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Pain—Mechanisms and Management

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In the past two decades there has been remarkable progress in understanding the neural mechanisms of pain. However, chronic pain is poorly understood and, by definition, poorly managed. In addition to hyperactivity of the sympathetic nervous system and damage to normal inhibitory mechanisms, social and psychological factors play a major role in producing the disability of chronic pain. New approaches to manage chronic pain include nonopiate drugs, transcutaneous electrcal nerve stimulation and psychological and behavioral methods. A nervous system network has recently been described that suppresses pain. This analgesic action is mediated by endogenous opioid peptides (endorphins) and by biogenic amines. The analgesia network can be activated either by electrcal stimulation or by opiates such as morphine or methadone.

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Pain is a warning signal that helps to protect the body from tissue damage. Potentially damaging stimuli activate and sensitize certain primary afferent nerve cells. The activity of these nerve cells projects to the spinal cord and from there to the brain, giving rise to the sensation of pain. Clinically, the sensation of pain elicits varying degrees of suffering and depression depending on its duration and a patient's psychosocial environment.

In the past two decades there has been rapid progress in our understanding of the physiology of pain. In this review we will first briefly outline current concepts of the mechanisms of pain transmission and modulation, then focus on those areas of pain management where concepts have changed, where new scientific findings have been applied to patient care or where existing knowledge has not been applied optimally.

Pain Transmission System

The first step leading to the sensation of pain is the activation of nociceptive primary afferents by intense thermal, mechanical or chemical stimuli. The mechanism of this activation (transduction) is poorly understood because the receptive region of the nociceptor is located in small, diffusely distributed, free nerve endings. Indirect studies of nociceptive transduction indicate that it involves chemical mediators that are released or synthesized in response to tissue damage (Figure 1). Physiologic concentrations of such inflammatory mediators either directly activate or sensitize nociceptors.[1] Because any intense stimulus could produce slight tissue damage, it is possible that such stimuli activate nociceptors through a common mechanism involving these mediators. A major breakthrough in our understanding of the transduction process was the finding that prostaglandins contribute to the activation of primary afferent nociceptors. Acetylsalicylic acid or other nonsteroidal anti-inflammatory agents (NSAIAs) prevent pain by inhibiting the metabolism of arachidonic acid to prostaglandins.[2] Other inflammatory mediators such as leukotrienes have also been shown to produce pain.[3] Because the cyclooxygenase pathway of arachidonic acid metabolism is not involved in leukotriene production, usual doses of NSAIAs do not prevent its production in injured tissue. Thus, the development of agents that block leukotriene synthesis could extend the clinical usefulness of NSAIAs.

The transduction process in the peripheral terminals

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ABBREVIATIONS USED IN TEXT

NSAIA = nonsteroidal anti-inflammatory agent
TENS = transcutaneous electrical nerve stimulation

of primary afferents leads to action potentials in their axons which propagate to the spinal cord. Sensory axons in a peripheral nerve fall into discrete groups based on diameter and conduction velocity. The most numerous group consists of the unmyelinated axons (C-fibers) that conduct very slowly (less than 3 ms^{-1}). They constitute 80% of all axons in cutaneous nerves. Most unmyelinated afferents can be activated by noxious stimuli. There are several groups of myelinated afferent axons, but only the smaller diameter, slower conducting ones are sensitive to noxious stimuli. The large-diameter myelinated sensory neurons respond maximally to innocuous stimuli.

In the spinal cord, the small-diameter sensory axons, which include all known nociceptors, enter the gray matter of the superficial dorsal horn to synapse on nerve cells contributing to pain-transmission pathways such as the spinothalamic tract (Figure 2). Besides pain-transmission neurons (projection cells), there are at least two other types of neurons located within the superficial dorsal horn (interneurons): one type relays information from primary afferents to the projection cells, the other *inhibits* the relay of information to the projection cells.[5,6] The inhibitory interneurons alter the pain message as soon as it enters the central nervous system (see Figure 2). Thus, although there are primary afferents specifically activated by noxious stimuli, the sensation of pain is a complex sum of activity in both nociceptive and nonnociceptive afferents.

One of the important controls over nociceptive transmission is exerted by the large-diameter primary afferents that respond to innocuous stimuli. These large myelinated afferents activate inhibitory interneurons that control pain transmission.[5,6] The functional importance of this inhibition is shown by the observation that when the large-diameter myelinated afferents in a nerve are blocked, the activity of the functioning unmyelinated afferents in the same nerve produces pain that is more severe than occurs when the myelinated afferents are conducting normally.[7,8] It is important to remember that when noxious stimuli are applied, *both* large- and small-diameter sensory fibers will be activated—that is, an intense stimulus will activate fibers that are also activated by mild stimuli. Thus the large-diameter myelinated primary afferents will normally *inhibit* the dorsal horn neurons that are excited by nociceptive primary afferents (Figure 2). This inhibitory effect explains the analgesic effect of transcutaneous electrical nerve stimulation (TENS) which selectively activates large fibers.

Our knowledge of the physiology of primary afferent nociceptors has been expanded by the recent discovery that they contain a variety of polypeptides. Substance P, somatostatin, vasoactive intestinal polypeptide and cholecystokinin are all present in different populations of small-diameter unmyelinated primary afferents, all of which terminate in the superficial dorsal horn.[10,11] Substance P is the best studied of these peptides. It excites pain-transmission neurons in the dorsal horn.[12] When the neurotoxin capsaicin is used to destroy substance P-containing primary afferent neurons, animals become unresponsive to a variety of noxious stimuli.[13] The role of the other neuropeptides in pain is less well understood.

