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TOPIC E: CELL & NUCLEAR DIVISION (MITOSIS & MEIOSIS)

Learning Outcome

Core Topic 1 – Cellular Functions

Candidates should be able to:

(l) Explain the importance of mitosis in growth, repair and asexual reproduction.

(m) Explain the need for the production of genetically identical cells and fine control of replication.

(n) Explain how uncontrolled cell growth can result in cancer, and identify causative factors (e.g. genetic, chemical carcinogens, radiation, loss of immunity) which can increase the chances of cancerous growth. (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.)

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(o) Describe, with the aid of diagrams, the behaviour of chromosomes during the mitotic cell cycle and the associated behaviour of the nuclear envelope, cell membrane and centrioles. (Names of the main stages are expected.)

(p) Explain what is meant by *homologous pairs* of chromosomes.

(q) Explain the need for reduction division (meiosis) prior to fertilisation in sexual reproduction.

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~~(p)~~(r) Explain how meiosis and random fertilisation can lead to variation.

(s) Describe, with the aid of diagrams, the behaviour of chromosomes during meiosis, and the associated behaviour of the nuclear envelope, cell membrane and centrioles. (Names of the main stages are expected, but not the subdivisions of prophase.)

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Content Outline

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1. The Role of Nucleus and Chromosomes in Cell Division
   - (a) Chromatin Structure
   - (b) Chromosome Structure
   - (c) Chromosome Number
   - (d) Homologous Chromosomes

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2. The Cell Cycle
   - (a) Interphase
   - (b) Mitosis
   - (c) Cytokinesis
   - ~~(c)~~(d) Significance of Mitosis
   - (e) Meiosis
   - ~~(d)~~(f) Significance of Meiosis
   - ~~(e)~~(g) Non-disjunction

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~~3. Significance of Nuclear Division~~
   - ~~(a) Importance of mitosis~~
   - ~~(b) Importance of meiosis~~

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~~4.~~3. The Control of Mitotic Cell Cycle

(a) Genes involved in control of cell cycle
(b) Onset of cancer
(c) Causative factors

References

1. Campbell, N. A. And Reece J.B. (2011~~08~~) Biology. Chapter 12 :The Cell Cycle and Chapter 1~~3~~3: Meiosis and Sexual Life Cycles. ~~8~~9th ed. Benjamin Cummings Publishing, Inc.

~~2. Clegg, C. J. And Mackean, D. J. (2000) Advanced Biology, Principles and Applications. Chapter 9: The Nucleus in Divison and Interphase. 2nd ed. John Murray Publishing (Ltd)~~

~~3. Jones, M. And Jones, G. (2004) Advanced Biology. Chapter 4: Cell Division. Cambridge University Press.~~

1. The Role of Nucleus and Chromosomes in Cell Division

All new cells are derived from pre-existing cells through cell division, a part of the **cell cycle** which includes:

- **Interphase** - cell growth and synthesis of cell materials
- **Nuclear division** - nucleus divides ~~first~~ to form two nuclei
- **Cytokinesis** - cytoplasm divides to form two daughter cells

The nucleus is responsible for carrying out cell division.

(a) Chromatin Structure

~~**Chromatin** is the **complex of DNA and proteins**:~~

- is the **complex of DNA and proteins**.
- ~~It~~ is the **less condensed** form of chromosome~~, present during **interphase**~~
- ~~D~~**dispersed** as a mass of long, thin fibres when cell is not dividing and during **interphase**.
- Two types of chromatin: **Heterochromatin (highly condensed)** and **euchromatin (less condensed).**
- The degree~~Level~~ of condensation may change~~ depending on circumstance~~:
  - Chromatin **condenses** by coiling to form chromosomes during cell division.
  - Chromatin **decondenses** for polymerases to gain access to specific regions of DNA for replication, gene expression or repair~~ or gene expression~~.

~~- Two types of chromatin: **Heterochromatin (highly condensed)** and **euchromatin (less condensed).**~~

10nm

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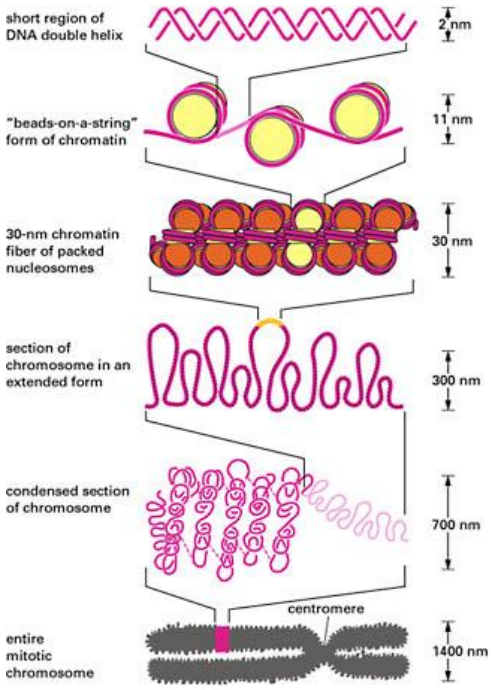

DNA packed into chromatin and chromosome

Eukaryotic DNA contains millions of nucleotides. In humans, the DNA material in a cell has a total length of about 1.8m long! However, the radius of the nucleus is only about 6µm. Hence, each DNA molecule must be packed into a compact structure that is about 50,000 times shorter that its extended length.

Condensation of chromatin into chromosome:

- Negatively-charged **double-helix DNA** (2nm) is wound twice around **histone proteins** that have **positively charged lysine and arginine** residues to form a **nucleosome**.
- **Nucleosomes** are joined by **linker DNA**, giving rise to **'beads-on-a-string'** structure **(10nm chromatin fibre)**.

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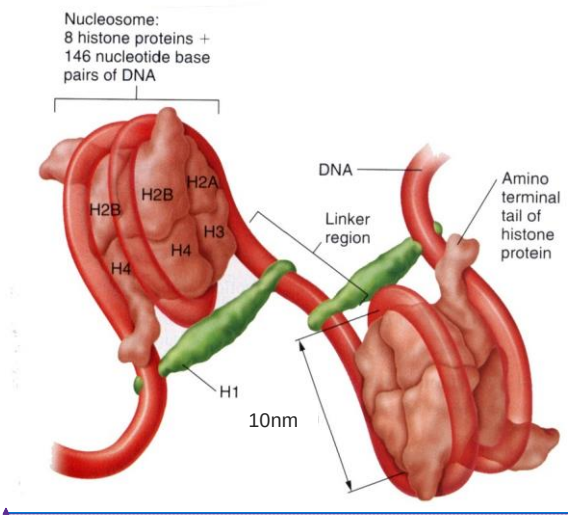

DNA wound around histone proteins

- Nucleosomes and linker DNA are coiled into a **solenoid structure**, forming a **30nm chromatin fibre**.
- 30nm chromatin fibres are folded into **looped domains** that are attached to **non-histone scaffolding proteins**, forming **300nm chromatin fibres**.
- 300nm chromatin fibres are further folded to form **700nm chromatin fibres** found on one of the sister chromatids on a duplicated **chromosome**.

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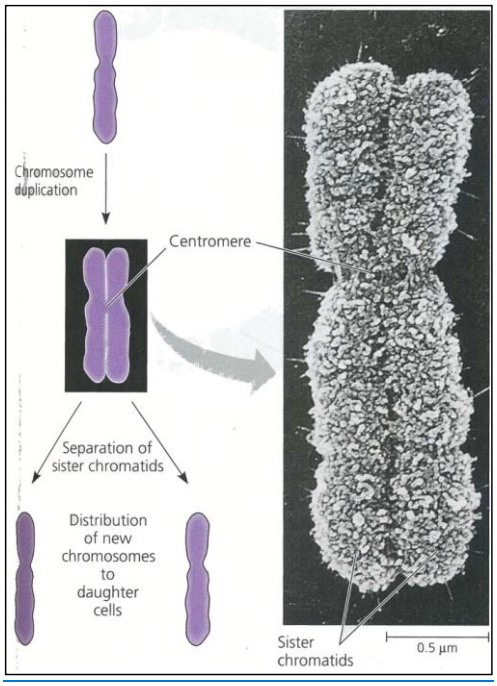
(b) Chromosome Structure

During cell division, chromatin condenses into **chromosomes**, which may exist as **unduplicated** chromosomes or **duplicated** chromosomes.



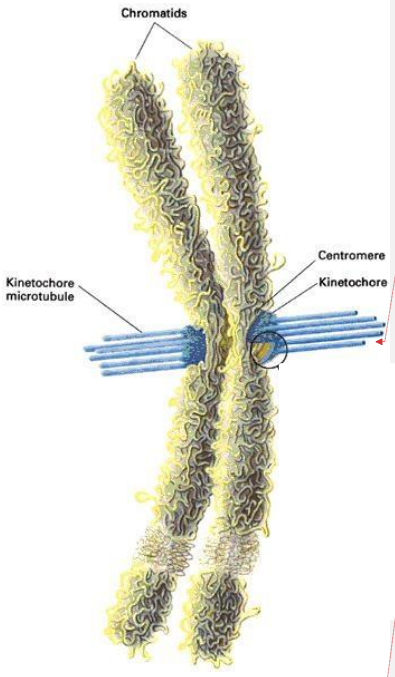


Diagram showing duplicated chromosome and unduplicated chromosome

(i) **Unduplicated chromosome**

- ~~Each unduplicated chromosome~~ consists of **a single DNA molecule**.

(ii) **Duplicated** chromosome (also known as **replicated** chromosome)

- Four-arm structure **visible under light microscope**
- consists of **two DNA molecules**
- consists of ~~T~~two **identical sister chromatids** ~~formed~~ joined at the **centromere**
  - Identical sister chromatids are formed due to **semi-conservative DNA replication during synthesis phase of Interphase**.
  - **Centromere** is a constricted region of **satellite DNA** (highly repetitive DNA sequence).
    - Bound to **kinetochore proteins** which allow for attachment of spindle fibres.
    - The **centromere holds two sister chromatids together** and are involved in **chromosome movement** during cell division.

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~~Centromere is a constricted region of satellite DNA (highly repetitive DNA sequence).~~

- ~~Bound to kinetochore proteins which allow for attachment of spindle fibres~~

~~The centromere holds two sister chromatids together (in examiner comments) and are involved in chromosome movement during cell division. (in campbell)~~

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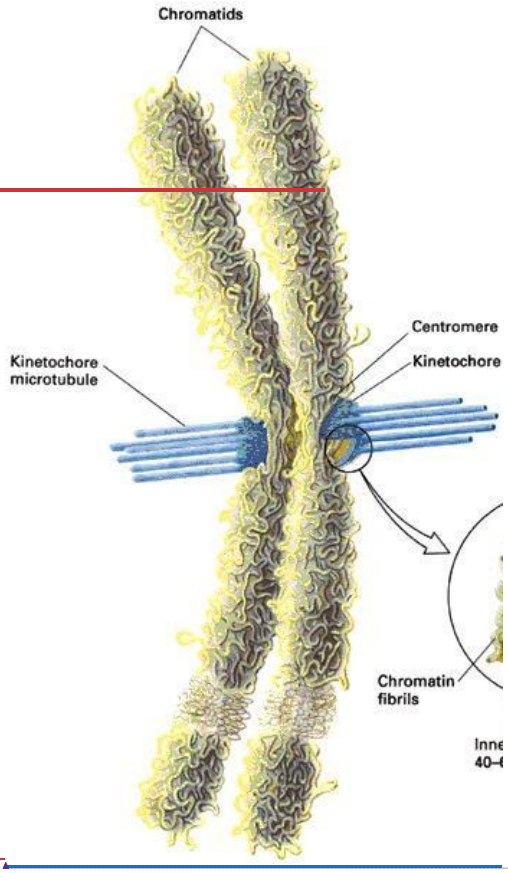

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~~Chromosome structure~~

(c) Chromosome Number

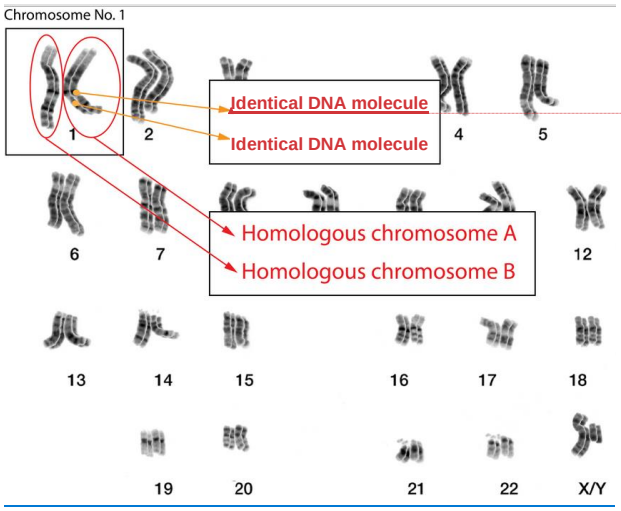
(i) Diploid

- ~~The number of chromosomes in **somatic cells** (i.e. all cells except sex cells) is fixed for a species. **Diploid** organisms have cells that contain **two sets of chromosomes**.~~
- Diploid cell has a **diploid number** of chromosomes, **2n**, where **n** represents **the number of chromosomes in a single set**.

  The number of chromosomes in **somatic cells** (i.e. all cells except sex cells) is fixed for a species. Each sexually reproducing species has a characteristic diploid number and haploid number.

  - For example, each human somatic cell has 46 chromosomes and the **diploid number** is 46.
  - Each somatic cell contains **two sets of chromosomes** (2n = 46). One set contains 23 different chromosomes (n = 23).
  - This can be clearly seen in a **karyotype**, an ordered display of chromosomes.

~~For example, humans have 46 chromosomes in each cell. Since humans are **diploid** organisms, the **diploid number** is 46. Each **somatic** cell contains **two sets of chromosomes** (2n = 46). One set contains 23 different chromosomes (n = 23). This can be clearly seen in a **karyotype**, an ordered display of chromosomes.~~



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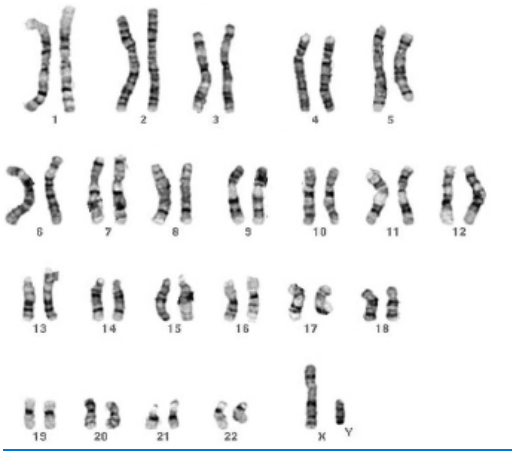
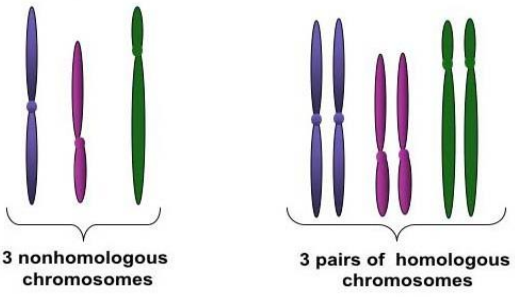


Karyotype of a human male

(ii) **Haploid**

- ~~organisms~~ **Gametes** (sex cells) contain **a single set of chromosomes**.
- **Haploid** cells have a **haploid number** of chromosomes (**n**).
  - For example, a human egg or human sperm has 23 chromosomes and the **haploid number** is 23.
  - Each sex cell contains **one set of chromosomes** (n = 23).
  - The 23 different chromosomes consist of the 22 **autosomes** plus a single **sex chromosome**.
  - A human egg contains 22 autosomes and an X chromosome,
  - A human sperm contains 22 autosomes and either an X or a Y chromosome.



