The University of Western Ontario - Neuroscience 9500

Notes for lecture by J. A. Kiernan (Department of Anatomy & Cell Biology)

The lecture begins with an introduction to the methods used to discover neuronal connectivity in functional systems within the brain and spinal cord. The pathways for general somatic sensation are then presented as examples of functional systems.

(A.) Neuroanatomical research methods

Summary

Exact information about connections between groups of neurons can be obtained only from experimental studies in animals.

The distribution of fragments of degenerating axons can provide evidence for the former existence of neuronal connections in the injured or diseased brain or spinal cord.

Investigations of neuronal activities, such as axonal transport and glucose or oxygen metabolism, are widely used in the study of connectivity and function in the central nervous system. Tracer substances may be transported anterogradely or retrogradely along axons, and their distributions can be correlated with information obtained about neurotransmitters and their actions upon postsynaptic cells. Certain viruses spread within neurons and across synapses, and these are used to identify chains of functionally connected neurons.

Most of the gross anatomical features of the nervous system were described centuries ago, and during the last two centuries, clinical investigators have been correlating disordered function with abnormalities found in different parts of the brain. Normal functions are deduced from the effects of destructive lesions. Experimentation with animals provides more precise information about the ways in which populations of neurons are interconnected. If the same connections are seen in a variety of mammalian species it is reasonable to suspect that the human nervous system is similarly organized.

Methods for investigating neural pathways and functions

Clinico-pathological correlations and functional imaging techniques show which parts of the brain and spinal cord are used for particular purposes, but they do not provide much information about the ways in which neurons, with their long axons, communicate between different parts of the nervous system.

In histological material from normal animals, it is seldom possible to follow an individual axon from its cell body of origin to the distant site in which it terminates. The small diameters and curved trajectories of axons, together with the fact that different pathways commonly occupy the

same territory, make the direct tracing of most connections impossible. It is, therefore, necessary to use experimental methods to determine the connectivity of the many groups of neurons in the brain and spinal cord. Results obtained in laboratory animals, especially the cat and monkey, may be applicable to the human brain. This transfer of data from animals to humans is usually justifiable when there are no major differences between the connections found in diverse groups of animals; a pathway present in rats, dogs, and monkeys is likely to occur also in humans. When variation among species is found, it is hoped that neuroanatomical information gained from primates, such as monkeys, will be helpful with respect to the human brain. Sometimes injury and disease in the human nervous system can cause degeneration of particular tracts of axons. Postmortem examination of the degenerated fibers provides valuable information about normal human neural connections.

Neuroanatomical methods based on degeneration

Until the introduction of methods based on axoplasmic transport, fiber tracts were traced by staining fibers undergoing wallerian degeneration after the placement of a destructive lesion at a selected site in the central nervous system of an animal. Although now largely of historical interest, such methods have contributed importantly to neuroanatomical knowledge.

The changes in neuronal cell bodies that follow axotomy (chromatolysis etc) have served to identify the sources of some tracts of fibers, but this approach is of limited value because many neurons fail to exhibit the changes. Axonal degeneration distal to a site of transection can be more reliably demonstrated.

The oldest staining method for anterograde degeneration is the **Marchi technique**, which depends on the staining of particles of degenerating myelin with osmium tetroxide in the presence of an oxidizing agent. The latter suppresses the staining of normal myelin, so that degenerating fibers appear as lines of black dots on a lighter background. The course of a tract can be followed in sections taken at appropriate intervals. The Marchi technique does not show the unmyelinated terminal branches of the degenerating axons, but it can nevertheless give useful results when applied to human postmortem material. There are several **Silver methods** for showing degenerating unmyelinated axons and synaptic terminals. Silver methods, which were much used for laboratory animals until about 1975, are not suited to the human nervous system because the degenerating axons are demonstrable only during a critical period of 4 to 8 days after placement of a lesion.

Degenerating axonal terminals can also be recognized in **electron micrographs**. When the general area of projection of a group of neurons or of a tract is known from light microscopy, the exact mode of termination of the fibers on the dendrites, somata, or axons of the postsynaptic cells may be determined. As with silver degeneration methods, electron microscopy usually cannot be applied to human material because the time of survival and the conditions of fixation of the tissue are critical.

Neuroanatomical methods based on axoplasmic transport

Research methods based on degenerating axons were replaced in the 1970s by much more sensitive techniques that reveal both the cells of origin and the sites of termination of axons. The results of the extensive use of methods based on axoplasmic transport have necessitated

substantial revisions of earlier accounts of neuronal connections in the central nervous system.

In the **autoradiographic method**, a small volume of a radioactively labeled amino acid solution, commonly [^{3}H]leucine, is injected into the region that contains the cell bodies of the neurons being investigated. The amino acid is taken up by the neurons and is incorporated into proteins, which are transported distally along the axons to the presynaptic terminals. The animal is killed 24 to 48 hours later and the appropriate parts of the nervous system are chemically fixed to immobilize the labeled proteins. Sections are cut, and autoradiographs are prepared in the usual way. High concentrations of silver grains, indicating the presence of tritium in the tissue, are seen over the site of injection, over the terminal field of projection of the neurons, and often over the axons between these two regions.

With this technique, it has been possible to trace connections previously undetectable by the use of degeneration methods. It also has the important advantage that the labeled amino acid enters only the cell bodies and dendrites of neurons. Axons that happen to be passing through the site of injection do not take up the tracer, thus avoiding the confusion that often complicated the interpretation of areas of terminal degeneration.

Research methods that exploited retrograde and anterograde changes following axotomy have been largely replaced by techniques that take advantage of the **uptake and axonal transport** of proteins and other substances. A histochemically detectable protein or a suitable fluorescent substance is injected into the region concerned. The foreign molecules are imbibed by presynaptic terminals in the region and transported retrogradely to their neuronal perikarya. The process takes 6 to 72 hours, according to the lengths of the axons and the substance used as a tracer. The animal is then killed and the tissue is removed and appropriately fixed and sectioned. A protein tracer is localized by histochemical means, thus revealing the neuronal cell bodies that innervated the site of the injection. A fluorescent tracer is observed directly by fluorescence microscopy.

The first protein to be used extensively as a tracer in this way was the enzyme peroxidase, extracted from the root of the horseradish plant. The more sensitive methods make use of **lectins**, which are carbohydrate-binding proteins of plant origin. Lectins bind strongly to cell surfaces, including those of axonal terminals, and are then taken up into the cytoplasm and transported. The lectin is rendered histochemically detectable by its covalent conjugation with an enzyme, usually horseradish peroxidase. Other tracers, detectable by similar methods, include simple polysaccharides and some bacterial toxins.

Many neurons in the brain have axons that send branches to widely separated places. It is possible to demonstrate such branching by injecting a different tracer into each suspected terminal field. Dyes that fluoresce in different colors are commonly used in this technique, which is known as **retrograde double labeling**. If both tracers are present in a single cell body, that neuron has axonal branches that go to both sites of injection.

Proteins and dyes are also taken up and transported retrogradely by injured axons of passage, so care must be taken not to cause undue physical damage when injecting into an area that contains nerve endings whose cells of origin are to be determined. Uptake by injured axons may be deliberately studied by applying protein tracers at the sites of transection of tracts or to cut peripheral nerves.

It is also possible to study also the **anterograde transport** of tracer proteins. The amount of protein taken up by cell bodies and dendrites is less than that absorbed by presynaptic terminals. However, an appreciable amount does enter the cell bodies and is transported orthogradely in the rapid component of the axoplasmic transport system. The protein is detected histochemically in the terminal and preterminal parts of axons, which have an appearance quite different from that of labeled perikarya. The method provides, for a smaller investment of time and effort, results comparable to those obtained by the autoradiographic method. Some lectins are especially suitable for anterograde tracing and provide remarkably clear delineation of the terminal branches of axons.