In addition to its proposed role as a neurotransmitter at the spinal cord terminals of nociceptors, substance P is also transported toward the peripheral terminals of these neurons.[14] Release of substance P from the peripheral terminals of nociceptors can produce cutaneous wheal and flare, a neurally mediated response

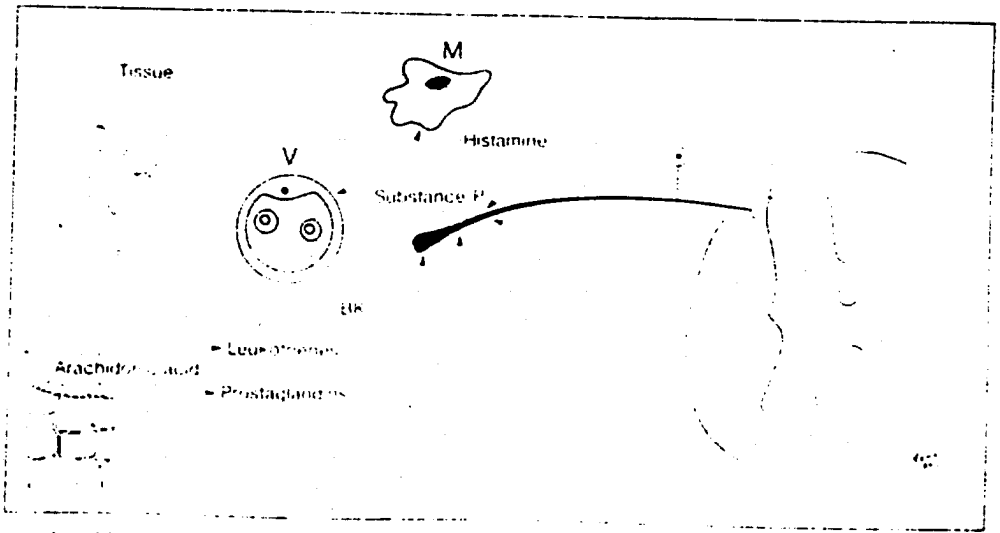

Figure 1.—A schematic representation of a primary afferent nociceptor—which transmits pain signals from injured tissue to dorsal horn of spinal cord—and its interaction with mediators of acute inflammation. Tissue injury stimulates the production of mediators or directly releases them from tissue stores. Mediator effects on primary afferent nociceptors include direct *activation* of the nociceptive afferent by bradykinin (BK) or histamine, and *sensitization* of the nociceptive afferent by prostaglandin products of arachidonic acid metabolism. The activated nociceptor releases neuropeptides such as substance P from its peripheral terminals which, in turn, may produce increases in vascular (V) permeability and mast (M) cell degranulation.

that occurs following noxious stimulation.[15] The inhibition of the peripheral actions of substance P by specific antagonists could provide a new therapeutic approach to the control of inflammation and pain. A number of antagonists for substance P have already been synthesized with this in mind.[16,17]

The processes initiated by noxious stimuli produce activity in pain-transmission neurons in the dorsal horn of the spinal cord that leads to a coherent message that is relayed to the brain. There are at least two major pathways in the spinal cord that are involved in this rostral projection of the pain message: the well-known spinothalamic tract and the larger but less appreciated spinoreticulothalamic tract. The latter tract runs with the spinothalamic tract in the spinal cord but separates from it in the brain stem to synapse on neurons in the reticular formation that in turn project to the thalamus. We know very little about differences in the function of these two pathways; however, there is some suggestion that activity transmitted via the spinoreticular pathway arises predominantly from deep and visceral structures.[18] Activity in the spinoreticular pathway may produce the more diffuse and emotionally disturbing pains that accompany many clinical conditions.[19]

These two pain pathways also have different sites of termination within the thalamus. The spinoreticulo-

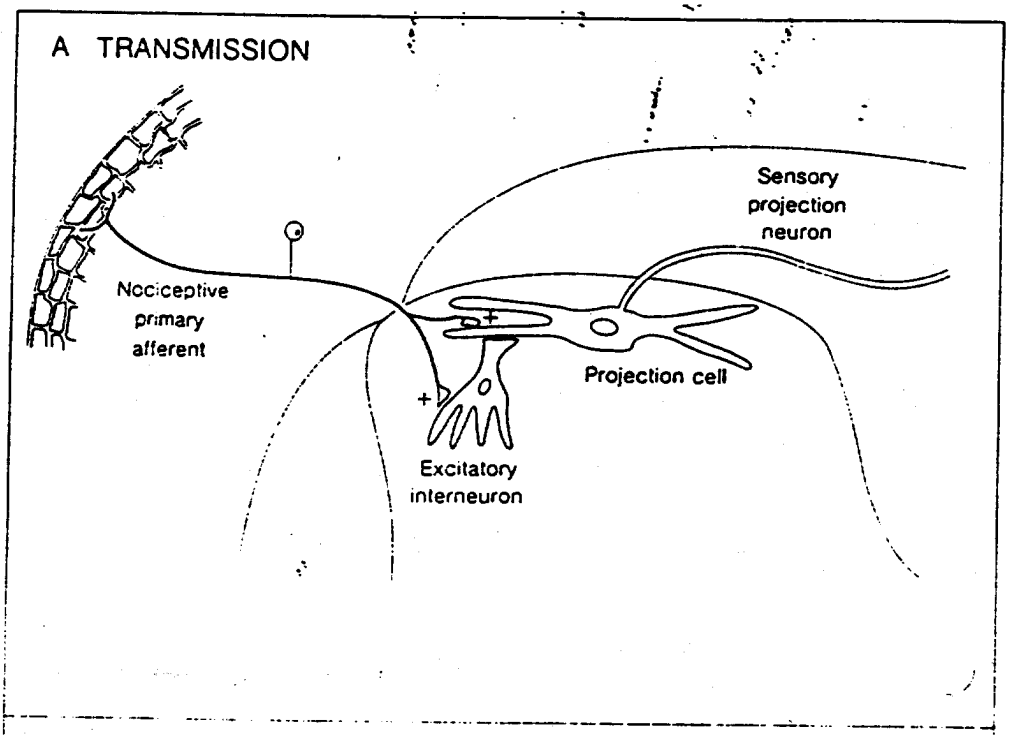

Figure 2.—A, A schematic representation of the central connections of the nociceptive primary afferent and projection cells in the pain-transmission pathway. In the dorsal horn of the spinal cord, nociceptive afferents synapse onto both projection cells that transmit pain signals rostrally to terminate in the thalamus, and onto local neurons that in turn synapse onto projection cells.

