Medical Genetics

LECTURE 2

CHROMOSOME ANOMALIES

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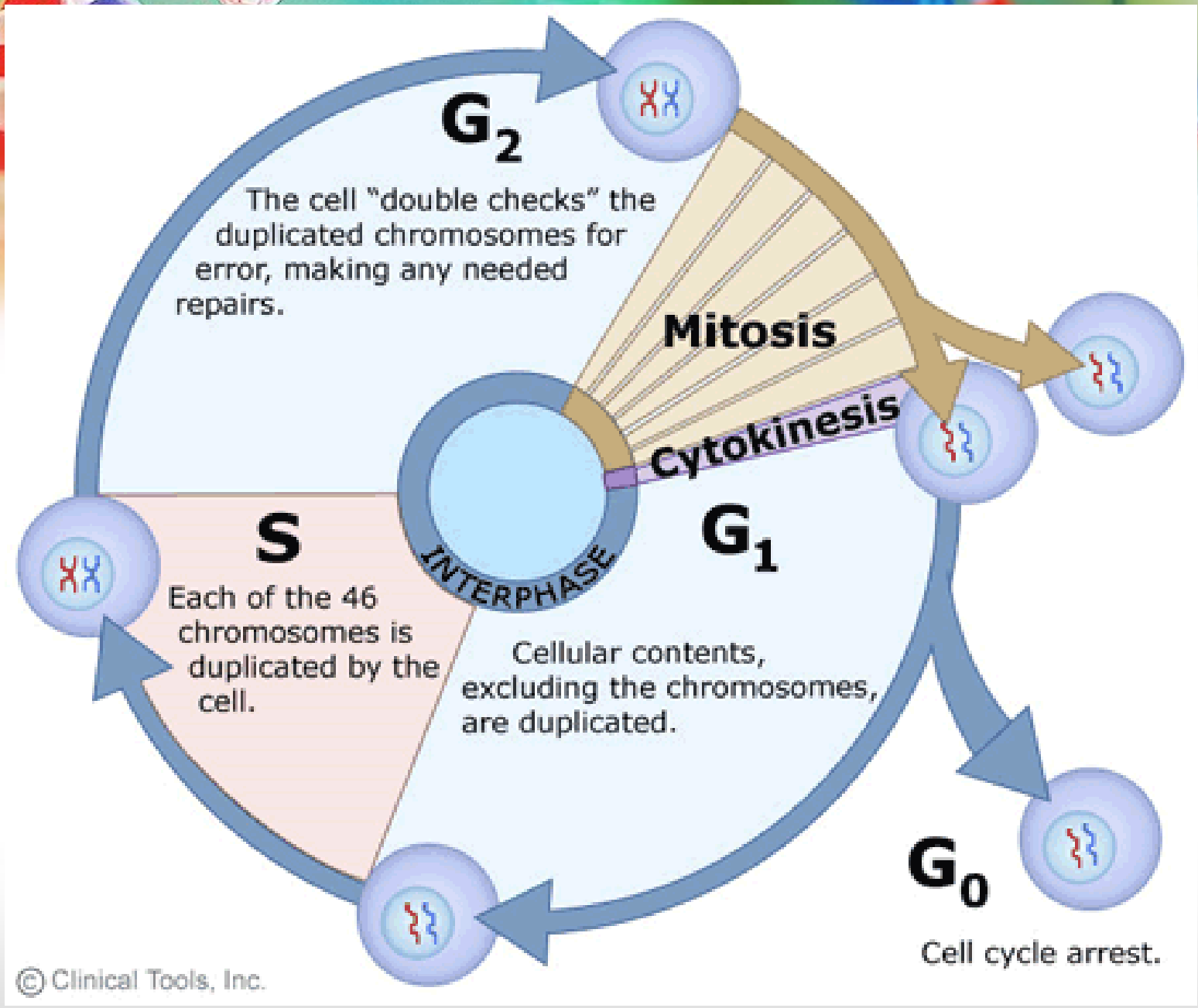
Lecture Objectives:

By the end of this lecture, the students should be able to:

- Describe and explain the events in mitosis & meiosis.
- Define non-disjunction and describe its consequences for meiosis and mitosis.
- Classify chromosomal abnormalities
- Understand the common numerical autosomal disorders: trisomies 21, 13, 18.
- Understand the common numerical sex chromosome disorders: Turner`s & Klinefelter`s syndromes
- Recognize the main structural anomalies in chromosomes


