CHAPTER 7
Spinal Cord: Structure and Function

Since the spinal cord is the best-understood and least complex of the major elements of the central nervous system, it is appropriate to begin the discussion of the CNS with it. The spinal cord has two fairly distinct functions. It conducts action potentials to and from the brain and it relates to "its" segment.

The spinal cord is segmented, one segment per vertebra, and in the less complex nervous system of fish, the region of the body relating to each segment is a cylindrical band the width of the vertebra. Into this spinal cord segment flows all of the sensory information from the body segment: information on pain, temperature, and position of the muscles, touch, and vibration. The axons that innervate the muscles of that body segment have their nuclei in the spinal cord segment.

In the human there is only a general relationship between the sensory segments and muscles innervated by the same segment of the cord. The size and shape of the regions vary considerably, but the principle remains the same - that of relating, in sensory reception and motor control, to a delimited region of the body. At each segmental level, incoming sensory information connects, in a stereotyped manner, to motor outflow. The knee jerk reflex and the reflexive withdrawal from pain are examples of segmental spinal cord activity.

In addition to relating these functions to specific regions, the spinal cord processes incoming sensory information and sends some of it on to the brain. This is a second and basically distinct function of the spinal cord: conduction to and from the brain. These two functions are anatomically separated. Inspection of a cross section of spinal cord shows white columns surrounding a butterfly-shaped interior gray column *(Fig. 7-1)*. The myelin sheaths of the thousands of axons running up and down in the white matter, the dorsal, lateral and ventral funiculi, produce the white color. The thousands of cell bodies in the center give that region a gray appearance. We speak, then, of gray matter, which contains cell bodies and synapses relating to the sensory and motor activities of the segment, and of white matter, which contains axons running to and from the brain.

Each spinal cord segment has four nerve roots attached to it *(Fig. 7-l)*. Each root is made up of many nerve bundles entering the body of the cord almost continuously. The two anterior roots, which carry axons out of the spinal cord to innervate muscles, are known as motor roots. The two posterior roots carry sensory information into the spinal cord. Since man stands vertically, we refer to posterior and anterior; in animals, dorsal and ventral. The cell bodies of all of the sensory fibers are in the posterior root ganglion. Damage to the right anterior root will paralyze motor units on the right side of the body. Damage to the left posterior root will interrupt all modalities of sensation from a small region on the left side of the body. The roots join just before they leave the spinal canal, through the intravertebral foramen, and form a single spinal nerve.

GROSS ANATOMY

The gross anatomy of the spinal cord is illustrated in *Figure 7-2.* The cord runs through the spinal canal of each vertebra, as is shown in

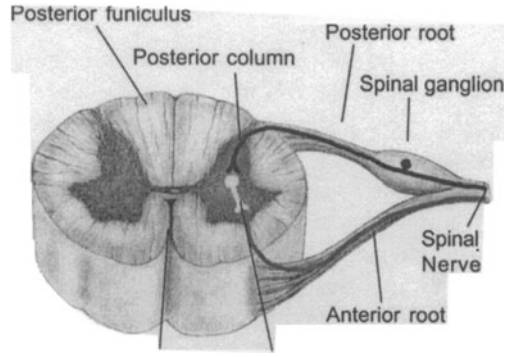

Figure 7-l. The posterior and anterior roots in relation to the gray and white matter of the spinal cord.

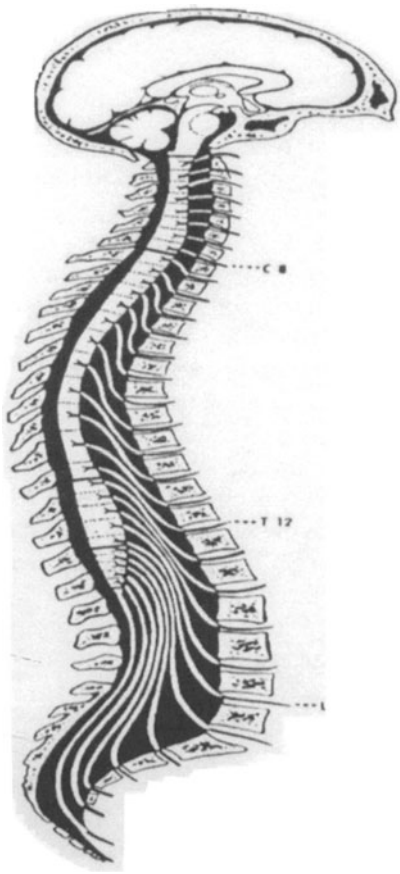

Figure 7-2. The lateral aspect of the spinal cord exposed within the vertebral canal. The spinous processes and the laminae of the vertebrae have been removed and the dura mater has been opened longitudinally. (From Clemente, C. (Ed) Gray's Anatomy, Philadelphia, Lea & Febiger,1985.)

Figure 7-3, and is protected by a number of layers of meninges. The pia mater is closely adherent to the cord. Cerebrospinal fluid occupies the subarachnoid space. The arachnoid lies snugly against the thick, tough dura. The spinal dura forms a protective tube beginning at the dura of the skull and tapering to a point in the region of the sacral vertebrae. Between the dura and the vertebrae lies the epidural space, usually filled with fat. The denticulate ligaments anchor the spinal cord to the dura.

The spinal cord and, more importantly, the spinal roots, are named in relation to the vertebral column. In humans there are 8 cervical, l2

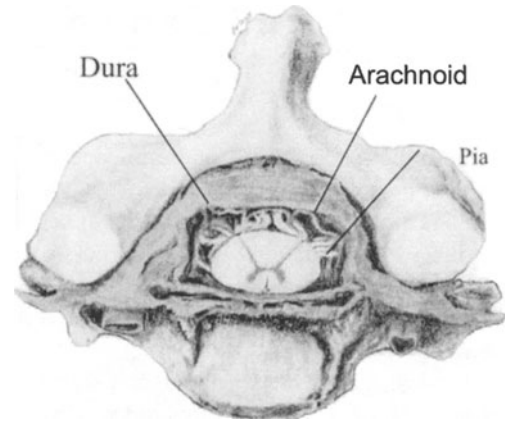

Figure 7-3. The relationships of the vertebral column, the meninges and spinal cord.

thoracic, 5 lumbar, and 5 sacral spinal cord segments. They are shown in relation to the vertebral column in Figure 7-2. There are 7 cervical vertebrae; the C8 in Figure 7-2 is the eighth cervical spinal nerve that arises from the anterior and posterior roots of the eighth cervical spinal cord segment. The eighth cervical nerve emerges below the seventh cervical vertebrae and above the first thoracic vertebrae. The spinal nerves are always named for the spinal cord segment of origin. The intervertebral disk and foramen (Fig 7-5) are normally named by the vertebrae above and below, i.e., L4, 5 disk; L5, Sl foramen.

During development and growth, particularly intrauterine growth, the vertebral column grows faster than the spinal cord it contains so that, in the adult, the spinal cord does not extend the length of the vertebral column (Fig 7-2). As a result, the spinal roots run interiorly before they leave the spinal canal. The spinal cord ends at the first or second lumbar vertebra, and below this level the spinal canal contains only spinal roots. This mass of roots reminded early anatomists of a horse's tail, so it was named cauda equina. The nerve roots run through the subarachnoid space, which is filled with cerebrospinal fluid. When a needle is inserted through the space between the fourth and fifth lumbar vertebra *(Fig 7-4)*, the point penetrates the dura and pushes aside the spinal roots. If the needle were inserted above L2 there would be danger of damaging the spinal cord. Samples of cerebrospinal fluid can be taken through this

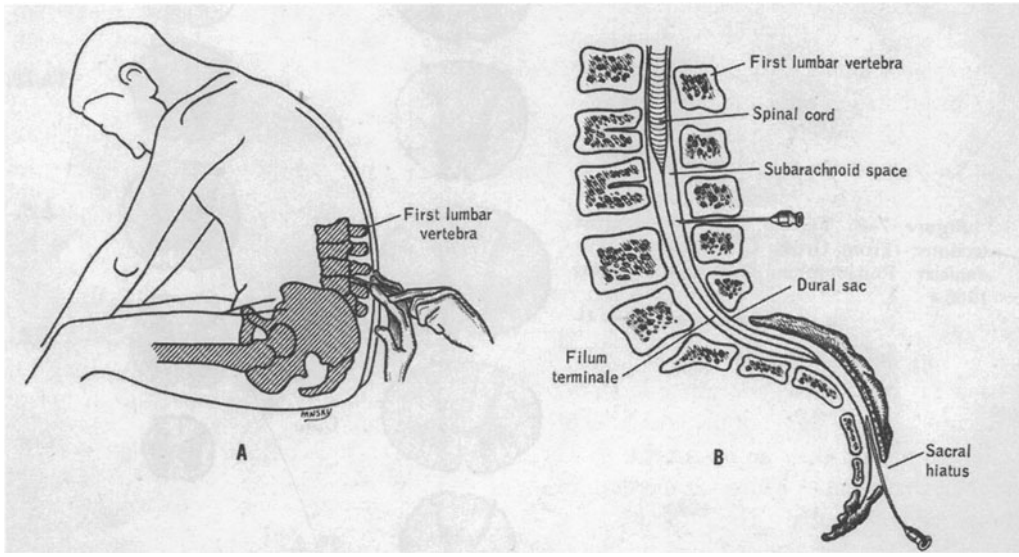

Figure 7-4. The technique of lumbar puncture. (From House and Pansky: A Functional Approach to Neuroanatomy. New York, McGraw-Hill, 1960.

needle; pressure can be measured or anesthetic agents or radio-opaque dyes (as in Fig 7-4) injected.

The anterior and posterior roots join to form a spinal nerve (Fig 7-1) just before leaving the vertebral canal through a recess in the posterior process of each vertebra as shown in *Figure 7-5.* The canal, the intervertebral neural foramina, is only a little larger than the nerve so that any swelling of the nerve or diminution of the diameter of the canal will pinch the nerve. It is not uncommon for the intervertebral disc to rupture posteriorly or laterally and press on a spinal nerve as it exits. The very intense pain this pressing causes is referred to the area of the skin where the nerve began. Frequent sites where the nerve roots are pinched are the intervertebral foramina between L2 and S1, which give rise to the sciatic nerve. The pinched nerve gives the patient the impression that a hot knife is being dragged along the posterior aspect of his calf.

Cross-sections.

The relative amounts of white and gray matter vary with the spinal cord level *(Fig 7-6).* White matter decreases in bulk as the sections are further from the brain. Motor tracts from the brain leave the white matter to enter the gray matter and synapse with motor neurons. Sensory fibers entering the cord, section by section, also form the white matter.

A section of the cervical cord contains sensory fibers running up to the brain from the thoracic, lumbar, and sacral sections. It also contains motor fibers running down to innervate motor axons of the thoracic, lumbar, and sacral sections. The white matter of a section of the lumbar cord, however, only contains fibers to and from the

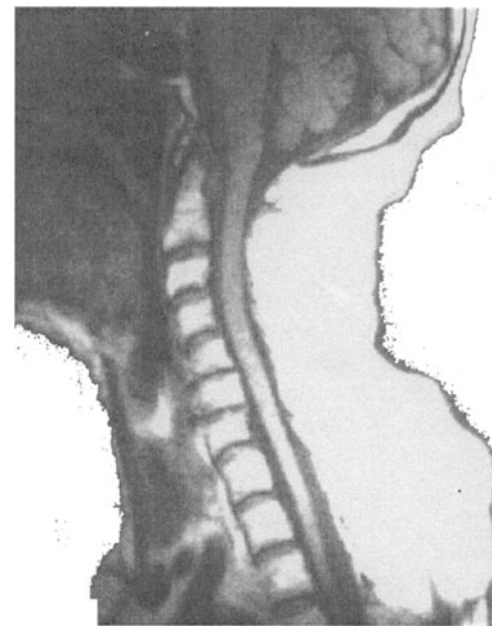

Figure 7-5. An MRI of a normal spinal cord in the spinal canal. Sagittal section.

lumbar segments inferior to it and the sacral segments. The white matter columns have the shape of thin pyramids with their bases at the foramen magnum and their tips at the last sacral section.

The situation in the gray matter is quite different. Since the gray matter innervates a segment, the size of the gray matter (the number of cells it contains) is related to the complexity of the segment. The hand, for example, is innervated by cervical segments 6, 7 and 8 (C6, C7 and C8) and the first thoracic segment (T1). The hand has the highest concentration of sensory receptors of any region of the body. All of these receptors send their axons into C6 to Tl where they synapse, thus increasing the girth of the posterior gray matter. The muscles of the hand can carry out very fine and intricate movements. They are innervated by nerves having their cell bodies in the gray matter of C6-Tl. Such movements require many motor nerves and many cell bodies in the anterior gray matter. Consequently, the cord is enlarged at C6-T1. The situation is much the same in the lumbar region. Sensory input from and motor output to the leg is complex and the gray matter is large. The thoracic and sacral segments, on the other hand, have very small gray matter areas since they innervate only a few muscles and receive relatively uncomplicated sensory messages.

