involved in receiving and processing incoming pain signals? Pain scientists are getting some idea, but much of the mystery remains.

Miles



William D. Willis

Pain signals leave the body and enter the brain via spinal cord nerves like this one.

Aside from rapidly delineating the physiological pathways of pain, researchers are also learning more about how existing pain treatments work. For instance, electrical stimulation of a particular region of the brainstem, the periaqueductal grey, can kill pain in chronic pain patients just as effectively as opiate drugs can. Both stimulation and opiates seem to perform this feat by getting nerves in the periaqueductal region that use serotonin as a neurotransmitter to inhibit the action of nerves ascending into the region with pain messages. Mayer has found that naloxone, a drug known to antagonize the action of the enkephalins, blocks the action of acupuncture but not that of hypnosis, suggesting that pain relief in the body does not always operate through the enkephalins.

Data from Sergio H. Ferreira of the University of São Paulo, Brazil, and from other scientists suggest that aspirin and narcotic drugs prevent pain in a similar fashion — by blocking prostaglandins' ability to sensitize nerves to pain messages — and that such blockage can occur both in peripheral nerves and in central nerves in the spinal cord and brain. According to R. Alan North of Loyola University in Maywood, Ill., both narcotics and enkephalins isolated and injected as drugs are able to prevent the firing of nerves in the spinal cord and thalamus that carry pain messages, and these drugs also interfere with neurotransmitter action. Whether neurotransmitter interference is the means by which the drugs actually prevent nerve firing, however, remains to be confirmed.

Pain scientists are also learning how to measure the effectiveness of pain treatments objectively, rather than having to rely on patients' subjective impressions. C. Richard Chapman and his colleagues at the University of Washington Medical School in Seattle have been using electrical stimulation to produce tooth pain in subjects, then analyzing the electroencephalogram responses of the subjects to the painful stimulus. "The size of the brain waves," Chapman says, "correlates nicely with the amount of pain the subjects report subjectively. So we now have a physiological correlate of pain and a means of objectively measuring the effectiveness of an analgesia."

New kinds of pain treatments are also being developed. Researchers first showed that severing of select pain-carrying nerves could abolish pain. Now they are demonstrating that stimulation of certain pain-carrying nerves can also abolish pain. How such stimulation works remains to be explained. One would think that stimulation of pain nerves would enhance rather than relieve pain, but Donlin M. Long of Johns Hopkins Medical Institutions and his co-workers have evidence that stimulation of peripheral nerves can relieve chronic pain that is of physiological origin, but not chronic pain of psychological origin. But the most promising advance in the use of stimulation to relieve pain, Long says, may come out of work done by Huda Akil and her colleagues at Stanford University School of Medicine in Palo Alto, Calif., where patients electrically stimulate their brains to relieve pain. After using the technique for a mean of 18 months, 18 out of 30 patients are still experiencing good to excellent pain relief from it. The patients suffer a wide range of illnesses, from low back pain (33 percent of all cases) to cancer, spinal cord paralysis, phantom limb pain and arthritis (SN: 6/17/78, p. 39).

Still another novel pain treatment is being explored by Wilbert E. Fordyce of the University of Washington Medical School. Pain behavior, Fordyce explains, is not the same as a pain stimulus, or even the same as a person's mental perception of the stimulus, but how a person reacts to the perception of pain. He and his colleagues have evidence that if chronic pain patients are not reinforced in their pain behavior, they pay less attention to their pain. In one of their experiments, for instance, chronic pain patients were told to exercise on a treadmill, but to stop when it hurt too much. The researchers found that the patients exercised much longer when they were not aware of how hard they were working than when they were given feedback on it. Fordyce and his colleagues are now attempting to try behavior therapy as a treatment for chronic pain; that is, to see whether they can condition chronic pain patients so that they do not react to their pain.

But more still needs to be learned about pain. What are the higher centers of the brain that process pain stimuli arriving in the thalamus and provide pain perception? Virtually no studies have been conducted on this subject to date. However, a little is known about how emotions alter pain perception. For instance, the discovery that anxiety can influence people's reaction to pain was published recently in the journal PAIN (4: 253-263, 1978), by Beat Von Graffenried and colleagues at the University of Berne in Switzerland.

Is there such a thing as a pain memory? Ronald Melzack of McGill University in Montreal reports how one of his patients who broke her jaw in a car accident and suffered excruciating pain experienced the same pain 10 years later. The reason? Melzack believes that the original painful stimulus may produce some permanent changes in nerves in her brain, creating a pain memory, and that 10 years later something activated these nerves, bringing back memory of the pain. But proof of pain memories is still to be had.

Does acute pain differ from chronic pain, and if so, how? Acute pain is a warning signal that something is wrong, but this is not true of chronic pain, Fordyce points out. Both acute and chronic pain are probably processed by the same nerves, conjectures Frederick W. L. Kerr of the Mayo Clinic in Rochester, Minn., but they may be expressed by different intensities and also modulated differently by higher centers in the brain. Acute pain is usually caused by tissue damage or disease and chronic pain by the mind, asserts John J. Bonica of the University of Washington, and since scientists know much less about the physiology of the mind, chronic pain is much harder to treat.

Finally, how can East Africans be so nonchalant about trephination? Do some higher brain centers help them ignore the ascending pain messages inflicted by the steel blade? And why is it that these patients claim that trephination relieves them of their headaches? Is it because the overwhelming, ascending pain messages from trephination close some pain "gate" in the dorsal horn of the spinal cord so that subsequent, less painful headache messages can no longer get through? This is the bold conjecture of Melzack, who with Patrick Wall proposed a gate control theory of pain several years ago, and who also points out that peoples other than East Africans have used brief painful stimuli to relieve intense chronic pain, whether it was the burning of a toe to assuage gout or the bruising of the back to mitigate back pain.

Melzack's pain gate, however, has not yet been proved to exist. So it will probably be a few years before pain researchers solve the mystery of East Africans' tolerance of trephination — as well as the other, still unanswered questions of pain science. □