Genetics (BTBio 211)

Lec. 2

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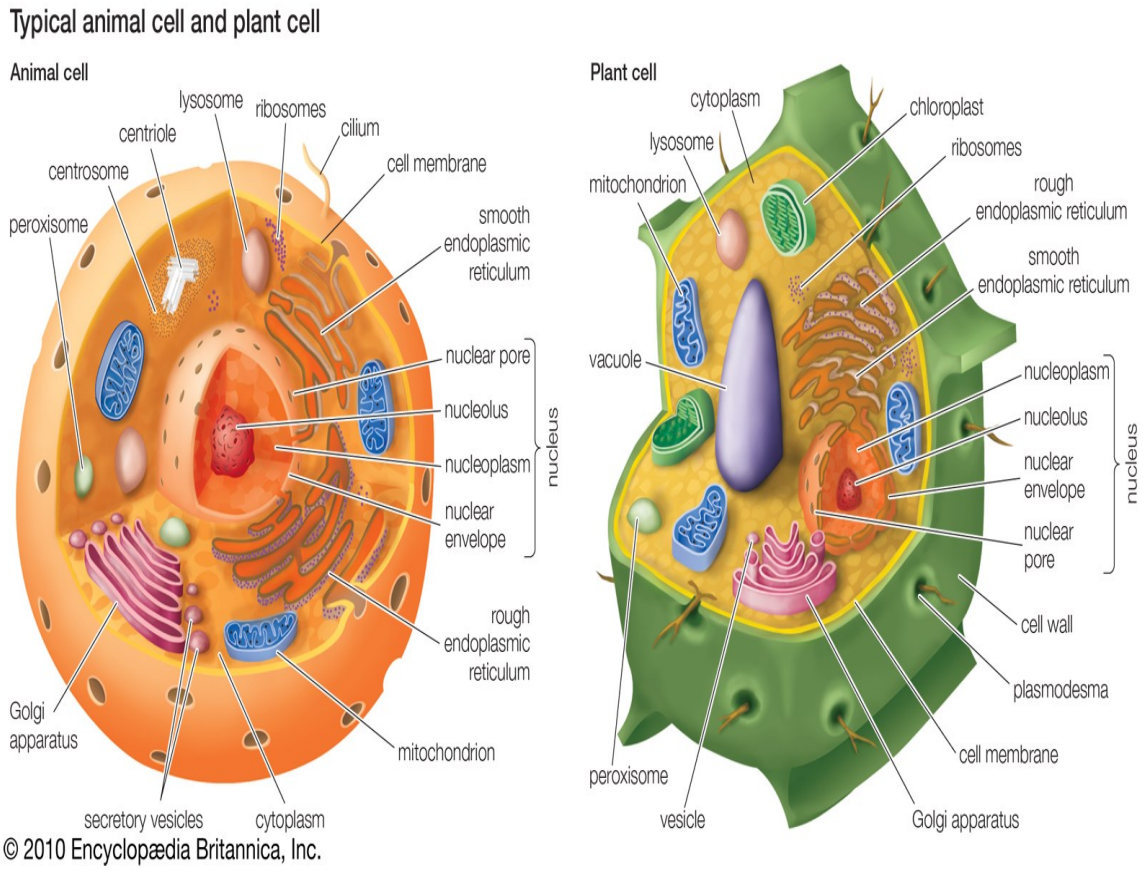
3. TRANSMISSION AND INHERITANCE OF CHROMOSOMES

EUKARYOTIC CELL STRUCTURE

Plant and animal cells have several differences and similarities (figure below):

Structurally, plant and animal cells are very similar because they are both eukaryotic cells. They both contain membrane-bound organelles such as the nucleus, mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, and peroxisomes. Both also contain similar membranes, cytosol, and cytoskeletal elements. The functions of these organelles are extremely similar between the two classes of cells (peroxisomes perform additional complex functions in plant cells having to do with cellular respiration).

The few differences that exist between plant and animals are very significant and reflect a difference in the functions of each cell. Plant cells can be larger than animal cells. The normal range for an animal cell varies from 10 to 30 micrometers while that for a plant cell stretches from 10 to 100 micrometers. Beyond size, animal cells do not have a cell wall or chloroplasts but plant cells do. Animal cells are round and irregular in shape while plant cells have fixed rectangular shapes.



We have two types of gene transmission and inheritance:

nuclear (happen in nucleus) and cytoplasmic (happen in plastids and mitochondria).

We will focus in this lecture on **the nucleus, nuclear transmission and inheritance,** while in another lecture we will study the cytoplasmic inheritance.

NUCLEUS

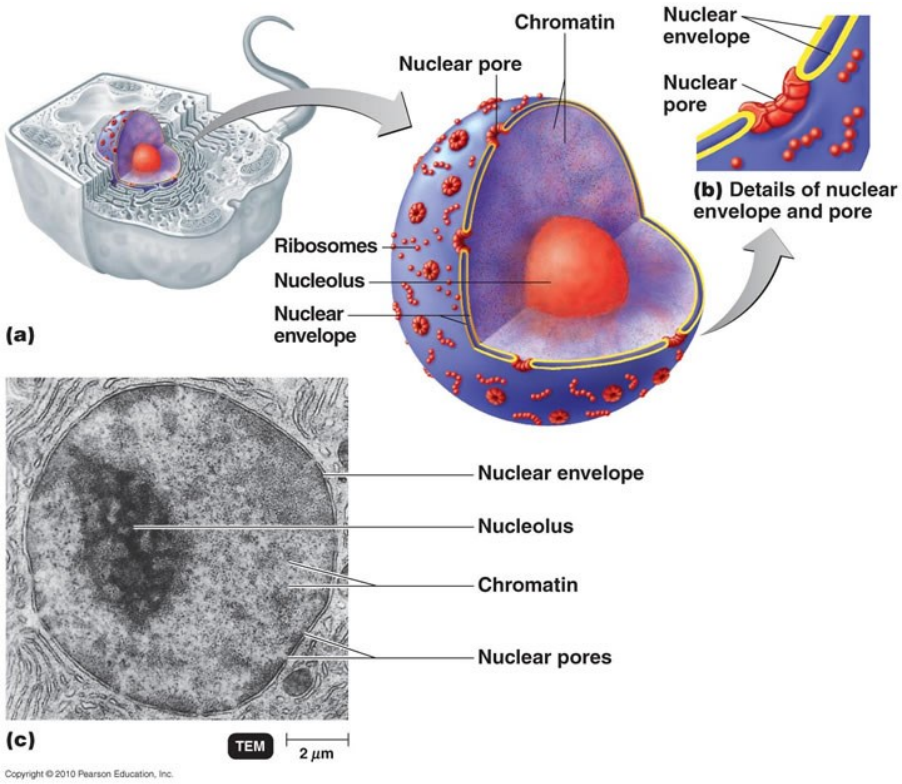
The nucleus in the cell is analogous to the brain in the body. It is a control center for a cell by maintaining the integrity of the genes and to control the activities of the cell by regulating gene expression. The nucleus stores all the information the cell needs to grow, reproduce, and function. This information is contained in long but thin molecules of deoxyribonucleic acid, or DNA. One of the functions of the nucleus is to

protect the cell's DNA from damage, but that is not all that it does. The nucleus is basically a large membranous sac (membrane-enclosed organelle) with a double membrane (an inner and an outer membrane separated from each other by 10 - 50 nm) that encloses it entirely and isolates its contents from the cellular cytoplasm. It serves as a barrier to prevent macromolecules from diffusing freely between the nucleoplasm (viscous liquid in nucleus) and the cytoplasm.

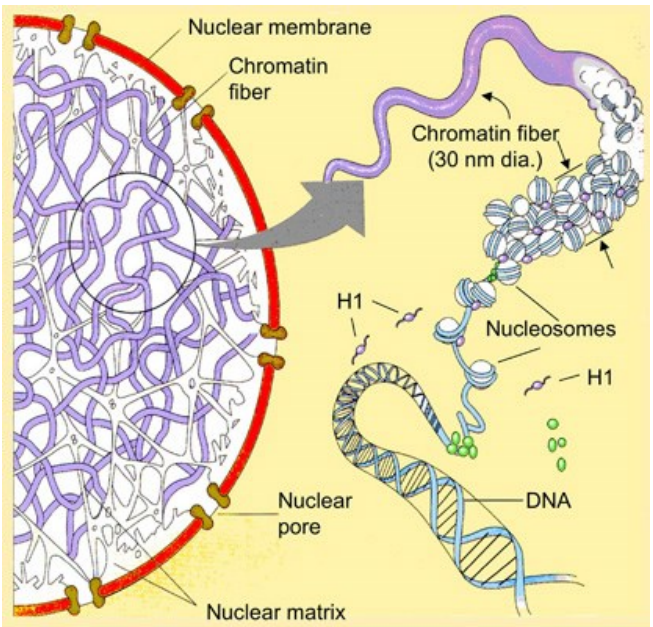
The nuclear membrane has pores through which the contents of the nucleus communicate with the rest of the cell. Nucleoporins, a family of 50 to 100 proteins, are the main components of the nuclear pore complex in eukaryotic cells. The nuclear membrane tightly controls what gets into the nucleus and what gets out. Movement of large water-soluble molecules such as proteins and RNA through the nuclear pores is required for both gene expression and the maintenance of chromosomes. Because the nuclear membrane is impermeable to large molecules, nuclear pores are required that regulate nuclear transport of molecules across this membrane. The pores cross both nuclear membranes, providing a channel through which larger molecules must be actively transported by carrier proteins while allowing free movement of small molecules and ions. This regulation of communication by the nuclear membrane has a great effect on what a cell looks like and what it does.

The nucleus also contains a small round body called a nucleolus, which is a discrete densely stained structure. It is not surrounded by a membrane, and is sometimes called a suborganelle. It is composed of proteins and nucleic acids found within the nucleus of eukaryotic cells. Its function is to transcribe ribosomal RNA (rRNA) and combine it with proteins to form almost-complete ribosomes. The nucleolus occupies up

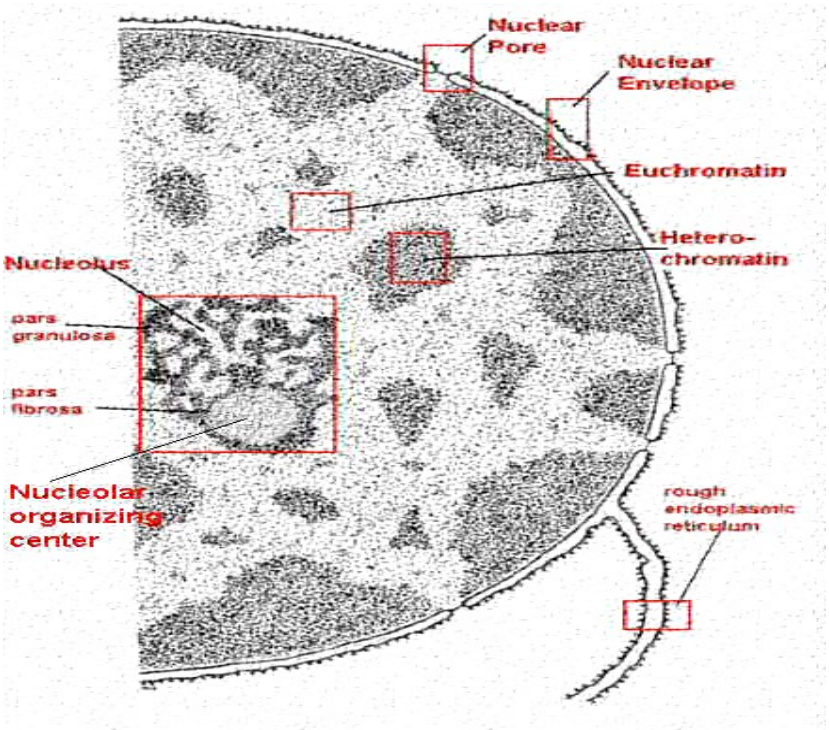
to 25% of the volume of the cell nucleus. Malfunction of nucleoli can be the cause of several human diseases.



Chromosomes are also located in the nucleus and are basically organized from DNA and proteins. In eukaryotes, the chromosomal DNA is packaged and organized into a condensed structure called chromatin (figure below).

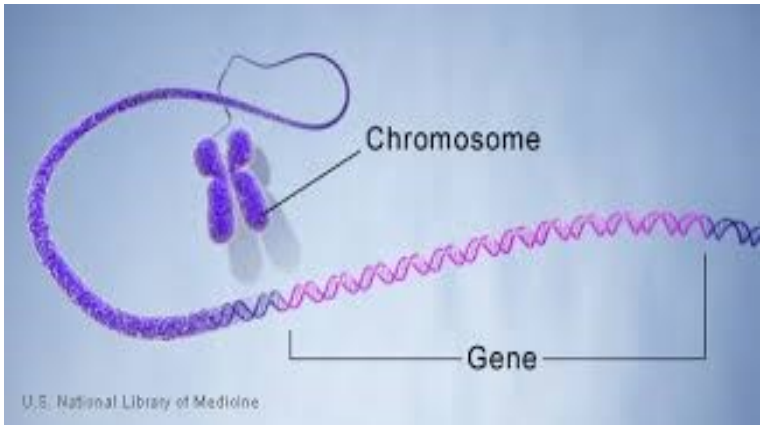


There are two types of chromatin: Euchromatin is the less compact DNA form, and contains genes that are frequently expressed by the cell. The other type, heterochromatin, is the more compact form, and contains DNA that is infrequently transcribed.

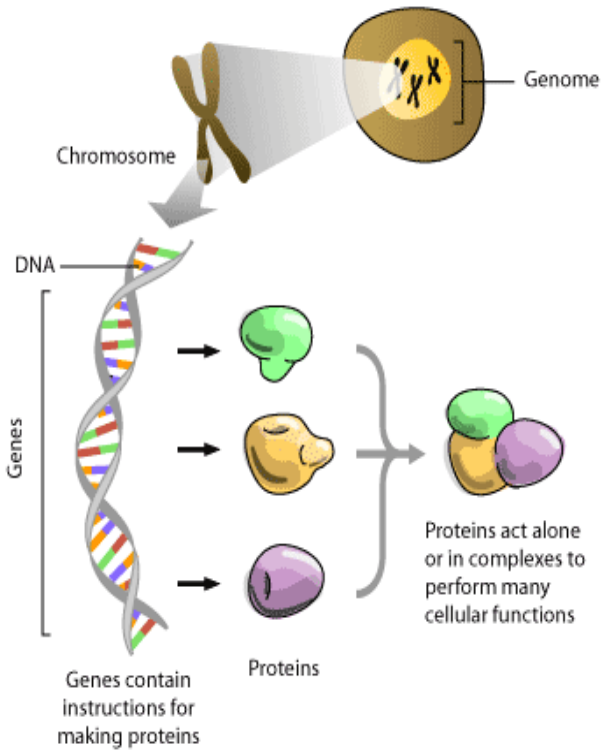


CHROMOSOMES

Chromosomes are single pieces of coiled double-stranded DNA along with genes, proteins, and nucleotides, and chromatin is a condensed package of chromosomes that basically allows DNA to fit inside the nucleus, so the genes within these chromosomes are known as the cell's nuclear genome.



In eukaryotic organisms, the DNA inside the nucleus is also closely associated with large protein complexes called histones. Along with the nuclear membrane, histones help control which messages get sent from the DNA to the rest of the cell. The information stored in DNA gets transferred to the rest of the cell by a very elegant process—a process so common and so important to life on Earth that it is called the central dogma of biology (DNA → RNA → Protein). Chromosomal DNA encodes most or all of an organism's genetic information.



The structure of chromosomes and chromatin varies through the cell cycle. Chromosomes are even more condensed than chromatin and are an essential unit for cellular division.

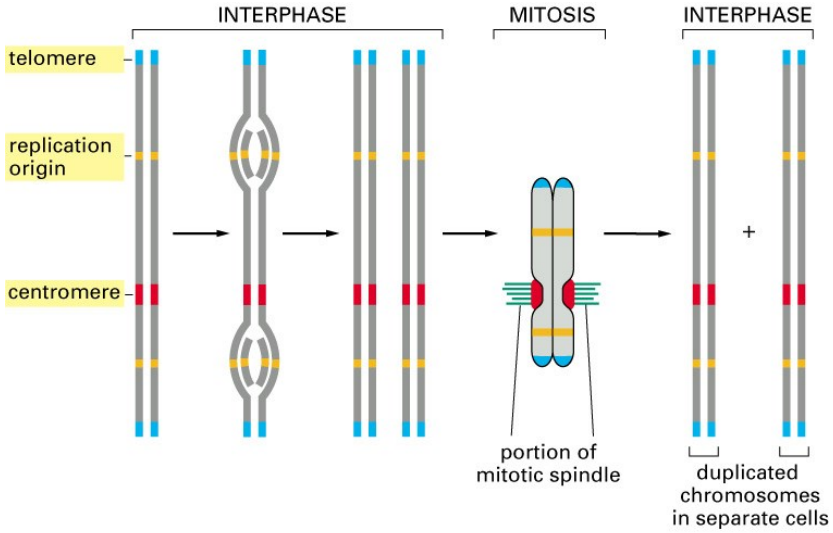
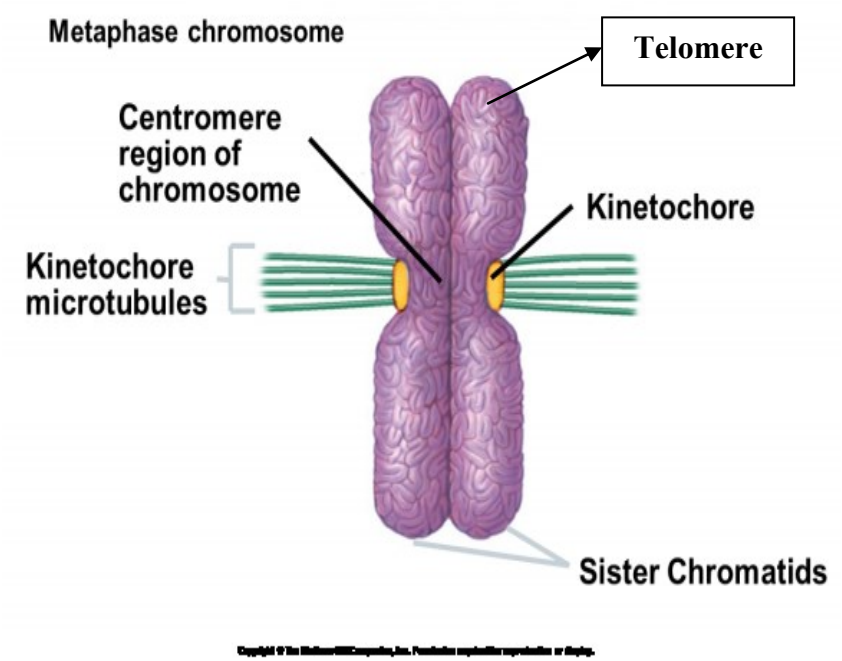


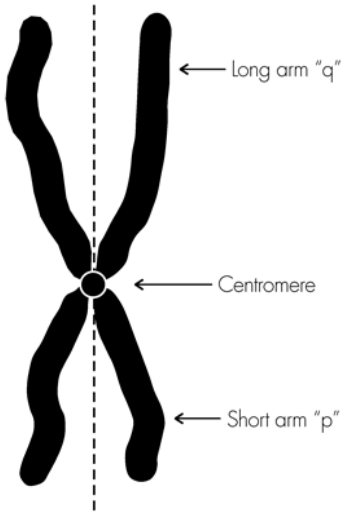
Figure 4–22. Molecular Biology of the Cell, 4th Edition.

