

Medical Genetics Course

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Lecture link: <https://youtu.be/IOovV7ZMn-I>

# History of Cytogenetics

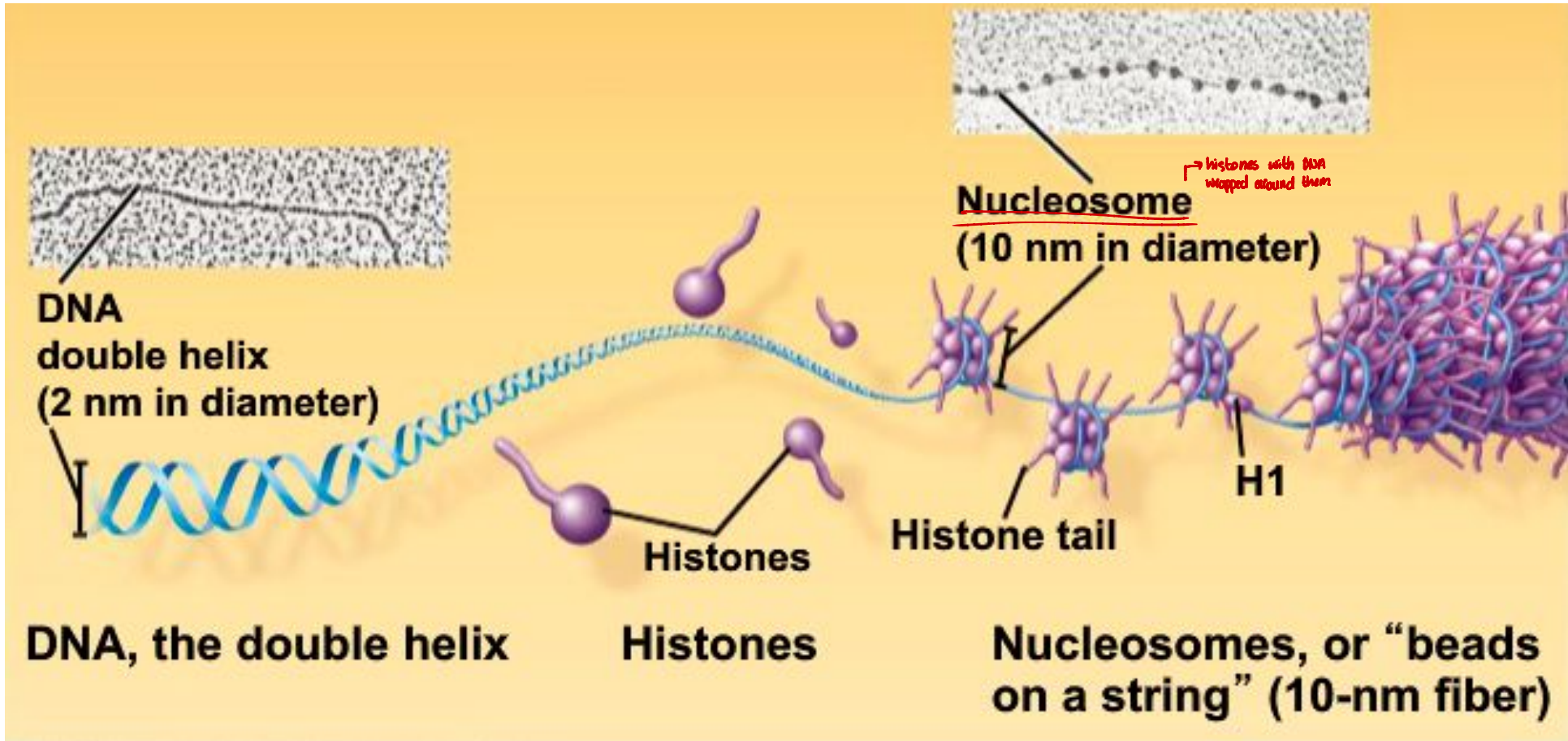
studying chromosomes &  
diseases related to chromosomal  
anomalies

True chromosome number  
established in 1956



*“ From their vantage through the microscope,  
the cytogeneticists’ view of the genome is still  
unrivalled in its scope, detail and color.”*

*Barbara J. Trask, 2002*



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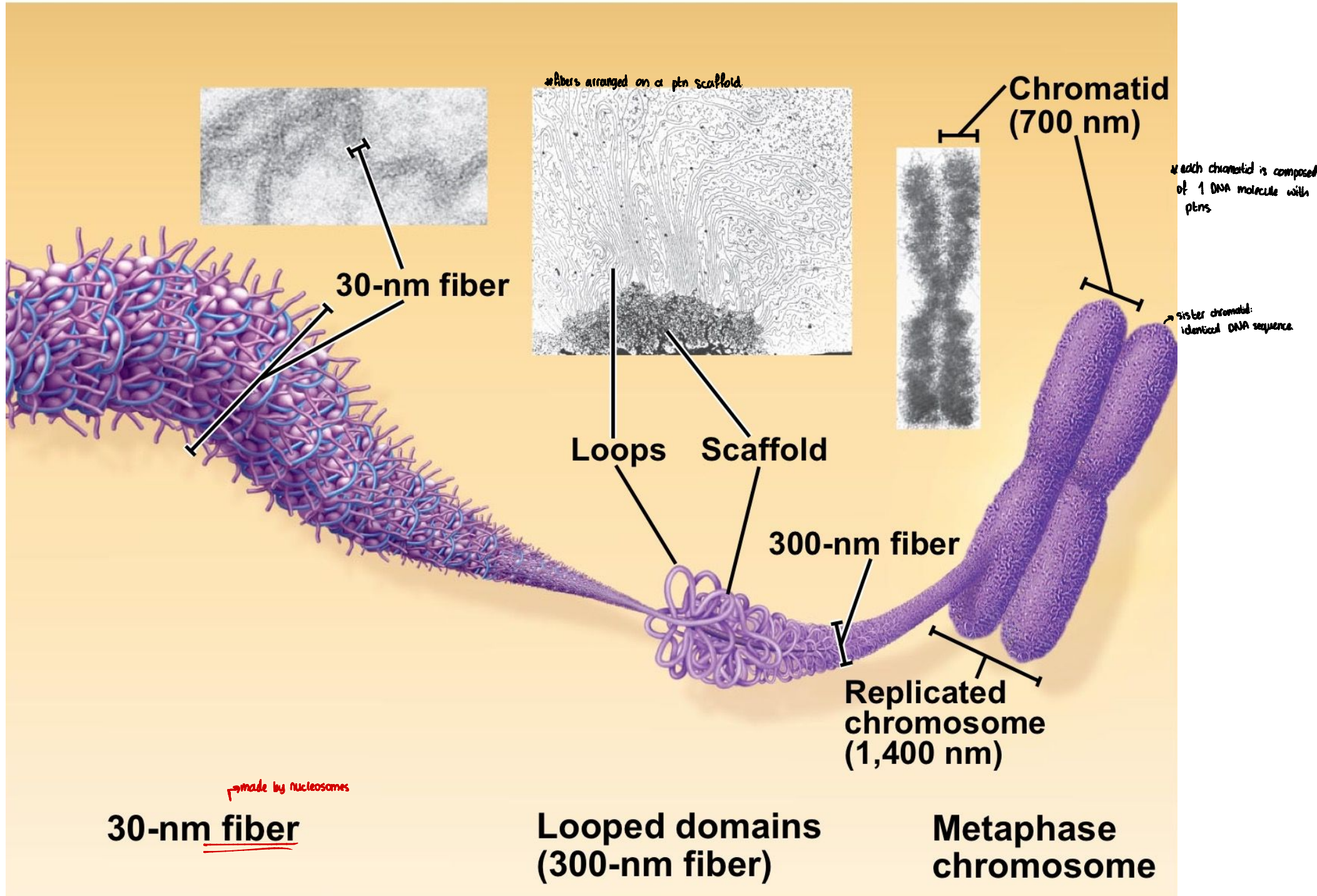
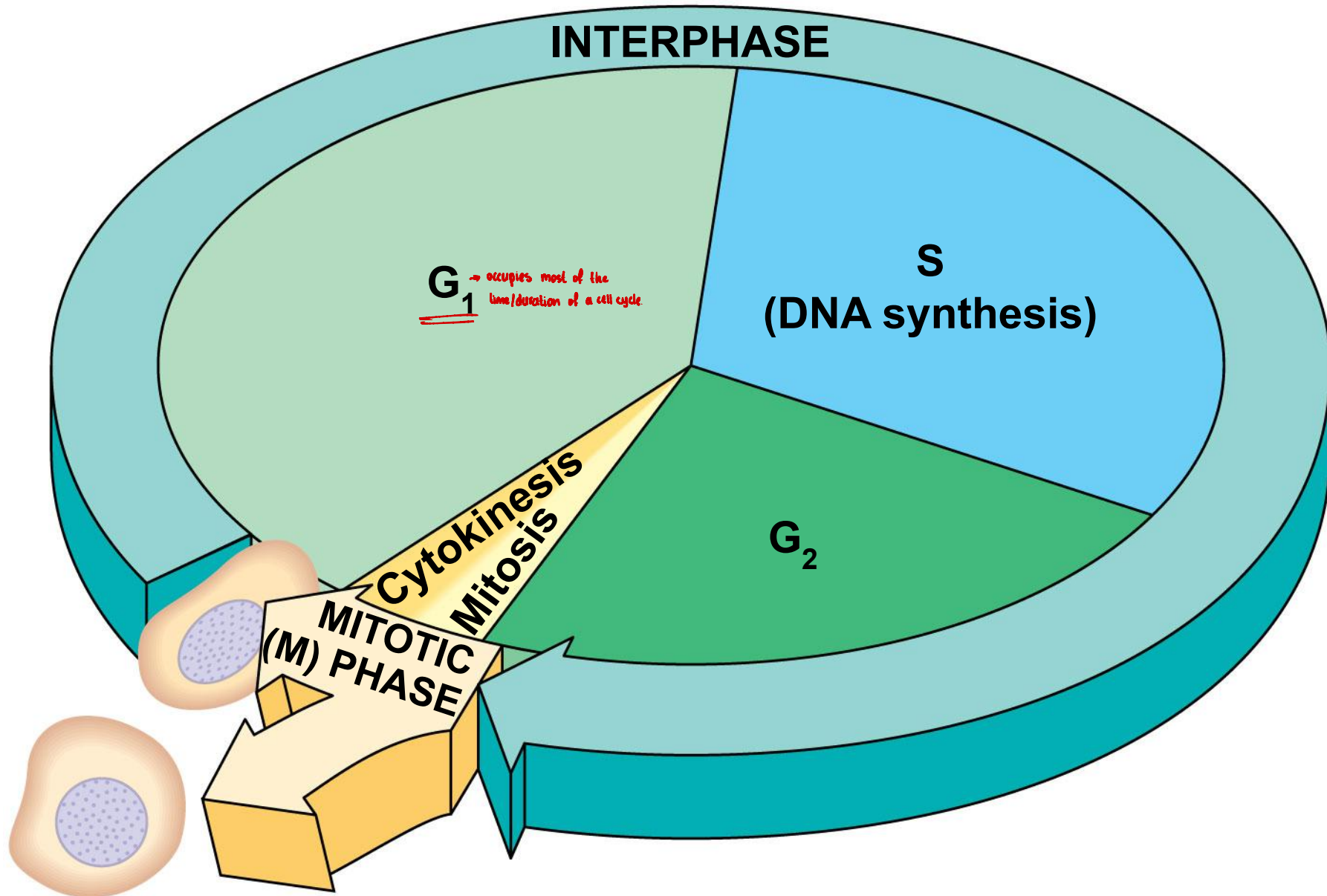


