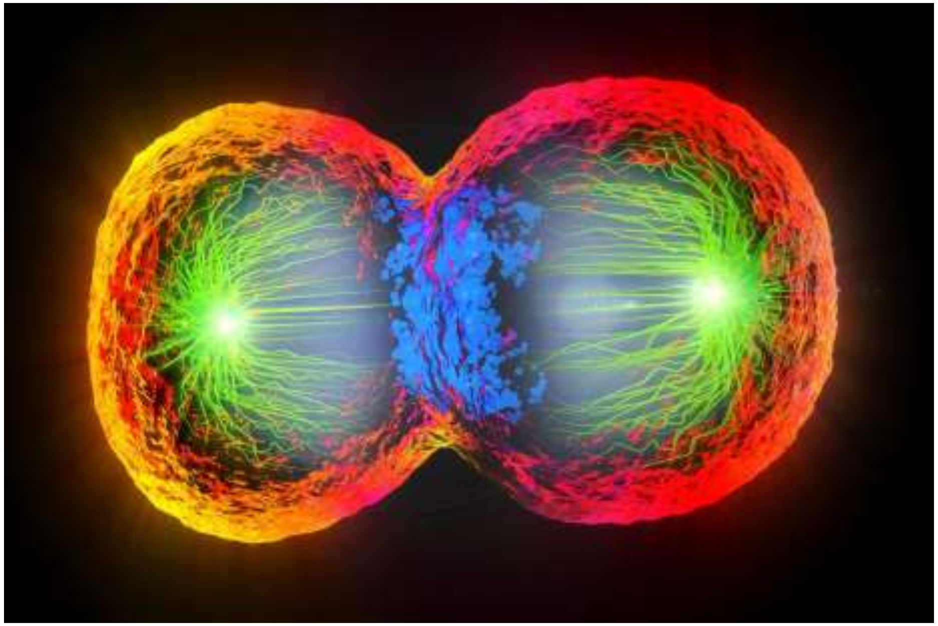
Lecture 8: Development, cancer and stem cells



Cells come together to form complex organisms: they divide, acquire specialized functions, etc.

Imagine the future (or actually the present)….

Blood Brothers for Life: A Family's Story

When Julie and Jonathan Henderson found out that their two-year old son Nicolas had T-cell lymphoma they were devastated. They had just found out that Julie was pregnant, and what was supposed to be an exciting time preparing for the new baby, turned into months of doctor visits, hospital stays and chemotherapy. After Nicolas' chemotherapy failed to work, the Henderson's doctor tried a relatively new transplant procedure using stem cells taken from the umbilical cord blood of their newborn baby, Nathaniel.

They worked with Cryo-Cell International, Inc., the world's first private cord blood bank and fastest growing Umbilical Cord Blood Stem Cell banking company, to process, test and store Nathaniel's umbilical cord blood. Today, Nicolas is a happy, energetic four-year-old who is in remission. He and his baby brother Nathaniel share a special bond.

HOW CAN UMBILICAL CORD CELLS BE USED TO CURE DISEASE?

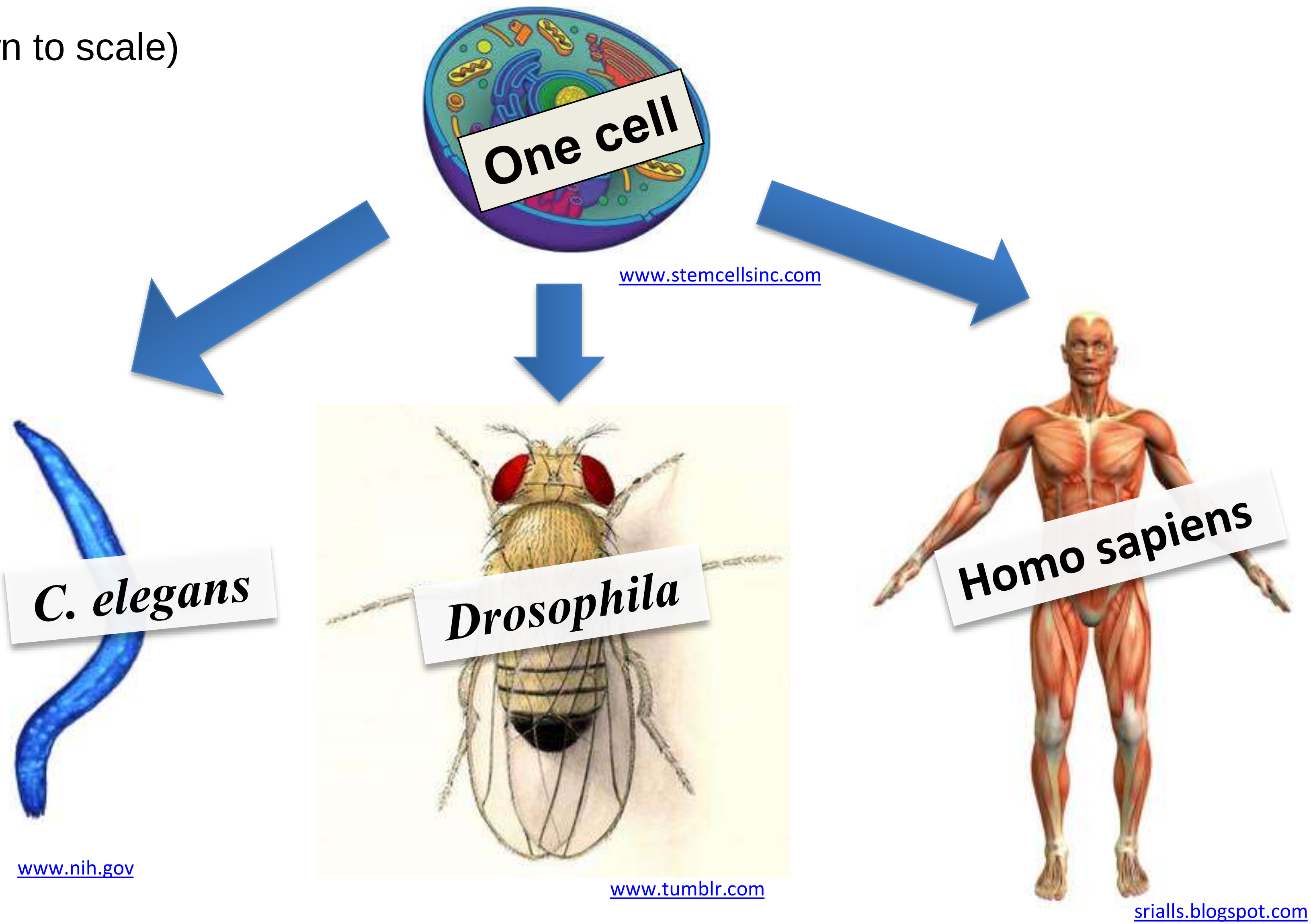
Development, stem cells and cancer

- Development: progressive changes in size, shape, and function during the life of an organism
- Stem cells: cells that can be made to form different types (have a property of being highly flexible)
- Cancer: cells that have bypassed the regular controls on cell division

- Different topics, but are connected…

Development of Multi-cellular Organisms

(not drawn to scale)



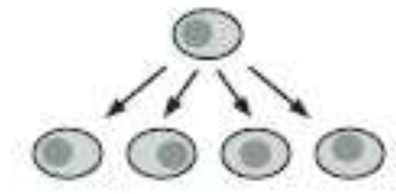
Development of Multi-cellular Organisms

- Four essential processes for multi-cellularity

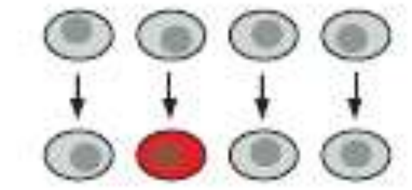
1) Proliferation (this lecture)
2) Specialization (regulation of gene expression lecture)
3) Interaction (communication lecture)
4) Movement (Ranjith's lecture)

- All processes are coordinated

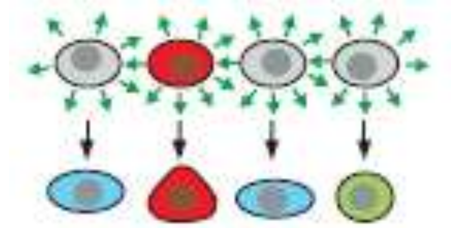
Proliferation



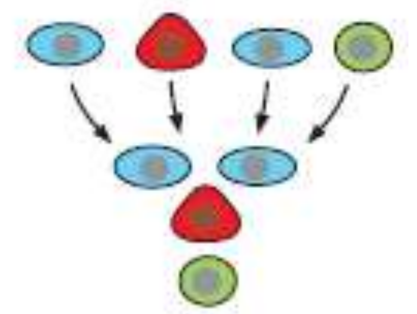
Specialization



Interaction



Movement

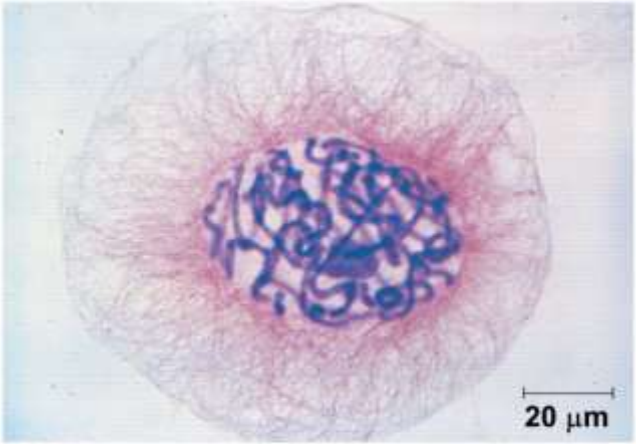


Development includes cell division

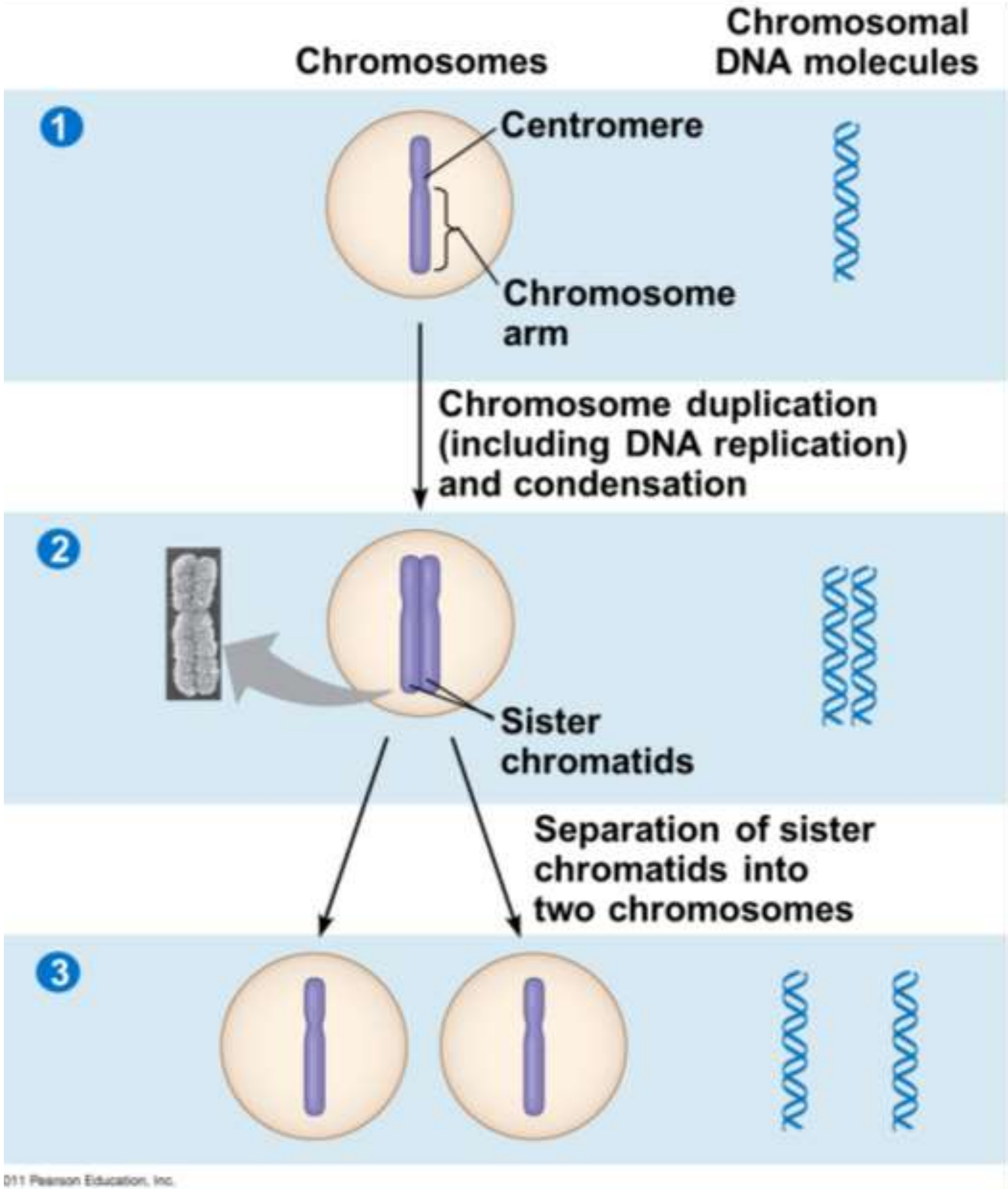
A genome can consist of a single DNA molecule (common in prokaryotic cells) or a number of DNA molecules (common in eukaryotic cells)

