River Valley High School
2025 JC1 H2 Biology

Lecture Topic 12: The Cell Cycle

Name: _____ ( ) Class: 25J____ Date: _____

References

Title	Author
Biology (9th edition)	Campbell and Reece
Biological Science 2: Systems, Maintenance & Change (3rd edition)	Taylor, Green and Stout
AS Level Biology	Bradfield, Dodds and Taylor
Molecular Biology of the Cell (5th edition)	Alberts, Johnson, Lewis, Raff, Roberts and Walter

Websites

URL	Description
Chromosome numbers during cell division	How to distinguish chromosomes numbers throughout replication, mitosis and meiosis
Mitosis	Clear, colourful and narrated 2D animations on mitosis
Cell cycle and cancer	How dysregulation of cell cycle checkpoints can lead to cancer
Meiosis	Clear, colourful and narrated 2D animations on meiosis
Mitosis and Meiosis - comparison	A comparison between mitosis and meiosis
Role of RAS protein in Cancer development	How RAS protein affects cancer development
Role of p53 in cancer	How p53 protein affects cancer development
Why is it so hard to cure cancer?	The complications of cancer

H2 Biology Syllabus 9477 (2025)

Candidates should be able to use the knowledge gained in the following section(s) in new situations or to solve related problems.

Related Topics	**Content**
DNA Replication	DNA structure and function
Inheritance	The passage of information from parent to offspring Linkage and crossing-over

Learning Outcomes

2E: The Cell Cycle

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

b. 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 & cancer is required, but detail of the mechanism is not required).

c. Identify the causative factors, including genetic, chemical carcinogens, ionising radiation and loss of immunity, which may increase the chances of cancerous growth.

d. Explain how the loss of function mutation of tumour suppressor genes, including *p53*, and gain in function mutation of proto-oncogenes, including *ras*, results in uncontrolled cell division.

e. Describe the development of cancer as a multi-step process that includes accumulation of mutations, angiogenesis and metastasis.

f. Describe the events that occur during the meiotic cell cycle and the main stages of meiosis (including the behaviour of chromosomes, nuclear envelope, cell surface membrane and centrioles) (names of the main stages are expected, but not the sub-divisions of prophase).

g. Explain the significance of the meiotic cell cycle (including how meiosis and random fertilisation can lead to variation).

Lecture Outline

I. Introduction

- A. Cell division & continuity of life
- B. Chromosomes
- C. Mitotic / Meiotic Spindle

II. The Cell Cycle

- A. Phases of the Cell Cycle
- B. Control of the Cell Cycle
- C. Detailed Events of Interphase
- D. Detailed Events of Mitotic Phase
- E. Significance of Mitosis

III. Cancer

- A. Cancer is a Genetic Disease
- B. Cancer is a Multistep Process
- C. The Progression of Cancer

IV. Meiosis

- A. Stages of Meiosis: Meiosis I and II
- B. Significance of Meiosis
- C. Comparison of Mitosis and Meiosis

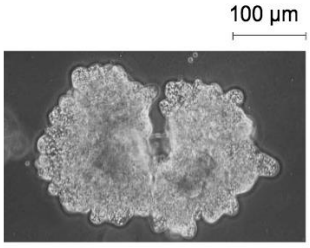
I. INTRODUCTION

A. Cell Division and the Continuity of Life

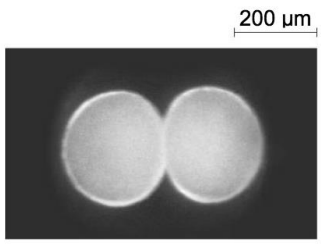
The ability of organisms to reproduce is one characteristic that distinguishes them from non-living matter. This unique capacity to procreate has a cellular basis. As modern cell theory states, the only way to make a new cell is to duplicate a cell that already exists.

This would imply that all living organisms, unicellular or multicellular, are products of repeated rounds of cell growth and division extending back in time to the beginnings of life on Earth.

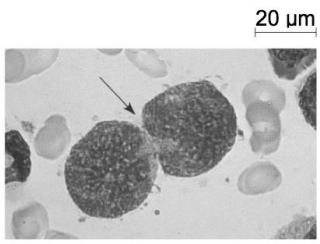
A cell reproduces by performing an orderly sequence of events in which it duplicates its contents and then divides in two. This cycle of duplication and division, known as the **cell cycle**, is the essential mechanism by which all living things reproduce.



(a) Reproduction. An amoeba, a single-celled eukaryote, is dividing into two cells. Each new cell will be an individual organism (LM).



(b) Growth and development. This micrograph shows a sand dollar embryo shortly after the fertilized egg divided, forming two cells (LM).



(c) Tissue renewal. These dividing bone marrow cells (arrow) will give rise to new blood cells (LM).

While the details of the cell cycle vary across organisms, certain characteristics are universal:

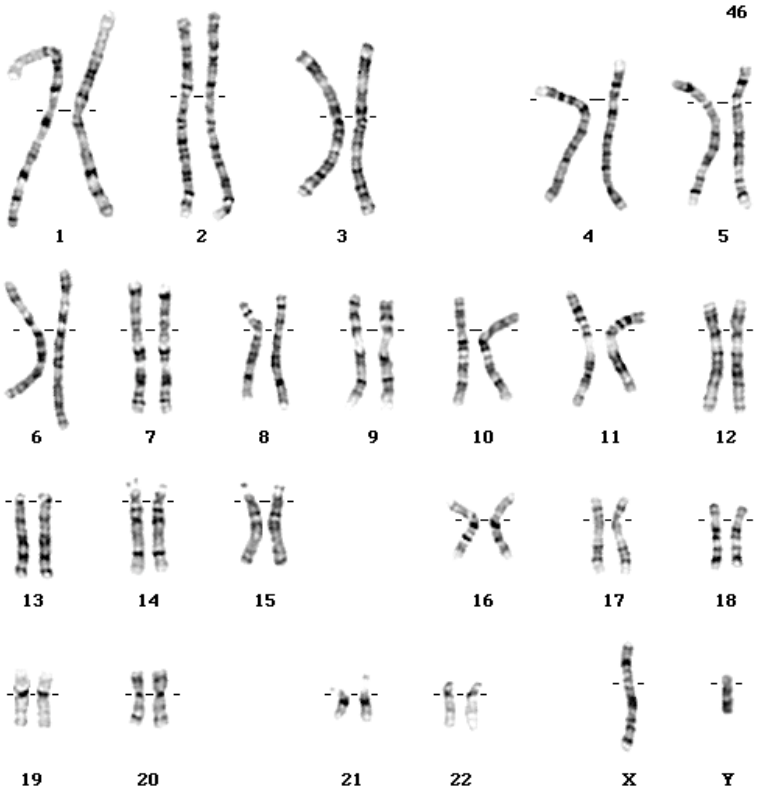
- The most fundamental task of the cell cycle is to allow the cell to pass on its genetic information accurately to the next generation of cells.
- To produce two genetically identical cells, the DNA in each chromosome must first be faithfully replicated to produce two complete copies, and the replicated chromosomes must then be accurately distributed to the two daughter cells, so that each receives a copy of the entire genome.

B. Chromosomes

Chromosome numbers and sets

- Every eukaryotic species has a characteristic number of chromosomes in each cell nucleus. The following table illustrates several examples:

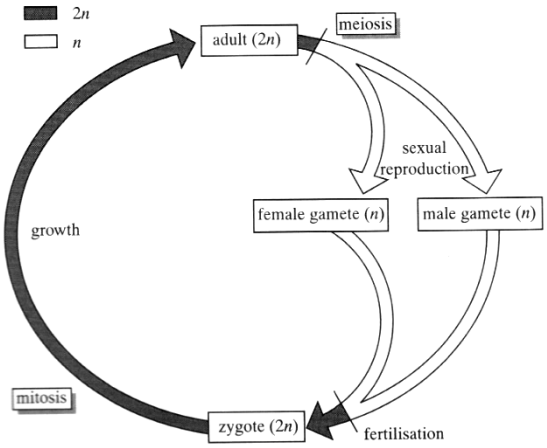
Common name	Species name	Chromosome number (in somatic cells)
Human	*Homo sapiens*	46
Monkey	*Macaca mulatta*	42
Mouse	*Mus musculus*	40
Mosquito	*Aedes aegypti*	6
Fruit Fly	*Drosophila melanogaster*	8
Flatworm	*Planaria torva*	16
Corn	*Zea mays*	20
Yeast	*S. cerevisiae*	32



Karyotype of a human male (with a normal 46, XY constitution). Homologous pairs of non-sex chromosomes (autosomes) are numbered from 1 to 22. There is 1 pair of sex chromosomes (X and Y).

- In particular, the nuclei of **human somatic cells** each contain 46 chromosomes.
  - If all the 46 chromosomes are lined up according to size it can be seen that there are in fact 23 distinct pairs of chromosomes.
  - The 23 pairs of chromosomes comprise 22 pairs of **autosomes** (non-sex chromosomes) and one pair of sex chromosomes, which determines the gender of the organism.
  - Each pair is known as a **homologous pair of chromosomes**, with each member of a pair called a **homologue**.
  - The 46 chromosomes are said to be made up of **two sets of 23 chromosomes**.
  - Each set of chromosomes is inherited from one parent. Hence, one set is called the **maternal set** and the other is called the **paternal set**.

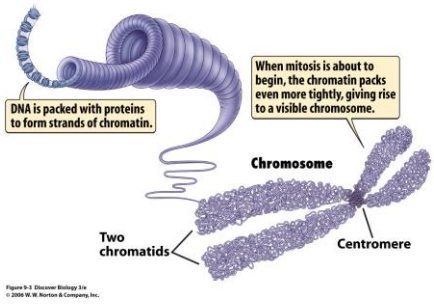
Haploid versus diploid



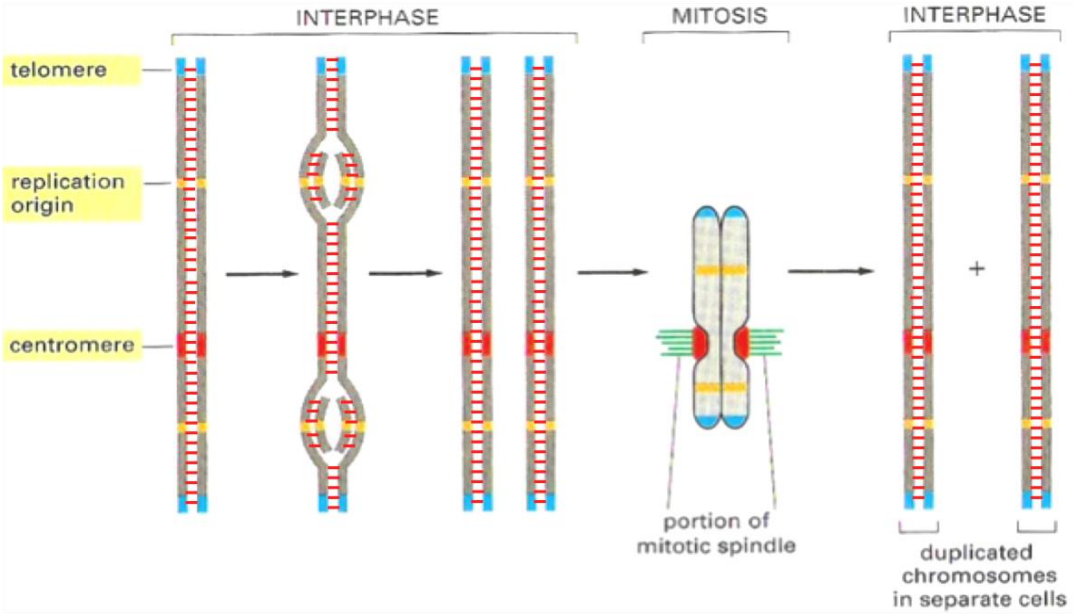
- Cells or organisms with **two** sets of chromosomes (i.e. contain both chromosomes from each homologous pair) are referred to as **diploid**, and given the symbol **2*n***.
- Cells or organisms with only **one** set of chromosomes (i.e. contain only one chromosome from each homologous pair) are referred to as **haploid**, and given the symbol ***n***.
- **Gametes**, or sex cells, are **haploid** cells.
- Fusion of two haploid gametes (sperm and ovum) during **fertilisation** restores the diploid condition, giving rise to a **zygote (2*n*)**.
- By the process of cell division involving **mitosis**, the zygote (2*n*) then divides to give rise to a mature organism with cells of the same genetic makeup (2*n*), thus conserving the number of chromosomes across generations of cells.
- **Haploid gametes (*n*)** are in turn produced via **meiosis**, whereby diploid parent cells (2*n*) divide to give rise to cells with half the number of chromosome

