Current topic 2:

Stem cells

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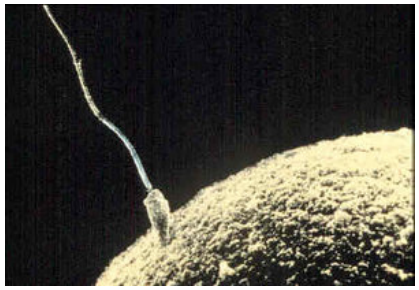
LT4- Part A- Human development in a nutshell

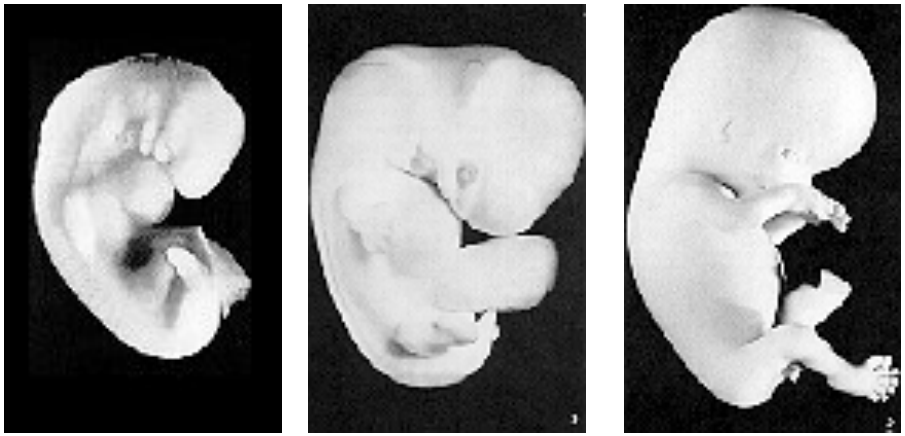
The question



How does a single cell (the fertilised egg) becomes

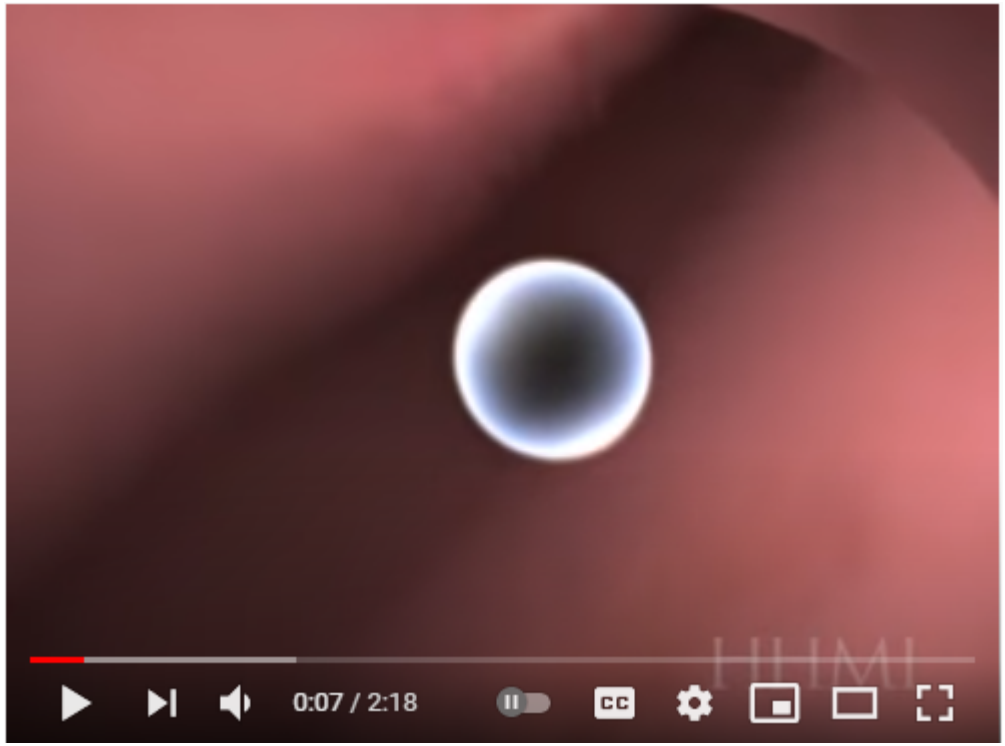
trillions of cells with

220 cell types organised in tissues and organs.

