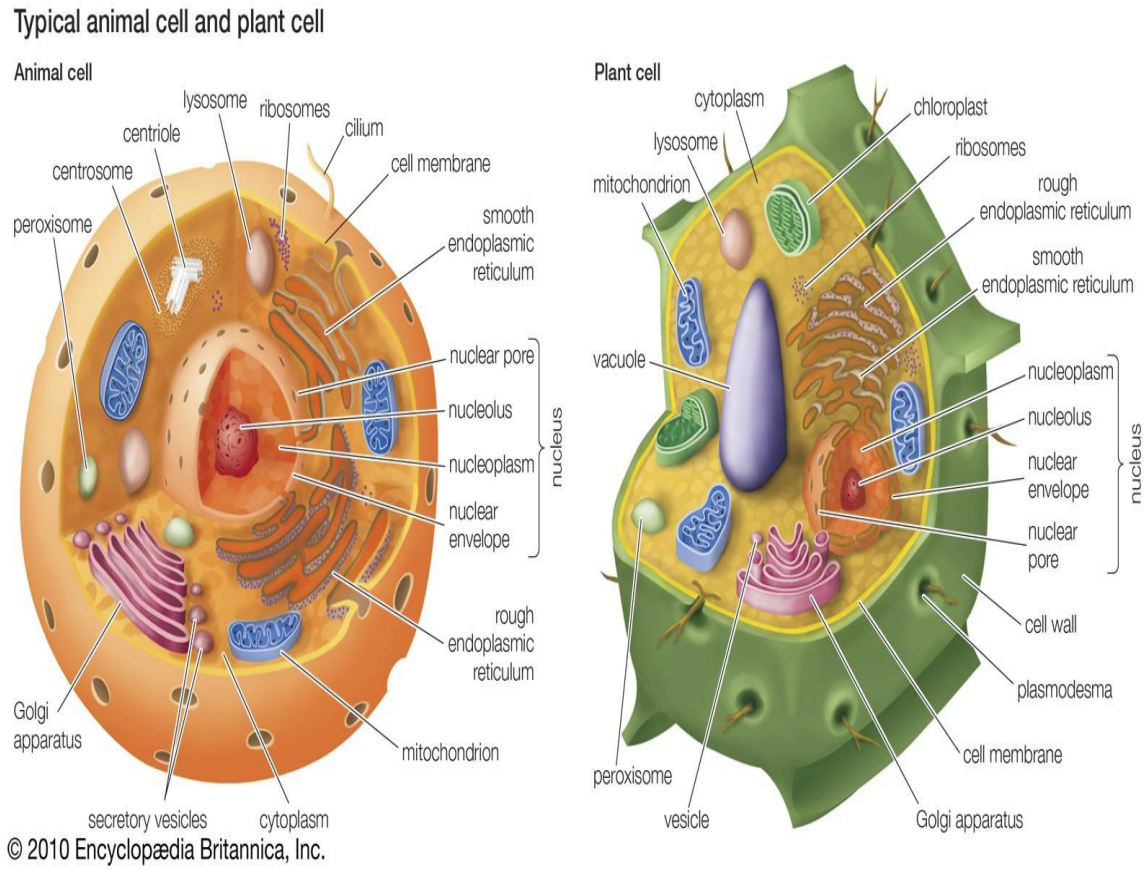
E U K A R Y O T I C C E L L S T R U C T U R E (read only)

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. In contrast to animal cells, plant cells often contain large central vacuoles occupying up to 90% of the total cell volume, pushing the nucleus against the cell wall.



TRANSMISSION AND INHERITANCE OF CHROMOSOMES

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

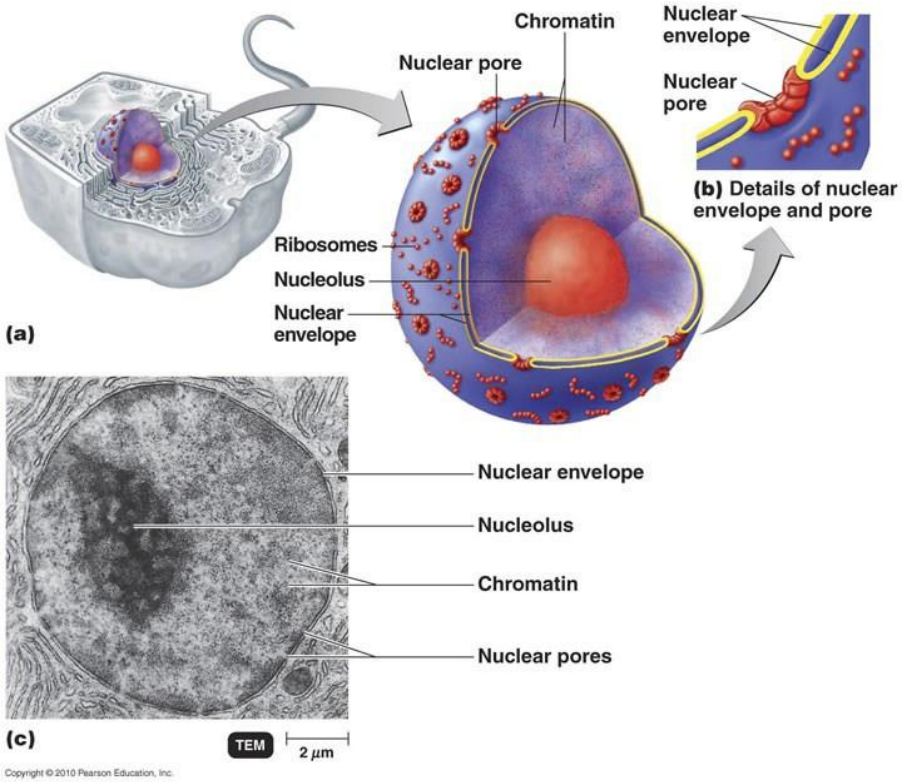
The nucleus in the cell is analogous to the brain in the body. It is a control center for a cell by maintaining the integrity of the genes and to control the activities of the cell by regulating gene expression. The

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.

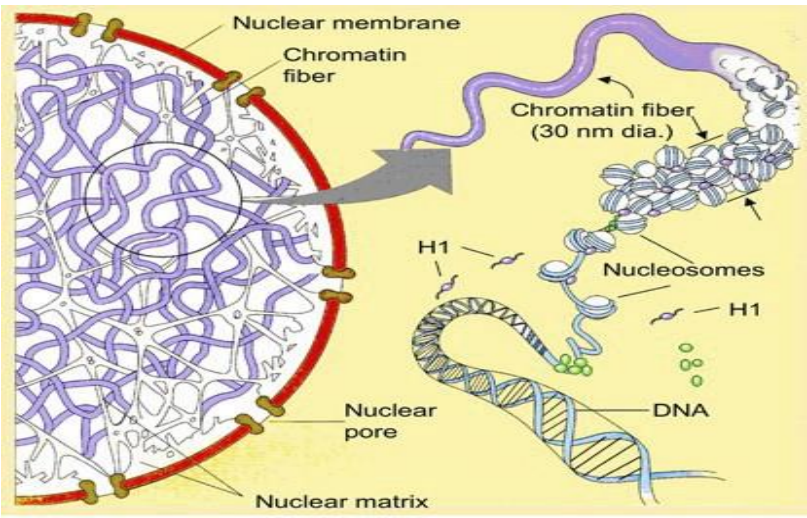
The nuclear membrane has pores through which the contents of the nucleus communicate with the rest of the cell. Nucleoporins, a family of 50 to 100 proteins, are the main components of the nuclear pore complex in eukaryotic cells. The nuclear membrane tightly controls what gets into the nucleus and what 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

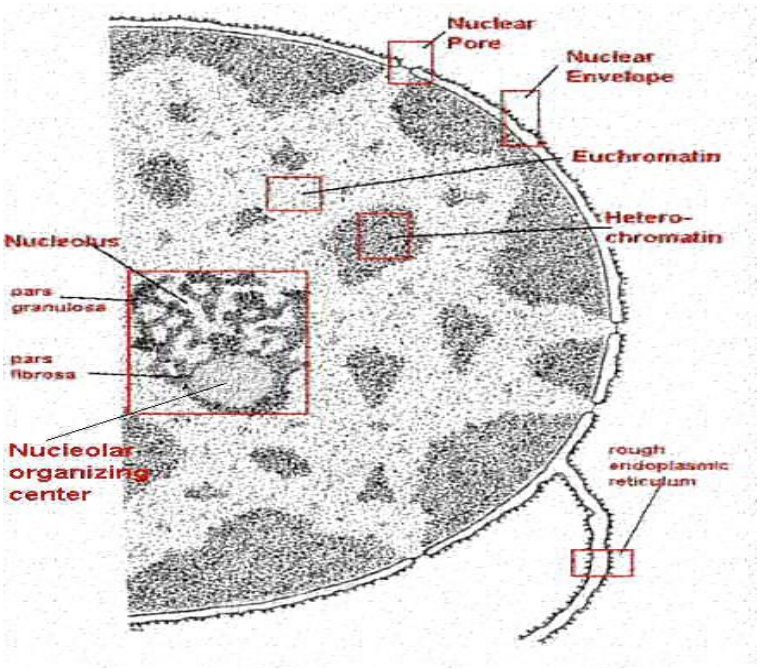
function is to transcribe ribosomal RNA (rRNA) and combine it with proteins to form almost-complete ribosomes. The nucleolus occupies up to 25% of the volume of the cell nucleus. Malfunction of nucleoli can be the cause of several human diseases.



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).

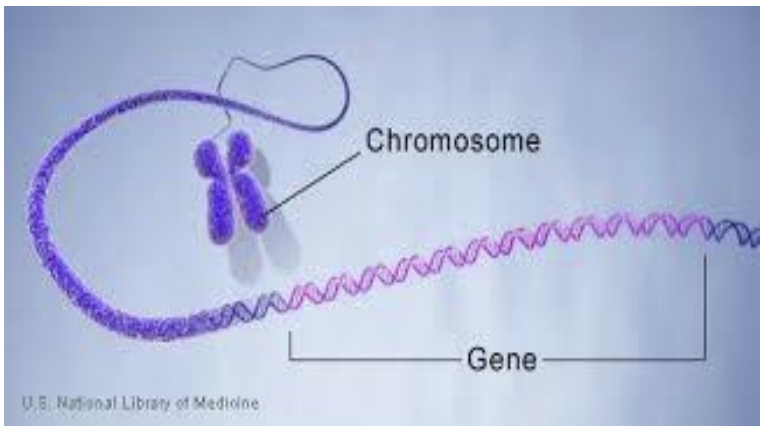


There are two types of chromatin: Euchromatin is the less compact DNA form, and contains genes that are frequently expressed by the cell. The other type, heterochromatin, is the more compact form, and contains DNA that is infrequently transcribed.

