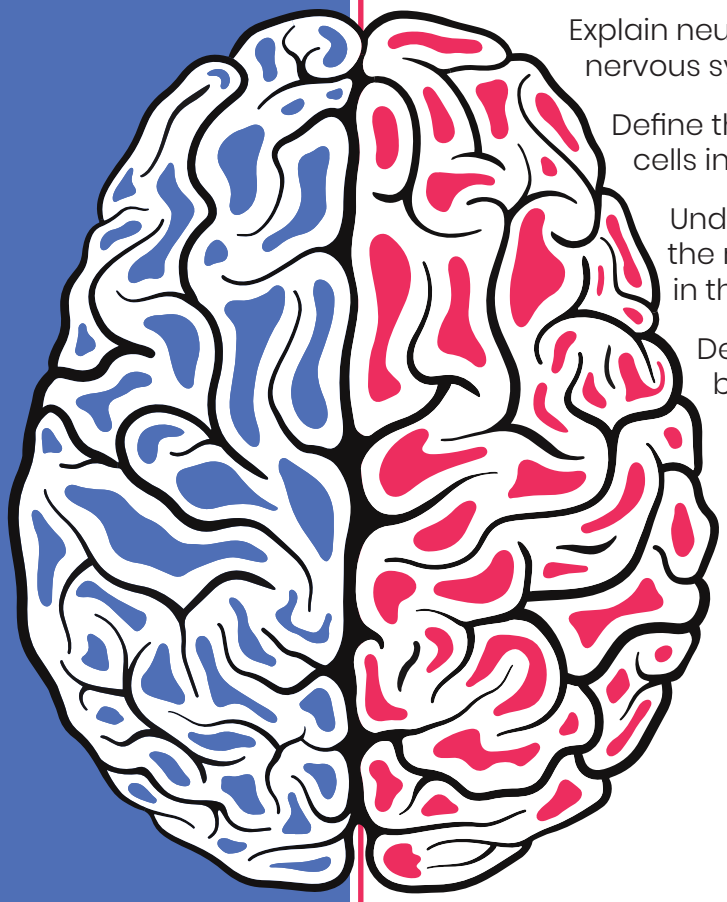
MEDICAL SCHOOL COMPANION

1

NEURULATION AND EARLY NEURAL DEVELOPMENT



Objectives

Explain neurulation and the early development of the nervous system.

Define the roles of neuroectoderm and neural crest cells in nervous system development.

Understand the time line and the importance of the notochord, neural plate, and neural groove in the formation of the neural tube.

Describe formation of primary and secondary brain vesicles in the fifth week.

Note the closure of the neural tube at the anterior and posterior neuropores in the fourth week.

Describe the types of neural tube defects (spinal bifida and anencephaly).

NEURULATION AND EARLY NEURAL DEVELOPMENT

Neurulation and Early Development

The nervous system begins its early development in the dorsal midline of the embryo. It develops from **ectoderm** in the latter half of the third week immediately after gastrulation. During gastrulation, the three germ cell layers (**ectoderm, mesoderm, and endoderm**) are formed by the migration of **epiblast cells.**

The major steps in neurulation and early developmental events that occur in the latter part of the third and fourth weeks are listed below and shown in Figure 1.1.

The three early stages of neurulation include the developments of the neural plate, neural groove, and the neural tube as described below.

1. The **notochord** develops at the end of gastrulation. The presence of the notochord induces a thickening in the dorsal, midline ectoderm to differentiate to form the **neural plate (neuroectoderm).** This marks the beginning of nervous system development. In the adult the notochord forms the nucleus pulposus of the intervertebral disc.

2. The neural plate grows from cranial to caudal in the dorsal midline and invaginates to form the midline **neural groove** by day 20. At the surface, the lateral margins of the neural groove thicken and elevate to form **neural folds**.

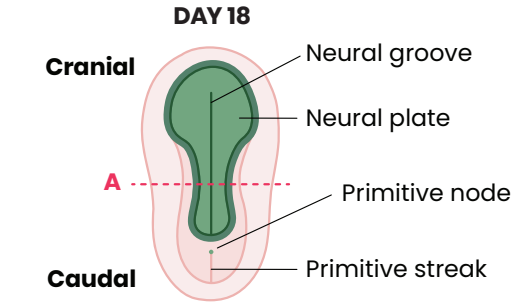
3. **Neural crest cells** are specialized cells that develop from the neuroectoderm within the lateral margins of the neural folds. These cells will eventually split away from the neural tube and migrate throughout the embryo during embryogenesis (3^{rd} – 8^{th} week) where they contribute to the development of multiple types of tissues.

