The Mitotic Cell Cycle

5.1 Replication & Division of Nuclei & Cells

Chromosomes: a structure made of DNA and histones, found in the nucleus of a eukaryotic cell; the term bacterial chromosome is now commonly used for the circular strand of DNA present in a prokaryotic cell. They contain DNA which contains genetic information in the form of genes.

- During interphase (S phase) the DNA replicates to create two identical strands of DNA called chromatids, joined together by a narrow region called the centromere.
- **DNA**: Chromosomes contain a long, coiled strand of DNA, which carries genetic information. The DNA is a double helix made of nucleotides, which include a phosphate group, a sugar (deoxyribose), and a nitrogenous base (A, T, C, or G). The sequence of these nucleotides encodes genetic information.
- **Histone Proteins**: DNA is tightly wrapped around proteins called histones. These histone proteins help organize the DNA into a compact structure. The DNA wraps around histone complexes, forming nucleosomes, which resemble "beads on a string." This packaging allows the long DNA strand to fit within the cell nucleus.
- **Sister Chromatids**: After DNA replication, each chromosome consists of two identical DNA strands, known as sister chromatids. These chromatids are exact copies of each other and are attached at a central point, preparing for cell division. The two chromatids that make up the double structure of a chromosome are known as 'sister chromatids.' It is important that the sister chromatids are identical (contain the same genes) because this is key to cell division, as one chromatid goes into one daughter cell and one goes into the other daughter cell during mitosis, ensuring the daughter cells are genetically identical. Each chromatid is made up of one very long, condensed DNA molecule, which is made up of a series of genes.
- **Centromere**: The centromere is the region where the two sister chromatids are most closely connected. It plays a crucial role during cell division (mitosis and meiosis), as it is the site where spindle fibers attach to pull the chromatids apart to opposite sides of the dividing cell.
- **Telomeres**: Telomeres are protective caps at the ends of each chromosome. They are composed of repetitive DNA sequences and protect the chromosome

from deterioration or fusion with neighboring chromosomes. Telomeres shorten with each cell division, playing a role in the aging process and cellular lifespan. The ends of the chromatids in chromosomes are 'sealed' with protective structures called telomeres.

Chromatin: the loosely coiled form of chromosomes during interphase of the cell cycle; chromatin is made of DNA and proteins and is visible as loosely distributed patches or fibres within the nucleus when stained.

Chromatid: one of two identical parts of a chromosome, held together by a centromere, formed during interphase by the replication of the DNA strand.

Passage of Information from Parent to Offspring:

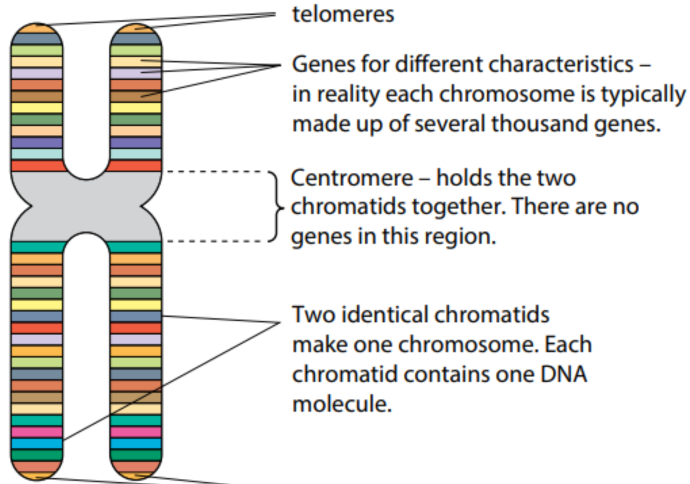
Homologous chromosomes (similar in position, structure, and evolutionary origin but not necessarily in function)

- Homologous chromosomes are two pieces of DNA within a diploid organism which carry the same genes, one from each parental source.
- There are 22 matching pairs of chromosomes called homologous chromosomes.
- Each pair is given a number. In the original zygote, one of each pair came from the mother, and one from the father.
- A non-matching pair called X and Y also exists.
- Hence there are 2 sets of 23 chromosomes- one set of 23 from the father and one set of 23 from the mother.
- A diploid cell is one that possesses two complete sets of chromosomes; the abbreviation for diploid is 2n. (2 Sets of Chromosomes. There is a pair od each type of chromosomes. There are 23 pairs in humans.)
- A haploid cell is one that possesses one complete set of chromosomes; the abbreviation for haploid is n. (Single Set of Chromosomes)

Significance of Telomerase:

- The ends of the chromatids in chromosomes are 'sealed' with protective structures called telomeres.

