13 Hypothalamus

CHAPTER OBJECTIVES

- To learn the location and boundaries of the hypothalamus and the various nuclei that make up this important area
- To review the main connections of the nuclei, especially the connections between the hypothalamus and the pituitary gland
- To review some of the common clinical problems involving the hypothalamus

A 16-year-old girl is taken by her mother to a pediatrician because she is rapidly losing weight. The mother states that the weight loss started about 1 year ago. The child's eating habits changed from eating practically anything put before her to being a very choosy eater. Her personality is also changed, and she fears meeting strangers. Her relatives notice that she is impatient and irritable and cries a great deal. On being urged to eat more food, the girl countered by saying she was getting fat and must diet to improve her figure. Although she would not admit to having anything wrong with her, she admitted that menstruation had ceased 3 months previously.

On being questioned by the pediatrician, the girl admits to calorie counting, and sometimes, when she feels she has overeaten, will force herself to vomit by sticking her fingers down her throat. On physical examination, she shows obvious signs of weight loss with hollow facial features, prominent bones, and wasted buttocks. Apart from having cold extremities and a low blood pressure of 85/60 mm Hg, no further abnormalities are discovered.

The pediatrician makes the diagnosis of anorexia nervosa and admits her to the local hospital. Psychological treatment includes getting the confidence of the patient by using nursing personnel who understood the condition. The primary treatment is to restore the patient's weight by persuading the individual to eat adequate amounts of food.

Anorexia nervosa is a disorder of feeding and endocrine function that is normally controlled by the hypothalamus. However, strong evidence suggests that it is also of psychogenic origin.

The hypothalamus, although small (0.3% of the total brain), is a very important part of the central nervous system. It is essential for life. It controls the autonomic nervous system and the endocrine system and thus indirectly controls body homeostasis. The hypothalamus is well placed for this purpose, lying in the center of the limbic system. It is the site of numerous converging and diverging neuronal pathways, and through its adequate blood supply, it is able to sample the blood chemistry. The hypothalamus makes appropriate controlling responses following the integration of its nervous and chemical inputs.

HYPOTHALAMUS

The hypothalamus is the part of the diencephalon that extends from the region of the optic chiasma to the caudal border of the mammillary bodies. It lies below the thalamus and forms the floor and the inferior part of the lateral walls of the third ventricle (Fig. 13-1). Anterior to the hypothalamus is an area that, for functional reasons, is often included in the hypothalamus. Because it extends forward from the optic chiasma to the lamina terminalis and the anterior commissure, it is referred to as the **preoptic area**. Caudally, the hypothalamus merges into the tegmentum of the midbrain. The lateral boundary of the hypothalamus is formed by the internal capsule.

When observed from below (Fig. 13-2), the hypothalamus is seen to be related to the following structures, from anterior to posterior: (1) the optic chiasma, (2) the tuber cinereum and the infundibulum, and (3) the mammillary bodies.

This small area of the brain will be seen in the following paragraphs to control body homeostasis, through

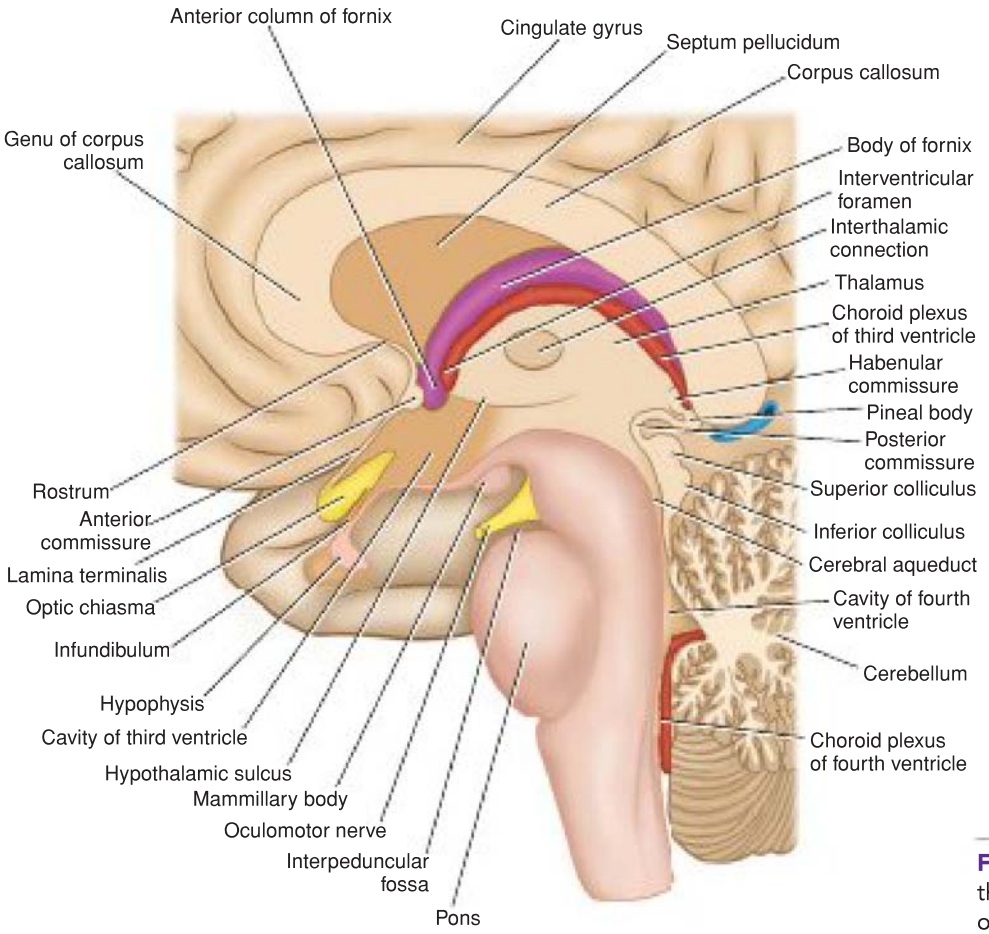


Figure 13-1 Sagittal section of the brain showing the position of the hypothalamus.

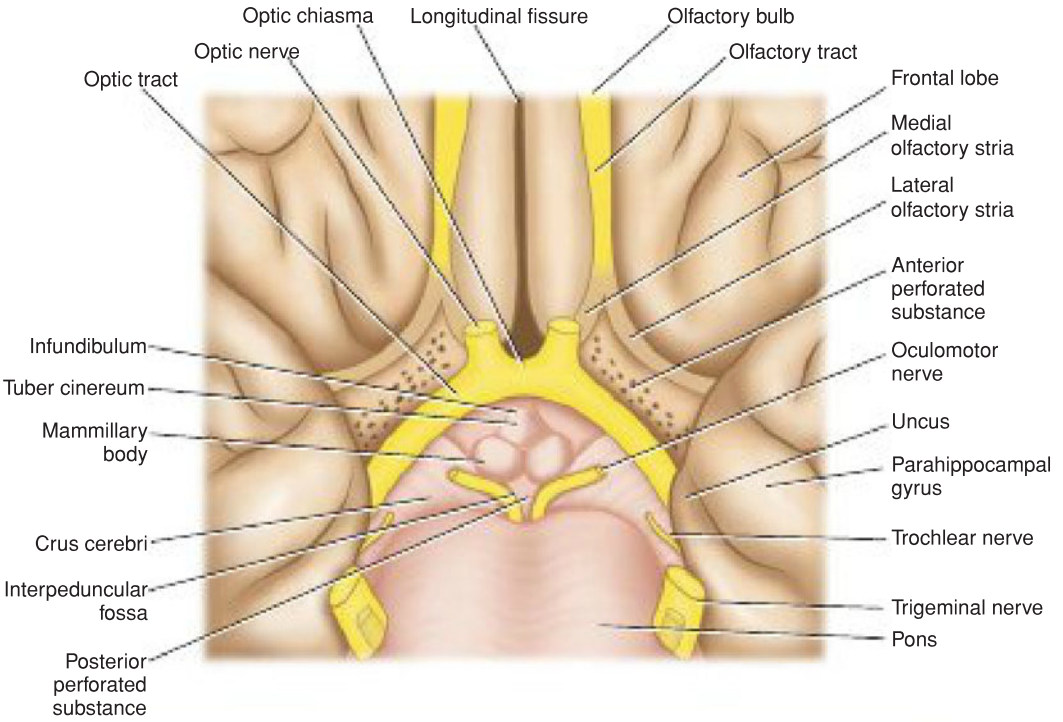


Figure 13-2 Inferior surface of the brain showing parts of the hypothalamus.

the autonomic nervous system and the neuroendocrine system, and to play a vital role in emotional behavior.

HYPOTHALAMIC NUCLEI

Microscopically, the hypothalamus is composed of small nerve cells that are arranged in groups or nuclei, many of which are not clearly segregated from one another. For functional reasons, the **preoptic area** is included as part of the hypothalamus. For purposes of description, the nuclei are divided by an imaginary parasagittal plane into medial and lateral zones (Fig. 13-3). Lying within the plane are the columns of the fornix and the mammillothalamic tract, which serve as markers (Fig. 13-4; also see Fig. 13-3).

Medial Zone

In the medial zone, the following hypothalamic nuclei can be recognized, from anterior to posterior: (1) part of the **preoptic nucleus**; (2) the **anterior nucleus**, which merges with the preoptic nucleus; (3) part of the **suprachiasmatic nucleus**; (4) the **paraventricular nucleus**;

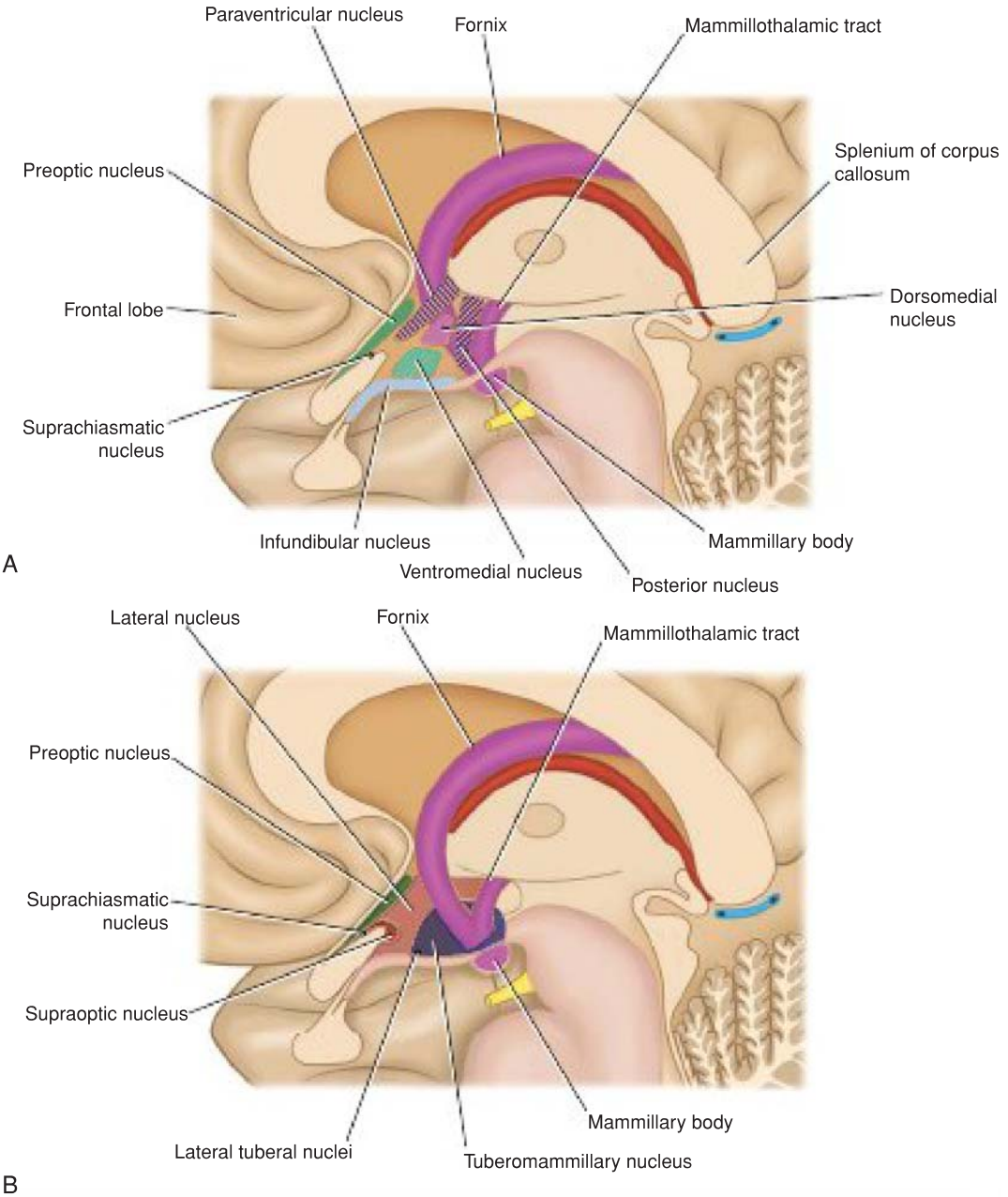


Figure 13-3 Sagittal section of the brain showing the hypothalamic nuclei. **A:** Medial zone nuclei lying medial to the plane of the fornix and the mammillothalamic tract. **B:** Lateral zone nuclei lying lateral to the plane of the fornix and the mammillothalamic tract.

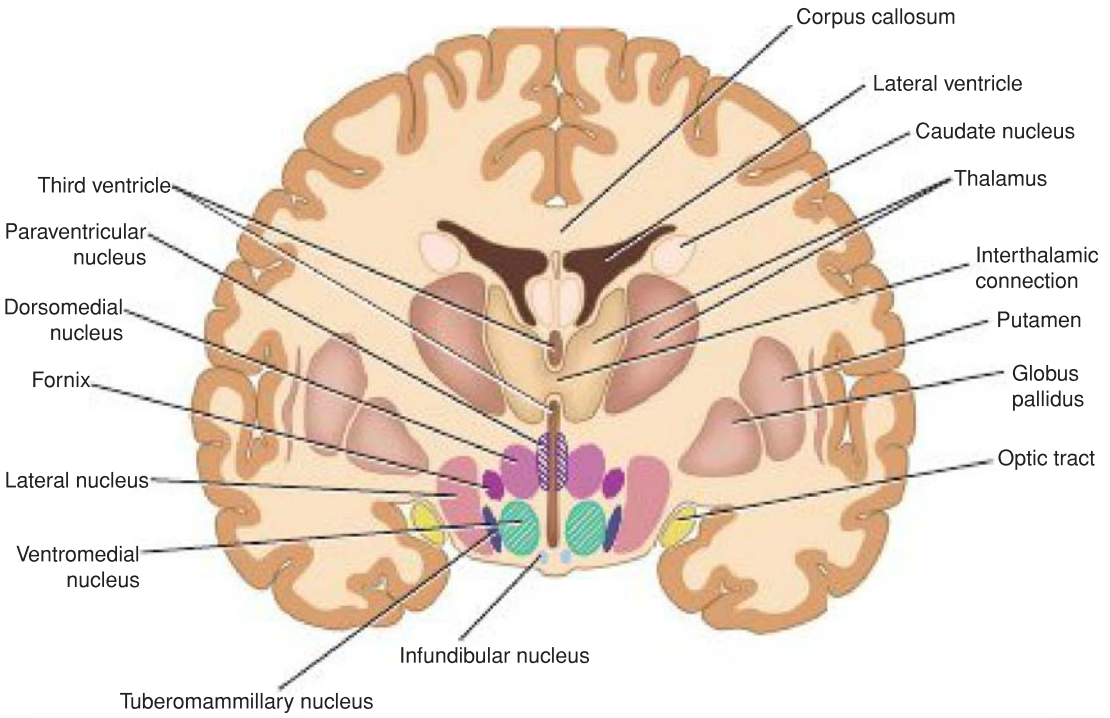


Figure 13-4 Coronal section of the cerebral hemispheres showing the position of the hypothalamic nuclei.

(5) the **dorsomedial nucleus**; (6) the **ventromedial nucleus**; (7) the **infundibular** (**arcuate**) **nucleus**; and (8) the **posterior nucleus**.

Lateral Zone

In the lateral zone, the following hypothalamic nuclei can be recognized, from anterior to posterior: (1) part of the **preoptic nucleus**, (2) part of the **suprachiasmatic nucleus**, (3) the **supraoptic nucleus**, (4) the **lateral nucleus**, (5) the **tuberomammillary nucleus**, and (6) the **lateral tuberal nuclei**.

Some of the nuclei, such as the preoptic nucleus, the suprachiasmatic nucleus, and the mammillary nuclei, overlap both zones. It should be emphasized that most of the hypothalamic nuclei have ill-defined boundaries. With the use of modern technology, including histochemical, immunochemical, and anterograde and retrograde tracer studies, groups of neurons and their connections are being more precisely identified. Unfortunately, as new nuclear groups are discovered and given names, the reader has difficulty coming to terms with the old and new nomenclature. Only the major nuclear groups with well-established names and their connections are described in this account.

HYPOTHALAMIC LINES OF COMMUNICATION

The hypothalamus receives information from the rest of the body through (1) nervous connections, (2) the bloodstream, and (3) cerebrospinal fluid (CSF). The neurons of the hypothalamic nuclei respond and exert their control via the same routes. The CSF may serve as a conduit between the neurosecretory cells of the hypothalamus and distant sites of the brain.

Afferent Nervous Connections

The hypothalamus, which lies in the center of the limbic system, receives many afferent fibers from the viscera, the olfactory mucous membrane, the cerebral cortex, and the limbic system.

The afferent connections are numerous and complex; the main pathways (Fig. 13-5) are as follows:

1. **Somatic and visceral afferents.** General somatic sensation and gustatory and visceral sensations reach the hypothalamus through collateral branches of the lemniscal afferent fibers and the tractus solitarius and through the reticular formation.
2. **Visual afferents** leave the optic chiasma and pass to the suprachiasmatic nucleus.
3. **Olfaction** travels through the medial forebrain bundle.
4. **Auditory afferents** have not been identified, but since auditory stimuli can influence the activities of the hypothalamus, they must exist.
5. **Corticohypothalamic fibers** arise from the frontal lobe of the cerebral cortex and pass directly to the hypothalamus.
6. **Hippocampohypothalamic fibers** pass from the hippocampus through the fornix to the mammillary body. Many neurophysiologists regard the hypothalamus as the main output pathway of the limbic system.

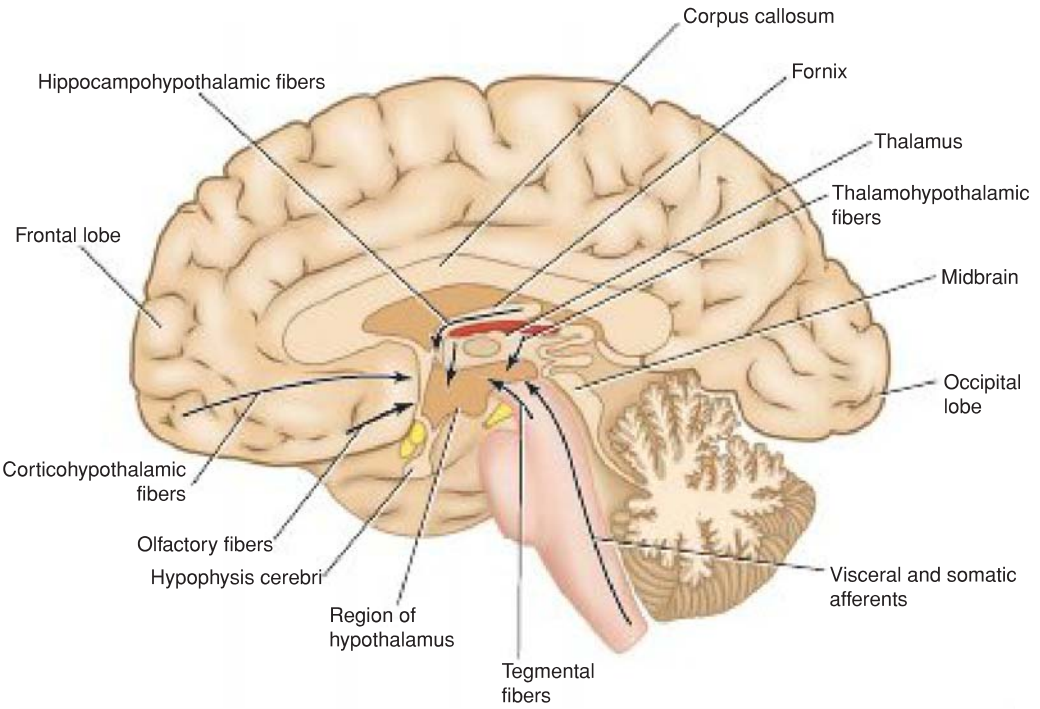


Figure 13-5 Sagittal section of the brain showing the main afferent pathways entering the hypothalamus.

7. **Amygdalohypothalamic fibers** pass from the amygdaloid complex to the hypothalamus through the stria terminalis and by a route that passes inferior to the lentiform nucleus.
8. **Thalamohypothalamic fibers** arise from the dorsomedial and midline thalamic nuclei.
9. **Tegmental fibers** arise from the midbrain.

The main afferent nervous connections of the hypothalamus are summarized in Table 13-1.

Efferent Nervous Connections

The efferent connections of the hypothalamus are also numerous and complex, and only the main pathways (Fig. 13-6) are described here:

1. **Descending fibers to the brainstem and spinal cord** influence the peripheral neurons of the autonomic nervous system. They descend through a series of neurons in the reticular formation. The hypothalamus is connected to the parasympathetic nuclei of the oculomotor, facial, glossopharyngeal, and vagus nerves in the brainstem. In a similar manner, the reticulospinal fibers connect the hypothalamus with sympathetic cells of origin in the lateral gray horns of the first thoracic segment to the second lumbar segment of the spinal cord and the sacral parasympathetic outflow at the level of the second, third, and fourth sacral segments of the spinal cord.
2. The **mammillothalamic tract** arises in the mammillary body and terminates in the anterior nucleus of the thalamus. Here, the pathway is relayed to the cingulate gyrus.
3. The **mammillotegmental tract** arises from the mammillary body and terminates in the cells of the reticular formation in the tegmentum of the midbrain.
4. Multiple pathways to the **limbic system**.

The main efferent nervous connections of the hypothalamus are summarized in Table 13-1.

Connections With the Hypophysis Cerebri

The hypothalamus is connected to the hypophysis cerebri (pituitary gland) by two pathways: (1) nerve fibers that travel from the supraoptic and paraventricular nuclei to the posterior lobe of the hypophysis and (2) long and short portal blood vessels that connect sinusoids in the median eminence and infundibulum with capillary plexuses in the anterior lobe of the hypophysis (Fig. 13-7). These pathways enable the hypothalamus to influence the activities of the endocrine glands.

Hypothalamohypophyseal Tract

The hormones **vasopressin** and **oxytocin** are synthesized in the nerve cells of the supraoptic and paraventricular nuclei. The hormones are passed along the axons together with carrier proteins called **neurophysins** and are released at the axon terminals (see Fig. 13-7). Here, the hormones are absorbed into the bloodstream in fenestrated capillaries of the posterior lobe of the hypophysis. The hormone vasopressin (antidiuretic hormone) is produced mainly in the nerve cells of the supraoptic nucleus. Its function is to cause **vasoconstriction**. It also has an important **antidiuretic function**, causing an increased absorption of water in

Table 13-1 Main Hypothalamic Afferent and Efferent Nervous Connections

Pathway	Origin	Destination
Afferent		
Medial and spinal lemnisci, tractus solitarius, reticular formation	Viscera and somatic structures	Hypothalamic nuclei
Visual fibers	Retina	Suprachiasmatic nucleus
Medial forebrain bundle	Olfactory mucous membrane	Hypothalamic nuclei
Auditory fibers	Inner ear	Hypothalamic nuclei
Corticohypothalamic fibers	Frontal lobe of cerebral cortex	Hypothalamic nuclei
Hippocampohypothalamic fibers; possibly main output pathway of limbic system	Hippocampus	Nuclei of mammillary body
Amygdalohypothalamic fibers	Amygdaloid complex	Hypothalamic nuclei
Thalamohypothalamic fibers	Dorsomedial and midline nuclei of thalamus	Hypothalamic nuclei
Tegmental fibers	Tegmentum of midbrain	Hypothalamic nuclei
Efferent		
Descending fibers in reticular formation to brainstem and spinal cord	Preoptic, anterior, posterior, and lateral nuclei of hypothalamus	Craniosacral parasympathetic and thoracolumbar sympathetic outflows
Mammillothalamic tract	Nuclei of mammillary body	Anterior nucleus of thalamus; relayed to cingulate gyrus
Mammillotegmental tract	Nuclei of mammillary body	Reticular formation in tegmentum of midbrain
Multiple pathways	Hypothalamic nuclei	Limbic system

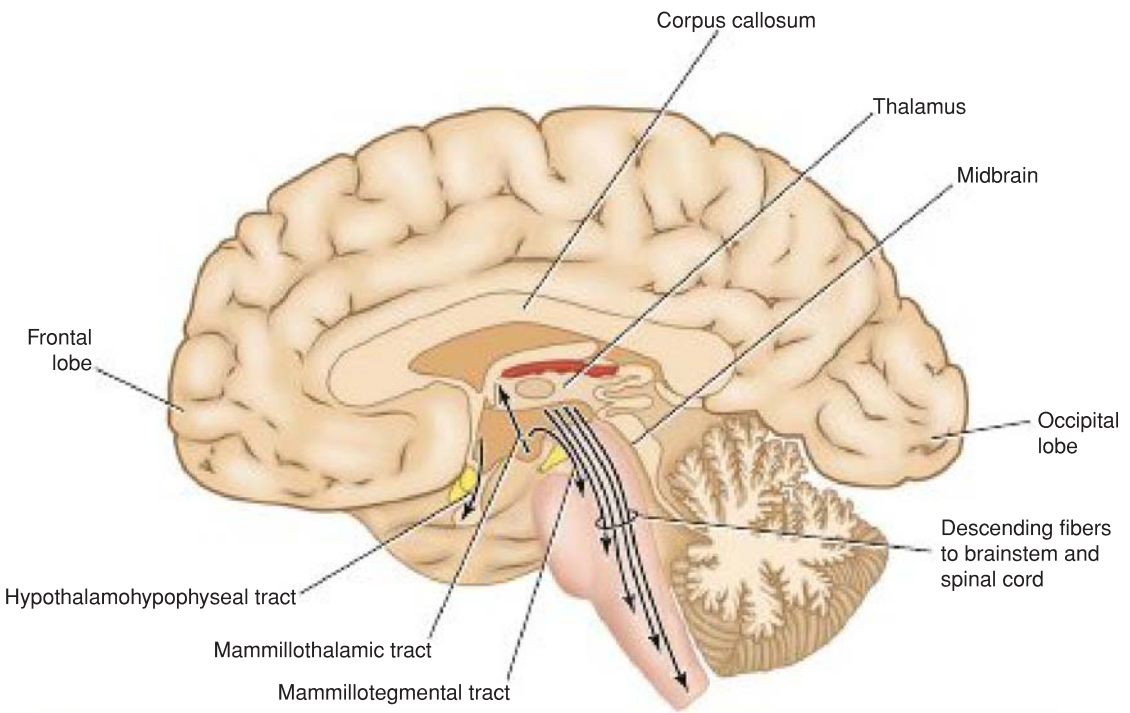


Figure 13-6 Sagittal section of the brain showing the main efferent pathways leaving the hypothalamus.

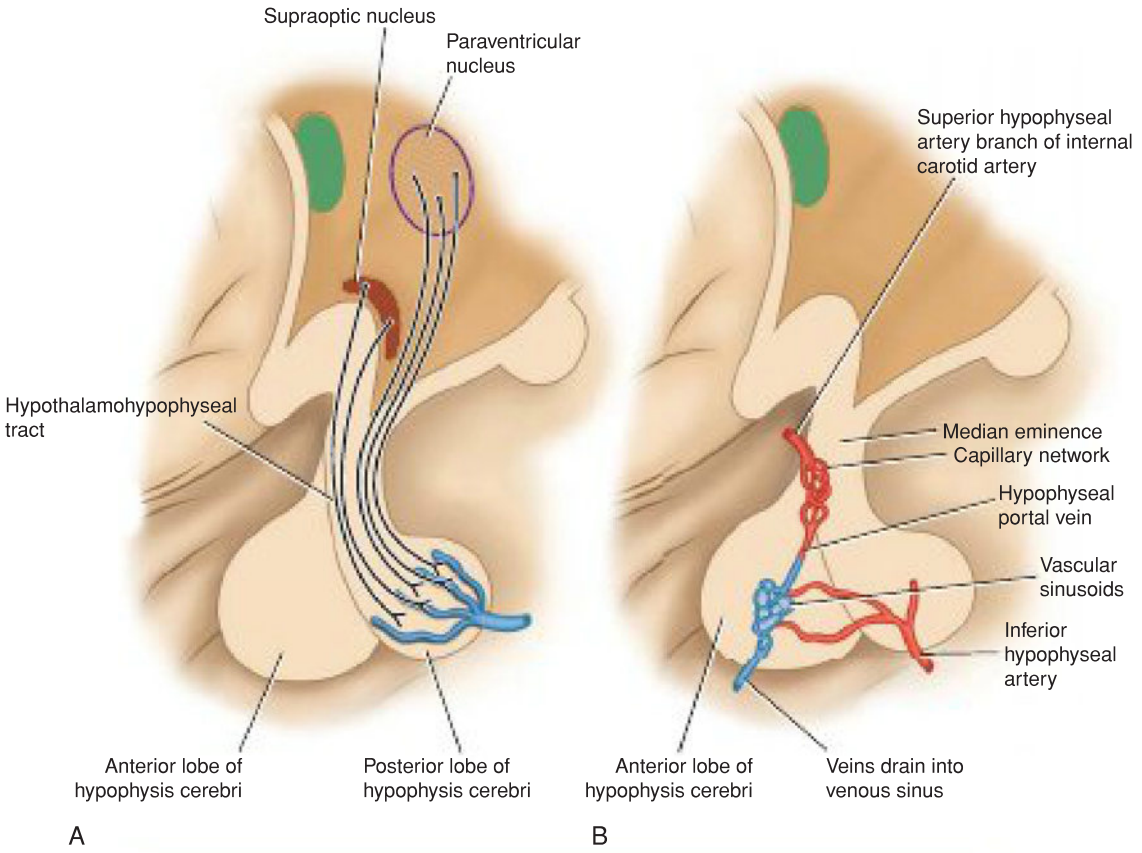


Figure 13-7 **A:** Hypothalamohypophyseal tract. **B:** Hypophyseal portal system.

the distal convoluted tubules and collecting tubules of the kidney. The other hormone is oxytocin, which is produced mainly in the paraventricular nucleus. Oxytocin stimulates the contraction of the smooth muscle of the uterus and causes contraction of the myoepithelial cells that surround the alveoli and ducts of the breast. Toward the end of pregnancy, oxytocin is produced in large amounts and stimulates labor contractions of the uterus. Later, when the baby suckles at the breast, a nervous reflex from the nipple stimulates the hypothalamus to produce more of the hormone. This promotes contraction of the myoepithelial cells and assists in the expression of the milk from the breasts.

The supraoptic nucleus, which produces vasopressin, acts as an **osmoreceptor**. Should the osmotic pressure of the blood circulating through the nucleus be too high, the nerve cells increase their production of vasopressin, and the antidiuretic effect of this hormone will increase the reabsorption of water from the kidney. By this means, the osmotic pressure of the blood will return to normal limits.

Hypophyseal Portal System

Neurosecretory cells situated mainly in the medial zone of the hypothalamus are responsible for the production of the **releasing hormones** and **release-inhibitory hormones.** The hormones are packaged into granules and are transported along the axons of these cells into the median eminence and infundibulum. Here, the granules are released by exocytosis onto fenestrated capillaries at the upper end of the hypophyseal portal system.

The hypophyseal portal system is formed on each side from the superior hypophyseal artery, which is a branch of the internal carotid artery (see Fig. 13-7B). The artery enters the median eminence and divides into tufts of capillaries. These capillaries drain into long and short descending vessels that end in the anterior lobe of the hypophysis by dividing into vascular sinusoids that pass between the secretory cells of the anterior lobe.

The portal system carries the releasing hormones and the release-inhibiting hormones to the secretory cells of the anterior lobe of the hypophysis. The releasing hormones stimulate the production and release of **adrenocorticotropic hormone** (**ACTH**), **follicle-stimulating hormone** (**FSH**), **luteinizing hormone** (**LH**), **thyrotropic hormone** or **thyroid-stimulating hormone** (**TSH**), and **growth hormone** (**GH**). The release of inhibiting hormones inhibits the release of the **melanocyte-stimulating hormone** (**MSH**) and **luteotropic hormone** (**LTH**). LTH (also known as the **lactogenic hormone** or **prolactin**) stimulates the corpus luteum to secrete progesterone and the mammary gland to produce milk. The GH inhibitory hormone (somatostatin) inhibits the release of GH. A summary of the hypothalamic-releasing and inhibitory hormones and their effects

Table 13-2 Hypothalamic-Releasing and Inhibitory Hormones and Their Effects on Hypophysis (Pituitary) Anterior Lobe

Hypothalamic Regulatory Hormone	Anterior Pituitary Hormone	Functional Result
Growth hormone–releasing hormone (GHRH)	Growth hormone (GH)	Stimulates linear growth in epiphyseal cartilages
Growth hormone–inhibiting hormone (GHIH) or somatostatin	Growth hormone (reduced production)	Reduces linear growth in epiphyseal cartilages
Prolactin-releasing hormone (PRH)	Prolactin (luteotropic hormone, LTH)	Stimulates lactogenesis
Prolactin-inhibiting hormone (PIH), dopamine	Prolactin (luteotropic hormone, LTH) (reduced production)	Reduces lactogenesis
Corticotropin-releasing hormone (CRH)	Adrenocorticotropic hormone (ACTH)	Stimulates adrenal gland to produce corticosteroids and sex hormones
Thyrotropin-releasing hormone (TRH)	Thyroid-stimulating hormone (TSH)	Stimulates thyroid gland to produce thyroxine
Luteinizing hormone–releasing hormone (LHRH)	Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	Stimulates ovarian follicles and production of estrogen and progesterone

on the anterior lobe of the hypophysis are shown in Table 13-2.

The neurons of the hypothalamus that are responsible for the production of the releasing hormones and the release-inhibiting hormones are influenced by the afferent fibers passing to the hypothalamus. They also are influenced by the level of the hormone produced by the target organ controlled by the hypophysis. Should the level of thyroxine in the blood fall, for example, then the releasing factor for the thyrotropic hormone would be produced in increased quantities. Table 13-3 summarizes the presumed nuclear origin of the pituitary-releasing and inhibitory hormones in the hypothalamus.

FUNCTIONS

Table 13-4 summarizes the functions of the main hypothalamic nuclei.

Table 13-3 Nuclear Origin[a] of the Hypophysis (Pituitary)-Releasing and Inhibitory Hormones in the Hypothalamus

Hypothalamic Regulatory Hormone	Presumed Nuclear Origin
Growth hormone–releasing hormone (GHRH)	Infundibular or arcuate nucleus
Growth hormone–inhibiting hormone (GHIH) or somatostatin	Suprachiasmatic nucleus
Prolactin-releasing hormone (PRH)	?
Prolactin-inhibiting hormone (PIH)	?
Corticotropin-releasing hormone (CRH)	Paraventricular nuclei
Thyrotropin-releasing hormone (TRH)	Paraventricular and dorsomedial nuclei and adjacent areas
Luteinizing hormone–releasing hormone (LHRH)	Preoptic and anterior nuclei

[a]Origin is presumed.

Table 13-4 Main Hypothalamic Nuclei Functions

Hypothalamic Nucleus	Presumed Function
Supraoptic nucleus	Synthesizes vasopressin (antidiuretic hormone)
Paraventricular nucleus	Synthesizes oxytocin
Preoptic and anterior nuclei	Control parasympathetic system
Posterior and lateral nuclei	Control sympathetic system
Anterior hypothalamic nuclei	Regulate temperature (response to heat)
Posterior hypothalamic nuclei	Regulate temperature (response to cold)
Lateral hypothalamic nuclei	Initiate eating and increase food intake (hunger center)
Medial hypothalamic nuclei	Inhibit eating and reduce food intake (satiety center)
Lateral hypothalamic nuclei	Increase water intake (thirst center)
Suprachiasmatic nucleus	Controls circadian rhythms

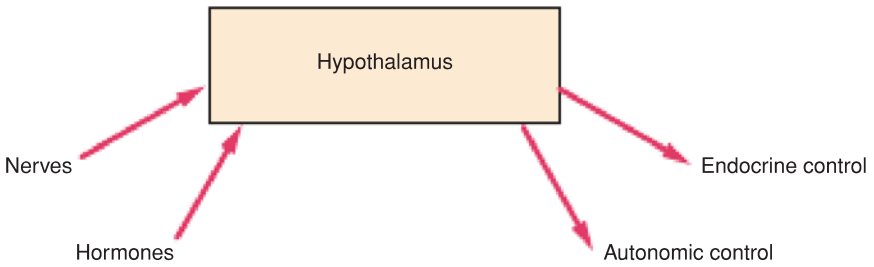


Figure 13-8 Diagram depicting the hypothalamus as the chief center of the brain for controlling the internal milieu of the body.

Autonomic Control

The hypothalamus has a controlling influence on the autonomic nervous system and appears to integrate the autonomic and neuroendocrine systems, thus preserving body homeostasis. Essentially, the hypothalamus should be regarded as a higher nervous center for the control of lower autonomic centers in the brainstem and spinal cord (Fig. 13-8).

Electrical stimulation of the hypothalamus in animal experiments shows that the anterior hypothalamic area and the preoptic area influence parasympathetic responses; these include lowering of the blood pressure, slowing of the heart rate, contraction of the bladder, increased motility of the gastrointestinal tract, increased acidity of the gastric juice, salivation, and pupillary constriction.

Stimulation of the posterior and lateral nuclei causes sympathetic responses, which include elevation of blood pressure, acceleration of the heart rate, cessation of peristalsis in the gastrointestinal tract, pupillary dilation, and hyperglycemia. These responses would lead one to believe that in the hypothalamus, there exists areas that might be termed *parasympathetic and sympathetic centers*. However, it has been shown that considerable overlap of function occurs in these areas.

Endocrine Control

The nerve cells of the hypothalamic nuclei, by producing the releasing factors or release-inhibiting factors (see Table 13-2), control the hormone production of the anterior lobe of the hypophysis (pituitary gland). The anterior lobe hormones include GH, prolactin (LTH), ACTH, TSH, LH, and FSH. Some of these hormones act directly on body tissues, while others, such as ACTH, act through an endocrine organ, which in turn produces additional hormones that influence the activities of general body tissues. It should be pointed out that each stage is controlled by negative and positive feedback mechanisms.

Neurosecretion

The secretion of vasopressin and oxytocin by the supraoptic and paraventricular nuclei is discussed on page 377.

Temperature Regulation

The anterior portion of the hypothalamus controls those mechanisms that dissipate heat loss. Experimental stimulation of this area causes dilatation of skin blood vessels and sweating, which lower the body temperature. Stimulation of the posterior portion of the hypothalamus results in vasoconstriction of the skin blood vessels and inhibition of sweating; there also may be shivering, in which the skeletal muscles produce heat.

Normally, the hypothalamus sets the body temperature at 98.08° to 98.68°F when measured orally and 18°F higher when measured rectally. The temperature set can be altered in response to extremes, such as in environmental temperatures or in infection.

Regulation of Food and Water Intake

Stimulation of the lateral region of the hypothalamus initiates the feeling of hunger and results in an increase in food intake. This lateral region sometimes is referred to as the **hunger center**. Bilateral destruction of this center results in anorexia, with the consequent loss in body weight. Stimulation of the medial region of the hypothalamus inhibits eating and reduces food intake. This area is referred to as the **satiety center**. Bilateral destruction of the satiety center produces an uncontrolled voracious appetite, causing extreme obesity.

Experimental stimulation of other areas in the lateral region of the hypothalamus causes an immediate increase in the desire to drink water; this area is referred to as the **thirst center**. In addition, the supraoptic nucleus of the hypothalamus exerts a careful control on the osmolarity of the blood through the secretion of vasopressin (antidiuretic hormone) by the posterior lobe of the hypophysis. This hormone causes a great increase in the reabsorption of water in the distal convoluted tubules and collecting tubules of the kidneys.

Emotion and Behavior

Emotion and behavior are a function of the hypothalamus, the limbic system, and the prefrontal cortex. Some authorities believe that the hypothalamus is the integrator of afferent information received from other areas of the nervous system and brings about the physical expression of emotion; it can produce an increase in the heart rate, elevate the blood pressure, cause dryness of

the mouth, flushing or pallor of the skin, and sweating. As well, it can often produce a massive peristaltic activity of the gastrointestinal tract.

Stimulation of the lateral hypothalamic nuclei may cause the symptoms and signs of rage, whereas lesions of these areas may lead to passivity. Stimulation of the ventromedial nucleus may cause passivity, whereas lesions of this nucleus may lead to rage.

Control of Circadian Rhythms

The hypothalamus controls many circadian rhythms, including body temperature, adrenocortical activity, eosinophil count, and renal secretion. Sleeping and wakefulness, although dependent on the activities of the thalamus, the limbic system, and the reticular activating system, are also controlled by the hypothalamus. Lesions of the anterior part of the hypothalamus seriously interfere with the rhythm of sleeping and waking. The suprachiasmatic nucleus, which receives afferent fibers from the retina, appears to play an important role in controlling the biologic rhythms. Nerve impulses generated in response to variations in the intensity of light are transmitted via this nucleus to influence the activities of many of the hypothalamic nuclei.

Clinical Notes

General Considerations

In summary, the activities of the hypothalamus are modified by information received along numerous afferent pathways from different parts of the central nervous system (especially from the limbic system and the prefrontal cortex) and by the plasma levels of circulating hormones. It exerts its influence on bodily functions through the autonomic nervous system and the endocrine system.

Although small, the hypothalamus should not be interpreted as a structure of little importance. It is the chief center of the brain for maintaining the internal milieu of the body (see Fig. 13-8). Hardly any tissue in the body escapes its influence.

The connections of the hypothalamus are extremely complicated, and only the major pathways should be committed to memory for use in clinical work.

Clinical Disorders Associated With Hypothalamic Lesions

The hypothalamus may be the site of inflammation, neoplasm, or vascular disorder. Because of its deep-seated central position, it can be pressed on by tumors of the surrounding brain tissue or may be compressed as the result of the development of internal hydrocephalus. Its widespread influence on many homeostatic and behavioral functions means that a lesion of the hypothalamus will produce a large number of different syndromes. Importantly, an acute lesion is more likely to produce signs and symptoms than is a slowly growing tumor.

Obesity and Wasting

Severe obesity can occur as the result of hypothalamic lesions. It is generally associated with genital hypoplasia or atrophy.

Wasting is less common than obesity in hypothalamic disease. Severe cachexia is suggestive of damage to the hypophysis (pituitary gland).

Sexual Disorders

In children, sexual retardation and, rarely, sexual precocity may result from hypothalamic lesions. After puberty, the patient with hypothalamic disease may have impotence or amenorrhea.

Hyperthermia and Hypothermia

Hyperthermia can follow lesions of the hypothalamus caused by head injury or following surgical operations in the region of the hypothalamus. The patient with hyperthermia is otherwise normal and has no signs of malaise, which occurs with pyrexia secondary to infections. Hypothermia also can follow a lesion of the hypothalamus.

Diabetes Insipidus

Diabetes insipidus results from a lesion of the supraoptic nucleus or from the interruption of the nervous pathway to the posterior lobe of the hypophysis. Characteristically, the patient passes large volumes of urine of low specific gravity. As a result, the patient is extremely thirsty and drinks large quantities of fluids. The condition must be distinguished from diabetes mellitus, which is characterized by glucosuria.

Sleep Disturbance

The occurrence of either frequent short periods of sleep during the waking hours or insomnia has been observed in patients with hypothalamic lesions.

Emotional Disorders

Attacks of unexplained weeping or laughter, uncontrollable rage, depressive reactions, and even maniacal outbursts all have been observed in patients with hypothalamic lesions.

Key Concepts

Hypothalamus

- The hypothalamus controls body homeostasis through the autonomic nervous and endocrine systems and plays a vital role in emotional behavior.

Hypothalamic Nuclei

- The nerve cells in the hypothalamus are arranged in many small groups, or nuclei, which are not clearly segregated from one another. However, some nuclei such as the preoptic, suprachiasmatic, and mammillary nuclei are distinct and demonstrate functional significance.
- The hypothalamus not only receives information through nervous connections but also through the bloodstream and CSF.

Hypothalamic Connections With the Hypophysis Cerebri

- The hypothalamus is connected with the pituitary gland by two pathways: 1) nerve fibers from supraoptic and paraventricular nuclei to the posterior lobe of the hypophysis, and 2) long and short portal blood vessels that connect sinusoids in the median eminence and infundibulum with capillary plexuses in the anterior lobe of the hypophysis.
- The hypothalamohypophyseal tract: Vasopressin and oxytocin hormones are synthesized in the nerve cells of the supraoptic and paraventricular nuclei, released at axon terminals, and absorbed into the bloodstream via fenestrated capillaries of the posterior lobe of the hypophysis.
- Hypophyseal portal system: Neurosecretory cells in the hypothalamus produce releasing hormones and release-inhibitory hormones that are packaged into granules and released by exocytosis into fenestrated capillaries at the upper end of the portal system.
- The portal system carries the releasing hormone to the anterior lobe of the pituitary gland, which then stimulates production and release of hormones or inhibits the release of different hormones.

Hypothalamic Functions

- The hypothalamus shows influence and control over the autonomic nervous system, the endocrine system, temperature regulation, regulation of food and water intake, emotion and behavior, and circadian rhythms.

Clinical Problem Solving

1. A 17-year-old boy is admitted into the medical ward for observation. The tentative diagnosis is Fröhlich syndrome. He has a 3-month history of severe headaches. More recently, he has attacks of vomiting, and 1 week ago he had noticed problems with his eyesight. The patient says that he has difficulty seeing objects on the lateral side of both eyes. His parents are concerned that he is putting on weight, as he has increased adiposity over the lower part of the trunk. On physical examination, the boy is found to be 6 ft 3 in tall; he has excessive trunk obesity. The testes and penis are small, and pubic and axillary hairs are absent. A lateral radiograph of the skull shows enlargement of the sella turcica with erosion of the dorsum sellae. An examination of the eye fields confirms that the patient has partial bitemporal hemianopia. Using your knowledge of neuroanatomy, explain the symptoms and signs of this patient.
2. A 40-year-old woman is involved in an automobile accident in which she sustains severe head injuries. Following a slow but uneventful recovery, she is released from the hospital without any residual signs or symptoms. Six months later, the patient starts to complain of frequency of micturition and is passing very large quantities of pale urine. She also says that she always seems thirsty and will often drink 10 glasses of water in one morning. Using your knowledge of neuroanatomy and neurophysiology, do you think a connection exists between the urinary symptoms and her automobile accident?
3. Do you think a patient with hydrocephalus could have a malfunctioning hypothalamus? If so, explain the connection.
4. Sherrington once stated in a scientific publication in 1947 that the hypothalamus should be regarded as the "head ganglion" of the autonomic nervous system (ANS). What is the relationship that exists between the hypothalamus and the ANS?
5. Explain what is meant by the terms *hypothalamohypophyseal tract* and *hypophyseal portal system*.

Answers and Explanations to Clinical Problem Solving

1. This boy was suffering from Fröhlich syndrome secondary to a chromophobe adenoma of the anterior lobe of the hypophysis. This space-occupying lesion had gradually eroded the sella turcica of the skull and had compressed the optic chiasma, producing bitemporal hemianopia. The size of the tumor was causing a raised intracranial pressure that was responsible for the headaches and attacks of vomiting. Pressure on the hypothalamus interfered with its function and resulted in the characteristic accumulation of fat in the trunk, especially the lower part of the abdomen. The hypogonadism and absence of secondary sex characteristics could have been due to pressure of the tumor on the hypothalamic nuclei and the consequent loss of control on the anterior lobe of the hypophysis, or it may have been due to the direct effect of the tumor pressing on the neighboring cells of the anterior lobe of the hypophysis.
2. Yes, the accident and the urinary symptoms are connected. This patient is suffering from diabetes insipidus caused by traumatic damage either to the posterior lobe of the hypophysis or to the supraoptic nucleus of the hypothalamus. In any event, production of vasopressin was inhibited. It should be pointed out that a lesion of the posterior lobe of the hypophysis is usually not followed by diabetes insipidus, since the vasopressin produced by the neurons of the supraoptic nucleus escapes directly into the bloodstream. The action of vasopressin on the distal convoluted tubules and collecting tubules of the kidney is fully explained on page 381.
3. Yes, it is possible. Hydrocephalus, caused by blockage of the three foramina in the roof of the fourth ventricle or by blockage of the cerebral aqueduct, will result in a rise in pressure in the third ventricle, with pressure on the hypothalamus. This pressure on the hypothalamus, which is situated in the floor and lower part of the lateral walls of the third ventricle, if great enough, could easily cause malfunctioning of the hypothalamus.
4. The hypothalamus is the main subcortical center regulating the parasympathetic and sympathetic parts of the autonomic system. It exerts its influence through descending pathways in the reticular formation.
5. The hypothalamohypophyseal tract is described on page 377, and the hypophyseal portal system is described on page 379. Remember that the hypothalamus exerts its control over metabolic and visceral functions through the hypophysis cerebri and the autonomic nervous system.

Review Questions

Directions: Each of the numbered items in this section is followed by answers. Select the ONE lettered answer that is CORRECT.

1. The following statements concern the hypothalamus:
   (a) It lies below the thalamus in the tectum of the midbrain.
   (b) It is not related to the limbic system.
   (c) The nuclei of the hypothalamus are divided by an imaginary plane formed by the columns of the fornix and the mammillothalamic tract into medial and lateral groups.
   (d) The suprachiasmatic nucleus does not receive nerve fibers from the retina.
   (e) The lateral boundary of the hypothalamus is formed by the external capsule.
2. The following statements concern the hypothalamus:
   (a) When seen from the inferior aspect, the hypothalamus is related to the following structures, from anterior to posterior: (i) the olfactory stria, (ii) the anterior perforated substance, and (iii) the mammillary bodies.
   (b) The margins of the different nuclei can be clearly seen with the naked eye.
   (c) The mammillary body does not overlap the medial and lateral groups of hypothalamic nuclei.
   (d) The preoptic area of the hypothalamus is located between the septum pellucidum and the optic chiasma.
   (e) The blood–brain barrier is absent in the median eminence of the hypothalamus, thus permitting the neurons to sample the chemical content of the plasma directly.
3. The following statements concern the afferent fibers passing to the hypothalamus:
   (a) Fibers pass from the hippocampus to the mammillary bodies, bringing information from the auditory system.
   (b) Olfactory impulses reach the hypothalamus through the lateral forebrain bundle.
   (c) The hypothalamus receives many afferent fibers from the viscera via the reticular formation.
   (d) The dorsomedial nucleus receives axons from the posterior lobe of the pituitary.
   (e) The pineal gland sends fibers via the habenular commissure to the hypothalamus.

4. The following statements concern the hypothalamus:
   (a) Somatic efferent fibers leave the hypothalamic nuclei via the medial and spinal lemnisci.
   (b) It does not integrate the autonomic and neuroendocrine systems.
   (c) The posterior portion of the hypothalamus controls those mechanisms that dissipate heat loss.
   (d) The nerve cells of the hypothalamus produce releasing and release-inhibiting hormones that control the production of various hormones in the anterior lobe of the hypophysis.
   (e) The hunger center is probably located in the posterior hypothalamic nuclei.
5. The following statements concern the functional activities of the hypothalamus:
   (a) The hypothalamus brings about the physical changes associated with emotion, such as increased heart rate and flushing or pallor of the skin.
   (b) The medial hypothalamic nuclei are concerned with fluid intake.
   (c) The corticotropin-releasing hormone (CRH) is produced in the anterior nucleus of the hypothalamus.
   (d) The suprachiasmatic nucleus plays no part in controlling circadian rhythms.
   (e) The hypothalamus controls the lower autonomic centers by means of pathways through the tectospinal tract.
6. The following statements concern the hypothalamohypophyseal tract:
   (a) Oxytocin inhibits the contraction of the smooth muscle of the uterus.
   (b) The nerve cells of the supraoptic and paraventricular nuclei produce the hormones vasopressin and oxytocin.
   (c) The hormones travel in lymph vessels with protein carriers called neurophysins.
   (d) Vasopressin stimulates the proximal convoluted tubules of the kidney, causing increased absorption of water from the urine.
   (e) The hormones are absorbed into the bloodstream in the capillaries of the anterior lobe of the hypophysis.
7. The following statements concern the hypophyseal portal system:
   (a) It carries releasing hormones and release-inhibiting hormones to the secretory cells of the anterior lobe of the hypophysis.
   (b) The production of the releasing hormones and the release-inhibiting hormones cannot be influenced by the level of the hormone produced by the target organ controlled by the hypophysis.
   (c) The blood vessels commence superiorly in the median eminence and end inferiorly in the vascular sinusoids of the posterior lobe of the hypophysis cerebri.
   (d) Efferent nerve fibers leaving the hypothalamus influence the production of the releasing hormones by nerve cells.
   (e) The neuroglial cells of the hypothalamus are responsible for the production of the release-inhibiting hormones.

Answers and Explanations to Review Questions

1. C is correct. The nuclei of the hypothalamus are divided by an imaginary plane formed by the columns of the fornix and the mammillothalamic tract into medial and lateral groups (see Fig. 13-3). A. The hypothalamus lies below the thalamus and not in the tectum of the midbrain (see Fig. 13-1). B. The hypothalamus lies in the center of the limbic system. D. The suprachiasmatic nucleus does receive nerve fibers from the retina. E. The lateral boundary of the hypothalamus is formed by the internal capsule.
2. E is correct. The blood–brain barrier is absent in the median eminence of the hypothalamus, thus permitting the neurons to sample the chemical content of the plasma directly. A. When seen from the inferior aspect, the hypothalamus is related to the following structures: (i) the optic chiasma, (ii) the tuber cinereum, and (iii) the mammillary bodies (see Fig. 13-2). B. The margins of the different hypothalamic nuclei are ill-defined and cannot be seen with the naked eye. C. The mammillary body overlaps both the medial and lateral groups of hypothalamic nuclei. D. The preoptic area of the hypothalamus is located between the lamina terminalis and the optic chiasma.
3. C is correct. The hypothalamus receives many afferent fibers from the viscera via the reticular formation. A. Fibers pass from the hippocampus to the mammillary bodies, bringing information from the limbic system. B. Olfactory impulses reach the hypothalamus through the medial forebrain bundle. D. The dorsomedial nucleus of the hypothalamus does not receive axons from the posterior lobe of the pituitary. E. The pineal gland does not send nerve fibers to the hypothalamus.
4. D is correct. The nerve cells of the hypothalamus produce releasing and release-inhibiting hormones that control the production of various hormones in the anterior lobe of the hypophysis. A. Somatic afferent fibers enter the hypothalamic nuclei via the medial and spinal lemnisci. B. The hypothalamus does integrate the autonomic and neuroendocrine systems, thus preserving homeostasis. C. The anterior portion of the hypothalamus controls those mechanisms that

dissipate heat loss. E. The hunger center is probably located in the lateral region of the hypothalamus.

