Medical Genetics

Sheet: 1 [Intro to Cytogenetic]

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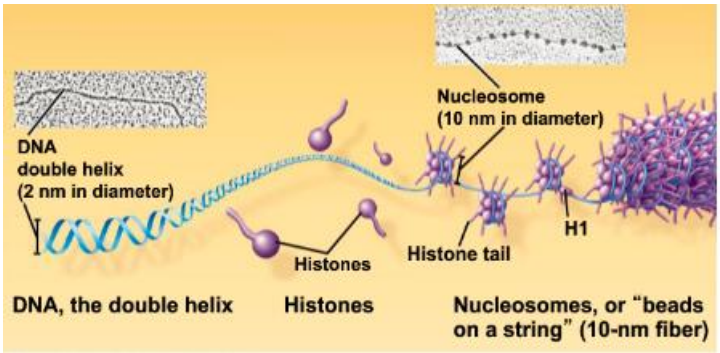
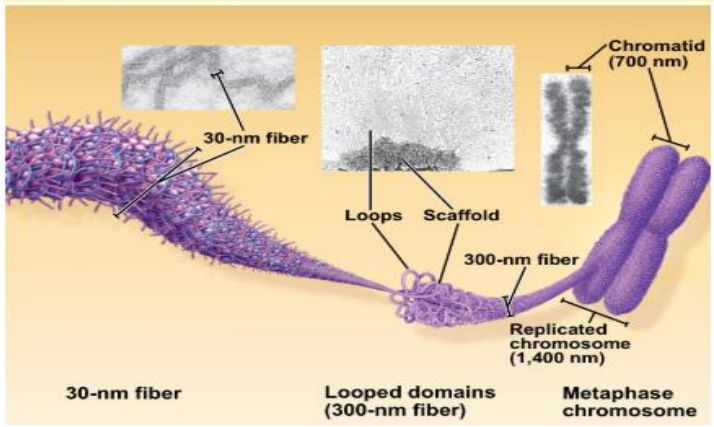
Before 1956, the human chromosome number was unknown. It was established through cytogenetics, the study of chromosomes.

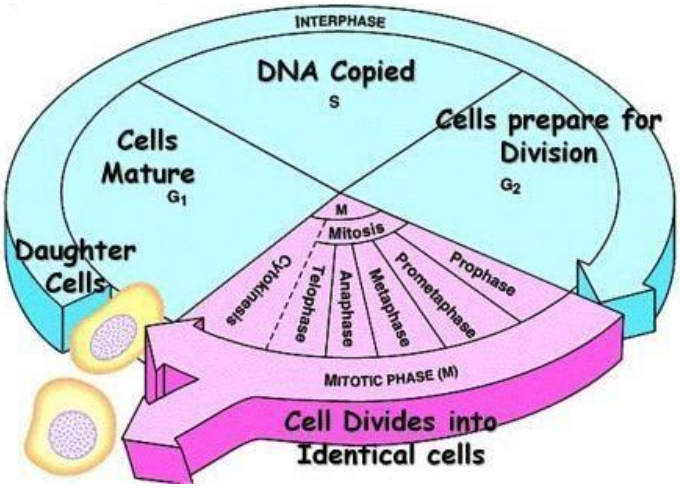
- ✓ **DNA structure:** A DNA molecule, which generally refers to double-stranded DNA, is wrapped around proteins called histones, forming a DNA-protein complex known as a nucleosome.
- ✓ Nucleosomes are packed together forming coils of chromatin.
- ✓ Chromatin is anchored onto what is called a scaffold, forming a chromatid.
- ✓ And an identical DNA molecule compromises the other sister chromatid.
- ✓ The 2 chromatids together form a chromosome.





