

The brain and spinal cord are organized through a series of developmental events. They start as a thickened neural plate and then transform into a simple tubular structure, the neural tube. The cranial end of the tubular structure enlarges to become the brain, whereas the remaining neural tube develops into the spinal cord. As precursor cells of the neural tube proliferate and differentiate into neurons and neuroglia, they migrate to appropriate target locations. This process of proliferation, differentiation, and migration is crucial for further developmental events, including outgrowth of axons and formation of synapses. Any interference with such developmental processes risks congenital malformations, perinatal mortality, and post-natal morbidity.

Formation of the neural tube

- 1 What embryonic germ layer becomes the nervous tissue?
- 2 Explain how the neural ectoderm forms the neural tube.

The development of the nervous system, like all other organ systems, starts at fertilization. An oocyte swept from the ovary is transported in the uterine tube to be fertilized. A fertilized ovum undergoes repeated cell division (also called cleavage). The first cleavage of the ovum results in two blastomeres, and successive cell divisions of blastomeres produce a spherical ball of cells. The blastomeres start to rearrange and a fluid-filled cavity, the blastocoel, is formed. The wall of the blastocyst is only a single cell in thickness, except the area where a cluster of cells, the **inner cell mass**, appears. The inner cell mass is destined to be concerned primarily with the formation of the embryonic body. Within the inner cell mass a cavity starts to develop, separating the amnion from the embryo-formative cells, the embryonic disc. The embryonic disc gives rise to the three germ

layers (endoderm, mesoderm, ectoderm) that form all the tissue and organs of the embryo.

The dorsomedial area of the ectoderm differentiates to become the **neural ectoderm** (Fig. 1.1). As the embryo develops, the neural ectoderm separates from the remaining ectoderm. Initially, the neural ectoderm is a flat area made of a single cell layer. There are three developmental stages (neural plate, neural fold, and neural tube) that form a tubular primordium of the central nervous system (CNS) (Fig. 1.2). The neural ectoderm thickens to become the neural plate, which folds into a neural groove. As the neural fold continues to become thicker, the groove becomes narrower and the dorsal edges of the fold fuse and the neural fold becomes the neural tube. The rostral end of the neural tube becomes the brain and the remaining neural tube develops into the spinal cord.

Neural plate

The **neural ectoderm** thickens to form a neural plate (Figs 1.1 and 1.2A). The first step in the formation of the brain and spinal cord is its transformation from a thickened neural plate into a tubular mass of cells.

Neural fold

The neural groove appears as a result of differential growth of the neural plate along the longitudinal axis of the embryo (Fig. 1.2B). The groove deepens and the elevated lateral margins of the neural plate form the neural fold. The neural folds, as they become more elevated, grow toward each other. The neural fold at the rostral end (also referred to as the cephalic end because the rostral neural fold develops into the brain) is much greater in size than it is further caudally. This results in the differentiation of the rostral neural fold into the brain and the remaining caudal portion into the spinal cord. At about the time the neural groove

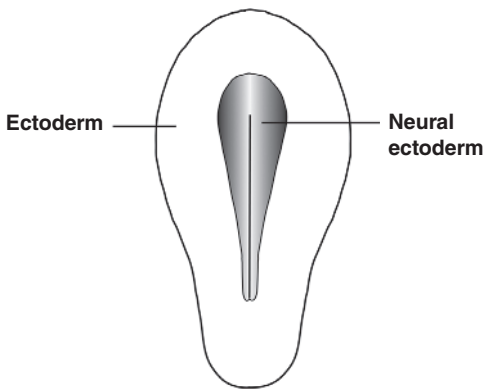


Fig. 1.1 The neural plate develops from the neural ectoderm that occupies the central portion of the ectoderm.

deepens, a cluster of cells appears and forms the **neural crest** at the area where the neural fold borders on the ectoderm. The neural crest detaches from the ectoderm to become ganglia of the cranial and spinal nerves. A cluster of cells associated with the cephalic end differentiates into the ganglia of the cranial nerves. Those cells associated with the remaining neural fold differentiate into the dorsal root ganglia and ganglia of the autonomic nervous system (ANS).

Neural tube

The neural tube results from fusion of the dorsal edges of the neural fold (Fig. 1.2C and D). Prior to the closure of the neural groove, the neural plate is continuous laterally with the ectoderm. When the two neural folds fuse with each other, the ectoderm also fuses to overlie the newly formed neural tube. The closure of the neural groove begins in the middle of the embryo and proceeds toward the two ends. However, progression of closure is more rapid towards the cephalic end than towards the caudal end (Fig. 1.3). As a result, three stages of neural development (i.e., the neural plate, fold, and tube) coexist simultaneously in different regions of the embryo. The cephalic end of the neural tube starts to enlarge and differentiate to become the brain. The rest of the neural tube remains relatively unchanged and becomes the spinal cord. The ectoderm separated from the neural ectoderm forms the epidermis.

Three primary brain regions and their subdivisions

- 1 What are the three vesicles stage and subsequent five vesicles stage of the developing brain?
- 2 What structures differentiate from each of the five vesicles of the developing brain?
- 3 Name the ventricular spaces associated with each of the five vesicles of the developing brain.
- 4 What developing vesicle gives rise to the eye and neurohypophysis?
- 5 Where are the choroid plexuses located?