Haploid Number = 3 **Diploid Number = 6**

Table showing chromosome numbers of human, fruit fly and dog

	Human	Fruit Fly	Dog
Diploid number	46	8	
Number of chromosomes in a gamete			
Number of different types of chromosomes			39

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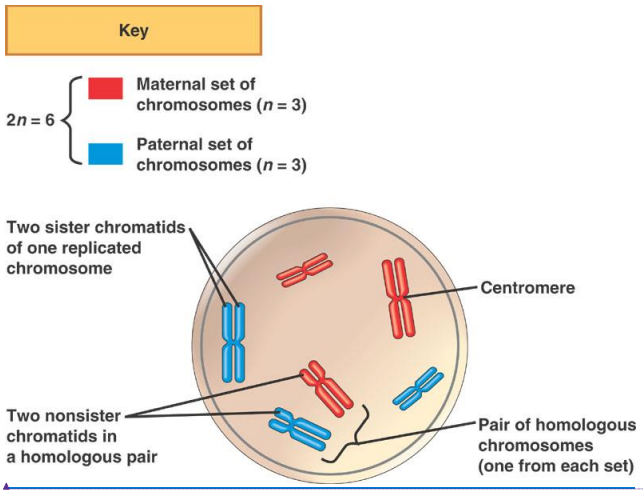

Diagram describing chromosome numbers

(d) Homologous Chromosomes

In a diploid cell, each type of chromosome exists as a pair of **homologous chromosomes**, with each chromosome known as a **homolog**.

In human diploid cell, we **inherit one chromosome of each pair from each parent**. Thus, the 46 chromosomes in our somatic cells are actually two sets of 23 chromosomes – a **maternal set** (from the female parent) and a **paternal set** (from the male parent).

Homologous chromosomes:

- have the **same length**,
- have the **same position of centromeres**.
- have the **same genes** at the **same loci**.
- Homologous chromosomes **may have different alleles** from each other.
  - Alleles are **alternative forms of the same gene** with a slight different nucleotide sequence.
- One homolog is derived from **maternal** parent while the other is derived from the **paternal** parent.
- Homologous chromosomes **pair to form bivalents** during prophase I of meiosis.
- Each homolog consists of **double structure containing two identical sister chromatids** during prophase I of meiosis.

The two **sex chromosomes** are an important exception to the general pattern of homologous chromosomes.

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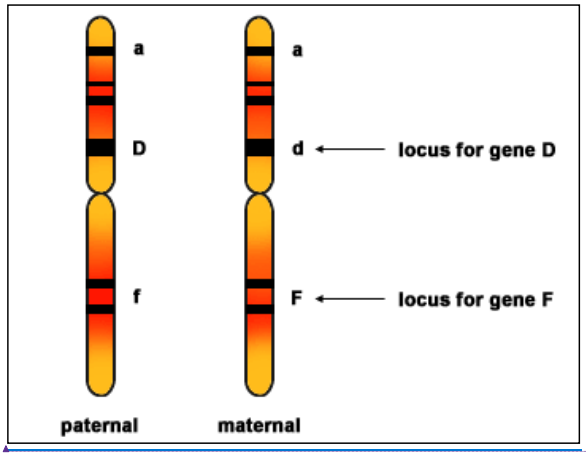

Homologous chromosomes

For example,

- When the two alleles coding for the gene *A*, on a pair of homologous chromosome are the same, this organism is **homozygous** for the trait.
- When the two alleles coding for the gene *D*, on a pair of homologous chromosome are different, the organism is **heterozygous** for the trait.
- When the genes that code for *A*, *D* and *F* are found on the same chromosome, they are said to be **linked (i.e. linked genes)**.

~~1.~~2. The Cell Cycle

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The **cell cycle** is the life of a cell from the time it is first formed from a dividing parent cell until its own division into two daughter cells.

- Three stages: **interphase, nuclear division** and **cytokinesis**.
- Two types of nuclear division:
  - **mitosis** for all **somatic** cells and
  - **meiosis** in **sexual reproductive organs** to form **gametes / sex cells.**
- The duration of cell cycle varies for different types of tissue within a single organism.

(a) Interphase

Cells prepare for mitosis or meiosis in 3 sub-phases:

- **First growth phase** or **G_1 phase**
- **Synthesis** or **S phase**

Phase	Events that occur
G_1	• **Synthesis of organelles** e.g. endoplasmic reticulum and mitochondria / chloroplasts (by binary fission) • **Nucleolus actively synthesises ribosomal RNA** for formation of ribosomes. • **Synthesis of proteins** • **Increase in cytoplasmic volume**, resulting in an increase of cell size.

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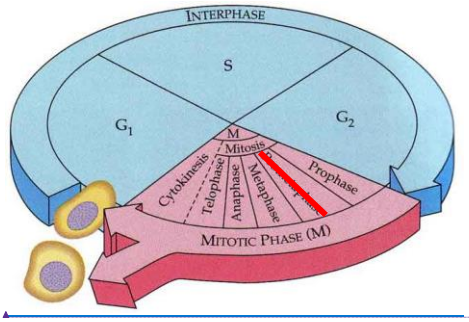
Synthesis	• **DNA semi-conservative replication** occurs, resulting in **doubling** of DNA content. • **Histone proteins are synthesized**. • Newly synthesized DNA molecules are wound tightly around the histone proteins. • Each chromatin fibre is composed of **two identical DNA molecules**.
G_2	• **Intensive synthesis of organelles** e.g. endoplasmic reticulum and mitochondria / chloroplasts (by binary fission) • **Replication of centrosome** to form 2 centrosomes. Each centrosome is made up of **a pair of centrioles** (in animal cells). • **Synthesis of proteins** – e.g. tubulins for assembly of microtubule in spindle fibre • **Synthesis of ATP** for energy.

- **Second growth phase** or **G_2 phase**



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Cell cycle

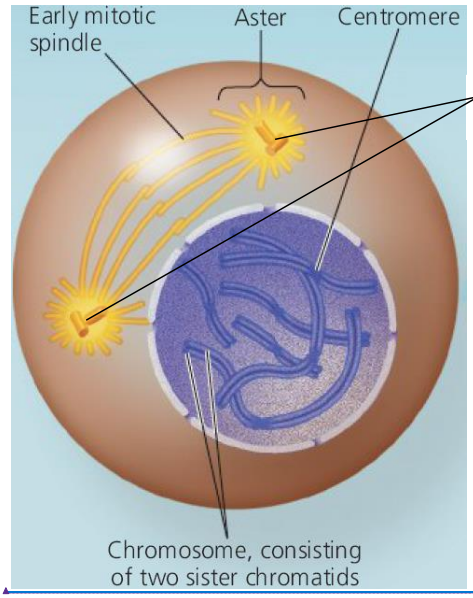
(b) Mitosis

Nuclear division:

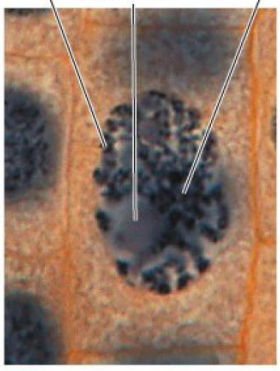
- **Nucleus of parent cell divides once** to produce two **genetically identical daughter nuclei** with **same number and types of chromosomes as parent nucleus**.
- Four main phases: **prophase**, **metaphase**, **anaphase**, **telophase**

(i) **Prophase**

- Chromatin fibre becomes more tightly coiled, **condensing into chromosomes**.
- Each duplicated chromosome appears as **two identical sister chromatids joined at their centromeres**.
- **Centrosome** organise microtubules into **spindle fibres** and the radial array of short microtubules extending from each centrosome are called **asters.**
- Centrosomes **migrate to opposite poles** of the cell by lengthening of microtubules.
  - In animal cells, each pair of centrioles migrates to opposite poles of the cell.
- **Nucleolus disperses** and **seems to disappear**.
- **Nuclear envelope fragments**.



Centrosome:
Animals have a pair of centrioles



Diagrams of Prophase

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(ii) **Metaphase (longest** phase in mitosis)

- Microtubules from centrosome attach to **kinetochore** at the centromere of each chromatid of chromosome, becoming **kinetochore microtubules**.
- **Centromeres of chromosomes are aligned along the metaphase plate** (an imaginary plane equidistant between the two poles of the cell) by microtubules.
- Non-kinetochore microtubules interact with those from the opposite pole of the spindle.

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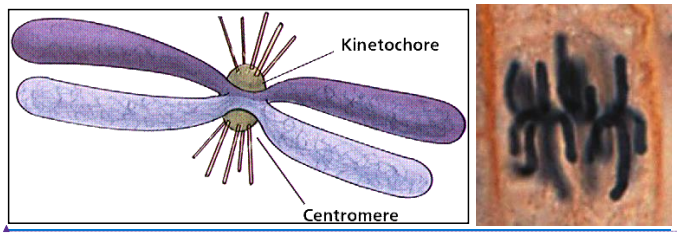

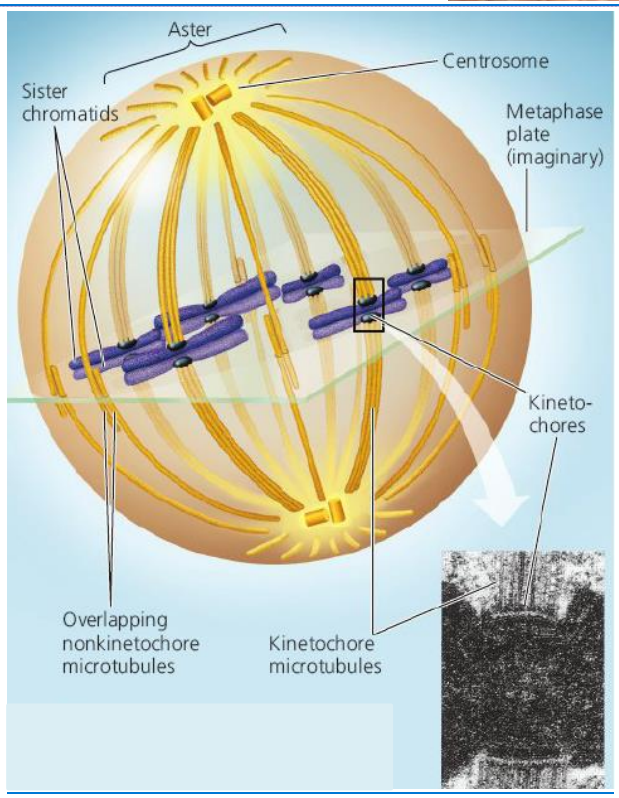

Diagrams showing Metaphase and chromosomes attached to kinetochore

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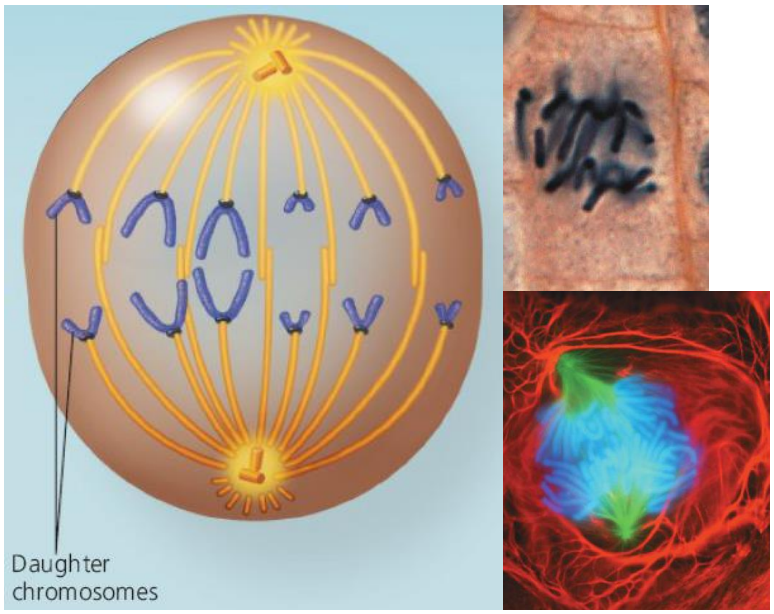
(iii) **Anaphase** (**shortest** phase in mitosis)

- **Centromere separates** and **two sister chromatids separate**, thus becoming two **daughter chromosomes**.
- **Daughter chromosomes migrate toward opposite poles of the cell, with the centromere leading the way** as **kinetochore microtubules shorten**.
- **Non-kinetochore microtubules lengthen,** leading to cell **elongation**.
- By the end of anaphase, the two poles of the cell have equivalent and complete set of chromosomes.



Diagrams showing Anaphase

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(iv) **Telophase**

- **Nuclear envelopes reform** from the fragments of the endomembrane system to form **two nuclei**.
- Nucleolus **reappears**.
- Chromosomes become **less condensed** to form **chromatin**.
- Microtubules **disperse** by depolymerising.

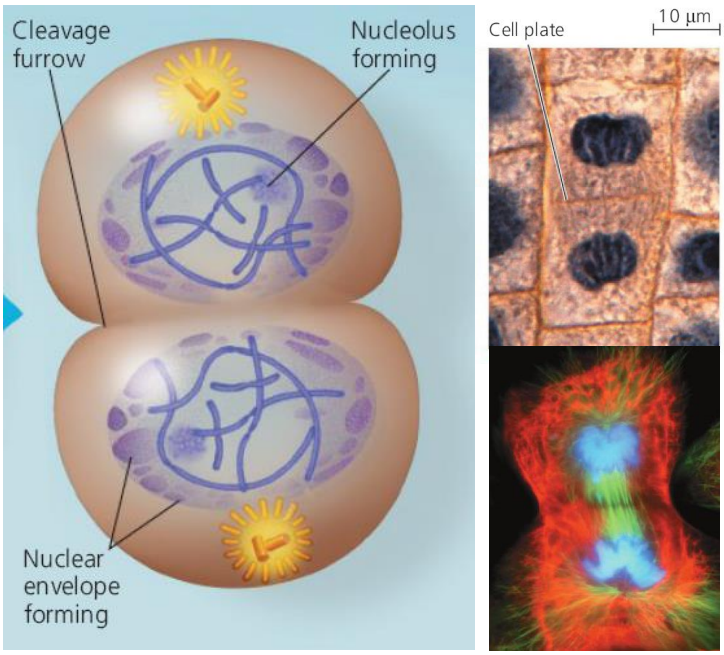

Diagram showing telophase with cytokinesis

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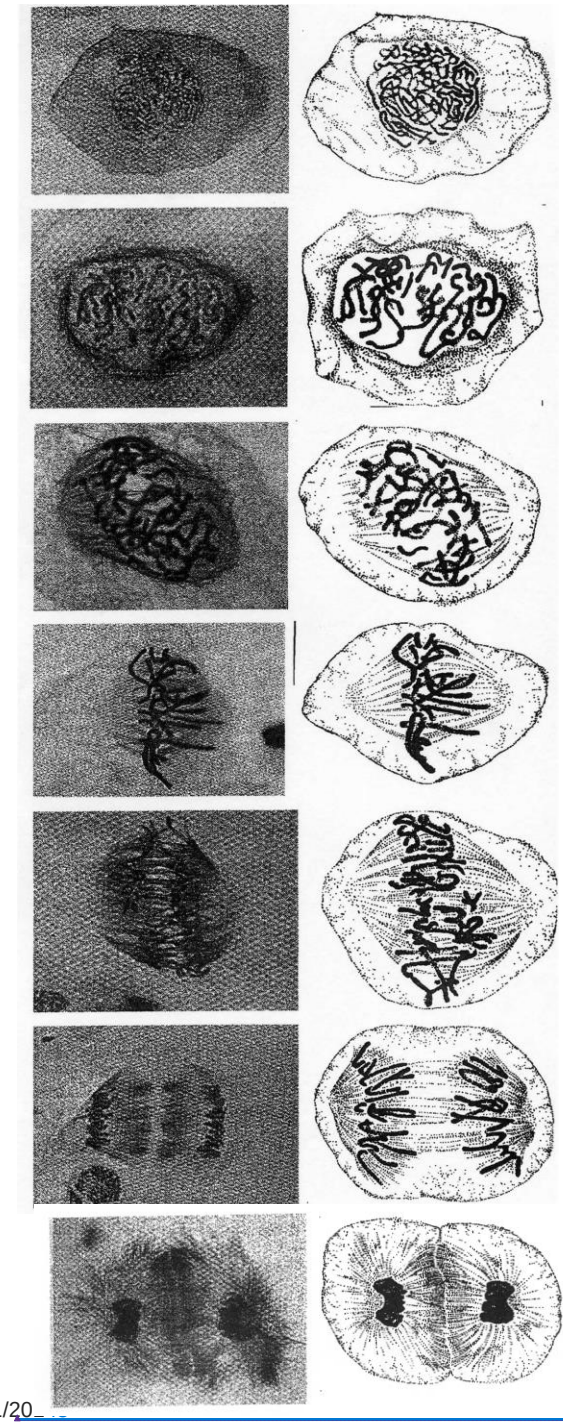

Early prophase

Mid prophase

Late prophase

Metaphase

Early anaphase

Late anaphase

Telophase

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(c) Cytokinesis

Cytokinesis usually occurs by **late telophase**, dividing the cytoplasm evenly between the two daughter cells that appear shortly after the end of mitosis.

