Cleavage

Cell Division – Cell Cycle Control

Morula – Compaction

Blastocyst – Hatching

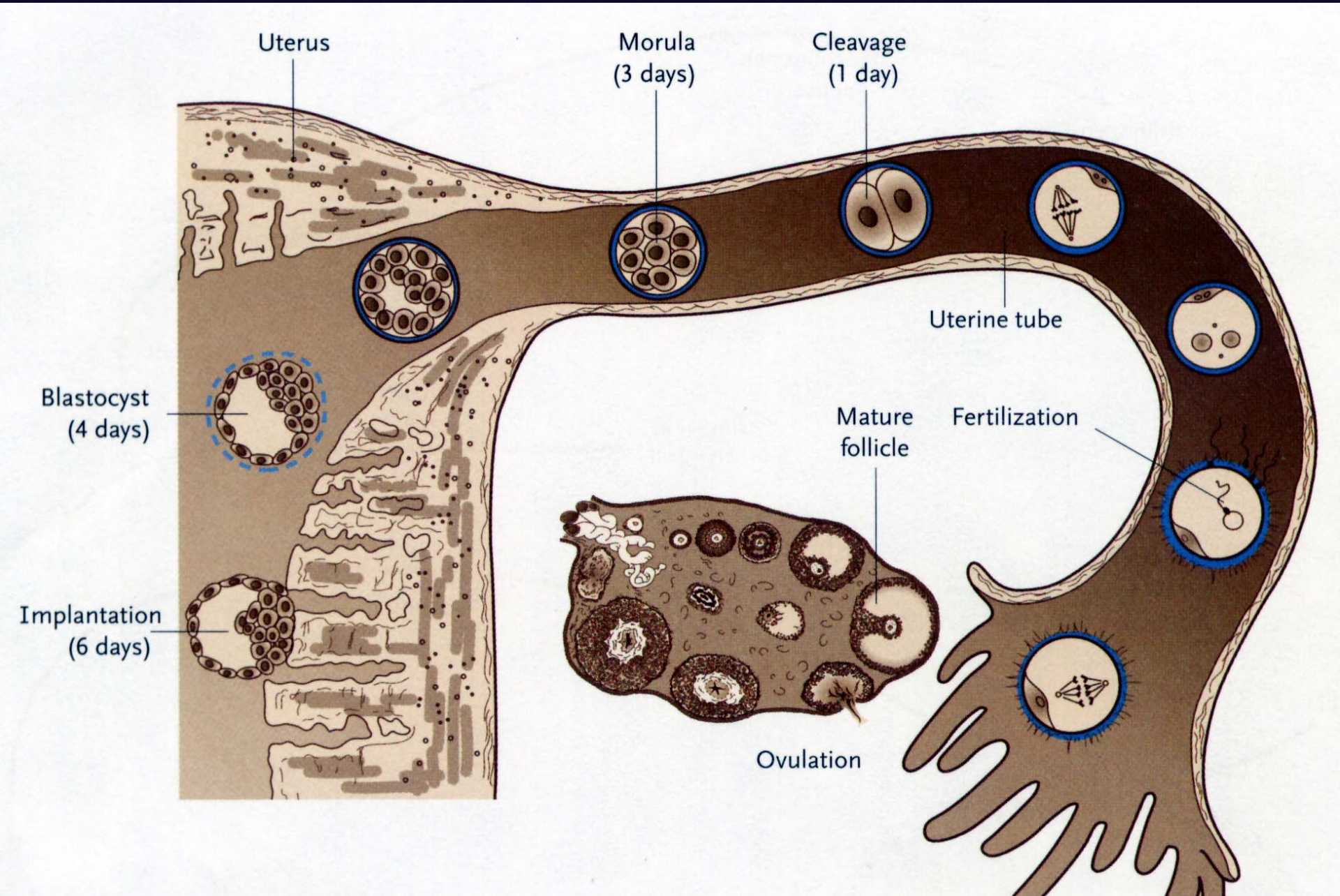
Implantation – Decidual Reaction

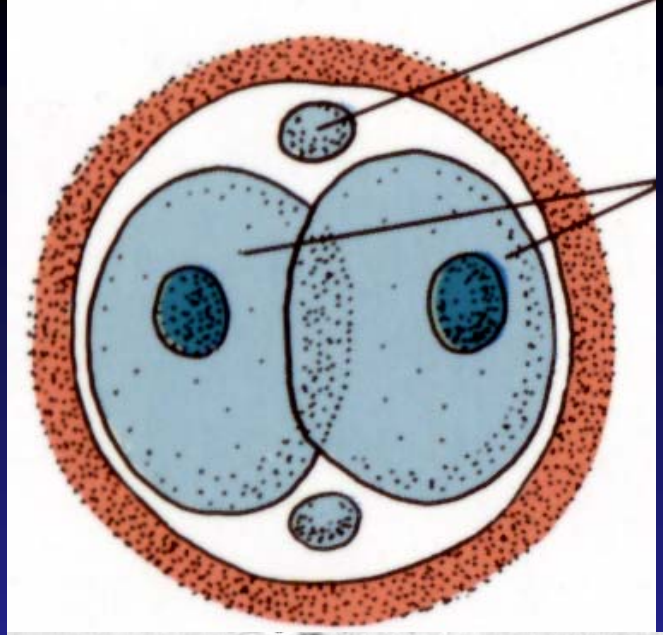
Early Cell Lineages

- Inner Cell Mass
- Trophoblasts (Extra-embryonic)

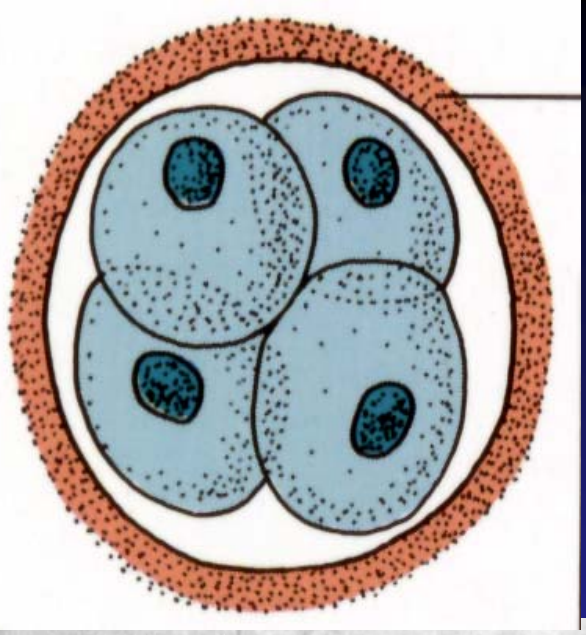
Anomalies

Cleavage


Uterus
Morula
(3 days)
Cleavage
(1 day)
Uterine tube
Blastocyst
(4 days)
Mature
follicle
Fertilization
Implantation
(6 days)
Ovulation



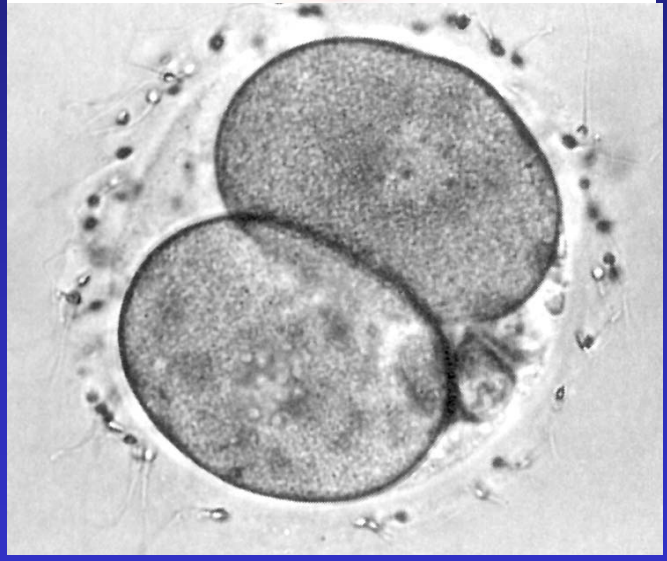
Cleavage



Blastomere

Equal

Asynchronous



40 hours – 4 cells

72 hours – 6-12 cells

96 hours – 16-32 cells

Cleavage – Molecular Events

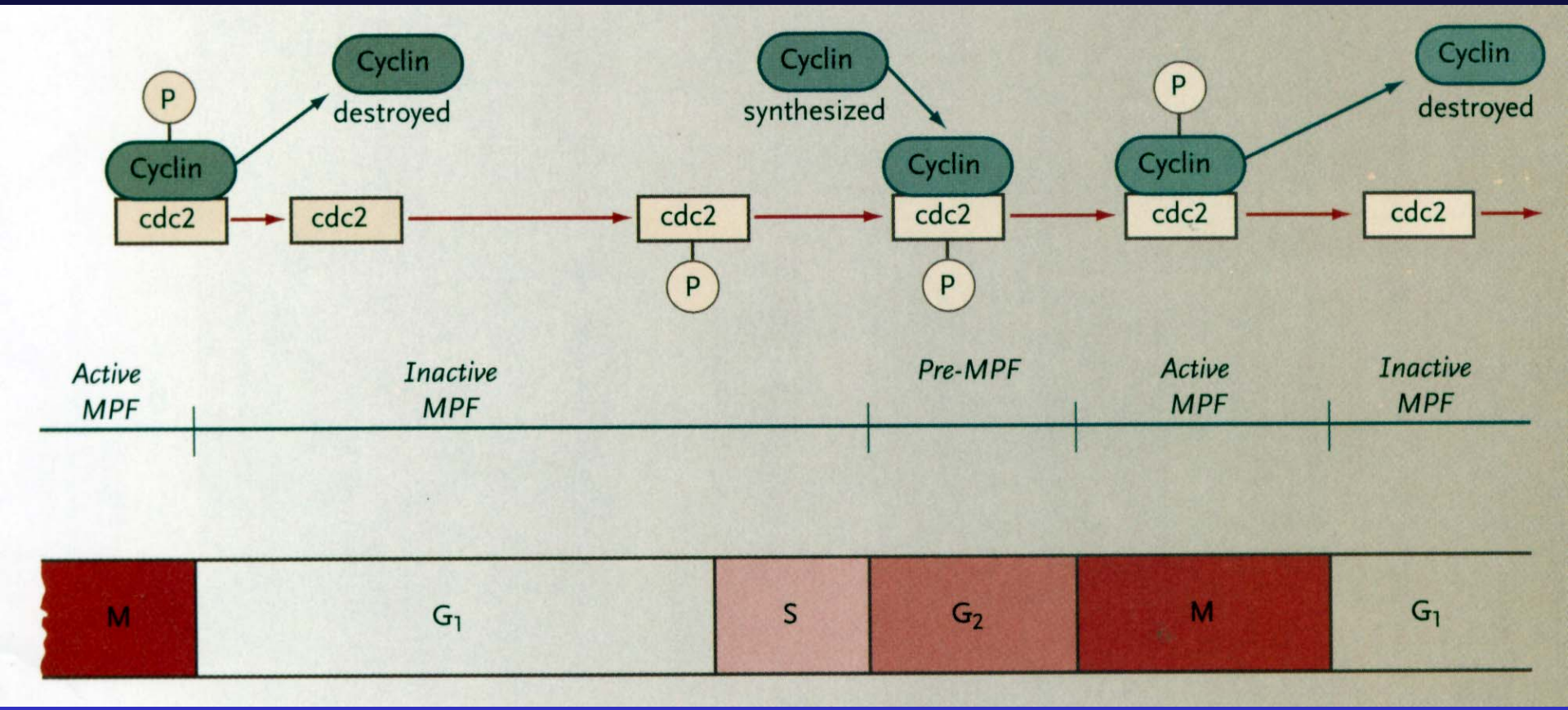
In mammals – no large maternal stores of RNA and ribosomes

Zygotic transcription begins by 2-4 cell stage

Oct-3 – Transcription factor expressed in egg

- KO in mouse – arrest at 1 cell stage
- Expressed in blastomeres up to morula stage
- Expressed in germ cells

Cell Cycle Control



MFP = Maturation-promoting factor, or mitosis-promoting factor

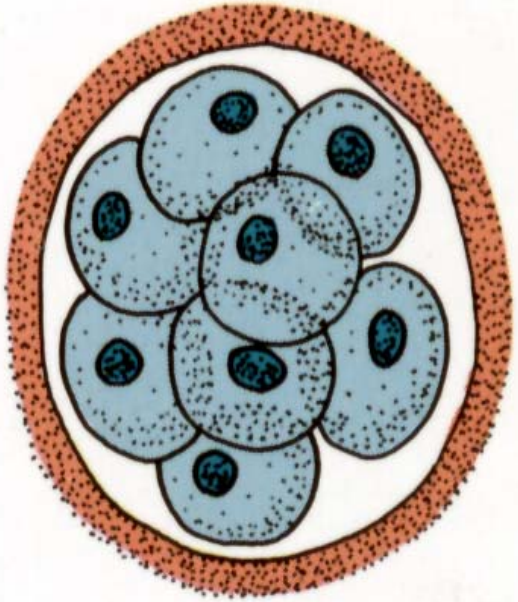
Cell Cycle Control

MPF – Mitosis Promoting Factor
- Heterodimer (cdc2 and cyclin B)
- Some Activities: Nuclear envelope breakdown, assembly of mitotic spindle

Cdc2 – Cell Division Cycle 2
- Phosphoprotein (P in S and G2)
- Constitutively expressed

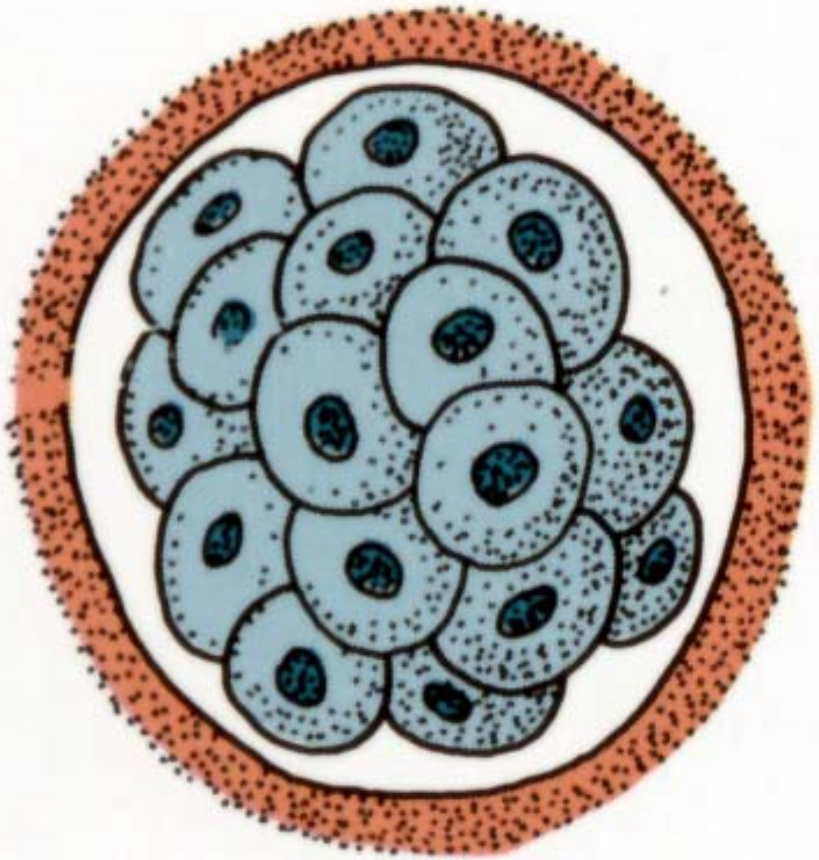
Cyclin B –present in G2 and M
- Bound to cdc2
- Phosphoprotein (P in M)
- Degraded in G1

Morula

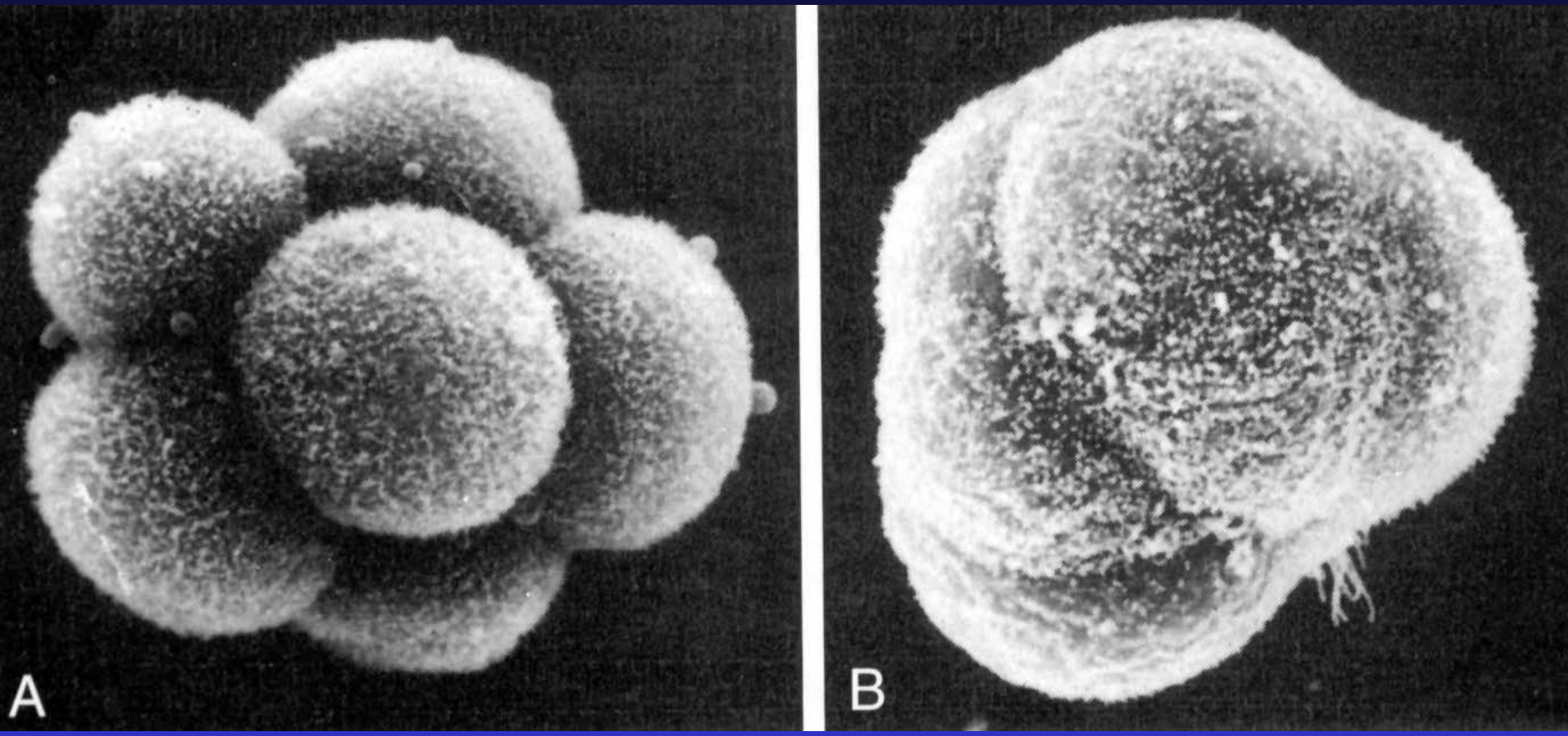


32 cell stage

‘Berry’ - appearance



Compaction

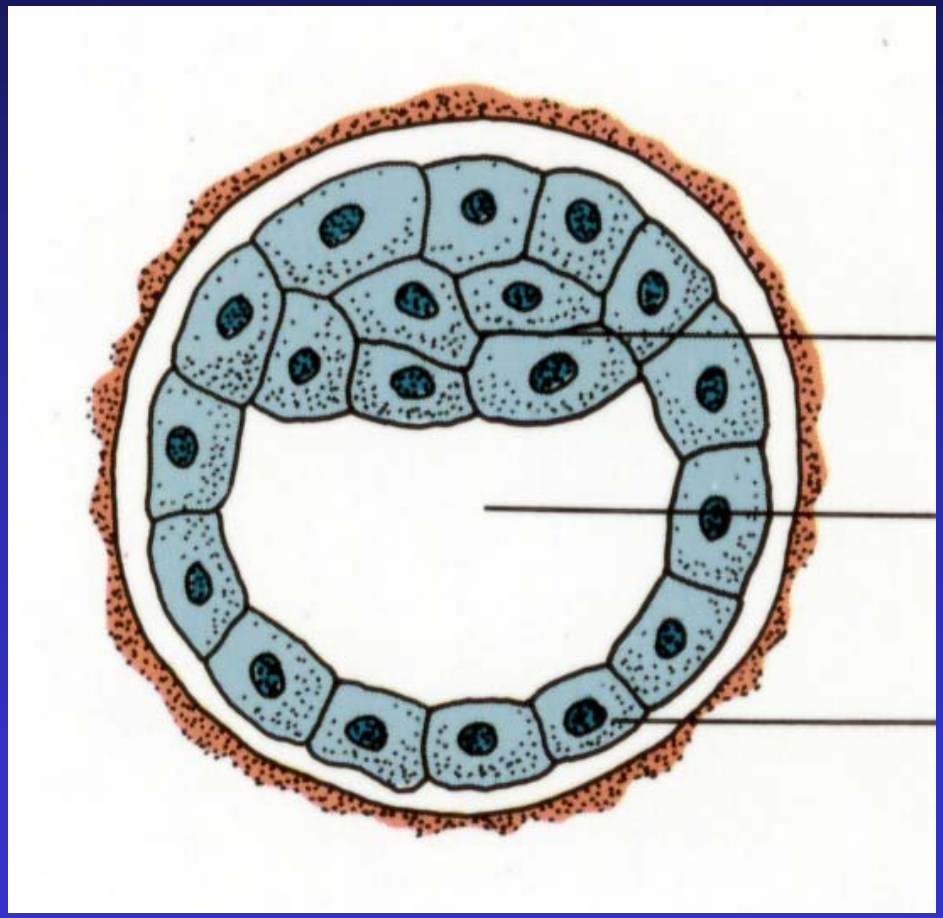


Compaction – blastomeres: loosely adherent → tightly adherent
cytoskeleton reorganization, tight junctions

