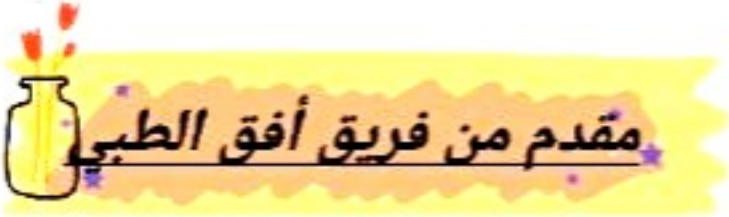

مقدم من فريق أفق الطبي


جامعة الأزهر - غزة
AL-AZHAR UNIVERSITY - GAZA
1412-1991


حركة الشبيبة الفتحاوية
جامعة الأزهر
Fateh Youth Movement

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

Histology

CYTOGENETICS

Notes BY

DR/ABDELWAHAB

@drabdelwahabb1

وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ ۚ وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا

cell cycle

- series of events within the cell that prepare the cell for dividing into two daughter cells

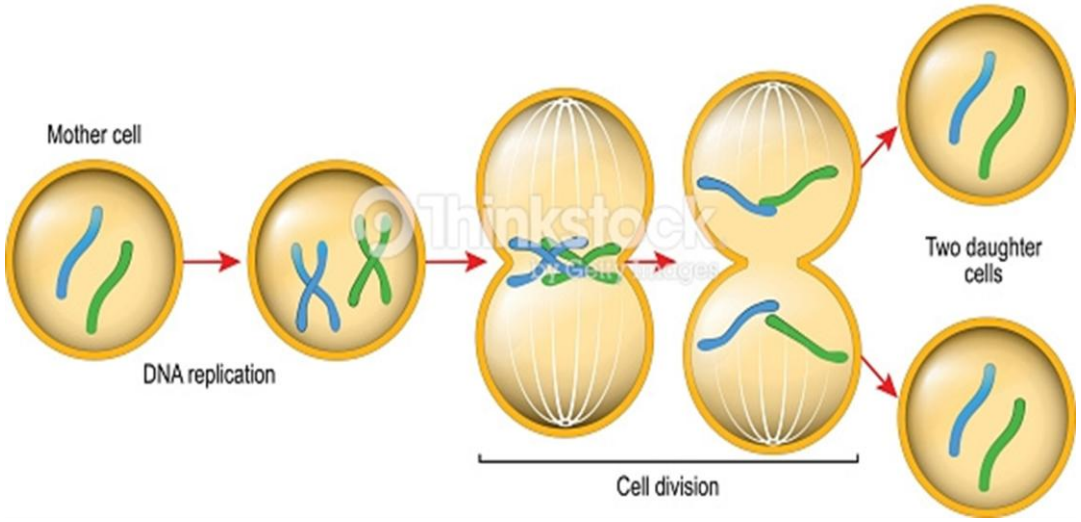
Two phases :

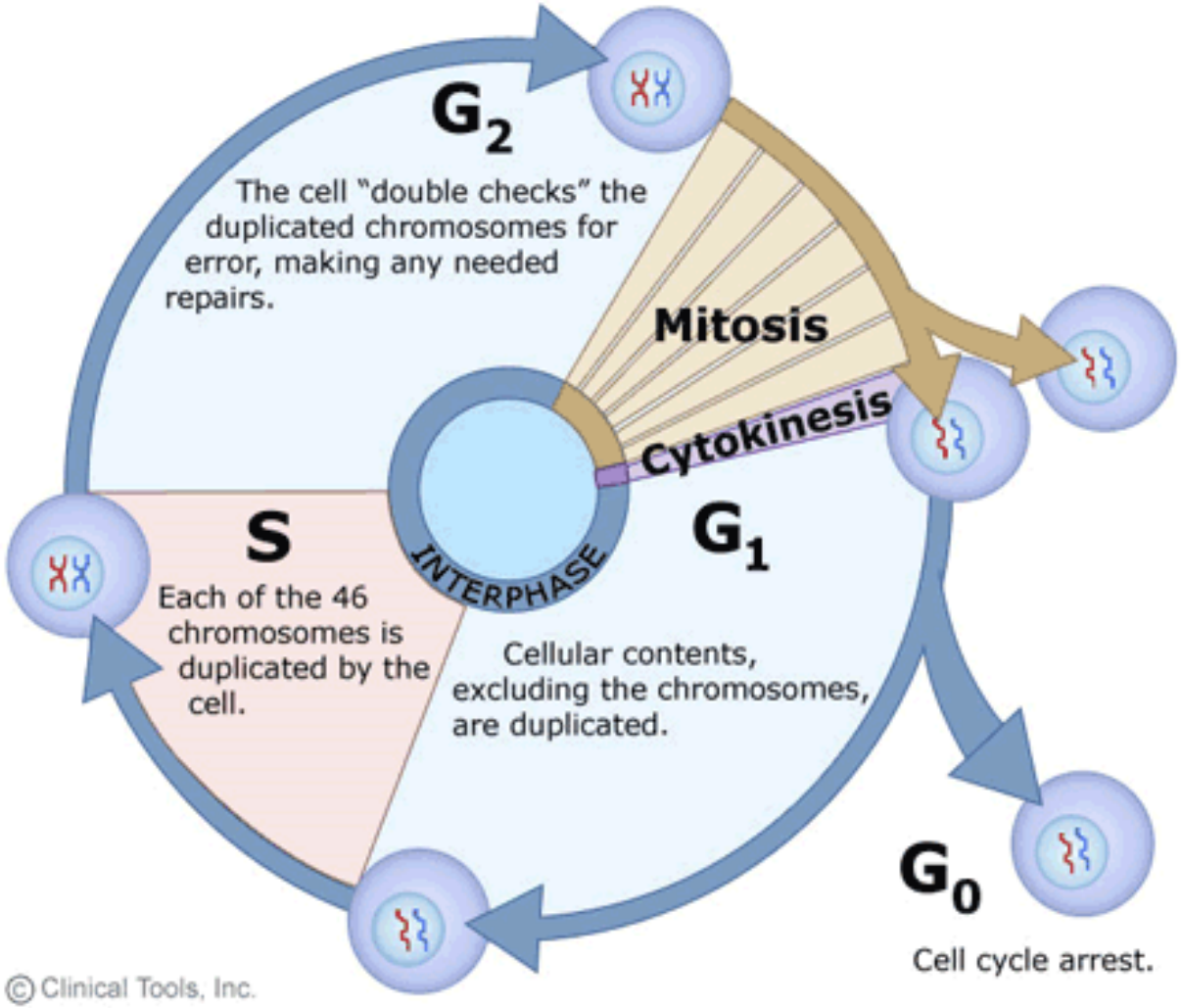
- ***Mitosis***:

- period in which the cell divides into 2 daughter cells
- lasts for short period (one hour)
- Changes are visible with microscope

- ***Interphase***:

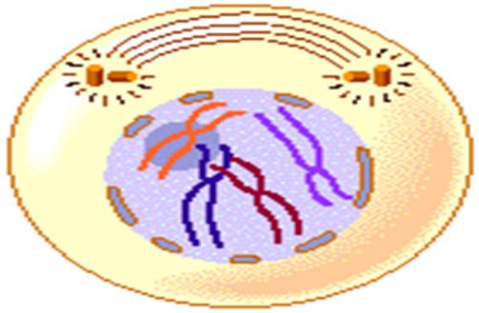
- period between two successive divisions
- lasts for 20 hours in rapidly dividing cells
- Changes cannot be detected with microscope





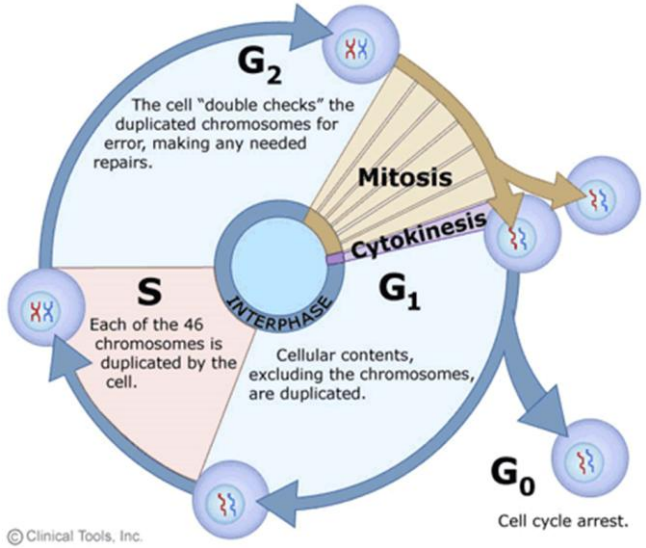
interphase is subdivided into three phases:

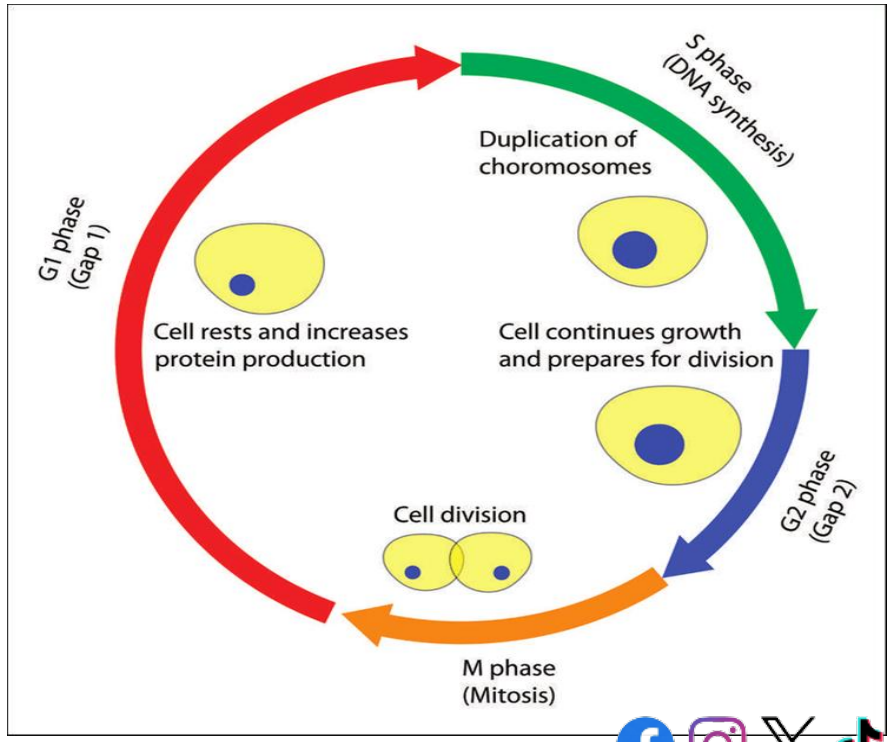
- **Gap 1 phase (GI phase):** *8 hours*
  - **cells become specialized working cells**
  The more specialized the cell, the longer the G1 -phase & the less rate of division
  It varies in duration depending on the rate of cell division and specialization (differentiation)
  - **cell Nucleus** contains **46 single chromosomes (s-chromosomes or chromatids)**
  - **cells grow in size & acquire energy (ATP)**
  - **RNA & protein synthesis required for duplication of DNA**
- **Synthesis phase (S phase):** *8 hours*
  - ***duplication***
  - **DNA** so each cell contains **46 d- chromosomes**
  - **centrioles**
- **Gap 2 phase (G2 phase):** *4 hours*
  - **Any error in DNA duplication (replication) is corrected**
  - ***for mitosis***
  - **RNA & protein synthesis**
  - **Tubulin is formed to build microtubules**
  - **Energy is stored**



Stable phase (GO phase):

- **Cells that have left the cell cycle**
- **in resting stage - GO (outside) phase - stable phase**





Cell Renewal

- Most of the working specialized cells are not in an active cycle

They perform their specific functions in prolonged GI phase

▶ **Specialized cells are classified according to their ability to reproduce themselves into:**

- **Non-renewing cells:**

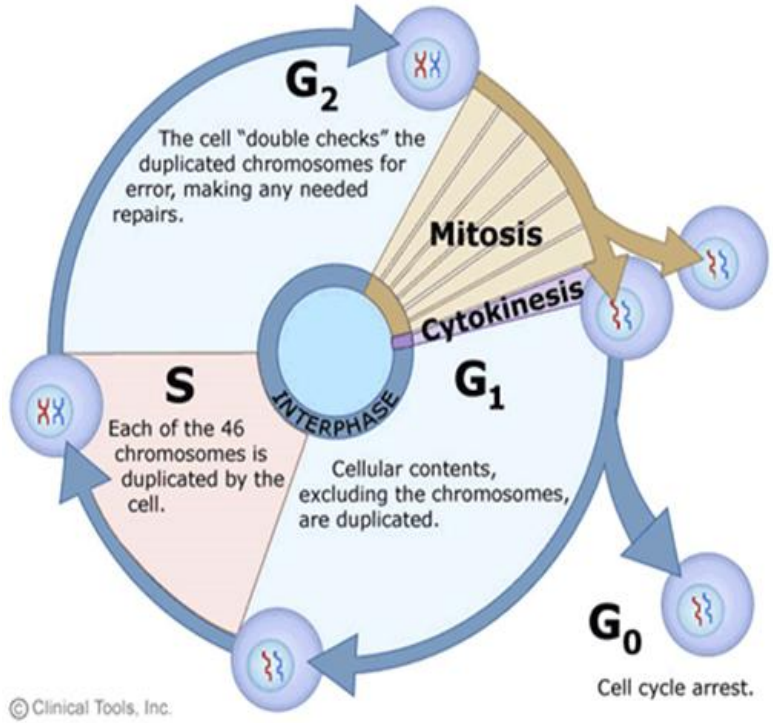
- Highly specialized cells leave cycle in GI forever & go to GO
  - never divide again (permanent exit)
  - If lost → not replaced with new cell
  - heart muscles - nerve cells

- **Potentially renewable cells:**

- Some specialized cells go to GO
  - can return to continue the cycle on need for replacement (transient exit)
  - liver cells (if destroyed or partially removed)

- **Continuously renewing cells:**

- Some highly specialized cells
  - end cells (cannot divide)
  - can be replaced from stem cells (blood cells - sperms)



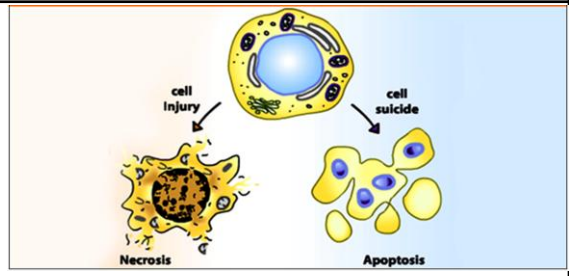
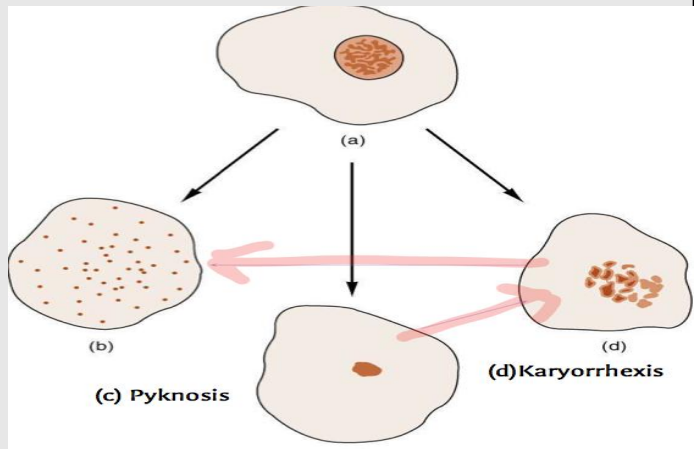
Stem Cells

- Undifferentiated cells that capable of self renewal

▶ **two types:**

- **Pluripotential or multipotential stem cells:**
  - have potential to produce more than one type of specialized cells
    - blood cells
    - cells lining gastro-intestinal tract
- **Unipotential stem cells:**
  - have potential to produce only one type of specialized cells
    - male germ cells

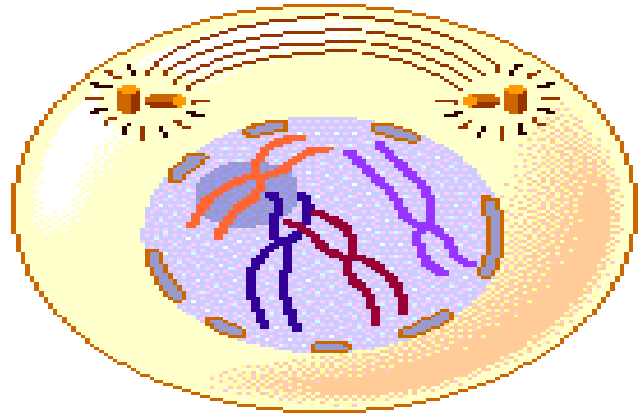
Cell Death

	Necrosis	Apoptosis
Definition	- Results from *anoxia - mechanical injury - exposure to toxins* - pathological condition	- active programmed cell death *occuring normally at end of cell life span* - pathological or Physiological
LM	**- Necrotic cells and their organelles:** • swell • burst releasing their content into extracellular space	**- Apoptotic cells:** • don't swell • decrease in size 
	nuclei & chromatin: • ***Pyknosis:*** Nuclei are small darkly sained with condensed chromatin • ***Karyorrhexis:*** fragmented into pieces by endonuclease enzyme • ***Karyolysis:*** dissolve then disappear	
Fate	Cells ***degenerate*** Phagocytosed by macrophages	Cells break into ***large vesicles*** Phagocytosed by macrophages

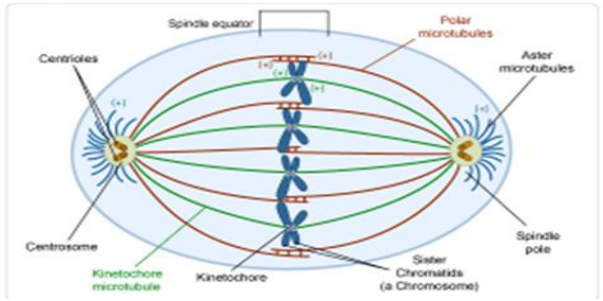
CELL DIVISION

1)Mitosis:

- Division of nucleus to produce 2 daughter cells genetically identical to parent cell

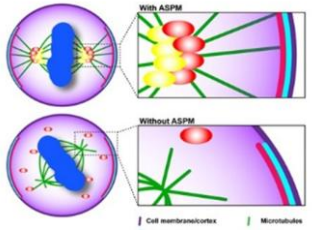


▶ **4 stages:**



- **Prophase:**
  - Chromosomes (46 d- chromosomes) *gradually become* ***shorter & darker*** ***(visible as fine threads)***
  - **disappearance of nucleoli & nuclear envelope**
  - **Centrioles move to opposite cell poles**

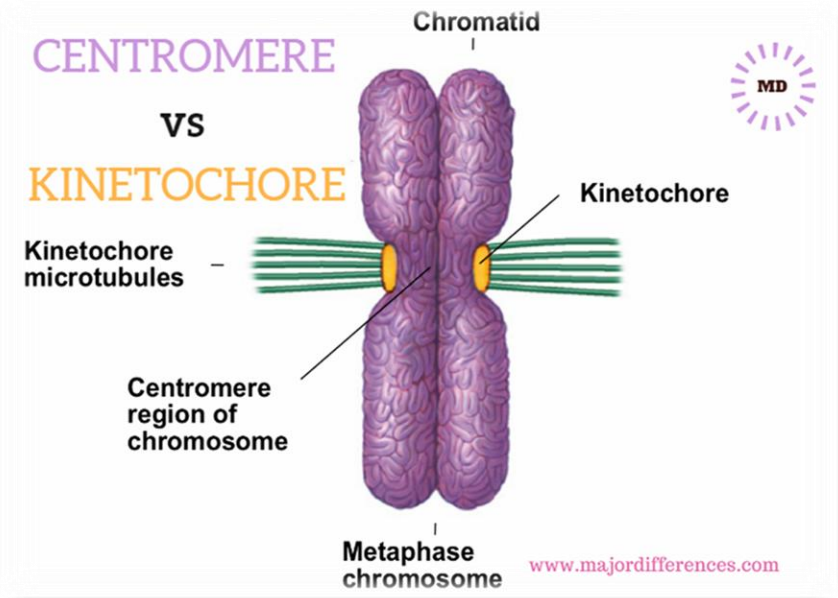
    by cytoplasmic microtubules radiating out from microtubular organizing centre (MTOC) around centrioles
  - **Microtubules organized to form spindle**
- **Metaphase:**
  - **Chromosomes migrate to equatorial plane of cell " meta phase plate“**
  - **At centromere of each chromosome dense plaque (kinetochore) as site of attachment of chromosomal microtubules**
  - ***Microtubules of mitotic spindle (arise from MTOC) are*:**



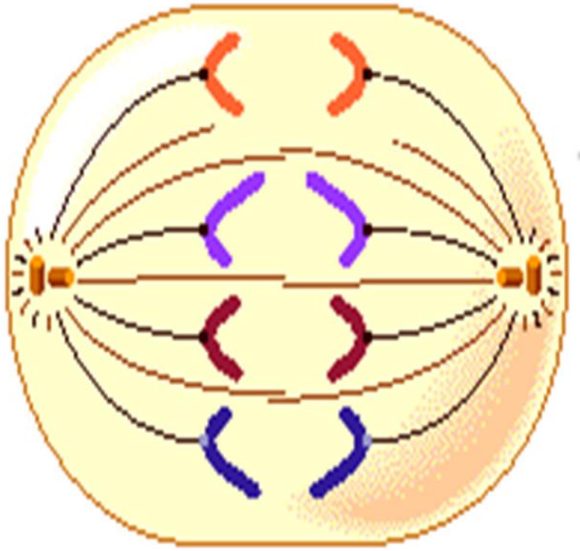
- ***Cytoplasmic microtubules*:**

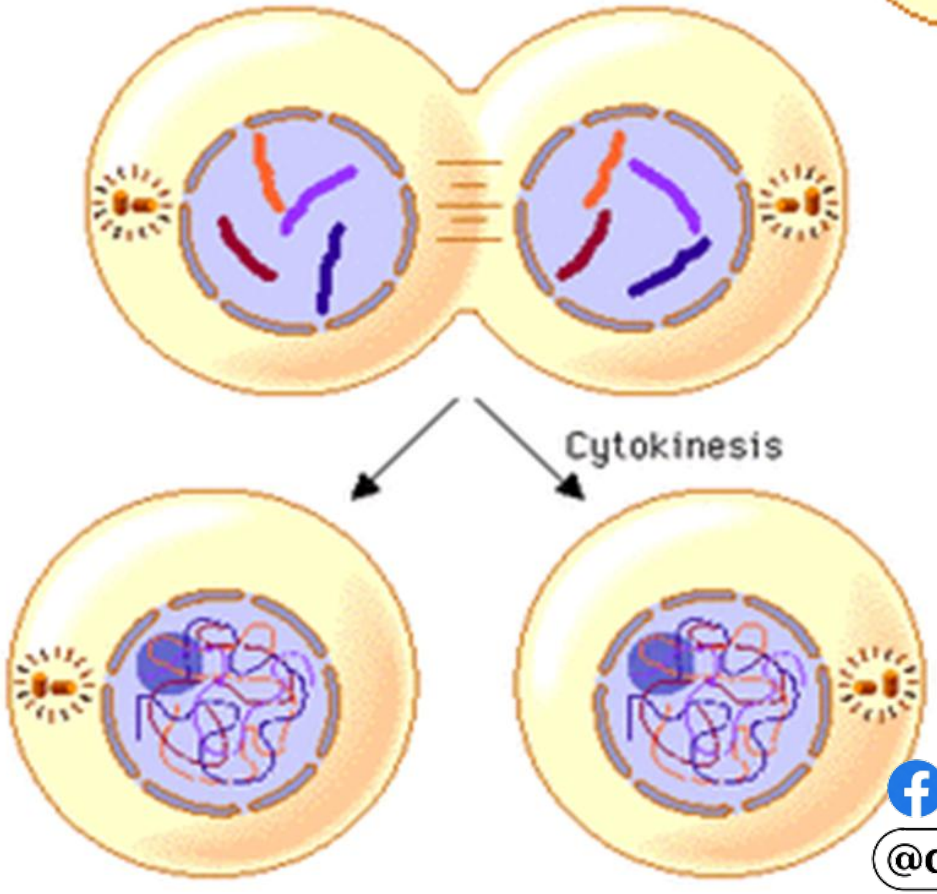
  for cell elongation
- ***Chromosomal microtubules*:**

  attached to kinetochores for arrangement of chromosomes in equatorial plane
- ***Astral microtubules:*** **"star like " around centrioles to establish spindle axis**