Segments can be recognized, then, by the amount of gray and white matter relative to the whole cross section. In the lower cervical segments the section is large, oval, and white matter and gray matter are nearly equal. The thoracic segments have much more white matter than gray matter and the shape of the gray matter, a thin H, is very characteristic. The lumbar segments have more gray matter than white matter, and the sacral segments are very small and have much more gray matter than white matter. The segments can also be recognized by the shapes of the gray matter. A careful review of Figure 7-6 and Spinal cord Figures 1-4 in descriptive atlas should provide a basis for recognizing the segmental levels of spinal cord sections. The area of the body which sends sensory fibers into a given spinal cord segment is called a dermatome. These have varying shapes and sizes. Figure 7-7 may help you to remember the general area

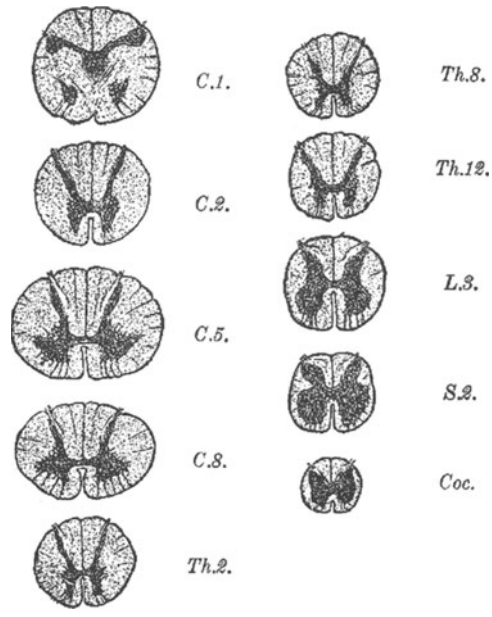

Figure 7-6. Typical spinal cord cross sections. (From Gross, C.M. (ed.): Gray's Anatomy. Philadelphia, Lea and Febiger.

served by the cord segments. The muscles underlying these areas have essentially the same innervation. More detailed areas are shown in chapter 8.

SEGMENTAL FUNCTION

Anterior horn Cells

The final effector cell of the spinal cord, the anterior horn cell *(Fig. 7-8)* is probably the best place to begin a discussion of the segmental function of spinal cord segments. The extensive dendritic tree allows upwards of 20-50,000 individual synaptic areas or knobs while the large cell body may have another l-2,000 synaptic knobs. Incoming axons may have more than one synaptic connection and hence exert greater control. Each anterior horn cell gives rise to one large (8 to l2 _m) axon, called an alpha motor neuron, which innervates a motor group or unit made up of 10 to 200 individual muscle fibers. There is only one motor end plate on each muscle. Therefore, for a motor group to contract, the anterior horn cell on the proximal end of the axon must fire an action potential. The muscle group is chained to its anterior horn cell. This anatomical relationship is often called the final common pathway. Activation of a specific ante-

rior horn cell precedes activity of a motor group. There are many ways to activate this anterior horn cell, many thousand axons synapse upon it and its extensive dendritic tree.

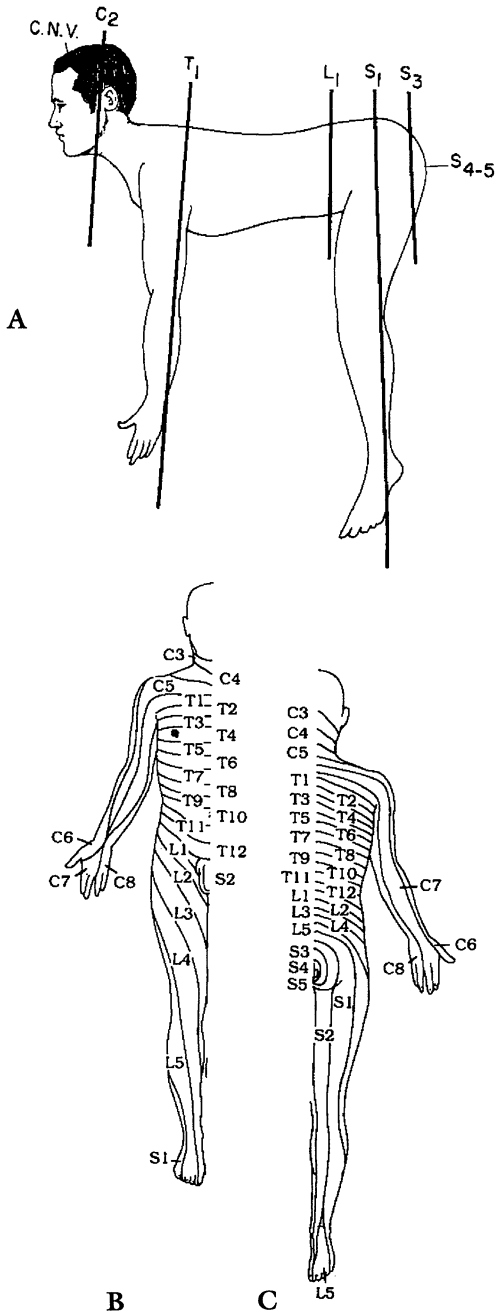

Figure 7-7. Key dermatome boundaries in man. A. Anatomical Position. B-anterior surface and C-posterior surface. From Zimmerman J and Jacobson S, Gross Anatomy, Little Brown 1990.

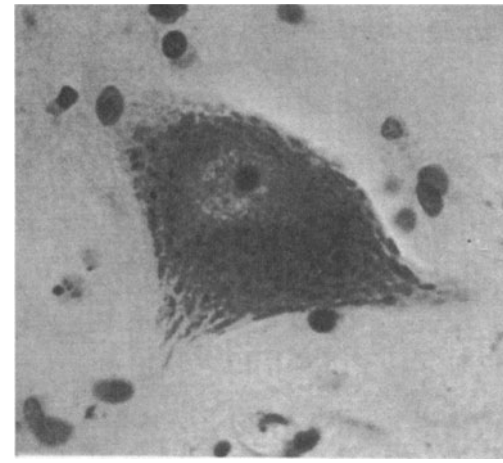

Figure 7-8. A motor neuron from the cervical spinal cord of a human with prominent Nissl substance(rough endoplasmic reticulum), AAThionin Stain <X 75>.

Neurons in the anterior horn can be divided into medial, and lateral groups *(Fig. 7-9)*.

1. The medial nuclear division is divided into posterior medial and anterior medial groups. The posterior medial nucleus is most prominent in the cervical and lumbar enlargement. The medial nucleus innervates the muscles of the axial skeleton.

2. The lateral nuclear division innervates the appendicular musculature. In the thoracic region the intercostal and associated muscles are innervated by this region. In the cervical and lumbar enlargement, these nuclei become especially prominent and are divided into individual columns of nuclei (Fig. 7-9) and these nuclei columns include anterior, anterior lateral, accessory lateral, posterior lateral and retroposterior lateral. These nuclei are represented functionally so that from medial to lateral one passes from midline spine, to trunk, upper and lower limb girdle, upper leg and arm and lower leg and arm to hand and foot. The most lateral nuclear groups innervate the muscles in the hand and foot.

3. The preganglionic autonomic nuclei lie in the intermediolateral column, a prominent lateral triangle in the gray matter (Fig 7-6; Th.2). There are two distinct groupings. The intermediolateral nucleus from C8 to L2 is the origin of the preganglionic sympathetic neurons which synapse again either in the sympathetic trunks or

in remote ganglia. The sacral nucleus in S2 to S4 is the origin of preganglionic parasympathetic fibers that run to several ganglions in the walls of the pelvic organs.

REFLEXES OF A SINGLE MUSCLE

All of the sensory axons entering the posterior roots are bipolar cells having their cell bodies in the posterior root ganglion. The axons can be divided into many classes by the sensory modality they carry. As far as we know, each axon carries information about only one modality, such as pain. The intensity of the pain or other sensation is coded as action potential frequency. Later in this chapter, the various modalities will be dis-

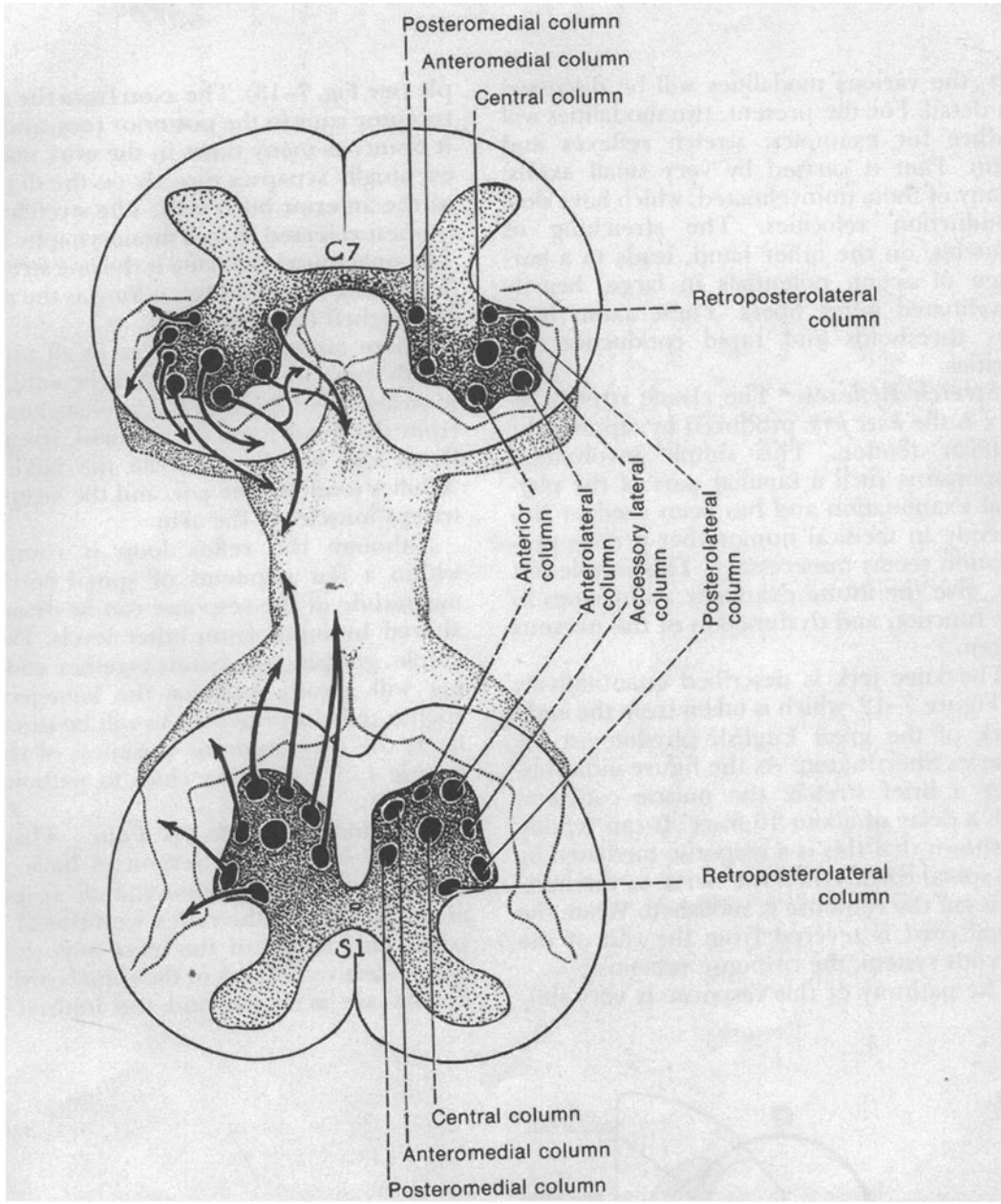

Figure 7-9. Functional localization within the anterior horns. (From Bossy: Atlas of Neuroanatomy. Philadelphia, W.B. Saunders, 1970.)

cussed in detail. For the present, two modalities will suffice for examples: muscle stretch and pain. Pain is carried by very small axons, many of them unmyelinated, which have high thresholds and slow conduction velocities. The stretching of muscles, on the other hand, leads to a barrage of action potentials in large, heavily myelinated nerve fibers. These axons have low thresholds and rapid conduction velocities.

Stretch Reflexes. The classic stretch reflex is the knee jerk, produced by tapping the patellar tendon. This simple involuntary response is such a familiar part of the physical examination and has been used so frequently in medical humor that precise description seems unnecessary. This simple test can give the astute examiner many clues to the function and dysfunction of the nervous system.

The knee jerk is described quantitatively by *Figure 7-l0,* which is taken from the early work of the great English physiologist Sir Charles Sherrington. As the figure indicates, after a brief stretch, the muscle contracts with a delay of about l0 msec. It can readily be shown that this is a response mediated by the spinal cord. When the nerve to the muscle is cut, the response is abolished. When the spinal cord is severed from the rest of the nervous system, the response remains.

Figure 7-10. A brief stretch reflex recorded from the quadriceps tendon. The initial small, sharp response is the quick stretch which initiated the large response. The time marks are 20 msec apart. (From Ballif, et al.: Proc. Roy. Soc., B98, 589, 1925.)

The pathway of this response is very simple *(Fig. 7-ll).* The axon from the stretch receptor runs into the posterior horn, and while it branches many times in the gray matter, it eventually synapses directly on the cell body of the anterior horn cells of the muscle stretched. The stretch reflex is often referred to as a monosynaptic reflex. The only muscle which contract is the one stretched. The reflex continues for as long as the muscle is stretched *(Fig. 7-l2).*

There are stretch reflexes in all muscles, but they are much stronger in the antigravity muscles, particularly the leg extensors. In addition to the familiar knee jerk from the quadriceps group, brisk stretch reflexes can be elicited from the ankle (the Achilles tendon), the jaw, and the biceps and triceps muscles in the arm.

Although the reflex loop is completed within a few segments of spinal cord, the magnitude of the response can be drastically altered by input from other levels. For example, grasping the hands together and pulling will greatly enhance the knee-jerk response (reinforcement). As will be discussed later, the magnitude or briskness of the response can give many clues to pathological processes.