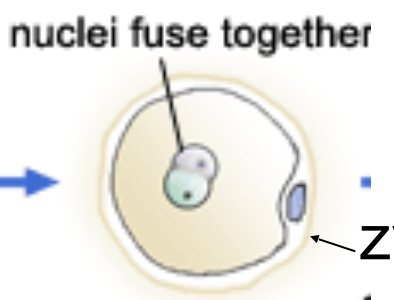


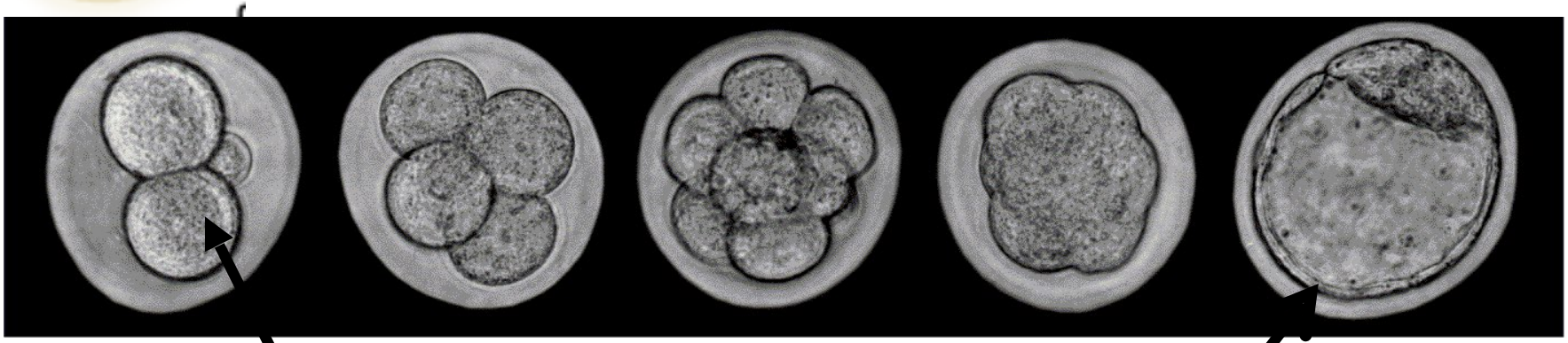
Video

http://www.youtube.com/watch?v=UgT5rUQ9EmQ&feature=related HHMI



Cleavage of the zygote

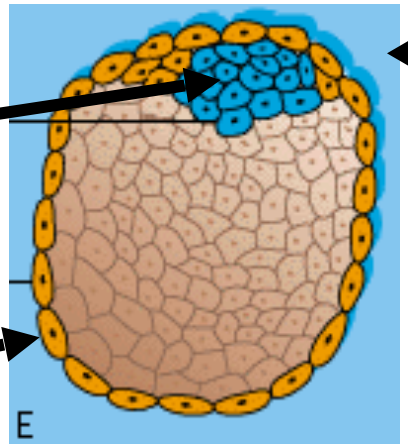




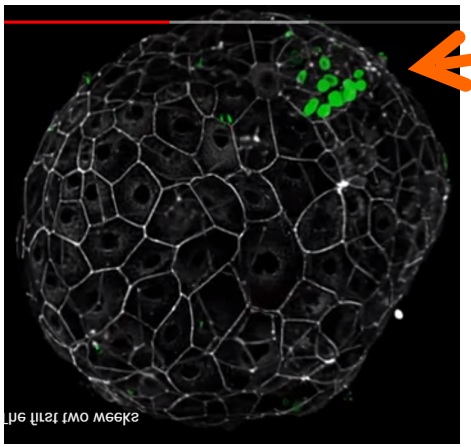
Blastomere

Inner cell mass (ICM) = embryo

Trophoblast = extra-embryonic membranes, e.g. placenta

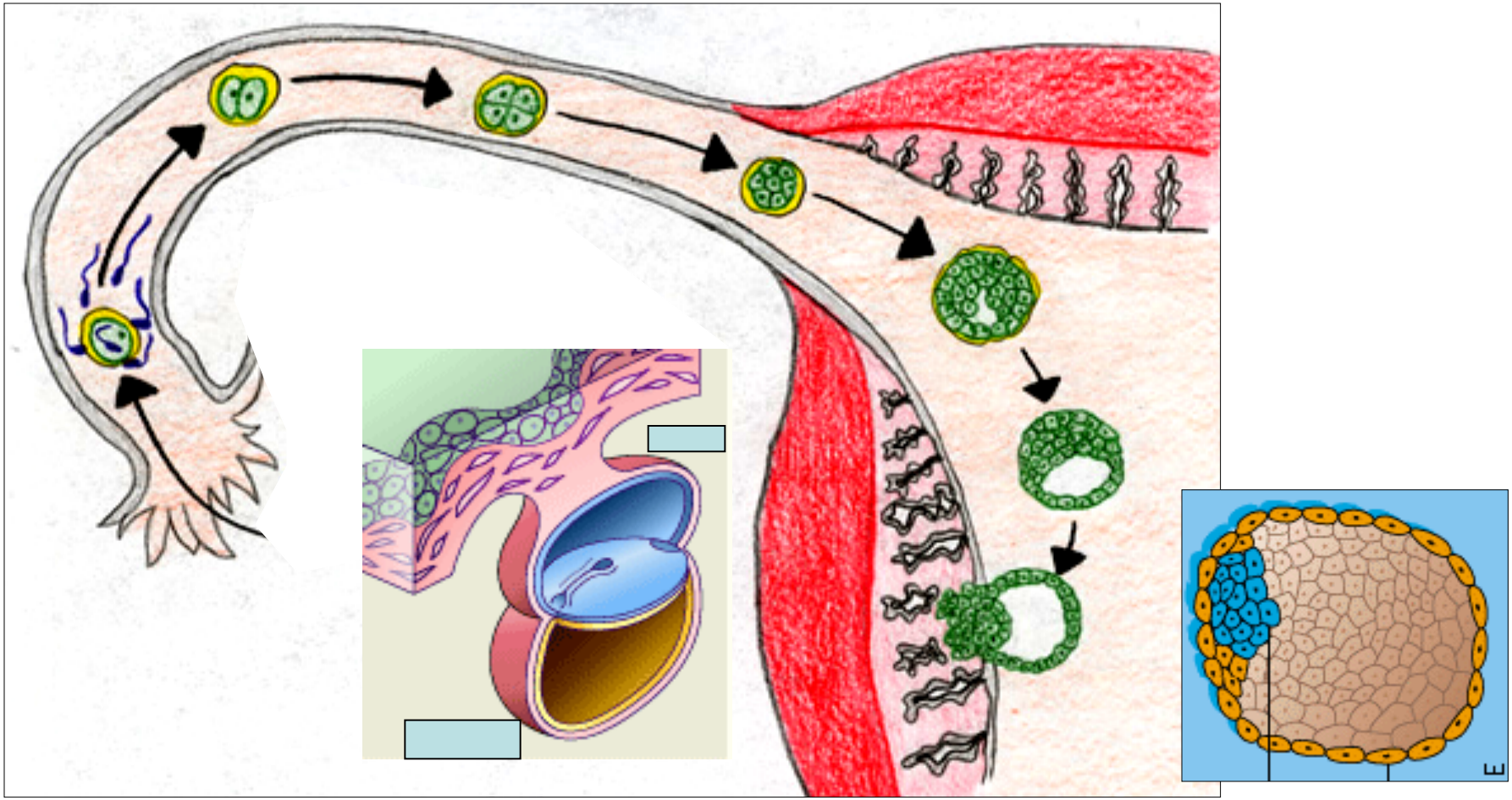


Blastocyst, 5 days



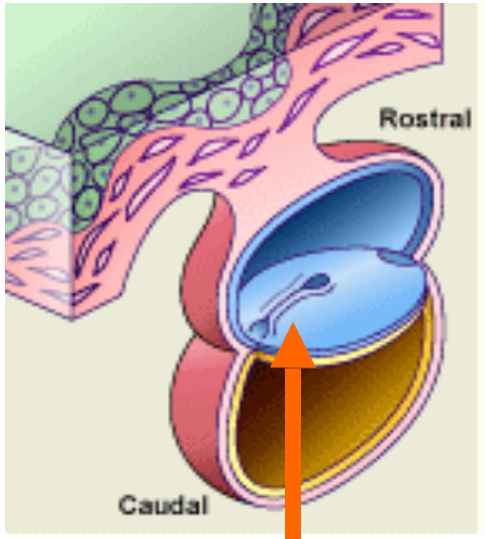
Multi-cellularisation (via mitosis) & partitioning of the zygote cytoplasm = From 1 cell type to 2 types

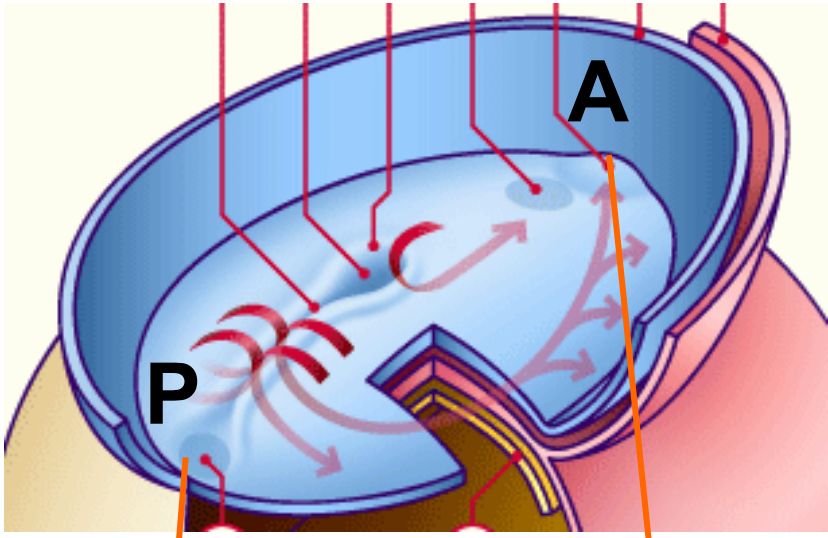
Uterine implantation



Driven by the trophobast. ICM expands and changes shape and location, but only one type of cell.

Setting the body axes =coordinates





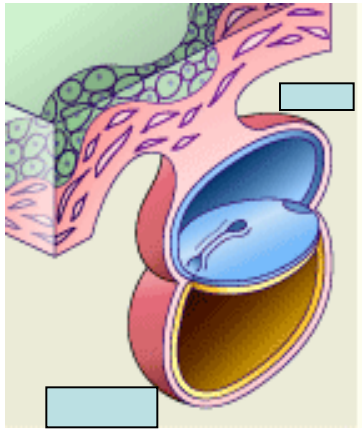
Primitive streak = Anterior Posterior (head to tail) axis

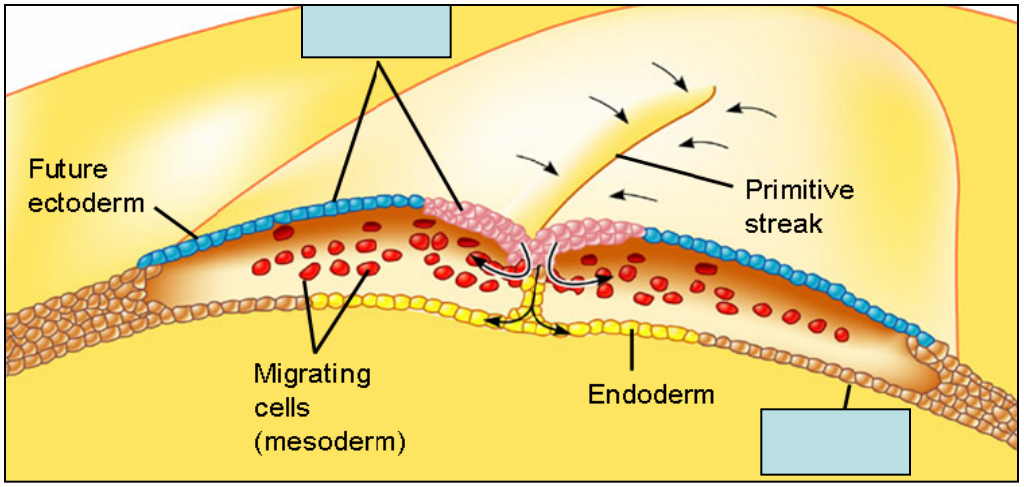
Bilateral symmetry along the anterior posterior axis.

