

ILA: Development of the CNS

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Reading Assignment

Langman's, Medical Embryology, 12th Edition, Chapter 6, pp. 63-70 & Chapter 18
Waxman figures as indicated below
Essential Clinical Anatomy, 4th edition pp. 285-6 "Spina bifida" (optional)
Young, Young, & Tolbert (Y.Y.&T.), Chapter 24 (optional)

Directions

Complete the reading assignment, and study the notes below. Watch the short videos at the links provided in the notes. Exam questions test the objectives that are covered in the notes. Drawing is highly encouraged.

Disclaimer: *Board Review Series Neuroanatomy 5th Edition* and *First Aid for the USMLE Step 1 2016* were used in composing this ILA.

Objectives

1. Describe the processes of primary (rostral) and secondary (caudal) neurulation. Be sure to mention germ layers, notochord, meninges, homeobox genes, sonic hedgehog protein, bone morphogenic protein, and nerve growth factor.
2. Distinguish between neural tube and neural crest. Include names and locations of neural crest derivatives, and focus on those that remain part of the nervous system.
3. Explain the development of brain vesicles, and name their derivatives in adult brain. Be sure to include locations and functional patterns of alar and basal plates, the names and locations of flexures, and neurocoele derivatives that contain cerebrospinal fluid in the adult.
4. Give the numbers of the gestational days on which the rostral and caudal neuropores close, and tell what protein is elevated in maternal serum when neuropores fail to close. Then name a vitamin women can take to prevent faulty closure, and tell when the vitamin must be taken.
5. List and describe specific malformations (neural tube defects) caused by either faulty rostral or caudal neuropore closure, and distinguish these from caudal mass defects. Mention location and severity.
6. Distinguish between dorsal and ventral induction defects as well as between problems with migration, proliferation, and organization. Name and describe clinical examples of each.

NOTES

The human central nervous system (CNS) forms by a process called “neurulation” and includes **primary neurulation** (formation of a **neural tube**) and **secondary neurulation** (formation of a **caudal mass**). Key points of neurulation are given below followed by more detailed information relevant to the process and then by clinical applications of neuroembryology.

I. NEURULATION KEY POINTS

A. Primary Neurulation (neural tube formation):

The **brain, brainstem,** and **C1-S1 spinal cord segments** are formed by a process called **primary neurulation**. Important events in primary neurulation can be summarized as follows:

- **Notochord induction** of a neuroectodermal **neural plate** and then **neural folds**
- **Fusion of neural folds dorsally** to form a **neural tube** by end of the 3rd gestational week
- **Neural crest** formation lateral to the neural tube followed by migration of neural crest cells
- **Neuropore closure** at both ends (rostral & caudal) of the neural tube

Primary neurulation begins when **ectoderm** (other than what will form skin) differentiates into **neuroectoderm** during **the 3rd week of gestation** in response to **induction factors** (e.g., sonic hedgehog) produced and released by an underlying **mesodermal notochord**. This neuroectoderm undergoes differentiation and growth to form either a **neural tube** or **neural crest** defined as:

1) NEURAL TUBE: a midline structure whose epithelial cells give rise to **CNS neurons** and **macroglial cells** (*astrocytes* and *oligodendroglia*). The **rostral** part of neural tube forms the **brain** and **brainstem**. The **caudal** part of the neural tube forms **spinal cord segments C1-S1**.

2) NEURAL CREST: the dorsal-most part of bilateral elevations of neuroepithelium that come together during neural tube formation. Neural crest differentiates into diverse cells that migrate to form peripheral nervous system (PNS) and other structures in various locations in the body, e.g., **sensory & autonomic ganglia neurons and satellite cells**.

Once the notochord induces neuroectoderm to form a neural plate, the plate **thickens** and develops a shallow **midline neural groove** (Langman, Figure 18.1). Subsequently, **sonic hedgehog protein** released from the notochord induces **neural folds** to **elevate** on each side of the groove causing the groove to become deeper. **These neural folds fuse dorsally** in the **midline** to form a **neural tube** beginning in the **cervical region** on **gestational day 20**, and this fusion progresses in **both a rostral (head) and a caudal (tail) direction**.

The **dorsal part** of the **neural folds** contain cells designated as **neural crest cells** (Langman, Figure 6.5) that initially move lateral to the neural tube and then migrate throughout the body to form the PNS and other structures (listed below). Disorders of neural crest origin can occur throughout the body. Absence of certain populations of neural crest cells can cause problems like **Hirschsprung’s disease** (megacolon) where parasympathetic ganglia don’t form or **Waardenburg syndrome** (FYI, not testable) inherited, hearing loss, one blue & one brown eye, premature patch of white hair.