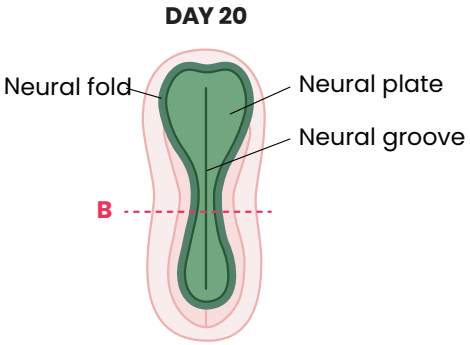
4. Neural folds elevate dorsally and arch across the dorsal midline. Their fusion initiates the closing of the neural groove to form the **neural tube.** The initial closure of the neural tube begins in the central region of the dorsal midline beginning on Day 22. The last parts of the neural tube to close are the **cranial and caudal neuropores** on days 25 and 27, respectively.

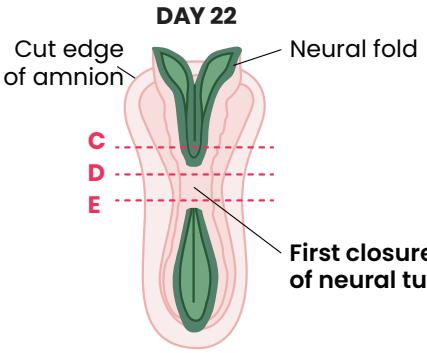
5. Further differentiation of the neuroectoderm of the neural tube results in the formation of the **basal** and **alar plates.** The **ventral part** of the neural tube (**basal plate**) forms **future motor neurons** and **pathways**. The **dorsal part** of the neural tube (**alar plate**) develops into future **sensory neurons** and **pathways.** The two plates are separated by the **sulcus limitans** separating the motor and sensory areas of the neural tube.

6. The **paraxial mesoderm** on either side of the notochord condenses to form somites. These blocks of mesoderm form segmentally and contribute to the development the axial skeleton and skeletal muscles of the limbs and trunk.

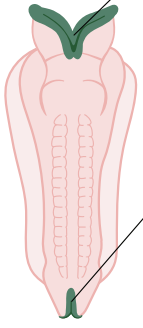
Dorsal View







Neural Tube Defects (NTDs)



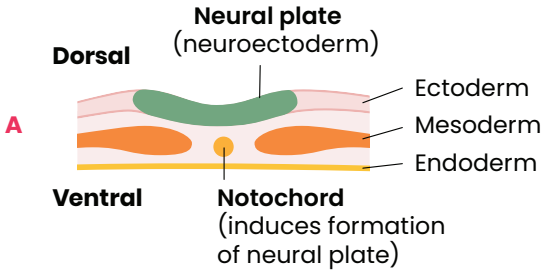
Rostral neuropore (closes at Day 25)

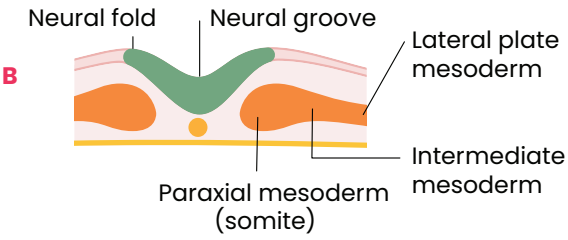
Failure to close results in **anencephaly,** resulting in polyhydraminos and increased a fetoprotein (AFP) and acetylcholinesterase (AChE) levels

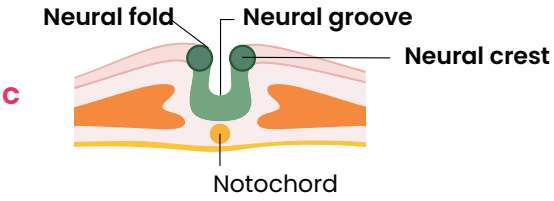
Caudal neuropore (closes at Day 27)

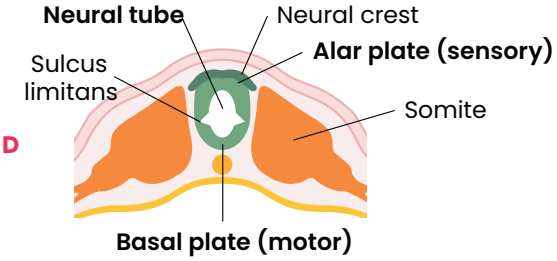
Failure to close results in **spina bifida** and increased a fetoprotein and acetylcholinesterase (AChE) levels

