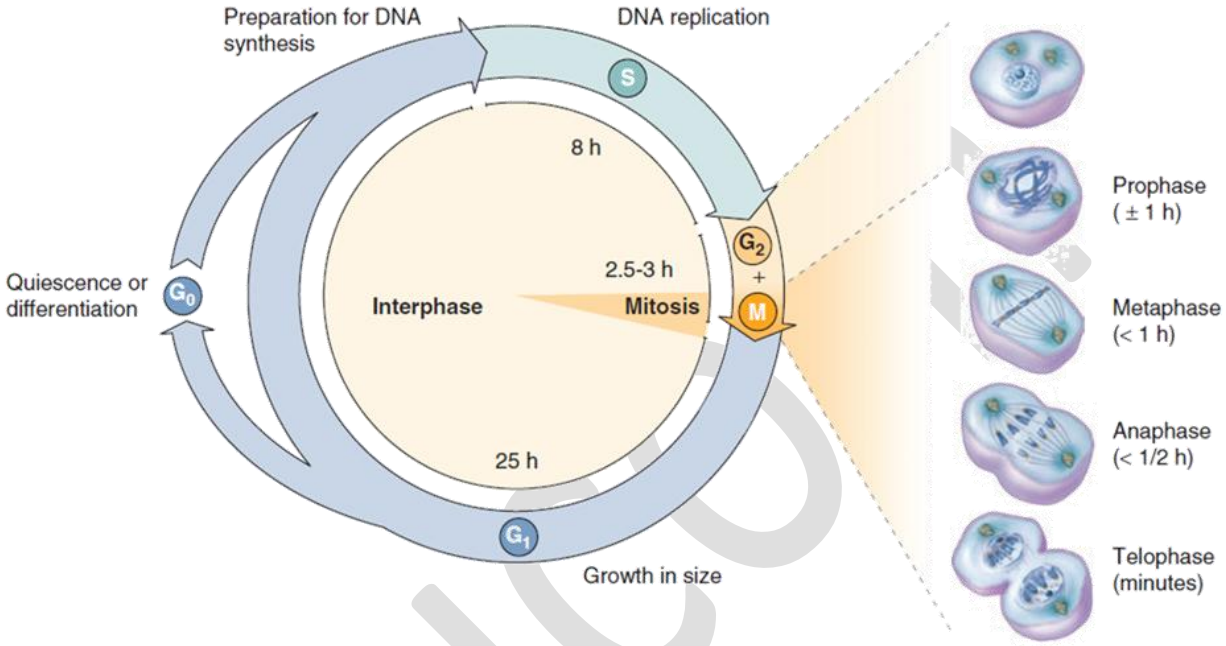
The cell cycle represents a self-regulated sequence of events that controls cell growth and cell division.

The cell cycle has four distinct phases:

1. G1 (the time gap between mitosis and DNA replication)
2. S (the period of DNA synthesis)
3. G2 (the gap between DNA duplication and the next mitosis).
4. M (mitosis or meiosis)



- **G1 phase** is usually the longest and most variable phase of the cycle and is a period of active RNA and protein synthesis, including proteins controlling progress through the cell cycle. Also in G1, the cell volume, reduced by half during mitosis, returns to its previous size.

The cell's progress through this phase is monitored by two checkpoints:

(1) **Restriction point (or "point of no return")**, which is sensitive to the size of the cell, the state of the cell's physiologic processes, and its interactions with extracellular matrix (Are cell nutrition, size, and environment favorable?).

(2) **G1 DNA-damage checkpoint**, which monitors the integrity of newly replicated DNA.

For instance, if the DNA has irreparable damage, the **G1 DNA-damage checkpoint** detects this damage and it does not allow the cell to enter the S phase. The cell will then most likely undergo programmed cell death (apoptosis).

The **restriction point** 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 G1 phase usually begins terminal differentiation by entering the **GO phase** ("O" stands for "outside" the cycle). Thus, the G1 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 non dividing cell.

- **S phase** is characterized by DNA replication, histone synthesis, and the beginning of centrosome duplication.

Presence of the **S DNA-damage checkpoint** in this phase monitors quality of replicating DNA. (Is all DNA intact?)

- **G2 phase,** in this phase the cell prepares for cell division.

This is a period of cell growth and reorganization of cytoplasmic organelles before entering the mitotic cycle.
Two checkpoints monitor DNA quality:

(1) **G2 DNA-damage checkpoint**
(2) **Unreplicated-DNA checkpoint**. The latter checkpoint prevents the progression of the cell into the M phase before DNA synthesis is complete.

G1 phase, S phase, and G2 phase are called interphase

- **M phase,** mitosis or meiosis occurs in this phase. Cell division nearly always includes both **karyokinesis** (division of the nucleus) and **cytokinesis** (division of the cell).

