9

Pain

1. A 59-year-old man came to the emergency room complaining of crushing pains in the chest. He was immediately admitted to the coronary care unit with a diagnosis of myocardial infarction (heart attack). Morphine was given by injection to relieve the pain.

2. A 23-year-old married woman was admitted to the obstetrics ward today as she developed labor pains. As he was waiting for her to deliver the baby, the husband also experienced severe crampy pains in his abdomen, which disappeared after his wife's delivery.

3. A 20-year-old single woman is still in severe pain after two weeks in the hospital. This is her seventh admission to the hospital in three years because of severe pains in the abdomen. During the first admission, an operation was done to rule out acute appendicitis. Her appendix was normal. She had two additional operations on the abdomen, because the cause of the pain was suspected to be adhesions from the first operation. All tests so far during this hospitalization have been normal, but she continues to have severe crampy pains and asks for frequent pain medications. When she asks for pain medication, she is given a saline injection (placebos) at the order of the physician, who believes that she is addicted to narcotic pain medications. The injection seems to help her for a couple of hours, but then she cries for another injection. According to the nurses, she seems to be always bitter and cynical.

4. A 27-year-old man who is a surgical patient in the hospital is complaining of severe shooting and stabbing pains in his right leg and foot. The patient had an amputation of the right leg and foot four weeks ago, after an industrial accident that crushed his right foot. This is an example of "phantom limb" pain—pain felt as coming from a limb that is no longer there.

These are only a few examples of patients with pain frequently seen in the hospital. Many patients with pain obviously do not present themselves to the physician, and almost all of us have from time to time had pain in some part of the body that we were able to ignore or that could be relieved with aspirin. It should be obvious from the foregoing cases that pain is not a simple phenomenon; it is determined and influenced by many factors. What, then, are the mechanisms and functions of pain, and what are the factors that affect this familiar but sometimes puzzling entity?

DEFINITIONS AND FUNCTIONS OF PAIN

Pain is an abstract concept that refers to a personal, private sensation of hurt, often as a result of a harmful stimulus that signals current or impending tissue damage, and an accompanying pattern of responses that operate to protect the organism from harm (Sternbach, 1968).

At a concrete level, pain is a perceptual experience like hearing or vision, but, unlike vision or hearing, pain experience is determined or modified to a greater extent by a multiplicity of factors such as the sufferer's psychological set, including expectations, suggestions, previous experiences, and sociocultural environment.

The function of pain is protective; it is usually a signal that tissue damage is occurring, and it alerts the person to take appropriate action or get away from it if possible. In this sense, pain as a signal of impending threat is analogous to anxiety. Anxiety occurs in anticipation of the threat, while pain occurs when the threatening situation is actually causing damage to the organism. Unlike anxiety, pain is usually perceived as emanating from a part of the body—it is *localizable.*

Like anxiety, pain may signify the presence of a *psychological state* without actual tissue damage. Pain *metaphors* describing emotional states are common, such as the "pain of loneliness" and "heartaches." In fact, descriptions of pain occurring from tissue damage are often also quite metaphorical, such as "splitting headaches," "stabbing pain," and "heartburn." These linguistic uses clearly indicate close association between the experience of pain and the *symbolic* meanings in the mental life of human beings. Thus, it is not surprising that some persons perceive certain psychological states as physical pain, attributable to a body organ.

Pain often generates anxiety; in many situations, anxiety is generated as a signal that a potentially painful process is in the making. *Anxiety may also generate pain;* pain is the most common heterothetic symptom resulting in doctor–patient contact (see Chapter 1).

Anxiety and pain are probably associated through a learning process (see Chapter 4). In childhood, physical punishment (pain) often occurs in a situation in which the child has anxieties about the possible loss of parental love; fear of the loss of bodily parts in injury is also accompanied by the sensation of pain. For many persons, therefore, pain is often associated with anxiety and anxiety with pain.

Pain is also a frequent symptom of depression, being present in 60–100% of depressed patients (VonKnorring, 1975; Ward *et al.*, 1979). There is evidence that chronic pain syndrome without evidence of underlying tissue damage may be a variant of depressive disorder (Blumer and Heilbronn, 1982). The evidence for this hypothesis is derived from the fact that chronic pain syndrome patients often show aspects of the depressive syndrome (although the depressive affect itself may be absent) and have family histories of affective disorder and that the chronic pain often responds to antidepressant drug treatment. On the other hand, depression may often develop as a consequence of severe and chronic pain due to tissue damage.

QUALITIES OF PAIN

Many different adjectives have been used to describe the qualitative aspects of pain. These include, among others, throbbing, pounding, shooting, stabbing, tender, aching, splitting, stinging, and grueling. Melzack and Torgerson (1971) classified 102 such descriptors into three major classes:

1. Words describing the *sensory* qualities of the experience, such as temporal, spatial, pressure, and thermal properties—e.g., pricking, scalding.
2. Words describing the *affective* qualities, such as tension and fear, and autonomic properties—e.g., sickening, exhausting, frightening, wretched.
3. Words *evaluating* the subjective overall intensity of pain—e.g., miserable, unbearable.

The quality of pain reported by patients is most important in helping the physician in diagnosis. For example, the crushing pain reported in vignette 1 is typical of a coronary disease, while a dull, aching pain in the same location (chest) is more likely to be from the chest wall, not

the heart. Elaborate metaphorical quality in the description of pain, such as "feeling as if someone is sitting on my stomach, cutting bowels out with a knife," often indicates that the pain is associated with elaborate fantasies of the patient.

Neurophysiological experiments show that pain sensation emanating from tissue damage can be classified into three major types:

1. Pricking pain: the type of pain caused by a needle pricking the skin or by incision of the skin. Strong irritation of a large area of the skin can also cause this sensation.
2. Burning pain: the type of pain felt when the skin is burned. This is often excruciating.
3. Aching pain: a low-intensity pain usually felt deep inside the body, not on the surface.

Pricking pain is conducted through small myelinated type A delta nerve fibers, while burning and aching pains are conducted by even smaller unmyelinated type C nerve fibers.

NATURE OF PAIN

Phenomenologically, pain is a *subjective experience* and falls into the realm of "private" data; that is, the experience of pain *cannot be shared* by others, but can only be reported. This is an important point, since physicians may tend spuriously to objectify pain, as though it were identical in degree to the pathology causing it.

Although certain events, such as injury, are usually associated with pain, under some circumstances, whether pain is experienced or not, and if so, how much, is dependent on factors other than tissue damage; for example, Beecher (1959b) reported that two thirds of the badly wounded men in a World War II battle did not complain of pain or ask for medications for it. This may be a manifestation of "stress anesthesia" that is mediated by release of endorphins under severe stress.

Beecher proposed that there are two *components* to a pain experience—a primary *sensory* component and a reactive *psychological* component. The primary component is the pain sensation itself, which includes the perception, discrimination, and recognition of the noxious stimulus. The secondary component is the suffering aspect of pain, which is an emotional aspect including anxiety. The reactive component is not always commensurate with the primary sensation. Physiological changes associated with pain, such as change in heart rate, blood pressure, and skin conductance, are thought to be related to the reactive component of pain.

Neurophysiology of Pain

The "pain receptors" are considered to be free nerve endings that are stimulated by tissue damage and stimuli that can cause tissue damage. There seem to be in the free nerve endings receptors that respond only to very strong mechanical stimuli and strong thermal stimuli evoking pain sensation. Also, various chemicals, such as lactic acid formed in the muscle due to lack of oxygen; polypeptides, such as bradykinin formed as a tissue breakdown product; amines (serotonin and histamine); and prostaglandins are known to cause intense pain. A novel type of C-fiber nocioceptors have been identified recently that do not respond to acute mechanical or thermal stimuli but respond to irritant chemicals associated with chronic inflammation ("silent nocioceptors"). These fibers do not respond even to severely noxious stimuli in healthy tissue, but may bombard the CNS with activity in inflamed or chronically injured tissue (McMahon and Koltzenburg, 1990).

The nerve impulses arising from the pain receptors (nocioceptors) travel through two types of nerve fibers in the sensory nerve: the type A delta fibers and the type C fibers. The A delta fibers have a conduction velocity of 3–20 m/sec, while the C fibers transmit at 0.5–2 m/sec. As mentioned earlier, the pricking type of pain is transmitted by the A delta fibers and the burning, aching pain by the type C fibers. Thus, a sudden painful stimulus can result in two perceptions, an initial pricking sensation followed by an aching or burning sensation a second or so later. The cell bodies of the pain fibers are in the dorsal root ganglia, and most pain fibers enter the spinal cord through the dorsal roots, then ascend or descend one or two segments in Lissauer's tract, terminating in the neurons in the gray matter of the dorsal horns (see Figures 14 and 15). Recent evidence has shown that significant numbers of unmyelinated C fibers enter the spinal cord via the ventral roots and then project to the dorsal horn.

In the dorsal horns, the signals pass through one or more short-fibered neurons, the last of which give rise to long fibers that cross to the contralateral side and ascend in the spinal cord as the *spinothalamic* and *spinoreticular tracts*.