Inner Cell Mass vs. Outer Cell Mass

Blastocyst

Embryo pole



abembryonic pole

Inner cell mass
(**embryoblast)**

Blastocoel

Outer cell mass
(**trophoblast)**

Hatching

(from zona pellucida)

Hatching: Enzymatic production by Trophoblasts - digestion of the Zona Pellucida

Zona Pellucida - Functions

Species-specific sperm penetration

Permanent block to polyspermy

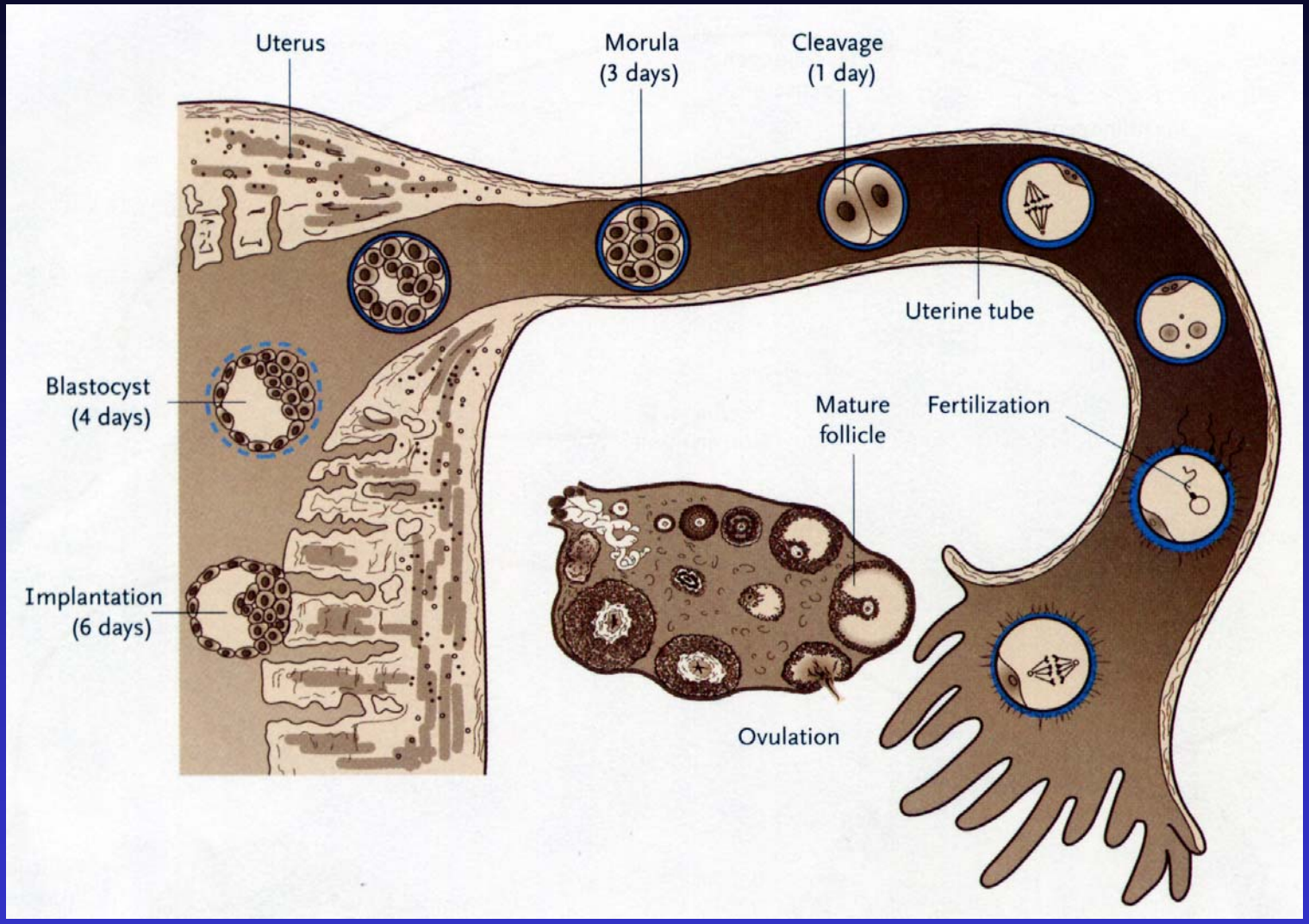
Acts as a porous selective filter - uterine tube signals

Immunological barrier - no HLA (histocompatibility antigens)

Keeps blastomeres together (loosely adherent)

Prevents premature implantation

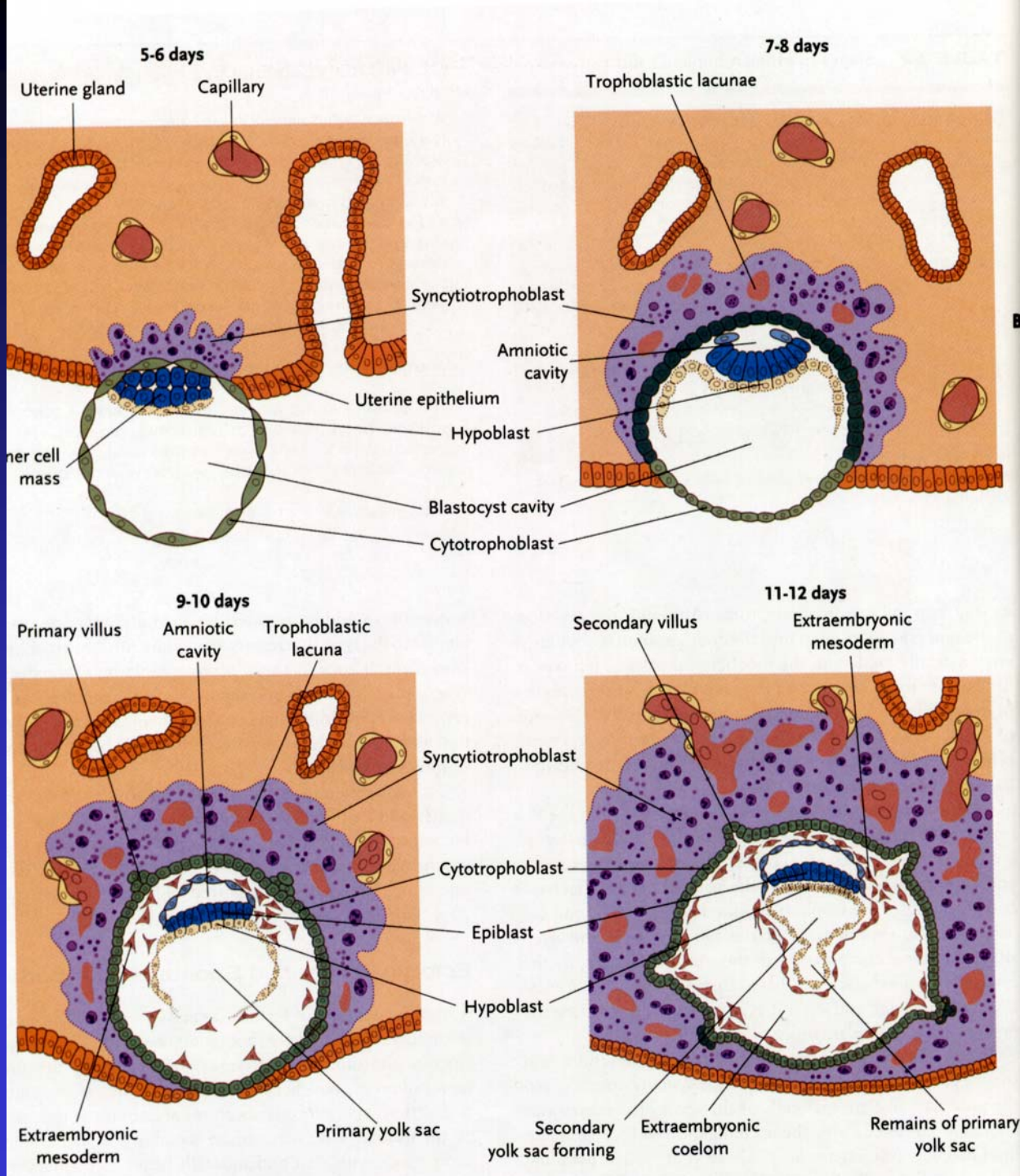
Implantation

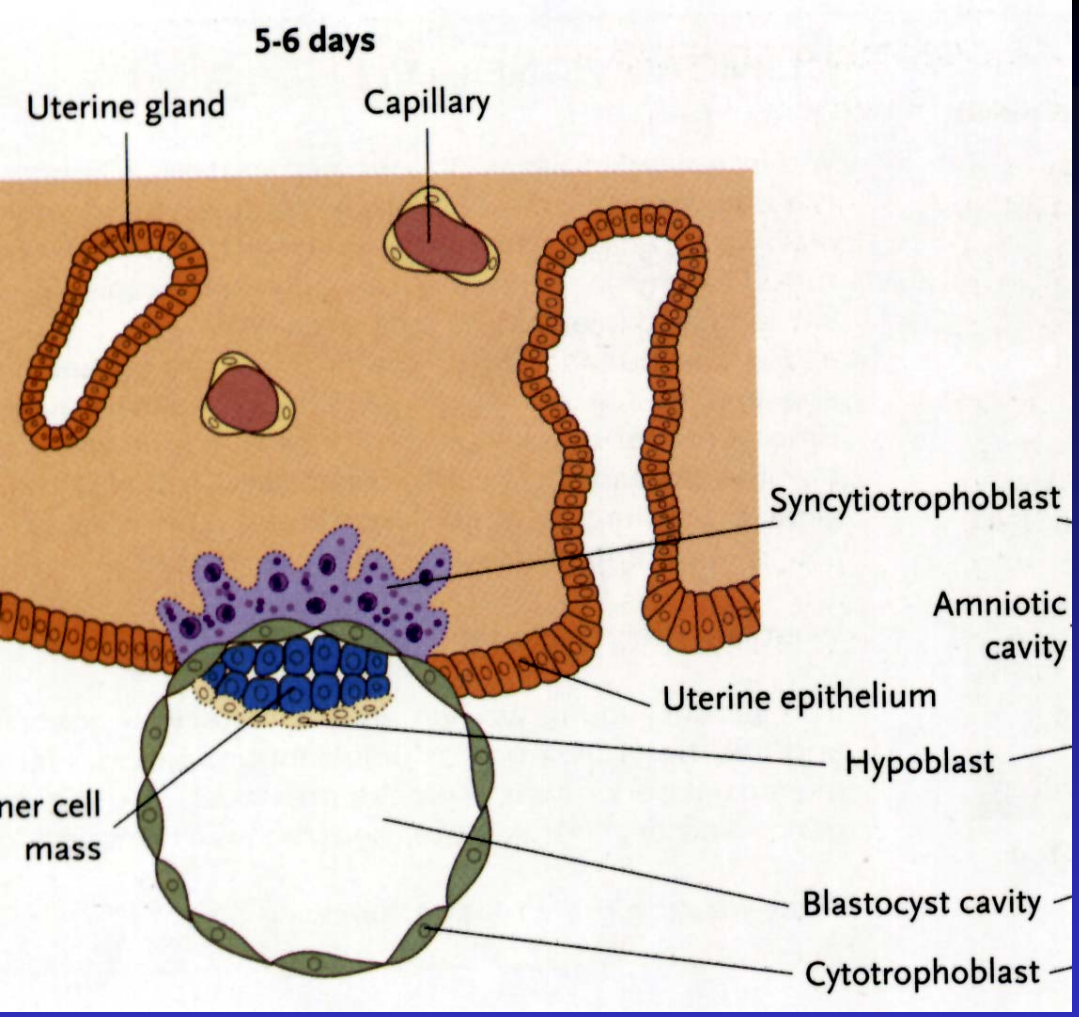


Decidual reaction – Progesterone induced endometrial cell conversion to secretory decidual cell

Implantation

- **Days 6 –12**
- **Adhesion, blastocyst to endometrium**
- **Trophoblast proliferation**
- **Syncytiotrophoblast**
- **Secretion of hydrolytic enzymes**
- **Breakdown of endometrium**





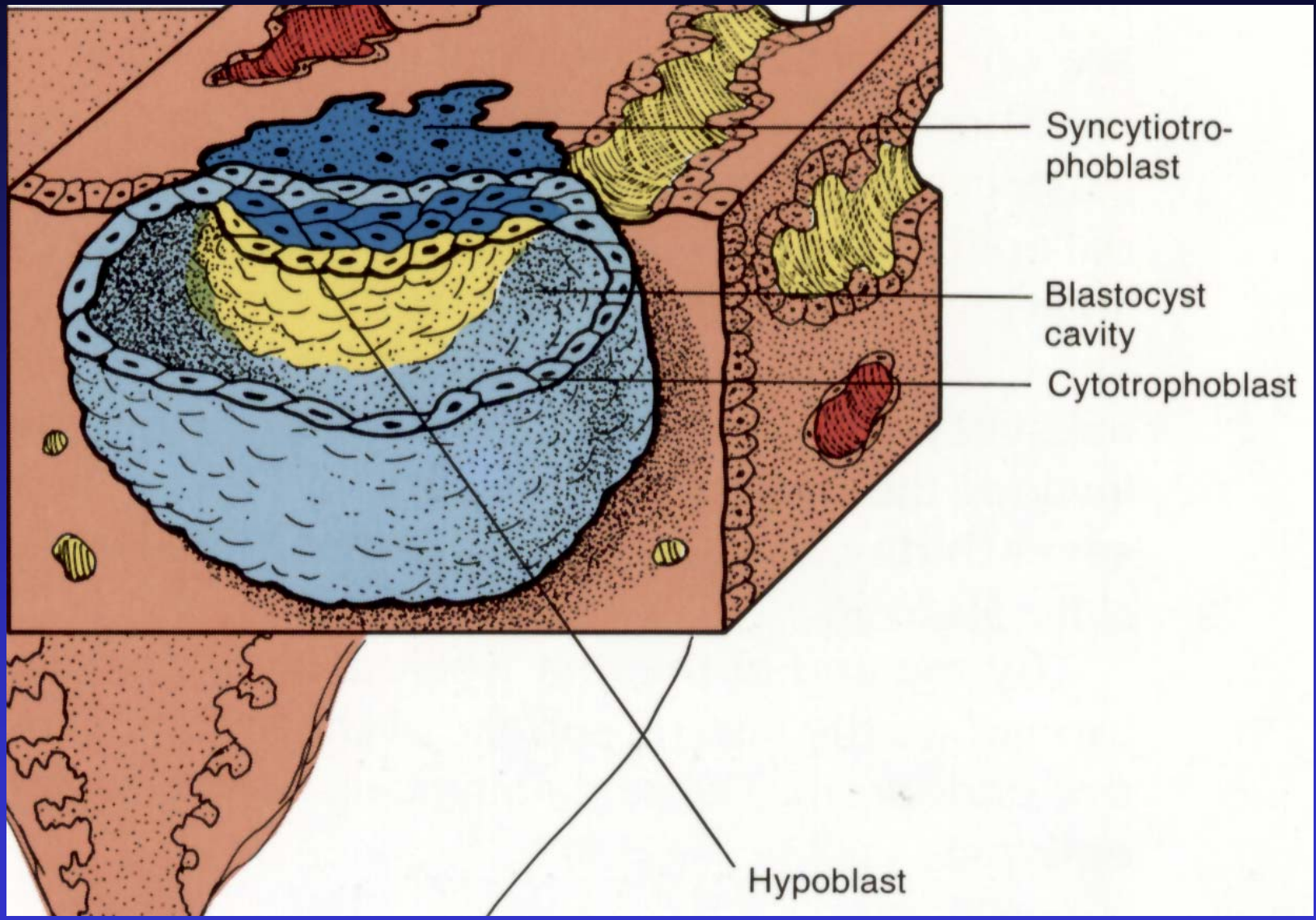
Day 6

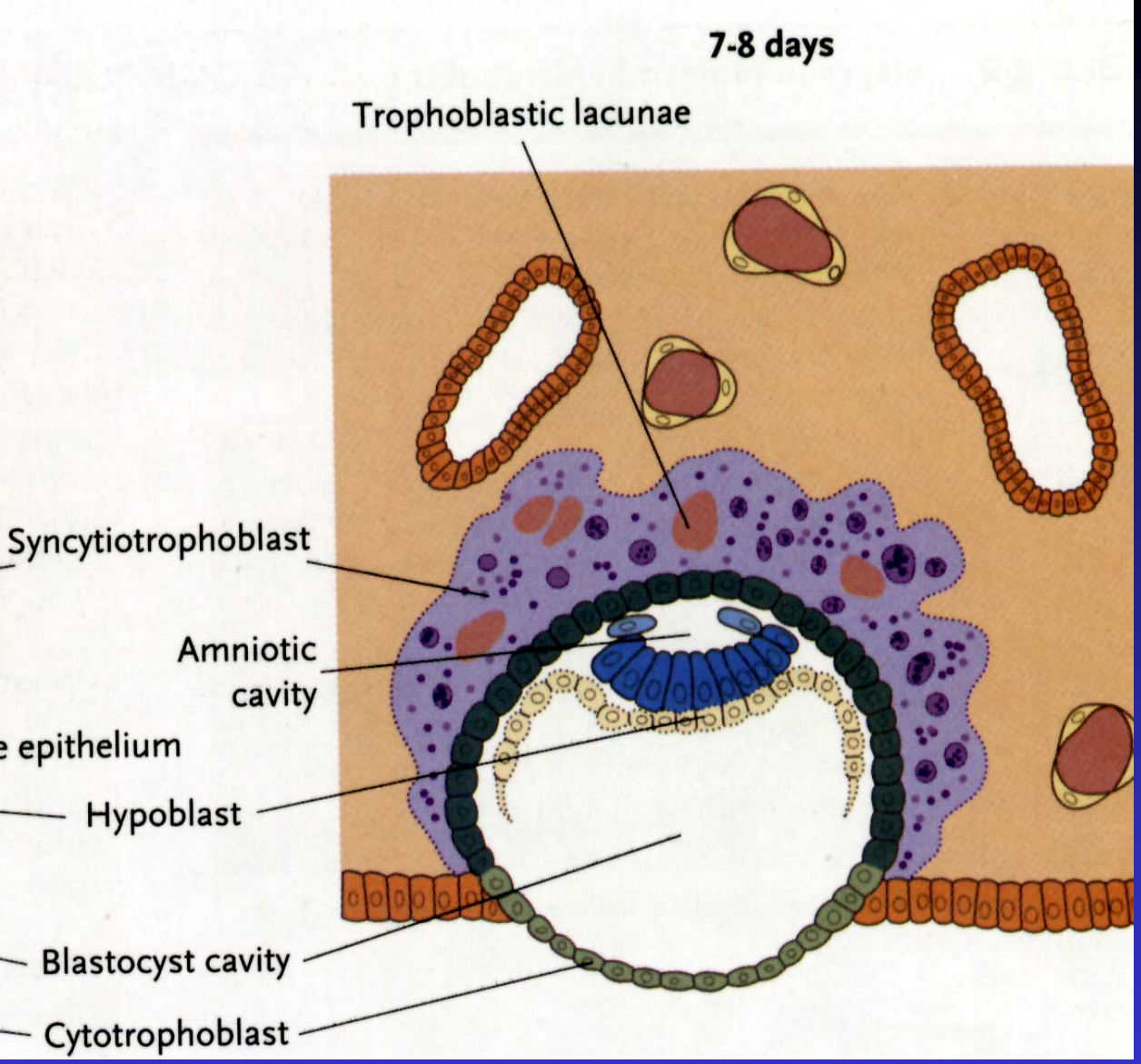
Blastocyst adheres to endometrium at embryo pole

