Bonica's Management of Pain

THIRD EDITION

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CHAPTER 8

Applied Anatomy Relevant to Pain

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This chapter contains information about those aspects of the gross anatomy and neuroanatomy relevant to painful disorders and is intended to complement the information contained in Chapters 3 and 4. The material is presented in two parts. The first section contains a description of the segmental and peripheral nerve supply to the skin, muscles, and bones and the segmental sensory and autonomic nerve supply to viscera. The second section is devoted to a general discussion of the autonomic nervous system (ANS) as relevant to its role in pain. The sensory supply of each region is discussed in more detail in the introductory chapter of each section of Part IV of the book and is also considered briefly in the introduction to some of the chapters. For example, Chapter 46, the first chapter of the section on pain in the head, contains a detailed discussion of the nerve supply to the head and precedes the chapters in which the various head pain syndromes are discussed. Some of the information is also repeated in the sections on neurologic and orthopedic examination of Part II and in connection with those chapters in Part V dealing with therapeutic modalities that require full knowledge of the relevant anatomy and physiology. The material is derived in part from updated reviews and other reliable sources (1–4).

SEGMENTAL AND PERIPHERAL NERVE DISTRIBUTION

Figures 8-1 and 8-2 are included as reference points with regard to the derivation of peripheral nerves from the spinal cord and brainstem. Figure 8-1 depicts the gross anatomy of the spinal cord and the attachment of rootlets of the posterior (dorsal) roots and anterior (ventral) roots. Figure 8-2 depicts the relationship of the segments of the spinal cord to the vertebral canal and column. The anatomy of the cranial nerves involved in nociception and their derivation from the brainstem are discussed in Chapter 46.

Segmental Distribution of Sensory Nerves

The distribution of sensory fibers, which, of course, contain nociceptive axons, is more or less segmental throughout the body. This is the result of the preservation by the sensory levels of the nervous system of the original embryologic division of the body into metameres. The spinal segments that provide sensory and motor innervation to one embryologic division constitute a *metamere*. The cutaneous area supplied by a single pair of sensory roots and their ganglia is known as a *dermatome*, and the area of bones supplied by a similar unit is known as a *sclerotome*. The ventral roots also innervate the dermatomes and sclerotomes, supplying them with sudomotor, pilomotor, and vasomotor fibers, but the distributions of the two classes of fibers, the sensory (afferent) and the motor (efferent), never exactly coincide. Furthermore, the ventral root supplies motor fibers to skeletal muscles, and the area supplied by each segment is often referred to as the *myotome*.

This distribution is particularly segmental for the ectodermal structures—the skin and subcutaneous tissue. The nerves supplying the viscera are also segmentally distributed; as mentioned in Chapter 3, however, visceral afferent fibers are few in number in comparison with the number of somatic primary afferents. It has been estimated that visceral afferents constitute only 10% of the total number of afferents in dorsal roots. This paucity of visceral afferents is compensated in part by the much larger area supplied by the visceral fibers in one root, the peripheral processes of which ramify widely. This is discussed later in this chapter in the section on segmental innervation of the viscera. Knowledge of the segmental distribution of sensory fibers is of critical importance in managing patients with acute and chronic pain.

Dermatomes

There are as many dermatomes as there are spinal segments, with the single exception of the first cervical segment, which in most individuals has no cutaneous distribution. Many investigators using various methods have mapped out the boundaries of the dermatomes. Although there were several investigations of the areas of skin supplied by dorsal roots during the nineteenth century, the first satisfactory delineation of the dermatomes came from the work of Sherrington in the 1890s (5,6). Sherrington's technique, known as the method of *residual sensibility*, was carried out in monkeys and consisted of sectioning several (usually three) dorsal (sensory) roots rostrad and three roots caudad to the root under consideration, which was allowed to remain intact. The area of sensation that remained in the otherwise unanesthetized area that resulted was the dermatome. Maps were drawn of the different dermatomes, and it was assumed that each dermatome resulted from the sensory axons that remain in the intact root.

Subsequently, the method of remaining sensibility was used extensively in humans by Foerster (7), who in the course of long experience with posterior root section (rhizotomy) for the management of intractable pain had the opportunity of determining every dermatome in the lower limbs and one dermatome in the upper limbs in humans. To fill the gap and to define other cervical and the thoracic dermatomes, he used what he called the *constructive method*, which consisted of dividing a series of contiguous posterior roots and testing sensitivity in the areas they supplied. Thus the superior border of the resulting anesthesia represented the inferior border of the dermatome supplied by the next higher intact root, and the inferior border of anesthesia marked the upper border of the next lower dermatome. The third method Foerster used was based on the antidromic response, in which the vasodilation that followed stimulation of the distal cut end of a dorsal root was mapped out. Foerster reported not only that great overlap existed among contiguous dermatomes, but also that significant variations existed in the cutaneous distribution of specific sensory roots, especially in the limbs, of different patients he studied. Figure 8-3 is based on reconstructions of Foerster's data by Haymaker and Woodhall (3) and by Lewis (8).

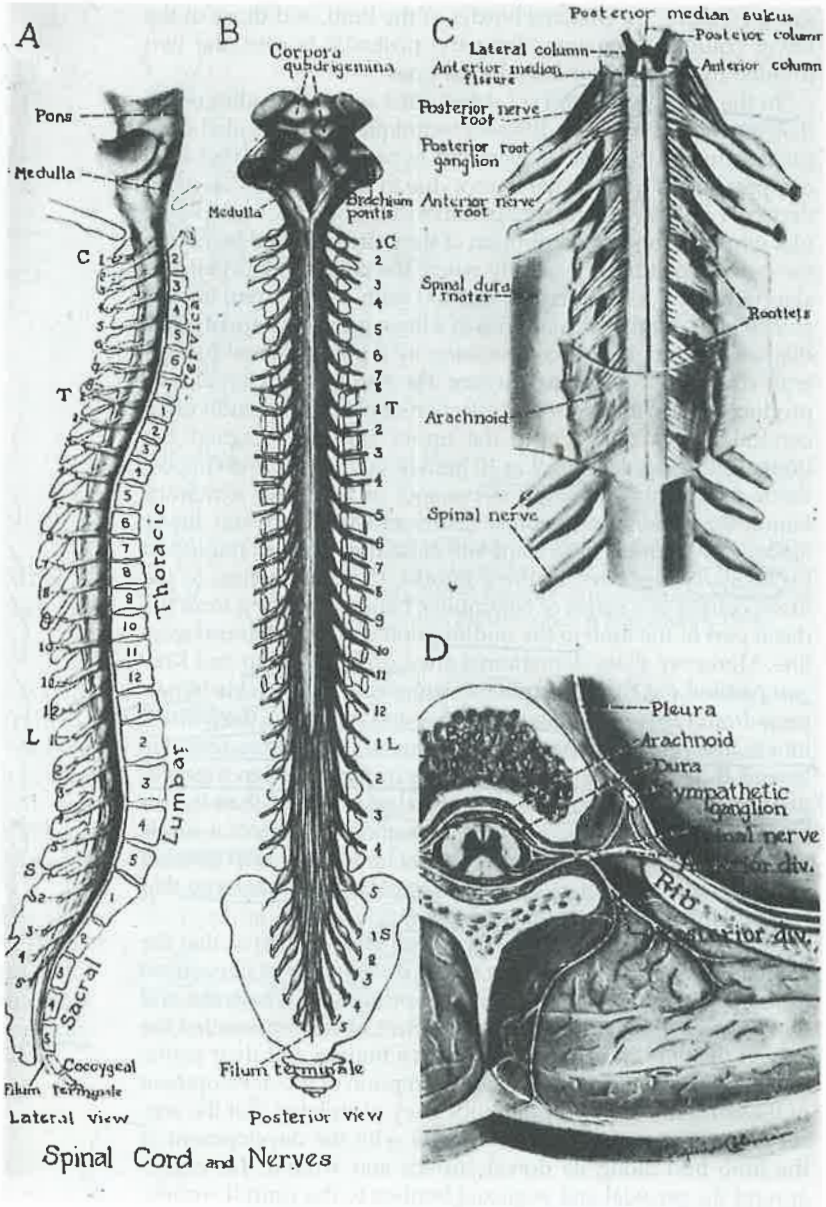

Figure 8-1. The spinal cord and the proximal portions of the spinal nerves. **A:** Lateral view of the spinal cord showing attachment of the nerves to the cord by their anterior and posterior roots. **B:** Posterior view of the spinal cord made possible by removal of the spinous processes and laminae. Note the relationship of the spinal cord segments and nerves to the vertebrae. In most individuals, the conus medullaris terminates at the lower border of the first lumbar vertebra. Caudal to the conus medullaris is the cauda equina, made up of rootlets that join together to form the anterior and posterior roots, near the point at which the latter join to create the formed nerve within the intervertebral foramina. **C:** Anterior view of the spinal cord with the dura-arachnoid removed from the upper portion of the specimen. The smaller anterior root fans out and divides into four to six rootlets, which form irregular rows attached to the cord in the anterolateral sulcus. The larger posterior root is composed of 6 to 10 rootlets attached to the spinal cord in a linear series along the posterolateral sulcus. These rootlets (fila radicularia) converge peripherally into two bundles, the fasciculi radiculi, which in turn unite near the dorsal root ganglion to form the posterior root. Within the intervertebral foramen the anterior and posterior roots join to make the formed spinal nerve. **D:** Cross section of the thoracic region showing the course and relation of a typical spinal nerve. Note its connection with the sympathetic ganglion. (div., division.)

At the same time as Sherrington's studies, Head (9), believing that herpes zoster was a disease of the posterior roots, closely observed and recorded the cutaneous eruptions of this affliction in the hope that it might accurately disclose the distribution of the posterior roots to the skin. Maps provided by a large number of cases of herpes zoster were examined and correlated with the borders of sensory loss arising from cord lesions at certain levels. Figure 8-4 is based on Head's preliminary data on cutaneous areas published in 1893 (9) and additional observations published in 1900 (10). It is important to note that there is little overlap in the trunk but some overlap in the lower limb. The patterns of Head's dermatomes in the lower limbs are similar to those reported by Foerster, but there are significant differences between the two patterns in the distribution of the upper limbs.

Many other investigators used Sherrington's technique of residual sensibility to produce dermatomal maps for many species. The major conclusions of these studies were that (a) the dermatomes overlap, and thus the area of the body wall supplied by the axons of a single dorsal root is greater than one segment; (b) because of this overlap, it is usually not possible to render an area of the body anesthetic by cutting only one dorsal root; (c) although the dermatomes overlap, the threshold for various stimuli is lowest in the central part of the dermatomal field; and (d) most of the dermatomes for the limbs do not extend to the midline of the body, so that dorsal and ventral axial lines are found in the extremities and result when the dermatomes from continuous spinal levels abut. Thus, the C-4 dermatome lies next to the T-2 dermatome and L-2 is next to S-2. This nonsegmental pattern of dermatomes in the limbs, published by Sherrington and Foerster, was based on the concept of dermatomic development proposed by Sherrington (5) and refined by others during the early part of the twentieth century. This concept suggests that whereas during embryonic life the spinal portion of the embryo is divided into metameres, this arrangement loses its uniformity when certain groups of metameres migrate into the limb buds, and as these extend more and more distally, the corresponding dermatomes also migrate. The dermatomes that have migrated become grouped parallel to the long axis of the future limb except at the distal part of the limb, at which they are arranged in loops over the expanding limb buds. Consequently, the dermatomes of the higher (rostral) segments are

grouped along the preaxial border of the limb, and those of the lower (caudal) segments along the postaxial border, the two divided by ventral and dorsal axial lines.

In the 1940s, Keegan (11) carried out a series of studies of the dermatomes using three different techniques. One detailed careful charting of the area of pain and hypalgesia associated with compression of a single nerve root due to herniation of an intervertebral disk. By careful preoperative examinations, with particular emphasis on the distribution of the pain (obtained by asking the patient to indicate precisely where the pain was located) and skin testing by a light scratch method with a safety pin, he was able to map out the dermatomes in a large group of patients. The diagnosis of single root compression by a posterolateral (unilateral) disk was verified at surgery. He also studied hypalgesia produced by (a) paravertebral injection of procaine on individual cervical nerves that supply the upper extremity, carried out under radiographic control in 10 human volunteers, and (b) posterior rhizotomy of a single nerve root in the lower extremity. Figure 8-5 shows dermatomal charts of the upper and lower limbs, and Figure 8-6 is a complete dermatomal chart, published by Keegan. As shown in these figures, the dermatomes to the limbs consist of a series of continuous bands extending from the distal part of the limb to the midline, and there is no dorsal axial line. Moreover, these dermatomal areas do not overlap, but Keegan pointed out that his outlines were areas of detectable hypalgesia from loss of a single nerve root and represent the *primary* innervation, not the entire distribution of each nerve root. He agreed there must be considerable secondary overlap innervation for each nerve root, otherwise analgesia (rather than hypalgesia) in the primary area would be found with loss of a single nerve root. He mentioned that at times he found a faint parallel strip of hypalgesia on each side of the primary dermatome that was half the width of the primary zone.

Keegan, in collaboration with Garrett (12), suggested that the primary zone, containing more dense distribution of fibers from the dorsal root, represented the true primitive dermatome and that the secondary zone, containing fewer fibers, represented the area of overlap. In support of Keegan's finding and their explanation, they presented a different conception of the development of the dermatome in the limb bud. They postulated that the sensory branches of the limb nerve grew with the development of the limb bud along its dorsal surface and wound themselves around the preaxial and postaxial borders to the ventral surface, meeting along the axial line. Figure 8-7 depicts the concept they proposed and the one proposed earlier.

More recently, studies of the dermatomes have been carried out by a number of other clinical investigators, including Hansen and Schliack (13), who, like Head, used the distributions of herpetic lesions and the zone of hyperalgesia associated with visceral disease and also used the pattern of hyperalgesia produced by a herniated intervertebral disk. Patterns published by these investigators are similar to those of Head for the trunk and somewhat similar to those of Keegan and Garrett (11,12) and Inman and Saunders (14) for the limbs. Bonica made observations of the pattern of dermatomes after paravertebral somatic nerve blocks, identifying the nerve by (a) the distribution of paresthesia upon contact with the needle point, (b) radiographic control of the precise location of the vertebral level of the bevel of the needle, and (c) injection of 2 mL of contrast medium and again verifying the location of the needle point. The nerve was then injected with a small volume (2 mL) of a local anesthetic (to avoid diffusion to adjacent segments), and the pattern of hypalgesia that developed was carefully ascertained. In the course of four decades, he used this technique experimentally in a group of human volunteers and as a diagnostic/prognostic procedure in evaluating more than 400 patients with segmental pain that was suspected to be due to herniation of an intervertebral disk, osteophyte, or other pathologic process that was subsequently proven at surgery.

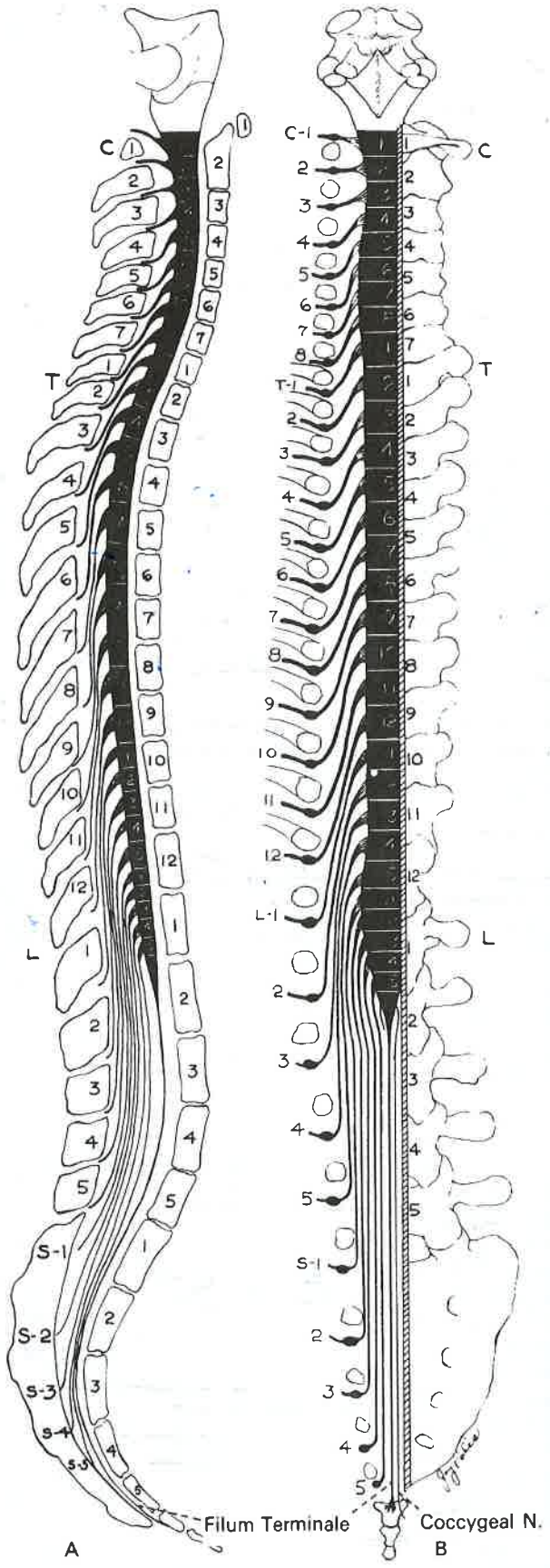

Figure 8-2. Schematic representation to show the relation of spinal column and the spinal cord, nerve roots, and the formed nerves. **A:** Lateral view. **B:** Posterior view. Note the direction of the spinal rootlets/roots in the various segments. The size of the spinal cord in relation to the spinal canal is exaggerated in **B** for the sake of clarity of the numbers of spinal cord segments and their relationship to the vertebrae. (C, cervical; L, lumbar; N, nerve; S, sacral; T, thoracic.)

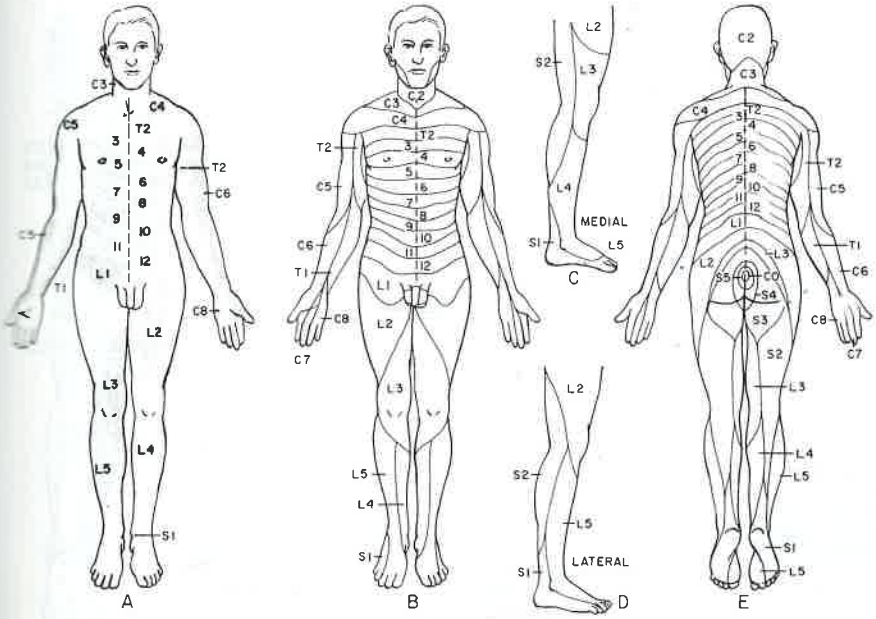

Figure 8-3. The dermatomes in humans according to the studies of Foerster. A, overlap of the dermatomes in the upper and lower limbs not depicted in **B** to **E**. (**A** modified from Lewis T. *Pain*. New York: Macmillan, 1946; **B** to **E** from Haymaker W, Woodhall B. *Peripheral nerve injuries: principles of diagnosis*. Philadelphia: WB Saunders, 1945.)

Bonica also used the technique to study the dermatomal pattern in surgical patients requiring an operation to a limited part of the trunk or the upper or lower limb. In these cases, each segment was injected with small amounts of fast-acting local anesthetic, observations were made as soon as hypalgesia developed, and the next segment was then injected. The procedure was also used to study the nociceptive pathways to the uterus in parturients (see Chapter 71).

Figure 8-8 has been developed on the basis of the dermatomal pattern published by Hansen and Schliack (13) and modified according to Bonica's observations. The dermatomal distribution to the anterior part of the lower limb is somewhat similar to that of Keegan, except that the first toe is predominantly supplied by L-5 and not L-4. It is difficult to rationalize the discrepant findings between Keegan and others with regard to the dermatomal pattern in the upper limb, particularly in regard to distribution of the dermatome to the midline anteriorly and posteriorly. Bonica was not able to demonstrate these patterns. Regional analgesia for operation on the neck, carried out with paravertebral block of C-2, C-3, and C-4 (deep cervical plexus block), invariably produces analgesia that extends anteriorly to the second, and often the third, thoracic dermatome on the trunk. In such patients, intense, noxious stimulation of the skin overlying the clavicle and just below that structure, which according to Keegan are supplied by C-5 and T-1, produced no sensation of pain. Similarly, deep cervical plexus block has been

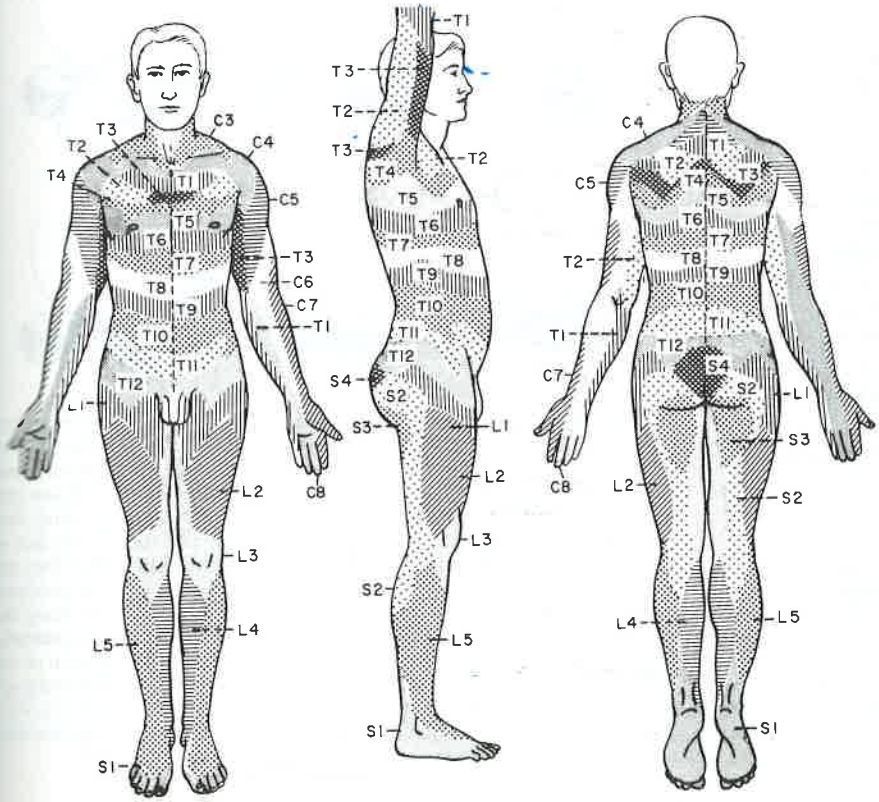

Figure 8-4. The dermatomes developed by Head, from observation of patients with herpes zoster lesions. There is no overlap of the dermatomes in the trunk, but there is some overlap of the dermatomes in the lower limbs. (Modified from Head H. On disturbance of sensation with special reference to the pain of visceral disease. *Brain* 1893;16:1; and Head H, Campbell AW. The pathology of herpes zoster and its bearing on sensory localization. *Brain* 1900;23:353.)