The M phase possesses two checkpoints:

(1) **Spindle-assembly checkpoint**, which prevents premature entry into anaphase.
(2) **Chromosome-segregation checkpoint**, which prevents the process of cytokinesis until all of the chromosomes have been correctly separated.
(Are all chromosomes attached to the mitotic spindle?)

As post mitotic cells begin to specialize and differentiate, cell cycle activities may be temporarily or permanently suspended, with the cells sometimes referred to as being in the **G0 phase.** Some differentiated cells, such as those of the liver, renew cycling under certain conditions; others, including most muscle and nerve cells, are *terminally differentiated*.

Progression through the cell cycle is halted by a variety of adverse conditions such as;

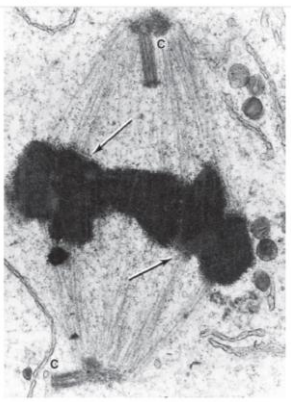
1. Inadequate nutrition (nutrient stress)
2. Inappropriate cellular microenvironments or DNA damage.

Nuclear DNA is monitored very closely, and damage here can arrest the cell cycle not only at the G1 restriction point but also during S or at a checkpoint in G2.
G1 arrest may permit repair of the damage before the cell enters S phase, so that the damaged DNA does not reproduce gene defects during replication. If the problem encountered at any checkpoint cannot be corrected fairly quickly, that cell's activity is redirected toward **cell suicide or apoptosis.**

DNA changes (mutations) resulting from damage are not always detected and corrected (or eliminated). Failure to detect unregulated cell cycling can lead to additional defects and the cellular changes found in the various types of **cancer.**

Mitosis

The period of somatic cell division, or **mitosis** (Gr. *mitos*, a thread), is the only cell cycle phase that can be routinely observed with the light microscope.
During mitosis, a parent cell divides and each of the two daughter cells receives a chromosomal set identical to that of the parent cell.
The chromosomes replicated during the preceding S phase are distributed to the daughter cells.



Mitotic spindle and metaphase

The long growth period between mitoses is also commonly called **interphase**.

The events of mitosis can be subdivided into four phases

1. **Prophase**

During the relatively long prophase, several changes occur:

1. The nucleolus disappears
2. The replicated chromatin condenses into threadlike chromosomes, each consisting of duplicate sister chromatids joined by cohesins.
3. At the centromere region of each chromosome, a large protein complex called the kinetochore serves as a site for attachment to microtubules.
4. The centrosomes with their now-duplicated centrioles separate and migrate to opposite poles of the cell.
5. The microtubules of the mitotic spindle polymerize between the two centrosomes.
6. Late in prophase, lamins and inner nuclear membrane are phosphorylated, causing the nuclear lamina and nuclear pore complexes to disassemble and disperse in cytoplasmic membrane vesicles.

2. **Metaphase**

During metaphase changes occur:

1. Chromosomes condense further
2. Each chromosome attaches to the mitotic spindle at large electron-dense protein complexes called kinetochores (Gr. *kinetos*, moving) at each centromere.
3. The cell is now more spherical
4. The chromosomes are moved to align at its equatorial plane.

3. **Anaphase**

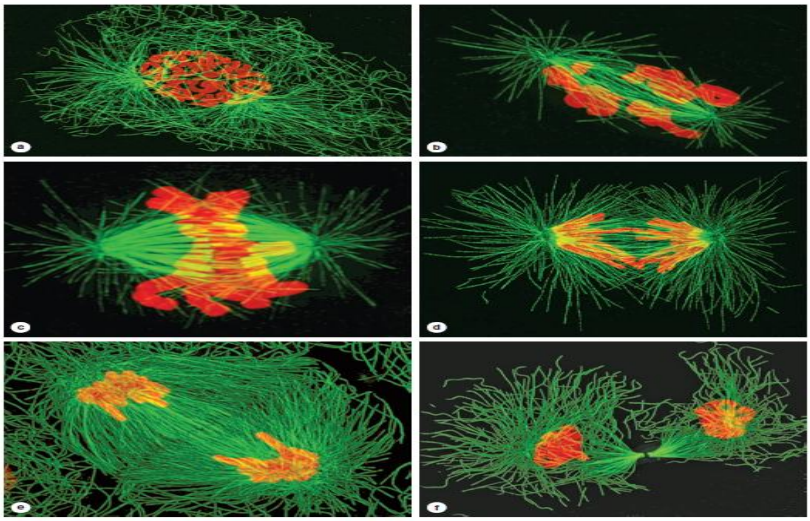
Sister chromatids (now called chromosomes) separate and move toward opposite spindle poles by a combination of microtubule motor proteins and dynamic changes in the lengths of the microtubules as the spindle poles move farther apart.