Trophoblast proliferation production of hCG (maintains corpus luteum)

Trophoblasts → Syncytiotrophoblast → hydrolytic enzymes → Embryo invasion

Trophoblasts → Cytotrophoblast


Syncytiotro-
phoblast
Blastocyst
cavity
Cytotrophoblast
Hypoblast



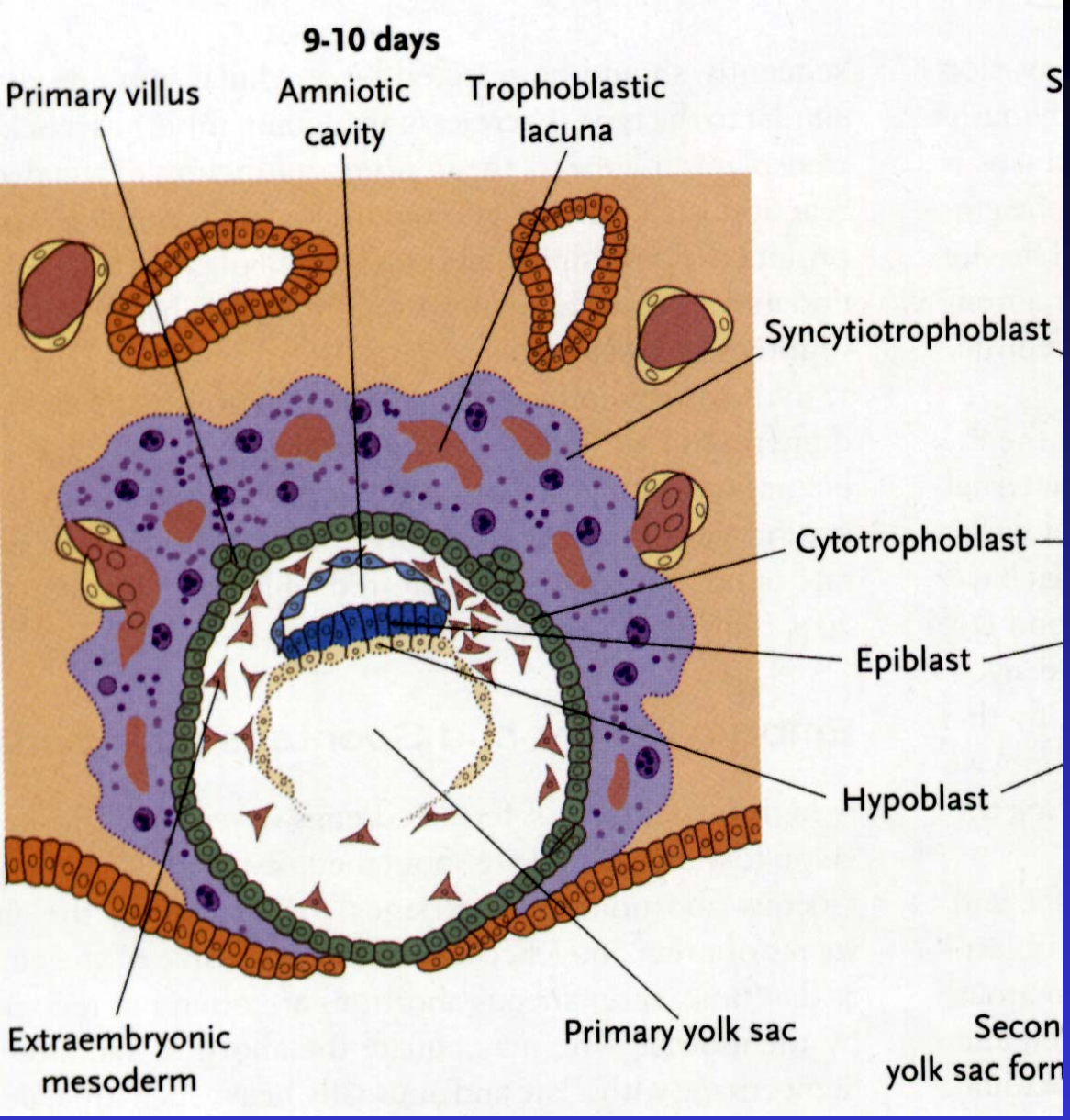
Day 7-8

- Syncytiotrophoblast expansion
- Lacunae form – filled with fluid (embryotroph)
- Embryotroph provides nutrients to the embryo. Derived from maternal blood.

Embryo - Bilaminar germ disc:

Epiblast layer – cavitates to form the amnionic cavity.

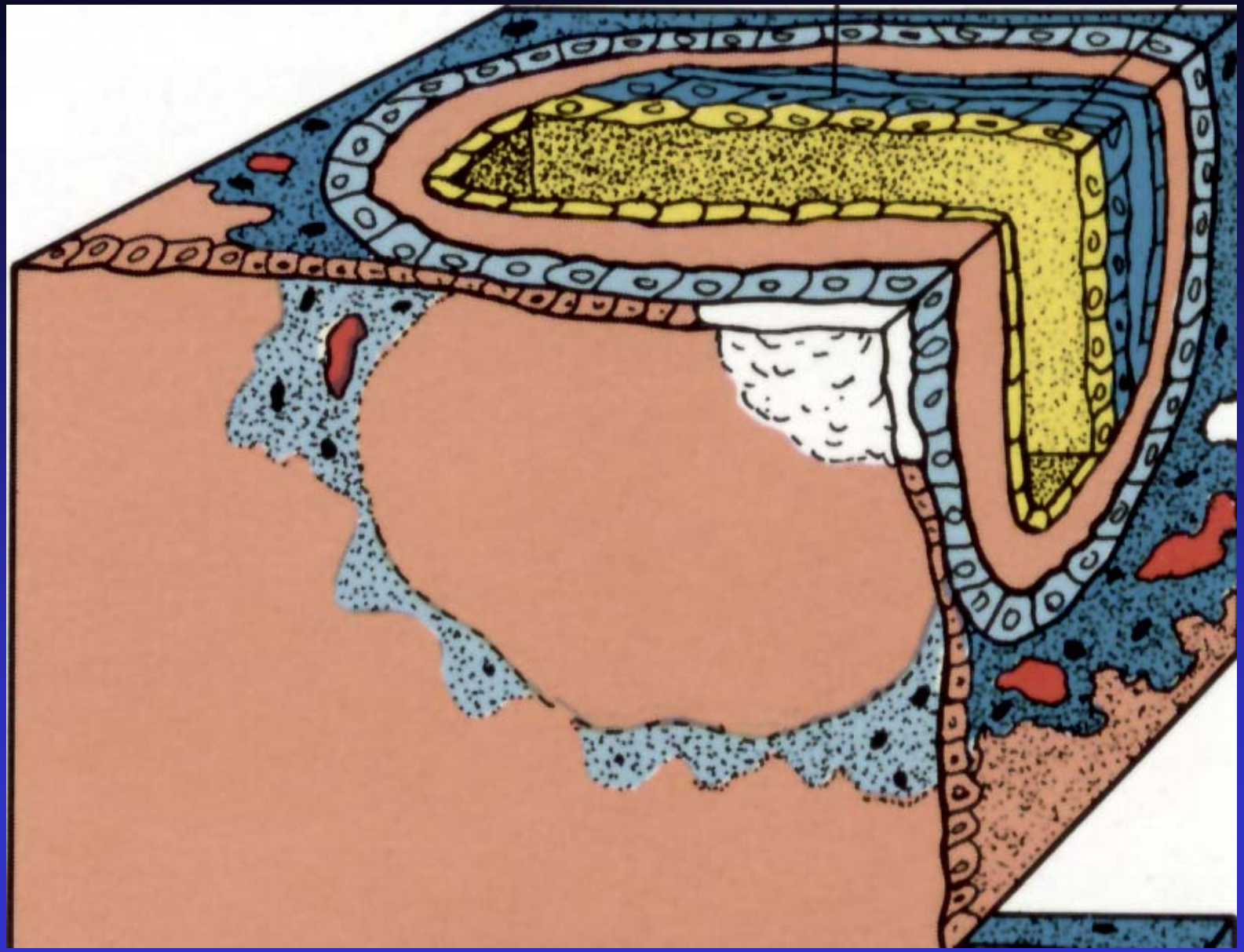
Hypoblast layer form the exocoelomic cavity / primary yolk sac

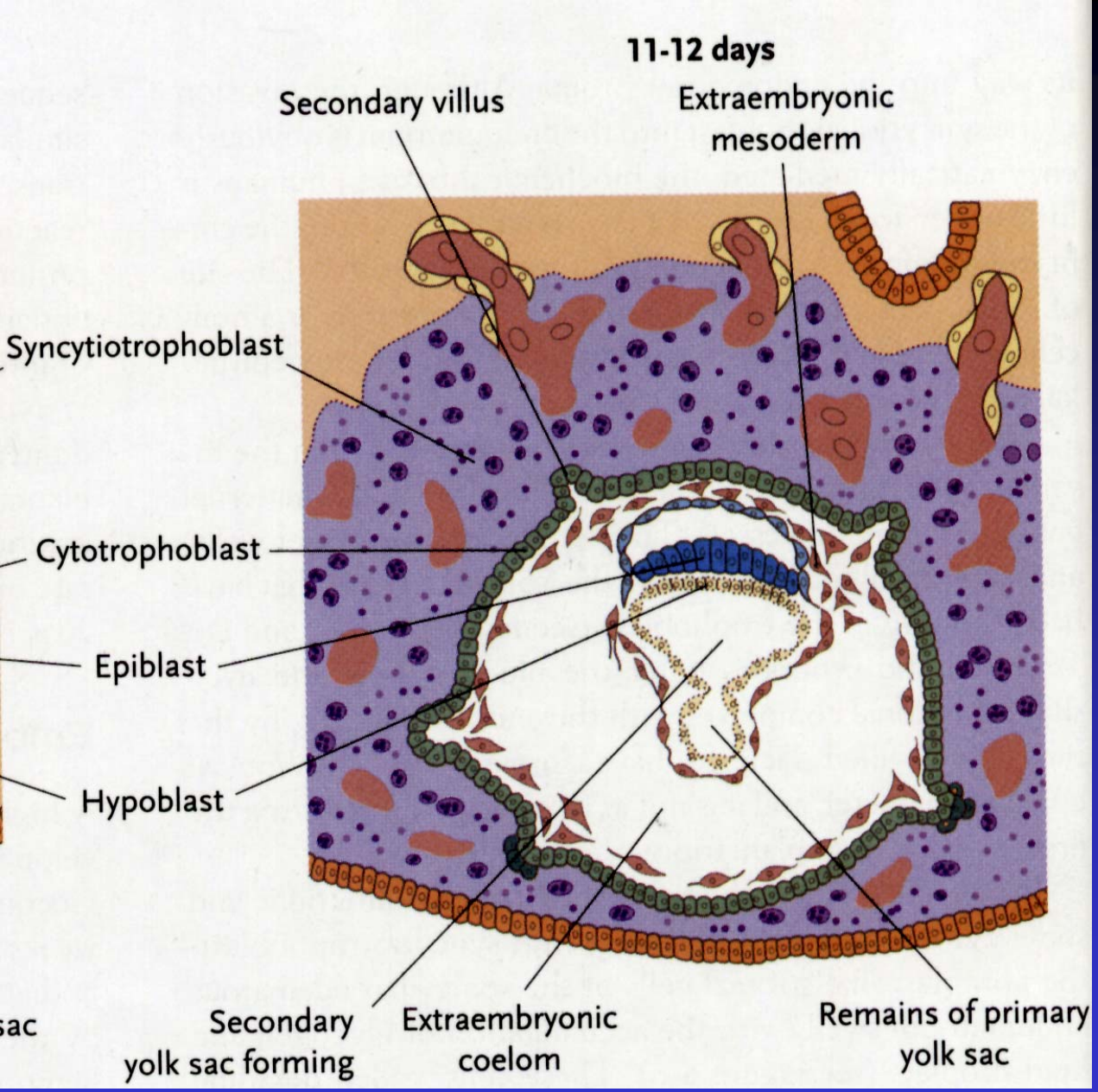


Day 9-10

- Lacunae enlarge
- Syncytiotrophoblast expands around entire blastocyst
- Cytotrophoblasts form primary villus – initiation of placenta formation
- Implantation Complete
- Coagulation Plug forms

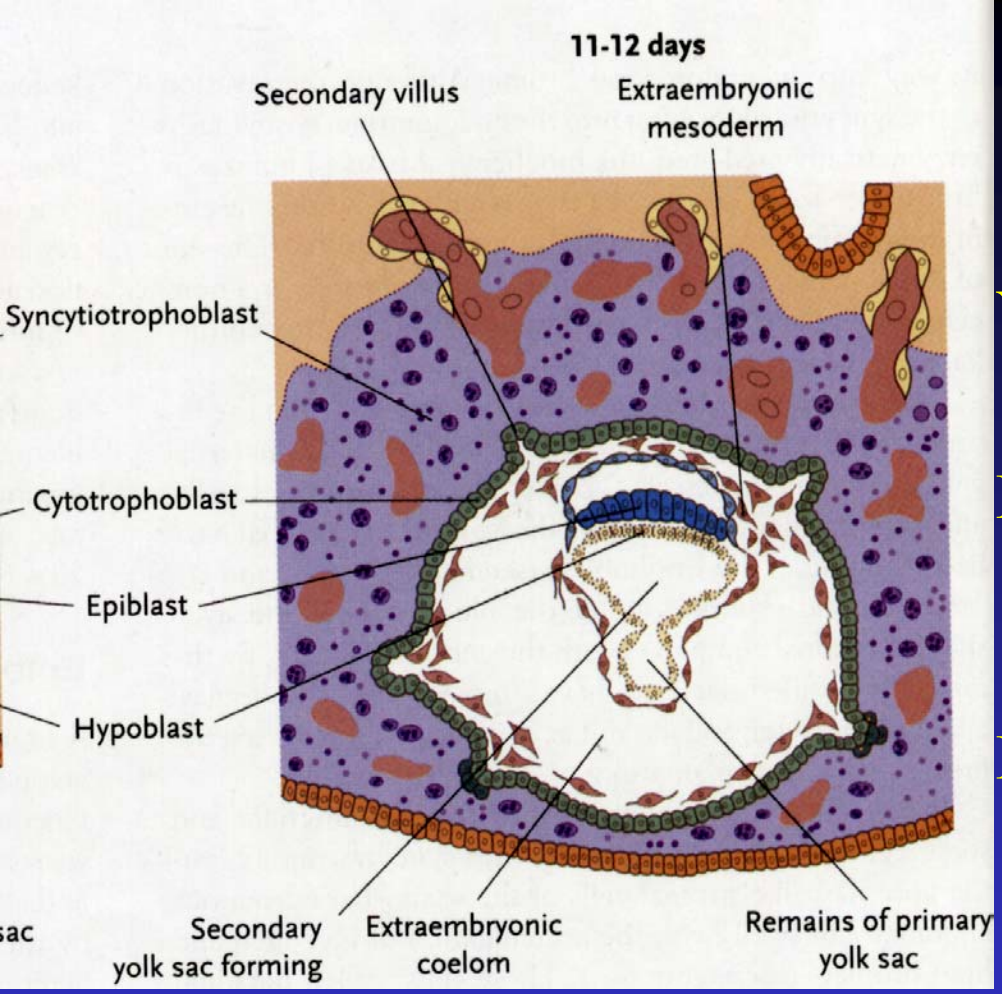
Embryo: hypoblast → exocoelomic membrane = Hauser's membrane
Extraembryonic mesoderm from yolk sac





Day 11-12

- Syncytiotrophoblast erode maternal capillaries – form sinusoids
- Syncytial lacunae become continuous with sinusoids
- Maternal blood to enter lacunae establishing the uteroplacental circulation



Day 11-12 – Embryo

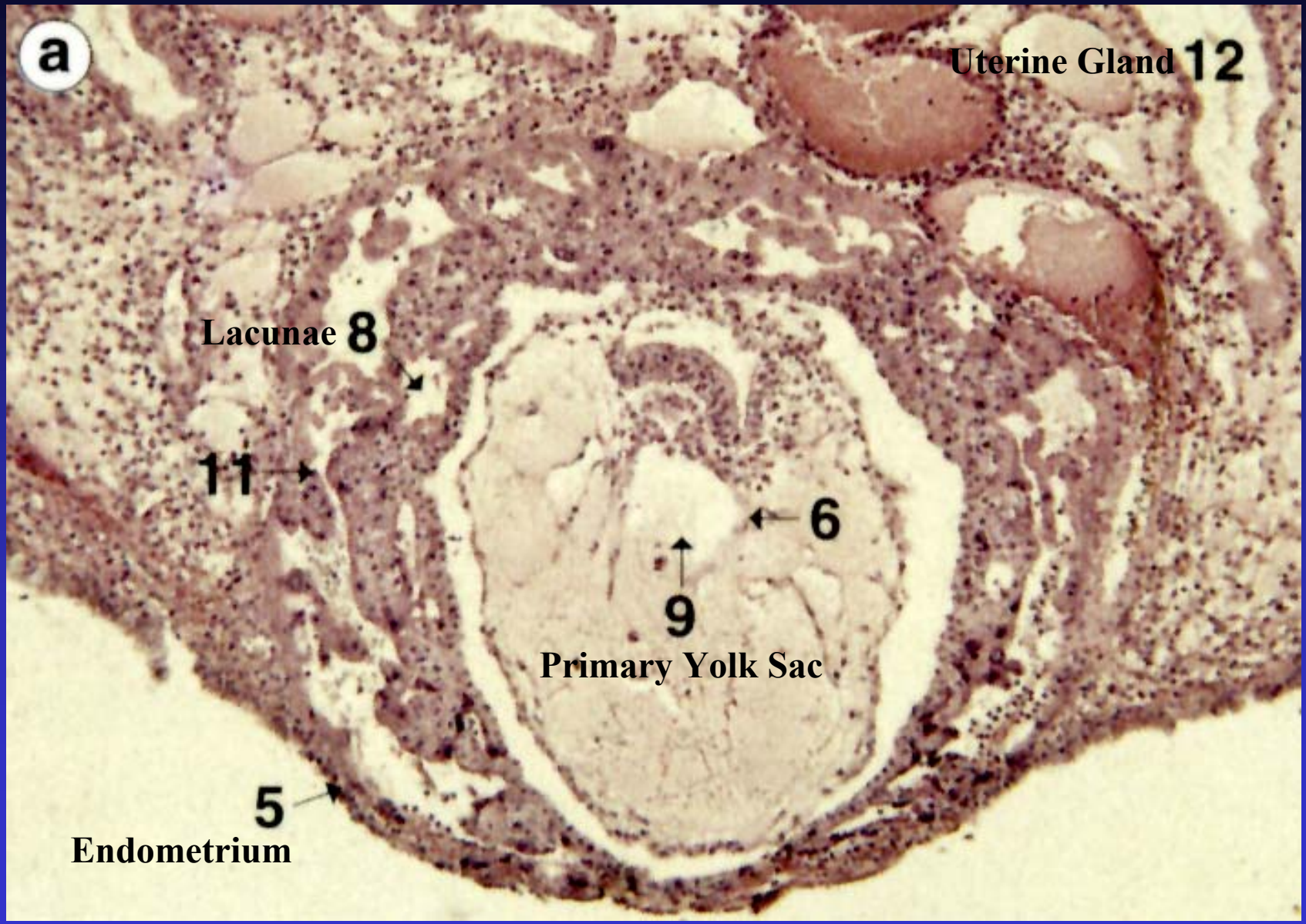
Yolk sac → extraembryonic mesoderm

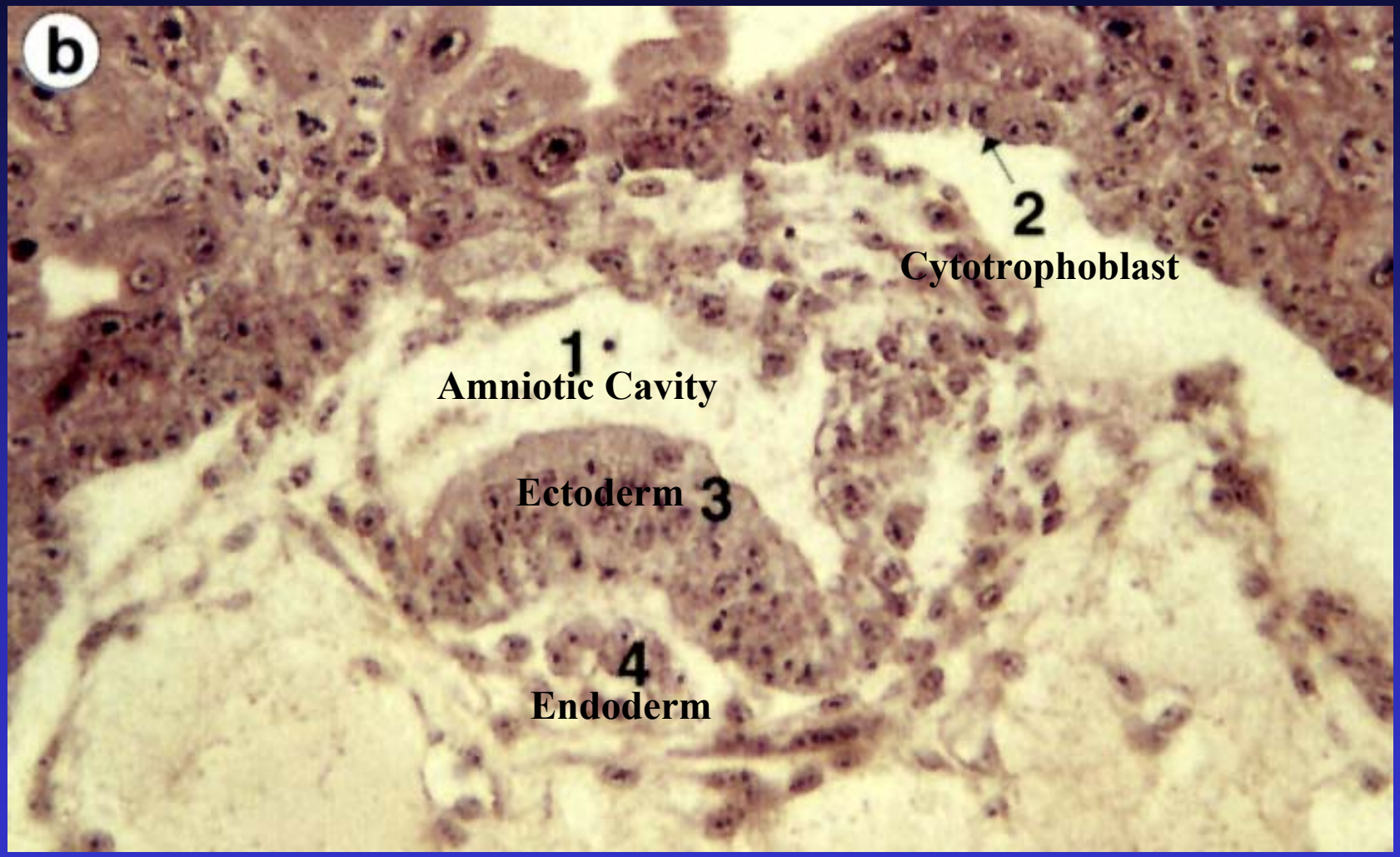
Extraembryonic Somatopleuric mesoderm - layer between amnion and cytotrophoblst