Figure 12.6

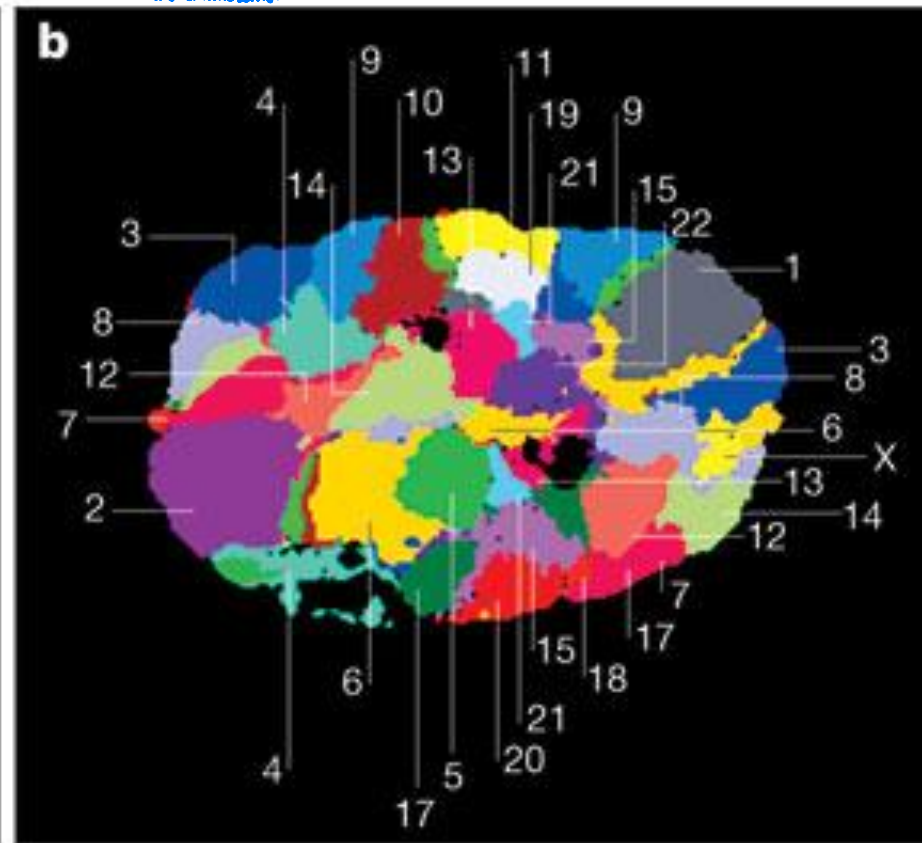
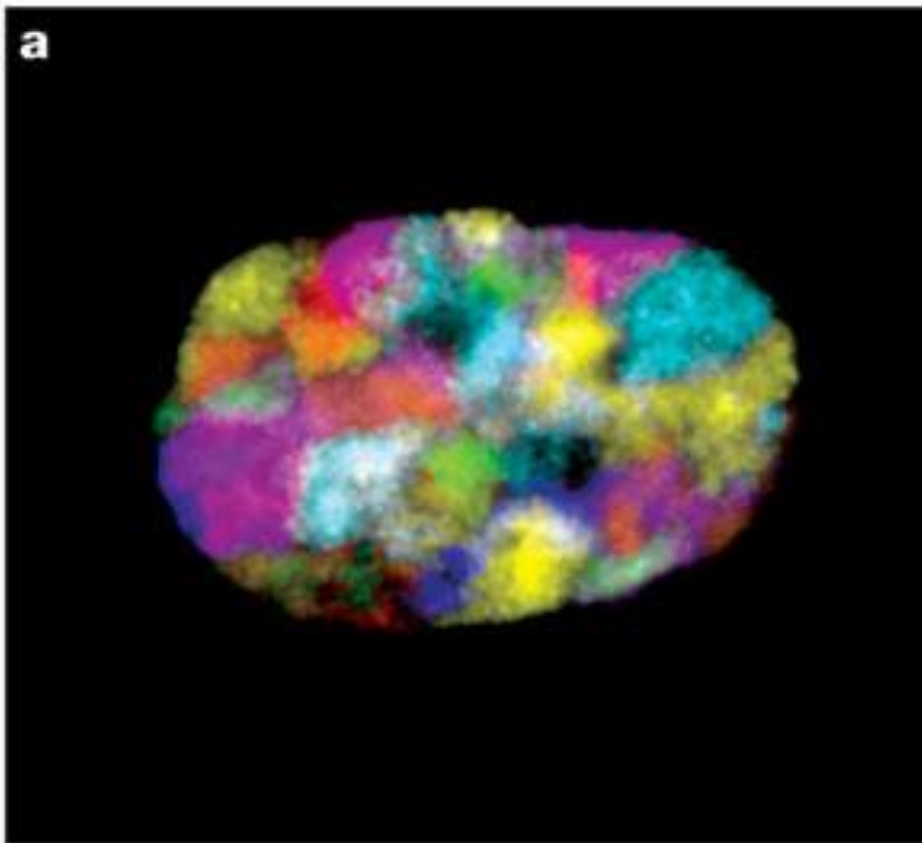
\* Cell cycle  
↳ interphase → G<sub>1</sub>  
↳ S  
↳ G<sub>2</sub>  
↳ mitotic phase



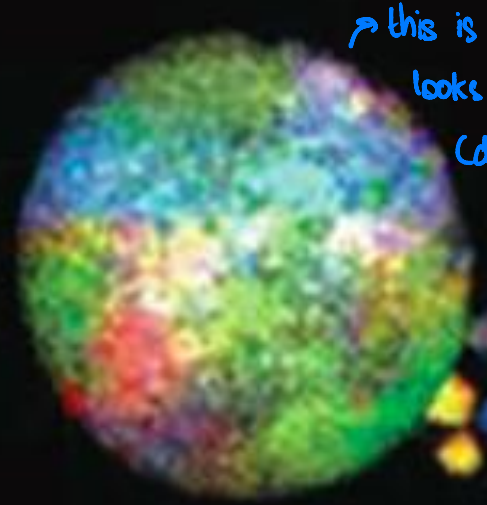
\* Chromosomes are NOT seen during interphase BUT chromatin can be seen.