Somatic cells (non-reproductive cells) have two sets of chromosomes
Gametes (reproductive cells: sperm and eggs) have half as many chromosomes as somatic cells

Cell division ensures that the genetic material and the cell contents are equally divided among the daughter cells



Distribution of Chromosomes During Eukaryotic Cell Division

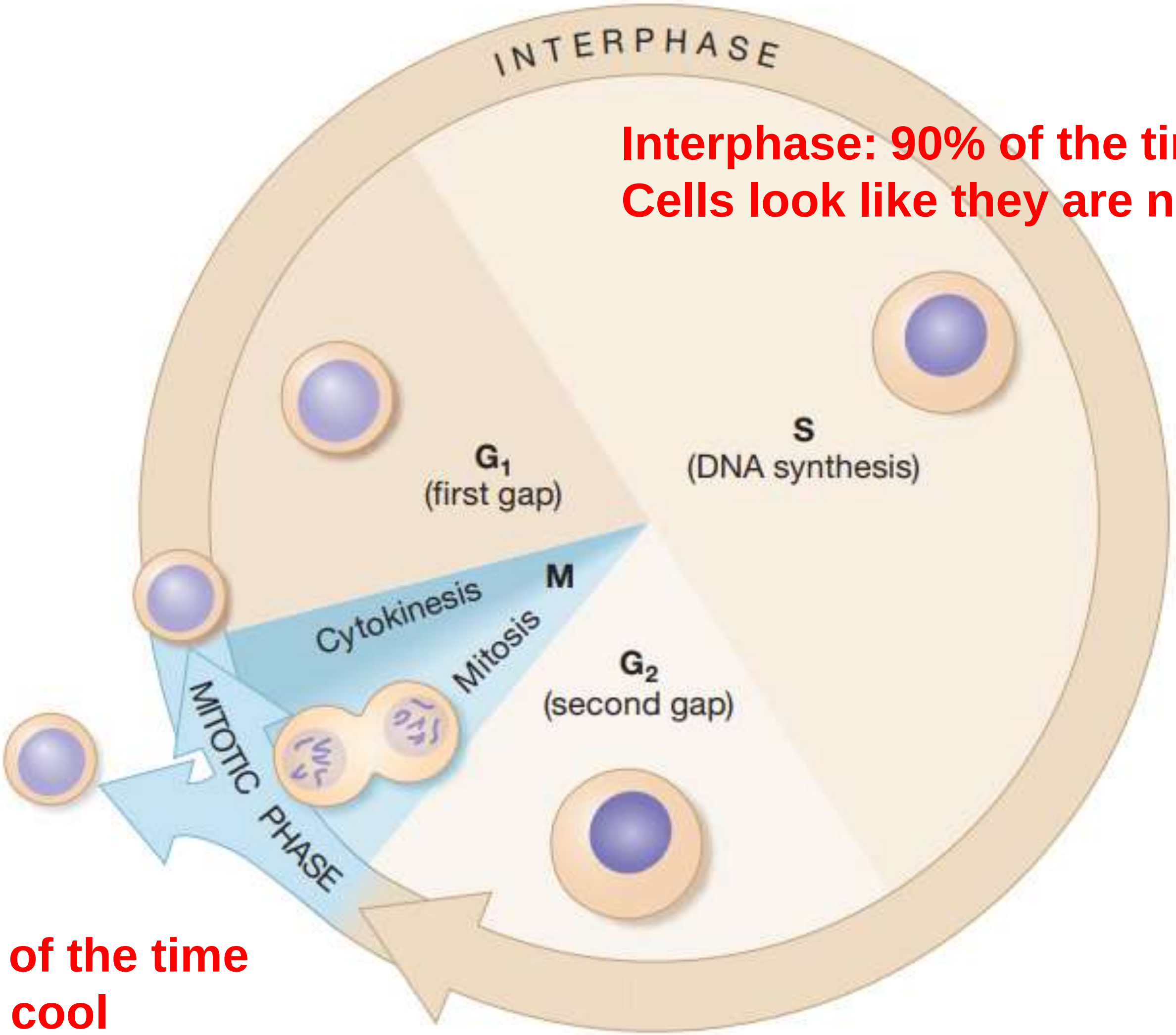


Cell division is accomplished during the Cell Cycle

Mitosis	Meiosis
•Division of somatic cells •Two daughter cells are produced with same amount of DNA as mother cell	•Division of gamete cells (sperm and ovum) •Four daughter cells are produced with half the amount DNA •We will not be discussing meiosis today

Mitotic cell cycle

Interphase: 90% of the time
Cells look like they are not doing much



Mitosis: 10% of the time
Visually very cool

▲ **Figure 8.4** The eukaryotic cell cycle. The relative size of each slice approximates the amount of time a typical human cell spends in that phase.

Mitotic cell cycle

Interphase

Constitutes 90% of cell cycle and can be divided into three sub phases:

1. G1 phase (first gap)
2. S phase (DNA synthesis phase)
3. G2 phase (second gap)

Mitotic phase

Constitutes only 10% cell cycle and can be divided into six sub phases:

1. Prophase
2. Prometaphase
3. Metaphase
4. Anaphase
5. Telophase
6. Cytokinesis

Lots of names! Don’t worry.

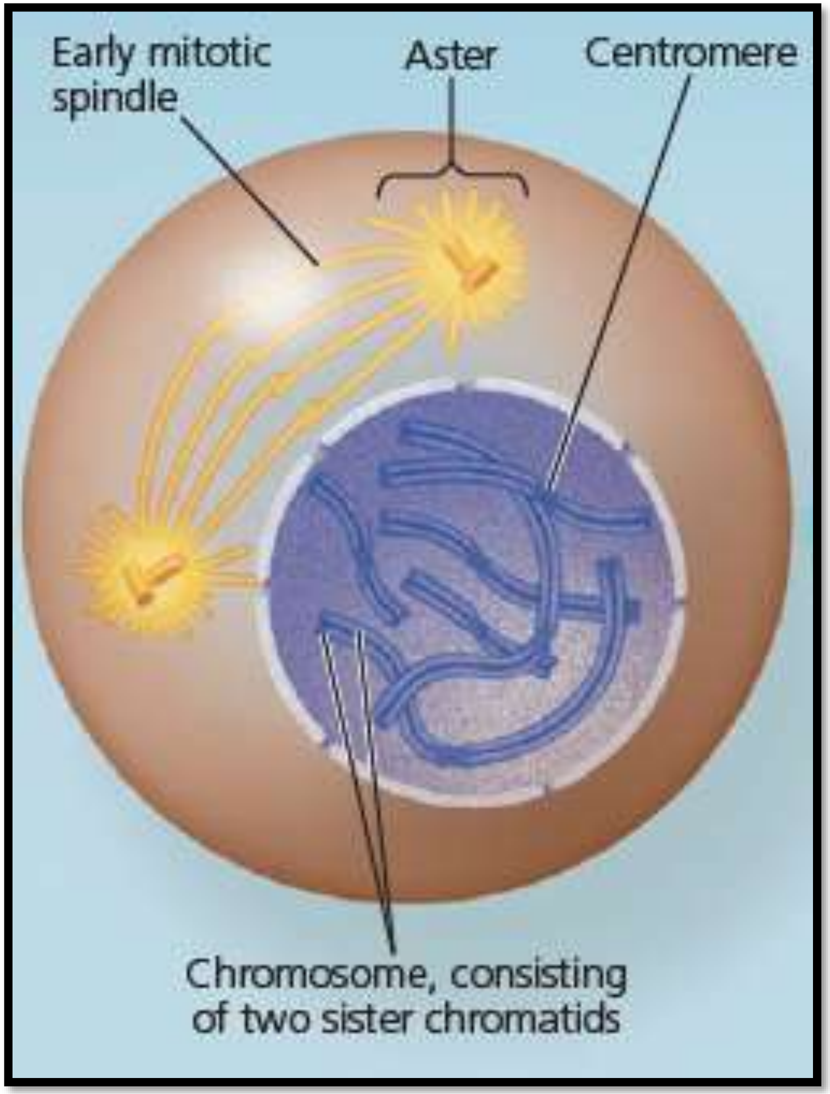
Mitosis

Prophase

•Chromatin (DNA) condenses into discrete chromosomes

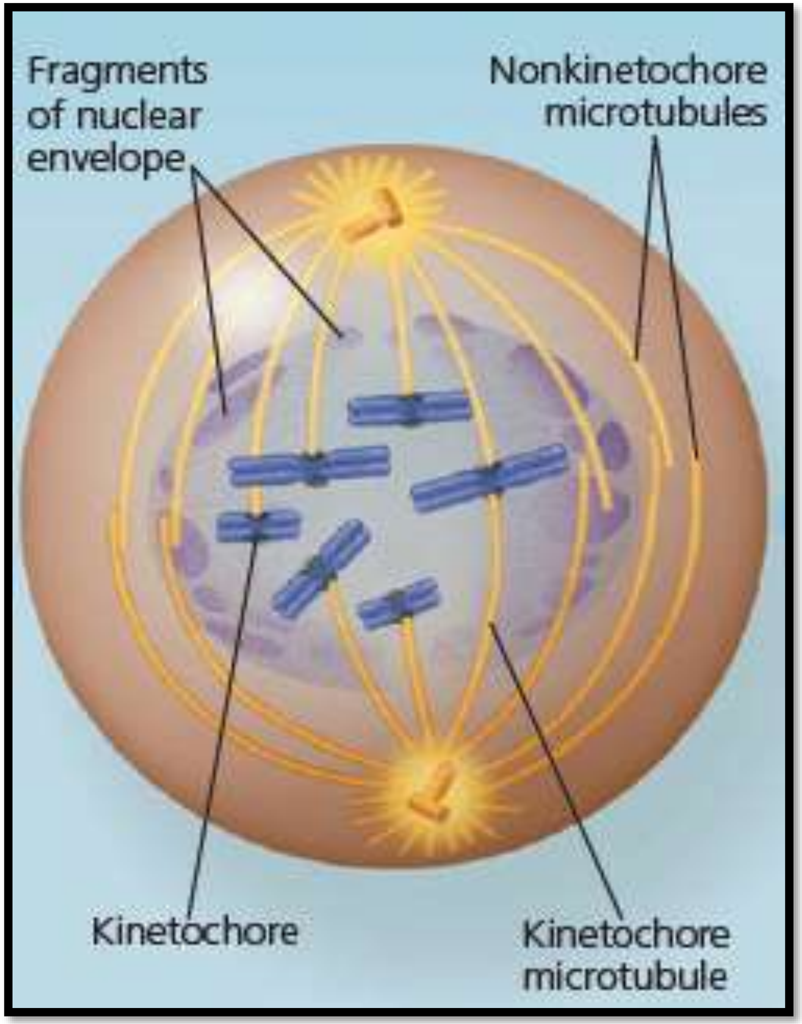
•Specialized structures called centrosomes (asters) move apart