5. A is correct. The hypothalamus probably brings about the physical changes associated with emotion, such as increased heart rate and flushing or pallor of the skin. B. The lateral hypothalamic nuclei are concerned with fluid intake. C. The CRH is produced in the paraventricular nuclei of the hypothalamus (see Table 13-3). D. The suprachiasmatic nucleus plays an important role in controlling circadian rhythms. E. The hypothalamus controls the lower autonomic centers by means of pathways through the reticular formation.
6. B is correct. The nerve cells of the supraoptic and paraventricular nuclei produce the hormones vasopressin and oxytocin. A. Oxytocin stimulates the contraction of the smooth muscle of the uterus. C. The hormones travel in the axons of the hypothalamohypophyseal tract with protein carriers called neurophysins. D. Vasopressin stimulates the distal convoluted tubules and collecting tubules of the kidney, causing increased absorption of water from the urine. E. The hormones leave the axons of the tract and are absorbed into the bloodstream in the capillaries of the posterior lobe of the hypophysis.
7. A is correct. The hypophyseal portal system carries releasing hormones and release-inhibiting hormones to the secretory cells of the anterior lobe of the hypophysis. B. The production of the releasing hormones and the release-inhibiting hormones can be influenced by the level of the hormone produced by the target organ controlled by the hypophysis. C. The blood vessels of the hypophyseal portal system commence superiorly in the median eminence and end inferiorly in the vascular sinusoids of the anterior lobe of the hypophysis cerebri. D. Afferent nerve fibers entering the hypothalamus influence the production of the releasing hormones by the nerve cells. E. The neuroglial cells of the hypothalamus are not responsible for the production of the release-inhibiting hormones.

14 Autonomic Nervous System

CHAPTER OBJECTIVES

- To understand the structure and physiology of the autonomic nervous system
- To understand the pharmacologic differences between the sympathetic and parasympathetic nervous systems

A 46-year-old man underwent a right-sided pneumonectomy for carcinoma of the bronchus and is seen by his thoracic surgeon for follow-up. The patient says that he feels surprisingly fit and is gaining some of the weight that he had lost prior to the operation. His wife comments that the upper lid of his right eye tends to droop slightly when he gets tired at the end of the day.

During a careful physical examination, the surgeon notices that in addition to the ptosis of the right eye, the patient's right pupil is constricted and that his face is slightly flushed on the right side. Further examination reveals that the skin on the right side of the face appears to be warmer and drier than normal. Palpation of the deep cervical group of lymph nodes reveals a large, hard, fixed node just above the right clavicle.

Based on his clinical findings, the surgeon makes the diagnosis of a right-sided Horner syndrome. These findings were not present before the operation. The presence of the enlarged right-sided deep cervical lymph node indicates that the bronchial carcinoma has metastasized to the lymph node in the neck and is spreading to involve the cervical part of the sympathetic trunk on the right side. This observation explains the abnormal eye and facial skin findings.

Knowledge of the sympathetic innervation of the structures of the head and neck enables the surgeon to make an accurate diagnosis in this patient.

The autonomic nervous system (ANS) and the endocrine system control the internal environment of the body. The ANS provides a fine discrete control over the functions of many organs and tissues, including heart muscle, smooth muscle, and the exocrine glands. The endocrine system, by means of its blood-borne hormones, exerts a slower more diffuse control.

The ANS, like the somatic nervous system, has afferent, connector, and efferent neurons. The afferent impulses originate in visceral receptors and travel via afferent pathways to the central nervous system (CNS), where they are integrated through connector neurons at different levels and then leave via efferent pathways to visceral effector organs. The majority of the activities of the autonomic system do not impinge on consciousness.

The efferent pathways of the autonomic system are made up of preganglionic and postganglionic neurons. The cell bodies of the preganglionic neurons are situated in the lateral gray column of the spinal cord and in the motor nuclei of the 3rd, 7th, 9th, and 10th cranial nerves. The axons of these cell bodies synapse on the cell bodies of the postganglionic neurons that are collected together to form **ganglia** outside the CNS.

The control exerted by the autonomic system is extremely rapid; it is also widespread, since one preganglionic axon may synapse with several postganglionic neurons. Large collections of afferent and efferent fibers and their associated ganglia form **autonomic plexuses** in the thorax, abdomen, and pelvis.

The visceral receptors include chemoreceptors, baroreceptors, and osmoreceptors. Pain receptors are present in viscera and certain types of stimuli, such as lack of oxygen or stretch, can cause extreme pain.

The information provided in this chapter is extensively used in clinical practice. The examples of autonomic innervations given are important and are commonly used by examiners to construct good questions.

ORGANIZATION

The ANS is distributed throughout the central and peripheral nervous systems. It is divided into two parts, the **sympathetic** and the **parasympathetic** and, as emphasized earlier, consists of both afferent and efferent fibers. This division between sympathetic and parasympathetic

is made on the basis of anatomic differences, differences in the neurotransmitters, and differences in the physiologic effects.

Both the sympathetic and parasympathetic divisions produce opposite effects in most organs and are thus considered as physiologic antagonists. However, both divisions operate in conjunction with one another and the balance in the activities maintains a stable internal environment.

Sympathetic Part

The sympathetic system is the larger of the two parts of the autonomic system and is widely distributed throughout the body, innervating the heart and lungs, the muscle in the walls of many blood vessels, the hair follicles and the sweat glands, and many abdominopelvic viscera.

The function of the sympathetic system is to prepare the body for an emergency. The heart rate is increased, arterioles of the skin and intestine are constricted, arterioles of skeletal muscle are dilated, and the blood pressure is raised. Blood is redistributed; thus, it leaves the skin and gastrointestinal tract and passes to the brain, heart, and skeletal muscle. In addition, the sympathetic nerves dilate the pupils; inhibit smooth muscle of the bronchi, intestine, and bladder wall; and close the sphincters. The hair is made to stand on end, and sweating occurs.

The sympathetic system consists of the efferent outflow from the spinal cord, two ganglionated sympathetic trunks, important branches, plexuses, and regional ganglia.

Efferent Nerve Fibers (Sympathetic Outflow)

The lateral gray columns (horns) of the spinal cord from the first thoracic segment to the second lumbar segment (sometimes third lumbar segment) possess the cell bodies of the sympathetic connector neurons (Fig. 14-1). The myelinated axons of these cells leave the cord in the anterior nerve roots and pass via the **white rami communicantes** (the white rami are white because the nerve fibers are covered with white myelin) to the **paravertebral ganglia** of the **sympathetic trunk**. Once these fibers (preganglionic) reach the ganglia in the sympathetic trunk, they are distributed as follows:

1. They synapse with an excitor neuron in the ganglion. The gap between the two neurons is bridged by the neurotransmitter **acetylcholine** (**ACh**). The postganglionic nonmyelinated axons leave the ganglion and pass to the thoracic spinal nerves as **gray rami communicantes** (the gray rami are gray because the nerve fibers are devoid of myelin). They are distributed in branches of the spinal nerves to smooth muscle in the blood vessel walls, sweat glands, and arrector pili muscle of the hairs of the skin.
2. They travel cephalad in the sympathetic trunk to synapse in ganglia in the cervical region (Fig. 14-2). The postganglionic nerve fibers pass via gray rami communicantes to join the cervical spinal nerves. Many of the preganglionic fibers entering the lower part of the sympathetic trunk from the lower thoracic and upper two lumbar segments of the spinal cord travel caudad to synapse in ganglia in the lower lumbar and sacral regions. Here again, the postganglionic nerve

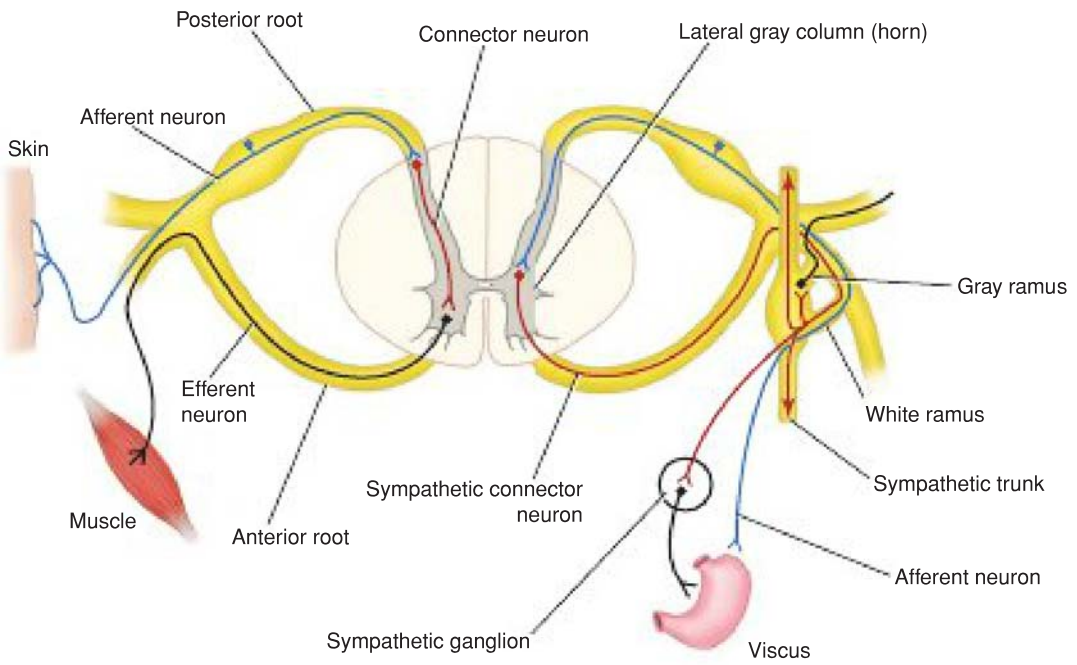


Figure 14-1 General arrangement of the somatic part of the nervous system (on **left**) compared with the autonomic part of the nervous system (on **right**).

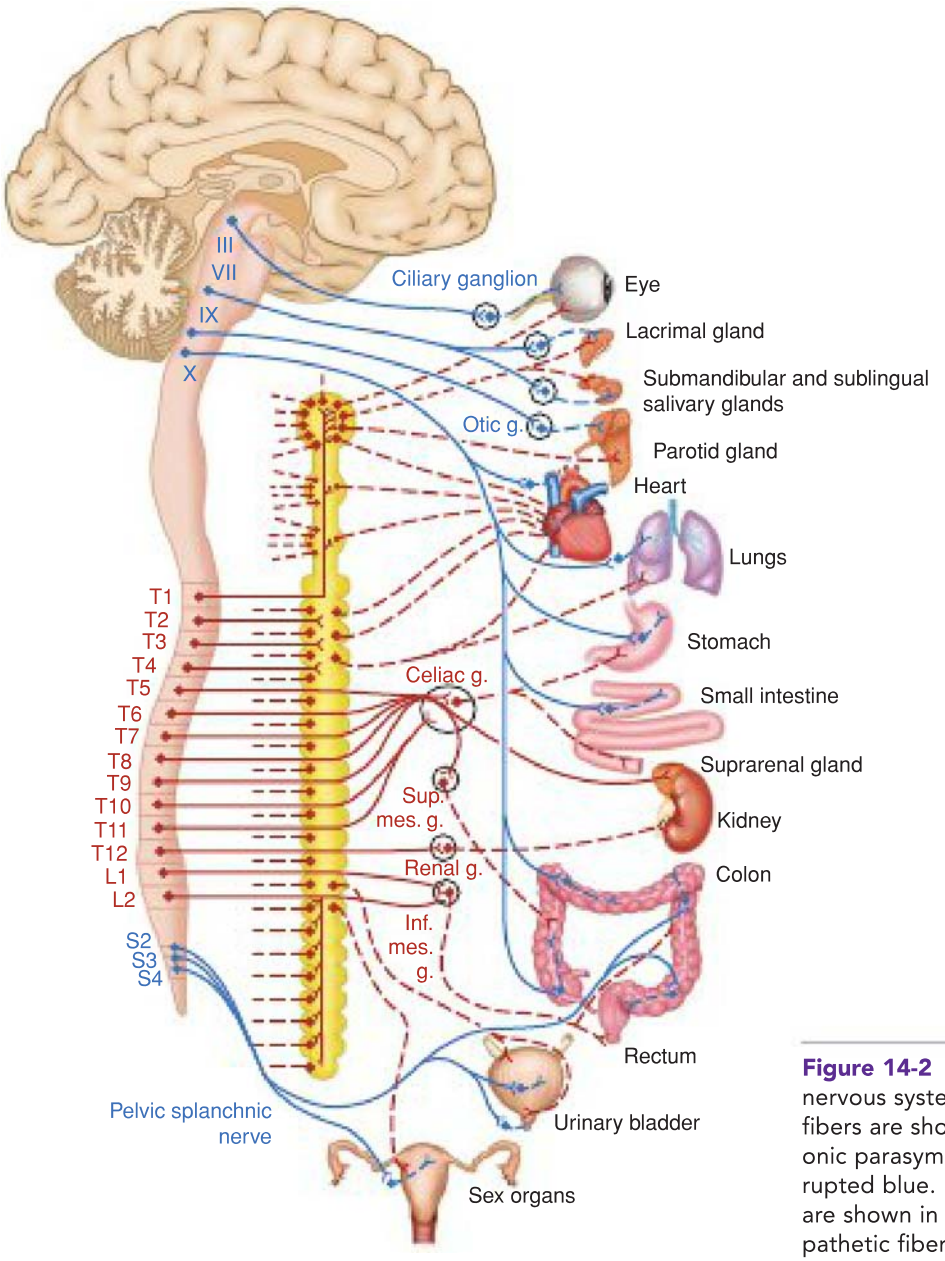


Figure 14-2 Efferent part of the autonomic nervous system. Preganglionic parasympathetic fibers are shown in solid blue and postganglionic parasympathetic fibers are shown in interrupted blue. Preganglionic sympathetic fibers are shown in solid red and postganglionic sympathetic fibers are shown in interrupted red.

fibers pass via gray rami communicantes to join the lumbar, sacral, and coccygeal spinal nerves.

3. They may pass through the ganglia of the sympathetic trunk without synapsing. These myelinated fibers leave the sympathetic trunk as the **greater splanchnic**, **lesser splanchnic**, and **lowest** or **least splanchnic nerves**. The greater splanchnic nerve is formed from branches from the fifth to the ninth thoracic ganglia. It descends obliquely on the sides of the bodies of the thoracic vertebrae and pierces the crus of the diaphragm to synapse with excitor cells in the ganglia of the **celiac plexus**, the **renal plexus**, and the suprarenal medulla. The lesser splanchnic nerve is formed from branches of the 10th and 11th thoracic ganglia. It descends with the greater splanchnic nerve and pierces the diaphragm to join excitor cells in ganglia in the lower part of the **celiac plexus.** The lowest splanchnic nerve (when present) arises from the 12th thoracic ganglion, pierces the diaphragm, and synapses with excitor neurons in the ganglia of the **renal plexus**. The splanchnic nerves, therefore, are formed of preganglionic fibers. The postganglionic fibers arise from the excitor cells in the peripheral plexuses and are distributed to the smooth muscle and glands of the viscera. A few preganglionic fibers, traveling in the greater splanchnic nerve, end directly on the cells of the **suprarenal medulla**. These medullary cells, which may be regarded as modified sympathetic excitor neurons, are responsible for the secretion of epinephrine and norepinephrine.

The ratio of preganglionic to postganglionic sympathetic fibers is about 1:10, permitting a wide control of involuntary structures.

Afferent Nerve Fibers

Afferent myelinated nerve fibers travel from the viscera through the sympathetic ganglia without synapsing. They pass to the spinal nerve via white rami communicantes and reach their cell bodies in the posterior root ganglion of the corresponding spinal nerve (see Fig. 14-1). The central axons then enter the spinal cord and may form the afferent component of a local reflex arc or ascend to higher centers, such as the hypothalamus.

Sympathetic Trunks

The sympathetic trunks are two ganglionated nerve trunks that extend the whole length of the vertebral column (see Fig. 14-2). In the neck, each trunk has 3 ganglia; in the thorax, 11 or 12; in the lumbar region, 4 or 5; and in the pelvis, 4 or 5. In the neck, the trunks lie anterior to the transverse processes of the cervical vertebrae; in the thorax, they are anterior to the heads of the ribs or lie on the sides of the vertebral bodies; in the abdomen, they are anterolateral to the sides of the bodies of the lumbar vertebrae; and in the pelvis, they are anterior to the sacrum. Below, the two trunks terminate by joining together to form a single ganglion, the **ganglion impar**.

Parasympathetic Part

The activities of the parasympathetic part of the autonomic system are directed toward conserving and restoring energy. The heart rate is slowed, pupils are constricted, peristalsis and glandular activity is increased, sphincters are opened, and the bladder wall is contracted.

Efferent Nerve Fibers (Craniosacral Outflow)

The connector nerve cells of the parasympathetic part of the ANS are located in the brainstem and the sacral segments of the spinal cord (see Fig. 14-2).

Those nerve cells located in the brainstem form nuclei in the following cranial nerves: the **oculomotor** (parasympathetic or Edinger–Westphal nucleus), the **facial** (superior salivatory nucleus and lacrimatory nucleus), the **glossopharyngeal** (inferior salivatory nucleus), and the **vagus** nerves (dorsal nucleus of the vagus). The axons of these connector nerve cells are myelinated and emerge from the brain within the cranial nerves.

The sacral connector nerve cells are found in the gray matter of the **second**, **third**, and **fourth sacral segments of the spinal cord**. These cells are not sufficiently numerous to form a lateral gray horn, as do the sympathetic connector neurons in the thoracolumbar region. The myelinated axons leave the spinal cord in the anterior nerve roots of the corresponding spinal nerves. They then leave the sacral nerves and form the **pelvic splanchnic nerves**.

The myelinated efferent fibers of the craniosacral outflow are preganglionic and synapse in peripheral ganglia located close to the viscera they innervate. Here again, acetylcholine is the neurotransmitter. The cranial parasympathetic ganglia are the **ciliary, pterygopalatine, submandibular**, and **otic**. In certain locations, the ganglion cells are placed in nerve plexuses, such as the **cardiac plexus, pulmonary plexus, myenteric plexus** (**Auerbach plexus**), and **submucosal plexus** (**Meissner plexus**); the last two plexuses are associated with the gastrointestinal tract. The pelvic splanchnic nerves synapse in ganglia in the **hypogastric plexuses**. Characteristically, the postganglionic parasympathetic fibers are nonmyelinated and of relatively short length compared with sympathetic postganglionic fibers.

The ratio of preganglionic to postganglionic fibers is about 1:3 or less, which is much more restricted than in the sympathetic part of the system.

Afferent Nerve Fibers

Afferent myelinated fibers span from the viscera to their cell bodies, located either in the sensory ganglia of the cranial nerves or in the posterior root ganglia of the sacrospinal nerves. The central axons then enter the CNS and take part in the formation of local reflex arcs or pass to higher centers of the ANS, such as the hypothalamus.

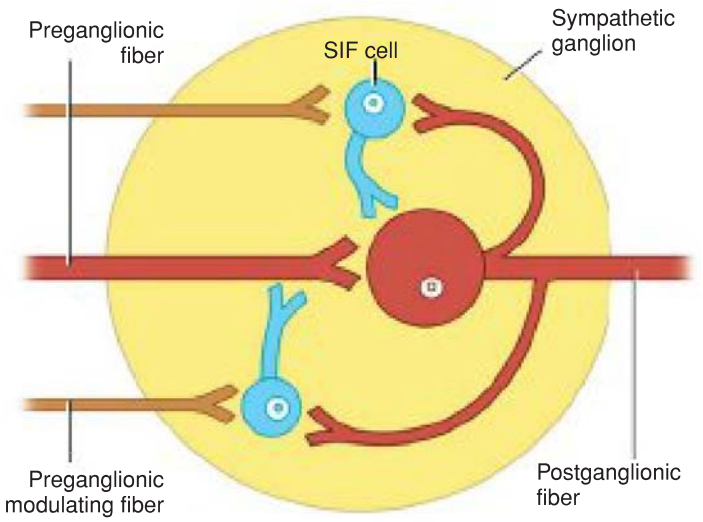
The afferent component of the autonomic system is identical to the afferent component of somatic nerves, and it forms part of the general afferent segment of the entire nervous system. The nerve endings in the autonomic afferent component may not be activated by such sensations as heat or touch but rather by stretch or lack of oxygen. Once the afferent fibers gain entrance to the spinal cord or brain, they are thought to travel alongside, or mixed with, the somatic afferent fibers.

LARGE AUTONOMIC PLEXUSES

Large collections of sympathetic and parasympathetic efferent nerve fibers and their associated ganglia, together with visceral afferent fibers, form **autonomic nerve plexuses** (a collection of nerve fibers that form a network, possibly containing nerve cells) in the thorax, abdomen, and pelvis. Branches from these plexuses innervate the viscera. The thorax contains the cardiac, pulmonary, and esophageal plexuses. In the abdomen, the plexuses are associated with the aorta and its branches, and subdivisions of these autonomic plexuses are named according to the branch of the aorta along which they are lying: celiac, superior mesenteric, inferior mesenteric, and aortic plexuses. The pelvis contains the superior and inferior hypogastric plexuses.

AUTONOMIC GANGLIA

The **autonomic ganglion** (a knotlike mass of nerve cells found outside the CNS) is the site where preganglionic



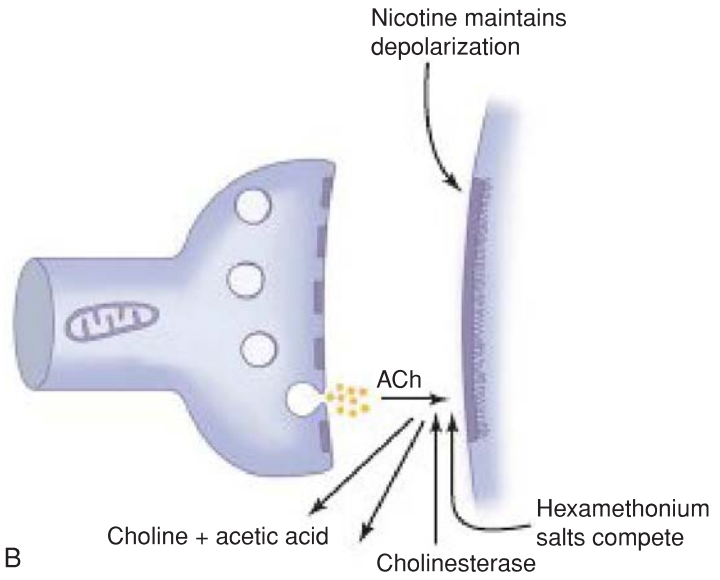


Figure 14-3 **A:** An autonomic ganglion as an integrator. Shows SIF cells. **B:** The liberation of acetylcholine (*ACh*) at an autonomic synapse.

nerve fibers synapse on postganglionic neurons (Fig. 14-3). Note that this term must be distinguished from the ganglion within the CNS consisting of nuclear groups (e.g., basal ganglia). Ganglia are situated along the course of efferent nerve fibers of the ANS. Sympathetic ganglia form part of the sympathetic trunk or are prevertebral in position (e.g., celiac and superior mesenteric ganglia). Parasympathetic ganglia, on the other hand, are situated close to or within the walls of the viscera.

An autonomic ganglion consists of a collection of multipolar neurons together with capsular or satellite cells and a connective tissue capsule. Nerve bundles are attached to each ganglion and consist of preganglionic nerve fibers that enter the ganglion, postganglionic nerve fibers that have arisen from neurons within the ganglion and are leaving the ganglion, and afferent and efferent nerve fibers that pass through the ganglion without synapsing. The preganglionic fibers are myelinated, small, and relatively slow-conducting B fibers. The postganglionic fibers are unmyelinated, smaller, and slower-conducting C fibers.

The structure of synapses in autonomic ganglia shows the characteristic membrane thickening and small clear vesicles as well as some larger granular vesicles. The smaller vesicles contain ACh; the content of the granular vesicles is unknown.

Although an autonomic ganglion is the site where preganglionic fibers synapse on postganglionic neurons, the presence of small interneurons has been recognized. These cells exhibit catecholamine fluorescence and are referred to as **small intensely fluorescent** (**SIF**) cells. In some ganglia, these interneurons receive preganglionic cholinergic fibers and may modulate ganglionic transmission. In other ganglia, they receive collateral branches and may serve some integrative function. Many SIF cells contain **dopamine**, which is thought to be their transmitter.

PREGANGLIONIC TRANSMITTERS

As the preganglionic nerve fibers approach their termination, they wind around and between the dendritic processes of the postganglionic neuron, making multiple synaptic contacts. When the wave of excitation reaches the synaptic contacts, the synaptic transmitter is liberated, crosses the synaptic cleft to reach the receptor, and excites the postganglionic neuron (see Fig. 14-3B).

The synaptic transmitter that excites the postganglionic neurons in both sympathetic and parasympathetic ganglia is **ACh** (Fig. 14-4). The action of ACh in autonomic ganglia is quickly terminated by hydrolysis by **acetylcholinesterase** (**AChE**).

Acetylcholine Receptors

ACh receptors are located on the outside of the cell membrane of postganglionic neurons. They are protein complexes that are bound to protein molecules that penetrate the cell membrane. Once the ACh molecule binds with the receptor, the structure of the protein molecule of the cell membrane changes and excitation or inhibition of the postganglionic neuron takes place. Two types of ACh receptors exist and are known as **nicotinic** and **muscarinic** receptors. These receptors are so named because nicotinic receptors respond specifically to nicotine (from tobacco), and muscarinic receptors respond specifically to muscarine (poison from toadstools). ACh is capable of binding to both of these receptors.

In both sympathetic and parasympathetic preganglionic neurons, the release of ACh binds predominantly with the nicotinic receptors on the postganglionic neurons.

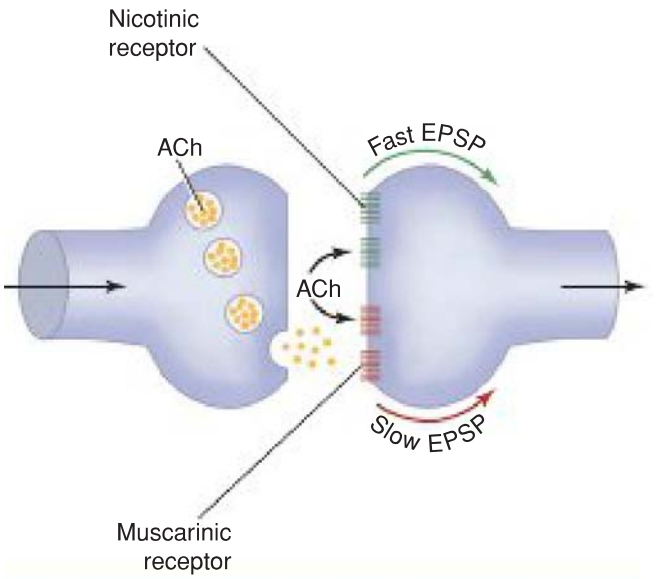


Figure 14-4 Example of the release of acetylcholine from a presynaptic terminal. A single presynaptic stimulus evokes a fast excitatory postsynaptic potential (*fast **EPSP***) at a nicotinic receptor. Further stimulation may lead to a slow excitatory postsynaptic potential (*slow **EPSP***) or a slow inhibitory postsynaptic potential (*slow **IPSP***) at a muscarinic receptor. In preganglionic neurons, both sympathetic and parasympathetic, the release of acetylcholine binds predominantly with the nicotinic receptors on the postganglionic neurons.

FAST, SLOW, AND INHIBITORY SYNAPTIC POTENTIALS

ACh activation of the postsynaptic nicotinic receptors on the dendrites and cell bodies of the postganglionic neurons results in a depolarization of the membrane, an influx of Na^+ and Ca^{2+} ions, and the generation of the fast excitatory postsynaptic potential (fast **EPSP**). Usually, several presynaptic axon terminals must fire simultaneously and summation has to occur for transmission along the postsynaptic axon to take place. The fast EPSP reaches a maximum within about 15 msec.

ACh is also believed to activate small numbers of postsynaptic muscarinic receptors. This results in the development of the slow excitatory postsynaptic potential (slow **EPSP**), which lasts for 2 to 5 seconds. The underlying mechanism is complicated, and the slow potential occurs when the Na^+ and Ca^{2+} channels are open and M-type K^+ channels close; this leads to membrane depolarization. Late slow **EPSP** lasting as long as 1 to 2 minutes can also be produced by neuropeptide transmitters.

The activation of postsynaptic muscarinic receptors may also result in the development of the slow inhibitory postsynaptic potential (slow **IPSP**), which lasts about 10 seconds. The IPSP results from the opening of K^+ channels, permitting K^+ ions to flow out into the synaptic space, producing hyperpolarization.

The existence of these complex postsynaptic potentials in both sympathetic and parasympathetic ganglia (see Fig. 14-4) illustrates how the postsynaptic membrane potential can be altered and ganglionic transmission modulated.

GANGLION-STIMULATING AGENTS

Stimulating drugs, such as nicotine, lobeline, and dimethylphenylpiperazinium, stimulate sympathetic and parasympathetic ganglia by activating the nicotinic receptors on the postsynaptic membrane and producing a fast EPSP.

GANGLION-BLOCKING AGENTS

The two types of ganglion-blocking agents are depolarizing and nonpolarizing. **Nicotine** in high concentrations acts as a blocking agent by first stimulating the postganglionic neuron and causing depolarization and then by maintaining depolarization of the excitable membrane. During this latter phase, the postganglionic

neuron will fail to respond to the administration of any stimulant, regardless of the type of receptor it activates.

Hexamethonium and **tetraethylammonium** block ganglia by competing with ACh at the nicotinic receptor sites.

POSTGANGLIONIC NERVE ENDINGS

The postganglionic fibers terminate on the effector cells without special discrete endings. The axons run between the gland cells and the smooth and cardiac muscle fibers and lose their covering of Schwann cells. At sites where transmission occurs, clusters of vesicles are present within the axoplasm (see Fig. 3-35). The site on the axon may lie at some distance from the effector cell; thus, the transmission time may be slow at these endings. The diffusion of the transmitter through the large extracellular distance also permits a given nerve to have an action on a large number of effector cells.

POSTGANGLIONIC TRANSMITTERS

Parasympathetic postganglionic nerve endings liberate **ACh** as their transmitter substance (Fig. 14-5). All neurons that release ACh at their endings are called **cholinergic** (work like ACh). The ACh traverses the synaptic cleft and binds reversibly with the cholinergic (**muscarinic**) receptor on the postsynaptic membrane. Within 2 to 3 msec, ACh is hydrolyzed into acetic acid and choline by the enzyme **AChE**, which is located on the surface of the nerve and receptor membranes. The choline is reabsorbed into the nerve ending and used again for synthesis of ACh.

Most sympathetic postganglionic nerve endings liberate **norepinephrine** as their transmitter substance. In addition, some sympathetic postganglionic nerve endings, particularly those that end on cells of sweat glands and the blood vessels in skeletal muscle, release **ACh**, which binds with muscarinic receptors on the postsynaptic membrane.

Sympathetic endings that use norepinephrine are called **adrenergic endings**. The two major kinds of receptors in the effector organs are called α and β **receptors**.

Two subgroups of α receptors (α_1 and α_2 receptors) and two subgroups of β receptors (β_1 and β_2 receptors) have been described. Norepinephrine has a greater effect on α receptors than on β receptors. **Phenylephrine** is a pure α stimulator. The bronchodilating drugs, such as **metaproterenol** and **albuterol**, mainly act on β_2 receptors. As a general rule, α receptor sites are associated with most of the excitatory functions of the sympathetic system (e.g., smooth muscle contraction, vasoconstriction, diaphoresis), whereas the β receptor sites are associated with most of the inhibitory functions (e.g., smooth muscle relaxation). β_2 Receptors are mainly in the lung, and stimulation results in

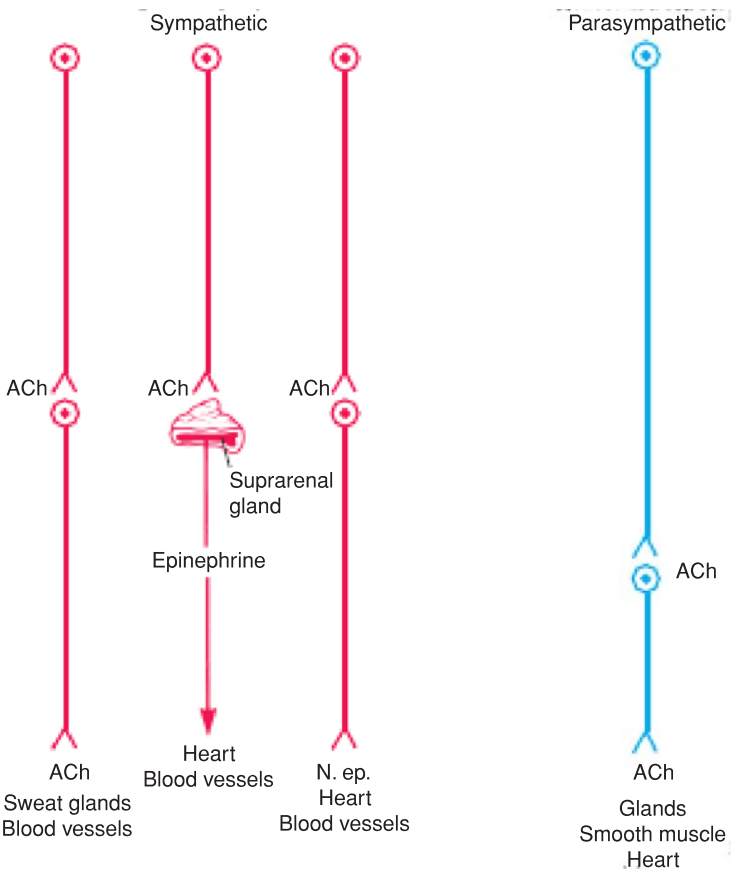


Figure 14-5 Efferent parts of the autonomic nervous system and the chemical transmitter substances released at the nerve endings. (ACh, acetylcholine; N. ep., norepinephrine.)

bronchodilation. β_1 Receptors are in the myocardium, where they are associated with excitation.

The action of norepinephrine on the receptor site of the effector cell is terminated by reuptake into the nerve terminal, where it is stored in presynaptic vesicles for reuse. Some of the norepinephrine escapes from the synaptic cleft into the general circulation and is subsequently metabolized in the liver.

OTHER POSTGANGLIONIC TRANSMITTERS

Sympathetic and parasympathetic postganglionic neurons have been shown to liberate substances other than ACh or norepinephrine at their endings; these include adenosine triphosphate (ATP), neuropeptide **Y**, and substance **P**. These substances may be released alone or from neurons that release ACh or norepinephrine; they have their own specific receptors. The function of these transmitters is probably to modulate the effects of the primary transmitter.

CHOLINERGIC RECEPTOR BLOCKADE

In the case of the parasympathetic and the sympathetic postganglionic nerve endings that liberate ACh as the transmitter substance, the receptors on the effector cells are **muscarinic**. This means that the action can be blocked by **atropine**. Atropine competitively antagonizes the muscarinic action by occupying the cholinergic receptor sites on the effector cells.

ADRENERGIC RECEPTOR BLOCKADE

The α-adrenergic receptors can be blocked by agents such as **phenoxybenzamine**, and the β-adrenergic receptors can be blocked by agents such as **propranolol**. The synthesis and storage of norepinephrine at sympathetic endings can be inhibited by **reserpine**.

HIGHER CONTROL

The hypothalamus has a controlling influence on the ANS and appears to integrate the autonomic and neuroendocrine systems, thus preserving body homeostasis (Fig. 14-6). Essentially, the hypothalamus should be regarded as a higher nervous center for the control of lower autonomic centers in the brainstem and spinal cord.

Stimulation of the anterior region of the hypothalamus can influence parasympathetic responses, whereas stimulation of the posterior part of the hypothalamus gives rise to sympathetic responses. In addition, lower brainstem centers such as **vasopressor**, **vasodilator**, **cardioaccelerator**, **cardiodecelerator**, and **respiratory centers** have been found in the reticular formation as the result of experimental stimulation in more primitive animals. The various levels of control are believed to be exerted as the result of interconnections of the different regions by ascending and descending pathways. The neurons of the thoracolumbar outflow of the sympathetic part of the system and the neurons of the craniosacral outflow of the parasympathetic part of the system receive their control through the descending tracts of the reticular formation.

Stimulation of different parts of the cerebral cortex and the limbic system produces autonomic effects, and this is presumably brought about through the hypothalamus. The ANS can be brought under voluntary control to some extent. This is seen, for example, in young individuals who may blush easily when embarrassed. As they mature, they are usually able to consciously train themselves to control this response. Also note that the higher centers of the brain can abnormally influence the activities of the ANS and induce diseases such as cardiac palpitations (arrhythmias) and even myocardial infarction.

ENTERIC NERVOUS SYSTEM

Two important plexuses of nerve cells and fibers extend continuously along and around the length of the gastrointestinal tract from the esophagus to the anal canal. The submucous or Meissner plexus lies between the mucous membrane and the circular muscle layer, and the myenteric or Auerbach plexus lies between the circular and longitudinal muscle layers. The submucous plexus is mainly concerned with the control of the glands of the mucous membrane, whereas the myenteric plexus controls the muscle and movements of the gut wall.

Different types of neurons have been recognized in the plexuses. Some neurons are bipolar or unipolar and are thought to be sensory and involved in local reflex activity; other neurons send axons to the celiac

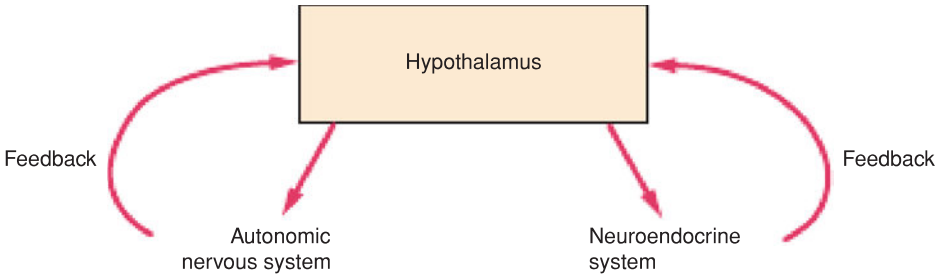


Figure 14-6 Hypothalamus as the control center for the autonomic nervous system and the neuroendocrine system.

and mesenteric plexuses. Preganglionic parasympathetic fibers synapse on nerve cells that give rise to postganglionic fibers that innervate the smooth muscle and glands. Postganglionic sympathetic fibers have been seen to terminate on parasympathetic nerve cells and probably exert an inhibitory role in parasympathetic activity. Internuncial neurons are also present. Interestingly, the nerve cells and their processes are surrounded by neuroglialike cells that closely resemble astrocytes in the CNS. It has been suggested that while the enteric plexuses can coordinate the activities of the gut wall, the parasympathetic and sympathetic inputs modulate these activities.

FUNCTIONS

The ANS, along with the endocrine system, maintains body homeostasis. The endocrine control is slower and exerts its influence by means of blood-borne hormones.

The ANS functions for the most part at the subconscious level. We are not aware, for example, that our pupils are dilating or that our arteries are constricting. The system should not be regarded as an isolated portion of the nervous system; it can play a role with somatic activity in expressing emotion and certain autonomic activities, such as micturition, can be brought under voluntary control. The various activities of the autonomic and endocrine systems are integrated within the hypothalamus.

The sympathetic and parasympathetic components of the ANS cooperate in maintaining the stability of the internal environment. The sympathetic part prepares and mobilizes the body in an emergency when sudden severe exercise, fear, or rage occurs. The parasympathetic part aims at conserving and storing energy, for example, in the promotion of digestion and the absorption of food by increasing the secretions of the glands of the gastrointestinal tract and stimulating peristalsis.

The sympathetic and parasympathetic parts of the ANS usually have antagonistic control over a viscus. For example, the sympathetic activity will increase the heart rate, whereas the parasympathetic activity will slow the heart rate. The sympathetic activity will make the bronchial smooth muscle relax, but the muscle is contracted by parasympathetic activity.

However, many viscera do not possess this fine dual control from the ANS. For example, the smooth muscle of the hair follicles (the arrector pili muscle) is made to contract by the sympathetic activity without parasympathetic control.

The activities of some viscera are kept under a constant state of inhibition by one or the other components of the ANS. The heart in a trained athlete is maintained at a slow rate by the activities of the parasympathetic system. This is of considerable importance because the heart is a more efficient pump when contracting slowly than when contracting very quickly, thus permitting adequate diastolic filling of the ventricles.

DIFFERENCES BETWEEN SYMPATHETIC AND PARASYMPATHETIC SYSTEMS

Important anatomic, physiologic, and pharmacologic differences between the sympathetic and parasympathetic parts of the ANS are shown in Table 14-1.

1. The sympathetic efferent nerve fibers originate (see Fig. 14-2) from nerve cells in the lateral gray column of the spinal cord between the first thoracic and second lumbar segments (the **thoracic outflow**). The parasympathetic efferent nerve fibers originate from nerve cells in the 3rd, 7th, 9th, and 10th cranial nerves and in the gray matter of the 2nd, 3rd, and 4th sacral segments of the cord (the **craniosacral outflow**).
2. The sympathetic ganglia are located either in the paravertebral sympathetic trunks or in the prevertebral ganglia, such as the celiac ganglion. The parasympathetic ganglion cells are located as small ganglia close to the viscera or within plexuses within the viscera.
3. The sympathetic part of the autonomic system has long postganglionic fibers, whereas the parasympathetic system has short fibers (see Fig. 14-5).
4. The sympathetic part of the system has a widespread action on the body as the result of the preganglionic fibers synapsing on many postganglionic neurons and the suprarenal medulla releasing the sympathetic transmitters epinephrine and norepinephrine, which are distributed throughout the body through the bloodstream. The parasympathetic part of the autonomic system has a more discrete control, since the preganglionic fibers synapse on only a few postganglionic neurons with no comparable organ to the suprarenal medulla.
5. The sympathetic postganglionic endings liberate norepinephrine at most endings and ACh at a few endings (e.g., sweat glands). The parasympathetic postganglionic endings liberate ACh.
6. The sympathetic part of the autonomic system prepares the body for emergencies and severe muscular activity, whereas the parasympathetic part conserves and stores energy.

To assist with the learning of the different actions of these two components of the autonomic system, imagine that sympathetic activity would be maximal in a man who finds himself suddenly alone in a field with a bull that is about to charge. His hair will stand on end with fear; his skin will be pale as the result of vasoconstriction, which causes a redistribution of blood away from the skin and viscera to the heart muscle and skeletal muscle. His upper eyelids will be raised and his pupils will be widely dilated so that he can see where to run. His heart rate will rise and the peripheral resistance of the arterioles will be increased, causing a rise in blood pressure. His bronchi will dilate to permit maximum respiratory flow of air. His peristaltic activity will be inhibited and his gut sphincters will be contracted. His vesical sphincter will also be contracted (this is certainly not the time to be thinking of defecation or

Table 14-1 Anatomic, Physiologic, and Pharmacologic Characteristics of Sympathetic Versus Parasympathetic Systems

	Sympathetic	Parasympathetic
Action	Prepares body for emergency	Conserves and restores energy
Outflow	T1–L2 (3)	Cranial nerves III, VII, IX, and X; S2–S4
Preganglionic fibers	Myelinated	Myelinated
Ganglia	Paravertebral (sympathetic trunks), prevertebral (e.g., celiac, superior mesenteric, inferior mesenteric)	Small ganglia close to viscera (e.g., otic, ciliary) or ganglion cells in plexuses (e.g., cardiac, pulmonary)
Neurotransmitter within ganglia	Acetylcholine	Acetylcholine
Ganglion-blocking agents	Hexamethonium and tetraethylammonium by competing with acetylcholine	Hexamethonium and tetraethylammonium by competing with acetylcholine
Postganglionic fibers	Long, nonmyelinated	Short, nonmyelinated
Characteristic activity	Widespread due to many postganglionic fibers and liberation of epinephrine and norepinephrine from suprarenal medulla	Discrete action with few postganglionic fibers
Neurotransmitter at postganglionic endings	Norepinephrine at most endings and acetylcholine at few endings (sweat glands)	Acetylcholine at all endings
Blocking agents on receptors of effector cells	α-Adrenergic receptors—phenoxybenzamine β-Adrenergic receptors—propranolol	Atropine, scopolamine
Agents inhibiting synthesis and storage of neurotransmitter at postganglionic endings	Reserpine	
Agents inhibiting hydrolysis of neurotransmitter at site of effector cells		Acetylcholinesterase blockers (e.g., neostigmine)
Drugs mimicking autonomic activity	Sympathomimetic drugs Phenylephrine: α receptors; Isoproterenol: β receptors	Parasympathomimetic drugs Pilocarpine Methacholine
Higher control	Hypothalamus	Hypothalamus

micturition). Glycogen will be converted into glucose for energy and he will sweat to lose body heat.

On the other hand, the parasympathetic activity will be great in a woman who has fallen asleep in an armchair after a satisfying meal. Her heart rate will be slow and her blood pressure will not be high. Her upper eyelids will droop or be closed and her pupils will be constricted. Her breathing will be noisy owing to bronchial constriction. Her abdomen may rumble owing to excessive peristaltic activity. She may feel the inclination to defecate or micturate.

AUTONOMIC INNERVATIONS

Some important ANS innervations are shown in Table 14-2.

Eye

Both sympathetic and parasympathetic nervous systems control involuntary function in the iris and lacrimal glands, whereas the eyelids are only affected by the sympathetic nervous system.

Upper Lid

The upper lid is raised by the levator palpebrae superioris muscle. The major part of this muscle is formed by skeletal muscle innervated by the oculomotor nerve. A small part is composed of smooth muscle fibers innervated by sympathetic postganglionic fibers from the superior cervical sympathetic ganglion (Fig. 14-7).

Iris

The smooth muscle fibers of the iris consist of circular and radiating fibers. The circular fibers form the sphincter pupillae and the radial fibers form the dilator pupillae.

The sphincter pupillae is supplied by parasympathetic fibers from the parasympathetic nucleus (Edinger–Westphal nucleus) of the oculomotor nerve.

Table 14-2 Autonomic Nervous System Effects on Body Organs

Organ		Sympathetic Action	Parasympathetic Action
Eye	Pupil	Dilates	Constricts
	Ciliary muscle	Relaxes	Contracts
Glands	Lacrimal, parotid, submandibular, sublingual, nasal	Reduce secretion by causing vasoconstriction of blood vessels	Increase secretion
	Sweat	Increases secretion	
Heart	Cardiac muscle	Increases force of contraction	Decreases force of contraction
	Coronary arteries (mainly controlled by local metabolic factors)	Dilates (β receptors), constricts (α receptors)	
Lung	Bronchial muscle	Relaxes (dilates bronchi)	Contracts (constricts bronchi)
	Bronchial secretion		Increases secretion
	Bronchial arteries	Constricts	Dilates
Gastrointestinal tract	Muscle in walls	Decreases peristalsis	Increases peristalsis
	Muscle in sphincters	Contracts	Relaxes
	Glands	Reduces secretion by vasoconstriction of blood vessels	Increases secretion
Liver		Breaks down glycogen into glucose	
Gallbladder		Relaxes	Contracts
Kidney		Decreases output due to constriction of arteries	
Urinary bladder	Bladder wall (detrusor)	Relaxes	Contracts
	Sphincter vesicae	Contracts	Relaxes
Erectile tissue of penis and clitoris			Relaxes, causes erection
Ejaculation		Contracts smooth muscle of vas deferens, seminal vesicles, and prostate	
Systemic arteries			
Skin		Constrict	
Abdominal		Constrict	
Muscle		Constrict (α receptors), dilate (β receptors), dilate (cholinergic)	
rector pili muscle		Contract	
prarenal			
Cortex		Stimulates	
Medulla		Liberates epinephrine and norepinephrine	

After synapsing in the **ciliary ganglion,** the postganglionic fibers pass forward to the eyeball in the **short ciliary nerves**. (The ciliary muscle of the eye is also supplied by the short ciliary nerves; see p. 406.)

The dilator pupillae is supplied by postganglionic fibers from the superior cervical sympathetic ganglion. The postganglionic fibers reach the orbit along the internal carotid and ophthalmic arteries. They pass uninterrupted through the ciliary ganglion and reach the eyeball in the **short ciliary nerves**. Other sympathetic fibers reach the eyeball in the **long ciliary nerves**.

Lacrimal Gland

The parasympathetic secretomotor nerve supply to the lacrimal gland originates in the **lacrimatory nucleus**

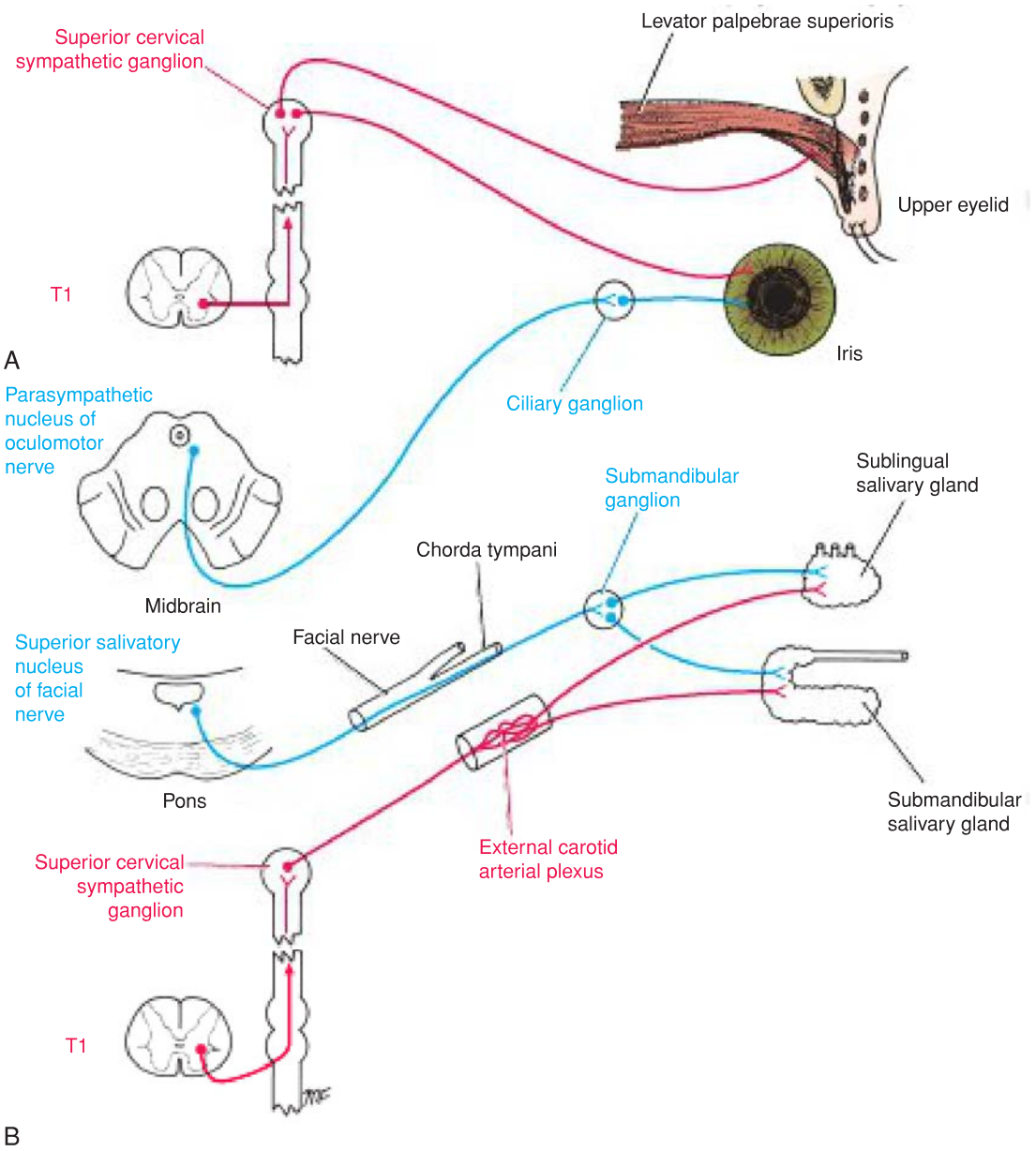


Figure 14-7 Autonomic innervation of the upper eyelid and iris (**A**) and the sublingual and submandibular salivary glands (**B**).

of the facial nerve (Fig. 14-8). The preganglionic fibers reach the **pterygopalatine ganglion** through the **nervus** intermedius and its **great petrosal branch** and through the **nerve of the pterygoid canal**. The postganglionic fibers leave the ganglion and join the maxillary nerve. They then pass into its **zygomatic branch** and the **zygomaticotemporal nerve.** They reach the lacrimal gland within the **lacrimal nerve**.

The sympathetic postganglionic fibers arise from the superior cervical sympathetic ganglion and travel in the plexus of nerves around the internal carotid artery. They join the **deep petrosal nerve,** the **nerve of the pterygoid canal**, the **maxillary nerve**, the **zygomatic nerve**, **zygomaticotemporal nerve**, and finally the lacrimal nerve. They function as vasoconstrictor fibers.

Salivary Glands

The involuntary action of the salivary glands is controlled by the ANS. These three, paired glands have similar sympathetic nerve origination but have unique parasympathetic origins.