G2
The cell "double checks" the duplicated chromosomes for error, making any needed repairs.
Mitosis
Cytokinesis
INTERPHASE
G1
Cellular contents, excluding the chromosomes, are duplicated.
S
Each of the 46 chromosomes is duplicated by the cell.
G0
Cell cycle arrest.
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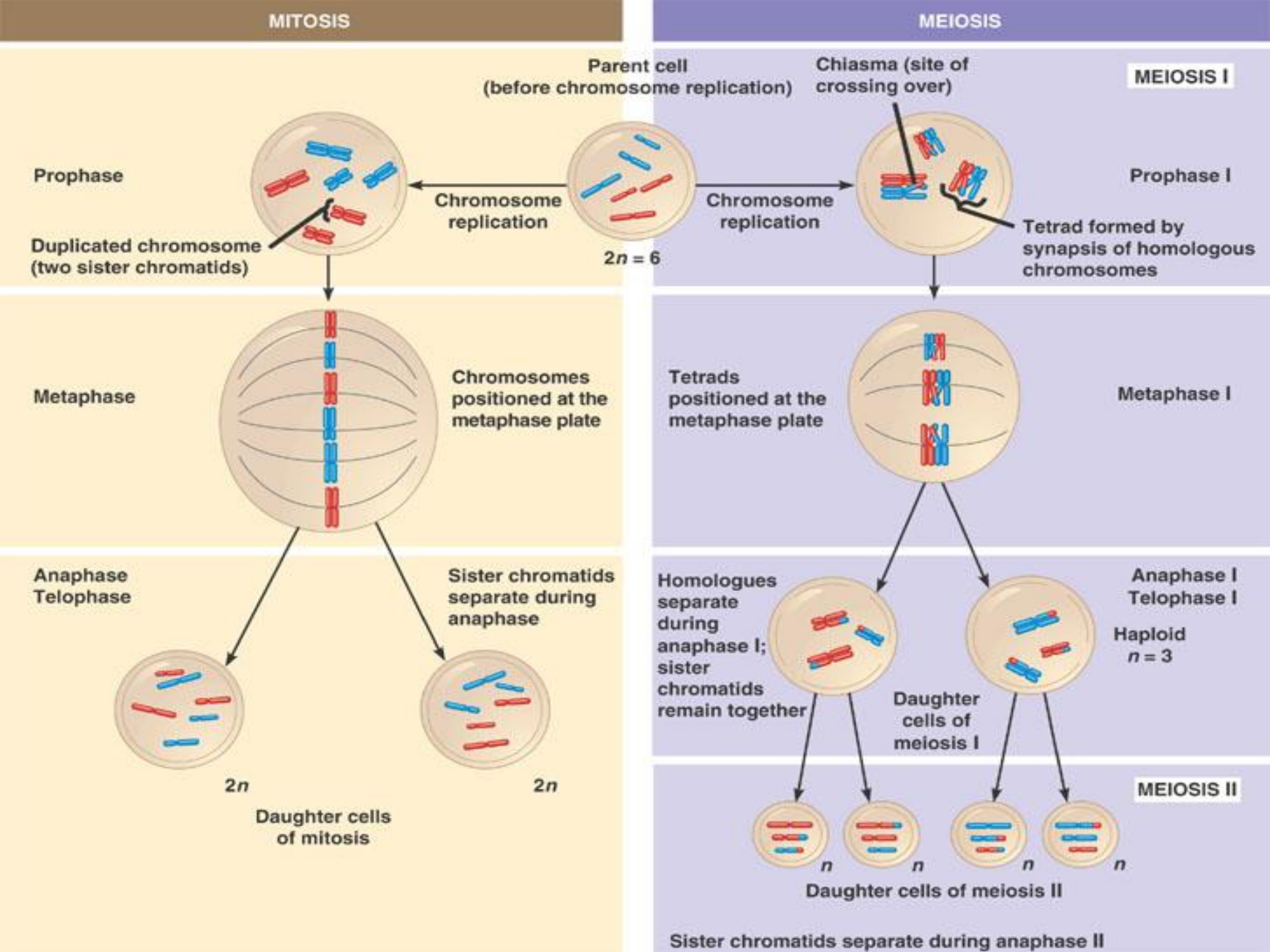
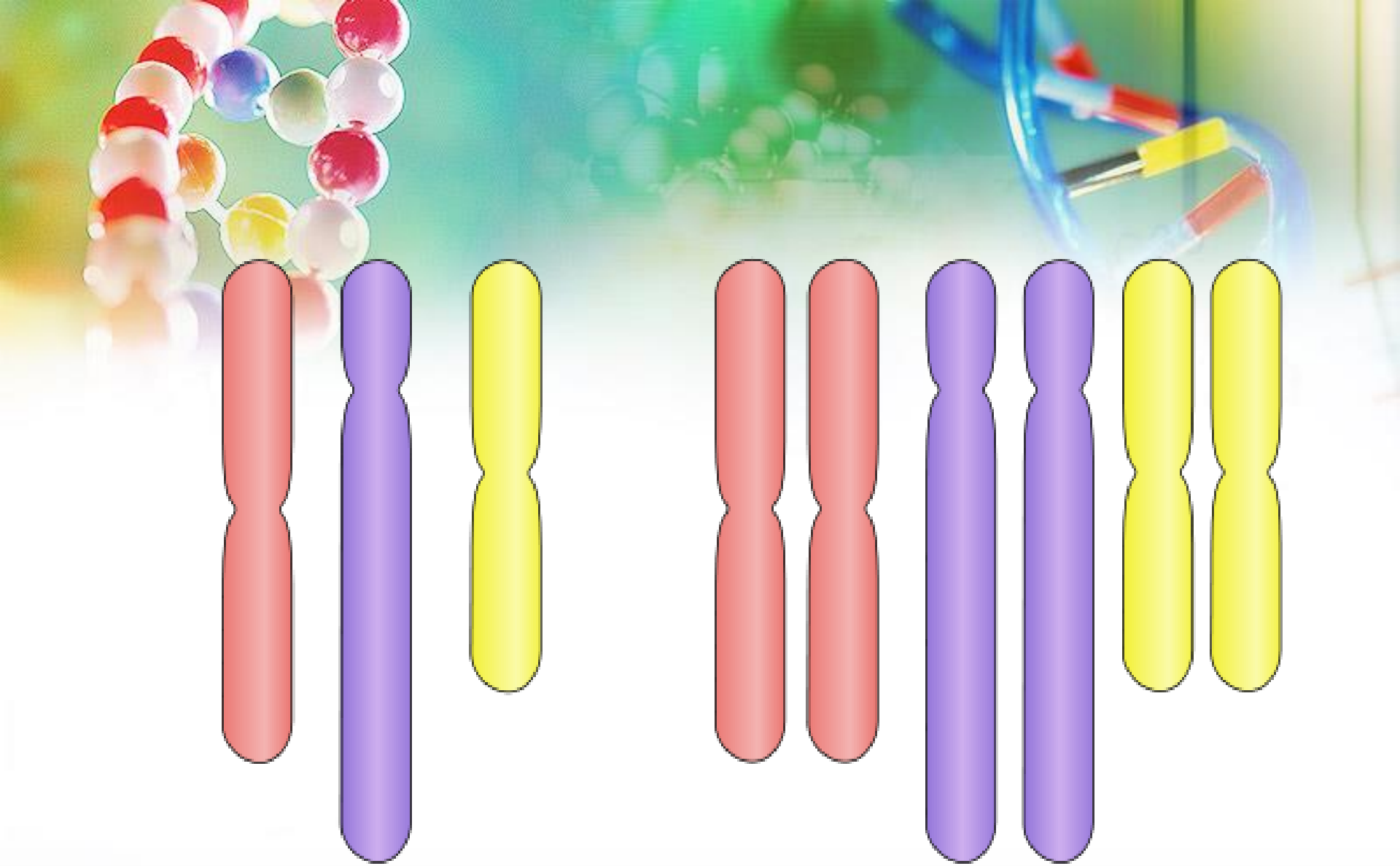
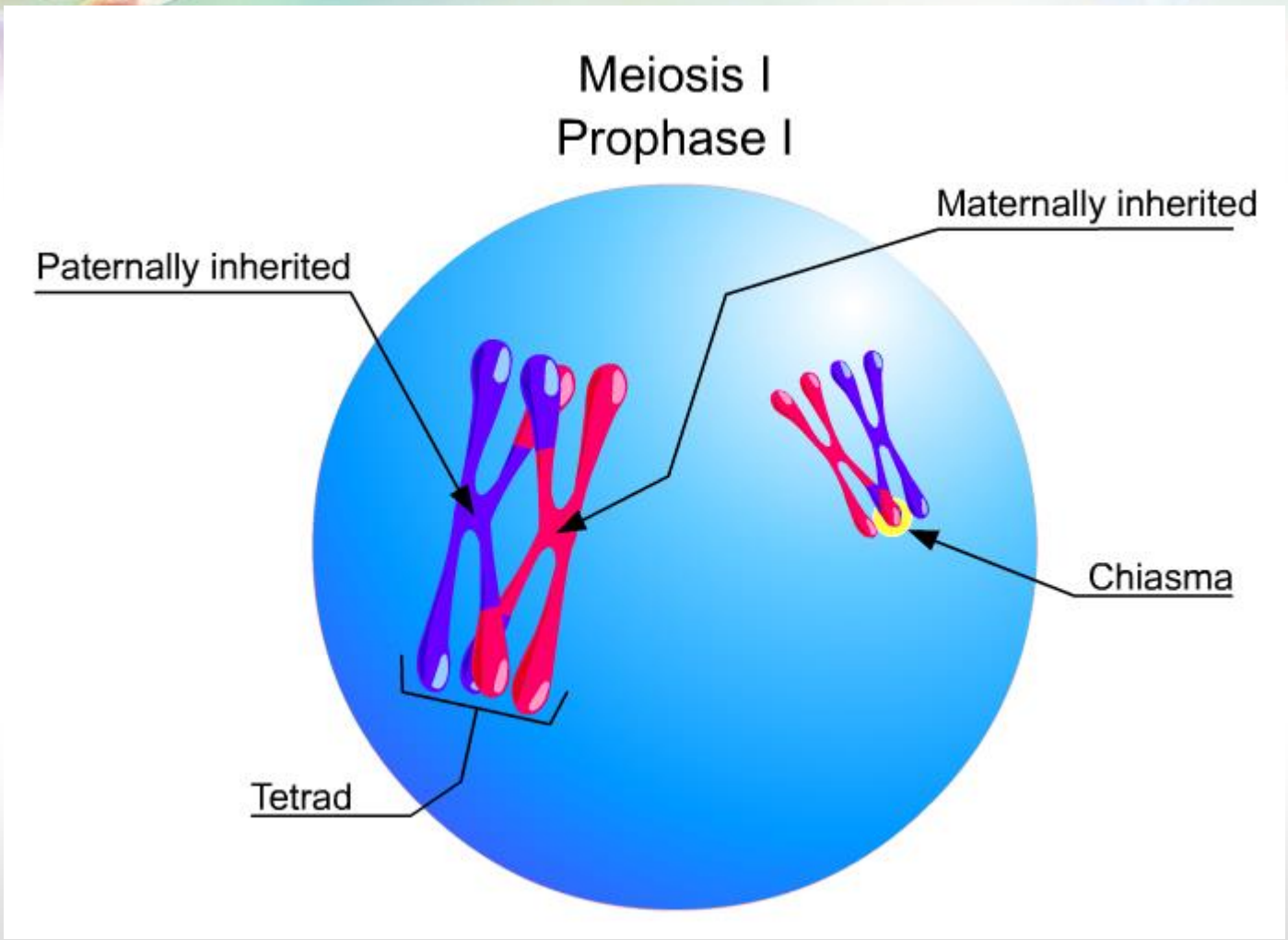
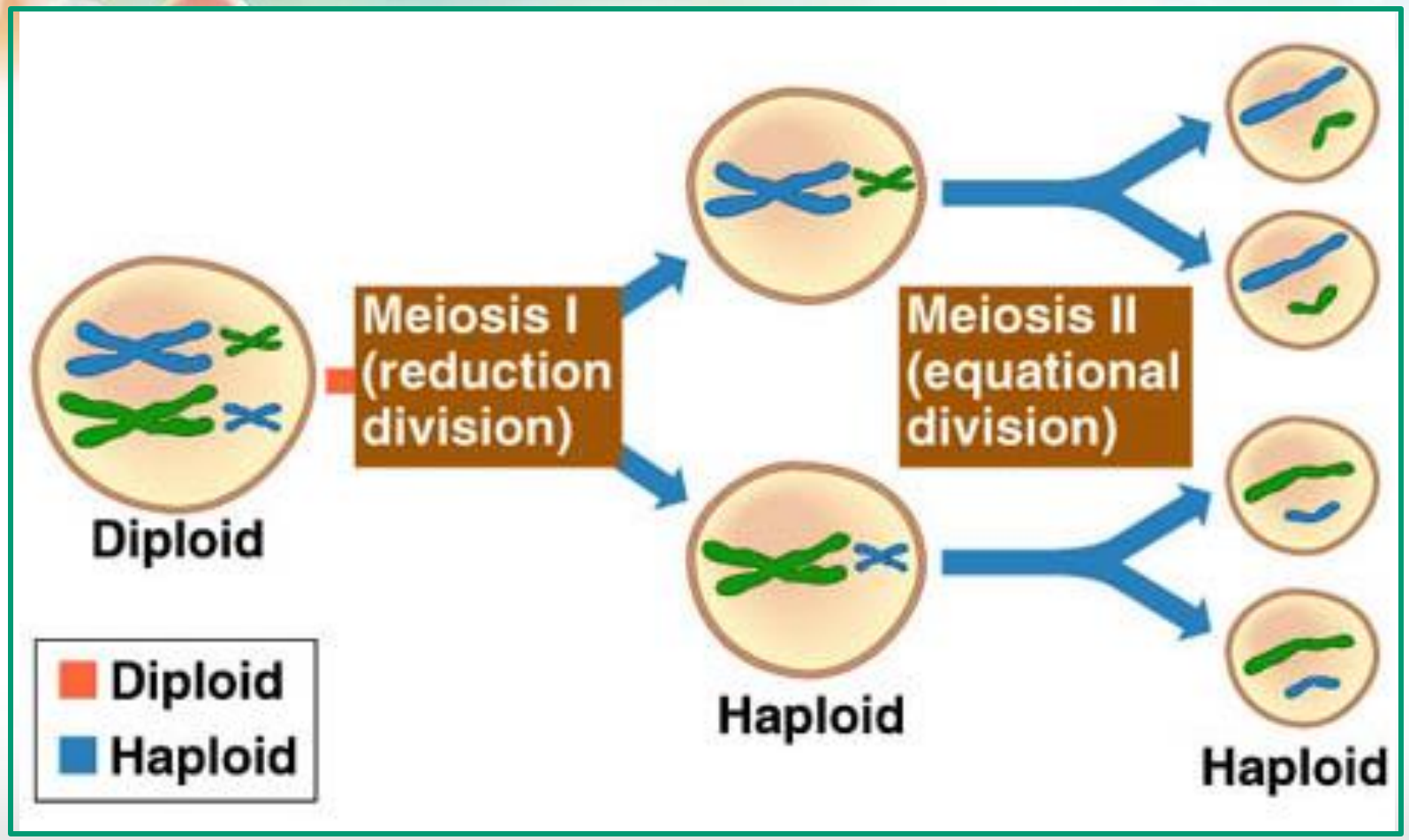