- **Anaphase:**
  - **Migration to opposite poles of cell**
    by elongation of cytoplasmic microtubules
  - **by pulling action of chromosomal microtubules**
    Each d-Chromosome splits longitudinally at centromere → its two sister chromatids separate
- **Telophase:**
  - **constriction develops at equatorial plane (cleavage furrow)**
    contraction of actin filaments → cytoplasm divided into 2 halves
  - **reappearance of nucleoli & nuclear envelope**
  - **46 chromatids (s-chromosomes)** *of each cell begin to*
    lengthen - uncoil - lose their visibility





2)Meiosis:

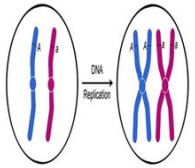
- special type of cell division in which
diploid cells in the testis & ovary undergo 2 successive divisions (without S-phase in between)
to produce haploid germ cells (sperms or ova)

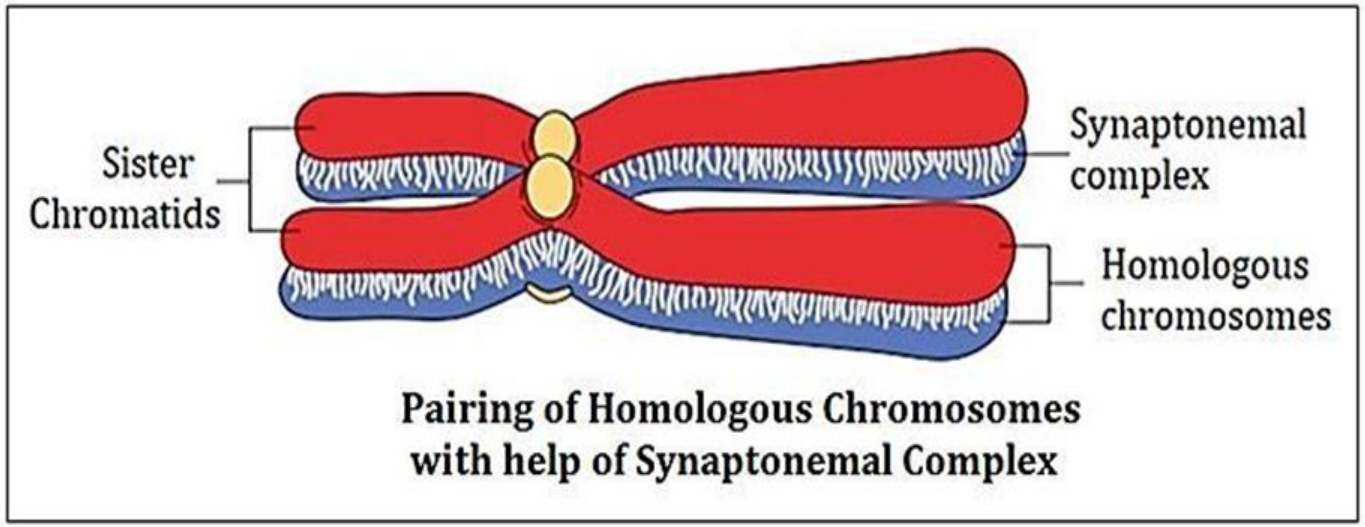
First Meiotic Division (Reduction Division):

- **Prophase I** *takes long period of time*
  - In male (spermatogenesis) → 22 days
  - In female (oogenesis) → 12-45 years to be completed

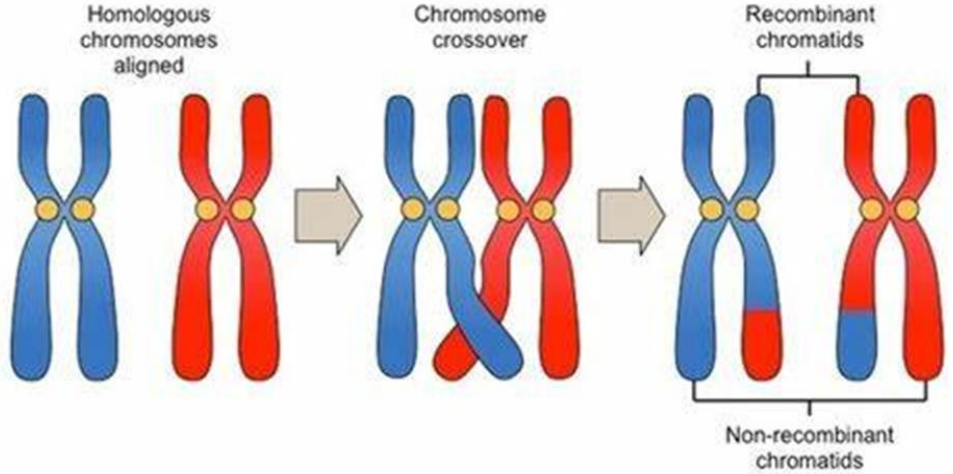
Prophase I includes the following stages:

- 46 d-chromosomes appear as long thin threads
- disappearance of nucleoli & nuclear envelope
  freeing chromosomes into the cytoplasm
- Chromosomes appear as 23 pairs (bivalents)
  - Each pair formed of
    2 homologous chromosomes (1 maternal 1 paternal)
- bivalents become shorter & thicker
  appear as tetrads (4 chromatids attached along their length)
- Crossing over occurs at the chiasmata (by help of recombinase enzyme)
  - in homologous chromosomes
    exchange of segments between non-sister chromatids
- Chromosomes begin to separate revealing chiasmata

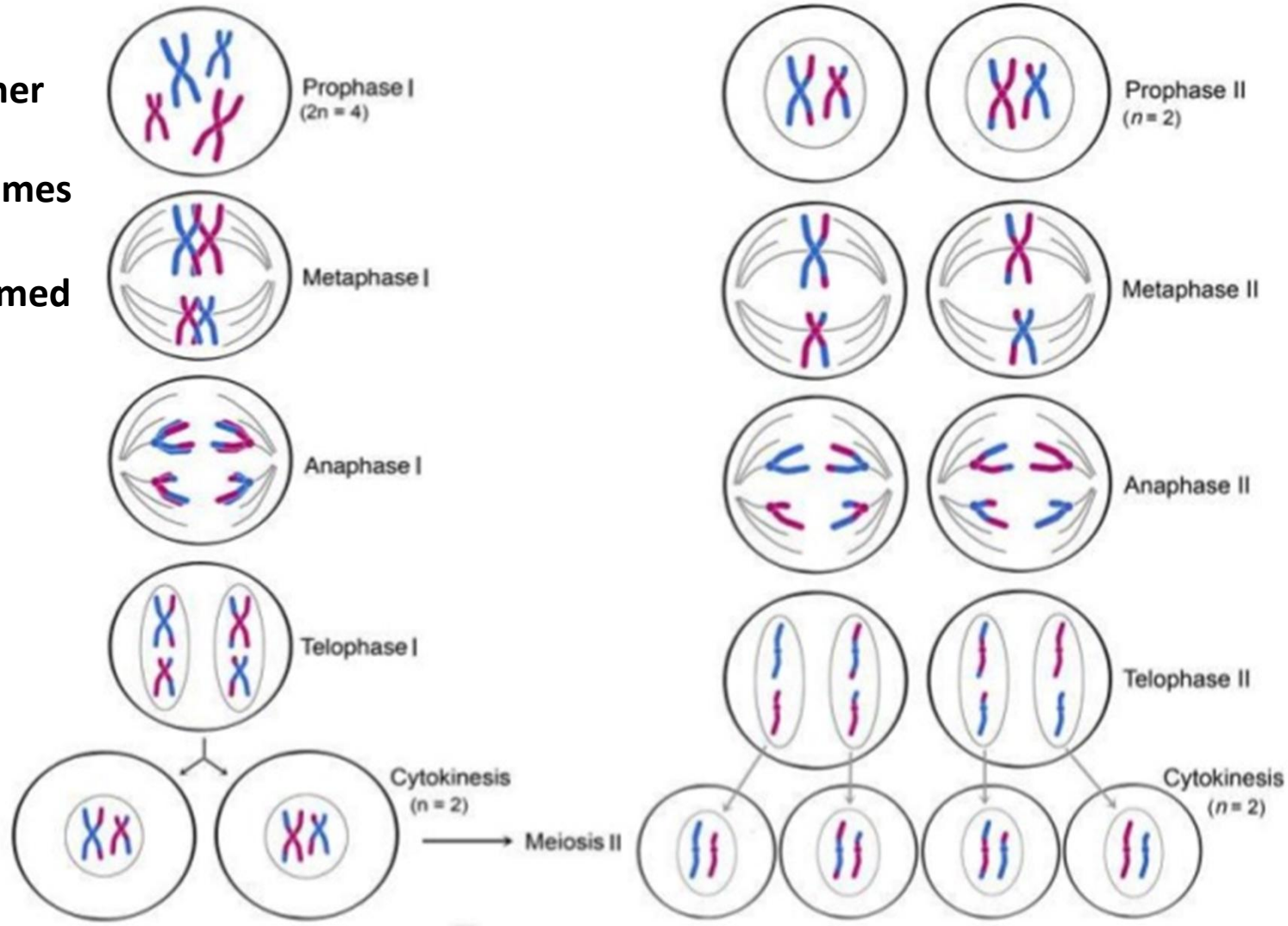




Pairing of Homologous Chromosomes
with help of Synaptonemal Complex



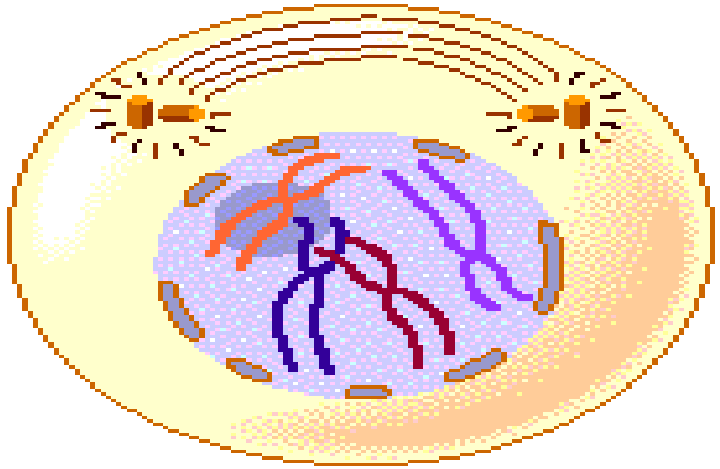
- **Metaphase I**
  - 23 bivalent d-chromosomes aligned as pairs in equatorial plane
  - attached to microtubules of mitotic spindle
- **Anaphase I**
  - bivalent d-chromosomes separate from one another
  - move to opposite poles of cell
  - Each cell receives one of homologous d-chromosomes
- **Telophase I**
  - At the end of this stage two daughter cells are formed
  - Each daughter cell has 23d -chromosomes

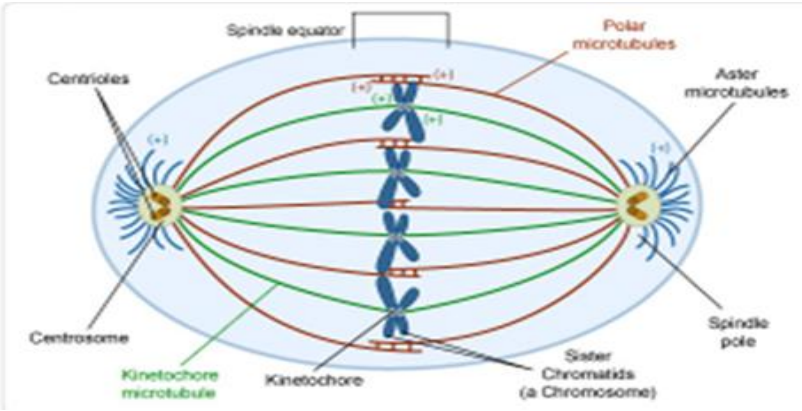


Second Meiotic Division (Equatorial Division):

- mitosis-like division
- occurs rapidly after the first division
- Very short interphase ((without S-phase)) each daughter cell has 23 d-chromosomes

- **Prophase II**
  - Chromosomes are shorter and thicker
  - Mitotic spindle starts to appear
- **Metaphase II**
  - 23 d-chromosomes are aligned at the equatorial plate
- **Anaphase II**
  - Each d-chromosome splits at centromere into two chromatids (s-chromosomes)
  - which move to opposite poles of cell
- **Telophase II**
  - 2 daughter cells separate
  - Each daughter cell has 23 s-chromosomes (haploid number of chromosomes)

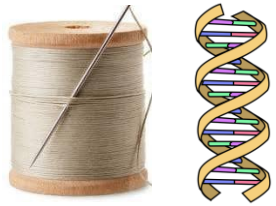


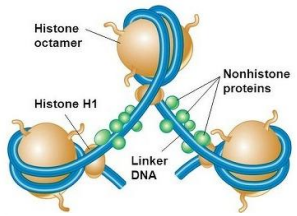


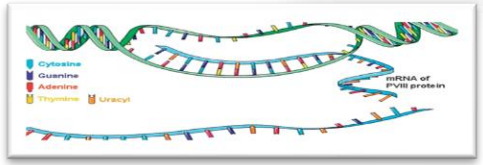
	Mitosis	Meiosis
Site	somatic cells	germ cells of testes & ovaries
Number of divisions	Single	Two successive divisions without S-phase in-between
Crossing over exchange of genes	Absent	Present
Separation	Each chromosome divides longitudinally at centromere into 2 chromatids	In 1st division each chromosome of bivalent moves towards one pole
Daughter cells	- Two (somatic cells) with diploid number of chromosomes - genetically identical	- Four (germ cells) with haploid number of chromosomes - show genetic variation

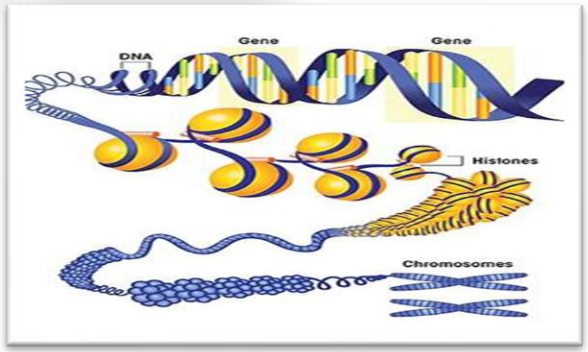
Human chromosome

▶ **chromatin fibers**
- formed of DNA molecule coiled around histone & non histone proteins
- condensed and tightly coiled during mitosis & meiosis
- visible with light microscope

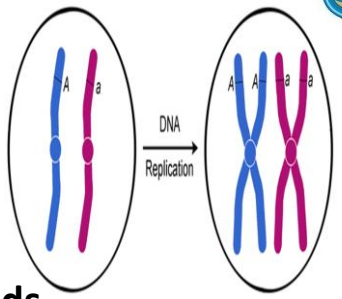


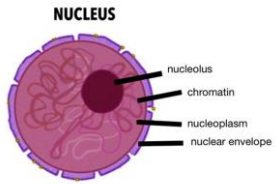






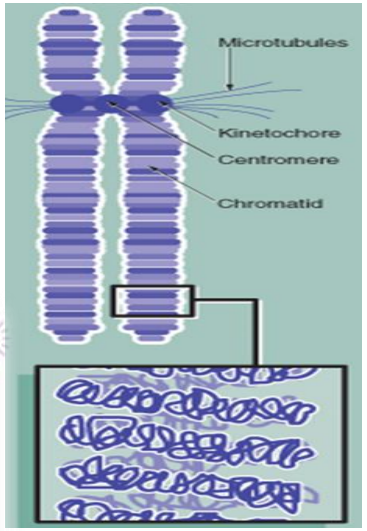
▶ **GI-Phase of interphase**
- chromosome formed of single-thread of DNA called s-chromosome or chromatid



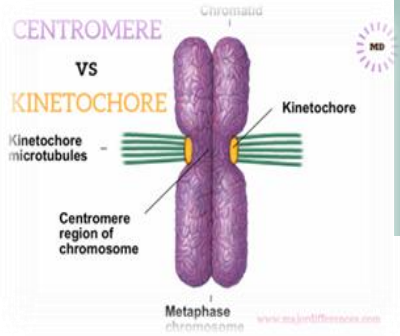


▶ **s-Phase of interphase**
- chromosome formed of double-threads called d-chromosome

▶ **During late prophase & metaphase**
- each chromosome formed of 2 chromatids *connected at centromere* that divides d- chromosome into short arm (P) - long arm (Q)

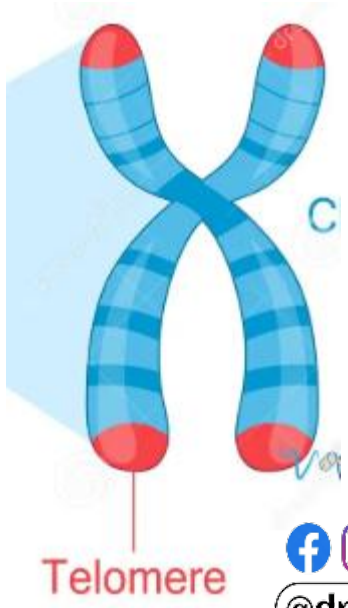


▶ **Kinetochores**
- 2 discs of protein located at the centromere
- to which spindle fibres are attached during cell division



▶ **Genes**
- segments of DNA code for formation of specific proteins
- Each gene has a precise position (locus) on the chromosome

▶ **Telomeres**
- regions of repeated sequence at chromosomal ends
- protect its end from destruction and prevent end to end fusion of chromosomes



Karyotyping:

- **Definition**

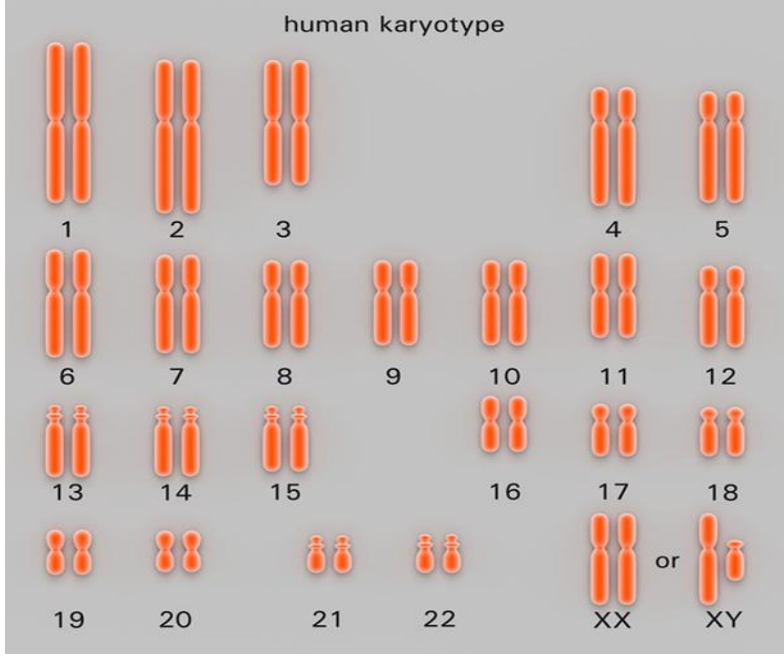
→ study of number & type of chromosomes according to
- their length
- position of centromere

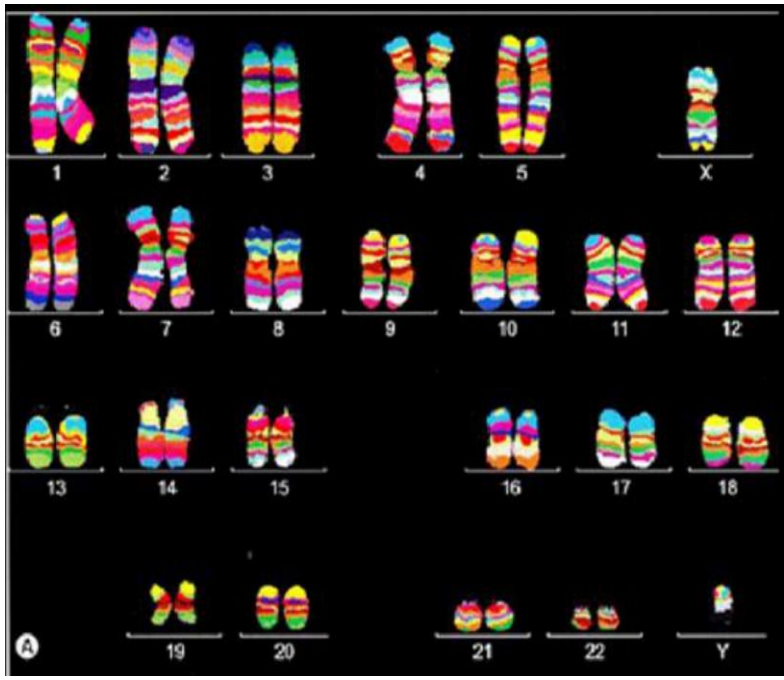
- **Technique**

→ best cells to study chromosomes (Leucocytes)
→ Cells allowed to divide by mitosis then stopped at metaphase
→ At metaphase Chromosomes are photographed & matched into pairs → arranged in descending order of length
→ Chromosomes are studied using specialized computer software programs

- **Banding technique**

→ better differentiate chromosomes by
- staining different segments (genes) with different colors





Classification of Chromosomes:

According to gene content:

- **Autosomes**

→ 22 homologous (identical) pairs

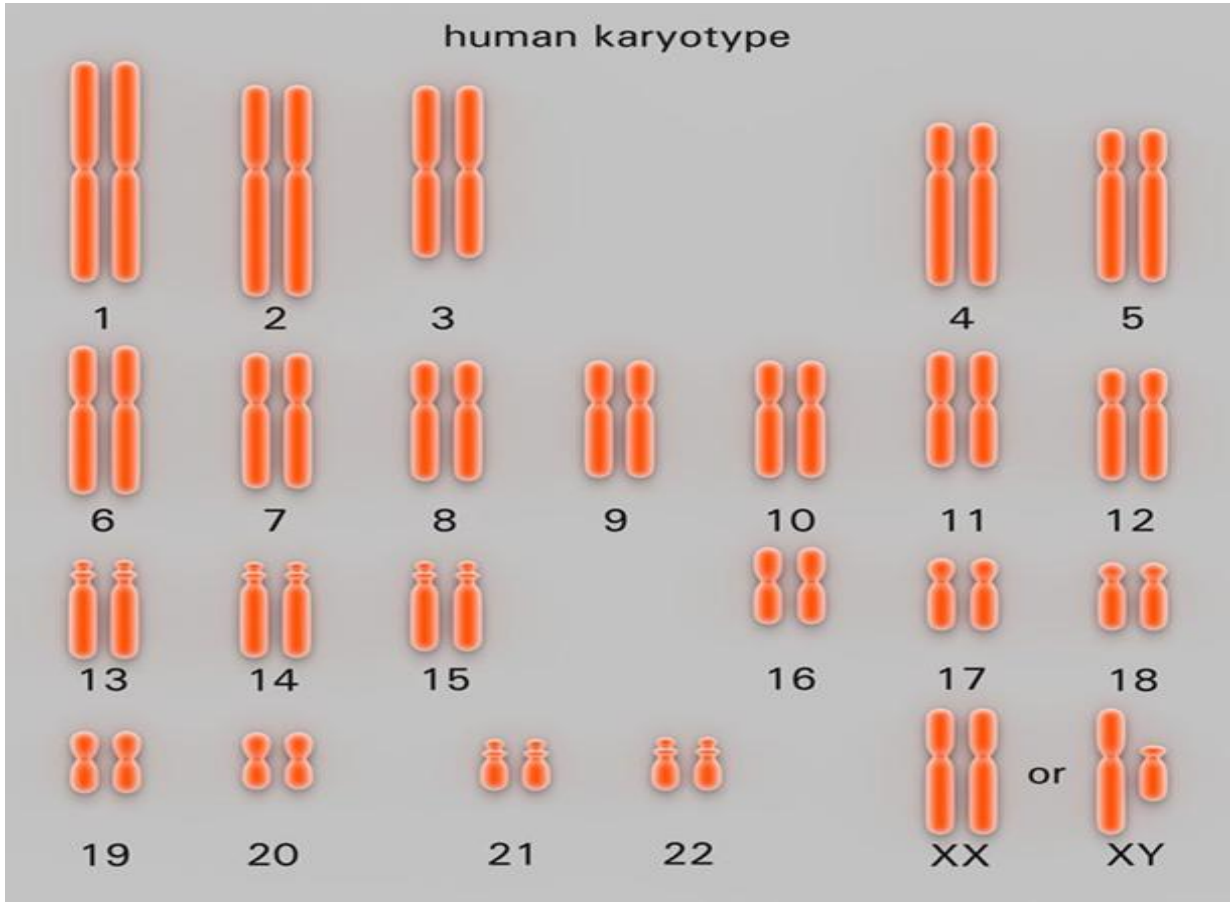
- control somatic characters

- **Sex chromosomes** one pair

→ homogonous (identical) in females (XX)

→ heterogonous (non-identical) in males (XY)

- control sex



According to chromosomal length:

- **Homologous 22 pairs**

→ **numbered** serially **from 1-22**

→then grouped into **7 groups** in descending order of **length** (A, B, C, D, E, F and G)

- **Sex chromosomes** one pair

→ (XX) OR (XY)

→ arranged **either alone or X** in group C & Y in group G

According to position of centromere:

- **Metacentric**

→ centromere at center of chromosome

→ two arms are equal (p = q)

- **Submetacentric**

→ centromere is midway between centre & upper end

→ short & long arms (p shorter than q)

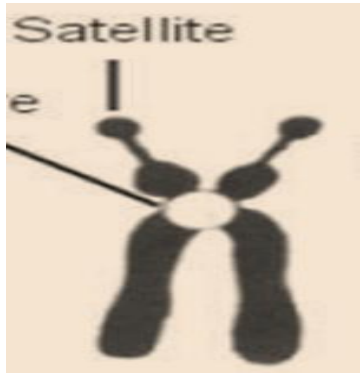
- **Acrocentric**

→ centromere is very close to upper end

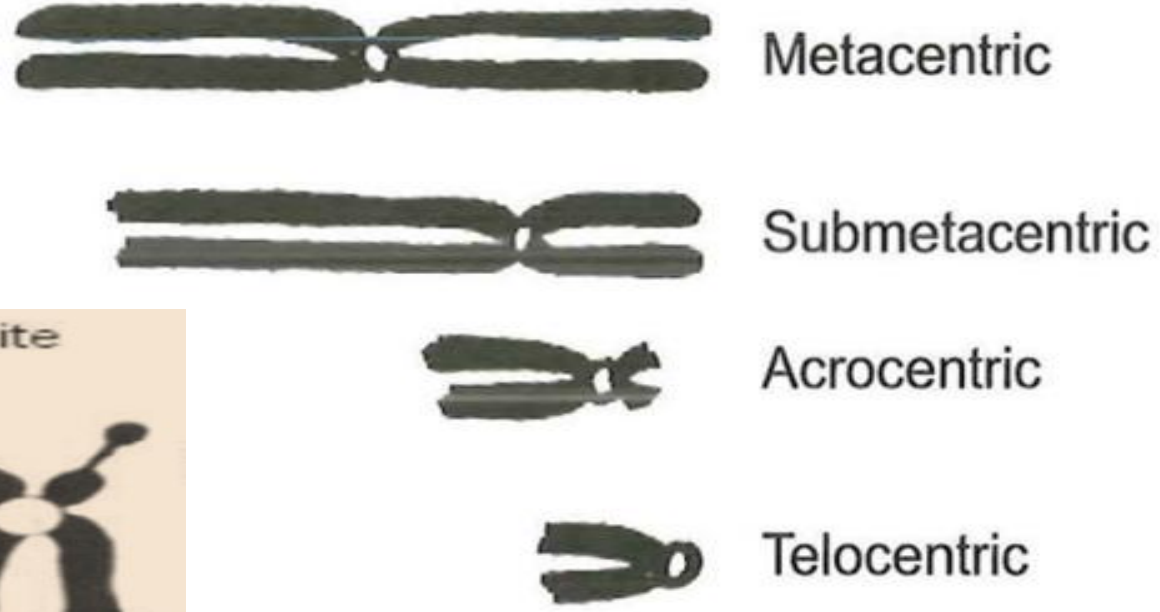
→ short & long arms (p is very short)

→ Some of these chromosomes except Y

- have small masses of chromatin (satellites)



attached to short arm by a narrow stalk (secondary constriction) containing genes for rRNA

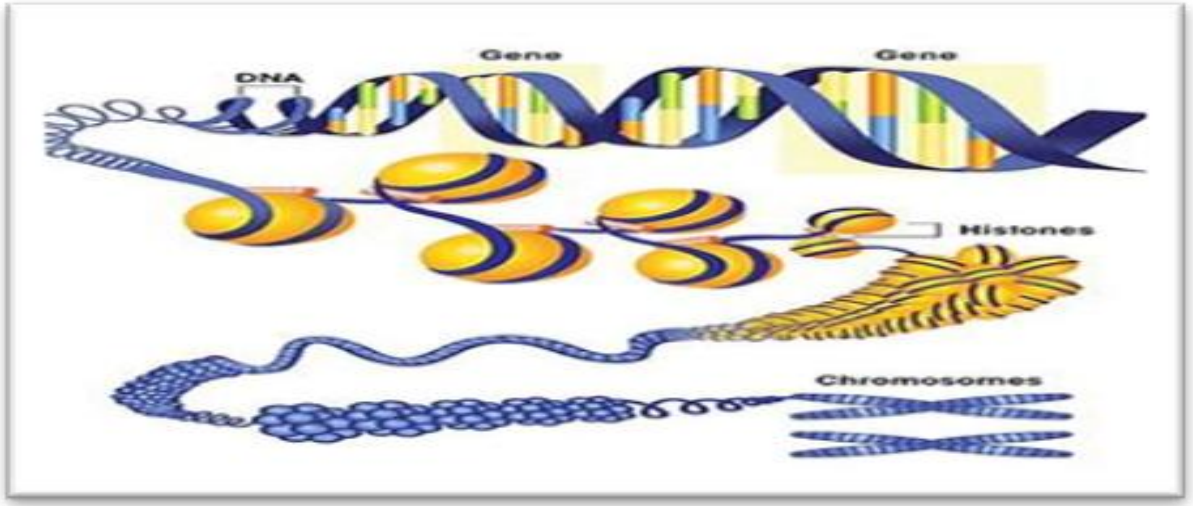


- **Telocentric**

→ centromere is terminal

→ not present in humans

Sex Chromatin (Barr Body):

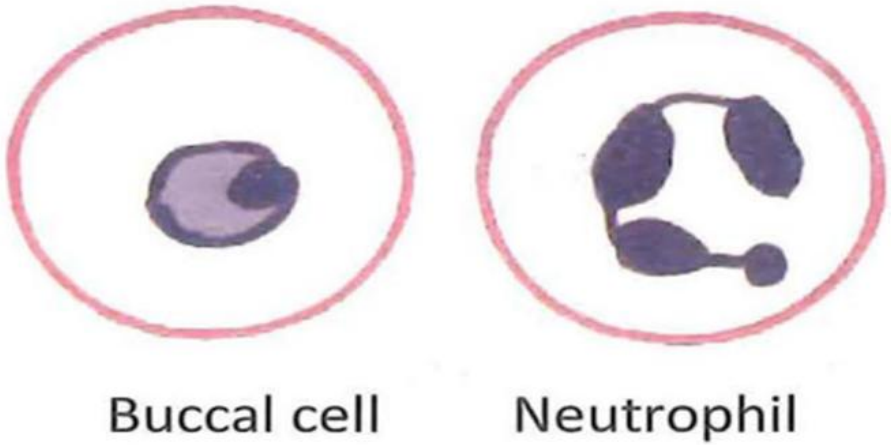


- **Definition & Nature**

→ darkly stained mass of chromatin
first seen by Murray Barr
→ inactive coiled dark stained (X) chromosome in
- nuclei of female cells
→ other (X) chromosome is active extended & non apparent

- **Site**

→ nuclear envelope (inner aspect) of
- 60% of female epithelial buccal cell nuclei
→ drumstick-like mass attached to nucleus
- 3-5% of female blood neutrophil



- **Important Rules**

→ Each somatic cell must have at least one (X) chromosome to be active
- carries other genes rather than sex determining genes
→ Barr body appears in:
- normal female cells (XX)
- male cells with an extra X chromosome (XXY, Klinefelter syndrome)
→ Barr body NOT apparent :
- normal male cells (XY)
- female cells with only one X chromosome (XO, Turner syndrome)

Clinical Importance of Chromosomal Examination:

→Diagnosis of **genetic sex in doubtful cases of hermaphroditism**

→Identification of fetal sex by

- staining cells obtained from amniotic fluid

→Diagnosis of **sex chromosome abnormalities** as in

- Turner's syndrome (XO)

- Klinefelter's syndrome (XXY)

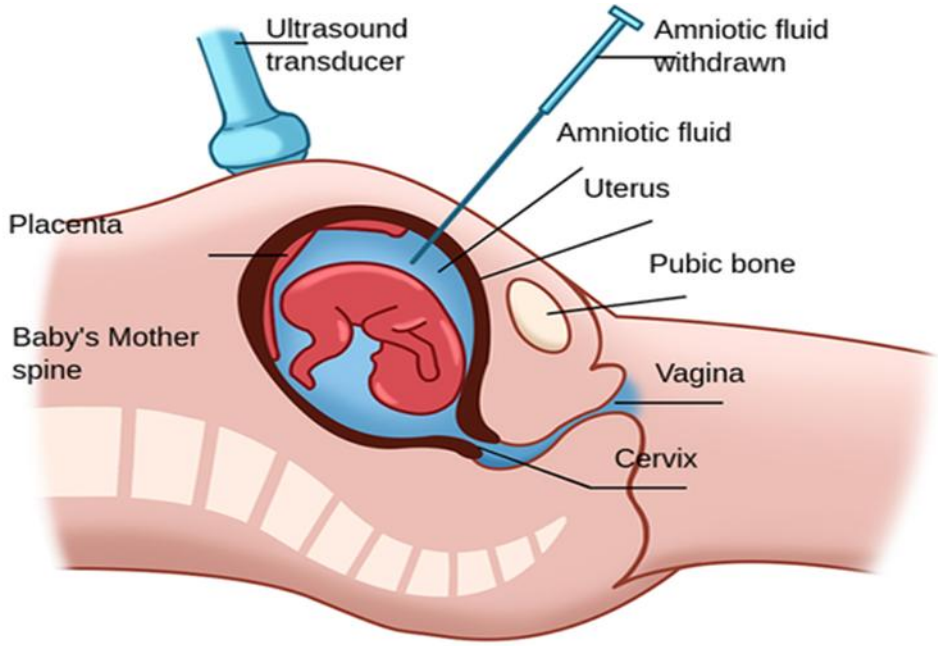
→Diagnosis of **structural abnormalities** in chromosomes

- Deletion in mental retardation

- Translocation in chronic myeloid leukemia

→Diagnosis of **numerical abnormalities** as in **mongolism**

→Medico-legal importance in forensic medicine



Chromosomal Aberrations (Abnormalities):

→Any deviation from normal number or structure

→Aberrations may occur in

- autosomes (22 pairs)
- sex chromosome pair

→Most types of aberrations cause

- Mental retardation
- developmental retardation

Causes of chromosomal aberrations:

- **Radiation**

→ chromosomal damage & non-disjunction

- **Viral infections**

→ german measle → fragmentation of chromosome

- **Pregnancy in old age**

→ increase risk of non-disjunction (very long prophase)

- **Drugs**

→ cytotoxic drugs e.g. colchicine → inhibit formation of mitotic spindle

- **Autoimmune diseases**

→ usually associated with non-disjunction

Numerical Aberrations:

→**Anomalies involving deviation from normal number of chromosomes**

→**occur in germ cell or somatic cell in form of:**

▶ Euploidy:

→Karyotyping shows **exact multiple of basic haploid number & exceeds diploid number**

- **Triploid (3n):**

→ **69 chromosomes**

- **Tetraploid (4n):**

→ **92 chromosomes**

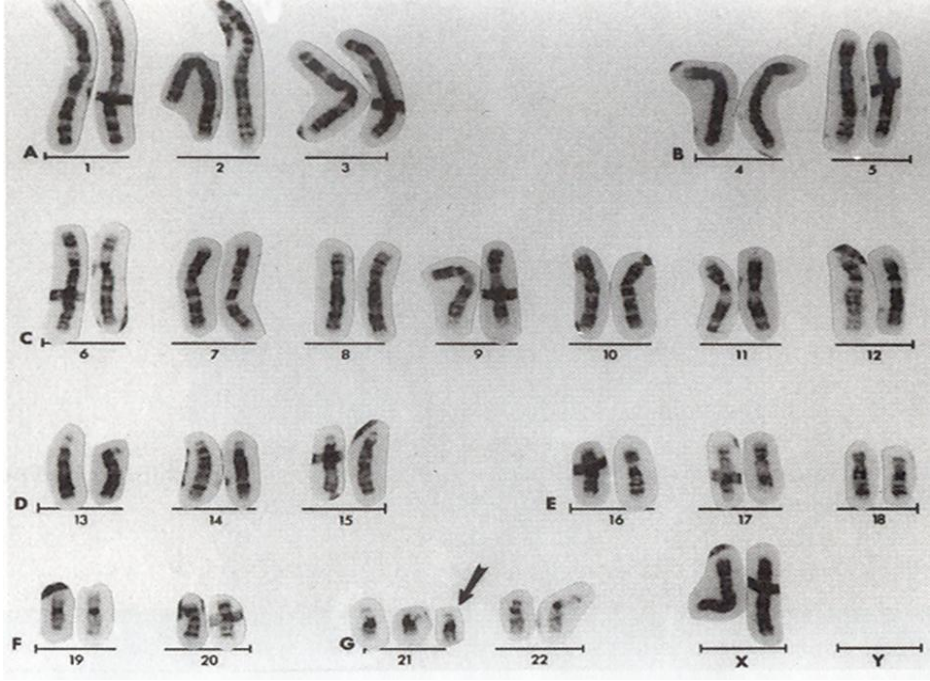
- **Polyploidy (5n, 6n, or more):**

→ **one or both gametes are not haploid**

Aneuploidy (abnormal ploidy):

→ abnormality is **not exact multiple** of **haploid** number

→ Karyotype shows **addition** or **loss** of **1 chromosome**



- **Trisomy**

→ **Addition of an extra chromosome → karyotype is (2n + 1)**

- 3 copies of chromosome instead of 2

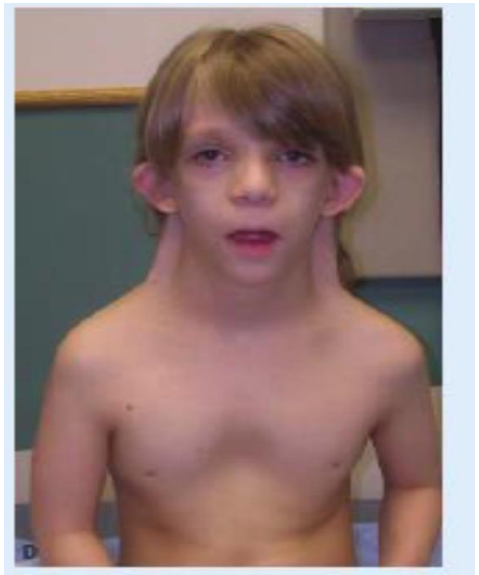
→ **Down syndrome (trisomy 21, mongolism)**

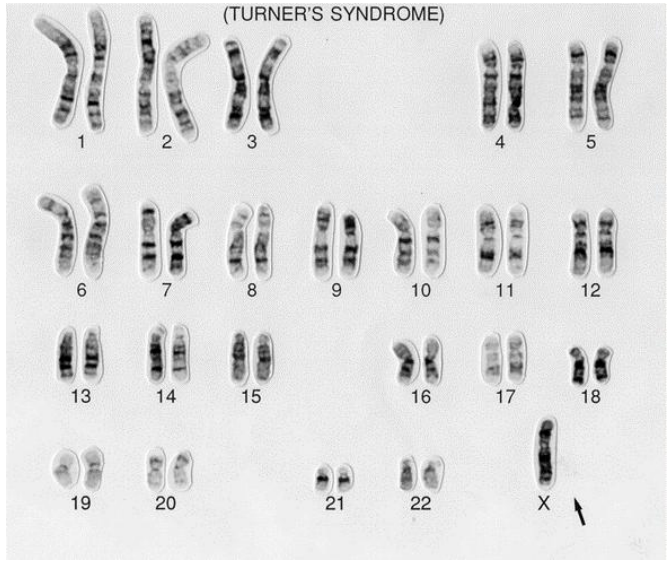
- **Monosomy**

→ **Missing of 1 chromosome → karyotype is (2n - 1)**

- 1 copy of chromosome instead of 2 in chromosomal pair

→ **Turner syndrome (45 chromosomes)**





Causes of aneuploidy:

▶ Non-disjunction:

- **Primary non-disjunction:**

→2 homologous (bivalent) chromosomes
- fail to separate during first meiotic division

→results in 4 abnormal daughter cells

- **Secondary non-disjunction:**

→2 chromatids
- fail to separate at centromere either during second meiotic division or mitosis

→results in 2 normal & 2 abnormal → meiosis

→results in 2 abnormal → mitosis

- **Mosaic:**

→Secondary non-disjunction
- occurs in mitosis after many normal divisions
- cells have more than one karyotype (46, 47, 45).

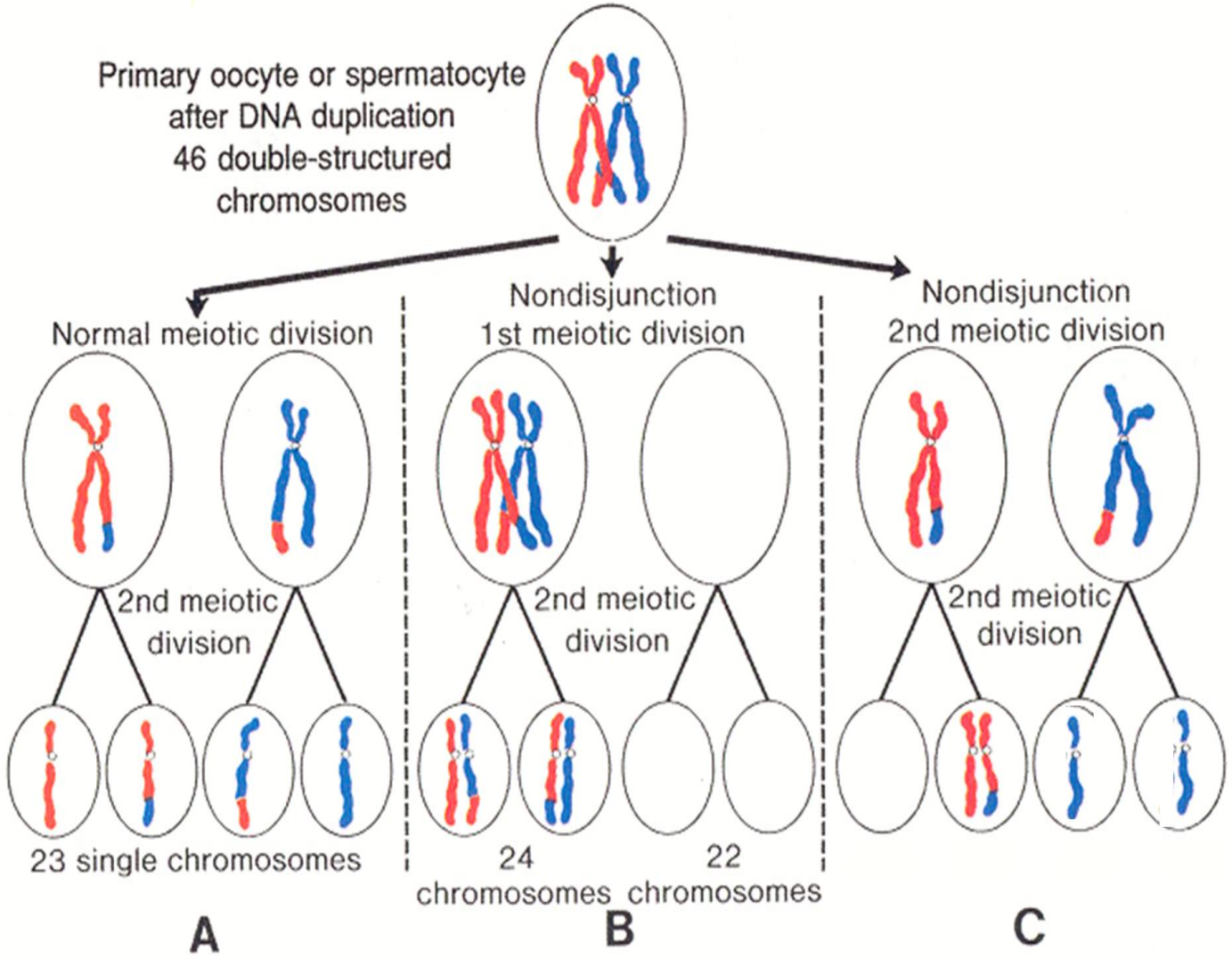


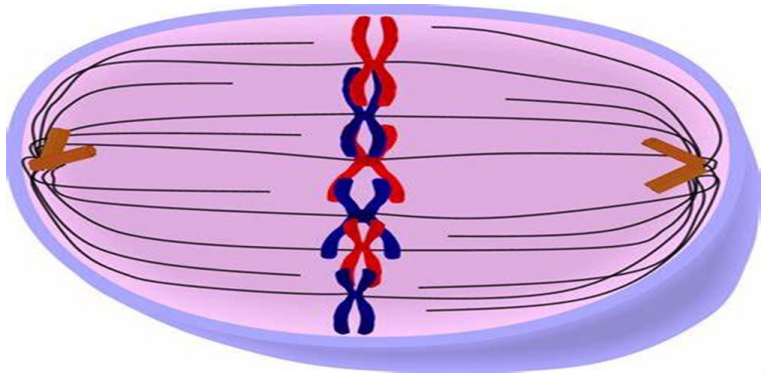
Figure 1.5. A. Normal maturation divisions. B. Nondisjunction in the first meiotic division. C. Nondisjunction in the second meiotic division.

