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# GENERAL EMBRYOLOGY

Week 13

## **Proliferation**

- Increase in the number of cells by mitotic divisions (symmetric or asymmetric)

## **Growth**

- Increasing the volume and mass of the organism by increasing the number of cells, the size of cells and the amount of extracellular matrix

## **Differentiation**

- Maturation of cells and their descendants during several successive cell cycles - unspecialized cells become specialized cells

## **Restriction and determination**

- From the early embryo, restriction occurs - the limitation of developmental possibilities. Determination - the ultimate degree of restriction when there is only one developmental path - differentiation into a specific cell type

## **Induction**

- Accelerating the proliferation of nearby or distant cells

## **Migration**

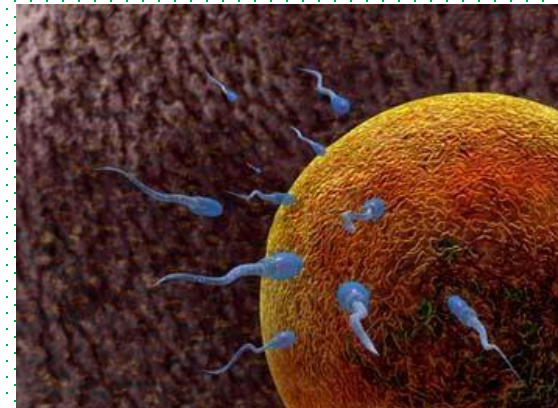
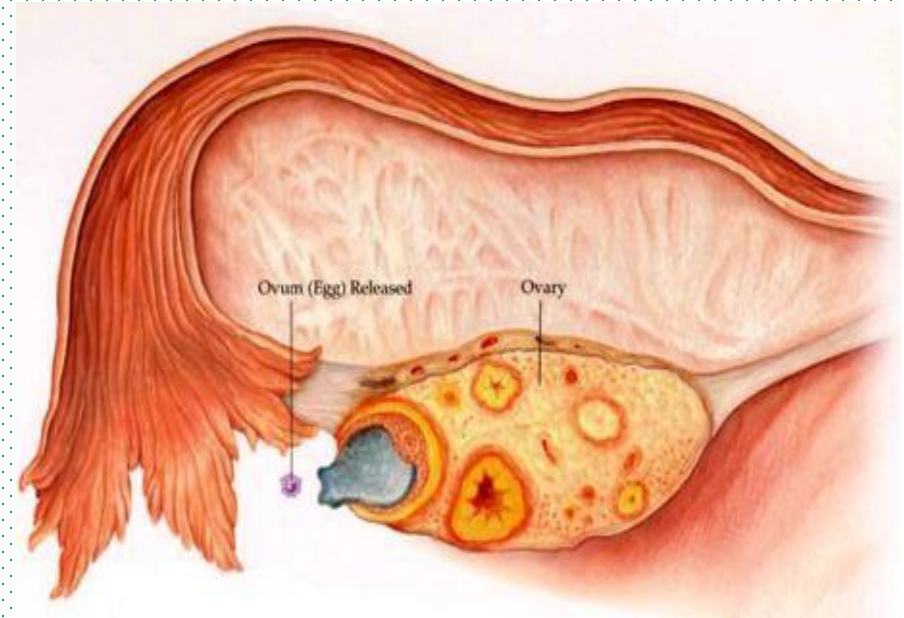
- The ability of the cell to move - to change position

## **Integration**

- Association of cells from different germ layers in the formation of organs

# Fertilization

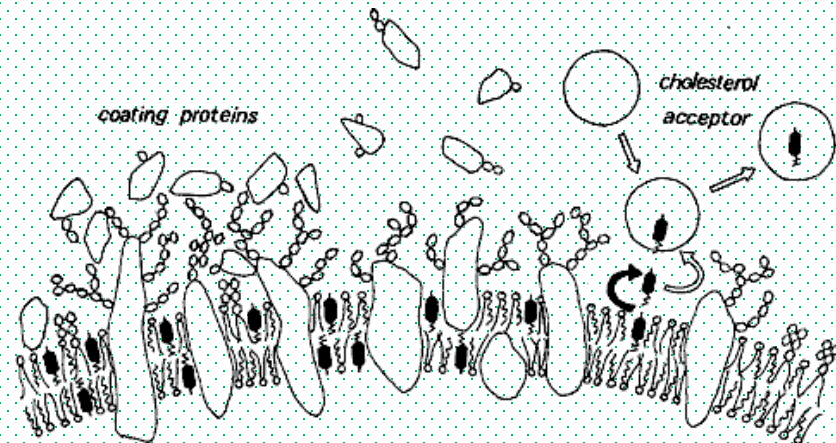
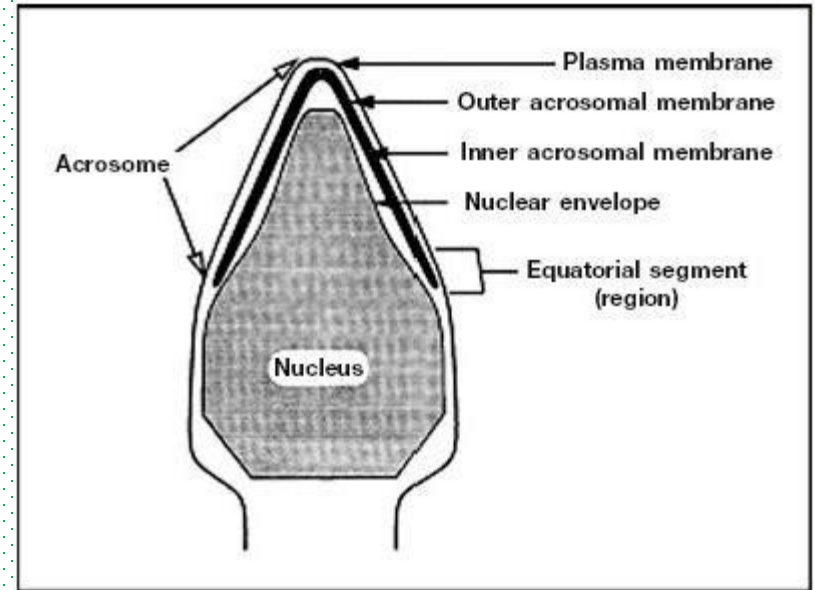
- Fertilization, the process by which male and female gametes fuse, occurs in the **ampullary region of the uterine tube**.
- The **egg cell** is released from the ovary during ovulation and retains the ability to fertilize for **12-24 hours** while **spermatozoa** retains that ability for **80 hours**



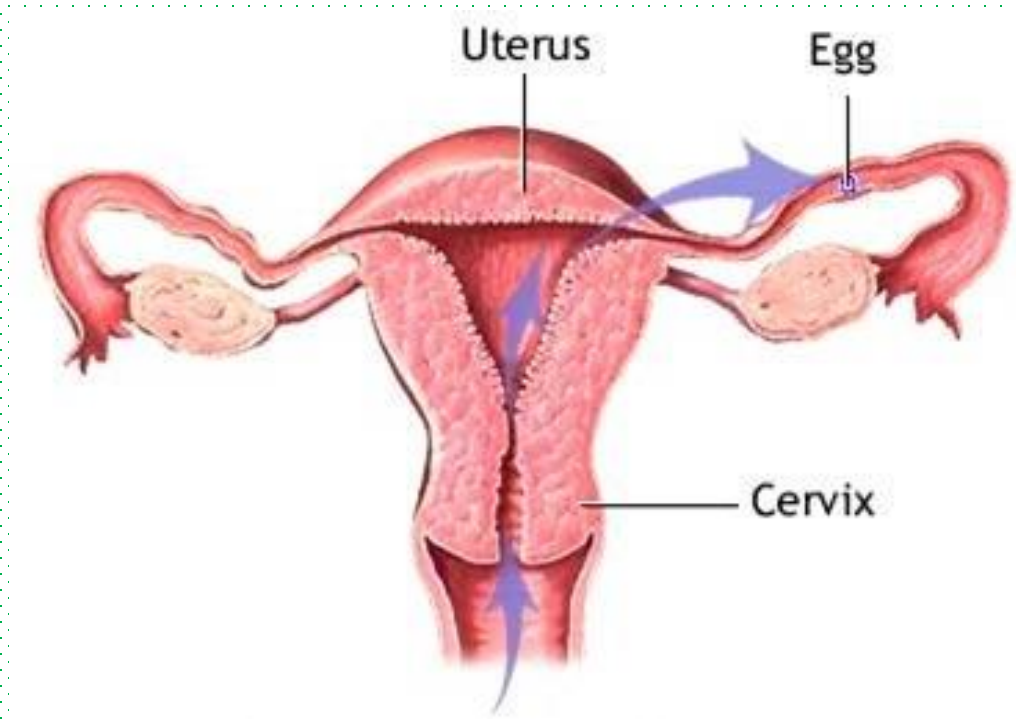
**Spermatozoa** are not able to fertilize the oocyte immediately upon arrival in the female genital tract but must undergo

- **capacitation and**
- **acrosome reaction** to acquire this capability

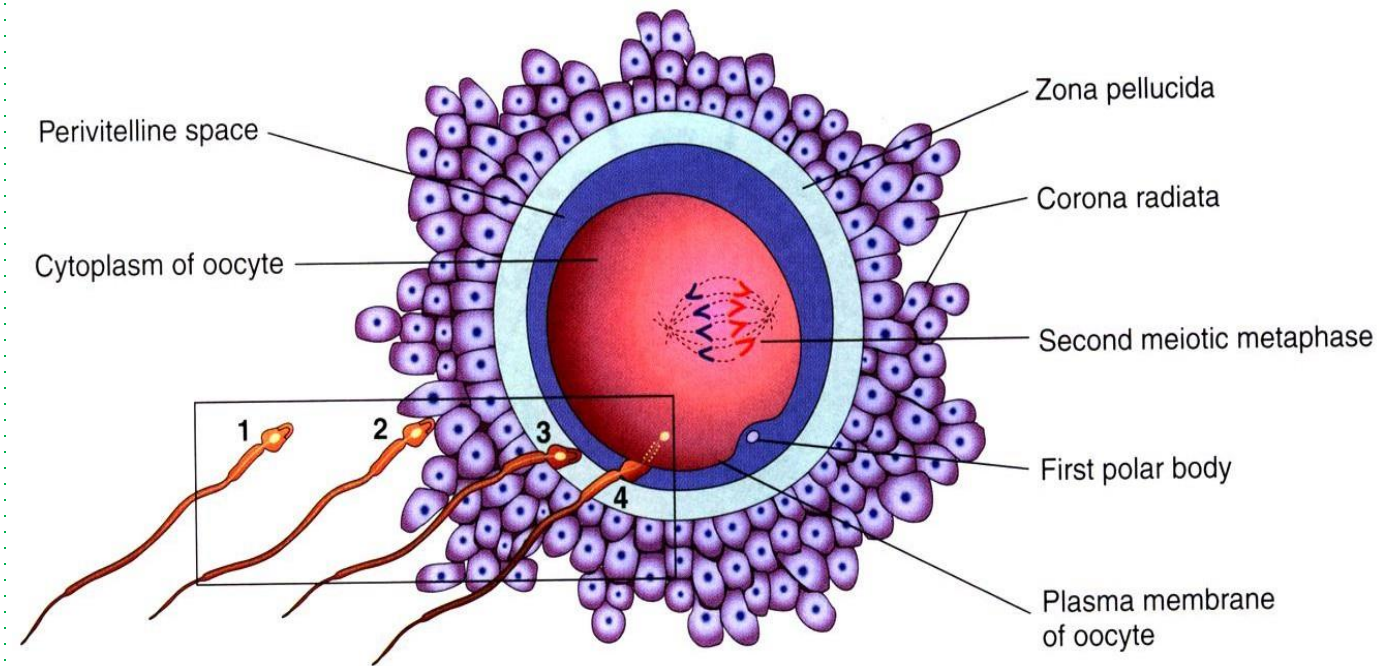
- **Capacitation** is a period of conditioning in the female reproductive tract that in the human lasts approximately 7 hours. Only capacitated sperm can pass through the corona cells and undergo the acrosome reaction.
- **Acrosome reaction**, which occurs after binding to the zona pellucida, is induced by zona proteins. Release of enzymes needed to penetrate the zona pellucida, including acrosin- and trypsin-like substances.



- 200-400 million sperm cells
- Only 1% of sperm deposited in the vagina enter the cervix and only 1 in a million reaches egg cell.
- The trip from cervix to oviduct can occur as rapidly as **30 minutes** or as slow as **6 days**



# Phases of fertilization

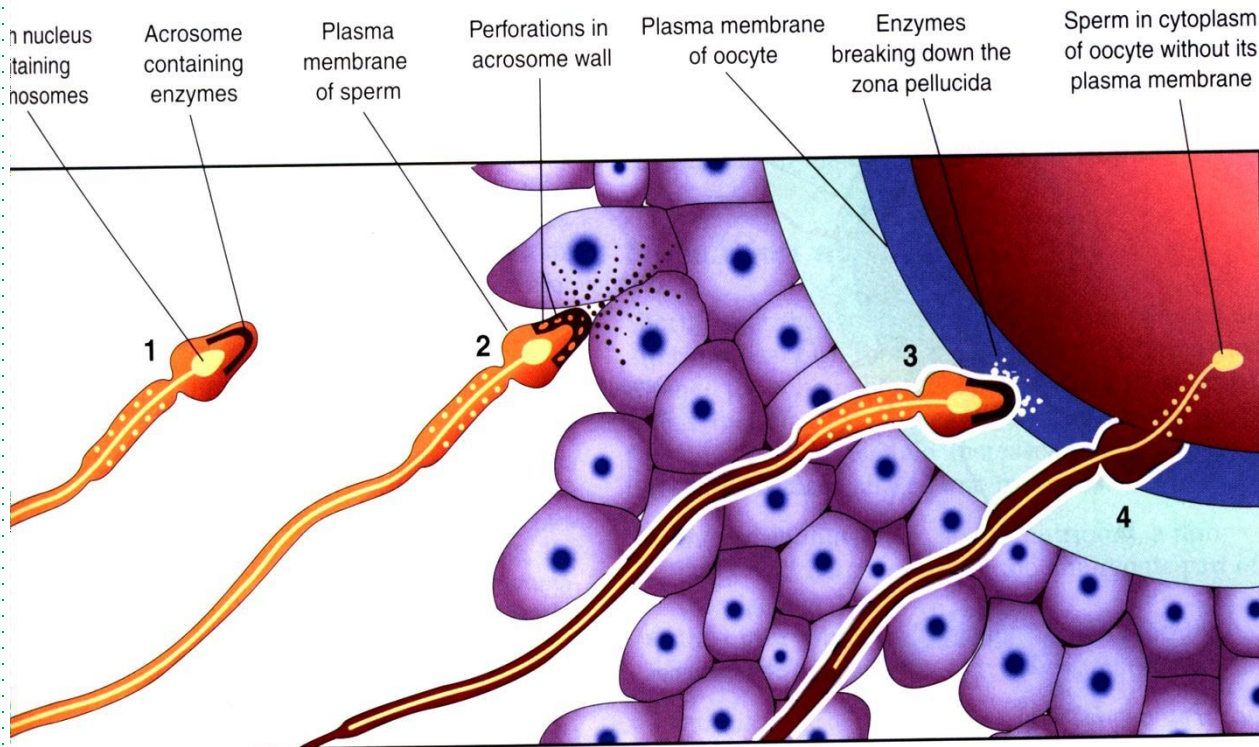


The phases of fertilization include

- Phase 1, **penetration of the corona radiata**
- Phase 2, **penetration of the zona pellucida**
- Phase 3, **fusion of the oocyte and sperm cell membranes**

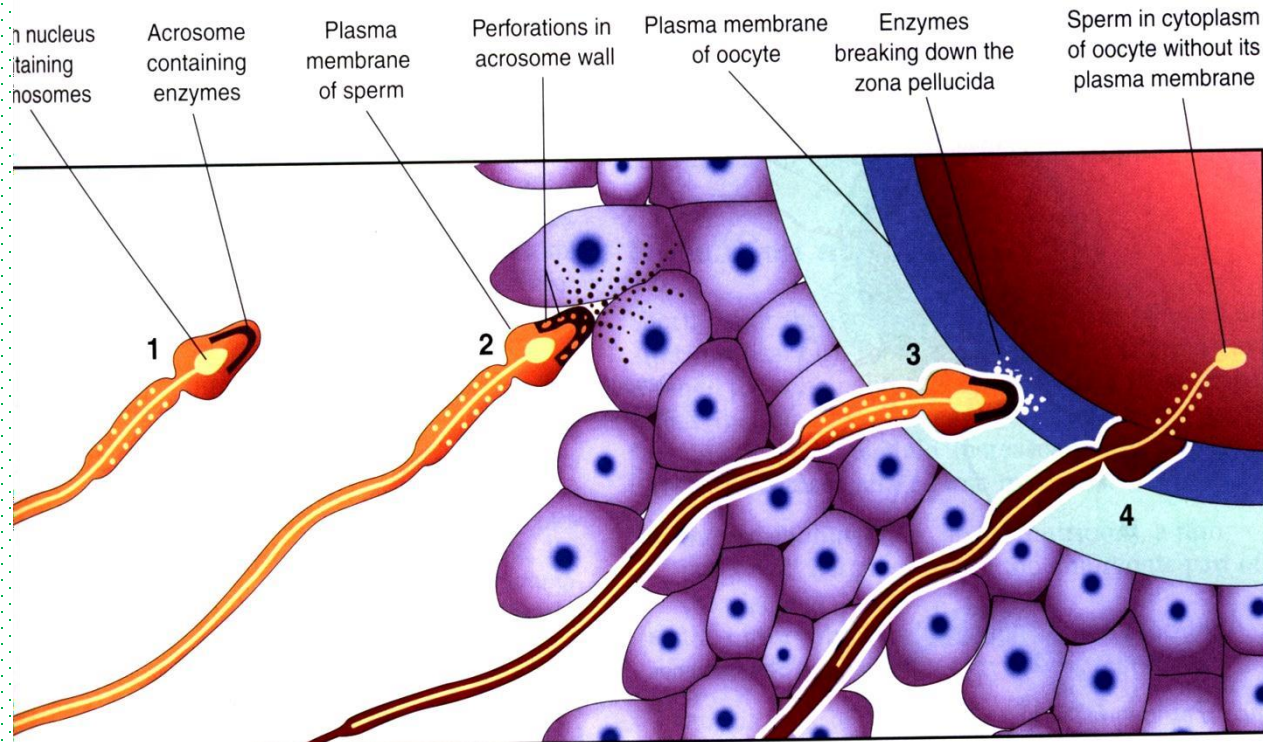


# Penetration of the corona radiata



- Sperm cell that is capacitated passes relatively easy through corona by virtue of **hyaluronidase enzyme**.