Submandibular and Sublingual Glands

The parasympathetic secretomotor supply originates in the **superior salivatory nucleus** of the facial nerve (see Fig. 14-7). The preganglionic fibers pass to the **submandibular ganglion** and other small ganglia close to the duct through the **chorda tympani nerve** and the **lingual nerve**. Postganglionic fibers reach the submandibular gland either directly or along the duct. Postganglionic

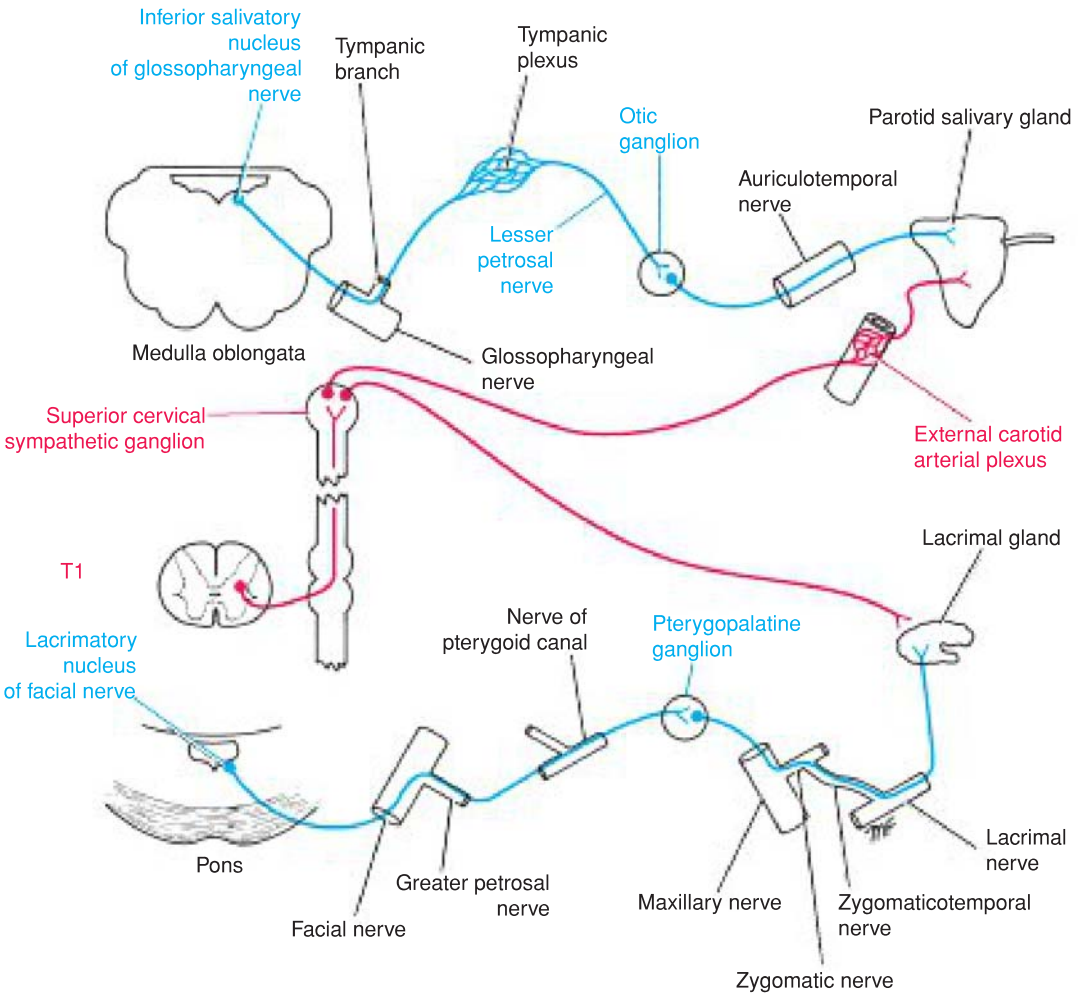


Figure 14-8 Autonomic innervation of the parotid salivary gland and lacrimal gland.

fibers to the sublingual gland travel through the lingual nerve.

Sympathetic postganglionic fibers arise from the superior cervical sympathetic ganglion and reach the glands as a plexus of nerves around the external carotid, facial, and lingual arteries. They function as vasoconstrictor fibers.

Parotid Gland

Parasympathetic secretomotor fibers from the **inferior salivatory nucleus** of the glossopharyngeal nerve supply the gland (see Fig. 14-8). The preganglionic nerve fibers pass to the otic ganglion through the **tympanic branch of the glossopharyngeal nerve** and the **lesser petrosal nerve**. Postganglionic fibers reach the gland through the auriculotemporal nerve.

Sympathetic postganglionic fibers arise from the superior cervical sympathetic ganglion and reach the gland as a plexus of nerves around the external carotid artery. They function as vasoconstrictor fibers.

Heart

The sympathetic postganglionic fibers arise from the cervical and upper thoracic portions of the sympathetic trunks (Fig. 14-9). Postganglionic fibers reach the heart by way of the **superior**, **middle**, and **inferior cardiac branches** of the cervical portion of the sympathetic trunk and a number of **cardiac branches** from the thoracic portion of the sympathetic trunk. The fibers pass through the **cardiac plexuses** and terminate on the **sinoatrial** and **atrioventricular nodes**, on cardiac muscle fibers, and on coronary arteries. Activation of these nerves results in cardiac acceleration, increased force of contraction of the cardiac muscle, and dilatation of the coronary arteries. The coronary dilatation is mainly produced in response to local metabolic needs rather than by direct nerve stimulation of the coronary arteries.

The parasympathetic preganglionic fibers originate in the **dorsal nucleus of the vagus nerve** and descend into the thorax in the vagus nerves. The fibers terminate by synapsing with postganglionic neurons in the **cardiac plexuses**. Postganglionic fibers terminate on the **sinoatrial** and **atrioventricular nodes** and on the coronary arteries. Activation of these nerves results in a reduction in the rate and force of contraction of the myocardium and a constriction of the coronary arteries. Here again, the coronary constriction is mainly produced by the reduction in local metabolic needs rather than by neural effects.

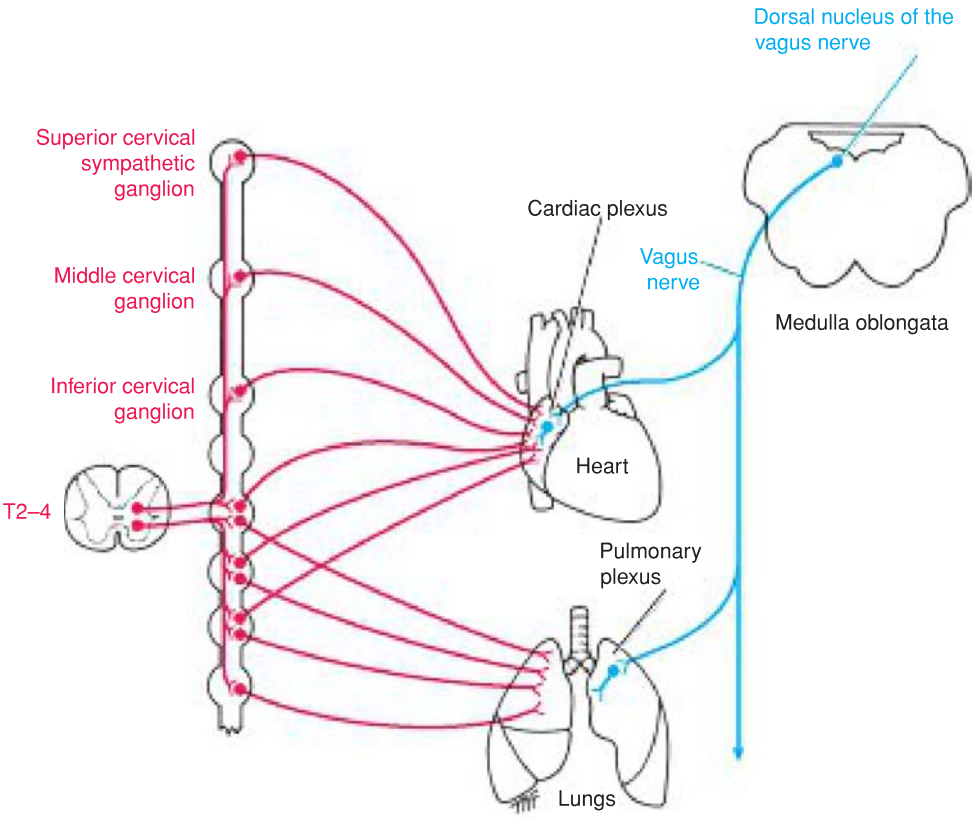


Figure 14-9 Autonomic innervation of the heart and lungs.

Lungs

The sympathetic postganglionic fibers arise from the second to the fifth thoracic ganglia of the sympathetic trunk (see Fig. 14-9). The fibers pass through the pulmonary plexuses and enter the lung, where they form networks around the bronchi and blood vessels. The sympathetic fibers produce bronchodilation and slight vasoconstriction.

The parasympathetic preganglionic fibers arise from the **dorsal nucleus of the vagus** and descend to the thorax within the vagus nerves. The fibers terminate by synapsing with postganglionic neurons in the pulmonary plexuses. The postganglionic fibers enter the lung, where they form networks around the bronchi and blood vessels. The parasympathetic fibers produce bronchoconstriction and slight vasodilation and increase glandular secretion.

Gastrointestinal Tract

Stomach and Intestine (to Splenic Flexure)

Preganglionic parasympathetic fibers enter the abdomen in the **anterior** (**left**) and **posterior** (**right**) **vagal trunks** (Fig. 14-10). The fibers are distributed to many abdominal viscera and to the gastrointestinal tract from the stomach to the splenic flexure of the colon. The fibers that pass to the gastrointestinal tract terminate on postganglionic neurons in the **myenteric** (**Auerbach**) and **submucosal** (**Meissner**) **plexuses**. The postganglionic fibers supply the smooth muscle and glands. The parasympathetic nerves stimulate peristalsis and relax the sphincters; they also stimulate secretion.

Sympathetic preganglionic nerve fibers pass through the thoracic part of the sympathetic trunk and enter the **greater** and **lesser splanchnic nerves**. These descend into the abdomen and synapse with postganglionic neurons in the **celiac** and **superior mesenteric ganglia**. The postganglionic nerve fibers are distributed to the stomach and intestine as nerve plexuses around the branches of the celiac and superior mesenteric arteries. The sympathetic nerves inhibit peristalsis and cause contraction of the sphincters; they also inhibit secretion (see the enteric nervous system, p. 394).

Descending Colon, Pelvic Colon, and Rectum

The preganglionic parasympathetic fibers originate in the gray matter of the spinal cord from the second to the fourth sacral segments (see Fig. 14-10). The fibers pass through the **pelvic splanchnic nerves** and the nerve plexuses around the branches of the inferior mesenteric artery. They terminate on postganglionic neurons in the myenteric (Auerbach) and submucosal (Meissner) plexuses. The postganglionic fibers supply the smooth muscle and glands. The parasympathetic nerves stimulate peristalsis and secretion.

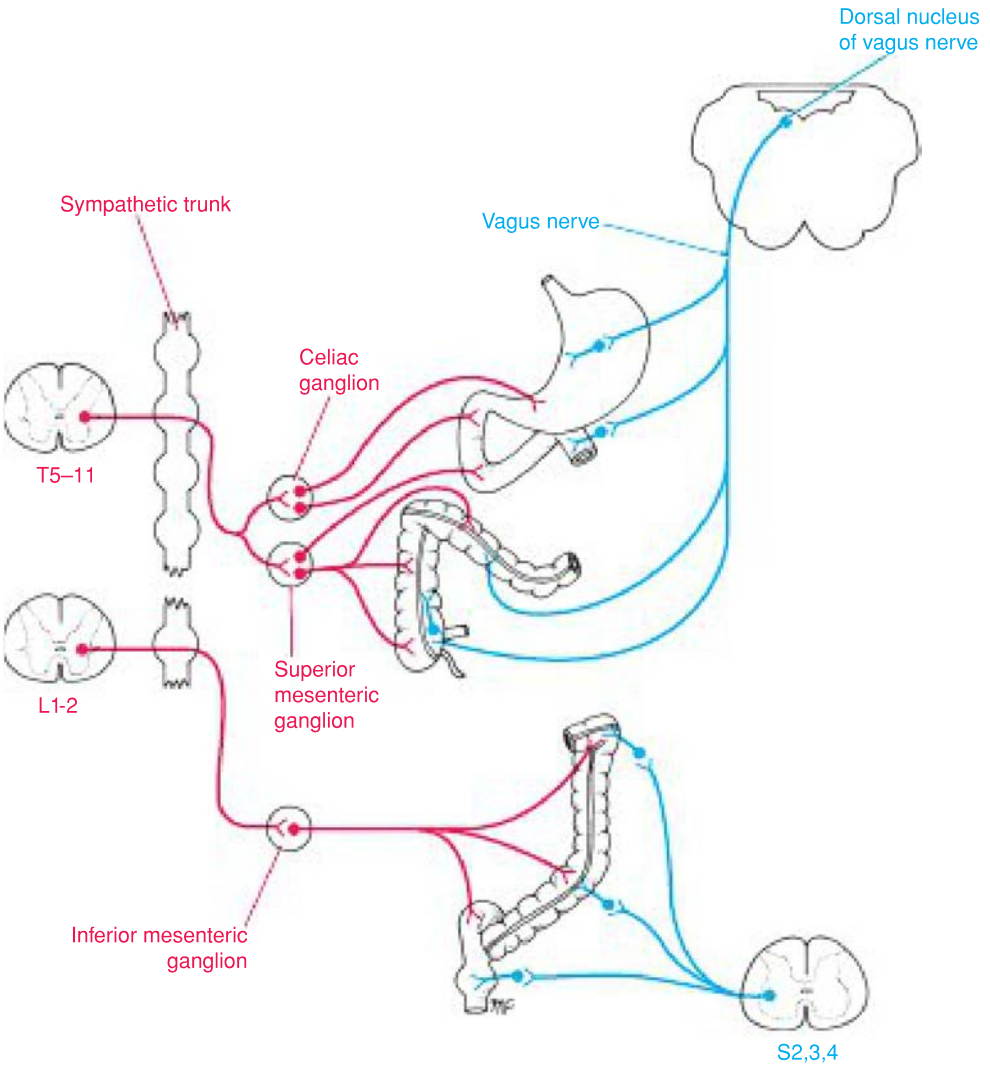


Figure 14-10 Autonomic innervation of the gastrointestinal tract.

The sympathetic preganglionic nerve fibers pass through the lumbar part of the sympathetic trunk and synapse with postganglionic neurons in the **inferior mesenteric plexus**. Postganglionic fibers are distributed to the bowel as nerve plexuses around the branches of the inferior mesenteric arteries. The sympathetic nerves inhibit peristalsis and secretion.

Gallbladder and Biliary Ducts

The gallbladder and biliary ducts receive postganglionic parasympathetic and sympathetic fibers from the hepatic plexus. Parasympathetic fibers derived from the vagus are thought to be motor fibers to the smooth muscle of the gallbladder and bile ducts and inhibitory to the sphincter of Oddi.

Autonomic afferent fibers are also present. Some of the fibers are believed to leave the hepatic plexus and join the right phrenic nerve, thus partially explaining the phenomenon of referred shoulder pain in the presence of gallbladder disease (see p. 410).

Kidney

Preganglionic sympathetic fibers pass through the lower thoracic part of the sympathetic trunk and the lowest thoracic splanchnic nerve to join the **renal plexus** around the renal artery (Fig. 14-11). The preganglionic fibers synapse with postganglionic neurons in the renal plexus. The postganglionic fibers are distributed to the branches of the renal artery. The sympathetic nerves are vasoconstrictor in action to the renal arteries within the kidney.

Preganglionic parasympathetic fibers enter the renal plexus from the vagus. Here, they synapse with postganglionic neurons whose fibers are distributed to the kidney along the branches of the renal artery. The parasympathetic nerves are thought to be vasodilator in action.

Suprarenal Gland Medulla

Preganglionic sympathetic fibers descend to the gland in the **greater splanchnic nerve**, a branch of the thoracic

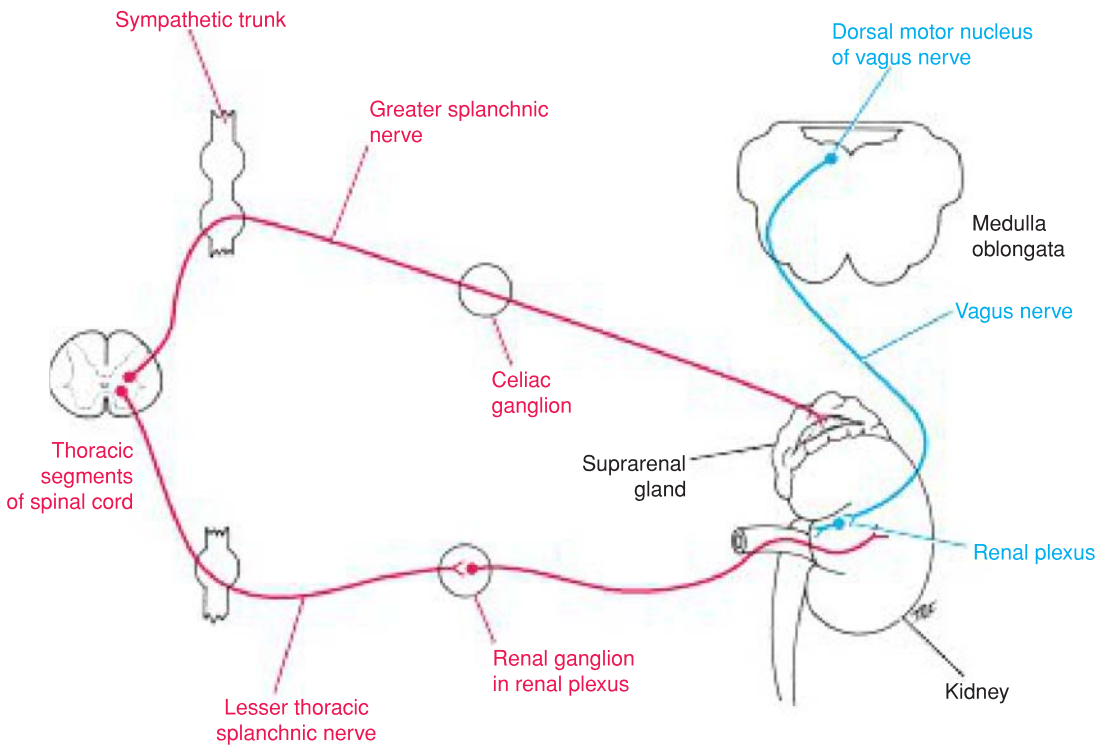


Figure 14-11 Autonomic innervation of the kidney and suprarenal gland.

part of the sympathetic trunk (see Fig. 14-11). The nerve fibers terminate on the secretory cells of the medulla, which are comparable to postganglionic neurons. ACh is the transmitter substance between the nerve endings and the secretory cells, as at any other preganglionic endings. The sympathetic nerves stimulate the secretory cells of the medulla to increase the output of epinephrine and norepinephrine. The medulla of the suprarenal gland lacks parasympathetic innervation.

Anal Canal Involuntary Internal Sphincter

The circular smooth muscle coat is thickened at the upper end of the anal canal to form the involuntary internal sphincter. The sphincter is innervated by postganglionic sympathetic fibers from the **hypogastric plexuses** (Fig. 14-12). Each hypogastric plexus receives sympathetic fibers from the **aortic plexus** and from the lumbar and pelvic parts of the sympathetic trunks. The sympathetic nerves cause the internal anal sphincter to contract.

Urinary Bladder

The muscular coat of the bladder is composed of smooth muscle, which at the bladder neck is thickened to form the **sphincter vesicae**. The nerve supply of the smooth muscle is from the hypogastric plexuses (see Fig. 14-12). The sympathetic postganglionic fibers originate in the first and second lumbar ganglia of the sympathetic trunk and travel to the hypogastric plexuses. The parasympathetic preganglionic fibers arise as the pelvic splanchnic nerves from the second, third, and fourth sacral nerves; they pass through the hypogastric plexuses to reach the bladder wall, where they synapse with postganglionic neurons.

The sympathetic nerves to the detrusor muscle have little or no action on the smooth muscle of the bladder wall and are distributed mainly to the blood vessels. The sympathetic nerves to the sphincter vesicae play only a minor role in causing contraction of the sphincter in maintaining urinary continence. However, in the male, the sympathetic innervation of the sphincter causes active contraction of the bladder neck during ejaculation (brought about by sympathetic action), thus preventing seminal fluid from entering the bladder. The parasympathetic nerves stimulate the contraction of the smooth muscle of the bladder wall and, in some way, inhibit the contraction of the sphincter vesicae.

Penile and Clitoral Erection

In erection, the genital **erectile tissue** becomes engorged with blood. The initial vascular engorgement is controlled by the parasympathetic part of the ANS. The parasympathetic preganglionic fibers originate in the gray matter of the second, third, and fourth sacral segments of the spinal cord (Fig. 14-13). The fibers enter the hypogastric plexuses and synapse on the postganglionic neurons. The postganglionic fibers join the internal pudendal arteries and are distributed along their branches, which enter the erectile tissue. The parasympathetic nerves

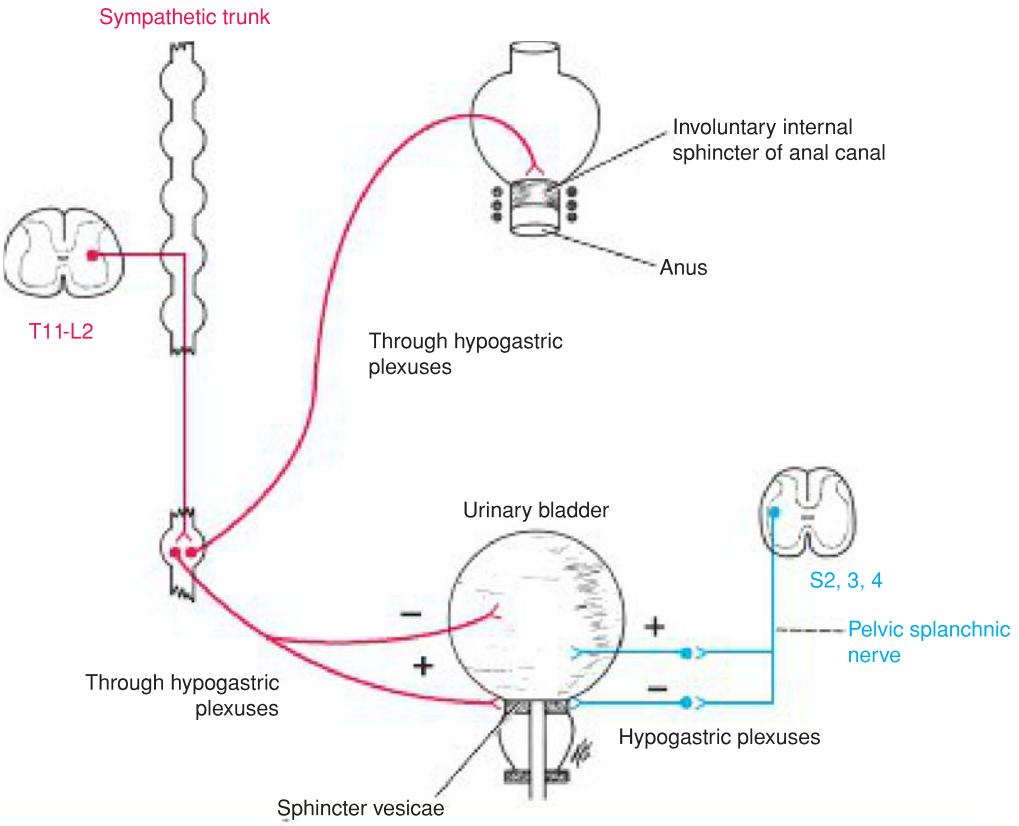


Figure 14-12 Autonomic innervation of the sphincters of the anal canal and urinary bladder.

cause vasodilatation of the arteries and greatly increase the blood flow to the erectile tissue.

Ejaculation

During the increasing sexual excitement that occurs during sex play, the external urinary meatus of the glans penis becomes moist as a result of the secretions of the bulbourethral glands. Friction on the glans penis, reinforced by other afferent nervous impulses, results in a discharge along the sympathetic nerve fibers to the smooth muscle of the duct of the epididymis and the vas deferens on each side, the seminal vesicles, and the prostate. The smooth muscle contracts and the spermatozoa, together with the secretions of the seminal vesicles and prostate, are discharged into the prostatic urethra. The fluid now joins the secretions of the bulbourethral glands and penile urethral glands and is then ejected from the penile urethra as a result of the rhythmic contractions of the bulbospongiosus muscles, which compress the urethra. Meanwhile, the sphincter of the bladder contracts and prevents a reflux of the spermatozoa into the bladder. The spermatozoa and the secretions of the several accessory glands constitute the **seminal fluid**, or **semen**. At the climax of male sexual excitement, a mass discharge of nervous impulses takes place in the CNS. Impulses pass down the spinal cord to the sympathetic outflow (T1–L2). The nervous impulses that pass to the genital organs are thought to leave the cord at the first and second lumbar segments in the preganglionic sympathetic fibers (see Fig. 14-13). Many of these fibers synapse with postganglionic neurons in the first and second lumbar ganglia. Other fibers may synapse in ganglia in the lower lumbar or pelvic parts of the sympathetic trunks. The postganglionic fibers are then distributed to the **vas deferens**, the **seminal vesicles**, and the **prostate** through the **hypogastric plexuses**. The sympathetic nerves stimulate the contractions of the smooth muscle in the walls of these structures and cause the spermatozoa, together with the secretions of the seminal vesicles and prostate, to be discharged into the urethra.

Uterus

Preganglionic sympathetic nerve fibers leave the spinal cord at segmental levels T12 and L1 and are believed to synapse with ganglion cells in the sympathetic trunk or possibly in the inferior hypogastric plexuses (Fig. 14-14). The postganglionic fibers supply the smooth muscle of the uterus. Parasympathetic preganglionic fibers leave the spinal cord at levels S2–S4 and synapse with ganglion cells in the inferior hypogastric plexuses. Although the uterine muscle is largely under hormonal control, sympathetic innervation may cause uterine contraction and vasoconstriction, whereas parasympathetic fibers have the opposite effect.

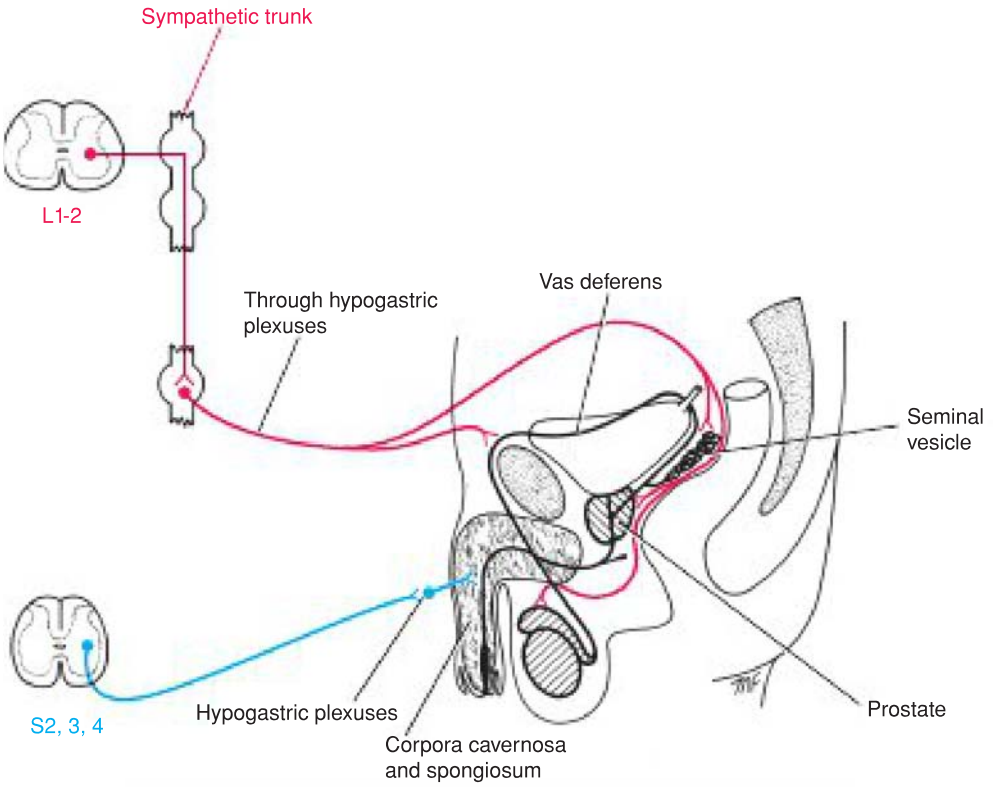


Figure 14-13 Autonomic innervation of the male reproductive tract.

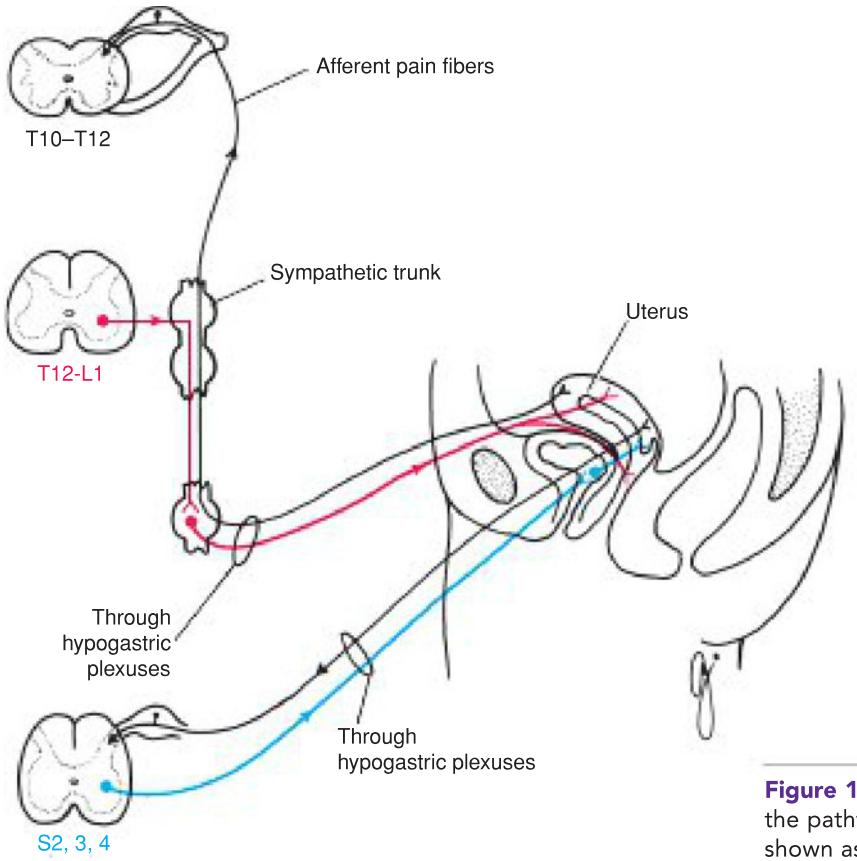


Figure 14-14 Autonomic innervation of the uterus; the pathway taken by the afferent sensory fibers is shown as well.

Afferent pain fibers from the fundus and the body of the uterus ascend to the spinal cord through the hypogastric plexuses, entering it through the posterior roots of the 10th, 11th, and 12th thoracic spinal nerves. Fibers from the cervix run in the pelvic splanchnic nerves and enter the spinal cord through the posterior roots of the second, third, and fourth sacral nerves.

Upper Limb Arteries

The arteries of the upper limb are innervated by sympathetic nerves. The preganglionic fibers originate from cell bodies in the second to the eighth thoracic segments of the spinal cord (Fig. 14-15). They pass to the sympathetic trunk through white rami and ascend in the trunk to synapse in the middle cervical, inferior cervical, first thoracic, or stellate ganglia. The postganglionic fibers join the nerves that form the brachial plexus and are distributed to the arteries within the branches of the plexus. The sympathetic nerves cause vasoconstriction of cutaneous arteries and vasodilatation of arteries that supply skeletal muscle.

Lower Limb Arteries

The arteries of the lower limb are also innervated by sympathetic nerves (see Fig. 14-15). The preganglionic fibers originate from cell bodies in the lower three thoracic and upper two or three lumbar segments of the spinal cord. The preganglionic fibers pass to the lower thoracic and upper lumbar ganglia of the sympathetic trunk through white rami. The fibers synapse in the lumbar and sacral ganglia and the postganglionic fibers reach the arteries through branches of the lumbar and sacral plexuses.

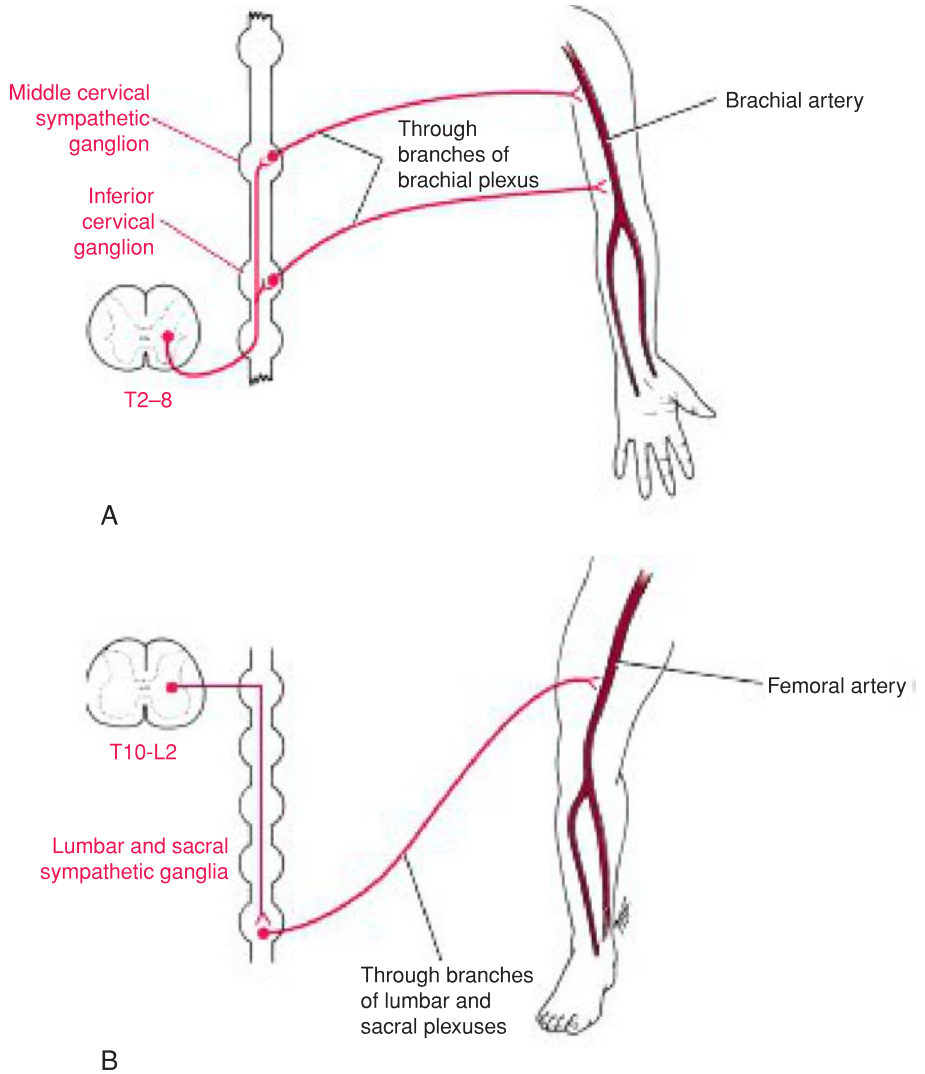


Figure 14-15 Sympathetic innervation of the arteries of the upper limb (**A**) and lower limb (**B**).

ANS PHYSIOLOGIC REFLEXES

The ANS is involved in important visual and cardiovascular reflexes.

Direct and Consensual Light Reflexes

Afferent nervous impulses travel from the retina through the optic nerve, optic chiasma, and optic tract (see Fig. 11-3). A small number of fibers leave the optic tract and synapse on nerve cells in the **pretectal nucleus**, which lies close to the superior colliculus. The impulses are passed by axons of the pretectal nerve cells to the parasympathetic nuclei (Edinger–Westphal nuclei) of the oculomotor nerve on both sides. Here, the fibers synapse and the parasympathetic nerves travel through the oculomotor nerve to the **ciliary ganglion** in the orbit. Finally, postganglionic parasympathetic fibers pass through the **short ciliary nerves** to the eyeball and to the constrictor pupillae muscle of the iris. Both pupils constrict in the consensual light reflex because the pretectal nucleus sends fibers to the parasympathetic nuclei on both sides of the midbrain.

Accommodation Reflex

When the eyes are directed from a distant to a near object, contraction of the medial recti brings about convergence of the ocular axes, the lenses thicken to increase their refractive power by contraction of the ciliary muscle, and the pupils constrict to restrict the light waves to the thickest central part of the lenses. The afferent impulses travel through the optic nerve, the optic chiasma, the optic tract, the lateral geniculate body, and the optic radiation to the visual cortex (see Fig. 11-3). The visual cortex is connected to the eye field of the frontal cortex. From here, cortical fibers descend through the internal capsule to the oculomotor nuclei in the midbrain. The oculomotor nerve travels to the medial recti muscles. Some of the descending cortical fibers synapse with the parasympathetic nuclei (Edinger–Westphal nuclei) of the oculomotor nerve on both sides. The parasympathetic preganglionic fibers then travel through the oculomotor nerve to the **ciliary ganglion** in the orbit where they synapse. Finally, postganglionic parasympathetic fibers pass through the **short ciliary nerves** to the ciliary muscle and the constrictor pupillae muscle of the iris.

Carotid Sinus and Aortic Arch Reflexes

The carotid sinus, located in the bifurcation of the common carotid artery, and the aortic arch serve as baroreceptors. As the blood pressure rises, nerve endings situated in the walls of these vessels are stimulated. The afferent fibers from the carotid sinus ascend in the glossopharyngeal nerve and terminate in the **nucleus solitarius** (see Figs. 11-16 and 11-17). The afferent fibers from the aortic arch ascend in the vagus nerve. Connector neurons in the medulla oblongata activate the parasympathetic nucleus (dorsal nucleus) of the vagus, which slows the heart rate. At the same time, reticulospinal fibers descend to the spinal cord and inhibit the preganglionic sympathetic outflow to the heart and cutaneous arterioles. The combined effect of stimulation of the parasympathetic action on the heart and inhibition of the sympathetic action on the heart and peripheral blood vessels reduces the rate and force of contraction of the heart and reduces the peripheral resistance of the blood vessels. Consequently, the blood pressure falls. The blood pressure of the individual is thus modified by the afferent information received from the baroreceptors. The modulator of the ANS, namely, the hypothalamus, in turn, can be influenced by other, higher centers in the CNS.

Bainbridge Right Atrial Reflex

This reflex is initiated when the nerve endings in the wall of the right atrium and in the walls of the venae cavae are stimulated by a rise of venous pressure. The afferent fibers ascend in the vagus to the medulla oblongata and terminate on the **nucleus of the tractus solitarius** (see Fig. 11-18). Connector neurons inhibit the parasympathetic nucleus (dorsal) of the vagus, and reticulospinal fibers stimulate the thoracic sympathetic outflow to the heart, resulting in cardiac acceleration.

Clinical Notes

General Considerations

Clearly, the ANS is not an isolated part of the nervous system. It should be regarded as the part of the nervous system that, with the endocrine system, is particularly involved in maintaining the stability of the internal environment of the body. Its activities are modified by the hypothalamus, whose function is to integrate vast amounts of afferent information received from other areas of the nervous system and to translate changing hormonal levels of the bloodstream into appropriate nervous and hormonal activities.

Because the ANS is so important in maintaining normal body homeostasis, not surprisingly, the system is subject to many pharmacologic interventions. Propranolol and atenolol, for example, are β-adrenergic antagonists that can be used in the treatment of hypertension and ischemic heart disease.

Autonomic Nervous System Injury

Trauma to the ANS is usually limited to either sympathetic or parasympathetic components, rarely both at the same time, due to their relative locations in the thorax or cranial cavity, respectively.

Sympathetic Injuries

The sympathetic trunk in the neck can be injured by stab and bullet wounds. Traction injuries to the first thoracic root of the brachial plexus can damage sympathetic nerves

destined for the stellate ganglion. All these conditions can produce a preganglionic type of Horner syndrome. Injuries to the spinal cord or cauda equina can disrupt the sympathetic control of the bladder (see p. 402).

Parasympathetic Injuries

The oculomotor nerve is vulnerable in head injuries (herniated uncus) and can be damaged by compression by aneurysms in the junction between the posterior cerebral artery and posterior communicating artery. The preganglionic parasympathetic fibers traveling in this nerve are situated in the periphery of the nerve and can be damaged. Surface aneurysmal compression characteristically causes dilation of the pupil and loss of the visual light reflexes.

The autonomic fibers in the facial nerve can be damaged by fractures of the skull involving the temporal bone. The vestibulocochlear nerve is closely related to the facial nerve in the internal acoustic meatus, so clinical findings involving both nerves are common. Involvement of the parasympathetic fibers in the facial nerve may produce impaired lacrimation in addition to paralysis of the facial muscles.

The glossopharyngeal and vagus nerves are at risk in stab and bullet wounds of the neck. The parasympathetic secretomotor fibers to the parotid salivary gland leave the glossopharyngeal nerve just below the skull; therefore, they are rarely damaged.

The parasympathetic outflow in the sacral region of the spinal cord (S2–S4) may be damaged by spinal cord and cauda equina injuries, leading to disruption of bladder, rectal, and sexual functions.

Degeneration and Regeneration of Autonomic Nerves

The structural changes are identical to those found in other areas of the peripheral and central parts of the nervous system. Functional recoveries following sympathectomy operations can be explained only by the assumption either that the operative procedure was inadequate and nerve fibers were left intact or regenerated or that alternative nervous pathways existed and were left undisturbed.

The denervation of viscera supplied by autonomic nerves is followed by their increased sensitivity to the agent that was previously the transmitter substance. One explanation is that following nerve section, there may be an increase in the number of receptor sites on the postsynaptic membrane. Another possibility, which applies to endings where norepinephrine is the transmitter, is that the reuptake of the transmitter by the nerve terminal is interfered with in some way.

Urinary Bladder Dysfunction

Injuries to the spinal cord are followed by disruption of the nervous control of micturition. The normal bladder is innervated as follows:

Sympathetic innervation is from the first and second lumbar segments of the spinal cord.

Parasympathetic innervation is from the second, third, and fourth sacral segments of the spinal cord.

Sensory nerve fibers enter the spinal cord at the above segments.

The **atonic bladder** occurs during the phase of spinal shock immediately following the injury and may last from a few days to several weeks. The bladder wall muscle is relaxed, the sphincter vesicae is tightly contracted (loss of inhibition from higher levels), and the sphincter urethrae is relaxed. The bladder becomes greatly distended and finally overflows. Depending on the level of the cord injury, the patient may or may not be aware that the bladder is full but has no voluntary control.

The **automatic reflex bladder** occurs after the patient has recovered from spinal shock, provided that the cord lesion lies above the level of the parasympathetic outflow (S2–S4). This is the type of bladder normally found in infancy. The descending fibers in the spinal cord are sectioned, so voluntary control is not possible. The bladder fills and empties reflexly. Stretch receptors in the bladder wall are stimulated as the bladder fills and the afferent impulses pass to the spinal cord (S2–S4). Efferent impulses pass down to the bladder muscle, which contracts; the sphincter vesicae and the urethral sphincter both relax. This simple reflex occurs every 1 to 4 hours.

The **autonomous bladder** is the condition that occurs if the sacral segment of the spinal cord is destroyed or if the cauda equina is severed. The bladder has no reflex control or voluntary control. The bladder wall is flaccid and the capacity of the bladder is greatly increased. It fills to capacity and overflows, which results in continual dribbling. The bladder may be partially emptied by manual compression of the lower part of the anterior abdominal wall, but infection of the urine and back pressure effects on the ureters and kidneys are inevitable.

Defecation

The act of defecation involves a coordinated reflex that results in the emptying of the descending colon, pelvic colon, rectum, and anal canal. It is assisted by a rise in the intra-abdominal pressure brought about by contraction of the muscles of the anterior abdominal wall. The involuntary internal sphincter of the anal canal normally is innervated by postganglionic sympathetic fibers from the hypogastric plexuses, and the voluntary external sphincter of the anal canal is innervated by the inferior rectal nerve. The desire to defecate is initiated by stimulation of the stretch receptors in the wall of the rectum.

Following severe spinal cord injuries (or cauda equina injuries), the patient is not aware of rectal distention. Moreover, the parasympathetic influence on the peristaltic activity of the descending colon, sigmoid colon, and rectum is lost. In addition, control over the abdominal musculature and sphincters of the anal canal may be severely impaired. The rectum, now an isolated structure, responds by contracting when the pressure within its lumen rises. This local reflex response is much more efficient if the sacral segments of the spinal cord and the cauda equina are intact. At best, however, the force of the contractions of the rectal wall is small and constipation and impaction are the usual outcome. The treatment of patients with spinal cord injuries is to empty the rectum with biweekly enemas; the use of suppositories also may be helpful.

Erection and Ejaculation

As described previously, erection of the penis or clitoris is controlled by the parasympathetic nerves that originate from the second, third, and fourth sacral segments of the spinal cord. Bilateral damage to the reticulospinal tracts in the spinal cord above the second sacral segment of the spinal cord will result in loss of erection. Later, when the effects of spinal shock have disappeared, spontaneous or reflex erection may occur if the sacral segments of the spinal cord are intact.

Ejaculation is controlled by sympathetic nerves that originate in the first and second lumbar segments of the spinal cord. Ejaculation brings about a flow of seminal fluid into the prostatic urethra. The final ejection of the fluid from the penis is the result of the rhythmic contractions of the bulbospongiosus muscles, which compress the urethra. The bulbospongiosus muscles are innervated by the pudendal nerve (S2–S4). Discharge of the seminal fluid into the bladder is prevented by the contraction of the sphincter vesicae, which is innervated by the sympathetic nerves (L1–L2). As in the case of erection, severe bilateral damage to the spinal cord results in loss of ejaculation. Later, reflex ejaculation may be possible in patients with spinal cord transections in the thoracic or cervical regions. Some individuals have a normal ejaculation without external emission, and the seminal fluid passes into the bladder owing to paralysis of the sphincter vesicae.

Diseases Involving the Autonomic Nervous System

The ANS can be affected by a variety of diseases that compromise the integrity of peripheral nerves containing sympathetic and parasympathetic fibers.

Diabetes Mellitus

Diabetes mellitus is a common cause of peripheral nerve neuropathy. This involves sensory and motor dysfunction and may also include autonomic dysfunction. The clinical features of autonomic dysfunction include postural hypotension, peripheral edema, pupillary abnormalities, and impaired sweating. The cause is probably associated with chronic hyperglycemia.

Horner Syndrome

Horner syndrome consists of (1) constriction of the pupil (miosis), (2) slight drooping of the eyelid (ptosis), (3) enophthalmos (which, although apparent, is not real and is caused by the ptosis; however, the orbitalis muscle is paralyzed, and involvement may be responsible), (4) vasodilation of skin arterioles, and (5) loss of sweating (anhydrosis). All these symptoms result from an interruption of the sympathetic nerve supply to the head and neck. Pathologic causes include lesions in the brainstem or cervical part of the spinal cord that interrupt the reticulospinal tracts descending from the hypothalamus to the sympathetic outflow in the lateral gray column of the first thoracic segment of the spinal cord. Such lesions include **multiple sclerosis** and **syringomyelia**. Traction on the stellate ganglion due to a **cervical rib** or involvement of the ganglion in a metastatic lesion may interrupt the peripheral part of the sympathetic pathway.

All patients with Horner syndrome have miosis and ptosis. However, a distinction should be made between lesions occurring at the first neuron (the descending reticulospinal fibers within the CNS), the second neuron (the preganglionic fibers), and the third neuron (postganglionic fibers). For example, the clinical signs suggestive of a first-neuron defect (central Horner syndrome) could include contralateral hyperesthesia of the body and loss of sweating of the entire half of the body. Signs suggesting a second-neuron involvement (preganglionic Horner syndrome) include loss of sweating limited to the face and neck and the presence of flushing or blanching of the face and neck. Signs suggesting third-neuron involvement (postganglionic Horner syndrome) include facial pain or ear, nose, or throat disease.

The presence or absence of other localizing signs and symptoms may assist in differentiating the three types of Horner syndrome.

Argyll Robertson Pupil

Argyll Robertson pupil is characterized by a small pupil, which is of fixed size and does not react to light but does contract with accommodation. It is usually caused by a neurosyphilitic lesion interrupting the fibers that run from the pretectal nucleus to the parasympathetic nuclei (Edinger–Westphal nuclei) of the oculomotor nerve on both sides. The fact that the pupil constricts with accommodation implies that the connections between the parasympathetic nuclei and the constrictor pupillae muscle of the iris are intact.

Adie Tonic Pupil Syndrome

In Adie tonic pupil syndrome, the pupil has a decreased or absent light reflex, a slow or delayed contraction to near vision, and a slow or delayed dilatation in the dark. This benign syndrome, which probably results from a disorder of the parasympathetic innervation of the constrictor pupillae muscle, must be distinguished from the Argyll Robertson pupil (see above), which is caused by neurosyphilis. Adie syndrome can be confirmed by looking for hypersensitivity to cholinergic agents. Drops commonly used for this test are 2.5% methacholine (Mecholyl) or 0.1% pilocarpine. The Adie tonic pupil should constrict when these drops are put in the eye. These cholinergic agents do not cause pupillary constriction in mydriasis caused by oculomotor lesion or in drug-related mydriasis.

Frey Syndrome

Frey syndrome is an interesting complication that sometimes follows penetrating wounds of the parotid gland. During the process of healing, the postganglionic parasympathetic secretomotor fibers traveling in the auriculotemporal nerve grow out and join the distal end of the great auricular nerve, which supplies the sweat glands of the overlying facial skin. By this means, a stimulus intended for saliva production instead produces sweat secretion.

A similar syndrome may follow injury to the facial nerve. During the process of regeneration, parasympathetic fibers normally destined for the submandibular and sublingual salivary glands are diverted to the lacrimal gland. This produces watering of the eyes associated with salivation, the so-called **crocodile tears**.

Hirschsprung Disease

Hirschsprung disease (megacolon) is a congenital condition in which the myenteric plexus (Auerbach plexus) fails to develop in the distal part of the colon. The involved part of the colon possesses no parasympathetic ganglion cells and peristalsis is absent. This effectively blocks the passage of feces and the proximal part of the colon becomes enormously distended.

Disease Caused by Botulinum Toxin

A very small amount of botulinum toxin binds irreversibly to the nerve plasma membranes and prevents the release of ACh at cholinergic synapses and neuromuscular junctions, producing an atropinelike syndrome with skeletal muscle weakness.

Disease Caused by Black Widow Spider Venom

The venom of a black widow spider causes a brief release of ACh at the nerve endings followed by a permanent blockade.

Disease Caused by Anticholinesterase Agents

AChE, which is responsible for hydrolyzing and limiting the action of ACh at nerve endings, can be blocked by certain drugs. Physostigmine, neostigmine, pyridostigmine, and carbamate and organophosphate insecticides are effective AChE inhibitors. Their use results in an excessive stimulation of the cholinergic receptors, producing the "SLUDG syndrome"—salivation, lacrimation, urination, defecation, and gastrointestinal distress.

Sympathectomy

Sympathectomy, or surgical removal of a sympathetic nerve ganglion, can be used to treat arterial disease.

Raynaud Disease

Raynaud disease is a vasospastic disorder involving the digital arteries of the upper limb. The disorder is usually bilateral and an attack is provoked by exposure to cold. Pallor or cyanosis of the fingers is seen as well as severe pain. Gangrene of the tips of the fingers may occur.

In mild cases of Raynaud disease, the treatment is the avoidance of cold and no smoking (smoking causes vasoconstriction). In more severe cases, drugs that inhibit sympathetic activity, such as reserpine, bring about arterial vasodilatation with consequent increase in blood flow to the fingers. Cervicothoracic preganglionic sympathectomy has been used, but the long-term results are disappointing.

Intermittent Claudication

Intermittent claudication, which is common in men, is due to arterial occlusive disease of the leg. Ischemia of the muscles produces a cramplike pain on exercise. Lumbar preganglionic sympathectomy may be advocated as a form of treatment in order to bring about vasodilatation and an increase in blood flow through the collateral circulation. Preganglionic sympathectomy is performed by removing the upper three lumbar ganglia and the intervening parts of the sympathetic trunk.

Hypertension

In the past, severe essential hypertension was treated by bilateral thoracolumbar sympathectomy to reduce the vasomotor control over the peripheral resistance and thus lower the blood pressure. Today, chemical blocking agents of the sympathetic system are widely used with great success and the resulting reduction in the force of myocardial contraction reduces the arterial blood pressure.

Referred Visceral Pain

Most viscera are innervated only by autonomic nerves. Therefore, it follows that visceral pain is conducted along afferent autonomic nerves. Visceral pain is diffuse and poorly localized, whereas somatic pain is intense and discretely localized. Visceral pain frequently is referred to skin areas that are innervated by the same segments of the spinal cord as the painful viscus (Fig. 14-16). The explanation for referred pain is not known. One theory is that the nerve fibers from the viscus and the dermatome ascend in the CNS along a common pathway and the cerebral cortex is incapable of distinguishing between the sites of origin. Another theory is that under normal conditions, the viscus does not give rise to painful stimuli, whereas the skin area

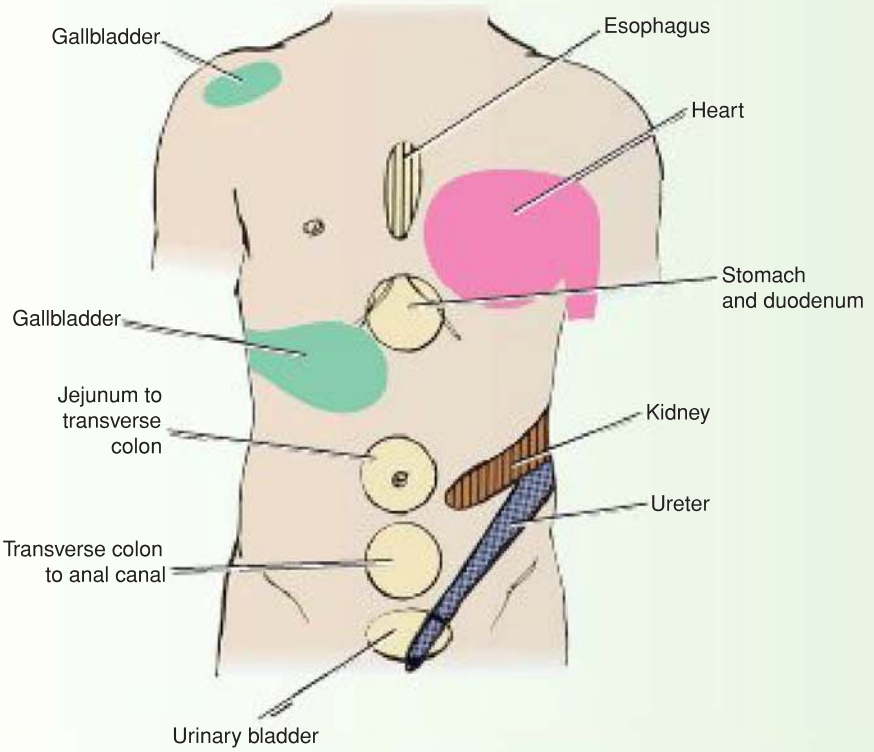


Figure 14-16 Some areas of referred pain from the viscera. In the case of the heart, the pain is usually referred to the left side of the thorax; occasionally, it is referred to both sides.

repeatedly receives noxious stimuli. Because both afferent fibers enter the spinal cord at the same segment, the brain interprets the information as coming from the skin rather than from the viscus. Pain arising from the gastrointestinal tract is referred to the midline. This can probably be explained by the fact that the tract arises embryologically as a midline structure and receives a bilateral nerve supply.