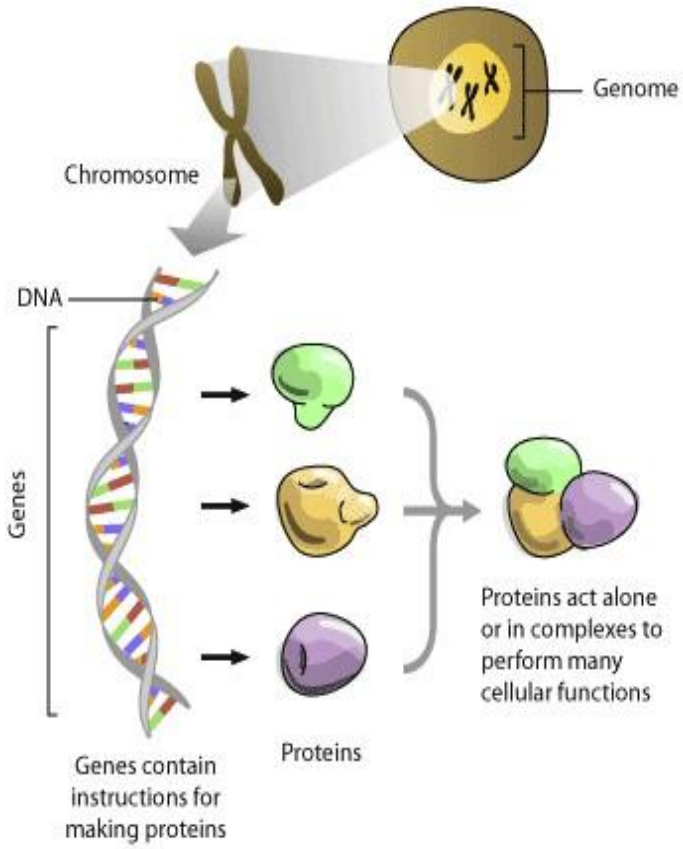


C H R O M O S O M E S

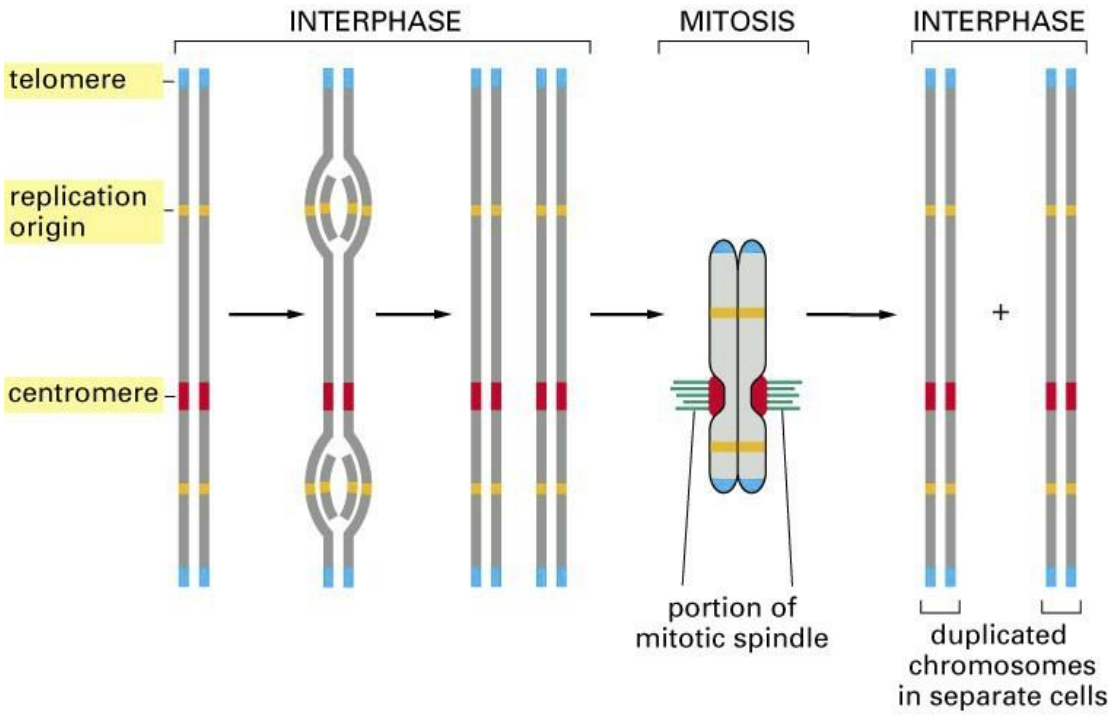
Chromosomes are single pieces of coiled double-stranded DNA along with genes, proteins, and nucleotides, and chromatin is a condensed package of chromosomes that basically allows DNA to fit inside the nucleus, so the genes within these chromosomes are known as the cell's nuclear genome.



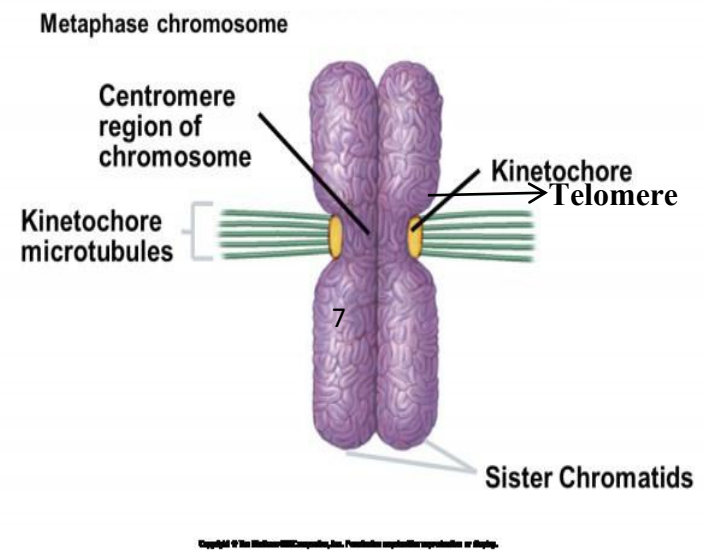
In eukaryotic organisms, the DNA inside the nucleus is also closely associated with large protein complexes called histones. Along with the nuclear membrane, histones help control which messages get sent from the DNA to the rest of the cell. The information stored in DNA gets transferred to the rest 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.



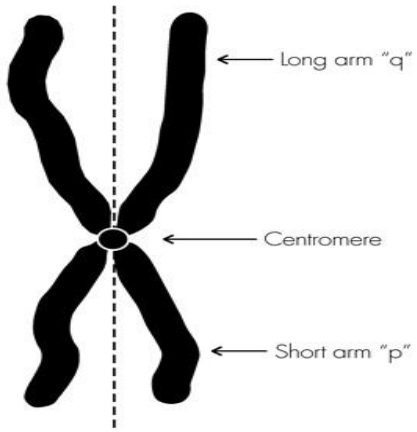
Chromosomes may exist as either duplicated (**dyad**) or unduplicated (**m o n a d**) in mitosis or as **t e t r a d** in meiosis. Unduplicated chromosomes are single linear chromatid strands contains one DNA molecule, which may be several inches long, whereas duplicated chromosomes contain two identical copies (called arm or chromatids or sister chromatids or 2 monads) joined by a **c e n t r o m e r e**. 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 **t e l o m e r e s**.


Metaphase chromosome
Centromere region of chromosome
Kinetochore
Telomere
Kinetochore microtubules
Sister Chromatids

7

C h r o m o s o m e C l a s s i f i c a t i o n :

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.



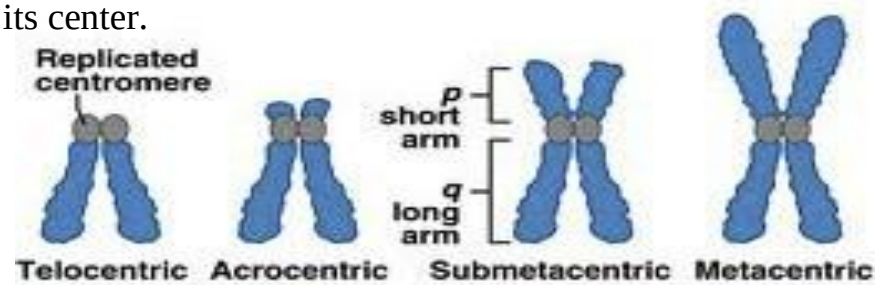
Chromosomes are classified according to centromere position to Metacentric, Sub-metacentric, Acrocentric and Telocentric (figure below).

M e t a c e n t r i c : 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.

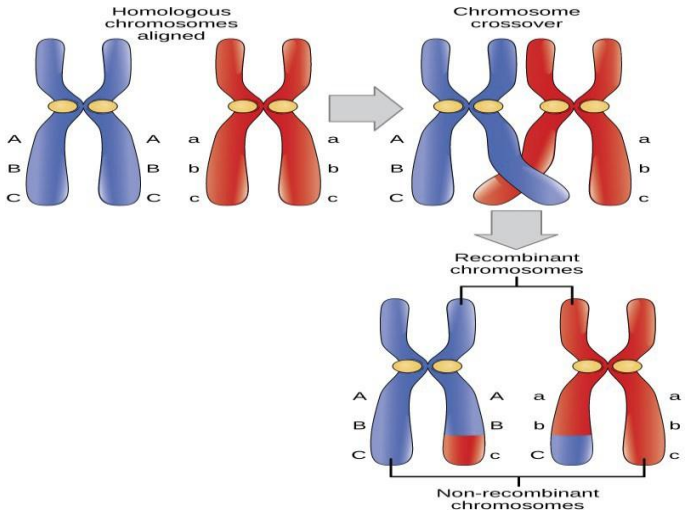
Acrocentric: The p (short) arm is so short that it is hard to observe, but still present, as the centromere is located near the terminal end of the chromosome.