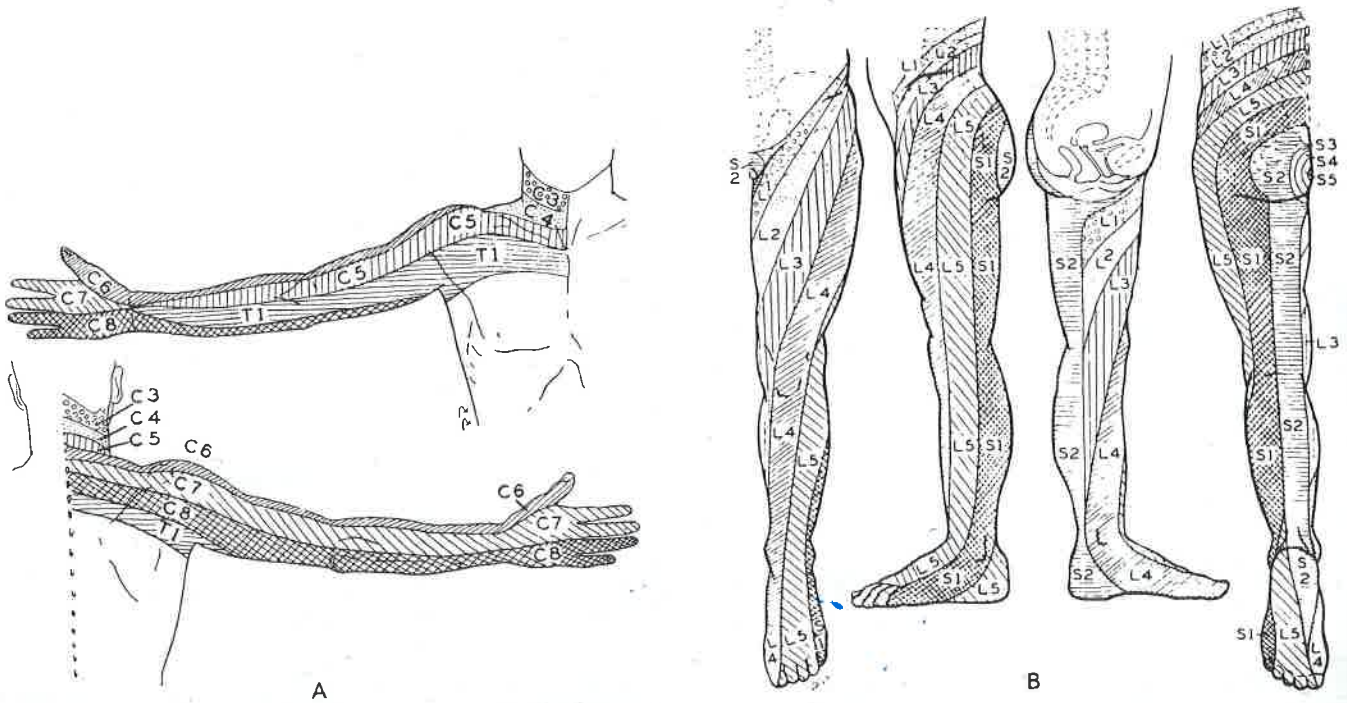

Figure 8-5. **A:** Dermatome chart of the upper extremity. **B:** Dermatome chart of the lower extremity. Dermatomes determined by pattern of hypalgesia from loss of a single nerve root. (A from Keegan JJ. Dermatome hypalgesia with posterolateral herniation of lower cervical intervertebral disc. *J Neurosurg* 1947;4:115; B from Keegan JJ. Neurosurgical interpretation of dermatome hypalgesia with herniation of the lumbar intervertebral disc. *J Bone Joint Surg* 1944;26:238.)

used to produce analgesia of the skin overlying the spinous process of the first, second, and third thoracic vertebrae and the skin of the adjacent paravertebral region. Perhaps the most important part of Keegan's pattern to rationalize is the difference in the distribution of the dermatomes in the back, discussed in the next paragraph.

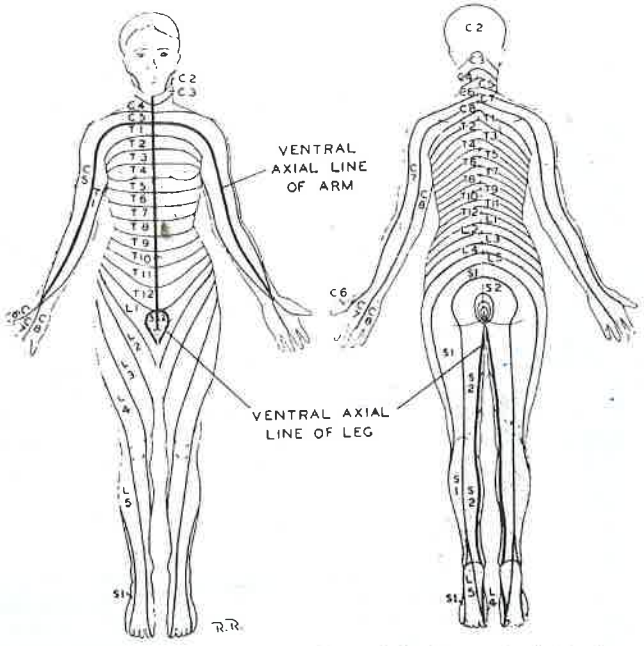

Figure 8-6. Composite dermatome chart of the human body developed by Keegan, from studies of the dermatomes in the upper and lower limbs and from a classical pattern of the dermatomes in the trunk. (From Keegan JJ. Dermatome hypalgesia with posterolateral herniation of lower cervical intervertebral disc. *J Neurosurg* 1947;4:115.)

Two clinically important features of the posterior part of the dermatomes need comment in relation to the distribution of the posterior primary divisions of the spinal nerves. One is the fact that the first cervical nerve does not supply any area of the skin but the posterior primary division of the second and third cervical nerves not only compensates for this but also innervates

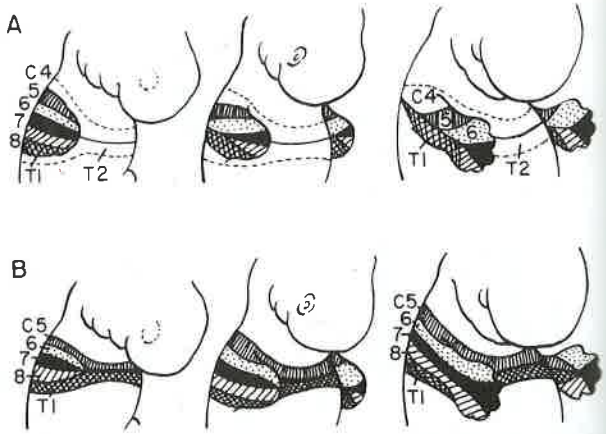

Figure 8-7. **A:** The classic concept of the development of the dermatome in the limb bud at three stages of development, following the scheme suggested by Sherrington and refined by Bolk. **B:** The concept proposed by Keegan and Garrett. In **A**, certain groups of metameres migrate into the limb buds, and as they extend distally the corresponding dermatomes also migrate and become grouped parallel to the long axis of the future limb bud, except at the distal part of the limb, where they are arranged in a semicircle. As a result, the rostral segments are grouped along the preaxial border of the limb and the caudal segments along the postaxial border, with the two divided by the ventral and dorsal axial lines. In **B**, the sensory branches of limb nerve grow with development of the limb bud along its dorsal surface and wind around the preaxial and postaxial borders of the ventral surface, meeting along the axial line. As a result, neighboring dermatomes across this line are noncontiguous with respect to number and overlap across the axial line is minimal.

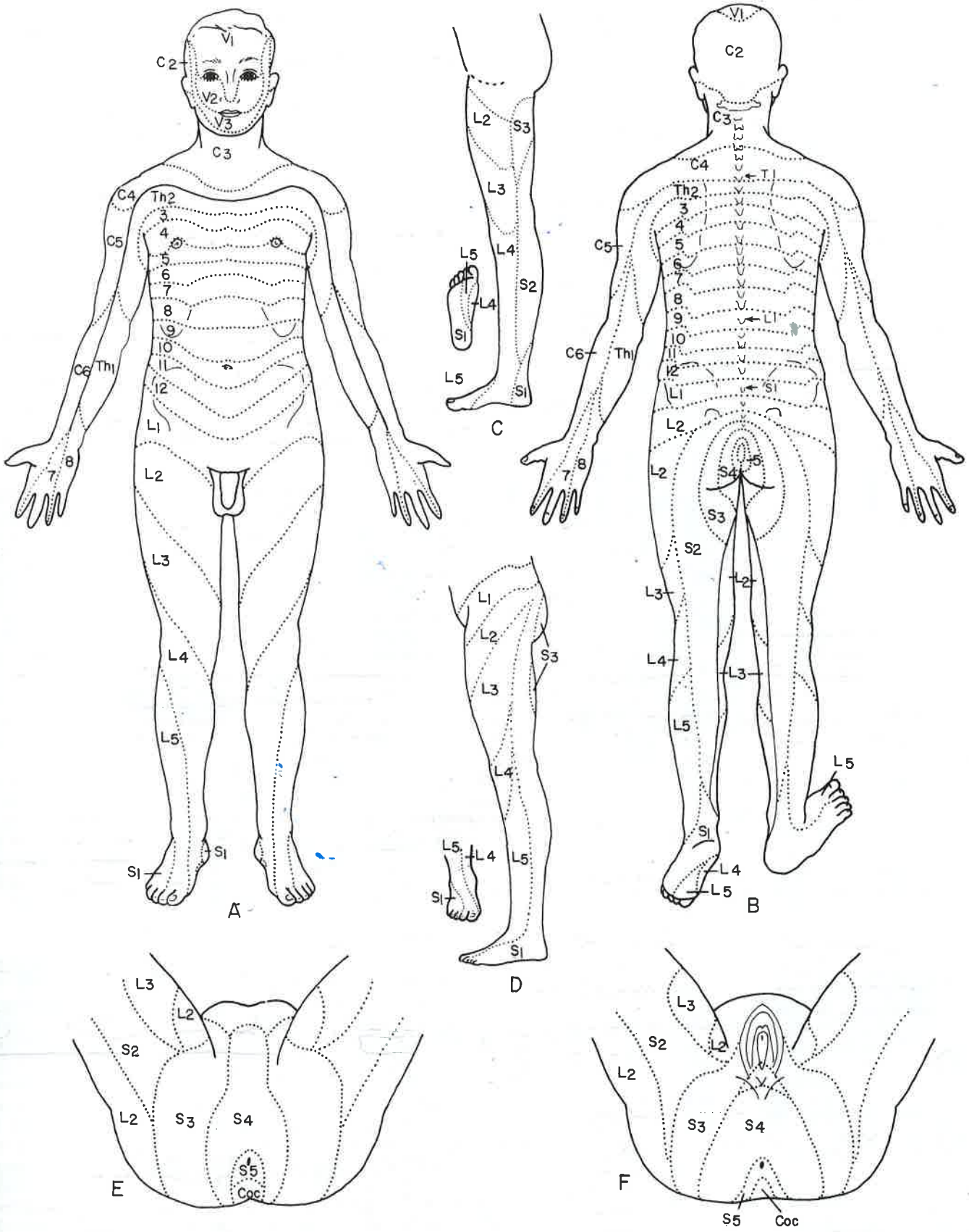

Figure 8-8. The dermatomes developed by Bonica on basis of personal observation and data published by others. See text for description.

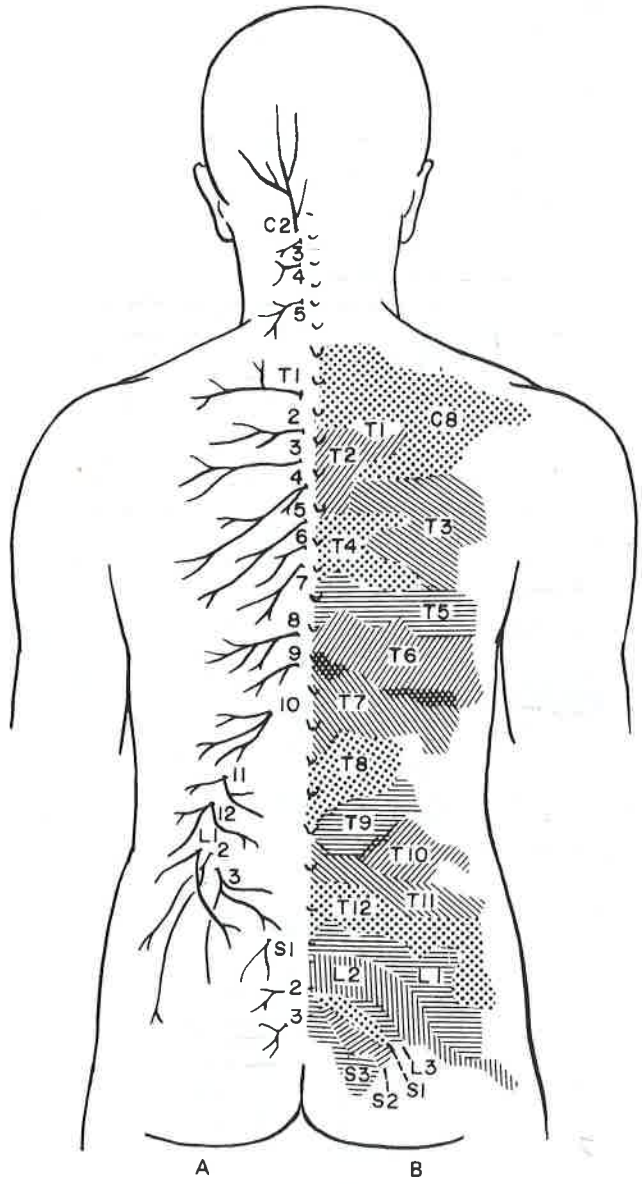

Figure 8-9. **A:** Caudad migration of the posterior primary division of the thoracic and lumbar spinal nerves. **B:** Distribution of these cutaneous nerves to the skin of the back.

the back of the scalp as far forward as the vertex and abut the first division of the trigeminal nerve. Moreover, the posterior primary rami of the sixth, seventh, and eighth cervical nerves, and of the fourth and fifth lumbar nerves, do not supply the skin. The second extremely important point is that beginning at approximately T-4 or T-5, the posterior division of each spinal nerve migrates within muscles caudally for a progressively greater distance before emerging from the muscles to supply the skin and subcutaneous tissue overlying the spinous processes, vertebrae, and the adjacent paravertebral region (Fig. 8-9, Table 8-1). These points are critically important when evaluating patients with back pain and attempting to identify the cutaneous nerve supply.

The differences of pattern of dermatomes suggest that these are not simple sensory patterns that are the result of anatomic distribution of sensory axons of each particular dorsal root. Instead, the interaction of primary afferent fibers from various segments with neurons whose axons are in Lissauer's tract prob-

TABLE 8-1. Distribution of cutaneous branches of posterior division of spinal nerves

Nerve of origin of cutaneous branch	Area of distribution[a]
T-2	T-4–5
T-3	T-5–6
T-4	T-6–7
T-5	T-8–9
T-6	T-9–10
T-7	T-10–12
T-8	T-12–L-1
T-9	L-1–2
T-10	L-2–3
T-11	L-3–4
T-12	L-5–S-1
L-1	S-1–2
L-2	S-2–3
L-3–5	Lower one-third of sacrum

[a]Skin overlying spinous process and paravertebral region.

ably determine not only the size of the dermatome but the quality of the sensation as well (15). This is suggested by the monkey study carried out by Denny-Brown and associates (15,16) with section of roots distal to the dorsal root ganglion rather than proximal (as all other investigators before them had done). These studies showed that the size of each dermatome was enlarged. Strychnine also greatly enlarged the size of each dermatome, as did section of the lateral part of Lissauer's tract. The size of the dermatome was decreased by cutting the medial part of the tract of Lissauer or by cutting six roots on each side of the intact isolated root. This form of neuronal plasticity was also described in patients who had had dorsal rhizotomies for the relief of pain; the area of sensory loss and pain relief was modified by orally administered drugs (17).

Notwithstanding these issues, careful mapping of the dermatome to help pinpoint the site of a lesion that involves the formed nerve (or nerves) before it divides as it makes its exit through the intervertebral foramen is an important clinical tool. Similarly, as will be noted, elicitation of the area of segmental hyperalgesia present in patients with painful diseases involving various thoracic and abdominal viscera helps in differential diagnosis.

Sclerotomes

The segmental nerve roots that supply bones (sclerotomes) are illustrated in Figure 8-10. Comparison of this figure with those showing the dermatomes makes it obvious that they do not agree in spatial relationship, particularly in the limbs. It is only occasionally that a dermatome overlies a portion of the corresponding sclerotome. Whereas dermatomes are arranged along preaxial and postaxial borders of the limb, sclerotomes extend distally for almost the entire length of a limb. In some instances the sclerotome is continuous, and in others it is interrupted. The skull is innervated by the trigeminal nerve in its anterior two-thirds and by the second and third cervical nerves in its posterior third. Each vertebra is supplied by the recurrent nerve derived from the posterior division of spinal nerves, whereas the ribs are supplied by the posterior and anterior primary divisions of their respective spinal nerves.

Myotomes

The segmental nerve supply of various muscles in the body is listed in Table 8-2 and is discussed in Chapter 13 in the sec-

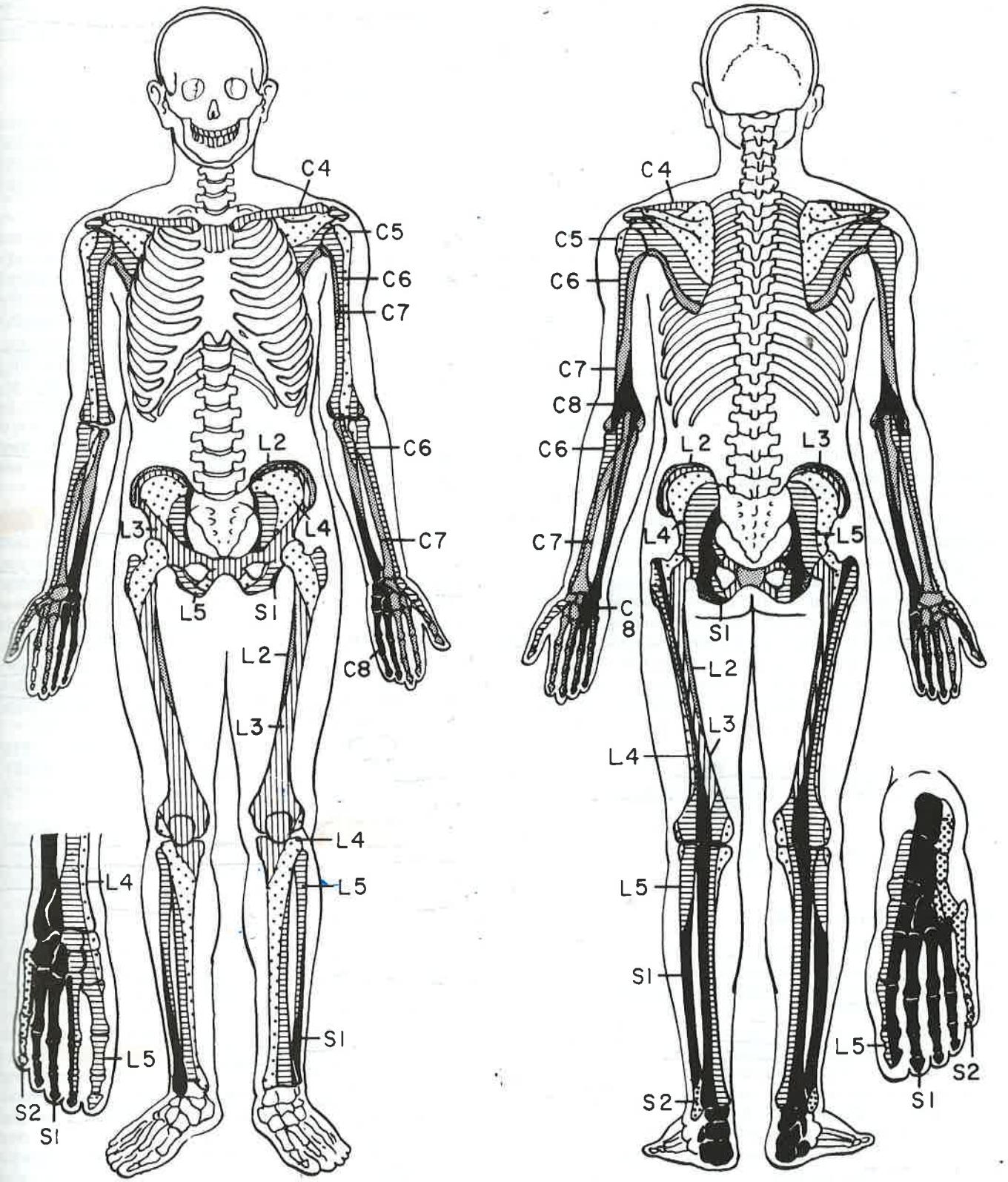

Figure 8-10. The sclerotomes in humans. Various patterns indicate the field of supply of each spinal segment. The skull is innervated by the trigeminal nerve in the anterior two-thirds and by C-2 and C-3 in the posterior third; the vertebrae are supplied by the posterior divisions of the spinal nerves, whereas the ribs are supplied by both posterior and anterior primary divisions of the spinal nerves. The inserts show the sclerotomes of the bones of the feet. (Modified from Déjerine J. *Sémiologie du système nerveux*. Paris: Masson, 1914.)

tion on evaluation of painful conditions by the use of electromyography.

Segmental Innervation of the Viscera

The viscera are supplied by sensory fibers, which are constituent fibers of the spinal and cranial nerves because they have their cell bodies in the posterior root ganglia of spinal nerves or the sensory ganglia of cranial nerves. The sensory fibers' central processes pass via the dorsal (and occasionally ventral) roots, whereas their distal processes accompany the sympathetic or parasympathetic nerves to end in the viscera. Usually, each viscus is supplied by dorsal roots of a number of spinal nerves.

Study of the segments that supply various thoracic and abdominal viscera was also initiated in the latter part of the nineteenth century when physiologists used the visceromotor reflex in animals. This method involves applying noxious stimuli to the stomach, for example, then determining the segmental reflex response of the abdominal muscles by systematically carrying out surgical dorsal rhizotomy until response is eliminated. At approximately the same time Head (9) also studied the segments supplying each viscus by carefully determining the extent of cutaneous hyperalgesia in patients with various visceral diseases. As is discussed in Chapter 9, nociceptive stimulation produces reflex responses, which include cutaneous hyperalgesia in the same segments that supply the viscera. After a long and very comprehensive study, Head developed the map of cutaneous hyperalgesia. In the 1920s, the knowledge he acquired in humans (10) and by experimental work in animals was confirmed in humans by various clinical investigators who used paravertebral somatic nerve block, discussed in Chapter 102 in patients with pain caused by disease of various viscera (18,19). Subsequently, the data were also confirmed by using rhizotomy or sympathectomy for permanent relief of various painful conditions such as cardiac pain (20).

Because the segmental sensory supply of the various viscera is via the sympathetic and parasympathetic nerves, it is presented after discussion of the ANS. It is also repeated in each chapter containing discussion of pain due to each specific type of visceral disease, together with depiction of the gross anatomy of the nerve supply to the particular viscus.

Peripheral Nerve Supply

With a few exceptions, each peripheral nerve contains fibers from two or more adjacent dorsal roots, as depicted in Figure 8-11. As with dermatomes, some overlap exists among peripheral nerves, but less than with dorsal roots. Interruption of the nerve produces an area of complete sensory loss surrounded by a field of altered or diminished sensibility. Both of these zones are smaller than the area of skin that the nerve supplies. Such an area is revealed only if the nerve is left intact and all of the adjacent nerves are cut. Figure 8-12 shows the peripheral nerve supply of the skin, and Figure 8-13 depicts the peripheral nerve supply of bones. It is important to note that the peripheral nerve supply of the skeleton is closely linked with the muscle innervation. Most of the bones receive their innervation from nerve twigs that have penetrated from the attached muscles. For example, the nerve to the quadratus femoris muscle sends twigs to that part of the bony pelvis to which this muscle is attached. Moreover, joints are usually supplied by two types of nerves: articular branches derived directly from major nerves that supply the joint exclusively, and "accessory" nerves that are short branches derived from nerves supplying the muscles near or surrounding the joint.

Pain Sensibility of Tissues and Structures

This section contains a brief summary of the pain sensibilities of various body tissues and organs. Although mention of these is made throughout Chapter 3, here they are presented in a unified fashion to obviate the need for the reader to search for the information in various parts of that chapter.