Membrane probes

Some hydrophobic fluorescent compounds, most notably a cyanine dye called **DiI**, enter the lipid domains of cell membranes, including the neuronal axolemma, and then diffuse in the plane of the membrane. This happens even in dead tissue, allowing the tracing of fiber tracts from a site of application of the dye. Diffusion within the axolemma is extremely slow and several months are needed to trace axons over distances of less than a centimeter. This method has been applied to human postmortem material but has not, as yet, yielded new neuroanatomical knowledge. DiI and certain other nontoxic fluorochromes are internalized by living neurons. This property has been exploited to label cells and trace the migrations of cell bodies and growth of axons in developing animals and also to examine axonal regeneration and other responses of neurons to injury.

Transsynaptic tracing of pathways

In some viral diseases, such as rabies, the infective agent spreads through the central nervous system by being passed from one neuron to another. Certain viruses are used for experimental neuronal tracing because they replicate within neurons, are transported within the axon, and are passed from one cell to another at synapses. The virus can be modified to make the cells that harbor it synthesize a histochemically detectable enzyme, or the viral protein may be stained immunohistochemically.

Techniques used for tracing neuronal pathway in laboratory animals are summarized in Table 1.
.

TABLE 1. **Neuroanatomical tracing methods used in research**

TECHNIQUE	COMMENTS
Degeneration methods	
Marchi's method	Anterograde tracing by staining degenerating myelin. Terminal parts of degenerating axons not shown, but the method can be used with human material.

Silver methods

Anterograde tracing by staining degenerating axons, including their preterminal and terminal parts. Suitable only for laboratory animals. Results may be confusing because lesions destroy axons of passage as well as neuronal cell bodies.

Electron microscopy

Shows exact locations of degenerating synaptic terminals. Uncertainty about origins of the degenerated axons, as for silver methods.

Methods based on axonal transport

Autoradiographic tracing

A locally injected radioactive amino acid is taken up by neuronal cell bodies and incorporated into proteins. These are transported to synaptic terminals, where they are detected by autoradiography.

Horseradish peroxidase (HRP)

The injected enzyme is taken up by axonal terminals (also by injured axons of passage) and transported retrogradely to neuronal cell bodies, where it is detected by histochemical staining for peroxidase activity.

Fluorescent dyes

Several fluorescent dyes, administered in the same way as HRP, may be used as retrograde tracers and detected by fluorescence microscopy. With two dyes it is possible to show that axonal branches from an individual neuron project to different sites: retrograde double labeling. Labeled dextrans (bacterial polysaccharides conjugated to fluorescent dyes) are also used as tracers.

Lectins

Carbohydrate-binding proteins that bind to the neuronal surface are then internalized and transported either retrogradely or anterogradely. A lectin may be labelled, usually by conjugation with HRP, or it may be detected immunohistochemically in sections of the tissue.

Membrane probes

Strongly hydrophobic fluorescent dyes that enter cell membranes

and diffuse in the plane of the membrane. The best known is DiI, a cyanine dye. Axons can be traced in living or dead material, but only over short distances in the latter.

Transsynaptic tracing

A virus such as pseudorabies is passed from neuron to neuron at synapses. The cells occupied by the virus are detected by immunohistochemistry. This method demonstrates pathways composed of functionally connected populations of neurons.

Metabolic marking methods

The sugar **2-deoxy-D-glucose** is an analog of ordinary D-glucose. It enters cells in the same way as glucose but cannot be metabolized. When cells are active, their glucose uptake increases. Therefore, if an active cell is supplied with 2-deoxyglucose, this sugar will accumulate in the cytoplasm. A laboratory animal may be given an intravenous infusion of radioactively labeled 2-deoxyglucose while part of its nervous system is made highly active; for example, its visual system may be stimulated by light or its auditory system by sound. The radioactive sugar accumulates in all the neurons in the active system and may be detected there autoradiographically. In the visual system, for example, activity is detected in the retina, in certain layers of cells in the lateral geniculate body, and in the calcarine.

The deoxyglucose method can reveal those structures in the brain that are active when a particular system of pathways is in use. It may thus be possible to determine which of a multitude of connections demonstrated by neuroanatomical tracing methods are the most important in relation to function.

The catalytic functions of certain enzymes used in the metabolic activities of all cells can be demonstrated histochemically. **Cytochrome oxidase** is a notable example, and in regions that contain active neurons, the activity of this enzyme is higher than in adjacent quiescent areas. Cytochrome oxidase histochemistry has been used with great success in the demonstration of columns of cells that respond to different visual stimuli in the cortex of the occipital lobe of the brain.

Physiological and pharmacological methods

Anatomical studies of neuronal pathways are often supplemented by electrically stimulating neurons and recording the potentials evoked elsewhere. Measurement of the time elapsed between stimulation and recording provides information that may help to determine the number of neurons, or synaptic delays, that are included in a pathway. This procedure, introduced by Dusser de Barenne in the 1930s, was called "physiological neuronography," a term that is now seldom used. In modern investigations of neuronal connections, anatomical tracing experiments are frequently combined with immunohistochemistry to identify neurotransmitters and

electrophysiological studies that ascertain the actions of transmitters upon postsynaptic neurons.

Electrophysiological investigations of the human central nervous system are necessarily more limited in scope than experiments using animals. Nevertheless, a great deal has been learned from observation of the effects of stimulating the cerebral cortex.

Several **toxic substances** are used in laboratory animals as adjuncts to the study of neuroanatomy. For example, **nicotine** was used a century ago by Langley to block synapses and thus establish their locations in autonomic ganglia. Nicotine is now known to stimulate (but in larger doses, to inhibit) some neurons that normally respond to acetylcholine. Local injection of **kainic acid** or **ibotenic acid** kills many types of neurons without causing transection of passing fibers. These substances are known as **excitotoxins** because they are analogs of glutamic acid, which is an excitatory transmitter. When kainic or ibotenic acid binds to glutamate receptors, there is an unusually long activation of nonspecific ligand-gated cation channels of the postsynaptic cells. Calcium ions that diffuse into the neurons activate proteolytic enzymes that destroy the cytoplasm. The result is a lesion more selective than one produced by physical methods. Cells that use monoamines as synaptic transmitters are selectively intoxicated by analogs of these substances or their metabolic precursors. Thus neurons that make use of dopamine or noradrenaline are selectively poisoned by **6-hydroxydopamine**, and serotonin cells are similarly sensitive to **5,6-dihydroxytryptamine**.

Some poisonous lectins (notably **ricin-60** from the castor bean) and other compounds (notably the antibiotic **doxorubicin**, which is used to treat some types of cancer) are taken up by axonal endings and by injured axons of passage and transported retrogradely to the neuronal cell bodies, where they inhibit nucleic acid and protein synthesis. This strategy, known as **suicide transport**, is also useful for producing selective lesions to provide experimental models of diseases in which certain populations of neurons degenerate spontaneously.

Suggested reading

Heimer L. Neuroanatomic Techniques. In: Heimer L, *The Human Brain and Spinal Cord*. 2nd ed. New York: Springer-Verlag, pp 172-84, 1995

Krassioukov AV, Bygrave MA, Puckett WR, Bunge RP, Rogers KA. Human sympathetic preganglionic neurons and motoneurons retrogradely labelled with DiI. *J Autonom Nerv Syst* **70**:123-128, 1998

Lukas JR, Aigner M, Denk M, Heinzl H, Burian M, Mayr R. Carbocyanine postmortem neuronal tracing: influence of different parameters on tracing distance and combination with immunocytochemistry. *J Histochem Cytochem* **46**:901-910, 1998

McLean JH, Shipley MT, Bernstein DI. Golgi-like transneuronal retrograde labelling with CNS injections of Herpes simplex virus type 1. *Brain Res Bull* **22**:867-81, 1989

Miklossy J, Van der Loos H: The long-distance effects of brain lesions: visualization of myelinated pathways in the human brain using polarizing and fluorescence microscopy. *J Neuropathol Exp Neurol* **50**:1-15, 1991

Purves D: Assessing some dynamic properties of the living nervous system. *Quart J Exp Physiol* **74**:1089-1105, 1989

Rajakumar N, Elisevich K, Flumerfelt BA. Biotinylated dextran: a versatile anterograde and retrograde neuronal tracer. *Brain Res* **607**:47-53, 1993

Vercelli A, Repici M, Garbossa D, Grimaldi A. Recent techniques for tracing pathways in the central nervous system of developing and adult mammals. *Brain Res Bull* **51**:11-28, 2000

The above notes on neuroanatomical research methods for Neuroscience 500 are a shortened version of part of Chapter 4 in *Barr's The Human Nervous System*, 9th edition, by J. A. Kiernan. Copyright © 2008 Lippincott, Williams & Wilkins, Baltimore. Chapter 4 in the book includes illustrations and also covers imaging methods for the human CNS.