\* Chromatin is the diffuse form of a chromosome

each chromosome has a unique DNA sequence → we can denature & break H-bonds of dsDNA within chromosome → Add DNA which is complementary to unique sequences on the chromosome. → this added DNA is stained with a dye (fluorophore) → this process is known as spectral karyotyping



\* Each chromosome occupies a region in the nucleus



→ this is how the nucleus looks like in the interphase (diffuse chromatin)

→ to allow for transcription & translation for protein synthesis (i.e. G<sub>1</sub> phase) & DNA replication (S phase)



→ this is how the nucleus looks like in the M phase (condensed chromosomes)

→ in order to allow proper arrangement & separation of each chromosome into daughter cells

(if misarrangement occurs it can lead to cancer or hereditary diseases)

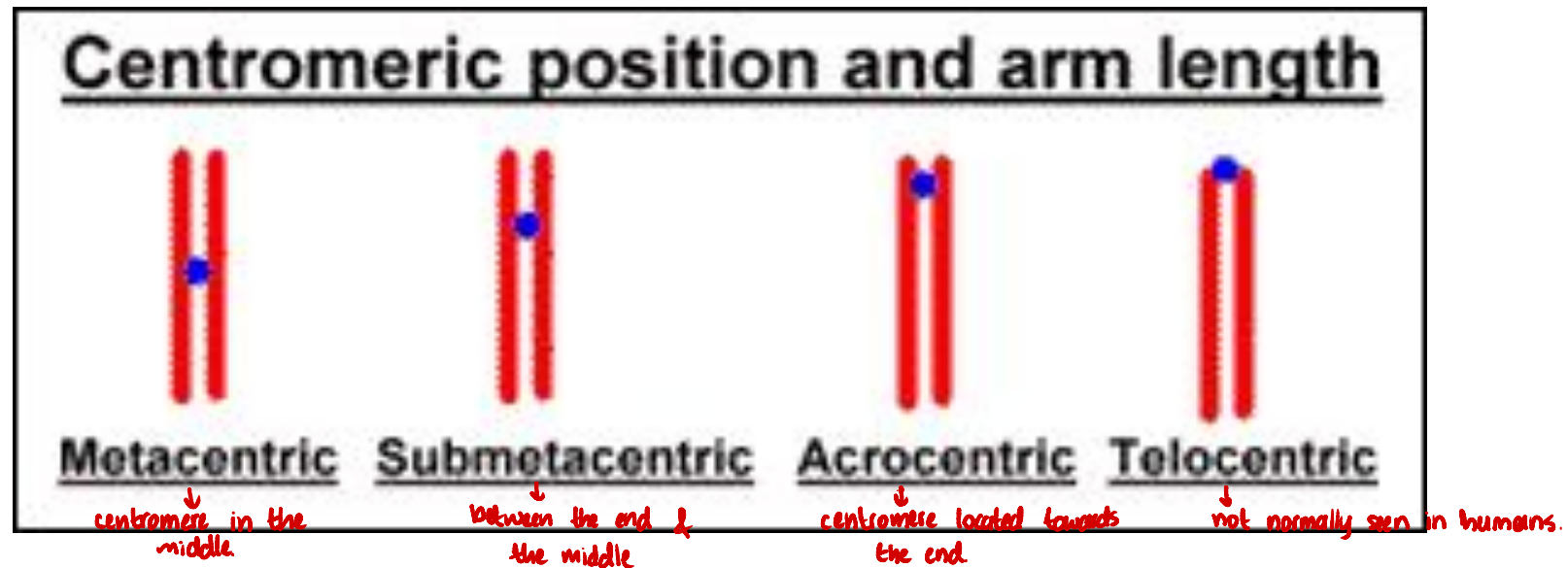
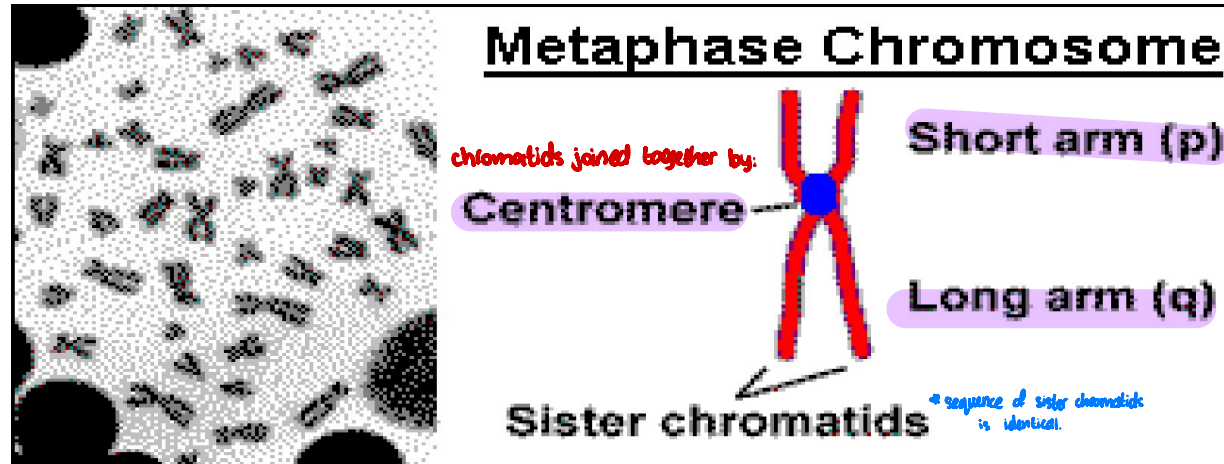
homologous chromosomes (1 from each parent)

2 sister chromatids 2 sister chromatids



\* chromosomes arranged & numbered according to size (ch. 1 is larger than others)

# Nomenclature of chromosomes

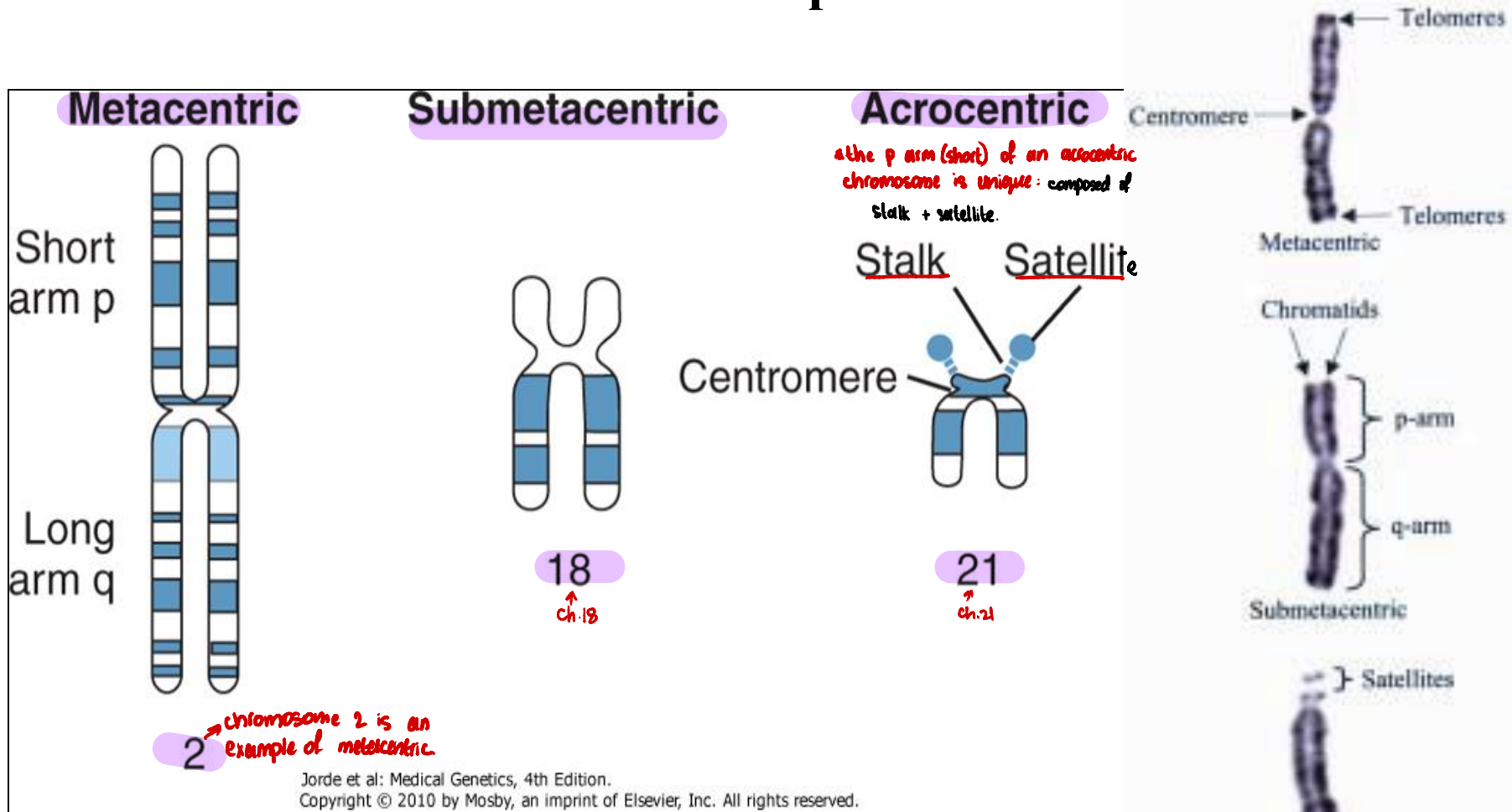


# Chromosome Shape

**Metacentric-** centromere is located in the middle of chromosome

**Submetacentric-** centromere is displaced from the center

**Acrocentric** – centromere is placed near the end



# Human chromosomes

- 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)

autosomal chromosomes

germ cells are ALL cells in our bodies EXCEPT gametes → germ cells: 46 ch. gametes: 23 ch.