Skin and Other Ectodermal Structures. The skin and mucous membranes in their entirety are pain sensitive to mechanical, thermal, or chemical injury, or a combination of these, and the pain is sharp, well localized, and often composed of two temporal parts: first pain and second pain. Other tissues of ectodermal origin, such as the *cornea* and the *dentin*, and the deeper structures of the *teeth* are also sensitive to noxious stimuli. The *conjunctivae* and the *glans penis*, like other mucous surfaces, are extremely sensitive to noxious mechanical and thermal stimuli. The subcutaneous tissues such as areolar tissue and fat are less pain sensitive because of the lesser number of nociceptive nerve endings. In contrast, deep fascia is very pain sensitive, mechanical or thermal injury causing moderately severe pain.

Musculoskeletal Structures. Skeletal muscles are sensitive to a variety of noxious stimuli, including injection of hypertonic saline or other algogenic substances, strong pressure, stretching, ischemia, and unduly forceful or sustained contraction during exercise. The severe pain and intermittent claudication caused by peripheral vascular disease are undoubtedly due to ischemia of the exercising muscle. Backaches, myalgias, and certain types of headaches are probably due to unduly prolonged contraction of the involved muscles. The tendons of muscles are sensitive to noxious stimuli, so strong pressure, injection of hypertonic saline, or squeezing causes pain.

Most joints are heavily supplied by nociceptors, including group IV and some group III afferents, which are markedly sensitized by chemical substances that are products of acute or chronic inflammation (see Chapter 3).

The periosteum is very sensitive to mechanical stimulation. Scraping with a periosteal elevator or stimulation of any kind results in moderately sharp pain. The cancellous portion of the bone is also pain sensitive, but the cortex is not.

Cranial Structures. Much of the *dura mater* can be incised, scratched, or cauterized painlessly in many patients. However, parts of the dura at the base of the brain and the dural arteries (particularly the middle meningeal and the great venous sinuses and their various tributaries from the surface of the brain) are uniformly pain sensitive. When these structures are pinched or stimulated electrically or stretched, pain is produced. The *cortex* of the brain and its pia-arachnoid covering can be stimulated electrically, burned, or incised without producing pain, but the *cerebral arteries* at the base of the brain, particularly the middle cerebral, vertebral, basilar, and posterior cerebral arteries, are sensitive, and noxious stimulation such as pinching, cutting, or electrical stimulation produces pain. Stimulation of the fifth, ninth, and tenth cranial nerves also produces pain. The *inner portion* of the brain, including its white matter, the ependymal lining of the ventricles, and the choroid plexus is not sensitive to nociceptive stimuli. The *meninges* of the spinal cord have the same relative sensitivity as those that cover the brain.

TABLE 8-2. Nerve supply of muscles

Region/muscle group/function[a]	Peripheral nerve supply	Segmental nerve supply[b]
Shoulder rotator cuff		
Supraspinatus	Suprascapular	C-5, 6
Infraspinatus	Suprascapular	C-5, 6
Subscapularis	N. to subscapularis	C-5, 6
Teres minor	Axillary	C-5, 6
Scapular motion		
Elevation		
Levator scapulae	Dorsal scapular	C-4, 5
Rhomboideus	Dorsal scapular	C-4, 5
Trapezius (superior fibers)	Spinal accessory	CN XI
Depression		
Trapezius (inferior fibers)	Spinal accessory	CN XI
Pectoralis major	Medial/lateral pectorals	C-5–8, T-1
Subclavius	N. to subclavius	C-5, 6
Upward rotation		
Serratus anterior	Long thoracic	C-5–7
Trapezius (upper, lower fibers)	Spinal accessory	CN XI
Downward rotation		
Levator scapulae	Dorsal scapular	C-4, 5
Rhomboideus	Dorsal scapular	C-4, 5
Pectoralis major, minor	Lateral/medial pectorals	C-5, 6, 7, 8, T-1
Latissimus dorsi	Thoracodorsal	C-6, 7, 8
Abduction (protraction)		
Serratus anterior	Long thoracic	C-5–7
Pectoralis major	Medial/lateral pectorals	C-5–8, T-1
Adduction (retraction)		
Trapezius (middle fibers)	Spinal accessory	CN XI
Rhomboideus	Dorsal scapular	C-4, 5
Latissimus dorsi	Thoracodorsal	C-6, 7, 8
Arm motion		
Flexion		
Pectoralis major (clavicle head)	Medial/lateral pectorals	C-5–8, T-1
Deltoid (anterior fibers)	Axillary	C-5, 6
Coracobrachialis	Musculocutaneous	C-6, 7
Biceps brachii	Musculocutaneous	C-5, 6
Extension		
Latissimus dorsi	Thoracodorsal	C-6, 7, 8
Teres major	Subscapular	C-5, 6
Deltoid (posterior fibers)	Axillary	C-5, 6
Triceps brachii	Radical	C-7, 8
Abduction		
Deltoid (middle fibers)	Axillary	C-5, 6
Supraspinatus	Suprascapular	C-5, 6
Infraspinatus	Suprascapular	C-5, 6
Teres minor	Axillary	C-5, 6
Adduction		
Pectoralis major, minor	Medial/lateral pectorals	C-5, 6, 7, 8, T-1
Latissimus dorsi	Thoracodorsal	C-6, 7, 8
Teres major	Subscapular	C-5, 6
Medial rotation		
Subscapularis	N. to subscapularis	C-5, 6
Latissimus dorsi	Thoracodorsal	C-6, 7, 8
Pectoralis major, minor	Medial/lateral pectorals	C-5–8, T-1
Lateral rotation		
Infraspinatus	Suprascapular	C-5, 6
Teres minor	Axillary	C-5, 6
Elbow/forearm motion		
Extension		
Triceps brachii	Radial	C-6, 7, 8
Anconeus	Radial	C-7, 8
Upper extremity		
Flexion		
Biceps brachii	Musculocutaneous	C-5, 6
Brachialis	Musculocutaneous	C-5, 6
Brachioradialis	Radial	C-5, 6
Wrist motion		
Flexion		
Flexor carpi radialis	Median	C-6, 7
Flexor carpi ulnaris	Ulnar	C-7, 8
Palmaris longus	Median	C-7, 8
Extension		
Extensor carpi radialis, longus/brevis	Radial	C-6, 7
Extensor carpi ulnaris	Radial (posterior interossei)	C-7, 8
Radial deviation		
Flexor carpi radialis	Median	C-6, 7
Extensor carpi radialis, longus/brevis	Radial	C-6, 7
Ulnar deviation		
Flexor carpi ulnaris	Ulnar	C-7, 8
Extensor carpi ulnaris	Radial (posterior interossei)	C-7, 8
Digits (2-5)		
Flexion		
Flexor digit superficialis	Median	C-7, 8, T-1
Flexor digit profundus	Median (anterior interossei)	C-7, 8, T-1
Extension		
Extensor digit communis	Radial (posterior interossei)	C-7, 8
Extensor digit minimi	Radial (posterior interossei)	C-7, 8
Extensor indicis	Radial (posterior interossei)	C-7, 8
Abduction		
Dorsal interossei	Ulnar	C-8, T-1
Adduction		
Palmar interossei	Ulnar	C-8, T-1
Motion of thumb		
Flexion		
Flexor pollicis longus	Median (anterior interossei)	C-7, 8
Extension		
Extensor pollicis longus	Radial (posterior interossei)	C-7, 8
Extensor pollicis brevis	Radial (posterior interossei)	C-7, 8
Abductor pollicis longus	Radial (posterior interossei)	C-7, 8
Adduction		
Adductor pollicis	Ulnar	C-8, T-1
Abduction		
Abductor pollicis brevis	Median	C-8, T-1
Opponens pollicis	Median	C-8, T-1
Opposition		
Opponens pollicis	Median	C-8, T-1
Hypothenar group (motion of fifth finger)		
Abductor digiti minimi	Ulnar	C-8, T-1
Flexor digiti brevis	Ulnar	C-8, T-1
Opponens digiti minimi	Ulnar	C-8, T-1

continued

TABLE 8-2. (*Continued*)

Region/muscle group/function[a]	Peripheral nerve supply	Segmental nerve supply[b]
Lower extremity		
Hip/thigh motion		
Extension		
Gluteus maximus	Inferior gluteal	L-5, S-1, 2
Semitendinosus	Sciatic (tibial)	L-5, S-1
Semimembranosus	Sciatic (tibial)	L-5, S-1
Biceps femoris (long head)	Sciatic (tibial)	L-5, S-1
Biceps femoris (short head)	Sciatic (peroneal)	L-5, S-1
Flexion		
Iliopsoas	Branches from lumbar plexus and femoral	L-2, 3, 4
Rectus femoris	Femoral	L-2, 3, 4
Adductor brevis	Obturator	L-2, 3, 4
Sartorius	Femoral	L-2, 3, 4
Abductor longus	Obturator	L-2, 3, 4
Tensor fasciae latae	Superior gluteal	L-4, 5, S-1
Abduction		
Gluteus medius	Superior gluteal	L-4, 5, S-1
Gluteus minimus	Superior gluteal	L-4, 5, S-1
Tensor fasciae latae	Superior gluteal	L-4, 5, S-1
Gluteus maximus	Superior gluteal	L-5, S-1
Adduction		
Adductor longus	Obturator	L-2, 3, 4
Adductor brevis	Obturator	L-2, 3, 4
Adductor magnus	Obturator/tibial	L-3, 4, 5
Gluteus maximus (lower fibers)	Inferior gluteal	L-5, S-1, 2
Pectineus	Femoral	L-2, 3, 4
Medial rotation (of free leg)		
Tensor fasciae latae	Superior gluteal	L-4, 5, S-1
Gluteus minimus	Superior gluteal	L-4, 5, S-1
Gluteus medius (anterior fibers)	Superior gluteal	L-4, 5, S-1
Semitendinosus	Sciatic (tibial)	L-5, S-1
Semimembranosus	Sciatic (tibial)	L-5, S-1
Lateral rotation		
Gluteus maximus	Inferior gluteal	L-5, S-1, 2
Knee/leg motion		
Extension		
Rectus femoris	Femoral	L-2, 3, 4
Vastus medialis, intermediate, and lateralis	Femoral	L-2, 3, 4
Sartorius	Femoral	L-2, 3, 4
Leg flexion		
Semitendinosus	Sciatic (tibial)	L-5, S-1, 2
Semimembranosus	Sciatic (tibial)	L-5, S-1
Biceps femoris (long head)	Sciatic (tibial)	L-5, S-1, 2
Gracilis	Obturator	L-2, 3
Biceps femoris (short head)	Sciatic (peroneal)	S-1, 2, 3
Gastrocnemius	Sciatic (tibial)	S-1, 2
Ankle/foot motion		
Dorsiflexion		
Tibialis anterior	Deep peroneal	L-4, 5, S-1
Peroneus longus, brevis	Superficial peroneal	L-4, 5, S-1
Plantar flexion		
Gastrocnemius	Tibial	S-1, 2
Soleus	Tibial	S-1, 2
Eversion		
Peroneus longus, brevis	Superficial peroneal	L-4, 5, S-1
Inversion		
Tibialis anterior	Deep peroneal	L-4, 5, S-1
Tibialis posterior	Tibial	L-5, S-1
Motion of toes		
Flexion		
Flexor digiti longus, brevis	Tibial	L-5, S-1
Flexor hallucis longus, brevis	Tibial	L-5, S-1
Flexor digiti minimi, brevis	Medial plantar	L-5, S-1
Quadratus plantae	Lateral plantar	L-5, S-1
Extension		
Extensor digiti longus, brevis	Deep peroneal	L-5, S-1
Extensor hallucis longus	Lateral plantar	L-5, S-1
Lumbricales	Medial plantar	L-5, S-1
Dorsal interossei	Lateral plantar	S-1, 2
Abduction		
Abductor hallucis	Medial plantar	L-5, S-1
Abduction digiti minimi	Lateral plantar	S-1, 2
Dorsal interossei	Lateral plantar	S-1, 2
Adduction		
Adduction hallucis	Lateral plantar	S-1, 2
Plantar interossei	Lateral plantar	S-1, 2
Head, neck, and trunk		
Head		
Muscles of mastication (masseter, temporalis, and pterygoids)	Mandibular nerve	CN V
Neck/head motion		
Flexion		
Longus colli	APDSN	C-2–6
Longus capitis		C-1–3
Rectus capitis		C-1, 2
Extension	PPDSN	
Splenius capitis		C-3–5
Splenius cervicis		C-1, 2
Lateral flexion		
Sternocleidomastoid	Spinal accessory (APDSN)	CN XI, C-2, 3
Scaleni (anterior, medial, posterior)	APDSN	C-3–8
Trunk		
Flexion/rotation		
Rectus abdominis	APDSN	T-6–12
External oblique		T-6–12
Internal oblique		T-7–12
Transversus abd.		T-7–12
Extension		
Iliocostocervicalis (cervical, thoracic, lumbar)	PPDSN	C-2–L-5
Longissimus (capit., cervical, thoracic)		C-2–L-5
Spinales (capit., cervical, thoracic)		C-2–T-12
Semispinalis		C-2–T-12
Multifidus		C-2–T-12
Respiration		
Intercostals	Intercostals	T-1–12
Diaphragm	Phrenic	C-2–4
Pelvis/perineum		
Levator ani	Pudendal nerve	S-2–4
Anal and urethral sphincters	Pudendal nerve	S-2–4

APDSN, anterior primary division of spinal nerve; N, nerve; PPDSN, posterior primary division of spinal nerve.
[a]Muscles listed under motion are the chief movers. Other muscles not listed may act as "accessory" movers and play a minor role in the movement.
[b]Underlining indicates main root(s).

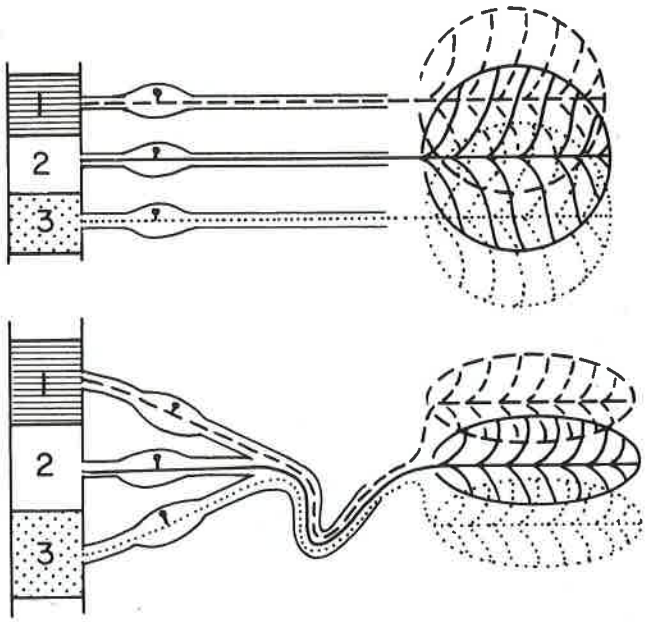

Figure 8-11. Simple diagrams to illustrate the overlap of cutaneous fields of segmental and peripheral nerves. In the upper figure three intercostal (segmental) nerves extending from the periphery to the spinal cord are represented. The lower figure illustrates a somewhat analogous but less extensive overlap in the peripheral nerves.

Thoracic Viscera. The *visceral pleura* and the lung parenchyma are insensitive to nociceptive stimuli, but the *parietal pleura*, being richly supplied with somatic nerve endings derived from the intercostal and phrenic nerves, is very sensitive to painful stimuli. The *pericardium*, with the exception of its lower portion, which is supplied with nociceptive fibers from the phrenic nerve, is insensitive to noxious stimuli but produces pain in the presence of inflammation. The *heart* is insensitive to touching or manipulation of the ventricular walls or aortic ring or any other mechanical stimulation, but myocardial ischemia, endocarditis, vascular insufficiency, and certain other pathologic processes give rise to pain.

The *esophagus* is pain sensitive to chemicals applied to its mucosa, and abnormal motor function produces pain.

Abdominal Viscera. The *parietal peritoneum* is richly supplied with nerve endings derived from the intercostals and other spinal nerves and is sensitive to stretch and to chemicals. The visceral peritoneum and mesentery are insensitive to cut, burn, or scratch, but traction on the mesentery or rapid distension of the visceral peritoneum covering the spleen and liver results in pain.

The *stomach* and the rest of the *gastrointestinal tract* are also insensitive to cut, crush, or burns, but traction, rapid distention, and strong contraction under isometric conditions produce pain. Similarly, the normal mucosa is relatively insensitive to touch or pressure, but when inflamed, it is extremely sensitive to touch and chemical stimuli.

The *parenchyma* of the liver is insensitive to ordinary stimuli because it can be cut, burned, or torn without pain, but rapid enlargement of this organ, such as occurs in cases of cardiac decompensation or rapidly growing tumors, gives rise to pain, probably due to stretching of the hepatic capsule. The *gallbladder* is insensitive to cutting or clamping, but traction or distension causes pain that is especially severe when the gallbladder is inflamed. The *pancreas* is insensitive to stimuli that produce pain when applied to the skin, but inflammatory lesions or necrosis of this organ gives rise to excruciating pain. The *spleen* is also insensitive to cutting or mechanical stimuli, but inflammation of its serosa can give rise to pain, probably due to involvement of the parietal peritoneum. Rapid enlargement of the spleen is usually accompanied by pain caused by distension of its covering.

The *renal parenchyma*, like other solid viscera, can be cut, torn, or cauterized without pain, but traction on the kidney gives rise to pain due to the pull on the renal blood vessels and the parietal peritoneum. Rapid distension of the *kidney, pelvis, ureters, bladder,* and *urethra* causes pain, especially in the presence of inflammation. *Kidney stones* are the most common cause of ureteral colic, one of the most painful disorders that can be experienced by humans.

The *body* of the uterus is insensitive to such mechanical stimuli as incision or gentle manipulation, but, as is well known, uterine contractions are invariably associated with pain. Stimulation of the *fallopian tubes* and *ovaries* gives rise to no sensations unless there is traction on the parietal peritoneum and the ligaments of the uterus. Faradic stimulation or rapid distension of the cervix causes pain referred to the lower abdominal wall, although this structure can be pinched with a forceps in conscious patients without invoking pain. The normal *vaginal mucosa* is insensitive to mechanical noxious stimuli. The *female external genitalia* have been found to be moderately pain sensitive to faradic stimulation; pain is felt at the site of stimulation. Pressure on the *testicle* causes excruciating pain, as does noxious heat.

AUTONOMIC NERVOUS SYSTEM

Because the ANS, especially sympathetic afferents and efferents, is frequently involved in various painful states, this is one of the most important portions of the nervous system to the physician involved in managing patients with acute and chronic pain. To properly manage the pain of angina pectoris, complex regional pain syndromes types I and II, pancreatitis, various peripheral vascular diseases, and other conditions, it is essential for the clinician to have thorough knowledge of the anatomy, physiology, and pharmacology of this system. For the anesthesiologist or other physician using nerve block therapy, it is also essential to have thorough knowledge and experience in techniques of blocking various portions of this system. These are discussed in Chapter 102. In this chapter, we discuss the general anatomic arrangement of the ANS and summarize the physiologic and pharmacologic considerations. As previously mentioned in Part IV, the sympathetic or parasympathetic nerves and the associated afferent nerves supplying various parts of the body are discussed in detail at the beginning of each section and also mentioned in some of the chapters contained in each section.

Anatomic Considerations

The ANS is composed of central and peripheral portions, as shown in Figure 8-14. The central portion consists of centers located in the cortex, hypothalamus, midbrain, and medulla and pathways located in the brainstem and spinal cord. The peripheral portion consists of afferent and efferent neurons, the axons of which are located outside of the central nervous system. The autonomic centers are discussed first, and then the peripheral parts of the system are considered. More detailed description can be found in the books by Hovelacque (21), Kuntz (22), Mitchell (23), and Pick (24) and the more recent paper by Janes et al. (25).

Autonomic Centers

In the central nervous system, aggregates of neurons are functionally connected with the ANS by extensive ramifications that influence and coordinate all autonomic functions and, among other things, particularly integrate the control of respi-

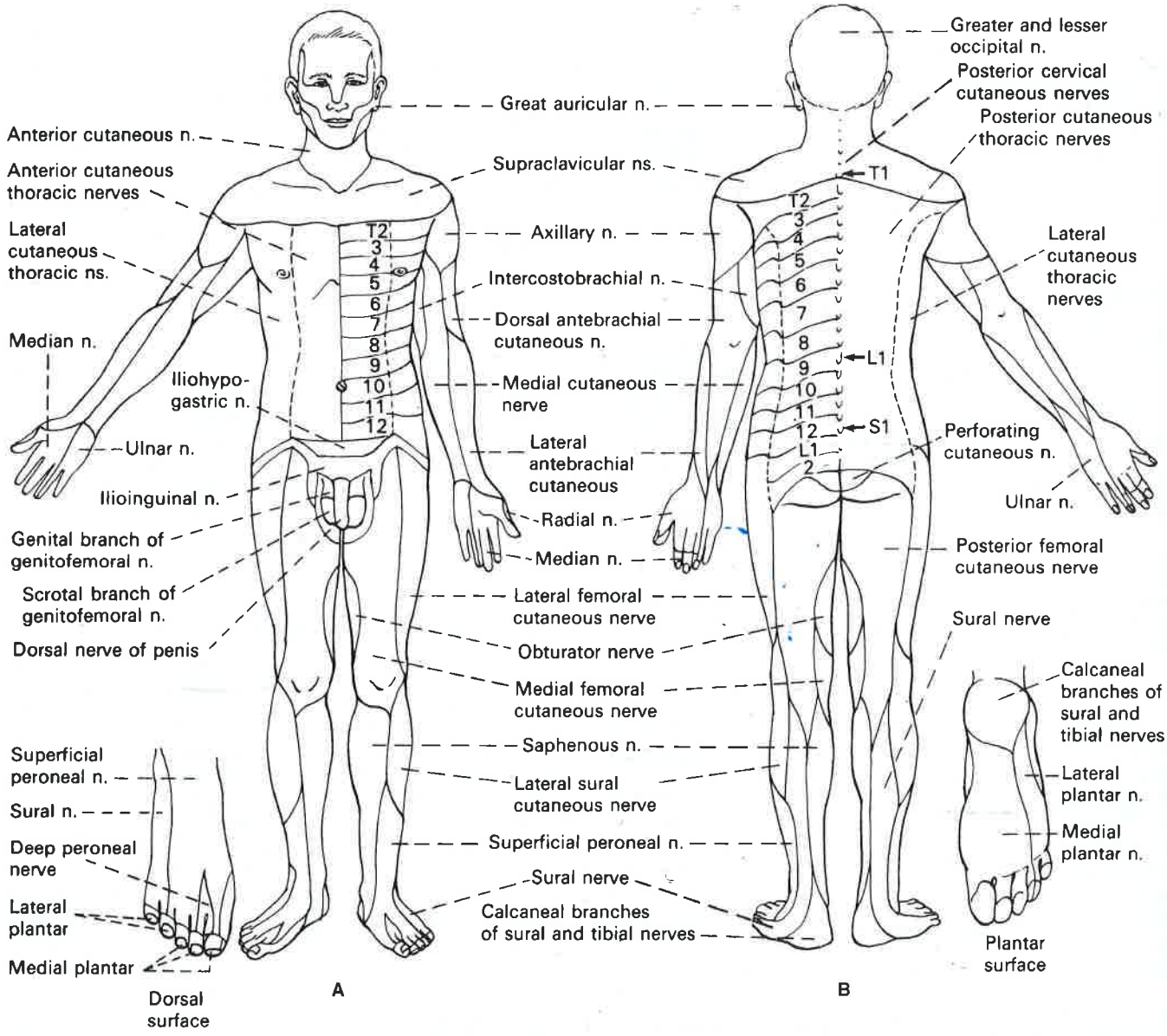

Figure 8-12. The cutaneous fields of peripheral nerves (n.). **A:** Anterior view. **B:** Posterior view. In both figures, the numbers on the trunk refer to the intercostal nerves. (Modified from Haymaker W, Woodhall B. *Peripheral nerve injuries: principles of diagnosis*. Philadelphia: WB Saunders, 1945.)

ration, blood pressure, body temperature, carbohydrate and fat metabolism, water balance, and sexual behavior.

