CELL CYCLE

The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division. The goal of the cell cycle is to produce two daughter cells, each containing chromosomes identical to those of the parent cell.

Rapidly renewing populations of human cells progress through the full cell cycle in about 24 hours, while other types of cells take longer time.

Phases of the Cell Cycle

The cell cycle incorporates two principal phases: the **interphase**, and the **M phase (mitosis)**.

A) Interphase:

It represents continuous growth of the cell and is subdivided into three phases, **G_1 (gap1) phase**, **S (synthesis) phase**, and **G_2 (gap 2) phase**.

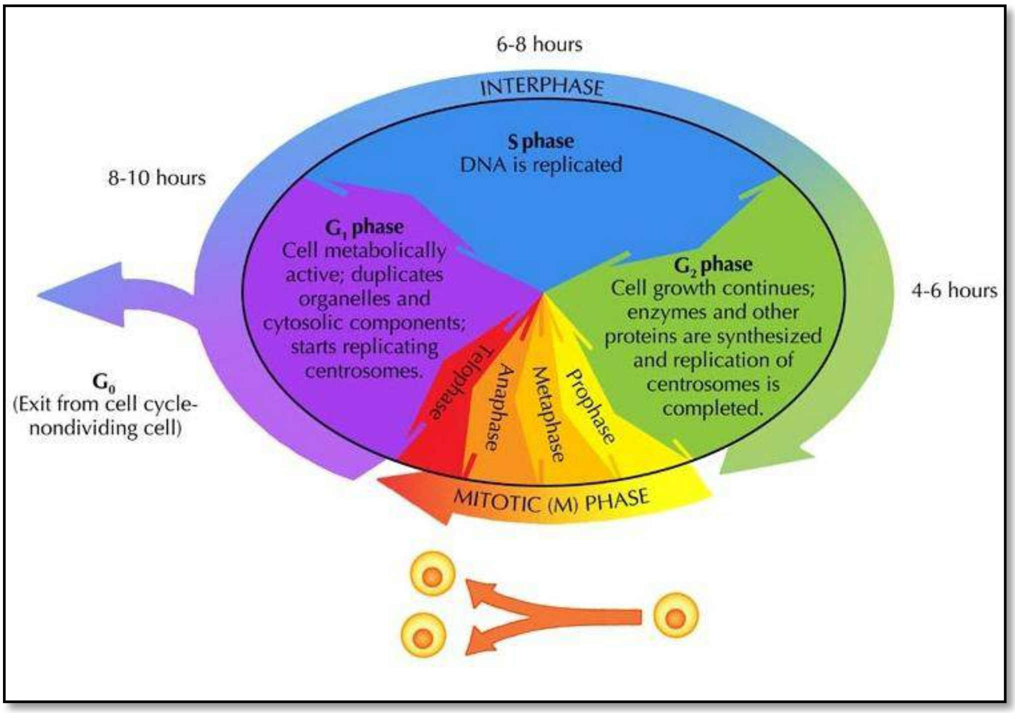
1) **The G_1 phase**
It is usually the longest and the most variable phase of the cell cycle, and it begins at the end of M phase. During the **G_1 phase**, the cell gathers nutrients and synthesizes RNA and proteins necessary for DNA synthesis and chromosome replication.

2) **The S phase (DNA replication)**
Initiation of DNA synthesis marks the beginning of the **S phase**, which is about 7.5 to 10 hours in duration. The DNA of the cell is doubled during the S phase, and new chromatids are formed.

3) **The G_2 phase (cell preparation for cell division)**
During this phase, the cell examines its replicated DNA in preparation for cell division. This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle. The **G_2 phase** may be as short as 1 hour in rapidly dividing cells or of nearly indefinite duration in some polyploid cells and in cells such as the primary oocyte that are arrested in G_2 for extended periods.

B) Mitosis (M) phase

Mitosis nearly always includes both **karyokinesis** (division of the nucleus) and **cytokinesis** (division of the cell) and lasts about 1 hour. Mitosis takes place in several stages described in more detail below. Separation of two identical daughter cells concludes the **M phase**.



