Lecture 4

ESS_2nd semester

- Outline of implantation of the blastocyst. Abnormal sites of implantation (extrauterine pregnancies)
- Development of the germ disc: Origin of the intraembryonic mesoderm. Notogenesis - development of the chorda dorsalis
- Somites and their derivatives
- Outline of development of fetal membranes: The amniotic sac, the yolk sac and chorion. Placenta - structure and function. Anomalies of the placenta
- The umbilical cord. Anomalies of the umbilical cord

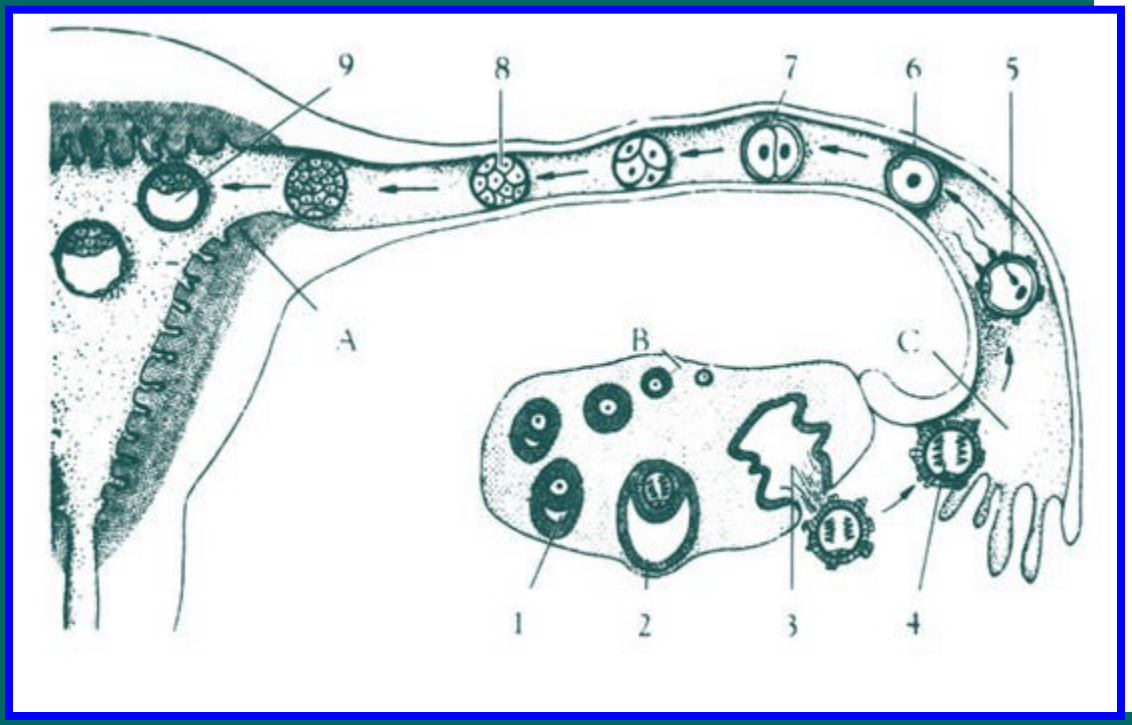
Cleavage of the zygote

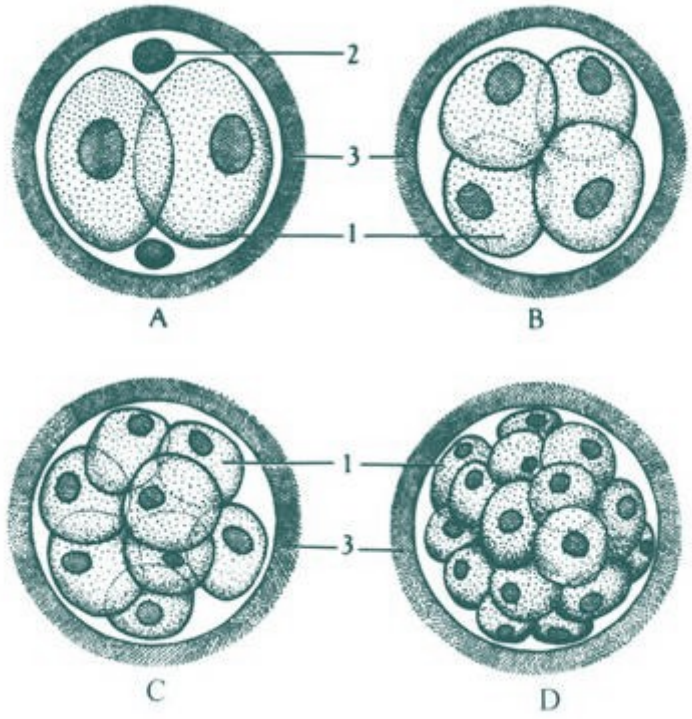
the phase of development characterized by mitotic divisions of the zygote resulting in formation of the blastocyst

cells are called **blastomeres** and become smaller with each division

the cleavage takes place partly in the **uterine tube** (during the first three days), partly in the **uterus** (from day 4 to 6)

the first division resulting in 2-cell stage needs about 24 to 30 hours, subsequent divisions follow in shorter intervals because blastomeres become progressively smaller





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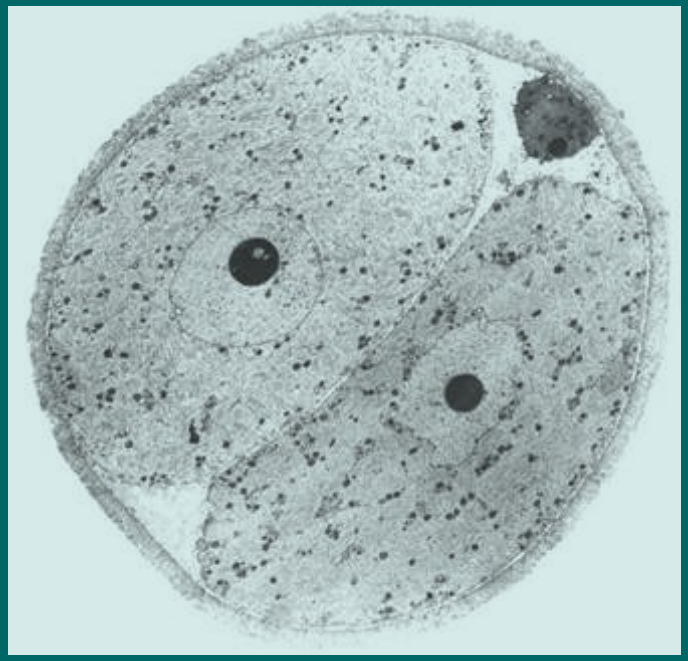

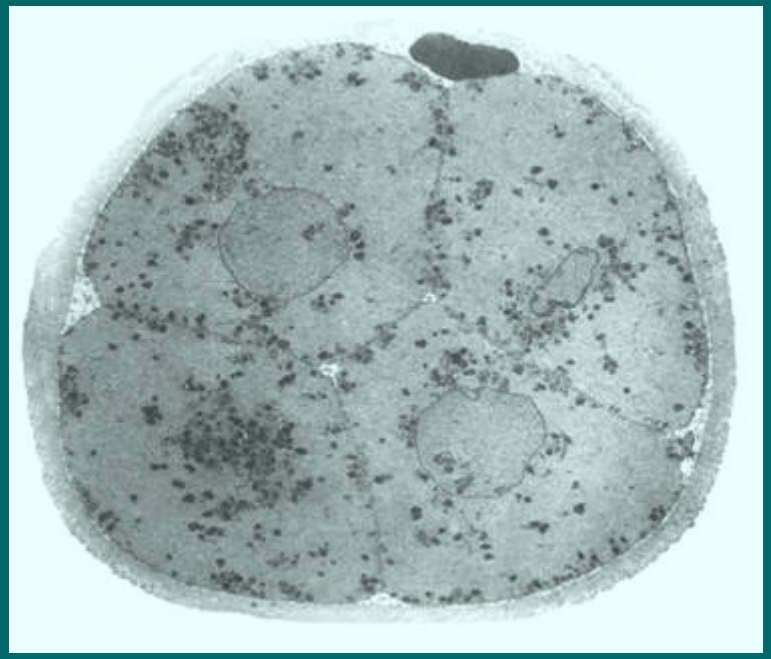

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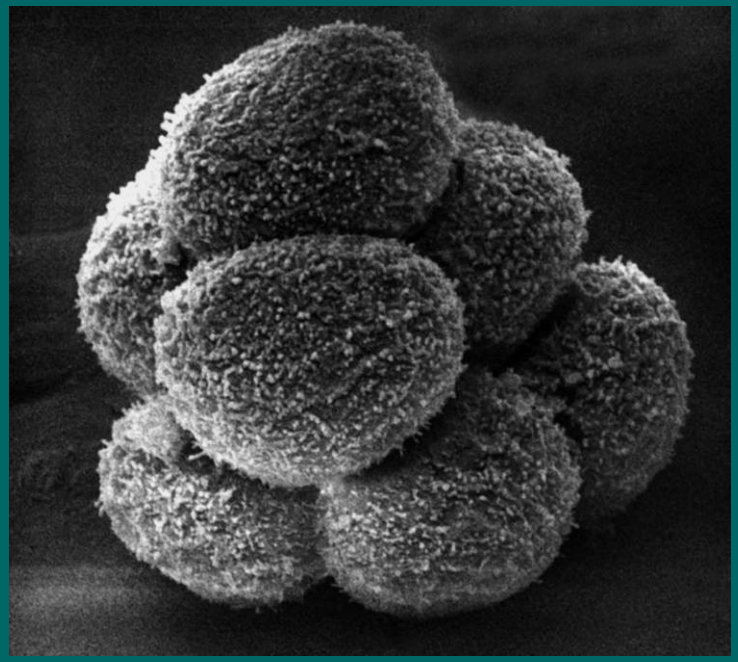
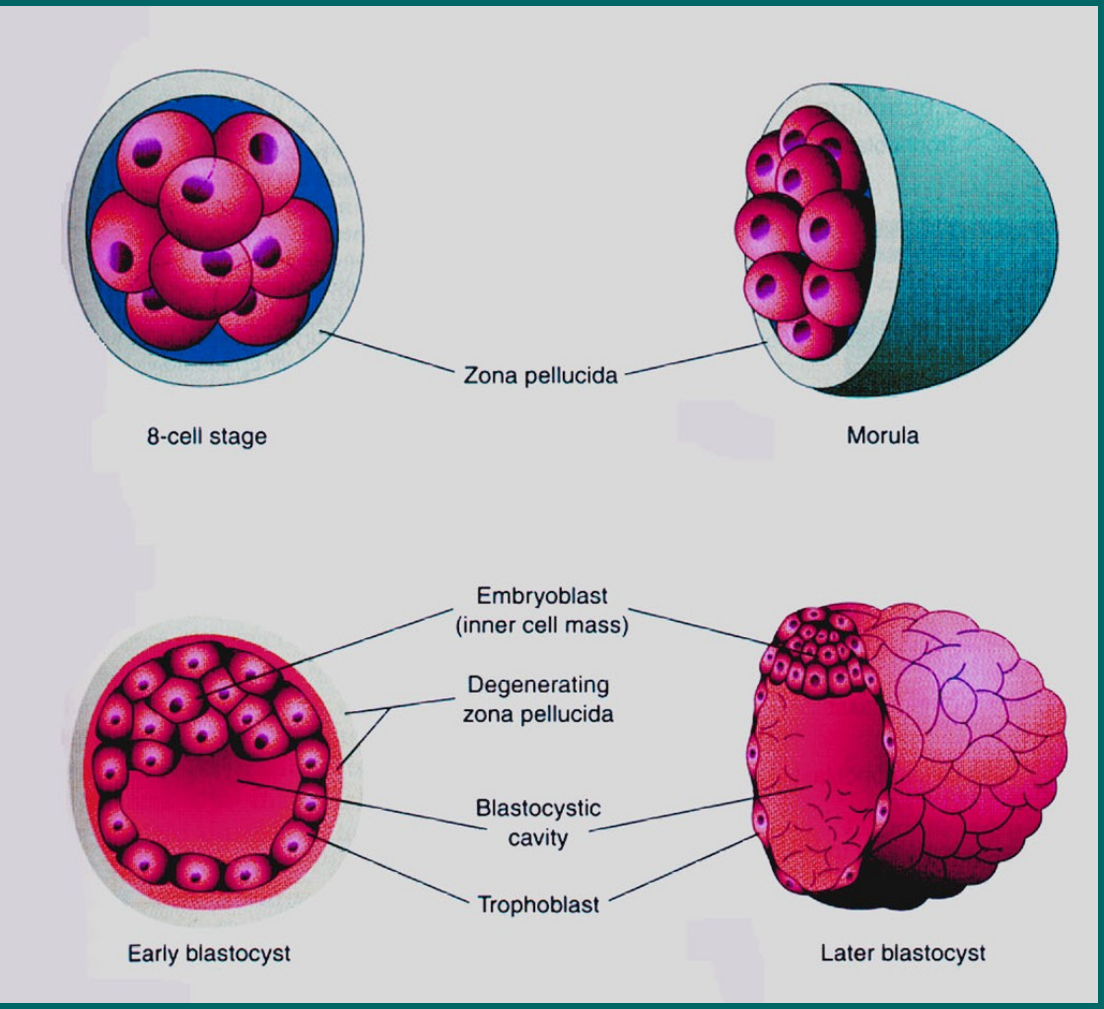


after the eight-cell stage, **the morula** stage follows
the morula - a solid ball consisting of 12 to 16 cells that lay on tightly each other (it shows resemblance to the fruit of mulberry tree)

the morula enters the uterine cavity where is transformed into the blastocyst



Formation of the blastocyst

shortly after the morula enters the uterus (on day 4), fluid from the uterine cavity passes through the zona pellucida to form a single fluid-filled space – blastocystic cavity (**primitive chorionic cavity**)