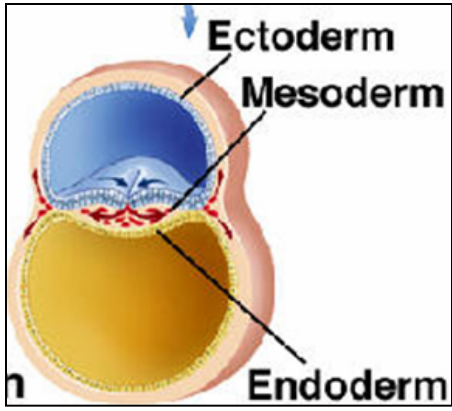
Coordinates AP, DV, Prox-Distal

Ventral = belly

Gastrulation

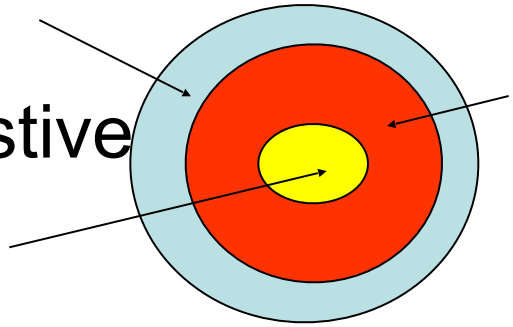






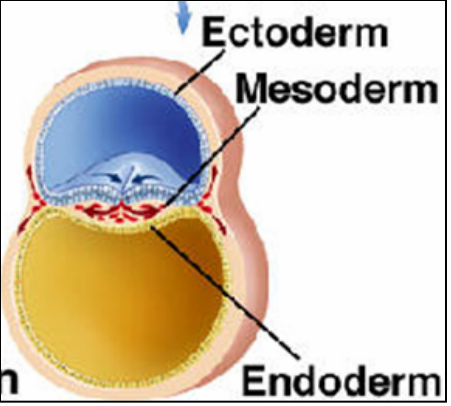
Ectoderm: Skin and nervous system

Endoderm: Digestive system, lungs,…

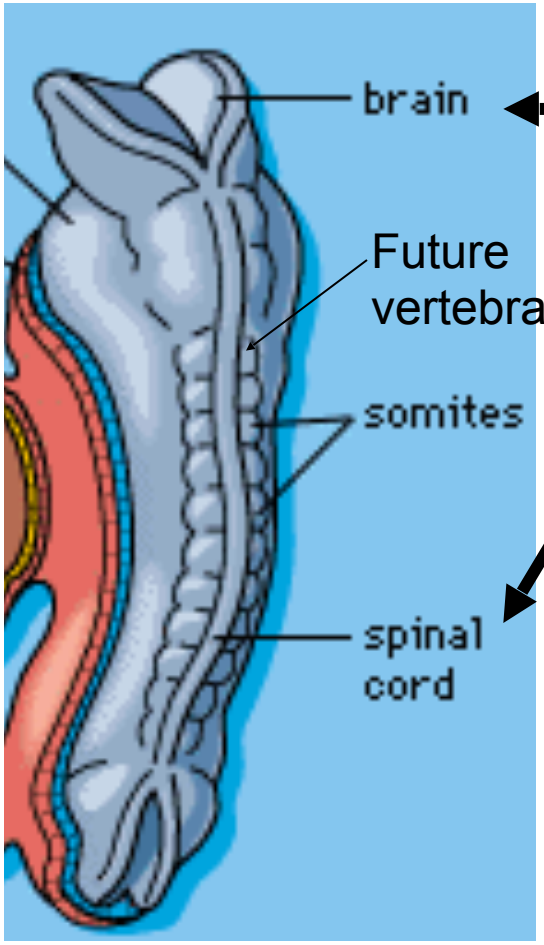


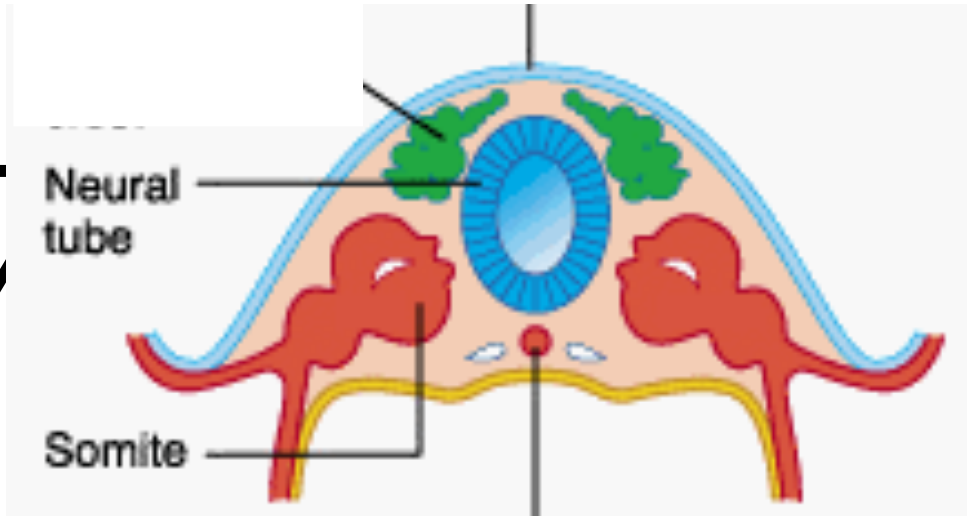
Mesoderm: Muscles, blood, skeleton, connective tissue, heart.

Highly coordinated cell movements: the ICM cells get organised into the three germ layers.



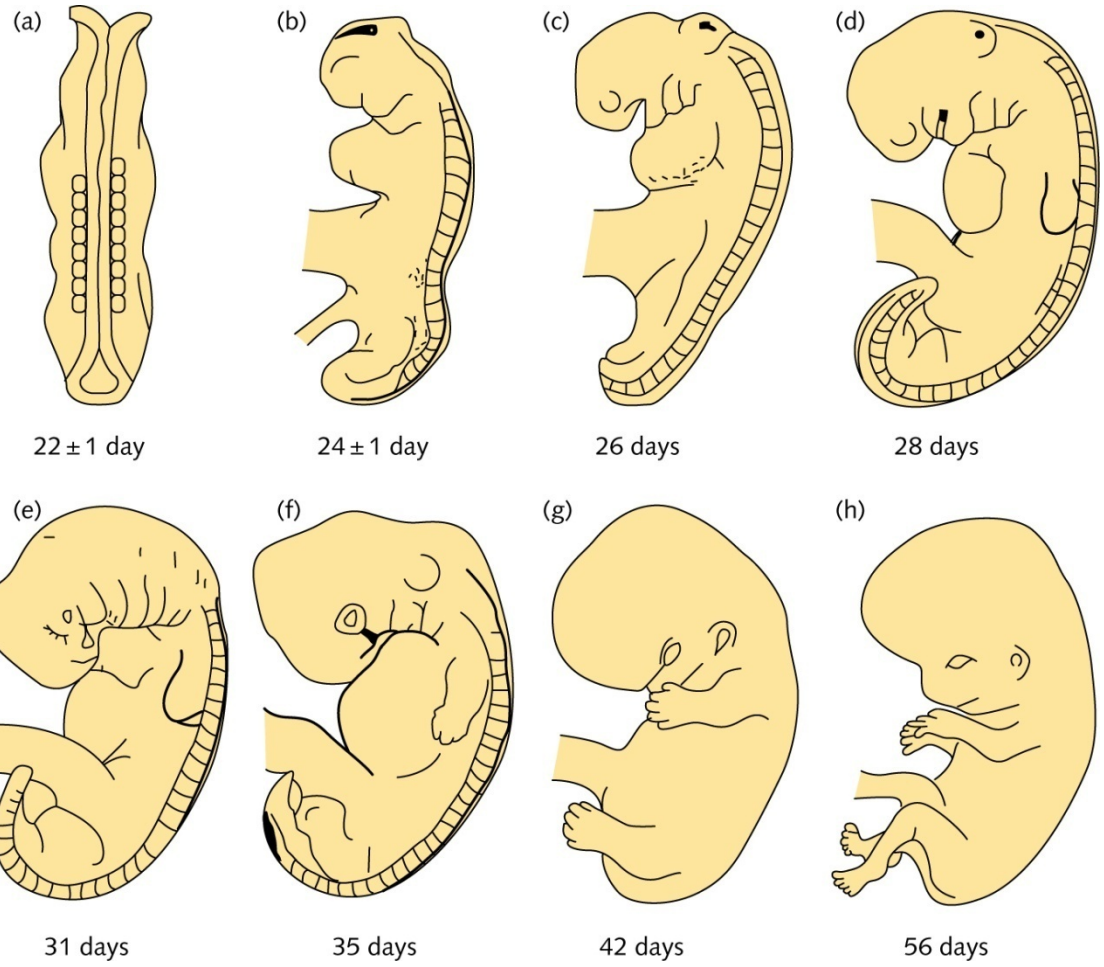
Neurogenesis along the AP axis –defines the framework