Cell Cycle Checkpoints

Throughout the cell cycle, several internal quality control mechanisms or **checkpoints** represented by biochemical pathways control transition between cell-cycle stages. The cell cycle stops at several checkpoints and can only proceed if certain conditions are met—for example, if the cell has reached a certain size. Checkpoints monitor and modulate the progression of cells through the cell cycle in response to intracellular or environmental signals.

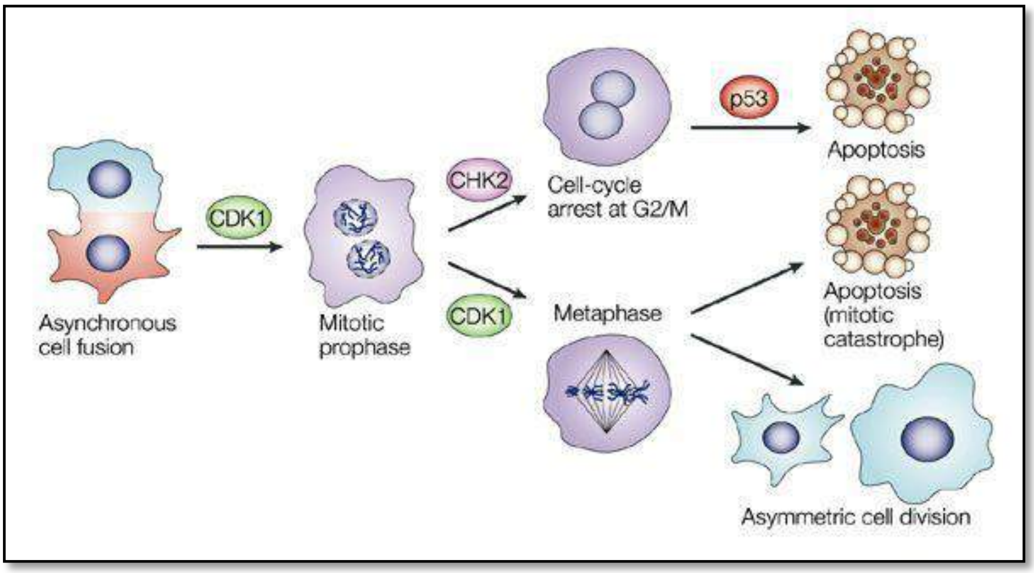
****The **restriction checkpoint (or "point of no return")** is the most important checkpoint in the cell cycle. At this checkpoint, the cell self-evaluates its own replicative potential before deciding to either enter the S phase and the next round of cell division or to retire and leave the cell cycle.*

*A cell that leaves the cycle in the G_1 phase usually begins terminal differentiation by entering the **G_0 phase** ("O" stands for "outside" the cycle). Thus, the G_1 phase may last for only a few hours (average 9 to 12 hours) in a rapidly dividing cell, or it may last a lifetime in a nondividing cell.*