In animal cells,

- **Cell surface membrane invaginates** towards the metaphase plate
- A ring of actin microfilaments contracts by interacting with myosin molecules.
- The **cleavage furrow deepens** until the parent cell is **pinched into two**, producing two daughter cells.

In plant cells,

- **Golgi vesicles** that contain cell wall material (cellulose) **move along microtubules**, towards the metaphase plate and fuse together to produce a **cell plate**.
- Cell plate **enlarges** as more vesicles fuse with it, until its **surrounding membrane fuses with cell surface membrane** along the perimeter of the cell.
- A new cell wall is formed between the two daughter cells.

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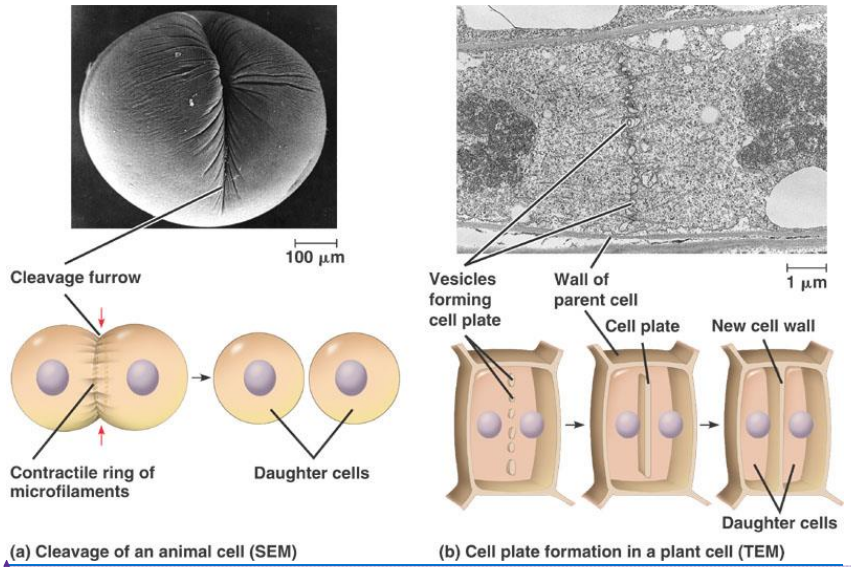

Diagram of animal and plant cytokinesis

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(d) Significance of mitosis

- Mitosis confers **genetic stability** between generations of cells.
- Each parent cell produces two **genetically identical** daughter cells with **same number and types of chromosomes as parent nucleus** (no variation in genetic information).
- The daughter cells have **identical genetic information** as the parent cell, due to **semi-conservative replication** of parental DNA during **synthesis phase of interphase**.
- This enables **growth, repair** and **asexual reproduction**.

(i) Organism **Growth**

- To grow from one cell to a multicellular organism, all daughter cells must be genetically identical to the parent cell. However, genetically identical cells are able to **differentiate** to different cell types due to **differential gene expression**.

(ii) Tissue **Repair**

- Cells that are **lost, damaged or worn-out** are **replaced** by genetically identical cells.

(iii) **Asexual reproduction**

- Involves **one single parent**, producing offsprings that are genetically identical to parent known as **clones**.
- This is common in:
  - plants - **vegetative propagation,** e.g. bulbs in onions,
  - less complex animals - **budding** in yeasts or **fragmentation** in starfish
  - and micro-organisms - **binary fission** in bacteria and yeasts).

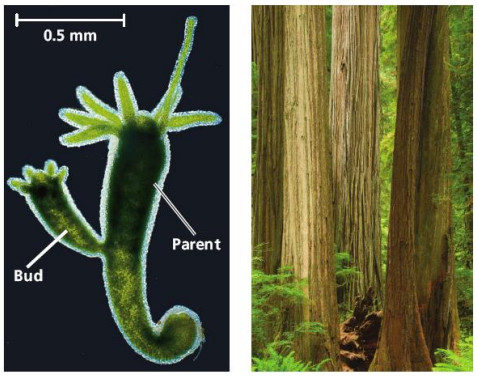

Diagram showing organisms that reproduce asexually

The organism on the left is the hydra, which reproduces by budding. The bud is a localised mass of mitotically dividing cells that develops into a small hydra and detaches from its parent.
The organism on the right is the redwood tree. All the trees in this circle of redwood arose asexually from a single parent tree, whose stump is in the centre of the circle.

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(e) Meiosis

Nuclear division:

- **Nucleus of a parent cell divides twice** to produce **four genetically non-identical haploid daughter nuclei**.
- Each daughter nuclei contains **half the number of chromosomes** in the parent nucleus by reducing two sets of chromosomes to **1 set of chromosomes**.
- It is vital for **sexual reproduction** and takes place in the **reproductive organs** of plants and animals.
- Meiosis occurs after **interphase**, followed by **cytokinesis**

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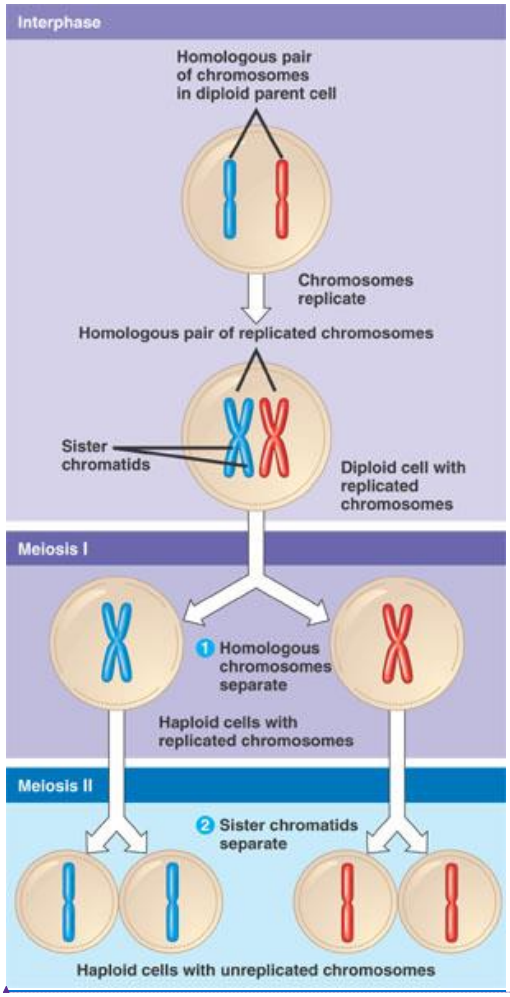

Overview of Meiosis

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(i) **Prophase I**

- Chromatin fibre becomes more tightly coiled, **condensing into chromosomes**.
- Each duplicated chromosome appears as **two identical sister chromatids joined at their centromeres**.
- **Homologous chromosomes pair** to form **bivalents** in a state called synapsis.
- **Crossing over** occurs **between non-sister chromatids of homologous chromosomes** resulting in **chiasmata** formation.
  - **the exchange of corresponding DNA segment between non-sister chromatids**.
- **Centrosome** organise microtubules into **spindle fibres** and the radial array of short microtubules extending from each centrosome are called **asters.**
- Centrosomes **migrate to opposite poles** of the cell by lengthening of microtubules.
  - In animal cells, each pair of centrioles migrates to opposite poles of the cell.
- **Nucleolus disperses** and **seems to disappear**.
- **Nuclear envelope fragments**.

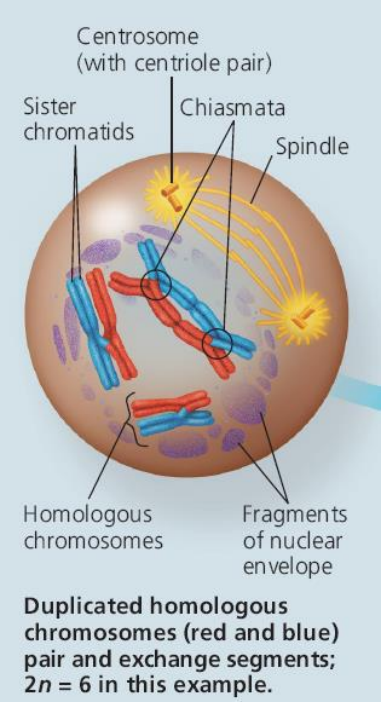

Diagram of Prophase I

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(ii) **Metaphase I**

- The **bivalents** (pairs of homologous chromosomes) **align** themselves at the **metaphase plate**, with one chromosome in each pair facing each pole.
- The arrangement of chromosome of each bivalent is **independent** of the arrangement of the other bivalents (i.e. **independent assortment**).
- Both chromatids of one homolog are attached to **kinetochore microtubules** from one pole; those of the other homolog are attached to microtubules from the opposite pole.
- Non-kinetochore microtubules interact with those from the opposite pole of the spindle.

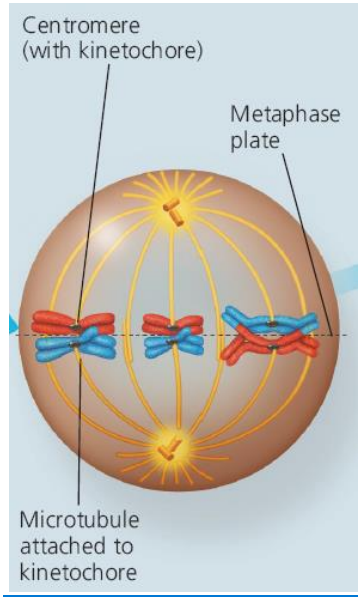

Diagram of Metaphase I

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(iii) **Anaphase I**

- **Each homolog of a bivalent separates / Homologous chromosomes separate** but not sister chromatids. Centromere of each chromosome does not separate.
- **Homologous chromosomes migrate toward opposite poles of the cell, with the centromere leading the way** as **kinetochore microtubules shorten**.
- **Non-kinetochore microtubules lengthen,** leading to cell **elongation**.

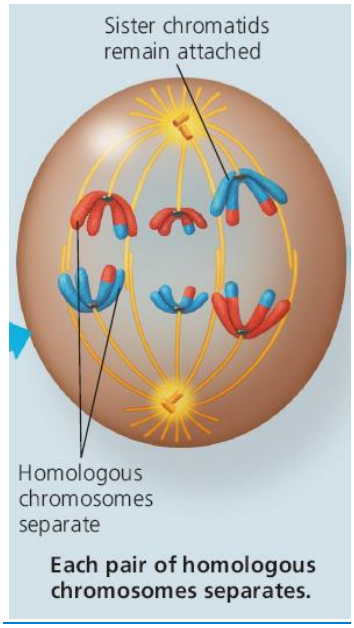

Diagram showing Anaphase I

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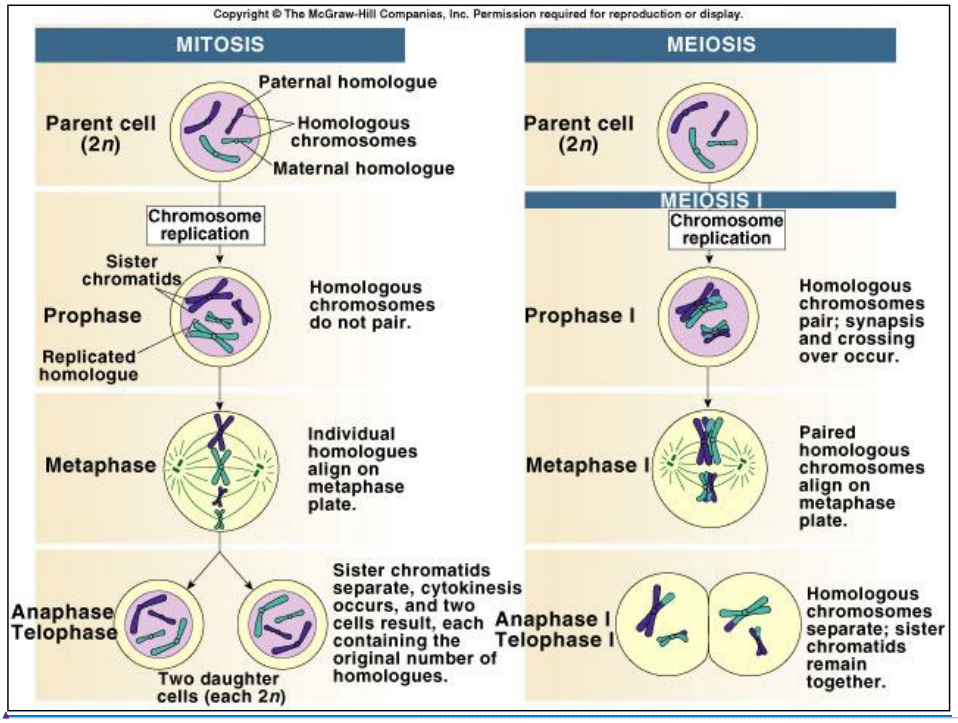
~~(ii)~~(iv) **Telophase I**

- In some species, **nuclear envelopes reforms** from the endomembrane system, forming **two nuclei**.
- Each nucleus has a **haploid** set of chromosomes (duplicated chromosomes).
- Thus meiosis I is known as the **reductional division** because it halves the number of chromosome sets per cell.
- Nucleolus **reappears**.
- Chromosomes become **less condensed** to form **chromatin**.
- Microtubules **disperse** by depolymerising.
- Cytokinesis usually occurs simultaneously with telophase I, forming two haploid daughter cells. No replication of DNA occurs between meiosis I and meiosis II.

- In other species, these processes (including the reforming of nuclear envelope) are skipped and the cell carries on directly to Prophase II.



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Comparison between Mitosis and Meiosis I

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~~(iii)~~(v) **Prophase II**

- Chromatin fibre becomes more tightly coiled, **condensing into chromosomes**.
- **Nucleolus disperses** and **seems to disappear**.
- **Nuclear envelope fragments**.

(vi) **Metaphase II**

- Microtubules from centrosome attach to **kinetochore** at the centromere of each chromatid of chromosome, becoming **kinetochore microtubules**. (Sister chromatids may no longer be identical as crossing over may have occurred in Prophase I).
- **Centromeres of chromosomes are aligned along the metaphase plate, perpendicular** to the metaphase plate in metaphase I by microtubules.
- Non-kinetochore microtubules interact with those from the opposite pole of the spindle.

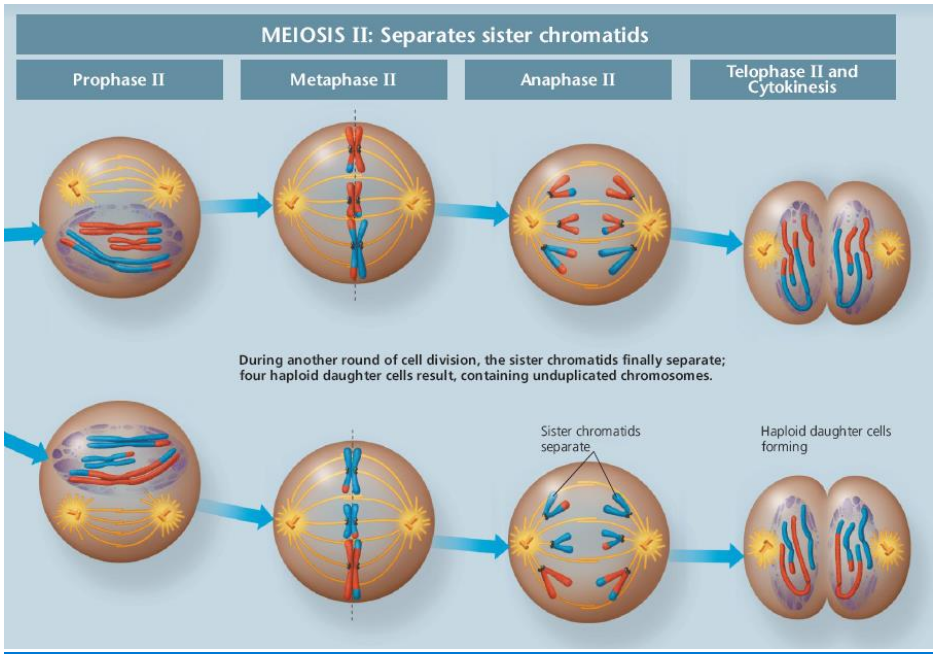

Diagram of Meiosis II

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(vii) **Anaphase II**

- **Centromere separates** and **two non-identical sister chromatids separate**, thus becoming two **daughter chromosomes**.
- **Daughter chromosomes migrate toward opposite poles of the cell, with the centromere leading the way** as **kinetochore microtubules shorten**.
- **Non-kinetochore microtubules lengthen,** leading to cell **elongation**.

