CHAPTER
39

Pain

Sensory mechanisms provide individuals with a continuous stream of information about their bodies, the outside world, and the interactions between the two. The somatosensory component of the nervous system provides an awareness of body sensations such as touch, temperature, limb position, and pain.

ORGANIZATION AND CONTROL OF SOMATOSENSORY FUNCTION

The somatosensory system is designed to provide the central nervous system (CNS) with information about the body. Sensory neurons can be divided into three types that vary in distribution and the type of sensation detected: general somatic, special somatic, and general visceral afferent neurons (see Chapter 36). *General somatic afferent neurons* have branches with widespread distribution throughout the body and with many distinct types of receptors that result in sensations such as pain, touch, and temperature. *Special somatic afferent neurons* have receptors located primarily in muscles, tendons, and joints. These receptors sense position and movement of the body. *General visceral afferent neurons* have receptors on various visceral structures and sense fullness and discomfort.

Sensory Systems

Sensory systems can be conceptualized as a serial succession of neurons consisting of first-order, second-order, and third-order neurons. The *first-order neurons* contain the sensory receptors and transmit sensory information from the periphery to the

CNS. The *second-order neurons* communicate with various reflex networks and sensory pathways in the spinal cord and contain the ascending pathways that travel to the thalamus. *Third-order neurons* relay information from the thalamus to the cerebral cortex (Fig. 39-1). Many interneurons process and modify the sensory information at the level of the second- and third-order neurons, and many more participate before coordinated and appropriate learned-movement responses occur.

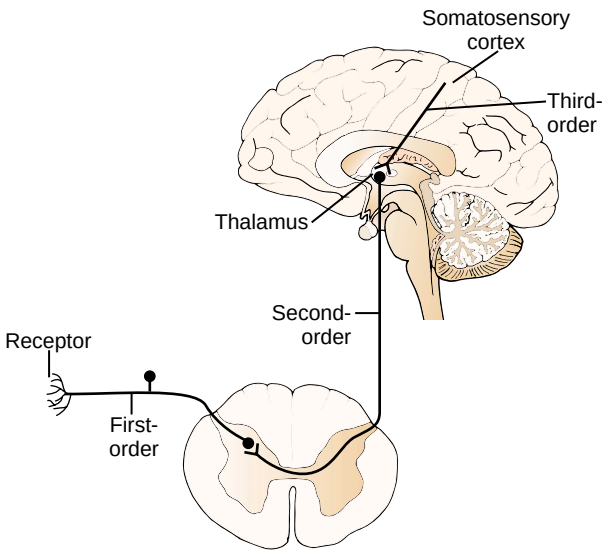
The Sensory Unit

The somatosensory experience arises from information provided by a variety of receptors distributed throughout the body. There are four major modalities of sensory experience: (1) discriminative touch, which is required to identify the size and shape of objects and their movement across the skin; (2) temperature sensation; (3) sense of movement of the limbs and joints of the body; and (4) nociception or pain sense.

Each of the somatosensory modalities is mediated by a distinct system of receptors and pathways to the brain. However, all somatosensory information from the limbs and trunk shares a common class of sensory neurons called *dorsal root ganglion neurons*. Somatosensory information from the face and cranial structures is transmitted by the trigeminal sensory neurons, which function in the same manner as the dorsal root ganglion neurons. The cell body of the dorsal root ganglion neuron, its receptor (which innervates a small area of periphery), and its central axon (which projects to the CNS) form a *sensory unit*. Individual dorsal root ganglion neurons respond selectively to specific types of stimuli because of their specialized peripheral terminals, or receptors.

Dermatomal Pattern of Dorsal Root Innervation

The somatosensory innervation of the body, including the head, retains a basic segmental organizational pattern that was established during embryonic development. The region of the body wall that is supplied by a single pair of dorsal root ganglia is called a *dermatome*. These dorsal root ganglion-innervated strips occur in a regular sequence moving upward from the second coccygeal segment through the cervical segments, reflecting the basic segmental organization of the body and the nervous system (Fig. 39-2). The cranial nerves that innervate the head send their axons to equivalent nuclei in the brain stem. Neighboring dermatomes overlap one another sufficiently so that a loss of one dorsal root or root ganglion results in reduced but not total loss of sensory innervation of a dermatome (Fig. 39-3). Dermatome maps are helpful in interpreting the level and extent of sensory deficits that are the result of segmental nerve and spinal cord damage.



■ **FIGURE 39-1** ■ Arrangement of first-order, second-order, and third-order neurons of the somatosensory system.

KEY CONCEPTS

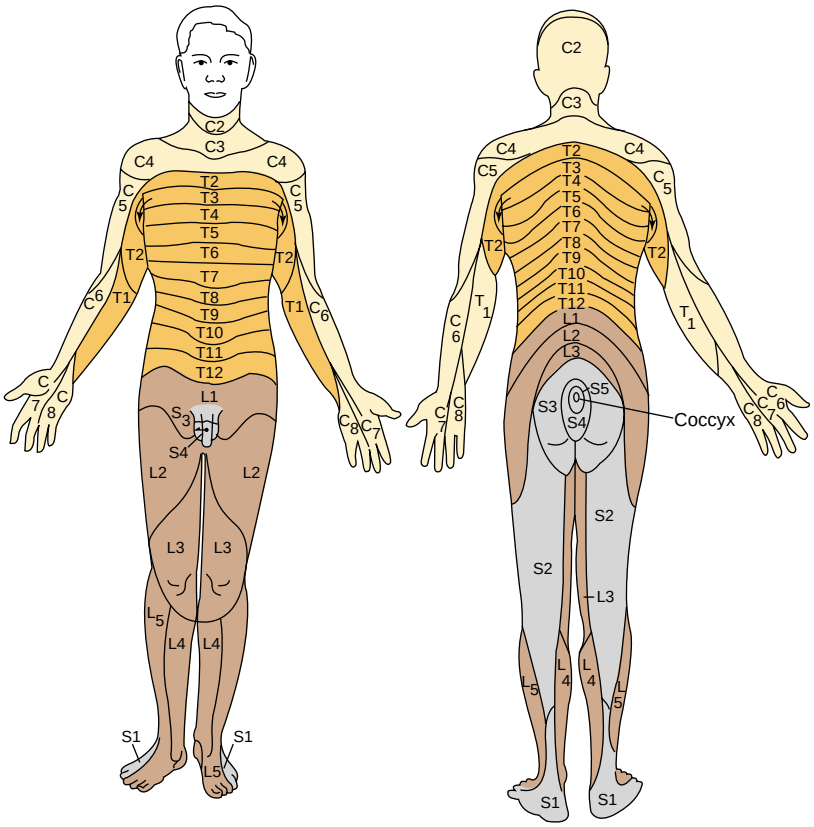
THE SOMATOSENSORY SYSTEM

- The somatosensory system relays information to the CNS about four major body sensations: touch, temperature, pain, and body position. Stimulation of receptors on regions of the body wall is required to initiate the sensory response.
- The system is organized into dermatomes, with each segment supplied by a single dorsal root ganglion that sequentially relays the sensory information to the spinal cord, the thalamus, and the sensory cortex.
- Two pathways carry sensory information through the CNS. The discriminative pathway crosses in the medulla and relays touch and body position. The anterolateral pathway crosses in the spinal cord and relays temperature and pain sensation from the opposite side of the body.

Spinal Circuitry and Ascending Neural Pathways

On entry into the spinal cord, the central axons of the somatosensory neurons branch extensively and project to nuclei in the spinal gray matter. Some branches become involved in local spinal cord reflexes and directly initiate motor reflexes (*e.g.*, flexor-withdrawal reflex). Two parallel pathways, the rapid conducting *discriminative pathway* and the slower conducting *anterolateral pathway,* transmit information from the spinal cord to the thalamic level of sensation, each taking a different route through the CNS.

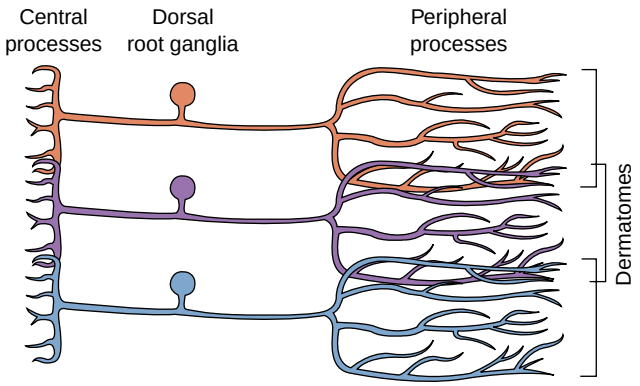
The Discriminative Pathway. The discriminative pathway, which crosses at the base of the medulla, is used for the rapid transmission of sensory information such as discriminative touch (Fig. 39-4). It contains branches of primary afferent axons that travel up the ipsilateral (*i.e.*, same side) dorsal columns of the spinal cord white matter and synapse with highly evolved somatosensory input association neurons in the medulla. The discriminative pathway uses only three neurons to transmit information from a sensory receptor to the somatosensory strip of parietal cerebral cortex of the opposite side of the brain: (1) the primary dorsal root ganglion neuron, which projects its central axon to the dorsal column nuclei; (2) the dorsal column neuron, which sends its axon through a rapid



■ **FIGURE 39-2** ■ Cutaneous distribution of spinal nerves (dermatomes). (Barr, M. [1993]. *The human nervous system.* New York: Harper & Row)

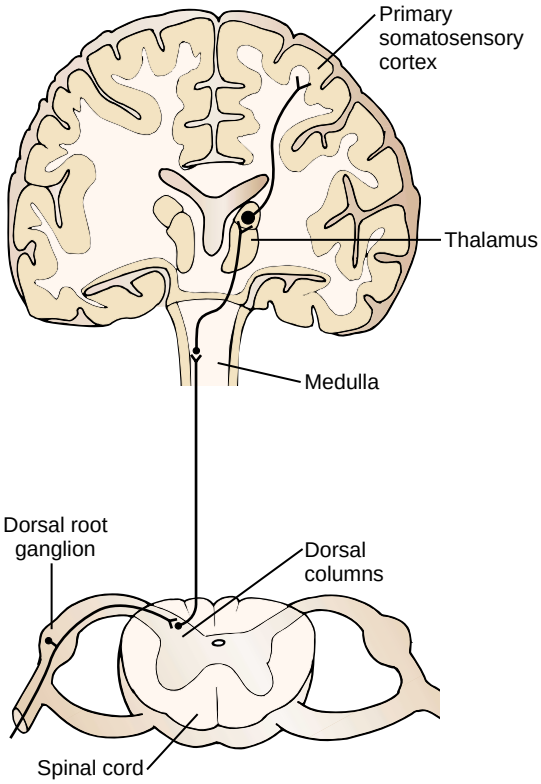
conducting tract, called the *medial lemniscus*, that crosses at the base of the medulla and travels to the thalamus on the opposite side of the brain, where basic sensation begins; and (3) the thalamic neuron, which projects its axons through the somatosensory radiation to the primary sensory cortex. The medial lemniscus is joined by fibers from the sensory nucleus of the trigeminal nerve (cranial nerve V) that supplies the face. Sensory information arriving at the sensory cortex by this route can be discretely localized and discriminated in terms of intensity.

One of the distinct features of the discriminative pathway is that it relays precise information regarding spatial orientation. This is the only pathway taken by the sensations of muscle and joint movement, vibration, and delicate discriminative touch, as is required to differentiate correctly the location of touch on the skin at two neighboring points (*i.e.*, two-point discrimination). One of the important functions of the discriminative pathway is to integrate the input from multiple receptors. The sense of shape and size of an object in the absence of visualization, called *stereognosis*, is based on precise afferent information from muscle, tendon, and joint receptors. For example, a screwdriver is perceived as being different from a knife in terms of its texture (tactile sensibility) and shape based on the relative position of the fingers as they move over the object. This complex interpretive perception requires that the discriminative system must be functioning optimally and that higher-order parietal association cortex processing and prior learning must have occurred. If the discriminative somatosensory pathway is functional but the parietal association cortex has become discretely damaged, the person can correctly describe the object but does not recognize that it is a screwdriver. This deficit is called *astereognosis*.

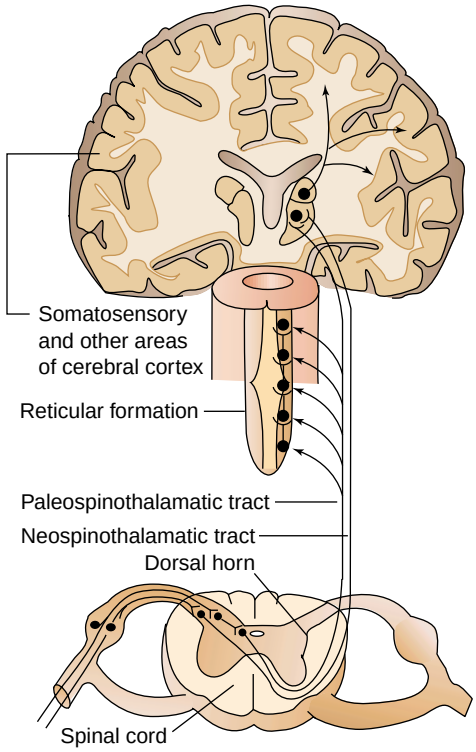


■ **FIGURE 39-3** ■ The dermatomes formed by the peripheral processes of adjacent spinal nerves overlap on the body surface. The central processes of these fibers also overlap in their spinal distribution.