The mitotic catastrophe

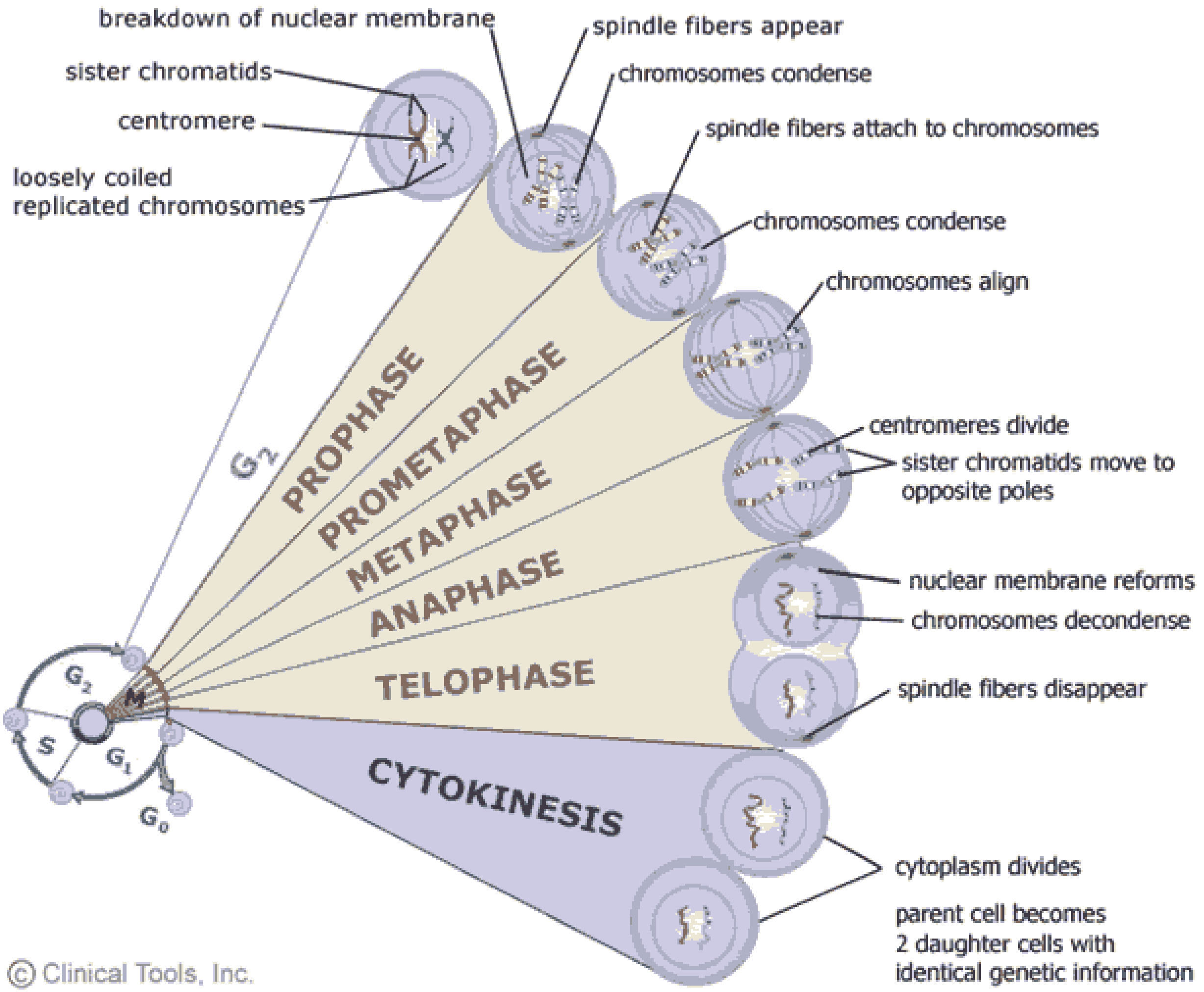
- Malfunction of any of the checkpoints at the **G_1**, **S**, and **G_2** phases of the cell cycle and the checkpoint at **M** phase may lead to a **mitotic catastrophe**.
- Mitotic catastrophe is defined as the failure to arrest the cell cycle before or at mitosis, resulting in abnormal chromosome separation.
- Under normal conditions, death in these cells will occur by activation of the apoptotic cycle.

- Cells that fail to execute the apoptotic cycle are likely to divide asymmetrically in the next round of cell division.
- This leads to the generation of **aneuploid cells** (cells containing abnormal chromosome numbers).
- Thus, a mitotic catastrophe may be regarded as one of the mechanisms contributing to **oncogenesis** (tumor cell development).