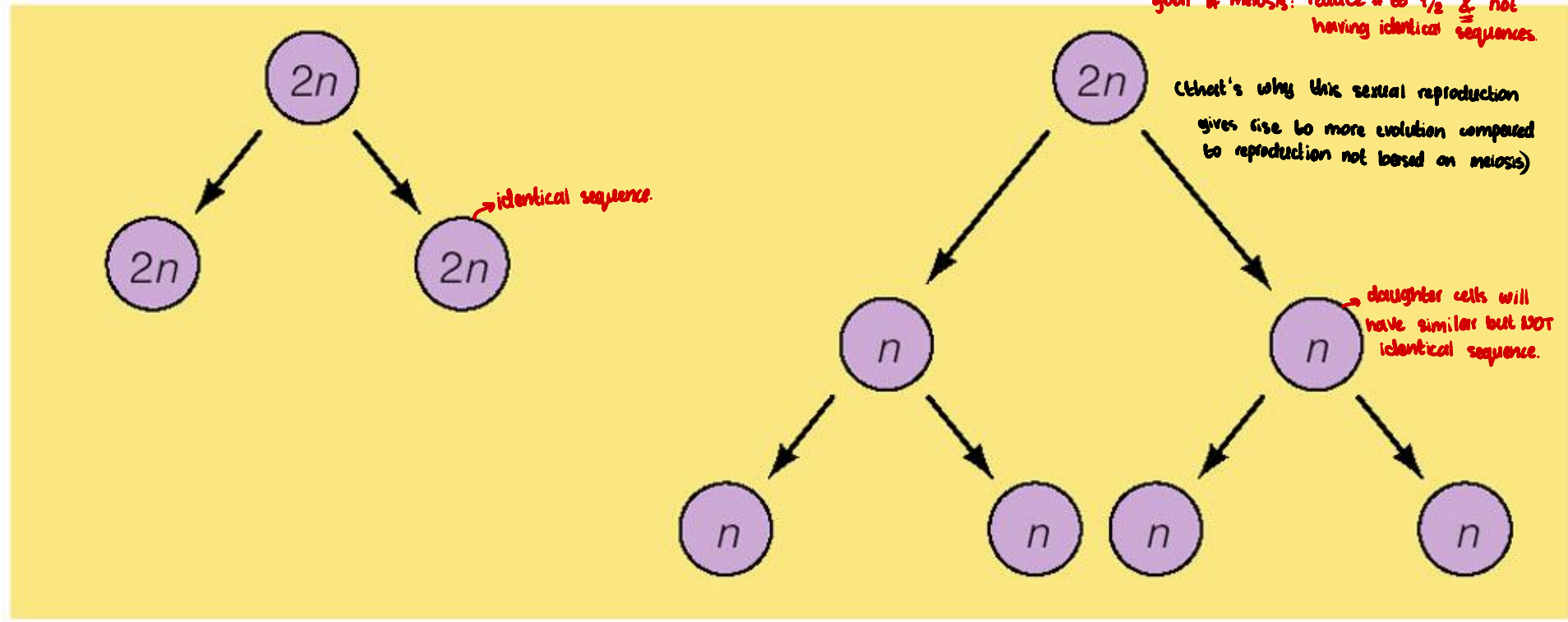
→ division resulting in an identical # of chromosomes in daughter cells

# Mitosis

→ Reduction phase: reduce # of chromosomes to 1/2

# Meiosis

46 → 23



# Interphase

- Gap 1 (G1)**— many cytoplasmic organelles are constructed; RNA, protein and other molecules are synthesized; cell almost doubles in size

*growth phase: cell is growing therefore it has \$\$\$ plus for synthesis of organelles, macromolecules, etc.*

*\* DNA in this phase has to be decondensed to allow for transcription & translation. → transcription factors + RNA polymerase can access DNA.*

*we will NOT see chromosomes, instead we see diffuse genetic material (chromatin)*
- Synthesis (S)**— DNA is replicated and chromosomes duplicate, forming 2 sister chromatids attached at the centromere

*↳ DNA polymerase & other plus (i.e. helicase, topoisomerase, etc.) need to access DNA in order to replicate it.*

*↳ DNA should be diffuse & loose*
- Gap 2 (G2)**— more cell growth; mitochondria divide; spindle precursors form

*↳ loose DNA as well*

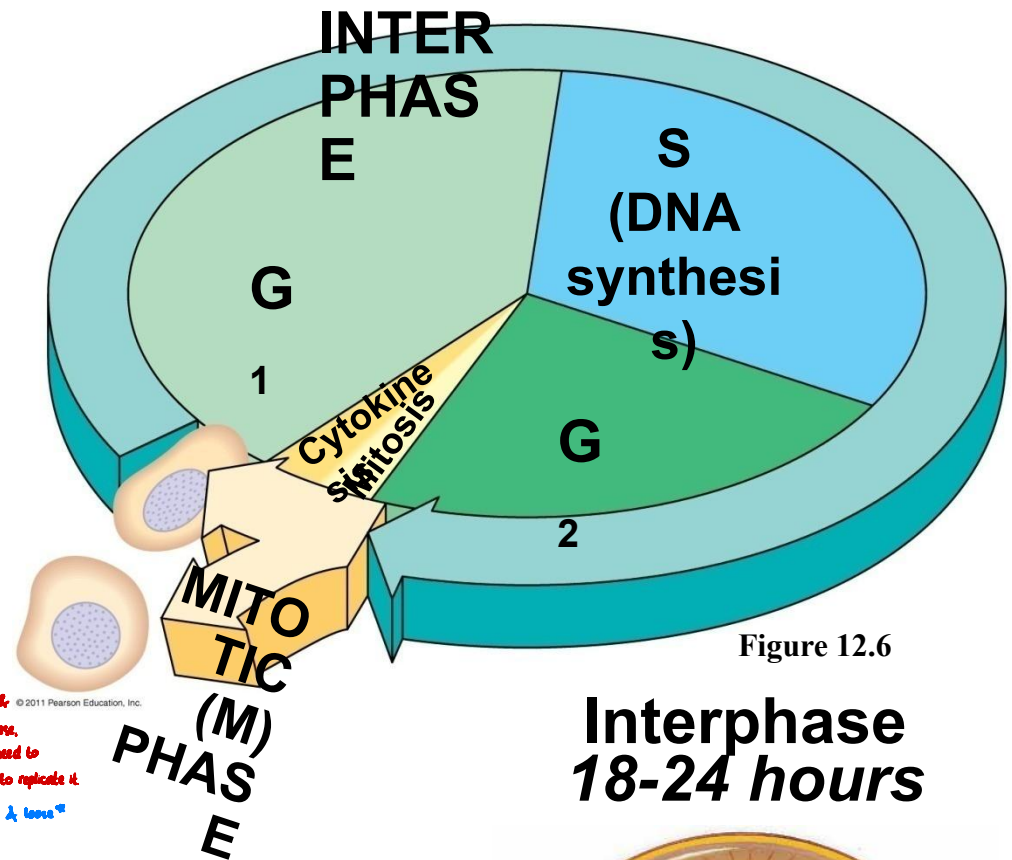


Figure 12.6

## Interphase 18-24 hours

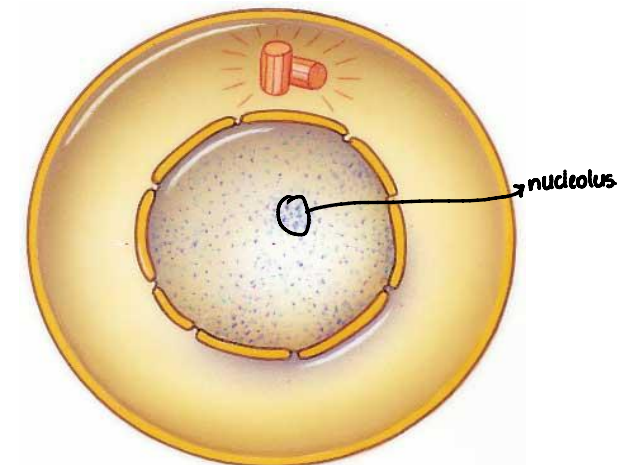
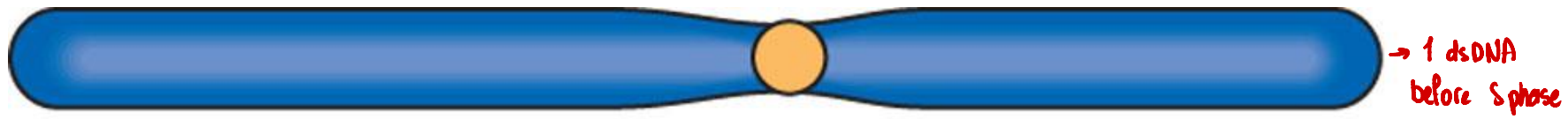
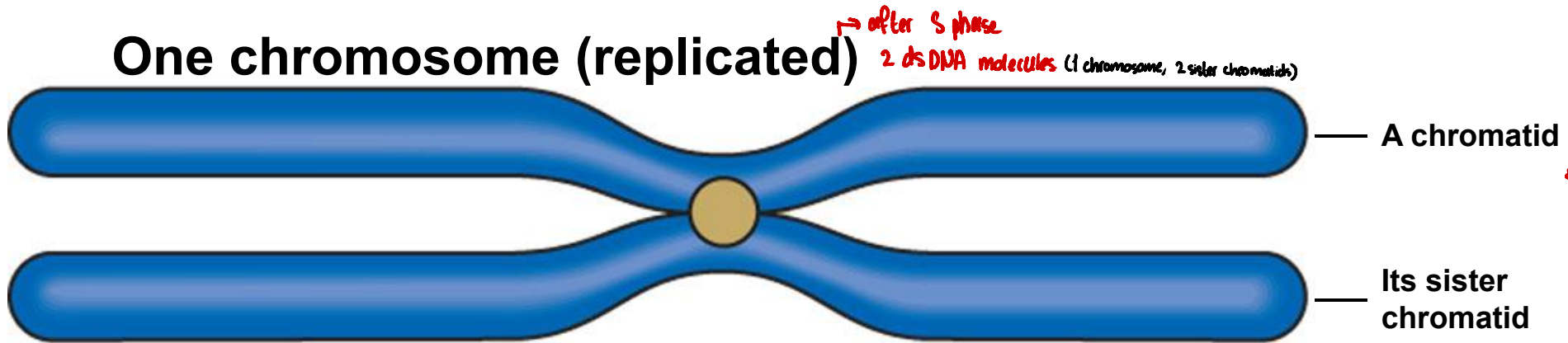


