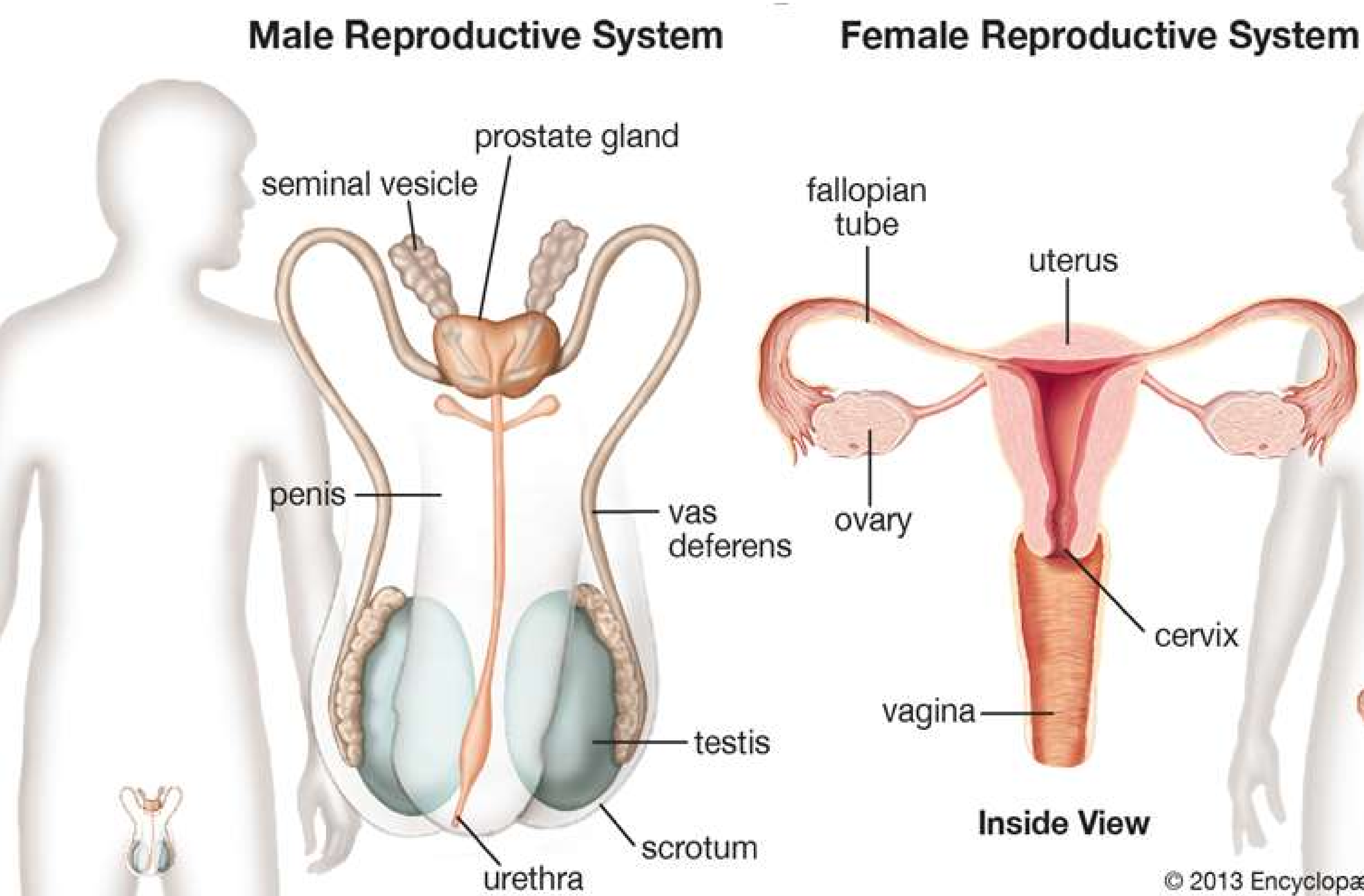
GAMETOGENESIS 1

Dr. Sawsan S. Shurrab


Male Reproductive System
Female Reproductive System
prostate gland
seminal vesicle
penis
vas deferens
testis
scrotum
urethra
fallopian tube
uterus
ovary
cervix
vagina
Inside View
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Male reproductive system

- **Primary sex organ**
- Testes: need lower temperature for normal function so situated in the scrotum outside the body

- **Secondary sex organs**
- Ducts system responsible for transportation of sperms to outside
- Epididymis
- Vas deferens   ampulla of vas
- Ejaculatory duct open in prostatic urethra
- Glands provide nutrition and activation of sperms

Female reproductive system

- **Primary sex organ**
- **Ovaries**
- **Responsible for formation of mature ova and secretion of female hormones**

- **Secondary sex organs**
- 1)fallopian tube:10cm,fertilization in lateral third
- 2)uterus : hollow pear shape muscular organ in middle of pelvic cavity where implantation of fertilized ovum occur

General Embryology

- Sequence of events that occur until the production of a new full-term human being from a single cell (Zygote) over a period of 9 months.

Human Development

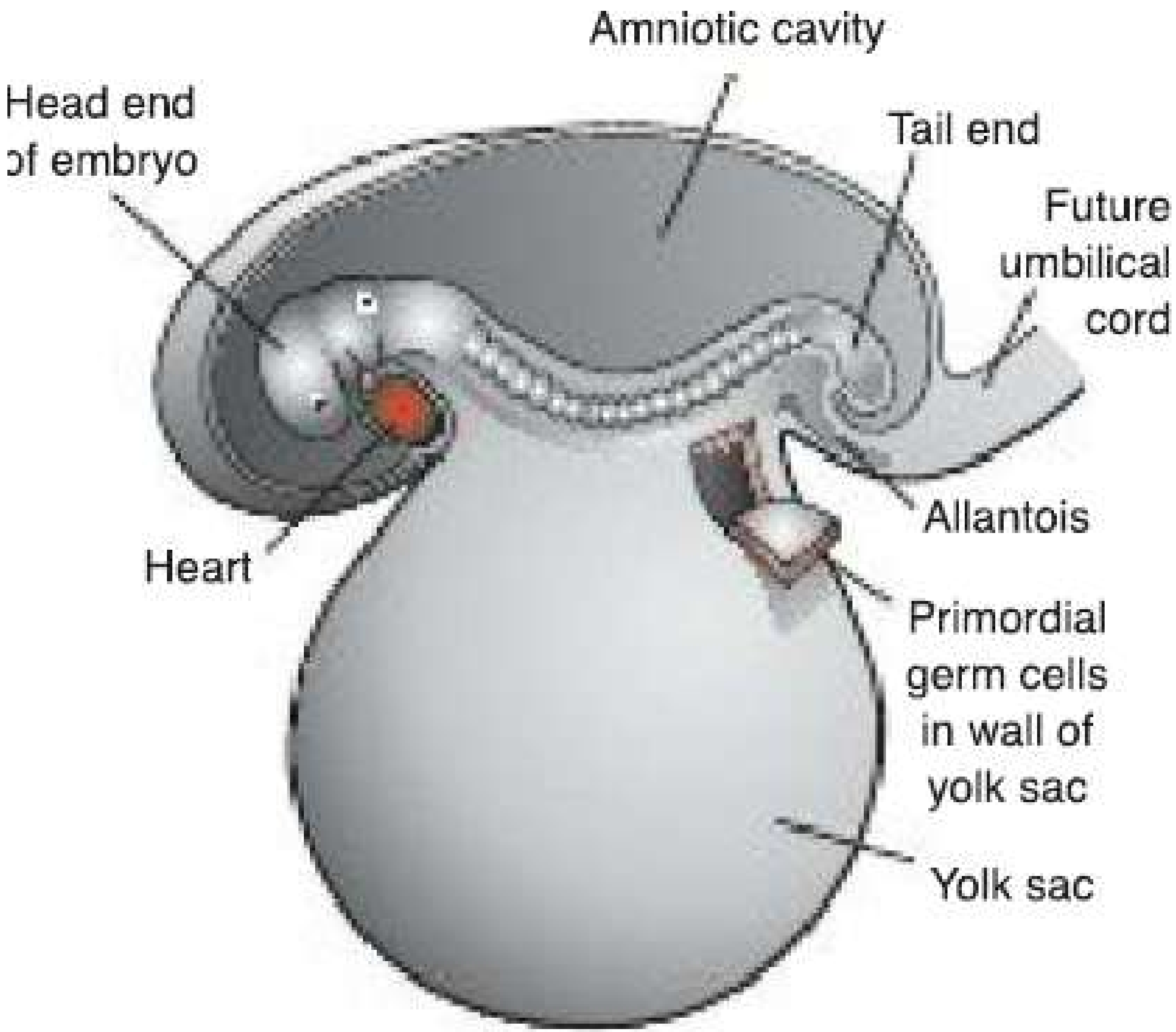
Embryonic period

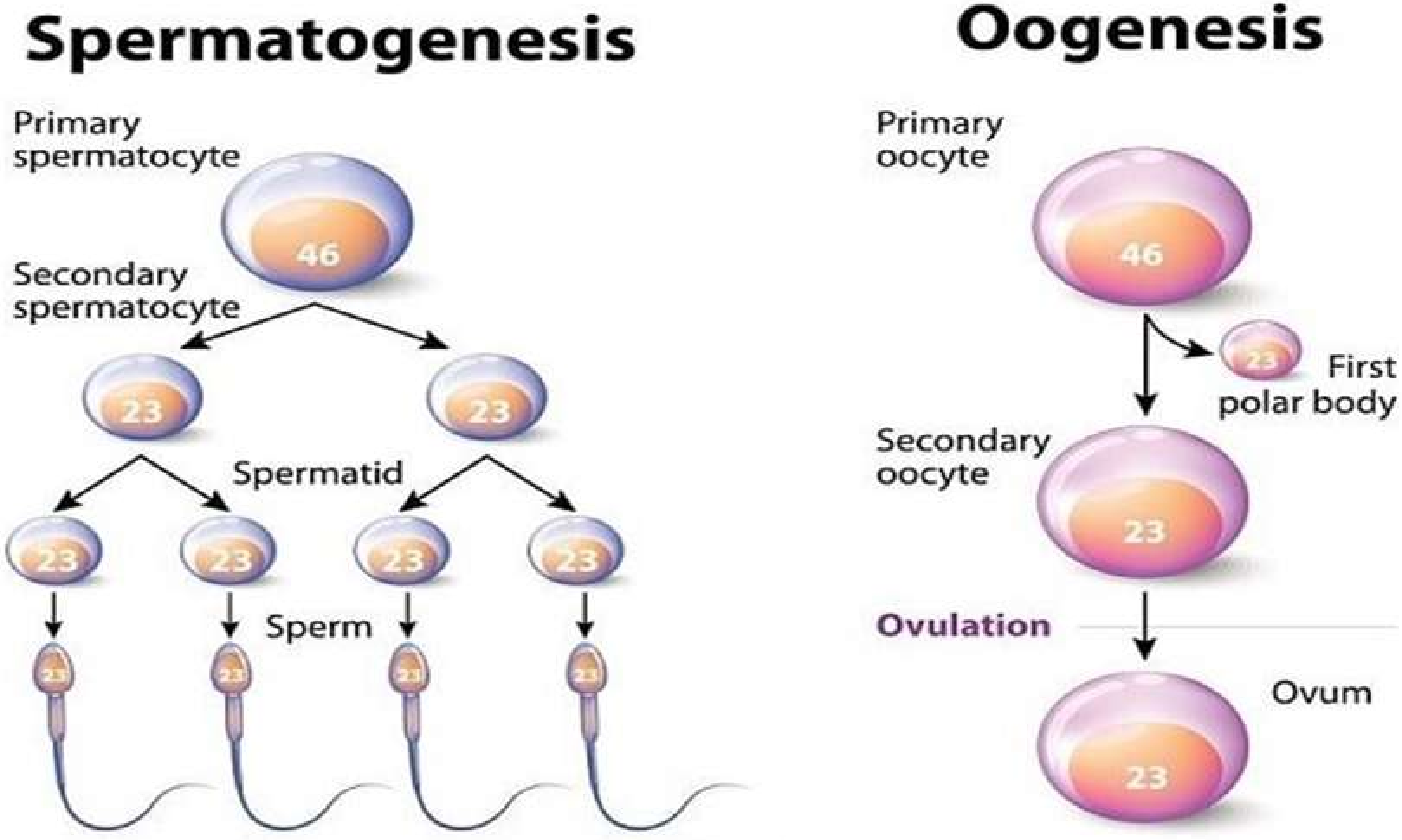
- First 8 weeks.
- Stage of organogenesis.

Fetal period

- From 9th week to the end of pregnancy.
- The fetus grows and gains weight.

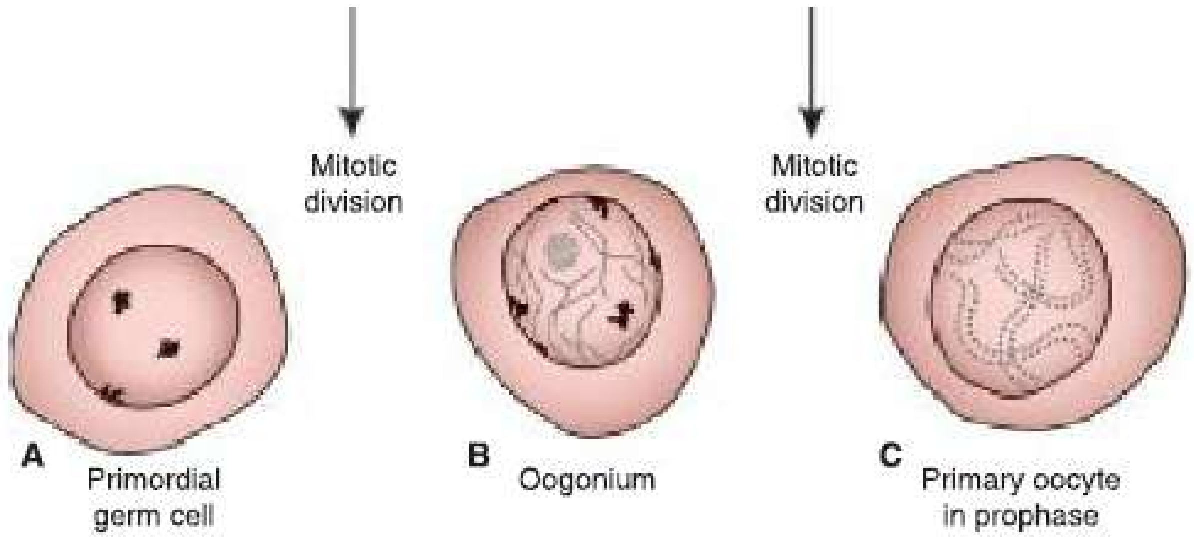
GAMETOGENESIS





Spermatogenesis
Primary spermatocyte
46
Secondary spermatocyte
23
23
Spermatid
23
23
23
23
Sperm
Oogenesis
Primary oocyte
46
23
First polar body
Secondary oocyte
23
Ovulation
Ovum
23

- Oogenesis is the process whereby oogonia differentiate into mature oocytes.



Maturation of Oocytes Begins Before Birth

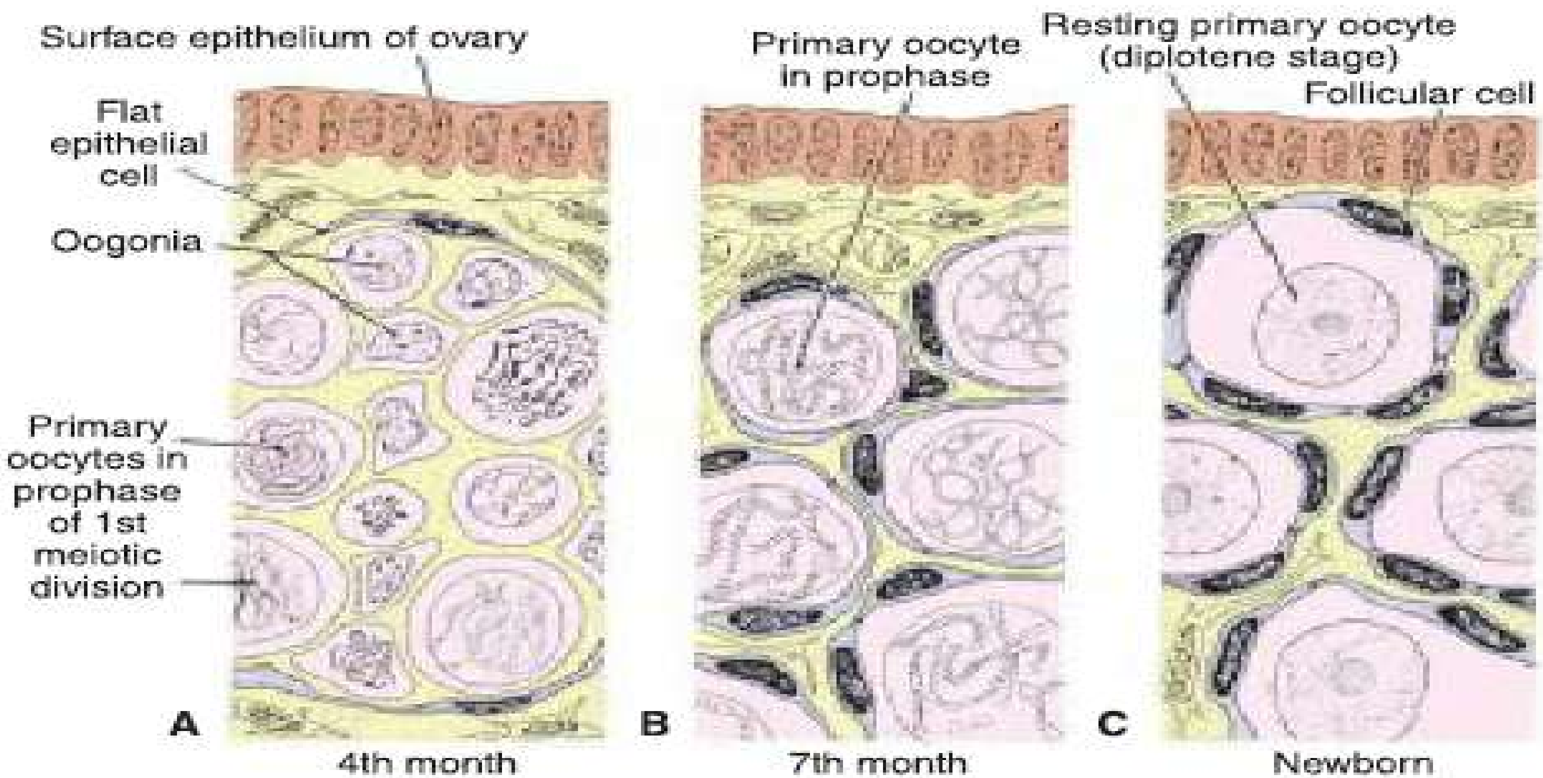
- Once PGCs have arrived in the gonad of a genetic female, they differentiate into oogonia.
- These cells undergo a number of mitotic divisions, and by the end of the third month, they are arranged in clusters surrounded by a layer of flat epithelial cells.

- Whereas all of the oogonia in one cluster are probably derived from a single cell, the flat epithelial cells, known as follicular cells, originate from surface epithelium covering the ovary

- The majority of oogonia continue to divide by mitosis, but some of them arrest their cell division in prophase of meiosis I and form primary oocytes .

- During the next few months, oogonia increase rapidly in number, and by the fifth month of prenatal development, the total number of germ cells in the ovary reaches its maximum, estimated at 7 million.

- At this time, cell death begins, and many oogonia as well as primary oocytes degenerate and become atretic



- By the seventh month the majority of oogonia have degenerated except for a few near the surface.
- All surviving primary oocytes have entered prophase of meiosis I, and most of them are individually surrounded by a layer of flat follicular epithelial cells.
- A primary oocyte, together with its surrounding flat epithelial cells, is known as a primordial follicle

Maturation of Oocytes Continues at Puberty

- Near the time of birth, all primary oocytes have started prophase of meiosis I, but instead of proceeding into metaphase, they enter the diplotene stage, a resting stage during prophase that is characterized by a lacy network of chromatin

- Primary oocytes remain arrested in prophase and do not finish their first meiotic division before puberty is reached

- This arrested state is produced by oocyte maturation inhibitor (OMI), a small peptide secreted by follicular cells.
- The total number of primary oocytes at birth is estimated to vary from 600,000 to 800,000.

- During childhood, most oocytes become atretic; only approximately 40,000 are present by the beginning of puberty, and fewer than 500 will be ovulated.
- Some oocytes that reach maturity late in life have been dormant in the diplotene stage of the first meiotic division for 40 years or more before ovulation

- Whether the diplotene stage is the most suitable phase to protect the oocyte against environmental influences is unknown.

- The fact that the risk of having children with chromosomal abnormalities increases with maternal age indicates that primary oocytes are vulnerable to damage as they age.

- At puberty, a pool of growing follicles is established .

- Each month, 15 to 20 follicles selected from this pool begin to mature.

- Some of these die, whereas others begin to accumulate fluid in a space called the antrum, thereby entering the antral or vesicular stage.

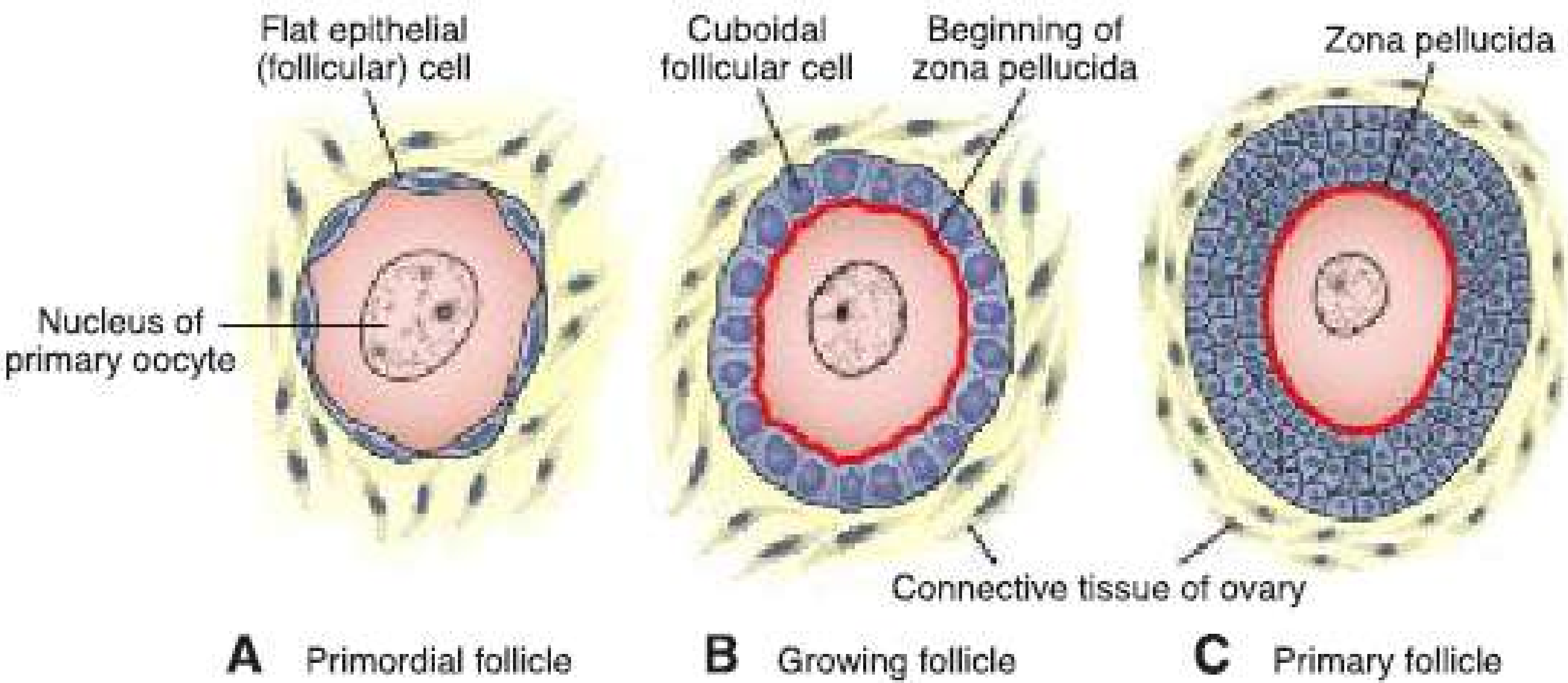
- Fluid continues to accumulate such that, immediately prior to ovulation, follicles are quite swollen and are called mature vesicular follicles or graafian follicles.

- The antral stage is the longest, whereas the mature vesicular stage is present 37 hours prior to ovulation.

- As primordial follicles begin to grow, surrounding follicular cells change from flat to cuboidal and proliferate to produce a stratified epithelium of granulosa cells, and the unit is called a primary follicle.

- Granulosa cells rest on a basement membrane separating them from surrounding ovarian connective tissue (stromal cells) that form the theca folliculi.

- Also, granulosa cells and the oocyte secrete a layer of glycoproteins on the surface of the oo-cyte, forming the zona pellucida

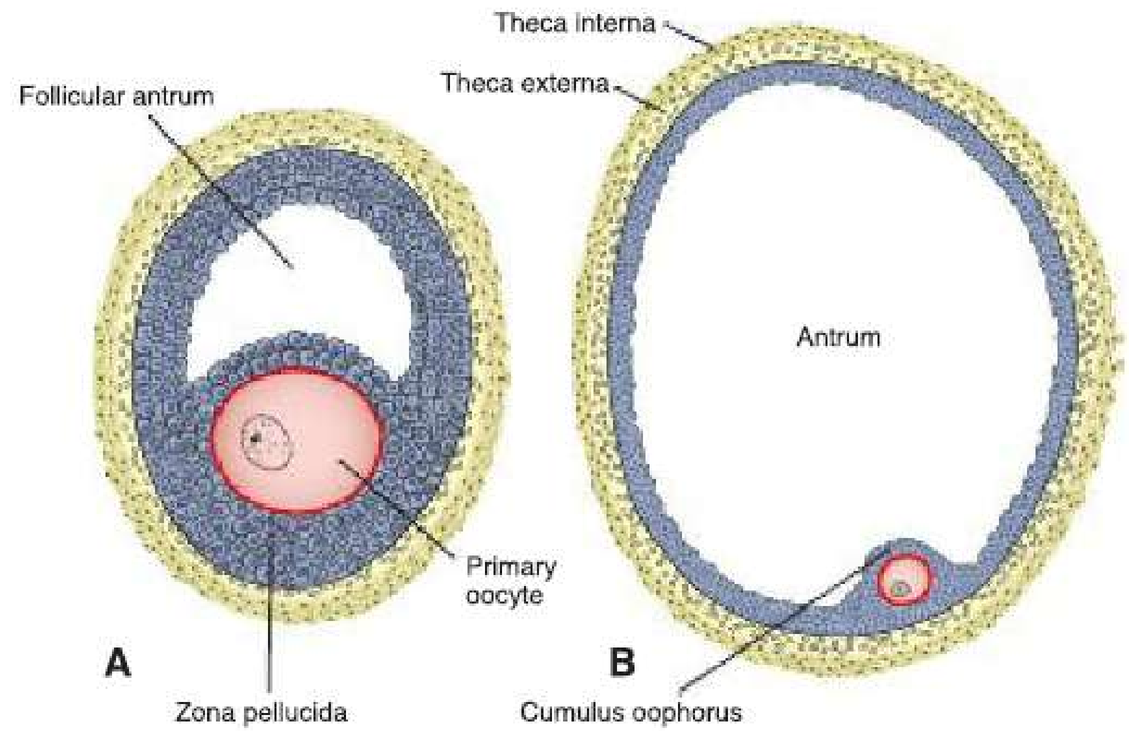


- As follicles continue to grow, cells of the theca folliculi organize into an inner layer of secretory cells, the **theca interna**, and an outer fibrous capsule, the **theca externa**.

- Also, small, fingerlike processes of the follicular cells extend across the zona pellucida and interdigitate with microvilli of the plasma membrane of the oocyte to transport of materials from follicular cells to the oocyte.

- As development continues, fluid-filled spaces appear between granulosa cells.
- Coalescence of these spaces forms the antrum, and the follicle is termed a vesicular or an **antral follicle**.
- Initially,the antrum is crescent-shaped, but with time, it enlarges .

- Granulosa cells surrounding the oocyte remain intact and form the cumulus oophorus.
- At maturity, the mature vesicular (graafian) follicle may be 25 mm or more in diameter



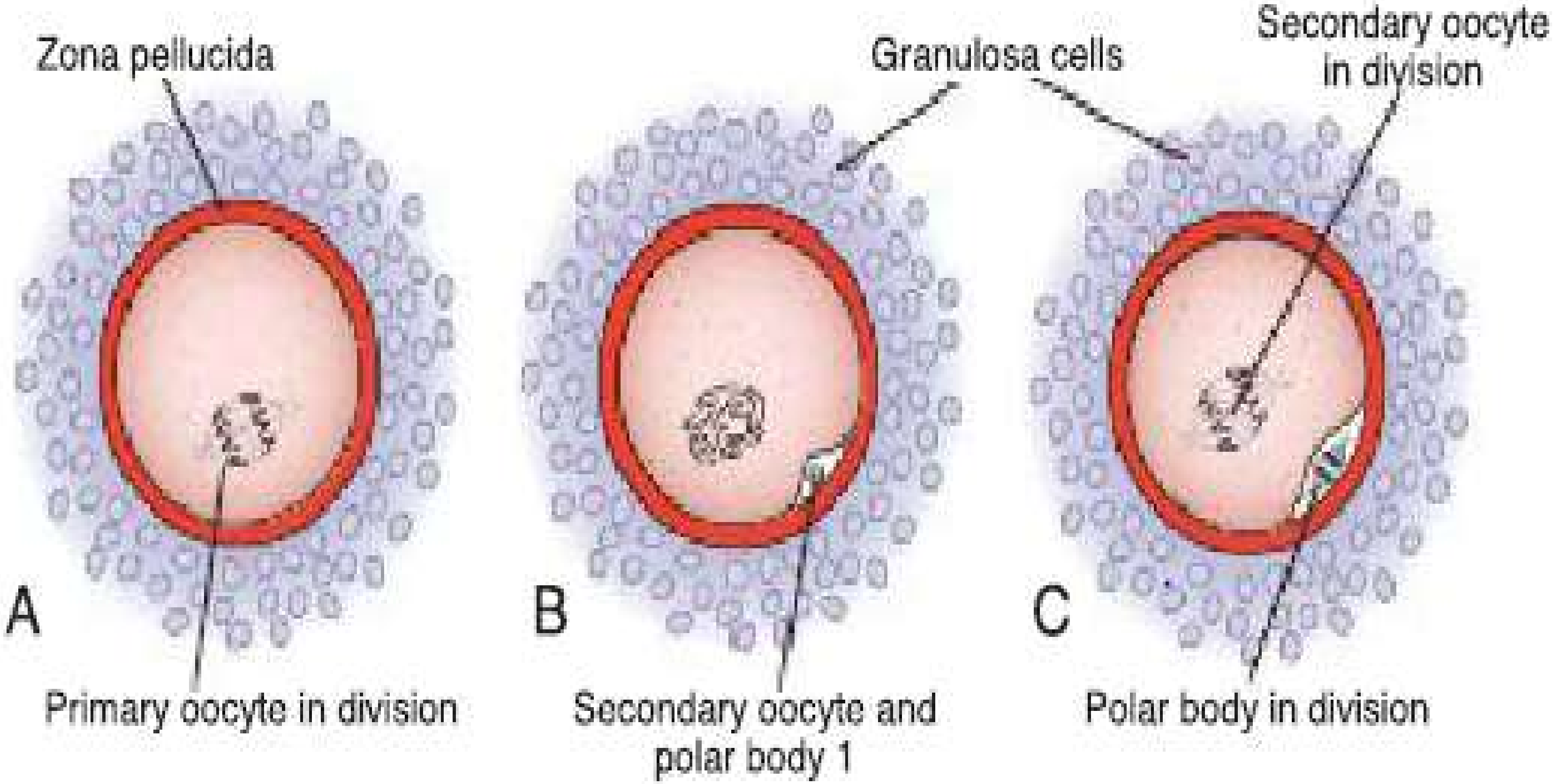
- It is surrounded by the theca interna, which is composed of cells which can secrete steroids, and the theca externa, which merges with the ovarian connective tissue .

- With each ovarian cycle, a number of follicles begin to develop, but usually, only one reaches full maturity.

- The others degenerate and become atretic.
- When the secondary follicle is mature, a surge in luteinizing hormone (LH) induces the pre ovulatory growth phase.

- Meiosis 1 is completed resulting in two daughter cells of unequal size, each with 23 chromosomes.
- One cell, the secondary oocyte, receives most of the cytoplasm; the other, the polar body, receives practically none.
- The first polar body lies between the zona pellucida and the cell membrane of the secondary oocyte in the perivitelline space

- The cell then enters meiosis II but arrests in metaphase approximately 3 hours before ovulation.
- Meiosis II is completed only if the oo-cyte is fertilized; otherwise, the cell degenerates approximately 24 hours after ovulation.
- The first polar body may undergo a second division.



Zona pellucida
Granulosa cells
Secondary oocyte
in division
A
B
C
Primary oocyte in division
Secondary oocyte and
polar body 1
Polar body in division

follicular cells
stromal cells

Ovarian cycle

Follicular phase

- **Follicular cells** from ovarian surface epithelium will give (granulosa cells), then will be separated from the oocyte by zona pellucida.
- **Stroma cells:** will form theca cells:

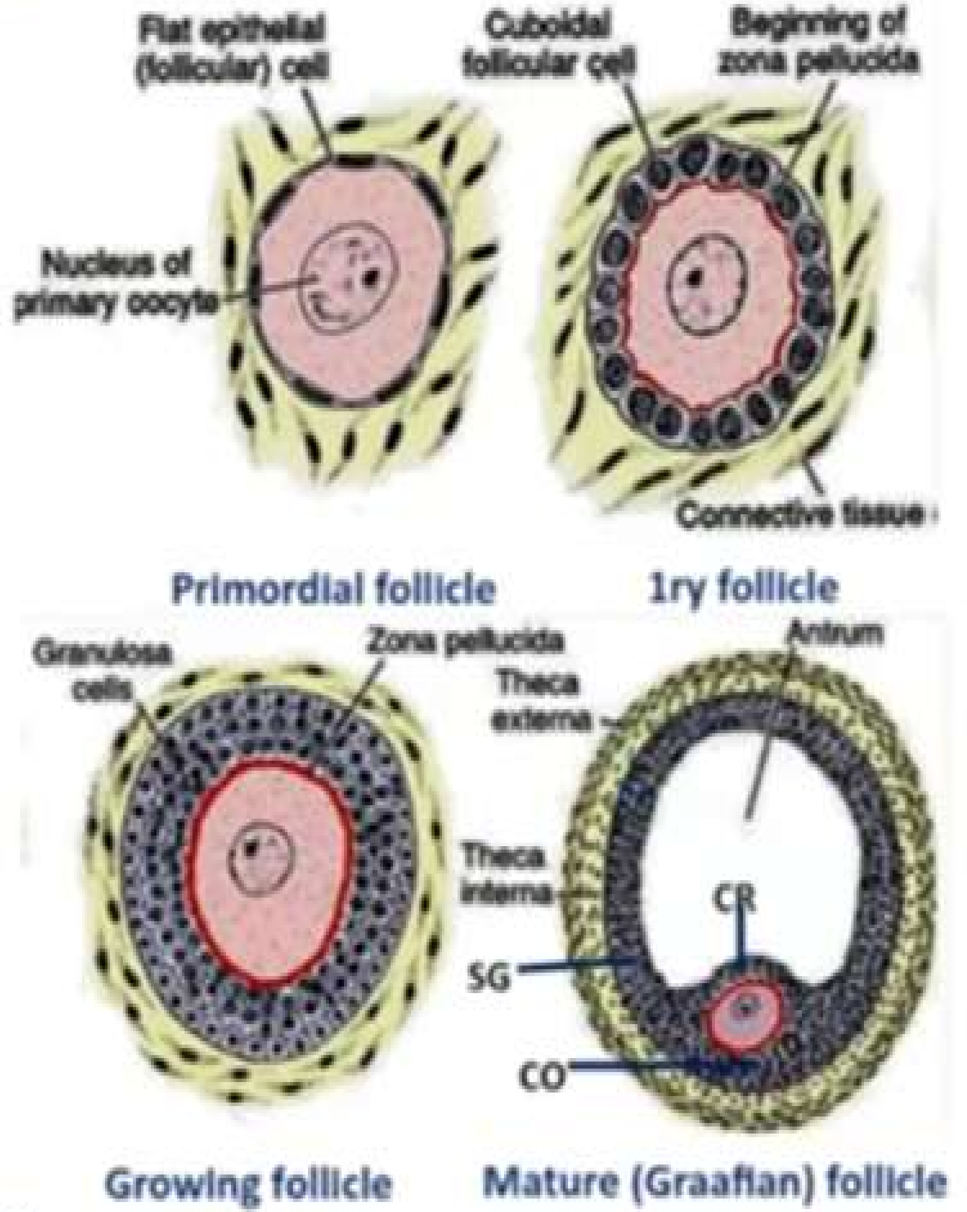
a) **Theca interna**: cells and blood capillaries, they secrete estrogen.

b) **Theca externa**: fibrous tissue and blood vessels.

- **Follicular antrum:** will be formed separating the granulosa cells

c) **Outer part**: (stratum granulosum).

d) **Inner part**: corona radiata (around the oocyte) + cumulus oophorus binding the oocyte to one side of the follicle.

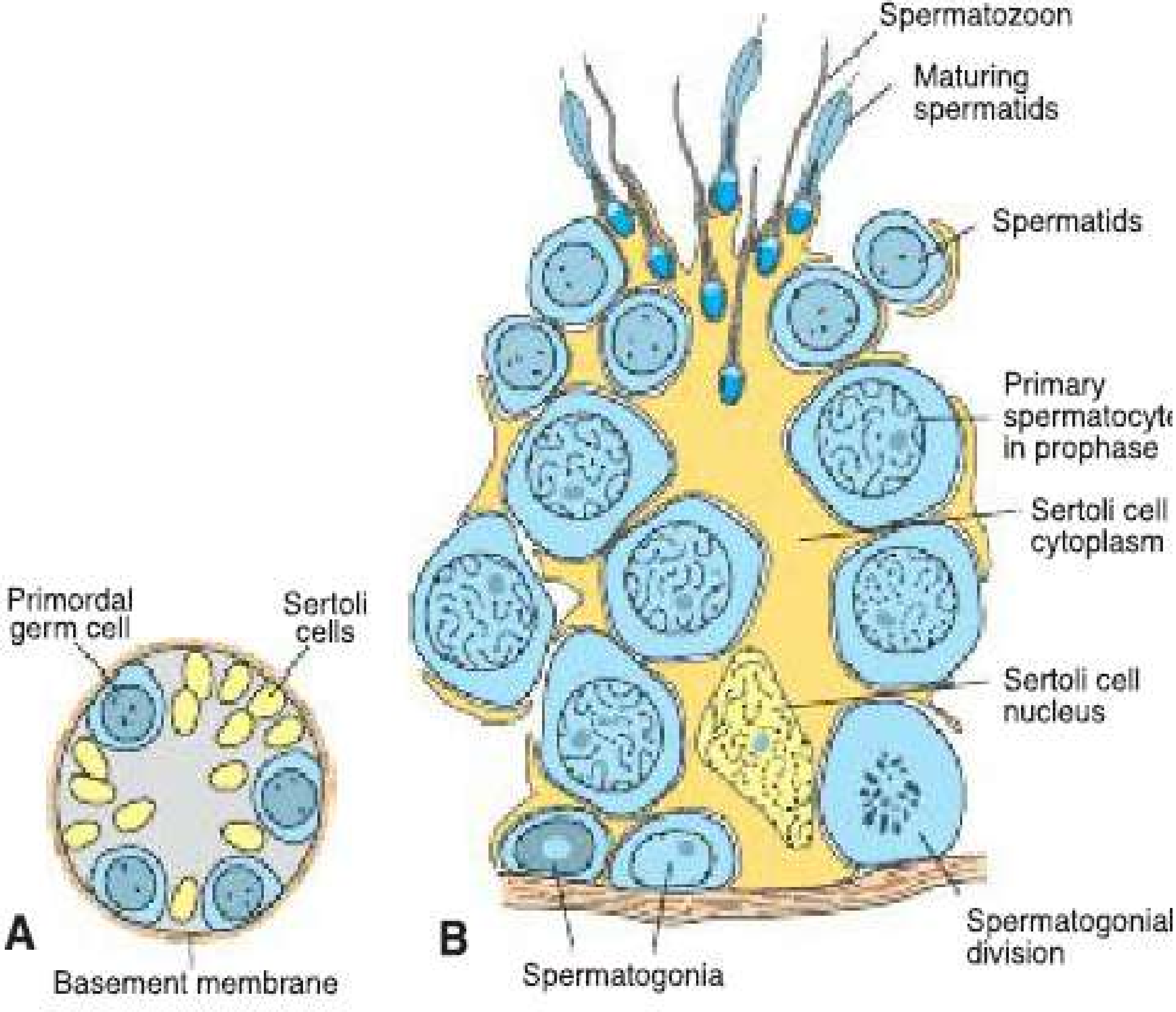


Spermatogenesis

- Spermatogenesis, which begins at puberty, includes all of the events by which spermatogonia are transformed into spermatozoa.

- At birth, germ cells in the male infant can be recognized in the sex cords of the testis as large, pale cells surrounded by supporting cells.

- Supporting cells, which are derived from the surface epithelium of the testis become sustentacular cells or **Sertoli cells** .



Primordal germ cell
Sertoli cells
A
Basement membrane
Spermatozoon
Maturing spermatids
Spermatids
Primary spermatocyte in prophase
Sertoli cell cytoplasm
Sertoli cell nucleus
B
Spermatogonia
Spermatogonial division

- Shortly before puberty, the sex cords acquire a lumen and become the seminiferous tubules.
- At about the same time, PGCs give rise to spermatogonial stem cells.
- At regular intervals, cells emerge from this stem cell population to form type A spermatogonia, and their production marks the initiation of spermatogenesis.

- Type A cells undergo a limited number of mitotic divisions to form clones of cells.
- The last cell division produces type B spermatogonia, which then divide to form primary spermatocytes

- Primary spermatocytes then enter a prolonged prophase (22 days) followed by rapid completion of meiosis I and formation of secondary spermatocytes.

- During the second meiotic division, these cells immediately begin to form haploid spermatids.

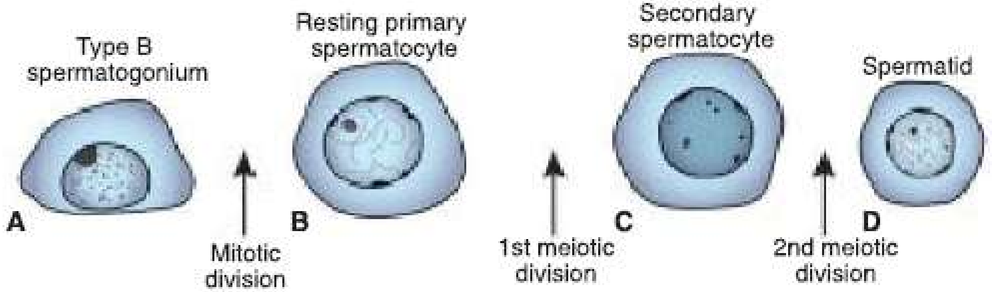
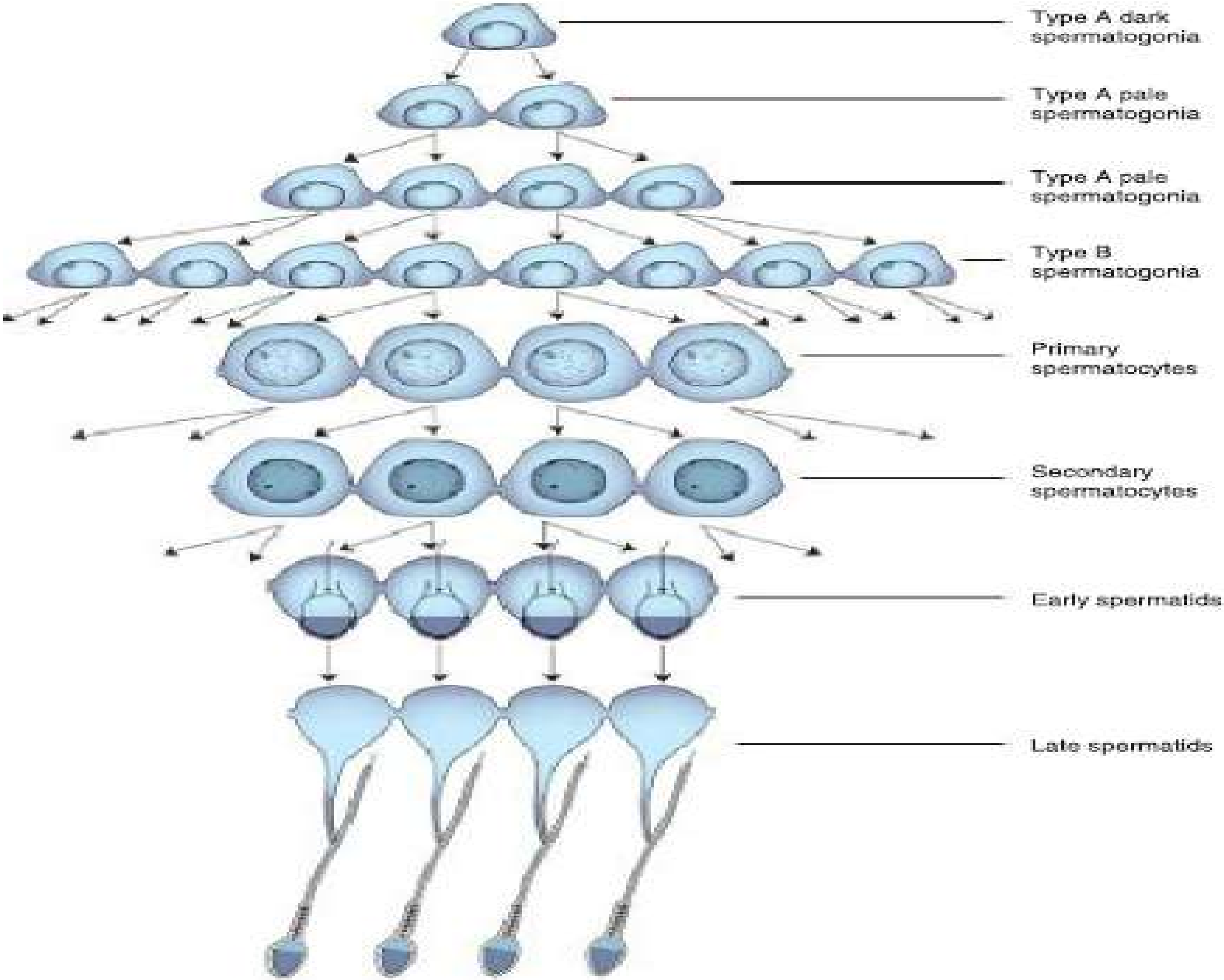


FIGURE 2.23 The products of meiosis during spermatogenesis in humans.

- From the time type A cells leave the stem cell population to formation of spermatids, cytokinesis is incomplete so that successive cell generations are joined by cytoplasmic bridges.


Type A dark spermatogonia
Type A pale spermatogonia
Type A pale spermatogonia
Type B spermatogonia
Primary spermatocytes
Secondary spermatocytes
Early spermatids
Late spermatids

- Furthermore, spermatogonia and spermatids remain embedded in deep recesses of Sertoli cells throughout their development.

- In this manner, Sertoli cells support and protect the germ cells, participate in their nutrition, and assist in the release of mature spermatozoa

- Spermatogenesis is regulated by LH production by the pituitary gland.

- LH binds to receptors on Leydig cells and stimulates testosterone production,
which in turn binds to Sertoli cells to promote spermatogenesis.

