CHAPTER 45

# The Autonomic Nervous System

The autonomic nervous system (ANS) is the system that controls nonstriated muscles and glands. There are three divisions of the ANS: sympathetic (thoracolumbar), parasympathetic (craniosacral), and enteric. The sympathetic and parasympathetic divisions are characterized by a two-neuron chain with two anatomic elements: a preganglionic (first-order) neuron within the central nervous system (CNS) that terminates in a ganglion outside the CNS and a postganglionic (second-order) neuron that carries impulses to a destination in the viscera. An overview of the anatomy of the sympathetic and parasympathetic division is shown in Figure 45.1. The enteric nervous system is located in the walls of the gastrointestinal tract. In addition, dorsal root ganglion neurons convey afferent visceral impulses that arise in both sympathetic and parasympathetic fibers. There are also autonomic neurons within the CNS at various levels from the cerebral cortex to the spinal cord. Autonomic functions are beyond voluntary control and for the most part beneath consciousness.

## THE PERIPHERAL AUTONOMIC NERVOUS SYSTEM

The parasympathetic division is composed of the general visceral efferent fibers of cranial nerves III, VII, IX, X, and bulbar portion of XI (the cranial outflow), together with fibers arising in the S2-S4 segments of the spinal cord (the sacral outflow). The parts of the parasympathetic division are widely separated, but because of anatomic characteristics, similarity in function, and similar pharmacologic responses, they are classified as parts of one system rather than as separate divisions. The parasympathetic nerves have long preganglionic fibers that end in peripheral ganglia near or in the viscera they supply, and short

postganglionic fibers that arise in proximity to or within the viscus innervated. One preganglionic fiber usually synapses with only one postganglionic neuron.

The anatomy of the cranial portion of the parasympathetic division is discussed with the individual cranial nerves. In brief, it consists of the Edinger-Westphal nucleus, the superior and inferior salivatory nuclei, the dorsal motor nucleus of the vagus, and neurons in the vicinity of the nucleus ambiguus. The sacral parasympathetic fibers arise from cells in the intermediolateral cell column at the S2-S4 levels of the sacral spinal cord, travel through the sacral nerves, and are collected into the pelvic splanchnic nerves (nervi erigentes), which proceed to the pelvic plexuses and their branches. Some postganglionic fibers may travel from these plexuses to the pelvic viscera, but most preganglionic fibers continue to small ganglia in or near the viscera, from where postganglionic fibers supply the bladder, descending colon, rectum, anus, and genitalia. The greatest parasympathetic outflow is via the vagus nerves. Peripheral parasympathetic ganglia include the ciliary, otic, submandibular, and sphenopalatine (Figure 45.2).

The sympathetic division is composed of preganglionic fibers that arise from cells in the intermediolateral columns from the T1 to the L3 segments of the spinal cord. The fibers exit through the ventral roots of the corresponding segmental nerves (Figure 24.3). These fibers terminate in the paravertebral ganglionic chain, prevertebral plexuses, and collateral ganglia, or occasionally in terminal ganglia (Figure 45.3). Postganglionic fibers go to the viscera. The sympathetic preganglionic fibers are typically short and terminate on ganglia some distance from the viscera they supply, with long postganglionic fibers that travel from the ganglia to the viscera. One preganglionic fiber may synapse with many postganglionic neurons.

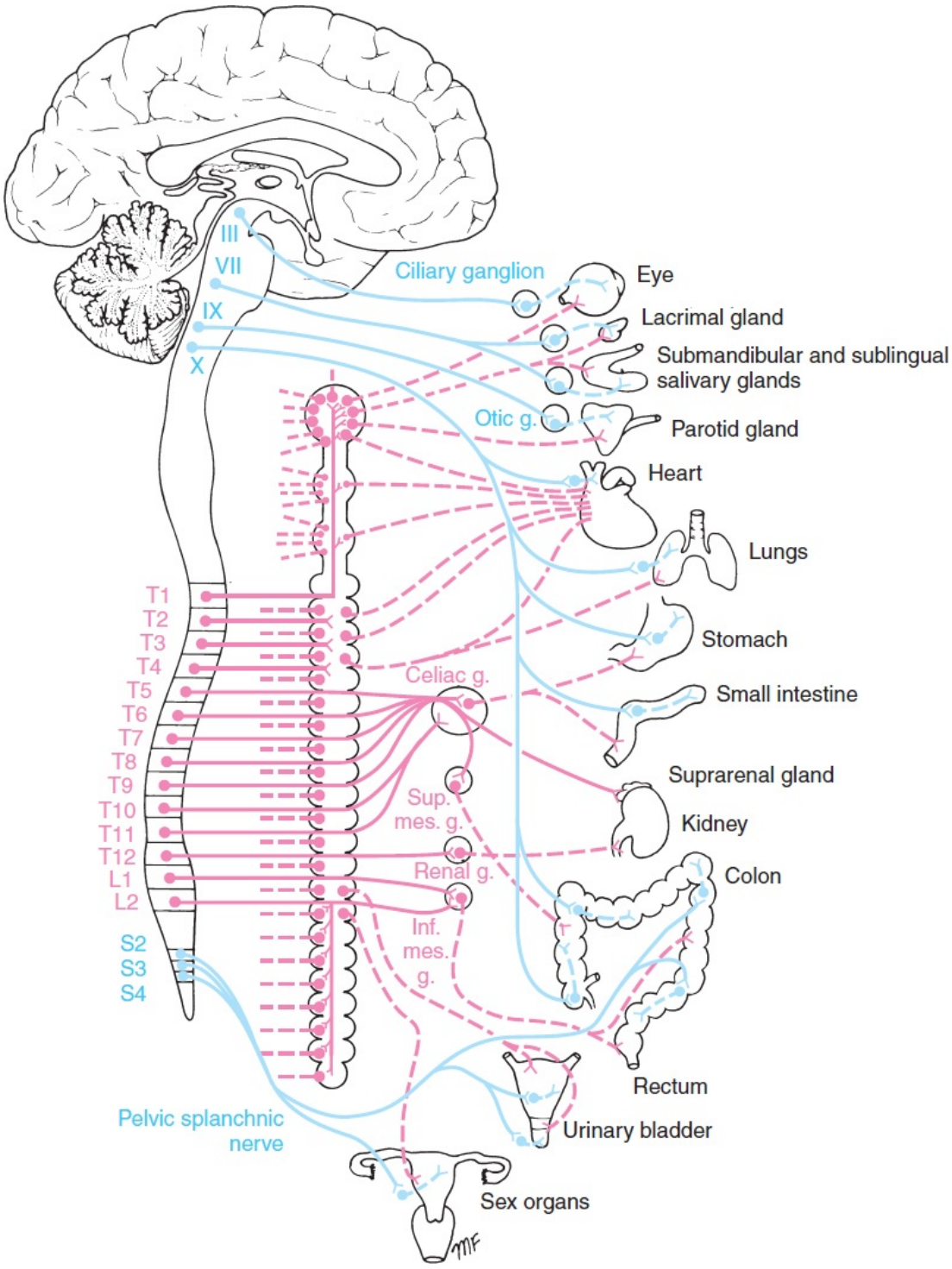


**FIGURE 45.1** General arrangement of the autonomic nervous system. The sympathetic components are shown in *red* and the parasympathetic component in *blue*. (Reprinted with permission from Snell R. *Clinical Neuroanatomy*. 7th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2009.)

The sympathetic ganglia are arranged into two plexuses: paravertebral and

prevertebral. The paravertebral ganglia lie alongside the vertebral column; the prevertebral ganglia lie anterior to the vertebral column. The prevertebral ganglia innervate the viscera of the abdomen and pelvis. The paravertebral sympathetic chain consists of two elongated plexuses, each composed of a series of ganglia that are segmentally arranged and bound together by ascending and descending nerve fibers. The sympathetic trunks have from 22 to 24 ganglia and extend from the level of C2 to the coccyx. There are 3 cervical, 10 to 12 thoracic, 4 lumbar, and 4 to 5 sacral ganglia. The chains usually join at the level of the coccyx in an unpaired coccygeal ganglion (ganglion impar). Preganglionic fibers leave the spinal cord through the anterior root and mixed spinal nerve to reach the anterior primary ramus and then exit as finely myelinated fibers (white rami communicantes) to enter the ganglionic chain. They may synapse immediately or ascend or descend before synapsing. The postganglionic fibers return to the anterior primary ramus as unmyelinated fibers (gray rami communicantes). The T1-T3 segments innervate the head and neck, the T3-T11 segments innervate the upper extremities and viscera in the thorax and abdomen, and the T12-L2 segments innervate the lower extremities and pelvic viscera.