In the brain, the ascending pain pathway separates into two separate pathways, the "pricking pain pathway" and the "burning pain pathway" (Guyton, 1976). The pricking pain pathway terminates in the caudalmost part of the ventrobasal complex of the thalamus. There are

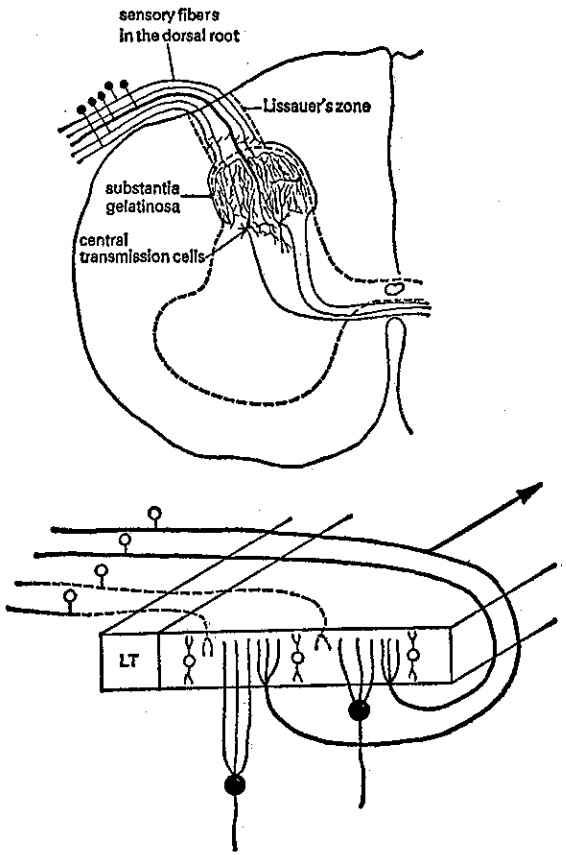

Figure 14. Top: Schematic drawing of the substantia gelatinosa in relation to somatosensory fibers and dorsal horn cells that project their axons across the cord to the anterolateral pathway. (After a figure originally published in AA Pearson, *Arch Neurol/Psychiatry* 68:515, 1952. Copyright 1952 by the American Medical Association.) Bottom: Main components of the cutaneous afferent system in the upper dorsal horn. The large-diameter cutaneous peripheral fibers are represented by thick lines running from the dorsal root and terminating in the region of the substantia gelatinosa; one of these, as shown, sends a branch toward the brain in the dorsal column. The finer peripheral fibers are represented by dashed lines running directly into the substantia gelatinosa. The large cells, on which cutaneous afferent nerves terminate, are shown as large black spheres with their axons projecting deeper into the dorsal horn. The open circles represent the cells of the substantia gelatinosa. The axons (not shown) of these cells connect them to one another and also run in Lissauer's tract (LT) to distant parts of the substantia gelatinosa. (Adapted from a figure originally published in PD Wall, *Prog Brain Res* 12:92, 1964. Courtesy of Oxford University Press.) (From Melzack, 1973. Copyright 1973 by Ronald Melzack and reproduced with his permission.)

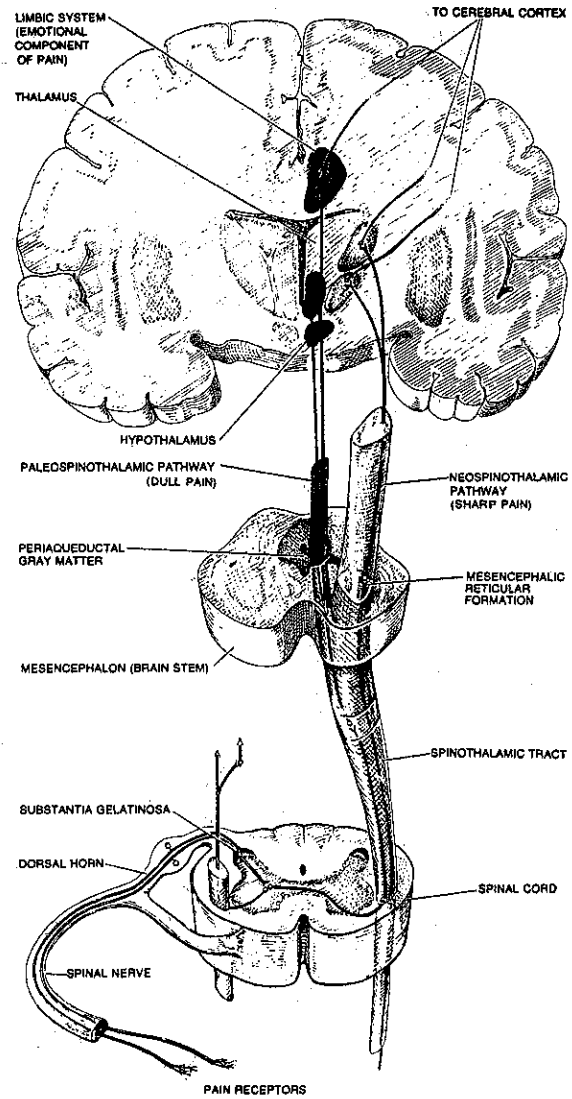

Figure 15. Two types of pain pathways carrying information from the periphery of the nervous system to the brain: the laterally located neospinothalamic pathway, which transmits sharp, localized pain, and the medially located paleospinothalamic pathway (shaded), which transmits less localized burning pain. Burning pain is best relieved by opiates, and opiate receptors have been found to be concentrated in the substantia gelatinosa and in the central thalamus. (From Snyder, 1977. Copyright 1977 by Scientific American, Inc. Reproduced with permission.)

neural connections between this complex and the somatosensory cortex and other areas of the thalamus.

The burning pain pathway terminates in the reticular formation of the brain stem and the intralaminar nucleus of the thalamus. The reticular formation and the intralaminar nuclei are parts of the reticular activating system (RAS) (see Figure 7 [Chapter 4]), the function of which is to regulate the level of arousal of the entire central nervous system. The pain signals activate this system, sending activating signals to the entire cortex, entire brain stem, thalamus, and hypothalamus, which controls the autonomic and neuroendocrine systems. Thus, through the RAS, pain causes a central nervous system state of arousal, promoting defensive reactions to get rid of the noxious stimulus (see Chapter 5).

Pain sensations from various parts of the body are represented in the thalamic nuclei in a somatotopical fashion somewhat like that in the sensory cortex. Although sensory modalities other than pain require intact sensory cortex to be perceived, the perception of pain seems to require the functional integrity of the nervous system *only up to the thalamic level.* The states of other parts of the nervous system, however, have a major impact on the degree of perception and on the interpretation of the perception and the organism's response to it. The cerebral cortex may affect the state of the neurons in the spinal column through efferent nerves, which might, in turn, affect the sensation itself.

The localization of pain seems to depend to a large extent on the simultaneous stimulation of tactile receptors. The signals transmitted by type C fibers are localizable only very grossly, since this pathway terminates very diffusely in the brain. As mentioned earlier, pain is a subjective experience that cannot be measured objectively. It is possible, however, to measure the least amount of stimulus on the skin necessary to elicit the report of pain from an individual *(pain threshold).* This threshold can be measured by projecting a beam of radiant heat onto the skin. The skin temperature at which pain is first perceived is remarkably uniform in different people, regardless of their ethnic or cultural background, sex, age, and other differences. Most people begin to feel the sensation of pain when the skin temperature reaches almost exactly 45 °C.

This uniformity of the threshold for pain, however, is valid only in precisely controlled laboratory situations, where the environmental factors are kept constant. The perception of pain is markedly modified in natural conditions by the person's psychological state, such as anticipation, attention, or suggestion. The pain threshold is lowered in injured skin reddened by vasodilatation. Sensitization of pain receptors

also occurs when a very strong stimulus is initially applied (Perl, 1976). "Adaptation" to stimuli also occurs, so that there is a decrease in pain sensation after repeated stimuli.

Historical Neurophysiological Theories of Pain Perception

Historically, there are three theories concerning the neurophysiological basis of pain perception: (1) the specificity theory, (2) the pattern theory, and (3) the gate control theory.

The *specificity theory* is the oldest theory; it postulates a specific pain receptor with specific pathways leading to a particular nucleus in the thalamus. In other words, according to this theory, the free nerve endings responsible for pain sensation have no function other than to detect pain, and there is no mechanism for detection of pain other than stimulation of these free nerve endings (receptors). The thalamus is considered to be the primary organ for the integration of pain sensation, according to this theory. In its classic form, this theory cannot account for pain phenomena in which there is no stimulation of the specific pain receptors, as in phantom pain (vignette 4) (see Figure 16).

The *pattern theory* postulates that particular types of input, whether or not they came from specific receptors, would set in motion a particular firing pattern in *reverberatory circuits* in the spinal cord internuncial neurons. This self-propagating nerve impulse in the dorsal horns would then send to the brain volleys of impulses that are perceived as pain. This theory can explain phantom limb pain, since the initial damage to the limb, or the amputation procedure itself, could initiate abnormal firing patterns in the reverberatory circuits in the dorsal horns. There is not good evidence, however, that reverberatory circuits initiating and perpetuating pain exist in the spinal cord.