The Anterolateral Pathway. The anterolateral pathways (anterior and lateral spinothalamic pathways), which crosses within the first few segments of entering the spinal cord, consists of bilateral multisynaptic slow-conducting tracts (Fig. 39-5). These pathways provide for transmission of sensory information such as pain, thermal sensations, crude touch, and pressure that does not require discrete localization of signal source or fine discrimination of intensity. The fibers of the anterolateral pathway originate in the dorsal horns at the level of the segmental nerve, where the dorsal root neurons enter the spinal cord. They cross in the anterior commissure of the cord, within a few segments of origin, to the opposite anterolateral pathway, where they ascend upward toward the brain. The spinothalamic tract



■ **FIGURE 39-4** ■ Discriminative pathway. This pathway is an ascending system for rapid transmission of sensations that relate joint movement (kinesthesis), body position (proprioception), vibration, and delicate touch. Primary afferents travel up the dorsal columns of the spinal cord white matter and synapse with somatosensory input association neurons in the medulla. Secondary neurons project through the brain stem to the thalamus and synapse with tertiary neurons, which relay the information to the primary somatosensory cortex on the opposite side of the brain.



■ **FIGURE 39-5** ■ Neospinothalamic and paleospinothalamic subdivisions of the anterolateral sensory pathway. The neospinothalamic tract runs to the thalamic nuclei and has fibers that project to the somatosensory cortex. The paleospinothalamic tract sends collaterals to the reticular formation and other structures, from which further fibers project to the thalamus. These fibers influence the hypothalamus and the limbic system as well as the cerebral cortex.

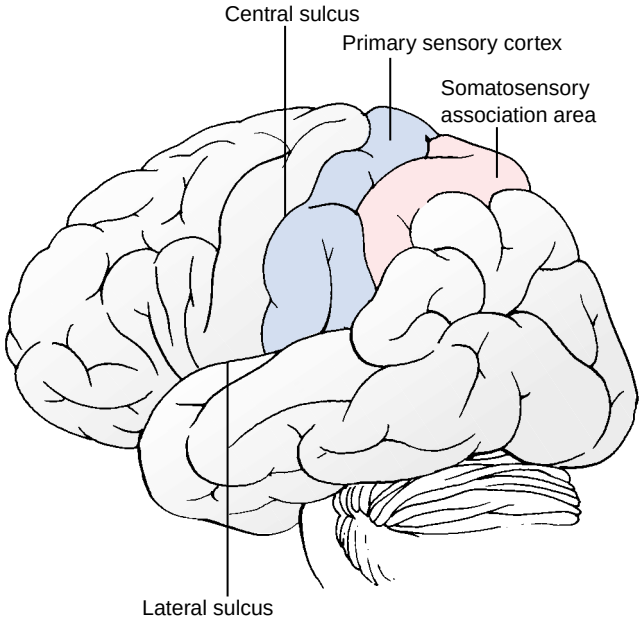
fibers synapse with several nuclei in the thalamus, but en route they give off numerous branches that travel to the reticular activating system of the brain stem. These projections provide the basis for increased wakefulness or awareness after strong somatosensory stimulation and for the generalized startle reaction that occurs with sudden and intense stimuli. They also stimulate autonomic nervous system responses, such as an increase in blood pressure and heart rate, dilation of the pupils, and the pale, moist skin that results from constriction of the cutaneous blood vessels and activation of the sweat glands.

There are two subdivisions in the anterolateral pathway: the outer *neospinothalamic tract* and the inner *paleospinothalamic tract* (Fig. 39-5). The neospinothalamic tract, which carries bright pain, consists of a sequence of at least three neurons with long axons. It provides for relatively rapid transmission of sensory information to the thalamus. The paleospinothalamic tract, which is phylogenetically older than the neospinothalamic system, consists of bilateral, multisynaptic slow-conducting tracts that transmit sensory signals that do not require discrete localization of signal source or discrimination of fine gradations in intensity. This slower-conducting pathway also projects into the intralaminar nuclei of the thalamus, which have close connections with the limbic cortical systems. This circuitry provides touch with its affective or emotional aspects.

Central Processing of Somatosensory Information

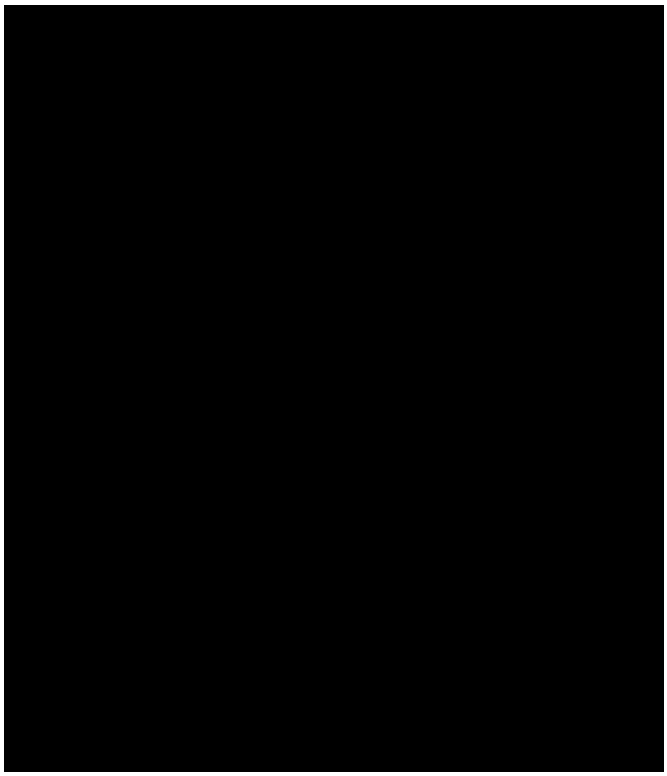
Perception, or the final processing of somatosensory information, involves awareness of the stimuli, localization and discrimination of their characteristics, and interpretation of their meaning. As sensory information reaches the thalamus, it begins to enter the level of consciousness. In the thalamus, the sensory information is roughly localized and perceived as a crude sense. The full localization, discrimination of the intensity, and interpretation of the meaning of the stimuli require processing by the somatosensory cortex.

The somatosensory cortex is located in the parietal lobe, which lies behind the central sulcus and above the lateral sulcus (Fig. 39-6). The strip of parietal cortex that borders the central sulcus is called the *primary somatosensory cortex* because it receives primary sensory information by way of direct projections from the thalamus. A distorted map of the body and head surface, called the *sensory homunculus*, reflects the density of cortical neurons devoted to sensory input from afferents in corresponding peripheral areas. As depicted in Figure 39-7, most of the cortical surface is devoted to areas of the body such as the thumb, forefinger, lips, and tongue, where fine touch and pressure discrimination are essential for normal function.



■ **FIGURE 39-6** ■ Primary somatosensory and association somatosensory cortex.

The somatosensory association cortex, which lies parallel to and just behind the primary somatosensory cortex, is required to transform the raw material of sensation into a meaningful experience. It is here that the stimulus pattern from the present sensory experience is integrated with past learning. For instance, a person's past learning plus present tactile sensation provide the perception of sitting on a soft chair, rather than on a hard bicycle seat.



Sensory Modalities

Somatosensory experience can be divided into *modalities*, a term used for qualitative, subjective distinctions between sensations such as touch, heat, and pain. Such experiences require the function of sensory receptors and forebrain structures in the thalamus and cerebral cortex. Sensory experience also involves quantitative sensory discrimination or the ability to distinguish between different levels of sensory stimulation.

The receptive endings of different afferent neurons are particularly sensitive to specific forms of physical and chemical energy. For instance, a receptive ending may be particularly sensitive to a small increase in local skin temperature. Other afferent sensory terminals are most sensitive to slight indentations of the skin, and their signals are subjectively interpreted as touch. Cool versus warm, sharp versus dull pain, and delicate touch versus deep pressure are all based on different populations of afferent neurons or on central integration of simultaneous input from several differently tuned afferents. For example, the sensation of itch results from a combination of high activity in pain- and touch-sensitive afferents, and the sensation of tickle requires a gently moving tactile stimulus over cool skin.

When information from different primary afferents reaches the forebrain, where subjective experience occurs, the qualitative differences between warmth and touch are called *sensory modalities*. Although the receptor-detected information is relayed to the thalamus and cortex over separate pathways, the experience of a modality, such as cold versus warm, is uniquely subjective.

Tactile Sensation

The tactile system, which relays sensory information regarding touch, pressure, and vibration, is considered the basic somatosensory system. Loss of temperature or pain sensitivity leaves the person with no awareness of deficiency. However, if the tactile system is lost, total anesthesia (*i.e.*, numbness) of the involved body part results.

Touch sensation results from stimulation of tactile receptors in the skin and in tissues immediately beneath the skin, pressure from deformation of deeper tissues, and vibration from rapidly repetitive sensory signals. There are at least six types of specialized tactile receptors in the skin and deeper structures: free nerve endings, Meissner's corpuscles, Merkel's disks, pacinian corpuscles, hair follicle end-organs, and Ruffini's end-organs[1,2] (Fig. 39-8).

Free nerve endings are found in skin and many other tissues, including the cornea. They detect touch and pressure. *Meissner's corpuscles* are present in nonhairy parts of the skin. They are particularly abundant in the fingertips, lips, and other areas where the sense of touch is highly developed. *Meissner's corpuscles* are particularly sensitive to movement of very light objects over the surface of the skin and to low frequency vibration. *Merkel's disks* are found in nonhairy areas and in hairy parts of the skin. They are responsible for giving steady-state signals that allow for continuous determination of touch against the skin.

The *pacinian corpuscle* is located immediately beneath the skin and deep in the fascial tissues of the body and is important in detecting tissue vibration. The *hair follicle end-organs* detect movement on the surface of the body. *Ruffini's end-organs* are found in the skin and deeper structures, including the joint

capsules. These receptors are important for signaling continuous states of deformation, such as heavy and continuous touch and pressure.

The sensory information for tactile sensation enters the spinal cord through the dorsal roots of the spinal nerves. All tactile sensation that requires rapid transmission is transmitted through the discriminative pathway to the thalamus by way of the medial lemniscus. This includes touch sensation requiring a high degree of localization or fine gradations of intensity, vibratory sensation, and sensation that signals movement against the skin. In addition to the ascending discriminative pathway, tactile sensation also uses the more primitive and crude anterolateral pathway. The second-order dorsal horn neurons of this pathway have many branches or collaterals. After several synapses, axons are projected up both sides of the anterolateral aspect of the spinal cord to the thalamus. Few fibers travel all the way to the thalamus. Most synapse on reticular formation neurons that then send their axons on toward the thalamus, where a crude, poorly localized sensation from the opposite side of the body is received. From the thalamus, some projections travel to the somatosensory cortex.

Because of these multiple routes, total destruction of the pathways for tactile sensation seldom occurs. The only time this crude alternative system becomes essential is when the discriminative pathway is damaged. Then, despite projection of the anterolateral system information to the somatosensory cortex, only a poorly localized, high-threshold sense of touch remains. Such persons lose all sense of joint and muscle movement, body position, and two-point discrimination.

Thermal Sensation

Thermal sensation is discriminated by three types of receptors: cold receptors, warmth receptors, and pain receptors. The cold and warmth receptors are located immediately under the skin at discrete but separate points. In some areas, there are more cold receptors than warmth receptors. For example, the lips have 15 to 25 cold receptors per square centimeter, compared with 3 to 5 in the same-sized area of the finger.[1] There are also correspondingly fewer warmth receptors in these areas. The gradations of heat and cold result from selective stimulation of the different types of thermal receptors. The thermal receptors are very sensitive to differences between the temperature of skin and temperature of objects that are touched. Warmth receptors respond proportionately to increases in skin temperature above resting values of 34°C and cool receptors to temperatures below 34°C.[3]

The thermal pain receptors are stimulated only by extremes of temperature such as "freezing cold" (temperatures below 5°C) and "burning hot" (temperatures above 45°C) sensations.[3] With the exception of pain receptors, thermal receptors tend to adapt rapidly during the first few minutes and then more slowly during the next 30 minutes or so. However, these receptors do not appear to adapt completely, as evidenced by the experience of an intense sense of heat on entering a tub of hot water or the extreme degree of cold initially sensed when going outside on a cold day. On entering the dorsal horn, thermal signals are transmitted by neurons whose axons then cross to the opposite side of the cord and ascend in the multisynaptic, slow-conducting anterolateral system to the opposite side of the brain.

Conduction of thermal information through peripheral nerves is quite slow compared with the rapid tactile afferents that travel through the discriminative system. If a person places a foot in a tub of hot water, the tactile sensation occurs well in advance of the burning sensation. The foot has been removed from the hot water by the local withdrawal reflex well before the excessive heat is perceived by the forebrain. Local anesthetic agents block the small-diameter afferents that carry thermal sensory information before they block the large-diameter axons that carry touch information.

