THE SOMATOSENSORY SYSTEM

I. Peripheral Nervous System

The somatosensory system consists of those components of the peripheral and central nervous systems that mediate sensations which we commonly identify as light pressure or touch of the skin, position of the limbs in space, warmth, cold or pain. The term “identify” distinguishes neural processes of which we are aware (if we are paying attention) from those which operate ‘automatically’. In clinical practice one evaluates the integrity of the former components of the nervous system by asking someone “do you feel this?”

Receptors. Somatosensory receptors are formed by the terminal processes of peripheral nerve fibers whose parent cell bodies are located in the dorsal root ganglia (Fig. 1, left). Functionally there are three types. Mechanoreceptors are activated by the displacement of tissue caused by mechanical force. Mechanoreceptors are of several different varieties according to the type of stimulus that best activates them (e.g., touch/pressure, skin stretch, vibration). Thermoreceptors are activated by non-painful warming or cooling of the skin. Nociceptors (from the word ‘noxious’) are activated by extremes of mechanical force, cold or heat that may cause actual tissue damage. Somatosensory receptors can be grouped into two major categories on the basis of their structural appearance (Fig. 1, right). Free-nerve endings: the terminal portion of the axon arborizes extensively among epithelial or connective tissue cells but is not associated with any specialized structure. Free nerve endings are found virtually everywhere in somatic and visceral tissue. Encapsulated endings: the nerve terminal is enveloped by or closely associated with specialized tissue. Examples include Pacinian corpuscles, which are sensitive to high-frequency vibratory stimuli, and Meissner’s corpuscles, which are located in the fingertips and are sensitive to light touch. The encapsulated endings are exclusively mechanoreceptive whereas the free nerve endings are thermoreceptors and/or nociceptors; some free nerve endings also function as mechanoreceptors.

![Figure 1](image_url)

**Figure 1** Left: Top: Low threshold, myelinated sensory unit (A-beta fiber) terminating in the skin as an encapsulated. Bottom: High threshold, lightly- or non-myelinated sensory unit (A-delta or C-fiber) terminating as a free nerve ending. Right: examples of receptive endings in the skin.
Receptors carry out the crucially important function of changing physical energy into a bioelectric signal. This process is called transduction. In somatic sensory receptors, the transduction sequence can be summarized as follows: stimulus > permeability change > generator current > generator potential > action potential. The generator potential is a product of the nerve terminal membrane, not the non-neural structures comprising the encapsulating tissue. It is thought that for mechanoreceptors physical deformation of the nerve terminal produces a conformational change in a membrane-spanning molecule which in turn causes an increase in membrane conductance to both Na\(^+\) and K\(^+\). This yields a net depolarization, which may lead to an action potential being produced at the first node of Ranvier. Some types of afferent fibers, called rapidly adapting, adapt quickly to a maintained deformation of the skin such that action potentials are produced only during changes in stimulus energy (for example, at the beginning and/or end of a skin indentation; Fig. 2 upper trace). Others continue to discharge in a more or less regular fashion as long as the stimulus energy is present; these are called slowly adapting (Fig. 2 lower trace). In nociceptors a chemical intermediary may be involved in the transduction process (see below).

**Figure 2** Rapidly adapting (RA) and slowly adapting (SA) sensory units display characteristic firing patterns to a sustained stimulus, e.g., skin indentation.

Peripheral nerve fibers and sensory units. The somatosensory receptors are formed by the terminals of dorsal root ganglion cells (Fig. 1, left). These are pseudo-unipolar cells having a central axon which enters the spinal cord and a peripheral axon which innervates the skin; they do not have dendrites. The peripheral processes of a single dorsal root ganglion neuron form only one kind of receptive ending. If a given fiber has several peripheral branches, each will terminate in the same type of receptive ending. A peripheral axon therefore responds to only one type of stimulus and is thus described as being modality specific (responding to only one type or modality of stimulation). A dorsal root ganglion cell, including all of its peripheral and central branches and its associated receptive ending, is called a sensory unit.

Peripheral nerve fibers differ with respect to axon diameter and degree of myelination, and hence conduction velocity. The most rapidly conducting sensory nerve fibers innervate muscle receptors, and are called A-alpha fibers; these are found in (deep) muscle nerves. In cutaneous nerves three fiber types are recognized; in decreasing order of conduction velocity, these are A-beta (30-70 m/s), A-delta (5-30 m/s) and C fibers (0.2-2 m/s). B-fibers are pre-ganglionic autonomic efferents. Experiments in which the modality property of a sensory unit is compared with its conduction velocity demonstrate that the rapidly conducting, A-beta fibers respond to small mechanical stimuli, i.e., they are low-threshold mechanoreceptors, whereas the slower conducting,
A-delta and C-fibers respond to temperature and/or pain.

