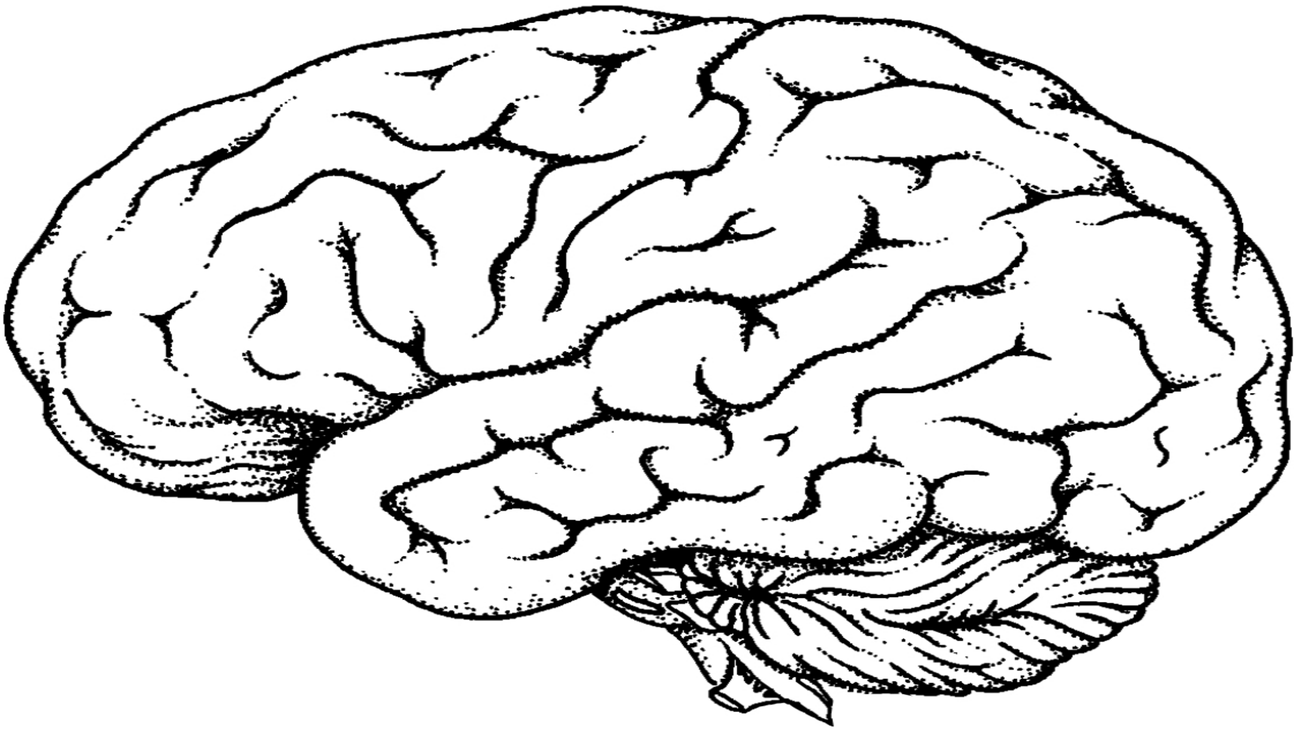
EMBRYOLOGY
Team 435

NERVOUS SYSTEM

هذا الملف للاستزادة واثراء المعلومات

Neuropsychiatry block.



قال تعالى: (وَلَقَدْ خَلَقْنَا الْإِنسَانَ مِن سُلَالَةٍ مِّن طِينٍ {١٢} ثُمَّ جَعَلْنَاهُ نُطْفَةً فِي قَرَارٍ مَّكِينٍ {١٣} ثُمَّ خَلَقْنَا النُّطْفَةَ عَلَقَةً فَخَلَقْنَا الْعَلَقَةَ مُضْغَةً
فَخَلَقْنَا الْمُضْغَةَ عِظَامًا فَكَسَوْنَا الْعِظَامَ لَحْمًا ثُمَّ أَنشَأْنَاهُ خَلْقًا آخَرَ فَتَبَارَكَ اللَّهُ أَحْسَنُ الْخَالِقِينَ {١٤})

Resources

- ✓ BRS Embryology Book.
- ✓ Pathoma Book (IN DEVELOPMENTAL ANOMALIES PART).