The *cortex* provides integration of somatic and vegetative functions, including the correlation of conditioned reflexes, visceral processes, and pain with mental states. Experimental and clinical data (26) indicate that the major portion of the cortical influence on autonomic function emanates from the motor, premotor, and orbital regions of the frontal lobes. The cortical regulation of a given visceral function emanates from areas that are closely related to the cortical areas that influence the corresponding somatic function. In addition, fibers originating in the cortex pass to the autonomic centers in the hypothalamus and brainstem.

In the *hypothalamus* the anatomic centers of the ANS are most distinct and consist of 16 nuclei, depicted in Figures 5-11 and 8-15. These include the supraoptic, paraventricular, suprachiasmatic, ventromedial hypothalamic, and dorsomedial hypothalamic nuclei, which are concerned with sympathetic function; the preoptic nucleus, which is concerned with parasympathetic function; and the mammillary nuclei, the actions of which are uncertain. In addition to these nuclei, autonomic nerve tracts in the hypothalamus integrate autonomic function among the various hypothalamic nuclei and between these and the limbic system, cerebral cortex, thalamus, and the reticular formation. A detailed discussion of the anatomy and physiology of the hypothalamus is given in Chapter 5.

The *cerebellum* plays a part in certain autonomic regulation, the anterior lobe being involved in the functions of respiration, circulation, and thermal regulation (27).

In the *midbrain*, *pons*, and *medulla* are located distinct autonomic centers that have been physiologically delineated. These include the nuclei, which give rise to the parasympathetic visceral efferent fibers of the cranial nerves, and special centers that regulate respiration and circulation.

The *thoracic and upper lumbar segments* of the spinal cord contain autonomic centers that regulate vasomotor activity, pilo-erection, and perspiration of the entire body as well as sympathetic and parasympathetic function of the viscera. The

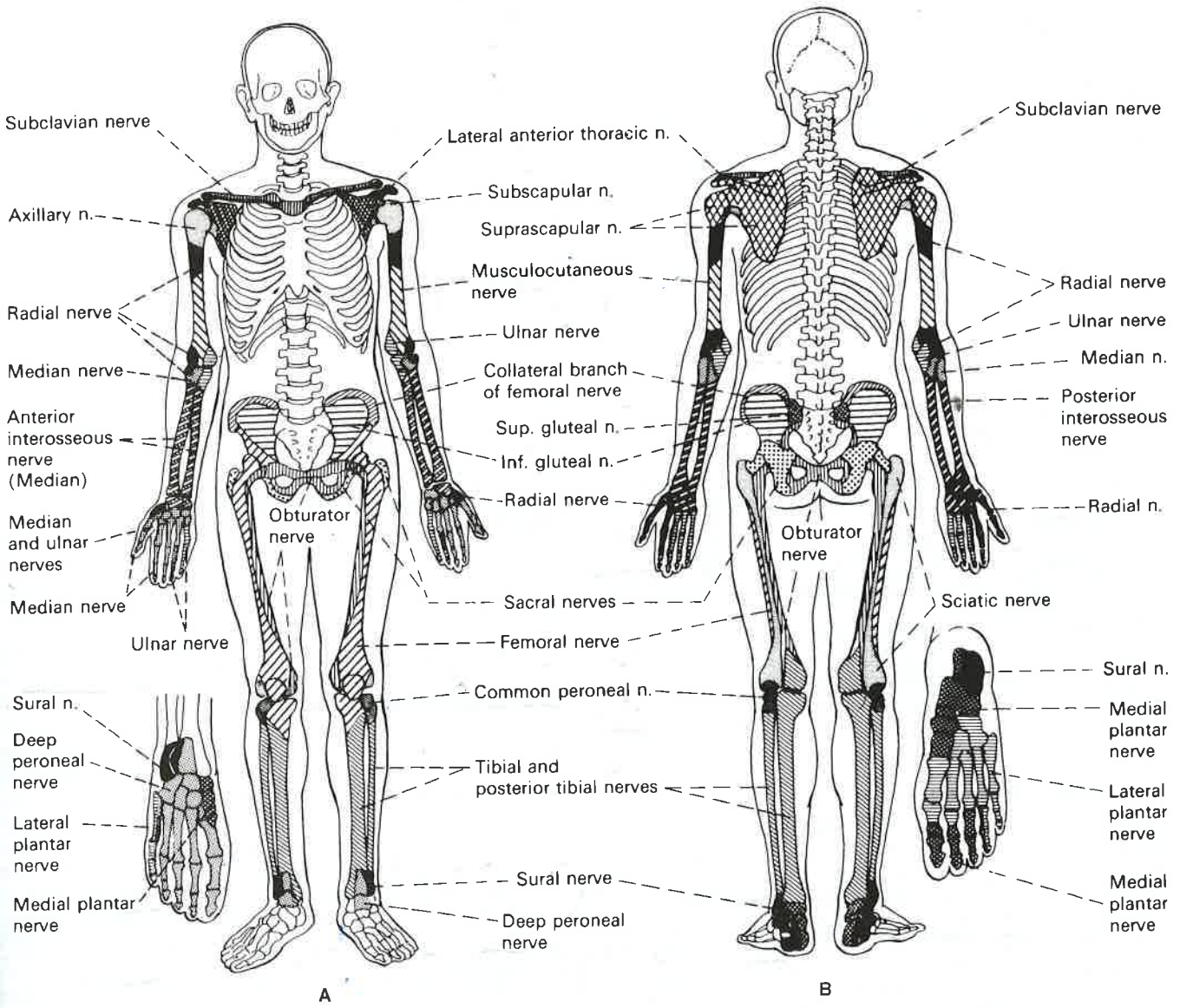

Figure 8-13. Peripheral nerve supply of the skeleton. **A:** Anterior view. **B:** Posterior view. The various peripheral nerve fields are indicated by different patterns. (Modified from Déjerine J. *Sémiologie du système nerveux*. Paris: Masson, 1914.)

locations of the cell bodies of preganglionic sympathetic and parasympathetic neurons, which mediate their function in various parts of the body, are listed in Table 8-3. Some autonomic functions, such as vasomotor control, are bilaterally represented, whereas others, such as pupillary dilation, are unilateral. With bilateral representation, visceral nerve conduction takes place more effectively on the ipsilateral than on the contralateral side. Figure 8-15 depicts the autonomic pathways that connect the preganglionic neurons in the intermediolateral horn of the spinal cord with the hypothalamus and other brainstem structures.

Peripheral Autonomic Nervous System

The peripheral portion of the ANS consists of pre- and postganglionic efferent fibers and afferent fibers from various body structures (22,23,28). These fibers are concerned with transmission of visceral sensation such as nociception, nausea, and fullness; with circulatory, respiratory, and visceral motor reflexes; and with the integration of visceral activities. Although many writers have followed the suggestion by Gaskell (29) and Langley (30) to restrict the term "autonomic nervous system" to efferent (motor) pathways, Mitchell (23), among others (28,31), points out the irrationality of this concept. If the role of the ANS is to regulate visceral function through reflex activity, it cannot do so without afferent and intercalary (connector) neurons as well as efferent (motor) neurons. In this book, the afferents associated with the ANS are referred to as "sympathetic afferents" and "parasympathetic afferents."

The peripheral efferent pathways consist of a two-neuron chain, a primary presynaptic or preganglionic neuron, and a secondary postsynaptic or postganglionic neuron. The cell bodies of the primary preganglionic neurons are located in the central nervous system, either in the intermediolateral cell column of the spinal cord or in the visceral efferent nuclei in the brainstem. The axons of these cell bodies travel toward the periphery either by way of the anterior roots of the spinal nerves or through the cranial nerves, to reach outlying autonomic ganglia, in which they affect synaptic connection with the postganglionic neurons. The cell bodies of the postganglionic neurons are located within these outlying autonomic ganglia, and their axons pass to their terminal distribution in the

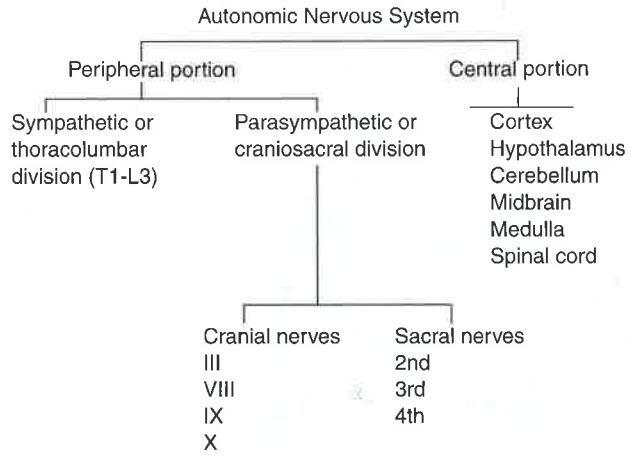

Figure 8-14. Autonomic nervous system.

TABLE 8-3. Autonomic centers (AC) in spinal cord

Structure	Location of AC in spinal cord
Head and neck	T-1–4
Upper limb	T-2–8/9
Upper trunk	T-2–8
Lower trunk	T-9–L-2
Lower limb	T-10–L-2
Viscera	
Thoracic (sympathetic)	T-1–5 (8)
Abdominal (sympathetic)	T-5–L-2
Pelvic (parasympathetic)	S-2–4

wall of the viscera or in the wall of the blood vessels and to sweat glands and other target organs. On the basis of anatomic, physiologic, and pharmacologic characteristics, the peripheral portion of the ANS is divided into two parts: the parasympathetic or craniosacral division and the sympathetic or thoracolumbar division.

The cell bodies of the postganglionic neurons are arranged in aggregates known as *ganglia*, wherein the synapses between pre- and postganglionic neurons take place. As shown in Figure 8-16, there are four general groups of these ganglia, two with the sympathetic division and two with the parasympathetic division.

Parasympathetic Division

Cranial Parasympathetics. The central portion of the parasympathetic division of the ANS consists of preganglionic fibers, which have their cell bodies in the gray matter of the brainstem, and their axons, which pass as component parts of the oculomotor, facial, glossopharyngeal, and vagus nerves (see Fig. 8-15). Those in the first three nerves synapse with short postganglionic fibers in the ciliary, sphenopalatine, otic, and submaxillary ganglia. The very long preganglionic parasympathetic fibers in the vagus terminate in intramural ganglia contained in the walls of the gastrointestinal tract, heart, and lungs, wherein they synapse with short postganglionic fibers that innervate the smooth muscles and glands in these organs.

Somatic afferent fibers are component parts of the facial, glossopharyngeal, and vagus nerves and transmit nociceptive and other somatosensory information from the ear, throat, back of the tongue, larynx, and tracheobronchial tree. Visceral afferents associated with the vagus nerve supply viscera in the chest and abdomen; transmit sensation of distension, fullness, and nausea; and constitute the afferent limb of reflex control of these structures.

Sacral Parasympathetics. The sacral portion of the parasympathetic division consists of preganglionic neurons, which have their cell bodies in the intermediolateral column of the gray matter of the second, third, and fourth sacral segments (see Figs. 8-15 and 8-17). Their axons leave the spinal cord via the anterior roots of the nerves and run directly as the pelvic splanchnic nerves (nervi erigentes) to the pelvic plexuses. They pass through the plexus without interruption and finally reach and terminate in the terminal ganglia in the pelvic plexus and vesical plexus, and some in intramural ganglia of the urinary bladder, the descending colon, the sigmoid colon and rectum, and the genital organs. Afferent fibers associated with sacral parasympathetics transmit nociceptive information from the urinary bladder, lower part of the ureter, the descending colon, and the sigmoid colon and rectum. Other afferent fibers are involved in autonomic reflexes relevant to the functions of these structures.

Sympathetic (Thoracolumbar) Division

The efferent portion of the sympathetic division of the ANS consists of preganglionic neurons, the two paravertebral (lateral) sympathetic chains, prevertebral and terminal ganglia, and postganglionic neurons (21–24) (see Figs. 8-15 and 8-17).

Preganglionic Neurons. The cell bodies of the preganglionic neurons are located primarily in the first thoracic to second lumbar spinal cord segments, inclusive. Most of the cell bodies of preganglionic neurons are located in the intermediolateral (lateral) column of the spinal cord, but some become aggregated and form a second, less definite column on the medial side of the intermediolateral gray matter, which has been termed the *intermediomedial (medial) column* (22,23). Evidence also exists that some cell bodies of preganglionic neurons exist in the eighth cervical and third lumbar segments, and in some instances the seventh cervical and fourth lumbar spinal segments (32,33). In some instances, the axons of preganglionic neurons in the cervical cord descend, whereas those in the third and fourth lumbar segments ascend within the spinal cord and emerge through the first thoracic and second lumbar segments, respectively. Others pass via the eighth cervical or third (and perhaps fourth) lumbar anterior root and the homologous white rami communicantes.

The axons of these preganglionic neurons are carried in the anterior nerve root of the spinal nerve of the same segments and then via the white rami communicantes to synapse with postganglionic neurons in the sympathetic ganglia outside the neuraxis (see Fig. 8-17). The paravertebral ganglia and interganglionic fibers make up the lateral sympathetic chain, to which axons of preganglionic neurons first pass. On entering the sympathetic chain or trunk, some preganglionic axons end in the first ganglion they reach; some pass cephalad or caudad for varying distances within the sympathetic trunk before they synapse in the trunk; others pass through the chain without interruption to terminate and synapse within one of the prevertebral ganglia. Preganglionic fibers pass to and through the adrenal medulla and synapse within chromaffin cells, which are homologous to postganglionic neurons.

Preganglionic fibers from the upper five thoracic segments either terminate in the first sympathetic ganglion they reach or turn upward within the sympathetic trunk to synapse in a ganglion at a higher level, particularly the inferior or stellate ganglion and the intermediate, middle, and superior cervical ganglia. Some preganglionic fibers from the fifth to the tenth thoracic segments terminate in the first ganglion they reach; some ascend or descend; others pass through the paravertebral

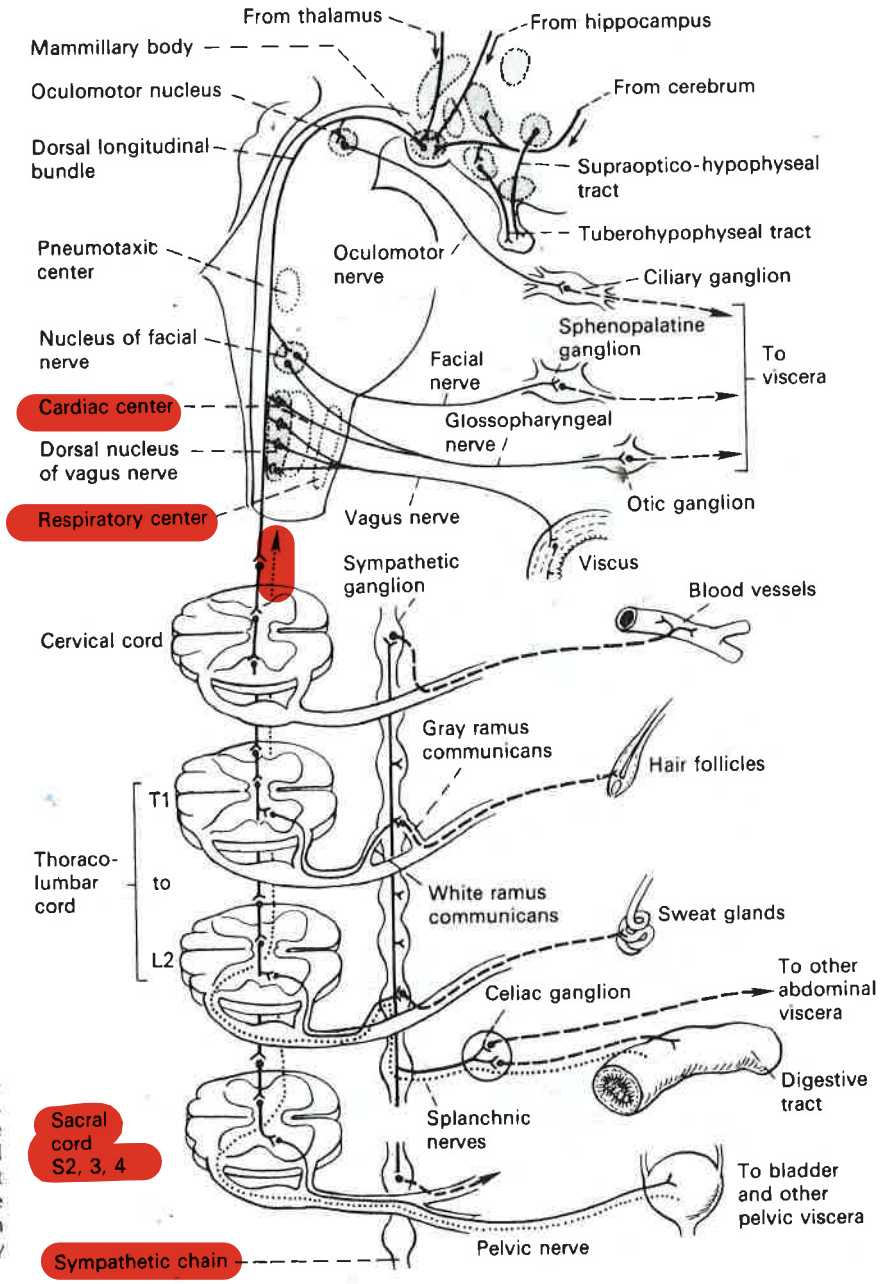

Figure 8-15. Schematic representation of autonomic pathways in the neuraxis and the efferent peripheral pathways. Note the connection among the various hypothalamic nuclei and between these structures and the nuclei and important autonomic centers in the brainstem and spinal cord. The dorsal longitudinal fasciculus (DLF) passes from the hypothalamus caudad through the central and tegmental portion of the mesencephalon and the tegmental portion of the pons to terminate in the reticular formation, the autonomic centers and cranial nerve nuclei in the brainstem, and in the intermediolateral cell column of the spinal cord. The DLF is composed of both crossed and uncrossed fibers, including some long ones and an extensive system of short fibers, which are arranged in the gray matter in frequent relays. Note also that the cell bodies of preganglionic sympathetic neurons are located only in spinal cord segments T-1 through L-2, whereas the parasympathetic neurons are located in cranial nerves and in S-2, S-3, and S-4. The solid lines represent preganglionic fibers, the dashed lines represent postganglionic fibers, and the dotted lines are afferent (sensory) fibers. Not shown are the sensory fibers contained in the facial, glossopharyngeal, and vagus nerves, which transmit nociceptive and other somatosensory information from the head.

ganglia without interruption to become the superior thoracic (greater) splanchnic nerves, which terminate within the celiac ganglia (see Fig. 8-17). Some of the preganglionic fibers from the tenth to the twelfth thoracic segments and first and second lumbar segments terminate in the first ganglion they reach; some pass caudad; and others pass through the ganglia uninterrupted to become the middle thoracic (lesser) splanchnic nerves and the inferior thoracic (least) splanchnic nerves. The middle thoracic splanchnic nerves enter the celiac plexus and synapse in the aorticorenal ganglion, and the inferior thoracic splanchnic nerves pass directly to the renal ganglion, in which each synapses with postganglionic fibers.

Many preganglionic axons converge on each postganglionic neuron, whereas the collaterals of each preganglionic axon diverge into many postganglionic neurons. An extraordinary variability exists among ganglia and the quantitative degree of convergence and divergence. The number of postganglionic neurons in a ganglion is usually considerably higher than the number of preganglionic axons innervating it. The divergent and convergent synaptic connections guarantee a high safety factor for the transmission of excitation in the ganglia.

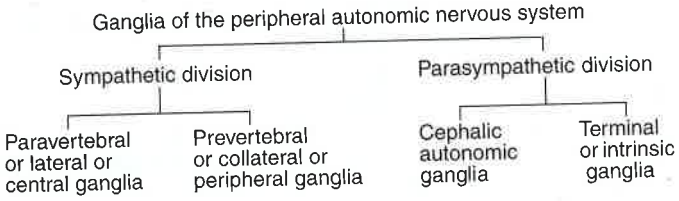

Figure 8-16. Ganglia of the peripheral autonomic nervous system.

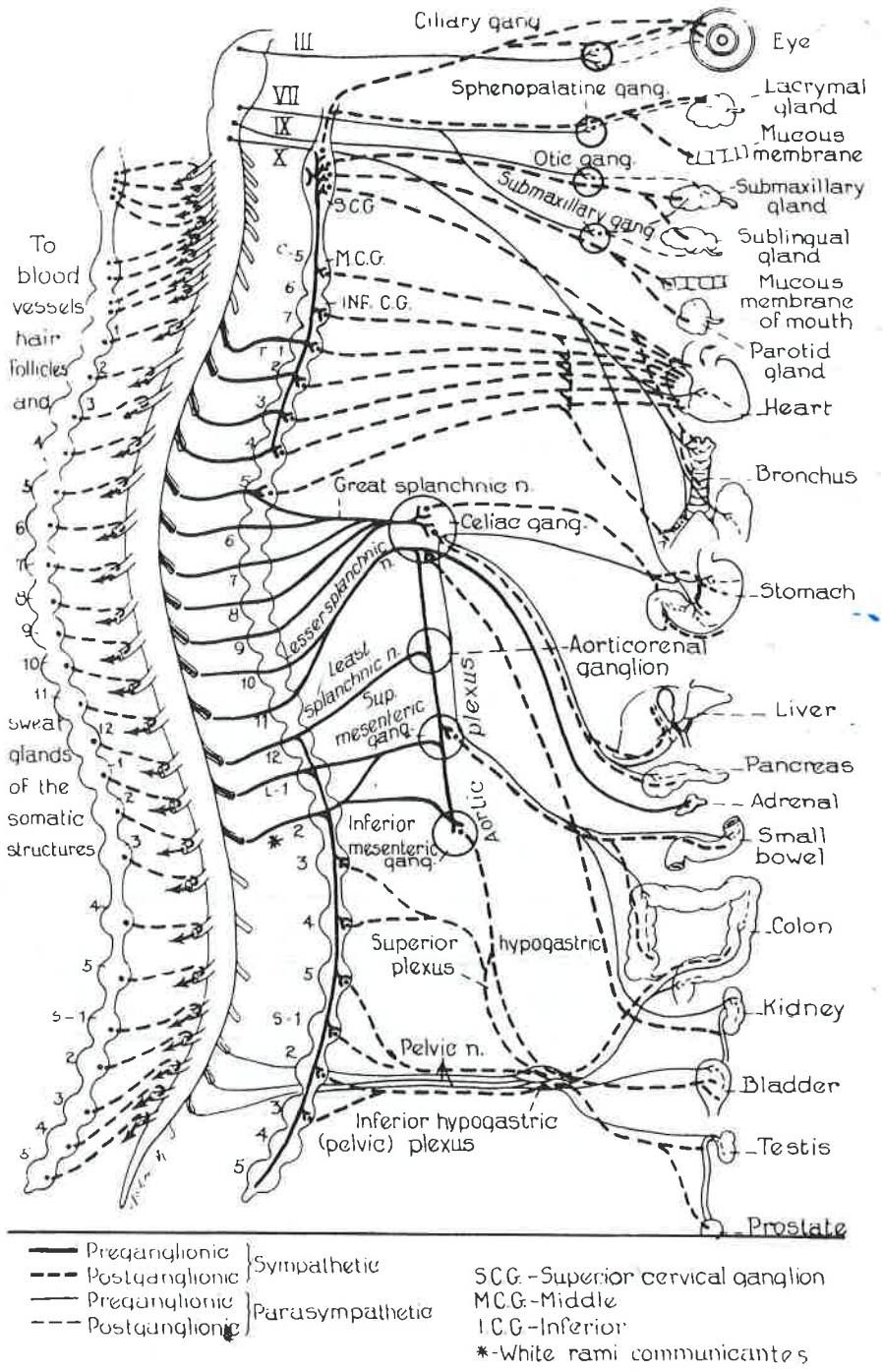

Figure 8-17. Distribution of peripheral autonomic nervous system to various structures of the body. On the reader's right are shown (from above downward) the four cranial nerves, which contain preganglionic parasympathetic fibers, the axons of preganglionic sympathetic fibers (which pass from the anterior root to the paravertebral sympathetic chain), and the parasympathetic preganglionic axons in S-2, S-3, and S-4. Note that the axons of all of the preganglionic sympathetic neurons pass via the white rami communicantes into the paravertebral chain, in which some synapse with postganglionic neurons, whereas others pass to the prevertebral sympathetic ganglia, in which they synapse with postganglionic fibers. On the reader's left are depicted the gray rami communicantes, containing postganglionic sympathetic fibers, which originate in the paravertebral chain and then pass to each of the spinal nerves to innervate blood vessels, hair follicles, and sweat glands in various parts of the body.