- Follicle-stimulating hormone (FSH) is also essential because its binding to Sertoli cells stimulates testicular fluid production and synthesis of intracellular androgen receptor proteins.

Spermiogenesis

- It is the series of changes resulting in the transformation of spermatids into spermatozoa which include:

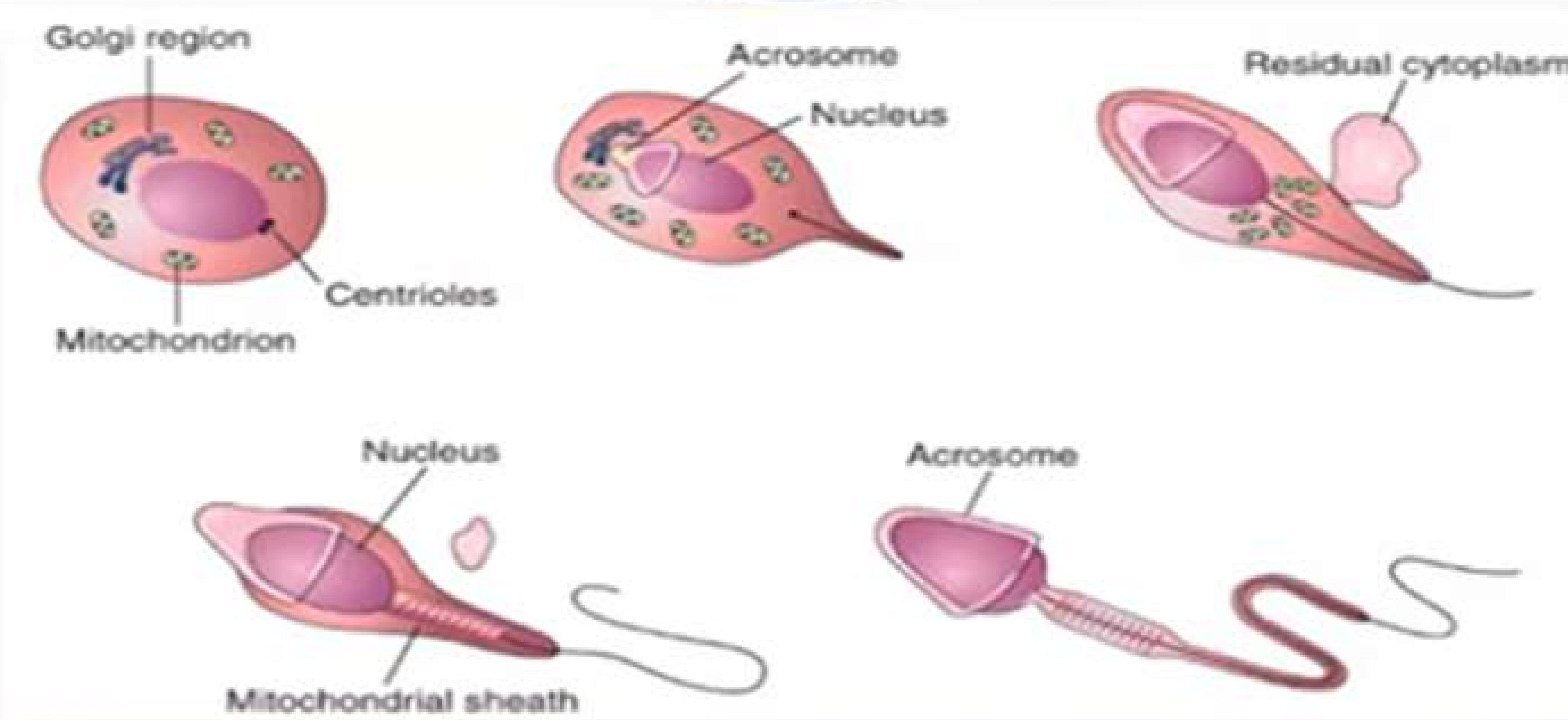
(1) Formation of the acrosome, which covers half of the nuclear surface and contains enzymes to assist in penetration of the egg and its surrounding layers during fertilization .

(2) Condensation of the nucleus;

(3) Formation of neck, middle piece, and tail

(4) Shedding of most of the cytoplasm as residual bodies that are phagocytized by Sertoli cells.

Spermiogenesis



- **Nucleus**: **condenses** to ovoid chromatin.
- **Golgi** complex: **aggregates** to form **acrosomal cap**.
- **Centrioles**: appear in the **neck** giving the **axial filament**.
- **Mitochondria**: **collect** in the **middle piece** as helical sheath arou the axial filament.
- **Cytoplasm**: mostly will be shed.

- In humans, the time required for a spermatogonium to develop into a mature spermatozoon is approximately 74 days, and approximately 300 million sperm cells are produced daily.

- When fully formed, spermatozoa enter the lumen of seminiferous tubules.
- From there, they are pushed toward the epididymis by contractile elements in the wall of the seminiferous tubules.
- Although initially only slightly motile, spermatozoa obtain full motility in the epididymis .

First Week of Development: Ovulation to Implantation 2

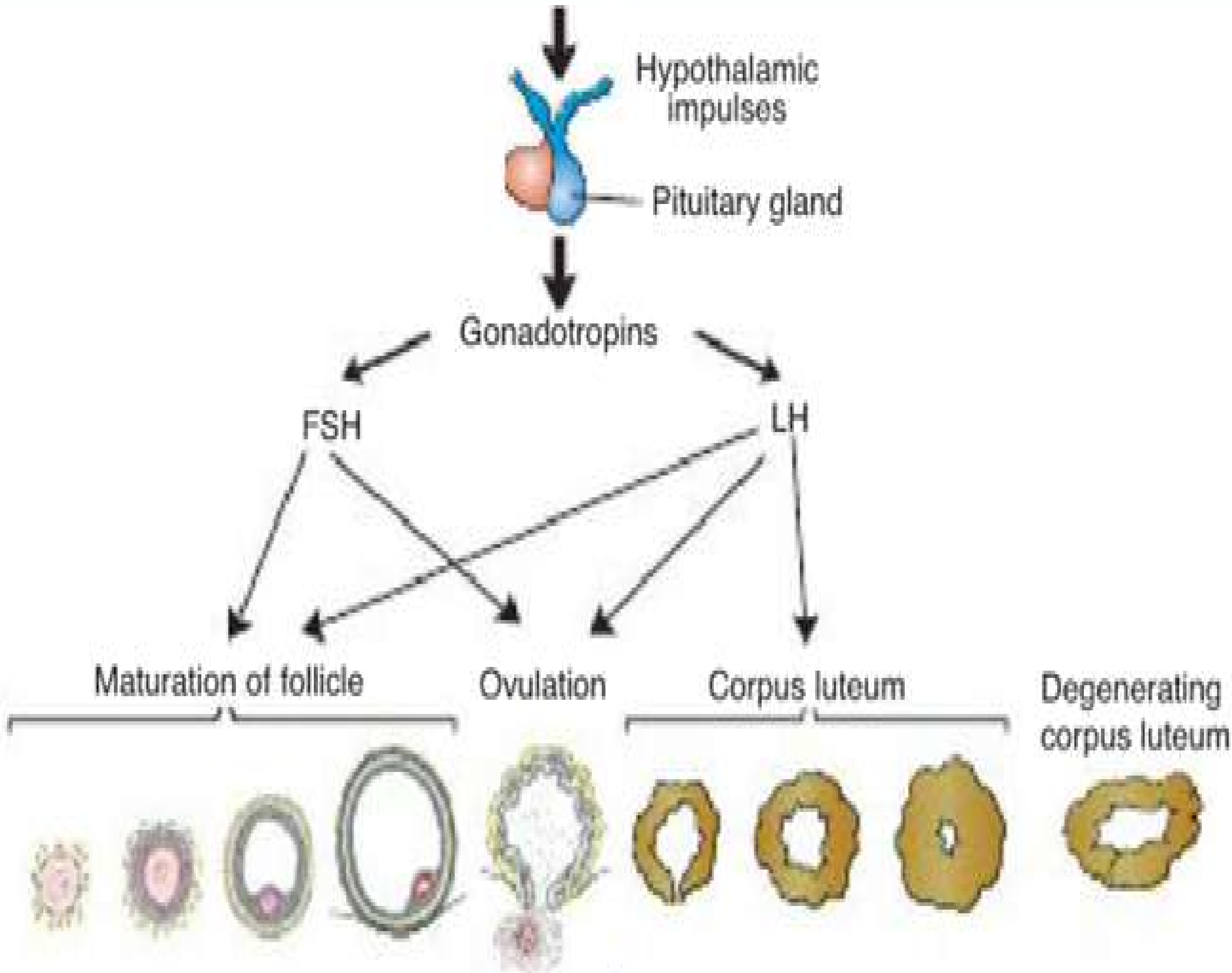
Dr. Sawsan S. Shurrab

OVARIAN CYCLE

- At puberty, the female begins to undergo regular monthly cycles which are controlled by the hypothalamus.
- Gonadotropin-releasing hormone (GnRH), produced by the hypothalamus, acts on cells of the anterior lobe of the pituitary gland, which secrets gonadotropins.

- At the beginning of each ovarian cycle, 15 to 20 primary-stage (preantral) follicles are stimulated to grow under the influence of FSH.
- Without it , they would be atretic.

- These hormones, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), stimulate and control cyclic changes in the ovary.


Hypothalamic impulses
Pituitary gland
Gonadotropins
FSH
LH
Maturation of follicle
Ovulation
Corpus luteum
Degenerating corpus luteum

- Thus, FSH rescues 15 to 20 of these cells from a pool of continuously forming primary follicles

- Under normal conditions, only one of these follicles reaches full maturity, and only one oocyte is discharged;others become atretic.

- In the next cycle, another group of primary follicle is recruited, and again, only one follicle reaches maturity.
- Consequently, most follicles degenerate without reaching full maturity and replaced by connective tissue

- FSH also stimulates maturation of follicular (granulosa) cells surrounding the oocyte.
- In turn, proliferation of these cells is mediated by growth differentiation factor 9, a member of the transforming growth factor-B (TGF-B) family.

- In cooperation, theca interna and granulosa cells produce estrogens:

- Theca interna cells produce androstenedione and testosterone and granulosa cells convert these hormones to estrone and 17 B-estradiol.

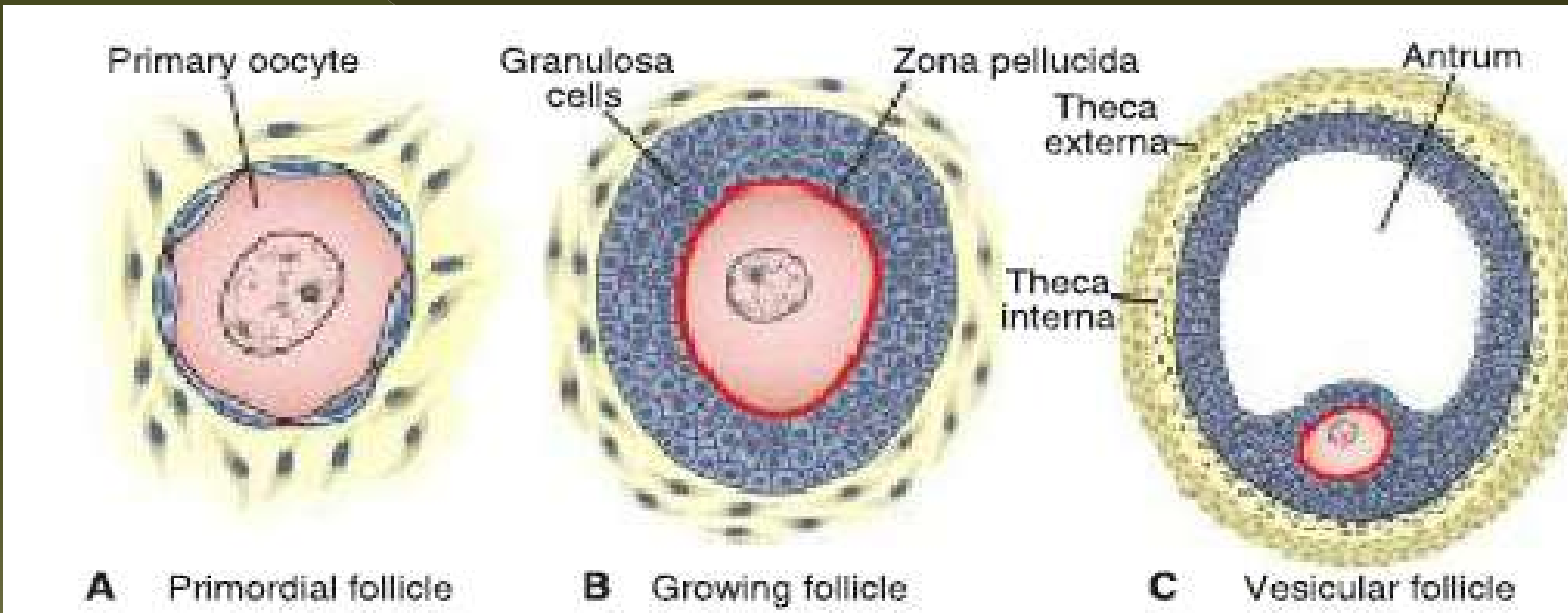
- The uterine endometrium enters the follicular or proliferative phase.
- Thinning of the cervical mucus occurs to allow passage of sperm.
- The anterior lobe of the pituitary gland is stimulated to secrete LH.

- At midcycle, there is an **LH surge** that:
  - Elevates concentrations of maturation promoting factor, causing oocytes to complete meiosis I and initiate meiosis II.
  - Stimulates production of progesterone by follicular stromal cells (luteinization)
  - Causes follicular rupture and ovulation

Ovulation

- In the days immediately preceding ovulation,under the influence of FSH and LH, the vesicular follicle grows rapidly to a diameter of 25 mm to become a mature vesicular (graafian) follicle.

- Coincident with final development of the vesicular follicle, there is an abrupt increase in LH that causes the primary oocyte to complete meiosis I and the follicle to enter the preovulatory mature vesicular stage


Primary oocyte
Granulosa cells
Zona pellucida
Antrum
Theca externa
Theca interna
A Primordial follicle
B Growing follicle
C Vesicular follicle

- Meiosis II is also initiated, but the oocyte is arrested in metaphase 3 hours before ovulation.
- The surface of the ovary begins to bulge locally, and at the apex, an avascular spot, the stigma, appears.

- LH increases collagenase activity, resulting in digestion of collagen fibers surrounding the follicle.

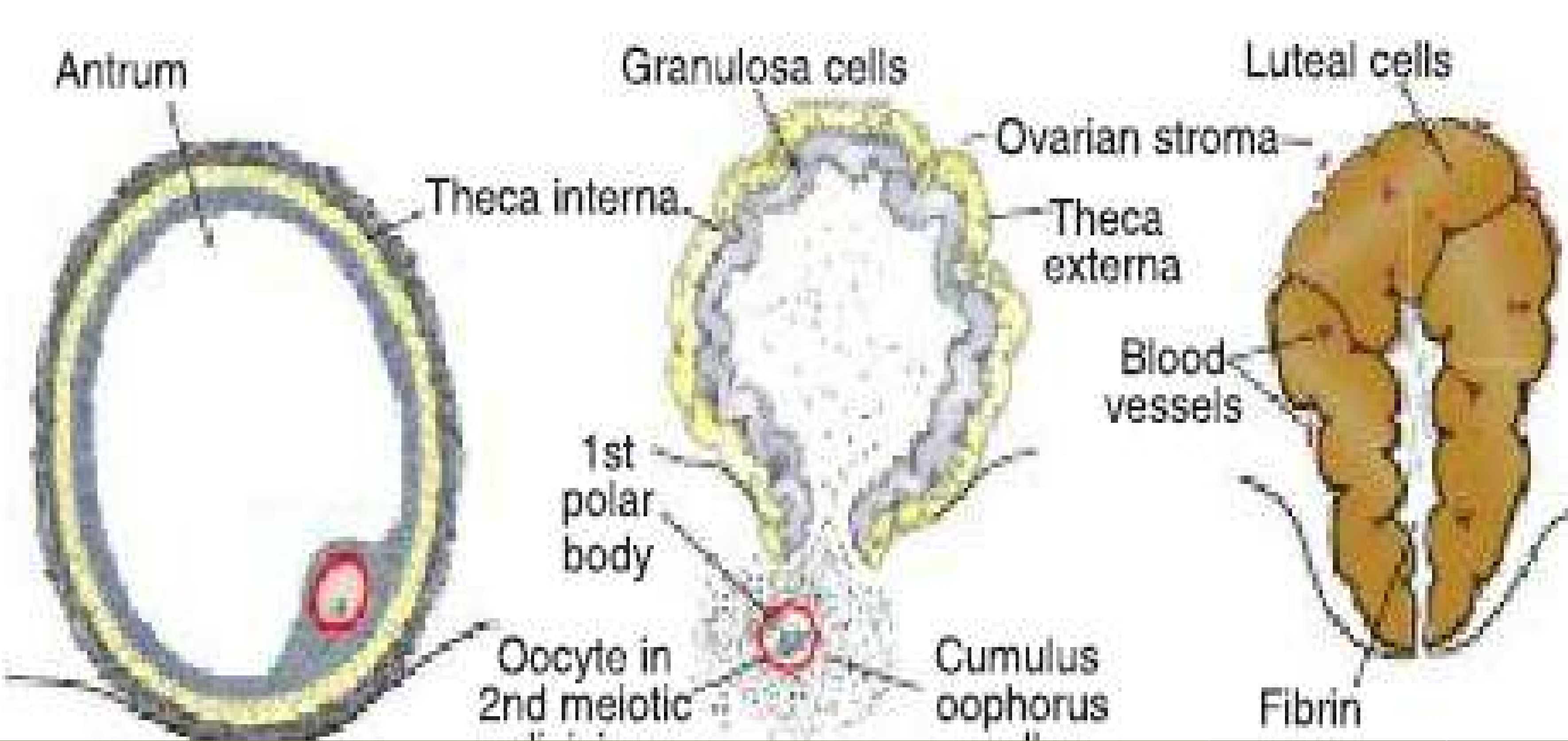
- Prostaglandin levels also increase in response to the LH surge and cause local muscular contractions in the ovarian wall.

- Those contractions extrude the oocyte, which together with its surrounding granulosa cells breaks free (ovulation) and floats out of the ovary .
- Some of the cumulus oophorus cells then rearrange themselves around the zona pellucida to form the **corona radiata.**

Corpus Luteum

- After ovulation, granulosa cells remaining in the wall of the ruptured follicle, together with cells from the theca interna, are vascularized by surrounding vessels.

- Under the influence of LH these cells develop a yellowish pigment and change into lutein cells, which form the corpus luteum and secrete estrogens and progesterone.

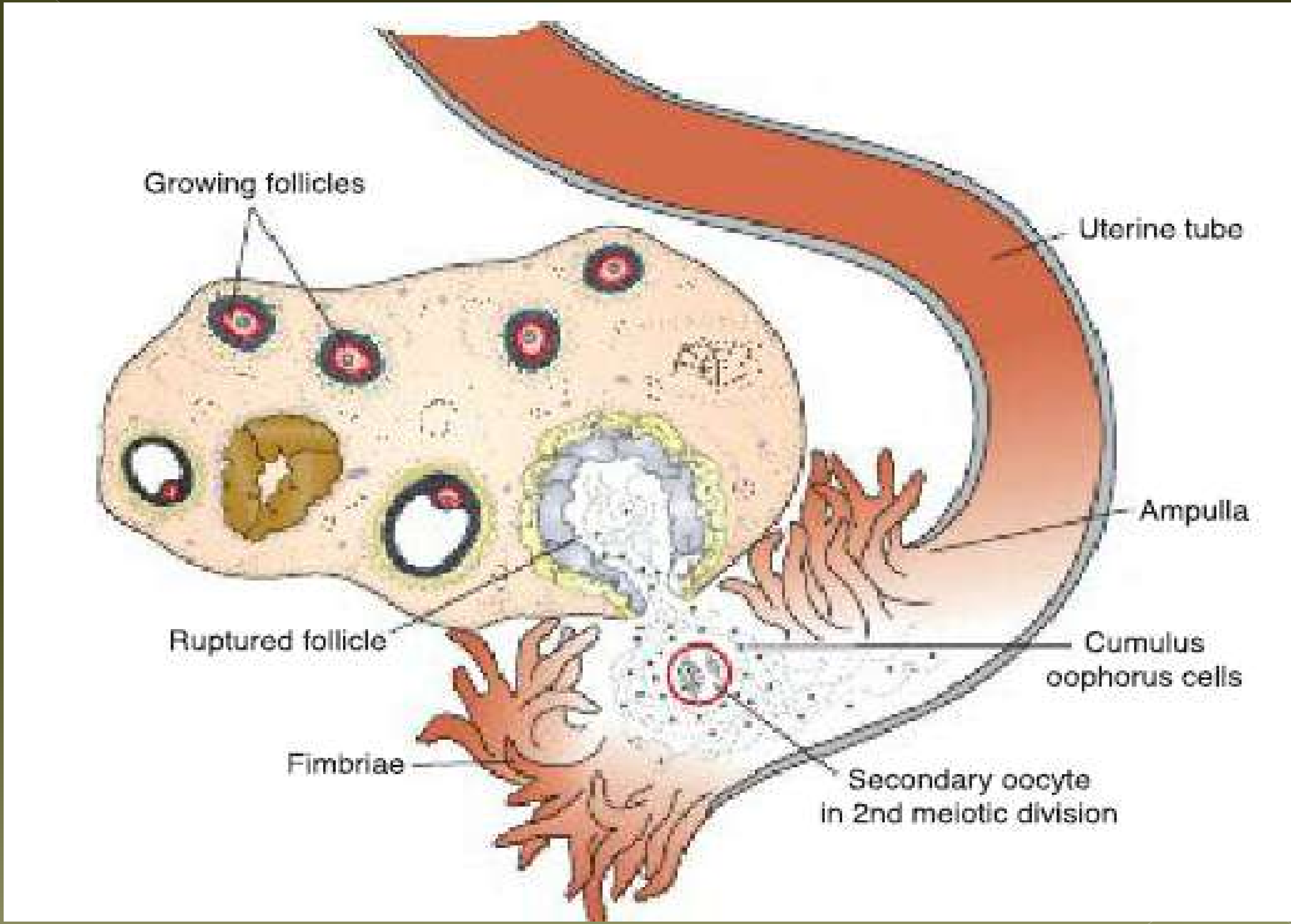


Antrum
Theca interna
Granulosa cells
Ovarian stroma
Theca externa
1st polar body
Oocyte in 2nd meiotic
Cumulus oophorus
Luteal cells
Blood vessels
Fibrin

- Progesterone, together with some estrogen, causes the uterine mucosa to enter the progestational or secretory stage in preparation for implantation of the embryo

Oocyte Transport

- Shortly before ovulation, fimbriae of the uterine tube sweep over the surface of the ovary and contracts rhythmically.
- The oocyte, surrounded by some granulosa cells is carried into the tube by these sweeping movements of the fimbriae and by motion of cilia on the epithelial lining.



Growing follicles
Uterine tube
Ampulla
Ruptured follicle
Cumulus
oophorus cells
Fimbriae
Secondary oocyte
in 2nd meiotic division

- Once the oocyte is in the uterine tube, it is propelled by peristaltic muscular contractions of the tube and by cilia in the tubal mucosa .
- The fertilized oocyte reaches the uterine lumen in approximately 3 to 4 days.

Corpus Albicans

- If fertilization does not occur, the corpus luteum reaches maximum development 9 days after ovulation.
- It can easily be recognized as a yellowish projection on the surface of the ovary.

- Subsequently, the corpus luteum shrinks because of degeneration of lutein cells and forms a mass of fibrotic scar tissue, the **corpus albicans**

- Simultaneously, progesterone production decreases, precipitating menstrual bleeding.
- If the oocyte is fertilized, degeneration of the corpus luteum is prevented by HCG, a hormone secreted by the syncytiotrophoblast of the developing embryo.

- The corpus luteum continues to grow and forms the corpus luteum of pregnancy.
- By the end of the third month, this structure may be one-third to one-half of the total size of the ovary.

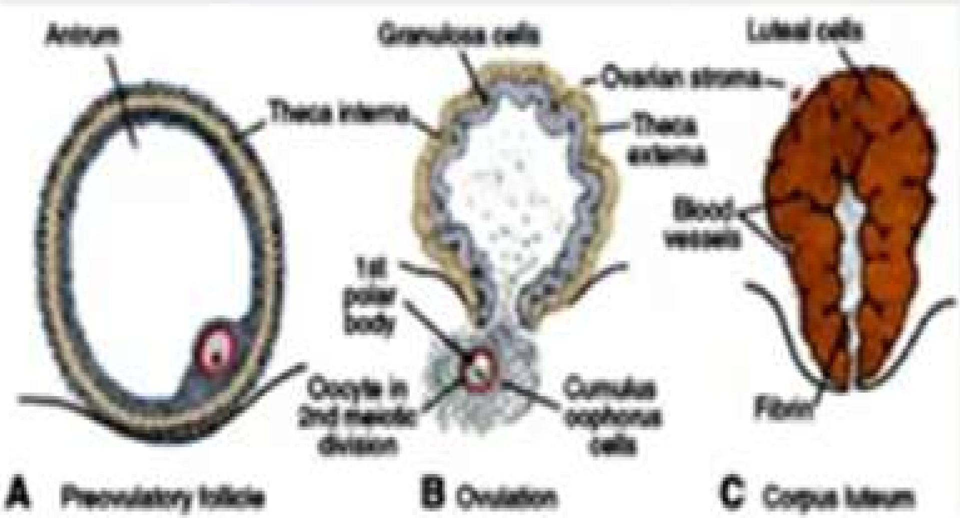
- Yellowish luteal cells continue to secrete progesterone until the end of the fourth month.
- Thereafter, they regress slowly as secretion of progesterone by the trophoblastic component of the placenta becomes adequate for maintenance of pregnancy.

Ovarian cycle

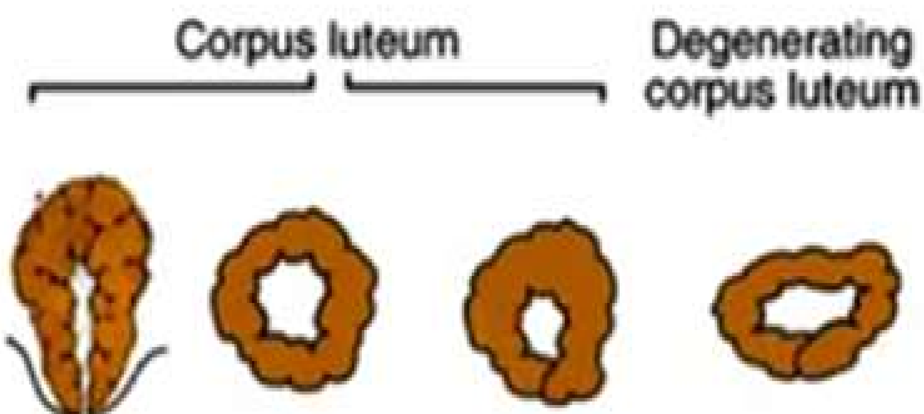
Follicular phase

Ovulation

Luteal phase



- Formation of corpus luteum by effect of (LH) hormone.
- It will secrete progesterone hormone (responsible for secretory stage of uterine



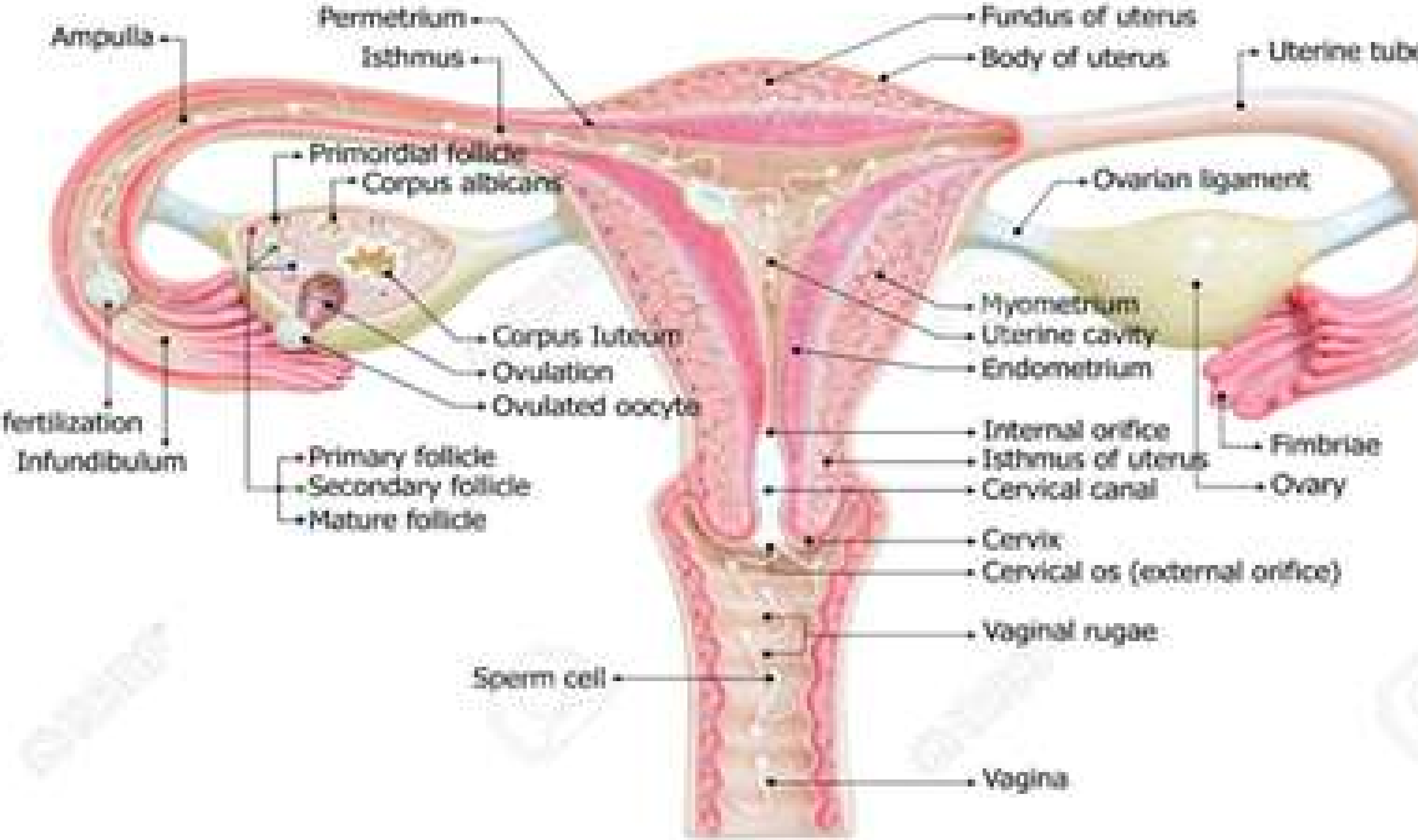
Fate of corpus luteum:

- If fertilization occurs: it will persist and secrete progesterone for 3-4 months till the formation of the placenta, then it will degenerate.
- If no fertilization: it will transform into white mass (corpus albicans), then it will

FERTILIZATION

- It is the process by which male and female gametes fuse.
- It occurs in the ampullary region of the uterine tube which is the widest part of the tube and is close to the ovary .
- Spermatozoa may remain viable in the female reproductive tract for several days

Diagram of Female Reproductive System



- Only 1% of sperm deposited in the vagina enter the cervix, where they may survive for many hours.
- Movement of sperm from the cervix to the uterine tube occurs by muscular contractions of the uterus and uterine tube and very little by their own propulsion.

- The trip from cervix to oviduct can occur as rapidly as 30 minutes or as slow as 6 days.
- After reaching the isthmus, sperm become less motile and cease their migration

- At ovulation, sperm again become motile, perhaps because of chemoattractants produced by cumulus cells surrounding the egg, and swim to the ampulla where fertilization usually occurs.

- Spermatozoa are not able to fertilize the oocyte immediately upon arrival

  in the female genital tract but must

  undergo:

  (1) capacitation

  (2) the acrosome reaction

Preparatory steps of fertilization

Sperm capacitation

- It is the final step in sperm maturation.
- Occurs in the female genital tract.
- It takes 7 hours.
- Includes removal of the glycoprotein coat from the cell membrane overlying the acrosomal region.

Acrosomal reaction

- Occurs after contact with zona pellucida.
- It includes secretion of enzymes helping to penetrate the zona pellucida:
- A) hyaluronidase: digests corona radiata.
- B) zonalysin and trypsin like substance: to penetrate zona pellucida.

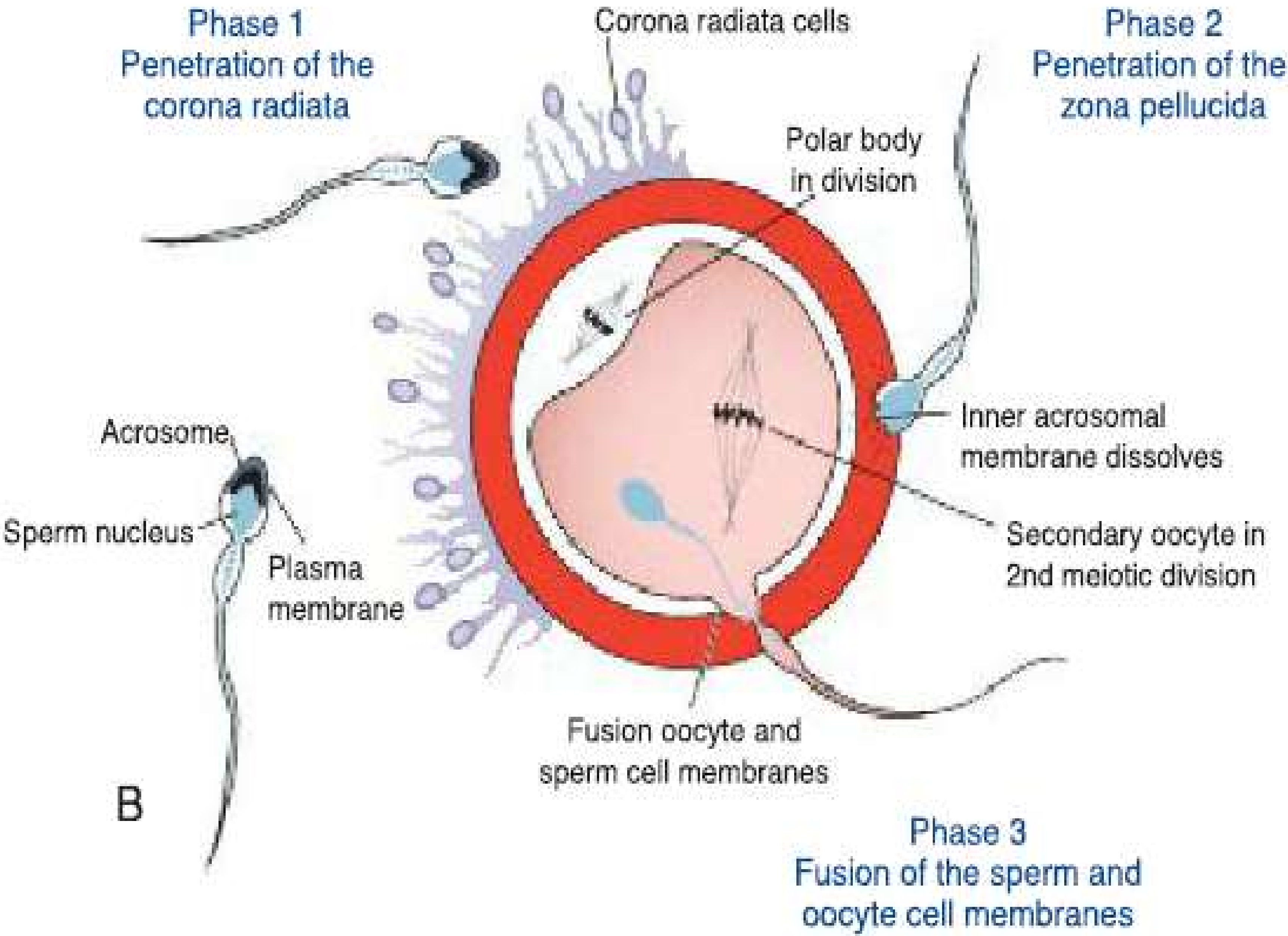
- Capacitation is a period of conditioning in the female reproductive tract that in the human lasts approximately 7 hours.
- Thus, speeding to the ampulla is not an advantage because capacitation has not yet occurred and such sperm are not capable of fertilizing the egg.

- Capacitation involves epithelial interactions between the sperm and the mucosal surface of the tube.
- During this time, a glycoprotein coat and seminal plasma proteins are removed from the plasma membrane that overlies the acrosomal region of the spermatozoa.

- Only capacitated sperm can pass through the corona cells and undergo the 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,

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



Phase 1
Penetration of the corona radiata
Corona radiata cells
Phase 2
Penetration of the zona pellucida
Polar body in division
Acrosome
Sperm nucleus
Plasma membrane
Inner acrosomal membrane dissolves
Secondary oocyte in 2nd meiotic division
Fusion oocyte and sperm cell membranes
B
Phase 3
Fusion of the sperm and oocyte cell membranes

:Phase 1
Penetration of the Corona Radiata

- Of the 200 to 300 million spermatozoa normally 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 .

Phase 2: 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 to prevent sperm penetration

- Other spermatozoa have been found embedded in the zona pellucida, but only one is able to penetrate the oocyte

:Phase 3
Fusion of the Oocyte and Sperm Cell Membranes

- The initial adhesion of sperm to the oocyte is mediated 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 .

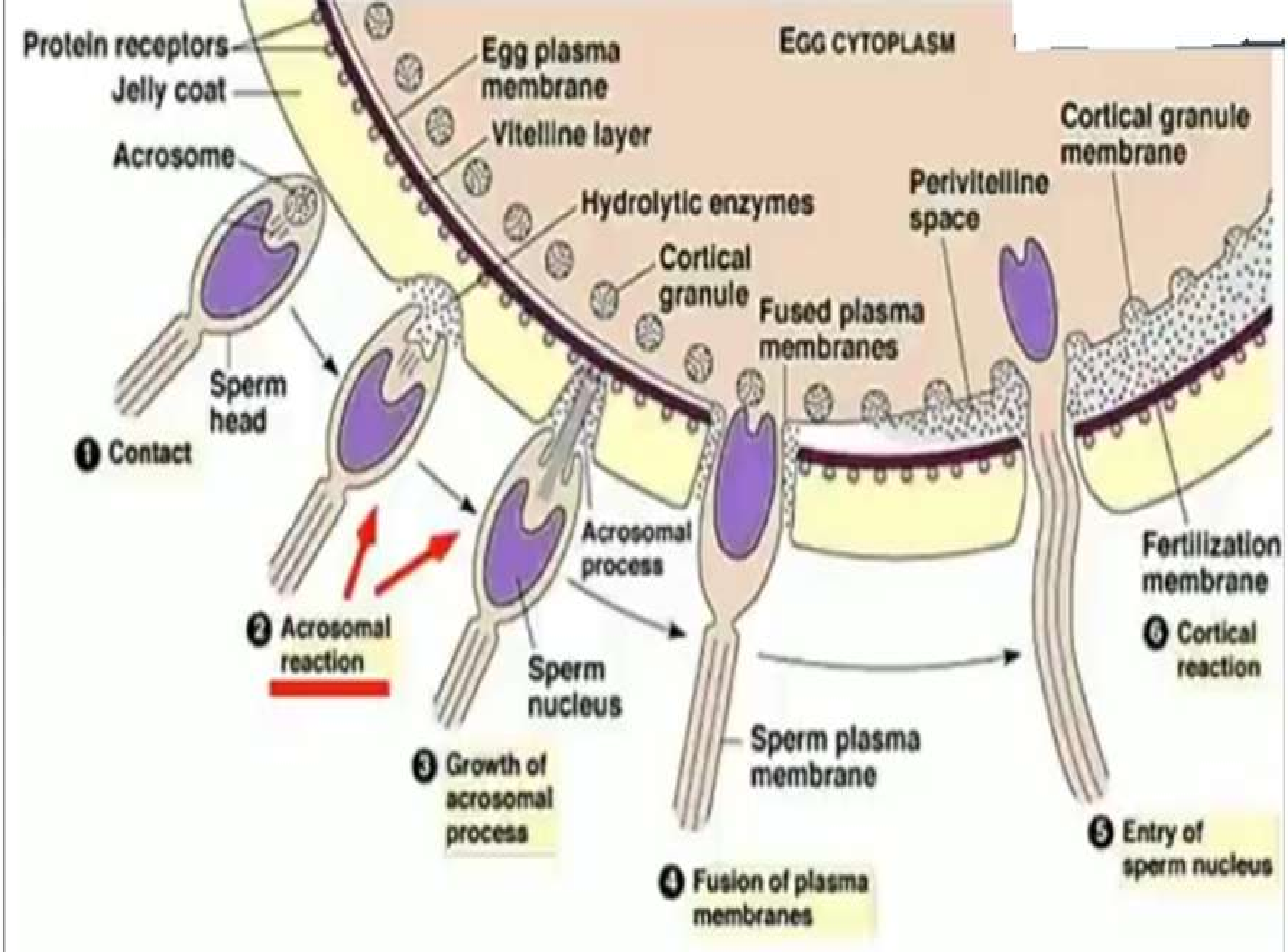
- In the human, both the head and the tail of the spermatozoon enter the cytoplasm of the oocyte, but the plasma membrane is left behind on the oocyte surface.
- As soon as the spermatozoon has entered the oocyte,the egg responds in three ways:

1. Cortical and zona reactions.

- As a result of the release of cortical oocyte granules, which contain lysosomal enzymes,

(1) the oocyte membrane becomes impenetrable to other spermatozoa,

(2) the zona pellucida alters its structure and composition to prevent sperm binding and penetration.



Protein receptors
Jelly coat
Acrosome
Egg plasma membrane
Vitelline layer
Hydrolytic enzymes
Cortical granule
EGG CYTOPLASM
Cortical granule membrane
Perivitelline space
Fused plasma membranes
Sperm head
1 Contact
2 Acrosomal reaction
Acrosomal process
Sperm nucleus
3 Growth of acrosomal process
Sperm plasma membrane
4 Fusion of plasma membranes
Fertilization membrane
6 Cortical reaction
5 Entry of sperm nucleus

2. **Resumption of the second meiotic division.**

- One of the daughter cells, which receives hardly any cytoplasm, is known as the second polar body; the other daughter cell is **the definitive oocyte**.

- Its chromosomes (22 plus X) arrange themselves in a vesicular nucleus known as the female pronucleus

3. Metabolic activation of the egg

- The activating factor is probably carried by the spermatozoon.
- Activation encompasses the initial cellular and molecular events associated with early embryogenesis

- The spermatozoon moves forward until it lies close to the female pronucleus.
- Its nucleus becomes swollen and forms the male pronucleus .
- The tail detaches and degenerates.
- Morphologically, the male and female pronuclei are indistinguishable, and eventually, they come into close contact and lose their nuclear envelopes .

- During growth of male and female pronuclei (both haploid), each pronucleus must replicate its DNA.
- Immediately after DNA synthesis, chromosomes organize on the spindle in preparation for a normal mitotic division

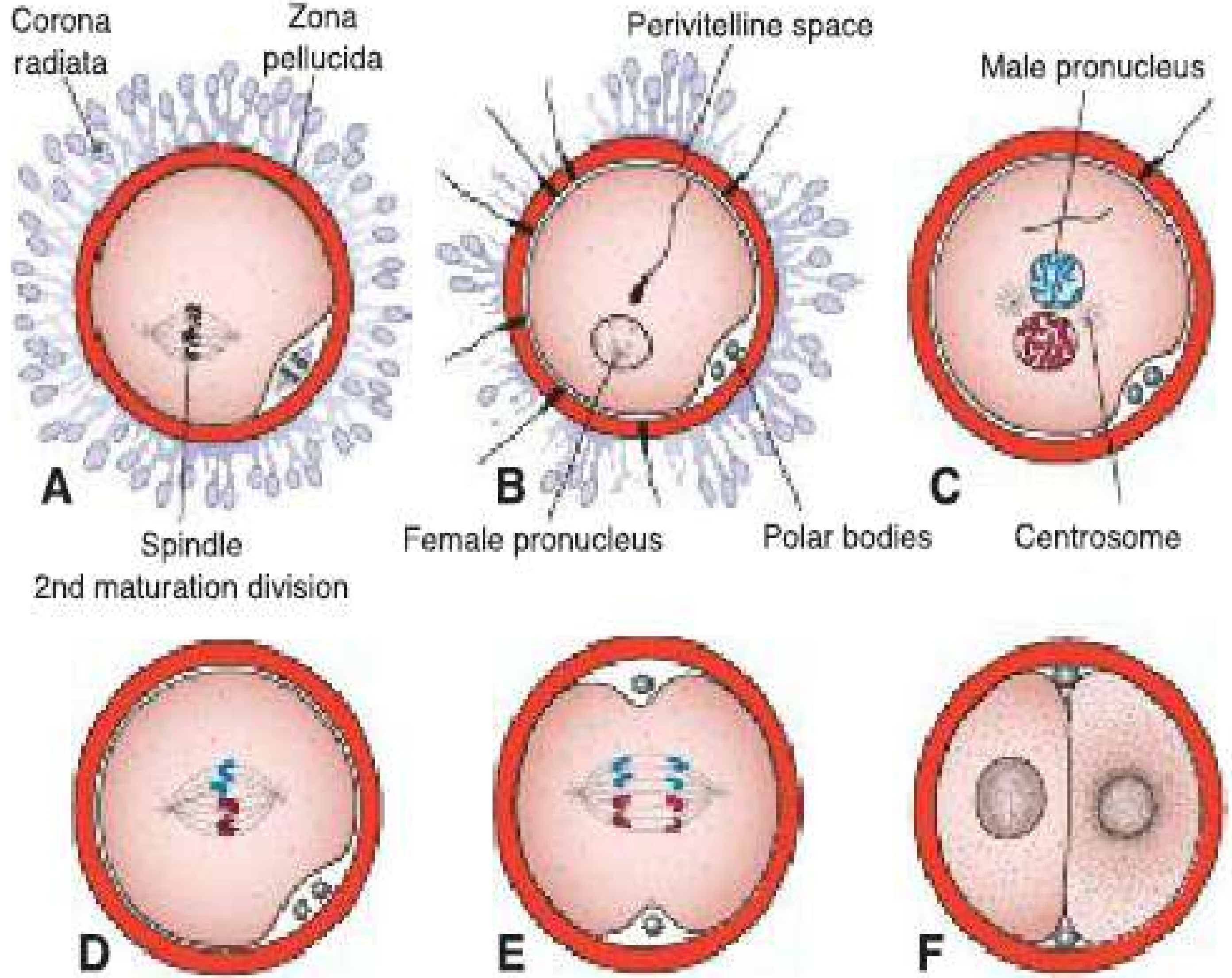


FIGURE 3.6 **A.** Oocyte immediately after ovulation, showing the spindle of the second meiotic division. **B.** A spermatozoon has penetrated the oocyte, which has finished its second meiotic division. Chromosomes of the oocyte are arranged in a vesicular nucleus, the female pronucleus. Heads of several sperm are stuck in the zona pellucida. **C.** Male and female pronuclei. **D,E.** Chromosomes become arranged on the spindle, split longitudinally, and move to opposite poles. **F.** Two-cell stage.

Actual steps of fertilization

penetration of coronal radiata

- By the effect of:
- A) hyaluronidase enzyme.
- B) tubal mucosal enzymes.
- C) movements of the sperm's tail.

Penetration of zona pellucida

- By the effect of zonalysin and trypsine-like enzymes.
- As the head of the sperm contacts the plasma membrane of the 2ry oocyte, cortical granules inside the oocyte release lysosomal enzymes to change the zona permeability to prevent further penetration by other sperms (zonal block).