MITOSIS
MEIOSIS
Parent cell
(before chromosome replication)
Chiasma (site of crossing over)
MEIOSIS I
Prophase
Chromosome replication
Chromosome replication
Prophase I
Duplicated chromosome
(two sister chromatids)
2n = 6
Tetrad formed by synapsis of homologous chromosomes
Metaphase
Chromosomes positioned at the metaphase plate
Tetrads positioned at the metaphase plate
Metaphase I
Anaphase
Telophase
Sister chromatids separate during anaphase
Homologues separate during anaphase I; sister chromatids remain together
Anaphase I
Telophase I
Haploid
n = 3
Daughter cells of meiosis I
2n
2n
Daughter cells of mitosis
MEIOSIS II
n
n
n
n
Daughter cells of meiosis II
Sister chromatids separate during anaphase II


Haploid (N)
Diploid (2N)


Meiosis I
Prophase I
Maternally inherited
Paternally inherited
Chiasma
Tetrad

The phases of meiosis I & II



CHROMOSOME ANOMALIES

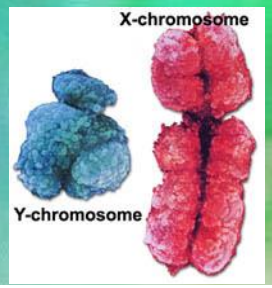
- **TYPES:**
  - **Numerical**
  - **Structural**
- **MECHANISMS**
- **NOMENCLATURE**
- **Etiology**

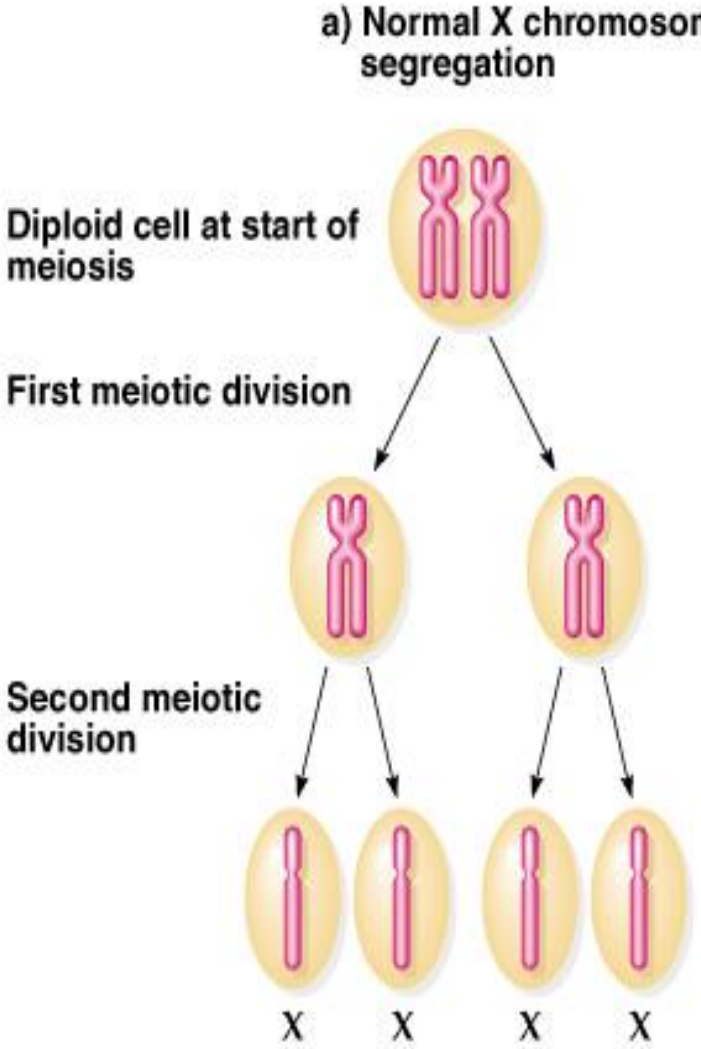
Non-disjunction in Meiosis

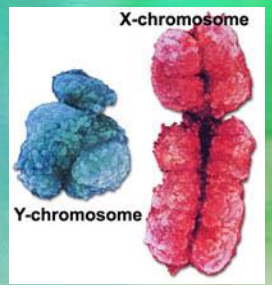
- **Nondisjunction** ("not coming apart") is the failure of chromosome pairs to separate properly during meiosis stage 1 or stage 2.

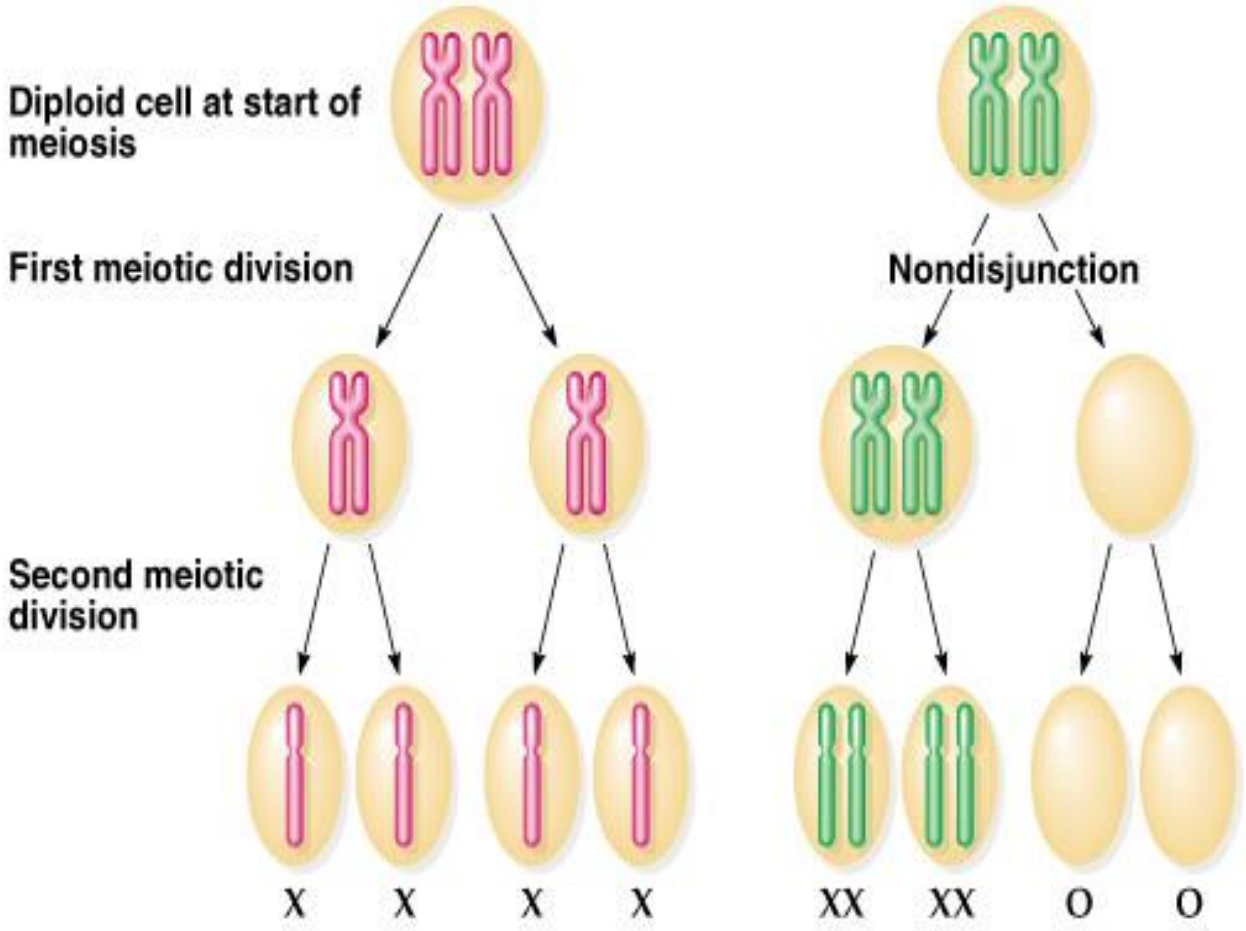
- As a result, one daughter cell has two chromosomes or two chromatids, and the other has none.

