VICTORIA JUNIOR COLLEGE
BIOLOGY DEPARTMENT
YEAR ONE LECTURE 2024 (H2 9744 & H1 8876)

CORE IDEA 2: GENETICS AND INHERITANCE
Mitotic Cell Cycle

Learning Outcomes:

Candidates should be able to:

(n) Describe the events that occur during the mitotic cell cycle and the main stages of mitosis (including the behaviour of chromosomes, nuclear envelope, cell membrane and centrioles).

(o) Explain the significance of the mitotic cell cycle (including growth, repair and asexual reproduction) and the need to regulate it tightly. (Knowledge that dysregulation of checkpoints of cell division can result in uncontrolled cell division and cancer is required, but detail of the mechanism is not required.)

Note: LO **(f) – (g)** in H1 syllabus

Contents:

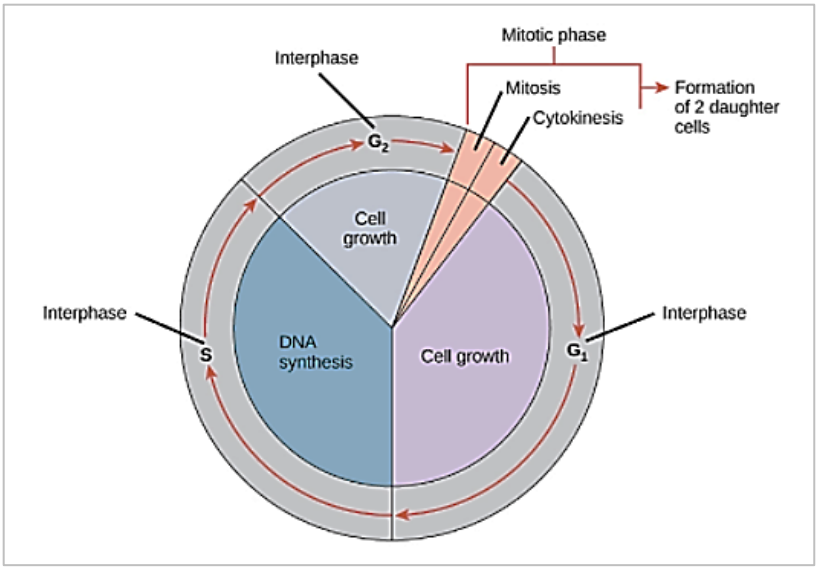
Need a song to get in beat with mitosis? (overview)	https://www.youtube.com/watch?v=pOsAbTi9tHw
	https://www.youtube.com/watch?v=f7Dmhfo7XXA

1. THE MITOTIC CELL CYCLE

Describe the events that occur during the mitotic cell cycle and the main stages of mitosis (including the behaviour of chromosomes, nuclear envelope, cell membrane and centrioles).

(a) Introduction to the cell cycle

- Recall the **Cell Theory** states that the cell is a fundamental unit of structure, function and organisation in all living organisms and new cells are formed from other existing cells.
- The cell cycle is an **ordered sequence of events** in cell division



Overview: Cell cycle (& Cancer)

Scan me

Fig. 1. Stages of the cell cycle.
Source: https://openstax.org/books/biology/pages/10-2-the-cell-cycle

1. **Mitosis** is the last part of the cell cycle. In fact, the **mitotic (M) phase**, which includes both mitosis and **cytokinesis**, is usually the shortest part of the cell cycle.
2. Mitotic cell division comes after a much longer stage called **interphase**, which often accounts for about 90% of the cycle. Interphase **consists of** three main stages: **G_1, S and G_2 phases**.

   *(While G stands for gap, you can use G1 and G2 mnemonically as **g**rowth phases, when the cell synthesizes a variety of proteins; For e.g., in G1 the synthesised proteins are required for DNA replication and in G2, microtubule proteins are required during mitosis.)*

G_1 phase	• Cell synthesises organelles such as mitochondria and ribosomes. • Builds up a large store of energy. • Manufactures proteins such as histones, ribosomal proteins and tubulin (a subunit of spindle fibres).
S phase	• DNA replication/ **S**ynthesis occurs. • A microtubule-organizing structure called the centrosome is also duplicated.
G_2 phase	• Cell continues to store energy and manufacture proteins and organelles. • Only cells with the right conditions can proceed to the **M phase** to ensure that damaged or incomplete DNA is not passed on to the daughter cells.
M phase	• Mitosis (nuclear division) • Cytokinesis

(b) Organisation of genetic materials during cell cycle

- During interphase, the genetic material of the cell are in the form of **chromatin**.
- In the first stage of mitosis, the chromatin condenses – The chromatin fibres become densely coiled, forming **chromosomes** which are much shorter and thicker, and are visible under the light microscope.
- Since DNA replication has already occurred in the S phase, each mitotic chromosome is already a duplicated structure, consisting of two **sister chromatids**.
- The two sister chromatids are **identical** DNA molecules attached to each other at the **centromere**.

