GENETICS

Sheet no.3

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Learning points for this lecture:

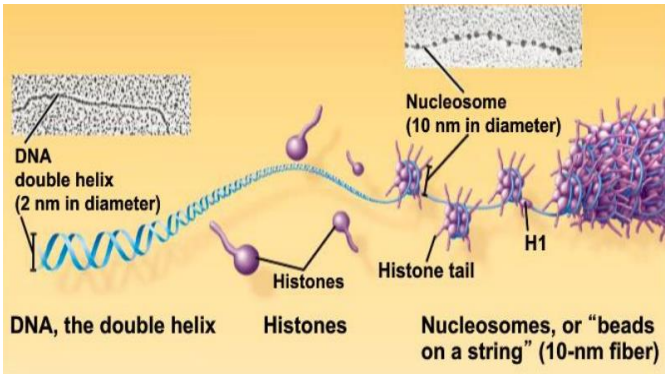
- Describe how chromosomes are packed during cell division
- Describe the results of mitosis and meiosis, and how these are achieved

Chromosomes compacting

Before going to cell division, we must put the DNA into the nucleus, and to add it we need compaction.

Chromatin: nuclear DNA plus all the proteins bound to it (50:50)

- 2 main groups of proteins involved in folding/packaging eukaryotic chromosomes:



• Histones:

- positively charged proteins filled with amino acids lysine and arginine that bond.
- Histone protein sequence is highly conserved among eukaryotes (the same function in every organism).
- DNA is wound around histone proteins twice to produce *nucleosomes (the building blocks of chromatin)*.

• Nonhistones:

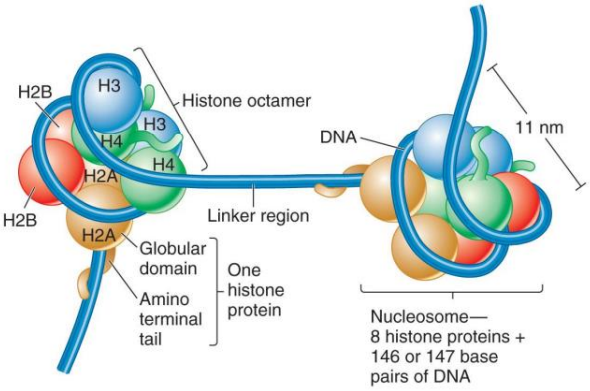
- less positive (Many are acidic and negatively charged)
- Highly variable in cell types, organisms, and at different times in the same cell type
- have role in compaction (which is looping – explained later)
- Scaffold Protein.

So, **Nucleosome** consist of DNA wrapped twice around protein, The protein is Histone Octamer (which is 2 copies of; H2A, H2B, H3, H4), So we have 8 histones in each nucleosome.

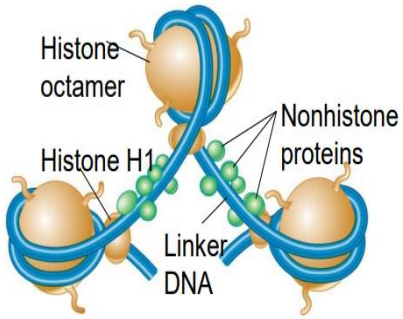
Note: The Wrapping helps to organize the negative charges of the DNA

Between every nucleosome and the other there is a DNA sequence called ***linker region***, so 146 bps per nucleosome core particle with 53 bps for linker DNA which is linked to **H1** (which is not one of the main octamer).

Once H1 binds with a nucleosome, it changes to **Chromatosome** (it is number of nucleosomes equals hundreds or thousands not a level of packing)



(a) Nucleosomes showing core histone proteins

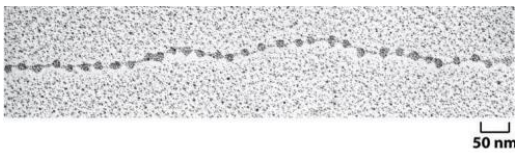


histone octomer
Chromatosome!

(c) Nucleosomes showing linker histones and nonhistone proteins

• Chromatin is linked together every 200 bps

• Chromatin arranged like "beads on a string" (electron microscope)



☼ The packaging of DNA into chromosomes involves several orders of DNA coiling and folding:

DNA is further compacted when the DNA nucleosomes associate with one another to produce **30 nm chromatin (Solenoid model)** which is a round structure and each turn (180°) it has 6 nucleosomes. It Is probably the major type of chromatin in the nucleus during interphase.