Consequently, the morula cells separate into two cell lines:

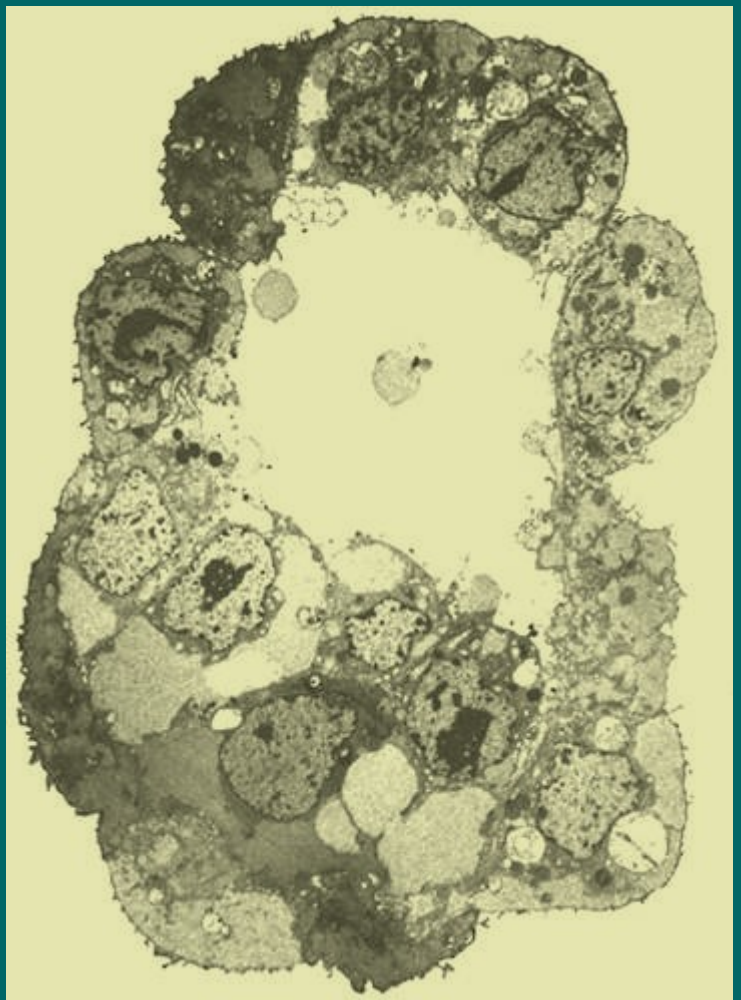
- an outer cell layer, the **trophoblast** (greek trophé = nutrition) - gives rise to chorion and finally fetal part of the placenta
- a group of centrally located cells, called as the **inner cell mass** or **embryoblast** - gives rise to the embryo

the blastocyst is enclosed with the zona pellucida and lies free in the uterus cavity

during the day 6, the zona pellucida becomes to digest by enzymes contained in the uterine fluid and soon disappears; the denuded blastocyst then expands up to diameter of 400 μm or more and is prepared to **start the implantation**

Early blastocyst
(with the zona)

Late (mature) blastocyst
(denuded)



Implantation

an adaptive process, during which the blastocyst establishes very close contact with the uterine mucosa (endometrium) of the maternal organism

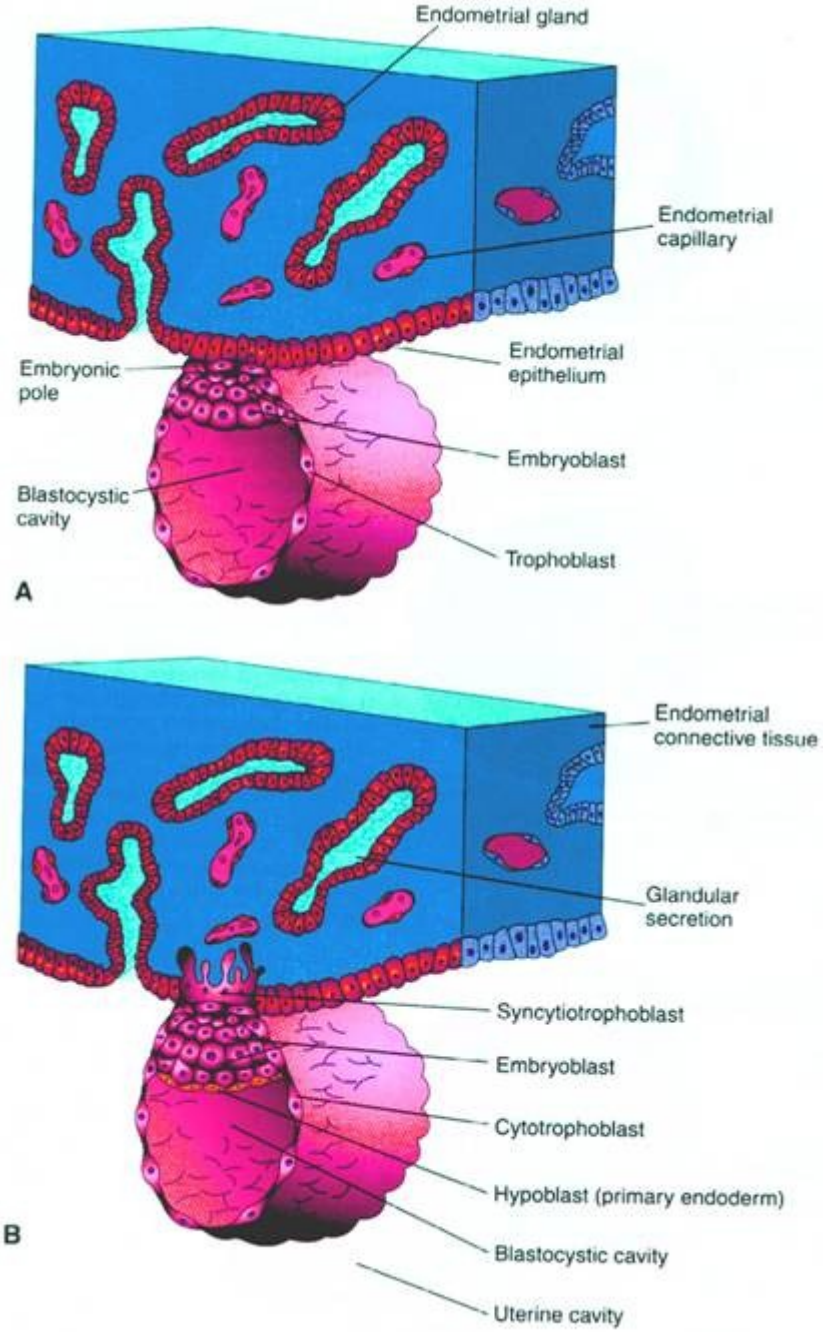
main goal is to provide nutrition of the embryoblast because yolk material has been completely utilized during cleavage and blastocyst formation

the implantation begins on **day 7 and ends on day 13**

the trophoblast cells play key role in this proces, they differentiate in the cytotrophoblast and the syncytiotrophoblast invading the uterine mucosa

Staging of the implantation:

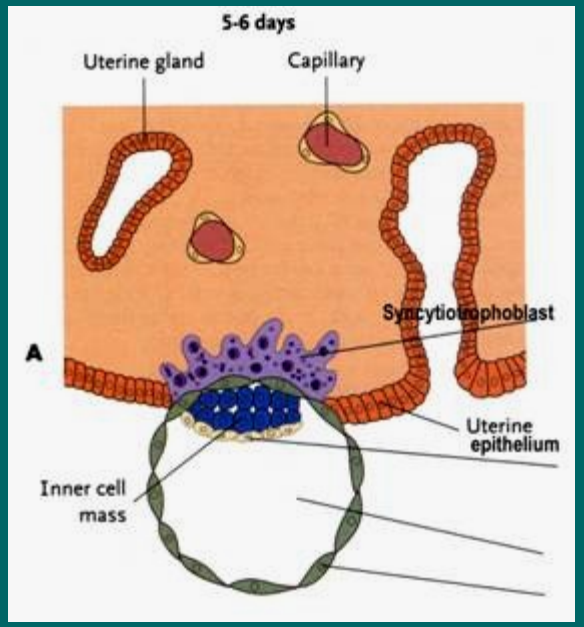
- **Attaching of the blastocyst to the endometrial epithelium**
- **Invasion of the trophoblast cells in the endometrium**
- **Reparation of implantation defect in the endometrium**
- **Formation of uteroplacental circulation**
- **Manifestation of decidual reaction**



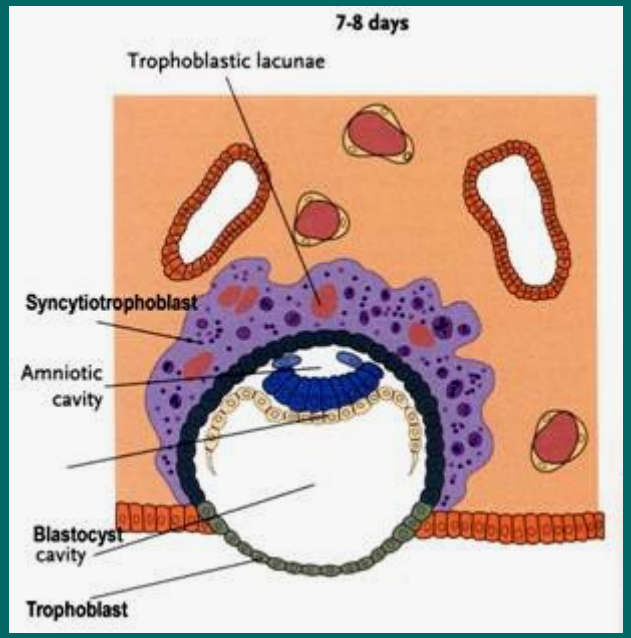
1. Attaching of the blastocyst to the endometrial epithelium
– it follows the zona pellucida lysis; the blastocyst attaches to the endometrium with embryonic pole (the pole, by which the embryoblast is placed)

2. Invasion of the trophoblast cells in the endometrium
follows as a result of contact of trophoblast with the endometrium
trophoblast cells proliferate and differentiate into 2 populations:

the **syncytiotrophoblast** located peripherally
– invades and erodes quickly the endometrial stroma and uterine glands
it forms around the blastocyst a large, thick and multinucleated mass without obvious cell boundaries
the erosion of the uterine mucosa is caused by proteolytic enzymes produced by syncytiotrophoblast cells



the **cytotrophoblast** (secondary trophoblast)
that gradually replaces the original trophoblast
the cytotrophoblast cells are mitotic active and form new cell generations - migrate into the blastocyst cavity where give rise to the extraembryonic mesoderm or migrate externally to complete masses of the syncytiotrophoblast



the trophoblast cell differentiation of the entire blastocyst needs about 3 days, i.e. on day 10 a conceptus is usually embedded within the endometrial stroma

3. Reparation of implantation defect in endometrium

after penetration of the blastocyst, the defect in the epithelium is filled with a **closing plug (operculum**) – a blood clot and cellular debris

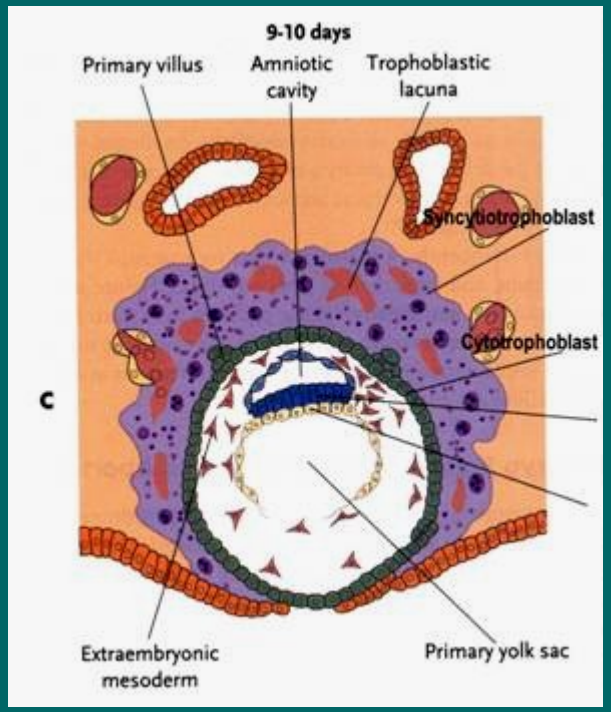
by day 12, the site of implanted conceptus appears as a minute elevation of the endometrial surface and is covered with regenerated epithelium