Chromosomes may exist as either duplicated (**dyad**) or unduplicated (**monad**). Unduplicated chromosomes are single linear chromatid strands contains one DNA molecule, which may be several inches long, whereas duplicated chromosomes contain two identical copies (called arm or chromatids or sister chromatids or 2 monads) joined by a **centromere**. The centromere is a constricted region of the chromosome containing a specific DNA sequence, to which is bound 2 discs of protein called **kinetochores**. Kinetochores serve as points of attachment for microtubules that move the chromosomes during cell division. The regions at both ends of chromosome are the **telomeres**.



Chromosome Classification:

1. Each chromosome has two arms, p (the short one) and q (the longer). The p arm is named for "petit" meaning 'small'; the q arm is named q simply because it follows p in the alphabet.



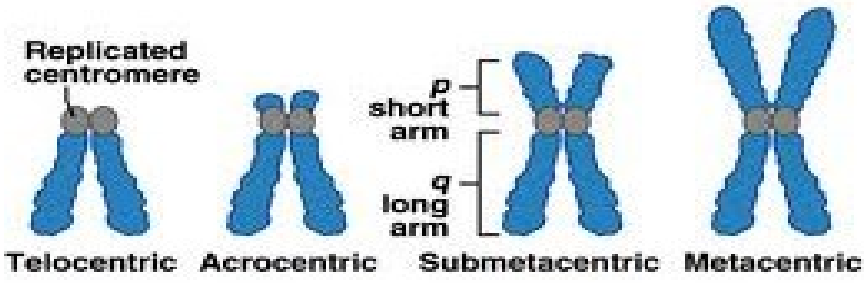
Chromosomes are classified according to centromere position to Metacentric, Sub-metacentric, Acrocentric and Telocentric (figure below)**.**

Metacentric: These are X-Shaped chromosomes, have centromere in the middle so that the two arms of the chromosomes are almost equal.

Submetacentric: The arms' lengths are unequal and the centromere is near the middle of the chromosome so, one arm is shorter than other.

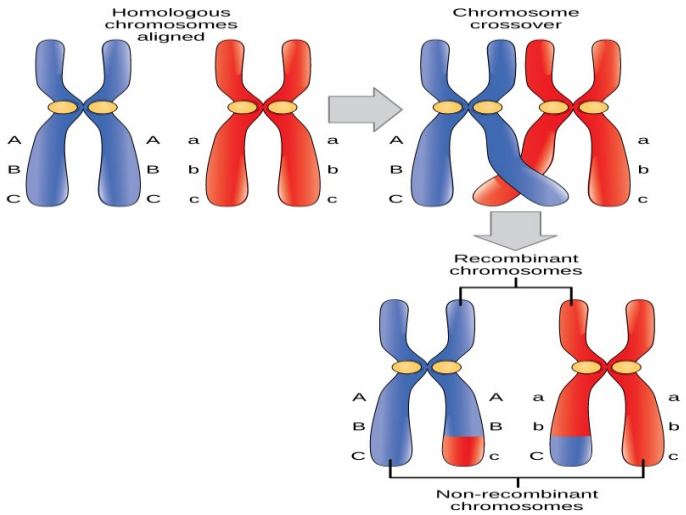
Acrocentric: The p (short) arm is so short that it is hard to observe, but still present, as the centromere is located near the terminal end of the chromosome.

Telocentric: The chromosome's centromere is located very close to its end than to its center.



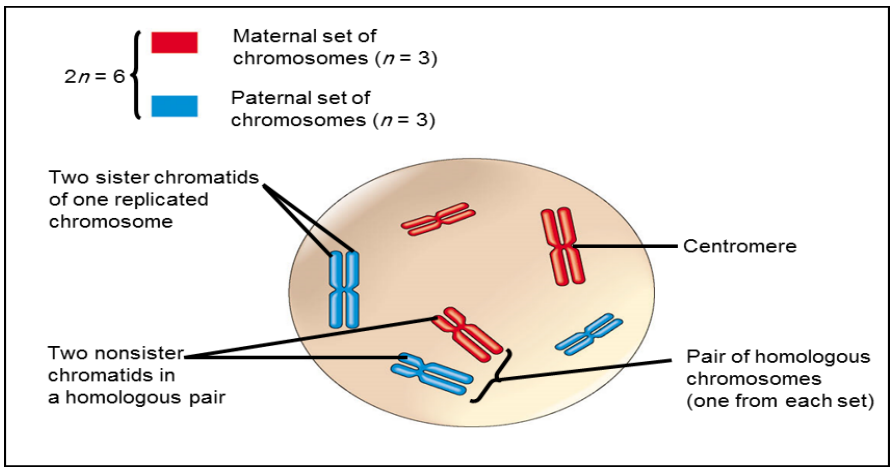
2. Chromosomes may be classified according to their types to either non-homologous, homologous or sex chromosomes.

Non-homologous chromosomes: look different and control different traits. Eg: chromosomes after crossover in meiosis

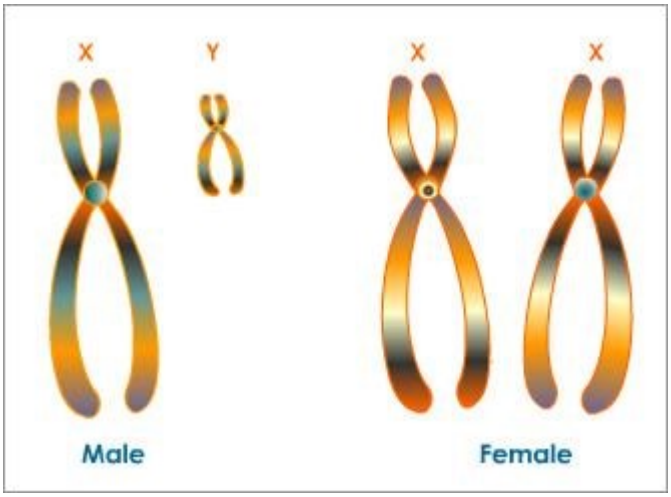


Homologous chromosomes- are chromosome pairs of approximately the same length, centromere position, and staining pattern, with genes for the same characteristics at corresponding loci (i.e. control the same traits).

May code for different forms of each trait and have independent origin - one homologous chromosome is inherited from the organism's mother; the other from the organism's father. They are usually not identical, but carry the same type of information i.e. similar but not identical. Eg: the 22 pairs of autosomes in human.



Sex chromosomes: Are distinct from each other in their characteristics and are represented as X and Y to determine the sex of the individual, XX being female **(homogametic)** and XY being male **(Heterogametic, hemizygotic)** Eg as in *Drosophila* and Human.



Other different sex determination mechanism:

1. Other Heterogametic male / homogametic female type: In grasshopper, the Y chromosome is absent in males and designed as X0

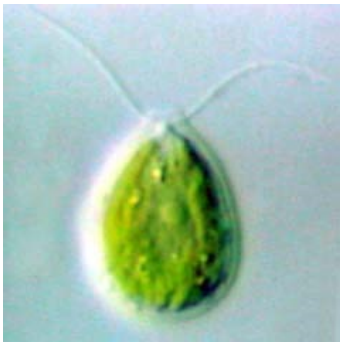
(heterogametic, hemizygotic) but females as two X chromosomes and signed as XX (homogametic).

2. Heterogametic female / homogametic male type: In Birds, the heterogametic female has one Z chromosome and one of W chromosome and signed ZW (heterogametic, hemizygotic), while the male has two Z chromosomes and signed ZZ (homogametic).

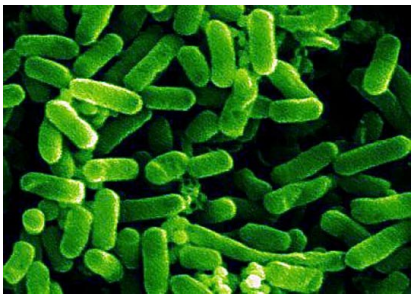
In moths, the heterogametic female has a single sex chromosome and designed as Z0 (heterogametic, hemizygotic), while the male has two of Z chromosomes and designed as ZZ (homogametic).

4. Haploid/Diploid type: Male bees are from unfertilized haploid eggs, while females (workers and Queeen) are from fertilized diploid eggs.

5. Mating type: Mating strains (eg: *Chlamydomonas*) are designated as (+) and (-) rather than ♂ and ♀, respectively.



6. Fertility factor: Donor cell (eg: Bacteria as *E. coli*) possesses a set of transfer genes that give its donor properties known as sex plasmid or Fertility plasmid or Fertility factor (signed as F). Maleness is presented as F^+ (presence of factor) and femaleness as F^- (absence of factor).

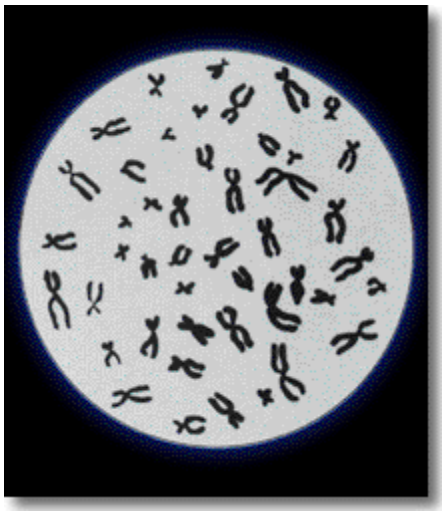


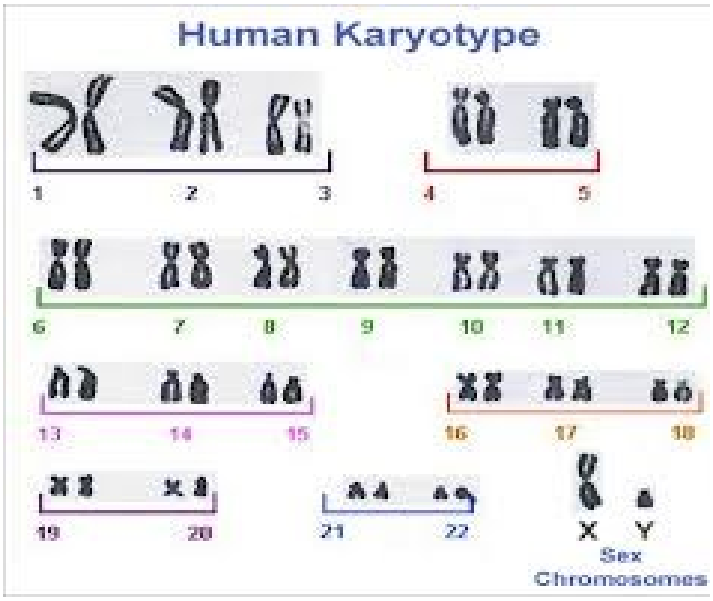
NOTE: An organism having only a single copy of a gene (genes on the single X chromosome in the male) instead of having two copies **or** having one sex chromosome (Y0 or Z0) are called **Hemizygous**.

KARYOTYPE

A **karyotype** is the particular array of the complete set of nuclear chromosomes in a species, or an individual organism. Karyotypes describe the number of chromosomes, and what they look like under a light microscope. Chromosomes are arranged in a karyotype for the

purpose of analysis. This arrangement of the chromosomes is based on their size, centromere position and banding patterns that are specific for each chromosome (figure below).



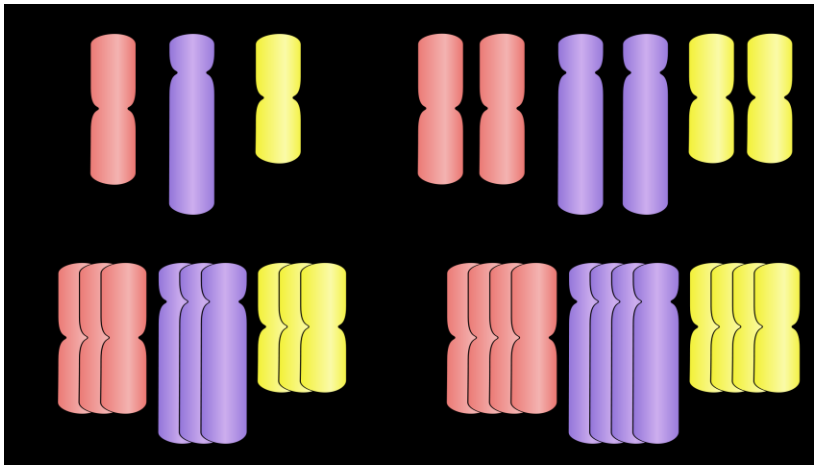


The cell may be classified according to the number of chromosomes copies (figure below) into either haploid (n) or diploid (2n) or polyploidy (n_s)**:**

Haploid - A cell possessing a single copy of each chromosome (human/plant sex cells).

Diploid - A cell possessing two copies of each chromosome (human/plant body cells). Most eukaryotes have between 10 and 50 chromosomes in their body cells. Human cells have 46 chromosomes: 22 nearly-identical pairs (autosomes) and a pair of sex chromosome.

Polyploid- A cell possessing numerous copies of each chromosome, so it may be triploid, tetraploid,…..



HOW THE CELL DIVIDE?

Cells spend a small part of their life dividing. Cell division is very tightly controlled, ensuring that everything happens at the right time and in the right order. Cells divide for reproduction, tissue renewal (wound healing), growth and development. Cell divisions include 2 main events: Cellular and Nuclear divisions. Cellular division refers to the process by which all the cellular components divide. Nuclear divisions refer to the process by which a nucleus divides. Two major nuclear divisions are involved in the genetic continuity of the nucleated cells: **Mitosis** and **Meiosis**. Mitosis is the process of cell division in which the daughter cells receive identical copies of DNA of the mother cell. Meiosis is the process of cell division that results in the formation of cells containing half the amount of DNA contained in the parent cell, and having different copies of DNA from one another. The cytoplasm and organelles are usually shared approximately

equally between the daughter cells. So, Mitosis creates genetically identical species, while Meiosis increases genetic diversity in a species.

CELL CYCLE

The cell cycle occurs from the completion of one division until the completion of the next division. It involves 2 phases: Interphase (G1, S and G2) and Mitosis (M) followed by Cytokinesis (C). The period between M and S is called G_1 stage and that between S and M is G_2 stage (figure below). The cell spends 90% of its time in Interphase and only 10% in Mitosis but, the duration of each phase and stage in eukaryotic cells depends on the cell type: For a typical rapidly proliferating normal human somatic cell with a total cycle time of 24 hours, the G1 phase might last about 11 hours, S phase about 8 hours, G2 about 4 hours, and M about 1 hour. Other types of cells, however, can divide much more rapidly as budding yeast and embryo cells: Yeast cell has a total cycle time of 2 hours, the G1 phase might last about 15 mins, S phase about 10 mins, G2 about 90 mins, and M about 5 mins.

Other example:

Cell Type	Total Time
fly embryo	8 minutes
bacteria	20 minutes
human skin	20 - 24 hours
human liver	1 year or more
human nerve	never, once mature

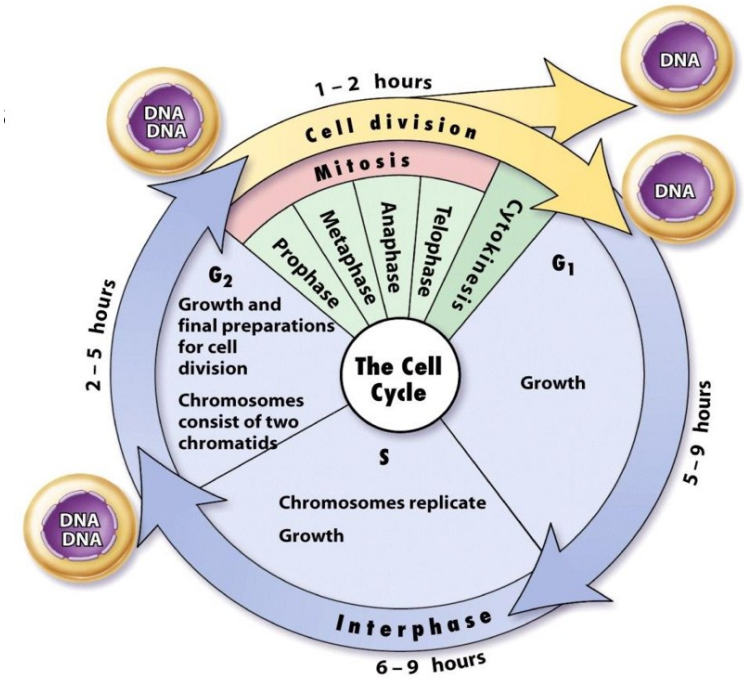


Figure 19-2 Biology of Humans, 2/e
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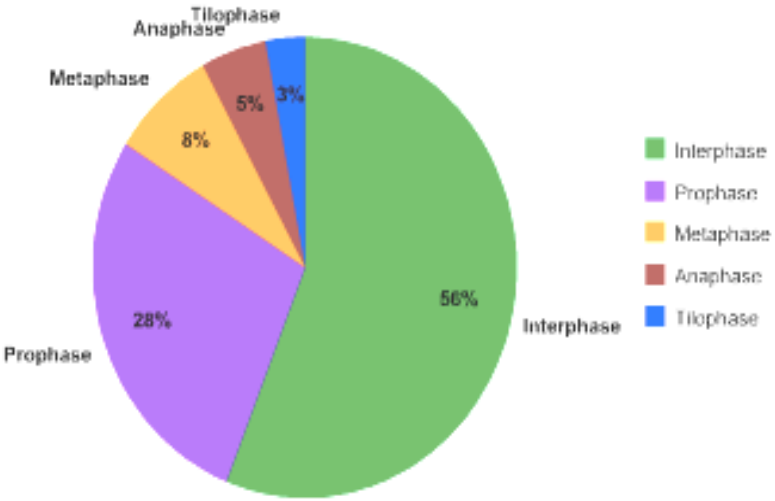
Length in Time of each phase of Mitosis



Interphase

The time between two successive mitotic divisions is known as Interphase (Resting or Growth stage). Eukaryotic cells spend most of their time (about 90%) in interphase. During interphase, the genetic material in the nucleus is in form of chromatin (uncoiled DNA), which appears only as dark granules within the nucleus. This appearance may be

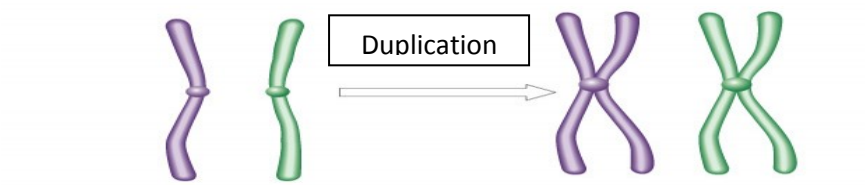
because they are uncoiled into long, thin strands. Both nucleolus and nuclear membranes are present and clearly visible.