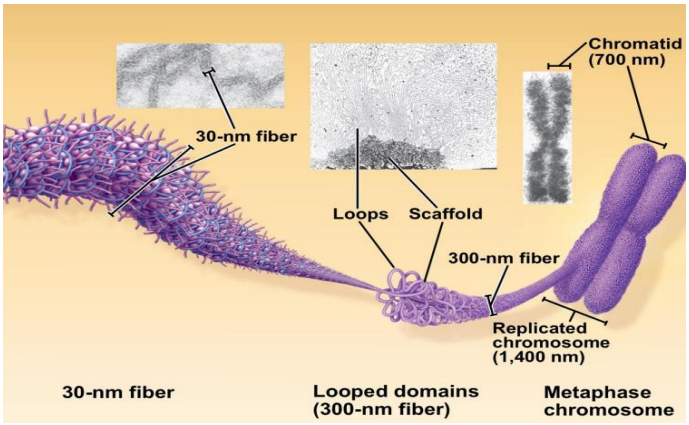
• Interestingly, histone H1 is very important in stabilizing chromatin higherorder structures, and 30-nanometer fibers form most readily when H1 is present.

Processes such as *transcription and replication require the two strands of DNA to come apart temporarily*, thus allowing polymerases access to the DNA template. However, the presence of nucleosomes and the folding of chromatin into 30-nanometer fibers pose barriers to the enzymes that unwind and copy DNA.

• It is therefore important for cells to have means of opening up chromatin fibers and/or removing histones transiently to permit transcription and replication to proceed.

The third step Is more compacting of the solenoid form, which gives you **Loop formation (Radial loops)** which is bound to scaffold protein which is a *nonehistone* proteins then will be further compaction of the loops and we will see the chromosomes as expected to see (Metaphase).

• DNA supercoiling is very important for DNA packaging by reducing the space required by the DNA.



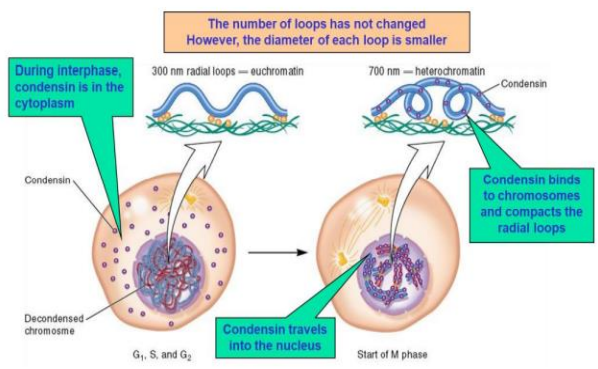
The formation of metaphase chromosomes is also promoted by two multi protein complexes (SMC proteins -> structural maintenance of chromosomes):

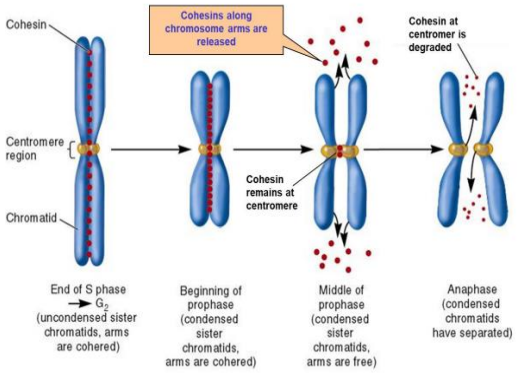
• **Condensin:** are responsible for condensing chromosomes at mitosis.

- group of proteins that bind to chromosomes as a cell enters prophase, causing the chromosomes to become more compact and visible under a light microscope by enhancing the supercoiling.