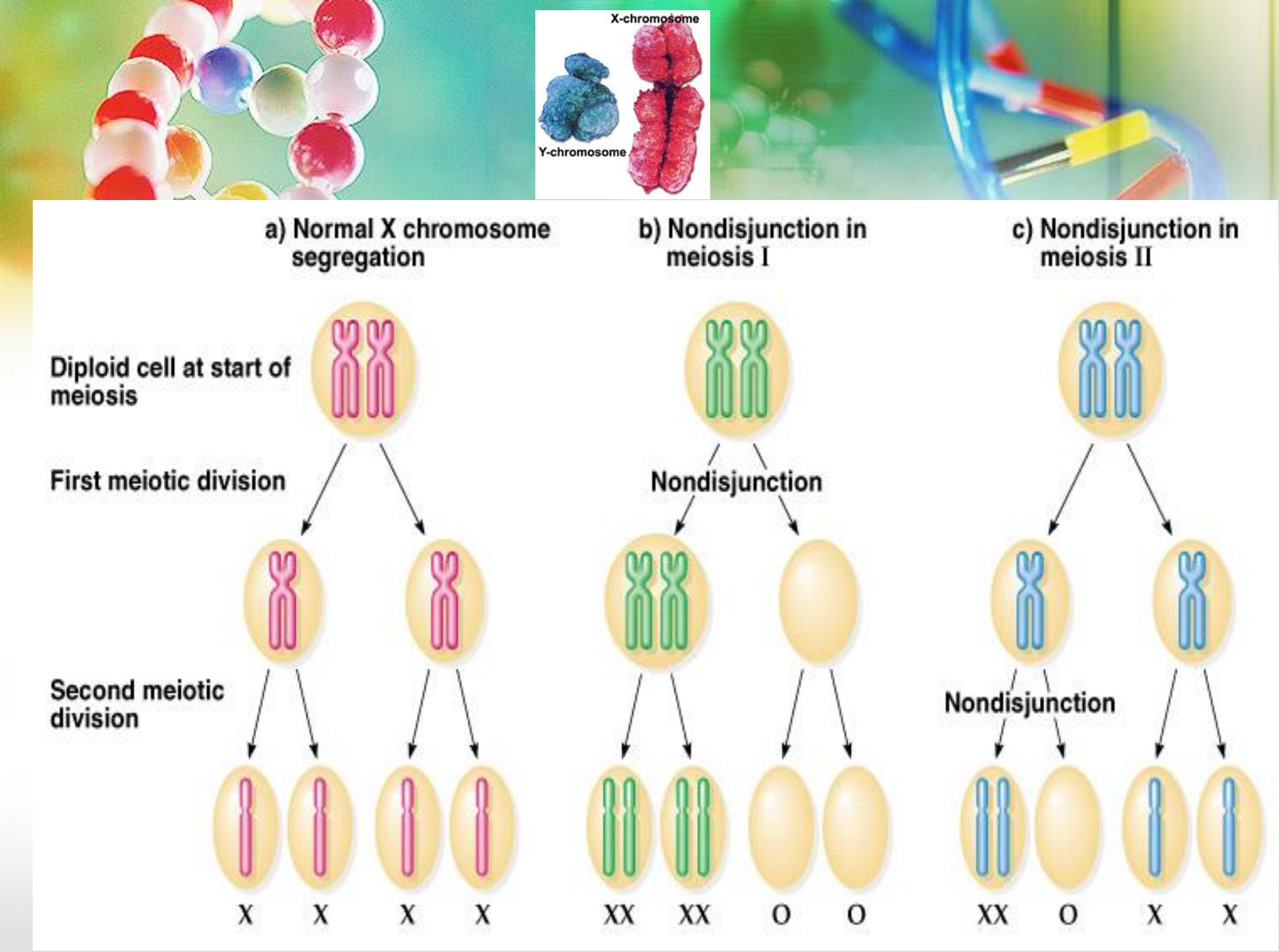
- The result of this error is a cell with an imbalance of chromosomes (Aneuploidy)


X-chromosome
Y-chromosome


a) Normal X chromosome segregation
Diploid cell at start of meiosis
First meiotic division
Second meiotic division
X
X
X
X


X-chromosome
Y-chromosome


a) Normal X chromosome segregation
b) Nondisjunction in meiosis I
Diploid cell at start of meiosis
First meiotic division
Second meiotic division
Nondisjunction
X
X
X
X
XX
XX
O
O


X-chromosome
Y-chromosome
a) Normal X chromosome segregation
b) Nondisjunction in meiosis I
c) Nondisjunction in meiosis II
Diploid cell at start of meiosis
First meiotic division
Second meiotic division
Nondisjunction
Nondisjunction
X X X X
XX XX O O
XX O X X

Meiotic non-disjunction

- can affect each pair of chromosomes
- is not a rare event
- non disjunction in first meiotic division produces 4 unbalanced gametes.
- non disjunction in second division produces 2 normal gametes & 2 unbalanced gametes:

Gamete with an extra autosome

Nullosomic gamete **(missing one chromosome)**

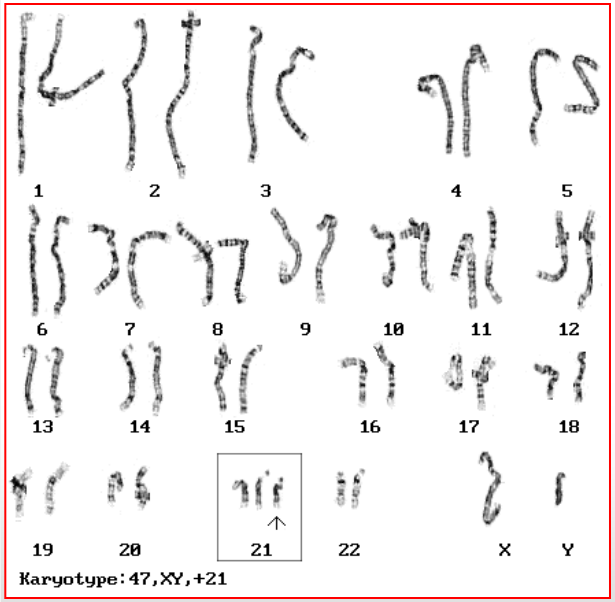
NUMERICAL CHROMOSOMAL ANOMALIES

Numerical anomalies in autosomes

Down syndrome, trisomy 21

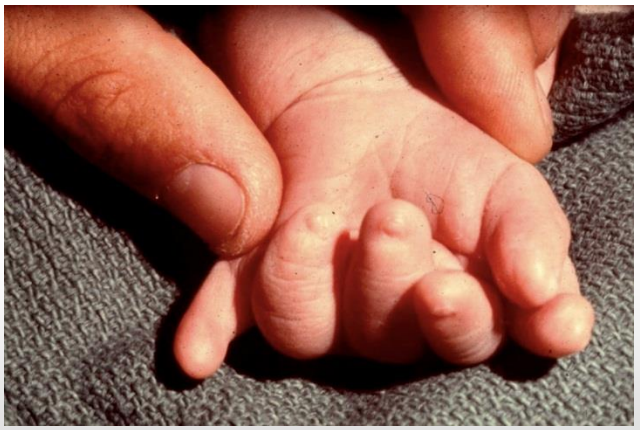
Karyotype: 47, XY, +21

- The incidence of trisomy 21 rises sharply with increasing maternal age
- Most cases arise from non disjunction in the first meiotic division
- The father contributing the extra chromosome in 15% of cases (i.e. Down syndrome can also be the result of nondisjunction of the father's chromosome 21)
- A small proportion of cases are mosaic and these probably arise from a non disjunction event in an early zygotic division.
- The symptoms include characteristic facial dysmorphologies, and an IQ of less than 50.