Mitosis

- Cell division is a crucial process that <u>increases the number of cells, permits renewal of cell populations, and allows wound repair.</u>
- **Mitosis** is a process of chromosome segregation and nuclear division followed by cell division that produces two daughter cells with the same chromosome number and DNA content as the parent cell.
- The process of cell division includes division of both the nucleus (**karyokinesis**) and the cytoplasm (**cytokinesis**).
- The process of cytokinesis results in distribution of nonnuclear organelles into two daughter cells.
- Before entering mitosis, cells duplicate their DNA in the *S* or *synthesis phase*.



Phases of Mitosis

1. **Prophase:**
   - The replicated chromatin condenses and become visible as chromosomes.
   - Each chromosome can be seen to consist of two **chromatids**.
   - The sister chromatids are held together by the ring of proteins at the **centromere**.
   - In late prophase, the nuclear envelope begins to disintegrate, and the nucleolus completely disappears.
   - In addition, a highly specialized protein complex called a **kinetochore** appears on each chromatid opposite to the centromere.

2. **Metaphase:**
   - Formation of the mitotic spindle, consisting of three types of microtubules, that becomes organized around the **centrosomes**, the **astral microtubules**, **the polar microtubules** and the **kinetochore microtubules**. When a kinetochore is finally captured by a kinetochore microtubule, it is pulled toward the centrosomes.
   - Kinetochore microtubules and their associated motor proteins direct the movement of the chromosomes to a plane in the middle of the cell, called the **equatorial** or **metaphase plate**.

3. **Anaphase:**
   - Separation of sister chromatids. This separation occurs when the proteins that have been holding the chromatids together break down.
   - The separated chromatids are pulled to opposite poles of the cell by the sliding along the kinetochore microtubules toward the centrosomes.

4. **Telophase:**
   - Reconstitution of a nuclear envelope around the chromosomes at each pole.
   - The chromosomes uncoil and become indistinct.
   - The nucleoli reappear, and the cytoplasm divides (cytokinesis) to form two daughter cells.

Cytokinesis

Cytokinesis begins with the furrowing of the plasma membrane midway between the poles of the mitotic spindle. The separation at the **cleavage furrow** is achieved by a **contractile ring** consisting of a very thin array of actin filaments positioned around the perimeter of the cell. As the ring tightens, the cell is pinched into two daughter cells.

- *Because the chromosomes in the daughter cells contain identical copies of the duplicated DNA, the daughter cells are genetically identical and contain the same kind and number of chromosomes. The daughter cells are **(2d)** in DNA content and **(2n)** in chromosome number.*

Meiosis

- **Meiosis** involves two sequential nuclear divisions followed by cell divisions that produce gametes (sex cells) containing half the number of chromosomes and half the DNA found in somatic cells.
- The **zygote** (the cell resulting from the fusion of an ovum and a sperm) and all the somatic cells derived from it are **diploid (2n)** in chromosome number (46 chromosomes in human); thus, their cells have two copies of every chromosome and every gene encoded on this chromosome.
- These chromosomes are called **homologous chromosomes** because they are similar but not identical; one set of chromosomes is of maternal origin, the other is from paternal origin.
- The **gametes**, having only one member of each chromosome pair, are described as **haploid (1n)**.
- During gametogenesis, reduction in chromosome number to the haploid state (23 chromosomes in humans) occurs through **meiosis.**