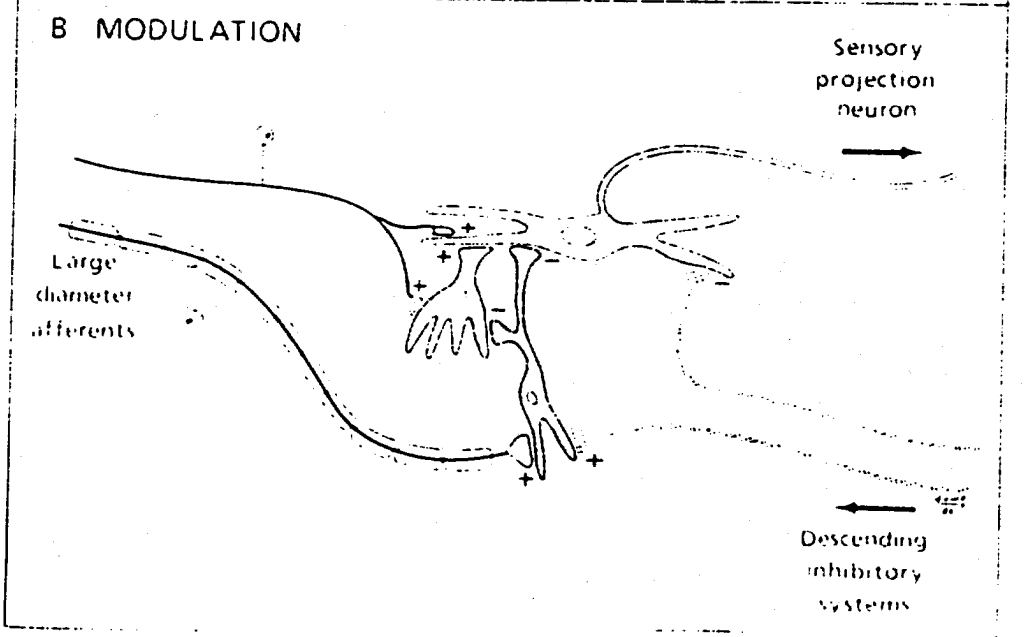

Figure 2.—B, A schematic of dorsal horn pain circuits including local (stippled) and descending (crosshatched) inhibitory systems. The local dorsal horn pain-inhibitory system can be activated both by descending inhibitory systems and by the large-diameter myelinated primary afferents that respond to nonnoxious stimuli. The plus (+) sign indicates an excitatory connection and the minus (−) sign an inhibitory synaptic connection between two neurons.

thalamic projection is more medial and the direct spinothalamic projection primarily lateral, ventral and caudal. The two thalamic regions project to different cortical sites, though in humans these sites are still unknown. It is established, however, that there is a cortical "representation" for pain because cortical and spinal and thalamic lesions can greatly impair the perception of pain.

Pain-Modulation System

The most important recent advances in our understanding of pain have come from the discovery of a specific central nervous system network for pain control and of endogenous opioid substances (referred to generically as endorphins) that are synthesized by nerve cells and have pharmacologic properties nearly identical to narcotic analgesic drugs. These discoveries have provided a basis for understanding the clinically well-known but scientifically puzzling variability of perceived pain.

The key observation leading to the discovery of the endorphin-mediated analgesia system was of the phenomenon of stimulation-produced analgesia. First described in rats, it occurs when certain parts of the brain are electrically stimulated. The inhibition of pain that occurs during stimulation is strikingly selective. Although animals are alert, active and respond normally to innocuous stimuli, noxious stimuli do not produce the expected vocalization, biting and escape. Its selectivity for pain received crucial confirmation from observations of patients with intractable pain who have had stimulating electrodes implanted at sites homologous to those from which stimulation-produced analgesia was elicited in animals.[20] Many patients with these electrodes report a gradual melting away of their pain. Although some report a feeling of warmth or sleepiness (or both), no other effects are consistently associated with pain relief. Thus, the system activated appears to be specifically designed for controlling pain.

Subsequent research has elucidated the anatomic, chemical and physiologic basis for this pain modulation. In Figure 3 is outlined what is known of its anatomy. The pain-modulating network consists of a series of neurons that run from the cortex to the dorsal horn of the spinal cord. Anatomic and physiologic studies have established that sites in the hypothalamus, midbrain periaqueductal gray and rostral medulla are also involved.[21,22] Although not tested in humans, electrical stimulation at the medullary level in animals produces analgesia and inhibits nociceptive spinothalamic tract cells. Thus the selectivity of the pain-modulating network apparently derives from its inhibition of spinal cord pain-transmission cells.