•Mitotic spindle begins to form from microtubules



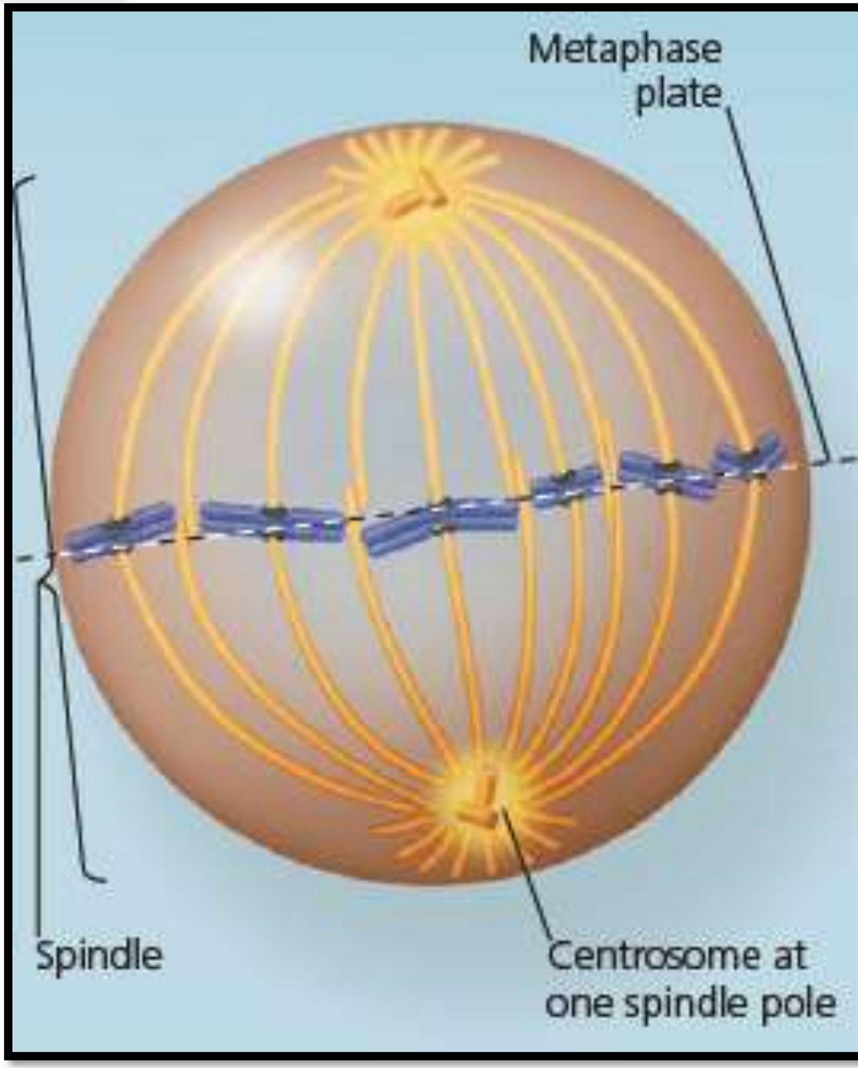
Prometaphase

- Nuclear membrane fragments
- Microtubules grow
- Each of the two chromatids have kinetochore proteins at centromere
- Some microtubules attach to kinetochores called “kinetochore microtubules”



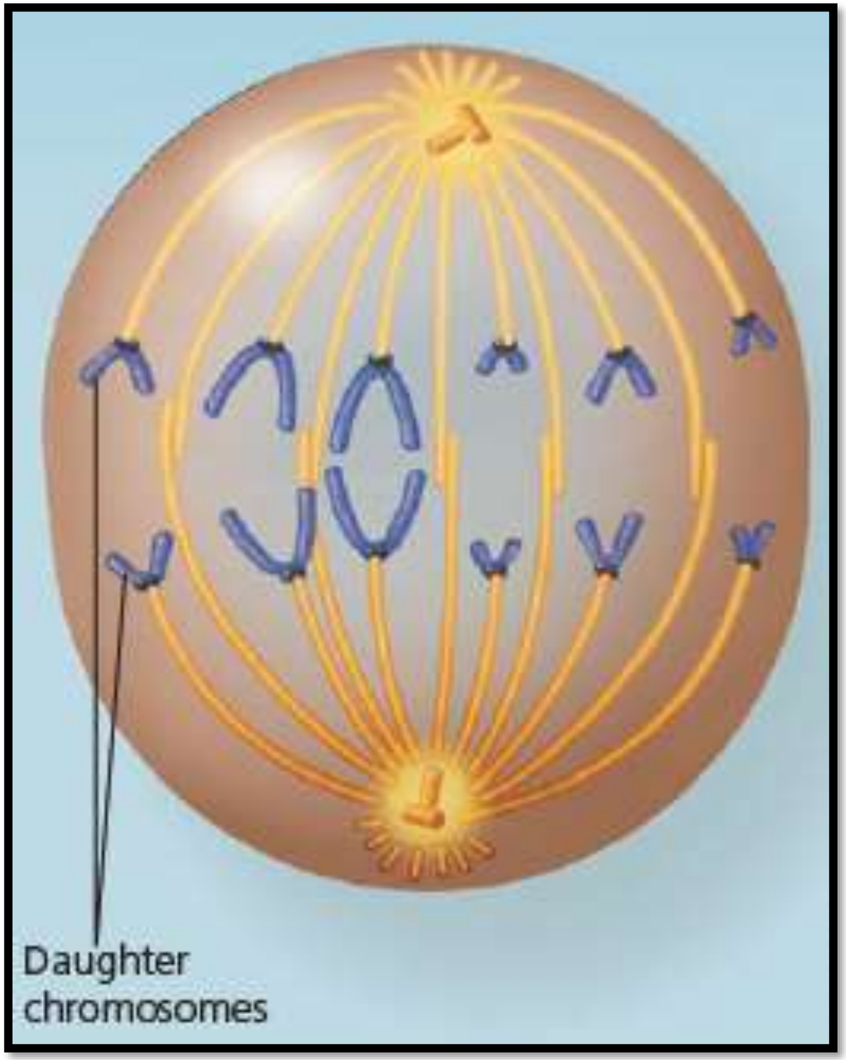
Metaphase

- All the chromosomes assemble at metaphase plate
- For each chromosome, sister chromatids are attached to kinetochore microtubules arising from opposite poles



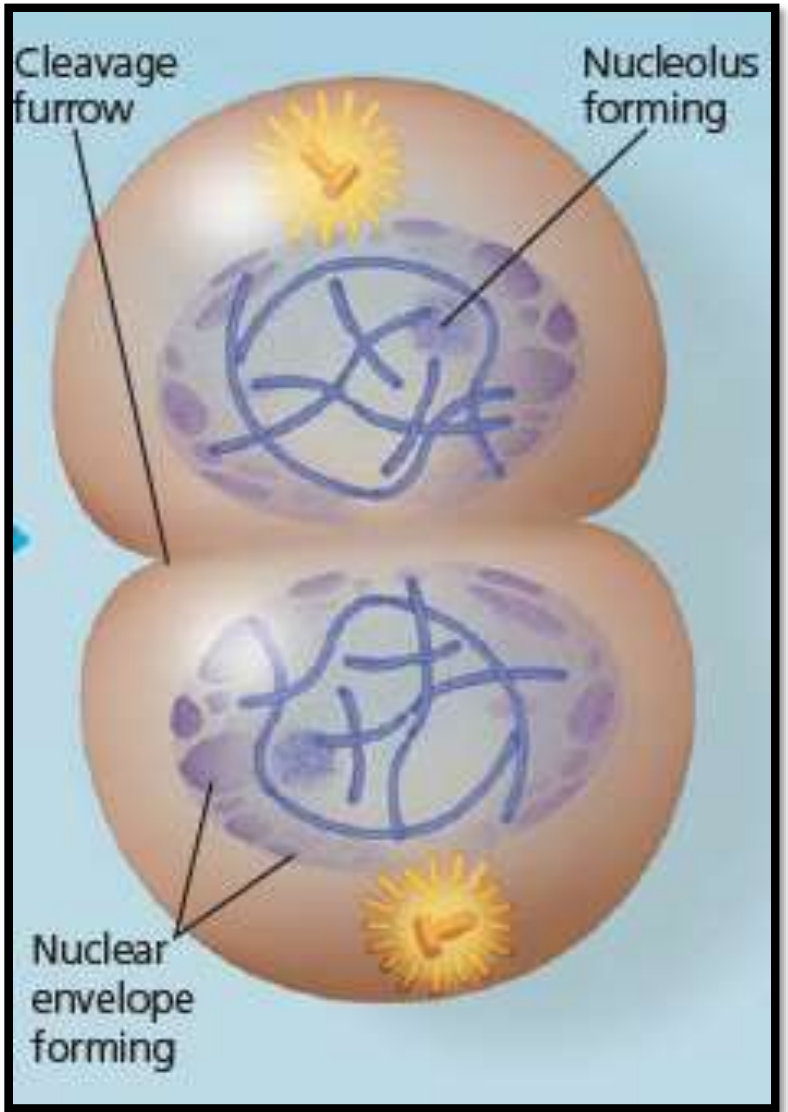
Anaphase

- Sister chromatids separate
- Each chromatid now behaves as a chromosome
- Daughter chromosomes move towards opposite poles due to shortening of kinetochore microtubules



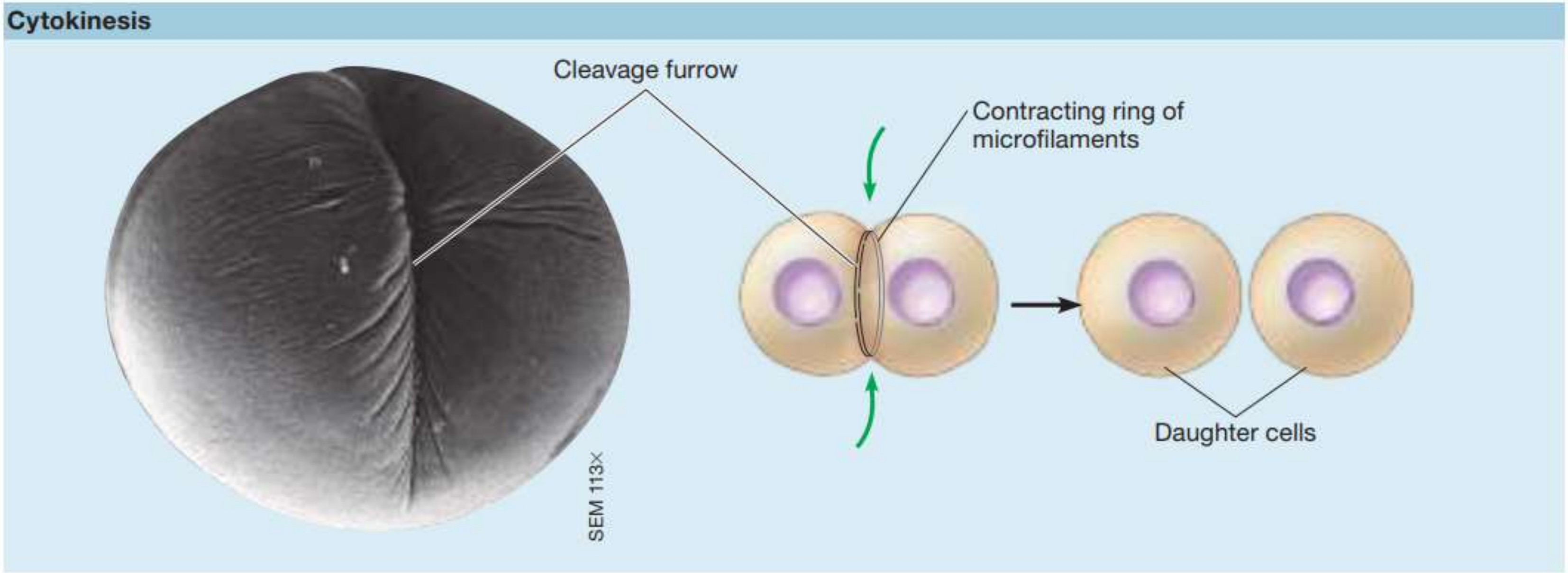
Telophase

- Two daughter nuclei form in the cell
- Nuclear envelope reappears
- Spindle microtubules depolymerize
- Chromosomes become less condensed



Cytokinesis

- Formation of cell furrow
- Division of cytoplasm to give rise to two daughter cells



▲ **Figure 8.6A** Cleavage of an animal cell https://www.youtube.com/watch?v=N97cgUqV0Cg

Control of the cell cycle

- The cell cycle is divided into two phases: Interphase and Mitosis
- Mitosis looks very exciting under the microscope, but Interphase is very important for control