(viii) **Telophase II**

- **Nuclear envelopes reform** from the fragments of the endomembrane system to form **two nuclei**.
- Nucleolus **reappears**.
- Chromosomes become **less condensed** to form **chromatin**.
- Microtubules **disperse** by depolymerising.
- **Four haploid daughter nuclei** will arise from one diploid parent nuclei.
- Cytokinesis then occurs as in mitosis.

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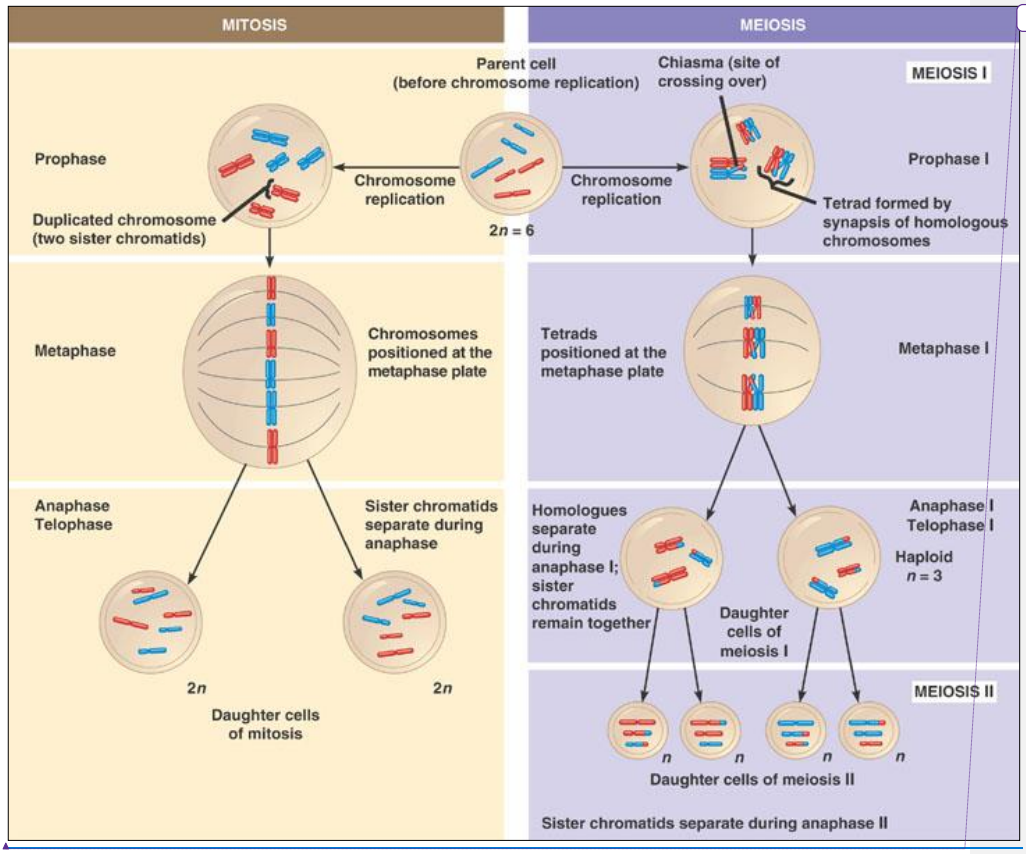

Comparison between Mitosis and Meiosis

~~(b)~~(f) Significance of meiosis

- The production of **haploid gametes** by meiosis is important prior to fertilisation in sexual reproduction, where **fusion of gametes** from different parents occurs to form a zygote.
- Meiosis ensures **maintenance of chromosomal number** in offspring and **prevent doubling of chromosomal numbers** during fertilisation

- Meiosis generates **genetic variation** in offspring by producing **recombinant gametes** through:
  (i) **Crossing over between non-sister chromatids of homologous chromosomes**
  (ii) **Independent assortment of homologous chromosomes**

There are three processes that contribute to the genetic variation arising from **sexual reproduction**:

(i) **Crossing over between non-sister chromatids of homologous chromosomes**

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(ii) **Independent assortment of homologous chromosomes** and
(iii) **Random fertilisation**

- Note: The source of **new** genetic variation is due to **spontaneous mutations** of DNA (e.g. errors that occur during semi-conservative replication), which results in **different nucleotide sequences** of a gene (alleles).
- Genetic variation in a population (genetically different individuals of the same species) is the basis for **natural selection**.

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(i) **Crossing over**

- **Crossing over** occurs **between non-sister chromatids of homologous chromosomes** resulting in **chiasmata** formation, during **prophase I of meiosis**.
- **Chiasmata** (singular = chiasma), the X-shaped regions exist at the point where crossing over has occurred.
- Crossing-over result in the **exchange corresponding DNA segment** of chromatids, thus **separating alleles of linked genes** and creating **new allelic combinations** in the chromatid.

- Crossing-over is a process that involves:
  - Breakage of a corresponding DNA segment from each non- sister chromatid,
  - Exchange of the corresponding DNA segment between non-sister chromatids, and
  - Rejoining of the DNA segment to the other chromatid, resulting in **chiasmata**.

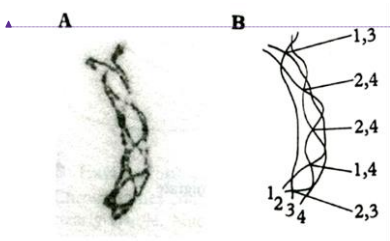

Figure 23.7 Chiasmata. **A** is a photomicrograph of a bivalent at late prophase from testis of grasshopper. **B** is an interpretive diagram. Chiasmata are numbered according to which chromatids are in contact. Note that chiasmata can be formed between any two non-sister chromatids. (*Bernard John, Australian National University*)

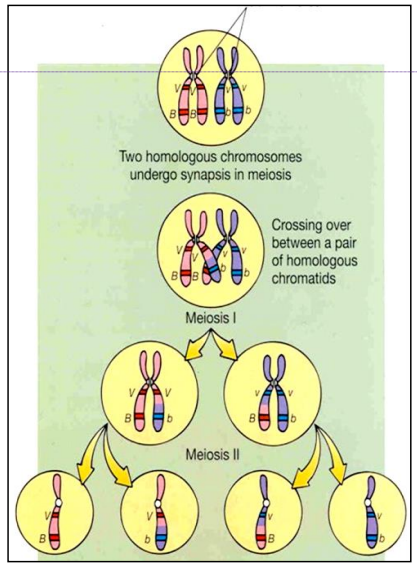

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Diagram of crossing over

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In the diagram above,

- Parental chromosome contains linked genes, V and B. One homolog contains dominant V and B alleles while the other contains recessive v and b alleles.
- Crossing over occurs between two non-sister chromatids, resulting in an exchange of allele for the gene B. This result in two **recombinant chromosomes**; one contains V and b alleles and the other contains v and B alleles.
- **Four different gametes** with different allelic combinations are produced: VB, Vb, vB and vB.

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(ii) **Independent assortment of homologous chromosomes**

- Independent assortment is the **random** orientation of pairs of homologous chromosomes along the metaphase plate **independent of other bivalents** during **metaphase I**
- Independent assortment of homologous chromosomes occurs during **metaphase I** leading to **independent segregation** during **anaphase I**.

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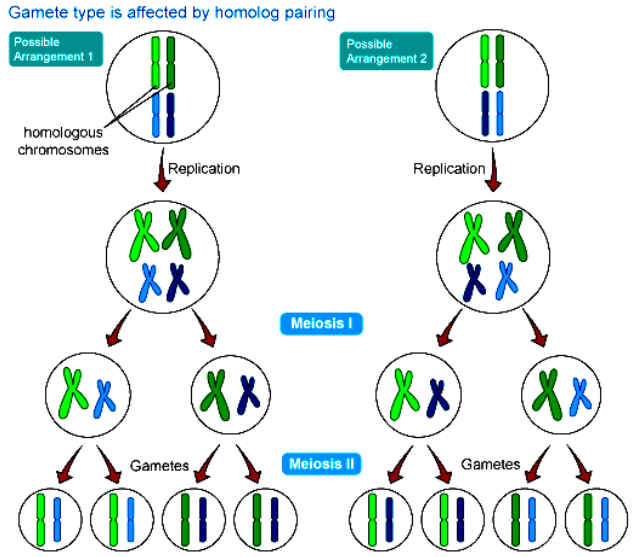

Diagram showing independent assortment and independent segregation

In the diagram above,

- During prophase I: Bivalents are aligned where the maternal homolog and paternal homolog faces each side of the pole
- At metaphase I: The two pairs of homologous chromosomes randomly orientate themselves along the metaphase plate. Thus, the first arrangement is **equally as likely** as the second arrangement.
- During anaphase I: Homologous chromosomes separate independently of other bivalents (i.e. independent segregation).
- Note: Only two of the four combinations of daughter cells shown would result from meiosis of a single diploid cell, because a single parent cell would have one or the other possible chromosomal arrangement at metaphase I, but not both.
- However, the population of daughter cells resulting from meiosis of a large number of diploid cells contains all **four types of gametes** in approximately **equal** numbers.

- The number of possible chromosomal combinations in a gamete is 2^n, where n = haploid number of the organism.

- In humans, the number of possible chromosomal combination is 2^{23}, thus 2^{23} different combinations of gametes can be produced by an individual.

(iii) **Random fertilisation**

- During fertilisation, **genetic material from two different individuals is combined** by **random fusion of gametes**.
  - In humans, the number of possible combinations of zygote is 2^{23} x 2^{23}.

(g) Non-disjunction

- An error during meiosis that result in chromosomal aberration, **aneuploidy**.

~~**Chromatin** is the **complex of DNA and proteins**:~~

- **Non-disjunction** occurs when:
  - A pair or pairs of homologous chromosome fail to separate during Anaphase I of meiosis or
  - sister chromatids fail to separate during Anaphase II of meiosis.
- This results in aberrant gametes:
  - gamete receives two of the same type of chromosome / extra chromosome (n+1) or
  - gamete with no copy of a particular type of chromosome / lacks a chromosome (n-1)

- If an aberrant gamete fuses with a normal gamete, the zygote will have an abnormal number of chromosomes (2n+1) or (2n-1), a condition known as **aneuploidy**.

  For example,
  - **Down syndrome** (trisomy 21),
  - Turner syndrome (XO),
  - Edwards syndrome (trisomy 18) and
  - Patau syndrome (trisomy 13).

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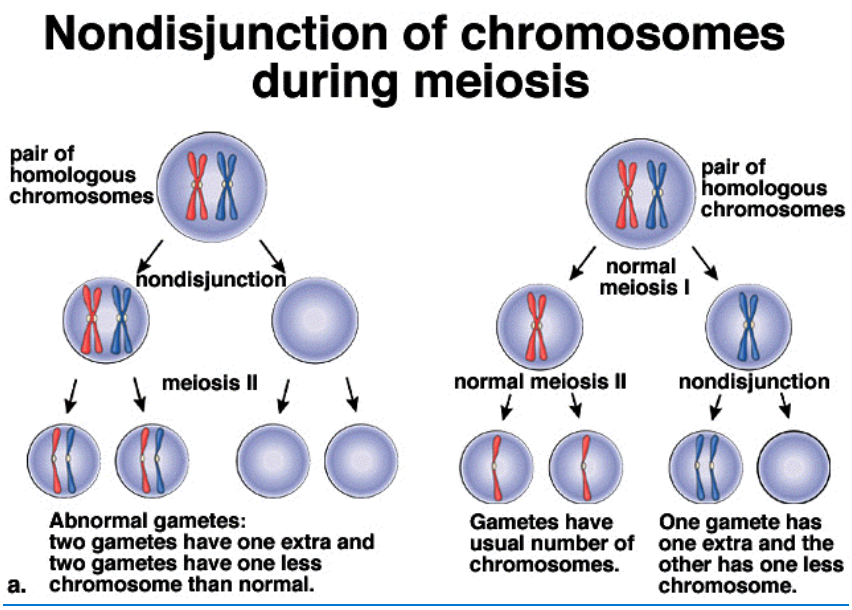

Diagram showing Non-disjunction

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The Control of the Mitotic Cell Cycle

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~~All new cells are derived from pre-existing cells through cell division, a part of the **cell cycle** which includes:~~

- ~~**Interphase** - cell growth and synthesis of cell materials~~
- ~~**Nuclear division** - nucleus divides first to form two nuclei~~
- ~~**Cytokinesis** - cytoplasm divides to form two daughter cells~~

~~The nucleus is responsible for carrying out cell division.~~

~~(a) Chromatin~~

~~Eukaryotic DNA, the cellular heredity material, contains **millions of nucleotides**. In human cells, DNA of total length 1.8m is packed into a compact structure to fit into the nucleus of 6µm.~~

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~~**Chromatin** is the **complex of DNA and proteins**:~~

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- ~~Present during **interphase**~~
- ~~Present during **interphase**~~
- ~~**Dispersed** as a mass of long, thin fibres~~
- ~~Able to **condense** by coiling and folding and **decondense** when necessary.~~

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~~**Figure 1**~~

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- Negatively-charged **double-helix DNA** (2nm) is wound twice around **histone proteins** that have **positively-charged lysine and arginine** residues to form a **nucleosome**.
  - **Nucleosomes** are joined by **linker DNA**, giving rise to **'beads-on-string' (10nm)**.
- Nucleosomes and linker DNA are coiled into **solenoid structure**, which are **30nm chromatin fibres**.
  - **Loosely condensed euchromatin** is lightly-stained under light microscope.
  - Genes located here are **frequently transcribed**.

Figure 2: Nucleosome on chromatin fiber (10nm) coiling into 30nm chromatin fiber

- 30nm fibres are folded into **looped domains** are attached to **scaffolding proteins**, forming **300nm chromatin fibers**.
- 300nm chromatin fibres are further folded to form **700nm fibres** found on chromatids on metaphase **chromosome**.

Figure 3: Fibers are looped around a protein scaffold, further coiled to form a sister chromatid.

Packing is highly specific and precise, resulting in particular genes always ending up at the same place in a chromosome.