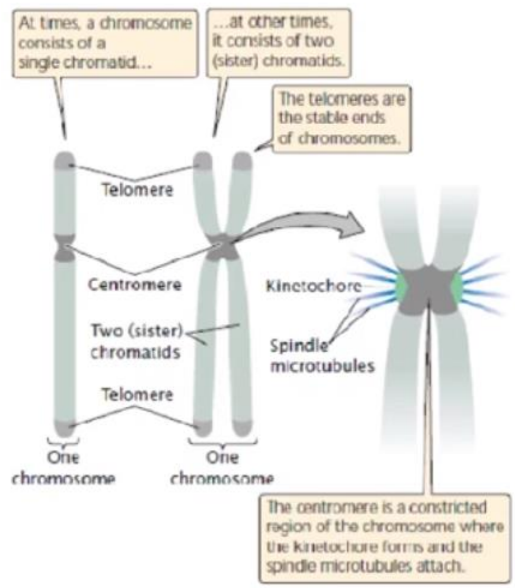
- They are made of non-coding DNA (DNA that does not contain genes) that is made up of short base sequences that are repeated many times (multiple repeat sequences).
- In telomeres, one strand is rich in the base guanine (G) and the other strand is rich in the complementary base cytosine (C).
- The main function of telomeres is to ensure that the very ends of the DNA molecules are included in DNA replication during mitosis.



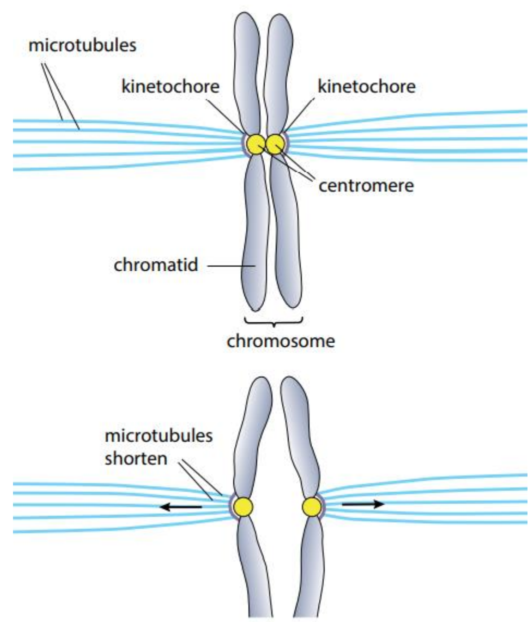
- This is because the copying enzyme responsible for DNA replication is unable to run right to the very end of the DNA molecule and stops a little short of the end. If this end part of the DNA molecule contained an important gene, that piece of genetic information would be lost during DNA replication.
- In each subsequent cell division, a little more genetic information would be lost.
- Telomeres therefore act as a 'buffer' region of non-essential DNA and ensure that no important coding sections near the ends of the DNA molecules are left out of the replication process.
- This ensures no genes are lost during cell division (the loss of vital genes can even result in cell death) and allows for continued replication of a cell. To avoid the risk of losing genes most cells have an enzyme called telomerase that adds additional bases at each end (the telomeres).
- Some cells (generally specialised cells) do not have telomerase to 'top up' their telomeres and therefore after a certain number of cell divisions the cell dies, this has been connected with the ageing process.
- The solution is to make the DNA a bit longer by adding some more bases.
- They have no useful information, but allow the copying enzyme to complete copying the meaningful DNA.
- As long as extra bases are added during each cell cycle, no vital information will be lost and the cell will be able to continue dividing successfully.
- The enzyme that performs this role is called telomerase.
- The extra DNA it adds is the telomere.

- THE MAIN FUNCTION OF TELOMERES IS THEREFORE TO PREVENT THE LOSS OF GENES DURING CELL DIVISION AND TO ALLOW CONTINUED REPLICATION OF A CELL.