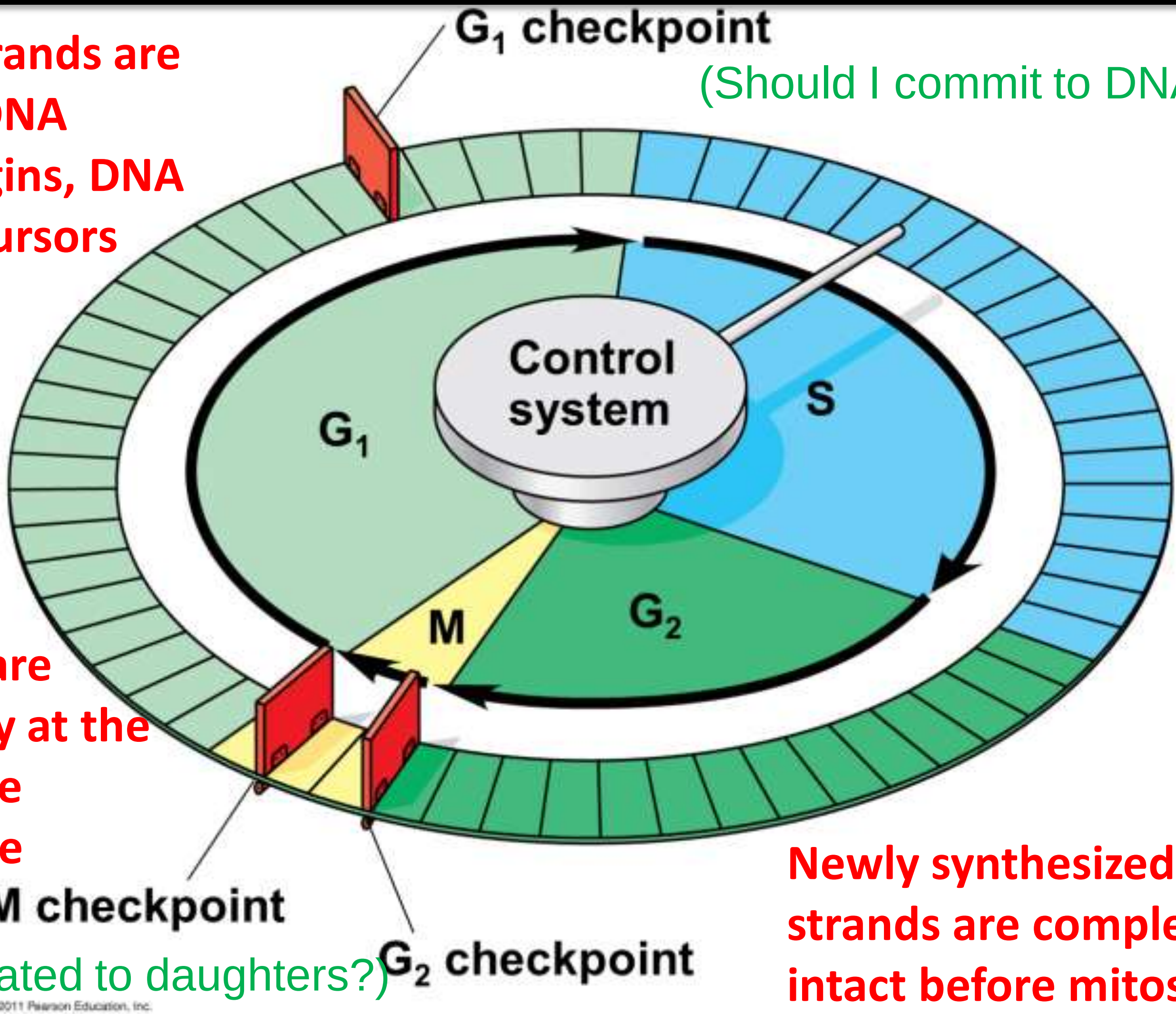
- Interphase consists of two “Gap” phases where the cell checks whether key steps have been accomplished before moving on
  - Should I commit to DNA synthesis? = G1
  - Let me double my DNA for my daughter cells = S
  - Is my DNA completely replicated? = G2
  - I decided to divide and doubled my DNA. Have I ensured that the DNA will be allocated equally to both my daughters? = M phase

Matthews, H. K., et al. (2022). "Cell cycle control in cancer." Nat Rev Mol Cell Biol 23(1): 74-88.

Checkpoints

Parent DNA strands are intact before DNA replication begins, DNA synthesis precursors available

(Should I commit to DNA synthesis?)



Chromosomes are aligned properly at the metaphase plate before anaphase

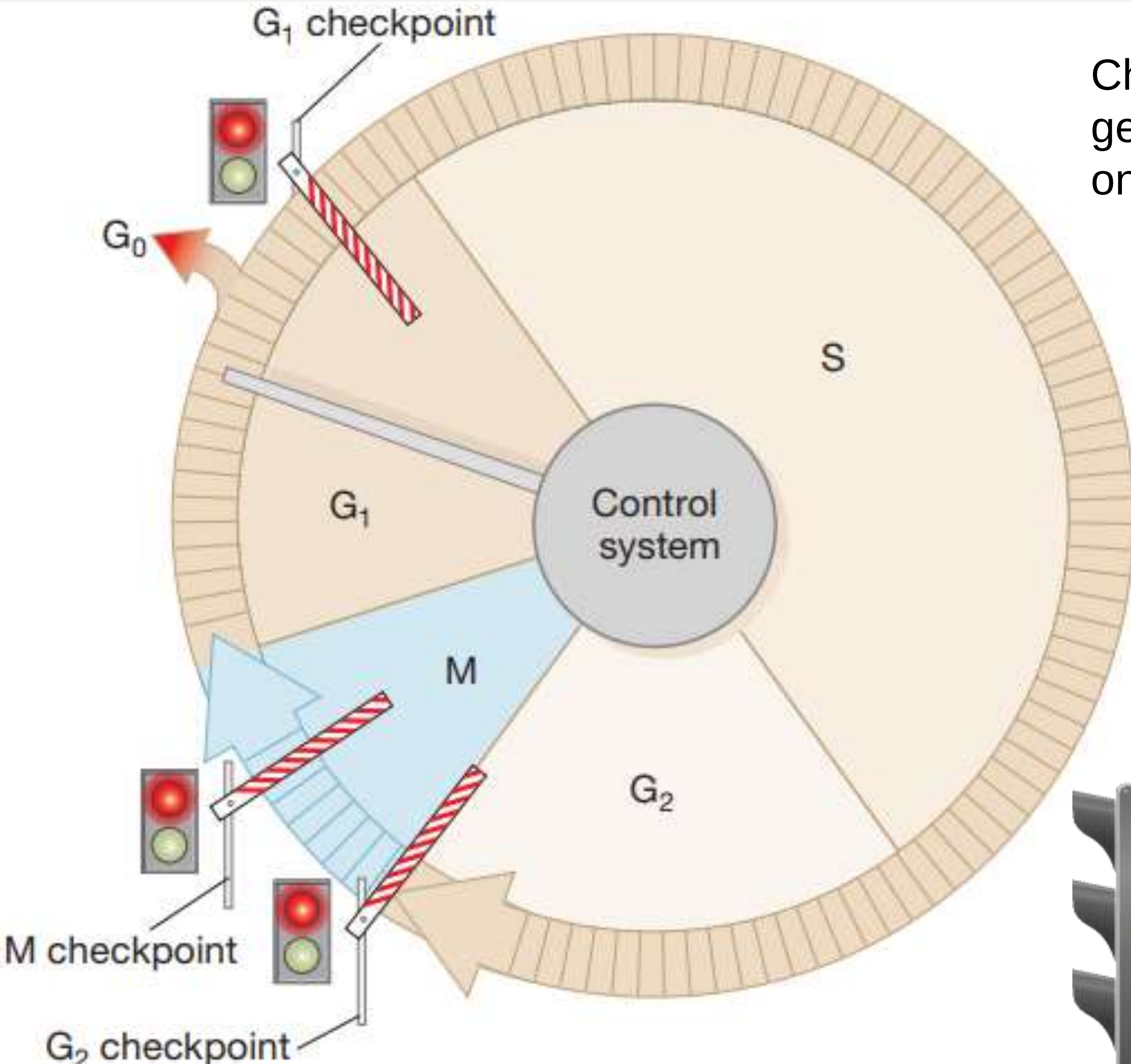
(Is my DNA allocated to daughters?)

Newly synthesized DNA strands are complete and intact before mitosis

(Is my DNA completely replicated?)

Checkpoints are essential for the correct distribution of complete chromosome sets between daughter cells

Checkpoints are a control system for the cell cycle



▲ **Figure 8.8A** A schematic model for the cell cycle control system

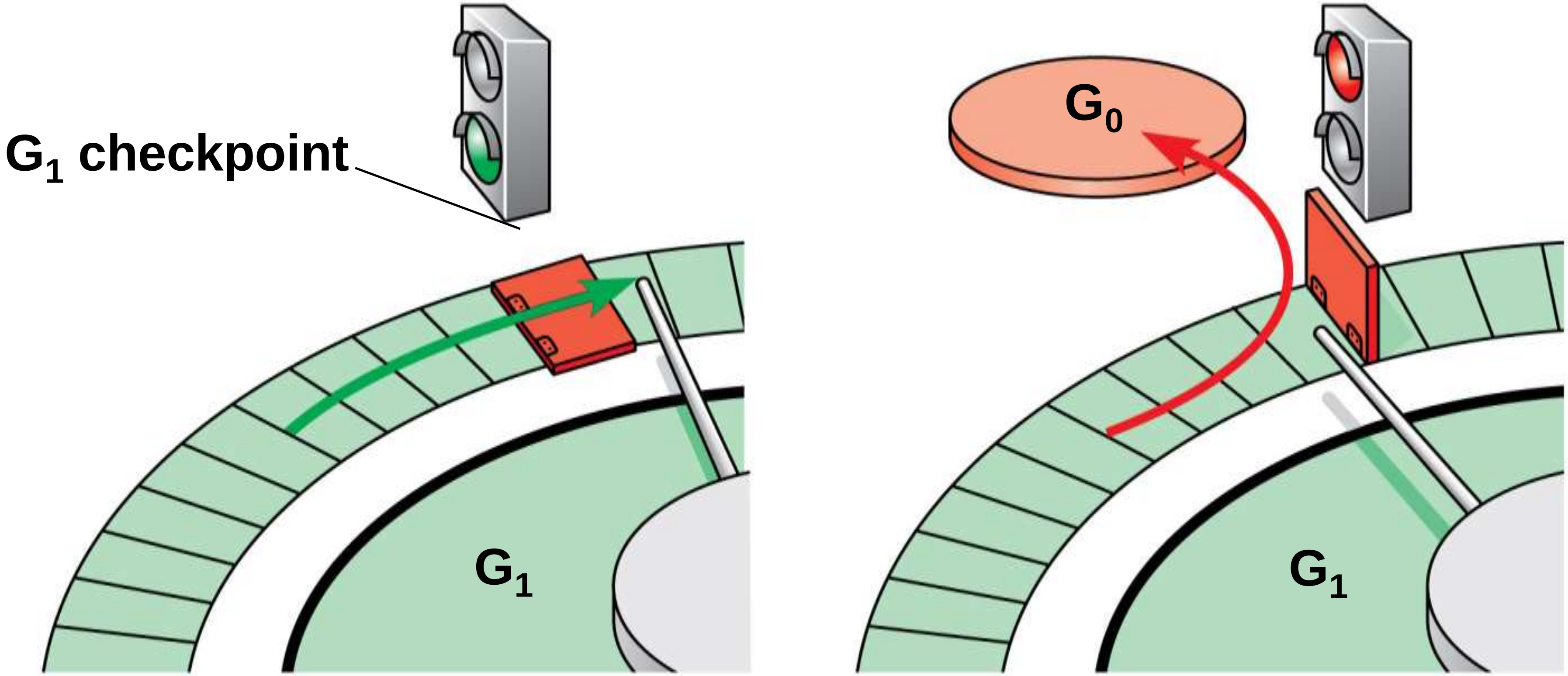
Checkpoints ensure that the genome is faithfully passed on to the daughter cells

Assess the situation at the checkpoint

Fix the problem

If problem fixed, proceed
If problem not fixed, die!