Position Sensation

Position sense refers to the sense of limb and body movement and position without using vision. It is mediated by input from proprioceptive receptors (muscle spindle receptors and Golgi tendon organs) found primarily in muscles, tendons, and joint capsules (see Chapter 38). There are two submodalities of proprioception: the stationary or static component (limb position sense) and the dynamic aspects of position sense (kinesthesia). Both of these depend on constant transmission of information to the CNS regarding the rate of change and degree of angulation of all joints. In addition, there are a number of mechanoreceptors in the joint capsules and ligaments. Many resemble Ruffini's end-organs, pacinian corpuscles, and Merkel's cells.

Signals from these receptors are processed through the discriminative pathway. It appears that information from the joint receptors is combined with that from the muscle spindles and Golgi tendon organs, and probably from skin receptors that estimate joint angle. Removing one source of information can be compensated by use of other sources.

In summary, the somatosensory component of the nervous system provides an awareness of body sensations such as touch, temperature, position sense, and pain. There are three primary levels of neural integration in the somatosensory system: the sensory units containing the sensory receptors, the ascending pathways, and the central processing centers in the thalamus and cerebral cortex. A sensory unit consists of a single dorsal root ganglion neuron, its receptors, and its central axon that terminates in the dorsal horn of the spinal cord or medulla. The part of the body innervated by the somatosensory afferent neurons of one set of dorsal root ganglia is called a *dermatome*. Ascending pathways include the discriminative pathway, which crosses at the base of the medulla, and the anterolateral pathway, which crosses within the first few segments of entering the spinal cord. Perception, or the final processing of somatosensory information, involves centers in the thalamus and somatosensory cortex. In the thalamus, the sensory information is crudely localized and perceived. The full localization, discrimination of the intensity, and interpretation of the meaning of the stimuli require processing by the somatosensory cortex. A distorted map of the body and head surface, called the *sensory homunculus*, reflects the density of cortical neurons devoted to sensory input from afferents in corresponding peripheral areas.

The tactile system relays the sensations of touch, pressure, and vibration. It uses two anatomically separate pathways to relay touch information to the opposite side of the forebrain: the dorsal column discriminative pathway and the anterolateral pathway. Delicate touch, vibration, position, and movement sensations use the discriminative pathway to reach the thalamus, where third-order relay occurs to the primary somatosensory strip of parietal cortex. Crude tactile sensation is carried by the bilateral slow-conducting anterolateral pathway. Temperature sensations of warm-hot and cool-cold are the result of stimulation to thermal receptors of sensory units projecting to the thalamus and cortex through the anterolateral system on the opposite side of the body. Proprioception is the sense of limb and body movement and position without using vision. It is mediated by input muscle spindle receptors and Golgi tendon organs found in muscles, tendons, and joint capsules and by mechanoreceptors (*e.g.*, Ruffini's end-organs, pacinian corpuscles, and Merkel's cells) in the joint capsules and ligaments.

PAIN

Pain is an "unpleasant sensory and emotional experience associated with potential tissue damage, or described in terms of such damage."[4] It involves anatomic structures, physiologic behaviors, and psychological, social, cultural, and cognitive factors. Pain can be a prepotent or overwhelming experience, often disruptive of customary behavior, and when severe, it demands and directs all of a person's attention. Pain is the most common symptom that motives a person to seek professional help. It sends those who suffer to a health care facility more often and with more speed than any other symptoms. Its location, radiation, duration, and severity provide important clues as to its cause. Despite its unpleasantness, pain can serve a useful purpose because it warns of impending tissue injury, motivating the person to seek relief. For example, an inflamed appendix could progress in severity, rupture, and even cause death were it not for the warning afforded by the pain.

Pain Theories

Traditionally, two theories have been offered to explain the physiologic basis for the pain experience. The first, *specificity theory*, regards pain as a separate sensory modality evoked by the activity of specific receptors that transmit information to pain centers or regions in the forebrain where pain is experienced.[5] The second theory includes a group of theories collectively referred to as *pattern theory*. It proposes that pain receptors share endings or pathways with other sensory modalities

KEY CONCEPTS

PAIN SENSATION

- Pain is both a protective and an unpleasant physical and emotionally disturbing sensation originating in pain receptors that respond to a number of stimuli that threaten tissue integrity.
- There are two pathways for pain transmission:
  - The fast pathway for sharply discriminated pain that moves directly from the receptor to the spinal cord using myelinated Aδ fibers and from the spinal cord to the thalamus using the neospinothalamic tract
  - The slow pathway for continuously conducted pain that is transmitted to the spinal cord using unmyelinated C fibers and from the spinal cord to the thalamus using the more circuitous and slower-conducting paleospinothalamic tract.
- The central processing of pain information includes transmission to the somatosensory cortex, where pain information is perceived and interpreted; the limbic system, where the emotional components of pain are experienced; and to brain stem centers, where autonomic nervous system responses are recruited.
- Modulation of the pain experience occurs by way of the endogenous analgesic center in the midbrain, the pontine noradrenergic neurons, and the nucleus raphe magnus in the medulla, which sends inhibitory signals to dorsal horn neurons in the spinal cord.

but that different patterns of activity (*i.e.*, spatial or temporal) of the same neurons can be used to signal painful and nonpainful stimuli.[5] For example, light touch applied to the skin would produce the sensation of touch through low-frequency firing of the receptor; intense pressure would produce pain through high-frequency firing of the same receptor. Both theories focus on the neurophysiologic basis of pain, and both probably apply. Specific nociceptive afferents have been identified; however, almost all afferent stimuli, if driven at a very high frequency, can be experienced as painful.

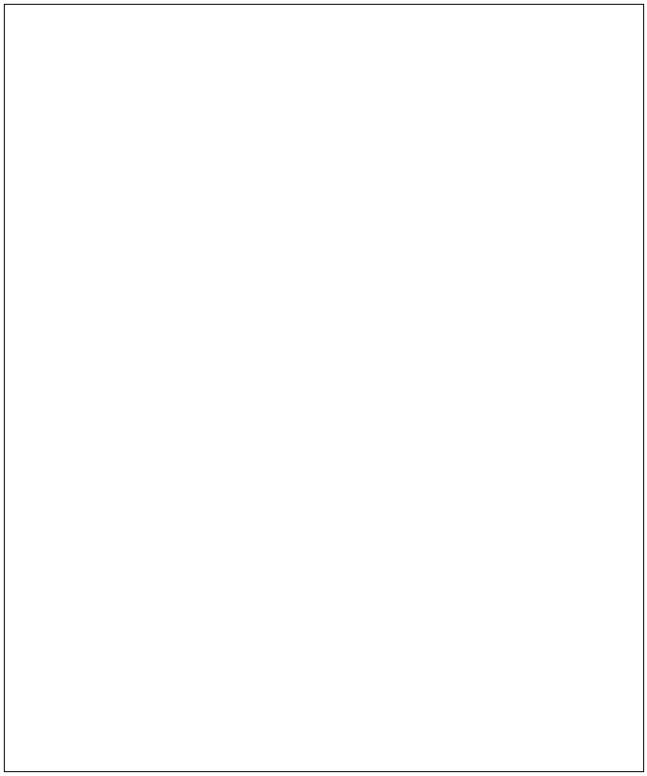
Gate control theory, a modification of specificity theory, was proposed by Melzack and Wall in 1965 to meet the challenges presented by the pattern theories.[6] This theory postulated the presence of neural gating mechanisms at the segmental spinal cord level to account for interactions between pain and other sensory modalities. According to the gate control theory, the internuncial neurons involved in the gating mechanism are activated by large-diameter, faster-propagating fibers that carry tactile information. The simultaneous firing of the large-diameter touch fibers has the potential for blocking the transmission of impulses from the small-diameter myelinated and unmyelinated pain fibers.

More recently, Melzack has developed the *neuromatrix theory* to address further the brain's role in pain as well as the multiple dimensions and determinants of pain.[7] This theory is particularly useful in understanding chronic pain and phantom limb pain, in which there is not a simple one-to-one relationship between tissue injury and pain experience. The neuromatrix theory proposes that the brain contains a widely distributed neural network, called the *body-self neuromatrix*, that contains somatosensory, limbic, and thalamocortical components. Genetic and sensory influences determine the synaptic architecture of an individual's neuromatrix that integrates multiple sources of input and evokes the sensory, affective, and cognitive dimensions of pain experience and behavior. These multiple input sources include somatosensory; other sensory impulses affecting interpretation of the situation; inputs from the brain addressing such things as attention, expectation, culture, and personality; intrinsic neural inhibitory modulation; and various components of stress-regulation systems.

Pain Mechanisms and Pathways

Pain usually is viewed in the context of tissue injury. The term *nociception*, which means "pain sense," comes from the Latin word *nocere* ("to injure"). Nociceptive stimuli are objectively defined as stimuli of such intensity that they cause or are close to causing tissue damage. Researchers often use the withdrawal reflex (*e.g.*, the reflexive withdrawal of a body part from a tissue-damaging stimulus) to determine when a stimulus is nociceptive. Stimuli used include pressure from a sharp object, strong electric current to the skin, or application of heat or cold of approximately 10°C above or below normal skin temperature. At low levels of intensity these noxious stimuli do activate nociceptors (pain receptors) but typically are perceived as painful only when the intensity reaches a level where tissue damage occurs or is imminent.

The mechanisms of pain are many and complex (Fig. 39-9). As with other forms of somatosensation, the pathways are composed of first-, second-, and third-order neurons. The first-order neurons and their receptive endings detect stimuli that threaten the integrity of innervated tissues. Second-order neurons are located in the spinal cord and process nociceptive information. Third-order neurons project pain information to the brain. The thalamus and cortex integrate and modulate pain as well as the person's subjective reaction to the pain experience.



■ **FIGURE 39-9** ■ Mechanisms of pain. Tissue injury leads to release of inflammatory mediators with subsequent nociceptor stimulation. Pain impulses are then transmitted to dorsal horn of the spinal cord, where they make contact with second-order neurons that cross to the opposite side of the cord and ascend via the spinothalamic tract to the reticular activating system (RAS) and thalamus. The localization and meaning of pain occurs at the level of the somatosensory cortex.

Pain Receptors and Mediators

Nociceptors, or pain receptors, are sensory receptors that are activated by noxious insults to peripheral tissues (Fig 39-9). Structurally, the receptive endings of the peripheral pain fibers are free nerve endings. These receptive endings, which are widely distributed in the skin, dental pulp, periosteum, meninges, and some internal organs, translate the noxious stimuli into action potentials that are transmitted by a dorsal root ganglion to the dorsal horn of the spinal cord. Nociceptive action potentials are transmitted through two types of afferent nerve fibers: myelinated Aδ fibers and unmyelinated C fibers. The larger Aδ fibers have considerably greater conduction velocities, transmitting impulses at a rate of 10 to 30 m/second. The C fibers are the smallest of all peripheral nerve fibers; they transmit impulses at the rate of 0.5 to 2.5 m/second. Pain conducted by Aδ fibers traditionally is called *fast pain* and typically is elicited by mechanical or thermal stimuli. C-fiber pain often is described as *slow-wave pain* because it is slower in onset and longer in duration. It typically is incited by chemical stimuli or by persistent

mechanical or thermal stimuli. The slow-wave potentials generated in C fibers are now believed to be responsible for central sensitization to chronic pain.

Stimulation of Nociceptors. Unlike other sensory receptors, nociceptors respond to several forms of stimulation, including mechanical, thermal, and chemical. Some receptors respond to a single type of stimuli (mechanical or thermal), and others, called *polymodal receptors*, respond to all three types of stimuli (mechanical, thermal, and chemical). Mechanical stimuli can arise from intense pressure applied to skin or from the violent contraction or extreme stretch of a muscle. Both extremes of heat and cold can stimulate nociceptors. Chemical stimuli arise from a number of sources, including tissue trauma, ischemia, and inflammation. A wide range of chemical mediators are released from injured and inflamed tissues, including hydrogen and potassium ions, prostaglandins, leukotrienes, histamine, bradykinin, acetylcholine, and serotonin. These chemical mediators produce their effects by directly stimulating nociceptors or sensitizing them to the effects of nociceptive stimuli; perpetuating the inflammatory responses that lead to the release of chemical agents that act as nociceptive stimuli; or inciting neurogenic reflexes that increase the response to nociceptive stimuli. For example, bradykinin, histamine, serotonin, and potassium activate and also sensitize nociceptors. Adenosine triphosphate, acetylcholine, and platelets act alone or in concert to sensitize nociceptors through other chemical agents such as prostaglandins. Aspirin and other nonsteroidal analgesic drugs are effective in controlling pain because they block the enzyme needed for prostaglandin synthesis.