The cell cycle

- ✓ DNA replication in the cell cycle occurs in the S phase (S stands for synthesis (i.e., DNA synthesis)). In this phase, the DNA polymerase uses each strand of the DNA molecule as a template to synthesize daughter strands (Now, I have 2 molecules which are the sister chromatids that compromise the chromosome).
- ✓ **In the interphase** (The G1-S-G2 phase; the stage preceding cell division), the DNA should be loose/accessible and available for the proteins to bind e.g. **the RNA polymerase in the G phase (Growth phase)** to create more mRNA molecules, proteins that are necessary for the cell to grow and divide, and **proteins that are used for replication** (**in the S phase**).

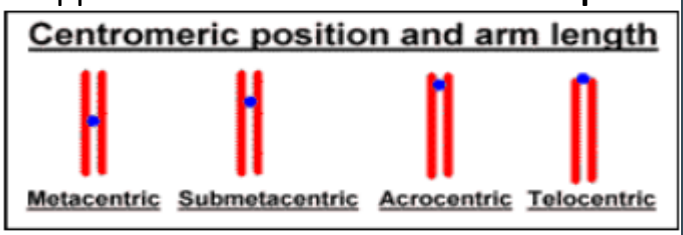


- ✓ Before S phase (i.e., DNA replication): a chromosome consists of one double-stranded DNA molecule (one chromatid), and it is STILL called a chromosome!
- ✓ At the end of S phase: a chromosome consists of two sister chromatids joined together in the center in a region called "**centromere**" (the chromatid itself is one long double-stranded DNA molecule).

- ✓ To summarize: each chromosome enters the S phase as one chromatid and comes out of it as two chromatids. Therefore, while the amount of the genetic information is doubled in the S phase, there is still the same number of chromosomes (46).
- ✓ In the **M phase** (or mitosis, cell division, etc.) DNA is **tightly packed** for easier separation of chromosomes.
- ✓ Chromosomes are only seen in M phase, particularly metaphase, which is when chromosomes are **most condensed** >>>>> **Chromosomes = condensed chromatin**. So theoretically, one can say that there are no chromosomes in the interphase, and that they only exist in M phase, because in the interphase, chromosomes are diffused chromatin.
- ✓ When you see a picture of chromosomes, you can say that this is the **M phase** and often the metaphase of mitosis (when they are most condensed).

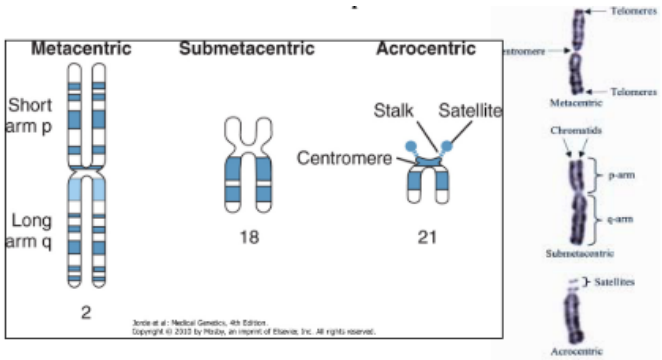
Nomenclature of chromosomes

- ✓ Chromosomes are classified based on **centromeric position and arm length.**
- ✓ There are 2 arms for each chromosome: the upper arm is **shorter** and called the **p** arm, and the lower arm is **longer** and called the **q** arm.



There are **4 types** of chromosomes:

- **Metacentric**: centromere is in the middle (p & q are not distinguishable).
- **Submetacentric**: centromere is displaced from the center (p & q are easily distinguishable).
- **Acrocentric**: there is barely a p arm.
- **Telocentric**: no p arm (it's considered an **abnormal** centromere position), normally it's not found in humans.



