Chapter – 4
CELL CYCLE

Introduction

- Every living cell has a power to grow and divide to form new cells of the same kind. The genetic materials are transmitted to the newly produced cells called as *daughter cells* during the course of division. This is also essential for body growth and for the replacement of dead cells of the body.
- Development of an organism from the zygote to the full-grown stage takes place by the division of cells. Even after full size is attained, replacement of cells takes place by the cell division. The process of cell division can be defined as *the process whereby the chromosomes are duplicated in one cell and distributed equally* or *reductionally to the daughter cells*.

History

Rudolf Virchow - Law of cell Lineage : *"Omnis cellula e cellula"* New cells arise from prexisting cells.

Strasburger - First study of cell division in plants.

Walter Flemming - First study of cell division in animals.

Boveri and **Flemming -** Studied details of somatic cell division.

Flemming - gave term **'Mitosis'.**

Van Beneden - discovered Meiosis.

Sutton, Winiwater and **Strasburger -** studied details of Meiosis.

Farmer and **Moore -** gave term '**Meiosis**'.

Gregoire used term **Meiosis I** and **Meiosis II.**

Factors Controlling Cell Divison

1. **Cell Size** When cells grow in size, its nucleo-cytoplasmic ratio and surface area - volume ratio decreases. To maintain these ratios cells divide as smaller cells have high ratios, therefore more active.
2. **Mitogens** are polypeptide growth factors that control cell proliferation. Common plant mitogen is hormone **cytokinin**. Mitogens in human beings include **lymphokines**, Epidermal growth factor (**EGF**) or platelet derived growth factor. **(PDGF)**

Generation time : Period between two successive divisions.

Cell Cycle : The entire sequence of events which takes place in a cell between one cell division and the next.

The cell cycle

- The cell cycle entails (i) S-phase when DNA is replicated, and (ii) The entry into M-phase when division occurs. In this regard following two timing events need to be moitored by the cells :
  - S-phase entry (when to initiate replication)
  - M-phase entry (when to begin chromosomal condensations)
- Related to above mentioned events, M-phase is regulated by following factors :
  - The accumulation of a specific cellular mass is a factor for somatic cells. This is called the mass factor.
  - Some cells need to obtain a specific growth rate for mitosis begin. This is called the growth rate factor.
  - The time between successive M-phases appears to be controlled by timer or oscillator genes. This is the time factor and appears to be a factor in embryo cells.

- The entry into the M-phase also requires completion of the S-phase. This insures that daughter cells receive complete DNA complements and is called the completion of chromosomal replication factor.

➢ For the cell to coordinate these different events, it must be able to monitor the cell cycle. An important biological question that needs to be resolved is how does the cell known where it is in the cell cycle. As you would expect, genetics and biochemical characterization have provided an extensive, but incomplete description of the process.

➢ Cell cycle research has primarily been performed on mutant strains of the fission yeast (*Schizosaccharomyces pombe*) and the budding yeast (*Saccharomyces cerevisae*) that have genetic lesions in some phase of the cell cycle. The cell division cycle (cdc) mutant strains have been quite useful in elucidating important steps. The cell cycle in yeast has two points where it is committed to proceed to the next stage in the cycle. The first point called start occurs near the end of the G1, and the cell becomes committed to DNA synthesis in the S phase of the cycle. The second commitment point is at the beginning of the M phase when the cell becomes committed to chromosomal condensation and the subsequent mitotic steps.

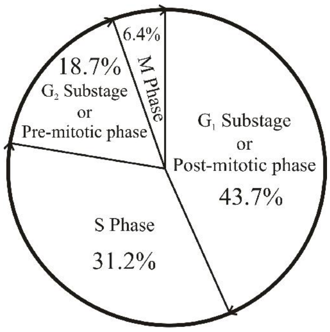

Fig. ***Cell cycle.***

Interphase

➢ Many cells undergo a continuous alternation between division and nondivision. The events occurring from the completion of one division until the end of the next division constitute the cell cycle.

➢ Initial stage of cycle, called interphase, as the interval between divisions. It was once thought that the biochemical activity during interphase was devoted solely to the cell's metabolism and growth. We not known that another biochemical step critical to the next mitotic division occurs during interphase; the replication of the DNA of each chromosome.

➢ These are designated G_1 (gap1) and G_2 (gap2), respectively. Particularly during G_1, intensive metabolic activity, cell growth, and cell differentiation occur. By the end of G_2, the volume of the cell has roughly doubled.