Extraembryonic Splanchnopleuric mesoderm - layer between Primary yolk sac and cytotrophoblast

Extraembryonic mesoderm becomes confluent and forms another cavity – extraembryonic coelom or chorionic cavity

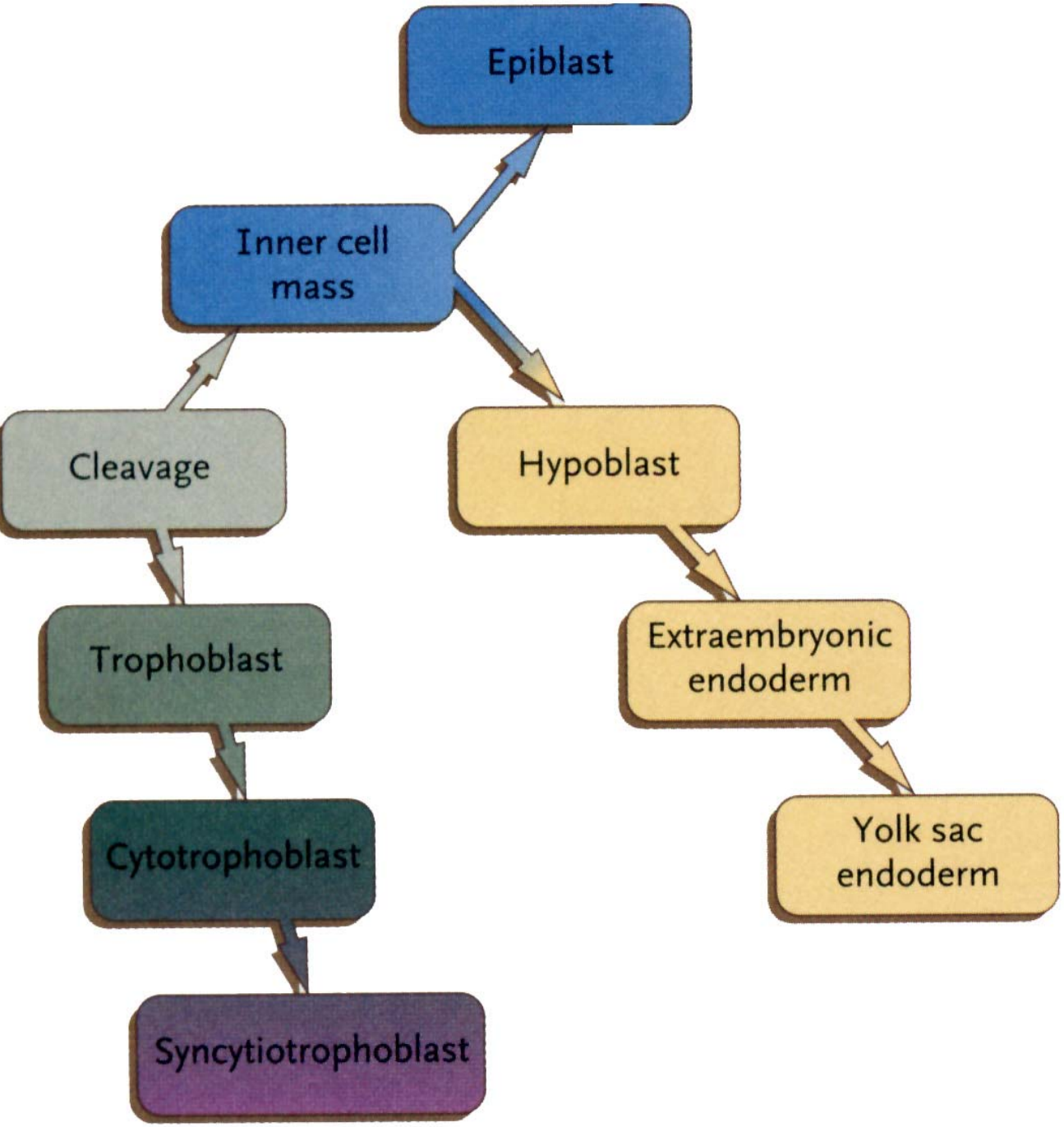
Implantation




b
2
Cytotrophoblast
1
Amniotic Cavity
Ectoderm 3
4
Endoderm

Summary

Day 0	Fertilization in Ampulla of uterine tube
Day 1	Zygotic transcription begins
Day 1-3	Cleavage – morula – compaction
Day 3-4	Transport to uterine cavity Relaxation of the uterotubal junction
Day 5	Maturation of blastocyst, hatching
Day 6-7	Attachment / penetration of uterine stroma
Day 7-9	Invasion of uterine stroma
Day 9-11	Lacuna formation, erosion of spiral arteries