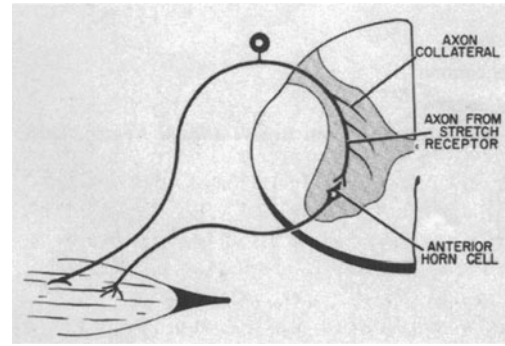

Figure 7-11. The pathway for the monosynaptic stretch reflex.

Reflexive Response to Pain. The majority of spinal cord responses have more flexibility than the monosynaptic response, as can be seen in the reflex withdrawal from pain. This is one of the most important of the protective reflexes of the spinal cord. The flexors are activated and the injured limb withdrawn. Figure 7-l2 shows the responses of the ankle flexor muscle, the tibialis anterior, to stimulation of the nerve branches leading to the skin - branches which contain predominantly pain fibers. It can immediately be seen that the combined response is considerably greater than the sum of the two. This augmentation of response is known as facilitation and is one of the most basic integrative responses of the nervous system. The reaction is graded in response to the intensity of the stimulus and the

area stimulated.

The mechanism of facilitation is shown in *Figure 7-13.* Stimulation of nerve A excites two anterior horn cells to threshold. Two more are excited in a subthreshold manner; they do not fire an action potential. Nerve B stimulates two totally different anterior horn cells to threshold and the same two to just below threshold. Simultaneous activation of nerves A and B brings all six cells to threshold and elicits a greater tension from the muscle.

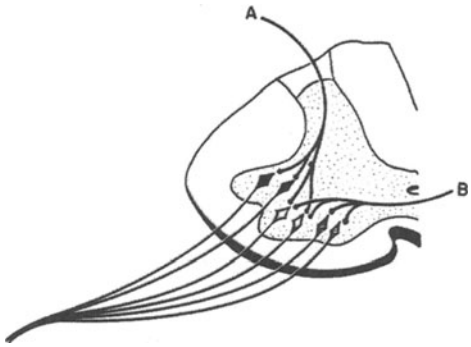

Figure 7-13. A mechanism of summation. Stimulation of nerve A fires the solid anterior horn cells and excites the clear cells. Stimulation of nerve B excites the lined cells to fire and excites the clear cells. Stimulation of both nerves fires all of the cells.

RECIPROCAL INNERVATION OF A JOINT

When the biceps femoralis muscle contracts, the opposing muscle, the quadriceps, is stretched because both muscles are connected to the tibia. The quadriceps group has a strong stretch reflex which is not elicited when the biceps femoralis contracts. When the quadriceps tendon is stretched, stretch reflex tension develops *(Fig. 7-14).* The tension is maintained until the biceps tendon is stretched; then the tension abruptly drops. This diminution or abolition is called inhibition. Inhibition is, together with facilitation, the keystone of the integrative action of the spinal cord and probably the entire nervous system.

The pathway for the inhibitory response is shown in *Figure 7-15.* A collateral (branch) of the stretch receptor nerve from the biceps muscle runs to an interneuron, which in turn synapses on the anterior horn cells of the quadriceps. As far as we know, all inhibitory responses are carried out through at least one interneuron. The endings of one nerve, such as the stretch receptor nerve, all have the same effect, either facilitation or inhibition. For the nerve pathway to exhibit the other type of function, an interneuron must intercede.

The pathway for the inhibition shown in *Figure 7-14.* Trains of action potentials from the stretch receptors of biceps enters the anterior root and stimulate biceps anterior horn cells and via an interneuron, inhibits the quadriceps muscle.

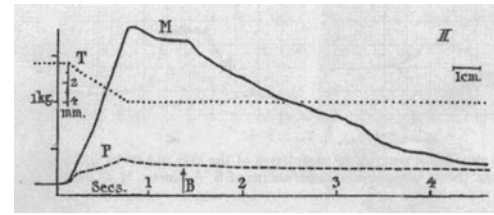

Figure 7-14. Inhibition of a stretch reflex (M) in an extensor muscle, quadriceps, by stretch, at B, of a flexor muscle, biceps. T is the applied stretch to the extensor tendon that initiated the stretch reflex. (From Liddell and Sherrington: Proc. Roy. Soc., B97, 267, 1925.)

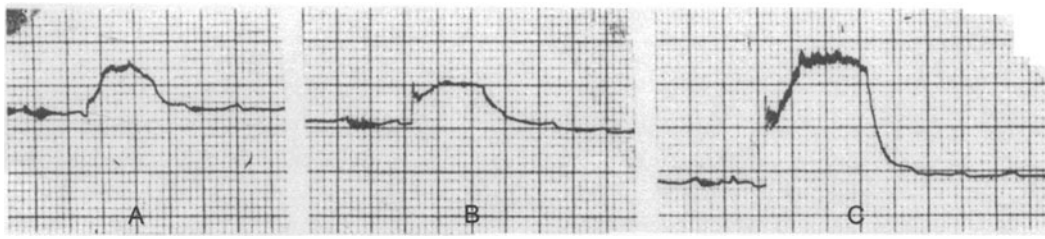

Figure 7-12. Tension response in the tibialis anterior to stimulation of the skin of (A) the ipsilateral foot, (B) ipsilateral calf, or (C) both. Stimulation of both sites results in a tension response greater than the sum of the individual responses: summation. Spinal rabbit. (From unpublished experiments of B.A. Curtis, M.C. Fleming, and E.M. Marcus.)

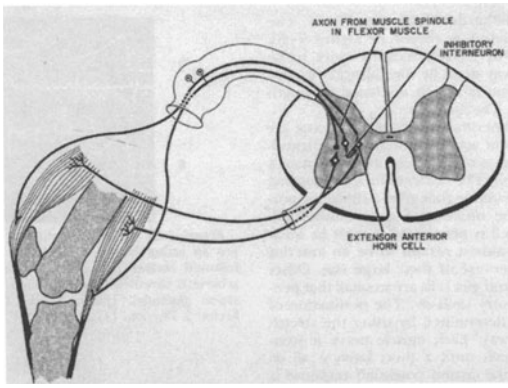

Figure 7-15. The pathway for the inhibition shown in Figure 7-14. Trains of action potentials from the stretch receptor of biceps enters the anterior root and stimulate biceps anterior horn cells and, via an interneuron, inhibits the quadriceps anterior horn cells.

MEMBRANE BASIS OF INTEGRATION

When a microelectrode is inserted into the anterior horn of the spinal cord, the tip, with luck, eventually penetrates an anterior horn cell. This penetration is signaled by the abrupt jump of voltage between the tip and the extracellular fluid from 0 to -70 mV. This intracellular work was pioneered by Sir John Eccles and his collaborators and is discussed at length in his book, *The Synapse*. In this experiment the anterior roots are cut to prevent action potentials, generated by the stimulator, from traveling up the motor axons antidromatically (backwards). Stimulation, then, mimics only sensory input. Low voltage stimulation activates only the larger, stretch receptor axons. The extracellular recording from the posterior root gives a signal proportional to the number of axons stimulated. After the cell is penetrated it must be identified; it is almost certain to be an anterior horn cell because of their large size. Other cell bodies and glia cells are so small that penetration is very unlikely. The destination of its axon is determined by using the stretch reflex pathway. Each muscle nerve is stimulated in turn until a short latency, all or nothing; spike (action potential) response is obtained. This is the equivalent of a monosynaptic stretch reflex. A spike response recorded from an anterior horn cell is the counterpart of muscle tension.

Excitatory Postsynaptic Potential, EPSP. When a flexor anterior horn cell has been located, the record in Figure 7-16 is obtained by stimulating a cutaneous nerve to mimic pain. When the nerve is stimulated at high voltage, many small pain fibers are stimulated. The response in the anterior horn cell can be the firing of an action potential, as in the lowest record. This response is the electrically recorded counterpart of the reflexive withdrawal from a painful stimulus, as shown in Figure 7-13. When the stimulus intensity is reduced, upper records; intensity is reached when no action potential is produced, yet the cell body still responds. The response is a subthreshold depolarization of the anterior horn cell called an excitatory postsynaptic potential, abbreviated EPSP. This response brings the anterior horn cell closer to threshold, that is, closer to firing an action potential that would cause contraction of a motor group. The EPSP is localized to the cell body and dendrites. The axon is unaffected. In contrast to the action potential, it is a graded response.

The EPSPs can add up until threshold is reached and an action potential is fired as is shown in Figure 7-17. Note that the second EPSP in A is larger (greater depolarization) than the first. The effect of the first had not yet "worn off" and the second could add on top of it. In B the second EPSP follows sooner and adds up to a threshold depolarization, initiating an action potential.

This is the basic mechanism of facilitation. The two classic types of facilitation, temporal and spatial, are the same in terms of a membrane response: the EPSP's add up. Spatial response refers to the EPSP's generated as a result of the activation of two different nerves as Figure 7-13. Temporal summation, as illustrated in Figure 7-20, means summation in time; its membrane basis depends upon the time course of the EPSP. The membrane repolarizes slowly following the initial rapid depolarization of an EPSP and a second EPSP can add upon the first. Frequently this "added boost" will bring the cell membrane to the threshold for firing an action potential in the axon.

Delay.

There is a delay of approximately 0.8 msec between the arrival of an action potential from a stretch receptor axon and response of an anterior

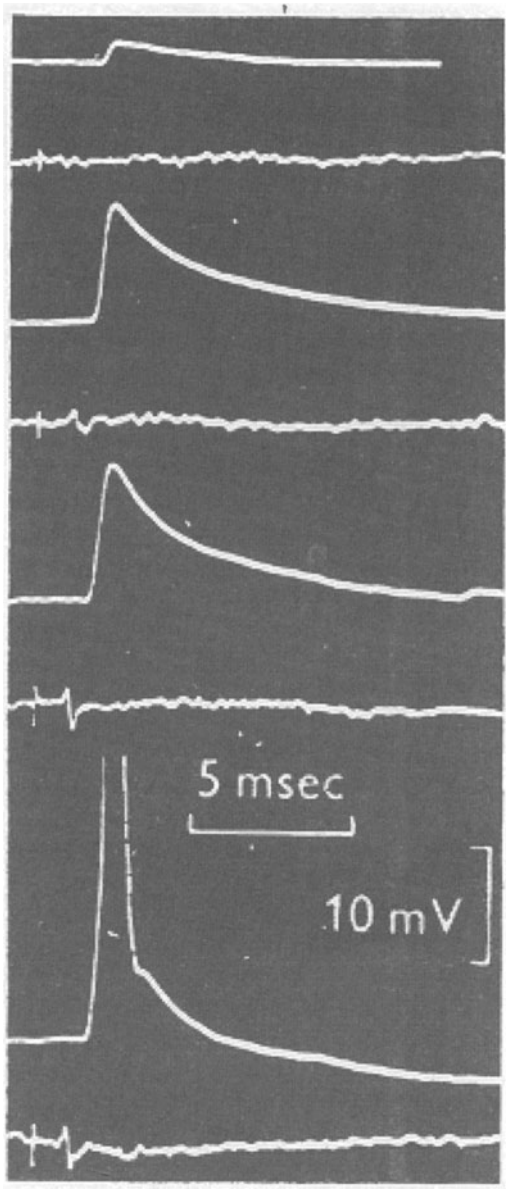

Figure 7-16. EPSP's: The upper trace of each pair is an intracellular record from a biceps anterior horn cell. The lower trace of each pair is the action current from the posterior root and is proportional to the number of sensory axons firing. As the number of axons firing increases, the depolarization (an EPSP) increases until threshold for the anterior horn cell is reached and an action potential fires. The bottom pair of records is the intracellular version of a stretch reflex. The rest of the action potential of the lower record is off the scale. The average resting potential is - 70 mV. (From Brock, Coombs, and Eccles: J. Physiol., 117, 431, 1952.)

horn cell. This delay and other features strongly support chemical transmission at the synapses on the anterior horn cell. The identity of the transmitter is still not entirely clear although there is a great deal of evidence to suggest that L-glutamate and L-aspartate are the transmitters for many of the excitatory synapses in the spinal cord.

These transmitters destroy the selective permeability of the postsynaptic membrane, just as acetylcholine does at the myoneural junction. The equilibrium potential is then zero millivolts. The membrane never reaches zero under the influence of excitatory transmitters since they are rapidly removed. At the anterior horn cell membrane, however, unlike the myoneural junction, the amount of excitatory transmitter released is not always sufficient to depolarize the cell body to threshold.

Inhibitory Postsynaptic Potential, IPSP. When the nerve leading to the quadriceps muscle is stimulated, the membrane of a flexor (an antagonist) anterior horn cell hyperpolarizes, as shown in the recordings in *Figure 7-18.* This hyperpolarizing response called an inhibitory postsynaptic potential (IPSP), moves the membrane further from threshold, making it more

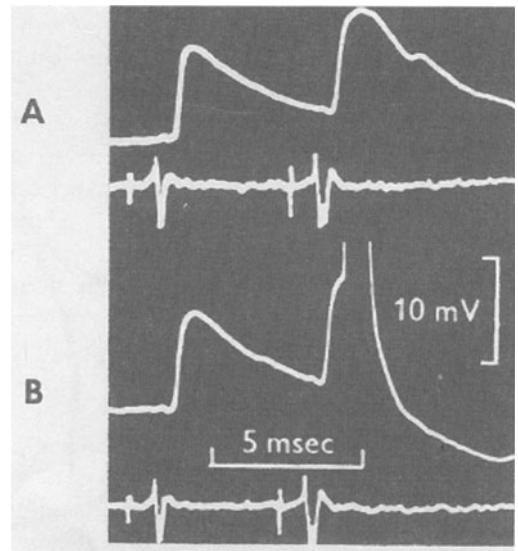

Figure 7-17. The summation of two EPSP's to fire an action potential. In B the second EPSP followed sooner and added upon the first to achieve a threshold depolarization, initiating an action potential. (From Brock, Coombs, and Eccles: J. Physiol., 117, 431, 1952.)