Postganglionic Neurons. The axons of some of the postganglionic neurons, which have their cell bodies in the paravertebral chain, become gray rami communicantes and join the spinal nerves and thus are distributed to the skin and various other somatic structures. The axons of other postganglionic neurons, which have their cell bodies in the paravertebral chain, pass to the thoracic and pelvic viscera, whereas the postganglionic neurons, which have their cell bodies in the prevertebral ganglia, become part of the prevertebral plexuses and thus are distributed to various viscera in the abdomen.

In addition to this classic distribution, some synapses take place in spinal nerves and thus bypass the sympathetic trunks (22,23) (Fig. 8-18). Moreover, some intermediary ganglia are located on the white rami communicantes or anterior spinal nerve roots and are thus located outside of the lateral sympathetic trunk (22,23). These anomalous sympathetic pathways are most frequent in the lower cervical and upper thoracic sympathetic trunk and in the lower thoracic and upper lumbar sympathetic trunk. As a result of these anomalies, the usual technique of surgical sympathectomy does not include them and may be responsible for incomplete sympathectomy of the limbs. In contrast, these anomalous pathways are invariably involved by sympathetic blocks because the local anesthetic solution diffuses to these various anomalous structures. The clinical implication of this is important: Even though a prognostic sympathetic block with local anesthetic produces complete

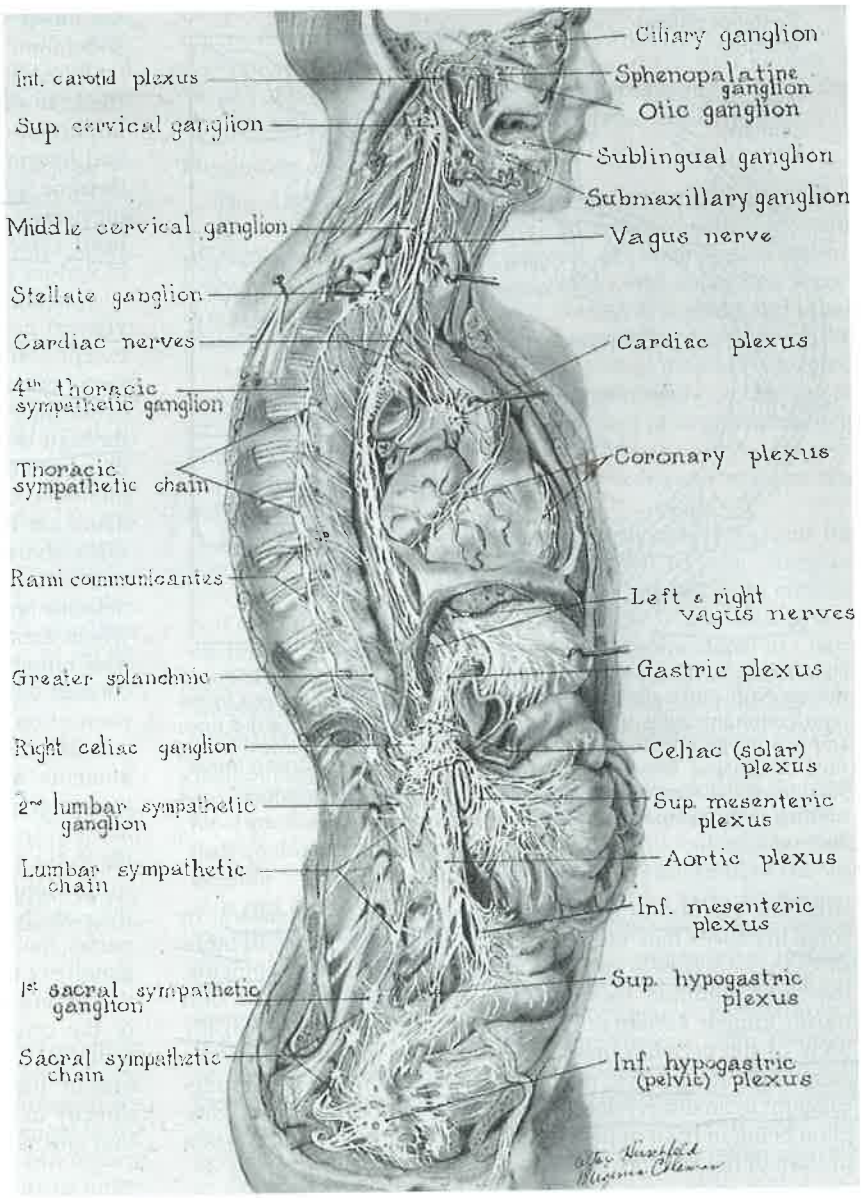

Figure 8-18. Gross anatomy of the peripheral autonomic nervous system. (After Hirschfeld L. *Traite et iconographie du système nerveux*, 2nd ed. Paris: Masson, 1865.)

sympathetic interruption (and pain relief), the sympathectomy might not. In such cases, the incomplete resection can be proven by a postsurgical sympathetic block, which invariably produces evidence of complete interruption and pain relief in sympathetically dependent pain syndromes.

Lateral Sympathetic Trunk. The paravertebral ganglia are segmentally arranged in two vertical rows, each ganglion being connected to the adjacent ganglia by longitudinal ascending and descending nerve fibers, thus forming what are commonly called the *two sympathetic trunks* (Fig. 8-19). These two trunks extend along the ventrolateral aspect of the vertebral column from the second cervical vertebra to the coccyx. The cervical ganglia lie ventral to the base of the transverse processes; the thoracic ganglia lie over the heads of the ribs; the lumbar ganglia lie on the anterolateral surface of the lumbar vertebrae; and the sacral ganglia lie on the anterior surface of the sacrum medial to the anterior sacral foramina (see Chapter 102 for illustrations). The cephalic end of each of the two trunks is continued upward as the internal carotid nerve, branches of which eventually become distributed to the head. The caudal end of the trunks converges and terminates in front of the coccyx as the ganglion impar.

In the cervical region, a condensation of the segmental ganglia has occurred, there being only four: the superior, middle, intermediate, and inferior ganglia. In 80% of subjects, the inferior cervical ganglion is fused with the first thoracic ganglion, forming the stellate ganglion (21,23). Below this level the paravertebral ganglia are segmentally arranged, there being 10 to 12 thoracic, three to five lumbar, four or five sacral, and one coccygeal.

Macroscopically, the lumbar sympathetic chain is the most variable portion of the peripheral sympathetic system, particularly with regard to the number of ganglia and the general forms of the two chains, which are extremely inconstant not only among different individuals, but also on each side of the same person. According to Hovelacque (21), it is almost exceptional to find five ganglia, as classically described in most textbooks; it is more common to find only four or three, and not uncommonly a fusion of the first lumbar and twelfth thoracic ganglia. In addition, one rarely finds a chain on one side that is the same shape and size and in a similar position as the one on the other

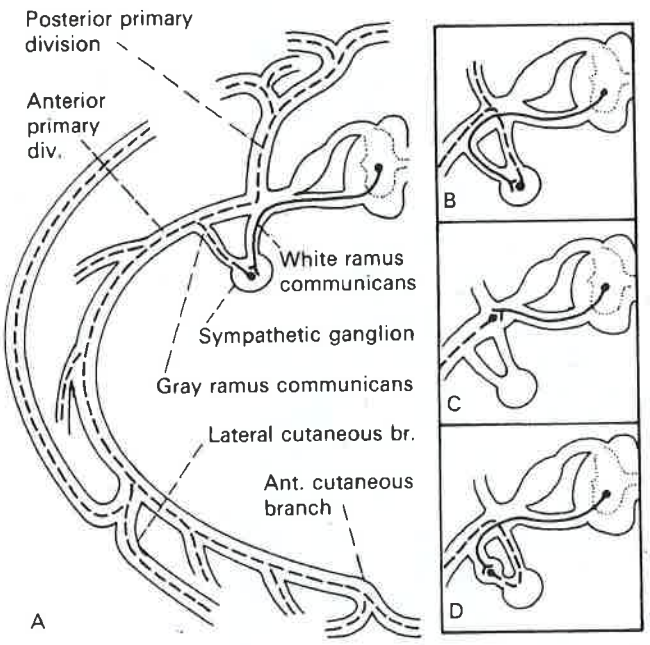

Figure 8-19. **A:** The course of sympathetic fibers in thoracic spinal nerves. Note particularly the course of the preganglionic fibers in the rami communicantes. Preganglionic fibers are shown as solid lines and postganglionic fibers as dashed lines. **B**, **C**, and **D** show unusual sites of synapse between preganglionic and postganglionic fibers. Section of the sympathetic ganglion in **C** would not produce interruption of the sympathetic pathways. (Ant., anterior; br., branch; div., division.)

side. The location of the lumbar ganglia is also inconstant. In some instances they are segmentally located, whereas in other cases they are closely grouped and lie over particular segments, the most common location being between the second and fourth lumbar vertebrae. The ganglia may be situated on the body of the vertebra immediately in front of the aponeurotic arcades giving origin to the psoas muscles, or they may lie antero-lateral to an intervertebral disk, the upper portion of the ganglion being in front of the vertebra above and the lower portion in front of the vertebra below.

Connections between Sympathetic Trunks and Spinal Nerves. The sympathetic trunks are connected to the spinal cord and spinal nerves by one or more rami communicantes and with visceral and somatic afferent fibers.

White Rami Communicantes. The white rami communicantes consist of myelinated preganglionic neurons and visceral afferent fibers. These are limited in their distribution and are present only in the thoracic and upper two or three lumbar segments, but usually not in the cervical, lower lumbar, or sacrococcygeal segments (see Fig. 8-17). These 14 or 15 pairs of white rami communicantes carry the only preganglionic fibers of the sympathetic outflow and are therefore the only connections between the central nervous system and the peripheral sympathetic system. All sympathetic motor impulses to the body and visceral sensory impulses to the central nervous system are conveyed through these anatomic bridges.

Gray Rami Communicantes. The gray rami communicantes consist of unmyelinated postganglionic sympathetic fibers, which pass from the sympathetic trunks to each of the spinal nerves to become distributed as vasomotor, sudomotor, and pilomotor fibers in the somatic areas. The vasoconstrictor fibers consist of unmyelinated postganglionic neurons, the cells of which arise in the ganglia of the sympathetic trunk, and the axons of which pass by way of the gray rami communicantes to all spinal nerves. By coursing peripherally through these nerves, they finally reach the blood vessels of the trunk and limbs. The pilomotor and sudomotor fibers have a similar course.

In addition to the gray rami communicantes, the sympathetic trunks give off rami that supply the viscera. The most important of these are the carotid nerve; the superior, middle, and inferior cardiac nerves; the superior, middle, and inferior thoracic splanchnic nerves; and the lumbar and sacral splanchnic nerves. They supply sympathetic fibers to the viscera of the head, chest, and abdomen. These are discussed in greater detail in various chapters of Part IV.

Sympathetic Afferents. Many sympathetic afferents mediate visceral pain from the heart and from the abdominal viscera, except some pelvic organs that are supplied by parasympathetic afferents. Although these fibers do not establish direct connections with the peripheral autonomic neurons, they pass through the ganglia of the sympathetic trunk, at which point they can be surgically or chemically interrupted. As previously mentioned, the cell bodies of visceral (and somatic) afferent fibers are located in the dorsal root ganglia of spinal nerves. Their short central processes pass to the spinal dorsal horn, where they make synaptic connection with dorsal horn interneurons and also with the cell bodies of neurons, the axons of which make up ascending pathways. Some dorsal horn neurons onto which primary afferents synapse pass anteriorly to connect with somatic motor neurons, and some make synaptic connection with preganglionic neurons in the intermediolateral cell column. Through these spinal segmental circuits, visceral afferents affect reflex connections, which are involved in increased skeletal muscle tension and increased sympathetic activity, and which in turn alter the function of the viscera (see Fig. 8-16).

The long peripheral processes of sympathetic afferents pass through the distal part of the posterior root, the formed spinal nerve, the white rami communicantes, and then through the ganglia of the sympathetic trunk without interruption to reach the viscera by one of two ways. One is by passing through one of the cardiac or splanchnic nerves and through the corresponding prevertebral plexus. The other is by passing through one of the nerves that passes from the sympathetic trunk directly to the viscera without traversing any of the prevertebral plexuses.

Ganglia and Plexuses of the Peripheral Autonomic Nervous System

Cephalic Ganglia. Autonomic ganglia include the ciliary, sphenopalatine, otic, and submaxillary ganglia, which are situated in relation to the third, fifth, and ninth cranial nerves. Each of these ganglia receives sympathetic postganglionic fibers, parasympathetic preganglionic fibers, and sensory fibers. The anatomy of these ganglia, as well as the sympathetic plexuses to the head, are discussed in Chapter 46, concerned with the anatomic and physiologic bases of pain in the head.

Autonomic Plexuses in the Chest. Three great prevertebral plexuses exist, consisting of aggregates of ganglia and interconnecting sympathetic, parasympathetic, and afferent fibers. These include the cardiac plexuses, the pulmonary plexuses, and the esophageal plexuses and are discussed in Chapter 60 in connection with the anatomic and physiologic bases of pain in the chest.

Abdominal Prevertebral Ganglia/Plexuses. As in the chest, three large prevertebral plexuses exist, which include prevertebral sympathetic ganglia as well as parasympathetic fibers from the vagus or the sacral parasympathetics and afferent fibers. These include (a) the celiac (solar) plexus, which breaks into approximately 10 important subsidiary plexuses that supply the abdominal viscera above the pelvis; (b) the superior hypo-

gastric plexus; and (c) the inferior hypogastric or pelvic plexus, which supplies the pelvic viscera. These are discussed in Chapter 65, concerned with the anatomic and physiologic bases of abdominal pain, and Chapter 70, concerned with the anatomic and physiologic bases of pelvic pain.

Sympathetics to the Limbs and Trunk. The sympathetic nerve supply to the limbs is discussed in Chapter 54, dealing with the anatomic and physiologic bases of pain in the upper limb, and in Chapter 75, concerned with the anatomic and physiologic bases of pain in the lower limbs.

Summary of Sympathetic and Nociceptive Supply to Body Structures

Table 8-4 summarizes the sympathetic and nociceptive pathways to various body structures. It is based on information contained in the first edition of this book and subsequent comprehensive reviews (28,34) and information published by Mitchell (23), Pick (24), Pick and Sheehan (35), Netter (4), and Meyer (36). The parasympathetic supply to these various structures is not included for the sake of clarity and also because the origins of preganglionic parasympathetic fibers, their routes, and the locations of postganglionic fibers have previously been mentioned and are discussed in detail in Chapters 46, 54, 60, 65, 70, and 75.

Pharmacology and Physiology of the Autonomic Nervous System

This section on the pharmacology and physiology of the ANS is included for the sake of completeness and is *not* intended to be all inclusive. A few pharmacologic principles and the physiologic action of sympathetic and parasympathetic nervous systems are considered. Detailed discussions can be found elsewhere (21,23,29,35).

Pharmacology

Neurohumeral transmission in the peripheral ANS occurs in principle by the same mechanism as that at the neuromuscular endplate and at central synapses (Fig. 8-20). In contrast to the endplate, however, the pre- and postsynaptic structures in the ANS are extremely variable (myocardial cells, smooth muscle cells, gland cells, and neurons). Moreover, the density of innervation varies greatly among different smooth muscles.

Acetylcholine. Acetylcholine is released at all preganglionic autonomic nerve endings, both sympathetic and parasympathetic, and also by most postganglionic parasympathetic neurons—so-called cholinergic neurotransmitters. Some sympathetic postganglionic neurons are also cholinergic—those to the sweat glands and perhaps the vasodilator neurons to the resistance vessels in the skeletal muscles. The action of acetylcholine on the postsynaptic membranes of the postganglionic neurons can be simulated by nicotine and its action on the effector cells by muscarine. This suggests there are two kinds of receptors to which acetylcholine reacts: nicotinic and muscarinic, respectively (37,38). It has long been known that there are drugs that selectively block one or the other action. The nicotinic action of acetylcholine on the postganglionic neurons can be blocked by quaternary ammonium bases, which are thus called *ganglionic blocking agents*. The muscarinic action of acetylcholine can be selectively blocked by atropine (see Fig. 8-20).

Norepinephrine. Norepinephrine (noradrenalin) is the transmitter substance in sympathetic postganglionic nerve endings, and these cells are called *adrenergic neurons*. The cells in the adrenal medulla, which are homologues of the postganglionic neurons, mainly release epinephrine (adrenaline) into the bloodstream (80% adrenaline and 20% noradrenaline). The response of organs to catecholamines is mediated by two types of receptors: α-adrenergic and β-adrenergic receptors. As is well known, a variety of pharmacologic agents can either enhance or block the α-adrenergic and β-adrenergic action of the catecholamines.

Physiology

The ANS regulates activities that are normally not under voluntary or conscious control, including such important physiologic processes as metabolism, circulation, respiration, body temperature, digestion, sweating, and endocrine secretion. The integrating action that is exerted over these and other physiologic processes helps to maintain the constancy of the internal environment. This integration of function, termed *homeostasis* by Cannon (39), frees the individual from having to pay constant attention to the management of bare existence. It thus obviates the necessity of always being alert to the constant danger to which a changing environment subjects the individual.

All portions of the ANS take part in homeostasis, and the function of some of these parts is relevant to pain. The part played by the central portions has been alluded to in connection with the anatomy. The functions of the hypothalamus and the limbic system in pain are discussed in some detail in Chapter 5. The part played by the peripheral portion of the ANS in the regulation of autonomic function and homeostasis deserves emphasis because of the significant role its dysfunction plays in some painful states.

The sympathetic and parasympathetic divisions of the ANS have mutually coordinated actions that are often antagonistic, thus maintaining a functional balance. This balance is made possible by the dual autonomic supply of almost all of the viscera and of the other parts of the body. The effects of stimulating either portion of the ANS and its impact on various organs, visceral structures, and effector cells are summarized in Table 8-5. It deserves strong emphasis that in most situations the two systems act in an exquisitely synergistic fashion. For example, a reduction in arterial blood pressure produces a reflex response on the part of the cardiovascular system that consists of an increase in the rate and contractility of the heart and an increase in peripheral vascular resistance. This increase in heart and peripheral vascular resistance is brought about by an increase in the activity of the sympathetic nervous system and a concomitant and exquisitely coordinated decrease in the activity of the parasympathetic system (functional synergy).

Close study of Table 8-5 makes it obvious that the sympathetic outflow is catabolic in function, a fact that is duly emphasized in discussing the pathophysiology of acute pain in Chapter 9. Although the sympathetic system is considered not absolutely essential to life, because in its absence one can survive in a very sheltered existence, it does have the important function of protecting the organism against adverse conditions by immediately and simultaneously activating all organs through rapid diffuse action. This prepares the individual for "fight" or "flight" by increasing cardiac output, through chronotropic and inotropic action and increase in peripheral resistance with consequent rise in blood pressure; an increase in blood sugar; contraction of the spleen with an increase in circulating red blood cells; constriction of all blood vessels (except those of the brain, heart, and skeletal muscles), resulting in redistribution of the blood to where it is needed most (the high-priority organs); and dilation of the bronchi and inhibition of the gastrointestinal and urinary functions. This rapid and diffuse action is made possible by the aforementioned vast synaptic connection of pre- and postganglionic fibers, a characteristic that is not common to the parasympathetic division, in which there is a one-to-one relationship between pre- and postganglionic neurons.

TABLE 8-4. Summary of sympathetic and nociceptive nerve supply to more important body structures

Region, structure, chapter reference	Sympathetic nerve supply			Nociceptive pathways	
	Location of cell body in spinal cord and course of preganglionic neurons	Site of synapse of preganglionic with postganglionic neurons	Course of postganglionic axons	Location of primary afferent pathway	Entrance into central nervous system
Head and neck					
Meninges and arteries of brain Chapters 46, 47	T-1, 2 (3)[b] To and through cervical sympathetic chain	All cervical sympathetic ganglia	Plexuses around internal carotid and vertebral arteries	Cranial nerves (CN) V, IX, X C-1–3	Trigeminal subnucleus caudalis C-1–3 spinal segments
Eye[a] Chapters 46, 51	T-1, 2, 3 (4) To and through cervical sympathetic chain	Superior cervical ganglion and ganglia in internal carotid plexus	Internal carotid and cavernosus plexuses→ciliary ganglion or nasociliary nerve→ciliary nerves or along ophthalmic artery	Ophthalmic branch of CN V	Trigeminal subnucleus caudalis
Lacrimal gland[a] Chapter 46	T-1, 2 To and through cervical sympathetic ganglia	Superior cervical sympathetic ganglion	Internal carotid plexus→vidian nerve→sphenopalatine ganglion→maxillary nerve→zygomatic/lacrimal nerves	Lacrimal nerve→ophthalmic branch of CN V	As above
Parotid gland[a] Chapter 46	As above	All cervical sympathetic ganglia	External carotid plexus→internal maxillary and middle meningeal plexus→to auriculotemporal nerve and plexus and to the parotid arterial plexuses	Parotid nerve→auriculotemporal nerve of mandibular division of CN V	As above
Submandibular and sublingual glands[a] Chapter 46	As above	As above	External carotid plexus→facial plexus→submandibular ganglion→direct glandular filaments or via lingual nerves or directly to glands along vessels	Submandibular branch of lingual nerve→mandibular division of CN V	As above
Thyroid gland Chapter 54	As above	Middle and inferior cervical sympathetic ganglia	Perivascular sympathetic plexuses accompanying superior and inferior thyroid arteries	Afferents accompanying sympathetic pathways	T-1 and 2 spinal cord segments
Blood vessels of skin and somatic structures Sweat glands Hair follicles Chapters 46, 54	T-1–4 To and through cervical sympathetic chain	All cervical sympathetic ganglia	In perivascular plexuses accompanying various branches of external and internal carotid arteries	Afferents accompanying sympathetic nerves CN V, IX, X C-2–4	T-1–4 spinal cord Subnucleus caudalis C2–4 spinal cord segments
Thoracic viscera					
Heart Chapters 60, 61	T-1–4 (5) To upper thoracic and cervical sympathetic chain	All cervical and upper four (5) thoracic ganglia	Superior, middle, and inferior cervical cardiac nerves and the four (5) thoracic cardiac nerves→cardiac plexuses	Afferents in middle and inferior cervical cardiac and the thoracic cardiac nerves	T-1–4 (5)
Larynx Chapter 52	T-1, 2 To and through cervical sympathetic chain	Superior cervical ganglion	Laryngeal branch of superior cervical ganglion→superior laryngeal nerve	Superior laryngeal nerve	Trigeminal subnucleus caudalis
Trachea, bronchi, and lungs Chapter 62	T-2–6 (7) To upper thoracic sympathetic chain	T-2–6 (7) Sympathetic ganglia	Pulmonary branches from sympathetic trunk→pulmonary plexuses	Afferents with sympathetics Afferents with vagus	T-2–6 (7) Nucleus tractus solitarius (medulla)

continued

Region, structure, chapter reference	Sympathetic nerve supply: Location of cell body in spinal cord and course of preganglionic neurons	Sympathetic nerve supply: Site of synapse of preganglionic with postganglionic neurons	Sympathetic nerve supply: Course of postganglionic axons	Nociceptive pathways: Location of primary afferent pathway	Nociceptive pathways: Entrance into central nervous system
Esophagus Chapter 62 Cervical	T-2–4 To and through upper thoracic sympathetic chain	All cervical sympathetic ganglia and pharyngeal plexus	From cervical ganglia to recurrent laryngeal nerve	Afferents in vagus Afferents with sympathetics	N. tractus solitarius T-2–4(?)
Thoracic	T-3–6 To and through upper thoracic sympathetic chain	Stellate and upper thoracic ganglia	Direct esophageal branches and through cardiac sympathetic nerves	Afferents with vagus Afferents with sympathetics	N. tractus solitarius T-3–6(?)
Abdominal	T-5–8 To thoracic sympathetic chain—superior thoracic splanchnic nerve	Celiac ganglia	Via plexuses around left gastric and inferior phrenic arteries	Afferents with sympathetics Afferents with vagus	T-5–8 N. tractus solitarius
Thoracic aorta Chapter 60	T-1–5 (6) To thoracic sympathetic chain	Synapse upper five (six) thoracic sympathetic ganglia	Branches from cardiac sympathetic nerves and direct fibers from thoracic sympathetic chain	Afferents with sympathetic pathways	T-1–5 (6)
Abdominal viscera					
Abdominal aorta Chapter 65	T-5–L-2 Some through splanchnic nerves and direct branches	Celiac ganglia and paravertebral sympathetic chain	Fibers that contribute to the aortic plexus	Afferents associated with sympathetics	T-5–L-2
Stomach and duodenum Chapters 65, 66	T-(5) 6–9 (10) (11) Superior (greater) and middle (lesser) thoracic splanchnic nerves and celiac plexus	Celiac ganglia	Right and left gastric and gastroepiploic plexuses	Afferents with sympathetics	T-(5) 6–9 (10) (11)
Gallbladder and bile ducts Chapters 65, 67	T-(5) 6–9 (10) Superior thoracic (greater) splanchnic nerves and celiac plexus	Celiac ganglia	Hepatic and gastroduodenal plexuses	Afferents associated with sympathetics	T-(5) 6–9 (10)
Liver Chapters 65, 67	T-(5) 6–9 (10) Superior thoracic (greater) splanchnic nerves and celiac plexus	Celiac ganglia	Hepatic plexus	Afferents associated with sympathetics	T-(5) 6–9 (10)
Pancreas Chapters 65, 67	T-(5) 6–10 (11) Superior thoracic (greater) splanchnic nerves and celiac plexus	Celiac ganglia	Direct branches from celiac plexus and offshoots from splenic, gastroduodenal, and pancreaticoduodenal plexuses	Afferents associated with sympathetics	T-5–10 (11)
Small intestines Chapters 65, 66	T-8–12 right T-8–11 left To superior (greater) and middle (lesser) thoracic splanchnic nerves to celiac plexus	Celiac and superior mesenteric ganglia	Superior mesenteric plexus→nerves alongside jejunal and ileal arteries	Follow sympathetic pathways through celiac and inferior mesenteric plexuses	T-(8) 9, 10 T-10, 11
Cecum and appendix[a] Chapter 66	T-10–12 Superior (greater) and middle (lesser) thoracic splanchnic nerves→celiac and superior mesenteric plexuses	Celiac and superior mesenteric ganglia	Nerves alongside ileocolic artery	Accompanying sympathetic pathways	T-10–12

continued

TABLE 8-4. (*Continued*)