Centromeres, Centrosomes & Centrioles:

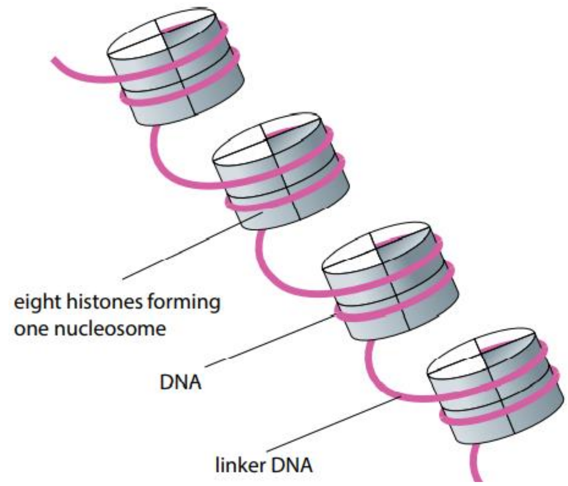


- The centromere is needed for the separation of chromatids during mitosis. It is visible as a constriction.
- It is the site of attachment of spindle microtubules.
- Each metaphase chromosome has two kinetochores at its centromere, one on each chromatid.
- These are made of protein molecules which bind specifically to the DNA in the centromere and also bind to microtubules.
- Bundles of microtubules called spindle fibres extend from the kinetochores to the poles of the spindle during mitosis.
- Construction of kinetochores begins before nuclear division starts (during the S phase of the cell cycle) and they are lost again afterwards. The microtubules attached to a given kinetochore pull the kinetochore, with the rest of its chromatid dragging behind, towards the pole.



- This is achieved by shortening of the microtubules, both from the pole end and from the kinetochore end. The poles of the spindle are where the centrosomes are located, one at each pole.
- The centrosome is an organelle found in animal cells that acts as the microtubule organising centre (MTOC) for construction of the spindle.
- Each centrosome consists of a pair of centrioles surrounded by a large number of proteins.
- It is these proteins that control production of the microtubules, not the centrioles.
- Plant mitosis occurs without centrosomes.

Nucleosomes:



- The nucleosome is cylindrical in shape, about 11 nm wide by 6 nm long.
- It is made up of eight histone molecules.
- The DNA is wrapped around the outside of the cylinder, making $1\frac{2}{3}$ turns (equivalent to 147 base pairs) before linking to the next nucleosome.
- The DNA between the nucleosomes (linker DNA, 53 base pairs in length) is also held in place by a histone molecule.
- Nucleosomes line up like a string of beads to form a fibre 10nm wide.
- This string can be further coiled and supercoiled, involving some non-histone proteins.
- The extent of coiling varies during the cell cycle, the period between one cell division and the next.
- The chromosomes seen just before nuclear division represent the most tightly coiled (condensed) form of DNA.
- Between nuclear divisions, some uncoiling occurs. In fact, chromatin exists in two forms – euchromatin and heterochromatin.
- Euchromatin is loosely coiled, whereas heterochromatin is tightly coiled, as in the chromosomes seen at nuclear division.
- During the period between divisions (interphase) the majority is in the form of euchromatin. This is where the active genes are located.
- The genes in the heterochromatin are mostly inactive.

Replication & Division of Nuclei & Cells: Eukaryotes have tightly wound DNA, which is present in supercoiled form to make condense structures called chromosomes. Chromosomes have proteins attached them known as histone proteins and they are responsible for gene regulation as well as supporting DNA supercoiling period since eukaryotes are more complex, their DNA molecules are also longer.

What is the need for Cell Division:

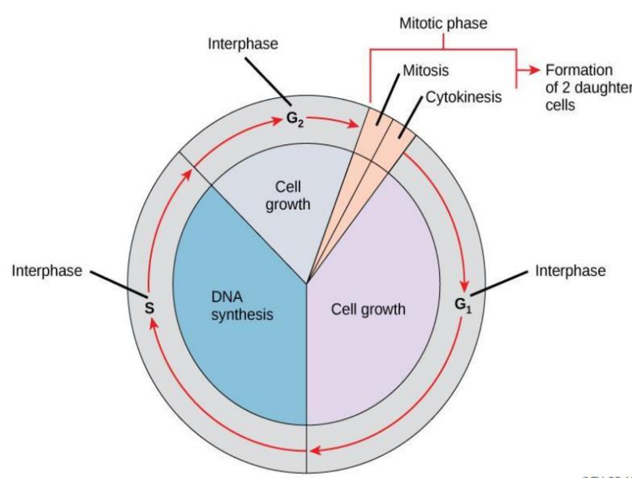
- New cells are produced from cells which already exist by cell division.
- Single celled organisms can reproduce in this way to make new organisms, whilst in multicellular organisms cell division leads to growth.
- In all cases cell division is the method of increasing the number of cells.