# Penetration of the zona pellucida

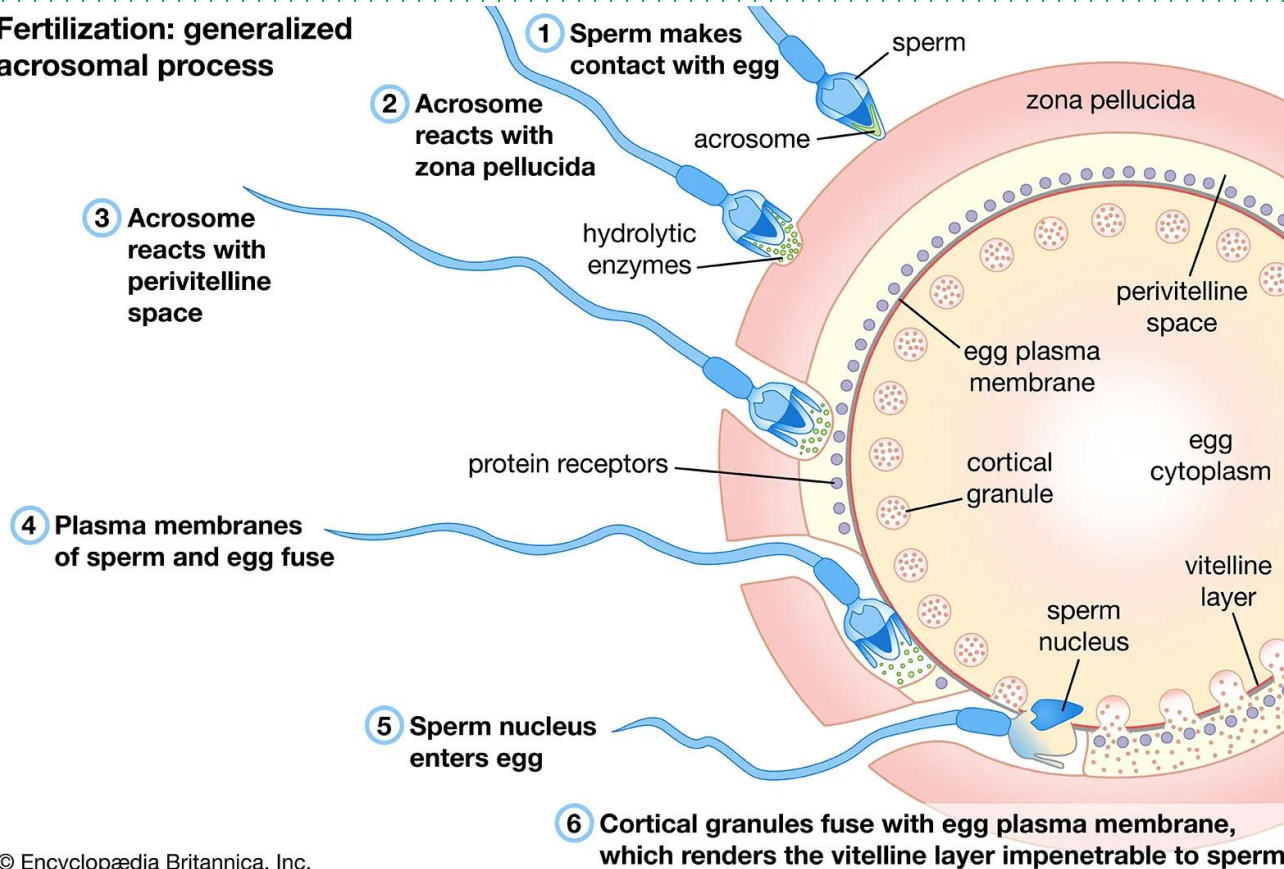


- Binding and the acrosome reaction are mediated by the ligand ZP3, a zona protein.
- **Acrosin** allows sperm to penetrate the zona, thereby coming in contact with the plasma membrane of the oocyte
- Release of lysosomal enzymes from **cortical granules** lining the plasma membrane of the oocyte. In turn, these enzymes alter properties of the zona pellucida (**zona reaction**) to prevent sperm penetration and inactivate species-specific receptor sites for spermatozoa on the zona surface.

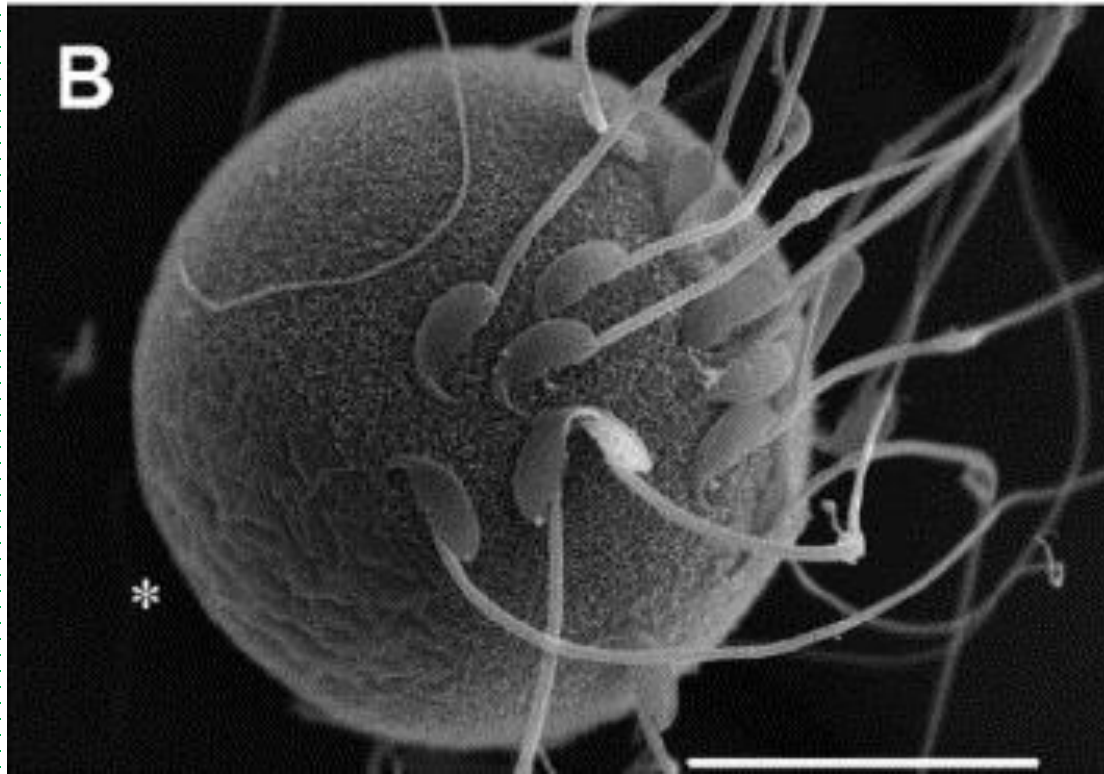


# Fusion .....

## Fertilization: generalized acrosomal process



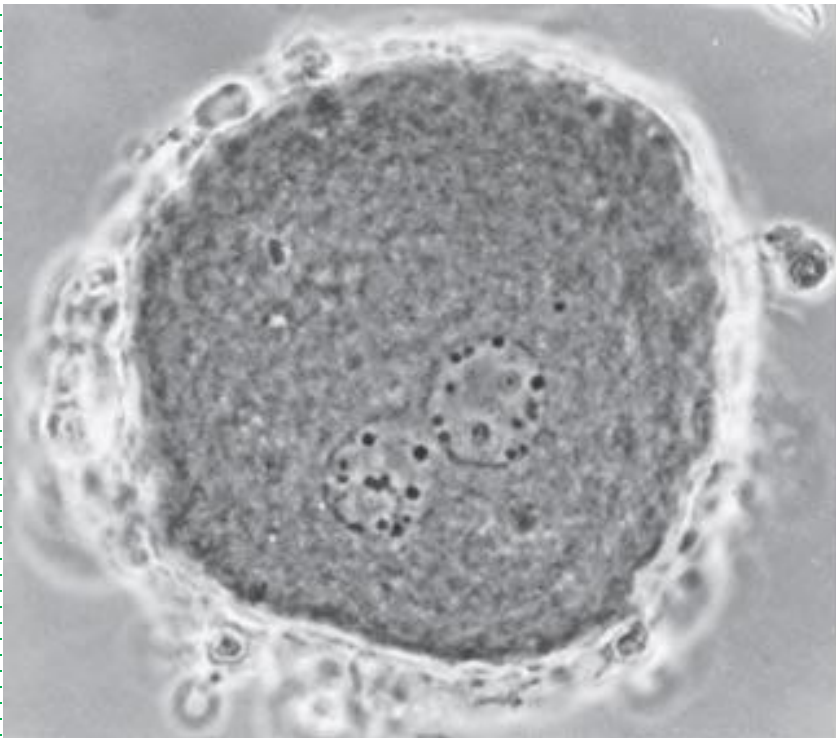
- Adhesion of sperm to the oocyte is mediated in part by the interaction of **integrins** on the oocyte and their ligands, **disintegrins**, on sperm. After adhesion, the plasma membranes of the sperm and egg fuse.



1. **Cortical and zona reactions.** After release of cortical oocyte granules, the oocyte membrane becomes impenetrable to other spermatozoa, and the zona pellucida alters its structure and composition to prevent **polyspermy** (penetration of more than one spermatozoon into the oocyte).
2. **Resumption of the second meiotic division.** The oocyte finishes its second meiotic division immediately after entry of the spermatozoon.
3. **Metabolic activation of the egg.**

# Zygote

- Restoration of the **diploid number** of chromosomes, half from the father and half from the mother.
- Determination of the sex of the new individual.
- Initiation of cleavage. Without fertilization, the oocyte usually **degenerates 24 hours after ovulation**.



# Human development

## **Preembryonic period**

- from fertilization to the end of the second week

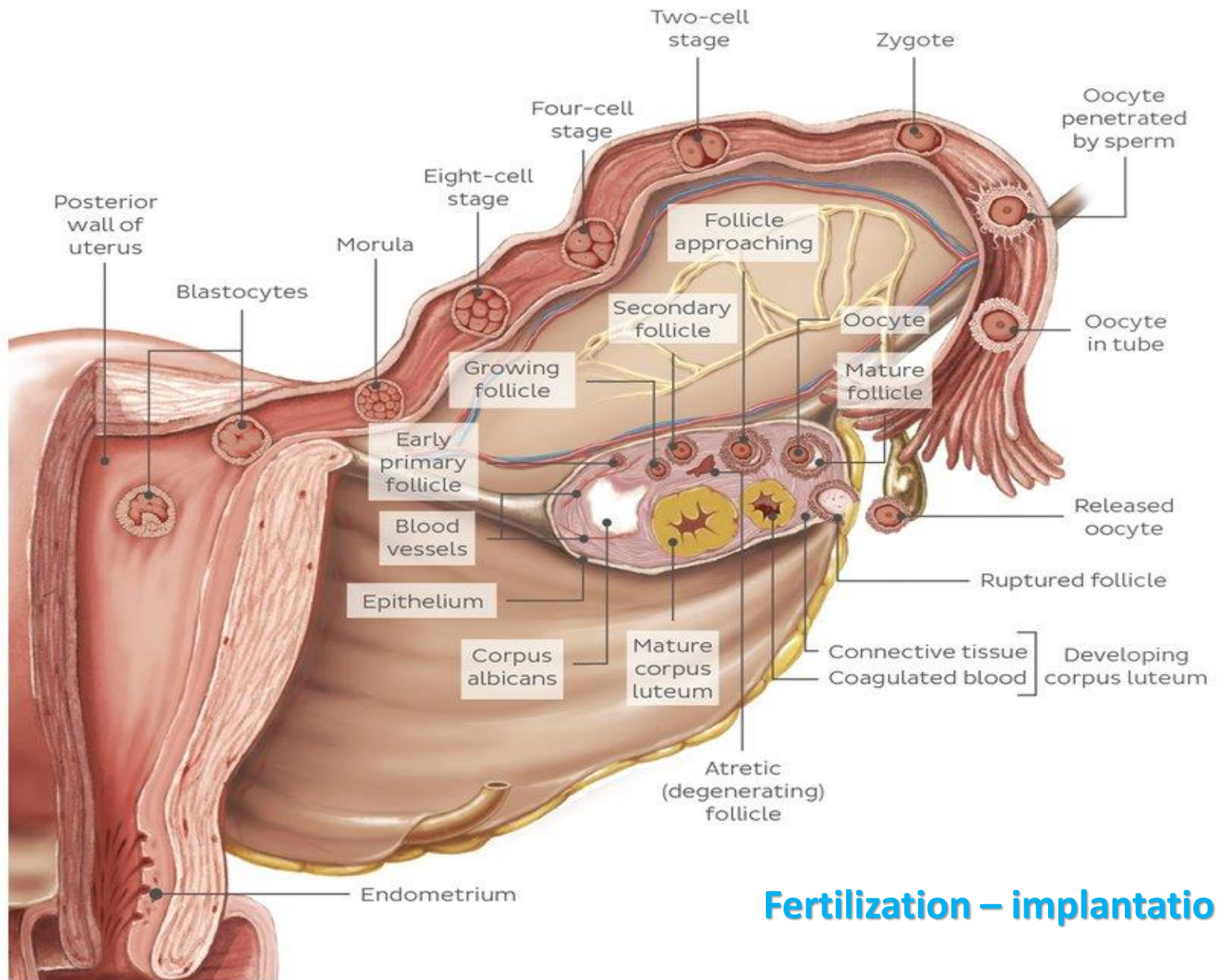
## **Embryonic period**

- from the beginning of the third to the end of the eighth week

## **Fetal period**

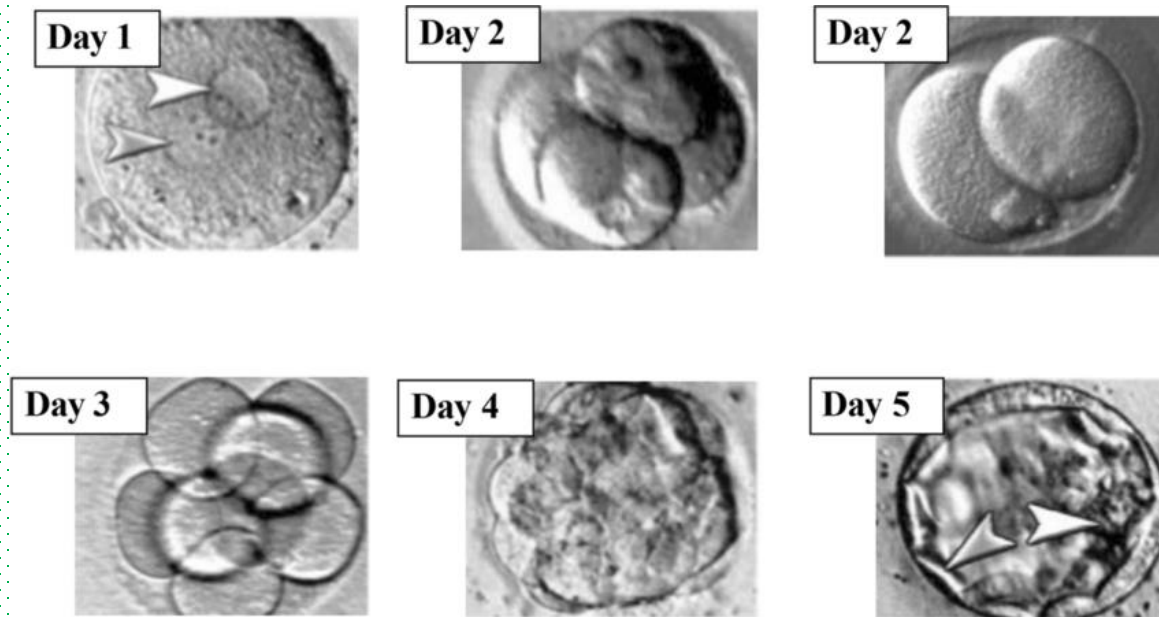
- from the beginning of the ninth week (from the 57th day) until delivery

# Week 1

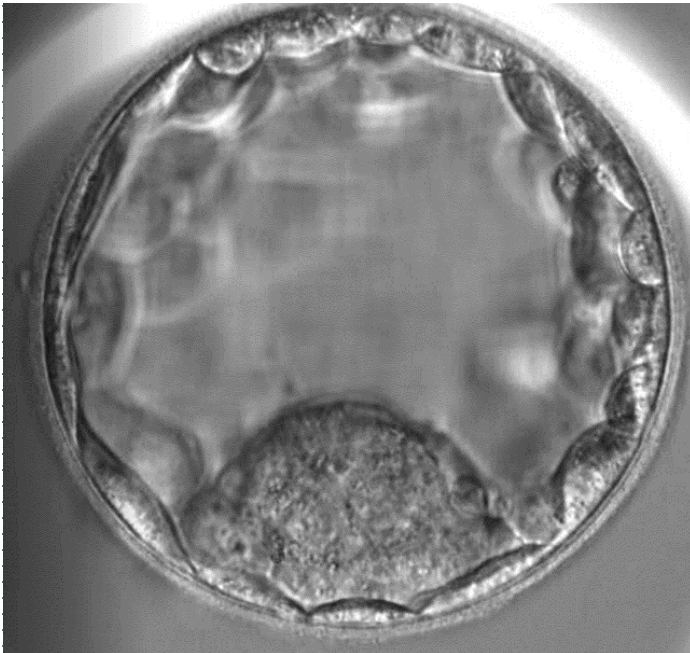
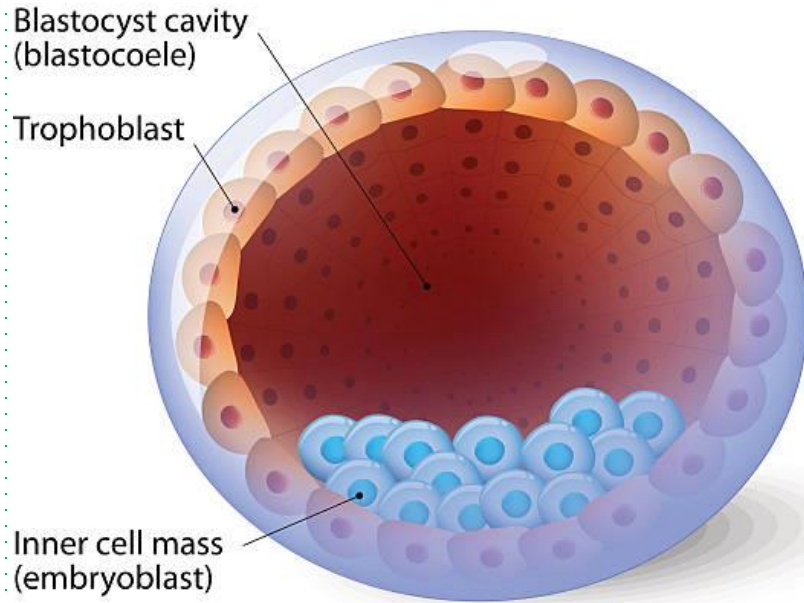




- Once the zygote has reached the two-cell stage, it undergoes a series of mitotic divisions, increasing the numbers of cells.
- During the second day there are **4 blastomeres**.
- Approximately 3-4 days after fertilization, cells of the compacted embryo divide again to form a **16-cell morula**
- Inner cells of the morula constitute the **inner cell mass**, and surrounding cells compose the **outer cell mass**.
- The inner cell mass gives rise to tissues of the embryo proper, and the outer cell mass forms the trophoblast, which later contributes to the placenta