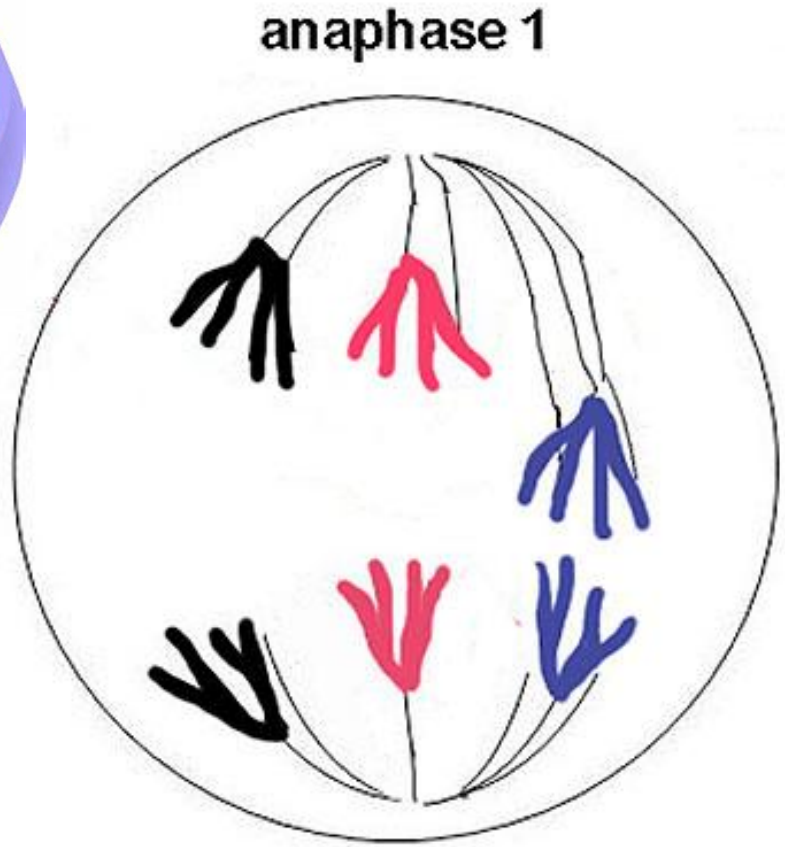
Failure of duplication:

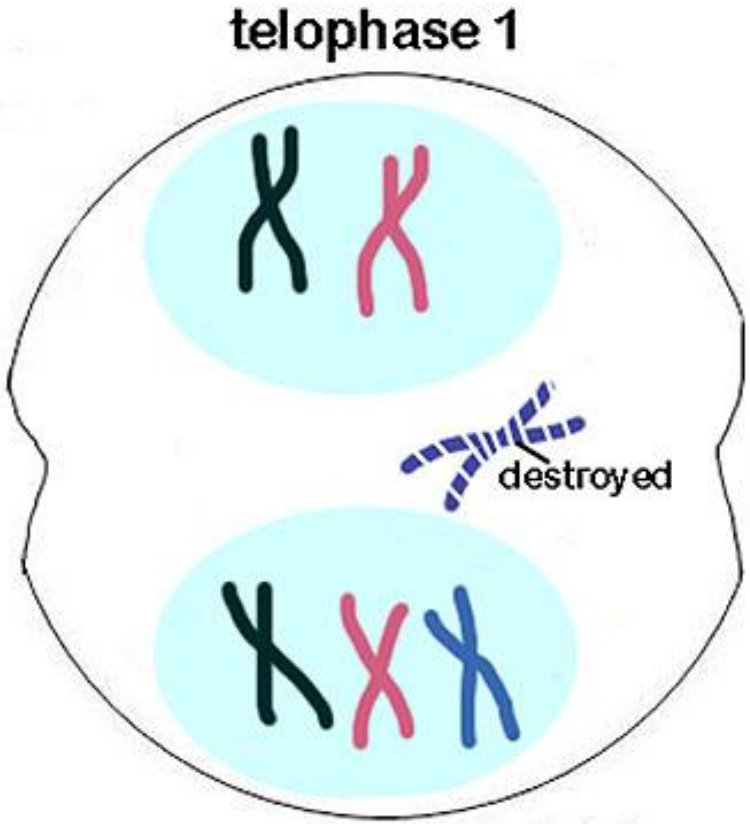
→ 1 chromatid (s-chromosome) fails to duplicate during S-stage

Simple loss:

→ failure of chromosome to align during metaphase or lagging to move in anaphase







Numerical aberrations in Autosomes

Down Syndrome (Mongolism): occurs as a result of

- 1)non-disjunction of chromosome 21 (Trisomy 21)

→ mongol child Cells contain 47 chromosomes

→ extra chromosome is similar to chromosome 21

- 2) Translocation (21 & 14)

Characteristic features

→ Cardiac abnormalities

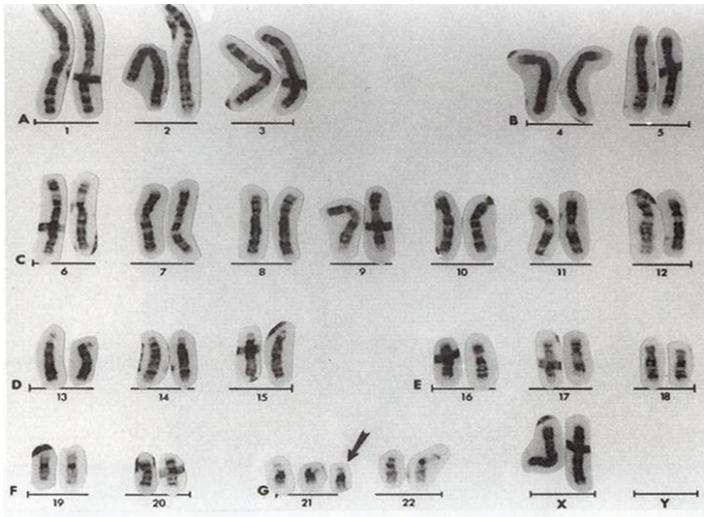
→ Mental retardation

→ Small genital organs

→ Lateral upward slope of eyes

→ Small ears

→ Short broad nose & neck



Numerical aberrations in Sex chromosomes

- **Causes:**

→ Non-disjunction in first meiotic division of primary oocyte

→ produced ovum may contain (XX) OR no X (0)

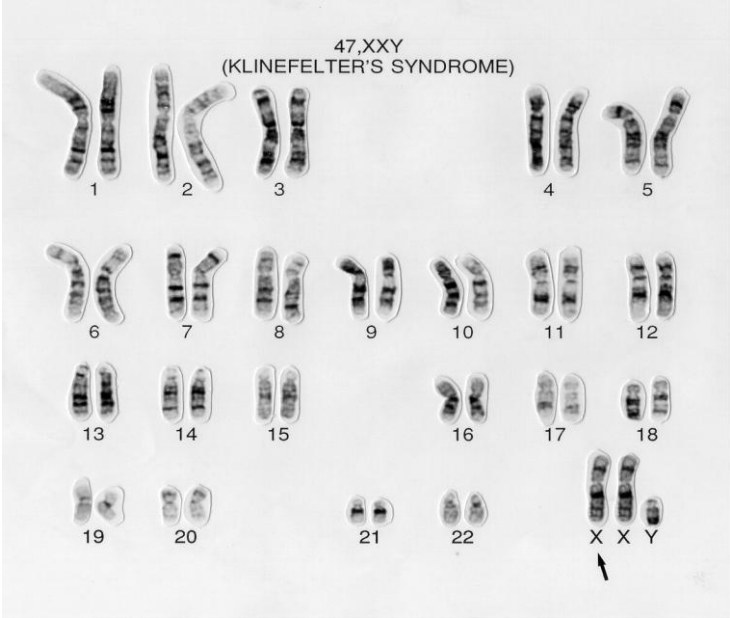
▶ Klinefelter's syndrome (47, XXY):

→ trisomy of sex chromosome

→ Male having additional X chromosome

→ non-disjunction of X chromosomes → 1st meiotic division of oocyte

- Ovum (2 X) fertilized with sperm (Y)



Characteristic features

→ Mentally retarded tall male

→ Small testis

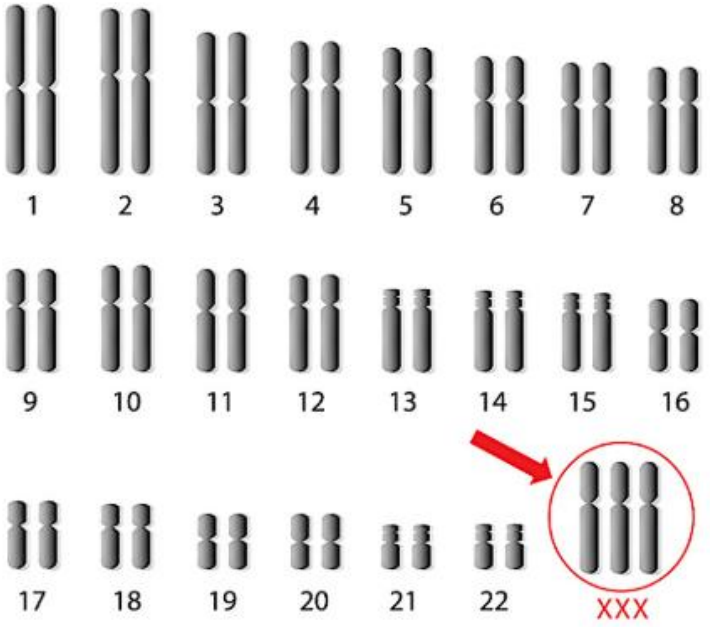
→ Large breast → Widely separated nipples

Multiple X Syndrome (47, XXX):

→ trisomy of sex chromosome
→ Female having additional X chromosome (triple X syndrome) → 2 Barr bodies
→ Same cause as Klinefelter but ovum fertilized by sperm having X

Characteristic features Girls show

→ delayed language development
→ auditory disorders
→ motor coordination problems

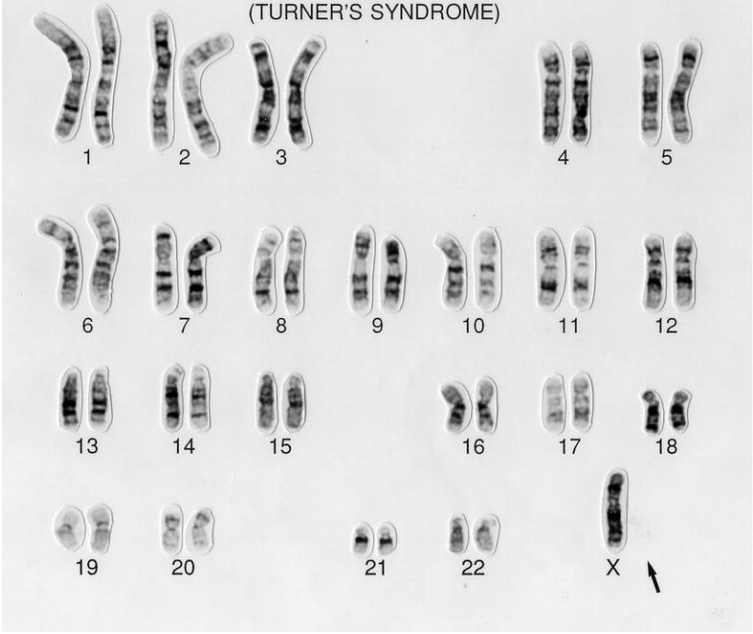


Turner's Syndrome (45, XO):

→ monosomy of sex chromosome
→ Female with only one X chromosome → No Barr bodies → missing of X chromosome
→ non disjunction of X chromosomes during first meiotic division in oocyte
→ ovum with no X is fertilized with a sperm having X chromosome

Characteristic features

→ Short female
→ Underdeveloped external genitalia
→ primary amenorrhea
→ Underdeveloped ovaries
→ mental retardation
→ Edema of limbs



Structural Aberrations of chromosomes (Mutation of Chromosomes)

- **Definition:**

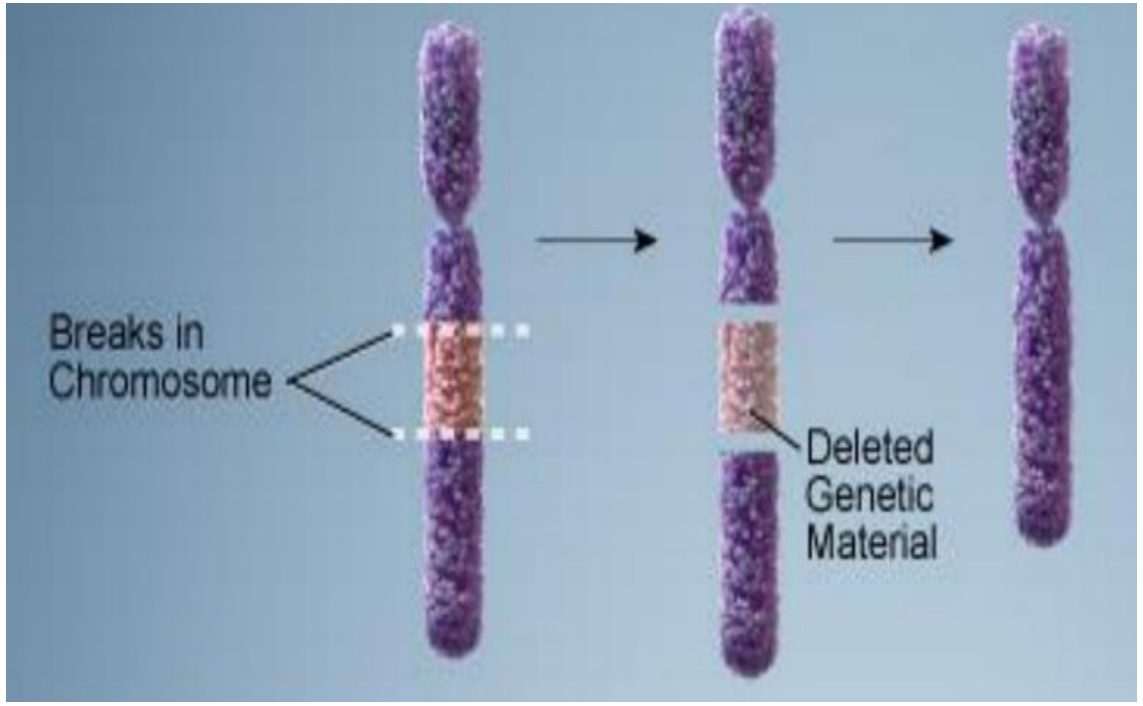
abnormalities in structure of chromosomes

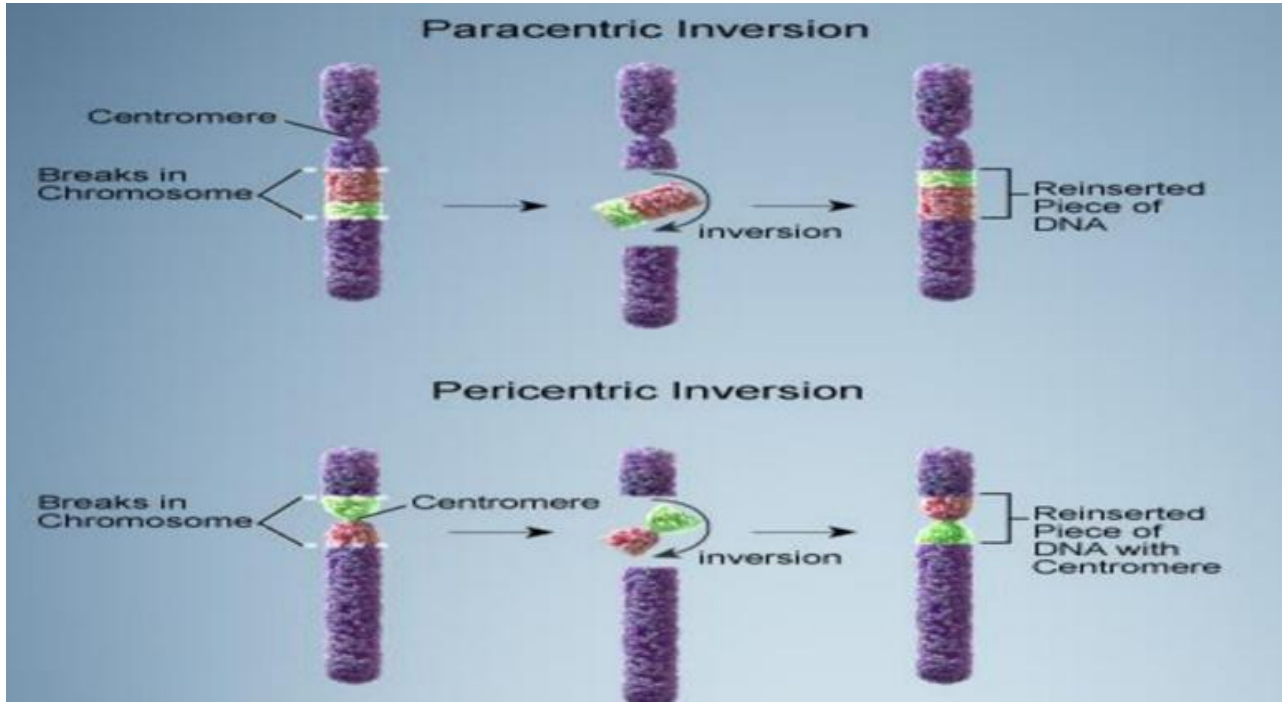
→ **Balanced aberration:**

- chromosome has normal complement of genetic information

→ **Unbalanced aberration:**

- additional or missing information → affected phenotype





Types of structural aberrations

- **1)Breaks**

→ Heal rapidly

→ reunion of the 2 sticky ends of the chromatids

- **2)Deletion**

→ Loss of a fragmented part of chromosome

▶ 3 types:

- *Terminal deletion*

→ loss of a segment from one end by 1 break

- *Interstitial deletion*

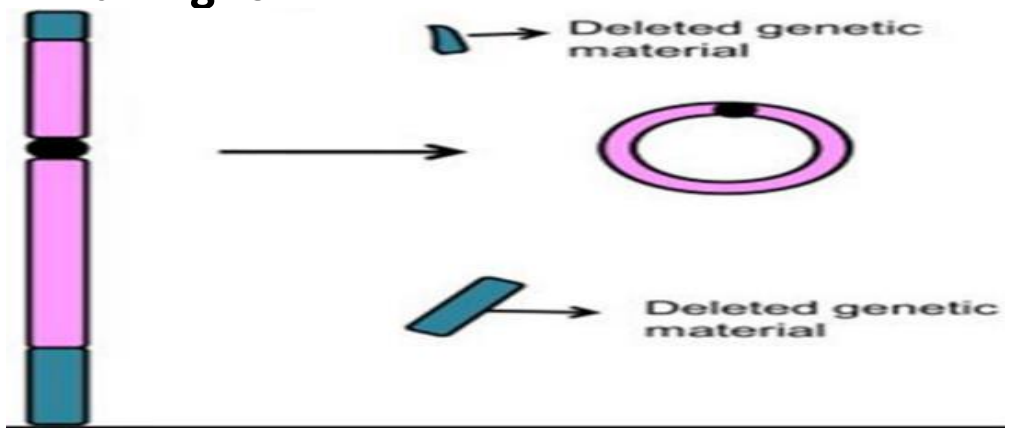
→ loss of fragments between 2 breaks in same arm