The *gate control theory* was proposed by Melzack and Wall (1965). This is an attempted integration of the theories concerning pain and postulates the following: A neural mechanism in the dorsal horns of the spinal cord acts like a gate that can increase or decrease the flow of nerve impulses from peripheral fibers to the central nervous system (Melzack, 1973). Once signals from receptors (which are specific for pain, as in the specificity theory) reach the spinal cord, their transmission from the afferent fibers to the cells that give ascending output into the brain (transmission, or T, cells) is modulated by the gating mechanism. The gating mechanism was thought to be located in the *substantia gelatinosa,* a group of small neurons located at the tip of the dorsal horn. The substantia gelatinosa receives impulses from many small and large fibers entering the spinal cord as well as from

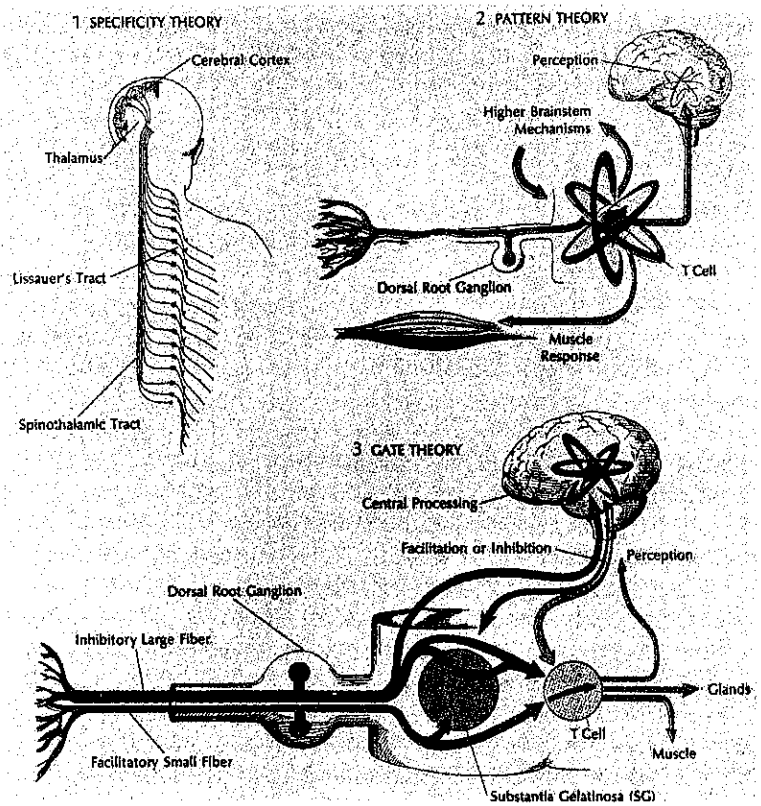

Figure 16. Schematic representation of three theories of pain transmission and perception. The earliest was the specificity theory (1), which held that pain stimuli enter the spinal cord through spinal nerves and synapse ipsilaterally, then rise several levels in Lissauer's tract. They then cross the cord and ascend to the thalamus, where they synapse again and rise to the cerebral cortex, where pain is perceived. The pattern theory (2) postulates stimuli entering from nerves through dorsal root ganglia into the spinal cord. The so-called T cell is in the lateral horn of the spinal cord. It sets up a response, part of which results in an impulse to higher brain stem mechanisms. These, in turn, modulate the response by action on the T cell, which fires and sends impulses to the brain, causing perception, and to striated muscle, facilitating response. The gate theory (3) depends on the concept of two "parallel" fibers, both with cell bodies in the dorsal root ganglia. The large fiber has basically an inhibitory effect on pain perception, the small fiber basically a facilitatory effect. The large fiber acts on and stimulates the substantia gelatinosa (SG). Such stimulation will prevent firing of the T cell, which is necessary for pain perception. The small fiber can overcome or modify the large fiber's influence on the SG, or it can directly stimulate the T cell to fire, or it can do both. The large fiber may also act directly on the brain's central processing mechanisms, although the pathways of this action have not been defined. Impulses may be either inhibitory or facilitatory. If the latter, the result will be firing of the T cell, producing pain perception and endocrine and muscle responses. (Reprinted with permission from Pearson, 1976. Drawings by Ms. Carol Donner.)

descending fibers from the brain, such as the reticulospinal tract. According to the gate control theory, large-diameter fibers, such as those responsible for position and touch, have an inhibitory effect on the gate control mechanism, reducing the flow of impulses transmitted to the brain. The small-diameter fibers, such as the pain fibers (both A delta and C), have a facilitatory effect. The descending fibers from the brain have an inhibitory effect; the brain stem reticular formation is also considered to exert a powerful inhibitory control over information projected by the spinal cord transmission cells.

A specialized system of large-diameter, fast-conducting fibers (probably in the dorsal column of the spinal cord and its projections), which is called the "central control trigger," is postulated to carry information concerning the pain (e.g., location). This system is considered to activate selective brain processes, such as memories of prior experiences, before the perception of pain and then to exert control selectively over the sensory input by modulating the gate control system through descending pathways, or by modulating the receptivity of the cortical neurons to the stimuli coming up more slowly through the pain pathways, or in both ways.

According to this theory, phantom limb pain can be explained on the basis of release from inhibition; the loss of large-diameter fibers from the amputated organ "opens the gate control mechanisms," so that the T cell fires at a very low threshold level or even spontaneously. This theory can also explain the pain-relieving effect of counterirritation (such as liniment and acupuncture), which stimulates the inhibitory large-diameter fibers. There is controversy concerning the existence of such a gating mechanism and the exact nature of the T cells.

In fact, phantom pain is not relieved even after complete surgical transection of the spinal cord with bilateral sympathetic block, nor after surgical removal of the somatosensory areas of the cortex or thalamus (Melzack, 1990). More recent findings indicate that there is a specific system of nocioception in which specific receptors that are activated only in case of tissue damage (e.g., high-intensity pressure) give rise to impulses in corresponding specific afferent nerves (high-threshold neurons as opposed to low-threshold neurons such as those subserving touch sensation), leading to activation of specific nocioceptive areas of the central nervous system (Kerr and Wilson, 1978). It is also clear, however, that this specific nocioceptive system is influenced and modified by many factors other than tissue damage, especially through descending fibers from the brain (see below).

Role of Endorphins in Pain Mechanisms

When specific receptors binding morphine were discovered in the human brain in the early 1970s, people wondered why human beings might have developed receptors to an alkaloid made by the poppy plant. Obviously, a more likely explanation was that these receptors were for some morphinelike substance made by our own brains. Recently, a number of substances that possess morphinelike properties have been identified in the brains and pituitary glands of many animals and humans. These properties include, among others, analgesia, respiratory depression, euphoria, and addictiveness. The chemical structures of these substances have been studied, and all have been found to be peptides. The generic name for the peptides with opiatelike properties is *endorphins*. The name *enkephalins* is given to certain specific pentapeptides belonging to the class of endorphins. Some large-molecule endorphins, such as β-endorphin, a potent opioid peptide containing 31 amino acids, contain in their structures the shorter 5-amino-acid sequences of the enkephalins.

All the endorphins, including enkephalins, are antagonized by narcotic antagonists such as naloxone. Thus, their actions seem to be mediated by binding to the opiate receptors discovered earlier. In addition to properties similar to those of morphine, some endorphins have other important behavioral and physiological effects when injected into the brain or the cerebrospinal fluid. For example, β-endorphin and metenkephalin (which forms a fragment of the structure of β-endorphin) cause catatonic behavior in rats, with a decrease in body temperature. These effects are reversible with naloxone (Bloom *et al.*, 1976).

The opiate receptors, the presumed site of action of both the endorphins and narcotic analgesics, are especially heavily distributed in the limbic brain, in the central thalamus, and in the substantia gelatinosa of the spinal cord. As previously discussed, these areas of the central nervous system are especially concerned with the perception of pain. The importance of the limbic brain in the perception of the emotional component of pain should be obvious from our discussion in Chapter 4. It is possible that the euphoriant effect of narcotics is closely related to the concentration of opiate receptors in the limbic system. The opiate receptors are also abundant in all areas the stimulation of which causes analgesia.

The endorphins and the smaller enkephalins (which have a weaker and shorter duration of action) may be neurotransmitters or neuromodulators that modify the perception of pain. The mechanism of action seems to be through inhibition of neurons related to pain perception by means

of a rather unusual mechanism of blocking the sodium influx elicited by excitatory neurotransmitters (Snyder, 1977).

Many forms of analgesia may occur through the release of endogenous endorphins, as demonstrable by their reversal by naloxone. These endorphin-dependent analgesias include: brain-stimulation analgesia, acupuncture and some forms of placebo anesthesia, and nitrous oxide anesthesia. Although endorphins may play a role in the inhibition of pain perception during stress, hypnoanesthesia has not been reversed by naloxone (Goldstein, 1976; Marx, 1977).