Chromosomes and Chromatids

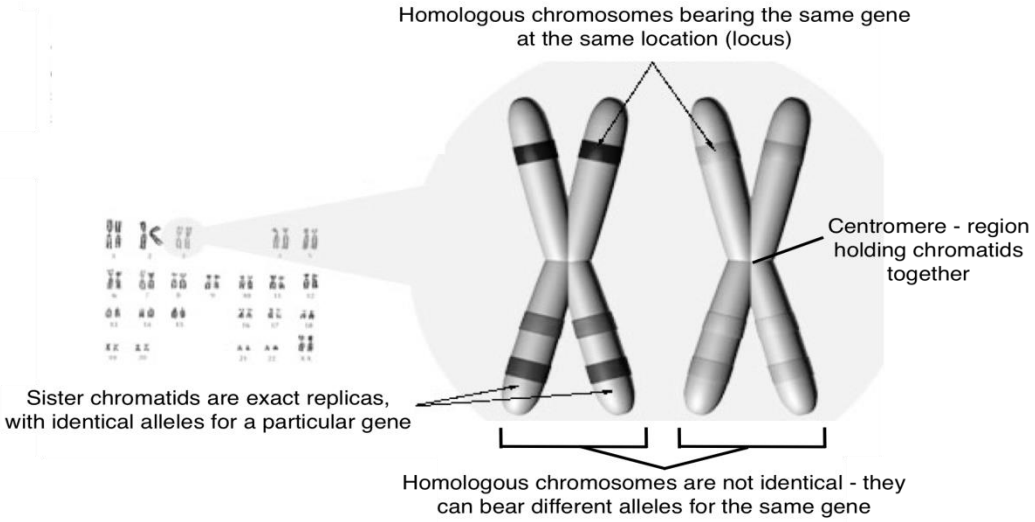
- **Definition of chromosome:** A cellular structure carrying genetic material, found in the nucleus of eukaryotic cells. Each chromosome consists of DNA and associated proteins.
- In a non-diving cell, each chromosome contains only one DNA molecule, i.e. only one DNA double helix.
- However, before the nucleus divides, DNA replication occurs (during interphase) each chromosome contains two identical DNA molecules, i.e. two identical DNA double helices.
- The chromatin becomes densely coiled and packaged into structures called **chromosomes**, so that at nuclear division the chromosome appears as a double arm structure (i.e. with 2 sister chromatids).



- The two parts of a replicated chromosome are referred to as **sister chromatids**. Each chromatid of a pair contains one of two identical DNA molecules.
- The sister chromatids are joined together at the **centromere**. It is also the region where kinetochore proteins and microtubules attach to the chromosome during cell division.
- **Definition of centromere**: Region of repetitive DNA base sequence in a mitotic chromosome where sister chromatids are joined together. It is also the site on the DNA where the kinetochore attaches.
- **Definition of kinetochore**: Complex structure formed from proteins on a mitotic chromosome to which microtubules attach and which plays an active part in the movement of chromosomes to the poles.



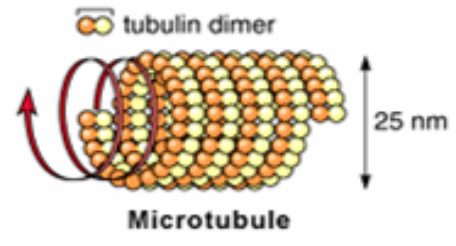
Sequence of events that a typical chromosome follows during a cell cycle. The DNA replicates in interphase, beginning at the origins of replication and proceeding bidirectionally from the origins. In M phase, the centromere attaches the duplicated chromosomes to the mitotic spindle so that one copy is distributed to each daughter cell during mitosis. The centromere also helps to hold the duplicated chromosomes together until they are ready to be moved apart. The telomeres form special caps at each chromosome end.



Homologous chromosomes vs. sister chromatids

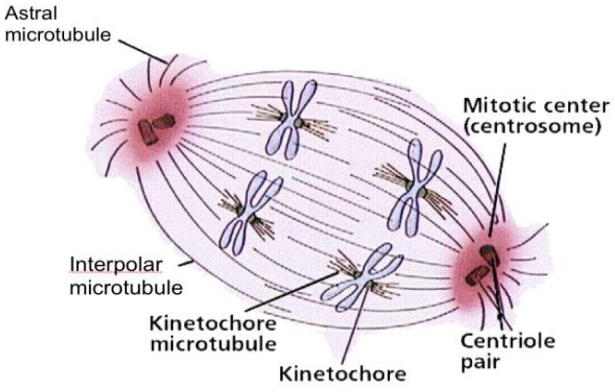
C. Mitotic / Meiotic Spindle

- Many of the events of cell division depend on the **mitotic / meiotic spindle**.
- The mitotic / meiotic spindle is a bipolar array of microtubules radiating from the **microtubule-organising centre (MTOC)**.
- In animal cells, the MTOC is known as the **centrosome**, which contains **a pair of centrioles**
  - During interphase in animal cells, the single centrosome replicates (i.e. synthesis of another centrosome), forming two centrosomes.
  - The two centrosomes move apart during prophase and prometaphase as microtubules grow out from them.
  - By the end of prometaphase, the two centrosomes, one at each pole of the spindle, are at opposite poles of the cell.



- The microtubules can **elongate** (polymerise) by incorporating more tubulin subunits, and **shorten** (depolymerise) by losing subunits.
- The **functions** of the spindle are to:
  1. Guide the movement of chromosomes during mitosis and meiosis, thus ensuring that each daughter cell receives an exact number of chromosomes. It achieves this by doing the following:
     a. Aligning chromosomes at the metaphase plate / equator of the spindle
     b. Segregating sister chromatids / homologous chromosomes to opposite poles of the cell during anaphase
  2. Elongate the cell in preparation for cytokinesis.

- The spindle comprises **three types of microtubules**:
  - **Kinetochore microtubules**
    - attached to sister chromatid pairs at large protein structures called **kinetochores**.
    - kinetochore microtubules align the chromosomes at the **metaphase plate** / **equator of spindle** during metaphase.
    - segregating sister chromatids / homologous chromosomes to opposite poles of the cell during anaphase
  - **Interpolar microtubules**
    - are not attached to the chromosomes and retain free ends that overlap along the metaphase plate.
    - These microtubules lengthen to push the two spindle poles apart during anaphase, resulting in cell elongation for cytokinesis to occur.
  - **Astral microtubules**
    - short microtubules that radiate outward from each centrosome. They help to position the spindle in the cell.



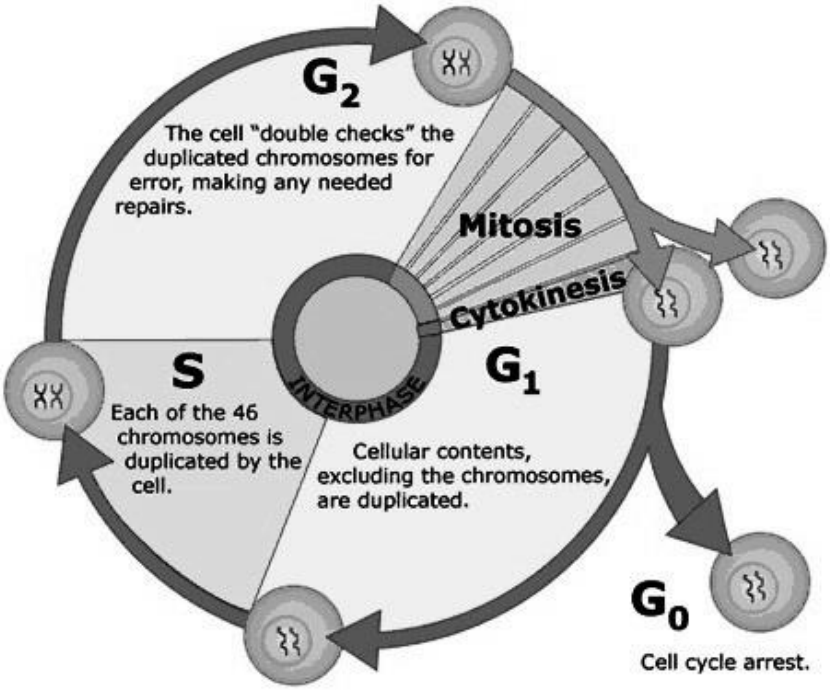
Three types of microtubules making up the spindle – kinetochore, interpolar and astral microtubules.

II. THE CELL CYCLE

A. Phases of the Cell Cycle

- The cell cycle is the sequence of events that occurs throughout the life of a cell, from its formation as a new cell by division, to its own division into two daughter cells.
    - Most types of cells never undergo the complete cell cycle, because they do not divide again after they have grown and become **specialised** (e.g. guard cells of stomata of plant epidermis; most neurons and skeletal muscle cells).
    - However some unspecialised cells retain the ability to divide and thus undergo the complete cell cycle. Some specialised cells can also be stimulated to re-enter the cell cycle via external cues (e.g. liver cells can be stimulated by growth factors during injury).
    - The length of the cycle is variable. It depends on internal factors such as the type of cell and external factors such as temperature, nutrients and oxygen supplies (e.g. bacteria may divide every 20 minutes, intestinal epithelial cells every 8-10 hours, onion root-tip cells every 20 hours).

- The cell cycle comprises two main stages:



1. **Interphase:** comprises **G_1 phase, S phase** and **G_2 phase**
2. **Mitotic phase (M phase)**: comprises **mitosis** (nuclear division) and **cytokinesis** (cytoplasmic division)

Interphase

- This is the longest phase of the cell cycle (about 90% of the total duration).
- It is a period of intense metabolic activity, where synthesis and growth occurs in preparation for cell division.
- Interphases can be divided into three subphases:
    - **G_1 phase** ("first gap")
    - **S phase** ("synthesis")
    - **G_2 phase** ("second gap")

- Throughout interphase, the cell grows by:

- Accumulating energy stores (e.g. ATP)
- Synthesising proteins and nucleic acids
- Synthesising new cytoplasmic organelles, e.g. centrioles, mitochondria, endoplasmic reticulum

- However, DNA replication, i.e. duplication of chromosomes occurs only during the **S phase**.
  - At the end of S phase, each chromosome comprises two identical DNA double helices, which exist as decondensed chromatin until prophase of mitosis.
  - The two gap phases of interphase (G_1 and G_2) are more than simple time delays to allow cell growth. They also provide time for the cell to monitor the internal and external environment, to ensure that conditions are suitable and preparations are complete before the cell commits to the massive upheavals of S phase and mitosis. *(Section B: Control of the Cell Cycle)*

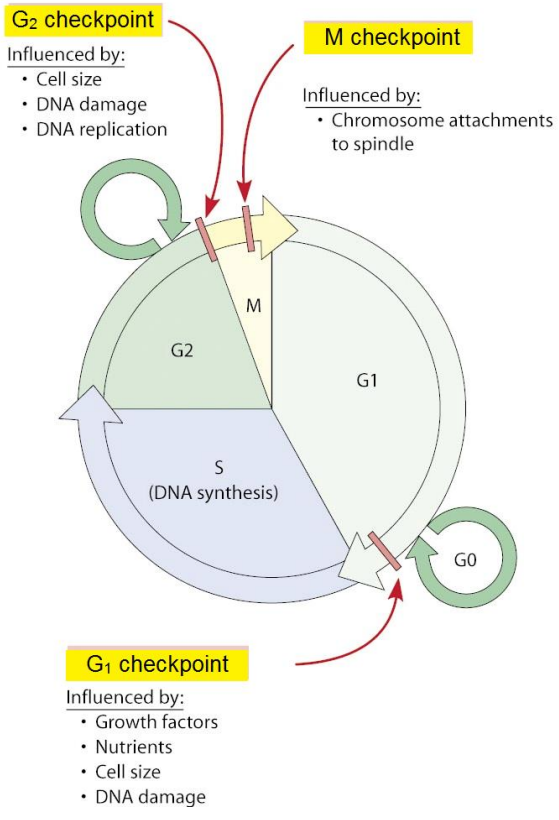
Mitotic phase (M phase)

- Following the completion of S phase and transition through G_2, the cell undergoes the dramatic upheaval of M phase.
- This begins with **mitosis**, during which sister chromatids are separated and distributed (*segregated*) to form a pair of identical daughter nuclei, each with its own copy of the genome.
- Mitosis comprises four stages – **prophase, metaphase, anaphase** and **telophase** – defined primarily on the basis of chromosome behaviour as seen in a microscope.
- As mitosis is completed, the second major event of M phase – **cytokinesis** – divides the cell into two halves, each with an identical nucleus.