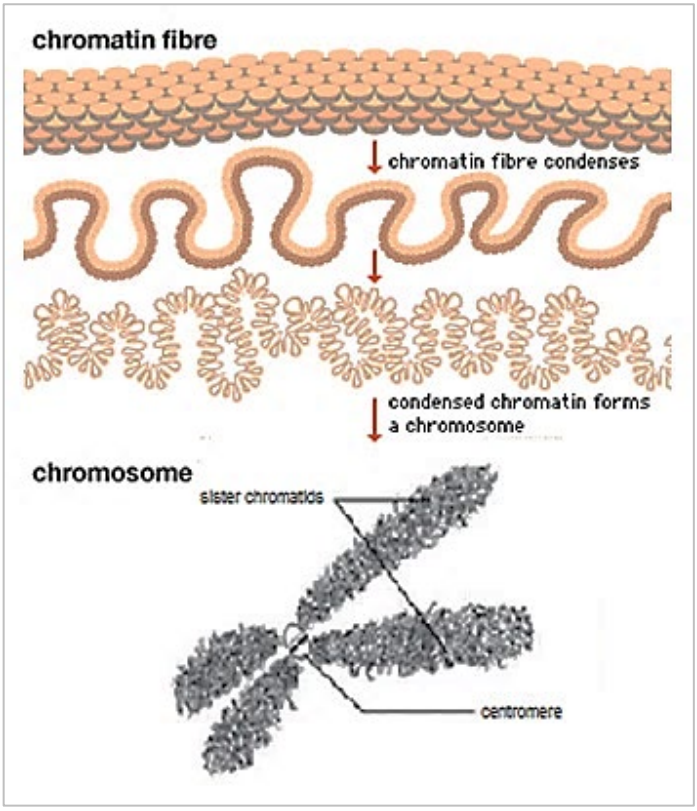


Fig. 2. Chromatin condensation into chromosomes

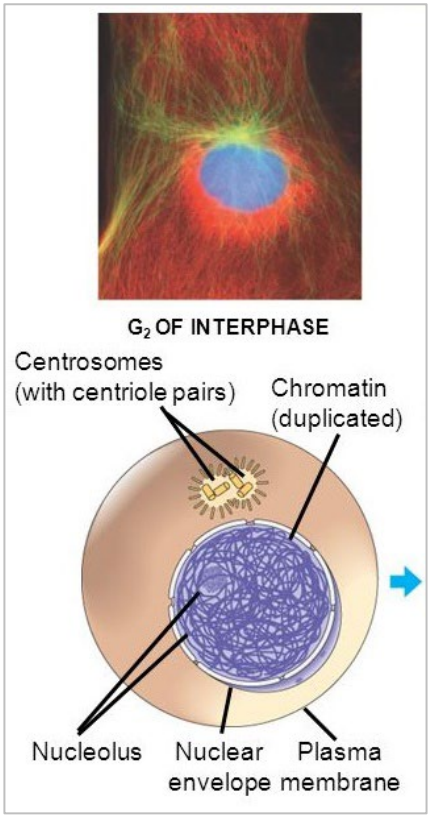
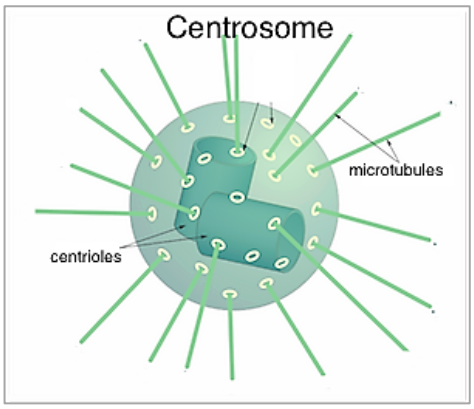


Fig. 3. Light micrograph of lung cell and representative drawing at G2 phase

- During mitosis, the two sister chromatids separate and move into the two daughter nuclei.
- Once they are separated, they are considered individual chromosomes.
- Thus, each daughter cell receives an **identical set of chromosomes as the parent cell.**

(c) Centrosomes, centrioles and spindle fibres



- **Centrosomes** are nonmembranous organelles found only in animal cells. They function as the **microtubule organizing center (MTOC)**, to organize the cell's microtubule throughout the cell cycle.
- In animal cells, each centrosome is composed of two **centrioles**, which are positioned perpendicular to each other.
- **Centrioles** are microtubule-based cylinders of defined length and diameter. They are found in animal cells but missing in most plant cells.
- Each centriole is approx. 500nm long and 200nm in diameter. Each is composed of 9 triplets of microtubules.

