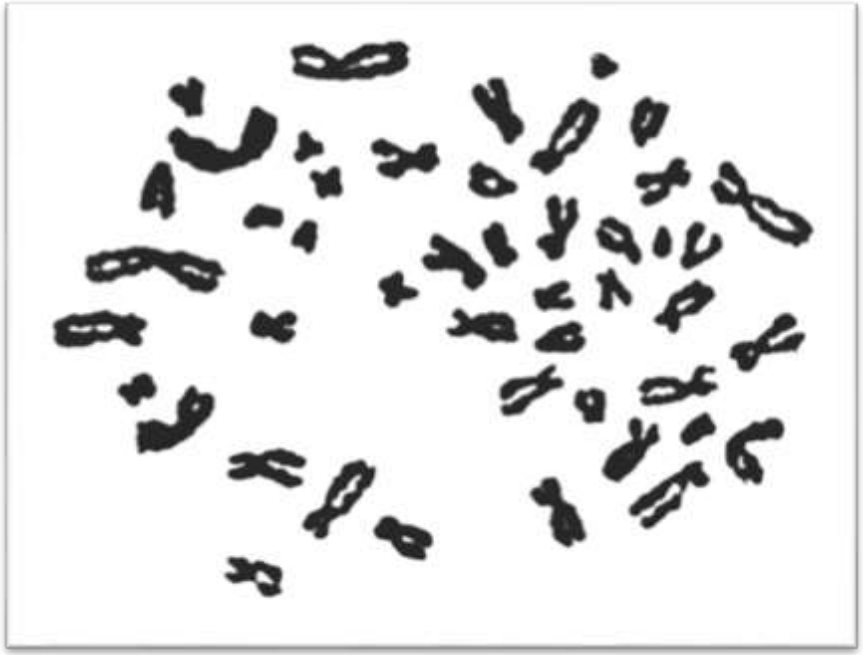
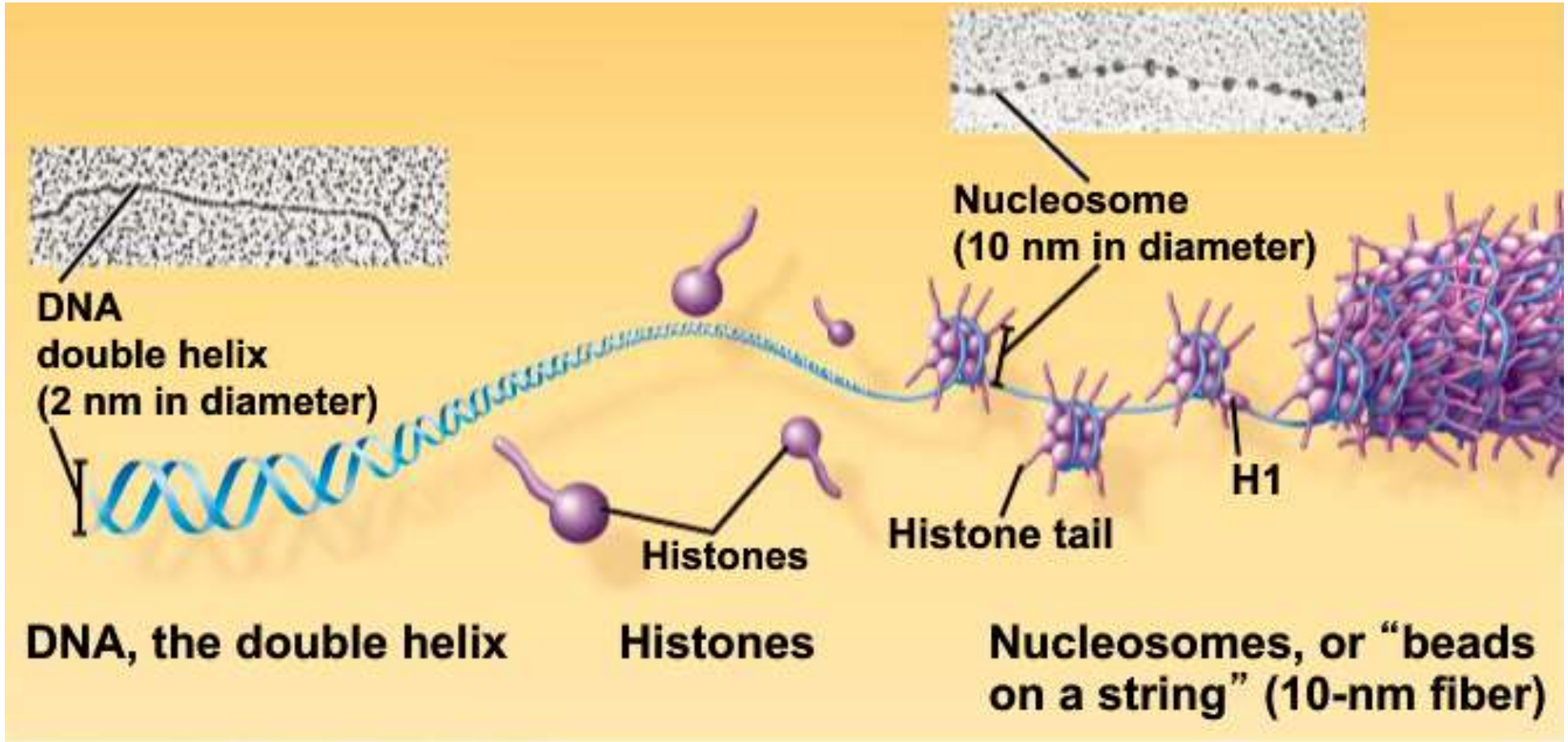
History of Cytogenetics