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

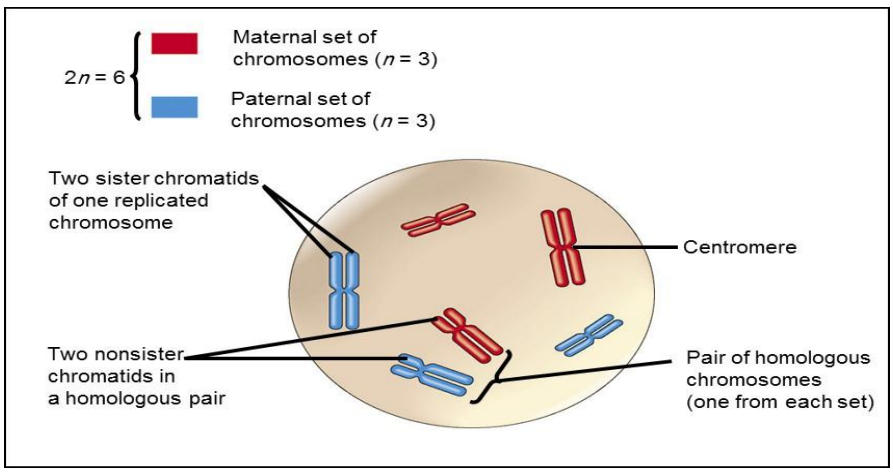


2. Chromosomes may be classified according to their types to either non-homologous, homologous or sex chromosomes.

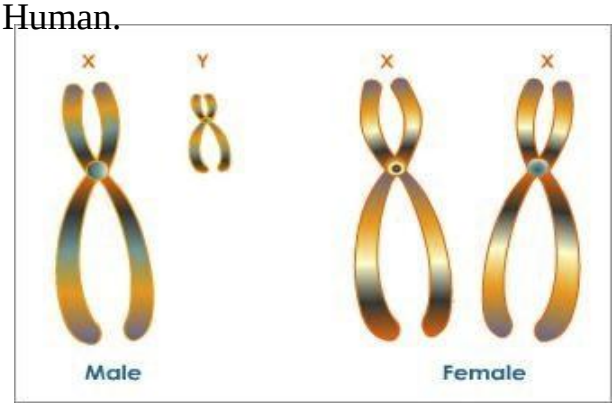
Non-homologous chromosomes: look different and control different Traits (characters). Eg: chromosomes after crossover in meiosis



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).

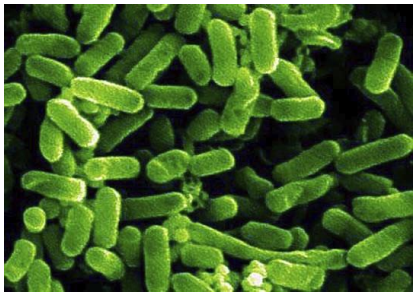
2. Heterogametic female / homogametic male type: In Birds, the heterogametic female has one Z chromosome and one of W chromosome and signed ZW (heterogametic, hemizygotic), while the male has two Z chromosomes and signed ZZ (homogametic).

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.

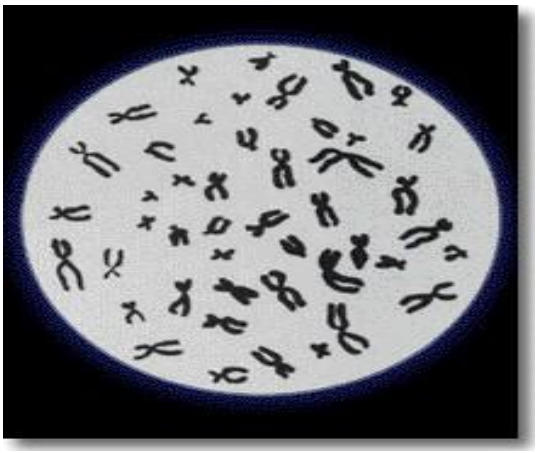
6. Fertility factor: Donor cell (eg: Bacteria as *E. coli*) possesses a set of transfer genes that give its donor properties known as sex plasmid or Fertility plasmid or Fertility factor (signed as F). Maleness is presented as F^+ (presence of factor) and femaleness as F^- (absence of factor).

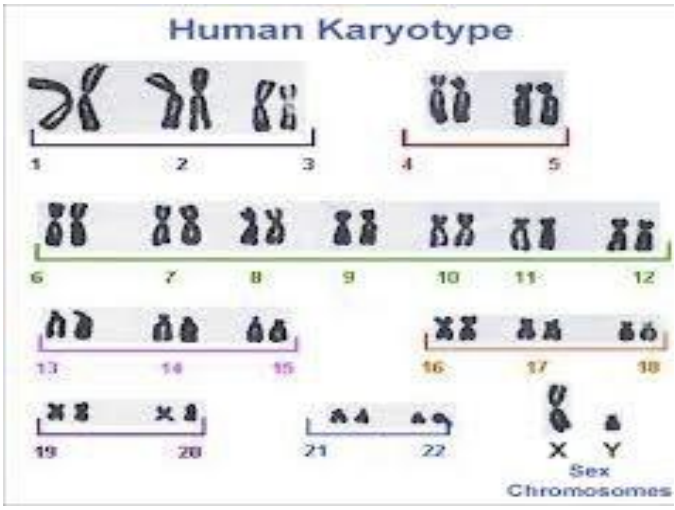


NOTE: An organism having only a single copy of a gene (genes on the single X chromosome in the male) instead of having two copies **o r** having one sex chromosome (Y0 or Z0) are called **H e m i z y g o u s**.

K A R Y O T Y P E

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).



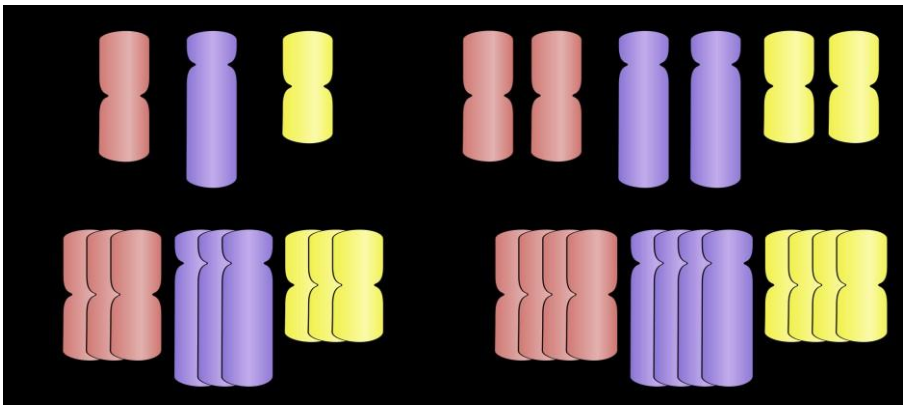


The cell may be classified according to the number of chromosomes copies (figure below) into either haploid (n) or diploid (2n) or polyploidy (n_s)**:**

H a p l o i d - A cell possessing a single copy of each chromosome (human/plant sex cells).

D i p l o i d - 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.

P o l y p l o i d - A cell possessing numerous copies of each chromosome, so it may be triploid, tetraploid,…..



H O W T H E C E L L D I V I D E ?

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: **M i t o s i s** and **M e i o s i s**.

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.

1. CELL CYCLE

The cell cycle occurs from the completion of one division until the completion of the next division. It involves 3 phases: **Interphase** (G1,S and G2), **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

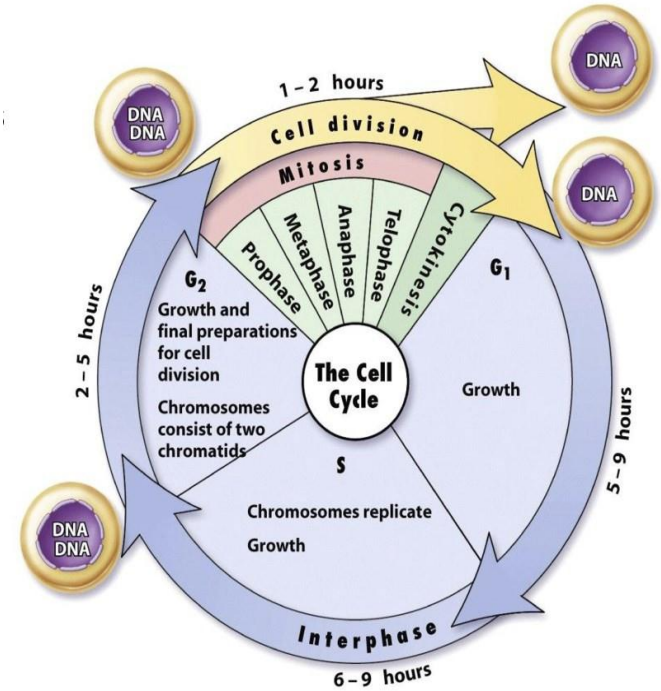


Figure 19-2 Biology of Humans, 2/e
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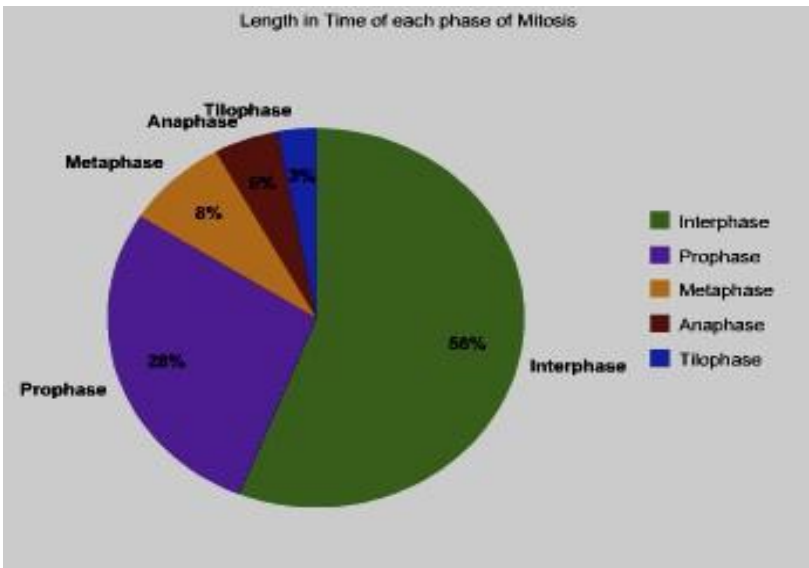


I n t e r p h a s e

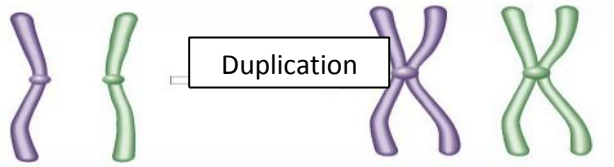
The time between two successive mitotic divisions is known as Interphase (Resting or Growth stage). Eukaryotic cells spend most of their time (about 90%) in interphase. During interphase, the genetic material in the nucleus is in form of chromatin (uncoiled DNA), which appears only as dark granules within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

G 1 s t a g e (g a p 1 , P r e - D N A s y n t h e s i s) : 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; formation of cytoplasmic strands as well as the cell organelles begin to increase in numbers, and the nucleus start to move to the center of the cell and enlarge so, cytoplasm enlarge, too and 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).