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OVERVIEW

A- **Central nervous system (CNS)** is formed in **week 3** of development, during which time the **neural plate** develops. The neural plate, consisting of **neuroectoderm**, becomes the **neural tube,** which gives rise to the **brain and spinal cord.**

B- **Peripheral nervous system (PNS)** is derived from three sources:
1. Neural crest cells
2. Neural tube, which gives rise to all **preganglionic** autonomic nerves (sympathetic and parasympathetic) and all nerves (-motoneurons and -motoneurons) that innervate skeletal muscles
3. Mesoderm, which gives rise to the **dura mater** and to connective tissue investments of peripheral nerve fibers (endoneurium, perineurium, and epineurium)

DEVELOPMENT OF THE NEURAL TUBE

Neurulation refers to the formation and closure of the neural tube. BMP-4 (bone morphogenetic protein), noggin (an inductor protein), chordin (an inductor protein), FGF-8 (fibroblast growth factor), and N-CAM (neural cell adhesion molecule) appear to play a role in neurulation. The events of neurulation occur as follows:

A- The **notochord** induces the overlying ectoderm to differentiate into **neuroectoderm** and form the **neural plate**. The notochord forms the **nucleus pulposus** of the intervertebral disk in the adult.

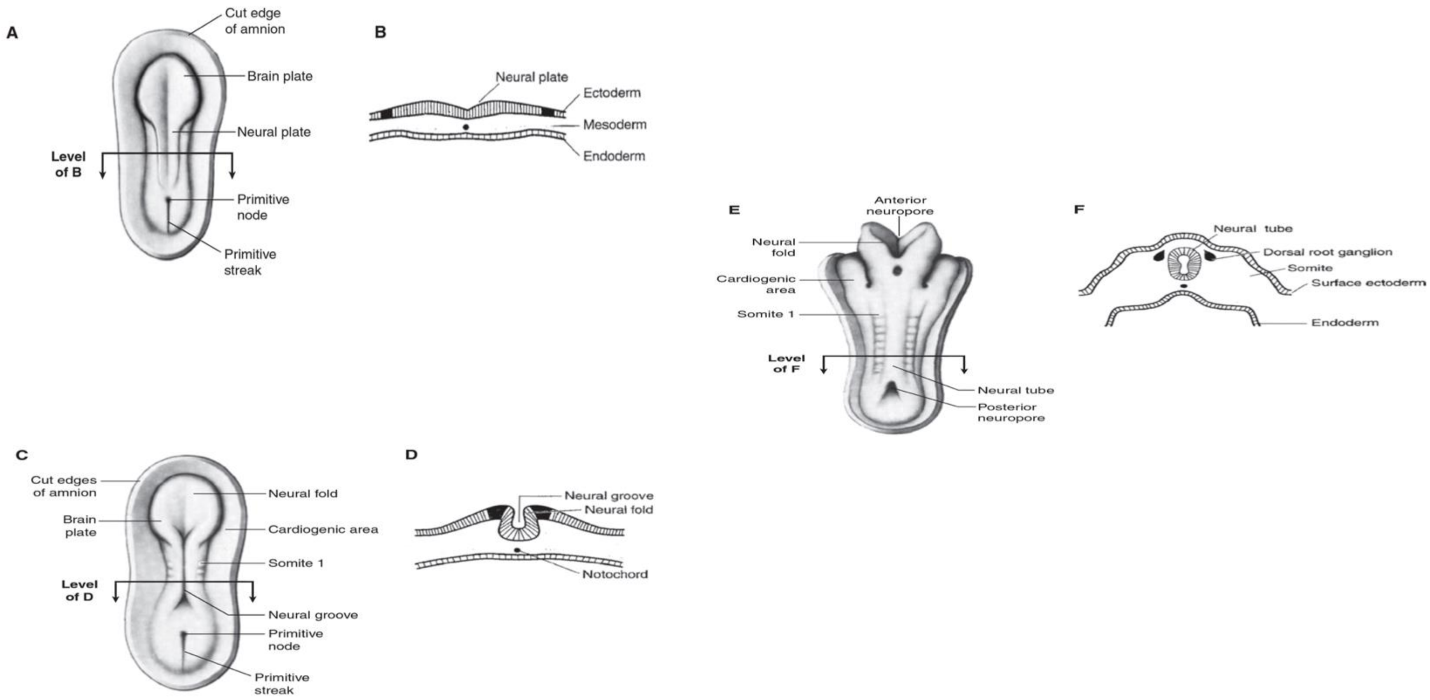
B- The neural plate folds to give rise to the neural tube, which is open at both ends at the **anterior** and **posterior neuropores**. The anterior and posterior neuropores connect the of the neural tube with the amniotic cavity.
1. The anterior neuropore closes during **week 4 (day 25)** and becomes the **lamina terminalis.** Failure of the anterior neuropore to close results in upper neural tube defects (NTDs; e.g., anencephaly).
2. The posterior neuropore closes during **week 4 (day 27).** Failure of the posterior neuropore to close results in lower NTDs (e.g., spina bifida with myeloschisis).