**** There will be a question in the exam about determining the type of chromosome, so pay attention!!*

10:00-20:00

Human chromosomes

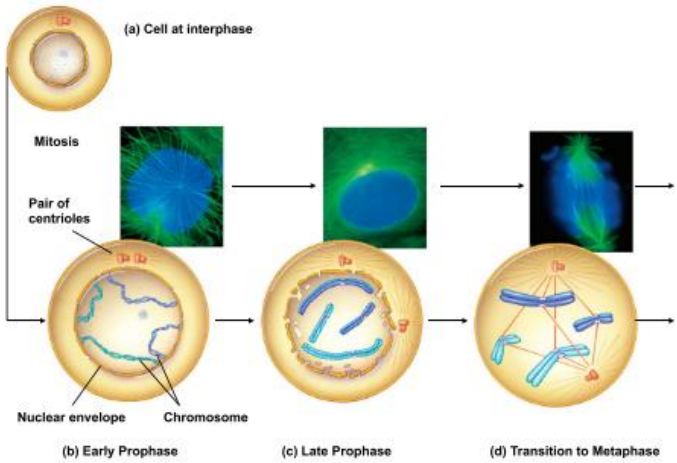
- ✓ We have 46 chromosomes in total; 23 pairs: one set from the mother and the other from the father [Maternal and paternal].
- ✓ Human somatic cells are **diploid** and have 22 pairs (autosomes), and the 23rd pair is the sex chromosome (XX or XY).
- ✓ All the cells in our bodies have 46 chromosomes, except the sex/germ cells which are **haploid** and have only 23 (22 chromosomes+ 1 sex chromosome X or Y).

Mitosis

- ✓ The division of cells to produce identical daughter cells (identical in the terms of the nucleus and DNA sequence, but not cytoplasm).
- ✓ Mitosis occurs in the zygote, the developmental process, repair, etc.
- ✓ It must happen accurately for cells to function properly.
- ✓ As we said before, prior to S phase a chromosome is one DNA molecule. And after S phase, it is 2 DNA molecules that have the same sequence (replicated) >>>> at M phase, the chromosome consists of 2 DNA molecules (2 sister chromatids).

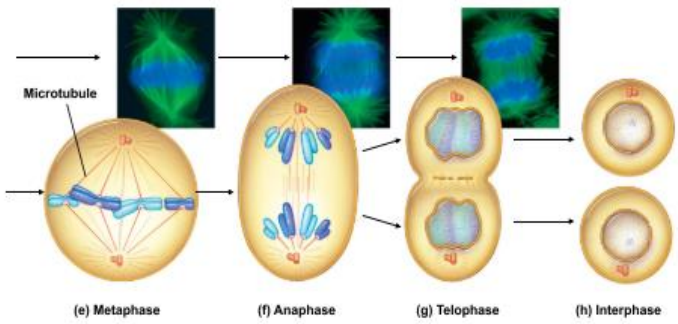
***<u>Phases</u> of mitosis (it's a continuous process but divided into distinct steps):**

1) **Prophase:** chromosomes begin to condense, nuclear envelope collapses, a pair of centrioles appears at opposite poles.
   Note: each chromosome is attached to spindle fibers at the centromere from both poles of the centrioles.
   Those fibers start from one centriole, pass through the centromeres of the chromosomes, and go to the opposite centriole.



2) **Metaphase:** each chromosome is aligned **<u>individually</u>** along the metaphase plate.

3) **Anaphase:** separation of sister chromatids (each chromatid is now called a chromosome so if we had 4 chromosomes to start with, we have 8 in this stage)
   Once the sister chromatids are separate from each other, each chromatid, by itself, is considered a chromosome.



4) **Telophase:** nuclear envelope reforms, two daughter nuclei forms, the chromosomes diffuse, and a cleavage furrow (contractile ring) forms producing two identical daughter cells in a process called cytokinesis; the division of cytoplasm.

