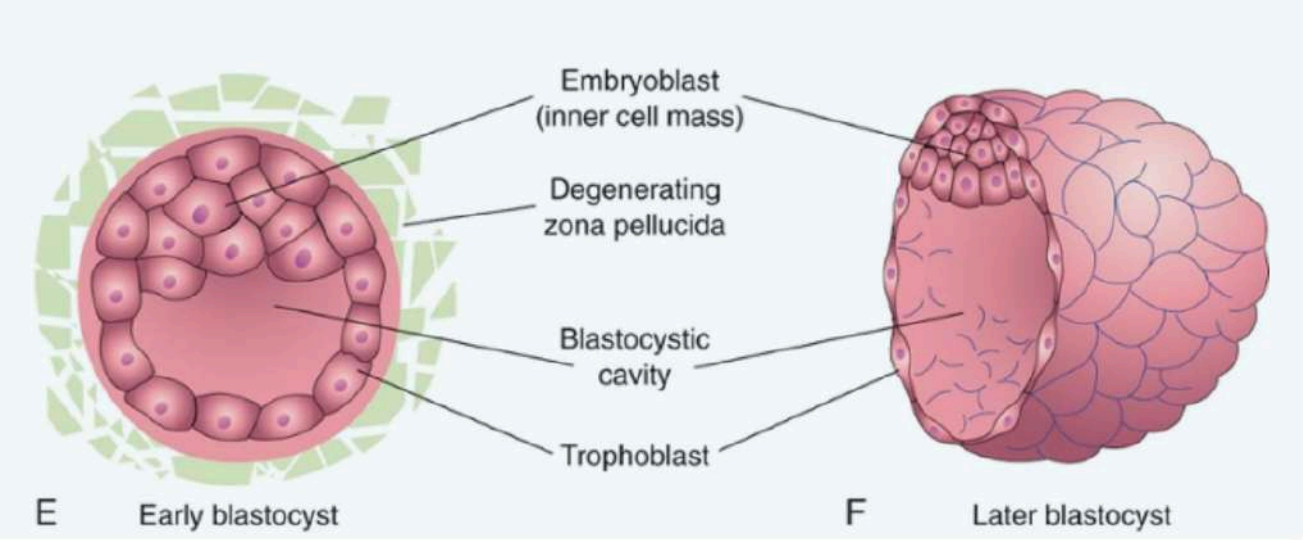
Embryology
Lesson 3

Embryoblast Formation

The inner cells of the morula—the **embryoblast** or **inner cell mass**—are surrounded by a layer of flattened blastomeres that form the **trophoblast**. *Hippo signaling is an essential factor in segregating the **inner cell** mass from the **trophoblast***.

An immunosuppressant protein—the **early pregnancy factor**—is secreted by the trophoblastic cells and appears in the maternal serum within 24 to 48 hours after implantation. The early pregnancy factor forms the basis for a pregnancy test applicable during the first 10 days of development



hCG

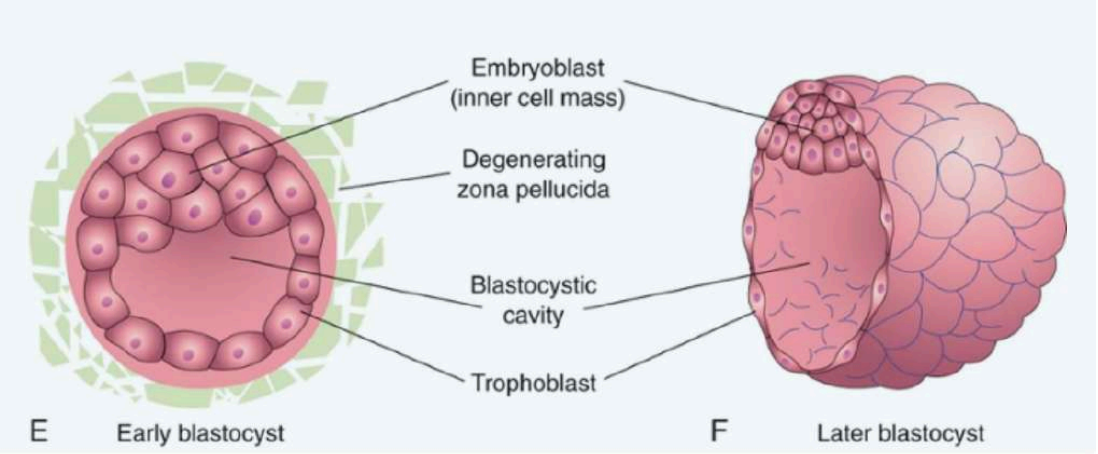
https://studentconsult.inkling.com/read/moore-before-we-are-born-9/chapter-3/cleavage-of-zygote

Formation of Blastocyst

Shortly after the morula enters the uterus (about 4 days after fertilization), uterine fluid passes through the zona pellucida to form a fluid-filled space—the **blastocystic cavity**—inside the morula.
As fluid increases in the cavity, the blastomeres are separated into two parts:

The **trophoblast**, the thin outer cells that give rise to the embryonic part of the placenta

The **embryoblast**, a discrete group of blastomeres that is the primordium of the embryo

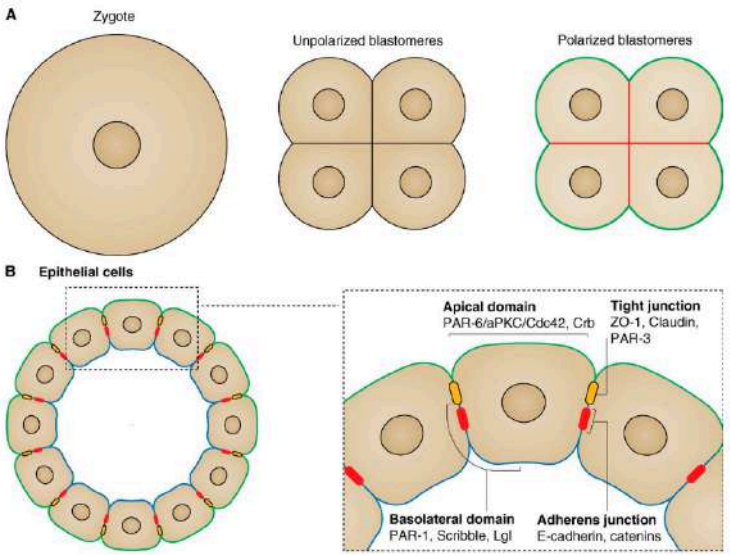


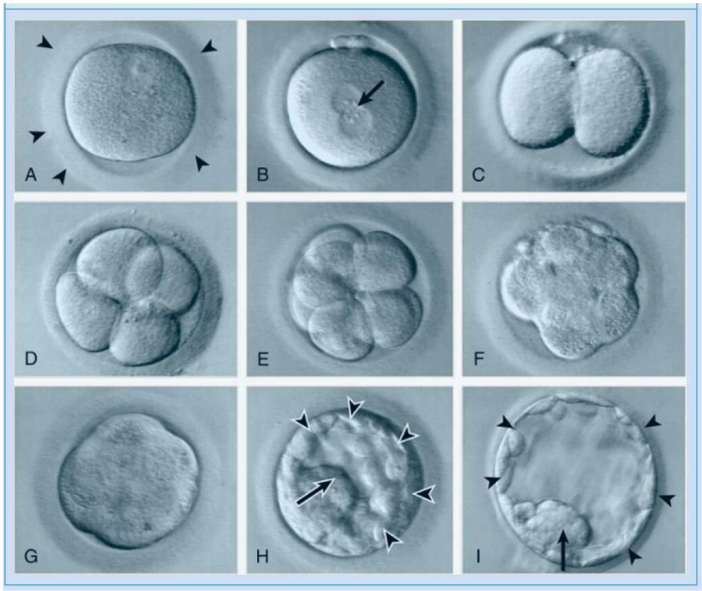
Beginning at 8-cell stage

1- At eight-cell stage of development,

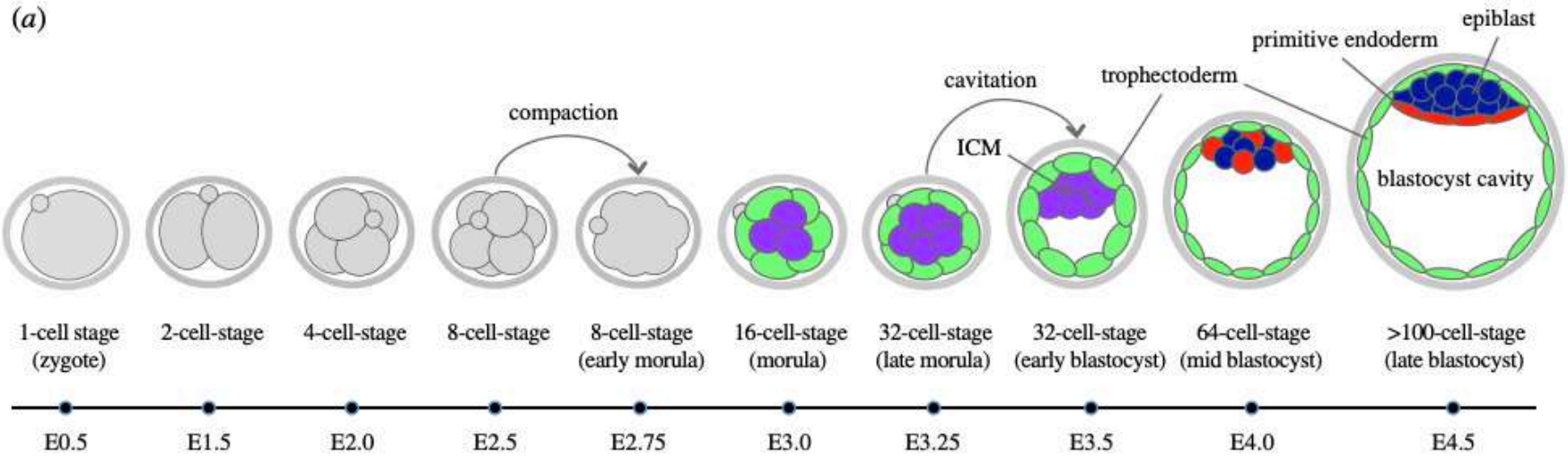
Intercellular adhesion are weak, and each blastomere is morphologically recognizable.

The first event is the increase of e-cadherin, with cell boundaries become less evident (**COMPACTION**)



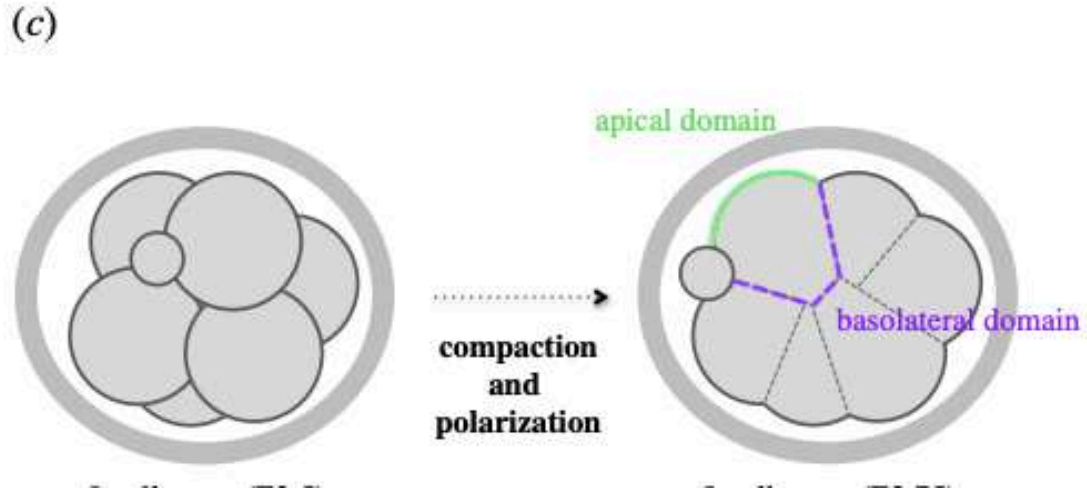


Although individual cells separated from the 4- or 8-cell stage mouse embryo cannot independently develop beyond implantation, they are, nevertheless, able to contribute to all tissues when combined with other blastomeres in experimentally derived chimaeras, indicating that they still retain their full developmental potential



As a result of compaction, adherens junctions form at the cell-to-cell contact sites, creating the embryonic structure commonly referred to as the morula.

In parallel with compaction, blastomeres undergo a process of intracellular polarization, resulting in the asymmetric distribution of defined cellular components, between the apical and basolateral membrane domains, thus defining the establishment of a radial, with respect to the embryo, apical–basolateral axis of cell polarity in each blastomere



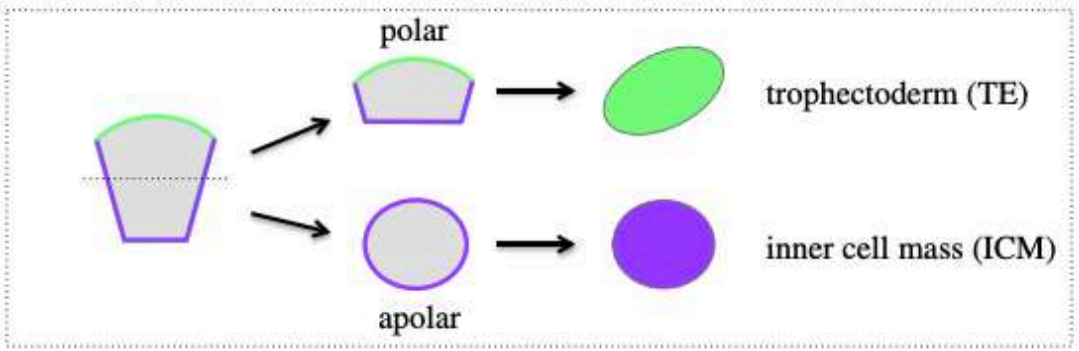
Role of E-Cadherin (cdh1) in cell-cell adhesion

Importantly, it is at this stage that **tight junction** formation is also initiated, at the border between the apical and basolateral regions, that ultimately serves to delineate these two membrane domains.

The initial differences in cells **position** (outer/inner) and intracellular **organization** (polarized/nonpolarized), will eventually segregate them into one of two different cell lineages, trophectoderm or ICM, in a process typically referred to **as the first cell-fate decision**

The classical ‘polarity’ and ‘positional’ models proposed to explain the first cell-fate decision.