Nociceptive stimulation that activates C fibers can cause a response known as *neurogenic inflammation* that produces vasodilation and an increased release of chemical mediators to which nociceptors respond. This mechanism is thought to be mediated by a dorsal root neuron reflex that produces retrograde transport and release of chemical mediators, which in turn causes increasing inflammation of peripheral tissues. This reflex can set up a vicious cycle, which has implications for persistent pain and hyperalgesia.[8] Local anesthetics (*e.g.*, procaine [Novocain]) can prevent the spread of sensitization and secondary hyperalgesia caused by stimulation of cutaneous nociceptors by blocking the dorsal root neuron reflex.[9]

Mediators in the Spinal Cord. In the spinal cord, the transmission of impulses between the nociceptive neurons and the dorsal horn neurons is mediated by chemical neurotransmitters released from central nerve endings of the nociceptive neurons. Some of these neurotransmitters are amino acids (*e.g.*, glutamate), others are amino acid derivatives (*e.g.*, norepinephrine), and still others are low–molecular-weight peptides composed of two or more amino acids. The amino acid glutamate is a major excitatory neurotransmitter released from the central nerve endings of the nociceptive neurons. Substance P, a neuropeptide, also is released in the dorsal horn by C fibers in response to nociceptive stimulation. Substance P elicits slow excitatory potentials in dorsal horn neurons. Unlike glutamate, which confines its action to the immediate area of the synaptic terminal, some neuropeptides released in the dorsal horn can diffuse some distance because they are not inactivated by reuptake mechanisms. In persistent pain, this may help to explain the excitability and unlocalized nature of many painful conditions. Neuropeptides such as substance P also appear to prolong and enhance the action of glutamate. If these neurotransmitters are released in large quantities or over extended periods, they can lead to secondary hyperalgesia, a condition in which the second-order neurons are overly sensitive to low levels of noxious stimulation. Understanding how chemical mediators function in nociception is an active area of research that has implications for the development of new treatments for pain.

Spinal Cord Circuitry and Pathways

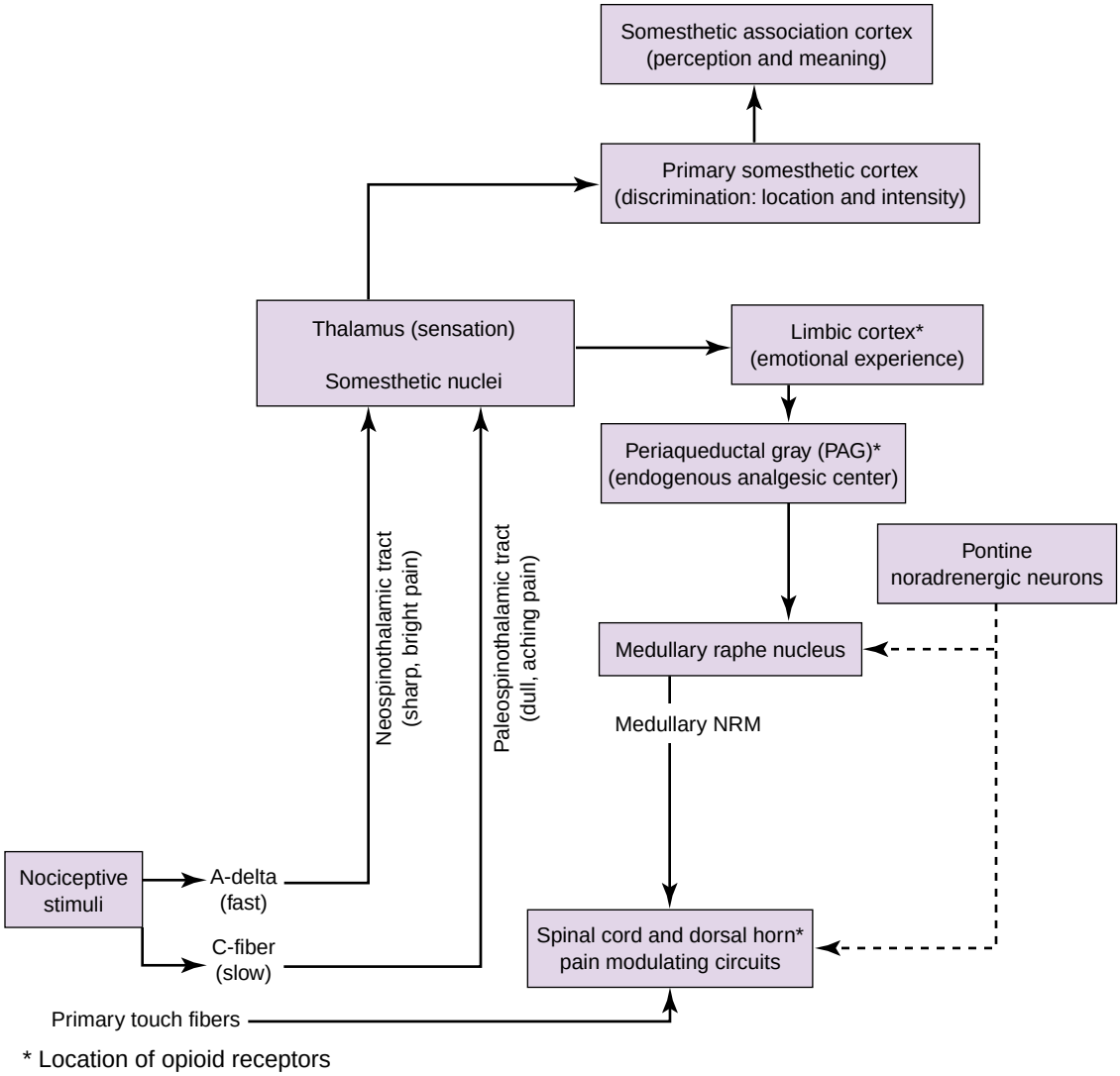
On entering the spinal cord through the dorsal roots, the pain fibers bifurcate and ascend or descend one or two segments before synapsing with association neurons in the dorsal horn. From the dorsal horn, the axons of association projection neurons cross through the anterior commissure to the opposite side and then ascend upward in the previously described neospinothalamic and paleospinothalamic pathways (Fig. 39-10).

The faster-conducting fibers in the neospinothalamic pathway (*i.e.*, lateral spinothalamic tract) are associated mainly with the transmission of sharp-fast pain information to the thalamus.[1] In the thalamus, synapses are made and the pathway continues to the contralateral parietal somatosensory area to provide the precise location of the pain. Typically, the pain is experienced as bright, sharp, or stabbing in nature. There is also a local cord-level withdrawal reflex that is designed to remove endangered tissue from a damaging stimulus.

The paleospinothalamic tracts are slower-conducting, multisynaptic pathways concerned with the diffuse, dull, aching, and unpleasant sensations that commonly are associated with chronic and visceral pain.[1] This information travels through the small, unmyelinated C fibers. Fibers of this system also project up the contralateral (*i.e.*, opposite) anterolateral pathway to terminate in several thalamic regions, including those that project to the limbic system, where it is associated with the emotional aspects of pain. Fibers from the spinoreticular tract project bilaterally to the reticular formation of the brain stem. This component of the paleospinothalamic system facilitates avoidance reflexes at all levels. It also contributes to an increase in the electroencephalographic activity associated with alertness and indirectly influences hypothalamic functions associated with sudden alertness, such as increased heart rate and blood pressure. This may explain the tremendous arousal effects of certain pain stimuli.

Brain Centers and Pain Perception

The basic sensation of hurtfulness, or pain, occurs at the level of the thalamus. In the neospinothalamic system, interconnections between the lateral thalamus and the somatosensory cortex are necessary to add precision and discrimination to the pain sensation. Association areas of the parietal cortex are essential to the learned meaningfulness of the pain experience. For example, if a person is stung on the index finger by a bee and only the thalamus is functional, the person reports pain somewhere on the hand. With the primary sensory cortex functional, the person can localize the pain to the precise area on the index finger. With the association cortex functional, the person can interpret the buzzing and sight of the bee that preceded the pain as being related to the bee sting. The paleospinothalamic system projects diffusely from the intralaminar nuclei of the thalamus to large areas of the limbic cortex. These



■ **FIGURE 39-10** ■ Primary pain pathways. The transmission of incoming nociceptive impulses is modulated by dorsal horn circuitry that receives input from peripheral touch receptors and from descending pathways that involve the limbic cortical systems (orbital frontal cortex, amygdala, and hypothalamus), periaqueductal endogenous analgesic center in the midbrain, pontine noradrenergic neurons, and the nucleus raphe magnus (NRM) in the medulla. Dashed lines indicate inhibition or modulation.

connections probably are associated with the hurtfulness and the mood-altering and attention-narrowing effect of pain.

Central Pathways for Pain Modulation

A major advance in understanding pain was the discovery of neuroanatomic pathways that arise in the midbrain and brain stem, descend to the spinal cord, and modulate ascending pain impulses. One such pathway begins in an area of the midbrain called the *periaqueductal* gray (PAG) region. Through research it was found that focal stimulation of the midbrain PAG regions produced a state of analgesia. The resultant analgesia lasted for many hours and was sufficient to permit abdominal surgery, although levels of consciousness and reactions to auditory and visual stimuli remained unaffected. A few years later, opioid receptors were found to be highly concentrated in this and other regions of the CNS where electrical stimulation produced analgesia. Because of these findings, the PAG area of the midbrain often is referred to as the *endogenous analgesia center*.

The PAG area receives input from widespread areas of the CNS, including the cerebral cortex, hypothalamus, brain stem reticular formation, and spinal cord by way of the paleospinothalamic and neospinothalamic tracts. This region is intimately connected to the limbic system, which is associated with emotional experience. The neurons of the PAG area in the midbrain have axons that descend into an area called the *nucleus raphe magnus* (NRM) in the rostral medulla. The axons of these NRM neurons project to the dorsal horn of the spinal cord, where they terminate in the same layers as the entering primary pain fibers (Fig. 39-10). Stimulation of the NRM is thought to inhibit pain transmission by dorsal horn projection neurons.[10] There also is evidence of noradrenergic neurons that can inhibit transmission of pain impulses at the level of the spinal cord.

The discovery that norepinephrine can block pain transmission led to studies directed at the combined administration of opioids and clonidine, a central-acting α-adrenergic agonist for some types of pain relief.

Serotonin also has been identified as a neuromodulator in the NRM medullary nuclei that project to the spinal cord. It has been shown that tricyclic antidepressant compounds, such as amitriptyline, have analgesic properties independent of their antidepressant effects. These drugs, which enhance the effects of serotonin by blocking its presynaptic uptake, have been found to be effective in the management of certain types of chronic pain.[11]

Endogenous Analgesic Mechanisms. There is evidence that the endogenous opioid peptides, morphine-like substances synthesized in many regions of the CNS including the spinal cord and PAG, modulate pain in the CNS. Three families of opioid peptides have been identified—the enkephalins, endorphins, and dynorphins. Although the endogenous opioid peptides appear to function as neurotransmitters, their full significance in pain control and other physiologic functions is not completely understood. Probably of greater importance in understanding mechanisms of pain control has been the characterization of receptors that bind the endogenous opioid peptides. The identification of these receptors has facilitated a more thorough understanding of the actions of available opioid drugs, such as morphine, and it also has facilitated ongoing research into the development of newer preparations that are more effective in relieving pain and have fewer side effects.

KEY CONCEPTS

TYPES OF PAIN

- Pain can be classified according to location, site of referral, and duration.
- Cutaneous pain is a sharp, burning pain that has its origin in the skin or subcutaneous tissues.
- Deep pain is a more diffuse and throbbing pain that originates in structures such as the muscles, bones, and tendons and radiates to the surrounding tissues.
- Visceral pain is a diffuse and poorly defined pain that results from stretching, distention, or ischemia of tissues in a body organ.
- Referred pain is pain that originates at a visceral site but is perceived as originating in part of the body wall that is innervated by neurons entering the same segment of the nervous system.
- Acute pain usually results from tissue damage and is characterized by autonomic nervous system responses.
- Chronic pain is persistent pain that is accompanied by loss of appetite, sleep disturbances, depression, and other debilitating responses.

Pain Threshold and Tolerance

Pain threshold and tolerance affect an individual's response to a painful stimulus. Although the terms often are used interchangeably, *pain threshold* and *pain tolerance* have distinct meanings. *Pain threshold* is closely associated with tissue damage and the point at which a stimulus is perceived as painful. *Pain tolerance* relates more to the total pain experience; it is defined as the maximum intensity or duration of pain that a person is willing to endure before the person wants something done about the pain. Psychological, familial, cultural, and environmental factors significantly influence the amount of pain a person is willing to tolerate. The threshold to pain is fairly uniform from one person to another, whereas pain tolerance is extremely variable.[12] Separation and identification of the role of each of these two aspects of pain continue to pose fundamental problems for the pain management team and for pain researchers.

Types of Pain

The most widely accepted classifications of pain are according to source or location, referral, and duration (acute or chronic). Classification based on associated medical diagnosis (*e.g.*, surgery, trauma, cancer, sickle cell disease, fibromyalgia) is useful in planning appropriate interventions.

Cutaneous and Deep Somatic Pain

Cutaneous pain arises from superficial structures, such as the skin and subcutaneous tissues. A paper cut on the finger is an example of easily localized superficial, or cutaneous, pain. It is a sharp, bright pain with a burning quality and may be abrupt or slow in onset. It can be localized accurately and may be distributed along the dermatomes. Because there is an overlap of nerve fiber distribution between the dermatomes, the boundaries of pain frequently are not as clear-cut as the dermatomal diagrams indicate.

Deep somatic pain originates in deep body structures, such as the periosteum, muscles, tendons, joints, and blood vessels. This pain is more diffuse than cutaneous pain. Various stimuli, such as strong pressure exerted on bone, ischemia to a muscle, and tissue damage, can produce deep somatic pain. This is the type of pain a person experiences from a sprained ankle. Radiation of pain from the original site of injury can occur. For example, damage to a nerve root can cause a person to experience pain radiating along its fiber distribution.