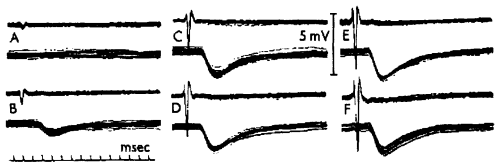

Figure 7-18. The response (an IPSP) of a biceps anterior horn cell to stimulation of the quadriceps nerve. The upper trace of each pair is the action current from the posterior root; the lower is the intracellular record. The greater the number of sensory axons firing the more negative and longer lasting is the IPSP. (From Coombs, Eccles, and Fatt: J. Physiol., 130, 396, 1955.)

difficult to fire an action potential and is a postsynaptic inhibition. The IPSP is the membrane equivalent of inhibition. As noted earlier, inhibition is effected through an interneuron (Fig. 7-l4).

The transmitters substances responsible for the IPSP include GABA and glycine. They specifically increase the chloride conductance of the anterior horn cell, typically for hundreds of msec. The membrane potential at rest is -74 mV, indicating there is considerable sodium conductance in relationship to potassium and chloride conductances. The calculated values for potassium, chloride, and sodium equilibrium voltages are: VK = -90 mV, VCl = -80 mV and VNa = +45 mV. A large increase in chloride conductance will result in a membrane potential of -80 mV and this is the equilibrium potential at the height of the IPSP.

Summation of IPSP's and EPSP's can occur as shown in *Figure 7-19*. The microelectrode is recording from an anterior horn cell innervating biceps (a flexor). When the stretch receptor nerve from the biceps is stimulated (Fig. 7-19A), an action potential fires; this is the stretch reflex. When the nerve to the quadriceps (an opposing extensor) is stimulated (Fig. 7-19B), a large IPSP is recorded; this is the inhibition of a stretch reflex of an opposing muscle. When the two are stimulated 45 msec apart (Fig. 7-19C), the cell fires. When the delay was reduced, the membrane depolarizes but does not reach threshold (Fig. 7-19D).

SYNAPTIC MECHANISMS

The dendritic tree and cell bodies of spinal cord neurons contain a varied collection of receptor mediated ionic channels that are sum-

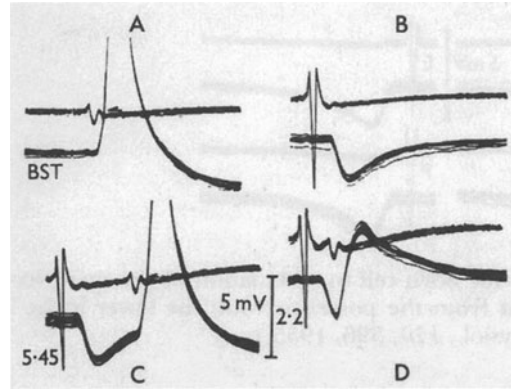

Figure 7-19. Summation of an IPSP and an EPSP. The lower trace of each pair is an intracellular recording from a biceps anterior horn cell. The upper trace is the action current in the posterior root. In A the nerve to the biceps was stimulated and an action potential evoked; this is the intracellular equivalent of a stretch reflex. In B the nerve to quadriceps was stimulated and an IPSP was evoked. In C the two were stimulated 45 msec apart and a spike resulted. In D the two were stimulated 2.2 msec apart and no action potential resulted; the IPSP generated by the quadriceps stimulus inhibited the biceps anterior horn cell. In C the hyperpolarization effect of the IPSP had declined by the time the second nerve was stimulated. (From Coombs, Eccles, and Fatt: J. Physiol., 130, 396, 1955.)

marized in Figure 7-19 along with some of the neurotransmitters implicated in their activation. All of these ionic channels act on a time scale of milliseconds to seconds.

The fast EPSP channel (A) is very similar to the ACh channel at the myoneuronal endplate. It opens to all small ions and depolarizes rapidly and decisively. The somewhat slower IPSP Cl-channel (B) is equally important. Selective increase in PK (C) usually occurs after action potential firing in the axon and is thought to be mediated by increasing Cai, possibly Ca entering during the very positive voltages of the action potential. All of these mechanisms depend on increasing ionic permeability (decreasing cell resistance) and to rapidly changing intracellular ionic concentrations which must be restored by energy expenditure.

The next two mechanisms (D,E) rely on decreases in permeability and are more energy efficient.

The active transport of unequal numbers of

ionic changes can result in changes in membrane voltage; 3Na/2K and 3Na/Ca are examples. The relative importance of this electrogenic mechanism is not clear.

Intermediate term changes in neuron baseline characteristics (more or less excitable) are produced by altering the number of active channels on the cell surface. For example, in response to noxious stimuli 5 HT is co-released from sensory a nerve which increases the C-AMP level of the interneuron causing rapid inactivation by dephosphorylation of potassium channels. Whenever an action potential enters the presynaptic region, the depolarization is prolonged because the normal increase in PK that hastens repolarization is lacking. Consequently, the voltage gated Ca channels remain open longer allowing greater Ca entry and hence greater transmitter release. This augmented response may last for several hours after 5 HT liberation. The key to specificity is both the type of receptor and the enzyme chain-second messenger system linked to it. Receptors for Epinephrine & Norepinephrine increase the number of phosphorylated, hence active, Ca channels.

Enhancement of synaptic transmission lasting one or more days occurs by increasing the amount of neurotransmitter released from each synaptic vesicle. Increase in synaptic vesicle content presumably reflects changes in gene expression that could last a very long time and might be the synaptic basis of long-term memory. This mechanism alters the importance of existing synapses. A synaptic junction that previously needed the cooperative effort of l0 other synaptic junctions to depolarize the cell body to threshold can now do so alone.

The only other major variants seen when recording from anterior horn cells are long-lasting (30 to 40 msec) responses. These are thought to involve many interneurons possibly arranged in a circular path so that an action potential "chases its tail" around the circuit for several revolutions, stimulating the anterior horn cells on each revolution. They may also be produced by long acting neurotransmitters co-released from the same axons that release the shorter acting neurotransmitters.

Slow Potentials. Action potentials in axons making synaptic contact with the dendrites or cell body of an anterior horn cell are expressed within the anterior horn cell as depolarizations (EPSP's, a very few of which will, by themselves, fire the cell) and hyperpolarization (IPSP's, which inhibit firing). The membrane potential of the cell is constantly changing under the influence of these two types of input. Whenever the membrane potential reaches the firing level of the axon (-55 mV), action potentials are generated with a frequency proportional to the depolarization past threshold. For the purposes of transmission, depolarization, more positive than threshold, is coded as frequency. When these action potentials bombard another cell they are once again decoded into changes in the membrane potential of that cell body.

It is not clear why the EPSP's and IPSP's recorded from the cell body are of different amplitude. This may be due to differences in the amount of transmitter released or may be due to the location of the synapse on the cell. Since the dendrites, like the cell body, conduct potential disturbances in a decremental, cable fashion, synapses close to the cell body will have a greater influence on the membrane potential.

It is possible to show inhibition of firing of anterior horn cells without any change in the resting membrane potential; no IPSP precedes the inhibition. The inhibition is thought to take place presynaptically, either at a nearby unidentified interneuron or more probably, in the junction region between the axon and the dendrite. We will discuss this type of inhibition later in this chapter.

STRETCH RECEPTORS

The Muscle Spindle. In the previous discussion of spinal reflexes, reference to stretch receptors was very general. The major dynamic stretch receptor is the muscle spindle. This is a bundle of modified muscle fibers that lie parallel to the rest of the muscle fibers. Its structure is shown in Figure 7-20; it is composed basically of three to five small muscle fibers each containing a specialized, nonstriated region in their center. The striated ends of the muscle fibers can contract and are innervated by small, gamma motor neurons. These gamma motor neurons have cell bodies in the anterior horn, just as do the large alpha fibers that innervate the bulk of the muscle.

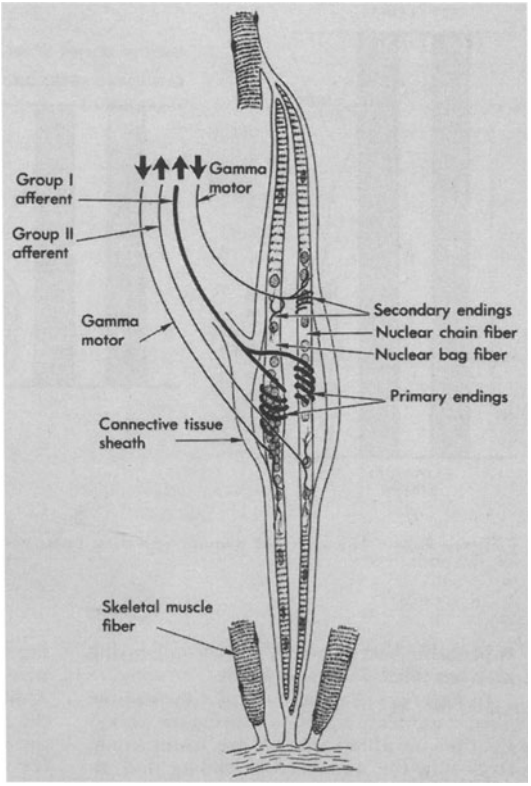

Figure 7-20. A muscle spindle. (From Gardner: Fundamentals of Neurology. Philadelphia, W.B. Saunders, 1968.)

The small muscle fibers in the spindle are called intrafusal fibers, and the large muscle fibers that make up the bulk of the muscle are referred to as extrafusal fibers. The extrafusal fibers are primarily innervated by large (8-12 μ) axons. The pattern is not exclusive and there is some dual innervation; alpha motor fibers to both intra and extrafusal fibers.

There are two sensory nerves which take origin from the unstriated center region of the muscle spindle. The largest, (12 μ) classified Ia, comes from the center of the sensory region. The unmyelinated ends of the nerve wrap around each of the muscle fibers and are called primary or annulospiral endings. From these endings arise the action potentials that stimulate the stretch reflexes. This axon gives off many types of collateral within the gray matter of the cord that then travel up and down the cord for several segments.

The second ending gives off a smaller nerve, classified IIa, from specialized, secondary or flower-spray endings on either side of the annulospiral ending. These axons rise to the ipsilateral cerebellum, carrying information on "unconscious position sense". They apparently play no part in the stretch reflex.

The basic function of the stretch receptor is to fire when the muscle is stretched. The response of the annulospiral ending is of short latency. The frequency of firing is at first high; it then slows down, but never adapts completely.

The Gamma System. The function of the intrafusal muscle fibers is more difficult to understand. The first function is to keep the muscle spindle tight as the extrafusal fibers contract; Figure 7-26 shows this. At the rest length (A) the spindle is tight. Any further stretch will set up a volley of action potentials in the Ia sensory nerve that will lead to a stretch reflex; contraction of the extrafusal fibers. When the extrafusal fibers contract because of firing in the alpha motor neuron alone, the spindle goes slack (B) and is no longer responsive to stretch. Indeed the muscle would have to be pulled out slightly further than the rest position for the spindle to react. To rectify this situation, the gamma motor neuron fires, thus contracting the intrafusal fiber, and the spindle is tight again (C). Through the mechanism of the gamma motor neurons the sensitivity of the stretch reflex is maintained throughout the entire range of the limb movement. For example, the knee-jerk reflex can be elicited in many positions of the lower leg.

Another function of the intrafusal fibers is to change the sensitivity of the annulospiral ending (Fig. 7-21). It can easily be seen, in the last column, that the response to 20 gm tension or an equivalent stretch can be drastically altered by activity of the intrafusal fiber. Apparently the annulospiral ending reacts to stretch or deformation whether it is from without, as in stretch, or from within, as in intrafusal muscle fiber activity.

Probably the most important function of the intrafusal fibers is to modulate contraction of the extrafusal fibers via the stretch reflex. It is clear from Figure 7-21 that activation of the gamma fibers and subsequent contraction of the intrafusal fibers sets up a response in the Ia sensory fibers which is indistinguishable from the response to stretch (compare response in the upper right and lower left in Figure 7-22. This

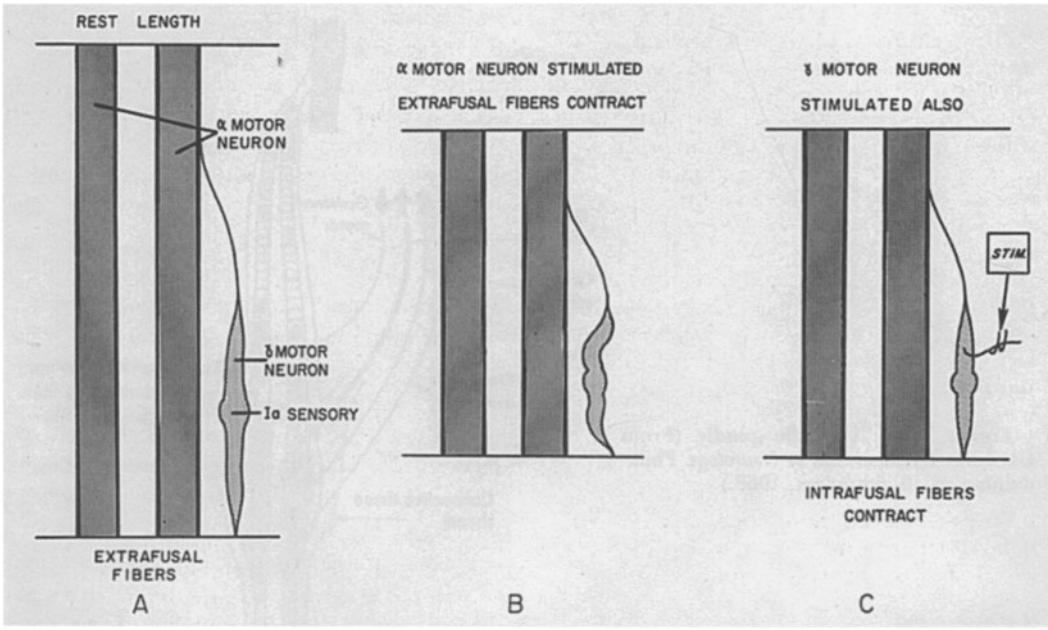

Figure 7-21. The effect of gamma activation of intrafusal muscle fibers upon maintenance of "tone" in the muscle spindle. When just the extrafusal fibers contract (B) the spindle becomes slack and unresponsive to small stretches. When both alpha and gamma systems are activated, the spindle is once again taut and responsive to small stretches.

activation of the Ia sensory fiber leads to contraction of the extrafusal fibers. This is probably best shown by the accompanying sketches (Figs. 7-22).