Union of the sperm and the 2ry oocyte

- Fusion of both cell membranes of the sperm and the oocyte.
- The oocyte (vitelline) membrane becomes impermeable to other sperms.

Results of fertilization

1. Restoration of diploid number of chromosomes.
2. Determination of the sex of the new individual.
3. Initiation of cleavage.

Without fertilization,the oocyte usually degenerates
24 hours after ovulation

First Week of Development: Ovulation to Implantation 3

Dr. Sawsan S. Shurrab

CLEAVAGE

- Once the zygote has reached the two-cell stage, it undergoes a series of mitotic divisions, increasing the numbers of cells.
- These cells, which become smaller with each cleavage division,are known as blastomeres
- Until the eight-cell stage, they form a loosely arranged clump .

- After the third cleavage, however, blastomeres maximize their contact with each other, forming a compact ball of cells held together by tight junctions .

- This process, compaction, segregates inner cells, which communicate extensively by gap junctions, from outer cells.
- 3 days after fertilization, cells of the compacted embryo divide again to form a 16-cell morula (mulberry).

- Inner cells of the morula constitute the inner cell mass, and surrounding cells compose the outer cell mass.
- line 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

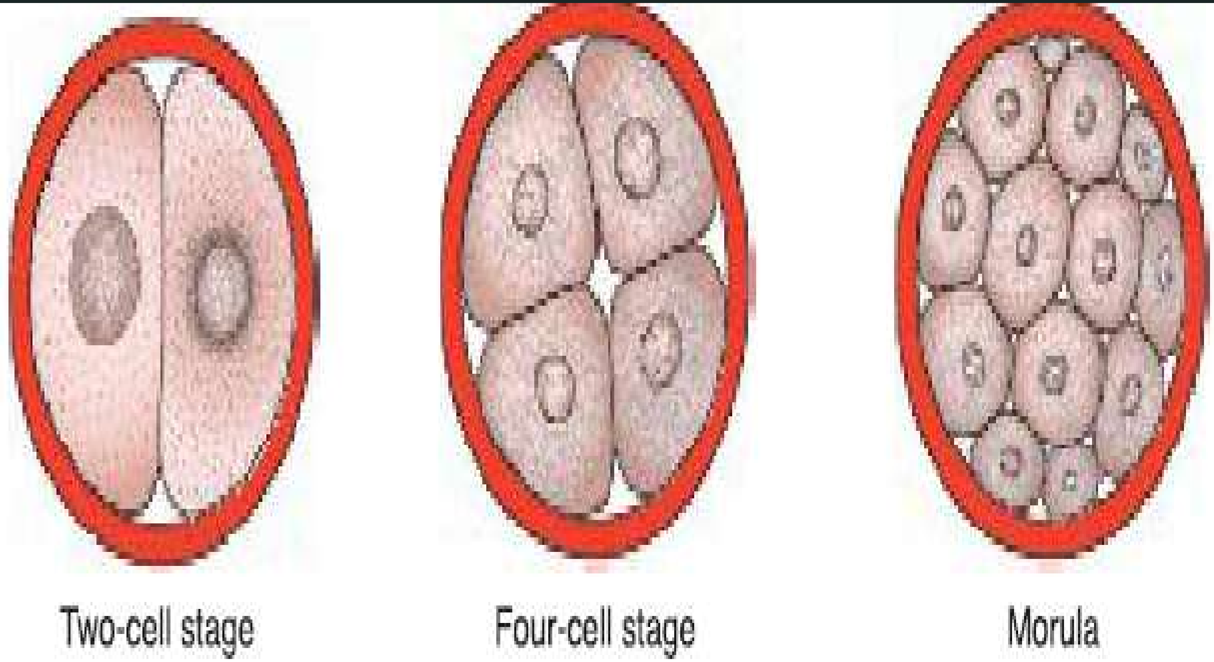


FIGURE 3.8 Development of the zygote from the two-cell stage to the late morula stage. The two-cell stage is reached approximately 30 hours after fertilization; the four-cell stage is reached at approximately 40 hours; the 12- to 16-cell stage is reached at approximately 3 days; and the late morula stage is reached at approximately 4 days. During this period, blastomeres are surrounded by the zona pellucida, which disappears at the end of the fourth day.

BLASTOCYST FORMATION

- About the time the morula enters the uterine cavity, fluid begins to 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 blastocele, forms .

- At this time, the embryo is a blastocyst.
- Cells of the inner cell mass, now called the embryoblast, are at one pole, and those of the outer cell mass, or trophoblast, flatten and form the epithelial wall of the blastocyst .
- The zona pellucida has disappeared, allowing implantation to begin.

- In the human, trophoblastic cells over the embryoblast pole begin to penetrate

between the epithelial cells of the uterine mucosa

on about the sixth day .

- L—selectin on trophoblast cells and its carbohydrate receptors on the uterine epithelium mediate initial attachment of the blastocyst to the uterus.

- Following capture by selectins, further attachment and invasion by the trophoblast involve integrins, expressed by the trophoblast and the extracellular matrix molecules laminin and fibronectin.

- Integrin receptors for laminin promote attachment, whereas those for fibronectin stimulate migration.

- Hence, by the end of the first week of development, the human zygote has passed through the morula and blastocyst stages and has begun implantation in the uterine mucosa.

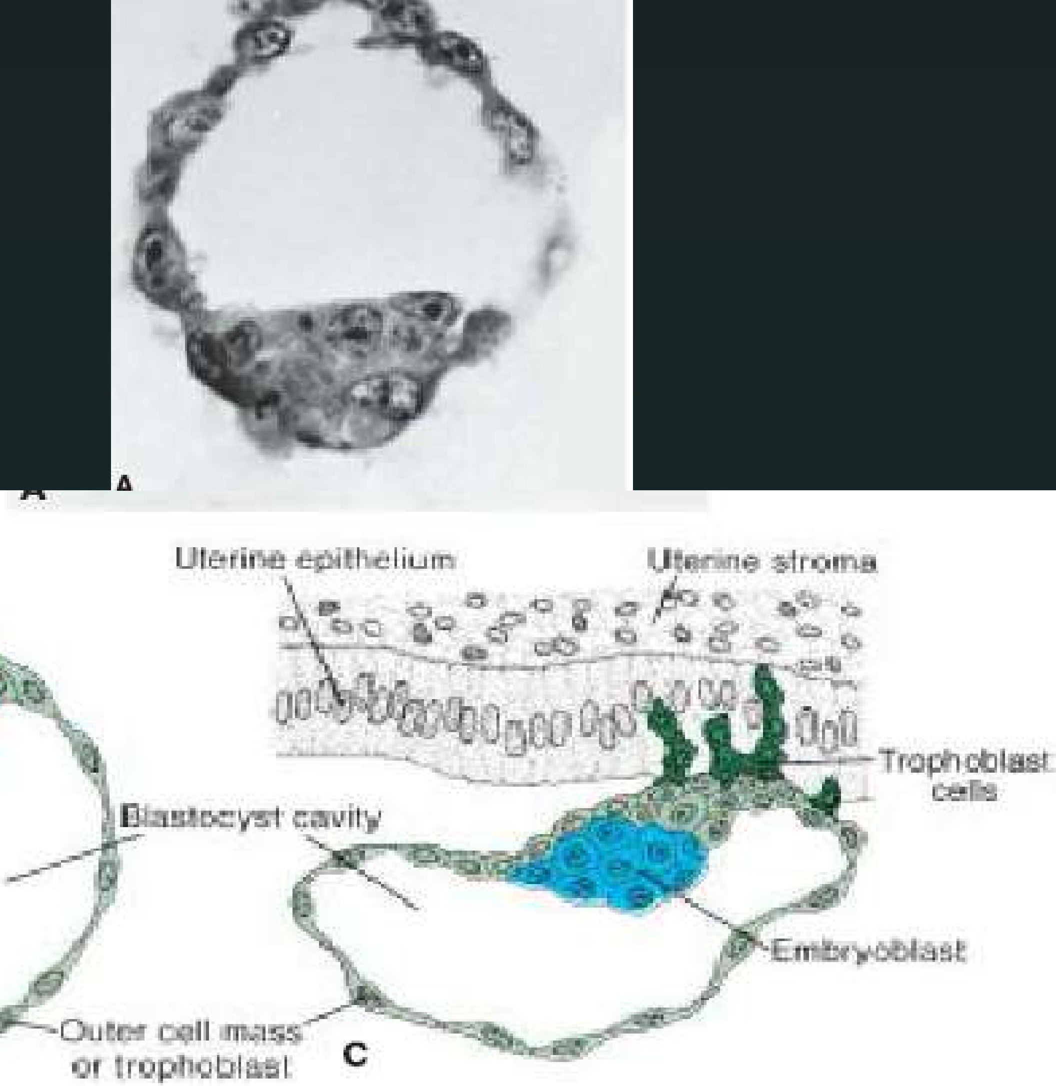


FIGURE 3.10 A. Section of a 107-cell human blastocyst showing inner cell mass and trophoblast cells. **B.** Schematic representation of a human blastocyst recovered from the uterine cavity at approximately 4.5 days. *Blue*, inner cell mass or embryoblast; *green*, trophoblast. **C.** Schematic representation of a blastocyst at the sixth day of development showing trophoblast cells at the embryonic pole of the blastocyst penetrating the uterine mucosa. The human blastocyst begins to penetrate the uterine mucosa by the sixth day of development.

EPIBLAST, HYPOBLAST, AND AXIS FORMATION

- Under the influence of fibroblast growth factors (FGFs) at the early blastocyst stage, cells in the embryoblast differentiate into epiblast and hypoblast cells .

- Initially, these cells are scattered in the embryoblast, but near the time of implantation, they segregate to become a layer of epiblast cells dorsally and hypoblast cells ventrally adjacent to the blastocyst cavity.

- Thus, a dorsal—ventral polarity is established in the embryo.

- In addition, some of the hypoblast cells are specified to form the anterior visceral endoderm (AVE), and these cells migrate to what will become the cranial end of the embryo

- AVE cells are classified as endoderm (as is the entire hypoblast) and are responsible for secreting nodal antagonists that act on adjacent epiblast cells to specify the cranial end of the embryo

- In the absence of these inhibitors, nodal establishes the primitive streak at the caudal end of the embryo.

- In this manner, the cranial—caudal embryonic axis is established near the time of implantation (days 5.5 to 6).

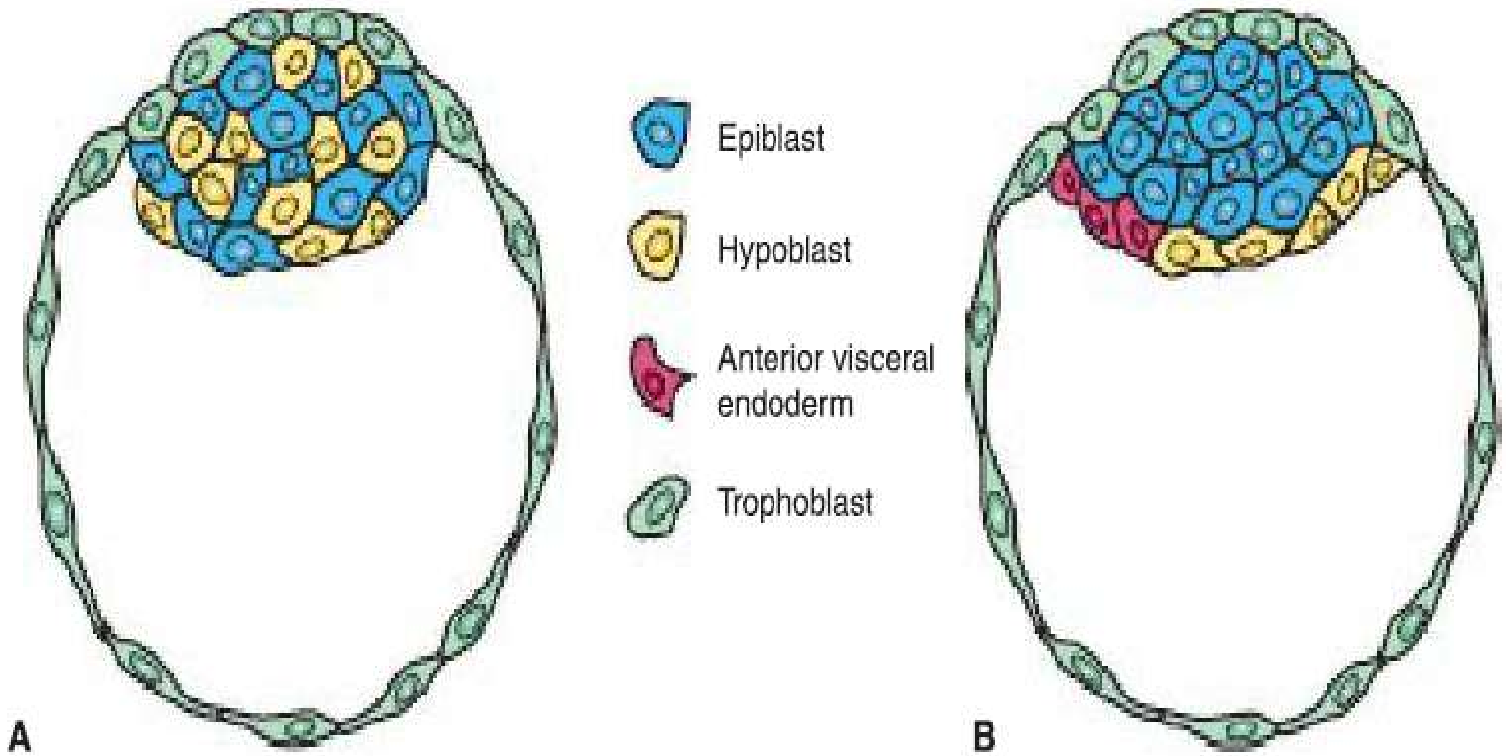


FIGURE 3.11 **A.** At the early blastocyst stage, cells are specified to form epiblast and hypoblast cells, which are scattered in the embryoblast. **B.** Near the time of implantation [5.5 to 6 days], hypoblast cells move to form a layer ventral to the epiblast and adjacent to the blastocyst cavity. In addition, some cells in the hypoblast form the anterior visceral endoderm [AVE], and these cells migrate to the future cranial end of the embryo. Here, they will signal nearby epiblast cells to form cranial structures. Notice that formation and positioning of the hypoblast and AVE establishes the dorsal-ventral and cranial-caudal embryonic axes, respectively.

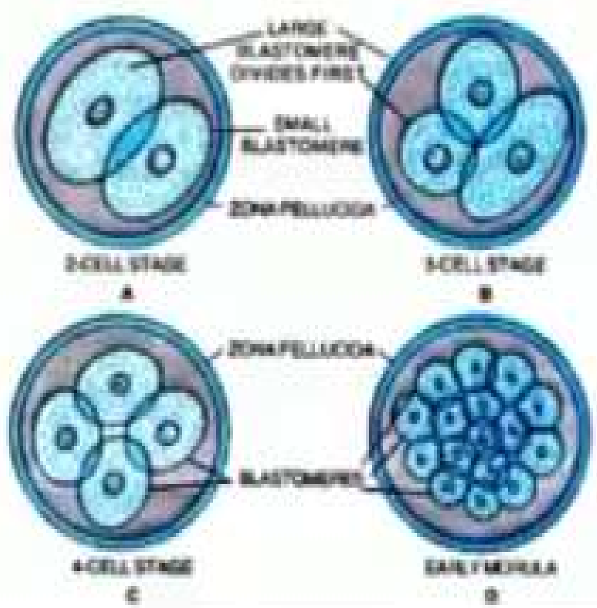
Cleavage of the zygote

30 hours after fertilization

- Zygote starts a series of mitotic divisions to be transformed to multicellular mass of embryonic cells (blastomeres) = increase number of cells and decrease size of cells.
- Zygote also moves towards the uterine cavity by the action of the tubal cilia.

72 hours after fertilization

- It reaches morula stage (12-16 cell stage)
- The morula will continue division.



4th day after fertilization

- Morula reaches the uterine cavity.
- It undergoes the following

a) zona pellucida: disappears.

b) Fluid is absorbed from the uterine cavity & □ccumulates inside the morula to form the blastocyst.

- The cavity of the blastocyst is called blastocele.
- Cells will be arranged into two masses:

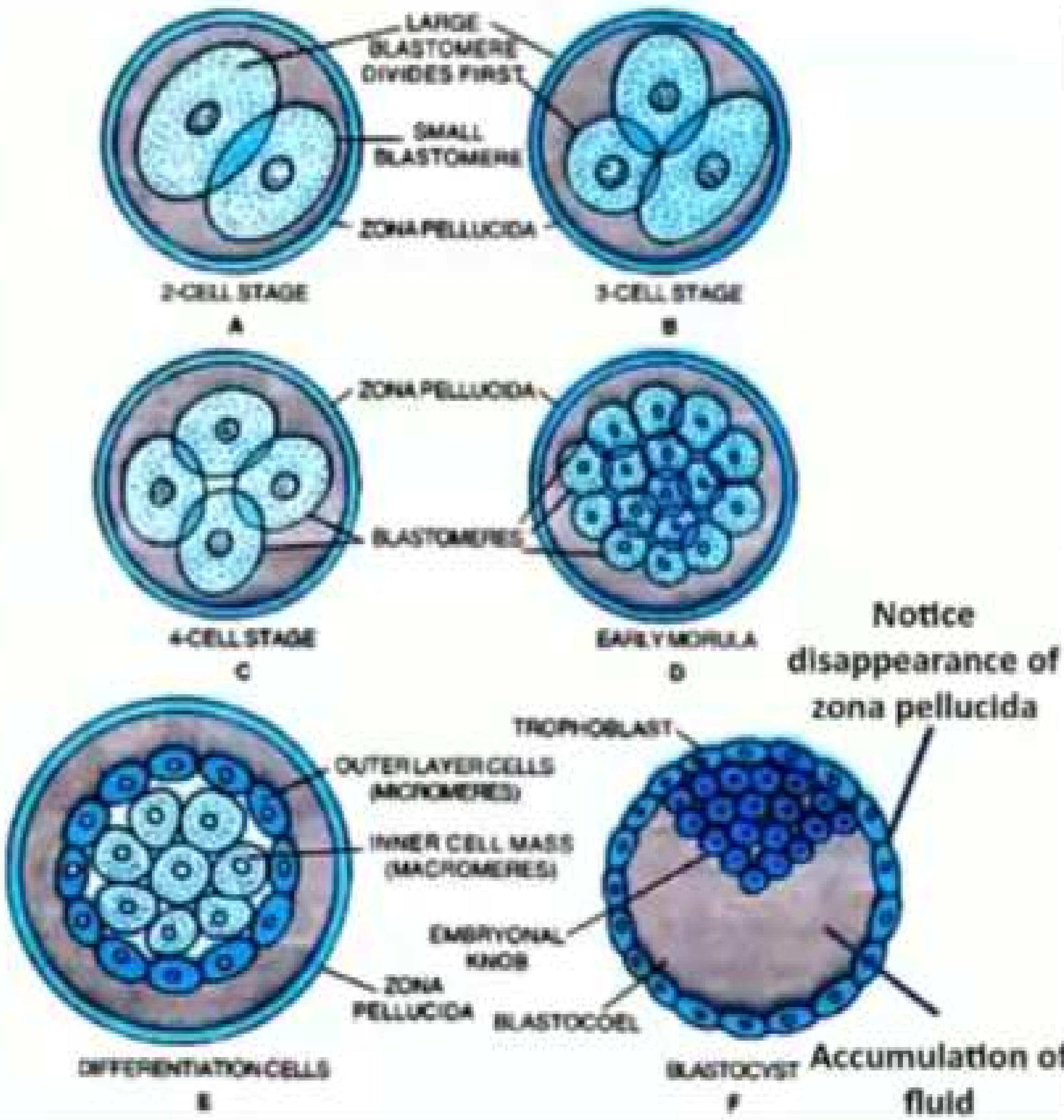
a) An outer cell mass: it forms the trophoblast.

b) An inner (formative) cell mass: it will give rise to the embryo.

- The blastocyst now has two poles:

c) Embryonic pole: at which the inner cell mas is attached.

d) Abembryonic pole: the opposite pole of the blastocyst.



Embedding of the blastocyst into the uterine wall.

Implantation

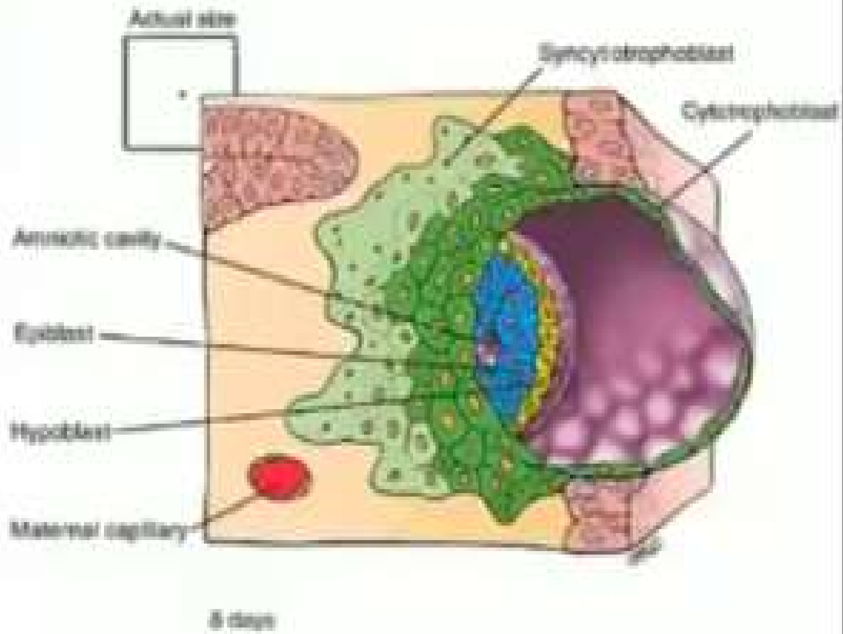
- Normally, it implanted in upper part of the body of the uterus, mainly the posterior wall, in the midline, near the fundus.

6th day after fertilization

- It is the start of implantation.
- The trophoblast over the embryonic pole adheres to the uterine wall and starts to erode the endometrium and the whole blastocyst progressively penetrates it.
- The trophoblastic cells rapidly proliferate as soon as they touch the endometrium and become formed of two layers:

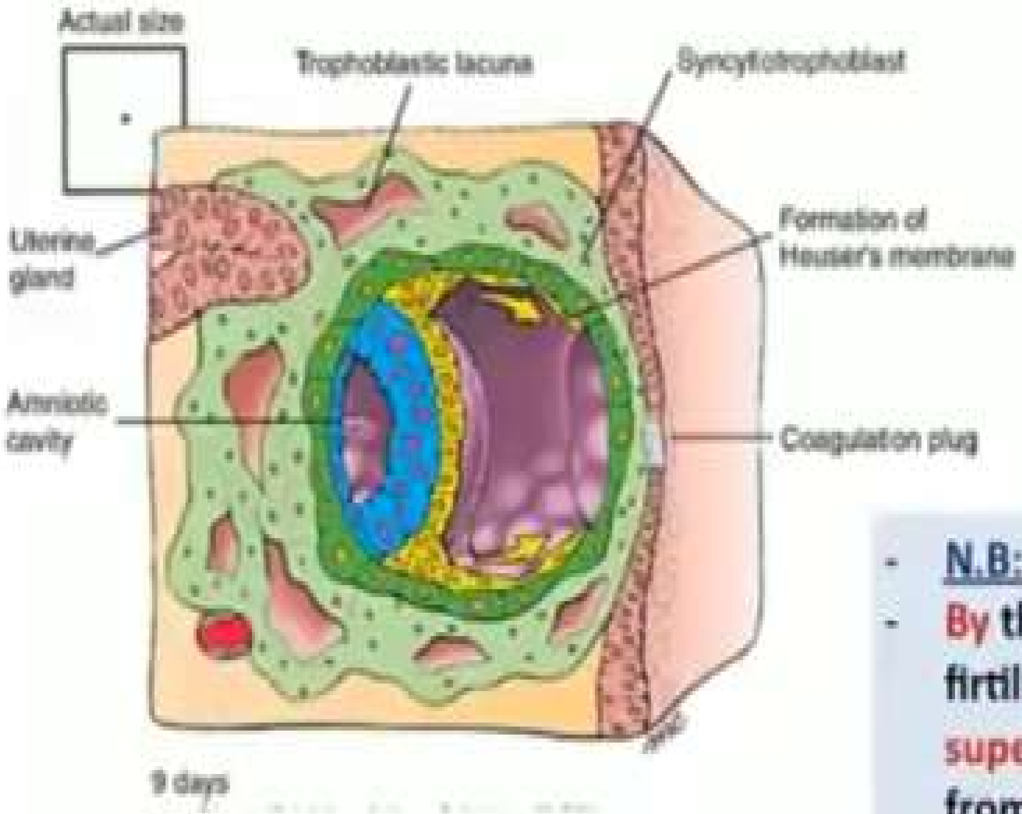
a) An outer syncytio-trophoblast layer: mass of protoplasm containing randomly dispersed nuclei.

b) An inner cyto-trophoblast: cells with well defined walls.



Implantation

6th day after fertilization



9th day after fertilization

- The blastocyst is completely
- The site of implantation is closed by a fibrin clot.

- N.B:
- By the end of 1st week (7th day) after firtilization, the blastocyst is implanted superficially getting its nourishment from the eroded endometrium.

Abnormal sites of implantation

Intra-uterine (placenta previa)

- It is the implantation in the lower uterine segment (very close to the cervix)
- It may be:

a) Placenta previa lateralis: just above the internal os.

b) Placenta previa marginalis: partially covers the internal os.

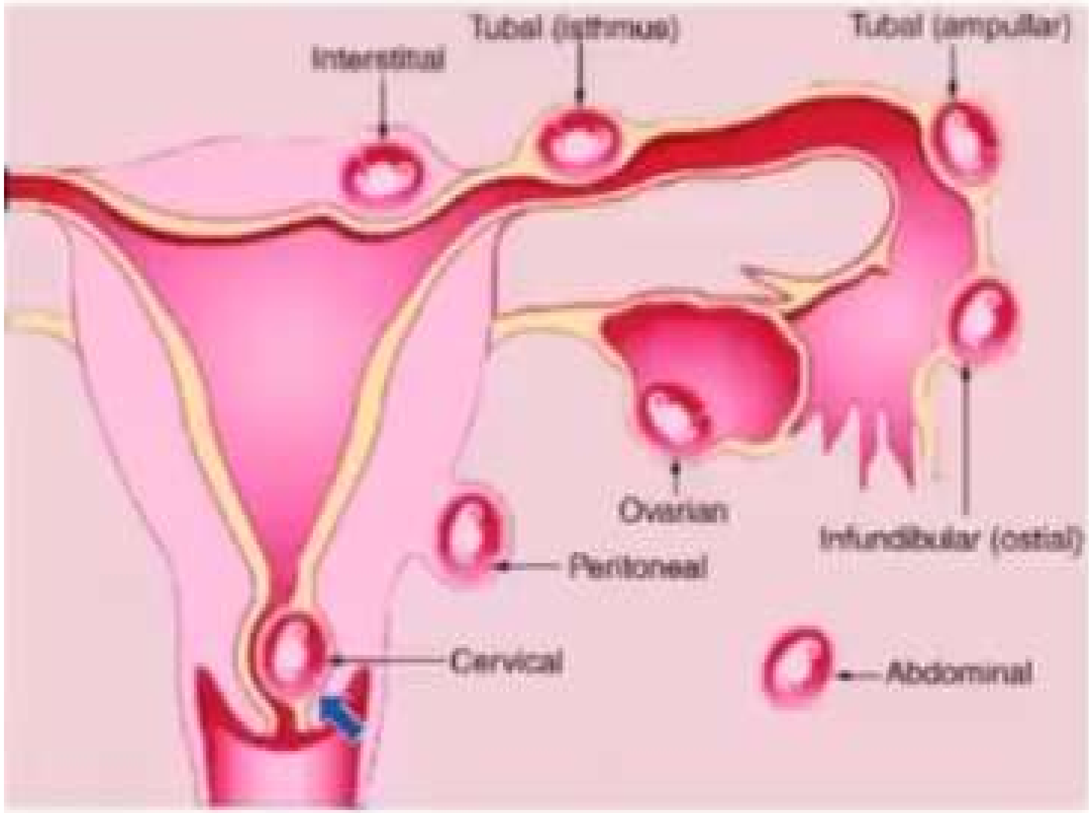
c) Placenta previa centralis : completely covers the internal os.

Placenta Previa

Abnormal sites of implantation

Intra-uterine (placenta previa)

Extra-uterine



- **It may be:**

A) **Tubal pregnancy:** in the fallopian tube.

B) **Abdominal pregnancy:** in the abdominal cavity.

C) **Ovarian pregnancy:** on the surface of the ovary.

- **N.B:**
- **Ectopic pregnancy can't reach the full term because of inadequate nutrition and the weak implantation site.**

UTERUS AT TIME OF IMPLANTATION

- The wall of the uterus consists of three layers:

1. Endometrium or mucosa lining the inside wall
2. Myometrium, a thick layer of smooth muscle
3. Perimetrium, the peritoneal covering lining the outside wall .

- From puberty (11 to 13 years) until menopause (45 to 50 years), the endometrium undergoes changes in a cycle of approximately 28 days under hormonal control by the ovaries.

- During this menstrual cycle, the uterine endometrium passes through three stages:

1. Follicular or proliferative phase
2. Secretory or progestational phase
3. Menstrual phase

- The proliferative phase begins at the end of the menstrual phase, is under the influence of estrogen, and parallels growth of the ovarian follicles.

- The secretory phase begins approximately 2 to 3 days after ovulation in response to progesterone produced by the corpus luteum.

- If fertilization does not occur, shedding of the endometrium (compact and spongy layers) marks the beginning of the menstrual phase.

- If fertilization does occur, the endometrium assists in implantation and contributes to formation of the placenta.

- Later in gestation, the placenta assumes the role of hormone production, and the corpus luteum degenerates.

- At the time of implantation, the mucosa of the uterus is in the secretory phase , during which time uterine glands and arteries become coiled and the tissue becomes succulent.

- As a result, three distinct layers can be recognized in the endometrium

- a superficial compact layer,
- an intermediate spongy layer
- a thin basal layer

- Normally, the human blastocyst implants in the endometrium along the anterior or posterior wall of the body of the uterus, where it becomes embedded between the openings of the glands .

- If the oocyte is not fertilized, venules and sinusoidal spaces gradually become packed with blood cells, and an extensive diapedesis of blood into the tissue is seen.
- When the menstrual phase begins, blood escapes from superficial arteries, and small pieces of stroma and glands break away

- During the following 3 or 4 days, the compact and spongy layers are expelled from the uterus, and the basal layer is the only part of the endometrium that is retained .

- This layer, which is supplied by its own arteries,the basal arteries, functions as the regenerative layer in the rebuilding of glands and arteries inthe proliferative phase .

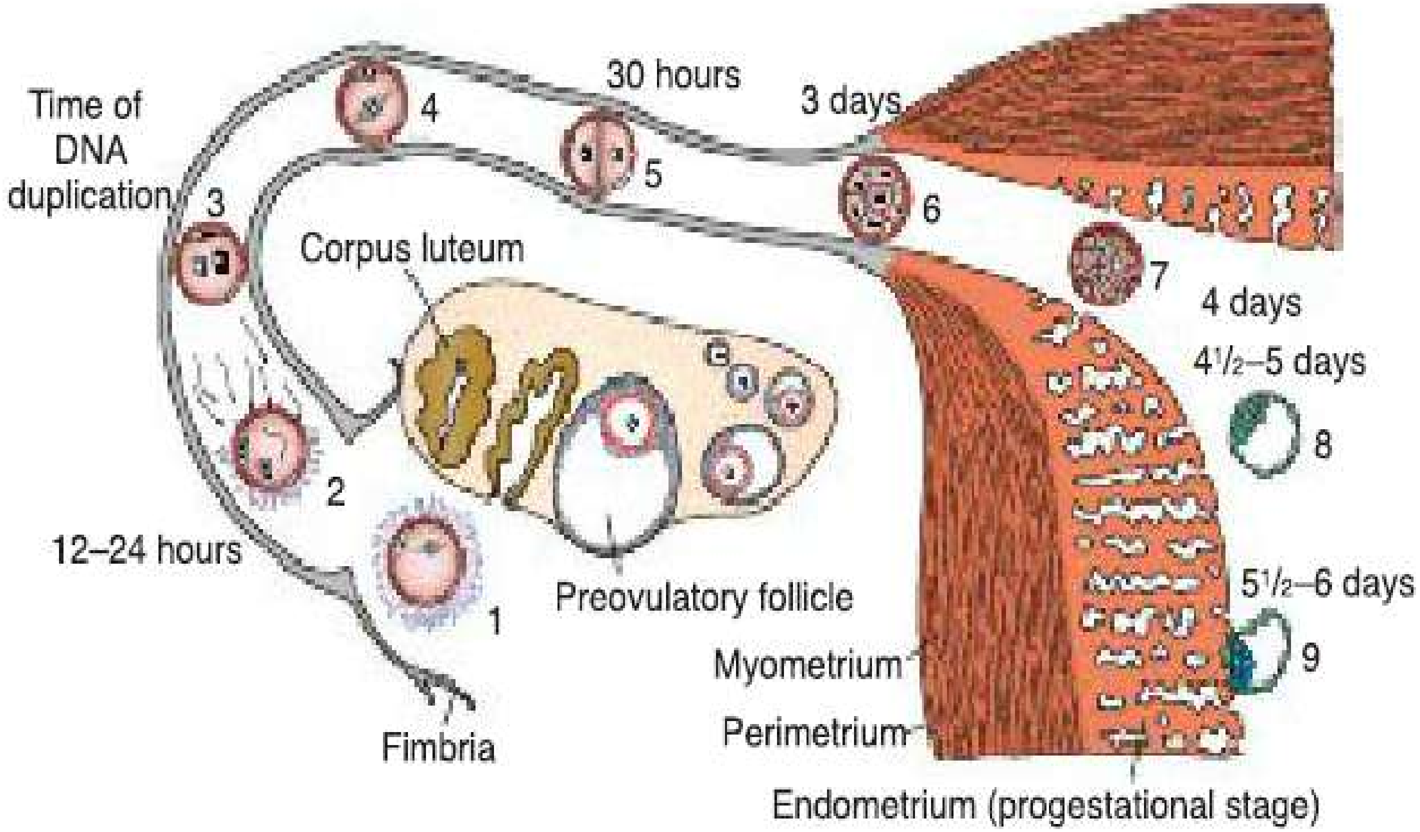


FIGURE 3.12 Events during the first week of human development. *1*, oocyte immediately after ovulation; *2*, fertilization, approximately 12 to 24 hours after ovulation; *3*, stage of the male and female pronuclei; *4*, spindle of the first mitotic division; *5*, two-cell stage (approximately 30 hours of age); *6*, morula containing 12 to 16 blastomeres (approximately 3 days of age); *7*, advanced morula stage reaching the uterine lumen (approximately 4 days of age); *8*, early blastocyst stage (approximately 4.5 days of age; the zona pellucida has disappeared); *9*, early phase of implantation (blastocyst approximately 6 days of age). The ovary shows stages of transformation between a primary follicle and a preovulatory follicle as well as a corpus luteum. The uterine endometrium is shown in the progestational stage.

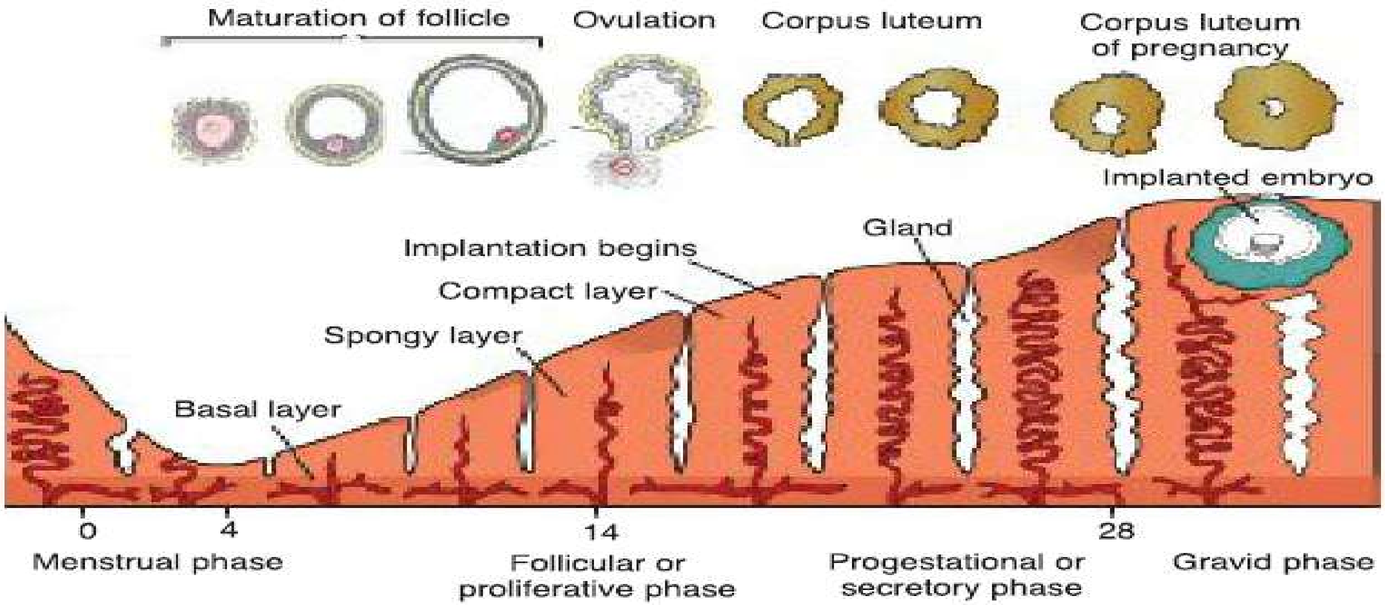
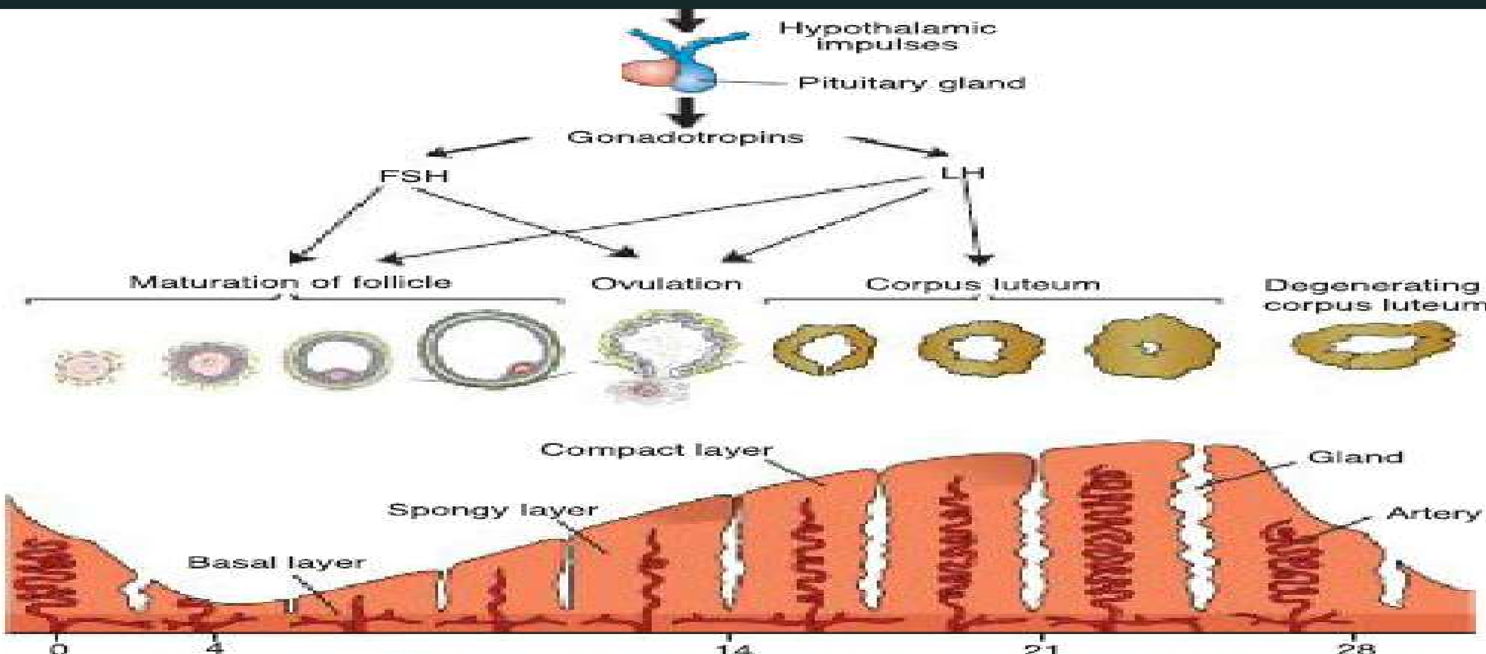


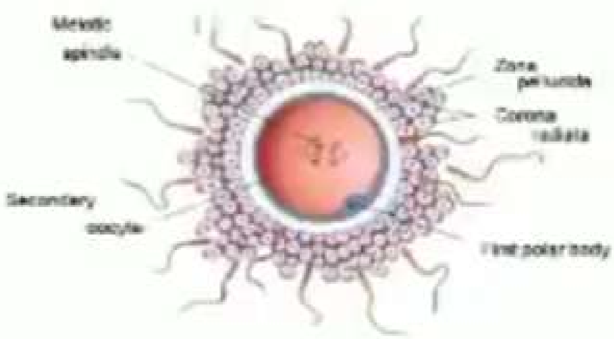
FIGURE 3.13 Changes in the uterine mucosa correlated with those in the ovary. Implantation of the blastocyst has caused development of a large corpus luteum of pregnancy. Secretory activity of the endometrium increases gradually as a result of large amounts of progesterone produced by the corpus luteum of pregnancy.



Events of the 1st week

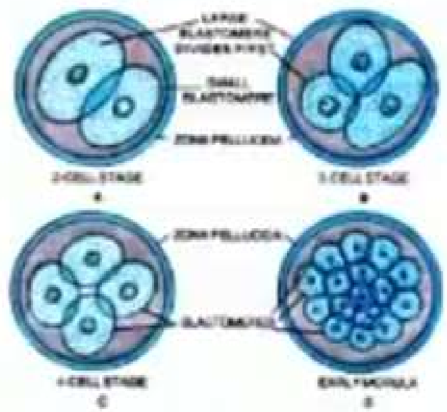
Fertilization

- It is the process of union between the male and female gametes (sperm & ovum) to form the zygote.



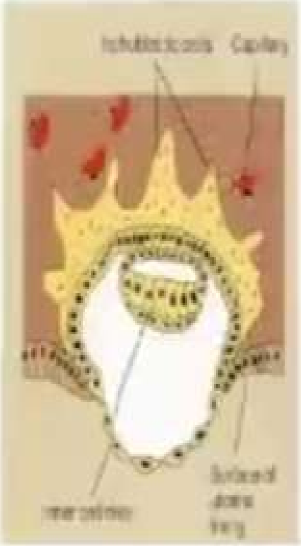
Cleavage

- It is repeated mitotic divisions by which the unicellular zygote is transformed to multicellular embryonic cells (blastomeres).



Implantation

- It is the process of embedding the blastocyst into the uterine wall.



- **The decidua:**
- It is the endometrium of the pregnant uterus (gravid endometrium).
- It is called decidua because it will be separated completely at the time of the child birth (decidua means a structure that will separate).
- **After fertilization, the endometrium will start a decidual reaction:**

A) uterine glands will e distended with secretions.

B) Stroma cells will be vacuolated and filled with lipids and glycogen.

- **Parts of the decidua:**

3) Decidua capsularis: lies superficial to the blastocyst, between it and the uterine cavity.

4) Decidua basalis: lies deep to the blastocyst, between it and the wall of the uterus.

5) Decidua Parietalis: lines the remaining wall of the uterus.

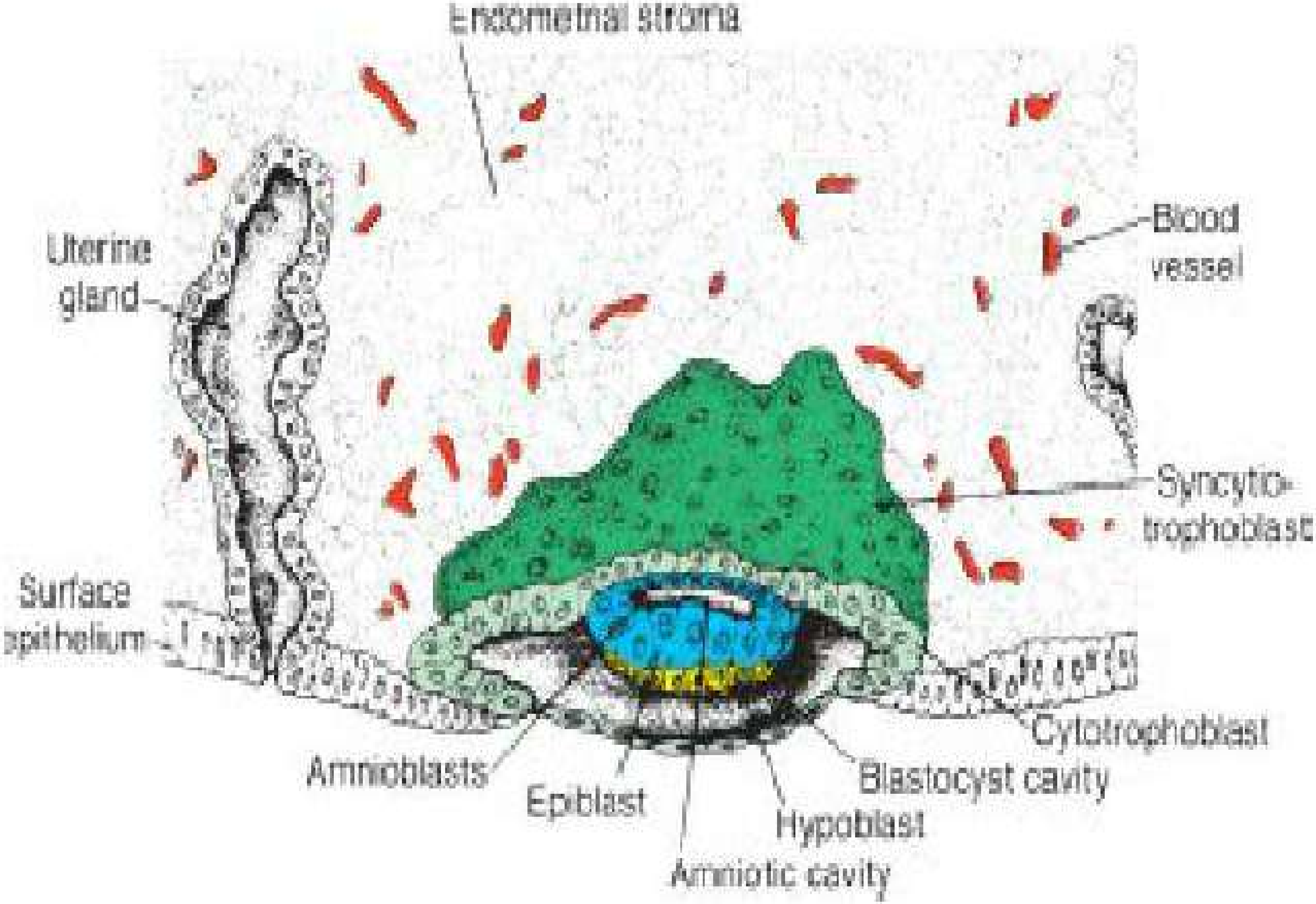
:Second Week of Development Bilaminar Germ Disc 4

Dr. Sawsan S. Shurrab

DAY 8

- At the eighth day of development, the blastocyst is partially embedded in the endometrial stroma.