LIST OF NEURAL CREST DERIVATIVES

Nervous System:

- 1) Leptomeninges (pia & arachnoid mater)
- 2) Sensory ganglia primary sensory neurons & satellite cells:
 - DRG (dorsal root ganglia)
 - Named sensory ganglia for cranial nerves (e.g., trigeminal, geniculate)
- 3) Autonomic ganglia motor neurons & satellite cells:
 - Parasympathetic:**
 - Cranial ganglia (ciliary, pterygopalatine, otic, & submandibular ganglia)
 - Sacral trunk /chain ganglia
 - Terminal ganglia (parasympathetic) in end organs
 - Sympathetic (Langman, Figure 18.41):**
 - Thoraco-lumbar trunk /chain ganglia
 - Prevertebral/preaortic ganglia (sympathetic)
- 4) Suprarenal medulla chromaffin cells (sympathetic; Langman, Figure 18.41)
- 5) Schwann cells (myelinate peripheral nerve axons of both spinal and cranial nerves)

Other (not testable for this ILA, but know for USMLE!!)

- 6) Skin melanocytes
- 7) Heart conotruncal septum
- 8) Tooth papilla, follicle, & odontoblasts (make dentin of teeth)
- 9) Pharyngeal arch mesenchyme (craniofacial skeleton, dermis of the face and neck),
- 10) C- cells of the thyroid gland
- 11) Face and skull connective tissue

Fusion of the neural folds is **completed by day 23** of gestation resulting in the formation of a **neural tube** that has **open neuropores** at the rostral (**anterior neuropore**) and caudal (**posterior neuropore**) ends. Without proper fusion of neural folds and bone severe **congenital malformations**, e.g., **rachischisis** (vertebral column not fused) or **craniorachischisis** (cranium & vertebral column not fused) can occur.

Anterior and **posterior neuropores** allow the **neurocoele (lumen)** of the neural tube to temporarily communicate with the **amniotic cavity**. These two neuropores must close for normal development otherwise neural tube defects occur. Gestational days of neuropore closure are:

Day 25 = Anterior neuropore

Day 27 to 28 = Posterior neuropore

Faulty neuropore closure causes measurable **increases** in both **maternal serum** and **amniotic fluid** levels of **alpha fetoprotein (AFP)**. So **neural tube defects** are suspected when increased AFP is detected in maternal serum. Acetylcholinesterase (**ACHE**) also leaks into **amniotic fluid** with neuropore closure defects so if **both AFP and ACHE** are found to be **elevated in amniotic fluid**, suspected presence of a neural tube defects is strengthened. **Prevention** of these defects is possible if women who might become pregnant take **400mcg of folate** per day.

B. Secondary Neurulation (caudal mass formation):

Secondary neurulation forms **spinal cord segments S2-Coccygeal segment 1** during **gestational days 20-40** although details of the process are not completely known in humans. Basically, a cluster of undifferentiated mesenchymal cells located caudal to the neural tube forms a **caudal mass/eminenence**. This mass then differentiates into several tissue types including a **neural cord** that **cavitates** by gestational day 24 and **attaches** to the caudal-most part of the neural tube (spinal cord S1 segment). Failure of the caudal mass to connect with the neural tube can result in **sacral hypoplasia** and in the worst-case scenario **caudal regression syndrome** mentioned again below.

Watch the very short movie at this link:

https://embryology.med.unsw.edu.au/embryology/index.php/Secondary_Neurulation_Movie

FYI but not testable, see the following link:

<http://ispn.guide/book/The%20ISPN%20Guide%20to%20Pediatric%20Neurosurgery/Congenital%20Disorders%20of%20the%20Nervous%20System%20in%20Children/Embryology%20of%20the%20Central-2>

C. Meninges

During both primary and secondary neurulation, connective tissue coats called “**meninges**” begin to form around CNS neural tissue. The **thin** leptomeninges (**arachnoid & pia** mater) are derived from both **neural crest** and **mesoderm** before the **thick** pachymeninx (**dura** mater) is derived from **mesoderm**. Certain neural tube defects are named based on involvement of the meninges, e.g., meningiocele.

II. ORGANIZATION OF NEURAL TUBE

The **neurocoele** is present throughout the neural tube and no longer communicates with the amniotic cavity after closure of both neuropores. Adult derivatives of the neurocoele are the:

Ventricular system of the brain

Central canal of the spinal cord

Midline dorsal and **ventral regions** of the early neural tube are called **roof plate** and **floor plate**, respectively, that become both the source of cerebral ventricular choroid plexus that makes the cerebrospinal fluid (CSF) and the location of axons that cross from one side to the other.