The length of A is the equilibrium point for the stretch reflex when there is no gamma activity; stretch of this muscle would lead to extrafusal contraction. At A the gamma fiber is suddenly activated. During the period B, the intrafusal fibers are contracting, stretching the annulospiral ending and altering the sensitivity of the primary stretch receptor to the dashed line. The Ia ending increases its rate of firing and causes reflexive shortening of the extrafusal fibers and shortening of the muscle as a whole, as is happening in C. This process continues in D until point E is reached. At E the muscle as a whole has contracted sufficiently to decrease the stress on the center region of the muscle spindle and reduce the rate of firing of the Ia fiber to threshold for the stretch reflex.

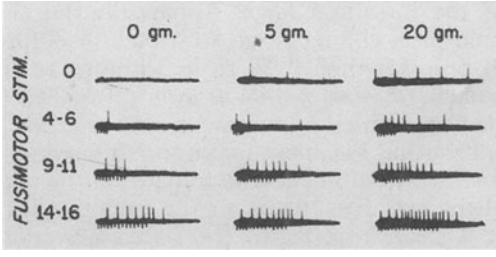

Figure 7-22. The response of an Ia fiber from an annulospiral ending to stretch and gamma activity. Notice that the number of action potentials fired increases with stretch (weight) and gamma activation. The downward deflections are stimulus artifacts of gamma stimulation. (From Kuffler, et al.: J. Neurophysiol, 14, 29, 1951.

The shortening and subsequent maintenance of muscle length and, consequently, of the joint angle was brought about by a constant gamma activation (Fig 7-24). The rate of firing of the gamma system, initiated by the brain, has not changed during the entire time. The new position (E) is not affected by the load the muscle had to move. If the load was light, the new position was reached quickly; if the load was heavy the new position was reached slowly. In any event, the new position was reached and maintained without further judgment from the motor centers of the brain.

This loop will provide good length control if movement is very slow. If movement is faster, this simple type of loop will begin oscillating because of nerve conduction and synaptic delays. As the muscle is contracting, its length at t=0 is

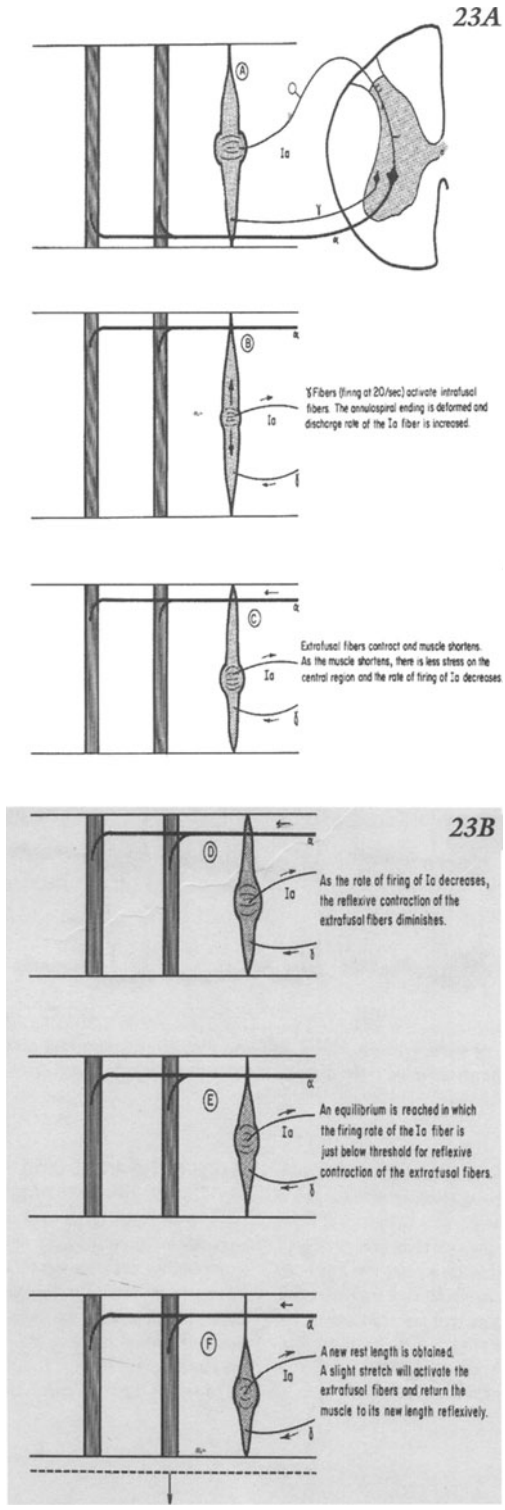

Figure 7-23A. & 23B The role of the gamma system in setting a new muscle length. (Refer to text for discussion.)

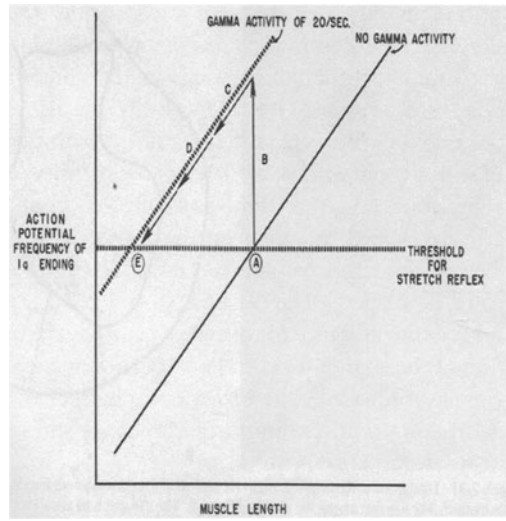

Figure 7-24. The effect of gamma activation upon maintenance of "tone" in the muscle spindle.

sent up the sensory nerve and arrives at the spinal cord at t+15 msec. After a 5 msec delay the rate of firing of the anterior horn cell varies. This variation arrives via the motor nerve at the muscle in another 15 msec. Thirty-five msec have elapsed, the muscle is no longer at its original length and the "correction" is no longer correct. This will lead to a cycle of over corrections around the intended length: oscillations.

The oscillations can be rectified if the control system is given information on the rate of change of position, velocity. With this information the control system in the spinal cord can figure out where the muscle will be at the end of the delay time and make corrections accordingly. Careful inspection of Figure 7-21, particularly the right hand column, will show that the firing rate at the beginning of movement is faster: there is velocity information in the signal from the stretch receptor.

The difficulty with the pure gamma stimulation of muscle activity theory is that recordings such as are shown in Figure 7-21 show that the alpha fibers are activated at about the same time as the gamma fibers, not 30-40 msec later as the theory predicts. Other evidence suggests that muscle movement probably gets started by direct alpha stimulation and is later reinforced by reflexive gamma stimulation. The termination point may well be found and maintained mainly through the gamma system.

Let us digress a moment and consider the simplest type of muscle movement - opposing the thumb to the palm. Cells in the anterior horn are activated by fibers from the large descending corticospinal tract, a direct pathway, of which more will be said later. The intensity of stimulation and the number of motor groups activated are determined by the motor cortex. The motor cortex basically sets the tension that is to be developed. The distance moved is a function of the resistance to movement and the duration of the stimulus. The extent of movement is visually controlled; when the thumb reaches the desired position, the motor cortex stops stimulating the anterior horn cells.

In contrast to this type of movement, which requires constant attention if the desired position is to be achieved, many of our movements, such as walking, require little attention beyond the decision to walk along the sidewalk. Most of us can even chew gum at the same time! These movements are probably carried out through mediation of the gamma system, which allows the brain to set a desired position and then forget about it. Compare, then a corticospinal system, which produces a force, and a second system, the gamma system, which produces a new position. Although it is not completely clear at this time, it would appear that the gamma anterior horn cells are innervated by descending motor tracts other than the corticospinal. This system is controlled by neurons in the brain stem; the reticular formation, the vestibular nucleus and the red nucleus.

Golgi Tendon Organs. Golgi tendon organs are a second type of stretch receptor found in the tendinous insertion of muscles. It contains no muscle fiber system. This receptor is in series with the muscle fibers and signals tension via Ib sensory fibers. It is much more sensitive to tension generated by the muscle than to stretch of the muscle. Activation of the sensory fibers from the tendon organ causes an inhibition of the contraction of the muscle. Among the functions of the tendon organ is to protect the insertion of the muscle from too great a stress which might tear the insertion from the bone. Tension information from the tendon organ is transmitted to higher centers via both dorsal and ventral spinocerebellar tracts.

INTERNEURONS

Only a very small portions of the cells of the gray matter of the spinal cord are anterior horn cells; the vast majority are interneurons - small cells with short dendrites and axons. These cells interconnect incoming sensory axons and descending spinal cord tracts with each other and with anterior horn cells.

One such interneuron is the Renshaw cell that must be studied in a somewhat roundabout fashion. After the posterior (sensory) roots have been cut, stimulation of a muscle nerve (for example, to the gastrocnemius) will result in action potentials traveling back up the motor nerve (antidromic) and entering the spinal cord. An extracellular electrode records a burst of high frequency action potentials from the Renshaw cell in response to a single volley of action potentials *(Fig. 7-26)*. Electrophoresing dye from a recording electrode has localized these cells. After a Renshaw cell has been characterized physiologically by its response to antidromic stimulation, dye is deposited at the tip of the electrode by passing current through the microelectrode. An example of this widely used technique is shown in Figure 7-27. When many such dots are placed together on a spinal cord cross section (Fig. 7-27) they all appear in the most anterior portion of the anterior horn. This is the same region in which the axons from the anterior horn cells branch.

The firing of anterior horn cells activates the Renshaw cell with acetylcholine as the neurotransmitter. Studies of a Renshaw cell show it to

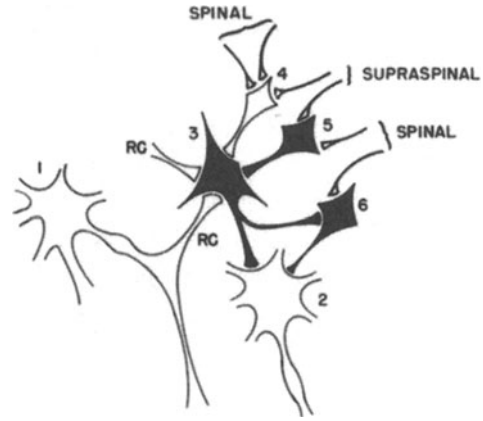

Figure 7-25. Major classes of input to Renshaw cell.

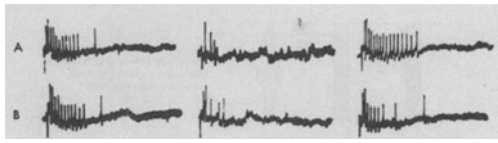

Figure 7-26. Renshaw cell activity, left hand responses are produced by stimuli to ventral roots conducted antidromically. This activity can be inhibited (right hand responses) by (A) a squeeze of the ipsilateral toe and (B) by stimulus to the contralateral biceps-semitendinous nerve. (From Wilson, Talbot and Kato: J. Neurophysiol., 27, 1063, 1964.)

be activated by antidromic stimulation of any of a great many motor nerve fibers; even from different muscles. These muscles, however, usually belong to a single functional grouping, such as knee flexors or ankle extensors. The effect of Renshaw cell activation upon other anterior horn cells is inhibitory; it depresses or totally inhibits firing. This is shown diagrammatically in Figure 7-25. Activity in anterior horn cell l will inhibit, via the Renshaw cell, anterior horn cell 2. This inhibition is usually to opposing muscle groups. The Renshaw cell itself can be inhibited by a variety of pathways, such as squeezing the ipsilateral toes and stimulating the muscle nerve on the contralateral side (Fig. 7-26). Note that in each case the response to the antidromic stimulation is much reduced.

Since the Renshaw cell is inhibitory to anterior horn cells, inhibiting the Renshaw cell will remove inhibition from the anterior horn cell 2 in Figures 7-26, 27, 28. The effect of inhibition of an inhibitory cell is called disinhibition. This doesn't mean that anterior horn cell 2 will fire, since that requires a facilitatory stimulus, but it does mean that no inhibition is being applied via that particular Renshaw circuit. This phenomenon of disinhibition is quite common in the nervous system.