For many cells the G1 checkpoint is an important checkpoint

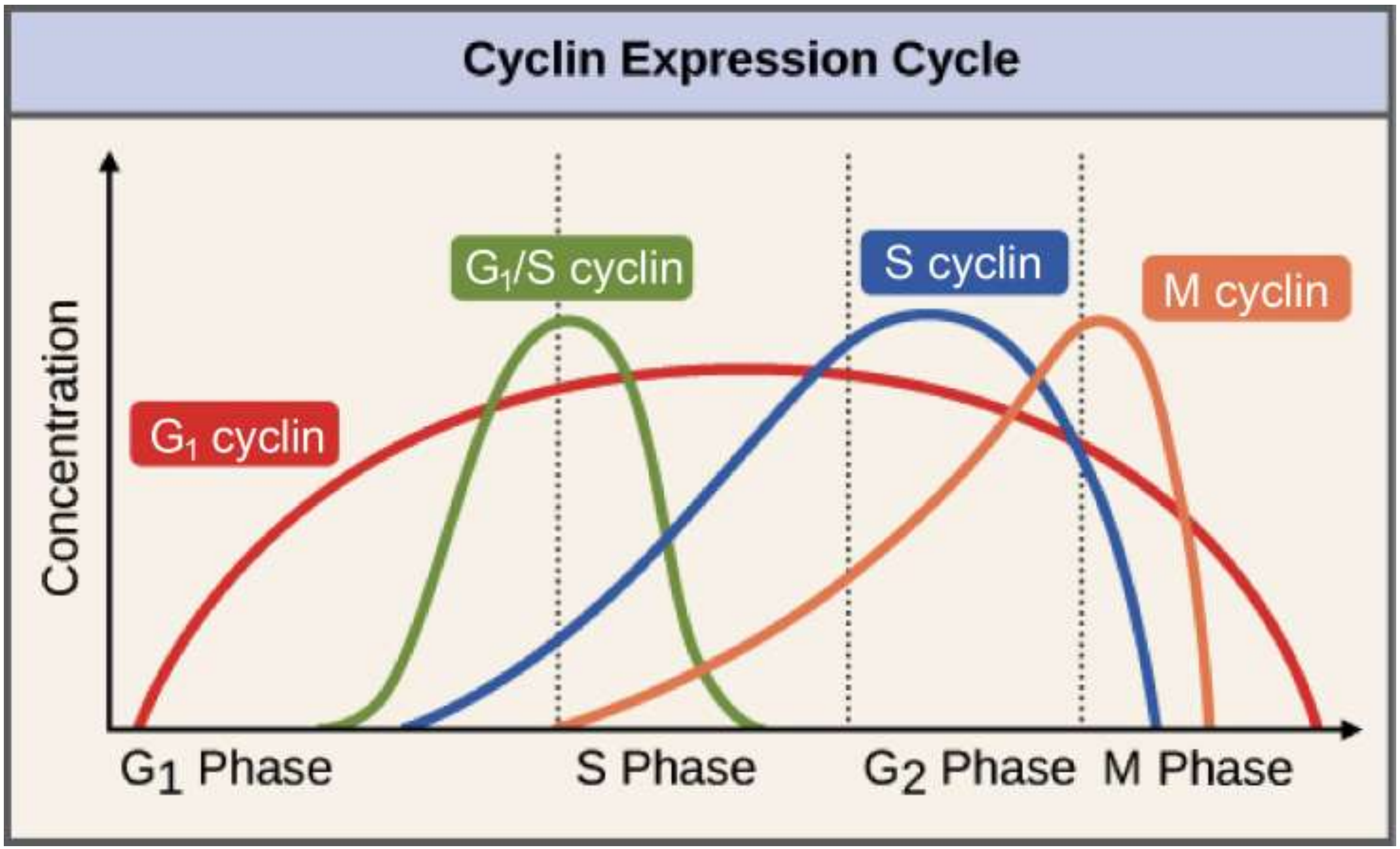


(a) Cell receives a go-ahead signal.

(b) Cell does not receive a go-ahead signal.

Cells that enter the G0 stage, stop dividing and become specialized cells (e.g. neurons), they can also undergo programmed cell death

Proteins called cyclins and cyclin-dependent kinases act at the checkpoints



https://educationalgames.nobelprize.org/educational/medicine/2001/cellcycle.html

External signals

- Nutrients

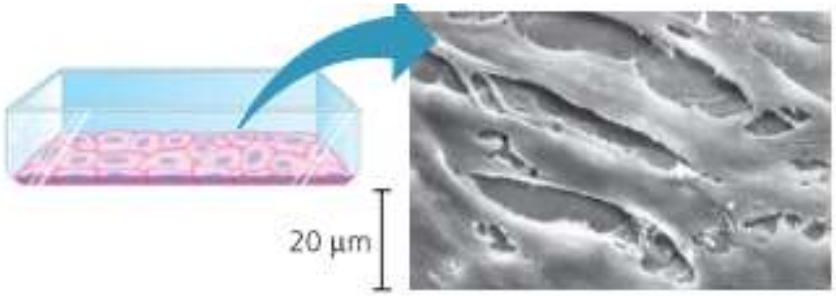
- Growth factors

- Space (crowded cells stop dividing) also known as **density dependent inhibition**

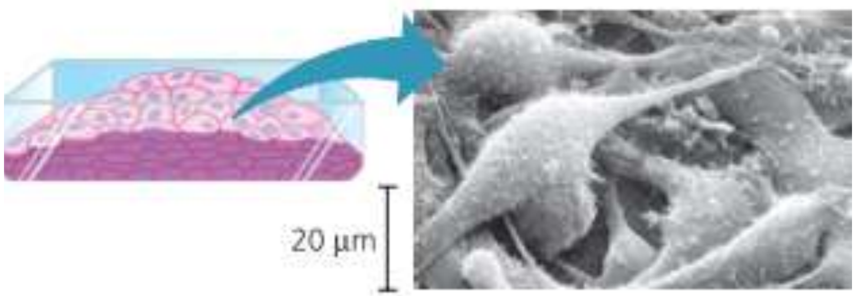
- Substratum for anchorage (**anchorage dependence**)

Cancer cells lose dependence on internal and external signals for proliferation

- Cancer cells do not stop at cell cycle checkpoints
- Continue to divide even after the presence of errors in the DNA
- Do not exhibit density dependent inhibition (form multiple layers of cells)
- Do not require anchorage with the substratum



Normal mammalian cells



Cancer cells

Some anti-cancer drugs and their targets

- Taxol, vinblastine: microtubules
- Methotrexate: block the synthesis of DNA precursors
- Cisplatin: forms chemical bonds with DNA
- Radiation therapy: cancers have lowered ability to repair damaged DNA as they have errors in their genomes that allow bypass of checkpoints

Cell division is one concept of the process called development; another concept is differentiation

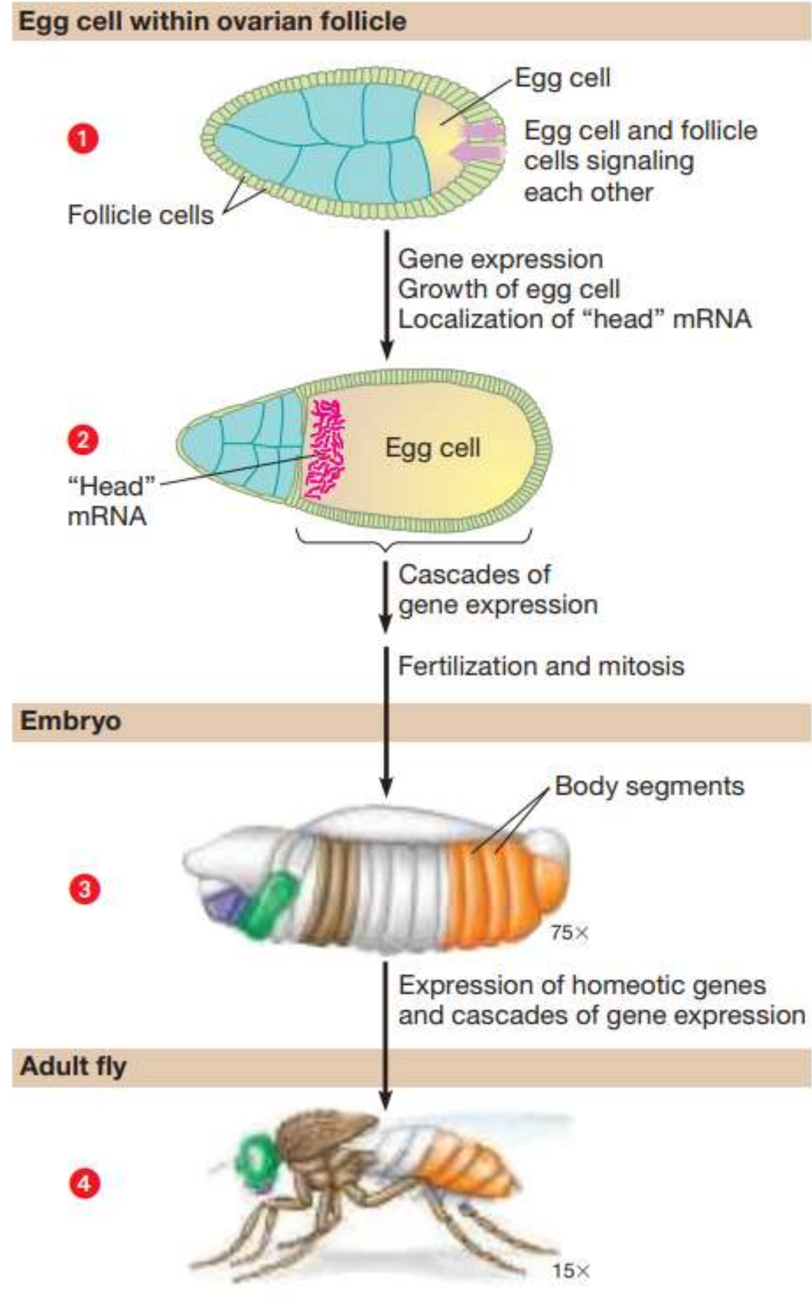
Development involves cells going from “undifferentiated” to” differentiated”.

Undifferentiated: no obvious phenotype, have the potential to become something else

Differentiated: have a distinct form and function (hair, nails, liver, muscle, etc)

During embryonic development, cells are given cues that depend on their position in the embryo.

These cues give rise to changes in gene expression (regulation of transcription) that result in specific genes being expressed.



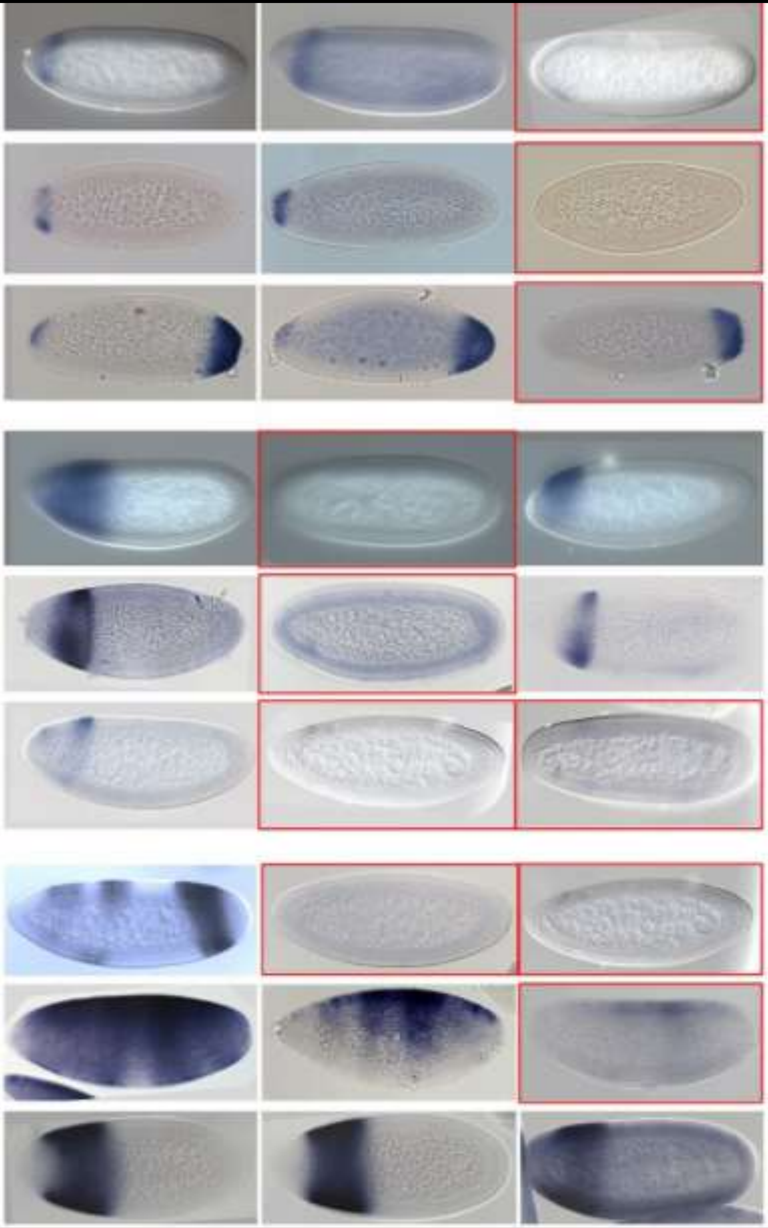
▲ Figure 11.8B Key steps in the early development of head-tail axis in a fruit fly

The early embryo looks like a blob, but it's not!