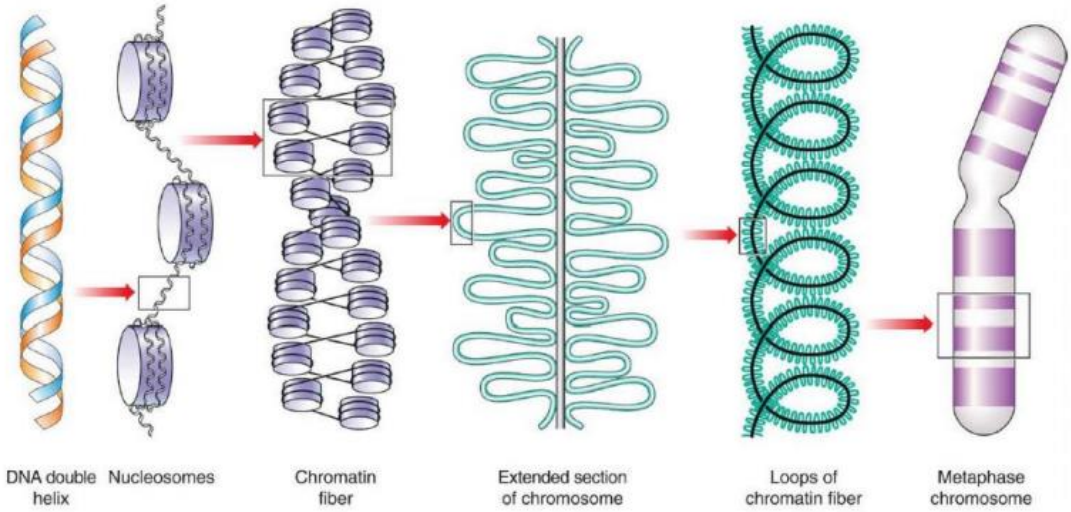
• **Cohesin:**

- Promote binding of the sister chromatids after S phase and until the middle of the prophase.
- At anaphase the cohesins bound to the centromere are degraded by a specific protease.





In summary we have a nucleosome then we have 30 nanometer fibers and we have radial coils then we have chromatid and chromosome.



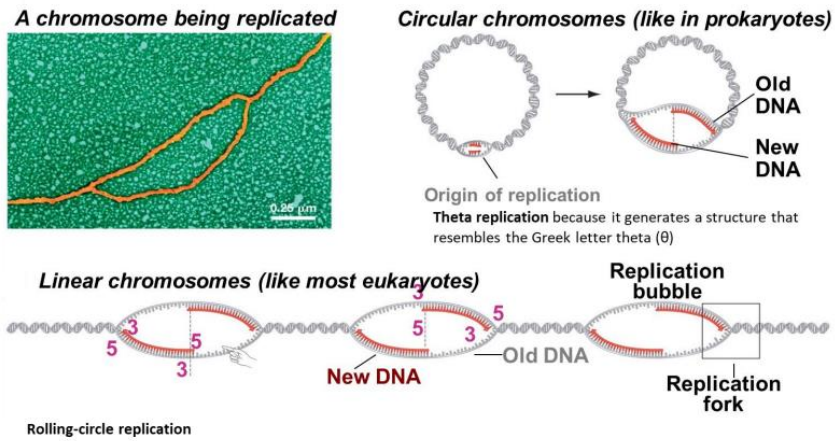
Chromosome Structure

Chromosomes contain three types of regions that are required for replication and segregation:

1. Origins of replication: certain DNA sequences along each chromosome at which DNA replication can be initiated

Bacteria has only one chromosome which means that it has only one origin of replication.

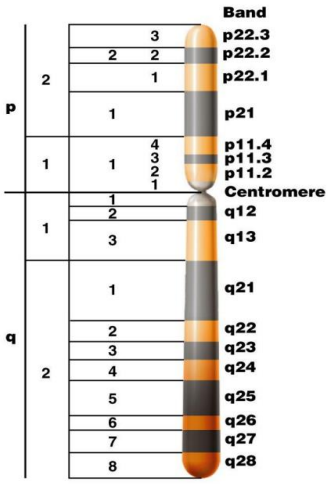
But in humans we have hundreds of thousands of origin of replication because in that way it will only take hours to make new cells instead of the dead cells (and that's the main reason why it goes in both directions to make amplification or duplication)



2. Centromere: constriction point which divides the chromosome into two sections, or "arms."

– The short arm of the chromosome is labeled the ***"p arm."***

– The long arm of the chromosome is labeled the ***"q arm."***



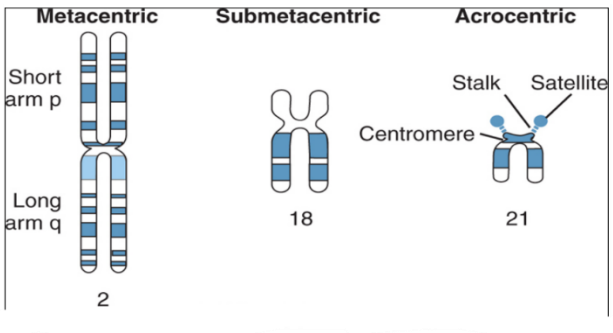
• The location of the centromere on each chromosome gives the chromosome its characteristic shape, and can be used to help describe the location of specific genes