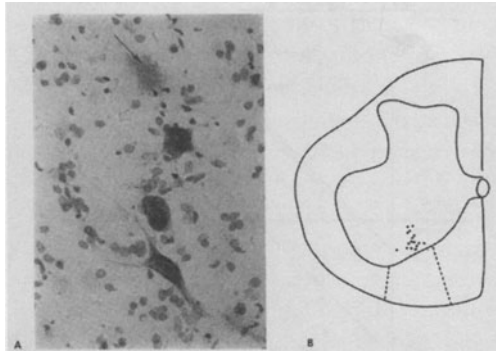

Figure 7-27. Localization of the Renshaw cells by the method of dye electrophoresis from the recording electrode. A, The dye spot among the anterior horn cells. The dye spot, arrow, is an azure blue while the cells are purple. B, The location of a number of dye spots superimposed upon a tracing of a lumbar spinal cord segment. (From Thomas and Wilson: Nature, 206:211, 1965.)

POSTERIOR HORN

Laminar Organization. The posterior horn contains the entry of the sensory fibers and their rich synaptic connections. Many names have been proposed for the regions of the posterior and intermediate horns to describe their anatomical and physiological variations. In order to clear up this confusion about the terminology of the organization of the gray matter of the cord, Rexed proposed a laminar organization of the cat spinal cord which has since been extended to all primates. The gray matter is divided into nine layers with a thin tenth region surrounding the central canal, *Figure 7-28.*

Lamina l forms the cap of the dorsal horn and is penetrated by many fibers. It includes the nucleus posterior marginalis. Many intersegmental pathways arise from this layer.

Lamina 2 corresponds to the substantia gelatinosa. This nucleus extends the entire length of the cord and is most prominent in the cervical and lumbar levels. Cells in this lamina also form intersegmental connections.

Lamina 3 is the broad zone containing many myelinated axons and receives many synapses from the dorsal root fibers.

Lamina 4 is the largest zone and consists primarily of the nucleus proprius of the dorsal horn. This nucleus is conspicuous in all levels.

Lamina 5 extends across the neck of the dorsal horn and in all but the thoracic region is divided into medial and lateral portions. The lateral portion consists of the reticular nucleus that is most conspicuous in the cervical levels. Corticospinal and posterior root synapses have been identified in this lamina.

Lamina 6 is a wide zone most prominent in the cervical and lumbar enlargements. In these levels, it is divided into medial and lateral zones. Terminals from the posterior roots end in the

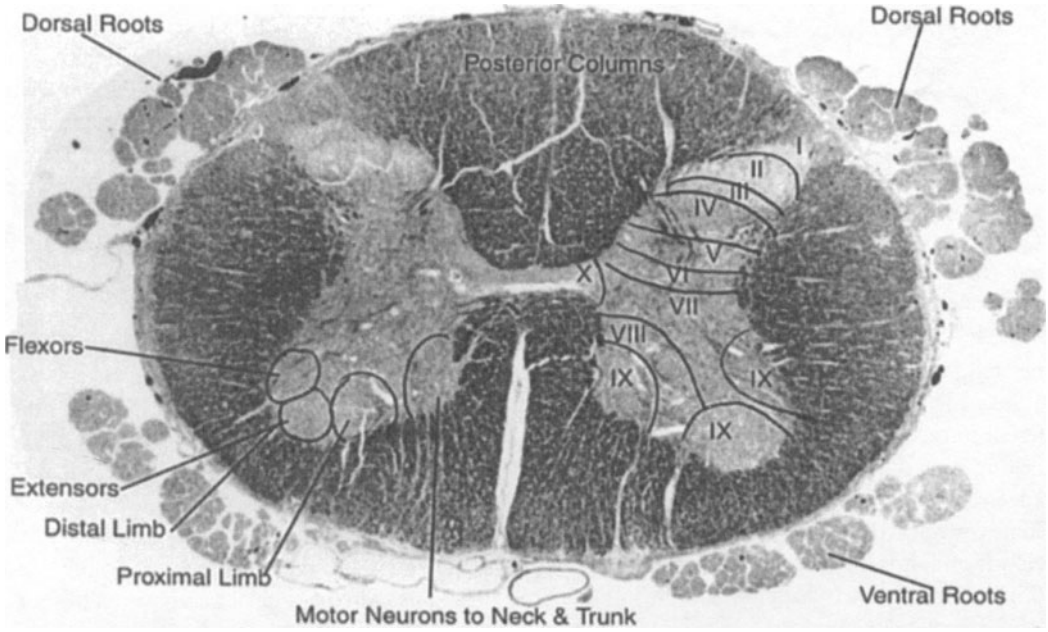

Figure 7-28. Rexed's lamination pattern of the spinal gray matter on the right and the location of ventral horn cells on the left, Lumbar Section. Myelin Stain,

medial region while descending fiber tracts project to the lateral zone.

Lamina 7 includes most of the intermediate region of the gray matter in the spinal cord. In this lamina are found the intermediolateral and intermediomedial nuclei. The nucleus dorsalis or nucleus spinal cerebellar of Clark is obvious in C8 through L2 levels. The axons arising from this nucleus form the posterior spinocerebellar tract. In the cervical and lumbar enlargements, this lamina includes many of the internuncials and the cell bodies of gamma efferent neurons. Axons from posterior roots, cerebral cortex and other systems end in lamina 7. Cells in lamina 7 form tracts that project to higher levels including cerebellum and thalamus. In the thoracic and sacral regions axons also leave this lamina to form preganglionic autonomic connections.

Lamina 8 in the cervical and lumbar enlargement is confined to the medial part of the anterior horn. Many of the axons from these nerve cells form commissural fibers in the anterior white column. Axons from descending pathways originating in the brain stem terminate here.

Lamina 9 includes the largest cell bodies in the spinal cord, the horn cells. The axons of these cells (alpha motor neurons) form much of the ventral rootlets that supply the extrafusal muscle fibers. The medial group innervates the muscles of the axial skeleton while the lateral group innervates the muscles of the appendicular skeleton.

Lamina 10 includes the commissural axons.

Posterior root fibers. Sensory nerve fibers enter the spinal cord gray matter (Figure 7-28) by a medial bundle of large, heavily myelinated fibers and a lateral bundle consisting of thinly myelinated and unmyelinated axons. The heavily myelinated medial bundles convey information from the large dorsal root ganglion cells subserving encapsulated somatic receptors (muscle spindles, pacinian corpuscles, Meissner's corpuscles), carrying information on touch, position and vibratory senses. Upon entering the spinal cord, the axons divide into ascending and descending processes, both giving off collaterals. Many of these collaterals end in the segments above or below the level of entry. Branches from the larger fibers enter the ipsilateral posterior funiculus and ascend to the medulla. The large myelinated axons also have numerous terminals in Clark's nucleus in lamina 7. Collaterals from posterior

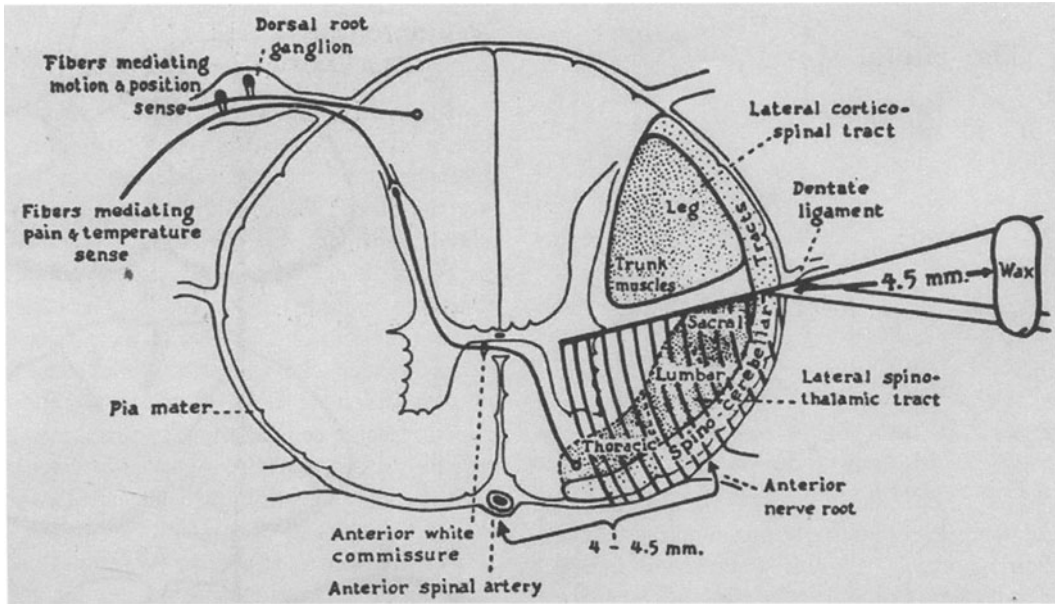

Figure 7-29. Diagram illustrating a chordotomy. The cross section of the spinal cord shows the lamination of the spinothalamic tract, the position of the pyramidal tract in relation to it, and the presence of other tracts in the lower quadrant. A piece of bone wax is mounted 4.5 mm. from the tip of the knife as a depth gauge. Heavy curved lines in the ventral quadrant indicate the sweep of the knife. Note that a desire to spare the lateral corticospinal tract would result in sparing the sacral dermatomes. (From Kahn and Rand: J. Neurosurg. 9:611-619, 1952.)

root fibers also enter Lamina 7 and 9 ending on internuncial neurons and anterior horn cells for reflex activity.

The smaller, lateral bundle of thin axons (A delta & C fibers) conveys information from free nerve endings, tactile receptors and other unencapsulated receptors. These fibers, conveying impulses of tissue damage, temperature and light touch sensation, enter Lissauer's tract (fasciculus dorsal lateralis) (Figures 7-28, 7-34). Axons from Lissauer's tract enter laminas I, II and III. Axons from this lamina ascend and descend in Lissauer's tract to reenter the same lamina,

NOCICEPTION AND PAIN

Any stimulus, such as heat, trauma or pressure, which produces tissue damage or irritation, is a nociceptive stimulus. Nociceptive stimuli are the afferent arm of many reflexes; locally, a red wheal develops around a cut, withdrawal of a limb from a hot pipe is a spinal cord reflex, while tachycardia from an electric shock to the finger is a brain stem autonomic reflex. Only when this nociceptive information reaches the thalamus and cerebral cortex should we talk about pain. Pain perception by these higher centers triggers affective responses and suffering behaviors. The pain experience varies enormously from person to person and the circumstances may alter the response. Contrast the pain of your thumb being hit with a hammer when you are: fixing your sail boat, doing a "chore" around the house or holding the nail for someone else.

As a gross oversimplification we perceive pain in two ways. As pricking, itching or sharp and easily localizable, such as a razor blade cut or a mosquito bite. This type of pain is usually short lasting, up to a day or so, and is usually tolerated. In contrast, pain may be described as dull, aching or burning and is poorly localized. This type of pain is longer lasting (rheumatoid arthritis) or repetitive (menstrual cramps) and is often poorly tolerated, frequently coloring the persons entire view of life.

Receptors. Tissue damage releases a variety of typical intracellular substances including K+, H+, bradykinin, as well as specialized compounds such as: serotonin from blood platelets,

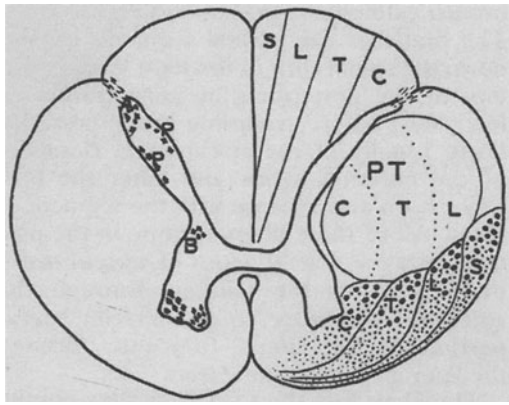

Figure 7-30. The lamination pattern of the major tracts of the spinal cord. (From Walker: Arch Neural. Psychiat. (Chicago), 43:284, 1940.)

substance P from nerve terminals and histamine from mast cells. All of these substances directly stimulate the free endings of small, myelinated A delta fibers (1-5 μ diameter) and smaller, non-myelinated C fibers (0.25-1.5 μ diameter). A second group of released substances including prostaglandin precursors and leukotrienes act as sensitizes. Many of these small fibers have collaterals ending in regions containing neurotransmitter vesicles that apparently amplify nociceptive stimuli by releasing substance P when the free nerve ending is stimulated.

In addition to these relatively non-specific receptors, the upper end of the range of stimuli to temperature and pressure receptors generates nociceptive responses. For example, heating a patch of skin to 40°C with a heat lamp gives a comfortable, warm sensation. Heating to 47°C generates a painful, but tolerable experience. Higher temperatures are perceived as unbearable pain.

Cold is a divers sensation and recently a cold channel has been identified (McKeeney, Neuhauser & Julius 2002). Cold and warmth are sensed by thermoreceptor proteins on the free nerve endings of the somatosensory neurons; one channel, vanilloid receptor subtype 1 (VR1) os activated by temperatures above 43° C, and by vanilloid compounds including capsaicin the component of hot chili peppers. The other vanilloid receptor type 1 (VRL-1) is sensitive to temperatures above 50°C. The cation channel that is methanol activated (CMR1-cold methanol type 1) is activated by temperatures of 8-30°C and is a member of the transient receptor potential family of ion channels with VR1 and VRL-1 also members of this family.

These nerve fibers carrying nociceptive information join peripheral nerves, segregate into spinal nerves and once inside the spinal dura, join posterior roots. Their cell bodies are in the posterior root ganglia while the axon continues and enters the spinal cord in the lateral bundle. Nociceptive information entering on one posterior root projects for 2-3 segments up and down the cord in lamina I-III. From centuries old clinical observation we know all nociceptive information reaching consciousness, had hence causing pain, crosses the neuro-axis close to the segment of entry and rises in the contralateral white column.