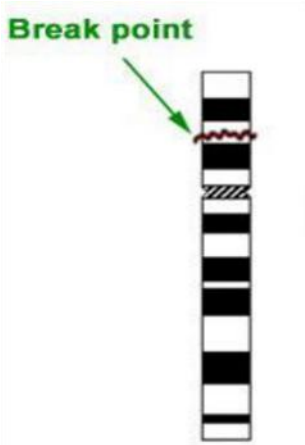
→ fusion at break sites

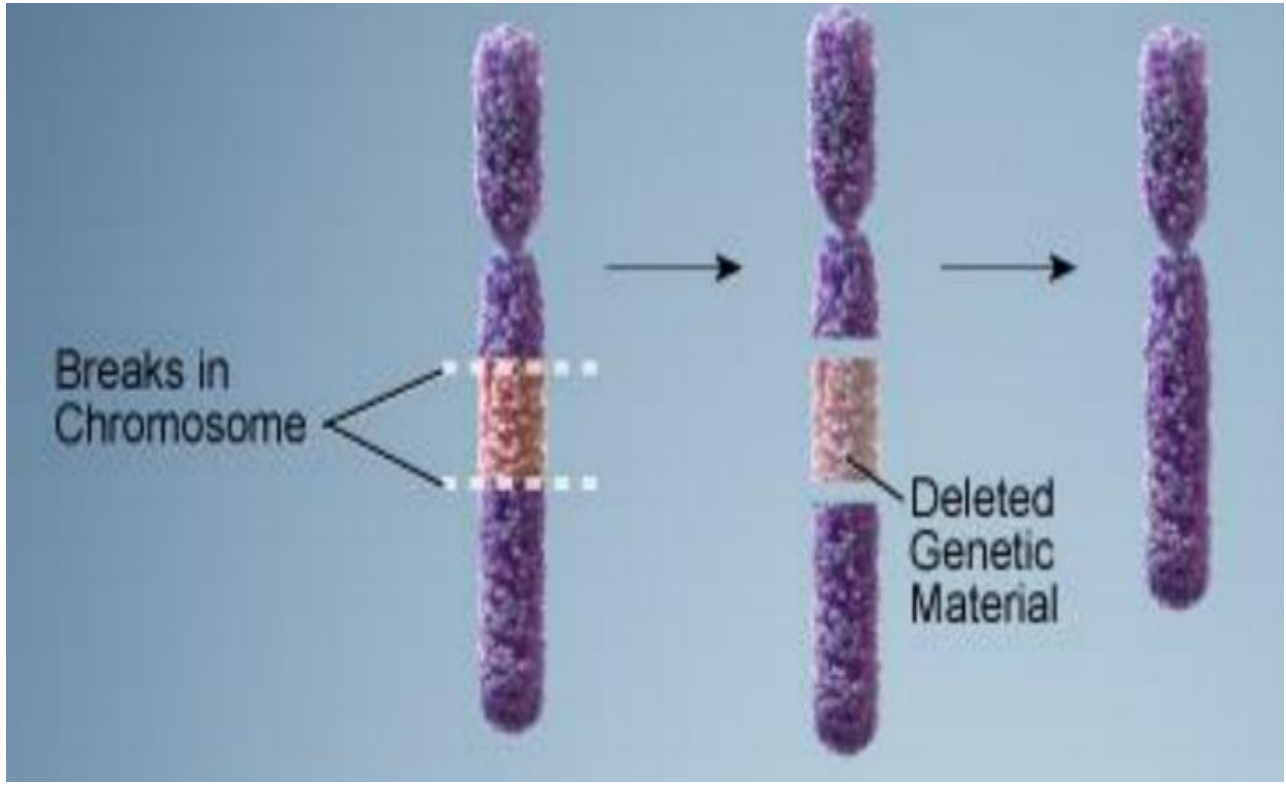
- *Ring chromosome*

→ 2 breaks → loss of fragments

→ reunion in a ring form







- **3)Inversion**

→2 breaks in chromosome followed by rejoining in inverted form

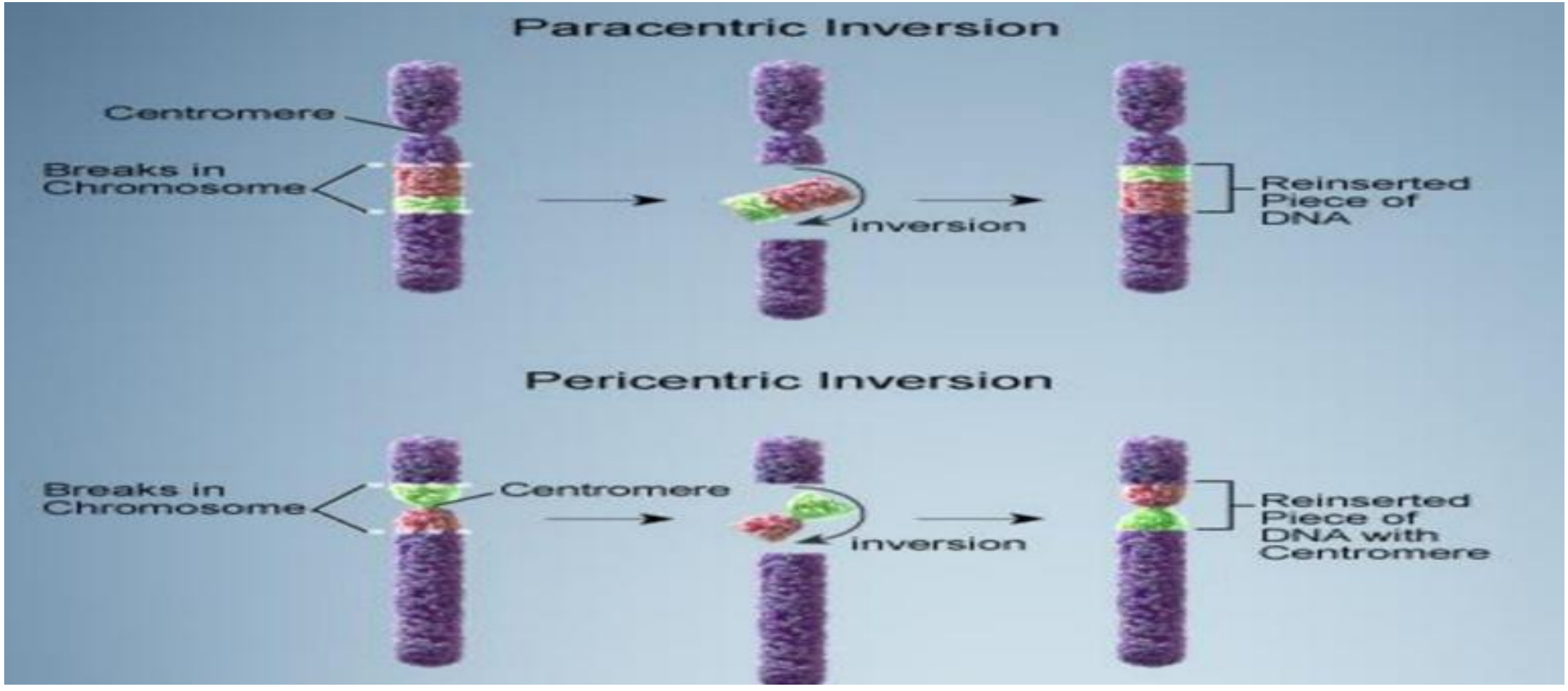
▶ **2 types:**

- ***Pericentric***

→ break occurs on either side of centromere

- ***Paracentric***

→ break occurs on one side of centromere



• 4)Translocation

→ transfer of chromosomal segment carrying genetic material to another non-homologous chromosome

▶ 2 types:

• ***Centric fusion*** *3-4% of cases of Down syndrome*

→ acrocentric chromosomes 21 & 14

→ fusion of long arms of chromosomes 21 & 14

"chromosome t" is formed

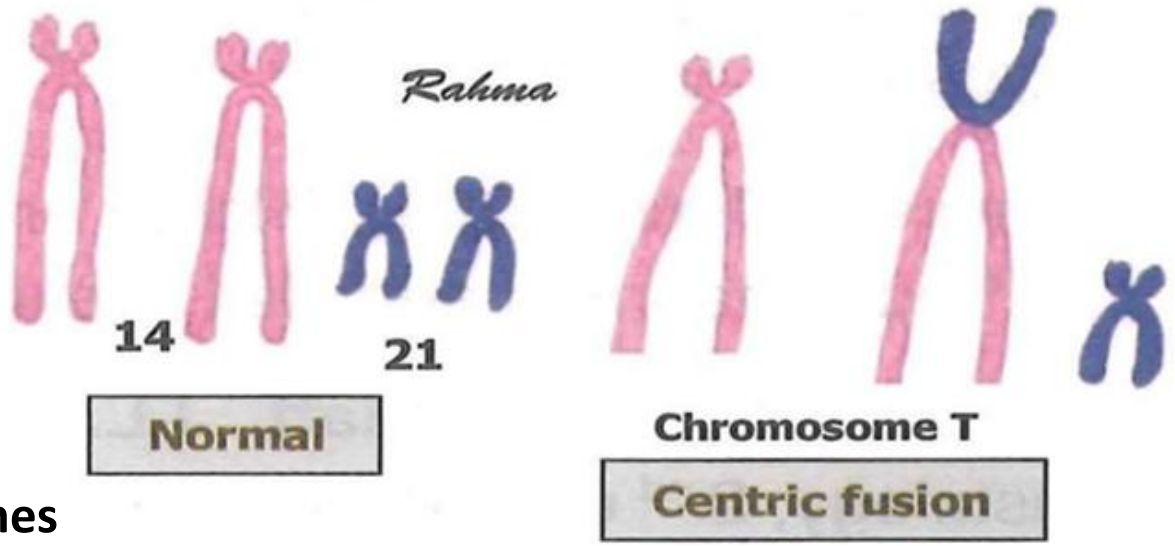
→ short arms of both chromosomes lost (insignificant)

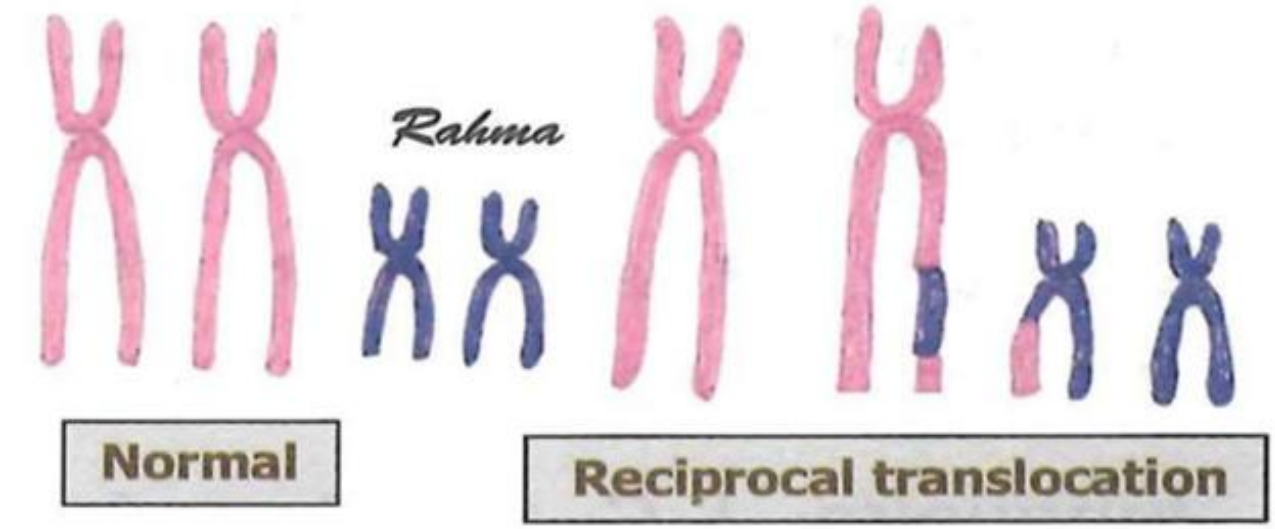
• ***Reciprocal translocation***

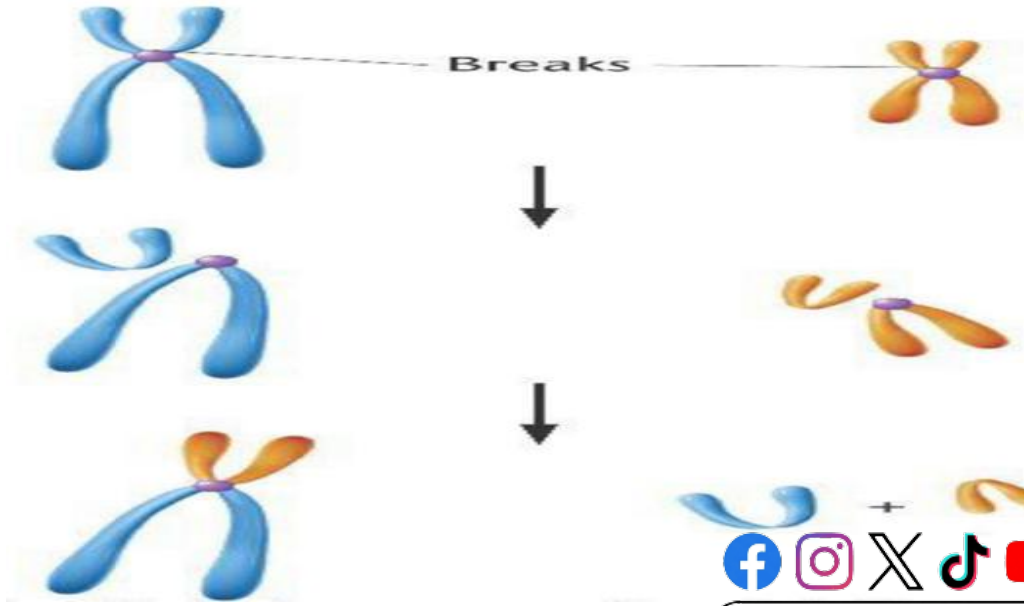
→ exchange of chromosomal material between 2 chromosomes

→ balanced

no chromosomal material is lost or added





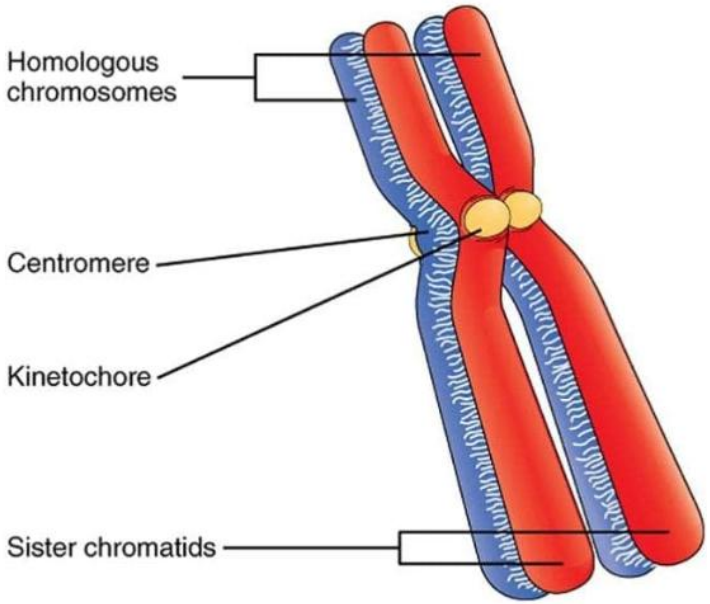


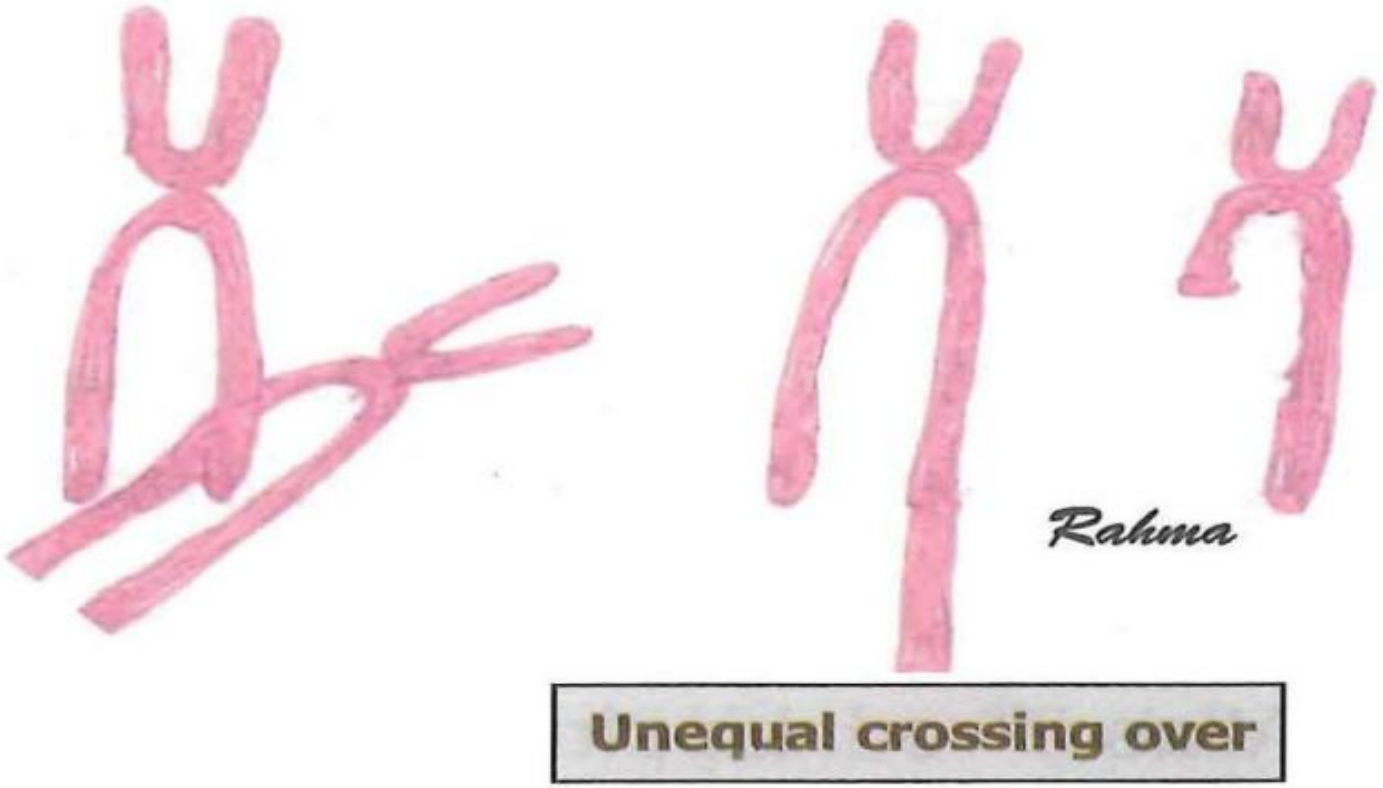
• 5)Duplication (Addition):

→ Addition of a fragmented segment of one chromosome as extra piece to homologous chromosome

→ unequal crossing over of homologous chromosomes

→ 2 copies of same genes on same chromosome (double dose of genes on chromosome)





• 6)Isochromosomes

→ mostly in **submetacentric chromosomes**

→ during **anaphase of mitosis**

- Chromosome divides transversely at centromere, not longitudinally

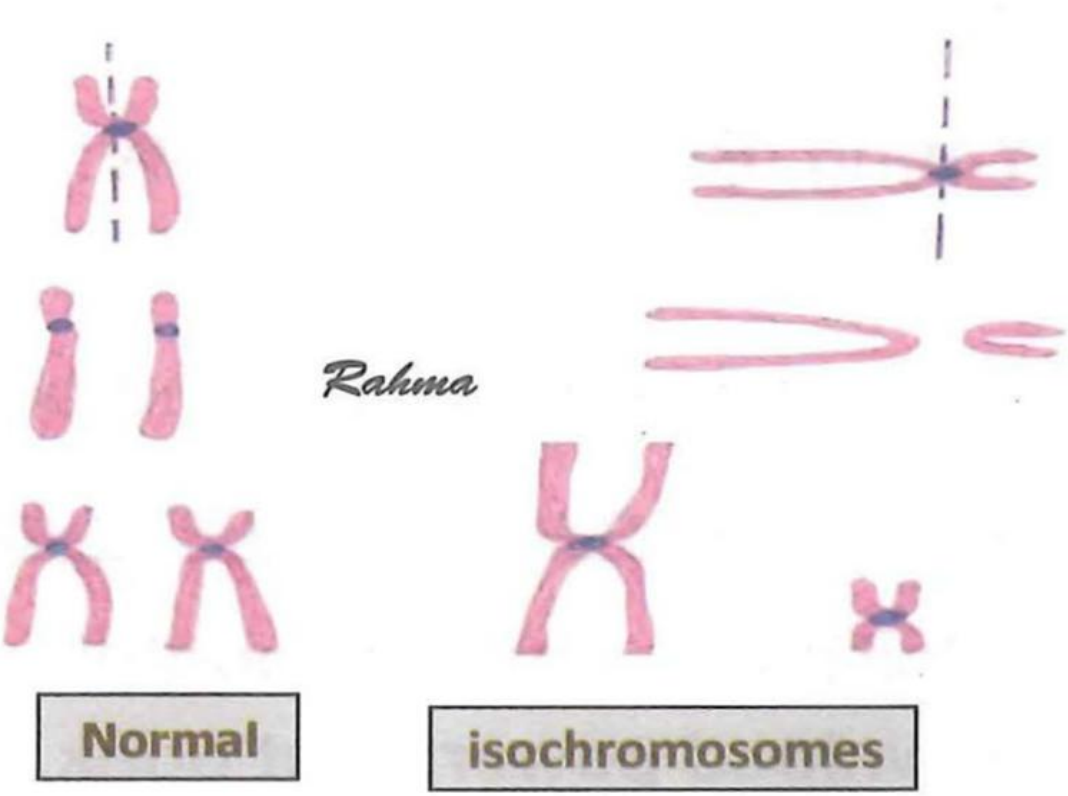
→ result → 2 chromatids → 1 short & 1 long

→ daughter cells → unequal chromosomes:

One with p & q arms → long

Another with p & q arms → short

(isochromosomes)



Read only topic

Philadelphia chromosome arises by reciprocal translocation between chromosomes 22 & 9. It is used to diagnose chronic myeloid leukaemia.

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HISTOLOGY

CYTOGENETICS

MODULE

104

2026

PREPARED BY

DR.MOHAMAD ABDELWAHAB

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Cell Cycle

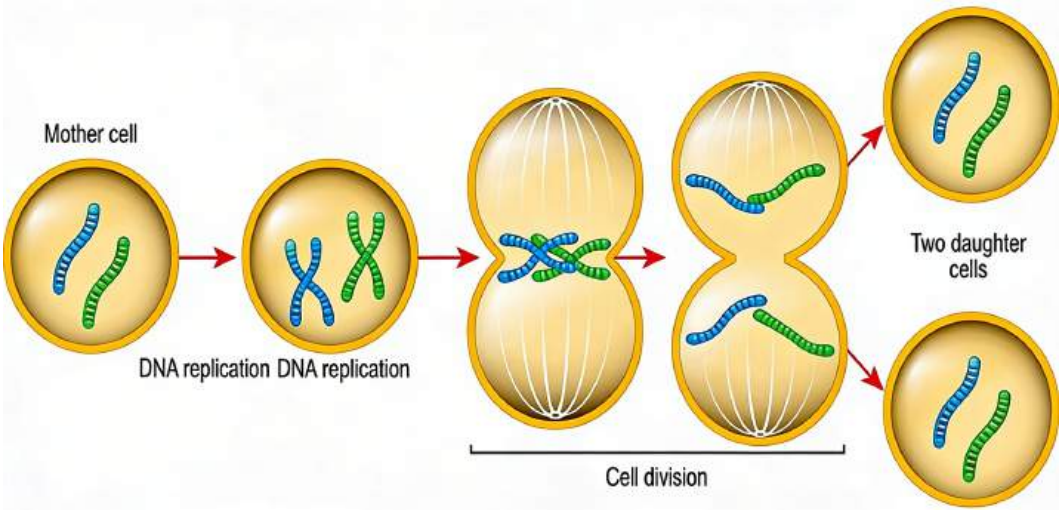
- Series of **events** within the cell that **prepare** the **cell** for **dividing into two daughter cells**.
- **Two phases:**

Mitosis

- Period in which the cell divides into 2 daughter cells
- Lasts for short period (one hour).
- Changes are visible with microscope.