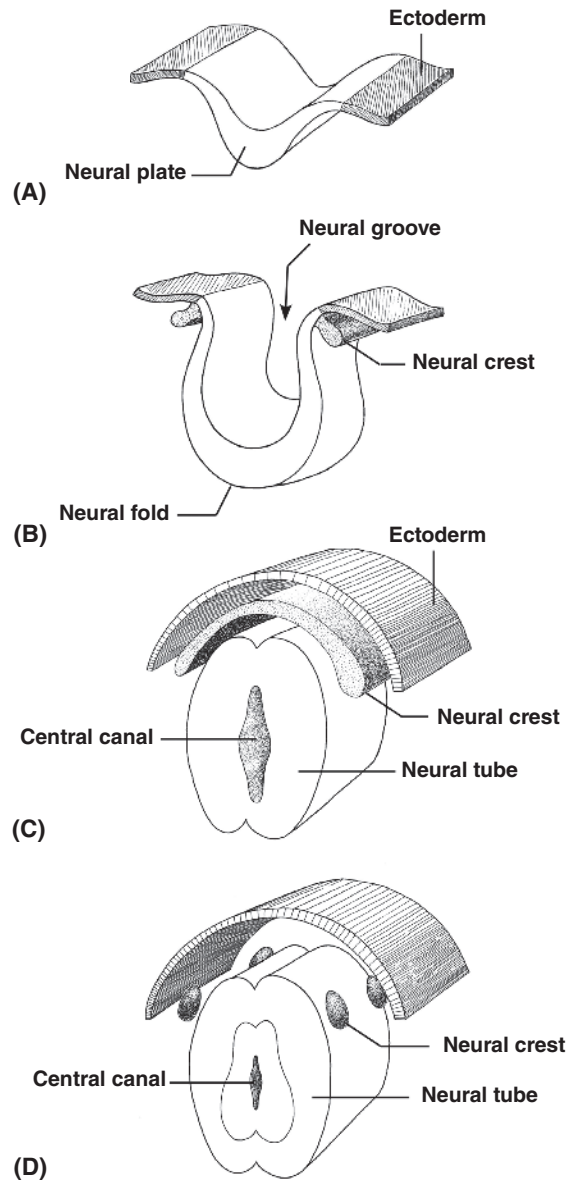


Fig. 1.2 Development of the neural tube and neural crest from the ectoderm. (A) Transverse section of the embryonic disc. The neural plate is the thickened area of the ectoderm. (B) Invagination of the neural plate to form the neural fold. The neural crest appears at the dorsolateral edge of the neural fold. (C) Fusion of the dorsal edges of the neural fold forms the neural tube. (D) The neural crest gives rise to small aggregates of cells that start to migrate ventrally to become ganglia.

The nervous system starts as a relatively straight neural tube. As the embryo develops, the neural tube at the cephalic end expands more rapidly. Subsequently, the cephalic end develops into three primary regions: the forebrain (also known as the prosencephalon), midbrain, and hindbrain (also known as the rhombencephalon) (Fig. 1.4A). The central neural space runs the length of the neural tube, and it remains open in spite of the development of the neural tube into the brain and spinal

cord. However, the shape and size of the space change greatly, reflecting the regional modification of the neural tube during development (Figs 1.5, 1.6, and 1.7).

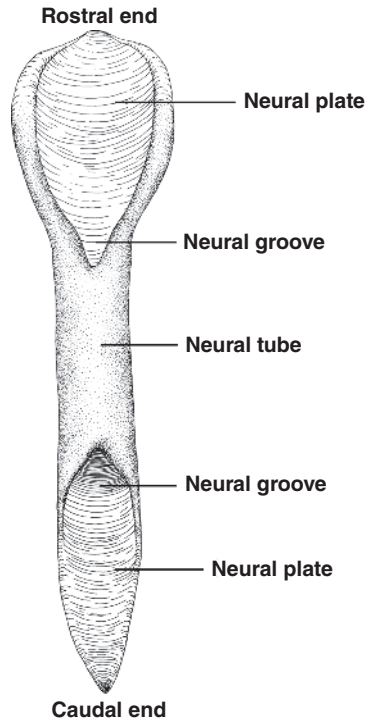


Fig. 1.3 Dorsal view of the embryo, showing transformation of the neural groove into a neural tube. Three developmental stages (neural plate, neural fold, and neural tube) of the nervous system coexist in different areas of the embryo. This is because closure of the neural groove starts at the middle of the embryo and proceeds toward the cephalic and caudal ends. The developing cerebrum becomes obvious even before the closure of the cephalic neural groove.

Forebrain

The forebrain (or prosencephalon) gives rise to two lateral evaginations: the **telencephalon** (Gr. *telos* end, *enkephalos* brain) (Fig. 1.4). These two evaginations at the end of the neural tube become the cerebral hemispheres. The junction between the two hemispheres is a narrow interhemispheric fissure (*L. fissura* groove) (Fig. 1.4B). Each hemisphere has a vault, called the future cerebral cortex, and a floor, called the future basal nuclei (Fig. 1.8B). The telencephalon is initially smooth in contour. However, convolution becomes apparent later in development. The neural space in each hemisphere becomes the lateral ventricle. It is lined with ependymal cells. A part of the medial wall of the hemisphere is made of the pia mater lined on the side of the neural space with ependymal cells. Invagination of this thin layer into the lateral ventricle forms the choroid plexus, a highly convoluted and vascularized structure (Fig. 1.8B). The choroid plexus secretes the cerebrospinal fluid into the ventricular space.

The floor of the telencephalon thickens to become the basal nuclei (Figs 1.8B and 3.20). The basal nuclei are under the influence of the cerebral cortex and serve as a key motor center that regulates motor nuclei in the brain stem (Fig. 3.27). The portion of the forebrain that remains medial to each telencephalon is the **diencephalon** (Gr. *dia* between) (Fig. 1.4). The neural space associated with the diencephalon is the third ventricle. The lateral ventricles of the telencephalon open into the third ventricle via the interventricular foramen. The mid-portion of the diencephalon differentiates to become the **thalamus**. The enormous growth of the thalamus in each hemisphere results in their fusion at the median line to become one massive area of gray matter consisting of many nuclei. The thalamus integrates sensory and motor information before projecting to the cerebral cortex.