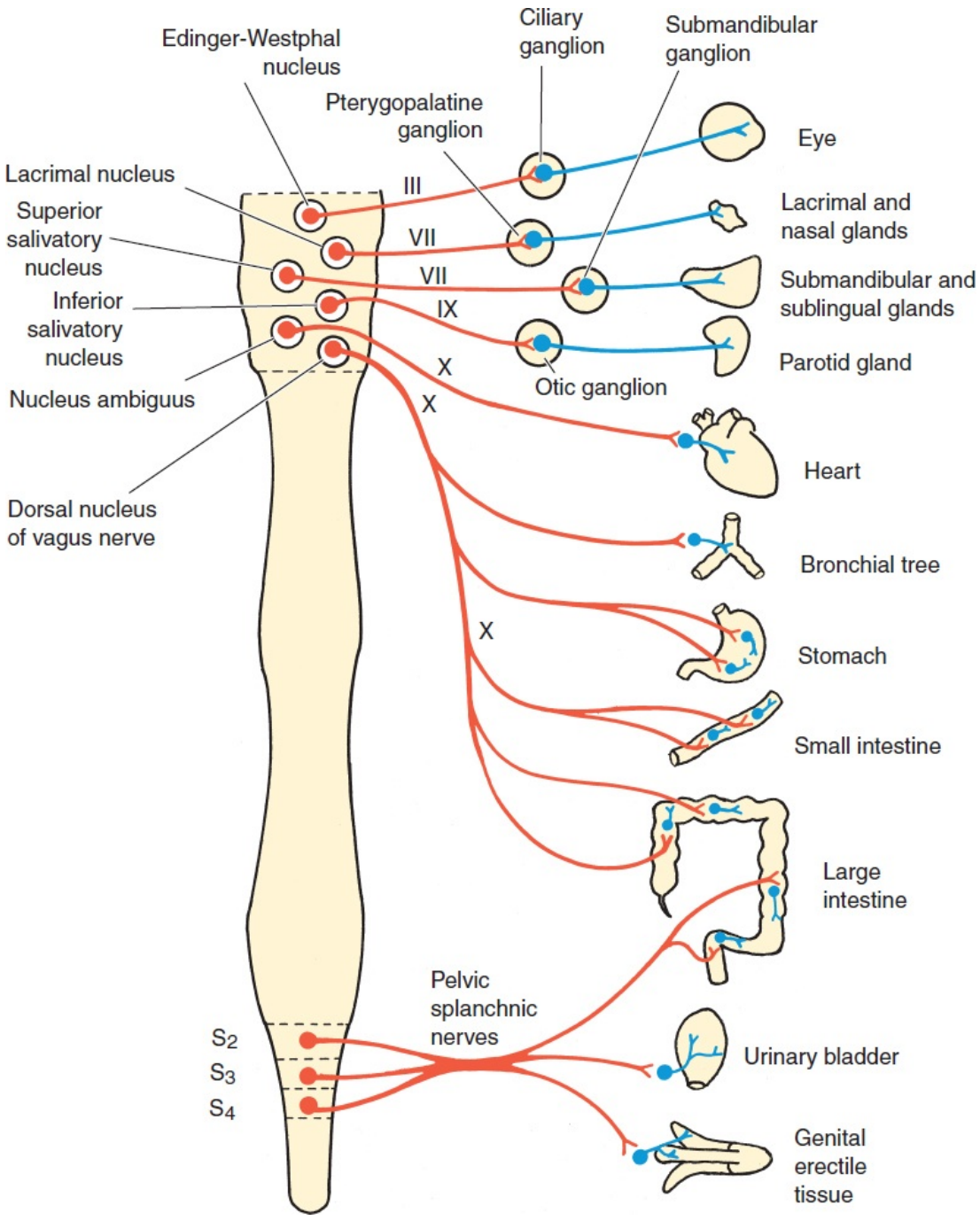


**FIGURE 45.2** The parasympathetic division. Preganglionic neurons are *red*, and postganglionic neurons are *blue*. (Reprinted with permission from Kiernan JA. *Barr's The Human Nervous System: An Anatomical Viewpoint*. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2009.)

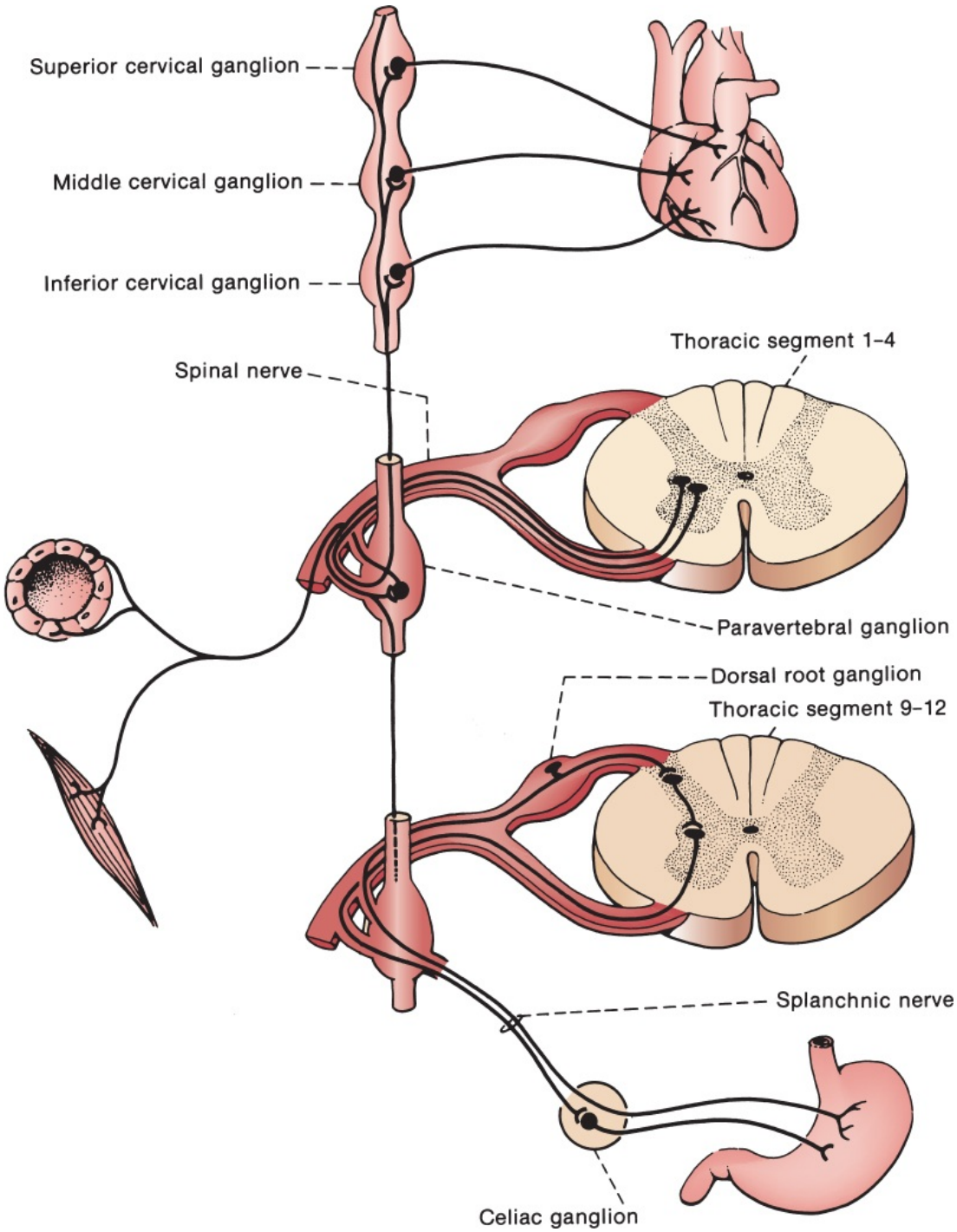


**FIGURE 45.3** The sympathetic outflow, showing connections with the paravertebral ganglionic chain, splanchnic nerves, and collateral ganglia.

The cervical portion of the sympathetic chain consists of the superior, middle, and inferior cervical ganglia. These innervate structures within the head, upper extremities, and thorax. The superior cervical ganglion, the largest, lies opposite the C2-C3 vertebrae and behind the internal carotid artery. It is primarily

supplied by the first two thoracic segments. The internal carotid nerve, a direct continuation of the superior cervical ganglion, gives rise to postganglionic filaments that supply the internal carotid, and terminates as the internal carotid and cavernous plexuses. Anterior branches from the ganglion form plexuses around the middle meningeal and external carotid and maxillary arteries. The sympathetic innervation of the ciliary ganglia travels through the long ciliary nerves from the cavernous plexus. The sphenopalatine ganglion is supplied by the internal carotid plexus through the deep petrosal and vidian nerves. The otic ganglion receives its sympathetic innervation from the plexus around the middle meningeal artery, and the submaxillary ganglion from that around the external maxillary artery. There are other connections from the superior cervical ganglion to other cranial nerves and the upper four cervical nerves, the pharyngeal plexus, the carotid sinus and body, the heart, and the superior cardiac nerves. The middle cervical ganglion communicates with the fifth and sixth cervical nerves to begin the middle cardiac nerve and sends other branches to the thyroid gland. The inferior cervical ganglion communicates with the seventh and eighth cervical nerves to form the inferior cardiac nerve and nerves to the blood vessels.

The paravertebral ganglia provide long unmyelinated axons to all sympathetically innervated tissues and organs except those in the abdomen, pelvis, and perineum. The superior cervical ganglion (T1-T2) provides pupillodilator and sudomotor fibers to the face. The stellate ganglion (T2-T6) innervates the upper limb through branches of the brachial plexus, and the lumbar sympathetic ganglia (T9-L1) innervate the lower limb through branches of the lumbosacral plexus. The postganglionic sympathetic fibers join the peripheral somatic nerves via the gray rami communicantes, and thus their distribution is similar to that of the corresponding somatic nerve.