(a) A schematic representation of the ‘polarity’ model showing that the differences required to set the trophectoderm (TE) and the ICM cell lineages apart arise as a result of an ***asymmetric partitioning*** of polarized subcellular components between daughter cells (e.g. differential inheritance of apical and basolateral membrane domains) upon asymmetric cell division; solid green and purple lines, respectively, mark the apical and basolateral membrane domains.



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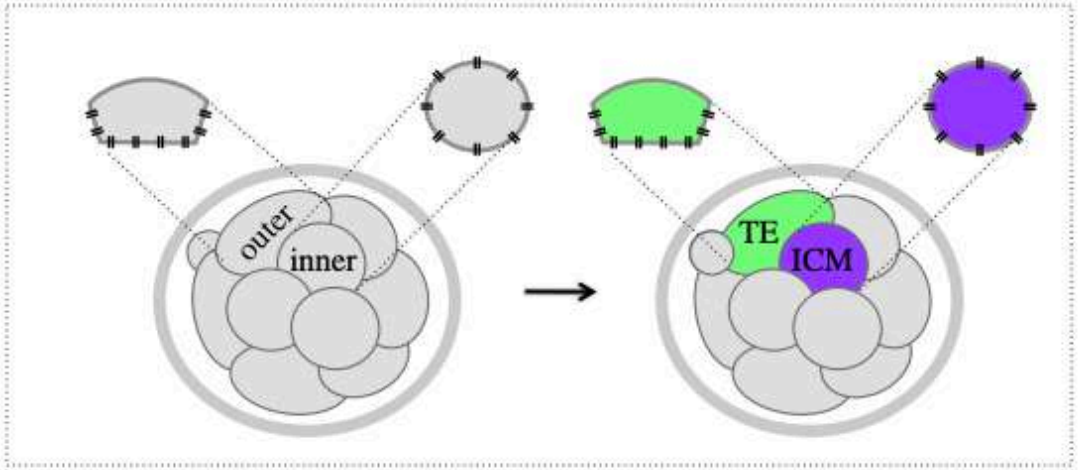
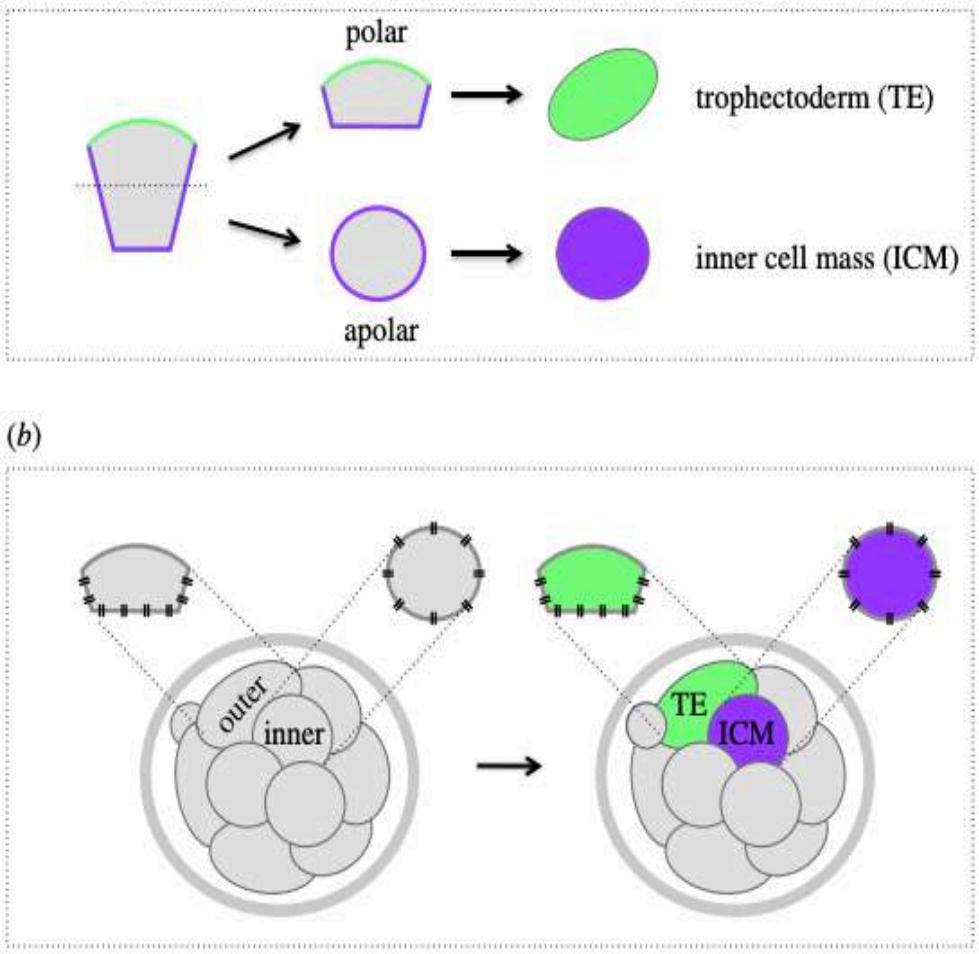


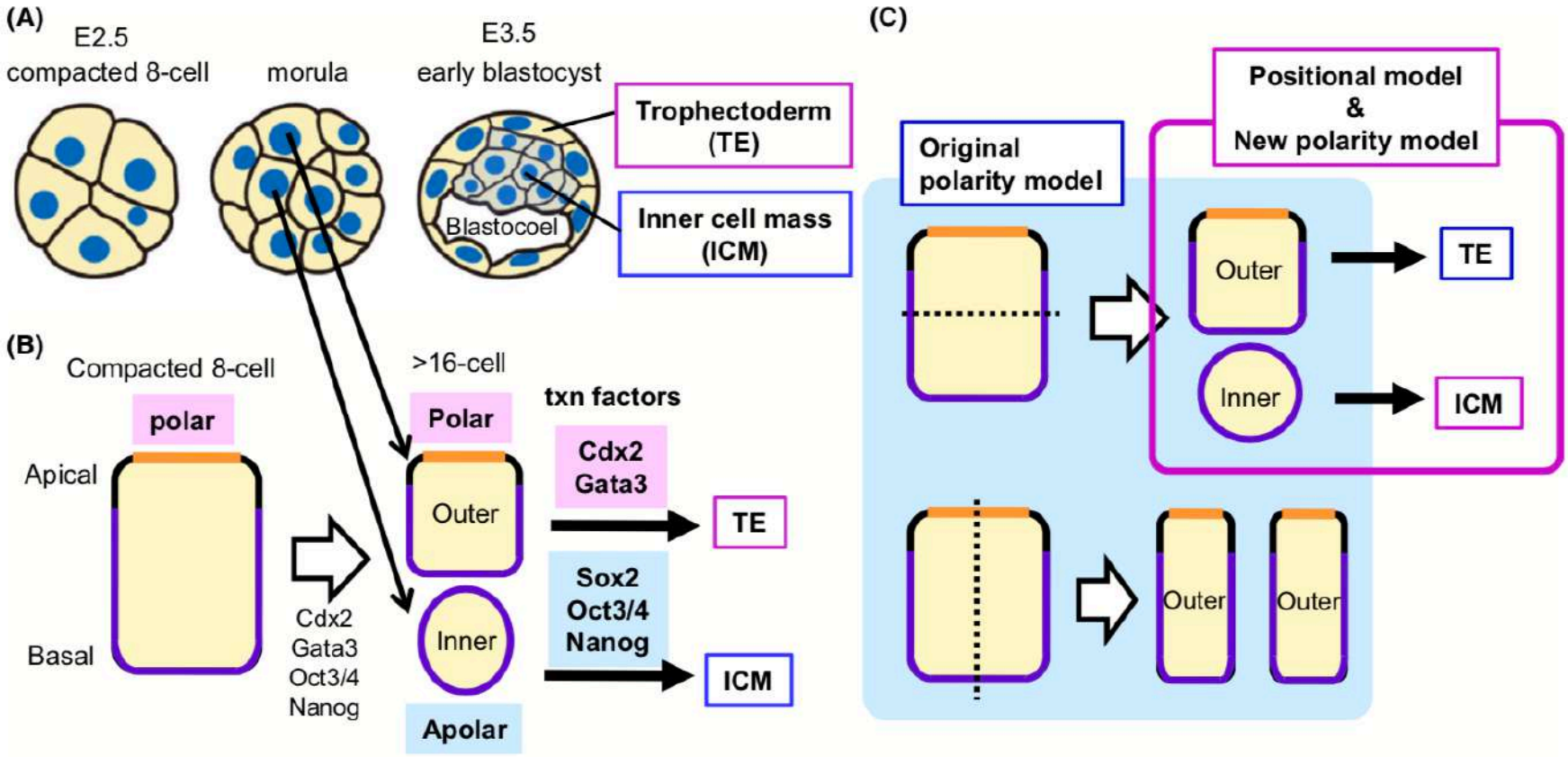
(a) A schematic representation of the 'positional' model showing that the differences required for the segregation of the TE and the ICM cell lineages originate in the differential extent of cell-to-cell contact between individual blastomeres, corresponding to their **relative position** in the embryo; the sites of the cell-to-cell contact are highlighted with two parallel black lines, reminiscent of adherens junctions.



At morula stage: >16 cells

Mouse embryo develop into a cyst-like structure

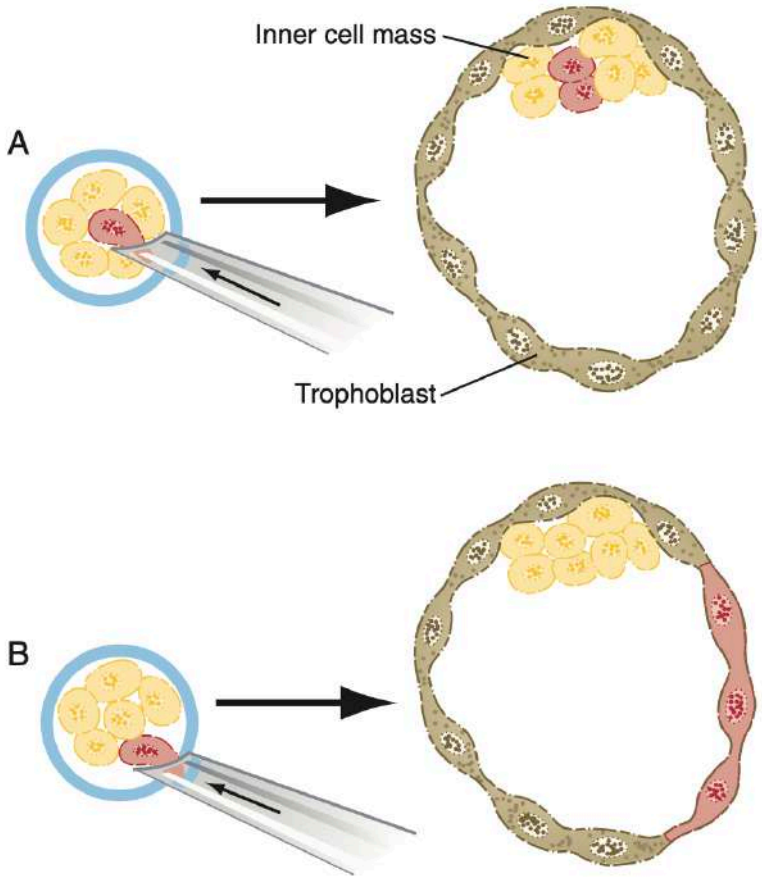
While the outer cells remain polarized, the inner cells **lose polarity**



At 16-cell stage cells of the inner cell mass, if transplanted to the outer surface of another embryo, can become trophoblast, and at least some of the outer cells can turn into inner cell mass if transplanted into the interior.

By the 32-cell stage, this capability for phenotypic transformation has become largely lost.

POSITIONAL inside-outside Hypothesis



Experiment illustrating the inside-outside hypothesis of cell determination in early mammalian embryos.

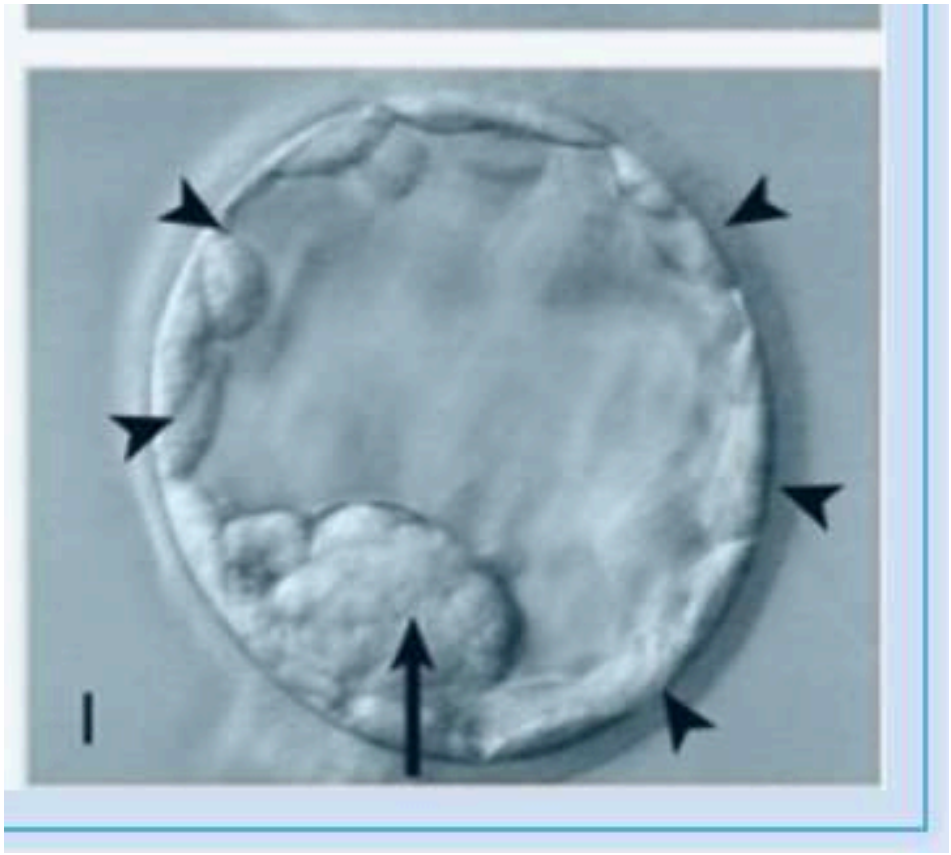
A, If a marked blastomere is inserted into the interior of a morula, it and its progeny become part of the inner cell mass.
B, If a marked blastomere is placed on the outside of a host moru it and its descendants contribute to the trophoblast.