(B.) Somatic sensory pathways

For some illustrations similar to those used in the lecture, see http://instruct.uwo.ca/anatomy/530/530notes.htm#SOMSENS

Summary

Neuronal signals from skin and deeper structures are segregated in the spinal cord. Transmission to the thalamus and cerebral cortex may occur through the spinothalamic tract or through the dorsal funiculus (posterior column) and medial lemniscus.

For pain, temperature, and the less discriminative aspects of touch, neurons in the dorsal horn have axons that cross the midline in the spinal cord and ascend as the spinothalamic tract, which is laterally situated in the spinal cord and brain stem.

For discriminative touch and conscious proprioception, the axons of primary sensory neurons ascend ipsilaterally in the dorsal funiculus and end in the gracile or cuneate nucleus. Lateral inhibition in these nuclei provides a mechanism for enhancing sensory discrimination between adjacent parts of the peripheral fields. Fibers arising in the gracile and cuneate nuclei cross in the medulla and ascend in the medial lemniscus, which is near the midline in the medulla and shifts to a lateral location in the midbrain.

For conscious proprioception from the lower limb, there is an additional pathway through the spinal cord and caudal part of the medulla. This involves the caudal part of the gracile fasciculus, the dorsal spinocerebellar tract, and nucleus Z.

Both the spinothalamic tract and the medial lemniscus end in the VPl nucleus of the thalamus. This thalamic nucleus projects to the primary somesthetic cortex of the postcentral gyrus, where the contralateral half of the body is represented as an upside-down homunculus.

The somesthetic pathways for the head include the trigeminal sensory nuclei and their projections to the contralateral VPm thalamic nucleus. Primary afferent axons for touch end in the pontine trigeminal nucleus. Pain and temperature fibers descend in the spinal trigeminal tract before ending in the caudal part of its nucleus.

Lesions in the spinal cord and brain stem can affect the somesthetic pathways separately, causing dissociated sensory loss.

The main pathways are supplemented by others, especially for pain, with relays in the reticular formation and thalamic nuclei other than the VPl or VPm. A pathway through the mediodorsal thalamic nucleus to the anterior cingulate cortex is active in the perception of pain.

The primary somatosensory area and associated parietal association cortex are necessary for localizing the source of a painful stimulus and for recognizing objects by touch.

Descending projections influence transmission in the ascending somatosensory pathways. These include the raphespinal tract, which inhibits the perception of stimuli that would be painful.

This is an account of the pathways from the general sensory receptors to the thalamus and thence to the cerebral cortex, where the sensations are appreciated subjectively. With an understanding of the anatomy of these pathways, an appraisal of sensory deficits provides information concerning the location of a lesion in the central nervous system.

Sensory axons that enter the spinal cord in dorsal roots of spinal nerves segregate in such a way that there are two main general sensory systems. The first of these, regarded as the more primitive, includes one or more synaptic relays in the dorsal gray horn. Spinal neurons give rise to axons that cross the midline and ascend in the ventrolateral white matter to the thalamus. This is the **spinothalamic system**. It carries signals that report the senses of pain and temperature, and is also the main pathway for the less discriminative tactile sensation usually called light touch and probably also for some other forms of touch, notably firm pressure.

The second system includes large numbers of primary afferent axons that turn rostrally in the ipsilateral dorsal funiculus of the spinal cord and do not end until they reach the medulla. Smaller numbers of axons, in the dorsal funiculus and in the dorsal part of the lateral funiculus, arise ipsilaterally from neurons in the dorsal horn. All of these axons terminate in certain nuclei in the lower medulla, from which axons cross the midline and then ascend as the medial lemniscus to the thalamus. Hence this second pathway is called the **medial lemniscus system**. It is concerned primarily with discriminative aspects of sensation, especially the awareness of position and movement of parts of the body and the tactile recognition of shapes and textures and of changes in the positions of stimuli that move across the surface of the skin. The medial lemniscus system is often called the **posterior column system**, especially in clinical usage, because it includes the dorsal funiculi ("posterior columns") of the spinal cord.

The **spinoreticulothalamic pathway**, which includes relays in the reticular formation of the brain stem, conducts some of the ascending signals generated by cutaneous sensation. It is, therefore, closely related functionally to the spinothalamic system. The association is seen especially in central conduction for pain. In fact, the spinothalamic pathway and the less direct spinoreticulothalamic pathway, with their projections to the cerebral cortex, may be combined under the term **ventrolateral (or anterolateral) system**. The comparable term **dorsomedial system** is then used for the medial lemniscus system. The various names for the pathways for general sensation are summarized in Table 2. Unfortunately all the terms are in fairly widespread use by anatomists, physiologists, and clinicians. The **trigeminothalamic** pathways serve the same functions as the spinothalamic and medial lemniscus systems, but for the head (central connections of somatic sensory components of the trigeminal, facial, glossopharyngeal, and vagus nerves).

TABLE 2. **Names and components of the somatic sensory pathways concerned with parts of the body below the head.**

Medial lemniscus system	**Spinothalamic system**
Alternative names:	*Alternative names:*
Dorsomedial system Posterior column system Dorsal column system	Ventrolateral system Anterolateral system
Neurons with cell bodies in peripheral nervous system	
Dorsal root ganglia	Dorsal root ganglia
Dorsal (posterior) funiculi (= dorsal or posterior columns) Each consisting of: Gracile fasciculus Cuneate fasciculus	Dorsolateral tract of Lissauer
Neurons with decussating axons that end in the thalamus	
Gracile and cuneate nuclei (also Nucleus Z*)	Dorsal horn of spinal gray
Decussation of the medial lemnisci	Ventral white commissure of spinal cord
Medial lemniscus	Spinothalamic tract (also spinoreticular fibers) Spinal lemniscus (= spinothalamic fibers in the brain stem) (also reticulothalamic fibers)
Thalamocortical neurons	

Ventral posterior nucleus of thalamus	Ventral posterior nucleus of thalamus and other thalamic nuclei (mediodorsal; posterior group; intralaminar group)
Internal capsule	Internal capsule
Cerebral cortex	
Primary somatosensory cortex Parietal association cortex	Primary somatosensory cortex Parietal association cortex Anterior cingulate cortex

---

* An additional pathway for conscious proprioception from the lower limb includes an additional relay in the nucleus thoracicus, with axons that ascend in the dorsal spinocerebellar tract and have branches in the medulla that synapse with neurons in nucleus Z.

The general sensory pathways are said to consist of primary, secondary, and tertiary neurons, with cell bodies in sensory ganglia, the spinal cord or brain stem, and the thalamus, respectively. The concept of a simple relay of three neurons is not accurate, however, because interneurons act upon the secondary and tertiary neurons of a pathway. In addition, the activity of the secondary neurons is influenced by descending axons that originate in the cerebral cortex and the brain stem.