The thoracic portion of the sympathetic trunk rests against the heads of the ribs. Occasionally the first thoracic ganglion is blended with the inferior cervical ganglion to form the stellate ganglion. The stellate ganglion receives preganglionic fibers from the T2-T6 levels, and its postganglionic fibers are distributed with the nerves of the brachial plexus to provide autonomic innervation to the upper extremity. The sympathetic fibers traveling in somatic nerves innervate vasomotor, sudomotor, and pilomotor structures in the distribution of the nerve in which they are carried.

The upper five ganglia provide branches to the cardiac and pulmonary plexuses. The abdominal portion of the sympathetic trunk is situated in front of the vertebral column along the medial margin of the psoas major muscle, and the

pelvic portion is in front of the sacrum. All of these ganglia send gray rami communicantes to the corresponding spinal nerves and many branches to the various plexuses and collateral ganglia. The postganglionic fibers terminate on blood vessels, sweat glands, and other smooth muscle and glandular structures.

Branches of the lower seven thoracic ganglia unite to form the three splanchnic nerves that penetrate the diaphragm and supply the abdomen and the pelvic viscera. These branches are white in color and primarily carry preganglionic fibers that pass through the ganglia without synapsing and terminate in the prevertebral plexuses or the collateral ganglia. The greater splanchnic nerve is formed by branches of the 5th through the 9th or 10th thoracic ganglia; it terminates in the celiac ganglion. The lesser splanchnic nerve is formed by branches of the 9th, 10th, and sometimes the 11th thoracic ganglia; it ends in the aorticorenal ganglion. The lower splanchnic nerve arises from the last thoracic ganglion; it ends in the renal plexus.

Within the thoracic, abdominal, and pelvic cavities are aggregations of nerves and ganglia known as the prevertebral plexuses and their collateral ganglia. These are composed of both parasympathetic and sympathetic fibers. The parasympathetic fibers are preganglionic and may synapse in the plexuses or go through without synapse to terminal ganglia. The sympathetic fibers, mainly from the splanchnic nerves, usually synapse in the plexuses. From these plexuses, branches are given off to the abdominal and pelvic viscera. The cardiac plexus is supplied by the cardiac branches of the vagus nerves and the cardiac nerves arising from the cervical and upper thoracic sympathetic ganglia. The cardiac plexus also communicates with the pulmonary and the esophageal plexuses, all supplied by the vagus nerve as well as the thoracic sympathetic ganglia.

The celiac plexus is the largest of the three sympathetic plexuses and innervates all the abdominal viscera except for the descending colon. The thoracic splanchnic nerves, carrying preganglionic fibers from the T5-T12 levels, perforate the diaphragm and form the celiac plexus, which lies in the abdomen at the level of the upper part of the first lumbar vertebra, behind the stomach and omental bursa, in front of the diaphragm and abdominal aorta, and between the adrenal glands. It is composed of the two celiac ganglia that are supplied by the greater splanchnic nerves and filaments from the right vagus nerve, and the aorticorenal ganglia, which receive the lesser splanchnic nerves. Other plexuses arise from or are connected with the celiac plexus, including phrenic, hepatic, splenic, and others. The superior (anterior) gastric plexus and

the hepatic plexus also receive branches from the left vagus nerve. The renal and inferior mesenteric plexuses and their branches are also supplied by the lowest splanchnic nerve.

The hypogastric plexus is located in front of the last lumbar vertebra and the promontory of the sacrum, between the two common iliac arteries, and is formed by the union of many elements from the aortic plexus and the lumbar sympathetic chain, together with some fibers from the inferior mesenteric plexus. It is divided into the two pelvic plexuses formed by fibers from the hypogastric plexus; preganglionic sympathetic fibers from the second, third, and fourth sacral nerves; and a few filaments from the sacral sympathetic ganglia. Branches are distributed to the pelvic viscera and the internal and external genitalia through the middle hemorrhoidal, vesical, prostatic, vaginal, and uterine plexuses.

The enteric nervous system consists of intrinsic and extrinsic components. The intrinsic component consists of Meissner's submucosal and Auerbach's myenteric plexi. The extrinsic component consists of preganglionic sympathetic, from prevertebral ganglia, and parasympathetic, from the dorsal motor nucleus of the vagus and the sacral parasympathetic centers, inputs that control peristalsis and secretion.

## Autonomic Afferents

General visceral afferent fibers convey both conscious and unconscious sensations from the viscera and are involved in autonomic reflexes. Small myelinated and unmyelinated fibers carry impulses from visceral receptors to cell bodies in the dorsal root and cranial nerve ganglia. The visceral afferents that enter the spinal cord synapse on neurons in the dorsal horn and intermediolateral gray column. Centrally, sensation from the viscera travels mainly in the spinothalamic and spinoreticular tracts, but some visceral afferents —especially those related to bowel and bladder control—are carried in the posterior columns. After a synapse in the thalamus, visceral sensory fibers project to areas of the cortex involved in autonomic function. Afferent autonomic fibers in the vagus nerve synapse in the nodose ganglion, and those in the glossopharyngeal nerve synapse in the petrosal ganglion. The vagal afferents transmit impulses from the heart, great vessels, lungs, and gastrointestinal (GI) tract; the glossopharyngeal afferents convey information from the carotid sinus. These afferents synapse in the nucleus of the solitary tract and are involved in

autonomic reflexes as well as such functions as coughing and swallowing.

## Neurotransmitters

Acetylcholine is the neurotransmitter at sympathetic and parasympathetic preganglionic neurons, and at postganglionic parasympathetic neurons. Norepinephrine is the primary postganglionic sympathetic neurotransmitter, except at sweat glands, which are cholinergic. There are two subtypes of acetylcholine receptor: nicotinic and muscarinic. Most of the postganglionic acetylcholine receptors are muscarinic. They mediate the cardiac effects and cause pupillary constriction, lacrimal and salivary secretion, bronchoconstriction, and erection. They also stimulate GI tract motility and cause evacuation of the bladder and rectum. There are two main subtypes of adrenergic receptors: alpha and beta. The alpha-adrenergic receptors mediate pupillary dilatation, vasoconstriction, and ejaculation, and they also control the internal sphincters of the bladder and rectum. Beta-adrenergic receptors control the heart, cause vasodilation and bronchial dilatation, and mediate metabolic effects. Some postganglionic sympathetic neurons also utilize adenosine triphosphate and neuropeptide Y, and some postganglionic parasympathetic endings may use vasoactive intestinal polypeptide or nitric oxide.

## The Physiology of the Peripheral Autonomic Nervous System

The ANS governs the activities of cardiac and smooth muscle, including the smooth muscle of the blood vessels and the functions of most glandular structures. It regulates such important functions as respiration, circulation, digestion, temperature adjustment, and metabolism—all vital to normal existence—and combats forces acting from within or without that would tend to cause undesirable changes in the normal function of the body. By homeostasis the constancy of the internal environment of the body and the uniformity and stability of the organism are maintained.

The sympathetic division supplies all parts of the body. Its functions are catabolic and directed toward the utilization of energy. It prepares the organism for combat or escape (fight-or-flight response). It acts whenever rapid adjustment to the environment is required. It accelerates the heart, dilates the

coronary vessels, increases the arterial blood pressure, empties the blood reservoirs, dilates the bronchi, liberates glucose, and inhibits GI activity. It is an emergency protective mechanism that is called into action under emotional stress and causes the individual to react strongly to stimuli of rage and fear. The parasympathetic division supplies special structures, such as the pupils, salivary glands, heart, lungs, GI tract, bladder, and portions of the genital system. In certain parasympathetic functions, as in bladder, rectal, and genital activity, contraction of striated muscles is closely integrated with that of smooth muscle. The parasympathetic division conserves energy. It controls anabolic, excretory, and reproductive functions, and conserves and restores bodily resources and energy.

**TABLE 45.1 Effects of Sympathetic and Parasympathetic Systems on Various Effector Organs**

| Organ | Sympathetic Effect | Parasympathetic Effect |
|---|---|---|
| Pupil | Pupillodilation (alpha) | Pupilloconstriction |
| Accommodation | Decreased | Increased |
| Heart | Positive chronotropic effect (beta) | Negative chronotropic effect |
| | Positive inotropic effect (beta) | Negative inotropic effect |
| Arteries | Vasoconstriction (alpha) | Vasodilation |
| | Vasodilation (beta) | |
| Veins | Vasoconstriction (alpha) | |
| | Vasoconstriction (beta) | |
| Tracheobronchial tree | Bronchodilation (beta) | Bronchoconstriction |

| | | |
|---|---|---|
| | | Increased bronchial gland secretions |
| Gastrointestinal tract | Decreased motility (beta) | Increased motility |
| | Contraction of sphincters (alpha) | Relaxation of sphincters |
| Bladder | Detrusor relaxation (beta) | Detrusor contraction |
| | Contraction of sphincter (alpha) | Relaxation of sphincter |
| Salivary glands | Scant, thick, viscid saliva (alpha) | Copious, thin, watery saliva |
| Skin | Piloerection (cutis anserina) | No piloerection |
| Sweat glands | Increased secretion (cholinergic) | Decreased secretion |
| Genitalia | | Erection |
| | Ejaculation | Ejaculation |
| Adrenal medulla | Catecholamine release | |
| Glycogen | Glycogenolysis (alpha and beta) | Glycogen synthesis |
| | Lipolysis (alpha and beta) | |

The viscera receive a dual autonomic supply, both sympathetic and parasympathetic. In general these two divisions are antagonistic and reciprocal in their functions, but there are exceptions. Table 45.1 compares the functions of the two divisions in the innervation of various effector organs.