- Hippo-signalling pathway demonstrated activity within inner cells and suppression in outer cells of the embryo, from the 16-cellstage onwards. Specifically, the **selective activation** of the Hippo-pathway component serine/ threonine protein kinases Lats1/2 (large tumour suppressor kinase 1 and 2), within completely surrounded **inner cells** that do not possess a cell contactless domain, leads to the phosphorylation-dependent cytoplasmic sequestration of the transcriptional co-activator protein Yap1 (a transcriptional co-activator of Tead4/TEA domain transcription factor 4— itself required **to activate transcription of trophectoderm related genes.**
- whereas in outer cells a failure to activate Lats1/2 kinases permits unphosphorylated Yap1 to enter the nucleus and enables Tead4-dependent transcription of trophectoderm-required genes.

Thus, such spatially distinct and differential activation of the Hippo-signalling pathway ensures that only outer cells can express trophectoderm genes, while inner cells are prevented from such inappropriately activated gene transcription, given that they will not contribute cells to any future trophectoderm

Embryoblast Formation

The inner cells of the morula—the **embryoblast** or **inner cell mass**—are surrounded by a layer of flattened blastomeres that form the trophoblast. *Hippo signaling is an essential factor in segregating the inner cell mass from the* ***trophoblast***.



Embryoblast Formation

The inner cells of the morula—the **embryoblast** or **inner cell mass**—are surrounded by a layer of flattened blastomeres that form the **trophoblast.**

Paternal genes are predominantly expressed in the trophoblast.
Called **parental imprinting**, the effects are manifest in different ways. It is possible to remove a pronucleus from a newly inseminated
mouse egg and replace it with a pronucleus taken from another inseminated egg at a similar stage of development.
If a male or female pronucleus is removed and replaced with a female pronucleus (resulting in a zygote with two female pronuclei),
however, the embryo itself develops fairly normally, but the placenta and yolk sac are poorly developed.
Conversely, a zygote with two male pro- nuclei produces a severely stunted embryo, whereas the pla- centa and yolk sac are nearly normal.
Parental imprinting occurs during gametogenesis

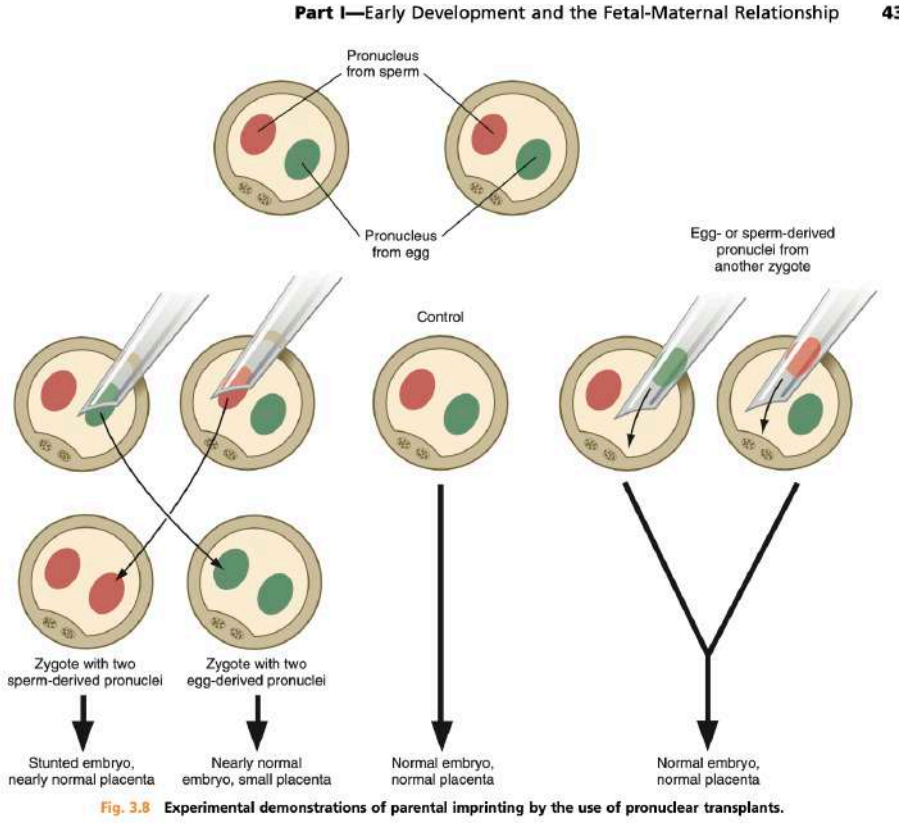


Fig. 3.8 **Experimental demonstrations of parental imprinting by the use of pronuclear transplants.**

Twinning: Monozygotic twins

A: Cleavage of the early embryo: each half developing as completely separated embryo

B: Cleavage of the inner cell mass results in two embryos enclosed within the same trophoblast

C: The inner cell mass does not completely separate. This may result in conjoined twins.”

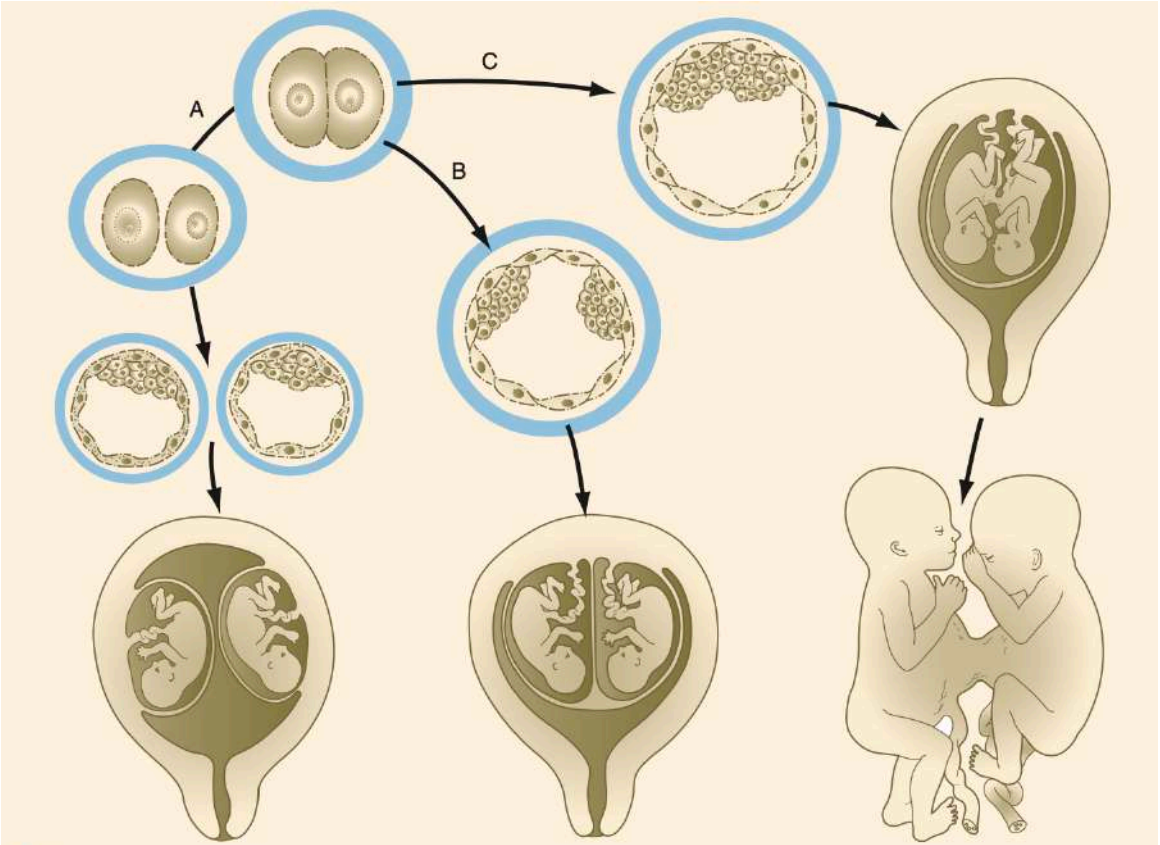


Fig. 3.14 **Modes of monozygotic twinning.** A, Cleavage of an early embryo, with each half developing as a completely separate embryo. B, Splitting of the inner cell mass of a blastocyst and the formation of two embryos enclosed in a common trophoblast. This is the most common mode of twinning. C, If the inner cell mass does not completely separate, or if portions of the inner cell mass secondarily rejoin, conjoined twins may result.

Box 3.1 Summary of Functions of the Zona Pellucida

1. It promotes maturation of the oocyte and follicle.
2. The zona pellucida serves as a barrier that normally allows only sperm of the same species access to the egg.
3. It initiates the acrosomal reaction.
4. After fertilization, the modified zona pellucida prevents any additional spermatozoa from reaching the zygote.
5. During the early stages of cleavage, it acts as a porous filter through which certain substances secreted by the uterine tube can reach the embryo.
6. Because it lacks histocompatibility (human leukocyte) antigens, the zona pellucida serves as an immunological barrier between the mother and the antigenically different embryo.
7. It prevents the blastomeres of the early cleaving embryo from dissociating.
8. It facilitates the differentiation of trophoblastic cells.
9. It normally prevents premature implantation of the cleaving embryo into the wall of the uterine tube.

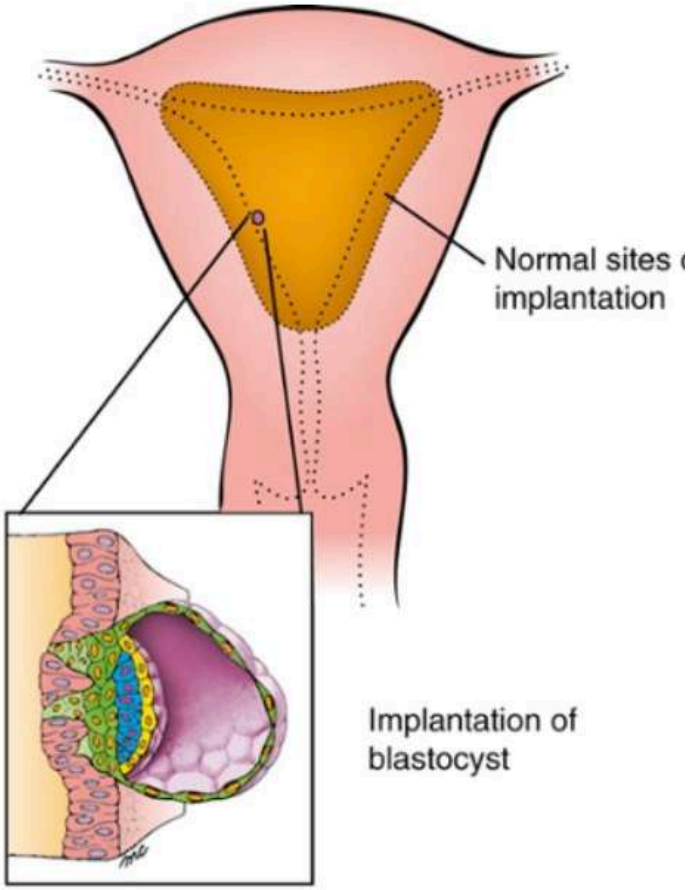
DAY 5 : blastocyst hatching

End of First Week: Initiating Implantation

Very soon after arriving in the uterus, the blastocyst becomes tightly adherent to the uterine lining.

Cells of the endometrial stroma respond to its presence and to the progesterone secreted by the corpus luteum by differentiating into metabolically active, secretory cells called **decidual cells**.
This response is called the **decidual reaction**.

The endometrial glands in the vicinity also enlarge, and the local uterine wall becomes highly vascularized.
It is thought that secretions of the decidual cells and endometrial glands include growth factors and metabolites that support growth of the implanting embryo.



If an embryo implants, cells of the trophoblast produce the hormone **human chorionic gonadotropin (hCG)**, which supports the corpus luteum and thus maintains the supply of progesterone (**maternal recognition of pregnancy**).

Implantation in Abnormal Site Results in Ectopic Pregnancy

Occasionally, a blastocyst implants in the
-peritoneal cavity,
-on the surface of the ovary,
-within the oviduct, or at an abnormal site in the uterus.

The epithelium at these abnormal sites responds to the implanting blastocyst with increased vascularity and other supportive changes, so that the blastocyst is able to survive and commence development.

These **ectopic pregnancies** often threaten the life of the mother because blood vessels that form at the abnormal site are apt to rupture as a result of growth of the embryo and placenta. Typically, ectopic pregnancy is revealed by symptoms of abdominal pain and/or vaginal bleeding.
Drug (methyltrexate, which blocks rapid division) or surgical intervention is usually required to interrupt the pregnancy.

Initiating the Implantation

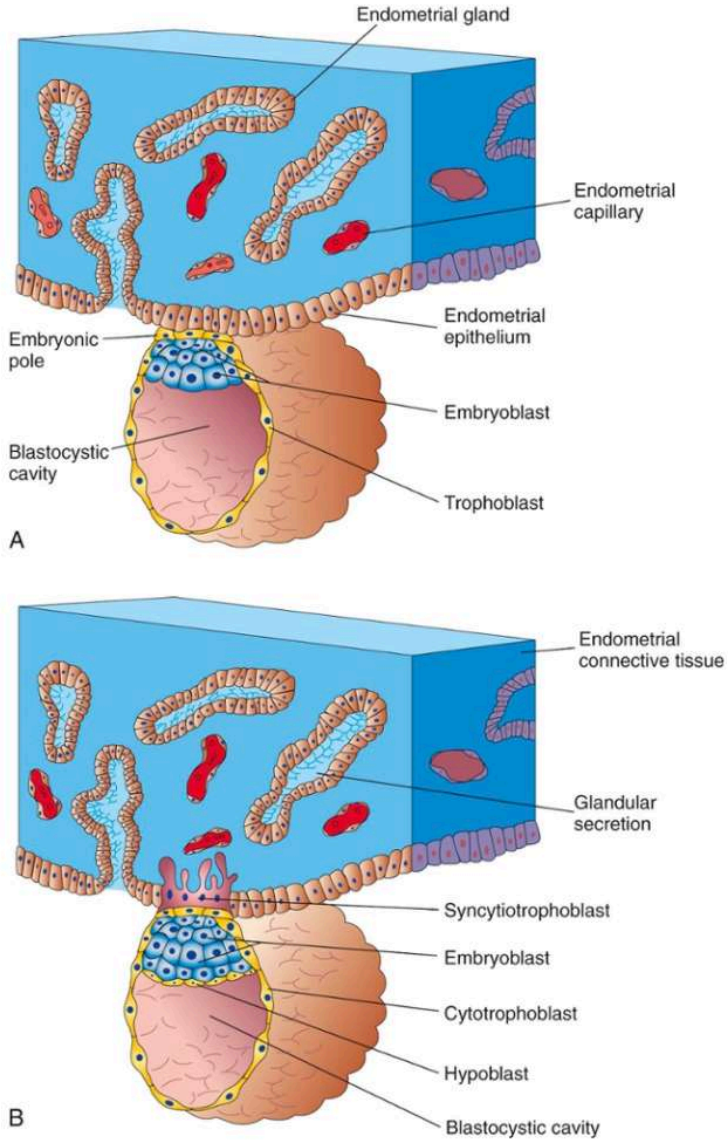
Approximately 6 days after fertilization, the blastocyst attaches to the endometrial epithelium.