Cardiac Pain

Pain originating in the heart as the result of acute myocardial ischemia is assumed to be caused by oxygen deficiency and the accumulation of metabolites, which stimulate the sensory nerve endings in the myocardium. The afferent nerve fibers ascend to the CNS through the cardiac branches of the sympathetic trunk and enter the spinal cord through the posterior roots of the upper four thoracic nerves. The nature of the pain varies considerably, from a severe crushing pain to nothing more than a mild discomfort.

The pain is not felt in the heart but is referred to the skin areas supplied by the corresponding spinal nerves. The skin areas supplied by the upper four intercostal nerves and by the intercostobrachial nerve (T2) are therefore affected. The intercostobrachial nerve communicates with the medial cutaneous nerve of the arm and is distributed to skin on the medial side of the upper part of the arm. A certain amount of spread of nervous information must occur within the CNS, as the pain is sometimes felt in the neck and the jaw.

Myocardial infarction involving the inferior wall or diaphragmatic surface of the heart often gives rise to discomfort in the epigastrium, just below the sternum. One must assume that the afferent pain fibers from the heart ascend in the sympathetic nerves and enter the spinal cord in the posterior roots of the seventh, eighth, and ninth thoracic spinal nerves and give rise to referred pain in the T7–T9 thoracic dermatomes in the epigastrium.

Because the heart and the thoracic part of the esophagus probably have similar afferent pain pathways, pain from **acute esophagitis** can mimic the pain of myocardial infarction.

Stomach Pain

Referred pain from the stomach is commonly felt in the epigastrium. The afferent pain fibers from the stomach ascend in company with the sympathetic nerves and pass through the celiac plexus and the greater splanchnic nerves. The sensory fibers enter the spinal cord at segments T5–T9 and give rise to referred pain in the dermatomes T5–T9 on the lower chest and abdominal walls.

Appendicular Pain

Visceral pain from the appendix is produced by distention of its lumen or spasm of its muscle. It travels in nerve fibers that accompany sympathetic nerves through the superior mesenteric plexus and the lesser splanchnic nerve to the spinal cord (T10 segment). The vague referred pain is felt in the region of the umbilicus, which is innervated by the 10th intercostal nerve (T10 dermatome). Later, when the inflammatory process involves the parietal peritoneum in the right iliac fossa, which is innervated by the 12th thoracic and 1st lumbar spinal nerves, the now somatic pain becomes severe and dominates the clinical picture. The somatic pain is localized precisely to the right lower quadrant of the anterior abdominal wall (T12–L1 dermatomes).

Gallbladder Pain

Visceral pain impulses from the gallbladder (acute cholecystitis, gallstone colic) travel in nerve fibers that accompany sympathetic fibers through the celiac plexus and the greater splanchnic nerves to the spinal cord (segments T5–T9). The vague referred pain is felt in the dermatomes (T5–T9) on the lower chest and upper abdominal walls. Should the inflammatory process spread to involve the parietal peritoneum of the anterior abdominal wall or peripheral diaphragm, the now severe somatic pain will be felt in the right upper quadrant of the anterior abdominal wall and through to the back below the inferior angle of the scapula. Involvement of the central diaphragmatic parietal peritoneum, which is innervated by the phrenic nerve (C3–C5), may give rise to referred pain to the tip of the shoulder, since the skin in this area is innervated by the supraclavicular nerves (C3–C4).

Causalgia

Causalgia is a painful condition of the arm or leg accompanied by trophic changes in the affected skin and nails. It commonly follows crushing or partial division of the median nerve in the arm or the tibial nerve in the leg. It is thought that the descending impulses in the sympathetic postganglionic fibers in some way evoke ascending impulses in the afferent pain fibers at the site of injury. In many instances, sympathectomy has relieved the pain of causalgia.

Key Concepts

Organization

- The ANS is divided into two parts, sympathetic and parasympathetic.
- The function of the sympathetic system is to prepare the body for emergency by increasing heart rate, constricting peripheral blood vessels, increasing blood supply to muscles, and increasing blood pressure. Thus, it redistributes blood to organs that need high performance in emergency situations.
- Efferent fibers of the sympathetic system originate in the lateral gray columns of the spinal cord. Myelinated axons leave the cord in the anterior root and pass via the white rami communicantes to the paravertebral ganglia of the sympathetic trunk.
- Once these presynaptic fibers reach the sympathetic trunks, they are distributed as follows:
  - Synapse with a postsynaptic sympathetic neuron in the ganglion.

  - Travel superiorly or inferiorly to synapse at a different level of the sympathetic trunk. For instance, T1 fibers must travel superiorly to the superior cervical ganglion.
  - Pass through the ganglia without synapsing, as the greater, lesser, or least splanchnic nerve, to synapse in a prevertebral sympathetic ganglion.
- Afferent information from the viscera travels through the sympathetic ganglia without synapsing and ascends to higher centers.
- The function of the parasympathetic system is to conserve and restore energy. The heart rate is slowed, pupils are constricted, peristalsis and glandular activity is increased, and the bladder walls are contracted.
- Efferent fibers of the parasympathetic system originate in the parasympathetic nuclei of cranial nerves III, VII, IX, and X and the sacral spinal cord segments S2–S4.
- Presynaptic parasympathetic fibers of cranial nerves II, VII, and IX synapse in the parasympathetic ganglia of the head—specifically—ciliary, otic, pterygopalatine, and submandibular.
- Afferent fibers from viscera travel with the cranial nerves and the pelvic splanchnic nerves.
- The sympathetic system has long postganglionic fibers, whereas the parasympathetic has short fibers.

Neurotransmitters

- The preganglionic fibers in both the sympathetic and parasympathetic systems are cholinergic, meaning they synthesize and release ACh at the synapse.
- The postganglionic fibers in the parasympathetic are also cholinergic.
- Most postganglionic sympathetic neurons release norepinephrine; however, fibers to sweat glands and blood vessels are cholinergic.

Important Autonomic Innervations

- The skin of the upper eyelid receives sympathetic innervation from the superior cervical ganglion.
- The pupil of the iris is constricted by parasympathetic from cranial nerve III and dilated by sympathetic fibers from the superior cervical ganglion.
- The lacrimal gland receives parasympathetic fibers from cranial nerve VII and sympathetic vasoconstrictor fibers from the superior cervical ganglion.
- Submandibular and sublingual glands receive parasympathetic innervation from cranial nerve VII and sympathetic fibers from the superior cervical ganglion.
- The parotid gland receives parasympathetic fibers from cranial nerve IX and sympathetic fibers from the superior cervical ganglion.
- The gastrointestinal tract, up to the splenic flexure, receives parasympathetic innervation from cranial nerve X and sympathetic fibers from the greater and lesser splanchnic nerves.
- The descending colon, sigmoid colon, and rectum receive parasympathetic innervation from the pelvic splanchnic nerves and sympathetic fibers from the lumbar part of the sympathetic trunk.

Clinical Problem Solving

1. A 35-year-old man is getting off the back of a truck when it starts to move. With his feet on the ground, he grabs a rail on the truck with his right hand and holds on. The truck continues along the road for one block before it stops. In the meantime, the man is dragged along the road as he holds onto the truck. He is seen in the emergency department in a state of shock, with cuts and abrasions to his legs. On careful examination of his right arm, the following muscles are found to be paralyzed: the flexor carpi ulnaris, flexor digitorum profundus, palmar and dorsal interossei, and the thenar and hypothenar muscles. Loss of sensation occurs on the medial side of the arm, forearm, and hand. The deep tendon reflex for the biceps brachii is present, but the triceps reflex is absent. The pupil of the right eye is constricted and the right upper eyelid droops. The right eyeball seems to be less prominent than the left. The skin of the right cheek feels warmer and drier and is redder in color than the left cheek. Using your knowledge of neuroanatomy, explain the clinical findings.
2. A 3-year-old boy with a history since infancy of chronic constipation and abdominal distention is taken to a pediatrician. The child's mother says that the constipation is getting progressively worse. It is not responding to laxatives and she is finding it necessary to give her son an enema once a week to relieve his abdominal distention. On physical examination, the child's abdomen is obviously distended and a doughlike mass is palpated along the course of the descending colon in the left iliac fossa.

Examination of the rectum shows it to be empty and not dilated. Following an enema and repeated colonic irrigation with saline solution, the patient is given a barium enema for a radiographic examination. The radiograph shows a grossly distended descending colon and an abrupt change in lumen diameter where the descending colon joined the sigmoid colon. Notably, the child fails to empty the colon of the barium. Using your knowledge of the autonomic nerve supply to the colon, what is the diagnosis? How would you treat this patient?

3. A nervous 25-year-old woman attends her physician because she is experiencing attacks of painful discoloration of the fourth and fifth fingers of both hands. She says that her symptoms started 2 years previously, during the winter, and affects her right hand first and, in subsequent attacks, her left hand as well. Her fingers turn white on exposure to cold and then become deep blue. The color change is confined to the distal half of each finger and is accompanied by an aching pain. Holding her hands over a hot stove or going into a hot room is the only treatment that relieves the pain. As the pain disappears, she says her fingers become red and swollen. She tells her physician that she notices that her fingers are moist with sweat during some of the attacks. Using your knowledge of neuroanatomy, make the diagnosis. What is the autonomic nerve supply to the blood vessels of the upper limb? How would you treat this patient?
4. An obese 45-year-old mother of six children is examined by her physician because her symptoms are suggestive of gallbladder disease. She complains of having severe attacks of colicky pain beneath the right costal margin, which radiate through to the back beneath the right scapula. The physician turns to a medical student and says, "Note that the patient complains of referred pain to the back." What does he mean by that statement? Explain the phenomenon of referred pain to the back and sometimes the right shoulder in gallbladder disease.
5. Examination of a patient with neurosyphilis indicates that the pupil of her left eye is small and fixed and does not react to light but contracts when she is asked to look at a near object. What is the innervation of the iris? Using your knowledge of neuroanatomy, state where you believe the neurologic lesion would be situated to account for these defects.
6. A 36-year-old man is admitted to the emergency department following a gunshot wound to the lower back. Radiographic examination reveals that the bullet is lodged in the vertebral canal at the level of the third lumbar vertebra. A complete neurologic examination reveals the symptoms and signs that indicate a complete lesion of the cauda equina. What is the autonomic nerve supply to the bladder? Is this patient going to have any interference with bladder function?
7. On routine medical examination, a 40-year-old black man is found to have essential hypertension. His blood pressure readings are 180 systolic and 100 diastolic (mm Hg). How would you treat this patient medically? What is the action of the various types of drugs that are commonly used in the treatment of hypertension?
8. What transmitter substances are liberated at the following nerve endings: (a) preganglionic sympathetic, (b) preganglionic parasympathetic, (c) postganglionic parasympathetic, (d) postganglionic sympathetic fibers to the heart muscle, and (e) postganglionic sympathetic fibers to the sweat glands of the hand?

Answers and Explanations to Clinical Problem Solving

1. As a result of holding onto the moving truck with the right hand, this man has sustained a severe traction injury of the eighth cervical and first thoracic roots of the brachial plexus. The various paralyzed forearm and hand muscles together with the sensory loss were characteristic of Klumpke paralysis. In this case, the pull on the first thoracic nerve was so severe that the white ramus communicans to the inferior cervical sympathetic ganglion was torn. This effectively cut off the preganglionic sympathetic fibers to the right side of the head and neck, causing a right-sided Horner syndrome (preganglionic type). This was exemplified by (a) constriction of the pupil, (b) drooping of the upper lid, and (c) enophthalmos. The arteriolar vasodilatation due to loss of sympathetic vasoconstrictor fibers was responsible for the red, hot cheek on the right side. The dryness of the skin of the right cheek also was due to the loss of the sympathetic secretomotor supply to the sweat glands.
2. This 3-year-old boy has Hirschsprung disease, a congenital condition in which the myenteric plexus (Auerbach plexus) fails to develop in the distal part of the colon. The proximal part of the colon is normal but becomes greatly distended due to the accumulation of feces. In this patient, the lower sigmoid colon, later at operation, was shown to have no parasympathetic ganglion cells. Thus, this segment of the bowel had no peristalsis and effectively blocked the passage of feces. Once the diagnosis had been confirmed by performing a biopsy of the distal segment of the bowel, the treatment was to remove the aganglionic segment of the bowel by surgical resection.
3. This patient has given a classic history of Raynaud disease. The disease is much more common in women than in men, especially those who have a nervous disposition. The initial pallor of the fingers is due to spasm of the digital arterioles. The cyanosis that follows is due to local capillary dilatation

due to accumulation of metabolites. Because blood flow through the capillaries is absent, deoxygenated hemoglobin accumulates within them. During this period of prolonged cyanosis, the patient experiences severe, aching pain. On exposing the fingers to warmth, the vasospasm disappears and oxygenated blood flows back into the very dilated capillaries. Reactive hyperemia results, as well as increased tissue fluid responsible for the swelling of the affected fingers. The sweating of the fingers during the attack probably is due to the excessive sympathetic activity, which may be responsible in part for the arteriolar vasospasm.

The arteries of the upper limb are innervated by sympathetic nerves. The preganglionic fibers originate from the cell bodies in the second to the eighth thoracic segments of the spinal cord. They ascend in the sympathetic trunk to synapse in the middle cervical, inferior cervical, and first thoracic or stellate ganglia. The postganglionic fibers join the nerves that form the brachial plexus and are distributed to the digital arteries within the branches of the brachial plexus.

In this patient, the attacks were relatively mild. The patient should be reassured and told to keep her hands warm as much as possible. However, should the condition worsen, the patient should be treated with drugs, such as reserpine, that inhibit sympathetic activity. This would result in arterial vasodilatation with consequent increase in blood flow to the fingers.

4. The patient was suffering from gallstone colic. The visceral pain originated from the cystic duct or bile duct and was due to stretching or spasm of the smooth muscle in its wall. The pain afferent fibers pass through the celiac ganglia and ascend in the greater splanchnic nerve to enter the fifth to the ninth thoracic segments of the spinal cord. The pain was referred to the fifth through the ninth thoracic dermatomes on the right side—that is, to the skin over and inferior to the right scapula.

   Referred pain to the right shoulder in gallbladder disease is discussed on page 410.

5. This patient has an Argyll Robertson pupil, which is a small fixed pupil that does not react to light but contracts with accommodation. The condition usually is due to a syphilitic lesion. The innervation of the iris is described on page 396. The neurologic lesion in this patient interrupted the fibers running from the pretectal nucleus to the parasympathetic nuclei of the oculomotor nerve on both sides.
6. The urinary bladder is innervated by sympathetic fibers from the first and second lumbar segments of the spinal cord and by parasympathetic fibers from the second, third, and fourth sacral segments of the spinal cord. In this patient, the cauda equina was sectioned at the level of the third lumbar vertebra. This meant that the preganglionic sympathetic fibers that descend in the anterior roots of the first and second lumbar nerves were left intact, since they leave the vertebral canal to form the appropriate spinal nerves above the level of the bullet. The preganglionic parasympathetic fibers were, however, sectioned as they descended in the vertebral canal within the anterior roots of the second, third, and fourth sacral nerves. The patient would therefore have an autonomous bladder and would be without any external reflex control. The bladder would fill to capacity and then overflow. Micturition could be activated by powerful contraction of the abdominal muscles by the patient, assisted by manual pressure on his anterior abdominal wall in the suprapubic region.
7. The precise cause of essential hypertension is unknown. Nevertheless, the objective of the treatment is to lower the blood pressure and keep it, if possible, within normal limits before the complications of cerebral hemorrhage, renal failure, or heart failure develop. The best way to accomplish this in patients with mild hypertension is to reduce the plasma fluid volume by the use of diuretics. β-Receptor–blocking agents are now extensively used. These reduce the rate and force of contraction of the cardiac muscle and lower the cardiac output.
8. (a) Acetylcholine, (b) acetylcholine, (c) acetylcholine, (d) norepinephrine, and (e) acetylcholine.

Review Questions

Directions: Each of the numbered items in this section is followed by answers. Select the ONE lettered answer that is CORRECT.

1. The following statements concern the autonomic nervous system (ANS):
   (a) The enteric nervous system is made up of the submucous plexus of Meissner and the myenteric plexus of Auerbach.
   (b) The nerve fibers of the enteric nervous system are naked axons.
   (c) The activities of the parasympathetic part of the ANS are used in an emergency.
   (d) The parasympathetic part of the autonomic system contains only efferent nerve fibers.
   (e) The pretectal nucleus is concerned with the auditory reflexes.

2. The following statements concern the autonomic nervous system:
   (a) An Argyll Robertson pupil indicates that the accommodation reflex for near vision is normal but that the light reflex is lost.
   (b) White rami communicantes are limited to the thoracic part of the sympathetic trunk.
   (c) White rami communicantes contain postganglionic sympathetic fibers.
   (d) The greater splanchnic nerves are formed of nonmyelinated axons.
   (e) The lesser splanchnic nerves arise from the eighth and ninth ganglia of the thoracic part of the sympathetic trunks.
3. The following general statements concern the autonomic nervous system (ANS):
   (a) The hypothalamus has little control over the ANS.
   (b) The cerebral cortex has no control over the ANS.
   (c) A patient with Adie tonic pupil syndrome has an increased light reflex and a fast pupillary contraction to near vision and a fast dilatation in the dark.
   (d) Pain arising in the gastrointestinal tract is referred to the midline.
   (e) Visceral pain frequently is referred to skin areas that are innervated by different segments of the spinal cord as the painful viscus.
4. The following statements concern Horner syndrome:
   (a) The pupil is dilated.
   (b) The upper eyelid is retracted.
   (c) The patient has vasodilation of the facial skin arterioles.
   (d) The patient has excessive facial sweating.
   (e) The patient has exophthalmos.

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or completions of the statement. Select the ONE lettered answer or completion that is BEST in each case.

5. The sympathetic outflow:
   (a) arises from nerve cells that are situated in the posterior gray column (horn) of the spinal cord.
   (b) has preganglionic nerve fibers that leave the spinal cord in the posterior roots of the spinal nerves.
   (c) is restricted to the T1–L2 segments of the spinal cord.
   (d) receives descending fibers from supraspinal levels that pass down the spinal cord in the posterior white column.
   (e) has many preganglionic nerve fibers that synapse in the posterior root ganglia of the spinal nerves.
6. Norepinephrine is secreted at the endings of the:
   (a) preganglionic sympathetic fibers.
   (b) preganglionic parasympathetic fibers.
   (c) postganglionic parasympathetic fibers.
   (d) postganglionic sympathetic fibers.
   (e) preganglionic fibers to the suprarenal medulla.
7. The parasympathetic innervation controlling the parotid salivary gland arises from the:
   (a) facial nerve.
   (b) oculomotor nerve.
   (c) vagus nerve.
   (d) carotid plexus.
   (e) glossopharyngeal nerve.
8. Which of the following statements best describes the parasympathetic part of the autonomic nervous system (ANS)?
   (a) It is associated with the thoracolumbar part of the spinal cord.
   (b) Effects are local and discrete due to preganglionic neurons synapsing with few postganglionic neurons.
   (c) It has short preganglionic axons.
   (d) It is active during an emotional crisis.
   (e) Its activity mobilizes glucose from glycogen.
9. Anticholinesterase drugs act at synapses by:
   (a) mimicking the action of acetylcholine at its receptor sites.
   (b) preventing the release of acetylcholine.
   (c) increasing the secretion of acetylcholine.
   (d) blocking the breakdown of acetylcholine.
   (e) preventing the uptake of acetylcholine by the nerve ending.
10. Atropine has the following effect on the autonomic nervous system:
    (a) It is an anticholinesterase drug.
    (b) It increases the activity of norepinephrine.
    (c) It blocks the action of acetylcholine on effector sites in the parasympathetic system.
    (d) It blocks norepinephrine reuptake by presynaptic terminals in the sympathetic system.
    (e) It blocks norepinephrine receptor sites.
11. The parasympathetic outflow in the spinal cord occurs at levels:
    (a) S1–S2
    (b) S3–S5
    (c) S1–S3
    (d) S2–S4
    (e) L1–L2

Directions: Each of the numbered items in this section is followed by answers. Select the ONE lettered answer that is CORRECT.

12. The following statements concern autonomic innervation of the urinary bladder:
    (a) The parasympathetic part brings about relaxation of the bladder wall muscle and contraction of the sphincter vesicae.
    (b) The sympathetic part in the male causes relaxation of the sphincter vesicae and does not prevent reflux of semen into the bladder during ejaculation.
    (c) The afferent fibers from the bladder reach the spinal cord at the first and second lumbar segments and the second, third, and fourth sacral segments.
    (d) The sympathetic part causes contraction of the sphincter urethrae.
    (e) The parasympathetic part innervates the blood vessels supplying the bladder wall.

13. The following statements concern the autonomic innervation of the heart:
    (a) The parasympathetic part causes dilation of the coronary arteries.
    (b) The postganglionic fibers do not terminate on the sinoatrial and atrioventricular nodes.
    (c) The sympathetic postganglionic fibers liberate acetylcholine at their nerve endings.
    (d) The sympathetic nerves cause cardiac acceleration and increased force of contraction of the heart.
    (e) The neural control of dilatation of the coronary arteries is more important than the chemical control exerted by the products of cardiac muscle metabolism.

Matching Questions. Directions: Match the numbered glands with the most appropriate lettered autonomic ganglion listed below. Each lettered option may be selected once, more than once, or not at all.

14. Submandibular gland	(a) Otic ganglion
15. Lacrimal gland	(b) Submandibular ganglion
16. Nasal glands	(c) Pterygopalatine ganglion
17. Parotid gland	(d) Ciliary ganglion
18. Sublingual gland	(e) None of the above

Match the numbered autonomic ganglia with the most appropriate lettered viscus or muscle listed below. Each lettered option may be selected once, more than once, or not at all.

19. Superior cervical ganglion	(a) Levator palpebrae superioris (smooth muscle only)
20. Ciliary ganglion	(b) Vermiform appendix
21. Celiac ganglion	(c) Constrictor pupillae
22. Inferior mesenteric ganglion	(d) Descending colon
23. Superior mesenteric ganglion	(e) None of the above

Match the numbered cranial nerves with the appropriate lettered nuclei listed below. Each lettered option may be selected once, more than once, or not at all.

24. Facial nerve	(a) Inferior salivatory nucleus
25. Oculomotor nerve	(b) Edinger–Westphal nucleus
26. Glossopharyngeal nerve	(c) Lacrimatory nucleus
27. Hypoglossal nerve	(d) None of the above

The following questions apply to Figure 14-17. Match the numbered areas of referred pain with the appropriate lettered viscus originating the pain listed below. Each lettered option may be selected once, more than once, or not at all.

28. Number 1	(a) Heart
29. Number 2	(b) Appendix
30. Number 3	(c) Gallbladder
31. Number 4	(d) Stomach
	(e) None of the above

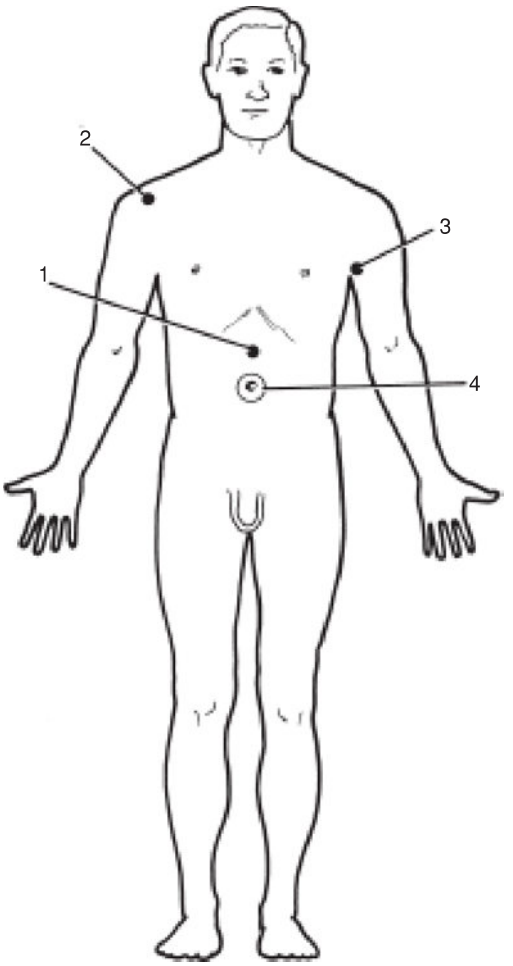


Figure 14-17 Areas of referred pain.

Answers and Explanations to Review Questions

1. A is correct. The enteric nervous system is made up of the submucous plexus of Meissner and the myenteric plexus of Auerbach. B. The nerve cells and the nerve fibers in the enteric nervous system are surrounded by neuroglialike cells that closely resemble astrocytes. C. The activities of the parasympathetic part of the ANS aim at conserving and restoring energy. D. The parasympathetic part of the autonomic system contains both afferent and efferent nerve fibers. E. The pretectal nucleus is concerned with the light reflex.
2. A is correct. An Argyll Robertson pupil indicates that the accommodation reflex for near vision is normal but that the light reflex is lost. B. White rami communicantes are found in the thoracic and first and second lumbar parts of the sympathetic trunk. C. Gray rami communicantes contain postganglionic sympathetic fibers. D. The greater splanchnic nerves are formed of myelinated axons. E. The lesser splanchnic nerves arise from the 10th and 11th ganglia of the thoracic part of the sympathetic trunks.
3. D is correct. Pain arising in the gastrointestinal tract is referred to the midline. A. The hypothalamus has great control over the ANS. B. The cerebral cortex can influence the ANS. C. A patient with Adie tonic pupil syndrome has a decreased or absent light reflex and a slow or delayed pupillary contraction to near vision and a slow or delayed dilatation in the dark. E. Visceral pain frequently is referred to skin areas that are innervated by the same segment of the spinal cord as the painful viscus.
4. C is correct. In Horner syndrome, the patient has vasodilation of the facial skin arterioles. A. The pupil is constricted. B. Ptosis of the upper eyelid occurs. D. Facial sweating is absent. E. Enophthalmos occurs.
5. C is correct. The sympathetic outflow is restricted to T1–L2 segments of the spinal cord (see Fig. 14-2).
6. D is correct. Norepinephrine is secreted at the endings of most postganglionic sympathetic fibers.
7. E is correct. The parasympathetic innervation controlling the parotid salivary gland is the glossopharyngeal nerve.
8. B is correct. The parasympathetic part of the ANS produces effects that are local and discrete due to preganglionic neurons synapsing with few postganglionic neurons.
9. D is correct. Anticholinesterase drugs act at synapses by blocking the breakdown of acetylcholine.
10. C is correct. Atropine blocks the action of acetylcholine on the effector sites in the parasympathetic part of the autonomic system.
11. D is correct. The parasympathetic outflow in the spinal cord occurs at the level of S2–S4 (see Fig. 14-2).
12. C is correct. The afferent sensory fibers from the bladder reach the spinal cord at the first and second lumbar segments and the second, third, and fourth sacral segments. A. The parasympathetic innervation of the bladder brings about contraction of the bladder wall muscle and relaxation of the sphincter vesicae. B. The sympathetic innervation of the bladder in the male causes contraction of the sphincter vesicae and prevents the reflux of semen into the bladder during ejaculation. D. The sphincter urethrae is not under the control of the autonomic nervous system; it is made to contract voluntarily by the internal pudendal nerve. E. The sympathetic nerves innervate the blood vessels supplying the bladder wall.
13. D is correct. The sympathetic nerves supplying the heart cause cardiac acceleration and increased force of contraction of the cardiac muscle. A. The parasympathetic part of the autonomic system brings about constriction of the coronary arteries. B. The postganglionic autonomic nerves to the heart do terminate on the sinoatrial and atrioventricular nodes. C. The sympathetic postganglionic fibers supplying the heart liberate norepinephrine at their endings. E. The local metabolic needs of the cardiac muscle exert a greater control over the degree of dilation of the coronary arteries than the neural control of the arteries.
14. B is correct. The submandibular salivary gland receives secretomotor parasympathetic nerves through the submandibular ganglion.
15. C is correct. The lacrimal gland receives secretomotor parasympathetic nerves through the pterygopalatine ganglion.
16. C is correct. The nasal glands receive secretomotor parasympathetic nerves through the pterygopalatine ganglion.
17. A is correct. The parotid salivary gland receives secretomotor parasympathetic nerves through the otic ganglion.
18. B is correct. The sublingual salivary gland receives secretomotor parasympathetic nerves through the submandibular salivary ganglion.
19. A is correct. The levator palpebrae superioris (smooth muscle only) is innervated by sympathetic fibers from the superior cervical sympathetic ganglion.
20. C is correct. The constrictor pupillae is innervated by parasympathetic nerves from the ciliary ganglion.
21. E is correct. The celiac ganglion gives rise to nerves that supply the smooth muscle of the gut from the gastroesophageal junction down to the middle of the second part of the duodenum; it also supplies the liver, the pancreas, and the spleen.
22. D is correct. The descending colon receives sympathetic nerves from the inferior mesenteric ganglion.
23. B is correct. The vermiform appendix receives sympathetic nerves from the superior mesenteric ganglion.
24. C is correct. Parasympathetic nerve fibers from the lacrimatory nucleus travel in the facial nerve and

its branches to the pterygopalatine ganglion, synapse, and then pass to the lacrimal gland.

25. B is correct. Parasympathetic nerve fibers from the Edinger–Westphal nucleus travel in the oculomotor nerve to the ciliary ganglion, synapse, and then pass to the constrictor pupillae and the ciliary muscle.
26. A is correct. Parasympathetic nerve fibers from the inferior salivatory nucleus travel in the glossopharyngeal nerve and its branches to the otic ganglion, synapse, and then pass to the parotid salivary gland.
27. D is correct. The hypoglossal nerve supplies the muscles of the tongue.
28. D is correct.
29. C is correct.
30. A is correct.
31. B is correct.

15 Meninges

CHAPTER OBJECTIVES

- To learn the structure and function of the three meninges that surround the brain and spinal cord
- To understand the venous sinuses within the skull and see how the meninges contribute to their walls
- To appreciate the relationship of the meninges to the different forms of cerebral hemorrhage

A 44-year-old woman is seen by a neurologist because she is experiencing intense pain in the right eye. On physical examination, she is found to have a slight medial strabismus of the right eye, and the right pupil is smaller than normal. Further examination reveals numbness over the right cheek. A computed tomography (CT) scan shows the presence of an aneurysm of the right internal carotid artery within the cavernous sinus. The aneurysm is about the size of a pea.

The location of the carotid aneurysm within the cavernous sinus explains the ocular pain; pressure on the right abducens nerve is responsible for the paralysis of the lateral rectus muscle producing the medial strabismus. The small pupil of the right eye is caused by the aneurysm pressing on the sympathetic plexus surrounding the carotid artery and producing paralysis of the dilator pupillae muscle. The numbness over the right cheek is due to pressure of the aneurysm on the right maxillary division of the trigeminal nerve as it passes forward through the lateral wall of the sinus.

This patient illustrates the necessity of knowing the relationships between the structures within the skull, especially in regions like the cavernous sinus, where so many important neural structures lie close to one another.

BRAIN MENINGES

The brain in the skull is surrounded by three protective membranes or meninges: the dura mater, the arachnoid mater, and the pia mater.

Dura Mater

The dura mater of the brain is conventionally described as two layers: the endosteal layer and the meningeal layer (Fig. 15-1). These are closely united except along certain lines where they separate to form **venous sinuses**.

The **endosteal layer** is nothing more than the periosteum covering the inner surface of the skull bones. At the foramen magnum, it does not become continuous with the dura mater of the spinal cord. Around the margins of all the foramina in the skull, it becomes continuous with the **periosteum** on the outside of the skull bones. At the sutures, it is continuous with the **sutural ligaments**. It is most strongly adherent to the bones over the base of the skull.

The **meningeal layer** is the dura mater proper. It is a dense, strong fibrous membrane covering the brain (Figs. 15-2 and 15-3) and is continuous through the foramen magnum with the dura mater of the spinal cord. It provides tubular sheaths for the cranial nerves as the latter pass through the foramina in the skull. Outside the skull, the sheaths fuse with the epineurium of the nerves (see Fig. 15-2B).

The meningeal layer sends inward four septa—the falx cerebri, falx cerebelli, tentorium cerebelli, and diaphragma sellae—which divide the cranial cavity into freely communicating spaces that lodge the subdivisions of the brain (see Figs. 15-1 and 15-3). The function of these septa is to restrict the displacement of the brain associated with acceleration and deceleration when the head is moved.

The **falx cerebri** is a sickle-shaped fold of dura mater that lies in the midline between the two cerebral hemispheres. Its narrow anterior end is attached to the internal frontal crest and the crista galli. Its broad posterior part blends in the midline with the upper surface of the

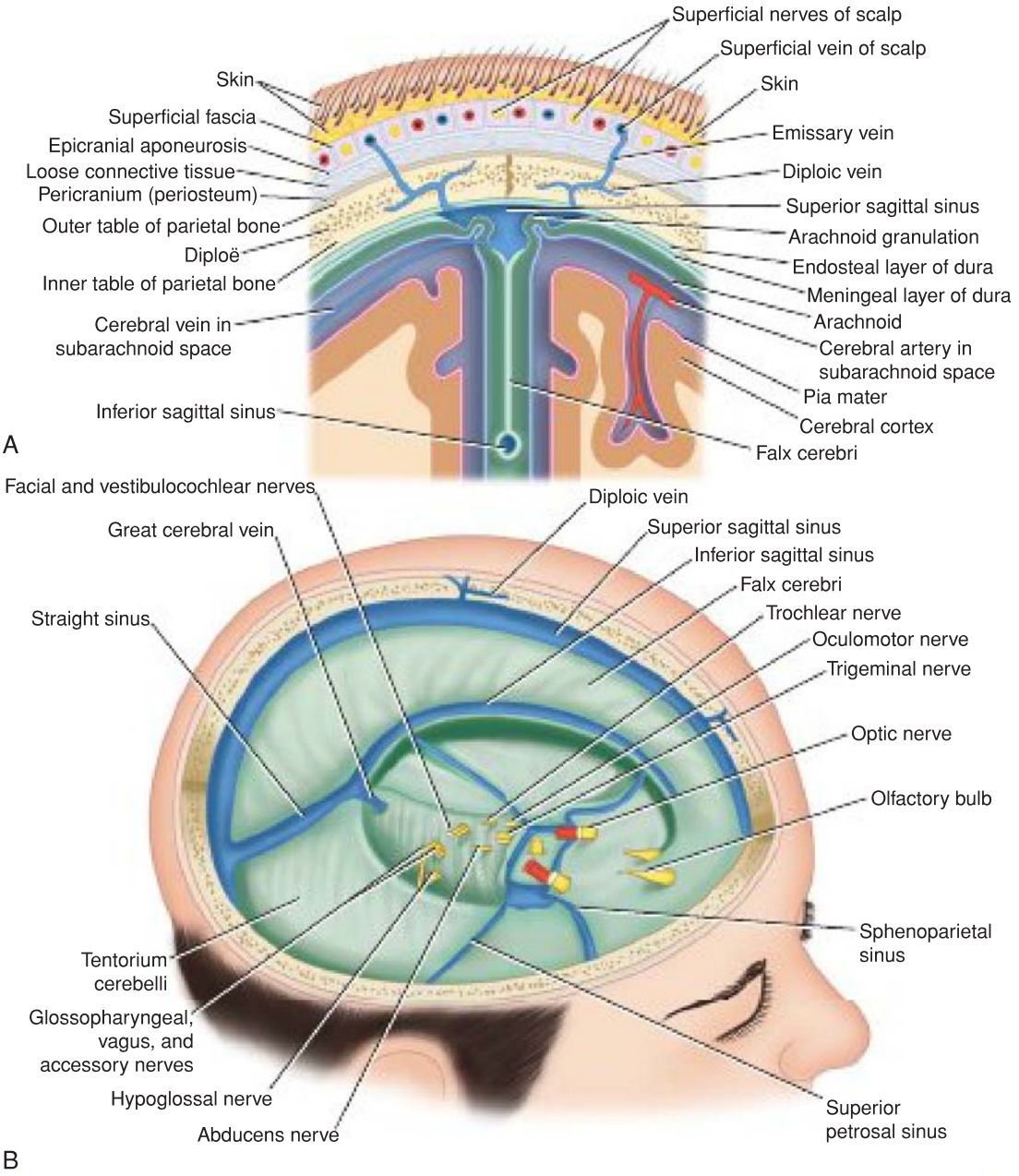


Figure 15-1 **A:** Coronal section of the upper part of the head showing the layers of the scalp, sagittal suture of the skull, falx cerebri, venous sinuses, arachnoid granulations, emissary veins, and relation of the cerebral blood vessels to the subarachnoid space. **B:** Interior of the skull showing the dura mater and its contained venous sinuses.

tentorium cerebelli. The **superior sagittal sinus** runs in its upper fixed margin, the **inferior sagittal sinus** runs in its lower concave free margin, and the **straight sinus** runs along its attachment to the tentorium cerebelli.

The **tentorium cerebelli** is a crescent-shaped fold of dura mater that roofs over the posterior cranial fossa (Fig. 15-1; also see Fig. 15-4). It covers the upper surface of the cerebellum and supports the occipital lobes of the cerebral hemispheres. In the anterior edge, a gap, the **tentorial notch**, allows passage of the midbrain, which produces an inner free border and an outer attached or fixed border. The fixed border is attached to the posterior clinoid processes, the superior borders of the petrous bones, and the margins of the grooves for the transverse sinuses on the occipital bone. The free border runs forward at its two ends, crosses the attached border, and is affixed to the anterior clinoid process on each side. At the point where the two borders cross, the third and fourth cranial nerves pass forward to enter the lateral wall of the cavernous sinus.

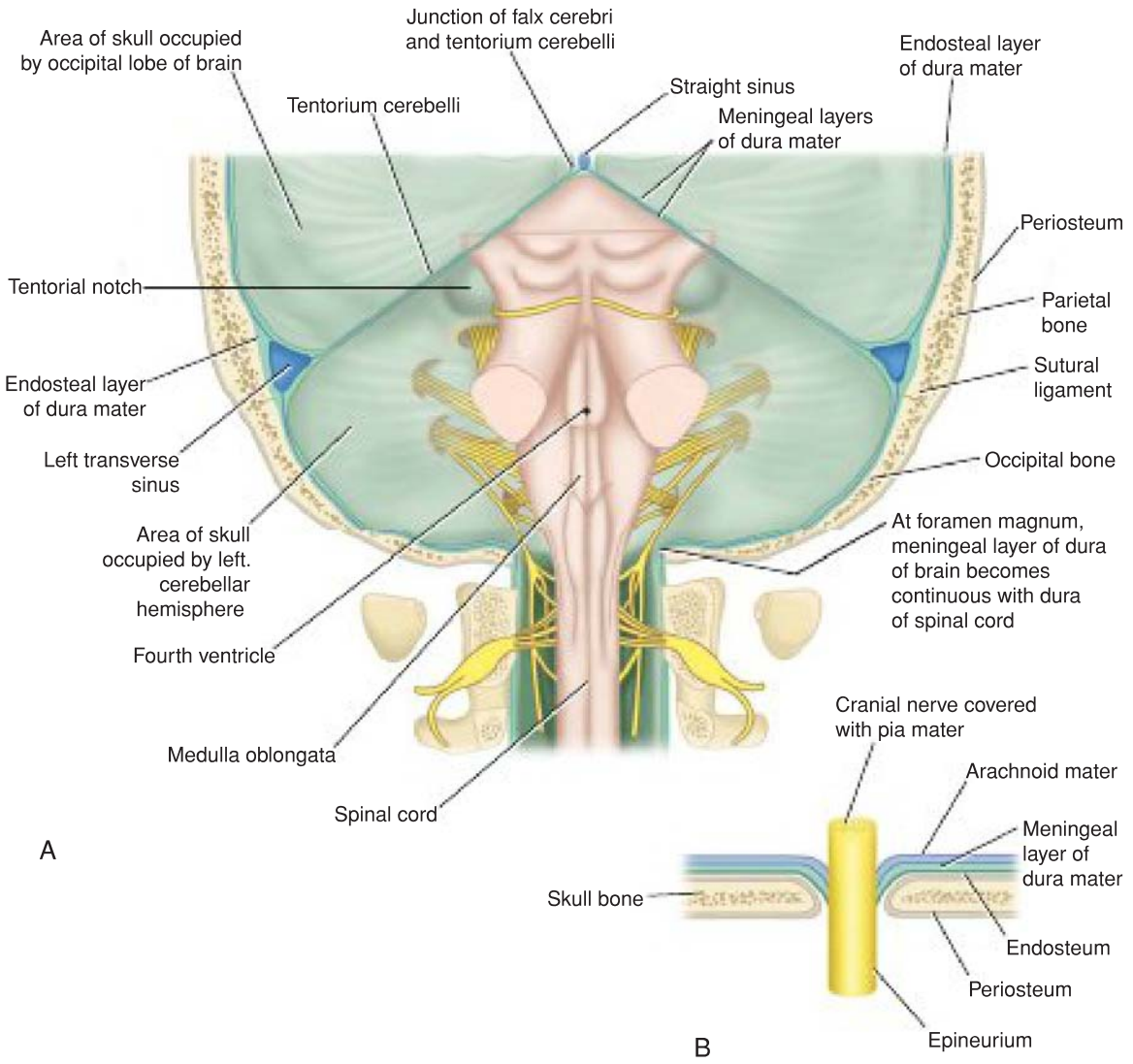


Figure 15-2 **A:** Posterior view of the interior of the skull after removal of the occipital and parietal bones showing the arrangement of the endosteal and meningeal layers of the dura mater. The brainstem has been left in situ. **B:** The arrangement of the meninges as a cranial nerve passes through a foramen in the skull.

Close to the apex of the petrous part of the temporal bone, the lower layer of the tentorium is pouched forward beneath the superior petrosal sinus to form a recess for the trigeminal nerve and the trigeminal ganglion.

The falx cerebri and the falx cerebelli are attached to the upper and lower surfaces of the tentorium, respectively. The straight sinus runs along its attachment to the falx cerebri, the superior petrosal sinus runs along its attachment to the petrous bone, and the **transverse sinus** runs along its attachment to the occipital bone (see Figs. 15-1 and 15-4).

The **falx cerebelli,** a small, sickle-shaped fold of dura mater attached to the internal occipital crest projects forward between the two cerebellar hemispheres. Its posterior fixed margin contains the **occipital sinus**.

The **diaphragma sellae** is a small, circular fold of dura mater that forms the roof for the sella turcica (Fig. 15-5). A small opening in its center allows passage of the stalk of the **hypophysis cerebri**.

Dural Nerve Supply

Branches of the trigeminal, vagus, and the first three cervical spinal nerves and branches from the sympathetic trunk pass to the dura.

The dura possesses numerous sensory endings that are sensitive to stretching, which produces the sensation of headache. Stimulation of the sensory endings of the trigeminal nerve above the level of the tentorium cerebelli produces referred pain to an area of skin on the same side of the head. Stimulation of the dural endings below the level of the tentorium produces pain referred

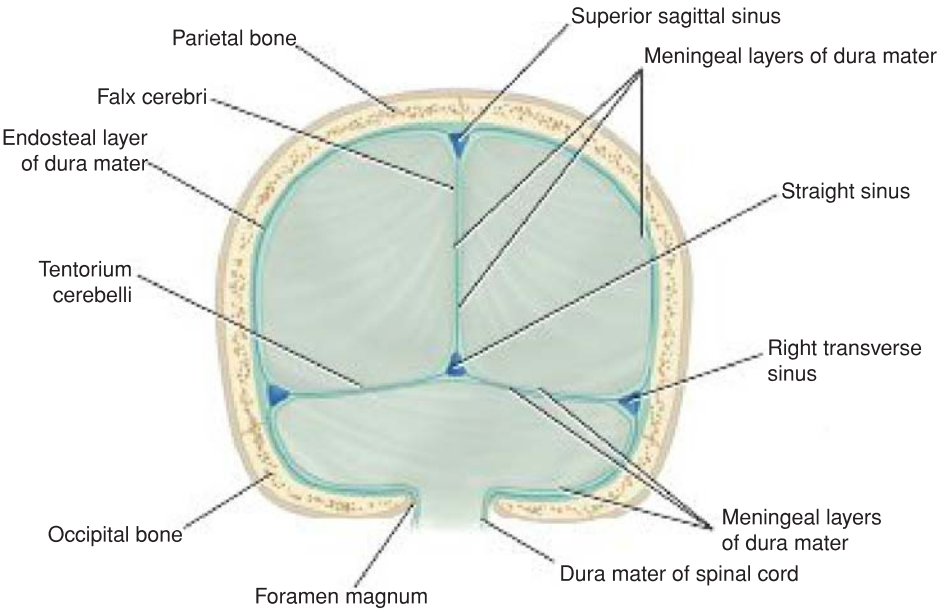


Figure 15-3 Falx cerebri and the tentorium cerebelli. Note the continuity between the meningeal layer of dura mater within the skull and the dura mater of the spinal cord at the foramen magnum.

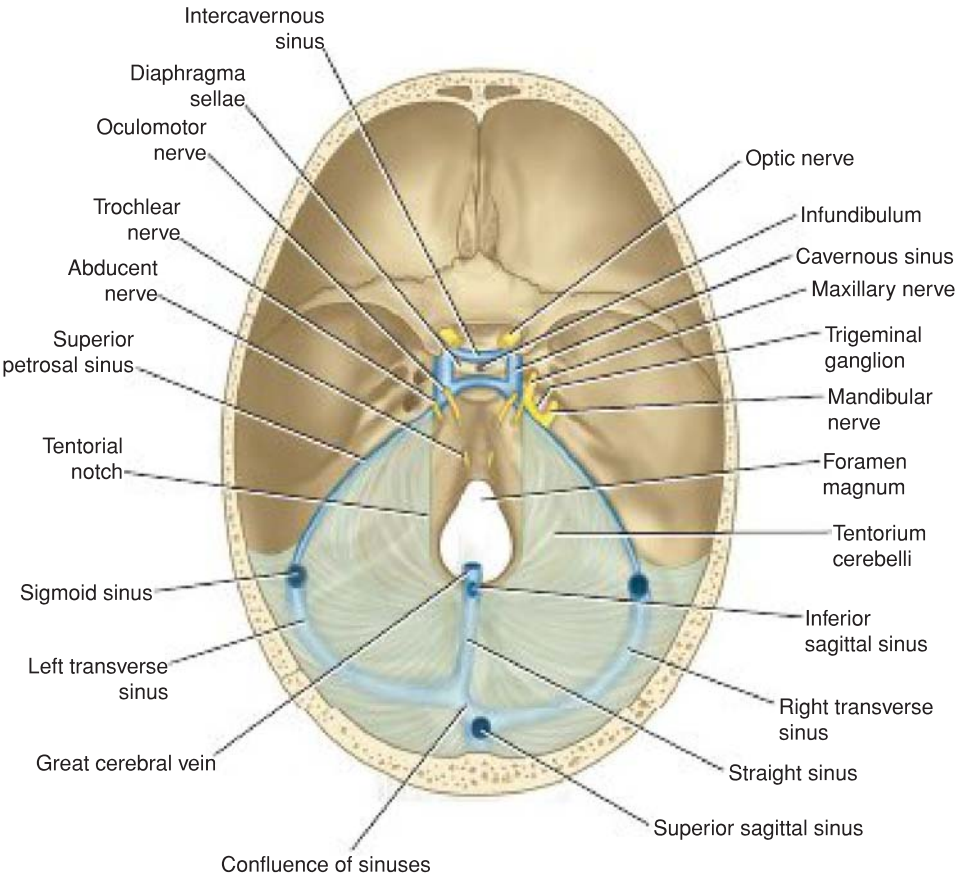


Figure 15-4 Superior view of the diaphragma sellae and tentorium cerebelli. Note the position of the cranial nerves and venous sinuses.

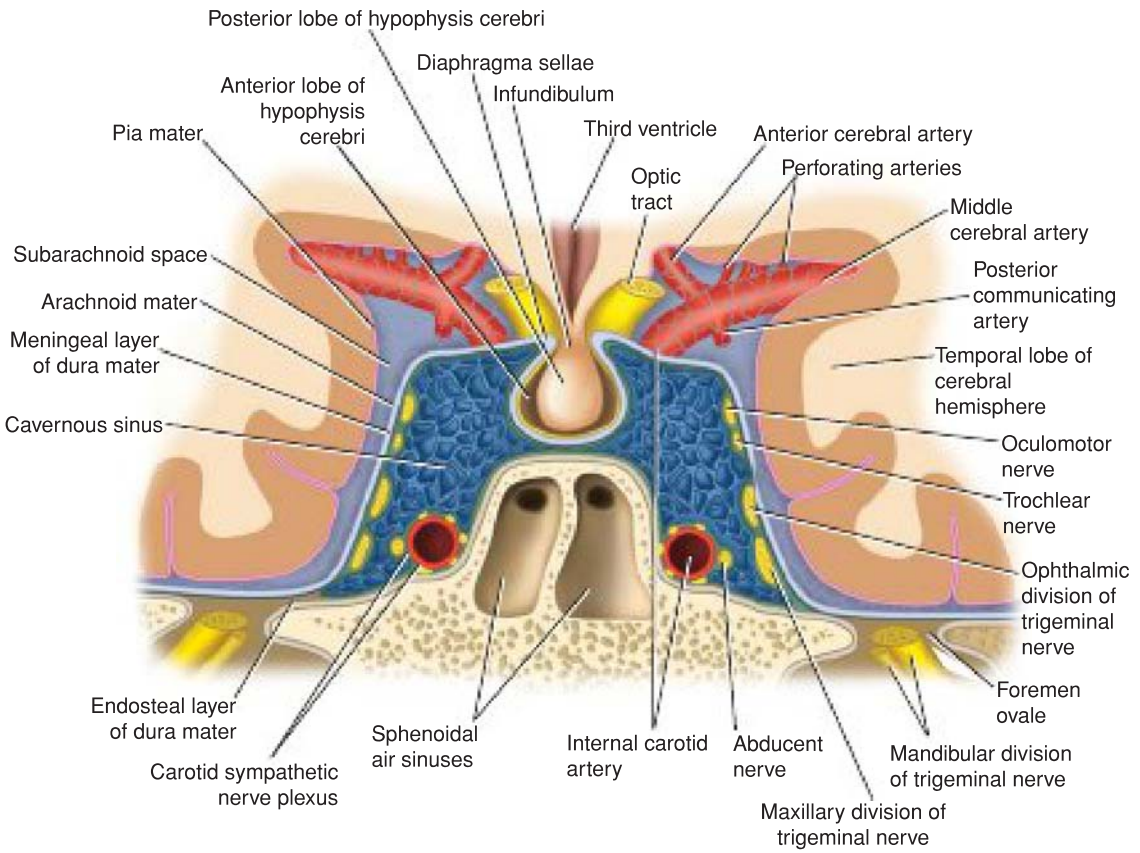


Figure 15-5 Coronal section through the body of the sphenoid bone showing the hypophysis cerebri and cavernous sinuses. Note the position of the internal carotid artery and the cranial nerves.

to the back of the neck and the back of the scalp along the distribution of the greater occipital nerve.

Dural Arterial Supply

Numerous arteries supply the dura mater from the **internal carotid, maxillary**, **ascending pharyngeal**, **occipital**, and **vertebral arteries**. From the clinical standpoint, the most important is the **middle meningeal artery**, which can be damaged in head injuries (Fig. 15-6).

The **middle meningeal artery** arises from the maxillary artery in the infratemporal fossa. It enters the cranial cavity through the **foramen spinosum** and then lies between the meningeal and endosteal layers of dura. The artery then runs forward and laterally in a groove on the upper surface of the squamous part of the temporal bone. The anterior branch deeply grooves or tunnels the anterior-inferior angle of the parietal bone, and its course corresponds roughly to the line of the underlying precentral gyrus of the brain. The posterior branch curves backward and supplies the posterior part of the dura mater (Fig. 15-7).

The **meningeal veins** lie in the endosteal layer of dura (see Fig. 15-6). The middle meningeal vein follows the branches of the middle meningeal artery and drains into the pterygoid venous plexus or the sphenoparietal sinus. The veins lie lateral to the arteries.

Dural Venous Sinuses

The venous sinuses of the cranial cavity are situated between the layers of the dura mater (see Figs. 15-3 to 15-5 and 15-7). Their main function is to receive blood from the brain through the cerebral veins and the cerebrospinal fluid (CSF) from the subarachnoid space through the **arachnoid villi** (see Fig. 16-18). The blood in the dural sinuses ultimately drains into the internal jugular veins in the neck. The dural sinuses are lined by endothelium, and their walls are thick but devoid of muscular tissue. They have no valves. **Emissary veins**, which are also valveless, connect the dural venous sinuses with the **diploic veins** of the skull and with the veins of the scalp (see Fig. 15-1).

The **superior sagittal sinus** occupies the upper fixed border of the falx cerebri (see Figs. 15-1 and 15-4). It begins anteriorly at the foramen cecum, where it occasionally receives a vein from the nasal cavity. It runs posteriorly, grooving the vault of the skull; at the internal occipital protuberance, it deviates to one or the other side (usually the right) and becomes continuous with the corresponding **transverse sinus.** The sinus

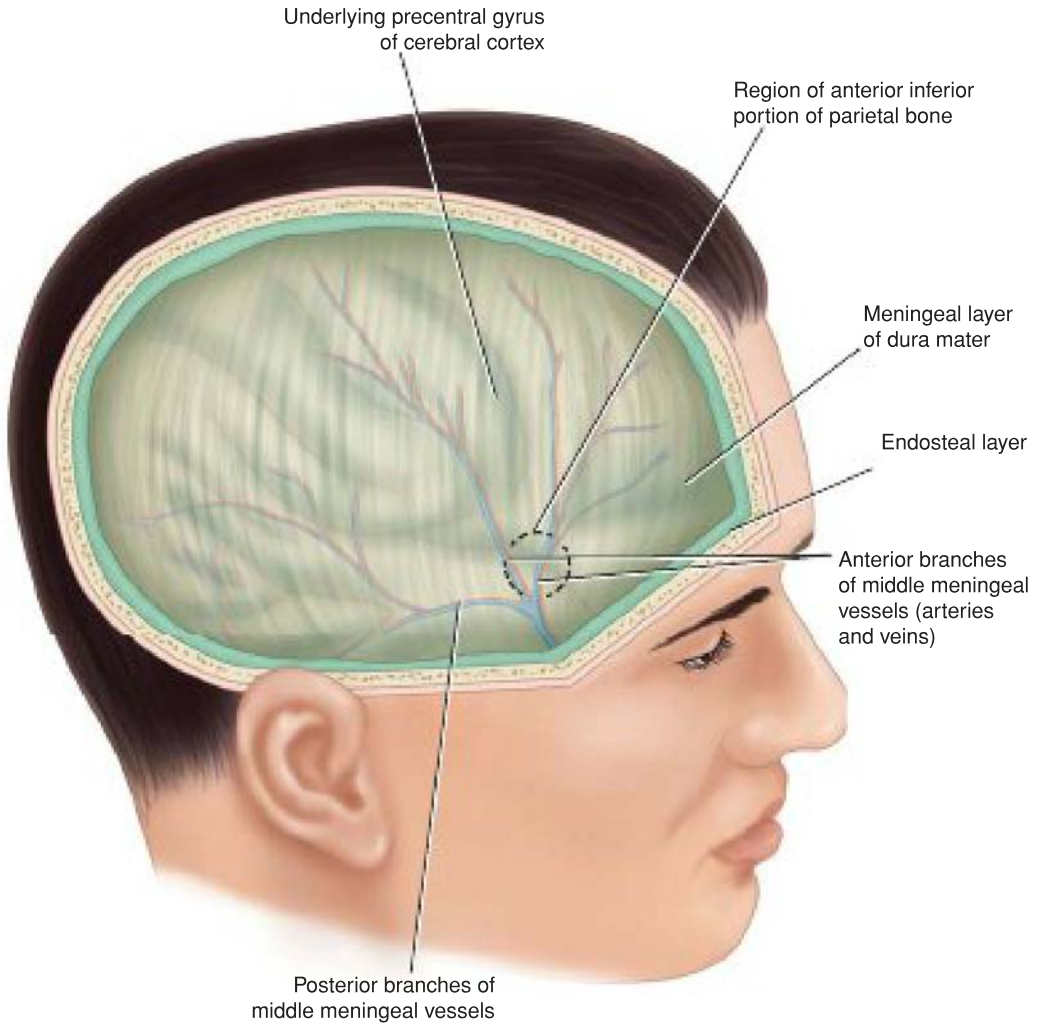


Figure 15-6 Right side of the head showing the relation of the middle meningeal vessels to the layers of the dura mater and the skull.

communicates through small openings with two or three irregularly shaped **venous lacunae** on each side (see Fig. 15-7). Numerous arachnoid villi and granulations project into the lacunae, which also receive the diploic and meningeal veins (see Fig. 15-1).