# BLASTOCYST

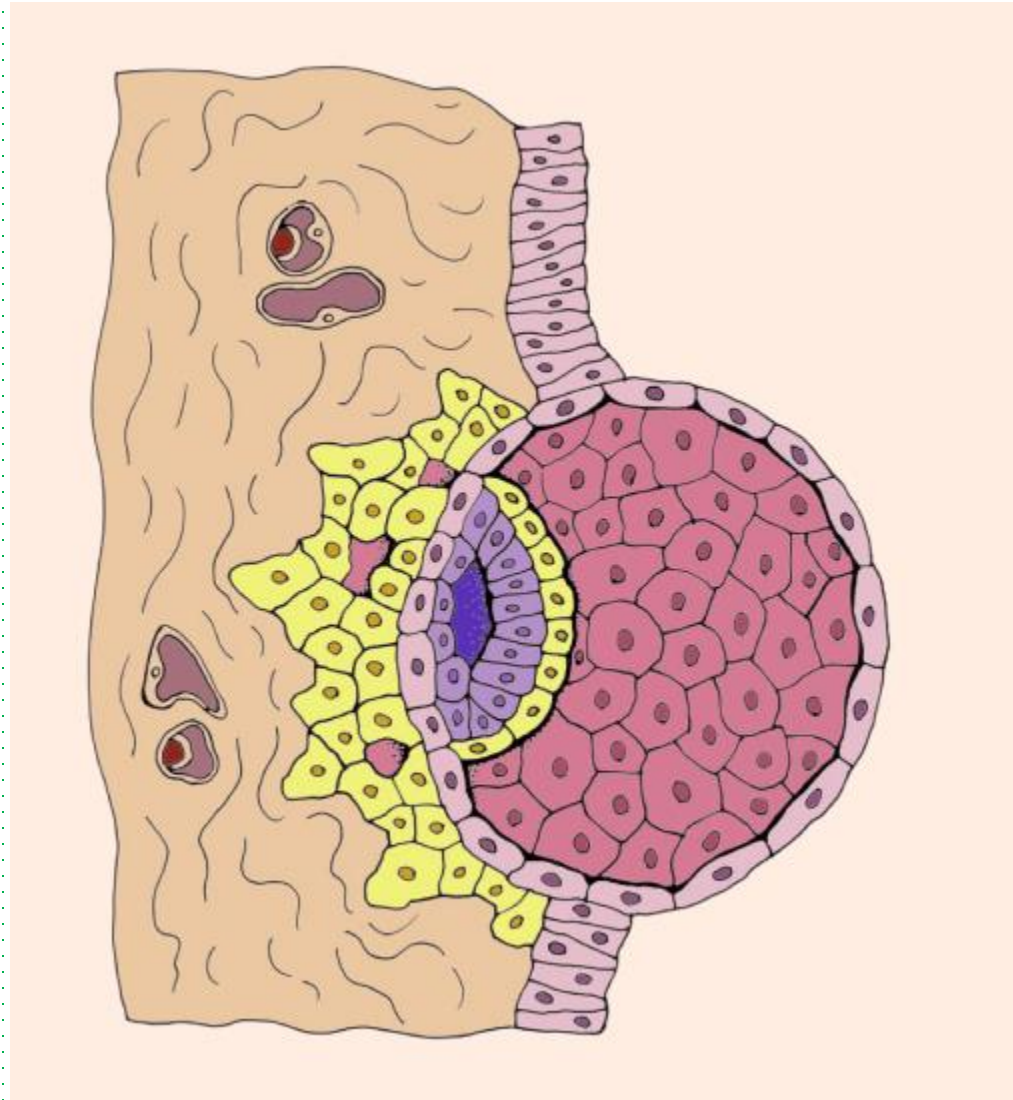


## Day 6

- Extracellular fluid accumulation begins from the product of the endometrial glands and blastocyst cavity or **blastocoele** is formed.
- The embryo at this stage of development is called a **blastocyst**.
- Inner cell mass, now called the **embryoblast**, and those of the outer cell mass, or **trophoblast**.

# Implantation

- Zona pellucida has disappeared, allowing **implantation** to begin.
- Trophoblastic cells begin to penetrate between the epithelial cells of the uterine mucosa on about the day 6.
- **Integrin** receptors for **laminin** promote attachment, while those for **fibronectin** stimulate migration. These molecules regulate trophoblast differentiation, so that implantation is the result of mutual trophoblastic and endometrial action.



# Week 2

## Week 2 events

Complete implantation

Blastocyst differentiation

Trophoblast differentiation

Formation of the two-layered embryonic disc (epiblast and hypoblast)

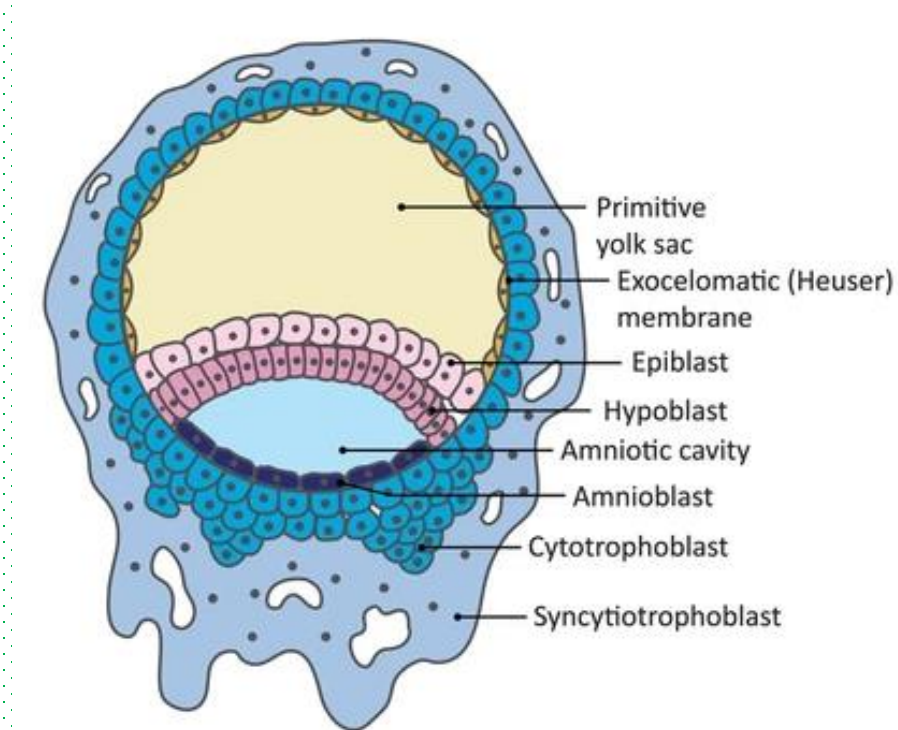
# Day 8

**Trophoblast** has differentiated into two layers:

- **Cytotrophoblast**, inner layer of mononucleated cells
- **Syncytiotrophoblast** outer multinucleated zone without distinct cell boundaries

**Embryoblast** also differentiate into two layers:

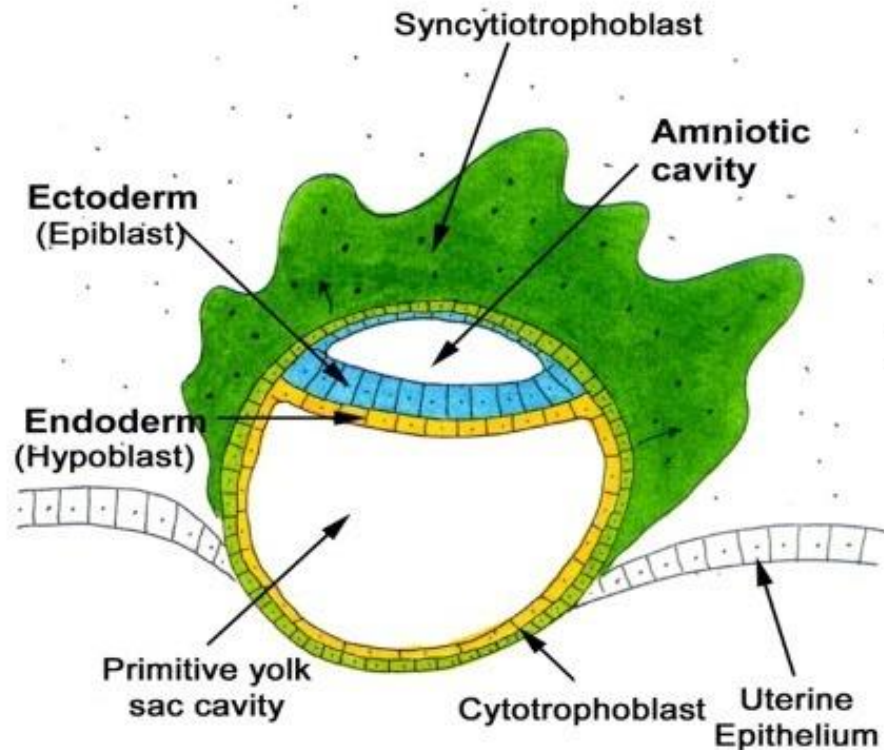
- **Hypoblast**, small cuboidal cells adjacent to the blastocyst cavity
- **Epiblast**, layer of high columnar cells adjacent to the amniotic cavity





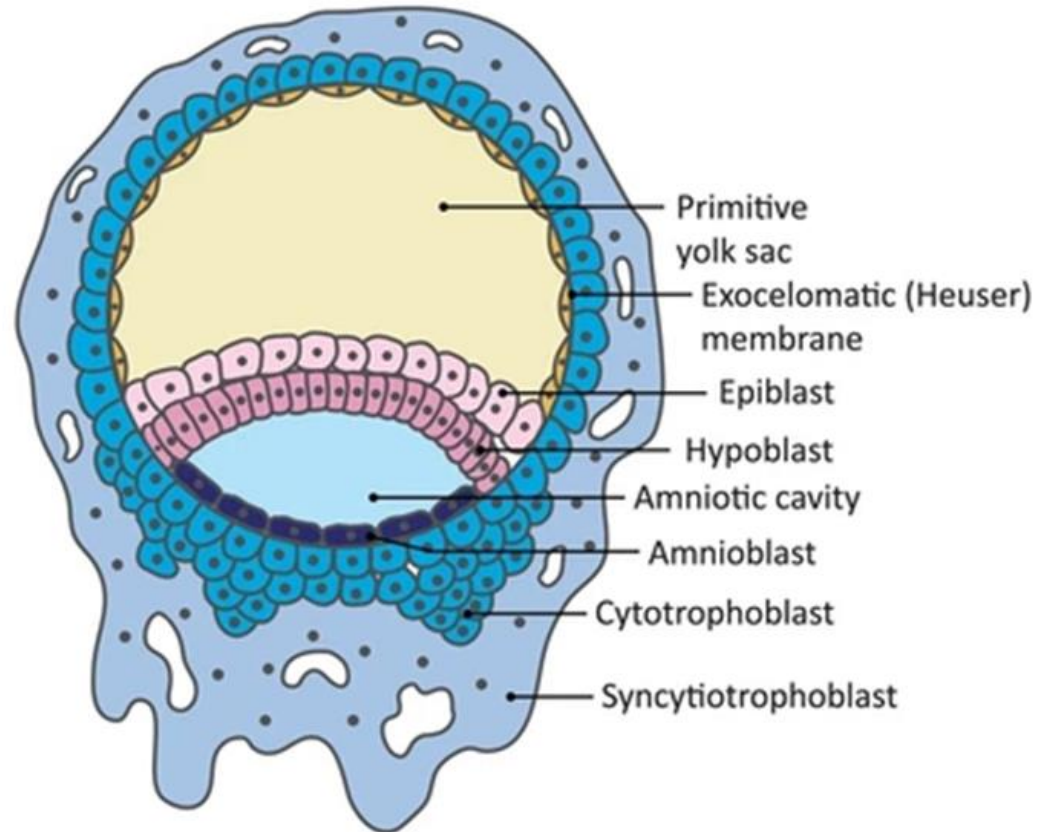
# Amniotic cavity

- Peripheral epiblast cells differentiate into elongated cells - **amnioblasts**.
- With a layer of epiblast cells, they limit the newly formed **amnion cavity**.
- The floor of the amniotic cavity builds a layer of **epiblast cells**, while its roof are made by **amnioblasts**.
- The amniotic cavity is filled with **amniotic fluid**.



# Day 9

- Cells probably originating from the hypoblast form a thin membrane, **the exocoelomic (Heuser's) membrane** that lines the inner surface of the cytotrophoblast.
- This membrane, together with the hypoblast, forms the lining of the exocoelomic cavity, or **primitive yolk sac**.

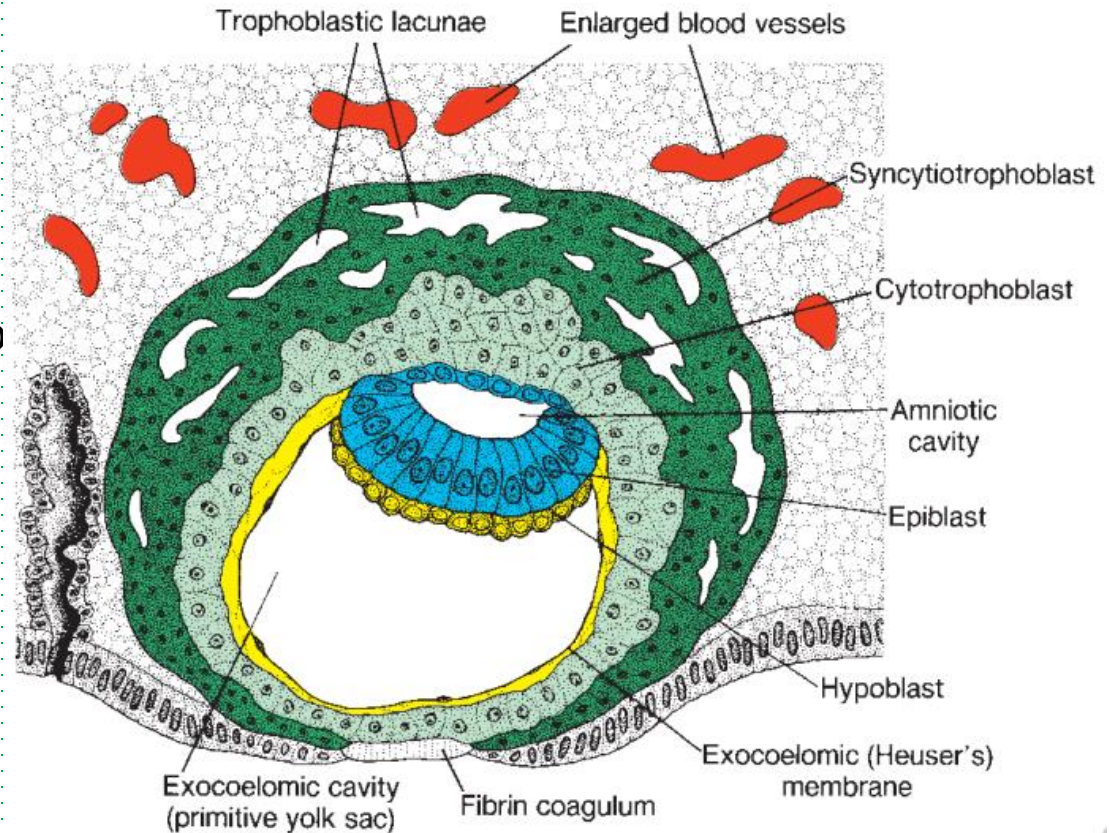


# END of Day 9

- The implantation is complete.
- The cells of the epiblast proliferate and differentiate into **amnioblasts**, which, together with epiblast cells, limit the **amniotic cavity**.
- Hypoblast cells line the blastocyst cavity, building **Heuser's membrane**.
- **Lacunae** are formed in the syncytiotrophoblast.
- The belt of peripherally placed syncytiotrophoblast expands so that it completely surrounds the blastocyst at the moment when it has completely sunk into the endometrium.
- The superficial epithelium becomes continuous again, although in some cases, a coagulation plug may form at the implantation site.

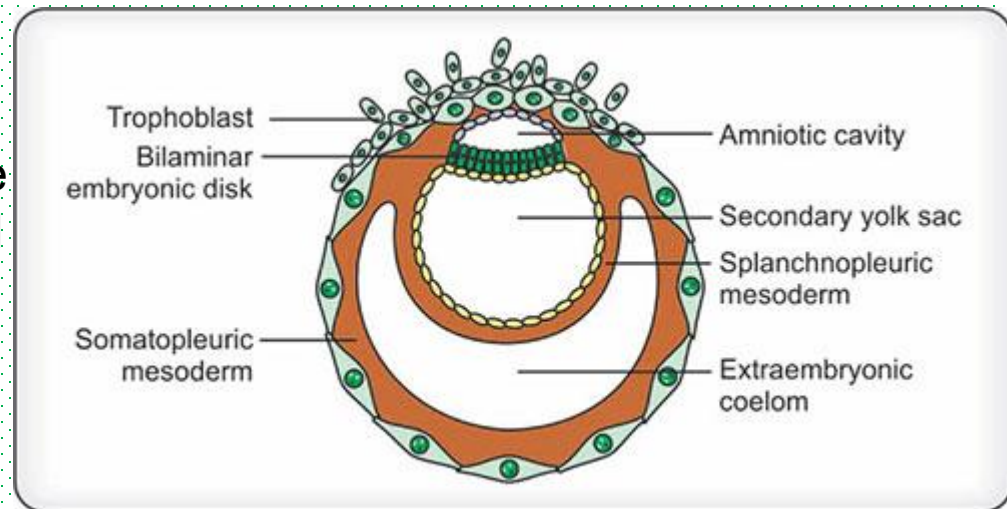
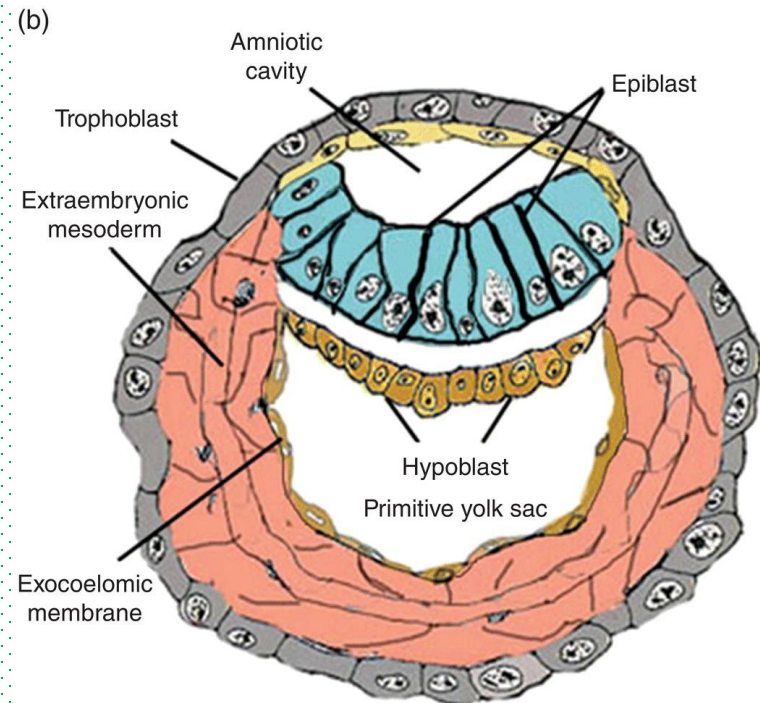
# Day 11-12

- Trophoblastic lacunae become continuous with the sinusoids, and maternal blood enters the **lacunar system**.
- As the trophoblast continues to erode more sinusoids, maternal blood begins to flow through the trophoblastic system, establishing the **uteroplacental circulation**.