Receptive fields and peripheral innervation density. The receptive field of a sensory unit is the area of skin which when stimulated evokes action potentials from it. Receptive fields of nerve fibers innervating the fingertips are smallest, those of nerve fibers innervating proximal limbs and trunk are largest (Figure 3). A given “patch” of skin is innervated by more than one afferent fiber and is therefore included in the receptive fields of more than one sensory unit. A 1 cm² region of fingertip skin is innervated by ~240 large myelinated fibers. The extent of overlap among receptive fields of different sensory units is least where receptive fields are smallest. Also, there are more sensory nerve fibers per surface area of skin in the fingertips than in more proximal areas. In other words, the receptive fields of individual sensory units are smallest and the overlap among receptive fields of different sensory units is least in skin areas having the greatest peripheral innervation density.

This relationship suggests that the ability to resolve detail in a textured surface should be especially good in the fingertips, much as a fine-grained video screen yields a particularly sharp image. One measure of our tactile acuity is the two-point discrimination threshold. To determine this a compass, or other object having two fine tips whose distance is adjustable, is lightly applied to the skin surface. The subject then says whether he/she perceives this stimulus as one or two separate points, and the spacing between the points is gradually reduced until only a single point is perceived. If the smallest distance between two separately perceived points is small, the measured threshold is low. Two-point discrimination thresholds are lowest on the lips, fingertips and toes and highest on the proximal leg, shoulder and back.

Stimulus coding. Peripheral nerve fibers can encode the nature of the peripheral stimulus in several ways (Figure 4). 1) The type of stimulus to which the receptor responds indicates stimulus quality, e.g., activity in Pacinian corpuscles signals the presence of a high-frequency vibratory stimulus. 2) A second code is temporal pattern. Rapidly adapting receptors can indicate stimulus onset, and sometimes stimulus offset, by responding to stimulus transients; slowly adapting receptors encode stimulus duration by firing throughout the stimulus period. Temporal coding also signals features of a time varying stimulus. For example, Pacinian corpuscles will fire one-for-one with each cycle of a vibratory stimulus. 3) A third means of encoding is threshold; a given receptor may fire only when the skin is indented a certain amount and/or at a certain velocity. 4) Yet another is a frequency code; a given fiber will discharge an increasing number of action potentials/sec with increasing stimulus intensity. Finally (5), a primary afferent fiber encodes location by discharging action potentials only when a stimulus is present within its receptive field. Responses are most vigorous when the stimulus is presented to the center of the receptive field (Figure 4, right).
In addition to their characteristic adaptation rates, different types of low threshold
mechanoreceptors have different thresholds and mechanical coupling to the skin (Fig. 1, right).
Meissner’s corpuscles and Merkel cells are located superficially in the skin, just deep to the
epidermis. Meissner’s corpuscles (rapidly adapting) have low mechanical thresholds and, in the
fingertip, are coupled to the edges of the papillary ridges; they are thus especially sensitive to small
movements of the skin, such as those produced by rubbing the fingertip across a textured surface or
sensing micro-slippage of an object gripped by the fingers. Merkel cells (slowly adapting) have
somewhat higher mechanical thresholds and, in the fingertip, are located directly beneath the center
of the papillary ridge. Small, steady indentations, e.g., produced by a small diameter probe, evoke
more spikes than larger indentations of the same force, e.g., produced by a flat or gently rounded
probe. Populations of nearby Merkel cells are thus well-suited for encoding shapes of small objects
pressed into the fingertip, like dots on a Braille letter. Pacinian corpuscles (RA) and Ruffini endings
(SA), located deeper within the dermis, are coupled to broad expanses of skin; they best signal
vibration (as when the hand grasps and releases a large object - like a block or ball) and skin stretch
(object shape), respectively.

II. Spinal Cord Pathways

In the peripheral nervous system there is a dichotomy between large, rapidly conducting
fibers that carry information from low-threshold mechanoreceptive endings and small, slowly
conducting fibers that are activated by thermal and noxious stimuli. As the central processes of
dorsal root ganglion cells enter the spinal cord, these two types of axons follow different courses
(Figs. 5). The central process of an A-beta fiber may 1) turn at right angles and ascend the spinal
white matter in the posterior columns on the same side, 2) ascend the posterior columns and also
distribute a collateral branch to the gray matter at its segment of entry or 3) terminate in the spinal
gray matter only. The small myelinated and unmyelinated A-delta and C fibers synapse on cells in
the spinal gray matter, mainly at or near their entry level; some axons however ascend or descend to
other spinal cord levels via the tract of Lissauer (located in the spinal white matter near the dorsal
root entry zone. Axons of some spinal cord cells that receive synapses from A-delta and C fibers decussate (or cross) to the other side in the anterior white commissure and ascend the spinal cord white matter as the spinothalamic (or anterolateral) system.