About the time that this pain-modulation network was being mapped, a parallel revolution was occurring in the world of pharmacology. Structure-activity rela-

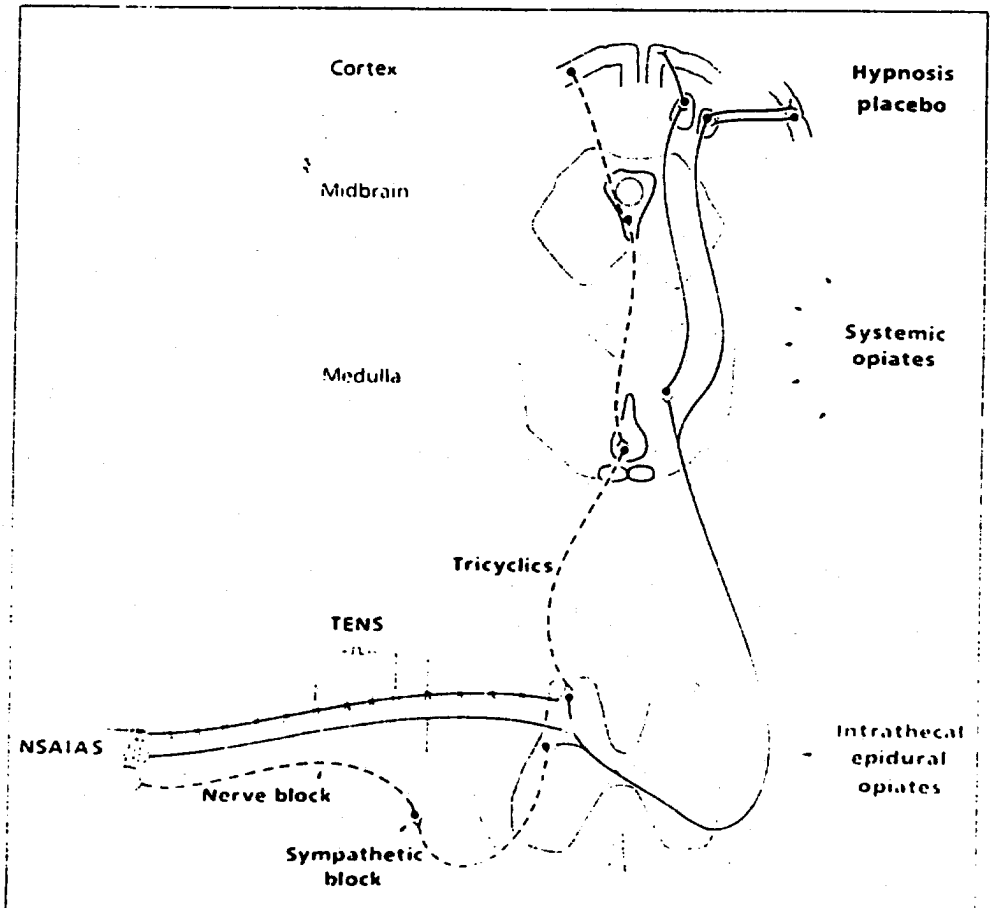

Figure 3.—A detailed schematic of the sites of action of commonly used pharmacologic and physiologic analgesic therapies. The aspirin-like nonsteroidal anti-inflammatory analgesics (NSAIAs) act at the level of the transduction process in the nociceptive primary afferent. Sympathetic blocks may have a similar locus of action. Peripheral nerve blocks work by blocking transmission. Transcutaneous electrical nerve stimulation (TENS) produces analgesia indirectly by activation of large-diameter afferents that normally respond to nonnoxious stimuli. These afferents, in turn, activate local analgesia circuits in the spinal cord and may also inhibit the sympathetic nervous system. Opiate analgesics act at multiple sites in the central nervous system to activate the descending inhibitory systems (shown by broken line). Application of opiates at the level of the spinal cord produces local analgesia. Tricyclic antidepressants appear to produce analgesia by an action on the same descending inhibitory system that mediates opiate-induced analgesia. This system may also be activated by suggestion and hypnosis via cortical circuits.

tions for clinically effective narcotic analgesics had been well worked out and bioassays were available to assess new opiate-like drugs.[24] The analgesic potency of these narcotic drugs was shown to correlate well with their binding affinity to certain membrane preparations from brain. This binding was shown to be stereospecific and to have a high affinity. In addition to the binding-potency relationship, the availability of a selective antagonist, naloxone, allowed these binding sites to be clearly identified as opiate receptors. This triggered the search for an endogenous ligand for the opiate receptor. In 1975 Hughes and co-workers[25] reported that two pentapeptides isolated from pig brain had a high affinity for the opiate receptor. These pentapeptides were active in bioassays and their action was blocked by the narcotic antagonist, naloxone. These two pentapeptides, leucine and methionine enkephalin, were the first endorphins discovered. It is beyond the scope of this review to enumerate all of the endorphins, their anatomic distribution, putative functions and metabolism. It is, however, important to point out that there are at least three distinct families of endorphins coded by separate genes and present in different cell populations of brain, pituitary, adrenal, gut and sympathetic nervous system.[26]

Many of the endorphin-containing cells of the brain are anatomically associated with the analgesia networks described above. For example, the enkephalins are present in nerve cells at midbrain, medullary and spinal loci implicated in pain modulation. Furthermore, there is a remarkably precise anatomic correlation between opiate receptor, endorphin distribution and the nuclei from which analgesia can be elicited by electrical stimulation or microinjection of opiates. This evidence provides convincing support for the idea that there is a discrete endorphin-mediated network designed specifically for modulating pain.

In addition to providing both an anatomic and a chemical explanation for the phenomenon of stimulation-produced analgesia, the discovery of the endorphin-mediated analgesia system has provided insights into how narcotic analgesics relieve pain. Thus, drugs like morphine sulfate, meperidine hydrochloride and Percodan (oxycodone hydrochloride and aspirin) presumably relieve pain by mimicking the action of endorphins at synapses in the pain-modulating networks.

Despite the importance of endorphins, it would be misleading to suggest that they are the only neurotransmitters involved in pain modulation. There is a good deal of evidence that both norepinephrine and serotonin also play a role, especially in the connection between the brain stem and the spinal cord.[27-32] These transmitters are of particular importance because they can be manipulated by a variety of pharmacologic agents, thus raising the possibility of new classes of centrally acting analgesic agents.