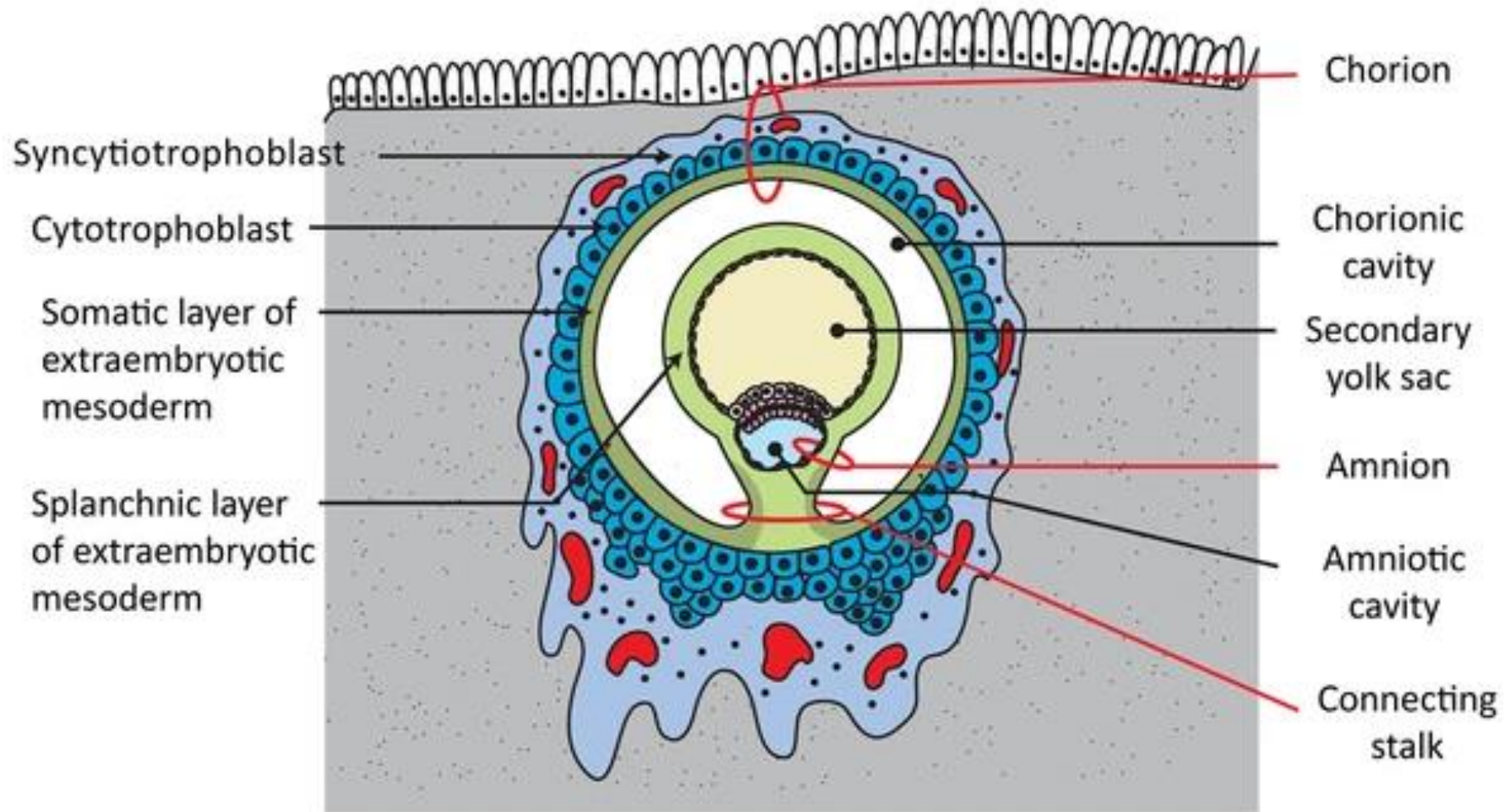




- Cells, derived from yolk sac cells, form loose connective tissue, the **extraembryonic mesoderm**, which eventually fills all of the space between the trophoblast externally and the amnion and exocoelomic membrane internally.
- Large cavities develop in the extraembryonic mesoderm, become confluent, they form a new space - the extraembryonic cavity, or **chorionic cavity**.
- Extraembryonic mesoderm lining the cytotrophoblast and amnion is called the **extraembryonic somatic mesoderm**; the lining covering the yolk sac is known as the **extraembryonic splanchnic mesoderm**.



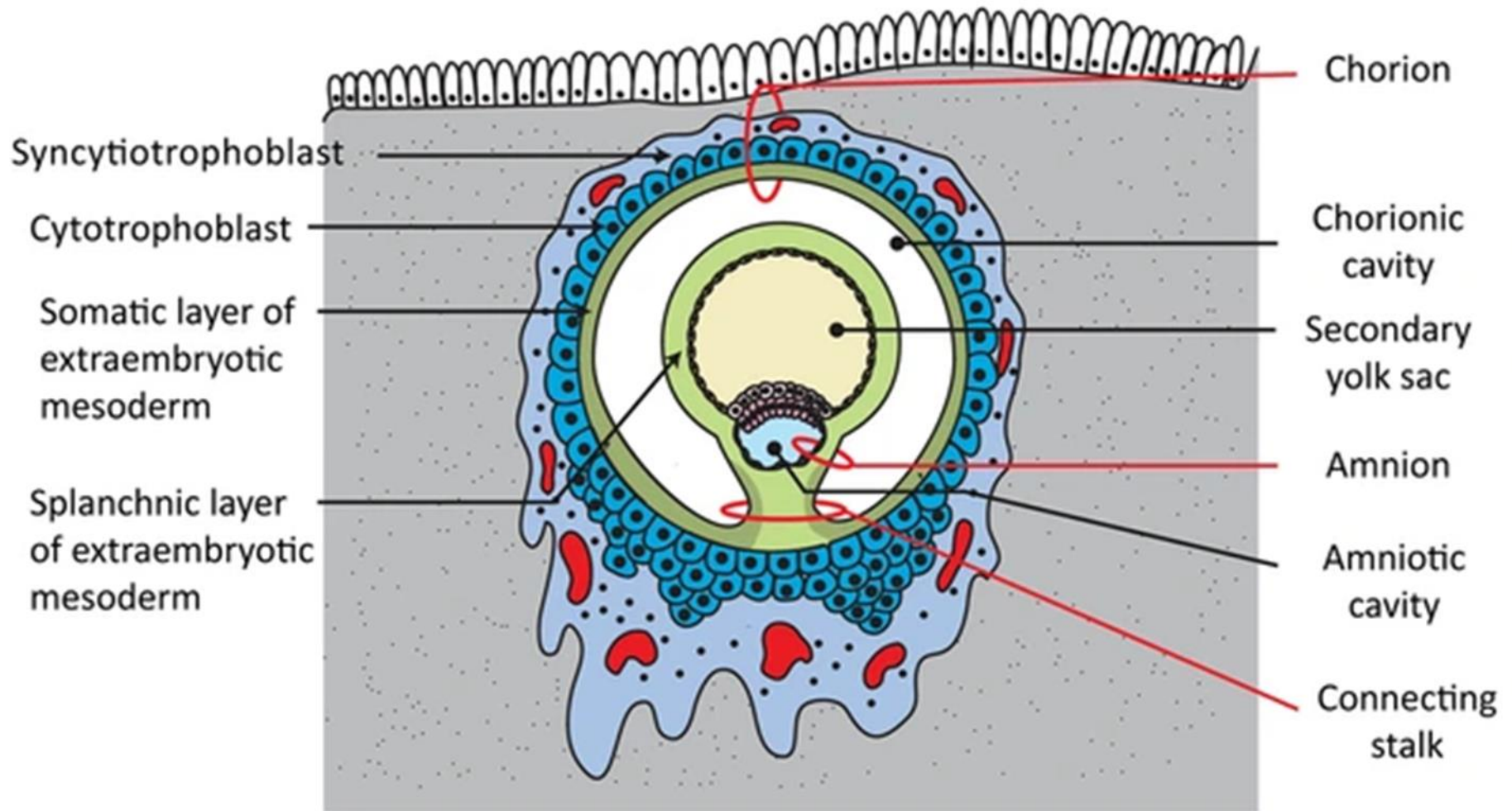




Cells of the endometrium, meanwhile, become polyhedral and loaded with glycogen and lipids; intercellular spaces are filled with extravasate, and the tissue is edematous. These changes, known as the **decidua reaction**.

# Amnion and chorion

- Extraembryonic mesoderm cells separate into two layers.
  - The **inner layer envelops the amniotic cavity and the primary yolk sac.**
  - The **outer (parietal) layer rests on the cytotrophoblast.**
  - In this way, two new extraembryonic structures are formed - **amnion and chorion.**
- 
- **Amnion** consists of the **amniotic epithelium and the inner layer extraembryonic mesoderm.**
  - **Chorions** build **the outer layer of extraembryonic mesoderm and trophoblast.**

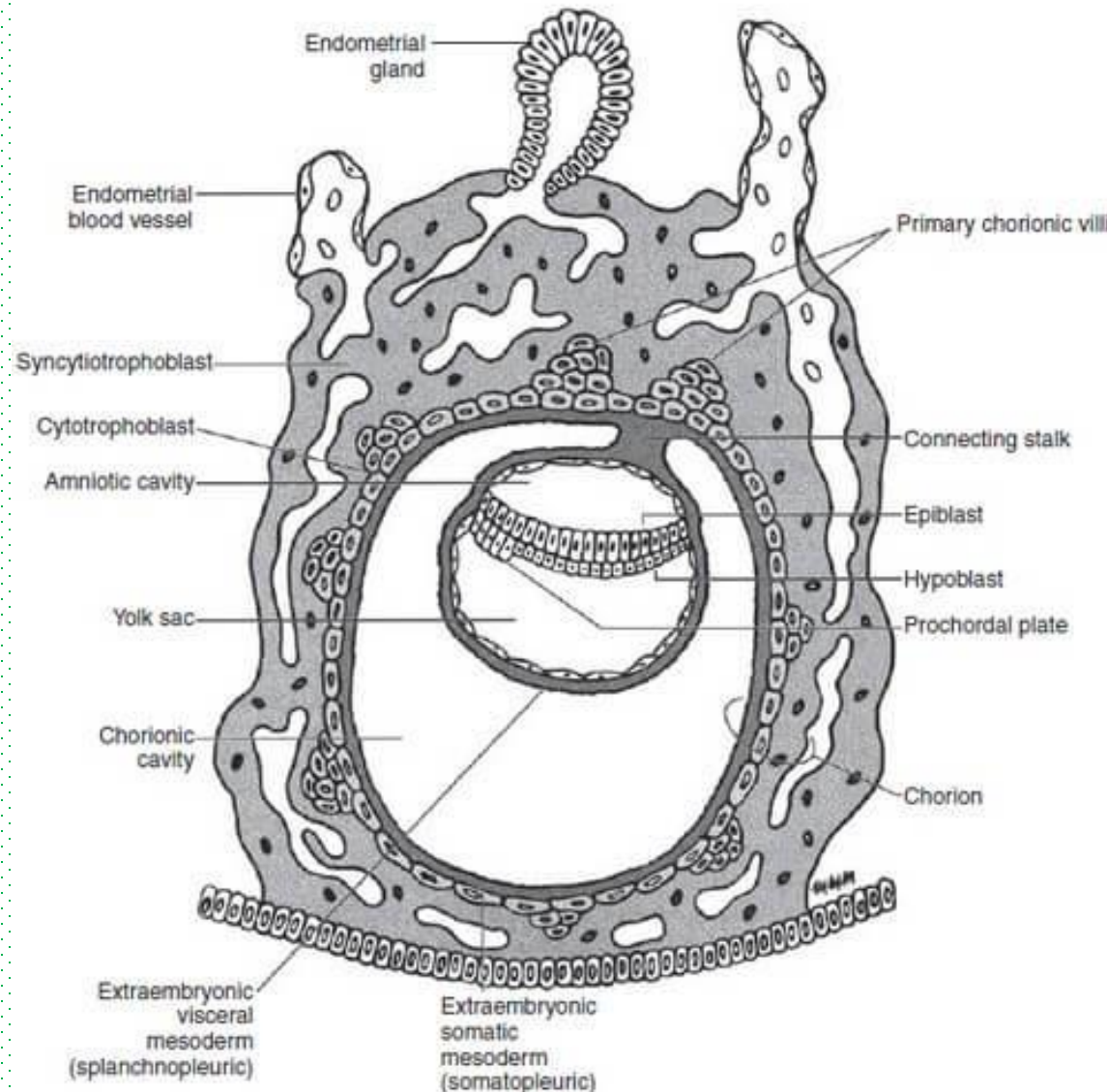


The inner layer of extraembryonic mesoderm, from the 12th to the 13th day, equatorially borders the primary yolk sac.

Thus, the primary yolk sac is divided into a definitive - **secondary yolk sac** and a small ventral remnant of the primary one, which is reduced.

# Chorionic cavity

- Between the two layers of extraembryonic mesoderm, at the end of the 2nd week of development, a newly formed **chorionic cavity** or extraembryonic coelom is clearly visible.
- The chorionic cavity does not completely separate the two layers of extraembryonic mesoderm.
- The layers of extraembryonic mesoderm become fused over **connecting stalk**.
- Umbilical cord** will develop from this stem.



..end of **second** week.....the rule of **2s**

**Two**-layered embryonic disc is made up of **epiblast and hypoblast**.

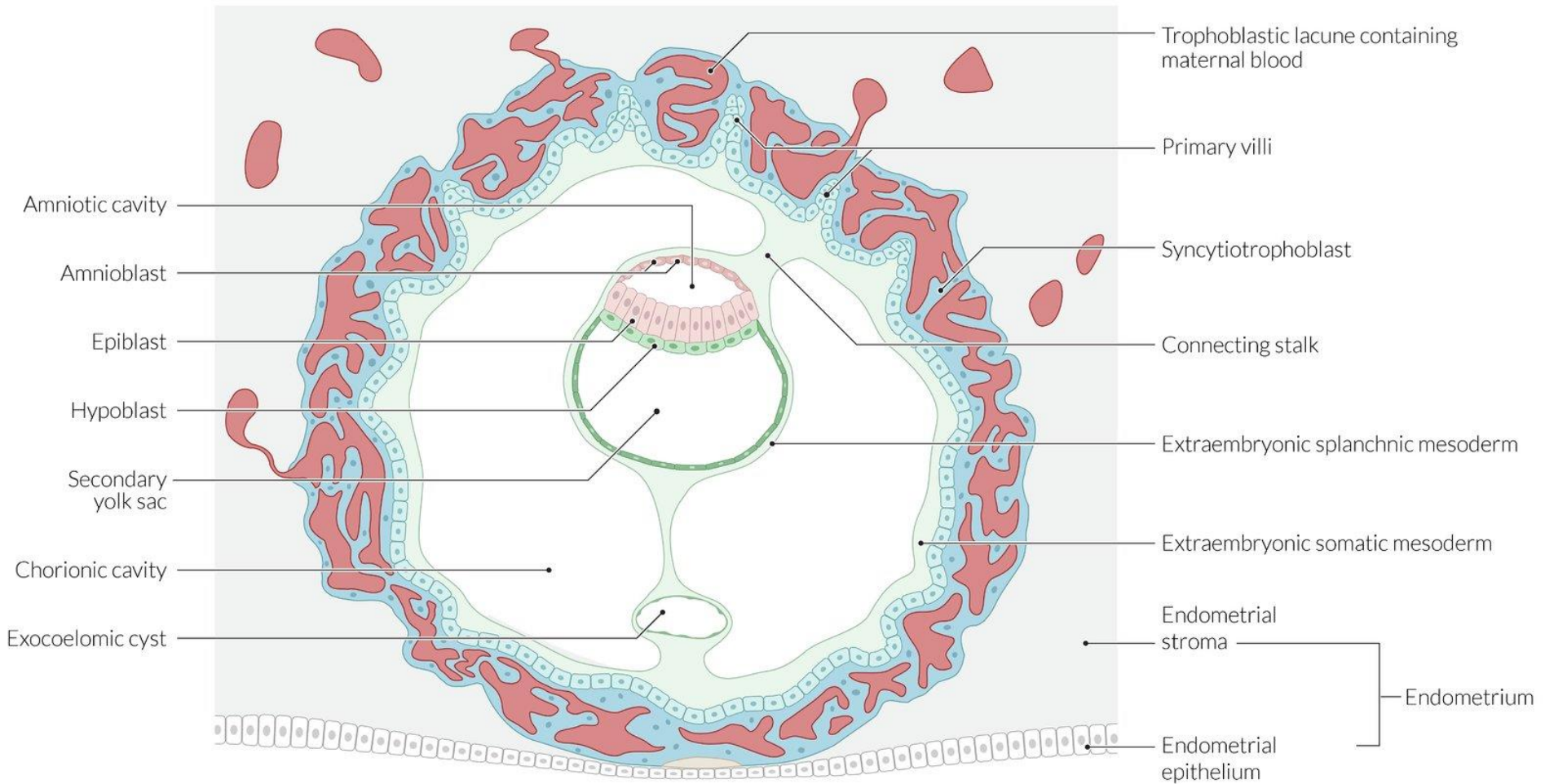
**Two** layers of **trophoblast**

**Two** cavities, **secondary yolk sac** and a **chorionic cavity** are formed,

**Two** sheets of **extraembryonic mesoderm** connected **connected stalk** (future umbilical cord).

**Secondary chorionic** villi are formed





# Chorionic villi

Stages in the formation of chorionic villi.