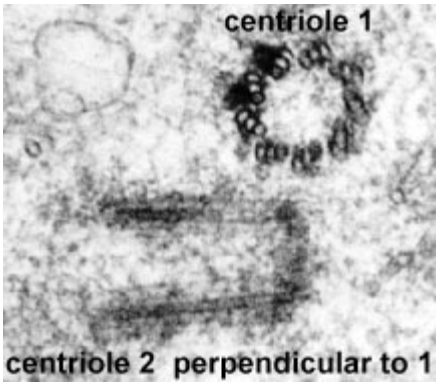


Fig. 4a: A pair of centrioles lying perpendicular to each other

(http://www.basic.northwestern.edu/g-buehler/eyes.htm)

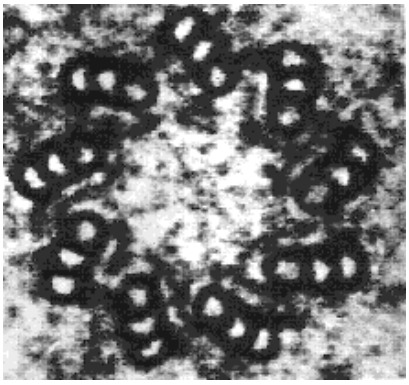


Fig. 4b. Electron micrograph showing a cross section of a centriole with its array of nine triplets of microtubules.

(https://www.biology-pages.info/C/Centrioles.html)

- At the beginning of nuclear division, long protein fibres (**microtubules**) extend from the centrioles. They form the **spindle fibres**. **Spindle fibres** are long, hollow tubes about 24-25nm in diameter. They are made up of protein subunits called **tubulin.**

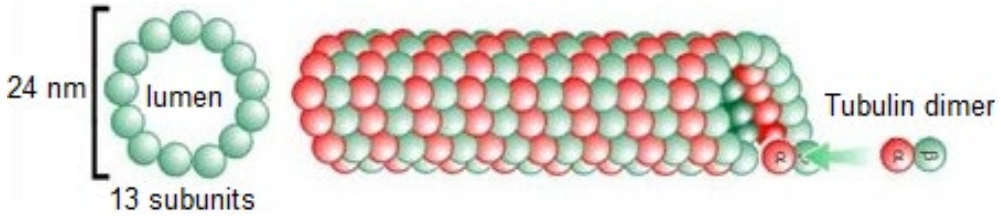


Fig. 5. Arrangement of tubulin in a spindle fibre

- Some of the spindle fibres attach to the kinetochores of the chromosomes are referred to as **kinetochore microtubules**. Shortening of these fibres by removal of tubulin subunits **separates** the chromatids and pull them to **opposite poles**.

- Spindle fibres that do not attach to kinetochores are referred to as nonkinetochore microtubules. They interact with nonkinetochore microtubules from the opposite pole of the cell. In a dividing animal cell, these microtubules are responsible for elongating the whole cell during anaphase.