Three **layers or zones** form in the two **lateral walls** of the early neural tube as shown in Waxman Figures 2-1 & 5-2 and are named as follows:

- 1) **Ventricular**
- 2) **Intermediate**
- 3) **Marginal**

The **ventricular layer/zone** or **proliferative layer** consists of a **pseudostratified neuroepithelium** surrounding the neurocoele. It is called “**proliferative**” because it gives birth to **neuroblasts** and

glioblasts that form the intrinsic cells of the CNS, i.e., **neurons** and **macroglia** (astrocytes and oligodendrocytes), respectively. An extrinsic cell-type (not from neural tube!) called **microglia** migrates into the CNS from **bone marrow** (Waxman, Table 2-2) and functions **similar to macrophages**. After cellular proliferation is completed, the ventricular/proliferative layer remains as the adult **ependymal cell layer**, a simple cuboidal or columnar *ciliated* epithelium that **lines** the cerebral **ventricles** (hence its name “**ventricular**” layer) and cerebral **aqueduct** as well as the **central canal** of the spinal cord.

Glioblasts differentiate into **radial glia** that are **bipolar in shape**, extending one process toward the ventricle and the other toward the external surface of the neural tube. **Neuroblasts migrate** from near the ventricle **along** these **radial glia** to reach specific locations within the wall of the neural tube. This migration process forms functional layers of the developing brain, brainstem, and spinal cord. **Timing** is important for normal brain development, e.g., if an insult occurs at the same time a certain population of neurons is developing, those neurons could be deleted from the CNS. Most glioblasts are formed after neuroblasts. Radial glia mature into **astroglia** when migration of neuroblasts is finished. (FYI: Langman’s use of the term glioblast is interchangeable with glioblast)

Watch this movie beginning at 2:23 minutes. <https://www.youtube.com/watch?v=xLXb5lyAXWY>

The **cerebral cortex** (brain gray matter) is formed from neuroblasts that migrated along radial glia from the ventricular zone to reside in the **marginal zone** toward the external surface of the CNS that is lined with pia mater. In contrast, neuroblasts that form **spinal cord** gray matter stop in the **intermediate zone (mantle layer)**. The **brainstem nuclei** (clusters of neurons, gray matter) initially form similar to the gray matter of the spinal cord but change orientation as fourth ventricle forms.

III. NEURAL TUBE CELLULAR DIFFERENTIATION

Differentiation of cells of the neural tube wall gives rise to neurons, macroglial cells, and ependymal cells; but NOT microglia (bone marrow origin). Pseudostratified cells of the neuroepithelial layer of the neural tube begin to differentiate into **neuroblasts** that first become **round** (apolar) cells. Subsequently, each round neuroblast grows **an axon** and **a dendrite** by a process of **elongation** which gives them a bipolar appearance. These **bipolar-shaped neuroblasts** are able to **migrate** along radial glia to reach their final location. Most neuroblasts differentiate into multipolar neurons once they have reached their final location. Formation and elongation of neural processes (axons and dendrites) and migration to the correct location are dependent upon **neurotrophins** produced by **target cells**.

Once neuroepithelial cells differentiate into **neuroblasts**, they typically **no longer divide**. Most populations of neurons are fixed postmitotics (non-dividing) after birth. By contrast, **glioblasts** and **glial cells** retain their ability to **divide** and replenish themselves throughout the life of the individual. Brain tumors called neuroblastomas and glioblastomas originate from neuroblasts or glioblasts, respectively. Whereas, **glioblastomas** are typically seen in **adults** and are usually **fatal**, **neuroblastomas** are the most common cancer found in **newborns** and have a high rate of **cure**.

Oligodendroglial **myelination** of axons and neuronal formation of synapses (**synaptogenesis**) within

the CNS **continue postnatally** throughout childhood and into adulthood. Further details of CNS neuronal differentiation, migration, and synaptogenesis are beyond the scope of this ILA (FYI but not tested see Y.Y. & T. Fig. 24-4).

IV. MOLECULAR BASIS OF NEUROEMBRYOLOGY

Initially, the neural tube is divided into major segmental subdivisions called **neuromeres**, which are established under the control of **Hox genes** (homeobox genes). These segments are important for development of the **rostral neural tube** primary and secondary **vesicles** and **cranial nerves** (pharyngeal arches) as well as **caudal neural tube spinal cord segments** and **spinal nerves**.

Dorsal (sensory) patterns in the neural tube are induced by **bone morphogenetic proteins**.

Ventral (motor) patterns in the neural tube are induced by **sonic hedgehog protein**.

Greater numbers of neurons are found in the brain of an early embryo than in the brain of a neonate. **Neurotrophins** are required for **survival** of neurons, and **specific targets** (i.e., other neurons within the CNS, neurons in autonomic ganglia, or skeletal muscle cells) produce these neurotrophins. Prevention of **apoptosis** (programmed cell death) of **specific subsets** of neurons by neurotrophins allows the CNS to develop specific functions. **Correct number** of neurons innervating a target is important for the wellbeing of both the target and the neurons that innervate the target.