Modulation of Pain Transmission. Transmission of pain information through the chain of neurons in the posterior root is influenced by many factors, some of them originating within the segment, some from higher centers. Most of us, after cutting or bruising ourselves, rub the surrounding area and obtain relief of the pain for as long as we rub. An animal that has been hurt will lick the wound, presumably to obtain relief of pain. This subjective phenomenon is frequently spoken of as counter irritation; stimulation of the large, myelinated touch fibers reduces the magnitude of transmission of pain sensation through the posterior horn. This modulation takes place in the substantia gelatinosa, lamina II, within the "Gate" proposed by Wall and Melzak.

Several clinical observations point to the importance of large fiber inhibition of nociceptive transmission, even in the absence of apparent nociceptive stimulation. Perhaps the most painful of these condition is avulsion, traumatic tearing out, of posterior roots. Surgical severing of posterior roots, instead of giving pain relief, often results in intolerable pain. In both cases large fiber input is lost. In contrast, destruction by a laser beam of the lateral dorsal root entry zone (for small fibers) is often highly successful in blocking the flow of nociceptive information up the neuro-axis. The large fiber input is largely spared because they enter in the medial zone.

Severed peripheral nerves often generate itching or burning sensations, causalgia, which

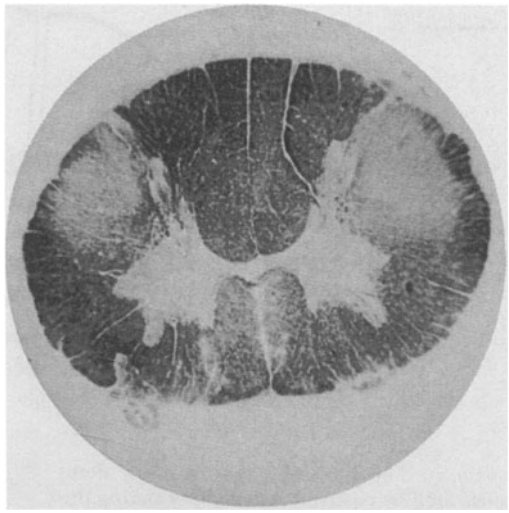

Figure 7-31. (A) The location of the corticospinal tracts as shown by degeneration caused by a lesion in the internal capsule. (From Wechsler: Clinical Neurology. Philadelphia, W.B. Saunders, 1963.) (B) The collateral branches of a corticospinal axon originating in the monkey motor cortex and innervating ulnar nerve motor neurons. The collaterals extend up and down the spinal cord for 2-3 mm (1 segment). From Futami, Brain Res. 164:279-284, 1979.

can be alleviated by stimulating the large diameter axons central to the cut. The large diameter axons have low thresholds so can be stimulated without stimulating the smaller, high threshold nociceptive fibers. Activity in the large fibers suppresses background nociceptive inflow. TENS, Trans Epithelial Nerve Stimulation, is often effective in preventing, or reducing, peripherally generated nociception from becoming pain; effective in closing the gate.

As mentioned earlier, branches of many incoming large axons enter the posterior column. Stimulation of the posterior column sends antidromically-conducted action potentials into the posterior horn and often reduces the pain experience.

Damaged small axons are prone to developing alpha2 adrenergic receptors, so the axon becomes sensitive to norepinephrine liberated by the peripheral sympathetic nerves. Pharmacological blocking or surgical severing sympathetic outflow often reduces pain.

The major excitatory neurotransmitter in the pain system is substance P that is found in abundance in the posterior horn, particularly lamina I and II. The mechanism of postsynaptic action is a reduction in potassium permeability leading to depolarization. The major inhibitory transmitters in the pain pathway are the enkephalin/endorphin series of peptides released from cells entirely within the posterior horn, mostly lamina II. Their action is closely mimicked by the opioid peptides. At least three modes of action have been shown, although all studies are complicated by the very small size of the cell bodies in the substantia gelatinosa (lamina II). An increase in potassium permeability has been shown which hyperpolarizes the cell and acts as an IPSP. Many studies suggest these compounds also compete with the excitatory transmitters of the region, substance P and glycine, for postsynaptic sites. Other studies suggest reduction of Ca++ influx into the presynaptic terminal in response to incoming depolarization and consequent reduction of the amount of excitatory transmitter released. Other studies implicate presynaptic inhibition (below).

Injection of opioids into the lumbar CSF often reduces nociceptive transmission and reduces the pain experience. The effect is blocked by the universal narcotic blocker, naloxone. Successful acupuncture increases endorphins in the lumbar CSF.

Descending axons in both the anterolateral and posterior white columns influence transmission across this chain of synapses.
Supraspinal control of these enkephalin/endorphin neurons is from the brain stem, particularly from the locus ceruleus (Norepinephrine) and Raphe nuclei (5HT), both in the medulla. These areas in turn are modulated by the periaqueductal gray of the midbrain that also contains an inhibitory endorphin/enkephalin system. Stimulation of these structures results in profound anesthesia (electroanesthesia).

While the descending pathways are not clear, we can suppress the flow of nociceptive information through the posterior horn by positive thinking, for example, all "pain" studies are bedeviled by a 40% placebo effect. Yes, the third, post surgical morphine injection can be replaced with saline and still "work" half the time.

Presynaptic Inhibition. In contrast to the cells in the anterior horn, the major mechanism of inhibition in the posterior horn is presynaptic.

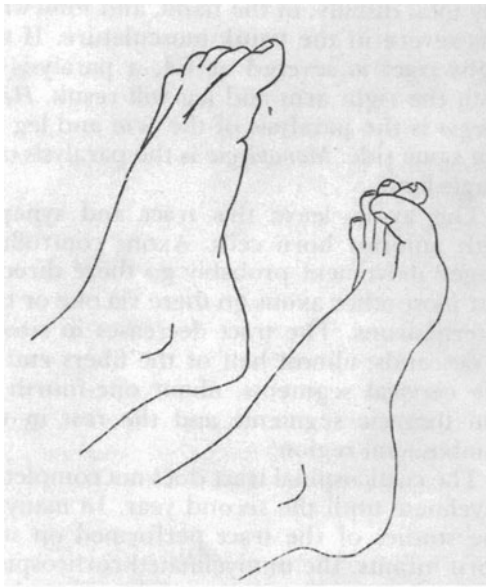

Figure 7-32. The Babinski response. Upper, The normal adult response to stimulation of the lateral plantar surface of the foot. Lower, The normal infant and abnormal adult response.

After a volley of action potentials enter the posterior root, prolonged depolarization can be measured in that and adjoining posterior root axons as well as in the substantia gelatinosa. All available evidence suggests that the next cell in the transmission pathway is not depolarized. If an action potential(s) enters the endplate region of cell II, a reduced amount of excitatory transmitter is released because of the existing depolarization. The reduced amount of transmitter released by cell II causes a smaller EPSP in cell III (panel C); in this example cell III does not reach threshold. Presynaptic inhibition appears to be particularly useful in the sensory system because specific inputs to cell III can be blocked; while other inputs (such as cell IV) have not lost their influence.

Projection fibers. After the extensive processing just described, large diameter, myelinated axons with cell bodies in lamina I and V cross the neuro-axis near the central canal (Fig 7-28) to join the anterior-lateral white matter. These fibers are described later in this chapter as the Spinothalamic tract as they project to the brainstem and ultimately the cerebral cortex.

TRACTS

The white matter of the cord contains axons which run up and down the spinal cord connecting segment to segment and the segments to the brain. (The white matter is divided into three regions that are delimited by the presence of the dorsal roots that separate the posterior from the lateral funiculi and the ventral roots that separates the lateral from the anterior funiculi Fig. 7-28).

The posterior funiculus consists primarily of the posterior columns. The lateral funiculus is a solid mass of myelinated nerve fibers containing many tracts with the ascending fibers on the outside and the descending fibers closer to the gray

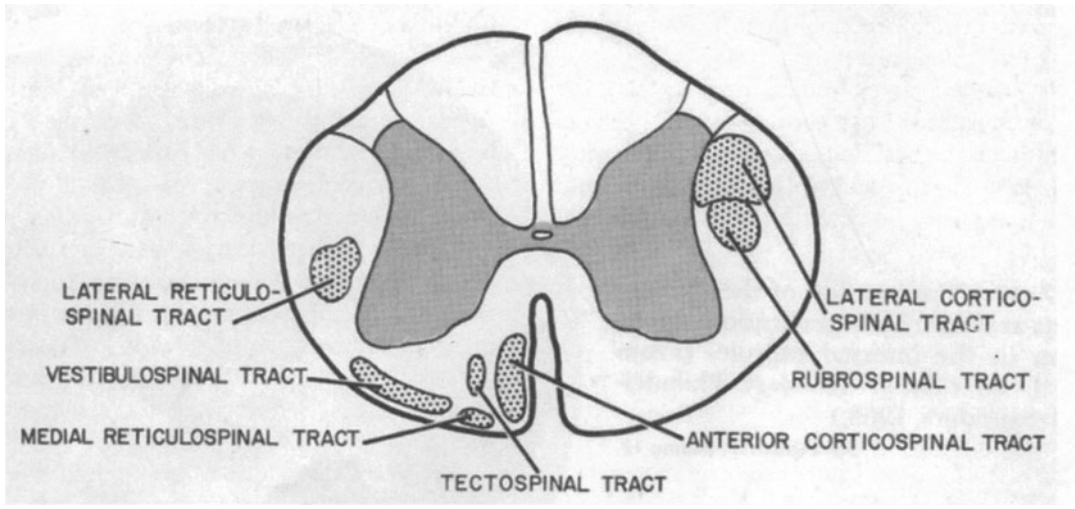

Figure 7-33. The major descending tracts in man.

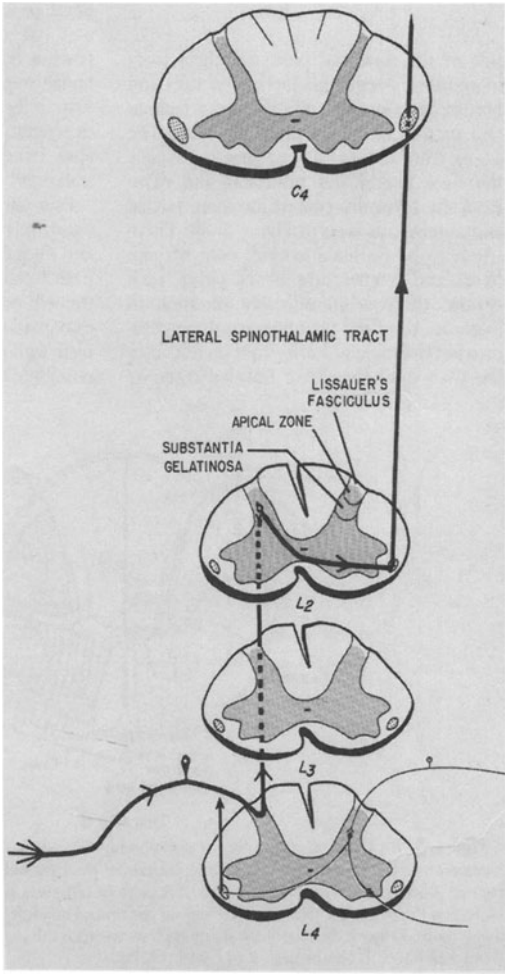

Figure 7-34. The spinothalamic tract/anterolateral system. Incoming fibers that are activated by tissue damaging stimuli may rise ipsilaterally for up to 3 spinal cord segments (as the fiber entering on the left) before synapsing and crossing the neuro-axis and entering the spinothalamic tract. The fiber entering on the right synapses at the level of entry, one axon crosses the neuro-axis and rises, the other axon enters the anterior horn to participate in local reflexes, such as withdrawal from a hot surface. The major projections of the spinothalamic tract are: midline medulla (o), periaqueductal grey of the midbrain , and two nuclear groups of the thalamus, the ventral posterior lateral nucleus which projects in turn to the post central gyrus, as well as the interlaminar nucleus which projects widely.

matter. The only way that the location of individual tracts can be determined is to examine sections after an injury in the nervous system. The anterior funiculus likewise carries many ascending and descending tracts. The location of the tracts must be determined by observing any degeneration caused by discrete lesions.

In this section we will provide an overview of the pathways in the spinal cord. A detailed discussion of the individual sensory and motor pathways are included in the diencephalic chapter 17. The discussion in this section will focus on topics relevant to only the spinal cord.

DESCENDING TRACTS IN the spinal cord.

Corticospinal Tracts. Commands for voluntary movement travel from the brain and through the spinal cord in the corticospinal tract. This tract has its origin in the cerebral cortex, most prominently from the motor and premotor cortex of the frontal lobe(see Chapter 17). At the junction between the medulla and the spinal cord (the level of the foramen magnum) most of the fibers cross the neuroaxis, decussate, and move laterally and posteriorly to form the lateral corticospinal tract (Fig. 7-36).

The location of this pathway in the human is determined by analyzing cord sections obtained at autopsy from cases where cortical destruction has occurred in the motor areas of the precentral gyrus or in the internal capsule and axons degenerated following death of the cell body (Fig 7-31).

The Lateral Corticospinal Tract is the major tract for voluntary control of skeletal muscle. Destruction of this tract leads to paralysis of skeletal muscle and the loss of voluntary movement. This paralysis is usually total distally, in the hand, and somewhat less severe in the trunk musculature. If the right tract is severed at Cl, a paralysis of both the right arm and leg will result, Hemiplegia, a paralysis of the arm and leg on the same side. Monoplegia is the paralysis of a single limb.

ASCENDING SENSORY TRACTS

All ascending sensory systems have three types of neurons;

1) Primary sensory neuron in dorsal root ganglion attached to each segment of the spinal cord

2) Second order neuron in dorsal horn of spinal cord or gracile and cuneate nuclei of medulla.