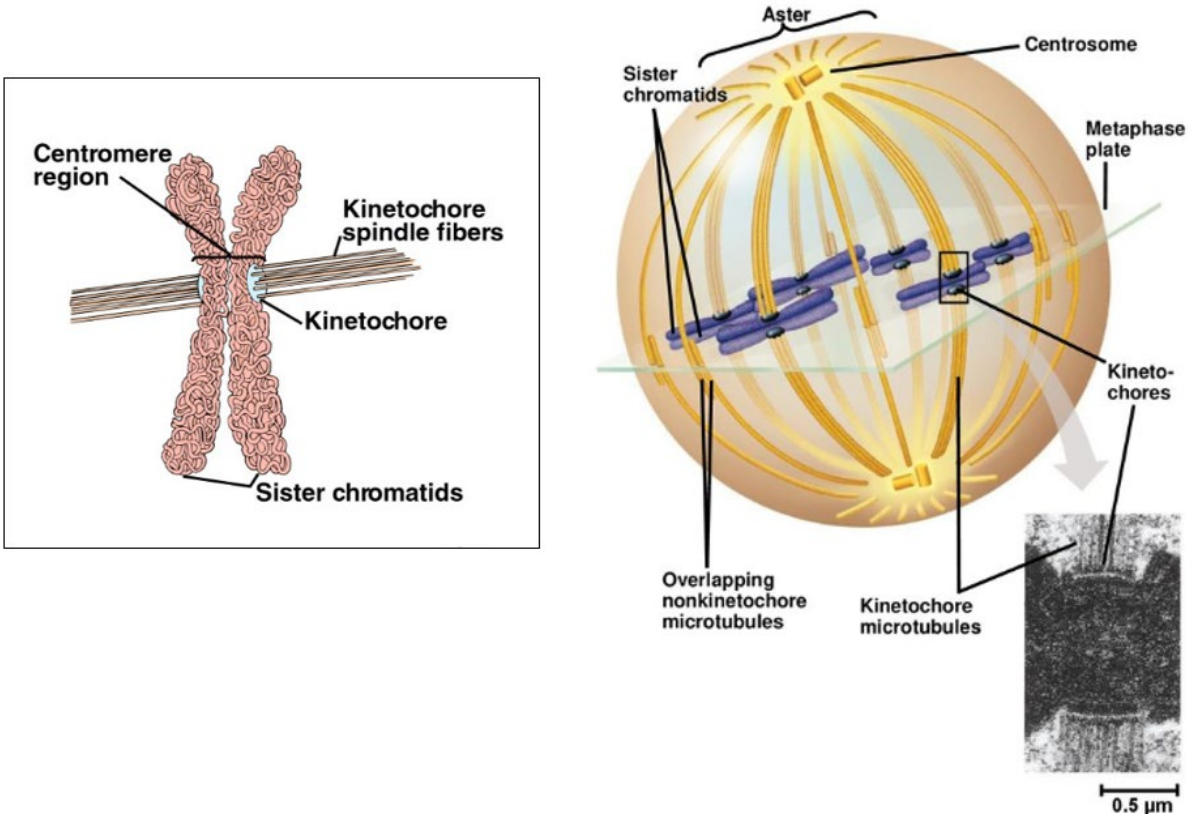


Fig. 6. Types of microtubules involved in mitosis

- **Colchicine** is a chemical commonly used to prevent formation of spindle fibre in actively dividing cells. As a result, sister chromatids remain attached in the metaphase plate. This allows the observation of the number and structure of chromosomes, as well as karyotyping.

(d) Process of mitosis

- Mitosis can be divided into four phases, namely **prophase**, **metaphase**, **anaphase** and **telophase**.

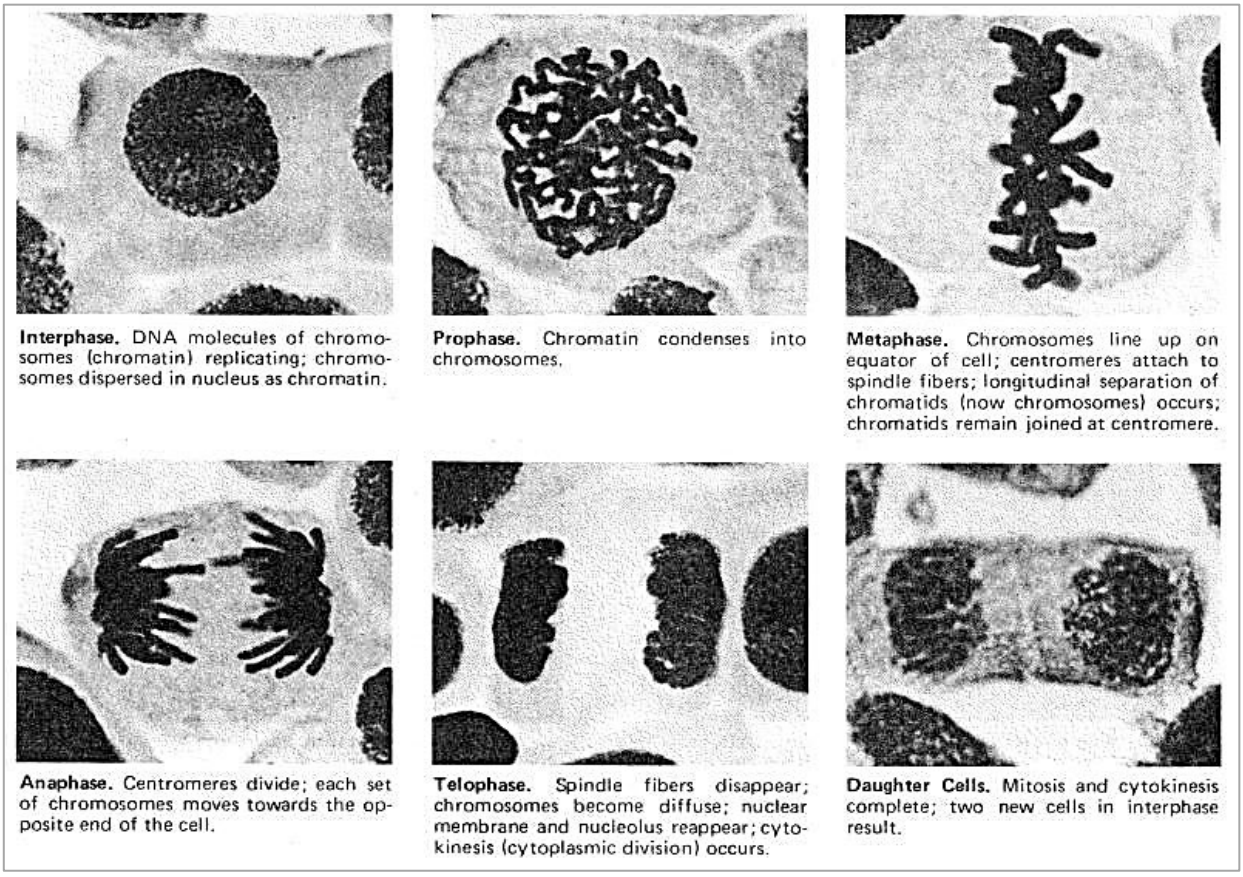
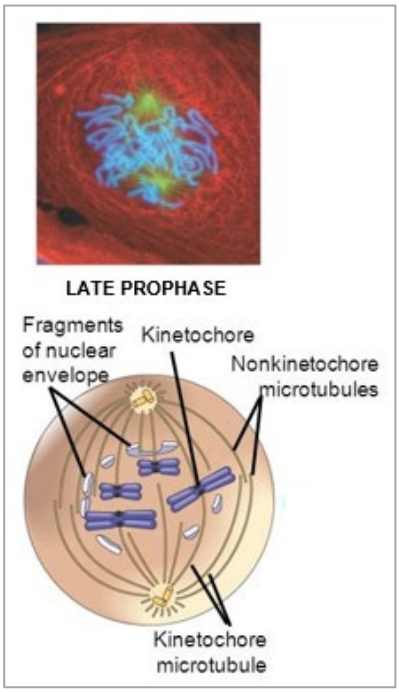