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



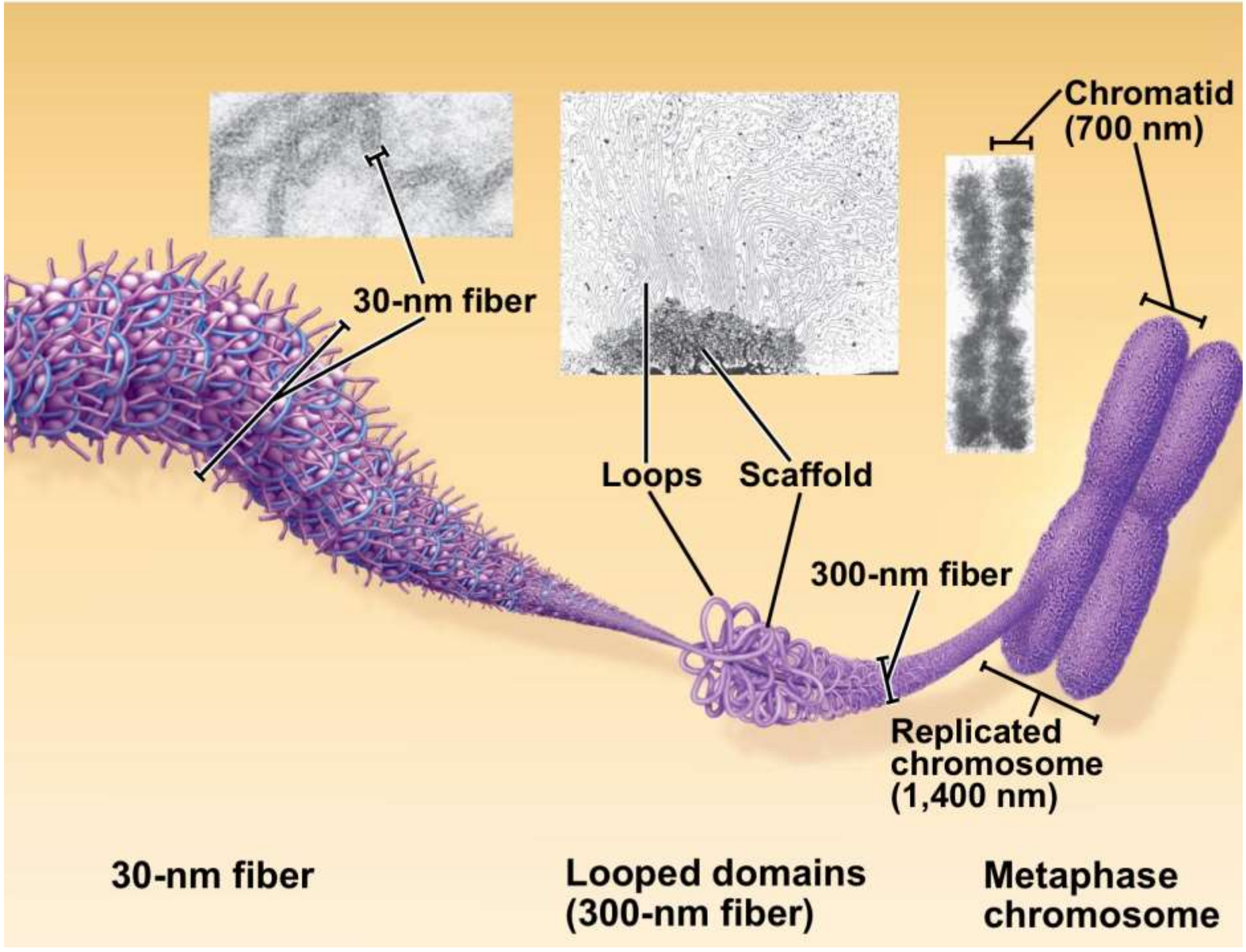
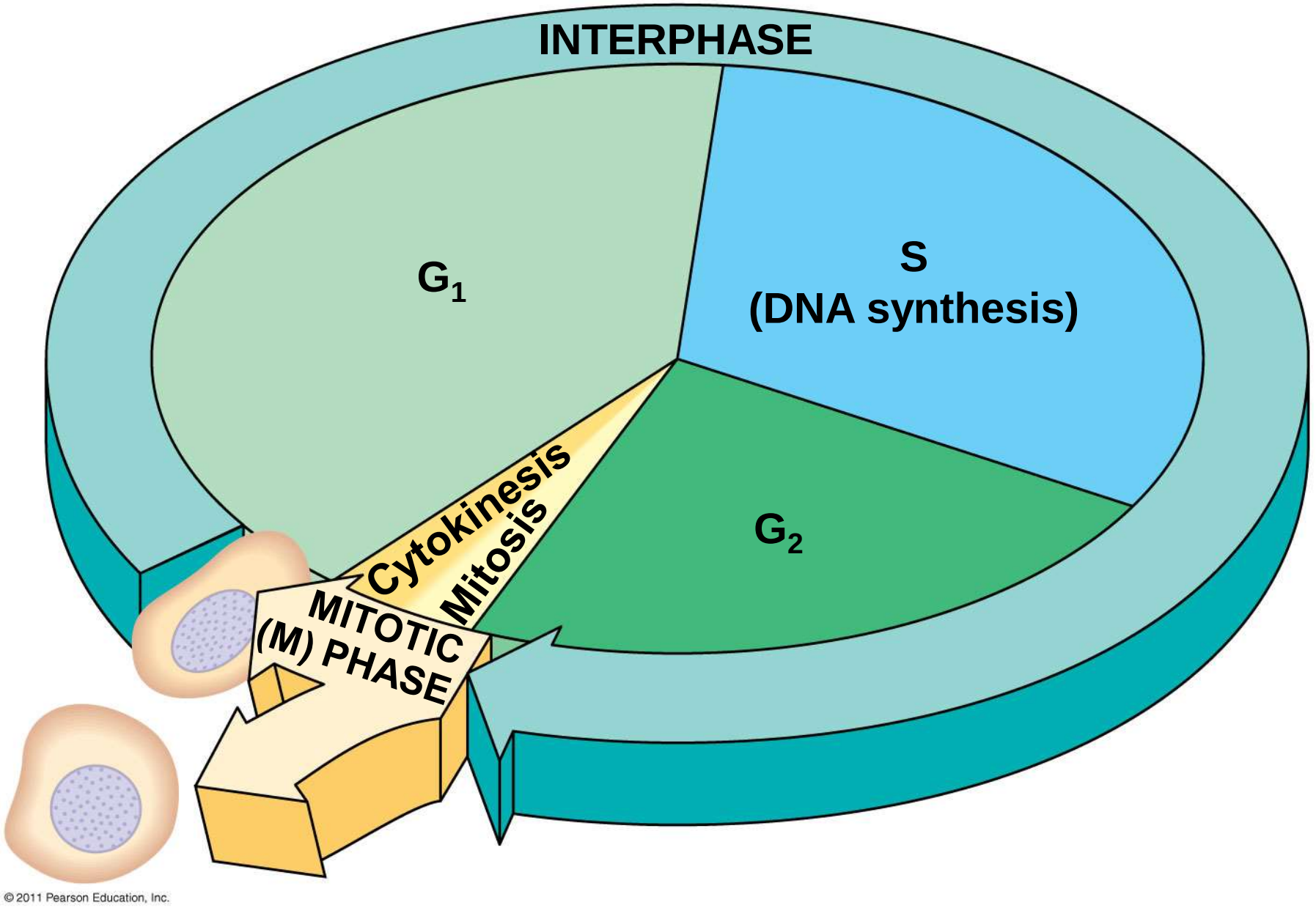