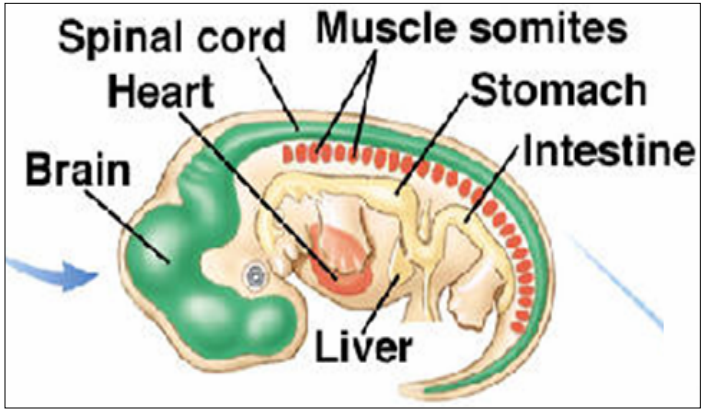




Somites → future muscles and vertebral column, and dermis of the skin. During development, they provide landmarks along AP for organ formation

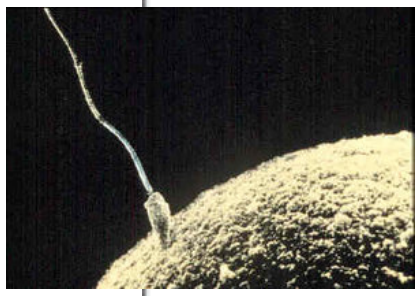
Organogenesis is progressive

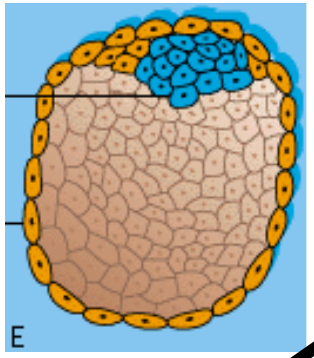


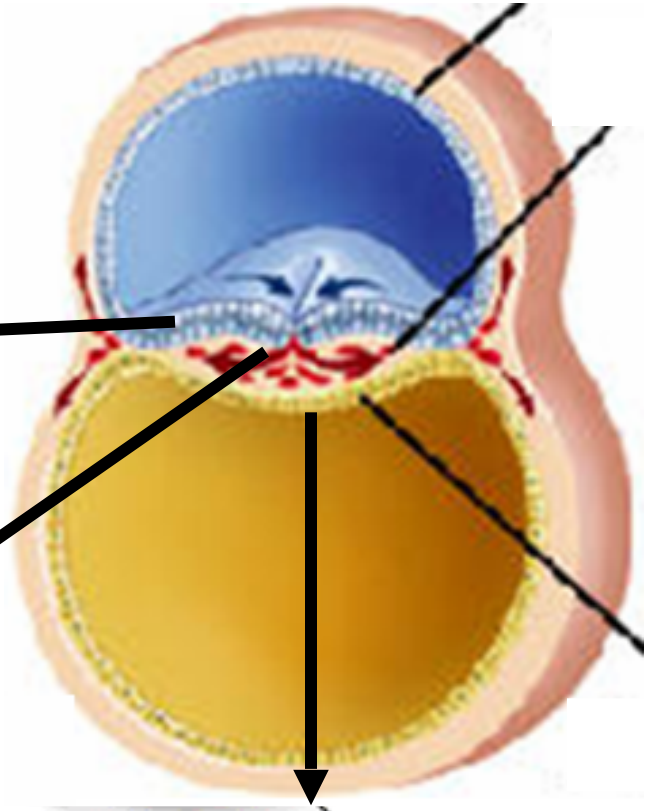


Using the head to tail framework as a reference axis, other cells move, get more specialised and organised into tissues and organs.

From one cell to 220 cell types







Skin Cells of Epidermis

Neuron of Brain

Pigment Cell

Ectoderm (External Lay

Mesoderm (Middle Layer)

Cardiac Muscle

Skeletal Muscle Cells

Tubule Cell of the Kidney

Red Blood Cells

Smooth Muscle (in Gut)

Endoderm (Internal Layer)

Lung Cell (Alveolar Cell)

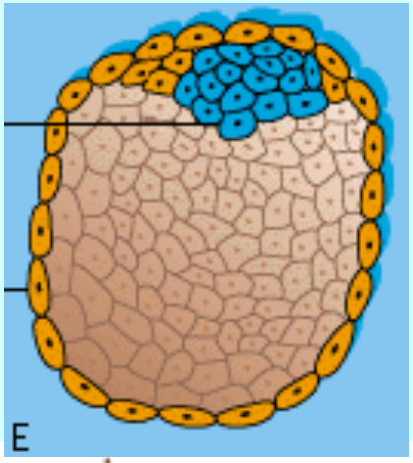
Thyroid Cell

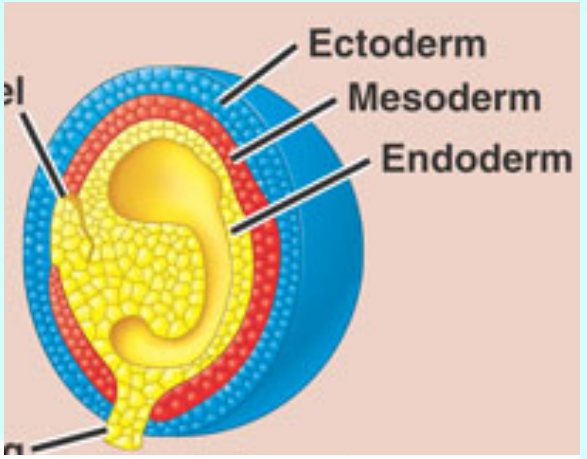
Pancreatic Cell

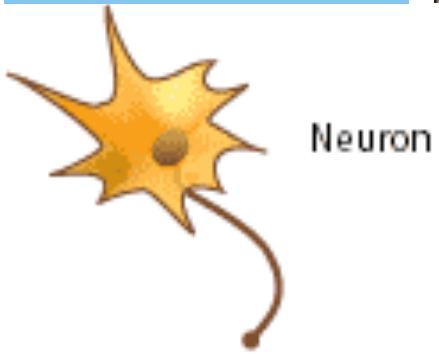
Part B- How do cells become different and specialised?

Undifferentiated cells all look the same but are different.

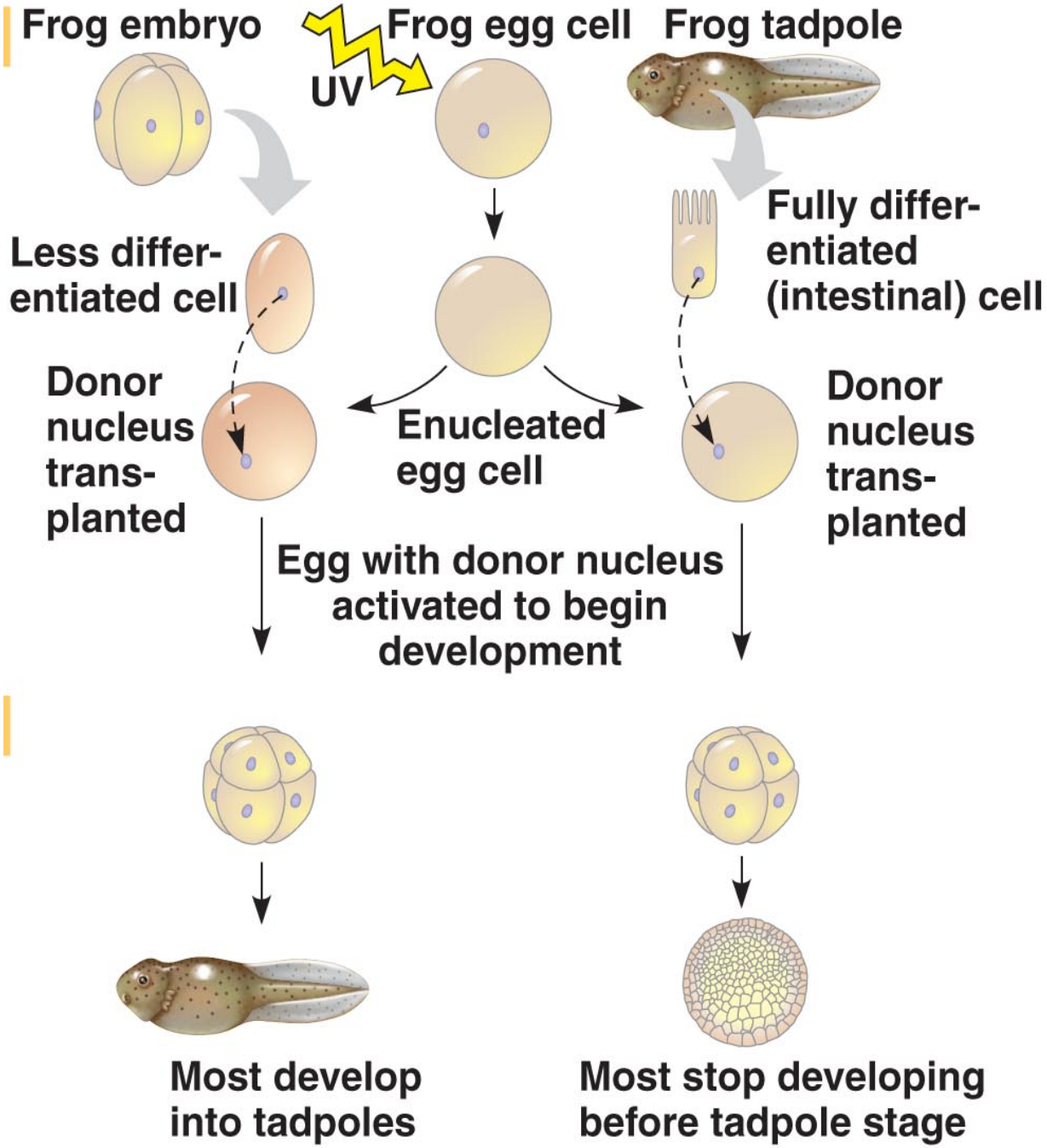
Differentiated cells: shape, structure and function is well defined.