*In vivo and in vitro studies have shown that attachment of the blastocyst occurs at the area above the inner cell mass (**embryonic pole**), a finding suggesting that the surfaces of the trophoblast are not all the same.*

As soon as it attaches to the epithelium, the trophoblast starts to proliferate and differentiate into two layers:

1- The **cytotrophoblast**, the inner layer of cells

2- The **syncytiotrophoblast**, the outer layer consisting of a multinucleate protoplasmic mass formed by the fusion of cells

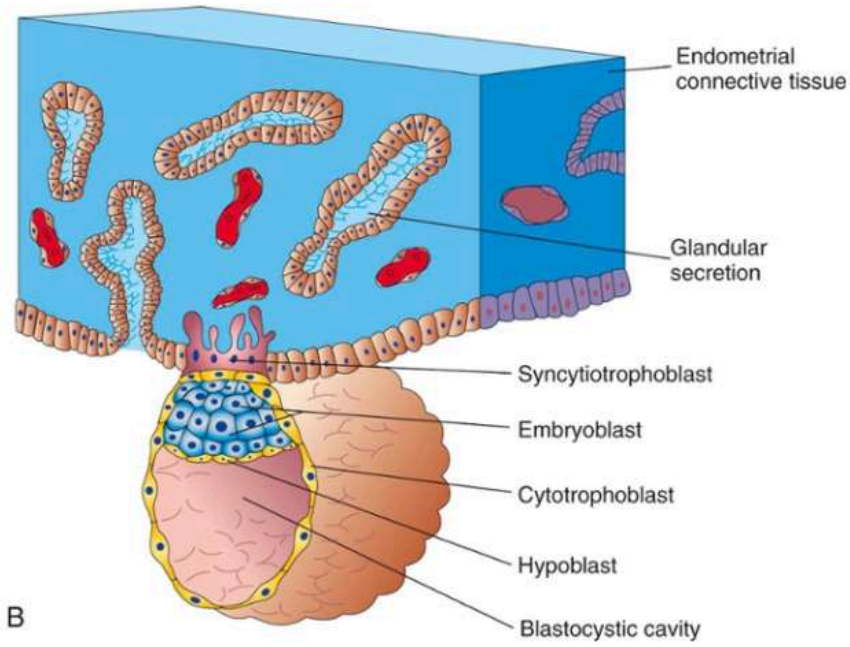


Trophoblast

The finger-like processes of the syncytiotrophoblast extend through the endometrial epithelium and invade the endometrial connective tissue.

By the end of the first week, the blastocyst is superficially implanted in the compact layer.

The highly invasive syncytiotrophoblast rapidly expands adjacent to the embryoblast—the **embryonic pole.**

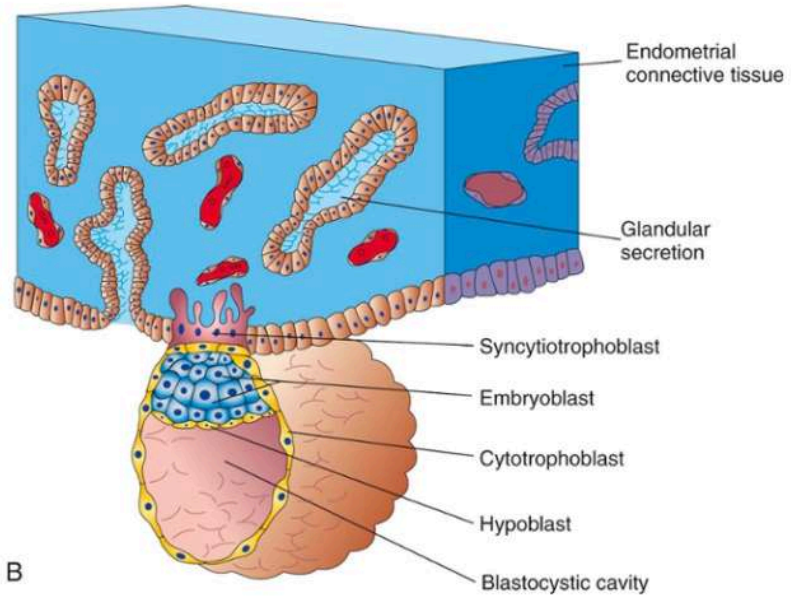


Trophoblast

The syncytiotrophoblast produces proteolytic enzymes that erode the maternal tissues, enabling the blastocyst to “burrow” into the endometrium.

Decidual cells also help to control the depth of penetration of the syncytiotrophoblast.

At the end of the first week, a <u>cuboidal layer of cells</u>, called the **<u>hypoblast</u>**, appears on the surface of the embryoblast, facing the blastocystic cavity.



Decidual reaction

While the embryo burrows into the endometrium, and some cytotrophoblastic cells fuse into syncytiotrophoblast, the **fibroblastlike stromal cells of the edematous endometrium** swell, with the accumulation of glycogen and lipid droplets.

These cells, called **decidual cells**, are tightly adherent and form a massive cellular matrix that first surrounds the implanting embryo and later occupies most of the endometrium. Concurrent with the **decidual reaction,** the leukocytes that have infiltrated the endometrial stroma during the late progestational phase of the endometrial cycle secrete **interleukin-2**, which prevents maternal recognition of the embryo as a foreign body during the early stages of implantation.

A primary function of the decidual reaction apparently is to provide an immunologically privileged site to protect the developing embryo from being rejected, but a real understanding of how this is accomplished has resisted years of intensive research.

Why Isn't the Conceptus Rejected by Its Mother?

An embryo is antigenically different from the mother and consequently should be rejected by a cellular immune react similar to the type that rejects an incompatible heart or kidney transplant.

Medawar (Nobel prize in 1960) proposed over fifty years ago three possibilities for why the developing conceptus is not rejected by its mother:

- fetal and maternal cells are physically separated from one another;
- the conceptus is antigenically immature;
- the maternal immune system is suppressed or becomes tolerant to the conceptus during pregnancy.

Why Isn't the Conceptus Rejected by Its Mother?

The trophoblast, which separates the actual tissues of the developing fetus from its mother, poorly expresses **MHC** molecules (antigenically immature…)

However, there is evidence that maternal T cells are activated during pregnancy.

it is likely that tolerogenic mechanisms block maternal T-cell responses and prevent fetal rejection.

The unique hormonal conditions of pregnancy that prepare the uterus for implantation and growth of the blastocyst apparently also induce tolerance. Such tolerance is specific for fetal antigens, for example, maternal antiviral immunity is not suppressed during pregnancy, as shown in HIV+ women who do not suffer from AIDS-like disease during pregnancy.

- **Formation of Amniotic Cavity, Embryonic Disc and Umbilical Vesicle**
- **Development of Chorionic Sac**
- **Implantation Sites of Blastocysts**

Bilaminar Embryonic Disc

Implantation of the blastocyst is completed during the second week of development with the formation of a **bilaminar embryonic disc** composed of two layers:

the epiblast and hypoblast (or **primitive endoderm)**

The **embryonic disc** gives rise to germ layers that form all the tissues and organs of the embryo.

Extraembryonic structures forming during the second week include the

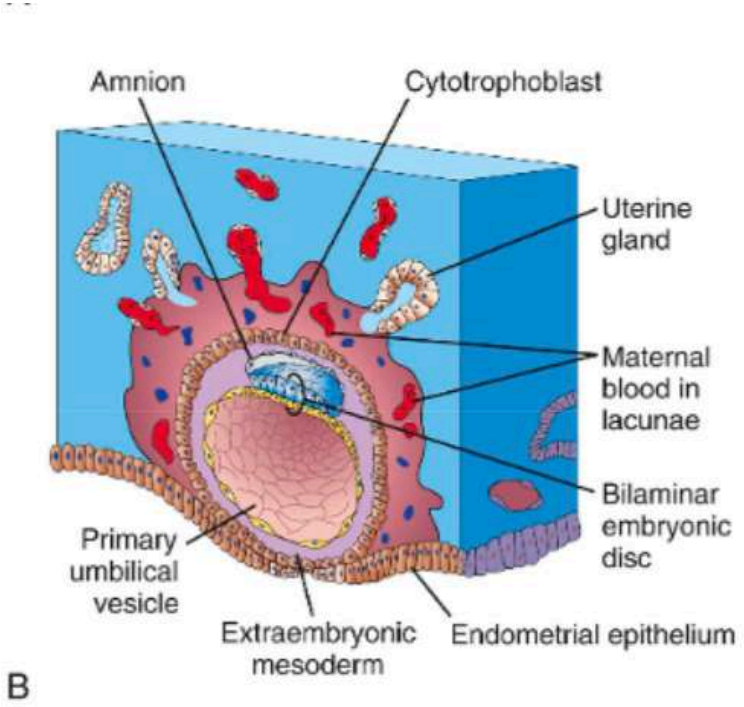
- amniotic cavity
- amnion
- **umbilical vesicle** (yolk sac)
- connecting stalk and chorionic sac.

Implantation

Syncytiotrophoblastic cells displace endometrial cells. Proteolytic enzymes produced by the syncytiotrophoblast are involved in this process.

The endometrial cells undergo ***apoptosis***, which facilitates implantation. The uterine connective tissue cells around the implantation site become loaded with glycogen and lipids. Some of these cells—**decidual cells**—degenerate providing a rich source of *embryonic nutrition*.

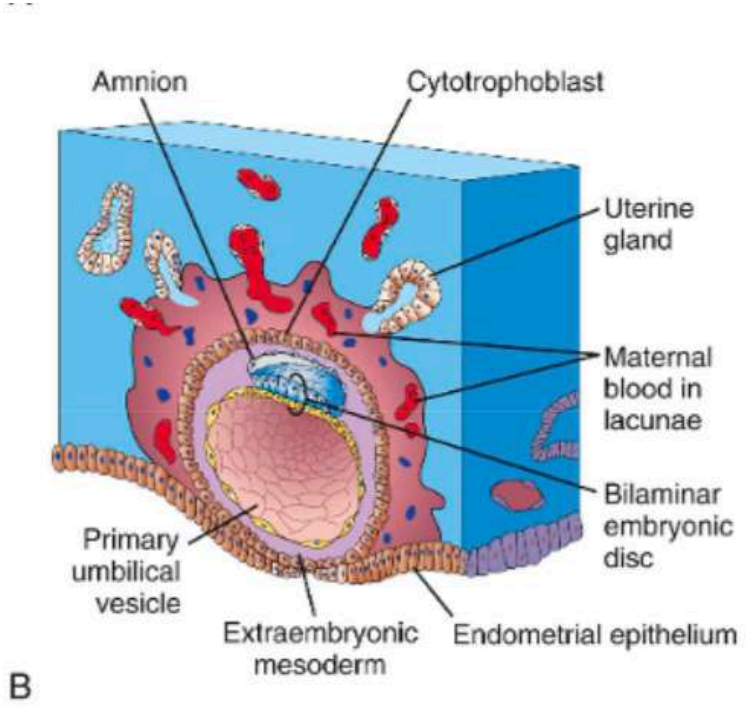
As the blastocyst implants, more trophoblast contacts the endometrium and continues to differentiate into two layers.



Implantation

The *cytotrophoblast*, a layer of mononucleated cells that is mitotically active. It forms new trophoblastic cells that migrate into the increasing mass of *syncytiotrophoblast*, where they fuse and lose their cell membranes.

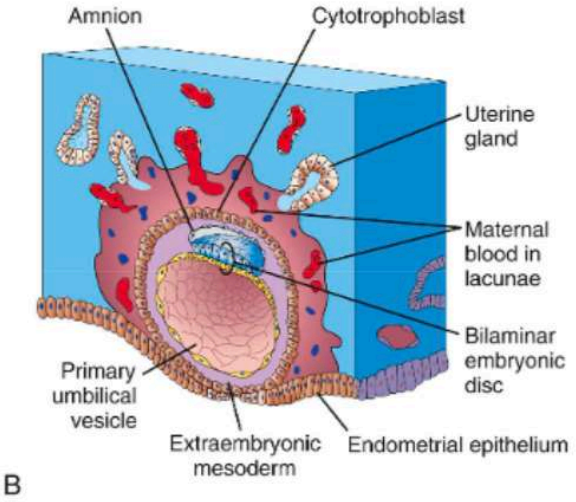
The syncytiotrophoblast, a rapidly expanding, multinucleated mass in which no cell boundaries are discernible.



Implantation

The **syncytiotrophoblast** produces a hormone, **human chorionic gonadotropin** (hCG), that enters the maternal blood in the lacunae in the syncytiotrophoblast.

hCG maintains the development of spiral arteries in the myometrium and formation of the syncytiotrophoblast. It also forms the basis for pregnancy tests. Highly sensitive assays are available for detecting hCG at the end of the second week even though the woman is probably unaware that she is pregnant.