Cross Section View









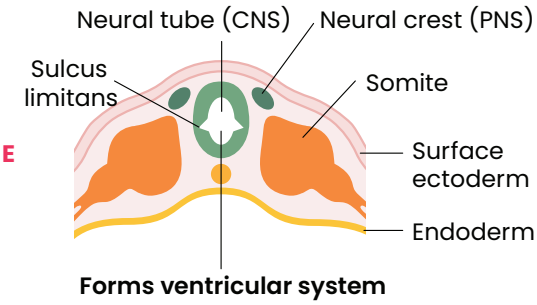


FIGURE 1.1 Early Development of the Nervous System

Note: 1. Folic acid taken prenatally reduces the rate of neural tube defects. **2.** Body wall defects (NTDs, omphalocele, and gastroschisis) can result in elevated levels of AFP during pregnancy

Fifth Week of Development

After neural tube closure at the end of the fourth week, the neural tube forms three cranial dilations called primary vesicles early in the fifth week (Fig. 1.2):

1. **Prosencephalon** (forebrain)
2. **Mesencephalon** (midbrain)
3. **Rhombencephalon** (hindbrain)

Immediately after the primary vesicles form in the fifth week, they then divide into **five secondary vesicles**. The progressive developments of the vesicles and their adult derivatives are shown below.

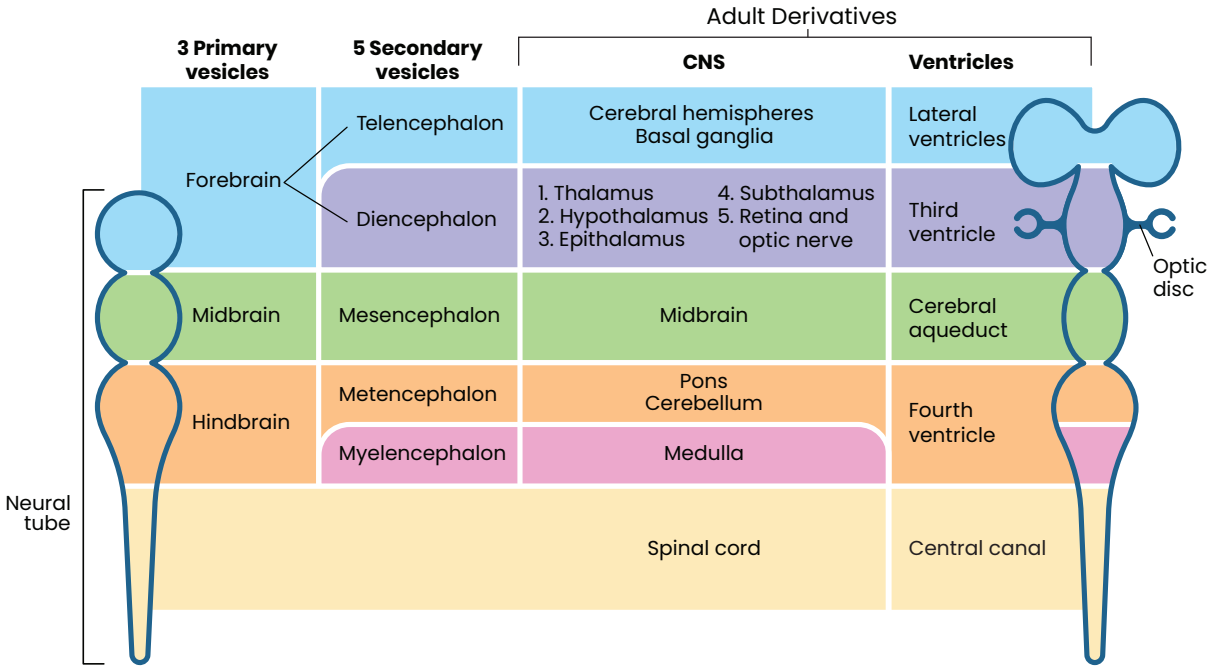


FIGURE 1.2 Fifth Week of CNS Development

Normal Neural Development from Germ Layers

Neuroectoderm (CNS):

- **Neural tube Forms:**
  1. Central nervous system
  2. Retina and optic nerve (actually a CNS tract from diencephalon)
  3. Posterior pituitary (Neurohypophysis)
  4. Astrocytes
  5. Oligodendrocytes (Myelinate CNS axons and CN II; damaged in multiple sclerosis)
- **Neural crest (PNS) Cells Form:**
  1. Sensory ganglia - pseudounipolar neurons (or unipolar)
  2. Autonomic ganglia - postganglionic motor neurons
  3. Schwann cells (Myelinate PNS axons; damaged in Guillain-Barre)

Abnormal Development of the Nervous System

Neural Tube Defects

Failure of the cranial or caudal neuropores to close by the end of fourth week results in **neural tube defects** (NTD) as listed below. Neural tube defects often result in elevated levels of **a fetoprotein (AFP)** and AChE level.