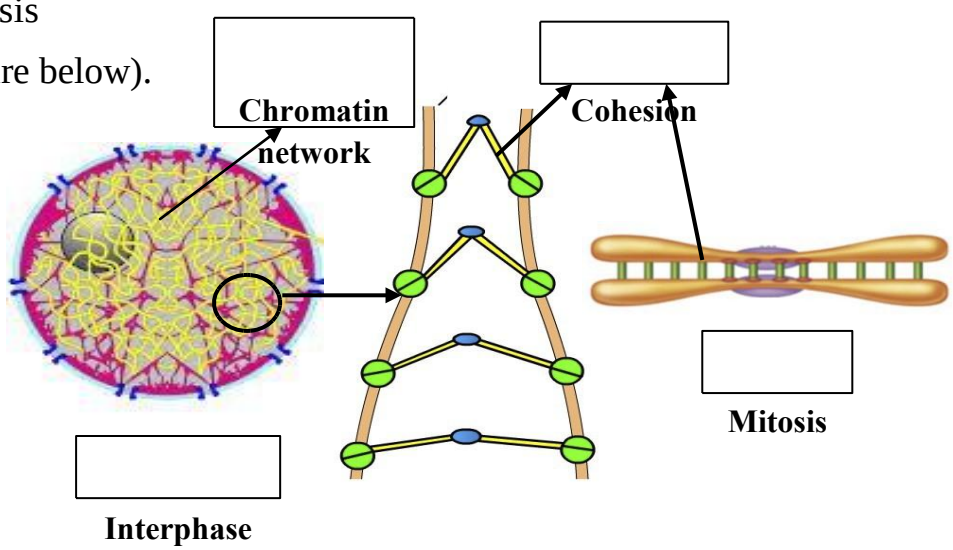
If the cells will never divide again but remain viable and metabolically active, it will refer as **G0 stage** (Prolonged G1 stage). It may be permanently arrested in G1 stage (never reenter the cell cycle) or can be stimulated to return to G_1 and thereby reenter the cell cycle.

S s t a g e (D N A s y n t h e s i s) : 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).

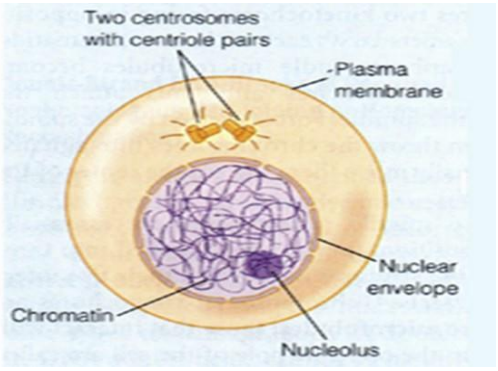


Two unduplicated chromosomes **Two duplicated chromosomes**

Sister chromatids are held together by a multi-subunit protein complex called **c o h e s i n** formed between them in interphase and mitosis
(figure below).

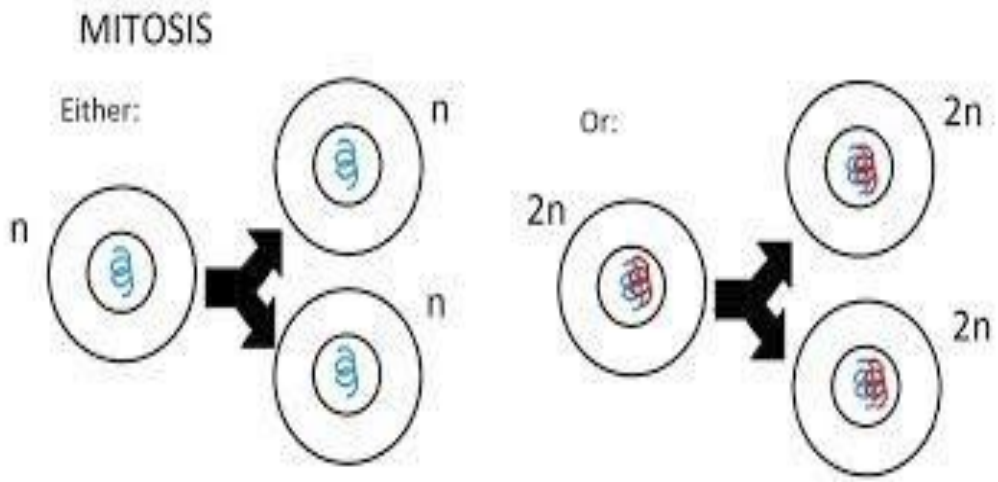


G 2 s t a g e (g a p 2 , P o s t - D N A s y n t h e s i s) : This stage lasting from 2-5 hours in some eukaryotic cells. In which the cell synthesis certain component required for mitosis as centrosomes and centrioles, proteins of spindle fiber, enzymes,... and go to the final preparations of the cell (2^{nd} 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.



M I T O S I S

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.

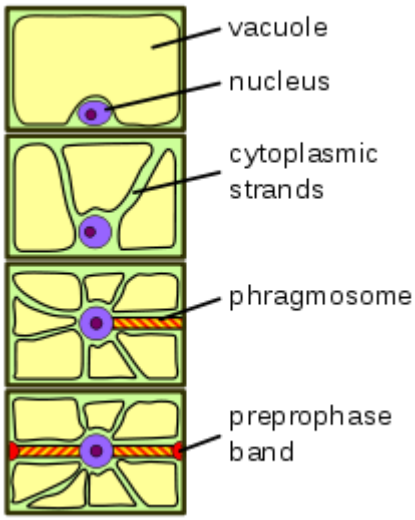


Mitosis consists of occurs in 4 stages (Karyokinesis) known as Prophase, Metaphase, Anaphase and Telophase (figure below).

In order for mitosis to occur, the nucleus has to move into the center of the cell. This happens during (G1 phase) of the cell cycle. Initially, cytoplasmic strands forms that penetrate the central vacuole and provide pathways for nuclear migration. Actin filaments along these cytoplasmic strands pull the nucleus into the center of the cell. These cytoplasmic strands fuse into a transverse sheet of cytoplasm along the plane of future cell division, forming the **phragmosome**. Phragmosome formation is only clearly visible in dividing plant cells that are highly vacuolated.

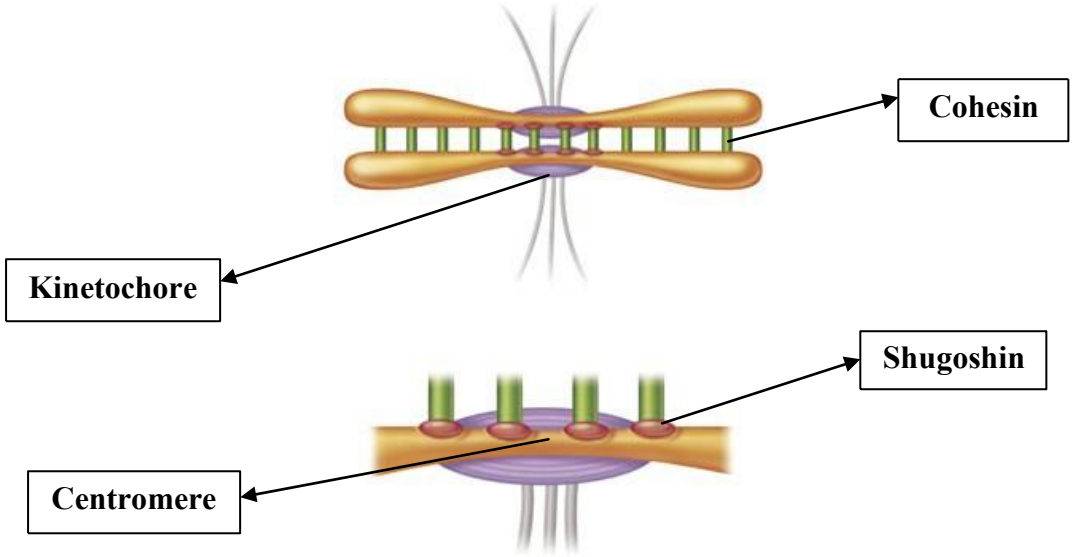
Just before mitosis, a dense band of microtubules appears around the phragmosome and the future division plane just below the plasma membrane.

This **preprophase band** marks the equatorial plane of the future mitotic spindle as well as the future fusion sites for the new cell plate with the existing cell wall. It disappears as soon as the nuclear envelope breaks down and the mitotic spindle forms.

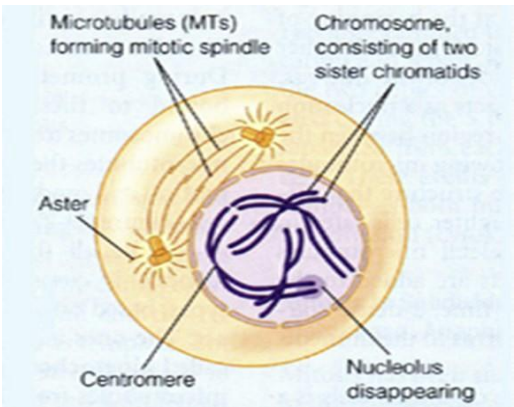


Prophase: In this phase, the sister chromatids condense (coiled) and thickened until they appear as thread-like chromosomes joined by centromere (2n double in structure). Sister chromatids are also held together along their length by cohesion but at centromeres region, they are held together by both cohesin and **S h u g o s h i n** 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).