# THE CENTRAL REGULATION OF AUTONOMIC FUNCTION

The peripheral ANS is under the control of higher centers in the cerebral cortex, especially the amygdala, hypothalamus, basal forebrain, ventral striatum, brainstem, and spinal cord that regulate and influence the function of its peripheral components. The centers in the CNS that are involved in autonomic function are referred to as the central autonomic network. The neurons of the central autonomic network are interconnected and make up a functional unit. The most important of these centers is the hypothalamus.

## The Hypothalamus

The hypothalamus (Figure 45.4) is part of the ventral diencephalon, lying just below the thalamus and above the pituitary gland. The entire area measures only about 14 × 18 × 20 mm and weighs only 4 g. It forms most of the floor and part of the lateral wall of the third ventricle, extending from the level of the chiasm to the interpeduncular fossa. From a strictly anatomic point of view it includes the optic chiasm, neurohypophysis (posterior pituitary), infundibulum, pars supraoptica, tuber cinereum, and mammillary bodies, but from a physiologic point of view the first three structures are not included. The supraoptic nucleus is located just above the optic chiasm. The mammillary bodies are a pair of small spherical gray matter masses that lie in the interpeduncular fossa rostral to the posterior perforated substance and contain the mammillary nuclei; they form the caudal portion of the hypothalamus. Beneath the hypothalamus a hollow, conical process, the infundibulum, or pituitary stalk, projects downward and forward and is attached to the posterior lobe of the hypophysis. The infundibulum contains the supraopticohypophyseal and tuberohypophyseal tracts. The tuber cinereum is a prominence that lies between the mammillary bodies and the infundibulum.

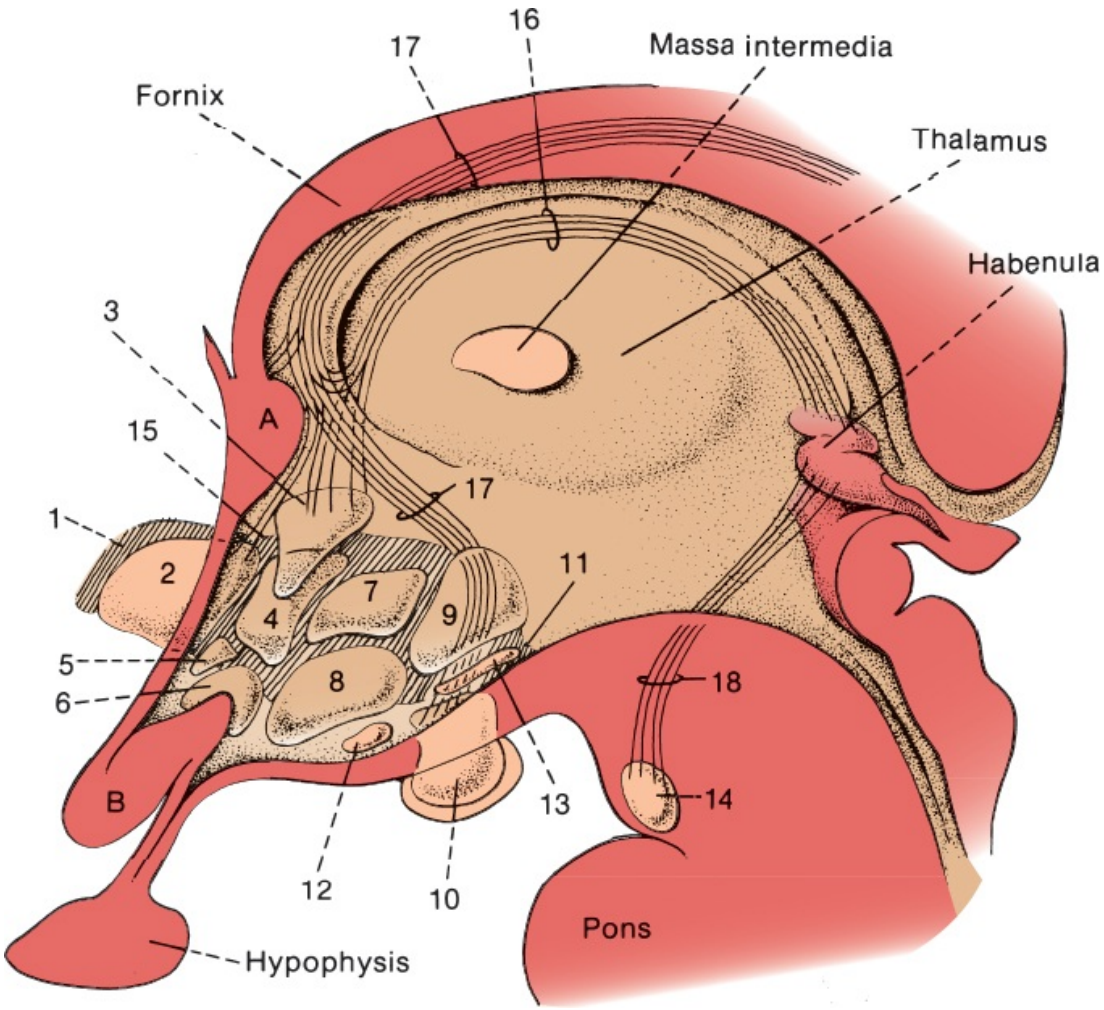


**FIGURE 45.4** Diagrammatic sketch of the human hypothalamus. **A.** Anterior commissure. **B.** Optic nerve. (*1*) Lateral preoptic area, permeated by the median forebrain bundle. (*2*) Medial preoptic area. (*3*) Paraventricular nucleus. (*4*) Anterior hypothalamic area. (*5*) Suprachiasmatic nucleus. (*6*) Supraoptic nucleus. (*7*) Dorsomedial hypothalamic nucleus. (*8*) Ventromedial hypothalamic nucleus. (*9*) Posterior hypothalamic area. (*10*) Medial mammillary nucleus. (*11*) Lateral mammillary nucleus. (*12*) Premammillary area. (*13*) Supramammillary area. (*14*) Interpeduncular nucleus. (*15*) Lateral hypothalamic area. (*16*) Stria habenularis. (*17*) Fornix. (*18*) Habenulopeduncular tract.

The boundaries of the hypothalamus are not sharply defined. Anteriorly it merges with the basal olfactory and preoptic areas, and caudally it is continuous with the central gray matter and tegmentum of the midbrain. Laterally it is continuous with the subthalamic region; superiorly it is separated from the thalamus proper by the hypothalamic sulcus. The preoptic area is the region just above and anterior to the chiasm, extending to the lamina terminalis and anterior commissure.

The hypothalamus is composed of numerous nerve cells, not uniformly distributed but arranged into more or less definite regions or nuclear groups. It can be divided into three longitudinal zones: periventricular, medial, and lateral, all of which send descending fibers to the brainstem and spinal cord. The paraventricular and supraoptic hypothalamic nuclei give rise to the supraopticohypophyseal tract and are important in osmotic balance. The paraventricular nucleus has subpopulations of neurons that produce vasopressin, oxytocin, corticotropin-releasing hormone, and other hormones involved in pituitary function. Destruction of the paraventricular and supraoptic nuclei causes diabetes insipidus. The paraventricular nucleus is important in cardiovascular regulation. Afferents to the paraventricular nucleus come from the medial prefrontal cortex, amygdalae, and insular and other hypothalamic nuclei.

The medial zone of the hypothalamus contains the medial preoptic nucleus, which controls gonadotropin release and is involved in thermoregulation, and the anterior nucleus, which is also involved in thermoregulation. The lateral zone contains the lateral preoptic and lateral hypothalamic nuclei and is traversed by the medial forebrain bundle. Stimulation of the lateral nucleus causes eating, whereas ablation causes starvation. The lateral zone is also involved in arousal and sleep mechanisms. The arcuate (infundibular) nucleus lies in the periventricular region of the tuber cinereum and gives rise to the tuberohypophyseal tract. It contains releasing factors that control release of hormones from the anterior pituitary. It also contains dopaminergic neurons that act to inhibit the release of prolactin.

The autonomic pathways that descend from the hypothalamus run primarily in the ipsilateral brainstem tegmentum. In the spinal cord the descending autonomic fibers are in the anterolateral fasciculus. They are widely distributed but run primarily in the reticulospinal tracts. Some fibers, especially those subserving bladder control, lie close to the lateral corticospinal tracts. Impulses carried through these pathways terminate at appropriate levels in the intermediolateral column of the spinal cord.