- In the area over the embryoblast, the trophoblast has differentiated into two layers:


Endometrial stroma
Uterine gland
Blood vessel
Syncytiotrophoblast
Surface epithelium
Cytotrophoblast
Amnioblasts
Epiblast
Blastocyst cavity
Hypoblast
Amniotic cavity

(1) An inner layer of mononucleated cells, the **cytotrophoblast**.

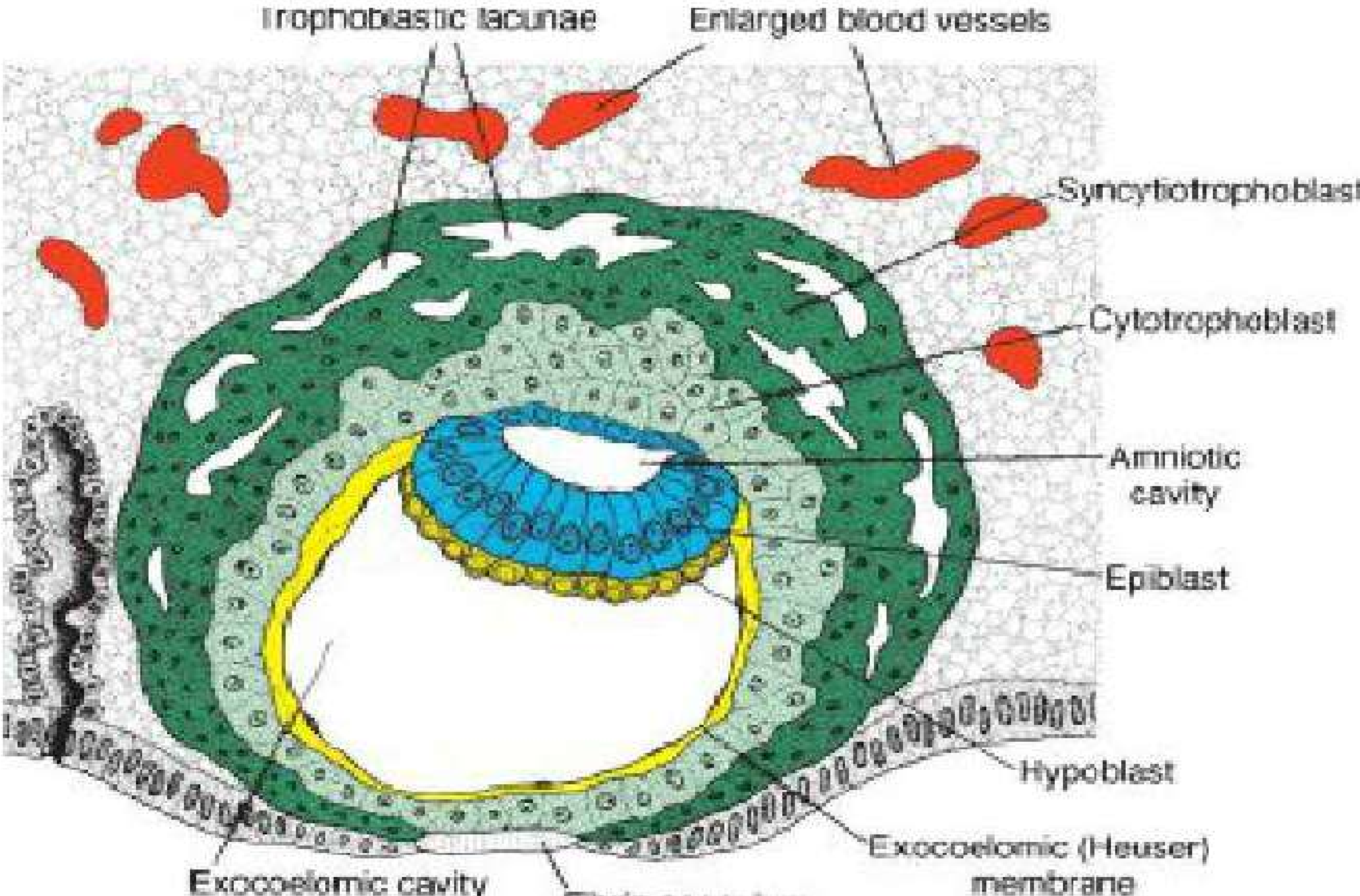
(2) An outer multinucleated zone without distinct cell boundaries, the **syncytiotrophoblast**

- Mitotic figures are found in the cytotrophoblast but not in the syncytiotrophoblast.
- Thus, cells in the cytotrophoblast divide and migrate into the syncytiotrophoblast, where they fuse and lose their individual cell membranes.

- Cells of the inner cell mass or embryoblast also differentiate into two layers forming a flat disc :

(1) A layer of small cuboidal cells adjacent to the blastocyst cavity, known as the **hypoblast layer**

(2) A layer of high columnar cells adjacent to the amniotic cavity, the **epiblast layer**


Trophoblastic lacunae
Enlarged blood vessels
Syncytiotrophoblast
Cytotrophoblast
Amniotic
cavity
Epiblast
Hypoblast
Exocoelomic (Heuser)
membrane
Exocoelomic cavity

- At the same time, a small cavity appears within the epiblast.
- This cavity enlarges to become **the amniotic cavity.**
- Epiblast cells adjacent to the cytotrophoblast are called amnioblasts; together with the rest of the epiblast, they line the amniotic cavity

- The endometrial stroma adjacent to the implantation site is edematous and highly vascular.
- The large, tortuous glands secrete abundant glycogen and mucus.

DAY 9

- Blastocyst is more deeply embedded in the endometrium, and the penetration defect in the, surface epithelium is closed by a fibrin coagulum

- The trophoblast shows considerable progress in development, particularly at the embryonic pole, where vacuoles appear in the syncytium.

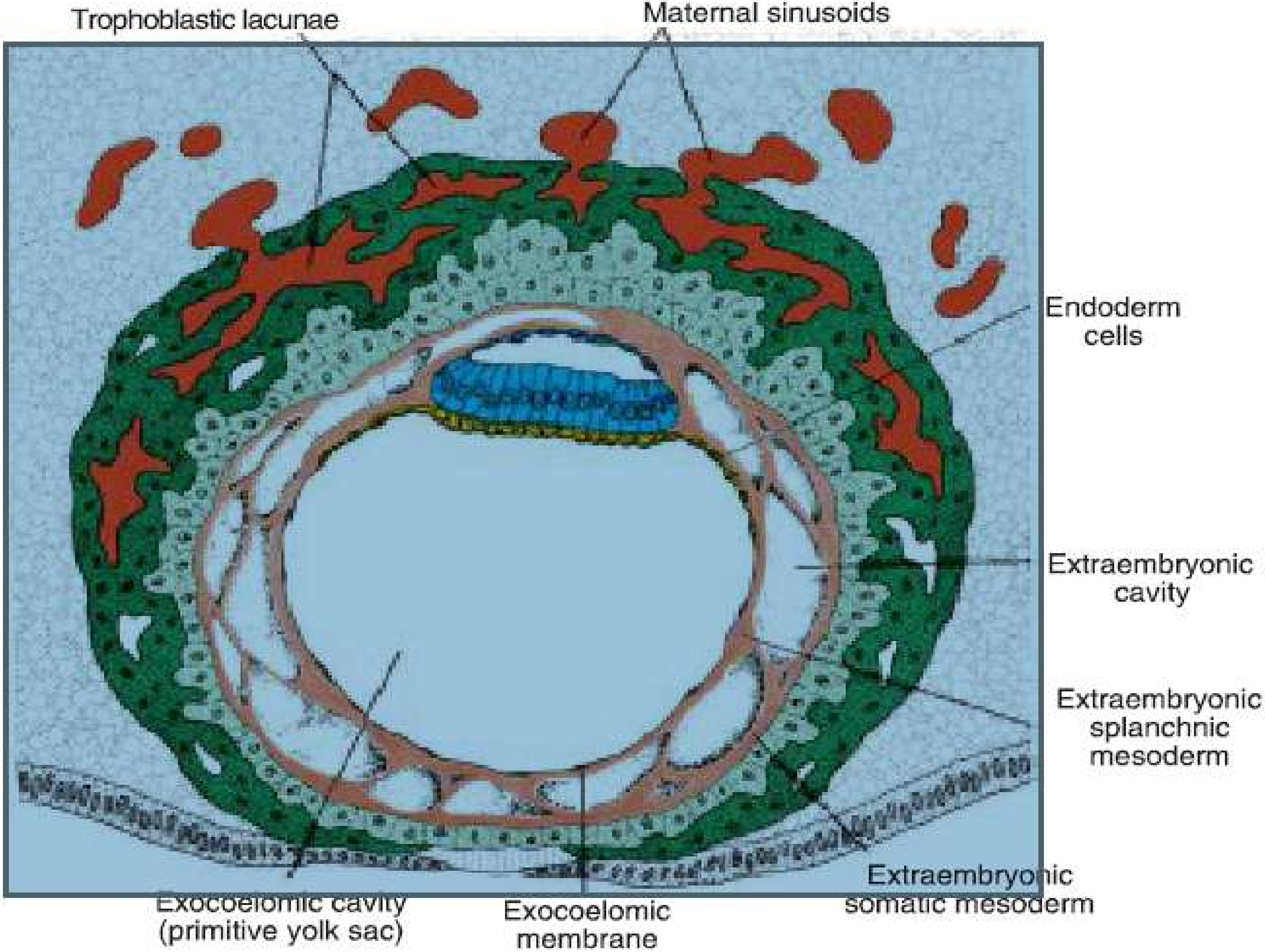
- When these vacuoles fuse, they form large lacunae, and this phase of trophoblast development is thus known as the lacunar stage

- At the abembryonic pole, meanwhile, flattened cells probably originating from the hypoblast form a thin membrane, the exocoelomic (Heuser) 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**.

DAYS 11 AND 12

- By the 11th to the 12th day of development, the blastocyst is completely embedded in the endometrial stroma, and the surface epithelium almost entirely covers the original defect in the uterine wall.



GURE 4.4 Human blastocyst of approximately 12 days. The trophoblastic lacunae at the embryoni
e in open connection with maternal sinusoids in the endometrial stroma. Extraembryonic mesoderm

- The blastocyst now produces a slight protrusion into the lumen of the uterus.
- The trophoblast is characterized by lacunar spaces in the syncytium that form an intercommunicating network.

- This network is particularly evident at the embryonic pole;

- At the abembryonic pole, the trophoblast still consists mainly of cytotrophoblastic cells

- Concurrently, cells of the syncytiotrophoblast penetrate deeper into the stroma and erode the endothelial lining of the maternal capillaries.
- These capillaries, which are congested and dilated, are known as sinusoids.
- The syncytial lacunae become continuous with the sinusoids,and maternal blood enters the lacunar system.

- As the trophoblast continues to erode more and more sinusoids, maternal blood begins to flow through the trophoblastic system, establishing the uteroplacental circulation.

- In the meantime, a new population of cells appears between the inner surface of the cytotrophoblast and the outer surface of the exocoelomic cavity.

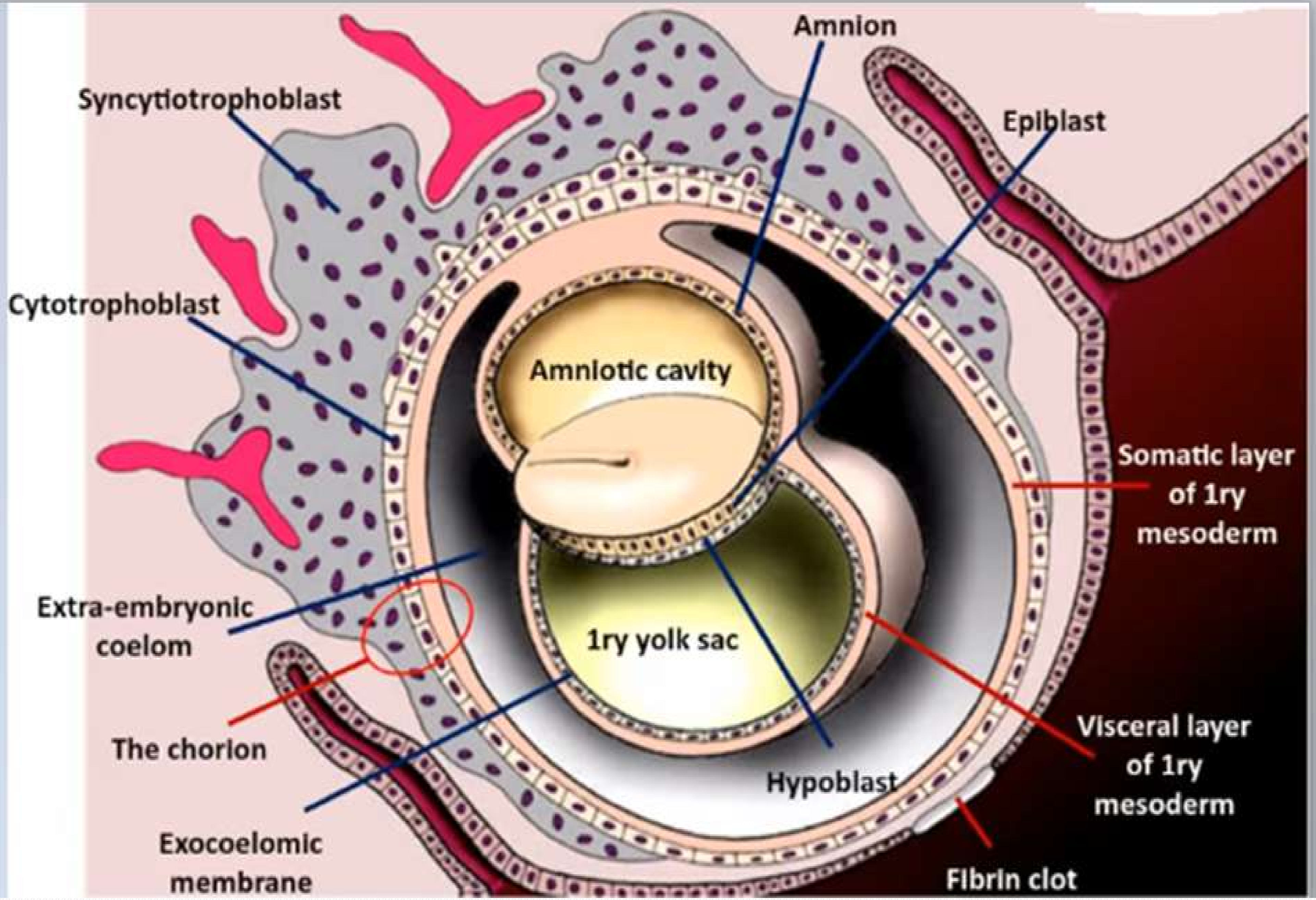
- These cells, derived from yolk sac cells, form a fine, loose connective tissue, the **extraembryonic mesoderm,** which fills all of the space between the trophoblast externally and the amnion and exocoelomic membrane internally .

- Soon, large cavities develop in the extraembryonic mesoderm, and when these become confluent, they form a new space known as the extraembryonic cavity, or chorionic cavity .

- This space surrounds the primitive yolk sac and amniotic cavity, except where the germ disc is connected to the trophoblast by the **connecting stalk**

- The 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**


Amnion
Syncytiotrophoblast
Epiblast
Cytotrophoblast
Amniotic cavity
Somatic layer
of 1ry
mesoderm
Extra-embryonic
coelom
1ry yolk sac
The chorion
Visceral layer
of 1ry
mesoderm
Hypoblast
Exocoelomic
membrane
Fibrin clot

- Growth of the bilaminar disc is relatively slow compared with that of the trophoblast; consequently, the disc remains very small (0.1 to 0.2 mm).

- Cells of the endometrium 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, at first, are confined to the area immediately surrounding the implantation site but soon occur throughout the endometrium

DAY 13

- By the 13th day of development, the surface defect in the endometrium has usually healed.
- Occasionally, however, bleeding occurs at the implantation site as a result of increased blood flow into the lacunar spaces.

- Because this bleeding occurs near the 28th day of the menstrual cycle, it may be confused with normal menstrual bleeding and, therefore, may cause inaccuracy in determining the expected delivery date.

- The trophoblast is characterized by villous structures.
- Cells of the cytotrophoblast proliferate locally and penetrate into the syncytiotrophoblast, forming cellular columns surrounded by syncytium.
- Cellular columns with the syncytial covering are known as **primary villi.**

- In the meantime, the hypoblast produces additional cells that migrate along the inside of the exocoelomic membrane .
- These cells proliferate and gradually form a new cavity within the exocoelomic cavity.

- This new cavity is known as the secondary yolk sac or definitive yolk sac .
- This yolk sac is much smaller than the original exocoelomic cavity, or primitive yolk sac.
- During its formation, large portions of the exocoelomic cavity are pinched off.
- These portions are represented by exocoelomic cysts, which are often found in the extraembryonic coelom or chorionic cavity

- Meanwhile, the extraembryonic coelom expands and forms a large cavity, the **chorionic cavity**.

- The extraembryonic mesoderm lining the inside of the cytotrophoblast is then known as the **chorionic plate.**

- The only place where extraembryonic mesoderm traverses the chorionic cavity is in the connecting stalk.
- With development of blood vessels, the stalk becomes **the umbilical cord**

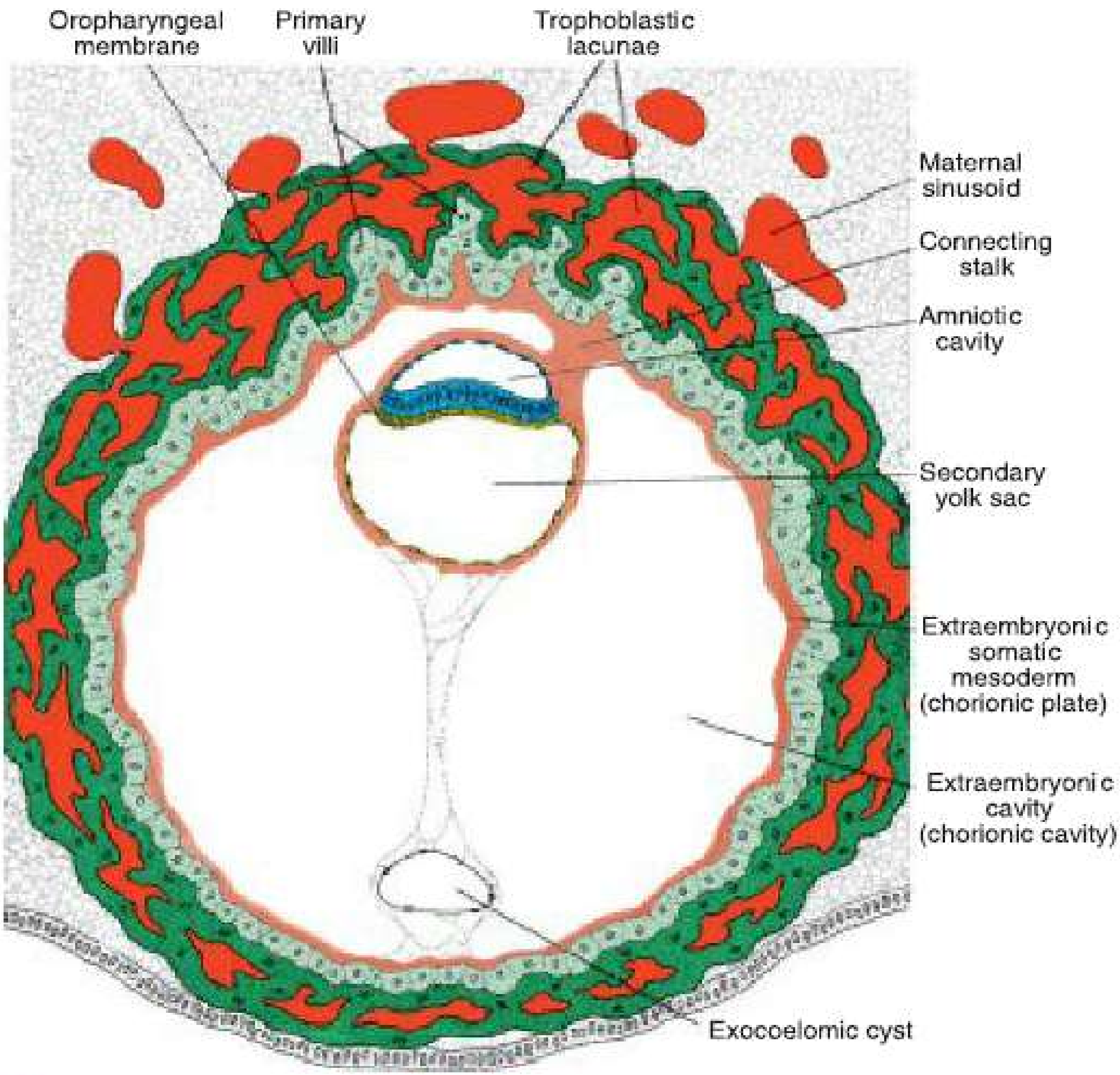
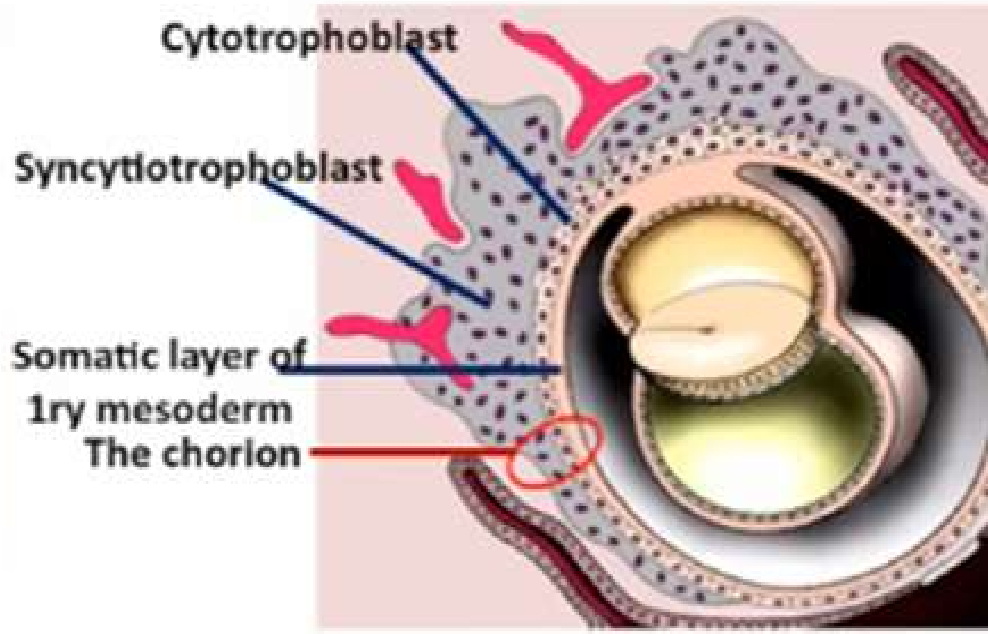


FIGURE 4.6 A 13-day human blastocyst. Trophoblastic lacunae are present at the embryonic as well as the abembryonic pole, and the uteroplacental circulation has begun. Note the primary villi and the extraembryonic coelom or chorionic cavity. The secondary yolk sac is entirely lined with endoderm.

The chorion

- It is the **wall** of the **chorionic vesicle**.
- It is **composed** of **three** layers, arranged **from outside inwards**:

1) Syncytiotrophoblast,
2) Cytotrophoblast,
3) Somatic layer of the 1ry mesoderm.



Events of the 2nd week

Bilaminar embryonic disc

- It is the formation of circular, transparent embryonic disc formed of 2 layers:

a) Epiblast: the future ectoderm.

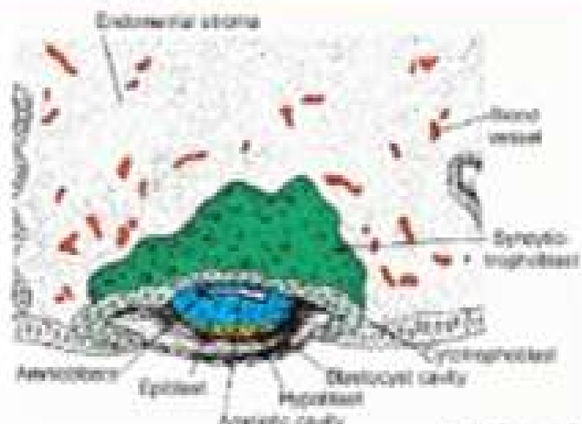
b) Hypoblast: the future endoderm.

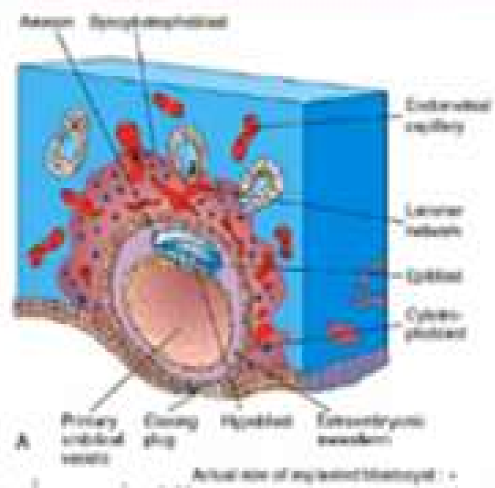
Extraembryonic mesoderm

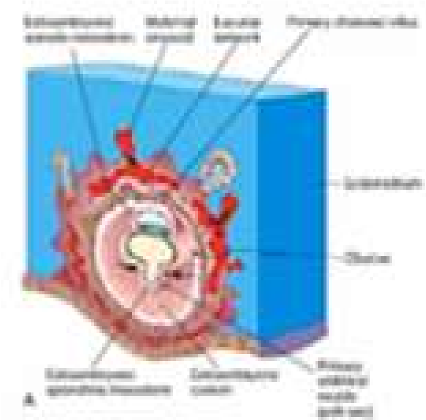
- Arises from the hypoblast.
- It surrounds the amnion and the yolk sac separating them from the trophoblast.

Chorion

- It is the wall of the chorionic vesicle.







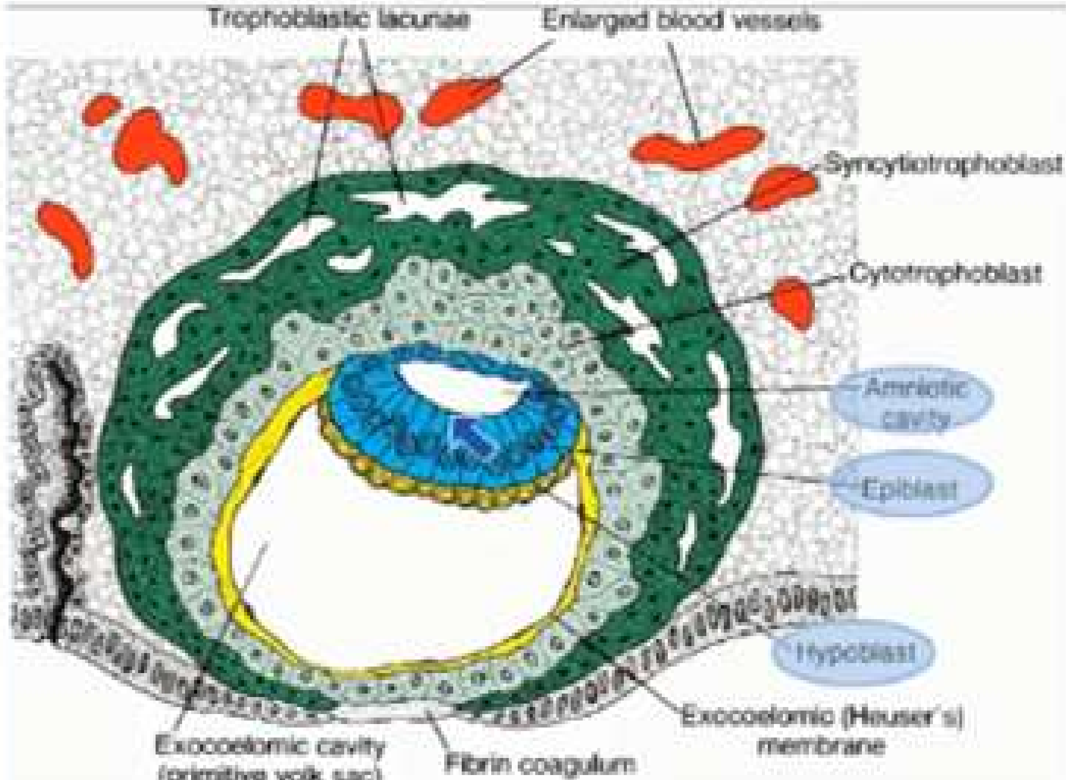
The bilaminar embryonic disc

- It is almost circular, transparent formed of two layers:

a) Epiblast: high columnar cells which will form the future ectoderm.

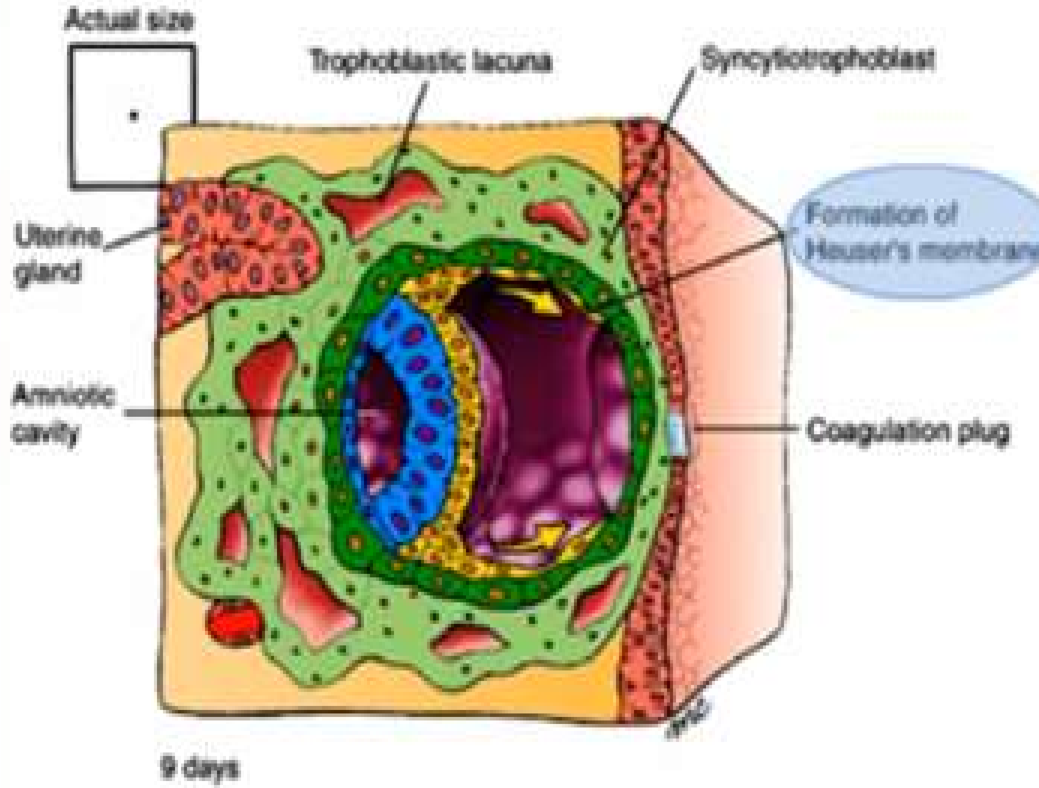
b) Hypoblast: small cuboidal cells which will form the future endoderm. They are adjacent to the exo-coelomic cavity (1ry yolk sac).

- A small cavity appears within the epiblast and enlarges (amniotic cavity).
- Epiblasts give rise to amnioblasts which surround the amniotic cavity and forming the amnion.



The bilaminar embryonic disc

- **The exocoelomic membrane:**
- It is formed by flattened cells arising from the hypoblast.
- It is a thin membrane lining the inner surface of the cytotrophoblast cells.
- It forms with the hypoblast cells the lining of the 1ry yolk sac.



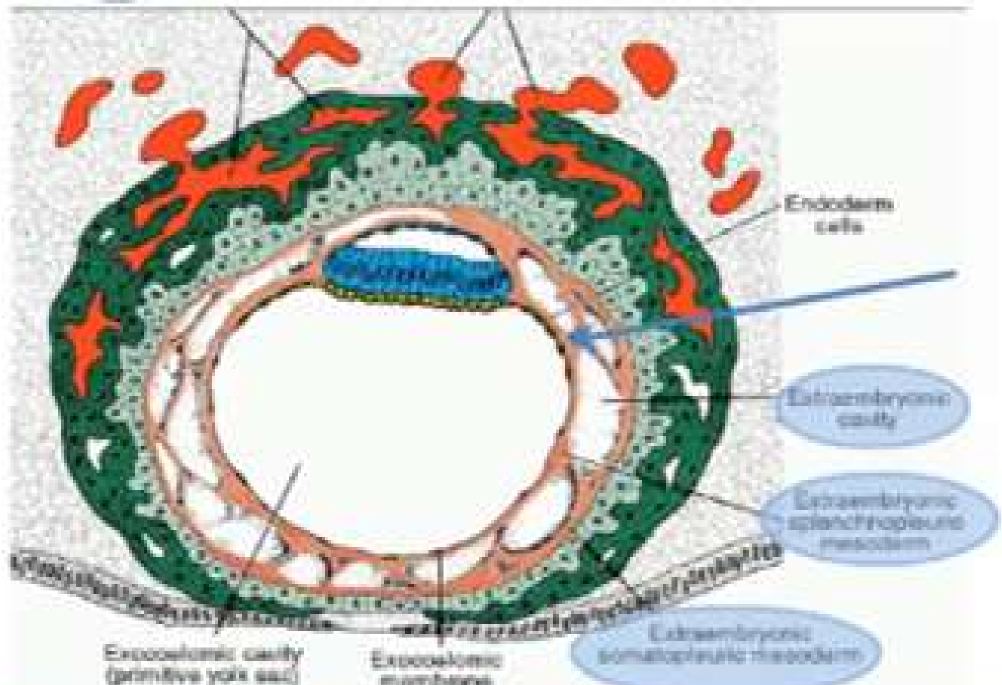
The extraembryonic mesoderm

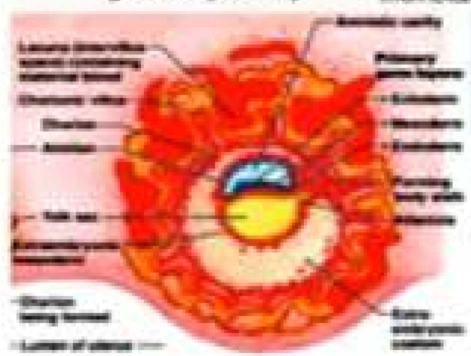
- It is the 1ry mesoderm.
- It arises from hypoblast cells.
- It surrounds the amnion and the 1ry yolk sac, separating them from the trophoblast .

- <u>The extra-embryonic coelom:</u>
- Small cavities appear in the mesoderm, these spaces coalesce together forming single cavity (the extra-embryonic coelom).
- Now the mesoderm is divided into two layers:

a) <u>An outer layer:</u> lining the trophoblast, it is the (somatic or parietal layer of this mesoderm).

b) <u>An inner layer:</u> covering the yolk sac, it is the (visceral layer of this mesoderm.





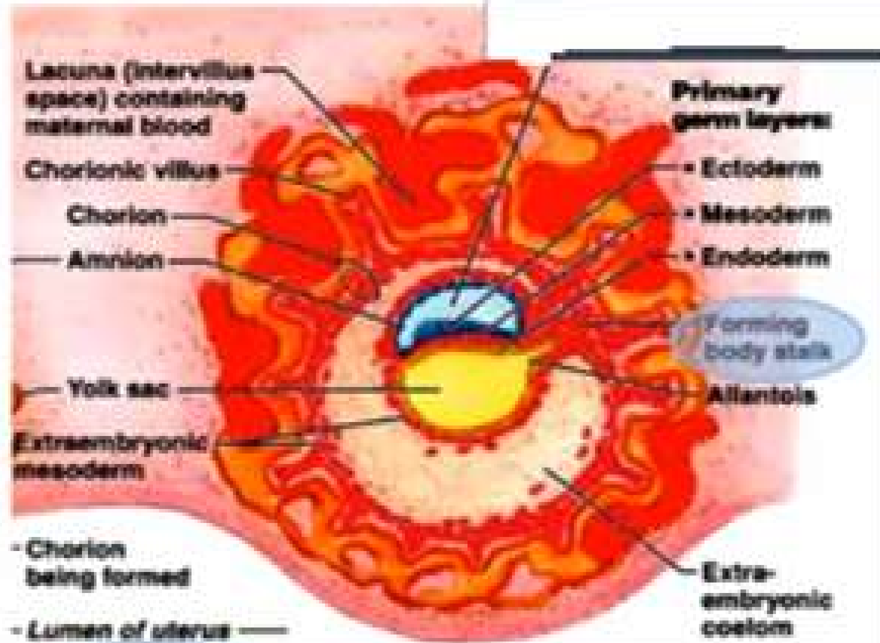
The blastocyst now is called the <u>chorionic vesicle</u>

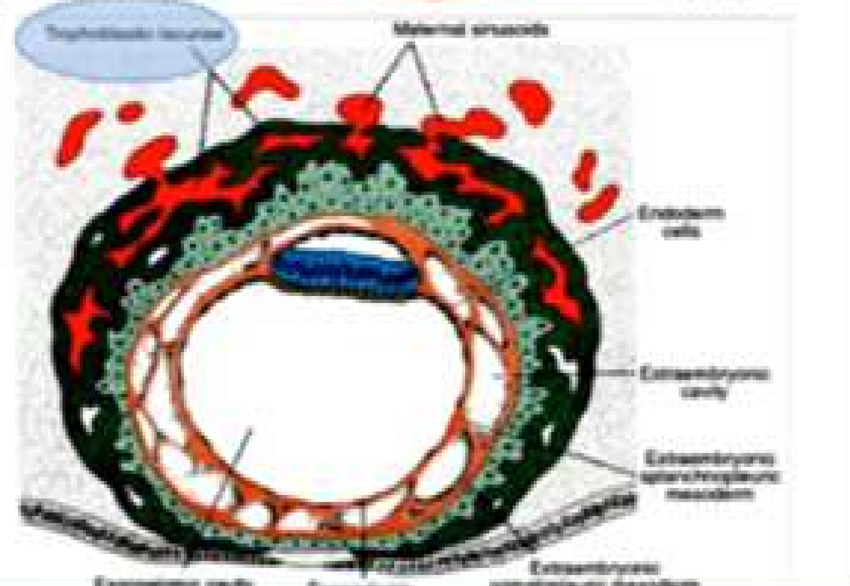
- **N.B:**

1) The extra-embryonic coelom incompletely surrounds the chorionic vesicle, because a part of the mesoderm stays without cavitation, this part forms the connecting stalk which connects the caudal part of the embryonic disc to the wall of the vesicle allowing fetal blood vessels to pass between the placenta to the fetus.

2) Spaces will appear in the syncytio-trophoblast forming a network (syncytial lacunae).

- With continuous erosion of the endometrium during implantation, the maternal sinusoids will be reached, now maternal blood can enter the lacunar system and flow inside the trophoblastic system (utero-placental circulation).



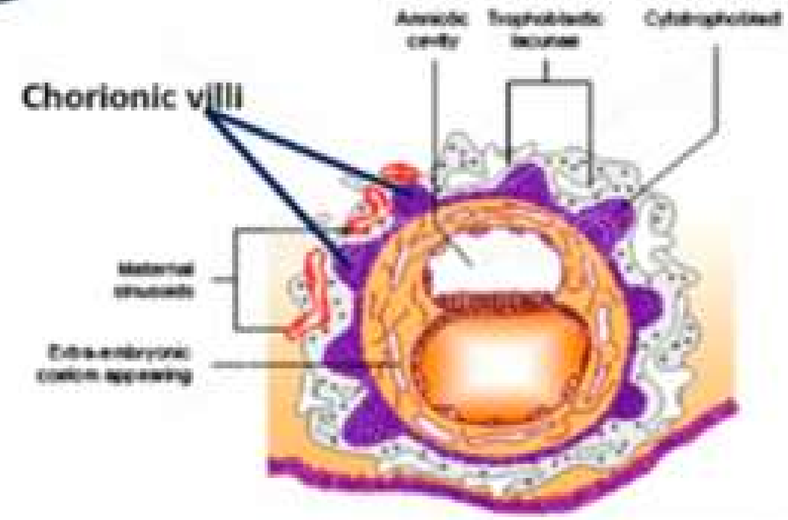


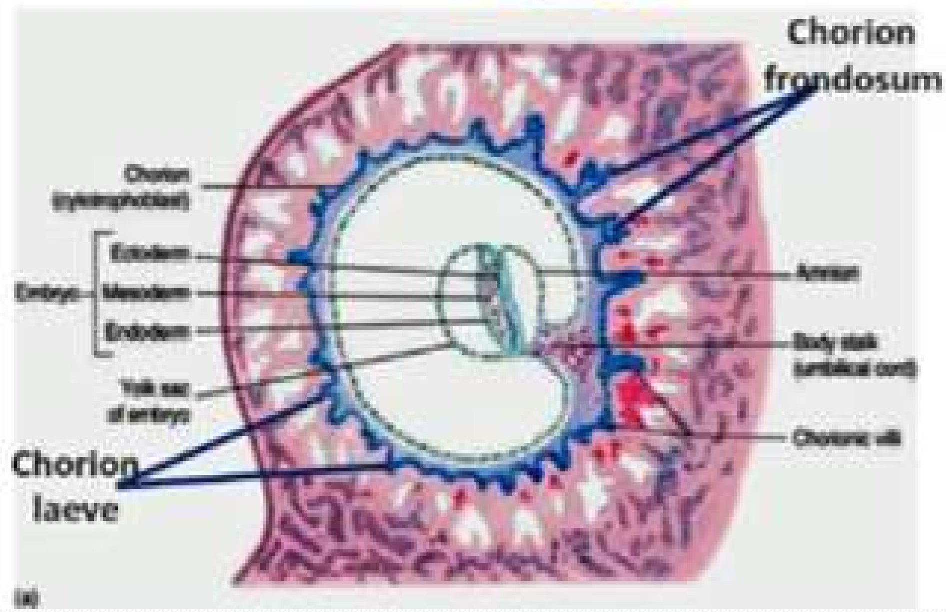
The chorion

- Large **number** of **proliferations** of the **cytotrophoblast** towards the **outer surface** of the **chorionic vesicle** will **form** the **chorionic villi**.
- These **proliferations** thought to be **induced** by the **underlying somatic** layer of the **1ry mesoderm**.

- **Chorionic villi** are **distributed** as follows:

1) Chorion frondosum: **well** developed villi lying **opposite** (**facing**) the **decidua basalis**.
2) Chorion laeve: **less** developed (**atrophic**) villi lying in **contact** with **decidua capsularis**.





Types of chorionic villi

Primary villi

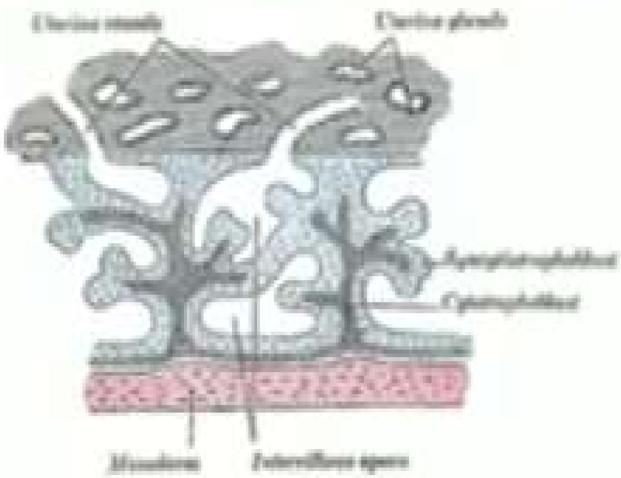
- Formed of the two layers of
- They are [illegible] by lacunae which is filled with maternal blood.

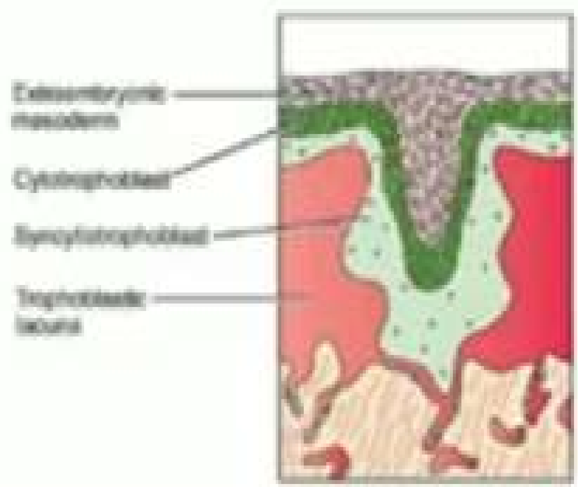
Secondary villi

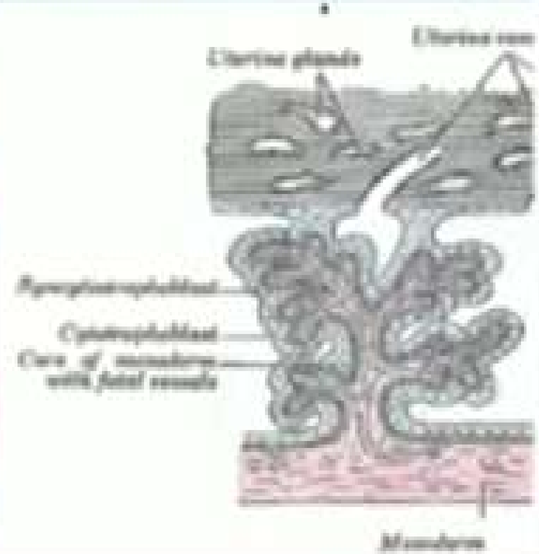
- They are the 1ry villi after they are invaded by cores of 1ry mesoderm.