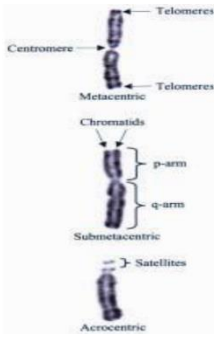
• The centromere is essential for chromosome segregation (during cell division). And is used for the formation of the ***kinetochore:*** A group of proteins (microtubules) that link the centromere to the spindle apparatus. (ensuring proper segregation of sister chromatids)!

❖ *Chromosome Shape:*

We have two types of classification of chromosomes shapes; one is depending on the size and shape where chromosome 1 is the largest and chromosome 22 the sex chromosome is the smallest.

In the second classification and the more important is depending **how far the centromere from the middle** so instead of 22 different chromosomes we will have 7 groups (we will see this in detail in cytogenetics)





Metacentric: centromere is located in the middle of chromosome.

Submetacentric: centromere is displaced from the center.

Acrocentric: centromere is placed near the end.

3. Telomere: essential for the stability of the chromosome tips.

The doctor explained it in a very long detailed way so I will summarize it for you as much as I can 😊:

During DNA replication, the DNA polymerase enzyme cannot replicate the very ends of linear chromosomes, leading to the gradual loss of telomeric DNA with each round of replication, Telomere contain Telomerase (reverse transcriptase) that contains both RNA and protein components. The RNA component serves as a template for the addition of telomeric DNA sequences. Telomerase extends the 3' end of the telomere by adding repetitive telomeric DNA sequences to prevent the loss of genetic material and maintain the stability of the chromosome.

• Each end of a linear chromosome is composed of a special DNA–protein structure called a telomere

• Telomeres -> prevent chromosomal rearrangements so brings stability. It prevents chromosomes shortening: They protects the chromosome from digestion via enzymes and the telomeres do replicate so the chromosomes do not become shortened

It has also **another function**, each chromosome has a single strand at the end of it so telomeres existence prevent the joining of two chromosomes together so maintain the stability.

Packaging of DNA into Chromosomes

• The compaction of interphase chromosomes is not completely uniform, there is 2 types of chromatins in it:

one with highly stained area called **heterochromatin** and the other with lightly stained area called **euchromatin.**

❖ **Heterochromatin:**

- ➢ diff types of condensed chromatin.
- ➢ Darkly stainable by many standard dyes used to make chromosomes.
- ➢ represents 10% of chromosomes.

- Tightly compacted regions of chromosomes.
- Transcriptionally inactive (in general, do not always encode proteins.)
- Responsible for function of telomeres, centromeres which indicate it has no or poor number of genes which means it is transcriptionally **inactive.**
- Replicate late S phase.
- Tight binding of histone H1.

☼ We have two subtypes of heterochromatin depending on its activity:

Constitutive heterochromatin: the chromosomal regions that are always heterochromatic and permanently inactive.

Facultative heterochromatin: chromatin that can occasionally interconvert between heterochromatin and euchromatin (X chromosome converting to a heterochromatic Barr body).

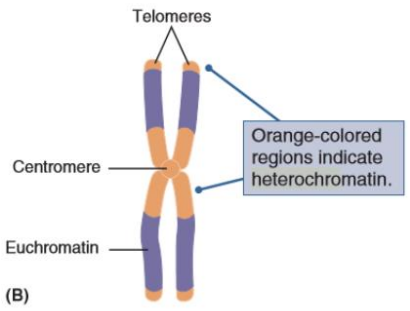
Note: The X chromosome from the father is randomly active or inactive (it is a 50:50 situation) if X from the mother is active. Not all genes in inactivated X will be inactivated (Some will go a thing called **escaping from inactivation**)

We have something called **skewed X inactivation;** normally in a recessive diseases; the *male (XY)* will have more probability than *female (XX)* of being diseased or have the signs or symptoms because he has 1X chromosome that is having the disease gene, in skewed X inactivation the females can show signs and symptoms or disease even though there is another X because the inactivated X is working instead of the activated X.