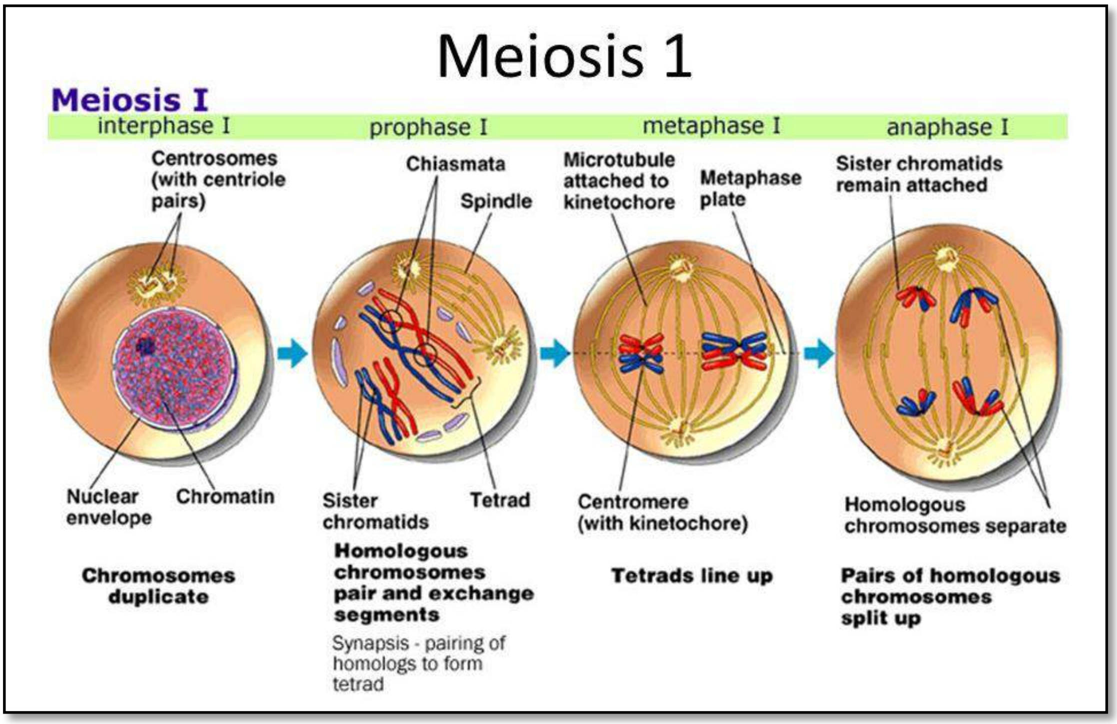
- This reduction is necessary to maintain a constant number of chromosomes in a given species.
- Reduction in chromosome number to **(1n)** in the first meiotic division is followed by reduction in DNA content to the haploid **(1d)** amount in the second meiotic division.
- During meiosis, the chromosome pair may exchange chromosome segments, thus altering the genetic composition of the chromosomes. This genetic exchange, called **crossing-over**, and the random assortment of each member of the chromosome pairs into haploid gametes give rise to infinite genetic diversity.

Differences in Meiosis between Male & Female

- The nuclear events of meiosis are the same in males and females, but the cytoplasmic events are markedly different.
- In males, the two meiotic divisions of a **primary spermatocyte** yield four structurally identical, although genetically unique, haploid **spermatids**. Each spermatid has the capacity to differentiate into a **spermatozoon**.
- In contrast, in females, the two meiotic divisions of a **primary oocyte** yield one haploid **ovum** and three haploid **polar bodies**. The ovum receives most of the cytoplasm and becomes the functional gamete. The polar bodies receive very little cytoplasm and degenerate.

