Head and Neck Embryology and Infant Skull Development

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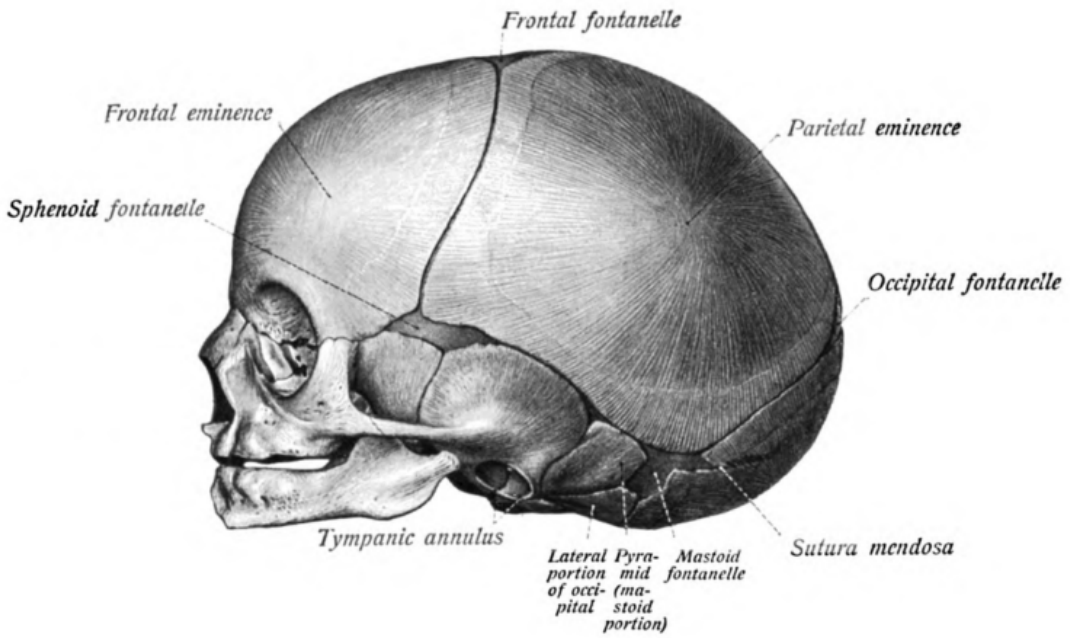
This article will help you understand how the brain develops in a human embryo from the very beginning: gastrulation, the formation, and fate of the primitive streak, neurulation with possible neurocristopathies, closure of the neuropores, embryonic folding, regionalization of the brain, and potential birth defects of the brain. After that, the article will focus on the development of the cranium and possible cranial birth defects.



Gastrulation

Infant development begins at fertilization as a one-cell zygote that forms a multicellular human being. The embryo develops into the trilaminar germ disk, consisting of the **ectoderm**, **mesoderm,** and **endoderm**.

Gastrulation is the name of the embryological process that forms the three germ layers. All embryonic tissues are derived from these germ layers; hence, gastrulation marks the beginning of morphogenesis, i.e., development of the body. This takes place in the **third week** of human development. This is also usually when the first symptoms of pregnancy start arising. **Gastrula** is the term used to describe the **trilaminar structure,** which helps convert the ball of cells known as blastula into a multilayered organism.

The entire nervous system is derived from the **neuroectoderm,** which is a part of the ectoderm. Various **signaling molecules** are involved in gastrulation and tissue

formation from the three germ layers. These molecules include **FGF** (Fibroblast Growth Factor), **sonic hedgehog**, **Tgifs** (TG-interacting factors), and **bone morphogenetic proteins**.