Tertiary villi

- They are the 2ry villi after they are invaded by fetal blood vessels within the core of the 1ry







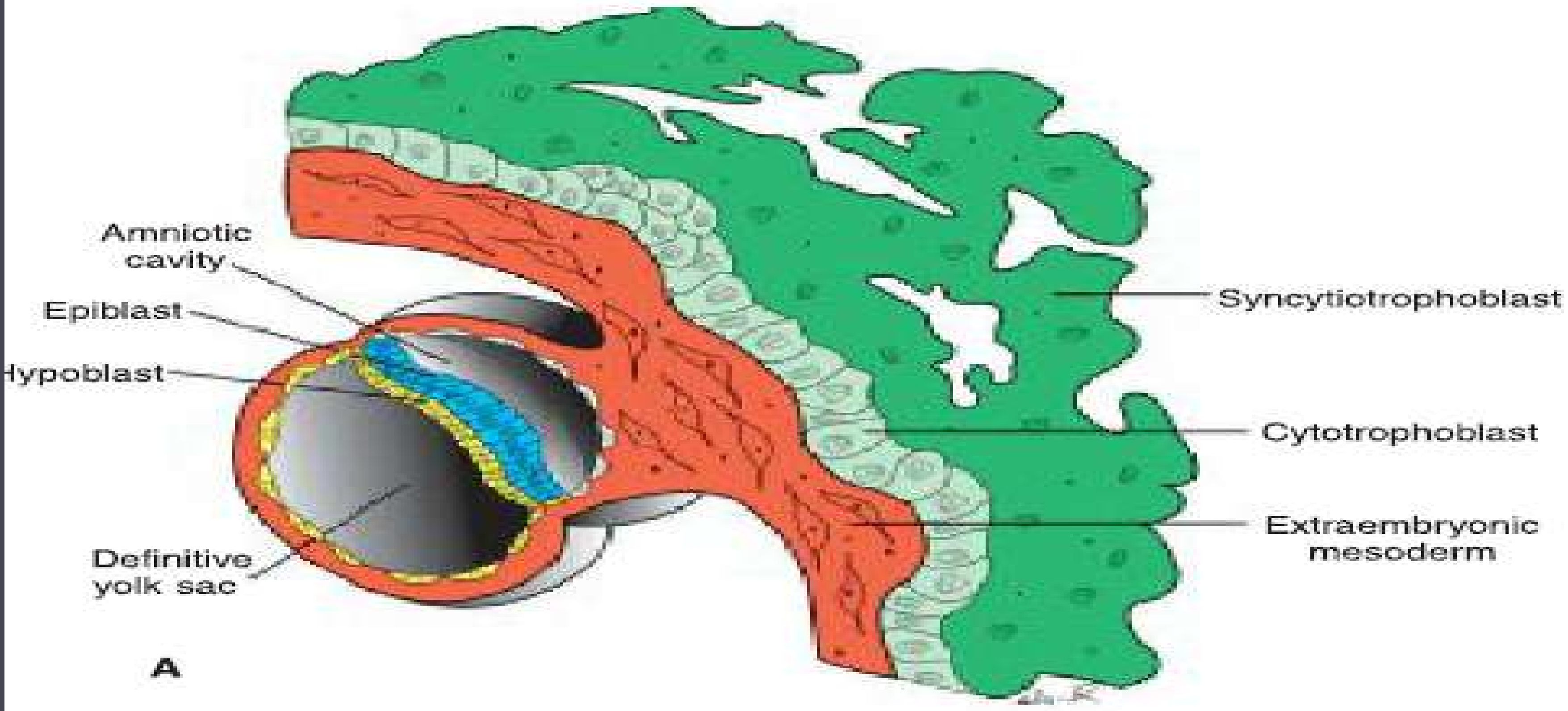
Third Week of Development: Trilaminar Germ Disc 5

Dr. Sawsan S. Shurrab

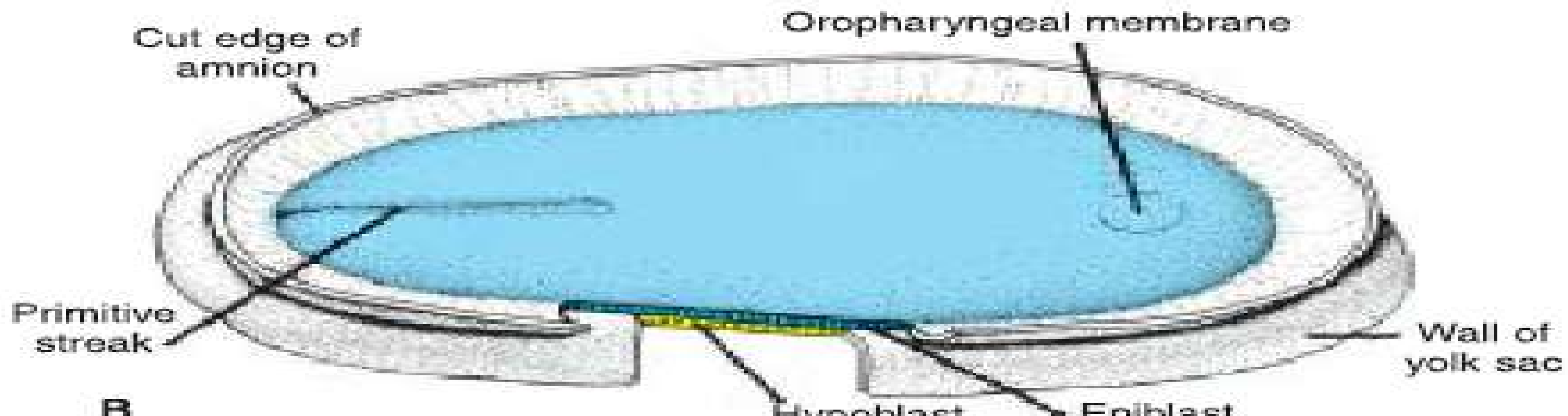
GASTRULATION: FORMATION OF MESODERM AND ENDODERM

- The most characteristic event occurring during the third week of gestation is **gastrulation**, the process that establishes all three germ layers (ectoderm, mesoderm, and endoderm)

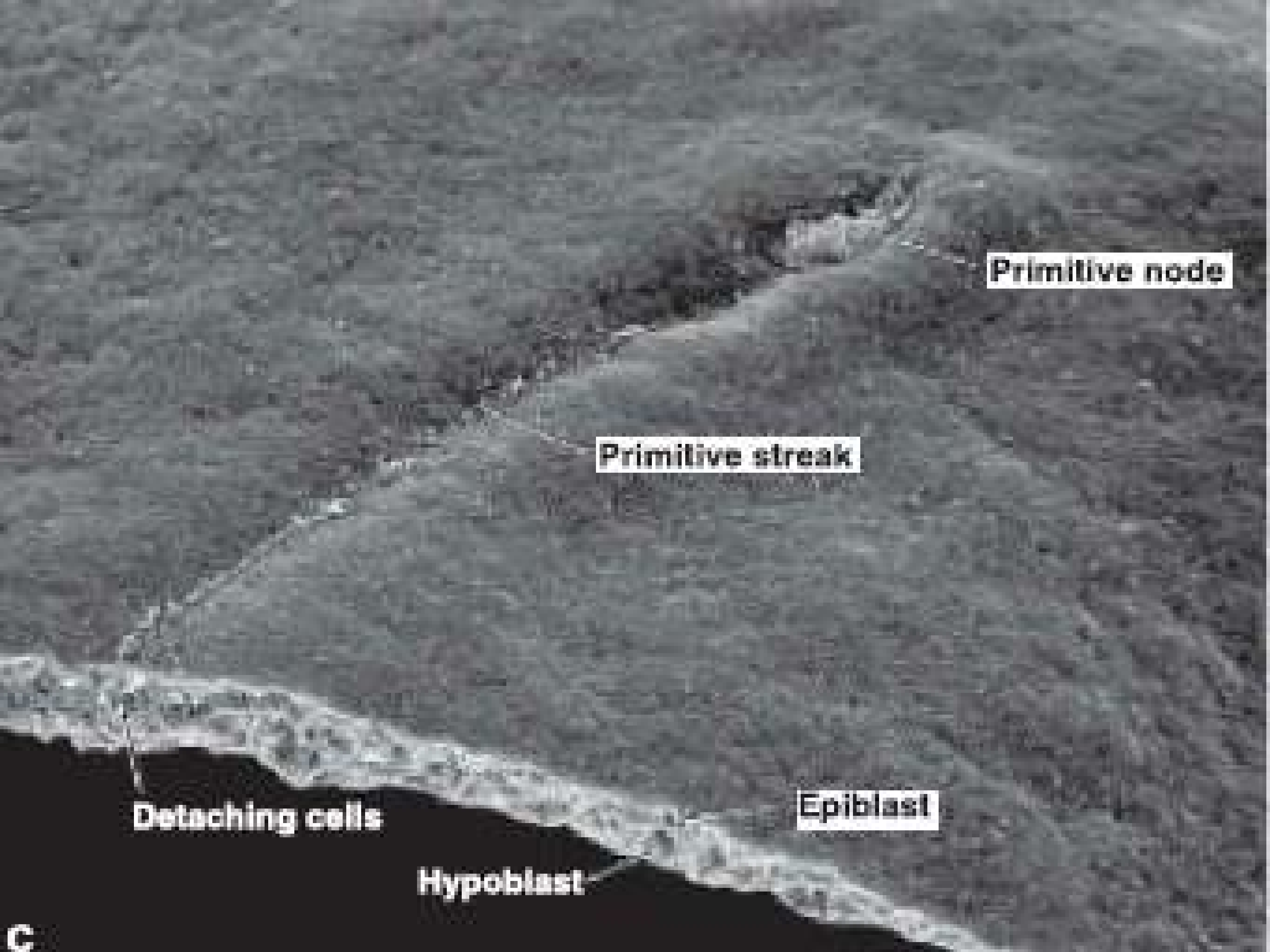
- Gastrulation begins with formation of the primitive streak on the surface of the epiblast


Amniotic cavity
Epiblast
Hypoblast
Definitive yolk sac
Syncytiotrophoblast
Cytotrophoblast
Extraembryonic mesoderm

A


Cut edge of amnion
Oropharyngeal membrane
Primitive streak
Wall of yolk sac
Hypoblast
Epiblast

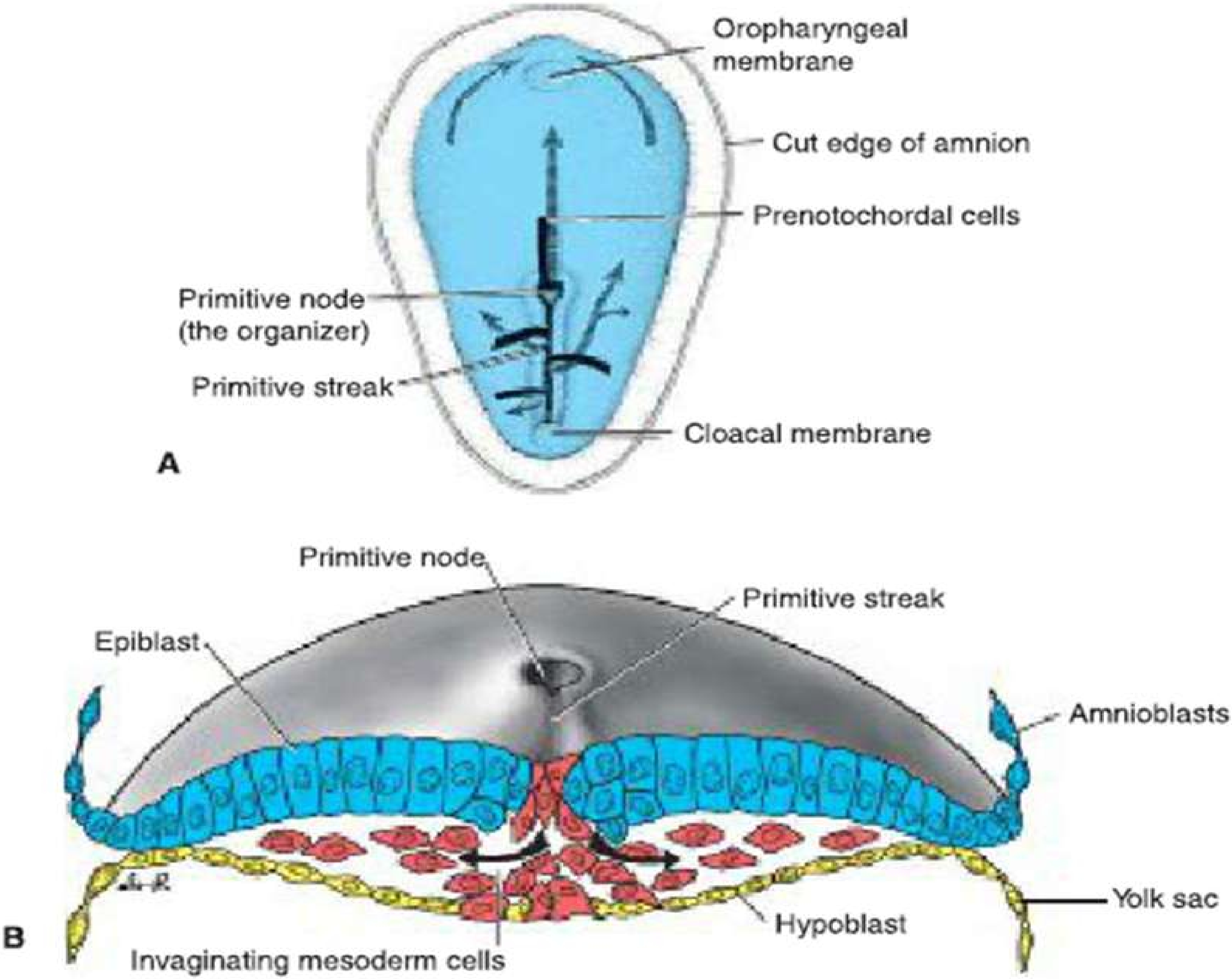
B



Primitive node
Primitive streak
Epiblast
Detaching cells
Hypoblast
C

- Initially, the streak is vaguely defined , but in a 15- to 16-day embryo, it is clearly visible as a narrow groove with slightly bulging regions on either side.
- The 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.
- Upon arrival in the region of the streak, they become flask-shaped, detach from the epiblast, and slip beneath it.
- This inward movement is known as invagination.


Oropharyngeal membrane
Cut edge of amnion
Prenotochordal cells
Primitive node (the organizer)
Primitive streak
Cloacal membrane
A
Primitive node
Primitive streak
Epiblast
Amnioblasts
Yolk sac
Hypoblast
B
Invaginating mesoderm cells

- Cell migration and specification are controlled by fibroblast growth factor 8 **(FGF8)** which is synthesized by streak cells themselves.
- It controls cell movement by downregulating E-cadherin, a protein that normally binds epiblast cells together.
- It controls cell specification into the mesoderm

- Once the cells have invaginated, some 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.

- Thus, 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.
- In the cephalic direction, they pass on each side of the prechordal plate

- The **prechordal plate** itself forms between the tip of the notochord and the oropharyngeal membrane and is derived from some of the first cells that migrate through the node in the midline and move in a cephalic direction.
- Later, the prechordal plate will be important for induction of the forebrain.

- The oropharyngeal membrane at the cranial end of the disc consists of a small region of tightly adherent ectoderm and endoderm cells that represents the future opening of the oral cavity.

FORMATION OF THE NOTOCHORD

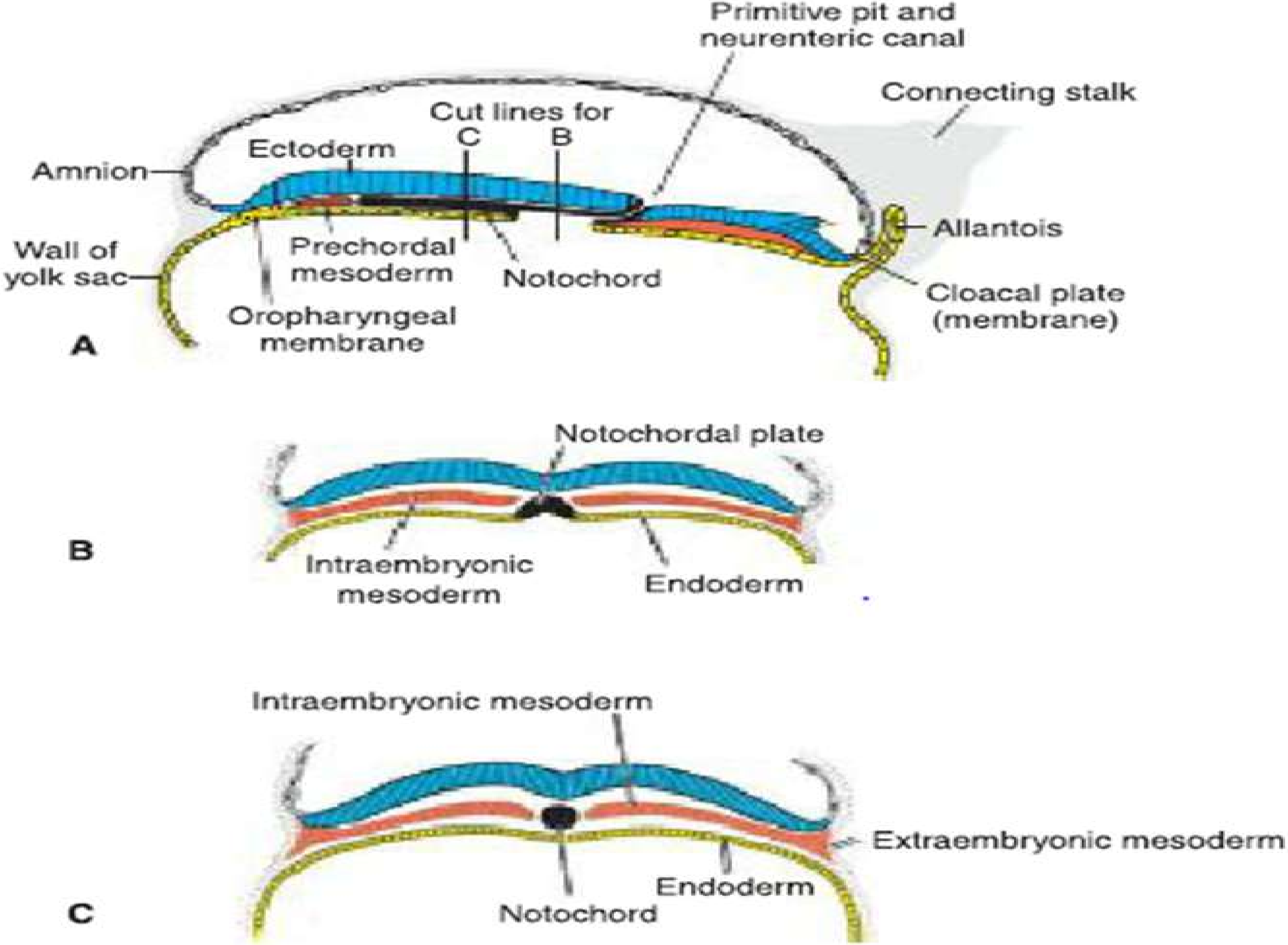
- Prenotochordal cells invaginating in the primitive node move forward cranially in the midline until they reach the prechordal plate.
- These prenotochordal cells become intercalated in the hypoblast so that for a short time, the midline of the embryo consists of two cell layers that form the notochordal plate.

- As the hypoblast is replaced by endoderm cells moving in at the streak, cells of the notochordal plate proliferate and detach from the endoderm.
- They then form a solid cord of cells, the definitive notochord which underlies the neural tube and is a signaling center for inducing the axial skeleton.

- Because elongation of the notochord is a dynamic process, the cranial end forms first, and caudal regions are added as the primitive streak assumes a more caudal position.

- The notochord and pre notochordal cells extend cranially to the prechordal plate and caudally to the primitive pit.

- At the point where the pit forms an indentation in the epiblast, the neurenteric canal temporarily connects the amniotic and yolk sac cavities .



Primitive pit and neurenteric canal
Connecting stalk
Cut lines for
C
B
Ectoderm
Amnion
Allantois
Wall of yolk sac
Prechordal mesoderm
Notochord
Cloacal plate (membrane)
Oropharyngeal membrane
A
Notochordal plate
B
Intraembryonic mesoderm
Endoderm
Intraembryonic mesoderm
Extraembryonic mesoderm
Endoderm
Notochord
C

- The cloacal membrane is formed at the caudal end of the embryonic disc .
- This membrane, which is similar in structure to the oropharyngeal membrane, consists of tightly adherent ectoderm and endoderm cells with no intervening mesoderm.

- When the cloacal membrane appears, the posterior wall of the yolk sac forms a small diverticulum (Allantois)that extends into the connecting stalk.

- Although in some lower vertebrates, the allantois serves as a reservoir for excretion products of the renal system, in humans, it remains rudimentary but may be involved in abnormalities of bladder development .

ESTABLISHMENT OF THE BODY AXES

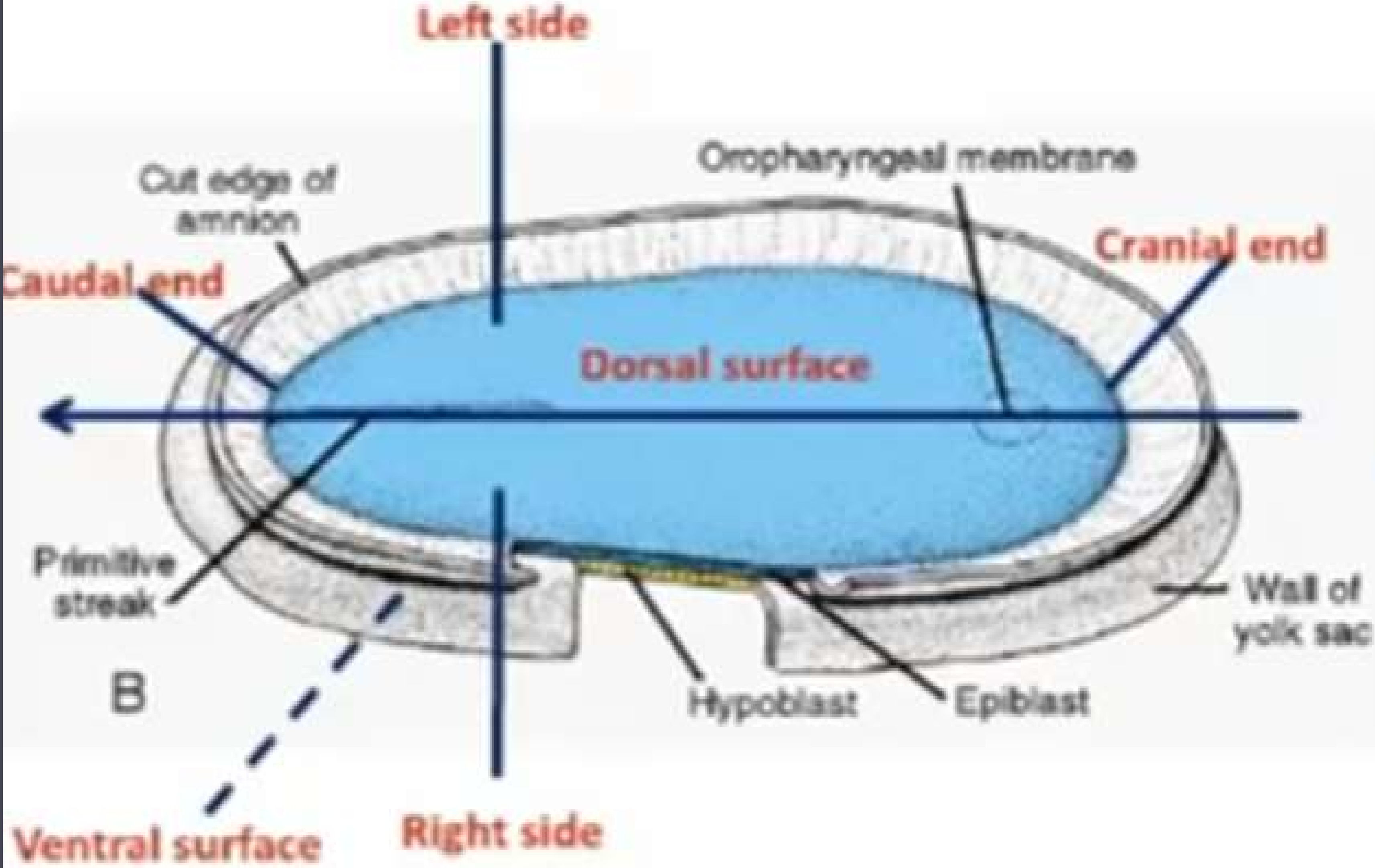
- Establishment of the body axes:

  - Anterior-posterior (A-P; craniocaudal),
  - Dorso-ventral (D-V),
  - left-right (L-R).

- By the blastocyst stage, the A-P axis is determined and cells that are destined to form the anterior visceral endoderm (AVE) migrate toward what will become the head region.

- At this bilaminar disc stage, cells in the AVE express genes essential for head formation, including the transcription factors which inhibit nodal activity, thereby establishing the cranial end of the embryo.

- The absence of these factors at the caudal end of the embryo allows nodal expression to continue, and this signal establishes and maintains the primitive streak.
- Once the streak is formed, formation of dorsal and ventral mesoderm and head and tail structures.



Left side
Oropharyngeal membrane
Cut edge of
amnion
Cranial end
Caudal end
Dorsal surface
Primitive
streak
Wall of
yolk sac
B
Hypoblast
Epiblast
Ventral surface
Right side

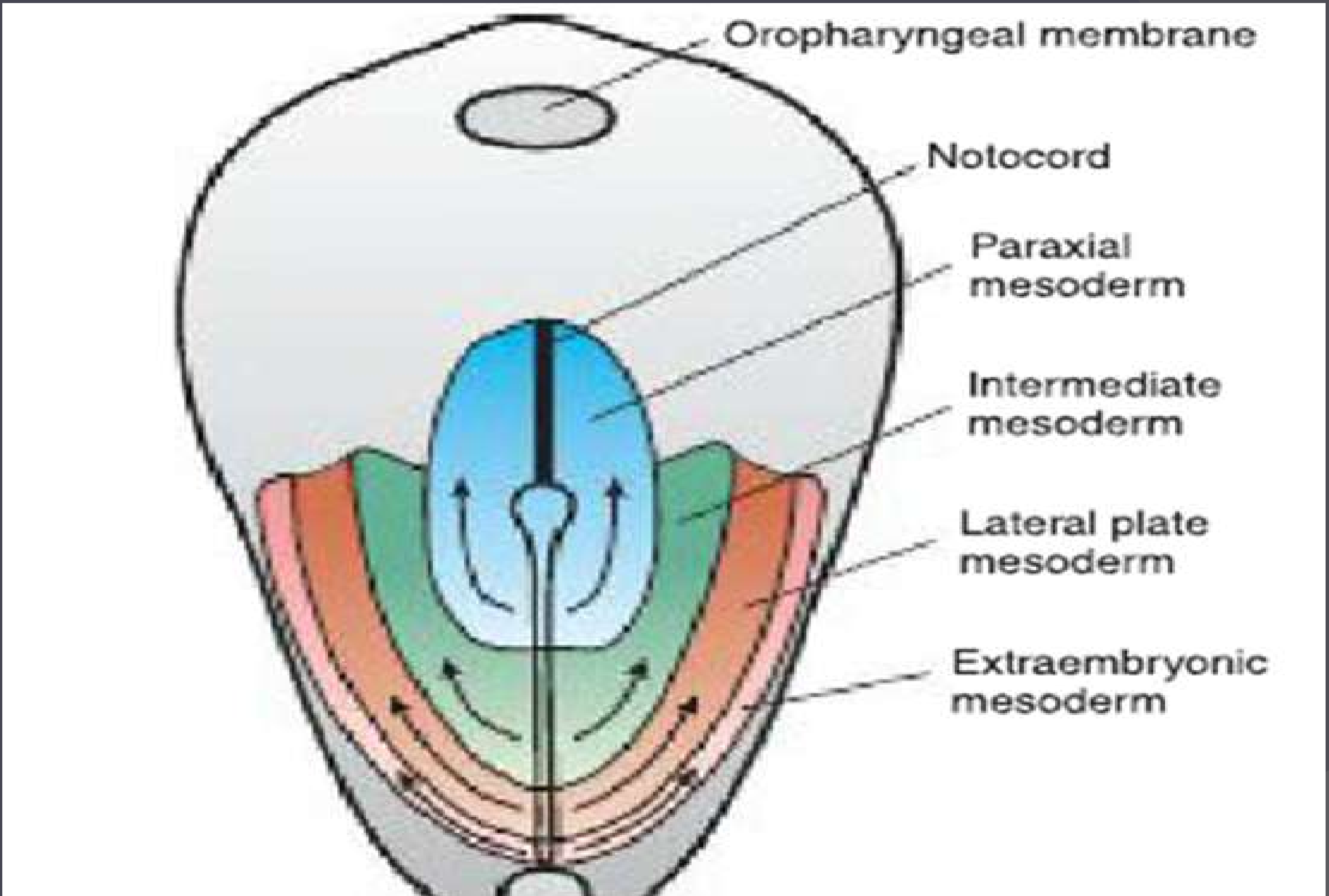
FATE MAP ESTABLISHED DURING GASTRULATION

- Cells that ingress through the cranial region of the node become prechordal plate and notochord,
- Cells migrating at the lateral edges of the node and from the cranial end of the streak become paraxial mesoderm
- Cells migrating through the midstreak region become intermediate mesoderm,.

- Cells migrating through the more caudal part of the streak form lateral plate mesoderm.

- Cells migrating through the caudal most part of the streak contribute to extraembryonic mesoderm.

(the other source of this tissue is the primitive yolk sac)


Oropharyngeal membrane
Notocord
Paraxial mesoderm
Intermediate mesoderm
Lateral plate mesoderm
Extraembryonic mesoderm
Cloacal membrane

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 .

- Expansion of the embryonic disc occurs mainly in the cephalic region; the region of the primitive streak remains more or less the same size.

- 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.

- Thus, gastrulation, or formation of the germ layers, continues in caudal segments

  while cranial structures are differentiating,

  causing the embryo to develop cephalocaudally

FURTHER DEVELOPMENT OF THE TROPHOBLAST

- By the beginning of the third week, the trophoblast is characterized by **primary villi** that consist of a cytotrophoblastic core covered by a syncytial layer .

- During further development, mesodermal cells penetrate the core of primary villi and grow toward the decidua.

  This is known as a **secondary villus**

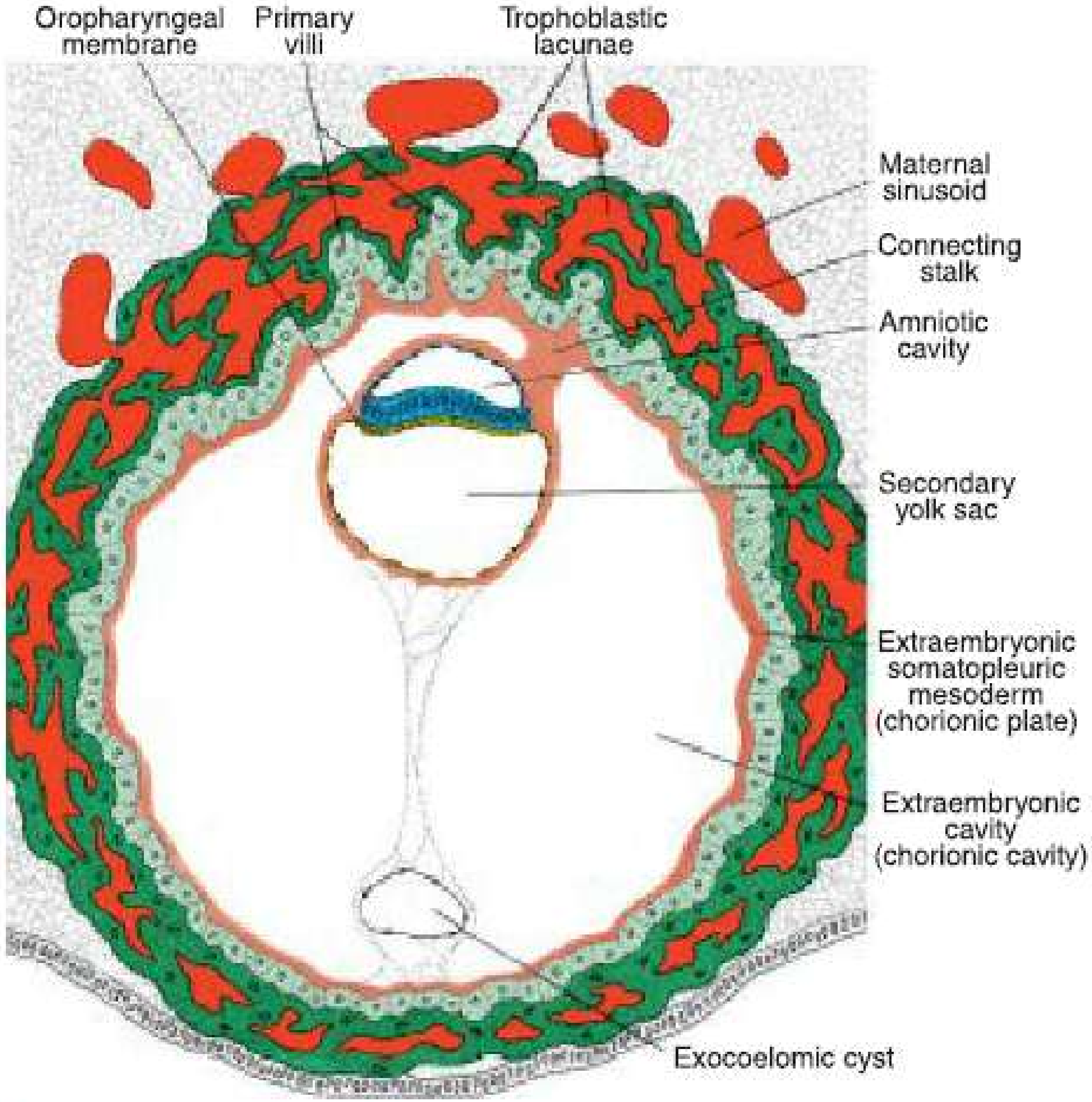


FIGURE 5.10 A 13-day-old implantation site showing primary villi of the trophoblastic shell just beginning to be invaded by mesoderm from the chorionic plate.

- By the end of the third week, mesodermal cells in the core of the villus begin to differentiate into blood cells and small blood vessels, forming the villous capillary system .

- The villus is now known as **a tertiary villus** or a definitive placental villus

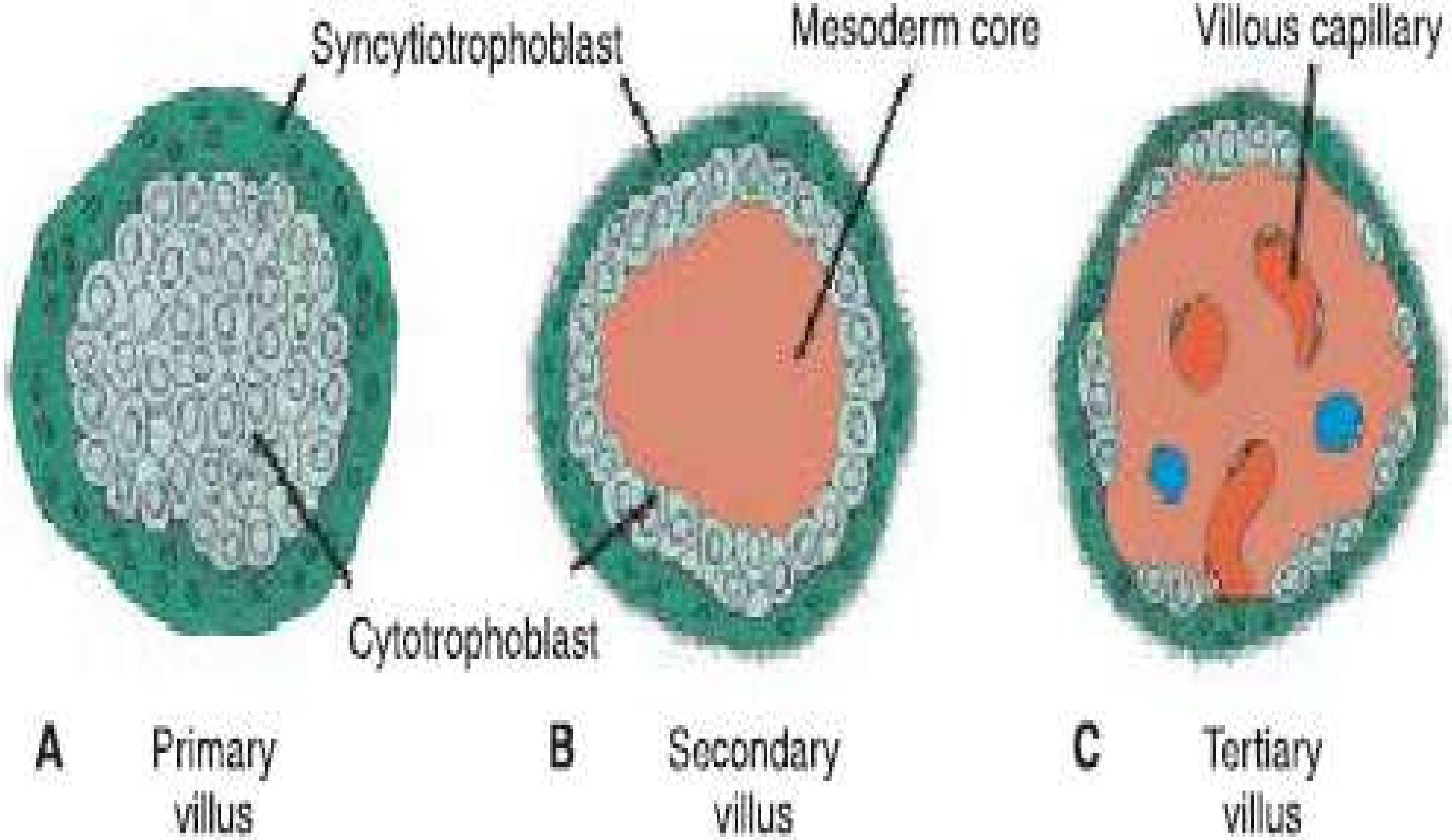


FIGURE 5.11 Development of a villus. **A.** Transverse section of a primary villus showing a core of cytotrophoblastic cells covered by a layer of syncytium. **B.** Transverse section of a secondary villus with a core of mesoderm covered by a single layer of cytotrophoblastic cells, which in turn is covered by syncytium. **C.** Mesoderm of the villus showing a number of capillaries and venules.

- Capillaries in tertiary villi make contact with capillaries developing in the mesoderm of the chorionic plate and in the connecting stalk .
- These vessels, in turn, establish contact with the intraembryonic circulatory system, connecting the placenta and the embryo.

- Hence, when the heart begins to beat in the fourth week of development, the villous system is ready to supply the embryo with proper essential nutrients and oxygen

- Meanwhile, cytotrophoblastic cells in the villi penetrate progressively into the overlying syncytium until they reach the maternal endometrium.

- Here, they establish contact with similar extensions of neighboring villous stems, forming a thin outer **cytotrophoblast shell.**

- This shell gradually surrounds the trophoblast entirely and attaches the chorionic sac firmly to the maternal endometrial tissue .

- Villi that extend from the chorionic plate to the decidua basalis are called stem or **anchoring villi**.

- Those that branch from the sides of stem villi are free **terminal villi**, through which exchange of nutrients and other factors will occur.
- The chorionic cavity, meanwhile, becomes larger, and by the 19th or the 20th day, the embryo is attached to its trophoblastic shell by a narrow connecting stalk .
- The connecting stalk later develops into the umbilical cord, which forms the connection between the placenta and embryo

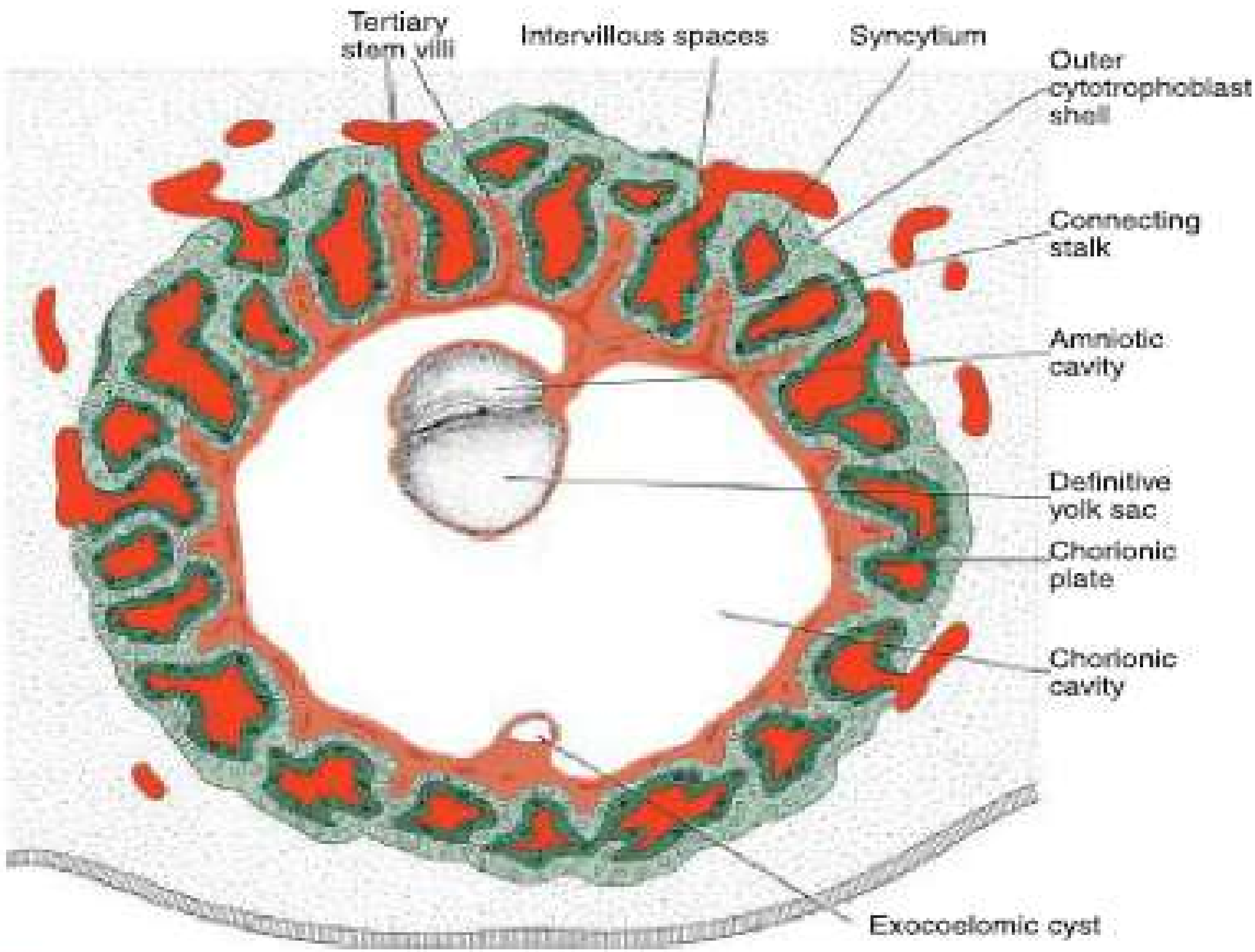


FIGURE 5.12 Presomite embryo and the trophoblast at the end of the third week. Tertiary and secondary stem villi give the trophoblast a characteristic radial appearance. Intervillous spaces, which are found throughout the trophoblast, are lined with syncytium. Cytotrophoblastic cells surround the trophoblast entirely and are in direct contact with the endometrium. The embryo is suspended in the chorionic cavity by means of the

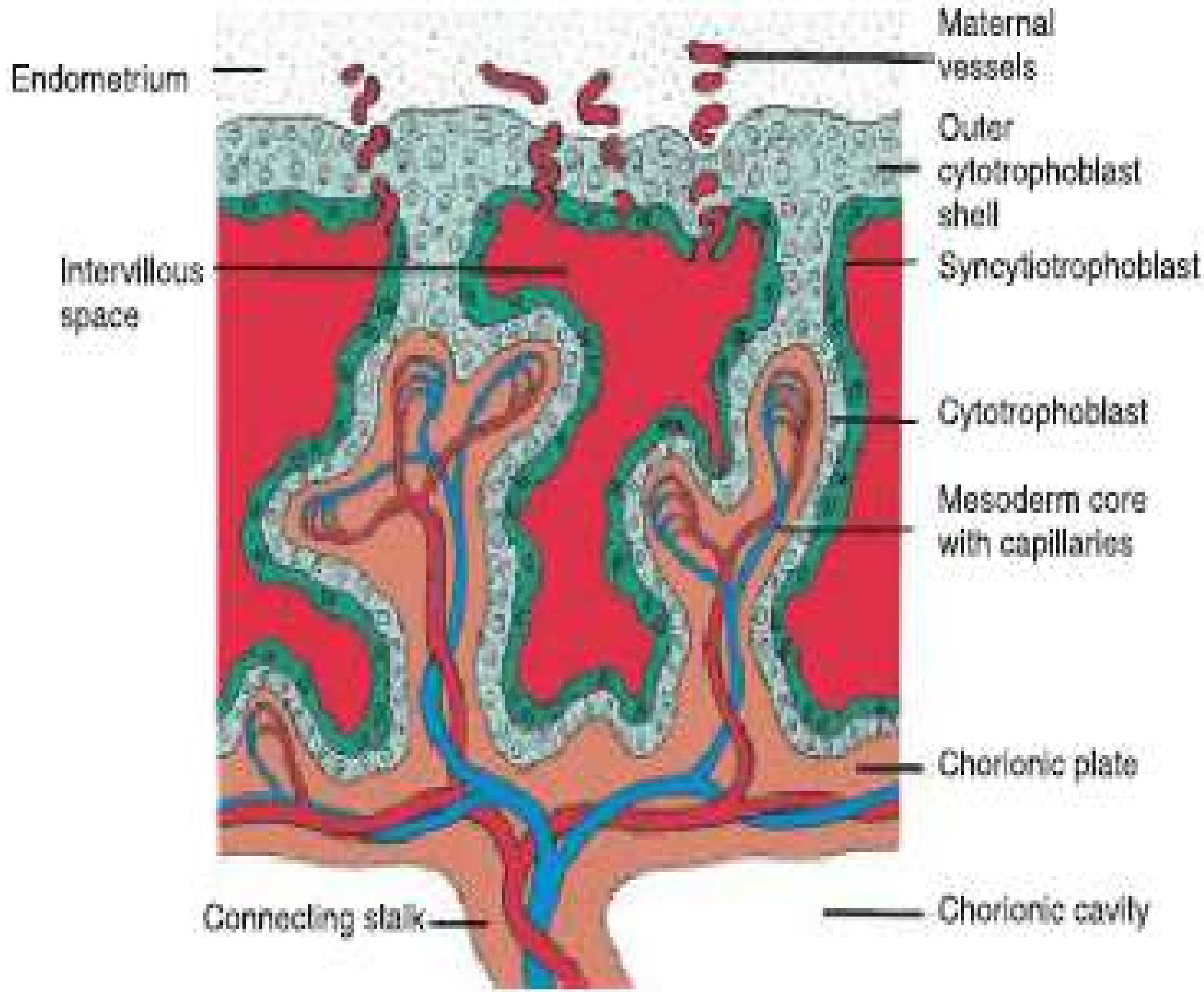


FIGURE 5.13 Longitudinal section through a villus at the end of the fourth week of development. Maternal vessels penetrate the cytotrophoblastic shell to enter intervillous spaces, which surround the villi. Capillaries in the villi are in contact with vessels in the chorionic plate and in the connecting stalk, which in turn are connected to intraembryonic vessels.

Third to Eighth Weeks:

The Embryonic Period 6

Dr. Sawsan S. Shurrab

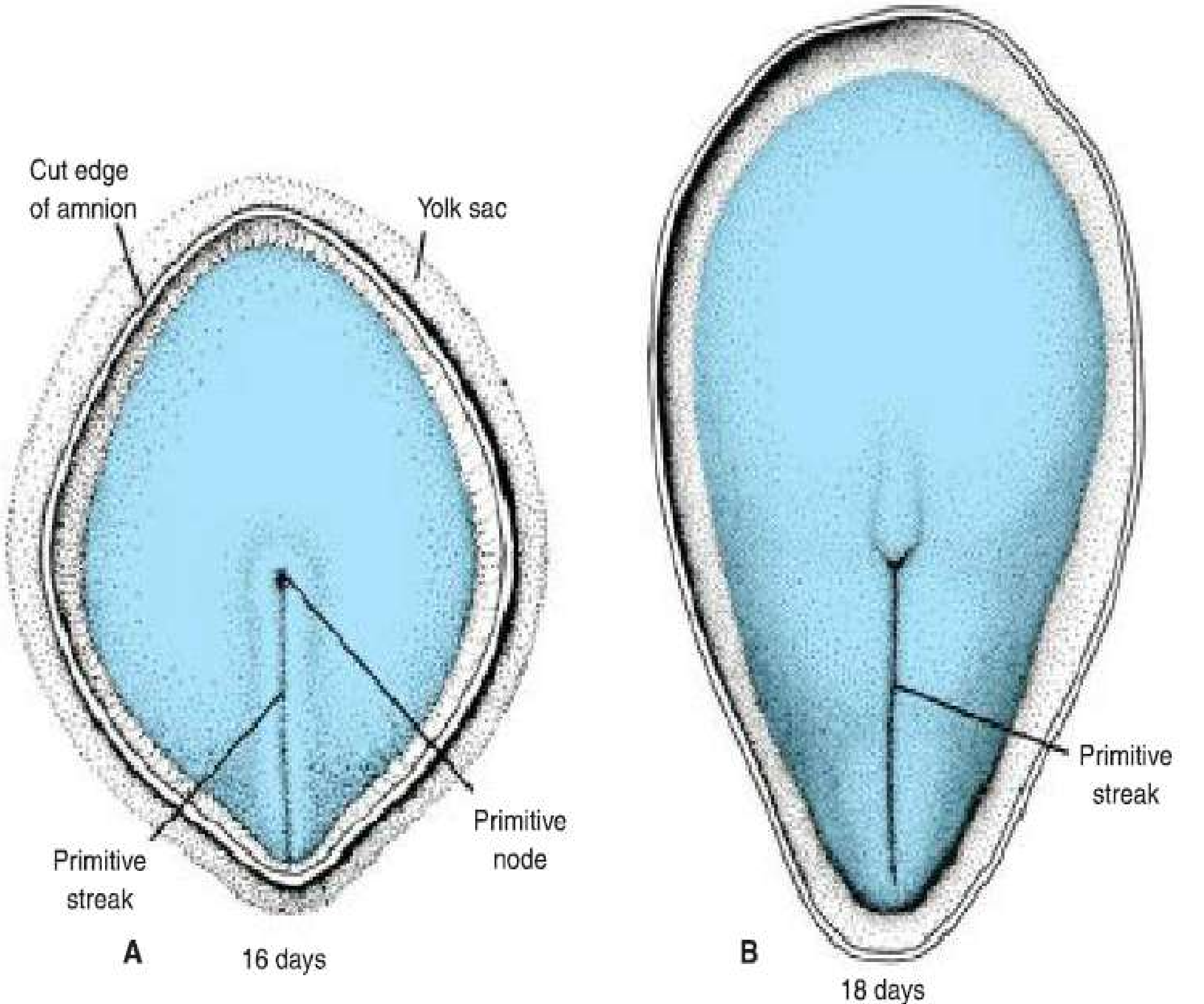
- The embryonic period, or period of organogenesis, occurs from the third to the eighth weeks of development

- It 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 bee established.
- The third to eighth weeks are the time when the majority of birth defects are induced.
- Prior to this time, any insult to the embryo results in its death and spontaneous abortion.