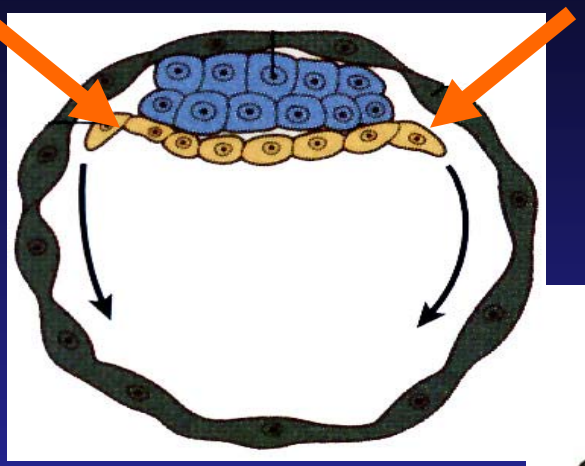
Early Cell Lineages

Extraembryonic Somatopleuric Mesoderm

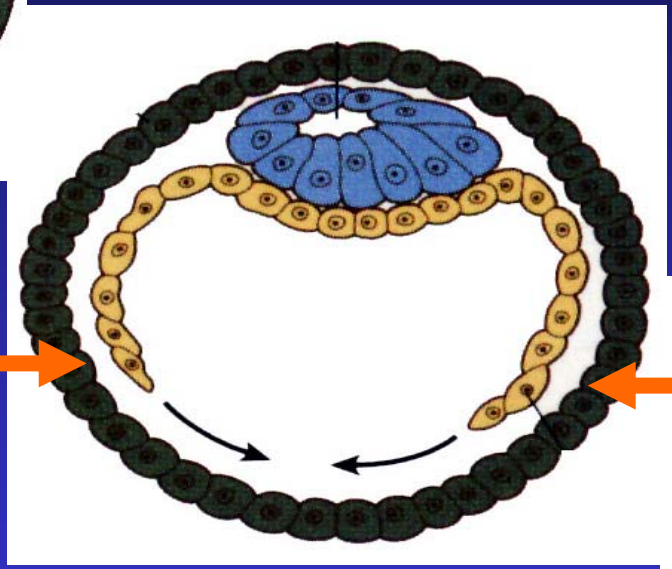
Extraembryonic Splanchnopluric Mesoderm

From BM Carlson, 1999

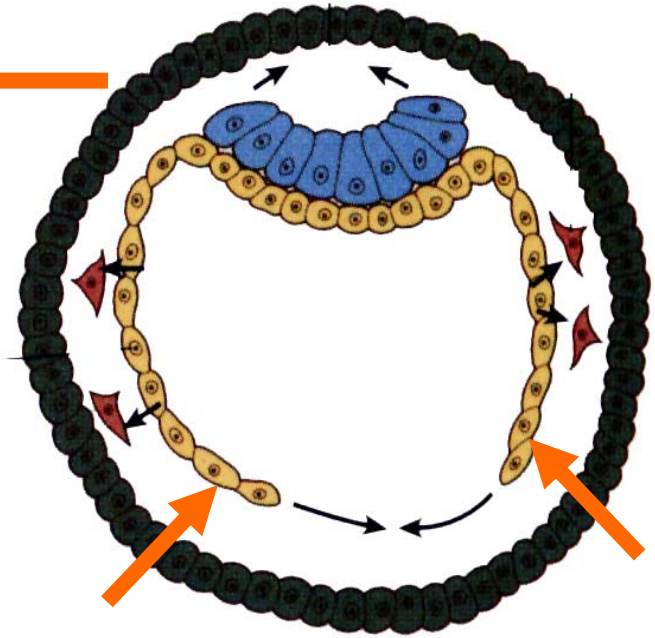
Extraembryonic Tissues



6 days



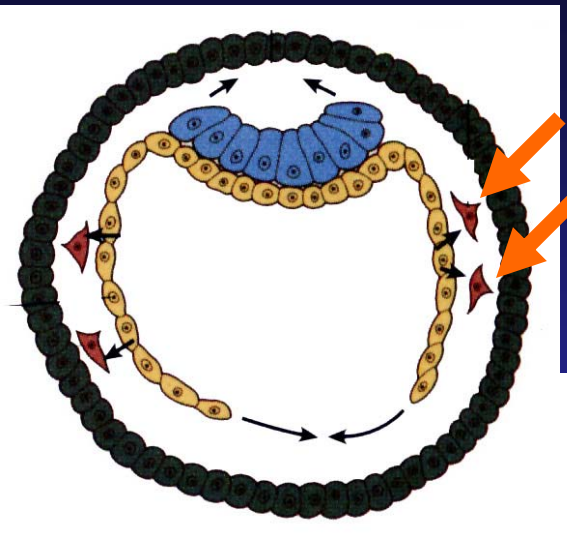
7 days



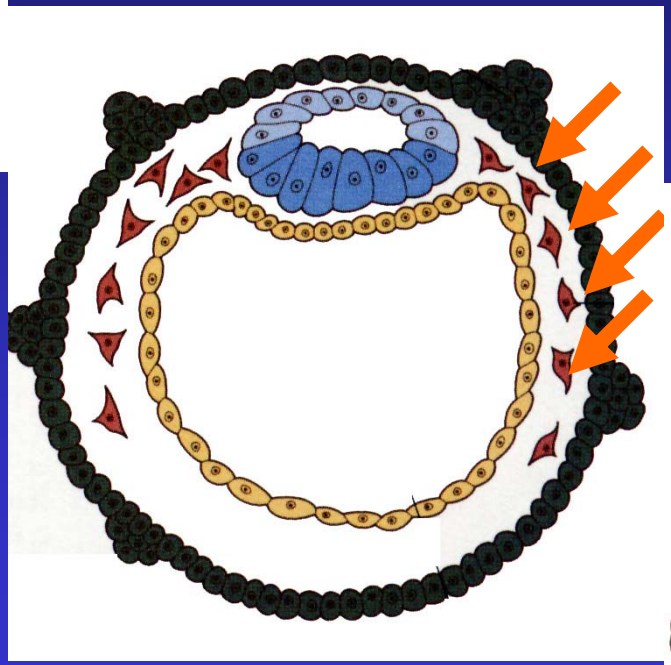
8 days

From BM Carlson, 1999

Extraembryonic Tissues

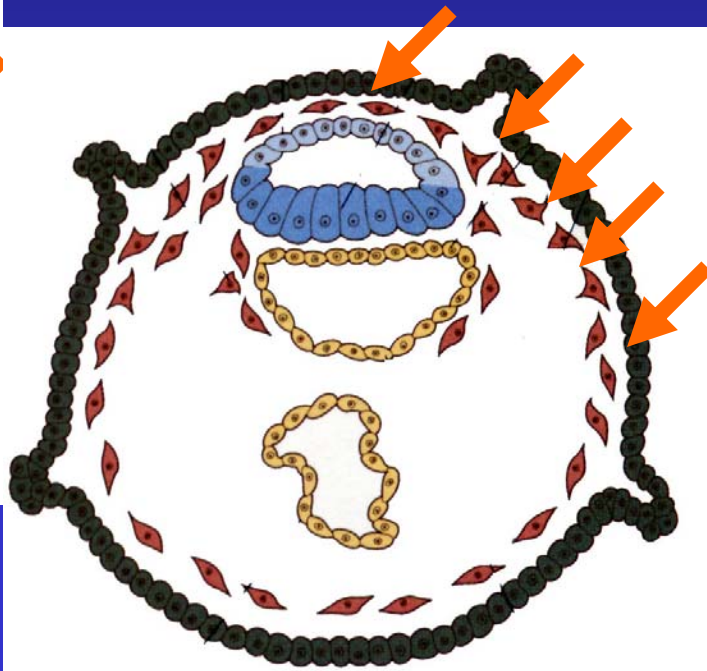


8 days

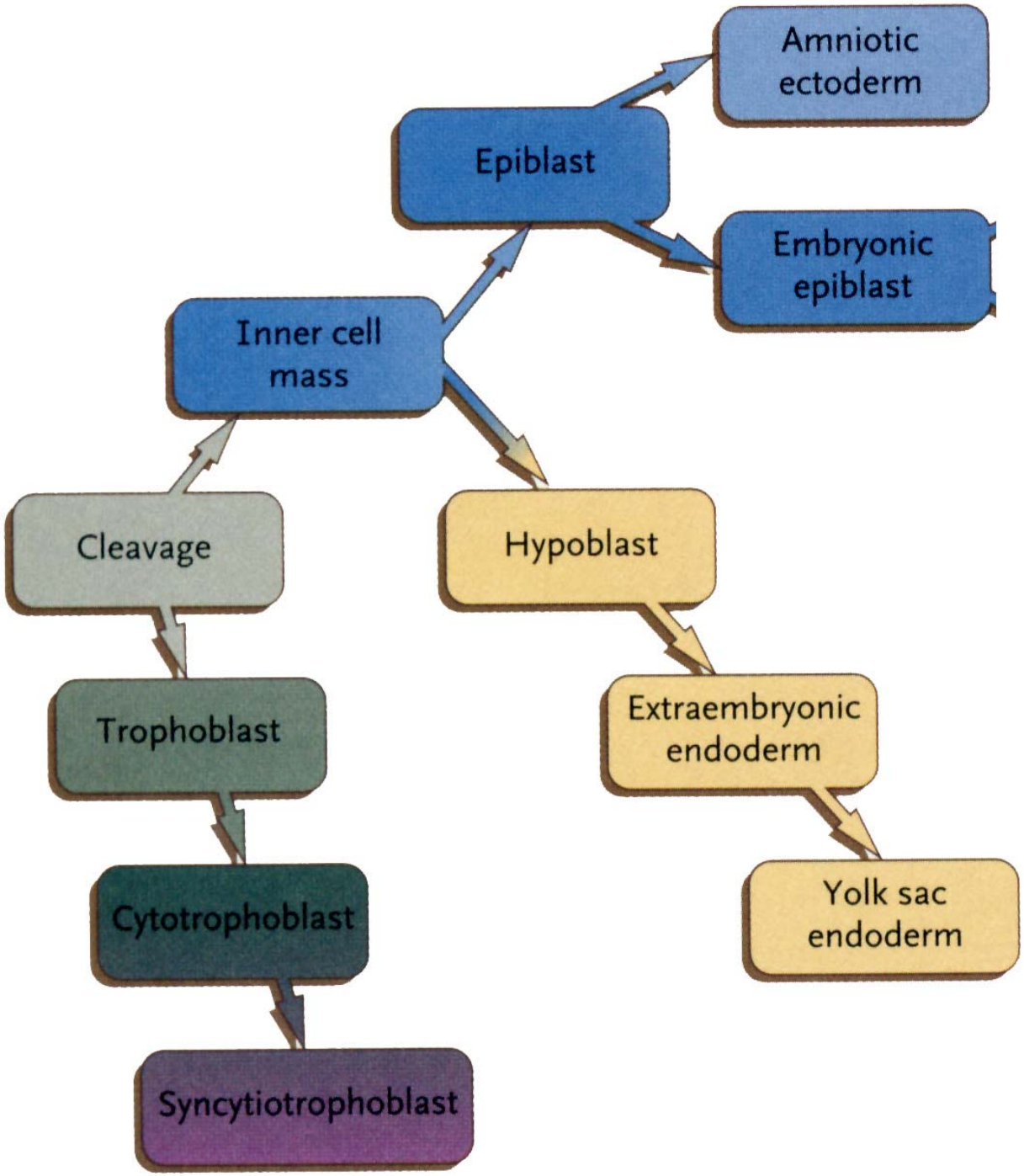


9 days

14 days



From BM Carlson, 1999



Amnion

Amnionic Cavity

Cavitation

From BM Carlson, 1999

From

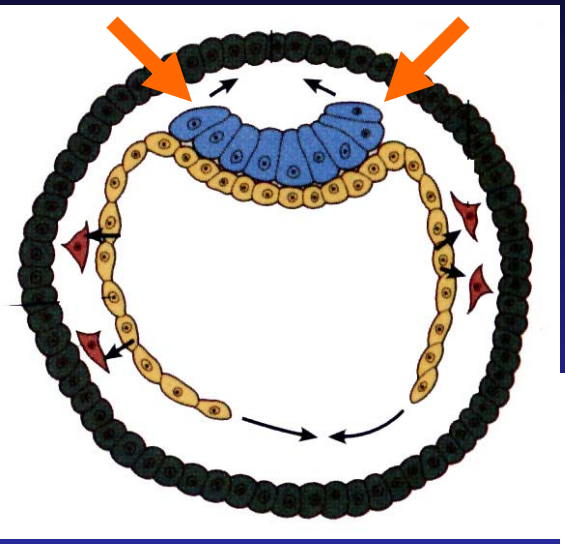
Extraembryonic Somatopleuric Mesoderm

BM

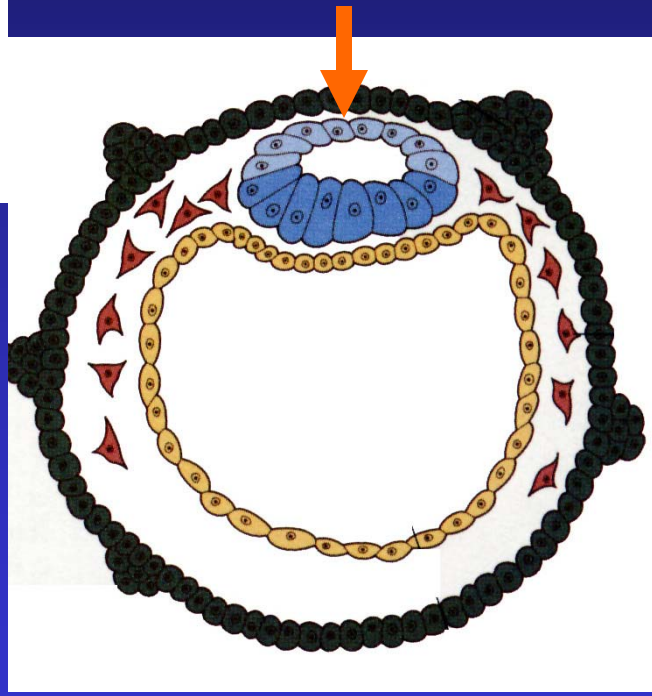
Carlson

Extraembryonic Splanchnopluric Mesoderm

Extraembryonic Tissues

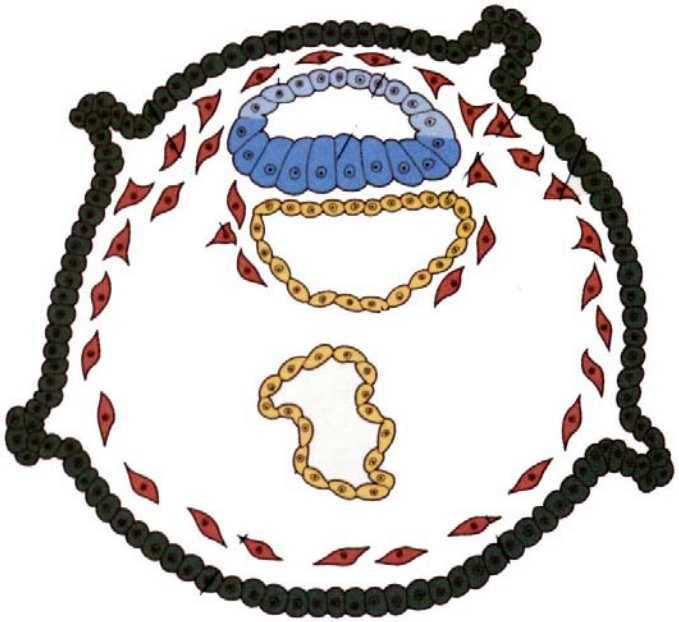


8 days



9 days

14 days

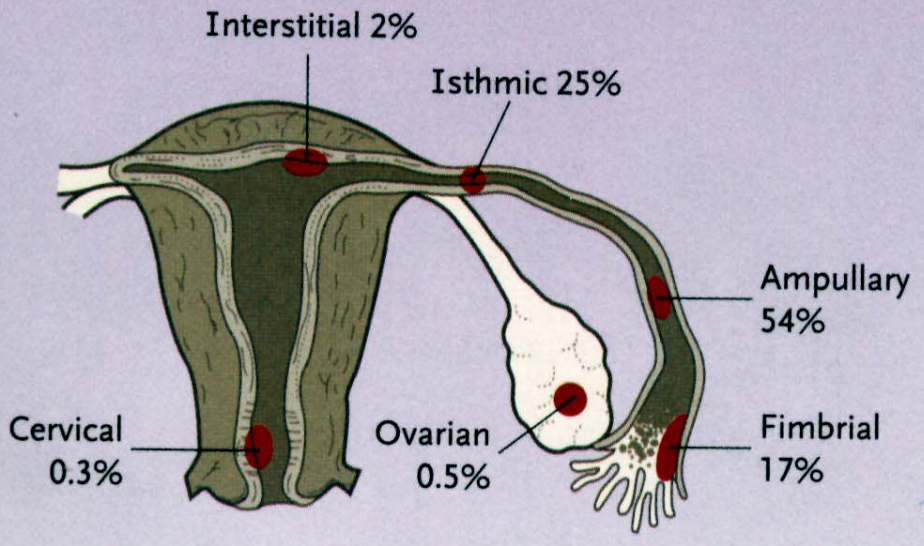


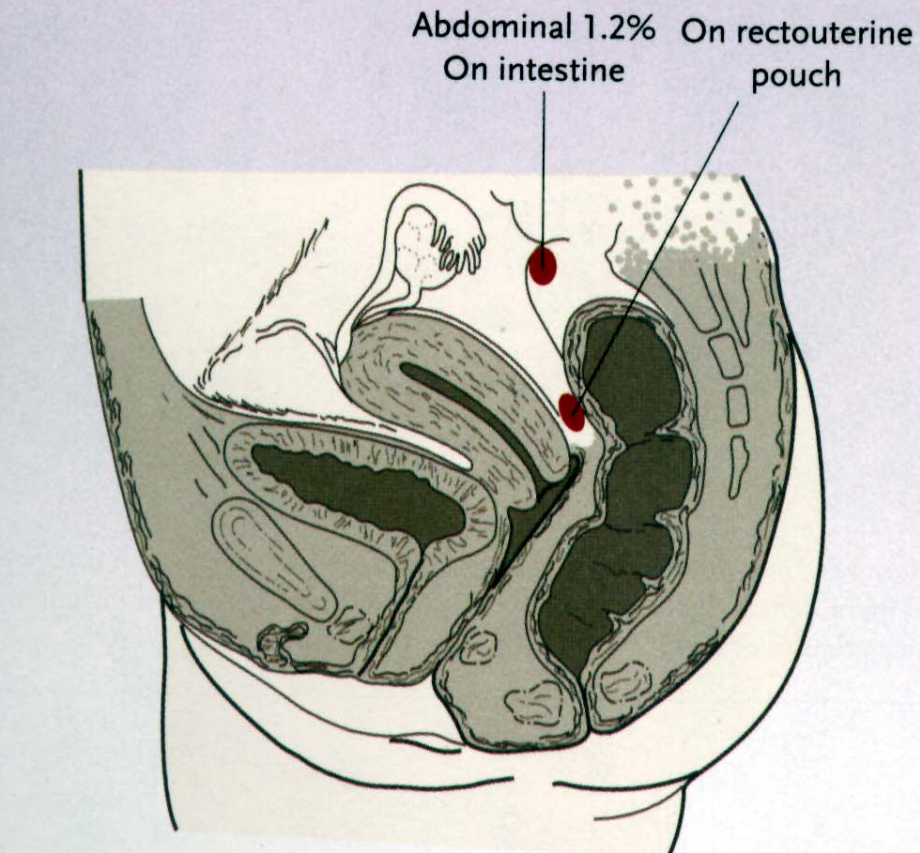
From BM Carlson, 1999

Implantation Sites

Typical - Mid-Uterus

Distribution of atypical implantation sites



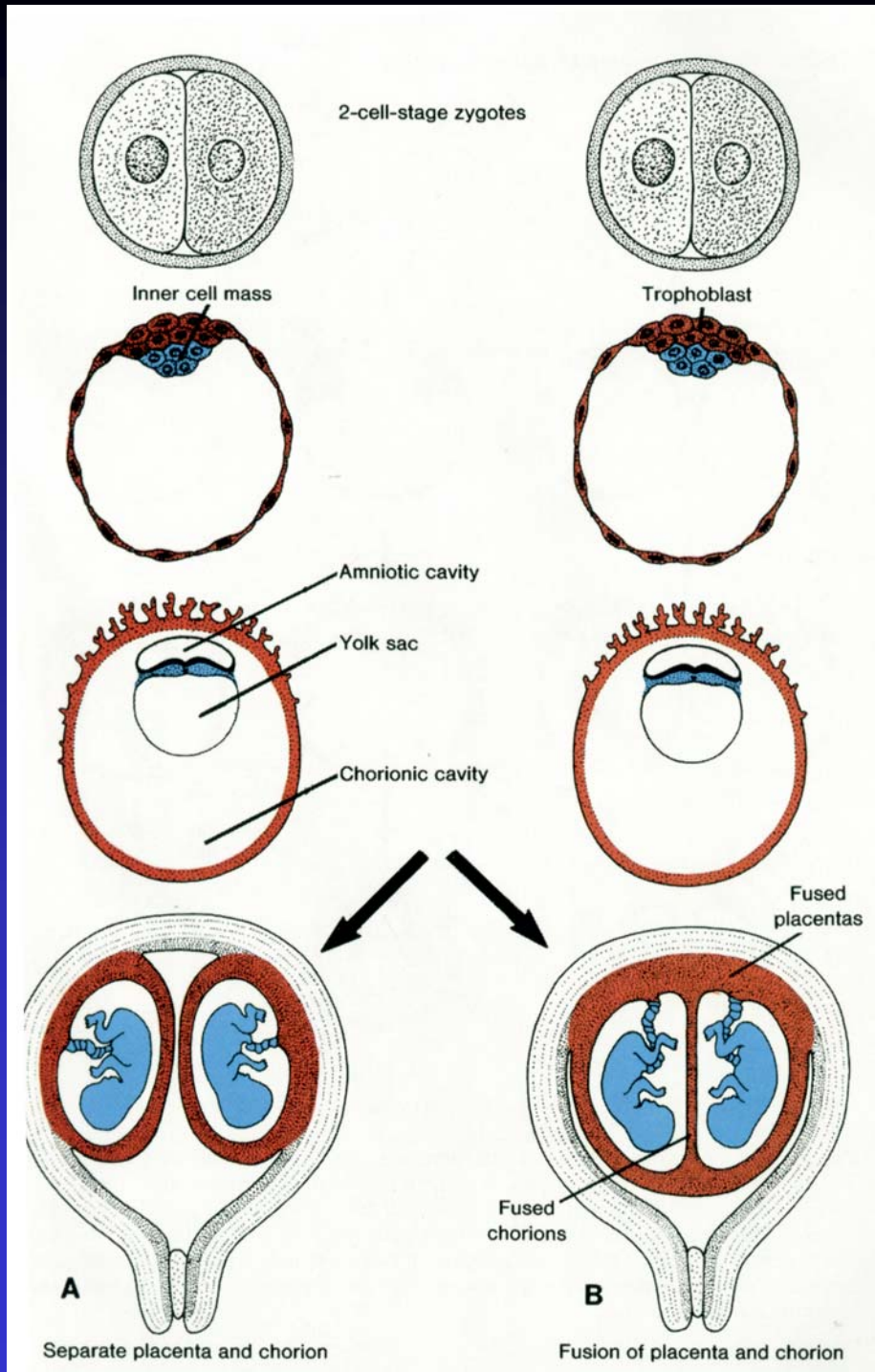


From BM Carlson, 1999

Dizygotic Twins

Dichorial

Monochorial



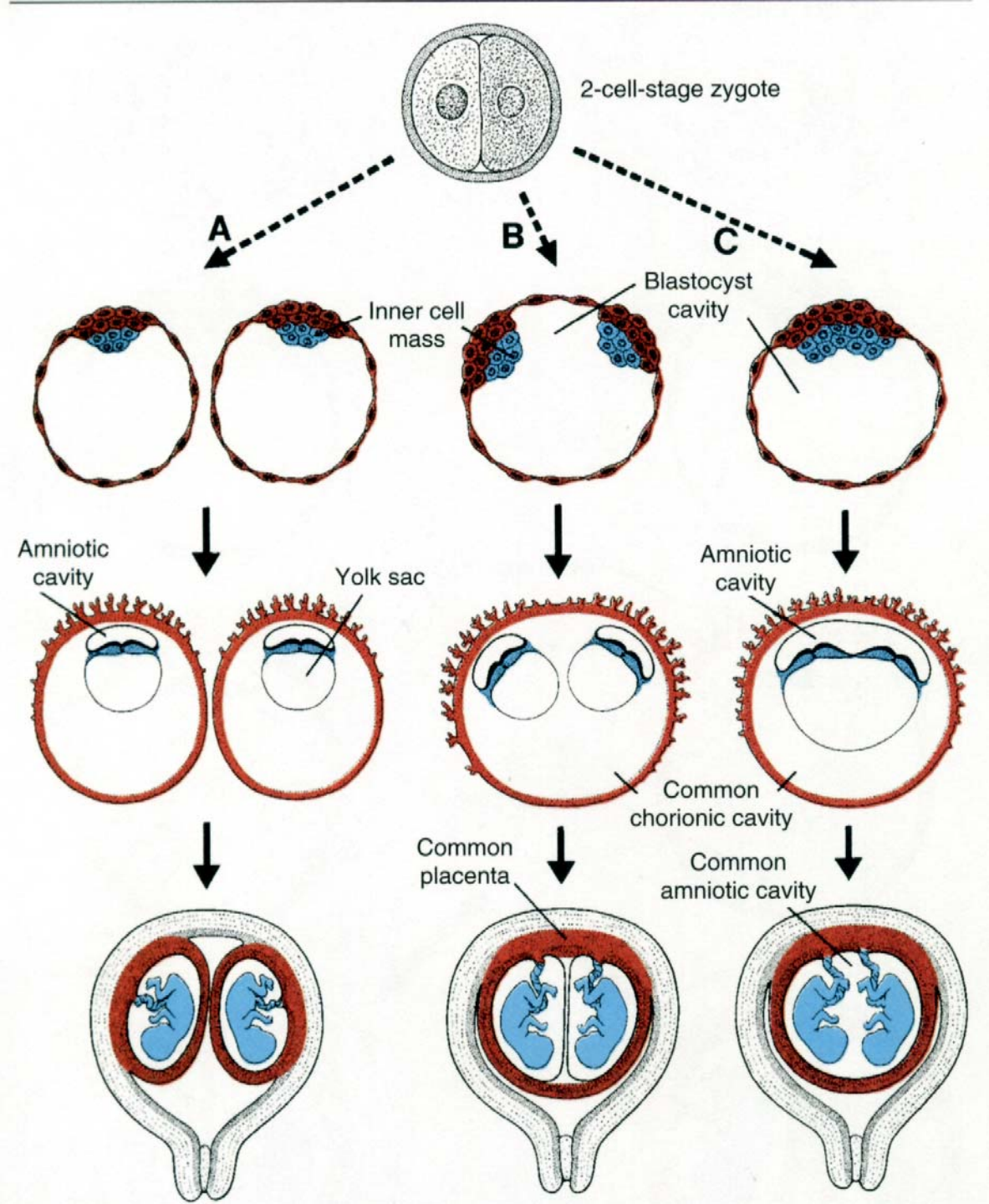
From TW Sadler, 2000

Monozygotic Twins

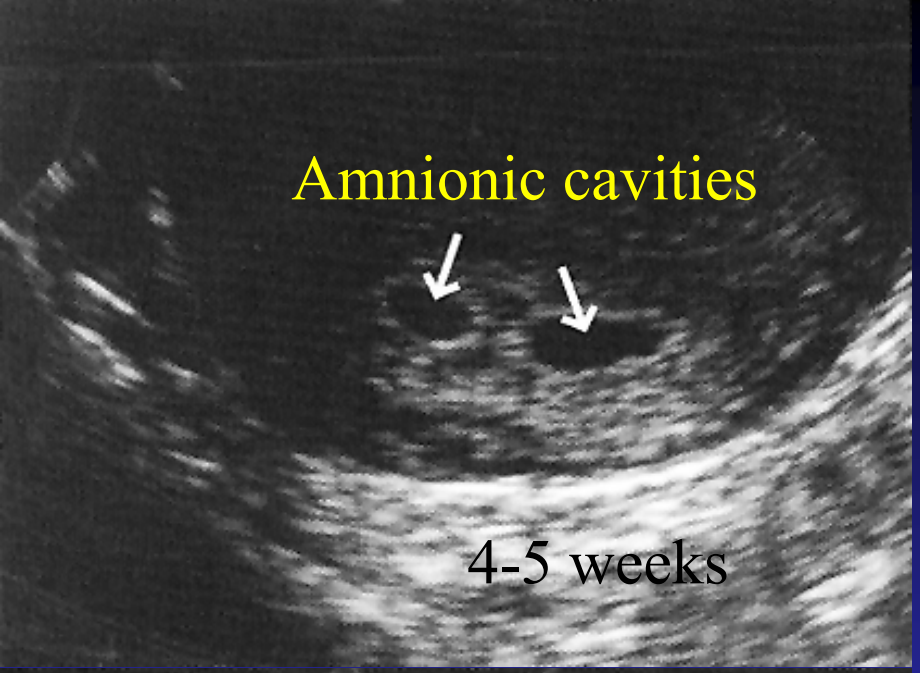
Dichorial/
Diamniotic (33%)

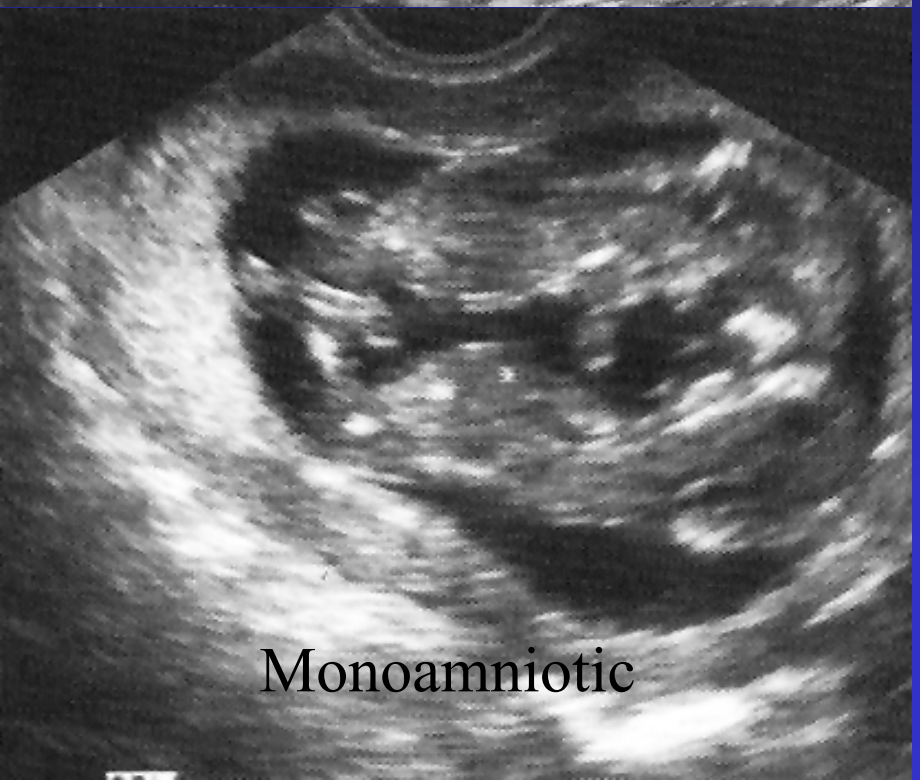
Monochorial/
Diamniotic (66%)

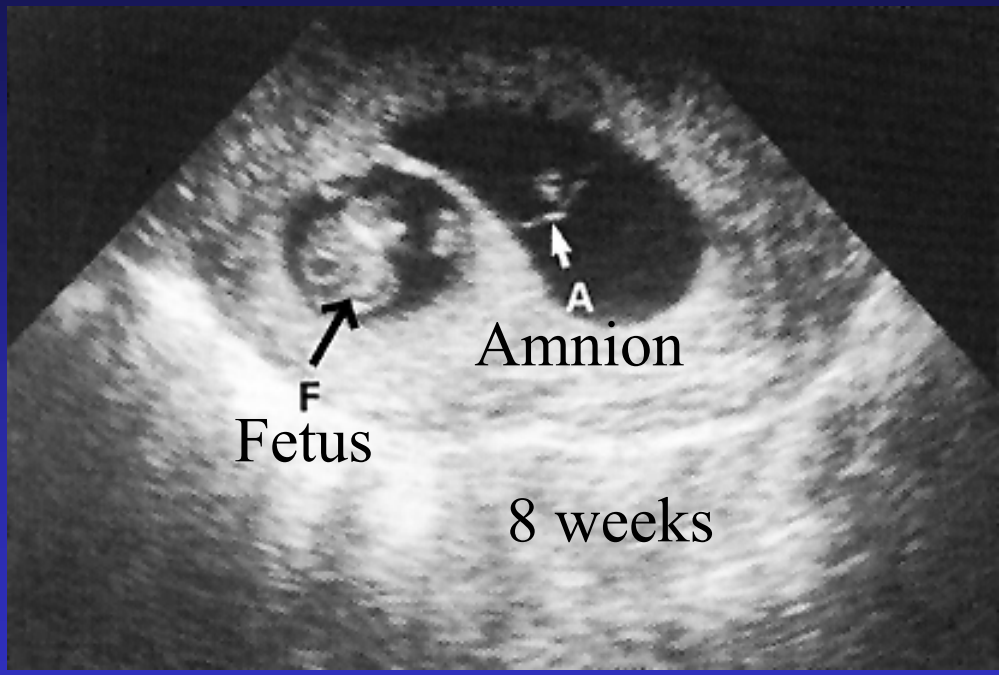
Monochorial/
Monoamniotic (rare)