B. Control of the Cell Cycle

Regulatory checkpoints

- The progression of the cell cycle is carefully controlled by a **cell-cycle control system**.
- This control system works much like a timer that triggers certain essential processes of the cell cycle in a set sequence, namely DNA replication, mitosis and cytokinesis.
  - Once each of these specific processes is triggered, it proceeds in a complete and irreversible fashion.
  - However, for each of these events to be launched and thus for the cell cycle to proceed, internal and external conditions must be favourable at certain regulatory transitions known as checkpoints
- The control system regulates cell-cycle progression at **three major checkpoints** in the cell cycle:
  1. First checkpoint (occurs in late G_1) is known as **G_1 checkpoint**, where the cell commits to DNA replication.
  2. If the control system does not receive a go-ahead signal at this checkpoint, it exits the cycle and switches into a non-dividing state called the **G_0 phase**.
  3. Second checkpoint (G_2-M transition) is the **G_2 checkpoint**, where the cell commits to mitosis.
  4. Third checkpoint (metaphase-to-anaphase transition) is the **M checkpoint**, where the cell commits to sister-chromatid separation and thus the eventual completion of mitosis and cytokinesis.
     - The M checkpoint ensures that all the chromosomes are properly attached to the spindle at the metaphase plate before anaphase.



The need for the cell cycle control system

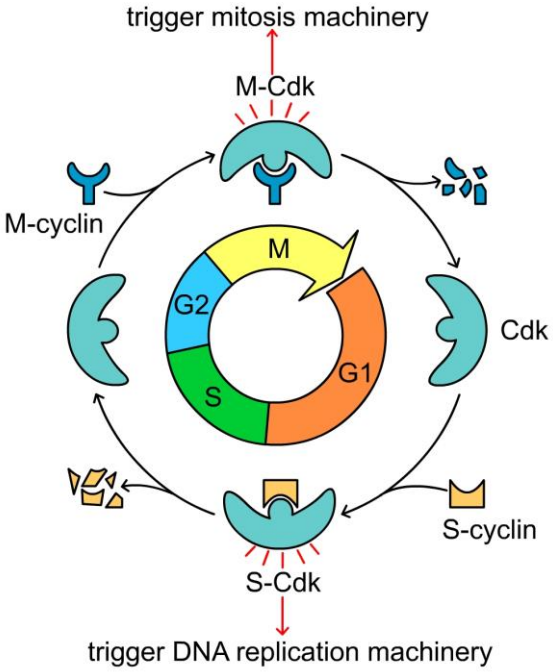
- If the control system detects unfavourable internal or external conditions, it blocks progression through each of these checkpoints.
- Such delays of cell-cycle progression at the checkpoints are crucial because:
  - They provide time for errors or malfunctioning cellular machinery to be repaired.
  - They prevent errors in cell division that may result if the cell cycle progressed prematurely to the next stage when conditions are still unfavourable.

Key components of the cell-cycle control system

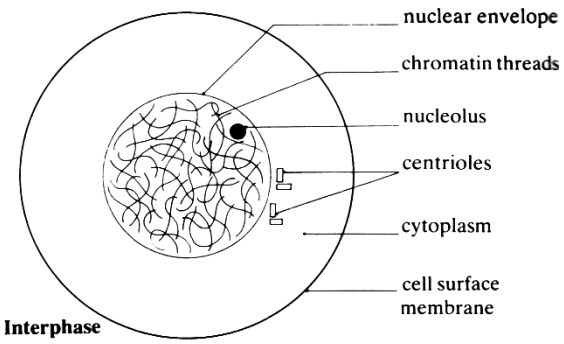
Rhythmic fluctuations in the abundance and activity of various cell cycle control molecules pace the sequential events of the cell cycle. These regulatory molecules are mainly proteins of two types – **cyclin-dependent kinases (Cdks),** and **cyclins**.

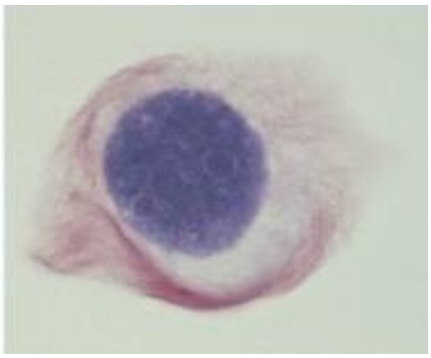
(Kinases are enzymes that transfer phosphate groups from high energy donor molecules, such as ATP, to specific substrates, thus activating or inactivating these substrates.)

- Many of the Cdks are present at constant concentration in the growing cell, but their activities rise and fall as the cell progresses through the cycle.
  - This leads to cyclical changes in the phosphorylation of other intracellular proteins that initiate or regulate major events of the cell cycle.
- Cdks, as their name implies, are dependent on cyclins for their activity. This is because to be **active**, a Cdk must be attached to a cyclin to form a specific **cyclin-Cdk complex**.
- Unlike Cdks, cyclins undergo a cycle of synthesis and degradation in each cell cycle, and thus their concentrations in the cell fluctuate cyclically (*hence their name*).
- Cyclical changes in cyclin protein levels result in the cyclic assembly and activation of the **cyclin-Cdk complexes**. This activation in turn triggers cell-cycle events.



C. Detailed Events of Interphase





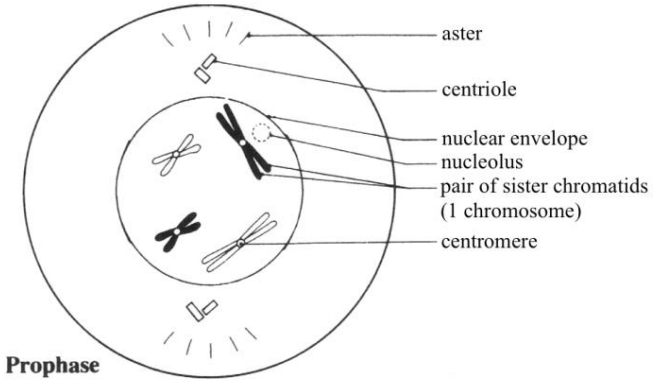
Phase	Major events occurring in cell
G_1	♦ Period of high metabolic activity due to **cell growth**. ♦ **Synthesis of proteins** including **histones**, **ribosomal proteins** and **tubulin** (to be used for spindle formation). ♦ **Synthesis of new cytoplasmic organelles** such as mitochondria and ribosomes. ♦ Cell builds up **energy stores** (e.g. ATP). ♦ **Centrioles replicate** just as the cell enters S phase.
S	♦ **DNA replication** occurs, **doubling DNA content of the cell.** Each DNA molecule is replicated forming an identical copy i.e. <u>each</u> chromosome is now made up of <u>two identical DNA molecules</u>.
G_2	♦ Cell continues to build up **energy stores**, and **synthesise proteins** and **cytoplasmic organelles**.

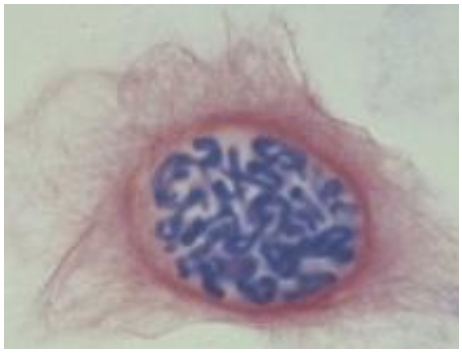
D. Detailed Events of Mitotic Phase (M Phase)

Mitosis (nuclear division)

- M phase begins with **mitosis**, the process by which a <u>cell nucleus divides to produce **two** daughter nuclei</u> containing the <u>same chromosome number</u> and the <u>same genetic makeup as the parent cell</u>.
- This is primarily achieved by <u>segregating the sister chromatids</u> to a <u>pair of identical daughter nuclei at opposite poles of the cell</u>.
- It is divided into four stages, defined primarily by chromosome behaviour as seen under a microscope: **Prophase, Metaphase, Anaphase** and **Telophase**.
- It is a continuous process with **no** sharp distinction between the phases, usually lasting around one hour.

Prophase





Behaviour of chromosomes

- Chromatin fibres become more tightly coiled, **condensing** into discrete **chromosomes** observable with a light microscope.
- Each duplicated chromosome now appears as **two identical sister chromatids**, joined together at the **centromere**.

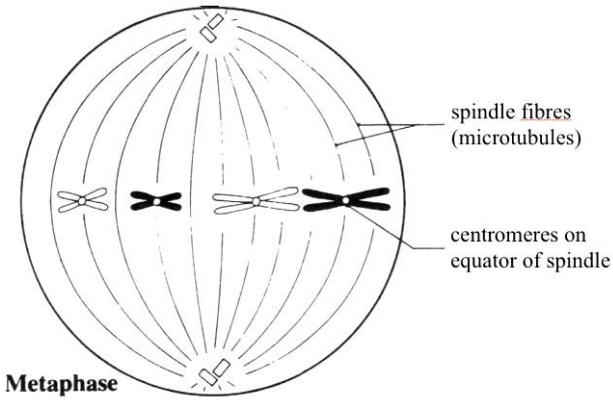
Nucleus

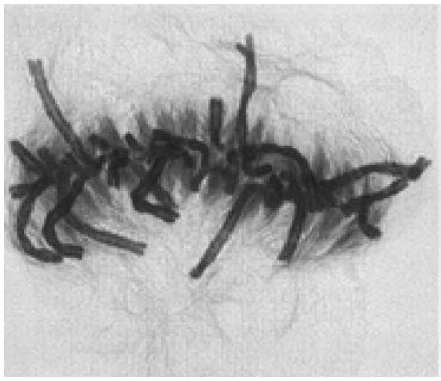
- **Nucleoli disappear** as their DNA passes to certain chromosomes.
- During late prophase (also known as prometaphase), the **nuclear envelope breaks down** into small vesicles which disperse.

Spindle fibres

- Outside the nucleus, duplicated pair of centrioles / centrosomes (in animal cells) move towards **opposite poles** of the cell.
- Short microtubules, known as **asters**, may be seen radiating from the centrioles.
- Microtubules extending from each centrosome then invade the nuclear area. Chromosomes **attach to kinetochore microtubules** via their **kinetochores** and thus undergo active movement.

Metaphase





Behaviour of chromosomes

- Chromosomes are **aligned** at the **metaphase plate / equator** of the cell.
- Kinetochore microtubules attach sister chromatids to opposite poles of the spindle.

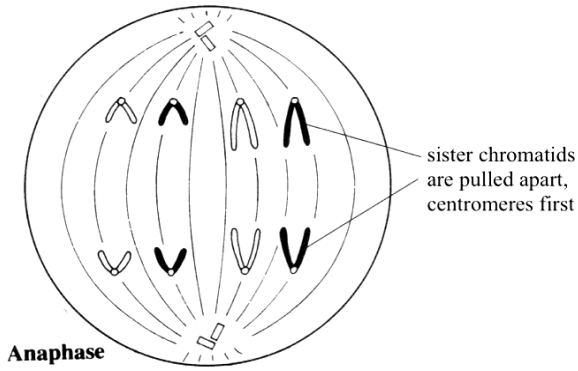
Nucleus

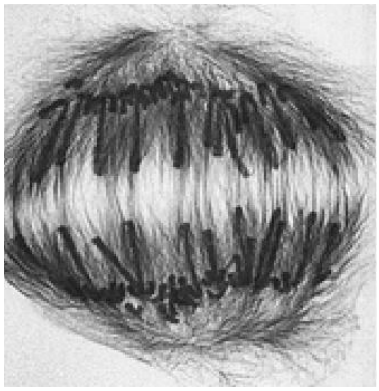
- Nucleus absent

Spindle fibres

- **Centrosomes** are now at **opposite poles** of the cell.

Anaphase





Behaviour of chromosomes

- The **centromere** of each chromosome **separates** into two, causing **sister chromatids** of each chromosome to **separate**.
- Each chromatid becomes a **daughter chromosome**.

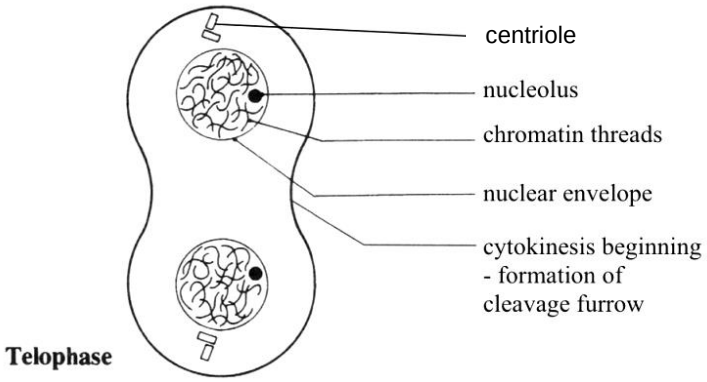
Nucleus

- Nucleus absent

Spindle fibres

- Kinetochore microtubules shorten, pulling the **daughter chromosomes** to opposite poles, **centromeres first**.
- Interpolar microtubules lengthen, causing spindle poles to move apart and the cell to **elongate**.

Telophase



Behaviour of chromosomes

- The two sets of daughter chromosomes **arrive at the opposite poles** of the spindle.
- Chromosomes **decondense** into chromatins.

Nucleus

- A new **nuclear envelope reassembles** around the chromosomes at each pole and the **nucleoli reappear**, completing the formation of two genetically identical daughter nuclei.