➢ Many cell types derived from mammals traverse the complete cell cycle in about 16 hours. The actual process of mitosis occupies only a small part of the cycle, often less than an hour.

➢ G_1 is of great interest in the study of cell proliferation and its control. At a point late in G_1, all cells follow one of two paths. They either withdraw from the cycle and enter a resting phase called G_0, or they become committed to initiating DNA synthesis and completing the cycle. Cells that enter G_0 remain viable and metabolically active, but are nonproliferative. Cancer cells apparently avoid entering G_0, or else they pass through it very quickly. Some cells enter G_0 and never reenter the cell cycle.

➢ Cytologically, interphase is characterized by the absence of visible chromosomes. Instead, the nucleus is filled with chromatin fibers that have formed as the chromosomes have uncoiled and dispersed following the previous mitosis.

➢ Once the G_1, S, and G_2 phases of interphase are completed, mitosis is initiated. Mitosis is a dynamic period of vigorous and continual activity.

MITOSIS

➢ The process of the cell division whereby the chromosomes are duplicated and distributed equally to the daughter cells is called as *mitosis*.

➢ Mitosis is also called as equational division. The mitotic cycle is divisible into five following phases; prophase, pro-metaphase, metaphase, anaphase and telophase.

Prophase

- Often, over half of mitosis is spent in prophase, a stage characterized by several significant activities. One of the early events in prophase of all animal cells involves the migration of two pairs of centrioles to opposite ends of the cell.
- Structures are found just outside the nuclear envelope in an area of differentiated cytoplasm called the centrosome. It is thought that each pair of centrioles consists of one mature unit and a smaller, newly formed centriole.
- Interestingly, cells of most plants, fungi, and certain algae seem to lack centrioles, spindle fibers are nevertheless apparent during mitosis. Therefore, centrioles are not universally responsible for the organization of spindle fibers.
- As the centrioles migrate, the nuclear envelope begins to break down and gradually disappears. In a similar fashion, the nucleolus disintegrates within the nucleus. While these events are taking place, the diffuse chromatin fibers begin to condense, continuing distinct threadlike structures, or chromosomes, become visible. It becomes apparent near the end of prophase that each chromosome is actually a double structure, split longitudinally, except at a single point of constriction, called the Centro mere. The two components of each chromosome are called chromatids. Because the DNA contained in each pair of chromatids represents the duplication of a single chromosome during the S phase of the previous interphase, these chromatids are genetically identical. Therefore, they are called *sister chromatids*.

Prometaphase and Metaphase

- The distinguishing event of the next stage of mitosis is the migration of each chromosome, led by its centrometric region, to the equatorial plane of the cell. The equatorial plane, also referred to as the *metaphase plate*, is the midline region of the cell.
- Migration is made possible by the binding of microtubules of the spindle fibers to a structure associated with the centromere of each chromosome called the kinetochore. The kinetechore, consisting of multilayered plates of proteins, forms on opposite sides of each centromere and becomes intimately associated with the two sister chromatids of each chromosome.
- Spindle fibers consist of microtubules, which themselves consist of molecular subunits of the protein tubulin. Microtubules seem to originate and grow out of the two centrosome regions at opposite poles of the cell. They are dynamic structures that lengthen and shorten as a result of the addition or loss of polarized tubulin subunits. It is interesting to not that the number of microtubules that bind to the kinetochore varies greatly between organisms.

Anaphase

- Events critical to chromosome distribution during mitosis occur during the shortest stage of mitosis, anaphase. During this phase, sister chromatids of each chromosome disjoin from each other and migrate to opposite ends of the cell. For complete disjunction to occur, each centrometric region must be split in two, signaling the initiation of anaphase. Once anaphase occurs, each chromatid is referred to as a daughter chromosome.
- Investigations have revealed that chromosome migration results from the activity of a series of specific proteins, generally called *motor proteins*. These proteins use the energy generated by the hydrolysis of

ATP, creating what are called molecular motors in the cell. These motors act at several positions within the dividing cell, but all are involve din the activity of microtubules and ultimately serve to propel the chromosomes to opposite ends of the cell. The centromeres of each chromosome appear to lead the way during migration, with the chromosome arms trailing behind. The location of the centromere determines the shape of the chromosome during separation.