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 in 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.



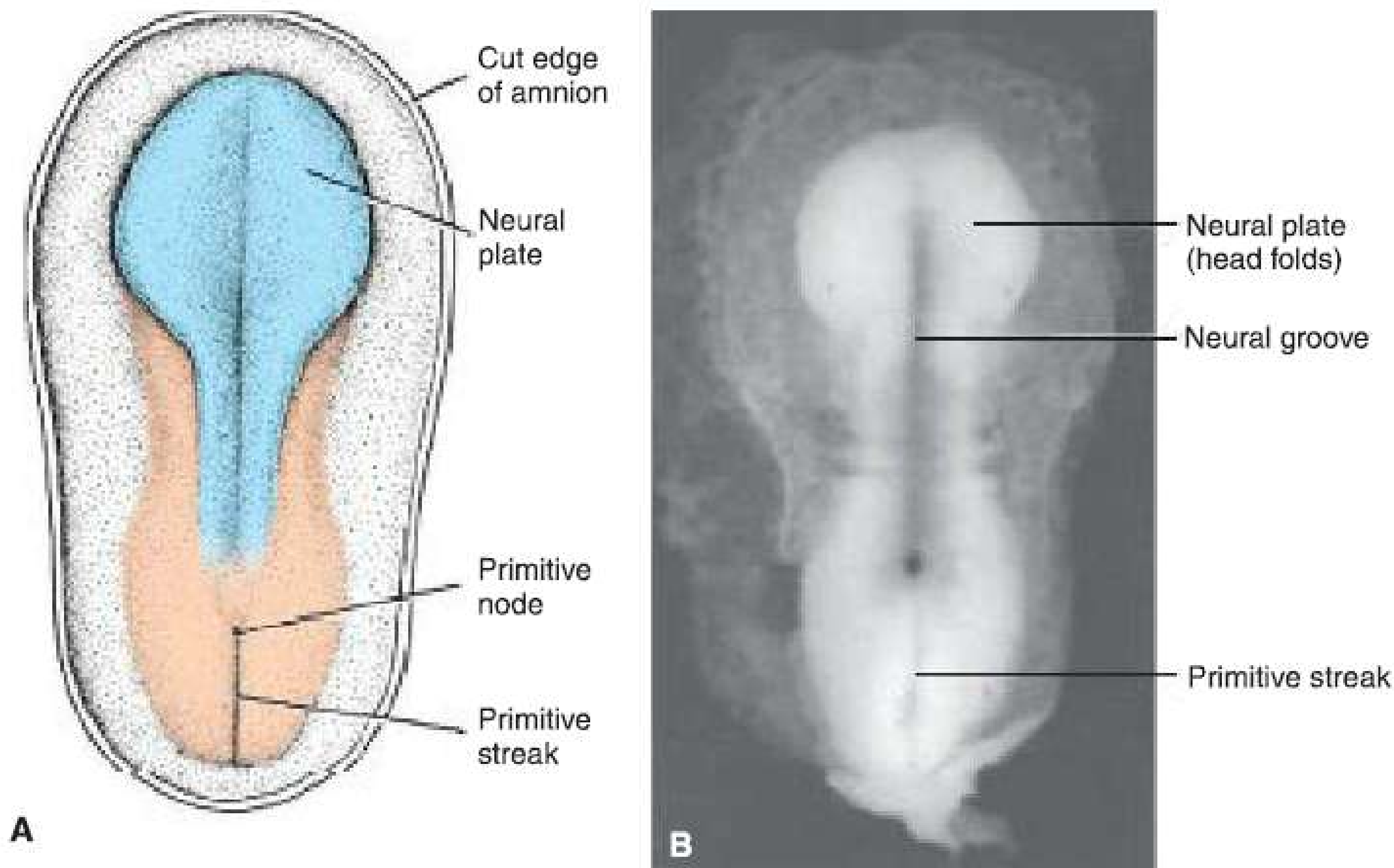
Cut edge
of amnion
Yolk sac
Primitive
node
Primitive
streak
A
16 days
Primitive
streak
B
18 days

Neurulation

- Neurulation is the process whereby the neural plate forms the neural tube

- As the neural plate lengthens, its lateral edges elevate to form neural folds,

  and the depressed mid region forms the neural groove .

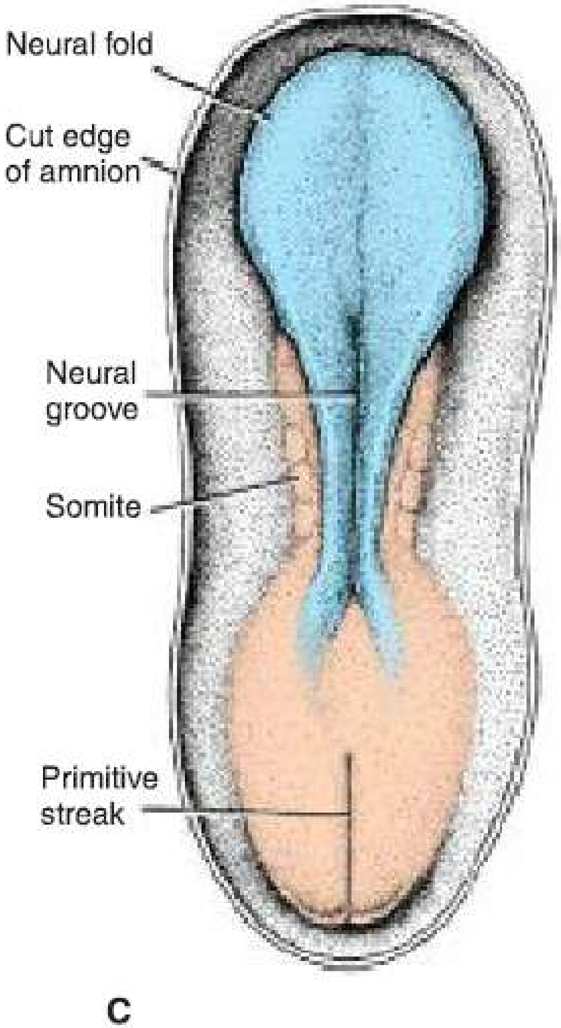

Cut edge of amnion
Neural plate
Primitive node
Primitive streak
A
Neural plate (head folds)
Neural groove
Primitive streak
B

19 days

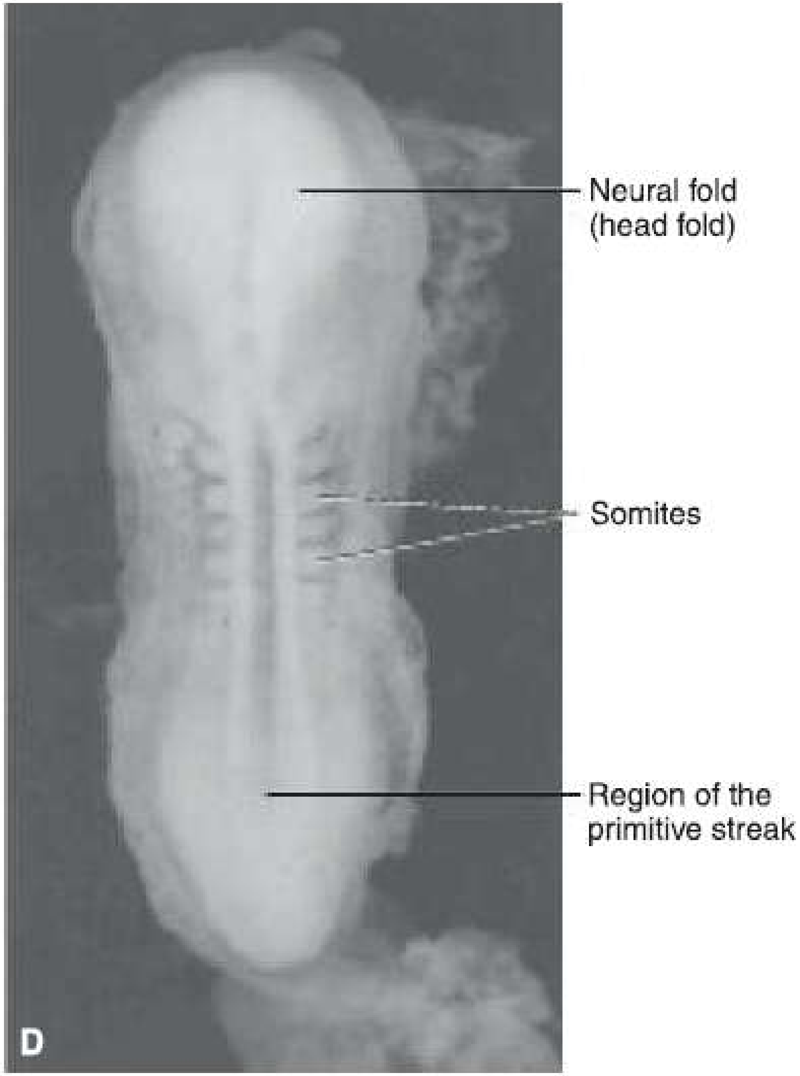
- Gradually, the neural folds approach each other in the midline, where they fuse .

- Fusion begins in the cervical region (fifth somite) and proceeds cranially and caudally.

- As a result, the neural tube is formed.



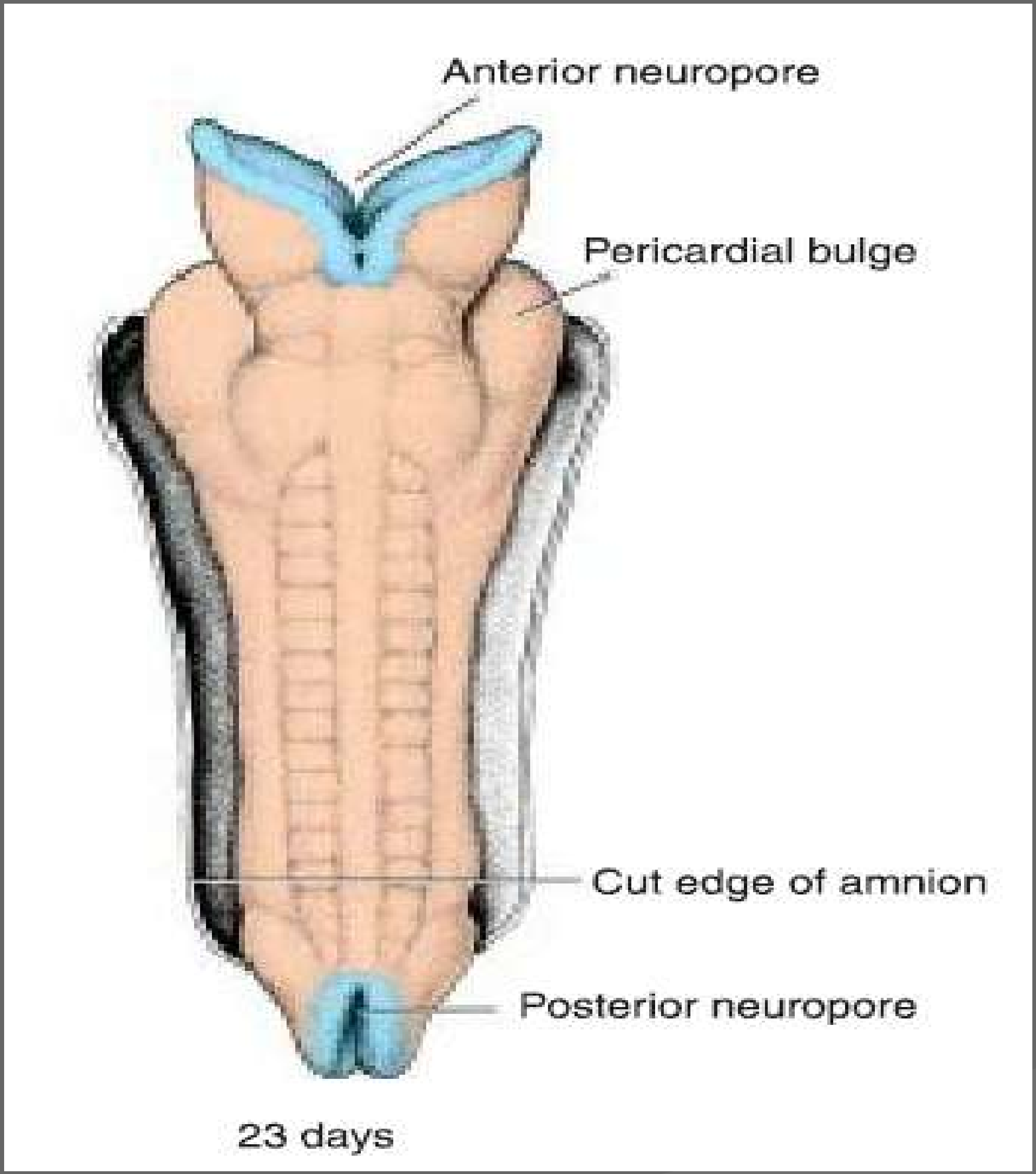
20 days



20 days

- 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.

- Closure of the cranial neuropore occurs at day 25 whereas the posterior neuropore closes at day 28 .


Anterior neuropore
Pericardial bulge
Cut edge of amnion
Posterior neuropore
23 days

- 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 .

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 neighbors.

- These neural crest cells undergoes an epithelial-to-mesenchymal transition as it leaves the neuroectoderm by active migration and displacement to enter the underlying mesoderm.

NOTE:

- Mesoderm refers to cells derived from the epiblast .
- Mesenchyme refers to loosely organized embryonic connective tissue

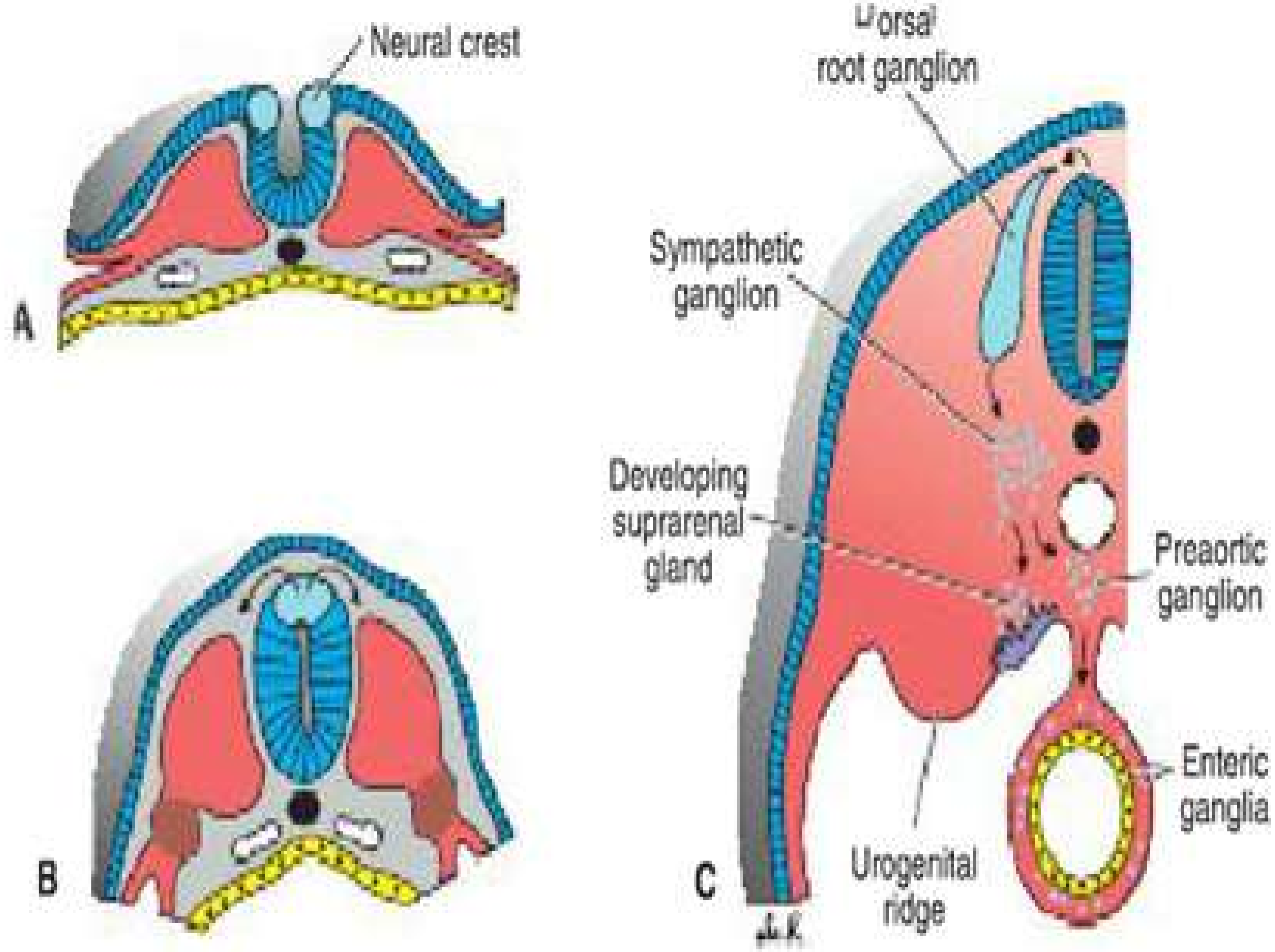
- Crest cells from the trunk region leave the neuroectoderm after closure of the neural tube and migrate along one of two pathways:

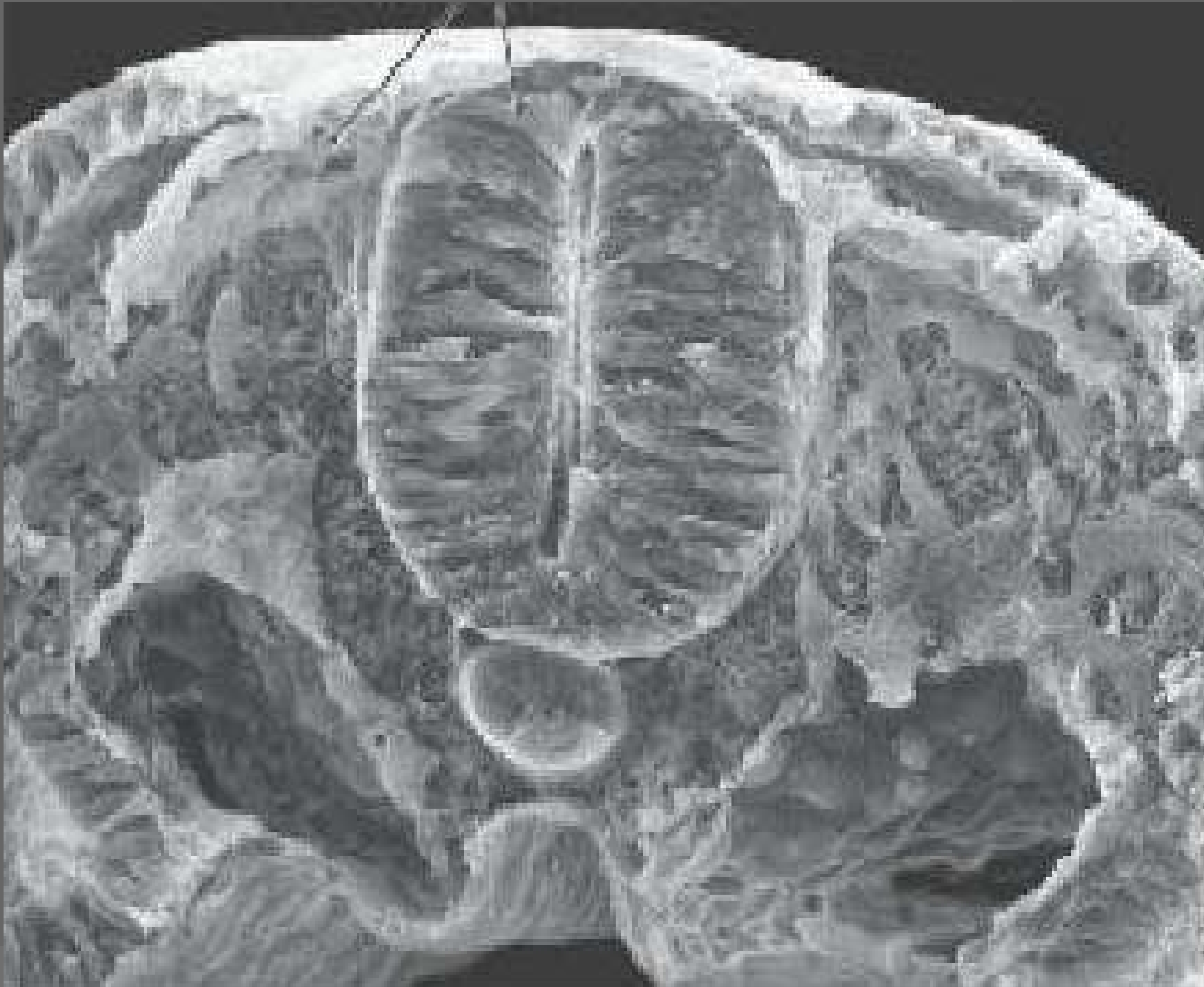
(1) **a dorsal pathway** through the dermis, where will enter the ectoderm through holes in the basal lamina to form melanocytes in the skin and hair follicles,

(2) **a ventral pathway** through the anterior half of each somite to become:

sensory ganglia, sympathetic neurons, Schwann cells, and cells of the adrenal medulla .

- NCC also form and migrate from cranial neural folds to contribute to the craniofacial skeleton as well as neurons for cranial ganglia, glial cells, melanocytes, and other cell types.


Neural crest
A
B
ᒧorsal
root ganglion
Sympathetic
ganglion
Developing
suprarenal
gland
Preaortic
ganglion
Enteric
ganglia
Urogenital
ridge
C

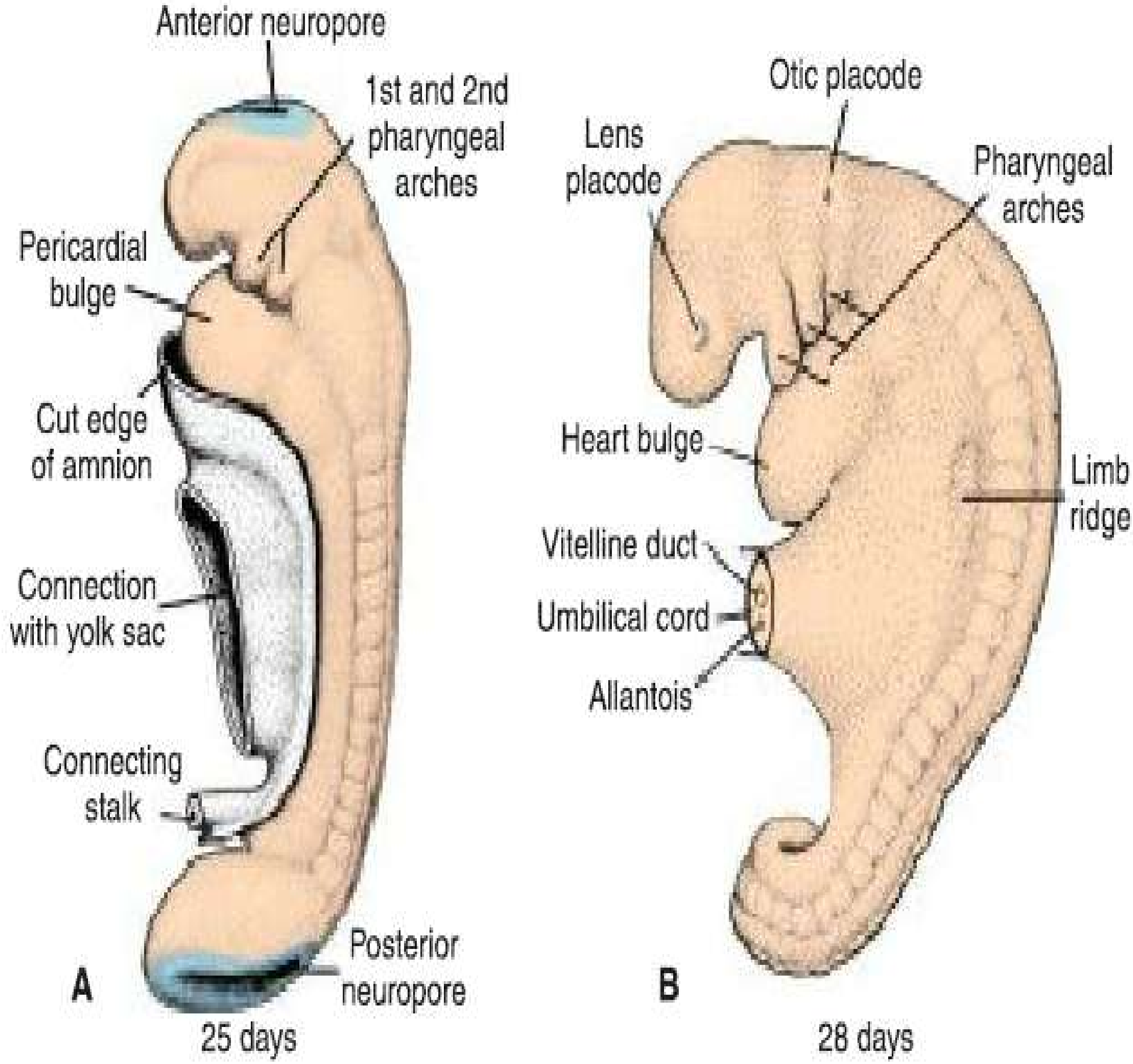


- NCC are so fundamentally important and contribute to so many organs and tissues that they are sometimes referred to as the fourth germ layer.
- They are also involved in at least one-third of all birth defects and manycancers,

- 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



Anterior neuropore
1st and 2nd pharyngeal arches
Pericardial bulge
Cut edge of amnion
Connection with yolk sac
Connecting stalk
Posterior neuropore
A
25 days
Otic placode
Lens placode
Pharyngeal arches
Heart bulge
Limb ridge
Vitelline duct
Umbilical cord
Allantois
B
28 days

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

- The central nervous system
- The peripheral nervous system
- The sensory epithelium of the ear, nose, and eye
- The epidermis, including the hair and nails
- The subcutaneous glands
- The mammary glands
- The pituitary gland
- 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 the 17th day, cells close to the midline proliferate and form as **paraxial mesoderm** .

- More laterally, the mesoderm layer 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 layer continuous with mesoderm covering the amnion, known as **the somatic or parietal** mesoderm layer
- 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

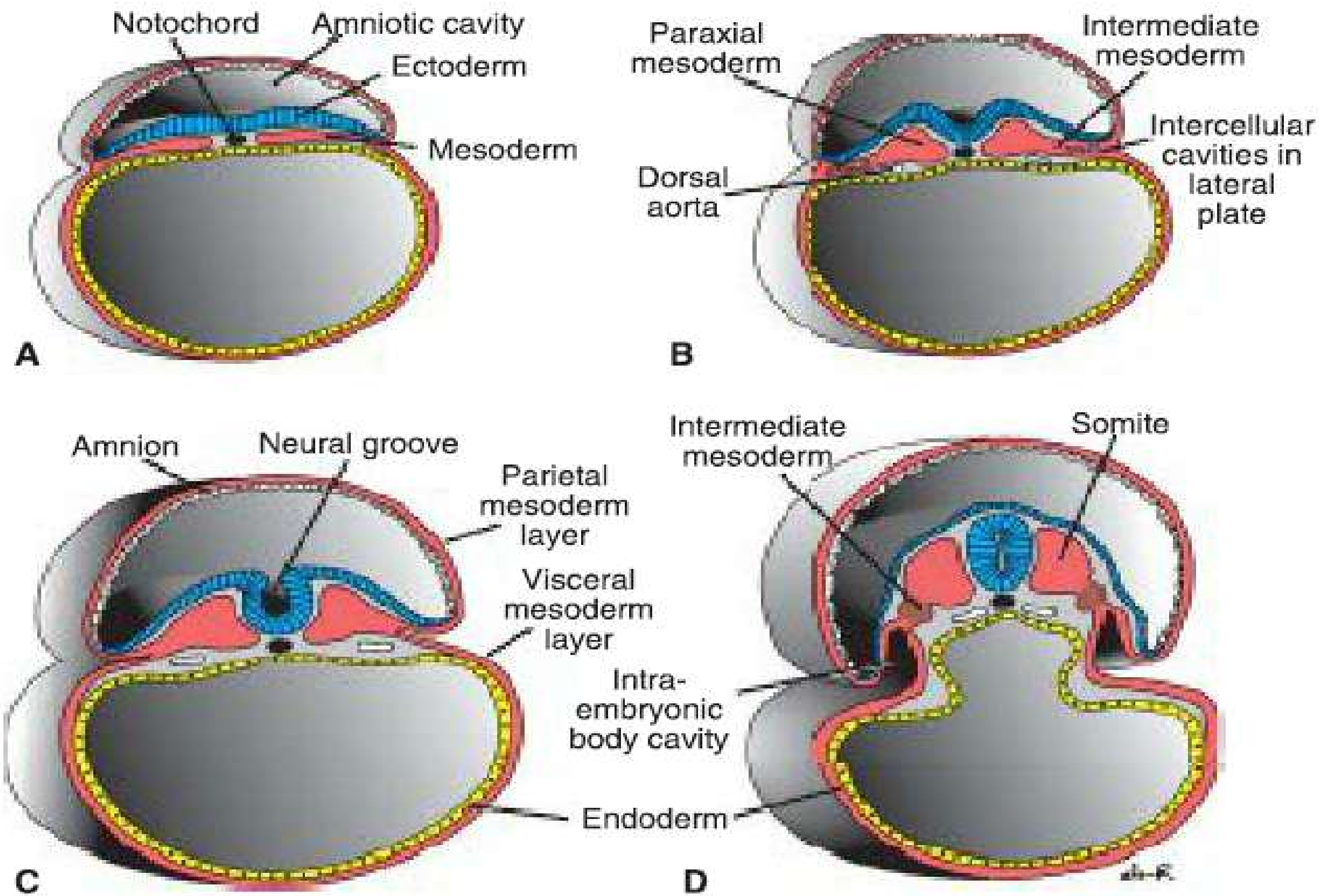
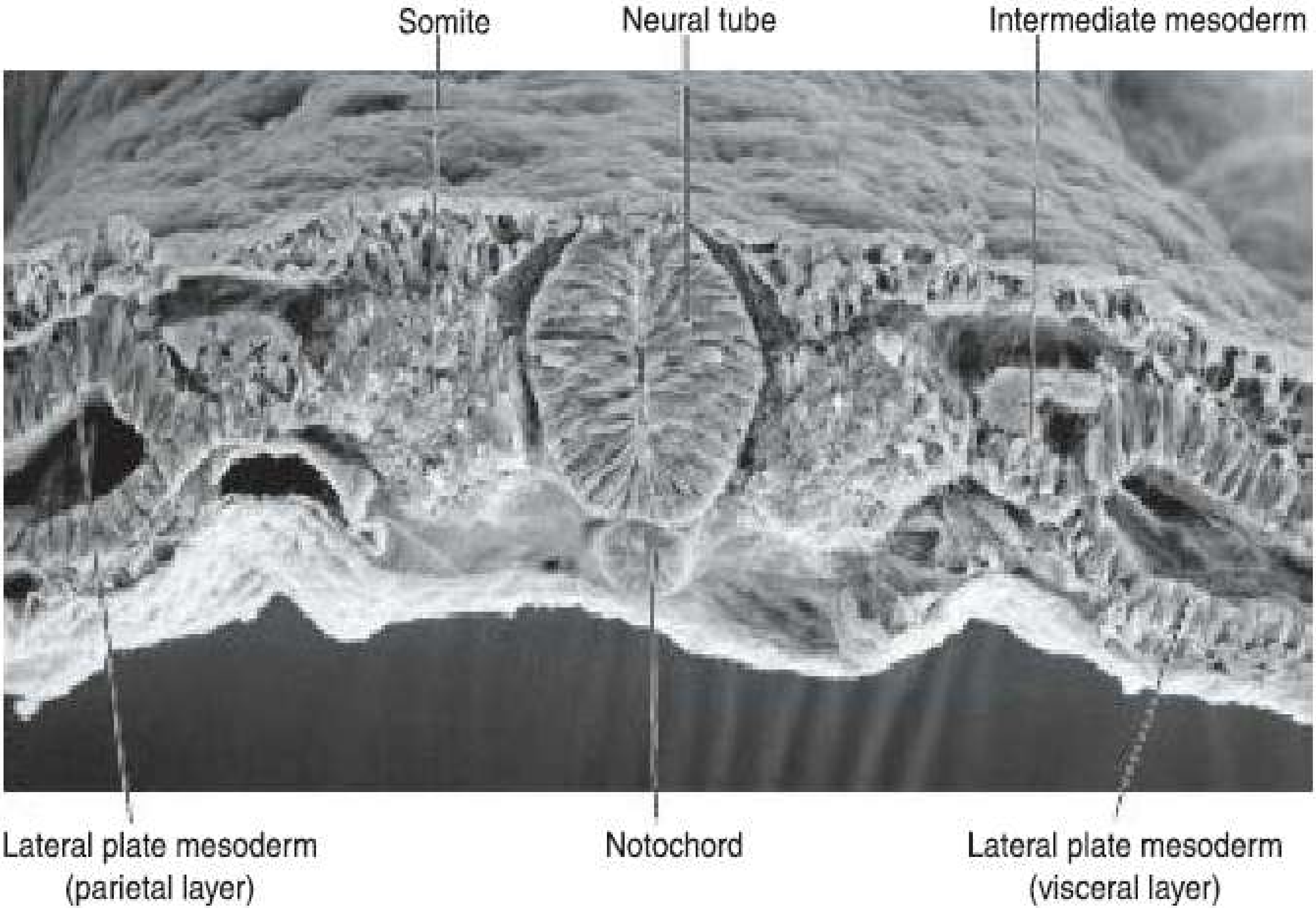


FIGURE 6.8 Transverse sections showing development of the mesodermal germ layer. **A.** Day 17. **B.** Day 19. **C.** Day 20. **D.** Day 21. The thin mesodermal sheet gives rise to paraxial mesoderm (future somites), intermediate mesoderm (future excretory units), and the lateral plate, which is split into parietal and visceral mesoderm layers lining the intraembryonic cavity.

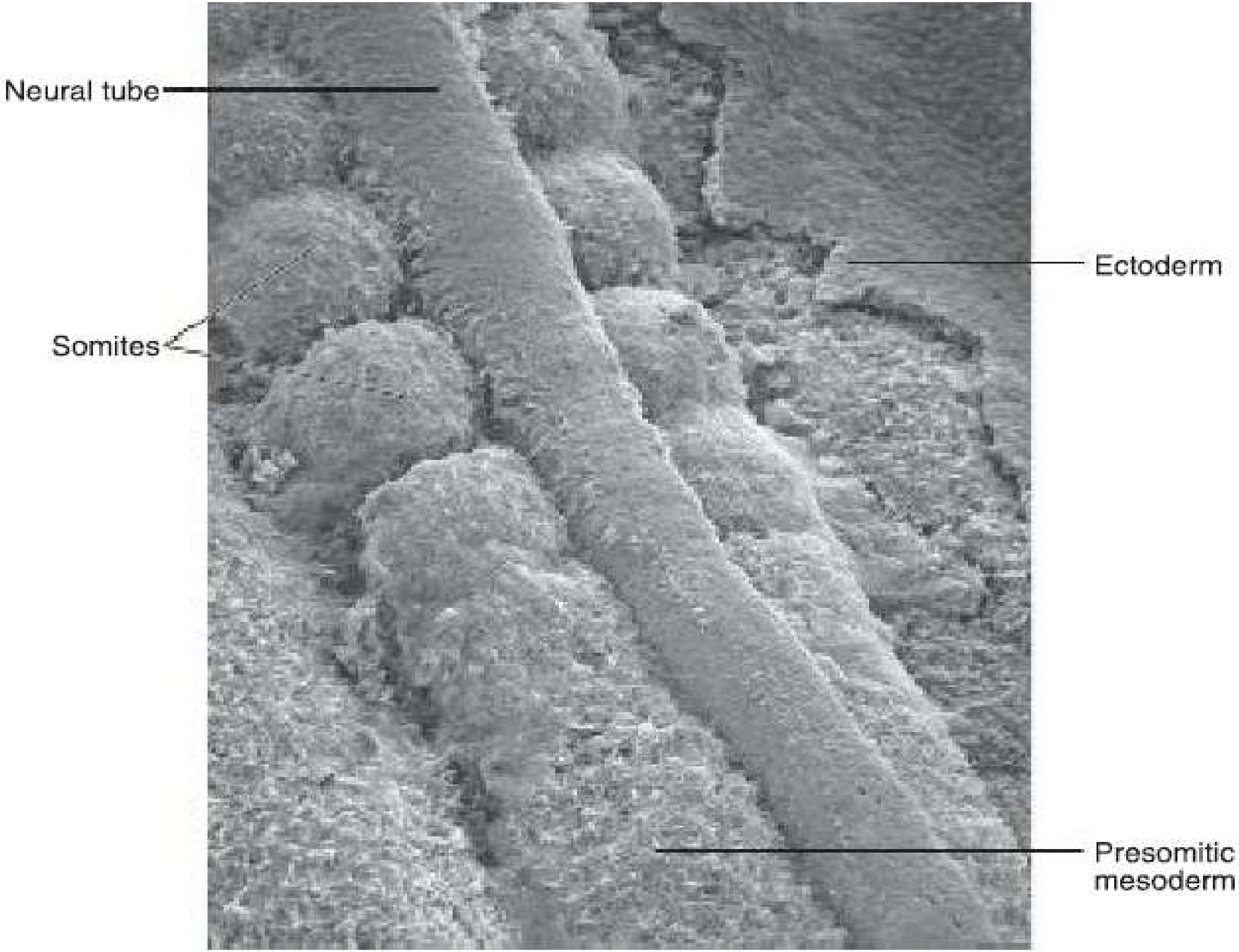


IGURE 6.9 Cross section through the somites and neural tube showing the organization of the paraxia
nesoderm into somites and intermediate and lateral plate mesoderm.

Paraxial Mesoderm

- By the beginning of the third week, paraxial mesoderm begins to be 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 segmentation of the neural plate into neuromeres and contribute to mesenchyme in the head
- From the occipital region caudally, somitomeres further organize into somites.


Neural tube
Ectoderm
Somites
Presomitic mesoderm

- The first pair of somites arises in the occipital region of the embryo at the 20th day .
- 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 .

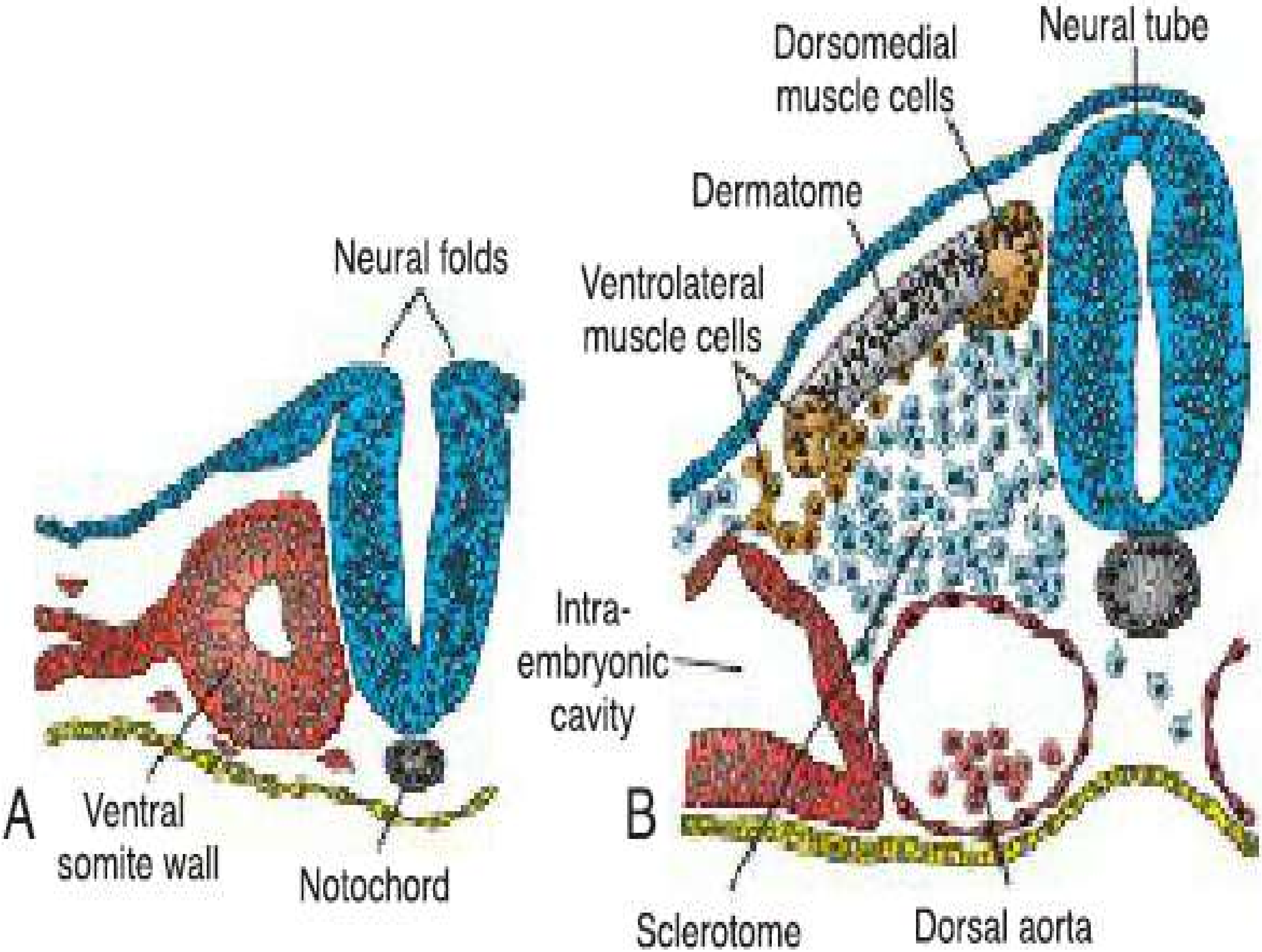
- There are 4 occipital, 8 cervical, 12 thoracic, 5 lumbar5 sacral, and 8 to 10 coccygeal pairs.
- The first occipital and the last five to seven coccygeal somites later disappear, whereas the remaining somites form the axial skeleton
- The age of an embryo can be accurately determined during this early time period by counting somites .

Somite Differentiation

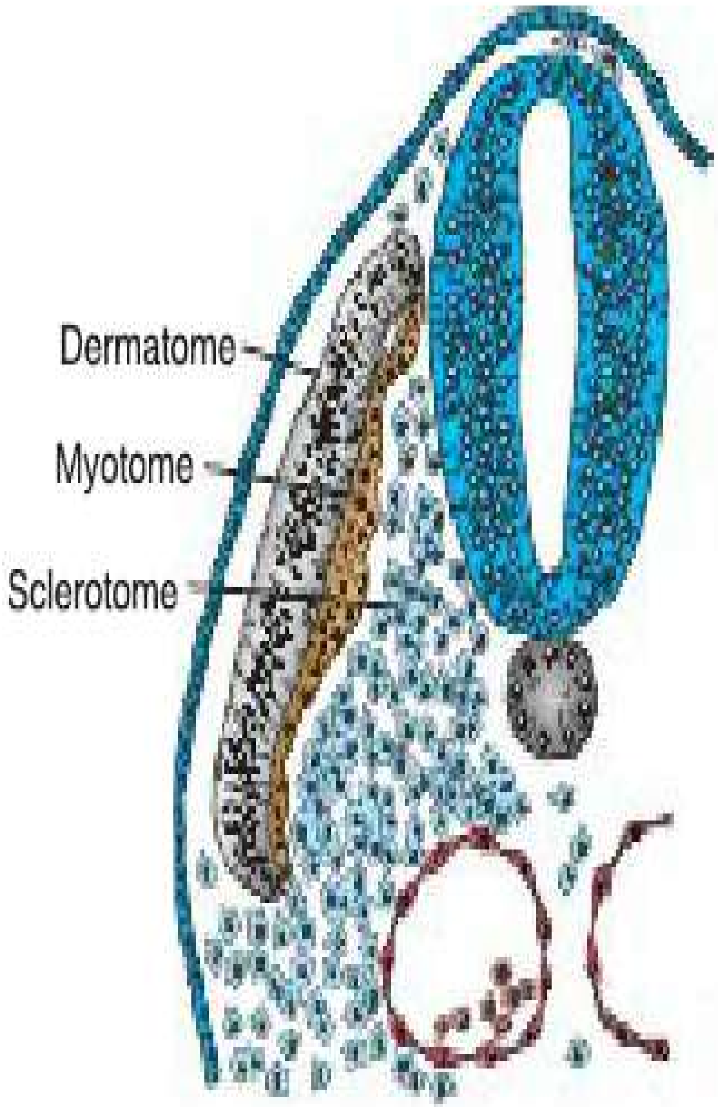
- When somites first form from presomitic mesoderm, they exist as a ball of mesoderm (fibroblast-like) cells.
- These cells then undergo a process of epithelization and arrange themselves in a donut shape around a small lumen

- By the beginning of the fourth week, cells in the ventral and medial walls of the somite lose their epithelial characteristics, become mesenchymal (fibroblast-like) again, and shift their position to surround the neural tube and notochord.