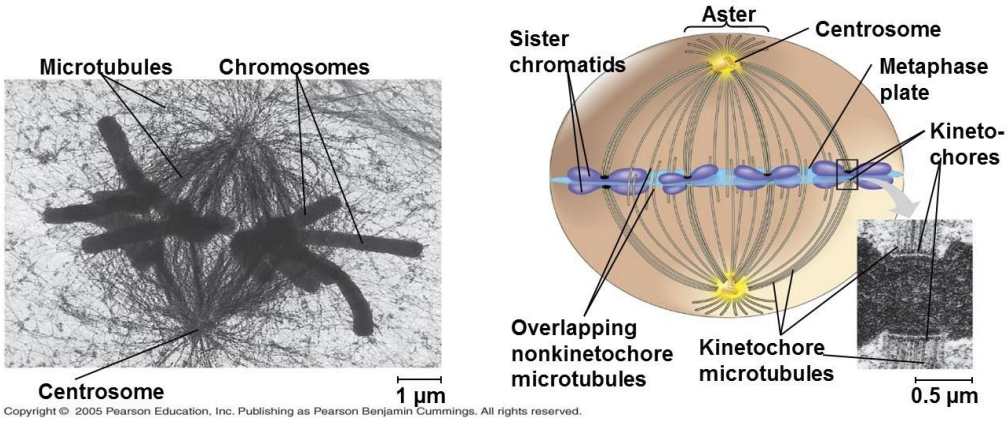
NOTE: The spindle apparatus includes the centrosomes (in animal cell but other in plant cell), the spindle microtubules, associated proteins and the asters (a radial array of short microtubules in animal cell). The centrosome replicates in interphase, forming two centrosomes each with 2 centrioles that 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.

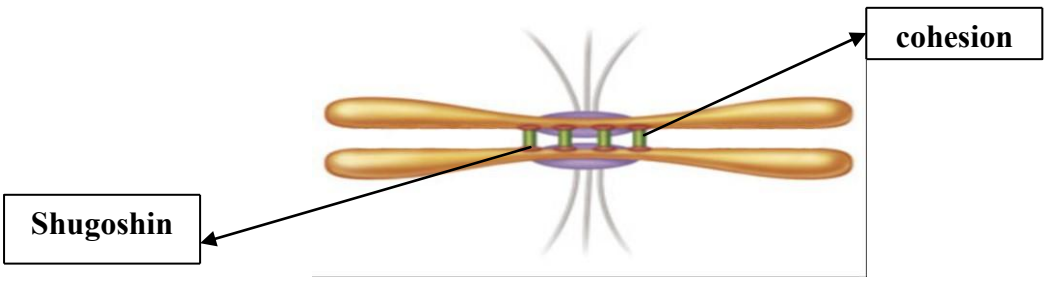


M e t a p h a s e : When the mitotic spindle is fully formed, the chromosomes

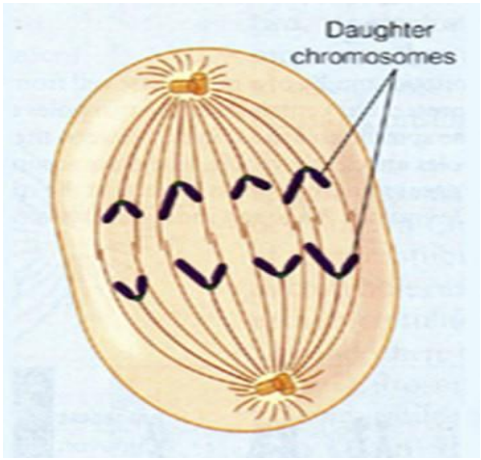
align themselves along the cell spindle in the middle of the cell (equator, equatorial plates). This movement is due to: Assembly and disassembly of microtubules provide force to move chromosomes with the help of the

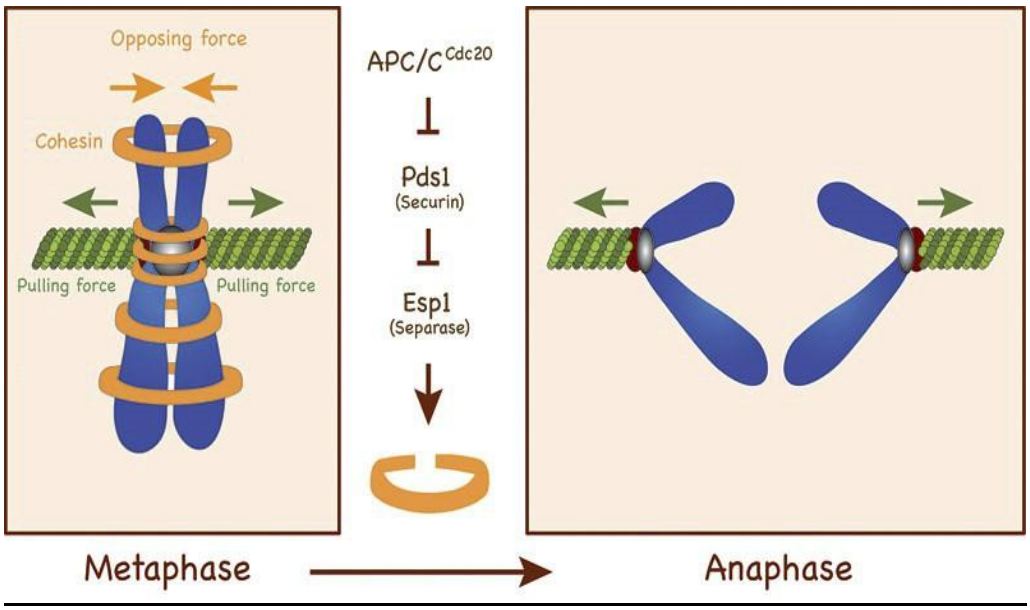
motor proteins located in kinetochore and poles of cell pull on microtubules to provide force. The metaphase chromosome (2n double in structure) appears as two sister chromatids join together by their centromeres and to the spindles by their kinetochore (figure below). At this stage, separase enzyme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



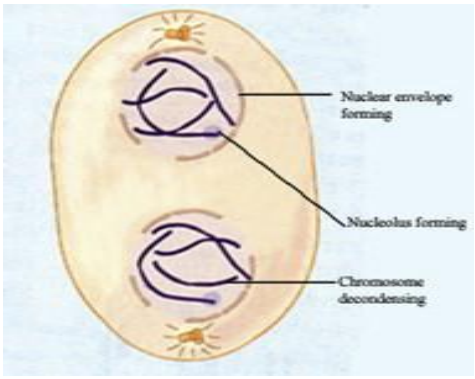


A n a p h a s e : Both cohesion and shugoshin dissolve by proteiolytic enzymes so, the sister chromatids (present in equator) split apart at their centromeres, begin to separate and move to opposite poles of the spindle, segregating one of the two sister chromatids to each of the opposite ends of the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

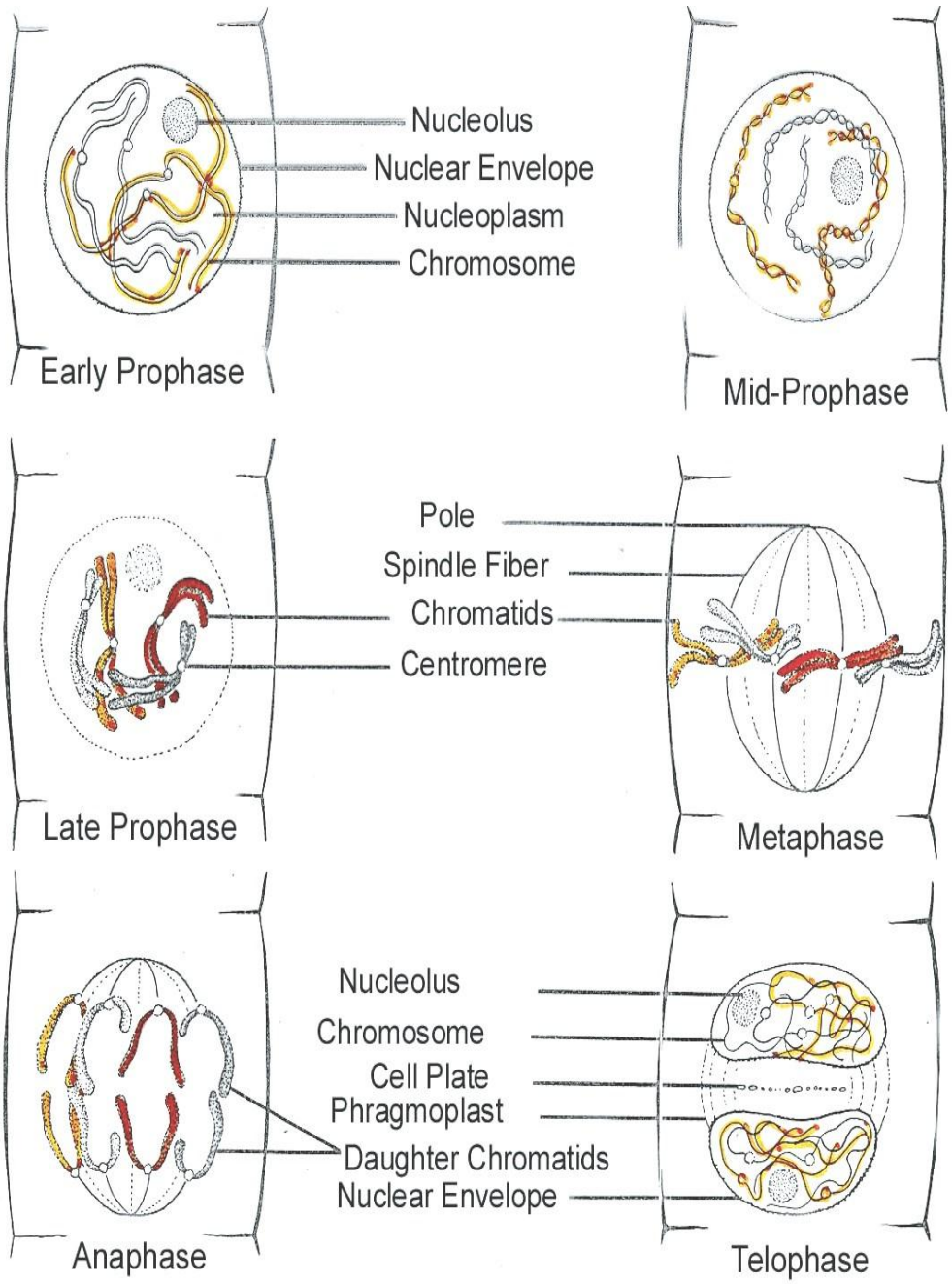




Telophase: A complete set of chromosomes reach each pole of the cell and begin to uncoil. The mitotic spindles, centrosomes and asters begin to disappear (microtubules are broken down into tubulin monomers). The nucleolus and the nuclear envelop reappear around the set of chromosomes. The chromosomes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