Telophase

- Telophase is the final stage of mitosis is depicted. At its beginning, there are two complete sets of chromosomes, one at each pole. The most significant event is cytokinesis, the division or partitioning of the cytoplasm. Cytokinesis is essential if two new cells are to be produced from one. The mechanism differs greatly in plant and animal cells. In plant cells, a cell plate is synthesized and laid down across the dividing cell in the region of the metaphase plate. The end result is the same. Two distinct cells are formed.
- The cell plate, laid down during telophase, becomes the middle lamella.
- In animals, complete constriction of the cell membrane produces the cell furrow characteristic of newly divided cells. They represent a general reversal of those that occurred during prophase.

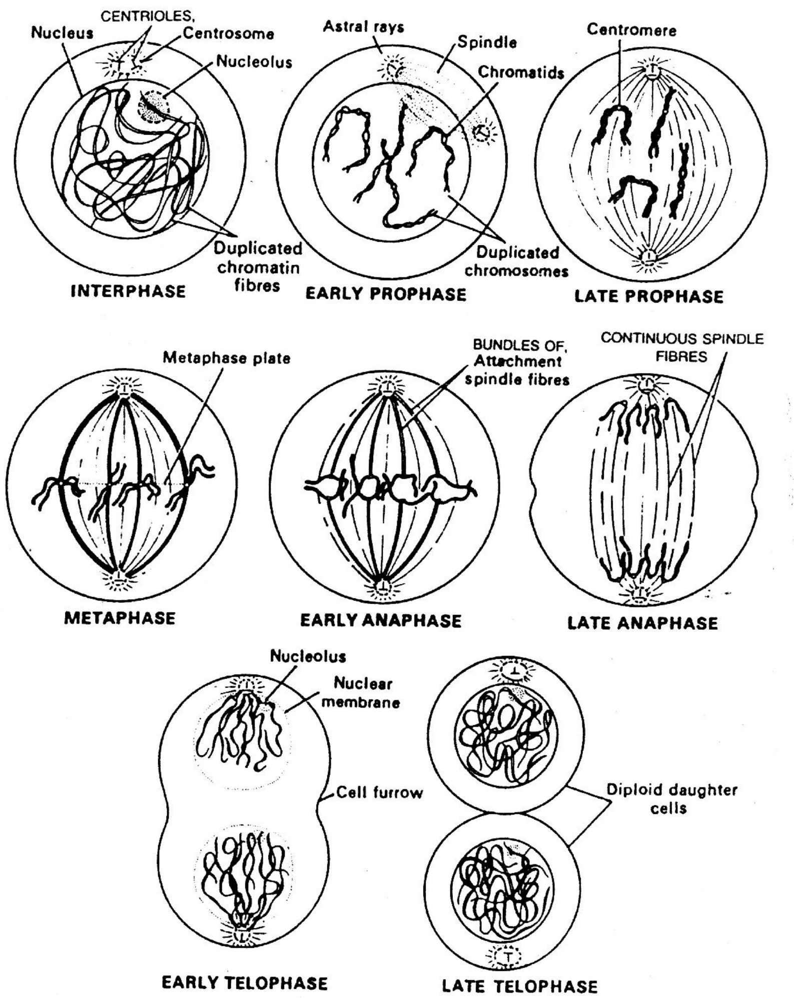

Fig. ***Different stages of mitotic cell division***

Cytokinesis

- This is the process by which cytoplasm of the cell divides into two parts. It starts with the formation of a constriction near the middle of the mother cell at the early telophase. The constriction deepens and joins together forming two daughter cells each with the same number of chromosomes equal to the chromosome number of the mother cell.
- When the nuclear division takes place without cytoplasmic division, it results in the formation of syncytium. The syncytium condition applies to a cell where large numbers of nuclei are present in a single cell.

Significance of meiosis

- Increase in the number: As two daughter cells are produced from one mother cell, there is an increase in the number of the cells.
- Constancy of chromosome number: In this division, the number of chromosomes remains the same in both the daughter cells as that of mother cell. This is essential to retain a constant number of chromosomes in a species.
- Equal distribution of genetic material: Chromosomes are the carriers of hereditary materials or the genes (DNA). During this division there is equal distribution of the genetic material in both the daughter cells. So the daughter cells have the similar characteristics as that of the mother cell.
- Growth: By this division growth in somatic structures takes place and it is the basic requirement for the growth in living organisms.
- Healing of wounds: Regeneration of organs and filling up of wounds in living organisms takes place by mitosis.
- Nucleo-cytoplasmic (N/C) ratio: This is the ratio between nucleus and cytoplasm of a cell. It has definite range for a particular type of cell. The growth of the cell results in an increase in N/C ratio, thereby the division maintains the N/C ratio. This is accomplished by mitosis.
- Maintains surface volume (S/V) ratio: To maintain the S/V ratio is another requirement for normal cells. If the cell only grows it will disturb the S/V ratio of the cell. So to restore the S/V ratio the cell should divide and it is accomplished by mitosis.