Thus pain and temperature information from the right side of the body ascends the spinal cord on the left side of the spinal cord. A fundamental point is that pain and temperature information ascends in the spinal cord on the side opposite from that of discriminative light touch and limb position sense. Unlike the posterior columns, the spinothalamic tract involves at least one synapse within the spinal cord itself.

The posterior columns can be damaged by direct trauma, by occlusion of the posterior spinal arteries, and by degenerative disorders. Lesions or disease states of the posterior columns yield sensory deficits that are characteristic of the loss of A-beta fiber inputs to the brain. Deficits include difficulty in the discriminative aspects of light touch, e.g., loss of vibration sense, elevated thresholds for two-point discrimination. Information about limb position is derived from cutaneous receptors that respond to skin stretch and from joint receptors that encode the amount of rotation of a limb about the joint. Damage to the posterior columns can thus lead also to loss of limb position sense (proprioceptive loss). Lesion-induced deficits are on the same side of the body as the lesion; they are described as being ipsilateral to the site of the lesion. Because the central processes of dorsal root ganglion cells that enter the spinal cord rostral to the lesion are not affected, the deficit is observed only on body regions at and below the level of the lesion. Pain and temperature sensations may be completely normal.

Damage to proprioceptive A-beta fibers can cause abnormal motor function, too. A patient with posterior column disease may have difficulty in standing, especially with eyes closed, and in walking in a coordinated fashion. In this case the sensory contribution to the motor deficit is the absence of proprioceptive information that is required by central brain regions for muscle
coordination (cerebellum).

**Spinothalamic or anterolateral system.** Recall that pain and temperature information ascends the spinal cord in the anterolateral white matter on the side of the spinal cord opposite to the site on the body where the stimulus is present. A-delta and C fibers in the peripheral nerve synapse in the spinal cord dorsal horn near or within a few segments of their level of entry through the dorsal root. The axons of the second-order cells cross the midline in the anterior white commissure and during the decussation they ascend one or two segments. Damage to the spinothalamic tract causes loss of pain and temperature sensation on the contralateral side of the body. The deficit occurs on the body slightly below the level of the lesion and extends caudally. Because discriminative touch and pain/temperature from the same side of the body ascend on opposite sides of the spinal cord, hemisection of the right side of the spinal cord will cause loss of discriminative touch on the right side of the body and loss of pain and temperature sensibility on the left side.

The anterior white commissure contains axons that cross from right to left as well as from left to right! Thus damage to these fibers yields bilateral deficits in pain and temperature sensibility. **Syringomyelia** is a degenerative disease that begins around the central canal, occurring most often at cervical levels. Patients would be likely to experience a progressive loss of pain and temperature sensation on both arms; these sensations on the rest of the body would be normal, provided that the lesion did not extend laterally into the anterolateral white matter. A large lesion might also damage anterior horn motor neurons, the spinothalamic tract and possibly the lateral corticospinal tract. Similar symptoms, but having acute onset, could follow occlusion of the anterior spinal artery.

**The Trigeminal System.** In the face, as in the body, large myelinated nerve fibers (A-beta) subserve discriminative touch and proprioception (for the jaw) whereas the smaller caliber A-delta and C fibers mediate pain and temperature sensibility. Sensory innervation of the head and face is supplied by peripheral nerves in cranial nerves 5,7,9 and 10. Largest among these is the trigeminal nerve, whose parent cell bodies lie in the trigeminal ganglion, a structure analogous to a dorsal root ganglion. The central processes of trigeminal ganglion cells terminate in the principal sensory nucleus of the pons and/or (by axon collaterals) in the spinal trigeminal nucleus. The latter extends throughout the medulla into the upper cervical spinal cord where it merges with the substantia gelatinosa. To reach it the central processes of the ganglion cells descend in the spinal trigeminal tract. A-beta fibers synapse on second-order neurons in the principal sensory nucleus and/or in the spinal trigeminal nucleus; A-delta and C fibers synapse in the spinal trigeminal nucleus but not in the principal sensory nucleus.