The superior sagittal sinus in its course receives the **superior cerebral veins** (Fig. 15-1; see Fig. 17-5). At the internal occipital protuberance, it is dilated to form the **confluence of the sinuses** (see Fig. 15-4). Here, the superior sagittal sinus usually becomes continuous with the right transverse sinus; it is connected to the opposite transverse sinus and receives the **occipital sinus.** The **inferior sagittal sinus** occupies the free lower margin of the falx cerebri (see Fig. 15-1). It runs backward and joins the **great cerebral vein** at the free margin of the tentorium cerebelli to form the straight sinus (see Figs. 15-1 and 15-4). It receives a few cerebral veins from the medial surface of the cerebral hemispheres.

The **straight sinus** occupies the line of junction of the falx cerebri with the tentorium cerebelli. It is formed by the union of the **inferior sagittal sinus** with the **great cerebral vein**. It ends by turning to the left (sometimes to the right) to form the **transverse sinus**.

The **transverse sinuses** are paired structures that begin at the internal occipital protuberance (see Figs. 15-3 and 15-4). The right sinus is usually continuous with the superior sagittal sinus, and the left is continuous with the straight sinus. Each sinus occupies the attached margin of the tentorium cerebelli, grooving the occipital bone and the posteroinferior angle of the parietal bone. The transverse sinuses receive the **superior petrosal sinuses**, the **inferior cerebral** and **cerebellar veins**, and the **diploic veins**. They end by turning downward as the **sigmoid sinuses** (see Fig. 15-4).

The **sigmoid sinuses** are a direct continuation of the transverse sinuses. Each sinus turns downward and medially and grooves the mastoid part of the temporal bone. Here, the sinus lies posterior to the mastoid antrum. The sinus then turns forward and then inferiorly through the posterior part of the jugular foramen to become continuous with the **superior bulb** of the **internal jugular vein**.

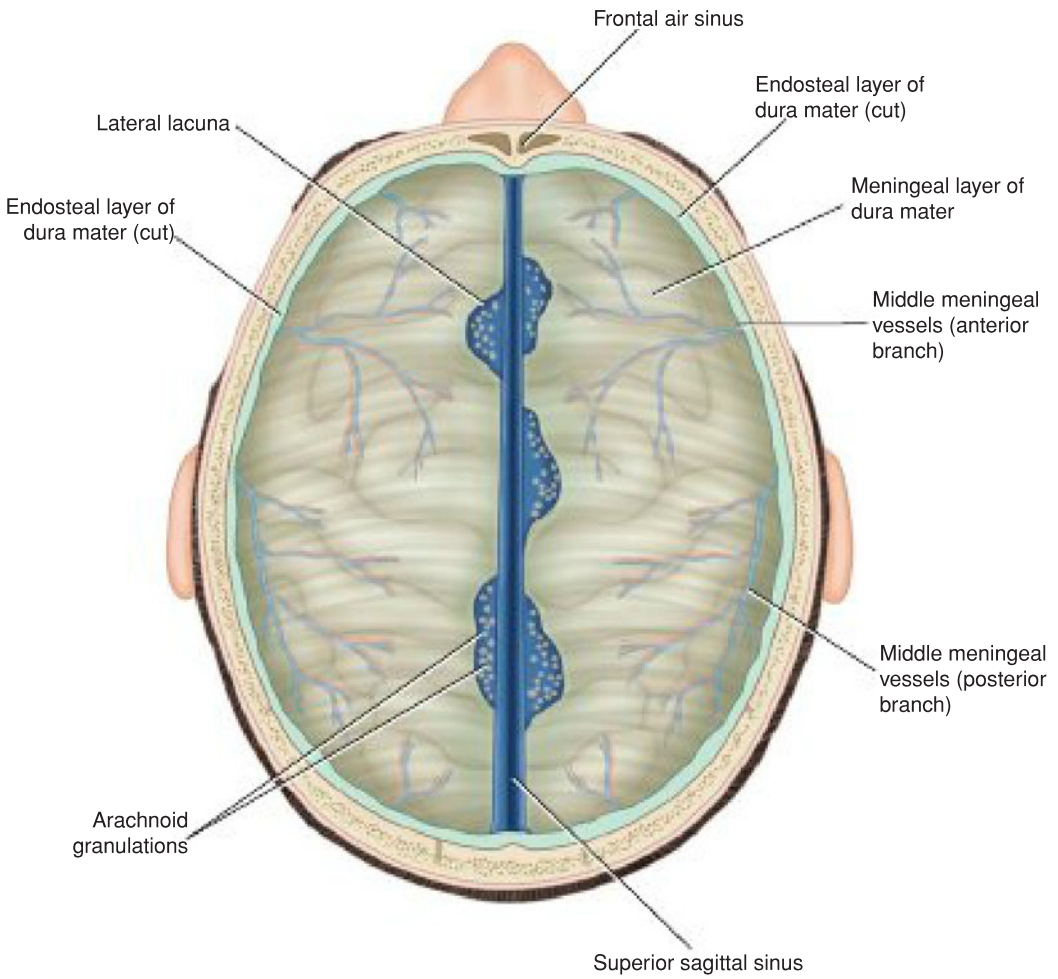


Figure 15-7 Superior view of the head with the calvarium removed. The greater part of the endosteal layer of dura mater has been removed, exposing the underlying meningeal layer of dura and the interior of the superior sagittal venous sinus.

The **occipital sinus** is a small sinus occupying the attached margin of the falx cerebelli. It commences near the foramen magnum where it communicates with the **vertebral veins** and drains into the **confluence of sinuses**.

The **cavernous sinuses** are situated in the middle cranial fossa on each side of the body of the sphenoid bone (see Fig. 15-5). Numerous trabeculae cross their interior, giving them a spongy appearance, hence the name. Each sinus extends from the superior orbital fissure in front to the apex of the petrous part of the temporal bone behind.

The **internal carotid artery**, surrounded by its **sympathetic nerve plexus**, runs forward through the sinus. The **abducens nerve** also passes through the sinus. The internal carotid artery and the nerves are separated from the blood by an endothelial covering.

The **third** and **fourth cranial nerves** and the **ophthalmic** and **maxillary divisions of the trigeminal nerve** run forward in the lateral wall of the sinus. They lie between the endothelial lining and the dura mater. The tributaries are the **superior** and **inferior ophthalmic veins**, the **inferior cerebral veins**, the **sphenoparietal sinus**, and the **central vein of the retina**.

The sinus drains posteriorly into the **superior** and **inferior petrosal sinuses** and inferiorly into the **pterygoid venous plexus**.

The two sinuses communicate with each other by means of the **anterior** and **posterior intercavernous sinuses**, which run in the diaphragma sellae anterior and posterior to the stalk of the hypophysis cerebri (see Fig. 15-4). Each sinus has an important communication with the facial vein through the superior ophthalmic vein. (This is a route by which infection can travel from the facial skin to the cavernous sinus.)

The **superior** and **inferior petrosal sinuses** are small sinuses situated on the superior and inferior borders of the petrous part of the temporal bone on each side of the skull. Each superior sinus drains the cavernous sinus into the transverse sinus, and each inferior sinus drains the cavernous sinus into the internal jugular vein.

Arachnoid Mater

The arachnoid mater is a delicate, impermeable membrane covering the brain and lying between the pia mater internally and the dura mater externally (see Fig. 15-1). It is separated from the dura by a potential space, the **subdural space**, filled by a film of fluid; it is separated from the pia by the **subarachnoid space**, which is filled with **CSF**. The outer and inner surfaces of the arachnoid are covered with flattened mesothelial cells.

The arachnoid bridges over the sulci on the surface of the brain, and in certain situations, the arachnoid and pia are widely separated to form the **subarachnoid cisternae**. The **cisterna cerebellomedullaris** lies between the inferior surface of the cerebellum and the roof of the fourth ventricle. The **cisterna interpeduncularis** lies between the two cerebral peduncles. All the cisternae are in free communication with one another and with the remainder of the subarachnoid space.

In certain areas, the arachnoid projects into the venous sinuses to form **arachnoid villi.** The arachnoid villi are most numerous along the superior sagittal sinus. Aggregations of arachnoid villi are referred to as **arachnoid granulations** (see Fig. 15-7). Arachnoid villi serve as sites where the CSF diffuses into the bloodstream.

The arachnoid is connected to the pia mater across the fluid-filled subarachnoid space by delicate strands of fibrous tissue.

Structures passing to and from the brain to the skull or its foramina must pass through the subarachnoid space. All the cerebral arteries and veins lie in the space, as do the cranial nerves (see Figs. 15-1 and 15-5). The arachnoid fuses with the epineurium of the nerves at their point of exit from the skull (see Fig. 15-2B). In the case of the **optic nerve**, the arachnoid forms a sheath for the nerve, which extends into the orbital cavity through the optic canal and fuses with the sclera of the eyeball (Fig. 15-8). Thus, the subarachnoid space extends around the optic nerve as far as the eyeball.

The **CSF** is produced by the **choroid plexuses** within the lateral, third, and fourth ventricles of the brain. It escapes from the ventricular system of the brain through the three foramina in the roof of the fourth ventricle and so enters the subarachnoid space. It now circulates both upward over the surfaces of the cerebral hemispheres and downward around the spinal cord. The spinal subarachnoid space extends down as far as the **second sacral vertebra** (see pp. 426-427). Eventually, the fluid enters the bloodstream by passing into the arachnoid villi and diffusing through their walls.

In addition to removing waste products associated with neuronal activity, the CSF provides a fluid medium in which the brain floats. This mechanism effectively protects the brain from trauma. In addition, the fluid is now believed to play a role in hormonal transport.

Pia Mater

The pia mater is a vascular membrane covered by flattened mesothelial cells. It closely invests the brain, covering the gyri and descending into the deepest sulci (see Fig. 15-1). It extends out over the cranial nerves and fuses with their epineurium. The cerebral arteries entering the substance of the brain carry a sheath of pia with them.

The pia mater forms the **tela choroidea** of the roof of the third and fourth ventricles of the brain, and it fuses with the ependyma to form the choroid plexuses in the lateral, third, and fourth ventricles of the brain.

SPINAL CORD MENINGES

Like the brain, the spinal cord in the vertebral column is also protected by three layers of meninges.

Dura Mater

The dura mater is a dense, strong, fibrous membrane that encloses the spinal cord and the cauda equina

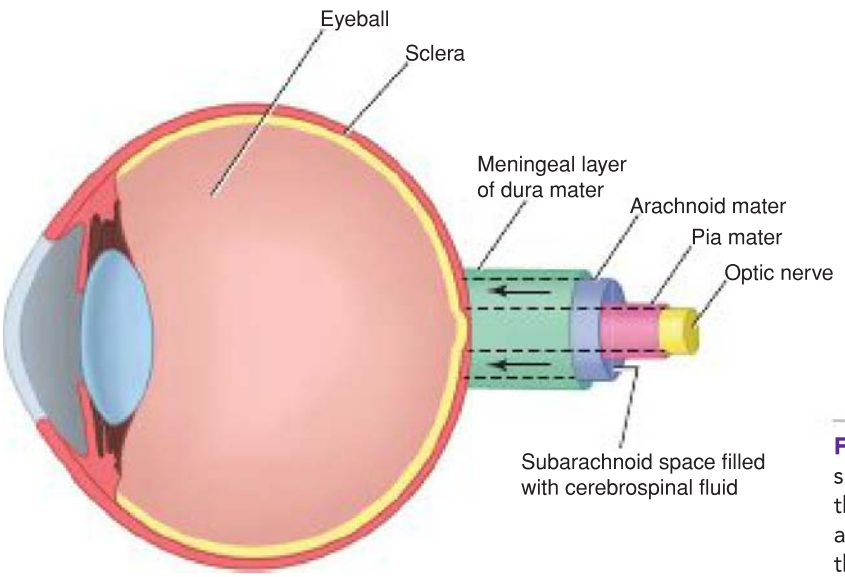


Figure 15-8 Sagittal section of the eyeball showing the attachment of the meninges to the sclera. Note the extension of the subarachnoid space around the optic nerve to the eyeball.

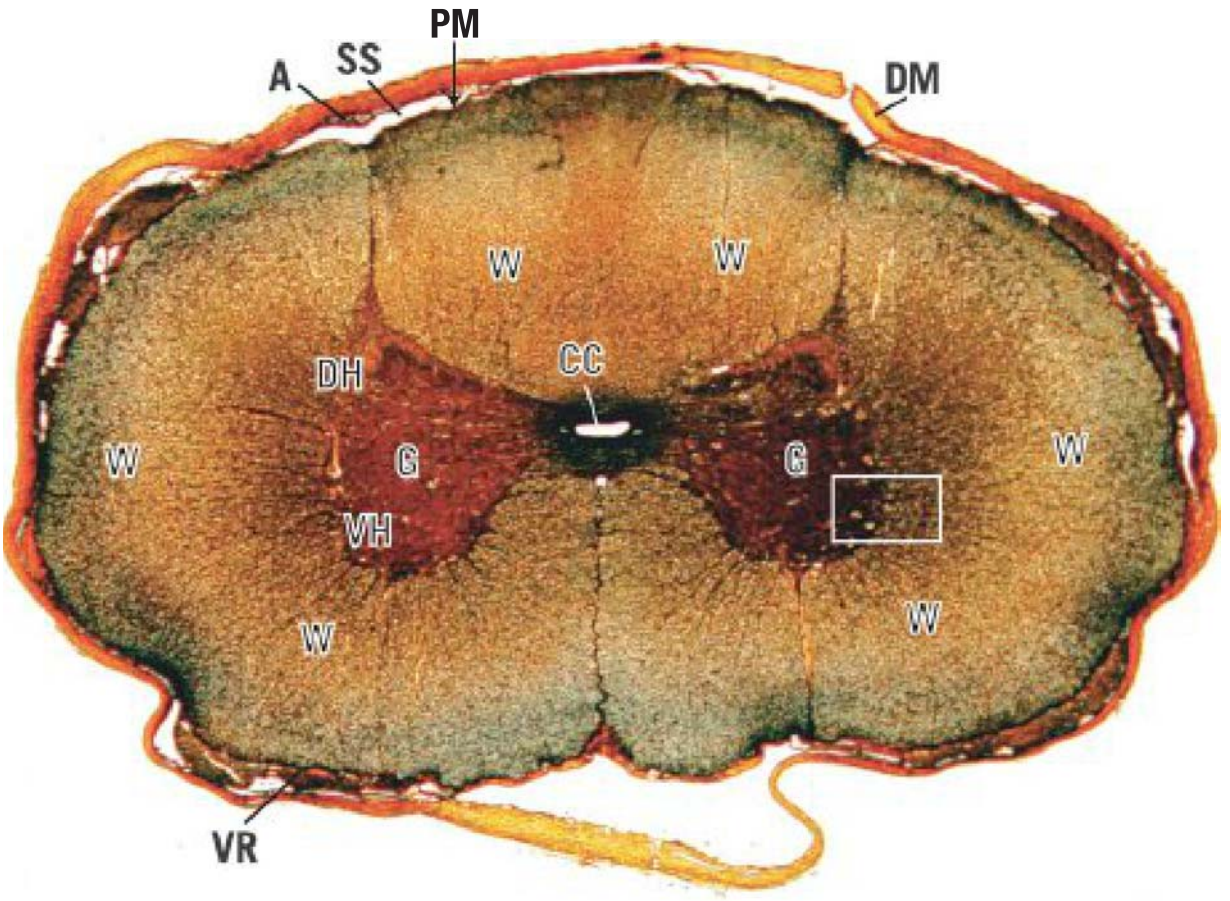


Figure 15-9 This silver stain of a cat spinal cord shows the spinal cord and its meninges: dura mater (DM), arachnoid mater (A) with its subarachnoid space (SS), and pia mater (PM). W, white matter; G, gray matter; DH, dorsal horn; VH, ventral horn; Gc, gray commissure; CC, central canal; VR, ventral roots; DR, dorsal roots. (From Gartner, L. P. (2018). *Color atlas and text of histology* (7th ed.). Baltimore, MD: Wolters Kluwer.)

(Figs. 15-9 to 15-11). It is continuous above through the foramen magnum with the meningeal layer of dura covering the brain. Inferiorly, it ends on the filum terminale at the level of the lower border of the second sacral vertebra. The dural sheath lies loosely in the vertebral canal and is separated from the wall of the canal by the **extradural space**. This contains loose areolar tissue and the **internal vertebral venous plexus**. The dura mater extends along each nerve root and becomes continuous with the connective tissue surrounding each spinal nerve (epineurium). The inner surface of the dura mater is in contact with the arachnoid mater (see Fig. 4-5).

Arachnoid Mater

The arachnoid mater is a delicate impermeable membrane that covers the spinal cord and lies between the pia mater internally and dura mater externally. It is separated from the pia mater by a wide space, the **subarachnoid space**, which is filled with **CSF**. The subarachnoid space is crossed by a number of fine strands of connective tissue. The arachnoid mater is continuous above through the foramen magnum with the arachnoid covering the brain. Inferiorly, it ends on the filum terminale at the level of the lower border of the second sacral vertebra (see Figs. 15-10 and 15-11). The arachnoid mater continues along the spinal nerve roots, forming small lateral extensions of the subarachnoid space.

Pia Mater

The pia mater, a vascular membrane that closely covers the spinal cord (see Fig. 15-9B), is thickened on either side between the nerve roots to form the **ligamentum denticulatum**, which passes laterally to adhere to the arachnoid and dura. By this means, the spinal cord is suspended in the middle of the dural sheath. The pia mater extends along each nerve root and becomes continuous with the connective tissue surrounding each spinal nerve.

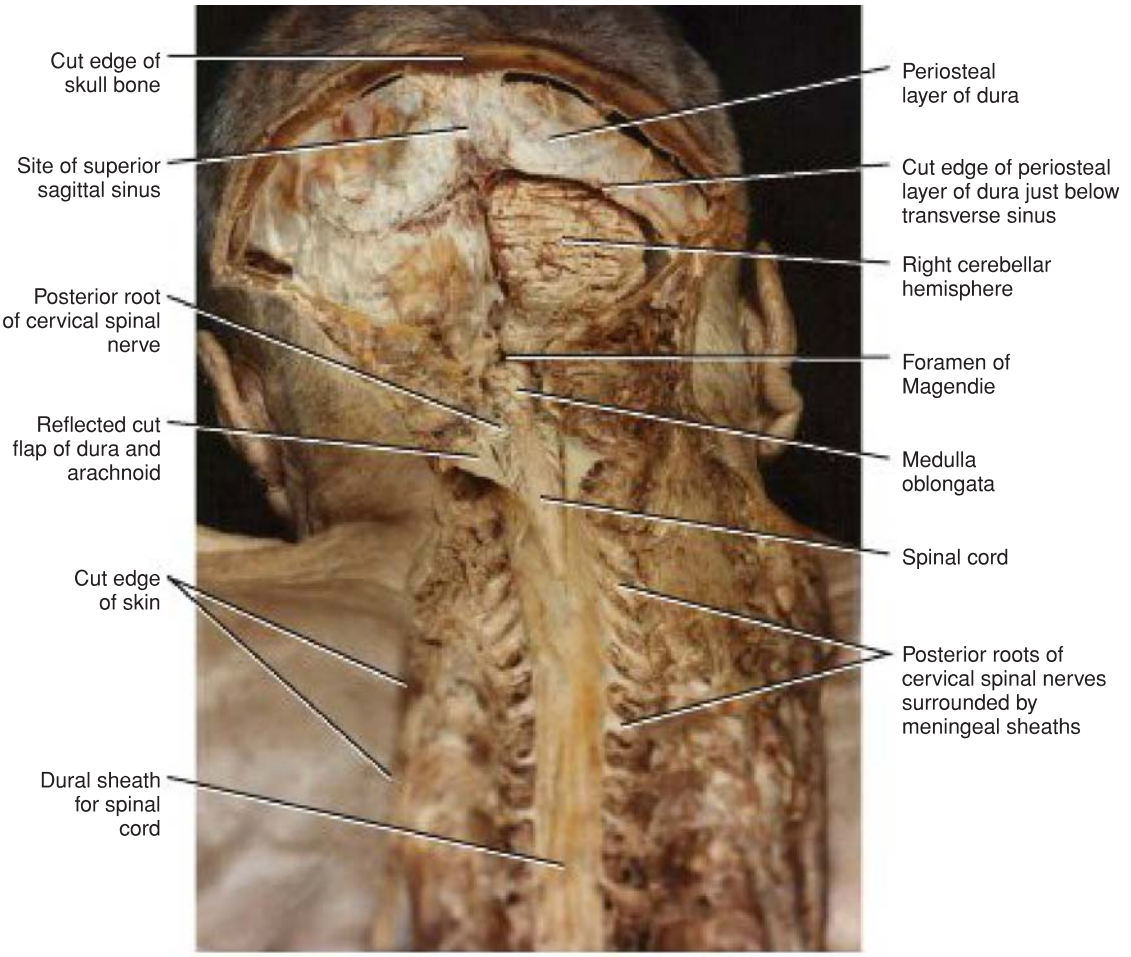


Figure 15-10 Dissection of the back of the head and neck. The greater part of the occipital bone has been removed, exposing the periosteal layer of dura. On the right side, a window has been made in the dura below the transverse venous sinus to expose the cerebellum and the medulla oblongata in the posterior cranial fossa. In the neck, the dura and arachnoid have been incised in the midline to expose the spinal cord and rootlets of the cervical spinal nerves. Note the cervical spinal nerves leaving the vertebral canal enveloped in a meningeal sheath.

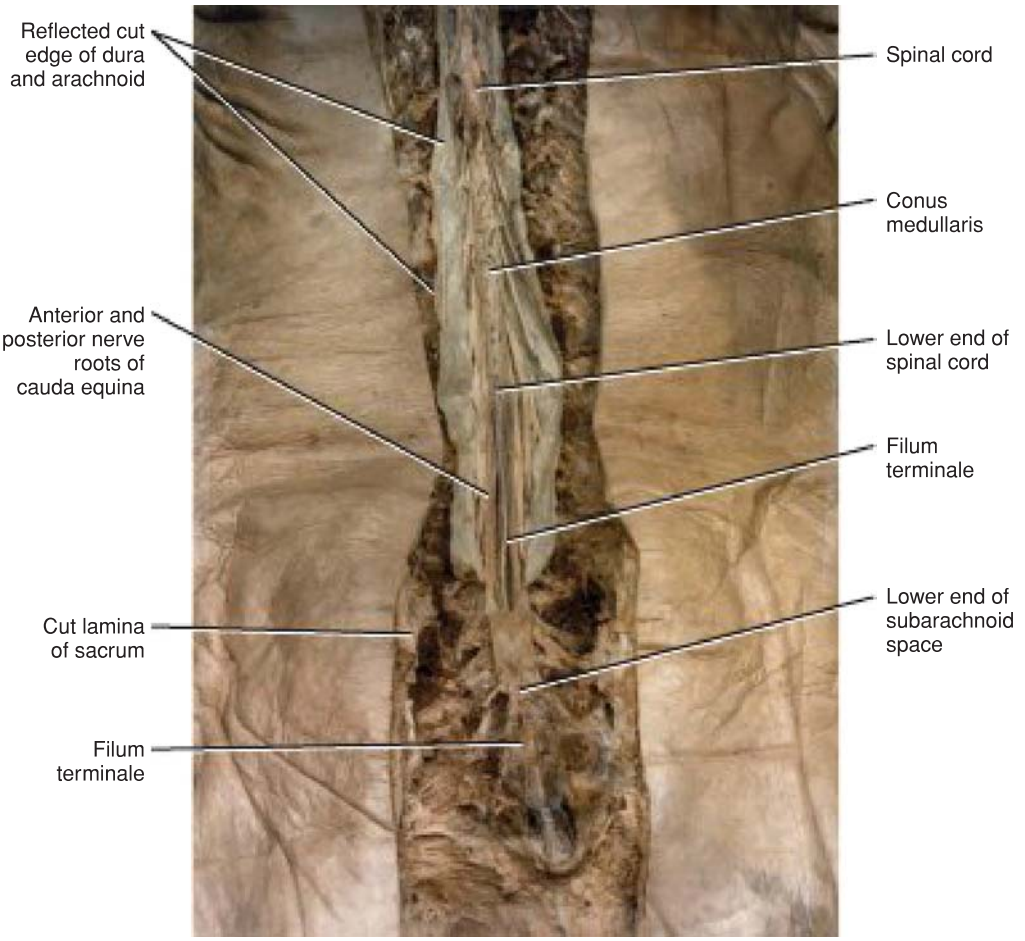


Figure 15-11 Dissection of the lower part of the back, including a complete laminectomy of the lumbar and sacral regions of the vertebral column. The meningeal sheath has been incised and reflected laterally, exposing the subarachnoid space, the lower end of the spinal cord, and the cauda equina. Note the filum terminale surrounded by the anterior and posterior nerve roots of the lumbar and sacral spinal nerves forming the cauda equina.

Clinical Notes

Functional Significance

The meninges of the brain and spinal cord form three concentric membranous coverings. The outermost covering, the dura mater, by virtue of its toughness, serves to protect the underlying nervous tissue. The dura protects the cranial nerves by forming a sheath that covers each cranial nerve for a short distance as it passes through foramina in the skull. The dura mater also provides each spinal nerve root with a protective sheath.

In the skull, the falx cerebri, which is a vertical sheet of dura between the cerebral hemispheres, and the tentorium cerebelli, which is a horizontal sheet that projects forward between the cerebrum and cerebellum, serve to limit excessive movements of the brain within the skull.

The arachnoid mater is a much thinner impermeable membrane that loosely covers the brain. The interval between the arachnoid and pia mater, the subarachnoid space, is filled with CSF. The CSF gives buoyancy to the brain and protects the nervous tissue from mechanical forces applied to the skull.

The pia mater is a vascular membrane that closely invests and supports the brain and spinal cord.

Excessive Brain Movement

When a moving patient's head is suddenly halted, the momentum of the brain causes it to travel onward until its movement is resisted by the skull or the strong septa of the dura mater. In lateral movements, the lateral surface of one hemisphere hits the side of the skull and the medial surface of the opposite hemisphere hits the side of the falx cerebri. In superior movements, the superior surfaces of the cerebral hemispheres hit the vault of the skull, and the

superior surface of the corpus callosum hits the sharp free edge of the falx cerebri; the superior surface of the cerebellum presses against the inferior surface of the tentorium cerebelli.

Movements of the brain relative to the skull and dural septa may seriously injure the cranial nerves that are tethered as they pass through the various foramina. Furthermore, the fragile cortical veins that drain into the dural sinuses may be torn, resulting in severe **subdural** or **subarachnoid hemorrhage**. The tortuous arteries, with their strong walls, are rarely damaged.

Intracranial Hemorrhage

Excessive brain movement or other cranial trauma can put significant traction on the cranial vessels, leading to rupture and hemorrhage. Intracranial hemorrhage is described based on its relationship to the adjacent layers of the meninges: epidural, subdural, and subarachnoid.

Epidural Hemorrhage

Epidural hemorrhage results from injuries to the meningeal arteries or veins. The most common artery to be damaged is the **anterior division of the middle meningeal artery**. A comparatively minor blow to the side of the head, resulting in fracture of the skull in the region of the anterior-inferior portion of the parietal bone, may sever the artery. Arterial or venous injury is especially liable to occur if the vessels enter a bony canal in this region. Bleeding occurs and strips up the meningeal layer of dura from the internal surface of the skull. The intracranial pressure rises and the enlarging blood clot exerts local pressure on the underlying motor area in the precentral gyrus. Blood also passes laterally through the fracture line to form a soft swelling under the temporalis muscle.

To stop the hemorrhage, the torn artery or vein must be ligated or plugged. The burr hole through the skull wall should be placed about 1½ in (4 cm) above the midpoint of the zygomatic arch.

Subdural Hemorrhage

Subdural hemorrhage results from tearing of the **superior cerebral veins** at their point of entrance into the superior sagittal sinus. The cause is usually a blow on the front or the back of the head, causing excessive anteroposterior displacement of the brain within the skull. Acute and chronic forms of the condition occur.

Computed Tomography Scans

The different appearances of the blood clots in these two conditions as seen on CT scans are related to the anatomy of the area (Fig. 15-12). In an epidural hemorrhage, the blood strips up the meningeal layer of the dura from the endosteal layer of dura (periosteum of the skull), producing a **lens-shaped** hyperdense collection of blood that compresses the brain and displaces the midline structures to the opposite side. The shape of the blood clot is determined by the adherence of the meningeal layer of dura to the periosteal layer of dura.

In patients with subdural hematoma, the blood accumulates in the extensive potential space between the meningeal layer of dura and the arachnoid, producing a long **crescent-shaped,** hyperdense rim of blood that extends from anterior to posterior along the inner surface of the skull. With a large hematoma, the brain sulci are obliterated and the midline structures are displaced to the opposite side.

Subarachnoid and Cerebral Hemorrhages

Subarachnoid and cerebral hemorrhages are described on page 474.

Intracranial Hemorrhage in the Infant

Intracranial hemorrhage may occur during birth and may result from excessive molding of the head. Bleeding may occur from the cerebral veins or the venous sinuses. Excessive anteroposterior compression of the head often tears the anterior attachment of the falx cerebri from the tentorium cerebelli. Bleeding then takes place from the great cerebral veins, the straight sinus, or the inferior sagittal sinus.

The shaken baby syndrome is described on page 22.

Headache

The brain itself is insensitive to pain; therefore, headaches are due to the stimulation of receptors outside the brain.

Meningeal Headaches

The dura mater receives its sensory nerve supply from the trigeminal and the first three cervical nerves. The dura above the tentorium is innervated by the trigeminal nerve, and the headache is referred to the forehead and face. The dura below the tentorium is innervated by the cervical nerves, and the headache is referred to the back of the head and neck. **Meningitis**, or inflammation of the meninges, causes severe headache over the entire head and back of the neck.

Headaches Caused by Cerebral Tumors

An expanding tumor with its associated raised intracranial pressure produces severe, continuous, and progressive headache caused by the irritation and stretching of the dura. A tumor above the tentorium tends to produce a headache referred to the front of the head, while a tumor below the tentorium produces a headache referred to the back of the head.

Migraine Headache

Migraine is a common form of headache, which may be unilateral or bilateral, recurring at intervals and associated with prodromal visual disturbances. The prodromal visual disturbances are thought to be due to sympathetic vasoconstriction of the cerebral arteries supplying the visual cortex. The headache is chiefly due to the dilation and stretching of other cerebral arteries and branches of the external carotid artery. The disease therefore appears to affect arteries both inside and outside the skull, and its cause is unknown, although genetic, hormonal, and biochemical factors may initiate an attack. β-blockers bring relief to some patients due to the reduction in cerebral vasodilation.

Alcoholic Headache

Alcoholic headache is due to the direct toxic effect of alcohol on the meninges.

Headaches Due to Diseases of the Teeth, Paranasal Sinuses, and Eyes

Dental infection and sinusitis are common causes of headache. The pain is referred to the skin of the face and the forehead along the branches of the trigeminal nerve. Tonic spasm of the ciliary muscle of the eye, when attempting to focus on an object for prolonged periods (e.g., reading small print), may cause severe orbital headache. This commonly occurs in individuals who need lenses for the correction of presbyopia.

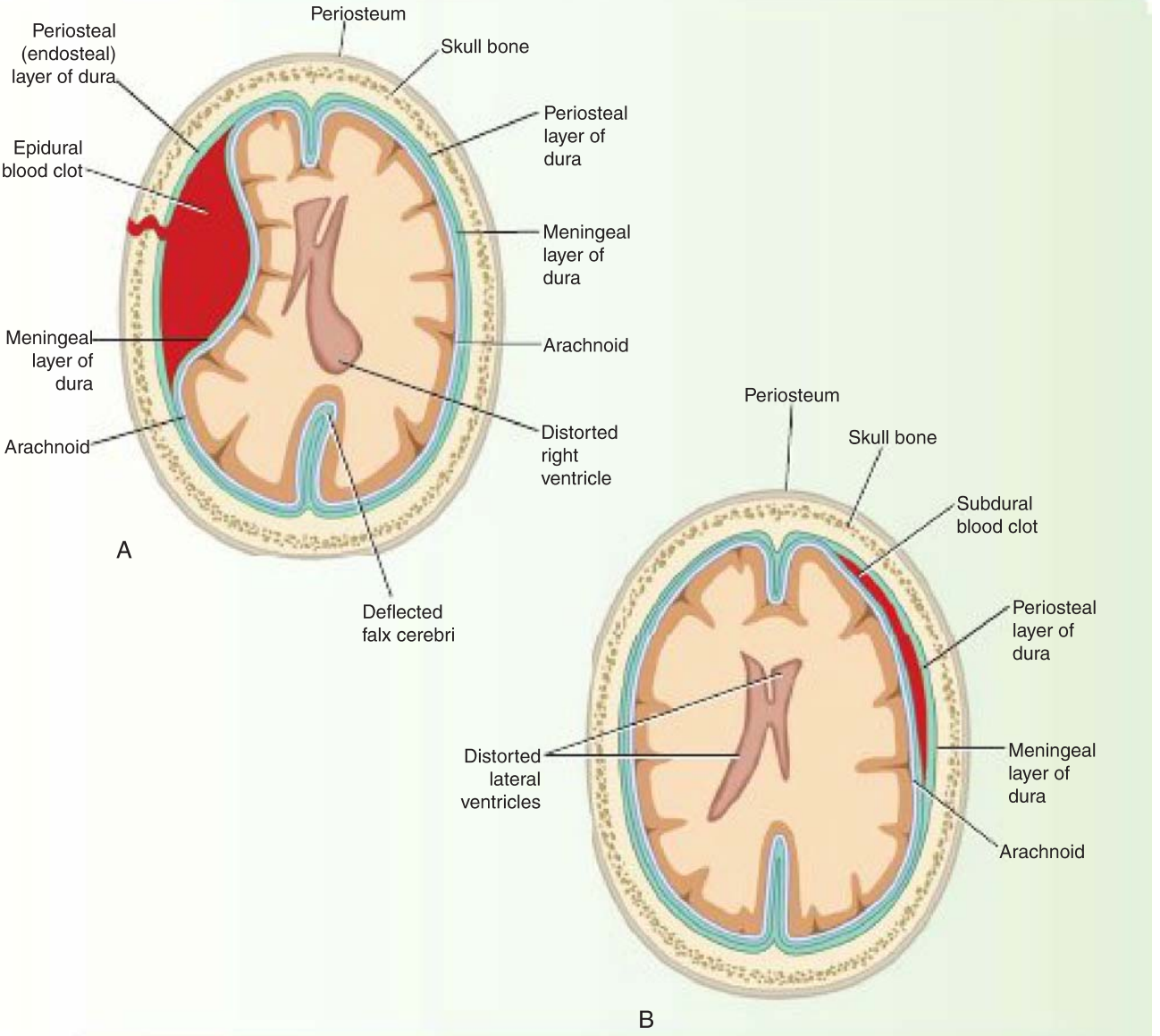


Figure 15-12 Diagrammatic representation of an epidural hemorrhage and a subdural hemorrhage. **A:** Epidural hemorrhage from the middle meningeal artery or vein on the left side. The hematoma is lens shaped and occupies the space between the endosteal layer of dura (periosteum of the skull) and the meningeal layer of dura (true dura, hence the name *epidural*). **B:** Subdural hemorrhage from the cerebral veins at the site of entrance into the venous sinus on the right side. The hematoma is crescent shaped and occupies the space between the meningeal layer of dura and the arachnoid (i.e., beneath the dura).

Key Concepts

Brain Meninges

- The brain in the skull and the spinal cord in the vertebral canal are surrounded by three protective membranes or meninges: dura mater, arachnoid mater, and pia mater.

Dura Mater

- In the skull, the dura mater has two layers, an endosteal layer and a meningeal layer. The endosteal layer is essentially the periosteum of the skull and therefore not present in the vertebral canal.
- The meningeal layer or dura mater proper is a dense, strong fibrous membrane that forms four inward septa, which divide the cranial cavity into freely communicating spaces.
- The falx cerebri is the largest dural fold and separates the two cerebral hemispheres at midline.
- The tentorium cerebelli is continuous with the falx cerebri and separates the cerebrum from the cerebellum.
- The falx cerebelli separates the two cerebellar hemispheres.
- The diaphragma sellae forms the roof over the sella turcica, which houses the pituitary gland.

DURAL NERVE SUPPLY

- Branches of the trigeminal, vagus, and the first three cervical spinal nerves innervate the cranial dura.

DURAL ARTERIAL SUPPLY

- Multiple arteries supply the dura but from the clinical standpoint, the middle meningeal artery is the most important as it is the only arterial vessel found between the meningeal and endosteal layers of dura.

DURAL VENOUS SINUSES

- The venous sinuses are found between the two layers of dura.
- The superior and inferior sagittal sinuses are located within the falx cerebri.
- The inferior sagittal sinus joins the straight sinus which is located at the junction of the falx cerebri and tentorium cerebelli.
- The occipital sinus is located within the falx cerebelli.
- The superior sagittal sinus, straight sinus, and occipital sinus come together at the confluence of sinuses, which then drains laterally into two transverse sinuses.
- The sigmoid sinuses are a direct continuation of the transverse sinuses and eventually exit the cranial cavity through the jugular foramen, at this point becoming the internal jugular vein.

Arachnoid Mater

- A delicate impermeable membrane lying between the dura mater and pia mater.
- It is separated from the pia mater by the subarachnoid space, which is filled with CSF.
- In certain areas, the arachnoid protrudes into the dural venous sinuses as arachnoid villi, which serve as sites where CSF diffuses into the bloodstream.
- The vasculature for the central nervous system is located in the subarachnoid space.

Pia Mater

- The pia mater is a vascular membrane that closely invests the brain, covering the gyri and descending into the deepest sulci.
- The cerebral arteries entering the substance carry a sheath of pia with them.

Spinal Cord Meninges

- The dura mater of the spinal cord is continuous with the meningeal layer of the cranial dura.
- The arachnoid mater is continuous with cranial arachnoid mater and maintains the same meningeal relationships in the vertebral canal as the cranial cavity.
- The pia mater closely covers the spinal cord and has multiple thickenings on either side, called denticulate ligaments, that form a means of suspension for the spinal cord in the dural sheath.

Clinical Problem Solving

1. In a head trauma accident, which structures within the skull limit damage to the cerebral hemispheres and other parts of the brain? Which blood vessels are damaged more commonly, the cerebral arteries or the cerebral veins? Are cranial nerves likely to be damaged in head injuries? If so, which ones are damaged most commonly and what is the reason for their increased susceptibility?
2. While performing an autopsy on a patient who had died of a meningioma, the pathologist explains to a group of students that these tumors arise from the arachnoid mater. She explains that they occur in those areas in which the arachnoid pierces the dura to form the arachnoid villi that project into the dural venous sinuses. She then asks the students where they would expect to find meningiomas. How would you answer that question?
3. A 10-year-old girl is admitted to hospital for surgical correction of medial strabismus of the right eye. Twenty-four hours after successful completion of the operation, her right eyeball is noted to project forward excessively (proptosis) and the conjunctiva of the right eye is inflamed. A watery, purulent discharge is expressed from beneath the eyelids. The ophthalmologist is greatly concerned because he does not want the complication of cavernous sinus thrombosis to occur. What is the connection between infection of the eye and cavernous sinus thrombosis? Is cavernous sinus thrombosis a serious condition?
4. On examination, a 41-year-old man is found to have paralysis of the lateral rectus muscle of his left eye; the left pupil is dilated but reacts slowly to light, and anesthesia of the skin over the left side of the forehead is noted. A carotid arteriogram reveals the presence of an aneurysm of the right internal carotid artery situated in the cavernous sinus. Using your knowledge of anatomy, explain the clinical findings on physical examination.
5. On ophthalmoscopic examination, a 45-year-old woman is found to have edema of both optic discs (*bilateral papilledema*) and congestion of the retinal veins. The cause of the condition is found to be a rapidly growing intracranial tumor. Using your knowledge of anatomy, explain the papilledema. Why does the patient exhibit bilateral papilledema?
6. A pediatrician is observing a 6-year-old boy playing with his toys. He notes that the child has perfectly normal use of his arms but that his legs are stiff; and when he walks, he tends to cross his legs and has a scissorlike gait. A diagnosis of cerebral diplegia secondary to birth injuries is made. (Note that congenital cerebral diplegia is believed by some authorities to occur early in fetal life and to be caused by a viral infection that arrests cerebral development.) Apparently, the child was born prematurely and he was a breech presentation. Using your knowledge of anatomy, explain what happens to the fetal skull bones during delivery. Why are the dural venous sinuses likely to be damaged at birth? Why is cerebral hemorrhage more likely to occur in a premature baby with a malpresentation?
7. A 25-year-old woman is admitted to the emergency department unconscious after being hit on the side of the head by a car while crossing the road. Within an hour, her state of unconsciousness deepens. On examination, she is found to have a large, doughlike swelling over the right temporalis muscle. She also has the signs of right-sided hemiplegia. Later, a right-sided, fixed, dilated pupil develops. A lateral radiograph of the skull shows a fracture line across the groove for the anterior division of the right middle meningeal artery. Her coma deepens and she dies 4 hours after the accident. Using your knowledge of neuroanatomy, make a diagnosis in this case. Explain the clinical findings. How could you account for the homolateral hemiplegia?
8. A 50-year-old woman complaining of a severe headache of 3 days' duration visits her physician. She says that the headache had started getting very severe about 1 hour after she hit her head on the mantelpiece after bending down to poke the fire. She is admitted to the hospital for observation. Three hours later, she becomes confused and also develops a right-sided hemiplegia on the side of the body opposite to the head injury. She has exaggeration of the deep reflexes and a positive Babinski response on the right side. Examination of the cerebrospinal fluid with a lumbar puncture shows raised pressure and the presence of blood in the fluid. Radiographic examination shows no fracture of the skull. A CT scan reveals the presence of a subdural hematoma. What exactly is a subdural hematoma?

Answers and Explanations to Clinical Problem Solving

1. The meninges and the cerebrospinal fluid afford a remarkable degree of protection to the delicate brain. The dural partitions, especially the falx cerebri and the tentorium cerebelli, limit the extent of brain movement within the skull.

   The thin-walled cerebral veins are liable to be damaged during excessive movements of the brain relative to the skull, especially at the point where the veins join the dural venous sinuses. The thick-walled cerebral arteries are rarely damaged.

   The small-diameter cranial nerves of long length are particularly prone to damage during head injuries. The trochlear, abducens, and oculomotor nerves are commonly injured.
2. Meningiomas arise from the arachnoid villi found along the dural venous sinuses. They are therefore most commonly found along the superior sagittal sinus and the sphenoparietal sinuses. They are rare below the tentorium cerebelli.
3. The anterior facial vein, the ophthalmic veins, and the cavernous sinus are in direct communication with one another. Infection of the skin of the face alongside the nose, ethmoidal sinusitis, and infection of the orbital contents can lead to thrombosis of the veins and ultimately cavernous sinus thrombosis. If untreated with antibiotics, this condition can be fatal, since the cavernous sinus drains many cerebral veins from the inferior surface of the brain.
4. The internal carotid artery passes forward on the lateral surface of the body of the sphenoid within the cavernous sinus. An aneurysm of the artery may press on the abducens nerve and cause paralysis of the lateral rectus muscle. Further expansion of the aneurysm may cause compression of the oculomotor nerve and the ophthalmic division of the trigeminal nerve as they lie in the lateral wall of the cavernous sinus. This patient had left lateral rectus paralysis and paralysis of the left pupillary constrictor muscle owing to involvement of the abducens and oculomotor nerves, respectively. The slight anesthesia of the skin over the left side of the forehead was due to pressure on the ophthalmic division of the left trigeminal nerve.
5. The optic nerves are surrounded by sheaths derived from the pia mater, arachnoid mater, and dura mater. The intracranial subarachnoid space extends forward around the optic nerve to the back of the eyeball. A rise in cerebrospinal fluid pressure due to an intracranial tumor will compress the thin walls of the retinal vein as it crosses the extension of the subarachnoid space in the orbital cavity. This will result in congestion of the retinal vein and bulging of the optic disc involving both eyes.
6. During the descent of the fetal head through the birth canal during labor, the bones of the calvarium overlap, a process known as molding. If this process is excessive or takes place too rapidly, as in malpresentations or in premature deliveries (when a small fetus is birthed rapidly), an abnormal strain is put on the falx cerebri. This stress involves the superior sagittal sinus, especially if the anteroposterior compression is excessive, and the sinus may tear where it joins the transverse sinus. The great cerebral vein may tear as well. The result is either a subarachnoid or subdural hemorrhage with accompanying brain damage.
7. The initial loss of consciousness was due to concussion or cerebral trauma. The swelling over the right temporalis and the radiographic finding of a fracture over the right middle meningeal artery were due to hemorrhage from the artery into the overlying muscle and soft tissue. This patient had an extradural hemorrhage. The right homolateral hemiplegia was due to the compression of the left cerebral peduncle against the edge of the tentorium cerebelli. This is unusual. A left hemiplegia due to pressure on the right precentral gyrus is more common. The right-sided, fixed, dilated pupil was due to the pressure on the right oculomotor nerve by the hippocampal gyrus, which had herniated through the tentorial notch.
8. A subdural hematoma is an accumulation of blood in the interval between the meningeal layer of dura and the arachnoid mater. It results from tearing of the superior cerebral veins at their point of entrance into the superior sagittal sinus. The cause is usually a blow on the front or the back of the head, causing excessive anteroposterior displacement of the brain within the skull. A subdural hematoma can be easily identified by CT as a dense rim of blood extending along the inner table of the skull, obliterating the cerebral fissures and displacing the cerebral structures to the opposite side.

Review Questions

Directions: Each of the numbered items in this section is followed by answers. Select the ONE lettered answer that is CORRECT.

1. The following statements concern the meninges of the brain:
   (a) Both layers of the dura mater covering the brain are continuous through the foramen magnum with the dura covering the spinal cord.
   (b) The periosteal layer of dura mater is not continuous with the sutural ligaments of the skull.
   (c) As each cranial nerve passes through a foramen in the skull, it is surrounded by a tubular sheath of arachnoid mater only.
   (d) The cranial venous sinuses run between the meningeal and endosteal layers of dura mater.
   (e) The meninges extend anteriorly through the optic canal and fuse with the periosteum of the orbital cavity.
2. The following general statements concern the meninges:
   (a) The cisterna cerebellomedullaris lies between the inferior surface of the cerebellum and the roof of the fourth ventricle and contains lymph.
   (b) The arachnoid mater is permeable to cerebrospinal fluid (CSF).
   (c) The CSF in the arachnoid villi is able to drain into the venous sinuses through small tubules lined with endothelial cells.
   (d) The arachnoid mater surrounding the spinal cord ends inferiorly on the filum terminale at the level of the lower border of the first sacral vertebra.
   (e) The extradural space that separates the dural sheath of the spinal cord and the walls of the vertebral canal contains the external vertebral venous plexus.
3. The following statements concern the tentorium cerebelli:
   (a) The free border is attached anteriorly to the posterior clinoid processes.
   (b) It is formed from the meningeal layer of the dura mater.
   (c) It separates the cerebellum from the temporal lobes of the brain.
   (d) The sigmoid sinus lies within its attached border to the occipital bone.
   (e) The anterior edge houses the occipital venous sinus.
4. The following statements concern headache:
   (a) Brain tissue is insensitive to pain.
   (b) Intracranial pain arises from receptors situated in the pia mater.
   (c) An expanding cerebral tumor located in the posterior cranial fossa would produce pain referred to the face.
   (d) Migraine headache is believed to be due to dilation of the cerebral veins.
   (e) Headaches associated with presbyopia are due to tonic spasm of the frontalis muscles of the forehead.
5. The following statements concern the subarachnoid space:
   (a) It is filled with cerebrospinal fluid (CSF).
   (b) It extends inferiorly as far as the fourth sacral vertebra.
   (c) The cerebral arteries and veins are not located in the subarachnoid space.
   (d) The cranial nerves lie outside the subarachnoid space in sheaths derived from the dura mater.
   (e) The arachnoid villi project into the venous sinuses as large outpouchings of the subarachnoid space.
6. The following statements concern the cavernous sinus:
   (a) The external carotid artery passes through it.
   (b) Its medial wall contains the oculomotor, trochlear, and ophthalmic divisions of the trigeminal nerve.
   (c) It drains directly posteriorly into the straight sinus.
   (d) It does not communicate with the facial vein.
   (e) It is related medially to the pituitary gland and the sphenoid air sinus.
7. The following structure limits rotatory movements of the brain within the skull:
   (a) Tentorium cerebelli
   (b) Diaphragma sellae
   (c) Falx cerebri
   (d) Dorsum sellae
   (e) Squamous part of the temporal bone
8. The following nerves are sensory to the dura mater:
   (a) Oculomotor nerve
   (b) Trochlear nerve
   (c) Sixth cervical spinal nerve
   (d) Trigeminal nerve
   (e) Hypoglossal nerve

Answers and Explanations to Review Questions

1. D is correct. The cranial venous sinuses run between the meningeal and endosteal layers of dura mater (see Fig. 15-3). A. The periosteal (endosteal) layer of dura covering the brain is continuous through the foramen magnum with the periosteum outside the skull; only the meningeal layer of dura covering the brain is continuous through the foramen magnum with the dura covering the spinal cord (see Fig. 15-3). B. The periosteal layer of dura mater is continuous with the sutural ligaments of the skull. C. As each cranial nerve passes through a foramen in the skull, the cranial nerve is surrounded by a tubular sheath of pia, arachnoid, and dura mater (see Fig. 15-2). E. The meninges within the skull extend anteriorly through the optic canal and fuse with the sclera of the eyeball (see Fig. 15-8).
2. C is correct. The CSF in the arachnoid villi is able to drain into the venous sinuses through small tubules lined with endothelial cells (see Fig. 16-18). A. The cisterna cerebellomedullaris is filled with CSF and lies between the inferior surface of the cerebellum and the roof of the fourth ventricle. B. The arachnoid mater is not permeable to CSF. D. The arachnoid mater surrounding the spinal cord ends inferiorly on the filum terminale at the level of the lower border of the second sacral vertebra (see Fig. 15-9). E. The extradural space that separates the dural sheath of the spinal cord and the walls of the vertebral canal is filled with loose areolar tissue and contains the internal vertebral venous plexus (see Fig. 1-3).
3. B is correct. The tentorium cerebelli is formed from the meningeal layer of the dura mater (see Fig. 15-3). A. The free border of the tentorium cerebelli is attached anteriorly to the anterior clinoid processes of the sphenoid bone. C. The tentorium cerebelli separates the cerebellum from the occipital lobes of the brain. D. The sigmoid sinus does not lie within the free border of the tentorium cerebelli. E. In the anterior edge of the tentorium cerebelli is the tentorial notch (see Fig. 15-4).
4. A is correct. Brain tissue is insensitive to pain. B. Intracranial pain arises from receptors situated in the dura mater. C. An expanding cerebral tumor located in the posterior cranial fossa would produce pain referred to the back of the neck. D. Migraine headache is believed to be due to dilation of cerebral arteries and branches of the external carotid artery. E. Headaches associated with presbyopia are due to tonic spasm of the ciliary muscles of the eyes.
5. A is correct. The subarachnoid space is filled with CSF. B. The subarachnoid space extends inferiorly as far as the second sacral vertebra (see Fig. 15-9). C. The subarachnoid space contains the cerebral arteries and veins. D. The cranial nerves lie inside the subarachnoid space. E. The arachnoid villi project into the venous sinuses as minute outpouchings of the subarachnoid space.
6. E is correct. The cavernous sinus is related medially to the pituitary gland and the sphenoid air sinus (see Fig. 15-5). A. The cavernous sinus has the internal carotid artery and the abducens nerve passing through it (see Fig. 15-5). B. The cavernous sinus has the oculomotor, trochlear, and ophthalmic divisions of the trigeminal nerve in its lateral wall (see Fig. 15-5). C. The cavernous sinus drains posteriorly into the superior and inferior petrosal sinuses (see Fig. 15-1). D. The cavernous sinus has an important clinical communication anteriorly via the superior ophthalmic vein with the facial vein.
7. C is correct. The falx cerebri limits rotatory movements of the brain within the skull.
8. D is correct. The trigeminal nerve is an important sensory nerve to the dura mater within the skull.

16 Ventricular System and Cerebrospinal Fluid

CHAPTER OBJECTIVES

- To learn the locations, functions, origins, and fate of cerebrospinal fluid
- To understand the structure and function of the blood–brain and blood–cerebrospinal fluid barriers
- To learn how certain parts of the brain are protected from potentially toxic drugs or other exogenous materials

A 26-year-old woman involved in an automobile accident is admitted to the emergency department. Her mother, who is also involved in the accident, told the physician that at the time of impact, her daughter's head was thrown forward against the windshield.

On examination, the patient is unconscious and shows evidence of a severe head injury on the left side. After a thorough physical examination, the physician decides to perform a spinal tap. The cerebrospinal fluid (CSF) pressure is 160 mm of water, and two samples of the fluid are collected. The specimens show red blood cells at the bottom of the tubes, and the supernatant fluid is blood stained. After standing for an hour, the supernatant fluid in both tubes becomes colorless.

The physician makes the diagnosis of subarachnoid hemorrhage secondary to the head injury. The blood could be originating from a severe fracture of the skull, damage to one of the cerebral blood vessels, or a tear involving the brain or meninges. The physician is confident that the blood in the CSF specimens did not originate from an accidental puncture of a vertebral vein during the spinal tap procedure. He eliminates this possibility by drawing two specimens of the fluid. If a local vein is accidentally punctured by the first needle, the first specimen will be blood stained, however, the second specimen most probably will be clear. With this patient, both specimens are uniformly blood stained, so the blood is in the subarachnoid space.