C- As the neural plate folds, some cells differentiate into **neural crest cells.**

D- The **rostral** part of the neural tube becomes the adult **brain**.

E- The **caudal** part of the neural tube becomes the adult **spinal cord.**

F- The **lumen** of the neural tube gives rise to the **ventricular system** of the brain and **central canal** of the spinal cord.



VESICLE DEVELOPMENT OF THE NEURAL TUBE

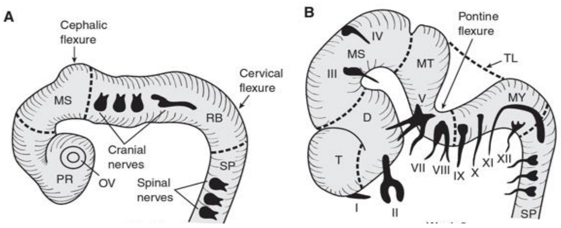
A- The <u>**three**</u> **primary brain vesicles** and **two associated flexures** develop during **week 4.**

1- **Primary brain vesicles ;**
   a. **Prosencephalon (forebrain)** is associated with the appearance of the **optic vesicles** and gives rise to the **telencephalon** and **diencephalon**.
   b. **Mesencephalon (midbrain)** remains as the **mesencephalon**.
   c. **Rhombencephalon (hindbrain)** gives rise to the **metencephalon** and **myelencephalon**.

2- **Flexures ;**
   a. **Cephalic flexure (midbrain flexure)** is located between the **prosencephalon and the rhombencephalon.**
   b. **Cervical flexure** is located between the **rhombencephalon and the future spinal cord.**

B- The <u>**five**</u> **secondary brain vesicles** become visible in **week 6** of development and form various adult derivatives of the brain.

1- **Telencephalon** gives rise to the **cerebral hemispheres**, caudate, and putamen.
2- **Diencephalon** gives rise to the **epithalamus, subthalamus, thalamus, hypothalamus,** mammillary bodies, neurohypophysis, pineal gland, globus pallidus, retina, iris, ciliary body, optic nerve (CN II), optic chiasm, and optic tract.
3- **Mesencephalon** gives rise to the **midbrain**.
4- **Metencephalon** gives rise to the **pons** and **cerebellum**.
5- **Myelencephalon** gives rise to the **medulla**.



BRAIN VESICLES AND THEIR ADULT DERIVATIVES

Primary Vesicles	Secondary Vesicles	Adult Derivatives
Prosencephalon	Telencephalon	Cerebral hemispheres, caudate, putamen, amygdaloid claustrum, lamina terminalis, olfactory bulbs, hippocampus
	Diencephalon	Epithalamus, subthalamus, thalamus, hypothalamus, mammillary bodies, neurohypophysis, pineal gland, globus pallidus, retina, iris, ciliary body, optic nerve (CN II), optic chiasm, optic tract
Mesencephalon	Mesencephalon	Midbrain
Rhombencephalon	Metencephalon	Pons, cerebellum
	Myelencephalon	Medulla

HISTOGENESIS OF THE NEURAL TUBE

The cells of the neural tube are neuroectodermal (or **neuroepithelial**) cells that give rise to the following cell types:

A- **Neuroblasts** form all neurons found in the CNS.