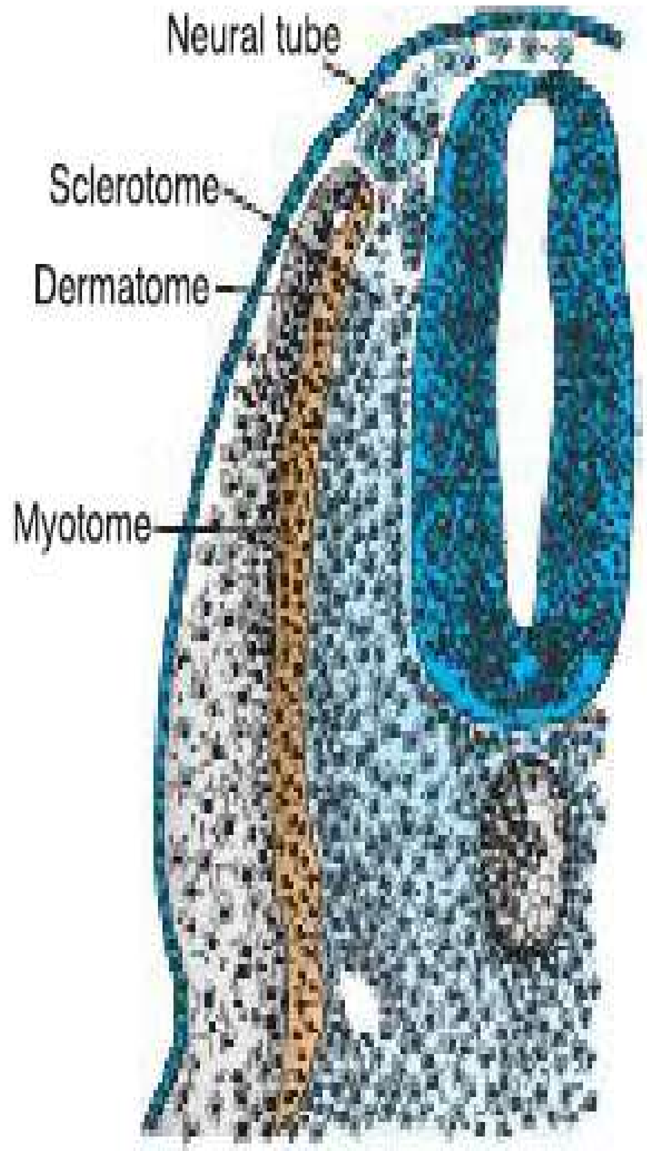
- These cells form the **sclerotome** that will differentiate into the vertebrae and ribs.
- Cells at the dorsomedial and ventrolateral edges of the upper region of the somite form precursors for muscle cells, whereas cells between these two groups form the dermatome .



Neural folds
A
Ventral
somite wall
Notochord
Dorsomedial
muscle cells
Neural tube
Dermatome
Ventrolateral
muscle cells
Intra-
embryonic
cavity
B
Sclerotome
Dorsal aorta


Dermatome
Myotome
Sclerotome

C


Neural tube
Sclerotome
Dermatome
Myotome

D

- Cells from both muscle precursor groups become mesenchymal again and migrate beneath the dermatome to create the dermomyotome .

- In addition, cells from the ventrolateral edge migrate into the parietal layer of lateral plate mesoderm to form most of the musculature for the body wall (external and internal oblique and transversus abdominis muscles) and most of the limb muscles .

- Cells in the dermomyotome ultimately form dermis for the skin of the back and muscles for the back, body wall (intercostal muscles), and some limb muscles.

- Each myotome and dermatome retains its innervation from its segment of origin, no matter where the cells migrate.
- Hence, each somite forms its own sclerotome (the tendon cartilage and bone component), its own myotome (providing the segmental muscle component), and its own dermatome, which forms the dermis of the back.
- Each myotome and dermatome also has its own segmental nerve component

Third to Eighth Weeks: The Embryonic Period 7

Dr. Sawsan S. Shurrab

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), but 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 (somatic) and visceral (splanchnic) layers, which line the intraembryonic cavity and surround the organs, respectively .

- Mesoderm from the parietal layer, together with overlying ectoderm, forms the lateral body wall folds

- These folds, together with the head (cephalic) and tail (caudal) folds, close the ventral body wall.

- The parietal layer of lateral plate mesoderm then forms the dermis of the skin in the body wall and limbs, the bones and connective tissue of the limbs, and the sternum.

- In addition, sclerotome and muscle precursor cells that migrate into the parietal layer of lateral plate mesoderm form the costal cartilages, limb muscles, and most of the body wall muscles .

- The visceral layer of lateral plate mesoderm, together with embryonic endoderm, forms the wall of the gut tube.

- Mesoderm cells of the parietal layer surrounding the intraembryonic cavity 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 form a thin serous membrane around each organ .

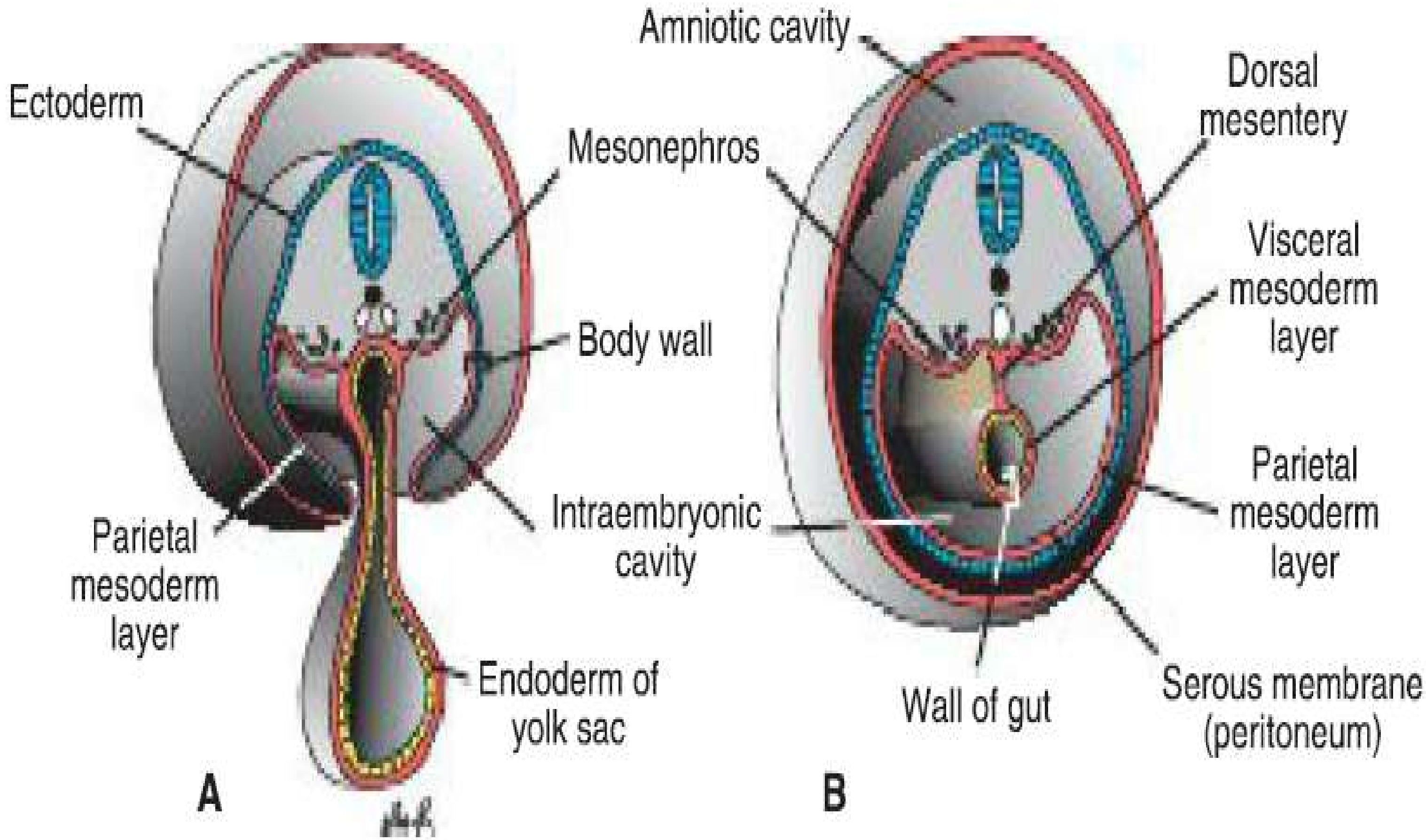
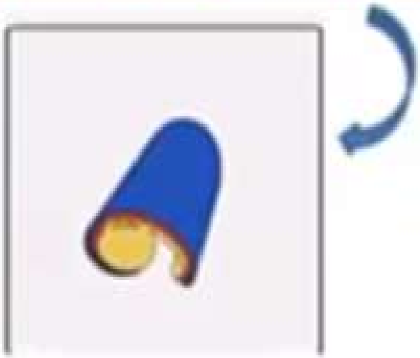


FIGURE 6.13 **A.** Cross section through a 21-day embryo in the region of the mesonephros showing parietal and visceral mesoderm layers. The intraembryonic cavities communicate with the extraembryonic cavity (chorionic cavity). **B.** Section at the end of the fourth week. Parietal mesoderm and overlying ectoderm form the ventral and lateral body wall. Note the peritoneal (serous) membrane.

Folding of the embryonic disc

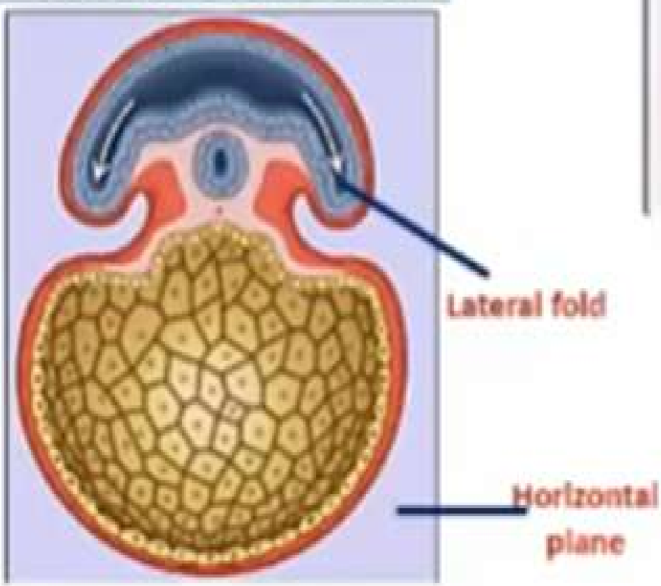
It is the ventral folding of the embryonic disc by the end of the 3rd week (20th day).

- The embryo will be changed from a tri-laminar disc into a cylinder.



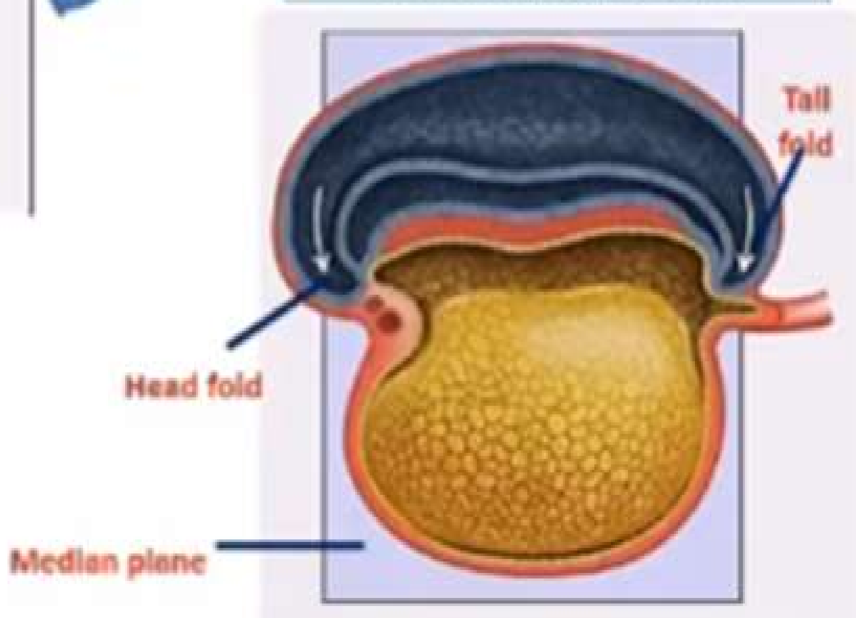
Folding in the horizontal plane

It results in the development of two lateral body folds.



Folding in the median plane

It results in development of the cranial (head) and caudal (tail) folds.



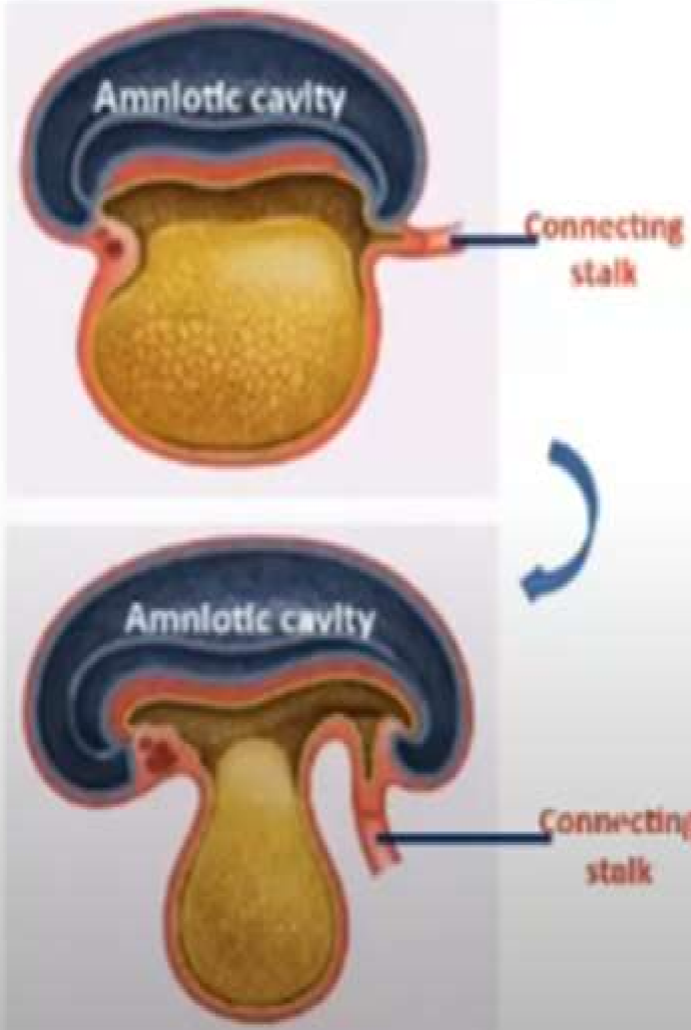
Folding is caused by different rates of growth of the embryonic structures :

- Rapid growth of the cranial end of neural tube,
- Growth of axial part of the embryo faster than its periphery, and
- Enlargement of the amniotic cavity.

Results of folding:

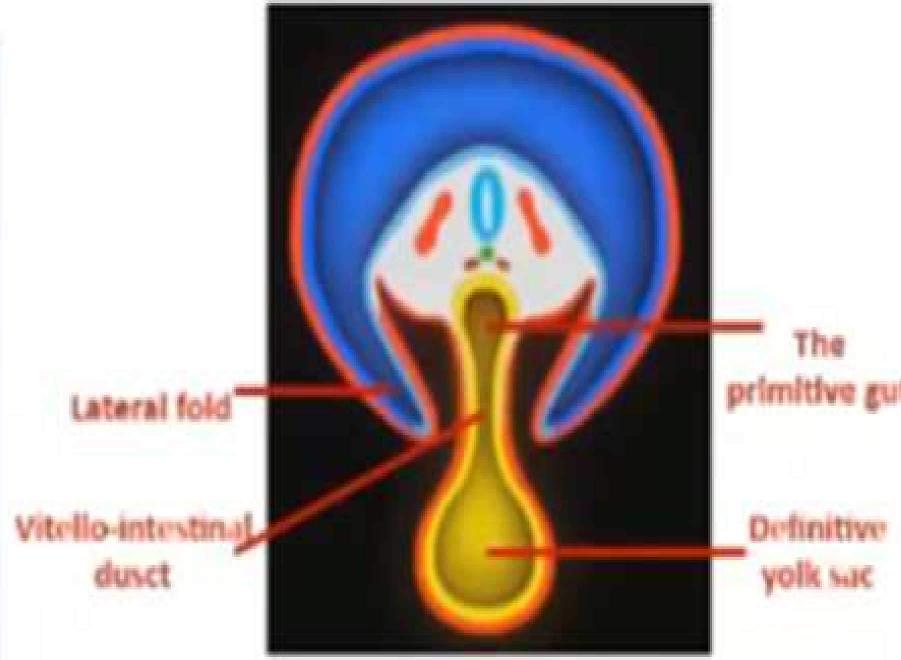
1) After folding, the embryonic disc becomes cylindrical and the embryo gains its characteristic features:

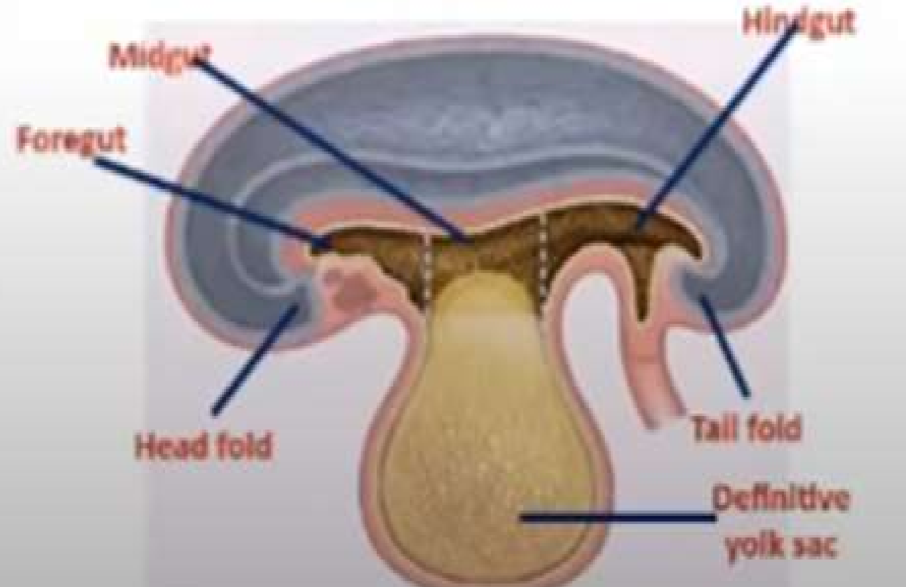
- A) the amniotic cavity almost completely surrounds the embryo.
- B) the connecting stalk comes to lie on the ventral aspect of the embryo, then it forms the umbilical cord.



2) Formation of the gut tube:

- As a result of the two lateral folds, the dorsal part of the endodermally-lined yolk sac is incorporated into the body of the embryo forming the primitive gut tube.
- As a result of the cranial and caudal folds, the primitive gut is divided into:
  - Foregut: inside the cranial fold.
  - Hindgut: inside the caudal fold.
  - Midgut: between foregut and hindgut.
- The part of the yolk sac which remains outside the embryo forms the definitive yolk sac which is connected to the gut by the vitello-intestinal duct.

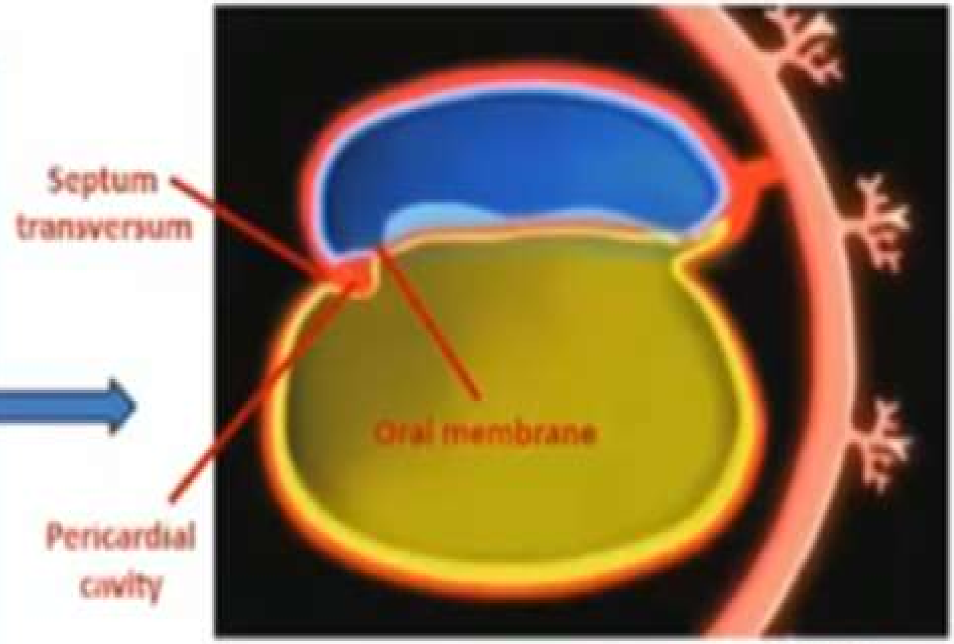


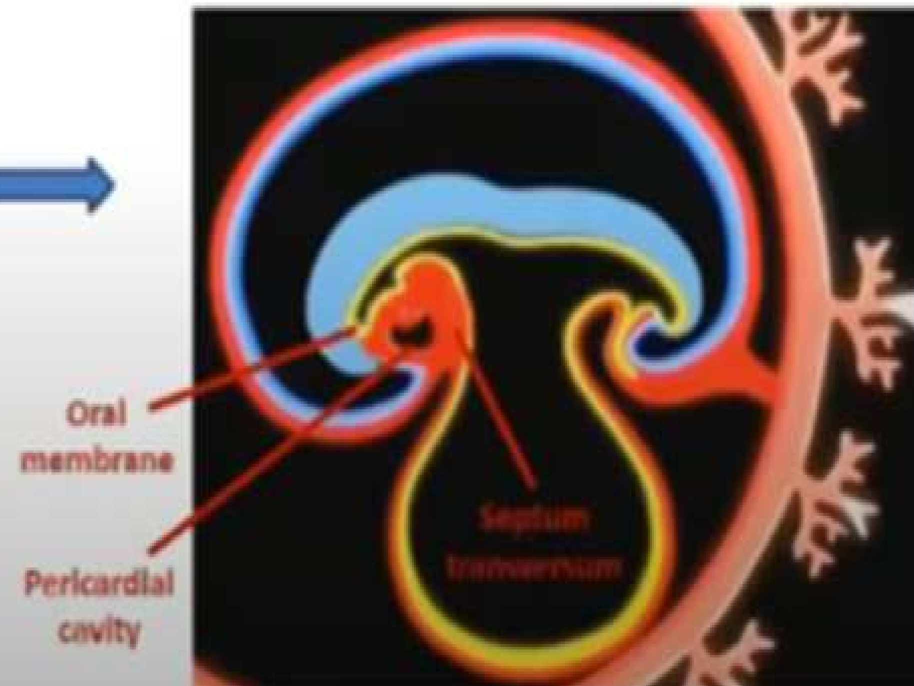


3) Change of positions of certain structures:

- Notice the arrangement of the septum transversum, pericardial cavity, and the oral membrane:
- Before folding: septum transversum is cranial, the oral membrane is caudal, and the pericardial cavity lies between them.
- After the cranial fold: the oral membrane becomes cranial, the septum transversum becomes caudal, and the pericardial cavity lies between them (caudal to oral membrane, and cranial to septum transversum).

Septum transversum forms the future diaphragm





DERIVATIVES OF THE ENDODERMAL 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.

- Lengthening of the neural tube now causes the embryo to curve into the fetal position as the head and tail regions (folds) move ventrally.

- Simultaneously, two lateral body wall folds form and also move ventrally to close the ventral body wall.

- As the head and tail and two lateral folds move ventrally, they pull the amnion down with them, such that the embryo lies within the amniotic cavity .

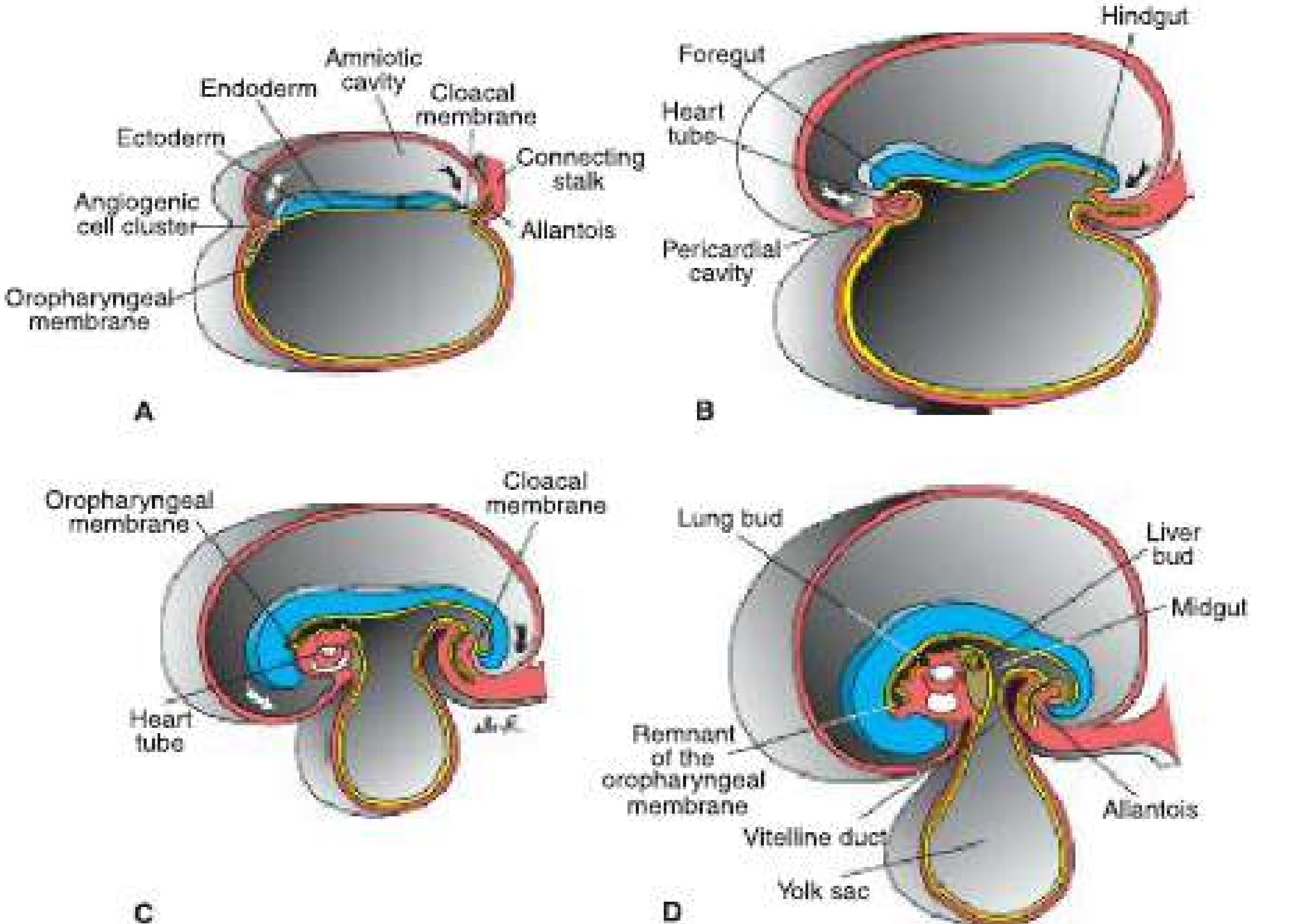


FIGURE 6.17 Sagittal midline sections of embryos at various stages of development to demonstrate cephalocaudal folding and its effect on position of the endoderm-lined cavity. **A.** 17 days. **B.** 22 days. **C.** 24 days. **D.** 28 days. *Arrows*, head and tail folds.

- The ventral body wall closes completely except for the umbilical region where the connecting stalk and yolk sac duct remain attached .

- Failure of the lateral body folds to close the body wall results in ventral body wall defects .

- As a result of cephalocaudal growth and closure of the lateral body wall folds, a continuously larger portion of the endodermal germ layer is incorporated into the body of the embryo to form the gut tube.

- The tube is divided into three regions: foregut, midgut, and hindgut .

- The midgut communicates with the yolk sac by way of a broad stalk, the vitelline (yolk sac) duct.

- This duct is wide initially, but with further growth of the embryo, it becomes narrow and much longer .

- At its cephalic end, the foregut is temporarily bounded by an ectodermal-endodermal membrane called the oropharyngeal membrane.

- This membrane separates the stomodeum, the primitive oral cavity derived from ectoderm, from the pharynx, a part of the foregut derived from endoderm.

- In the fourth week, the oropharyngeal membrane ruptures, establishing an open connection between the oral cavity and the primitive gut.

- The hindgut also terminates temporarily at an ectodermal-endodermal membrane, the cloacal membrane .

- This membrane separates the upper part of the anal canal, derived from endoderm, from the lower part, called the proctodeum, which is formed by an invaginating pit lined by ectoderm.

- The membrane breaks down in the seventh week to create the opening for the anus.

- Another important result of cephalocaudal growth 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 umbilical region

- The role of the yolk sac is not clear.
- It may function as a nutritive organ during the earliest stages of development prior to the estabilshment of blood vessels.
- It also contributes some of the first blood cells, although this role is very transitory.

- One of its main functions is to house germ cells that reside in its posterior wall and later migrate to the gonads to form eggs and sperm .

- 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,endoderm gives rise to the following:

- The epithelial lining of the respiratory tract.
- The parenchyma of the thyroid, parathyroids, liver, and pancreas .
- The reticular stroma of the tonsils and the thymus
- The epithelial lining of the urinary bladder and the urethra .
- The epithelial lining of the tympanic cavity and auditory tube .

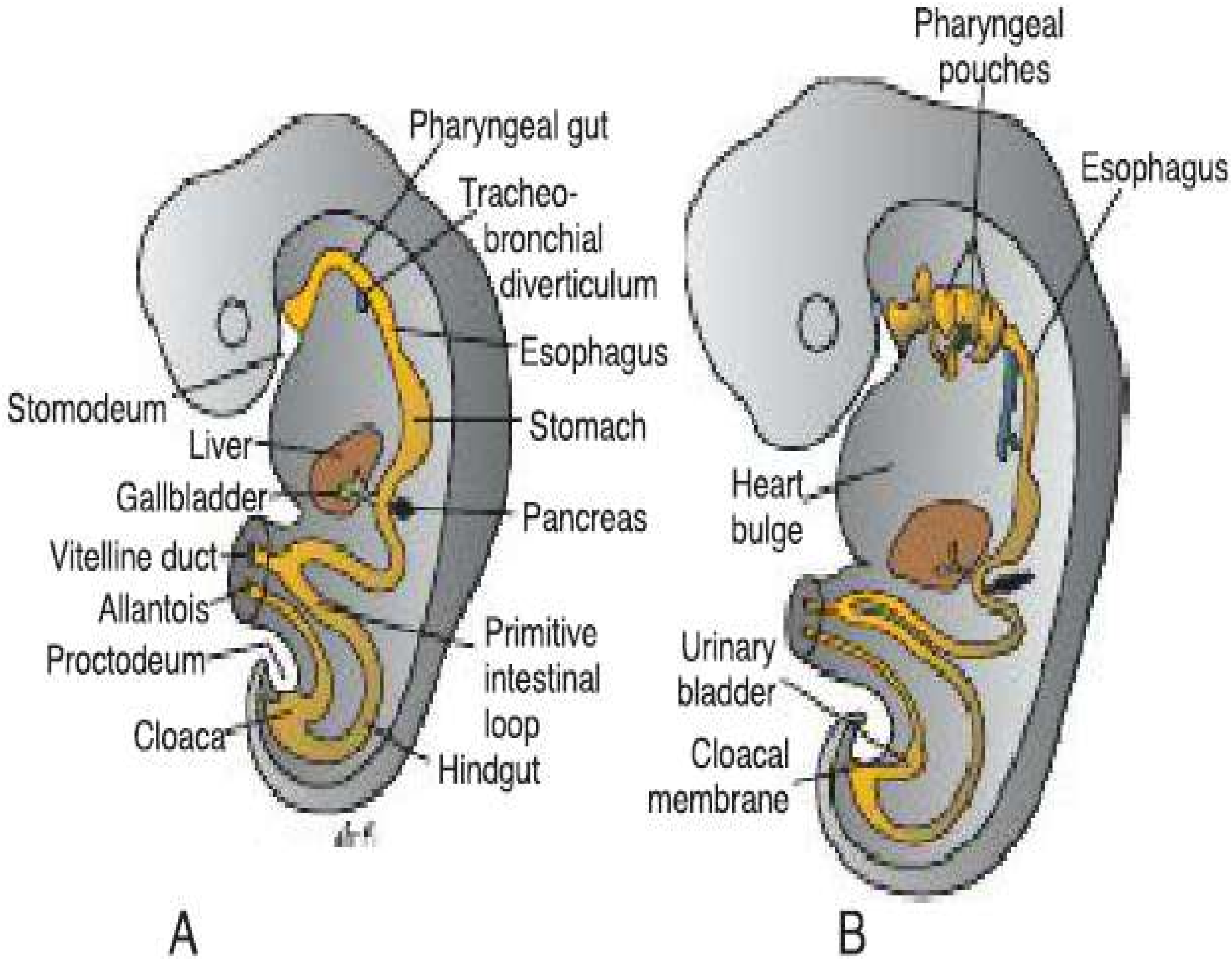


FIGURE 6.19 Sagittal sections through embryos showing derivatives of the endodermal germ layer. **A.** Pharyngeal pouches, epithelial lining of the lung buds and trachea, liver, gallbladder, and pancreas. **B.** The urinary bladder is derived from the cloaca and, at this stage of development, is in open connection with the allantois.

General Embryology,

Lecture XII,

Fetal Membranes & Placenta, part I

Fetal membranes & Placenta

- By the beginning of the 2nd month, the trophoblast is characterized by a great number of 2ry & tertiary villi that give it a radial appearance (Fig. 7.1).)
- The villi are anchored in the mesoderm of the chorionic plate and are attached peripherally to the maternal decidua by way of the outer cytotrophoblast shell. (Fig.7.2, A,C).
- During the following months, numerous small extensions sprout from existing villous stems into the surrounding lacunar or intervillous spaces. The syncytium & endothelial wall of the blood vessels are then the only layers that separate the maternal & fetal circulations (Fig. 7.2, *B & D)*.
- Frequently, the syncytium becomes very thin, & large pieces containing several nuclei may break off & drop into the intervillous blood lakes. These pieces, known as syncytial knots

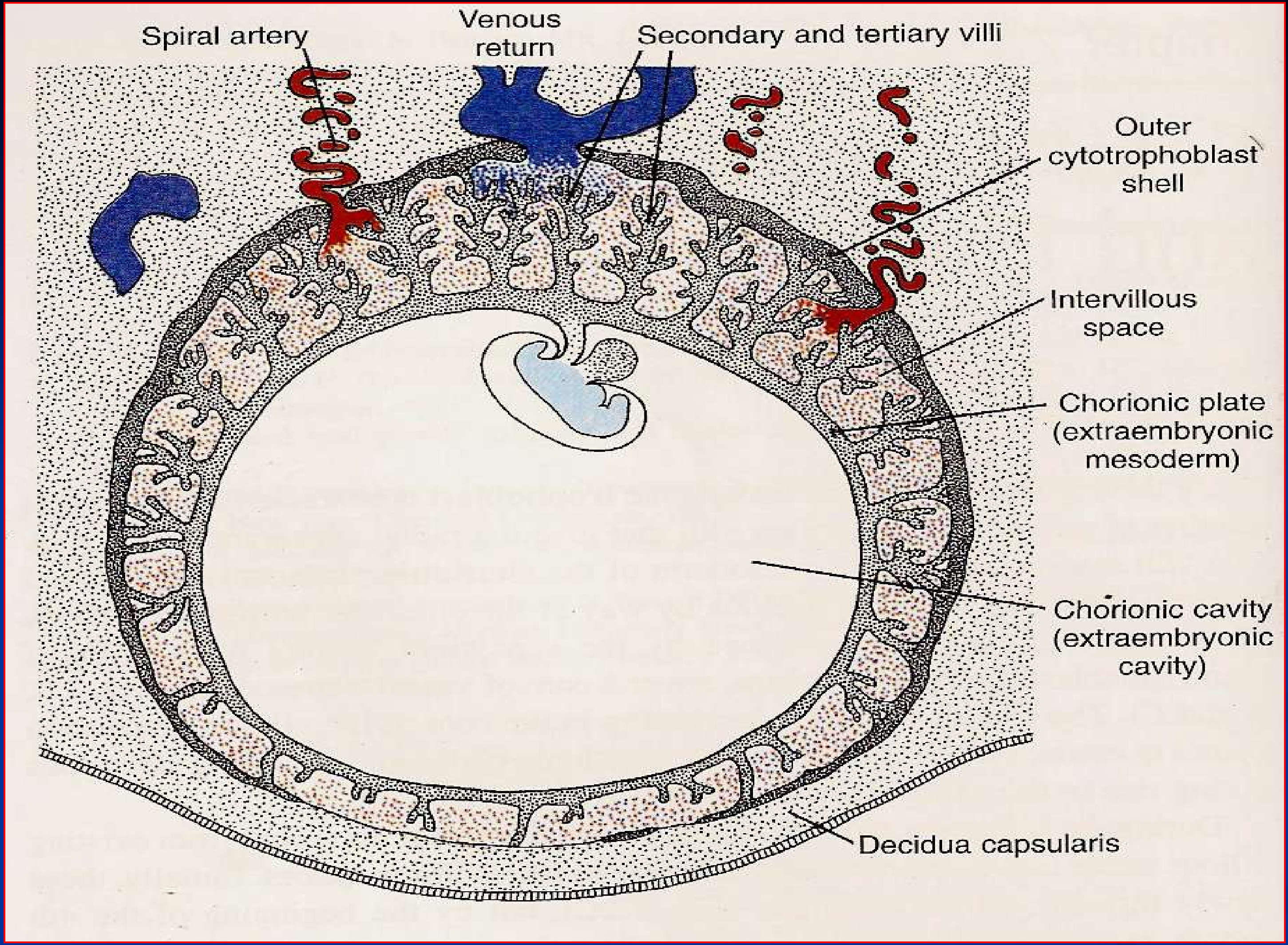


Figure 7.1. Schematic representation of a human embryo at i beginning of i 2nd month of development. At i embryonic pole, villi are numerous & well formed; at the apembryonic pore, they are few in number & poorly developed.

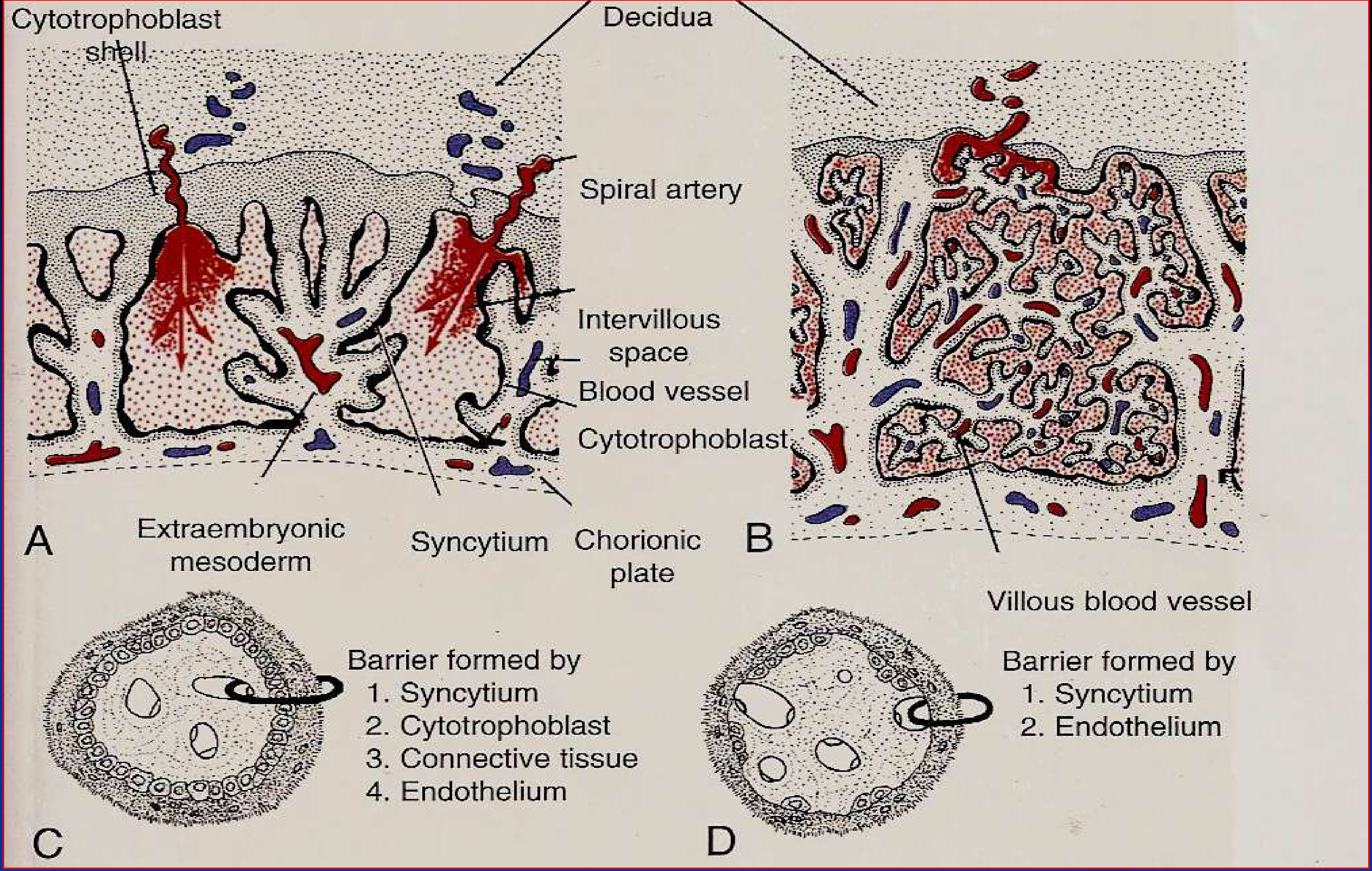


Figure 7.2. Structure *of* villi at various stages *of* development. A. During the 4th week B. During the 4th month. In many small villi the wall *of* the capillaries is in direct contact with the syncytium. C and D. Enlargement *of* the villus as shown in A and B, respectively.

Chorion Frondosum and Decidua Basalis

- As pregnancy advances, villi on i embryonic pole continue to grow and to form chorion frondosum (bushy chorion).
- by the 3rd month side of the chorion is smooth & is known as the chorion laeve (Figs. 7.3 and 7.4 *A)*.

- The decidua basalis_ which is over the chorion frondosum, has a layer, the decidual plate, is tightly connected to the chorion.
- The decidual layer over the abembryonic pole is known as the decidua capsularis (Fig. 7 *.4A)*. *Which* becomes stretched & degenerates lately.

- Subsequently, the chorion laeve comes into contact with the uterine wall (decidua parietalis), and the two fuse (Figs. 7.4-7.6), thereby obliterating the uterine lumen. Hence, the only portion of the chorion participating in the exchange process is the chorion frondosum, which, together with the decidua basalis, makes up the placenta.
- Similarly, fusion of the amnion and chorion to form the amniochorionic membrane obliterates the chorionic cavity (Fig. 7 .4, *A &B)*.

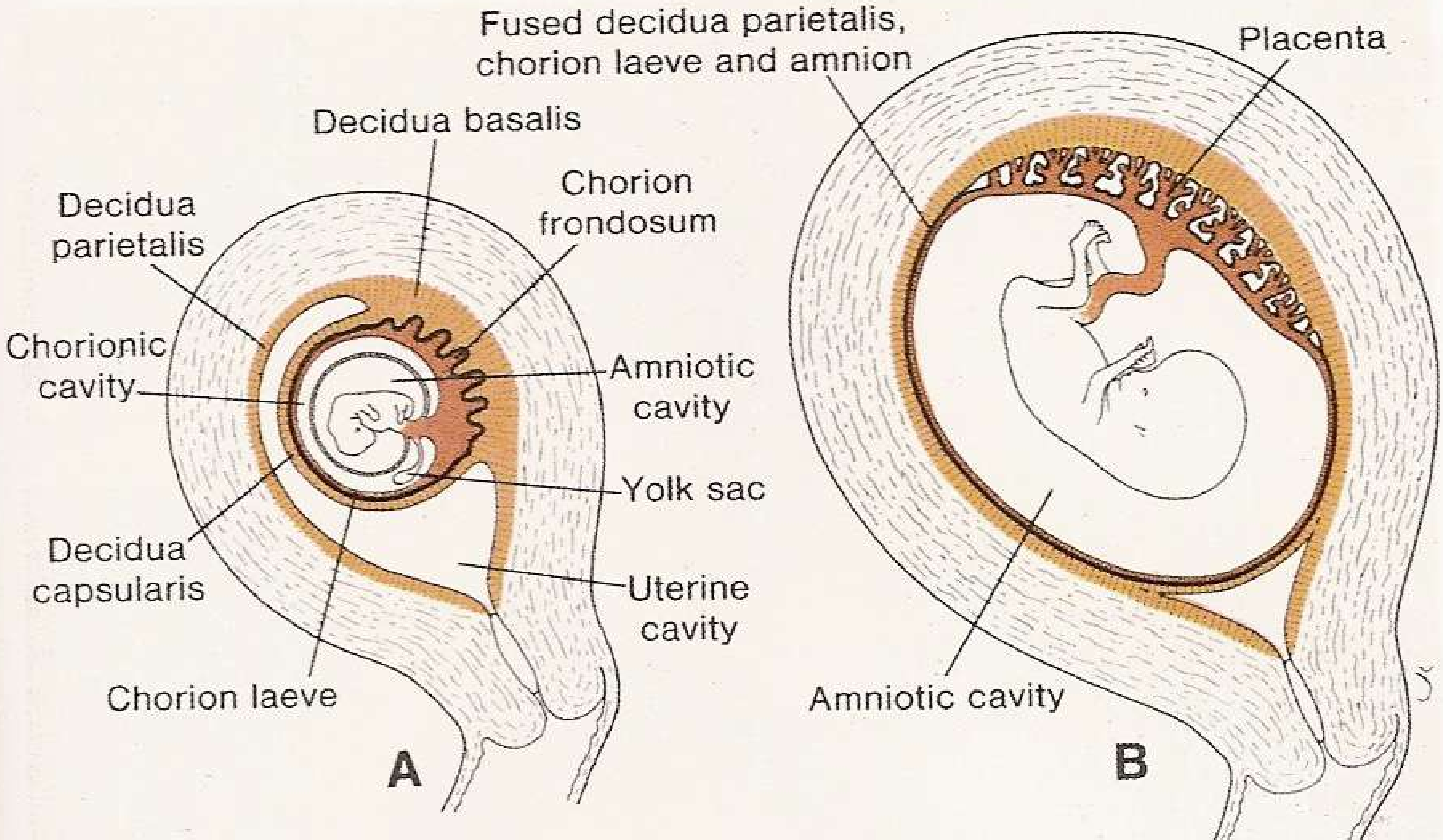


Fig. 7.4. Relation of fetal membranes & wall of i uterus. A. End of i 2nd mo. Note i yolk sac in i chorionic cavity bet. i amnion & chorion. At the abembryonic pole, villi have disappeared (chorion laeve). B. End of i 3rd m. The amnion & chorion have fused, & i uterine cavity is obliterated by fusion of i chorion laeve & i decidua parietalis.