It seems, then, that endorphins play an important role in the *self-regulation* of the perception and tolerance of pain by the brain through their action on *pain at the spinal cord all the way up to the emotional reactions* to the pain sensation mediated by the limbic system. In chronic pain, the endogenous endorphin levels may be elevated; on the other hand, insufficient endorphin release due to genetic or other reasons might predispose a person to feel excessive pain. *Some patients may require greater amounts of narcotic analgesics* for control of minor pain because of insufficient or depleted endorphin-release mechanisms in the central nervous system.

Descending Influences from the Brain

A number of descending systems from the brain influence the state of the spinal cord. Brain stem stimulation can cause a change in the excitability of spinal cord cells (Wall, 1976). Stimulation of the sensorimotor cortex inhibits low-threshold neurons, but the high-threshold units are unaffected (Coulter *et al.*, 1974). A cold block of the spinal cord rostral to the recording site has a tonic inhibitory effect on nocioceptive neurons (Handwerker *et al.*, 1975).

Electrical stimulation of certain areas of the brain produces potent analgesia, called stimulus-produced analgesia (SPA). SPA can also be produced by stimulation of peripheral nerves, although not as consistently as by brain stimulation. The areas of the brain that produce analgesia on stimulation include the periaqueductal gray, the dorsal raphe nucleus, the nucleus raphe magnus of the medulla, the gray matter surrounding the third ventricle, and the septal area (Illis, 1990; Kerr and Wilson, 1978) (see Figure 15). The analgesia produced by brain stimulation specifically inhibits the activation of the nocioceptive neurons in the dorsal horn without affecting the low-threshold neurons (Beall *et al.*, 1976; Oliveras *et al.*, 1974). SPA produced by brain stimulation is effective against visceral as well as somatic pain.

Injection of very small amounts of morphine into some of the brain areas that can cause SPA also produces a marked elevation in pain threshold, and the analgesia produced by electrical stimulation of the brain areas is reversed by the administration of or pretreatment with naloxone, an opiate antagonist (Kerr and Wilson, 1978).

Animal and human data indicate that there are at least four classes of descending pathways for centrally induced analgesia: neural–opiate, neural–nonopiate, hormonal–opiate, and hormonal–nonopiate (Watkins and Mayer, 1982). In animals, certain environmental stresses such as centrifugal rotation and injection of intraperitoneal hypertonic saline cause potent nonopiate analgesia that is not reversed by naloxone.

If the stressor is electrical shock to the feet, either opiate- or nonopiate-mediated analgesia occurs, depending on the location of the shock; front-paw shock activates the opiate system, while hind-paw shock activates a nonopiate analgesic system. When animals are exposed to the nonelectrified grid following repeated sessions of electric shock to the front paws, potent analgesia develops, which is reversed by naloxone. Thus, the nonelectrified grid may serve as a conditioned stimulus to produce the activation of the opiate analgesic system.

Analgesias induced by front-paw shock, by morphine, and by classical conditioning are quite similar; none is attenuated by the ablation of pituitary or adrenal glands, all are reversed or attenuated by naloxone, and all are subject to the development of morphine tolerance. Thus, they belong to the neural-opiate class of descending analgesia. Hind-paw shock activates the neural–nonopiate system. Shock-produced analgesia seems to induce both neural–opiate and neural–nonopiate analgesia. The dorsolateral funiculus of the spinal cord seems to be a final common pathway of all neurally mediated analgesia, since they are all reversed by lesioning this structure (Watkins and Mayer, 1982).

Acupuncture analgesia, analgesia induced by prolonged shock of all four paws, and immobilization-induced analgesia are also reversed by naloxone, but are distinguishable from neural analgesia in that they are abolished or attenuated by the removal of the pituitary or adrenal glands. Thus, they are examples of hormonal–opiate analgesia. Analgesia induced by cold water swims, on the other hand, requires the integrity of the pituitary gland but is not reversed by naloxone, being an example of hormonal–nonopiate analgesia.

Central Neuropharmacology of Pain

Biogenic amines play an important role in pain perception. Tetrabenazine, a substance that depletes brain monoamines, markedly reduces

the analgesia produced by stimulation of the periaqueductal gray in rats (Akil and Liebeskind, 1975). This effect can be reversed by the administration of serotonin or L-dopa.

Dopamine and *serotonin* seem to decrease pain mechanisms in the brain. Stimulation of dopamine receptors in the brain by apomorphine produces a marked increase in brain-stimulation-induced analgesia, while the blockade of dopamine receptors with pimozide impairs the analgesia. The administration of *p*-chlorophenylalanine, an inhibitor of serotonin synthesis, results in decreased brain-stimulation analgesia. This effect is reversed by the administration of the serotonin precursor 5-hydroxytryptophan.

Brain *norepinephrine* seems to have an effect on pain mechanisms opposite to that of dopamine and serotonin. Disulfiram, a substance that blocks norepinephrine synthesis from dopamine, causes a significant increase in brain-stimulation-induced analgesia.

The effect of morphine and endorphins may be modulated by brain monoamine levels. For example, reserpine antagonizes experimental morphine anesthesia (Kerr and Wilson, 1978).

Substance P is a peptide that has striking depolarizing effects on neurons. It is present in large concentrations in the dorsal roots and substantia gelatinosa, as well as in the hypothalamus and substantia nigra. Many nocioceptive neurons in the spinal cord respond to substance P.

Glutamate, another substance found in high concentrations in the dorsal roots and ganglia, may be a neurotransmitter concerned with nocioception.

Somatostatin (growth-hormone-release-inhibiting hormone) is also a peptide recently found to be in some small-sized neurons in the dorsal root ganglia. There also appears to be a dense plexus of somatostatin-containing fibers in the substantia gelatinosa. Somatostatin has potent depressant activity on neuronal firing and may be an inhibitory transmitter for the perception of pain.

PSYCHOSOCIAL FACTORS THAT INFLUENCE PAIN EXPERIENCE

Although the pain-sensation threshold seems to be more or less the same for most people in laboratory situations, as described earlier, the *response* to pain, perceptual intensity, and meaning of pain in natural situations are influenced by a number of psychosocial factors. Even in laboratory situations, persons of differing backgrounds show marked

differences in pain *tolerance,* the level of pain at which the subject refuses to tolerate any more pain.

Cultural expectations are known to exert a powerful influence on the experience of pain. In some cultures, for example, childbirth is perceived to be quite painful, while in others, especially in the South American cultures that practice *couvade* (Kroeber, 1923), it is accompanied by no visible distress to the woman. In the latter cultures, the woman often works in the field until the time she is about to deliver, and after the delivery of the baby with no signs of pain, she returns to the field to complete her work. Her husband, however, takes to bed while his wife is delivering and moans and groans as though he were in severe pain. Even in our culture, symptomatic variants of "couvade syndrome" are occasionally seen (vignette 2). In some parts of India, a religious ritual is still practiced in which a chosen man hangs on two steel hooks inserted into the back, which are suspended by a rope, and blesses the children and crops. During the ritual, the man reportedly feels no pain, but rather a "state of exaltation" (Kosambi, 1967) (see Figure 17).

One study in the United States showed that whites tolerated more pain than Orientals, with blacks occupying an intermediate position (Woodrow *et al.,* 1972). In a study of pain involving Old American, Irish, Italian, and Jewish housewives (Sternbach and Tursky, 1964), those of Italian origin were found to have a lower pain tolerance to electric shocks, and the Old Americans showed a more rapid physiological adaptation to repeated shock. Other studies, however, failed to demonstrate such ethnic differences in pain tolerance (Merskey and Spear, 1964; Winsberg and Greenlick, 1967). Ethnic differences in the attitude toward pain have already been discussed (Chapter 1).

What is the mechanism by which cultural and psychosocial factors influence pain experience? Although the exact mechanisms are not known, the descending influences and the recent discovery of the role of endorphins in pain-inhibition mechanisms provide a conceptual framework in which the state of the central nervous system, such as attention, anxiety, depression, and past experiences, and values ingrained in the mind and brain can influence the perception of pain.

Age may also affect pain experience. Tolerance to cutaneous pain is reported to increase with age, while tolerance to deep pain decreases with age (Woodrow *et al.,* 1972).