The interphase involves 3 stages called G1, S and G2, respectively.

G1 stage (gap1, Pre-DNA synthesis): It lasting in a range of 4-9 hours depending on the type of eukaryotic cells. The cells become metabolically active (1^{ry} growth) producing RNA and ribosomes for protein synthesis; the cell organelles begin to increase in numbers, and the nucleus and cytoplasm enlarge so, the cell reach their mature size (small in size from previous division). The chromosomes are 2n in number, fully extended and single in structure i.e. a chromatid with a centromere (unduplicated chromosome).

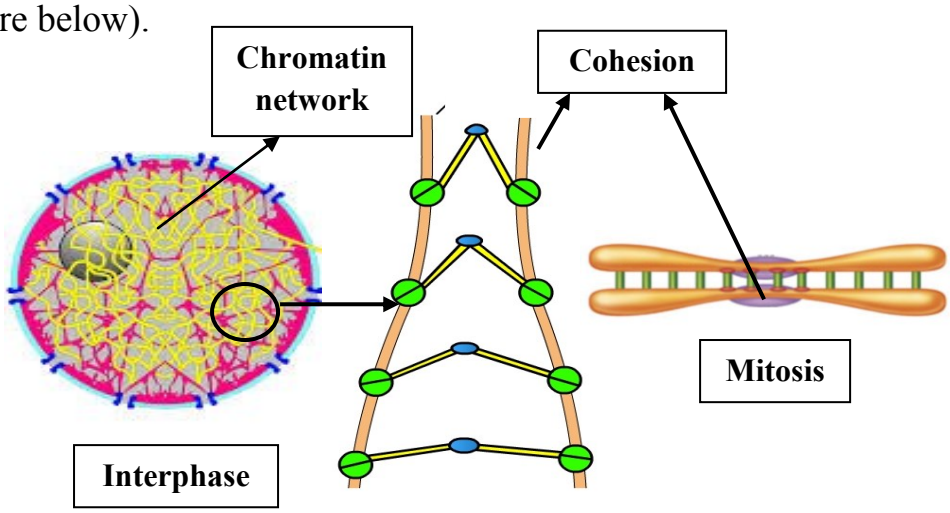
If the cells will never divide again but remain viable and metabolically active, it will refer as **G0 stage** (Prolonged G1 stage). It may be permanently arrested in G1 stage (never reenter the cell cycle) or can be stimulated to return to G_1 and thereby reenter the cell cycle.

S stage (DNA synthesis): DNA and histone syntheses lasting in a range of 6-9 hours depending on the type of eukaryotic cells. DNA and histone are the main component of chromatids (previously mentioned). At the end of this stage, the chromosomes have been duplicated and became 2n double in structure i.e. with 2 sister chromatids (duplicated chromosome) joined by a centromere (figure below).

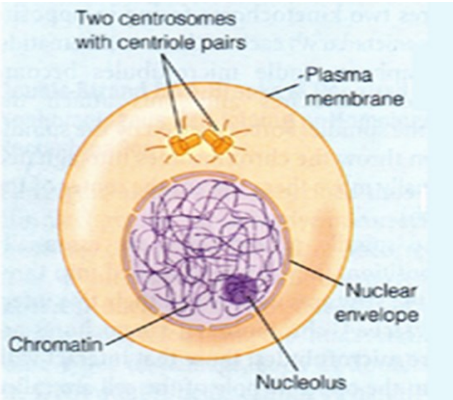


Two unduplicated chromosomes **Two duplicated chromosomes**

Sister chromatids are held together by a multi-subunit protein complex called **cohesin** formed between them in interphase and mitosis (figure below).

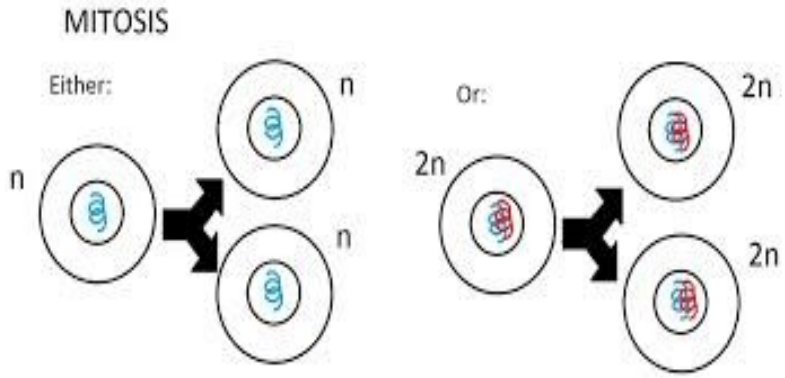


G2 stage (gap2, Post-DNA synthesis): This stage lasting from 2-5 hours in some eukaryotic cells. In which the cell synthesis certain component required for mitosis as centrosomes and centrioles, proteins of spindle fiber, enzymes,... and go to the final preparations of the cell (2nd growth) before divisions. The chromosomes are 2n double in structure but invisible in this form (uncoil) and the nucleus is filled with chromatin fibers that are formed when the chromosomes are uncoil.



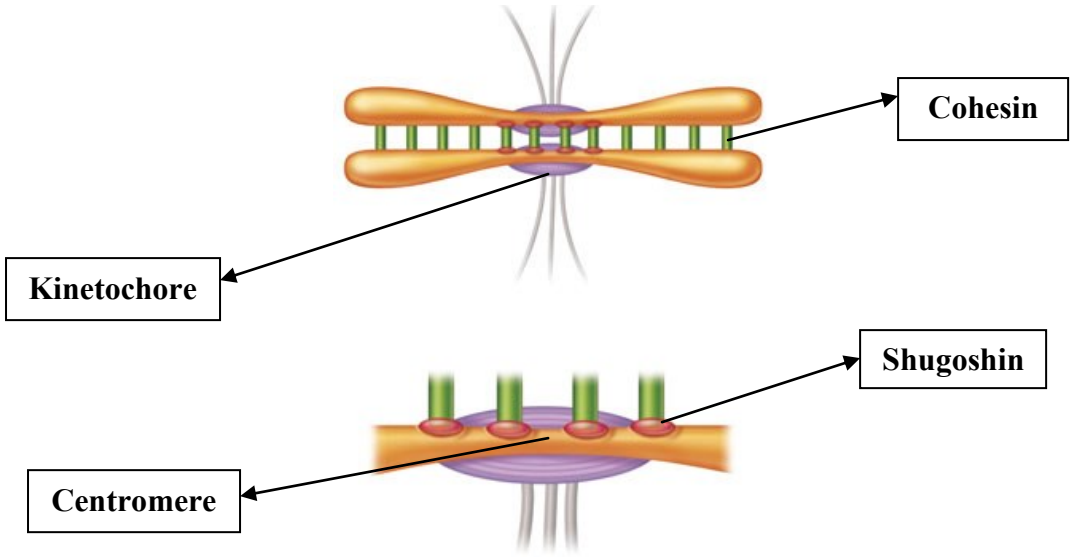
MITOSIS

It is the process by which a cell produces two identical daughter cells with complete set of chromosomes. This means that all the chromosomes must be duplicated and separated into two full sets, one at each end of the cell that is splitting in two (figure below). The cell organelles and other material that makes up the cell also split in two.

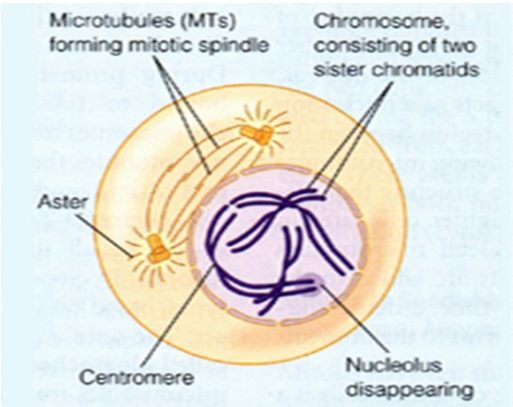


Mitosis consists of occurs in 4 stages (Karyokinesis) known as Prophase, Metaphase, Anaphase and Telophase (figure below).

Prophase: In this phase, the sister chromatids condense (coiled) and thickened until they appear as thread-like chromosomes joined by centromere (2n double in structure). Sister chromatids are also held together along their length by cohesion but at centromeres region, they are held together by both cohesin and **Shugoshin** proteins (Figure below). Both nuclear envelope and nucleoli start to disappear, while the mitotic spindles begin to form from the centrosomes to control chromosome movement during mitosis (figure below).

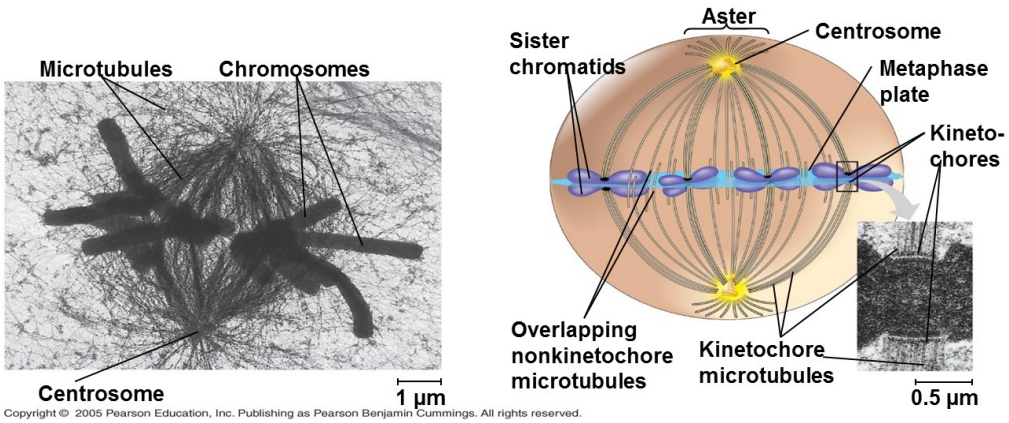


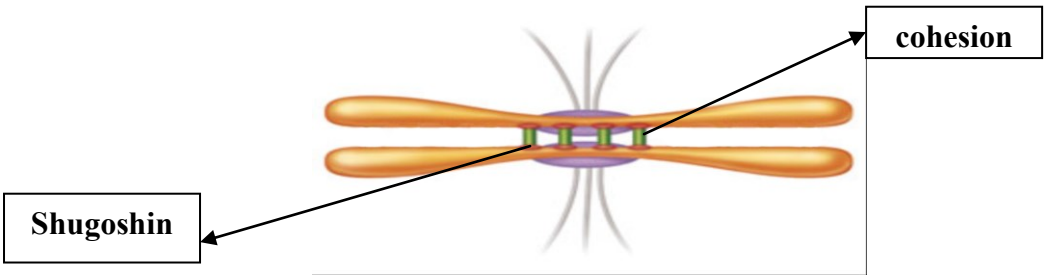
NOTE: The spindle apparatus includes the centrosomes (in animal cell but other in plant cell), the spindle microtubules, associated proteins and the asters (a radial array of short microtubules in animal cell). The centrosome replicates in interphase, forming two centrosomes each with 2 centrioles that migrate to opposite ends of the cell in prophase. Assembly of spindle microtubules begins in the centrosome (the microtubule organizing center) and an aster extends from each centrosome.



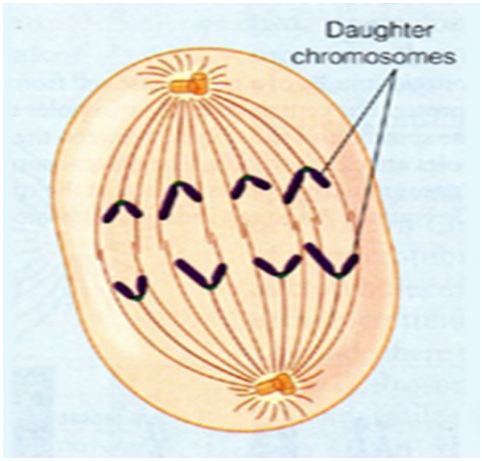
Metaphase: When the mitotic spindle is fully formed, the chromosomes align themselves along the cell spindle in the middle of the cell (equator, equatorial plates). This movement is due to: Assembly and disassembly of microtubules provide force to move chromosomes with the help of the

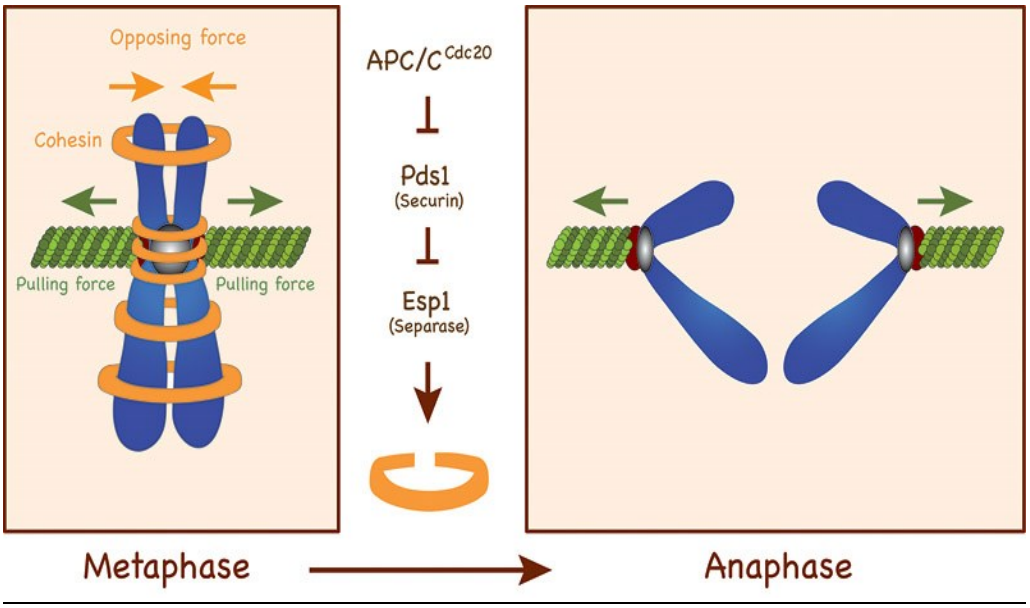
motor proteins located in kinetochore and poles of cell pull on microtubules to provide force. The metaphase chromosome (2n double in structure) appears as two sister chromatids join together by their centromeres and to the spindles by their kinetochore (figure below). At this stage, separase enzyme (and others) dissolves the cohesion protein along the 2 sister chromatids except at centromere were both cohesion and Shugoshin proteins remains (Figure below).



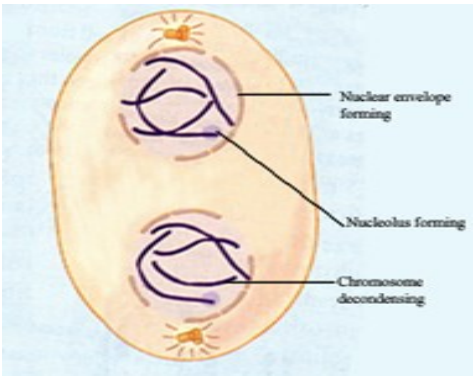


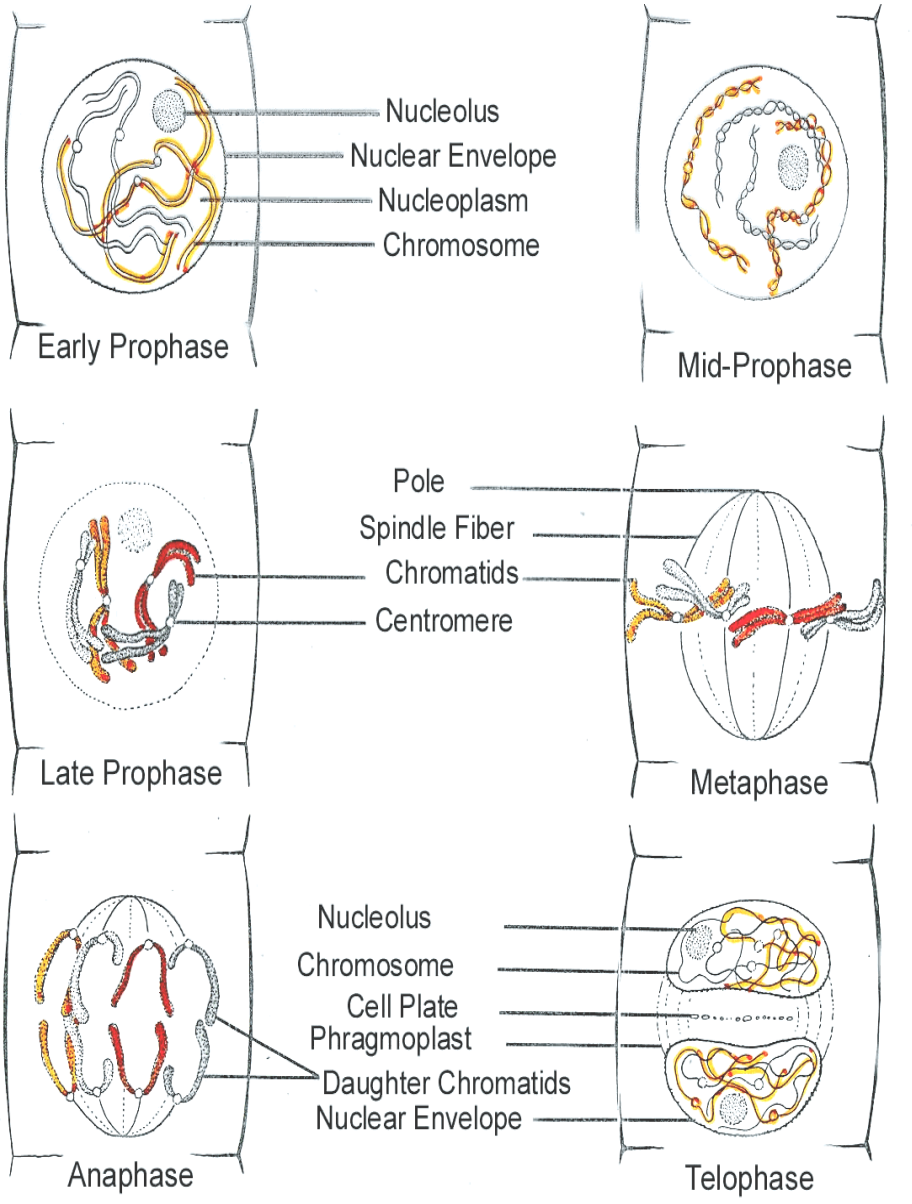
Anaphase: Both cohesion and shugoshin dissolve by proteiolytic enzymes so, the sister chromatids (present in equator) split apart at their centromeres, begin to separate and move to opposite poles of the spindle, segregating one of the two sister chromatids to each of the opposite ends of the cell. In this case, each chromatid became a chromosome. The chromosomes are 2n single in structure (2n monad).