Edward's syndrome, Trisomy 18
Karyotype: 47, XY, +18

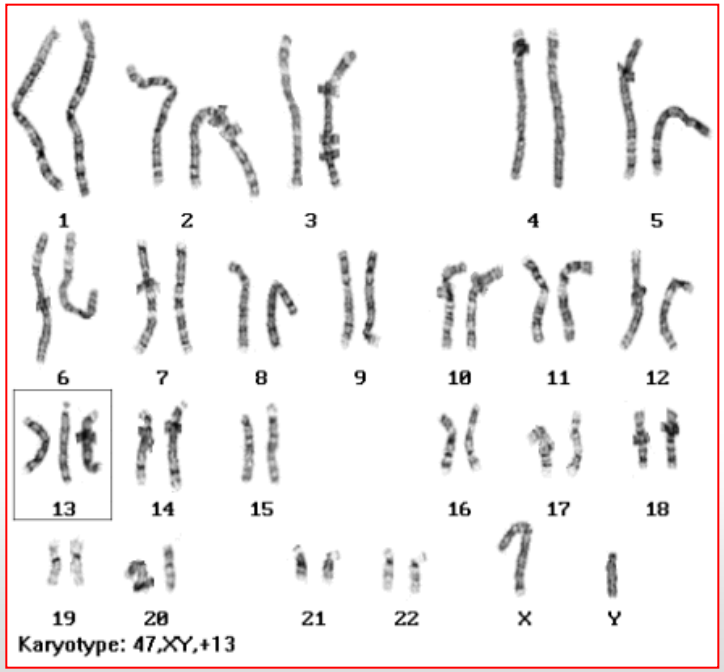
- It is the second most common autosomal trisomy, after Down syndrome, that carries to term
- It occurs in around one in 6,000 live births and around 80 percent of those affected are female
- Most babies die in the first year and many within the first month & has a very low rate of survival
- Common anomalies are heart abnormalities, kidney malformations, and other internal organ disorders



Patau Syndrome, Trisomy 13

Karyotype: 47, XY, +13

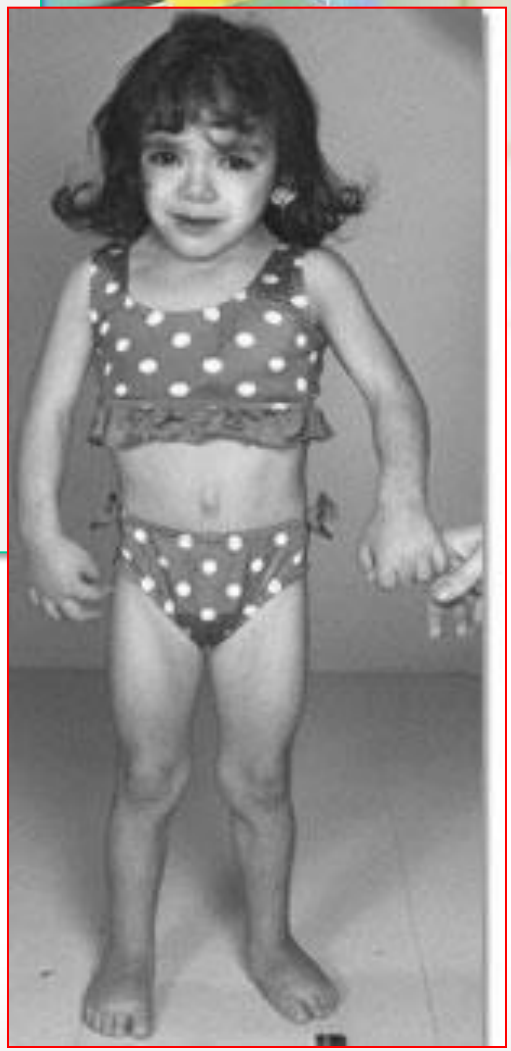
- Fifty % of these babies die within the first month and very few survive beyond the first year.
- There are multiple dysmorphic features.
- Most cases, as in Down's syndrome, involve maternal non-disjunction.

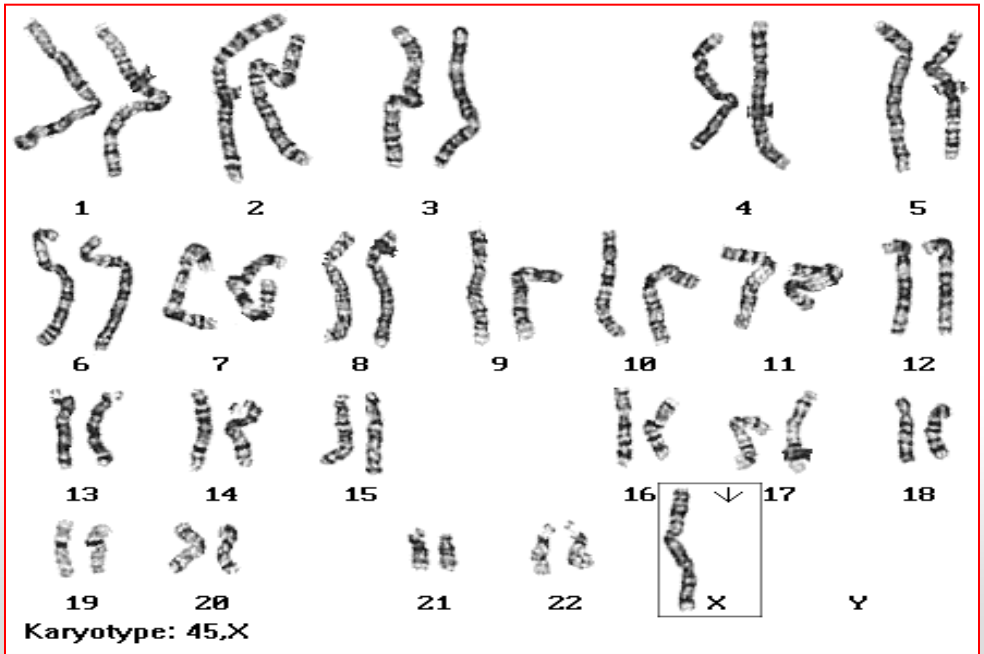


Numerical anomalies in Sex chromosomes

Monosomy X (Turner's syndrome, 45, XO)

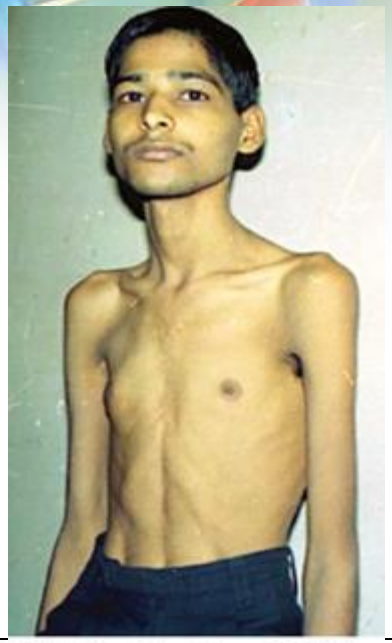
- Occurring in 1 in 5000 phenotypic females
- The only viable monosomy in humans
- Characteristics: Webbed neck, Individuals are genetically female, not mature sexually, Sterile, Short stature, Broad chest, Low hairline, Streak ovaries, Normal intelligence, Normal life span

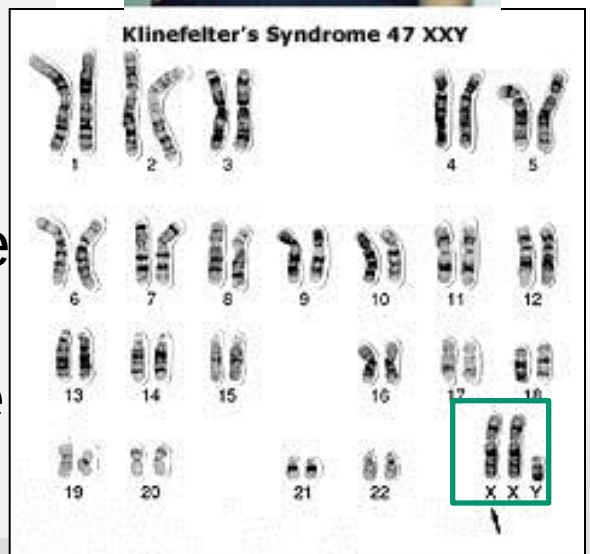




Klinefelter Syndrome: 47,XXY males

- Male sex organs; unusually small testes which fail to produce normal levels of testosterone→ breast enlargement (gynaecomastia) and other feminine body characteristic
- Patients are taller and thinner than average and may have a slight reduction in IQ but generally they have normal intelligence
- No spermatogenesis → sterile
- Very rarely more extreme forms of Klinefelte syndrome occur where the patient has 48, XXXY or even 49, XXXXY karyotype. These individuals are generally severely retarded.