Formation and Fate of the Primitive Streak

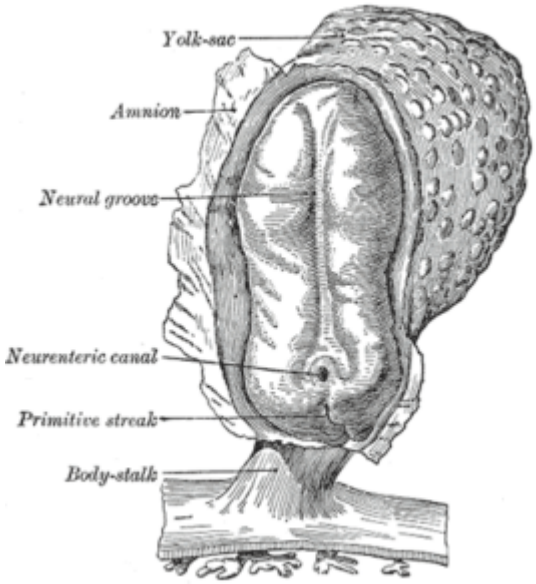


Image: "The Primitive Streak." by Henry Vandyke Carter, Henry Gray (1918) Anatomy of the Human Body. Bartleby.com: Gray's Anatomy, Plate 17. License: Public Domain

The primitive streak, the first sign of gastrulation on the **blastula** (the previous bilaminar structure), establishes bilateral symmetry in a human body. It gives the embryo a craniocaudal axis, helping to distinguish its cranial and caudal ends, dorsal and ventral surfaces, and left and right sides.

The primitive streak occurs caudally on the median plane of the embryonic disc's dorsal surface. It keeps getting longer as more and more cells are added to its caudal surface. At its cranial surface, cells proliferate to produce a **primitive node**.

The primitive groove, an invagination of the primitive streak continuous with the invagination in the primitive node, is called the **primitive pit**.

Cells from the deeper surface of the primitive streak leave to form the **mesoderm**, which forms various supportive embryonic tissues. The cells from the primitive node, **epiblast,** and other areas of the primitive streak form the **endoderm**. Cells that remain in the epiblast (the most external layer of the blastula) form the **ectoderm**.

Once the primitive streak has given rise to mesoderm and the remaining germ layers, it regresses by the end of the fourth week. It remains an insignificant structure in the embryo's sacrococcygeal region. A **sacrococcygeal teratoma** is the result of persisting remnants of the primitive streak.

Neurulation

Neurulation is the **neural tube** formation process through the development of the **neural plate** and the closing of the **neural folds**. The neural tube develops into the

brain and spinal cord, while the neural crest cells formed during this process migrate away from the neural tube to form a variety of cell types, including pigment cells and neurons.

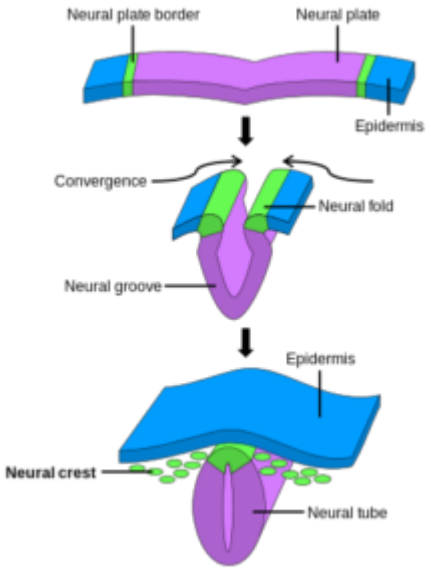


Image: “Neural Crest Formation during Neurulation.” by NikNaks – File:Neural_Crest.png. License: Public Domain

Neurulation begins in the fourth week. The location of neurulation is initially **between the 4th to 6th somite** (bilateral blocks of paraxial mesoderm that align themselves along the neural tube and form the vertebrae, ribs, muscles, and skin). It begins with the formation of the neural plate that arises from the thickening of the ectoderm caused by cuboidal epithelial cells that become columnar. The cells change in shape and adhesion, creating a rise that finally meets in the middle to form the neural tube.

The following molecules play vital roles in neurulation:

- **Noggin** – an inductor protein
- **BMP-4** – bone morphogenetic protein
- **N-CAM** – a neural cell adhesion molecule
- **FGF-8** – fibroblast growth factor

The notochord is the structure responsible for inducing **neuroectoderm** formation (which gives rise to the nervous system). The notochord is a median cellular cord that develops during the migration of mesenchymal cells from the cranial aspect of the primitive node and pit. The notochord, once acquiring a lumen, transforms into the **notochordal canal**. The notochord also makes the **nucleus pulposus** of the intervertebral disc in an adult.

The notochord induces neural plate formation by thickening and elongating the embryonic ectoderm lying over it. The neural plate, in turn, gives rise to the neuroectoderm that forms the central nervous system.