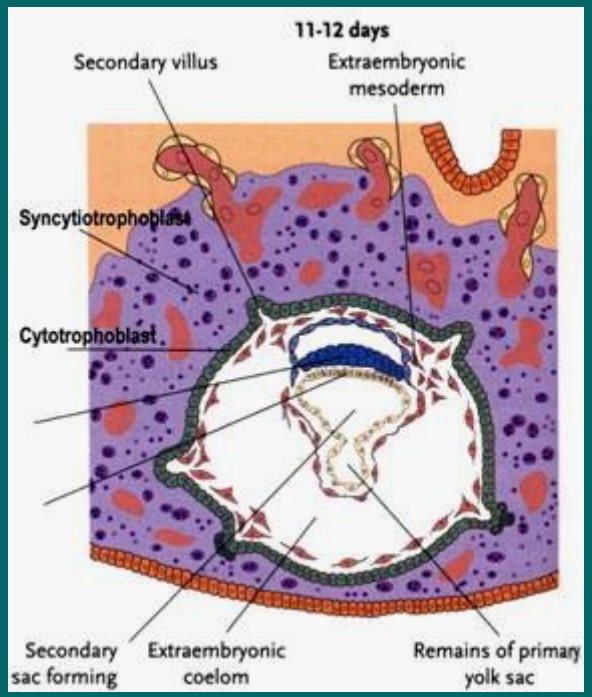
4. Formation of uteroplacental circulation

around day 9, isolated spaces (cavities) called **lacunae** are formed in the syncytiotrophoblast

they become filled with nutrition secretions from eroded endometrial glands and with maternal blood from ruptured maternal capillaries – **histiotroph**

later, between day 11 and 13, adjacent lacunae fuse to form lacunar network in which maternal vessels open and through which maternal blood flows





5. Manifestation of decidual reaction

the conceptus evokes reaction of the entire endometrium

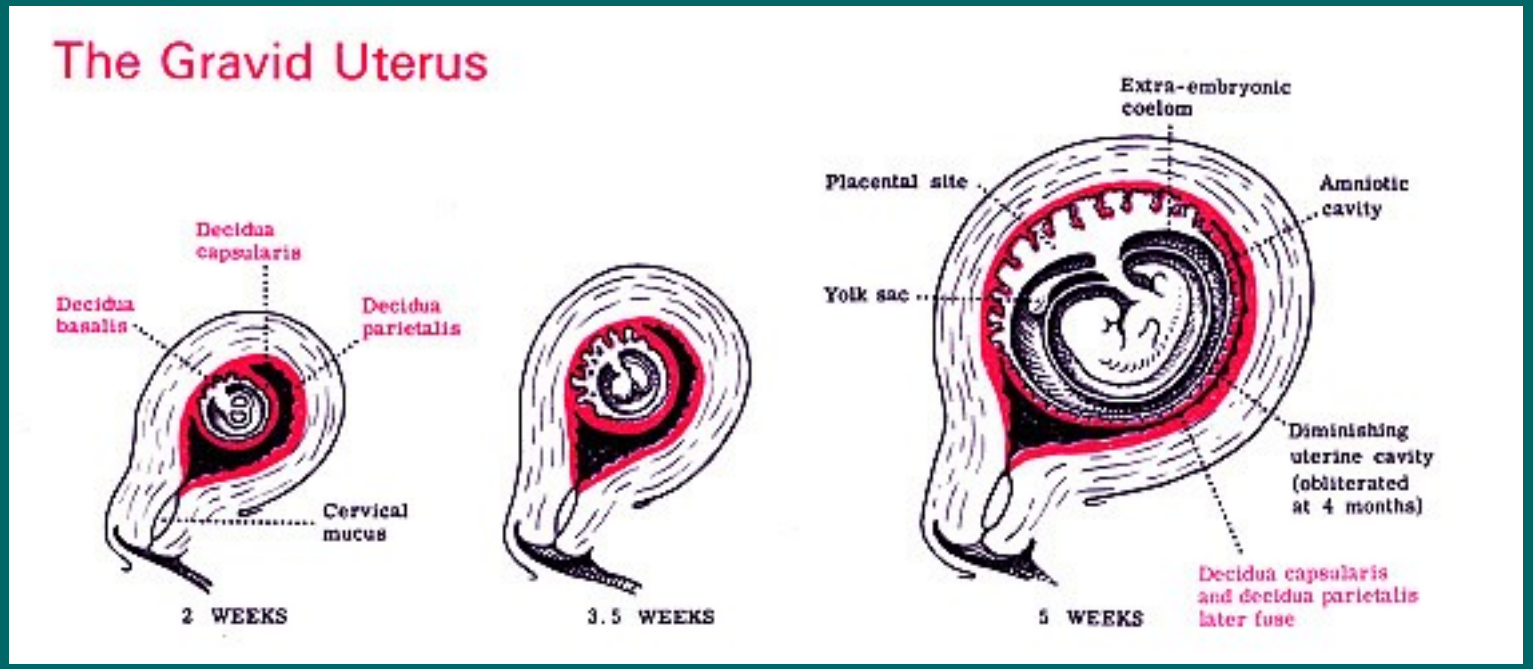
consists in endometrial stromal cell changes that enlarge and accumulate glycogen and lipid droplets, in vascular alterations (capillary network around the conceptus becomes denser), and glandular alterations – uterine glands increase their activity

changes are referred to as the **decidual reaction**

and the decidual transformed endometrium to as the **decidua**

The decidua involves 4 distinct regions as follows:

- **basal decidua - under the conceptus**
- **marginal decidua - at the side of the conceptus**
- **capsular decidua - above the conceptus**
- **parietal decidua - has no contact with the conceptus**



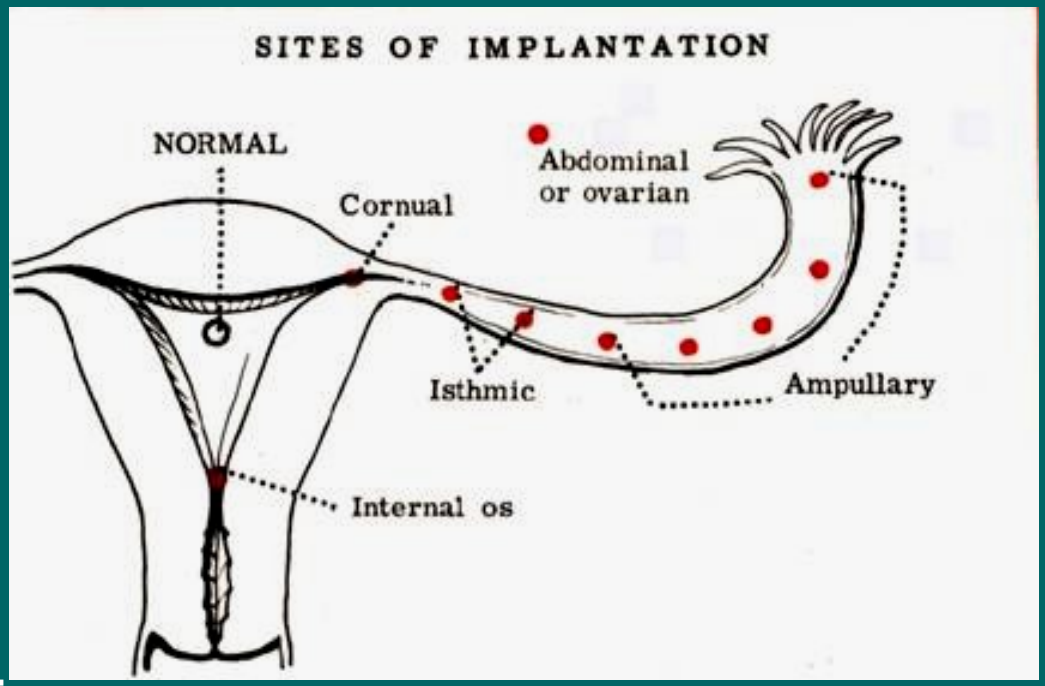
Implantation sites of the blastocyst

Intrauterine sites:

normally, the blastocyst implants on the posterior wall of the midportion of the uterus body

important: nidation near the internal ostium – the developing placenta covers the internal ostium as **placenta previa**

it causes severe bleeding during pregnancy (it usually occurs in the 28th week) or during the labor



Extrauterine sites:

if blastocyst achieves the mature blastocyst stage (without zona pellucida), it starts to implant in the site where is just

- implantation in the uterine tube (**ectopic tubal pregnancy**) - is represents about 90 % ectopic pregnancies; tubal pregnancy usually results in rupture of the uterine tube and hemorrhage during the first 8 weeks, followed by death of the embryo
- implantation in the ovary (**ectopic ovarian pregnancy**)

ectopic pregnancies are connected with profuse hemorrhage

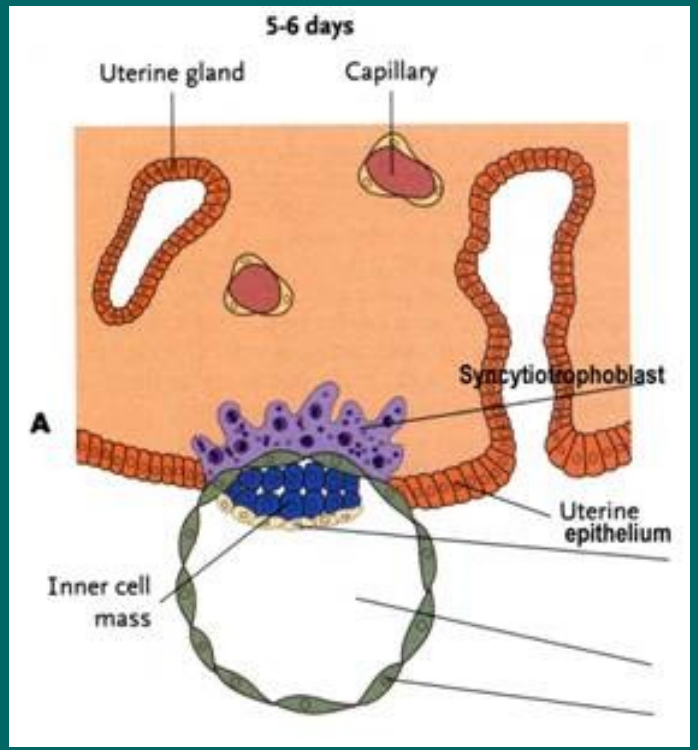
Changes within the blastocyst during implantation - development of the germ disc

simultaneously with the beginning of the blastocyst implantation (on day 7), the embryoblast differentiates into two layers:

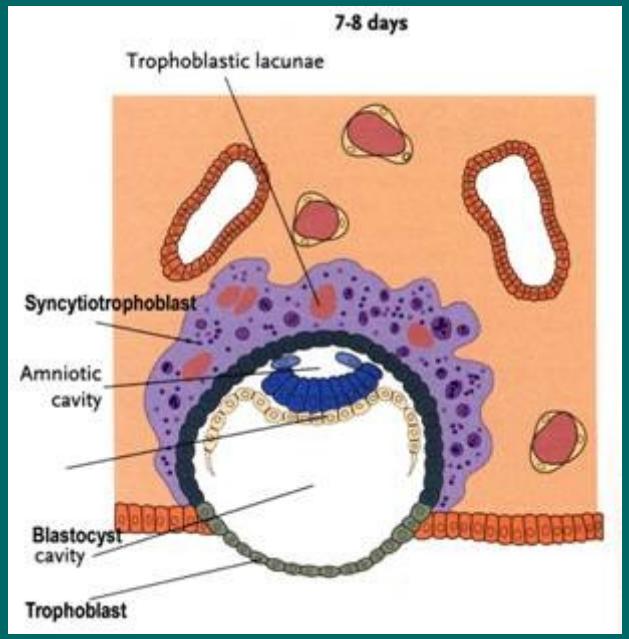
- **the ectoderm** (or epiblast) consisting of high columnar cells being in a close contact with the cytotrophoblast cells of the embryonic pole - future **dorsal aspect**
- **the endoderm** (or hypoblast) consisting of cuboidal cells adjacent to blastocyst cavity - the side corresponds to the **future ventral aspect**

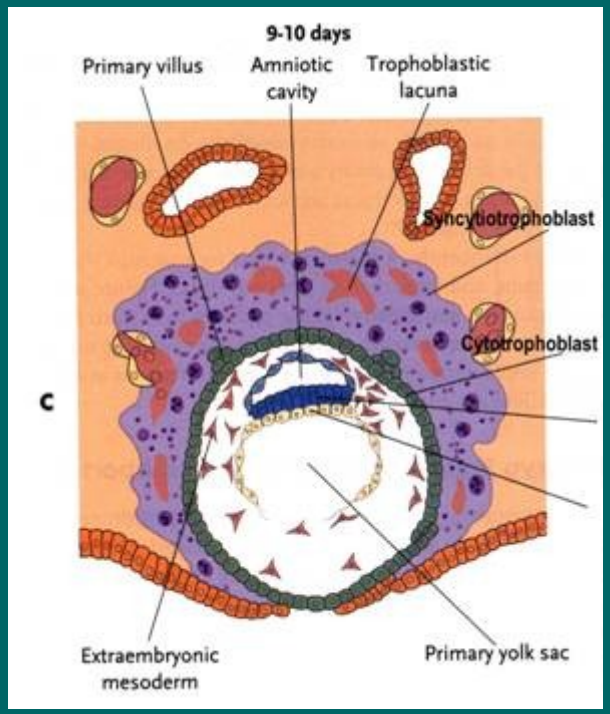
according to the terminology convention, the bilaminar stage is termed as **gastrula** in the human, the gastrula is developed by the mean of splitting off - or **delamination**

Remember: the gastrula is stage,
in which dorsal and ventral sides (aspects)
of the embryo arre firstly identified



to the end of day 7, small cavities appear between the ectoderm and the cytotrophoblast they fuse together and form a single **amniotic cavity**
during the next days the amniotic cavity enlarges by proliferation and migration of **amnioblast cells**
are cells that derive from the cytotrophoblast that is in contact with ends of the ectodermal plate