Sex chromosome unbalance
Of much less deleterious effect

47, XYY

May be without any symptoms. Males are tall but normally proportioned. 10 - 15 points reduction in IQ compared to sibs.

XXX females

It seems to do little harm, individuals are fertile and do not transmit the extra chromosome. They do have a reduction in IQ comparable to that of Kleinfelter's males

Numerical anomalies affecting the number of complete haploid set (n) of chromosomes

Polyploidy

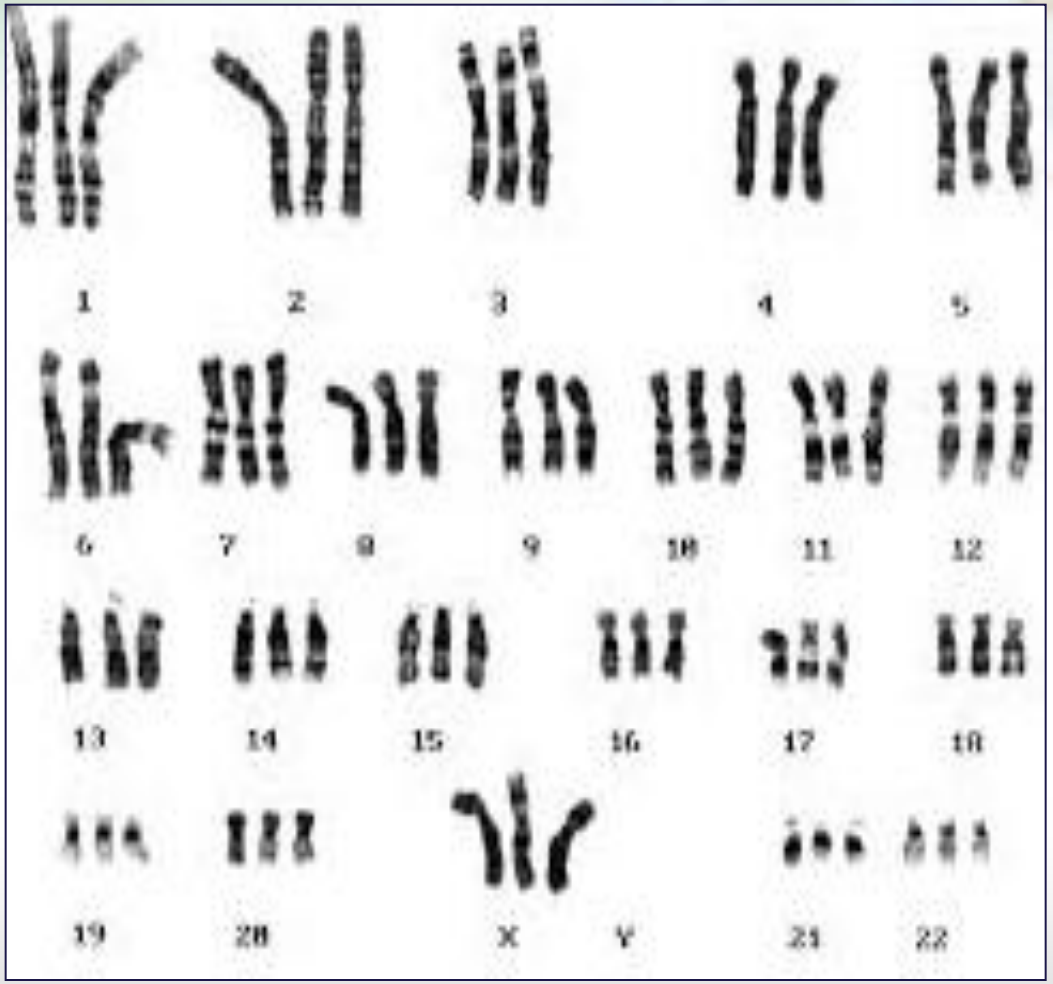
- **Triploidies are the most frequent,**

  - 3N = 69 chromosomes: e.g. 69, XXX, or 69, XXY, or 69, XYY.

  - Are found in 20 % of spontaneous miscarriages.

- **Tetraploidy,**

  4N = 92 chromosomes.



Can an individual have A combination of cells:

- some cells with normal chromosomal numbers, &
- some cells with numerical chromosomal anomalies?

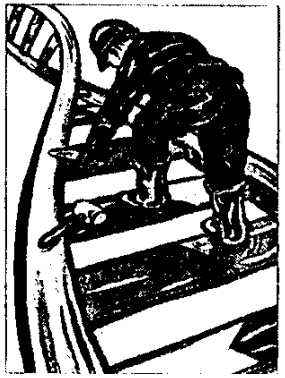
MOSAICISM

- A mosaic individual is made of 2 (or more) cell populations, coming from only 1 zygote
- Is denoted by a slash between the various clones observed e.g.46, XY / 47, XY, +21).
- Numerical mosaic anomaly is usually due to a mitotic non-disjunction
- A mosaic must not be confused with a chimeras.
- Chimerism is the presence in an individual of two or more genetically distinct cell lines derive from more than one zygote (e.g. 2 sperms fertilize 2 ova → 2 zygotes that fuse to form 1 embryo

STRUCTURAL CHROMOSOMAL ANOMALIES

STRUCTURAL CHROMOSOMAL ANOMALIES

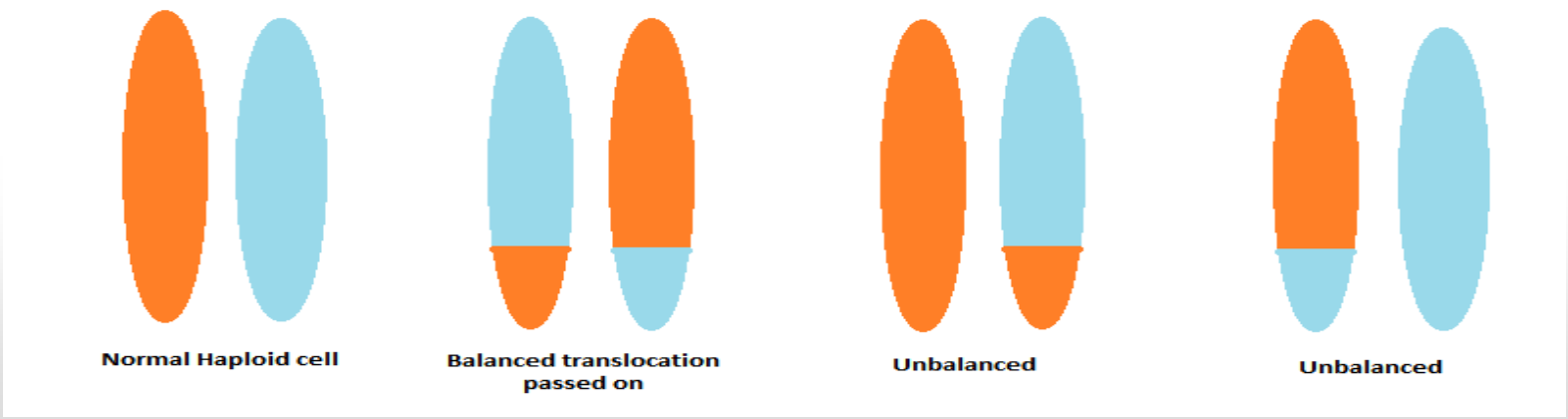
- **The most frequent Structural anomalies are:**
  - **Translocations**
  - **Inversions**
  - **Deletions (terminal or interstitial)**
  - **Isochromosome (i)**
  - **Ring formation (Ring chromosome)**



Reciprocal translocation:

A mutual exchange between terminal segments from the arms of 2 chromosomes.

Provided that there is no loss or alteration at the points of exchange, the new rearrangement is genetically balanced, and called a Balanced rearrangement.