1. **Primary villi** are avascular and contain cytotrophoblast surrounded by syncytiotrophoblast. (13-15 day)
2. **Secondary villi** are also avascular and formed when parietal sheet of the extraembryonic mesoderm penetrates in primary. (16-21 day)
3. **Tertiary villi** are formed when branches of the umbilical artery and umbilical vein grow into the mesoderm, and in this way the chorionic villi are vascularized. (17-22 day)



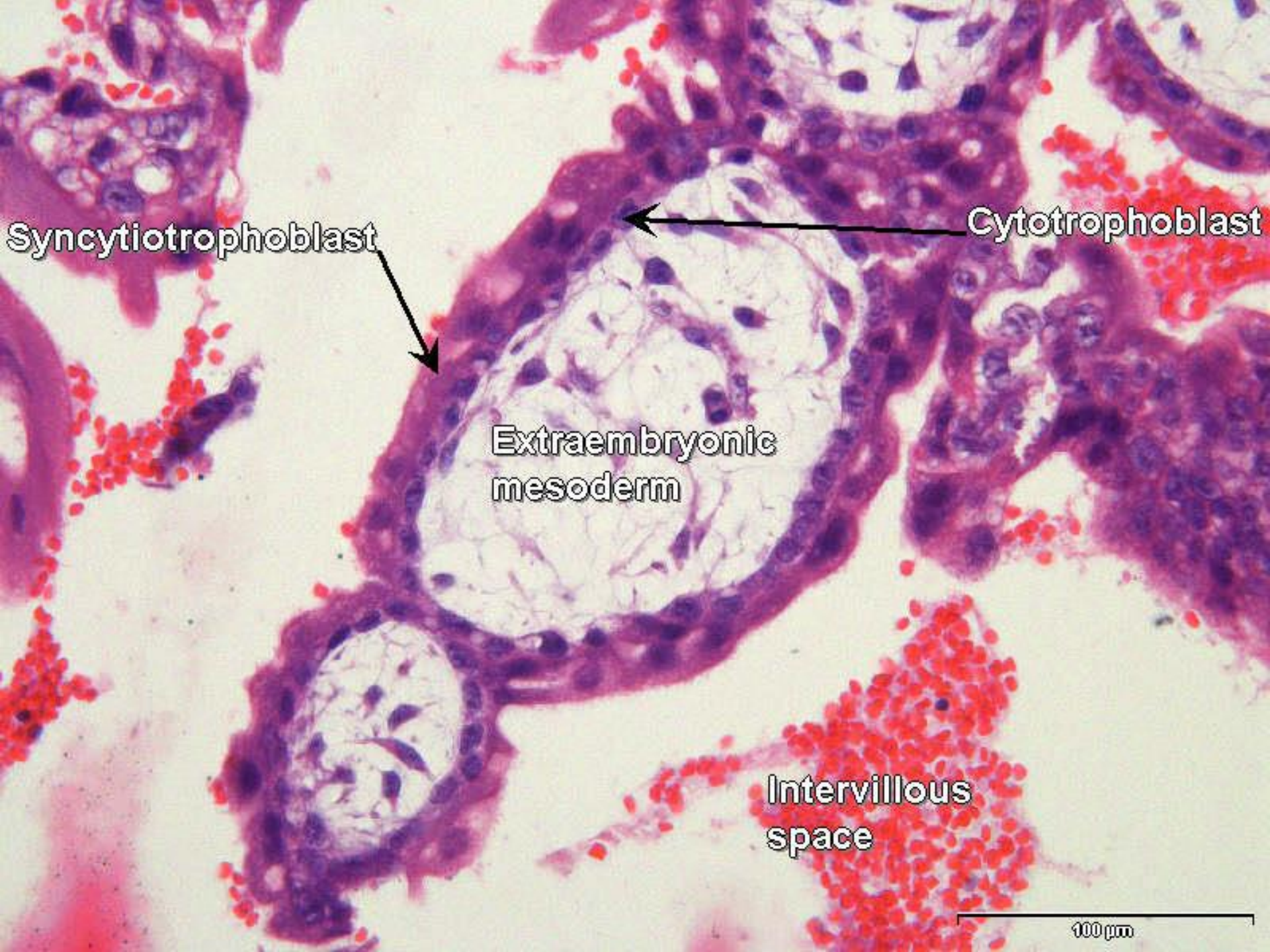
Syncytiotrophoblast

Cytotrophoblast

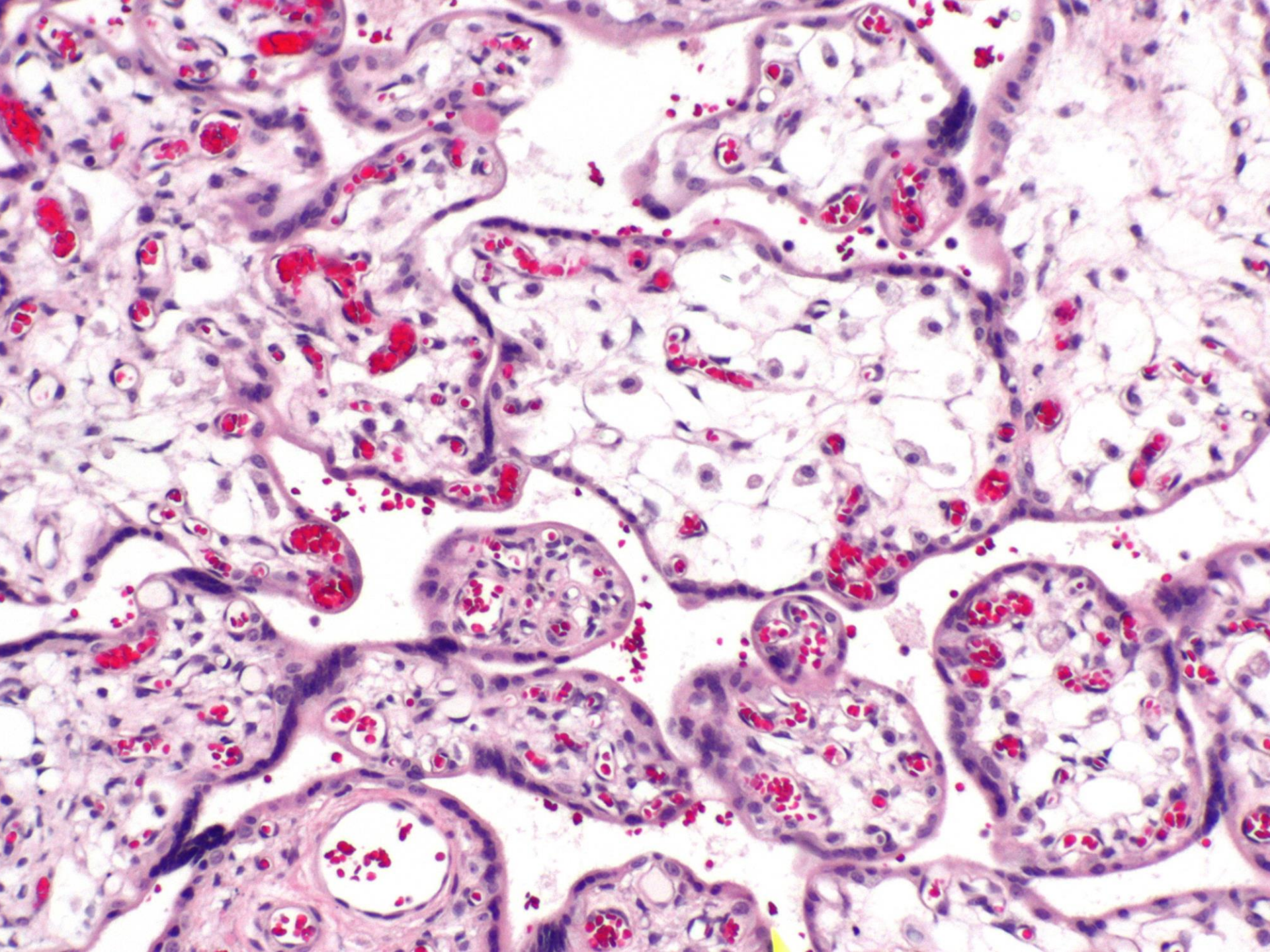
Extraembryonic  
mesoderm

Intervillous  
space

100  $\mu$ m





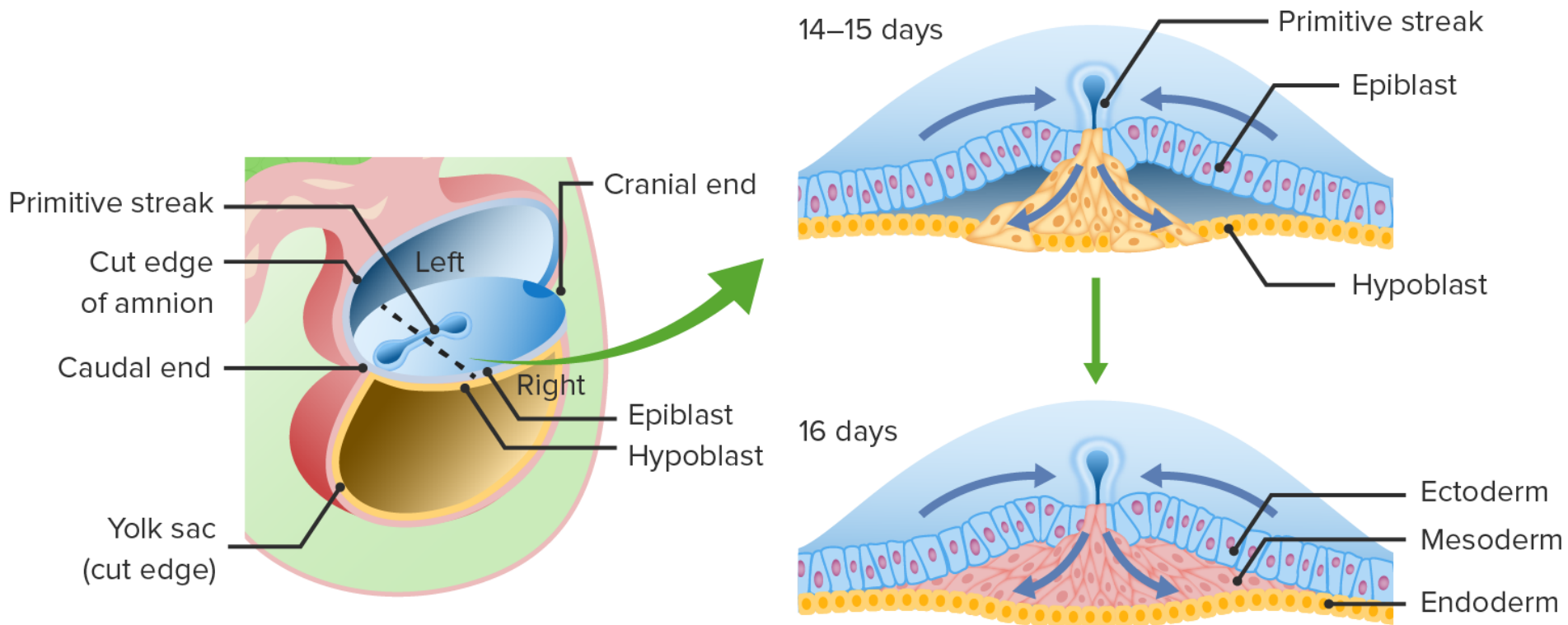


# Embryonic period

- It lasts from the beginning of the third to the **end of the eighth week**.
- In this period is called an **embryo**.
- The embryonic period is marked by the growth of the embryo and the differentiation of the germ layers.



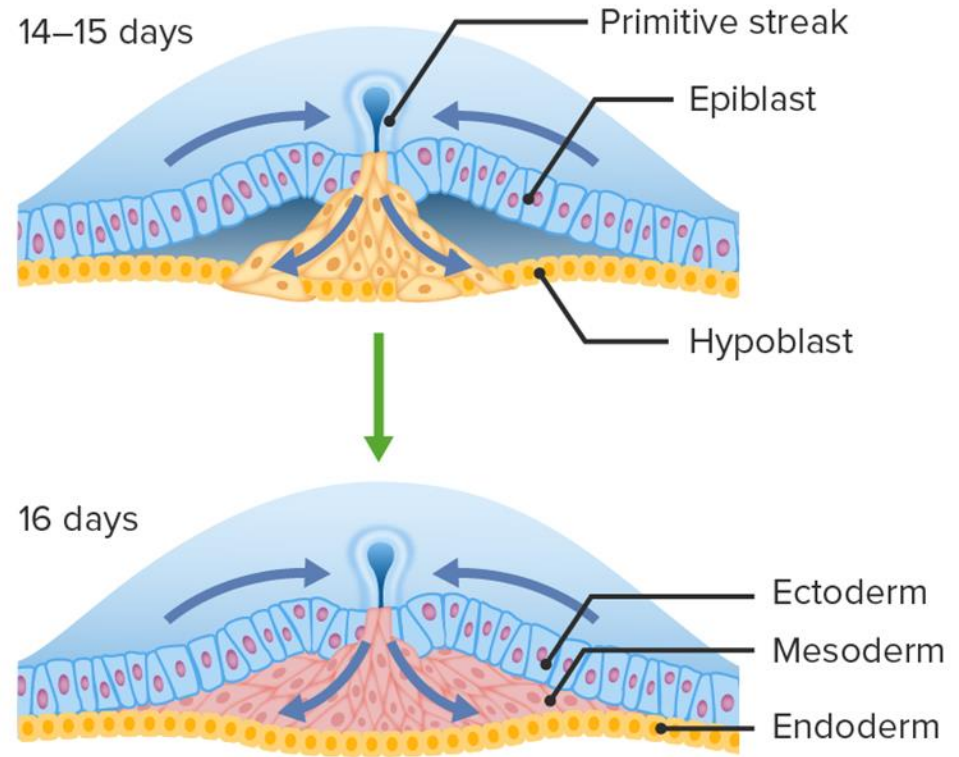
# Week 3..... Gastrulation

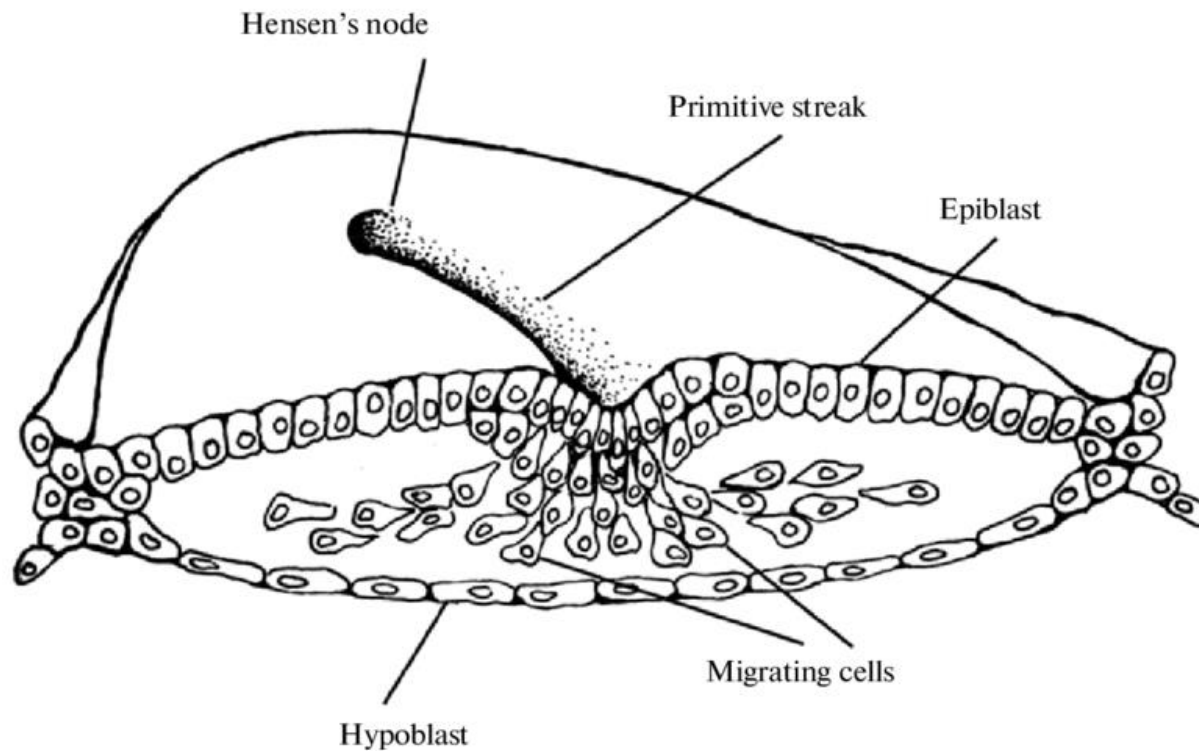


The most characteristic event occurring during the third week of gestation is **gastrulation**, the process that establishes all three germ layers

1. **Ectoderm,**
2. **Mesoderm,**
3. **Endoderm**

- Gastrulation begins with formation of the **primitive streak** on the surface of the epiblast
- Cephalic end of the streak, the **primitive node**, consists of a slightly elevated area surrounding the small **primitive pit**
- Cells of the epiblast migrate toward the primitive streak, detach from the epiblast, and slip beneath it then undergo **epithelial to mesenchymal transition** in a process known as **ingression**.



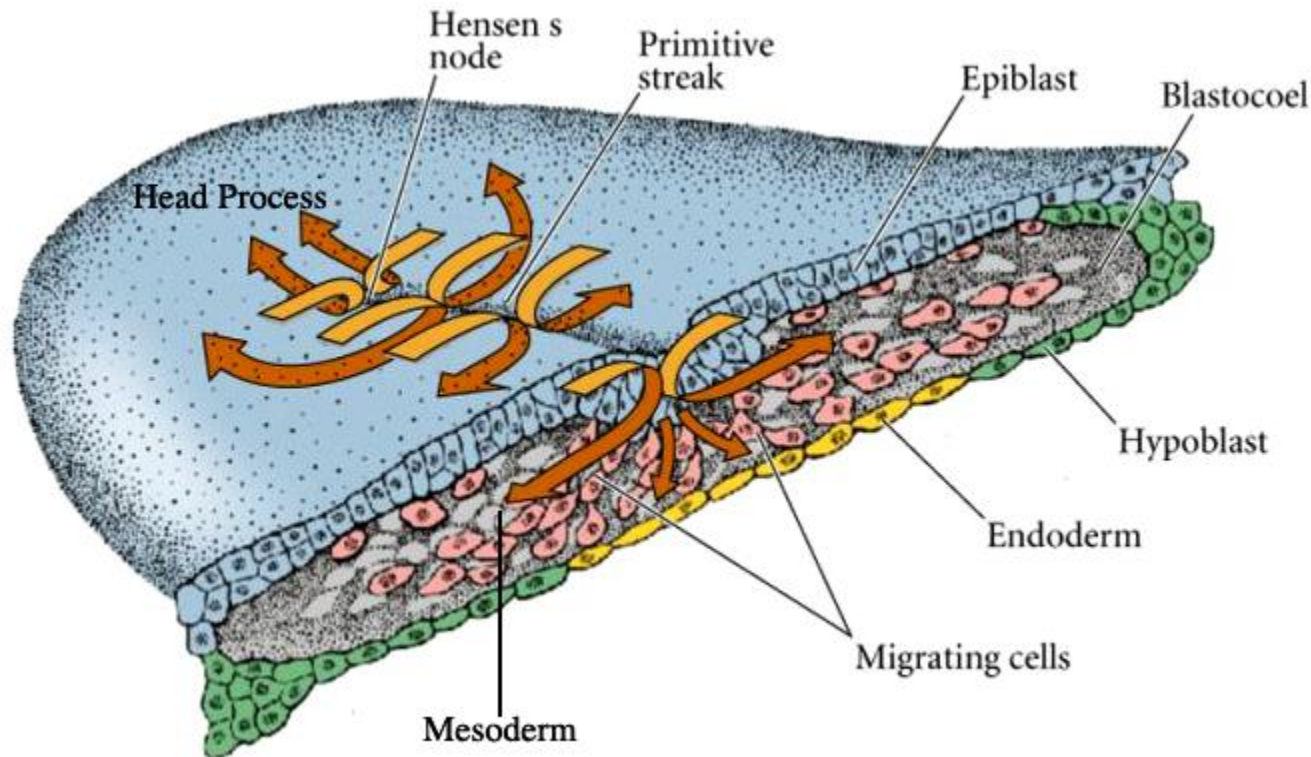


The cranial (head) and caudal (tail) poles are differentiated on the two-layered embryonic disc.

