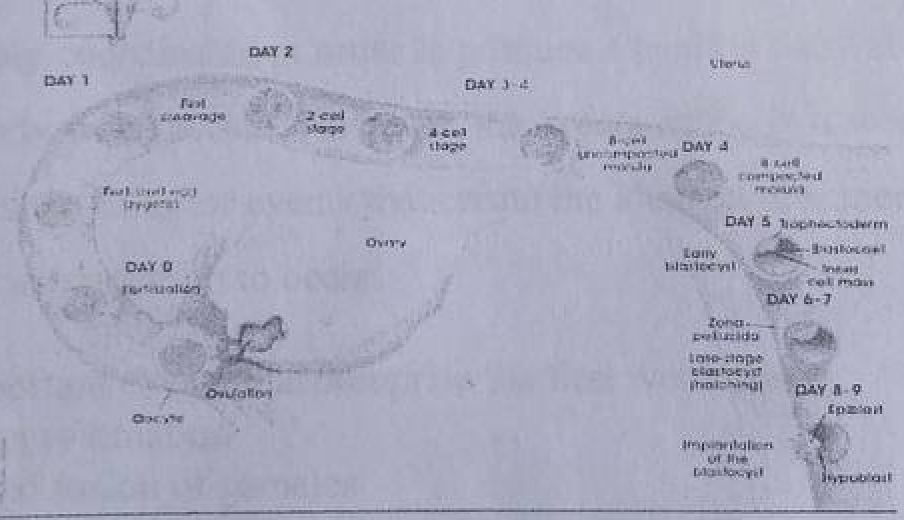
① أمبريو ١

EMBRYOLOGY1

Human embryogenesis is a complicated process by which the fertilized egg develops into an embryo it's the branch of biology that studies the development of gametes (sex cells), fertilization, and development of embryos and fetuses . Additionally, embryology is the study of congenital disorders that occur before birth.

Human embryology is the study of this development during the first eight weeks after fertilization. The normal period of gestation (pregnancy) is nine months or 38 weeks. Embryogenesis covers the first eight weeks of development; at the beginning of the ninth week the embryo is termed a fetus .

In comparison to the embryo, the fetus has more recognizable external features and a more complete set of developing organs.During the first eight weeks of development, the concepts shifts from a single-celled zygote into a multi-leveled, multi-dimensional fetal body plan which utilizes primitively functioning organs.



The female reproductive system

The female reproductive system is made up of the internal and external sex organs that function in human reproduction. These organs are involved in the production and transportation of gametes and the production of sex hormones. The female reproductive system also facilitates the fertilization of ova by sperm and supports the development of offspring during pregnancy and infancy.The female reproductive system is immature at birth and develops to maturity at puberty to be able to produce gametes, and to carry a fetus to full term.

The human female reproductive system performs the following functions
a) Formation of eggs
b) Reception of sperms during copulation
c) Providing a conducive environment for fertilization
d) Providing shelter and nourishment to the growing embryo

The first week of embryonic development is filled with an eclectic arrangement of physical and biochemical changes. Each step is a part of a cascade of events that must be intricately coordinated in order to produce a healthy baby at the end of the thirty eight to forty week period. However, the events of the first week of gestation are highly dependent on prior events that create the ideal environment for fertilization and implantation to occur.

Some of the important events that comprise the first week are:

- Gamete approximation
- Contact and fusion of gametes
- Fertilization
- Mitotic cleavage of the blastomeres
- Morula formation
- Blastocyst formation
- Implantation of the blastocyst

At puberty, the female begins to undergo regular monthly cycles controlled by the hypothalamus which secretes gonadotropins. These hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), stimulate and control cyclic changes in the ovary.At the beginning of each ovarian cycle, 15 to 20, follicles are stimulated to grow under the influence of FSH. Under normal conditions, only one of these follicles reaches full maturity, and only one oocyte is discharged; the others degenerate and become atretic. When a follicle becomes atretic, the oocyte and surrounding follicular cells degenerate and are replaced by connective tissue.

Ovulation

In the days immediately preceding ovulation, under influence of FSH and LH, the follicle grows rapidly to become a mature vesicular ***graafian follicle***,the surface of the ovary begins to bulge locally, Before ovulation, the oocyte and some cells of the cumulus oophorus (*Cumulus oophorus is a cluster of cells that surround the oocyte both in the ovarian follicle and after ovulation*) dettach from the inside of the distended follicle.

At ovulation, there is a "surge" of LH release, the stigma balloons out, forming a surface vesicle, then it ruptures, expelling the oocyte with follicular fluid.

The oocyte is covered by the zona pellucida and one or more layers of follicular cells which radially arrange themselves as the corona radiate.

After ovulation the follicle turns into the corpus luteum which is made up of large conical yellowish cells. Corpus luteum serves as a temporary endocrine gland, by releasing female sex hormones namely progesterone and estrogen. The corpus luteum reaches máximum development approximately 9 days after ovulation. It can easily be recognized as a yellowish projection on the surface of the ovary. Subsequently, the corpus luteum shrinks and forms a mass of fibrotic scar tissue, the Corpus albicans.

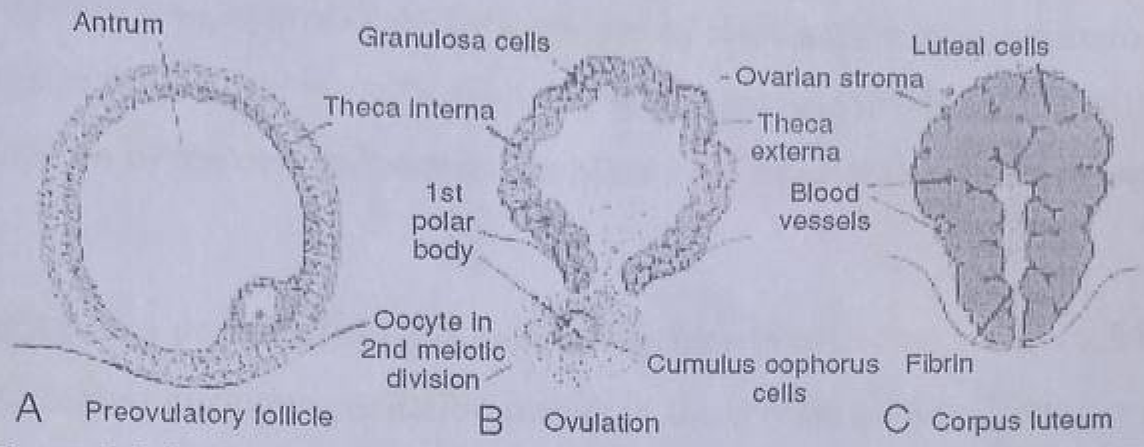


Figure 2.2 A. Preovulatory follicle bulging at the ovarian surface. **B.** Ovulation. The oocyte, in metaphase of meiosis II, is discharged from the ovary together with a large number of cumulus oophorus cells. Follicular cells remaining inside the collapsed follicle differentiate into lutean cells. **C.** Corpus luteum. Note the large size of the corpus luteum, caused by hypertrophy and accumulation of lipid in granulosa and theca interna cells. The remaining cavity of the follicle is filled with fibrin.

While the follicle and ovum are maturing, the follicle secretes hormones that prepare the uterine lining (the endometrium). The endometrium gets thicker and is well supplied with blood vessels.If fertilization does not occur, or for any other reason a blastocyst (future embryo) fails to implant within the endometrium, the built-up endometrial lining degenerates .

The egg that is released is picked up by the fimbriae of the uterine tube(*fingerlike projections at the end of the fallopian tubes, through which eggs move from the ovaries to the uterus*), and the egg is transported toward the uterus. If fertilization does not occur, the egg degenerates, and menstruation occurs.

Fertilization

Fertilization is commonly known as conception ,is a process by which male and female gametes fuse, occurs in the ampulary region of the uterine tube(*the widest part of the tube and is close to the ovary*). Once the fertilized gamete (ovum) implants itself in the uterine lining, pregnancy begins. The process of fertilization occurs in several steps and the interruption of any of them can lead to failure.

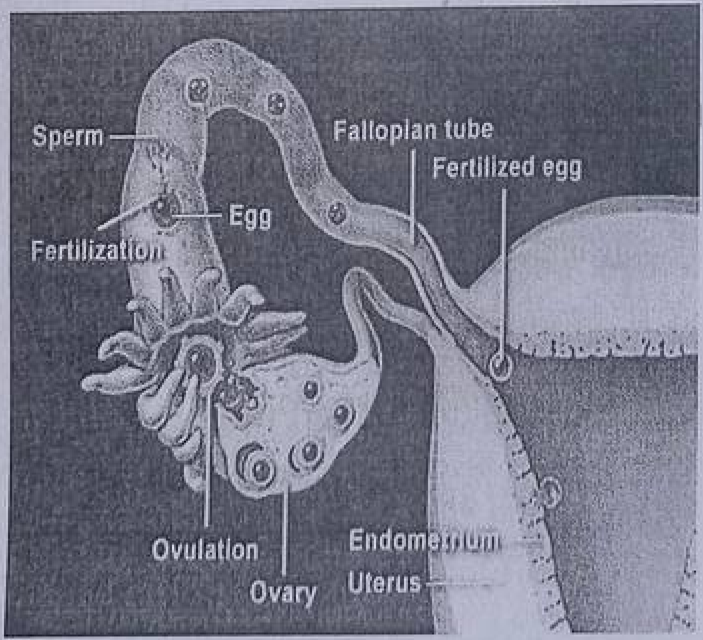
Prior to fertilization, sperm undergo a process of capacitation in response to conditions in the female reproductive tract, which include increases in motility and destabilization of the cell membrane that allows the head of the sperm to penetrate the egg.

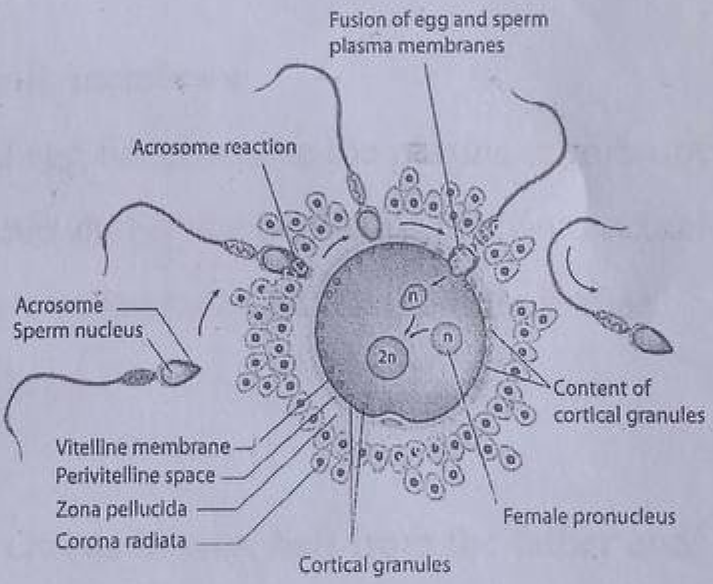
Capacitation is a period of conditioning in the female reproductive tract .Much of this conditioning during capacitation occurs in the uterine tube and involves epithelial interactions between the sperm and the mucosal surface of the tube..

Only capacitated sperm can pass through the corona cells and undergo the acrosome reaction.

Acrosome reaction

The acrosome reaction, which occurs after binding to the zona pellucida, is induced by zona proteins. This reaction culminates in the release of enzymes needed to penetrate the zona pellucida, including acrosin- and trypsin-like substances .





Phases of fertilization :

PhaseI: Penetration of the corona radiata

Of the 200 to 300 million spermatozoa deposited in the female genital tract,only 300 to 500 reach the site of fertilization. Only one of these fertilizes the egg. It is thought that the others aid the fertilizing sperm in penetrating the barriers protecting the female gamete. Capacitated sperm pass freely through corona cells

.**PhaseII** : Penetration of the zona pellucida

The zona is a glycoprotein shell surrounding the egg that facilitates and maintains sperm binding and induces the acrosome reaction. Release of acrosomal enzymes (acrosin) allows sperm to penetrate the zona, thereby coming in contact with the plasma membrane of the oocyte.Permeability of the zona pellucida changes when the head of the sperm comes in contact with the oocyte surface. This contact results in release of lysosomal enzymes from cortical granules lining the plasma membrane of the oocyte.In turn, these enzymes alter properties of the zona pellucida (zona reaction).

PhaseIII :Fusion of oocyte and sperm cell membrane

The plasma membranes of the sperm and egg fuse,because the plasma membrane covering the acrosomal head cap disappears during the acrosome reaction, actual fusion is accomplished between the oocyte membrane and the membrane that covers the posterior region of the sperm head.

Results of fertilization :

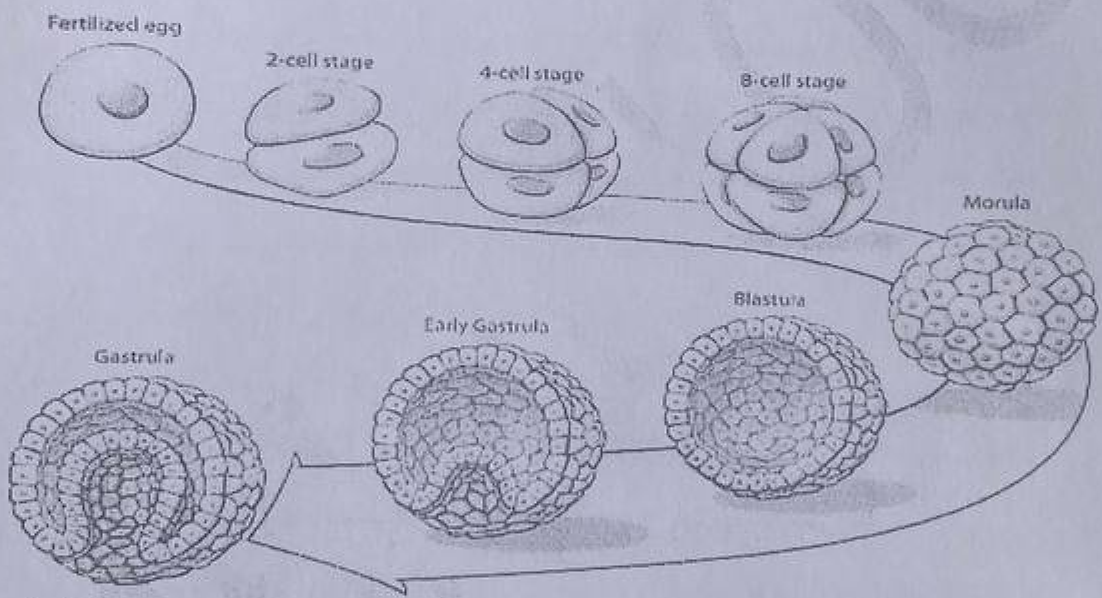
A- Restoration of the diploid number of chromosomes, half from the father and half from the mother. Hence, the zygote contains a new combination of chromosomes different from both parents.