The management of this patient in the emergency department and the evaluation of the spinal tap specimen depends on knowledge of the CSF system and the anatomy involved in the spinal tap procedure.

VENTRICULAR SYSTEM

The ventricles are four fluid-filled cavities located within the brain; these are the two lateral ventricles, the third ventricle, and the fourth ventricle (Fig. 16-1; see also Atlas Plates 3, 4, 7, and 8). The two **lateral ventricles** communicate through the **interventricular foramina** (of Monro) with the **third ventricle**. The third ventricle is connected to the **fourth ventricle** by the narrow **cerebral aqueduct** (**aqueduct of Sylvius**). The fourth ventricle, in turn, is continuous with the narrow **central canal** of the spinal cord and, through the three foramina in its roof, with the subarachnoid space. The central canal in the spinal cord has a small dilatation at its inferior end, referred to as the **terminal ventricle**.

The ventricles are lined throughout with **ependyma** and are filled with **CSF**. The ventricles are developmentally derived from the cavity of the neural tube.

Lateral Ventricles

One of each of the two large lateral ventricles is present in each cerebral hemisphere (Fig. 16-2). The ventricle is a roughly C-shaped cavity and may be divided into a **body** which occupies the parietal lobe and from which **anterior**, **posterior**, and **inferior horns** extend into the frontal, occipital, and temporal lobes, respectively. The lateral ventricle communicates with the cavity of the third ventricle through the **interventricular foramen** (Figs. 16-3 and 16-4; also see Fig. 16-2). This opening, which lies in the anterior part of the medial wall of the ventricle, is bounded anteriorly by the anterior column of the fornix and posteriorly by the anterior end of the thalamus.

The **body of the lateral ventricle** extends from the interventricular foramen posteriorly as far as the posterior end of the thalamus. Here, it becomes continuous

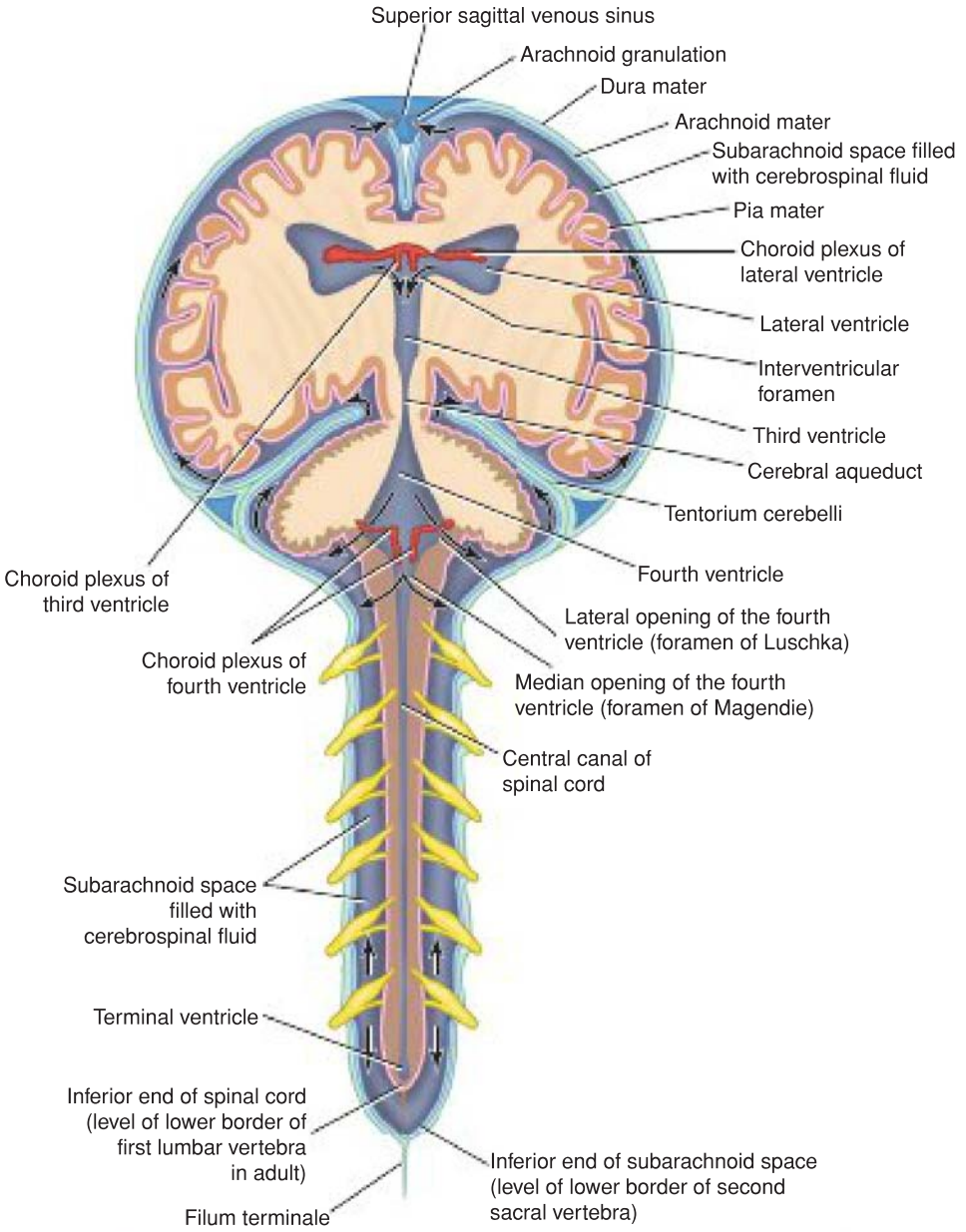


Figure 16-1 Origin and circulation of the cerebrospinal fluid.

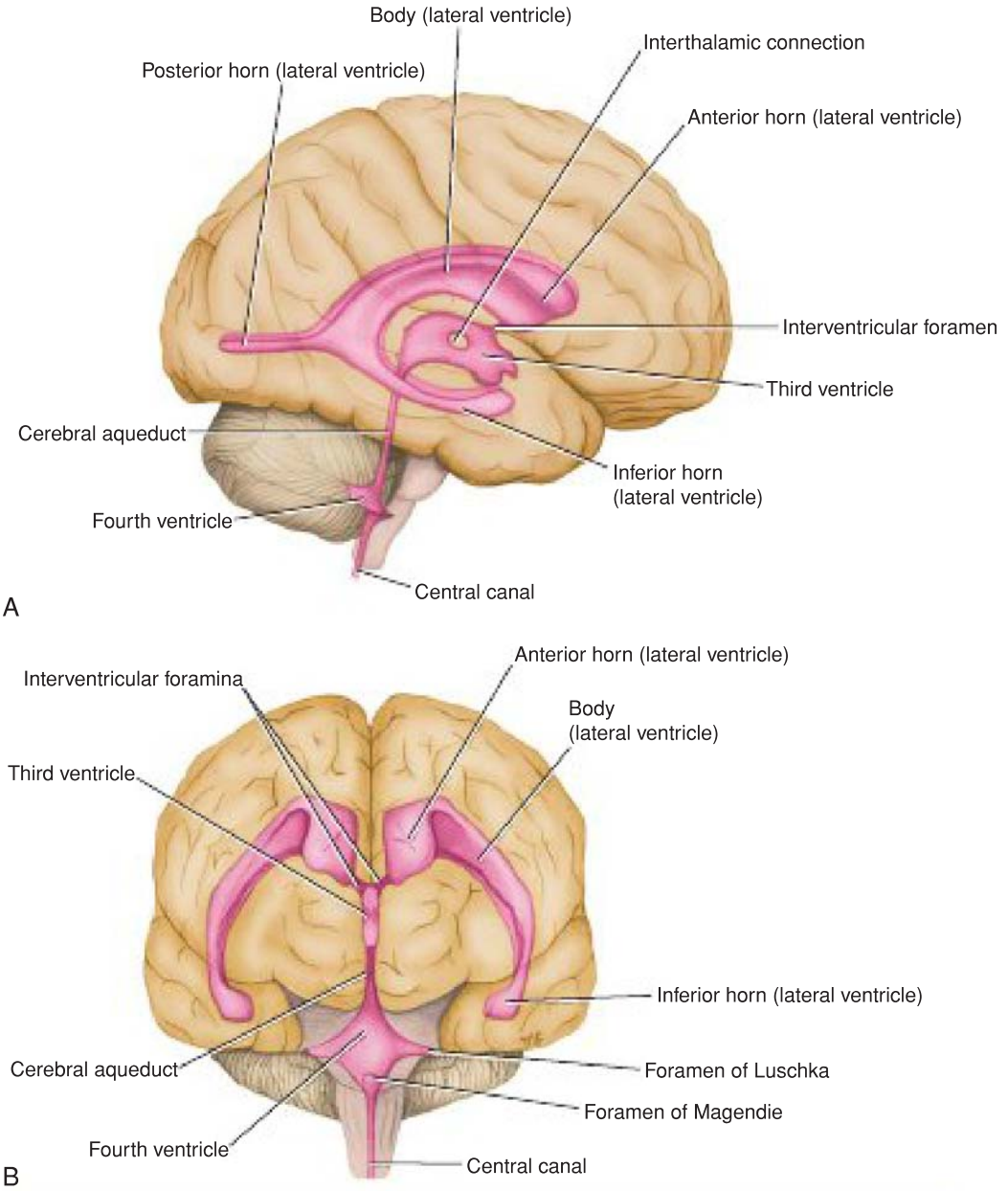


Figure 16-2 Cast of the ventricular cavities of the brain. **A:** Lateral view. **B:** Anterior view.

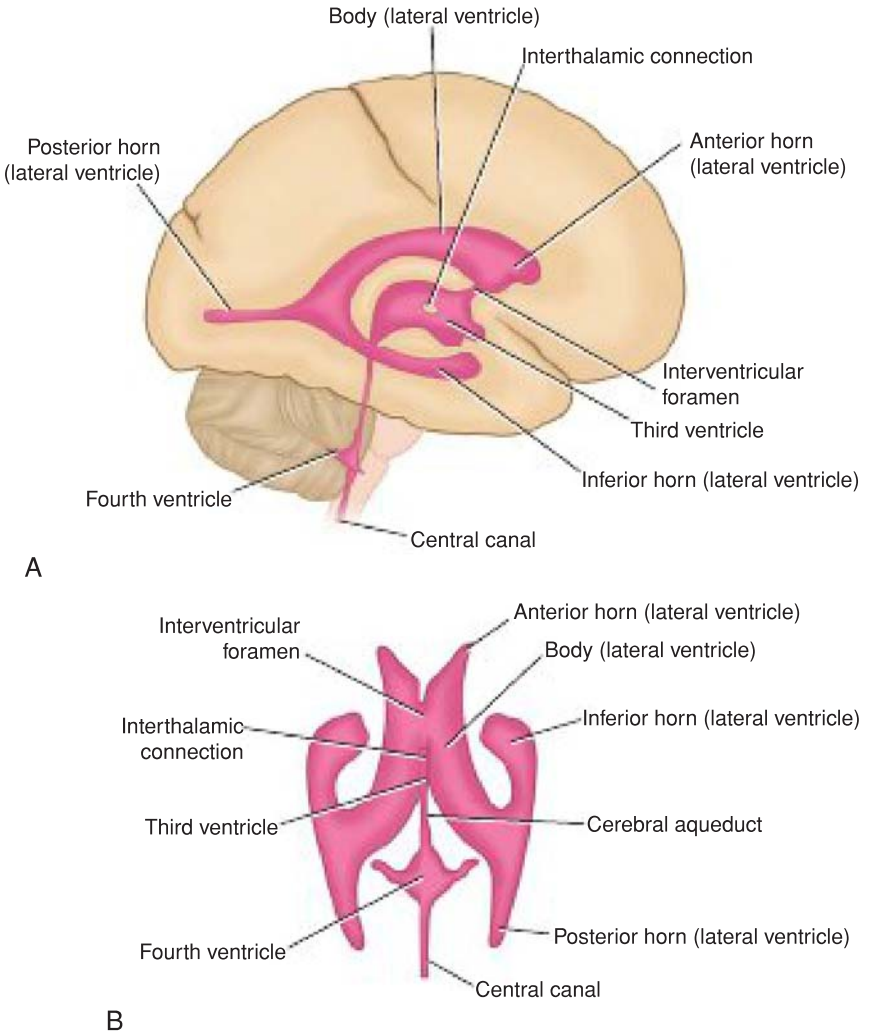


Figure 16-3 Ventricular cavities of the brain. **A:** Lateral view. **B:** Superior view.

with the posterior and the inferior horns. The body of the lateral ventricle has a roof, a floor, and a medial wall (Fig. 16-5).

The **roof** is formed by the undersurface of the **corpus callosum**. The **floor** is formed by the body of the **caudate nucleus** and the lateral margin of the thalamus. The superior surface of the thalamus is obscured in its medial part by the **body of the fornix**. The **choroid plexus** of the ventricle projects into the body of the ventricle through the slitlike gap between the body of the fornix and the superior surface of the thalamus. This slitlike gap is known as the **choroidal fissure**; through it, the blood vessels of the plexus invaginate the pia mater of the tela choroidea and the ependyma of the lateral ventricle. The **medial wall** is formed by the **septum pellucidum** anteriorly; posteriorly, the roof and the floor come together on the medial wall.

The **anterior horn of the lateral ventricle** extends forward into the frontal lobe (see Figs. 16-2 and 16-3). It is continuous posteriorly with the body of the ventricle at the interventricular foramen. The anterior horn has a roof, a floor, and a medial wall. The **roof** is formed by the undersurface of the anterior part of the **corpus callosum**; the **genu of the corpus callosum** limits the anterior horn anteriorly (see Fig. 16-5A). The **floor** is formed by the rounded **head of the caudate nucleus**; medially, a small portion is formed by the superior surface of the **rostrum of the corpus callosum**. The **medial wall** is formed by the **septum pellucidum** and the **anterior column of the fornix**.

The **posterior horn of the lateral ventricle** extends posteriorly into the occipital lobe (see Figs. 16-2 and 16-3). The **roof** and **lateral wall** are formed by the fibers of the **tapetum of the corpus callosum.** Lateral to the tapetum are the fibers of the **optic radiation** (see Fig. 16-5C). The **medial wall** of the posterior horn has two elevations. The superior swelling is caused by the splenial fibers of the corpus callosum, called the **forceps major**, passing posteriorly into the occipital lobe; this superior swelling is referred to as the **bulb of the posterior horn**. The inferior swelling is produced by the **calcarine sulcus** and is called the **calcar avis**.

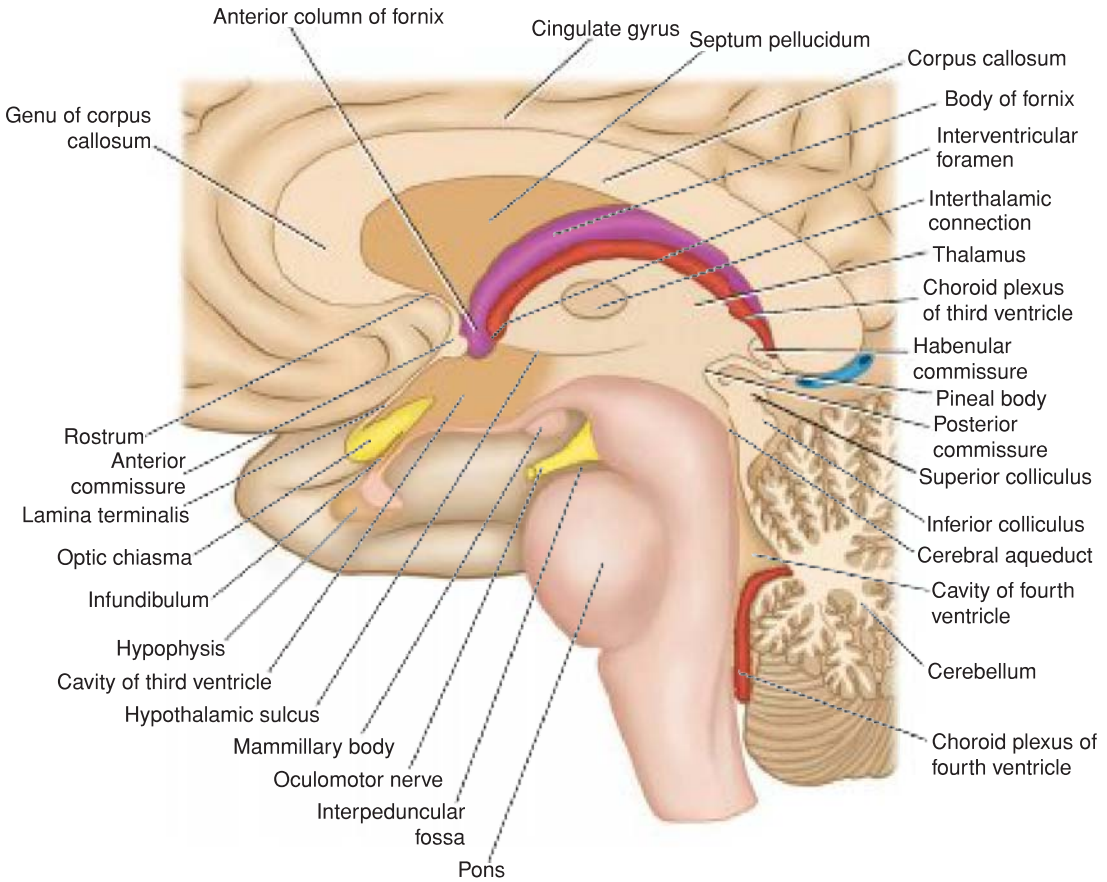


Figure 16-4 Sagittal section of the brain showing the third ventricle, the cerebral aqueduct, and the fourth ventricle.

The **inferior horn of the lateral ventricle** extends anteriorly into the temporal lobe (see Figs. 16-2 and 16-3). The inferior horn has a roof and a floor (see Fig. 16-5B).

The **roof** is formed by the inferior surface of the **tapetum of the corpus callosum** and by the **tail of the caudate nucleus** (see Fig. 9-5). The latter passes anteriorly to end in the **amygdaloid nucleus**. Medial to the tail of the caudate nucleus is the **stria terminalis**, which also ends anteriorly in the amygdaloid nucleus.

The **floor** is formed laterally by the **collateral eminence**, produced by the **collateral fissure**, and medially by the hippocampus (see Figs. 9-3 and 9-4). The anterior end of the hippocampus is expanded and slightly furrowed to form the **pes hippocampus**. The hippocampus is composed of gray matter; however, the ventricular surface of the hippocampus is covered by a thin layer of white matter called the **alveus**, which is formed from the axons of the cells of the hippocampus. These axons converge on the medial border of the hippocampus to form a bundle known as the **fimbria**. The fimbria of the hippocampus becomes continuous posteriorly with the **posterior column of the fornix**.

In the interval between the stria terminalis and the fimbria is the temporal part of the choroidal fissure. Here, the lower part of the **choroid plexus** of the lateral ventricle invaginates the ependyma from the medial side and closes the fissure (Fig. 16-6).

Choroid Plexus

The **choroid plexus** projects into the ventricle on its medial aspect and is a vascular fringe composed of pia mater covered with the ependymal lining of the ventricular cavity (Fig. 16-7). The choroid plexus is, in fact, the irregular lateral edge of the tela choroidea, which is a two-layered fold of pia mater situated between the fornix superiorly and the upper surface of the thalamus (see Fig. 16-6A). At the junction of the body of the lateral ventricle and the inferior horn, the choroid plexus is continued into the inferior horn and projects through the choroidal fissure. The function of the choroid plexus is to produce CSF.

Third Ventricle

The third ventricle is a slitlike cleft between the two thalami. It communicates anteriorly with the lateral ventricles through the interventricular foramina (of Monro) and posteriorly with the fourth ventricle through the cerebral aqueduct (of Sylvius) (see Fig. 16-4). The walls of the third ventricle are described on page 363.

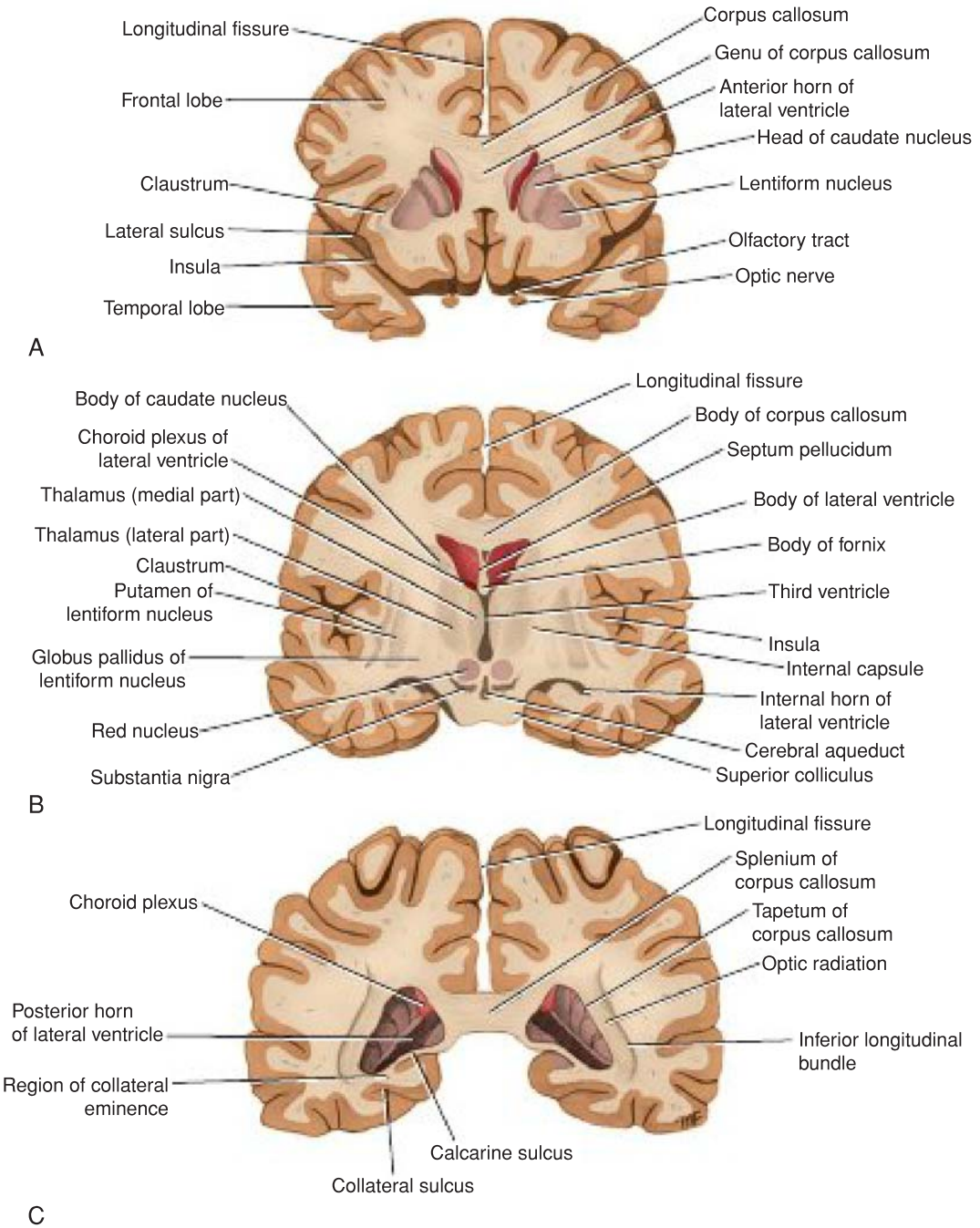


Figure 16-5 Coronal sections of the brain passing through the anterior horn of the lateral ventricle (**A**), the body of the lateral ventricle (**B**), and the posterior horn of the lateral ventricle (**C**).

Choroid Plexuses

The choroid plexuses are formed from the tela choroidea situated above the roof of the ventricle (see Fig. 16-7). The vascular tela choroidea projects downward on each side of the midline, invaginating the ependymal roof of the ventricle. The two vascular ridges or fringes that hang from the roof of the third ventricle form the choroid plexuses. The function of the choroid plexuses is to produce CSF.

The blood supply of the tela choroidea and, therefore, also of the choroid plexuses of the third and lateral ventricles is derived from the **choroidal branches of the internal carotid and basilar arteries**. The venous blood drains into the internal cerebral veins, which

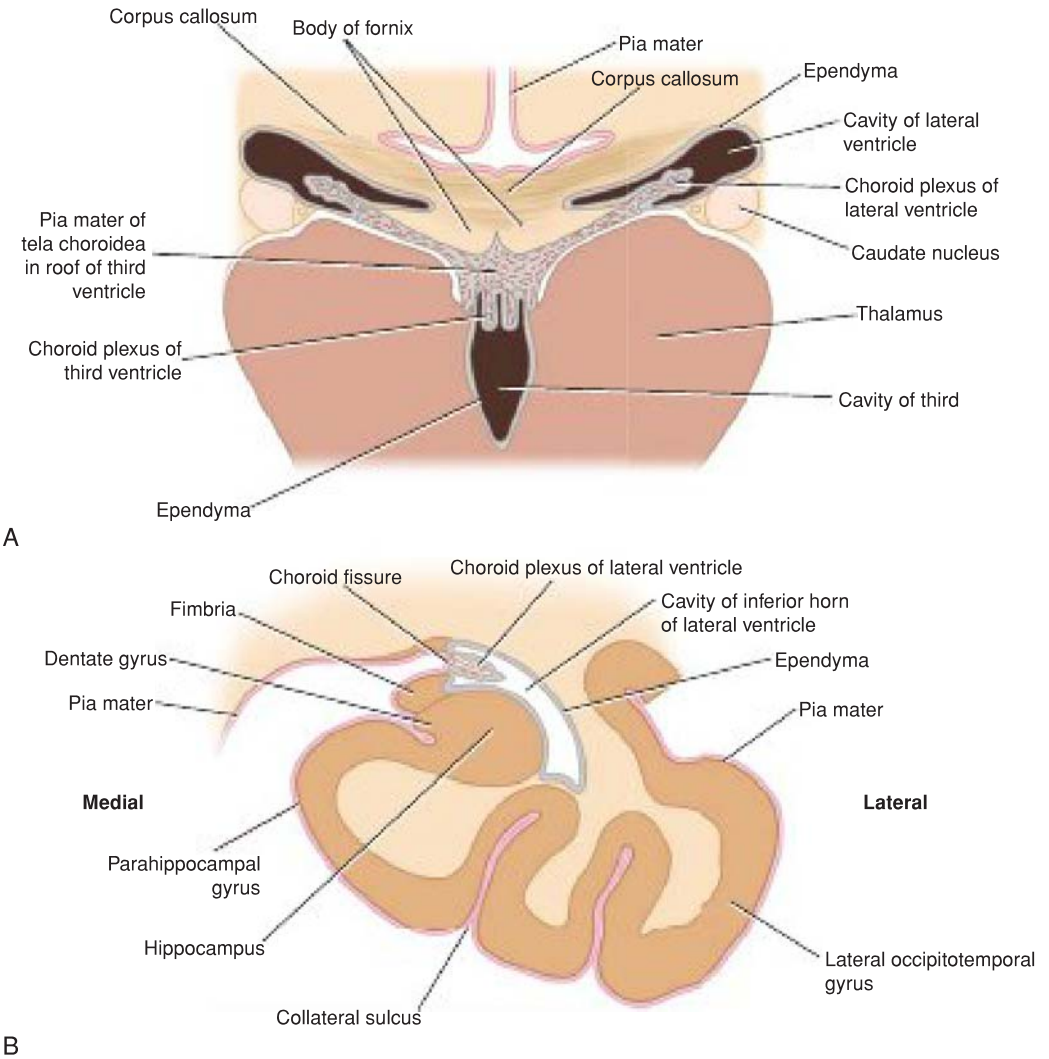


Figure 16-6 Coronal section of the cavities of the third and lateral ventricles (**A**) and the cavity of the inferior horn of the lateral ventricle (**B**).

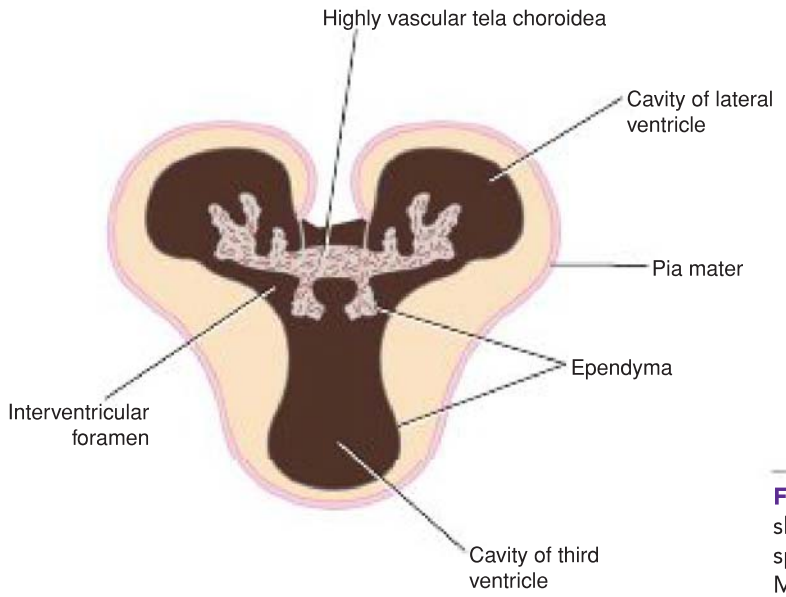


Figure 16-7 Sagittal section of the fourth ventricle showing the origin and circulation of the cerebrospinal fluid. Note the position of the foramen of Magendie.

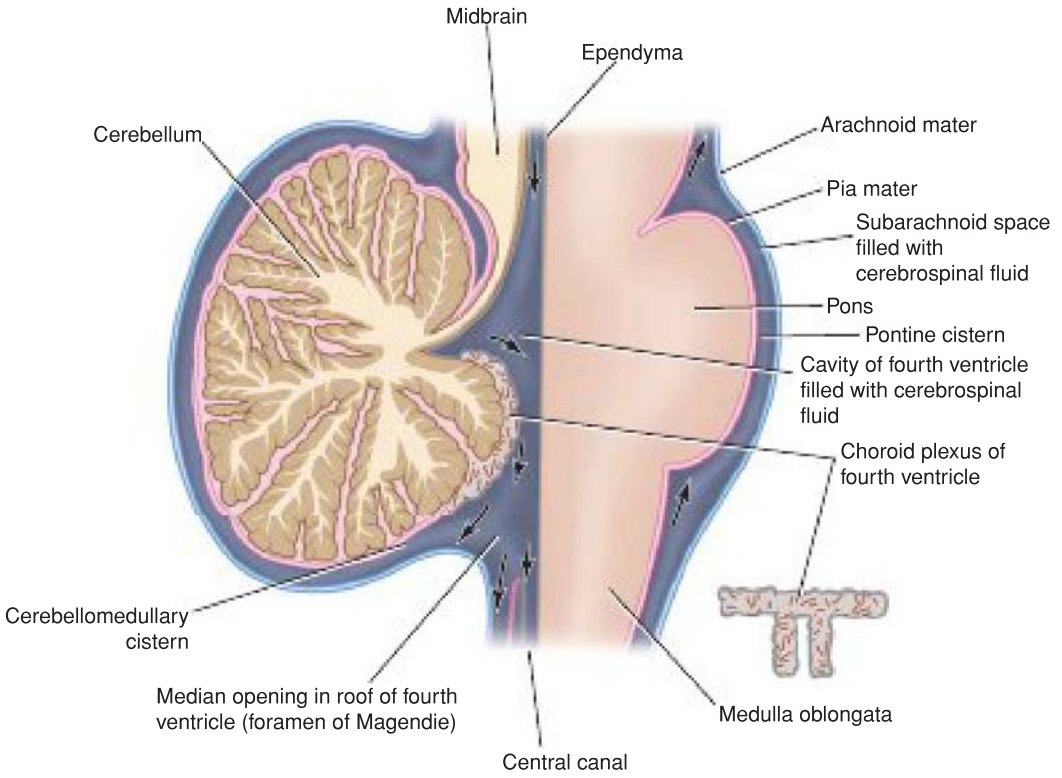


Figure 16-8 Schematic diagram of a coronal section of the third and lateral ventricles at the site of the interventricular foramina showing the structure of the tela choroidea and its relationship with the ependyma and pia mater.

unite to form the great cerebral vein. The great cerebral vein joins the inferior sagittal sinus to form the straight sinus.

Cerebral Aqueduct

The cerebral aqueduct (aqueduct of Sylvius), a narrow channel about 3/4 of an inch (1.8 cm) long, connects the third ventricle with the fourth ventricle (see Figs. 16-2 and 16-3). It is lined with ependyma and is surrounded by a layer of gray matter called the **central gray**. The direction of CSF flow is from the third to the fourth ventricle. The cerebral aqueduct does not have a choroid plexus.

Fourth Ventricle

The fourth ventricle is a tent-shaped cavity filled with CSF. It is situated anterior to the cerebellum and posterior to the pons and the superior half of the medulla oblongata (Figs. 16-8 and 16-9; also see Fig. 16-4). It is lined with ependyma and is continuous above with the cerebral aqueduct of the midbrain and below with the central canal of the medulla oblongata and the spinal cord (Fig. 16-3). The fourth ventricle possesses lateral boundaries, a roof, and a rhomboid-shaped floor.

Lateral Boundaries

The caudal part of each lateral boundary is formed by the inferior cerebellar peduncle (Fig. 16-10). The cranial part of each lateral boundary is formed by the superior cerebellar peduncle.

Posterior Wall (Roof)

The tent-shaped roof projects into the cerebellum (see Figs. 16-8 and 16-9). The superior part is formed by the medial borders of the two superior cerebellar peduncles and a connecting sheet of white matter called the **superior medullary velum** (Fig. 16-11). The inferior part of the roof is formed by the **inferior medullary velum**, which consists of a thin sheet devoid of nervous tissue and formed by the ventricular ependyma and its posterior covering of pia mater (Fig. 16-12). This part of the roof is pierced in the midline by a large aperture, the **median aperture** or **foramen of Magendie**. Lateral recesses extend laterally around the sides of the medulla and open anteriorly as the **lateral openings of the fourth ventricle**, or the **foramina of Luschka** (Fig. 16-13). Thus, the cavity of the fourth ventricle communicates with the subarachnoid space through a single median opening and two lateral apertures. These important openings permit CSF flow from the ventricular system into the subarachnoid space.

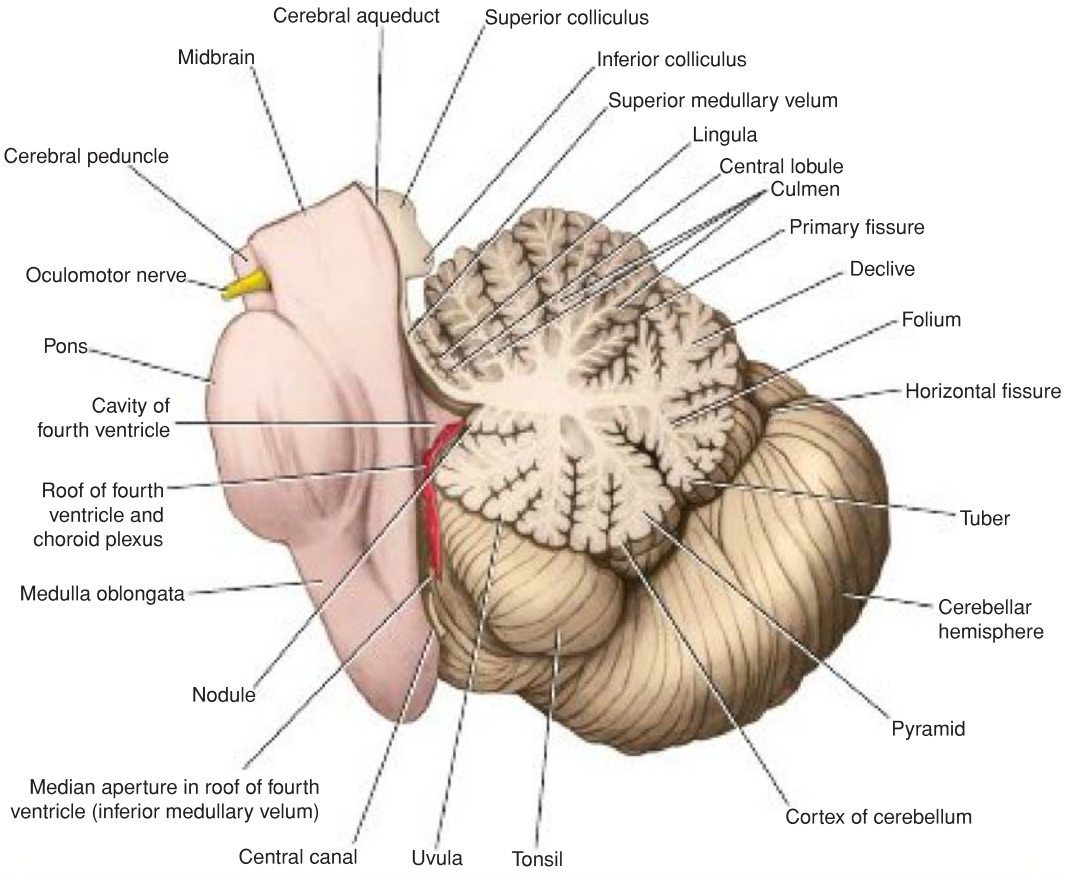


Figure 16-9 Sagittal section through the brainstem and the cerebellum showing the fourth ventricle.

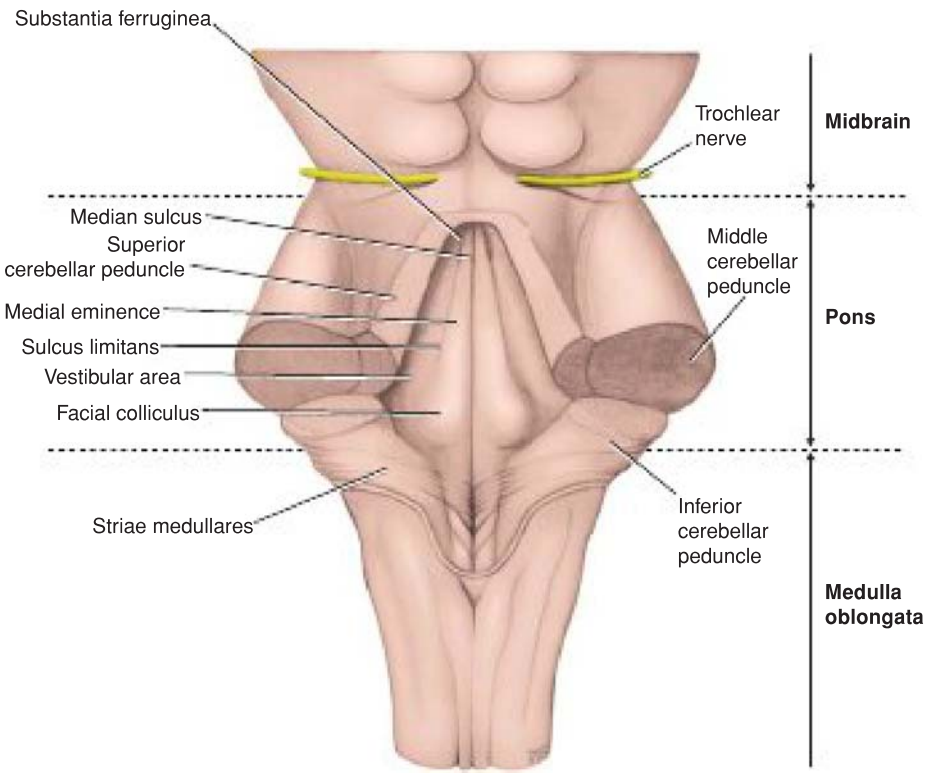


Figure 16-10 Posterior surface of the brainstem showing the floor of the fourth ventricle. The cerebellum has been removed.

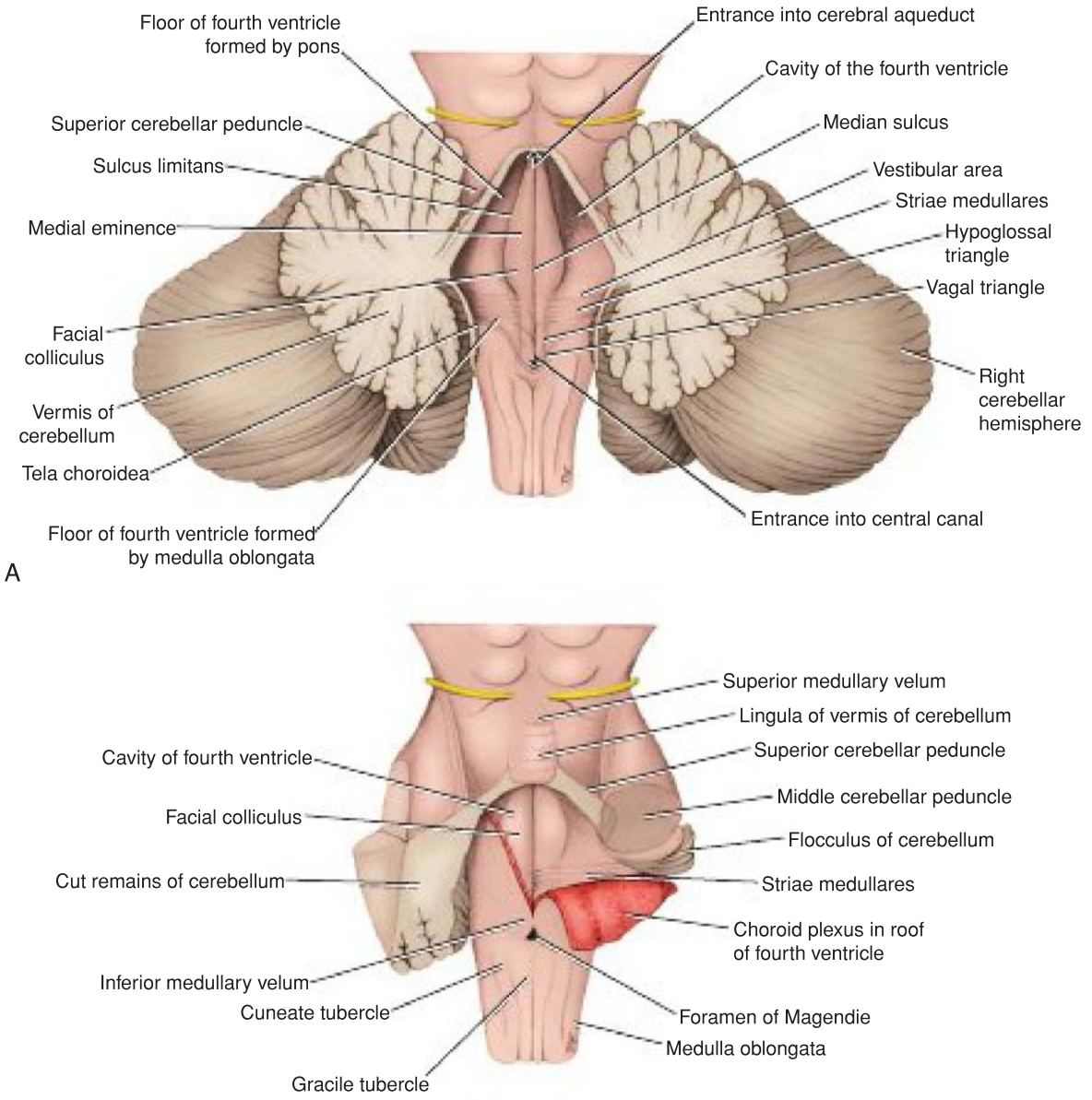


Figure 16-11 Posterior view of the cavity of the fourth ventricle. **A:** The vermis of the cerebellum has been divided in the midline and the cerebellar hemispheres have been displaced laterally. **B:** The greater part of the cerebellum has been removed, leaving the superior and inferior medullary vela. Note that the right half of the inferior medullary velum has been reflected inferiorly to reveal the choroid plexus.

Rhomboid Fossa (Floor)

The diamond-shaped floor is formed by the posterior surface of the pons and the cranial half of the medulla oblongata (see Fig. 16-10). The floor is divided into symmetrical halves by the **median sulcus**. On each side of this sulcus, an elevation, the **medial eminence**, is bounded laterally by another sulcus, the **sulcus limitans**. Lateral to the sulcus limitans is an area known as the **vestibular area** (see Figs. 16-10 and 16-11). The vestibular nuclei lie beneath the vestibular area.

The **facial colliculus** is a slight swelling at the inferior end of the medial eminence that is produced by the fibers from the motor nucleus of the facial nerve looping over the abducens nucleus (Fig. 16-14). At the superior end of the sulcus limitans, a bluish gray area is produced by a cluster of nerve cells containing melanin pigment; the cluster of cells is called the **substantia ferruginea**. Strands of nerve fibers, the **stria medullaris**, derived from the arcuate nuclei, emerge from the median sulcus and pass laterally over the

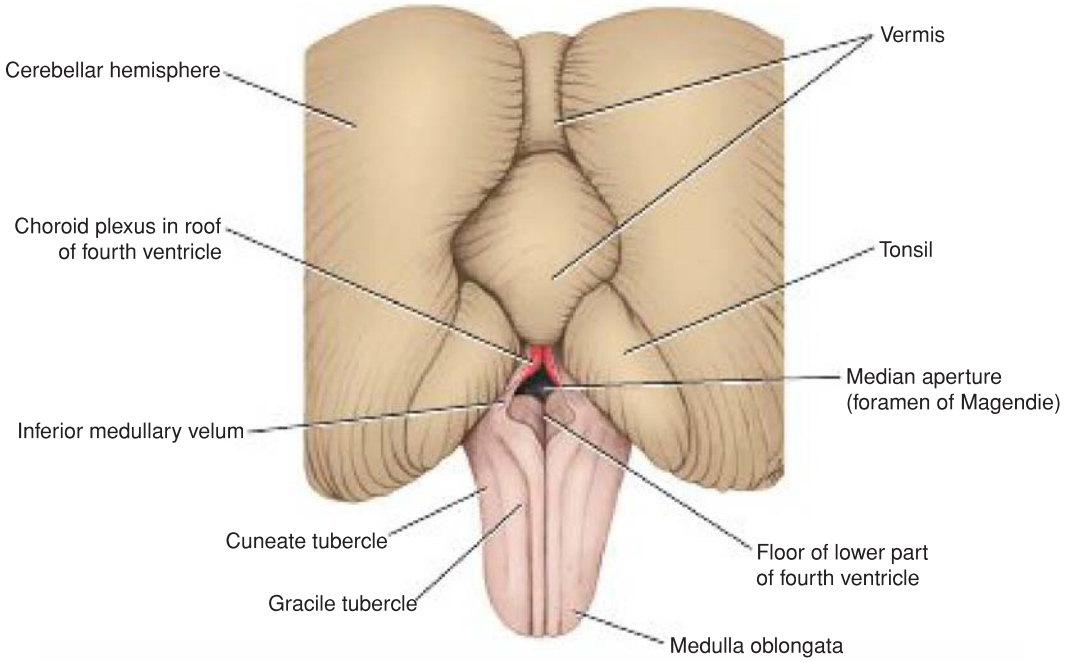


Figure 16-12 Posterior view of the roof of the fourth ventricle. The cerebellum has been displaced superiorly to show the large median aperture (foramen of Magendie).

medial eminence and the vestibular area and enter the inferior cerebellar peduncle to reach the cerebellum (see Fig. 16-10).

Inferior to the stria medullaris, the following features should be recognized in the floor of the ventricle. The most medial is the **hypoglossal triangle**, which indicates the position of the underlying **hypoglossal nucleus** (see Fig. 16-11). Lateral to this is the **vagal triangle**, beneath which lies the dorsal motor nucleus of the vagus. The **area postrema** is a narrow area between the vagal triangle and the lateral margin of the ventricle, just rostral to the opening into the central canal. The inferior part of the vestibular area also lies lateral to the vagal triangle.

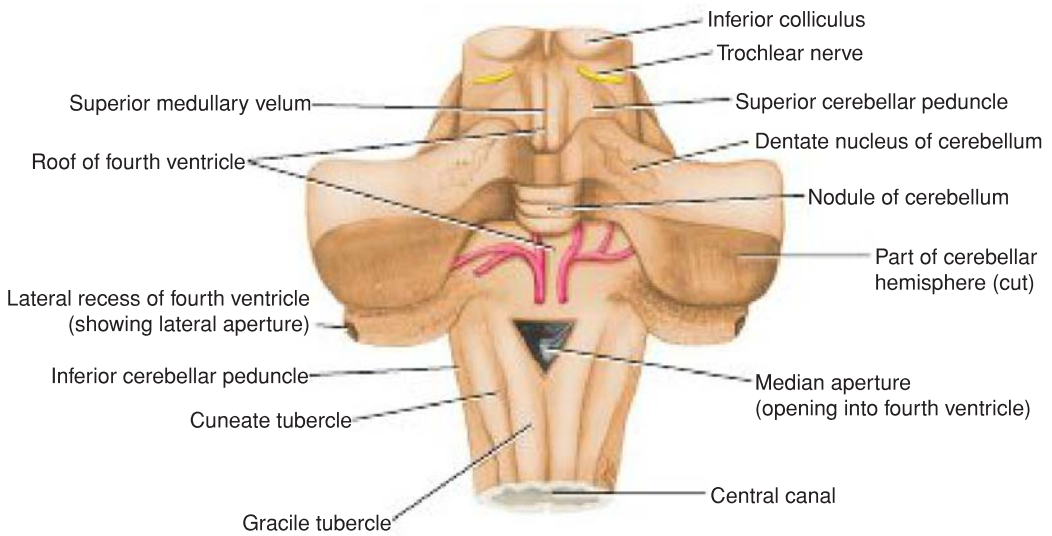


Figure 16-13 Posterior view of the roof of the fourth ventricle after removal of the greater part of the cerebellum. Shows the lateral recess and aperture (foramina of Luschka).

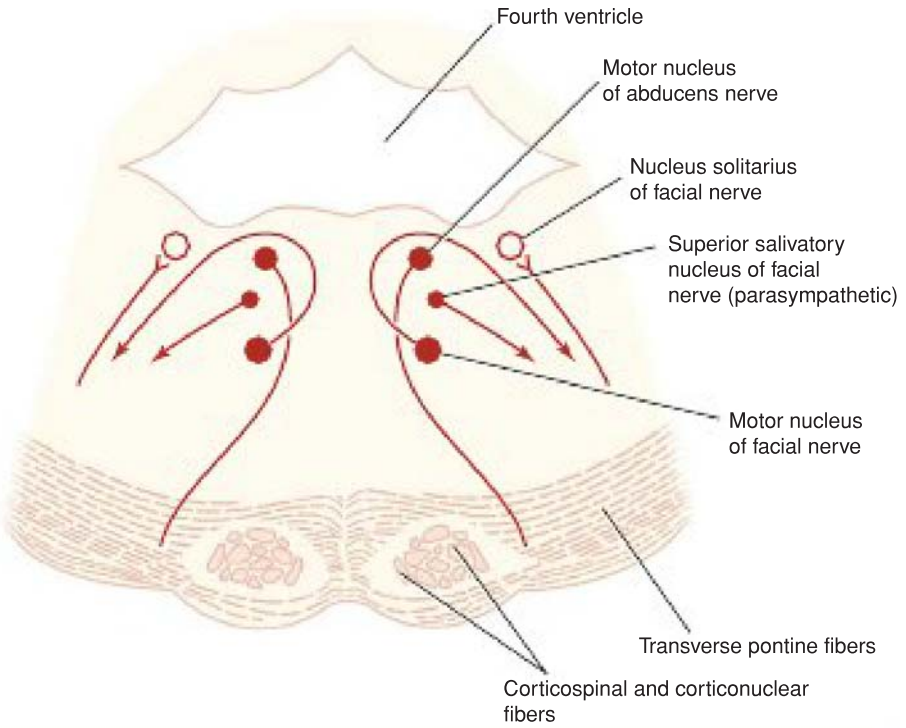


Figure 16-14 Transverse section through the fourth ventricle and the pons showing the nuclei of the facial nerve and their relationship to the nucleus of the abducens nerve.

Choroid Plexus

The choroid plexus has a T shape; the vertical part of the T is double (see Fig. 16-8). It is suspended from the inferior half of the roof of the ventricle and is formed from the highly vascular tela choroidea. The tela choroidea is a two-layered fold of pia mater that projects through the roof of the ventricle and is covered by ependyma. The blood supply to the plexus is from the **posterior inferior cerebellar arteries**. The function of the choroid plexus is to produce CSF.

Central Canal

The central canal opens superiorly into the fourth ventricle. Inferiorly, it extends through the inferior half of the medulla oblongata and through the entire length of the spinal cord. In the conus medullaris of the spinal cord, it expands to form the **terminal ventricle** (see Fig. 16-1). The central canal is closed at its lower end, is filled with CSF, and is lined with ependyma. The central canal is surrounded by gray matter, the **gray commissure**. The central canal does not have a choroid plexus.

SUBARACHNOID SPACE

The subarachnoid space is the interval between the arachnoid mater and pia mater and, therefore, is present where these meninges envelop the brain and spinal cord (see Fig. 16-1). The space is filled with CSF and contains the large blood vessels of the brain (Fig. 16-15). This space is traversed by a network of fine trabeculae, formed of delicate connective tissue. The subarachnoid space completely surrounds the brain and extends along the olfactory nerves to the mucoperiosteum of the nose. The subarachnoid space also extends along the cerebral blood vessels as they enter and leave the substance of the brain and stops where the vessels become an arteriole or a venule.

In certain situations around the base of the brain, the arachnoid does not closely follow the surface of the brain. In such a case, the subarachnoid space expands to form **subarachnoid cisterns**. The descriptions of the **cerebellomedullary cistern**, the **pontine cistern**, and the **interpeduncular cistern**, which are the largest cisterns, are on page 449.

Inferiorly, the subarachnoid space extends beyond the lower end of the spinal cord and invests the **cauda equina** (see Fig. 1-15). The subarachnoid space ends below at the level of the interval between the second and third sacral vertebrae.

The subarachnoid space surrounds the cranial and spinal nerves and follows them to the point where they leave the skull and vertebral canal. Here, the arachnoid mater and pia mater fuse with the perineurium of each nerve.