Nerve growth factor (**NGF**) was the **first neurotrophin discovered** for its promotion of the **survival** of neural crest cells that formed dorsal root ganglion (**DRG**) **neurons** in an experimentally **dose dependent** fashion. Administering more NGF lead to the survival of a greater number of DRG neurons in mice that lacked the gene for NGF. Depending on amounts of NGF, the skin of these mice was either innervated by large numbers of DRG neurons or small numbers of DRG neurons. Two other examples of neurotrophins are brain-derived neurotrophic factor (**BDNF**) and ciliary neurotrophic factor (**CNTF**) with functions and mechanisms of action beyond the scope of this ILA.

V. CAUDAL NEURAL TUBE BECOMES SPINAL CORD

The spinal cord, down to level S2, develops during primary neurulation from the caudal portion of the neural tube and retains the following **three-layered architecture**:

- 1) **Ependyma** (proliferative layer, lines the central canal)
- 2) **Gray matter** (intermediate/mantle layer)
- 3) **White matter** (marginal layer, most external)

Dorsal (alar) and **ventral (basal)** thickenings occur in the neural tube **mantle layer** (see Y.Y. & T. Fig. 24-3; Waxman, Fig. 5-1). These thickenings become the following plates (Langman Figure 18.8):

Alar Plate (dorsal) - **sensory** neuroblasts; becomes the **dorsal horn** of the spinal cord

Basal Plate (ventral) - **motor** neuroblasts; becomes the **ventral horn** of the spinal cord

The **sulcus limitans** separates the two plates and serves as a **topographical landmark** between **dorsal (sensory)** and **ventral (motor)** spinal cord.

Neuroblasts that differentiate into **autonomic neurons** cluster between the developing dorsal and ventral horns to form an **intermediate horn**. Developing preganglionic autonomic **sympathetic** neurons locate in the intermediate horn at **spinal cord levels T1-L3**. Developing preganglionic autonomic **parasympathetic** neurons locate in the intermediate horn at spinal cord levels **S2-4**. Helpful Hint: be careful not to confuse spinal cord levels with vertebral levels when studying the nervous system.

White matter **tracts** consisting of **myelinated axons** develop throughout the **marginal layer**. In the ventral midline of the marginal layer (white matter) **axons** cross from one side to the other as a very important **decussation** called the **anterior white commissure** of the spinal cord. This commissure and spinal cord white matter tracts will be covered in spinal cord lectures.

(NOTE: spinal cord levels S2-Co1 form by secondary neurulation, not primary neurulation.)

VI. ROSTRAL NEURAL TUBE BECOMES BRAIN AND BRAINSTEM

The walls of the rostral neural tube obtain varying thicknesses and balloon out into **vesicles** that will become the **brain and brainstem** (see Y.Y. & T. Fig. 24-2; Langman, Chapter 18). The neurocoele in this region develops into brain ventricles and the cerebral aqueduct. **Three primary** vesicles initially form and later give rise to **five secondary** vesicles that form the brain and brainstem. Primary vesicles are summarized as follows:

Three Primary Vesicles (draw and label Langman, Figure 18.4):

Prosencephalon - **forebrain** - supratentorial (anterior and middle cranial fossae)

Mesencephalon - **midbrain** - infratentorial (posterior cranial fossa)

Rhombencephalon - **hindbrain** - infratentorial (posterior cranial fossa)

As the three vesicles continue to grow, **three** important **flexures** (bends) occur to eventually obtain the adult anatomical configuration of the CNS. Draw and label Langman, Figure 18.17, which only labels the pontine flexure so use the summary below to find and label all flexures in the drawing:

Two VENTRAL brain flexures form the:

Cervical flexure between the hindbrain and spinal cord

Cephalic flexure at the midbrain region

One DORSAL brain flexure forms the:

Pontine flexure gives rise to the fourth ventricle (rhomboid fossa)

The walls continue to thicken, become more complex, and the three vesicles are further subdivided into **five secondary** vesicles as follows:

Prosencephalon becomes **telencephalon** + **diencephalon**

Mesencephalon remains **mesencephalon**

Rhombencephalon becomes **metencephalon** + **myelencephalon**

The Five Secondary Vesicles form Adult Structures as follows:

Telencephalon (“end” brain) - cerebral hemispheres & basal ganglia

Diencephalon (“tween” brain) - all structures with the word “thalamus” in them

Mesencephalon (“mid” brain) - midbrain

Metencephalon (“after” brain) - pons & cerebellum

Myelencephalon (“marrow” brain) - medulla

Watch the following movie for these basics, <https://www.youtube.com/watch?v=Tp25wrm-AoA>

Individual vesicles are discussed in more detail below. Each time adult structures are mentioned, refer to the **whole brain** and **half brain** laboratories and the Haines Atlas. Continue to use the illustrations in **Langman, Chapter 18** while studying these notes that emphasize important material.