Despite its small size, the hypothalamus has extensive and complex connections, some organized into definite bundles or tracts, others diffuse and difficult to trace (Figure 45.5). It is involved in the functions of the ANS, the endocrine system, and the limbic system. The hypothalamus receives impulses from the primary olfactory area, septal area, and orbitofrontal cortex through the medial forebrain bundle; from the amygdaloid nucleus through the stria

terminalis; from the hippocampal formation through the fornix; and from the raphe nuclei, locus caeruleus, and tegmental nuclei of the brainstem. It sends efferent fibers through the medial forebrain bundle to the septal area and brainstem, via the mamillothalamic tract to the anterior nucleus of the thalamus, by the stria terminalis to the amygdala, and to the dorsomedial nucleus of the thalamus. The tuberohypophyseal tract and hypophyseal portal system connect the hypothalamus to the adenohypophysis and the supraopticohypophyseal tract connects it to the neurohypophysis.

## Other Components of the Central Autonomic Network

Other important centers involved in autonomic control include the periaqueductal gray matter (PAG) in the midbrain, other brainstem nuclei, the cerebral cortex, and the amygdala. The PAG is important in the micturition reflex, pain mechanisms—including opiate responsiveness—and the fight-or-flight response. Descending pathways from the PAG modulate, primarily inhibit, pain. The nucleus of the solitary tract (NST) in the medulla is involved in cardiopulmonary and GI function. It receives afferents from arterial baroreceptors and chemoreceptors, and mediates important autonomic reflexes. The medullary cardiorespiratory centers consist of cells in the reticular formation of the ventral medulla that control blood pressure and respiration and mediate cardiorespiratory reflexes. Afferents from baroreceptors, chemoreceptors, and cardiac and pulmonary receptors travel into the brainstem through the glossopharyngeal and vagus nerves and synapse in the NST. Projections from the NST activate the nucleus ambiguus and dorsal motor nucleus of the vagus, which send parasympathetic fibers to the heart and lungs. Bilateral lesions of the NST cause acute neurogenic hypertension. There are also projections from the NST to the reticular formation neurons involved in respiratory rhythmogenesis, and to cells that send sympathetic fibers to the intermediolateral column of the spinal cord. Reticular formation interneurons, along with the NST, are also involved in such functions as coughing, sneezing, and vomiting. The reticulospinal pathways involved in cardiovascular and respiratory function descend in the ventral part of lateral columns of the spinal cord.

Neurons in the nucleus ambiguus are part of the system of cardiac parasympathetic innervation and are involved in the automatic control of

respiration. The parabrachial nuclear complex lies in the dorsolateral pontine tegmentum. It includes the medial and lateral parabrachial nuclei and the Kölliker-Fuse nucleus. The parabrachial complex is involved in the processing of visceral information, pain modulation, and automatic control of respiration.

The primary cortical areas involved in autonomic function include the cortex of the insula, the medial prefrontal cortex, the cingulate gyrus, and the nucleus of the amygdala. The medial prefrontal cortex is activated by stress and is involved in autonomic and affective responses. Sensory input from the viscera project to the insula. It connects with the limbic system and projects to the amygdalae. There are wide connections with other cortical regions. It is an important area in cardiovascular regulation. Damage to the insula in cerebrovascular disease may mediate hypertension, arrhythmias, myocardial injury, and an increased risk of sudden death. The amygdala communicates with the hypothalamus, PAG, and the brainstem autonomic nuclei. It is important in regulating vigilance, memory modulation, emotional learning, and fear mechanisms.

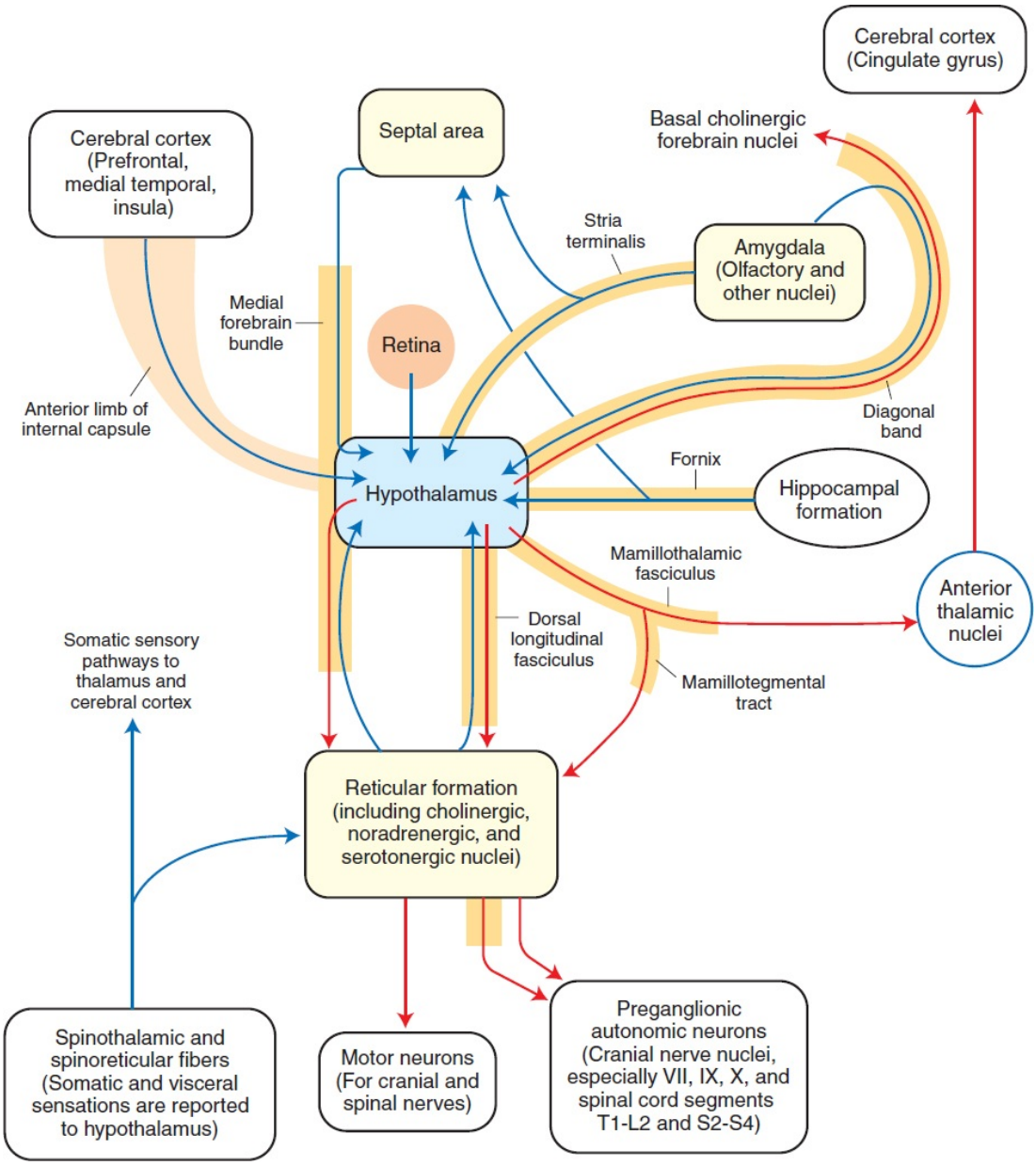


**FIGURE 45.5** Direct and indirect neural connections of the hypothalamus with other parts of the brain and spinal cord. (Reprinted with permission from Kiernan JA. *Barr's The Human Nervous System: An Anatomical Viewpoint*. 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins, 2009.)

## EXAMINATION

The history in patients with autonomic insufficiency may reveal symptoms related to orthostatic hypotension, abnormalities of sweating, or dysfunction of the GI or genitourinary tracts. Symptoms of orthostasis include dizziness or

light-headedness, feelings of presyncope, syncope, palpitations, tremulousness, weakness, confusion, or slurred speech, all worse with standing. Occasional patients complain only of difficulty walking. The symptoms of orthostasis are often worse postprandially, after a hot bath or ingestion of alcohol, or following exercise. Sweating abnormalities may produce abnormal dryness of the skin, sometimes with excessive sweating in uninvolved regions. Other symptoms include constipation, dysphagia, early satiety, anorexia, diarrhea (particularly at night), weight loss, erectile dysfunction, ejaculatory failure, retrograde ejaculation, urinary retention, urinary urgency, recurrent urinary tract infections, and urinary or fecal incontinence.

The general physical and neurologic examinations may reveal a variety of abnormalities in patients with disorders of the ANS. Acromegaly, dwarfism, or signs of endocrine imbalance or sexual immaturity may indicate a hypothalamic abnormality. Abnormal dryness of the skin may be a sign of sudomotor failure and could occur in a localized distribution, as with a peripheral nerve injury, or be generalized, as in diffuse dysautonomia. Lack of normal moisture in the socks may indicate deficient sweating. A simple bedside test to demonstrate the distribution of abnormal skin dryness related to loss of sweating is to note the resistance to stroking of the skin with a finger or an object such as the barrel of a pen or a spoon. When a spoon is drawn over the skin, it pulls smoothly over dry (sympathectomized) skin but irregularly and unevenly over moist, perspiring skin. It is often possible to see the sweat droplets on the skin, especially on the papillary ridges of the fingers, using the +20 ophthalmoscope lens. Other cutaneous signs of autonomic dysregulation include changes in skin temperature or color, mottling, alopecia, hypertrichosis, thickening or fragility of the nails, absent piloerection, decreased hand wrinkling in water, and skin atrophy. Acral vasomotor dysregulation may lead to pallor, acrocyanosis, mottling, erythema, or livedo reticularis. Patients with dysautonomia associated with a regional pain syndrome may have allodynia and hyperalgesia in addition to the autonomic changes.