Expression of different genes at different positions (there are different signaling molecules at different positions) …

PNAS, 114 (31) 8295-8300

Cells move to reach their positions in the embryo (gastrulation)
https://youtu.be/j87y7EAj8qE



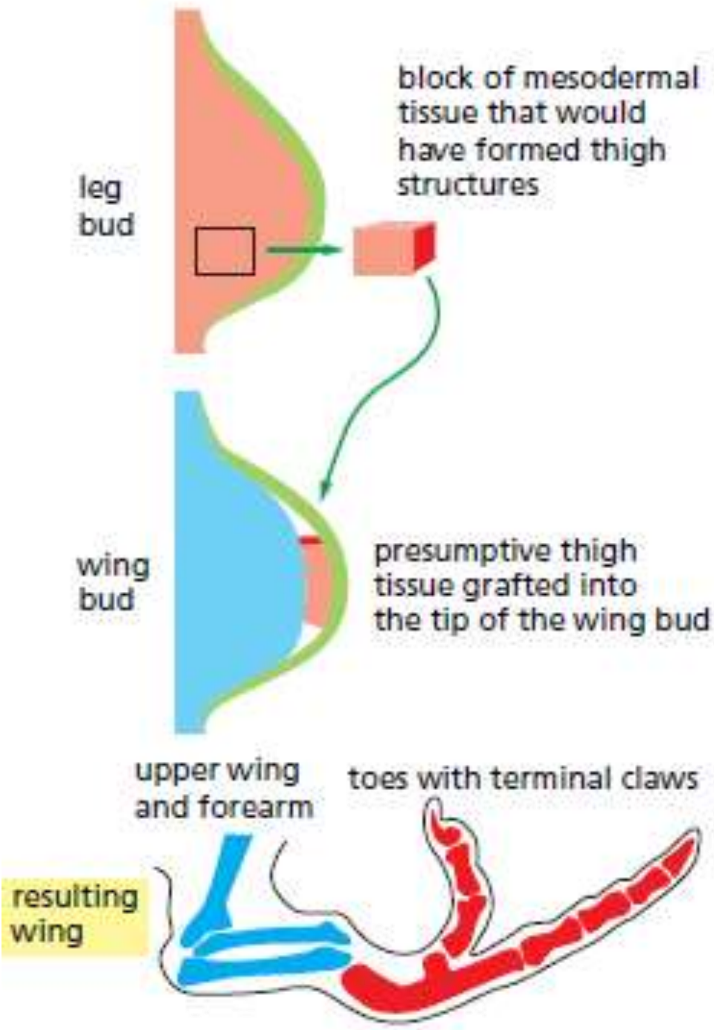
The position of a cell affects its differentiation

- Developmental decisions are made long before a visible change

- Cell's state of determination can be tested by transplanting it to altered environments

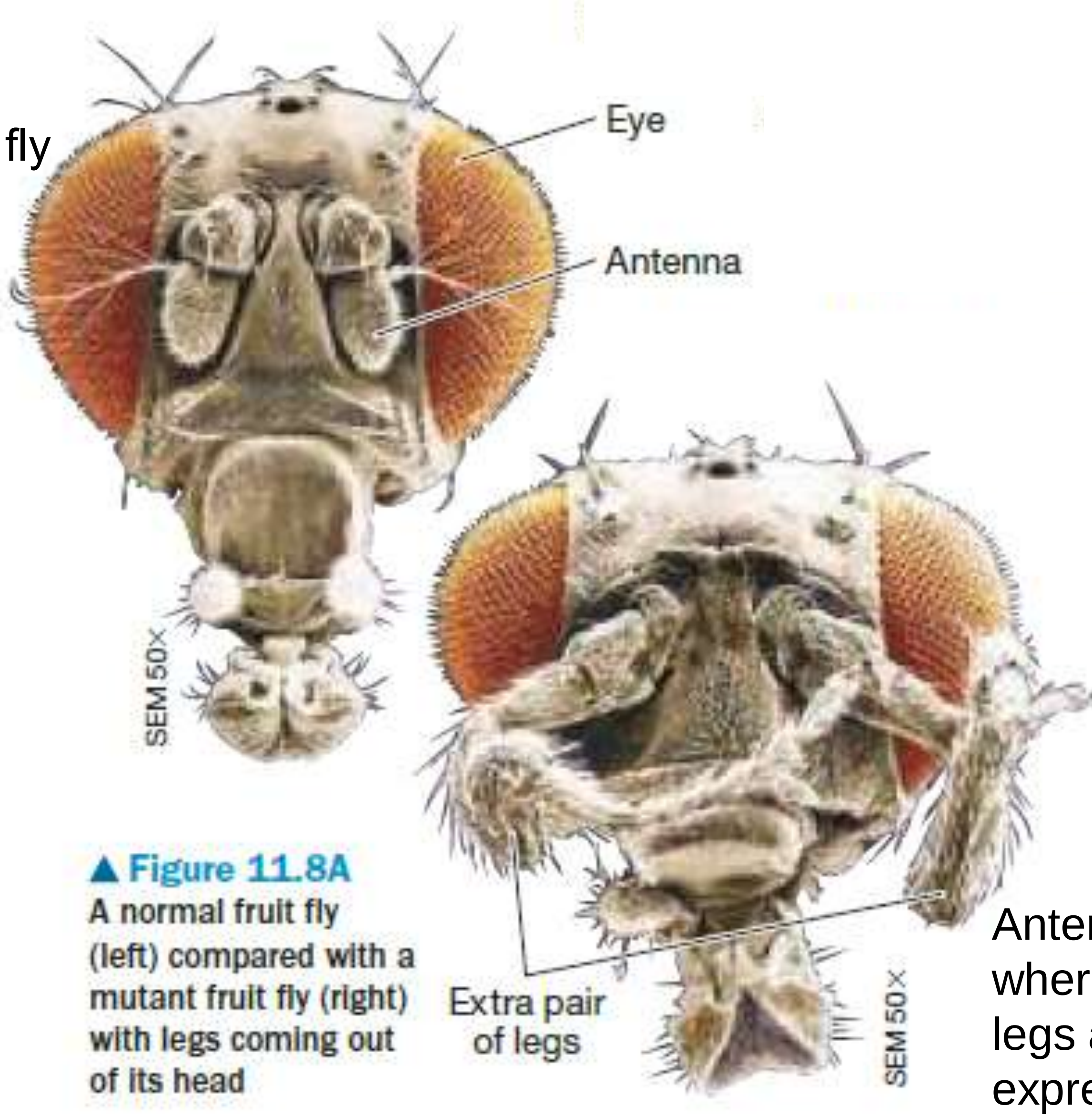
- Between extremes of the fully determined and the completely undetermined cell, there is a whole spectrum of possibilities

- **POSITIONAL VALUES**



Frankenstein flies: proteins for "legs" expressed in the head

"Normal" fly



▲ Figure 11.8A
A normal fruit fly (left) compared with a mutant fruit fly (right) with legs coming out of its head

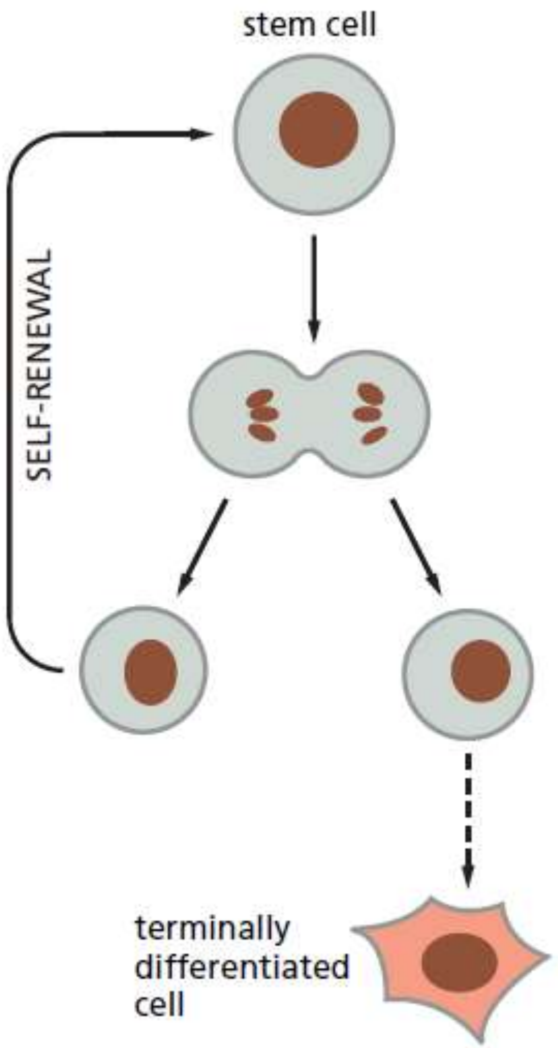
Antennapedia mutant where the proteins for legs are wrongly expressed in the head

Stem Cells: cells that have not yet achieved their final fate/identity

Properties:

- Able to divide
- Capable of differentiation*
- Not terminally differentiated
- Daughter cells can remain in undifferentiated state or differentiate

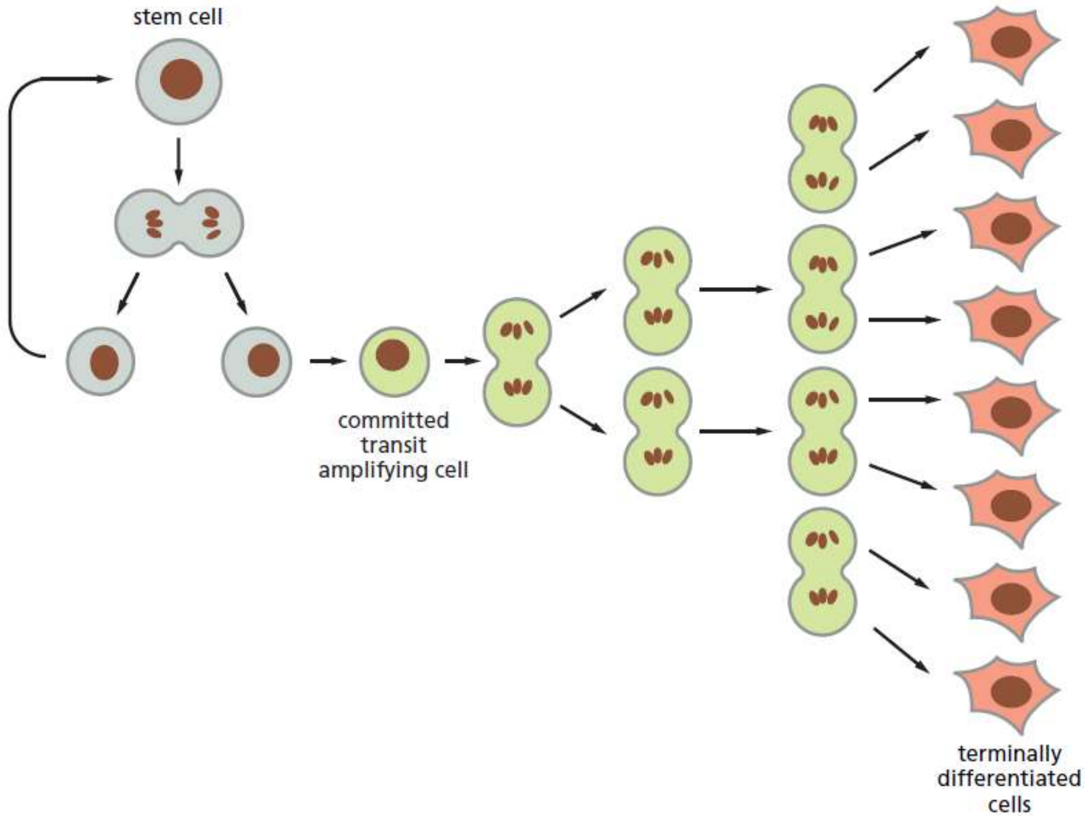
Examples: Epidermal stem cells, hematopoietic stem cells (found in adults) and many embryonic cells (found in the developing embryo)