Telophase: A complete set of chromosomes reach each pole of the cell and begin to uncoil. The mitotic spindles, centrosomes and asters begin to disappear (microtubules are broken down into tubulin monomers). The nucleolus and the nuclear envelop reappear around the set of chromosomes. The chromosomes are 2n single in structure. Then the cell prepares to split in two identical daughter cells by a process called cytokinesis.



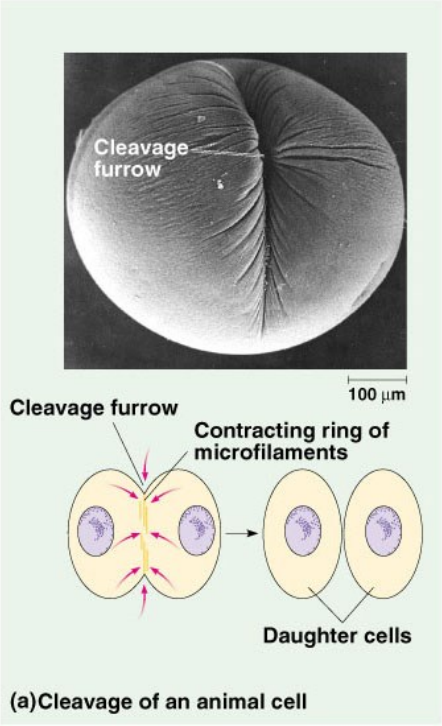


CYTOKINESIS

It usually initiates during the late stages of mitosis (at the end of telophase), and sometimes meiosis, splitting a cell in two, to ensure

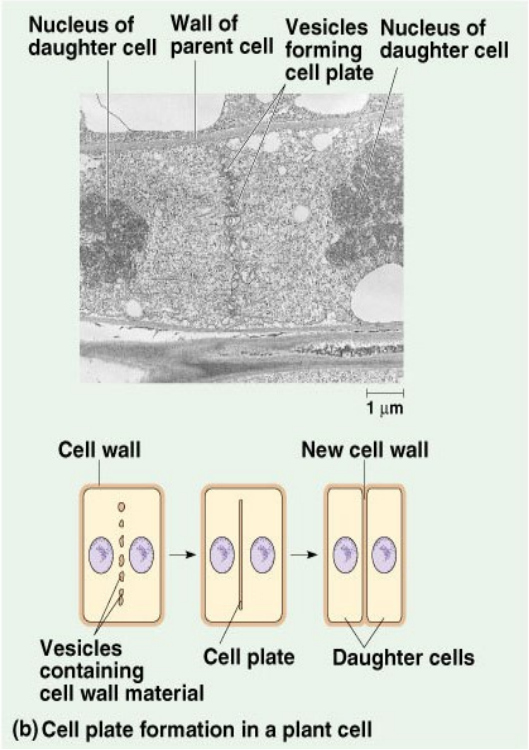
that chromosome number is maintained from one generation to the next or one cell to another.

In animal, the cell membranes on opposite sides of the cell become pinched-in (constriction) allowing for the cell to divide. The initial structure that forms is called a **cleavage furrow**. The cleavage furrow continues to pinch in, until the two sides are touching. At this point, there will be two new cells.



In plant cells, a structure known as a **cell plate** (originates from vesicles of Golgi apparatus) begins to grow and elongate in the center of the cell (at the region of the metaphase plate), with each end heading toward the opposite cell walls. This linear wall-like structure continues to grow until it reaches the actual cell walls. Once the cell plate has divided the cell into two cells, it forms the **middle lamella.** In the same time the **plasma membrane** of the maim cell split and begin to reform in the both daughter cells. Subsequently, the cell will develop new primary and

secondary layers of **cell wall** (figure). This stage is followed by a stage of G1-interphase.



NOTE: The cytoplasm and organelles are usually shared approximately equally between the daughter cells.

NOTE: Cyclins are a family of proteins that control the progression of cells through the cell cycle by activating cyclin-dependent kinase (Cdk) enzymes.

Differences between Mitosis in Animal and Plant cells:

DIFFERENCES BETWEEN MITOSIS IN PLANT AND ANIMAL CELLS	
MITOSIS IN ANIMAL CELLS	**MITOSIS IN PLANT CELLS**
1. Centrioles are involved	1. Centrioles are absent
2. Asters are formed	2. No aster formation
3. Cytokinesis occurs by furrowing of cytoplasm	3. Cytokinesis occurs by cell plate formation
4. Occurs in tissues throughout the body	4. Occurs mainly in the meristems

CELL CYCLE CHECKPOINTS

Maintenance of genomic stability is needed for cells to survive many rounds of division throughout their lifetime without disruption. Key to the proper inheritance of intact genome is the tight temporal and spatial coordination of cell cycle events to monitor the proper execution of cell cycle processes to avoid uncontrolled cell division characterizing malignancy. Those keys are the cell cycle checkpoints.

Multiple checkpoints have been identified: G1 checkpoint, G2 checkpoint, DNA replication checkpoints, Mitotic spindle checkpoint and antephase checkpoint.

G1 checkpoint (restriction point) is located at the end of the G_1 phase, just before entry into S phase (G_1/S) to monitor the size the cell has achieved since its previous mitosis, nutrition, growth factors and also to evaluate the condition of the DNA. It is a vital checkpoint making the key decision of whether the cell should divide, delay division, or enter a resting stage. If all conditions are "normal", then the cell is allowed to proceed from G1 to the S phase of the cycle. If the cell has not reached an adequate size or if the DNA has been damaged, further progress through the cycle is arrested until these conditions are "corrected."

NOTE:

As we have outlined previously, the cell cycle consists of four primary stages, G1 (GAP 1, 1^{ry} growth), S (Synthesis), G2 (GAP 2, 2^{nry} growth) and M (Mitosis). Each stage contributes to the successful replication of a cell in its own unique way. But in order for each of the stages to have good participation in the cycle, DNA must clear all the checkpoints which it encounters along the way.

The check for DNA damage in eukaryotic cell division is to successfully pass accurate DNA strands (mutation free) from parental genomes to

daughter cells as cells mitotically replicates. The passing of mutation-free DNA will ensure the cycle procedures healthy and functional cells. However, DNA does not always exist as mutation free and DNA with mutations (due to either irradiation or chemical modification) will likely lead to cancer. For the prevention of passing DNA which could cause replication of cancerous cells, the cell cycle includes an impressive system of checkpoints that, more or less, scan the DNA passing through the cycle for mutations (or any damages) by sensor mechanisms i.e. those checkpoints verify (and assess) whether the processes (done before or needed) at each phase along the cell cycle have been accurately completed before progression into the next phase (Figure below).

Checkpoints along the cycle not only assess the DNA for damage but can actually act upon it in effort to correct any mutation which is hindering its advancement in the cycle. Signal Mechanisms within the checkpoints can delay (or stall) the cycle until mutations are corrected. If the G1 checkpoint deems the DNA unsuitable for progression it can stop or delay the process sending it into an optional resting phase known as G0. A special protein referred to as P53 is essential in the function of the G_1 restriction point as P53 has the ability to detect mutations in the genes which pass through the checkpoint. If mutations are irreversible, they can tag a cell for self-destruction via **apoptosis** (effector mechanism) and thereby eliminating the chance that mutated DNA will be replicated. However, as we all know, this process is not always flawless, causing the spread of mutation filled, cancerous cells.

The **DNA replication checkpoint** is located at the end of the S phase to ensure the good replication of DNA before entering G2 phase.

The **G2 checkpoint** is another checkpoint (after completing S and G2 phases) in which DNA must overcome to complete a successful cycle. In

order for this checkpoint to be passed, the cell has to check a number of factors, including DNA, to ensure that the cell is ready for advancing to the M or mitosis phase. A successful transition through this checkpoint will trigger the start of mitosis. Often time's damage can occur to the DNA before it reaches this checkpoint and therefore, in efforts to stop the transmission of mutated genes to daughter cells, it is likely that the cycle will be inhibited at this point. If this checkpoint is passed, the cell initiates the many molecular processes that signal the beginning of mitosis.

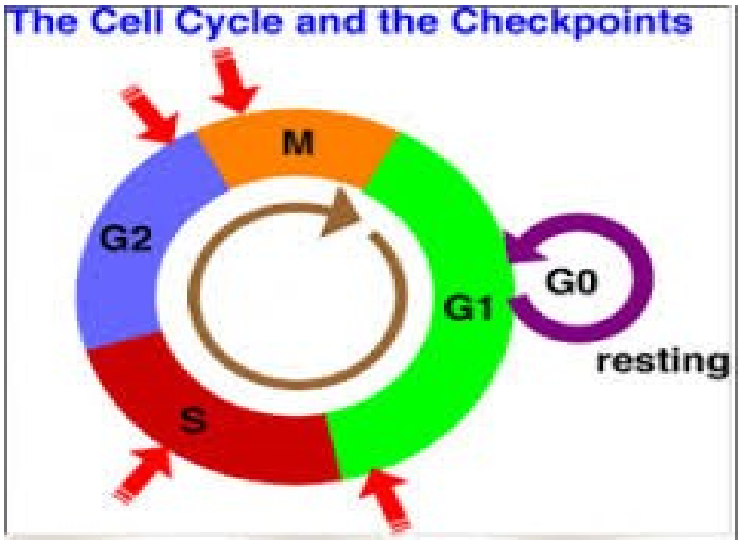
Without DNA damage checkpoints throughout the process of cell division and replication, the transferring of mutated genes would be more likely. Viable checkpoints are necessary to ensure that DNA being replicated is mutation free. Cancer may spread with more amplification and at a must quicker rate if it weren't for the detection of checkpoints in the process of cell division.

The **antephase checkpoint** has recently been gaining attention. The term "antephase" refers to the time in late G_2 phase when signs of chromosome condensation first become visible until commitment to mitosis. This checkpoint plays an important role in preventing mitotic entry in the presence of various stress conditions by preventing chromosome condensation.

The **mitotic spindle checkpoint** (spindle assembly checkpoint) occurs at metaphase where all the chromosomes should/have aligned at the mitotic plate (equator) and be under bipolar tension (tension of both poles). The tension created by this bipolar attachment is what is sensed, which initiates the anaphase entry i.e. the anaphase will be blocked if the chromatids are not properly assembly on mitotic spindle by their kinetochores. In addition, if this failure to attach correctly to the spindle

passes, it causes an unequal segregation of chromosomes, which can lead to cell death or disease.

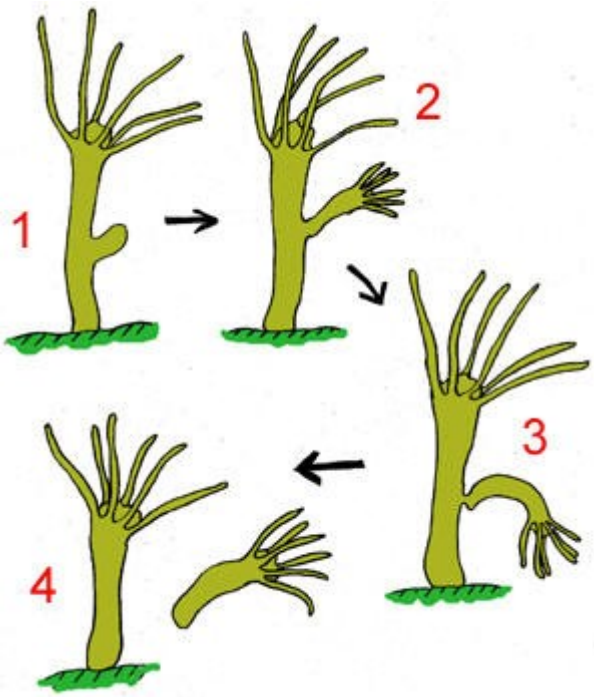
The DNA damage and spindle assembly checkpoints are surveillance mechanisms that ensure genomic integrity by delaying cell cycle progression in the presence of DNA or spindle damages, respectively until all chromosomes are correctly attached in a bipolar fashion to the mitotic spindle.



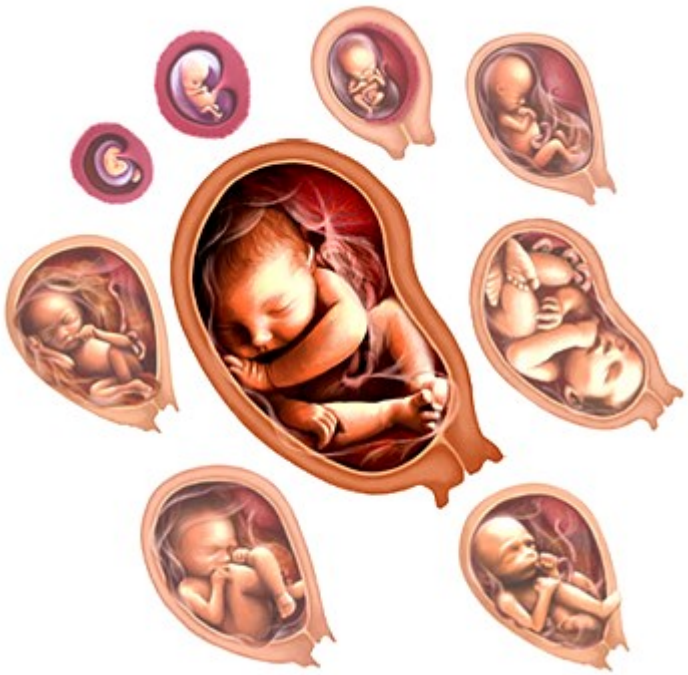
IMPORTANCE OF MITOSIS:

Following are the occasions in the lives of organism where mitosis happens:

Asexual Reproduction: Some organisms produce genetically similar offspring through asexual reproduction. For example; hydra reproduces asexually by budding. The cells at the surface of hydra undergo mitosis and form a mass called bud. Mitosis continues in the cells of bud and it grows into a new individual. The same division happens during asexual reproduction or vegetative propagation in plants and microbes.



Development and growth: The number of cells within an organism increase by mitosis. This is the basis of the development of a multicellular body from a single cell i.e., zygote and also the basis of the growth of a multicellular body. In the fetus, babies and growing children mitosis occurs in most tissues.

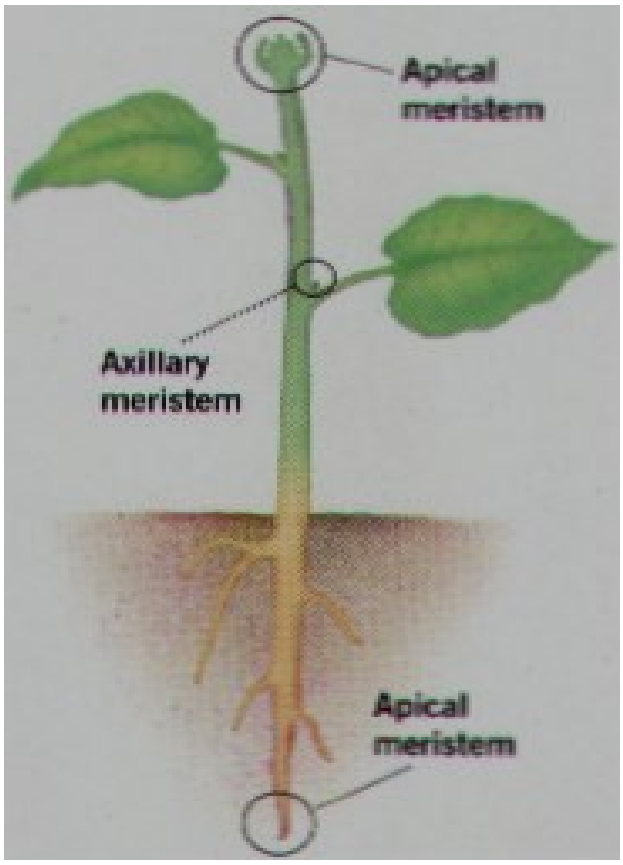


While in adults, however, most tissues do not proliferate but mitosis occurs regularly at the following sites:

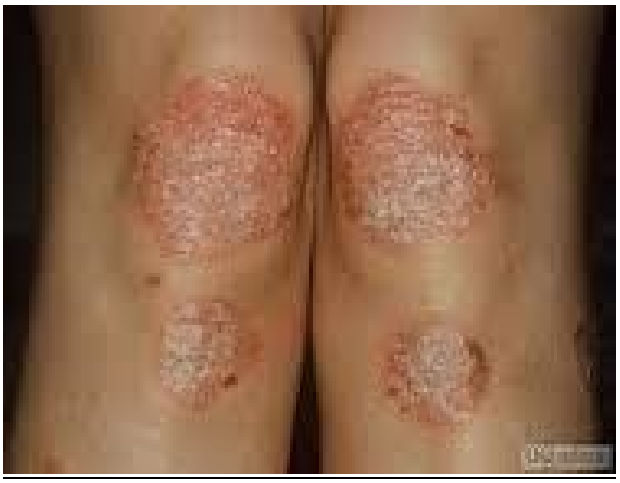
1. Red bone marrow – for production of blood cells (erythropoiesis)
2. Lymphoid tissue - formation of lymphocytes (lymphooiesis)
3. Testes – for spermatogenesis (production of spermatozoa)
4. Epidermis - replacement of superficial skin cells
5. Hair follicles - hair growth
6. Gastro-intestinal tract - renewal of epithelium

Note that most of the neural cells do not perform mitosis so; any damage in them cannot be repair.