On the 18th day, an invagination takes place in the middle of the neural plate, forming the **neural groove** with neural folds on either side. The **neural folds** begin to fuse on the median plane; once fused together, they convert the neural plate into the **neural tube**. A fusion of the neural folds happens at the 5th somite level and continues both cranially and caudally.

The neural tube further differentiates into **primary brain vesicles** that convert into different regions of the human brain. The **neural canal**, a lumen of the neural tube, communicates openly with the amniotic fluid in the cavity and gives rise to the ventricular system of the brain and spinal cord.

Neural crest cells are neuroectodermal cells found along the lateral border of the neural plate on the internal margin of the neural folds. During neural fold fusion, the cells disassociate themselves from the inner margins of the neural folds, lose their epithelial nature, and form the neural crest, which is located between the neural tube and the overlying ectoderm layer. This process is mediated by **BMP-4** and **BMP-7**.

Wnt/β-catenin is the signaling molecule that activates the **Gbx2 gene,** which is vital to neural crest formation. Neural crest cells migrate to different regions of the embryo and give rise to various structures. The neural crest cells migrate to the **somites** via redefined pathways because of the molecular interaction of particular signaling molecules, transcription factors, and genes like **FoxD3**, **Sox9,** and **Sox10**.

Neurocristopathy refers to the disorders that occur due to maldevelopment of the neural crest cells.

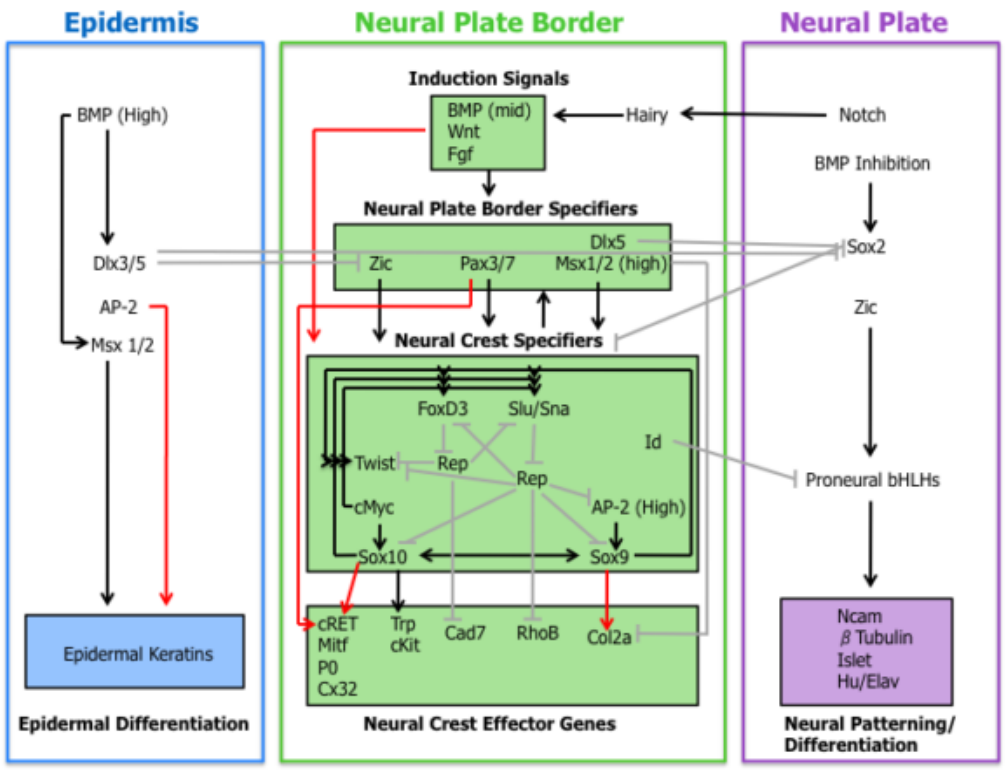


Image: "Molecular interaction of various genes, transcription factors, and signaling molecules to allow migration of neural crest cells to different regions." License: Public Domain

Examples of diseases with neural crest cell origin include **medullary carcinoma of the thyroid**, **Hirschsprung disease**, **Digeorge syndrome**, **Schwannoma,** and **neurofibromatosis type 1**.