Fig. 7. A series of micrographs of a dividing animal cell.

(i) Prophase

- Genetic material becomes visible under light microscope as chromosomes due to **condensation** of chromatin.
- Each chromosome consists of two identical **sister chromatids**, which are joined at the **centromere**.
- The **nucleolus** disappears.
- In animal cells, **centrosomes** move to opposite ends of the cell. Short microtubules develop from each pair of centrioles in the centrosomes. This forms a star-shaped structure called an **aster**.
- Phosphorylation of various proteins on inner surface of the nuclear envelope causes the **nuclear envelope** to **disintegrate** into small membrane vesicles.
- Microtubules extend from the centrioles to form **spindle fibres.** The two ends of the spindle are known as its **poles**.
- A specialised protein structure, **kinetochore** assembles at the centromere of the chromosome.



- Some of the spindle fibres (microtubules) extend to attach specifically to the kinetochores becoming 'kinetochore microtubules".
- Nonkinetochore / polar microtubules are spindle fibres that extend from one pole to the opposite pole.

(ii) Metaphase

- Metaphase is the longest stage of mitosis, often lasting about 20 minutes.
- The centrosomes are now at opposite poles of the cell.
- The chromosomes align on the **metaphase plate / equator**, an imaginary plane that is equidistant between the spindle's two poles. The chromosomes' centromeres lie on the metaphase plate.
- Spindle fibres (kinetochore microtubules) are now attached to the kinetochores located at the centromere of each chromosome.

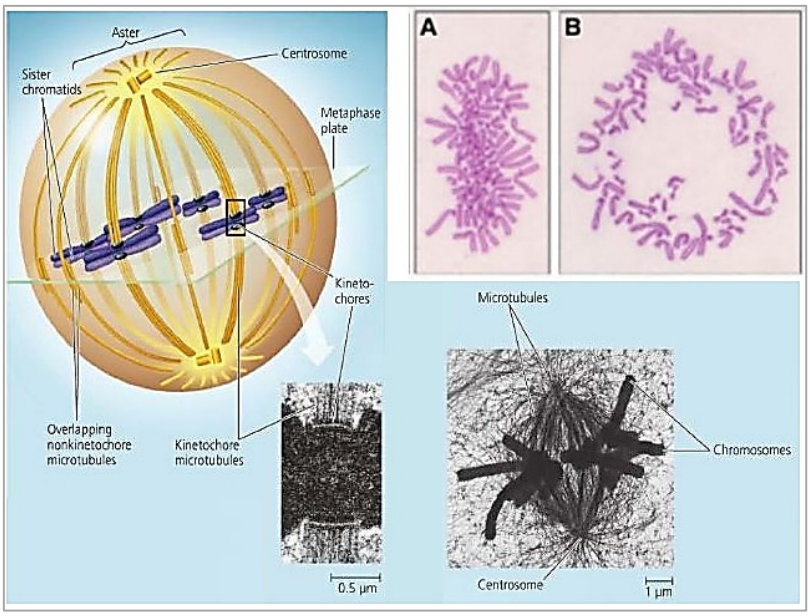
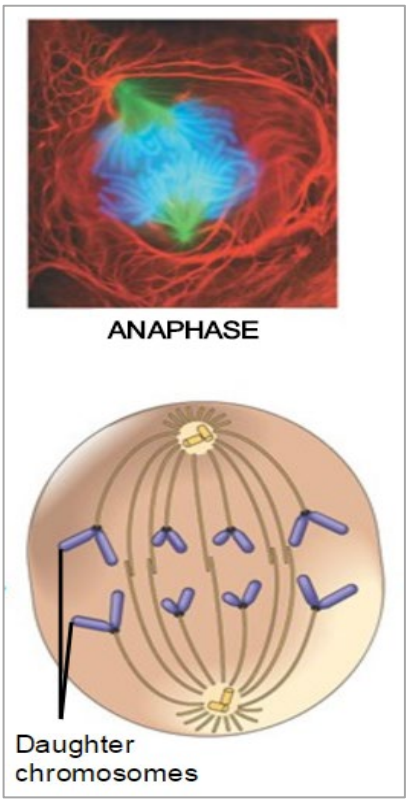