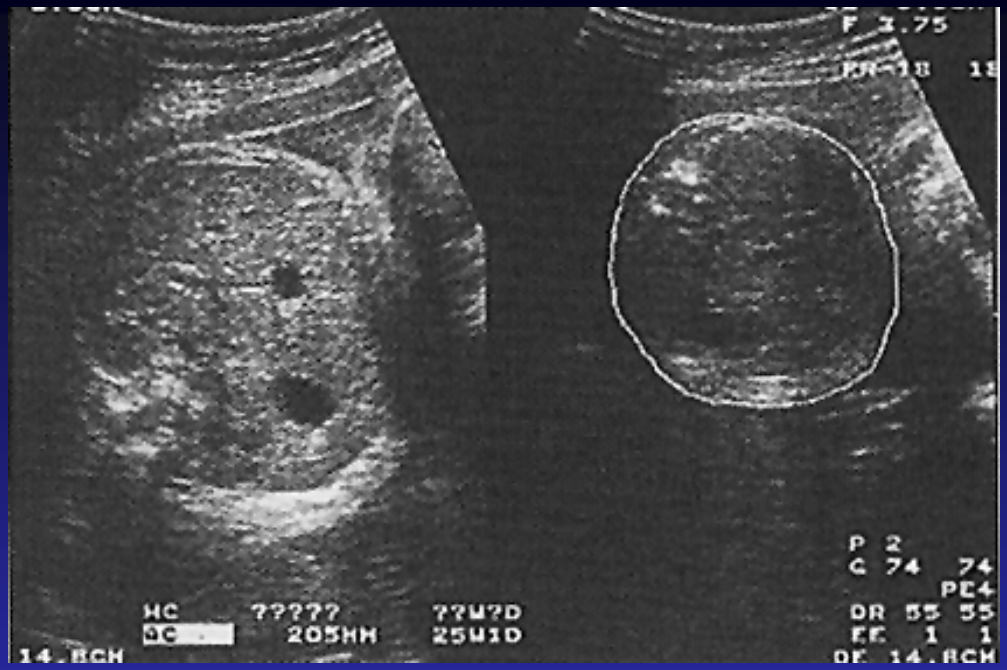


From TW Sadler, 2000


Amnionic cavities
4-5 weeks


Monoamniotic


A
Amnion
F
Fetus
8 weeks



Vanishing twins (triplets)

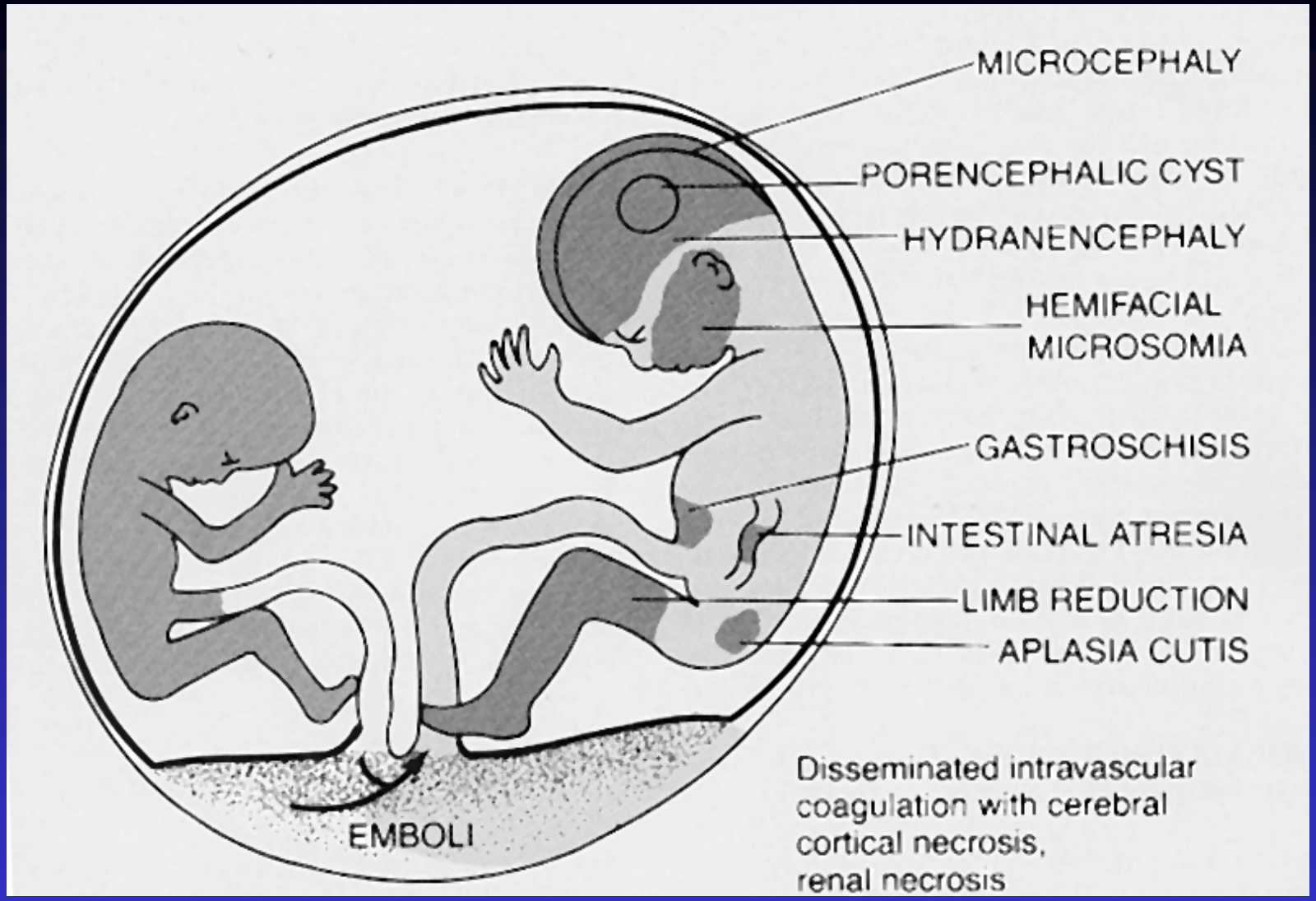
20% of twin pregnancies

Chromosomal or Structural abnormalities

Twins, Discordant Growth

Abdominal circumference, 3rd Trimester

>25% - associated with increased morbidity



Papyraceus – Death of a monochorionic co-twin
Circulatory interactions can cause problems

Table 16.1
Twinning rates per 1000 maternities by zygosity in different countries

	Monozygotic	Dizygotic	Total
Nigeria	5.0	49.0	54.0
USA			
black	4.7	11.1	15.8
white	4.2	7.1	11.3
England and Wales	3.5	8.8	12.3
India	3.3	8.1	11.4
Japan	3.0	1.3	4.3

Table 16.2
Different monozygotic twin types

Time of division	Type of twinning
< 4 days	Dichorionic diamniotic
4–8 days	Monochorionic diamniotic
8–13 days	Monochorionic monoamniotic
> 13 days	Conjoined twins

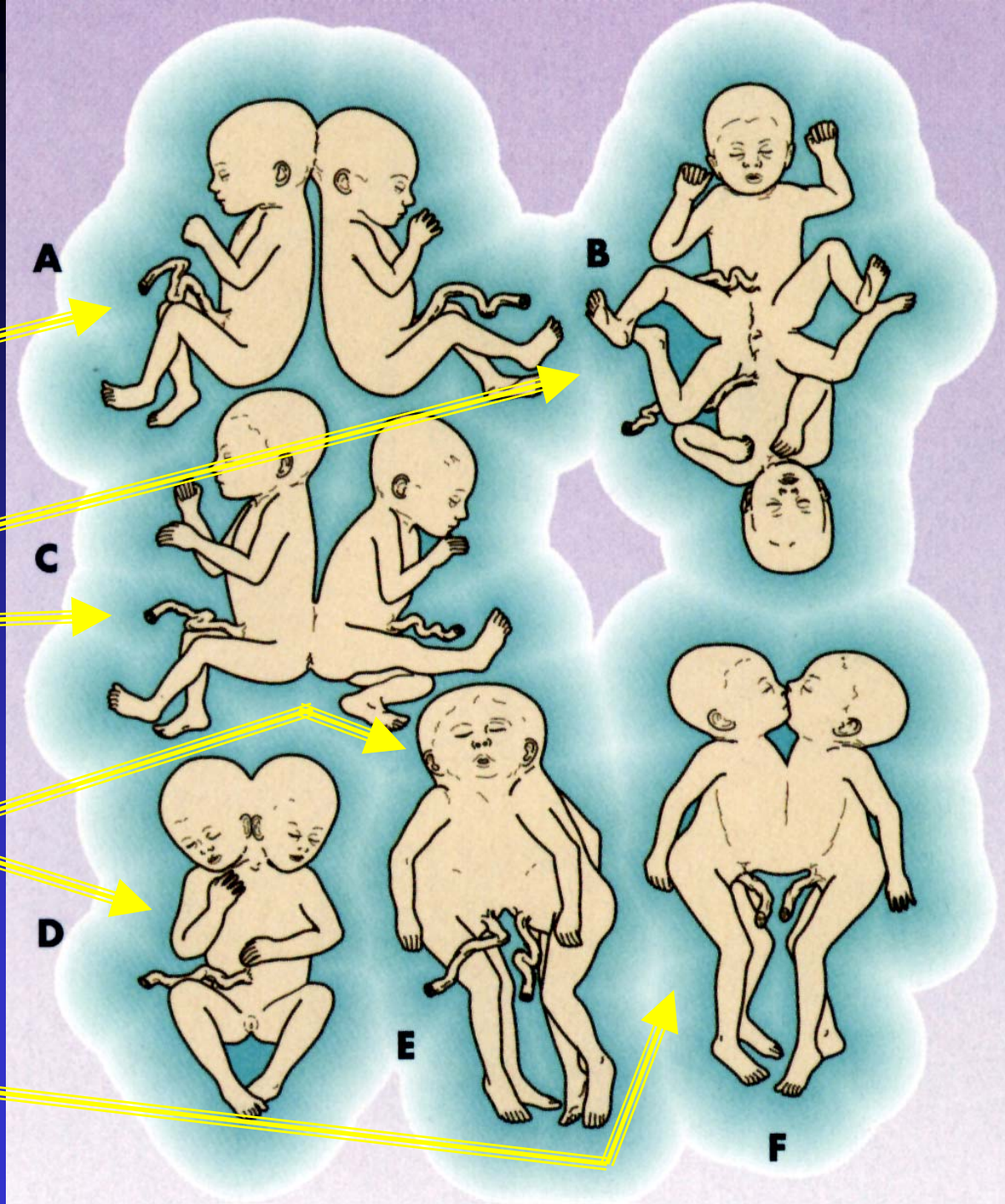
Conjoined Twins

Cephalopagus

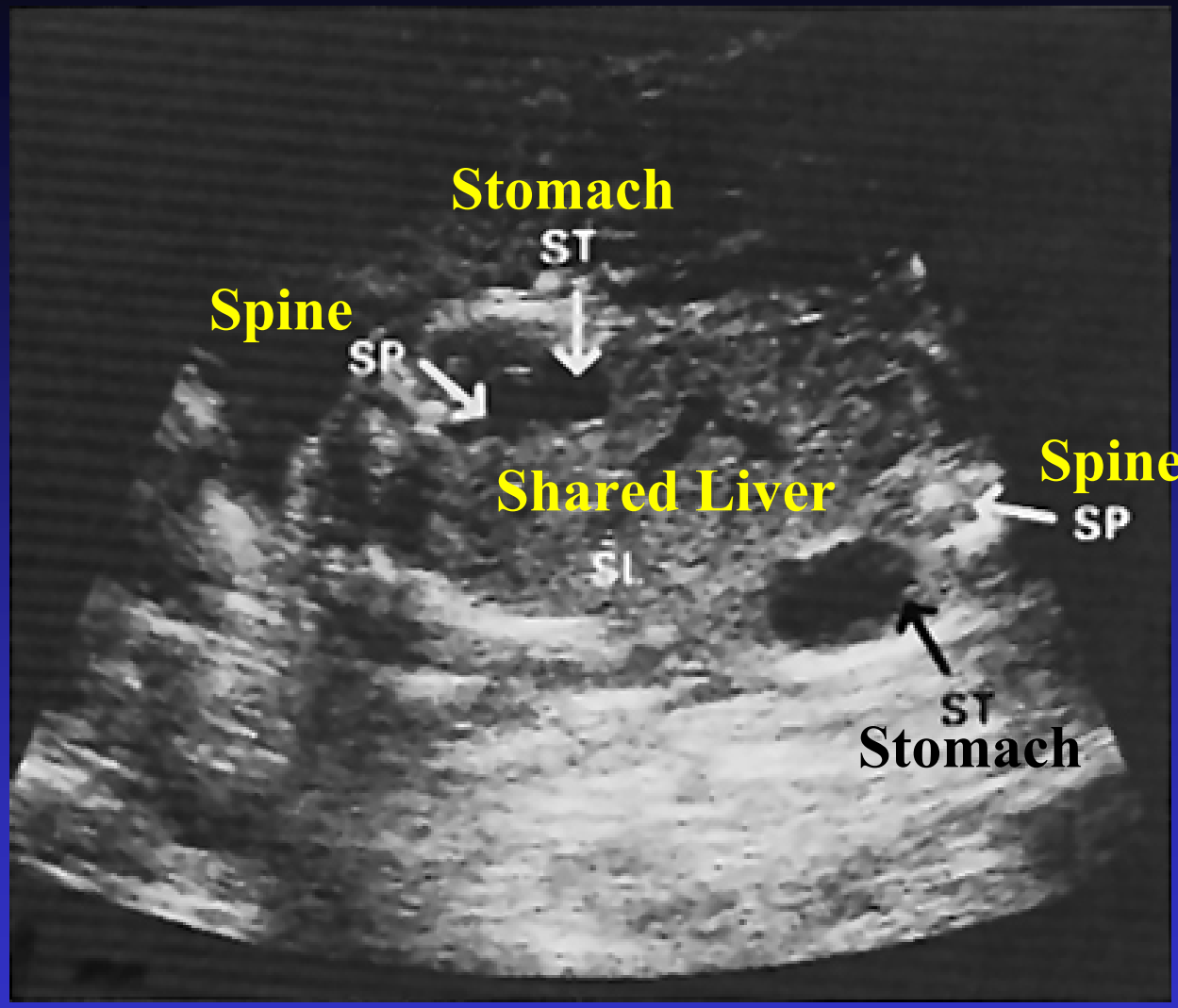
Pygopagus

Cephalothoracopagus

Thoracopagus



From BM Carlson, 1999

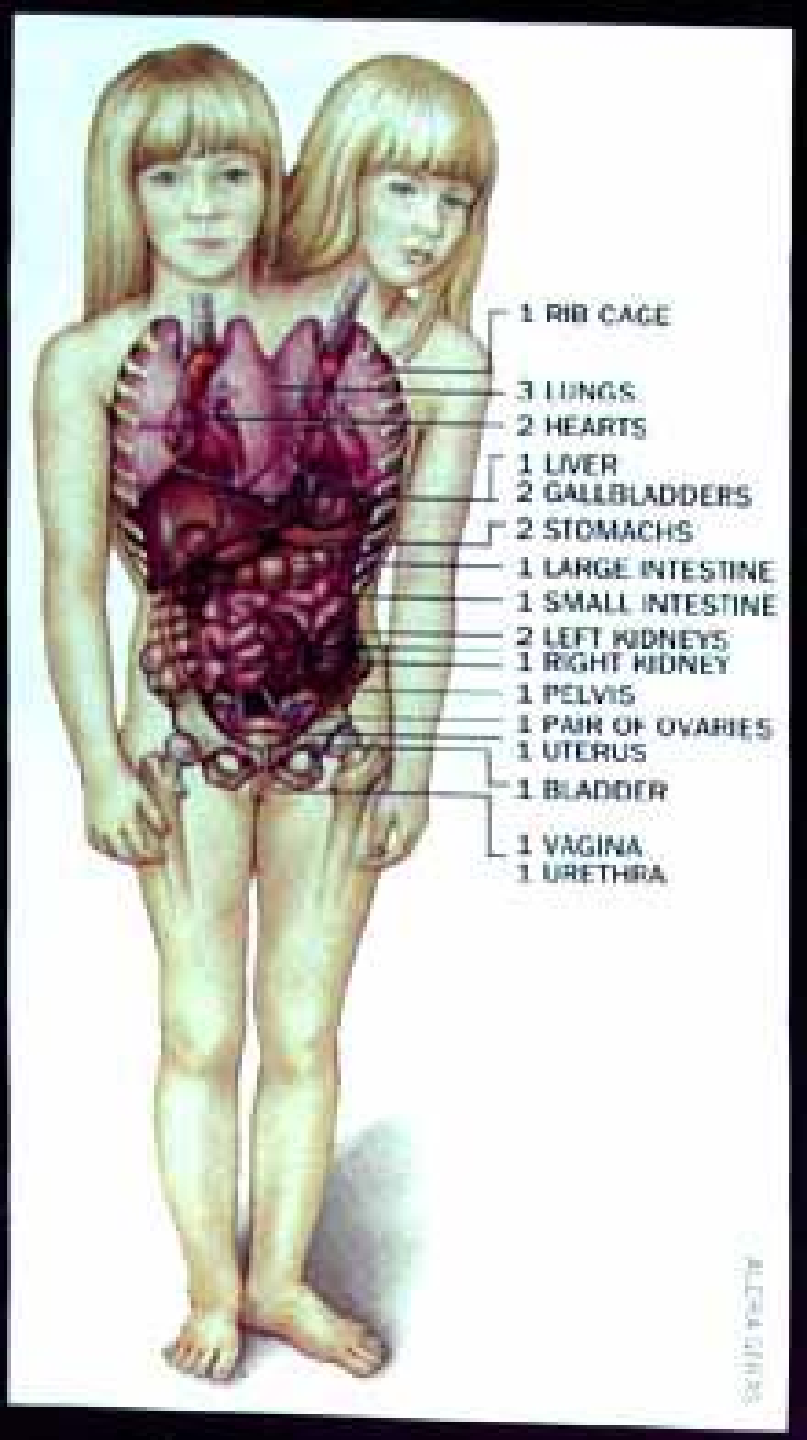


Ultrasound of conjoined twins

Pygopagus

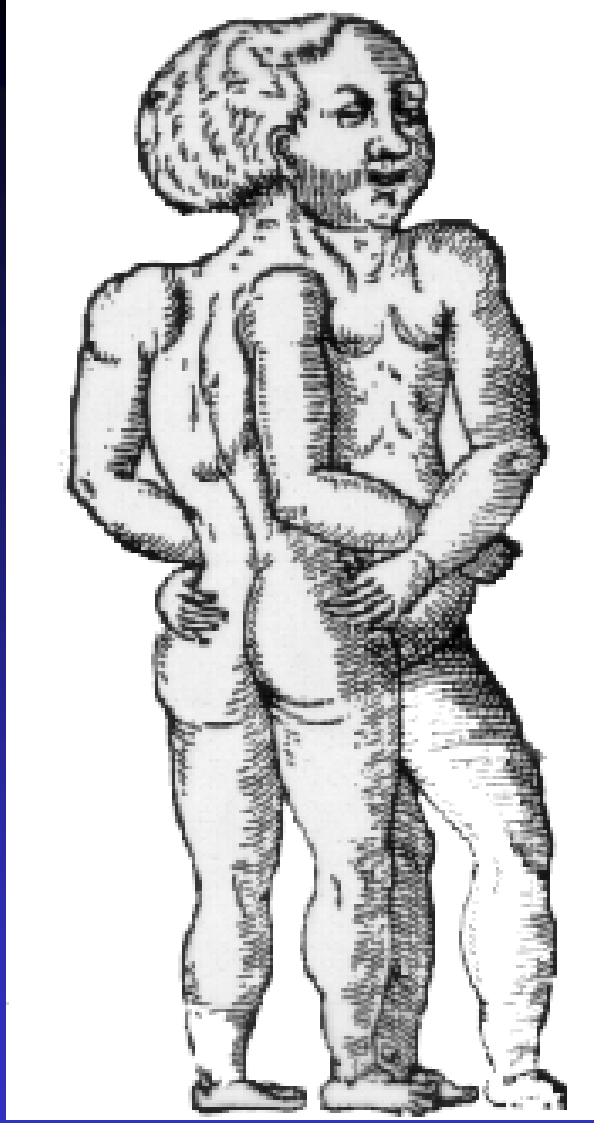
Posterior union of the rump
19% of all conjoined twins.