Fig. 2.8a



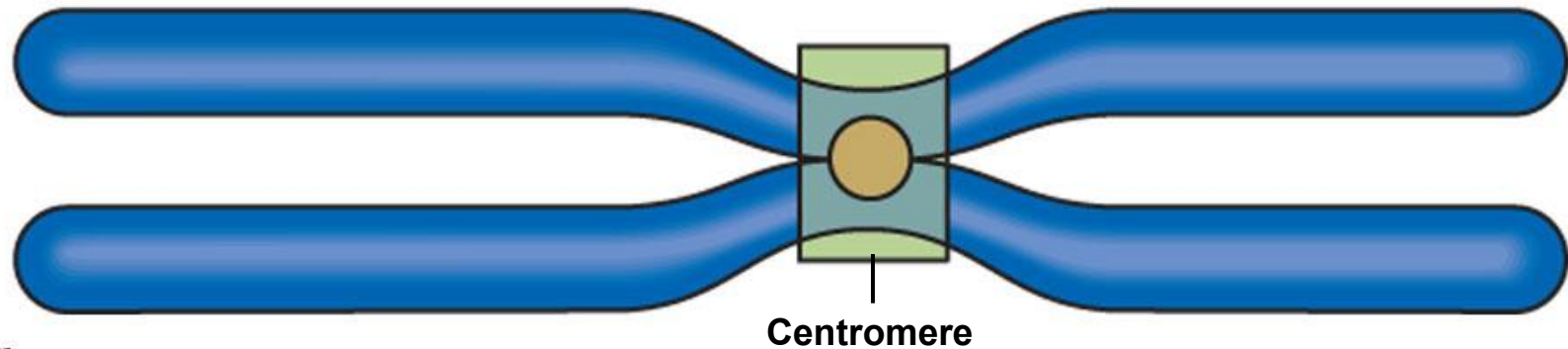
One chromosome (unreplicated)



One chromosome (replicated)

\* sister chromatids are only considered so when they are joined together.

↓  
once they separate, they will no longer be sister chromatids & each one becomes a chromosome on its own



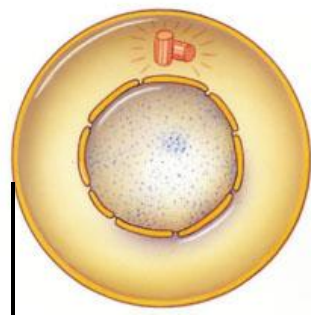
# Mitosis

- Produces identical daughter cells <sup>on a genetic level</sup>
  - (46 chromosomes)
- It must be accurate for cells to function properly
- Continuous process but divided into distinct steps:
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase

↳ there's some cytoplasmic heterogeneity in daughter cells after division (i.e. # of mitochondria, plasm..)

↳ down syndrome:  
47 chromosomes

after mitosis → 47 identical chromosomes in daughter cells  
(daughter cells will have the same numerical anomaly)

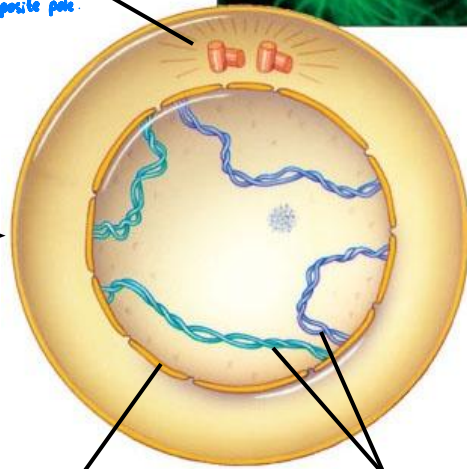
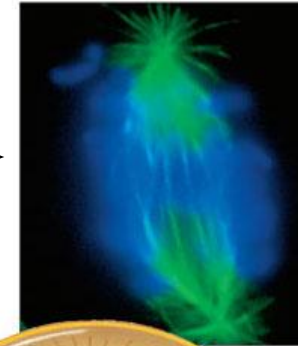
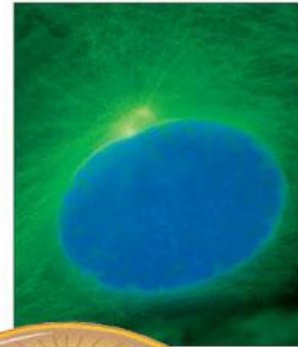
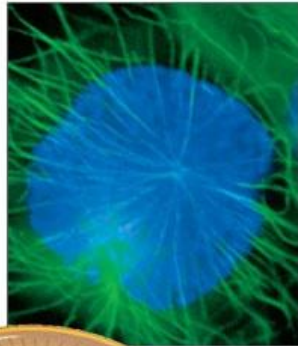


(a) Cell at interphase → x chromosomes

Mitosis

Pair of centrioles

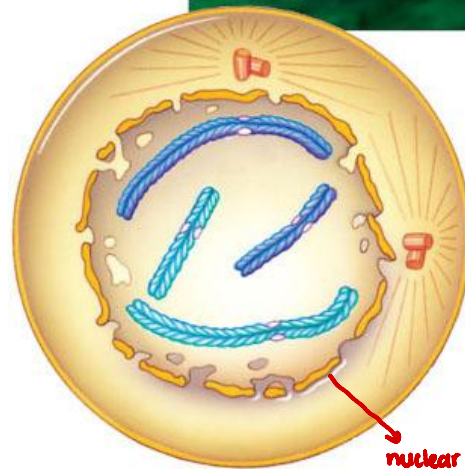
each pair will travel to the opposite pole



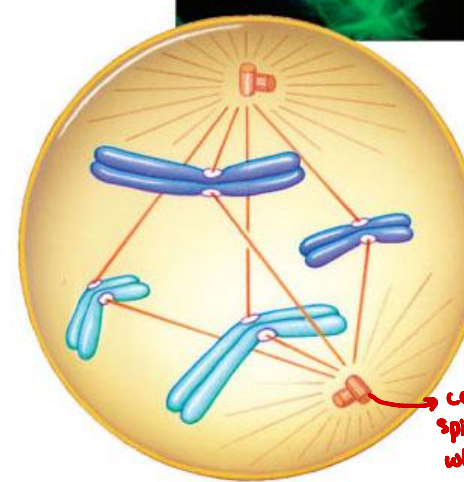
Nuclear envelope

Chromosome

start to condense & become visible



nuclear envelope starts to degrade



centriole containing spindle fibers (microtubules) which will attach to centromeres from both poles/sides

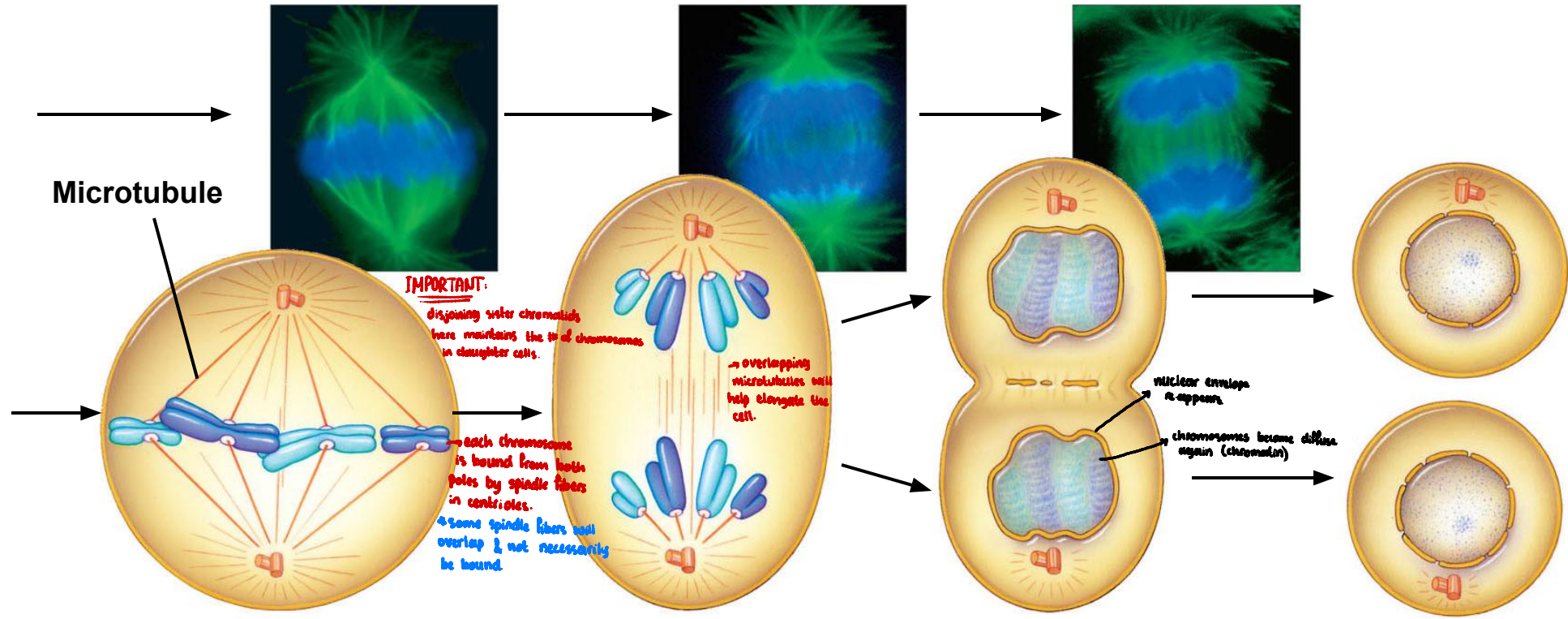


(b) Early Prophase

(c) Late Prophase

(d) Transition to Metaphase  
(still in prophase)

Stepped Art



Microtubule

**IMPORTANT:**  
 disjoining sister chromatids here maintains the # of chromosomes in daughter cells.

→ overlapping microtubules will help elongate the cell.

nuclear envelope reappears  
 chromosomes become diffuse again (chromatin)

**(e) Metaphase**

chromosomes will align individually in the middle of the cell

→ each chromosome is bound from both poles by spindle fibers in centrioles.  
 → some spindle fibers will overlap & not necessarily be bound.