   *** Mitosis happens during prenatal development, newborn and adult, also for tissue repair, wound healing, and proliferation of immune cells.*

Meiosis

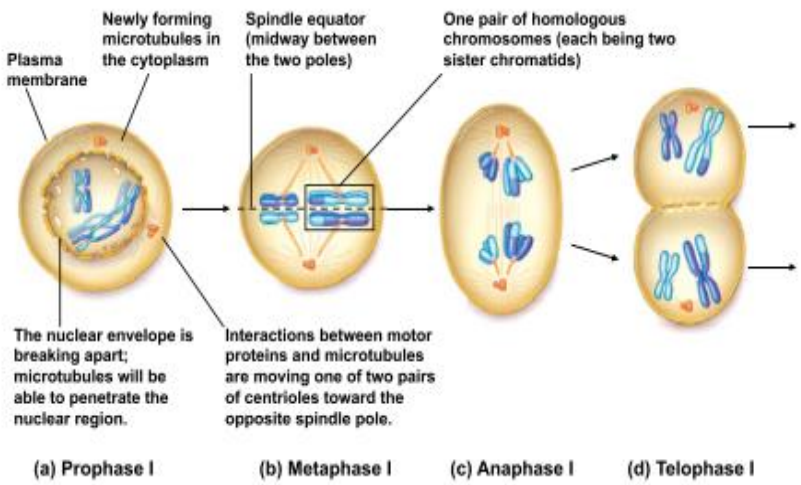
- ✓ Unlike mitosis, meiosis does not produce identical daughter cells. It gives daughter cells with half the number of chromosomes and with varying DNA sequences.
- ✓ Only happens to produce sperms and eggs.

20:00-30:00

Meiosis have 2 stages: meiosis I where the two homologous chromosomes separate, and meiosis II where the two sister chromatids separate.

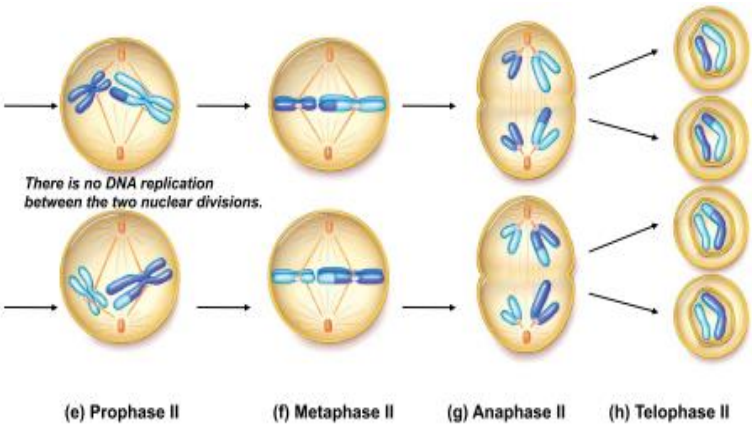
Meiosis I:

a. **Prophase I**: condensation of chromosomes, the nuclear envelope disappears, spindle fibers appear from centrioles, and centrioles migrate to the opposite poles… (prophase I is when **recombination** happens, Prophase I takes the most time out of all stages).
b. **Metaphase I**: the chromosomes are aligned **in pairs (homologs)** and each chromosome is attached to spindle fibers of only one centriole on one pole of the cell.
c. **Anaphase I:** consists of the disjunction of homologous chromosomes (and not sister chromatids), reducing the chromosomes number to half.
d. **Telophase I**: the 2 haploid cells separate. The end of meiosis I is when the haploid chromosome number is first seen.
*** Reduction of the number of chromosomes occurring in meiosis I, not in meiosis II.*



Meiosis II consists of 4 stages as the adjacent picture implies:

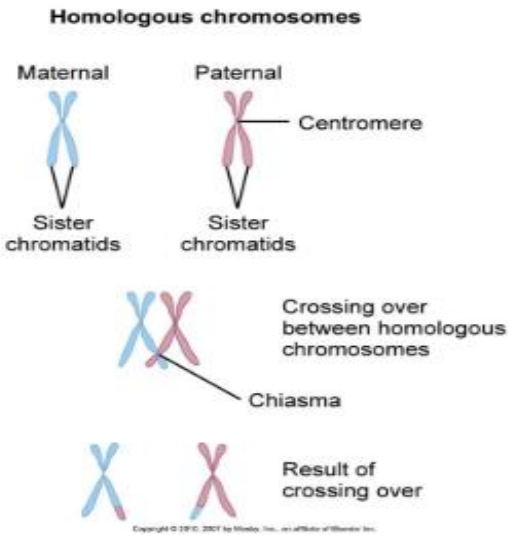
- ✓ It happens immediately after meiosis I (no interphase).
- ✓ Anaphase II: separation of sister chromatids.
- ✓ Product: 4 non-identical daughter cells (sperms/eggs)
- ✓ Meiosis II stages are the same as mitosis stages (the same things happen to the cells that enter mitosis).