B -Determination of the sex of the new individual. An X-carrying sperm produces a female (XX) embryo, and a Y-carrying sperm produces a male

(XY) embryo. Hence, the chromosomal sex of the embryo is determined at fertilization.

C- Initiation of cleavage :

Following fertilization a series of rapid cell divisions called cleavage occur with no significant growth and decrease the cells' size with each subsequent division and produces a cluster of cells that is the same size as the original zygote. At least four initial cell divisions occur, resulting in a dense ball of at least sixteen cells called the morula. The different cells derived from cleavage, up to the blastula stage, are called blastomeres.



Cell Cleavage
Process by which the number of cells in a developing embryo is multiplied through cell division.

EMBRYOLOGY امبريو محاضرة ٢ ، تكوين

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EMBRYOLOGY2

Second week of development

The second week of human development is concerned with the process of implantation and the differentiation of the blastocyst into early embryonic and مشيمة placental forming .structures

Morula

: During the first week the zygote undergoes cleavage divisions, which is

Theprocess by which the zygote rapidly divides without any increase in the size it ➢ .)becomes multicellular(cells are termed blastomeres

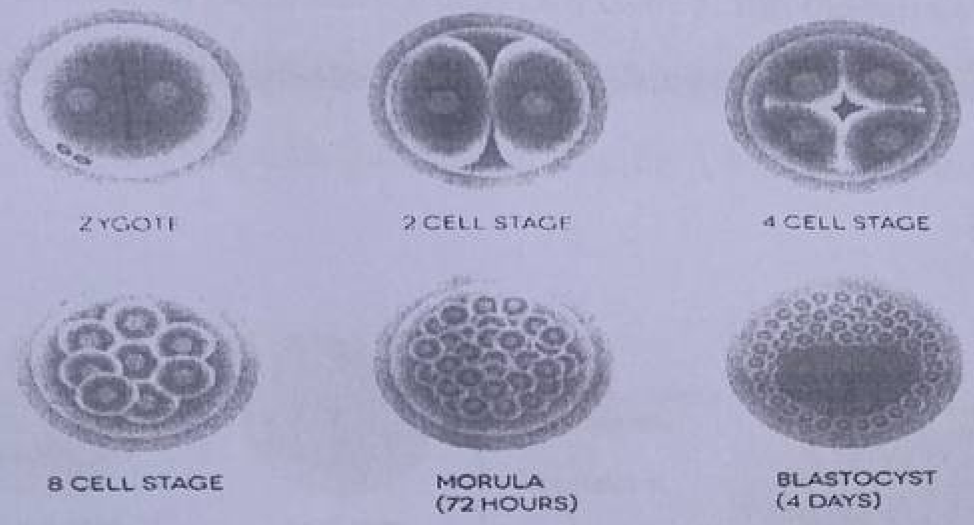
Firstdivision occurs about a day after fertilization ,and subsequent divisions ➢ occur every 12-24hrs after that. When the cell's number is around sixteen the solid sphere of cells within the zona pellucida is referred to as a *morula*

Aboutthe time the morula enters the uterine cavity, fluids begin t o penetrate ➢ . through the zona pellucida into the intercellular spaces of the inner cell mass

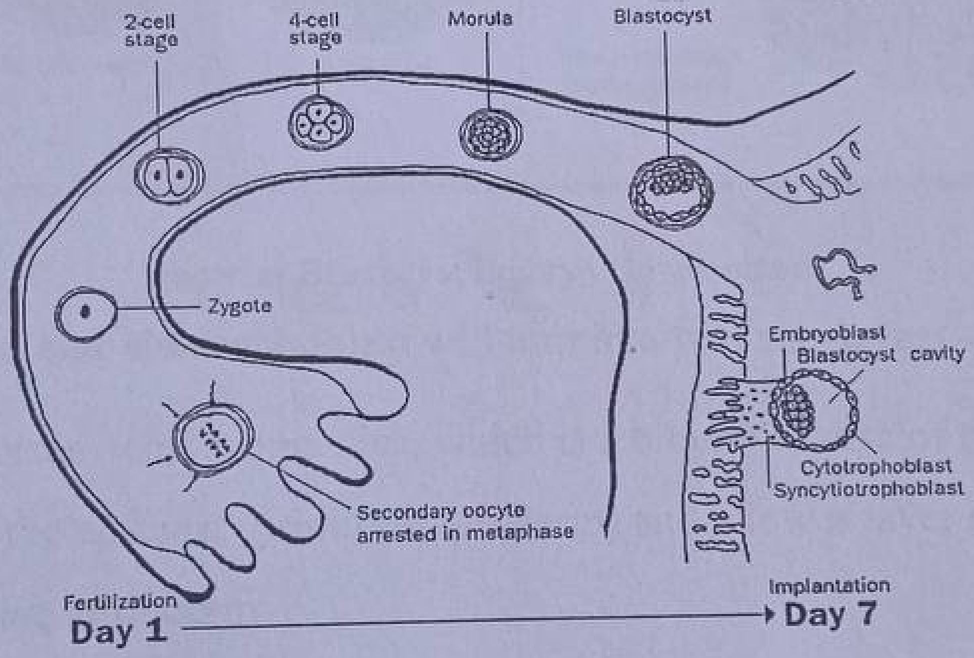
Gradually,the intercellular spaces become confluent, and finally, a single cavity, ➢ . the blastocole forms

Cleavagecontinues as cellular differentiation . and then a blastocyst, consisting of ➢ . embryoblast and trophoblast

Duringthis week development is predominately associated with implantation of ➢ the blastocyst into the uterine wall to establish a source of nutrition. As it migrates towards the uterus, the zona pellucida surrounding the blastocyst prevents direct contact with the epithelial ظهان lining of the fallopian tubes, ensuring implantation in .approximately 99% of pregnancies will occur within the uteru



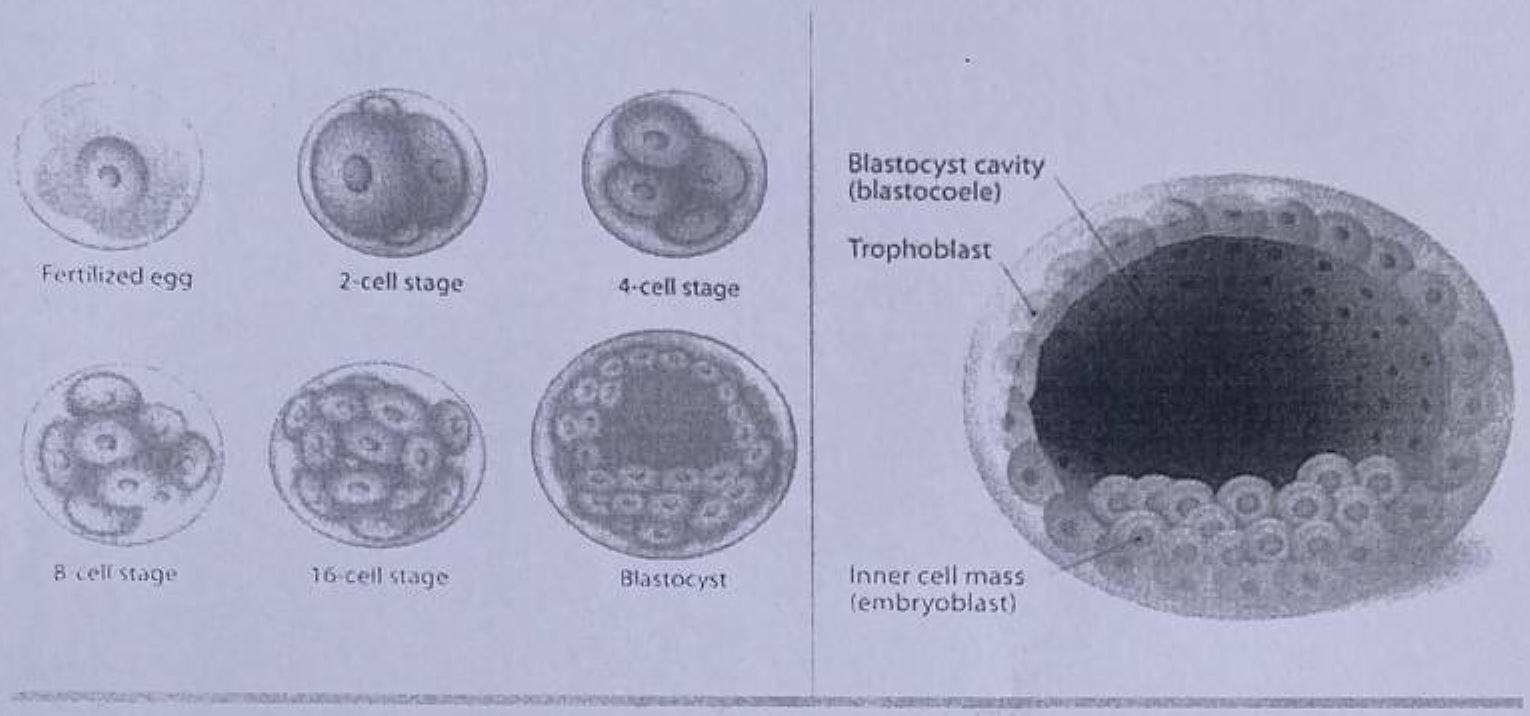
Once the blastocyst enters the uterus, the zona pellucida degenerates to expose the underlying trophoblast layer, thus enabling it to attach to the endometrium.



Blastulation(Blastocyst formation)

The blastocyst possesses an inner cell mass (ICM) which subsequently forms the embryo. The outer layer of the blastocyst consists of cells collectively called the trophoblast. This layer surrounds the inner cell mass and a fluid-filled cavity known as the blastocoel.

Cells differentiate into an outer layer of cells called the trophoblast and an inner cell mass. The inner mass of cells differentiate to become embryoblasts and polarise at one end. They close together and form gap junctions, which facilitate cellular communication. This polarisation leaves a cavity, the blastocoel, creating a structure that is now termed the blastocyst. The resulting increase in size of the blastocyst causes it to hatch through the zone pellucida , which then disintegrates.



Stages of Blastocyst Embryo Development

The embryoblast and the trophoblast will turn into two sub-layers.

- Theembryoblast forms embryonic disc, which is a bilaminar disc of two layers, an upper layer called the epiblast (primitive ectoderm) and a lower layer called the . (hypoblast(primitive endoderm

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- Thedisc is stretched between what will become the amniotic cavity and the yolk : sac.The trophoblast will develop two sub-layers

Cytotrophoblast

Syncytiotrophoblas

- Implantation:afterovulation, the endometrial lining becomes thickened, with its secretory glands becoming elongated, and is increasingly vascular in preparation for accepting the embryo. The placenta develops once the blastocyst is implanted, .connecting the embryo to the uterine wal

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EMBRYOLOGY

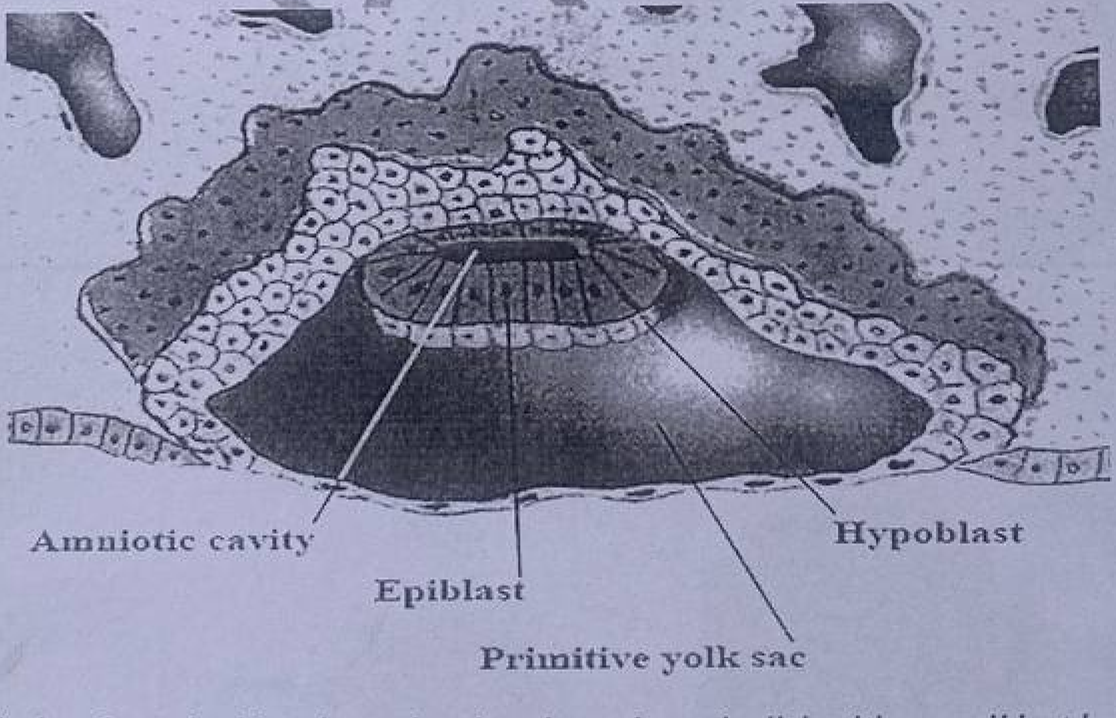
EMBRYOLOGY3

Third week of development

During the third week of human development the embryo forms all three of it's layers of endoderm, mesoderm, and ectoderm through gastrulation. The notochord also develops, which forms the midline axis, and the cephalic and caudal ends of the embryo develop.