**(f) Anaphase**

→ sister chromatids separate (once they separate, each one become a chromosome by itself)  
 → microtubules will pull them in opposite directions disjoining them.

**(g) Telophase**

this phase occurs in conjunction with cytokinesis (division of cytoplasm) resulting in 2 daughter cells with identical DNA material.

**(h) Interphase**

# The Stages of Meiosis

- After chromosomes duplicate, two divisions follow
  - Meiosis I (reductional division): homologs pair up and separate, resulting in two haploid daughter cells with replicated chromosomes
  - Meiosis II (equational division) sister chromatids separate
- The result is four haploid daughter cells with unreplicated chromosomes

Figure 13.7-1

## Interphase

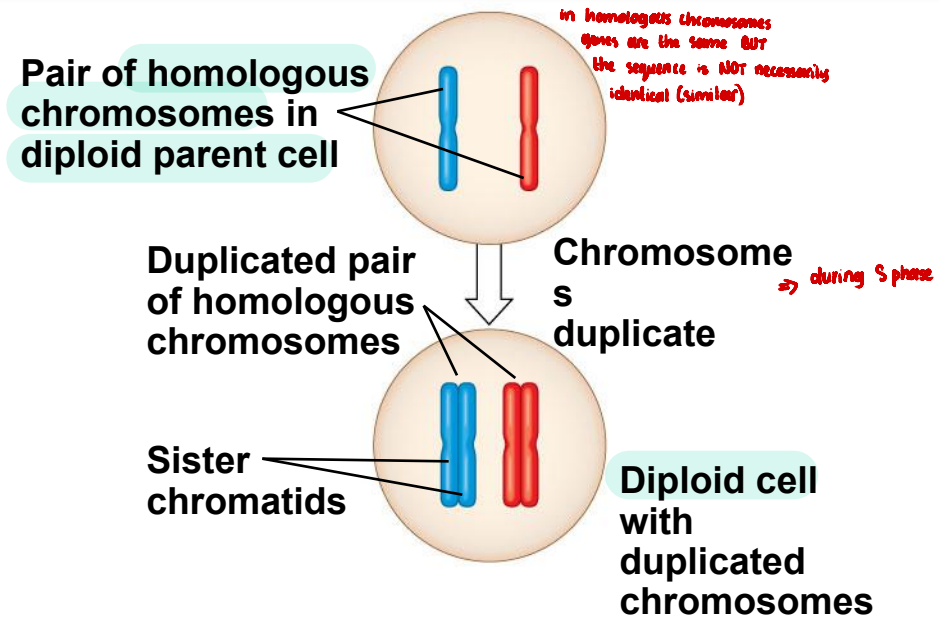


Figure 13.7-2

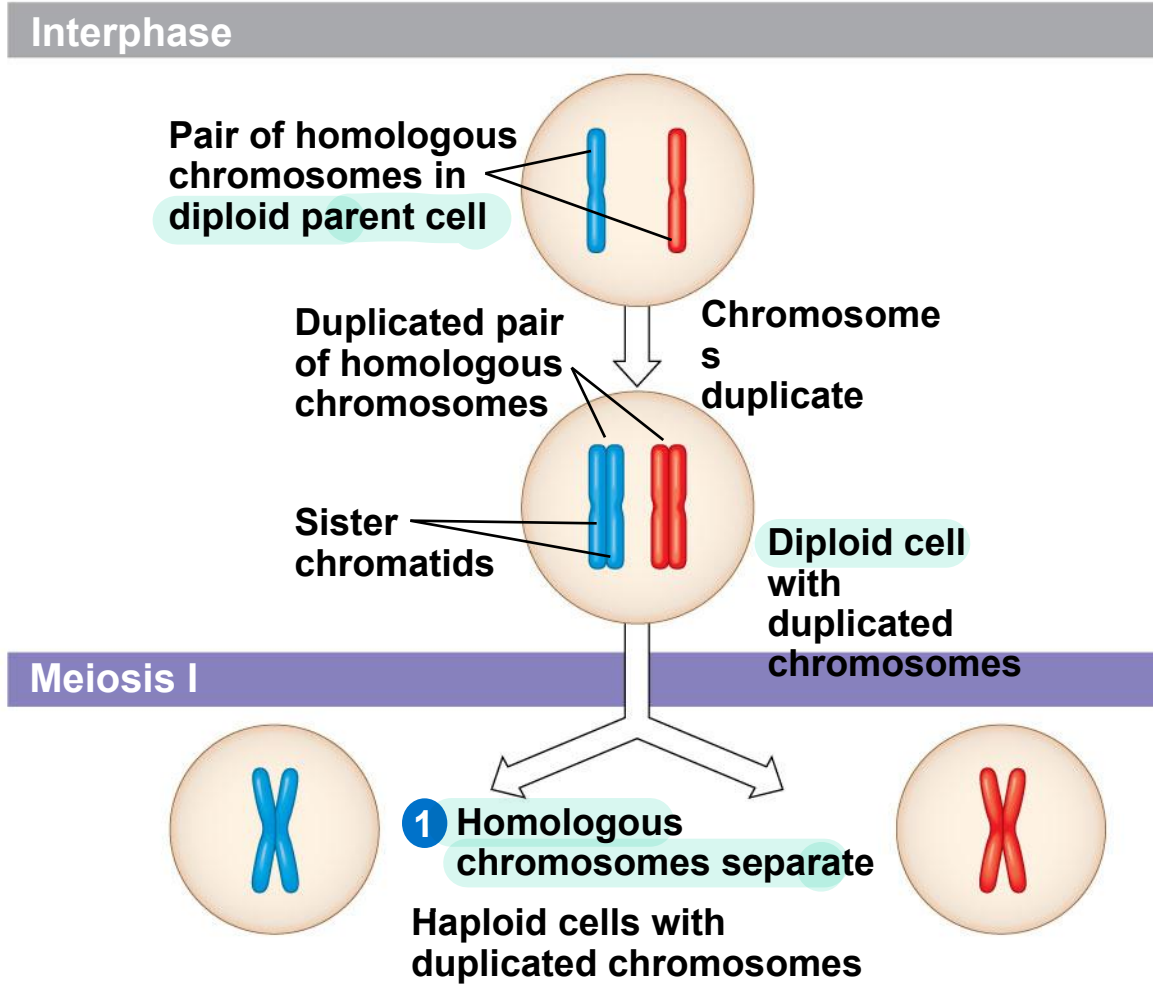
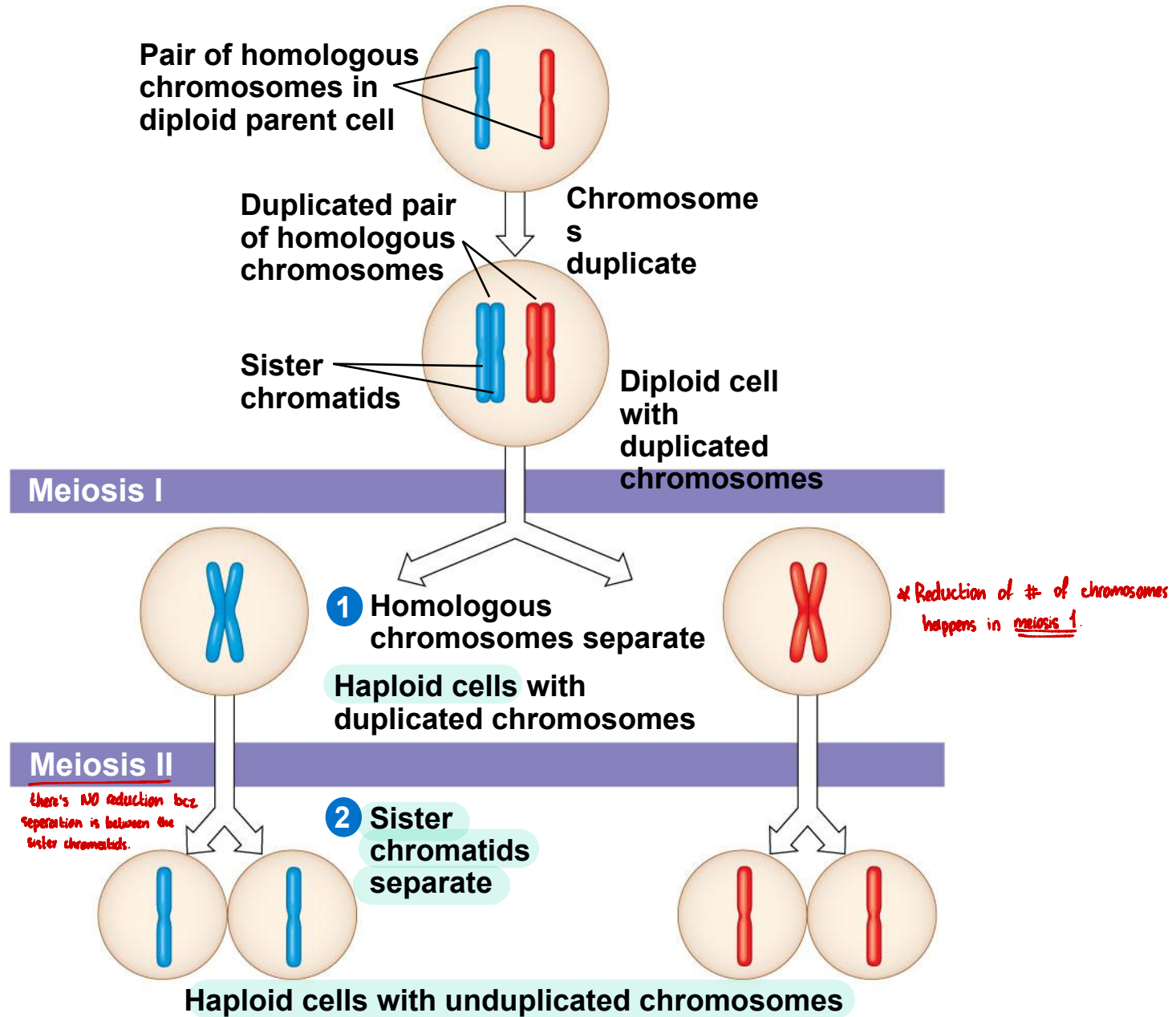