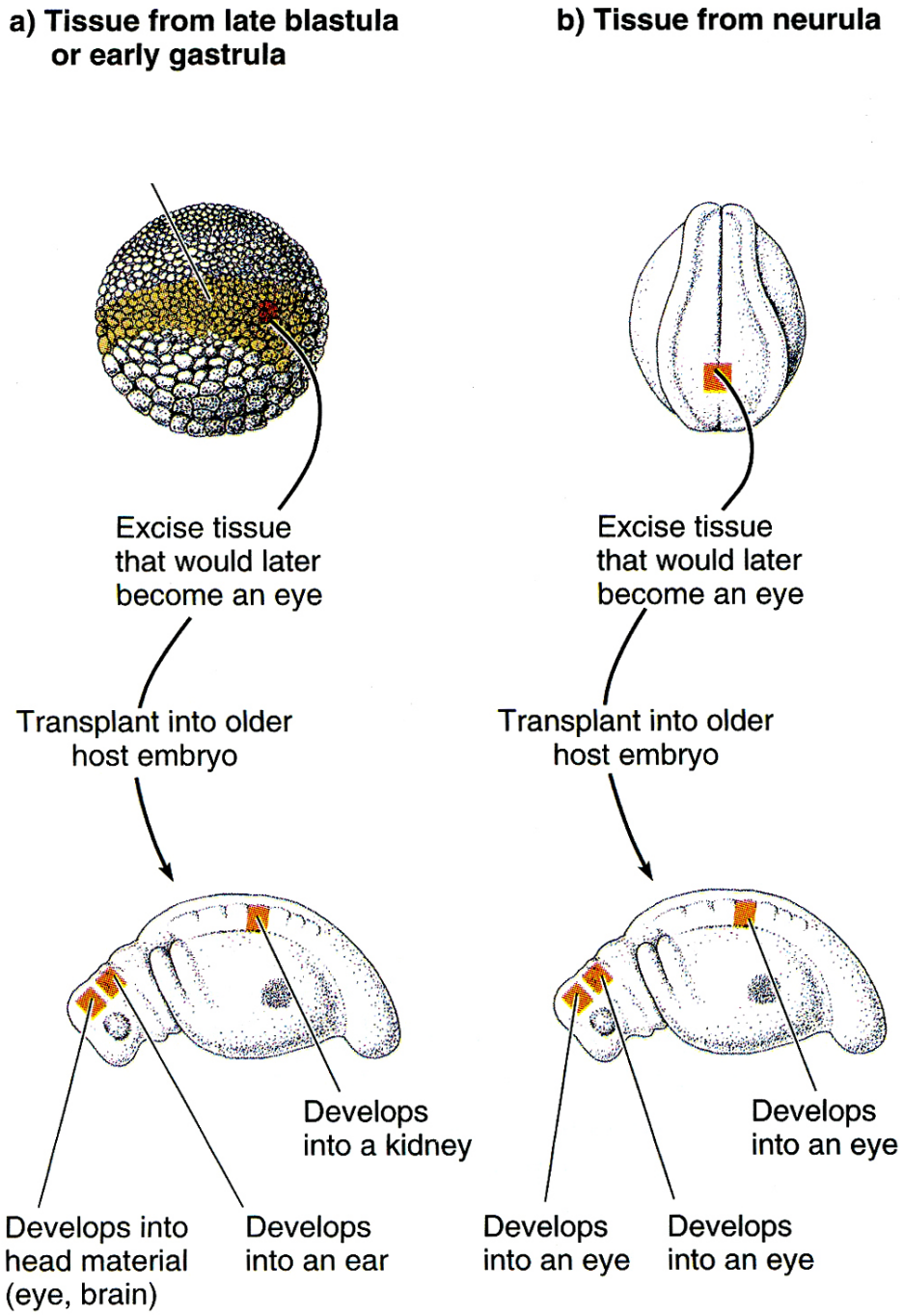
The Gurdon cloning experiment.



A cell's developmental potential (**potency**)

1. decreases as it gets more specialised?
2. increases during development?

Grafting experiments



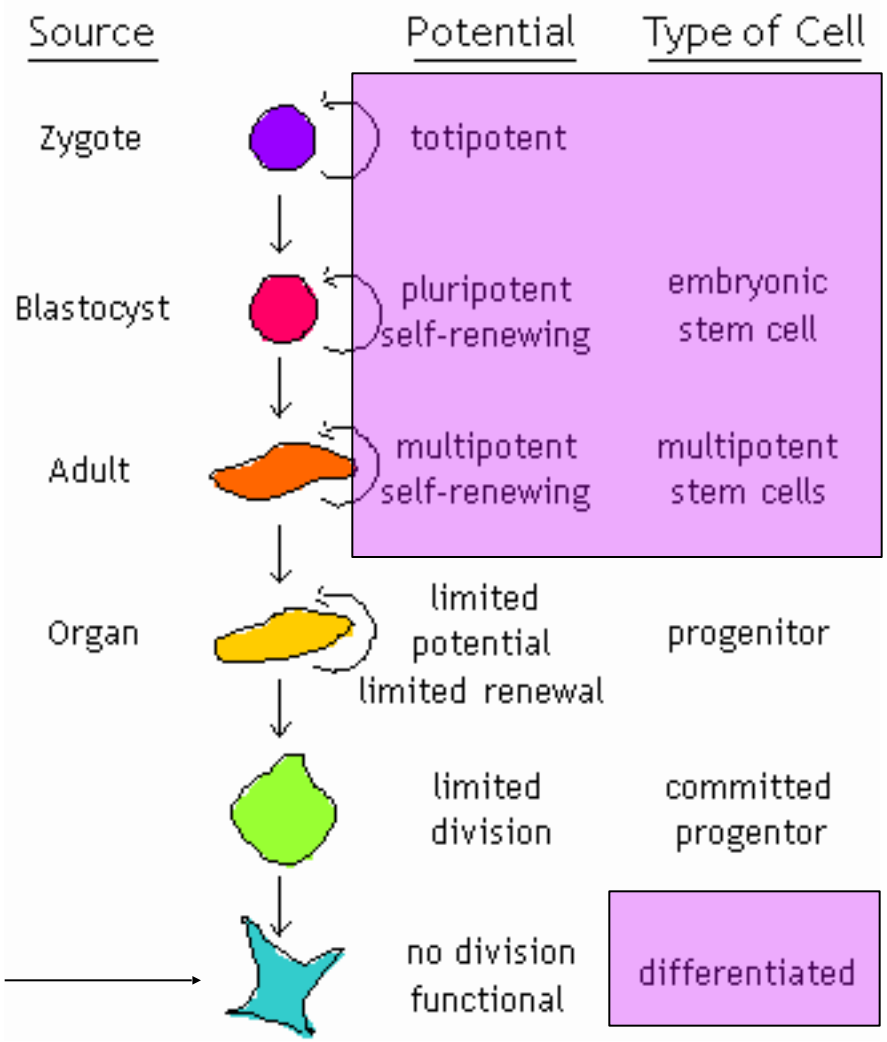
A cell fate

1. is never locked before differentiation?