*Differentiation: expressing genes that give form and function

Transit Amplifying Cells

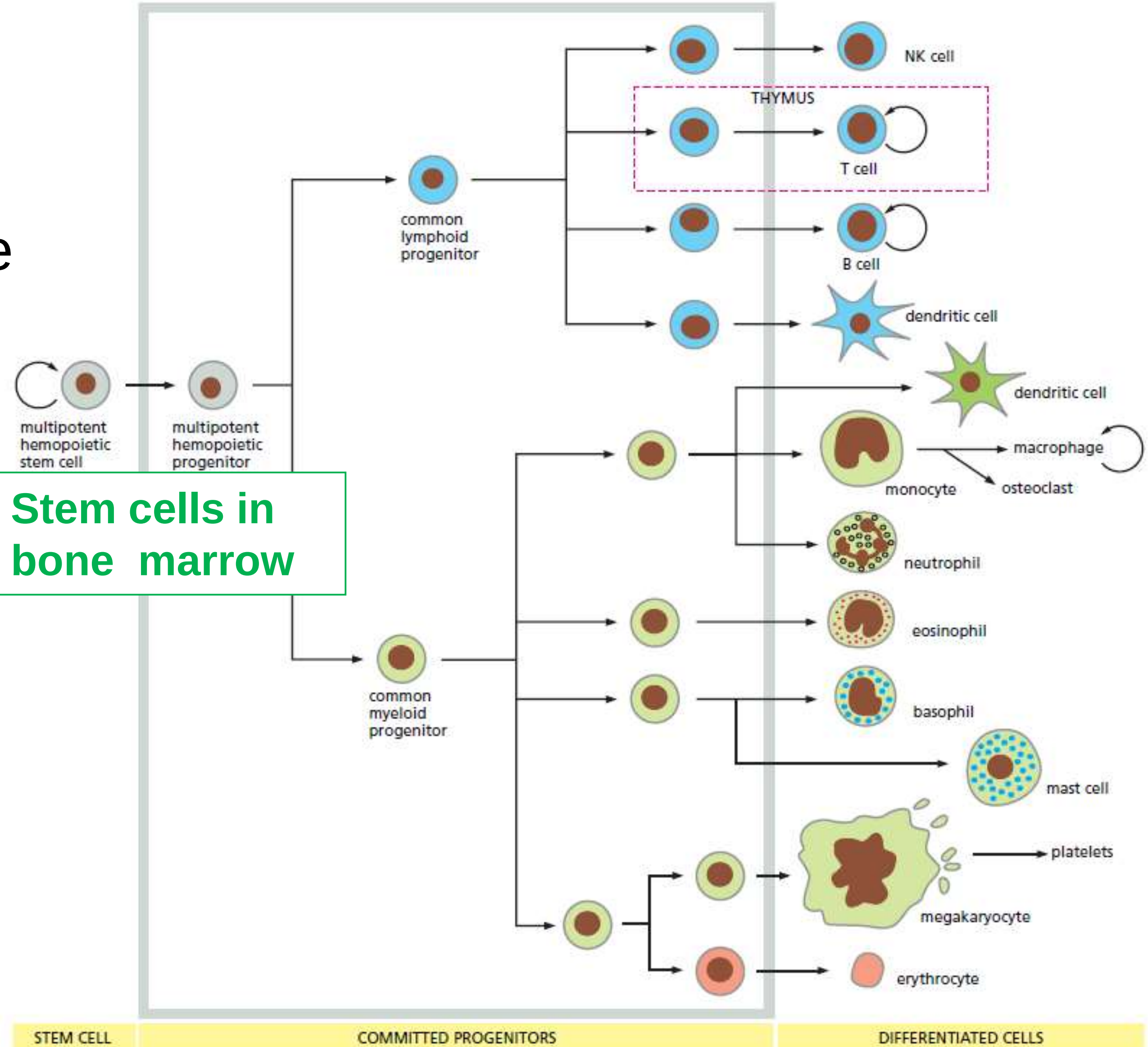
- Daughter cells that divide rapidly before differentiation
- Growth control strategy
- Short range signals for growth and feedback signals for growth halt



An example of Transit Amplifying cells: Hematopoiesis

- Stem cells are multipotent, can give rise to the complete range of blood cell types

- Commitment is a stepwise process followed by terminal differentiation

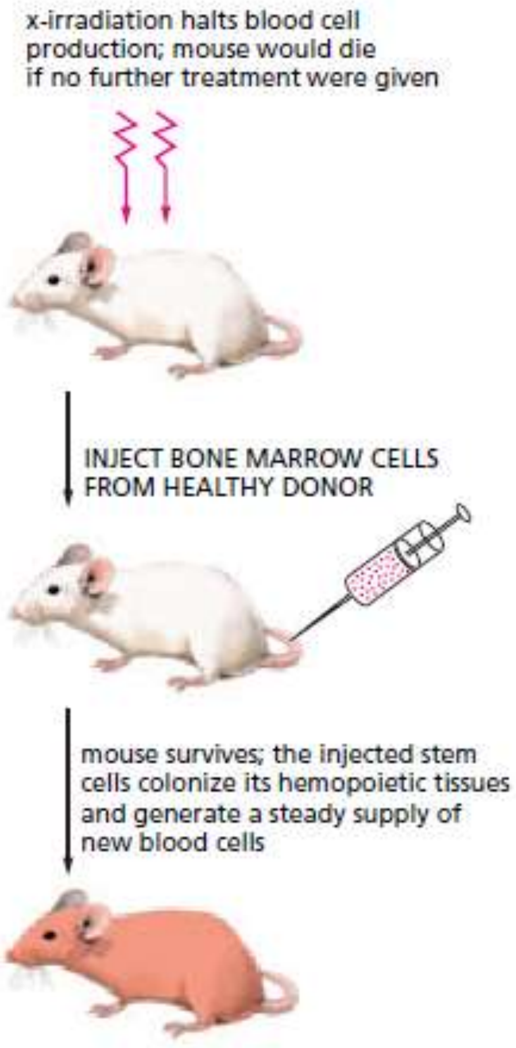


Experiments showed that stem cells can be transplanted

• X-ray irradiated mouse can be saved by transfusion of cells taken from the bone marrow of a healthy, immunologically compatible donor

• Stem cell population in bone marrow is low (~ 1 in 10000)

• Hematopoietic stem cells can be isolated from bone marrow using Fluorescence Activated Cell Sorter (FACS)



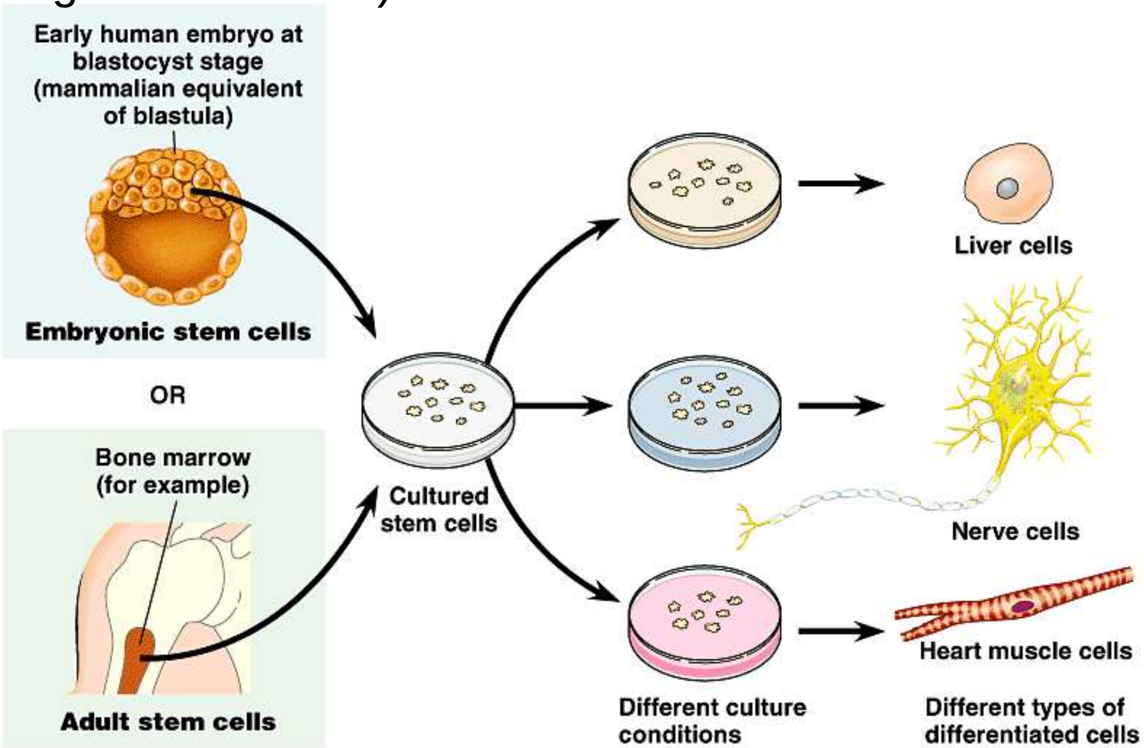
Embryonic Stem Cells

- **Why?** Stem Cells in the adult body are tissue-specific

Each type of specialized cell has a memory of its developmental history and seems fixed in its specialized fate.

- ES cells can make any part of the body!

(have a large range of final fates)



(have a smaller range of final fates)

Embryonic Stem Cells

• ES cells can be derived from early human embryos and from human fetal germ cells

• ES cells can be induced to differentiate into a wide variety of cell types in culture, by treatment with appropriate combinations of signal proteins and growth factors

• But, ethical objections to use of human embryos as stem cell reservoir

Solution to the problem: Conversion of adult cells to ES cell by manipulating gene expression (Gurdon & Yamanaka, Nobel Prize in Physiology & Medicine, 2012)

How can Nathaniel's umbilical cord cells be used to cure his brother Nicolas?

What information is relevant?

- Umbilical cord cells have sub-populations of ES cells
- They can be enriched and differentiated into many different cell types
- T-cell lymphoma is a cancer of immune cells (T-cells)

- Strategy: remove all cancerous T-cells (chemotherapy and radiation) followed by repopulating the body with non-cancerous T-cells derived from ES cells

How are Nicolas and Nathaniel “blood brothers”?

(1) Treat Nicolas to destroy his bone marrow cells (chemotherapy and radiation therapy)

Nicolas

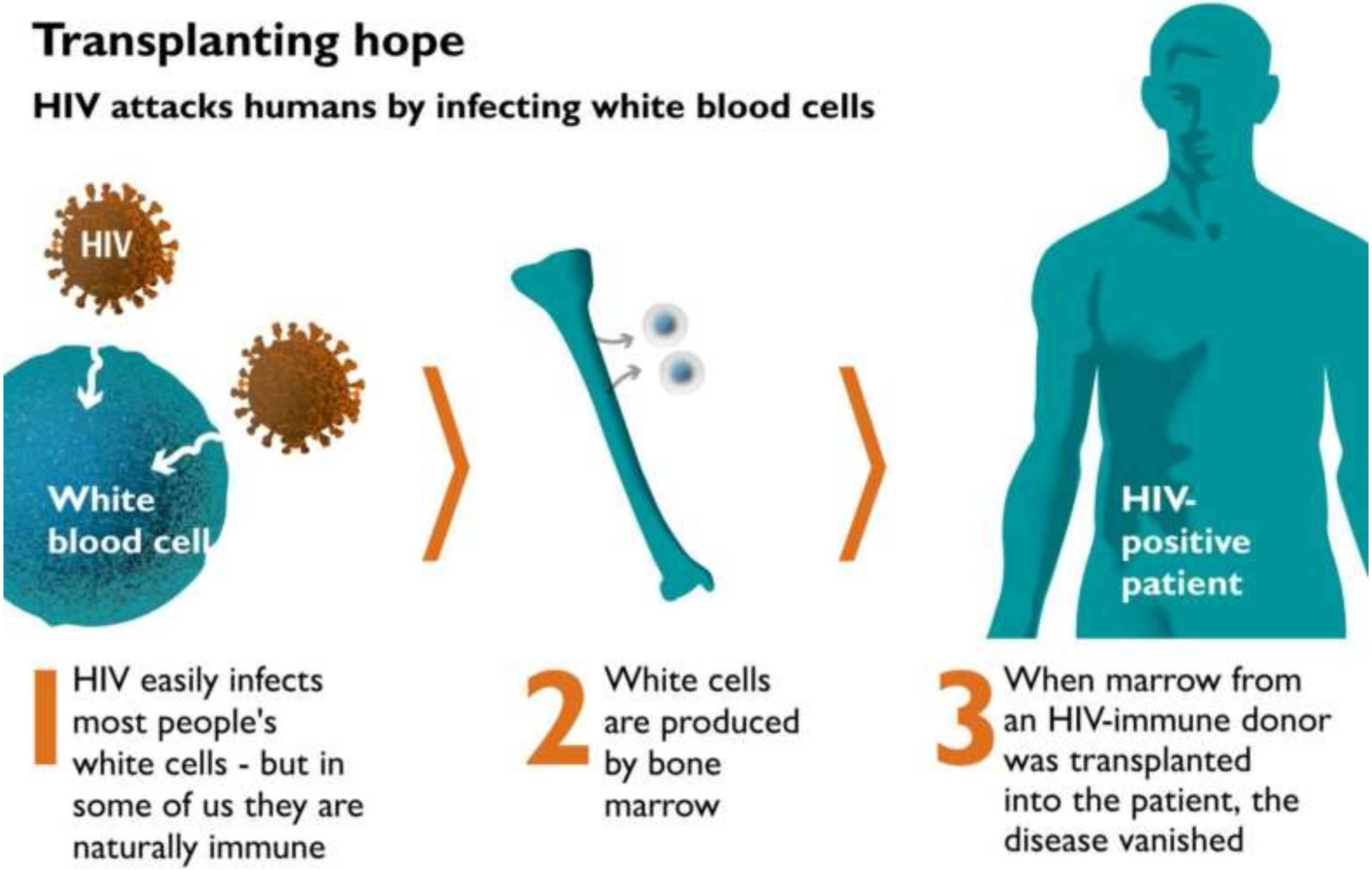
(2) Collect embryonic stem cells (hematopoietic cells) from Nathaniel’s umbilical cord blood