The *personality* of the individual has an important effect on his reaction to pain; conversely, the experience of prolonged or severe pain may also have an effect on the personality. For example, extroversion is associated with greater pain tolerance and, at the same time, with a

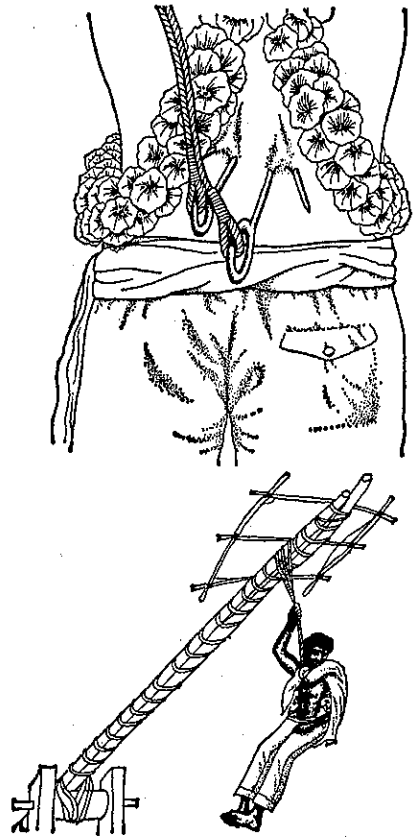

Figure 17. Annual hook-swinging ceremony practiced in remote Indian villages. Top: Two steel hooks are thrust into the small of the back of the "celebrant," who is decked with garlands. The celebrant is later taken to a special cart that has upright timbers and a cross-beam. Bottom: The celebrant is shown hanging onto the ropes as the cart is moved from one village to the next. After he blesses each child and farm field in a village, he swings free, suspended only by the hooks. The crowds cheer at each swing. During the ceremony, the celebrant is in a state of exaltation and shows no sign of pain. (Originally published in Kosambi, 1967.) (From Melzack, 1973. Copyright 1973 by Ronald Melzack and reproduced with his permission.)

tendency to exaggerate the pain experience, as compared to introversion (Eysenck, 1961; Lynn and Eysenck, 1961).

Persons with the "defensive" or "repressive" coping styles seem to have an elevated pain tolerance (Jamner and Schwartz, 1986).

Persistent pain is common in psychiatric disorders, especially those characterized by anxiety, such as neuroses (Merskey, 1965a, b). Chronic pain is also thought to *increase* anxiety and "neuroticism" of patients (Bond, 1971), whether the pain is "organic" or "psychiatric" (Woodforde and Merskey, 1972). Patients with chronic pain also tend to develop a feeling of being out of control of their lives and a sense of suspicion and anger toward others, whom they attempt to "manipulate and control" (Timmermans and Sternbach, 1974). *Depression* is also a common consequence of chronic pain (Robinson *et al.*, 1972). These findings indicate that evidence of depression, anxiety, or "neurotic tendencies" in a patient with pain does not justify an automatic diagnosis of "psychogenic" pain.

Among the psychological states that affect the experience of pain are *depression* and *expectancy*. Physical sensations can be accentuated in a state of depressive withdrawal, when the individual's attention is directed toward himself and his bodily sensations. In this instance, any minor discomfort can become magnified and be experienced as serious pain. Depression also tends to result in a vicious cycle of pain escalation—pain causes depression, and then, because of the depressed state, the intensity of pain is accentuated. In cases of pain with signs of depression, antidepressant therapy might be useful to halt this vicious cycle as well as, in some cases, to alleviate the precipitating cause of the pain (see Chapter 6).

Pain has been shown to be associated with *aggression*. In patients with persistent pain, there are often heightened feelings of hostility that are not overtly expressed (Sternbach, 1968). Pain is also implicated in triggering of aggressive behavior in animals. It may be an *unconditioned stimulus for aggressive behavior* (Ulrich *et al.*, 1965). Aggression induced by pain can be conditioned, for example, at the presentation of a tone (Vernon and Ulrich, 1966) (see Chapter 4 for a discussion of conditioning). These studies imply that pain may be exacerbated or exaggerated when patients are angry and that pain may, in turn, provoke angry feelings and aggressive behavior. A non-anxiety- and non-aggression-provoking environment, then, would seem to contribute to *prevention* of these undesirable problems of exacerbation of pain or aggressive behavior.

Expectations concerning pain play a major role in the person's experience of pain. In experimental pain situations, subjects who were told to expect severe pain had better pain tolerance than those who were not so prepared (Kanfer and Goldfoot, 1966), and when subjects had an opportunity to obtain information concerning forthcoming electric shocks and, in fact, requested such information, they tended to have decreased anxiety concerning the anticipated shock (Jones *et al.*, 1966).

Another dimension related to expectations concerning pain is the placebo effect, which we will discuss next.

PLACEBO EFFECT

Although a placebo is a substance that is considered to be pharmacologically inert, it is by no means "nothing." According to Beecher (1955), it is a powerful therapeutic tool, on the average about one half to two thirds as powerful as morphine in the usual dose (10 mg/70 kg body weight) in relieving severe pain. Although the placebo effect is most often described in pain relief, it occurs in many other situations, such as depression and anxiety. It can produce relief from any or all symptoms for which it is given (Sternbach, 1968).

A placebo, like any other pharmacological agent, can have *side effects*, and the side effects may be "toxic" in appearance at times.

The placebo effect is not always consistent. In one study, about 50% of patients receiving both morphine and placebos for postoperative pain were relieved of the pain when the dispensing of the medication was not prolonged (Lasagna *et al.*, 1954). Of the patients who had *more than one dose of placebo, only 14%* consistently obtained relief from the placebos, 55% had inconsistent responses, and 31% consistently never received relief.

It is now recognized that approximately *one third of the general population are placebo responders* in clinical situations, whether the pain is from surgery, angina pectoris, cancer, or headache (Beecher, 1959a, 1960). There are no generally accepted tests to differentiate placebo responders from nonresponders. Although placebo reactors were reported to be more anxious, dependent, self-centered, emotionally labile, and preoccupied with internal bodily processes than nonreactors by the Rorschach test (Lasagna *et al.*, 1954), there were no superficial behavioral characteristics—that is, the reactors were not "whiners," but rather had less "self-critical inhibition" of expressing dependency needs. The placebo reactors might be able to receive considerable pain relief through the comfort from nursing care as well as from the confidence in the efficacy of the medications. In fact, the study found that the reactors had a less painful postoperative course and received fewer medications than the nonreactors.

Placebo responses are not simply alterations in the mental state of affective response to pain. Placebo administration can also produce physiological responses (Sternbach, 1968).

The *mechanism* for the placebo effect is probably quite complex, including psychological and psychodynamic factors. The basic neurophysiological mechanism probably includes the *endorphin* pain inhibition system as well as other systems. In one recent study, placebo analgesia was reversed by the administration of naloxone (Levine *et al.*, 1978). Psychologically, gratification of dependency needs in the form of a medication may play a role. On the other hand, Herrnstein (1962) formulated a simple classic conditioning model of the placebo response. In rats, scopolamine depressed lever-pressing behavior, while saline alone did not. When saline was followed by scopolamine in a conditioning paradigm, saline resulted in depression of the lever-pressing behavior. Herrnstein postulated that a similar type of *conditioned placebo response* might also occur in humans, although increased in complexity.

This model suggests that relief of pain was associated in childhood with certain persons and behaviors as well as affects. Love, comfort, and caring, as well as reduction of anxiety, are related to relief from pain, as are such behaviors as "mother kissing the hurt and making it better." Taking a pill is also often associated with the relief of pain. When the patient is exposed to a situation similar to those in which relief was obtained in the past, such as taking a pill or being cared for by a motherlike person (nurse), the pain may disappear (as in conditioned response).

Sternbach (1968) hypothesizes that the production of an "approach-avoidance conflict" concerning reaction to pain might contribute to the inconsistencies in the response to placebos.

In early childhood, complaining of pain usually brings about comfort and relief. In the course of growing up, however, a child learns that complaining about pain is seen negatively by others, such as, "Don't be a crybaby." This may result in a classic approach-avoidance conflict. In clinical situations, there is both pain and the sick-role expectation of being in a passive and dependent position. This is conducive to *regression* (discussed in Chapter 5)—and evocation of the approach-avoidance conflict.

Thus, patients may experience a conflict between the wish to complain of pain, to experience pain relief and comfort, and the fear that this would be seen as immature and "like a sissy" or otherwise negatively. Some of these patients may become angry and particularly resistant to pain relief even with active drugs.

Although the placebo effect has been considered to be similar to hypnosis, it appears that there is in susceptible persons a specific hypnotic analgesic effect over and above the placebo effect (McGlashan *et al.*, 1969).

USE OF PLACEBOS IN MEDICAL PRACTICE

It should be clear from the preceding discussions that favorable nonspecific effects brought about by the patient's coming into contact with the health-care system might very well be considered to be related to the placebo effect. This general type of response is an inherent part of medical practice and may be related to what Parsons called "unconscious psychotherapy" (see Chapter 3).

Placebos in a narrower sense, such as saline injections with specific symptoms as targets, may also be administered in a medical-treatment setting, but they are more often than not misused.

The most common *misuse* of placebos is *as a diagnostic tool.* A surgeon had asked the psychiatrist to see a patient who was suspected of having pain as a hysterical conversion symptom. When the surgeon was told by the nurses that a saline injection had brought on relief of the patient's pain, he turned to the psychiatrist and exclaimed, "Q.E.D.! Now you don't even have to see her; you can just transfer her to the psychiatry ward." This was an incorrect conclusion. Even patients with severe pain caused by demonstrable tissue damage (e.g., such as that associated with metastatic cancer to bone) frequently respond to placebos. *Placebos should never be used to make a differential diagnosis between an "organic" and a "functional" pain, since it is impossible to make such differentiation with placebos* (Shapiro, 1960).