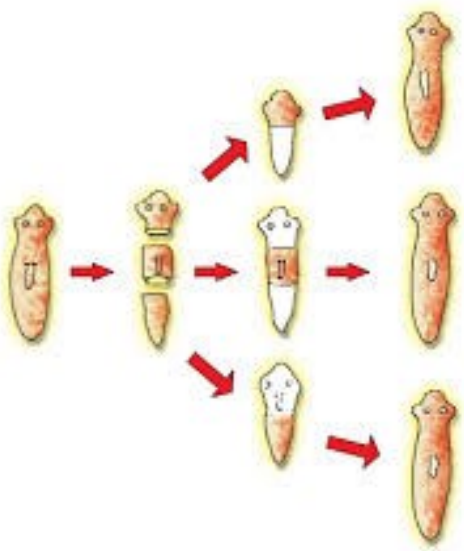
In plants, mitotic cell division mainly takes place in special regions called meristems. They are either present in Shoot apex or axillary buds or root tips of the plants for development and growth.



Cell Replacement: In some parts of body, e.g. skin and digestive tract, cells are constantly sloughed off and replaced by new ones. New cells are formed by mitosis and so are exact copies of the cells being replaced. Similarly, RBCs have short life span (only about 4 months) and new RBCs are formed by mitosis.



Regeneration: Some organisms can regenerate (form *de novo*) their parts of bodies. The production of new cells is achieved by mitosis. For example; sea star and flat worms regenerate their lost part through mitosis.



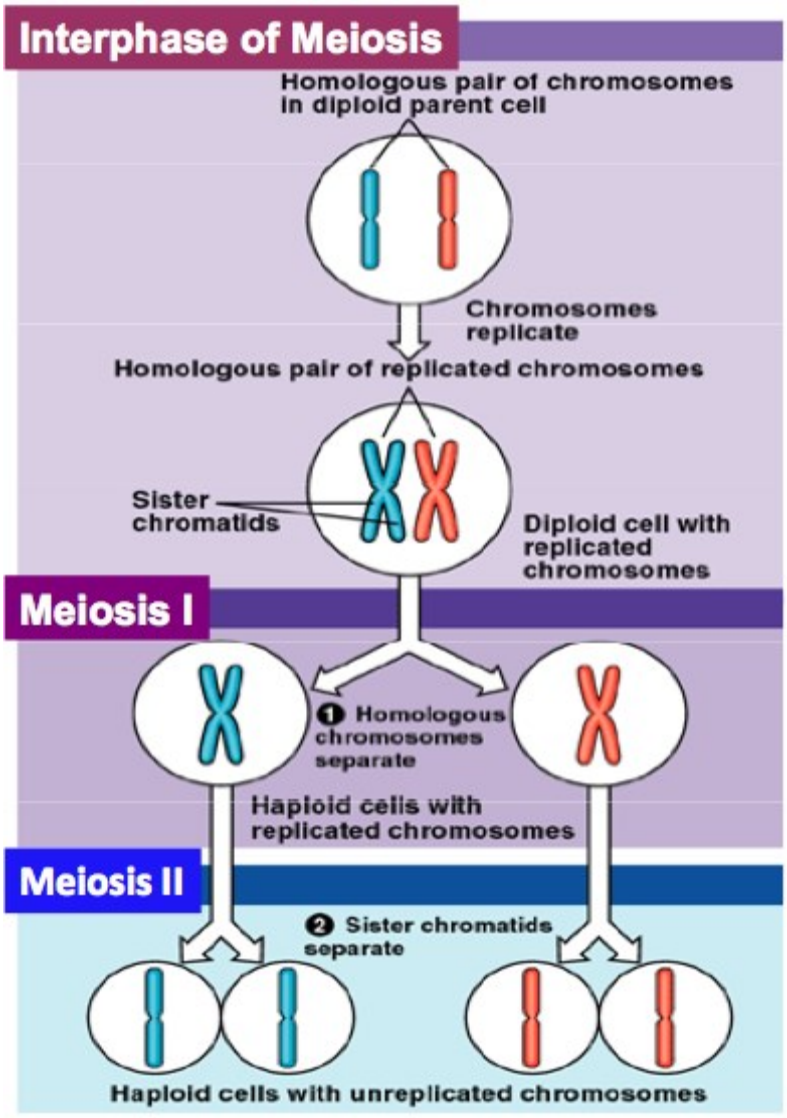
CLINICAL APPLICATIONS:

Cancer cells undergo uncontrolled cell proliferation. As such, they are defects of the control of the cell cycle. Oncogenes (الجينات المسرطنه) are mutations in the genes that normally control the cell cycle. Chemotherapy of cancers is aimed towards interrupting the cell cycle and preventing the cancer cells from proliferating. As a side effect, however, also the normal sites of cell proliferation are affected resulting in hair loss, intestinal disorders, anemia and infertility, which return back in normal state after ending the treatment.

Student assessment: What are the different between Normal and Cancer Cell Cycle?

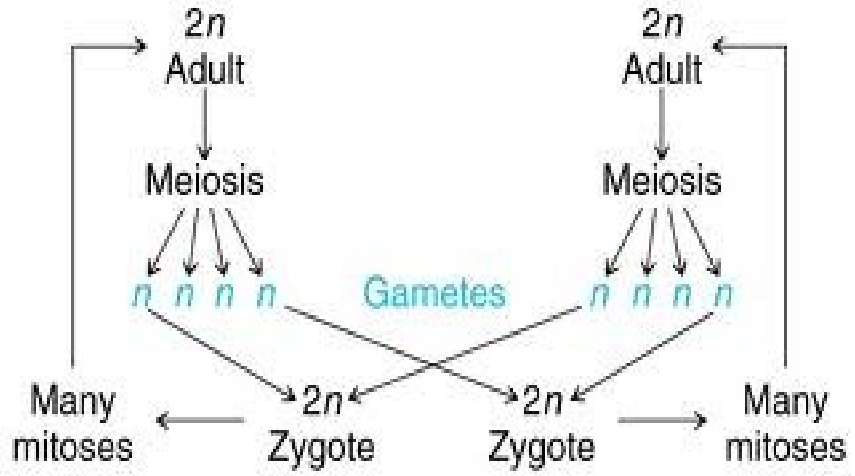
MEIOSIS AND SEXUAL REPRODUCTION

Meiosis is a special type of cell division necessary for sexual reproduction, in eukaryotes, such as animals, plants and fungi, to produce gametes (figure below). The process includes: 1) number of sets of chromosomes in the cell undergoing meiosis is reduced to half the original number, typically from two sets (diploid) to one set (haploid). 2) the chromosome is reduced from double to single structure.



In many organisms, including all animals and land plants (but not some other groups such as fungi), gametes are called sperm in males and egg cells (or ova) in females. Since meiosis has halved the number of sets of chromosomes, when two gametes fuse during fertilization, the number of

sets of chromosomes in the resulting zygotes restored to the original number.



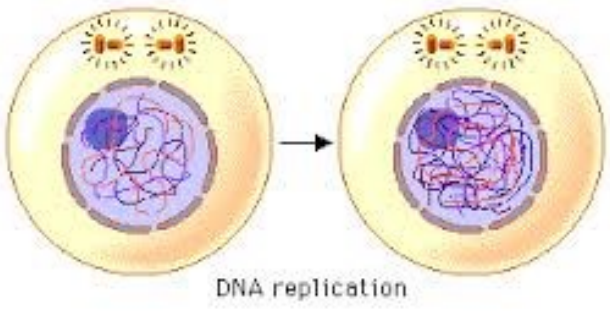
Meiosis is divided into two stages, meiosis I and meiosis II which are further divided into Karyokinesis I (prophase I, metaphase I, anaphase I, telophase I) and Cytokinesis I then Karyokinesis II (prophase II, metaphase II, anaphase II, telophase II) and Cytokinesis II, respectively, dividing the cells once at each stage.

The first stage (Meiosis I) begins with a diploid cell that has two copies of each type of chromosome, one from each the mother and father (homologous chromosomes). All homologous chromosomes pair up and may exchange genetic material with each other in a process called crossover. Each pair then separates as two haploid cells are formed, each with one chromosome from every homologous pair.

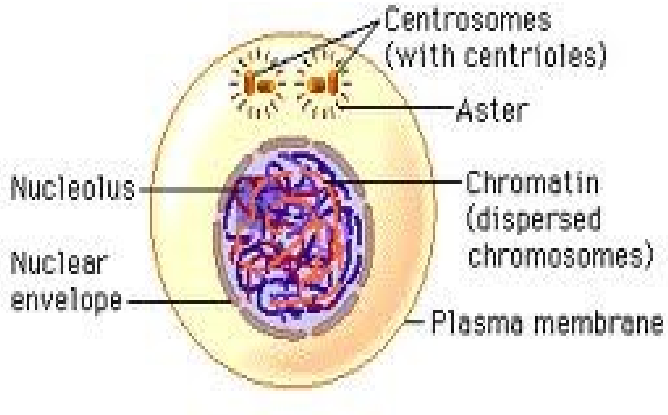
In the second stage (Meiosis II), each chromosome splits into two, with each half, called a sister chromatid, being separated into two new cells, which are still haploid. This occurs in both of the haploid cells formed in meiosis I. Therefore from each original cell, four genetically distinct (genetically different) haploid cells are produced. These cells can mature into gametes.

Meiosis I (reduction division)

Because meiosis is a "one-way" process, it cannot be said to engage in a cell cycle as mitosis does. However, the preparatory steps that leads up to meiosis are identical in pattern and name to the interphase of the mitotic cell cycle i.e. interphase is not a part of meiosis. So, just before meiosis I there is Interphase I where there is DNA replication, organelle synthesis and an increase in energy stores.

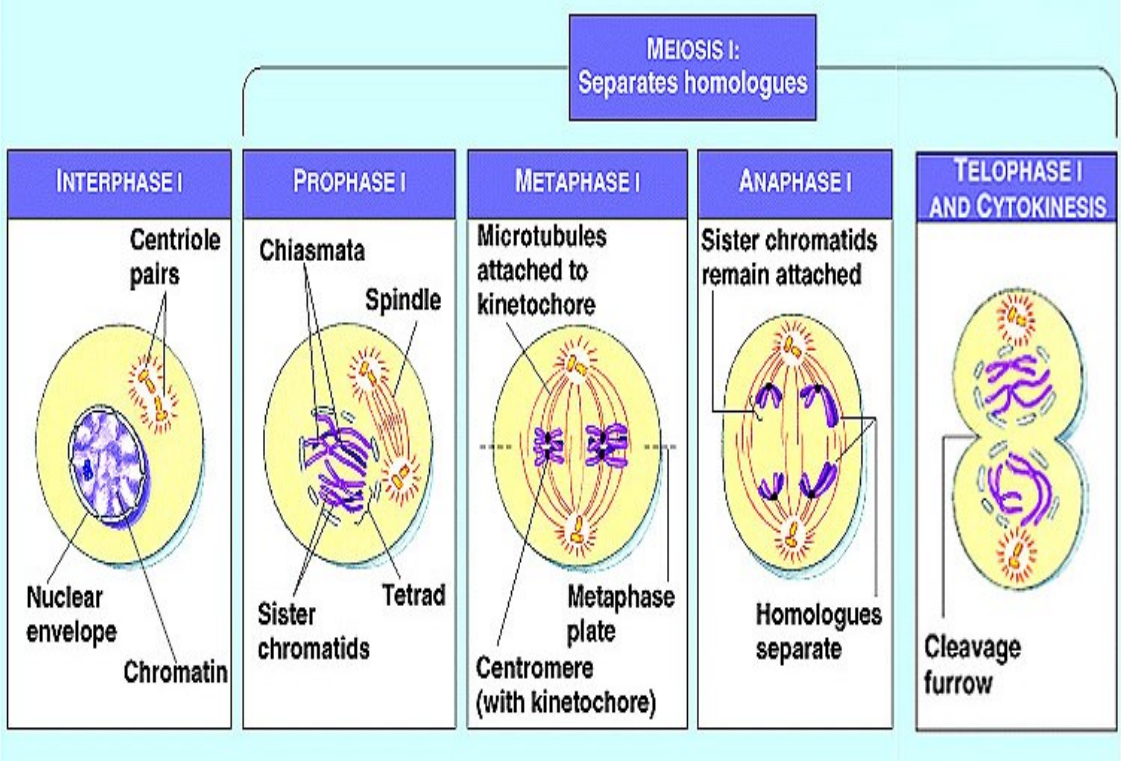


Interphase I

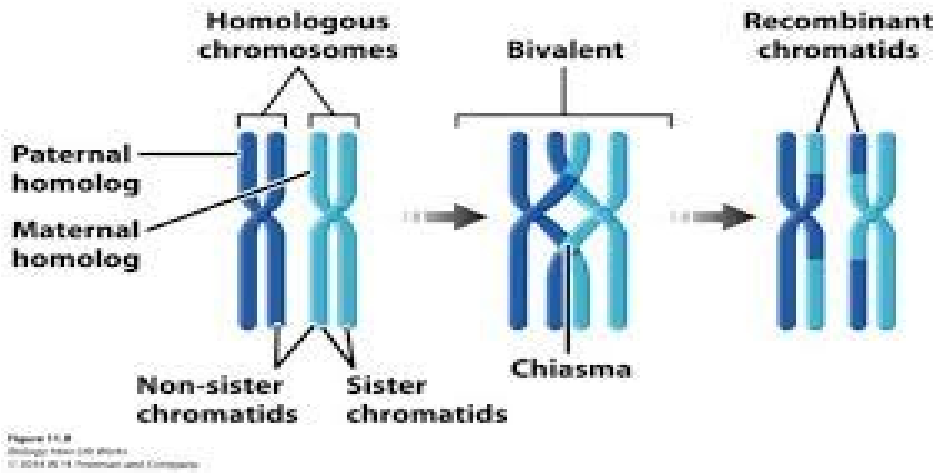


In Meiosis I, the number of sets of chromosomes in the cell undergoing meiosis I is reduced to half the original number, typically from diploid to haploid (reduction division or separates homologues), but the chromosome structure remains double.

Meiosis I is divided into Karyokinesis I (prophase I, metaphase I, anaphase I, telophase I) and Cytokinesis I (figure below).

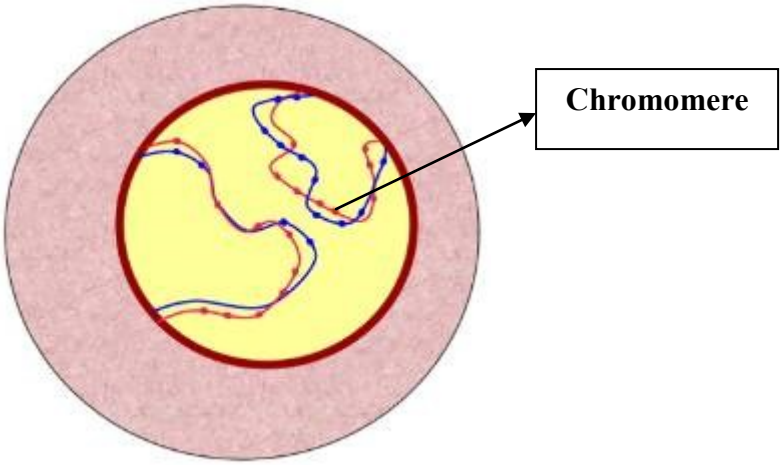


Prophase I: It is the longest phase of meiosis. During prophase I, DNA is exchanged between homologous chromosomes in a process called homologous recombination. This often results in chromosomal crossover. The new combinations of DNA created during crossover are a significant source of genetic variation, and may result in beneficial new combinations of alleles. The process of pairing the homologous chromosomes is called **synapsis**. The paired and replicated chromosomes (synapsed structure) are called **bivalents or tetrads**, which have two chromosomes (2 dyads) with four chromatids, with one chromosome coming from each parent (figure below). At this stage, non-sister chromatids may cross-over at points called **chiasmata** (singular chiasma). Both nuclear envelope and nucleoli start to disappear by the end of prophase I, while 2 pairs of centrioles would have moved to opposite poles of the cell forming the spindles, which in turn control the chromosome movement during the next phases.