Visceral Pain

Visceral, or splanchnic, pain has its origin in the visceral organs. Common examples of visceral pain are renal colic, pain caused by cholecystitis, pain associated with acute appendicitis, and peptic ulcer pain. Although the viscera are diffusely and richly innervated, cutting or burning of viscera, as opposed to similar noxious stimuli applied to cutaneous or superficial structures, is unlikely to cause pain. Instead, strong abnormal contractions of the gastrointestinal system, distention, or ischemia affecting the walls of the viscera can induce severe visceral pain. Anyone who has had severe gastrointestinal distress or ureteral colic can readily attest to the misery involved.

Visceral pain is transmitted by small unmyelinated pain fibers that travel with the axons of the autonomic nervous system and project to visceral input association neurons of the cord or brain stem. In addition to sending projections to the forebrain, these input association neurons also project through the paleospinal and spinoreticular pathways into visceral reflex circuits. Visceral pain typically is accompanied by autonomic nervous system responses such as nausea, vomiting, sweating, and pallor and, less commonly, is followed by shock.

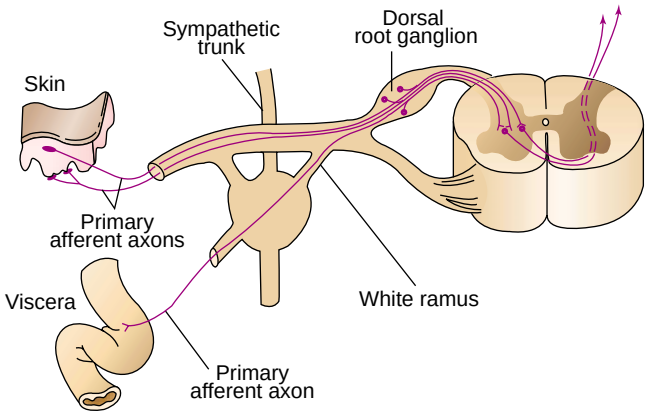
The visceral pain pathways travel with the parasympathetic distribution for the upper and lower viscera and with the sympathetic distribution for the intervening viscera. Pain from the viscera may be localized only with difficulty. There are several explanations for this. First, innervation of visceral organs is poorly represented at the forebrain levels (*i.e.*, perception). A second possible explanation is that the brain does not easily learn to localize sensations that originate in organs that are only imprecisely visualized. For example, a cut on the third finger of the right hand can be readily seen, identified, and localized, whereas an inflamed internal organ can be localized only vaguely. A third explanation is that sensory information from thoracic and abdominal viscera can travel by two pathways to the CNS.

Referred Pain

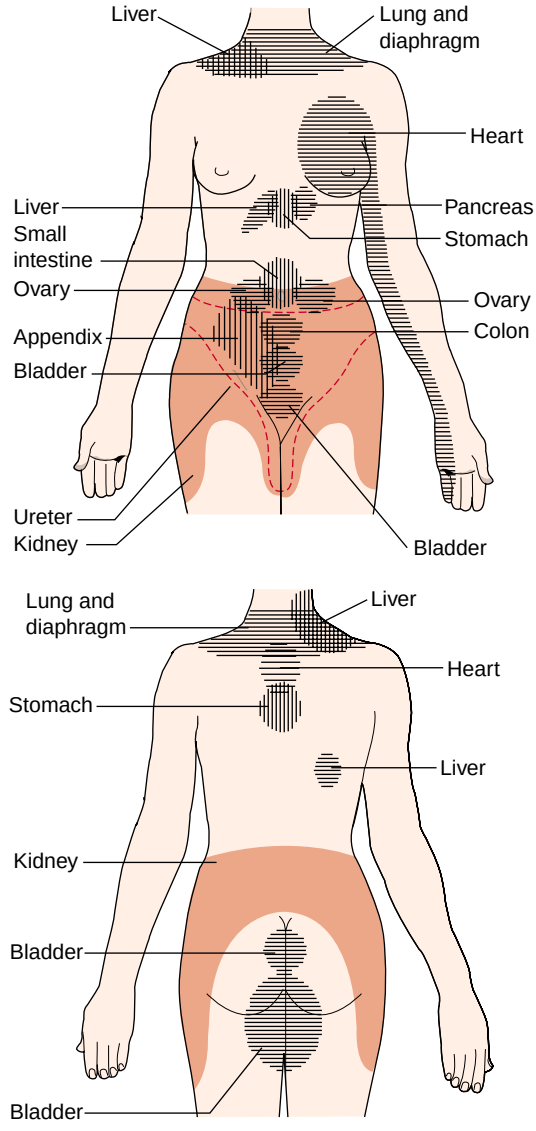
Referred pain is pain that is perceived at a site different from its point of origin but innervated by the same spinal segment. It is hypothesized that visceral and somatic afferent neurons converge on the same dorsal horn projection neurons (Fig. 39-11). For this reason, it can be difficult for the brain to correctly identify the original source of pain. Pain that originates in the abdominal or thoracic viscera is diffuse and poorly localized and often perceived at a site far removed from the affected area. For example, the pain associated with myocardial infarction commonly is referred to the left arm, neck, and chest.

Referred pain may arise alone or concurrent with pain located at the origin of the noxious stimuli. This lack of correspondence between the location of the pain and the location of the painful stimuli can make diagnosis difficult. Although the term *referred* usually is applied to pain that originates in the viscera and is experienced as if originating from the body wall, it also may be applied to pain that arises from somatic structures. For example, pain referred to the chest wall could be caused by nociceptive stimulation of the peripheral portion of the diaphragm, which receives somatosensory innervation from the intercostal nerves. An understanding of pain referral is of great value in diagnosing illness. The typical pattern of pain referral can be derived from our understanding that the afferent neurons from visceral or deep somatic tissue enter the spinal cord at the same level as the afferent neurons from the cutaneous areas to which the pain is referred (Fig. 39-12).

The sites of referred pain are determined embryologically with the development of visceral and somatic structures that share the same site for entry of sensory information into the CNS and then move to more distant locations. For example, a person with peritonitis may report pain in the shoulder. Inter-



■ **FIGURE 39-11** ■ Convergence of cutaneous and visceral inputs onto the same second-order projection neuron in the dorsal horn of the spinal cord. Although virtually all visceral inputs converge with cutaneous inputs, most cutaneous inputs do not converge with other sensory inputs. (From Conn P.M. [1995]. *Neuroscience in medicine.* Philadelphia: J.B. Lippincott)



■ **FIGURE 39-12** ■ Areas of referred pain. (**Top**) Anterior view. (**Bottom**) Posterior view.

nally, there is inflammation of the peritoneum that lines the central part of the diaphragm. In the embryo, the diaphragm originates in the neck, and its central portion is innervated by the phrenic nerve, which enters the cord at the level of the third to fifth segments (C3 to C5). As the fetus develops, the diaphragm descends to its adult position between the thoracic and abdominal cavities, while maintaining its embryonic pattern of innervation. Thus, fibers that enter the spinal cord at the C3 to C5 level carry information from both the neck area and the diaphragm, and the diaphragmatic pain is interpreted by the forebrain as originating in the shoulder or neck area.

Muscle spasm, or *guarding*, occurs when somatic structures are involved. Guarding is a protective reflex rigidity; its purpose is to protect the affected body parts (*e.g.*, an abscessed appendix or a sprained muscle). This protective guarding may cause blood vessel compression and give rise to the pain of muscle ischemia, causing local and referred pain.

Acute and Chronic Pain

It is common to classify pain according to its duration. Pain research of the past three decades has emphasized the importance of differentiating acute pain from chronic pain. The diagnosis and therapy for each is distinctive because they differ in cause, function, mechanisms, and psychological sequelae (Table 39-1).

Acute Pain. The classic definition of acute pain is pain that lasts less than 6 months. This somewhat arbitrary cutoff point reflects the notion that acute pain is the result of a tissue-damaging event, such as trauma or surgery, and usually is self-limited, ending when the injured tissues heal. The purpose of acute pain is to serve as a warning system. Besides alerting the person to the existence of actual or impending tissue damage, it prompts a search for professional help. The pain's location, radiation, intensity, and duration as well as those factors that aggravate or relieve it provide essential diagnostic clues.

Acute pain can lead to anxiety and secondary reflex musculoskeletal spasms, which in turn tend to worsen the pain.[13] Interventions that alleviate the pain usually alleviate the anxiety and musculoskeletal spasms as well. Inadequately treated pain can provoke physiologic responses that alter circulation and tissue metabolism and produce physical manifestations, such as tachycardia, reflective of increased sympathetic activity. Inadequately treated acute pain tends to decrease mobility and respiratory movements such as deep breathing and coughing to the extent that it may complicate or delay recovery.

Chronic Pain. Chronic pain classically has been defined as pain lasting 6 months or longer. However, in practice one does not wait an arbitrary 6 months before deciding that the pain is chronic; rather, one considers the normal expected healing time for the underlying cause of the pain. The International Association for the Study of Pain defines chronic pain as that which persists beyond the expected normal time of healing.[13] Chronic pain can be quite variable. It may be unrelenting and extremely severe, as in metastatic bone pain. It can be relatively continuous with or without periods of escalation, as with some forms of back pain. Some conditions with recurring episodes of acute pain are particularly problematic because they have characteristics of both acute and chronic pain. These include the pain associated with sickle cell crisis or migraine headaches.

TABLE 39-1 Characteristics of Acute and Chronic Pain

Characteristic	Acute Pain	Chronic Pain
Onset	Recent	Continuous or intermittent
Duration	Short duration (<6 months)	6 months or more
Autonomic responses	Consistent with sympathetic fight-or-flight response* Increased heart rate Increased stroke volume Increased blood pressure Increased pupillary dilation Increased muscle tension Decreased gut motility Decreased salivary flow (dry mouth)	Absence of autonomic responses
Psychological component	Associated anxiety	Increased irritability Associated depression Somatic preoccupation Withdrawal from outside interests Decreased strength of relationships
Other types of response		Decreased sleep Decreased libido Appetite changes

*Responses are approximately proportional to intensity of the stimulus.

Chronic pain is a leading cause of disability in the United States. Unlike acute pain, persistent chronic pain usually serves no useful function. In contrast, it imposes physiologic, psychological, familial, and economic stresses and may exhaust a person's resources.

Persons with chronic pain may not exhibit the somatic, autonomic, or affective behaviors often associated with acute pain. As painful conditions become prolonged and continuous, autonomic nervous system responses decrease. Decreased pain tolerance, which may result from the depletion of serotonin and endorphins, and depression are common in individuals with chronic pain. There is often loss of appetite, sleep disturbances, and depression.[14] The link between depression and decreased pain tolerance may be explained by the similar manner in which both respond to changes in the biologic pathways of serotonergic and noradrenergic systems.[14] Tricyclic antidepressants and other medications with serotonergic and noradrenergic effects have been shown to relieve a variety of chronic pain syndromes, lending credence to the theory that chronic pain and depression share a common biologic pathway.[14]

Pain Management

Assessment

Careful assessment of pain assists clinicians in diagnosing, managing, and relieving the patient's pain. Assessment includes such things as the nature, severity, location, and radiation of the pain. As with other disease states, it is preferable to eliminate the cause of the pain, rather than simply to treat the symptom. A careful history often provides information about the triggering factors (*i.e.*, injury, infection, or disease) and the site of nociceptive stimuli (*i.e.*, peripheral receptor or visceral organ). Although the observation of facial expression and posture may provide additional information, current AHCPR practice guidelines emphasize that "the single most reliable indicator of the existence and intensity of acute pain—and any resultant affective discomfort or distress—is the patient's self report."[15,16] A comprehensive pain history should include pain onset; description, localization, radiation, intensity, quality, and pattern of the pain; anything that relieves or exacerbates it; and the individual's personal reaction to the pain.

Unlike many other bodily responses, such as temperature and blood pressure, the nature, severity, and distress of pain cannot be measured objectively. To overcome this problem, various methods have been developed for quantifying a person's pain. Most of these are based on the patient's report. They include numeric pain intensity, visual analog, and verbal descriptor scales.

Treatment

The therapeutic approaches to acute and chronic pain differ markedly. In acute pain, therapy is directed at providing pain relief by interrupting the nociceptive stimulus. Acute pain should be aggressively managed and pain medication provided before the pain becomes severe. This allows the person to be more comfortable and active and to assume a greater role in directing his or her own care. Because the pain is self-limited, in that it resolves as the injured tissues heal, long-term therapy usually is not needed.

Chronic pain management is much more complex and is based on multiple considerations. It usually requires early attempts to prevent pain and adequate therapy for acute bouts of pain. Specific treatment depends on the cause of the pain, the natural history of the underlying health problem, and the life expectancy of the individual. If the organic illness causing the pain cannot be cured, noncurative methods of pain control become the cornerstone of treatment. Treatment methods for chronic pain can include pharmacological and nonpharmacological interventions. Pharmacological treatment includes the use of non-narcotic and narcotic medications. Non-narcotic medications such as tricyclic antidepressants, antiseizure medications, and nonsteroidal anti-inflammatory drugs (NSAIDs) serve as useful adjuncts to opioids for the treatment of different types of chronic pain. Nonpharmacological interventions include neural blockade, electrical modalities (*e.g.*, transcutaneous electrical nerve stimulation [TENS]), physical therapy, and cognitive behavioral interventions (*e.g.*, imagery and relaxation strategies). Chronic pain is best handled by a multidisciplinary team that includes specialists in areas such as anesthesiology, nursing, physical therapy, social services, and surgery.