As previously mentioned, placebos may also have *side effects.* In addition to expected "pharmacological" side effects such as nausea, blushing, and tachycardia, there is an important social interpersonal side effect that can occur with the use of placebos in a medical setting. An atmosphere of *"trickery"* and deception often develops when placebos are used to treat a patient with persistent pain. When a saline injection is ordered for a patient, the nurse's attitude and feelings are often affected; that is, a feeling of "tricking" the patient, and perhaps anger at the patient for being put in such a position, may ensue. Such an attitudinal change is often sensed by the patient, who then feels deceived and badly treated (vignette 3). Patients with guarded, suspicious personality styles may

become quite angry and upset in this situation and may even leave the hospital prematurely ("against medical advice").

PSYCHOLOGICAL MEANINGS OF PAIN

We have already mentioned that pain is often associated with anxiety and anxiety-provoking situations in childhood. Such associations are, of course, unique to individual patients, and the specific meanings of a particular pain will also be unique to the patient. Punishment, threat, loss, and even reward are "meanings" that pain may acquire. Pavlov (1927, 1928) found that dogs can be conditioned to *associate pain with pleasure* (food). Dogs normally have violent negative reactions to electric shock applied to a paw. Shock regularly presented to a hungry dog before feeding changed the reaction—the animal would salivate and start to wag its tail and turn toward the food dish immediately after the shock. In these experiments, the electric-shock experience acquired the meaning of a signal of a reward to follow (food). Such learning might account for the behavior of some patients who seem to be deliberately seeking painful experiences and suffering, for example, patients who are "addicted to surgery" (vignette 3). The "secondary gain" of being sick might be a powerfully motivating "reward experience" for some patients. Sexual excitation may be associated with painful experiences, for example, genital stimulation with pain, an association that may have first been experienced during spanking.

Pain is a *regressive stimulus.* In the presence of severe pain, the sufferer's thoughts and actions tend to become like those of a child. Sternbach (1968) writes:

> It is not only that we cry with the pain; what we say, aloud and to ourselves, is childlike. We ask what we have done to deserve such pain, and think back to make a connection between some action of ours and the onset of the pain. We implore others to help us, to take away the hurt. We promise that once the pain is removed we will be different—we will be kinder to others, do good works. We beg for forgiveness, we say we are sorry. We ask God for help, we ask Him to save us.

Many memories of childhood, associated with pain, with punishment, and with relief of pain, may be reactivated in the presence of pain. Sometimes conflictual feelings about other issues may be activated by the experience of pain. For example, some patients cannot tolerate even small amounts of pain because they are afraid of becoming like a child, the regressive meaning of having pain.

Pain may have *different meanings according to personality type.* For a patient who has a long-suffering, self-sacrificing personality style, pain may be the symbol of expiation of his guilt feelings and justification for receiving care. For a patient with a dramatizing, emotional personality, pain may mean that he is no longer attractive. For a patient with an orderly, controlling personality, pain may mean a loss of control (see Chapter 18).

"PSYCHOGENIC" PAIN

The terms *functional* or *psychogenic* pain refers to pain experienced without demonstrable peripheral tissue damage; by implication, it may be thought to be "caused" by psychological or psychodynamic factors. Still, pain, no matter what its cause, acquires psychological meaning and may be accompanied by signs of psychological distress. Furthermore, pain may signal early tissue damage or dysfunction that is not yet demonstrable. For these reasons, extreme caution must be exercised in the use of these terms. Nevertheless, there are some persons who suffer long-standing and severe chronic pain without demonstrable tissue damage, in whom the existence of pain can be explained on the basis of psychological factors (like the hallucinations experienced in dreams) and whose improvement depends largely on successful psychological management. Additionally, there are certain people who experience pain with unusual intensity and frequency, in whom the presence or absence of associated tissue damage is only weakly correlated with the quality and intensity of pain and in whom even removal of the lesion may fail to bring relief from pain. Engel (1959) called such patients "pain prone" and identified a marker of personality characteristically encountered in them. He proposed that the physician consider the following questions in evaluating patients with severe pain problems: (1) Are there pathological processes affecting nerve endings and leading to disordered patterns in nerve pathways that would be expected to produce pain? (2) If such processes are present, can the character of the pain experience reported by the patient be fully, partially, or not at all accounted for by the distinctive characteristics of the peripheral pathological process? (3) How are psychological processes operating to determine the ultimate character of the pain experience for the patient and the manner in which it is communicated to the physician? A number of factors and findings may suggest that

the pain is psychogenic or psychogenically exacerbated. They include the following:

1. Psychogenic pain tends to be described in a dramatic and metaphorical fashion (such as "a man sitting on my chest").
2. The location of the pain tends to correspond to the patient's subjective body image rather than to anatomical distribution of peripheral nerves and central nervous system pain pathways.
3. Such pain tends to occur at emotionally charged times (e.g., in anticipation of a loss or at the anniversary of such an event).
4. There is a "complaining" quality to the patient's description of the pain, which is usually exacerbated during an interview when an emotionally charged subject is discussed.
5. Psychogenic pain almost never wakes a patient from sleep.

The past histories of pain-prone patients often include similar episodes of obscure pain in the past in which the pain was used as a means of getting attention and love or as a means of atonement for feelings of guilt. The personality style, obviously, is likely to be the long-suffering, self-sacrificing type (see Chapter 18). It is not unusual to find that these patients had been close to someone who suffered from chronic or severe pain and that the patient's pain might even have started shortly after the loss of such a person. In such an instance, identification with the lost person would be an important psychological defense mechanism involved in the development of the symptom (see Chapter 6).

In some cases of psychogenic pain, *secondary gain* might play an important role. This term refers to gratification or advantages that accrue to the person by virtue of the illness but did not contribute to its causation. Secondary gains may then reinforce the symptom and make it hard to give up. They include attention- and love-getting, the opportunity to be "unusually" angry and aggressive, and financial gain such as disability compensation payments. In cases in which pain occurs as a "depressive equivalent" or in pain associated with the depressive syndrome (see Chapter 6), signs of depression, such as suicidal ideas and guilt feelings, may be found as well as such physiological signs of depression as sleep disturbance, weight loss, anorexia, constipation, and loss of *sexual interest.*

Blumer and Heilbronn (1982) proposed that the chronic pain syndrome without identifiable tissue pathology should be considered to be a variant of depressive disorder. On the basis of extensive studies of "psychogenic" pain patients, they identified the following characteristics:

Demographic data. Female/male ratio approximately 2:1; highest age of onset between 45 and 50; mostly lower-middle-class blue collar workers.

Clinical features. Chronic pain that is continuous, hypochondriacal preoccupation, strong desire for a surgical solution, strong guilt feelings, strong denial of difficulties in interpersonal relationships, idealization of spouse (despite frequent history of physical abuse by spouse), insomnia, usually normal appetite, anergia, anhedonia, little emotional expression.

Premorbid characteristics. Hard-working, "workaholic," "solid citizen," frequent history of abuse by spouse.

Family history. High incidence of affective disorders in first-degree relatives, high incidence of disability or deformity in a next of kin.

Psychodynamic considerations. The pain syndrome patients are considered to have strong needs to be accepted and to be dependent. These infantile dependency needs are denied, and, instead, the future patient compensates for inner insecurity through hard work and relentless activity. A shift occurs following a significant loss or disappointment, with or without painful injury or illness. The solid citizen is transformed into an invalid who can justifiably be dependent and taken care of. This, however, creates a painful dilemma, since the dependency needs continue to be denied, and value is placed on being well and working. Thus, the pain is seen consciously to be the "only problem" and the desire is for it to be eliminated by surgery or other magical means.

We should caution again that while the presence of these indicators should alert the physician that there may be psychogenic components to the patient's pain experience, these findings in and of themselves *by no means* indicate *absence* of organic pathology. Coexistence of psychogenic and tissue factors in pain is not at all unusual. *One of the most common ways in which psychogenic pain is expressed, in fact, is as an elaboration of pain arising in damaged tissue.*

MANAGEMENT OF PAIN

The management of pain obviously requires a comprehensive approach. Relief from pain is important not only as direct relief from suffering itself, but also because of the untoward effects of physiological concomitants of pain that might be harmful to the patient (such as the increase in cardiac work in myocardial infarction) and the fact that anxiety associated with pain may in time aggravate its intensity as well as the intensity of psychophysiological reactions to it.

For most acute pain, effective *pharmacological agents* are available. They include the nonsteroidal anti-inflammatory agents (NSAIDs) such as acetaminophen and narcotic analgesics. In severe pain, narcotic analgesics should be used in effective doses.

There is some evidence, however, that narcotics are *underutilized* in treating acute pain situations for fear of addiction (Kilwein, 1989; Marks and Sachar, 1973; Schechter, 1989). Even terminally ill patients with severe pain are often undertreated with narcotic analgesics. It should be pointed out that the actual *risk of causing narcotic addiction in a hospitalized patient with pain is quite negligible* (less than 1% [Marks and Sachar, 1973]). Underusage of narcotic analgesics may reinforce the patient's preoccupation with the medication and his drug-seeking behavior, such as calling for the medication before the scheduled time to prevent the development of more severe pain.