Interphase

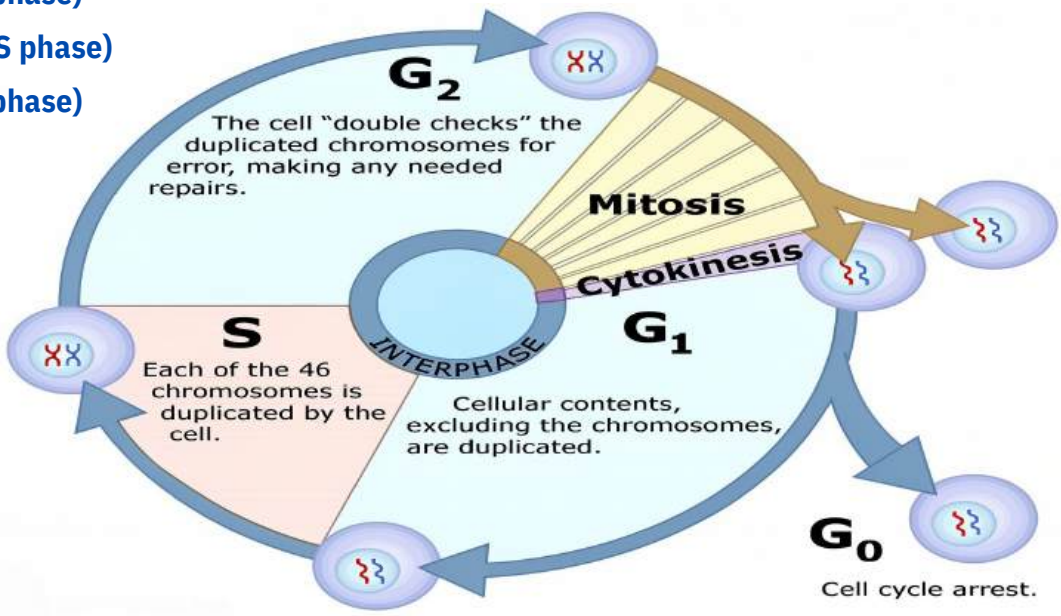
- Period between two successive divisions
- Lasts for 20 hours in rapidly dividing cells
- Changes cannot be detected with microscope.



Interphase

Subdivided into three phases:

- Gap 1 phase **(G1 phase)**
- Synthesis phase **(S phase)**
- Gap 2 phase **(G2 phase)**



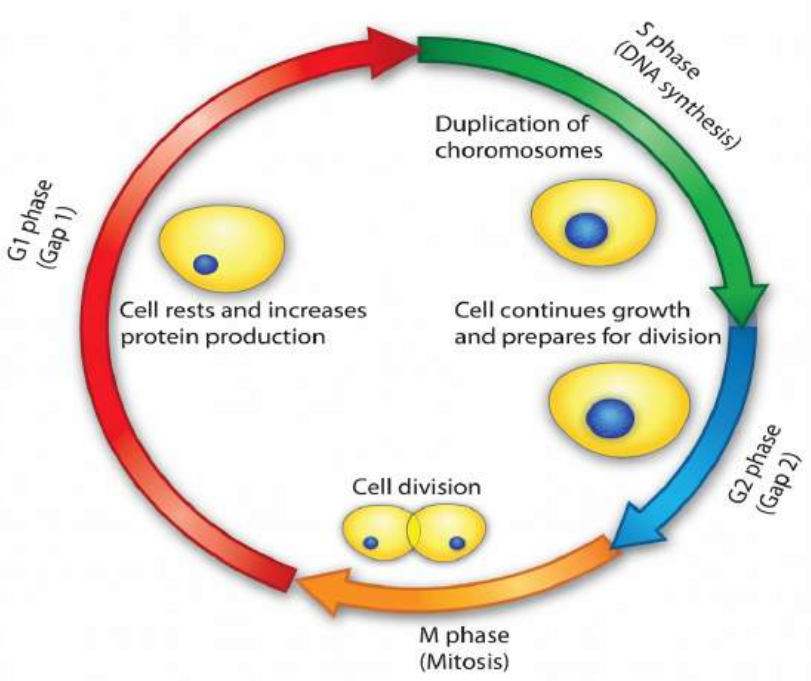
Gap 1 phase (G1 phase): 8 hours	• **Cells become specialized working cells:**
	  ◦ The more specialized the cell, the longer the G1 -phase & the less rate of division
	  ◦ It varies in duration depending on the rate of cell division and specialization (differentiation)
	• Cell Nucleus contains **46 single** chromosomes **(s-chromosomes or chromatids)**
	• **Cells grow in size & acquire energy (ATP)**
	• **RNA & protein synthesis** required for **duplication** of DNA

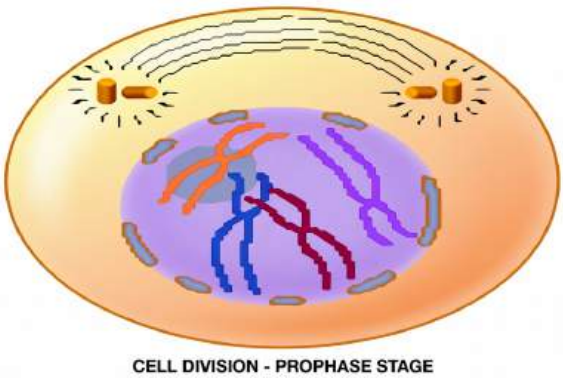
Synthesis phase (S phase): 8 hours	• **Duplication:**
	  ◦ DNA so each cell contains **46 d-** chromosomes
	  ◦ **Centrioles**

Gap 2 phase (G2 phase): 4 hours	• Any error in DNA **duplication** (replication) is corrected
	• **For mitosis:**
	  ◦ **RNA & protein synthesis**
	  ◦ Tubulin is formed to build microtubules
	  ◦ Energy is stored

Stable phase (GO phase):

- Cells that have left the cell cycle
- In resting stage - GO (outside) phase - stable phase




CELL DIVISION - PROPHASE STAGE

Cell Renewal

- **Most of the working specialized cells are not in an active cycle**
  - They perform their specific functions in prolonged **G1** phase

Specialized cells are classified according to their ability to reproduce themselves into:

Non-renewing cells

- **Highly specialized cells leave cycle in G1 forever & go to G0**
  - Never divide again **(permanent exit)**
  - If lost → not replaced with new cell
  - **Heart** muscles - **Nerve** cells

Potentially renewable cells

- **Some specialized cells go to G0:**
  - Can return to continue the cycle on need for replacement **(transient exit)**
  - **Liver** cells (if destroyed or partially removed)

Continuously renewing cells

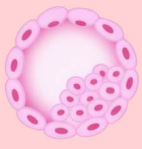
- **Some highly specialized cells:**
  - End cells (cannot divide)
  - Can be replaced from stem cells (blood cells - sperms)

Stem Cells

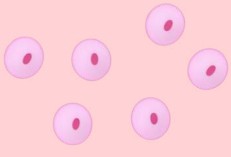
- Undifferentiated cells that capable of self renewal
- **Two types:**

Pluripotential or multipotential Stem cells

- Have potential to produce **more than one type** of specialized cells.
- Blood cells.
- Cells lining gastro-intestinal tract.



Pluripotent Stem Cell



Multipotent Stem Cell

Unipotential Stem cells

- Have potential to produce **only one type** of specialized cells.
- Male germ cells.

Cell Death

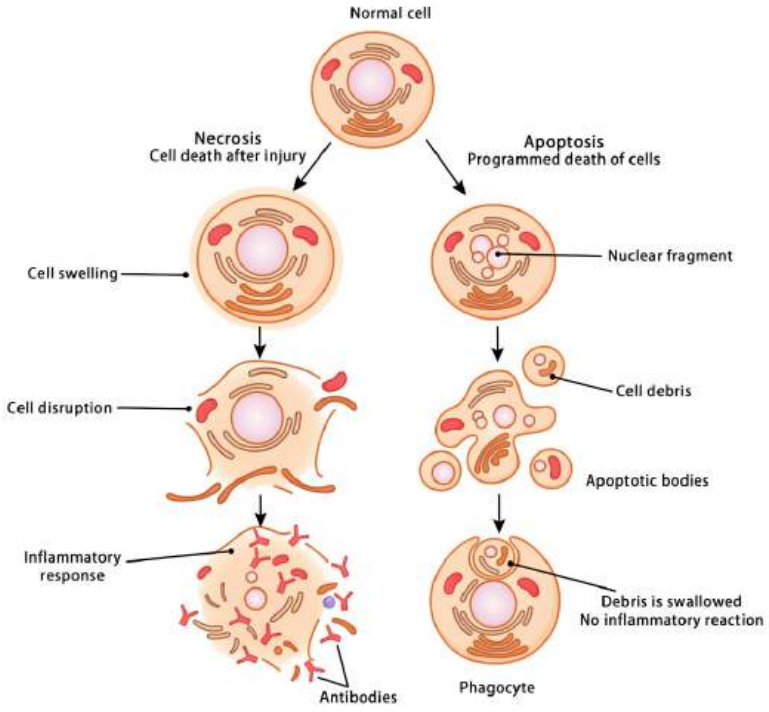
	Necrosis	Apoptosis

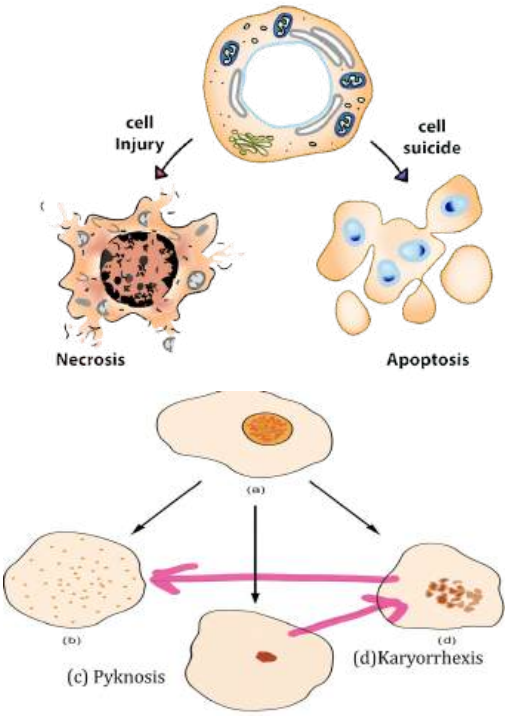
Definition	• **Results from:**
	  ◦ Anoxia
	  ◦ Mechanical injury
	  ◦ Exposure to toxins
	• **Pathological condition**
		• **Active programmed cell death:**
		  ◦ Occuring normally at end of cell life span
		• **Pathological** or **Physiological**

LM	• **Necrotic cells and their organelles:**
	  ◦ Swell
	  ◦ Burst releasing their content into
	• **Extracellular space**
		• **Apoptotic cells:**
		  ◦ Don't swell
		  ◦ Decrease in size

	• **Nuclei & chromatin:**
	  ◦ **Pyknosis:**
	  ▪ Nuclei are small darkly sained with condensed chromatin
	  ◦ **Karyorrhexis:**
	  ▪ Fragmented into pieces by endonuclease enzyme
	  ◦ **Karyolysis:**
	  ▪ Dissolve then disappear	

Fate	• Cells **degenerate** • Phagocytosed by macrophages	• Cells break into **large vesicles** • Phagocytosed by macrophages





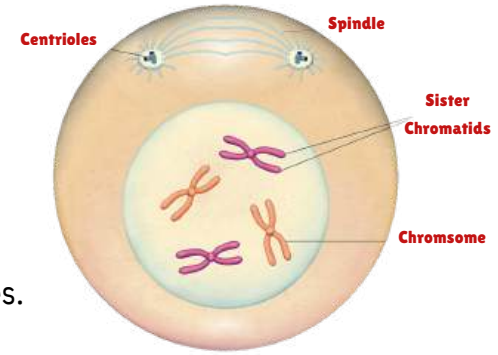
Cell Division

I. Mitosis

- Division of nucleus to produce **2 daughter cells** genetically identical to parent cell.
- **4 stages:**

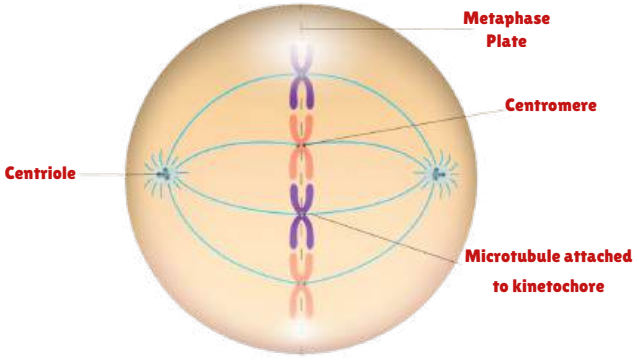
1. Prophase

- **Chromosomes (46 d- chromosomes) gradually become:**
  - **Shorter & darker** (visible as fine threads)
- **Disappearance of nucleoli & nuclear envelope**
- **Centrioles move to opposite cell poles:**
  - By cytoplasmic microtubules radiating out from microtubular organizing centre (MTOC) around centrioles.
- **Microtubules organized to form spindle.**

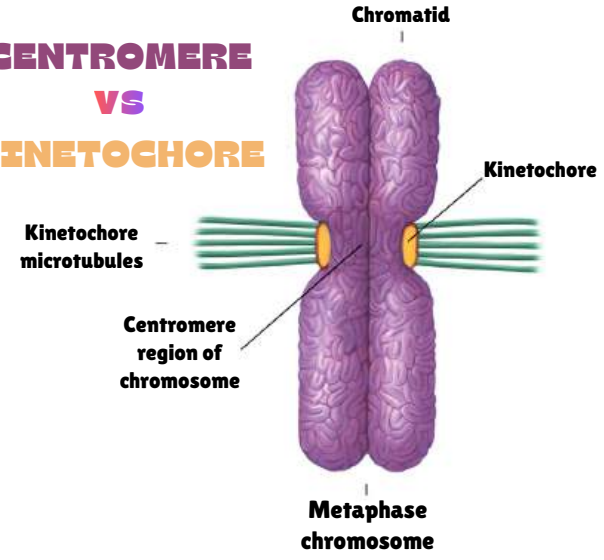


2. Metaphase

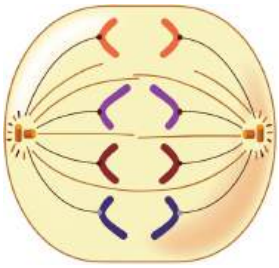
- **Chromosomes migrate to equatorial plane of cell "meta phase plate"**
- **At centromere of each chromosome:**
  - Dense plaque **(kinetochore)** as site of attachment of chromosomal microtubules
- **Microtubules of mitotic spindle (arise from MTOC) are:**
  - **Cytoplasmic microtubules:**
    - For cell **elongation**
  - **Chromosomal microtubules:**
    - Attached to kinetochores for arrangement of chromosomes in **equatorial plane**
  - **Astral microtubules: "star like "**
    - Around centrioles to establish spindle **axis**



CENTROMERE VS KINETOCHORE

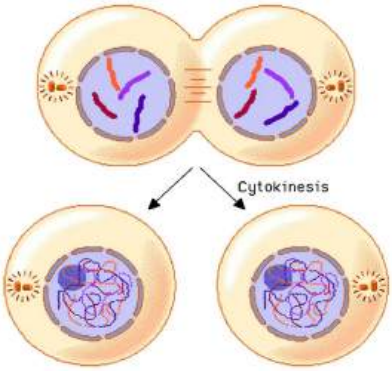


3. Anaphase

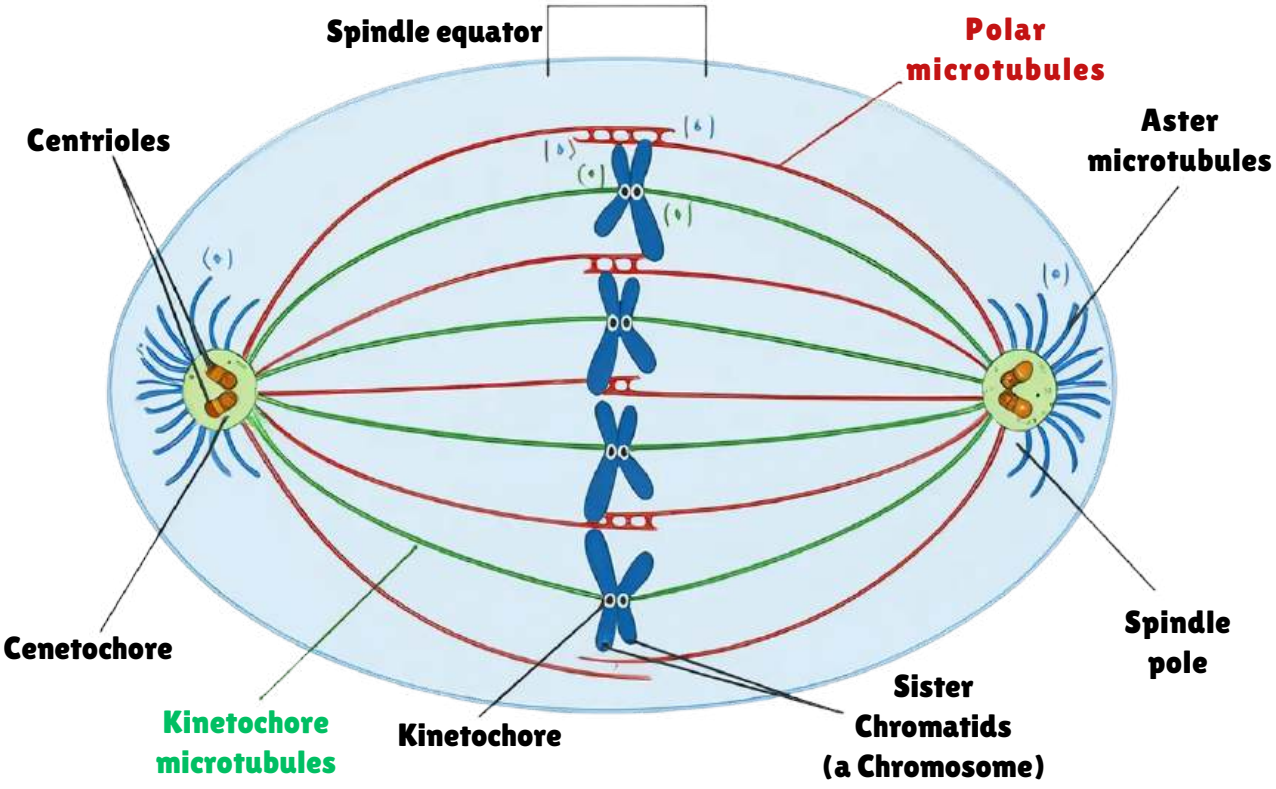


- **Migration to opposite poles of cell:**
  - by elongation of cytoplasmic microtubules.
- **By pulling action of chromosomal microtubules:**
  - Each d-Chromosome splits longitudinally at centromere → its two sister chromatids separate.

4. Telophase



- **Constriction develops at equatorial plane (cleavage furrow):**
  - Contraction of actin filaments → cytoplasm divided into 2 halves
- **Reappearance of nucleoli & nuclear envelope**
- **46 chromatids (s-chromosomes) of each cell begin to:**
  - Lengthen - uncoil - lose their visibility



II. Meiosis

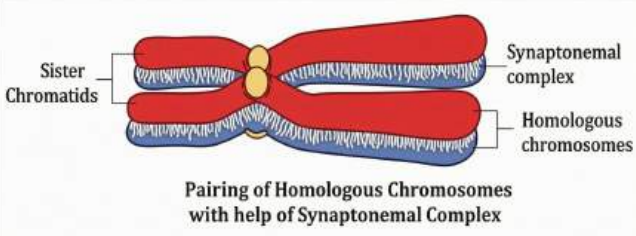
- Special type of cell division in which diploid cells in the testis & ovary undergo 2 successive divisions **(without S-phase in between)** to produce haploid germ cells **(sperms or ova)**.

First Meiotic Division (Reduction Division):

1. Prophase [1]

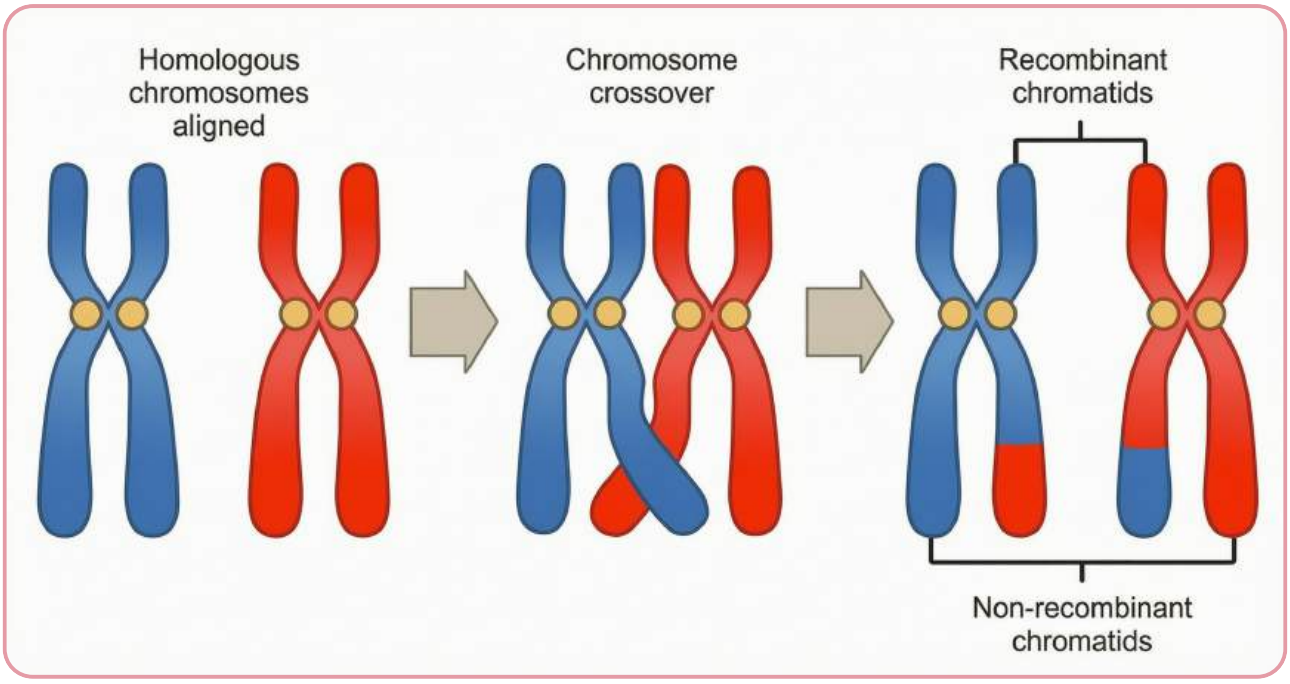
- **Takes long period of time**
- **In male (spermatogenesis) → 22 days**
- **In female (oogenesis) → 12-45 years** to be completed

Prophase I includes the following stages:



Pairing of Homologous Chromosomes with help of Synaptonemal Complex

- **46 d-chromosomes** appear as long thin threads
- **Disappearance of nucleoli & nuclear envelope:**
  - Freeing chromosomes into the cytoplasm
- **Chromosomes appear as 23 pairs (bivalents):**
  - Each pair formed of 2 homologous chromosomes (1 maternal 1 paternal)
- **Bivalents become shorter & thicker:**
  - Appear as tetrads (4 chromatids attached along their length)
- **Crossing over occurs at the chiasmata (by help of recombinase enzyme):**
  - In homologous chromosomes exchange of segments between non-sister chromatids
- **Chromosomes begin to separate revealing chiasmata**