As the secondary vesicles develop, **choroid plexus** is formed by an inward growth of **blood vessels** and **pia mater** together with modified **ependymal cells** inside the cerebral ventricles and makes CSF (Waxman Figures 11-2, 11-3, 11-10, & 11-15). Choroid plexus arises from the:

Floor plate of **Lateral** ventricles of **Telencephalon** (Langman, Figures 18.25 & 18.27)

Roof plate of **Third** ventricle of **Diencephalon** (Langman, Figure 18.30)

Roof plate of **Fourth** ventricle (rhomboid fossa) of **Rhombencephalon** (Langman Figure 18.21)

PROSENCEPHALON (Tel + Di)

Telencephalon (cerebral hemispheres & basal ganglia):

The **rostral** part of the **prosencephalon** forms the telencephalon, which balloons out laterally on each side to eventually form the two **cerebral hemispheres**. Clusters of neuroblasts in the **medial** wall of the telencephalon become nuclei called **corpus striatum** (Langman, Figures 18.24, 18.25, & 18.27) that give rise to adult **basal ganglia** (FYI but not testable for this ILA, e.g., caudate and lentiform nuclei). Lateral growth of the cerebral hemispheres together with the formation of the cephalic flexure causes the developing hemispheres to cover the lateral aspects of the diencephalon, mesencephalon, and metencephalon (Langman, Figure 18.17).

Closure of the rostral (anterior) neuropore forms a thin tissue called the **lamina terminalis** at the rostral-most extent of the telencephalon (Langman, Figures 18.24 & 18.25). As the **cephalic flexure** forms, the lamina terminalis becomes located **rostral to the third ventricle** where it remains **in the adult** brain.

Diencephalon:

The **caudal** part of the prosencephalon forms two bilateral thick masses of neuroblasts in the **mantle layer**. These thickenings are called **alar plates** that will become adult structures having “**thalamus**” in their names (i.e., thalamus, subthalamus, and hypothalamus) except

for the epithalamus (pineal gland), which forms from roof plate of the neural tube (Langman Figures 18.24 & 18.25). The alar plate develops a sulcus between the developing thalamus and hypothalamus and is called the **hypothalamic sulcus** in the adult (Langman Figure 18.24). Sometimes with rapid growth, a midline cluster of **alar plate neurons** connects the two thalami together and is called **massa intermedia**. Laterally on each side of the diencephalon, **optic vesicles** form and invaginate to become **optic cups** that give rise to neural and pigmented components of the eyes. A portion of the **floor of the diencephalon** grows toward the oral cavity and forms the pituitary **infundibulum** (stalk) that gives rise to the **pars nervosa** (Langman, Figure 18.26) comprising the pituitary **posterior lobe**. The **anterior lobe** of the pituitary, adenohypophysis, forms from upward growth of **oral ectoderm (Rathke's pouch)**.

MESENCEPHALON (Mes)

Mesencephalon (midbrain):

The primary vesicle known as mesencephalon **remains as a secondary vesicle** by the same name, mesencephalon. Clusters of neuroblasts form an **alar (sensory) plate dorsally** and a **basal (motor) plate ventrally** in the **mantle layer** of the neural tube. These plates are separated medially by a **sulcus limitans**. Study the illustrations in Langman, Figures 18.23.

Sensory: The **alar plates** form two longitudinal columns of sensory nuclei (clusters of neuroblasts) that become the **two superior (anterior)** and the **two inferior (posterior) colliculi** of the midbrain (Langman, Figure 18.20). **Visual** signals are relayed by the superior colliculi, and **auditory** signals by the inferior colliculi.

Motor: The **basal plates** contain neuroblasts that become the “lower” motor neurons (to skeletal muscle) of the **oculomotor (III)** and **trochlear (IV)** cranial nerves. The **marginal layer** external to the basal plates enlarges to form the **crus cerebri**, which eventually contain **axons** coming from “upper” motor neurons in the cerebral cortex to innervate the “lower” motor neurons in the brainstem (i.e., corticobulbar axons) and spinal cord (i.e., corticospinal axons).

RHOMBENCEPHALON (Met + Mye)

Neural tube that forms rhombencephalon develops thickened clusters of neuroblasts that form **alar (sensory)** and **basal (motor) plates** in the **mantle layer**. These plates change their orientation as the **fourth ventricle** forms, and they become specific brainstem nuclei associated with cranial nerves. Specific named rhombencephalon-derived brainstem nuclei will be covered in the brainstem lectures, not here. Only the **locations of functional categories of developing brainstem nuclei** are important to know for this ILA. Additionally, the **alar plate** forms the **cerebellum**. Pay attention to the **sulcus limitans** between alar and basal plates and to what happens with these plates as the **fourth ventricle** forms.