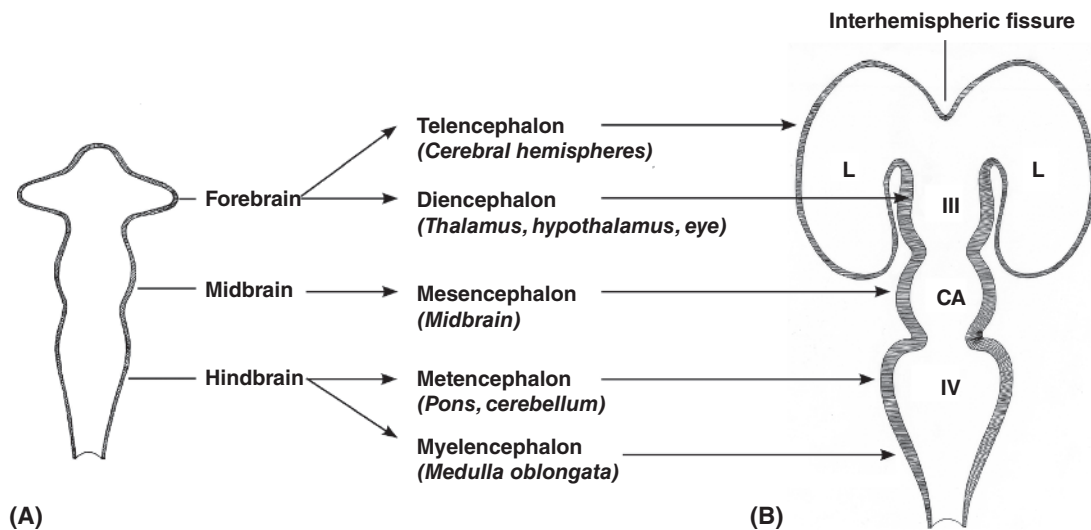


Fig. 1.4 Dorsal view of the developing brain from the three vesicles stage to the five vesicles stage. (A) Three enlargements appear at the cephalic end of the neural tube: the forebrain, midbrain, and hindbrain. (B) The forebrain develops into the telencephalon and diencephalon. The hindbrain further differentiates into the metencephalon and myelencephalon. L: lateral ventricle; III: third ventricle; CA: cerebral aqueduct; IV: fourth ventricle.

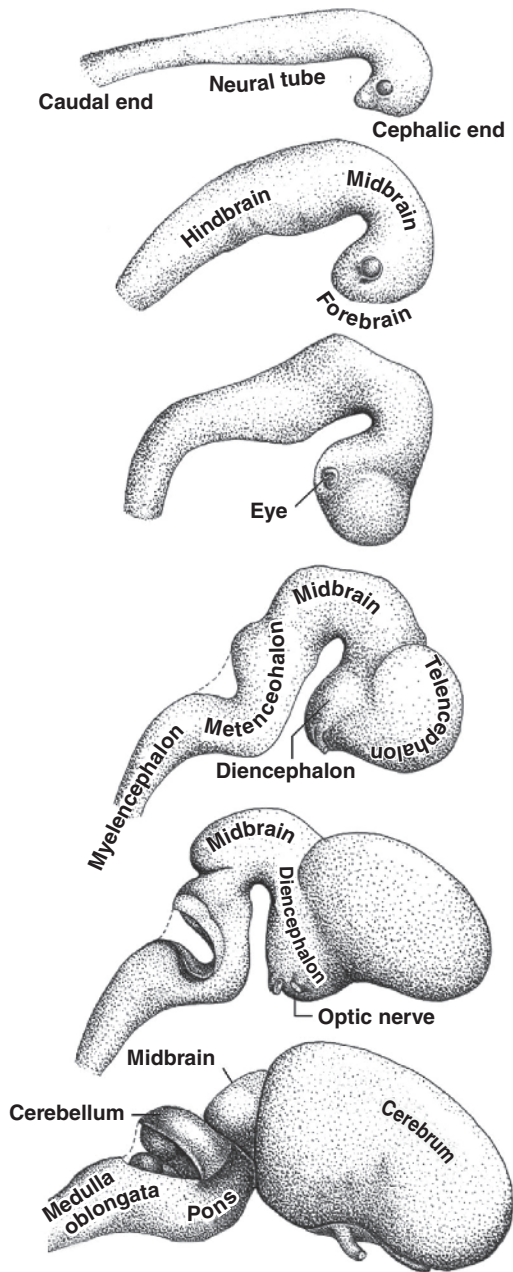


Fig. 1.5 The brain and spinal cord each start as a relatively straight neural tube. The cranial portion of the neural tube is dramatically modified by unequal growth and the appearance of flexures. This results in the formation of three enlargements: the forebrain, midbrain, and hindbrain. The shape and size of the neural tube vary greatly, reflecting the regional modification of the neural tube during the development.