4. **Telophase**

At telophase the following occur:

1. The two sets of chromosomes are at the spindle poles and begin reverting to their decondensed state.
2. The spindle depolymerizes.
3. The nuclear envelope begins to reassemble around each set of daughter chromosomes.
4. A belt-like contractile ring of actin filaments associated with myosins develops in the peripheral cytoplasm at the cell's equator.

- During **cytokinesis** at the end of telophase, constriction of this ring produces a cleavage furrow and progresses until the cytoplasm and its organelles are divided into two daughter cells, each with one nucleus.
- Most tissues undergo **cell turnover** with slow cell division and cell death. Nerve tissue and cardiac muscle are exceptions because their differentiated cells cannot undergo mitosis. A capacity for mitosis within a tissue, either by differentiated cells or by reserve cells, largely determines that tissue's potential to regeneration. The cell turnover rate is rapid in the epithelium lining the digestive tract and uterus or covering the skin. Mitotic cells are usually difficult to identify conclusively in sections of adult organs but may often be detected in rapidly growing tissues by their condensed chromatin.



Stages of mitosis in cultured cells

Meiosis is a specialized process involving *two* unique and closely associated cell divisions that occurs only in the cells that will form sperm and egg cells.

I. Meiosis I (Reduction Division): Reduces the chromosome number by half.

1. Prophase I: The longest and most complex stage. Homologous chromosomes pair, exchange genetic material, and prepare for division. (In human spermatogenesis prophaseI normally lasts for 3 weeks; oocytes arrest in this meiotic phase from the time of their formation in the fetal ovary through the woman's reproductive maturity, that is, for about 12 years to nearly five decades!)

It includes **five substages**:

• **Leptotene**
- Chromatin condenses and chromosomes become visible.
- Homologous chromosomes begin to move toward each other.

• **Zygotene**
- **Synapsis** begins: homologous chromosomes pair closely.
- Formation of the **synaptonemal complex** that holds the homologs together.

• **Pachytene**
- Synapsis is complete.
- **Crossing-over** occurs, exchanging DNA segments between homologous chromosomes.

• **Diplotene**
- The synaptonemal complex dissolves.
- Homologs start to separate but remain attached at **chiasmata**, indicating sites of crossing-over.

• **Diakinesis**
- Chromosomes condense maximally.
- Nuclear envelope breaks down and the nucleolus disappears.

2. Metaphase I
- Paired homologous chromosomes align at the cell's equatorial plate.

- Spindle fibers attach to kinetochores near the centromeres.

3. Anaphase I

- Homologous chromosomes move to opposite poles.
- **Sister chromatids remain together** because the centromeres do not split.

4. Telophase I

- Chromosomes reach the poles.
- Cytokinesis occurs, producing two cells that are:
  - **Haploid in chromosome number (1n)**
  - **Diploid in DNA content (2d)** since each chromosome still has two chromatids.

II. Meiosis II (Equational Division)

Similar to mitosis; separates sister chromatids. **Stages:**
Prophase II – Chromosomes condense again.
Metaphase II – Chromosomes align at the equator.
Anaphase II – Sister chromatids separate after cohesin is cleaved by separase.
Telophase II – Chromatids reach opposite poles; cytokinesis follows.
Final Outcome of Meiosis produces four daughter cells that are:

- Haploid (1n)
- With haploid DNA content (1d)
- Genetically unique, due to crossing-over and independent assortment of chromosomes

Two key features characterize meiosis.

(1) Early in the process the homologous chromosomes of each pair (one from the mother, one from the father) come together in an activity termed **synapsis**. During synapsis double-stranded breaks and repairs occur in the DNA, some of which result in reciprocal DNA exchanges called **crossovers** between the aligned maternal and paternal chromosomes. Crossing over produces new combinations of genes in the chromosomes in the germ cells so that few if any chromosomes are exactly the same as those in the mother and father.

(2) The cells produced are **haploid**, having just one chromosome from each pair present in the body's somatic cells. The union of haploid eggs and sperm at fertilization forms a new diploid cell (the zygote) that can develop into a new individual.