B- **Glioblasts (spongioblasts)** are, for the most part, formed after cessation of neuroblast formation. Radial glial cells are an exception and develop before neurogenesis is complete. Glioblasts form the supporting cells of the CNS and include the following:

- **a- Astrocytes** : play a role in the metabolism of neurotransmitters , buffer the [K] of the CNS extracellular space, form the external and internal glial-limiting membrane in the CNS, form glial scars in a damaged area of the CNS.
- **b- Oligodendrocytes** : produce the myelin in the CNS.
- **c- Ependymocytes** : line the central canal and ventricles of the brain.
- **d- Tanycytes**.
- **e- Choroid plexus cells**: secrete CSF.
- **f- Microglia (Hortega cell) :** are the macrophages of the CNS.

a

FIGURE 7.5. Protoplasmic astrocyte.

b

FIGURE 7.6. Oligodendrocyte.

c

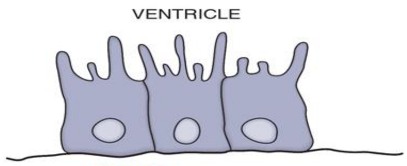


FIGURE 7.7. Ependymal cells.

d

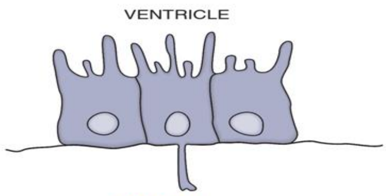


FIGURE 7.8. Tanycyte.

e

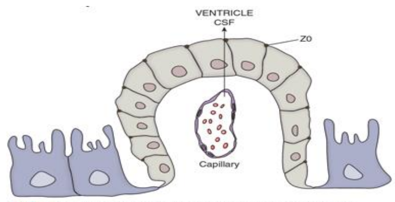


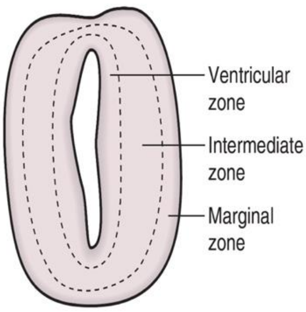
FIGURE 7.9. Choroid plexus cells. CSF = cerebrospinal fluid; ZO = zonula occludens.

f

FIGURE 7.10. Microglial cell.

LAYERS OF THE EARLY NEURAL TUBE

A- **Ventricular Zone :** The early neural tube consists of neuroectoderm arranged in a **pseudostratified columnar** arrangement.



B- **Intermediate Zone :**

1-The intermediate zone contains **neuroblasts**, which differentiate into **neurons with dendrites and axons.**

2. The intermediate zone also contains **glioblasts**, which differentiate into **astrocytes and oligodendrocytes.**

3. The intermediate zone forms the **gray matter** of the central nervous system.

4. The intermediate zone is divided into the **alar plate,** associated with **sensory** (afferent) functions, and the **basal plate,** associated with **motor** (efferent) functions.

C- **Marginal Zone :**

1-The marginal zone contains **axons** from neurons within the intermediate zone.

2. The marginal zone also contains **glioblasts**, which differentiate into **astrocytes** and **oligodendrocytes**.

3. The marginal zone forms the **white matter** of the central nervous system.

DEVELOPMENT OF THE SPINAL CORD

The spinal cord develops from the neural tube **caudal** to the **fourth pair of somites.**

- **Alar (sensory) plate:**
  1. The **alar plate** is a dorsolateral thickening of the **intermediate** zone of the neural tube.

2. The alar plate gives rise to **sensory** neuroblasts of the **dorsal horn** (general somatic **afferent** [GSA] and general visceral **afferent** [GVA] cell regions).
3. The alar plate receives axons from the dorsal root ganglia that become the **dorsal (sensory) roots.**
4. The alar plate becomes the **dorsal horn of the spinal cord.**