- Two types of cell division occur in eukaryotes: Mitosis & Meiosis.

Mitosis	**Meiosis**
Nuclear division giving rise to genetically identical cells in which the chromosome number is maintained.	Reduction division because the number of chromosomes are reduced by ½.
Genetically identical to parents (same number of chromosomes as the parent nucleus). Same number and type of chromosomes. • Growth of multicellular organisms: The two daughter cells formed allow the growth of multicellular organisms from unicellular zygotes. Growth may occur over the entire body, as in animals, or be confined to certain regions, as in the meristems (growing points) of plants. • Replacement of damaged or dead cells: This is possible using mitosis followed by cell division. • Repair of tissues by cell replacement • Asexual reproduction: genetically identical. Asexual reproduction can take many forms. For a unicellular organism such as *Amoeba*, cell division inevitably results in reproduction. For multicellular organisms, new individuals may be produced which bud off from the parent in various ways. • Immune Response: The cloning of B- and T- lymphocytes during the immune response is dependent on mitosis.	Nuclear division for genetically different cells.
Somatic (body cells): homologous. A human body (somatic) cell nucleus contains 46 chromosomes. These are difficult to distinguish when packed inside the nucleus, so scientists separate them and arrange them according to size and appearance. The outcome is called a karyotype. There are pairs of chromosomes.	Gamete (sex cells): each gamete has one member of each pair of homologous chromosomes. Otherwise, they would be double the number of chromosomes after they join at fertilisation in the zygote. The only pair that do not necessarily match is chromosome pair 23: the 'sex chromosomes'.

	The Y chromosome is much smaller than the X chromosome.
2 identical diploids.	Four haploid cells after two divisions.
When an organism develops into a zygote; All body cells are to divide by mitosis.	

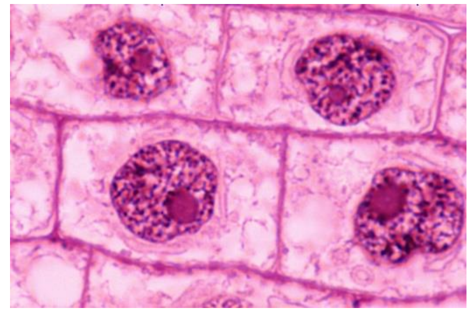
Cell Cycle:



- The cell cycle is the regular sequence of events that takes place between one cell division and the next.
- It has 3 phases, namely interphase, nuclear division and cell division.
- I-PMAT-C
  - **I**-Interphase
  - **P**-Prophase (chromosomes become (Prominent)
  - **M**-Metaphase (chromosomes align at the (Middle) of equator of the spindle fibre
  - **A**-Anaphase (chromosomes move (Away)) towards the opposite poles, centromeres first
  - **T**-Telophase (Two daughter nuclei)
  - **C**-Cytokinesis (Cytoplasm divides)

<u>Interphase:</u>

- Cell is NOT dividing.

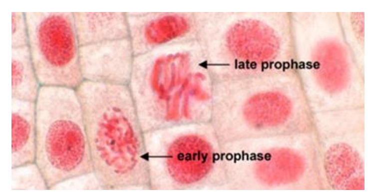


- Chromosomes are not visible.
- DNA is in the form of chromatin, which appears as a dark mass in the nucleus.
- DNA replicates.
- Centrioles replicate
- Interphase consists of G1, S and G2 phases. Cells are in this phase 80% of the time.
- During G1 (Cell Growth): Cells make the RNA, enzymes and other proteins needed for growth. At the end of G1, the cell becomes committed to dividing or not dividing.
- During S (DNA Synthesis): Follows the G1 phase and is when DNA replication occurs. Chromosomes are replicated forming two sister chromatids each. (Centrioles Divide)
- During G2 (Cell Growth): The cell continues to grow and new DNA is checked and any errors are usually repaired. Preparations are also made to begin the process of division. (Corrections)