Spinothalamic system

The spinothalamic or ventrolateral system is known also as the "pathway for pain and temperature" because these modalities of sensation are transmitted to the brain in the spinothalamic tract. It is also concerned with tactile sensation, as has already been noted.

Receptors

The **receptors for pain** (**nociceptors**) consist of unencapsulated endings of peripheral nerve fibers; these axons are the smaller components of group A, with thin myelin sheaths (group Aδ), and unmyelinated group C axons. These simple endings are not exclusively concerned with pain, but they appear to be the only receptors that respond to painful stimuli. Pain may be felt as two waves separated by an interval of a few tenths of a second. The first wave is sharp and localized, with conduction by group A fibers. The second wave, which is rather diffuse and still more disagreeable, depends on group C fibers, with a slow conduction speed. The two waves are most easily noticed in the feet (as when treading on something sharp) because of the greater lengths of the conducting axons in the nerves of the lower limb.

The mechanism of perception of pain is inseparable from that of the initiation of **inflammation**, which is the response of living tissue to any kind of injury. Injured cells release several substances

known as mediators, which act on venules and nerve endings. The venules dilate, causing redness of the affected area, and become permeable to blood plasma, which leaks out to cause swelling of the tissue. Simultaneous stimulation of the nociceptive endings results in perception of pain. Nerve impulses, however, do not pass solely to the central nervous system: they are also propagated antidromically along other peripheral branches of the afferent axon. In the case of cutaneous group C axons, the impulses cause a peptide neurotransmitter known as substance P to be released into the interstitial tissues of the dermis. This acts upon arterioles and in the dermis, which dilate. Substance P also causes degranulation of mast cells, which release more mediators, thereby enhancing the dilation of arterioles and sometimes also causing edema in the area surrounding the injury. In the skin, the total result constitutes the **triple response** (of Lewis): a red mark and a wheal, surrounded by a flare of neurogenic arteriolar vasodilation. A neurally mediated phenomenon such as this, which does not involve any synapses, is called an **axon reflex**. Other examples are known experimentally, but the axon reflex just described is the only one of clinical interest.

The question of identity of **receptors for temperature** has not yet been resolved. They are probably morphologically nondescript free nerve endings, similar to those for pain. The axons are of similar caliber to those that conduct impulses for pain. The **receptors for light touch** are unencapsulated nerve endings, Merkel and peritrichial endings, and Meissner's corpuscles. Ruffini endings respond to firm pressure on the skin, especially when this causes the dermis do move on the underlying subcutaneous tissue. Conduction for light touch and pressure in peripheral nerves is by myelinated group A fibers of medium diameter. (Descriptions of the specialized sensory nerve endings can be read in Chapter 3 of *Barr's The Human Nervous System*.)

Ascending central pathway

Synapses and interneurons in the dorsal horn

Cell bodies of small and intermediate size in the dorsal root ganglia have central processes that constitute the lateral divisions of the dorsal rootlets. These axons conduct impulses from pain and temperature receptors. Afferents for light touch and pressure enter the dorsal gray horn through the medial division of the dorsal rootlets. The pain and temperature fibers enter the **dorsolateral tract** (of Lissauer) of the spinal cord, in which ascending and descending branches travel, in most instances, for lengths that correspond to one segment. A few of the axons travel as far as four segments rostral or caudal to their levels of entry.

The terminals and the collateral branches of the axons in the dorsolateral tract enter the dorsal horn, where they branch profusely. Lamina II (the **substantia gelatinosa** of Rolando), near the tip of the dorsal horn, is an important region in which patterns of incoming sensory impulses are modified. The dendrites of the gelatinosa cells are contacted not only by primary afferent axons, but also by reticulospinal fibers, notably those derived from the raphe nuclei of the medulla. (Descending pathways that modulate transmission in the ascending sensory pathways are discussed later.) The axons of the cells in the substantia gelatinosa ascend and descend in the dorsolateral tract and in adjacent white matter, mostly for about the length of one segment. Throughout its length, the axon of a gelatinosa cell gives off branches that end by synapsing with the dendrites of **tract cells**, whose axons constitute the spinothalamic tract.

The dendrites of the tract cells are contacted by excitatory primary afferent axons for pain and temperature, by inhibitory axons of the gelatinosa cells, and by excitatory primary afferents for light

touch and pressure. These connections enable a tract cell to decide whether a potentially harmful stimulus is intense enough to initiate the onward transmission of a signal of pain perception. The neuronal circuitry for pain is discussed in more detail later.

Spinothalamic tract

Most of the tract cells have their cell bodies in the **nucleus proprius** (laminae IV and V-VI). The large neurons at the tip of the dorsal horn (lamina I) also contribute a proportion of the spinothalamic fibers, notably those concerned with pain. The axons of the tract cells cross the midline in the ventral white commissure. Continuing through the ventral horn of gray matter, the axons ascend in the **spinothalamic tract**, situated in the ventral part of the lateral funiculus and in the adjoining region of the ventral funiculus. Proceeding rostrally, axons are continually being added to the internal aspect of the tract. At upper cervical levels, therefore, fibers from sacral segments are most superficial, followed by fibers from lumbar and thoracic segments. The fibers from cervical segments are closest to the gray matter.

The ascending tracts of the spinal cord continue into the medulla without appreciable change of position initially. At the level of the inferior olivary nucleus, the spinothalamic tract traverses the lateral medullary zone (Monakow's area) between the inferior olivary nucleus and the spinal trigeminal nucleus, where it is close to the lateral surface of the medulla. At this level and throughout the remainder of the brain stem, the spinothalamic axons constitute most of the **spinal lemniscus**, which also includes axons of the spinotectal (spinomesencephalic) tract destined for the superior colliculus. The spinal lemniscus continues through the ventrolateral region of the dorsal pons. In the midbrain it is close to the surface of the tegmentum, running along the lateral edge of the medial lemniscus. In their passage through the brain stem, the spinothalamic axons give off collateral branches that terminate in the medullary and pontine reticular formation and in the periaqueductal gray matter of the midbrain. There are also **spinoreticular fibers** that go no further rostrally than the pons.

Thalamus and cerebral cortex

Most of the spinothalamic axons end in the **ventral posterior nucleus of the thalamus**. This nucleus consists of two parts: the ventral posterolateral division (**VPl**), in which spinothalamic axons and the medial lemniscus terminate, and the ventral posteromedial division (**VPm**), which receives trigeminothalamic axons. The somatotopic organization is such that the contralateral lower limb is represented dorsolaterally and the contralateral upper limb is represented ventromedially in the VPl; the opposite side of the head is represented in the VPm.

The thalamocortical projection consists of neurons in the ventral posterior nucleus whose axons traverse the **posterior limb of the internal capsule** and corona radiata to reach the **primary somesthetic area** in the parietal lobe. The contralateral half of the body, exclusive of the head, is represented as inverted in the dorsal two-thirds of the primary somesthetic area. Beginning ventrally, the sequence is, therefore, hand, arm, trunk, and thigh, followed by representation of the remainder of the lower limb and the perineum on the medial surface of the hemisphere. The cortical area for the hand is disproportionately large, providing for maximal sensory discrimination. The somatotopic arrangement at various levels of the sensory pathways forms the basis for recognition of the site of stimulation.

Experimental tracing in monkeys reveals that the sites of origin and termination of the spinothalamic tract and the positions of the axons in the spinal cord are more varied than the classic projections described earlier. Substantial numbers of axons have been demonstrated in the dorsal part of the lateral funiculus, and there are some axons (mainly from regions of gray matter other than the dorsal horn) that ascend ipsilaterally. The existence of such axons may account for the eventual recovery of sensibility to pain that follows transection of the ventrolateral quadrant of the spinal white matter.