Assessment of orthostatic changes in blood pressure (BP) and heart rate (HR) are basic tests of cardiovascular autonomic function. At the bedside, BP and pulse are taken with the patient supine and after standing for variable periods; typically the BP is determined at 1, 3, and 5 minutes after standing. Tilt table testing is more precise. Normally, systolic blood pressure (SBP) on standing does not decrease by more than 20 mm Hg, and the diastolic blood pressure (DBP) by not more than 10 mm Hg. There are more stringent diagnostic criteria

that permit a 30-point drop in SBP or a 15-point drop in DBP in normals. When BP measurement is done with a standard sphygmomanometer, the cuff should be kept at heart level to minimize hydrostatic influence on the measurement. When routine measurements are unrevealing, orthostatic blood pressure declines can sometimes be detected by having the patient perform 5 to 10 squats and then repeating the measurements.

The HR should not increase by more than 30 beats per minute above baseline on standing. In hypovolemia, the most common cause of orthostasis, a reflex tachycardia develops in response to the fall in standing blood pressure. When autonomic cardiovascular reflexes are impaired, the reflex tachycardia may not occur. Patients with the postural tachycardia syndrome will develop a brisk tachycardia without orthostatic hypotension (increased pulse rate more than 30 beats per minute above baseline or more than 120 beats per minute). The sustained hand grip, mental stress, and cold pressor tests all look for increases in DBP of at least 15 mm Hg or an increase in HR of greater than 10 beats per minute in response to peripheral vasoconstriction induced, respectively, by isometric hand exercise, mental arithmetic, or immersion of the hand in cold water. The cold face test assesses the trigeminovagal (diving) reflex. Resting tachycardia may be a sign of parasympathetic dysfunction.

Clinical assessment of bladder function is done by looking for evidence of distension by palpation and percussion, and by checking the anal wink and bulbocavernosus reflexes. The bulbocavernosus and superficial anal reflexes are somatic motor reflexes; the internal anal and scrotal reflexes are autonomic reflexes. The internal anal sphincter reflex is contraction of the internal sphincter on insertion of a gloved finger into the anus. If the reflex is impaired there is decreased sphincter tone and the anus does not close immediately after withdrawal. Postvoid residual urine volume is determined by catheterization after voiding.

Tear production by the lacrimal glands can be evaluated in a number of ways by ophthalmologists. A convenient and simple bedside assessment can be obtained with the Schirmer test, done by placing a strip of sterile filter paper in the lower conjunctival sac and measuring the degree of wetting over 5 minutes. Additional eye findings include excessive dryness with redness and itching, and ptosis. Examination of the pupil is discussed in Chapter 14. When autonomic failure occurs as part of a neurologic illness, there may be findings related to the underlying condition such as extrapyramidal or cerebellar signs, abnormal eye movements, weakness, sensory loss, or reflex abnormalities.

## Autonomic Function Testing

Many different procedures have been developed to test the sympathetic and parasympathetic nervous systems. Tests of cardiac vagal tone include assessment of heart rate variability to deep breathing, standing, and performing Valsalva. The beat-to-beat changes in heart rate in response to autonomic reflexes occur quickly, often too quickly for bedside assessment to be accurate. It is possible at the bedside to determine if heart rate variability with respiration or to Valsalva is present and obvious (probably normal), present but minimal (possibly abnormal), or absent (abnormal). More precise testing requires equipment, and may include an indwelling arterial catheter to follow BP changes.

Normal sinus arrhythmia is the beat-to-beat variability in heart rate that occurs with respiration. It is most prominent in healthy young people. Sinus arrhythmia normally becomes less prominent with age, and it may be markedly impaired or abolished when vagal innervation of the heart is compromised. The heart rate response to deep breathing ($HR_{DB}$) shows maximal variability at a breathing rate of 5 to 6 per minute. The $HR_{DB}$ can be assessed at the bedside simply by noting pulse variability; it can be measured more quantitatively by measuring the R-R interval with cardiac monitoring. The expiratory-to-inspiratory ratio quantitates the variability in $HR_{DB}$. The heart rate response to standing (30:15 ratio) is another method of evaluating the baroreflex arc. The most dramatic changes in HR normally occur in the first 30 seconds after standing, with an initial tachycardia, followed by bradycardia about 20 seconds later. The 30:15 (tachycardia:bradycardia) ratio is the ratio of the R-R interval at beat 30/R-R interval at beat 15; normal is >1.04.

The respiratory variability in heart rate is exaggerated when a Valsalva maneuver is performed. The cardiovascular responses to Valsalva are divided into four phases. Phases I and II occur during breath holding and phases III and IV after release. The BP and HR responses are mirror images: when BP increases, HR reflexly decreases. Measuring HR alone is adequate for some aspects of the Valsalva response, but a complete evaluation requires measurement of BP. In phase I there is a brief rise in BP because of increased intrathoracic pressure constricting the great vessels; in phase II, there is a gradual fall in BP because of impaired venous return that reaches a plateau because of peripheral vasoconstriction, with a compensatory tachycardia; in phase III, there is a brief fall in BP because of removal of the intrathoracic pressure constricting the great vessels. Phase IV occurs after the Valsalva is

released and the patient resumes normal breathing; the BP begins to recover and slowly rises. About 15 to 20 seconds after release, there is a rebound overshoot of BP to a level above baseline, accompanied by a reflex bradycardia with an HR below baseline, lasting for approximately 1 minute. The Valsalva ratio is the ratio of the fastest HR during phase II to the slowest HR during phase IV, or the longest R-R interval during phase IV to the shortest R-R interval during phase II. Normal is approximately ≥1.45, but age specific reference values are more precise. A lack of rebound overshoot of BP during phase IV is an early indicator of autonomic dysfunction. A lack of overshoot can also occur in some non-neurologic conditions, such as congestive heart failure. The BP changes occur quickly, and it is not possible to follow the complete cycle at the bedside with a BP cuff. The rebound overshoot in phase IV, however, can be detected by inflating a cuff to just at SBP and then having the patient Valsalva. Without changing the cuff pressure, the sounds will disappear during breath holding, and on release the sounds will return and can be followed up to detect the rebound overshoot in BP.

Tilt-table testing evaluates the integrity of autonomic reflexes. Autonomic laboratories use different degrees of tilt, but usually in the range of 60 to 80 degrees and for different durations. In neurocardiogenic (vasovagal, vasodepressor) syncope, or fainting, hypotension is accompanied by bradycardia, rather than the tachycardia that should occur. It occurs in response to emotional upsets such as fear, stress, or the sight of blood; occasionally in relation to micturition (micturition syncope) or coughing (cough syncope); and sometimes without identifiable provocation. Tilt-table testing has shown that a neurocardiogenic mechanism is responsible for a large proportion of the patients with recurrent, unexplained syncope.

Tests for thermoregulatory and sudomotor function include the sympathetic skin response (SSR), QSART (Quantitative Sudomotor Axon Reflex Test), sweat imprint, and thermoregulatory sweat test (TST). The SSR assesses peripheral sympathetic function by detecting changes in skin resistance in response to sudomotor discharges. The TST assesses both the central and peripheral sympathetic components by analyzing the sweating response to a rise in body temperature. The QSART assesses the postganglionic sudomotor fibers by measuring the sweat output in response to iontophoresis into the skin of acetylcholine. The sweat imprint test quantitates sweat output by visualizing the imprints sweat droplets make on a plastic or silicone mold. A TST combined with a test of postganglionic function can localize the site of a process producing

anhidrosis. If the postganglionic function test is abnormal, the cause is postganglionic. But if the postganglionic test is normal and the TST is abnormal, the cause is preganglionic. Sudoscan measures electrochemical skin conductance of the hands and feet through reverse iontophoresis. This technique is another method for measuring sudomotor function in small fiber neuropathy.

## DISORDERS OF THE AUTONOMIC NERVOUS SYSTEM

Autonomic disorders can be divided into those that affect the central autonomic elements and are typically associated with other evidence of CNS disease and those that affect the peripheral autonomic nervous system. Disorders may be local or generalized, and primary or secondary. Adie's pupil is an example of localized and acute pandysautonomia an example of generalized dysfunction. Pure autonomic failure is an example of primary and amyloid neuropathy an example of secondary dysautonomia. Autonomic dysfunction is usually manifest by underactivity, but hyperactivity occurs under some circumstances. Paroxysmal dysautonomia is common in spinal cord injury. Orthostatic hypertension occurs because of overactive pressor reflexes. A massive trigeminal-parasympathetic discharge causes the lacrimation and nasal secretion during attacks of cluster headache.

Multiple system atrophy (MSA) is a degenerative neurologic disorder, which is usually accompanied by prominent dysautonomia (Chapter 30). The autonomic failure in MSA results from involvement of preganglionic neurons in the brainstem and spinal cord in the degenerative process. Autonomic failure produces orthostatic hypotension, impotence, constipation, and urinary incontinence; it may be associated with respiratory symptoms such as laryngeal stridor and sleep apnea. Autonomic dysfunction may also occur in patients with Parkinson's disease, but usually late in the illness and not to the degree typical of MSA. Autonomic disturbances may accompany seizures, including cardiovascular changes, flushing, pallor, sweating, shivering, piloerection, vomiting, and respiratory abnormalities. Seizure-induced cardiovascular abnormalities include sinus tachycardia, bradyarrhythmia, sinus arrest, and ventricular tachyarrhythmias, including ventricular fibrillation. Autonomic dysfunction may also be a major feature of dementia with Lewy bodies, MS, and Wernicke's encephalopathy.