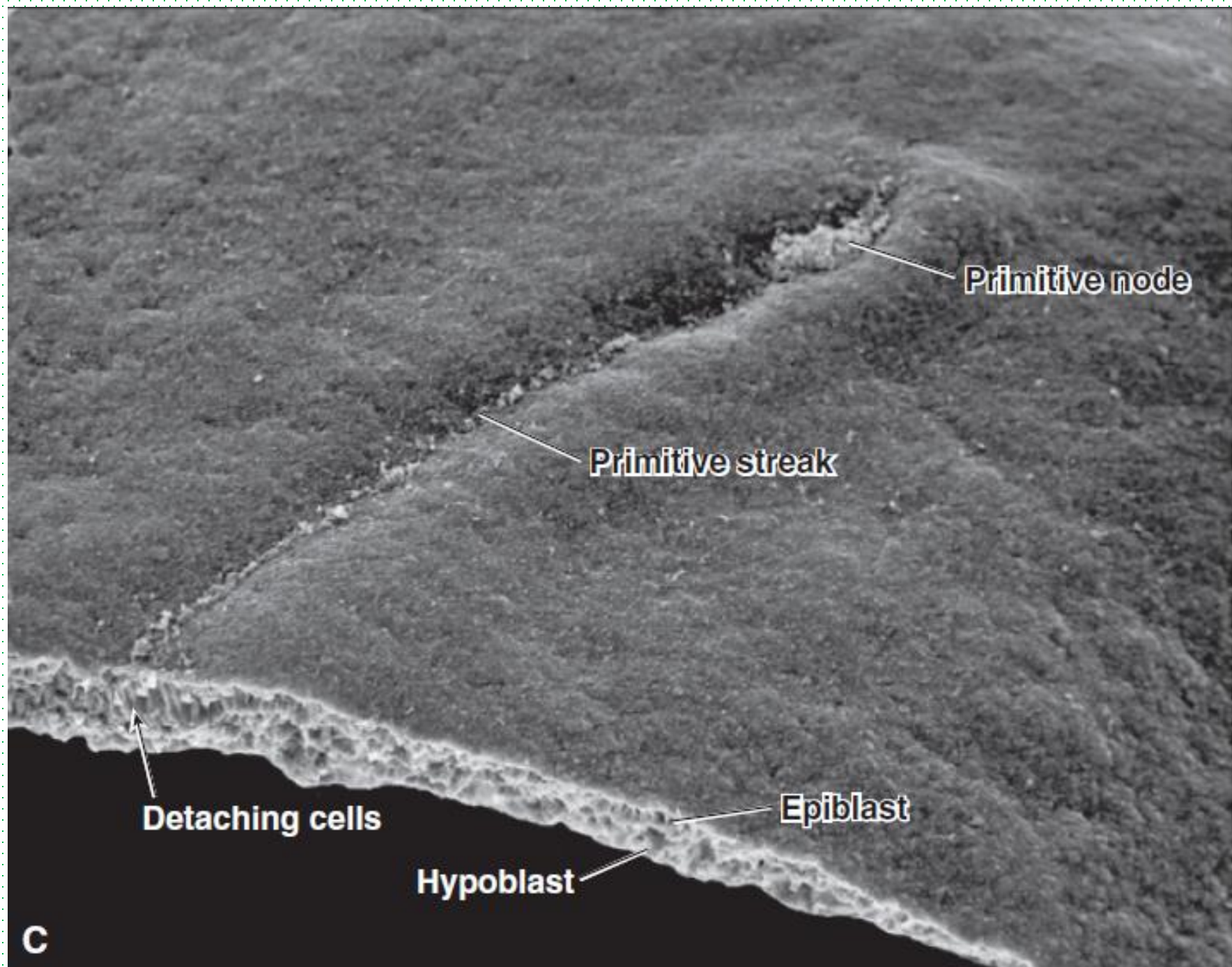
The **oropharyngeal membrane** is located on the cranial pole, and on the caudal half of the **cloacal membrane**.

Behind the oropharyngeal membrane is a limited thickening of the endoderm called the **prechordal plate**.

- ❖ Cells ingress through the streak and invade the hypoblast layer to form **embryonic endoderm**.
- ❖ Cells continue ingress the following day between the epiblast and endoderm layers to form **mesoderm**.
- ❖ Cells remaining in the epiblast then form **ectoderm**.





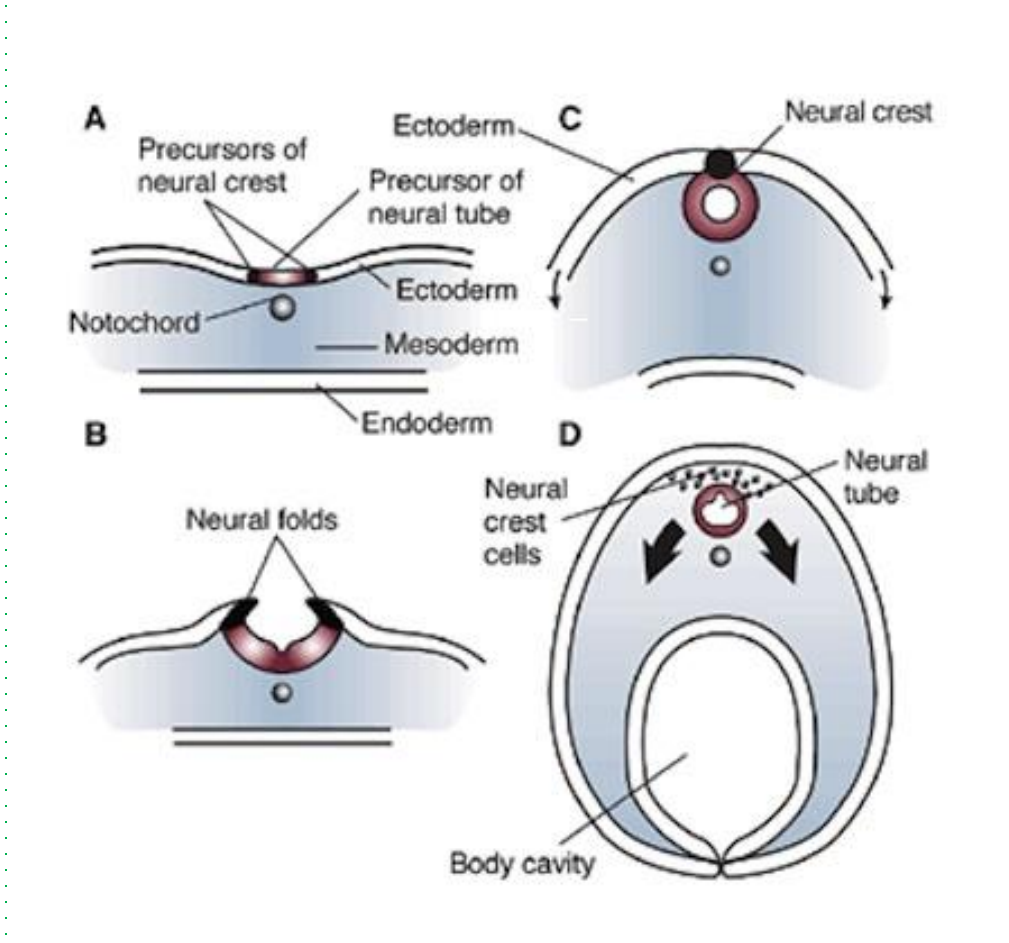




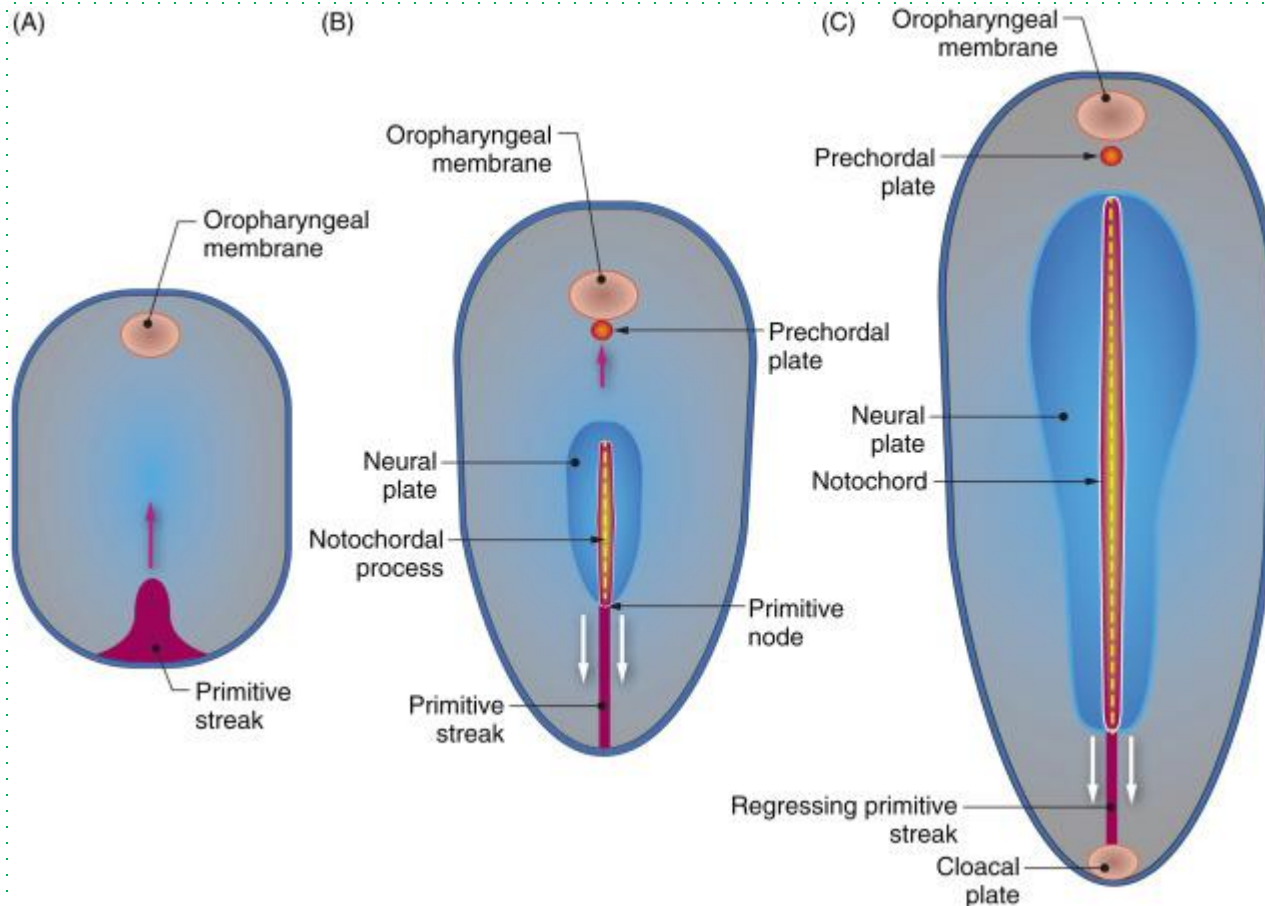
# In brief.....

- Blastocyst 14.-15. days of development contains epiblast and hypoblast.
- On the 15th day of development of an epiblast cell from the region of the primitive streak proliferate and migrate to the hypoblast.
- They take the place of hypoblastic cells and form the endoderm.
- Proliferation and migration of epiblast cells continues, with the newly formed cells populating the area between the epiblast (the future **ectoderm**) and the forming endoderm, forming the intraembryonic **mesoderm**.

# FORMATION OF THE NOTOCHORD



- **Prenotochordal cells** invaginating in the primitive node move forward cranially in the midline until they reach the **prechordal plate**

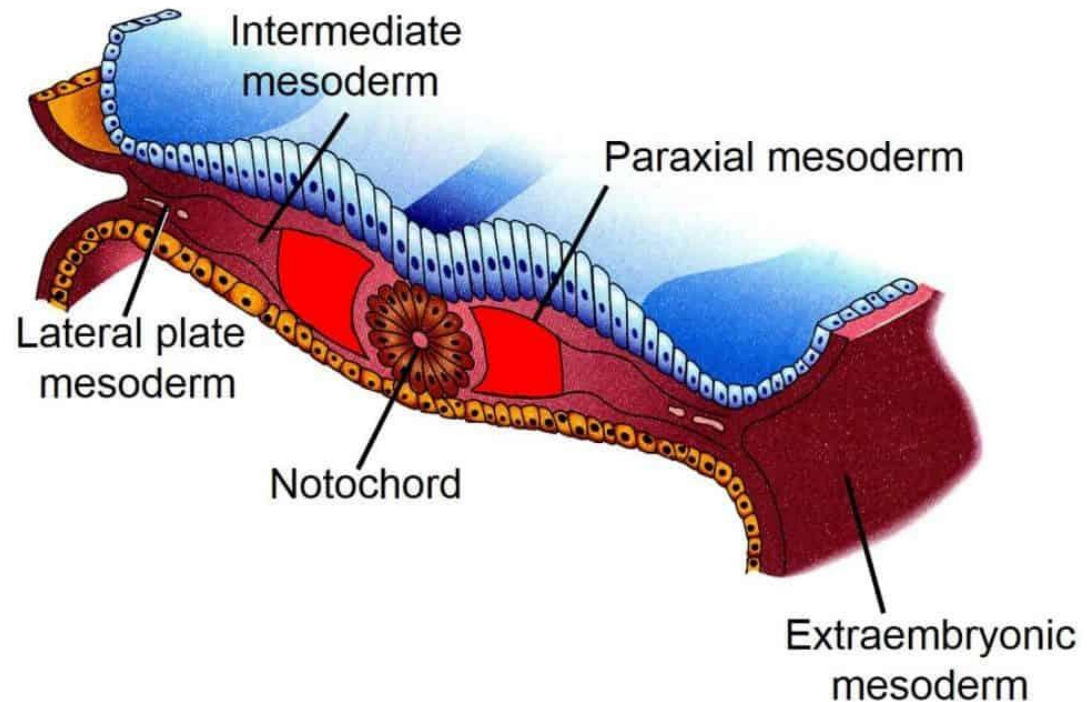


- Midline of the embryo consists of two cell layers that form the **notochordal plate**
- Cells of the notochordal plate proliferate and detach from the endoderm.
- They then form a solid cord of cells, the definitive **notochord**

# Mesoderm derivatives

The mesoderm is then segmented into:

- **axial**
- **paraxial mesoderm**
- **intermediate mesoderm**
- **lateral plate mesoderm**



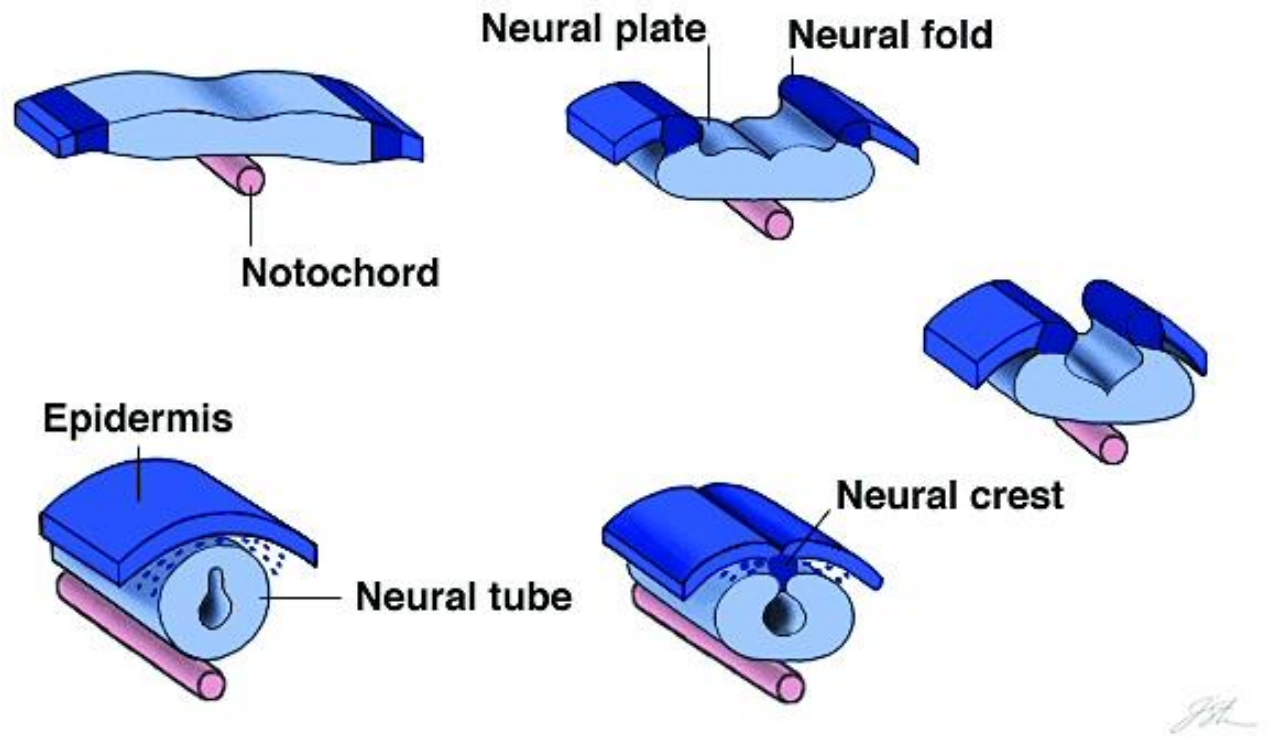
- Paraxial mesoderm gives rise to **somitomes**.
- The intermediate mesoderm divides into a **nephrotome**.
- Lateral mesoderm splits into **parietal** and **visceral** sheets

# Ectoderm .....

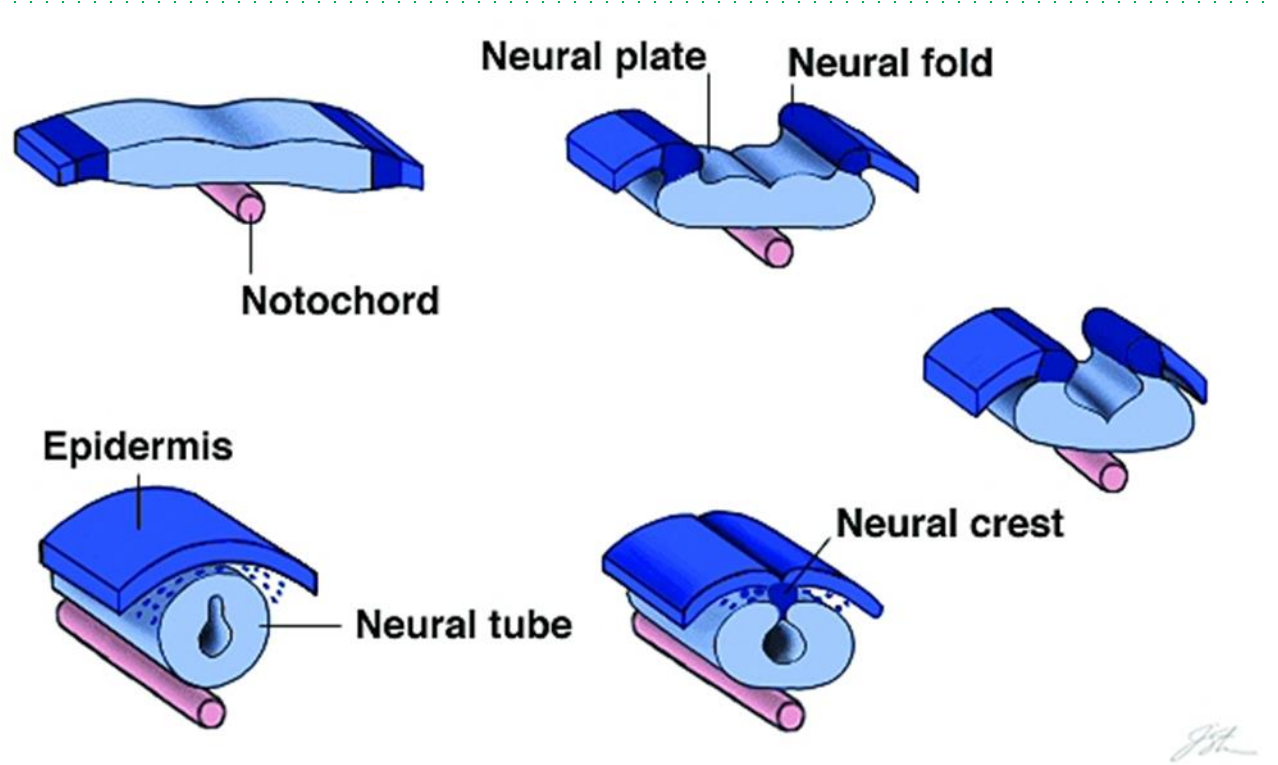
- The cells of the ectoderm in its central part become more cylindrical than those on the periphery - they will give the **epidermis of the skin**.
- These cells will serve as the basis from which the nervous system develops - **neuroectoderm**.
- Bending of this part creates a **neural tube**.



# Neurulation



- **Neurulation** is the process of **neural tube** formation and takes place from the middle 3rd to the end of the 4th week of development under the inductive effect of the notochord.