2. can be locked before differentiation?

Cell potency gets progressively restricted

Cell now has a clear-cut identity and expresses specific proteins for morphology or function.



Can develop into a whole organism

Can develop into a any cell type in body

Can develop into some cell types

Choice between 2 to 6 cell fates (particular tissue)

Determined. Cell fate is locked: Ongoing differentiation

Stops dividing

Cell potency and germ layers

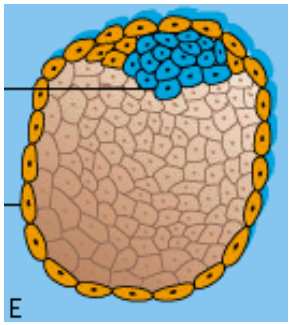
Totipotent embryonic stem cell

→ Up to 8 cells in human

Pluripotent embryonic stem cells

Human embryonic stem cell

Induced pluripotent stem cells



Inner cell mass cells are pluripotent

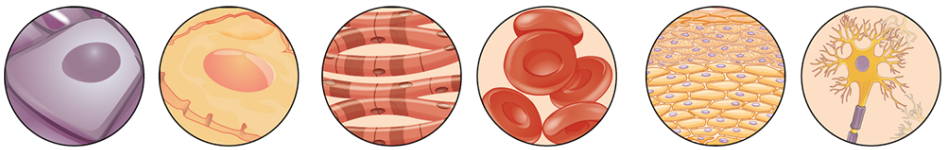
Multipotent stem cells

Adult bone marrow, skin, cord blood, deciduous teeth

Endoderm

Mesoderm

Ectoderm



Lung | Pancreas | Heart muscle | Red blood cell | Skin | Neuron

What accounts for cell differences?

A cell's ID

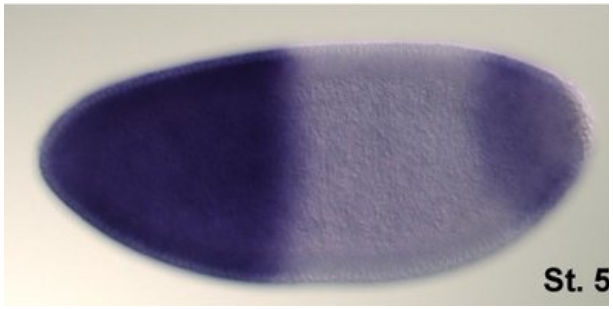
depends on the proteins present in that cell

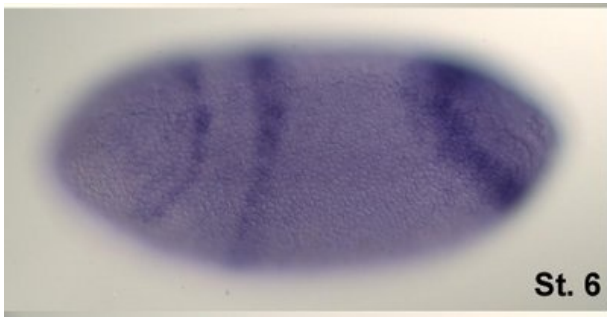
so it depends on the genes it expresses.

Cells do not express all their genes.
Examples with fly embryo.

Gene A (dark blue),

Two time points.

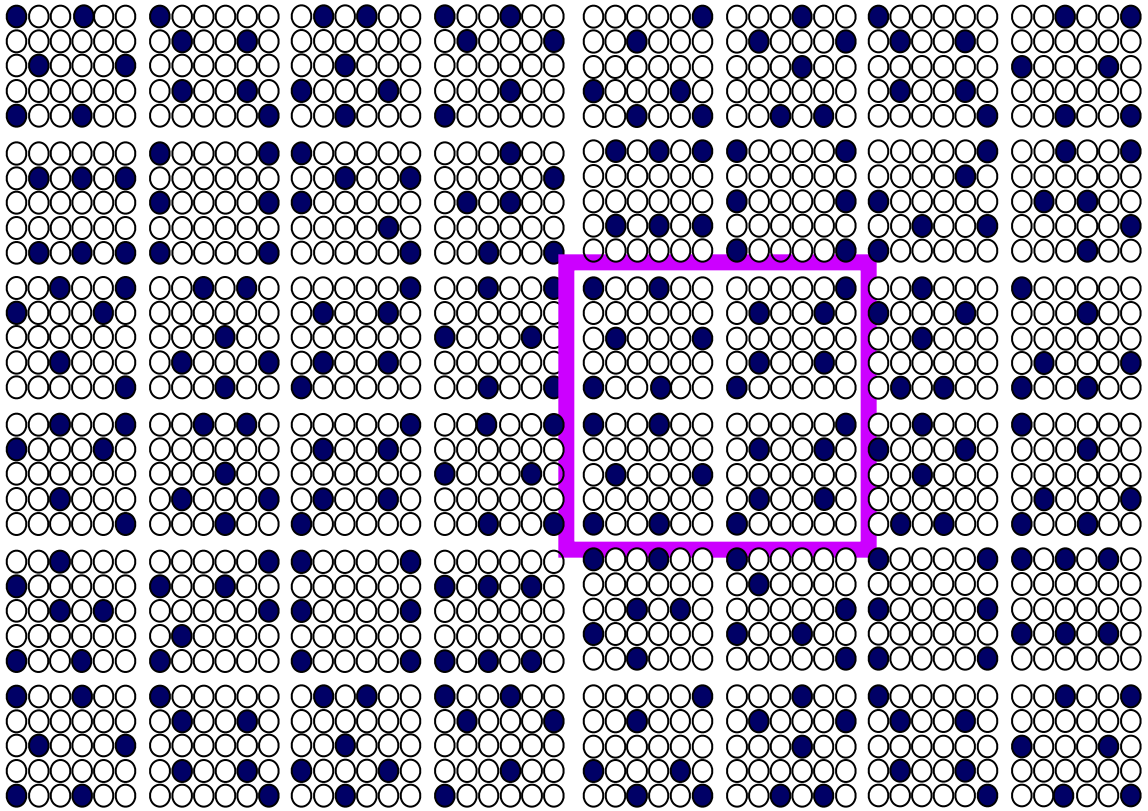




Genes A, B and C (white).

One time point.

Gene expression profile of 1 cell



At any given time, each cell expresses ~ **20%** of its genes. Genes switched ON are in blue.

10% of these (20%) genes are **developmental genes**. **Changes in the expression of these genes create differences amongst cells.**

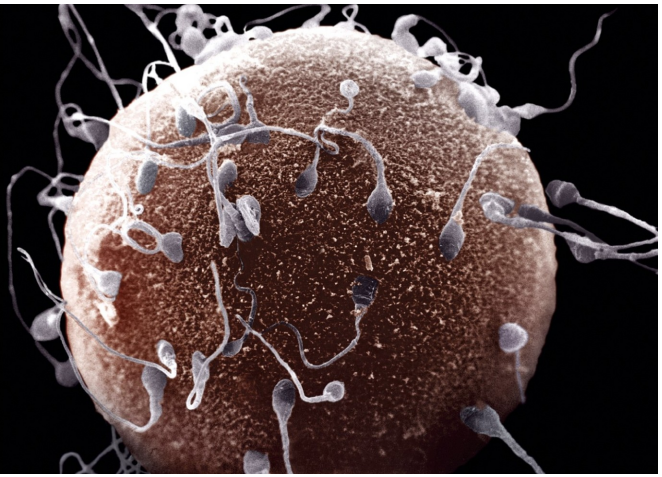
Developmental genes code for

- Proteins that regulate gene expression, i.e. turn genes ON or OFF.
- Proteins involved in cell communication/signalling. Through cell signals, cells can tell each other which genes to turn ON or OFF.
- So developmental genes overall control the expression or silencing of other genes (often other developmental genes).
- As a result, one initial difference in gene expression leads easily to many differences down stream (cascade /snow ball effect).