From zygote to blastocyst formation, the surrounding zona pellucida, which is a layer of the extracellular matrix that plays a role in the protection and prevention of implantation into the uterine tubes. During blastocyst formation, the zona pellucida begins to disappear from the blastocyst, allowing the ball of cells to proliferate, differentiate, change shape, and eventually implant into the uterine wall.

Development of the bilaminar disc directly precedes gastrulation, where the end goal during week 3 of development is to transform the human blastocyst into a multilayered gastrula with endoderm, mesoderm, and ectoderm.



drawing of a late 2-week-old embryo showing the embryonic disk with an epiblast layer and a the hypoblast below it. This is the bilaminar embryo just before gastrulation.

Gastrulation:

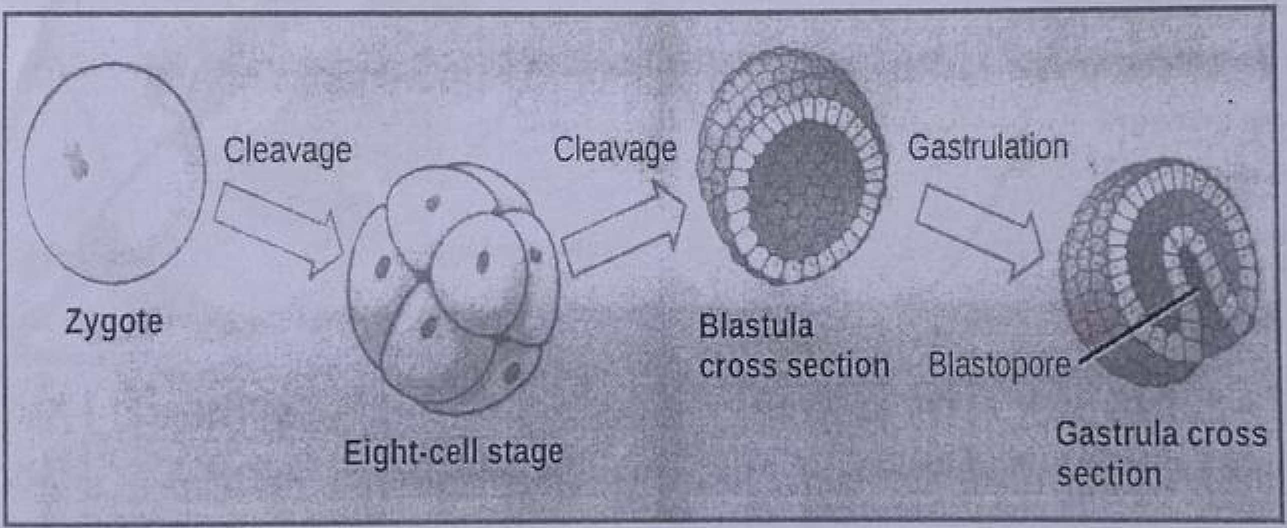
Gastrulation takes place after cleavage and the formation of the blastula and the primitive streak. It is followed by organogenesis, when individual organs develop within the newly-formed germ layers. Each layer gives rise to specific tissues and organs in the developing embryo.

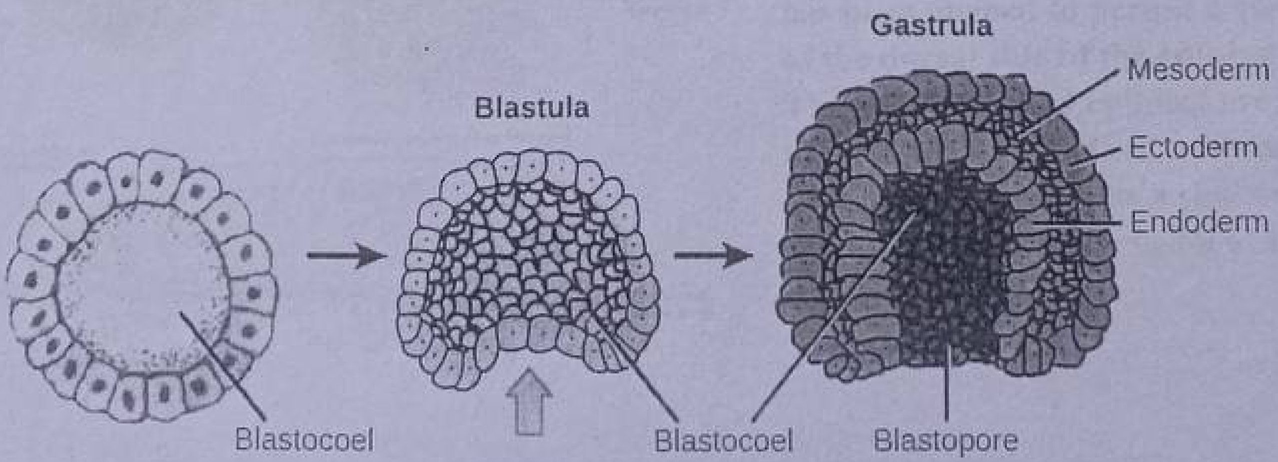
Gastrulation occurs in the following sequence:

a-The embryo becomes asymmetric.

b-The primitive streak forms.

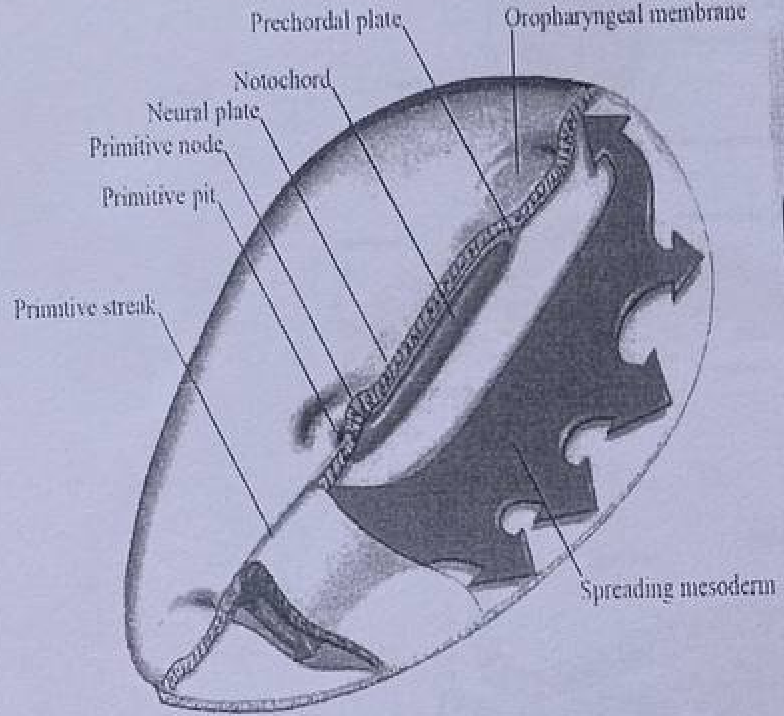
c-Cells from the epiblast at the primitive streak undergo an epithelial to mesenchymal transition and ingress at the primitive streak to form the germ layers.

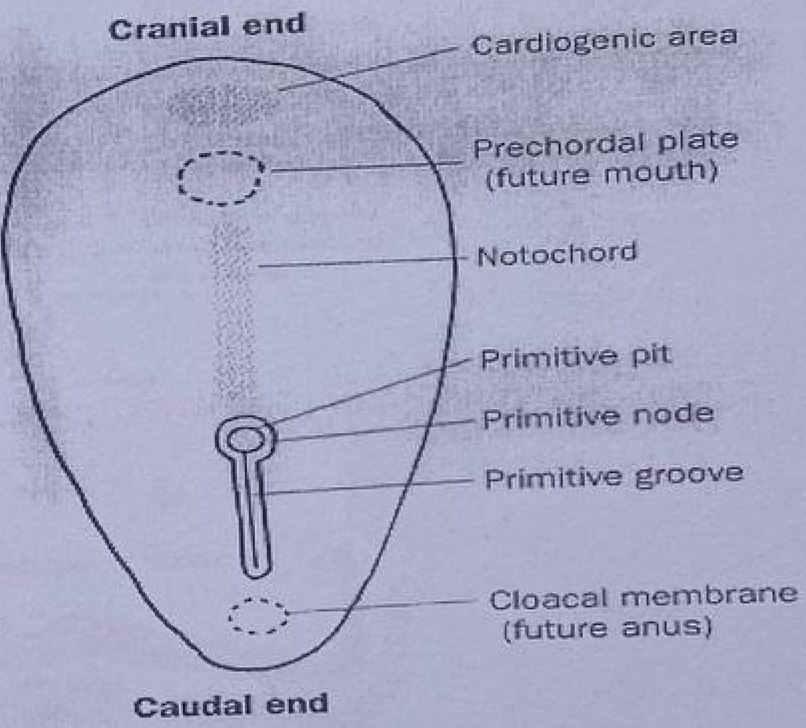


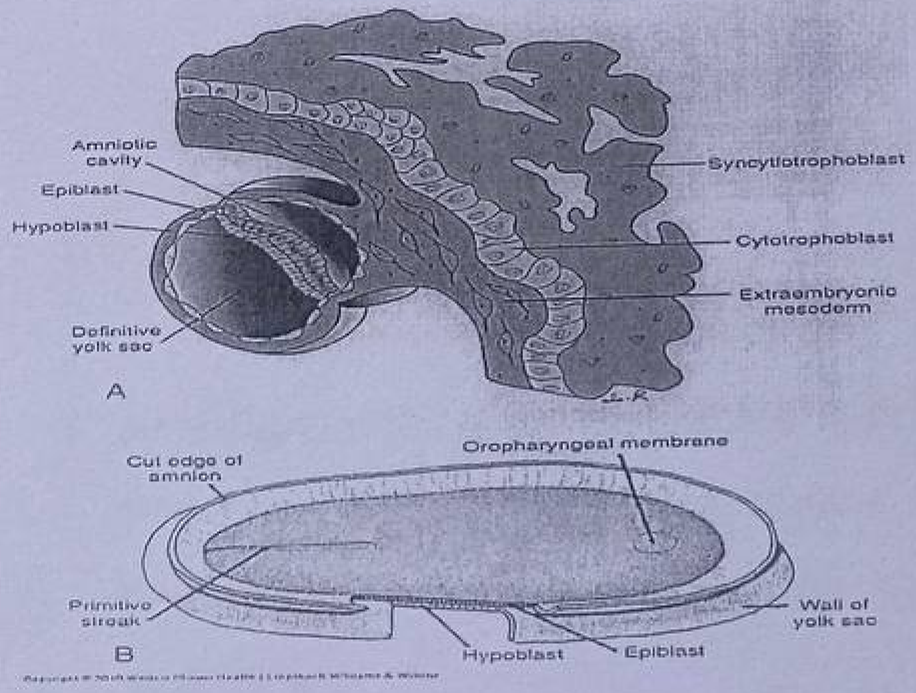


Primitive streak:

It is the first sign of gastrulation appears near the end of 2nd week and it appears by the 15th-16th day as a thickened linear band in the caudal end of the dorsal aspect of the embryonic disk. It's appearance enables identification of embryonic axes, cranial and caudal ends, top and bottom surfaces, and sides of the embryo. The cephalic end of the streak, the primitive node, consists of a slightly elevated area surrounding the small primitive pit.

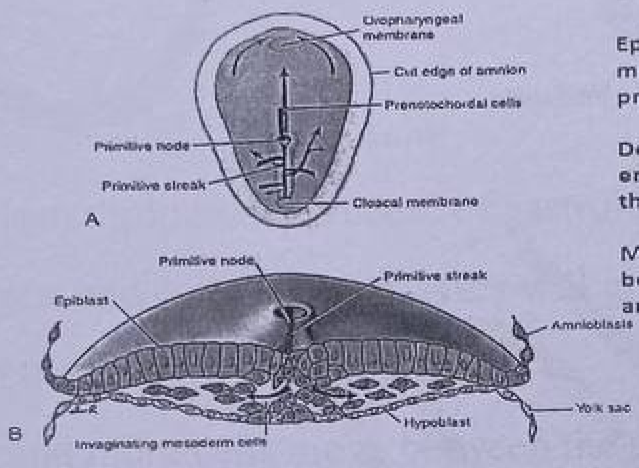






A.Implantation site at the end of the second week.
B. View of the germ disc at the end of the second week of development. The amniotic cavity has been opened to permit a view of the dorsal side of the epiblast. The hypoblast and epiblast are in contact with each other, and the primitive streak forms a shallow groove in the caudal region of the embryo.

- Cells of the epiblast migrate toward the primitive streak . Upon arrival in the region of the streak, they become flask-shaped, detach from the epiblast, and slip beneath it .
- Some cells displace the hypoblast, creating the embryonic endoderm, and others come to lie between the epiblast and newly created endoderm to form mesoderm. Cells remaining in the epiblast then form ectoderm.