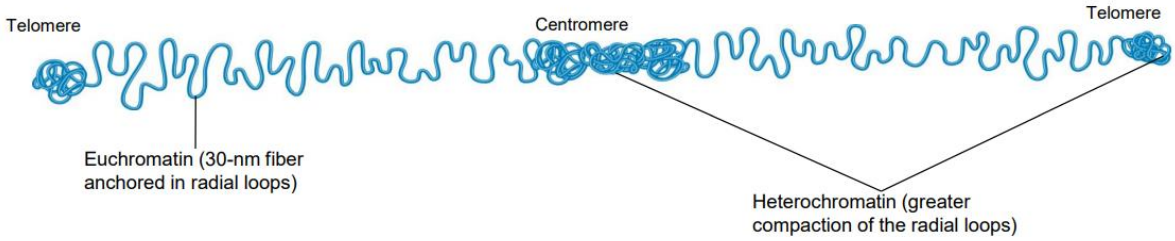
(Everything said here is just for information we will take it in epigenetics)

❖ **Euchromatin:**

- Less condensed regions of chromosomes.
- Usually, areas where gene expression is occurring.
- Composed of all types of chromatins structures30 nm fibers, loops, etc.



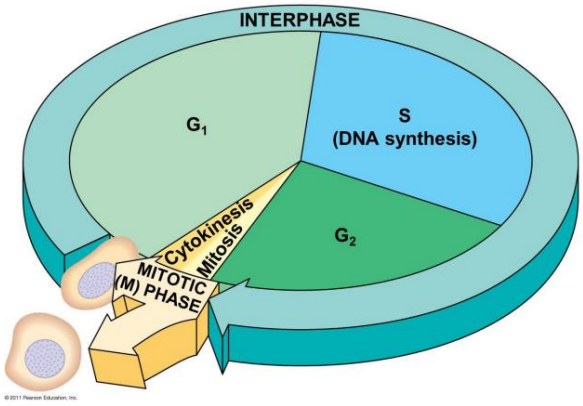
- 90% of chromatin.
- Replicate throughout S phase.
- Weak binding of histone H1 molecules.



	Heterochromatin	Euchromatin
	More condensed	Less condensed
	No or poor of genes	Has genes
	Dark stain	Light stain
	10% of chromosome	90% of chromosome
	Tight binding to H1	Weak binding to H1
	Replication: late phase S	**Replication:** through phase S

Metaphase Chromosomes:

- compaction is part of the cell cycle.
- Interface is the phase where the chromosome has the most relaxation and which have 3 stages G1G2 and S.
- By the end of prophase, sister chromatids are entirely heterochromatic
- Two parallel chromatids have an overall diameter of 1,400 nm



- As cells enter M phase, the level of compaction changes dramatically These highly condensed metaphase chromosomes undergo little gene transcription, after metaphase chromosomes will divide it into two daughter cells.

Cell Cycle

• DNA and associated proteins are organized into chromosomes

• Human somatic cells are diploid and have 22 pairs of autosomes AND 1 set of sex chromosomes (XX or XY)= total of 46 – Females XX – Males XY

• Germ cells are haploid and contain 22 chromosomes plus 1 sex chromosome (X or Y)

• An understanding of cell division is basic to an understanding of cytogenetics. Dividing cells are needed in order to study chromosomes using traditional cytogenetic techniques, and many cytogenetic abnormalities result from errors in cell division.