Some axons of the spinal lemniscus end in thalamic nuclei other than the VPl, notably those of the **posterior** and **intralaminar** groups and the **mediodorsal nucleus**. The posterior group projects to the insula and to adjacent parietal cortex, including that of the second somatic sensory area, which is at the lower end of the postcentral gyrus. The intralaminar nuclei project diffusely to the frontal and parietal lobes of the cerebral cortex and to the striatum. They may be involved in the maintenance of a conscious, alert state. The mediodorsal nucleus is connected with the frontal lobes, especially their medial and orbital surfaces: cortical regions concerned with affect, decision making and foresight. A projection of the mediodorsal nucleus to the anterior part of the cingulate gyrus is activated by painful stimuli.

Two spinothalamic pathways

Two populations of spinothalamic axons are recognized on the basis of experiments with various mammals and from human clinical studies. The **neospinothalamic tract**, which is prominent in primates, arises from lamina I and laminae IV-VI (nucleus proprius) in the dorsal horn. Its fibers do not have collateral branches in the reticular formation, but there are branches to the periaqueductal gray matter. The neospinothalamic fibers end in the VPl nucleus of the thalamus. Those from lamina I project also to the dorsomedial nucleus. The **paleospinothalamic tract**, which predominates in lower mammals, has more extensive spinal origins (including laminae VII, VIII, and X, which are not in the dorsal horn). Its axons send branches to the reticular formation and end in the intralaminar nuclei (especially the central lateral nucleus), the posterior group of nuclei, and the dorsomedial nucleus. The rather diffusely projecting paleospinothalamic tract, together with spinoreticular and reticulothalamic projections, are involved in the recognition of somatic sensory stimuli and in involuntary motor responses such as changes in facial expression. The topographically organized neospinothalamic pathway is necessary for localization of the stimuli.

Pain

Pain is a common complaint, and it is, therefore, necessary to become conversant with the anatomy, physiology, and pharmacology of this symptom. The central pathways concerned with pain are now discussed.

Spinal mechanisms

Perception of pain is thought to be modified by neural mechanisms in the dorsal horn. In addition to the influence of reticulospinal and corticospinal fibers, to be discussed later, the transmission of impulses for pain to the brain is altered by dorsal root afferents for other sensory modalities. Afferent axons of larger diameter, especially those for touch and deep pressure, have branches that synapse

with the dendrites of the gelatinosa cells. Trains of impulses coming through the larger axons can stimulate the gelatinosa cells, causing these interneurons to inhibit those tract cells that are concerned with nociception. The inhibitory effect can be overcome by sufficient nociceptive input to the tract cells. This postulated mechanism, known as the **gate control theory** of pain, enables the neurons in the spinal cord to determine, on the basis of all incoming sensory stimuli, whether a particular event should be reported to the brain as being painful. A similar mechanism is presumed to exist in the caudal part of the spinal trigeminal nucleus, which is the rostral continuation of the tip of the dorsal horn. The gate mechanism probably operates when pain arising in deep structures such as muscles and joints is relieved by stimulating sensory endings in the overlying skin (for example, by rubbing or by applying warmth or a mild chemical irritant such as a liniment).

A simpler, direct pathway is provided by the large neurons (Waldeyer cells) at the tip of the dorsal horn. These are activated by nociceptive primary afferent fibers and have axons that travel in the spinothalamic tract to the ventral posterior and mediodorsal thalamic nuclei.

The simplest defensive reflex initiated by pain is the **flexor reflex**, which involves at least two synapses in the spinal cord and causes flexion of a limb to withdraw it from the source of a sudden painful stimulus. In quadrupeds, there is also a **crossed extensor reflex** in which the withdrawal is assisted by extension of the contralateral limb. In normal humans, the crossed extensor reflex is largely suppressed as a result of activity in descending tracts of the spinal cord, but both it and the flexor reflex are conspicuous and, because of a lowered threshold, troublesome in paraplegic patients.

Ascending pathways

Impulses that signal pain are transmitted rostrally in the spinothalamic and spinoreticular tracts. Additional axons with this function appear to be present in the dorsolateral funiculus. Tractotomy or surgical transection of the ventrolateral region of the spinal cord, which contains the spinothalamic and spinoreticular tracts, results in almost complete loss of the ability to experience pain on the opposite side of the body below the level of the lesion. The sensibility usually returns gradually over several weeks. The recovery is probably a consequence of synaptic reorganization and increased usage of intact alternative pathways. A surgical cut in the midline of the spinal cord (commissural myelotomy) causes prolonged analgesia in the segments affected by the lesion.

Pain is still felt, although poorly localized, after destruction of the primary somesthetic area. This clinical observation led to an early assumption that painful sensations reached the level of consciousness within the thalamus. It is more likely that spinothalamic and reticulothalamic afferents to the intralaminar and mediodorsal thalamic nuclei are responsible for the persistence of sensibility to pain after destruction of the primary somesthetic area. These thalamic nuclei are connected with most of the neocortex, including the prefrontal areas and the anterior part of the cingulate gyrus. A unilateral painful stimulus is associated with increased blood flow in both cingulate gyri. The ventral posterior nucleus of the thalamus and the primary somesthetic area are undoubtedly necessary for the accurate localization of the site of the painful stimulus.

Descending pathways

Descending pathways modify the activity of all ascending systems; they are prominent in controlling the conscious and reflex responses to noxious stimuli. Both the subjective awareness of pain and the occurrence of defensive reflexes may be suppressed under circumstances of intense emotional stress.

This effect may be mediated by **corticospinal fibers** that originate in the parietal lobe and terminate in the dorsal horn.

Control of a subtler kind is exerted by certain reticulospinal pathways. The best understood of these is the **raphespinal tract**, which arises from neurons in the raphe nuclei of the medullary reticular formation, mainly those of the nucleus raphes magnus. The unmyelinated axons of this tract traverse the dorsal part of the lateral funiculus of the spinal cord and are believed to use serotonin as a neurotransmitter. The highest density of serotonin-containing synaptic terminals (observable by histochemical methods) is seen in the substantia gelatinosa (lamina II). The nucleus raphes magnus is itself influenced by descending fibers from the periaqueductal gray matter of the midbrain. Electrical stimulation of the nucleus raphes magnus or the periaqueductal gray matter causes profound analgesia. This is reversed either by transection of the dorsolateral funiculus or by administration of naloxone or similar drugs that antagonize the actions of morphine and related alkaloids of opium. Furthermore, the analgesic action of opiates is suppressed by transection of the dorsolateral funiculus.

The actions of the opiates and their antagonists are attributable to selective binding molecules (**opiate receptors**) on the surfaces of neurons in several parts of the brain. The normal function of the opiate receptor is to bind naturally occurring **opioid peptides**, of which the best understood are two pentapeptides, known as **enkephalins**. These serve either as neurotransmitters or as neuromodulators. Neurons that contain enkephalins have been identified immunohistochemically and include some of the gelatinosa cells of lamina II and some of the large tract cells (Waldeyer cells) of lamina I. Enkephalins also occur in the periaqueductal gray matter and the nucleus raphes magnus. These same regions also have high concentrations of opiate receptors. The analgesic action of morphine and related opiates can be attributed to simulation of the effects of endogenously secreted enkephalins on neurons that bear opiate receptors on their surfaces. Major anatomical sites of action evidently include the periaqueductal gray matter, nucleus raphes magnus, the dorsal horn, and probably the thalamus. Many other parts of the central nervous system contain enkephalins, mainly in local circuit neurons. These regions may be the sites of other pharmacological actions of the opiates, such as nausea, suppression of coughing, euphoria, and the development of addiction.

Information about the descending pathways that modulate pain has led not only to increased understanding of the sites of action of the opium alkaloids, but also to a technique occasionally used for the relief of chronic pain. An electrode stereotaxically implanted into the periaqueductal gray matter enables a patient to relieve pain instantly by switching on an electrical stimulator. The analgesia often lasts for several hours after cessation of stimulation.