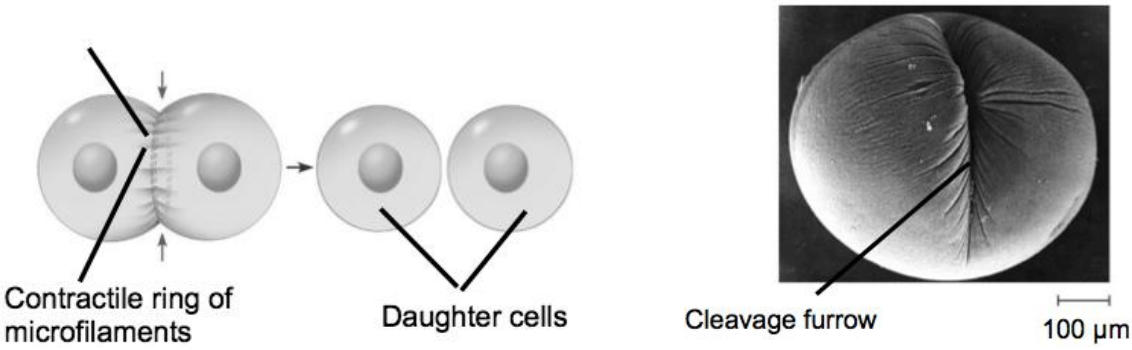
Spindle fibres

- Microtubules dis-assemble.

Cytokinesis (cytoplasmic division)

- Cytokinesis is the final step of the cell cycle and involves **division of the cytoplasm**.
- It typically overlaps with the later stages of mitosis.

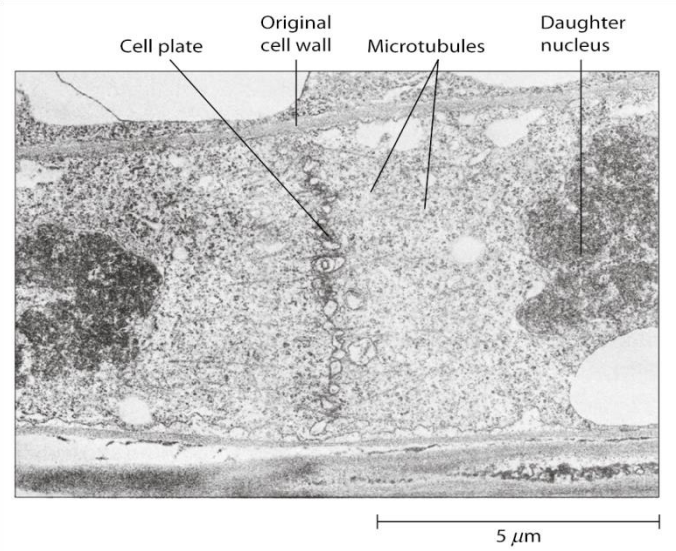
Cytokinesis in animal cells

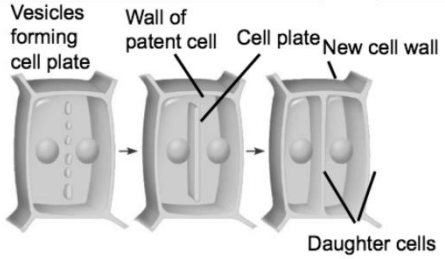


Cleavage in an animal cell. Just beneath the plasma membrane, a contractile ring of microfilaments at the former spindle equator contracts, so that its diameter shrinks all around the cell. The contractions continue and cut the cell into two.

- In most animal cells cytokinesis begins in anaphase and ends shortly after the completion of mitosis in telophase.
- In animal cells, cytokinesis involves the formation of a **cleavage furrow** – a shallow groove on the cell surface near the old metaphase plate. The furrow rapidly deepens until it completely divides the cell into two.
    - The structure underlying this process is a **contractile ring of actin microfilaments** that contracts to pinch the cell into two.
- This results in the formation of two daughter cells with identical nuclei.

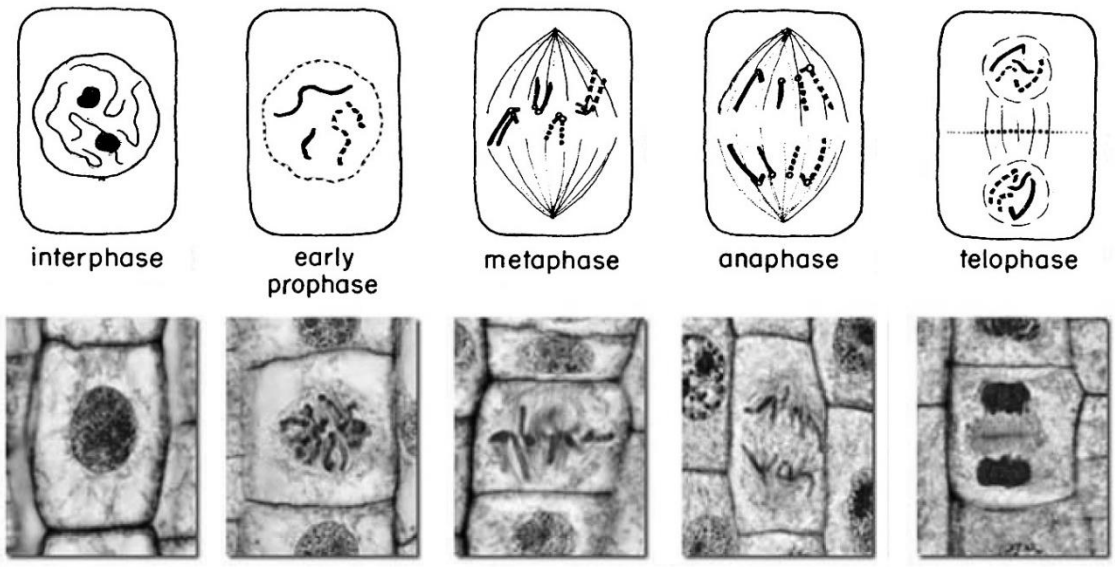
Cytokinesis in plant cells



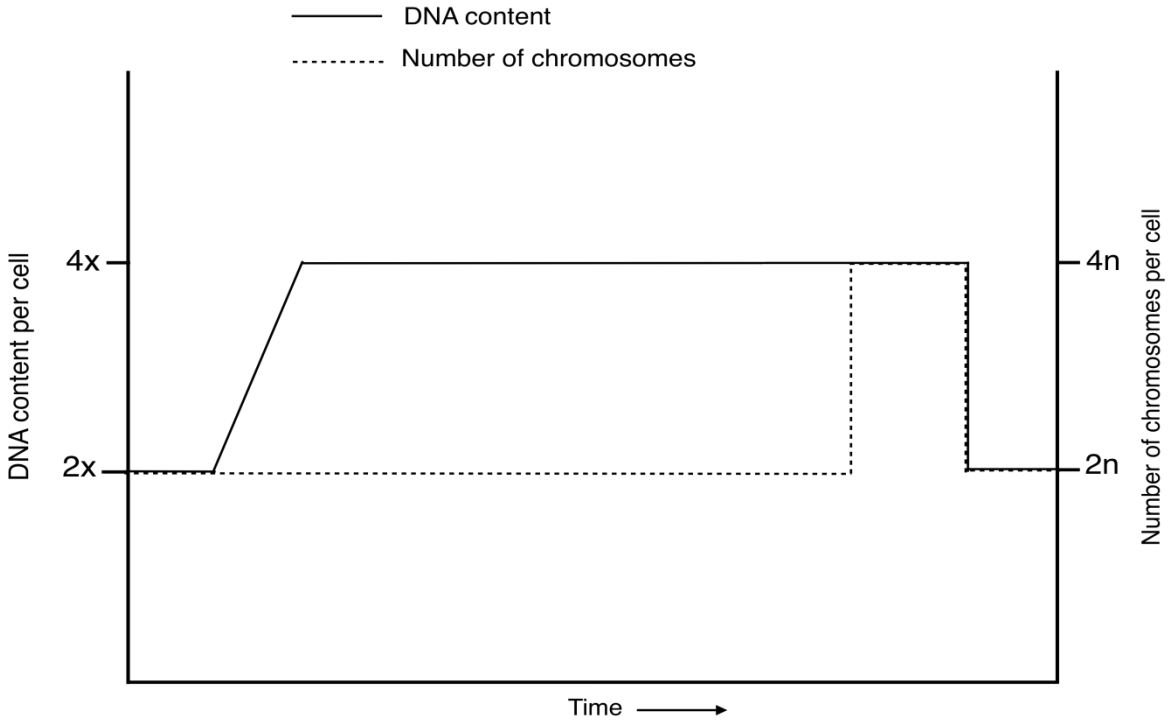


- During cytokinesis in plant cells, the cytoplasm is partitioned from the inside out (as opposed to outside in for animal cells) by the construction of a new cell wall, called the **cell plate**, between the two daughter nuclei.
- Assembly of the cell plate begins in late anaphase.
- **Vesicles derived from the Golgi apparatus** move along microtubules to the middle of the cell, where they **fuse** to form a **cell plate**. Cell wall materials carried in the vesicles, e.g. polysaccharides and glycoproteins, collect in the cell plate as it grows.
- Cell plate enlarges by further vesicle fusion until it reaches the plasma membrane and original cell wall and divides the cell in two.
- Later, cellulose microfibrils are laid down within the matrix of the cell plate to complete construction of the new cell wall.

Summary of the Events of Cell Division in an Onion Cell as Seen under a Microscope



Graph showing changes in DNA content and number of chromosomes *per cell* throughout *one cell cycle*



E. Significance of Mitosis

- **Genetic stability** – Mitosis produces two daughter nuclei that have the same number of chromosomes as the parent cell. These chromosomes of daughter cells were derived from parental chromosomes by replication of their DNA, hence they will be genetically identical to the parent chromosomes – no variation in genetic information. This results in genetic stability within populations of cells derived from the same parental cells. Genetically identical daughter cells can then function harmoniously as part of the same tissue, organ and organism.
- **Growth** – Mitosis allows the growth and development of a zygote into a multicellular organism, by forming new cells that are genetically identical to the existing cell(s) making up the individual.
- **Cell replacement** – It supplies new cells required to repair worn-out or damaged tissues. Damaged and worn cells must be replaced by exact copies of the originals to return a tissue to its former condition.
- **Regeneration** – Some animals are able to regenerate whole parts of the body, e.g. legs in crustacean, arms in starfish. Production of new genetically identical daughter cells involves mitosis.
- **Asexual reproduction** – Cells of a parent organism can divide by mitosis to produce genetically identical daughter cells that can form new offspring. The production of genetically identical individuals (**clones**) enables the species to reproduce rapidly in an environment that the parent plant is well adapted to. By exploiting favourable conditions, the species therefore colonises the habitat much more quickly than if it used sexual reproduction to propagate.

III. CANCER

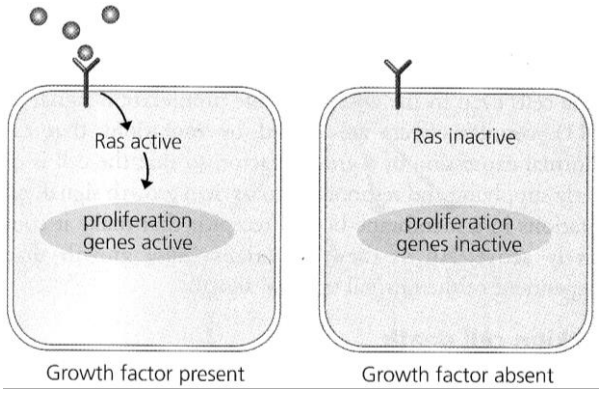
A. Cancer is a Genetic Disease

Definition

Cancer is a disease in which abnormal cells divide in an uncontrolled fashion, invade and colonise areas that are normally reserved for other cells. Cancer results from mutations in proto-oncogenes and tumour suppressor genes.

Genes are involved in regulation of cell proliferation

Cell division (a.k.a. proliferation) during the cell cycle is a highly regulated process. This regulation involves genes that code for (i) growth factors; (ii) their receptors; and (iii) the intracellular molecules of signal transduction pathways.



Regulation of cell division

Cell division is normally stimulated when (i) intercellular growth factors bind to transmembrane receptors and (ii) activate an intracellular signal transduction mechanism, involving the Ras protein, which (iii) results in the activation of genes required for cell cycle progression.

When the growth factor is absent, the cell does not divide.

Environmental factors can alter genes in cells.

Mutations that alter genes involved in cell cycle regulation can lead to cancer. The agent of such genetic alternation can be random spontaneous mutation.