• **The aims of cell division:**

1- Replace died cells

2- Repair of the damaged cells such as wound cells

3- Reproduction of living organisms

• There are two types of cell division: **mitosis** and **meiosis.**

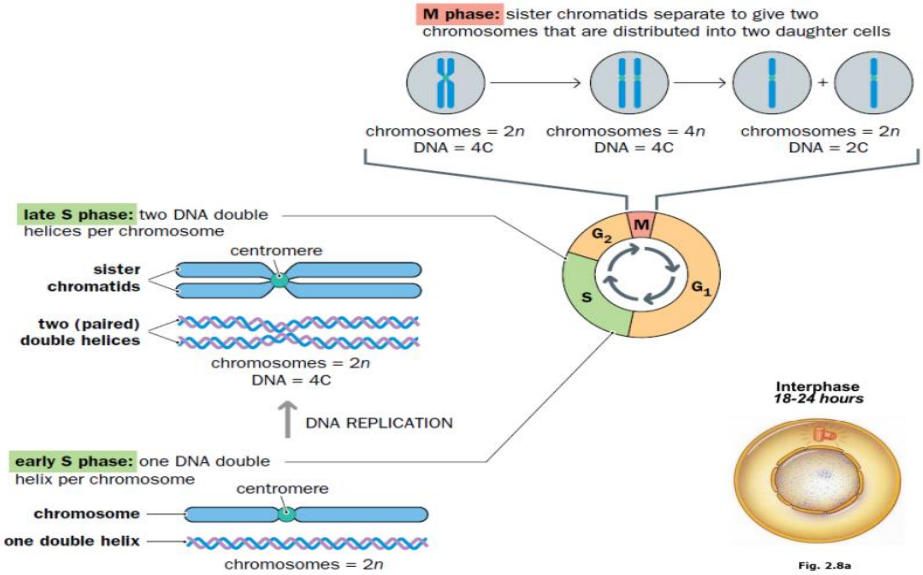
• **Mitosis** is the division of somatic cells, whereas **meiosis** is a special type of division that occurs only in gametic cells.

❖ ***cell cycle:***

- it is the series of growth and development steps; a cell undergoes between its "birth"—formation by the division of a mother cell—and reproduction—division to make two new daughter cells
- **Stages of the cell cycle:** To divide, a cell must complete several important tasks: it must grow, copy its genetic material (DNA), and physically split into two daughter cells.
- Cells perform these tasks in an organized, predictable series of steps that make up the cell cycle.
- The cell cycle is a cycle, rather than a linear pathway, because at the end of each go-round, the two daughter cells can start the exact same process over again from the beginning.

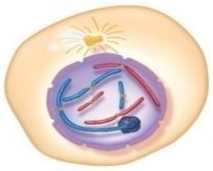
• The cell cycle consists of the alternation of cell division (**mitosis** and **cytokinesis** which is cytoplasm division) and **interphase**.

• DNA replication and protein synthesis take place during interphase which takes 18-24 hours compared to mitoses which takes two hours.



❖ Interphase consists of three parts:

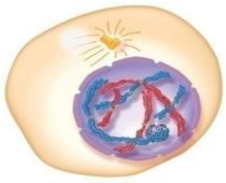
1st: Gap 1 (G1) (46 or 2n): many cytoplasmic organelles are constructed; RNA, protein and other molecules are synthesized; cell almost doubles in size in order to be mature enough to be ready for the next phase.


G_1 phase

After G1 and before S phase there is a **checkpoint phase** (مراحل تفتيش) that has routines the check on G1 materials and size and see if it has damage or not in this phase we still have 46 chromosomes.

2nd: Synthesis (S):

In **early S phase** number of chromosomes is same as G1, in **late S phase** DNA is replicated and number of chromosomes gets duplicated **(92 or 4n),** forming 2 sister chromatids attached at the centromere. It also does repair of DNA.


S phase

3rd: Gap 2 (G2) (92 or 4n):

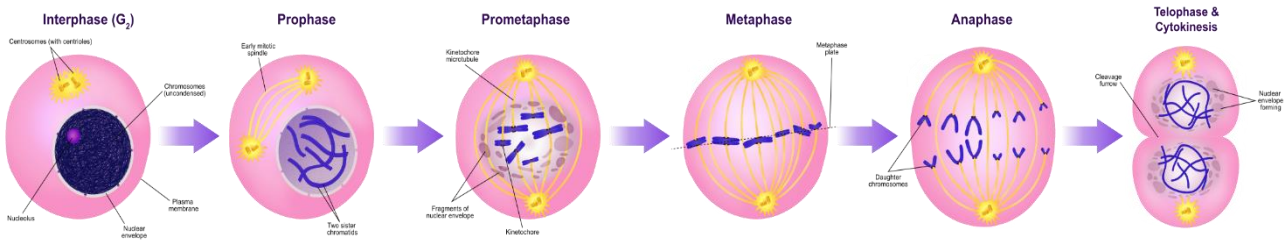
More cell growth; mitochondria, Golgi divide; spindle precursors form to **be ready for mitosis** (it's like having two cells in 1, it has the components of two cells (the double of everything).

Mitosis (M phase):

• The primary purpose of mitosis is to distribute the replicated chromosomes equally to the two daughter cells

• This stage is known as **equational division** (Cells have the same equal No. of chromosomes).