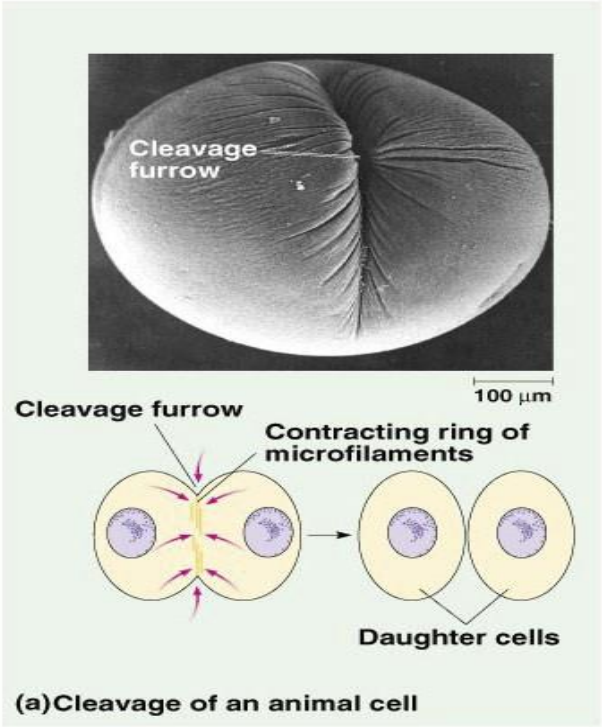
O v e r a l l s t e p s :



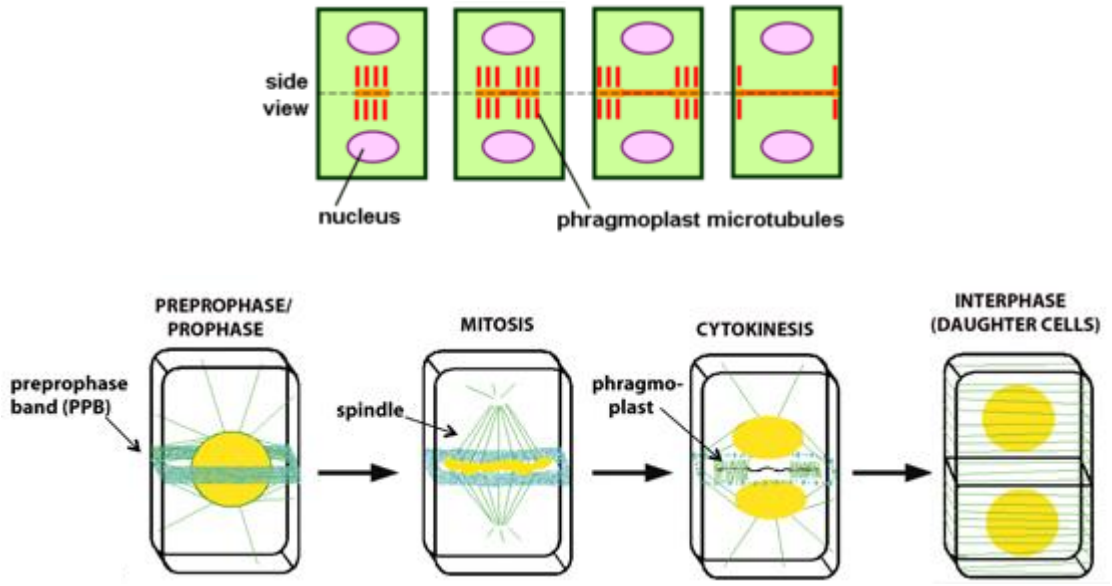
CYTOKINESIS

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.

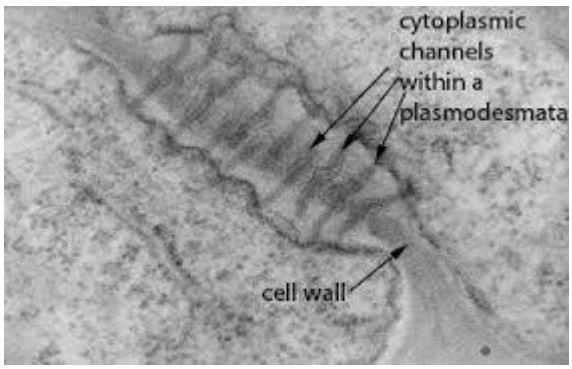


The **phragmoplast** is a plant cell specific structure that forms during late cytokinesis. It serves as a scaffold for cell plate assembly and subsequent formation of a new cell wall separating the two daughter cells.



The phragmoplast is a complex assembly of microtubules (MTs), microfilaments (MFs), and endoplasmic reticulum (ER) elements, that assemble in two opposing sets perpendicular to the plane of the future cell plate during anaphase and telophase. It is initially barrel-shaped and forms from the mitotic spindle between the two daughter nuclei while nuclear envelopes reassemble around them. The cell plate initially forms as a disc between the two halves of the phragmoplast structure. While new cell plate material is added to the edges of the growing plate, the phragmoplast microtubules disappear in the center and regenerate at the edges of the growing cell plate. The two structures grow outwards until they reach the outer wall of the dividing cell. If a phragmosome was present in the cell, the phragmoplast and cell plate will grow outwards through the space occupied by the phragmosome. They will reach the parent cell wall exactly at the position formerly occupied by the preprophase band.

The microtubules and actin filaments within the phragmoplast serve to guide vesicles with cell wall material to the growing cell plate. Actin filaments are also possibly involved in guiding the phragmoplast to the site of the former preprophase band location at the parent cell wall. While the cell plate is growing, segments of smooth endoplasmic reticulum are trapped within it, later forming the **plasmodesmata** (a narrow thread of cytoplasm that passes through the cell walls of adjacent plant cells and allows communication between them).



The phragmoplast can only be observed in Embryophytes, that is the bryophytes and vascular plants as well as a few advanced green algae. Some algae use another type of microtubule array, a phycoplast, during cytokinesis.

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 main cell split and begin to reform in the both daughter cells. Subsequently, the cell will develop new primary and secondary layers of cell wall. This stage is followed by a stage of G1-interphase.

N O T E : The cytoplasm and organelles are usually shared approximately equally between the daughter cells.

D i f f e r e n c e s b e t w e e n M i t o s i s i n A n i m a l a n d P l a n t c e l l s :

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

C E L L C Y C L E C H E C K P O I N T S

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.‖

N O T E :

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 (cell suicide) via apoptosis** (effector mechanism) and thereby block progression through the cell cycle by 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 **G 2 c h e c k p o i n t** is another checkpoint (after completing S and G2 phases) in which DNA must overcome to complete a successful cycle.

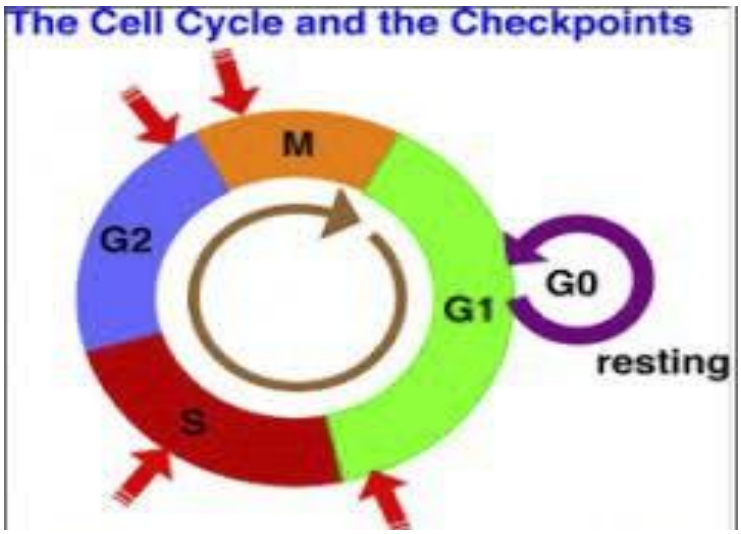
In order for this checkpoint to be passed, the cell has to check a number of factors, including DNA, to ensure that the cell is ready for advancing to the M or mitosis phase. A successful transition through this checkpoint will trigger the start of mitosis. Often time's damage can occur to the DNA before 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.



Regulation of Eukaryotic Cell Cycle

Not all cells proceed through the stages of the cell cycle at the same rate. Embryonic cells divide very rapidly, while mature cells might divide rarely, or in response to signals such as wounding or growth factors, or not at all.

It should seem obvious that the processes that drive a cell through the cell cycle must be highly regulated and required a number of control mechanisms to ensure that the resultant daughter cells are viable and each contains the complement of DNA found in the original parental cell. They control the timing of events so that each individual process is turned on and off at the appropriate time, mechanisms to initiate each event in the correct order and to also ensure that each event is triggered only once

per cell cycle, controls to ensure events occur in a linear, irreversible direction, redundancy, or back-ups to ensure the cycle functions properly even in the context of some malfunctioning parts, and systems that are adaptable so that cell cycle events can be modified in the context of different cell types and/or environmental conditions.

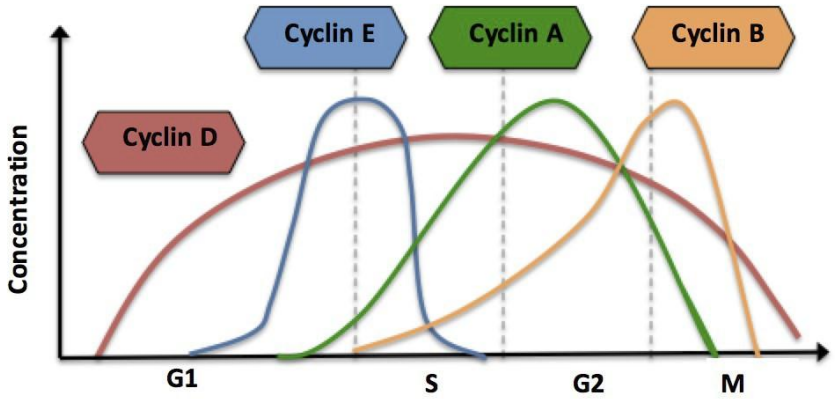
Two key classes of regulatory proteins: cyclins and cyclin-dependent kinases (CDKs) determine a cell's progress through the cell cycle. Many of the cell division cycle genes (cdc genes) encoding cyclins and CDKs are conserved among all eukaryotes, but in general more complex organisms have more elaborate cell cycle control systems that incorporate more individual components.

What Are Cyclins and Cyclin-Dependent Kinases?

CDKs are the most important of multifunctional enzymes that can modify various protein substrates involved in cell cycle progression by phosphorylate them (transferring phosphate groups from ATP to specific stretches of amino acids in the protein). Different types of eukaryotic cells contain different types and numbers of CDKs. For example, yeast has only a single CDK, whereas vertebrates have four different ones.

Cyclins are a family of proteins that form the regulatory subunits, while CDKs are the catalytic subunits of the activated complex; cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin. Each cyclin associates with one or two cyclin-dependent kinases to be partially activated.