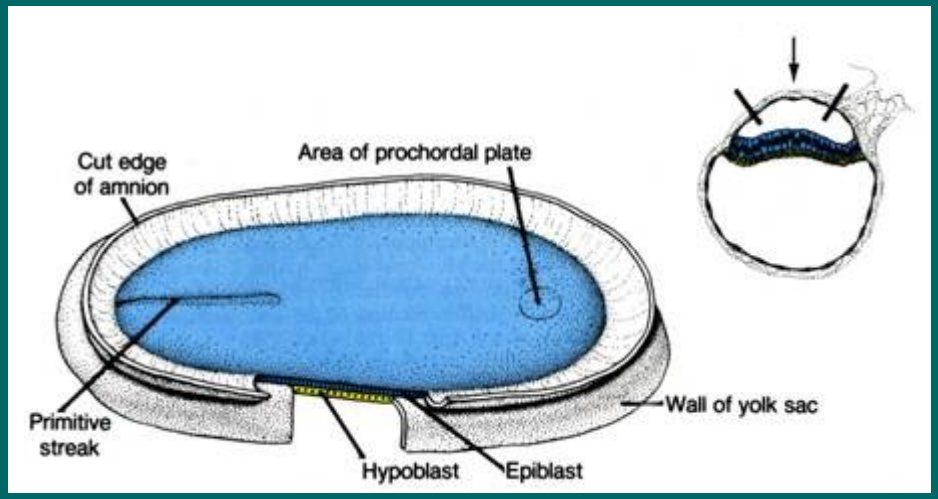
at this time, concurrently, the cytotrophoblast cells of abembryonic blastocyst pole migrate into the blastocyst cavity where they give rise to the **extraembryonic mesoderm**
during the 10th day several extraembryonic cells become continuous with the endoderm and form **exocoelomic membrane**
it circumscribes cavity termed as **primary yolk sac**
due enlargement of the amniotic sac, the bilaminar embryo is migrating step by step in the centre of the blastocyst
to the end of the 2nd week, the embryo has a form of a disc (1 mm) - **embryonic disc**

Development of the trilaminar embryo

begins on about day 14 and ends on day 20
the third germ layer - **mesoderm** develops as a new layer

the process is accompanied with differentiation of special structures in the midline of the embryonic disc called the **axial structures**

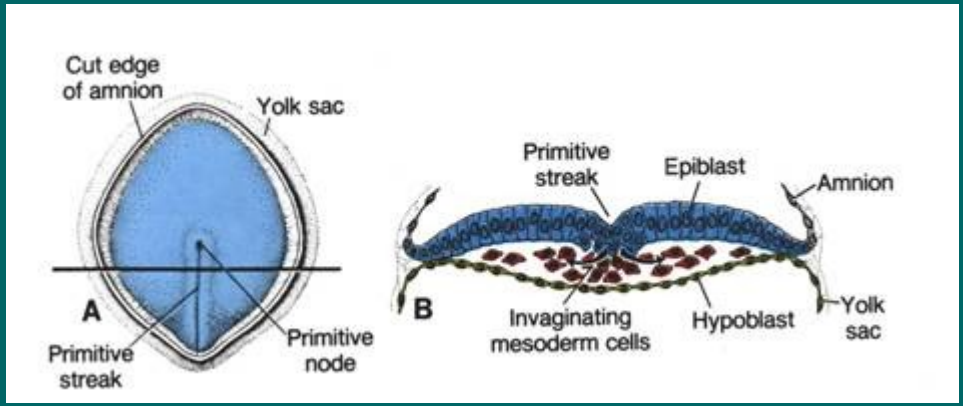
- **primitive streak with primitive groove**
- **primitive knob with primitive pit**
- **cloacal membrane**
- **notochordal process**
- **prochordal plate**



the **primitive streak** appears as a thickened linear band of the ectoderm caudally in the midline of the embryonic disc on the dorsal aspect

the ectodermal cells rapidly proliferate and migrate ventrally and laterally between the ectoderm and endoderm
they give rise to the **intraembryonic mesoderm**

a shallow primitive groove is visible at the site of migration of the ectodermal cells



Remember: as the primitive streak develops in the caudal part of the embryonic disc, the craniocaudal polarity and side orientation /left – right/ of the embryo are determined

the **cloacal membrane** is a small circular area located near the caudal portion of the primitive streak seen on day 15, originates by fusion of the ectoderm and the endoderm

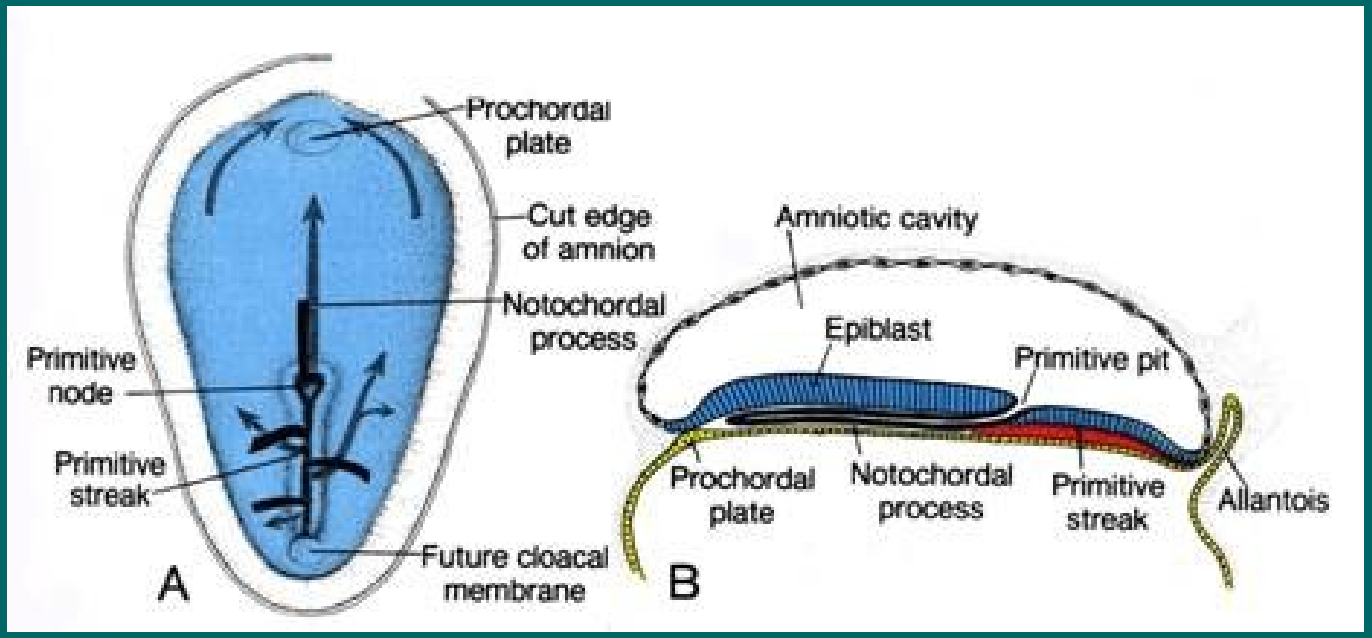
the **primitive knob** /node/ develops on about day 16

the cranial portion of the primitive streak becomes thicker by mitotic divisions, soon shallow depression termed as **primitive pit** occurs

during the day 17 the ectodermal cells of the primitive knob proliferate and migrate in cranial direction as a midline cord called the **notochordal process**, it grows so long as it reaches the prochordal plate

the **prochordal plate** is a small circular area of columnar endodermal cells located near the cranial end of the embryonic disc

cells of the plate migrate between the endo- and the ectoderm and give rise to the mesoderm



Notogenesis = development of notochord (= chorda dorsalis)

notochord is a cellular rod that differentiates from the notochordal process and forms the primitive axis of the embryo

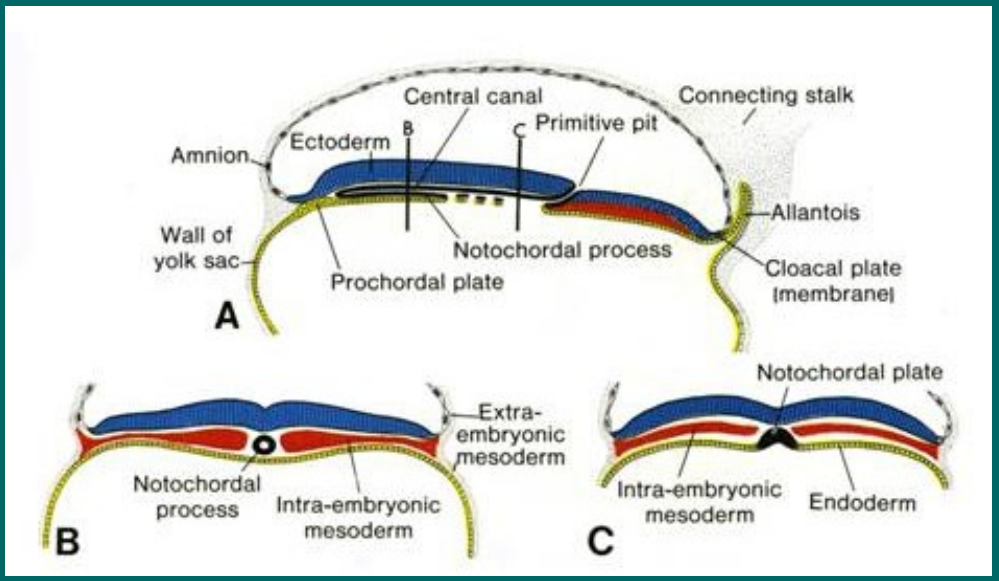
as the notochordal process elongates, the primitive pit extends into it to form a lumen known as the **notochordal canal** (canal of Lieberkuhn)

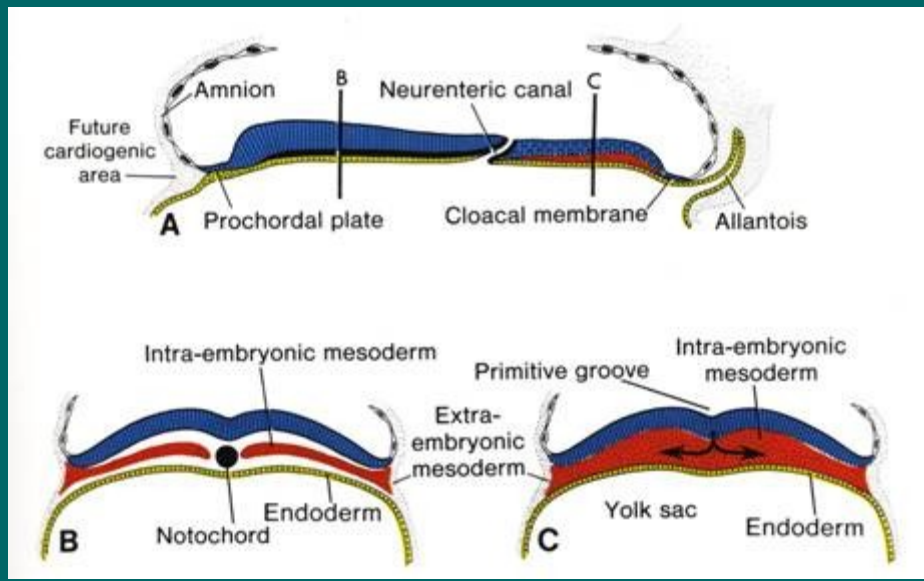
floor of the notochordal process fuses with underlying embryonic endoderm and cells of fused regions degenerate so that small multiplied openings arise in the floor of the notochordal process, via these openings the notochordal canal communicates with a yolk sac cavity

later, the openings rapidly become confluent and the floor of the notochordal canal disappears completely

a rest of the notochordal process forms a flattened grooved plate - the notochordal plate that differentiate as follows:

- the central part of the plate gives rise to the **notochord** (chorda dorsalis)
- the paired peripheral parts of the plate give rise to the **embryonic mesoderm**





Origin of the embryonic mesoderm – conclusion:

it derives from 3 different sources:

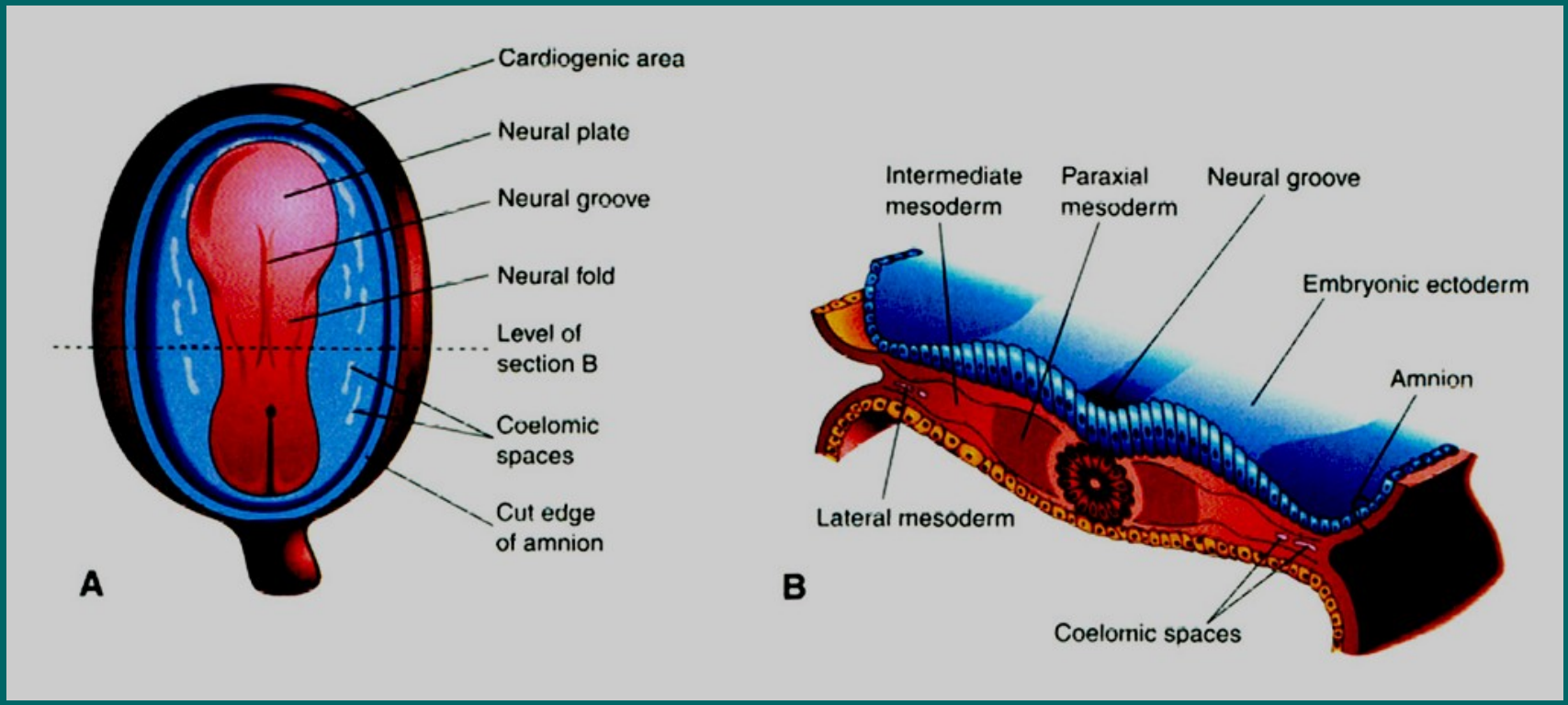
- the **primitive streak** - mesoderm of the caudal end of the embryo
- the **prochordal process** - mesoderm of the middle part of the embryo
- the **prochordal plate** - mesoderm of the cephalic region of the embryo

Remember:
notochord is the structure around which the vertebral column forms
in adult, the notochord persists only as the nuclei pulposi of intervertebral discs
it always degenerates in vertebral bodies

Development of somites

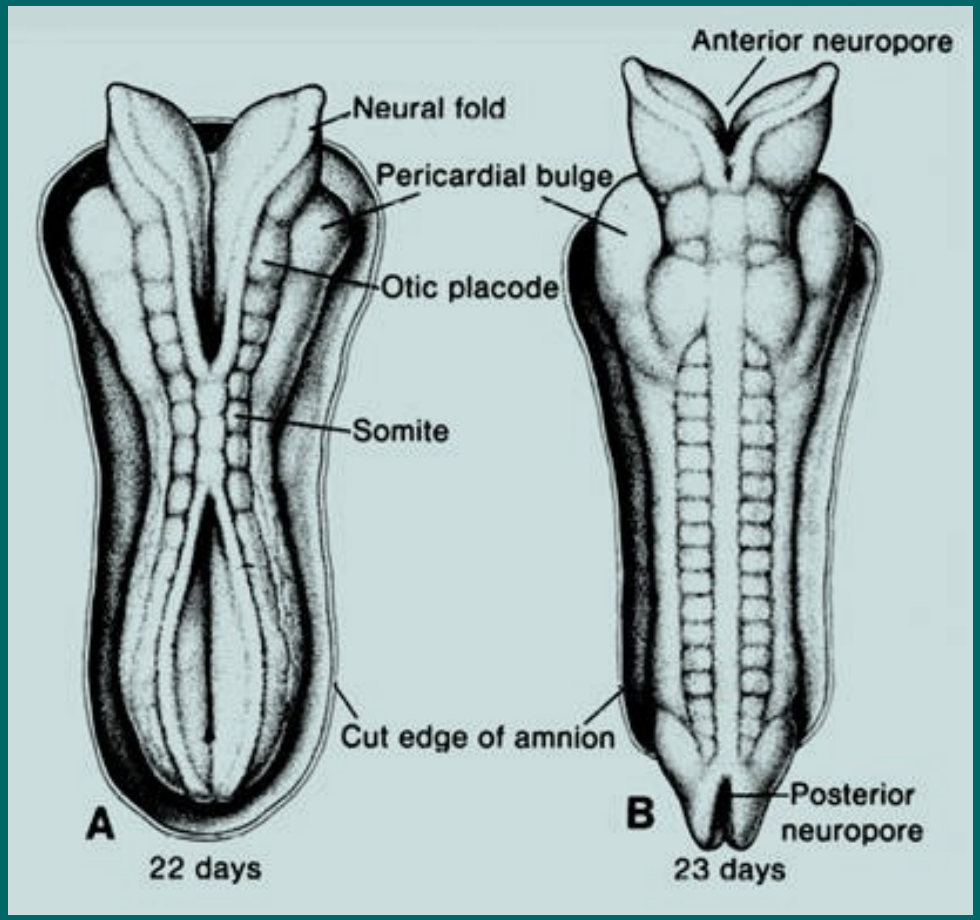
as the notochord and the neural tube form, the intraembryonic mesoderm on each side thickens to form longitudinal column of

- the **paraxial mesoderm**
  each paraxial column is continuous laterally with
- the **intermediate mesoderm**
  it thins gradually into a layer of
- the **lateral mesoderm**
  (is continuous with the extraembryonic mesoderm covering the yolk sac and amnion)



by days 20 to 21, the paraxial mesoderm begins to divide into paired cuboidal bodies - **somites**
first somites form in the future occipital region of the embryo, further ones follow caudally
to the end of the 5th week, **42 to 44** pairs of somites are costituted - **4 occipital, 8 cervical, 12 thoracical, 5 lumbar, 5 sacral, and 8 to 10 coccygeal**

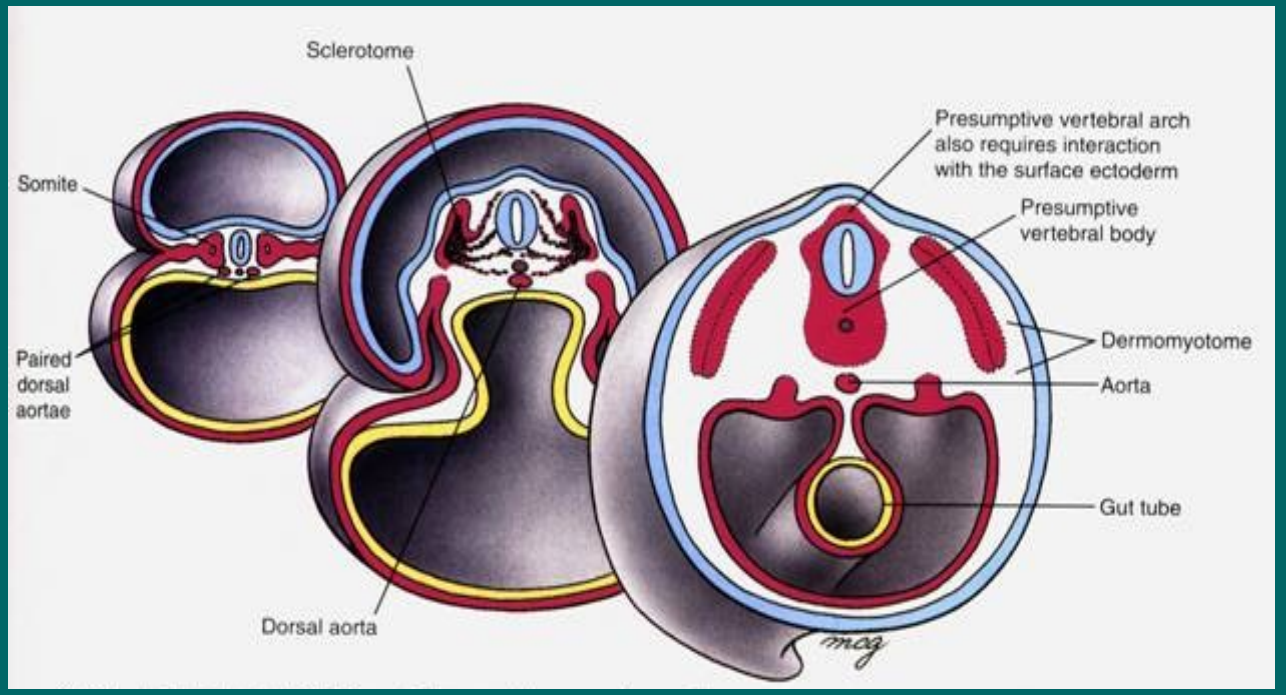
number of somites is used to determining an embryo´s age



somites differentiate into 3

- **sclerotome** - axial skeleton
- **myotome** - skeletal muscles
- **dermatome** - dermis

the intermediate mesoderm - nephrotomes gives rise to the urinary system (pro-, meso-, and metanephros)

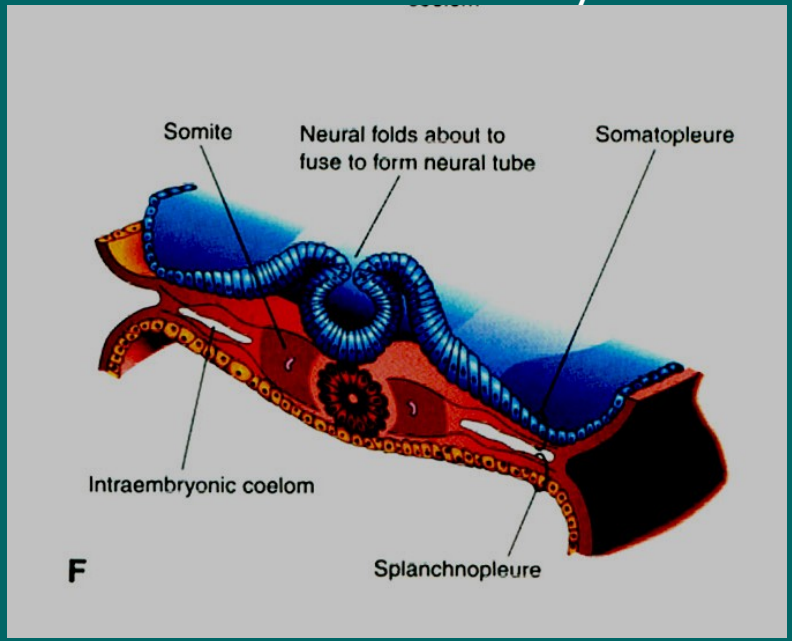


the lateral mesoderm is originally solid but divides later into two layers:

- a **somatic** (parietal) layer adjacent to the ectoderm

- a **splanchnic** (visceral) layer adjacent to the endoderm

(they border the **intraembryonic coelom**)



Fetal membranes and placenta. The umbilical cord

fetal membranes serve for protection and nutrition of the conceptus

there are 3: the amniotic sac or amnion, the yolk sac with allantois and the chorion

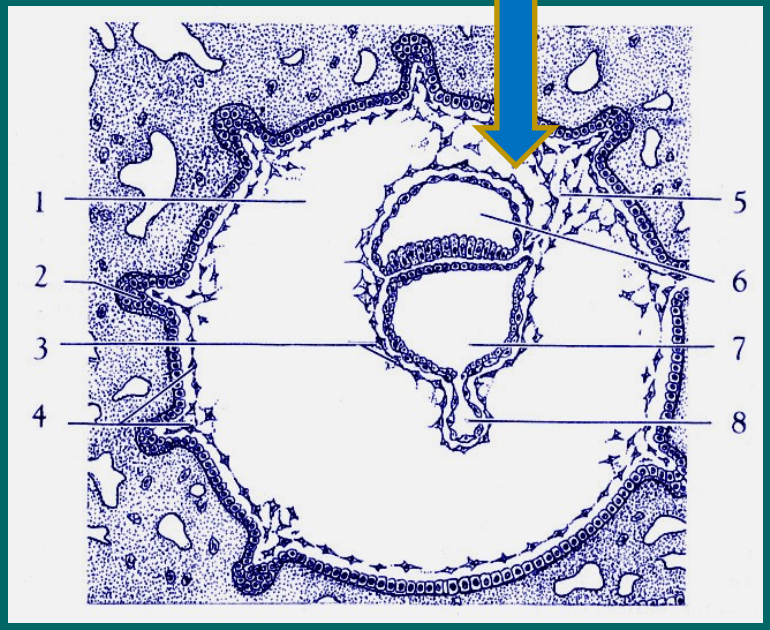
membranes develop from the trophoblast and do not form any part of the embryo body except a portion of the yolk sac and allantois