Parapagus



Lateral union of the lower half

Cephalopagus

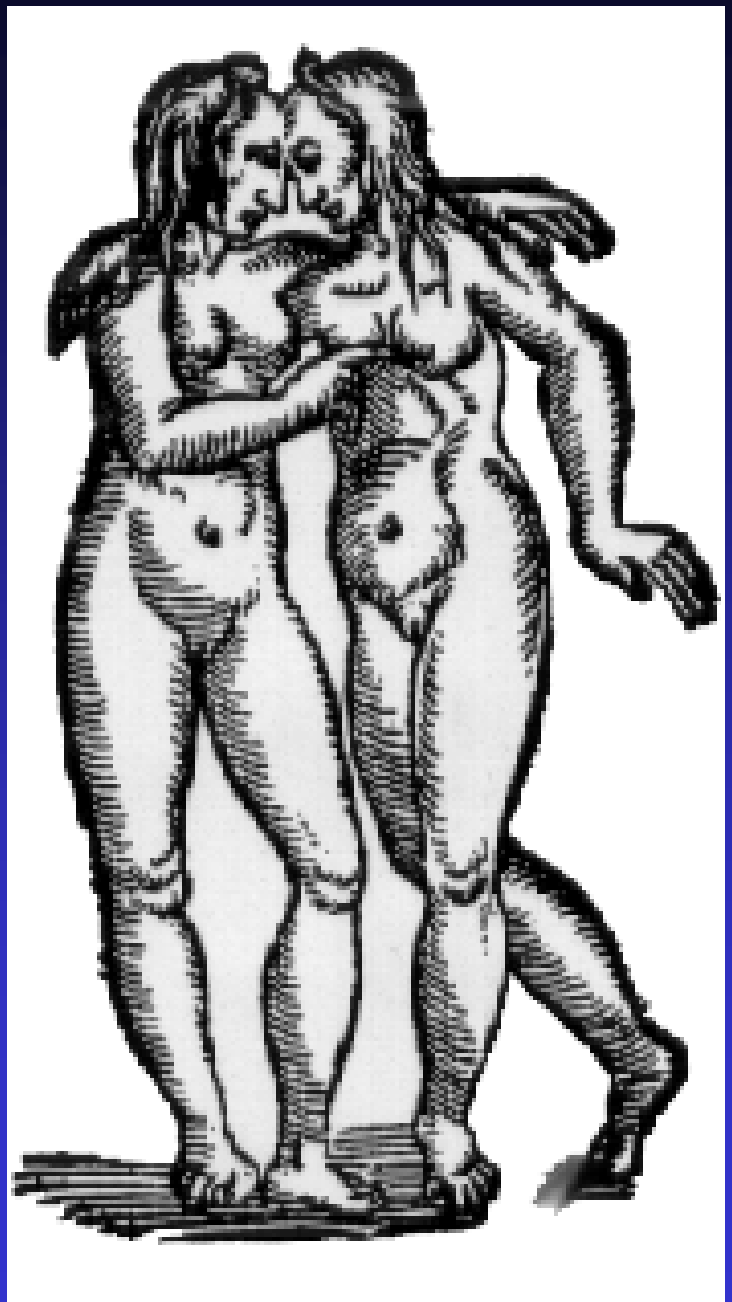


Anterior union of the upper half of the body with two faces on opposite sides of a conjoined head.

The heart is sometimes involved.

Cephalothoracopagus

Union of head and chest
There is only one brain
Hearts and gastrointestinal tracts
are fused.



Craniopagus

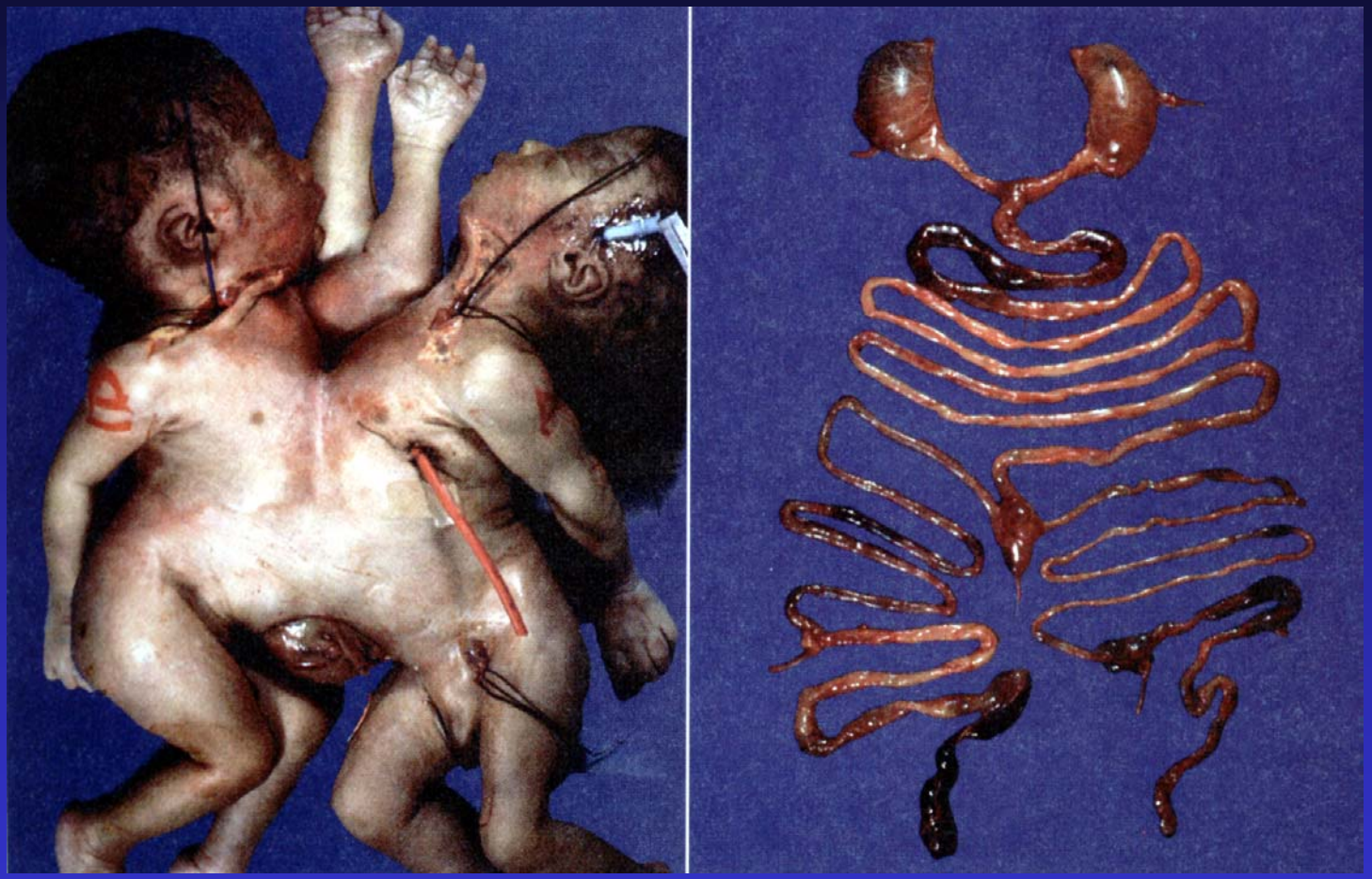
Cranial fusion only

Parasitic Conjoined Twins

One twin without brain or heart

From BM Carlson, 1999

Thoracopagus



Anterior union of the upper half of the trunk.
The most common form of conjoined twins (about 75%)
Always sharing the heart.

Hydatidiform Mole

Pregnancy without an embryo (complete or partial mole)

Complete Mole = Only a placenta / No fetus – Diploid but with 2 sets of paternal chromosomes, no maternal contribution

Partial Mole = Triploid (Maternal, 1N; Paternal, 2N)

Diagnosis – high hCG levels; ploidy analysis (flow cytometry)

1:1200 pregnancies in US; 1:200 pregnancies in Latin America/Asia

Hydatidiform Mole

Snow Storm appearance

Cystic Areas (white arrows)

No fetus

Placenta (open black arrows)

Partial Mole – cystic areas present

Fetus is present
- commonly triploid
- twin with mole in one sac (rare)

From BM Carlson, 1999

Imprinting

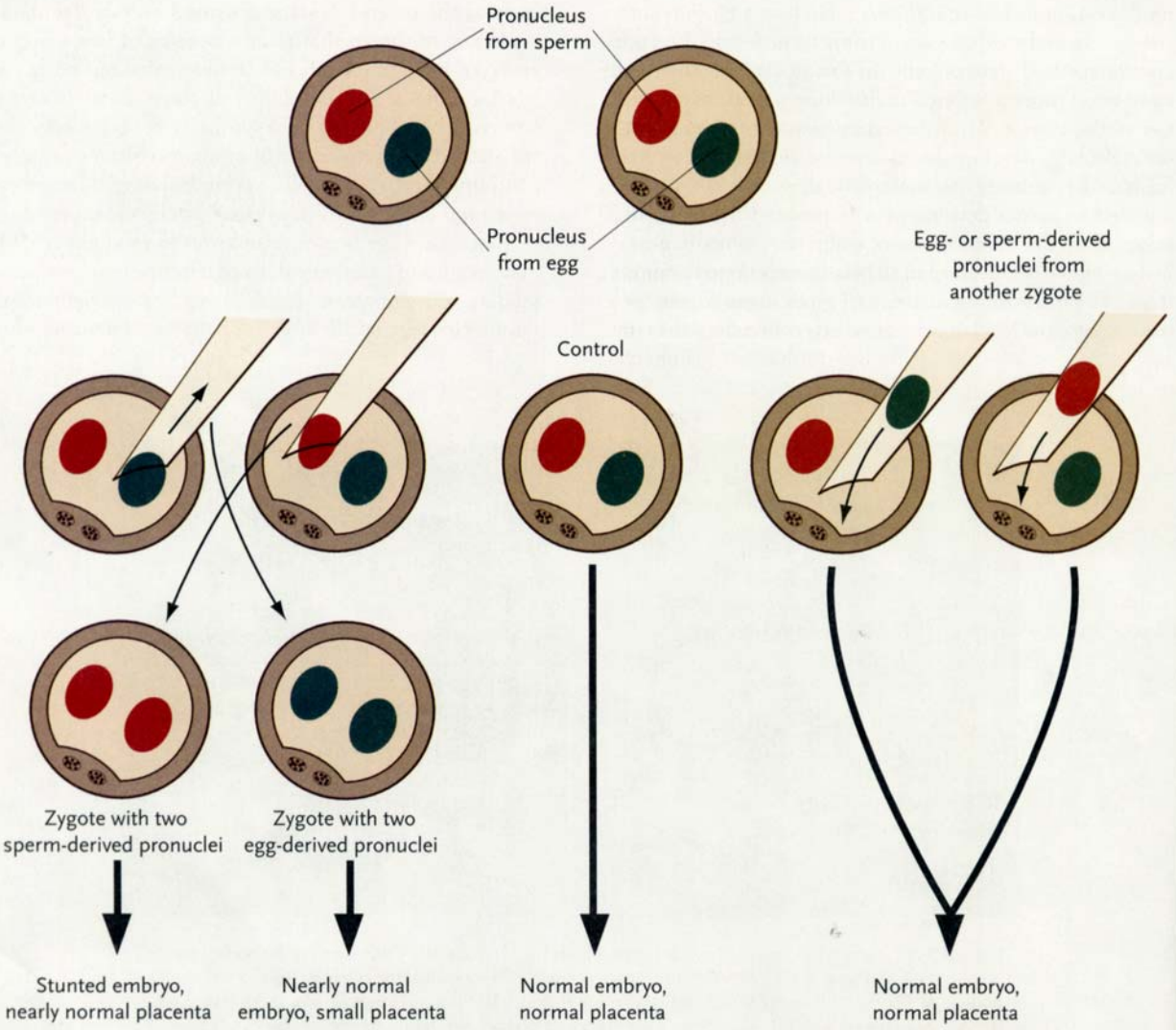


Figure 3-5 Experimental demonstrations of parental imprinting by the use of pronuclear transplants.

Parental Imprinting

Identical genes derived from maternal and paternal DNA display differential expression

Selected genes are turned off during gametogenesis by methylation of certain bases

Imprinted patterns are not passed on to progeny, imprints erased during gametogenesis

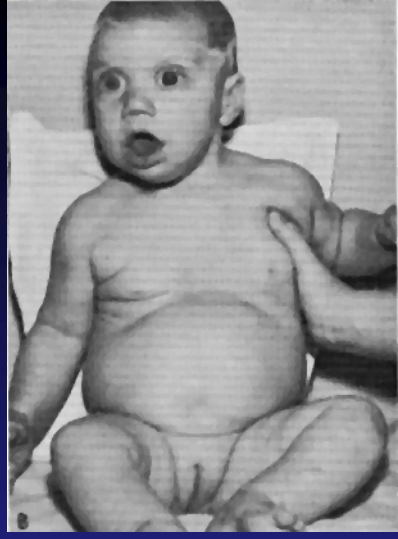
Beckwith-Wiedemann syndrome - *Igf2*

Long arm Chr 15 deletion

Angelman's syndrome - Maternal deletion

Prader-Willi syndrome - Paternal deletion

Beckwith-Wiedemann Syndrome



Chromosome 11

- *Igf2* (Insulin-like Growth Factor) – growth promoter
- H19 – a growth suppressor

Mental deficiency – mild to moderate

Macrosomia – excessive growth, muscle, subcutaneous tissues

Macroglossia – protruding tongue, overgrowth of other craniofacial structures

Organ Hyperplasia – kidneys, pancreas

Angelman's Syndrome

"Happy Puppet Syndrome"

Maternal long arm of Chromosome 15 deletion

Severe mental deficiency – marked delays in motor milestones, absent speech, frequent laughter, frequent seizures

Puppet like gait

Widely spaced teeth

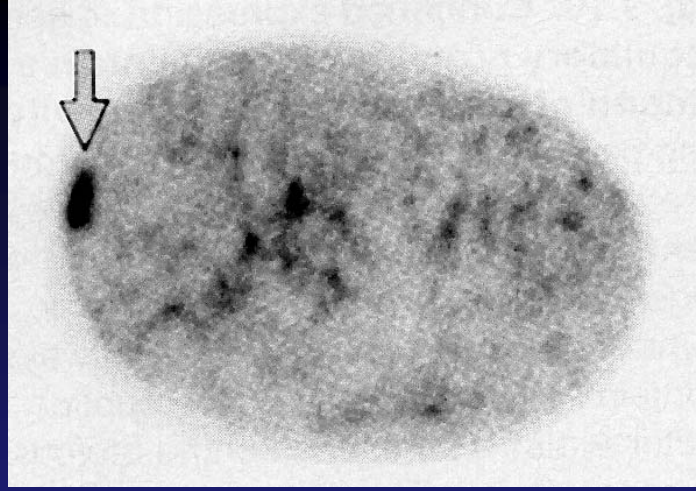
Macroglossia

Decreased occular pigment → pale blue eyes

Prader-Willi Syndrome

- Paternal long arm of Chromosome 15 deletion
- Mental deficiency – mild-moderate
- Normal birth size – decreased growth rate
- Short stature / Obesity
- Very small hands, feet, genitalia
- Fair skin, blue eyes, sun-sensitivity
- Craniofacial – almond-shaped, narrow bifrontal diameter

X-Chromosome Inactivation



Inequality of Genetic Expression

Female-specific, 1 X-chromosome is inactive
Barr body – extreme condensation

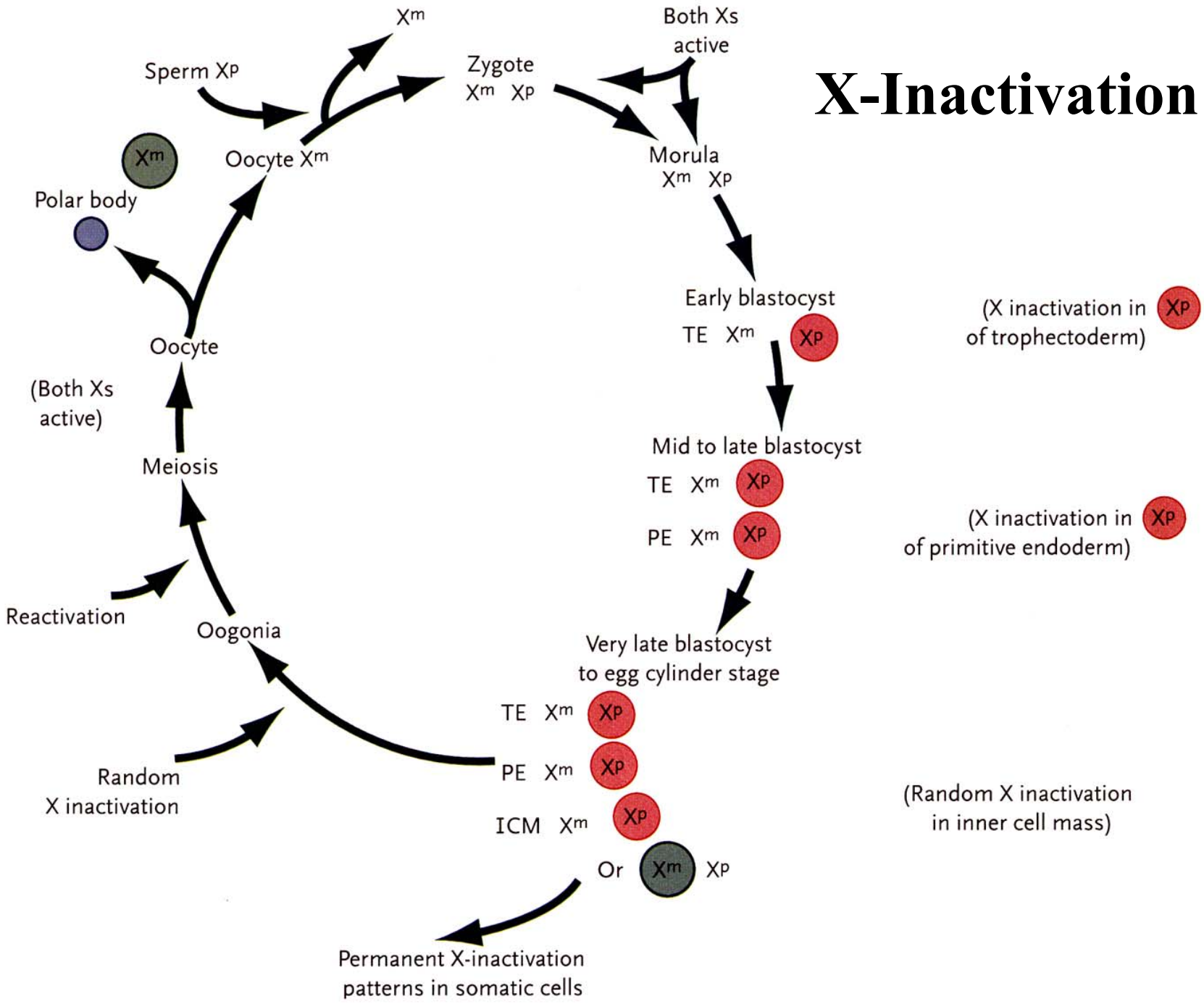
Both Xs are active thru cleavage

Blastocyst - Trophoblast – paternal X inactivated
Inner Cell Mass – both are active

Egg cylinder stage – differential X inactivation in cell lineages

Oogenesis – both Xs become active

X-Inactivation



Regulative Development

Ability of an embryo or organ to develop normally after removal or addition of parts