(b) Chromosome Structure

During cell division, chromatin condenses into **chromosome**, which may exist as **unduplicated** or **duplicated.**

(i) **Unduplicated** chromosome
- **Single DNA molecule** (present during Anaphase and Telophase)

(ii) **Duplicated** chromosome (also known as **replicated** chromosome)
- Four-arm structure **visible under light microscope**
  - Figure 4: Chromosome micrograph
  - **Two sister chromatids**
  - **Identical** due to **semi-conservative DNA replication during synthesis phase of Interphase**
- Centromere holds two sister chromatids together
- constricted region of highly repetitive (satellite) DNA sequence
  - **Kinetochore**
  - Wrapped around the centromere
  - consists of **proteins**, with higher organisms having kinetochore containing **proteins and some RNA in a trilaminar structure**

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- **~~Interface between attached spindle fibre and DNA of the centromere~~**

~~The **kinetochore** and **centromere** are involved in **chromosome movement** during cell division.~~

~~**Figure 5:** Chromosome structure~~

~~(c) Chromosome Number~~

~~The number of chromosomes in **somatic cells** (i.e. all cells except sex cells) is fixed for a species. **Diploid** organisms have cells that contain **two sets of chromosomes**. The total number of chromosomes is known as the **diploid number**, **2n**, where **n** depicts **a single set of chromosomes**.~~

~~For example, humans have 46 chromosomes in each cell. Since humans are **diploid** organisms, the **diploid number** is 46. Each **somatic** cell contains **two sets of chromosomes** (2n = 46). Each set contains 23 different chromosomes (n = 23). This can be clearly seen in a **karyotype**, an ordered display of chromosomes.~~

~~**Figure 6: Karyotype of a human male**~~

~~**N** is also known as the **haploid number**. **Gametes** (sex cells) contain **a single set of chromosome**s, thus they are known as **haploid**.~~

~~For example, human spermatozoan cell or an oocyte is a **haploid gamete**, with **a single set of chromosomes**. The **haploid number** is 23 (n = 23).~~

~~Fill in Table 1 below. The first column has been done as an example.~~

~~**Table 1: Chromosome numbers of human, fruit fly and dog**~~

~~(d) Homologous Chromosomes~~

~~(e) Each chromosome type exists as a pair of **homologous chromosomes**, with each chromosome known as a **homologue**. We **inherit one chromosome of each pair from each parent.**~~

~~The **two sets of chromosomes** present in **diploid** organism is a result of sexual reproduction. Each set of chromosomes is from each parent. Thus, the 46 chromosomes in our human somatic cells are actually two sets of 23 chromosomes – a **maternal set** (from the female parent) and a **paternal set** (from the male parent).~~

~~The **two sets of chromosomes** present in **diploid** organism is a result of sexual reproduction. Each set of chromosomes is from each parent. Thus, the 46 chromosomes in our human somatic cells are actually two sets of 23 chromosomes – a **maternal set** (from the female parent) and a **paternal set** (from the male parent).~~

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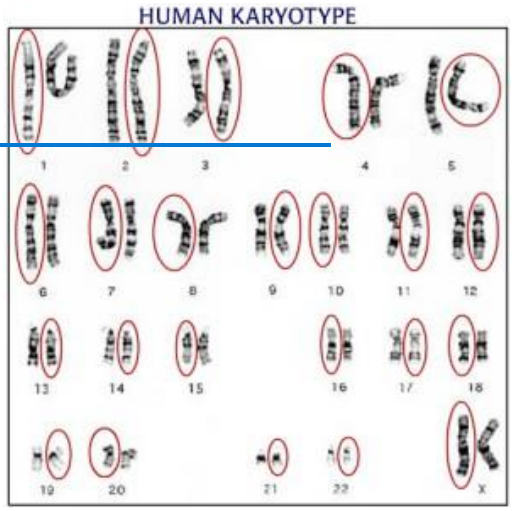

~~Each chromosome type exists as a pair of~~ **~~homologous chromosomes~~**~~, with each chromosome known as a~~ **~~homologue~~**~~. We~~ **~~inherit one chromosome of each pair from each parent~~**~~.~~

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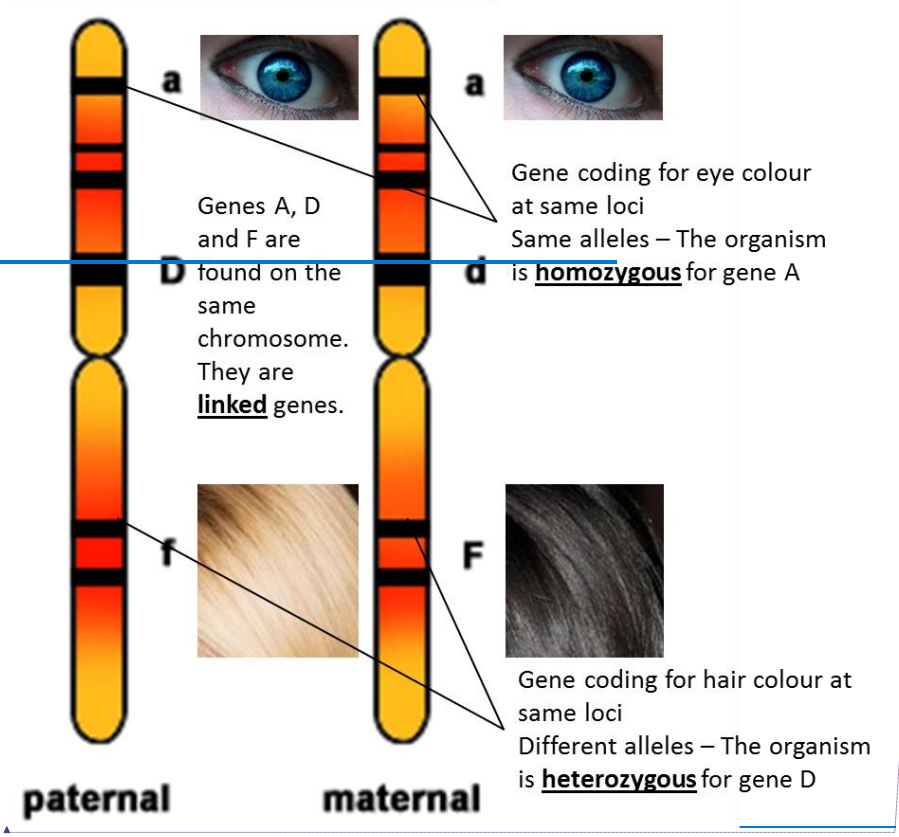
~~Homologues~~

- **~~Same length, centromere position, and staining pattern~~** ~~and~~ **~~genes for the same characteristics at corresponding loci~~**~~.~~
- ~~Different nucleotide sequence →~~ **~~alternative forms of the same gene (i.e. alleles)~~**~~.~~



- ~~**Homozygous** → same alleles on a pair of homologous chromosomes~~

~~**Heterozygous** → different alleles on a pair of homologous chromosomes~~

- ~~**Linked** → two alleles found on same chromosome~~
- ~~Exception: **Sex Chromosomes**. All other chromosomes known as **autosomes**~~
  - ~~Human females: Homologous pair of **X-chromosomes**~~
  - ~~Human males: one **X-chromosome** and one **Y-chromosome**~~

~~3. The Cell Cycle~~

~~The **cell cycle** is a sequence of events between successive cell division:~~

- ~~Duration: depends on tissue type and age of an organism.~~
- ~~Three stages: **interphase**, **nuclear division** and **cytokinesis**.~~
- ~~Two types of nuclear division: **mitosis** (all **somatic** cells) and **meiosis** (in **sexual reproductive organs**).~~

~~(a) Interphase~~

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~~Cells prepare for mitosis or meiosis in 3 sub-phases:~~

- ~~**First growth phase** or **G_1 phase**~~
- ~~**Synthesis** or **S phase**~~
- ~~**Second growth phase** or **G_2 phase**~~

~~Phase~~	~~Events that occur~~
~~G_1~~	~~**Synthesis of new organelles**~~**~~Nucleolus actively synthesises ribosomal RNA~~** ~~for synthesis of ribosomal subunits~~ ~~**Increase in cytoplasmic volume**, resulting in cell growth~~
~~**Synthesis**~~	~~**DNA semi-conservative replication** occurs → DNA content **doubles**~~ ~~**Histone proteins are synthesized**~~ ~~Newly synthesized DNA molecules are wound tightly around the histone proteins~~ ~~Each chromatin fibre is composed of **two identical DNA molecules**.~~
~~G_2~~	~~**Intensive synthesis / division of organelles**, e.g. division of mitochondria and chloroplasts (in plants) occur~~ ~~**Centrosome replicates** to form 2 centrosomes (in animals and lower plants, each centrosome is made up of **a pair of centrioles**)~~ ~~**Synthesis of spindle proteins** (tubulin)~~ ~~**Synthesis of ATP** for energy~~

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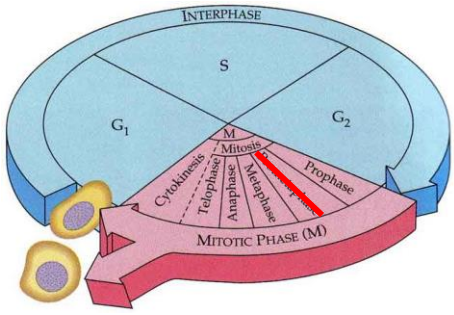

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~~**(c) Mitosis**~~

~~**Nuclear division:**~~

- ~~Process: **Parent cell nucleus divides once**~~
- ~~Four main phases: **prophase**, **metaphase**, **anaphase**, **telophase**~~
- ~~Product: **Two genetically identical diploid daughter nuclei**~~
- ~~**same number of chromosomes and same genes** as parent nucleus.~~

~~(i) Prophase~~

~~Chromosome:~~

- ~~Chromatin become **more tightly coiled, condensing into duplicated chromosomes**~~

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- Appears as **two identical sister chromatids joined together at their centromeres**.

Spindle fibres:

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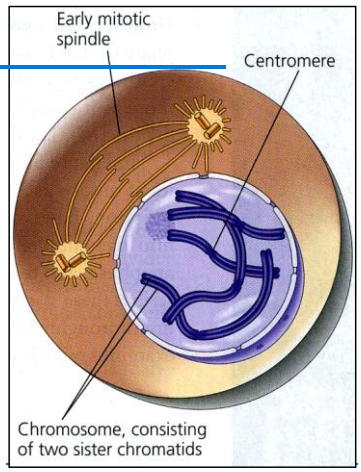
- **Formation of mitotic spindle which are centrosomes and extending microtubules** called **asters**.
- Microtubules lengthen → centrosomes **migrate to opposite poles** of the cell.

Nucleus:

- **Nucleolus disperses** and **seems to disappear**.
- **Nuclear envelope fragments** into smaller vesicles.



(ii) Metaphase (**longest** phase in mitosis)

- Microtubules from centrosome attach to **kinetochore** at the centromere of each chromatid of chromosome, becoming **kinetochore microtubules**.
- Chromosomes are aligned by the microtubules until the **centromeres of chromosomes are laid along the metaphase plate** (imaginary plane **equidistant** between the two spindle's two poles).

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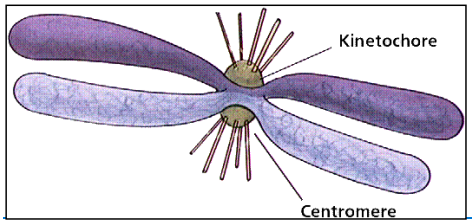

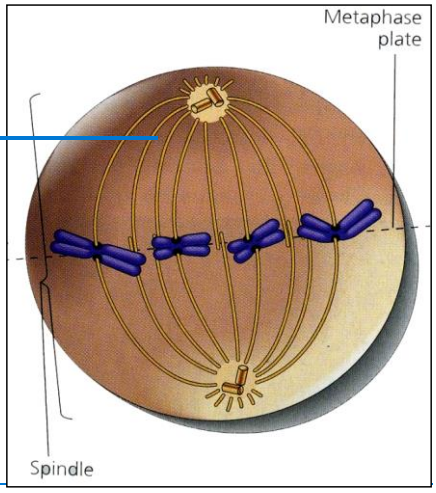

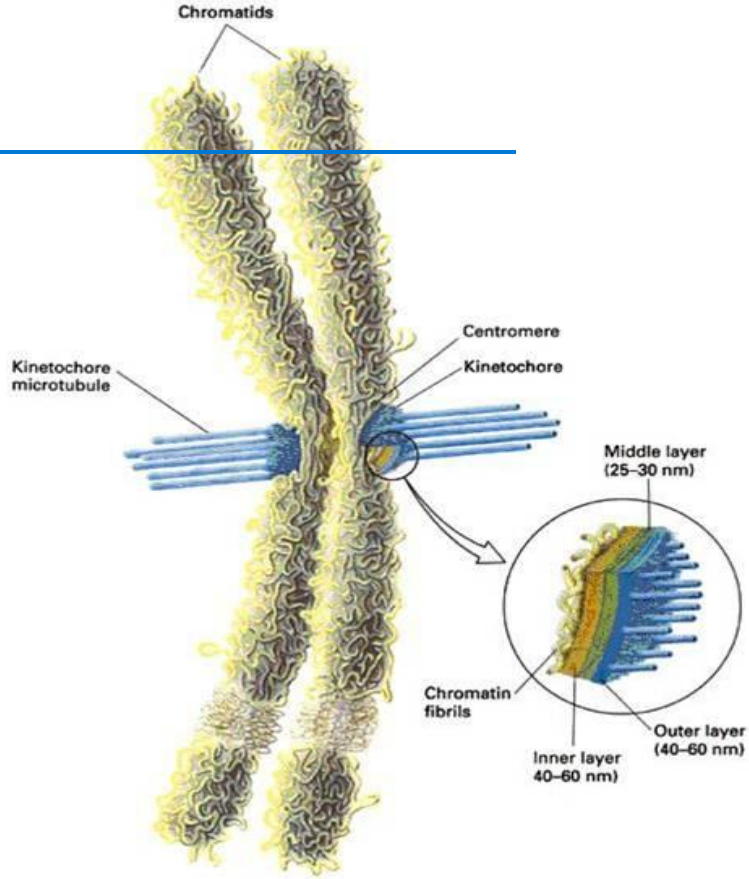

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~~(iii) Anaphase (**shortest** phase in mitosis)~~

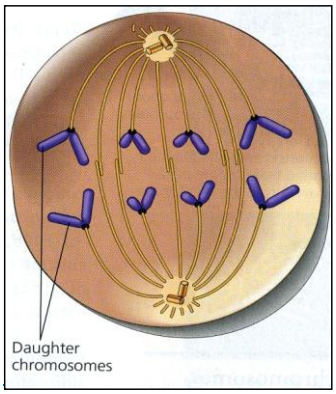
~~Each chromosome → two separate daughter chromosomes~~

- ~~**Centromere separates** → **two sister chromatids part suddenly** → two separate **daughter chromosome**.~~

~~Microtubules:~~

- ~~**Kinetochore microtubules shorten** → pulling on centromere → two separated daughter chromosomes **migrate toward opposite poles of the cell**, **with the centromere leading the way** .~~
- ~~**Non-kinetochore microtubules lengthen** → cell **elongation**.~~

~~After anaphase, the two poles of the cell have equivalent and complete set of chromosomes.~~



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~~(iv) Telophase~~

- ~~**Nuclear envelopes reforms** from the fragments of the parent cell's nuclear envelope and other portions of the endomembrane system, forming **two nuclei**.~~
- ~~Nucleolus **reappears**.~~
- ~~The chromosomes becomes **less condensed** (i.e. exists as chromatin).~~
- ~~Mitotic spindle microtubules **disintegrate**.~~
- ~~Nucleolus **reappears**.~~

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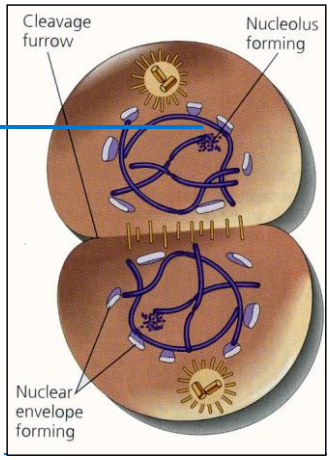

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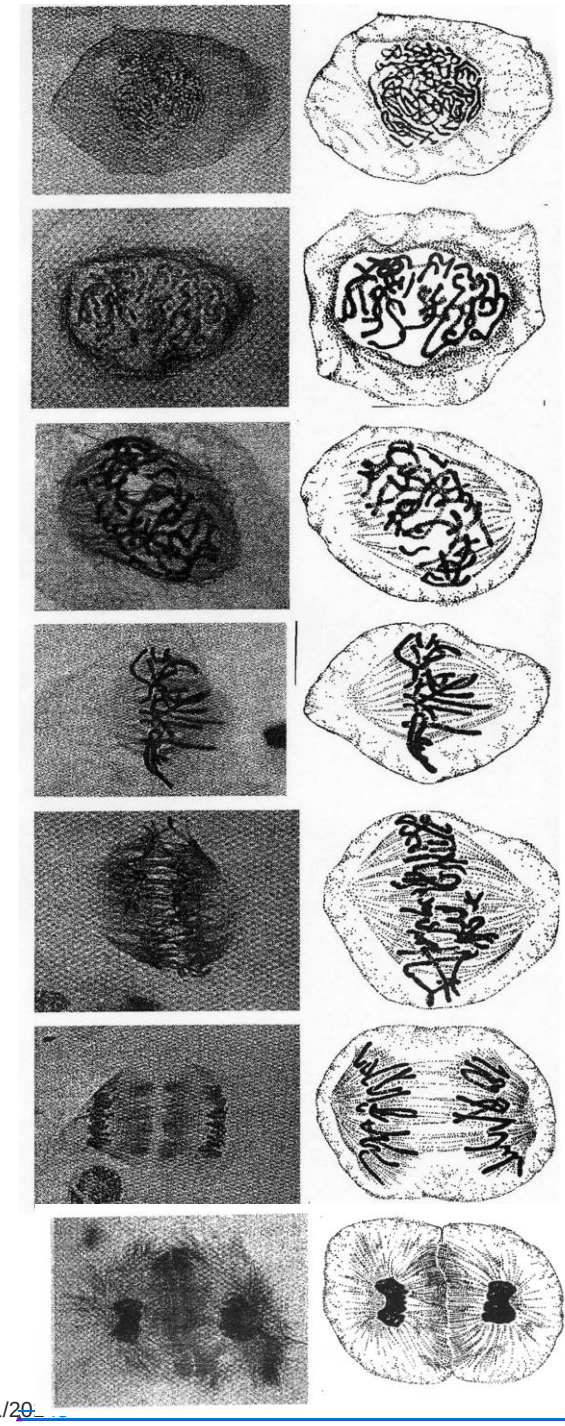