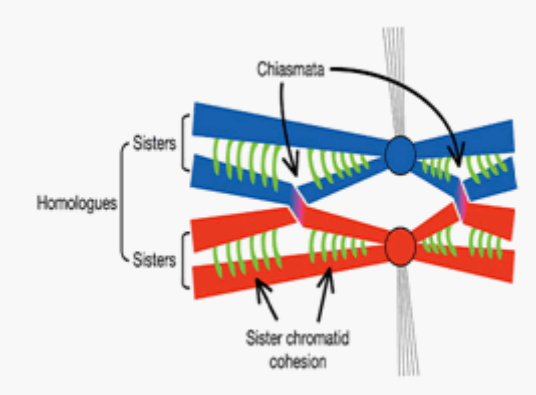


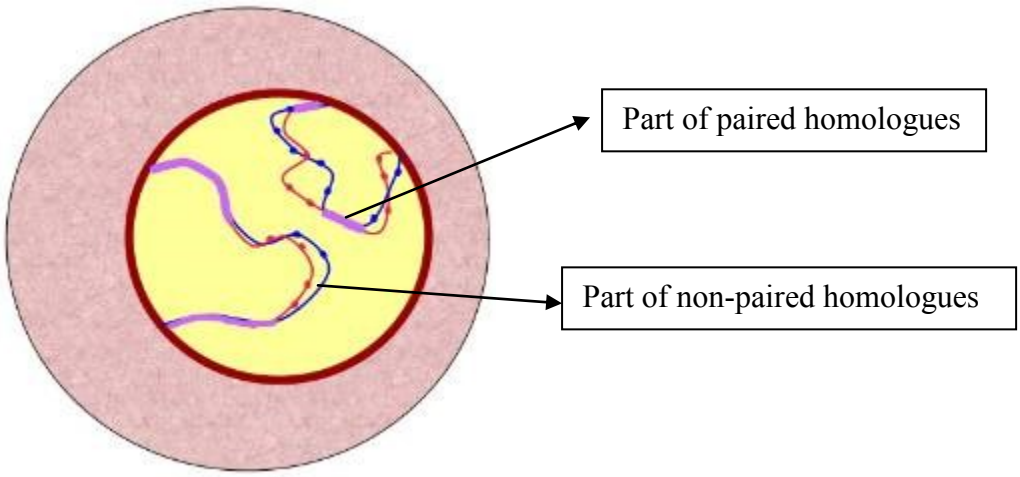
Prophase I is subdivided into the following 5 substages (figure below):

Leptotene (leptonema)**:** The first stage of prophase I that means "thin threads". This stage is of very short duration in which the individual chromosomes (each consisting of two sister chromatids, **Dyad**) change from the diffuse state they exist in during the cell's period of growth and condense (supercoil) into visible strands within the nucleus but they are not yet fully condensed. Along each chromosome some localized condensations are present and resemble beads on a string known as **chromomeres**. The chromosomes, while they have this threadlike form, are called *chromatonemata* (sing. chromonema; *-nema* is Greek for *thread*). The chromosomes appear single because the sister chromatids are still so tightly bound to each other that they cannot be separately seen. Sister chromatids of each dyad are held together along their length by cohesin and at centromeres region, they are held together by both cohesin and Shugoshin proteins. During this stage both telomeres of each chromosome are turned toward, and probably attached to, the same region of the nuclear envelope. The chromosomes are 2n and double in structure.

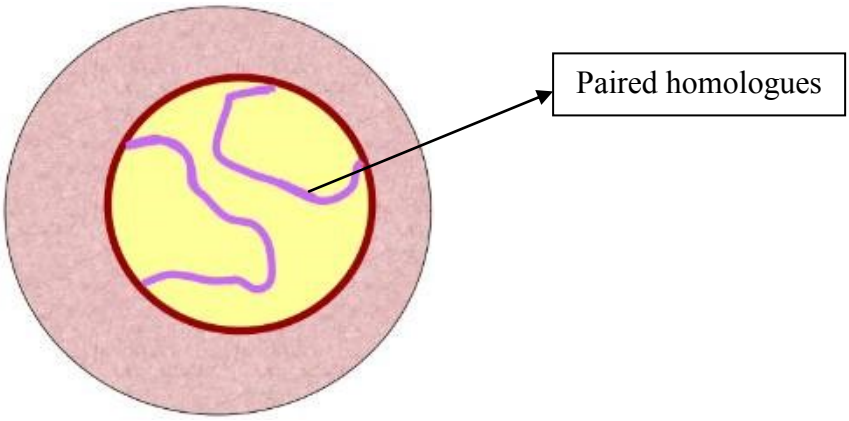


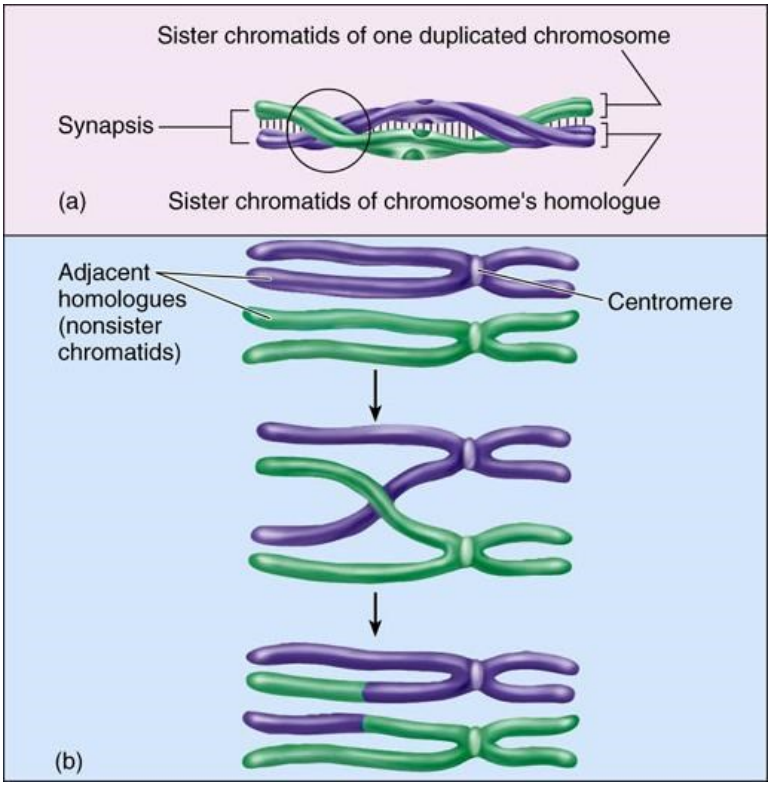
Zygotene (zygonema)**:** This stage means "paired threads", in which the chromosomes continue to shorten and thicken and approximately line up with each other into homologous chromosome pairs. This is called the bouquet or ladder-like stage because of the way the telomeres cluster at one end by synaptonemal proteins. At this stage, the synapsis (pairing/coming together) of homologous chromosomes take place so, the fused homologs look like a single chromosome under the light microscope, but they are actually double. **Synapsis** is the process of fusion that occurs between homologs by *synaptonemal complex* and begins at various points along the chromosome and extends outward in a zipper-like fashion until it completes the entire lengths in the next step. Individuals of a pair are equal in length and in position of the centromere thus pairing is highly specific and exact. The paired chromosomes are called bivalent or tetrad chromosomes. Sister chromatids of each dyad still held together along their length by cohesin and at centromeres region, they also held together by both cohesin and Shugoshin proteins (figure below).





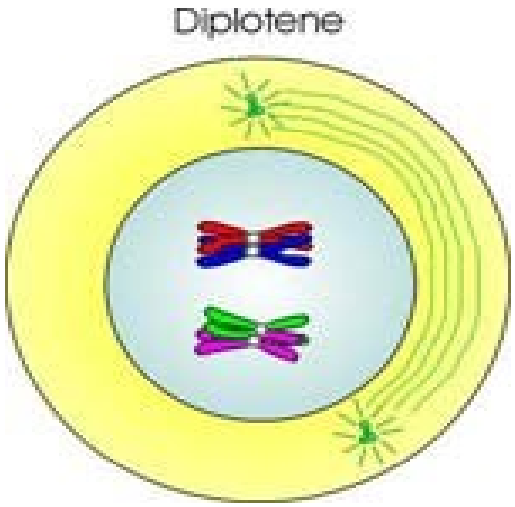
Pachytene (pachynema): it means "thick threads". At this stage, chromosomes become thicker and synapsis is completed chromosomal crossover occurs. Non-sister chromatids of homologous chromosomes may twist and start to exchange segments over regions of homology. Sex chromosomes, however, are not wholly identical, and only exchange information over a small region of homology. At the sites where exchange happens, **chiasmata form**. The exchange of information between the non-sister chromatids results in a recombination of information (mixed info) in a certain part, while the rest is the information it had before. The chromosomes are n bivalent.



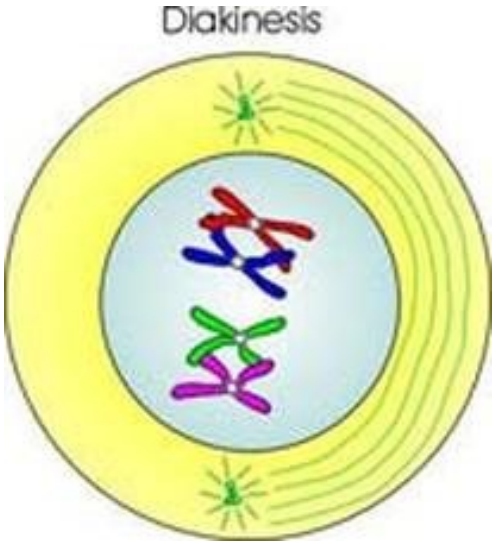


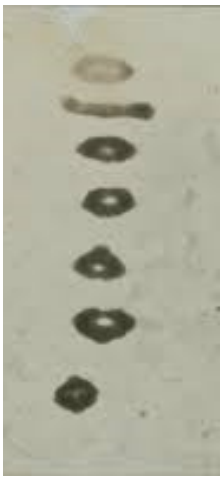
Diplotene (diplonema)**:** It means "two threads". During this stage, the crossover appears clearly due to the degradation of the synaptonemal complex (disassembly) that separate a little the homologous chromosomes from one another leading them to uncoil a bit (desynapsis). However, the homologous chromosomes of each bivalent remain tightly bound at chiasmata, the regions where crossover occurred. Chiasmata appear to "peristalse" to the tips of the chromatids, where they remain attached in a process known as **terminalization**. The chiasmata

remain on the chromosomes until they are separated in anaphase I. The chromosomes still n bivalent.



Diakinesis: It means "moving through". Chromosomes condense further during this stage. This is the first point in meiosis where the four parts of the tetrads are actually visible. Sites of crossover entangle together, effectively overlapping, making chiasmata more visible. The **terminalization** of the tetrads continues to get either ring or rod bivalents when it is completed or intermediate chiasmata may be formed due to incomplete terminalization in same/other chromosomes. The chromosomes still n bivalent. Other than this observation, the rest of the stage closely resembles late prophase of mitosis; the nucleoli disappear, the nuclear membrane disintegrates into vesicles, and the meiotic spindle begins to form and attach to kinetochores. Both nuclear envelope and nucleoli start to disappear, while the spindles begin to form from the centrosomes to control chromosome movement during meiosis I.

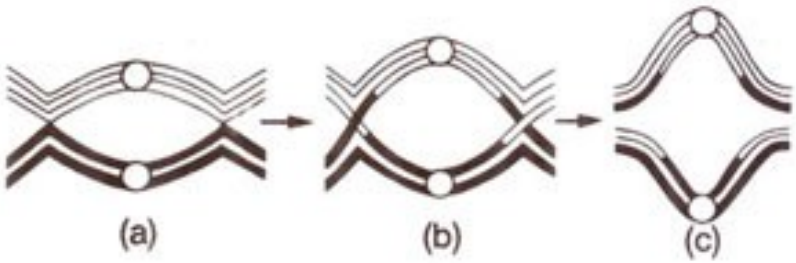




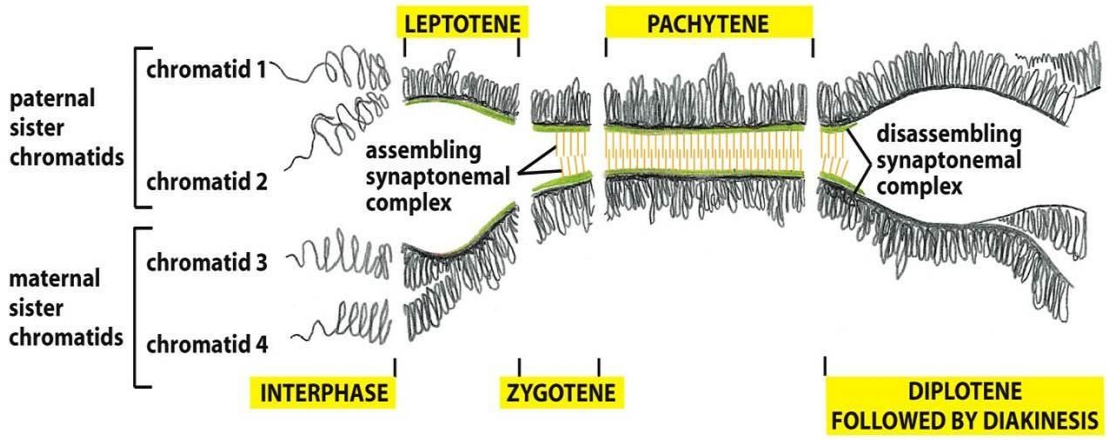
ring or rod bivalents

Terminalization of Chiasma:

The movement of chiasma to the ends of paired, non-sister chromatids. This movement starts in the diplotene and may continue until diaknesis or even metaphase I. As chiasma terminalization reaches completion, the total number of chiasma among the paired chromosomes decreases, and those that remain become concentrated near to, or at the ends of, each bivalent.



Assembling and disassembling of Synaptonemal Complex in Prophase I:



The **synaptonemal complex** (SCs) is a tripartite protein structure consisting of two parallel lateral elements, numerous transverse elements and a central element formed in the interface where two homologs unite. Three specific components of the synaptonemal complex have been characterized: SC protein-1 (SYCP1), SC protein-2 (SYCP2), and SC protein-3 (SYCP3).

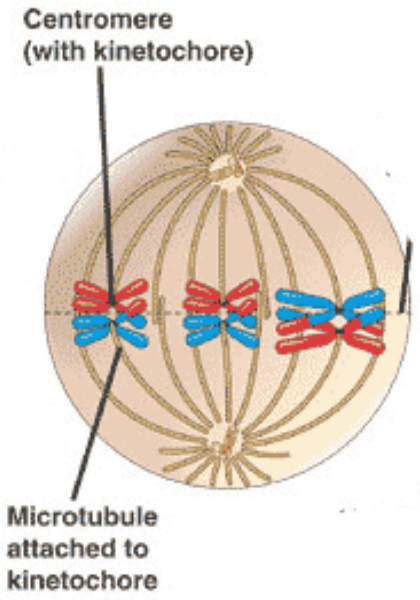
It works as zipper which assembled between homologous chromosomes during the prophase of the first meiotic division. Their assembly and disassembly correlate with the successive chromatin rearrangements of meiotic prophase, namely the condensation, pairing, recombination and disjunction of homologous chromosomes.

This "tripartite structure" is seen during the pachytene stage of the first meiotic prophase, both in males and in females during gametogenesis. Previous to the pachytene stage, during leptonema, the lateral elements begin to form and they initiate and complete their pairing during the zygotene stage. After pachynema ends, the SC usually becomes disassembled and can no longer be identified.

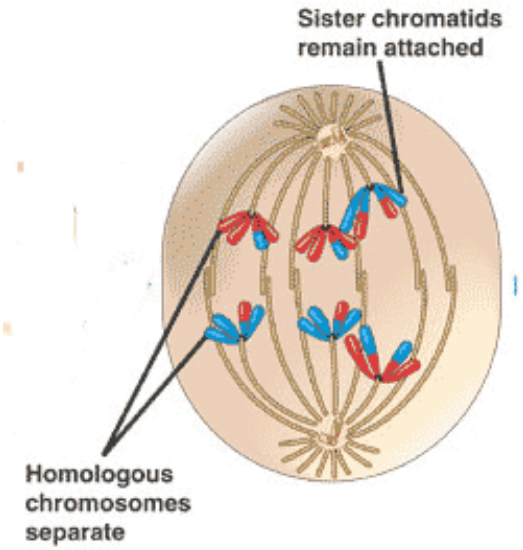
It is currently thought that the SC functions primarily as a scaffold to allow interacting chromatids to complete their crossover activities by mediating chromosome pairing, synapsis, and recombination.

SCs are now considered to be structures that control both the number and distribution of reciprocal exchanges between homologous chromosomes (crossovers) and convert crossovers into functional chiasmata.

Metaphase I: Homologous pairs move together along the metaphase plate: As kinetochore microtubules from both centrioles (of centromeres) attach to their respective kinetochores, the homologous chromosomes align along an equatorial plane that bisects the spindle fibers, due to continuous counterbalancing forces exerted on the bivalents by the microtubules emanating from the two kinetochores of homologous chromosomes. The physical basis of the independent assortment of chromosomes is the random orientation of each bivalent along the metaphase plate, with respect to the orientation of the other bivalents along the same equatorial line. Complete disappearance of nuclear membrane and nucleolus. The chromosomes still n bivalent.



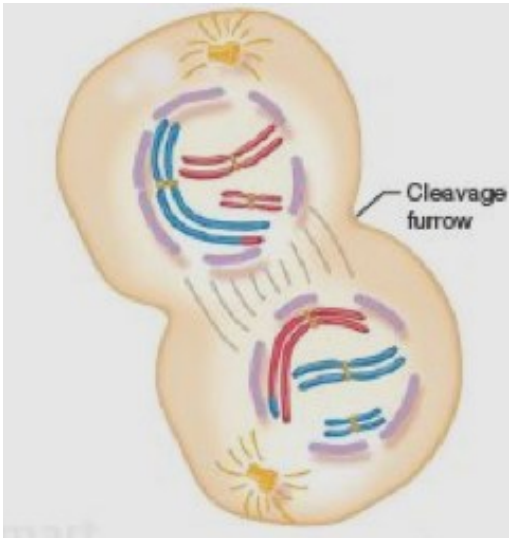
Anaphase I: Cohesin protein is degraded between sister chromatids, except at the centromere where they still connected (presence of both cohesin and shugoshin complex). Microtubules of spindle shorten leading to breaking of chiasmata, so spindle fibers separate the 2 dyads, carrying them to opposite poles. Each pole receives n number double in structure (reduction in number). The cell elongates in preparation for division down the center.



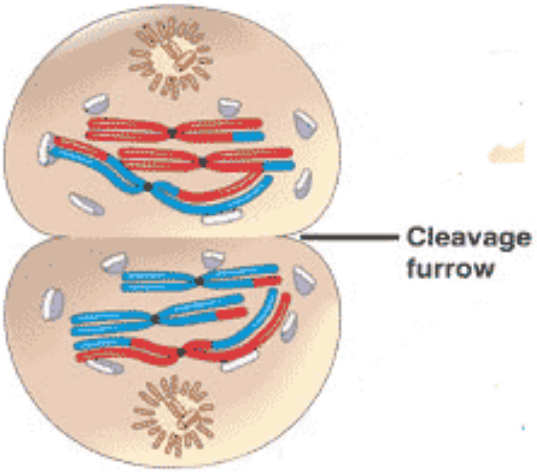
NOTE:

If crossover had not occurred in the first meiotic prophase, each dyad at each pole would consist of either paternal or maternal chromatids. However, the exchanges produced by crossover create mosaic (mix) chromatids from both paternal and maternal origin.