Closure of the Neuropores

Closure of the neuropores holds **clinical significance.** If they do not close, there may be various congenital neural tube defects.

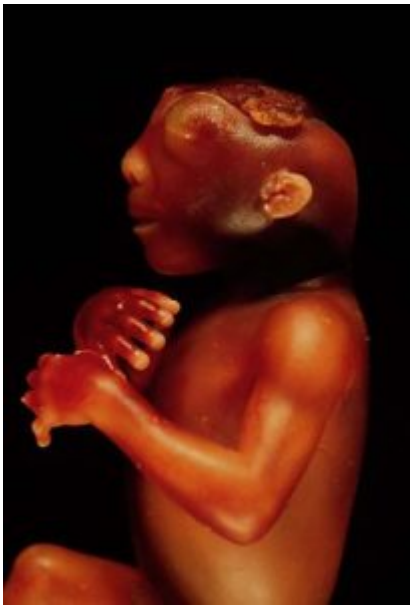


Image: “A Side View of the Anencephalic Fetus.” by Ed Uthman, MD – http://www.geocities.com/HotSprings/Falls/7780/images/anencephaly.html. License: Public Domain

a. The **middle part** is the first part of the neural tube to close, on the 22nd day.
b. The **rostral part**, i.e., the rostral neuropore is the second part to close, on the 25th day.
c. The **caudal neuropore** is the last part to close, on the 27th day.

In all **neural tube defects**, there will be higher levels of **alpha-fetoprotein** and **acetylcholinesterase** in the amniotic fluid. These two markers help identify neural tube defects in the fetus. Examples of neural tube defects include **anencephaly** and **spina bifida**.

Anencephaly: the upper neuro tube defect occurs when the anterior (rostral) neuropore does not close during the 4th week of development. The brain and bony cranial vault that encases it does not develop, which is incompatible with life. This disorder is easily diagnosed by ultrasound.

Image: “An Illustration of an Infant with Spina Bifida.” by Centers for Disease Control and Prevention – License: Public Domain

Spina bifida: the caudal neuropore does not close, so it does not induce bone development around it. There are four types. The mildest form is **spina bifida occulta** (which is asymptomatic except for a tuft of hair over the defect), and the severest form is **spina bifida with myeloschisis** (the spinal cord is outside the vertebral column, which is incompatible with life).

Embryonic Folding

Neural tube growth causes two types of embryonic folding: longitudinal and transverse (flexion). This converts the flat trilaminar structure into a cylindrical-shaped embryo.

These foldings occur at the same time.

- **Longitudinal folding**

a. **Headfold** – neural folds project dorsally into the amniotic cavity, whereas the forebrain grows and projects cranially, hanging over the primitive heart
b. **Tailfold** – folding of the caudal end because of the caudal and dorsal growth of the neural tube. The primitive streak moves from cranial to the caudal position after folding takes place

- **Transverse folding/flexion** – the embryo detaches from its embryonic membranes, attached only by the umbilical cord. It produces the right and left lateral folds since the two lateral parts of the body roll inwards towards the midline

Regionalization of the Brain

The neural tube initially gives rise to three primary vesicles, which further divide into five primary vesicles that give us the fully formed brain and spinal cord.

The three primary vesicles and two flexures develop in the 4th week.

- **Three vesicles**

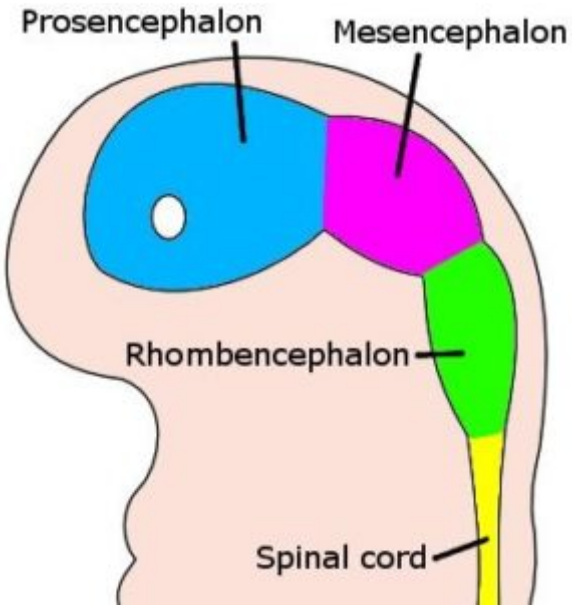


Image: “Brain of a four-week-old human embryo.” by Kurzon – Own work. License: Public Domain

a. Prosencephalon – forebrain
b. Mesencephalon – midbrain
c. Rhombencephalon – hindbrain