Early prophase

Mid prophase

Late prophase

Metaphase

Early anaphase

Late anaphase

Telophase

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~~(d) Cytokinesis~~

~~Cytokinesis~~ ~~usually occurs by **late telophase**, so the two daughter cells appear shortly after the end of mitosis. In this process, the cytoplasm is distributed evenly between the daughter cells.~~

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~~In animal cells,~~

- ~~**Cell surface membrane invaginates** towards the region once occupied by the metaphase plate, using **a ring of actin microfilaments that interact with myosin** molecules, thereby causing the **ring to contract**.~~
- ~~The **cleavage furrow deepens** until the parent cell is **pinched into two**, producing two completely separated daughter cells.~~

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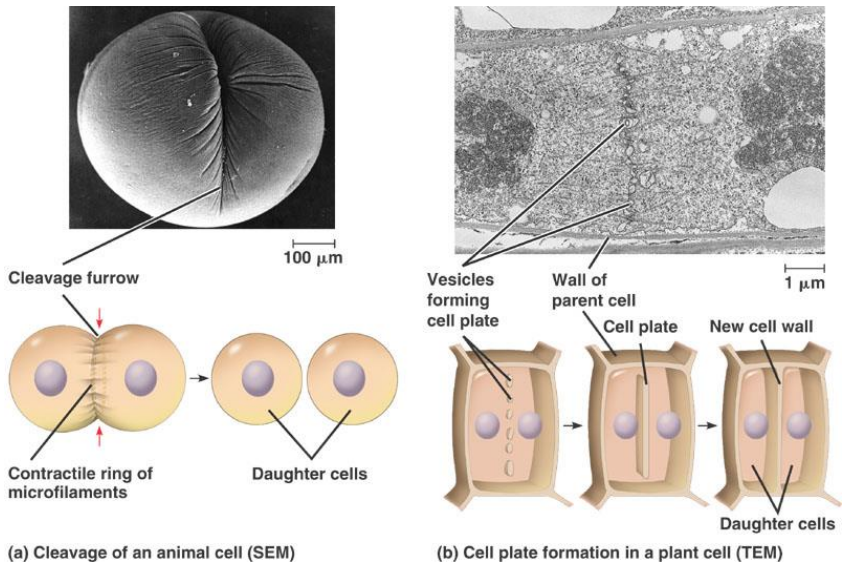
~~In plant cells,~~

- ~~**Vesicles from the Golgi apparatus move along microtubules**, towards the region once occupied by the metaphase plate.~~
- ~~These vesicles (**containing pectin, hemicellulose and cellulose**) fuse together, producing a **cell plate**, which will become the middle lamella that joins plant cells togethe.~~
- ~~Cell wall materials carried in the vesicles collect in the cell plate as it grows.~~
- ~~The cell plate **enlarges** until its **surrounding membrane fuses with the plasma membrane along the perimeter of the cell**.~~
- ~~Two daughter cells results, each with its plasma membrane.~~
- ~~Meanwhile a new cell wall arising from the contents of the cell plate has formed between the daughter cells.~~



(a) Cleavage of an animal cell (SEM)

(b) Cell plate formation in a plant cell (TEM)

~~(e) Meiosis~~

~~Meiosis is a type of **nuclear division** where the **nucleus of a parent cell divides twice** to produce **four genetically non-identical haploid daughter nuclei**.~~

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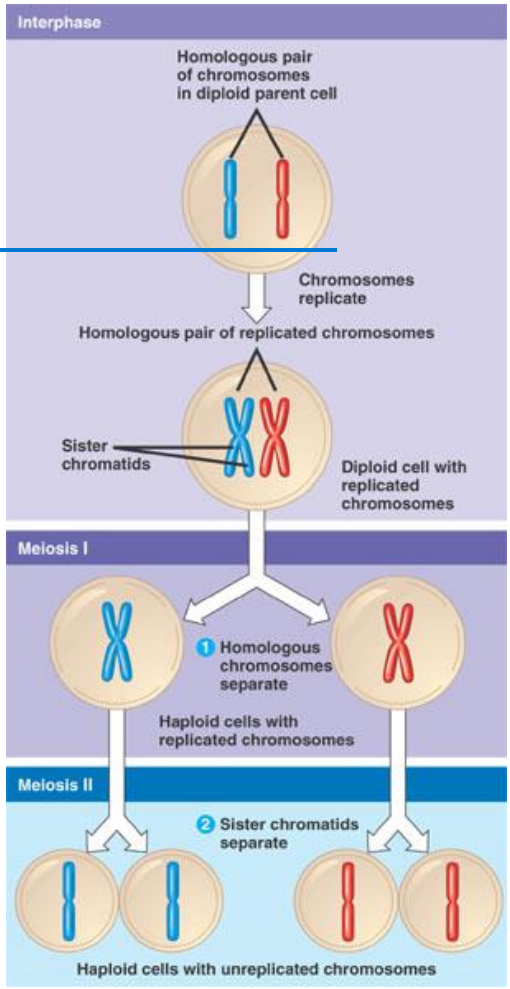
- ~~contains **half the amount of genetic material** found in the parent nucleus, i.e. it has only **1 complete set of chromosomes.** It is vital for **sexual reproduction** and takes place in the **reproductive organs** of plants and animals. In animals, gametes are formed in the male and female reproductive organs, testes and ovary, respectively. Testes produce sperm while ovary produces ovum. In flowering plants, male gametes (pollen) are produced in the anther (pollen sac) and female gametes (ovule) are produced in the ovary.~~
- ~~Each daughter nucleus contains **half the amount of genetic material** found in the parent nucleus, i.e. it has only **1 complete set of chromosomes**.~~
- ~~Like mitosis, meiosis is **preceded by interphase** and **followed by cytokinesis**.~~



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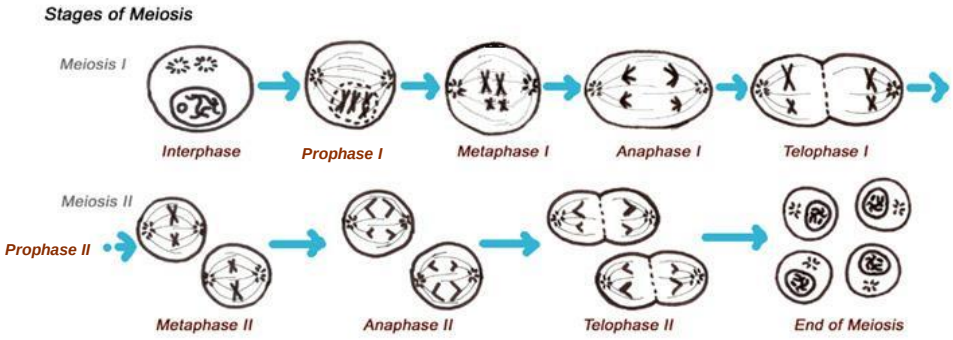

~~(i) **Prophase I**~~

- ~~The chromatin fibres become **more tightly coiled, condensing into chromosomes**.~~
- ~~Each duplicated chromosome appears as **two identical sister chromatids joined together at their centromeres**.~~
- ~~In mid-prophase, **homologous chromosomes pair** to form **bivalents** (in **synapsis**, i.e. held tightly together by proteins along their lengths, aligned gene by gene).~~
- ~~When homologous chromosome pair, **chiasmata** may be formed that may result in **crossing over**, i.e. **the exchange of corresponding segments of genetic materials between non-sister chromatids.**~~
- ~~The **nucleolus disperses** such that it **seems to disappear**.~~
- ~~Each duplicated chromosome appears as **two identical sister chromatids joined together at their centromeres**.~~
- ~~In mid-prophase, **homologous chromosomes pair** to form **bivalents** (in **synapsis**, i.e. held tightly together by proteins along their lengths, aligned gene by gene).~~
- ~~When homologous chromosome pair, **chiasmata** may be formed that may result in **crossing over**, i.e. **the exchange of corresponding segments of genetic materials between non-sister chromatids**.~~
- ~~The **spindle fibres** begin to form; it is composed of the **centrosomes and the microtubules that extend from them**.~~
- ~~The centrosomes then **migrate to opposite poles** of the cell.~~
- ~~The **nucleolus disperses** such that it **seems to disappear**.~~
- ~~**Nuclear envelope fragments** into smaller vesicles which are indistinguishable from bits of endoplasmic reticulum.~~

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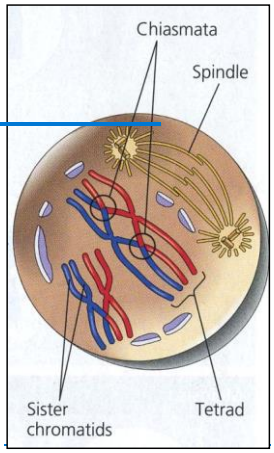
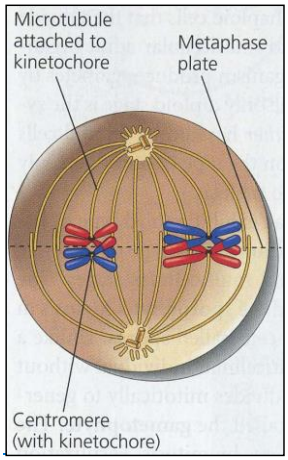


~~(ii)~~ **~~Metaphase I~~**

- ~~The bivalents (homologous pairs of chromosomes) arrange themselves at the~~ **~~metaphase plate~~**~~, with one chromosome in each pair facing each pole.~~
- ~~The arrangement of chromosome of each bivalent is~~ **~~independent~~** ~~of the arrangement of the other bivalents (i.e.~~ **~~independent assortment~~**~~).~~
- ~~Both chromatids of one homologue are attached to~~ **~~kinetochore microtubules~~** ~~from one pole; those of the other homologue are attached to microtubules from the opposite pole.~~



~~(iii)~~ **~~Anaphase I~~**

- **~~Each homologue of a bivalent separates~~** ~~but sister chromatids remain attached at their centromeres. (The centromere of each chromosome does not divide.)~~
- ~~As a spindle fibre shortens, each homologue of each bivalent separates and~~ **~~moves toward opposite poles, guided by the spindle fibres, with the centromere leading the way~~**~~.~~

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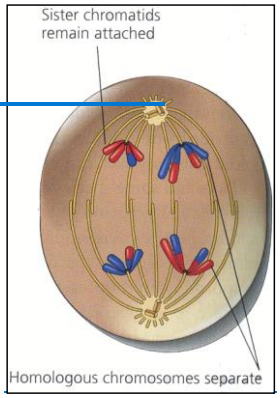

~~(iv) **Telophase I**~~

- ~~In some species, **nuclear envelopes reforms** from the fragments of the parent cell's nuclear envelope and other portions of the endomembrane system, forming **two nuclei**. Each nucleus now has a **haploid** set of chromosomes. Thus meiosis I is known as the **reductional division** because it halves the number of chromosome sets per cell.~~
- ~~The chromosomes may become **less condensed** (i.e. exists as chromatin), spindle fibres may **disintegrate**, and the nucleolus may **reappear**. In other species, these processes (including the reforming of nuclear envelope) are skipped and the cell carries on directly to Prophase II.~~
- ~~Cytokinesis usually occurs simultaneously with telophase I, forming two haploid daughter cells. No replication of DNA occurs between meiosis I and meiosis II.~~

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~~(v) **Prophase II**~~

- ~~Chromatin condenses, nucleolus disperses and the nuclear envelope fragments.~~
- ~~Microtubules reorganise to form spindle fibres, which attach to the centromeres holding **two chromatids** (may no longer be identical sister chromatids as crossing over may have occurred in Prophase I) together.~~

~~(vi) **Metaphase II**~~

- ~~The centromeres of chromosomes are positioned along the metaphase plate, which is **perpendicular** to the metaphase plate in metaphase I.~~

~~(vii) **Anaphase II**~~

- ~~The **centromere of each chromosome separates** and the **two chromatids of each chromosome part suddenly**. Each chromatid now becomes a **daughter chromosome**.~~
- ~~The two separated daughter chromosomes begin **migrate toward opposite poles of the cell**, **with the centromere leading the way.** This movement occurs as their **kinetochore microtubules shorten**.~~
- ~~Unlike mitosis, the chromatids that separate here may or may not be identical.~~

~~(viii) **Telophase II**~~

- ~~**Nuclear envelopes reforms** from the fragments of the parent cell's nuclear envelope and other portions of the endomembrane system, forming distinct nuclei.~~
- ~~The chromosomes becomes **less condensed** (i.e. exists as chromatin).~~

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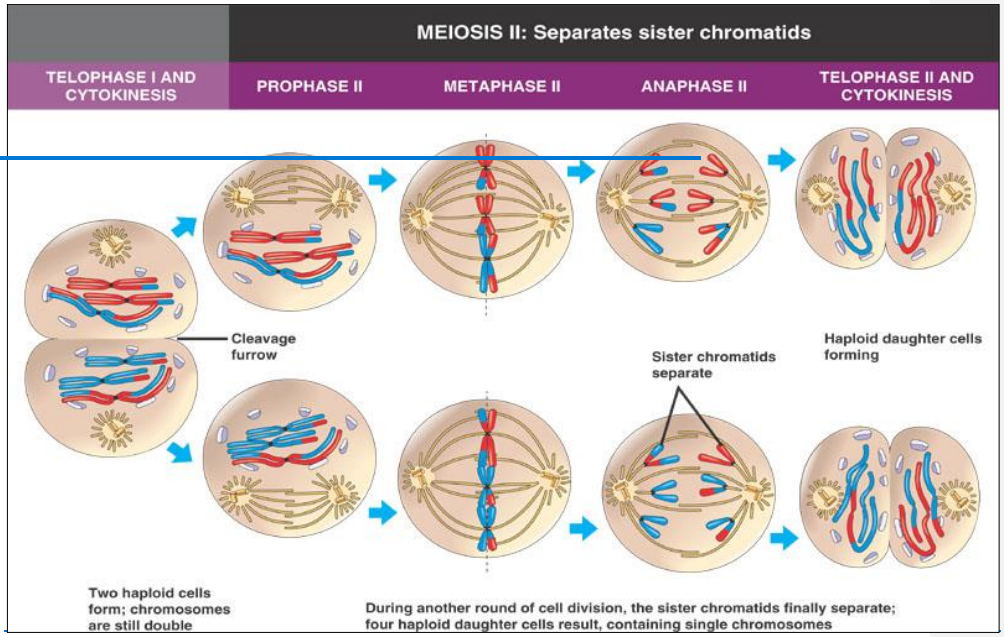
- ~~Spindle fibres **disintegrate**.~~
- ~~Nucleolus **reappears**.~~
- ~~**Four haploid daughter nuclei** will arise from one diploid parent nuclei.~~
- ~~Cytokinesis then occurs as in mitosis.~~



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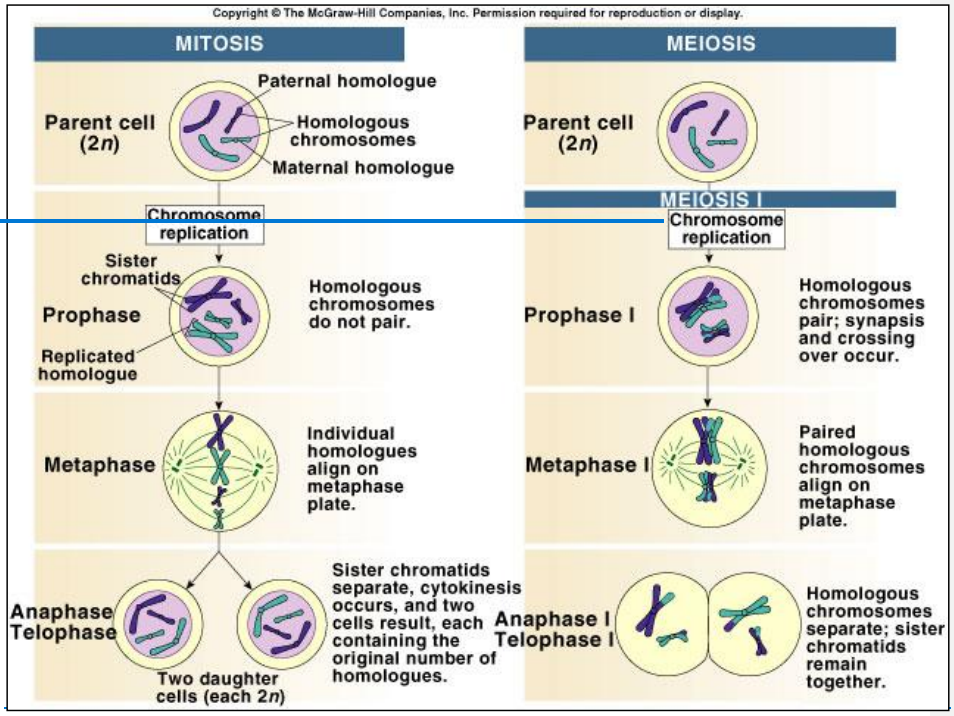