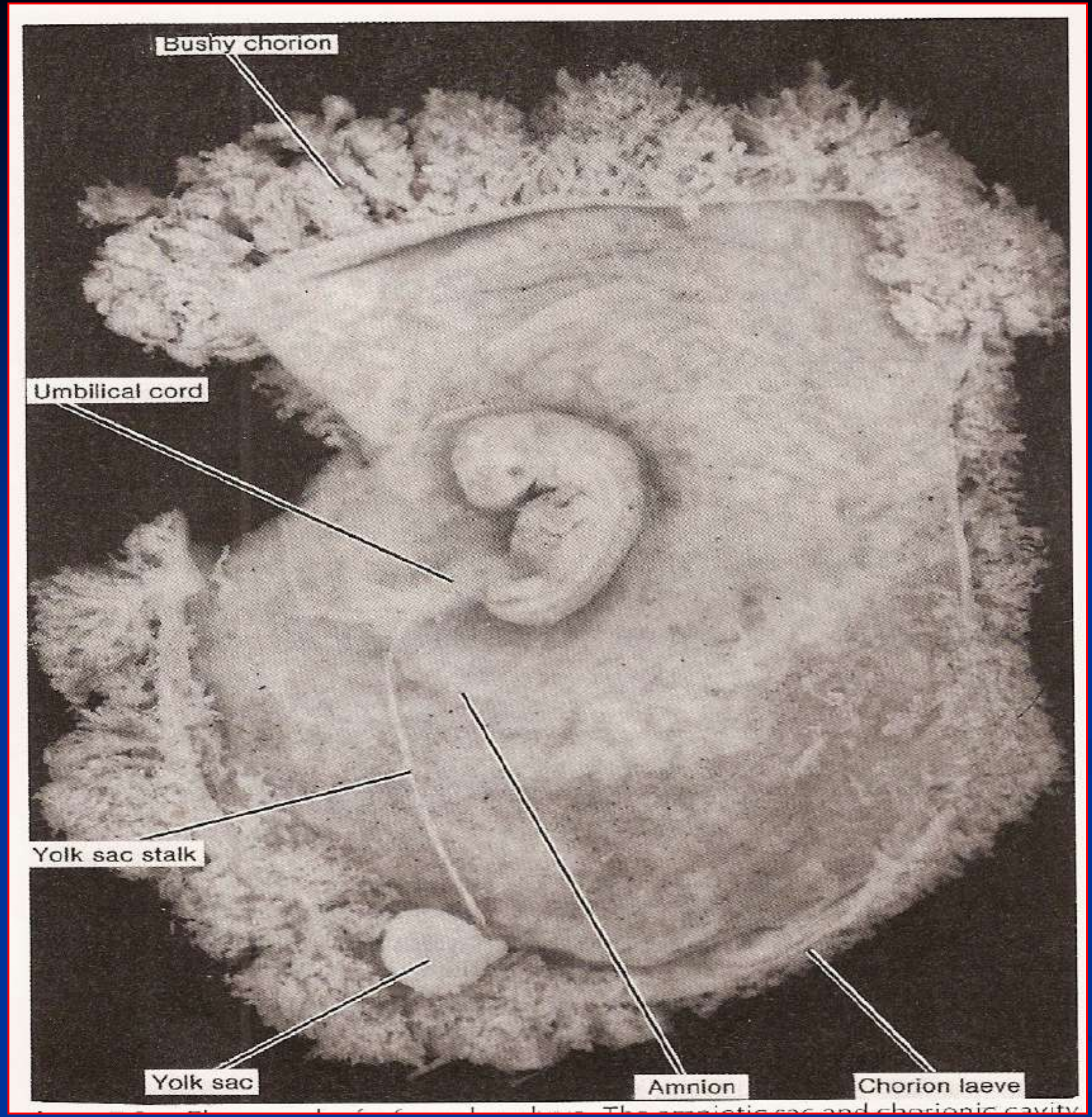


Figure 7.3. Photograph of 6-week embryo. The amniotic sac and chorionic cavity have been opened to expose the embryo. Note the bushy appearance of the trophoblast at the embryonic pole in contrast to small villi at the abembryonic pole. Note also i connecting stalk and yolk sac with its extremely long duct.

Structure of the Placenta

- By i beginning of i 4th month, i placenta has 2 comps. :

(a) A fetal portion, formed by the chorion frondosum;

(b) A materna1 portion,formed by the decidua basalis **Fig.7.4B** On the fetal side, the placenta is bordered by the chorionic plate (Fig.7.7); on its maternal side, it is bordered by the decidua basalis, *of* which the decidual plate is incorporated into the Placenta.

- During 4th & 5th months, the decidua forms a number *of* septa, the decidual septa, which project into intervillous spaces but do not reach the chorionic plate (Fig. 7.7). As a result *of* this septum form., the placenta is divided into a No. of compartments or cotyledons (Fig. 7.8).
- The placenta enlarges with growth of the fetus. Its increase in surface area roughly parallels that of the expanding uterus, & throughout pregnancy it covers approximately 15-30%.

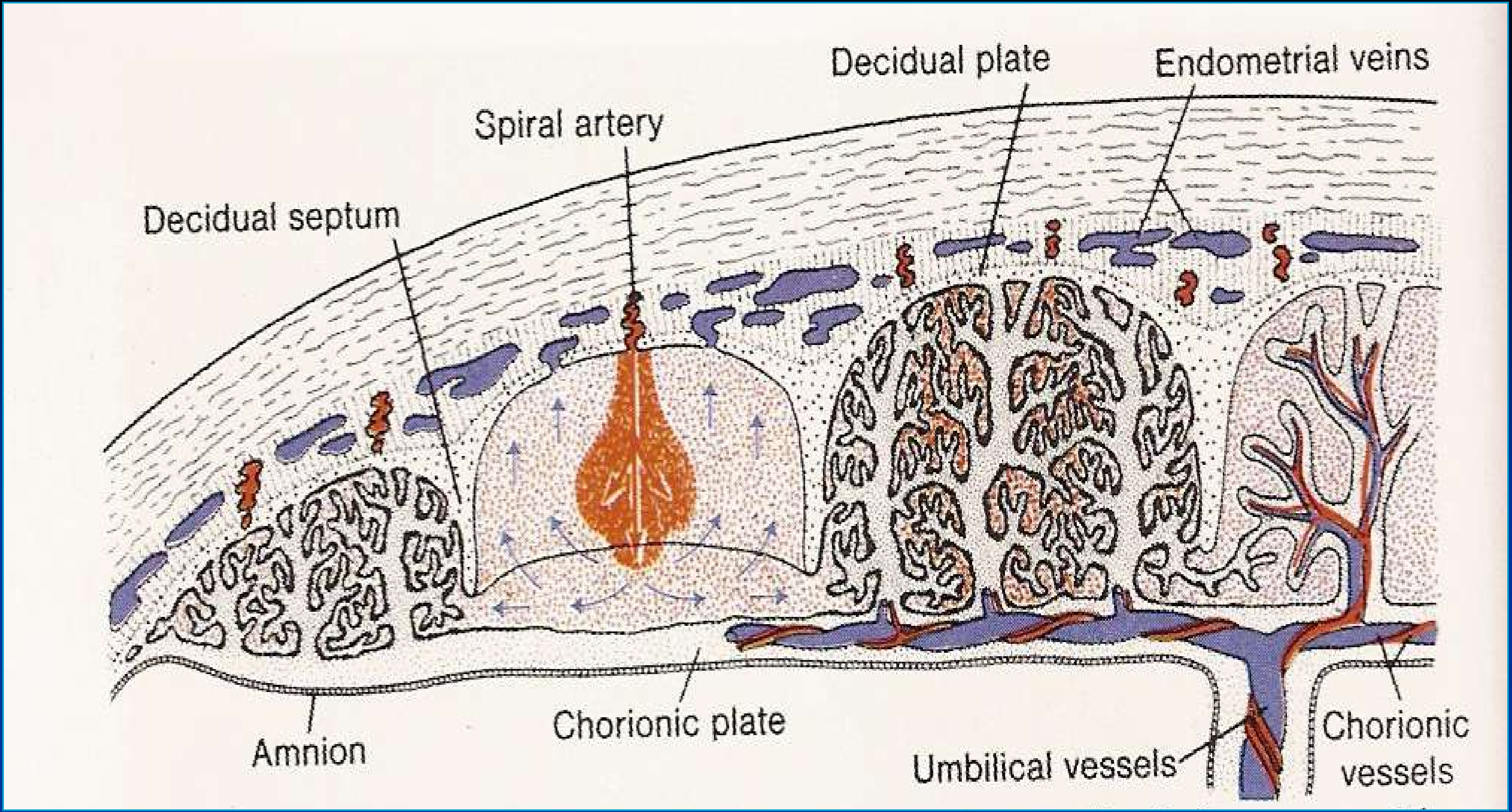


Figure 7.7. Composite drawing of the placenta in i second half of pregnancy. The cotyledons are partially separated from each other by the decidual (maternal) septa. Note that most of the intervillous blood returns to the maternal .circulation by way of the endometrial veins

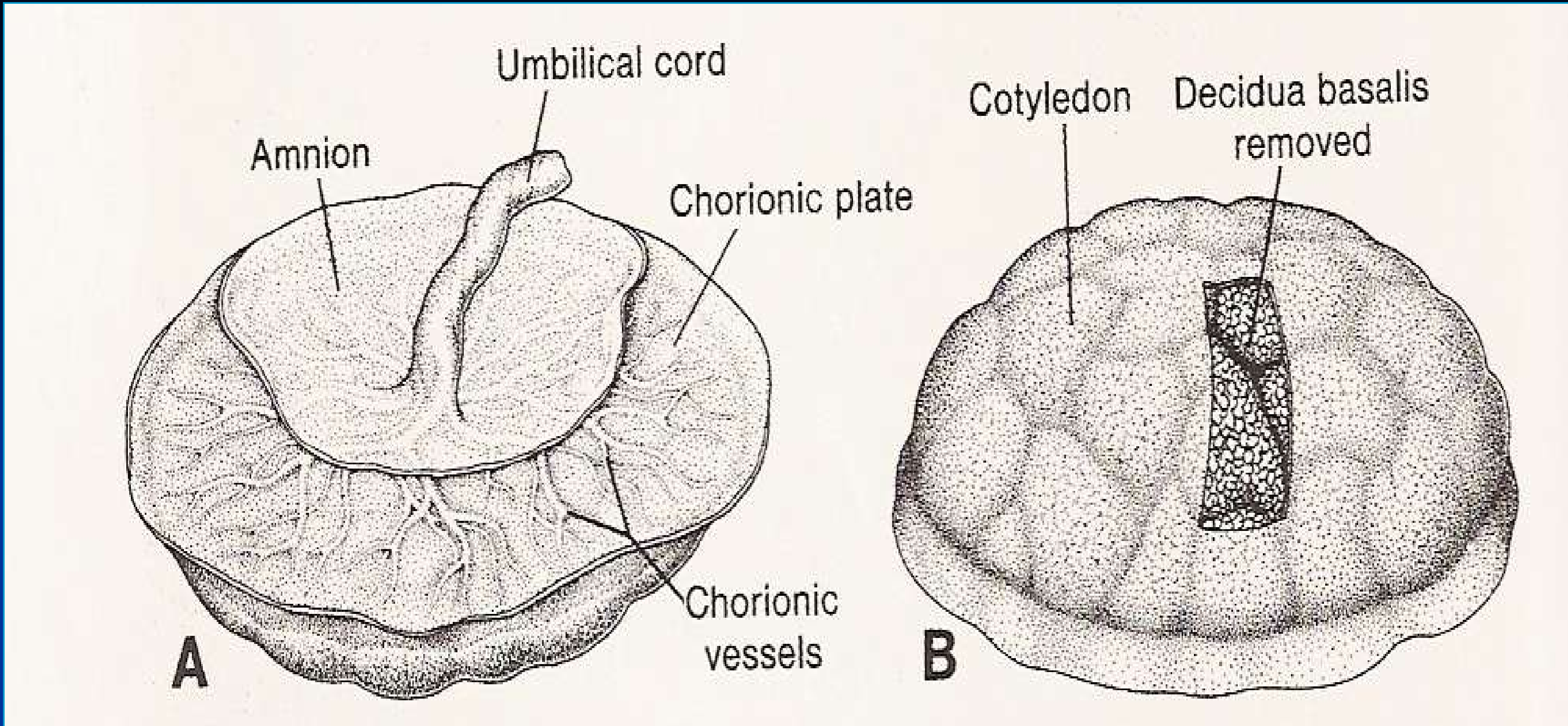


Figure 7.8. Full-term placenta. A. As seen from the fetal side. Note that the chorionic plate and umbilical cord are covered by amnion. B. As seen from i maternal side. Note i cotyledons. In one area, the decidua has been removed. The maternal side .of the placenta is always carefully

Full-Term Placenta

- At full term. the placenta has a discoid shape. a diameter of 15-25 cm. is approximately 3 cm thick, and weight of about 500-600 gm.

- At birth, it is torn from the uterine wall and, approximately 30 minutes after birth of the child. is expelled from the uterine cavity.

  (Fig. *7.8B)* (Fig. *7.8A)*.

THANK YOU

General Embryology, Lecture XIII, Fetal Membranes & Placenta, Part II

Circulation of the Placenta

- Cotyledons receive their blood through 80--100 spiral arteries that pierce the decidual plate and enter the intervillous spaces at more or less regular intervals (Fig. 7.7).
- The lumen of the spiral artery is narrow, resulting in an increased blood pressure when entering the intervillous space. This pressure forces the blood deep into the intervillous spaces and bathes the numerous small villi of the villous tree in oxygenated blood.
- As the pressure decreases, .blood flows back from the chorionic plate toward the decidua, Hence, blood from the intervillous lakes drains back into the maternal circulation through the endometrial veins.

- Collectively, the intervillous spaces of a mature placenta contain approximately 150 ml of blood, which is replenished about 3 or 4 times/minute, This blood moves along the chorionic villi,.

- The placental membrane separates maternal & fetal bl. & is initially composed of four layers: *(a)* the endothelial lining of fetal vessels; *(b) the* connective tissue in the villus core; *(c) the* cytotrophoblastic layer; & *(d) the* syncytium (Fig. 7.2C).

- From the 4th month on, the placental membrane becomes much thinner. since the endothelial lining of the vessels comes in intimate contact with the syncytial membrane, thus greatly increasing the rate of exchange (Fig. 7.2D). Sometimes called the placental barrier.

Function of the Placenta

- EXCHANGE OF GASES

  Exchange *of* gases. such as oxygen, carbon dioxide, and carbon monoxide. Is done by simple diffusion. At term, the fetus extracts 20-30 mL *of* oxygen per minute from the maternal circulation
- EXCHANGE OF NUTRIENTS AND ELECTROLYTES

  Exchange *of* nutrients and electrolytes, such as amino acids. free fatty acids, carbohydrates. and vitamins
- TRANSMISSION OF MATERNAL ANTIBODIES

  Maternal antibodies are taken up by the syncytiotrophoblast and subsequently transported to fetal capillaries. Specially lgG
- HORMONE PRODUCTION

  Probably, all hormones are synthesized in the syncytial trophoblast

  By the end *of the* 4th month, the placenta produces progesterone

  estrogenic hormones

  Syncytiotrophoblast also produces gonadotropins (hCG),

  Another hormone produced by the placenta is somatomammotropin (placental lactogen). It is a growth hormonelike substance

CLINICAL CORRELATES

- Rh incompatibility

  Erythroblastosis fetalis or hemolytic disease of the newborn (HDN)

- Most maternal hormones do not cross the placenta.

- Some synthetic progestins that cross the placenta at a rapid rate and may cause masculinization in female fetuses.

- Dangerous has been the use of the synthetic estrogen diethylstilbestrol, which easily crosses the placenta. This compound produces carcinoma of the vagina and abnormalities of the testes

- Placental barrier act as a protective mechanism against damaging factors, many viruses, such as rubella, cytomegalovirus, Coxsackie, variola, varicella, measles, and poliomyelitis virus, traverse the placenta without difficulty. Once in the fetus, some viruses cause infections, which may result in cell death and birth defects.

- Most drugs & drug metabolites traverse the placenta without difficulty & many cause serious damage to the embryo.

Amnion and Umbilical Cord

- The line of reflection between the amnion & embryonic ectoderm (amnioectodermal junction) is oval and is known as the primitive umbilical ring.
- At the 5th week of development, the following structures pass through the ring (Fig. 7.9, *A* and C):

(a) The connecting stalk, containing the allantois & the umbilical vessels consisting of two arteries & one vein;

(b) The yolk stalk (vitelline duct) accompanied by the vitelline vessels;

(c) the canal connecting the intraembryonic & extraembryonic coelomic cavities (Fig. *7.9C).*

The yolk sac proper occupies a space in the chorionic cavity, i.e. the space bet. the amnion & chorionic plate (Fig. *7.9B).*

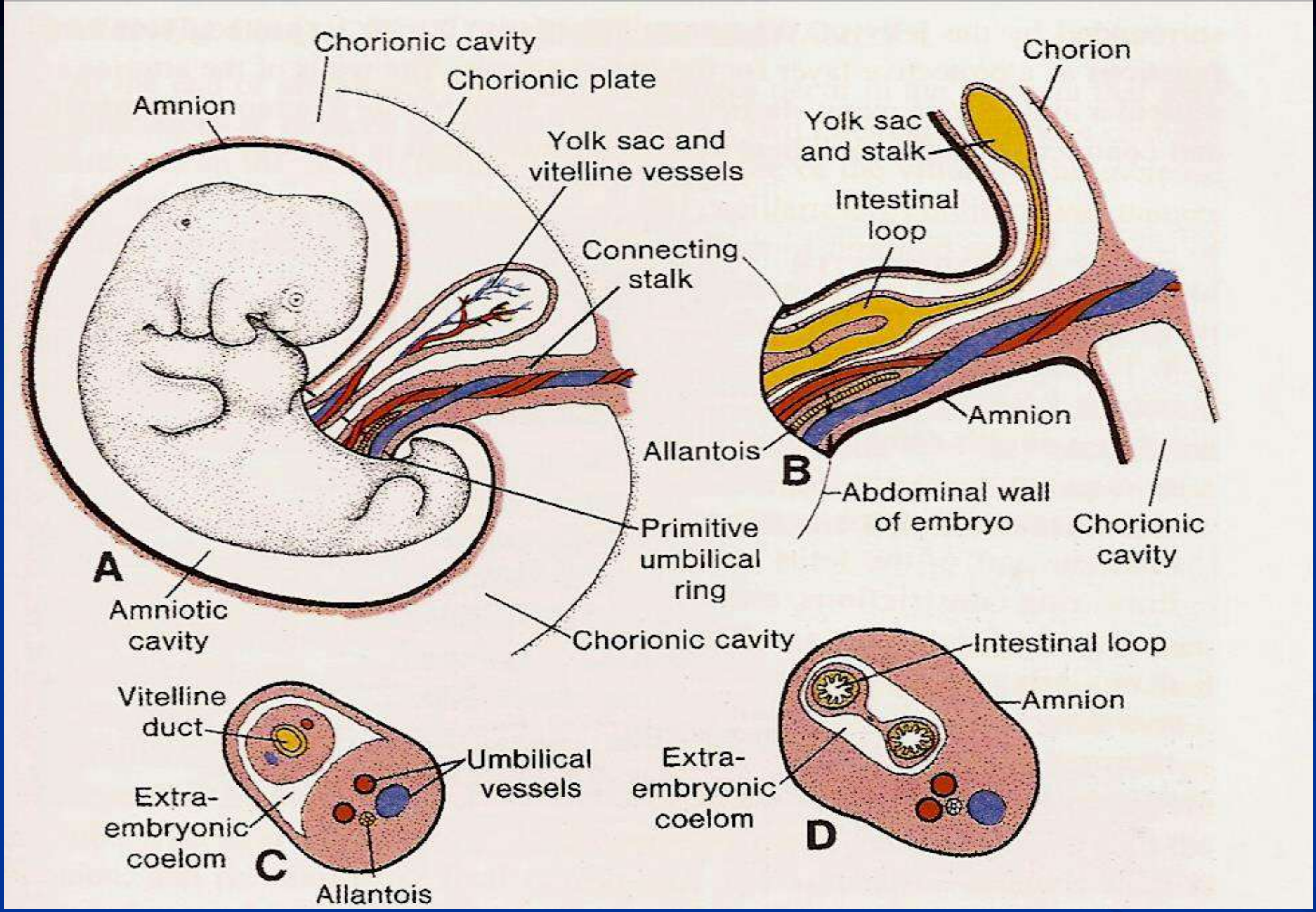


Figure 7.9. A. 5-week embryo to show structures passing through the primitive umbilical ring. B. primitive umbilical cord of a 10-week embryo. C. Transverse section through the structures at the level of the umbilical ring. D. Transverse section through the primitive umbilical cord, showing intestinal loops protruding in the cord.

CLINICAL CORRELATES

- Normally, there are two arteries and one vein in the umbilical cord.
- In 1 in 200 newborns, only one artery is present, & these babies have an approximately (20 %) chance of having cardiac and other vascular defects.
- Occasionally, tears in the amnion result in amniotic bands that may encircle part of the fetus, particularly the limbs & digits. Amputations, ring constrictions, & other abnormalities may result, including craniofacial deformations (Fig.7.10)
- Origin of the bands is probably from infections or toxic insults that involve either the fetus, fetal membranes, or both. Bands then form from the amnion, like scar tissue, constricting fetal structures.

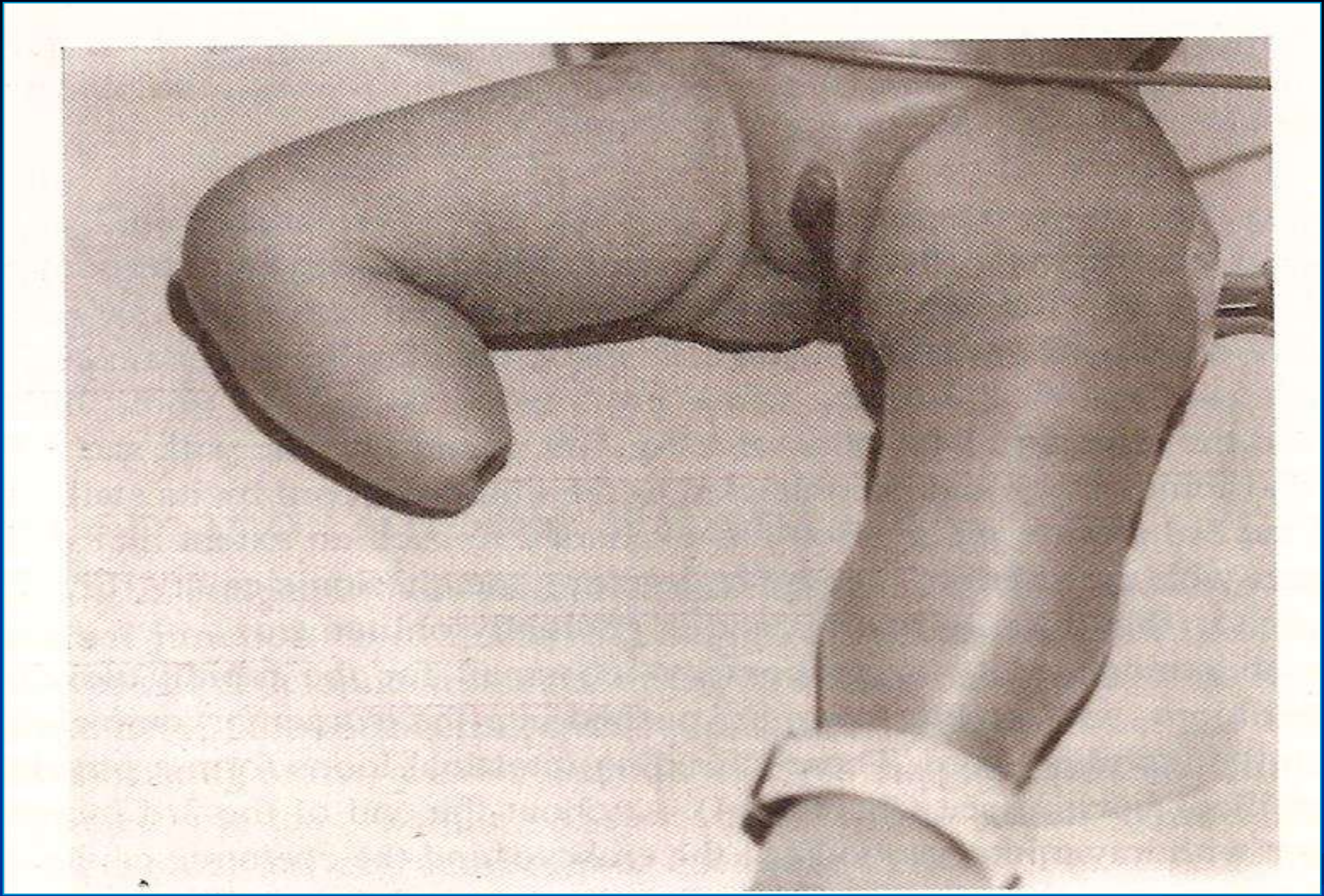


Figure 7.10. Photograph of infant showing limb amputation resulting from otic bands

Placental changes at the end of pregnancy :

- At the end *of* pregnancy, a number *of* changes occur in the placenta. These changes include:

  *(a)*Increase in fibrous tissue in the core *of* the villus,

  *(b)*Increase in thickness of basement membranes in fetal capillaries,

  *(c)*Obliterative changes in small capillaries *of* the villi.

  (d)Deposition *of* fibrinoid on the surface of the villi in the junctional zone and in the chorionic plate, which frequently causes infarction *of* an intervillous lake or *of* an entire cotyledon.

- At birth, the umbilical cord is approximately 2 cm in diameter and 50--60 cm long. It is tortuous, causing false knots.

AMNIOTIC FLUID

- The amniotic cavity is filled with a clear, watery fluid that is produced, in part, by amniotic cells but is derived primarily from maternal blood Amount *of* fluid increases from 30 ml at 10 weeks gestation, to 350 ml at 20 weeks, to 800--1000 ml at 37 weeks.

- During the early months *of* pregnancy, the embryo is suspended by its umbilical cord in this fluid. which serves as a protective cushion.
- The fluid *(a)* absorbs jolts, *(b)* prevents adherence *of the* embryo to the amnion, *(c)* allows for fetal movements. The volume *of* amniotic fluid is replaced every 3 hours..

- Fetal urine is added daily to the amniotic fluid in the 5th month, but this urine is mostly water, since the placenta is functioning as an exchange for metabolic wastes.

CLINICAL CORRELATES

- Premature rupture of the amnion occurs in 10% of pregnancies & represents the most common cause of preterm labor.

- Clubfoot & lung hypoplasia may be caused by oligohydramnios (amount less than 400 mL) following amnion rupture.
- Causes for rupture are largely unknown, but in some cases, trauma plays a role.
- Hydramnios or polyhydramnios is the term used to describe an excess of amniotic fluid (1500-2000 ml),
- Both conditions are associated with an increased incidence of birth defects.
- Primary causes *of* hydramnios include idiopathic causes (35%), maternal diabetes(25%), & congenital malformations.

THANK YOU

General Embryology,
Lecture XIV,
Fetal Membranes & Placenta,
Part III

Fetal Membranes in Twins

- Arrangement of fetal membranes in twins varies considerably and is dependent on the type of twins as well as on the time of separation of monozygotic twins.

DIZYGOTIC TWINS

- Approximately two-thirds of twins are dizygotic or fraternal, and their incidence of 7-11/1000 births increases with increasing maternal age.

- They result from simultaneous shedding of two oocytes and fertilization by two different spermatozoa., the twins have no more resemblance than brothers or sisters. They may or may not be of different sex.

- Both zygotes implant individually in the uterus, and each develops its own placenta, amnion, and chorionic sac (fig.7 .11A).

MONOZYGOTIC TWINS

- The 2nd type of twins develops from a single fertilized ovum and is known as monozygotic or identical twins. The rate is 3-4/1000.

- They result from splitting of the zygote at various stages of development. The earliest separation is believed to occur at the two-cell stage, in which case two separate zygotes develop.
- Both blastocysts implant separately, and each embryo has its own placenta and chorionic sac (Fig. 7.12A).

- In most cases, splitting of the zygote occurs at the early blastocyst stage. The inner cell mass splits into 2 separate groups of cells within the same blastocyst cavity (Fig. 7.12B).

- The 2 embryos have a common placenta, & a common chorionic cavity but have separate amniotic cavities (Fig. *7.12B).*

- Rarely, i separation occurs at the bilaminar germ disc stage just before i appearance of the primitive_streak (Fig.7.12c).
- This method of splitting results in form. of 2 partners with a single placenta & a common chorionic & amnion sac.

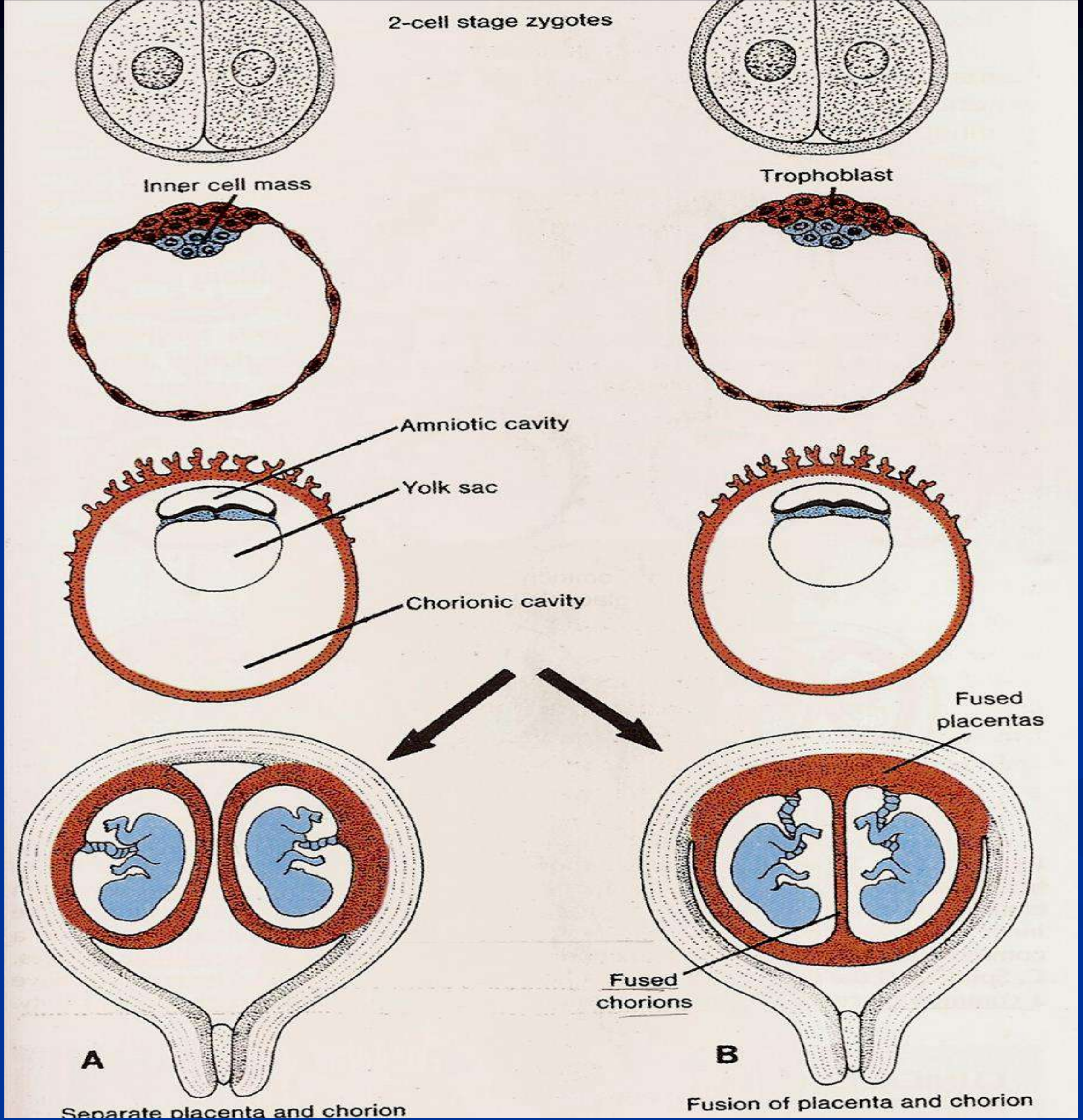


Figure 7.11.development of dizygotic twins. Normally, each embryo has its own amnion, chorion, & placenta **(A),** but sometimes the placentas are fused **(B),** Each embryo usually receives i appropriate amount of bl.

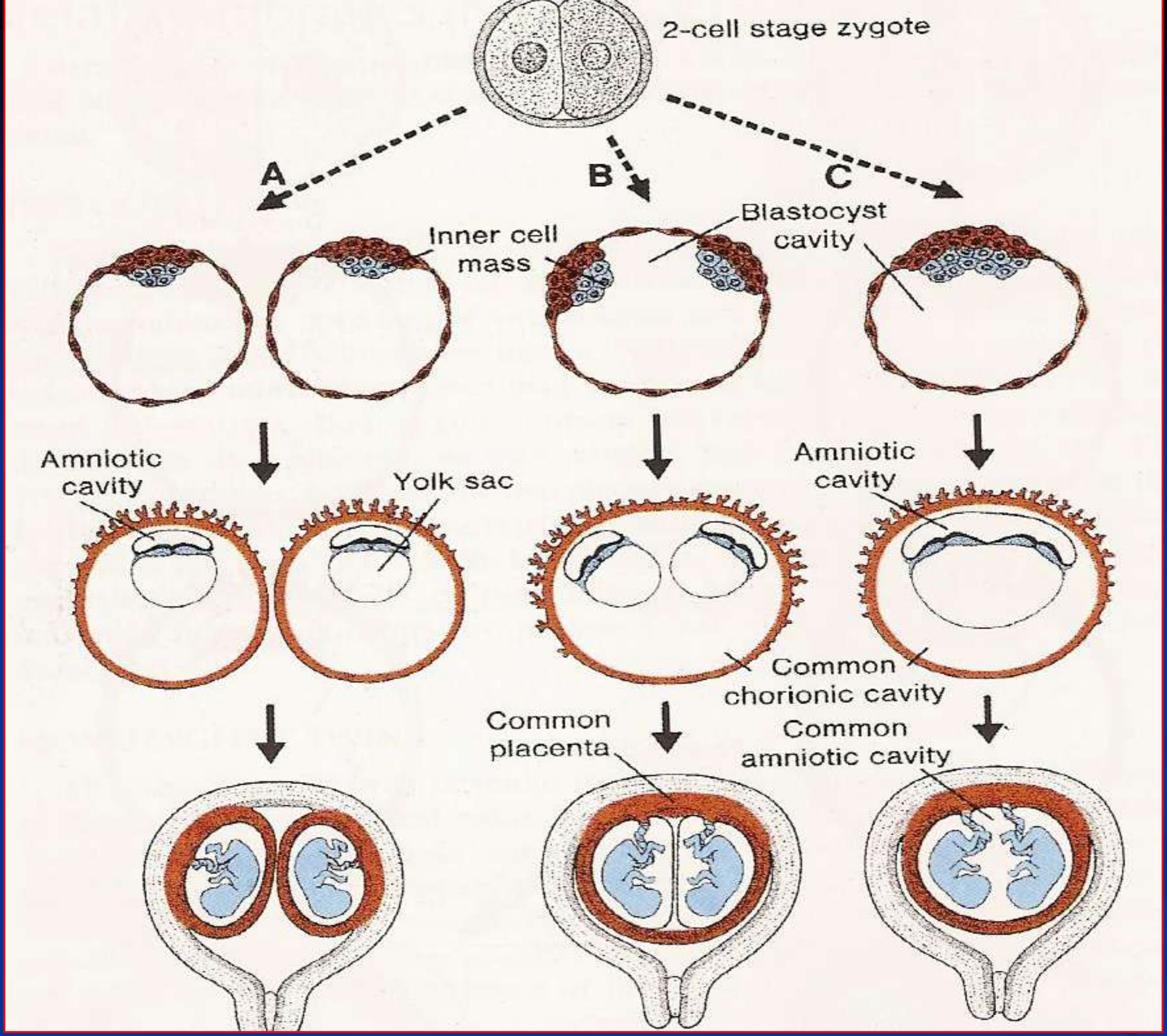


Fig 7.12. Possible relations of fetal membranes in monozygotic twins. A, Splitting occurs at i 2-cell stage & each embryo has its own placenta, amniotic & chorionic cavity. B, Splitting of i inner cell mass into 2 completely separated groups. The 2 embryos have a common placenta & a common chorionic sac but have separate amniotic cavities. C, Splitting of i inner cell mass at a late stage of develop. The embryos have a common placenta ,a common amniotic & common chorionic cavit.

CLINICAL CORRELATE

- Twin pregnancies have a higher incidence of perinatal mortality & morbidity & tendency toward preterm delivery.

- Nearly 12% of premature infants result from twin pregnancies, & twins are usually smaller at birth.
- Low birth weight & prematurity place infants of twin pregnancies at great risk, & about 10-20% of them will die compared with only 2%, of infants from single pregnancies.

- Some studies indicate that only 29% of women pregnant with twins actually give birth to two infants.

- The term vanishing twin refers to the death of one fetus. This disappearance occurs in the 1st trimester or early 2nd trimester & may result from resorption or formation of a fetus papyraceus (Fig. 7.13).

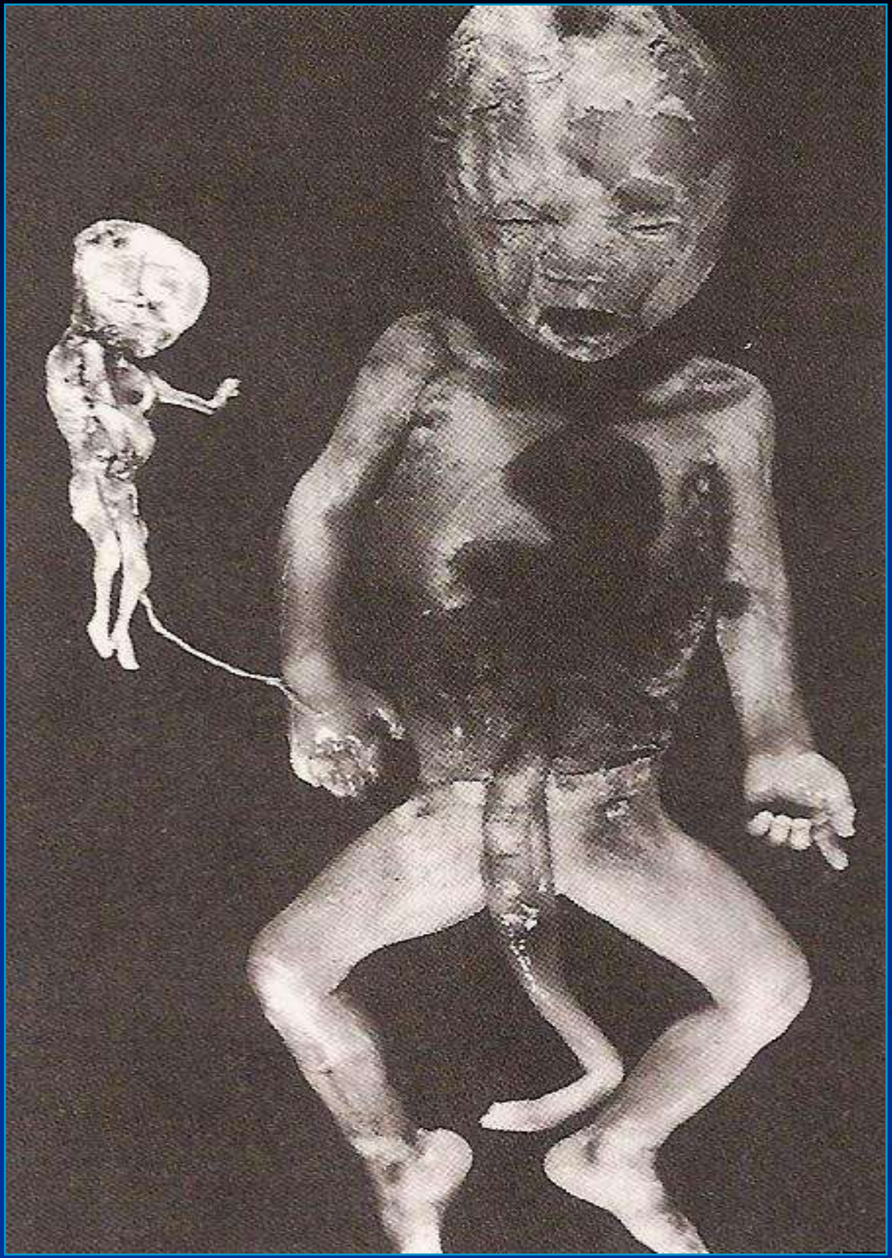


Figure 7.13 fetus papyraceus . One twin is larger , while the other has been compressed and mummified, hence the term papyraceus

- Twin transfusion syndrome, increased mortality among twins which occurs in 5-15%, of monochorionic monozygotic pregnancies.
- In this condition, placental vascular anastomoses, which occur in a balanced arrangement are disturbed, one twin receives most of the blood flow (Fig. 7.14). Death of both twins occurring in 60-100% of cases.

- Splitting of the zygote during later stages of development may result in an abnormal or incomplete splitting of the axial area of the germ disc. Such incompletely separated discs lead to formation of conjoined (Siamese) twins. According to the nature & degree of the union, they are classified as thoracopagus, pygopagus, & craniopagus (Figs.7.15 & 7.16)

Fig. 7.14; Monozygotic twins with twin transfusion syndrome. Placental vascular anastomosis produced unbalanced blood flow to i

2 fetuses

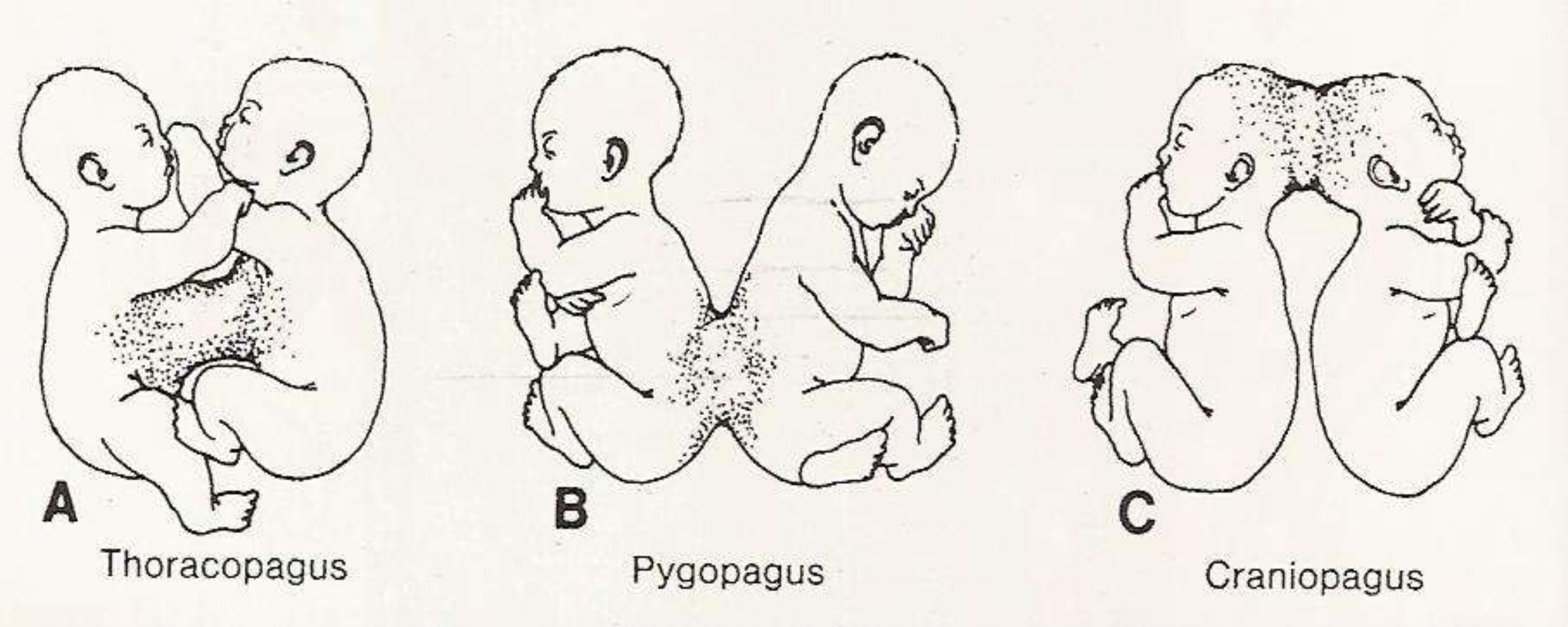


Figure 7.15. Schematic drawings of thoracopagus, pygopaus, and craniopagus twins. Conjoined twins can be separated only if they have no vital parts in common.

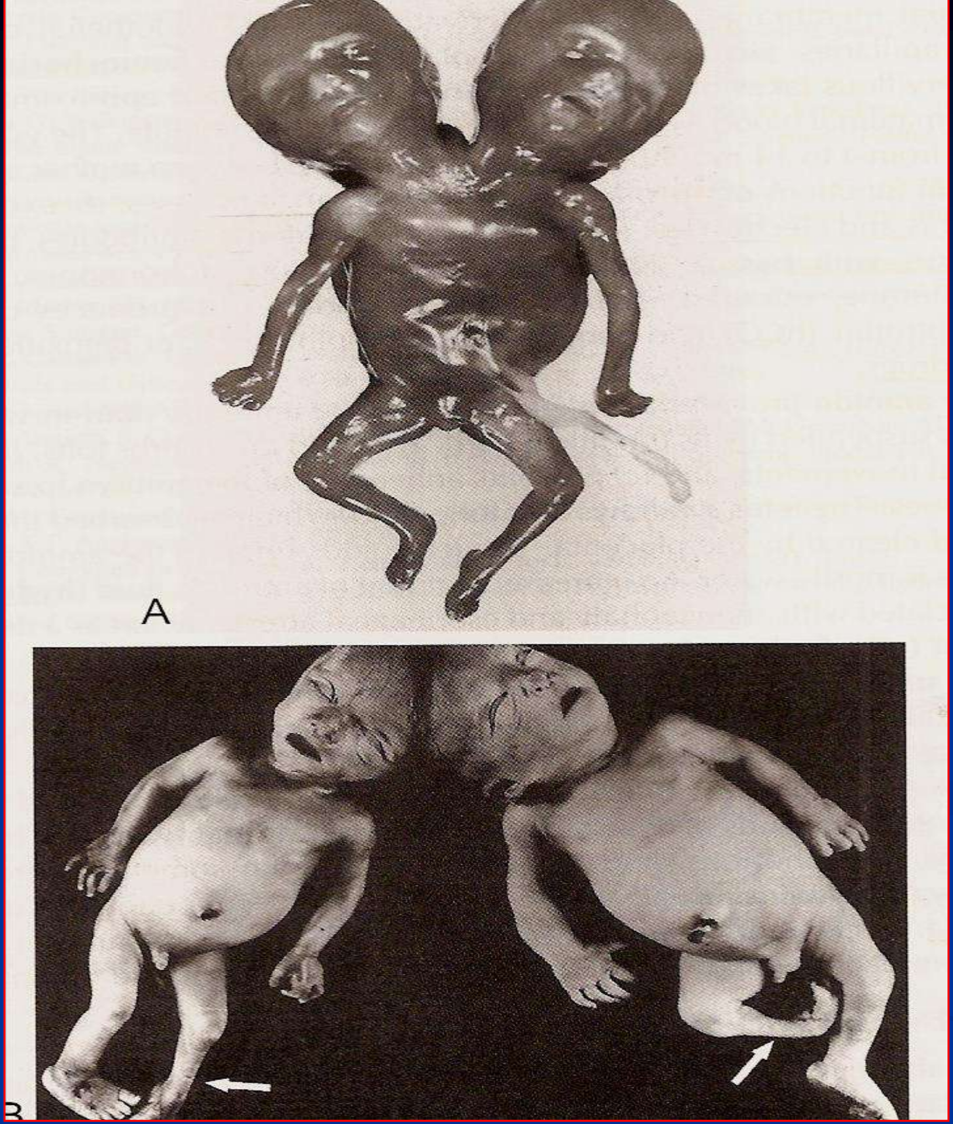


Figure 7.16. Examples of conjoined twins. A. Twins with 2 heads, a broad thorax, two spines, two partially fused hearts, four lungs, & a duplicated gut down to the ileum. B. Twins joined at the head (craniopagus) with multiple deformations of the limbs

THANK YOU