Telophase I: The first meiotic division effectively ends when the chromosomes arrive at the poles. Each daughter cell now has half the number of the tetrad but each chromosome consists of a pair of chromatids (dyad). The microtubules that make up the spindle network disappear, and a new nuclear membrane surrounds each haploid set. The chromosomes uncoil back into chromatin. Sister chromatids remain attached as dyads during telophase I.

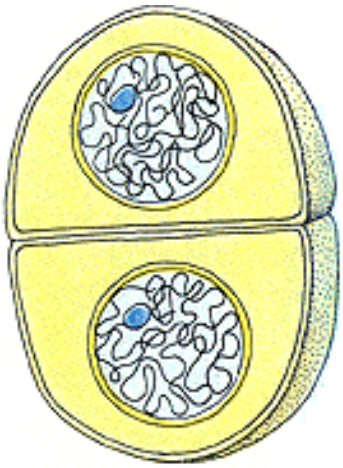


Cytokinesis I: the pinching of the cell membrane in animal cells or the formation of the cell wall in plant cells may or may not occur for completing the creation of two daughter cells. Like Mitosis, the cytoplasm and organelles are usually shared approximately equally between the daughter cells.



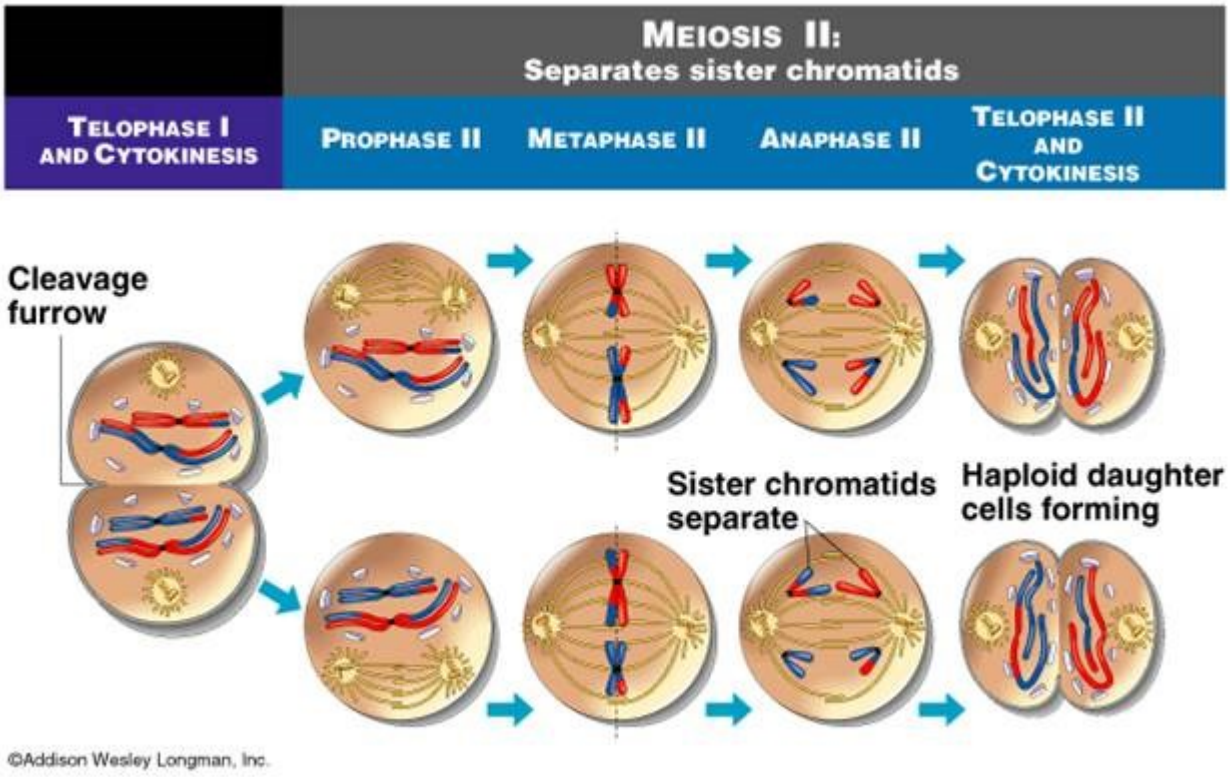
NOTE:

Cells may enter a period of rest known as **interkinesis or interphase II** where no DNA replication occurs. Like Mitosis, the genetic material in the nucleus is in form of chromatin, which appears only as dark granules because they are uncoiled into long, thin strands. Both nucleolus and nuclear membranes are present and clearly visible.

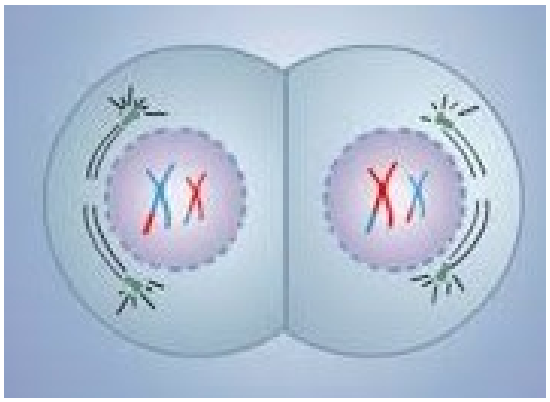


Meiosis II (similar to mitosis, reduction in structure)

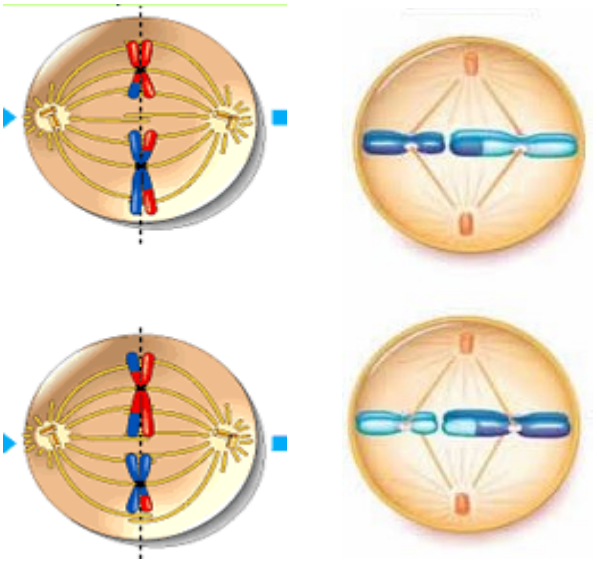
In this process, the two haploid cells (n dyads) produce 4 haploid (n monads) genetically different known as gametes. This division is physically the same as Mitosis, but the genetics of the cells are different. Meiosis II consists of Karyokinesis II (prophase II, metaphase II, anaphase II, telophase II) and Cytokinesis II (figure below).



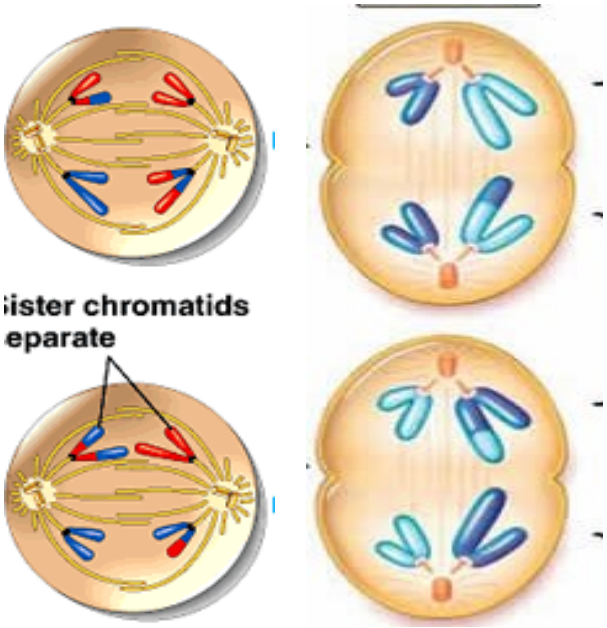
Prophase II: we see the disappearance of the nucleoli and the nuclear envelope again as well as the shortening and thickening of the chromatids which appear as dyads. Centrioles move to the polar regions and arrange spindle fibers for the second meiotic division.



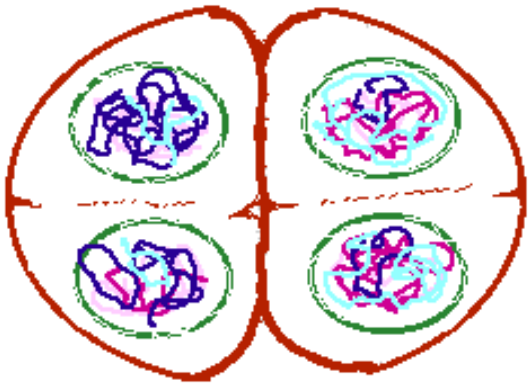
Metaphase II: The kinetochores of the dyads attach to spindle fibers formed from the centrosomes (centrioles) at each pole (i.e. directed towards the opposite poles). The chromatids of the dyads (non-homologous chromosomes) are joined by their centromeres with cohesin and shugoshin complex and aligned along the equator. In case of ♀ mother cells: the new equatorial metaphase plate is parallel to the spindle of metaphase I. In case of ♂ mother cells: the new equatorial metaphase plate is perpendicular (rotated by 90 degrees) to the previous plate of metaphase I.



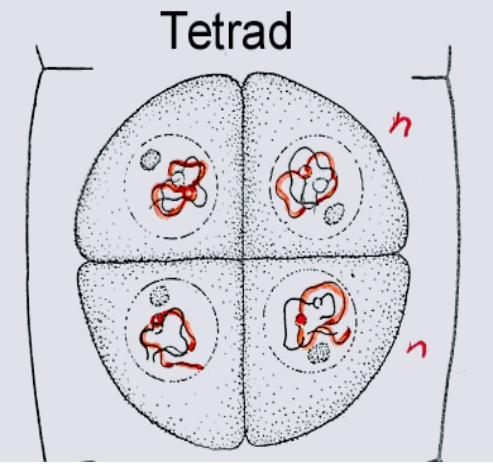
This is followed by **Anaphase II (reduction in structure)**, where the centromeres are cleaved by degrading cohesin and shugoshin complex, allowing microtubules attached to the kinetochores to pull the sister chromatids apart. The sister chromatids by convention are now called chromosomes (monads) as they move toward opposing poles (n single structure to each direction).



The Karypkinesis II process ends with **Telophase II**, which is similar to telophase I, and is marked by uncoiling and lengthening of the chromosomes and the disappearance of the spindle. Nuclear envelopes and nucleolus are reformed. Now we have 4 new haploid nuclei with monad chromosomes in one cell.



Cytokinesis II: Meiosis is now complete and ends up with four new cells by cleavage of the cell membrane in animal cells or the formation of the cell wall in plant cells producing a total of four cells, each with a haploid set of chromosomes which are single structure.



Gametogenesis:

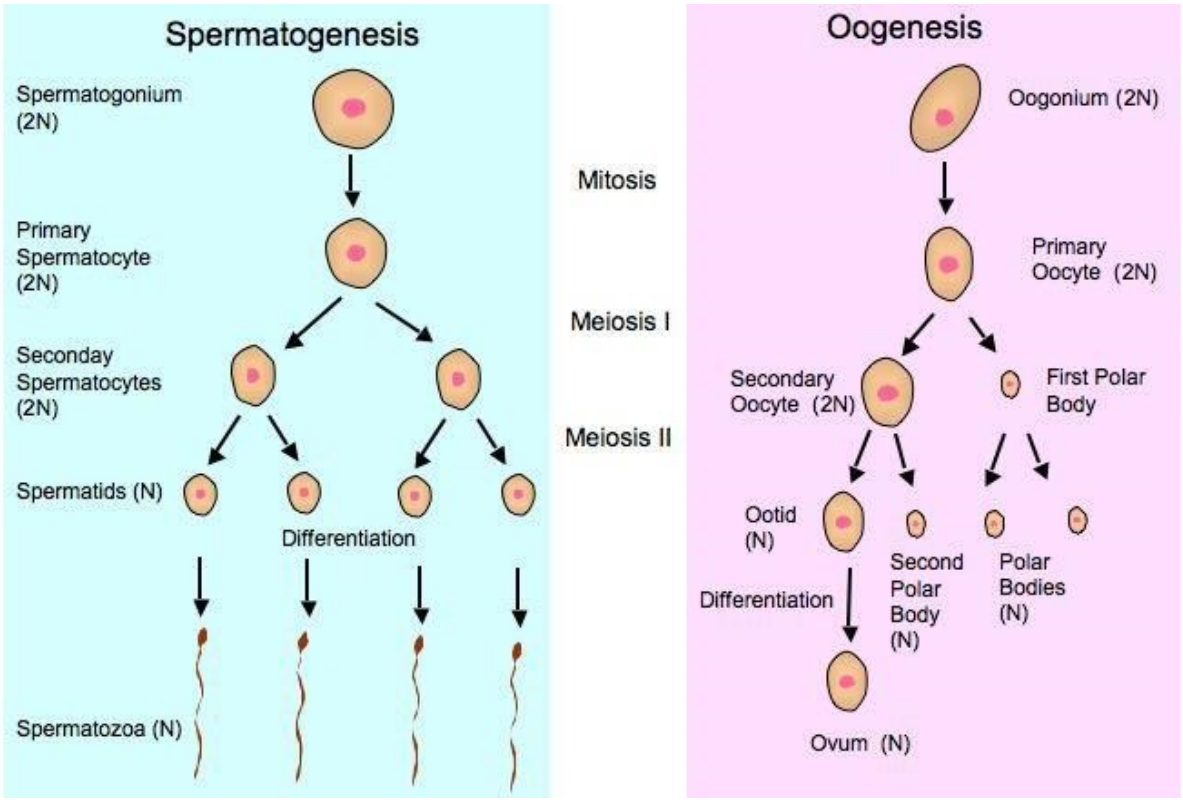
It is the process by which the produced 4 haploid cells undergo some differentiation and developmental events to produce gametes (haploid sex cells, germ cells). It includes the formation of ♂ gametes (spermatogenesis in animals and microsporogenesis in plants) or the formation of ♀ gametes (oogenesis in animals and megasporogensis in plants) i.e. all the sex cells whether are in plants or animals undergo meiosis.

In Animal or Human:

The formation of sperm cells, or **spermatogenesis**, begins with a germ cell called spermatogonium (2n) that suffers mitosis and gives birth to the spermatocyte I (2n). The spermatocyte I undergoes meiosis I and generates two spermatocyte II (n) that then undergo meiosis II and produce four spermatids (n). Each spermatid undergoes a maturation process called spermatogenesis and four sperm cells appear (figure below).

The formation of egg cells begins with a germ cell called oogonium (2n) that undergoes mitosis and gives birth to the oocyte I (2n). The oocyte I undergoes meiosis I that however is interrupted at prophase. After puberty during each menstrual cycle, an oocyte I finishes the meiosis I and generate one oocyte II (n) and the first polar body (n) i.e. uneven division. The first polar body is very small and almost lacks cytoplasm; it disintegrates after a period of time or stays attached to the oocyte II. With fecundation the oocyte II then undergoes meiosis II and produces the mature egg cell (n) and the second polar body (n) i.e. another uneven division. The second polar body is a very small cell that almost lacks cytoplasm and disintegrates or stays adnexal to the egg cell. The entire cytoplasmic content of the oocyte II passes to the egg cell. This process is known as **Oogenesis** and one mature egg appears (figure below).

The polar bodies are the byproducts of the primary and secondary oocyte at each point of meiotic division in oogenesis. The polar body allows for the oocyte to get rid of chromosomes while at the same time taking the least amount of resources (cytoplasm) from the oocyte. Each meiotic division serves as a means of moving the oocyte toward its need haploid number of chromosomes for fertilization. So the polar bodies function as a means of cellular structure conservation. They help ensure that the oocyte remains nutrient/resource rich while at the same time helping the oocyte reach its haploid number.