Perhaps the most important unanswered questions concerning the endogenous opioid-mediated analgesia system relate to its physiologic functions. Why does the brain need this pain-modulating system? When is it activated? How are its actions manifest? At the present time, our answers are teleologic or simply descriptive. Part of the problem is that we are dealing with a modulatory system whose activity is best studied in patients with clinically significant pain.

Early studies of nerve cells in the nuclei involved in pain modulation indicated that the majority were excited by noxious stimuli. This suggested that the network might function simply as a negative-feedback system to dampen responses to painful stimuli. Thus, if a given noxious stimulus activates both transmitting and modulating networks, the pain is less severe than it would be if only the transmission system were activated.

Because it is difficult to directly study the activation of the modulatory system in humans or in awake animals, this hypothesis required an indirect approach for its confirmation. Assuming that the action of endogenous opioids would be antagonized by administration of the narcotic antagonist, naloxone (Narcan), researchers used naloxone to block the analgesia network. The results of such studies have led to a tentative formulation of how the analgesia network is activated.

The responses to brief superficial painful stimuli are not altered by naloxone.[28,29] Noxious stimuli must be above the pain threshold and have prolonged duration to produce analgesic actions that are blocked by naloxone. Second, stimuli that are stressful, inescapable or associated with anxiety are particularly effective for producing naloxone-reversible (and thus presumably endorphin-mediated) analgesia.[30] Finally, naloxone can block the analgesia that results from consistently presenting an innocuous cue, such as a tone or light with a stressful pain.

Studies in humans, though somewhat complicated by the rich panoply of emotional and environmental factors that colors reports of subjective experiences, generally support the existence of an endorphin-mediated analgesia system. Although initial reports showed no effect of 0.4 to 10 mg of naloxone on experimentally induced pains, subsequent work has consistently shown that 10 mg of naloxone makes clinical pain worse. The studies on clinical pain compared the action of naloxone with that of a placebo and the worsening of pain with naloxone raised the possibility that the phenomenon of placebo analgesia might be accounted for by the action of this endorphin-mediated analgesia system. Subsequent work suggests that this is at least partly true. Our own studies of placebo analgesia show that stress, pain, environmental cues and expectation all activate the endorphin-mediated analgesia system.[31] Because of these complex factors and the possibility that placebo analgesia is endorphin mediated, early studies suggesting that acupuncture, transcutaneous electrical nerve stimulation and hypnosis all produce an opioid-mediated analgesia need to be reevaluated.

In summary, we have outlined the known properties of an endorphin-mediated analgesia system and have presented preliminary evidence that suggests that its

activation is part of a stress response and subject to complex environmental factors. In addition to the endorphins, there are other transmitter systems that play an important role in controlling pain transmission. The discovery of endorphin-mediated pain-modulating neural circuits has provided an explanation for how narcotic analgesics work and, perhaps more important, has greatly advanced our understanding of the variability of clinical pain.

The Management of Pain

In the following sections we will discuss the rationale for various methods in common use for pain management. Although treatment of the underlying disease should always be the primary goal, in many cases even when the cause is known, pain management is the major objective—for example, postoperative pain, labor pain or cancer pain. Because we cannot cover all methods of pain management in detail, we will focus on the optimal use of those therapeutic tools that are of greatest value for a broad range of physicians and discuss some general issues in pain management.

Behavioral Methods and Chronic Pain

Up to this point we have provided a very mechanistic description of the physiologic processes that result in the sensation of pain. The implication is that with this knowledge we should be able to achieve satisfactory control of pain in the overwhelming majority of patients. There are patients, however, who continue to complain of pain despite the use of potent analgesic drugs and repeated surgical treatments. Many patients with chronic low back or abdominal pain fall into this category and it would be misleading to discuss pain mechanisms and management without at least a brief discussion of recent developments in our knowledge of chronic pain.

Essential to an understanding of chronic pain is the distinction between the sensation of pain and the reaction or suffering aspect of pain.[39-42] The sensory aspect is usually studied by measuring pain threshold and is fairly uniform between human subjects. On the other hand, the subjective unpleasantness of or tolerance for pain varies greatly. A pain that one person would hardly notice would cause another to seek medical help. A simple way of thinking about this is that the sensory level (intensity) required for detection (pain threshold) is rather constant, whereas the intensity level required to elicit spontaneous complaints (tolerance "threshold") is highly variable.

For many acute pains such as occur during labor or following trauma or myocardial infarction, the pain intensity may well be above tolerance and lead to grimaces, groans, tears, splinting immobility and desperate calls for help. In addition to these overt behaviors, on physical examination there are often signs of increased sympathetic discharge such as a rapid pulse, increased blood pressure and sweating. These acute pains respond well to adequate doses of narcotic analgesics and need not pose a management problem.

On the other hand, many pains that are less severe initially, such as in some cases of arthritis, headaches and back pain, become clinically significant simply because of their chronicity—that is, they are distracting, irritating and eventually depressing. Patients with these latter types of problems rarely groan, cry or show any of the usual sympathetic discharge that patients with acute severe pain do. They will, nonetheless, show up at clinics and hospital emergency rooms claiming that they have unbearable pain.

Until recently, most physicians have had great difficulty managing patients with subacute or chronic pain. Unable to cure the underlying disease—or in some cases to diagnose it—and appropriately unwilling to use potent narcotic analgesics on a long-term basis for nonmalignant disease, physicians tend either to dismiss these patients as crocks or to tell them they must "learn to live with the problem" without telling them how to do it.

In response to a growing awareness of this class of patients, a new approach to treatment has been developed, the behaviorally oriented, multidisciplinary pain clinic. These pain clinics tend to emphasize psychological, behavioral and physical rather than pharmacologic or surgical approaches.[33,34] Among the methods in common use are hypnosis, psychotherapy, biofeedback and behavioral modification techniques. Heat, ice, massage, physical therapy and transcutaneous electrical nerve stimulation are also used. What seems to distinguish successful pain management programs is that they tend to be patient oriented rather than disease oriented.