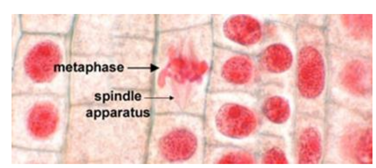
5.2 Chromosome Behavior in Mitosis

Mitosis/Nuclear Division:

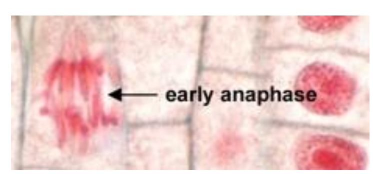
- Nuclear division follows interphase.
- This may be referred to as the M phase (M for mitosis). Growth stops temporarily during mitosis. After the M phase, when the nucleus has divided into 2, the whole cell divides to create two genetically identical cells.
- Cells are in this stage 10% of the time.
    - Prophase: Chromosomes become visible as they condense, shorten and thicken. Centrioles migrate to the poles. Nuclear membrane disintegrates/dissolves. Nucleolus disintegrates/dissolves. Spindle formation occurs.



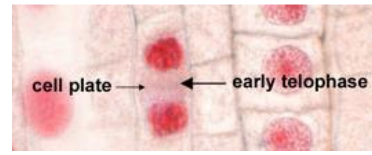
    - Metaphase: Chromosomes line up along the equator. Each sister chromatid is attached at the centromere to a spindle fibre originating from opposite poles.



    - Anaphase: Spindle fibers contract and pull individual chromatids apart at the centromere. Certain spindle fibers begin to elongate the cell. Sister Chromatids now called chromosomes move to opposite poles of the cell.



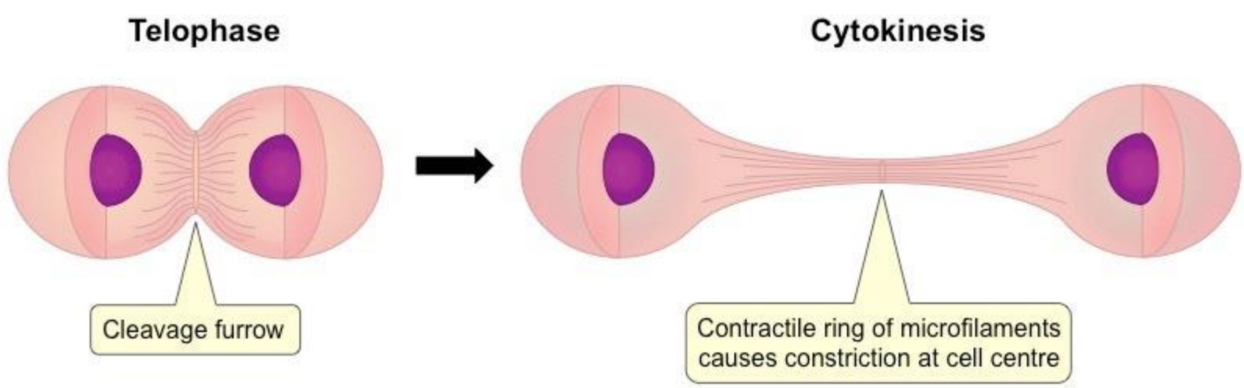
The energy required is provided by aerobic respiration in mitochondria, which gather around spindle fibers.



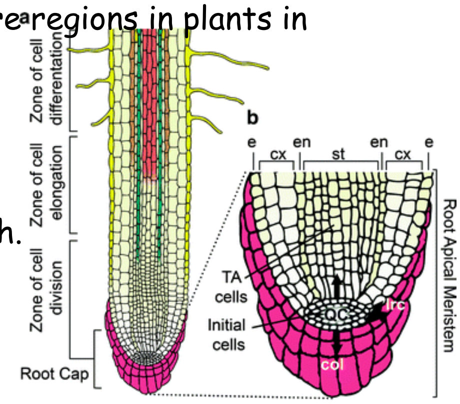
- Telophase: Chromosomes uncoil and become indistinct (becomes chromatin). Reformation of nuclear membrane occurs. Nucleoli reappears. Spindle disintegrates.