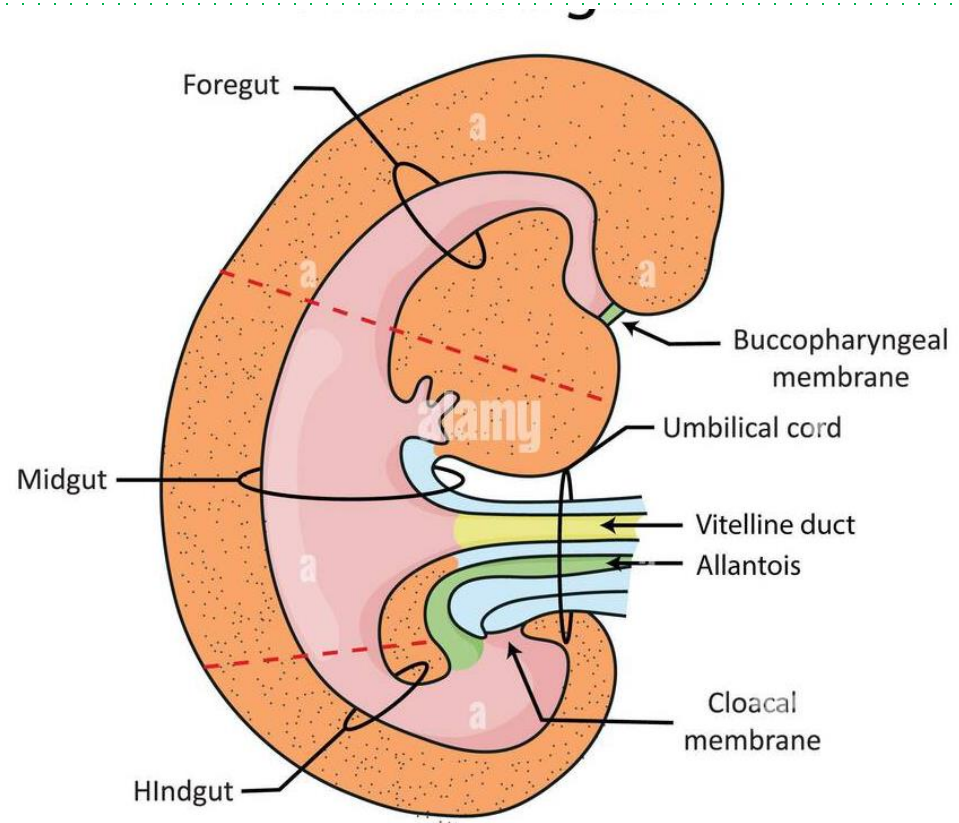
- First, a **neural plate** is formed in the form of a thickened ectoderm, then the plate indents and forms a **neural fold**, and finally the **neural tube** and **neural crest** form from the neural groove.

# Neural crest derivatives....

Connective tissue and bones of the face and skull
Cranial nerve ganglia (see Table 17.2)
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
Meninges (forebrain)
Melanocytes
Smooth muscle cells to blood vessels of the face and forebrain

# Endoderm .....

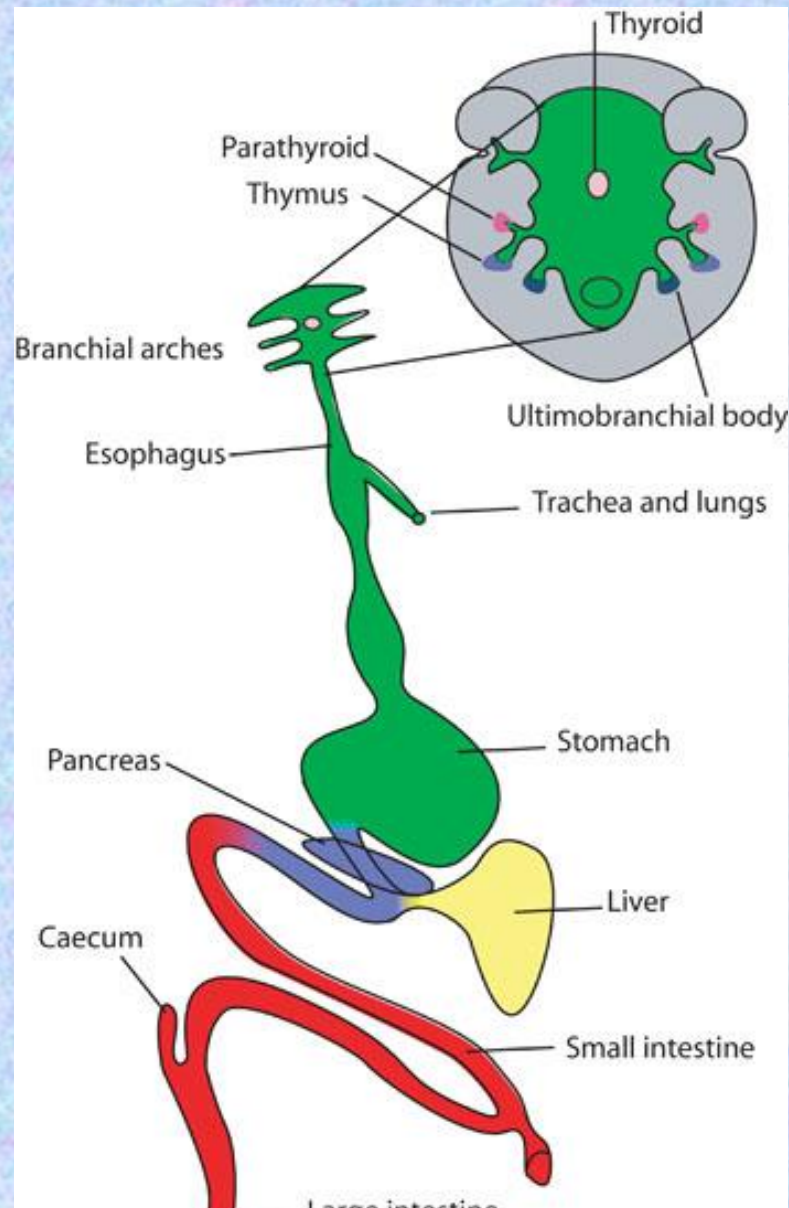
- As a result of the folding of the embryonic disc, the endoderm is formed into a tubular structure - the **primitive gut**.
- The primitive intestine is divided in the cephalocaudal direction into the **foregut**, **midgut** and **hindgut**.
- **Midgut** communicates with the yolk sac by **vitelline duct**.
- **Foregut** begins with the oropharyngeal membrane and gives ventral buds (evaginations) - **respiratory bud** and **liver bud**, which further differentiates.
- **Hindgut** is closed by the cloacal membrane.





# Derivatives of the Endodermal Germ Layer

- it gives rise to
- (a) the epithelial lining of the respiratory tract;
- (b) the Parenchyma of the thyroid, parathyroids, liver, and pancreas
- (c) the reticular stroma of the tonsils and thymus;
- (d) the epithelial lining of the urinary bladder and urethra; and
- (e) the epithelial lining of the tympanic cavity and auditory tube





# Ectoderm derivatives....

## Superficial ectoderm

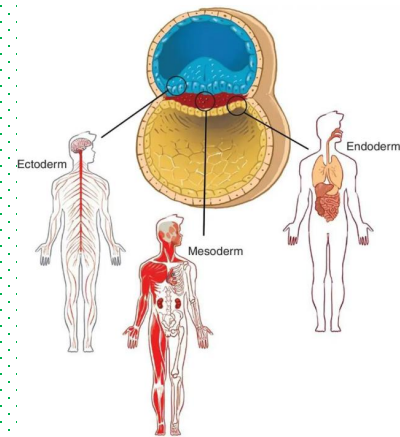
- skin epithelium and its derivatives
- epithelium of the oral cavity and salivary glands, enamel, adenohypophysis
- nose, eye lens and ear
- epithelium of the cornea, external ear canal and inner ear

## Neuroectoderm

- neural tube
- CNS (brain and spinal cord)
- neurohypophysis and pineal gland
- retina

## Neural crest

- PNS (spinal and vegetative ganglia), Schwann and satellite cells
- melanocytes
- odontoblasts
- connective tissue, cartilage and bones of the head and neck
- adrenal medulla
- C-cells of the thyroid



# Mesoderm derivatives

## ➤ Axial mesoderm (notochord)

- Vertebral column

## ➤ Paraxial mesoderm

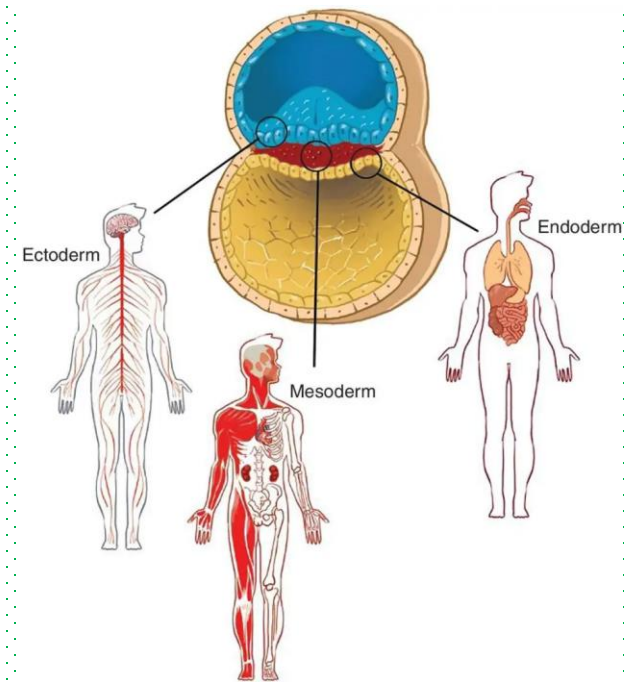
- dermatomes (dermis of the skin)
- sclerotomes (connective tissue, cartilage and bones of the body and limbs)
- myotomes (skeletal muscles)

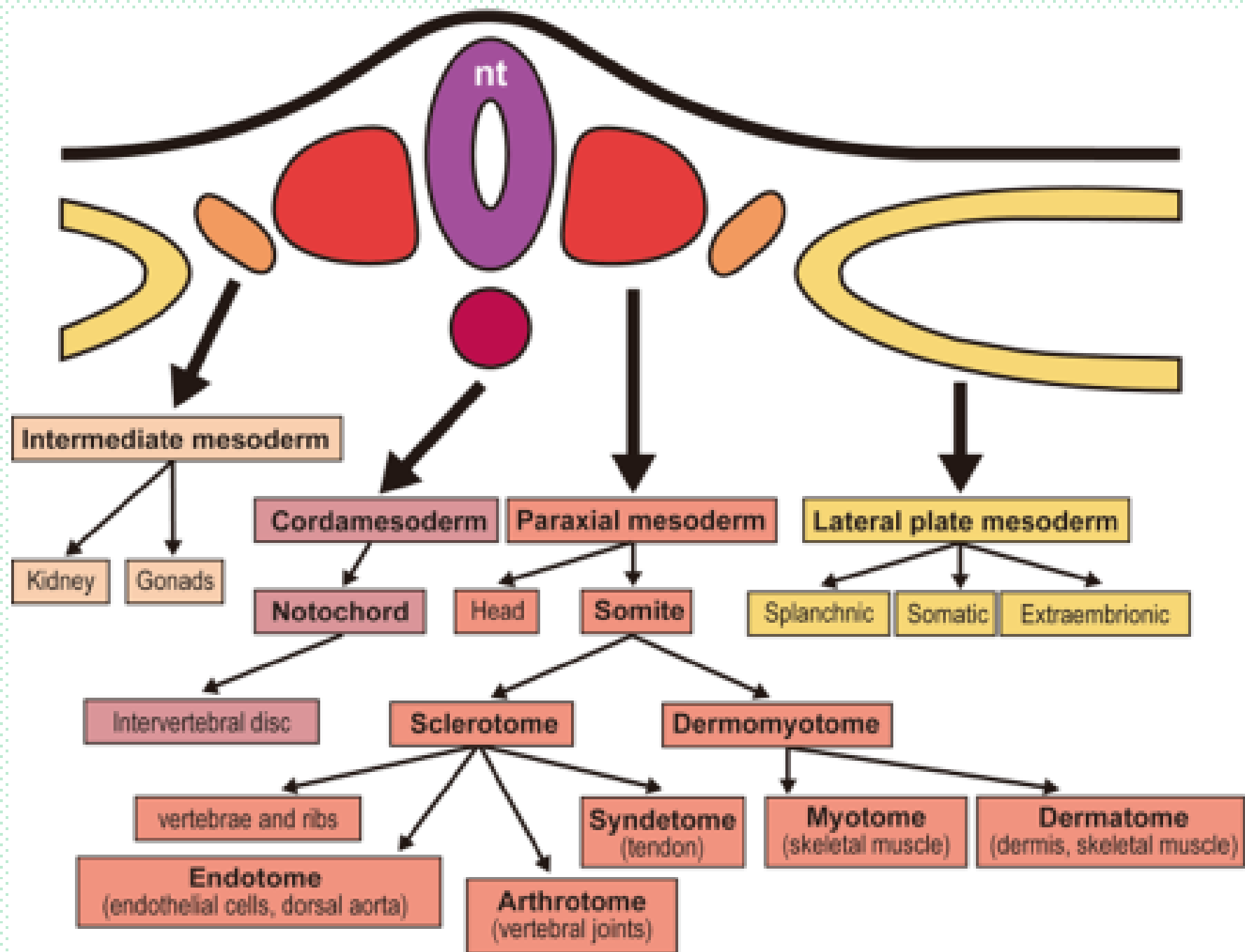
## ➤ Intermediate mesoderm

- epithelium of the urogenital system (kidneys, ureters, gonads, genital canals)

## ➤ Lateral mesoderm

- **parietal mesoderm**
  - dermis of the trunk, parietal sheets of the pericardium, pleura and peritoneum
- **visceral mesoderm**
  - connective tissue and smooth muscles of the digestive, respiratory and urogenital systems, visceral sheets of serous membranes





End of 3<sup>rd</sup> week - 2mm in length



# Extraembryonic membranes

Extraembryonic membranes include:

- amnion
  - chorion
  - yolk sac
  - allantois
- 
- umbilical cord
  - decidua
  - placenta