Therefore, 1: the principal sensory nucleus is to the face as the gracile (cuneate) nucleus is to the leg (arm), and 2: the spinal trigeminal nucleus is to the face as the dorsal horn of the spinal cord is to the body. Be sure you understand why these two analogies are both anatomically and functionally correct! Clinically, damage to the principal sensory nucleus yields deficits in discriminative touch whereas damage to the spinal trigeminal nucleus produces loss of pain and temperature. In both cases, the deficit is ipsilateral to the site of the lesion. Surgical transection of the spinal trigeminal tract (trigeminal tractotomy) is sometimes performed to alleviate intractable facial pain.
III. The Posterior Column/Medial Lemniscus System

Somatosensory information that reaches the cortical hemispheres, and hence consciousness, does so by way of a `chain' of neurons (Fig. 6). The axons of dorsal root ganglion cells ascend the spinal cord in the posterior columns and make the system’s first synapse in the gracile and cuneate nuclei of the brainstem. These second-order cells have axons that cross the midline and ascend to the ventral posterior thalamus via the medial lemniscus. From there, the third-order thalamic neurons project to the cerebral cortex via the internal capsule.

![Anatomical organization of the posterior-column medial lemniscus system](image)

**Figure 6** Anatomical organization of the posterior-column medial lemniscus system. Note that the first synapse occurs in the brainstem (gracile and cuneate nuclei for leg and arm; principal sensory nucleus for the face). Axons of the second-order cells than cross the midline and project to the ventral posterior nucleus.

**Somatotopic organization.** At each synaptic station, cells are organized into a somatotopic map wherein adjacent regions of skin are represented by adjacent neurons or small groups of neurons. The resulting map is called a homunculus (little man; Fig. 7). Within these maps there is a disproportionately large volume of tissue devoted to processing information from the fingertips and toes. Thus the somatopic map is distorted, reflecting the peripheral innervation density of a particular skin area, not its geometric size.
Figure 7 Example body maps in the posterior column/medial lemniscus system illustrating distortions of the central representation in different species. A large volume of neural tissue devoted to a given skin region reflects greater peripheral innervation density of the afferent fibers (more sensory units per unit of skin area). Regions of high peripheral innervation density are associated with greater tactile acuity.

Modality specificity. Like the A-beta sensory units, central neurons in the posterior column/medial lemniscus system are modality specific. There is also an anatomical segregation of neurons of different functional types. For example, proprioceptive cells responding to deep pressure or joint rotation tend to cluster together in patches separate from small clusters of cells responding to light touch of the skin.

Spatial and temporal integration. At each central synaptic station there are relay cells, whose long-projecting axons transmit information to the next level of processing, and inhibitory or excitatory interneurons, whose axons ramify locally, contacting relay cells and other interneurons (Fig. 8, left). Thus, a cell’s receptive field has both excitatory and inhibitory components. Inhibition can be observed in single cells as a diminution or abolition of their stimulus-evoked excitatory activity by preceding or concurrent stimulation of an adjacent region of skin. A neuron's receptive field can be thus described as displaying lateral (or surround) inhibition whereby it has an excitatory “center” and an inhibitory “surround”. For example, the left-most skin probe in Figure 8 (left) can evoke disynaptic inhibition in the center cuneate nucleus neuron via a local inhibitory interneuron. Inhibition produced in the cuneate nucleus neuron prevents it from firing, enhancing the difference in activity levels produced initially in the Abeta dorsal root ganglion cells (i.e., three spikes vs one spike in peripheral neurons becomes three spikes vs no spikes in the cuneate nucleus neurons). Surround inhibition first appears at the level of the dorsal column nuclei in caudal medulla. Stimulation of two nearby skin points, as in the two-point discrimination test, evokes within the somatotopic map two foci of excitatory activity separated by a focus of reduced (inhibited) activity. Also, since cells in the brainstem and thalamus receive (descending) synaptic inputs from the postcentral gyrus, the cerebral cortex can modify the sensory signal that it will eventually receive.
In the posterior column/medial lemniscus system afferent inhibition has an important temporal component. The decay time constants of EPSP’s are on the order of milliseconds, whereas IPSP’s decay over several 10's of msec (Fig. 8, right). One effect is to limit excitatory activity to a short period of time following a stimulus. Such focusing of activity in time is undoubtedly important for discriminating objects by active touch, for example “reading” the bumps and valleys on Braille letters. Indeed the processing of tactile information in the temporal domain may be the hallmark of posterior column/medial lemniscus function. A sensitive clinical test for posterior column function is the use of spatiotemporally patterned stimuli, e.g., movement of a cotton-tipped swab across the skin.