- **Basal (motor) plate:**

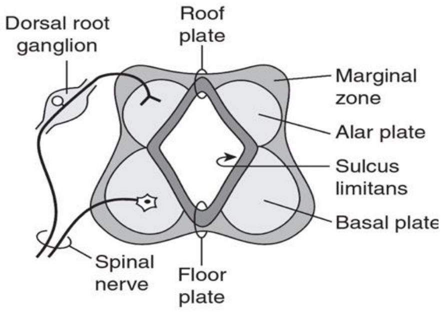
1.The basal plate is a **ventrolateral** thickening of the intermediate zone of the neural tube.
2. The basal plate gives rise to motor neuroblasts of the **ventral and lateral horns** (general somatic **efferent** [GSE] and general visceral **efferent** [GVE] cell regions).
3. The basal plate projects axons from **motor** neuroblasts, which exit the spinal cord and become the ventral (motor) roots.
4. The basal plate becomes the **ventral horn of the spinal cord.**

- **Sulcus limitans (SL):**

1.The SL is a **longitudinal groove** in the lateral wall of the neural tube that appears during **week 4** of development and **separates the alar and basal plates.**

2. The SL disappears in the adult spinal cord but is retained in the rhomboid fossa of the brain stem.

3. The SL extends from the spinal cord to the rostral midbrain.



- **The roof plate is the nonneural roof of the central canal, which connects the two alar plates.**
- **The floor plate is the nonneural floor of the central canal, which connects the two basal plates. The floor plate contains the ventral white commissure.**
- **Myelination:**

1.Myelination of the spinal cord begins during **month 4** in the ventral (motor) roots.
2. **Oligodendrocytes** accomplish myelination in the **CNS**.
3. **Schwann cells** accomplish myelination in the **PNS**.
4. **Myelination** of the corticospinal tracts is not completed until the end of **2 years** of age (i.e., when the corticospinal tracts become myelinated and functional).
5. **Myelination** of the association neocortex extends to **30 years** of age.

- **Positional changes of the spinal cord:**

1.**At week 8** of development, the spinal cord extends the length of the **vertebral canal.**

2. **At birth,** the **conus medullaris** extends to the level of the third lumbar vertebra (**L3**).

3. **In adults,** the **conus medullaris** terminates at **L1–L2** interspace.

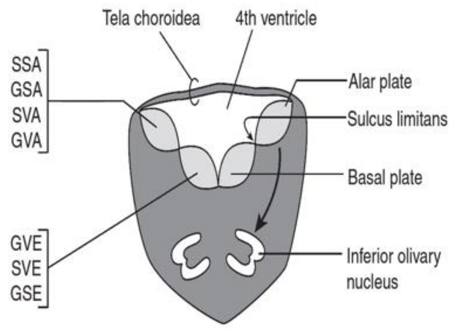
4. **Disparate** growth between the vertebral column and the spinal cord results in the formation of the **cauda equina,** consisting of dorsal and ventral roots (L3–Co), which descends below the level of the conus medullaris.

5. Disparate growth results in the nonneural **filum terminale,** which anchors the spinal cord to the coccyx.

DEVELOPMENT OF THE MYELENCEPHALON

The **myelencephalon** develops from the **caudal** rhombencephalon and gives rise to the **medulla oblongata.**

A- **Alar plate sensory neuroblasts** give rise to the following:
- Cochlear and vestibular nuclei.
- Spinal trigeminal nucleus.
- Solitary nucleus.
- Dorsal column nuclei.
- Inferior olivary nuclei.

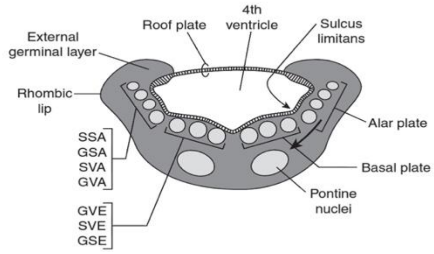


B- **Basal plate motor neuroblasts** give rise to the following:
- Dorsal motor nucleus of the vagus nerve (CN X) and the inferior salivatory nucleus of the glossopharyngeal nerve (CN IX).
- Nucleus ambiguus.
- Hypoglossal nucleus.

C- **The roof plate** forms the roof of the **fourth ventricle.**
D- **The open (rostral) medulla** extends from the obex to the stria medullares of the rhomboid fossa.