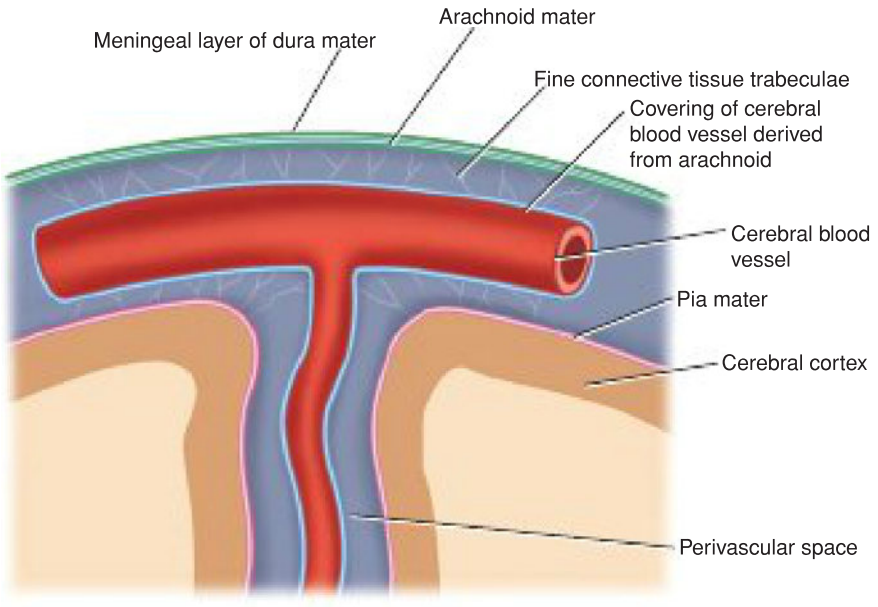


Figure 16-15 Diagram of the subarachnoid space around the cerebral hemisphere showing the relationship of the cerebral blood vessel to the meninges and cerebral cortex.

CEREBROSPINAL FLUID

The CSF is found in the ventricles of the brain and in the subarachnoid space around the brain and spinal cord. It has a volume of about 150 mL. It is a clear, colorless fluid and possesses, in solution, inorganic salts similar to those in the blood plasma. The glucose content is about half that of blood, with only a trace of protein. Only a few cells are present, and these are lymphocytes. The normal lymphocyte count is 0 to 3 cells per cubic millimeter. CSF pressure is **kept remarkably constant**. In the lateral recumbent position, the pressure, as measured by spinal tap, is about 60 to 150 mm of water. This pressure may be raised by straining, coughing, or compressing the internal jugular veins in the neck (see p. 256). Table 16-1 summarizes CSF physical characteristics and composition.

Functions

CSF, which bathes the external and internal surfaces of the brain and spinal cord, serves as a cushion between the central nervous system (CNS) and the surrounding bones, thus protecting it against mechanical trauma. Because the density of the brain is only slightly greater than that of the CSF, the CSF provides mechanical buoyancy and support for the brain. The close relationship of the fluid to the nervous tissue and the blood enables it to serve as a reservoir and assist in the regulation of the contents of the skull. For example, if the brain volume or the blood volume increases, CSF volume decreases. Because the CSF is an ideal physiologic substrate, it probably plays an active part in the nourishment of the nervous tissue; it almost certainly assists in the removal of products of neuronal metabolism. Secretions of the pineal gland possibly influence the activities of the pituitary gland by circulating through the CSF in the third ventricle (see p. 253).

Table 16-2 summarizes CSF functions.

Formation

CSF is formed mainly in the choroid plexuses of the lateral, third, and fourth ventricles; some originates from the ependymal cells lining the ventricles and from the brain substance through the perivascular spaces.

Table 16-1 Cerebrospinal Fluid Physical Characteristics and Composition

Appearance	Clear and colorless
Volume	c. 150 mL
Rate of production	0.5 mL/min
Pressure (spinal tap with patient in lateral recumbent position)	60–150 mm of water
Composition	
Protein	15–45 mg/100 mL
Glucose	50–85 mg/100 mL
Chloride	720–750 mg/100 mL
Number of cells	0–3 lymphocytes/mm^3

Table 16-2 Cerebrospinal Fluid Functions

1. Cushions and protects the central nervous system from trauma
2. Provides mechanical buoyancy and support for the brain
3. Serves as a reservoir and assists in the regulation of the contents of the skull
4. Nourishes the central nervous system
5. Removes metabolites from the central nervous system
6. Serves as a pathway for pineal secretions to reach the pituitary gland

The choroid plexuses have a much-folded surface, and each fold consists of a core of vascular connective tissue covered with cuboidal epithelium of the ependyma (Fig. 16-16). Electron-microscopic examination of the epithelial cells shows that their free surfaces are covered with microvilli. The blood of the capillaries is separated from the ventricular lumen by endothelium, a basement membrane, and the surface epithelium. The epithelial cells are fenestrated and permeable to large molecules.

The choroid plexuses **actively secrete** CSF and this creates a small pressure gradient. At the same time, they actively transport nervous system metabolites from the CSF into the blood. Active transport also explains why concentrations of potassium, calcium, magnesium, bicarbonate, and glucose are lower in CSF than in blood plasma.

The CSF is produced continuously at a rate of about 0.5 mL/min and with a total volume of about 150 mL; this corresponds to a turnover time of about 5 hours.

Importantly, CSF production is not pressure regulated (as in the case of blood pressure) and it continues to be produced even if the reabsorption mechanisms are obstructed.

Circulation

The circulation begins with its secretion from the choroid plexuses in the ventricles (and a small amount from the brain surface). The fluid passes from the lateral ventricles into the third ventricle through the interventricular foramina (Fig. 16-17; also see Fig. 16-1). It then passes into the fourth ventricle through the narrow cerebral aqueduct. The circulation is aided by the arterial pulsations of the choroid plexuses and by the cilia on the ependymal cells lining the ventricles.

From the fourth ventricle, CSF passes slowly through the median aperture and the lateral foramina of the lateral recesses of the fourth ventricle and enters the subarachnoid space. It then moves through the cerebellomedullary cistern and pontine cisterns and flows superiorly through the tentorial notch of the tentorium

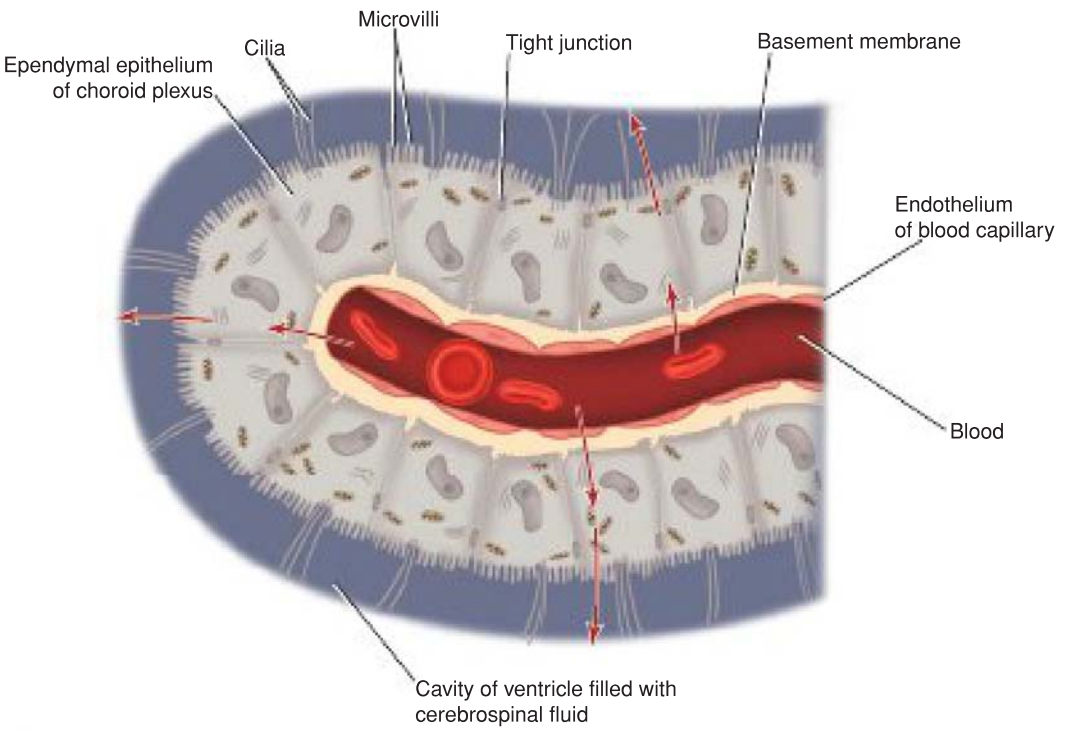


Figure 16-16 Microscopic structure of the choroid plexus showing the path taken by fluids in the formation of cerebrospinal fluid.

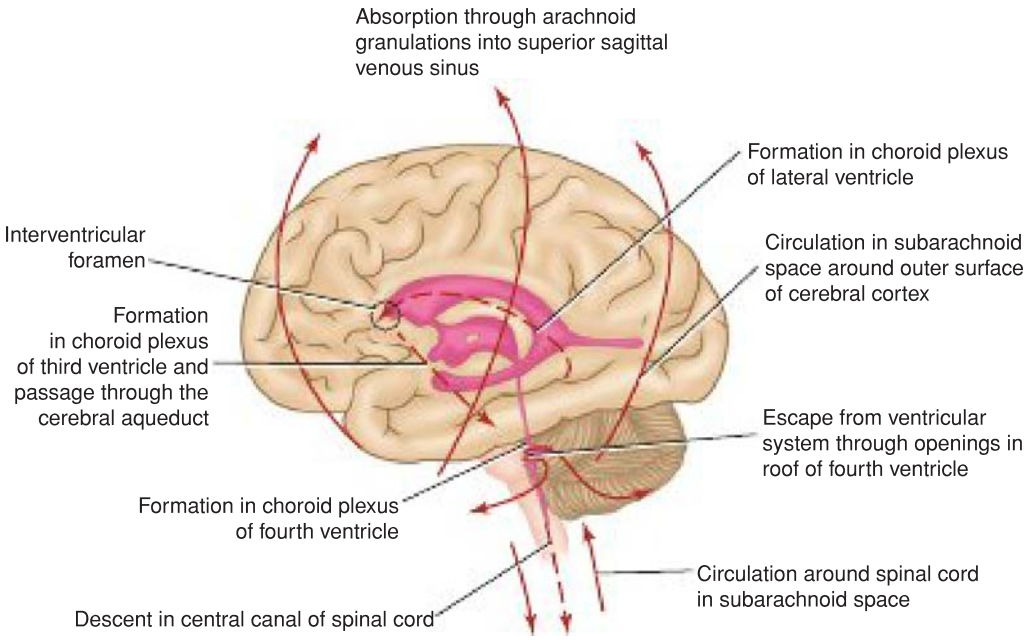


Figure 16-17 Circulation of the cerebrospinal fluid. The *dashed line* indicates the course taken by fluid within the cavities of the central nervous system.

cerebelli to reach the inferior surface of the cerebrum. It then moves superiorly over the lateral aspect of each cerebral hemisphere, assisted by the pulsations of the cerebral arteries. Some moves inferiorly in the subarachnoid space around the spinal cord and cauda equina. Here, it reaches a dead end and its further circulation relies on the pulsations of the spinal arteries and the movements of the vertebral column, respiration, coughing, and the changing of the positions of the body.

CSF not only bathes the ependymal and pial surfaces of the brain and spinal cord but also penetrates the nervous tissue along the blood vessels.

Absorption

The main sites for CSF absorption are the **arachnoid villi** that project into the dural venous sinuses, especially the **superior sagittal sinus** (Fig. 16-18). The arachnoid villi tend to be grouped together to form elevations known as **arachnoid granulations**. Structurally, each arachnoid villus is a diverticulum of the subarachnoid space that pierces the dura mater. The arachnoid diverticulum is capped by a thin cellular layer, which, in turn, is covered by the endothelium of the venous sinus. The arachnoid granulations increase in number and size with age and tend to become calcified with advanced age.

CSF absorption into the venous sinuses occurs when CSF pressure exceeds the venous pressure in the sinus. Electron-microscopic studies of the arachnoid villi indicate that fine tubules lined with endothelium permit a direct flow of fluid from the subarachnoid space into the lumen of the venous sinuses. Should the venous pressure rise and exceed CSF pressure, compression of the tips of the villi closes the tubules and prevents the reflux of blood into the subarachnoid space. The arachnoid villi thus serve as valves.

Some CSF probably is absorbed directly into the veins in the subarachnoid space and some possibly escapes through the perineural lymph vessels of the cranial and spinal nerves.

Because CSF production from the choroid plexuses is constant, the rate of CSF absorption through the arachnoid villi controls CSF pressure.

Subarachnoid Space Extensions

A sleeve of the subarachnoid space extends around the optic nerve to the back of the eyeball (Fig. 16-19). Here, the arachnoid mater and pia mater fuse with the sclera. The central artery and vein of the retina cross this extension of the subarachnoid space to enter the optic nerve, and they may be compressed in patients with raised CSF pressure.

Small extensions of the subarachnoid space also occur around the other cranial and spinal nerves. Here, some communication may occur between the subarachnoid space and the perineural lymph vessels.

The subarachnoid space also extends around the arteries and veins of the brain and spinal cord at points where they penetrate the nervous tissue (see Fig. 16-15). The pia mater, however, quickly fuses with the outer coat of the blood vessel below the surface of the brain and spinal cord, thus closing off the subarachnoid space.

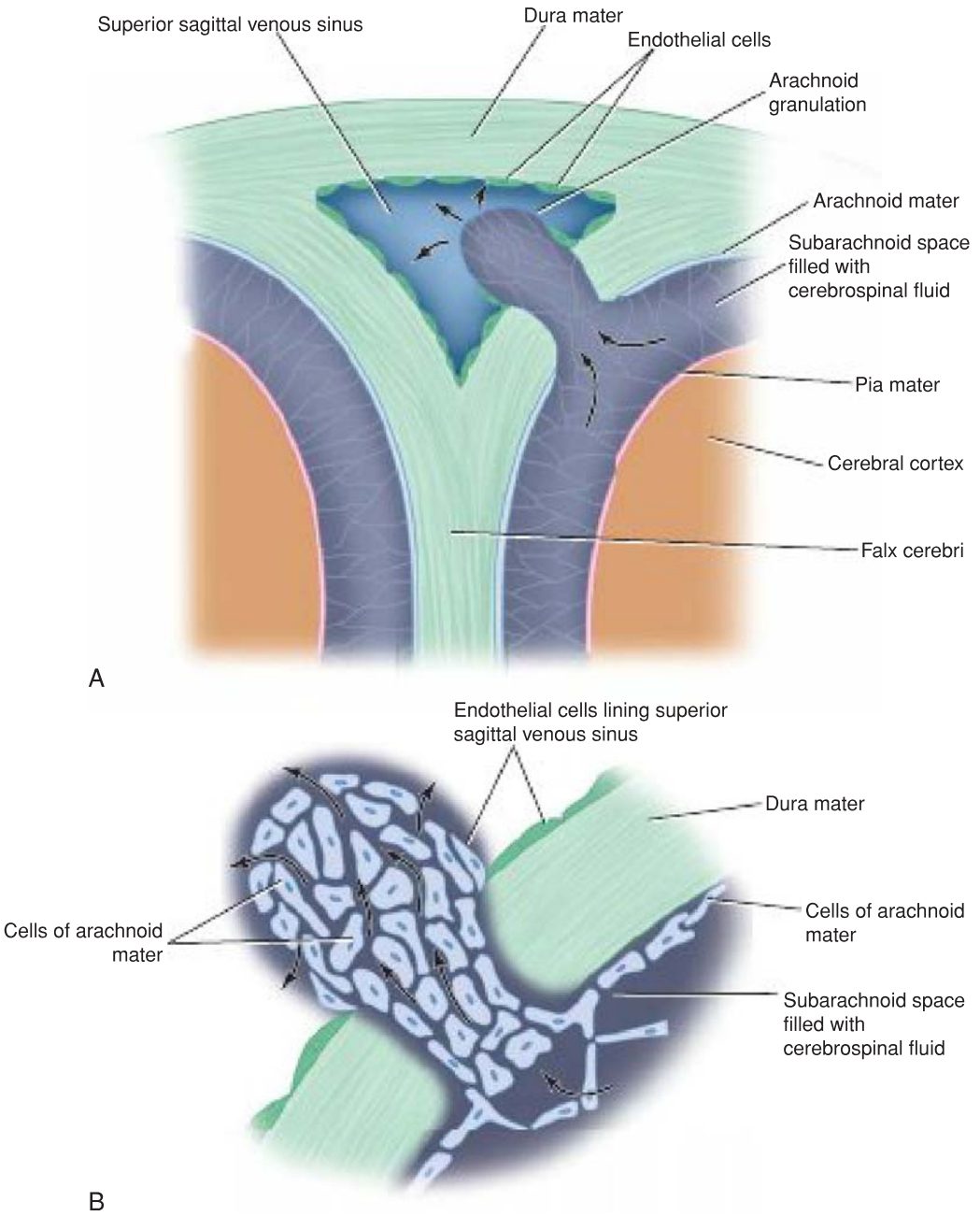


Figure 16-18 **A:** Coronal section of the superior sagittal sinus showing an arachnoid granulation. **B:** Magnified view of an arachnoid granulation showing the path taken by the cerebrospinal fluid into the venous system.

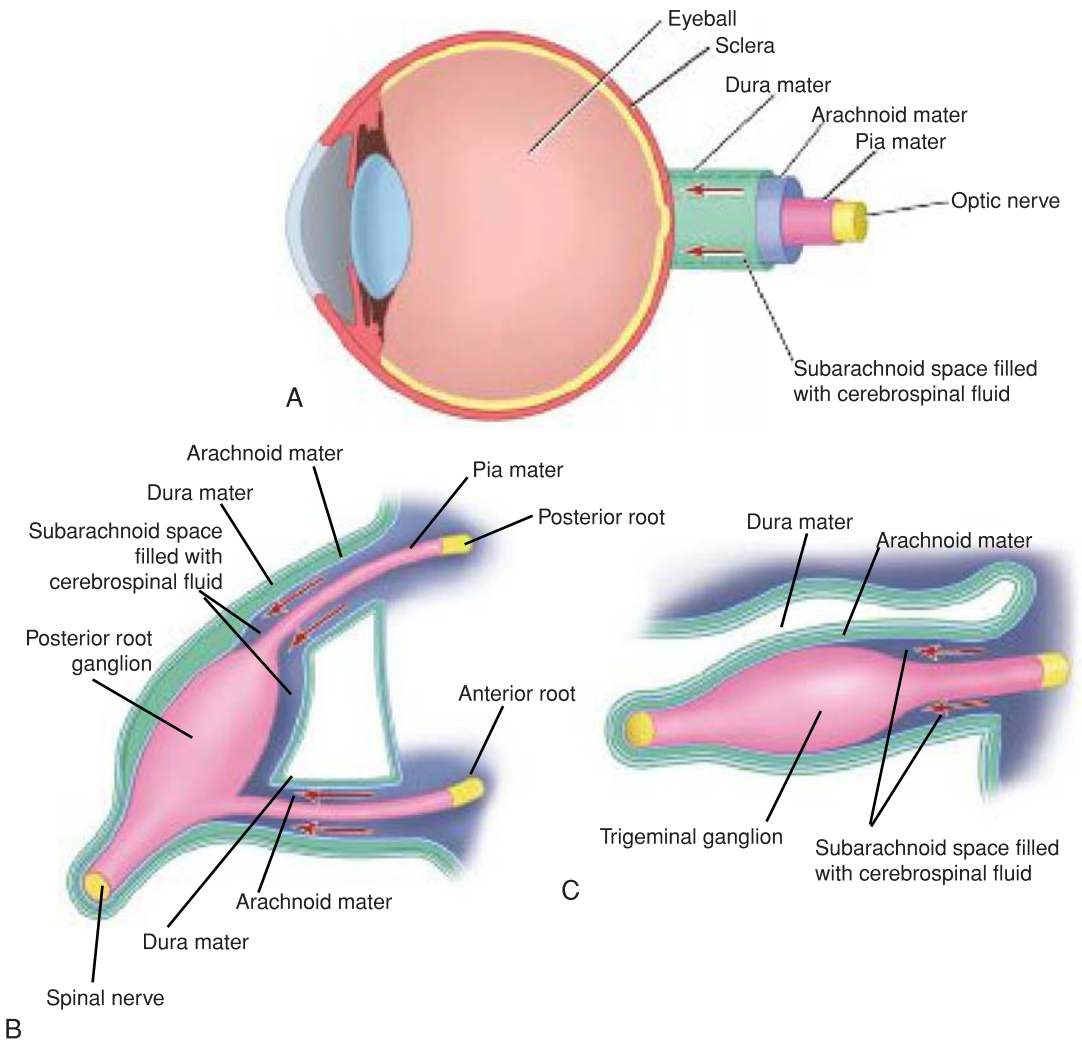


Figure 16-19 Course taken by cerebrospinal fluid around the optic nerve (**A**), the roots of a spinal nerve (**B**), and the trigeminal nerve (**C**).

BLOOD–BRAIN AND BLOOD–CEREBROSPINAL FLUID BARRIERS

The CNS requires a very stable environment in order to function normally. This stability is provided by isolating the nervous system from the blood by the existence of the so-called blood–brain barrier (BBB) and the blood–cerebrospinal fluid barrier.

Blood–Brain Barrier

The experiments of Paul Ehrlich in 1882 showed that living animals injected intravascularly with vital dyes, such as trypan blue, demonstrated staining of all the tissues of the body except the brain and spinal cord. Later, researchers demonstrated that although most of the brain is not stained after the intravenous injection of trypan blue, the following areas do become stained: the pineal gland, the posterior lobe of the pituitary, the tuber cinereum, the wall of the optic recess, and the vascular area postrema (area of the medulla on the floor of the fourth ventricle just rostral to the opening into the central canal). These observations led to the concept of a BBB (for which blood–brain–spinal cord barrier would be a more accurate name).

BBB permeability is inversely related to the size of the molecules and directly related to their lipid solubility. Gases and water pass readily through the barrier, whereas glucose and electrolytes pass more slowly. The barrier is almost impermeable to plasma proteins and other large organic molecules. Compounds with molecular weights of about 60,000 and higher remain within the blood circulatory system. This would explain why in the early experiments with trypan blue, which quickly binds to the plasma protein albumin, the dye did not pass into the neural tissue in the greater part of the brain.

Structure

Examination of a CNS electron micrograph shows that the lumen of a blood capillary is separated from the

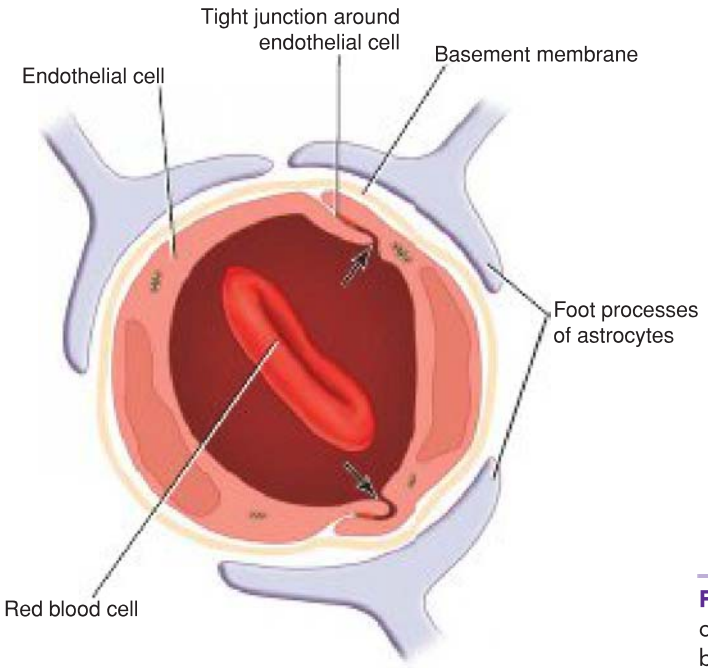


Figure 16-20 Cross section of a blood capillary of the central nervous system in the area where the blood–brain barrier exists.

extracellular spaces around the neurons and neuroglia by the following structures: (1) the endothelial cells in the wall of the capillary, (2) a continuous basement membrane surrounding the capillary outside the endothelial cells, and (3) the foot processes of the astrocytes that adhere to the outer surface of the capillary wall (Fig. 16-20).

The use of electron-dense markers such as lanthanum and horseradish peroxidase has shown that these substances do not penetrate between the endothelial cells of the capillaries because of the presence of tight junctions that form belts around the cells. When the dense markers are introduced into the extracellular spaces of the neuropil, they pass between the perivascular foot processes of the astrocytes as far as the endothelial lining of the capillary. This evidence demonstrates that the tight junctions between the endothelial cells of the blood capillaries are responsible for the BBB. (Peripheral nerves are isolated from the blood in the same manner as those of the CNS. The endothelial cells of the blood capillaries in the endoneurium have tight junctions; thus, there is a blood–nerve barrier.) In molecular terms, the BBB is thus a continuous lipid bilayer that encircles the endothelial cells and isolates the brain tissue from the blood. This explains how lipophilic molecules can readily diffuse through the barrier, whereas hydrophilic molecules are excluded.

Although a BBB exists in the newborn, it is likely more permeable to certain substances than it is in the adult.

BBB structure is not identical in all CNS regions: In those areas where it appears to be absent, the capillary endothelium contains fenestrations across which proteins and small organic molecules may pass from the blood to the nervous tissue (Fig. 16-21). The area

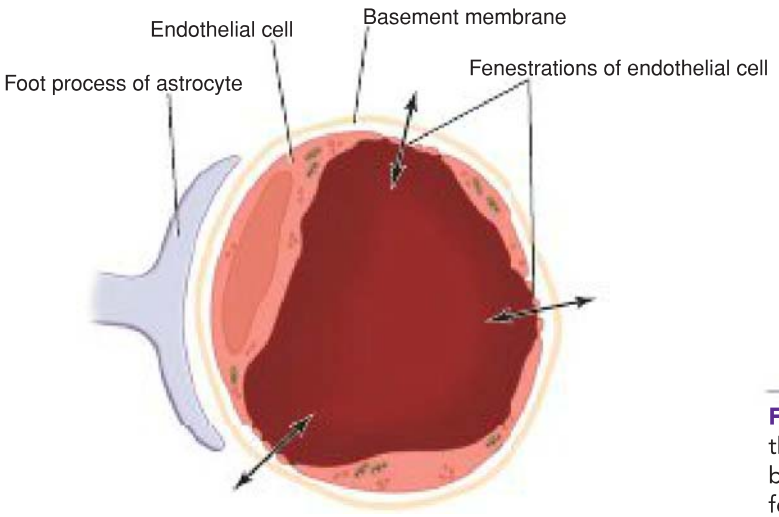


Figure 16-21 Cross section of a blood capillary of the central nervous system where the blood–brain barrier appears to be absent. Note the presence of fenestrations in the endothelial cells.

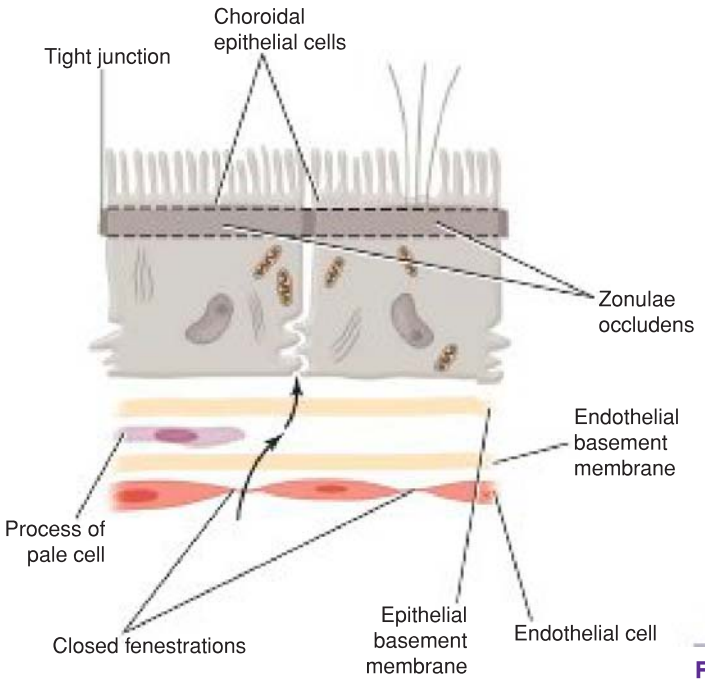


Figure 16-22 Section of villus of choroid plexus.

postrema of the floor of the fourth ventricle and the hypothalamus may serve as sites at which neuronal receptors may sample the chemical content of the plasma directly. The hypothalamus, which is involved in the regulation of the metabolic activity of the body, might bring about appropriate modifications of activity, thereby protecting the nervous tissue.

Blood–Cerebrospinal Fluid Barrier

Water, gases, and lipid-soluble substances pass freely from the blood to the CSF. Macromolecules such as proteins and most hexoses other than glucose are unable to enter the CSF. A barrier similar to the BBB may exist in the choroid plexuses.

Structure

Electron-microscopic examination of a villus of a choroid plexus shows that the lumen of a blood capillary is separated from the lumen of the ventricle by the following structures: (1) the endothelial cells, which are fenestrated and have very thin walls (the fenestrations are not true perforations but are filled by a thin diaphragm); (2) a continuous basement membrane surrounding the capillary outside the endothelial cells; (3) scattered pale cells with flattened processes; and (4) a continuous basement membrane, on which rest (5) the choroidal epithelial cells (Fig. 16-22). The use of electron-dense markers has not been entirely successful in localizing the barrier precisely. Horseradish peroxidase injected intravenously appears as a coating on the luminal surface of the endothelial cells and in many areas examined, it did pass between the endothelial cells. Tight junctions between the choroidal epithelial cells probably serve as the barrier.

Cerebrospinal Fluid–Brain Interface

Although vital dyes given by intravenous injection do not gain access to most brain tissues, if the dyes are injected into the subarachnoid space or into the ventricles, they soon enter the extracellular spaces around the neurons and glial cells. Thus, a comparable physiologic barrier between CSF and the CNS extracellular compartment does not exist. However, three structures separate CSF from nervous tissue: (1) the pia-covered surface of the brain and spinal cord, (2) the perivascular extensions of the subarachnoid space into the nervous tissue, and (3) the ependymal surface of the ventricles (Fig. 16-23).

The pia-covered surface of the brain consists of a loosely arranged layer of pial cells resting on a basement membrane. Beneath the basement membrane are the astrocyte foot processes. No intercellular junctions exist between adjacent pial cells or between adjacent astrocytes; therefore, the extracellular spaces of the nervous tissue are in almost direct continuity with the subarachnoid space.

The prolongation of the subarachnoid space into the central nervous tissue quickly ends below the surface of the brain, where the fusion of the outer covering of the blood vessel with the pial covering of the nervous tissue occurs.

The ventricular surface of the brain is covered with columnar ependymal cells with localized tight junctions.

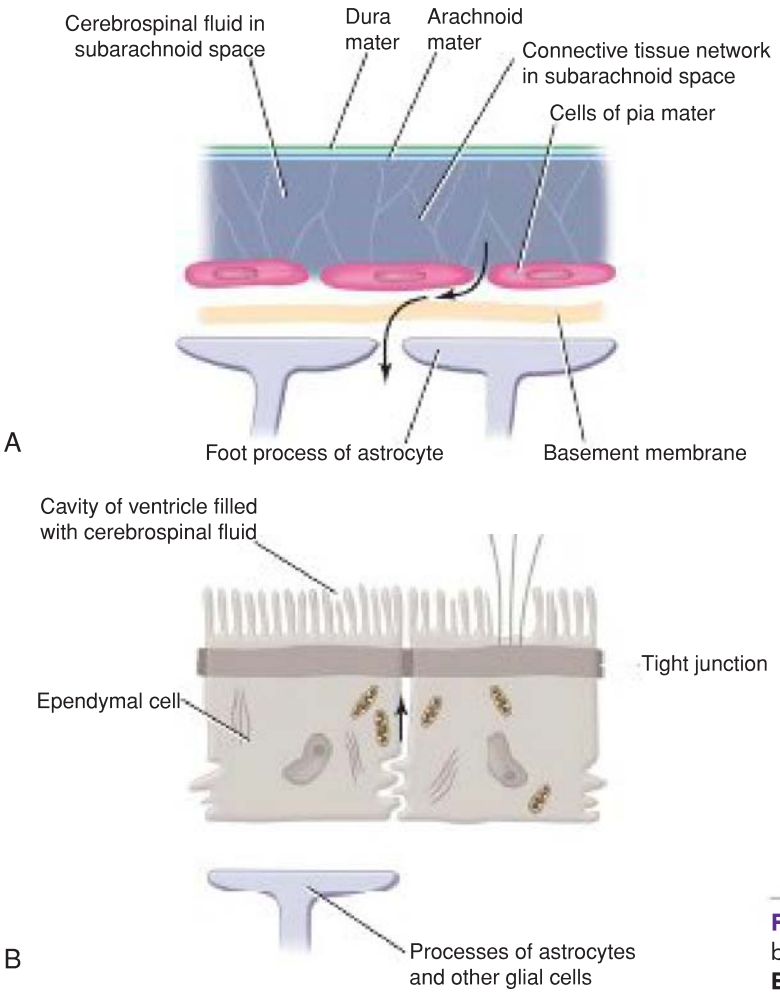


Figure 16-23 Section of the cerebrospinal fluid–brain interface. **A:** Outer surface of the brain. **B:** Ventricular surface of the brain.

Intercellular channels permit free communication between the ventricular cavity and the extracellular neuronal space. The ependyma does not have a basement membrane, and specialized astrocytic foot processes are absent because the neuroglia cells are loosely arranged.

Functional Significance of the Barriers

In normal conditions, the BBB and blood–cerebrospinal fluid barrier are two important semipermeable barriers that protect the brain and spinal cord from potentially harmful substances while permitting gases and nutriments to enter the nervous tissue.

Clinical Notes

Optic Nerve and Papilledema

The optic nerves are surrounded by sheaths derived from the pia mater, arachnoid mater, and dura mater. The intracranial subarachnoid space extends forward around the optic nerve to the back of the eyeball (see Fig. 16-19A). A rise of CSF pressure caused by an intracranial tumor will compress the thin walls of the retinal vein as it crosses the extension of the subarachnoid space to enter the optic nerve. This will result in congestion of the retinal vein, bulging forward of the optic disc, and edema of the disc; the last condition is referred to as **papilledema**. As both subarachnoid extensions are continuous with the intracranial subarachnoid space, both eyes will exhibit papilledema. Persistent papilledema leads to optic atrophy and blindness.

Hydrocephalus

Hydrocephalus is an abnormal increase in CSF volume within the skull. If the hydrocephalus is accompanied by raised CSF pressure, then it is due to one of the following: (1) abnormal increase in CSF formation, (2) blockage of CSF circulation, or (3) diminished CSF absorption. Rarely, hydrocephalus occurs with normal CSF pressure; these patients exhibit compensatory hypoplasia or atrophy of the brain substance.

Two varieties of hydrocephalus are described: In **noncommunicating hydrocephalus**, the raised CSF pressure is due to blockage at some point between its formation at the choroid plexuses and its exit through the foramina in the roof of the fourth ventricle. In **communicating hydrocephalus**, no obstruction exists within or to the outflow from the ventricular system; the CSF freely reaches the subarachnoid space and is found to be under increased pressure.

Excessive Cerebrospinal Fluid Formation

Excessive CSF formation is a rare condition that may occur with a tumor of the choroid plexuses.

Blockage of Cerebrospinal Fluid Circulation

An obstruction of the interventricular foramen by a tumor will block the drainage of the lateral ventricle on that side. Continued CSF production by the choroid plexus of that ventricle will cause distention of that ventricle and atrophy of the surrounding neural tissue.

An obstruction in the cerebral aqueduct may be congenital or may result from inflammation or pressure from a tumor. This causes a symmetrical distention of both lateral ventricles and distention of the third ventricle.

Obstruction of the median aperture (foramen of Magendie) in the roof of the fourth ventricle and the two lateral apertures (foramina of Luschka) in the lateral recesses of the fourth ventricle by inflammatory exudate or by tumor growth will produce symmetrical dilatation of both lateral ventricles and the third and fourth ventricles.

Sometimes, inflammatory exudate secondary to meningitis will block the subarachnoid space and obstruct CSF flow over the outer surface of the cerebral hemispheres. Here again, the entire ventricular system of the brain will become distended.

Diminished Cerebrospinal Fluid Absorption

Interference with CSF at the arachnoid granulations may be caused by inflammatory exudate, venous thrombosis or pressure on the venous sinuses, or obstruction of the internal jugular vein.

Clinical Investigation of the Cerebral Ventricles

The size of the cerebral ventricles may be investigated clinically by the use of (1) computed tomography (CT) and magnetic resonance imaging (MRI) and, if necessary, (2) intracranial pneumography.

CT and **MRI** are safe and easy to perform. The outline of the ventricles may be demonstrated by using these methods (see Figs. 1-24 and 1-25). Apart from ventricular distention or distortion, the cerebral tumor causing the condition also may be demonstrated.

Intracranial pneumography is essentially the replacement of CSF within the ventricles and subarachnoid space with air or oxygen. Because the air or gas is less dense than CSF or neural tissue, the ventricles and cerebral gyri can be visualized. In an **encephalogram**, the air or oxygen is introduced through a spinal tap and radiographs of the skull are then made. In a **ventriculogram**, the air or oxygen is introduced into the lateral ventricle through a needle inserted through a hole in the skull (in a young child, the needle may be inserted through a suture) and skull radiographs are made. In ventriculography, only the ventricles are visualized.

Cerebrospinal Fluid Pressure and Composition in Disease

CSF examination can be of great assistance in making a neurologic diagnosis.

Clinical measurement of CSF pressure by means of a spinal tap is described on page 19. An increase in pressure is usually due to meningitis or an increase in volume of the brain produced by edema, tumor formation, a cerebral abscess, or the presence of a hematoma.

The gross appearance of a specimen of CSF is of great value. Normally, it is clear and colorless. Cloudiness usually indicates the presence of polymorphonuclear leukocytes or an excessive quantity of protein. An increase in the white cells would suggest inflammation of the meninges or encephalitis. An increase in protein content implies a change in the vascular permeability, and protein escapes into the CSF. Raised protein content is seen in tuberculous meningitis and poliomyelitis. In multiple sclerosis, the gamma globulin is elevated due to production of immunoglobulins in the brain and spinal cord.

Normal CSF does not contain red blood cells. Gross blood in the CSF is usually caused by contamination brought about by puncture of a vertebral vein by the spinal tap needle. Uniform blood staining is found in subarachnoid hemorrhage. Yellow coloration or **xanthochromia** is caused by the presence of oxyhemoglobin in the fluid some hours after subarachnoid hemorrhage.

Normal CSF contains fewer than four white cells. In bacterial infections, many thousands of cells may be present per cubic millimeter. In viral infections of the nervous system, a moderate lymphocyte reaction may occur. A slight rise in lymphocyte count may also occur in cerebral tumors, cerebral infarction, and multiple sclerosis.

The glucose level in the CSF may disappear completely in acute bacterial meningitis but remains normal in viral infections.

Normal CSF physical characteristics and composition are summarized in Table 16-1.

Subarachnoid Space Blockage

A block of the subarachnoid space in the vertebral canal may be caused by a tumor of the spinal cord or the meninges. Performing a spinal tap is of great value in making a diagnosis. The normal pressure of CSF with the patient lying quietly on his or her side and breathing through the mouth is between 60 and 150 mm of water. If CSF flow in the subarachnoid space is blocked, the normal variations in pressure corresponding to the pulse and respiration are reduced or absent. Compression of the internal jugular veins in the neck raises the cerebral venous pressure and inhibits CSF absorption in the arachnoid villi and granulations, thus producing a rise in the manometric reading of CSF pressure. If this fails to occur, the subarachnoid space is blocked and the patient is exhibiting a positive **Queckenstedt sign**. Should the tumor completely occupy the vertebral canal in the region of the cauda equina, no CSF can flow out of the spinal tap needle.

Normally, CSF is clear. In the presence of a tumor, it may be yellow and clot spontaneously owing to the rise in protein content.

Fourth Ventricle Tumors

Tumors may arise in the vermis of the cerebellum or in the pons and invade the fourth ventricle. **Ependymomas** arising from the ependymal cells lining the ventricle also

occur. Tumors in this region may invade the cerebellum and produce the symptoms and signs of cerebellar deficiency, or they may press on the vital nuclear centers situated beneath the floor of the ventricle; the hypoglossal and vagal nuclei, for example, control movements of the tongue, swallowing, respiration, heart rate, and blood pressure.

Blood–Brain Barrier in the Fetus and Newborn

In the fetus, newborn child, and premature infant, the BBB is not fully developed, and toxic substances such as bilirubin can readily enter the CNS and produce yellowing of the brain and kernicterus. This is not possible in the adult.

Brain Trauma and the Blood–Brain Barrier

Any injury to the brain, whether it be due to direct trauma or to inflammatory or chemical toxins, causes a breakdown of the BBB, allowing free diffusion of large molecules into the nervous tissue. This is believed to be brought about by actual destruction of the vascular endothelial cells or disruption of their tight junctions.

Drugs and the Blood–Brain Barrier

The systemic administration of **penicillin** results in only a small amount entering the CNS. This is fortunate because penicillin in high concentrations is toxic to nervous tissue. In the presence of meningitis, however, the meninges become more permeable locally at the site of inflammation, thus permitting sufficient antibiotic to reach the infection. **Chloramphenicol** and the **tetracyclines** readily cross the BBB and enter the nervous tissue. The **sulfonamide** drugs also easily pass through the BBB.

Lipid-soluble substances such as the anesthetic agent **thiopental** rapidly enter the brain after intravenous injection. On the other hand, water-soluble substances such as exogenous **norepinephrine** cannot cross the BBB. **Phenylbutazone** is a drug that becomes bound to plasma protein, and the large drug protein molecule is unable to cross the barrier. Most tertiary amines such as **atropine** are lipid soluble and quickly enter the brain, whereas the quaternary compounds such as **atropine methyl nitrate** do not.

In Parkinson disease, the neurotransmitter dopamine is deficient in the corpus striatum. Unfortunately, dopamine cannot be used in the treatment, as it will not cross the BBB. L-Dopa readily crosses the barrier and has been used with great success.

Tumors and the Blood–Brain Barrier

Brain tumors frequently possess blood vessels that have no BBB. Anaplastic malignant astrocytomas, glioblastomas, and secondary metastatic tumors lack the normal barriers. However, slow-growing tumors often have normal vascular barriers.

Key Concepts

Ventricular System

- The ventricles are fluid-filled cavities located within the brain.
- The ventricles are lined throughout with ependyma and are filled with CSF.
- Lateral ventricles are the largest ventricles and are described as having a body, and anterior, posterior, and lateral horns.
- The lateral ventricles communicate with a singular, medially located third ventricle via the interventricular foramen.
- The third ventricle is found between the two thalami.
- The cerebral aqueduct of the midbrain communicates CSF between the third and fourth ventricles.
- The fourth ventricle is located between the pons/medulla and the cerebellum.
- CSF exits the fourth ventricle through the singular median opening (foramen of Magendie) and two lateral openings (foramina of Luschka).
- The choroid plexus is found within the lateral ventricles and produces CSF.
- Blood–Brain and Blood–Cerebrospinal Fluid Barriers
- The BBB freely allows gases and water, slowly allows glucose and electrolytes, but restricts passage of plasma proteins and other large organic molecules.
- The structure of the BBB is formed by the endothelial capillary walls, a continuous basement membrane around the vessels, and the foot processes of astrocytes that adhere to the capillary wall.
- Tight junctions between endothelial cells are responsible for the restriction of large molecules but yet allow lipophilic molecules to cross the barrier.
- Water, gases, and lipid-soluble substances pass freely from the blood to the CSF but macromolecules are restricted, suggesting a similar barrier exists in the choroid plexus.

Clinical Problem Solving

1. A 55-year-old man is being investigated for signs and symptoms that suggest the presence of a cerebral tumor. Examination of the CT scan shows gross enlargement and distortion of the left lateral ventricle. What other investigation might be carried out in this patient to display the ventricles of the brain? Using your knowledge of neuroanatomy, determine the location of the tumor in this patient.
2. A 3-year-old child is referred to the children's hospital because the circumference of his head greatly exceeds the normal limit for his age. After a careful history is taken and a detailed physical examination is performed, a diagnosis of hydrocephalus is made. What is your definition of hydrocephalus? Name three common causes of hydrocephalus in young children.
3. A 50-year-old man is found on ophthalmoscopic examination to have edema of both optic discs (bilateral papilledema) and congestion of the retinal veins. The cause of the condition is found to be a rapidly growing intracranial tumor. Using your knowledge of neuroanatomy, explain the papilledema. Why does the patient exhibit bilateral papilledema?
4. A 38-year-old man is admitted to the neurosurgery ward with symptoms of persistent headache and vomiting and some unsteadiness in walking. The headache started 6 weeks previously and became progressively worse. On examination, he cannot sit up in bed unsupported. The limbs on the right side of the body show some loss of tone. Examination of the patient when he is standing up shows a marked loss of equilibrium. Examination of the cranial nerves shows central deafness of the right ear. Ophthalmoscopic examination shows severe bilateral papilledema. Using your knowledge of neuroanatomy, explain the symptoms and signs experienced by this patient and try to make a diagnosis.
5. A 4-year-old girl is found to have tuberculous meningitis. She is immediately admitted to the hospital and administration of streptomycin and isoniazid is commenced. As soon as this therapy is started, she is also administered steroid hormones to reduce the incidence of adhesions. She recovers fully with no complications. Using your knowledge of neuroanatomy, explain why preventing adhesion formation in the subarachnoid space is important.
6. A 5-year-old girl with symptoms of headache, general malaise, and vomiting is admitted to the children's hospital. On examination, the body temperature is found to be 104°F and the pulse rate is rapid. Attempts to flex the neck produce pain and result in the patient flexing her hip and knee joints. A spinal tap is performed; the cerebrospinal fluid (CSF) is seen to be cloudy and the pressure is raised to 190 mm of water. Microscopic examination of the fluid shows a large number of polymorphonuclear leukocytes. A diagnosis of meningitis is made. Subsequent culture reveals the infection to be a meningococcal meningitis. The resident vaguely remembers reading in a textbook the importance of the blood–brain barrier (BBB) in the use of antibiotics for the treatment of meningitis. What is the BBB? Does the presence of the BBB influence your choice and dose of antibiotics to be used in this patient?
7. During a ward round in the children's hospital, the pediatrician informs the students that a 4-day-old baby with jaundice has a serum indirect bilirubin level of 45 mg/100 mL and that by now the bile pigment is staining the brain a yellow color (kernicterus). The neuronal damage is revealed clinically by lethargy and poor feeding habits and by occasional muscle spasms. She says the prognosis is very poor. One of the students observes that he cannot understand why the bile pigment is having such a dramatic effect on the baby. Recently, he examined a patient who was dying of inoperable carcinoma of the head of the pancreas with total obstruction of the common bile duct. In that patient, the skin was a deep yellow, but apart from complaints of the intense skin irritation owing to the high concentration of bile salts in the blood and loss of weight, the patient had no symptoms and no neurologic abnormalities. Explain why the baby had neuronal damage and the adult did not.
8. Name five areas of the brain where the blood–brain barrier (BBB) appears to be absent. What do you think is the significance of the fact that in a few areas of the brain, the barrier is absent?

Answers and Explanations to Clinical Problem Solving

1. An MRI shows the outline of the ventricles very well. Occasionally, when these methods show insufficient detail, a ventriculogram can be obtained. This procedure consists of the introduction of air or oxygen into the lateral ventricle through a needle inserted through a burr hole in the skull. Since the left lateral ventricle was the only part of the ventricular system that showed distention and distortion, one can assume that the tumor had closed off the left interventricular foramen and, therefore, was in the vicinity of that foramen. This was confirmed on the CT scan.
2. Hydrocephalus is an abnormal increase in the volume of cerebrospinal fluid within the skull. Congenital atresia of the cerebral aqueduct, meningitis, tumors, and blockage of the arachnoid granulations by subarachnoid bleeding or inflammatory exudate are common causes of this condition in young children.
3. The intracranial subarachnoid space extends forward around the optic nerve to the back of the eyeball. A rise in cerebrospinal fluid pressure caused by an intracranial tumor will compress the thin walls of the retinal vein as it crosses the extension of the subarachnoid space to enter the optic nerve. This will result in congestion of the retinal vein, bulging of the optic disc, and edema of the disc. Since both subarachnoid extensions are continuous with the intracranial subarachnoid space, both eyes will exhibit papilledema.
4. This man was operated on and was found to have a large astrocytoma of the vermis of the cerebellum. The tumor had severely encroached on the cavity of the fourth ventricle, producing internal hydrocephalus and pressure on the floor of the ventricle. The symptoms of headache and persistent vomiting were produced by a raised intracranial pressure caused by the enlarging tumor. The tumor also blocked off the median and lateral apertures in the roof of the fourth ventricle, causing an internal hydrocephalus, which further raised the intracranial pressure. The bilateral papilledema was secondary to the raised intracranial pressure. The inability to sit up in bed (truncal ataxia) and the loss of equilibrium on standing were due to the tumor involvement of the vermis of the cerebellum. The loss of tone of the muscles of the right limbs indicated spread of the tumor to involve the right cerebellar hemisphere. Central deafness on the right side was due to involvement of the right eighth cranial nerve nuclei by the tumor mass. The patient died 6 months after neurosurgical exploration.
5. Steroid hormones (e.g., prednisone) inhibit the normal inflammatory reaction and thereby reduce the incidence of fibrous adhesions. Preventing adhesion formation is important, as it can block the openings in the roof of the fourth ventricle thus preventing the escape of cerebrospinal fluid (CSF) into the subarachnoid space from within the ventricular system. Adhesions also can prevent the flow of CSF over the cerebral hemispheres or reduce the absorption of the fluid into the arachnoid granulations. Thus, adhesions of the meninges may result in hydrocephalus.
6. The BBB is a semipermeable barrier that exists between the blood and the extracellular spaces of the nervous tissue of the brain. It permits the passage of water, gases, glucose, electrolytes, and amino acids, but it is impermeable to substances with a large molecular weight. Yes, the presence of the BBB does affect the choice and dose of antibiotics. The antibiotic penicillin, when injected intramuscularly into a normal individual, is found in much lower concentrations in the CSF than in the blood; this is due to the existence of the BBB and the blood–cerebrospinal fluid barrier. Inflammation of the meninges results in an increased permeability of the meningeal blood vessels, and consequently, the concentration of penicillin rises in the CSF. However, for treatment to be effective in patients with meningitis, very large doses of penicillin must be given intravenously. By contrast, chloramphenicol and the sulfonamides rapidly cross the blood–brain and blood–cerebrospinal fluid barriers; therefore, an adequate concentration in the CSF can easily be maintained.
7. The blood–brain barrier in the newborn child is not fully developed and is more permeable than that in the adult. Indirect bilirubin readily crosses the barrier in the newborn but does not do so in the adult. Once the bile pigment reaches the extracellular spaces of the brain tissue in the newborn, it passes into the neurons and neuroglia cells. This results in abnormal cell function and eventually neuronal death.
8. The pineal gland, the posterior lobe of the pituitary, the tuber cinereum, the wall of the optic recess, and the vascular area postrema at the inferior end of the fourth ventricle are parts of the brain where the capillary endothelium contains open fenestrations across which proteins and small organic molecules may pass. In these areas, a BBB appears to be absent. The significance of the absence of the barrier in the pineal gland is not understood. To function normally, pinealocytes possibly require a close relationship with the blood plasma in order to sample the concentrations of hormones. The absence of the BBB in the region of the hypothalamus may allow this area of the brain to sample the chemical content of the plasma, so appropriate modifications of metabolic activity may take place, thus protecting the nervous tissue as a whole.

Review Questions

Directions: Each of the numbered items in this section is followed by answers. Select the ONE lettered answer that is CORRECT.

1. The following statements concern the ventricular system:
   (a) The cerebral aqueduct connects the third ventricle with the fourth ventricle.
   (b) The two lateral ventricles communicate directly with one another through the foramen of Monro.
   (c) The ventricles are developed from the embryonic endoderm.
   (d) It is lined throughout with squamous epithelium.
   (e) Choroid plexuses are found only in the lateral ventricles.
2. The following statements concern the ventricular system:
   (a) The fourth ventricle has a rectangular-shaped floor.
   (b) The pineal body is suspended from the roof of the fourth ventricle.
   (c) The nerve centers controlling the heart rate and blood pressure lie beneath the floor of the third ventricle.
   (d) The choroid plexus of the lateral ventricle projects into the cavity on its medial side through the choroidal fissure.
   (e) The foramen of Magendie is an aperture in the roof of the third ventricle.
3. The following statements concern the blood–brain barrier (BBB):
   (a) It protects the brain from toxic compounds of low molecular weight.
   (b) It is present in the pineal gland.
   (c) The endothelial cells of the blood capillaries are nonfenestrated.
   (d) The endothelial cells of the blood capillaries are held together by localized tight junctions.
   (e) L-Dopa has difficulty passing through it in the treatment of Parkinson disease.
4. The following statements concern the blood–brain barrier (BBB):
   (a) Chloramphenicol and the tetracyclines cannot cross the barrier.
   (b) In the newborn child, the BBB is not fully developed.
   (c) Cerebral trauma or inflammation has little effect on BBB integrity.
   (d) Gases and water pass with difficulty through the barrier.
   (e) Glucose and electrolytes pass quickly through the barrier.
5. The following statements concern the blood–cerebrospinal fluid barrier:
   (a) The beltlike tight junctions between the choroidal ependymal cells form the barrier.
   (b) The proteins and most hexoses, other than glucose, are able to cross the barrier.
   (c) Gases and water cannot pass through the barrier.
   (d) Lipid-soluble substances have difficulty passing through the barrier.
   (e) The basement membrane of the endothelial cells plays a vital part in the formation of the barrier.
6. The following structures are associated with the roof of the fourth ventricle:
   (a) Tectum of the midbrain
   (b) Choroid plexus
   (c) Pineal gland
   (d) Corpus callosum
   (e) Temporal lobes of the cerebral hemispheres
7. The following statements concern the cerebrospinal fluid (CSF) in the fourth ventricle:
   (a) It is produced mainly by the choroid plexus of the cerebral aqueduct.
   (b) It leaves the midbrain through the interventricular foramina.
   (c) It enters the spinal cord through the foramen of Luschka.
   (d) It is dark yellow in color.
   (e) It escapes into the subarachnoid space through the apertures in the roof of the fourth ventricle.
8. The lateral boundaries of the fourth ventricle are formed by:
   (a) the tentorium cerebelli.
   (b) the sulcus limitans.
   (c) the cerebellar peduncles.
   (d) the cerebral peduncles.
   (e) the striae medullares.
9. The following important nuclei lie beneath the floor of the fourth ventricle:
   (a) Oculomotor nucleus
   (b) Trochlear nucleus
   (c) Trigeminal nucleus
   (d) Hypoglossal nucleus
   (e) Olfactory nucleus
10. The following statements concern the third ventricle:
   (a) It is situated between the two thalami.
   (b) It communicates with the lateral ventricles through the cerebral aqueduct.
   (c) It is continuous with the fourth ventricle through the interventricular foramen.
   (d) The choroid plexus is located on the floor.
   (e) The choroid plexus receives its arterial supply through the posterior cerebral arteries.