Fig. 8. The **mitotic spindle at metaphase** with TEMs showing each kinetochore is attached to a cluster of kinetochore microtubules extending from the nearest centrosome, and nonkinetochore microtubules overlap at the metaphase plate. **A, B** are chromosomes at metaphase - side and polar views.

(**A, B** from: https://openi.nlm.nih.gov/detailedresult.php?img=PMC1820851_pone.0000318.g004&req=4)

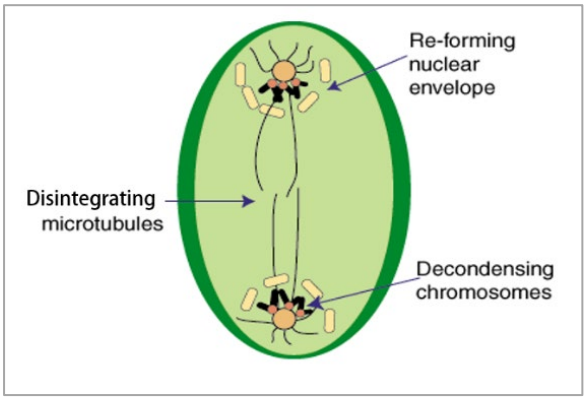
(iii) Anaphase

- Anaphase is the shortest stage of mitosis, often lasting only a few minutes.
- The **centromere of each chromosome divides** and the two **sister chromatids of each chromosome separate**.
- Each chromatid thus becomes a full-fledged chromosome.
- The two daughter chromosomes move, **centromere first**, to the **opposite poles** of the spindle, due to the shortening of their spindle fibres (kinetochore microtubules).
- This results in a distinct V-shape of the chromosome.
- The cell elongates as the nonkinetochore microtubules lengthen.



(iv) Telophase

- The chromosomes reach their respective poles to become the genetic material of daughter nuclei.
- The chromosomes **uncoil** and return to their chromatin form.
- **Spindle fibres disintegrate.**
- **Nuclear envelope reforms** around the chromosomes at each pole.
- **Nucleolus reappears** in each new nucleus.



3D animation of mitosis stages	

(e) Process of cytokinesis

- The division of the cytoplasm into two parts with each part enclosing one of the newly formed nuclei is usually well under way by late telophase, so the two daughter cells appear shortly after the end of mitosis.
- **Cytokinesis** occurs differently in plant and animal cells:

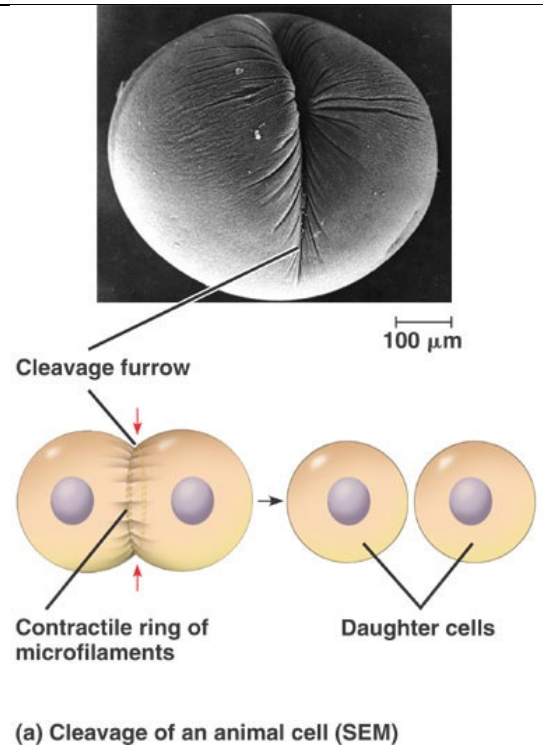
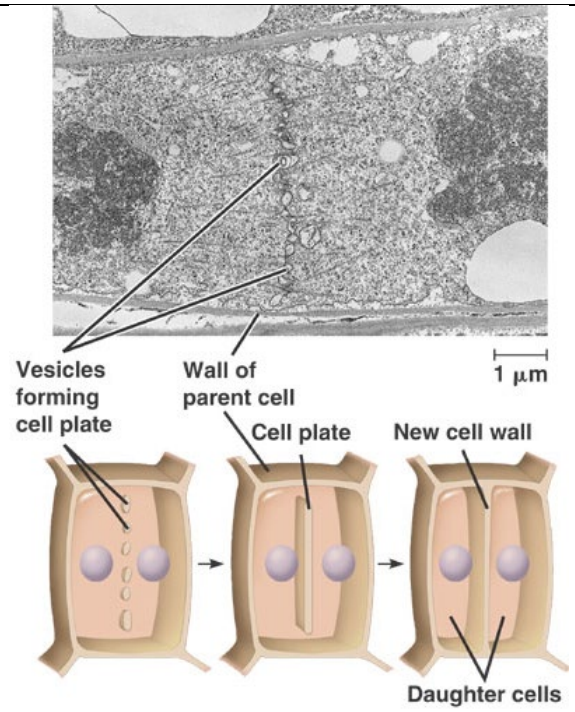
Animal cells	Plant cells
• A **cleavage furrow** develops in the cell membrane. The cell membranes in the furrows eventually join up and completely separate the two daughter nuclei	• A series of Golgi vesicles line up in the middle of the parent cell. They fuse to form the **cell plate**, which extends outwards across the equator of the parent cell. • The content of the Golgi vesicles contributes to the cell wall of the daughter cell while their membranes form the cell membranes of the daughter cells. • The cell plate eventually fuses with the parent cell wall and cell membrane, separating the two daughter cells.
	

Fig. 9. Cytokinesis in animal and plant cells.

(Taken from: http://celldivisionandreproduction.weebly.com/how-does-plants-mitosis-differ-from-animals.html)

2. IMPORTANCE OF MITOSIS AND REGULATION OF THE MITOTIC CELL CYCLE

Explain the significance of the mitotic cell cycle (including growth, repair and asexual reproduction) and the need to regulate it tightly.

(a) Significance of Mitosis

- Mitosis ensures that the two daughter nuclei formed contained **genetically identical** sets of chromosomes as the parent nuclei – Same number of chromosomes, same genetic make-up.
    - Hence, daughter cells will be **genetically identical** to the parent cell after cytokinesis. i.e. they are **clones** of the parent cell

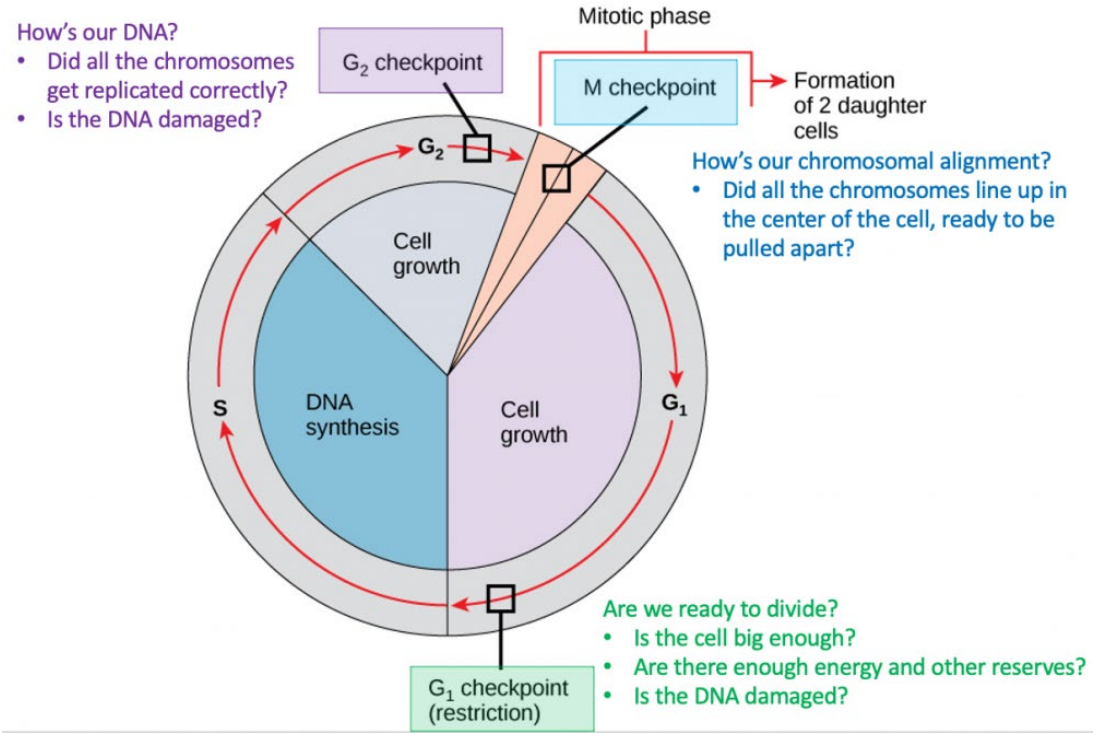
- Mitosis maintains the **genetic stability** of an organism and is important in the following processes:
    - Mitosis occurs during the **(i) growth** of a multicellular organism. E.g. in the development of a seedling into an adult plant. Cell division enables multicellular eukaryotes to develop from a single cell, the fertilized egg. *(Note: Larger organisms do not generally have larger cells than smaller organisms; they simply have more cells.)*
    - Mitosis occurs during the **(ii) repair** of worn-out parts of the body.
    - Mitosis is the basis of **(iii) asexual reproduction** – the production of an offspring without the fusion of gametes. E.g. budding of a hydra, vegetative propagation of certain plants like potato, onion and ginger.