DEVELOPMENT OF THE METENCEPHALON

The **metencephalon** develops from the **rostral** rhombencephalon and gives rise to the **pons and cerebellum.**



A. Pons

1. **Alar plate sensory neuroblasts** give rise to the following:
   - Cochlear and vestibular nuclei.
   - Spinal and principal trigeminal nuclei.
   - Solitary nucleus.
   - Pontine nuclei.
2. **Basal plate motor neuroblasts** give rise to the following:
   - Superior salivatory nucleus.
   - Facial (CN VII) and motor trigeminal (CN V) nuclei
   - Abducent (CN VI) nucleus
3. **Base of the pons.** The base of the pons contains the following:
   - Pontine nuclei from the alar plate
   - Corticobulbar, corticospinal, and corticopontine fibers, whose cell bodies are located in the cerebral cortex
   - Pontocerebellar fibers

B. Cerebellum

1.The **cerebellum** is formed from the **rhombic lips**, which are the two dorsolateral thickened alar plates.

2. The rhombic lips thicken at **week 6** to form the **cerebellar plate,** which has a dumbbell appearance.

3. The cerebellar plate is separated into **cranial and caudal** portions by a **transverse groove.**

4. The **caudal** portion forms the flocculonodular lobe, which is the most **primitive** part of the cerebellum.

5. The **cranial** portion forms the **vermis** and the **cerebellar hemispheres**, both of which undergo extensive formation of **fissures and folia.**

6. Like the rest of the neural tube, the rhombic lips consist of **neuroectoderm** arranged in the ventricular zone, intermediate zone, and marginal zone.

7. In **month 3**,the neuroectoderm in the ventricular zone undergoes another wave of proliferation to form the internal germinal layer.The **internal germinal layer** gives rise to the following:

- Deep cerebellar nuclei (i.e., dentate, emboliform, globose, and fastigial nuclei)
- Purkinje cells
- Golgi cells

8. Some **neuroectodermal** cells from the **internal germinal layer** migrate through the marginal zone to form the external germinal layer.The external germinal layer gives rise to the following:

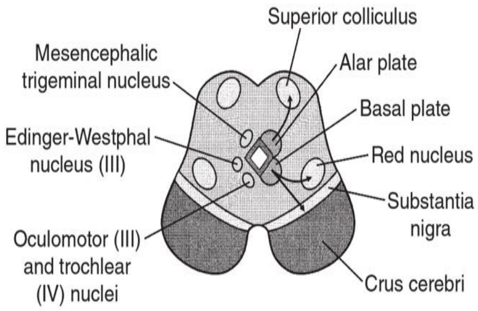
- Basket cells
- Granule cells

- Stellate cells

9. Both the **external and internal germinal layers** give rise to **astrocytes**, **Bergmann** cells, and **oligodendrocytes** within the cerebellum.

DEVELOPMENT OF THE MESENCEPHALON

The **mesencephalon** remains unchanged during primary to secondary vesicle formation and gives rise to the **midbrain**.

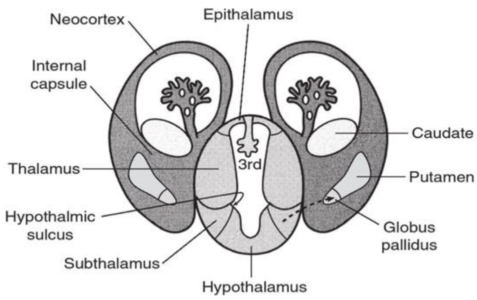


DEVELOPMENT OF THE DIENCEPHALON, OPTIC STRUCTURES, AND HYPOPHYSIS

A- **Diencephalon** develops from the **prosencephalon** within the walls of the primitive **third ventricle**. The alar plates remain prominent in the prosencephalon, but the basal plates regress. The diencephalon gives rise to the epithalamus, thalamus, subthalamus, and hypothalamus.

B- **Optic vesicles, cups, and stalks** are derivatives of diencephalon. They give rise to the retina, iris, ciliary body, optic nerve (CNII), optic chiasm, and optic tract.

C- **Hypophysis (pituitary gland)** is attached to the **hypothalamus** by the <u>pituitary stalk</u> and consists of the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis).