However, it is likely that many cancer-causing mutations result from environmental influences, such as

- Exposure to ultraviolet radiation and ionising radiation (e.g. X-rays, nuclear radiation) – These various types of radiation can cause various types of DNA damage.
- Exposure to carcinogenic chemicals (e.g. asbestos, benzene, tar, ethidium bromide, carbon tetrachloromethane) – Likewise, these chemical carcinogens can cause DNA damage.
- Infection by certain viruses that carry oncogenes, which may then be introduced into cells.
    - E.g. Hepatitis B virus and hepatitis C virus can cause liver cancer
    - E.g. Human papilloma virus (HPV) can lead to cervical cancer.
- Loss of immunity - A weakened immune system (due to factors such as HIV/AIDS, poor nutrition) is less able to destroy cancer cells and fight viral infections that may lead to cancer.
- Genetic predisposition – Cancers can result from certain heritable gene mutations (e.g. loss-of-function mutations in tumour suppressor genes).
- Lifestyle factors
    - Smoking is a known cause of lung cancer.
    - Heavy alcohol use can increase the risk of liver cancer.
    - Diet – e.g. consumption of red meat, saturated fat and excess calories – also appears to be a vital factor.
- Age – The chances of developing cancer increase dramatically with age.

Genetic alterations can cause cancer.

It is now established that cancer is a disease caused by genetic alterations to cells.

1. In some cases, predisposition to cancer is genetic.

   For example, individuals with xeroderma pigmentosum lack one of the DNA excision repair enzymes. The result is a dramatically increased sensitivity to sunlight and incidence of cancer.

2. However, cancer is not necessarily an inherited disease.

   In fact, the majority of cancers are sporadic (i.e. there is no family history). In these cancers, genetic changes accumulate in somatic cells during the lifetime of the individual, resulting in the development of cancer.

Cancer is caused by mutation of proto-oncogenes and tumour suppressor genes.

1. The study of genes that are mutated in cancer cells has revealed two different classes of genes:
   a. oncogenes; and
   b. tumour suppressor genes.
2. The proteins encoded by many proto-oncogenes and tumour suppressor genes are components of signal transduction pathways (a.k.a. cell signalling pathways). The focus is on the products of two key genes:
   a. the *ras* proto-oncogene – mutation of which causes 30 % of human cancers; and
   b. the *p53* tumour suppressor gene – mutation of which causes more than 50 % of human cancers.

Proto-oncogenes and Oncogenes

Definitions

Proto-oncogene: Normal gene, whose products is concerned with the promotion of normal cell division. The proto-oncogene can be converted into cancer-promoting oncogene by mutation.

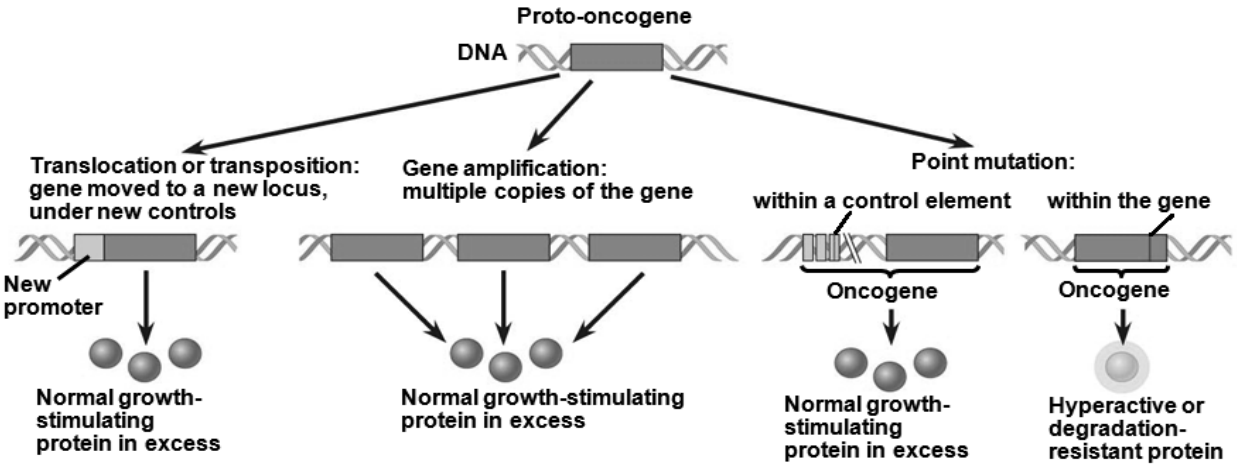
Oncogene: An oncogene is produced by a gain-in-function mutation of a proto-oncogene, whose product can act in a dominant fashion to make a cell cancerous, i.e. results in overstimulation of cell division. An oncogene can code for hyperactive / degradation-resistant proteins OR code for an excess of normal proteins.

Proto-oncogenes mutate to become oncogenes

1. Research on tumour viruses led to the discovery of cancer-causing genes called oncogenes (from Greek *onco*, tumour) in certain retroviruses. Subsequently, close counterparts of these oncogenes were found in the genomes of humans and other animals!
   - The normal versions of the cellular genes, called proto-oncogenes, code for proteins that stimulate normal cell division.
2. How might a proto-oncogene - a gene that has an essential function in normal cells become a cancer-causing gene?

   In general, an oncogene arises from a genetic change that leads to an increase either (i) in the amount of the proto-oncogene's protein product; or (ii) in the intrinsic activity of each protein molecule. The genetic changes that convert proto-oncogenes to oncogenes fall into three main categories:

   a. movement of DNA within the genome;
   b. amplification of a proto-oncogene; or
   c. point mutations in a control element or in the proto-oncogene itself.



Source: Biology (8th Edition) pp. 374

a. Translocation

Cancer cells are frequently found to contain chromosomes that have broken and rejoined incorrectly, translocating fragments from one chromosome to another.

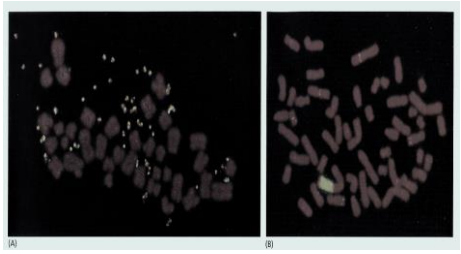
If a translocated proto-oncogene ends up near an especially active promoter (or other control element), its transcription may increase, making it an oncogene.

(Related Topic: Mutation)

b. Gene amplification

Gene amplification increases the number of copies of the proto-oncogene in the cell

(Related Topic: Control of Gene Expression - Eukaryotes)



c. Point mutation

Scenario 1:

A point mutation in the coding sequence, changes the gene's product to a protein that is (i) more active; or (ii) more resistant to degradation than the norm.

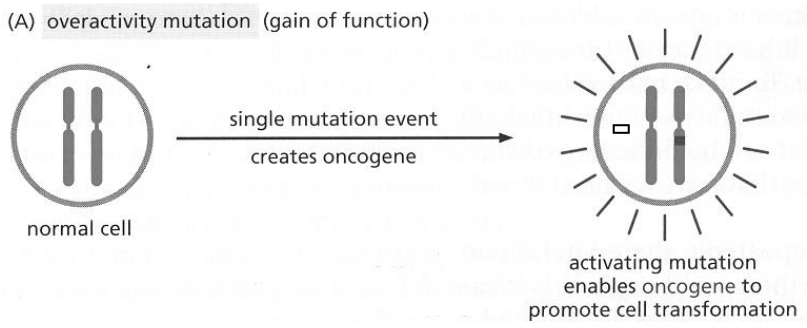
Scenario 2:

A point mutation in the promoter or an enhancer that controls a proto-oncogene causes an increase in its expression.

(Related Topic: Mutation)

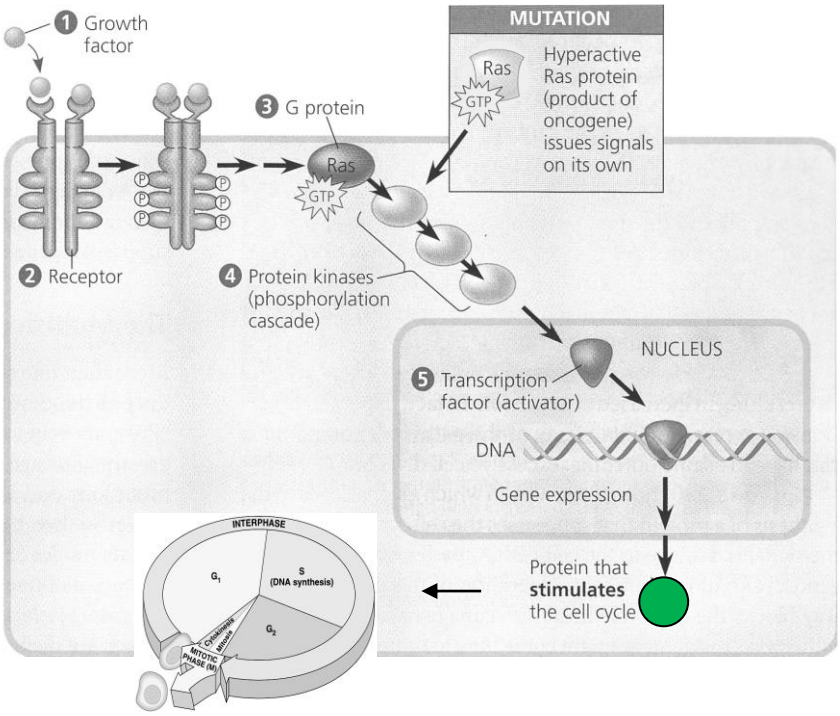
Oncogenes results from a gain in function mutation

The cellular phenotype of oncogenes is dominant, i.e. only one mutated copy is required to cause the cancer phenotype, as in gain in function mutation.



Source: Molecular Biology of the Cell (5th Edition) pp. 1232

Case study: The ras proto-oncogene



Cell cycle–stimulating pathway.
This pathway is triggered by 1 a growth factor that binds to 2 its receptor in the plasma membrane. The signal is relayed to 3 a G protein called Ras. Like all G proteins, Ras is active when GTP is bound to it. Ras passes the signal to 4 a series of protein kinases. The last kinase activates 5 a transcription activator that turns on one or more genes for proteins that stimulate the cell cycle. If a mutation makes Ras or any other pathway component abnormally active, excessive cell division and cancer may result.

Source: Biology (8th Edition) pp. 375

1. The **Ras protein**, encoded by the ***ras* gene** (named for rat sarcoma, a connective tissue cancer), is a G protein that relays a signal from a growth factor receptor on the plasma membrane to a cascade of protein kinases. *(Related Topic: Signal Transduction)*
2. The cellular response at the end of the pathway is the synthesis of a protein that stimulates the cell cycle. Normally, such a pathway will not operate unless triggered by the appropriate growth factor.
3. But certain mutations in the *ras* gene can lead to production of a hyperactive Ras protein that triggers the kinase cascade even in the absence of growth factor, resulting in increased cell division.
    - In fact, hyperactive versions or excess amounts of any of the pathway's components can have the same outcome: excessive cell division.

Tumour Suppressor Genes

Definition

Tumour suppressor gene: A gene whose protein product inhibits cell division, thereby preventing the uncontrolled cell division that contributes to cancer.

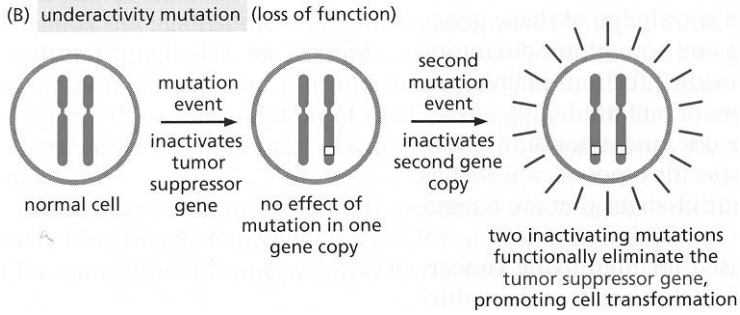
Role of tumour suppressor gene

1. In addition to genes whose products promote cell division, cells contain genes whose products inhibit cell division.
    - Such genes are called tumour suppressor genes because the proteins they encode help prevent uncontrolled cell division.
    - Any mutation that decreases the normal activity of a tumour suppressor protein may contribute to the onset of cancer, in effect stimulating cell division through the absence of suppression.

2. The protein products of tumour suppressor genes have various functions:
    a. Tumour suppressor proteins could be components of signal transduction pathways that inhibit the cell cycle.
    b. Other tumour suppressor proteins repair damaged DNA - a function that prevents the cell from accumulating cancer-causing mutations.
    c. Yet other tumour suppressor proteins induce cell death by **apoptosis**, when the damaged DNA is beyond repair.