Cancer is a common cause of chronic pain. The goal of chronic cancer pain management should be pain alleviation and prevention.[16] Preemptive therapy tends to reduce sensitization of pain pathways and provides for more effective pain control. Pharmacological and nonpharmacological interventions are the same as those used for other types of chronic pain. Depending on the form and stage of the cancer, other treatments such as palliative radiation, antineoplastic therapies, and palliative surgery may help to control the pain. The World Health Organization has created an analgesic ladder for cancer pain that assists clinicians in choosing the appropriate analgesic medications.[17]

Pharmacologic Treatment. An analgesic drug is a medication that acts on the nervous system to decrease or eliminate pain without inducing loss of consciousness. Analgesic drugs do not cure the underlying cause of the pain, but their appropriate use may prevent acute pain from progressing to chronic pain. Pain medications are commonly divided into three categories: non-narcotic analgesics, opioid or narcotic analgesics, and adjuvant analgesics.

Non-narcotic Analgesics. Common non-narcotic oral analgesic medications include aspirin, other NSAIDs, and acetaminophen. Aspirin, or acetylsalicylic acid, acts centrally and peripherally to block the transmission of pain impulses. It also has antipyretic and anti-inflammatory properties. Aspirin and the other NSAIDs inhibit several forms of prostaglandins through the inhibition of cyclooxygenase, an enzyme in the prostanoid pathway. Prostaglandins affect the sensation of pain by sensitizing nociceptors to chemical mediators such as bradykinin and histamine. Independent of prostaglandins, NSAIDs also decrease the sensitivity of blood vessels to bradykinin and histamine, affect lymphokine production by T lymphocytes, reverse vasodilation, and decrease the release of inflammatory mediators from granulocytes, mast cells, and basophils. Acetaminophen is an alternative to the NSAIDs. Although usually considered equivalent to aspirin as an analgesic and antipyretic agent, it lacks anti-inflammatory properties.

Opioid Analgesics. The term *opioid* or *narcotic* is used to refer to a group of medications, natural or synthetic, with morphine-like actions. The opioids (*e.g.*, morphine, codeine, and many other semisynthetic congeners of morphine) exert their action through opioid receptors. There are three major categories of opioid receptors in the CNS, designated mu (μ, for "morphine"), delta (δ), and kappa (κ).[18] Analgesia, as well as respiratory depression, miosis, reduced gastrointestinal motility (causing constipation), feelings of well-being or euphoria, and physical dependence result principally from morphine and morphine-like opioid analgesics that act at mu receptors. Part of the pain-relieving properties of exogenous opioids such as morphine involves the release of endogenous opioids.[18]

Opioids are used in the management of acute and chronic pain. When given for temporary relief of severe pain, such as that occurring after surgery, there is much evidence that opioids given routinely before the pain starts or becomes extreme are far more effective than those administered in a sporadic manner. Persons who are treated in this manner seem to require fewer doses and are able to resume regular activities sooner. Opioids also are used for persons with chronic pain such as that caused by cancer. Too often, because of undue concern about the possibility of addiction, many individuals with chro-

nic pain receive inadequate pain relief. Addiction is not considered a problem in patients with cancer.[19] Most pain experts agree that it is appropriate to provide the level of opioid necessary to relieve the severe intractable pain of persons whose life expectancy is limited. Morphine remains the most useful strong opioid, and the World Health Organization has recommended that oral morphine be part of the essential medication list and made available throughout the world as the medication of choice for cancer pain.[20]

Adjuvant Analgesics. Adjuvant analgesics include medications such as tricyclic antidepressants, antiseizure medications, and neuroleptic anxiolytic agents. The fact that the pain suppression system has nonendorphin synapses raises the possibility that potent, centrally acting, nonopiate medications may be useful in relieving pain. Serotonin has been shown to play an important role in producing analgesia. The tricyclic antidepressant medications block the removal of serotonin from the synaptic cleft to produce pain relief in some persons. These medications are particularly useful in some chronic painful conditions, such as postherpetic neuralgia. Certain antiseizure medications, such as carbamazepine and phenytoin, have analgesic effects in some pain conditions. These medications, which suppress spontaneous neuronal firing, are particularly useful in the management of pain that occurs after nerve injury. Other agents, such as the corticosteroids, may be used to decrease inflammation and nociceptive stimuli responsible for pain.

Surgical Intervention. The effects of surgical interventions may be curative or palliative. Surgical interventions that remove the source of the pain (*e.g.*, inflamed appendix) are curative. In other instances, surgery is used for symptom management, rather than for cure. Surgery for severe, intractable pain of peripheral or central origin has met with some success. It can be used to remove the cause or block the transmission of intractable pain from phantom limb pain, severe neuralgia, inoperable cancer of certain types, and causalgia.

In summary, pain is an elusive and complex phenomenon; it is a symptom common to many illnesses. It is a highly individualized experience that is shaped by a person's culture and previous life experiences, and it is difficult to measure. Traditionally, there have been two principal theories of pain: the specificity and pattern theories. Scientifically, pain is viewed within the context of nociception. Nociceptors are receptive nerve endings that respond to noxious stimuli. Pain receptors respond to mechanical, thermal, and chemical stimuli. Nociceptive neurons transmit impulses to the dorsal horn neurons using chemical neurotransmitters. The neospinothalamic and the paleospinothalamic paths are used to transmit pain information to the brain. Several neuroanatomic pathways as well as endogenous opioid peptides modulate pain in the CNS.

Pain can be classified according to location, referral, and duration as well as associated medical diagnoses. Pain can arise from cutaneous, deep somatic, or visceral locations. Referred pain is pain perceived at a site different from its origin. Acute pain is self-limiting pain that ends when the injured tissue heals, whereas chronic pain is pain that lasts much longer than the anticipated healing time for the underlying cause of the pain. Pain threshold, pain tolerance, age, gender, and other factors affect an individual's reaction to pain.

Treatment modalities for pain include the use of nonpharmacologic and pharmacologic agents used singly or in combination. It is becoming apparent that even with chronic pain, the most effective approach is early treatment or even prevention. After pain is present, the greatest success in pain assessment and management is achieved with the use of an interdisciplinary approach.

ALTERATIONS IN PAIN SENSITIVITY AND SPECIAL TYPES OF PAIN

Alterations in Pain Sensitivity

Sensitivity and perception of pain varies among persons and in the same person under different conditions and in different parts of the body. Irritation, mild hypoxia, and mild compression of a peripheral nerve often result in hyperexcitability of the sensory nerve fibers or cell bodies. This is experienced as unpleasant hypersensitivity (*i.e.*, *hyperesthesia*) or increased painfulness (*i.e.*, *hyperalgesia*). Possible causes of increased sensitivity to noxious stimuli include a decrease in the threshold of nociceptors, an increase in pain produced by suprathreshold stimuli, and the windup phenomenon. Primary hyperalgesia occurs at the site of injury. Secondary hyperalgesia occurs in nearby uninjured tissue.

Hyperpathia is a syndrome in which the sensory threshold is raised, but when it is reached, continued stimulation, especially if repetitive, results in a prolonged and unpleasant experience. This pain can be explosive and radiates through a peripheral nerve distribution. It is associated with pathologic changes in peripheral nerves, such as localized ischemia. Spontaneous, unpleasant sensations called *paresthesias* occur with more severe irritation (*e.g.*, the pins-and-needles sensation that follows temporary compression of a peripheral nerve). The general term *dysesthesia* is given to distortions (usually unpleasant) of somesthetic sensation that typically accompany partial loss of sensory innervation.

More severe pathologic processes can result in reduced or lost tactile (*e.g.*, *hypoesthesia, anesthesia*), temperature (*e.g.*, *hypothermia, athermia*), and pain sensation (*i.e.*, *hypalgesia*). *Analgesia* is the absence of pain on noxious stimulation or the relief of pain without loss of consciousness. The inability to sense pain may result in trauma, infection, and even loss of a body part or parts. Inherited insensitivity to pain may take the form of congenital indifference or congenital insensitivity to pain. In the former, transmission of nerve impulses appears normal, but the appreciation of painful stimuli at higher levels appears to be absent. In the latter, a peripheral nerve defect apparently exists such that transmission of painful nerve impulses does not result in perception of pain. Whatever the cause, persons who lack the ability to perceive pain are at constant risk of tissue damage because pain is not serving its protective function.

Allodynia (Greek *allo*, "other," and *odynia*, "painful") is the term used for the puzzling phenomenon of pain that follows a non-noxious stimulus to apparently normal skin. This term is

intended to refer to instances in which otherwise normal tissues may be abnormally innervated or may be referral sites for other loci that give rise to pain with non-noxious stimuli. It may be that an area is hypersensitive because of inflammation, injury, or another cause, and a normally subthreshold stimulus is sufficient to trigger the sensation of pain. This response is thought to be chemically mediated, possibly the result of tissue damage in the surrounding area. *Trigger points* are highly localized points on the skin or mucous membrane that can produce immediate intense pain at that site or elsewhere when stimulated by light tactile stimulation. Myofascial trigger points are foci of exquisite tenderness found in many muscles and can be responsible for pain projected to sites remote from the points of tenderness. Trigger points are widely distributed in the back of the head and neck and in the lumbar and thoracic regions. These trigger points cause reproducible myofascial pain syndromes in specific muscles. These pain syndromes are the major source of pain in clients at chronic pain treatment centers.

Special Types of Pain

Neuropathic Pain

When peripheral nerves are affected by injury or disease, it can lead to unusual and sometimes intractable sensory disturbances. These include numbness, paresthesias, and pain. Depending on the cause, few or many axons could be damaged and the condition could be unilateral or bilateral. Causes of neuropathic pain can be categorized according to the extent of peripheral nerve involvement. Conditions that can lead to pain by causing damage to peripheral nerves in a single area include nerve entrapment, nerve compression from a tumor mass, and various neuralgias (*e.g.*, trigeminal, postherpetic, and post-traumatic). Conditions that can lead to pain by causing damage to peripheral nerves in a wide area include diabetes mellitus, long-term alcohol use, hypothyroidism, renal insufficiency, and drug treatment with neurotoxic agents.[21] Injury to a nerve also can lead to a multisymptom, multisystem syndrome called *complex regional pain syndrome* (previously known as *causalgia* or *reflex sympathetic dystrophy*). Nerve damage associated with amputation is believed to be a cause of phantom limb pain.

Neuropathic pain can vary with the extent and location of disease or injury. There may be allodynia or pain that is stabbing, jabbing, burning, or shooting. The pain may be persistent or intermittent. The diagnosis depends on the mode of onset, the distribution of abnormal sensations, the quality of the pain, and other relevant medical conditions (*e.g.*, diabetes, hypothyroidism, alcohol use, rash, or trauma). Injury to peripheral nerves sometimes results in pain that persists beyond the time required for the tissues to heal. Peripheral pathologic processes (*e.g.*, neural degeneration, neuroma formation, and generation of abnormal spontaneous neural discharges from the injured sensory neuron) and neural plasticity (*i.e.*, changes in CNS function) are the primary working hypotheses to explain persistent neuropathic pain.

Treatment methods include measures aimed at restoring or preventing further nerve damage (*e.g.*, surgery to resect a tumor causing nerve compression, improving glycemic control for diabetic patients with painful neuropathies), and interventions for the palliation of pain. Although many adjuvant analgesics are used for neuropathic pain, pain control often is difficult. The initial approach in seeking adequate pain control is to try these drugs in sequence and then in combination. If there has been a poor response to the adjuvant analgesics, opioids also can be used. Nonpharmacologic therapies such as electrical stimulation of the peripheral nerve or spinal cord can be used for radiculopathies and neuralgias. As a last resort, neurolysis or neurosurgical blockade sometimes is used.

Neuralgia

Neuralgia is characterized by severe, brief, often repetitive attacks of lightning-like or throbbing pain. It occurs along the distribution of a spinal or cranial nerve and usually is precipitated by stimulation of the cutaneous region supplied by that nerve.

Trigeminal Neuralgia. Trigeminal neuralgia, or *tic douloureux*, is one of the most common and severe neuralgias. It is manifested by facial tics or grimaces and characterized by stabbing, paroxysmal attacks of pain that usually are limited to the unilateral sensory distribution of one or more branches of the trigeminal nerve, most often the maxillary or mandibular divisions. Although intermittent, the pain often is excruciating and may be triggered by light touch. The treatment of trigeminal neuralgia may include carbamazepine, an antiseizure drug, or surgery to release the vessels or scar tissue, or destroy or block branches of cranial nerve V. Other interventions include avoidance of precipitating factors (*e.g.*, stimulation of trigger spots) and eye injury caused by irritation; provision for adequate nutrition; and avoidance of social isolation.

Postherpetic Neuralgia. Postherpetic pain is pain that persists as a complication of herpes zoster or shingles. It describes the presence of pain more than 1 month after the onset of the acute attack. Postherpetic neuralgia develops in from 10% to 70% of patients with shingles[22]; the risk increases with age. The pain of postherpetic neuralgia occurs in the areas of innervation of the infected ganglia. During the acute attack of herpes zoster, the reactivated virus travels from the ganglia to the skin of the corresponding dermatomes, causing localized vesicular eruption and hyperpathia (*i.e.*, abnormally exaggerated subjective response to pain). In the acute infection, proportionately more of the large nerve fibers are destroyed. Regenerated fibers appear to have smaller diameters. Because there is a relative loss of large fibers with age, elderly persons are particularly prone to suffering because of the shift in the proportion of large- to small-diameter nerve fibers. Older patients have pain, dysesthesia, and hyperesthesia after the acute phase; these are increased by minor stimuli.