The dorsal portion of the diencephalon gives rise to the **epithalamus** (Gr. *epi* over; above the thalamus), and the ventral portion to the **hypothalamus** (Gr. *hypo* under; under the thalamus) (Fig. 3.29). The pineal gland, a small evagination of the epithalamic structure, appears at the caudal part of the dorsal diencephalon. It lies rostral to the groove between the two rostral colliculi of the midbrain (Fig. 3.31A). The pineal gland is

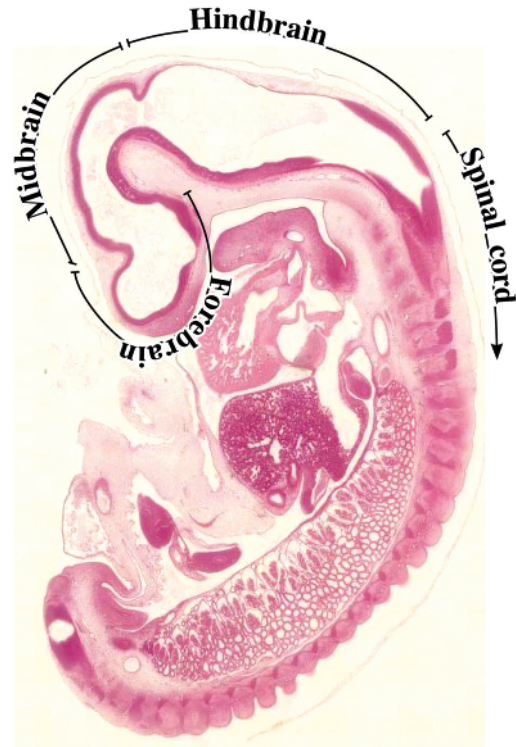


Fig. 1.6 Midsagittal section of the developing brain. 10 mm pig embryo. The forebrain is beginning its division into telencephalon and diencephalon. The spinal cord is not visible as it is not cut exactly at the midsagittal plane.

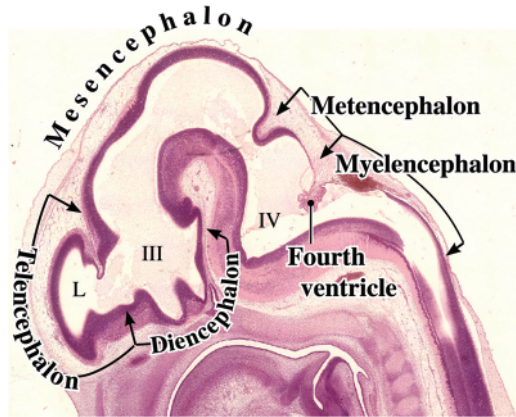


Fig. 1.7 Midsagittal section of the developing brain. 15 mm pig embryo. The ventricles occupy a large portion of the brain. L: lateral ventricle; III: third ventricle; IV: fourth ventricle.

the endocrine gland that regulates gonadal function by releasing melatonin. The levels of melatonin circulating in the blood regulate certain physiological rhythms; for example, behavioral rhythms of sleep and waking.

The floor of the diencephalon gives rise to the neural tissue of the **eye** and neural lobe of the **hypophysis** (Fig. 1.9). The hypothalamus is made of numerous nuclei. It has close structural and

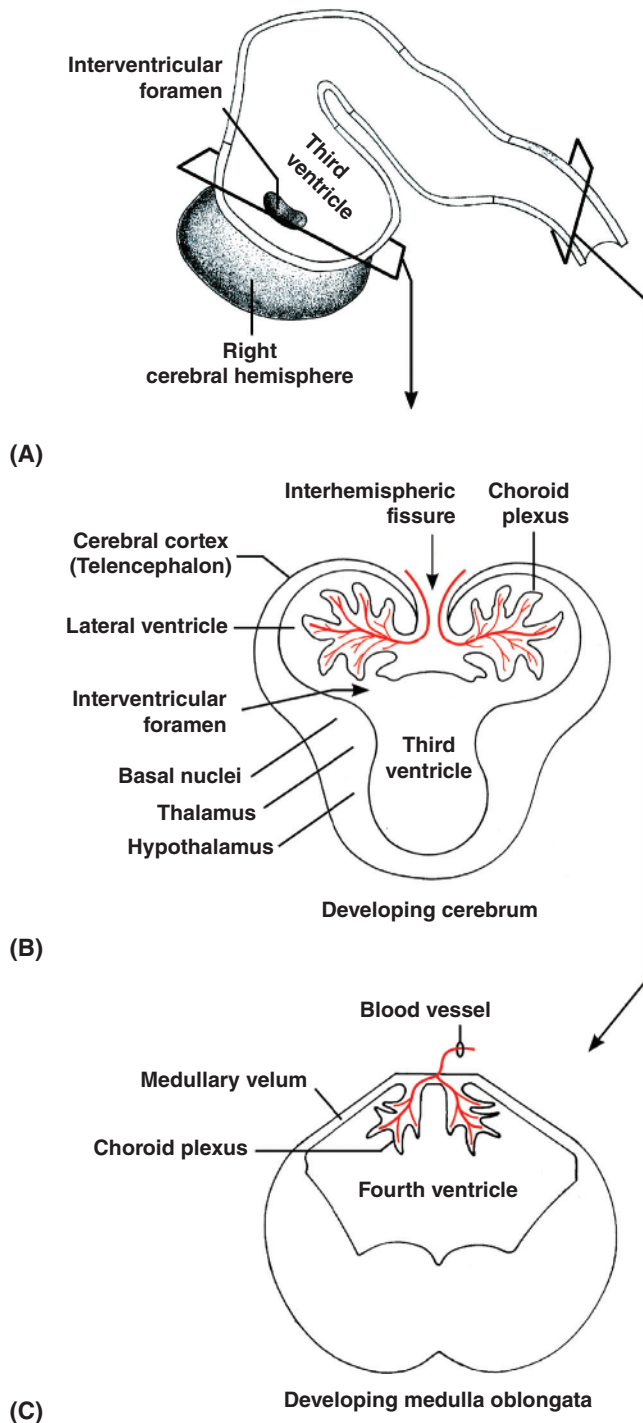


Fig. 1.8 (A) Midsagittal view of the developing brain, exposing the interventricular foramen and the third ventricle. (B) Transverse view of the telencephalon and diencephalon. The medial hemispheric wall invaginates to form the choroid plexus. (C) Transverse view of the myelencephalon (medulla oblongata) showing the choroid plexus in the fourth ventricle.

functional relationships with the hypophysis and the ANS. This allows the hypothalamus to monitor and regulate visceral and endocrine functions, playing a role in emotion, sleep, eating, drinking, sexual behavior, and temperature regulation.