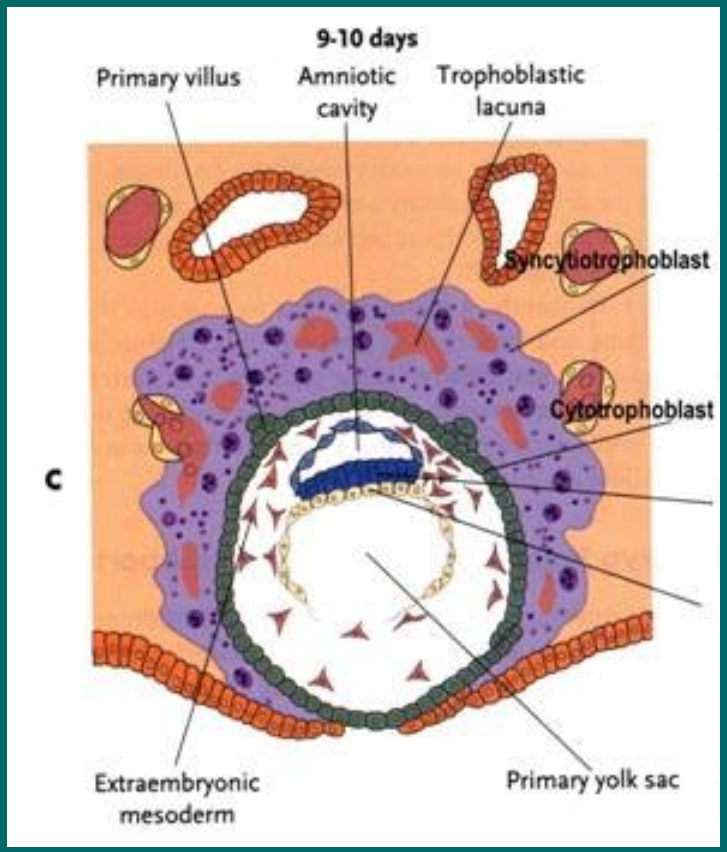
(the dorsal part of the yolk sac is incorporated into the embryo as the primordium of the primitive gut; the allantois persists in adults as a fibrous cord, the medium umbilical ligament, it extends from the apex of the urinary bladder to the umbilicus)

the amniotic cavity - develops as the first to the end of day 7 between the ectoderm and cytotrophoblast

shortly after its formation, extraembryonic mesodermal cells condense at the top of amniotic sac to form a solid cellular stalk called **connecting stalk**

it attaches the embryonic disc to the c otrophoblast, lately to the chorion

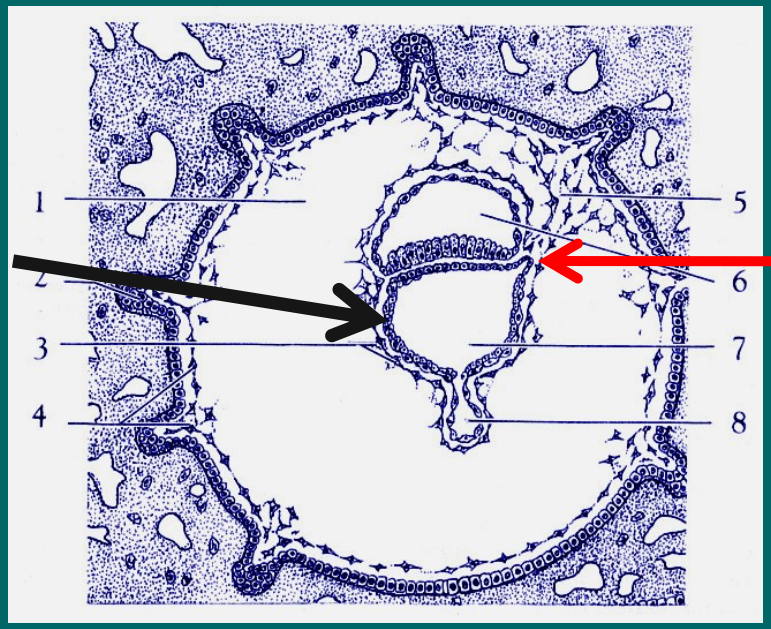


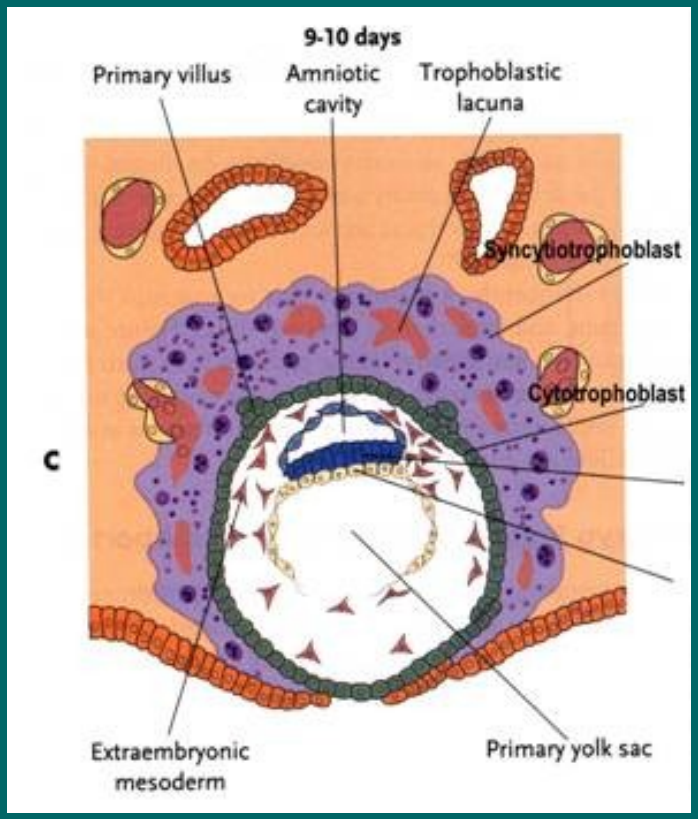


the yolk sac - 2 stages

- **primary yolk sac** - has a wall composed of only of extraembryonic mesoderm cells that are organized in the exocoelomic membrane (of Heuser) - on day 10

- **the secondary yolk sac** - has 2-layered wall lined by **the endoderm** that has been proliferated along the inner surface of the exocoelomic membrane from the embryonic disc - on day 13





a finger-like outpouching from the caudal part of the secondary yolk sac projecting in the connecting stalk and is called the **allantois** - day 16

in human embryos, the allantois is rudimentary

(partly is involved in early blood formation, partly is associated with development of the urinary bladder - as the bladder enlarges, the allantois becomes the urachus)

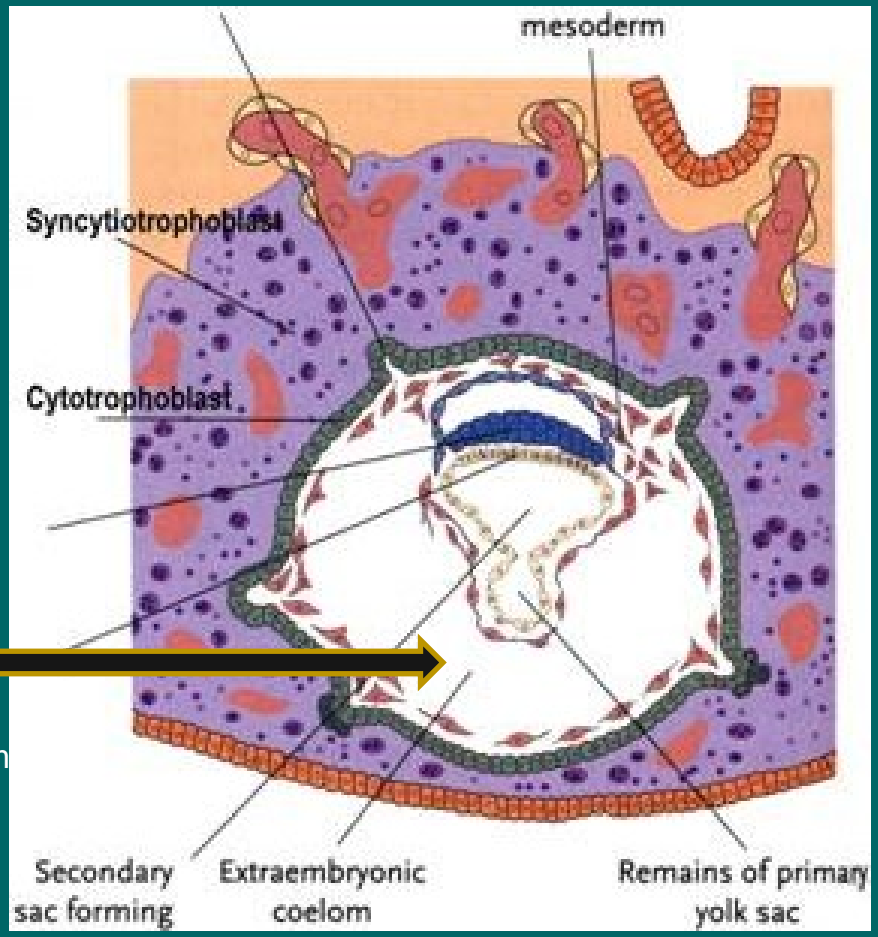
the chorionic sac or chorion - a membrane that covers conceptus externally

it consists of the cytotrophoblast and extraembryonic somatic mesoderm

within the chorion the embryo and amniotic and yolk sacs are suspended by the connecting stalk

the space extending between both sacs and the chorion is called as exocoelomic space or **extraembryonic coelom**

during flexion of the embryo the extraembryonic space is substan reduced



Development of chorionic villi

begins to form early and development of villi undergoes 3 stages: primary, secondary and tertiary villi

- **primary chorionic villi** develop on the entire surface of the chorionic sac - they appear as

local masses of the cytotrophoblast

- **secondary chorionic villi** occur on day 13 to day 14, when the extraembryonic mesoderm proliferates and grows into cytotrophoblast masses forming a core of loose connective tissue

❖ **tertiary chorionic villi** are vascularized , they contain already anlage blood vessels

chorionic villi was originally developed around the entire surface of implanted conceptus

later with the growth of conceptus

❖ **villi adjacent to capsular and marginal decidua** become rare and shorter up to evetually disappear

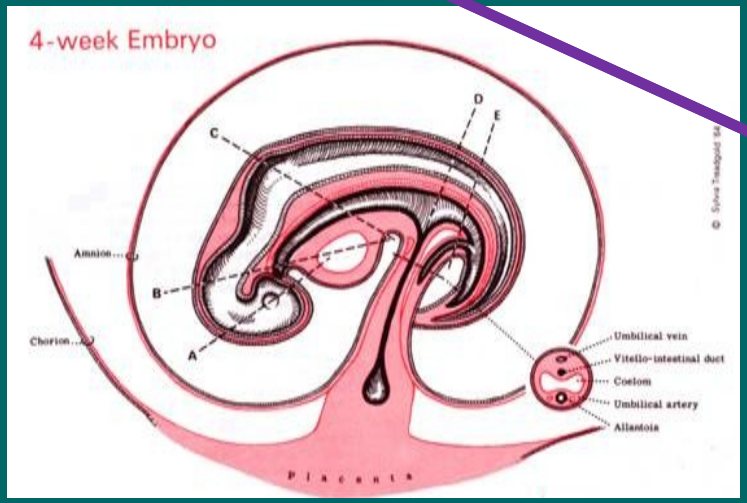
while

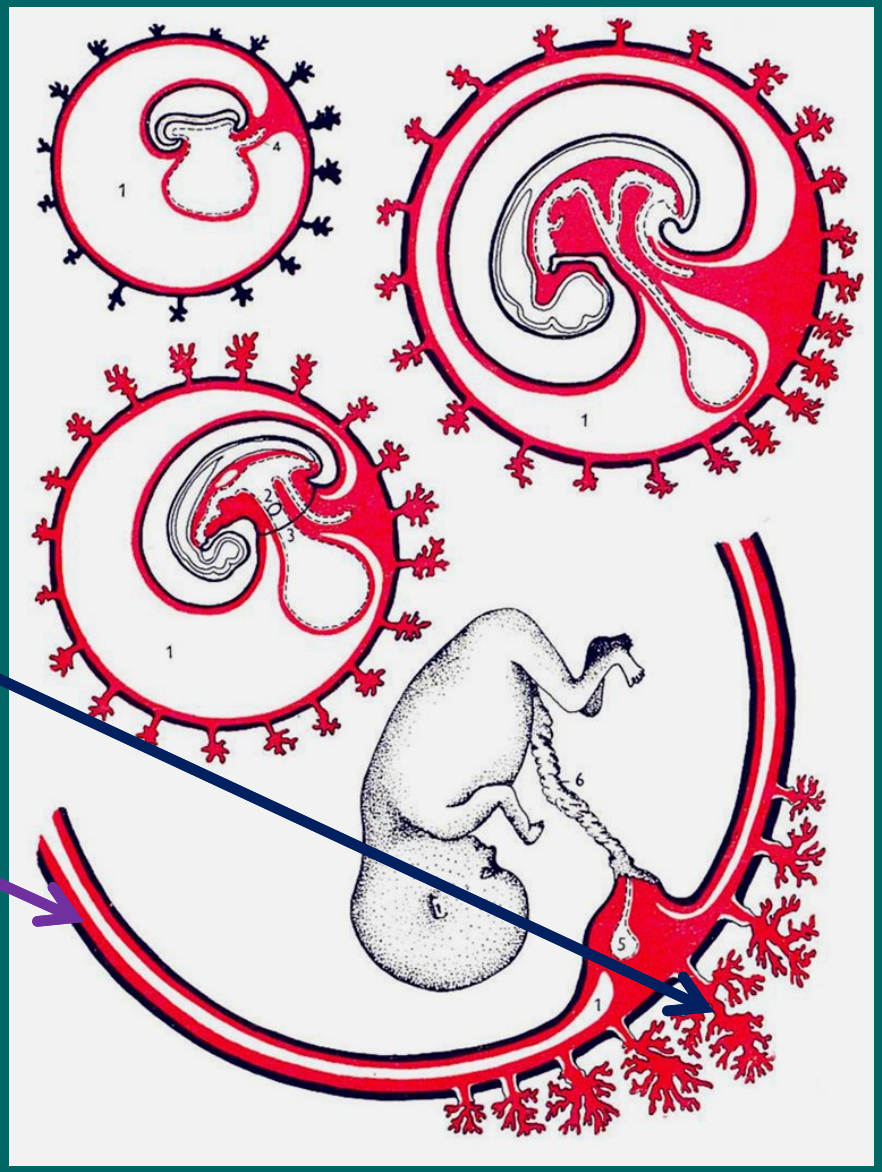
❖ **villi adjacent to basal decidua** become long and branched