Loss of function mutation in tumour suppressor genes results in cancer

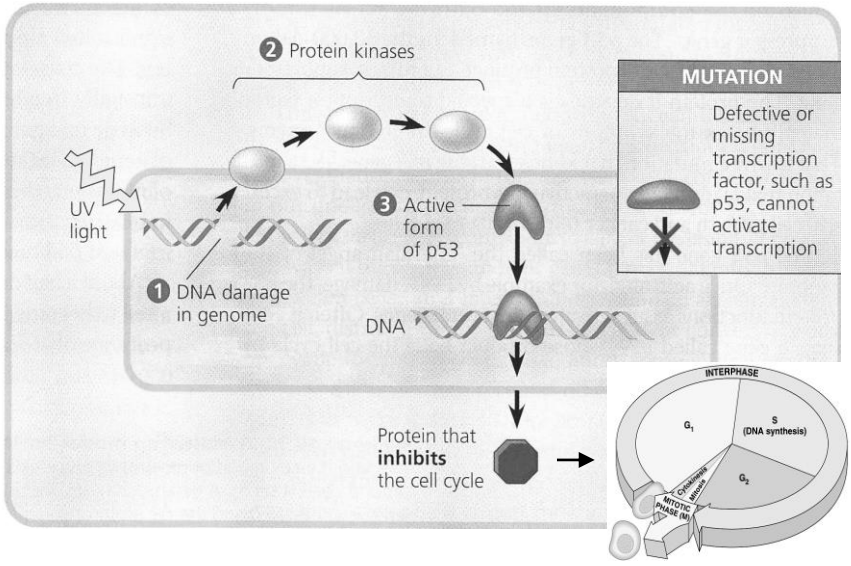
The cellular phenotype of tumour suppressor genes is recessive, i.e. mutations in both copies are required to cause the cancer phenotype, as in loss of function mutation.



Source: Molecular Biology of the Cell (5th Edition) pp. 1232

Case study: The p53 tumour suppressor gene

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. Mutations causing deficiencies in any pathway component can contribute to the development of cancer.



Source: Biology (8th Edition) pp. 375

1. In the above pathway, a signal leads to the synthesis of a protein that inhibits / suppresses the cell cycle.
2. In this case, the signal is the damage to the cell's DNA, perhaps as the result of exposure to ultraviolet light. Operation of this signal transduction pathway inhibits / blocks the cell cycle until the damage has been repaired. Otherwise, the damage might contribute to tumour formation by causing mutations or chromosomal abnormalities. Thus, the genes for the components of the pathway act as tumour suppressor genes.

a. The ***p53* gene**, named for the 53,000-dalton molecular weight of its protein product, is a tumour-suppressor gene.

b. The protein it encodes is a specific transcription factor that promotes the synthesis of cell cycle-inhibiting proteins.

c. That is why a mutation that knocks out the *p53* gene can lead to excessive cell growth and cancer.

3. The p53 gene has been called the 'guardian angel of the genome'.

   Once activated, the **p53 protein** functions as a transcription factor for several genes:

   a. Often, it facilitates the transcription of a gene called *p21*, whose product stops the cell cycle by binding to cyclin-dependent kinases ⇨ this allows the cell to repair the DNA in the meantime.

   b. The p53 protein can also turn on genes directly involved in DNA repair.

   c. When DNA damage is irreparable, p53 activates "suicide" genes, the products of which cause cell death by apoptosis.

B. Cancer is a Multistep Process

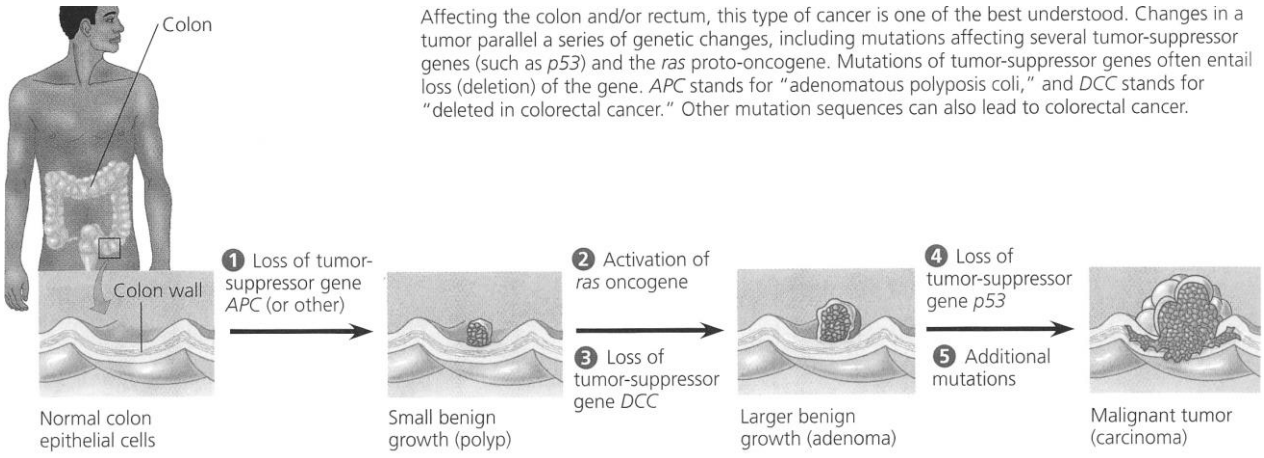
1. More than one somatic mutation is generally needed to produce all the changes characteristic of a full-fledged cancer cell.

   - This may help explain why the incidence of cancer increases greatly with age.

     If cancer results from an accumulation of mutations and if mutations occur throughout life, then the longer we live, the more likely we are to develop cancer.

2. The model of a multistep path to cancer is well supported by studies of one of the best-understood types of human cancer, colorectal cancer.

   About 135,000 new cases of colorectal cancer are diagnosed each year in the United States, and the disease causes 60,000 deaths each year.



Affecting the colon and/or rectum, this type of cancer is one of the best understood. Changes in a tumor parallel a series of genetic changes, including mutations affecting several tumor-suppressor genes (such as *p53*) and the *ras* proto-oncogene. Mutations of tumor-suppressor genes often entail loss (deletion) of the gene. *APC* stands for "adenomatous polyposis coli," and *DCC* stands for "deleted in colorectal cancer." Other mutation sequences can also lead to colorectal cancer.

Source: Biology (8th Edition) pp. 376

3. Like most cancers, colorectal cancer develops gradually:
   a. The first sign is often a polyp – a small, benign growth in the colon lining.
   b. The cells of the polyp look normal, although they divide unusually frequently.
   c. The tumour grows and may eventually become **malignant**, gaining the invasive property to extend into the surrounding tissue. Such malignant cells displays disorganized pattern of growth with ragged borders.

4. The development of a malignant tumour is paralleled by a gradual accumulation of mutations that gain in function mutation converting proto-oncogenes to oncogenes and causes loss of function of tumour-suppressor genes. A *ras* oncogene and a mutated *p53* tumour-suppressor gene are often involved.
    - About half dozen changes must occur at the DNA level for a cell to become fully cancerous.
    - These usually include the appearance of at least one active oncogene and the mutation or loss of several tumour-suppressor genes.
    - Furthermore, since mutant tumour-suppressor alleles are usually recessive, in most cases mutations must knock out both alleles in a cell's genome to block tumour suppression. Most oncogenes, on the other hand, behave as dominant alleles.

C. The Progression of Cancer

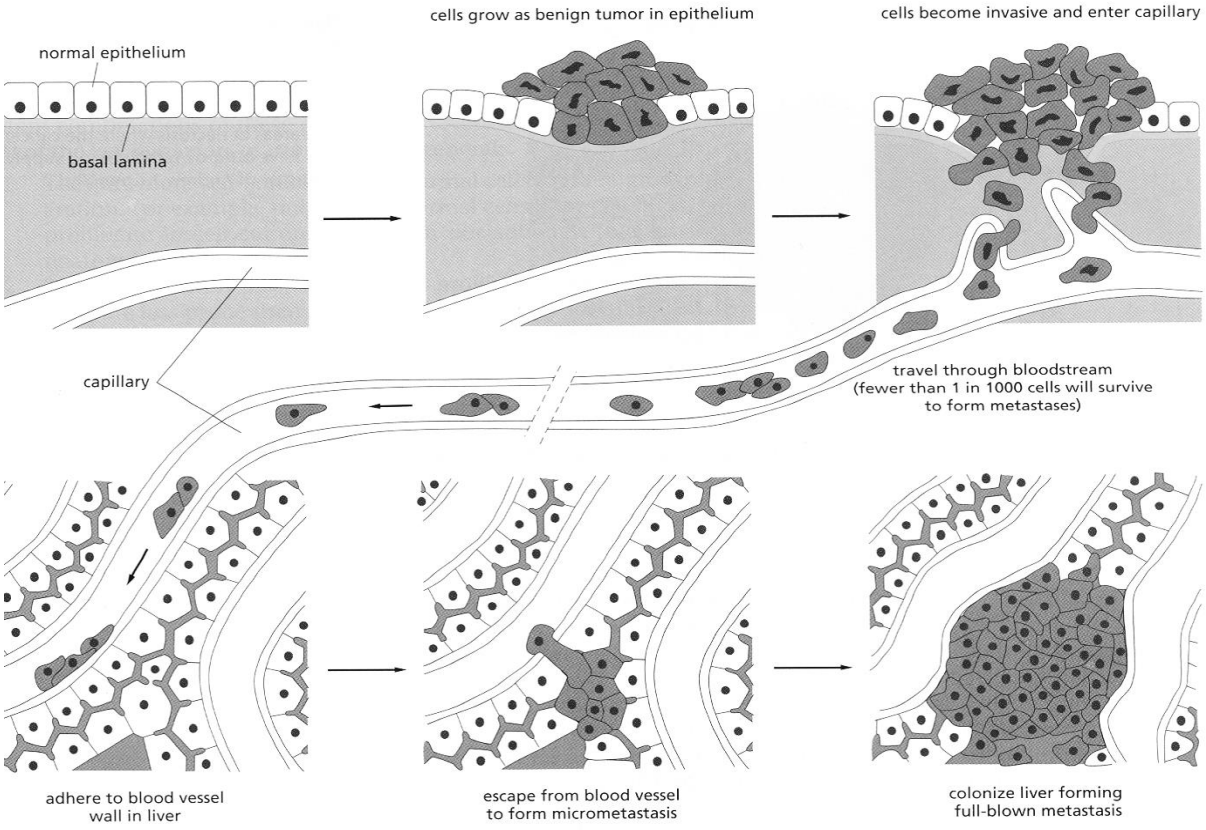


Figure 20–17 Steps in the process of metastasis. This example illustrates the spread of a tumor from an organ such as the bladder to the liver. Tumor cells may enter the bloodstream directly by crossing the wall of a blood vessel, as diagrammed here, or, more commonly perhaps, by crossing the wall of a lymphatic vessel that ultimately discharges its contents (lymph) into the bloodstream. Tumor cells that have entered a lymphatic vessel often become trapped in lymph nodes along the way, giving rise to lymph-node metastases. Studies in animals show that typically far fewer than one in every thousand malignant tumor cells that enter the bloodstream will colonize a new tissue so as to produce a detectable tumor at a new site.

1. Malignant cancer cells may also gain the ability to **metastasize**. The cancer cells can penetrate a blood vessel or a lymphatic vessel, exit from a vessel elsewhere in the body, and then establish new cellular colonies at distant sites.
    - Metastasis is the most deadly aspect of cancer, being responsible for 90% of cancer-associated deaths.
    - By spreading throughout the body, a cancer becomes almost impossible to eradicate by either surgery or localized irradiation.

2. In many malignant tumours, the gene for telomerase is activated. This enzyme reverses the shortening of chromosome ends during DNA replication. Production of telomerase in cancer cells removes a natural limit on the number of times the cells can divide.

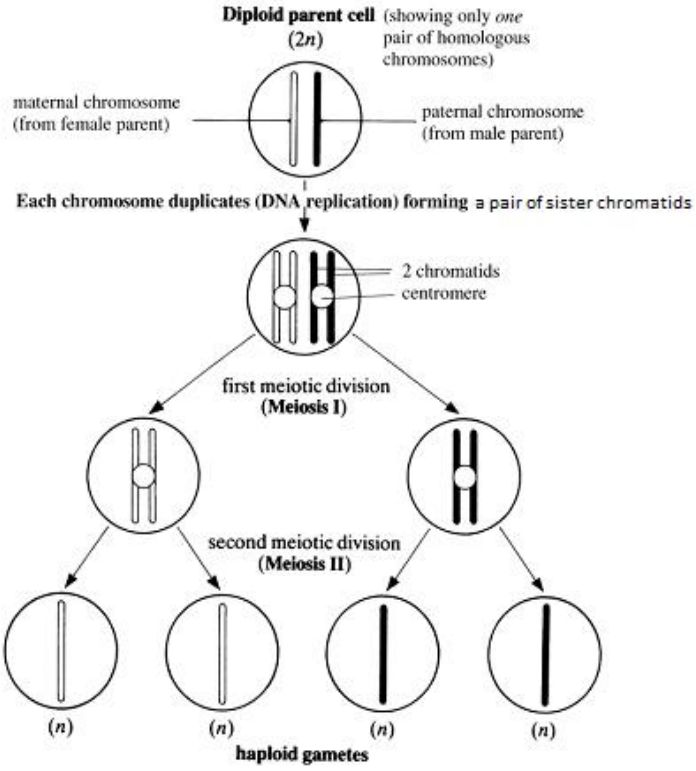
3. In addition, for tumours to grow large, a tumour must recruit adequate blood supply to ensure that it gets sufficient oxygen and nutrients. Thus, **angiogenesis**, the formation of new blood vessels, is required for tumour growth beyond a certain size.
    - Like normal tissues, tumours attract a blood supply by secreting angiogenic signals. These signals are produced in response to hypoxia, which begins to affect the cells as the tumour enlarges beyond 1mm in diameter.
    - The vasculature in that grows into tumour is leaky, increasing to possibility of tumour cells escaping into the blood or lymphatic vessels.