2. Metaphase [1]

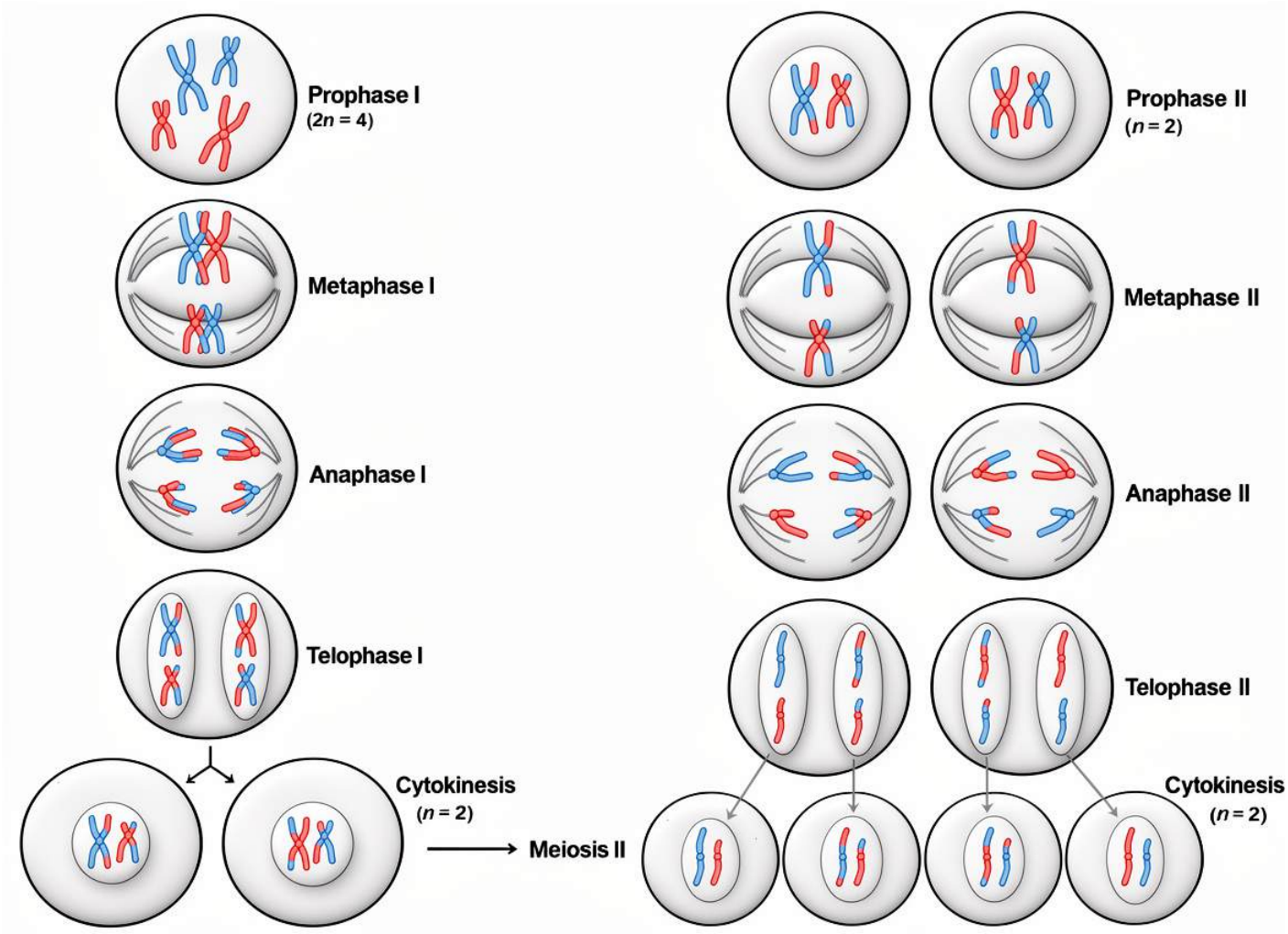
- **23 bivalent d-chromosome**s aligned as pairs in equatorial plane
- Attached to microtubules of mitotic spindle

3. Anaphase [1]

- Bivalent d-chromosomes separate from one another
- Move to opposite poles of cell
- Each cell receives one of **homologous d-chromosomes**

4. Telophase [1]

- At the end of this stage two daughter cells are formed
- Each daughter cell has **23d -chromosomes**

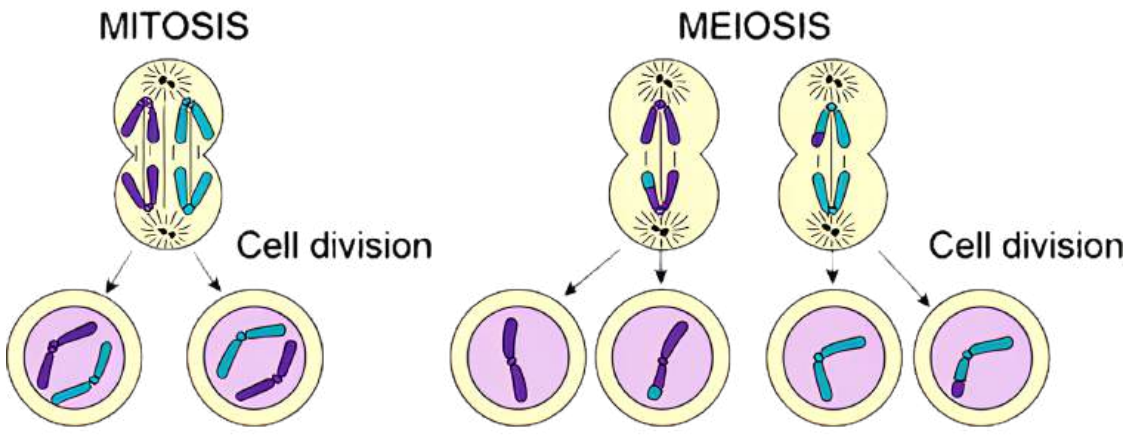


Second Meiotic Division (Equatorial Division):

- Mitosis-like division
- Occurs rapidly after the first division
- Very short interphase ((without S-phase)) each daughter cell has **23 d-chromosomes**

- **Prophase II:**
  - Chromosomes are **shorter** **and** **thicker**
  - Mitotic spindle starts to appear
- **Metaphase II:**
  - **23 d-chromosomes** are aligned at the equatorial plate
- **Anaphase II:**
  - Each d-chromosome splits at centromere into two chromatids **(s-chromosomes)**
  - which move to opposite poles of cell
- **Telophase II:**
  - 2 daughter cells separate
  - Each daughter cell has **23s-chromosomes** (haploid number of chromosomes)

	Mitosis	Meiosis
Site	• Somatic cells	• germ cells of testes & ovaries
Number of divisions	• Single	• Two successive divisions • **Without S-phase in-between**
Crossing over exchange of genes	• **Absent**	• **Present**
Separation	• Each chromosome divides longitudinally at centromere into **2 chromatids**	• **In 1st division:** each chromosome of bivalent moves towards one pole
Daughter cells	• **Two (somatic cells)** *with **diploid number** of chromosomes* • **Genetically identical**	• **Four (germ cells)** *with **haploid number** of chromosomes* • Show **genetic variation**



Human chromosome

Chromatin fibers:

- Formed of **DNA** molecule coiled around histone & non histone proteins
- **Condensed** and tightly **coiled** during **mitosis** & **meiosis**
- Visible with light microscope

GI-Phase of interphase:

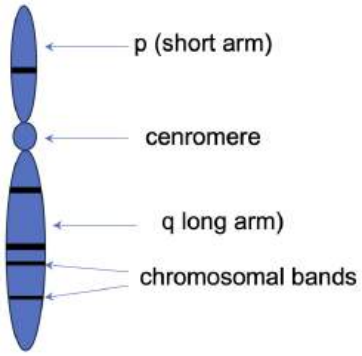
- Chromosome formed of single-thread of DNA called **s-chromosome** or **chromatid**

s-Phase of interphase:

- Chromosome formed of **double**-threads called **d-chromosome**

During late prophase & metaphase:

- Each chromosome formed of 2 chromatids connected at centromere **that divides d-chromosome into :**
  - Short arm (P)
  - Long arm (Q)



Kinetochores:

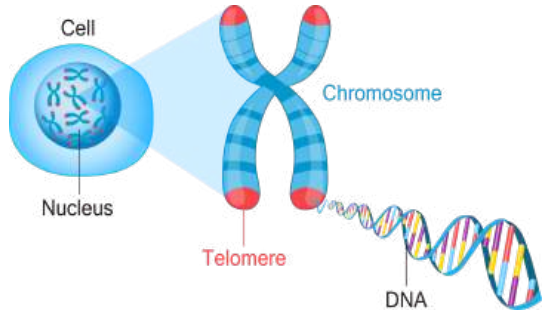
- 2 discs of protein located at the centromere
- To which spindle fibres are attached during cell division

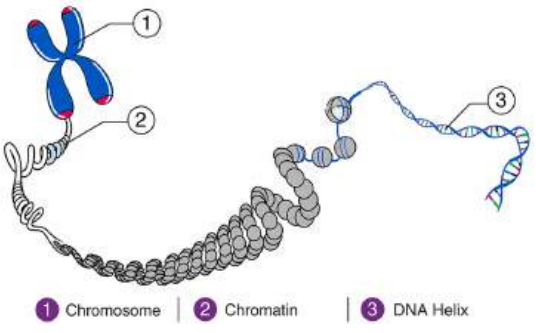
Genes:

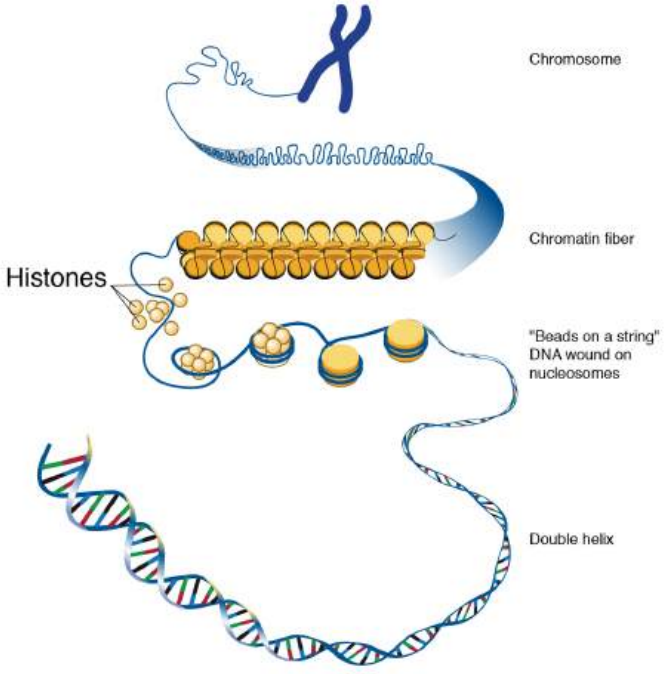
- Segments of DNA code for formation of specific proteins
- Each gene has a precise position **(locus)** on the chromosome

Telomeres:

- Regions of **repeated** sequence at chromosomal ends
- Protect its end from destruction and prevent end to end fusion of chromosomes

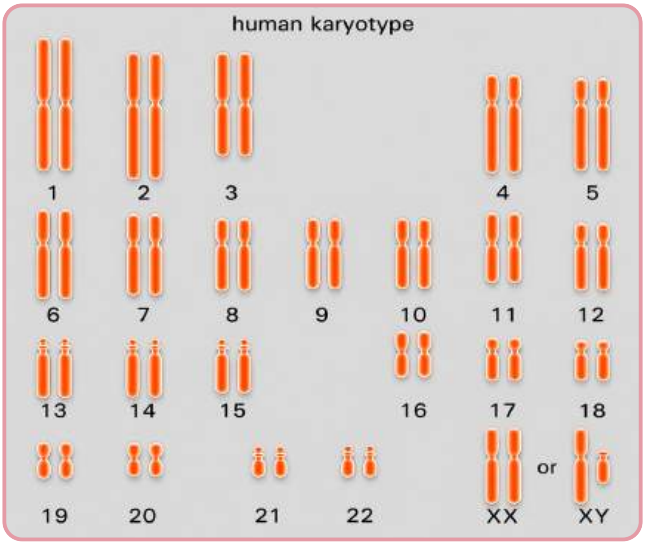


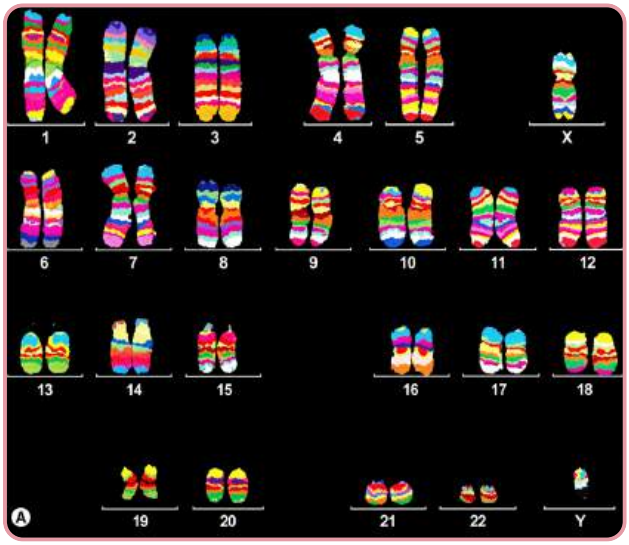




Karyotyping

- **Definition:**
  - **Study of number & type of chromosomes according to:**
    - Their length
    - Position of centromere
- **Technique:**
  - **Best cells** to study chromosomes **(Leucocytes)**
  - Cells allowed to divide by **mitosis** then **stopped** at **metaphase**
  - At metaphase Chromosomes are **photographed & matched into pairs** → arranged in descending order of length
  - Chromosomes are studied using specialized computer software programs
- **Banding technique:**
  - **Better differentiate chromosomes by:**
    - Staining **different segments** **(genes)** with **different colors**





Classification of Chromosomes

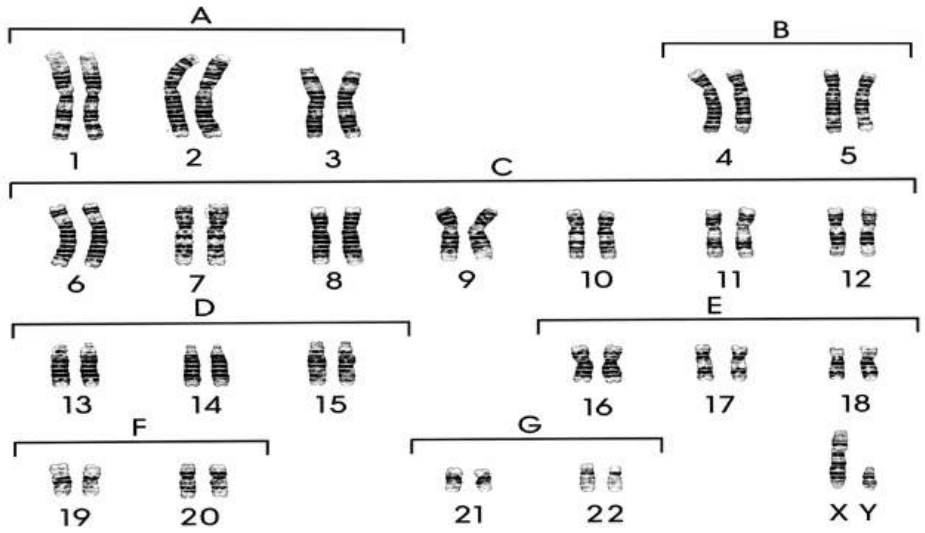
According to gene content

Autosomes	Sex chromosomes [One pair]

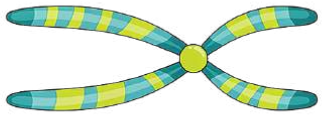
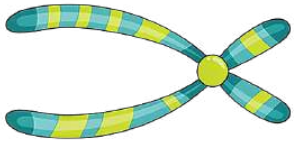
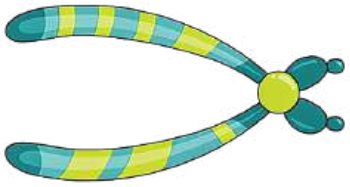
• **22 homologous (identical) pairs:**
  ◦ Control somatic characters
	• **Homogonous (identical):**
	  ◦ In females (XX)
	• **Heterogonous (non-identical):**
	  ◦ In males (XY)
	• **Control sex**

According to chromosomal length

Homologous 22 pairs	Sex chromosomes [One pair]
• Numbered serially **from 1-22** • Then grouped into **7 groups** in descending order of **length** (A, B, C, D, E, F and G)	• **(XX)** OR **(XY)** • → arranged either alone or **X** in group **C** & **Y** in group **G**



According to position of centromere

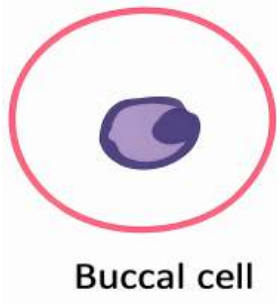
Metacentric	• **Centromere** at **center** of chromosome • Two **arms** are **equal** (p = q)	
Sub-metacentric	• **Centromere** is **midway** between **centre** & **upper end** • **Short** & **long** arms (p shorter than q)	
Acrocentric	• **Centromere** is **very close** to **upper end** • **Short** & **long** arms (p is very short) • Some of these chromosomes except Y • Have **small masses** of **chromatin** **(satellites)** • Attached to short arm by a narrow stalk (secondary constriction) containing genes for rRNA	
Telocentric	• **Centromere** is **terminal** • Not present in humans	

Sex Chromatin [Barr Body]

- **Definition & Nature:**
  - **Darkly stained mass of chromatin:**
    - First seen by Murray Barr
  - **Inactive coiled dark stained (X) chromosome in:**
    - Nuclei of female cells
  - **Other (X)** chromosome is **active** extended & non apparent


Neutrophil

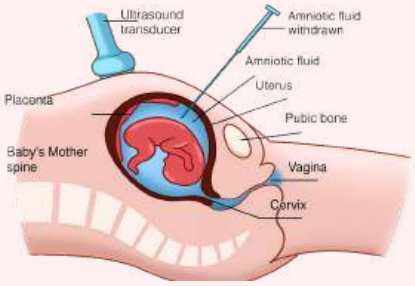
- **Site:**
  - **Nuclear envelope (inner aspect) of :**
    - **60%** of female epithelial buccal cell nuclei
  - **Drumstick-like mass attached to nucleus:**
    - **3-5%** of female blood neutrophil


Buccal cell

- **Important Rules:**
  - **Each somatic cell must have at least one (X) chromosome to be active:**
    - Carries other genes rather than sex determining genes
  - **Barr body appears in:**
    - Normal **female** cells (X**X**)
    - Male cells with an **extra X** chromosome (**X**XY, Klinefelter syndrome)
  - **Barr body NOT apparent :**
    - Normal **male** cells (XY)
    - Female cells with **only one X** chromosome (XO, Turner syndrome)

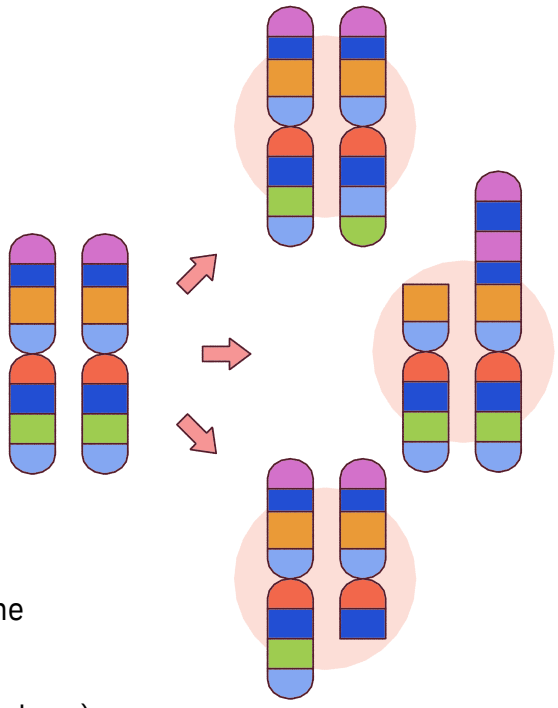
Clinical Importance of Chromosomal Examination

- **Diagnosis of genetic sex in doubtful cases of hermaphroditism**
- **Identification of fetal sex by:**
  - Staining cells obtained from amniotic fluid
- **Diagnosis of sex chromosome abnormalities as in:**
  - Turner's syndrome (XO)
  - Klinefelter's syndrome (XXY)
- **Diagnosis of structural abnormalities in chromosomes:**
  - Deletion in mental retardation
  - Translocation in chronic myeloid leukemia
- **Diagnosis of numerical abnormalities as in mongolism**
- **Medico-legal importance in forensic medicine**



Chromosomal Aberrations [Abnormalities]

- **Any deviation from normal number or structure**
- **Aberrations may occur in:**
  - Autosomes (22 pairs)
  - Sex chromosome pair
- **Most types of aberrations cause:**
  - Mental retardation
  - Developmental retardation



Causes of chromosomal aberrations

- **Radiation:**
  - Chromosomal damage & **non-disjunction**
- **Viral infections:**
  - German measle → fragmentation of chromosome
- **Pregnancy in old age:**
  - Increase risk of **non-disjunction** (very long prophase)
- **Drugs:**
  - Cytotoxic drugs e.g. **colchicine** → **inhibit** formation of **mitotic spindle**
- **Autoimmune diseases:**
  - Usually associated with **non-disjunction**

Numerical Aberrations

- **Anomalies involving deviation from normal number of chromosomes.**
- **Occur in germ cell or somatic cell in form of:**

I. Euploidy

Karyotyping shows **exact multiple of basic haploid number & exceeds diploid number**

Triploid (3n)	Tetraploid (4n)	Polyploidy (5n, 6n, or more)
69 chromosomes	**92 chromosomes**	**One or both gametes are not haploid**

II. Aneuploidy (abnormal ploidy)

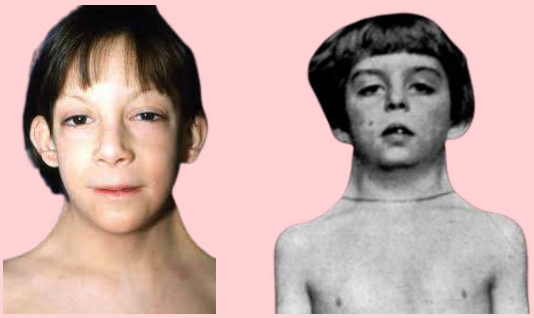
- Abnormality is **not exact multiple** of **haploid** number
- Karyotype shows **addition** or **loss** of **1 chromosome**