Metencephalon (pons & cerebellum):

Metencephalon **dorsal** to the fourth ventricle forms the **cerebellum**. Metencephalon **ventral** to the fourth ventricle forms the **pons** (Langman, Figures 18.19, 18.20, & 18.21). The base of the pons (bridge) contains neurons and axons that serve to bridge together the cerebral cortex, cerebellum and spinal cord.

Note that the neurocoele of the metencephalon widens **dorsally** forming the **fourth ventricle**. Compare early **closed** neurocoele shown in Langman, Figures 18.8A & 18.23A (early metencephalon is similar to these) to **open** neurocoele of later developing metencephalon in Langman, Figure 18.19.

Specific named brainstem nuclei derived from the metencephalon will be covered in brainstem lectures, not here. Learn only the **locations of functional categories** of nuclei shown in **Langman Figure 18.19. Draw and label this figure**. Note that efferent (**motor, red**) clusters of neuroblasts are **medial** to afferent (**sensory, blue**) clusters that are **lateral**. Note also that **somatic** (supply body wall) clusters of neuroblasts are located most-medially as well as most laterally with **visceral** (supply internal organs) clusters sandwiched **in between** them. General and Special categorizations do not need to be learned.

Sensory: Metencephalon **alar plate neuroblasts** form **sensory nuclei** in the **pons**. Note that the alar (wing) plates change their orientation to look more like wings as the fourth ventricle forms. The **sulcus limitans** separates sensory nuclei from motor nuclei.

Motor: Metencephalon **basal plate neuroblasts** form the **motor nuclei** in the **pons** that become located **medial to** the **alar plate** neuroblasts as fourth ventricle forms.

Cerebellum forms from the dorsolateral lips of the **alar plates** of the metencephalon that approach each other in the midline (Langman, figure 18.20) although the function of the cerebellum is to coordinate motor (skeletal muscle) movement. Cellular layers need not be learned at this time. Congenital lack of development of the **vermis** of the cerebellum is found in **Dandy-Walker Syndrome**, a genetic disorder characterized by growth of a large posterior cranial fossa cyst that blocks drainage of the fourth ventricle.

Myelencephalon (medulla):

Similar to metencephalon above, formation of the fourth ventricle causes **rostral** (upper) myelencephalon to **open dorsally**. However, **caudal** (lower) myelencephalon nearer to spinal cord remains **closed**. Compare Langman Figure 18.8A (closed neurocoele) to Langman Figure 18.18B&C (open neurocoele).

Rostral (open) myelencephalon will become the adult **open** medulla (fourth ventricle), and **caudal** (closed) myelencephalon will become the adult **closed** medulla.

Specific named brainstem nuclei derived from the myelencephalon will be covered in

brainstem lectures, not here. Learn only the **locations of functional categories** of nuclei in shown in the illustrations in Langman Figure 18.18B&C. **Draw and label Langman Figure 18.18C.** Note that efferent (**motor, red**) clusters of neuroblasts are **medial** to afferent (**sensory, blue**) clusters that are **lateral**. Note also that **somatic** (body wall) clusters are the most medial and the most lateral clusters with **visceral** (internal organ) clusters sandwiched **in between** them. General and Special categorizations do not need to be learned.

Sensory: Myelencephalon **alar plate neuroblasts** form the **sensory nuclei** of the **medulla**. Note that **rostrally**, the sensory **alar (wing) plates** change orientation to have more of a wing-shaped appearance as the fourth ventricle forms. **Caudally**, the sensory **alar plates** stay close to each other, as the neurocoele remains **closed**. (NOTE: only the rostral open myelencephalon is shown in Langman, Figure 18.18.) The **sulcus limitans** separates sensory from motor nuclei.

Motor: Myelencephalon **basal plate neuroblasts** form **motor nuclei** in the **medulla**. **Rostrally**, the motor **basal plates** become **medial** to the alar plates as the fourth ventricle forms. **Caudally**, the motor **basal plates** remain **ventral** to the alar plates. (Only the rostral open myelencephalon is shown in Langman, Figure 18.18.) Motor brainstem nuclei of the medulla are derived from myelencephalon basal plates.

VII. CLINICAL APPLICATION OF NEUROEMBRYOLOGY

A. DORSAL INDUCTION DEFECTS

Normal dorsal induction causes normal growth of embryonic **brain, brainstem, and spinal cord**.

Dorsal Induction Neural Tube Defects include:

1. **Primary** neurulation defects located from **lumbar spinal cord up**
2. **Secondary** neurulation defects located **below the lumbar cord**

Maternal **folate** deficiency, maternal **diabetes, hyperthermia**, or maternal **valproate** use are risk factors for neural tube defects. **Study Langman, Figures 18.15 and 18.35.** Notice how the terms are descriptive of the defects.