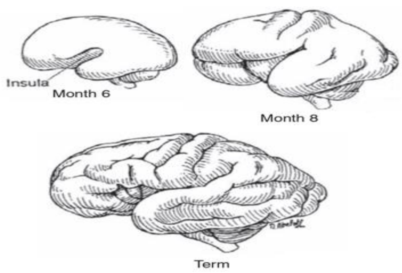


DEVELOPMENT OF THE TELENCEPHALON

The **telencephalon** develops from the **prosencephalon**. The telencephalon gives rise to the **cerebral hemispheres**, caudate, putamen, amygdaloid, claustrum, lamina terminalis, olfactory bulbs, and hippocampus.

A- **Cerebral hemispheres :** develop as bilateral evaginations of the lateral walls of the **prosencephalic vesicle** and contain the **cerebral cortex, cerebral white matter, basal ganglia, and lateral ventricles.**

<u>**The cerebral hemispheres are interconnected by three commissures:**</u> the corpus callosum, anterior commissure, and hippocampal (fornical) commissure. Continuous hemispheric growth gives rise to frontal, parietal, occipital, and temporal lobes, which overlie the insula and dorsal brain stem. The diagram shows the development of the cerebral cortex at **month 6, month 8,** and term. Note the change in the cerebral cortex from a smooth surface or lissencephalic structure to a convoluted surface or gyrencephalic structure. As growth proceeds, a complex pattern of **sulci** (grooves) and **gyri** (elevations) develops.



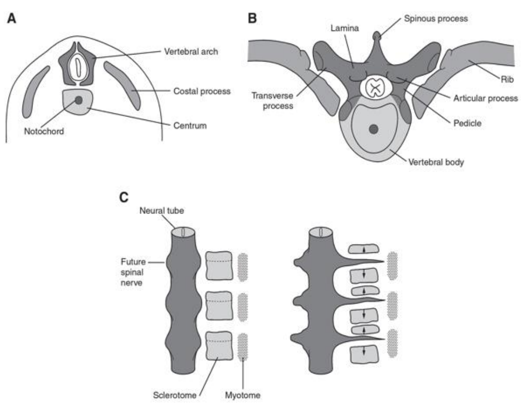
B- **Corpus striatum (striatal eminence) :**

1.The corpus striatum appears in **week 5** of development in the floor of the telencephalon vesicle.

2. The corpus striatum gives rise to the **basal ganglia**: the caudate nucleus, putamen, amygdaloid nucleus, and claustrum.
3. The corpus striatum is divided into the **caudate nucleus** and the **lentiform nucleus** by corticofugal and corticopetal fibers (which make up the internal capsule).
4. The neurons of the **globus pallidus** (also a basal ganglion) have their origin in the subthalamus, and these neurons migrate into the telencephalic white matter and become the medial segments of the lentiform nucleus.

DEVELOPMENT OF VERTEBRAL COLUMN

- Vertebrae in general
  1. Mesodermal cells from the sclerotome migrate and condense around the notochord to form the centrum, around the neural tube to form the vertebral arches, and in the body wall to form the costal processes.
  2. The centrum forms the vertebral body.
  3. The vertebral arches form the pedicles, laminae, spinous process, articular processes, and the transverse processes.
  4. The costal processes form the ribs.
- Intersegmental position of vertebrae
  1. As mesodermal cells from the sclerotome migrate towards the notochord and neural tube, they split into a cranial portion and a caudal portion.
  2. The caudal portion of each sclerotome fuses with the cranial portion of the succeeding sclerotome, which results in the intersegmental position of the vertebra.
  3. The splitting of the sclerotome is important because it allows the developing spinal nerve a route of access to the myotome, which it must innervate.
  4. In the cervical region, the caudal portion of the fourth occipital sclerotome (O4) fuses with cranial portion of the first cervical (C1) sclerotome to form the base of the occipital bone, which allows C1 spinal nerve to exit between the base of the occipital bone and C1 vertebrae.



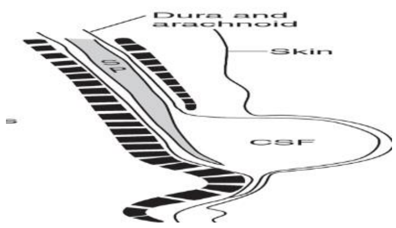
- Curves

The primary curves	The secondary curves
are thoracic and sacral curvatures that form during the fetal period.	are cervical and lumbar curvatures that form after birth as a result of lifting the head and walking, respectively.