by this way, the chorion is divided into regions of different surface

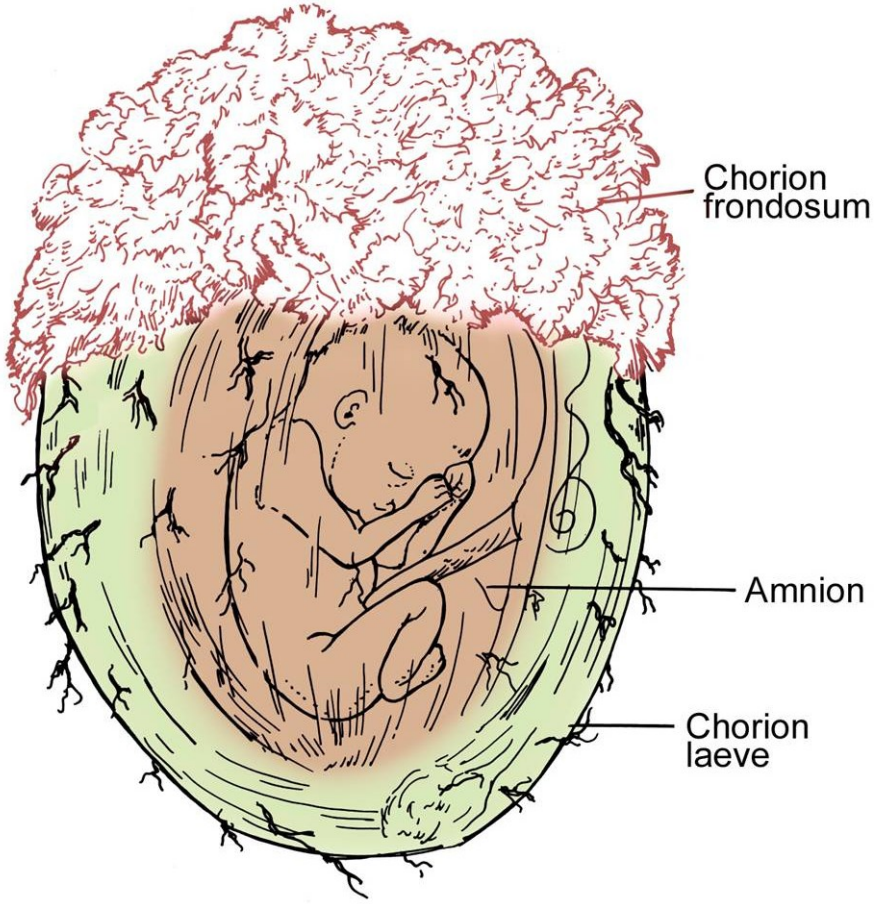
villous chorion /chorion frondosum,/ - against the basal decidua

smooth chorion/ chorion laeve - against the marginal and capsular decidua

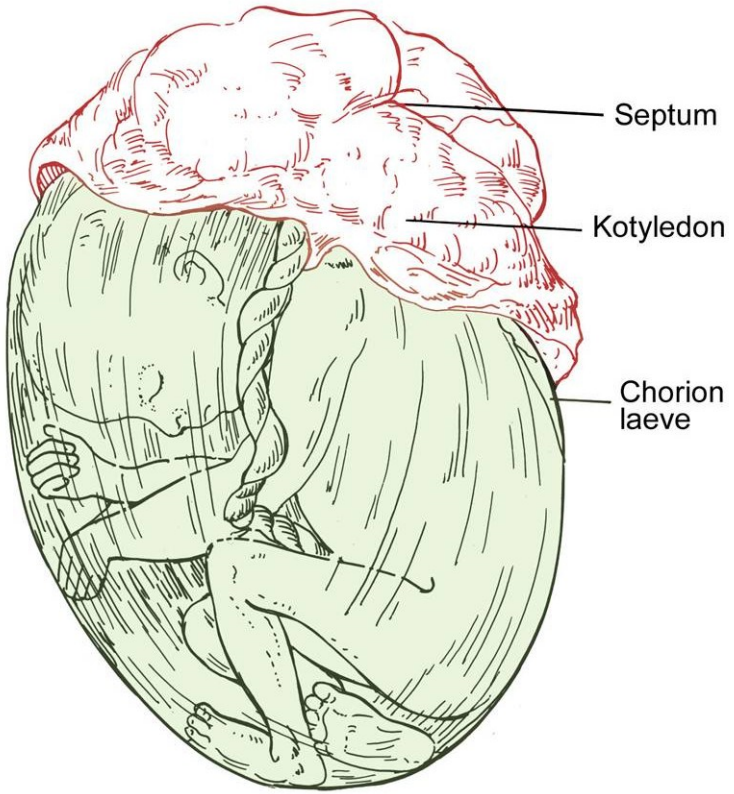




Chorionic sac - 4th month



Placenta - 6th month maternal aspect



Placenta

a membrane-like and temporary organ that develops between the 3 - 8 weeks
the site of nutrient and gas exchange between the mother and fetus

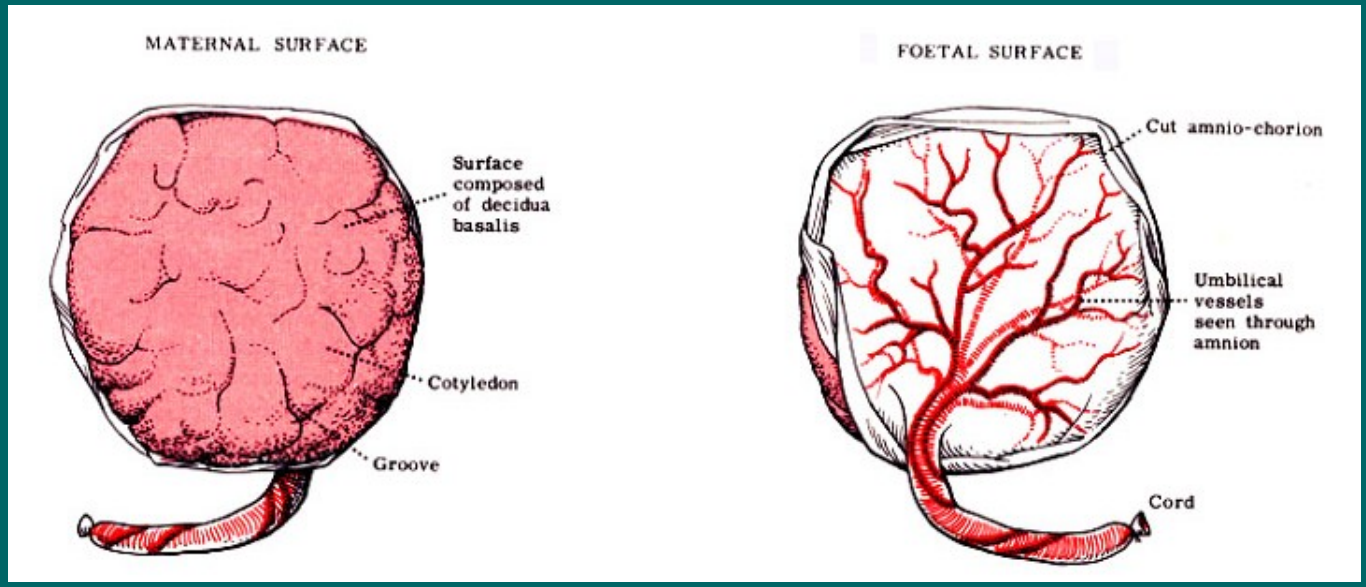
the full term human placenta is a **discoid,** a diameter 15 - 25 cm and 2- 3 cm thick
it weighs 500 to 600 g
the human placenta is **hemochorionic -** the blood of mother enters the intervillous space and flows slowlyaround the villi, allowing an exchange metabolic and gaseous products with fetal blood
shortly after birth a baby, the placenta and fetal membranes are expelled from the uterus as the **afterbirth**

2 parts close associated each other of the placenta:

- **the fetal part or villous chorion -** smooth with insertion of umbilical cord and outlines of umbilical vessels that are seen through the amnion

- **the maternal part or decidua basalis**

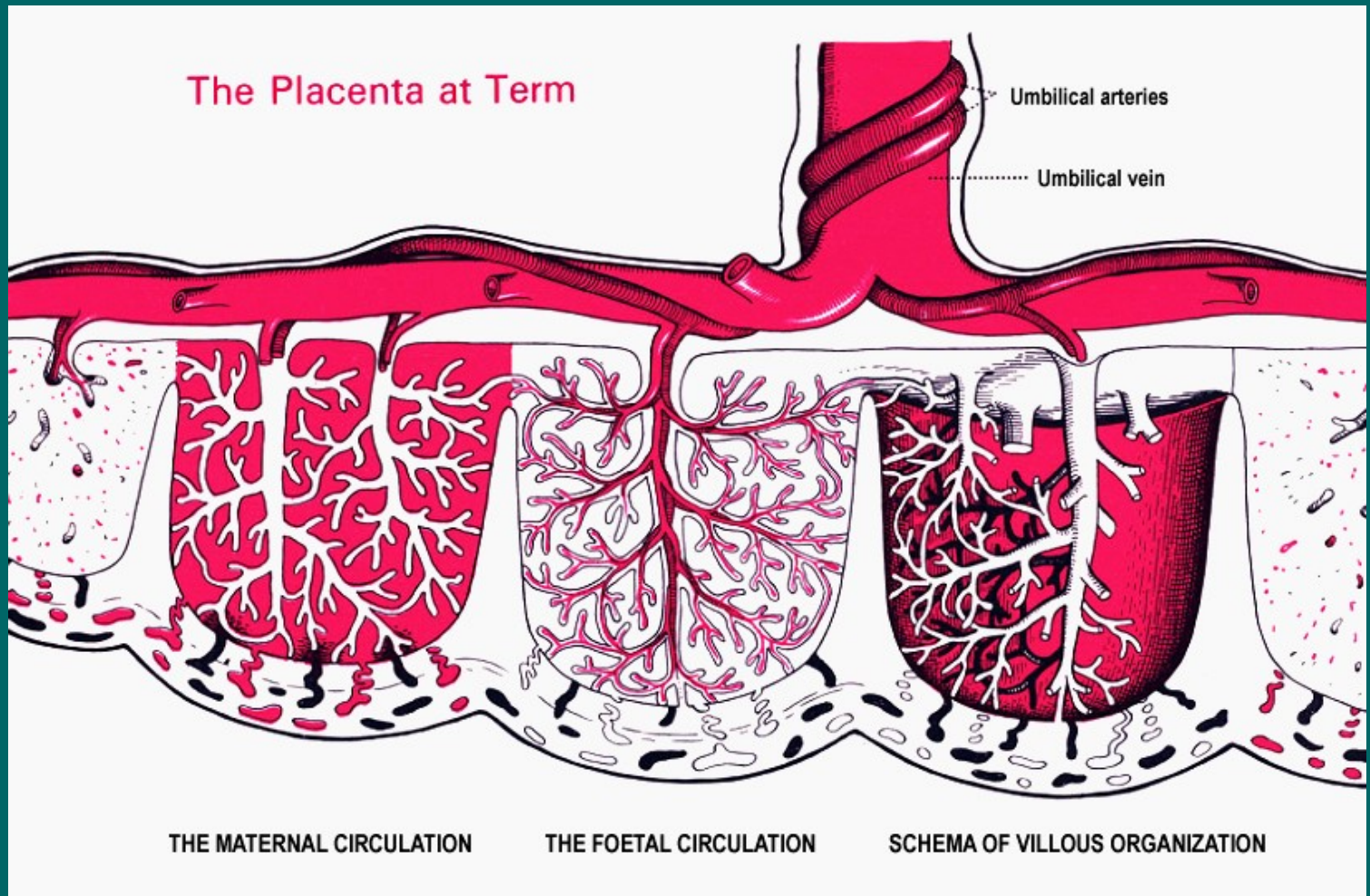
- is divided into irregular convex areas - **cotyledons** seperated by **placental septa**



Fetal part: a chorionic plate + chorionic villi

project into the intervillous space (is deriving from the lacunae developed in the syncytiotrophoblast during the 2nd week)
chorionic villi may be either free or anchored to the decidua basalis = main stem villi, one main stem villus forms a unit of the fetal part of the placenta known as - the **cotyledon**, they are separated each other by **septa** of placenta

maternal blood circulates through the intervillous space, bringing nutritive and other substances necessary for embryonic and fetal growth, and taking away the waste products of fetal metabolism