## Extraembryonic Membranes

chorion

amnion

embryo

allantois

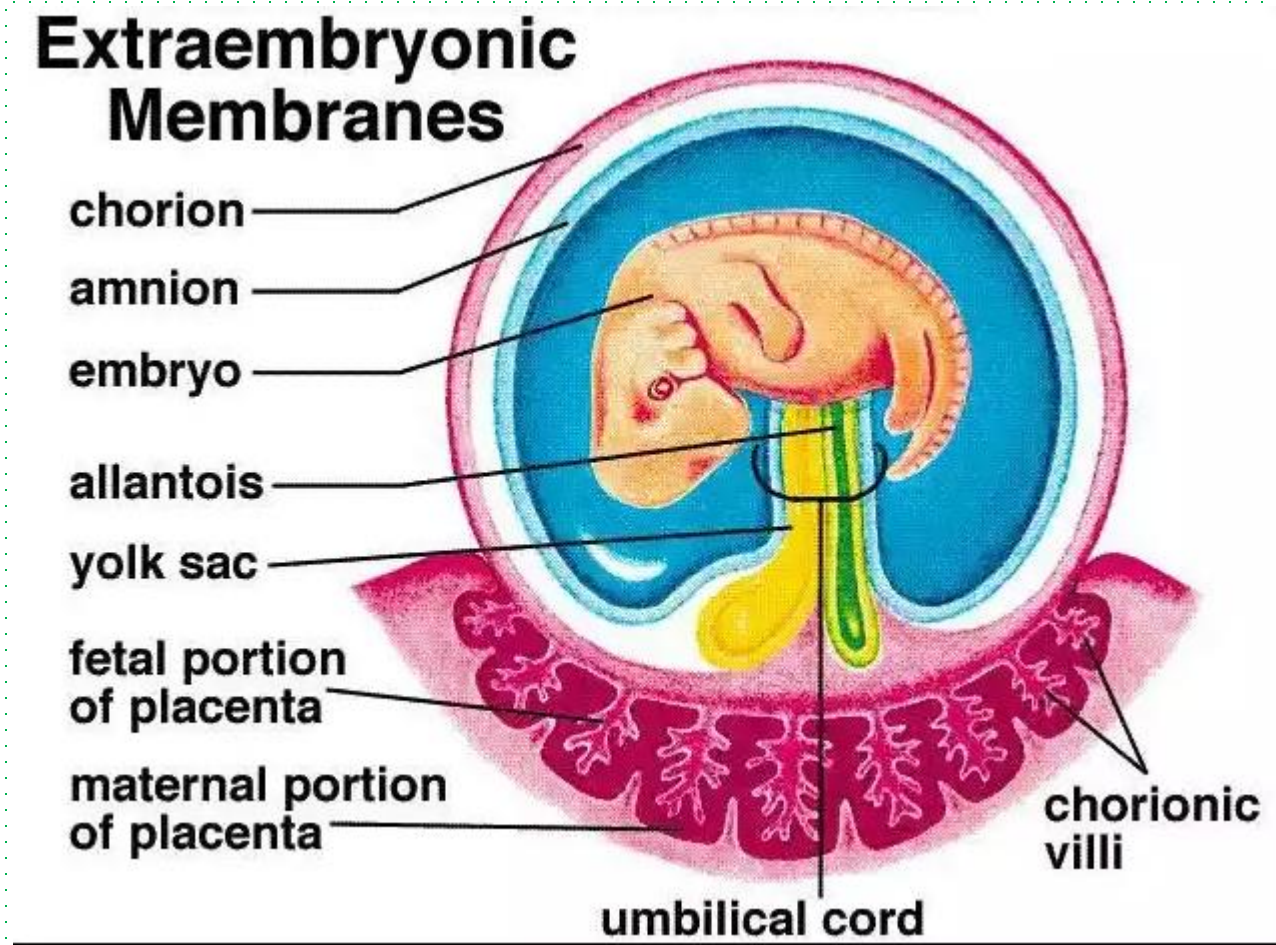
yolk sac

fetal portion  
of placenta

maternal portion  
of placenta

umbilical cord

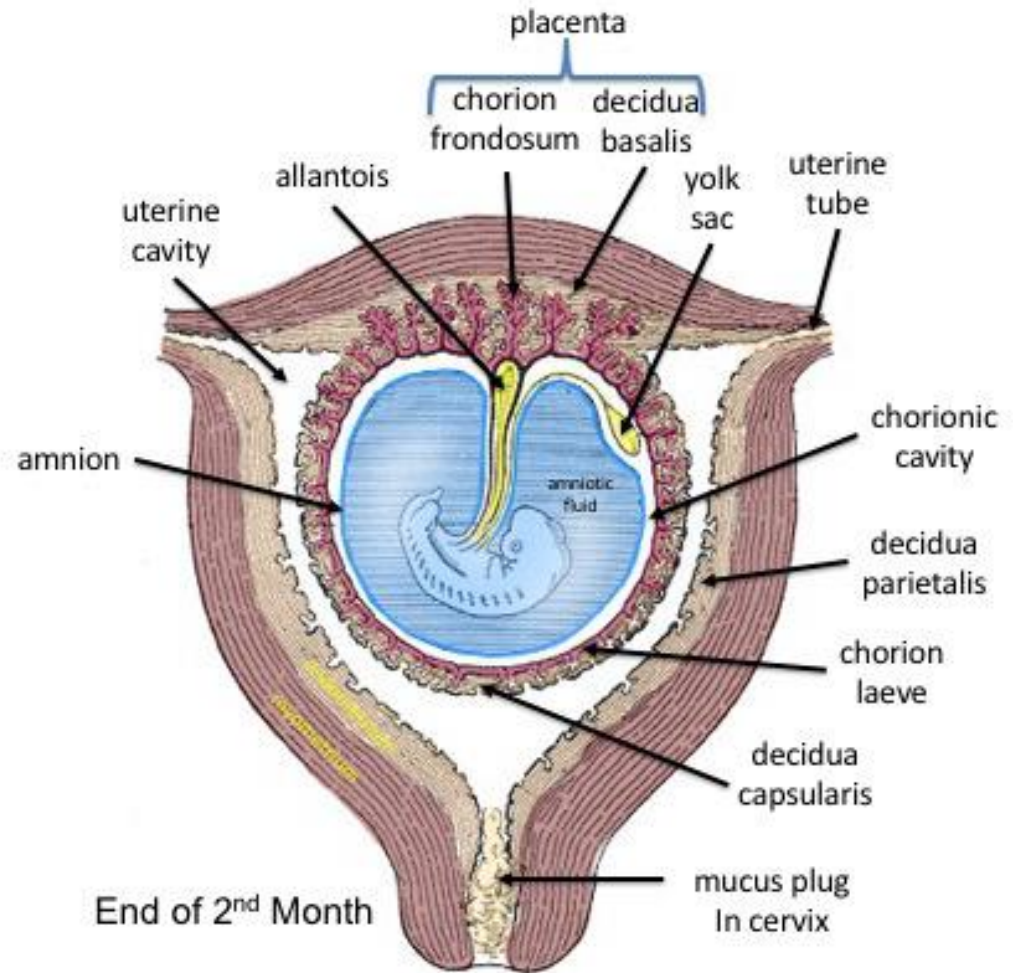
chorionic  
villi





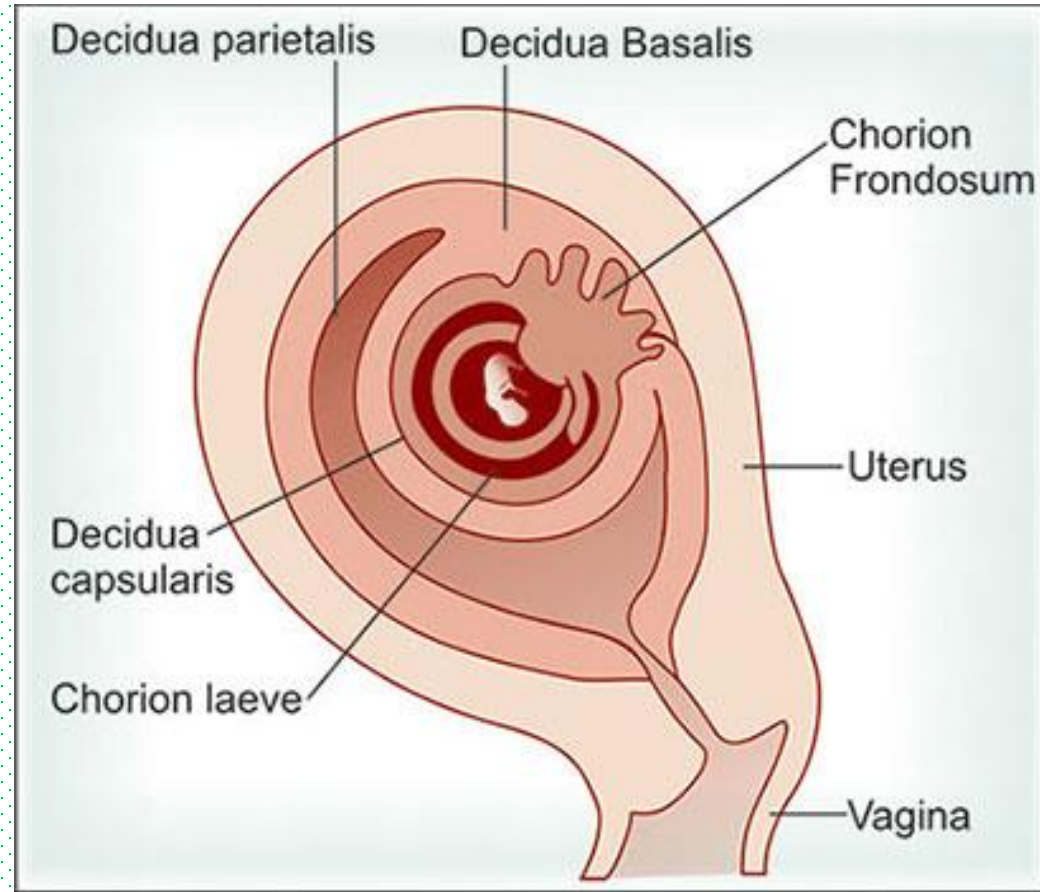
# Amnion

- It develops on the 8th day, and on the 12<sup>th</sup> week of fusion with the chorion occurs - **amniochorionic membrane**
- It is made up of **amniotic epithelium** and **visceral sheet of extraembryonic mesoderm**.
- The amnion is filled with amniotic fluid (amniotic fluid).
- From the 5th month, the embryo swallows amniotic fluid, about 400 ml/day.
- After the 14th week, **amniocentesis** can be performed.



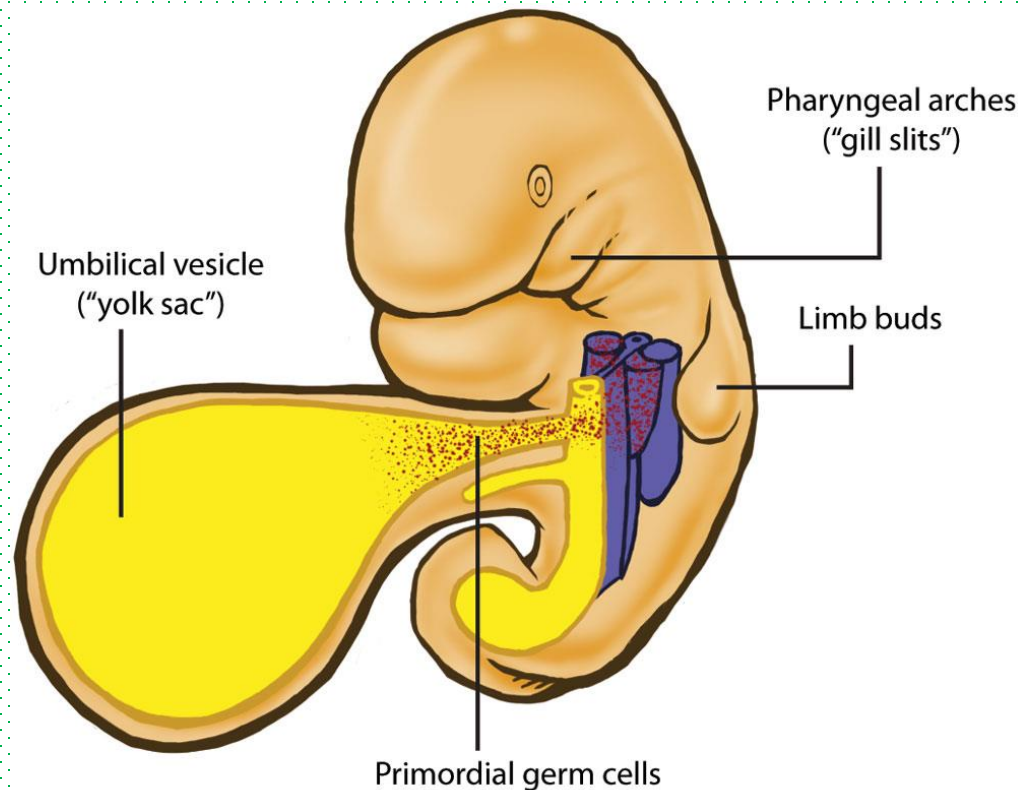
# Chorion

- The outer covering of the embryo.
- It consists of **trophoblasts and parietal layer of extraembryonic mesoderm**.
- There are **chorion laeve** (smooth) and **chorion frondosum** (bushy).
- The smooth chorion is part of the **amniochorionic membrane**, and the bushy one is part of the **placenta**.



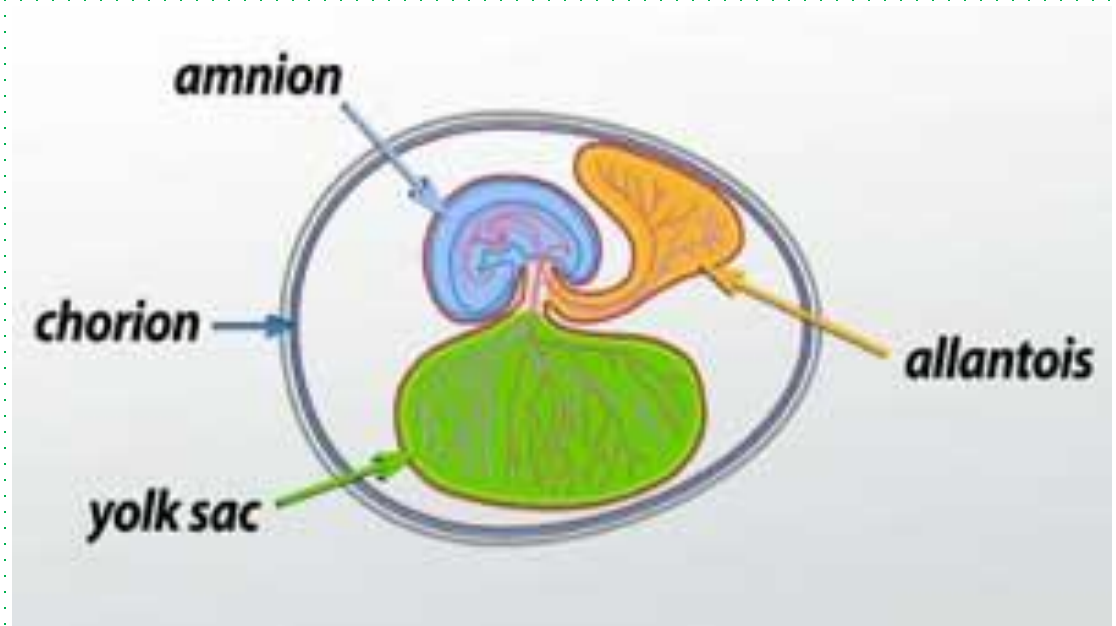
# Yolk sac

- **Primary yolk sac** is formed at the beginning of the second week and at the end of the same week, a **secondary yolk sac** is formed.
- It consists of epithelial cells of **hypoblastic origin** and **visceral layer of extraembryonic mesoderm**.
- The yolk sac reduces in size, communicates ventrally with the developing embryo via the yolk stalk, and later regresses.



# Allantois

- Arise as a pouch or sac from the **hindgut**.
- Will serve as an axis for the future **umbilical cord**.
- In the wall of the allantois, blood vessels develop, which give rise to two umbilical arteries and one vein.



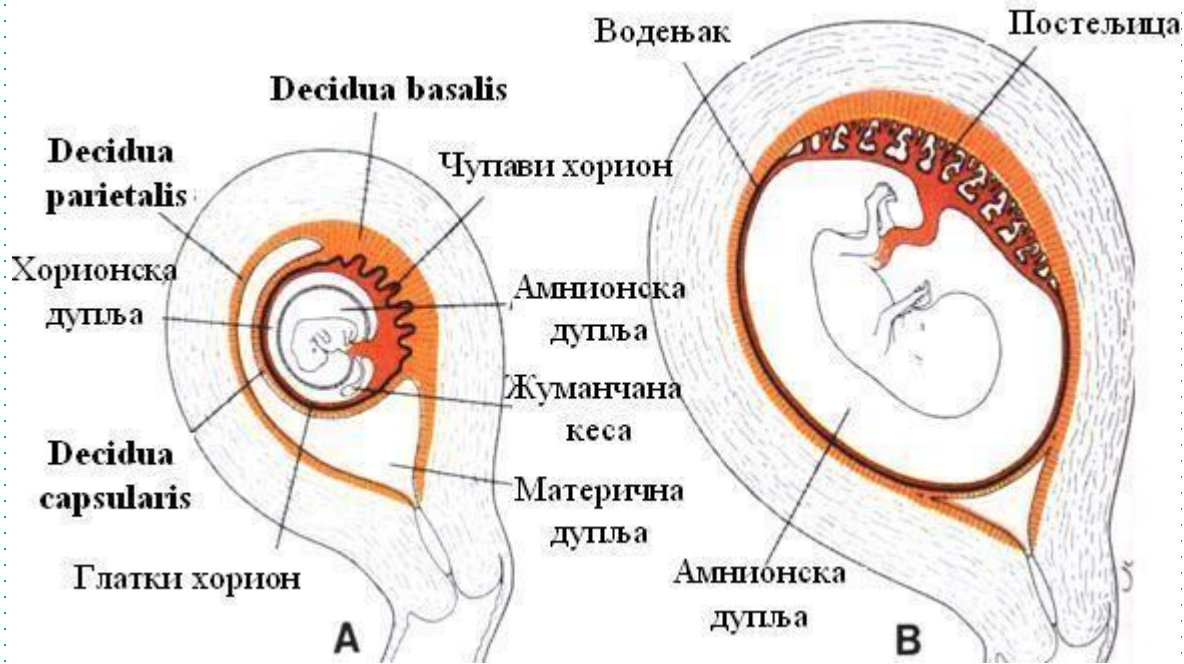
# Umbilical cord

- The umbilical cord connects the fetus to the placenta.
- Through the umbilical cord, the embryo is supplied with oxygen and nutrients, and it releases carbon dioxide and decomposition products.
- Histologically, the umbilical cord consists of a mucoid CT lined with amniotic epithelium.
- **Two umbilical arteries and one vein** pass through the ligament.





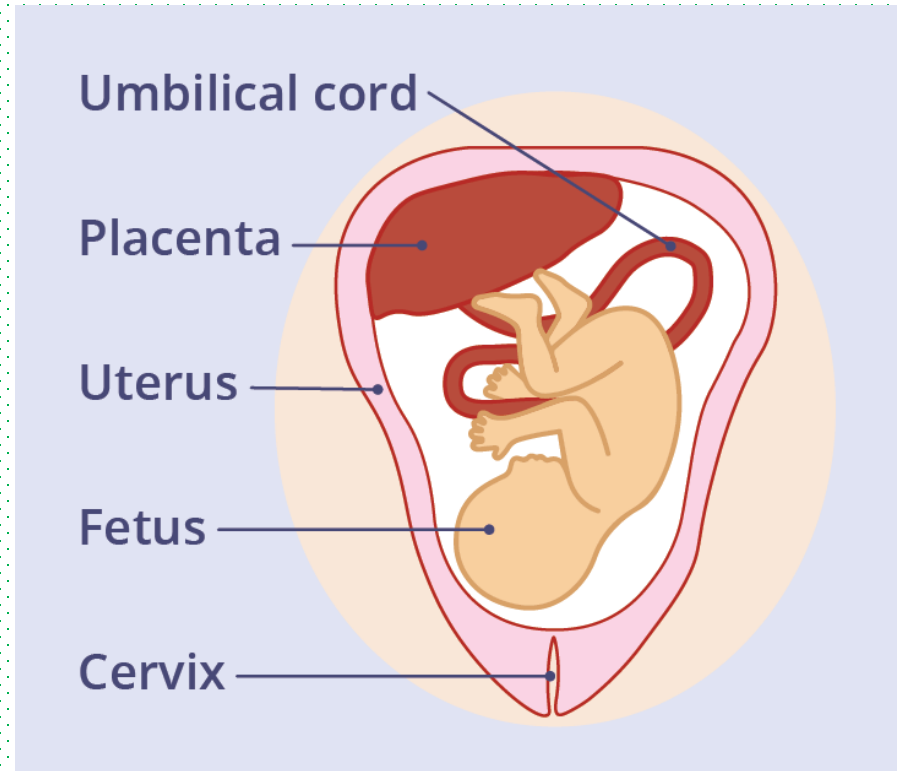
# Децидуа



- Децидуа је плодова овојница која потиче од функционалног слоја ендометријума.
- Топографска подела:
  - **decidua basalis** - налаже на чупави хорион и са њим гради постељицу
  - **decidua parietalis** - налаже на глатки хорион и са њим гради водењак
  - **decidua capsularis** - постепено дегенерише и ишчезава

# Placenta

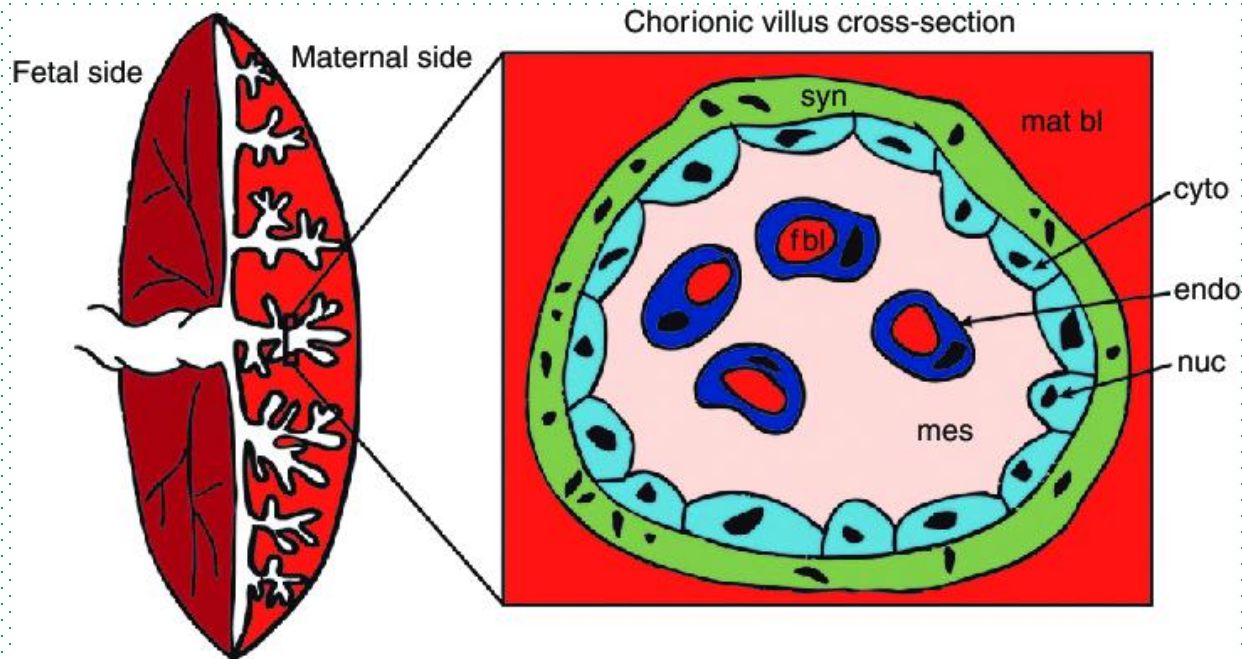
- Beginning of the fourth month, the placenta has two components:
- **fetal portion**, formed by the **chorion frondosum**
- **maternal portion**, formed by the **decidua basalis**



# Placental barrier

➤ Between the blood of the mother and the blood of the fetus there is a biological membrane, the so-called placental barrier consisting of:

1. trophoblast
2. trophoblast basement membrane
3. chorionic connective tissue
4. capillary endothelium
5. capillary basement membrane



# Placental functions

## **Respiratory role**

- It transports oxygen to the fetus and carbon dioxide in the opposite direction

## **Nutritional role**

- It transports nutrients to the fruit

## **Excretory role**

- Eliminates decay products of metabolism

## **Endocrine role**

- It secretes a number of hormones, such as human chorionic gonadotropin,
- progesterone, estrogen

## **Metabolic role**

- It metabolizes glycogen, cholesterol, and fatty acids that are used to nourish the fetus