Medial lemniscus system

The set of sensory pathways known as the medial lemniscus system is for proprioception, discriminative touch, and (although not exclusively) vibration. In contrast to the spinothalamic system, in which ascending axons cross the midline at spinal segmental levels, the pathways that constitute the medial lemniscus system ascend ipsilaterally in the cord and cross the midline in the caudal half of the medulla.

Receptors

The medial lemniscus (or dorsomedial) system is especially important in humans because of the discriminative quality of the sensations as perceived subjectively and their value in the learning process. The characteristics of fine or discriminative touch are that the subject can recognize the location of the stimulated points with precision and is aware that two points are touched simultaneously even though they are close together (two-point discrimination). These qualities accentuate recognition of textures and of moving patterns of tactile stimuli. Of the **tactile receptors**, Meissner's corpuscles, which have been found only in primates, have a special significance in discriminative touch. These rapidly adapting receptors occur in the ridged, hairless skin of the palmar surface of the hands, which are moved over surfaces to feel texture and other small irregularities. Several additional touch receptors, noted in connection with the spinothalamic system, also produce sensations through the medial lemniscus system. Pacinian corpuscles are the principal receptors for the sense of **vibration**, although this modality, once believed to be served exclusively by the dorsal funiculi, is now known to be carried also in the lateral white matter of the spinal cord.

With respect to **proprioception**, the dorsomedial pathway provides information concerning the precise positions of parts of the body; the shape, size, and weight of an object held in the hand; and the range and direction of movement. The proprioceptors are neuromuscular spindles, neurotendinous spindles, and endings in and near to the capsules and ligaments of joints. Conscious proprioception (kinesthesia) was once thought to depend mainly on receptors in joints, but it is now realized that the input from muscle spindles probably is of greater significance than the input from other proprioceptors.

Ascending central pathways

Identical pathways transmit discriminative touch and proprioception from the limbs and trunk. In addition, there is a supplementary pathway for proprioceptive signals from the lower limbs. The pathways for the two main sensory modalities of the medial lemniscus system are, therefore, described separately.

Discriminative touch

The primary sensory neurons for discriminative touch (and for proprioception) are the largest cells in the dorsal root ganglia; their processes are large group A fibers with thick myelin sheaths. The central processes are in the medial group of axons of each rootlet, and they bifurcate on entering the **dorsal funiculus**. The short descending branches are described later. Most of the ascending branches proceed ipsilaterally to the medulla. Above the midthoracic level, the dorsal funiculus consists of a medial **gracile fasciculus** and a lateral **cuneate fasciculus**. The axons of the gracile fasciculus, which enter the spinal cord below the midthoracic level, terminate in the **gracile nucleus**; axons of the cuneate fasciculus, coming from the upper thoracic and cervical spinal nerves, end in the **cuneate nucleus**. More precisely, there is a lamination of the dorsal funiculus according to segments. Axons that enter the spinal cord in lower sacral segments are most medial, and axons from successively higher segments are added in an orderly manner and ascend along the lateral side of those already present.

Axons of neurons in the gracile and cuneate nuclei curve ventrally as **internal arcuate fibers**, cross the midline of the medulla in the decussation of the medial lemnisci, and continue to the thalamus as the **medial lemniscus**. This substantial tract is situated between the midline and the inferior olivary nucleus in the medulla, in the most ventral portion of the tegmentum of the pons, and lateral to the

red nucleus in the tegmentum of the midbrain. The medial lemniscus and spinothalamic tract intermingle in the dorsal region of the subthalamus before entering the lateral division of the **ventral posterior nucleus of the thalamus**. The fibers of the medial lemniscus, in contrast to those of the spinothalamic tract, all terminate in the VPl nucleus.

A topographic arrangement of axons is maintained throughout the medial lemniscus. In the medulla, the larger dimension of the lemniscus is vertical as seen in cross section; fibers for the lower limb are most ventral (adjacent to the pyramid), and fibers for the upper part of the body are most dorsal. On entering the pons, the medial lemniscus "rotates" through 90 degrees; from here to the thalamus, fibers for the lower limb are in the lateral part of the lemniscus, and those for the upper part of the body are in its medial portion. This pattern conforms with the representation of the body in the VPl nucleus of the thalamus. The pathway is completed by a projection from this nucleus to the **primary somesthetic cortex** of the parietal lobe.

Proprioception

The central pathways for conscious awareness of position and movement are similar to those for discriminative touch, but for the lower limb there is an additional pathway. The pathway for the **upper limb** corresponds exactly with the one just described. That is, the ascending branches of primary afferent fibers terminate in the cuneate nucleus, from which the impulses are relayed through the medial lemniscus to the ventral posterior nucleus of the thalamus and thence to the first somatic sensory area of the cerebral cortex.

An equivalent pathway exists for the **lower limb**, but by way of the gracile fasciculus and gracile nucleus. The accessory pathway for conscious proprioception from the **lower limb** is different, being a series of four populations of neurons. **(1)** The primary afferent fibers enter the cord from the lumbar and sacral dorsal roots; they bifurcate into ascending and descending branches in the dorsal funiculus, but some of the former go only part of the way up the spinal cord. They terminate in the upper lumbar and lower thoracic segments in the **nucleus thoracicus** (nucleus dorsalis; Clarke's column), which is a column of large cells on the medial side of the dorsal horn in segments C8 to L3. **(2)** The neurons in the caudal part of the nucleus thoracicus give rise to axons that ascend ipsilaterally as the **dorsal spinocerebellar tract** in the dorsolateral funiculus. Before entering the inferior cerebellar peduncle, some of the axons of this tract give off collateral branches, which remain in the medulla. These collaterals are concerned with conscious proprioception from the lower limb. They end in the **nucleus Z** of Brodal and Pompeiano. This is rostral to the gracile nucleus, of which it may be functionally an outlying part. **(3)** The cells of nucleus Z give rise to internal arcuate fibers that cross the midline and join the medial lemniscus. The remainder of the pathway is the same as for the upper limb, with a synapse in the ventral posterior thalamic nucleus (VPl). **(4)** Thalamocortical fibers project to the leg area of the primary somatosensory cortex.

The existence of an accessory pathway for proprioception from the lower limb has clinical implications. The dorsal funiculi conduct impulses concerned with proprioception in the upper and lower limbs. A lesion at a high cervical level that transects the dorsal funiculus but spares the dorsal spinocerebellar tract results in clumsiness and other symptoms of impaired impaired position sense in the upper and lower limbs. Simple clinical testing in such cases shows loss of awareness of position and movement of the joints of the upper limb, and preservation of these senses in the lower limb. The patient's daily experience, however, indicates quite severe proprioceptive impairment of the leg and foot. The pathway involving the dorsal spinocerebellar tract and nucleus Z evidently is

sufficient to account for conscious proprioception when this modality is specifically tested in patients with dorsal funiculus lesions. This accessory pathway may be the principal one for lower limb proprioception in monkeys.

Enhancement of discrimination in the gracile and cuneate nuclei

It is convenient to think of sensory signals being "relayed" through the gracile or cuneate nucleus and the VPl nucleus of the thalamus to the cerebral cortex. Simple interruptions in the pathway would serve only to retard transmission, however. The real purpose of the nuclei is to modify the message, increasing the sensitivity of the cerebral cortex to the tiny differences in shape, texture or movement that stimulate the peripheral receptors. The way this happens is most easily understood by considering the circuitry of the gracile or cuneate nucleus in relation to stimulation of a point on the skin. This circuitry includes the excitatory synapses of the dorsal root ganglion neurons (*blue*) and a population of inhibitory interneurons (*black*) in the nucleus. Both are connected with the principal cells of the nucleus, whose axons (*red*) go to the thalamus.