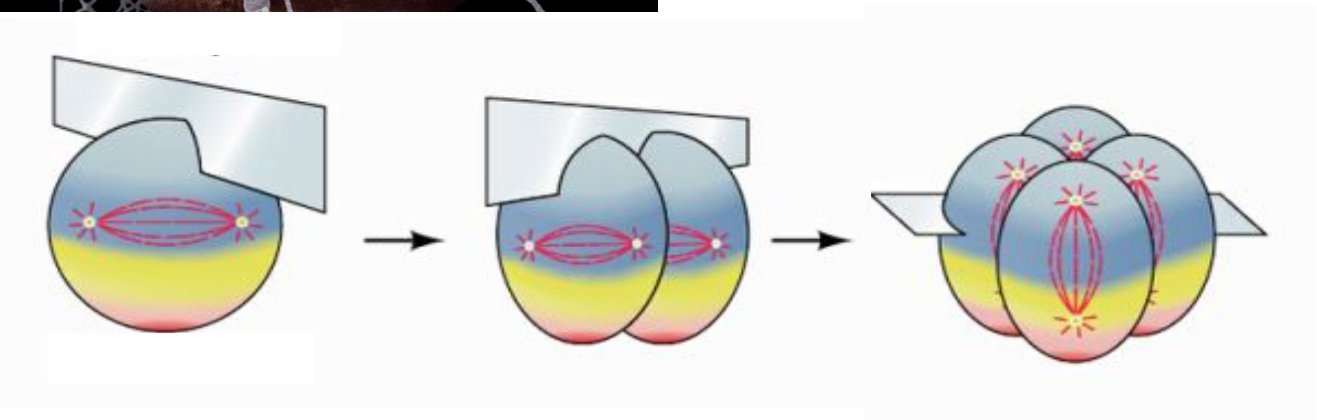
How does it all start?

What is the initial spark?

Cells become different because of maternal proteins deposited in egg -1.



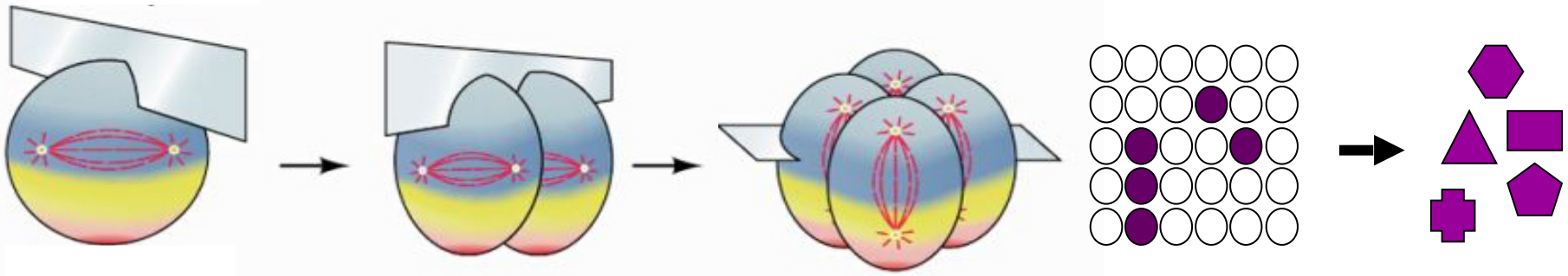
The egg = largest cell in the female body because it contains essential maternal proteins for the first steps of development. These are transcription factors and are not distributed uniformly.



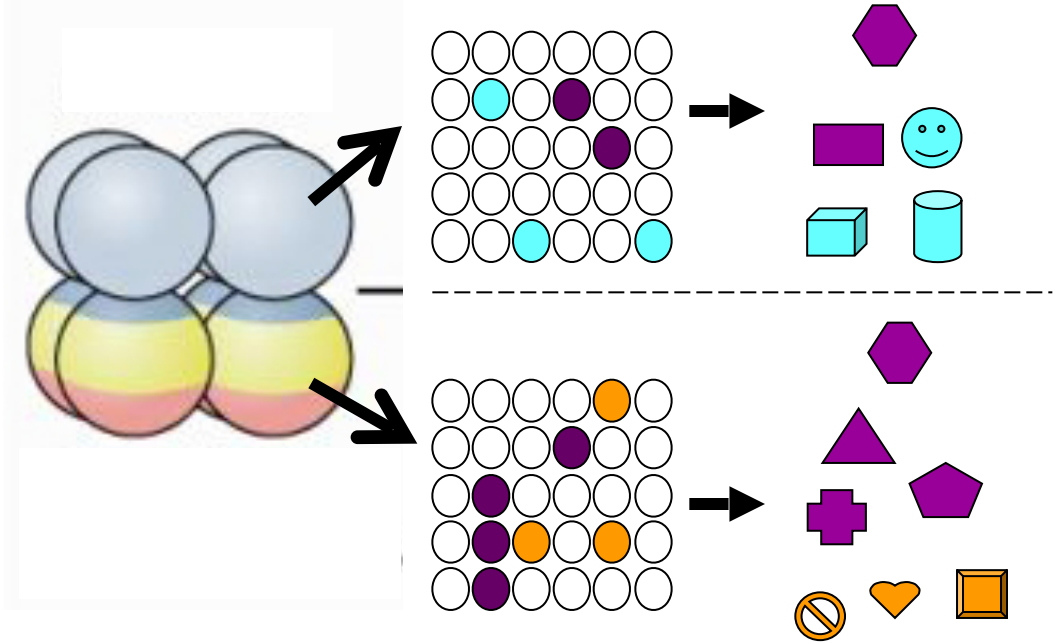
After two **cleavage divisions**, the blastomeres have the same maternal proteins in their cytoplasm.

Do you think that the four blastomeres express the same genes?

Cells become different because of maternal proteins deposited in egg -2.

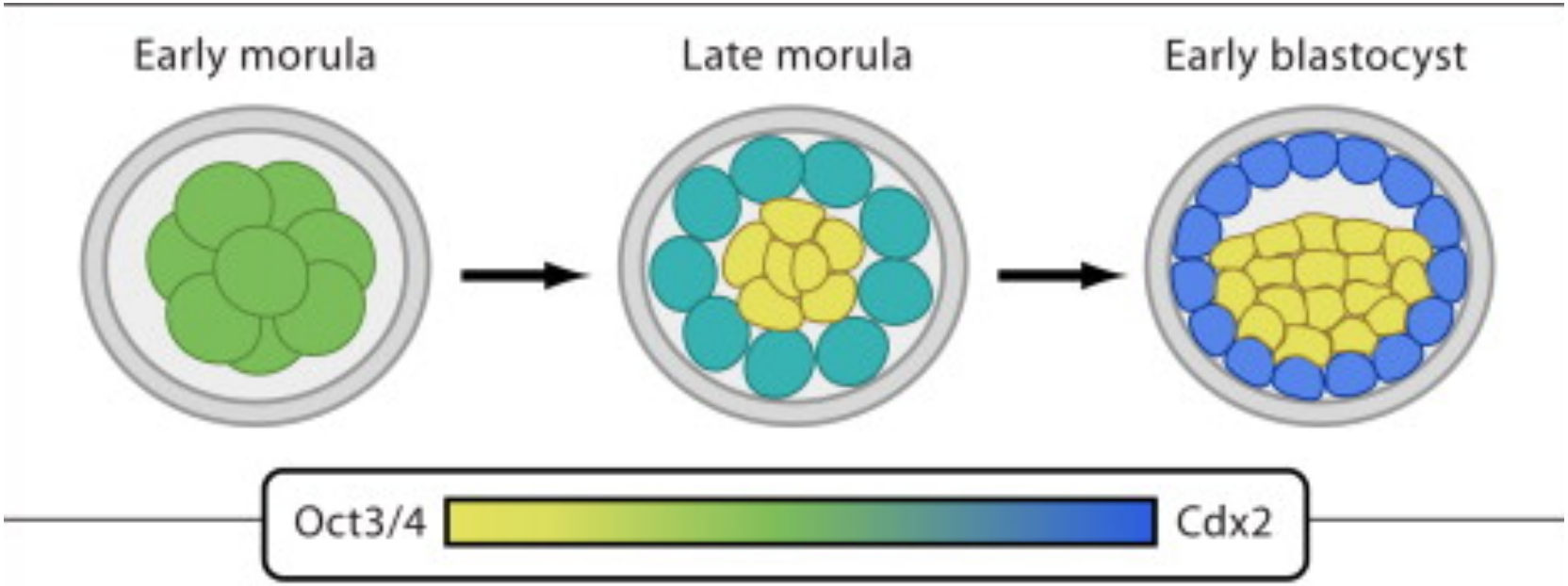


After **division II**, the blastomeres all express the same genes (i.e proteins which are transcription factors at this stage). → all cells are the same