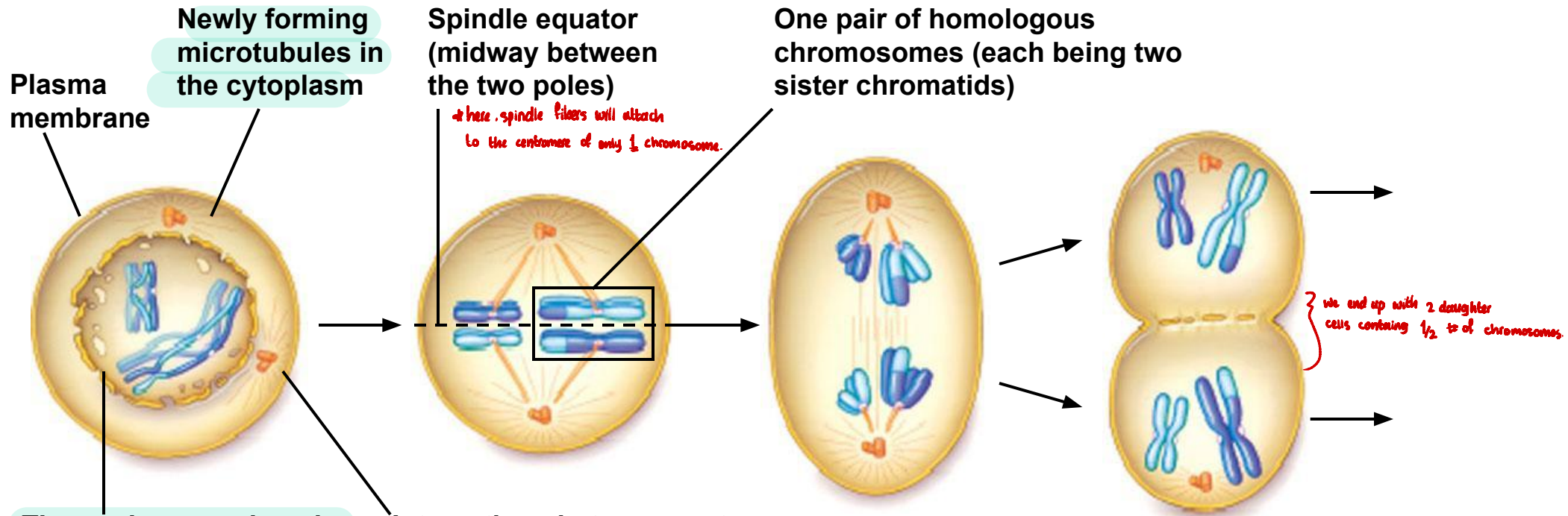
Figure 13.7-3

## Interphase



# Meiosis I

→ similar to mitosis with some differences.



The nuclear envelope is breaking apart; microtubules will be able to penetrate the nuclear region.

Interactions between motor proteins and microtubules are moving one of two pairs of centrioles toward the opposite spindle pole.

→ here, spindle fibers will attach to the centromere of only 1 chromosome.

we end up with 2 daughter cells containing 1/2 of chromosomes.

(a) Prophase I

↳ recombination (crossing-over) is a unique process that takes place in meiotic prophase I

(b) Metaphase I

chromosomes align as pair in the midline (in mitosis they align individually)

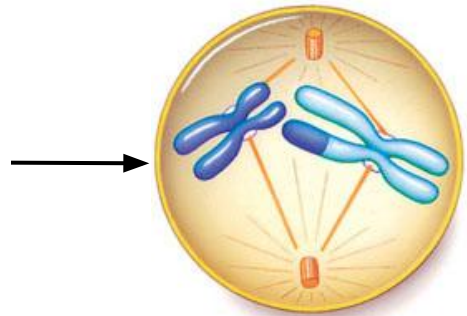
(c) Anaphase I

disjoining of homologous chromosomes

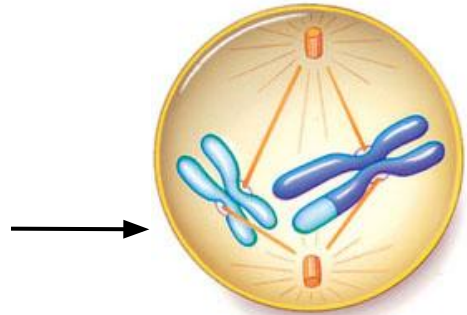
(d) Telophase I

# Meiosis II

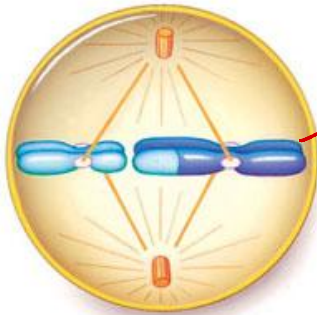
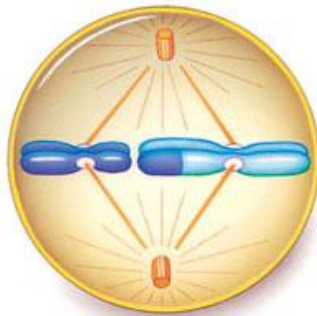
Meiosis II proceeds w/o an interphase before (immediately)



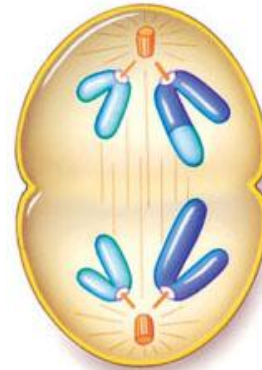
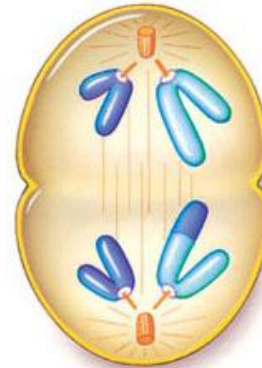
There is no DNA replication between the two nuclear divisions.