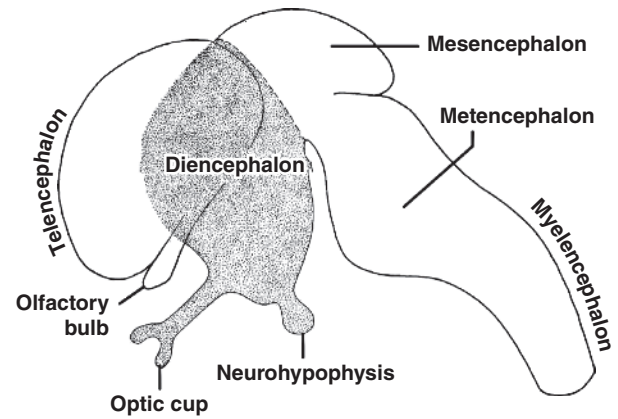


Fig. 1.9 Lateral view of the developing brain. The olfactory bulb and olfactory tract develop at the ventrorostral portion of the telencephalon. The eye and neurohypophysis develop at the floor of the diencephalon (shaded).

Midbrain

The midbrain develops from the middle enlargement of the three primary brain regions (Figs 1.4, 1.5, and 1.6). It is also referred to as the **mesencephalon** (Gr. *mesos* middle). The walls of the midbrain thicken markedly; consequently, the lumen becomes a narrow canal, the **cerebral aqueduct**. The dorsal midbrain thickens to become two pairs of colliculi (*L. colliculus* a mound or hill), the rostral and caudal (Figs 3.25B and 3.34). The **rostral colliculi** mediate visual reflexes (Figs 20.13 and 20.14), whereas the **caudal colliculi** mediate auditory reflexes (Fig. 19.15). The base of the midbrain also thickens and forms the substantia nigra and crus cerebri (Fig. 10.2A). The substantia nigra, which lies dorsal to the crus cerebri, is part of the motor system. It works closely with the basal nuclei. The crus cerebri is made of descending motor tracts originating in the cerebral cortex and terminating in the brain stem and spinal cord (Fig. 16.4C).

Hindbrain

The hindbrain (or rhombencephalon) develops into the rostral **metencephalon** (Gr. *meta* hindmost) and the caudal **myelencephalon** (Gr. *myelos* medulla) (Figs 1.4, 1.5, and 1.6). The spinal cord starts at the caudal end of the myelencephalon. Cells of the metencephalon and myelencephalon make massive lateral and ventral migration, resulting in the thin roof of the fourth ventricle, the medullary velum (Fig. 1.8C). This velum is made of a richly vascularized pia mater, lined on the inner surface by a single layer of ependymal cells. Near the center of the medullary velum, the ependymal cell layer and pia mater invaginate into the fourth ventricles as the choroid plexus (Figs 1.7 and 1.8C).

The metencephalon further differentiates to become the cerebellum and pons. The **cerebellum** starts as a bilateral thickening of the rostral metencephalon. These thickened areas come together and fuse at the midline. Initially, two portions of the cerebellum appear: the vermis (*L. vermis* worm; it resembles an

earthworm) and two lateral masses, the lateral lobes. The **nodulus** arises from the ventral portion of the vermis and the **flocculus** from each lateral lobe (Fig. 17.2). The nodulus and two flocculi constitute the flocculonodular lobe, phylogenetically the oldest part of the cerebellum. The flocculonodular lobe plays an important role in maintaining equilibrium and gaze. The lateral lobes further enlarge to become the cerebellar hemisphere, an important area for dexterity and smooth execution of body movements. Development of the cerebellar hemispheres parallels that of the cerebral hemispheres. The **pons** lies ventral to the cerebellum, and massive tracts, the cerebellar peduncles, connect the cerebellum to the pons. The cerebellum communicates with the rest of the CNS through the cerebellar peduncles.

The myelencephalon becomes the **medulla oblongata**. This portion of the brain stem plays a role in coordinating locomotion, posture, and visceral control. The medulla oblongata is also crucial for life as it contains the vital centers that regulate heart rate and blood pressure, waking and sleeping, breathing and swallowing. Thus, any lesions to the medulla oblongata bring serious consequences, even death.

Development of the spinal cord

- 1 What ectodermal cells differentiate to become neurons and neuroglia?
- 2 Explain the process involved in the development of the spinal cord from the neural tube.
- 3 What structures are derived from the embryonic mantle and marginal layers?
- 4 What is the functional difference between the alar and basal plates?
- 5 Where do neuroblasts of the neural crest migrate during the development of the embryo?

The ectoderm of the neural groove and early neural tube is made of a thick pseudostratified epithelium. These ectodermal cells have high mitotic activity. They differentiate to form **neuroblasts** (precursors of neurons) and **spongioblasts** (precursors of neuroglia). At the time of neural tube closure, neuroblasts develop cell processes and become neurons. Neuroblasts stop dividing a few weeks after birth. In contrast, spongioblasts remain mitotic and further differentiate into neuroglia cells. The spongioblasts that line the ventricles of the brain and central canal of the spinal cord become ependymal cells. Cell proliferation of neuroblasts and spongioblasts forms the thick, multilayered wall of the neural tube, the mantle layer (Fig. 1.10).