IV. MEIOSIS

A. Stages of Meiosis: Meiosis I and II

Definition: Meiosis (*meio*, to reduce) is the process by which a cell nucleus divides to produce **four** daughter nuclei, each containing half the number of chromosomes found in the original nucleus. A single diploid cell would give rise to four haploid cells**,** each carrying only a single set of chromosome.

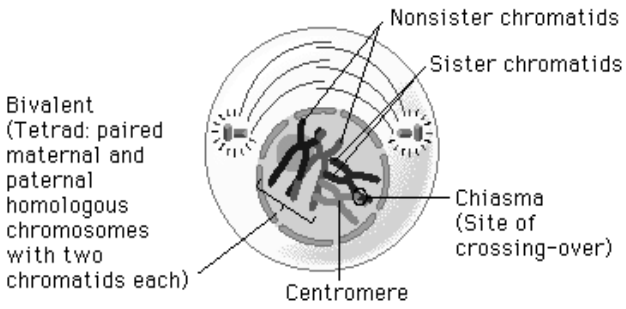
- Meiosis is preceded by DNA replication during interphase in the parent cell. This is then followed by **two** cycles of nuclear and cytoplasmic divisions.
    - The first nuclear division is known as **meiosis I** (the first meiotic division), and the second nuclear division is known as **meiosis II** (the second meiotic division).
    - Meiosis is a continuous process and can be divided into the phases of prophase, metaphase, anaphase and telophase in both meiosis I and II.

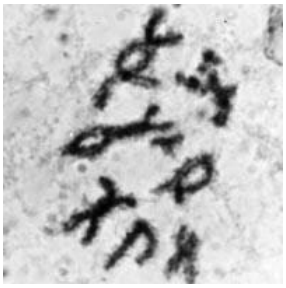


The basic characteristic of meiosis showing one chromosome duplication followed by two nuclear and cell divisions.

Meiosis I

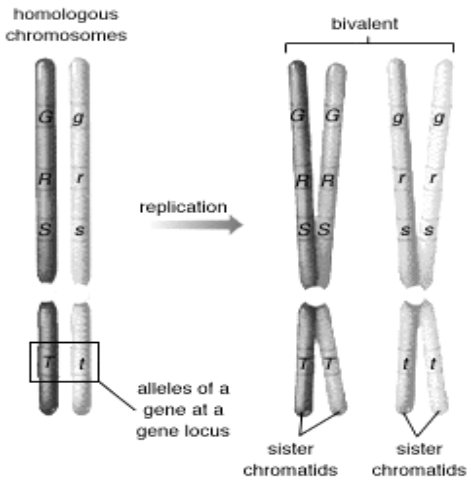
Prophase I



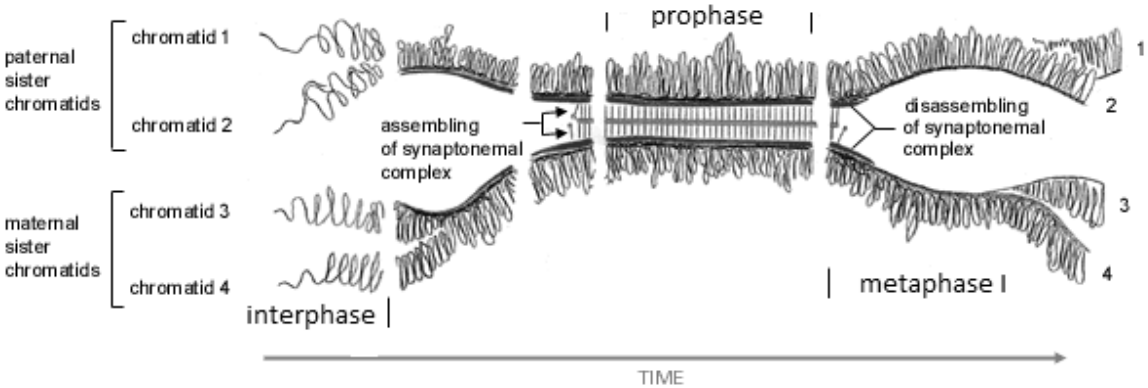


Behaviour of chromosome

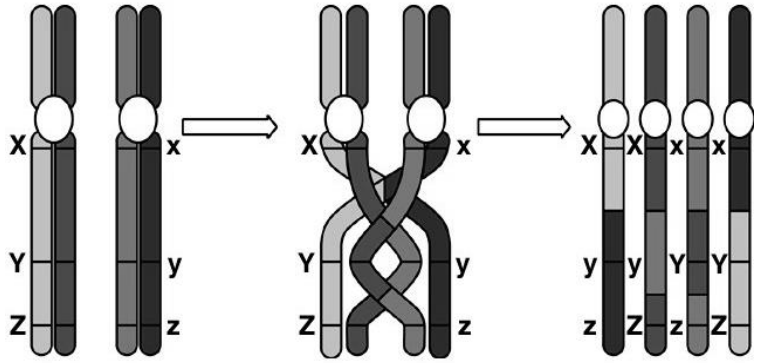
- Chromatin becomes more tightly coiled, condensing into discrete chromosomes.
- Each chromosome = two identical sister chromatids joined together at the centromere.
- Homologous chromosomes pair up to form a **bivalent** (or **tetrad**), via the process called **synapsis**.
    - This involves the assembly of protein complexes between homologues, forming the synaptonemal complex that holds homologous chromosomes together.
    - Significance of synapsis: This process is precise and brings the gene loci on homologous chromosomes into precise alignment *(essential for exchange of genetic material during crossing over)*.
- The bivalents shorten and thicken further, partly by coiling.



- The homologous chromosomes appear to repel each other and partially separate.

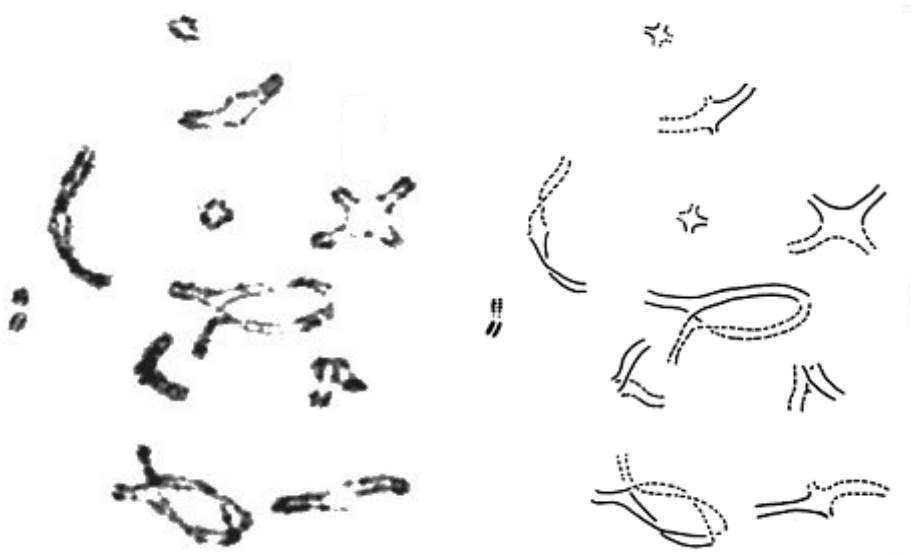


Chromosome synapsis and desynapsis during the different stages of meiosis.



Crossing over during meiosis.

- A process known as **crossing over** occurs between **non-sister chromatids of homologous chromosomes**.
    - One chromatid of the paternal chromosome and one chromatid of the maternal chromosome join each other at one or several points known as **chiasmata** (singular: chiasma).
    - Each chiasma is the site of an exchange of genetic material / alleles[1] between non-sister chromatids of homologous chromosomes.
    - At each chiasma, the chromatid may break and rejoin with a non-sister chromatid of the other chromosome in the bivalent. This gives rise to **new combinations of alleles** in the resulting chromatids.



Crossing over in prophase I, showing chiasmata, in the locust Locusta migratoria*. Bivalents are present with 1 or 2 chiasmata each. Paternal and maternal chromosomes are represented by solid and dotted lines respectively in the drawing. At each chiasma, a genetic exchange has occurred.*

- The bivalents assume particular shapes, varying from cross shape to ring shape, depending on the number and position of chiasmata.

[1] Allele: One of a set of alternative form of a gene. In a diploid cell each gene will have two alleles, each occupying the same position (locus) on homologous chromosomes.
Gene: Base sequence of DNA that controls a phenotype, usually corresponding to a polypeptide chain.

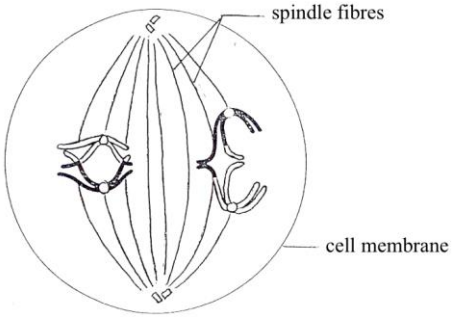
Nucleus

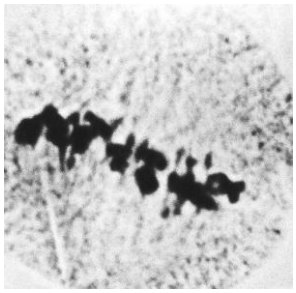
- By late prophase, the nucleoli **disappear** and nuclear envelope **disintegrates**.

Spindle fibres

- Outside the nucleus, the mitotic spindle assembles between the two centrosomes (in animal cells), which move towards **opposite poles** of the spindle.
- Astral microtubules radiate from the centrioles.
- Kinetochore microtubules attach to centromeres of chromosomes via kinetochore proteins.
- Kinetochore microtubules from one pole of the cell attach to one homologous chromosome of each bivalent, while those from the opposite pole attach to the other homologous chromosome of each bivalent.

Metaphase I





Behaviour of chromosome

- Homologous pairs of chromosomes (bivalents) are aligned on the metaphase plate of the spindle, with one chromosome in each bivalent facing each pole.
- **Independent assortment of homologous chromosomes** occurs, i.e. the orientation of each bivalent along the metaphase plate is **random** and **independent** of the orientation of other bivalents. *(This has implications on genetic variation among the resulting daughter cells)*

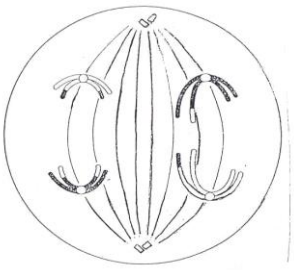
Nucleus

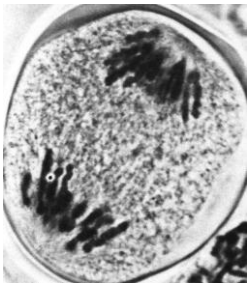
- Nucleolus and nuclear envelope absent.

Spindle fibres

- Centromeres of chromosomes are attached to kinetochore microtubules via kinetochore protein. Active movement of the microtubules places each bivalent on the metaphase plate, with each centromere equidistant above and below it.

Anaphase I





Behaviour of chromosome

- **Homologous chromosomes** move towards opposite poles of the spindle.
  (*Note: Sister chromatids do not separate during anaphase I, thus each chromosome still comprises a pair of sister chromatids. Sister chromatids will remain attached at the centromeric region until anaphase II.)*
- This separates the chromosomes into two haploid sets, one set at each end of the spindle i.e. reduction by halving the chromosome numbers in daughter cells.

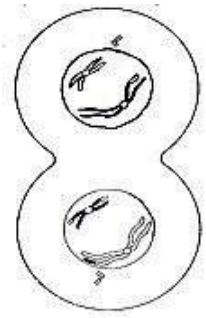
Nucleus

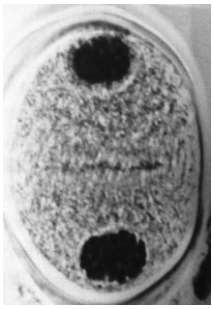
- Nucleolus and nuclear envelope absent.

Spindle fibres

- Kinetochore microtubules shorten, pulling **homologous chromosomes**, centromeres leading, towards opposite poles of the spindle.
- Interpolar microtubules lengthen, causing spindle poles to move apart and the cell to elongate.