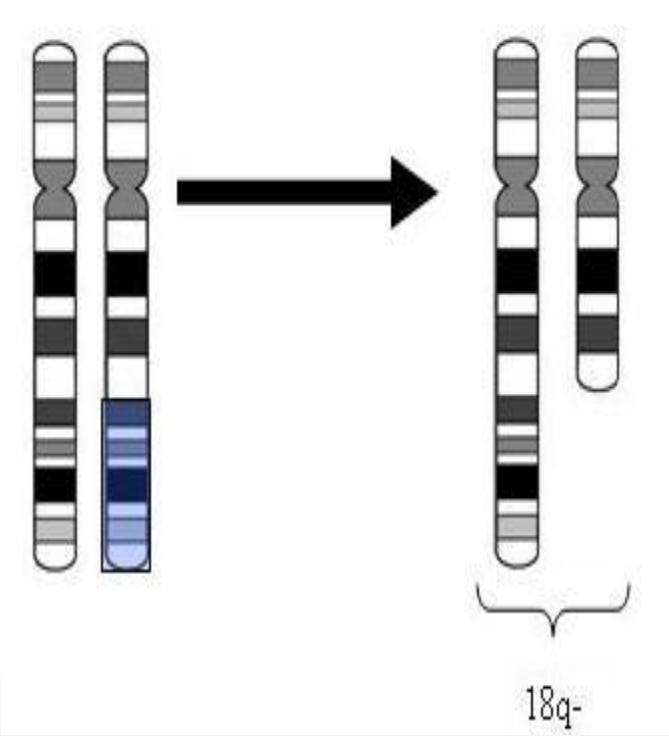


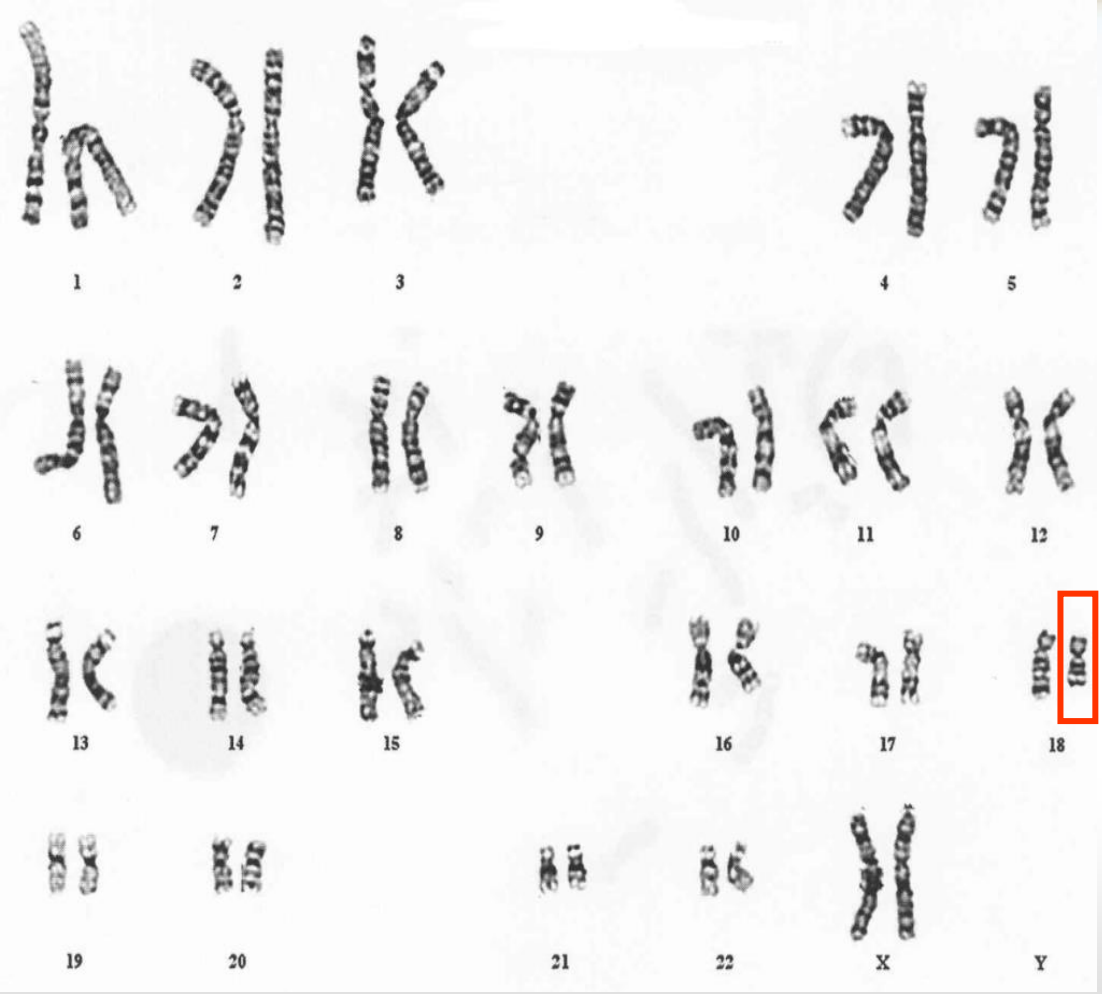
Deletion

- Loss of a segment from a chromosome, either terminal or interstitial
- Invariably, but not always, results in the loss of important genetic material
- Deletion is therefore an unbalanced rearrangement.
- Recorded as del

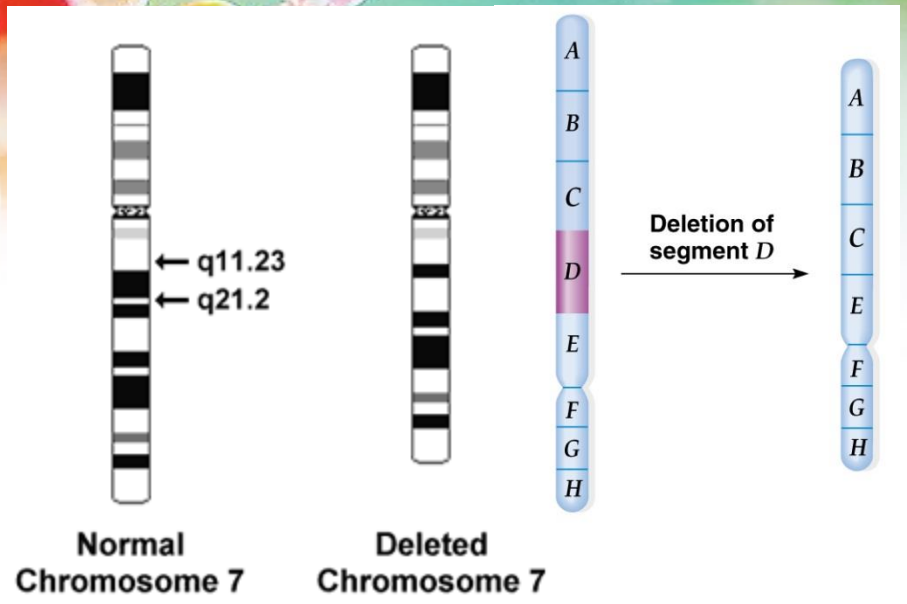
Terminal Deletion

46,XX,del(18)(q21.3).

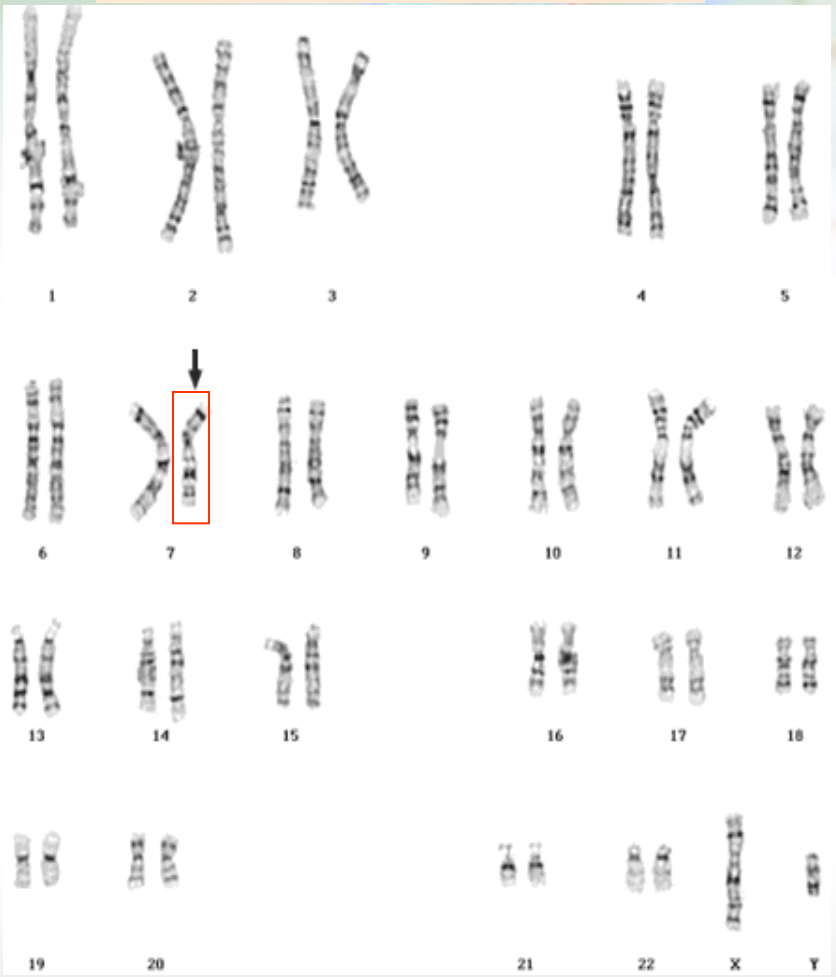




Interstitial deletion (7 Karyotype)