Sometimes there may even be an interesting paradoxical pattern in the use of powerful analgesics. The more pain the patient feels, the more he complains, the less likely he is to receive potent pain medications (Pilowsky, 1969). It is no wonder, then, that aggravated aggressive behavior is often found in such patients, especially in view of the fact that pain itself may generate aggressive feelings.

For chronic pain, serotonergic tricyclic antidepressants such as amitriptyline may be effective whether the patient is depressed or not.

Relief of anxiety is also important in managing pain. This calls not only for a reassuring attitude on the physician's part but also for *informing patients about treatment plans,* especially about procedures that themselves might be painful. Preparing the patient for the pain will help. As pointed out earlier, experimental subjects anticipating severe pain showed a higher tolerance for it and reduced perception of pain when motivated to endure it (Sternbach, 1968).

As mentioned earlier, pain is a powerful regressive stimulus. An unambivalent, caring attitude on the part of the health-care personnel, particularly nurses, can prevent or neutralize anxious and defensive reactions in patients who are embarrassed by regressive needs and behavior.

A comprehensive approach is also particularly necessary in managing patients with *psychogenic or psychologically aggravated pain.* In addition to symptomatic and etiological treatment of underlying disease processes in tissue, the psychological meaning of the pain should be evaluated and a plan for psychological treatment made. This may involve using *antidepressants* (see Chapters 6 and 21), as well as providing interpersonal contact, social support, and psychotherapy when indicated.

Another important reason for recognizing and treating psychogenic pain factors is to prevent unnecessary surgical and other drastic treatments.

SUMMARY

Pain is one of the most common experiences leading to help-seeking behavior. Pain, like anxiety, subserves a protective function. *Anxiety* often accentuates, and occasionally is perceived as, pain, and pain is, as a rule, accompanied by anxiety.

The quality of pain is important in the diagnosis of the underlying disease. Tissue damage or very strong stimuli result in stimulation of the pain receptors (free nerve endings). The pricking type of pain and burning and aching pain are conducted by separate types of nerve fibers, small type A delta fibers and even smaller type C fibers, respectively. *Pricking pain is* ultimately projected to the brain in the thalamus and the somatosensory cortex, while the aching and burning pain pathways are projected diffusely in the *reticular activating system* of the brain and thus influence not only the state of arousal, but also emotional and neuroendocrine responses. The nerve impulses that conduct pain are modified at the spinal-cord level by various influences, including those coming from the brain. Information concerning the nature and location of pain may be transmitted to the brain before the perception of pain, allowing the brain to modify the perception itself (at both brain and spinal-cord levels). Opiate and nonopiate intrinsic pain-control mechanisms are present. The distribution of opiate receptors in the limbic system, thalamus, and spinal cord implies that control of pain perception is closely related to emotional states and memory functions subserved by the limbic system. These mechanisms may provide a basis for known modifying influences on pain perception, such as the psychological state of the individual, his past experiences, and his cultural background.

Although the pain sensation threshold is very similar in most people, tolerance for and reaction to pain may be strongly influenced by psychological and social factors.

The *placebo effect* is found in approximately one third of the general population. The placebo response is a complex phenomenon that includes suggestion, anticipation, and conditioned responses. Endorphins are probably involved in the placebo response. Placebos are powerful and can *never* differentiate pain arising from tissue damage from "psychogenic"

pain. Many nonspecific beneficial effects of the health-care system can be attributed to the placebo effect.

Psychogenic pain, pain in the absence of observable tissue damage, is a complex phenomenon. It might be due to increased sensitivity to otherwise mild or negligible pain as a concomitant or variant of depression or a conversion mechanism (e.g., symbolization of a psychological meaning). Since all pain sensation can be associated with a psychological meaning, the discovery of a psychological meaning or the presence of a "secondary gain" should not exclude the possibility that there might be an underlying "organic" disease in a patient complaining of pain. Pain-seeking behavior may be a conditioned response or may also be a motivated behavior with complex psychological meaning.

The *management* of pain requires a comprehensive approach in the biological, psychological, and social dimensions. In addition to the treatment of tissue damage, the cultural and psychological dimensions of the pain should be understood and treated appropriately.

IMPLICATIONS

For the Patient

Pain is a *subjective* experience that cannot be shared objectively. When a patient presents with pain, he is suffering not only from the sensation but also from anxiety that accompanies the pain. His reaction to pain is influenced by a diversity of factors, such as cultural expectations, ethnic background, and personality. Thus, the probability that a certain level of pain will reach the limit of tolerance or anxiety for a given patient to result in help-seeking behavior is determined not only by the actual intensity of the stimulus but also by the social and psychological factors.

For the Physician

The existence or the absence of pain can never be proven in a given patient by a physician. Current understanding of the neurophysiology of pain clearly indicates that the *brain* has an important role in the perception of pain and that sensation of pain can occur without peripheral tissue damage. Whenever possible, *alleviation* of suffering from pain, regardless of the underlying pathology, can facilitate the formation of a cooperative doctor–patient relationship.

Attention to the *description* of pain is important in diagnosing the underlying condition.

An understanding of the cultural background and *social expectations,* as well as the patient's personality, obtained through *questions* and the patient's *demographic data,* helps the physician understand the differing reactions to pain in different patients and also can help him to anticipate and to take appropriate measures to forestall adverse reactions to pain that some patients might manifest. Adverse reactions may be nonreporting of pain in certain stoic individuals, as well as overreaction to it in others.

Because information about pain increases the tolerance for it, physicians should inform patients about potentially painful procedures and prepare them.

Because relief of pain by *placebos* occurs regularly in patients with severe tissue damage, placebos should *never* be used to differentiate organic from functional pain. The deceptive use of placebos in the hospital often undermines the patient's trust in the health-care personnel.

In treating a patient for pain relief, *adequate analgesics* should be given. Since narcotics probably interact with endogenous endorphin systems, some patients may require more narcotics for the relief of pain from the same stimulus if the endorphin system is inadequate or depleted. Narcotic addiction in the course of treatment with narcotic analgesics for pain is rare indeed, the incidence being less than 1%.

Pain may be experienced in the absence of tissue damage. This perception may be determined by *guilt feelings* (expiation), as a *body language* expression of the need for emotional caring, as a result of *depression* with bodily preoccupation, or as a conditioned response to *anxiety.* Pain-prone patients often come from a milieu in which pain was used as a means of getting attention and love as well as of atoning for guilt feelings. Pain perceived in the absence of peripheral-tissue damage is usually attributed to a part of the body according to the patient's body image and the meaning of the body part, rather than according to the distribution of nerve pathways. Psychogenic pain, however, is often presented as an *added-on* symptomatology to an organic condition, and the presence of secondary gain, or psychological meaning attributable to pain, should not rule out the possibility that there might be an organic disease yet undetected.

For the Community and the Health-Care System

Differences in reaction to pain seen in different ethnic and cultural groups often result in a breakdown of communication between patients

and health-care personnel. An understanding by health-care personnel of the cultural expectations of patients can help overcome this. Since anxiety often increases pain perception, the hospital *environment* should be such that patients are exposed to a minimum of anxiety-provoking situations.

The medical community should be aware that the use of narcotics in the treatment of pain is effective and when properly managed is not likely to result in addiction. Medical schools and hospitals should emphasize *adequate relief* of pain through the use of narcotic analgesics, rather than overemphasize the possibility of iatrogenic addiction.

Cultural change and assimilation may result in changes in pain experiences, and ethnic differences in reaction to pain may disappear as cultural stereotypes change.

REFERENCES

Akil H, Liebeskind JC: Monoaminergic mechanism of stimulation-produced analgesia. *Brain Res* 94:279–296, 1975.

Beall JE, Martin RF, Applebaum AE, *et al.*: Inhibition of primate spino-thalamic tract neurons by stimulation in the region of the nucleus raphe magnus. *Brain Res* 114:328–333, 1976.

Beecher HK: The powerful placebo. *J Am Med Assoc* 159:1602–1606, 1955.

Beecher HK: Generalization from pain of various types and diverse origins. *Science* 130:267–268, 1959a.

Beecher HK: *Measurement of Subjective Responses.* New York, Oxford Press, 1959b.

Beecher HK: Increased stress and effectiveness of placebos and "active" drugs. *Science* 132:91–92, 1960.

Bloom F, Segal D, Ling N, *et al.*: Endorphins: Profound behavioral effects in rats suggest new etiological factors in mental illness. *Science* 194:630–632, 1976.

Blumer D, Heilbronn M: Chronic pain as a variant of depressive disease. *J Nerv Ment Dis* 170:381–406, 1982.

Bond MR: The relation of pain to the Eysenck Personality Inventory, Cornell Medical Index, and Whitely Index of Hypochondria. *Br J Psychiatry* 119:671, 1971.