Hypothalamic disorders may cause many abnormalities of autonomic function, including deficiencies in osmoregulation and thermoregulation; abnormalities of appetite and body weight; sleep disturbances; changes in carbohydrate, fat, and water metabolism; and respiratory abnormalities together with, in many instances, behavioral abnormalities and personality changes. Hypothalamic lesions may cause either hyperthermia or hypothermia. Hyperthermia generally results from involvement of the tuberal region, especially the supraoptic nuclei or the rostral portion of the anterior hypothalamus. It is a common manifestation of third ventricular tumors, and may occur after head trauma or cranial surgery; terminal hyperthermia is a frequent manifestation of neurologic disease. Hypothermia tends to occur with involvement of the posterior hypothalamic area and mammillary bodies. Disorders of the anterior hypothalamus tend to cause loss of the ability to regulate against heat and disorders of the posterior hypothalamus, loss of the ability to regulate against cold.

The hypothalamus is closely related anatomically and physiologically to the pituitary gland (Figure 45.6). Because the hypothalamus controls the release of many of the anterior pituitary hormones, abnormalities of hypothalamic function may have a close relationship to some endocrine disorders. Lesions of the supraoptic nuclei or the supraopticohypophyseal tract cause diabetes insipidus. Diabetes insipidus is a common manifestation of tumors in the parasellar region, encephalitis, and meningitis, and it may develop after intracranial surgery or head injury. Lesions involving the hypothalamus may also cause disturbances of fat metabolism. The Froehlich, or adiposogenital, syndrome was the first hypothalamic syndrome described. It is characterized by disturbances of fat metabolism and sexual underdevelopment.

Abnormalities of respiration may be caused by hypothalamic dysfunction. These include hyperpnea, apnea, Cheyne-Stokes respirations, and Biot breathing. Disturbances of the sleep cycle may occur with hypothalamic lesions, especially those involving its posterior portions, including the mammillary bodies. There may be hypersomnolence, inversion of the sleep cycle, or insomnia. In the Kline-Levin syndrome there are periodic attacks of hypersomnolence, accompanied by bulimia, irritability, behavioral changes, and uninhibited sexuality. Neurons in the lateral hypothalamus synthesize hypocretin, a chemical involved in the pathogenesis of narcolepsy, and project to brainstem regions involved in rapid-eye-movement sleep. Disturbances of sexual function and sexual development occur with hypothalamic lesions, including precocious

puberty and sexual infantilism.

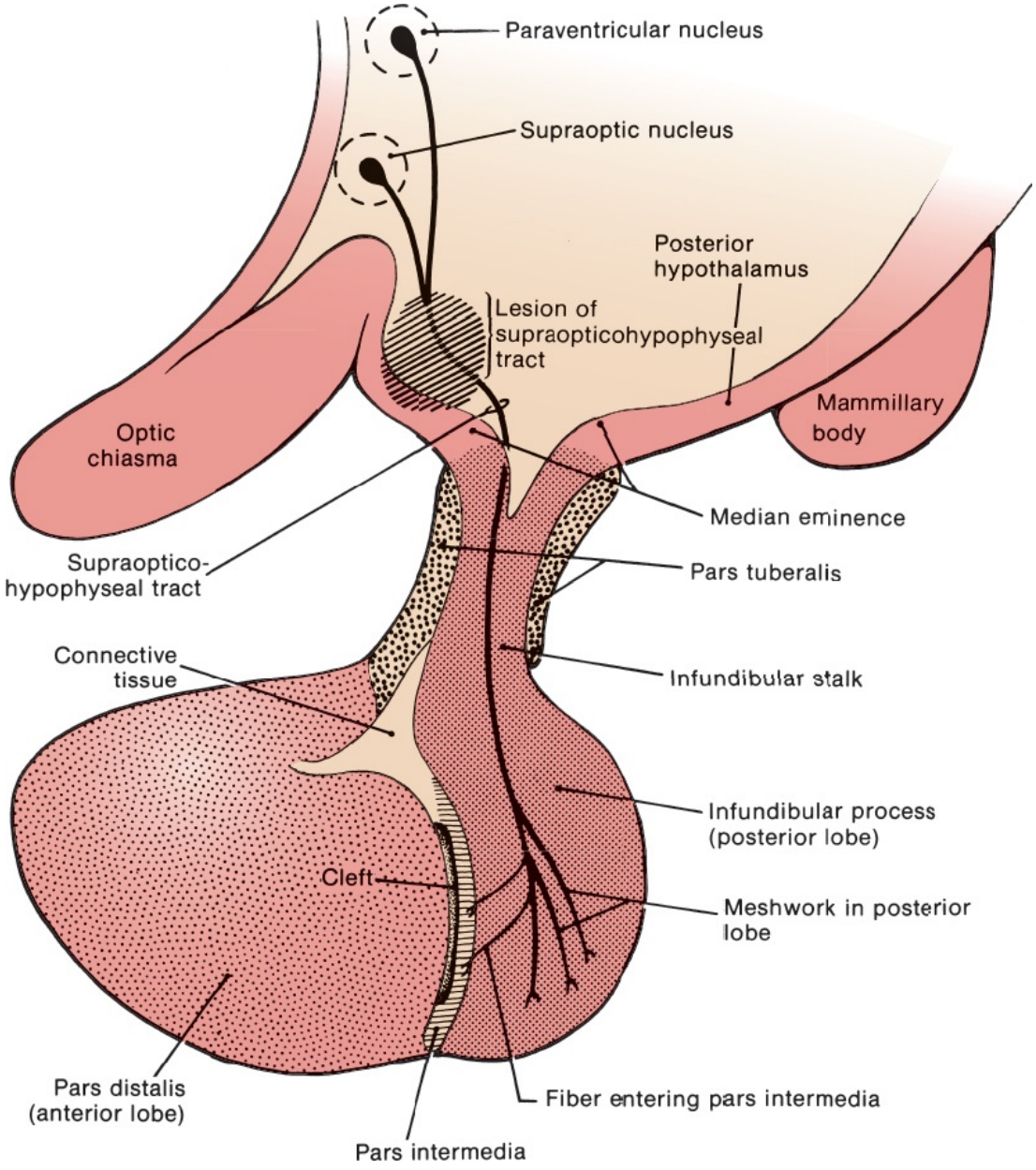


**FIGURE 45.6** Longitudinal section through the human hypothalamus and hypophysis.

The hypothalamus is involved with emotions. It is the center that coordinates the neural and humoral mechanisms of emotional expression. Hypothalamic lesions in animals may cause “sham rage,” with pupillary dilatation, increased pulse rate and BP, piloerection, and other signs of sympathetic overactivity. These physical manifestations suggest an intense emotional reaction is taking place, but there is no change in affect.

Brainstem disorders commonly cause autonomic dysfunction, including paroxysmal hypertension, profound bradycardia, intractable vomiting, central hypo- and hyperventilation, neurogenic pulmonary edema, and Horner's syndrome. The automatic and the voluntary breathing pathways are separated in the brainstem and upper spinal cord. Selective damage of the pathways subserving automatic breathing may cause respiratory insufficiency during sleep, with preserved respiration during wakefulness (Ondine's curse). The Cushing reflex, or Cushing triad, is bradycardia, hypertension, and slow, irregular respirations due to brainstem compromise and has ominous prognostic implications. Myelopathy, particularly spinal cord injury, is often associated with severe dysautonomia.

Peripheral autonomic failure results from disorders that involve the autonomic ganglia or postganglionic nerve fibers. The syndrome of pure autonomic failure is a slowly progressive, degenerative disorder of the ANS in which dysautonomia occurs in isolation, without other evidence of neurologic disease. Dysautonomia occurs commonly in some peripheral nerve disorders. It may develop acutely in Guillain-Barré syndrome, porphyria, and some paraneoplastic neuropathies. Acute pandysautonomia is a condition probably akin to Guillain-Barré syndrome but in which dysautonomia occurs in isolation. Chronic neuropathies often associated with major autonomic dysfunction include diabetes mellitus, alcoholism, amyloidosis, hereditary sensory autonomic neuropathy type III (Riley-Day syndrome), Fabry's disease, and vincristine toxicity. The most common cause of autonomic neuropathy is diabetes mellitus. Patients typically develop orthostatic hypotension, impotence, gastroparesis, constipation alternating with diarrhea, nocturnal diarrhea, and difficulty voiding. Autoimmune attack on autonomic ganglia may cause severe autonomic failure.