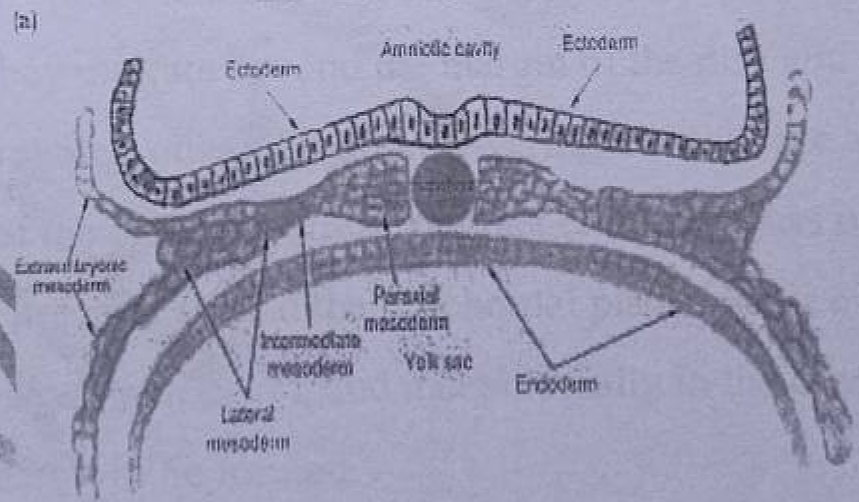
Langman's fig 5.3

Gastrulation:

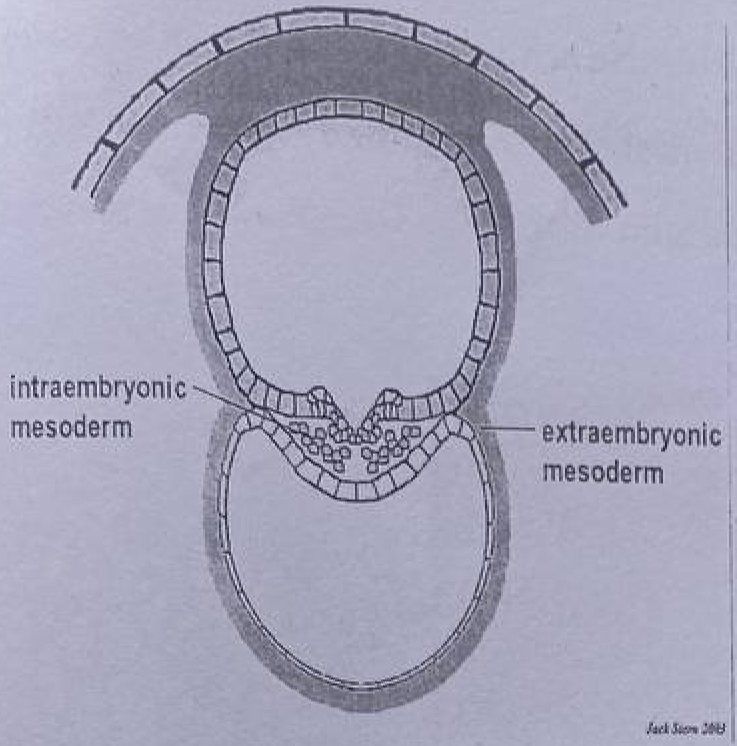
Epiblast cells migrate through the primitive streak.

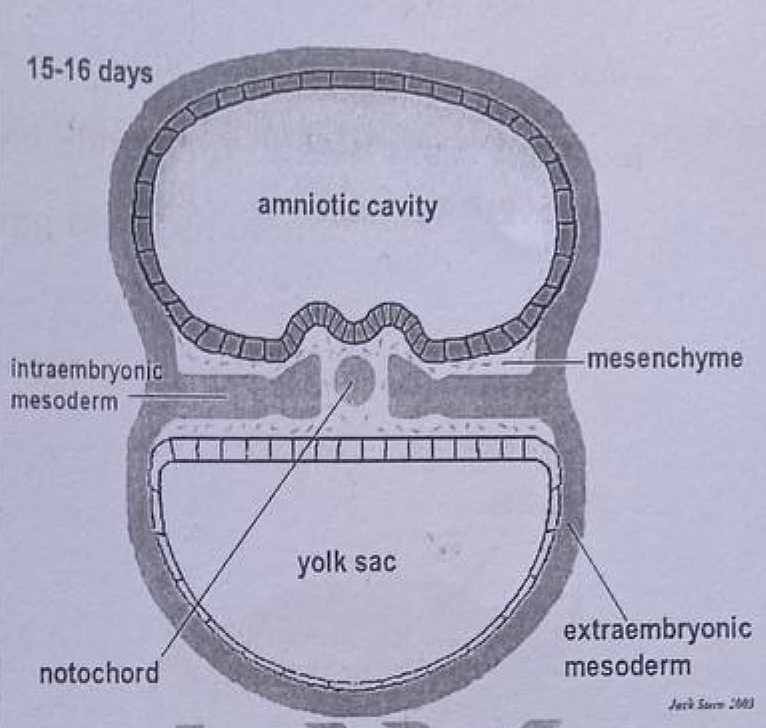
Definitive (embryonic) endoderm cells displace the hypoblast.

Mesoderm spreads between endoderm and ectoderm.



- At about day 16 cells of the epiblast migrate medially toward the streak, enter the primitive groove, then migrate laterally between the embryonic ectoderm and endoderm to organize into a layer, the <u>intraembryonic mesoderm</u> .
- Mesoderm also lies outside the embryo as <u>extra-embryonic mesoderm.</u>





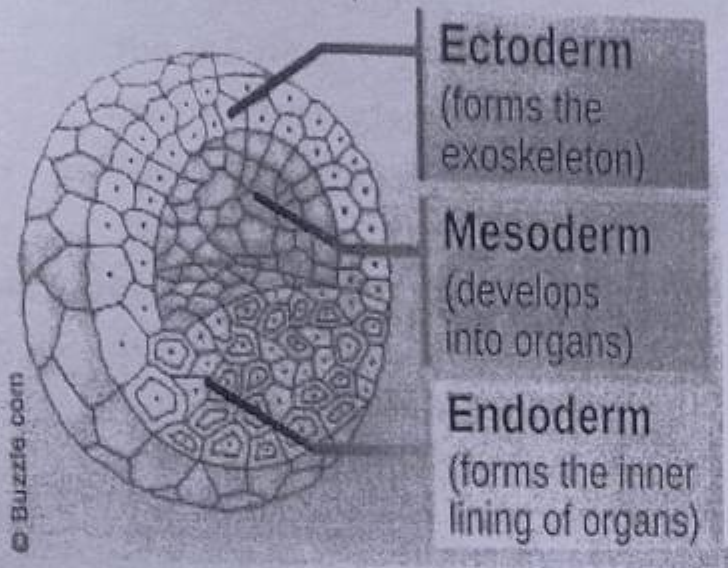
- The epiblast, through the process of gastrulation, is the source of all of the germ layers, and cells in these layers will give rise to all of the tissues and organs in the embryo.
- As more and more cells move between the epiblast and hypoblast layers, they begin to spread laterally and cranially .
- Gradually, they migrate beyond the margin of the disc and establish contact with the extraembryonic mesoderm covering the yolk sac and amnion.
- Some cells of the primitive streak migrate cranially, pass on each side of the notochordal process, around the prochordal plate(*small circular area of columnar endodermal cells*), and meet cranially in the cardiogenic area where the heart will be formed.

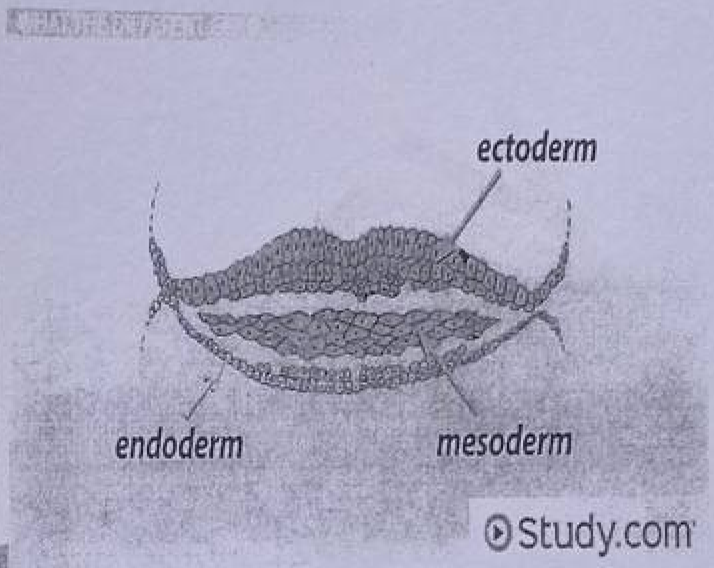
By the middle of week 3, intraembryonic mesoderm separates the ectoderm and endoderm everywhere except at :

a- oropharyngeal membrane cranially

b- cloacal membrane caudally

c- in the midline, cranial to the primitive knot where the notochordal process extends, because embryonic ectoderm and endoderm fuse at these sites and prevent mesenchymal cells from migrating between them.





Growth of the embryonic disc

- The embryonic disc, initially flat and almost round, gradually becomes elongated, with a broad cephalic and a narrow caudal end . Growth and elongation of the cephalic part of the disc are caused by a continuous migration of cells from the primitive streak region in a cephalic direction.
- Invagination of surface cells in the primitive streak and their subsequent migration forward and laterally continues until the end of the fourth week.
- At that stage, the primitive streak shows regressive changes, rapidly shrinks, and soon disappears.
- In the cephalic part, germ layers begin their specific differentiation by the middle of the third week, whereas in the caudal part, differentiation begins by the end of the fourth week.
- Gastrulation, or formation of the germ layers,continues in caudal segments while cranial structures are differentiating, causing the embryo to develop cephalocaudally.

Germ layers and their derivatives

Ectoderm gives rise to the

1- central nervous system (the brain and spinal cord)
2- the peripheral nervous system
3- the sensory epithelia of the eye, ear, and nose
4- the epidermis and its appendages (the nails and hair)
5- the mammary glands;
6- the pituitary gland
7- the subcutaneous glands
8- the enamel of the teeth

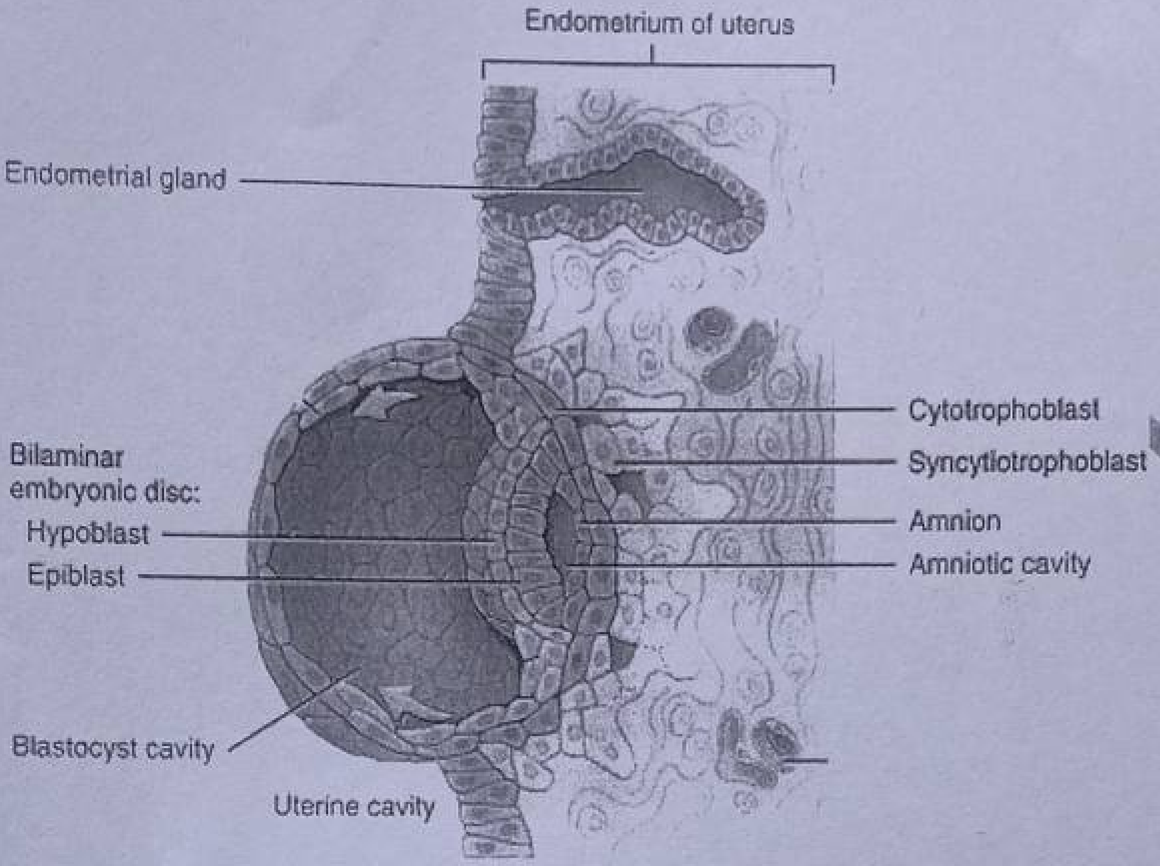
Mesoderm gives rise to

1- connective tissue
2- cartilage, and bone
3- striated and smooth muscles;
4- heart walls,
5- blood and lymph vessels and cells
6- kidneys
7- gonads (ovaries and testes) and genital ducts
8- the serous membranes lining the body cavities
9- the spleen
10- the adrenal cortices

Endoderm gives rise to :

1- epithelial lining of the gastrointestinal and respiratory tracts
2- the parenchyma of the tonsils, the liver, the thymus, the thyroid, the parathyroids, and the pancreas
3- the epithelial lining of the urinary bladder and urethra
4- the epithelial lining of the tympanic cavity, tympanic antrum, and auditory tube

5-Flexion takes the embryo from a flat disk to its basic embryonic body form. The primitive gut originates from endoderm at the time of its flexion.