Three principal cells (*red*) of the gracile or cuneate nucleus are shown receiving input that is strongest (highest frequency of action potentials) from the centre of the area of skin represented at the bottom of the diagram. The inhibitory interneurons (*black*) that surround the principal cells receive more stimulation from the more active primary afferent (*blue*) neurons. The stimulated interneurons inhibit neighboring principal cells, thereby reducing the frequency of signals that relate to the area of skin surrounding the stimulus. Activation of inhibitory interneurons by collateral branches of afferent axons is called **feed-forward inhibition**. The same effect is produced also by recurrent collateral branches of the axons of the principal cells ending on interneurons. The action due to recurrent collaterals is known as **feedback inhibition**. Both types occur in the gracile and cuneate nuclei, and are collectively known as **lateral inhibition**.

Lateral inhibition occurs at synaptic stations in all sensory pathways. It has been thoroughly studied in the retina, and it occurs also in the thalamic "relay" nuclei (including the ventral posterior nucleus) and within the cerebral cortex.

Inhibitory interneurons are also stimulated by a corticonuclear neurons. This arrangement provides **distal inhibition**, with the somatosensory cortex setting the sensitivity of the principal cells of the gracile and cuneate nuclei. Other examples of distal inhibition in sensory pathways include the raphespinal tract, mentioned earlier, and the olivocochlear projection of the auditory system.

Sensory pathways for the head

The back of the head and much of the external ear are supplied by branches of the second and third cervical nerves, whose central connections are with the spinothalamic and medial lemniscus systems. General sensations that arise elsewhere in the head are mediated almost entirely by the trigeminal nerve. Small areas of the skin and larger areas of mucous membrane are supplied by the facial, glossopharyngeal, and vagus nerves, but the central connections of the general sensory components of these nerves are the same as for the trigeminal nerve.

The cell bodies of primary sensory neurons of the trigeminal nerve, with the exception of those in the mesencephalic nucleus, are in the trigeminal ganglion. The peripheral processes have a wide distribution through the ophthalmic, maxillary, and mandibular divisions of the nerve. The central

processes enter the pons in the sensory root. Some of these axons end in the pontine trigeminal nucleus; many descend in the spinal trigeminal tract and end in the associated nucleus, and still others bifurcate, with a branch ending in each nucleus.

There is a spatial arrangement of axons in the sensory root and spinal tract that corresponds to the divisions of the trigeminal nerve. In the sensory root, ophthalmic fibers are dorsal, mandibular fibers ventral, and maxillary fibers in between. Because of a rotation of the axons as they enter the pons, the mandibular fibers are dorsal and the ophthalmic fibers ventral in the spinal trigeminal tract. The most dorsal part of this tract includes a bundle of fibers from the facial, glossopharyngeal, and vagus nerves. The cell bodies of the primary sensory neurons are in the geniculate ganglion of the facial nerve and in the superior ganglia of the glossopharyngeal and vagus nerves. Somatic sensory axons in the facial and vagus nerves supply parts of the external ear and tympanic membrane. The glossopharyngeal and vagus nerves supply the mucosa of the back of the tongue, pharynx, esophagus, larynx, auditory (eustachian) tube, and middle ear.

Pain and temperature

Primary afferent fibers for pain and temperature end in the **pars caudalis of the spinal trigeminal nucleus**; the pars caudalis is in the lower medulla and upper two or three cervical segments of the spinal cord. (There is some evidence that the pars interpolaris receives pain afferents from the teeth.) The part of the pars caudalis in the cervical cord receives sensory data from areas of distribution of the trigeminal nerve and upper cervical spinal nerves. The cellular characteristics of the pars caudalis are similar to those of the tip of the dorsal gray horn of the spinal cord. The continuity of the substantia gelatinosa (lamina II) with a layer of small cells in the pars caudalis is particularly conspicuous.

Neurons in the reticular formation immediately medial to the pars caudalis correspond to the nucleus proprius of the spinal gray matter. The tract cells whose axons project to the thalamus are in both the spinal trigeminal nucleus and the adjacent reticular formation. The axons of these second-order neurons cross to the opposite side of the medulla and continue rostrally in the **ventral trigeminothalamic tract**. The tract terminates mainly in the **medial division of the ventral posterior nucleus of the thalamus** (**VPm**), and thalamocortical fibers complete the pathway to the inferior (ventral) one-third of the **primary somesthetic area** of cortex. The axons of the tract cells associated with the pars caudalis, like those of the spinothalamic tract, have branches that end in the intralaminar, posterior and mediodorsal nuclei of the thalamus, thus providing for distribution of the sensory information to areas of cortex beyond the confines of the first somatic sensory area. From the foregoing description, it is evident that the pathway for pain and temperature from the head corresponds to the spinothalamic system.

Touch

The central pathway for tactile sensation from the head is similar to that just described for pain and temperature, differing mainly in the sensory trigeminal nuclei involved. For light touch, the second-order neurons are in the **pars interpolaris and pars oralis** of the spinal trigeminal nucleus and in the **pontine trigeminal nucleus**. For discriminative touch, they are in the pontine trigeminal nucleus and the pars oralis of the spinal trigeminal nucleus. The second-order neurons project to the contralateral ventral posterior nucleus of the thalamus (VPm) through the ventral trigeminothalamic tract. In addition, smaller numbers of axons, crossed and uncrossed, proceed from the pontine

trigeminal nucleus to the VPm in the **dorsal trigeminothalamic tract**. The two sets of trigeminothalamic fibers often are named together as the **trigeminal lemniscus**.

Proprioception

The primary sensory neurons for proprioception in the head are unique in that most of their cell bodies are in a nucleus in the brain stem instead of in a sensory ganglion. Constituting the **mesencephalic trigeminal nucleus**, they are unipolar neurons similar to most primary sensory neurons elsewhere. The peripheral branch of the single process proceeds through the trigeminal nerve without interruption; these axons supply proprioceptors in the trigeminal area of distribution, such as those related to the muscles of mastication. The other branch of the single process has branches that (a) terminate in the trigeminal motor nucleus for reflex action, or (b) synapse in the adjacent reticular formation with neurons whose axons join the **dorsal trigeminothalamic tract**. Some neurons of the mesencephalic trigeminal nucleus send peripheral branches to receptors in the sockets of the teeth. These receptors detect **pressure on the teeth**, a sense functionally related to muscle proprioception because it participates in the reflex control of the force of biting.

The only other type of sensation perceived by a tooth is **pain**, for which the sensory pathway has already been described. Pain may originate from the dentin, the pulp, or the periodontal tissues.

Clinical considerations

Spinothalamic system

Irritation of a peripheral nerve or dorsal root, by external pressure or local inflammation, stimulates pain and temperature fibers, causing painful and burning sensations in the area supplied by the affected roots or nerves. An example is pressure on a dorsal root of a spinal nerve by a **herniated intervertebral disk**. An effect opposite to that of irritation is produced by **local anesthetic** drugs. These are most effective in blocking the conduction of impulses along group C fibers, so that low doses may reduce pain perception while having little or no effect on tactile sensibility. **Ischemia** of a nerve, such as that resulting from a tight tourniquet, preferentially blocks conduction in group A fibers. Pain with a burning character is the only sensation that can be perceived before the failure of conduction in an ischemic nerve becomes complete.

Degenerative changes in the region of the central canal of the spinal cord interrupt pain and temperature axons as they decussate in the ventral white commissure. The best example is **syringomyelia**, a disease in which cavities slowly develop in the center of the spinal cord. When the process is most marked in the cervical enlargement, as is frequently the case, the area of anesthesia includes the hands, arms, and shoulders (cape-like anesthesia). A classical presenting symptom is a burn that is not painful.