CDKs are constitutively expressed in cells whereas cyclins are synthesized at specific stages of the cell cycle, in response to various molecular signals. All CDKs exist in similar amounts throughout the entire cell cycle. In contrast, cyclin manufacture and breakdown varies by stage with cell cycle progression dependent on the synthesis of new cyclin molecules.



All eukaryotes have multiple cyclins, each of which acts during a specific stage of the cell cycle. All cyclins are named according to the stage at which they assemble with CDKs. Common classes of cyclins include G_1-phase cyclins, G_1/S-phase cyclins, S-phase cyclins, and M-phase cyclins (table below).

Cyclin-CDK	**Cyclin**	CDK Partners
G_1-CDK	cyclin D (D1, D2, D3)	CDK4, CDK6
G_1/S-CDK	cyclin E	CDK2
S-CDK	cyclin A	CDK2
G_2-CDK	cyclin B	CDK1
M-CDK		

Specific function of cyclins-CDKs complexes:

1. **G_1 phase cyclins** (cyclin D) form G_1-CDK complexes at the beginning of G_1 and guide the cell's progress through the G_1 phase to coordinates cell growth with the entry to a new cell cycle.

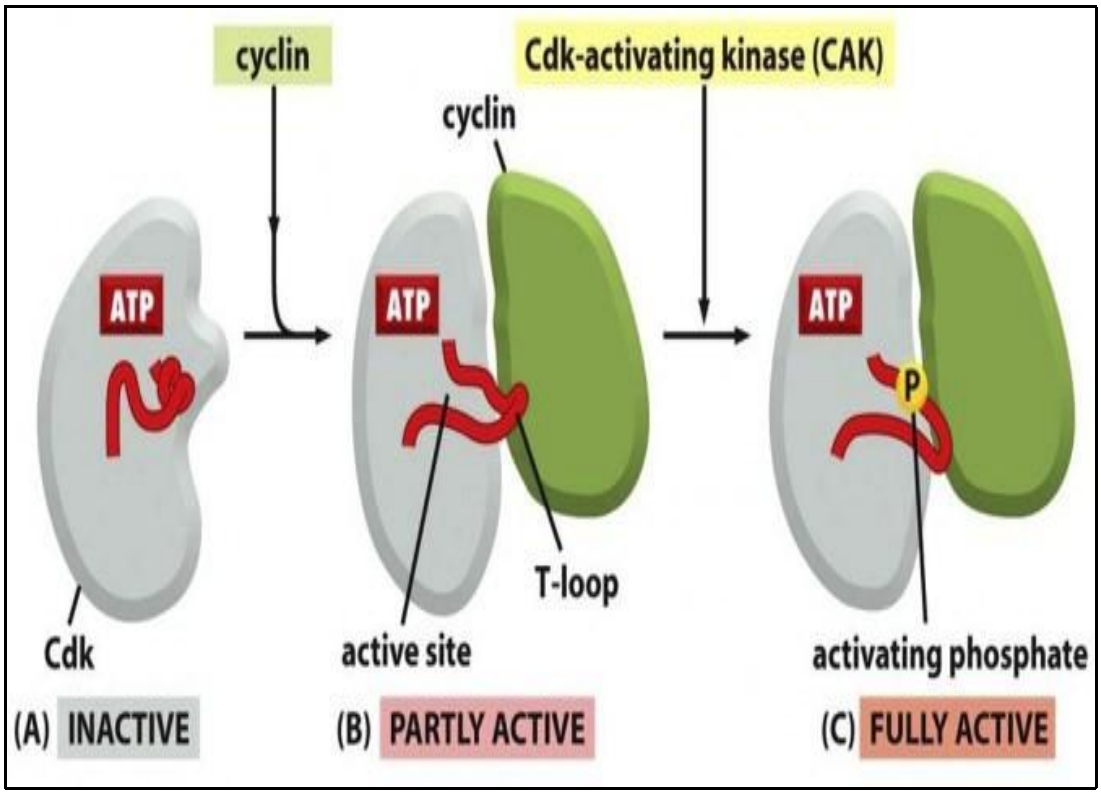
2. **G_1/S-cyclins (cyclin E)** bind to their cognate CDKs at the end of G_1 and it is this interaction that is required to commit the cell to the process of DNA replication in S-phase.
3. **The S-cyclins** (cyclin A) bind to their cognate CDKs during S-phase and it is this interaction that is required for the initiation and induction of DNA synthesis.
4. **The G2-cyclins** (cyclin B) bind to their cognate CDKs during G_2-phase and it is important for the transition into M phase, and plays a role in the following regulatory and structural processes.
5. **M-phase cyclins** (cyclin B) form M-CDK complexes (known as maturation promoting factor or mitosis promoting factors or **MPF**) and drive the cell's entry to promote the events of mitosis like the assembly of mitotic spindles and alignment of sister-chromatids along the spindles. The destruction of M cyclins during metaphase and anaphase, after the Spindle Assembly Checkpoint is satisfied, causes the exit of mitosis and cytokinesis. This complex activation causes breakdown of nuclear envelope and initiation of prophase, and subsequently, its deactivation causes the cell to exit mitosis.

How Do CDKs Control the Cell Cycle?

Interestingly, CDKs require the presence of **cyclins** to become partially active. CDKs must also be in a particular phosphorylation state, with some sites phosphorylated and others dephosphorylated, in order for activation to occur. When activated by a bound cyclin, CDKs perform a common biochemical reaction called phosphorylation that activates or inactivates target proteins to orchestrate coordinated entry into the next phase of the cell cycle.

Although CDKs are inactive unless bound to a cyclin, there is more to the activation process than just the interaction of the two parts of the

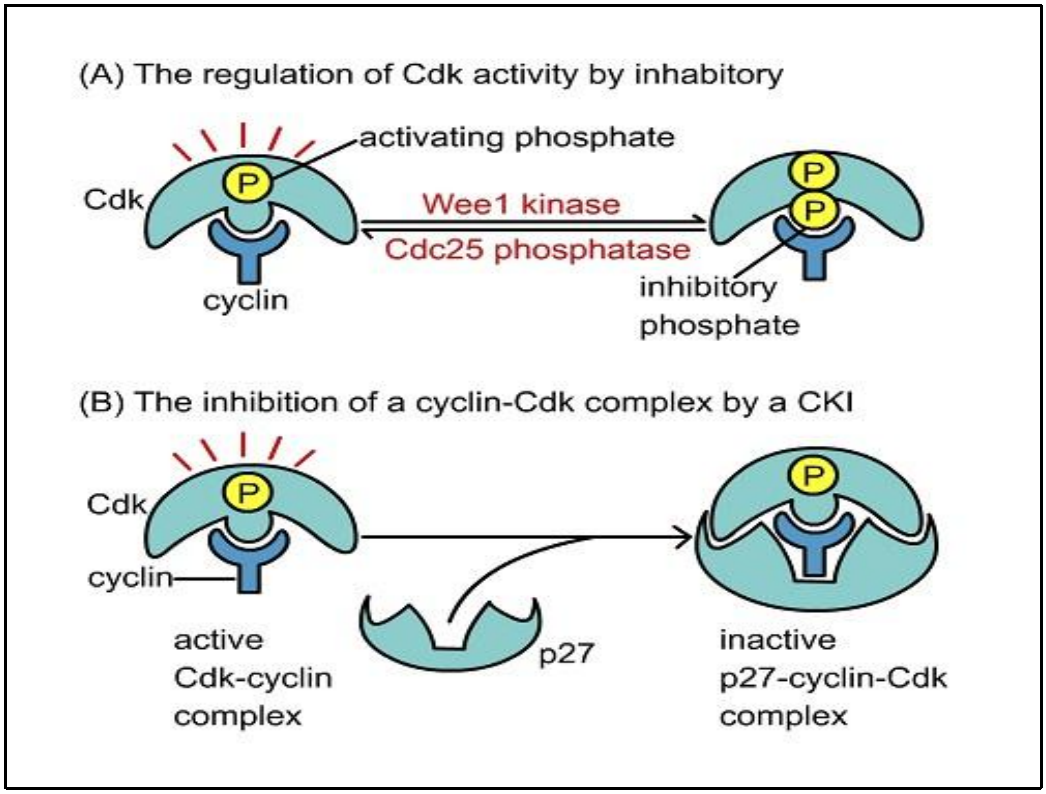
complex. When cyclins bind to CDKs they alter the conformation of the CDK resulting in exposure of a spot that is the site of phosphorylation by another kinase called **CDK-activating kinase (CAK)**. Following phosphorylation the cyclin-CDK complex is fully active (figure below).



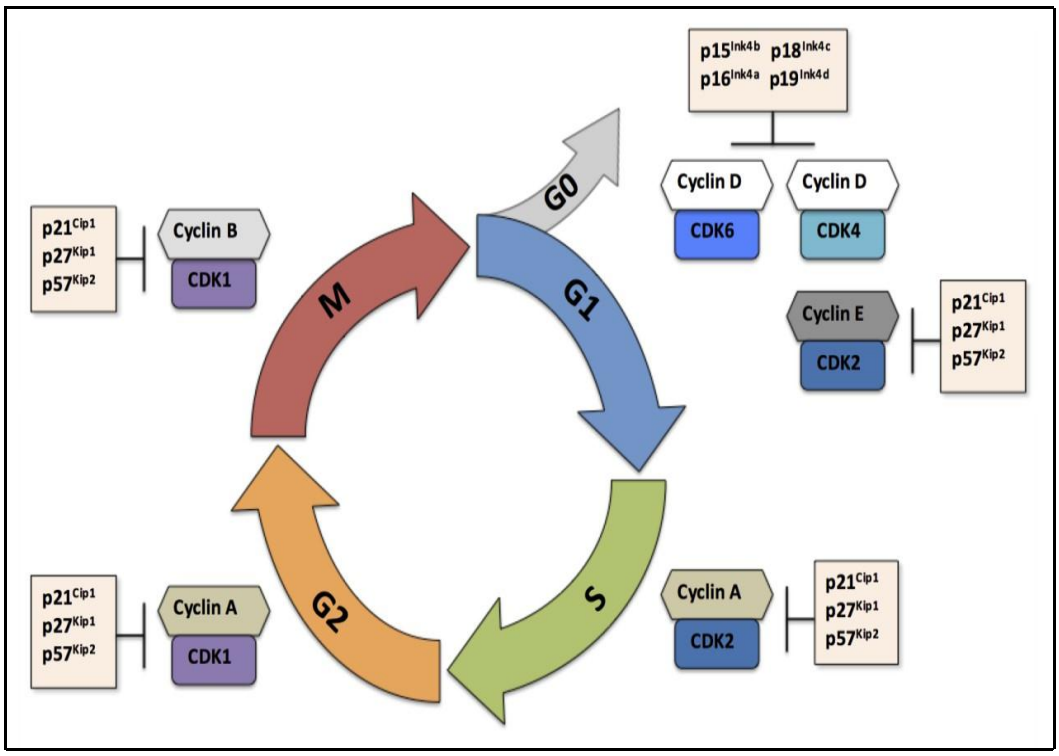
Cyclin degradation is equally important for progression through the cell cycle and specific enzymes break down cyclins are present at defined times in the cell cycle. When cyclin levels decrease, the corresponding CDKs become inactive. Cell cycle arrest can occur if cyclins fail to degrade.