Endometrium of uterus
Endometrial gland
Cytotrophoblast
Syncytiotrophoblast
Bilaminar embryonic disc:
Hypoblast
Epiblast
Amnion
Amniotic cavity
Blastocyst cavity
Uterine cavity

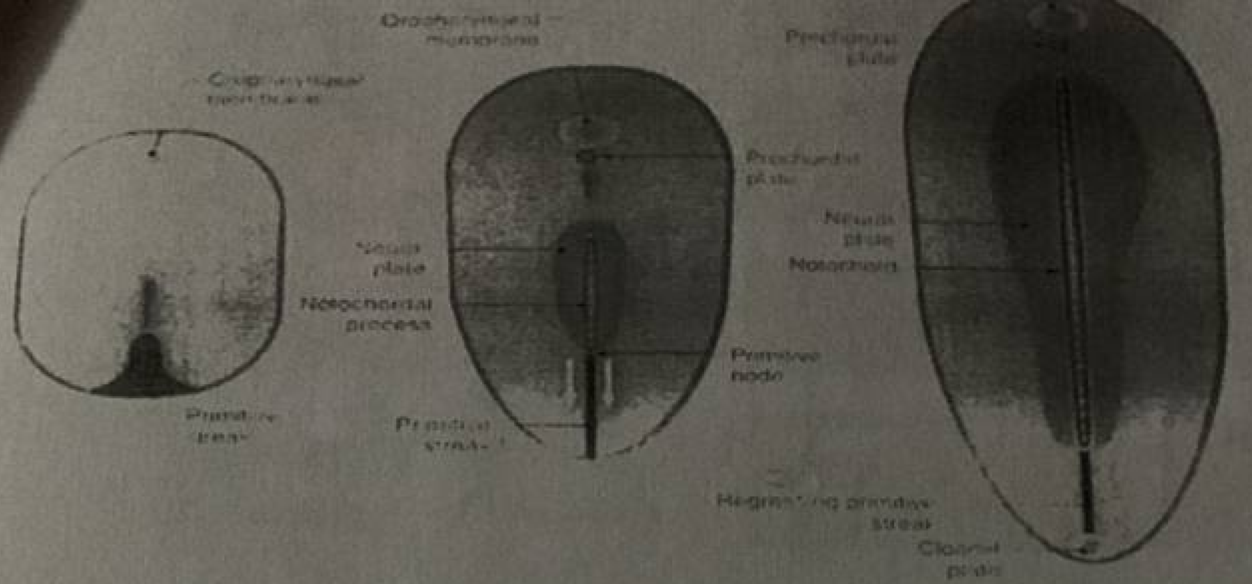
EMBRYOLOGY4

(Notochord development(Notogenesis) & Neurulation

Fourth week of embryonic development is the beginning of organogenesis (organogensis is usually extended to cover until 8 weeks of development as specific tissues and systems are beginning to differentiate from the trilaminar embryo.

Following gastrulation, the next major development in the embryo is neurulation, which occurs during weeks three and four after fertilization. This is a process in which the embryo develops structures that will eventually become the nervous system.Notochord development starts during gastrulation (3rd week) by the epiblasts where progenitor cells of notochord are derived start migrating from the primitive node and pit.

The notochord is a cellular rod that forms the first longitudinal midline axis around which the vertebral bodies are organized and is the basis for the axial skeleton. By day 12 or 13, the notochord is visible throughout the length of the embryo and around it are layered concentrations of cells, representing the primordia of the future vertebral bodies.



neural plate
shaping elongate
and depression
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and
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tube
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neural
crest

Neurulation refers to the folding process in vertebrate embryos, which includes the transformation of the neural plate into the neural tube. The embryo at this stage is termed the neurula. The neural plate folds in upon itself to form the neural tube, which will later differentiate into the spinal cord and the brain, eventually forming the central nervous system.

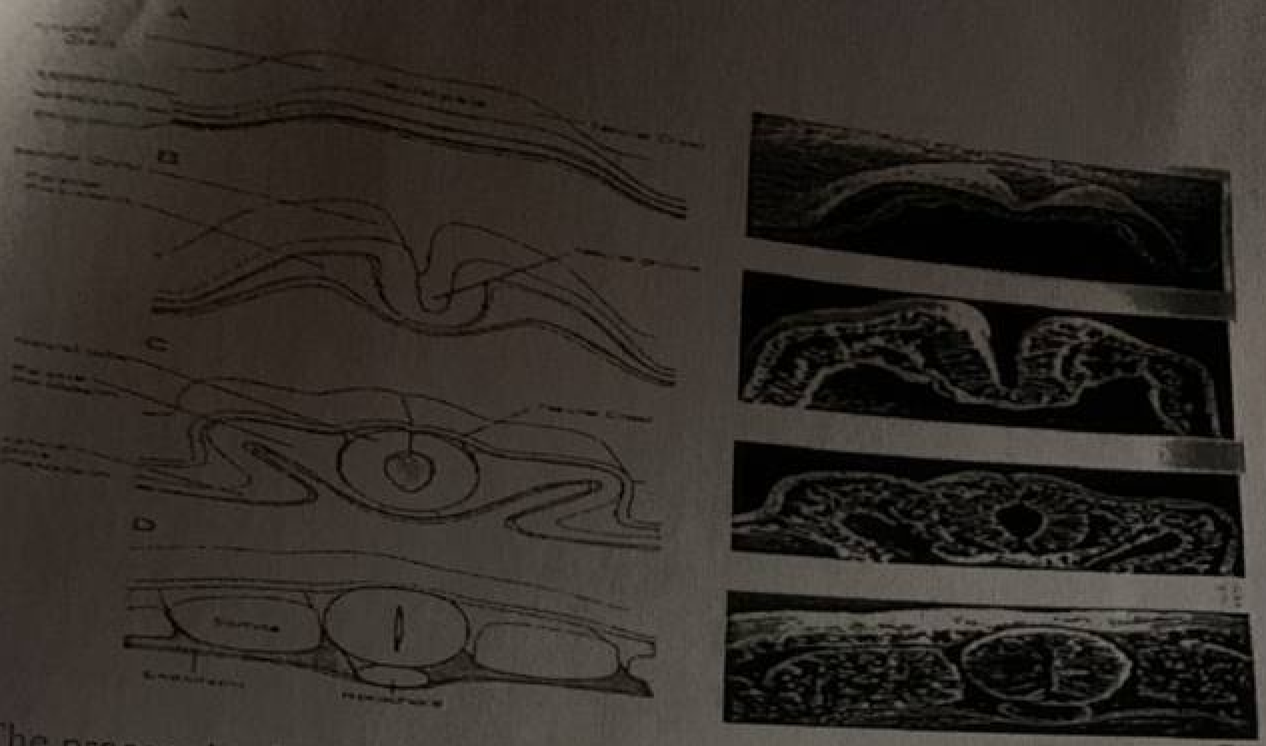
Neurulation occurs in four stages :

a- transformation of the central portion of the embryonic ectoderm into a thickened neural plate

b- shaping and elongation of the neural plate

c- bending of the neural plate around a medial groove followed by elevation of the lateralfolds

d- closure of the neural tube.



notochord
هو اللي بيحفز تكوين الاعصاب عن طريق الاشارات لل ecto derm

The process begins when the notochord induces the formation of the central nervous system (CNS) by signaling the ectoderm germ layer above it to thicken and form the neural plate. Cells of the plate make up the *neuroectoderm*, and their induction represents the initial event in the process of neurulation.

① Lengthening of the neural plate and body axis by the phenomenon of *convergent extension* whereby there is a lateral to medial movement of cells in the plane of the ectoderm and mesoderm.

② As the neural plate lengthens, its lateral edges elevate to form neural folds, and the depressed midregion forms the neural groove.

③ Gradually, the neural folds approach each other in the midline, where they fuse forming the neural tube(the neural tube will later differentiate into the spinal cord and the brain), eventually forming the central nervous system.

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- Until fusion is complete, the cephalic and caudal ends of the neural tube communicate with the amniotic cavity by way of the anterior (cranial) and posterior (caudal) neuropores respectively.

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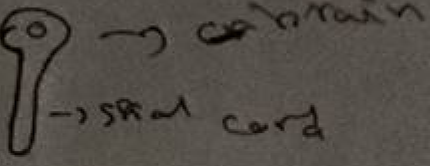
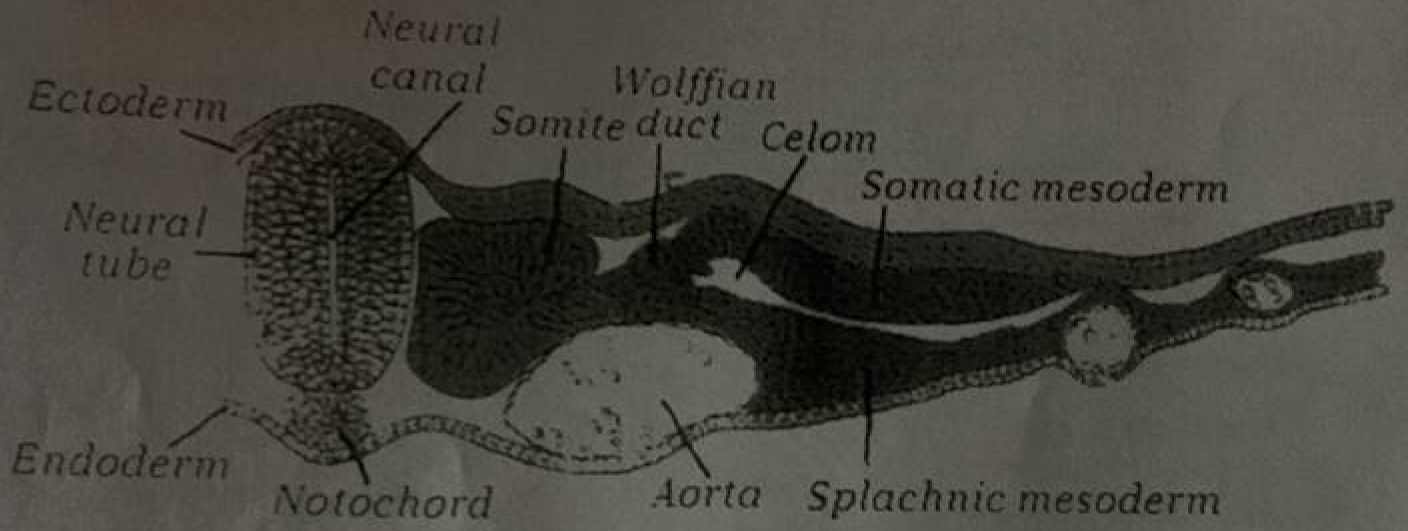


- Closure of the cranial neuropores occurs at approximately day 25, whereas the posterior neuropore closes at day 28.
- Neurulation is then complete, and the central nervous system is represented by a closed tubular structure with a narrow caudal portion, the spinal cord, and a much broader cephalic portion characterized by a number of dilations which are the brain vesicles .



The intraembryonic mesoderm

As the notochord and neural tube developed, the intraembryonic mesoderm on each side forms three longitudinal columns which are:

1- Paraxial mesoderm

2- Intermediate mesoderm

3-Lateral mesoderm

Paraxial mesoderm gives final count of approximately 42-44 pairs of somites. The somites form distinct surface elevations and are triangular in shape when seen in a transverse section

- These somites further differentiate into 3 components:

ⓐ Sclerotome (cartilage and bone)

b- Myotome (muscles)

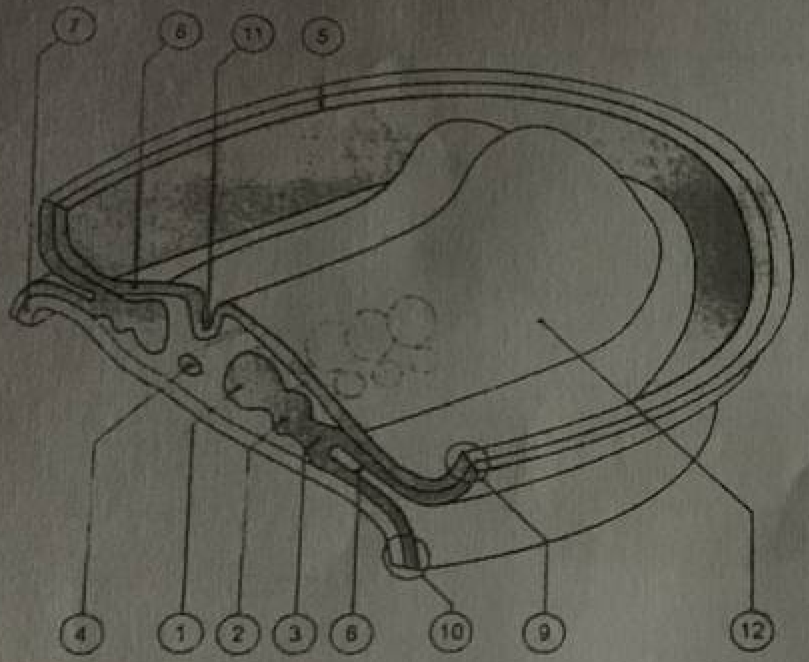
c- Dermatome (dermis of skin)

- Intermediate mesoderm (gives kidneys& genital system)
- Lateral mesoderm differentiates into:

a-**Somatopleure** (gives the voluntary muscles of chest and abdomen and the parietal layer of pleura and peritoneum)

b- **Splanchnopleure** (gives the involuntary muscles of heart, bronchial tree, and gut and the visceral layer of pleura and peritoneum).

The cavity between these two layers is the intraembryonic coelom.



Intraembryonic mesoderm

1 Paraxial mesoderm
2 Intermediate mesoderm
3 Lateral plate mesoderm
4 Chordal process
5 Amnion
6 Intraembryonic coelom
7 Endoblast
8 Ectoblast
9 Somatopleural (mesoderm and ectoderm)
10 Splanchnopleural (mesoderm and endoderm)
11 Neural groove
12 Neural plate

Neural crest cells

As the neural folds elevate and fuse, cells at the lateral border or crest of the neuroectoderm begin to dissociate from their neighbours.