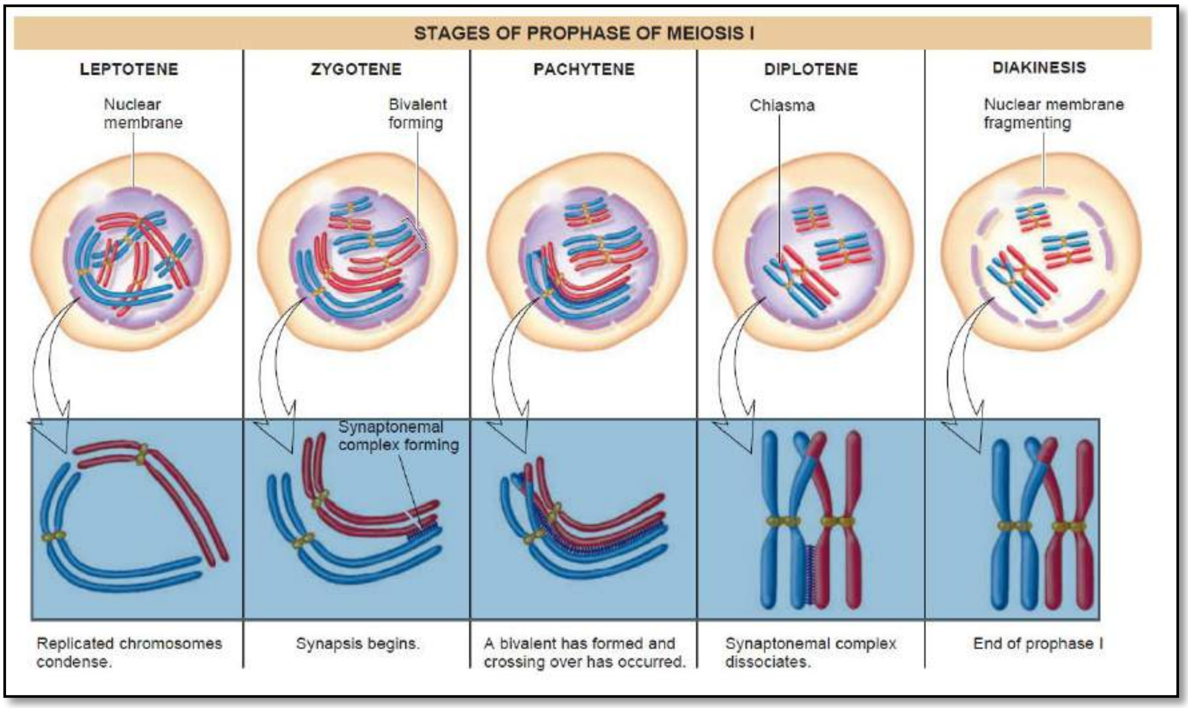
Divisions & Phases of Meiosis

- **Meiosis** consists of two successive mitotic divisions without the additional **S phase** between the two divisions.
- During the S phase that precedes meiosis, DNA is replicated forming sister chromatids (two parallel strands of DNA) joined together by the centromere. The DNA content becomes **(4d)**, but the chromosome number remains the same **(2n)**.
- The cells then undergo a **reductional division (meiosis I)** and an **equatorial division (meiosis II)**.
- During **meiosis I**, as the name *reductional division* implies, the chromosome number is reduced from diploid **(2n)** to haploid **(1n)**, and the amount of DNA is reduced from the **(4d)** to **(2d)**.
- No DNA replication precedes **meiosis II**.
- The division during meiosis II is always equatorial because the number of chromosomes does not change. It remains at **(1n)**, although the amount of DNA represented by the number of chromatids is reduced to **(1d)**.