The afferent inputs to the posterior column/medial lemniscus system are the rapidly conducting A-beta fibers. Moreover, only three synapses intervene between the peripheral receptors and cortical neurons (one each in the brainstem, thalamus and cortical layer IV). Afferent information reaches the cortex with a delay of only 20-30 msec! The posterior columns can therefore provide the rapidly updated sensory information that is necessary for the planning and execution of ongoing skilled movements.
Somatosensory Cortex. The representation of the face and body in the postcentral gyrus is called the primary or first somatosensory cortex (SI) (Fig. 9, left). Cells there have relatively small, well-defined receptive fields but these are somewhat larger than those at lower levels of the afferent system. Cortical neurons are modality specific and, as in the brainstem and thalamus, they are grouped together according to functional type (Fig. 9, right).

The principle of grouping in the cortex is called functional columnar organization. As illustrated in Figure 10, within a vertically oriented region of tissue from pia to white matter all neurons 1. have similar or overlapping receptive fields, 2. are of the same modality, and 3. respond to a peripheral stimulus with relatively short, though not identical, latencies. (“Cells of a feather columnate together”). The functional properties of neurons often change abruptly at horizontal intervals of 0.500-1.00 mm. Connections among cells within a column make microcircuits that process and transform information. For example, some cortical neurons respond selectively to a stimulus moving in a particular direction across the skin surface, a property not observed at lower levels, e.g., thalamus.

**Figure 9** Left: the cerebral cortex contains several distinct somatosensory representations in the parietal lobe. Regions of the insula and temporal lobes also receive somatosensory input. Right: cytoarchitecture and function of different body maps within the postcentral gyrus (CS denotes central sulcus; anterior is to the left).

**Figure 10** Functional columnar organization. Left: Receptive fields (RFs) encountered in two vertical microelectrode penetrations through the hand representation. RFs vary in size and location but within a penetration all have a common intersection on the skin. Right: Movement of the electrode across the cortical surface encounters groups of vertically aligned neurons having common RF properties that change at ~.5 to 1.0 mm steps. Electrodes 1 and 2 correspond to tracks 1 and 2 at left.
A column is a functional unit of information processing. Indeed, the cortex appears to be organized according to a principle of division of labor on both macro- and microscopic scales. In the case of cortical columns each small region of cortex contains neuronal machinery for analyzing a small part of the sensory world. On a larger scale, many columns are organized to make a map of the sensory periphery, and there are multiple interconnected somatosensory maps within parietal cortex, each performing somewhat different, but highly related tasks. The primate postcentral gyrus itself is now known to contain at least four such maps, two of which respond to stimulation of the skin surface, the other two responding to stimulation of deep tissues, including muscles and joints. Other regions of parietal cortex also contain body maps of one sort or another, and there may be as many as 10 or more somatosensory maps within each cortical hemisphere. How these maps interact to produce in us a perception of a unified body surface is not yet understood.

In humans, lesions of posterior parietal cortex, particularly in the right (non-language) hemisphere, can produce a syndrome known as sensory neglect. Patients have difficulty recognizing and using the left side of their body and attending to the left side of their world. Electrophysiological studies of single neurons in behaving monkeys have shown that cells in posterior parietal cortex are maximally active when the stimulus occurs in the context of an attended task. Parietal association cortex thus appears to be more involved with constructing a unified perception of the individual’s world or extrapersonal space than with overseeing the more “mundane” details of tactile discrimination. The concept of extrapersonal space, and the important role of parietal cortex in defining it, can be appreciated by considering a blind person with a cane. Using information provided by mechanoreceptors in the hand and by proprioceptors in the arm, the individual can construct a sufficiently accurate internal representation or “map” of the world to permit him to get on a bus in Squirrel Hill and find his way to work in a particular building, in a particular room, at a particular desk. A more common experience is the use of tools. We are aware of the pencil’s point or the end of the screwdriver’s blade, not the subtle gradients of pressure on our index fingers or hand where the tool actually contacts the skin surface. Nevertheless, it is precisely these subtle patterns of neural activity, established first in the A-beta sensory units and ultimately interpreted by posterior parietal cortex, that underlie this remarkably human behavior.

IV. Pain and The Anterolateral System

Imagine striking your thumb with a hammer, i.e., a frequent, unintended use of tools! The immediate sensation is one of painful contact followed by a longer-lasting discomfort often described as a burning sensation. A typical response is to rub or shake vigorously the hand, odd behavior that nonetheless makes your thumb feel better. Subsequently, the skin on the thumb becomes inflamed and often the inflammation spreads to adjacent regions of skin that were not specifically contacted by the hammer. The thumb becomes abnormally sensitive so that for periods up to several hours even gentle touching of the affected area hurts.