Telophase I





Behaviour of chromosome

- Homologous chromosomes reach opposite poles of the cell, thus marking the end of meiosis I.
- Chromosomes decondense to form chromatin.

Nucleus

- Nucleolus **reappears** and nuclear envelope reforms.

Spindle fibres

- Spindle fibres disassemble.

Cytokinesis

- Cytokinesis (via cleavage in animal cells or cell wall formation in plant cells) occurs as in mitosis. The cell subsequently undergoes **interphase II**, a short rest period during which there is no S phase, i.e. no DNA replication occurs.

Meiosis II

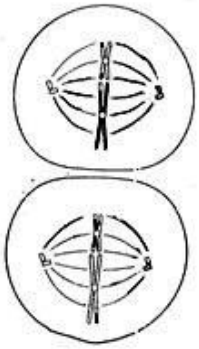
Prophase II

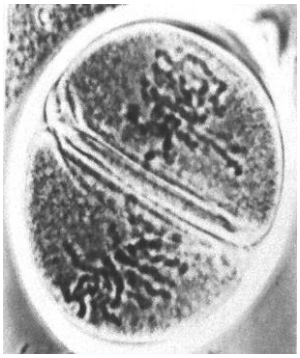
Behaviour of chromosome
- Chromatin becomes more tightly coiled, condensing into discrete chromosomes.
  - Each chromosome = two non-identical sister chromatids joined together at the centromere.
  - The two sister chromatids of each chromosome might not be genetically identical due to crossing over in prophase I.

Nucleus
- Nucleoli **disappear** and nuclear envelopes disintegrates.

Spindle fibres
- Centrioles / centrosomes move to opposite poles of the cells.
- New microtubules appear and become attached to kinetochore region of the chromosomes. Microtubules from each pole of the spindle are attached to one of the two sister chromatids making up each chromosome.
- The new spindle microtubules are oriented at **right angles** to the original spindle microtubules of meiosis I.

Metaphase II



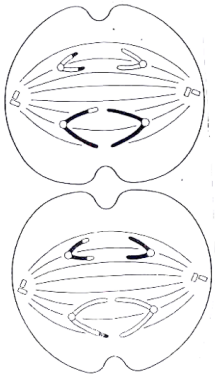


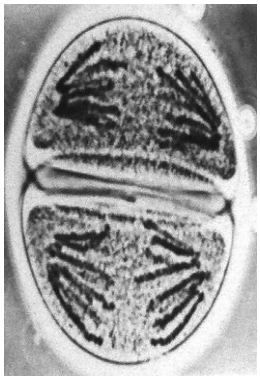
Behaviour of chromosome
- Chromosomes, each with its two non-identical sister chromatids, are aligned individually along the metaphase plate.

Nucleus
- Nucleolus and nuclear envelope absent.

Spindle fibres
- Kinetochore microtubules attach each of the two sister chromatids of a chromosome to opposite poles of the spindle.

Anaphase II



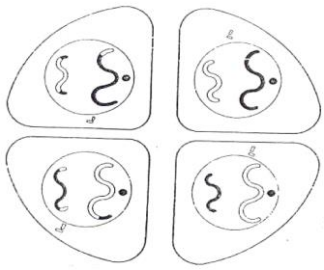


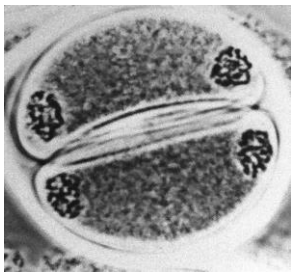
Behaviour of chromosome
- Centromeres separate, sister chromatids separate at the centromeric region. Each sister chromatid is now known as a daughter chromosome.

Nucleus
- Nucleolus and nuclear envelope absent.

Spindle fibres
- Kinetochore microtubules shorten, pulling the daughter chromosomes to opposite poles, centromeres leading.
- Interpolar microtubules lengthen, causing spindle poles to move apart and the cell to elongate.

Telophase II





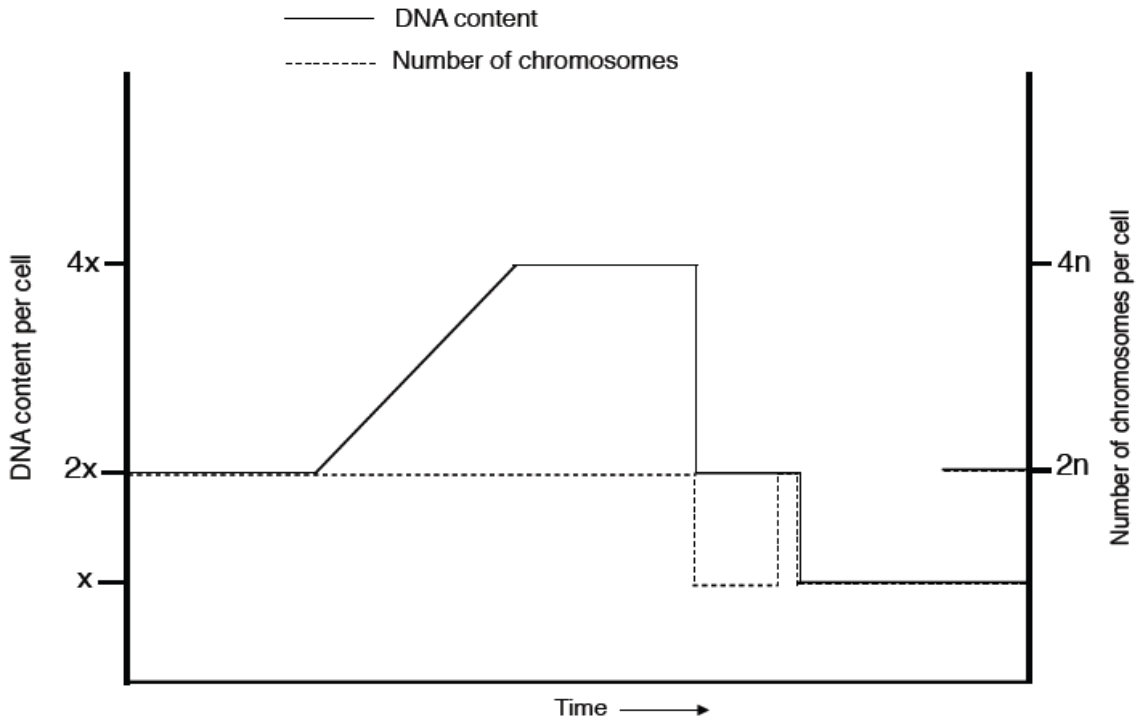
Behaviour of chromosome
- Daughter chromosomes reach opposite poles of the cell.
- Chromosomes decondense to chromatin.

Nucleus
- Nuclear envelopes reform around each nucleus and nucleoli reappears, completing the formation of four **daughter nuclei**.

Spindle fibres
- Spindle fibres disassemble.

Cytokinesis
- Subsequent cytokinesis (via cleavage for animal cells and cell wall formation for plant cells) produce **four haploid daughter cells** that are **genetically different** from the parent cell.

Graph showing changes in DNA content and number of chromosomes *per cell* as a cell undergoes *meiosis*



B. Significance of Meiosis

Sexual reproduction

- Meiosis occurs in all organisms carrying out sexual reproduction, producing haploid gametes.
- During fertilisation, the nuclei of two haploid gametes fuse, producing a diploid zygote, thus **restoring the fixed diploid number of chromosomes** for the particular species.
- If meiosis did not occur to produce gametes with half the number of chromosomes as somatic cells, fusion of gametes would result in the doubling of chromosome number for each successive sexually reproduced generation.

Genetic variation

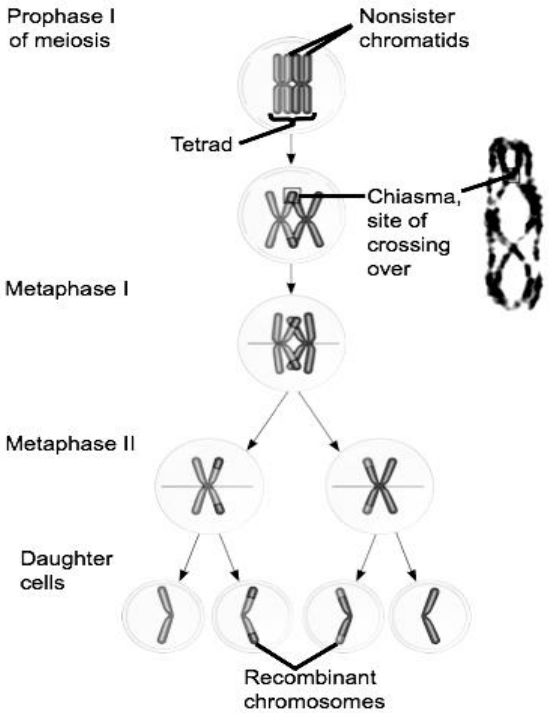
Meiosis provides opportunities for **new combinations of alleles** to occur in gametes.

- This in turn leads to **genetic variation in offspring** produced by sexual reproduction. Offspring are genetically different from one another and their parents.
- The presence of genetic variability allows species to constantly evolve and have a higher chance of adapting to and surviving environmental changes. This helps to ensure the **long term survival** of a species. (*KIV: Diversity & Evolution*)
- Meiosis brings about **genetic variation** in two ways:

  1) Crossing over between homologous chromosomes in prophase I, and

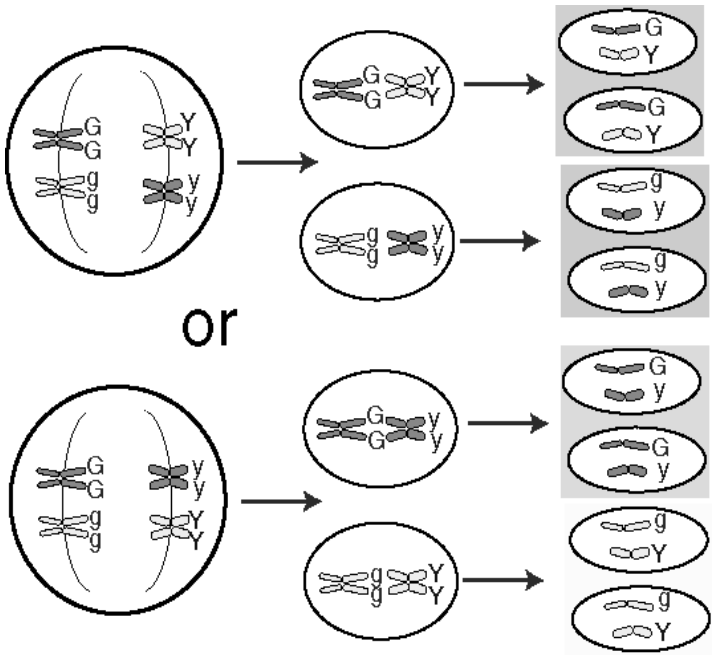
  2) Independent assortment of homologous chromosomes in metaphase I.

Crossing over between homologous chromosomes in prophase I



- Crossing over between non-sister chromatids of homologous chromosomes during prophase I produce **recombinant chromosomes**, which contain new combinations of alleles that are inherited from both parents. This increases genetic variation. (*Without crossing over, each chromosome would be exclusively maternal or paternal in origin.*)

Independent assortment of homologous chromosomes in metaphase I



- During **metaphase I of meiosis**, the orientation of each bivalent at the metaphase plate is **random and independent** of other bivalents.
- There is a 50% chance that a particular daughter cell of meiosis I will get the maternal chromosome of a certain homologous pair, and a 50% chance it will receive the paternal chromosome instead.

- This eventually results in **random sorting of paternal and maternal chromosomes** to each of the resulting daughter nuclei in meiosis I, producing various combinations of paternal and maternal alleles in daughter cells. The more bivalents there are the more variation is possible among the daughter nuclei.
- Generally, the number of possible combinations when chromosomes sort independently during meiosis I is 2^n where n is the haploid number of chromosomes for the organism.
- In humans, where n = 23 the total number of possible combinations is 2^{23}.

Random Fertilisation Further Adds to Genetic Variation Arising from Meiosis

- The random nature of fertilisation adds to the genetic variation arising from meiosis.
- Any male gamete can fuse with any female gamete.
- In humans, each male or female gamete represents one of about 8.4 million (2^{23}) possible chromosome combinations due to independent assortment alone. (Crossing over introduces even greater genetic variation among gametes.)
- The resulting zygote formed from the random fusion of a male gamete with any female gamete during fertilisation can therefore contain any of at least 70 trillion (2^{23} X 2^{23}) possible diploid combinations of chromosomes.

In summary, all three mechanisms (independent assortment, crossing over and random fertilisation) result in **genetic variability in populations** of sexually reproducing organisms, by reshuffling the **alleles** carried by individual members of a population.

C. Comparison of Mitosis and Meiosis