Region, structure, chapter reference	Sympathetic nerve supply			Nociceptive pathways	
	Location of cell body in spinal cord and course of preganglionic neurons	Site of synapse of preganglionic with postganglionic neurons	Course of postganglionic axons	Location of primary afferent pathway	Entrance into central nervous system
Colon to splenic flexure[a] Chapter 66	T-10–L-1 Middle (lesser) and inferior (least) thoracic and first lumbar splanchnic nerves	Superior and inferior mesenteric ganglia	Mesenteric plexus→nerves alongside right, middle, and superior left colic arteries	Associated with sympathetics, pass through superior and inferior mesenteric plexuses and splanchnic nerves and to spinal cord	T-10–L-1
Splenic flexure to rectum[a] Chapter 66	L-1, 2 (left side) S-2–4 Lumbar and sacral splanchnic nerves→inferior mesenteric and inferior hypogastric pelvic plexuses	Inferior mesenteric ganglion and ganglia in superior and inferior hypogastric plexuses	Nerves alongside inferior left colic and rectal arteries	Afferents with parasympathetic nerves and pudendal nerves	S-2–4
Suprarenal (adrenal) glands[a] Chapter 68	T-(7) 8–L-1 (2) Superior (greater), middle (lesser), and inferior (least) thoracic splanchnic nerves and first (second) lumbar splanchnic nerves	Chromaffin cells of adrenal medulla	Within the gland		
Kidneys[a] Chapter 68	T-10–12, L-1 (2) Middle (lesser) and inferior (least) thoracic splanchnic nerves and first (second) lumbar splanchnic nerves→celiac and renal plexuses	Celiac and aorticorenal ganglia	Along renal plexus	Accompanies sympathetic pathways	T-10–12 (L-1, 2)
Ureters[a] Upper two-thirds Chapter 68	T-(10), 11, 12, L-1, 2 Middle and inferior thoracic splanchnic and upper two lumbar splanchnic nerves	Celiac and aorticorenal ganglia	Superior mesenteric and renal plexuses→superior and middle ureteric nerves	Associated with sympathetics	T-10–12 (L-1, 12)
Ureters Lower one-third Chapter 68	T-11–L-1, S-2–4	Aorticorenal ganglion and sacral sympathetic ganglia	Aortic, superior hypogastric, and inferior hypogastric (pelvic) plexuses and sacral splanchnic nerves	Accompany sympathetic and parasympathetic nerves	T-10–12
Pelvic viscera					
Bladder Chapter 73	T-(11), 12, L-1, 2 Middle and inferior thoracic splanchnic nerves	Inferior mesenteric ganglion and sacral paravertebral ganglia	Superior and inferior hypogastric plexuses and sacral splanchnic nerves to vesical plexus	Predominantly afferents of parasympathetic nerves; also some sympathetic afferents	S-2–4
Uterus Chapter 71	T-(6–9) 10–12, L-1 (2) Splanchnic nerves to aortic and ovarian plexuses and superior and inferior hypogastric plexuses	Celiac ganglion and various paravertebral ganglia	Lumbar and sacral splanchnic nerves; superior, middle, and inferior hypogastric plexuses→uterine plexus	Accompanying sympathetic pathways	T-11–L-2

continuec

Region, structure, chapter reference	Sympathetic nerve supply: Location of cell body in spinal cord and course of preganglionic neurons	Sympathetic nerve supply: Site of synapse of preganglionic with postganglionic neurons	Sympathetic nerve supply: Course of postganglionic axons	Nociceptive pathways: Location of primary afferent pathway	Nociceptive pathways: Entrance into central nervous system
Testes, ductus deferens, epididymis, seminal vesicles, prostate Chapter 73	T-10–L-1 inclusive Splanchnic nerves→ aortic and superior hypogastric plexus	Prevertebral ganglia and inferior mesenteric ganglion	Follow various vascular plexuses in sacral splanchnic nerves	Testes (ovaries) Prostate Parasympathetic afferents	T-10 S-2–4
Trunks and limbs (Innervation of vessels, sweat glands, and hair follicles)					
Trunk	T-1–12	T-1–12 paravertebral sympathetic ganglia	Gray rami communicantes→thoracic spinal nerves	Primary afferents in spinal nerves	T-2–L-1
Upper extremities	T-2–8 (9) To and through upper thoracic and lower cervical sympathetic chain	Middle and stellate ganglia; T-2 and 3 ganglia	Gray rami communicantes to roots of brachial plexus→brachial plexus and its major nerves; some directly to plexuses around subclavian, axillary, and upper brachial arteries	Brachial plexus and its branches	C-5–T-1
Lower extremities	T-10–12, L-1, 2 To and through lumbar and upper sacral sympathetic chain	L-1–5, S-1–3 paravertebral ganglia	Gray rami communicantes→ lumbosacral plexus and its major nerves; direct branches to perivascular plexuses as far as upper femoral artery	Lumbosacral plexus	L-1–S-3

[a]Unilateral innervation.
[b]Segments in parentheses are inconstant.

In contrast to the catabolic function of the sympathetic system, stimulation of which often gives rise to an extraordinary liberation of energy, the parasympathetic function is anabolic and most essential for life. It is concerned with conserving and storing energy, by slowing the heart rate, by enhancing digestion and absorption of food through stimulating the gastrointestinal tract, and by emptying the hollow organs, including the lower colon and urinary bladder, thus aiding in the elimination of waste products.

The functional balance that is normally maintained by the two systems is disturbed in certain disease states, either by the hyperactivity of one or hypoactivity of the other, or a combination of these. The resultant disturbance in autonomic function, if persistent, can prove deleterious to the entire organism. Linkages exist between the autonomic and immune systems that may be important in the production of disease states and the response to neoplasia and other chronic disease that may lead to pain (40). Pain itself may alter the immune response and thereby alter the progression of a disease (41). Animal and human physiologic and pharmacologic studies of visceral as well as somatic pain have demonstrated both plasticity and functional characteristics that are far more complex than the basic anatomy described in this chapter; entire books have been written, for example, on visceral pain (42). Some of these issues are discussed in Chapters 3 to 5.

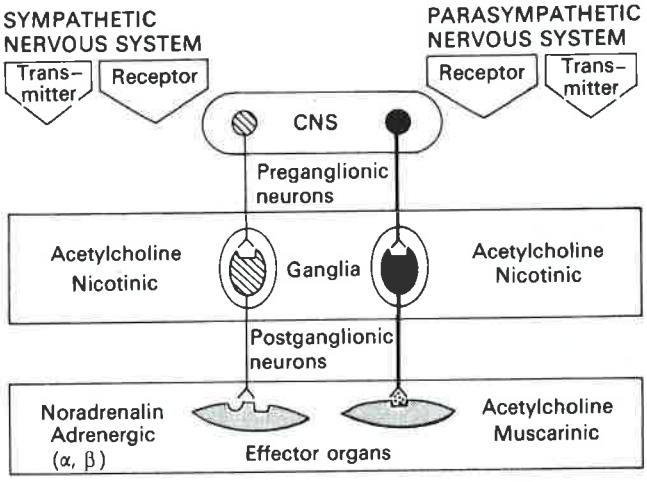

Figure 8-20. Transmitter substances in the peripheral autonomic nervous system. (Modified from Jänig W. The autonomic nervous system. In: Schmidt RF, Thews G, eds. *Human physiology.* Berlin: Springer-Verlag, 1983:111.)

TABLE 8-5. Physiologic responses to autonomic stimulation

Structures/organs	Sympathetic stimulation	Adrenergic receptors	Parasympathetic stimulation
Eye			
Ciliary muscle	Relaxed for far vision	β	Contraction (accommodation for near vision)
Pupillary muscles			
Dilator	Dilated (mydriasis)	α	—
Sphincter	—		Contraction (miosis)
Lacrimal gland	—		Secretion
Salivary glands			
Parotid	Sparse, thick secretion	α	Profuse serous secretion
Sublingual			
Submaxillary			
Thyroid gland	Stimulated		—
Tracheobronchial tree			
Bronchial muscles	Relaxed	β	Contracted
Bronchial glands	—(?)		Secretion
Heart			
Rate	Increased	β	Decreased
Output	Increased	β	Decreased
Esophagus			
Motility	Decreased	α and β	Increased
Sphincters	Contracted	α	Relaxed
Stomach			
Motility	Decreased	α and β	Increased
Sphincters	Contracted	α	Relaxed
Secretion	Inhibited	α	Increased
Liver	Glycogenolysis, gluconeogenesis	β	—
Gallbladder and biliary ducts	Relaxed	β	Contracted
Pancreas			
Blood vessels	Constriction		Dilation
Insulin secretion	Reduced	α	Increased
Spleen	Contraction of capsule	α	—
Intestines			
Motility	Decreased	α and β	Increased
Sphincters	Relaxed	β	Contracted
Secretion	Decreased	α	Increased
Adrenal gland	Secretion of 80% epinephrine/20% norepinephrine	α	—
Kidneys			
Arterioles	Constriction	α	Dilation
Ureter			
Tone and motility	Decreased	α	Increased
Urinary bladder			
Detrusor muscles	Relaxed	β	Contracted
Trigone and sphincter	Contracted	α	Relaxed
Genital organs			
Seminal vesicles	Contraction	α	—(?)
Vas deferens	Contraction	α	—(?)
Uterus	Contraction	α	Depends on species and hormonal status
	Relaxation	β	
Blood vessels			
Coronary arteries	Constriction	α	—
	Dilation?	β	—
Arteries in skeletal muscles	Constriction	α[a]	—
	Dilation	β	
Arteries in penis or clitoris	—(?)		Dilation
All other arteries	Constriction	α	Dilation
Veins	Constriction	α	—

[a]By circulating epinephrine only.

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adrenal glands for the release of cortisol, increased release of glucagon, decreased insulin release, decreased insulin sensitivity, activation of plasma cyclic adenosine monophosphate, release of arginine vasopressin, and decreased free water excretion from the kidneys. This process results in mobilization of substrates or a catabolic state in an effort to sustain the organism. This catabolic state can last for hours to weeks.

The neuroendocrinologic response producing a catabolic state was probably at one point advantageous, in that it allowed the organism while incapable of hunting and gathering to mobilize substrates to nourish vital organ systems and the damaged tissues. It is interesting that the length of this catabolic state corresponds well with the level of tissue injury and theoretically the level of incapacitation. No clear benefit exists for a catabolic state when the organism has a safe harbor and adequate nutrition can be provided. Nutritional support and modulation of the catabolic state are beneficial to the patient.

The limbic system may also act disproportionately in certain circumstances (see Chapter 5). At a primitive level, it is advantageous for an organism to recognize threat from an instinctive standpoint as well as to be able to learn from previous experiences with threatening stimuli. It is important to be able to determine when to appropriately choose fight or choose flight and, if one survives, postinjury maintenance of a high level of arousal and vigilance for the likely return of a predator is beneficial. It is interesting that peak catecholamine levels do not occur until 24 to 48 hours after injury, sustaining the adrenergic state. However, in modern society with our current medical system, this level of sympathetic response is probably not beneficial and can be detrimental.

The patient may have an elevation in the pain response mediated by the somatomotor reflex system and muscle spasm, the sympathetic nervous system via vasoconstriction and release of norepinephrine and epinephrine, and by increased local ischemia or an enhanced inflammatory response. The central nervous system does exert a descending inhibition system, mediated by cortical diencephalic and mesencephalic tracts, periaqueductal gray matter and other opioid-receptor-rich tracts, and the dorsolateral funiculus from the locus ceruleus and the nucleus raphe magnus, sending noradrenergic and serotonergic transmission to the dorsal horn.

Gamma-aminobutyric acid (GABA) receptor–specific medications act presynaptically in the large primary afferents, 1-A afferents for muscle, to decrease somatomotor reflex activity, thus the rationale for the use of GABA-specific receptor medications such as the benzodiazepines for decreasing reflex muscle spasm in response to pain. Some α-adrenergic agonist receptors, when stimulated, inhibit pain transmission and possibly somatomotor reflex activity. This is the rationale for the use of medications such as clonidine and tizanidine in the management of pain, spasticity, and spasm. Endogenous opioids, enkephalins, and endorphins can inhibit nociceptive transmission. The pituitary adrenal axis also exerts effects on stress, pain perception, and pain behaviors.

It is interesting to note that mood and emotional state are modulated by norepinephrine, serotonin, and GABA, as are the descending pain inhibitory pathways. Dopamine may have a small role in pain modulation, primarily through the arousal matrix.

Summary

The stress response appears to work best for preventing excessive morbidity or mortality in response to the physical assault of predators. However, hypercoagulability, catabolism, and hypervigilance are not adaptive when no physical threat exists, or the threat has been removed. The stress response can lead to multiple negative physical and psychological complications of trauma. Because the inflammatory and stress response systems can be exuberant and prolonged, medical modulation can be beneficial to the patient to relieve physical and emotional pain, promote healing, and prevent the development of chronic pain syndromes and the potential negative psychological sequelae of trauma.

TISSUE INJURIES

Connective tissue functions to support or contain other tissues or organs and to transmit mechanical forces. Components of connective tissue include collagen, ground substance (proteoglycans and water), and cells. The collagen fiber type and arrangement designate the classification of soft tissues. In general terms there are *loose* and *dense* connective tissues. Because of the high density and organization of the collagen in tendons and ligaments, these are referred to as dense connective tissue. The strength of connective tissue is a result of the triple helical structure protein, collagen. The ground substance is relatively amorphous. Proteoglycans and water are the main elements of the ground substance. Glycosaminoglycans, chondroitin sulfate, keratin sulfate, and hyaluronate make up the carbohydrate component of the proteoglycans. The main cellular component of connective tissue is fibroblasts. The collagen fibers give the tissue a high tensile strength. The ground substance allows diffusion of nutrients to the tissue. As well, it helps to minimize friction within the tissue and gives the tissue its compressive properties. Fibroblasts are responsible for the production of the collagen and the ground substance.

Tendons and ligaments have a high volume of type I collagen and a relatively low quantity of proteoglycan. They are particularly tolerant to tensile loads. Articular cartilage is composed of type II collagen and a large amount of proteoglycan-laden ground substance, making this a better tissue to handle compressive forces and associated frictional forces seen with weight-bearing activities. Also seen within connective tissue are circulating blood cells, including microphages acting as scavengers of dead cells, bacteria, and foreign particles and mediators of the inflammatory response; and mast cells (containing vasoactive substances) including histamine, serotonin, and possibly other kinins playing a key role in the control of blood flow and the inflammatory process. Lymphocytes and polymorphonuclear neutrophils can be seen within connective tissues.

The mechanical properties of soft tissues are not only determined by their structural components but also by temperature, activity, and age. Tendons and ligaments are stiffer when cold and become less viscous and more extensible with elevating temperature. Stretching results in creeping of the collagen fibers and change in the viscoelastic properties of that tissue, changes that can protect tissues from injury. In sports medicine, stretching has been recommended to prevent injury (4,5). In rehabilitation, stretching is used as a method to regain range of motion and improve function (6,7). Static stretching is the preferred technique for gaining sustained tissue elongation with minimal risk of injury. Ballistic stretching should be avoided. To get an adequate sustained elongation of soft tissues (i.e., stretch), it is helpful if the tissues are warm before stretching (8–10).

In sports medicine, active warming up with low-resistance, high-frequency exercise until a light perspiration has broken out on the skin (indicating an elevated body temperature and tissue temperature) should be performed before stretching. It may in fact be this warm-up procedure that is most responsible for injury prevention during the athletic activity that immediately follows. Stretching and resultant increased flexibility not only help prevent injury in the athletic activity immediately after, but if done on a consistent basis over time, also leads to a further

reduction in soft tissue injuries and improved performance over time, as the athlete's baseline level of flexibility improves (11,12). An injury prevention program should include routine stretching five to seven times per week with warm-up and stretching before and stretching after any strenuous activity.

It should be noted that warming up not only improves the viscous properties of tissue, leading to increased flexibility and increased range of motion, but also leads to increased enzymatic activity, increased force production, perhaps secondary to increased enzymatic activity, an increase in the dissociation of oxygen from hemoglobin and myoglobin, increase in muscle blood flow, increase in the sensitivity of nerve receptors, and increase in the speed of nerve conduction velocities. The improvement in nerve conduction times leads to improved proprioception, coordination, and reaction times as well as pain response times. All of these can lead to further reduction in injury rates (13).

The changes in tissues discussed previously can also be achieved with passive warming of these tissues. These passive methods are used in the rehabilitation process and therapeutically use the multiple benefits of warming soft tissues to promote healing of injured tissue and reverse the tissue changes that may have resulted from immobilization (14,15).

The old adage that an ounce of prevention is worth a pound of cure holds for acute and chronic musculoskeletal injury and pain. In many cases it is as simple as warming up and stretching. These should be done in this temporal sequence: warming up and then stretching before any strenuous activity, whether that strain is cumulative, based on the volume of repetitive activity or from relatively low repetition activity but with high force production in the musculotendinous unit. Stronger muscles are also less likely to be injured than weaker muscles. This is an argument for strength training, not only to be used for performance enhancement but also for injury prevention (16).

The pathophysiology of tendon, ligament, and muscle injury and pain is similar. Soft tissue injuries can be classified in terms of etiology: (a) direct injuries, usually caused by blunt trauma; and (b) indirect injuries, which include the following types: Acute injuries occur with the sudden overloading of musculotendinous units. Chronic or overuse injuries are caused by repetitive overloading, frictional resistance, which occurs in highly repetitive activities, or both. Acute or chronic injuries are caused by sudden rupture of a persistent lesion (e.g., rupture of Achilles tendon with chronic tendinitis).

Collagen fibers are the major building blocks of the soft tissues. Normal physiologic loading may produce 2% to 5% strain in collagen fibers and still result in return to resting length after removal of the load. Strain equals the increase in length divided by the original length multiplied by 100. This is characterized as the elastic deformation property of the tissue. At 7% or 8% strain, collagen fiber failure begins. Beyond this one sees plastic deformation, or failure to resume original length after removal of the load. Microscopically collagen failure occurs. Healing of soft tissue injuries occurs by fibrous repair (scar tissue).

Okes and van der Muelen have described the phases of healing postinjury (17,18). An early phase is associated with the sympathetic response or early stress response to tissue injury, vasoconstriction, which may last up to 10 minutes. Beyond this early phase, there is phase 1, described as the acute inflammatory phase (Okes) or the reaction phase (van der Muelen). Phase 2 has been described as the repair phase by Okes, and the regeneration phase by van der Muelen. Phase 3 has been described by both as the remodeling phase.

Phase 1

This phase may last for up to 72 hours, depending on the severity of the injury. It has both cellular and humeral components. Disruption of the cells and surrounding connective tissue occurs. The injury to the small vessels and capillaries results in leaking or bleeding. The local cellular damage also leads to extravasation of intracellular substances. The inflammatory cascade is initiated with further edema formation. Within 24 hours macrophages are present in the tissue, releasing antibacterial and antiinflammatory substances and enzymes for the breakdown of damaged tissues and subsequently the phagocytosis of the residual debris. The complement system is also activated, resulting in antigen–antibody complexes, stimulating chemotaxis and phagocytosis. Degranulation of mast cells occurs with release of histamine and serotonin. Granulocytes release prostaglandin, further increasing vasodilatation and chemotaxis. Phase 1 is characterized by inflammation, swelling, redness, warmth, and acute pain.

Phase 2

Phase 2 may last from 48 hours to 6 weeks. As early as 24 hours postinjury, macrophages are present in the tissue, releasing antibacterial and antiinflammatory substances as well as enzymes for the breakdown of damaged tissue, and subsequently allowing phagocytosis of the residual debris. The repair of tissue only takes place when the site has become clean with the removal of cellular debris. Phagocytosis by the granulocytes of devitalized tissue and bacteria is the essential first step in the healing process.

Early postinjury low oxygen tension occurs in the tissues because of blood vessel injury and poor perfusion, as well as the hypoxia created from the tissue edema. Aerobic bacteria do poorly in this environment; however, macrophages and granulocytes are able to perform their functions in a hypoxic environment, because of their capacity for anaerobic metabolism (i.e., glycolysis). The low oxygen tensions serve to stimulate vascular budding in the repair phase. There is usually relative immobilization and collagen contraction, which can help to protect the injured tissue, but also leads to a loss of flexibility and range of motion.

Phase 3

Phase 3, the remodeling phase, may last from 3 weeks to 12 months or possibly more, depending on the severity of the injury. This phase primarily involves the remodeling of collagen to increase the functional capabilities of the tendon or ligament to withstand the stresses of routine activities. The tensile strength of the collagen is related to the forces imposed on it during the remodeling phase. To fully rehabilitate the patient and prevent future injury, the rehabilitation program must incorporate highly specific but controlled exercises.

The collagen tissues in phase 2 are relatively disorganized. In phase 3 a higher level of organization occurs with appropriate orientation and improvement in the tensile strength of the tissues. Normal ligaments are composed of type I collagen. In a damaged, healing, or healed ligament a higher level of type III collagen is seen, having a fewer number of cross-linkages between and within the tropocollagen subunits. The quality of the tissue improves over time, but may never obtain the same tensile strength as an undamaged ligament (19).

Repair Processes

Phagocytosis by the granulocytes of devitalized tissue and bacteria is an essential first step in the healing process. Excessive edema can inhibit cellular migration to the devitalized tissues. Therefore, it makes sense to try to control this initial response to tissue damage, minimizing the extravasation of fluid and the amount of devitalized cellular material, both of which increase the workload for the phagocytes. In the early stage after injury it is important to control the exuberant inflammatory response and minimize bleeding and edema formation. This facilitates mac-

CHAPTER 81

Nonspecific Treatment Effects

Judith A. Turner

An understanding of the role of nonspecific effects in patient-provider interactions can help clinicians improve the outcomes and satisfaction of their patients. This chapter summarizes the findings from studies of placebo or nonspecific treatment effects that are relevant for clinicians who treat patients with pain problems. Knowledge of this literature may also help clinicians to evaluate critically the literature on various pain treatments to make informed decisions in treatment planning.