❖ ***This reduction is necessary to maintain a constant number of chromosomes in a given species.***

In summary, meiosis and mitosis share many aspects of chromatin condensation and separation, but differ in key ways:

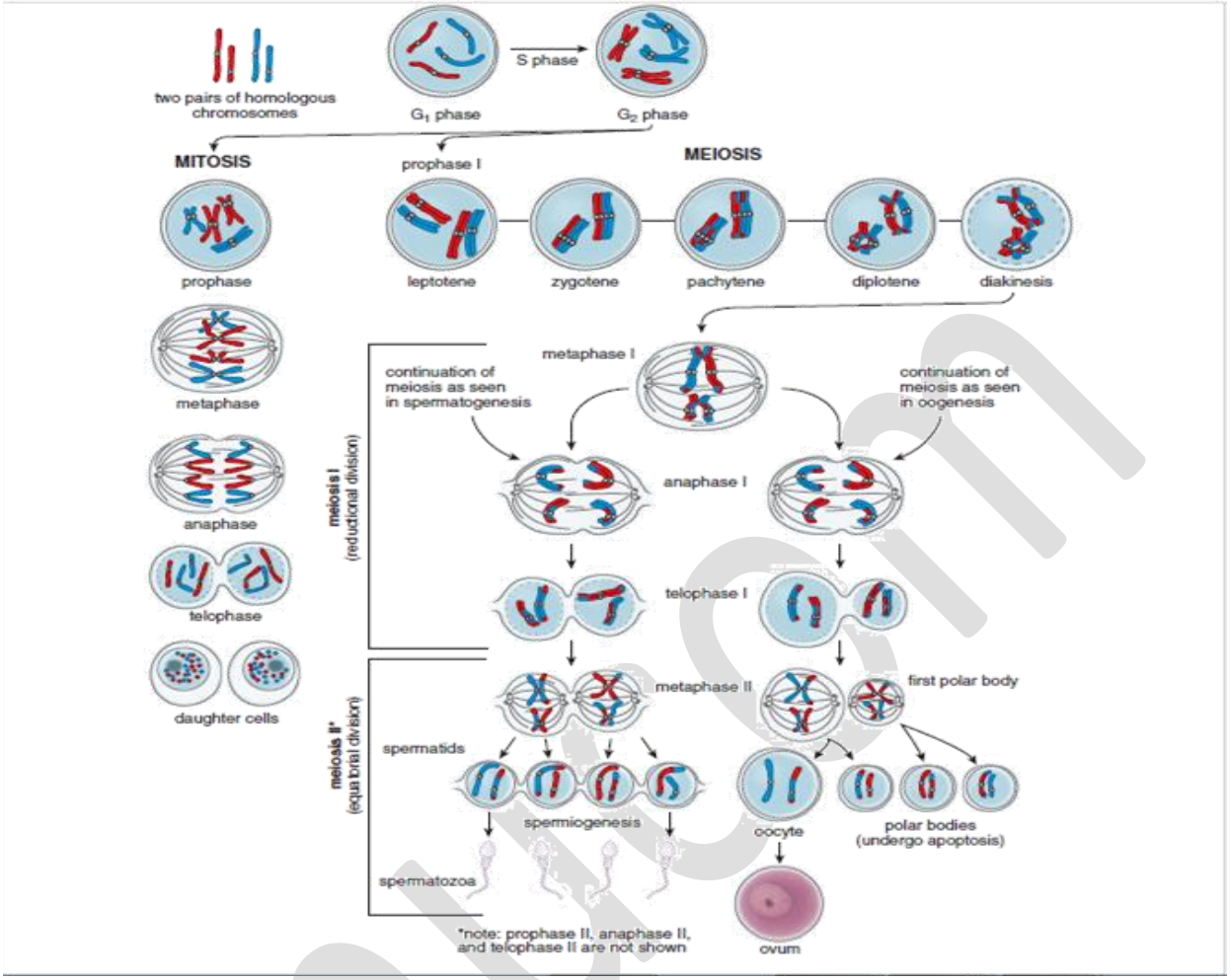
■■ Mitosis is a cell division that produces *two diploid cells*.
Meiosis involves two cell divisions and produces *four haploid cells*.

■■ During meiotic crossing over, new combinations of genes are produced and every haploid cell is genetically unique. Lacking synapsis and the opportunity for DNA recombination, mitosis yields two cells that are the same genetically.

MEDICAL APPLICATION

In humans chromosome 21 is a very small chromosome and the one most likely to be "overlooked" at the metaphase/ anaphase checkpoint. Failure of these homologous chromosomes to separate (nondisjunction) in the first meiotic division also occurs with greater frequency in older oocytes (or sperm progenitor cells). A gamete retaining this chromosome

pair forms a viable zygote after fertilization, but the developing trisomy 21 individual has morphologic and cognitive impairments associated with Down syndrome.



- **The nuclear events of meiosis I are similar in males and females, but the cytoplasmic events associated with meiosis differ in the male and female.**
- The nuclear and cytoplasmic events of meiosis occur in spermatogenesis and oogenesis.
- The events of meiosis through metaphase I are the same in both sexes. Therefore, the differences in the process diverge after metaphase I.
- **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.