Cytokinesis:

- Cytoplasm divides to form 2 new daughter cells.
- Organelles divided: division of cytoplasm & eventually cell surface membrane.
- Daughter cells are genetically identical.
- Cells return to interphase.
- Cytokinesis takes two forms depending on the cell.
- In animal cells: A cleavage furrow separates the daughter cells. In animal cells during cytokinesis, a cell surface membrane begins to invaginate along the plane of the equator. This forms a cleavage furrow. Gradually furrow is deepened and combined. Eventually membranes of the furrow join up and completely separate it into two cells. During this, organelles of the mother cell randomly divide among the two daughter cells.
- In plant cells: A cell plate, a precursor to the new cell wall, separates the daughter cells. In plant cells during cytokinesis, a cell plate is secreted by vesicles. Then the primary cell wall is laid on it by two daughter cells dividing the cytoplasm into two cells.



Mitosis in Meristems (Tips of Roots & Shoots): Meristems are regions in plants in which mitosis takes place.



- Apical Meristems: are at the tips of shoots and roots and contribute to increases in length.
- Lateral Meristems: are responsible for increases in girth.

Prokaryotic Cell Division:

Binary fission:

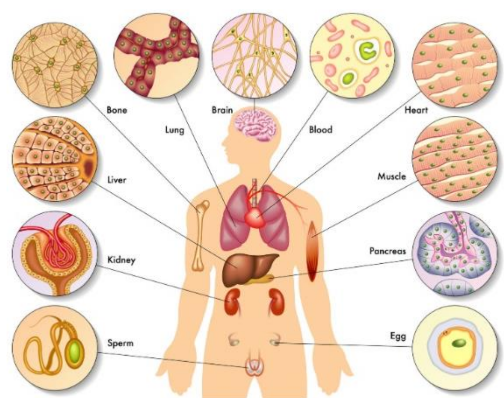
- Prokaryotes such as bacteria reproduce by binary fission.
- It involves the replication of the circular DNA and of plasmids.
- The division of the cytoplasm to produce two daughter cells, each with a single copy of the circular DNA and a variable number of copies of plasmids.

Virus Reproduction:

A minimal virus is a parasite that requires replication in a host cell. Being non-living, they do not undergo cell division. The virus cannot reproduce itself outside the hosts because it lacks the complicated machinery that a host cell possesses. The host's cellular machinery allows viruses to produce RNA from their DNA and to build proteins based on the instructions encoded in their RNA.

- The virus attaches itself to a specific host cell.
- Then injects its genetic material into the host cell.
- The host cell uses the genetic material to make new viruses.
- The host cell splits open, releasing the viruses.

Stem Cells:



Stem cells are unspecified, undifferentiated cells that divide by mitosis to produce daughter cells with the capacity to become specialised for specific functions & multiply into the 200 cell types that form a human being.

- A stem cell is an unspecilized cell that can divide an unlimited number of times (by mitosis).
- When it divides, each new cell has the potential to remain a stem cell or to develop (differentiate) into a specialised cell such as a blood cell or muscle cell.
- The extent of the power of a stem cell to produce different cell types is variable and is referred to as its potency.
- Stem cells that can produce any type of cell are described as totipotent.
- The zygote formed by the fusion of a sperm with an egg at fertilisation is totipotent, as are the cells up to the 16-cell stage of development in humans.
- After that, some cells become specialised to form the placenta, while others lose this ability but can form all the cells that will lead to the development of

the embryo and later the adult. These embryonic stem cells are described as pluripotent.

- The more 'committed' cells become to particular roles, the more they lose the ability to divide until, in the adult, most cells do not divide.
- However, for growth and repair it is essential that small populations of stem cells remain which can produce new cells.
- Adult stem cells have already lost some of the potency associated with embryonic stem cells and are no longer pluripotent. They are only able to produce a few types of cell and may be described as multipotent.
- For example, the stem cells found in bone marrow are of this type. They can replicate any number of times, but can produce only blood cells, such as red blood cells, monocytes, neutrophils and lymphocytes. Mature blood cells have a relatively short life span, so the existence of these stem cells is essential. For example, around 250 thousand million (250 billion) red blood cells and 20 billion white blood cells are lost and must be replaced each day.