Structure of villi:

a **connective tissue core** deriving from the extraembryonic mesoderm

is surrounded by the **cytotrophoblast** and the **syncytiotrophoblast**

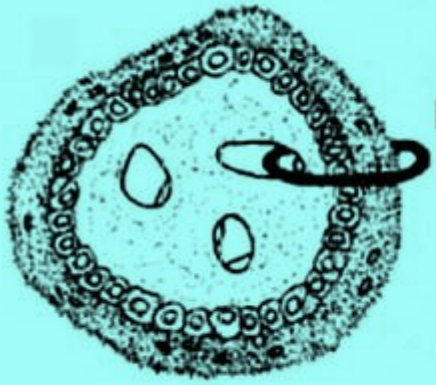
the cytotrophoblast disappears cca in a half of pregnancy while the syncytiotrophoblast is retained to the end

fetal and maternal blood streams in the placenta are separated by the **placental membrane (barrier)**

a composite membrane consisting of

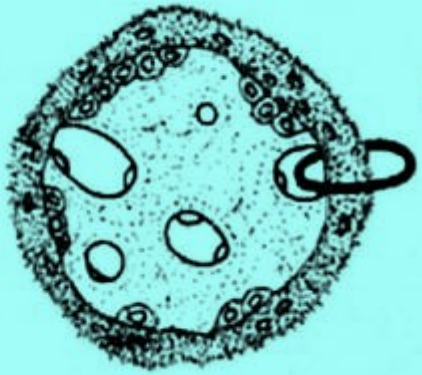
- **the endothelium with basal lamina of the fetal capillaries**
- **the connective tissue in the interior of the villus**
- **the cytotrophoblast + its basal lamina**
- **the syncytiotrophoblast**

- **the endothelium with basal lamina of the fetal capillaries**
- **the connective tissue in the interior of the villus**
- **the syncytiotrophoblast**



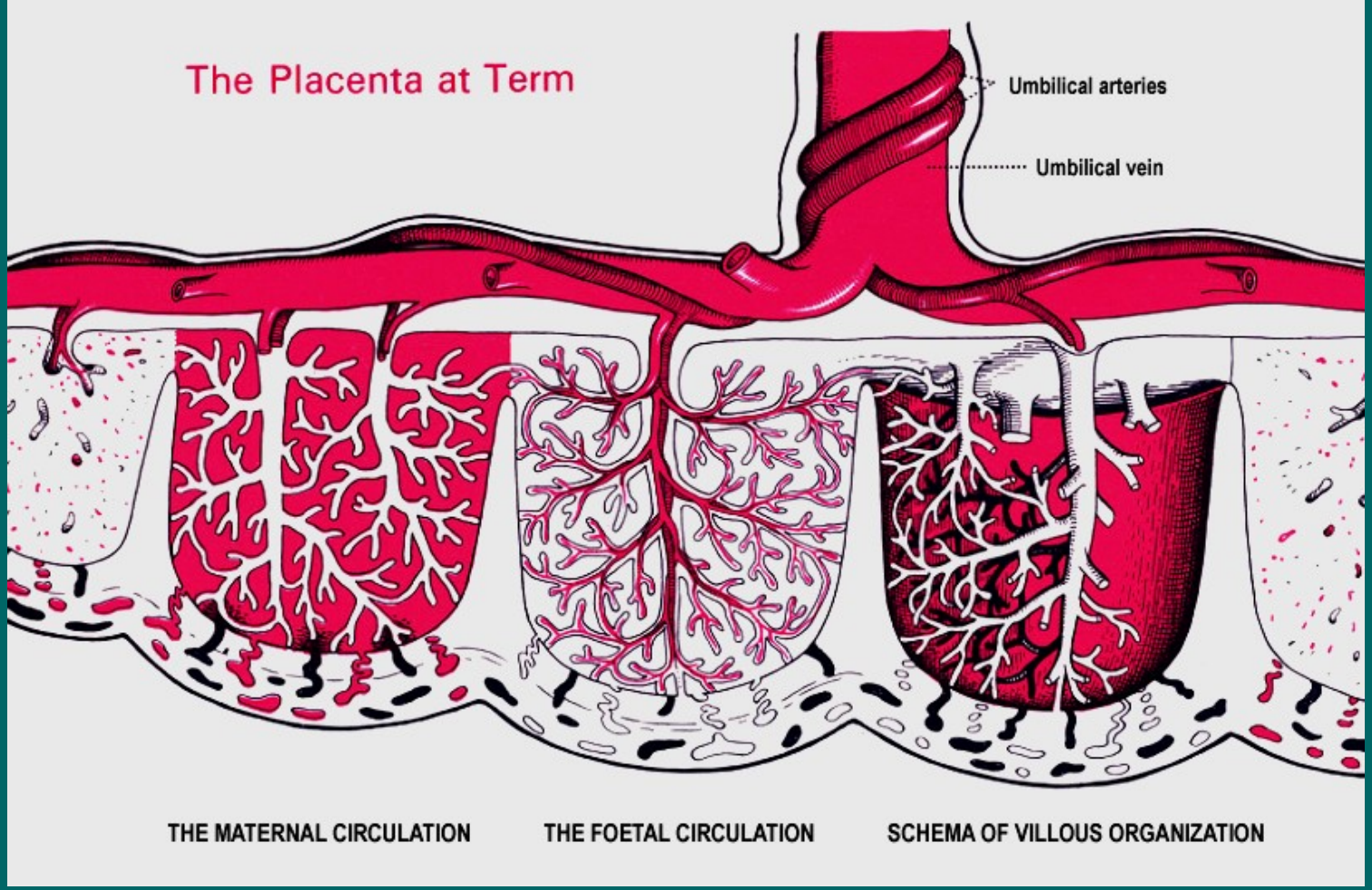
Barrier formed by
1. Syncytium
2. Cytotrophoblast
3. Connective tissue
4. Endothelium

until about 20 weeks



Barrier formed by
1. Syncytium
2. Endothelium

after the 20th week



Maternal part: is decidua basalis that usually forms a compact layer known as the **basal plate**

protrudes between individual cotyledons as **placental septa**

Placental circulation

Fetoplacental circulation: Deoxygenated blood leaves the fetus and passes through the 2 umbilical arteries to the placenta, arteries branch and ultimately give rise to capillaries of chorionic villi, oxygenated fetal blood returns to the fetus through the one umbilical vein

Maternal-placental circulation: 80 to 100 spiral arteries (are branches of the uterine artery) open in the middle of the placenta; blood flows into the intervillous space and passes over villus surfaces toward the chorionic plate; the maternal blood leaves the intervillous space through the endometrial veins (located near the periphery of the placenta)

normally, no intermingling of fetal and maternal blood occurrs

Placental activities

has three main functions: metabolic, transport of gases and nutrients, and endocrine secretion

Placental metabolism - placenta, in particular during early pregnancy, synthesizes glycogen, cholesterol, and fatty acids that all serve as a source of nutrients and energy for the embryo

Placental transport - is bidirectionally (between the placenta and maternal blood and vice versa)

gases, nutrients, hormones, electrolytes, antibodies, wastes, and also several drugs are transported across the placental membrane

4 main transport mechanisms are utilized: simple cell diffusion, facilitated diffusion, active transport, and pinocytosis

Placental endocrine secretion: the syncytiotrophoblast is endocrine active and produces hormones of 2 categories:

protein hormones: human chorionic gonadotropin (hCG), human chorionic somatomammotropin (hCS) or placental lactogen, human chorionic thyrotropin (hCT), and human chorionic corticotropin (hCACTH)

steroid hormones: progesterone + estrogens

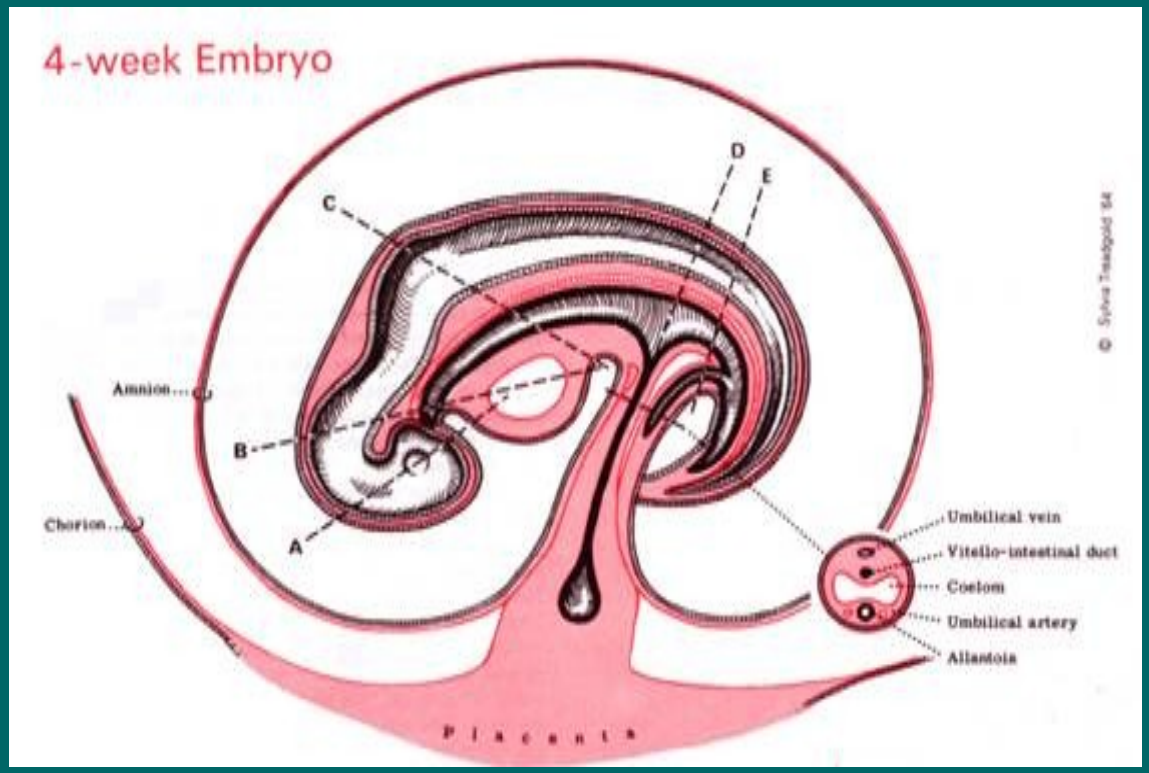
The umbilical cord

at the end of the second month, the amniotic sac enlarges and sheathes the umbilical cord

core od the cord si formed by the material of the connecting stalk

surface of the cord is covered with the amniotic ectoderm

the umbilical cord contains **2 umbilical arteries**, **1 vein**, rarely rests of the allantois

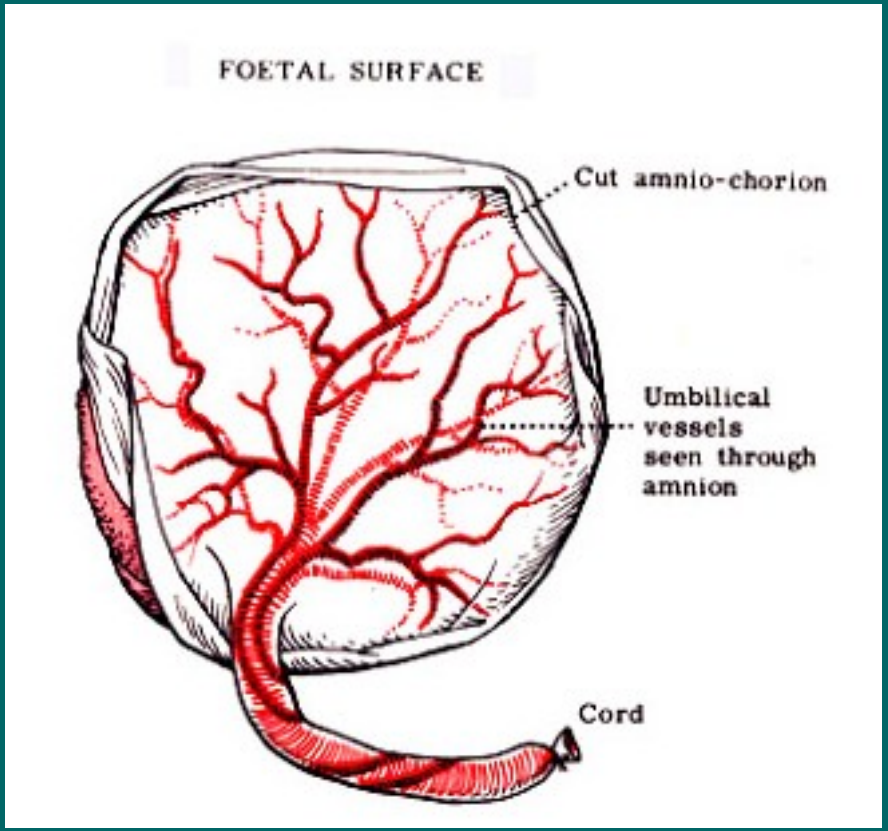


Due an enlargement of the amniotic sac, the extraembryonic coelom disappears and amnion lies to close vicinity of the chorionic sac, both membranes ultimately fuse in one common layer known as **amniochorionic membrane**

in the full term fetus, the umbilical cord measures 1-2 cm in diameter and 30-90 cm in length (average 55 cm)

the cord is usually attached near the center of the placenta

(**central insertion)**



other ways of insertion are:

marginal and

velamentous one