The **mantle layer** is the primordium of the spinal cord's gray matter. It differentiates into the **alar plate**, the primordium of the dorsal horn, and the **basal plate**, the future ventral horn (Fig. 1.10). These two plates are initially marked by a lateral groove of the central canal, the sulcus limitans. As the alar plates thicken, the facing ependymal layers fuse, forming a median seam called the dorsal median septum (Fig. 1.10E). This septum

reduces the extent of the central canal. The thickenings of the basal plates do not meet and fuse, resulting in a longitudinal furrow, the ventral median fissure.

As the mantle layer increases in mass, the marginal layer that surrounds the outer mantle layer also increases in thickness (Fig. 1.10C and D). The marginal layer is composed mostly of myelinated axons. It is the primordium of the white matter of the spinal cord (Fig. 1.10E). The white matter of a fresh spinal cord has a whitish appearance, reflecting the presence of myelinated nerve fibers. In contrast, the gray matter, where cell bodies of neurons are located, appears grayish. The marginal layer thickens as the numbers of ascending and descending axons increase. Most spongioblasts migrate throughout the mantle and marginal layers, and differentiate to become astrocytes and oligodendrocytes.

The cluster of neuroblasts located at the border of the neural ectoderm and the non-neural ectoderm is the neural crest (Figs 1.2B and 1.10A), the primordium of the dorsal root ganglia of the spinal nerves and other ganglia of the peripheral nervous system. Cells that give rise to the neural crest are initially located at the area where the neural fold meets the ectoderm. Later, they detach from the ectoderm and form the neural crest on either side of the neural tube. The neural crests migrate in the ventrolateral direction and give rise to neuroblasts. The central processes of the neuroblasts grow toward the dorsal portion of the neural tube and form the dorsal root. They enter the spinal cord and either (1) synapse with neurons in the alar plate (the primordium of the dorsal horn) or basal plates (the primordium of the ventral horn), or (2) enter the marginal layer to ascend or descend in the developing spinal cord, reaching neurons at various levels of the spinal cord or brain stem. Peripheral processes of the neuroblasts grow toward the periphery and form the sensory axons of the spinal nerves. Axons of neuroblasts in the basal plate leave the ventral spinal cord, forming the ventral roots of the spinal nerves. They innervate the muscles. Peripheral processes from the neural crest and ventral root of the spinal cord merge to form the main trunk of the spinal nerve (Fig. 1.10D and 1.10E).

Functional specialization of the neural crest

Neuroblasts of the neural crest migrate to form the dorsal root ganglia, sympathetic trunk ganglia, collateral ganglia, and terminal ganglia (Fig. 1.11). The neural crest cells that form dorsal root ganglia first assume a bipolar shape, with one process entering the dorsal portion of the spinal cord and the other process forming a spinal nerve (Fig. 1.10E). Subsequently, the two proximal processes that emerge from the cell body fuse to become unipolar (Fig. 2.2). The dorsal root ganglia mediate sensory impulses from sensory receptors to the spinal cord.

Some neuroblast cells from the neural crest migrate past the dorsal root ganglia to the region of the aorta and form segmentally arranged cell aggregates, the sympathetic trunk ganglia. These cell aggregates are linked by nerve fibers, forming the sympathetic trunk. The sympathetic trunk ganglia are