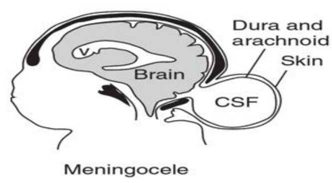
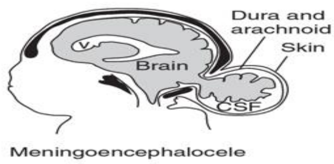
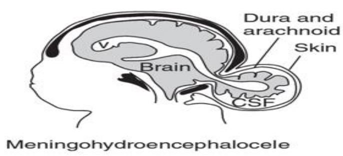
CONGENITAL MALFORMATIONS OF THE CENTRAL NERVOUS SYSTEM

A- Variations of spina bifida. Spina bifida occurs when the bony vertebral arches fail to form properly, thereby creating a vertebral defect, usually in the **lumbosacral** region.

1- Spina bifida occulta	is evidenced by a **tuft of hair** in the **lumbosacral** region. It is the **least severe** variation and occurs in 10% of the population. **The spinal cord is intact.**	

2- Spina bifida with meningocele	occurs when the **meninges protrude** through a vertebral defect and form a **sac filled with CSF.**	
3- Spina bifida with meningomyelocele	occurs when the **meninges and spinal cord protrude** through a vertebral defect and form a **sac filled with CSF.**	
4- Spina bifida with rachischisis	occurs when the posterior neuropore of the **neural tube fails to close during week 4 of development.**	

B- **Variations of cranium bifida** . Cranium bifida occurs when the bony skull fails to form properly, thereby creating a skull defect, usually in the occipital region.

1- Cranium bifida with meningocele	occurs when the meninges protrude through the skull defect and form a sac filled with CSF. The photograph in Figure 7.25 shows a fetus with an occipital meningocele	
2- Cranium bifida with meningoencephalocele	occurs when the meninges and brain protrude through the skull defect and form a sac filled with CSF	
3- Cranium bifida with meningohydroencephalocele	occurs when the meninges, brain, and a portion of the ventricle protrude through the skull defect.	

C- Anencephaly (meroanencephaly	is a type of upper NTD that occurs when the anterior neuropore fails to close during week 4 of development. This results in **failure of the brain to develop** (however, a rudimentary brain is present). Anencephaly is incompatible with extrauterine life.	
D-Arnold-Chiari malformation	occurs whenthe caudal vermis and tonsils of the cerebellum and the medulla oblongata herniate through the foramen magnum.	

DEVELOPMENTAL ANOMALIES (FROM PATHOMA)

1- NEURAL TUBE DEFECTS:

A- **Spina bifida** is failure of the posterior vertebral arch to close, resulting in a vertebral defect (disruption of the caudal end of the neural tube).
   a. Spina bifida occulta presents as a dimple or patch of hair overlying the vertebral defect.
   b. Spina bifida presents with cystic protrusion of the underlying tissue through the vertebral defect.
      - Meningocele-protrusion of meninges
      - Meningomyelocele-protrusion of meninges and spinal cord

B- **Anencephaly** is absence of the skull and brain (disruption of the cranial end of the neural tube).
   a. Leads to a 'frog-like' appearance of the fetus
   b. Results in maternal polyhydramnios since fetal swallowing of amniotic fluid is impaired

2- CEREBRAL AQUEDUCT STENOSIS:

- **Congenital stenosis** of the channel that drains cerebrospinal fluid (CSF) from the 3rd ventricle into the 4th ventricle
- Leads to **accumulation** of CSF in the ventricular space; most common cause of **hydrocephalus** in newborns;
   a. CSF is produced by the choroid plexus lining the ventricles.
   b. Flows from the lateral ventricles into the 3rd ventricle via the interventricular foramen of Monro
   c. Flows from the 3rd ventricle into the 4th ventricle via the cerebral aqueduct
   d. Flows from the 4th ventricle into the subarachnoid space via the foramina of Magendie and Luschka
- Presents with **enlarging head** circumference due to dilation of the ventricles (cranial suture lines are not fused)

Done by : Afnan Almalki.