• **In humans for example:** The 46 pairs of sister chromatids are separated and sorted; each daughter cell thus receives 46 chromosomes.



❖ The five stages of mitosis and their major events:

1) Prophase: chromosomes condense and become visible.

2) Prometaphase: spindle forms and sister chromatids attach to microtubules from opposite centrosomes.

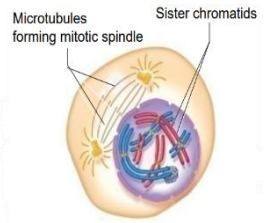
3) Metaphase: chromosome align at the cell's equator.

4) Anaphase: sister chromatids separate and move to opposite poles.

5) Telophase: chromosomes decondense and are enclosed in two nuclei (Separate completely).

▪ ***Cytokinesis*** overlaps the latter stages of mitosis.

1) Prophase:

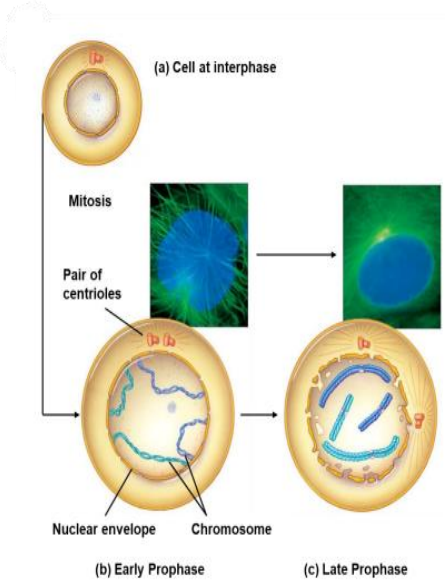


• Chromosomes condense and become visible (I can distinguish between them).

• The nuclear envelope starts dissociation into smaller vesicles.

• **Centrosomes or Centrioles (microtubules-producing center)** separate and move apart toward opposite poles & the **mitotic spindle apparatus** is formed which is Composed of microtubules (MTs)

❖ The Mitotic Spindle Apparatus:

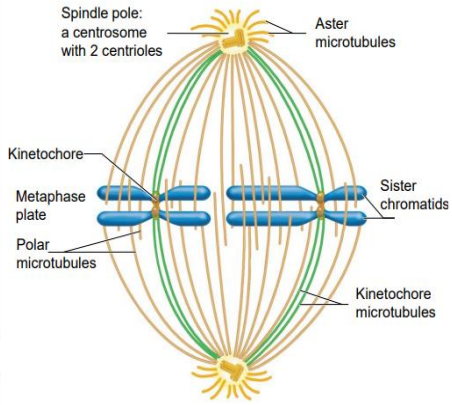


• Spindle apparatus is formed from microtubule organizing centers (MTOCs: called centrosomes)

• Microtubules are formed by rapid polymerization of tubulin proteins – Centrosomes lie at each spindle pole – A pair of centrioles is within each centrosome that enhance the dividing of cells equally **but don't reach the sister chromatids yet.**

• Some plants do not have centrosomes; The nuclear envelope functions as an MTOC.

➢ There are three types of spindle microtubules:

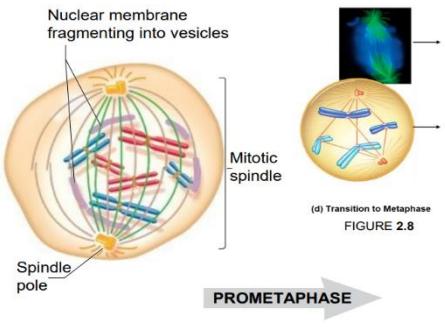


1. Aster microtubules: Help position the spindle at the poles of cells.

2. Polar microtubules: Help to "push" the poles away from each other (يزيد طولها حتى يسهل انفصالها)

3. Kinetochore microtubules: Attach to the kinetochore, which is bound to the centromere of each individual chromosome (In green).

2) Prometaphase:



• each centriole is in a pole already.

• Nuclear envelope breaks down (completely degraded)

• Centrosomes move to opposite ends of the cell, forming the spindle poles

• Spindle fibers interact with the sister chromatids **(they become in full intact with the sister chromatids)**

• Kinetochore microtubules grow from the two poles; The two kinetochores on a pair of sister chromatids are attached to kinetochore MTs on opposite poles.