Early treatment of shingles with high doses of systemic corticosteroids and an oral antiviral drug such as acyclovir or valacyclovir, a medication that inhibits herpesvirus DNA replication, may reduce the incidence of postherpetic neuralgia. Initially, postherpetic neuralgia can be treated with a topical anesthetic agent. A tricyclic antidepressant medication may be used for pain relief. Regional nerve blockade (*i.e.*, stellate ganglion, epidural, local infiltration, or peripheral nerve block) has been used with limited success.

Complex Regional Pain Syndrome

Recently, the International Association for the Study of Pain created the terms *complex regional pain syndrome I* and *complex regional pain syndrome II*. These terms refer, respectively, to re-

flex sympathetic dystrophy and causalgia. Trauma, frequently minor, to a nerve is the major cause. However, injury to soft tissue or a broken bone also can cause these pain syndromes. The hallmark is pain and mobility problems more severe than the injury warrants. Characteristically, the pain is severe and burning with or without deep aching. Usually, the pain can be elicited with the slightest movement or touch to the affected area; it increases with repetitive stimulation; and it lasts even after the stimulation has stopped. The pain can be exacerbated by emotional upsets or any increased peripheral sympathetic nerve stimulation. The variations of complex regional pain syndromes include sympathetic components. These are characterized by vascular and trophic (*e.g.*, dystrophic or atrophic) changes to the skin, soft tissue, and bone, and can include rubor or pallor, sweating or dryness, edema (often sharply demarcated), skin atrophy, and with time, patchy osteoporosis.

According to the clinical practice guideline the cornerstone of treatment is promoting normal use of the affected part to the extent possible.[23] Initially, oral analgesics (including the adjuvant analgesics), TENS, and physical activity are used. Interruption of sympathetic innervation may considered. If treatment by sympathetic blockade provides relief from pain, sympathectomy may be considered. If not, electrical stimulation of the spinal cord or narcotics may be considered.

Phantom Limb Pain

Phantom limb pain, a type of neurologic pain, follows amputation of a limb or part of a limb. As many as 70% of those who under amputation experience phantom pain.[24] The pain often begins as sensations of tingling, heat and cold, or heaviness, followed by burning, cramping, or shooting pain. It may disappear spontaneously or persist for many years. One of the more troublesome aspects of phantom pain is that the person may experience painful sensations that were present before the amputation, such as that of a painful ulcer or bunion.

Several theories have been proposed as to the causes of phantom pain.[24] One theory is that the end of a regenerating nerve becomes trapped in the scar tissue of the amputation site. It is known that when a peripheral nerve is cut, the scar tissue that forms becomes a barrier to regenerating outgrowth of the axon. The growing axon often becomes trapped in the scar tissue, forming a tangled growth (*i.e.*, neuroma) of small-diameter axons, including primary nociceptive afferents and sympathetic efferents. It has been proposed that these afferents show increased sensitivity to innocuous mechanical stimuli and to sympathetic activity and circulating catecholamines. A related theory moves the source of phantom limb pain to the spinal cord, suggesting that the pain is caused by the spontaneous firing of spinal cord neurons that have lost their normal sensory input from the body. In this case, a closed self-exciting neuronal loop in the posterior horn of the spinal cord is postulated to send impulses to the brain, resulting in pain. Even the slightest irritation to the amputated limb area can initiate this cycle. Other theories propose that the phantom limb pain may arise in the brain. In one hypothesis, the pain is caused by changes in the flow of signals through somatosensory areas of the brain. Treatment of phantom limb pain has been accomplished by the use of sympathetic blocks, TENS of the large myelinated afferents innervating the area, hypnosis, and relaxation training.

In summary, pain may occur with or without an adequate stimulus, or it may be absent in the presence of an adequate stimulus—either of which describes a pain disorder. There may be analgesia (absence of pain), hyperalgesia (increased sensitivity to pain), hypalgesia (a decreased sensitivity to painful stimuli), hyperpathia (an unpleasant and prolonged response to pain), hyperesthesia (an abnormal increase in sensitivity to sensation), hypoesthesia (an abnormal decrease in sensitivity to sensations), paresthesia (abnormal touch sensation such as tingling or "pins and needles" in the absence of external stimuli), or allodynia (pain produced by stimuli that do not normally cause pain).

Neuropathic pain may be caused by trauma or disease of neurons in a focal area or in a more global distribution (*e.g.*, from endocrine disease or neurotoxic medications). Neuralgia is characterized by severe, brief, often repetitiously occurring attacks of lightning-like or throbbing pain that occurs along the distribution of a spinal or cranial nerve and usually is precipitated by stimulation of the cutaneous region supplied by that nerve. Trigeminal neuralgia, or tic douloureux, is one of the most common and severe neuralgias. It is manifested by facial tics or grimaces. Postherpetic neuralgia is a chronic pain that can occur after shingles, an infection of the dorsal root ganglia and corresponding areas of innervation by the herpes zoster virus. Complex regional pain syndrome is an extremely painful condition that may follow sudden and traumatic deformation of peripheral nerves. Phantom limb pain, a neurologic pain, can occur after amputation of a limb or part of a limb.

HEADACHE

Headache is a common health problem. Seventy-six percent of women and 57% of men report at least one headache a month.[25] Headache is caused by a number of conditions. Some headaches represent primary disorders, and others occur secondary to other disease conditions in which head pain is a symptom.

The most common types of primary or chronic headaches are migraine headache, tension-type headache, and cluster headache. In 1988, the International Headache Society published a proposed classification of headaches that lists diagnostic criteria for both primary headache syndromes and headaches that occur secondary to other medical conditions (see Chart 39-1 for a summary of the components of the system).[26]

Although most causes of secondary headache are benign, some are indications of serious disorders, such as meningitis, brain tumor, or cerebral aneurysm. The sudden onset of a severe, intractable headache in an otherwise healthy person is more likely related to a serious intracranial disorder, such as subarachnoid hemorrhage or meningitis, than to a chronic headache disorder. Headaches that disturb sleep, exertional headaches, and headaches accompanied by neurologic symptoms such as drowsiness, visual or limb disturbances, or altered mental status also are indicative of underlying intracranial lesions or other pathology.

CHART 39-1 Classification and Diagnostic Criteria for Headache Disorders, Cranial Neuralgias, and Facial Pain

1. Migraine
   - 1.1 Migraine without aura
   - 1.2 Migraine with aura
   - 1.3 Ophthalmoplegic migraine
   - 1.4 Retinal migraine
   - 1.5 Childhood periodic syndromes that may be precursors to or associated with migraine
   - 1.6 Complications with migraine
   - 1.7 Migrainous disorder not fulfilling above criteria
2. Tension-type headache
   - 2.1 Episodic tension-type headache
   - 2.2 Chronic tension-type headache
   - 2.3 Headache of the tension type not fulfilling the above criteria
3. Cluster headache and chronic paroxysmal hemicrania
4. Miscellaneous headaches unassociated with structural lesion
5. Headache associated with head trauma
6. Headache associated with vascular disorders
7. Headache associated with nonvascular intracranial disorders
8. Headache associated with substances or their withdrawal
9. Headache associated with noncephalic infection
10. Headache associated with metabolic disorder
11. Headache or facial pain associated with disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
12. Cranial neuralgias, nerve trunk pain, and deafferentation pain
13. Headache not classifiable

(Adapted from Oleson J. [1988]. Classification and diagnostic criteria for headache disorders, cranial neuralgias, and facial pain. *Cephalgia* 8 [Suppl 7], 13–19)

The diagnosis and classification of headaches often is difficult. It requires a comprehensive history and physical examination to exclude secondary causes. The history should include factors that precipitate headache, such as foods and food additives, missed meals, and association with the menstrual period. A careful medication history is essential because many medications can provoke or aggravate headaches. Alcohol also can cause or aggravate headache. A headache diary in which the person records his or her headaches and concurrent or antecedent events may be helpful in identifying factors that contribute to headache onset. Appropriate laboratory and imaging studies of the brain may be done to rule out secondary headaches.

Migraine Headache

Migraine headaches affect more than 10 million persons in the United States. They occur more frequently in women than men and result in considerable time lost from work and other activities.[27] Migraine headaches tend to run in families and are thought to be inherited as an autosomal dominant trait with incomplete penetrance.[25]

There are two categories of migraine headache—migraine without aura, which accounts for approximately 85% of migraines, and migraine with aura, which accounts for most of the remaining migraines. Migraine without aura is a pulsatile, throbbing, unilateral headache that typically lasts 1 to 2 days and is aggravated by routine physical activity. The headache is accompanied by nausea and vomiting, which often is disabling, and a sensitivity to light and sound. Visual disturbances occur quite commonly and consist of visual hallucinations such as stars, sparks, and flashes of light. Migraine with aura has similar symptoms, but with the addition of visual or neurologic symptoms that precede the headache. The aura usually develops over a period of 5 to 20 minutes and lasts less than an hour. Although only a small percentage of persons with migraine experience an aura before an attack, many persons without aura have prodromal symptoms, such as fatigue and irritability, that precede the attack by hours or even days.

Subtypes of migraine include ophthalmoplegic migraine, hemiplegic migraine, aphasic migraine, and retinal migraine, in which transient visual and motor deficits occur. Ophthalmoplegic migraine is characterized by diplopia, caused by a transient paralysis of the muscles that control eye movement (usually the third cranial nerve), and localized pain around the eye. Migraine headache also can present as a mixed headache, including symptoms typically associated with tension-type headache or chronic daily headache. These are called *transformed migraine* and are difficult to classify.

The mechanisms of migraine attacks are poorly understood. There is increasing evidence to support a neurogenic basis for migraine. Supporting this neurogenic concept is the common presence of premonitory symptoms before the headache begins; the presence of focal neurologic disturbances, which cannot be explained in terms of cerebral blood flow; and the numerous accompanying symptoms, including autonomic and constitutional dysfunction.[25] The pathophysiologic process of migraine probably involves alterations in serotonin function and occurrence of inflammatory disturbances in the trigeminal vascular system.[25] Hormonal variations, particularly in estrogen levels, play a role in the pattern of migraine attacks. For many women, migraine headaches coincide with their menstrual periods. The greater predominance of migraine headaches in women is thought to be related to the aggravating effect of estrogen on the migraine mechanism.[25] Dietary substances, such as monosodium glutamate, aged cheese, and chocolate, also may precipitate migraine headaches. The actual triggers for migraine are the chemicals in the food, not allergens.

The treatment of migraine headaches includes preventative and abortive nonpharmacologic and pharmacologic treatment. In 1998, the U.S. Headache Consortium, a multidisciplinary panel, produced a set of evidence-based guidelines for the nonpharmacologic and pharmacologic management and prevention of migraine headaches in primary care settings.[27]

Nonpharmacologic treatment includes the avoidance of migraine triggers, such as foods, that precipitate an attack. Many persons with migraines benefit from maintaining regular eating and sleeping habits. Measures to control stress, which also can precipitate an attack, also are important. During an attack, many persons find it helpful to retire to a quiet, darkened room until symptoms subside.

Pharmacologic treatment involves both abortive therapy for acute attacks and preventive therapy. A wide range of medications is used to treat the acute symptoms of migraine headache.[28] These include 5-HT_1 (serotonin) receptor agonists (*e.g.*, the triptans), ergotamine derivatives, analgesics (*e.g.*, acetylsalicylic acid, acetaminophen, and NSAIDs such as naproxen sodium), sedatives (*e.g.*, butalbital), and antiemetic medications. Frequent use of abortive headache medications may cause rebound headache or perpetuate chronic daily headaches.

Preventative pharmacologic treatment may be necessary if migrainous headaches are disabling or occur more than two or three times a month. In most cases, preventative treatment must be taken daily for months to years. The β-adrenergic blocking medications are usually the first choice for prophylactic treatment because of empiric support for their effectiveness, safety, efficacy, and favorable side effect profile. Several other medications that may be effective prophylactically for migraine headache are antidepressants, selective serotonin reuptake inhibitors, calcium channel blockers, antiseizure medications (*e.g.*, divalproex sodium, valproic acid), ergot derivatives (methysergide), and NSAIDs (naproxen sodium).[29] When a decision to discontinue preventive therapy is made, the medications should be gradually withdrawn.

There may be serious side effects with some of the antimigraine medications. Because of the risk of coronary vasospasm, the serotonin receptor agonists should not be given to persons with coronary artery disease. Ergotamine preparations can cause uterine contractions and should not be given to pregnant women. They also can cause vasospasm and should be used with caution in persons with peripheral vascular disease.

Migraine Headache in Children

Migraine headaches occur in children as well as adults.[30,31] Before puberty, migraine headaches are equally distributed between the sexes. The essential diagnostic criterion for migraine in children is the presence of recurrent headaches separated by pain-free periods. Diagnosis is based on at least three of the following symptoms or associated findings: abdominal pain, nausea or vomiting, throbbing headache, unilateral location, associated aura (visual, sensory, motor), relief during sleep, and a positive family history.[31] Symptoms vary widely among children, from those that interrupt activities and cause the child to seek relief in a dark environment, to those detectable only by direct questioning. A common feature of migraine in children is intense nausea and vomiting. The vomiting may be associated with abdominal pain and fever; thus, migraine may be confused with other conditions such as appendicitis. More than half of children with migraine undergo spontaneous prolonged remission after their 10th birthday. Because headaches in children can be a symptom of other, more serious disorders, including intracranial lesions, it is important that other causes of headache that require immediate treatment be excluded.