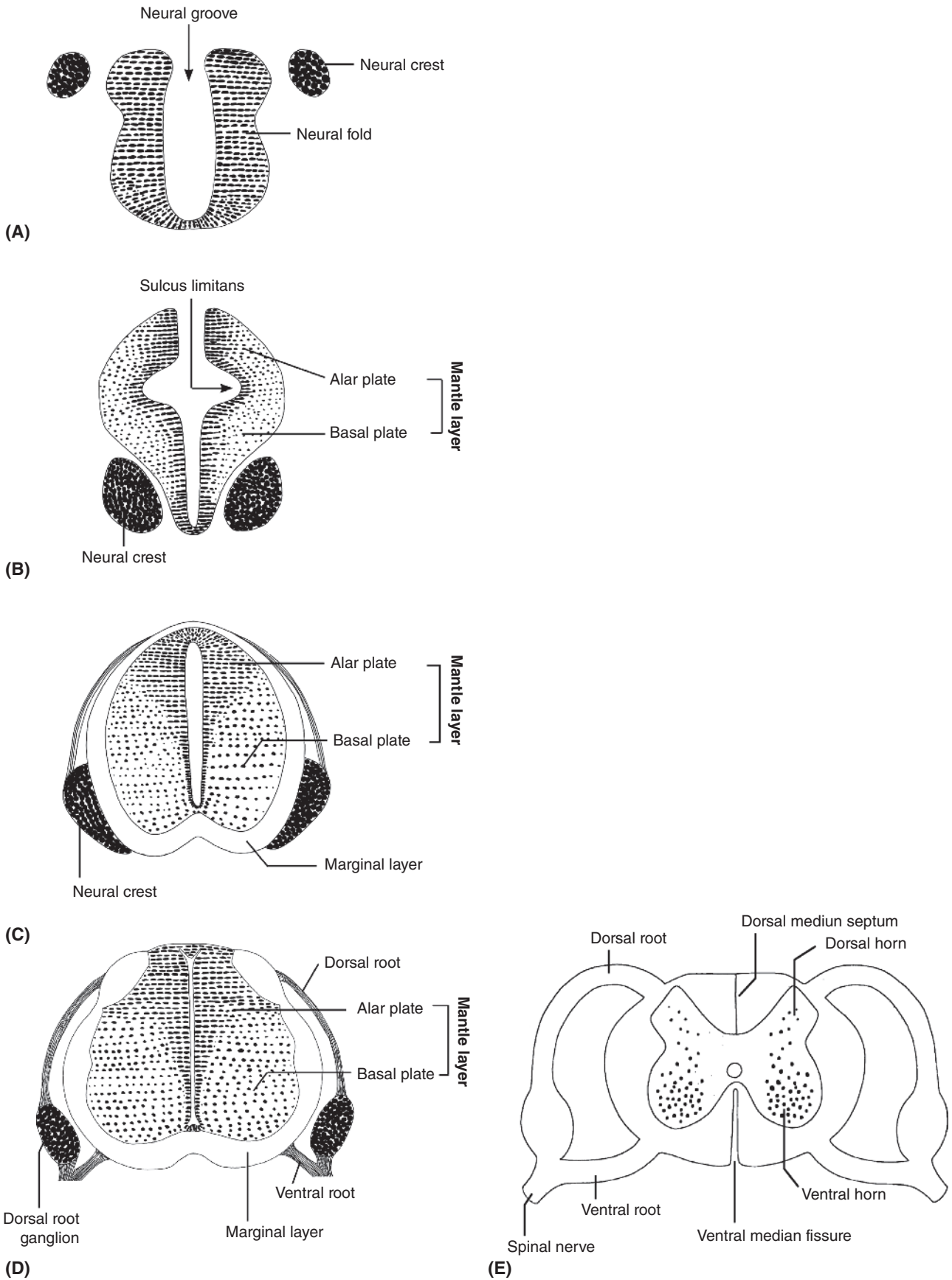


Fig. 1.10 Developing spinal cord. (A) The neural plate invaginates to form the neural fold. The neural ectoderm becomes the mantle layer, the future gray matter. The neural crest, the primordium of the dorsal root ganglia, lies dorsolateral to the neural fold. (B, C) The mantle layer of the neural tube further differentiates into the alar plate (the primordium of the dorsal horn) and basal plate (the primordium of the ventral horn). As these two plates increase in thickness, the marginal layer, the future white matter, appears at the peripheral portion of the mantle layer. (D) As the mantle layer thickens, so does the marginal layer that surrounds the mantle layer. (E) An adult spinal cord showing the dorsal and ventral horns of the gray matter.

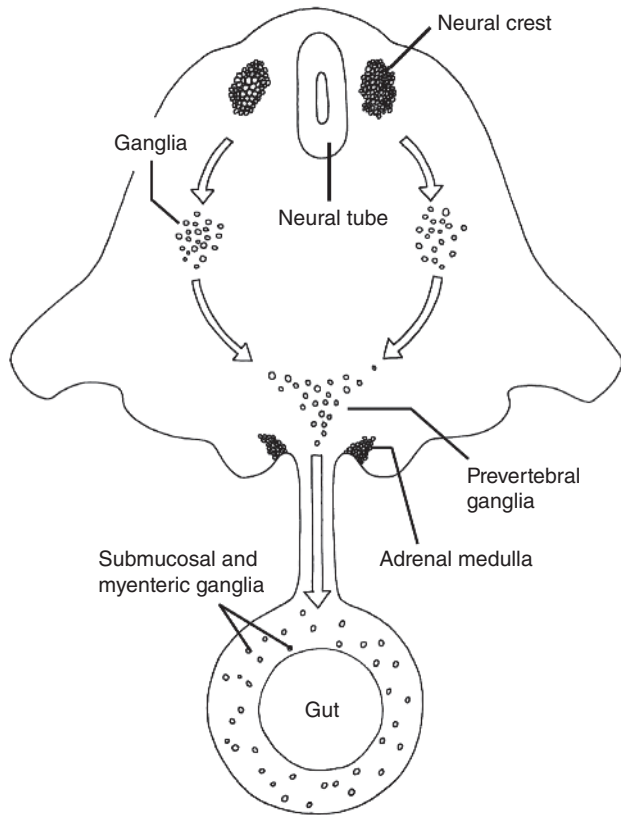


Fig. 1.11 Migration of the neuroblasts from the neural crest to form various ganglia. Neurons of the myenteric and submucosal plexus in the intestine are derived from the neural crest. The myenteric plexus lies between the circular and longitudinal layers of smooth muscles. It contains multipolar ganglion cells. The submucosal plexus is in the submucosa. Most of the submucosal ganglion cells are unipolar or bipolar, suggesting a sensory function. Their peripheral processes extend to the mucous membrane and their central processes synapse upon myenteric neurons.

distributed along both sides of the vertebral column. Some neuroblasts further migrate into the visceral cavity and either associate with some of the larger arteries as collateral ganglia or lie in various visceral organs as terminal ganglia. These cells are multipolar neurons (Fig. 2.2).

Clinical correlations

Developmental defects are often encountered in dogs, and their effects on the CNS are often incompatible with life. Examples of developmental disorders of the cerebral hemispheres (anencephaly, lissencephaly) and the spinal cord (spina bifida) are mentioned in this section. Hydrocephalus is also an important clinical problem and is mentioned in Chapter 4 (Meninges and Ventricular System).