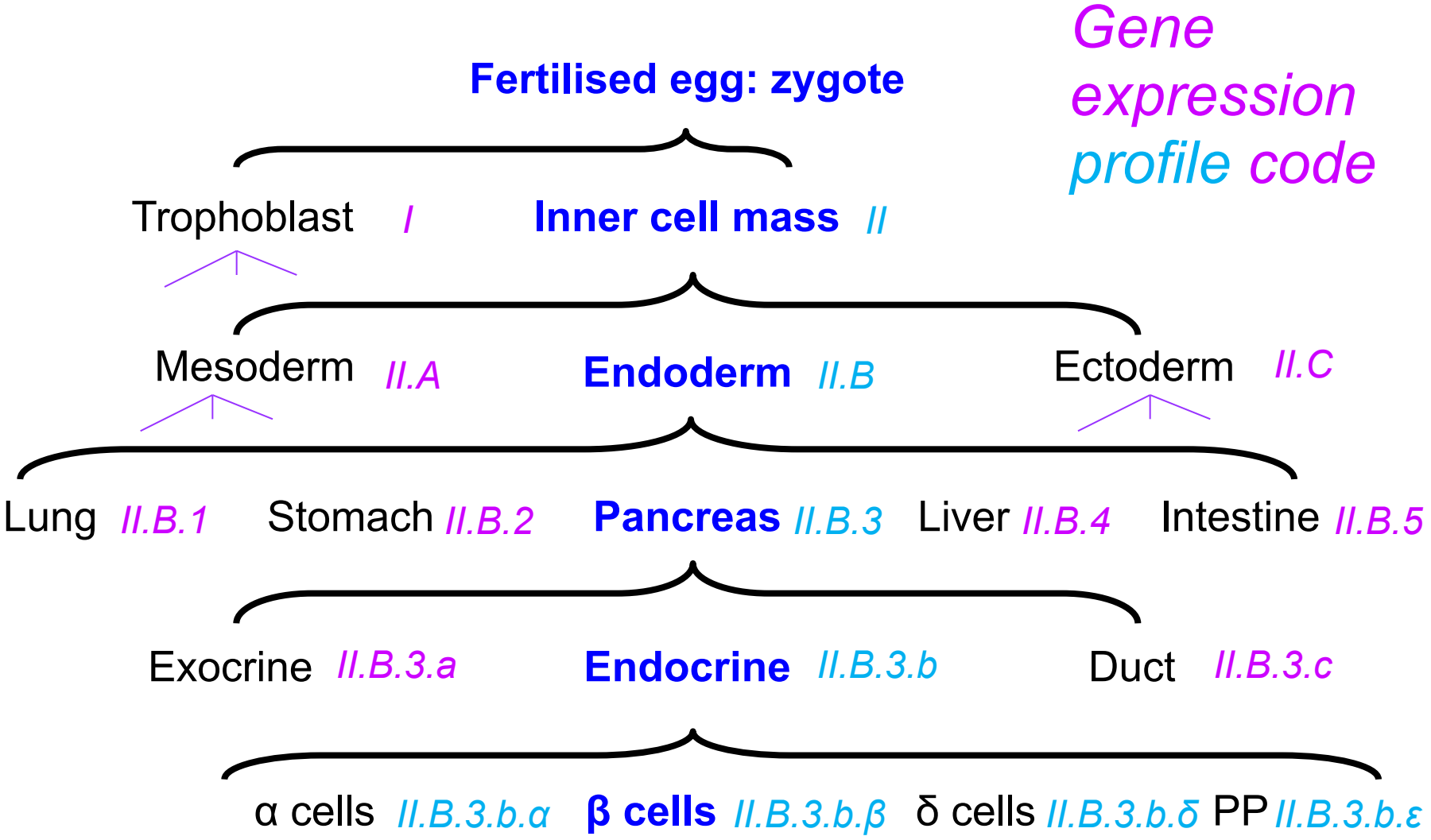


After division III, top and bottom blastomeres do not have the same maternal proteins in their cytoplasm → different gene expression profile → different proteins expressed (transcription factors and signalling factors) → more differences occur at each division.

In mammals: we have a two gene battle



Cell fate becomes progressively restricted: e.g. cell lineage of insulin producing cells



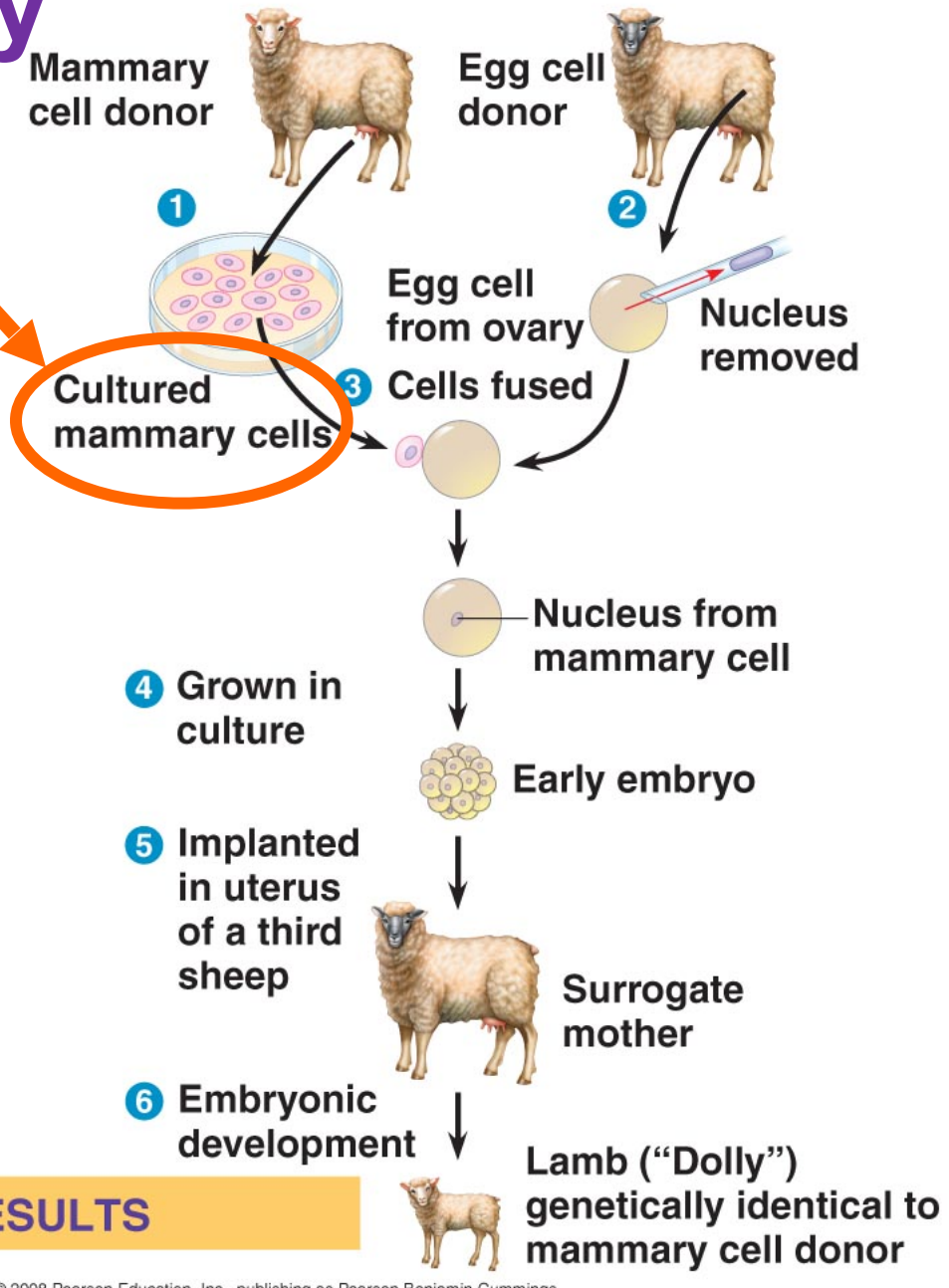
1997: Cloning Dolly

DNA reprogrammed

A differentiated cell can give rise to a new organism (totipotent)

1. Genes are lost as a cell specializes
2. Genes are not lost as a cell specializes.

Cells are genomically equivalent, but DNA needed to be reprogrammed to retrieve totipotency.



Summary

The embryo starts with a zygote (totipotent)

It becomes a blastocyst with trophoblast and ICM (pluripotent)

The ICM becomes ectoderm, mesoderm, endoderm (each multipotent).

Then cells from one or several germ layers collaborate and progressively differentiate to become organs and tissues.

Before the full differentiation, cells become locked in their fate – determined.

At the gene level, cells become different by expressing different developmental genes.

The initial difference stem from the maternal developmental proteins being unevenly distributed in the egg cytoplasm. As the blastomeres form through cleavage divisions, they end up not receiving the same developmental proteins.