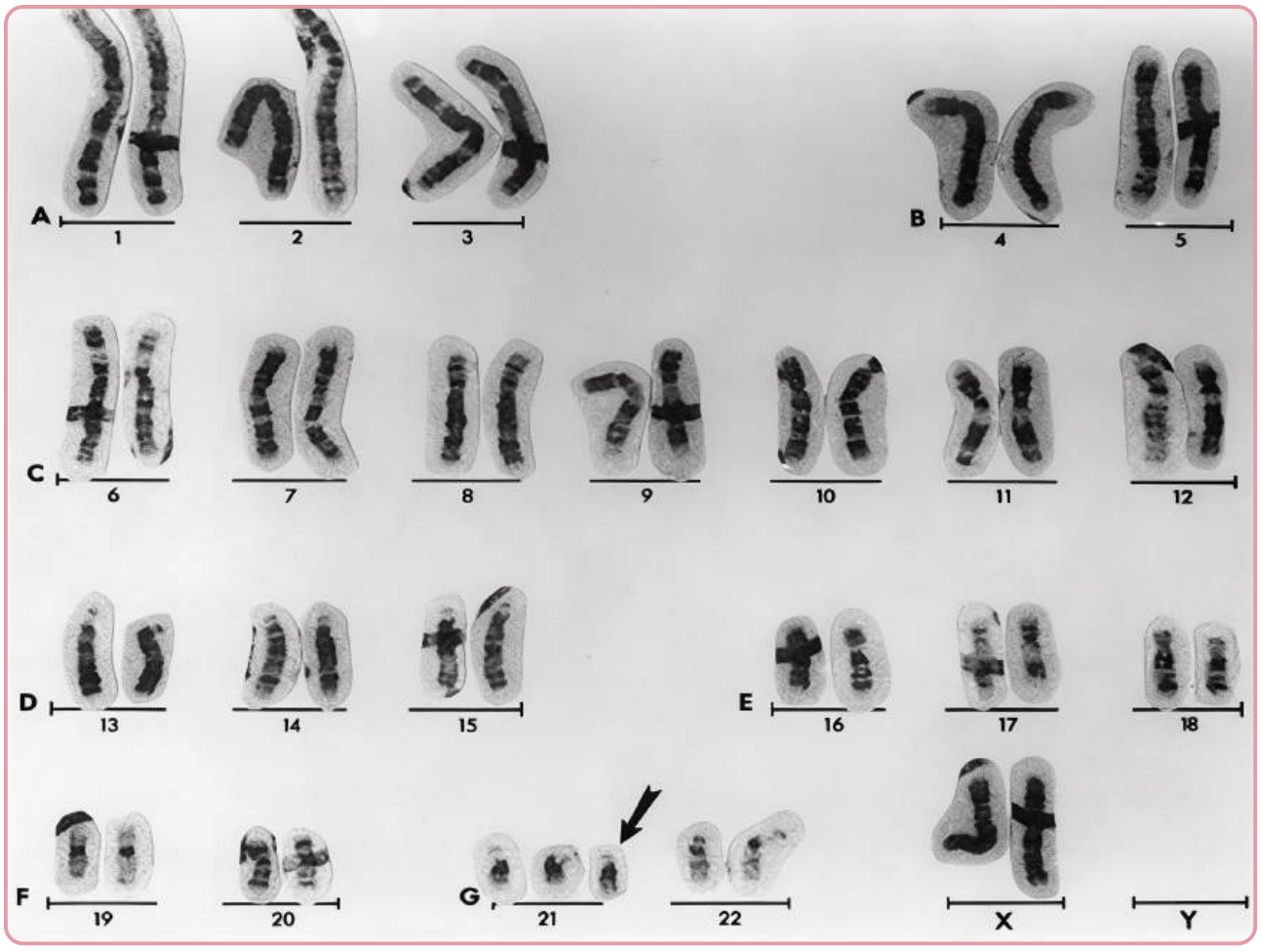
Trisomy

- Addition of an **extra** chromosome → karyotype is (2n + 1)
  - 3 copies of chromosome instead of 2
- ***Down syndrome*** (trisomy 21, mongolism)

Monosomy

- **Missing** of 1 chromosome → karyotype is (2n - 1)
- 1 copy of chromosome instead of 2 in **chromosomal pair**
- ***Turner syndrome*** (45 chromosomes)





Causes of aneuploidy

Non-disjunction:

- **Primary non-disjunction:**
  - **2 homologous (bivalent) chromosomes:**
    - Fail to separate during **first** meiotic division
  - Results in **4** abnormal daughter cells
- **Secondary non-disjunction:**
  - **2 chromatids:**
    - Fail to separate at centromere either during **second** meiotic division or mitosis
  - Results in **2** normal & **2** abnormal → meiosis
  - Results in **2** abnormal → mitosis

Mosaic:

- **Secondary non-disjunction**
  - occurs in mitosis after many normal divisions
  - cells have more than one karyotype (46, 47, 45).

Failure of duplication:

- 1 chromatid (s-chromosome) fails to duplicate during S-stage

Simple loss:

- Failure of chromosome to align during metaphase or lagging to move in anaphase

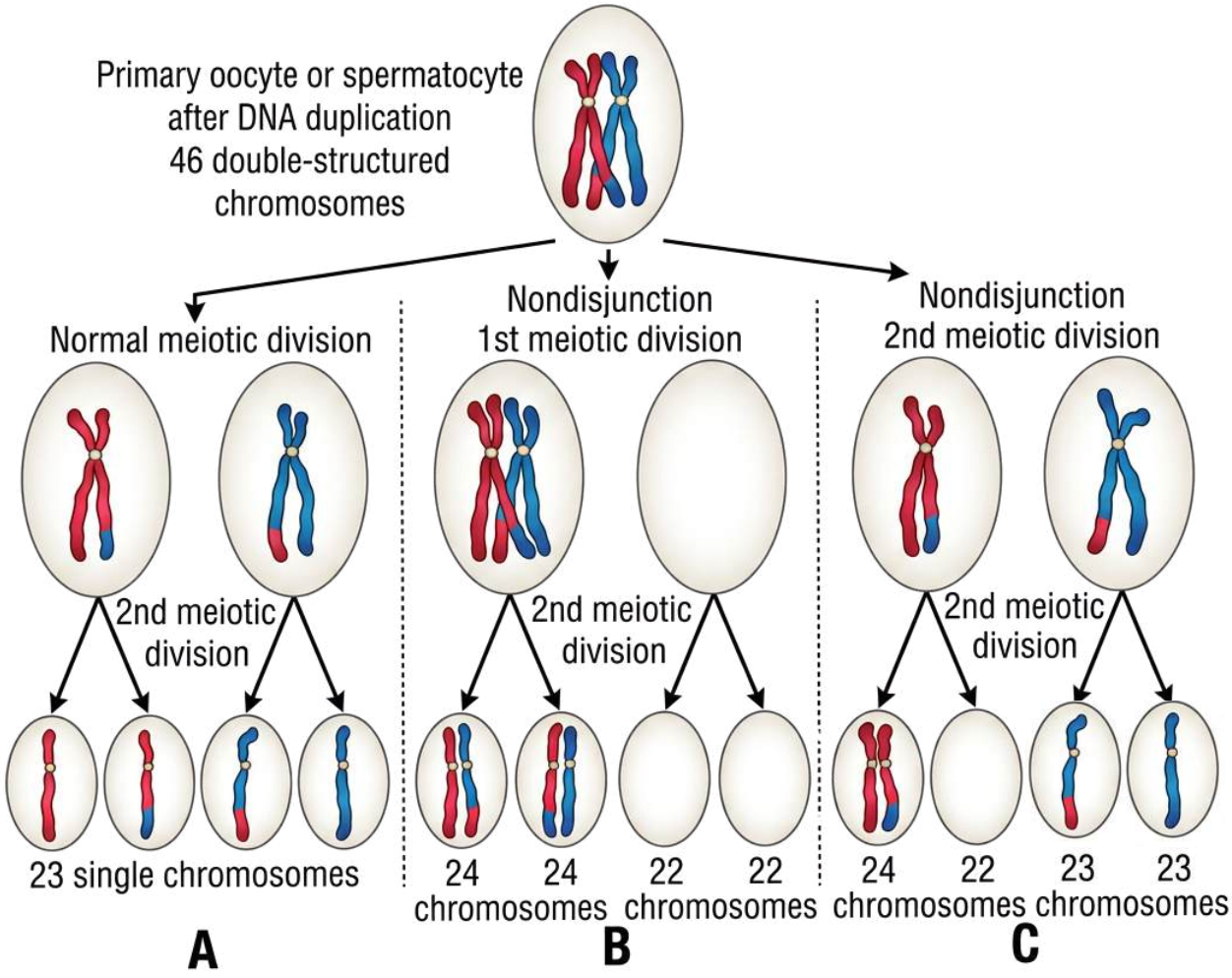


Figure 1.5. A. Normal maturation divisions. **B.** Nondisjunction in the first meiotic division. **C.** Nondisjunction in the second meiotic division.

Numerical aberrations in Autosomes

Down Syndrome (Mongolism)

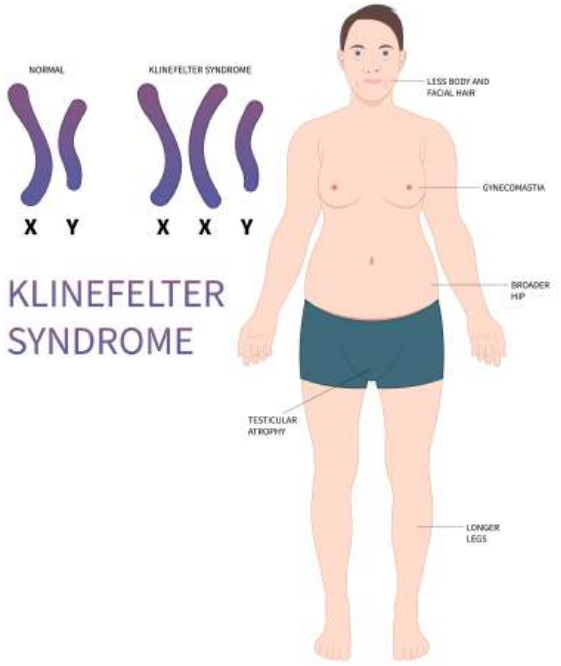
Occurs as a result ofL

1. **Non-disjunction of chromosome 21 (Trisomy 21):**
   - Mongol child Cells contain **47** chromosomes
   - **Extra** chromosome is similar to chromosome **21**
2. **Translocation (21 and 14):**
   - **Characteristic features:**
     - Cardiac abnormalities
     - Mental retardation
     - Small genital organs
     - Lateral upward slope of eyes
     - Small ears
     - Short broad nose & neck

Numerical aberrations in Sex chromosomes

- **Causes:**
  - **Non-disjunction** in **first** meiotic division of primary oocyte
  - Produced ovum may contain (XX) OR no X (0)

Klinefelter's syndrome (47, XXY)



- **Trisomy of sex chromosome**
- **Male** having additional X chromosome
- **Non-disjunction of X chromosomes → 1st meiotic division of oocyte:**
  - **Ovum (2 X)** fertilized with **sperm (Y)**

Characteristic features:

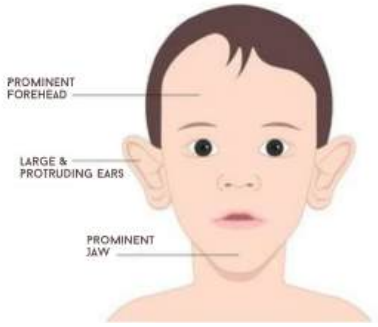
- Mentally retarded tall male
- Small testis
- Large breast → Widely separated nipples

Multiple X Syndrome (47, XXX)

- **Trisomy** of sex chromosome
- Female having **additional X chromosome** (triple X syndrome) → **2 Barr** bodies
- Same cause as Klinefelter but ovum fertilized by sperm having X

Characteristic features [Girls show] :

- Delayed language development
- Auditory disorders
- Motor coordination problems

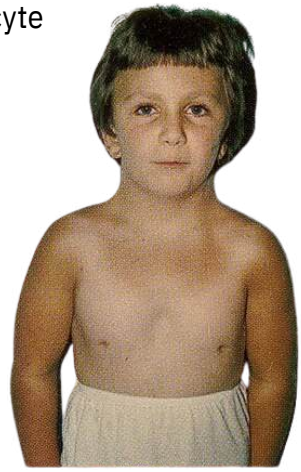


Turner's Syndrome (45, XO)

- **Monosomy of sex chromosome**
- Female with only one X chromosome → No Barr bodies → missing of X chromosome
- Non disjunction of X chromosomes during first meiotic division in oocyte
- Ovum with no X is fertilized with a sperm having X chromosome

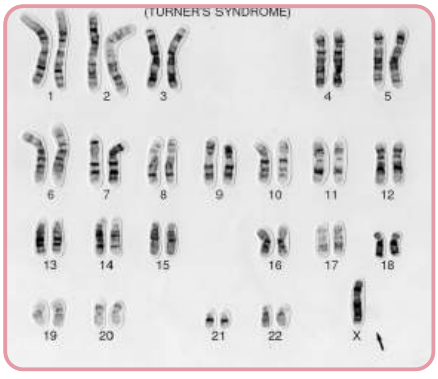
Characteristic features:

- Short female
- Underdeveloped external genitalia
- Primary amenorrhea
- Underdeveloped ovaries
- Mental retardation
- Edema of limbs

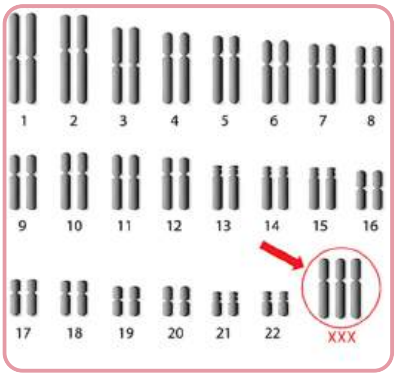


Klinefelter's syndrome

Turner's Syndrome



Multiple X Syndrome



Structural Aberrations of chromosomes (Mutation of Chromosomes)

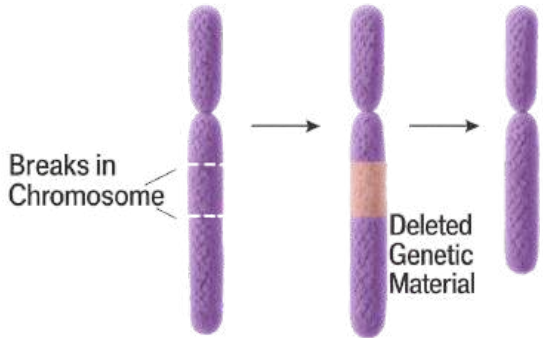
Definition:

- **Abnormalities in structure of chromosomes**
  - **Balanced aberration:**
    - Chromosome has normal complement of genetic information
  - **Unbalanced aberration:**
    - Additional or missing information → affected phenotype

Types of structural aberrations:

1. Breaks

- **Heal rapidly**
- **Reunion of the 2 sticky ends of the chromatids**

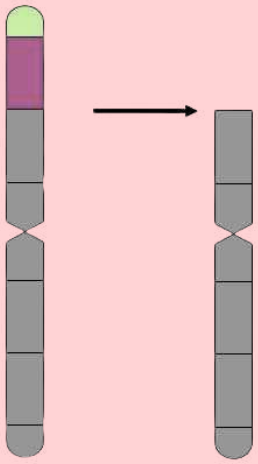


2. Deletion

Loss of a fragmented part of chromosome

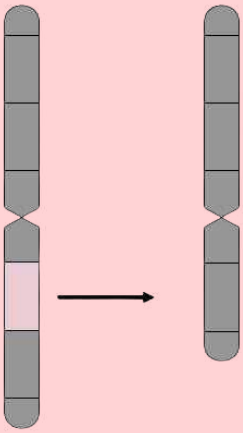
Terminal deletion

- Loss of a segment from **one end** by **1 break**



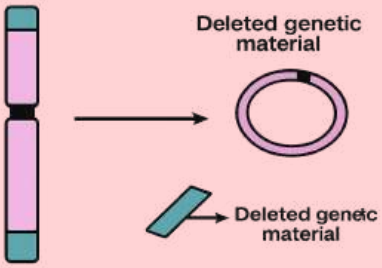
Interstitial deletion

- Loss of fragments between **2 breaks** in **same arm**
- Fusion at break sites



Ring chromosome

- **2 breaks** → loss of fragments
- Reunion in a **ring form**

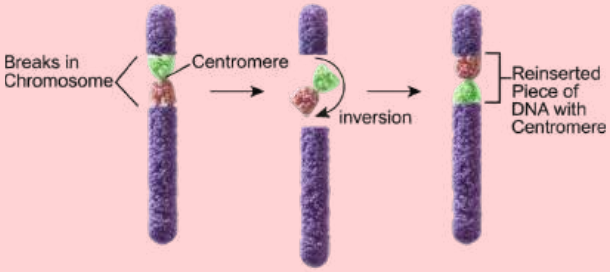


3. Inversion

2 breaks in chromosome followed by rejoining in inverted form

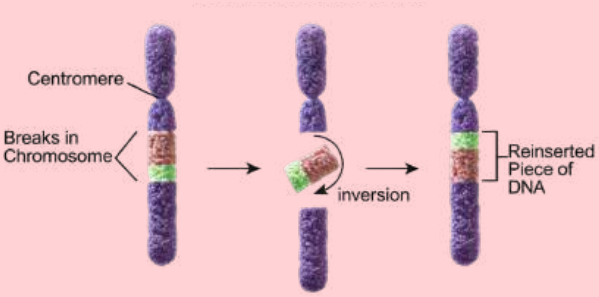
Pericentric

- Break occurs on **either side** of centromere



Paracentric

- Break occurs on **one side** of centromere



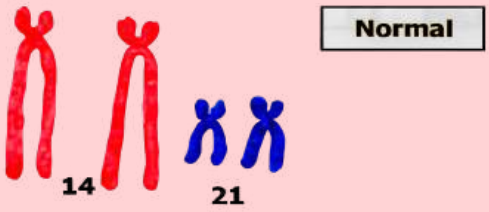
4. Translocation

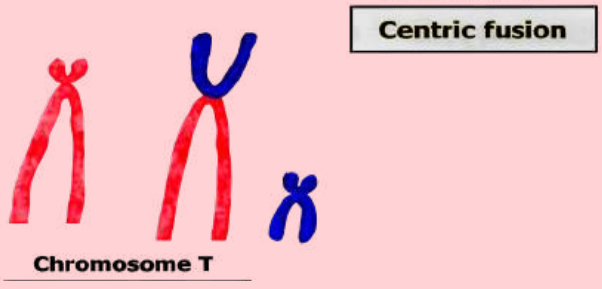
Transfer of chromosomal segment carrying genetic material to another **non-homologous** chromosome

Centric Fusion

3-4% of cases of Down syndrome

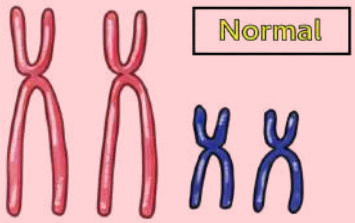
- Acrocentric chromosomes **21** & **14**
- Fusion of **long arms** of chromosomes **21** & **14**
  - **"chromosome t"** is formed
- **Short arms** of both chromosomes lost (insignificant)

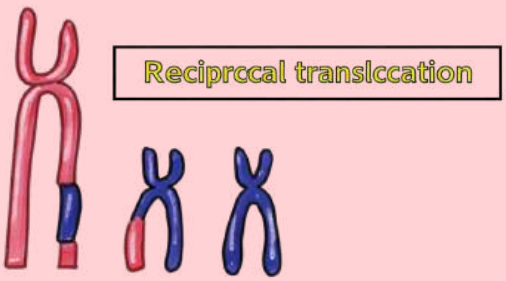




Reciprocal Translocation

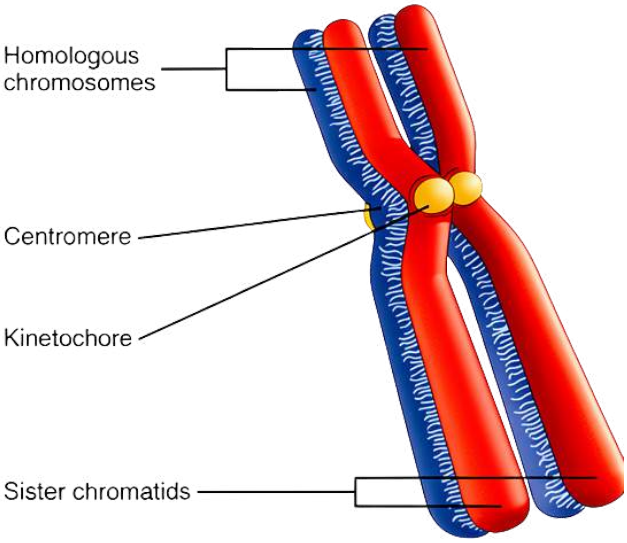
- Exchange of chromosomal material between **2 chromosomes**
- **Balanced:**
  - No chromosomal material is lost or added

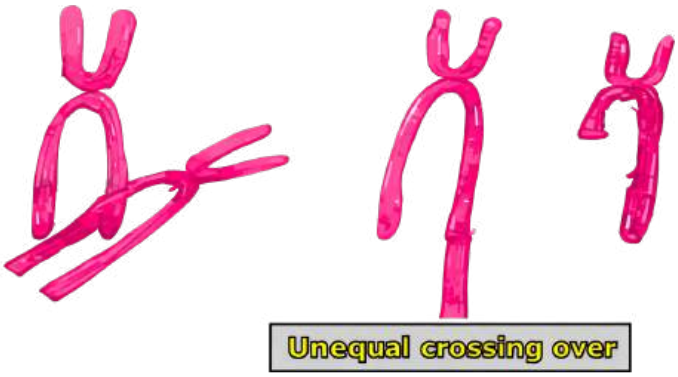




5. Duplication (Addition)

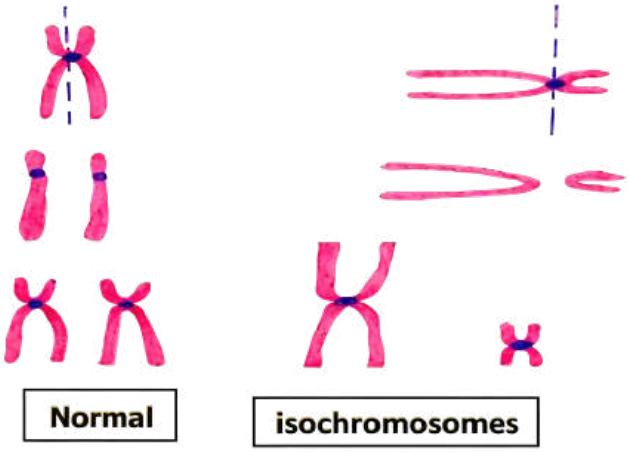
- **Addition of a fragmented segment of one chromosome:**
  - As extra piece to **homologous** chromosome
- **Unequal crossing over of homologous chromosomes**
- **2 copies of same genes on same chromosome :**
  - (double dose of genes on chromosome)





6. Isochromosomes

- Mostly **in submetacentric chromosomes**
- **During anaphase of mitosis**
  - Chromosome divides transversely at centromere, not longitudinally
- **Result → 2 chromatids → 1 short & 1 long**
- **Daughter cells → unequal chromosomes:**
  - One with **p** & **q** arms → **long**
  - Another with **p** & **q** arms → **short** *(isochromosomes)*



READ ONLY

- **Philadelphia chromosome :**
  - Arise by reciprocal translocation between chromosomes 22 & 9
  - It is used to diagnose chronic myeloid leukemia.