A number of factors may influence patient outcomes after any treatment for pain (Table 81-1). These factors fall into three general categories. The first category includes *specific effects of the treatment*, attributable solely to the characteristic content or process of the therapy. The second category includes *natural history and regression to the mean*. Most acute and some chronic pain problems improve or even resolve completely, regardless of treatment. Headache and low back pain are two examples of conditions that for many individuals recur episodically with periods of no or mild pain between episodes. Patients with chronic conditions typically have fluctuating symptoms and seek medical care (and enroll in research studies) when symptoms are at their worst. Thus, the next change is likely to be an improvement. When a group of patients with extreme scores on symptom measures is selected for study or treatment, over time the average scores in the group will decrease due to fluctuations toward more typical values. This tendency is known as *regression to the mean* (1). Apparent improvement may also reflect measurement error or random variation in patient symptoms over time (1). Clinicians and patients alike may mistakenly attribute a decrease in a patient's symptoms to a treatment when, in fact, the change is simply a fluctuation in a cycle of waxing and waning symptoms. The third category includes *nonspecific effects of treatment*—that is, change due to factors not specific to the particular drug or therapy. These include physician attention, interest, and concern in a healing setting; patient and physician expectations of treatment effects; the reputation, expense, and impressiveness of the treatment; and characteristics of the setting that influence patients to report improvement. The term *placebo effect* is often used synonymously with *nonspecific effects*.

TABLE 81-1. Factors that influence patient outcomes

1. Specific treatment effects
2. Natural history, regression to the mean
3. Nonspecific treatment effects (placebo effects)

The word *placebo* was first used in the English language in the fourteenth century as the name given to vespers sung for the dead (2). The first line of these vespers was the Latin version of a psalm (translated, "I shall walk before the Lord in the land of the living"). Apparently because of a translation error, "I shall walk" became *placebo* ("I shall please") (2). Because these vespers were sung for a substantial fee, the term "placebo" had a negative connotation. The word appeared in Hooper's *Medical Dictionary* in 1811, defined as "any medicine adopted to please rather than to benefit the patient" (3). In the past 30 years, many definitions of placebo have been advanced. A useful definition was proposed by Brody (4): an intervention designed to simulate medical therapy but that is not believed to be a specific therapy for the target condition, or an inefficacious treatment believed efficacious at the time of use. Brody (4) further defines *placebo effect* as a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property. Thus, a placebo effect can occur with any treatment, not just with a placebo. A *placebo response*, in contrast, refers to any change in a patient's behavior or condition after the administration of a placebo (5). These distinctions are not always made in the literature, however.

The following sections summarize what is currently known concerning placebo response rates, the pharmacologic and other characteristics of placebo responses (including magnitude and duration), nocebo effects, factors that influence nonspecific effects, and explanations that have been proposed for placebo effects. Finally, the implications of this literature for researchers and clinicians are discussed.

PLACEBO RESPONSE RATES

A common misconception is that approximately one-third of patients will show a placebo response in any clinical trial. This figure is based on Beecher's (6) classic article, a review of 15 studies (seven of which were Beecher's) of patients with a variety of conditions (postoperative pain, cough, angina pectoris, headache, drug-induced mood changes, seasickness, anxiety and tension, and the common cold). Beecher (6) reported that symptoms were "satisfactorily relieved" by a placebo in 35% of patients on average across these studies. However, it is important to note that the placebo response rate ranged from 15% to 58% across the studies. Since Beecher's review, placebo response rates have been observed to vary widely, often greatly exceeding 35%. Since Beecher's review, placebo responses have been observed in other settings and for other conditions [e.g., acute postoperative pain (7), peptic ulcers (8), angina pectoris (9,10), temporomandibular disorders (11)]. Roberts et al. (12) reviewed uncontrolled studies of medical and surgical treatments that were originally believed efficacious but later abandoned because they were found to be no better than placebo. On average, 70% of 7,000 patients included in the studies reviewed had excellent or good outcomes (12). Some studies reported success rates of 100%. Another review of 31 randomized trials found that, on average, 48% of patients showed healing of peptic ulcers, based on endoscopy, after treatment with only a placebo (8). In some of these studies, the rate was as high as 90%.

Even patients with a long history of chronic pain show clinically and statistically significant improvement with placebo. For example, Deyo et al. (13,14) found that, despite the chronicity of their pain (average duration of 4 years), back pain patients' scores on measures of pain severity, pain frequency, and functional status improved on average 20% to 40% after sham transcutaneous electrical nerve stimulation plus hot packs.

NONSPECIFIC EFFECTS OF SURGERY

Beecher (15) emphasized that surgery could evoke a placebo effect and urged caution in interpreting the results of new operations. Two classic studies (9,10) conducted in the 1950s demonstrated substantial and sustained improvement in angina pectoris after sham surgery (skin incision alone). These double-blind randomized trials compared a procedure believed at the time to help angina pectoris (internal mammary artery ligation) with skin incision alone (with vessel exposure but no ligation). In one study, 6 months after the operation, 63% of the ligated patients and 56% of the patients who had skin incision only were substantially improved (9). In the other study, all patients who had skin incision only reported greater than 50% improvement during the subsequent year (10). Benefits were not limited to decreased pain; they also included reduction in nitroglycerin use and increased exercise tolerance.

Improvement in pain after spine surgery may be due in part to some combination of natural history and nonspecific effects. A review of long-term outcomes for 2,504 patients undergoing diskectomies for lumbar disk disease found that, among patients who had no disk herniation (negative surgical exploration), 37% had complete relief of sciatica and 43% had complete relief of back pain (16). Given the lack of known therapeutic effects of surgical exploration of the spine, these outcomes appear to be due to nonspecific effects and/or natural history. The success rates that have been reported for operations for painful lumbar spine disorders are similar to success rates reported for discredited therapies for other conditions. Across 74 studies of surgery for lumbar spinal stenosis, an average of 64% of patients had good or excellent outcomes at long-term follow-ups (17). Similarly, across 47 studies of lumbar spinal fusion, 68% of patients had good or excellent results at long-term follow-ups (18). The lack of randomized controlled trials makes it impossible to draw conclusions concerning the extent to which the outcomes of these operations are due to specific surgery effects, nonspecific effects, or natural history. The weak association between radiologic findings and symptoms (19–24), and between technical success of surgery (e.g., solid fusion) and symptom improvement (25,26), also suggests the possibility that improvement after back surgery may to some extent be attributable to factors such as natural history and patients' and surgeons' expectations of improvement.

In sum, rates of good patient outcomes after medical and surgical treatments that have no specific therapeutic effects for painful conditions vary considerably across studies but, on average, are strikingly high. This makes obvious the need for studies that compare the short- and long-term clinical outcomes of treatments and procedures believed to relieve pain with those of placebo or control therapies. Although case series reports may provide some useful information, such as rates of specific complications, they cannot provide information concerning whether the outcomes are due to natural history, specific therapy effects, or nonspecific effects.

CHARACTERISTICS OF PLACEBO RESPONSES

Placebos have been demonstrated to have in common with active medications time-effect curves and peak effects, cumulative effects (greater effects with repeated administrations), and carryover effects after cessation of treatment (27). Furthermore, when a placebo is administered to people with pain after they have received an analgesic drug, the pain-relieving effect of the placebo is proportional to that of the drug that preceded it (28). Dose-response effects have also been demonstrated—for example, one study found that two placebo capsules produced more pronounced effects than one (29).

Nonspecific effects of treatments are not always positive; adverse effects have been demonstrated to occur after the administration of inactive pills or procedures. It is well known that placebos are associated with side effects. The most common are drowsiness, headaches, nervousness, insomnia, nausea, and constipation (30). A review of 109 double-blind drug trials found that, overall, 19% of healthy volunteers reported adverse events during placebo administration (31). Complaints were most frequent after repeated dosing and in elderly subjects. The type of side effect varied according to the therapeutic drug it was being compared with in the drug trial. Sham treatments can also worsen preexisting symptoms. For example, in a double-blind study of a magnetic device purported to relieve pain, 13 of 58 patients with pain discontinued treatment after one or two treatments because their pain was worse (32). Six months later, three of these patients believed the treatment made their pain permanently worse.

The duration of response to placebos has not been well studied. Fedele et al. (33) found a gradual decrease in the effectiveness of placebo treatment of dysmenorrhea over three consecutive menstrual cycles. However, patients with angina pectoris in the placebo arm of a double-blind randomized trial had a 77% reduction in anginal attacks after 6 months on placebo (34), and some patients with rheumatoid arthritis who were given placebos reported moderate to marked improvement for as long as 20 months (35). Patients with painful diabetic neuropathy reported a decrease in pain intensity over the first 3 weeks they received a placebo but then showed a partial return toward baseline levels during weeks 4 to 6 (36). In one of the studies of sham surgery for angina pectoris, clinically significant improvement in angina symptoms was maintained for up to 1 year (10). Of course, the extent to which these responses reflected natural history/regression to the mean versus placebo effects cannot be determined. It is likely that the magnitude and duration of placebo responses will vary with varying characteristics of patients, conditions, treatments, providers, measures, and settings. These are discussed in later sections of this chapter.

NOCEBO EFFECTS

The nocebo effect has been defined as the causation of sickness (or death) by expectations of sickness (or death) and by associated emotional states (37). For example, pain can be produced in normal subjects by the power of suggestion. Headaches were reported by 70% of college students told that a (nonexistent) electric current was passing through their heads (38). This study was later replicated by a different group of researchers, who also found that the subjects' pain ratings increased when they believed the electrical current had been increased (39). Hahn (37) distinguishes nocebo effects from placebo side effects, which occur when expectations of healing produce symptoms. Hahn (37) also points out that the act of giving a patient a diagnosis may have a placebo or a nocebo effect, and that failure to give the patient a diagnosis may have a nocebo effect.

One general practitioner randomly assigned his patients with symptoms but no abnormal signs, in whom no definite diagnosis could be made, to a positive or a negative encounter with him (40). In the positive encounter, patients were given a diagnosis and told they would be better in a few days. In the negative encounter, the doctor told patients he was not certain what was the matter with them. Two weeks later, 64% of the positive encounter group, but only 39% of the negative encounter group, reported that they had gotten better (a statistically significant dif-

ference). The author speculated that these minor illnesses would be expected to resolve spontaneously by 2 weeks in the majority of patients and that the 61% nonimprovement rate in the negative encounter group reflected adverse effects of the encounter. Another study also suggests that diagnostic testing may have a placebo effect and/or that not testing may have a nocebo effect. Patients thought to have noncardiac chest pain of unclear etiology were assigned randomly to diagnostic testing or no testing (41). Patients not tested were more than twice as likely to report short-term disability. Other examples of nocebo effects are presented in the next section of this chapter.

FACTORS THAT INFLUENCE NONSPECIFIC EFFECTS

Patient Factors

No personality, demographic, or other patient characteristics have been shown consistently to predict placebo responses (42). Specifically, placebo effects have not been found to relate consistently to age, gender, ethnicity, educational level, intelligence, locus of control, extraversion, introversion, neuroticism, or suggestibility (42). In fact, individuals who have a placebo response in one situation may not show a placebo response in a different situation (43,44). For example, one study found that positive responses to a placebo given for labor pain were not correlated significantly with the responses to a placebo given to the same women in the postpartum period (44).

The patient factors that have been shown to influence nonspecific effects are listed in Table 81-2. Patients' positive attitudes toward the provider and toward the treatment have been shown to predict improvement in studies of psychiatric outpatients treated with placebo, psychotropic drugs, or psychotherapy (42). There is also some evidence that highly anxious subjects may show the greatest placebo responses (42).

Patient expectations of treatment effects have been shown to influence their responses, at least in some situations. For example, when subjects in one study were given a pill containing only a magnet to measure stomach contractions, the contractions increased, decreased, or did not change according to the effects they were told the pill would cause (45). In a study of asthmatic patients, isotonic saline produced increases or decreases in airway resistance according to what patients were told to expect (46). Furthermore, when patients were given a true bronchodilator, its effects were about twice as great if patients were told it would produce this effect than if they were told it would produce the opposite effect. A later study (47) also demonstrated both nocebo and placebo responses in asthmatic patients, according to their expectations. When patients believed they were inhaling an irritant chemical, which was in fact water, they showed a bronchoconstrictive response. This nocebo effect was shown in the same study to be *abolished* by a placebo. When subjects inhaled an inactive substance they thought was a powerful new drug *before* inhaling the water solution they thought was an irritant, they had no bronchoconstriction in response to the irritant. In yet another study (48), after subjects drank a beverage they believed was caffeinated coffee but in fact was decaffeinated, motor skill task performance was either enhanced or impaired according to what effects they were told the beverage would have.

Expectations of adverse events have been shown repeatedly to be associated with the subsequent occurrence of such adverse events. An extreme example of this is voodoo death, death that can occur in some cultures by unknown mechanisms, believed to be due to the belief of the victim that death is imminent (49). In Western culture today, the belief that one is susceptible to heart attacks has been shown to be a risk factor itself for coronary death. Analysis of the Framingham study data (50) revealed that among middle-aged female homemakers free of coronary disease, those who believed they were more likely than others to develop heart disease were 3.7 times more likely to have a myocardial infarction (MI) in the next 20 years, even after controlling for commonly recognized cardiac risk factors.

TABLE 81-2. Patient factors that influence nonspecific effects

1. Positive attitudes toward provider, treatment
2. Anxiety
3. Expectations of effects
4. Treatment adherence

Symptoms may also occur when an individual becomes aware of symptoms in others and believes that he or she may also be vulnerable to the condition. A well-recognized form of this phenomenon is *mass hysteria*. Kerckhoff and Back (51) carefully examined the spread of such a sociogenic illness, the 1962 "June Bug" outbreak in a Montana mill. Sixty-two of 965 workers were affected, fainting or complaining of pain, nausea, or disorientation. All of those affected worked in dressmaking departments. Persons affected were 62% more likely to have worked overtime at least two or three times a week, 2.2 times more likely to be sole breadwinners, 5.6 times more likely to be divorced, and 30% more likely to have a child younger than age 6. These facts strongly implicate the role of physical and emotional stress in such conditions.

Other studies have also demonstrated the ability of expectations to produce symptoms. After being told that a medicine administered through a skin patch would induce seizures within 30 seconds, 77% of psychogenic seizure patients showed seizure behavior when the patch, which actually contained only alcohol, was applied (52). Symptoms included nonresponsiveness, generalized violent thrashing, and uncoordinated movements. Nineteen percent of the patients reported auras and 44% showed postictal confusion or sleepiness, or both. A double-blind study designed to evaluate a controversial method of food allergy testing compared the effect of injecting the food substances with the effect of injecting a saline solution (53). Twenty-seven percent of patients given the food substance injection and 24% of those given saline experienced symptoms of nose itching, watering or burning eyes, plugged ears, tight or scratchy throat, nausea, dizziness, sleepiness, and depression.

Another factor demonstrated to be associated with nonspecific treatment effects is treatment adherence. Patients who adhere closely to a prescribed regimen may have better outcomes than those who do not, even when taking a placebo. This observation was first made in a double-blind randomized trial that compared the efficacy of a lipid-lowering drug with placebo on mortality in men who had survived an acute MI (54). Although the lipid-lowering drug was no better than placebo in reducing 5-year mortality, men who adhered closely to the prescribed regimen (i.e., who took 80% or more of the capsules) had a marked reduction in mortality compared with poor adherers (i.e., who took less than 80% of the capsules). Surprisingly, this reduction in mortality was similar in the placebo and lipid-lowering drug groups. Even after controlling for 40 known or suspected coronary risk factors, the placebo noncompliers had a 5-year mortality rate 57% higher than that of the placebo compliers.

The effects of adherence on mortality after MI were further explored in data from the Beta Blocker Heart Attack trial (55). This multicenter randomized double-blind trial compared propranolol with placebo in men surviving an acute MI. Men with poor adherence—that is, who took 75% or less of the placebo or active medication—were 2.6 times more likely to have died

CHAPTER 86

Anticonvulsants and Local Anesthetic Drugs

Michael C. Rowbotham and Karin L. Petersen

Anticonvulsants and local anesthetic drugs have been used for decades to treat chronic pain. Sufficient basic and clinical scientific evidence has accrued to firmly establish anticonvulsants and local anesthetic drugs as specialized analgesics. Neither class of drug has clearly established analgesic efficacy for musculoskeletal, nociceptive, or idiopathic pain. However, both classes can dramatically relieve neuropathic pain.

Research in animals with experimental nerve injury and humans with chronic neuropathic pain has highlighted one clinically important mechanism for the production of neuropathic pain: ectopic impulse generation by damaged, dysfunctional primary sensory neurons and their axons. This abnormal, ectopic discharge can be suppressed by anticonvulsants and local anesthetics with sodium channel blocking effect at concentrations orders of magnitude lower than needed to block the propagation of action potentials in normal nerves (1,2). Because the process of ectopic impulse generation is far more sensitive to sodium channel blockade than is normal impulse conduction, these drugs can be given systemically or regionally without fatal toxicity from failure of normal nerve conduction. Anticonvulsants that do not block sodium channels, such as gabapentin, are also highly effective analgesic agents. Discerning the neuronal basis for the analgesic effect of these drugs has been the subject of much research.

In this chapter, anticonvulsants and systemic local anesthetics are discussed in the context of current concepts of the pathophysiology of neuropathic pain. First, the mechanisms behind neuropathic pain and ectopic neuronal activity are summarized, and the mechanisms by which membrane stabilizing drugs suppress ectopic firing are reviewed: (a) Na-channel blockade and (b) non–Na-channel blockade. Then, the clinical literature relating to their use and efficacy in the treatment of neuropathic pain is reviewed. Finally, the currently available anticonvulsants and systemic local anesthetic drugs are reviewed.

NEUROPATHIC PAIN AND ECTOPIC NEURONAL ACTIVITY

In teased axon recordings from dorsal roots in rats and rabbits with chronic nerve injury, Wall and Gutnick (3) and Kirk (4) demonstrated an increased level of ongoing discharge in afferent A and C fibers compared to normal intact dorsal root and dorsal root just after acute nerve section. Subsequent studies identified two principal sources of this activity: the nerve injury site (e.g., neuroma or nerve compression zone) (5,6; reviewed in 7) and the associated dorsal root ganglia (DRG) (8–10). In addition to spontaneous firing, ectopic discharge at both of these locations can be produced by gentle tapping and by a range of chemical stimuli. In contrast to the nerve injury site, the DRG have not yet been investigated as a potential source of ectopic firing in humans despite the strong experimental evidence in animals.

Ectopic neuronal activity contributes to pain in three ways. First, abnormal afferent barrages that propagate into the central nervous system (CNS) directly will elicit paraesthesias, dysesthesias, and pain. For example, continuous discharge in C fibers produces continuous sensations of burning pain, and intermittent spontaneous bursts in A-δ or A-β fibers produce lancinating dysesthesias or paresthesias. Second, ectopic sites are abnormally likely to generate action potentials (single or prolonged bursts of neuronal activity) spontaneously and in response to gentle mechanical stimulation, sympathetic efferent activity, and circulating catecholamines. Third, abnormally increased afferent input via nociceptors can trigger and maintain "central sensitization." Central neurons become sensitized in response to a brief but intense barrage of nociceptor input or sustained low-level nociceptor input (11). Once central neurons are sensitized, even innocuous mechanoreceptor stimulation from an area around the nerve injury is perceived as painful (12–14). This effect of ectopic firing in neuropathic pain is best illustrated under conditions in which a well-localized focus of abnormal neuronal discharge can be identified. Sheen and Chung (15), for example, severed the spinal nerve of DRG L-5 and L-6 in rats, creating a focus of ectopic discharge in the L-5 and L-6 neuromas and DRG. The result was behavioral signs of ongoing pain, presumably due to the ectopic firing, and allodynia in the hindlimb skin served by the neighboring L-4 root that was presumed to be due to central sensitization triggered by the ectopic firing. Blocking central propagation of the abnormal ectopic discharge by secondarily cutting the L-5 and L-6 dorsal roots eliminated the ongoing pain and normalized sensation in the L-4 territory.

Confirmatory evidence in humans has been gathered using the method of percutaneous microneurographic recording from single nerve fibers (16). Microneurography allows a direct comparison of neural discharge and sensation. A small number of such studies in patients with neuropathic pain have appeared (17–21). Spontaneous and evoked discharges were strikingly correlated with neuropathic paresthesias and pain. As reported by Cline and colleagues (17), patients who complained of burning pain and hyperalgesia had spontaneous activity in unmyelinated primary afferents. Nystrom and Hagbarth (19) documented ongoing discharge in the peroneal nerve in a lower extremity amputee. Their patient had ongoing phantom foot pain that was augmented by percussion of the neuroma. Each percussion elicited an intense burst of spike activity, mostly in slowly conducting axons. Local anesthetic block of the neuroma eliminated percussion-evoked neuronal activity and pain. In a patient with radicular pain after surgery for disk herniation, straight-leg lifting (Lasegue's sign) produced dysesthesias referred to the foot as well as ectopic impulse bursts in the sural nerve, the intensity of which waxed and waned in close correlation with the abnormal sensation (18).

There is some clinical evidence that large areas of touch-evoked allodynia are due to a state of central sensitization maintained by ectopic impulse generation from the area of most severe neuropathic pain. Rowbotham and Fields (22) reported dramatic shrinkage of the area of allodynia with local anesthetic skin infiltration of just the area of maximum pain in a small series of patients with postherpetic neuralgia. Gracely et al. (23) reported a patient whose painful scar near the knee was surrounded by touch-evoked allodynia extending up the thigh

and down the calf. Local anesthetic block of the scar eliminated the extended allodynia as well as the scar pain for the duration of the block. The interpretation offered was that noxious input originating in the scar triggered a spinal central sensitization state that amplified, and rendered painful, A-β touch input from the thigh and calf. More difficult to explain are those rare patients in whom a brief infusion of systemic lidocaine will reproducibly relieve neuropathic pain for days or weeks.

CONTRIBUTION OF NA^+ CHANNEL BLOCKADE TO PAIN RELIEF

Na^+ channels are membrane proteins found in all nerve cells. Among many functions, Na^+ channels constitute a major component of the impulse-generating machinery. Impulse propagation along axons is critically dependent on the functioning of Na^+ channels. The development of ectopic hyperexcitability is thought to be due to remodeling of the local electrical properties of the axon membrane via changes in Na^+ channel distribution (7). The principal underlying mechanism appears to be the accumulation of excess voltage-sensitive Na^+ channels in terminal swellings of axonal sprouts in the region of injury and in patches of demyelination (24).

Research suggests that there may be ten or more different Na^+ channel subtypes. Na^+ channels are classified as tetrodotoxin (TTX)-sensitive or TTX-resistant based on the response to TTX, an extremely potent selective Na^+ channel blocker. TTX inhibits neuronal activity in animal neuropathic pain models by blocking TTX-sensitive Na^+ channels in the injured nerve but also blocks TTX sensitive Na^+ channels throughout the nervous system. A TTX-resistant Na^+ channel named *PN3* (or alpha-SNS) has been identified. In contrast to previously identified Na^+ channels, PN3 is located only in the PNS on small neurons in the DRG (25). The PN3 Na^+ channel is suggested to be of specific importance to pain transmission. Experimental nerve damage leads to changes in PN3 expression in the DRG (26–28). Using immunolabeling, migration of PN3 Na^+ channels from the DRG to C and A-δ fibers has been demonstrated, implying that ectopic neural activity after nerve injury may be due to a dynamic redistribution of pain-specific Na^+ channels. Developing an analgesic agent specifically targeting the PN3 Na^+ channel has potentially important implications, since clinical use of nonselective Na^+ channel blockers are limited by systemic side effects presumed due to actions on cardiac and CNS Na^+ channels.