CAK phosphorylation is exerted to inhibit CDK activity through interaction with inhibitory proteins or by inhibitory phosphorylation events (dephosphorylation). Thus, there is extremely tight control on the overall activity of each CDK. Proteins that bind to and inhibit

cyclin-CDK complexes are called **C D K i n h i b i t o r y p r o t e i n s** (CKI, for cyclin-kinase inhibitor), figures below.



Cdk activity can be suppressed both by inhibitory phosphorylation and by inhibitory proteins.

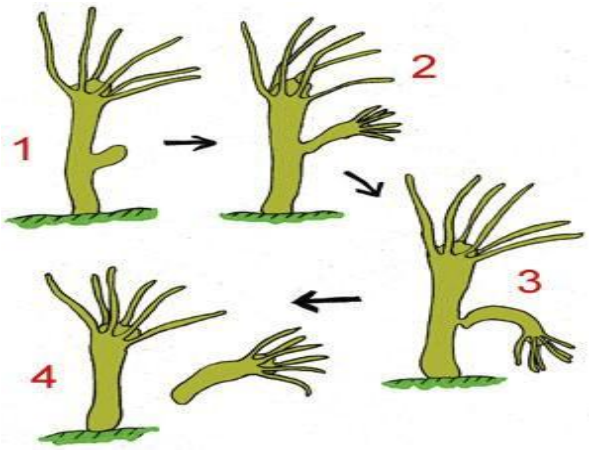


Eukaryotic cell cycle phases with respective cyclin-CDK complexes and inhibitors (CDKs)

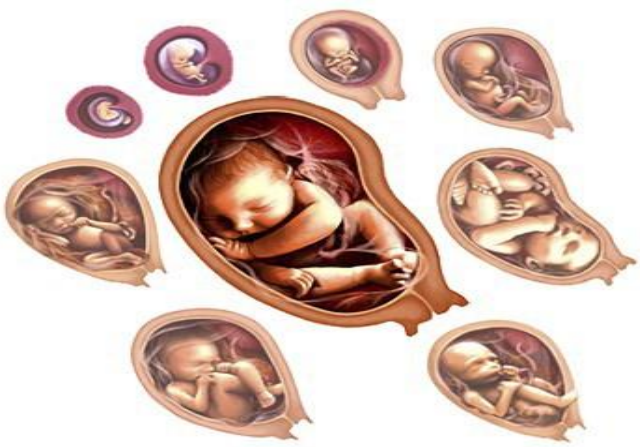
I m p o r t a n c e o f m i t o s i s:

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.

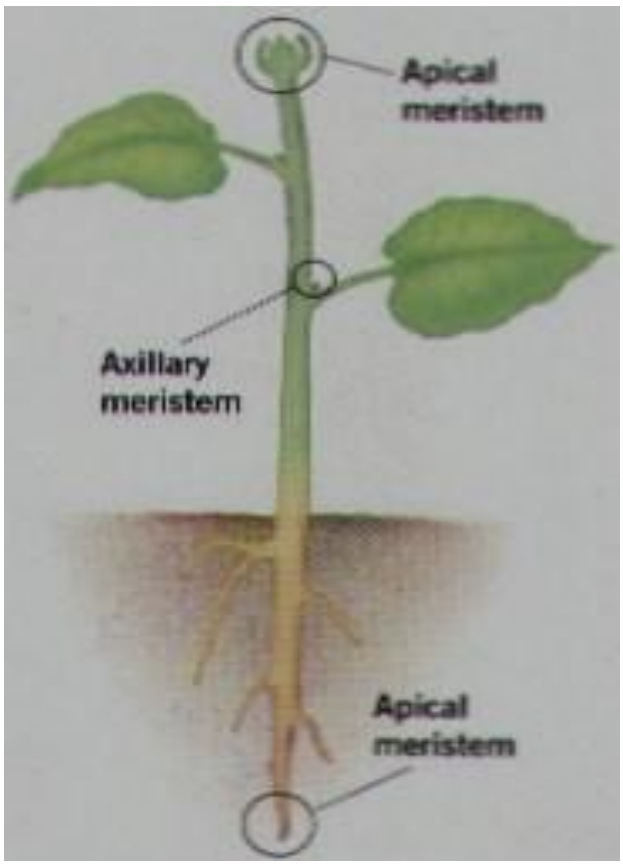


While in adults, however, most tissues do not proliferate but mitosis occurs regularly at the following sites:

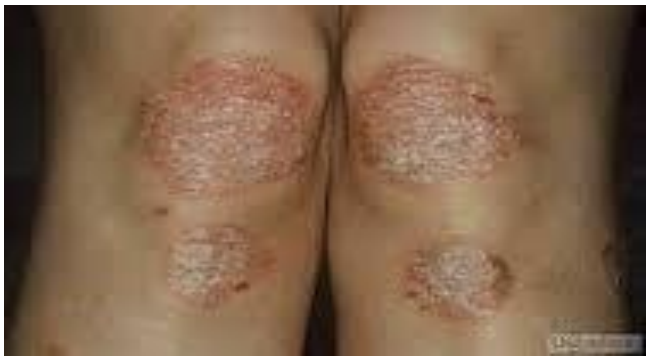
1. Red bone marrow - for production of blood cells (erythropoiesis)
2. Lymphoid tissue - formation of lymphocytes (lymphooiesis)
3. Testes - for spermatogenesis (production of spermatozoa)
4. Epidermis - replacement of superficial skin cells
5. Hair follicles - hair growth
6. Gastro-intestinal tract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

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

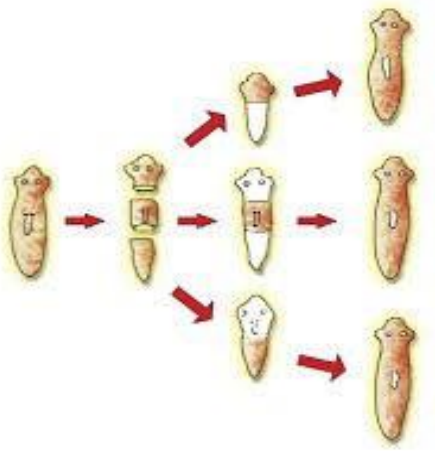
In plants, mitotic cell division mainly takes place in special regions called meristems. They are either present in Shoot apex or axillary buds or root tips of the plants for development and growth.



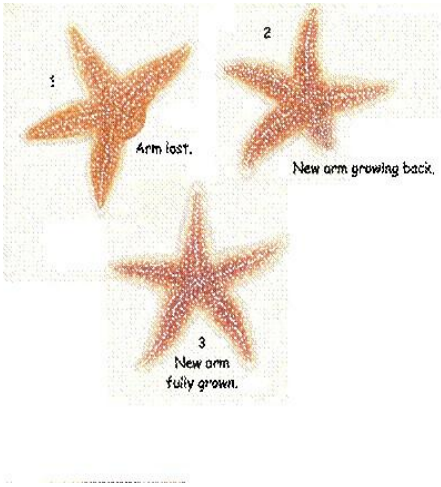
Cell Replacement: In some parts of body, e.g. skin and digestive tract, cells are constantly sloughed off and replaced by new ones. New cells are formed by mitosis and so are exact copies of the cells being replaced. Similarly, RBCs have short life span (only about 4 months) and new RBCs are formed by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



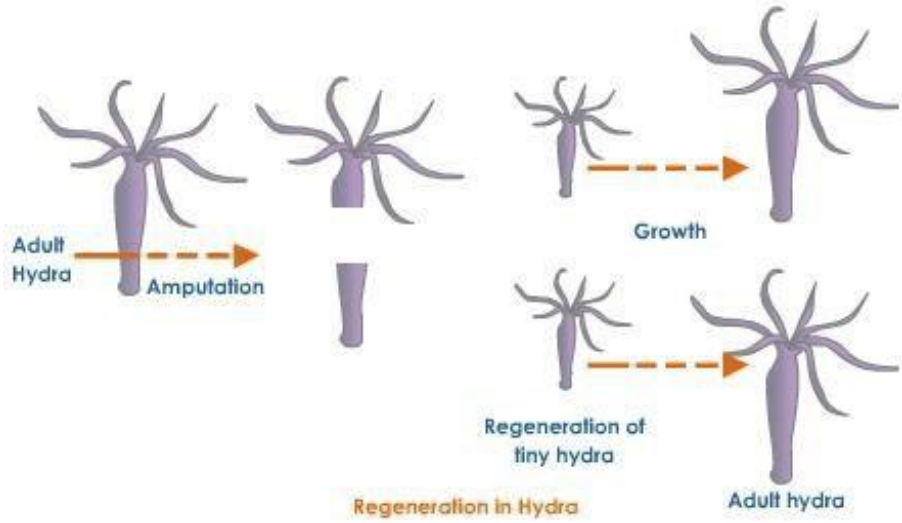
R e g e n e r a t i o n : Some organisms can regenerate (form *de novo*) their parts of bodies. The production of new cells is achieved by mitosis. For example; hydra, sea star and flat worms regenerate their lost part through mitosis.



Flat worm



Sea Star



C L I N I C A L A P P L I C A T I O N S :

Cancer cells undergo uncontrolled cell proliferation. As such, they are defects of the control of the cell cycle. Oncogenes (هنطرسملا نيجلاYئت) 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.

A n i m a t i o n s :

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 . Cell cycle checkpoint and regulation

https://www.youtube.com/watch?v=1EB8q9aR8Hk

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)
4. **Verma, D.S. (2001):** Cytokinesis and building of the cell plate in plants. Annual Review of Plant Biology 52:751-784 (online)
5. **Baskin, T.I. and Cande, W. Z. (1990):** The Structure and Function of the Mitotic Spindle in Flowering Plants. Annual Review of Plant Physiology and Plant Molecular Biology 41: 277-315(online)