This cell population, the neural crest, will undergo an epithelial-to-mesenchymal transition as it leaves the neuroectoderm by active migration and displacement to enter the underlying mesoderm. Neural crest cells are so fundamentally important

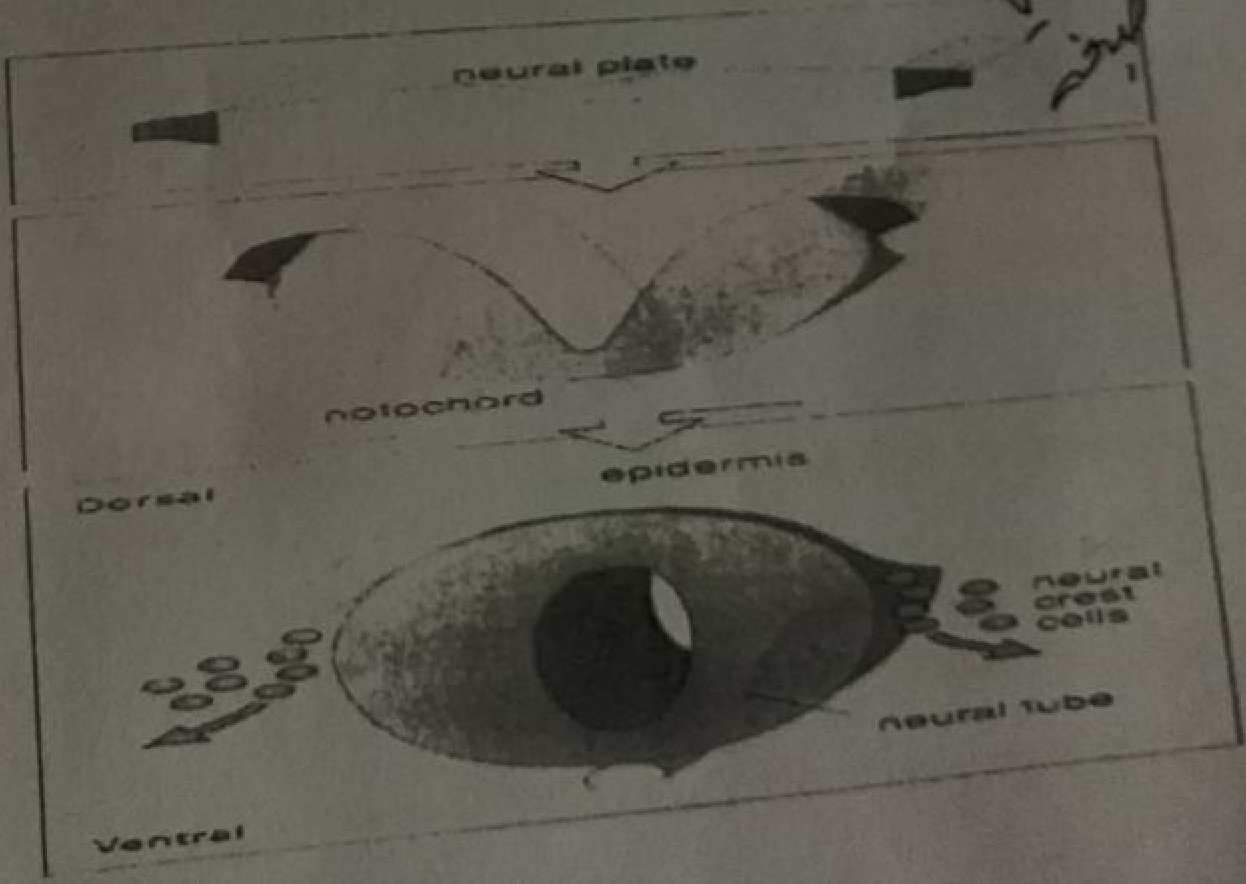
Like

and contribute to so many organs and tissues that they are sometimes referred to as (the fourth germ layer) Neural crest cells eventually give rise to :

1 (-The dorsal root ganglia)
2 (-Schwann cells) →
3 -The autonomic nervous system
4 -Meninges
5 -Sensory ganglia
6 -Bones of the face
7 -Teeth
8 -Lens of the eyes
9 -Melanocytes
10 -Adrenal medulla &many glands.

تدعم العصبي وتبقي على قيد الحياة

نفس الميلانين الي بتعطي صبغة



coelom

امبريو دكا نقوريب

Third to Eighth Week: The Embryonic Period

The embryonic period or period of organogenesis, occurs from the **third to the eighth weeks** of development and is the time when each of the three germ layers, **ectoderm, mesoderm,** and **endoderm,** gives rise to a number of specific tissues and organs. By the end of the embryonic period, the main organ systems have been established, rendering the major features of the external body form recognizable by the end of the second month.

Derivatives of the Ectodermal Germ Layer

At the beginning of the third week of development, the ectodermal germ layer has the shape of a disc that is broader in the cephalic than the caudal region . Appearance of the notochord and prechordal mesoderm induces the overlying ectoderm to thicken and form the **neural plate** . Cells of the plate make up the **neuroectoderm** and their induction represents the initial event in the process of **neurulation.**

NEURULATION

Once induction has occurred, the elongated, slipper-shaped neural plate gradually expands toward the primitive streak . By the end of the third week, the lateral edges of the neural plate become more elevated to form **neural folds,** and the depressed midregion forms the **neural groove** . Gradually, the neural folds approach each other in the midline, where they fuse. Fusion begins in the cervical region (fifth somite) and proceeds cranially and caudally . As a result, the **neural tube** is formed. Until fusion is complete, the cephalic and caudal ends of the neural tube communicate with the amniotic cavity by way of the **cranial and caudal neuropores,** respectively . Closure of the cranial neuropore occurs at approximately day 25 (18- to 20-somite stage), whereas the posterior neuropore closes at day 27 (25-somite stage). Neurulation is then complete, and the central nervous system is represented by a closed tubular structure with a narrow caudal portion, the **spinal cord,** and a much broader cephalic portion characterized by a number of dilations, the **brain vesicles** .

As the neural folds elevate and fuse, cells at the lateral border or crest of the neuroectoderm begin to dissociate from their neighbors. This cell population, the **neural crest** , will undergo an epithelial-to-mesenchymal transition as it leaves the neuroectoderm by activemigration and displacement to enter the underlying mesoderm. (**Mesoderm** refers to cells derived from the epiblast and extraembryonic tissues. **Mesenchyme** refers to loosely organized embryonic connective tissue regardless of origin.) Crest cells from the trunk region leave the neural folds after closure of the neural tube and migrate along one of two pathways: 1) a dorsal pathway through the dermis, where they will enter the ectoderm through holes in the basal lamina to form **melanocytes** in the skin and hair follicles; and 2) a ventral pathway through the anterior half of each somite to become **sensory ganglia, sympathetic and enteric neurons,**

Schwann cells, and cells of the adrenal medulla. Neural crest cells also form and migrate from cranial neural folds, leaving the neural tube before closure in this region. These cells contribute to the **craniofacial skeleton** as well as **neurons for cranial ganglia, glial cells, melanocytes,** and other cell types. Induction of neural crest cells requires an interaction between adjacent neural and overlying ectoderm. **Bone morphogenetic proteins (BMPs),** secreted by non-neural ectoderm, appear to initiate the induction

By the time the neural tube is closed, two bilateral **ectodermal thickenings,** the **otic placodes** and the **lens placodes,** become visible in the cephalic region of the embryo. During further development, the otic placodes invaginate and form the **otic vesicles,** which will develop into structures needed for hearing and maintenance of equilibrium. At approximately the same time, the **lens placodes** appear. These placodes also invaginate and, during the fifth week, form the **lenses** of the eyes.

In general terms, the ectodermal germ layer gives rise to organs and structures that maintain contact with the outside world:

(*a*) the central nerve system.
(*b*) the peripheral nervous system.
(*c*) the sensory epithelium of the ear nose, and eye
(*d*) the epidermis, including the hair and nails

In addition ,it gives rise to subcutaneous glands, the mammary glands, the pituitary gland, and enamel of the teeth.

Derivatives of the Mesodermal Germ Layer

Initially, cells of the mesodermal germ layer form a thin sheet of loosely woven tissue on each side of the midline. By approximately the 17th day, however, cells close to the midline proliferate and form a thickened plate of tissue known as **paraxial mesoderm**. More laterally, the mesoderm layer remains thin and is known as the **lateral plate.**

With the appearance and coalescence of intercellular cavities in the lateral plate, this tissue is divided into two layers :

(*a*) a layer continuous with mesoderm covering the amnion, known as the **somatic** or **parietal mesoderm layer**.

(*b*) a layer continuous with mesoderm covering the yolk sac, known as the **splanchnic or visceral mesoderm layer**. Together, these layers line a newly formed cavity, the **intraembryonic cavity**, which is continuous with the extraembryonic cavity on each side of the embryo. **Intermediate mesoderm** connects paraxial and lateral plate mesoderm .

TABLE :Neural Crest Derivatives
Connective tissue and bones of the face and skull
Cranial nerve ganglia
C cells of the thyroid gland
Conotruncal septum in the heart
Odontoblasts
Dermis in face and neck
Spinal (dorsal root) ganglia
Sympathetic chain and preaortic ganglia
Parasympathetic ganglia of the gastrointestinal tract
Adrenal medulla
Schwann cells
Glial cells
Arachnoid and pia mater (leptomeninges)
Melanocytes

PARAXIAL MESODERM

By the beginning of the third week, paraxial mesoderm is organized into segments. These segments, known as **somitomeres**, first appear in the cephalic region of the embryo, and their formation proceeds cephalocaudally. Each somitomere consists of mesodermal cells arranged in concentric whorls around the center of the unit In the head region somitomeres form in association with ectoderm segmentation of the neural plate into **neuromeres** and contribute to mesenchyme in the head. From the occipital region caudally,somitomeres further organize into somites. The first pair of somites arises in the occipital region of the embryo at approximately the 20th day of development.From here, new somites appear in craniocaudal sequence at a rate of approximately three pairs per day until, at the end of the fifth week, 42 to 44 pairs are present . There are four occipital, eight cervical,12 thoracic, five lumbar, five sacral, and eight to 10 coccygeal pairs. Thefirst occipital and the last five to seven coccygeal somites later disappear, while the remaining somites form the axial skeleton . During this period of development, the age of the embryo is expressed in number of somites.By the beginning of the fourth week, cells forming the ventral and medial walls of the somite lose their compact organization, become polymorphous,and shift their position to surround the notochord .

These cells, collectively known as the **sclerotome**, form a loosely woven tissue, the **mesenchyme**. They will surround the spinal cord and notochord to form the vertebral column . Cells at the dorsolateral portion of the somite also migrate as precursors of the limb and body wall musculature . After migration of these muscle cells and cells of the sclerotome, cells at the dorsomedial portion of the somite proliferate and migrate down the ventral side of the remaining dorsal epithelium of the somite to form a new layer, the myotome . The remaining dorsal epithelium forms the dermatome, and together these layers constitute the dermomyotome . Each segmentally arranged myotome contributes to muscles of the back (epaxial musculature;), while dermatomes disperse to form the dermis and subcutaneous tissue of the skin . Furthermore, each myotome and dermatome retains its innervation from its segment of origin, no matter where the cells migrate. Hence each somite forms its own

TABLE : Number of Somites Correlated to Approximate Age in Days

Approximate Age (days)	No. of Somites
20	1–4
21	4–7
22	7–10
23	10–13
24	13–17
25	17–20
26	20–23
27	23–26
28	26–29
30	34–35

sclerotome (the cartilage and bone component), its own **myotome** (providing the segmental muscle component), and its own **dermatome**, the segmental skin component. Each myotome and dermatome also has its own segmental nerve component.

cartilage- and bone-forming genes for vertebral formation. Expression of *PAX3*, regulated by WNT proteins from the dorsal neural tube, marks the dermomyotome region of the somite. WNT proteins from the dorsal neural tube also target the dorsomedial portion of the somite, causing it to initiate expression of the muscle-specific gene *MYF5* and to become epaxial musculature. Interplay between the inhibiting protein BMP-4 (and probably FGFs) fromthe lateral plate mesoderm and activating WNT products from the epidermis directs the dorsolateral portion of the somite to express another muscle-specific gene, *MYOD*, and to form limb and body wall muscles. The midportion of the dorsal epithelium of the somite is directed by **neurotrophin** 3 (NT-3), secreted by the dorsal region of the neural tube, to form dermis.

INTERMEDIATE MESODERM

Intermediate mesoderm, which temporarily connects paraxial mesoderm with the lateral plate differentiates into urogenital structures.
In cervical and upper thoracic regions, it forms segmental cell clusters (future **nephrotomes**), whereas more caudally, it forms an unsegmented mass of tissue, the **nephrogenic cord**. Excretory units of the urinary system and the gonads develop from this partly segmented, partly unsegmented intermediate mesoderm .

LATERAL PLATE MESODERM

Lateral plate mesoderm splits into parietal and visceral layers, which line the intraembryonic cavity and surround the organs, respectively . Mesoderm from the parietal layer, together with overlying ectoderm, will form the lateral and ventral body wall. The visceral layer and embryonic endoderm will form the wall of the gut . Mesoderm cells of the parietal layer surrounding the intraembryonic cavity will form thin membranes, the **mesothelial membranes,** or **serous membranes,** which will line the peritoneal, pleural, and pericardial cavities and secrete serous fluid . Mesoderm cells of the visceral layer will form a thin serous membrane around each organ .