MEIOSIS

- Reproduction is one of the most important characteristics of the living system by which we can make a distinction between living entities from a non-living system. There is a need of dissimilar types of gametes (male gamete and female gamete) to achieve the process of reproduction. If the gametes were diploid i.e., $2n$ number of chromosomes, the resulting zygote or new individual would have twice the diploid chromosomes number. But every organism contains a definite number of chromosomes and to maintain this, there is a special type of division in the cells responsible for the production of gametes. This special type of cell division in the gamete producing cells is referred to as *meiosis* or *meiotic division*.
- The meiosis can be defined as *the process of division in the cells whereby one cell undergoes division to produce four daughter cells with the reduction of chromosomes from diploid (2n) to haploid (n)*.

Process of meiotic cell division

- In the meiotic division, each mother cell with diploid number of chromosomes (2*n*) divides to form four daughter cells. The entire process includes two divisions of the cells but the chromosomes divide only once.
- The process of the meiotic division includes following two divisions of cells:
  - Meiosis I or heterotypical division or reduction division resulting in the formation of two daughter cells with half the chromosome number.
  - Meiosis II or homotypical division or equational division during which each daughter cell divides into two, the chromosomes of each daughter cell divides into chromatids which are equally distributed to two new daughter cells. So four cells formed will have haploid (*n*) number of chromosomes.
- The meiotic division takes place at the end of the G_2 phase of the interphase, similar to mitotic division. The important stages involve during meiosis are as follows:
  - Two successive divisions without any DNA replication occurs between them.
  - Formation of chiasmata and crossing over.
  - Segregation of homologous chromosomes and
  - Separation of sister chromatids

Reductional division (Meiosis I)

[A] Karyokinesis

Prophase I

- It is the longest phase of the meiotic division and most complicated too. This also takes maximum time for its completion. This phase is further divisible into following five sub-stages:

  Leptotene: The characteristics of leptotene are as follows:
  - Nucleus enlarges
  - Chromosomes become distinct, long, interwoven, thin filamentous structure called as *chromonemata*
  - The number of chromosomes is equal to the number found in the other somatic cells
  - Chromosomes look single rather than double
  - Chromosomes have a definite polarization of form loops whose ends are attached to the nuclear envelop near centiriole. This arrangement of chromosome is called *bouquet type*.

  Zygotene: The features of this sub-stage are as follows:
  - The pairing of chromosomes takes place. Only two homologous chromosomes do this pairing in which each one comes from two parents. The pairing of the homologous chromosomes is referred to as *synapsis*.
  - The pairing is completed in three different manners which are as follows:
    - Proterminal pairing: The two homologous chromosomes bring about pairing at the terminals, which gradually progresses towards the centromere.
    - Procentric pairing: This type of pairing starts at the centromere and moves towards the end.
    - Intermediate or random pairing: In this type of pairing, the pairing may start at many points towards the end.
  - The two homologous chromosomes are brought together through a characteristic ladder-like structure called as *synaptonemal complex*

- The pairing of homologous chromosomes or synapsis results in the formation of *bivalents*

Pachytene: The salient features of this stage are as follows:

- It is the longest period of the prophase I and large recombination nodules appear at intervals on synaptonemal complex.
- These recombination nodules mediate for chromosomal recombination
- The non-sister chromatids twist around and exchange segments with each other

Zygotene: The characteristic features of this sub-stage are as follows:

- The bivalents repel each other and begin to separate but the separation is not complete, as chromosomes remain united by centromere. This leads to the formation of X-like structure called as *chiasmata*
- Homologous chromosomes start separating from one another and the centromere progress towards the ends. This process of separation is regarded as *terminalization*.

Diakinesis: The characteristics of diakinesis are as follows:

- The chromosomes continue to contract the terminalization still continues.
- The bivalents appear as rounded bodies near the nuclear membrane.
- Late in this stage, nucleolus and nuclear membrane completely disappear.