Cluster Headache

Cluster headaches are relatively uncommon headaches that affect men more often than women. These headaches tend to occur in clusters over weeks or months, followed by a long, headache-free remission period. Typically the symptoms in cluster headaches include severe, unrelenting, unilateral pain located, in order of decreasing frequency, in the orbital, retroorbital, temporal, supraorbital, and infraorbital region. The pain is of rapid onset and builds to a peak in approximately 10 to 15 minutes, lasting for 15 to 180 minutes. The pain behind the eye radiates to the ipsilateral trigeminal nerve (*e.g.*, temple, cheek, gum). The headache frequently is associated with one or more symptoms such as conjunctival redness, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema. Because of their location and associated symptoms, cluster headaches are often mistaken for sinus infections or dental problems.[25]

The underlying pathophysiologic mechanisms of cluster headaches are unknown. Hypotheses include the interplay of vascular, neurogenic, metabolic, and humoral factors. Although the trigeminovascular system appears to be involved in the pathogenesis of cluster headache, a theory to explain the symptoms, periodicity, and circadian regularity of cluster headaches does not exist. The regularity in the timing of cluster headache may be caused by dysfunction of the hypothalamic biologic clock mechanisms. Ipsilateral lacrimation, nasal stuffiness, and rhinorrhea are thought to result from parasympathetic overactivity. Pain and vasodilation are thought to result from activation of the trigeminovascular system.

Because of the relatively short duration and self-limited nature of cluster headache, oral preparations typically take too long to reach therapeutic levels. The most effective treatments are those that act quickly (*e.g.*, oxygen inhalation and subcutaneous sumatriptan). Intranasal lidocaine also may be effective.[25] Oxygen inhalation may be indicated for home use. Prophylactic medications for cluster headaches include ergotamine, verapamil, methysergide, lithium carbonate, corticosteroids, sodium valproate, and indomethacin.

Tension-type Headache

The most common type of headache is tension-type headache. Unlike migraine and cluster headaches, tension-type headache usually is not sufficiently severe that it interferes with daily activities. Tension-type headaches frequently are described as dull, aching, diffuse, nondescript headaches, occurring in a hatband distribution around the head, and not associated with nausea or vomiting or worsened by activity. They can occur infrequently or be episodic or chronic.

The exact mechanisms of tension-type headache are not known, and the hypotheses of causation are contradictory. One popular theory is that tension-type headache results from sustained tension of the muscles of the scalp and neck; however, some research has found no correlation between muscle contraction and tension-type headache. Many authorities now believe that tension-type headaches are forms of migraine headache.[25] It is thought that migraine headache may be transformed gradually into chronic tension-type headache. Tension-type headaches also may be caused by oromandibular dysfunction, psychogenic stress, anxiety, depression, and muscular stress. They also may result from overuse of analgesics or caffeine. Daily use of caffeine, whether in beverages or medications, can produce addiction, and a headache can develop in such persons who go without caffeine for several hours.[25]

Tension-type headaches often are more responsive to nonpharmacologic techniques, such as biofeedback, massage, acupuncture, relaxation, imagery, and physical therapy, than are

other types of headache. For persons with poor posture, a combination of range-of-motion exercises, relaxation, and posture improvement may be helpful.[26]

The medications of choice for acute treatment of tension-type headaches are analgesics, including acetylsalicylic acid, acetaminophen, and NSAIDs. Persons with infrequently occurring tension-type headaches usually self-medicate using over-the-counter analgesics to treat the acute pain and do not require prophylactic medication. These agents should be used cautiously because rebound headaches can develop when the medications are taken regularly.

Because the "dividing lines" between tension-type headache, migraine, and chronic daily headache often are vague, addition of medications as well as the entire range of migraine medications may be tried in refractory cases. Other medications used concomitantly with analgesics include sedatives (*e.g.*, butalbital), anxiolytics (*e.g.*, diazepam), and skeletal muscle relaxants (*e.g.*, orphenadrine). Prophylactic treatment can include antidepressants (*e.g.*, amitriptyline, doxepin).

Temporomandibular Joint Pain

A common cause of head pain is temporomandibular joint (TMJ) syndrome. It usually is caused by an imbalance in joint movement because of poor bite, bruxism (*i.e.*, teeth grinding), or joint problems such as inflammation, trauma, and degenerative changes.[32] The pain almost always is referred and commonly presents as facial muscle pain, headache, neck ache, or earache. Referred pain is aggravated by jaw function. Headache associated with this syndrome is common in adults and children and can cause chronic pain problems.

Treatment of TMJ pain is aimed at correcting the problem, and in some cases this may be difficult. The initial therapy for TMJ should be directed toward relief of pain and improvement in function. Pain relief often can be achieved with use of the NSAIDs. Muscle relaxants may be used when muscle spasm is a problem. In some cases, the selected application of heat or cold, or both, may provide relief. Referral to a dentist who is associated with a team of therapists, such as a psychologist, physical therapist, or pain specialist, may be indicated.[32]

Head pain is a common disorder that is caused by a number of conditions. Some headaches represent primary disorders and others occur secondary to another disease state in which head pain is a symptom. Primary headache disorders include migraine headache, tension-type headache, and cluster headache. Although most causes of secondary headache are benign, some are indications of serious disorders, such as meningitis, brain tumor, or cerebral aneurysm. TMJ syndrome is one of the major causes of headaches. It usually is caused by an imbalance in joint movement because of poor bite, teeth grinding, or joint problems such as inflammation, trauma, and degenerative changes.

PAIN IN CHILDREN AND OLDER ADULTS

Pain frequently is underrecognized and undertreated in both children[33,34] and the elderly.[35] In addition to the common obstacles to adequate pain management, such as concern about the effects of analgesia on respiratory status and the potential for addiction to opioids, there are additional deterrents to adequate pain management in children and the elderly. With regard to both children and the elderly, there are stereotypic beliefs that they feel less pain than do other patients.[33–36] These beliefs may affect a clinician's opinion about the need for pain control. In very young children and confused elderly, there are several additional factors. These include the extreme difficulty of assessing the location and intensity of pain in individuals who are cognitively immature or cognitively impaired, and the argument that even if they feel pain, they do not remember it.

Pain in Children

Human responsiveness to painful stimuli begins in the neonatal period and continues through the life span. Although the specific and localized behavioral reactions are less marked in the younger neonate or the more cognitively impaired individual, protective or withdrawal reflexes in response to nociceptive stimuli are clearly demonstrated. Pain pathways, cortical and subcortical centers, and neurochemical responses associated with pain transmission are developed and functional by the last trimester of pregnancy. As infants mature and children grow, their responses to pain become more complex and reflective of their maturing cognitive and developmental processes.[36] Children do feel pain and have been shown reliably and accurately to report pain at as young as 3 years of age. They also remember pain, as evidenced in studies of children with cancer, whose distress during painful procedures increases over time without intervention, and in neonates in intensive care units, who demonstrate protective withdrawal responses to a heel stick after repeated episodes.

The assessment of pain in children is somewhat complicated, but research has led to the development of a variety of developmentally appropriate measurement tools. These include scales with faces of actual children or cartoon faces that can be used to elicit a pain report from young children. In older children and adolescents, numeric scales (*i.e.*, 1 to 10) and word graphic scales (*i.e.*, "none," "a little," "most I have ever experienced") can be used. Another strategy for assessing a child's pain is to use a body outline and ask the child to indicate where the hurt is located. Particular care must be taken is assessing children's reports of pain because their report may be influenced by a variety of factors, including age, anxiety and fear levels, and parental presence.

The management of children's pain basically falls into two categories: pharmacologic and nonpharmacologic. In terms of pharmacologic interventions, many of the analgesics used in adults can be used safely and effectively in children and adolescents. However, it is critical when using specific medications to determine that the medication has been approved for use with children and that it is dosed appropriately according to the child's weight. As with any person in pain, the type of analgesic used should be matched to the type and intensity of pain; and whether the patient is a child or adult, the management of chronic pain may require a multidisciplinary team. The overriding principle in all pediatric pain management is to treat each child's pain on an individual basis and to match the analgesic agent with the cause and the level of pain. A second principle involves maintaining the balance between the level of side effects and pain relief such that pain relief is obtained with

as little opioid and sedation as possible. One strategy toward this end is to time the administration of analgesia so that a steady blood level is achieved and, as much as possible, pain is prevented. This requires that the child receive analgesia on a regular dosing schedule, not "as needed."

Nonpharmacologic strategies can be very effective in reducing the overall amount of pain and amount of analgesia used. In addition, some nonpharmacologic strategies can reduce anxiety and increase the child's level of self-control during pain. In full-term infants, ingesting 2 mL of a sucrose solution has been found to relieve the pain from a heel stick.[37] Children as young as 4 years of age can use TENS, and they can be taught to use simple distraction and relaxation and other techniques such as application of heat and cold.[38] Other nonpharmacologic techniques can be taught to the child to provide psychological preparation for a painful procedure or surgery. These include positive self-talk, imagery, play therapy, modeling, and rehearsal. The nonpharmacologic interventions must be developmentally appropriate and, if possible, the child and parent should be taught these techniques when the child is not in pain (*e.g.*, before surgery or a painful procedure) so that it is easier to practice the technique.

Pain in Older Adults

Among adults, the prevalence of pain in the general population increases with age.[35] It is estimated that from 25% to 50% of community-dwelling elders[39] and 80% of individuals in long-term care facilities report experiencing pain.[40] Research is inconsistent about whether there are age-related changes in pain perception. Some apparent age-related differences in pain may be attributable to differences in willingness to report the pain, rather altered pain perception. The elderly may be reluctant to report pain so as not to be a burden or out of fear of the diagnoses, tests, medications, or costs that may result from an attempt to diagnose or treat their pain.

The assessment of pain in the elderly may be relatively simple in a well-informed, alert, cognitively intact individual with pain from a single source and no comorbidities. In contrast it may to extraordinarily difficult to assess pain in a frail individual with severe dementia and many concurrent health problems. When possible, patient report of pain is the gold standard, but outward signs of pain should be considered as well. Accurately diagnosing pain when the individual has many health problems or some decline in cognitive function can be particularly challenging. In recent years, there has been increased awareness of the need to address issues of pain in individuals with dementia. The Assessment for Discomfort in Dementia Protocol is one example of the efforts to improve assessment and pain management in these individuals. It includes behavioral criteria for assessing pain and recommended interventions for pain. Its use has been shown to improve pain management.[35,41]

Treatment of pain in the elderly can be complicated. The elderly may have physiologic changes that affect the pharmacokinetics of medications prescribed for pain management. These changes include decreased blood flow to organs, delayed gastric motility, reduced kidney function, and decreased albumin related to poor nutrition. Physiologic changes may affect the choice of medications or dosing. In addition, the elderly often have many coexisting health problems, leading to polypharmacy. When multiple medications are being taken, there is an increased risk of drug interactions and of noncompliance because of the complexity of the treatment regimen.

In summary, children experience and remember pain, and even fairly young children are able accurately and reliably to report their pain. Recognition of this has changed the clinical practice of health professionals involved in the assessment of children's pain. Pain management in children is improving as exaggerated fears and misconceptions concerning the risks of addiction and respiratory depression in children treated with opioids also are dispelled. Pharmacologic (including opioids) and nonpharmacologic pain management interventions have been shown to be effective in children. Nonpharmacologic techniques must be based on the developmental level of the child and should be taught to both children and parents.

Pain is a common symptom in the elderly. Assessment, diagnosis, and treatment of pain in the elderly can be challenging. The elderly may be reluctant or cognitively unable to report their pain. Diagnosis and treatment can be complicated by comorbidities and age-related changes in cognitive and physiologic function.

REVIEW QUESTIONS

- Compare the tactile, thermal, and position sense modalities in terms of receptors, adequate stimuli, ascending pathways, and central integrative mechanisms.
- Describe the organization of the somatosensory system in terms of first-, second-, and third-order neurons.
- Compare the discriminative pathway with the anterolateral pathway, and explain the clinical usefulness of this distinction.
- Differentiate among the specificity, pattern, gate control, and neuromatrix theories of pain.
- State the difference between the Aδ- and C-fiber neurons in the transmission of pain information.
- Trace the transmission of pain signals with reference to the neospinothalamic, paleospinothalamic, and reticulospinal pathways, including the role of chemical mediators and factors that modulate pain transmission.
- Differentiate acute pain from chronic pain in terms of mechanisms, manifestations, and treatment.
- Describe the mechanisms of referred pain, and list the common sites of referral for cardiac and other types of visceral pain.
- Describe the cause and characteristics and treatment of neuropathic pain, trigeminal neuralgia, postherpetic neuralgia, and complex regional pain syndrome.
- Differentiate between the periodicity of occurrence and manifestations of migraine headache, cluster headache, tension-type headache, and headache caused by temporomandibular joint syndrome.
- State how the pain response may differ in children and older adults.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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