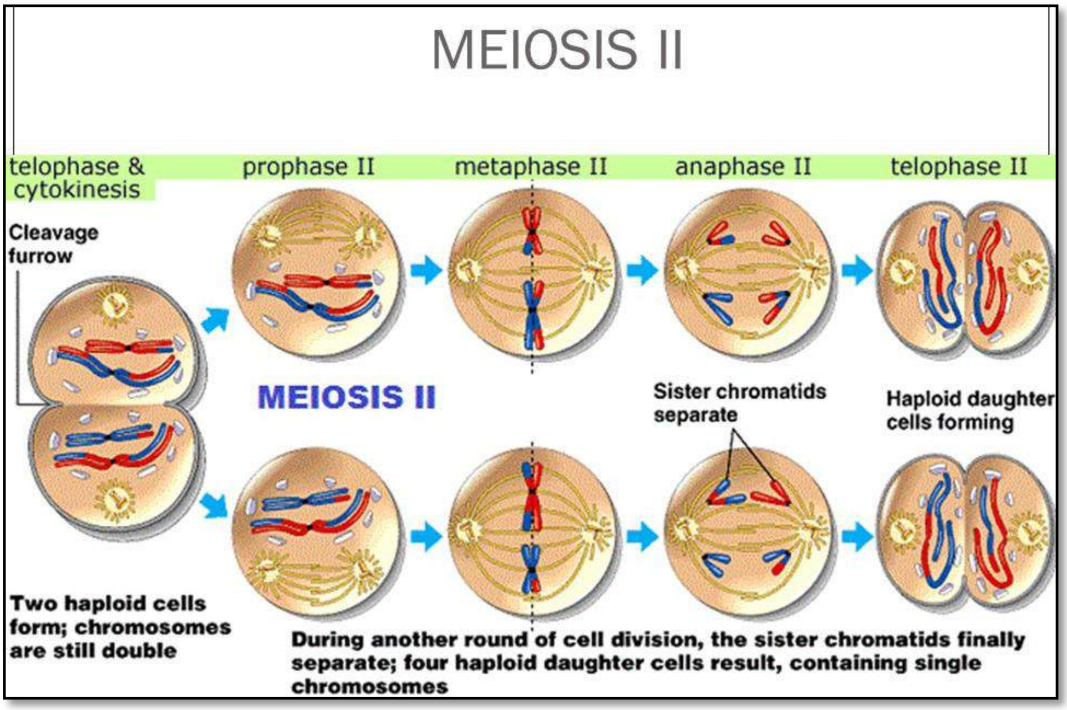


Phases of Meiosis I

1. **Prophase I:** It is an extended phase that is subdivided into the following five stages:
   Leptotene: chromosomes start to condense.
   Zygotene: homologous chromosomes become closely associated (synapsis) to form pairs of chromosomes (bivalents) consisting of four chromatids (tetrads).
   Pachytene: crossing over between pairs of homologous chromosomes to form chiasmata (sing. chiasma).
   Diplotene: homologous chromosomes start to separate but remain attached by chiasmata.
   Diakinesis: homologous chromosomes continue to separate, and chiasmata move to the ends of the chromosomes.



2. **<u>Metaphase I:</u>** Metaphase I is similar to the metaphase of mitosis except that the paired chromosomes are aligned at the **equatorial plate** with one member on either side.
   - The chiasmata are cut, and the homologous chromosomes separate completely.
   - The spindle microtubules begin to interact with the chromosomes through the **kinetochore** at the centromere.
   - The chromosomes undergo movement to ultimately align their centromeres along the equatorial plate with one member of the homologous chromosomes on either side.
3. **<u>Anaphase I</u>**:
   - The sister chromatids, held together by protein complexes and by the centromere, remain together.
   - A maternal or paternal member of each homologous pair moves to each pole.
   - **Segregation** or **random assortment** occurs because the maternal and paternal chromosomes of each pair are randomly aligned on one side or the other of the metaphase plate, thus contributing to genetic diversity.
4. **<u>Telophase I:</u>**
   - Homologous chromosomes, each consisting of two sister chromatids, are at the opposite poles of the cell.
   - Reappearance of the nucleolus and nuclear envelope.
   - At the completion of meiosis I, the cytoplasm divides. Each resulting daughter cell is haploid in chromosome number **(1n)** and contains one member of each homologous chromosome pair. The cell is still diploid in DNA content **(2d)**.



<u>Phases of Meiosis II:</u>

- After meiosis I, the cells quickly enter meiosis II <u>without passing through an S phase</u>.
- **Meiosis II** is an equatorial division and resembles mitosis.
- During this phase, the sister chromatids will separate at anaphase II and move to opposite poles of the cell.
- During meiosis II, the cells pass through **prophase II**, **metaphase II**, **anaphase II**, and **telophase II**.
- These stages are essentially the same as those in mitosis except that they involve a haploid set of chromosomes **(1n)** and produce daughter cells that have only haploid DNA content **(1d)**.
- <u>Unlike the cells produced by mitosis, which are genetically identical to the parent cell, the cells produced by meiosis are genetically unique.</u>

<u>By the end of meiosis II, each parent cell (2n) give rise to 4 daughter cells with haploid number of chromosomes (1n) and each daughter cell is genetically different from the parent cell.</u>