Metaphase I: The characteristics of this stage are as follows:

- Spindle formation is complete and it occupies the nuclear region.
- Chromosomes arrange themselves in the equatorial region and each member of a chromosome pair is attached by spindle fibres at the centromere.
- Centromeres of two chromosomes of a bivalent lie on opposite sides of the equatorial plate.
- The arms of chromosomes are always away or opposite from the poles.

Anaphase I: This phase has following characteristics:

- The two centromeres of a pair of homologous chromosomes repel each other and the chromosomal spindles give pull to the centromeres resulting in the migration of two chromosomes of each homologous pair to opposite poles.
- Centromeres do not divide and the chromatids do not separate.
- The entire chromosomes with its two chromatids move to the opposite poles.
- By the end of the anaphase I, each pole of the cell has half the number of chromosomes as compared to number of chromosomes in the parent cell.
- Each set of chromosomes consists of a mixture of paternal and maternal chromosome segments.

Telophase I: The characteristics of this phase are as follows:

- Chromosomes at both poles become elongated and threadlike, forming a network of chromatin material.
- Nucleolus reappears and nuclear membrane is formed around each set of chromosomes.
- At each pole, a daughter nucleus is formed containing half the number of chromosomes.

[B] Cytokinesis

- The telophase of the division is immediately followed by the division of cytoplasm i.e., cytokinesis resulting in the formation of two daughter cells each with haploid number of chromosomes.

Equational division (Meiosis II)

- There is a short resting period called *interkinesis* between meiosis I and II. In interphase proceeding first meiotic division there is synthesis of DNA but in interkinesis replication of DNA does not take place. This is immediately followed by meiosis II.

[A] Karyokinesis

- The meiosis II resembles the mitotic division but there is no further reduction of chromosome number. This second meiotic division includes following stages :

  Prophase II: The characteristics of this phase are as follows:
  - Chromosomes with chromatids become very thick and distinct.
  - Centrioles migrate to opposite poles and spindle fibres are formed.
  - Nucleolus and nuclear membrane disappear.

  Metaphase II: The characteristics of this phase are as follows:
  - Spindle fibres occupy the place of the nucleus.
  - Chromosomes move towards the equatorial plane and centromeres get attached with the spindle fibres.
  - Centromere still joins a pair of chromatids of one chromosome.

  Anaphase II: The characteristics of this phase are as follows:
  - Centromere of each chromosome divides and each chromatid now becomes a daughter chromosome.
  - Each daughter chromosome now moves towards opposite poles by the shortening of the spindle attached with centromere and the centriole.
  - The number of chromatids *i.e.,* daughter chromosomes is the same at each pole (haploid).

  Telophase II: The characteristics of this phase are as follows:
  - Each group of daughter chromosomes forms the chromatin network.
  - Nuclear membrane is formed around each group of chromosomes.
  - Nucleolus reappears.

[B] Cytokinesis

- The cytoplasm of each cell now divides and form each cell two new or daughter cells are formed. The end result of meiosis I and II is the formation of four daughter cells with haploid number of chromosomes(n).