BLOOD AND BLOOD VESSELS

Blood vessels form in two ways: **vasculogenesis,** whereby vessels arise from blood islands and **angiogenesis,** which entails sprouting from existing vessels. The first blood islands appear in mesoderm surrounding the wall of the yolk sac at 3 weeks of development and slightly later in lateral plate mesoderm and other regions . These islands arise from mesoderm cells that are induced by fibroblast growth factor 2 (FGF-2) to form **hemangioblasts,** a common precursor for vessel and blood cell formation. Hemangioblasts in the center of blood islands form **hematopoietic stem cells,** the precursors of all blood cells, whereas peripheral hemangioblasts differentiate into **angioblasts,** the precursors to blood vessels. These angioblasts proliferate and are eventually induced to form endothelial cells by **vascular endothelial growth factor (VEGF)** secreted by surrounding mesoderm cells This same factor then regulates coalescence of these endothelial cells into the first primitive blood vessels.

Once the process of vasculogenesis establishes a primary vascular bed, additional vasculature is added by angiogenesis, the sprouting of new vessels . This process is also mediated by VEGF, which stimulates proliferation of endothelial cells at points where new vessels are to be formed. Maturation and modeling of the vasculature are regulated by other growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β), until the adult pattern is established.

As mentioned, the first blood cells arise in the blood islands of the yolk sac, but this population is transitory. The definitive hematopoietic stem cells arise from mesoderm surrounding the aorta in a site called the **aorta-gonad-mesonephros region (AGM).** These cells will colonize the liver, which becomes the major hematopoietic organ of the fetus. Later, stem cells fromthe liver will colonize the bone marrow, the definitive blood-forming tissue.

Derivatives of the Endodermal Germ Layer

The gastrointestinal tract is the main organ system derived from the endodermal germ layer. This germ layer covers the ventral surface of the embryo and forms the roof of the yolk sac. With development and growth of the brain vesicles, however, the embryonic disc begins to bulge into the amniotic cavity and to fold **cephalocaudally.** This folding is most pronounced in the regions of the head and tail, where the **head fold** and **tail fold** are formed. As a result of cephalocaudal folding, a continuously larger portion of the endoderm-lined cavity is incorporated into the body of the embryo proper . In the anterior part, the endoderm forms the **foregut;** in the tail region, it forms the **hindgut.** The part between foregut and hindgut is the **midgut.** The midgut temporarily communicates with the yolk sac by way of a broad stalk, the **vitelline duct**. This duct is wide initially, but with further growth of the embryo, it becomes narrow and much long.

At its cephalic end, the foregut is temporarily bounded by an ectodermalendodermal membrane called the **buccopharyngeal membrane** . In the fourth week, the buccopharyngeal membrane ruptures, establishing an open connection between the amniotic cavity and the primitive gut . The hindgut also terminates temporarily at an ectodermalendodermal membrane, the **cloacal membrane**, which breaks down in the seventh week to create the opening for the anus.

As a result of rapid growth of the somites, the initial flat embryonic disc also
folds laterally, and the embryo obtains a round appearance . Simultaneously,
the ventral body wall of the embryo is established except for a small
part in the ventral abdominal region where the yolk sac duct and connecting

stalk are attached.

While the foregut and hindgut are established, the midgut remains in communication with the yolk sac. Initially, this connection is wide but as a result of body folding, it gradually becomes long and narrow to form the **vitelline duct** . Only much later, when the vitelline duct is obliterated, does the midgut lose its connection with the original endoderm-lined cavity and obtain its free position in the abdominal cavity.

Another important result of cephalocaudal and lateral folding is partial incorporation of the allantois into the body of the embryo, where it forms the **cloaca** . The distal portion of the allantois remains in the connecting stalk. By the fifth week, the yolk sac duct, allantois, and umbilical vessels are restricted to the region of the umbilical ring .

In humans, the yolk sac is vestigial and in all probability has a nutritive role only in early stages of development. In the second month of development, it lies in the chorionic cavity .

Hence, the endodermal germ layer initially forms the epithelial lining of the primitive gut and the intraembryonic portions of the allantois and vitelline duct . During further development, it gives rise to (*a*) the epithelial lining of the respiratory tract; (*b*) the parenchyma of the thyroid, parathyroids, liver, and pancreas (see Chapters 13 and 15); (*c*) the reticular stroma of the tonsils and thymus; (*d*) the epithelial lining of the urinary bladder and urethra (see Chapter 14); and (*e*) the epithelial lining of the tympanic cavity and auditory tube .

External Appearance During the Second Month

At the end of the fourth week, when the embryo has approximately 28 somites, the main external features are the somites and pharyngeal arches .

The age of the embryo is therefore usually expressed in somites .

Because counting somites becomes difficult during the second month of development, the age of the embryo is then indicated as the **crown-rump length (CRL)** and expressed in millimeters . CRL is the measurement from the vertex of the skull to the midpoint between the apices of the buttocks.

During the second month, the external appearance of the embryo is changed by an increase in head size and formation of the limbs, face, ears, nose, and eyes. By the beginning of the fifth week, forelimbs and hindlimbs appear as paddle-shaped buds . The former are located dorsal to the pericardial swelling at the level of the fourth cervical to the first thoracic somites, which explains their innervation by the **brachial plexus.** Hindlimb buds appear slightly later just caudal to attachment of the umbilical stalk at the level of the lumbar and upper sacral somites. With further growth, the terminal portions of the buds flatten and a circular constriction separates them from the proximal, more cylindrical segment . Soon, four radial grooves separating five slightly thicker areas appear on the distal portion of the buds, foreshadowing formation of the digits .

These grooves, known as rays, appear in the hand region first and shortly afterward in the foot, as the upper limb is slightly more advanced in development

than the lower limb. While fingers and toes are being formed ,

a second constriction divides the proximal portion of the buds into two segments,

and the three parts characteristic of the adult extremities can be recognized.

CLINICALCORRELATES

Birth Defects

Most major organs and organ systems are formed during the third to eighth week. This period, which is critical for normal development, is therefore called the period of organogenesis. Stem cell populations are establishing each of the organ primordia, and these interactions are sensitive to insult fromgenetic and environmental influences. Thus, this period is when most gross structural birth defects are induced. Unfortunately, the mother may not realize she is pregnant during this critical time, especially during the third and fourthweeks, which are particularly vulnerable. Consequently, she may not avoid harmful influences, such as cigarette smoking and alcohol. Understanding the main events of organogenesis is important for identifying the time that a particular defect was induced and, in turn, determining possible causes for the malformation.

Pharyngeal arches(branchial arches)

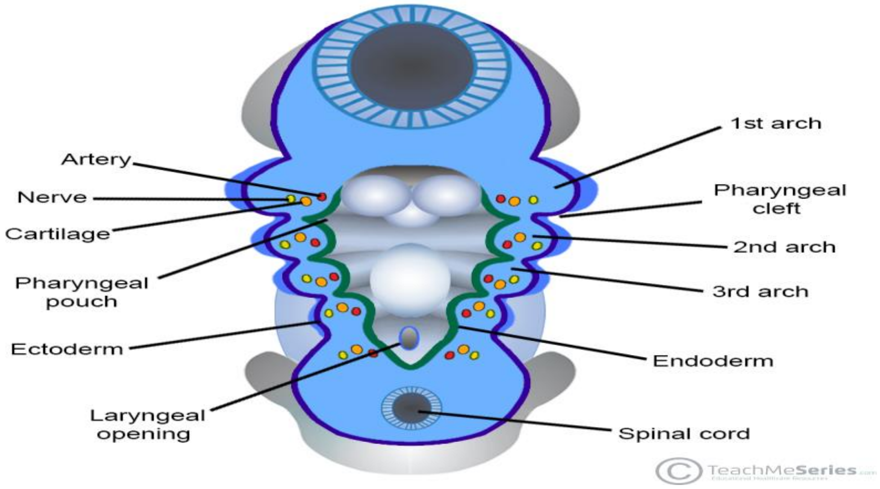
They are series of five paired swellings that surround the embryonic foregut, they are wedged between the developing heart and brain and give rise to the structures of the head and neck . The pharyngeal arches are formed by cells that are derived from ectoderm, endoderm, mesoderm and neural crest.

They develop in a rostral to caudal sequence,during human and all vertebrate development, pharyngeal arch pairs project forward from the back of the embryo toward the front of the face and neck. Each arch develops its own artery, nerve that controls a distinct muscle group, and skeletal tissue. These arches grow and join in the ventral midline.

The first arch, as the first to form, separates the mouth pit or stomodeum from the pericardium. The 1st pharyngeal arch appears at about the beginning of the 4th week and others are added more caudally later such that there are ultimately 5 arches by the end of the 4th week.

During embryological development, the pharyngeal arches appear as C-shaped rolls in a stack, separated by clefts. There are initially six arches, but only four are externally visible on the embryo.

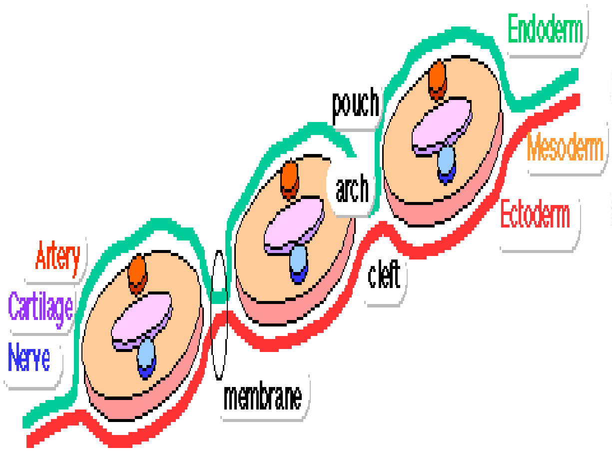
The fifth arch regresses before development is complete.These arches are numbered 1,2,3,4, and 6,the reason for this numbering is that some vascular component of a fifth pharyngeal arch occasionally develops transiently and then is lost.

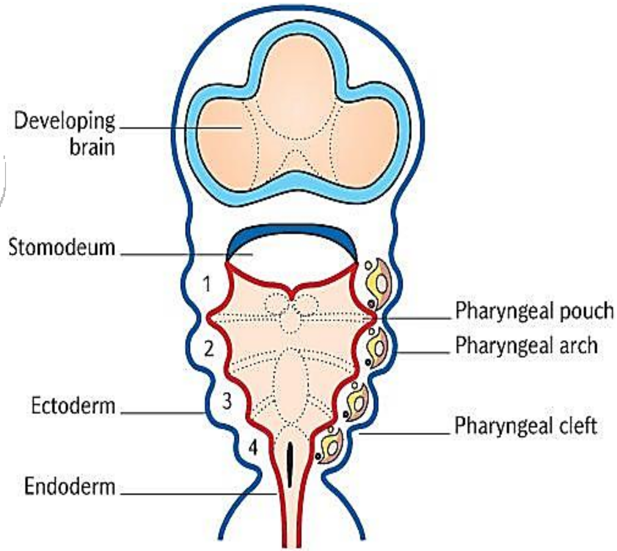


The Pharyngeal Arches - Clefts - Pouches -

Pharyngeal pouches are developed from the endoderm and they open towards the pharyngeal clefts.The external surface is composed of ectoderm and the internal surface is lined with endoderm.

- The entire pharyngeal apparatus consists of paired pharyngeal arches, pharyngeal pouches, pharyngeal clefts (or grooves), and pharyngeal membranes .
- The arches are covered by ectoderm,the ectoderm between the arches form clefts called pharyngeal clefts (grooves).
- Medially each of the pharyngeal arches is separated by a pharyngeal pouch,which approach the corresponding branchial cleft
- The arches are bordered medially by the pharynx which is lined by endoderm.
- The approximation of the ectoderm of the pharyngeal cleft with the endoderm of the pharyngeal pouch forms the *pharyngeal membrane.*
- The grooves and pouches are named (numbered) the same as the preceding arch.





Derivatives of pharyngeal archs:

1-The first pharyngeal arch(mandibular arch)

Skeletal elements

- Malleus & Incus of the middle ear
- maxilla & mandible

Muscles

- Muscles of mastication (chewing)
- Mylohyoid muscle
- Digastric muscle, anterior belly
- Tensor palati muscle
- Tensor tympani muscle

Nerve

Trigeminal nerve

Artery

Maxillary artery

2-The second pharyngeal arch

The second pharyngeal arch or hyoid arch (or second branchial arch) assists in forming the side and front of the neck.

Skeletal elements

- Stapes
- Temporal styloid process,
- Stylohyoid ligament
- Lesser horn of the hyoid bone.

Muscles

- Muscles of face
- Occipitofrontalis muscle
- Platysma
- Stylohyoid muscle
- Posterior belly of digastric
- Stapedius muscle
- Auricular muscles

Nerve supply

Facial nerve

3-The third pharyngeal arch

Skeletal elements

- Hyoid (greater horn),and lower part of body),thymus,inferior parathyroids.

Muscles

Stylohpharyngeus

Nerve

Glossopharyngeal nerve(IX)

Artery

Common carotid ,internal carotid artery.

4-The fourth pharyngeal arch

Skeletal elements

Thyroid cartilage , parathyroid ,Epiglottic cartilage.

Muscles

- Cricothyroid muscle
- All intrinsic muscles of the soft palate

Artery

- Right 4th aortic arch: subclavian artery
- Left 4th aortic arch .

5-The sixth pharyngeal arch

Skeletal elements

- Cricoid cartilage
- Arytenoid cartilage
- Corniculate cartilage

Muscles

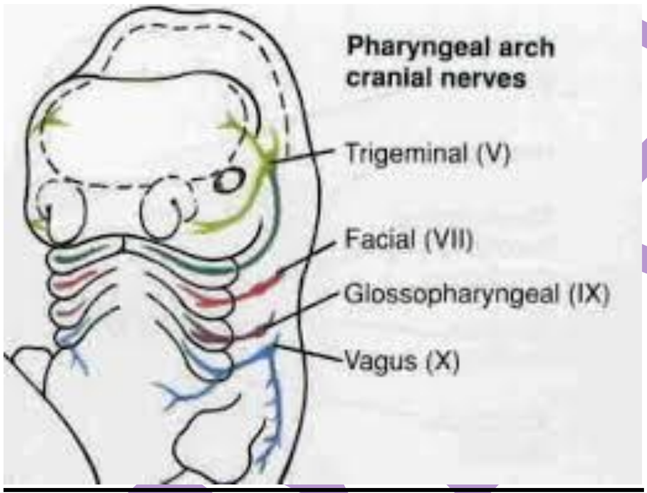
- All intrinsic muscles of larynx except the cricothyroid muscle

Nerve

- All the pharyngeal muscles of the fourth and sixth arches are innervated by the superior laryngeal and the recurrent laryngeal branches of the vagus nerve.