A lesion that transects axons in the **ventrolateral part of the spinal cord** on one side results in loss of pain and temperature sensibility below the level of the lesion and on the opposite side of the body. If, for example, the spinothalamic and spinoreticular tracts are interrupted on the right side at the level of the first thoracic segment, the area of anesthesia includes the left leg and the left side of the trunk. Careful testing of the upper margin of sensory impairment shows that cutaneous areas supplied by the first and second thoracic nerves are spared. Some signals from these levels reach the

contralateral pathways above their interruption because of the ascending branches of dorsal root axons in the dorsolateral tract. Surgical section of the pathway for pain (**tractotomy** or **chordotomy**) may be required for relief of intractable pain. Tractotomy is most likely to be considered in later stages of malignant disease of a pelvic organ; interruption of the pain pathway may be unilateral or bilateral, depending on circumstances prevailing in the particular patient. It was pointed out earlier that mobilization of alternative ascending pathways can lead to the return of pain several weeks after a tractotomy. An alternative analgesic procedure, effective for longer times, is **commissural myelotomy**, in which decussating spinothalamic and spinoreticular axons are cut by a median incision at and a few segments above the level of the source of the pain.

The spinal lemniscus may be included in an area of infarction in the brain stem. An example is provided by Wallenberg's **lateral medullary syndrome**; the area of infarction usually includes the spinal lemniscus and the spinal trigeminal tract and nucleus. The principal sensory deficit is for pain and temperature sensibility on the side of the body opposite the lesion, but on the same side for the face. The insensitivity to normally painful stimuli is sometimes accompanied by **allodynia**, a condition in which innocuous stimuli are felt as pain. This change may be due to reorganization of connections in the thalamus.

The standard method of testing for integrity of the pain and temperature pathway is to stimulate the skin with a pin and to ask whether it feels sharp or blunt. Light touch is tested with a wisp of cotton. Temperature perception usually need not be tested separately; if such testing is required, the method used is to touch the skin with test tubes containing warm or cold water.

Medial lemniscus system

Defective proprioception and discriminative touch result from interruption of the medial lemniscus system anywhere along its course. For example, the dorsal and dorsolateral funiculi are sites of symmetrical demyelination in **subacute combined degeneration** of the spinal cord), and conduction may be interrupted at any level by trauma, infarction, or the plaques of multiple sclerosis.

The usual test for proprioception is to move the patient's finger or toe, asking him to state when the movement begins and the direction of movement. In the **Romberg test**, any abnormal unsteadiness is noted when the patient stands with the feet together and the eyes closed, thereby evaluating proprioception in the lower limbs. Another useful test is to ask the patient to identify an object held in the hand with the eyes closed. Proprioception is especially helpful in recognizing the object on the basis of shape and size (**stereognosis**) as well as weight. This is a sensitive test that the patient may perform unsuccessfully when there is a lesion in the parietal association cortex, even though the pathway to the somesthetic area is intact.

For testing **two-point touch discrimination**, two pointed objects are applied lightly to the skin simultaneously. A suitable test object can be devised from a paper clip. Simultaneous stimuli are normally detected in a fingertip when the points are 3 to 4 mm apart, or even less. Thorough testing of two-point discrimination is a tedious procedure. A simpler test is for the examiner to ask the subject to identify simple figures "drawn" on the skin with the finger or with some other blunt object. This test relies on the ability to recognize the distance and direction of movement of the stimulus across the surface of the skin. It is highly specific for the dorsal funiculi of the spinal cord, provided there is no lesion in the cerebral cortex that is causing aphasia or agnosia.

Another sensory test is to ask the patient whether **vibration** as well as touch or pressure is felt when a tuning fork, preferably with a frequency of 128 Hz, is placed against a bony prominence such as an ankle or a knuckle. The sense of vibration often is reduced in elderly people, but even slight vibration should be felt in young people. For identifying the site of a lesion in the central nervous system, this test is less valuable than the examination of proprioception and discriminative touch. Diminished perception of vibration is often the first sign of disease affecting the largest myelinated axons in a peripheral nerve, some of which innervate pacinian corpuscles. **Peripheral neuropathy** is a term that embraces many disease processes that impair conduction in nerves, causing motor weakness or sensory deficits.

Sensation from the head

The commonest sensory abnormality affecting the face and scalp is **herpes zoster**. This disease is caused by a virus (the same one that causes chicken-pox) that infects the neurons in sensory ganglia. Burning pain and itching, commonly in the field of distribution of one of the three divisions of the trigeminal nerve, is accompanied by a skin eruption. This can be a serious condition if corneal ulceration results from infection of the ganglion cells concerned with the ophthalmic division of the trigeminal nerve. Occasionally the disability is prolonged, especially in elderly people, by **postherpetic neuralgia**. This may be particularly painful and recalcitrant to treatment. Relief can be obtained by applying capsaicin to the affected skin. Capsaicin first stimulates and then damages the terminal branches of nociceptive group C axons. Herpes zoster may also affect the geniculate ganglion or the superior vagal ganglion, causing an eruption on the tympanic membrane and parts of the external auditory canal and concha of the auricle; this is classical clinical evidence for the anatomy of the dual cutaneous innervation of this region.

A less common condition that causes episodes of severe pain in the fields of distribution of one or more divisions of the trigeminal nerve is **trigeminal neuralgia**. The more frequent types of headache, including migraine, are not due to anatomically discrete lesions in sensory pathways.

Thalamic lesions

Surgically or pathologically produced lesions in the ventral posterior nucleus of the thalamus cause profound loss of all sensations other than pain on the opposite side of the body. The intralaminar and posterior groups of nuclei in the thalamus are probably almost as important as the ventral posterior nucleus in the central pathway for pain.

Central neurogenic pain, which is not caused by activity in peripheral sensory axons, can be caused by lesions that interrupt the somatosensory pathways at any level. A destructive lesion that involves the VP nucleus of the thalamus may result in the **thalamic pain syndrome**, characterized by exaggerated and exceptionally disagreeable responses to cutaneous stimulation. This syndrome may include spontaneous pain and evidence of emotional instability, such as unprovoked laughing and crying.

Suggested reading

Apkarian AV, Hodge CJ: Primate spinothalamic pathways. I, II and III. *J Comp Neurol* **288**:447-511, 1989

Brodal P: *The Central Nervous System. Structure and Function.* 3rd ed. New York: Oxford University Press. 2004

Broman J: Neurotransmitters in subcortical somatosensory pathways. *Anat Embryol* **189**:181-214, 1994

Cook AW, Nathan PW, Smith MC: Sensory consequences of commissural myelotomy. A challenge to traditional anatomical concepts. *Brain* **107**:547-568, 1984

Craig AD: Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* **26**:1-30, 2003

Craig AD, Bushnell MC, Zhang ET, Blomqvist A: A thalamic nucleus specific for pain and temperature sensation. *Nature* **372**:770-773, 1994

De Broucker Th, Cesaro P, Willer JC, Le Bars D: Diffuse noxious inhibitory controls in man. Involvement of the spinoreticular tract. *Brain* **113**:1223-1224, 1990

Dickenson AH: Gate control theory of pain stands the test of time. Brit J Anaesth 88: 755-757, 2002

Hodge CJ, Apkarian AV: The spinothalamic tract. *Crit Rev Neurobiol* **5**:363-397, 1990

Nathan PW, Smith MC, Cook AW: Sensory effects in man of lesions of the posterior columns and of some other afferent pathways. *Brain* **109**:1003-1041, 1986

Proske U. Kinesthesia: the role of muscle receptors. *Muscle & Nerve* **34**: 545-558, 2006

Vogt BA, Derbyshire S, Jones AKP: Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. *Eur J Neurosci* **8**:1461-1473, 1996

Wall PD, Noordenbos W: Sensory functions which remain after complete transection of dorsal columns. *Brain* **100**:505-524, 1977

Willis WD, Westlund KN: Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol* **14**:2-31, 1997

The above notes on somatic sensory pathways for Neuroscience 500 are a shortened version of part of Chapter 19 in *Barr's The Human Nervous System*, 9th edition, by J. A. Kiernan. Copyright © 2009 Lippincott, Williams & Wilkins, Baltimore (published Oct. 2008). ISBN 9780781782562. Chapter 19 in the book includes diagrams of the pathways similar to those used in the lecture.

Updated October 2008