11. The following statements concern the subarachnoid space:
    (a) It contains cerebrospinal fluid (CSF) and the cerebral arteries but not the cerebral veins.
    (b) It does not communicate with the cisterns.
    (c) The fourth ventricle drains into it through a single foramen.
    (d) The space does not surround the cranial and spinal nerves where they leave the skull and the vertebral canal.
    (e) It is the interval between the arachnoid mater and the pia mater.
12. The following statements concern cerebrospinal fluid (CSF) formation:
    (a) None of the fluid originates from the brain substance.
    (b) It is largely formed by the choroid plexuses.
    (c) It is passively secreted by the ependymal cells covering the choroid plexuses.
    (d) It is produced continuously at a rate of about 5 mL/min.
    (e) It is drained into the subarachnoid space from the lymphatic vessels of the brain and spinal cord.
13. The following statements concern the cerebrospinal fluid (CSF):
    (a) Its circulation through the ventricles is not aided by the pulsations of the choroid plexuses.
    (b) It extends inferiorly in the subarachnoid space to the level of the fifth sacral vertebra.
    (c) The CSF pressure in the subarachnoid space rises if the internal jugular veins in the neck are compressed.
    (d) It exits from the ventricular system through the ventricular foramina.
    (e) Its circulation in the subarachnoid space is aided by the pulsations of the cerebral and spinal veins.
14. The following statements concern cerebrospinal fluid (CSF) absorption:
    (a) The fluid is passed into the blood by active transport through the cells forming the arachnoid villi.
    (b) The major sites for its absorption are into the veins in the subarachnoid space and the perineural lymph vessels.
    (c) Arachnoid villi play an important role in its absorption.
    (d) Fine tubules found within the arachnoid villi play a minor role in CSF flow into the venous sinuses.
    (e) In communicating hydrocephalus, flow is obstructed within the ventricular system and to the outflow from the ventricular system to the subarachnoid space.

Matching Questions. Directions: The following questions apply to Figure 16-24. Match the numbers listed on the left with the appropriate lettered structures listed on the right. Each lettered option may be selected once, more than once, or not at all.

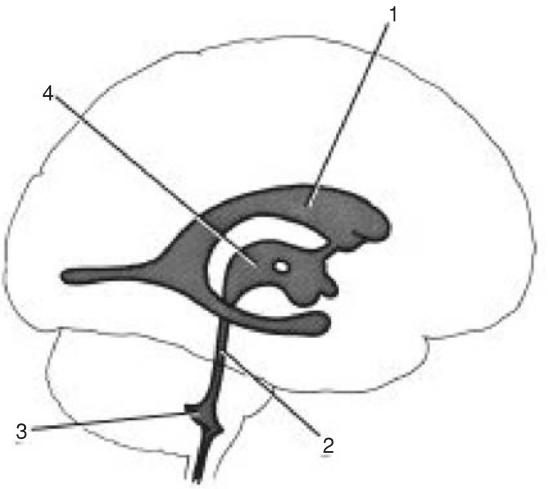


Figure 16-24 Lateral view of the brain showing an outline of ventricular cavities.

15. Number 1
16. Number 2
17. Number 3
18. Number 4

(a) Cerebral aqueduct
(b) Body of lateral ventricle
(c) Third ventricle
(d) Fourth ventricle
(e) None of the above

Directions: Each case history is followed by questions. Read the case history, then select the ONE BEST lettered answer.

A 24-year-old woman complaining of recent onset of severe headaches and several attacks of morning vomiting was seen by a neurologist. A thorough physical examination revealed findings suggesting that she might have an intracranial tumor involving the cerebellum. The physician ordered an MRI of the patient's brain with particular reference to the contents of the posterior cranial fossa.

19. Figure 16-25 is a coronal MRI (contrast enhanced) through the fourth ventricle. The radiologist made the following correct observations in his report except:
    (a) The bones of the skull showed nothing abnormal. The cerebral cortex appeared to be normal.
    (b) The midline structures were not deflected to one or the other side.
    (c) The cavity of the fourth ventricle was distorted and larger than normal.
    (d) The body of the lateral ventricle had a normal appearance.

A 21-year-old pregnant woman was invited to a reunion party and during the course of the evening, she drank several gin and tonics. The party was followed by several others extending over a 3-week period during which she drank heavily. Six months later, she gave birth to a boy who was diagnosed as having congenital hydrocephalus.

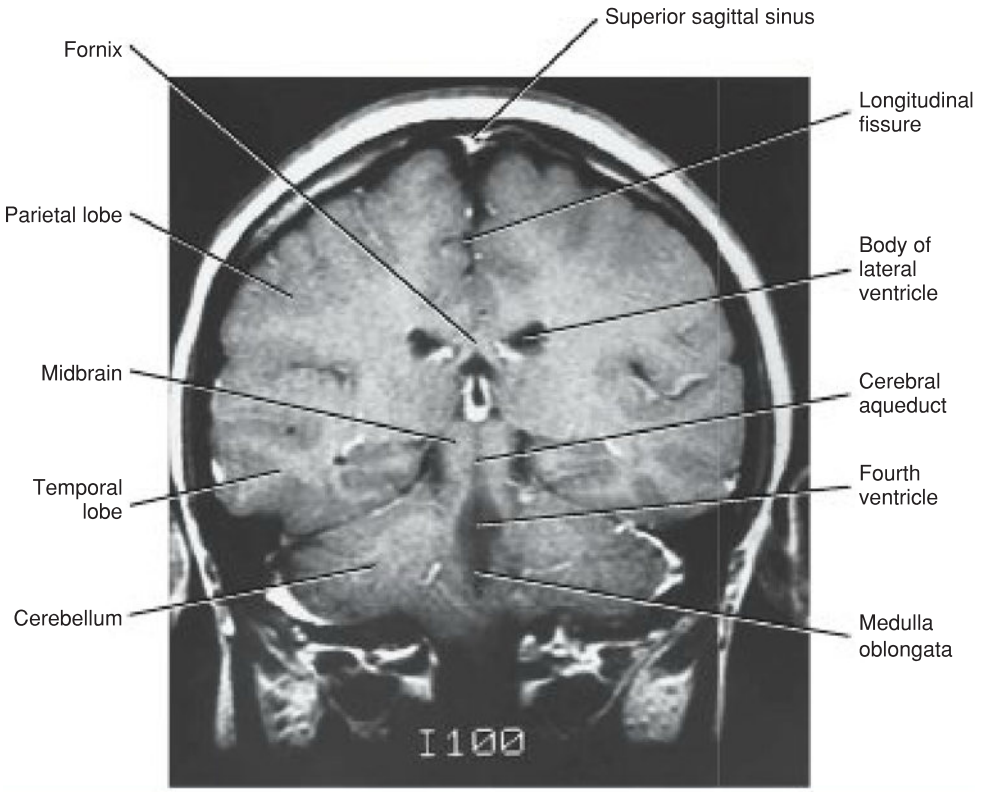


Figure 16-25 A coronal MRI (contrast enhanced) through the hindbrain showing the fourth ventricle and the surrounding neural and bony structures.

20. The pediatric neurologist carefully questioned the mother and came to the following correct conclusions except:
    (a) The consumption of a large amount of alcohol during pregnancy usually has no adverse effects on the developing fetus.
    (b) The high alcoholic intake coincided with the first trimester.
    (c) The alcohol had crossed the placental barrier and entered the fetal circulation.
    (d) The alcohol had probably also crossed the fetal blood–brain barrier (BBB) and entered the brain.
    (e) The neurologist was of the opinion that the toxic effect of alcohol was probably responsible for the hydrocephalus.

Answers and Explanations to Review Questions

1. A is correct. The cerebral aqueduct connects the third ventricle with the fourth ventricle (see Fig. 16-4). B. The two lateral ventricles do not communicate directly with one another through the interventricular foramen (foramen of Monro) (see Fig. 16-2). C. The ventricles are developed from the neural tube in the embryo. D. The ventricular system is lined throughout with ependyma, which is a single layer of cuboidal or columnar cells. E. The choroid plexuses are found in the lateral ventricles and the third and the fourth ventricles.
2. D is correct. The choroid plexus of the lateral ventricle projects into the cavity on its medial side through the choroidal fissure (see Fig. 16-7). A. The fourth ventricle has a diamond-shaped floor called the rhomboid fossa (see Fig. 16-11). B. The pineal body is not suspended from the roof of the fourth ventricle (see Fig. 16-4). C. The nerve centers controlling the heart rate and blood pressure lie beneath the floor of the fourth ventricle (see Fig. 16-11). E. The foramen of Magendie is an aperture in the roof of the fourth ventricle (see Fig. 16-12).
3. C is correct. The endothelial cells of the blood capillaries in the BBB are nonfenestrated. A. The BBB protects the brain from toxic compounds of high molecular weight. B. The BBB is not present in the pineal gland. D. The endothelial cells of the blood capillaries of the BBB are not held together by localized tight junctions; they pass around the endothelial cells. E. L-Dopa readily passes through the BBB in the treatment of Parkinson disease.

4. B is correct. In the newborn child, the BBB is not fully developed. A. Chloramphenicol and the tetracyclines can cross the BBB. C. Cerebral trauma and inflammation may have a great effect on the integrity of the BBB. D. Gases and water pass readily through the BBB. E. Glucose and electrolytes pass slowly through the BBB.
5. A is correct. In the blood–cerebrospinal fluid barrier, the beltlike tight junctions between the choroidal ependymal cells form the barrier. B. The proteins and most hexoses, other than glucose, are unable to cross the blood–cerebrospinal fluid barrier. C. Gases and water pass readily through the barrier. D. Lipid-soluble substances have no difficulty passing through the barrier. E. The basement membrane of the endothelial cells plays no part in the formation of the barrier.
6. B is correct. The choroid plexus is present in the roof of the fourth ventricle (see Fig. 16-8).
7. E is correct. The CSF in the fourth ventricle escapes into the subarachnoid space through apertures in the roof of the ventricle (see Fig. 16-13). A. The CSF in the fourth ventricle is produced mainly in the choroid plexuses of the lateral, third, and fourth ventricles. B. It leaves the midbrain through the cerebral aqueduct (Fig. 16-17). C. The CSF in the fourth ventricle enters the spinal cord through the central canal (see Fig. 16-7). D. The CSF is clear and colorless.
8. C is correct. The lateral boundaries of the fourth ventricle are formed by the cerebellar peduncles (see Fig. 16-10).
9. D is correct. The hypoglossal nucleus lies beneath the floor of the fourth ventricle (see hypoglossal triangle in Fig. 16-11).
10. A is correct. The third ventricle lies between the thalami (see Fig. 16-5). B. The third ventricle communicates with the lateral ventricles through the interventricular foramina (see Fig. 16-2). C. The third ventricle is continuous with the fourth ventricle through the cerebral aqueduct (see Fig. 16-3). D. The choroid plexus of the third ventricle is situated in the roof (see Fig. 16-6). E. The choroid plexus of the third ventricle receives its arterial supply from the internal carotid and basilar arteries.
11. E is correct. The subarachnoid space is the interval between the arachnoid mater and the pia mater (see Fig. 16-1). A. The subarachnoid space contains CSF, the cerebral arteries, and the cerebral veins. B. The subarachnoid space is in free communication with the cisterns. C. The fourth ventricle drains into the subarachnoid space through three openings in its roof (see Fig. 16-1). D. The subarachnoid space surrounds the cranial and spinal nerves to the point where they leave the skull and the vertebral canal.
12. B is correct. The CSF is largely formed by the choroid plexuses. A. Some of the fluid originates from the brain substance. C. The CSF is actively secreted by the ependymal cells covering the choroid plexuses. D. The CSF is produced continuously at a rate of 0.5 mL/min. E. The brain and spinal cord have no lymphatic vessels.
13. C is correct. The CSF pressure in the subarachnoid space rises if the internal jugular veins in the neck are compressed. A. The circulation of the CSF through the ventricles is aided by the pulsations of the arteries in the choroid plexuses. B. The CSF extends inferiorly in the subarachnoid space in the vertebral column to the level of the lower border of the second sacral vertebra (see Fig. 16-1). D. The CSF exits from the ventricular system of the brain through the foramina of Luschka and Magendie (see Fig. 16-1). E. The circulation of the CSF in the subarachnoid space is aided by the pulsations of the cerebral and spinal arteries.
14. C is correct. The arachnoid villi play an important role in the absorption of CSF into the cranial venous sinuses. A. The CSF does not pass into the blood by active transport through the cells forming the arachnoid villi. B. The veins in the subarachnoid space and the perineural lymph vessels are minor sites for the absorption of CSF. D. The fine tubules found within the arachnoid villi play a major role in the flow of the CSF into the venous sinuses. E. In communicating hydrocephalus, flow of the CSF is not obstructed within the ventricular system or to the outflow from the ventricular system to the subarachnoid space.

For answers to Questions 15 to 18, study Figure 16-21.

15. B is correct; 1 is body of the lateral ventricle.
16. A is correct; 2 is cerebral aqueduct.
17. D is correct; 3 is fourth ventricle.
18. C is correct; 4 is third ventricle.
19. C is correct. The size and the shape of the cavity of the fourth ventricle were within normal limits.
20. A is correct. Many chemical substances when consumed are toxic to the central nervous system (CNS), and alcohol in large quantities is one of the worst offenders. During the first trimester, alcohol can readily access the brain at a time when it is particularly vulnerable. Before a physician prescribes a therapeutic drug, he or she must know whether the drug will cross the BBB and what effect, if any, that drug will have on the CNS.

17 Blood Supply of the Brain and Spinal Cord

CHAPTER OBJECTIVES

- To review the main arteries and veins supplying the brain and spinal cord
- To learn the areas of the cerebral cortex and spinal cord supplied by a particular artery and to understand the dysfunction that would result if the artery were blocked
- To review the circle of Willis as well as the blood supply to the internal capsule

A 61-year-old woman collapsed in the supermarket and was in a coma when admitted to the emergency department of the local hospital. Twenty-four hours later, she recovered consciousness and was found to have paralysis on the left side of her body, mainly involving the lower limb. There was also some sensory loss of the left leg and foot. She was able to swallow normally and did not appear to have difficulty with her speech. The left-sided hemiplegia and hemianesthesia strongly suggested a cerebrovascular accident involving the right cerebral hemisphere. The limitation of the paralysis and anesthesia to the leg and foot indicated that the right anterior cerebral artery or one of its branches was blocked by a thrombus or embolus. The diagnosis was confirmed by positron emission tomography (PET), which showed an absence of blood flow through the leg area on the medial surface of the right cerebral hemisphere.

Cerebrovascular accidents (stroke) remain the third leading cause of morbidity and death in the United States. Consequently, clinicians must know the areas of the cerebral cortex and spinal cord supplied by a particular artery and to understand the dysfunction that would result if the artery were blocked. The internal capsule that contains the major ascending and descending pathways to the cerebral cortex is commonly disrupted by arterial hemorrhage or thrombosis.

ARTERIES OF THE BRAIN

The brain is supplied by the two internal carotid and the two vertebral arteries. The four arteries lie within the subarachnoid space, and their branches anastomose on the inferior surface of the brain to form the circle of Willis.

Internal Carotid Artery

The internal carotid artery begins at the bifurcation of the common carotid artery (Fig. 17-1), where it usually possesses a localized dilatation, called the **carotid sinus**. It ascends the neck and perforates the base of the skull by passing through the carotid canal of the temporal bone. The artery then runs horizontally forward through the cavernous sinus and emerges on the medial side of the anterior clinoid process by perforating the dura mater. It now enters the subarachnoid space by piercing the arachnoid mater and turns posteriorly to the region of the medial end of the lateral cerebral sulcus. Here, it divides into the **anterior** and **middle cerebral arteries** (Fig. 17-2; also see Fig. 17-1).

Cerebral Portion Branches

1. The **ophthalmic artery** arises as the internal carotid artery emerges from the cavernous sinus. It enters the orbit through the optic canal below and lateral to the optic nerve. It supplies the eye and other orbital structures, and its terminal branches supply the frontal area of the scalp, the ethmoid and frontal sinuses, and the dorsum of the nose.
2. The **posterior communicating artery** is a small vessel that originates from the internal carotid artery close to its terminal bifurcation. The posterior communicating artery runs posteriorly above the oculomotor nerve to join the posterior cerebral artery, thus forming part of the **circle of Willis**.
3. The **choroidal artery**, a small branch, also originates from the internal carotid artery close to its terminal

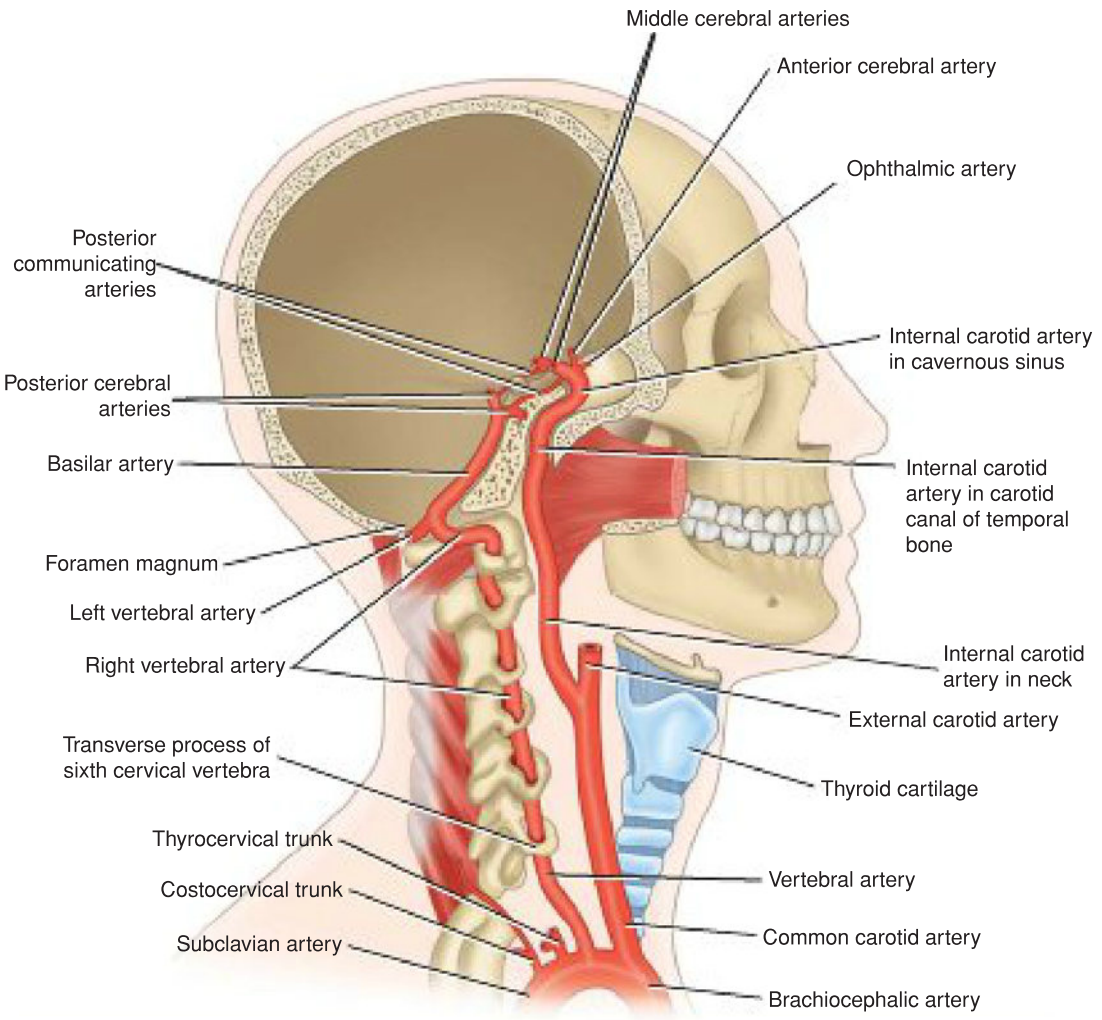


Figure 17-1 Origin and courses of the internal carotid and vertebral arteries as they ascend the neck to enter the skull.

bifurcation. The choroidal artery passes posteriorly close to the optic tract, enters the inferior horn of the lateral ventricle, and ends in the choroid plexus. It gives off numerous small branches to surrounding structures, including the crus cerebri, the lateral geniculate body, the optic tract, and the internal capsule.

4. The **anterior cerebral artery** is the smaller terminal branch of the internal carotid artery. It runs forward and medially superior to the optic nerve and enters the longitudinal fissure of the cerebrum. Here, it is joined to the anterior cerebral artery of the opposite side by the **anterior communicating artery**. It curves backward over the corpus callosum and, finally, anastomoses with the posterior cerebral artery (Fig. 17-3; also see Fig. 17-8). The **cortical branches** supply the entire medial surface of the cerebral cortex as far back as the parieto-occipital sulcus. They also supply a strip of cortex about 1 in (2.5 cm) wide on the adjoining lateral surface. The anterior cerebral artery thus supplies the "leg area" of the precentral gyrus. A group of **central branches** pierces the anterior perforated substance and helps to supply parts of the lentiform and caudate nuclei and the internal capsule.
5. The **middle cerebral artery,** the largest branch of the internal carotid, runs laterally in the lateral cerebral sulcus (see Fig. 17-2). **Cortical branches** supply the entire lateral surface of the hemisphere except for the narrow strip supplied by the anterior cerebral artery, the occipital pole, and the inferolateral surface of the hemisphere, which are supplied by the posterior cerebral artery (see Fig. 17-3). This artery thus supplies the entire motor area except the "leg area." **Central branches** enter the anterior perforated substance and supply the lentiform and caudate nuclei and the internal capsule (Fig. 17-4).

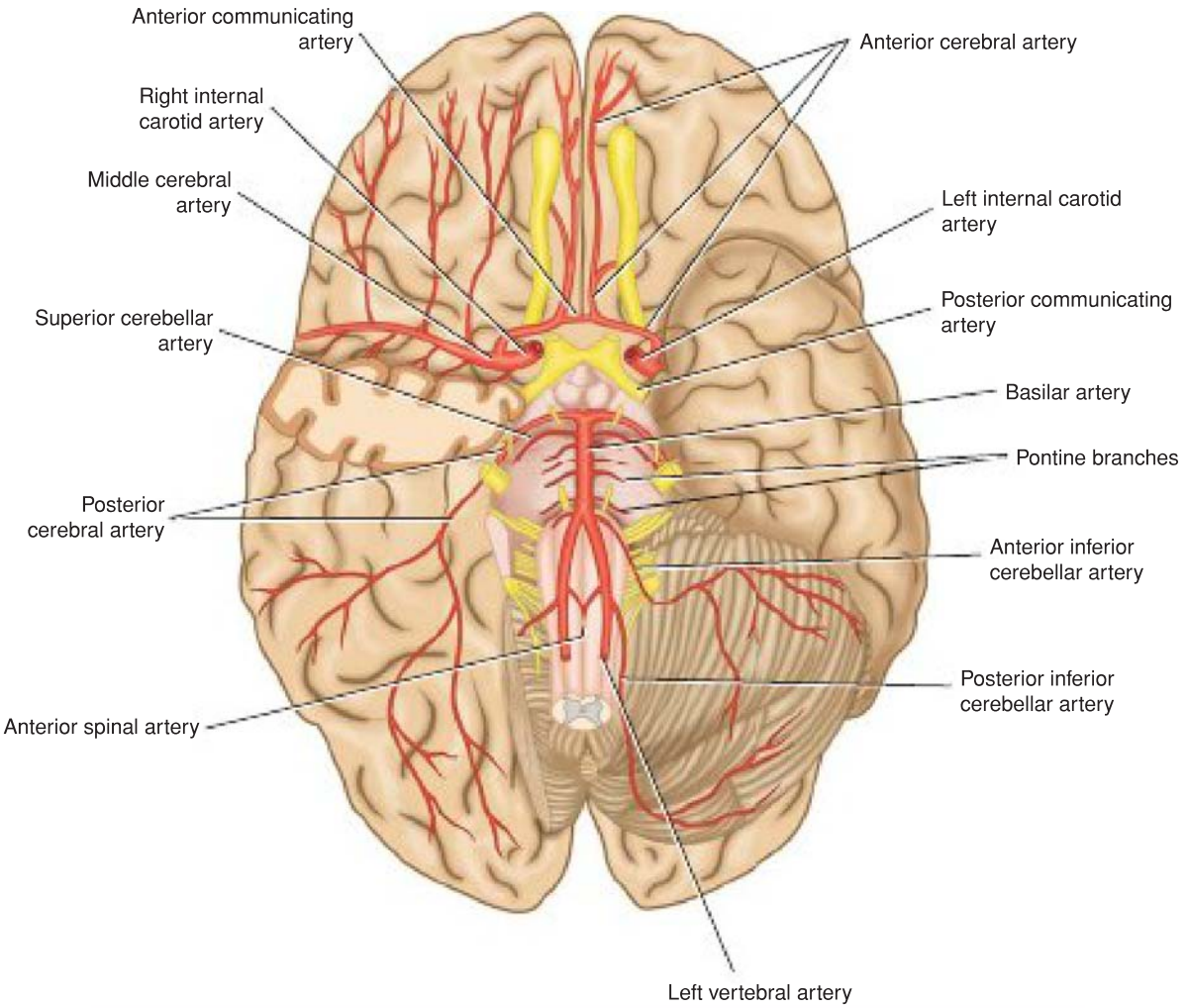


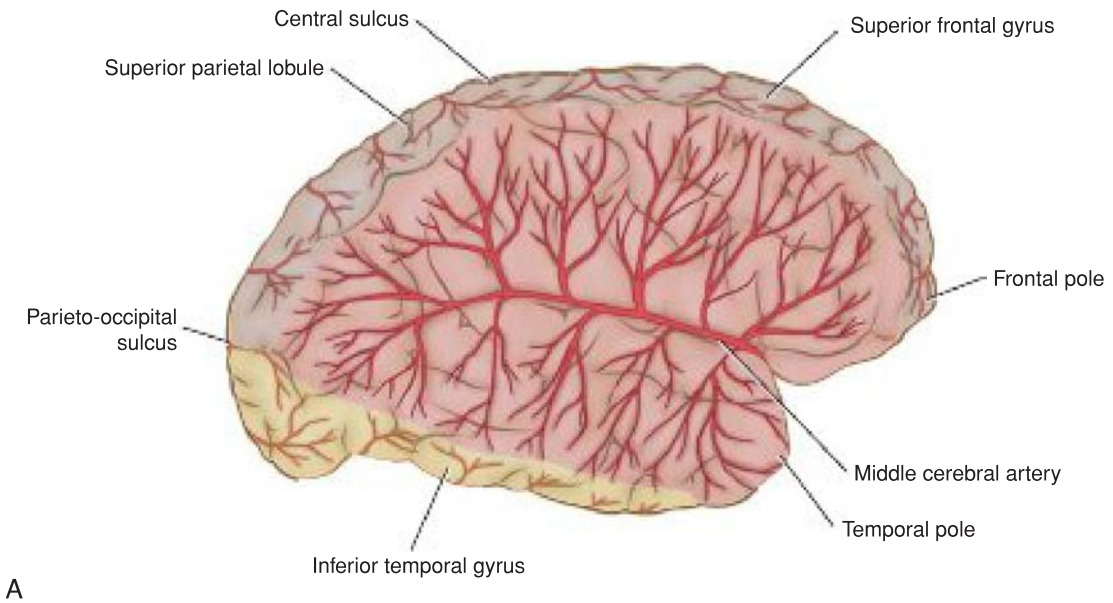
Figure 17-2 Arteries of the inferior surface of the brain. Note the formation of the circle of Willis. Part of the right temporal lobe has been removed to show the course of the middle cerebral artery.

Vertebral Artery

The vertebral artery, a branch of the first part of the subclavian artery, ascends the neck by passing through the foramina in the transverse processes of the upper six cervical vertebrae (see Fig. 17-1). It enters the skull through the foramen magnum and pierces the dura mater and arachnoid to enter the subarachnoid space. It then passes upward, forward, and medially on the medulla oblongata (see Fig. 17-2). At the lower border of the pons, it joins the vessel of the opposite side to form the **basilar artery**.

Branches of the Cranial Portion

1. The **meningeal branches** are small and supply the bone and dura in the posterior cranial fossa.
2. The **posterior spinal artery** may arise from the vertebral artery or the posterior inferior cerebellar artery. It descends on the posterior surface of the spinal cord close to the posterior roots of the spinal nerves. The branches are reinforced by radicular arteries that enter the vertebral canal through the intervertebral foramina. For the detailed distribution of this artery, see page 471.
3. The **anterior spinal artery** is formed from a contributory branch from each vertebral artery near its termination (see Fig. 17-2). The single artery descends on the anterior surface of the medulla oblongata and spinal cord and is embedded in the pia mater along the anterior median fissure. The artery is reinforced by radicular arteries that enter the vertebral canal through the intervertebral foramina. For the detailed distribution of this artery, see page 472.
4. The **posterior inferior cerebellar artery**, the largest branch of the vertebral artery, passes on an irregular course between the medulla and the cerebellum (see Fig. 17-2; also see Figs. 17-12 and 17-14). It supplies the inferior surface of the vermis, the central nuclei of the cerebellum, and the undersurface of the cerebellar hemisphere; it also supplies the medulla oblongata and the choroid plexus of the fourth ventricle.



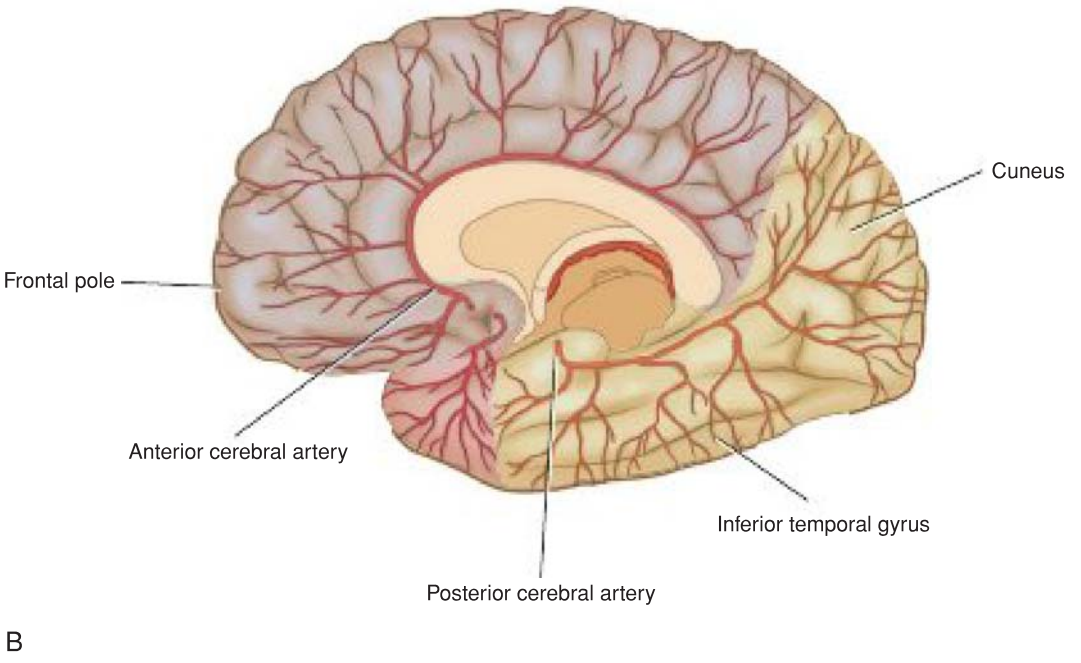


Figure 17-3 Areas supplied by the cerebral arteries. **A:** The lateral surface of the right cerebral hemisphere. **B:** The medial surface of the right cerebral hemisphere. The area supplied by the anterior cerebral artery is colored blue, the area supplied by the middle cerebral artery is pink, and the area supplied by the posterior cerebral artery is brown.

5. The **medullary arteries** are very small branches that are distributed to the medulla oblongata.

Basilar Artery

The basilar artery, formed by the union of the two vertebral arteries (see Fig. 17-1), ascends in a groove on the anterior surface of the pons (see Fig. 17-2; also see Figs. 17-13 and 17-14). At the upper border of the pons, it divides into the two posterior cerebral arteries.

Branches

1. The **pontine arteries** are numerous small vessels that enter the substance of the pons.
2. The **labyrinthine artery** is a long, narrow artery that accompanies the facial and the vestibulocochlear nerves into the internal acoustic meatus and supplies the internal ear. It often arises as a branch of the anterior inferior cerebellar artery.

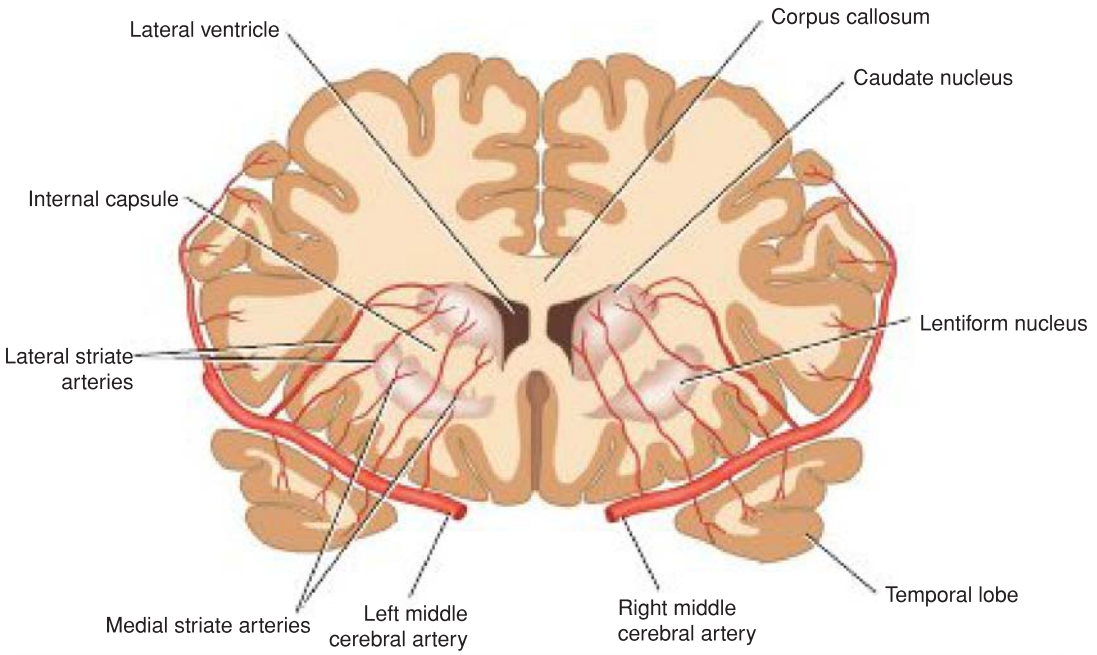


Figure 17-4 Coronal section of the cerebral hemispheres showing the arterial supply to the deep cerebral structures from the middle cerebral artery.

3. The **anterior inferior cerebellar artery** passes posteriorly and laterally and supplies the anterior and inferior parts of the cerebellum. A few branches pass to the pons and the upper part of the medulla oblongata.
4. The **superior cerebellar artery** arises close to the termination of the basilar artery (see Fig. 17-2; also see Figs. 17-11 to 17-14). It winds around the cerebral peduncle and supplies the superior surface of the cerebellum. It also supplies the pons, the pineal gland, and the superior medullary velum.
5. The **posterior cerebral artery** curves laterally and backward around the midbrain and is joined by the posterior communicating branch of the internal carotid artery (see Figs. 17-1 and 17-2; also see Figs. 17-11 to 17-14). **Cortical branches** supply the inferolateral and medial surfaces of the temporal lobe and the lateral and medial surfaces of the occipital lobe (see Fig. 17-3). Thus, the posterior cerebral artery supplies the visual cortex. **Central branches** pierce the brain substance and supply parts of the thalamus and the lentiform nucleus as well as the midbrain, the pineal, and the medial geniculate bodies. A **choroidal branch** enters the inferior horn of the lateral ventricle and supplies the choroid plexus; it also supplies the choroid plexus of the third ventricle.

Circle of Willis

The circle of Willis lies in the interpeduncular fossa at the base of the brain. It is formed by the anastomosis between the two internal carotid arteries and the two vertebral arteries (see Fig. 17-2). The anterior communicating, anterior cerebral, internal carotid, posterior communicating, posterior cerebral, and basilar arteries all contribute to the circle. The circle of Willis allows blood that enters by either internal carotid or vertebral arteries to be distributed to any part of both cerebral hemispheres. Cortical and central branches arise from the circle and supply the brain substance.

Variations in the sizes of the arteries forming the circle are common, and the absence of one or both posterior communicating arteries has been reported.

Arteries to Specific Brain Areas

The **corpus striatum** and the **internal capsule** are supplied mainly by the medial and lateral striate central branches of the middle cerebral artery (see Fig. 17-4); the central branches of the anterior cerebral artery supply the remainder of these structures.

The **thalamus** is supplied mainly by branches of the posterior communicating, basilar, and posterior cerebral arteries.

The **midbrain** is supplied by the posterior cerebral, superior cerebellar, and basilar arteries.

The **pons** is supplied by the basilar and the anterior, inferior, and superior cerebellar arteries.

The **medulla oblongata** is supplied by the vertebral, anterior and posterior spinal, posterior inferior cerebellar, and basilar arteries.

The **cerebellum** is supplied by the superior cerebellar, anterior inferior cerebellar, and posterior inferior cerebellar arteries.

Nerve Supply of Cerebral Arteries

The cerebral arteries receive a rich supply of sympathetic postganglionic nerve fibers. These fibers are derived

from the superior cervical sympathetic ganglion. Stimulation of these nerves causes vasoconstriction of the cerebral arteries. However, under normal conditions, the local blood flow is mainly controlled by the concentrations of carbon dioxide, hydrogen ions, and oxygen present in the nervous tissue; a rise in the carbon dioxide and hydrogen ion concentrations and a lowering of the oxygen tension bring about a vasodilatation.

VEINS OF THE BRAIN

The veins of the brain have no muscular tissue in their very thin walls, and they possess no valves. They emerge from the brain and lie in the subarachnoid space. They pierce the arachnoid mater and the meningeal layer of the dura and drain into the cranial venous sinuses (Fig. 17-5).

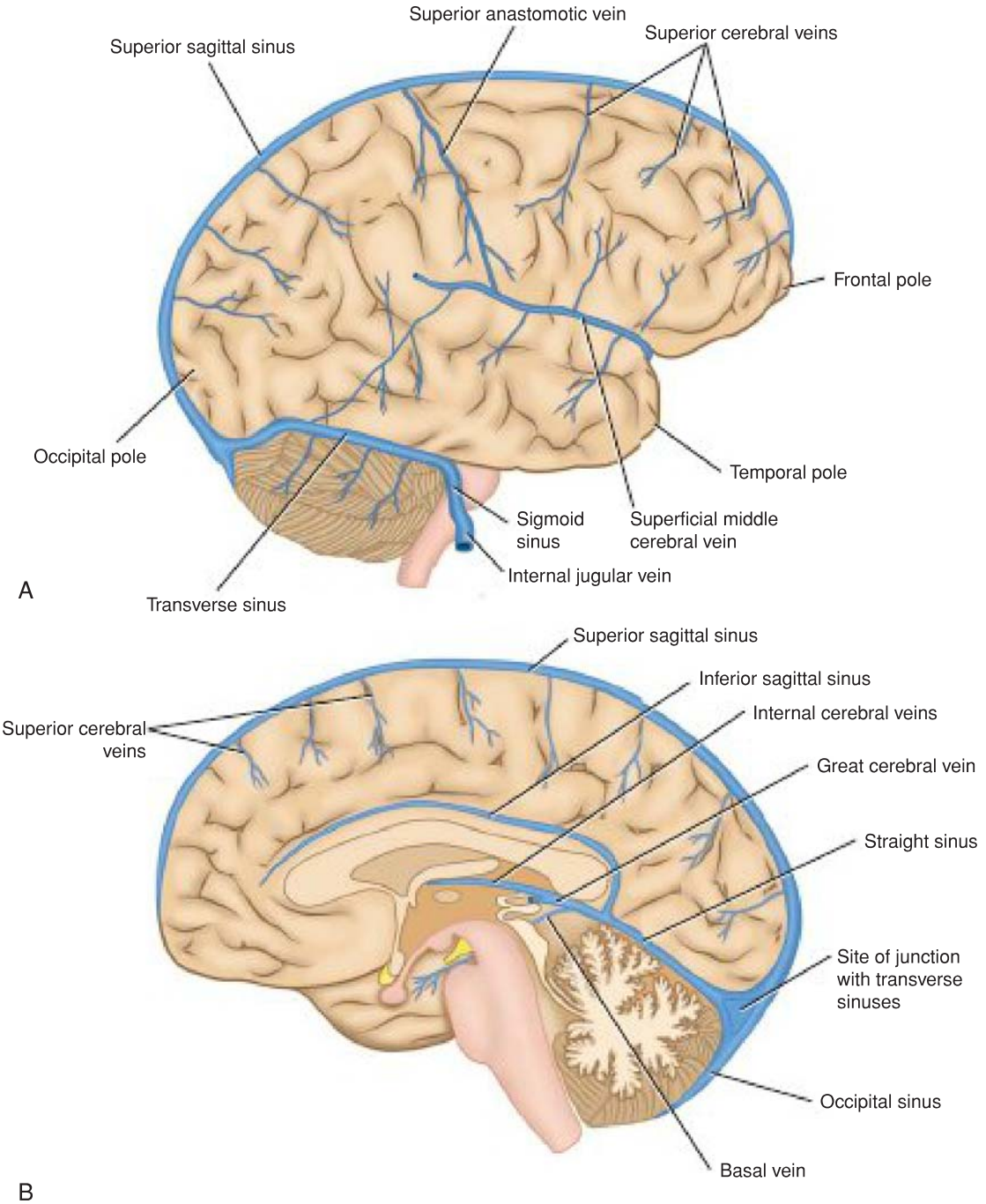


Figure 17-5 Venous drainage of the right cerebral hemisphere. **A:** Lateral surface. **B:** Medial surface.

External Cerebral Veins

The **superior cerebral veins** pass upward over the lateral surface of the cerebral hemisphere and empty into the superior sagittal sinus.

The **superficial middle cerebral vein** drains the lateral surface of the cerebral hemisphere. It runs inferiorly in the lateral sulcus and empties into the cavernous sinus.

The **deep middle cerebral vein** drains the insula and is joined by the **anterior cerebral** and **striate veins** to form the **basal vein**. The basal vein ultimately joins the great cerebral vein, which in turn drains into the straight sinus.

Internal Cerebral Veins

The two internal cerebral veins are formed by the union of the **thalamostriate vein** and the **choroid vein** at the interventricular foramen. The two veins run posteriorly in the tela choroidea of the third ventricle and unite beneath the splenium of the corpus callosum to form the great cerebral vein, which empties into the straight sinus.

Veins of Specific Brain Areas

The **midbrain** is drained by veins that open into the basal or great cerebral veins.

The **pons** is drained by veins that open into the basal vein, cerebellar veins, or neighboring venous sinuses.

The **medulla oblongata** is drained by veins that open into the spinal veins and neighboring venous sinuses.

The **cerebellum** is drained by veins that empty into the great cerebral vein or adjacent venous sinuses.

BRAIN CAPILLARIES

The capillary blood supply to the brain is greater in the gray matter than in the white matter. This is to be expected, since the metabolic activity in the neuronal cell bodies in the gray matter is much greater than in the nerve processes in the white matter. The blood–brain barrier isolates the brain tissue from the rest of the body and is formed by the tight junctions that exist between the endothelial cells in the capillary beds (see pp. 452-453).

CEREBRAL CIRCULATION

The blood flow to the brain must deliver oxygen, glucose, and other nutrients to the nervous tissue and remove carbon dioxide, lactic acid, and other metabolic by-products. The brain has been shown to be supplied with arterial blood from the two internal carotid arteries and the two vertebral arteries. The blood supply to half of the brain is provided by the internal carotid and vertebral arteries on that side, and their respective streams come together in the posterior communicating artery at a point where the pressure of the two is equal and they do not mix (Fig. 17-6). If, however, the internal carotid or vertebral artery is occluded, the blood passes forward or backward across that point to compensate for the reduction in blood flow. The arterial circle also permits the blood to flow across the midline, as shown when the internal carotid or vertebral artery on one side is occluded. It also has been shown that the two streams of blood from the vertebral arteries remain separate and on the same side of the lumen of the basilar artery and do not mix.

Although the cerebral arteries anastomose with one another at the circle of Willis and by means of branches on the surface of the cerebral hemispheres, once they enter the brain substance, no further anastomoses occur.

The most important factor in forcing the blood through the brain is the arterial blood pressure. This is opposed by such factors as a raised intracranial pressure, increased blood viscosity, and narrowing of the vascular diameter. Cerebral blood flow remains

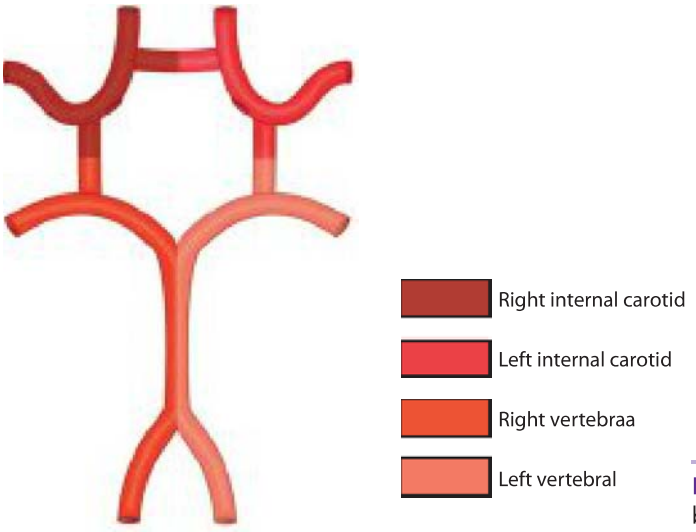


Figure 17-6 Circle of Willis showing the distribution of blood from the four main arteries.

remarkably constant despite changes in the general blood pressure. This autoregulation of the circulation is accomplished by a compensatory lowering of the cerebral vascular resistance when the arterial pressure is decreased and a rising of the vascular resistance when the arterial pressure is increased. Needless to say, this autoregulation does not maintain an adequate blood flow when the arterial blood pressure falls to a very low level.

The diameter of the cerebral blood vessels is the main factor contributing to the cerebrovascular resistance. While cerebral blood vessels are innervated by sympathetic postganglionic nerve fibers and respond to norepinephrine, they apparently play little or no part in the control of cerebrovascular resistance in normal human beings. The most powerful vasodilator influence on cerebral blood vessels is an increase in carbon dioxide or hydrogen ion concentration; a reduction in oxygen concentration also causes vasodilatation. It has been shown, using PET, that an increase in neuronal activity in different parts of the brain causes a local increase in blood flow. For example, viewing an object will increase the oxygen and glucose consumption in the visual cortex of the occipital lobes. This results in an increase in the local concentrations of carbon dioxide and hydrogen ions and brings about a local increase in blood flow.

The cerebral blood flow in patients can be measured by the intracarotid injection or inhalation of radioactive krypton or xenon. Normal cerebral blood flow, per minute, is around 50 to 60 mL/100g of brain tissue.

SPINAL CORD ARTERIES

The spinal cord receives its arterial supply from three small arteries: the two posterior spinal arteries and the anterior spinal artery. These longitudinally running arteries are reinforced by small segmentally arranged arteries that arise from arteries outside the vertebral column and enter the vertebral canal through the intervertebral foramina. These vessels anastomose on the surface of the cord and send branches into the substance of the white and gray matter. Considerable variation exists as to the size and segmental levels at which the reinforcing arteries occur.

Posterior Spinal Arteries

The posterior spinal arteries arise either directly from the vertebral arteries inside the skull or indirectly from the posterior inferior cerebellar arteries. Each artery descends on the posterior surface of the spinal cord close to the posterior nerve roots and gives off branches that enter the substance of the cord (Fig. 17-7). The posterior spinal arteries supply the posterior third of the spinal cord.

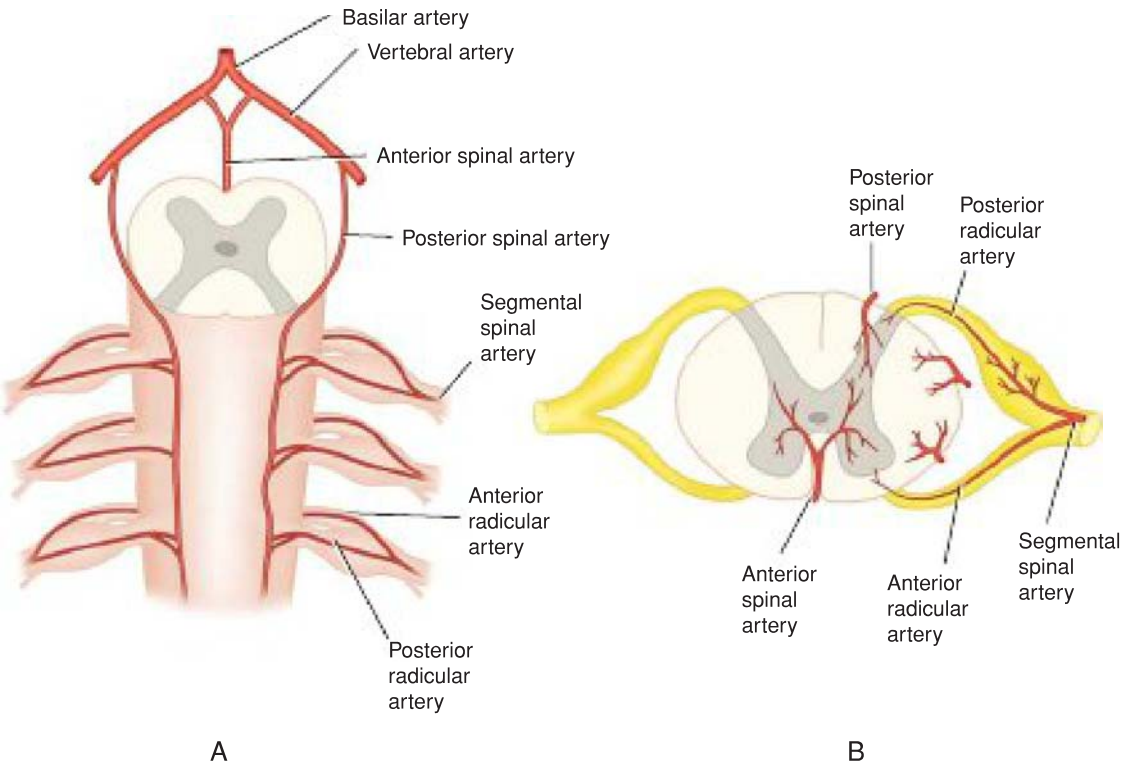


Figure 17-7 **A:** Arterial supply of the spinal cord showing the formation of two posterior spinal arteries and one anterior spinal artery. **B:** Transverse section of the spinal cord showing the segmental spinal arteries and the radicular arteries.

The posterior spinal arteries are small in the upper thoracic region, and the first three thoracic segments of the spinal cord are particularly vulnerable to ischemia should the segmental or radicular arteries in this region be occluded.

Anterior Spinal Artery

The anterior spinal artery is formed by the union of two arteries, each of which arises from the vertebral artery inside the skull. The anterior spinal artery then descends on the anterior surface of the spinal cord within the anterior median fissure. Branches from the anterior spinal artery enter the substance of the cord and supply the anterior two-thirds of the spinal cord.

In the upper and lower thoracic segments of the spinal cord, the anterior spinal artery may be extremely small. Should the segmental or radicular arteries be occluded in these regions, the fourth thoracic and the first lumbar segments of the spinal cord would be particularly liable to ischemic necrosis.

Segmental Spinal Arteries

At each intervertebral foramen, the longitudinally running posterior and anterior spinal arteries are reinforced by small segmental arteries on both sides. The arteries are branches of arteries outside the vertebral column (deep cervical, intercostal, and lumbar arteries). Having entered the vertebral canal, each segmental spinal artery gives rise to **anterior** and **posterior radicular arteries** that accompany the anterior and posterior nerve roots to the spinal cord.

Additional **feeder arteries** enter the vertebral canal and anastomose with the anterior and posterior spinal arteries; however, the number and size of these arteries vary considerably from one individual to another. One large and important feeder artery, the **great anterior medullary artery of Adamkiewicz**, arises from the aorta in the lower thoracic or upper lumbar vertebral levels; it is unilateral and, in the majority of persons, enters the spinal cord from the left side. The importance of this artery lies in the fact that it may be the major source of blood to the lower two-thirds of the spinal cord.

SPINAL CORD VEINS

The veins of the spinal cord drain into six tortuous longitudinal channels that communicate superiorly within the skull with the veins of the brain and the venous sinuses. They drain mainly into the internal vertebral venous plexus.

Clinical Notes

The brain receives about 15% of the resting cardiac output. The arterial blood reaches the brain through the two internal carotid and the two vertebral arteries; the internal carotid arteries are the major supply of arterial blood.

The distributing arteries—the anterior, middle, and posterior cerebral arteries—that arise from the circle of Willis pass over the outer surface of the brain and anastomose with one another. They give rise to branches that penetrate the brain at right angles. In the brain substance, further branching occurs, but no further anastomoses take place. Anastomoses on the brain surface provide the vital collateral circulation should one of the arteries be occluded by disease.

Despite the recent decrease in cerebrovascular disease, which has been brought about by the treatment of high blood cholesterol and the aggressive treatment of hypertension, cerebrovascular disease is still responsible for about 50% of all adult neurologic hospital admissions.

Cerebral Ischemia

Unconsciousness occurs in 5 to 10 seconds if the blood flow to the brain is completely cut off. Irreversible brain damage with death of nervous tissue rapidly follows complete arrest of cerebral blood flow. Neuronal function is estimated to cease after about 1 minute, and irreversible changes start to occur after about 4 minutes, although this time may be longer if the patient's body has been cooled. (However, brain damage might be reversed if the blood flow can be restored even after 5 minutes.) Cardiac arrest due to coronary thrombosis is the most common cause of this condition.

Cerebral Circulation Interruption

Vascular lesions of the brain are extremely common and the resulting neurologic defect will depend on the size of the artery occluded, the state of the collateral circulation, and the area of the brain involved.

CEREBRAL ARTERY SYNDROMES

Clinical studies and the examination of postmortem material have focused attention on the high frequency of lesions in the common carotid, internal carotid, and vertebral arteries in the neck.

ANTERIOR CEREBRAL ARTERY OCCLUSION

If the occlusion of the anterior cerebral artery is proximal to the anterior communicating artery, the collateral circulation is usually adequate to preserve the circulation. Occlusion distal to the communicating artery may produce the following signs and symptoms:

1. Contralateral hemiparesis and hemisensory loss involving mainly the leg and foot (paracentral lobule of cortex)
2. Inability to identify objects correctly, apathy, and personality changes (frontal and parietal lobes)

MIDDLE CEREBRAL ARTERY OCCLUSION

Occlusion of the middle cerebral artery may produce the following signs and symptoms, but the clinical picture will vary according to the site of occlusion and the degree of collateral anastomoses:

1. Contralateral hemiparesis and hemisensory loss involving mainly the face and arm (precentral and postcentral gyri)