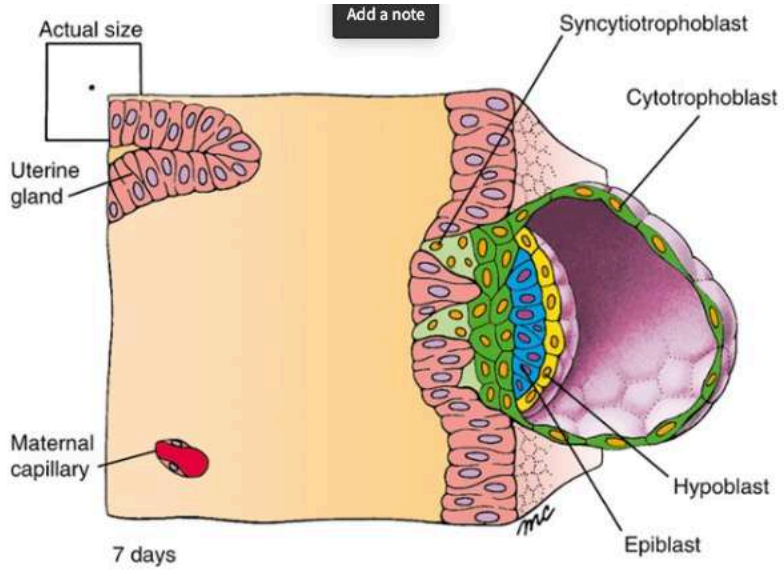


Human chorionic gonadotropin (hCG)

- hCG is a realiable marker of preganancy
- Enough hCG is produced by the syncytiotrophoblast at the end of the second week to give a positive pregnancy test
- Level of hCG remains to sustain Corpus Luteum
- High hCG remains high till placent develops and can produce enough hormones on its own to mantain pregnancy

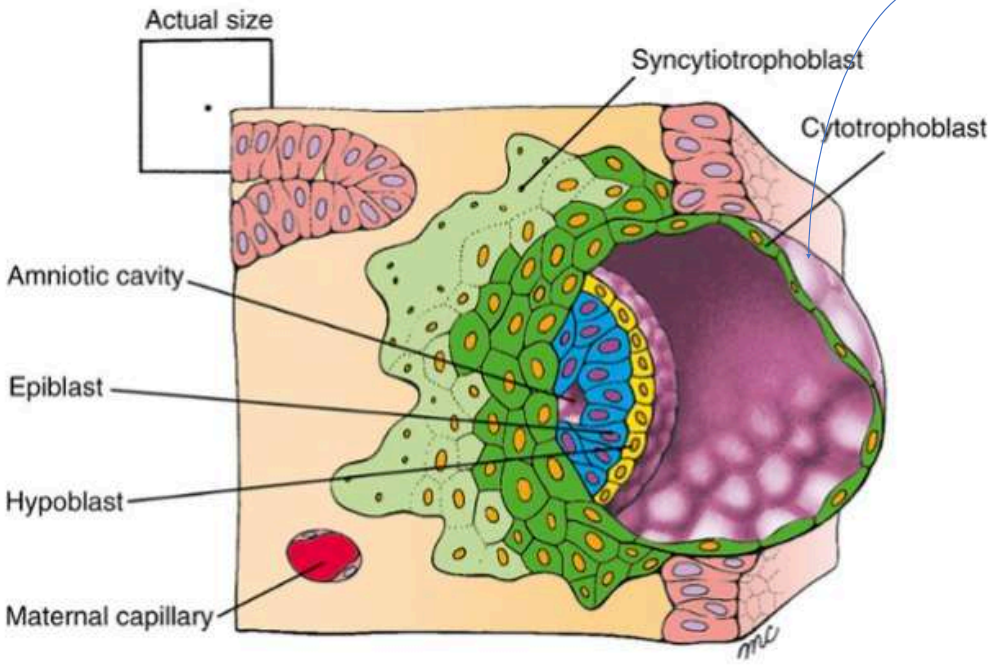
Implantation

The blastocyst adheres to the uterine wall at the end of the first week. Contact with the uterine endometrium induces the trophoblast at the embryonic pole to proliferate. Some of these proliferating cells lose their cell membranes and coalesce to form a syncytium (a mass of cytoplasm containing numerous dispersed nuclei) called the **syncytiotrophoblast.**



Implantation

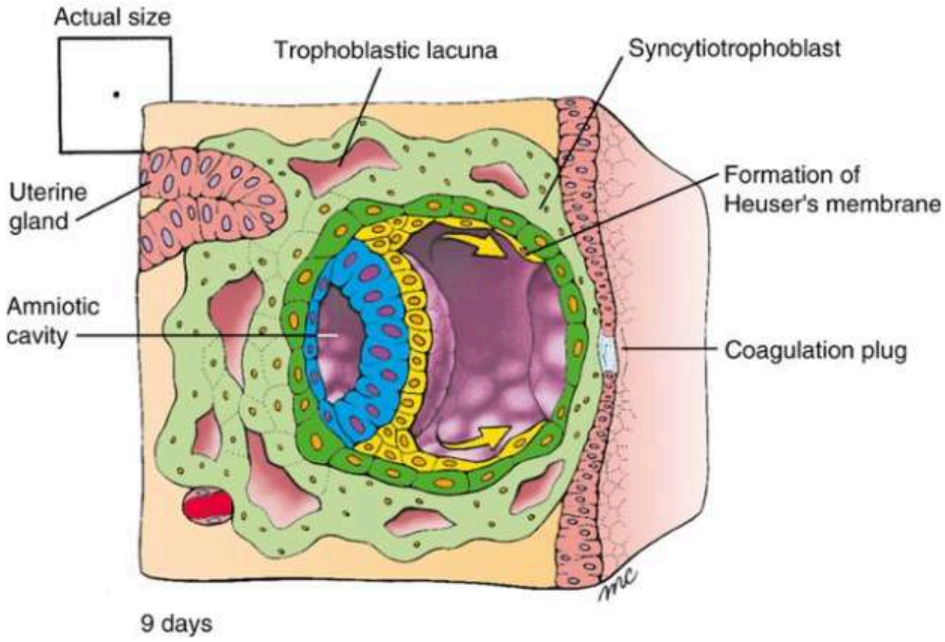
The cells of the trophoblast that line the wall of the blastocyst retain their cell membranes and constitute the **cytotrophoblast**. The syncytiotrophoblast increases in volume throughout the second week as cells detach from the proliferating cytotrophoblast at the embryonic pole and fuse with the syncytium



Implantation

As implantation progresses, the expanding syncytiotrophoblast gradually envelops the blastocyst.

By day nine, the syncytiotrophoblast blankets the entire blastocyst, except for a small region at the embryonic pole.
A plug of acellular material, called the **coagulation plug**, seals the small hole where the blastocyst implanted, temporarily marking this point in the endometrial epithelium



What Regulates the Initial Phase of Implantation: Blastocyst Adherence to the Uterine Epithelium?

The uterus cycles through receptive and non-receptive stages, during which implantation is possible, is controlled by estrogen and progesterone.

Estrogen, acting through the **estrogen receptor**, stimulates the uterine endometrium to undergo proliferation by inducing the production of growth factors such as **insulin-like growth factor 1** and it also prevents **programmed cell death** within the uterine epithelium.

What Regulates the Initial Phase of Implantation: Blastocyst Adherence to the Uterine Epithelium?

Progesterone, in turn, acting through the **progesterone receptor**, blocks continued endometrial growth and allows implantation to occur.

In the receptive stage, its apical **glycocalyx** (a polysaccharide matrix surface coating of epithelial cells including—in the case of the uterine epithelium—abundant high–molecular-weight mucin glycoproteins) decreases in amount.

Moreover, apical **microvilli**, which are normally abundant, retract to establish a flattened surface in many areas of the epithelium, and large apical protrusions called **pinopodes** form.

What Regulates the Initial Phase of Implantation: Blastocyst Adherence to the Uterine Epithelium?

Zona Pellucida prevents blastocyst attachment, but also experimental removal of the zona a few days earlier demonstrates that the blastocyst itself is still at the attachment-incompetent stage.

As blastocysts mature to the attachment stage, they express **perlecan**, a **heparan sulfate proteoglycan**, on their surface. Heparan sulfate proteoglycans will specific bind to various extracellular matrix proteins and growth factors/cytokines and thus could serve as attachment factors.

What Regulates the Initial Phase of Implantation: Blastocyst Adherence to the Uterine Epithelium?

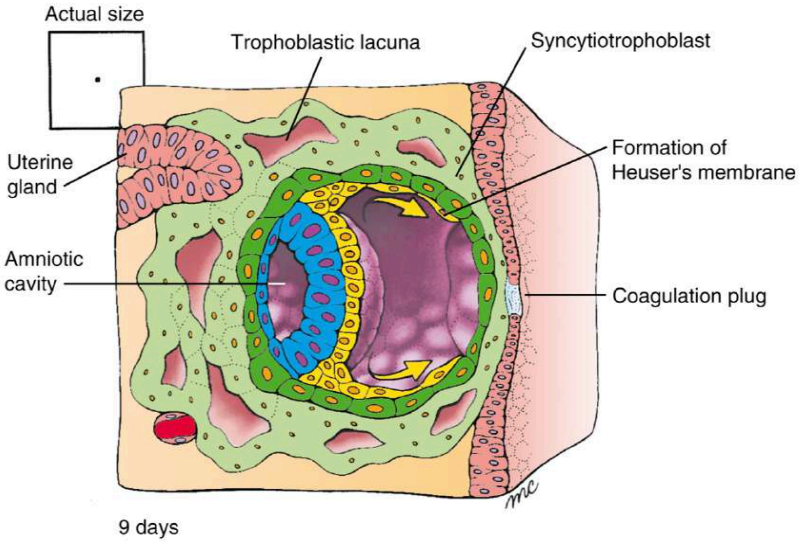
The uterus at the time of implantation upregulates expression of **heparin-binding epidermal growth factor–like growth factor (Hb-Egf)** at implantation sites, presumably in response to blastocyst signaling. Studies have shown that binding of Hb-Egf to the blastocyst requires that the blastocyst expresses both the Egf receptor and heparan sulfate proteoglycan.

Perlecan-null mice do not exhibit defects in implantation, suggesting that perlecan has functional redundancy with other heparan sulfate proteoglycans that can substitute (or are compensatorily upregulated) in its absence.

Embryoblast Reorganizes into Epiblast and Hypoblast

By day eight, the embryoblast consists of a distinct external (or upper) layer of columnar cells, called the **epiblast**, and an internal or lower layer of cuboidal cells, called the **hypoblast**. An extracellular basement membrane is laid down between the two layers as they become distinct.

The resulting two-layered embryoblast is called the **bilaminar embryonic disc**, or **bilaminar blastoderm**. With formation of the bilaminar embryonic disc, the primitive **dorsal-ventral axis** of the embryo is defined (i.e., epiblast is dorsal, hypoblast is ventral).



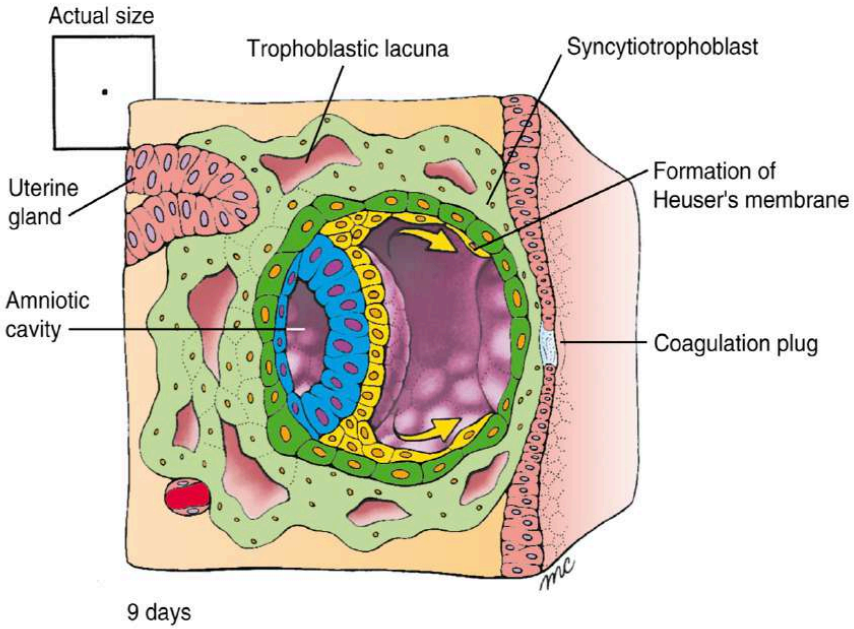
Epi→dorsal

Hypo→Ventral

Amniotic Cavity - day 8

The first new cavity to form during the second week—the **amniotic cavity**—appears on day eight as fluid begins to collect between cells of the epiblast and overlying trophoblast.

A layer of epiblast cells expands toward the embryonic pole and differentiates into a thin membrane separating the new cavity from the cytotrophoblast. This membrane is the lining of the **amnion**, one of four extraembryonic membranes (i.e., amnion, chorion, yolk sac, and allantois)

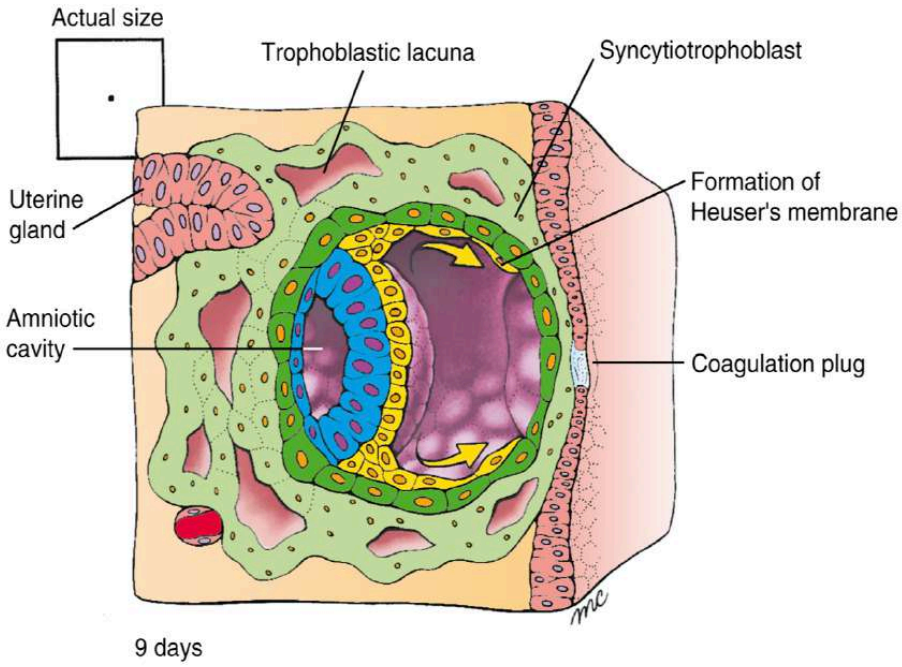


Amniotic Cavity- day 8

Slowly the amniotic cavity will be filled with a secretion of fluid, the amniotic fluid, which serves as a shock absorber to the developing embryo while preventig its desiccation.