- Five primary vesicles, derived from the three primary vesicles

a. Prosencephalon: telencephalon and diencephalon
b. Mesencephalon remains as it is
c. Rhombencephalon: metencephalon and myelencephalon

- Adult brain structures derived from the five primary vesicles

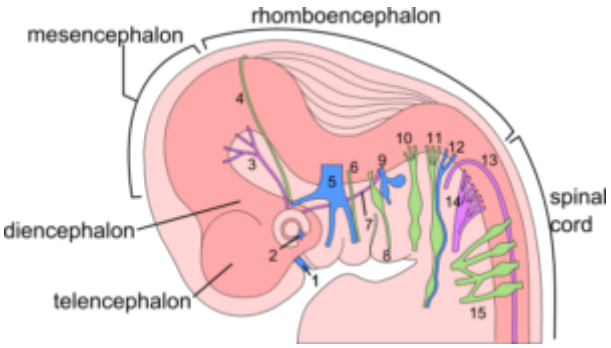


Image: "A diagram showing the brain and major nerves of a 6-week old human embryo. 1. olfactory 2. optic 3. oculomotor 4. trochlear 5. trigeminal sensory 6. trigeminal motor 7. abducens 8. facial 9. vestibulocochlear 10. glossopharyngeal 11. vagus 12. cranial accessory 13. spinal accessory 14. hypoglossal 15. cervical I, II, III, and IV" by Kurzon – Own Work. License: Public Domain

a. Telencephalon – cerebral hemisphere, caudate, putamen, amygdaloid, hippocampus, claustrum, olfactory bulbs, and lateral ventricles
b. Diencephalon – thalamus, hypothalamus, subthalamus, epithalamus (also known as pineal gland), retina, optic, mammillary bodies, neurohypophysis, optic chiasm, optic tract nerve, as well as the third ventricle
c. Mesencephalon – midbrain and the cerebral aqueduct
d. Metencephalon – pons, cerebellum, and the fourth ventricle
e. Myelencephalon – medulla, spinal cord, and the central canal

Note: all ventricles are derived from the neural canal remnant.

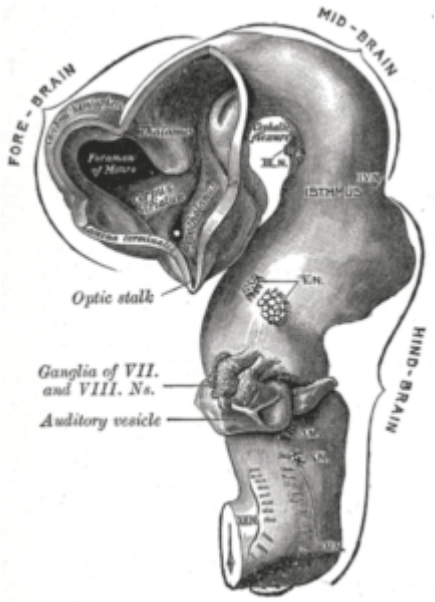


Image: "The Cephalic Flexure." by Henry Vandyke Carter, Henry Gray (1918) Anatomy of the Human Body. Bartleby.com: Gray's Anatomy, Plate 651. License: Public Domain

Cephalic flexure, also called the midbrain flexure, occurs between the prosencephalon and rhombencephalon, whereas the **cervical flexure** is located between the prosencephalon and the future spinal cord. **The pontine flexure** is the junction between the metencephalon and myelencephalon.

The cephalic flexure helps bend the forebrain over the anterior part of the notochord and foregut, so the floor of the forebrain is on the same level as the hindbrain. Due to the cephalic flexure, the midbrain temporarily holds the most dorsal and prominent position in the embryo.