Peripheral nerves. In considering the neural bases for these phenomenon, we need first to return to peripheral nerves. Recall that different classes of sensory units conduct action potentials at particular velocities depending on the diameter of the axon and the presence or degree of
myelination. Peripheral nerves are differentially sensitive to asphyxia produced by a cuff around the arm. Conduction fails first in A-beta fibers, followed by A-delta and then C-fibers. Experiments in human volunteers have shown that well-localized 'fast' pain is mediated by A-delta fibers whereas slower, more persistent and unpleasant pain is mediated by C-fibers. Reverse sequences of conduction block and sensory deficits can be produced by local anesthetics.

A-delta and C-fibers terminate in the skin as free nerve endings, and those that respond to painful stimuli are called nociceptors. (Note: some A-delta fibers respond to innocuous warming or cooling of the skin; these are non-nociceptive). A-delta nociceptors respond to extremely high intensity mechanical stimulation or extreme heat (tissue-damaging stimuli). C-fibers, on the other hand, can respond to moderately intense mechanical, thermal or chemical stimuli as well as to very intense stimuli; because they are activated by several different stimulus modalities (mechanical, thermal, chemical), these receptors are called polymodal nociceptors. Some polymodal C-fibers respond with increasing rates of discharge to increasingly intense stimuli. Interestingly, following tissue damage the background discharge rates of C-fibers increase and remain elevated for several hours; during this period, a low intensity stimulus will evoke more action potentials than it did prior to the insult. These findings parallel behavioral observations that an injured area of skin is associated with a prolonged, burning type of pain and that even gentle touching of the affected area can be painful.

Transduction. Transduction in nociceptors is thought to involve a chemical intermediary. The evidence for this is that injection of extracts from damaged skin, e.g. blister fluid, is very painful, as is injection of some known neurotransmitters (acetylcholine, serotonin), peptides that are thought to act as neurotransmitters and that are present in C-fibers (bradykinin, substance P), and solutions high in potassium. Tissue damage itself causes elevations in extracellular $K^+$ . Tissue-damaging stimuli are thought to cause a release of a chemical substance from the damaged tissue which binds to the nerve terminal membrane, leading to permeability change, generator current, generator potential and action potential.

The nerve terminal itself releases a chemical involved in the pain response (Fig. 11). Tissue damage leads to the release of peptides from nociceptive sensory endings that causes release of histamine from mast cells, thereby sensitizing nerve terminal endings. Release of peptides by the nerve terminals also contributes to the local reddening of damaged skin which extends beyond the actual site of tissue damage. This vasodilation is prevented by nerve section and subsequent degeneration of the peripheral nerves. The findings suggest that action potentials generated in one branch of a nociceptive axon are conducted antidromically into other peripheral branches of the same axon where they invade the terminal endings and evoke a vasomotor response; this is called the axon reflex. Prostaglandins are synthesized and released by damaged cells and may sensitize nociceptors and exacerbate the local inflammation. Commonly used analgesics such as aspirin and acetaminophen inhibit the biosynthesis and release of prostaglandins.
There is increasing recognition that peripheral nerves contain many 'silent' nociceptors. These afferent fibers do not respond to acute noxious mechanical or thermal stimuli but become responsive after long-term exposure to painful stimuli, e.g., chronic pain. The emergence of stimulus-evoked responsiveness in C-fibers has been observed in experimental models of arthritis and bladder irritation. The recruitment of a previously unresponsive population of afferent fibers with connections to pain processing centers in the spinal cord could mediate symptoms of chronic pain that develop after prolonged tissue inflammation or irritation.

Visceral Pain: Peripheral axons subserving pain in the viscera are A-delta and C fibers whose parent cell bodies reside in dorsal root ganglia. These axons course to the periphery via autonomic nerves. The innervation density of viscera is less than that of skin. Nevertheless, visceral tissues are sensitive to noxious stimuli, such as excessive distention of the gut or bladder or inflammation from infection. Frequently, pain arising from visceral organs is perceived as if it is arising from a distant site on the skin surface. This inaccurately localized pain is called referred pain; it is 'referred' to skin areas innervated by the same dermatome as the affected visceral organ. A well-known example is cardiac pain, which is often felt as if it is occurring on the inner aspect of the left arm. Interestingly, referred pain can sometimes be alleviated by local anesthetics applied to the reference site on the skin. The mechanism responsible for referred pain is not known with certainty but is probably due to convergence of visceral and somatic pain fibers in the dorsal horn of the spinal cord.