The axons of the second order sensory neuron cross the neuro-axis, become contralateral, and form ascending pathways within the spinal cord and brainstem that terminate on third order neurons.

3) Third order neurons in the thalamus. Third order neurons project to the ipsilateral sensory area of the cerebral cortex.

Tactile Discrimination-Posterior columns. Fibers in the posterior fasciculus, also known as the dorsal column, *(Fig. 7- 35)*, are the major, if not exclusive, pathway for signals conveying joint position sense, tactile localization, 2 point discrimination, and vibratory sensation. Fibers conveying touch sensation rise both in the posterior column and several other fasciculi. The fibers in this region consist primarily of heavily myelinated dorsal root ganglion fibers. Upon entering the posterior fasciculus via the medial entry root zone, these fibers divide into ascending and descending branches.

Ascending fibers from lower levels (sacral levels) lie medially while those from upper levels lie laterally. In uppermost thoracic and all cervical levels, the posterior column is divided into the medially placed fasciculus gracilis that includes fibers from the lower extremity and lower thorax and the laterally placed fasciculus cuneatus which include fibers from the neck, upper extremity and upper thorax. The axons in the dorsal column are primary uncrossed axons and continue with-

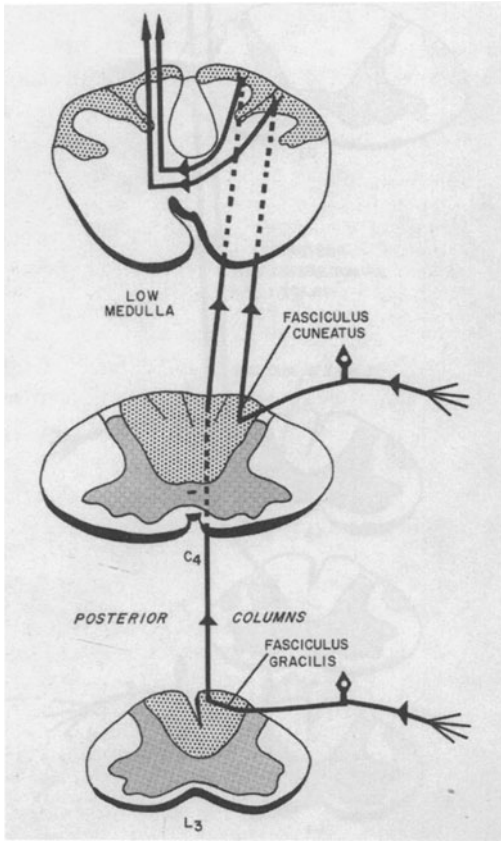

Figure 7-35. The posterior columns

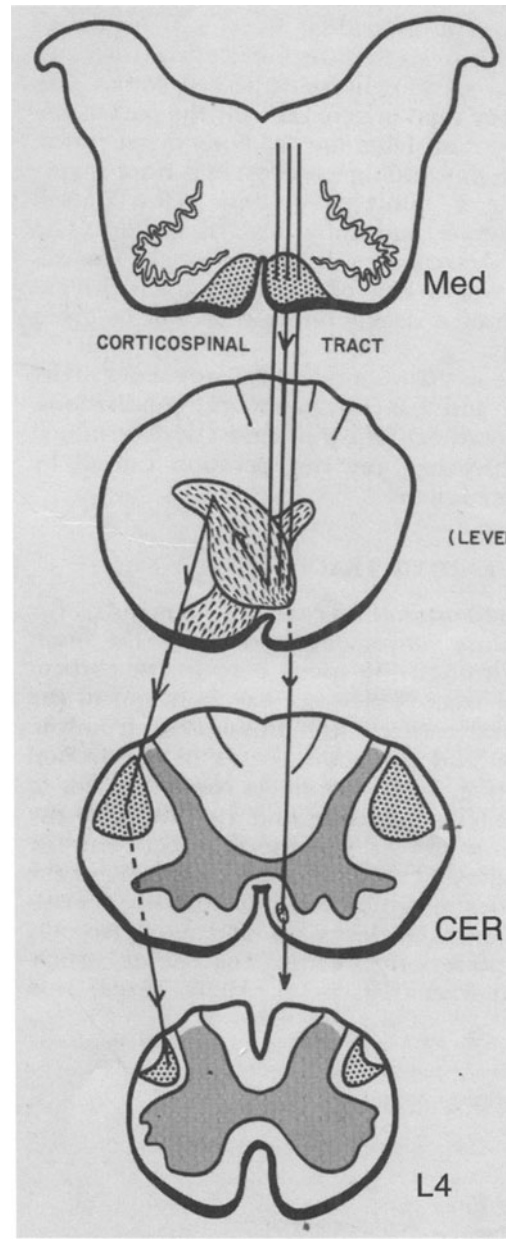

Figure 7-36. The corticospinal tracts.

out a synapse ipsilaterally up to the lower medulla where the secondary neurons begin. The axon of the secondary neuron crosses to the contralateral side and forms the medial lemniscus that ascends through pons and midbrain to the ventral posterior lateral nucleus of the thalamus. The third order neuron in the thalamus sends their axons ipsilaterally by the posterior limb of the internal capsule onto the postcentral gyrus of the cortex.

Lesions in this pathway usually diminish tactile localization, 2-point discrimination and vibratory sensation. There is also loss of ability to appreciate weight differences. Position and movement sense is also affected. These deficits are most pronounced in the fingers and extremities than in the thorax or abdomen. These

TABLE 7-1: MAJOR PATHWAYS IN THE SPINAL CORD

Pathway	Origin	Termination	Function
Corticospinal Contralateral	Motor Cortex	Lamina 7 and 9 in spinal cord	Voluntary movement of limbs
Rubrospinal Contralateral	magnocellular portion of red nucleusin midbrain	Lamina 7 and 9	Involuntary Support of movement. Facilitates flexor and inhibits extensor motor neurons, particularly arm flexors
Tectospinal Contralateral	Deep layers of superior colliculus	Lamina 7 & 9 of cervical spinal cord	Support corticospinal pathway
Vestibulospinal Uncrossed	Lateral vestibular nucleus of Cranial nerve VIII	All levels of cord lamina 7&8	Coordination of eye and neck movements
Reticulospinal	Nucleus reticularis gigantiocellularis in the medulla and from nucleus reticularis pontus caudalis and oralis of the pons	Lamina 7 & 8 of all levels of cord but especially cervical and lumbar enlargements	nfluence gamma motor system Facilitory to extensor motor neurons.
MLF	Cranial nerves iii, v,vi, vii & VIII, XI	Cervical cord	Coordination of eye and neck movements
Descending Autonomic Pathways Bilateral	Hypothalamus and brain stem	Sympathetic to lamina 7 in C8-L2 Parasympathetic to Sacral nucleus of S2-S4	
Spino-spinal System.	All spinal cord levels intersegmental and dorsal root fibers	Lamina	involved in intersegmental connections or taking part in the 2-neuron reflex arch.
Posterior spinal cerebellar some of largest myelinated axons origin of group IA and IB afferent fibers. Ipsilateral	Clark's nucleus in lamina 7 from C2-L2	Ipsilateral vermis of cerebellum	unconscious tactile and proprioceptor information. Encapsulated(Golgi tendon organs, stretch receptors and muscle spindles
Anterior spinocerebellar Contralateral	lamina 5, 6 & 7 from most levels	Contralateral vermis of cerebellum	unconscious tactile proprioception
Cuneocerebellar Ipsilateral	accessory cuneate nucleus in low medulla	anterior lobe and also go into the pyramis and uvula of the cerebellum.	unconscious tactile and proprioceptive information for upper extremity and neck

deficits also produce poorly coordinated movements; posterior column ataxia.

The Anterolateral pathway. Fibers carrying information on pain and temperature sense from the body all rise in the contralateral spinothalamic tract *(Fig.7-34)*. Compression, intrinsic disease or deliberate section all result in anesthesia of the contralateral body beginning 3 segments below the level of disruption.

Pain and Temperature. Primary Cell Bodies-Cutaneous receptors for pain and temperature send axons to small and medium sized dorsal root ganglion cells. These axons enter the spinal cord via the lateral aspects of the dorsal root entry zone. Most of these fibers enter Lissauer's tract and branch extensively (over 2 or 3 segments on either side of the segment of entry) before entering the posterior horn, lamina I, II and III (Fig. 7-28).

The secondary neurons arise primarily from cell bodies in lamina I and V that give origin to large axons which cross in the anterior white commissure and ascend in the contralateral anterior-lateral funiculus. As discussed earlier in the chapter (Nociception and Pain) many factors modulate information transfer across the posterior horn; between incoming nociceptive fibers and outgoing spinothalamic fibers.

There is a somatotopic arrangement in the spinothalamic tract (Fig. 7-34) with the most lateral and external fibers representing sacral levels while the most intermediate and anterior fibers representing cervical levels. Pain fibers are located anteriorly to the more posteriorly placed temperature fibers.

Perhaps as many as half the fibers in the tract, often called the spinoreticular tract, end in the brainstem, while many of the rest send collaterals into the brainstem on their way to the thalamus (Chapter 15). There are endings in two major nuclei of the thalamus: the ventral posterior medial nucleus and the intralaminar nuclei. (see Chapter 15)

Recordings from individual spinothalamic neurons reveal four major functional categories, all contralateral.

1) low threshold units, activated only by gentle stimuli, for example, by stroking hairs on the arm.

2) wide dynamic range units, activated by many types of stimuli of both high and low intensity with response graded by intensity.

3) high threshold units, activated only by nociceptive stimuli.

4) thermosensitive units, with high action potential frequency signaling nociception.

All of these units have small receptive fields peripherally and larger fields toward the midline. The posterior horn seems to tease apart what stimulus from what part of the body. Recording from the thalamic endings of these fibers also shows this separation of function as well as adding a wake up function- ouch! A unilateral section of this tract (Fig. 7-29) for relief of pain produces a complete absence of pain and temperature from the opposite side of the body lasting for 6-9 months, but pain sensation slowly returns. Nociceptive information probably rises in Lissauer's tract until it is above the cut and then crosses.

There are several "pain" responses to nociceptive stimuli. A direct spinothalamic pathway to the contralateral ventral posterior medial nucleus of the thalamus with third order projection to the postcentral gyrus probably mediates sharp, localizable pain. Stimulation of the post central gyrus, however, rarely generates the sensation of pain. Pain is rarely reported by patients during epileptic (cortical) seizures. Apparently the thalamus tells us what (pain) and the post central gyrus tells us where. We test this pathway with the light prick of a pin and expect the patient can tell us, or point to, the location of the pin prick.

The dull throbbing quality of the pain probably ascends by a multi-synaptic pathway via brain stem synapses to the midbrain and then to interlaminar thalamic nuclei with much wider cortical projection including the limbic system. The limbic system (Chapter 22) has much to do with our outlook upon life. The thalamus alone can signal poorly localized pain to consciousness.

In addition to the spinal thalamic and spinal reticular pathways, there are other pathways that may convey pain and thermal information to the thalamus. The cervicothalamic pathway originates from the lateral cervical nucleus in the lateral column at level Cl and C2 and projects to the brain stem and thalamus. Another is the spinotectal tract running from the spinal cord to

deep

Upper and Lower Motor Neurons. Causes of muscle weakness or paralysis can be grouped functionally into two categories. If the difficulty is located in the corticospinal or other descending motor tract the problem is called an upper motor neuron lesion. If the problem is in the anterior horn cell, its axon, or its motor group, the problem is called a lower motor neuron lesion.

Weakness, hyperreflexia, the Babinski sign, and a type of increased resistance to passive movement at a joint, spasticity, characterize the upper motor neuron syndrome. Passively moving or rotating the ankle, knee, hip, shoulder, elbow, or wrist joints easily demonstrates the increased tone. In the normal individual, the joints all move easily. When spasticity is present, the joint is easy to move for a short interval, then resistance to movement increases rapidly; upon further pressure, the resistance suddenly gives way. This latter phenomenon is often referred to as a clasp-knife reflex. In the leg, spasticity is greatest in the extensors, whereas in the arm the flexors are more affected.

Upper Motor Neuron Dysfunction vs	Lower Motor Neuron Dysfunction
Spasticity	Flaccidity
Hyyperreflexia	Hyporeflexia
Babinski Sign	Fasciculation
Very little atrophy	Severe muscle atrophy

Descending motor tracts normally exert an inhibitory effect on spinal cord reflexes. Hyperreflexia is a sure sign of decreased corticospinal function. Decreased function of the corticospinal tract also effects a curious reflex of the foot, Babinski's sign. If a moderately sharp object such as a key, is drawn over the lateral boundary of the sole of the foot, the toes of an adult flex (curl). In very young children and in adults with corticospinal tract destruction, the toes extend and fan out as shown in Figure 7-22.

Weaknesses, loss of reflexes, extreme muscle wasting, and a flaccid tone, hyporeflexia, to the muscles, characterize the lower motor neuron syndrome. The reasons for the weakness and muscle wasting are discussed in Chapter 6 and relate to the loss of the anterior horn cell or the motor axon. The loss of reflexes and the flaccid tone of the muscles relate to the loss of the motor side of the stretch reflex pathway. Often, it is possible to observe spontaneous twitching of the muscle, fasciculayers of the superior colliculus. It also conveys pain and thermal information with some synaptic interruption before reaching the thalamus.

Other Spinal Pathways. We have just listed the major ascending pathways. There are also pathways from the spinal cord to reticular formation of the brain stem to the vestibular nuclei of the medulla and pons, the inferior olive of the medulla and to nuclei and pons and midbrain.

(See Chapter on functional localization in the Brain Stem and the Major Pathways –Chapter 15).