Anencephaly is a very, severe birth defect resulting from failure of the cranial neuropore to close at day 25. This results in failure of the cranial bones to form and failure of the brain to develop. This is incompatible with life and most are stillborn. The inability to swallow results in **polyhydramnios**. There are **increased AFP** and AChE levels during pregnancy.

Spina bifidas (Fig. 1.3) occur with failure of the caudal neuropore to close at day 27. Spina bifidas are classified into several types and are shown in the figures to the right.

A. **Spina bifida occulta** is not a true NTD and is actually a defect of **mesoderm** development resulting in the failure of the laminae and spines of the vertebral arches to fuse around the spinal cord at one or more of the lumbar vertebrae. There is no cord herniation or neurological defects present. No increased AFP.

B. **Cysticas.** The following represent NTDS (cysticas) with variable degrees of neurological defects. Spina bifida cysticas share the same vertebral arch defect described in occulta above but also include spinal cord and meningeal malformations. The three major types are described below:

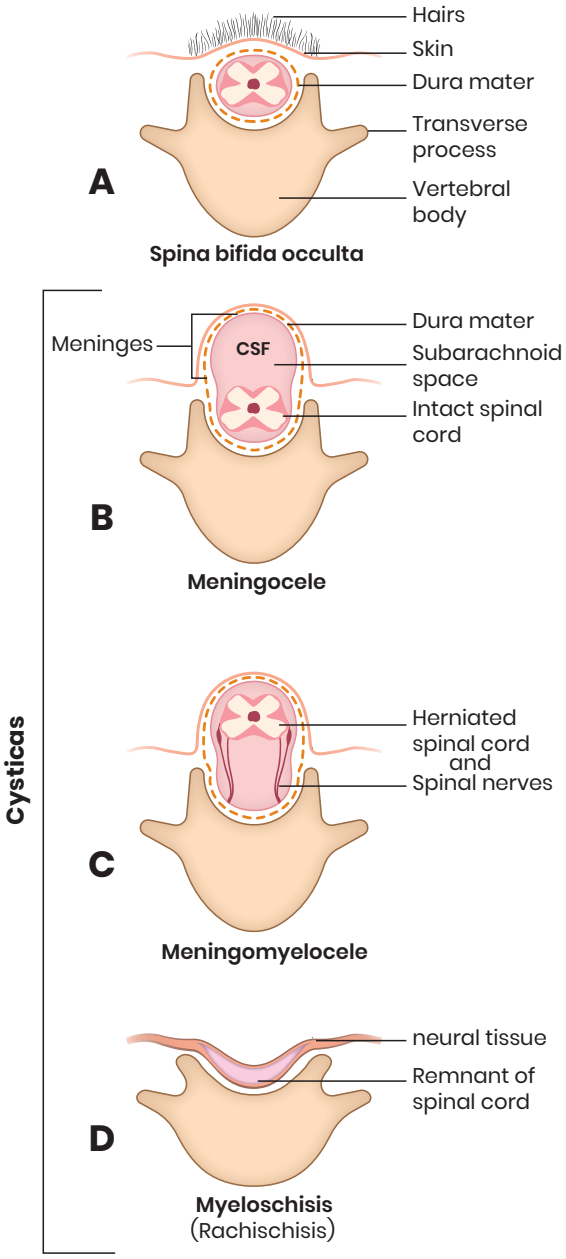


FIGURE 1.3 Spina Bifidas

1. **Meningocele** with spina bifida is a failure of the caudal neuropore to close resulting in a cyst containing CSF lined by meninges. Meningocele occurs in the dorsal midline with limited neurological defects. Increased AFP and AChE levels.

2. **Meningomyelocele** with spina bifida is a significant neural tube defect that involves herniation of the meninges with parts of the lumbar spinal cord and spinal nerves. Major motor and sensory defects are present in the lower limbs with incontinence of bladder and bowel functions. Frog-leg posture is seen with lumbosacral nerve damage. Often seen with Arnold-Chiari II. Increased AFP and AChE levels.

3. **Myeloschisis (rachischisis)** is the most sever type of spina bifida with an open neural tube and limited lower spinal cord development. There are severe motor and sensory lower limb defects seen in these newborns. Increased AFP and AChE levels.

Dandy-Walker Syndrome

1. Partial or complete congenital agenesis or hypoplasia of the vermis of the cerebellum
2. Absence of or failure of the foramina of Luschka and Magendie to open; dilated fourth ventricle
3. Results in trunk (cerebellar) ataxia (loss of motor function, coordination, and development of motor skills) and hydrocephalus

Arnold-Chiari Malformation: Type II (newborn)

1. Congenital displacement and herniation of the medulla and cerebellar tonsils through the foramen magnum into the vertebral column
2. Compresses fourth ventricle and flow of CSF
3. Results in cerebellar dysfunction and hydrocephalus
4. Often seen with meningomyelocele and syringomyelia