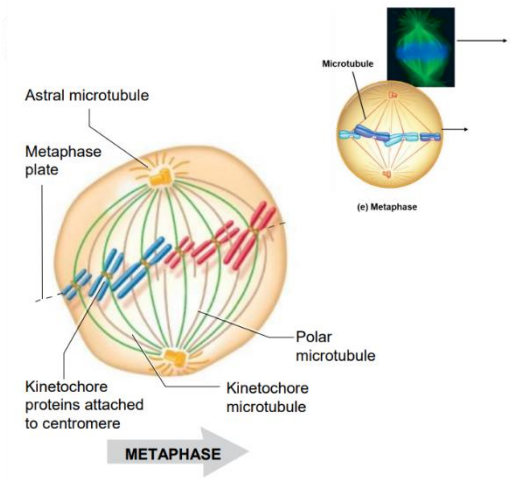
• The cells become longer.

3) Metaphase:

• The highest level of compaction.

• Chromosomes become arranged in a single plane, ***the metaphase plate***, between the two centrosomes.

• The chromosomes are arranged equally (by the help of microtubules) in a way that each sister chromatid face a pole.



• Each pair of chromatids is attached to both poles by kinetochore microtubules.

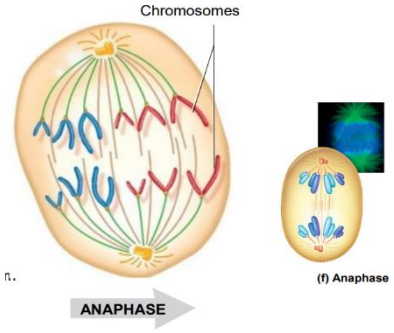
• Forces pushing and pulling chromosomes to or from each pole are in balanced equilibrium.

4) Anaphase:

• Anaphase begins when the sister chromatids separate and move toward opposite spindle poles.

• The connection holding the sister chromatids together is broken **(cohesion degradation).**

• Each chromatid, now an individual chromosome, is linked to only one pole **and make V shape.**



• As anaphase proceeds – Kinetochore MTs shorten (قوى سحب)

• Chromosomes move to opposite poles – Polar MTs lengthen (قوى دفع)

• Poles themselves move further away from each other.

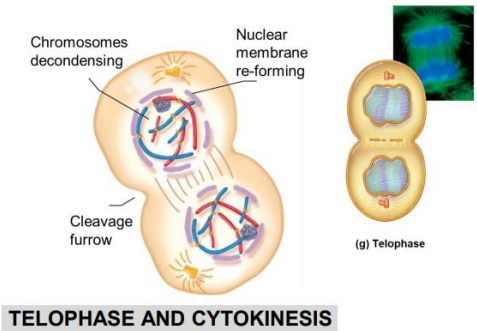
5) Telophase & Cytokinesis:

• Chromosomes reach their respective poles

• **Nuclear membrane** reforms to form two separate nuclei

• Spindle fibres disperse

• The chromosomes relax and lengthen, once again disappearing from view (decondensed).



• In most cases, mitosis is quickly followed by **cytokinesis (Cleavage furrow).**

Note: in all phases of mitosis there's 92 chromosomes or 4n until it separates in telophase.

That's it ;).

Past Papers:

1) This chromosome is:

A. Metacentric

B. Acrocentric

C. Submetacentric

D. Interphase chromosome

E. Telocentric

2) How many double stranded DNA molecules are in a somatic human cell that is in present G2 phase:

A. 46

B. 23

C. 92

D. There are no double stranded DNA molecules in G2

E. 69

3) All of the following regarding telomeres is true EXCEPT:

A. Telomeres consist of a repeated sequence of TTAGGG.

B. Telomeres are shortened by each cycle of DNA replication.

C. It codes for important genes.

D. Prevents end-to-end fusion of chromosomes.

E. Cancer cells are characterized by high telomerase activity.

4) A cell is in G0 phase. How many chromosomes does it have?

A. 46

B. 23

C. 92

5) The shortest stage in cell cycle:

A. M

B. G0

C. G1

D. S

E. G2

6) Which phase of the cycle is most likely to be interrupted for smaller abnormalities detection?

A. Metaphase

B. Prometaphase

C. S phase

D. G phase

E. Anaphase

Questions	Answers
1	C
2	C
3	C
4	A
5	A
6	B

V2

Page 11: (S) is **92** or 4n not 96.