Coulter JC, Maunz RA, Willis WD: Effects of stimulation of sensory motor cortex on primate spinothalamic neurons. *Brain Res* 65:351–356, 1974.

Engel GL: "Psychogenic" pain and the pain-prone patient. *Am J Med* 26:899–918, 1959.

Eysenck SBG: Personality and pain assessment in childbirth of married and unmarried mothers. *J Ment Sci* 107:417–430, 1961.

Goldstein A: Opioid peptides (endorphins) in pituitary and brain. *Science* 193:1081–1086, 1976.

Guyton AC: *Textbook of Medical Physiology.* Philadelphia, WB Saunders, 1976.

Handwerker HO, Iggo Z, Zimmerman M: Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. *Pain* 1:147–165, 1975.

Herrnstein RJ: Placebo effect in the rat. *Science* 138:677–678, 1962.

Illis IL: Central pain. *Br Med J* 300:1284–1286, 1990.

Jamner LD, Schwartz GE: Self-deception predicts self-report and endurance of pain. *Psychosom Med* 48:211–223, 1986.

Jones A, Bentler PH, Petry G: The reduction of uncertainty concerning future pain. *J Abnorm Psychol* 71:87–94, 1966.

Kanfer FH, Goldfoot DA: Self-control and tolerance of noxious stimulation. *Psychol Rep* 18:79–85, 1966.

Kerr FWL, Wilson PR: Pain. *Annu Rev Neurosci* 1:83–102, 1978.

Kilwein JH: Undertreating pain—caution or cruelty? *J Clin Pharm Ther* 14:419–422, 1989.

Kosambi DD: Living prehistory in India. *Sci Am* 216:105–114, 1967.

Kroeber AL: *Anthropology.* New York, Harcourt-Brace, 1923.

Lasagna L, Mosteller F, von Felsinger JM, *et al.*: A study of the placebo response. *Am J Med* 16:770–779, 1954.

Levine JD, Gordon NC, Fields HL: The mechanism of placebo analgesia. *Lancet* 2:654–657, 1978.

Lynn R, Eysenck HJ: Tolerance for pain, extraversion, and neuroticism. *Percept Mot Skills* 12:161–162, 1961.

Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med* 78:173–181, 1973.

Marx JL: Analgesia: How the body inhibits pain perception. *Science* 195:471–473, 1977.

McGlashan TH, Evans FJ, Orne MT: The nature of hypnotic analgesia and placebo response to experimental pain. *Psychosom Med* 31:227–246, 1969.

McMahon SB, Koltzenburg M: Novel classes of nocioceptors: Beyond Sherrington. *Trends Neurosci* 13:199–201, 1990.

Melzack R: *The Puzzle of Pain.* New York, Basic Books, 1973.

Melzack R: Phantom limbs and the concept of neuromatrix. *Trends Neurosci* 13:88–92, 1990.

Melzack R, Torgerson WS: On the language of pain. *Anesthesiology* 34:50–59, 1971.

Melzack R, Wall PD: Pain mechanisms: A new theory. *Science* 150:971–979, 1965.

Merskey H: The characteristics of persistent pain in psychological illness. *J Psychosom Res* 9:291–298, 1965a.

Merskey H: Psychiatric patients with persistent pain. *J Psychosom Res* 9:299–309, 1965b.

Merskey H, Spear FG: The reliability of the pressure algometer. *Br J Clin Psychol* 3:130–136, 1964.

Oliveras JL, Besson JM, Builbaud G, *et al.*: Behavioral and electrophysiological evidence of pain inhibition from midbrain stimulation in the cat. *Exp Brain Res* 20:32–44, 1974.

Pavlov IP: *Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex* (Anrep GV, trans-ed). London, Oxford University Press, 1927.

Pavlov IP: *Lectures on Conditioned Reflexes* (Gantt WH, trans). New York, International Publishers, 1928.

Pearson DH: Pain pathways: An overview. *Hosp Pract* (special report), Jan 14–18, 1976.

Perl ER: Sensitization of nocioreceptors and its relation to sensation, in Bonica JJ, Albe-Fessard DG (eds): *Advances in Pain Research and Therapy.* New York, Raven Press, 1976, vol 1.

Pilowsky I: Pain and its management in malignant disease. *Psychosom Med* 31:400–404, 1969.

Robinson H, Kirk RF, Frye RF, *et al.*: A psychological study of patients with rheumatoid arthritis and other painful diseases. *J Psychosom Res* 16:53–56, 1972.

Schechter NL: The undertreatment of pain in children: An overview. *Pediatr Clin N Am* 36:781–794, 1989.

Shapiro AK: Attitudes toward the use of placebos in treatment. *J Nerv Ment Dis* **130**:200–211, 1960.

Snyder SH: Opiate receptors and internal opiates. *Sci Am* **236**:44–57, 1977.

Sternbach RA: *Pain: A Psychophysiological Analysis.* New York, Academic Press, 1968.

Sternbach RA, Tursky B: Ethnic differences among housewives in psychophysical and skin potential responses to electric shock. *Psychophysiology* **1**:241–246, 1964.

Timmermans G, Sternbach RA: Factors of human chronic pain: An analysis of personality and pain reaction variables. *Science* **184**:806–808, 1974.

Ulrich RE, Hutchinson RR, Azrin NH: Pain-elicited aggression. *Psychol Rec* **15**:111–126, 1965.

Vernon J, Ulrich RE: Classical conditioning of pain-elicited aggression. *Science* **152**:668–669, 1966.

VonKnorring L: The experience of pain in depressed patients. *Neuropsychobiology* **1**:155–165, 1975.

Wall PD: Modulation of pain by non-painful events, in Bonica JJ, Albe-Fessard D (eds): *Advances in Pain Research and Therapy.* New York, Raven Press, 1976, vol 1.

Ward NG, Bloom VL, Friedel RO: The effectiveness of tricyclic antidepressants in the treatment of coexisting pain and depression. *Pain* 7:331–341, 1979.

Watkins LR, Mayer DJ: Organization of endogenous opiate and nonopiate pain control systems. *Science* **216**:1185–1192, 1982.

Winsberg B, Greenlick M: Pain response in Negro and white obstetrical patients. *J Health Soc Behav* 8:222–227, 1967.

Woodforde JM, Merskey H: Personality traits of patients with chronic pain. *J Psychosom Res* **16**:167–172, 1972.

Woodrow KM, Friedman CD, Siegelaub AB, *et al.*: Pain tolerance: Differences according to age, sex, and race. *Psychosom Med* 34:548–556, 1972.

RECOMMENDED READING

Bass C (ed): Somatization—The somatic presentation of psychiatric illness. *J Psychosom Res* **33**(6), 1989. This special issue of the journal has a good discussion of somatization disorders including epidemiology and treatment approaches.

Bonica JJ, Albe-Fessard DB (eds): *Advances in Pain Research and Therapy.* New York, Raven Press, 1976, vol 1. A very comprehensive multiauthor volume on various aspects of pain, from neurophysiology to psychological factors and surgical management. An excellent up-to-date reference.

Engel GL: "Psychogenic" pain and the pain-prone patient. *Am J Med* **26**:899–918, 1959. A classic paper describing the possible nature of "psychogenic" pain and backgrounds of "pain-prone" patients.

Marks RM, Sachar EJ: Undertreatment of medical inpatients with narcotic analgesics. *Ann Intern Med* 78:173–181, 1973. This is a must for medical students and physicians to understand the degree of undertreatment of pain rampant in our hospitals. The conclusion is based on interviews with patients being treated for pain and on questionnaires completed by house staff physicians in two major hospitals in New York.

Ness TJ, Gebhart GF: Visceral pain: A review of experimental studies. *Pain* **41**:167–234, 1990. A comprehensive review of the experimental literature concerning visceral pain. The review includes sections on anatomy, electrophysiological studies of primary afferents, and various stimuli including electrical, mechanical, ischemia, and chemical, and concludes with models and theories concerning visceral pain.

Shafii M, Shafii SL: *Biological Rhythms, Mood Disorders, Light Therapy, and the Pineal Gland.* Washington, DC, American Psychiatric Press, 1990. An up-to-date review of the role of pineal gland and the melatonin system in biological rhythm disorders. This volume contains excellent discussions on seasonal affective disorder as well as light therapy.

Snyder SH: Opiate receptors and internal opiates. *Sci Am* **236**:44–57, 1977. This is a comprehensive and lucid discussion of the endorphins (enkephalins) and their actions by one of the discoverers of the opiate receptors in the human brain. Recommended especially for those who would like to read more about the structures and mechanisms of action of the endorphins and the distribution of opiate receptors.

Sternbach RA: *Pain: A Psychophysiological Analysis.* New York, Academic Press, 1968. This is a comprehensive and concise monograph presenting clinical and experimental studies concerning pain. A beautifully written, well-integrated book that also deals with the psychology of pain.

Watkins LR, Mayer DJ: Organization of endogenous opiate and nonopiate pain control systems. *Science* **216**:1185–1192, 1982. This is a comprehensive and interesting review of experimental data concerning the intrinsic pain-control systems and their clinical implications.