Posterior Horn of the Spinal Cord. The central processes of A-delta and C fibers enter the spinal cord and terminate in the gray matter at the segment of entry (Fig. 12); they also send collaterals to other spinal segments via the tract of Lissauer. A-beta (and A-alpha) fibers also synapse in the posterior horn as do axons descending from the brainstem reticular formation. The posterior horn is comprised of three major somatosensory-related nuclei (Fig. 12). The posteromarginal zone (nucleus) comprises the outermost margin of the posterior horn and contains
neurons whose axons project rostrally via the anterolateral white matter. An important cell grouping, called the substantia gelatinosa, is located just deep to the posteromarginal zone and contains mostly local interneurons (most of which are inhibitory). These cells receive synaptic contacts from cells located at other spinal levels and from brainstem neurons via reticulospinal pathways. They also receive inputs from nociceptive and non-nociceptive primary afferent fibers. Because of the diversity of their inputs, their local axonal projections and their inhibitory effects on other neurons, substantia gelatinosa cells are strategically placed to influence the nature of the pain signals that are sent from the spinal cord to higher centers in the brainstem and thalamus. This may account, in part, for why vigorously shaking an injured thumb, a behavior that strongly activates A-beta fibers, provides some amelioration of the pain. A third main nucleus, located near the base of the posterior horn and called nucleus proprius, contains neurons that also project more rostrally, via the anterolateral white matter.

Figure 12 Simplified diagram of posterior horn of spinal cord. The outermost cells in the gray matter (posteromarginal zone) receive inputs from nociceptive A-delta and C-fibers (a C-fiber input is not shown here). Cells in the nucleus proprius, located near the base of the posterior horn) have dendrites that extend towards the apex of the posterior horn; these dendrites receive excitatory inputs from A-beta, A-delta and C-fibers and inhibitory inputs from interneurons in the substantia gelatinosa (S.G.) Both posteromarginal zone and nucleus proprius cells send axons across the midline to ascend in the anterolateral white matter contralateral to site of the peripheral (skin or viscera) stimulus.

Some projection neurons (spinothalamic tract cells) are exclusively nociceptive, receiving inputs only from A-delta and C fibers. Most of these arise from the posteromarginal zone, the outermost layer of the gray matter. By contrast, other cells are multimodal, responding to light touch (from A-beta fibers), innocuous heating or cooling (A-delta fibers) and to noxious chemical, thermal and mechanical stimulation (A-delta and C fibers). Because these cells respond to stimuli over a broad range of stimulus intensities, they are called wide dynamic range cells. The cell bodies of these cells are in nucleus proprius, located at the base of the dorsal horn. In addition to convergence of modality information, there is convergence of place information so that many wide dynamic range cells also have large, and sometimes bilateral, cutaneous receptive fields. Such cells can also respond to visceral stimulation, providing a potential mechanism for the phenomenon of referred pain.
In the presence of severe and continuing tissue injury, cells in the dorsal horn become progressively more excitable and responsive to nociceptive stimuli, a phenomenon called ‘wind-up’. C-fibers use glutamate as a neurotransmitter at their central synapses. Because ‘wind-up’ can be prevented by NMDA-receptor blockade, central sensitization of pain circuits in the spinal cord are thought to be due to strengthening of the C-fiber synapse via NMDA receptors. It has been found that supplementing general anesthesia with direct spinal application of local anesthetics can ameliorate post-operative pain following surgery. The local anesthetic presumably prevents engagement of spinal circuitry by nociceptive inputs, thereby avoiding central sensitization.

The Anterolateral System. As a population, dorsal horn neurons whose axons travel through the anterolateral white matter project to many regions of the brainstem and diencephalon, not just the thalamus. Some dorsal horn neurons do project to the thalamus, that is, they comprise a true spinothalamic tract (Fig. 13). Spinothalamic axons that terminate in the ventral posterior nucleus are nociceptive, end in topographically appropriate parts of the nucleus and have relatively small receptive fields. Their terminations are segregated from those of medial lemniscus axons, preserving modality separation in VP.

Figure 13 Anatomical organization of the anterolateral system. Ascending tracts include the spinothalamic tract, which involves only one synapse from periphery to thalamus, and the spinoreticuloencephalic pathway, which is polysynaptic and projects to many regions of the brainstem and diencephalon. Note how the topographic organization of the spinothalamic tract (leg, lateral; arm medial) matches that of the medial lemniscus (Figure 6).

Most axons in the anterolateral white matter project to the brainstem reticular formation of the medulla, pons and mesencephalon and to the superior colliculus. From the brainstem pain
information projects to the diencephalon either directly or indirectly via synaptic relays in the pons and mesencephalon. Projection sites in the diencephalon include thalamic nuclei other than VP (some of which in turn project widely throughout the cortex) and the hypothalamus, thus providing nociceptive inputs to the limbic system, which is involved in emotional reactivity. The overall pathway is thus called a spino-reticulo-diencephalic pathway (Fig. 13, 14, left).