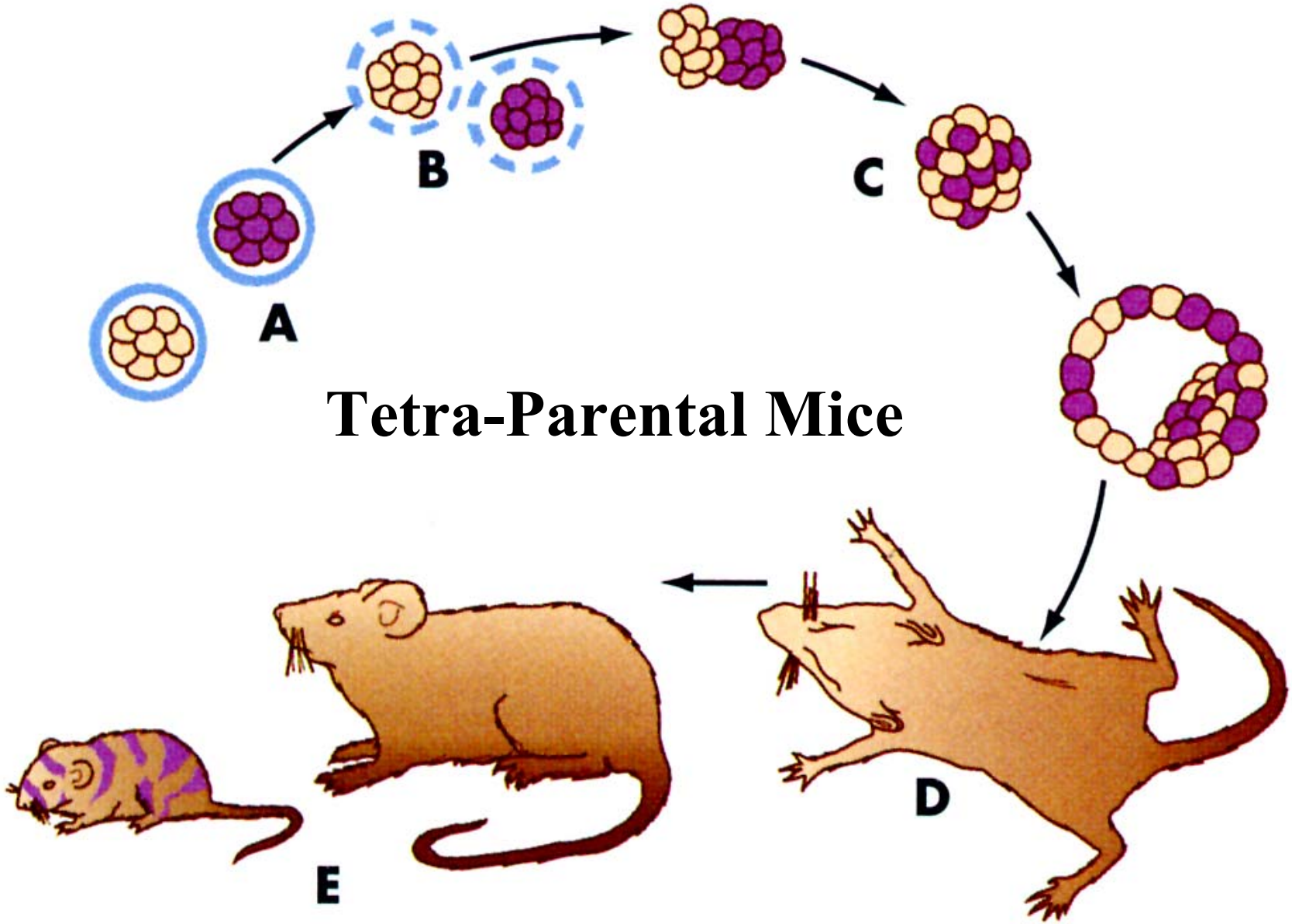
Fate of cells is not irreversibly fixed – influenced by environment

Contrast Mosaic Development

Fate Mapping studies

Developmental Potency – Totipotency

Stem Cells

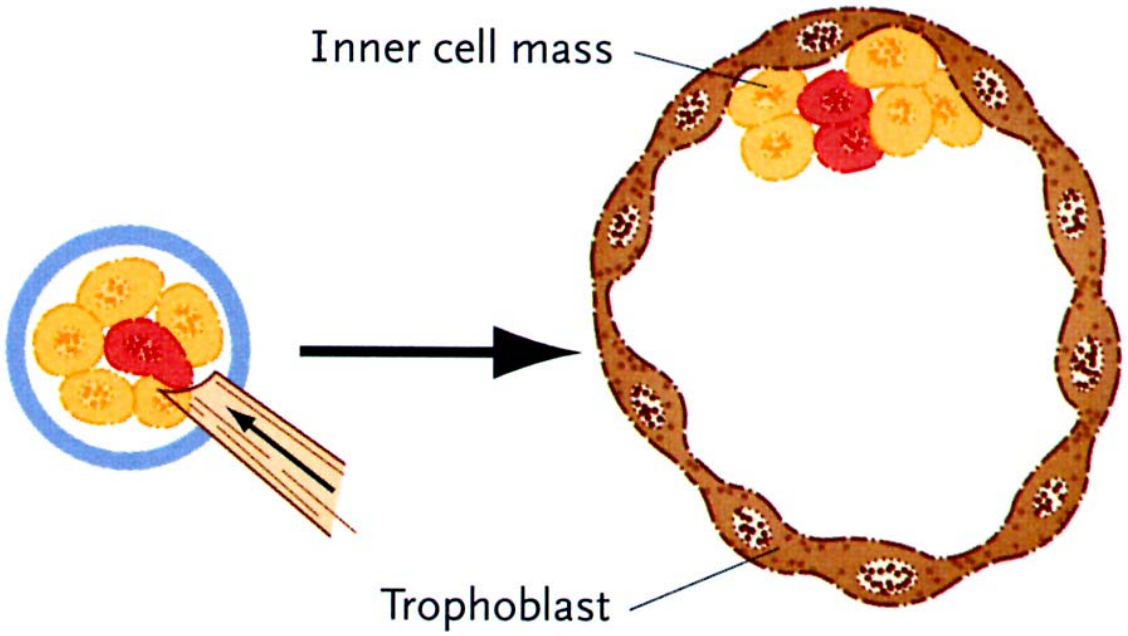


Tetra-Parental Mice

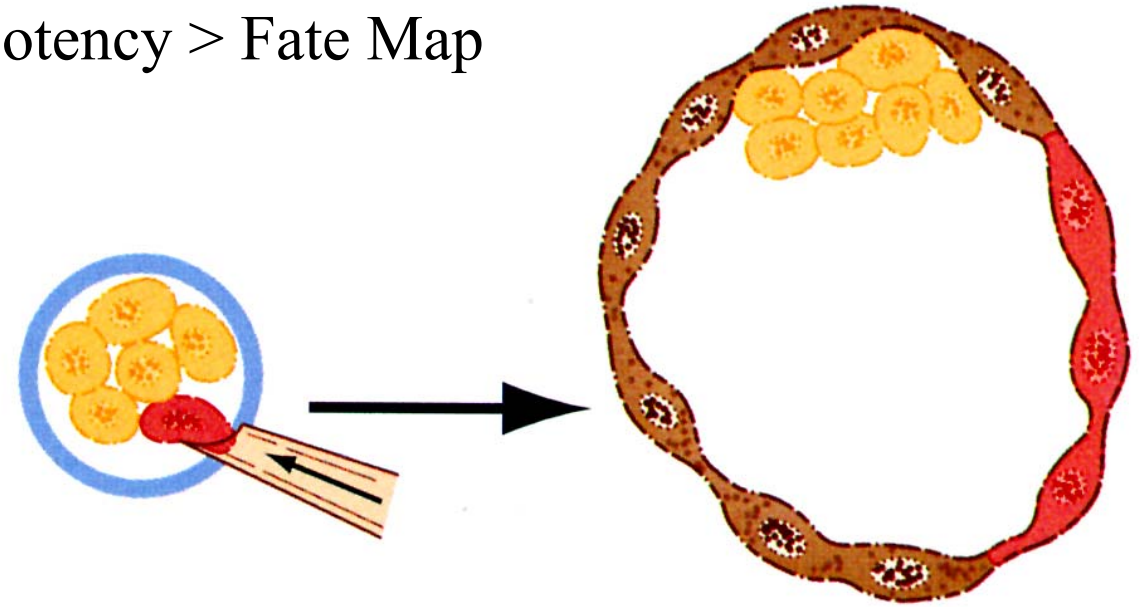
Position-Specific Differentiation

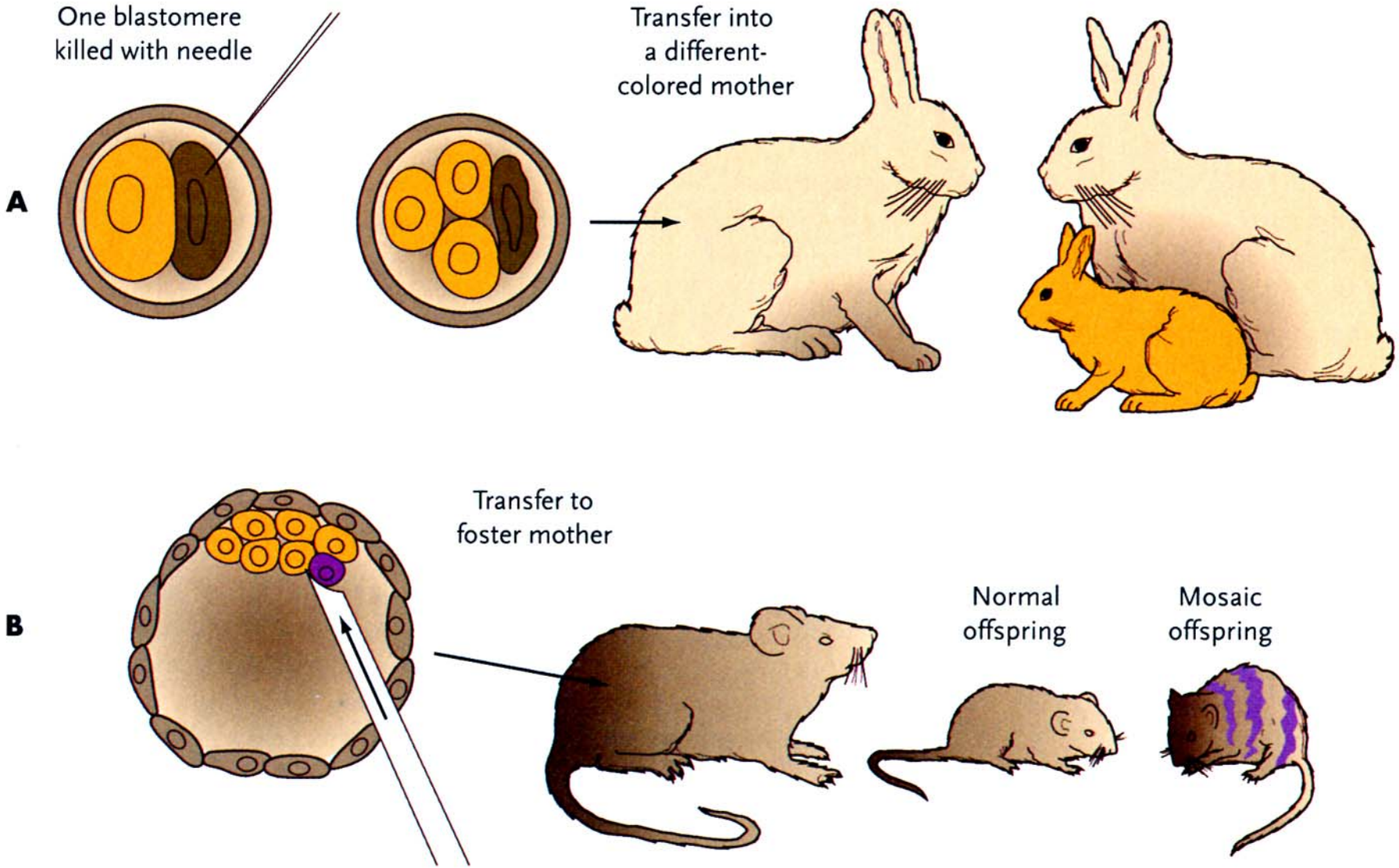
Inside-Outside Hypothesis

8-16 Cell Stage - Totipotent

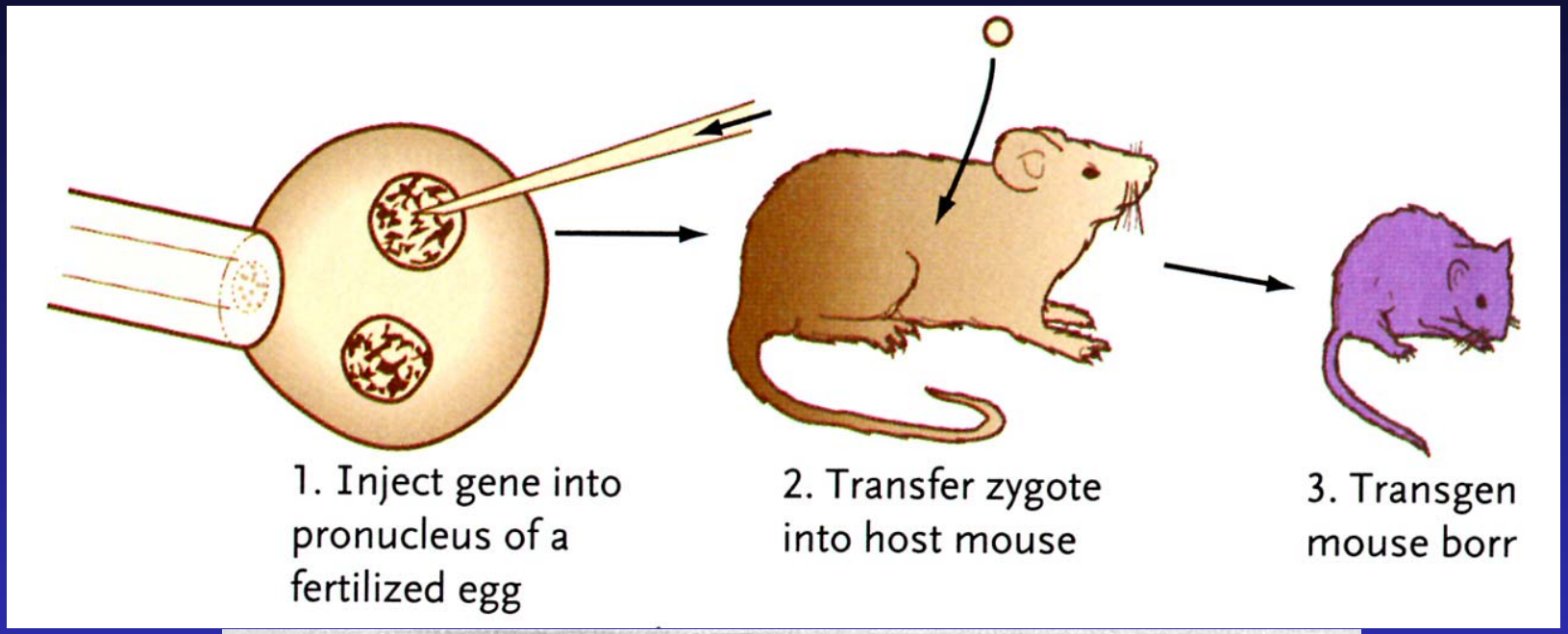


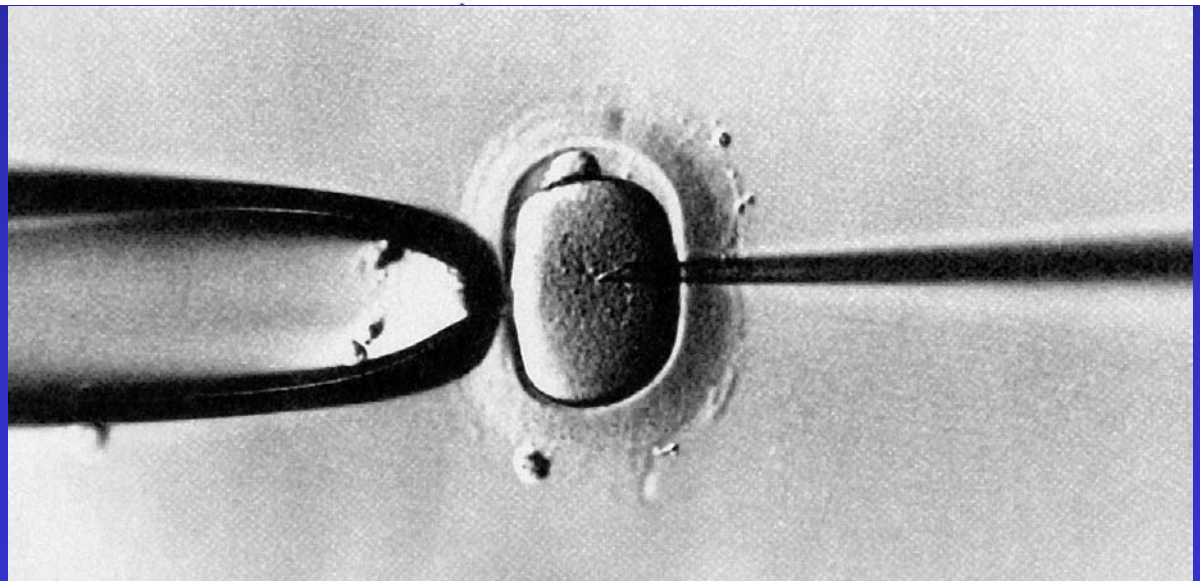
Potency > Fate Map

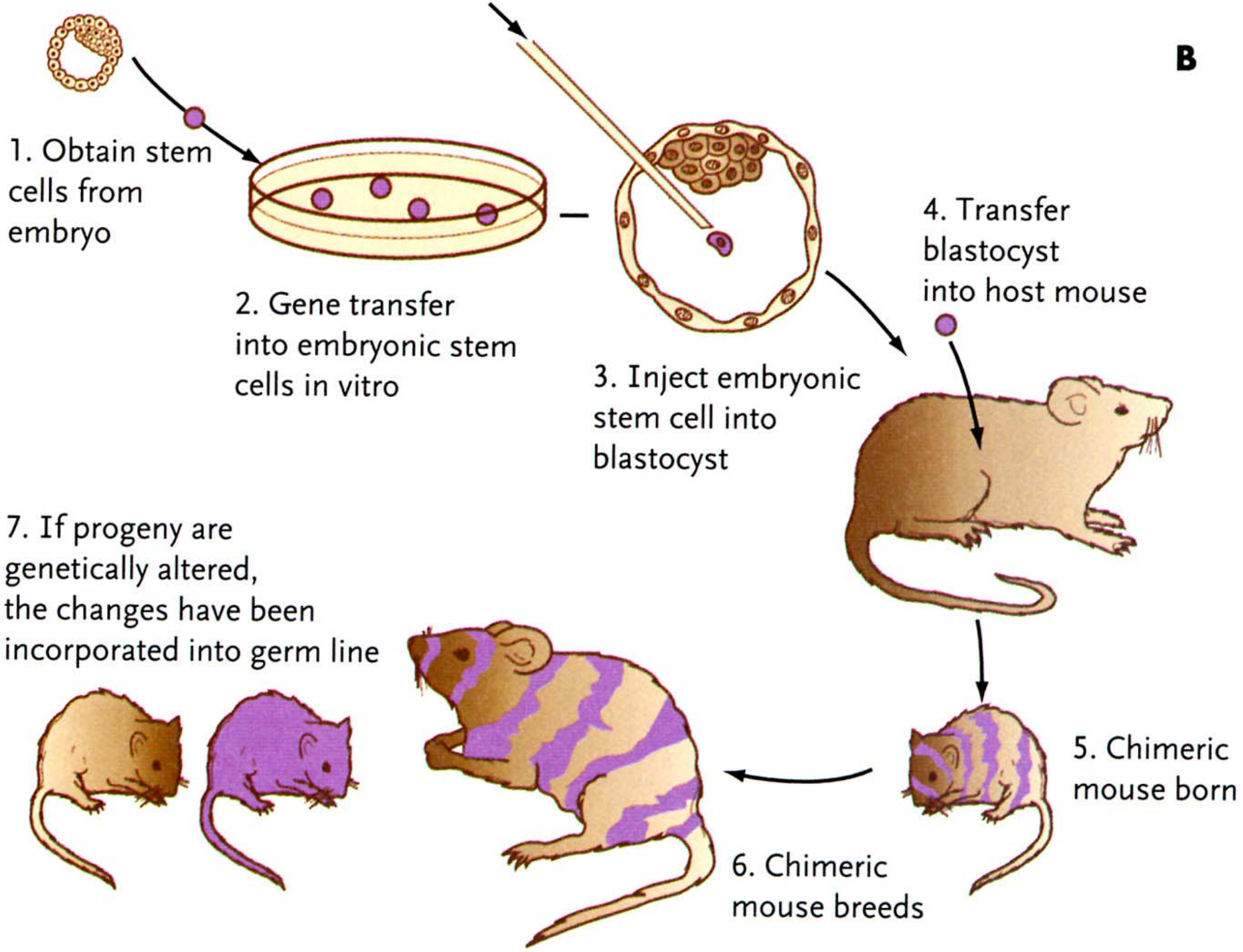



A
One blastomere killed with needle
Transfer into a different-colored mother
B
Transfer to foster mother
Normal offspring
Mosaic offspring

Transgenic Mice






B
1. Obtain stem cells from embryo
2. Gene transfer into embryonic stem cells in vitro
3. Inject embryonic stem cell into blastocyst
4. Transfer blastocyst into host mouse
5. Chimeric mouse born
6. Chimeric mouse breeds
7. If progeny are genetically altered, the changes have been incorporated into germ line

Cloning Dolly