While not denying that a patient may have a "real" or an "organic" pathologic process that initially triggered the pain, these behaviorally oriented programs recognize that there are environmental factors that tend to reinforce illness behavior.[35] For example, a patient may have suffered an acute low back strain and have been put to bed, staying home from work for several days and receiving attention and sympathy or reprieve from responsibilities at work or at home. A prescription for tranquilizers or powerful opiate drugs, or both, may also have been given. Furthermore, people become more supportive, understanding and concerned about a person when he or she is ill. In short, being sick or at least having a valid complaint suggesting significant illness may have both primary and secondary gains for a patient. These rewards constitute reinforcement for illness behavior. Behavioral programs attempt to disconnect the illness behavior from the reward system by making patients more responsible for their own care and rewarding "normal" behavior such as increased activity or reduced drug intake. The goals include a return to productive life (which is something that can be verified objectively) rather than total elimination of pain.

Transcutaneous Electrical Nerve Stimulation

Although the therapeutic indications for transcutaneous electrical nerve stimulation (TENS) remain to

be fully spelled out, it is in common use in pain clinics and by physical therapists, neurologists, orthopedic surgeons and, in some centers, by general surgeons for postoperative pain.[36]

Because large-diameter myelinated axons have lower electrical thresholds than do small-diameter axons and do not produce pain when activated, it is possible to stimulate them selectively without producing discomfort. The earliest reports, on small groups of patients, indicated that TENS can produce dramatic relief of pain. These studies provide the impetus for larger clinical trials that have generally confirmed the usefulness of this approach.

The most carefully designed clinical trials, which have been carried out in patients with postoperative pain, show that TENS produces significant pain relief. It is routinely used for postoperative pain in some hospitals. Because postoperative pain has a consistent natural history and responds predictably to narcotic analgesics, these studies are all the more important. The evidence that TENS is effective in the treatment of chronic pain is not good; there are reports, however, of dramatic results in patients with pain syndromes associated with nerve damage. In these patients, TENS is most effective when stimulation is applied to the injured nerve proximal to the site of injury, where one can be assured of stimulating intact large-diameter axons. Recently encouraging results using TENS in the management of pain following spinal cord injury have also been reported.

This form of therapy is attractive because it is noninvasive, selective for pain and has few side effects. Its use requires detailed instruction, however, and patients will commonly have to experiment to find the most effective electrode positions. Thus, good cooperation is necessary for outpatient use.

Psychotropic Drugs

There is increasing evidence that psychotropic drugs have a place in pain management. Obviously, patients receiving psychotropic drugs could clinically improve for a variety of reasons. For example, pain that is a manifestation of depression would be expected to fade when the depression is relieved. However, there is evidence that certain psychotropic drugs may produce analgesia by acting directly on pain-modulation systems.

The most useful group of psychotropic drugs presently used in pain management is the tricyclic antidepressants. The effectiveness of tricyclics may relate to their actions in the central nervous system on biogenic amines such as serotonin (5-hydroxytryptamine) and norepinephrine. As mentioned above, both serotonin and norepinephrine-containing neurons form integral links in the endorphin-mediated analgesia system. Because tricyclic antidepressants, especially the methylated forms (imipramine, amitriptyline and doxepin), block serotonin reuptake, they would be expected to enhance its actions. Studies in animals have shown that tricyclics can produce "analgesia" directly or by enhancing the action of opiates.[37-39] Thus, there are good theoretical and experimental reasons for expecting clinical pain relief from this class of drugs. In controlled studies, tricyclics have ameliorated tension and migraine headaches.[39,40] In patients with postherpetic neuralgia, amitriptyline hydrochloride has had a pain-relieving effect that is rapid in onset and independent of relief of depression.[41] There are also anecdotes of its effectiveness in a variety of patients with chronic pain.

Phenothiazines are the other major class of psychotropic drugs that are used in pain management, usually as adjuncts to narcotic analgesics. Careful studies have shown that these drugs have little if any analgesic action either alone or in combination with opiates.[42] There is some evidence, however, that phenothiazines are useful when combined with tricyclic drugs in managing neuropathic pain.

Opiate Analgesia

Opium derivatives have been used for centuries to provide pain relief and remain the most potent analgesics available. Despite the long history of their use by physicians, it is well documented that patients, especially women and children, are often inadequately treated with narcotic analgesics.[43,44] This is due to several factors, including a physician's or nurse's fear that the patient will become addicted and a lack of knowledge of either appropriate dose or time course of the drugs' effects. Another source of difficulty is that the dose of a narcotic analgesic required to produce adequate pain relief varies greatly between patients[45] and the therapeutic endpoint is subjective. Thus, to assure adequate analgesia, additional doses must be given until a patient either reports relief or has unacceptable respiratory depression or sedation. Such a therapeutic approach requires that the patient be asked directly if the analgesic drug was effective. Unfortunately, this is often not done.

The finding of opiate receptors located in the dorsal horn of the spinal cord suggested that local application of opiates might produce a local analgesia without the side effects seen when these drugs are systemically administered. In fact, morphine has been given either epidurally (2.0 to 5.0 mg) or intrathecally (0.5 to 10.0 mg) to many patients for postoperative, posttraumatic and labor pain.[46,47] These doses of opiates are highly effective and, when given intrathecally, may produce analgesia lasting up to 24 hours. More recently, implantable infusion pumps have been used to epidurally deliver a continuous infusion of morphine to patients with cancer pain in the lumbosacral region. Although tolerance does develop within weeks, these devices can provide reasonable pain relief in terminally ill patients who no longer respond to very high doses of morphine given systemically.[48] Although useful, intrathecal and epidural administration of opiates produces dose-related side effects such as pruritus, urinary retention, nausea and vomiting and late respiratory depression in a significant proportion of patients. For-

fortunately, most of the side effects can be reversed by doses of the narcotic antagonist, naloxone, which does not reverse analgesia. Commercially available morphine or meperidine preparations are probably not safe for intrathecal use because of preservatives.