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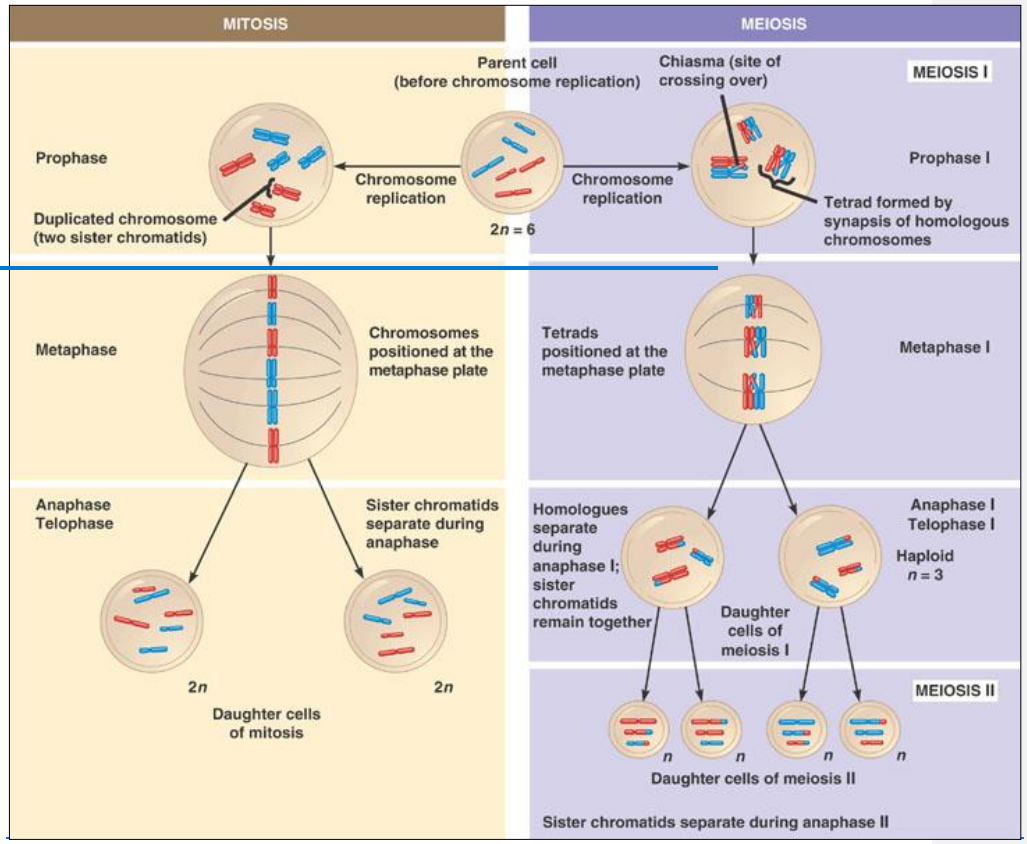

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~~(f) Non-disjunction~~

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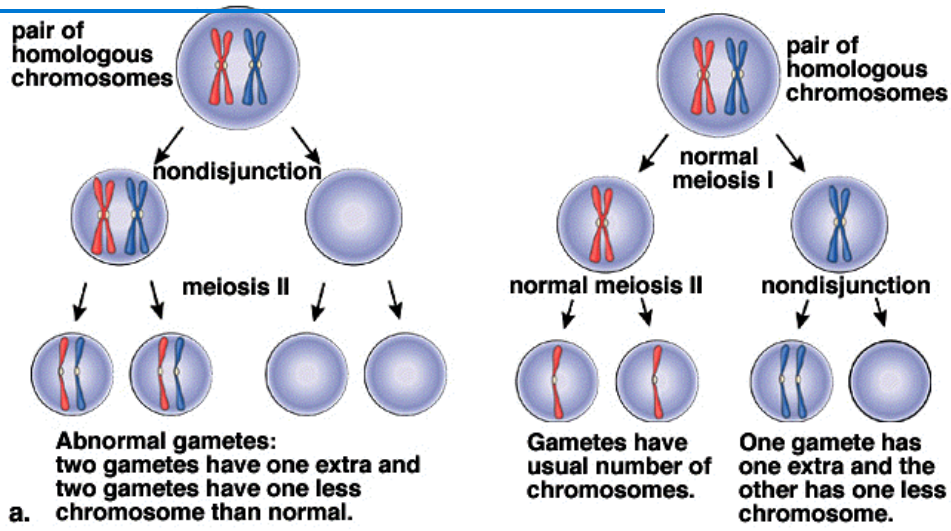
~~**Non-disjunction** occurs when homologous chromosome pairs do not separate properly during either Anaphase I or when non-identical sister chromatids do not separate properly during Anaphase II. This results in an **aneuploid** gamete, where the gamete has either a loss of a single chromosome (n-1) or a gain in a single chromosome (n+1).~~

~~In the event that an aneuploidic gamete is fertilized, a number of syndromes might result. These include individuals with Turner syndrome (XO), Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and Patau syndrome (trisomy 13). Most aneuploidic zygotes do not survive.~~

Nondisjunction of chromosomes during meiosis



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~~4. Significance of Nuclear Division~~

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~~The two types of nuclear division perform different biological function.~~

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~~(a) Significance of mitosis~~

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~~Mitotic cell cycle is important to the cells as it ensures **genetic stability** with each generation of cells. This enables growth, repair and asexual reproduction to occur.~~

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- ~~**Genetic stability** exists since mitosis makes each parent cell produce two **genetically identical** daughter cells (i.e. **no variation in genetic information**).~~

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- ~~Each daughter nucleus contains identical number of chromosomes to parent cell.~~

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- ~~The chromosomes in the daughter cells have identical genetic information as those in the parent cell, due to semi-conservative replication of parental DNA during synthesis phase of interphase).~~

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~~As mitosis ensures genetic stability, the following can occur:~~

~~(i) **Growth**~~

- ~~To grow from one cell to a multicellular organism, all daughter cells must be genetically identical to the parent cell. All cells in a multicellular organism carry identical genetic information. However, the information is expressed differently, i.e. **differential gene expression**, to give rise to cells with different functions, i.e. **differentiation**.)~~

~~(ii) **Repair**~~

- ~~The number of cells in our body must be maintained at a certain number. Mitosis ensures that when cells are **lost, damaged or worn-out**, they are **replaced** by cells that are identical to them.~~

~~(iii) **Asexual reproduction**~~

- ~~This is a type of reproduction involving only one parent (male or female). There is no fusion of gametes from male and female parents. Since mitosis is involved in such reproduction, the offspring are identical to the parents, i.e. **clones** of the parents.~~
- ~~Asexual reproduction is carried out when rapid production of offspring is required. These identical offspring can differ only if mutation of the genetic material takes place. In nature, this form of reproduction takes place commonly in plants (**vegetative propagation**, e.g. bulbs in onions), less complex animals (e.g. **budding** in yeasts or **fragmentation** in starfish) and micro-organisms (e.g. **binary fission** in bacteria and yeasts).~~
- ~~Most animals reproduce using sexual reproduction that involves meiosis, not mitosis.~~

~~(b) Significance of meiosis~~

~~Meiosis is a very important step for **sexual reproduction**. In sexual reproduction, **two haploid cells (gametes) fuse to form a diploid zygote**. The fusion of male and female gametes (haploid, n) **restores the diploid (2n) state** of parent cells. It also generates **genetic variation**, which gives rise to genetic differences between individuals of the same species. Meiosis produce variations in offspring by giving rise to **recombinant gametes** through the following processes:~~

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(iii) **Crossing over of non-sister chromatids of homologous chromosomes** at the **chiasmata**, during **prophase I**. This allows **corresponding sections** of chromatids to be exchanged, thus **separating linked genes** and creating **new combinations of alleles** in the chromatid.

Crossing over of non-sister chromatids of homologous chromosomes

In prophase I of meiosis, homologous chromosomes pair to form a bivalent. The non-sister chromatids of homologous chromosomes overlap, producing an X- shaped figure called chiasmata (singular = chiasma).

- Chiasma formation is followed by exchange of genetic material between non-sister chromatids.
- Crossing-over is a process that involves:
  - **Breakage** of a corresponding section from each chromatid at the chiasma.
  - **Exchange** of the section between non-sister chromatids, and
  - **Rejoining** of the section to a new sister chromatid.

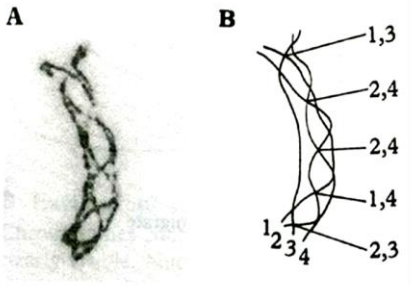

Figure 23.7 Chiasmata. **A** is a photomicrograph of a bivalent at late prophase from testis of grasshopper. **B** is an interpretive diagram. Chiasmata are numbered according to which chromatids are in contact. Note that chiasmata can be formed between any two non-sister chromatids. (*Bernard John, Australian National University*)

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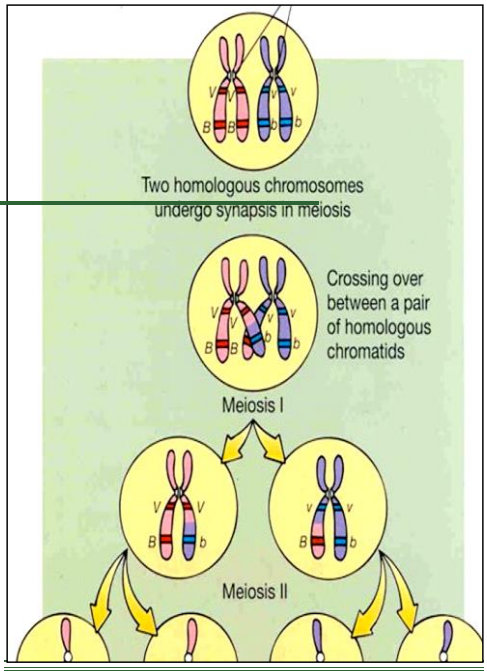

~~In the diagram on the right, parental chromosome contains linked genes, V and B. One homologue contains dominant V and B alleles while the other contains recessive v and b alleles.~~

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- ~~Crossing over occurs between two non-sister chromatids, resulting in an exchange of allele for the B gene. Now, one chromatid contains V and b alleles and the other contains v and B alleles.~~
- ~~**Four different gametes** with different allele combinations are produced: VB, Vb, vB and vB.~~

~~(iv) **Independent assortment of chromosomes** during **metaphase I**. The orientation of the homologous pair of chromosomes along the metaphase plate is **independent of other bivalents**, i.e. **random**. This is followed by **independent segregation** during **anaphase I**. Thus, there is a 50% chance that a particular daughter nucleus produced by meiosis I, will receive either one of the chromosome in the homologous pair. The number of possible chromosomal combinations in a gamete is 2^n, where n = number of homologous pairs of chromosomes. Thus there can be a possibility of having 2^{23} or about 8 million different combinations of gametes.~~

~~During **fertilization**, **random fusion of gametes** occurs (i.e. any egg cell can be fertilised by any sperm cell). This results in 8 million x 8 million possible combinations of a zygote. **Another source of genetic variation is spontaneous mutations of DNA (e.g. errors that occur during semi-conservative replication). All these are the basis for natural selection.**~~

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~~Crossing over of non-sister chromatids of homologous chromosomes~~

~~In prophase I of meiosis, homologous chromosomes pair to form a bivalent. The non-sister chromatids of homologous chromosomes overlap, producing an X-shaped figure called chiasmata (singular = chiasma).~~

- ~~Chiasma formation is followed by exchange of genetic material between non-sister chromatids.~~
- ~~Crossing-over is a process that involves:~~
  - ~~**Breakage** of a corresponding section from each chromatid at the chiasma,~~
  - ~~**Exchange** of the section between non-sister chromatids, and~~
  - ~~**Rejoining** of the section to a new sister chromatid.~~

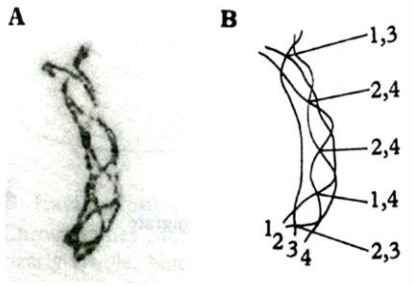

Figure 23.7 Chiasmata. **A** is a photomicrograph of a bivalent at late prophase from testis of grasshopper. **B** is an interpretive diagram. Chiasmata are numbered according to which chromatids are in contact. Note that chiasmata can be formed between any two non-sister chromatids. (*Bernard John, Australian National University*)

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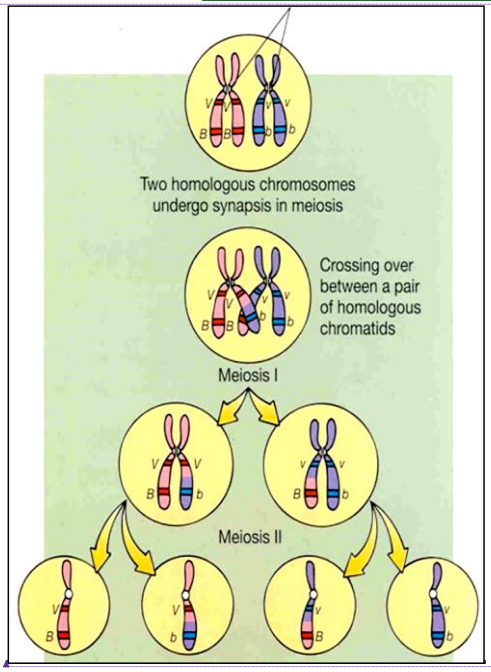

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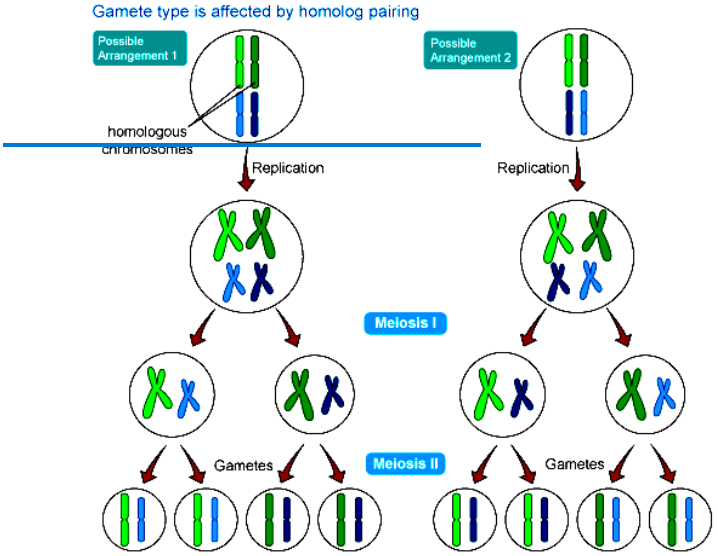
~~In the diagram on the right, parental chromosome contains linked genes, V and B. One homologue contains dominant V and B alleles while the other contains recessive v and b alleles.~~

- ~~Crossing over occurs between two non-sister chromatids, resulting in an exchange of allele for the B gene. Now, one chromatid contains V and b alleles and the other contains v and B alleles.~~
- ~~**Four different gametes** with different allele combinations are produced: VB, Vb, vB and vB.~~

~~Independent assortment of chromosomes~~

~~Independent assortment involves both **random arrangement** and **independent segregation**. It starts from late prophase I and ends at anaphase I.~~



~~During prophase I:~~

- ~~Bivalents are aligned where the maternal and paternal homologue faces each side of the pole.~~

~~At metaphase I:~~

- ~~The two pairs of homologous chromosomes randomly orientate themselves along the metaphase plate.~~
- ~~Thus, the first arrangement is **equally as likely** as the second arrangement.~~

~~During anaphase I,~~

- ~~Homologous chromosomes separate independently (i.e. independent segregation).~~
- ~~All **four resultant gametes are different from each other**. The **probability of having any of the four gametes is approximately equal**.~~

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~~4. The Control of Mitotic Cell Cycle~~

~~Cells are constantly being lost and are replaced by the process of cell division, e.g. if an injury occurs, the rate of cell division increases but slows down when the wound is healed. Normally, t~~The rate of cell division is **highly regulated** at ~~. There are~~ various **checkpoints** in the cell cycle ~~to control the rate of cell division.~~ – control points to determine if the cell will proceed to the next stage.