** During **prophase I, recombination occurs (crossing over)** which is the exchange of genetic material between **non-sister chromatids** of **homologous chromosomes.**

Prophase I is subdivided into even Five stages: (important)

1) **Leptotene**: initiation of condensation; homologous (replicated) chromosomes align (for recombination).
2) **Zygotene**: synapsis & tetrad formation (the point of synapsis is called chiasma)
3) **Pachytene:** Synapsis is complete, and each pair of homologs is called a tetrad (bivalent)and crossing over (recombination) happens.
4) **Diplotene**: chromosomes separate but remain bound at chiasmata, why?? Because in the metaphase after a while, we need the chromosomes to be aligned as PAIRS.
5) **Diakinesis**: further condensation (until we reach the metaphase (the most condensed))

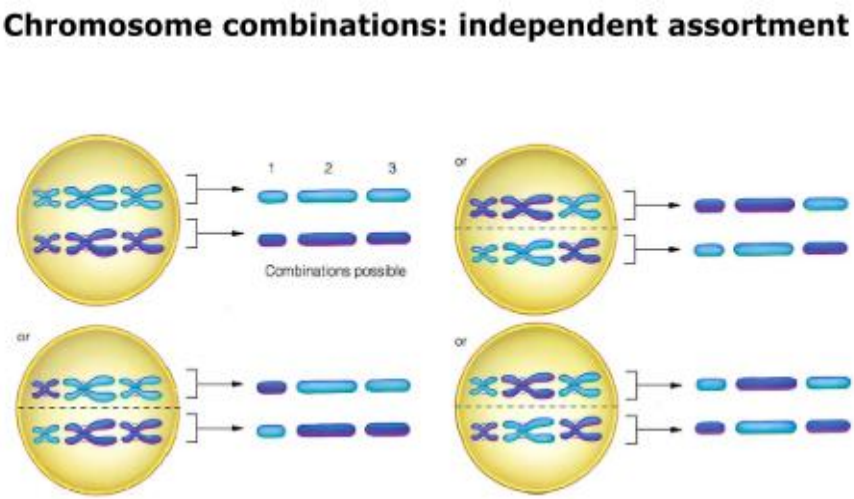


30:00-36:21

Gregor Mendel's Laws

1. **Law of Segregation** (in the context of chromosomes): each homologous chromosome will separate and appear in a different daughter cell, such that each gamete receives one allele for a given trait.
2. **Law of Independent Assortment**: chromosomes are aligned at the metaphase plate **independently** of each other, meaning that traits are inherited independently of each other.

- ✓ Each pair of homologous chromosomes is assorted independently of other pairs.
- ✓ How many different combinations of chromosomes in gametes could result from the adjacent cell? 8 combination. (the rule is 2^n where n= the number of pairs of homologous chromosomes)



Genetic consequences of meiosis:

- Reduction of chromosomes number.
- Diploid to haploid (essential for gametes).
- Random assortment of maternal and paternal chromosomes.
  - genes on different chromosomes.
  - maternal/paternal chromosomes.
  - Number of possible chromosomal combinations = 2^{23} or 8,388,608.
  - Recombination between chromosome pairs increases the possible combinations.
- Segregation of alleles.
- Recombination/crossing-over
  - Allows new combinations of genes to be produced.
  - Important for normal chromosome disjunction.
  - Ensures genetic diversity.