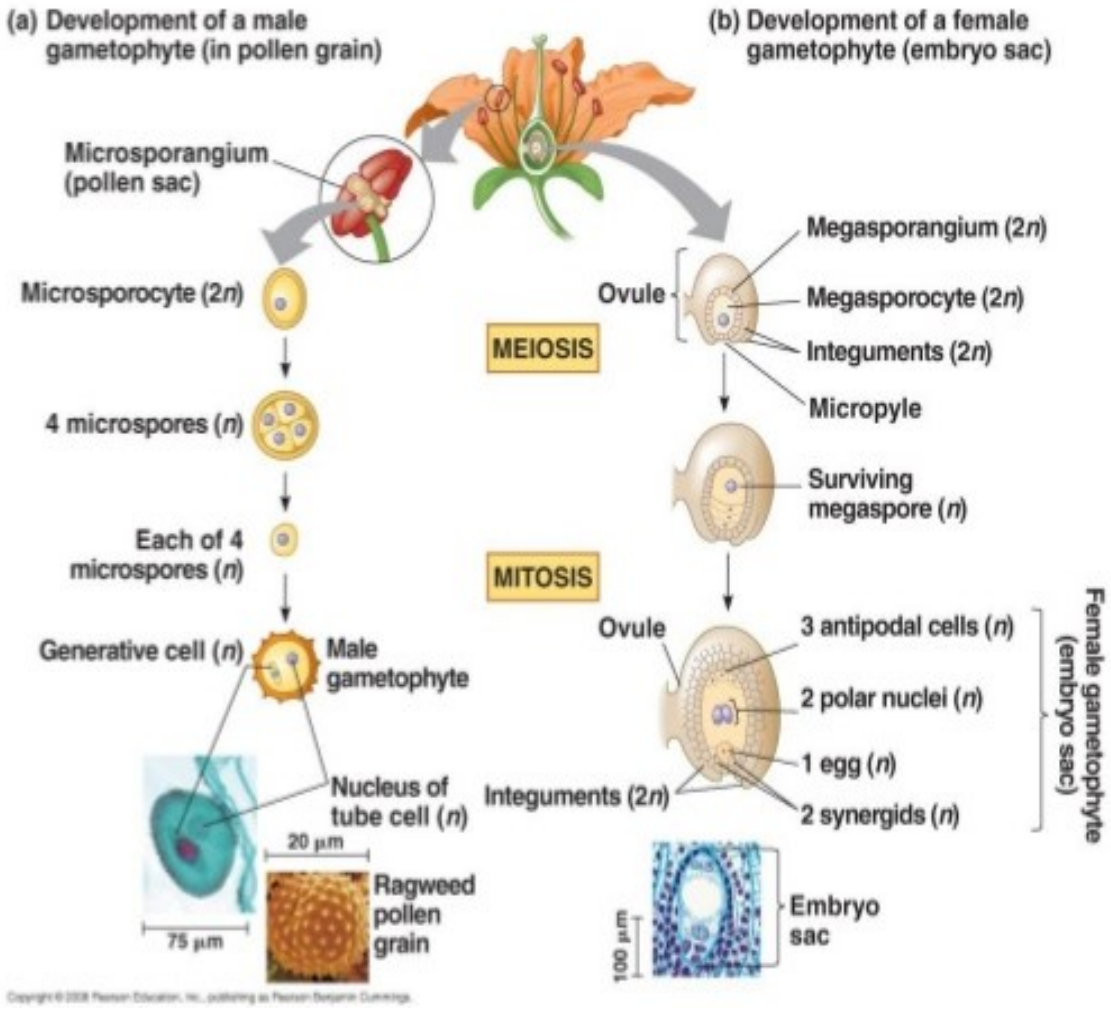


In Flowering Plants:

The microspore mother cell present in anther tissue undergoes a meiotic division (Meiosis I and II) to form 4 haploid functional microspores. This is **microsporogenesis**. From microspore the pollen grains are developed. The pollen grain contains two cells. One – **tube cell and generative cell**. Generative cell undergoes a division to form **two sperm nuclei.**

The meristematic tissue of the ovary wall called Ovule primordia. Within the nucellus of the ovule, one cell known as Archesporial cell (2n) develops larger than the surrounding cells, having a large nucleus and denser cytoplasm called know Megaspore mother cell (MMC). MMC undergoes a meiotic division (Meiosis I and II), giving rise to **four megaspores** (n). Among the four cells, **one megaspore** survives to give rise to an **embryo sac**, whereas other three aborts. **Development of functional megaspore from MMC is called megasporogenesis**. The nucleus within the functional magaspore undergoes three successive

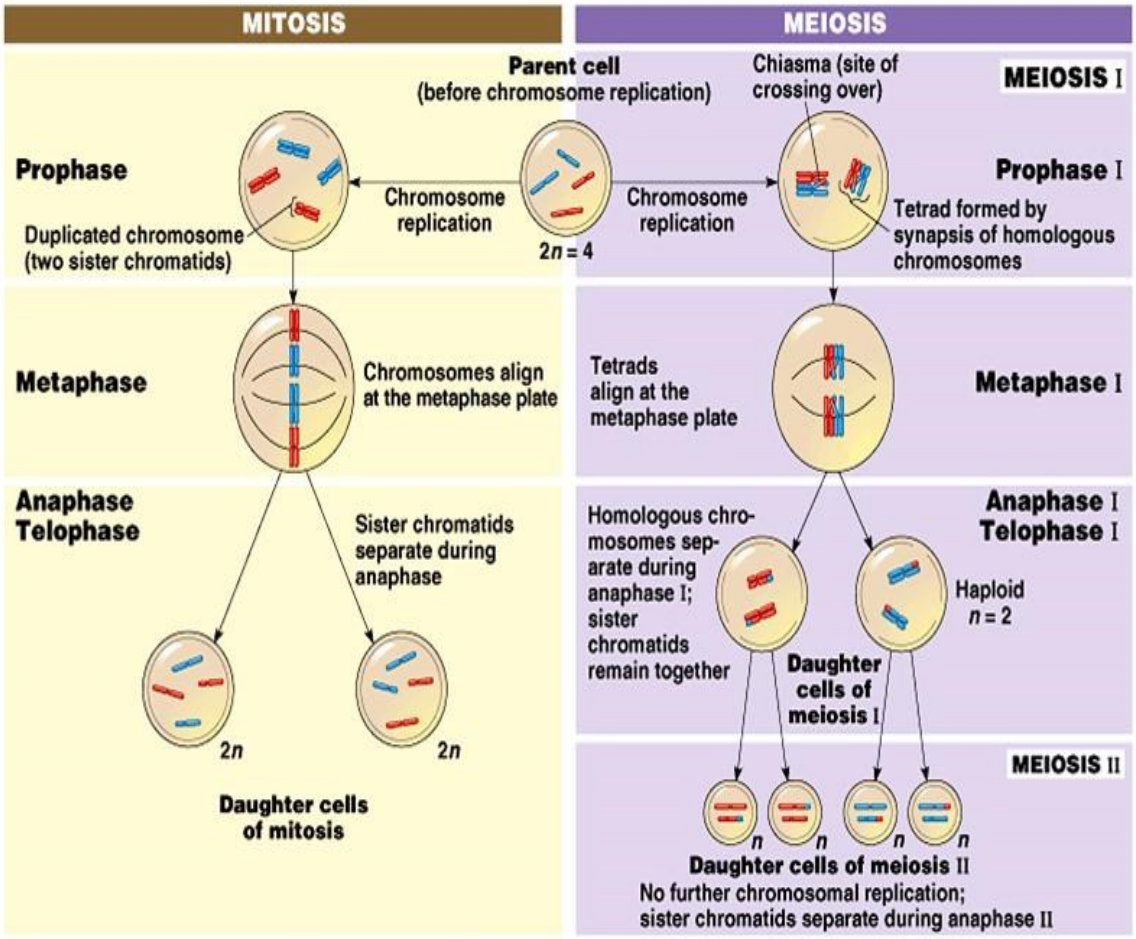
divisions to form eight nuclei, which are arranged as **three antipodal** cells at one **end**, two **central polar nuclei**, **one egg cell with two synergids at the other** end. **Development of eight celled embryo sac from the functional magaspore is called as magagametogenesis**.



NOTE: the Y chromosome essentially is reproduced **via cloning** from one generation to the next. This prevents mutant Y chromosome genes from being eliminated from male genetic lines except by inactivation or deletion. The Y chromosome has about one tenth the genetic variation that occurs on all other chromosomes. Subsequently, the Y chromosome now has few active genes and mostly contains genetic junk rather than genes.

Differences between Mitosis and Meiosis:

	Mitosis	**Meiosis**
Number of divisions	1	2
Number of produced cells	2	4
Genetically identical?	Yes	No
Chromosome #	Same as parent	Half of parent
Where	Somatic cells	Germ cells
Synapsis and crossover	Absent	Present
Centromere in Anaphase	Divided at anaphase	Not divided at anaphase I but at Anaphase II
When	Throughout life	At sexual maturity
Role	Growth, development, regeneration and repair	Sexual reproduction



THE RELATION BETWEEN MENDEL LAWS AND CHROMOSOMES IN MEIOSIS

The function of Meiosis I is very different from that of either Mitosis or Meiosis II. In both Mitosis and Meiosis II sister chromatids are separated during anaphase to produce identical daughter cells. In Anaphase I of Meiosis I, members of homologous chromosome pairs are separated. This results accounts for the law of segregation of genes into the two gametes. The principle of segregation is one of two core ideas in genetics proposed by Gregor Mendel.

The alignment of homologous pairs along the metaphase 1 plate accounts for the law of independent assortment (the segregation of any one pair of chromosomes is independent of any other pair). Assortment of chromosomes from each pair to the two daughter cells is random. The

number of possible genetic combinations (distribution probability) in the resulting gametes is therefore very large. This model works for genes that are on separate (non-homologous) chromosomes, but not necessarily for genes that are on the same chromosome.

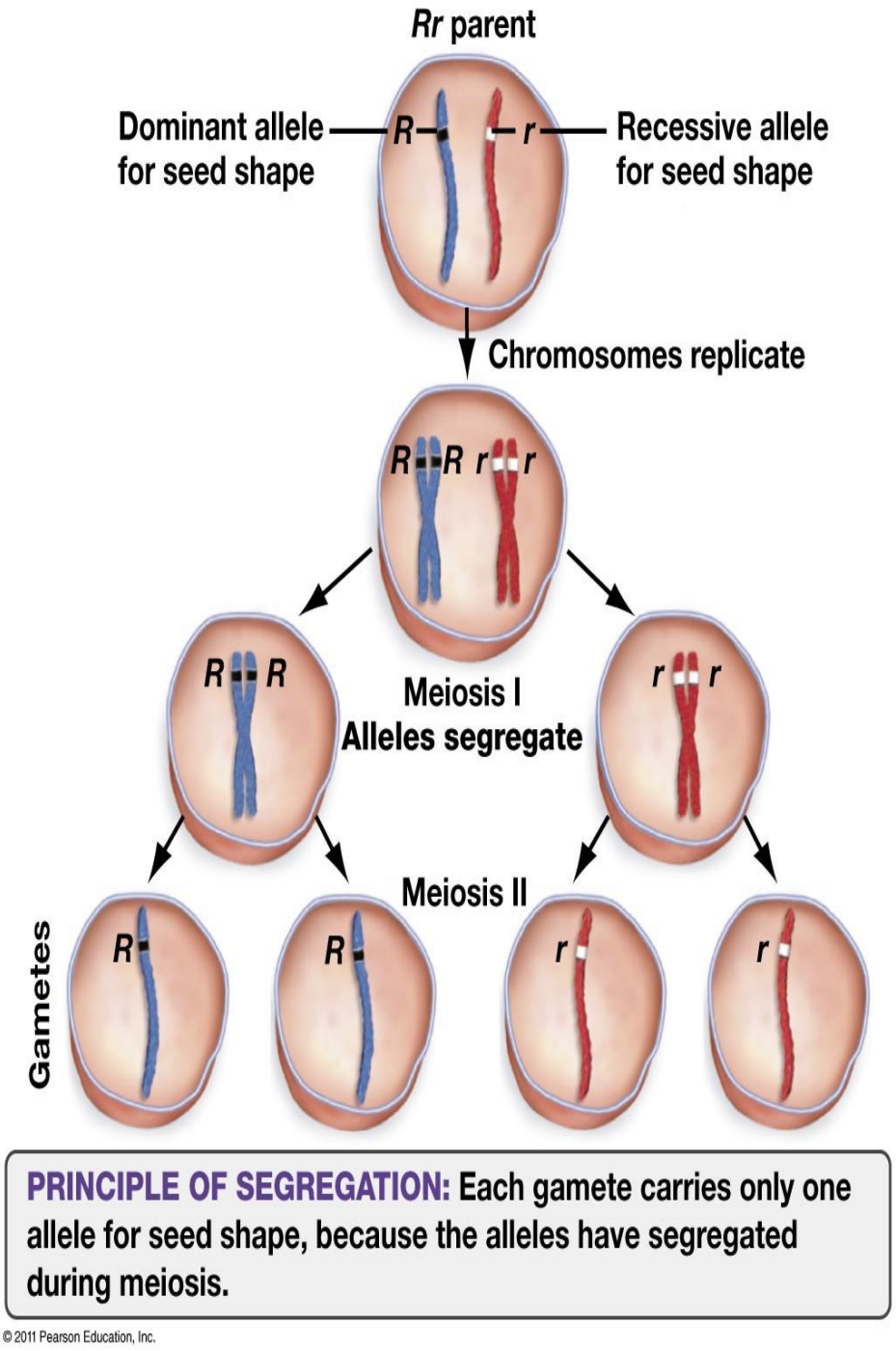
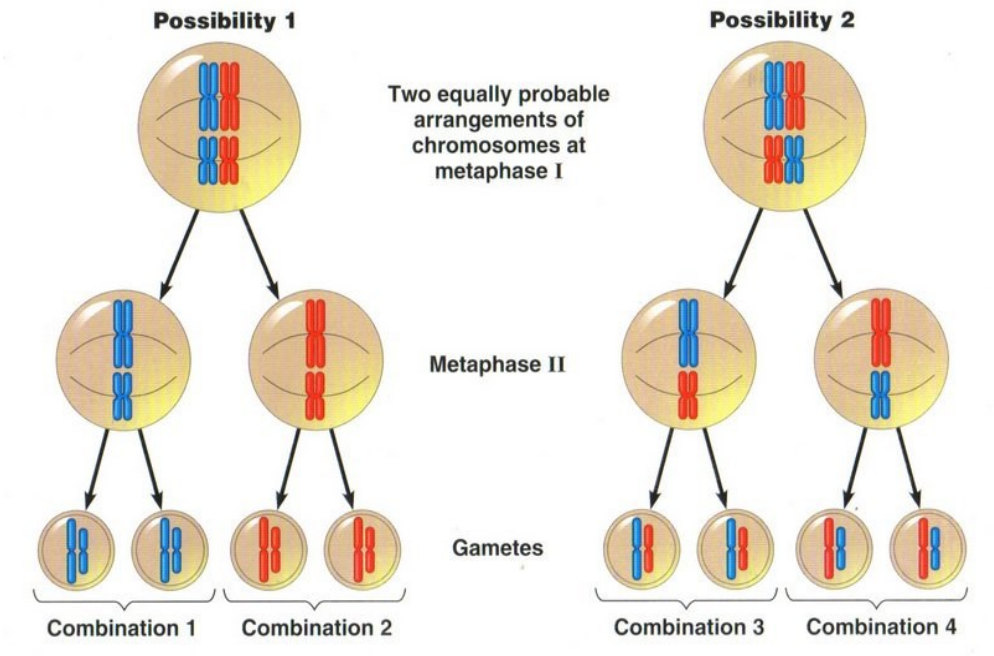
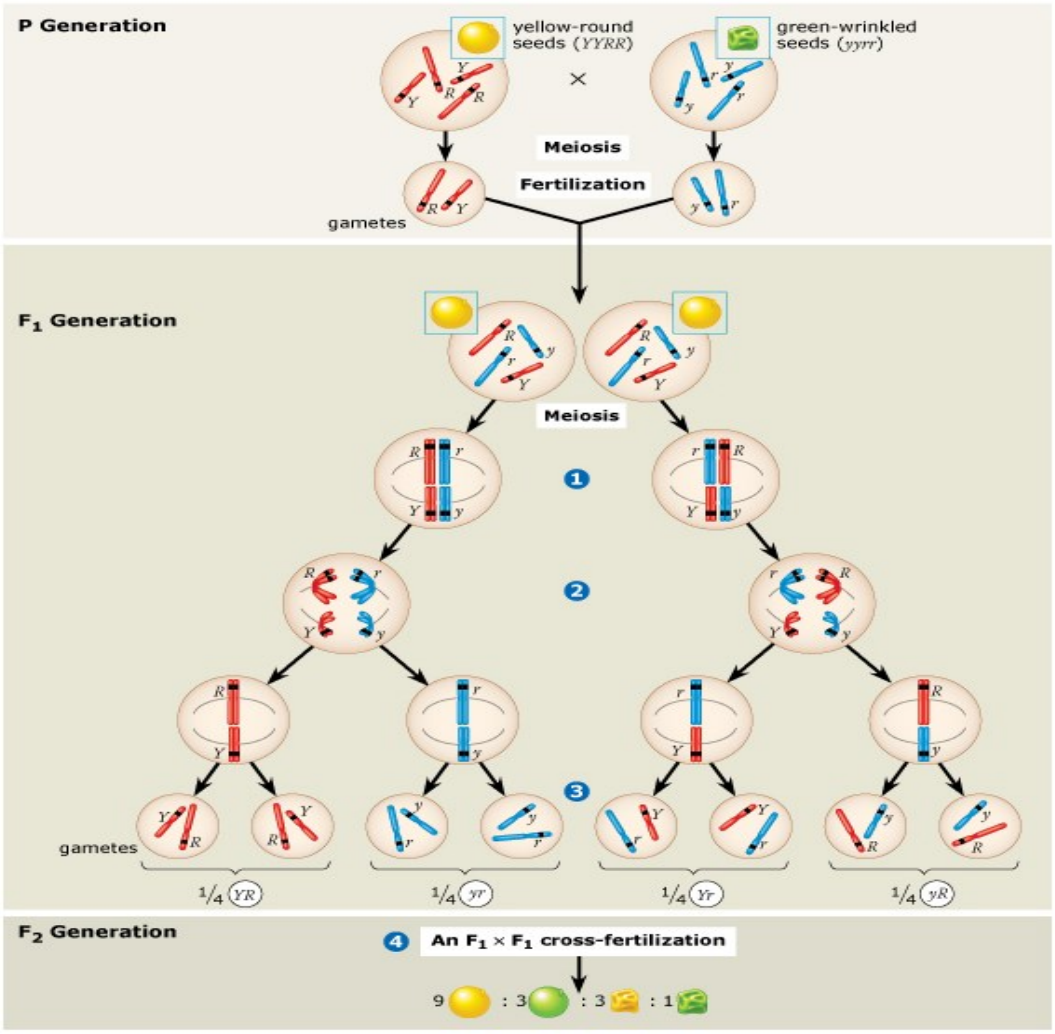


Figure 8.16 Results of the independent orientation of chromosomes at metaphase I





Adapted from *Campbell Biology* by Reece et al. © Pearson Education, Inc.

IMPORTANCE OF MEIOSIS:

- Meiosis generates genetic diversity through:
  1. the exchange of genetic material (crossover) between homologous chromosomes during Prophase I-Meiosis I.
  2. the random alignment of chromosomes in Meiosis I and Meiosis II.
- Meiosis maintains the chromosome number in sexually reproducing organisms.

Animations:

1. **Cell cycle**

http://youtu.be/JcZQkmooyPk

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter2/animation__how_the_cell_cycle_works.html

2. **Mitosis**

http://highered.mcgraw-hill.com/sites/0072495855/student_view0/chapter2/animation__mitosis_and_cytokinesis.html

3. **Meiosis**

http://highered.Mcgraw-hill.Com/sites/0072495855/student_view0/chapter28/animation__how_meiosis_works.Html

4. **Cancer cell cycle and chemotherapy:**
   http://www.youtube.com/watch?v=lpAa4TWjHQ4

For more reading: (in Botany and Microbiology Department Library)

1. The world of the cell:international edition, 6th edition, 2006, Becker, Kleinsmith and Hardin (eds.).
2. Biology, 8th edition, 2008, Losos, Mason and Singer (eds.)
3. Concepts of Genetics, William S. Klug, Michael R. Cummings, Charlotte A. Spencer and Michael A. Palladino, 10th edition, 2012, Pearson Education Inc. (also present online)