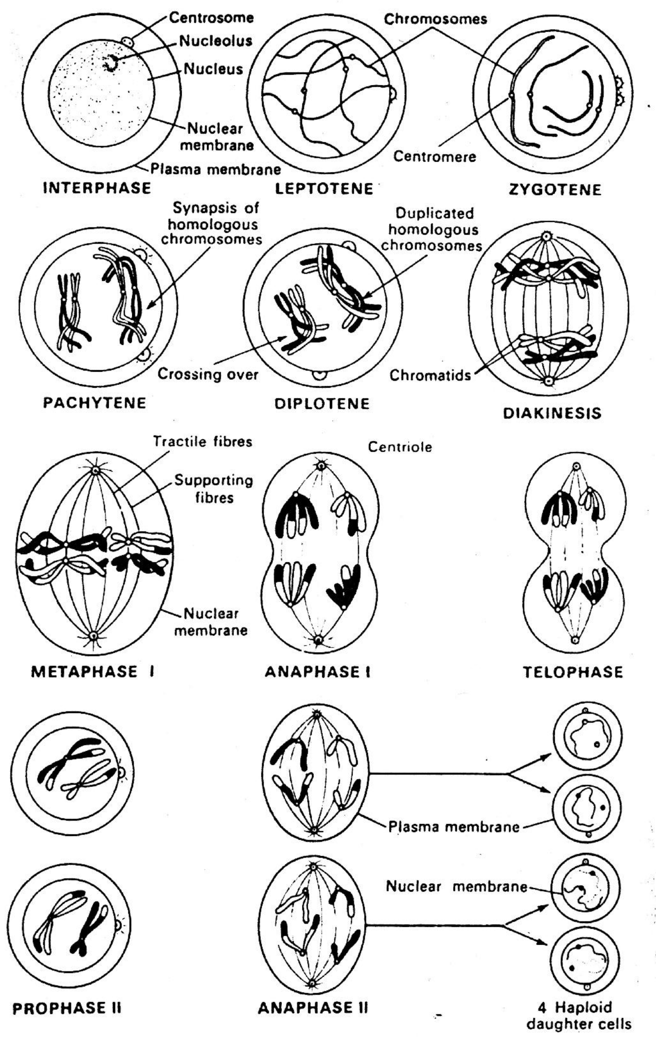

Fig. ***Different stages of meiosis cell division***

Types of Meiosis

Cells undergoing meiosis are called **meiocytes**. Three types of meiosis.

(1) **Gametic/Terminal Meiosis :** Division takes place during gamete formation which fuse to form zygote. This type of meiosis results in diplontic life cycle and occurs in animals.

(2) **Zygotic/Initial Meiosis :** Division takes place in zygote and the resulting organisms have haplontic life cycle. Occurs in plants of thallophyta group.

(3) **Sporic/Intermediate Meiosis :** Division takes place during formation of spores resulting in diplohaplontic life cycle. Occurs in all plants except thallophyta.

Table 3.1. Differences between Mitosis and Meiosis

Characters	**Mitosis**	**Meosis**
1 Occurrence	Somatic cells	Reproductive cells and also in zygotes and spore producing cells
2. No. of chromosomes in daughter cells	Each DNA or chromosome replication is followed by one nuclear division, thereby maintaining the amount of DNA and the number of chromosomes per cell constant from generation to generation.	Each DNA or chromosome replication is followed by two successive divisions of the nucleus. Thus, each of the daughter cells contains half as many chromosomes and half as much DNA as its parent cell.

Characters	Mitosis	Meosis
3. DNA replication	Only takes place during interphase. DNA replicates once for one cell division.	Takes place during interphase I but not in interphase II (interkinesis). DNA replicates once for two cell divisions.
4. Prophase	Comparatively simple and not so time taking affair.	Comparatively longer and may take many hours to several days.
5. Sub-divisions of prophase	No sub-division	Prophase is divisible into; leptotene, zygotene, pachytene, diplotene and diakinesis.
6. Crossing over	Absent	Chromatids of two homologous chromosomes exchange segments during crossing over.
7. No. of chromatids	Each chromosome consists of two chromatids, united by a centromere.	Two homologous chromosomes form bivalents or tetrads, each bivalent has four chromatids and two centromeres.
8. Direction of arms of prophase chromatid	Close to each other	Widely separated
9. Metaphase	All the centromeres line up in the same plane.	The centromeres are line up in two planes which are parallel to each other.
10. Metaphase plate	Made up of paired chromosomes	Made up of tetrads
11. Centromere	Division of centromere takes place	No division of centromere during anaphase I, centromere divides during anaphase II.
12. Fate of Nucleolus and Spindles fibres	Spindle fibres disappear completely, nucleolus reappear	Spindle fibres do not disappear completely during telophase I, nucleolus reappear in telophase II not in telophase I.
13. No. of chromosomes in Daughter cells	Remains same	Reduce to half (diploid to haploid).
14. Daughter Cells	Identical to mother cell	Different genetical constitution due to crossing over. The chromosomes of daughter cells contain a mixture of maternal and paternal genes.

AMITOSIS

Amitosis is also termed as **Direct division** because in this nucleus divides directly (without prophase, metaphase, anaphase and telophase) into two parts. Discovered by **Remak** and is a very primitive type of division.

- Spindle fibres are not formed during the division.
- There is no sequential change during the division.
- The exchange of genetic material is not necessary during Amitosis.
- A rapid division completed approximately in 20-30 minutes.

Division of prokaryotic animals (organisms), also occurs in some eukaryotes like yeast, ciliate protozoans and foetal membrane of vertebrates