Stem Cell Therapy:

- In the adult, stem cells are found throughout the body – for example in the bone marrow, skin, gut, heart and brain.
- Research into stem cells has opened up some exciting medical applications.
- Stem cell therapy is the introduction of new adult stem cells into damaged tissue to treat disease or injury.
- Bone marrow transplantation is the only form of this therapy that has progressed beyond the experimental stage into routine medical practice, but in the future it is hoped to be able to treat conditions like diabetes, muscle and nerve damage, and brain disorders such as Parkinson's and Huntington's diseases.
- Experiments with growing new tissues, or even organs, from isolated stem cells in the laboratory have also been conducted.

Cancer: Mitosis is a controlled process & hence part of the precisely controlled process called the cell cycle. Uncontrolled cell division can lead to the formation o f tumours and cancers. Many Cancer treatment are directed at controlling the rate of cell division. Cancer forms as a result of uncontrolled cell division.

- Sometimes cells divide repeatedly and form a tumour, which is an irregular mass of cells. The cells usually show abnormal changes in shape.

- Some tumours do not spread from their site of origin, and are known as benign tumours; warts are a good example.
- It is only tumours that spread through the body, invade other tissues and destroy them that cause cancer, and these are known as malignant tumours.
- Malignant tumours interfere with the normal functioning of the area where they have started to grow.
- They may block the intestines, lungs or blood vessels.
- Cells can break off and spread through the blood and lymphatic system to other parts of the body to form secondary growths.
- The spread of cancers in this way is called metastasis. It is the most dangerous characteristic of cancer, since it can be very hard to find secondary cancers and remove them.

Oncogenes:

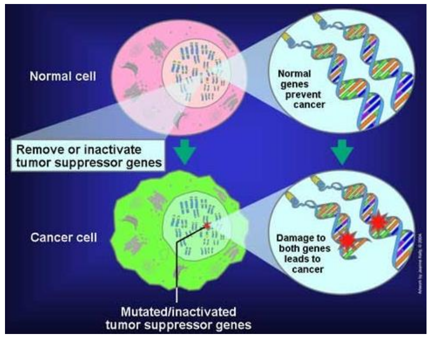
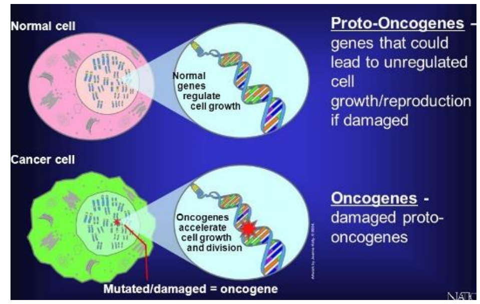
- Genes known as proto-oncogenes code for proteins that stimulate cell division.
- Mutated forms, called oncogenes, cost military proteins to be overactive, with the result that cells proliferate excessively.
- Gain of function mutations.

What is a tumour suppressor?

- Tumour suppressor genes are genes that regulate the growth of cells. When these genes are functioning properly, they can prevent and inhibit the growth of tumours.
- When tumour suppressor genes are altered or inactivated due to a mutation, they lose the ability to make a protein that controls cell growth.
- The protein made by tumour suppressor genes normally inhibits cell growth, preventing tumour formation.
- Mutations in these genes result in cells that no longer show normal inhibition of cell growth and division.
- The products of tumour suppressor genes may act at the cell membrane in the cytoplasm or in the nucleus.
- Mutations in these genes results in a loss of function that is the ability to inhibit cell growth.

Comparison of Proto-Oncogenes & Tumour Suppressor:

Property	**Tumour Suppressor Genes**	**Proto-Oncogenes**
Alleles mutated in cancer	Both alleles	1 allele
Germ line transmission of mutant allele.	Frequent	Rare (1 example)

Somatic Mutations	Yes	Yes
Functions of Mutant Allele	Loss of function (recessive allele)	Gain of function (dominant allele)
Effects on Cell Growth	Inhibit cell growth	Promote cell growth
Pictures		

<u>Role of Telomeres & Telomerase in Cancer:</u>

- Cancer cells often avoid cell death by maintaining their telomeres despite repeated cell divisions.
- This is possible because the cancer cells activate an enzyme called telomerase, which adds genetic units onto the telomeres to prevent them from shortening to the point of causing cell death.