It is thought that the faster, more somatotopically precise spinothalamic projection to the ventral posterior thalamus mediates sensations of pricking pain, which rise to consciousness quickly and which can be well localized. The slower, polysynaptic and more anatomically diffuse spino-reticulo-diencephalic pathway is known to be strongly activated by C-fiber stimulation and is thought to mediate slow, burning pain and the emotions of anxiety and suffering that may accompany it. Pain and temperature sensation for the face is mediated by pathways originating in the spinal trigeminal nucleus.

The role of the cerebral cortex in pain perception is poorly understood. Some clinical studies

Figure 13 Descending control of pain transmission in the posterior horn. Left: Overview of anterolateral system and descending pathways (dashed line) from the brainstem to the spinal cord. Right: simplified circuitry in the posterior horn (see Fig. 12). A serotonergic axon from the brainstem reticular formation excites a local inhibitory interneuron in the substantia gelatinosa that uses an endogenous opiate-like compound (Enk: enkephalin) as a transmitter. The interneuron makes inhibitory synapses on the dendrite of a nucleus proprius cell and also a presynaptic inhibitory synapse on a substance-P containing C-fiber. Nociceptive signals in the wide dynamic range spinothalamic cell of the nucleus proprius can be suppressed while preserving signals arising from low-threshold, e.g., touch, pressure, A-beta fibers.
report diminished pain sensibility after lesions of parietal cortex. Interestingly, lesions of prefrontal cortex or of the cingulate gyrus can produce a condition in which patients are aware of the occurrence of painful sensations but are not bothered by them. Thus, neural substrates underlying the perception of pain differ from those underlying behavioral or psychological responses to it.

The posterior thalamus is the first common site of termination for cells of the posterior column/medial lemniscus system and for cells of the spinothalamic system. Lesions here, due for example to occlusion of the posterior cerebral artery or some of its branches, may produce a complete absence of somatic sensation on the contralateral body. Such lesions can also produce a quite different phenomenon called the thalamic pain syndrome. This is a tragic and horrifying situation in which even gentle tactile stimulation elicits severe pain, a condition called hyperpathia. The thalamic pain syndrome is one example of neurogenic pain, which is pain experienced in the absence of any obvious peripheral source of nociceptive activity. Another example is phantom limb pain; in this syndrome patients experience pain within a limb that has been previously amputated.

Neurogenic pain is difficult to alleviate surgically or pharmacologically. These types of unusual pain syndromes suggest a disruption of a normal balance of activity between the posterior column/medial lemniscus and the spinothalamic systems. This is suggested further by findings that electrical stimulation of the posterior columns can sometimes alleviate pain. Also, stimulation of large myelinated afferent fibers by vibrating needles may underlie analgesic effects that reportedly occur with acupuncture. Central pain syndromes may also reflect pathology of descending pain control systems.

Descending Pain Control Systems. The brainstem reticular formation is involved in many functions that regulate, among other things, arousal and consciousness. Neurons may receive inputs from multiple sensory modalities, e.g., auditory, somatic, visual, and project rostrally to thalamic nuclei, e.g. intralaminar nuclei, that project to widespread regions of the cerebral cortex and are thought to control overall cortical excitability. Regions of the brainstem reticular formation also project to the spinal cord where they can selectively suppress nociceptive-evoked activity in spinal cord neurons. The effects are mediated by reticulospinal neurons that project to the dorsal horn via the dorsolateral funiculus of the spinal cord and that use serotonin as their neurotransmitter (Fig. 14, right). Since these same brainstem regions receive afferent input from spinoreticular cells by way of the anterolateral system, the circuit can function as a negative feedback system. Electrical stimulation of the brainstem reticular formation, particularly the grey matter surrounding the cerebral aqueduct in the mesencephalon, produces analgesia in experimental animals and in human patients. Sites of stimulus-produced analgesia are co-extensive with regions that have a high binding affinity for opiates such as morphine, and injection of opiates into these areas also produces analgesia. Both stimulus-produced analgesia and opiate-produced analgesia are blocked by systemic injection of naloxone. Descending control of pain perception is thought to involve the release of opiates by substantia gelatinosa neurons which, when excited by serotonergic reticulospinal fibers, produce presynaptic inhibition at the central terminals of A-delta and C-fibers. Both opioid and non-opioid systems are thought to be involved with stress-induced analgesia, an elevation of perceptual pain thresholds that sometimes accompanies severe environmental conditions.