- Two features of mitosis ensure that daughter nuclei formed receive exactly the **same number and type of chromosomes as the parent nucleus.**
    - **Semi-conservative replication** of DNA must occur before mitosis, to ensure that each chromosome of the parent nucleus is duplicated to form two **identical sister chromatids**.
    - Proper arrangement of the chromosomes along the equator ensures that the chromosomes are shared **equally** between the two daughter nuclei, as each sister chromatid of every chromosome is pulled towards opposite poles.

      Therefore, proper formation and subsequent shortening of the mitotic spindle also plays a key role in ensuring the proper separation of chromosomes during mitosis.

(b) Cell cycle checkpoints

- A **cell cycle checkpoint** is a critical control point where the stop and go-ahead signals can regulate the cycle.
- These checkpoints are important as they ensure the cell is **only allowed to proceed to the next phase of the cell cycle if it has properly completed the previous phase.**
- The checkpoints basically monitor for **DNA replication, DNA damage and chromosome-to-spindle attachments.**



Mitosis and cell cycle checkpoints (mechanism details not required)

Fig.10. Checkpoints in the cell cycle
https://openoregon.pressbooks.pub/mhccbiology112/chapter/10-3-control-of-the-cell-cycle/html

- There are 3 major checkpoints in the cell cycle found in the G_1, G_2 and M phases.

Checkpoint	Factors to be checked / Requirements for progression
G_1 (also known as restriction/ start checkpoint)	• This is the primary point where the cell decides whether to divide or not. **G_1** checkpoint checks for ✓ **Size** of cell – ensures that the cell is large enough to divide. ✓ **Nutrients** availability – ensures enough nutrients are available to support daughter cells. ✓ **DNA integrity** – ensures that genome is intact. Damage to DNA can halt the cycle at this point. ✓ Molecular **signals** – ensures that cell has received an appropriate growth signal. • If a cell does not receive the growth signal, it will exit the cell cycle and switch to a non-dividing state called G_0. • Most cells in the human body are in G_0 phase.

G_2 (also known as G_2/M checkpoint)	**G_2** checkpoint checks for ✓ **DNA integrity** – ensures that DNA is undamaged. ✓ **DNA replication** – ensures that DNA replication was successfully completed. • If DNA damage are detected or DNA is not accurately replicated, the cell can stall the cycle at the **G_2** checkpoint to allow for DNA repairs. • If DNA damage is extensive/ beyond repair, **p53** triggers the cell to undergo programmed cell death (apoptosis). This ensures that damaged DNA is not passed on to daughter cells. • *FYI: A growth factor known as M-phase-promoting factor (MPF) must be present.* o *MPF is sensitive to agents that disrupt DNA replication or damage DNA.* o *MPF phosphorylates various proteins of the nuclear lamina to disintegrate the nuclear envelope.* o *MPF also activates other kinases to phosphorylate proteins on the outer nuclear membrane.*
M (also known as spindle or metaphase checkpoint)	**M** checkpoint checks for ✓ all chromosomes are attached to spindle fibres (kinetochore microtubules) to prepare for anaphase. ✓ Proper tension is placed on the paired kinetochores. • *FYI: The go-ahead signal is transmitted via a protein complex known as anaphase promoting complex (APC).* o *APC removes the inhibitors of a protease that digest cohesin (a protein holding sister chromatids together during metaphase).*