1. PRIMARY NEURULATION DEFECTS (listed most severe to least severe and by location):

Brain, Brainstem, & Spinal Cord:

Craniorachischisis totalis,

Brain:

Anencephaly

Encephalocele

Cerebellum & Brainstem:

Arnold-Chiari malformation

Spinal Cord:

Myeloschisis

Myelomeningocele

Meningocele

a. **CRANIORACHISCHISIS TOTALIS** is total failure of neurulation. **Cranium and vertebral column** do not form dorsally. The neural plate lateral edges never fuse at any point so there is no brain, brainstem, or spinal cord (Langman, Figure 18.37B). Survival is not possible, resulting in spontaneous abortion or stillbirth.

b. **ANENCEPHALY** is a defect of anterior neuropore closure. **Cranium** does not form dorsally. The initial cervical point of fusion down to the posterior neuropore is normal while **no fusion rostral to the brainstem** occurs. There are **no cerebral hemispheres** but a rudimentary brainstem might be present (Langman, Figure 18.37A). Anencephaly can cause stillbirth, but if live-born, the infant typically dies within days. Incidence is 1 per 1000 births (testable).

c. **ENCEPHALOCELE** occurs with only partial failure of anterior neural tube closure. An outpouching of **neural tissue** typically occurs in the **occipital region** but can be between the forehead and nose (Langman, Figure 18.35 and 18.36). If the outpouching includes meninges, it is called **meningoencephalocele**. If it includes meninges and a cerebral ventricle, it is called **meningohydroencephalocele**. The tissues included are stated in these names. Maternal **hyperthermia** from fever or from saunas/hot tubs between gestational **days 20-25** is a risk factor. (FYI but not testable: Incidence is 1 per 12,000 births.)

d. **ARNOLD-CHIARI MALFORMATION** consists of inferior displacement of posterior fossa structures such as **cerebellum and brainstem** due to bony **defects of the foramen magnum** and upper cervical vertebrae. Hydrocephalus (Langman, Figure 18.38) with myelomeningocele can occur. Survival rate is good with neurosurgery.

e. **MYELOSCHISIS** is a defect of posterior neuropore closure. The neural plate **inferior to the neck** that forms **spinal cord** fails to fuse so spinal cord is split, and there is usually **no bone or skin covering it dorsally (RACHISCHISIS)**. All are stillborn.

f. **MYELOMENINGOCELE** is defect of partial failure of posterior neural tube closure. It most frequently occurs over the **lumbar area** (last region to close) of the **spinal cord**. Consists of exposed **neural tissue** covered by **meninges** not by bone and only possibly by a sack of skin. **Hydrocephalus** occurs in most. Level of defect determines problems, e.g., loss of sensory and motor function, sphincter dysfunction. Genetic (5% chance of 2nd sibling affected) and environmental risk factors possible. Survival rate can be good with neurosurgery. (FYI but not testable: Incidence of up to 5/1000 births.)

g. **MENINGOCELE** is a malformation the occipital bone or spine of vertebrae through which **meninges** but no neural tissue protrudes. It can occur dorsally anywhere from the occipital region to lumbar region. Survival rate is good with neurosurgery.

NOTE: Spina bifida is a larger category encompassing: myeloschisis (most severe), myelomeningocele (less severe), meningocele (least severe), and spina bifida occulta (not involving neural tube so no neurological problems).

2. SECONDARY NEURULATION DEFECTS

Defects of **caudal mass** formation are distinguished by **caudal location** and **closed skin over the lesion**. Due to the closed skin, these defects might go undetected so they are called **OCCULT dysraphic states**.

a. CAUDAL REGRESSION SYNDROME is characterized by **caudal dysplasia** or **sacral agenesis** and occurs with increased frequency in infants of diabetic mothers. **Sacral hypoplasia** and hypoplastic femurs can occur. Sometimes caudal dysplasia is correlated with **sirenomelia** (mermaid syndrome) where only one femur is present.

b. TETHERED CORD is characterized by the caudal end of the spinal cord being fixed by fibrous bands associated with the filum terminale. Fat pads (LIPOMAS) are frequently present and sometimes also a split spinal cord, which occurs due to notochord splitting.

FYI not testable: split cord is called diastamatomyelia; tethered cord is caused by a persistence of the neurenteric canal, a temporary connection with the notochord canal (Langman, Figure 5.3A).

B. VENTRAL INDUCTION DEFECTS

Normal **ventral induction** occurs via **prechordal mesoderm** (rostral to notochord) and causes normal growth of the **ventral side** of the **rostral end** of the embryo, i.e., **face and forebrain**.