A variety of anticonvulsant and local anesthetic drugs that suppress abnormal discharge originating at nerve injury sites and associated DRG act on Na^+ channels (29). These include the anticonvulsants carbamazepine, phenytoin, and lamotrigine (30,31); the antiarrhythmics mexiletine and tocainide (32); and lidocainelike local anesthetics (33). Each of these prevents the generation of spontaneous ectopic impulses at much lower concentrations than are required to block normal impulse propagation. Abram and Yaksh (34) compared the effect of systemic lidocaine in three rat pain models: the formalin test (which uses a chemical stimulus to produce a two-phase nociceptive response), partial ligation of the sciatic nerve (which produces neuropathic hyperalgesia), and normal paw withdrawal to noxious heat. Doses of lidocaine that markedly reduce neuropathic hyperalgesia leave the withdrawal latency to noxious heat in the normally innervated paw and both phases of the formalin unaffected. Higher doses of lidocaine reduce only the second phase of the formalin test, which is thought to be due, in part, to the development of central sensitization. In a study of rat sciatic neuromas by Chabal and colleagues (32), lidocaine, mexiletine, and tocainide abolished spontaneous activity and markedly suppressed the ability of gentle mechanical stimulation to evoke abnormal activity. Other studies in animal models of neuropathic pain demonstrate that systemic lidocaine sometimes relieves cutaneous hypersensitivity for a longer time than would be expected from the serum half-life of the drug (35). In sum, these results suggest the following rank ordering of lidocaine effects on pain: (a) Low plasma levels suppress ectopic impulse generation in chronically injured peripheral nerve; (b) higher levels suppress central sensitization and central neuronal hyperexcitability; (c) high levels have general analgesic effects; (d) very high levels are associated with seizure activity, cardiac arrhythmias, and cardiovascular collapse; and (e) supralethal systemic levels block normal axonal impulse conduction.

ANALGESIC EFFECTS INDEPENDENT OF NA^+ CHANNEL BLOCKADE

Some anticonvulsant drugs are highly effective in controlling pain but seem to do so without blocking Na^+ channels. Proposed mechanisms of analgesic actions for non-Na^+ channel blocking drugs revolve around effects on sensitized central neurons, such as direct or indirect inhibition of the release of excitatory amino acids, blockade of neuronal calcium channels, and augmentation of CNS inhibitory pathways via increasing GABA-ergic transmission.

The best example of an effective non-Na^+ channel blocking anticonvulsant is gabapentin, a lipophilic GABA analog. Two large multicenter clinical trials of gabapentin for neuropathic pain demonstrated efficacy (36,37). Gabapentin does not reduce acute nociceptive pain (38,39). However, gabapentin does reduce signs of central sensitization in animals after experimentally induced hyperalgesia and may do so by reducing the sensitization of dorsal horn sensory neurons (39–41). Furthermore, it has been demonstrated in animal models that gabapentin reduces hyperalgesia following experimental nerve injury (38,42). Despite intensive study, the basis for gabapentin analgesia remains uncertain. Gabapentin was developed as an analog to the neurotransmitter GABA but has since been shown not to interact with either $GABA_A$ or $GABA_B$ receptors [for review, see Taylor et al. (41)]. Since gabapentin is excreted unmetabolized, active metabolites cannot explain the analgesic effect in humans. GABA-ergic function could be potentiated without direct interaction with GABA sites by increasing the concentration of GABA in neuronal tissue through release of GABA from nerve terminals (43), enzyme effects, or decreased GABA breakdown (for review, see 41 and 44). Another possible mechanism is mobilization of intracellular GABA via gabapentin-sensitive transporters. However, the best evidence to date comes from studies rank-ordering effects of gabapentin and related drugs on a specific gabapentin-binding protein found in brain and spinal cord. The binding site, called $\alpha_2\delta$, is a subunit of an N-type voltage-gated calcium channel found in high density in the cerebral cortex, superficial dorsal horn, cerebellum, and hippocampus (38,41,45). Studies in spinal cord dorsal horn preparations have found that gabapentin binding is primarily postsynaptic and is resistant to neonatal capsaicin treatment and rhizotomy. GABA itself has no activity at this binding site, but gabapentin analogs that bind to the $\alpha_2\delta$-subunit do appear to have analgesic activity. At this time, it is not certain which, if any, of the suggested mechanisms may be relevant to the analgesic efficacy of gabapentin.

CLINICAL USE OF LOCAL ANESTHETICS, ANTIARRHYTHMICS, AND ANTICONVULSANTS IN TREATMENT OF CHRONIC PAIN

Systemic administration of local anesthetics for analgesia has a long history (46). Beginning in the 1930s, procaine and later lidocaine have been given systemically for a broad variety of

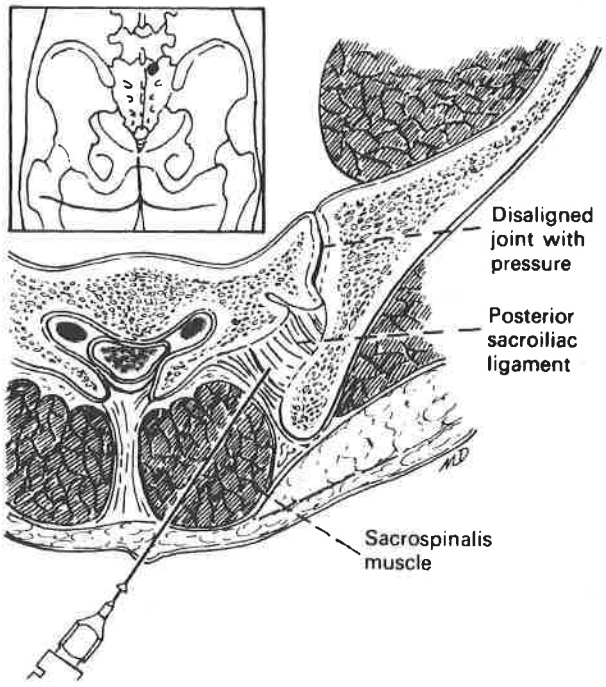

Figure 102-5. Injecting the ligaments of the right sacroiliac joint, which is shown subluxated. Inset: The skin wheal (*black dot*) used to anesthetize the skin for insertion of a larger needle is made in the midline at the level of the posterior superior spines of the ilium. The needle is inserted toward the affected side to make an angle of 45 degrees with the midsagittal section. Once the point is in the ligament, the LA is injected. Then an attempt is made to advance the needle into the subluxated joint, where 3 to 5 mL of solution is injected.

Infiltration of an LA into a muscle can also be used as a diagnostic and therapeutic procedure in the rare cases of pyriformis or scalenus anticus syndrome.

Chronic Pain

Painful Scars. It is unusual for a whole scar to be painful but "trigger points" may be found in a scar. These can be associated with hyperesthesia and radiation of the pain along dermatomes from the scar. Infiltration of the scar with a dilute solution of bupivacaine (e.g., 0.25%) on about six occasions at 3- to 5-day intervals may produce persistent relief. If pain relief does not persist following a series of injections of LA, transcutaneous electrical nerve stimulation should be tried. If this fails, consideration should be given to injection of 1 mL of alcohol into the specific trigger points, which is said to produce a high incidence of success (56).

Neuromata. Neuromata can develop in nerves idiopathically, due to nerve entrapment, subsequent to traumatic nerve section or after surgery or amputation. Infiltration of the neuroma with an LA is a useful diagnostic procedure for determining whether the pain is arising from the neuroma. Moreover, injection of a solution containing an LA (without adrenalin) and a depot corticosteroid such as methylprednisolone (Depo-Medrol) into the neuroma can suppress the spontaneous ectopic discharges that are probably producing pain and paresthesia. Experimental studies have shown that the steroid stabilizes the nerve membrane for 2 weeks or longer (57). Therefore, patients with painful neuromata can be given a trial with this combination at 1- to 2-week intervals for the first month and at 2- to 3-month intervals thereafter. The management of patients with this type of pain is discussed in detail in Chapter 21.

Myofascial Syndromes with Trigger Points. One of the most effective clinical applications of infiltration of LA, with or without steroids, is in the management of myofascial pain syndromes with trigger points. Trigger points can develop in almost every muscle in the body, as well as in tendons and ligaments, producing local and referred pain, tenderness, reflex muscle spasm, and other signs and symptoms. In some patients, such trigger points can be in the vicinity of classic acupuncture points (58). Repeated injections of trigger points with an LA alone or combined with steroid or with saline solution usually produce permanent relief of pain and eliminate the other signs and symptoms (59) (see Chapter 29).

Arthritis. An intraarticular injection of a dilute solution of LA alone or in combination with steroids is also indicated as a diagnostic and therapeutic procedure in patients with pain of chronic arthritis involving major joints in the limbs or spine (Figs. 102-5 and 102-6). It has been suggested that injection of corticosteroids into tender spots along the nerves supplying an osteoarthritic joint produces much better relief of pain than intrasynovial injection of

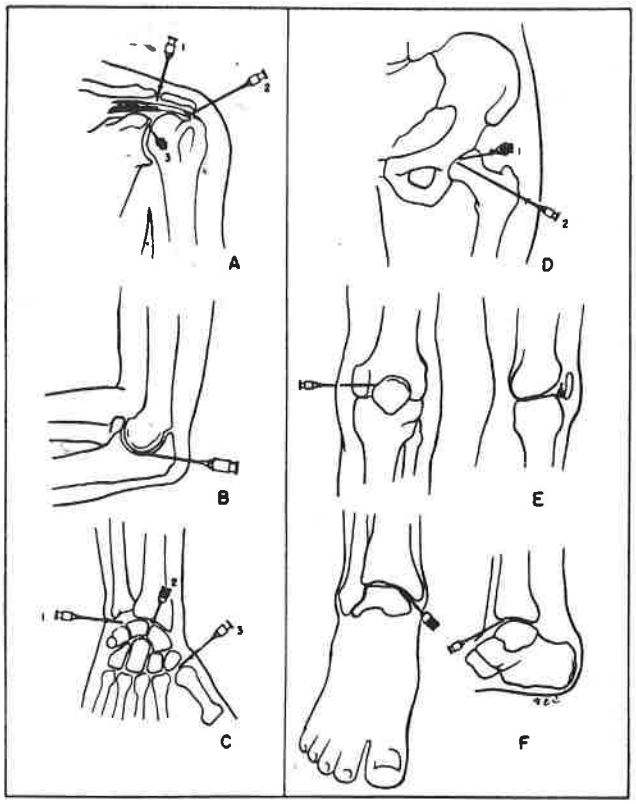

Figure 102-6. Intraarticular injection of various joints. **A:** Techniques for injecting part of the shoulder using a 22- or 25-gauge, 5-cm needle: the acromioclavicular joint (1), the supraspinatus tendon for treatment of tendinitis (2), and the scapulohumeral joint (3). **B:** Injecting the elbow (humeroulnar) joint. **C:** Intraarticular injection of the wrist, ulnar approach (1), dorsal approach (2), and injection into the carpometacarpal joint of the thumb (3). **D:** Injection of the left hip joint by the anterior (1) and lateral (2) approaches. Note the direction of the shaft of the needle to the bone. When inserted just anterior to the greater trochanter in a sagittal direction and pointed toward the middle of Poupart's ligament, the needle point slides anterior to the periosteum and enters the joint space anteriorly near the upper reflection of the synovial sac. **E:** Injecting the knee joint: anterior and lateral views. After a skin wheal is made on the anteromedial surface of the knee, 1 to 2 cm from the medial border of the patella, a needle is inserted in a lateral and slightly posterior direction, in a line, with the goal of sliding it between the posterior surface of the patella and the patellar groove of the femur. Synovial fluid can be aspirated as soon as the joint cavity is entered. **F:** Injecting the ankle joint: anterior and lateral views. (Reprinted from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks.* Springfield, IL: Charles C Thomas Publisher, 1959, with permission.)

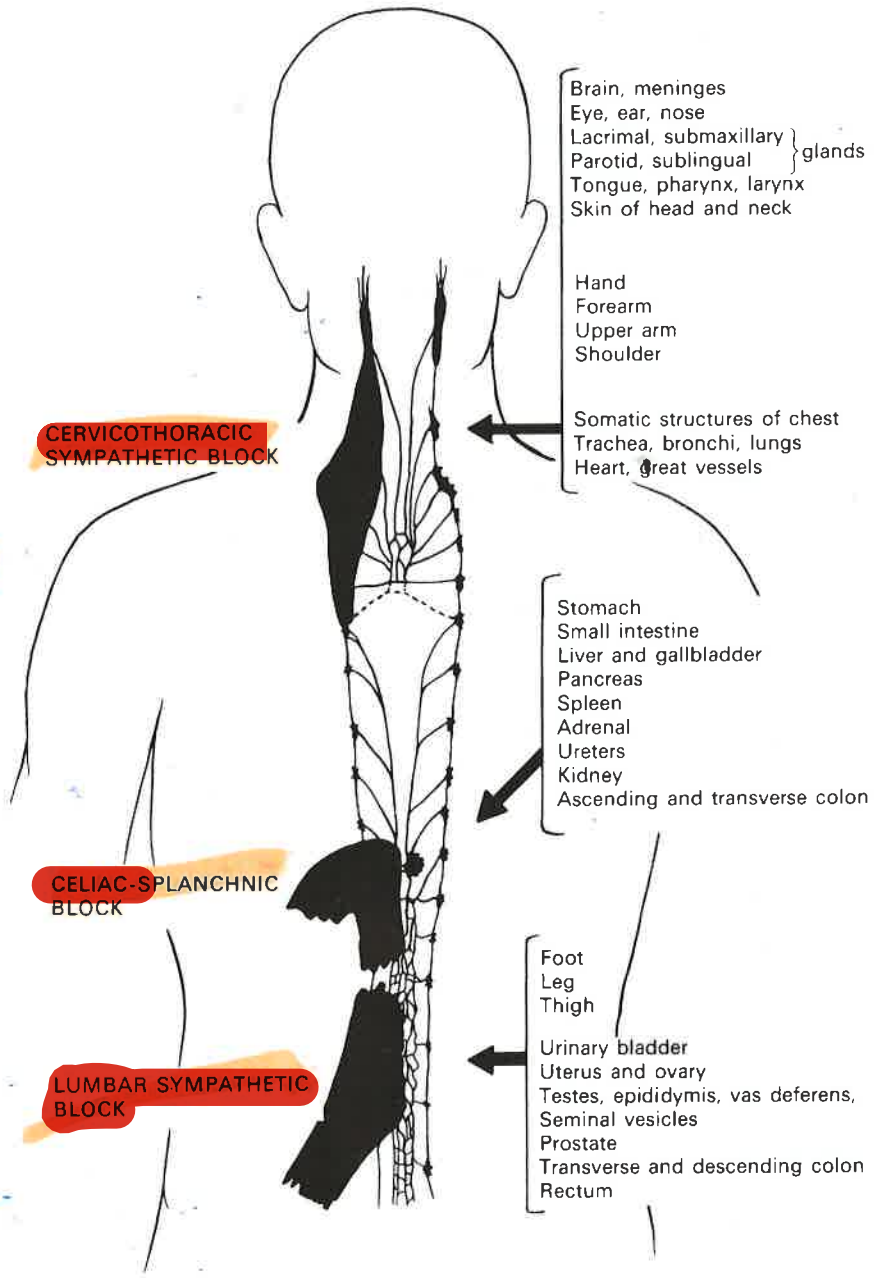

Figure 102-47. Three critical sites that can be used to interrupt the peripheral sympathetic nervous system. Left: Pattern of diffusion (*black*) of local anesthetic solutions injected in the vicinity of the cervicothoracic (stellate) ganglion, celiac plexus, and lumbar sympathetic ganglia. Injection of 15 to 20 mL of local anesthetic solution into the proper fascial plane near the stellate ganglion spreads sufficiently to involve the sympathetic chain from the lower portion of the superior cervical ganglion to the T-5 ganglion, so that all the sympathetic fibers to the head and neck, upper extremities, and the heart, and most of the fibers to the esophagus and lungs, are interrupted. Injection of 15 to 25 mL of solution bilaterally near the celiac plexus spreads sufficiently to interrupt all the sympathetic (and vagal) efferent fibers to and afferent fibers from the viscera in the upper abdomen. Injection of 15 to 20 mL of solution through a needle with its tip at the anterolateral surface of the L-2 or L-3 vertebra interrupts all the sympathetic fibers to the ipsilateral lower extremity and pelvis. These sympathetic nerve structures are apparently contained within fascial planes that can be considered as relatively closed spaces (or even pouches) that facilitate the spread of the local anesthetic solution, so that an extensive sympathetic block is produced. Right: Names of the structures that are denervated with each block. (Modified from Bonica JJ. *Clinical applications of diagnostic and therapeutic nerve blocks*. Springfield, IL: Charles C Thomas Publisher, 1959.)

When performing the paratracheal technique the tip of the needle is close to the vertebral artery and dural cuff of the C-8 nerve. Hence when LA is injected, it is important to ensure that the needle is not intravascular or subarachnoid by aspiration of the needle in two planes and the use of a test dose (1 mL of injectate) and waiting a few minutes to ensure no adverse CVS or CNS effects.

Stellate ganglion blocks for head and neck disorders can be accomplished with 3 to 5 mL of LA. If the block is intended to interrupt all sympathetic fibers to the ipsilateral upper extremity, 12 to 15 mL of solution is injected. This is sufficient to spread to and block all the sympathetic nerves that supply the upper limb, even in a patient with the anomalous Kuntz's nerves. If the block is intended to interrupt the afferents and efferents to the heart, 20 mL of solution is injected, with the patient in a semirecumbent or sitting position (Fig. 102-52).

Successful block of sympathetic fibers to the head is indicated by the appearance of Horner's syndrome (ptosis, miosis, enophthalmos, anhidrosis of the neck and face). Successful block of sympathetic fibers to the upper limb is indicated by engorgement of the veins in the back of the hand, a rise in skin temperature, absence of a skin conductance response, plethysmography, thermography, a sweat test, or a combination of these. Maximal evidence of an arm sympathectomy may take 15 to 20 minutes.

Complications

Complications of the anterior paratracheal technique include inadvertent intraarterial or intravenous injection of LA, pneumothorax; unintentional brachial plexus block, recurrent laryngeal nerve block, or accidental subarachnoid injection. These complications, their prophylaxis, and treatment have been discussed (see Basic Considerations, earlier in this chapter).

Block of the Thoracic Sympathetic Chain

Block of one, or more, of the thoracic sympathetic ganglia and the intervening interganglionic chain is indicated as a diagnostic procedure for identifying specific nociceptive pathways or as a therapeutic measure for treating herpes zoster or other chest wall

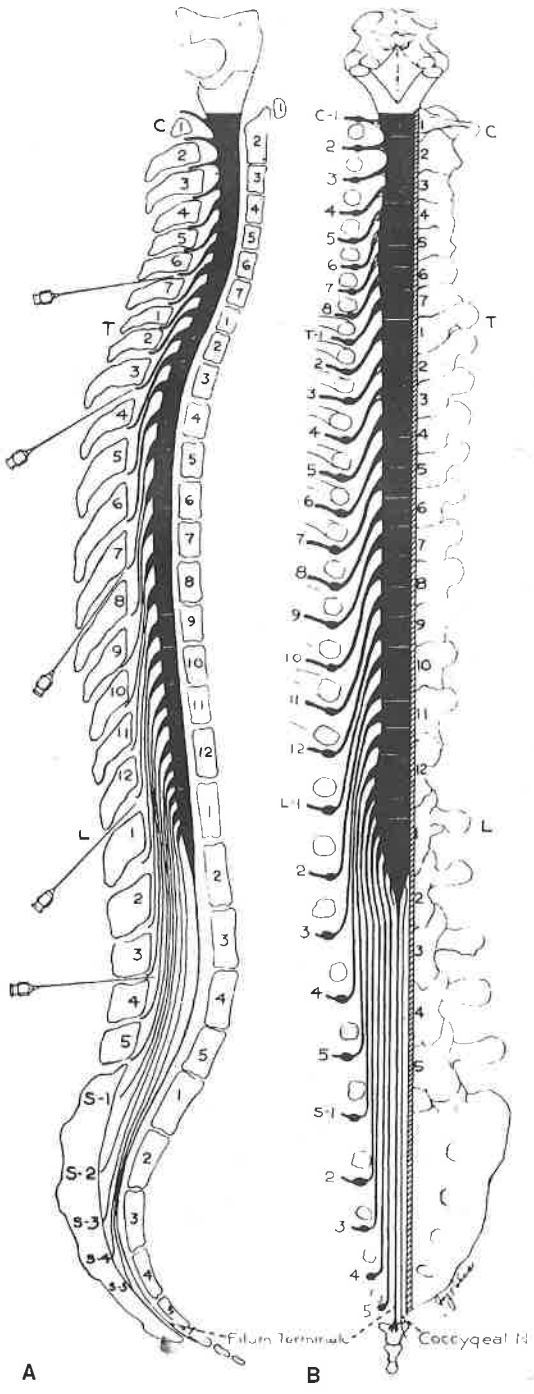

Figure 104-23. Schematic of relationships of the spinal column, spinal cord, spinal nerves, and sites of attachment of their rootlets. **A:** Lateral view showing the angles of the shafts of needles inserted for dural puncture at different vertebral levels. **B:** Posterior view showing relationships of the vertebrae to the spinal cord segments and to the rootlets of various spinal nerves.

It has been claimed that subarachnoid alcohol or phenol does not produce the same beneficial effect in the upper thoracic and cervical segments (67,68). Several factors are involved. The dural sheath in which the neurolytic agent "settles" in the cervical segments is relatively short, and the cervical nerve roots and rootlets have a short intrathecal course and therefore have less exposure to the neurolytic agent. Also, the spinal canal is narrow, with a stronger current of CSF that tends to carry the neurolytic agent away from the target nerve rootlets. Bonica obtained good results, however, by inserting a needle through each of the interspinous spaces involved and injecting 0.2 mL of absolute alcohol in 0.05-mL aliquots through each of two or three needles (see Fig. 104-20). Others have used extradural or subdural injection of phenol for this purpose.

Results. Various reports on the results of therapy using subarachnoid neurolytic blockade are difficult to compare because of differences in the assessment of pain and of pain relief, the types and sites of tumor for which the procedure was done, and the sites and doses of alcohol injection. Moreover, many of the reports lack specific data on the incidence, severity, and duration of side effects and complications.

Table 104-3 summarizes some of the most important reports of results with subarachnoid alcohol, and Table 104-4 summarizes some reports of results obtained with phenol in glycerin. *Good* pain relief means the patient obtained complete or almost complete relief of pain for which the procedure(s) was done until the patient's death; *fair* relief means complete relief of pain for less than 1 month or pain relief of 50% or more until the patient's death; and *poor* relief means that the patient experienced partial relief for a few days or no relief at all. In many cases, more than one block was done to achieve the reported results. Based on personal experience, Bonica believed that in those reports in which the incidence of combined good and fair relief was lower than 60%, an improper technique was used. For example, the neurolytic agent was injected into the lumbar region and then change in posture was used in an attempt to direct the neurolytic agent to the affected segments in the mid- or high thoracic area. As Bonica (2) emphasized, this practice not only produces inadequate pain relief but also results in an unacceptably high complication rate.

In 1951, Bonica (56) presented the first report analyzing the results obtained in 194 patients with cancer pain who were treated with various neurolytic techniques, including 68 patients who received 107 subarachnoid blocks with alcohol. As noted in Table 104-3, 37 patients (54%) obtained complete or almost complete relief of pain, which permitted the gradual reduction in dosage of strong opioids in those who had received them. Another 22 patients (32%) had partial relief and were made comfortable with moderate doses of opioids and adjuvants (usually less than half the amount they had been receiving at the time of the block). Despite one or even two reinjections, nine patients (14%) derived only transient relief of pain and required strong opioids.

Seven years later, in 1958, Bonica published a summary (75) of the results obtained in an additional 114 patients, which was added to the results of the first group and shown as a second series in Table 104-3. Although the results regarding pain relief were similar, those in the second group experienced a lower incidence of complications (Table 104-5), because the earlier experience (when one needle was used to inject 1.0 to 1.5 mL of alcohol to block several segments) prompted him to adopt the multiple-needle technique and to inject small volumes of alcohol as explained above. In the ensuing 19 years, Bonica carried out subarachnoid block with alcohol in an additional 167 patients, who received a total of 228 blocks (see Table 104-3) (*unpublished data*). As noted in Tables 104-3 and 104-5, the analgesia improved slightly, with a further decrease in complications, reflecting a more conservative attitude and a more careful selection of patients.

It is generally acknowledged that, in the hands of those who have experience extensive enough with one or the other agent to be considered an "expert," the results of therapy with subarachnoid alcohol are similar to those obtained with phenol in glycerin. Pain relief appears to be better and to last longer with