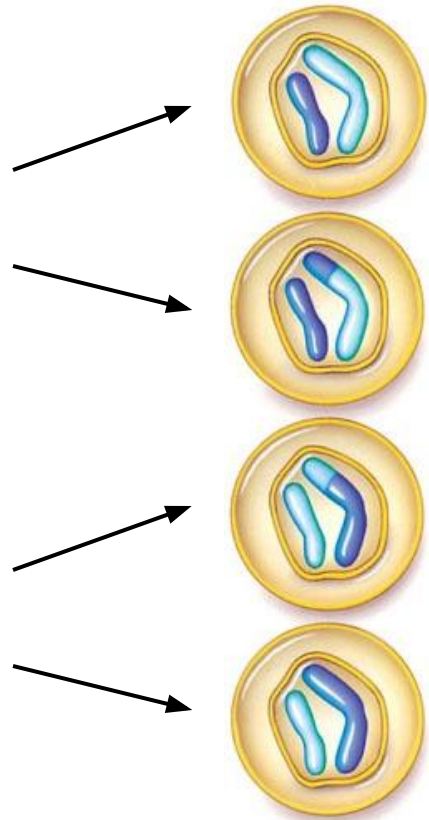
(e) Prophase II



(f) Metaphase II

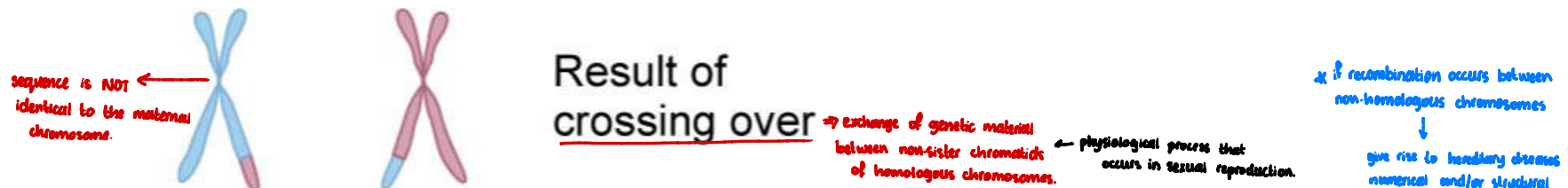
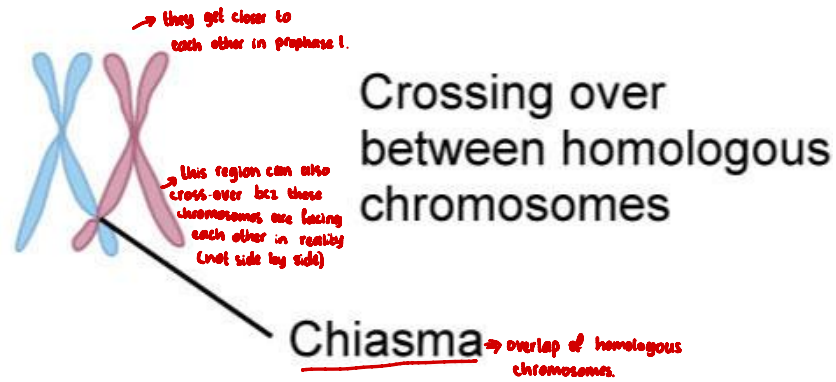
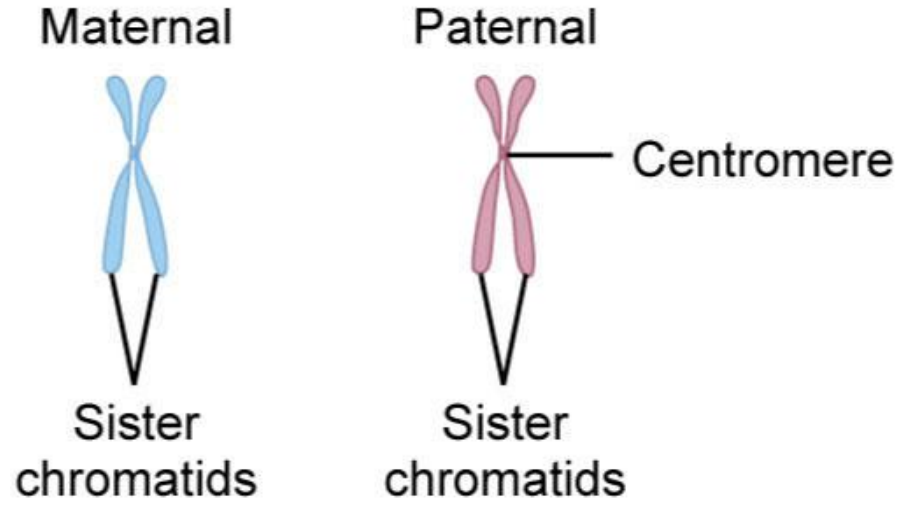


(g) Anaphase II  
↳ separation of sister chromatids



(h) Telophase II

# Homologous chromosomes

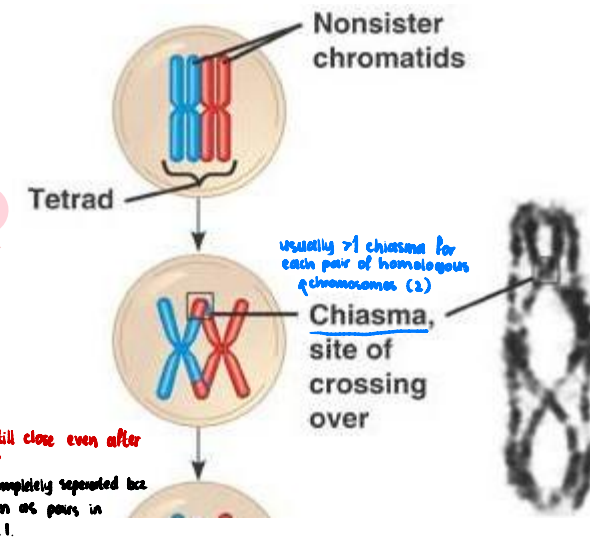
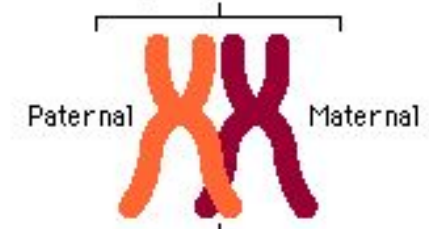


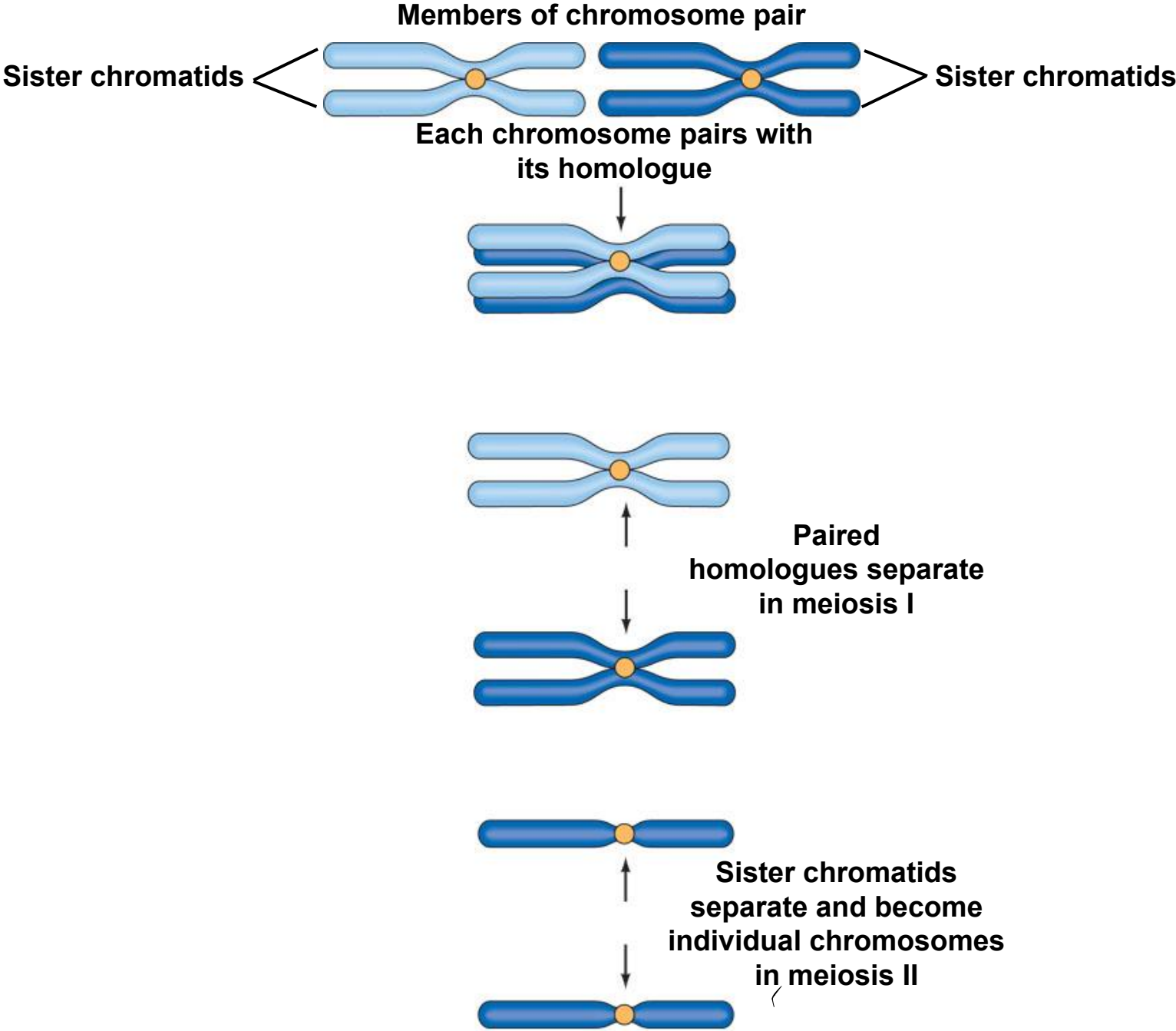
# Prophase I

\* recombination is subdivided into categories:

- **Leptotene**
  - Replicated chromosomes align and begin to condense condensation of chromatin → chromosomes.
- **Zygotene**
  - homologous chromosomes pair along entire length (**synapsis**)
  - synaptonemal complex forms
- **Pachytene**
  - Synapsis is complete and each pair of homologues is called a **tetrads (bivalent)** → they appear as 4 chromatids. (started in zygotene BUT visibly clearer in pachytene)
  - **Crossing over** occurs (recombination at **chiasmata**)
- **Diplotene**
  - Homologous chromosomes separate some but remain bound at chiasmata
    - usually 2 chiasmata/chromosome, more frequent in females) during oogenesis.
- **Diakinesis** can still be seen.
  - Further chromosome condensation; tetrads viable

Synapsis: Pairing of homologous chromosomes





# Genetic consequences of meiosis

- Reduction of chromosome number
- Diploid to haploid (essential for gametes)  
they will carry 1 set of chromosomes.  
22 autosomes + 1 sex chromosome.
- Random assortment of maternal and paternal chromosomes  
(next slide)
  - genes on different chromosomes
  - maternal/paternal chromosomes
  - Number of possible chromosomal combinations =  $2^{23}$  or 8,388,608  
→ for a primordial cell to generate a sperm cell  
> 8.4 million sperms should be made in order to find 2 sperms → same goes for oogenesis  
with the combination (assortment) of chromosomes
  - 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

# Chromosome combinations: independent assortment

4 combination possibilities

Random alignment of paternal & maternal chromosomes.

4 in this example:  
6 chromosomes  
combinations possible = 8 different combinations

$2^n$  →  $n=23$  in humans