Dysautonomia may accompany disorders of neuromuscular transmission, particularly Lambert-Eaton syndrome and botulism, in which the defect is presynaptic and acetylcholine release is impaired at autonomic synapses as well as at neuromuscular junctions. Some autonomic disorders occur in a restricted distribution or involve a particular organ system. Autonomic disorders of the pupil include Argyll Robertson and Adie's pupils, Horner's syndrome, and third cranial nerve palsy. Dysautonomia primarily involving the vascular system may cause Raynaud's phenomenon, acrocyanosis, erythromelalgia (Weir Mitchell syndrome), and livedo reticularis. Autonomic dysfunction of the genitalia causing erectile dysfunction and other abnormalities is common, especially in diabetes mellitus. Abnormalities of sweating occur frequently and are sometimes

the only manifestation of the autonomic disturbance. Autonomic dysregulation is a common component of complex regional pain syndromes (reflex sympathetic dystrophy) and occurs in the same distribution as the pain.

## The Bladder

Bladder function involves both the autonomic and the voluntary nervous systems, and disorders of bladder function may follow lesions of the paracentral lobule, hypothalamus, descending pathways in the spinal cord, pre- or postganglionic parasympathetic nerves, or pudendal nerve. The detrusor muscle of the bladder is innervated by parasympathetic neurons located in the S2-S4 intermediolateral column (Figure 45.7). Onuf's nucleus consists of additional motor neurons located in the nearby anterior horn at the same levels. The axons from Onuf's nucleus innervate the external urethral sphincter. There is a curious preservation of the Onuf nucleus neurons in amyotrophic lateral sclerosis. The internal urethral sphincter at the neck of the bladder receives its innervation from the intermediolateral column at the T12-L1 level, via the sympathetic prevertebral plexus and the hypogastric nerve.

Micturition is a spinobulbospinal reflex. In response to stretch, afferent impulses are carried to the sacral spinal cord. Sacral cord projections to the PAG are relayed to the pontine micturition center (Barrington's nucleus) in the dorsomedial pontine tegmentum, near the locus caeruleus, which sends descending fibers to the preganglionic parasympathetic motoneurons in the sacral cord innervating the bladder. The pontine micturition center is under the control of centers in the forebrain. Descending impulses activate the efferent centers in the sacral cord, causing contraction of the detrusor muscle and relaxation of the internal sphincter. In the infant, bladder function is purely reflex, but with cortical maturation and the completion of myelination inhibitory control over this reflex develops, as well as voluntary regulation of the external sphincter. Normal micturition requires intact autonomic and spinal pathways, and cerebral inhibition and control of the external sphincter must be normal.

Forebrain lesions may cause loss of voluntary bladder control, but do not affect the spinobulbospinal reflex mechanisms. Disruption of the bulbospinal pathway from the pontine micturition center to the sacral cord, and lesions affecting the afferent and efferent connections between the bladder and the conus medullaris, may cause severe disturbances in bladder function.

The term neurogenic bladder refers to bladder dysfunction caused by disease

of the nervous system. Symptoms of bladder dysfunction are often among the earliest manifestations of nervous system disease. Frequency, urgency, precipitate micturition, massive or dribbling incontinence, difficulty in initiating urination, urinary retention, and loss of bladder sensation may occur. One practical classification of neurogenic bladder dysfunction is based on urodynamic criteria and includes the following types: uninhibited, reflex, autonomous, sensory paralytic, and motor paralytic.

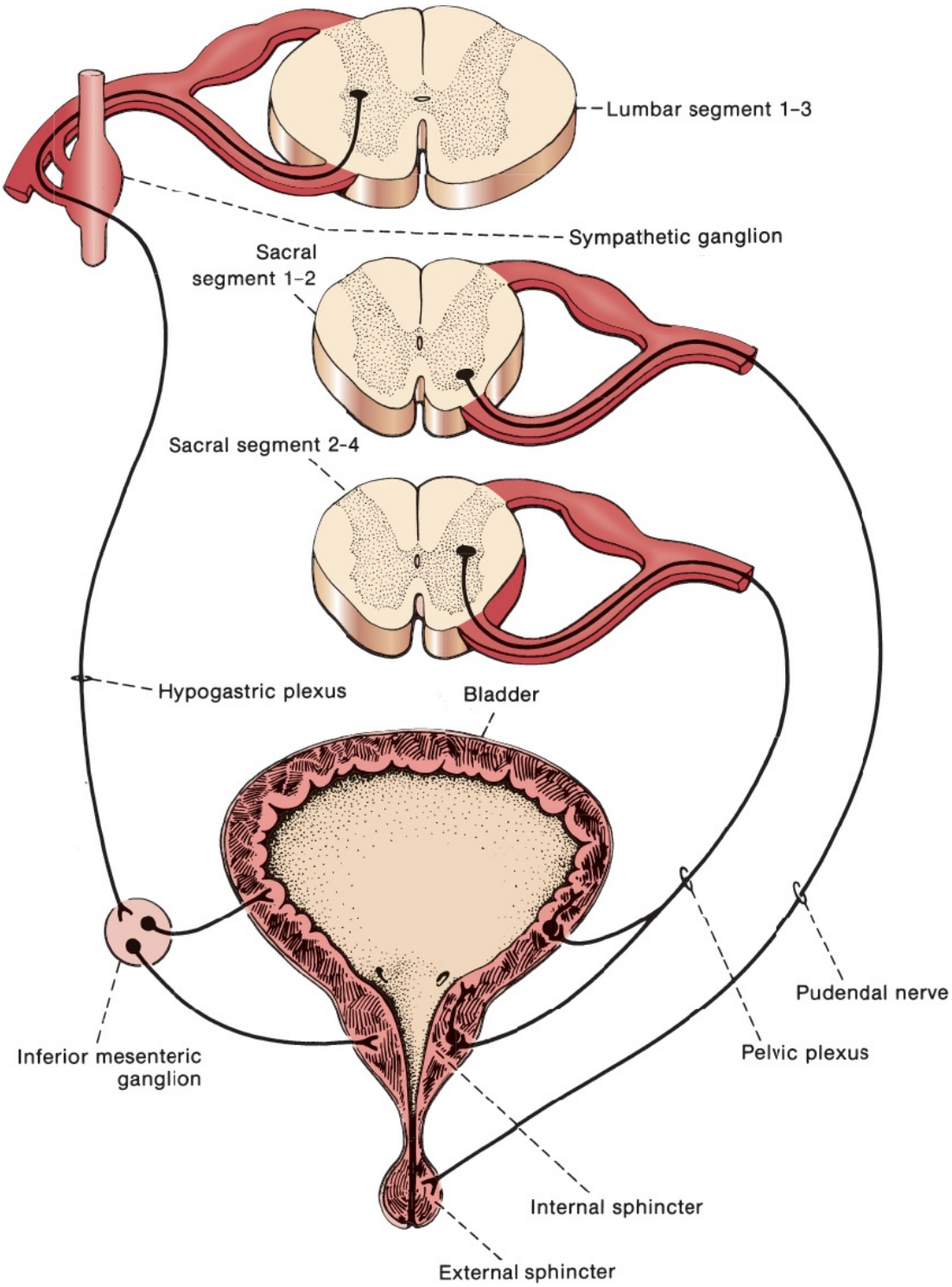


**FIGURE 45.7** Innervation of the urinary bladder.

In the uninhibited neurogenic bladder, there is a loss of the cortical inhibition of reflex voiding, although bladder tone remains normal. Bladder distention causes contraction in response to the stretch reflex. There is frequency, urgency,

and incontinence that are not associated with dysuria. Hesitancy may precede urgency. Bladder sensation is usually normal. There is no residual urine. The reflex neurogenic bladder occurs with severe myelopathy or extensive brain lesions causing interruption of both the descending autonomic tracts to the bladder and the ascending sensory pathways above the sacral segments of the cord. The bladder capacity is small, and micturition is reflex and involuntary. The residual urine volume is variable. An autonomous neurogenic bladder is one without external innervation. It is caused by neoplastic, traumatic, inflammatory, and other lesions of the sacral spinal cord, conus medullaris or cauda equina, S2-S4 motor or sensory roots, or the peripheral nerves, and with congenital anomalies such as spina bifida. There is destruction of the parasympathetic supply. Sensation is absent, and there is no reflex or voluntary control of the bladder; contractions occur as the result of stimulation of the intrinsic neural plexuses within the bladder wall. The amount of residual urine is large, but the bladder capacity is not greatly increased. A sensory paralytic bladder is found with lesions that involve the posterior roots or posterior root ganglia of the sacral nerves, or the posterior columns of the spinal cord. Sensation is absent, and there is no desire to void. There may be distention, dribbling, and difficulty both in initiating micturition and in emptying the bladder. There is a large amount of residual urine. A motor paralytic bladder develops when the motor nerve supply to the bladder is interrupted. The bladder distends and decompensates, but sensation is normal. The residual urine and bladder capacity vary.

## Sexual Function

Disturbed sexual function is common in dysautonomia. In the genital (sex, ejaculatory, coital) reflex, arousal causes penile erection and sometimes ejaculation. Erection is a parasympathetic function mediated through S2-S4; ejaculation is a largely sympathetic function mediated by the lumbar nerves. Autonomic insufficiency usually causes impotence, but pathologic exaggeration of the sexual reflex may occur as part of the mass reflex, a spinal defense reflex seen in severe myelopathy (see Chapter 40), and may produce priapism and occasionally ejaculation after minimal stimulation. In autonomic neuropathy, especially from diabetes, retrograde ejaculation may precede the development of impotence. Because the internal vesical sphincter does not close, semen goes into the bladder rather than externally through the urethra. The patient with retrograde ejaculation may notice milky-appearing urine.

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