Although the amniotic cavity is at first smaller than the blastocyst cavity, it expands steadily. By the eighth week, the amnion encloses the entire embryo.

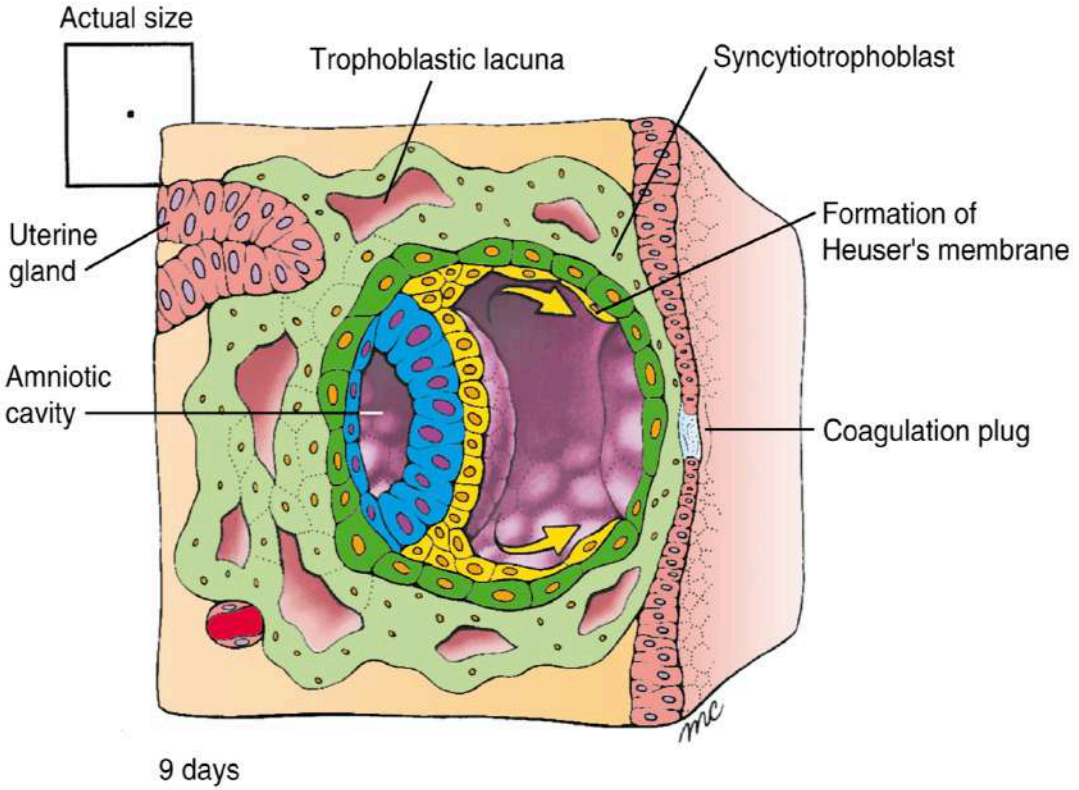
The embryonic epiblast is believed to contain all the cells that will generate the actual embryo.



Development of Yolk Sac and Chorionic Cavity

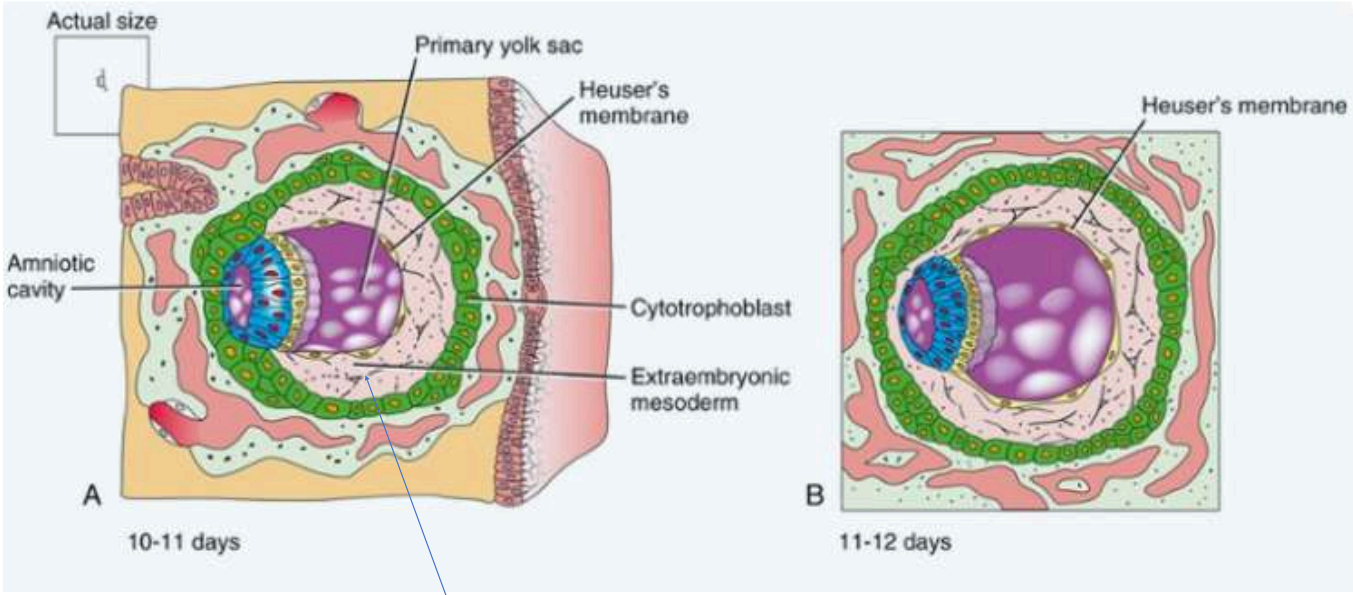
!!Proliferation of hypoblast cells, followed by two successive waves of cell migration, will form the yolk sac membranes or Heuser's membrane, which extend from the hypoblast into the blastocyst cavity.

The first wave of migration begins on day eight and forms the primary **yolk sac** (the **exocoelomic membrane**, or **Heuser's membrane**).



Development of Yolk Sac and Chorionic Cavity

Simultaneously, the **extraembryonic mesoderm** forms, filling the blastocyst cavity with loosely arranged cells. This early extraembryonic mesoderm (outside the embryo) is believed to originate in humans from the hypoblast

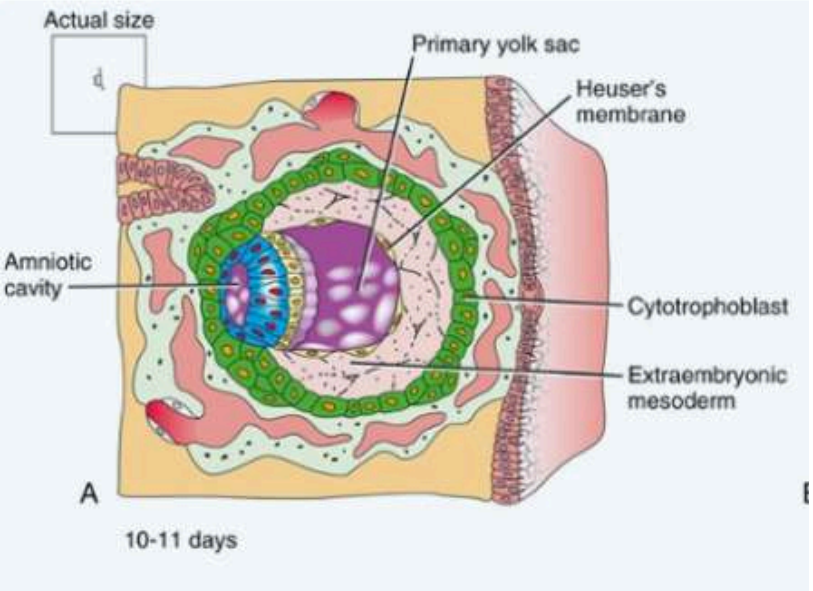


extraembryonic mesoderm

Extraembryonic mesoderm

The extraembryonic mesoderm joins the trophoblastic extension and give rise to the blood vessels that carry nutrients from the mother to the embryo.

- The narrow connecting stalk of extraembryonic mesoderm that links the embryo to the trophoblast eventually form the vessels of the umbilical cord.
- The fully developed organ, consisting of **trophoblast tissue and blood vessels containing mesoderm is called chorion**, that eventually fuses with the uterine wall to create the placenta. Thus the placenta will have both the maternal portion (the uterine endometrium modified during the pregnancy) and a fetal component: the chorion



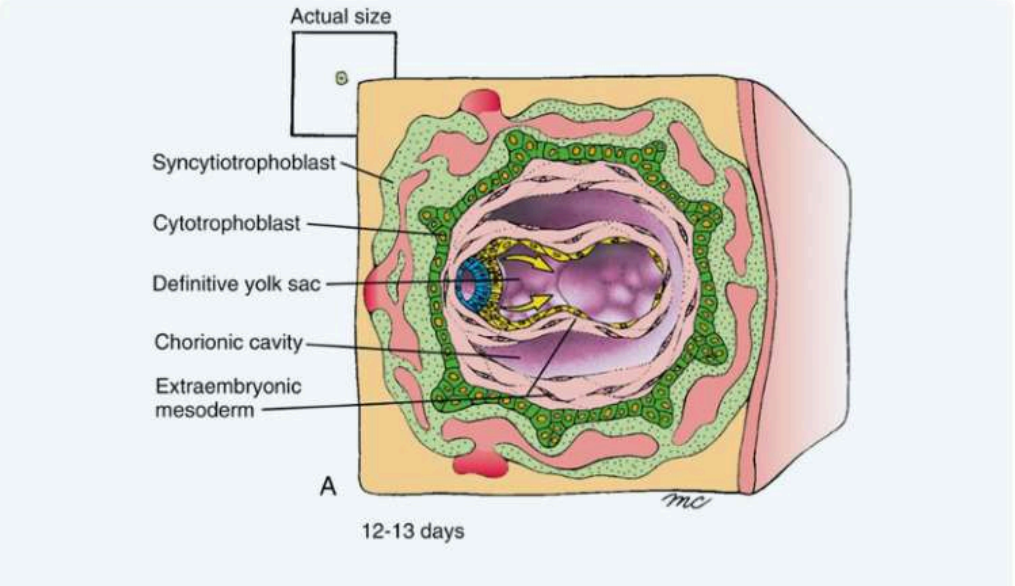
Development of Yolk Sac and Chorionic Cavity

The **extraembryonic coelom**, or **chorionic cavity**—is formed by splitting of the extraembryonic mesoderm into two layers.

1- yolk sac

2- the chorion

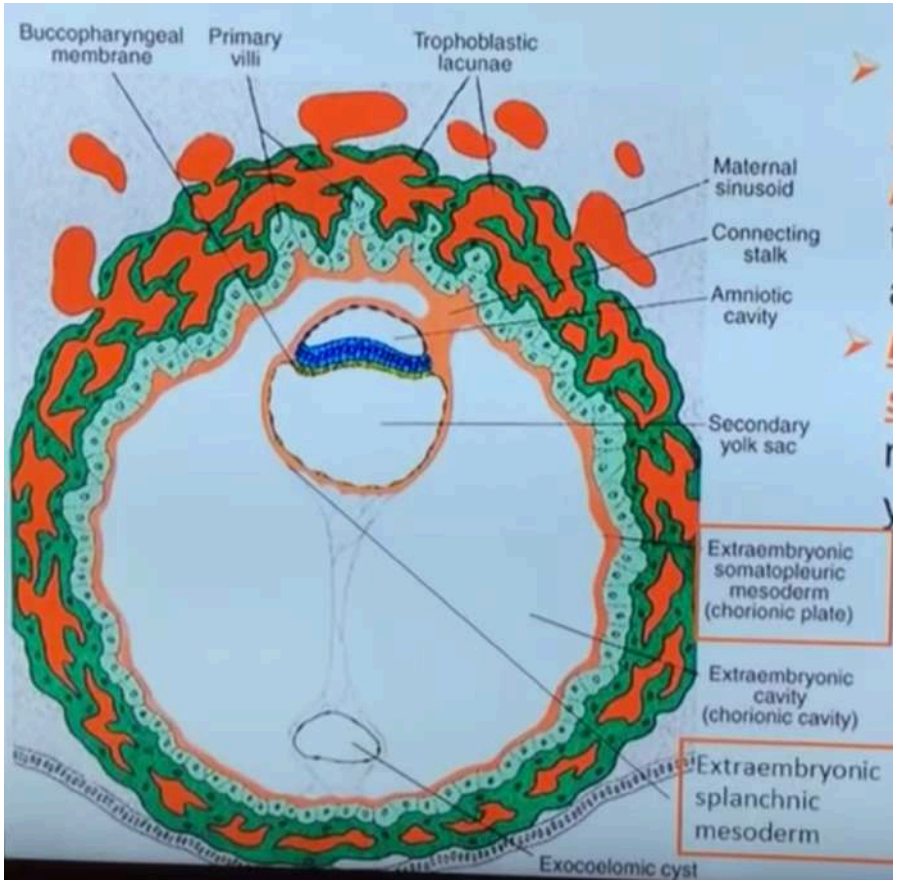
By day 13, the embryonic disc with its dorsal amnion and yolk sac is suspended in the chorionic cavity solely by a thick stalk of extraembryonic mesoderm called the **connecting stalk**