1. HOLOPROSENCEPHALY (Cyclops) occurs due to defective ventral induction during gestational weeks 5 – 6 (face formation) and includes **failure of forebrain cleavage**, resulting in lack of formation of paired cerebral hemispheres. A single nose (cebocephaly) can be found above a single eye (cyclopia). Mutations in **SHH gene** and maternal **diabetes** are possible causes. See Langman, Figure 18.34, and search the Internet for photos of holoprosencephaly showing cebocephaly and cyclopia.

C. NEURONAL PROLIFERATION DISORDERS

Proliferation disorders occur by 2 - 4 months gestation. These manifest as either:

- 1. MEGALENCEPHALY** (large brain size): genetic cause; seen with autism and epilepsy
- 2. MICROCEPHALY** (small brain size): results from genetics, intrauterine infection (e.g. zika virus), alcohol, or decreased oxygen among other causes.

D. NEURONAL MIGRATION DISORDERS

These occur by 3 - 5 months gestation causing **abnormal** development of **gyri** due to genetics and/or disruptions of **neurotrophins**. Seizures, cognitive, and motor problems can be present.

- 1. SCHIZENEPHALY** refers to a **cleft brain**, sometimes occurs bilaterally. If the defect is **small** and does not extend long distances along the dorsoventral axis, then the term **PORENCEPHALY** can be used.
- 2. LISSENCEPHALY** refers to a **smooth** brain with few or no gyri.
- 3. PACHYGYRI** refers to a brain with **broad, fewer** than usual gyri (Pachyderm = thick skin).
- 4. POLYMICROGYRI** (POLYGYRI) refers to a brain that has regions with **too many small** gyri. Histological examination may reveal that many more additional gyri are present than can be detected grossly.
- 5. HETEROTOPIAS** are the least severe of migration defects, referring to normal islands of tissue deposited in the **wrong place**.

Photos of neuronal migration disorders below are FYI and not testable for this ILA:

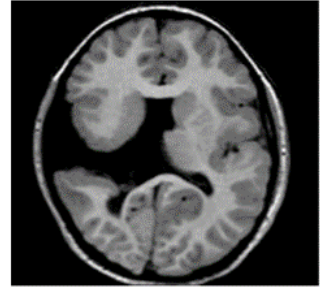
Disorders of Migration: Effects on Cerebral Cortical Gyri



Normal Brain



Schizencephaly: cleft brain



Lissencephaly:
smooth brain (few gyri)



Pachygyri:
broad gyri, too few gyri



Polymicrogyri:
small gyri

E. ORGANIZATION DEFECTS

Organization defects involve notable changes at 6 months gestation to several years of age. They can involve a **paucity of synapses** and have **genetic or environmental** (e.g., starvation, intra- or extra-uterine events) or unknown causes. On the gaussian curve of human intelligence they would represent the lowest 3% of the population. Examples are:

- Some cases of mental retardation
- Down's syndrome
- Perinatal insult
- Several rare diseases

Sample Questions (See also optional practice questions at the link on Oasis)

1. A newborn girl exhibits a developmental defect arising from the failure of the anterior neuropore to completely close. The child exhibits a pouch in the occipital area that contains clear fluid and some neural tissue. Which of the following developmental defects does this child exhibit?

- A. Craniorachischisis totalis
- B. Encephalocele
- C. Holoprosencephaly
- D. Polymicrogyri
- E. Schizencephaly

2. A stillborn male infant exhibits the absence of a brain or spinal cord that arose due to a failure of neurulation (i.e., the neural plates never fused to form the neural tube). Which of the following developmental defects does this child exhibit?

- A. Craniorachischisis totalis
- B. Myelomeningocele
- C. Encephalocele
- D. Meningocele
- E. Spina bifida occulta

3. It is recommended that all women of reproductive age supplement their diet with 400 ug of folic acid per day since this is known to decrease the incidence of neural tube defects. Supplementation must precede pregnancy because by the time someone may realize they are pregnant it is often too late since neural tube fusion is completed on embryonic day _____.

- A. 18
- B. 20
- C. 21
- D. 25
- E. 27

4. A 16-year-old male has been experiencing progressive motor and sensory dysfunction in his legs. An MRI confirms the diagnosis of tethered cord syndrome. This defect arises due to a problem in the normal development of the caudal eminence. Which of the following spinal cord level(s) is derived from the caudal eminence?

- A. Lumbar only
- B. Sacral only
- C. Coccygeal only
- D. Lumbar, sacral and coccygeal
- E. Sacral and coccygeal

5. Proper migration of neural crest cells is an important stage of embryonic development. Which of the following cell types would exhibit normal development in an embryo in which there is a defect of neural crest migration?

- A. Schwann cells
- B. Sympathetic ganglion cells
- C. Dorsal root ganglion cells
- D. Spinal motor neurons
- E. Melanocytes

Answers: 1. B, 2. A, 3. E, 4. E, 5. D