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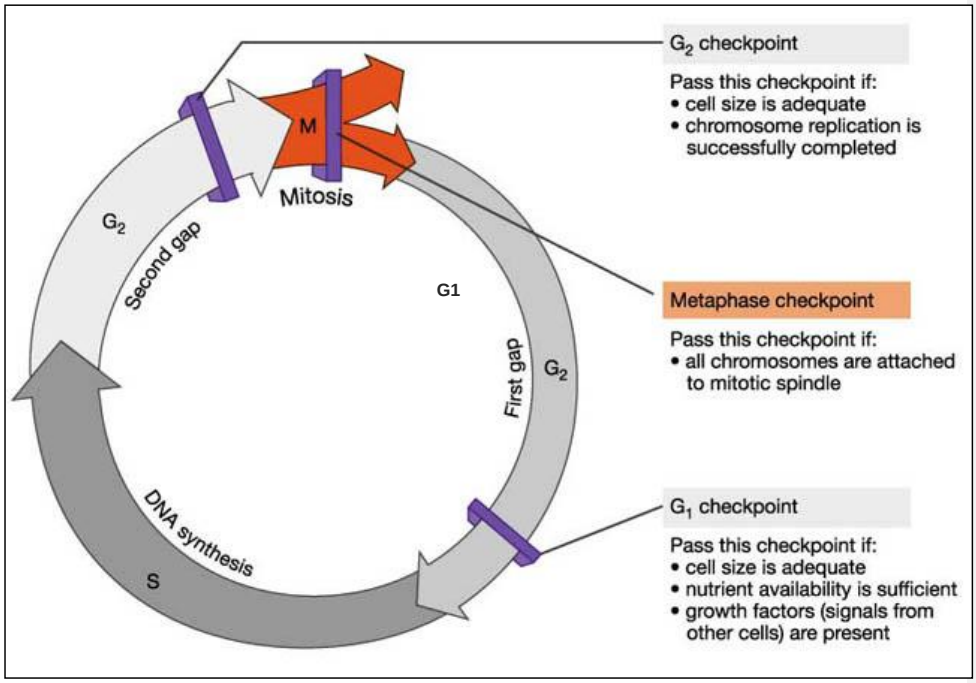

Diagram showing Cell Cycle Control

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There are three checkpoints during the mitotic cell cycle at **G_1, G_2 and metaphase**.

- G_1 checkpoint ensures that the **cell size is adequate** and there are **sufficient nutrients** available and **growth factors** present for cell to undergo mitosis.
  - If the cell does not pass the G_1 checkpoint, the cell will exit the cycle, switching into a nondividing state called the **G_0 phase**.
- G_2 checkpoint ensures that the **cell size is adequate** and **semi-conservative DNA replication has been completed** successfully.
- Metaphase checkpoint ensures that **all chromosomes are attached to spindle fibres / microtubules** at the metaphase plate before proceeding to anaphase.
- When all checkpoints are passed, cell cycle continues to the next stage.

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(a) Genes involved in control of cell cycle

Many genes interact to ~~A number of factors appear to influenc~~determine if ~~e whether or not a~~ a cell divides and how rapidly it divides ~~how rapidly it does~~. ~~The most important factor is the cell's own genes. Many genes are known to interact to determine when the cell divides.~~ In a healthy cell, ~~the activity of these genes~~ these are~~is~~ balanced and controlled by external factors so that cell division only takes place ~~as and~~ when ~~it is~~ required.

Two classes of genes that regulate cell division are **proto-oncogenes** and **tumour suppressor genes**.

(i) Proto-oncogenes

- Proto-oncogenes ~~in the cell~~ encode ~~many types of~~ proteins that **stimulate normal cell division**.
- The **gain-of-function mutation** of proto-oncogenes to **oncogenes** leads to **increase in amount of proto-oncogene's protein product** or **permanently activated proteins**.
- This will result in **uncontrolled cell division~~growth~~**, possibly leading to **cancer**.
- **Gain-of-function** mutation result in a **dominant allele** as the effect of the normal allele is masked by the mutated allele. Only **one** allele of a gene needs to be mutated to have an effect.
  - E.g.~~One important proto-oncogene is~~ **Ras gene**~~, which~~ codes for **Ras protein**, is a G protein that relays a signal from growth factor receptor on cell surface membrane to a cascade of protein kinases which result in ~~. Ras protein eswhich~~ normal ~~s~~ cell division.
  - ~~, which will~~ Ras oncogene codes for a permanently activated Ras protein which triggers the kinase cascade in the absence of growth factor, resulting in uncontrolled cell division.

- There are five main classes of proto-oncogenes, namely those which codes for:
  - ~~One important proto~~growth factors,
  - growth factor receptors,
  - signal transducers,
  - transcription factors and
  - programmed cell death regulators.

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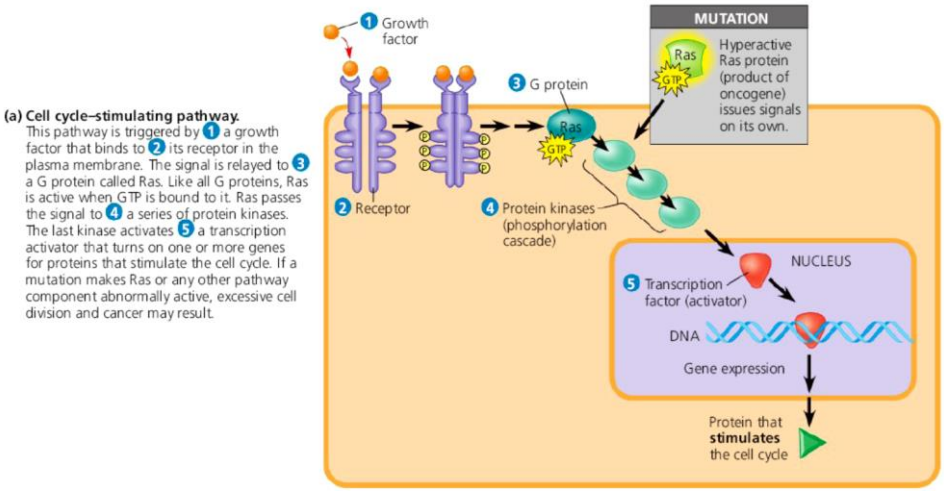

Diagram showing function of Ras protein

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(ii) Tumour suppressor genes

- Tumour suppressor genes encode proteins that ~~in one way or another~~ **inhibit cell division** or **promote apoptosis** (controlled cell death).
- The **loss-of-function mutation** of tumour suppressor genes to mutated tumour suppressor genes leads to **no protein product** or **decrease in amount of protein product** or **permanently deactivated proteins**.
- This will result in **uncontrolled cell division~~growth~~**, possibly leading to **cancer**.
- **Loss-of-function** mutation result in a **recessive allele** as the normal dominant allele encodes functional protein. **Two alleles** of a gene need to be mutated to have an effect.
  - E.g.~~One important proto-oncogene is~~ **p53 gene**~~, which~~ codes for **p53 protein**, is a transcription factor that promotes synthesis of protein that triggers cell cycle arrest or promote apoptosis when DNA damage is detected.
  - ~~, which will~~ Mutated p53 tumour suppressor genes result in no p53 being produced. Cells with damaged DNA which are not supposed to proliferate will continue to divide, resulting in uncontrolled cell division.
- There are five main classes of tumour suppressor genes, namely those which codes for:
  - Intracellular proteins that inhibit progression into a specific stage of cell cycle.
  - Receptors for secreted hormones that function to inhibit cell proliferation.
  - Checkpoint-control proteins that arrest the cell cycle if DNA is damaged.
  - Proteins that promote apoptosis.
  - Enzymes that participate in DNA repair.

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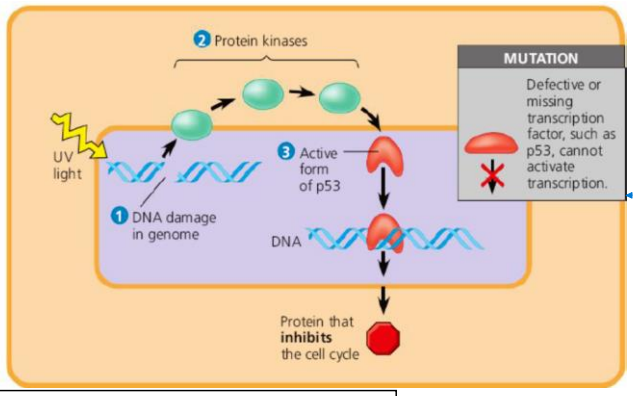
(b) Cell cycle–inhibiting pathway. In this pathway, 1 DNA damage is an intracellular signal that is passed via 2 protein kinases and leads to activation of 3 p53. Activated p53 promotes transcription of the gene for a protein that inhibits the cell cycle. The resulting suppression of cell division ensures that the damaged DNA is not replicated. If the DNA damage is irreparable, the p53 signal leads to programmed cell death (apoptosis). Mutations causing deficiencies in any pathway component can contribute to the development of cancer.



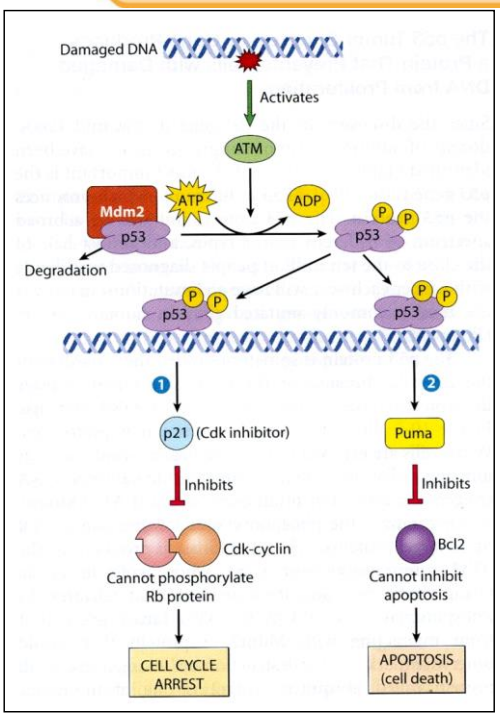


Diagram showing function of p53 protein

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(b) Onset of cancer

When the ~~mechanisms that~~ control of the cell cycle is ~~are~~ defective, **cells divide uncontrollably**. These cells are called cancer cells.

- ~~Cancer cells **divide uncontrollably to form a clump of overlapping cells** known as a **tumour**.~~

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- Cancer cells exhibit ~~One of the reasons for development of tumour is the~~a **loss of anchorage dependence** ~~in cancer cells~~. Normal cells need to anchor to a surface before they can divide. Cancer cells are able to divide without a surface to anchor. ~~However, cancer cells continue to divide even when not anchored to the basement membrane, causing a tumour to form~~.
- ~~An~~Cancer cells exhibit a ~~**other reason for the development of tumour is the**~~ **lack of density-dependent inhibition** ~~in cancer cells~~. Normal c~~C~~ells ~~normally only~~ divide as a single layer and stop dividing ~~when they come into~~upon contact with another cell. C~~.~~ ~~However, c~~ancer cells continue to divide ~~upwards~~ even after a layer of cells had been formed.
  - ~~This causes a tumour to form.~~

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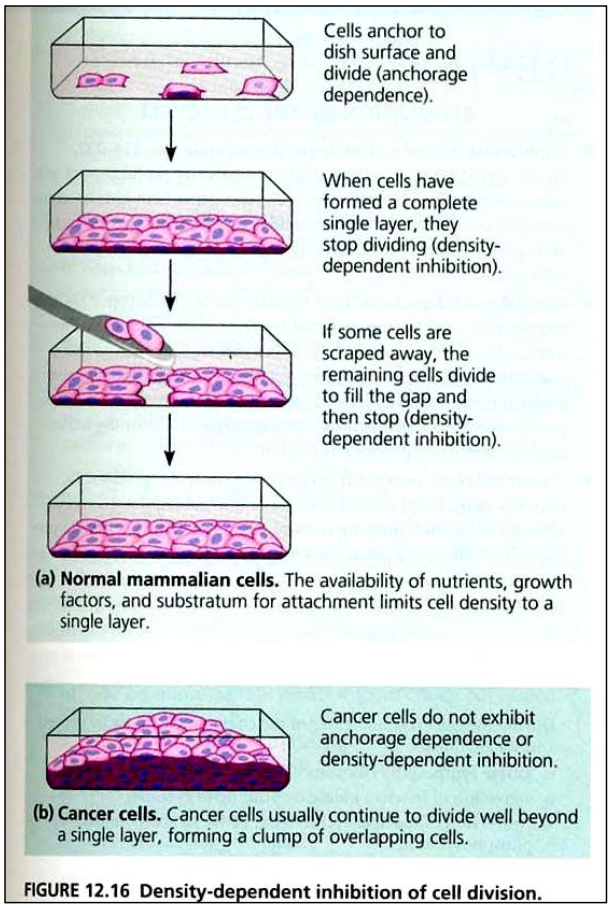

FIGURE 12.16 Density-dependent inhibition of cell division.

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Diagram of cancer cell

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As a result, **a clump of overlapping cells** is formed called **tumour**. There are 2 main types of tumour:

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- **Benign tumour**
  - a mass of abnormal cells that grows and remains ~~locally (i.e.~~ at the original location~~) and does not invade neighbouring tissues or spread to other parts of the body~~.
  - Can be completely removed by
- **Malignant tumour:**
  - an uncontrolled, growing mass of cells which may lose their attachment to neighbouring cells and ~~. They~~ can **invade** surrounding tissue ~~migrate to nearby tissue or enter the circulatory or lymphatic system to~~.
  - This spread of cancer cells to distant sites is called **metastasis**.
  - An individual with a malignant tumor is said to have **cancer**.

~~The escape of cancer cells from normal cell cycle control can be due to:~~

~~(i) Mutation of proto-oncogenes to oncogenes (**gain-of-function mutation**) would produce proteins that can provide an uncontrolled growth signal to stimulate cell proliferation.~~

- ~~e.g. Ras oncogene~~
- ~~The Ras proto-oncogene is a normal gene that produces a protein involved in a normal pathway that stimulates cell proliferation. However, a point mutation of DNA sequence causes it to become an oncogene. It causes a number of cancers including colon cancer.~~
- ~~Oncogenes can cause cancer by producing proteins that trigger cell proliferation, e.g. G proteins, protein kinases, growth factors. This leads to uncontrolled cell division and formation of tumours.~~

~~(ii) Mutation of the tumour suppressor genes (**loss-of-function mutation**) causes them to be not expressed / permanently inactivated. The result of these mutations may lead increased cell proliferation and decreased cell death, thus greatly increasing the probability of these cells becoming cancer cells.~~

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(c) Causative factors

Cancer usually develops when cells escape normal cell cycle due to oncogenes or mutated tumour suppressor genes.

There are various factors, physical, chemical and biological, that can cause mutation of these genes and increase the chances of cancer.

(i) **Physical factors:**

- **Ionising radiation:** α / β / γ radiation, X-ray
  - Radiation causes formation of chemically active ions in the cells which are capable of damaging and breaking DNA.
- **Ultra-violet light**
  - Absorption of UV causes DNA to increase in energy level, causing damage to DNA double helix by creating kinks. .

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(ii) **Chemicals factors (carcinogens):** ethidium bromide, asbestos, coal dust

- Mutagens that cause chemical changes in bases resulting in incorrect base pairing, results in insertion or deletion of base pair.

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(iii) **Biological:**

- **Viruses**: retrovirus, DNA virus.
  - These viruses alter DNA sequence of host leading to formation of oncogenes, e.g. Human papilloma virus causing cervical cancer.
- **Fungus**
  - Stored grains and peanuts contaminated with *Aspergillus flavus*, fungal poison called mycotoxins can cause liver cancer.

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(iv) **Genetic factor**: inherited cancer-causing-gene from parent

- Mutated genes such as either oncogenes or mutated tumour suppressor genes found in **gametes** of parents.
  - e.g. Colon cancer usually runs in the family.