46,XY,del(7)(q11.23q21.2)

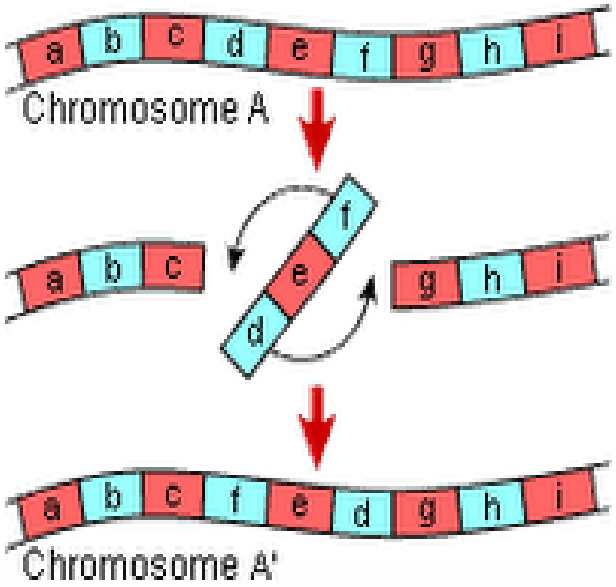


The key to the karyotype description is as follows:

- 46: the total number of chromosomes.
- XY: the sex chromosomes (male).
- del(7): deletion in chromosome 7.
- (q11.23q21.2): breakpoints of the deleted segment.

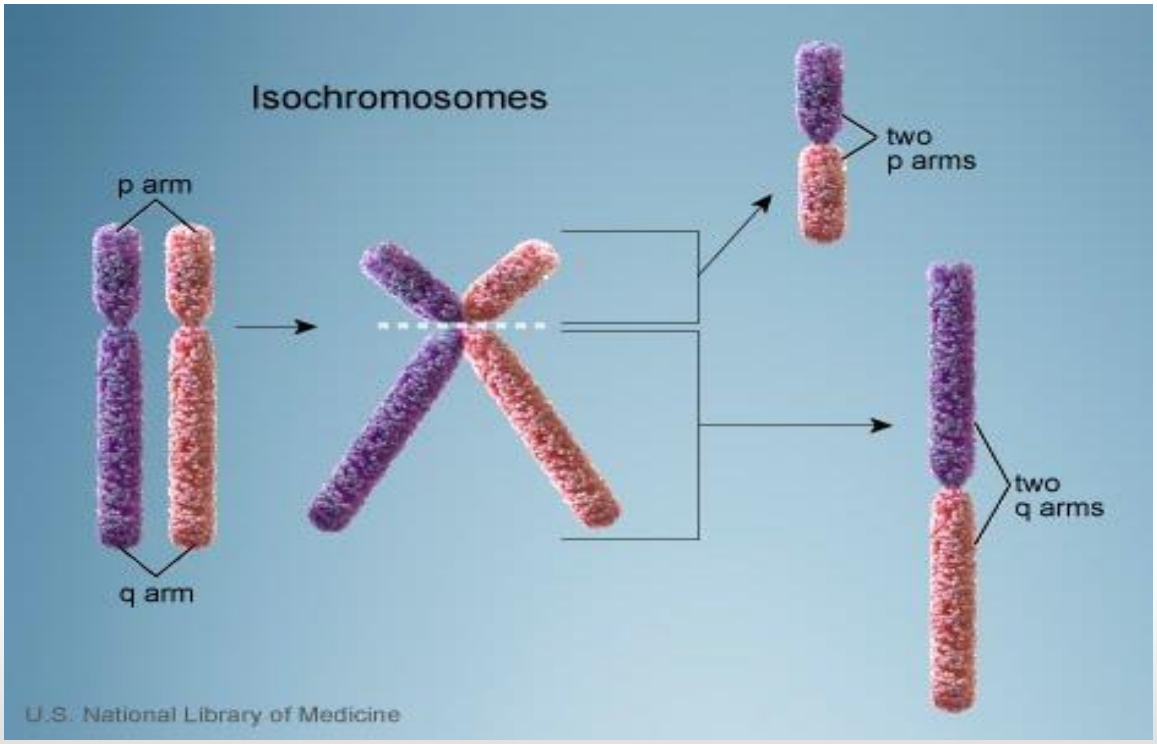
Inversion

- **Inversion occurs when a segment of chromosome breaks, and rejoining within the chromosome effectively inverts it.**
- **Recorded as inv.**
- **Only large inversions are normally detected.**
- **They are balance rearrangements that rarely cause problems in carriers**



Isochromosome

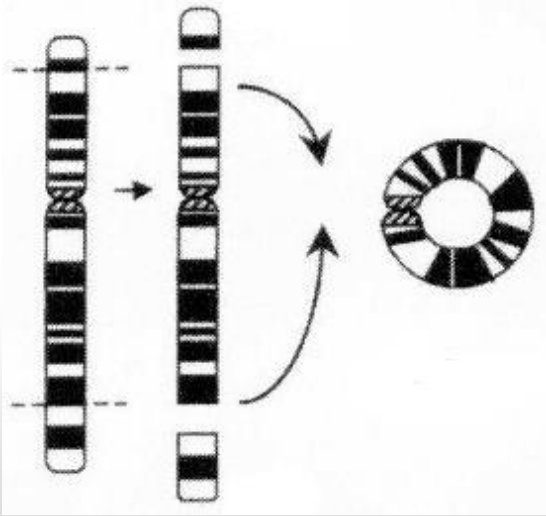
- The most probable explanation for isochromosome is that the centromere has divided transversely rather than longitudinally



Ring formation (Ring chromosome)

A break on each arm of a chromosome → two sticky ends on the central portion → Reunion of the ends as a ring → loss of the 2 distal chromosomal fragments

Ring chromosomes are often unstable in mitosis



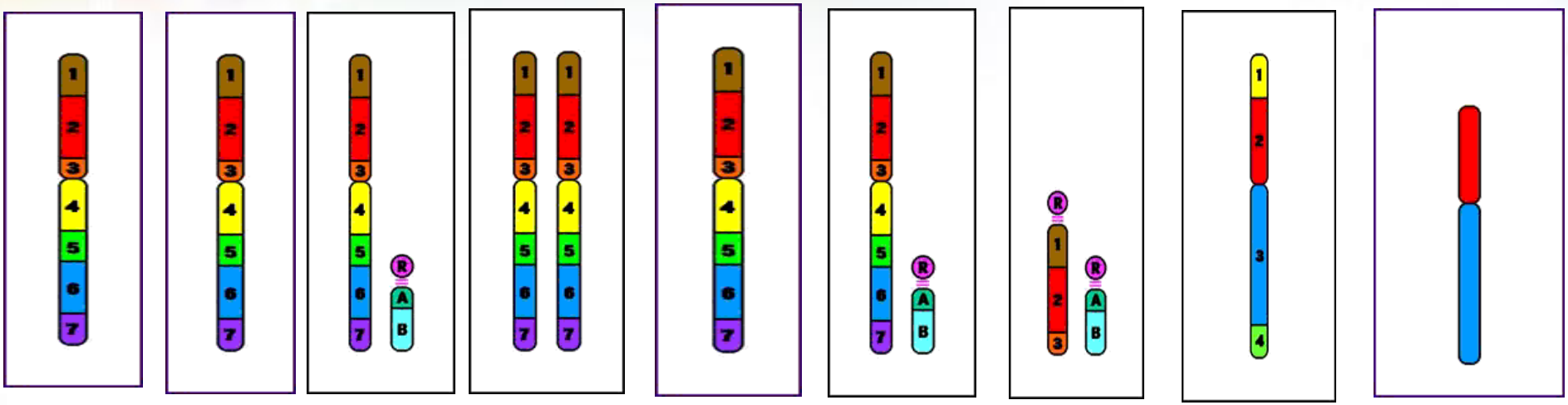
STRUCTURAL CHROMOSOMAL ANOMALIES

Deletion

Duplication

Reciprocal translocation

Ring Chromosome



Terminal Deletion

Insertion

Inversion

Robertsonian Translocation

Isochromosomes

Take home message

- Chromosome abnormalities can be numerical or structural.
- Numerical abnormalities include aneuploidy and polyploidy.
- In trisomy, a single extra chromosome is present, usually as a result of non-disjunction in the 1^{st} or 2^{nd} meiotic division.
- In polyploidy, ≥3 complete haploid sets are present instead of the usual diploid complement.
- Structural abnormalities include translocations (balanced or unbalanced), inversions, deletions, isochromosome & rings.

THANK YOU ☺