Artery

- Right 6th aortic arch :pulmonory artery
- Left 6th aortic arch: pulmonary artery, ductus arteriousus.



Nerves of PhA

Pharyngeal pouches

Pharyngeal or branchial pouches form on the endodermal side between the branchial arches.

- First pouch

The endoderm lines the future auditory tube (Pharyngotympanic Eustachian tube), middle ear, mastoid antrum, and inner layer of the tympanic membrane.

- Second pouch

Contributes to the middle ear, palatine tonsils, supplied by the facial nerve.

- Third pouch

Third pouch possesses dorsal and ventral wings. Derivatives of the dorsal wings include the inferior parathyroid glands, while the ventral wings fuse to form the cytoreticular cells of the thymus. The main nerve supply to the derivatives of this pouch is glossopharyngeal nerve.

- Fourth pouch:

Superior parathyroid glands and ultimobranchial body which forms the parafollicular C-Cells of the thyroid gland.

Musculature and cartilage of larynx (along with the sixth pharyngeal pouch).

- Fifth pouch

Rudimentary structure, becomes part of the fourth pouch contributing to thyroid C-cells.

- Sixth pouch

Along with the fourth pouch, the contributes to the formation of the musculature and cartilage of the larynx.

Pharyngeal clefts

Ectodermal lined recesses that appear on the outside of the pharynx between the arches .

- Pharyngeal cleft1

Develops into the external auditory meatus(the corresponding 1st pharyngeal pouch develops into the auditory or eustacian tube, and the intervening membrane develops into the typanic membrane.

- Pharyngeal cleft 2,3 and 4 are overgrown by expansion of the 2nd pharyngeal arch arch and usually obliterated.

Fate of pharyngeal arches

- The pharyngeal arches contribute exclusively to the formation of the face, nasal cavities, mouth, larynx, pharynx and neck.
- During the fifth week, the second pharyngeal arch enlarges and overgrows the third and fourth arches, forming the ectodermal depression called cervical sinus.
- By the end of seventh week the second to fourth pharyngeal grooves and the cervical sinus have disappeared, giving the neck a smooth contour

Branchial arch anomalies:

Branchial cysts are the most common branchial arch anomaly and usually arise from the second and third arches. They often present with cutaneous drainage tracts and most commonly present in childhood.

Branchial cyst is a congenital epithelial cyst that arises on the lateral part of the neck usually due to failure from an incompletely closed branchial cleft.

Remnants of pharyngeal clefts 2-4 can appear in the form of cervical cysts or fistulas found along the anterior border of the sternocleidomastoid muscle.

Most branchial cleft fistulae are asymptomatic, but they may become infected.

Treatment:Conservative (i.e. no treatment), or surgical excision. With surgical excision, recurrence is common, usually due to incomplete excision. Often, the tracts of the cyst will pass near important structures, such as the internal jugular vein, carotid artery, or facial nerve, making complete excision impractical.

Embryology 6

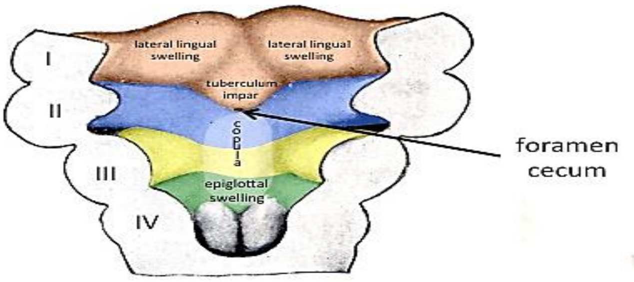
Development of the tongue

The tongue is an extremely sensitive organ that performs on a complex muscle background. In the first stage of development, lingual and medial swellings appear:

- **Two lateral lingual swellings**– derived from the 1st pharyngeal arch. Contributes to the mucosa of the anterior 2/3 of the tongue.
- **Three medial swellings (x3):**
  - Tuberculum impar – derived from the 1st pharyngeal arch. Contributes to the mucosa of the anterior 2/3 of the tongue.
  - Cupola (hypobranchial eminence) – derived from the 2nd, 3rd and 4th pharyngeal arches. Forms the mucosa of the posterior 1/3 of the tongue.
  - Epiglottal swelling – derived from the 4th pharyngeal arch. Forms the epiglottis.

During the 4th week, the lateral lingual swellings overgrow the tuberculum impar and **merge** together – forming the mucosa of the anterior 2/3 of the tongue. Their line of fusion is marked by the median sulcus of the tongue.

Within the **cupola**, the 3rd pharyngeal arch component overgrows the 2nd arch, and forms the mucosa of the posterior 1/3 of the tongue. The anterior 2/3 and posterior 1/3 fuse – forming a V-shaped groove known as the terminal sulcus. At the center of this groove is the foramen cecum, a pit which represents the place of origin of the thyroid gland.



4 weeks

Innervation of the anterior 2/3rd of the tongue*:*

-Sensory innervation of the mucosa is via the lingual branch of the trigeminal nerve

-Taste bud innervation is via the chorda tympani branch of the facial nerve,

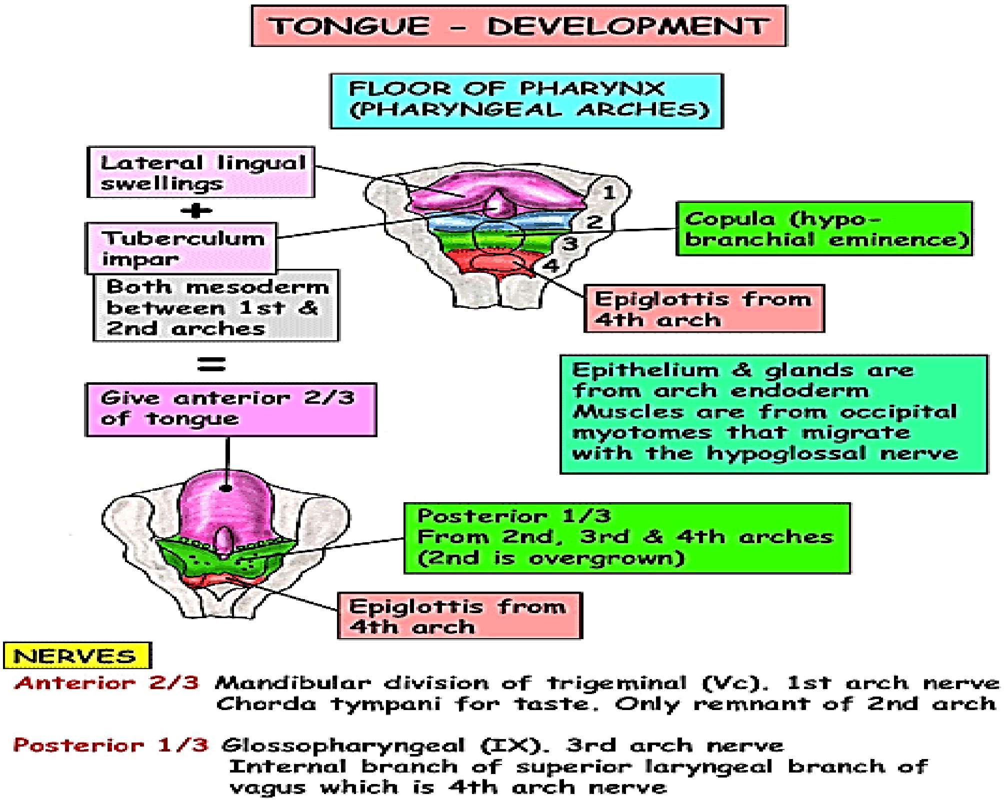
-The taste buds in the circumvallate papilla that present in the posterior most part of the anterior 2/3rd of the tongue are innervated by glossopharyngeal nerve.

Innervation of the posterior 1/3rd of the tongue:

- Sensory innervation of the mucosa is mostly via the glossopharyngeal nerve (and some vagus)

-Taste innervation is mostly via the glossopharyngeal nerve (and some vagus)

Motor innervation of the intrinsic skeletal muscles is via the hypoglossal nerve.



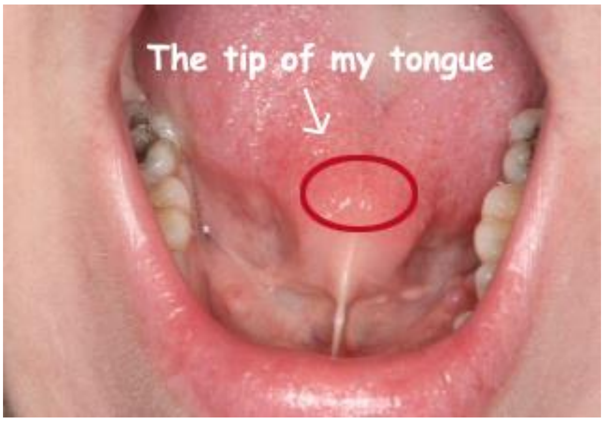
Anterior 2/3 Mandibular division of trigeminal (Vc). 1st arch nerve
Chorda tympani for taste. Only remnant of 2nd arch

Posterior 1/3 Glossopharyngeal (IX). 3rd arch nerve
Internal branch of superior laryngeal branch of vagus which is 4th arch nerve

Abnormalities:

Ankyloglossia (Tongue-Tie)

Ankyloglossia (tongue-tie) is the general clinical term for the short lingual frenulum (less than 2 cm), that limits the range of movement of the tongue, This is associated with speech development and feeding disorders. In the most common form of ankyloglossia, the frenulum extends to the tip of the tongue.



Macroglossia

Macroglossia is the medical term for an unusually large tongue. Sever enlargement of the tongue can cause cosmetic and functional difficulties in speaking, eating, swallowing and sleeping. Macroglossia is uncommon, and usually occurs in children. There are many causes can be associated with a number of genetic abnormalities including: trisomy 21 (Down syndrome), acromegaly. Treatment is dependent upon the exact cause(A).

Microglossia

This is a rare condition where the size of the tongue is abnormally small. Cases of complete absence of the tongue have been reported. A tiny tongue will pose many difficulties related to speech and swallowing. There is no treatment for this condition, and the affected person will have to train their tongue to the best of their abilities(B).

Thyroid gland

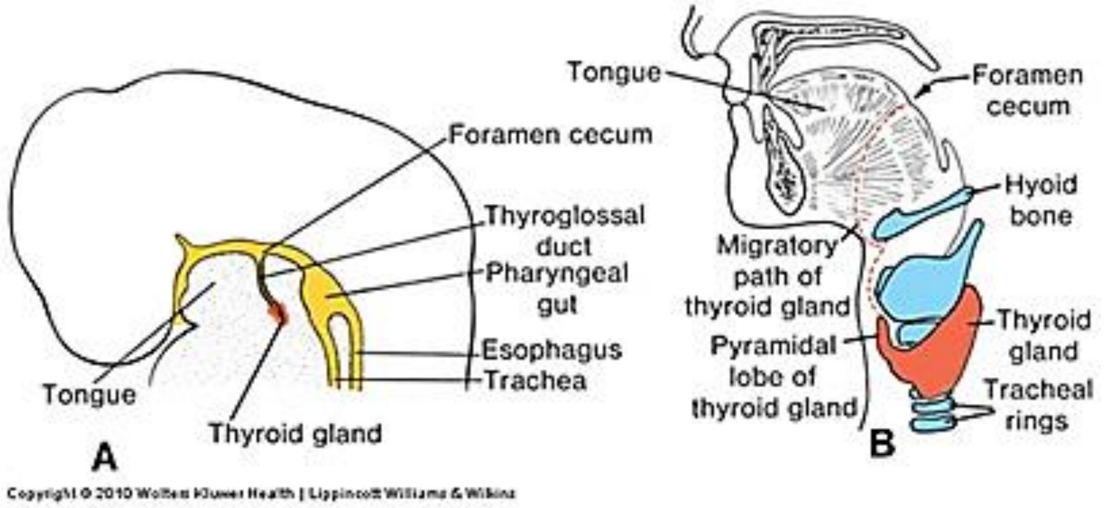
- The thyroid gland appears as an epithelial proliferation at a point indicated by the foramen ceacum . Subsequently, the thyroid descends in front of the pharyngeal gut as a bilobed diverticulum .
- During this migration, the thyroid remains connected to the tongue by the *thyroglossal duct* which later disappears.

- With further development, the thyroid gland descends in front of the hyoid bone and the laryngeal cartilages. It reaches its final position in front of the trachea in the 7th week.
- The thyroid begins to function at approximately the end of the third month, at which time the first follicles containing colloid become visible.
- Follicular cells produce the colloid that serves as a source of:

  Triiodothyronine(T3)

  Thyroxine (T4)

  Parafollicular, or C, cells derived from the ultimobranchial body(derived from (4th pharyngeal pouch) , serve as a source of **calcitonin.**



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A. The thyroid primordium arises as an epithelial diverticulum in the midline of the pharynx
B. Position of the thyroid gland in the adult(Broken line, the path of migration).

Thyroglossal cyst

A thyroglossal cyst may lie at any poínt along the migratory pathway of the thyroid gland but is always near or in the midline of the neck.

It is a cystic remnant of the thyroglossal duct,they may also be found at the base of the tongue or close to the thyroid cartilage.Sometimes, a thyroglossal cyst is connected to the outside by a fistulous canal, a thyroglossal fístula. Such a fistula usually arises secondarily after rupture of a cyst but may be present at birth.