(3) Transfer Nathaniel’s ES cells into Nicolas and they will repopulate the bone marrow

Nathaniel

https://www.lls.org/treatment/types-of-treatment/stem-cell transplantation/allogeneic-stem-cell-transplantation

Cure of an HIV patient using this technology



https://www.thetimes.co.uk/article/yes-i-cured-a-man-of-hiv-but-now-i-need-to-pick-up-my-daughter-from-school-qlmxh5r70

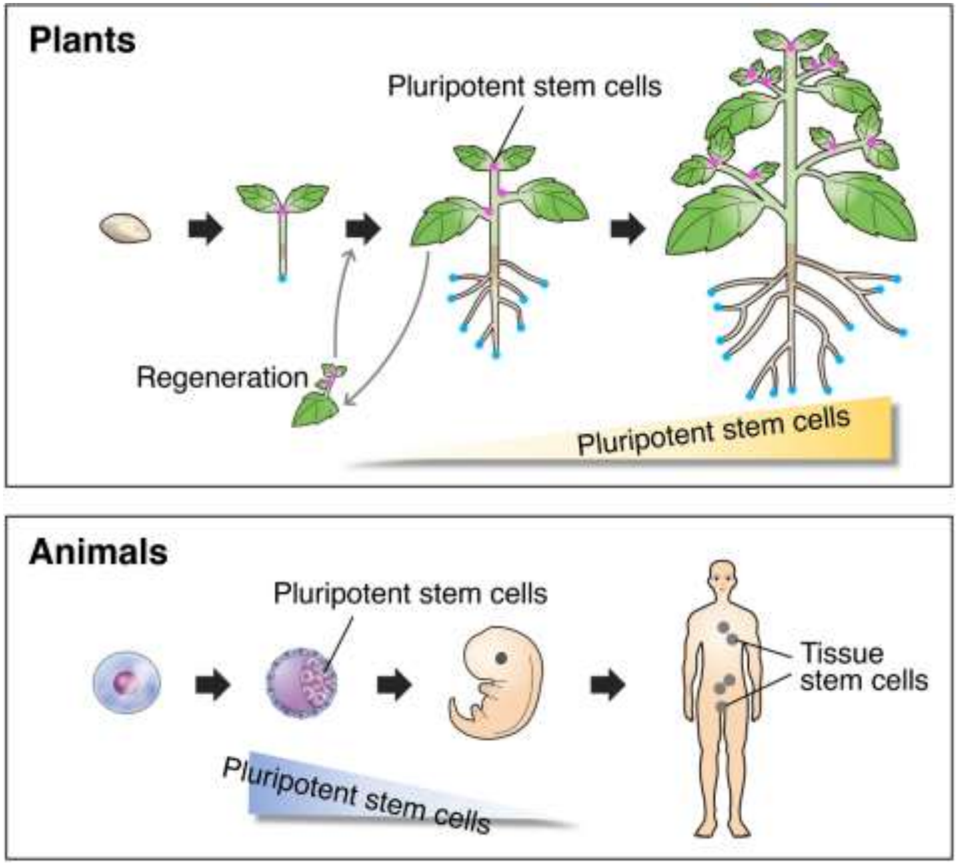
Plant Stem Cells

Thanks to Rajesh Patkar for the slides

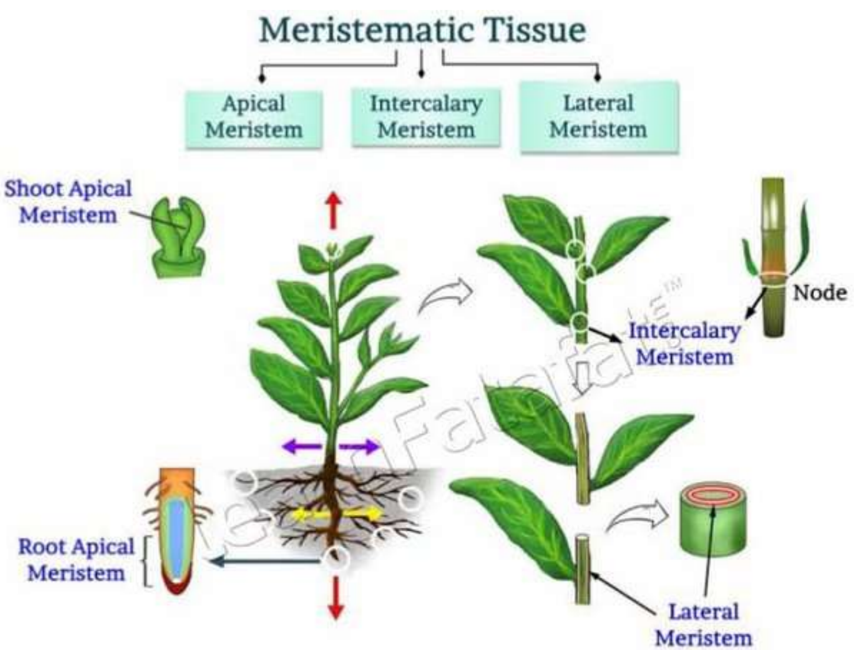
Difference between

Stem cells in plants and animals

Different Meristematic Tissues & their sites in a plant



Umeda et al. The Plant Journal. 2021

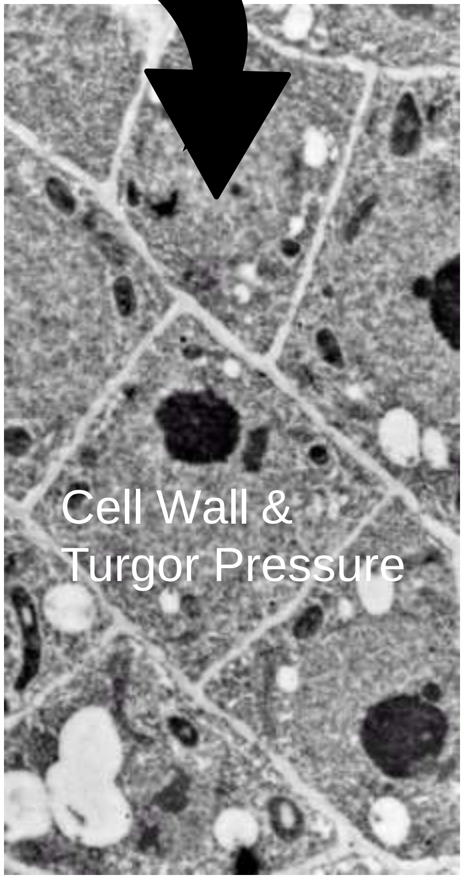


Meristem: a region of plant tissue, found chiefly at the growing tips of roots and shoots, consisting of actively dividing cells forming new tissue

https://www.quora.com/What-is-the-name-of-the-tissue-in-plants-that-contain-stem-cells

Animal Stem Cells respond to Growth Factors (proteins)

Plant Stem Cells Respond to Mechanical Forces

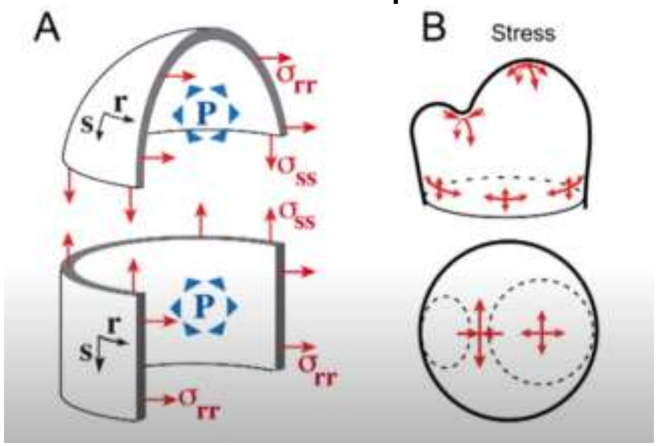


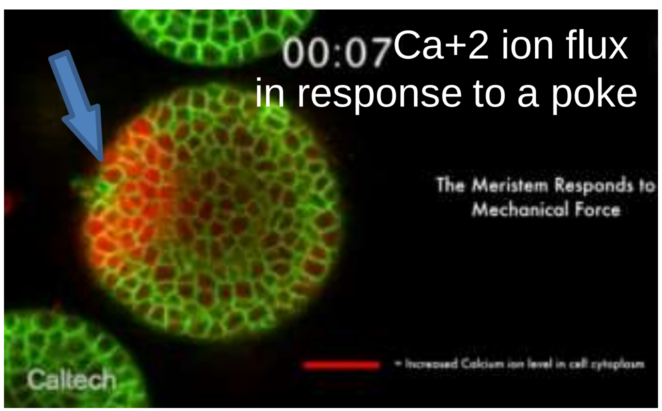
Courtesy: Prof. Elliot Meyerowitz, Caltech

Mechanical Force alters Calcium ion flux & Microtubule alignment in Shoot Apical Meristem

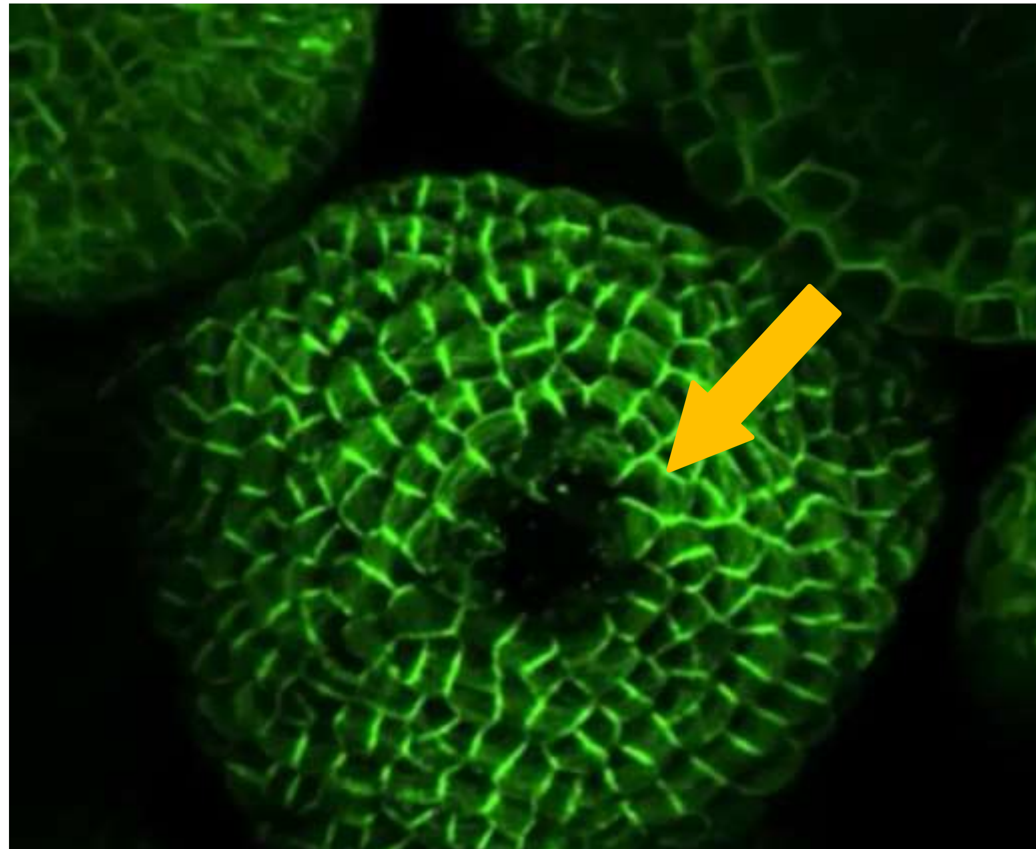
Thin-wall pressure vessel

Plant Shoot Apical Meristem





Courtesy: Prof. Elliot Meyerowitz, Caltech



Microtubule Re-alignment in response to mechanical stress

More than 50% of world' food energy comes from 3 "Mega-Crops" – Rice, Wheat and Maize

Research on plant stem cells helps us to optimize food production