Division of the extrambryonic mesoderm

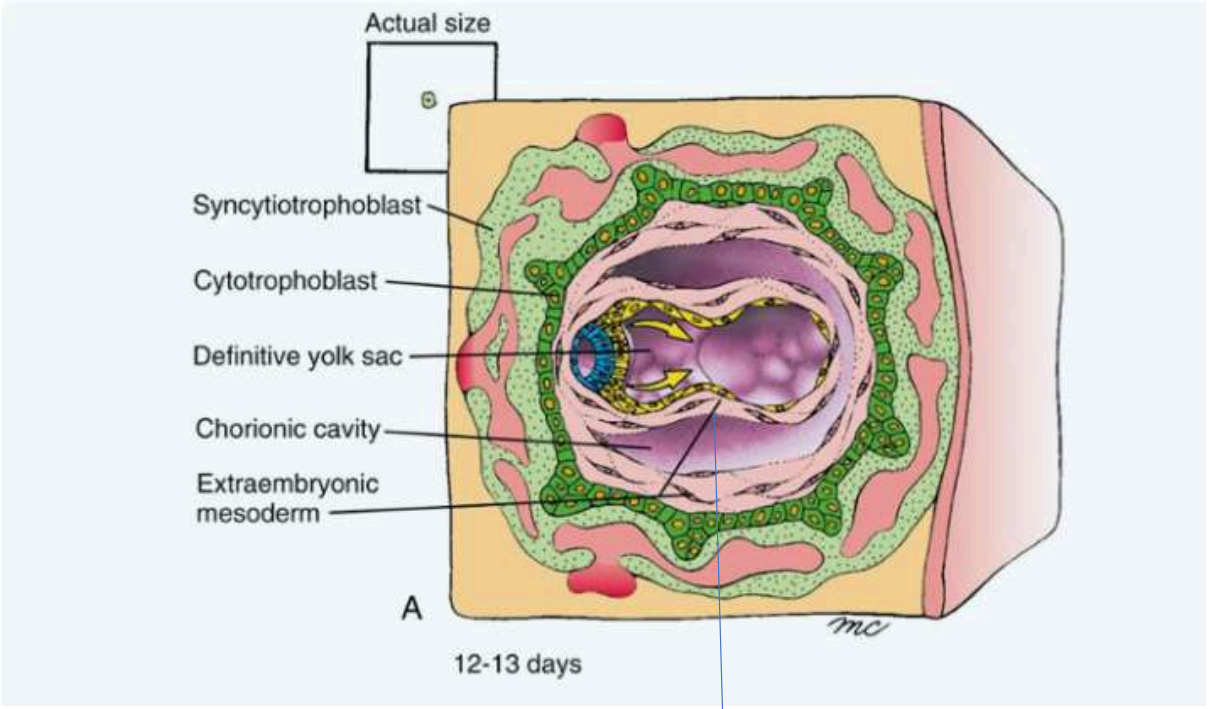
- Extra embryonic **somatic** mesoderm (chorionic plate) is the mesoderm lining the cytotrophoblast and amnion

- Extraembryonic **splanchnic** mesoderm-the mesoderm covering the yolk sac



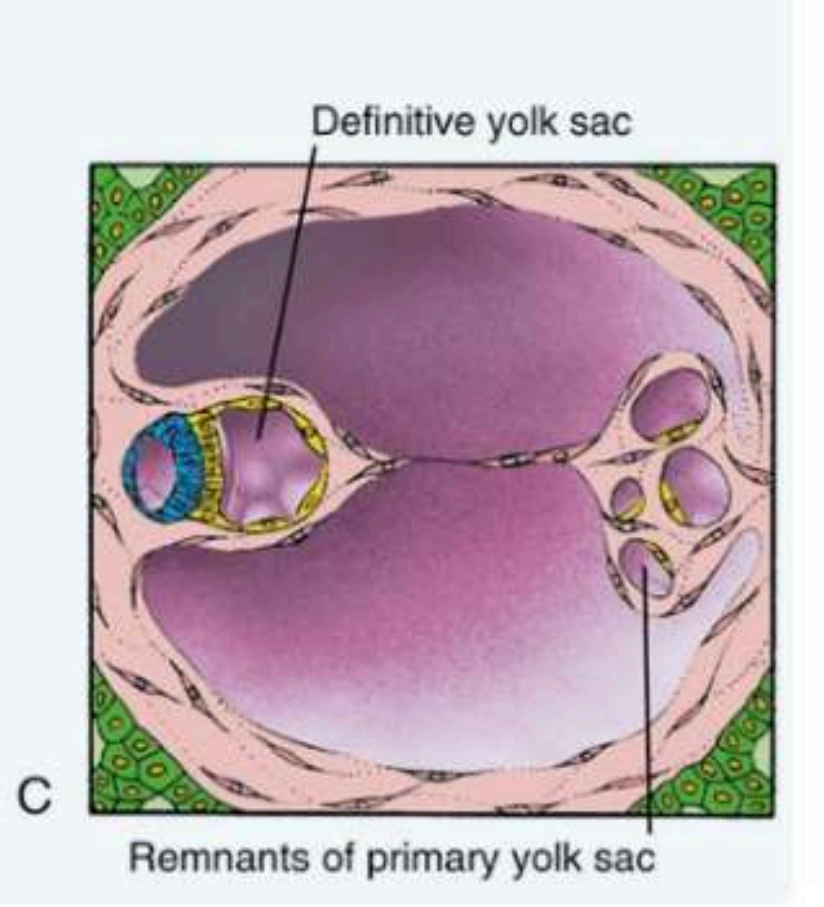
Development of Yolk Sac and Chorionic Cavity

By day 12, the primary yolk sac is displaced (and eventually degenerates) *by the second wave of migrating hypoblast cells*, which forms the secondary yolk sac.



Development of Yolk Sac and Chorionic Cavity

The **Chorionic cavity** expand and it will surround also the amniotic cavity and primitive yolk sac separating from the cytotrophoblast, except at one area where germ disc is connected to the trophoblast by the <u>connecting stalk.</u>



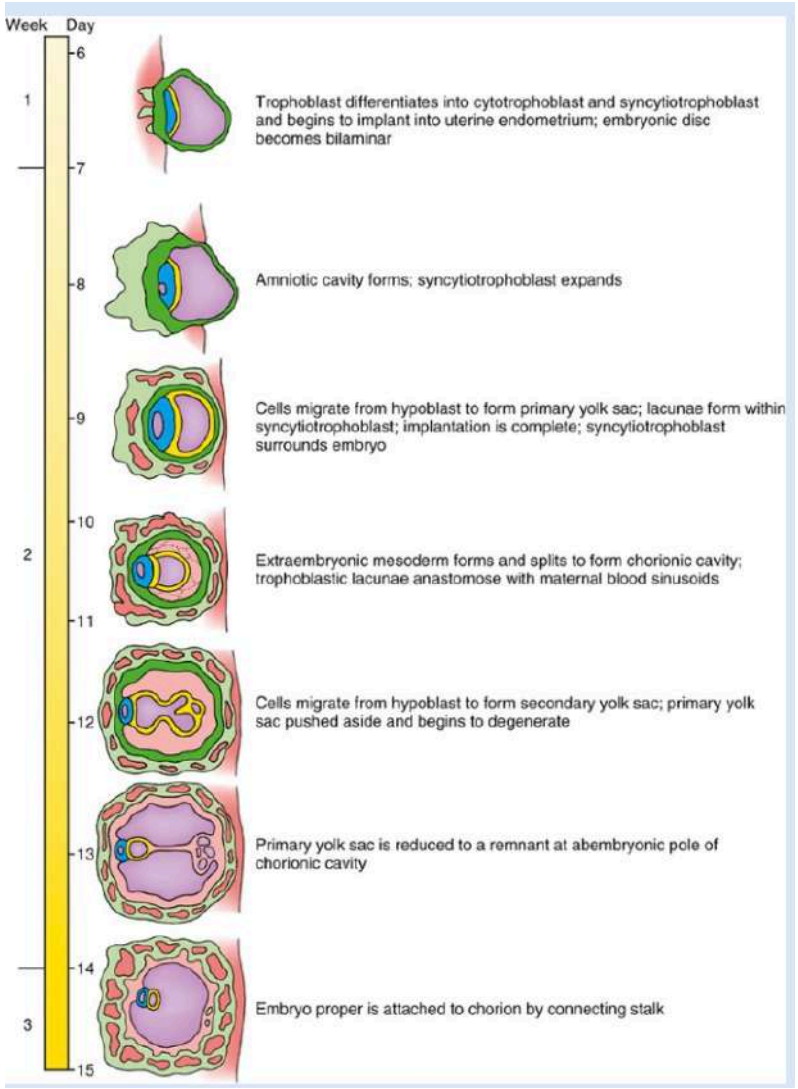
The **definitive yolk sac** remains a major structure associated with the developing embryo through the fourth week and performs important early functions.

Extraembryonic mesoderm forming the outer layer of the yolk sac is a major site of **hematopoiesis** (blood formation).

After the fourth week, the yolk sac is rapidly overgrown by the developing embryonic disc.

The yolk sac normally disappears before birth, but on rare occasions it persists in the form of a digestive tract anomaly called **Meckel's diverticulum**

Time Line of the second week of development



- https://studentconsult.inkling.com/read/moore-before-we-are-born-9/animations/implantation

Uteroplacental Circulatory System Begins to Develop during Second Week

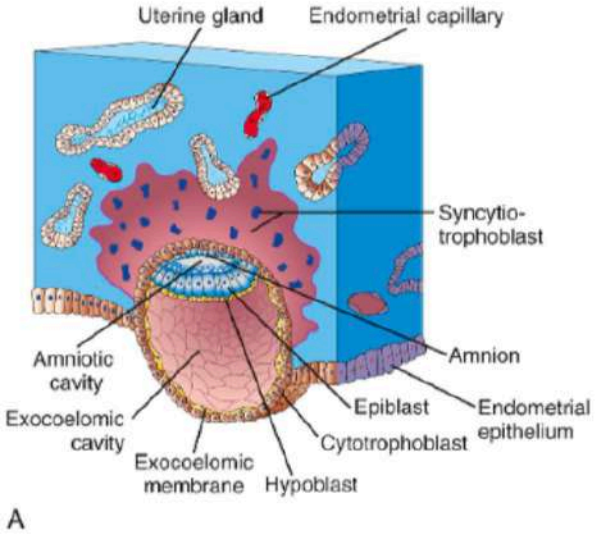
During the first week of development, the embryo obtains nutrients and eliminates wastes by simple diffusion.

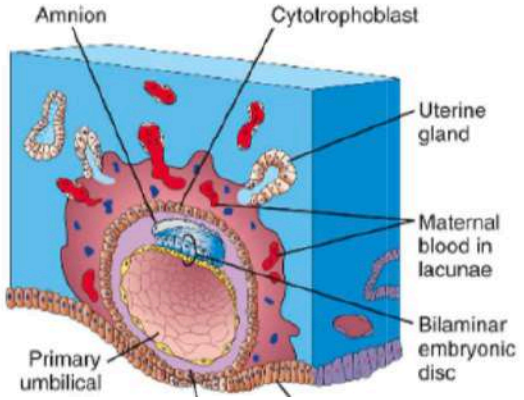
Rapid growth of the embryo makes a more efficient method of exchange imperative. **Uteroplacental circulation**—the system by which maternal and fetal blood flowing through the **placenta** come into close proximity and exchange gases and metabolites by diffusion.

Primordial Uteroplacental Circulatory System Begins to Develop during Second Week

This system begins to form on day nine, as vacuoles called **trophoblastic lacunae** open within the syncytiotrophoblast. Maternal capillaries near the syncytiotrophoblast then expand to form **maternal sinusoids** that rapidly anastomise with the trophoblastic lacunae.

Between days eleven and thirteen, these anastomoses continue to develop, and the cytotrophoblast proliferates locally to form extensions that grow into the overlying syncytiotrophoblast.





Uteroplacental Circulatory System Begins to Develop during Second Week

When maternal blood flows into the lacunae, oxygen and nutritive substances become available to the extraembryonic tissues over the large surface of the syncytiotrophoblast.

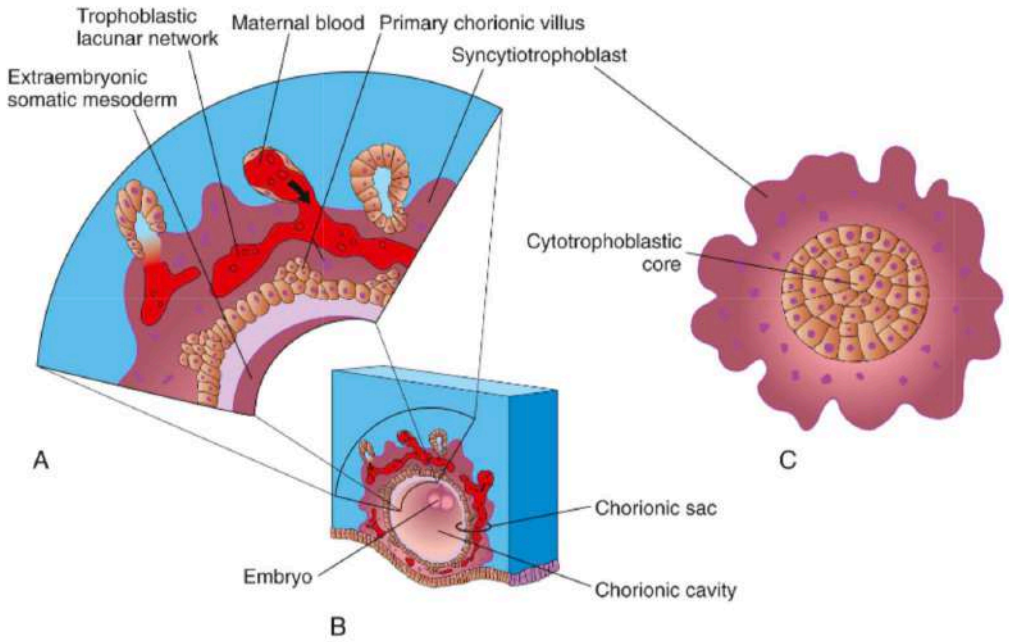
Oxygenated blood passes into the lacunae from the *spiral endometrial arteries* in the endometrium;

deoxygenated blood is removed from the lacunae through endometrial veins.

Uteroplacental Circulatory System Begins to Develop during Second Week

The extensions of cytotrophoblast grow-out into the blood-filled lacunae, carrying with them a covering of syncytiotrophoblast.