Another newly developed approach for opiate administration is the use of continuous *intravenous* infusion. This can produce effective analgesia without excessive risk. The general applicability of this technique is limited, however, by the fact that the dose required may vary over a period of a day, and for technical reasons it is difficult to change the infusion rate to meet changing drug requirements. An alternate approach, patient-controlled "on-demand" analgesia, has proved highly effective and has been associated with a decrease in side effects when compared with nurse or physician administration of drug.[49,50] Even in the most enlightened medical environment, a patient must request medication, be evaluated by nursing personnel and wait for the drug to be obtained, a sequence of events that might easily take half an hour. In studies with a bedside on-demand analgesia apparatus, patients regulate pain effectively with moderate dosage and, in the case of postoperative pain, decrease drug use over time. This type of administration of analgesics has been used in Europe for some time and is not that dissimilar to the oral outpatient use of narcotics in the United States. It is likely that machines for patient-controlled analgesia will be licensed and available in this country within a year.

A discussion of narcotics for chronic pain is often limited to their use in patients whose pain is associated with malignancy. They have, however, been used successfully for nonmalignant chronic pain of musculoskeletal origin. Guidelines for narcotics use in these conditions need more systematic formulation. Starting with weaker opiates such as codeine, it may be possible to control chronic pain for years on dosing regimens that are stable. Obviously, patients need to be informed about the risk of tolerance and addiction.

Recent studies of the factors affecting analgesic response to opiates suggest some preliminary guidelines for the clinical use of this important class of drugs in patient subgroups.[51] Middle-aged patients require smaller doses than younger patients and the elderly less than middle-aged patients. Patients who describe their pain as dull obtain more relief than those who describe it as sharp. Finally, pain originating from the abdomen requires less medication than thoracic or upper-extremity pain.

Another approach to therapy suggested by the discovery of endorphins is to use pharmacologic agents that prolong their action. For example, there are enkephalinases that rapidly degrade enkephalins. One such enkephalinase inhibitor, thiorphan, has been reported to produce analgesia.[51] Furthermore, enkephalin analogs have been synthesized that resist degradation and retain analgesic potency. At present, these compounds are experimental agents.

Opiates, along with NSAIAs, are the mainstay of management for severe pain. The recent advances in their routes of administration have extended their clinical applications, and recent discoveries about their mechanism of action suggest that further advances are forthcoming.

Nonsteroidal Anti-inflammatory Agents

Nonsteroidal anti-inflammatory agents (NSAIAs), including aspirin and acetaminophen, are the most commonly used analgesics. Although the new NSAIAs have altered dosing regimen and toxicity, direct evidence for greater efficacy of this class of drugs is scanty. In fact, the major impact of newer agents that need to be taken only once or twice a day may be better compliance. Another possibility is that they are more effective simply because they contain a higher and thus more effective dose. Although it is commonly done with aspirin, no other NSAIA has been systemically administered at doses that are near toxic levels.

Additional recent changes in the clinical use of NSAIAs are broadening our perspectives on their role in pain management. For example, the availability of preparations suitable for parenteral administration may allow NSAIAs to be used for the treatment of pain syndromes for which they have not previously been considered applicable because of gastrointestinal toxicity or because of the severity of the pain. Both renal and biliary colic have been treated in this manner with apparent good results.[52,53]

The effectiveness of parenteral administration of NSAIAs in these conditions, generally considered to be associated with severe pain, raises doubt about the traditional teaching that these agents are only effective for pain of mild to moderate severity. Although renal and biliary colic and dysmenorrhea often produce severe pain, the fact that the pain is associated with local inflammation makes them candidates for treatment with NSAIAs. In this case, it is the *mechanism* of the pain rather than its *severity* that makes NSAIAs effective analgesics.

In part because of their popularity, NSAIAs have been used in different combinations with other drugs that have not been found to have established analgesic efficacy. Combinations such as NSAIAs plus mild stimulants, sold as over-the-counter preparations, may owe part of their efficacy to a placebo response perhaps enhanced by psychoactive actions of compounds such as caffeine.

A final clinical area in which NSAIAs have recently been applied with remarkable success is in preventing postoperative pain. Prophylactic administration before a surgical procedure is associated with less pain and swelling and decreasing requirements for postoperative narcotic analgesics.[54] The success of this therapeutic regimen could have been predicted from the mechanism of action of NSAIAs. Trauma invariably produces inflammation via prostaglandin synthesis, which in turn sensitizes the peripheral terminals of nociceptive afferents.

In conclusion, a better understanding of the mechanisms of peripheral nociceptive transduction processes and of the NSAIAs provides a rationale for the optimal use of these analgesic agents and has extended their therapeutic use to a broader range of clinical conditions. As discussed earlier, the recent elucidation of the role of the lipoxygenase pathway of arachidonic acid metabolism in pain promises to provide additional insights into the peripheral mechanisms of nociception and the possibilities for new classes of analgesic agents.

Sympatholytic Therapy

A number of pain syndromes are associated with increases in sympathetic nervous system activity localized to the painful region.[52,56] That sympathetic nervous system activity is causally related to the pain associated with these diseases is suggested by the observation that the pain is often exacerbated by stressors that increase sympathetic tone, and is abolished by selective regional sympathetic blockade.[57]

A mechanism by which sympathetic nervous system activity could produce pain is suggested by recent physiologic studies of regenerating fibers in a region of peripheral nerve injury.[58-60] The neuroma that forms near the regenerating end of the nerve contains a predominance of small-diameter axons, including both nociceptive primary afferents and sympathetic efferents. The afferents show increased sensitivity to sympathetic activity and circulating catecholamines. The clinical relevance of these observations is dramatically illustrated in patients with causalgia and reflex sympathetic dystrophy, where sympathetic blockade can dramatically reduce the pain. More recently, sympathetic block induced by regional intravenous or intra-arterial injection of the catecholamine-depleting agents, guanethidine and reserpine, has been shown to significantly ameliorate causalgia, minor causalgia and other forms of reflex sympathetic dystrophy.[61-63] The duration of pain relief varies from hours to permanent termination of the condition.