The neural tube forms gradually from the neural plate by “zippering” in caudal and cephalic directions from the cervical region (Fig. 1.3). The last portions of the neural tube to close are the rostral and caudal neuropores (i.e., the opening of the neural

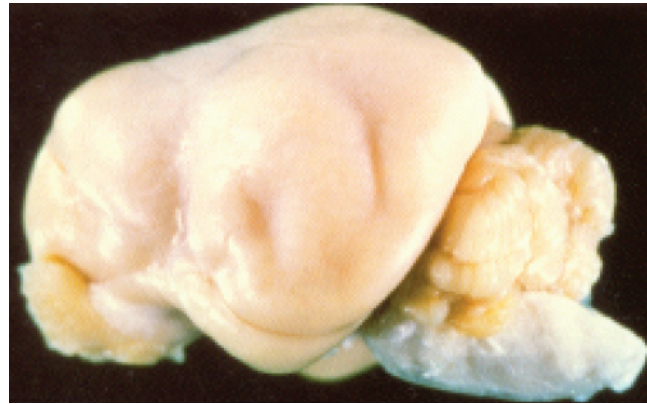


Fig. 1.12 The cerebrum with lissencephaly features smooth cerebrum with rudimentary or absent gyri (agyria) or sulci. The cerebral cortex is thin and neurons are randomly arranged in the deeper cortical layers, suggesting arrested neuronal migration during cerebral development. *Source:* Reprint with permission from *Neurology for the Small Animal Practitioner*, Chrisman *et al.*, copyright 2003 Teton NewMedia, Jackson, Wyoming USA.

tube). **Anencephaly** (*an* neg. + Gr. *enkephalos* brain, absence of the cerebral hemispheres) results from defects in anterior neural tube closure early in gestation. The brain is absent and the skull and meninges are often absent or defective in this condition. However, the basal ganglia, brain stem, and cerebellum are not affected. The rudimentary nerve tissue present in anencephaly shows many immature, and only a few mature, neurons, reflecting a failure of brain development and cellular differentiation at an early stage. Successful closure of the rostral neural tube and subsequent development of cerebral hemispheres are not a guarantee for normal development of the brain. Arrested migration of neurons may prevent the development of the surface folding of the cerebrum, resulting in **lissencephaly** (Gr. *lissos* smooth + *enkephalos* brain, brain with little or no gyri and sulci). Lissencephaly is a rare developmental defect characterized by a small, smooth-appearing cerebrum with rudimentary or absent gyri (**agyria**) or sulci (Fig. 1.12). Lissencephaly features a thin cerebral cortex and neurons that are randomly arranged in the deeper cortical layers, suggesting the arrested neuronal migration. Lissencephaly involves only the neocortex, as the hippocampal and olfactory lobes are normal. Lhasa apsos are most commonly affected, although this anomaly may affect other breeds of dogs (e.g., wire-haired fox terriers, Irish setter, and Samoyed). Clinical signs appearing in dogs younger than 1 year of age may include deficient or poor learning capabilities, or erratic behavior patterns, like episodic aggression, dementia, confusion, depression, hyperactivity, visual deficits, and seizures. The absence of gyri and sulci and thin cortex can be seen by magnetic resonance imaging (MRI).

Midline defects of the developing neural tube also occur during its closure in caudal and cephalic directions. **Spina bifida** is an example of such a defect and is among the most common developmental defects of the CNS. Spina bifida refers to a group

of developmental defects characterized by incomplete closure of the dorsal vertebral arches that may occur with or without protrusion or **dysplasia** (Gr. *dys*, combining form signifying difficult+*plassein* to form, abnormality of development) of the spinal cord or its meninges, or both. English bulldogs are most frequently affected with this condition. Puppies with spina bifida are born with one or more vertebrae that failed to develop normally. The spinal cord is exposed to the outside by a gap created from missing dorsal vertebral bone. This condition makes the exposed portion of the spinal cord liable to damage and further complications, such as urinary and fecal incontinence. The prognosis and life expectancy for dogs with spina bifida is variable. If the exposed spinal cord stays in place and its roots are not damaged, the animal is unlikely to develop any neurologic problems and lives without any treatment. However, if a dog has significant spinal cord damage with severe signs of neurological deficits (e.g., pain, inability to walk normally, fecal and urinary incontinence), prognosis for having normal quality of life is questionable. The cause of spina bifida is not known, but the overgrowth theory suggests that hyperplasia (or overgrowth) of the cells of the dorsal neural tube prevents fusion of the neural tube and adjacent vertebral arches.

The developing spinal cord may develop cavitation of the parenchymal tissue known as **syringomyelia** or dilation of the central canal called **hydromyelia**. They are rare congenital malformations that result from incomplete closure or development of the neural tube. Syringomyelia and hydromyelia may occur separately or together (hydrosyringomyelia) and may affect a few or many segments of the spinal cord.

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Self-evaluation questions

- The neural plate develops from the:
 - Ectoderm
 - Mesoderm
 - Endoderm
- The neural crest gives rise to the dorsal root ganglia.
 - True
 - False
- The thalamus is derived from the:
 - Telencephalon
 - Diencephalon
 - Mesencephalon
 - Metencephalon
 - Myelencephalon
- The lateral ventricle is part of the:
 - Telencephalon
 - Diencephalon
 - Mesencephalon
 - Metencephalon
 - Myelencephalon
- The eyes develop from the:
 - Telencephalon
 - Diencephalon
 - Mesencephalon
 - Metencephalon
 - Myelencephalon

6 Neurons are derived from:

- A Spongioblasts
- B Neuroblasts

7 The choroid plexus is not present in the:

- A Lateral ventricles
- B Third ventricle
- C Cerebral aqueduct
- D Fourth ventricle

8 The gray matter of the spinal cord derives from the:

- A Marginal layer
- B Mantle layer
- C Neural crest

9 Submucosal and myenteric ganglia of the intestine derive from the:

- A Neural crest
- B Alar plate
- C Basal plate
- D Marginal layer