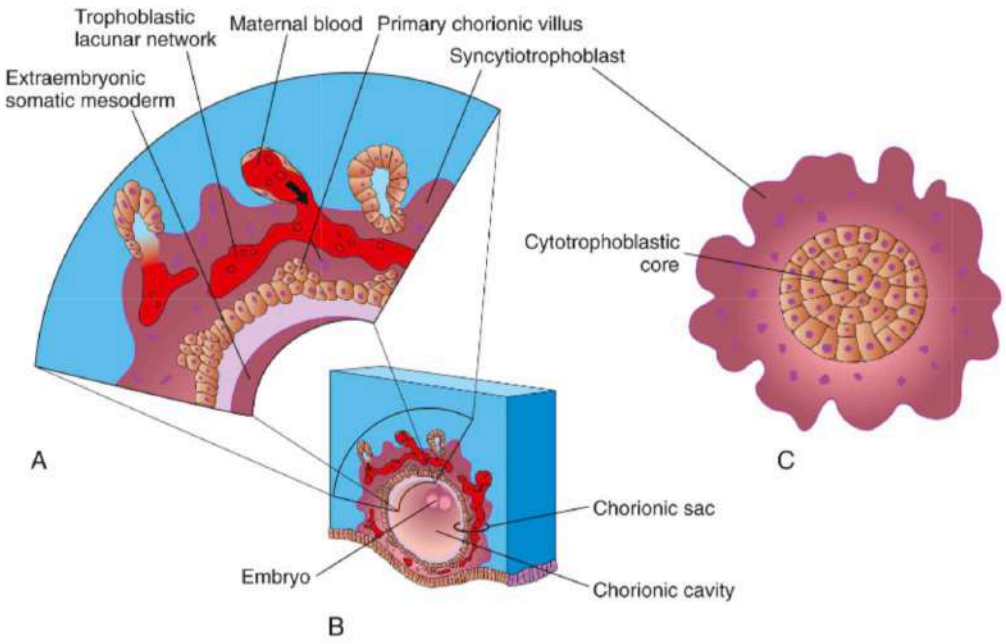
The resulting outgrowths are called **primary chorionic stem villi**.



The growth of these cytotrophoblastic extensions is believed to be induced by the underlying **extraembryonic somatic mesoderm**.

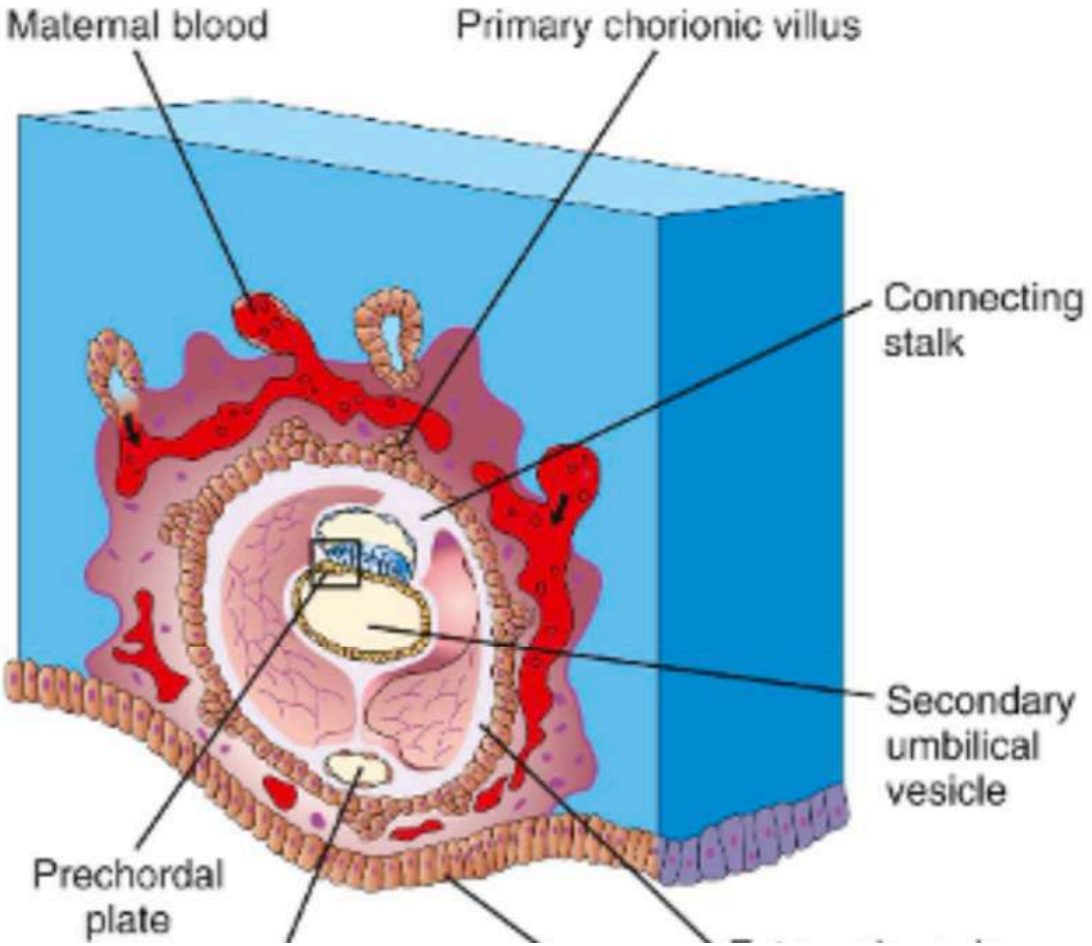
The extraembryonic somatic mesoderm and the two layers of trophoblast form the **chorion**.

The chorion forms the wall of the chorionic sac.



The embryo, amniotic sac, and Yolk Sac (umbilical vesicle) are suspended in the **chorionic cavity** by the connecting stalk. Transvaginal ultrasonography (endovaginal sonography) is used to measure the diameter of the chorionic sac.

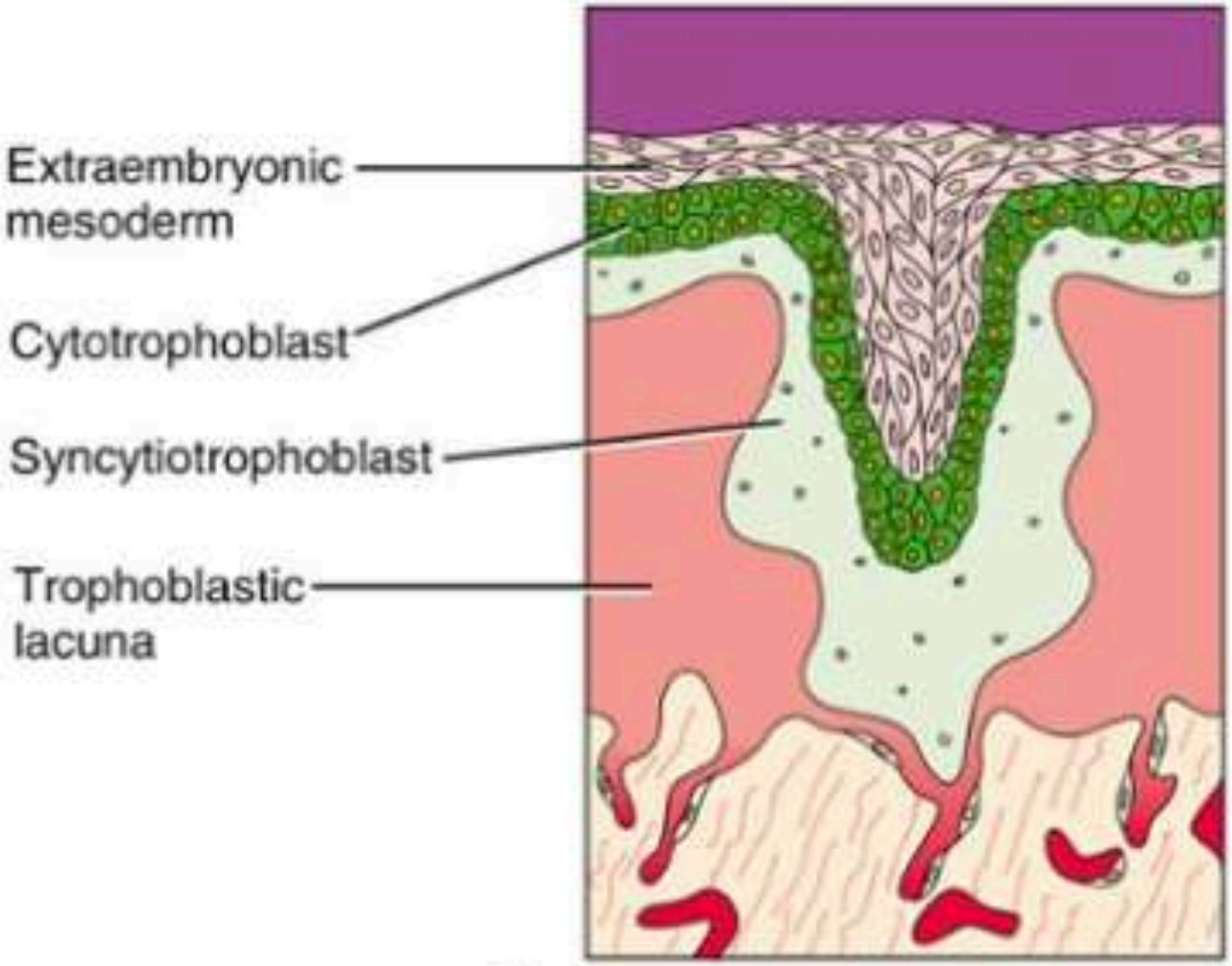
This measurement is valuable for evaluating early embryonic development and pregnancy outcome.



Uteroplacental Circulatory System Begins to Develop during Second Week

By day sixteen the extraembryonic mesoderm associated with the cytotrophoblast penetrates the core of the primary stem villi, thus transforming them into **secondary chorionic stem villi**.

By the end of the third week, this villous mesoderm has given rise to blood vessels that connect with the vessels forming in the embryo proper, thus establishing a working uteroplacental circulation, the primitive heart starts beating on day twenty-two.



B Secondary stem villus (16 days)

Uteroplacental Circulatory System Begins to Develop during the Second Week

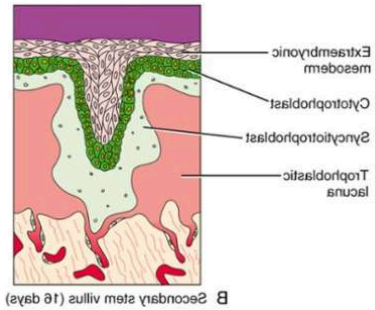
The gases, nutrients, and wastes that diffuse between the maternal and fetal blood must cross four tissue layers:

1 endothelium of the villus capillaries

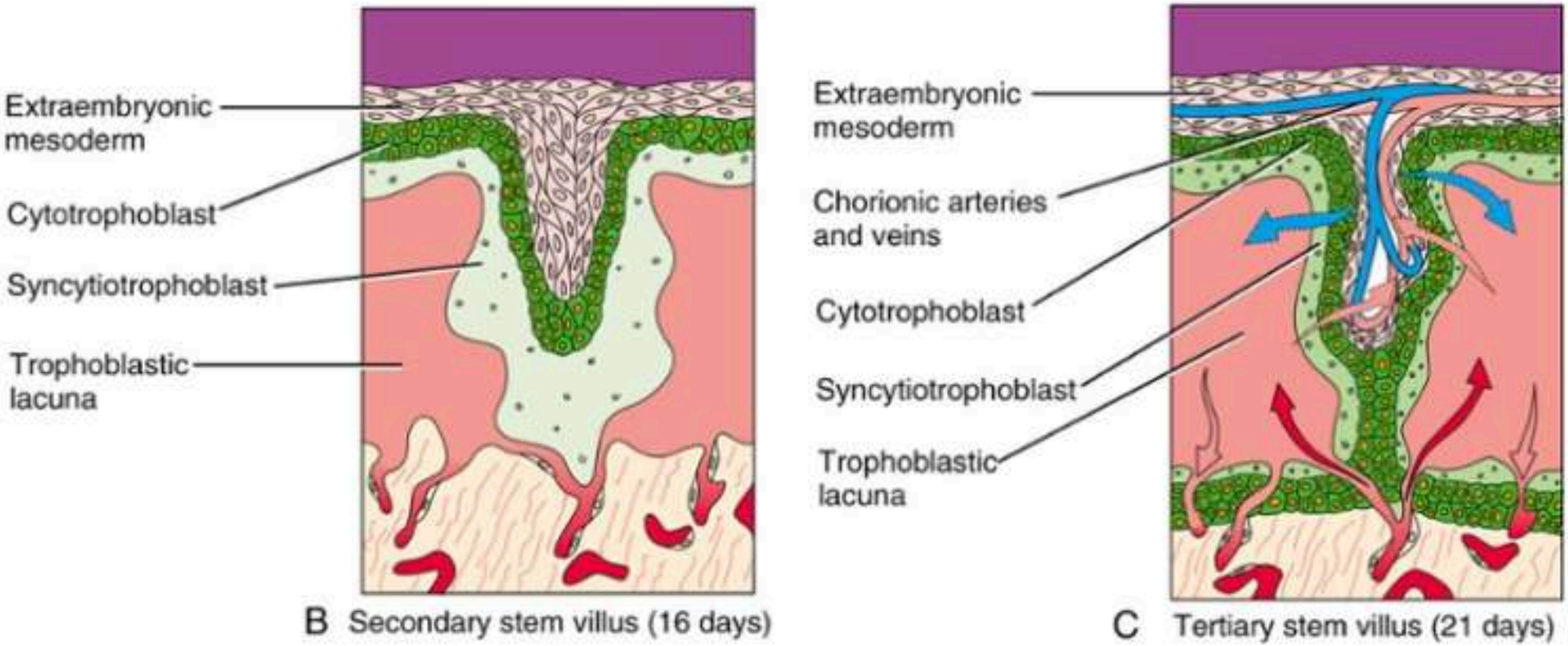
2 the loose connective tissue in the core of the villus (extraembryonic mesoderm)

3 layer of cytotrophoblast

4 layer of syncytiotrophoblast



The **endothelial lining of the maternal sinusoids** does not invade the trophoblastic lacunae, so a maternal layer does not need to be crossed.



https://studentconsult.inkling.com/read/larsen-human-embryology-schoenwolf-5/videos/animation-2-2

The rule of Twos

Many events occur in twos during the second week. Thus, a “rule of twos” constitutes a handy mnemonic for remembering events of the second week.

During the second week,
the embryoblast splits **into two layers**: the epiblast and the hypoblast.
The trophoblast also gives rise to **two tissues**: the cytotrophoblast and the syncytiotrophoblast.
Two yolk sacs form, first the primary and then the secondary.
Two new cavities form: the amniotic cavity and the chorionic cavity.
The **extraembryonic mesoderm splits into the two layers** that line the chorionic cavity, and the **amnion, yolk sac, and chorion** all become two-layered membranes.