Our knowledge about the central nervous system control of the autonomic nervous system and the relation of this to clinical pain is poor. There is evidence that activity in large-diameter sensory neurons inhibits the sympathetic nervous system at the level of the spinal cord.[64] Regenerating sensory fibers in a neuroma are spontaneously active and respond to innocuous mechanical stimuli and, as mentioned above, to sympathetic nervous system activity. The mechanical hypersensitivity and spontaneous activity in the small-diameter afferent fibers in the absence of the normal inhibitory effect of the larger fibers has been proposed as the cause of the excruciating burning pain and superficial hypersensitivity that is reported by many patients. The dramatic relief of this pain by TENS in some patients supports the idea that reduced large-fiber input contributes to the pain and that large-fiber inhibition of activity in the sympathetic nervous system contributes to the analgesic effect of TENS. Other commonly used therapies such as ice, vibration, massage or other physical manipulations may have a similar mechanism.

Despite the intriguing observations described above, it is not clear how the autonomic nervous system "normally" affects pain perception. In part this is due to the difficulties in determining what aspects of autonomic function are specific to pain. We hope the recently renewed interest in the association of autonomic function and pain will provide an impetus for further insight.

Summary and General Treatment Strategies

The major components of the neural networks relevant to pain transmission and modulation are outlined in Figure 3. After transduction in peripheral terminals, signals are relayed to the spinal cord by small-diameter primary afferents. In the spinal cord, this signal is modified by simultaneously arriving inhibitory input from large-diameter primary afferents that have been activated by nonpainful stimuli. The pain message is then relayed by dorsal horn neurons to thalamocortical circuits, either directly or via the brain-stem reticular formation.

The pain-transmission system is continually modified by networks running from cortex to spinal dorsal horn. This modulatory system has both endorphin and biogenic amine links active at several brain levels. It is activated by pain, stress and a variety of other poorly understood environmental factors.

Given this complex system with its numerous neuronal links for transmission and modulation, it is clear that there are many possible sites at which the perception of pain can be altered. The two general approaches that have been used clinically are to either reduce transmission or to enhance modulation.

The two most commonly used classes of analgesic agents are the NSAIAs, which reduce transmission by interfering with the transduction mechanism at the peripheral receptor, and narcotics, which powerfully activate the modulating system by an action in the central nervous system. Because their mechanisms of producing analgesia are different, combining these two classes of drug to enhance analgesia has a strong rationale. On the other hand, the use of more than one drug within each class makes little sense.

Other major methods of blocking transmission include applying local anesthetic to peripheral nerve or spinal cord, giving narcotic analgesics epidurally or intrathecally and surgical lesions to interrupt the spinothalamic tract.

Sympathetic blocks and TENS make use of independent modulatory mechanisms. Sympathetic block reduces abnormal excitatory influences on peripheral nociceptors and TENS inhibits nociceptive transmission cells and, perhaps, sympathetic preganglionic fibers in the spinal cord. It should be possible to enhance sympatholytic therapy using catecholamine-depleting agents such as reserpine or guanethidine. These have been reported to work in some painful conditions

but only when given by regional perfusion in relatively high concentrations. Because TENS and sympathetic block work by unique mechanisms, their effects, if partial, should add to the analgesia produced by systemic drugs.

The descending pain-modulating networks can be activated by narcotic analgesics and, in some patients by suggestion (placebo) in the setting of significant pain and stress. It is also possible that certain physical methods such as heat, massage, biofeedback and acupuncture function, at least in part, by activating or enhancing pain-modulating networks.

Another therapeutic approach using pain-modulating networks is to enhance their nonopioid links. For example, there is experimental evidence that tricyclic antidepressants enhance opiate analgesia by potentiating biogenic amine links in the endorphin circuit. Thus, opiate-tricyclic combinations may be clinically useful. Opiate-tricyclic-NSAIA combinations might also have a place in treating patients who have an inflammatory component to their painful condition, if the pain is resistant to therapy with single drugs.

One of the major practical problems in managing pain is knowing when to refer patients for behaviorally or psychologically oriented treatments such as hypnosis, biofeedback, guided imagery, psychotherapy or a psychologically oriented inpatient program. Many patients are unwilling to take this approach, while more will find it an unsupportable financial burden. Physicians tend to use every medical option before requesting psychological referral. However, because chronic pain produces anxiety, depression and other emotional problems, it is useful to obtain psychiatric evaluation of these cases early. In some patients there will be a major psychological problem that is contributing to the intractability of the pain. In most cases, however, the contribution of psychological factors to the painful condition cannot be determined with certainty and an empiric approach, however unsatisfactory, must be taken. If some evidence of response to medical management or rehabilitation is not observed within a few weeks and the medical condition is stable, psychological evaluation and behavioral approaches to management should be considered.

One of the great challenges in pain management is to develop ways of evaluating the efficacy of behavioral therapies. Only then can we begin to define which patients will benefit. At present we must rely on anecdotal studies suggesting that pain clinics are helpful to patients with chronic pain.

In summary, in the past two decades there has been a remarkable expansion of our knowledge of pain mechanisms. Some of this progress has had an impact on patient care, but great challenges remain. Because pain is subjective and subject to complex physiologic and psychological factors, its management requires patience and sensitivity. Despite this complexity, or in some cases because of it, therapeutic interventions are often dramatically successful and rewarding to both patients and physicians.

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