Birth Defects of the Brain

Microcephaly

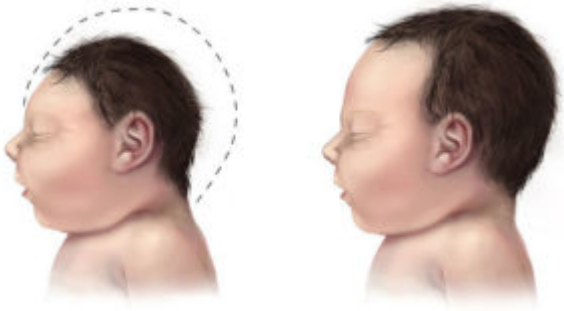


Image: "Side-view illustration of a baby with microcephaly (left) compared to a baby with typical head size." by Centers for Disease Control and Prevention. License: Public Domain

This is a developmental disorder in which the brain and **calvaria** are small in size with a normal size face. It presents at birth or a few months later. The infant has severe **neurological deficits,** like seizures, along with decreased cognitive, speech, and motor functions. Dwarfism may also be present.

Primary microcephaly is autosomal recessive. However, various external etiologies have been linked to microcephaly onset. These include exposure to radiation, infections by viruses such as rubella, cytomegalovirus, and the Zika virus. Maternal alcohol abuse during pregnancy is also a known cause.

Encephalocele

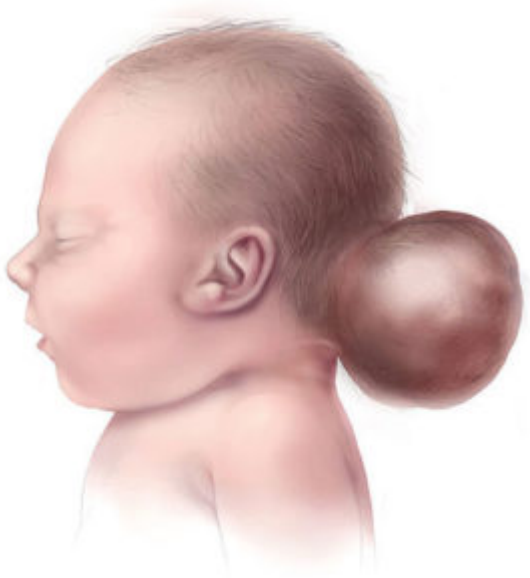


Image: "Illustration of a Baby with Encephalocele." by the Centers for Disease Control and Prevention – License: CC0

Also known as **cranium bifidum**, this condition is a neural tube defect in which the brain and its membranes herniate out through defects in the cranium, usually in the occipital region. It occurs once in every 2,000 births. There are three types of encephalocele:

a. **Meningocele**: the herniation only contains the meninges. The sac is filled with CSF (cerebrospinal fluid).
b. **Meningoencephalocele**: the herniation includes the meninges as well as a part of the brain. The herniation is filled with CSF. Diagnosed with MRI.
c. **Meningohydroencephalocele**: herniation includes the meninges, a part of the brain as well as the part of the ventricular system.

Germ Layers and Their Derivatives

The **ectoderm** is the most distal/outer layer of the gastrula.

The ectoderm can be divided into two categories:

1. **Surface ectoderm**, which forms the epidermis (skin), nails, hair, eye lens, teeth enamel, inner and external ear structures, and the anterior pituitary (which is derived from the **Rathke's pouch**).
2. **Neuroectoderm**, which is further divided into the neural tube and neural crest cell, forming the entire central and peripheral nervous systems.

The structures derived from the neural tube are as follows:

- **Central nervous system** (brain and spinal cord)
- **Neurohypophysis** (posterior pituitary)

- **Oligodendrocytes** (myelinating cells of the CNS)
- **Pineal gland**
- **Retina and optic nerve** (although optic nerve is considered to be a cranial nerve, it is, in fact, an extension of the diencephalon; therefore, its involvement is seen as optic neuritis in multiple sclerosis, a demyelinating disease of the CNS)
- **Astrocytes**

The structures derived from the neural crest cells are as follows:

1. **Adrenal medulla**
2. **Sensory and autonomic (postganglionic) ganglia**
3. **Pharyngeal arch cartilage**
4. **Melanocytes** (pigment cells) – neural crest cells migrate to the stratum basalis of the skin epidermis
5. **Schwann cell** (myelinating cells of the PNS)
6. **Meninges** – arachnoid and pia mater, whereas the dura mater is derived from the mesoderm

Neural crest cells also play an important role in the development of the **aorticopulmonary septum.** A defect can lead to congenital heart diseases, like **Tetrology of Fallot**. If the cells do not migrate to the first pharyngeal arch, then **first arch syndromes** with craniofacial abnormalities, like **Treacher Collins syndrome** and **Pierre Robin syndrome,** may occur.

The mesoderm forms the muscles, bones, cartilage, blood vessels, and all serous membranes of the body and connective tissue layers of the peripheral nerves, known as the **endoneurium**, **perineurium,** and **epineurium**.

The endoderm forms the body's epithelial linings and the parenchyma of various viscera, such as the liver, pancreas, thyroid, and salivary glands.

Development of the Cranium

Neurocranium – bones that encase the brain.

Viscerocranium – bones that make up the facial features, which are derived from the pharyngeal arches.

The skull develops from the mesenchyme that surrounds the brain. **Desmocranium mesenchyme** is the primordium of the cranium and the ossification centers within the desmocranium, initiating cranium formation.

Transforming growth factors beta (TGF- β) are very important molecules that regulate osteoblast differentiation and lead to cranium formation.

The neurocranium can be divided into the cartilaginous neurocranium and the membranous neurocranium.

Cartilaginous neurocranium

The fusion of numerous cartilages creates a cartilaginous base, which, after ossification, forms the base of the cranial bones. For example, the base of the occipital bone is derived from the parachordal cartilage, which forms around the cranial end of the notochord and fuses with the surrounding cartilage to form the base of the occipital bone.

It later expands and forms the boundaries of the **foramen magnum**.

Similarly, hypophysial cartilage forms alongside the developing pituitary and later gives rise to the sphenoid bone body. **Trabeculae cranii** give rise to the body of the **ethmoidal bone,** whereas ala orbit fuse together to form the lesser wing of the sphenoid.

Membranous neurocranium

This forms the **calvaria**, also known as the skull cap. It occurs on the top and sides of the head. Calvaria sutures are dense connective tissue membranes found between the bones of the calvaria. **Fontanelles** are where sutures meet. Fontanelles, along with the soft bones of the calvaria, allow the fetal cranium to mold during birth.

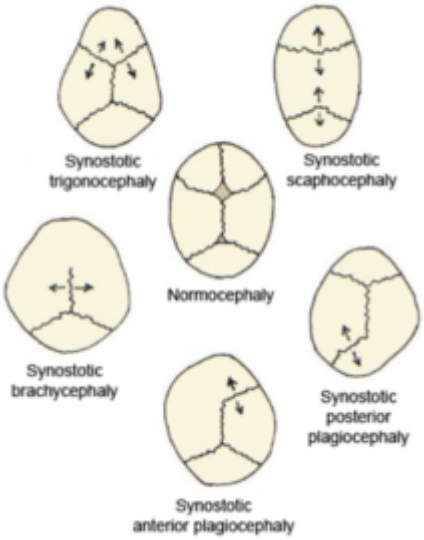


Image: “Skull Deformities Associated with Single Suture Synostosis.” by Xxjamesxx – Own Work. License: CC BY-SA 3.0

The **sutures’** flexibility allows the brain to grow and develop after birth. The most rapid postnatal growth of the brain occurs in the first two years. Calvaria growth continues until the age of 16, followed by 3-4 years of thickening of the bones.

Cranial Birth Defects

Premature closing of sutures can give rise to the following cranial defects:

- **Scaphocephaly**: early closure of the sagittal suture
- **Brachycephaly**: early closure of the coronal suture
- **Plagiocephaly**: the coronal suture closes early on one side
- **Trigonocephaly**: premature closure of the frontal suture

References

Keith L. Moore. (2013). The developing human 9th edition. Philadelphia: Elsevier Inc.

Embryonic Folding and Flexion of The Embryo via lifemapsc.com

Brain regionalization: Of signaling centers and boundaries via wiley.com

Notes