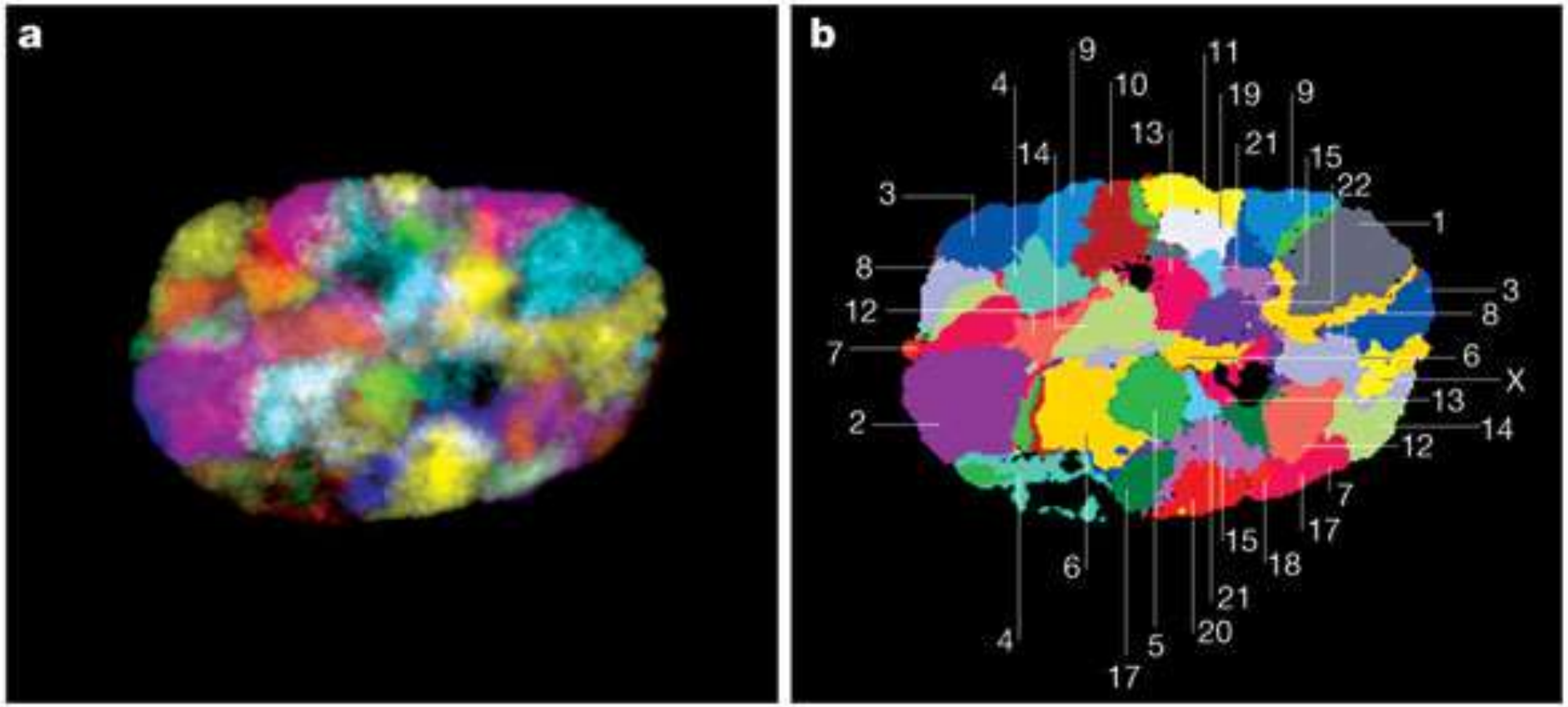
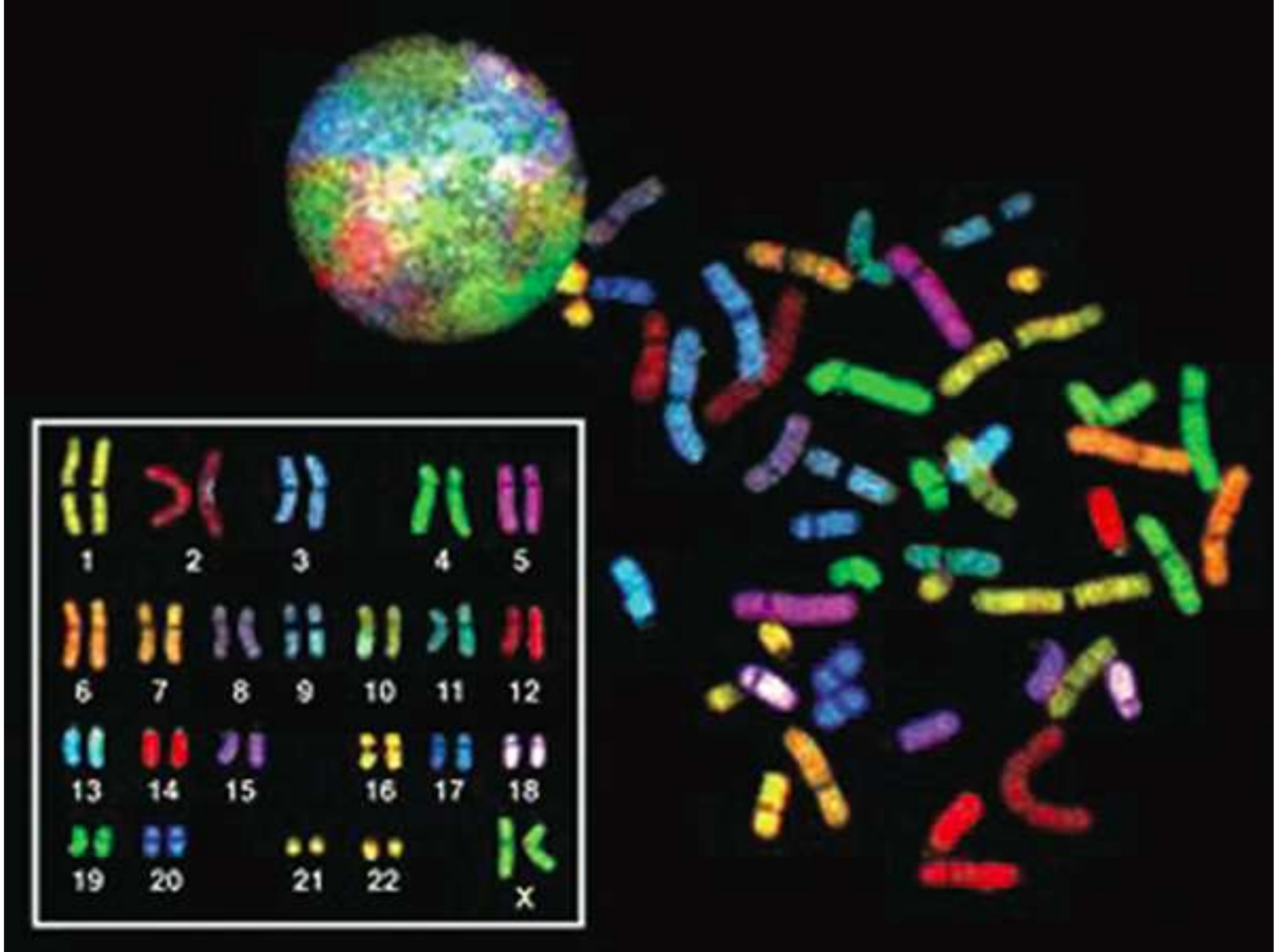

Chromatid
(700 nm)
30-nm fiber
Loops
Scaffold
300-nm fiber
Replicated
chromosome
(1,400 nm)
30-nm fiber
Looped domains
(300-nm fiber)
Metaphase
chromosome

Figure 12.6


INTERPHASE
G1
S
(DNA synthesis)
G2
Cytokinesis
Mitosis
MITOTIC
(M) PHASE
© 2011 Pearson Education, Inc.

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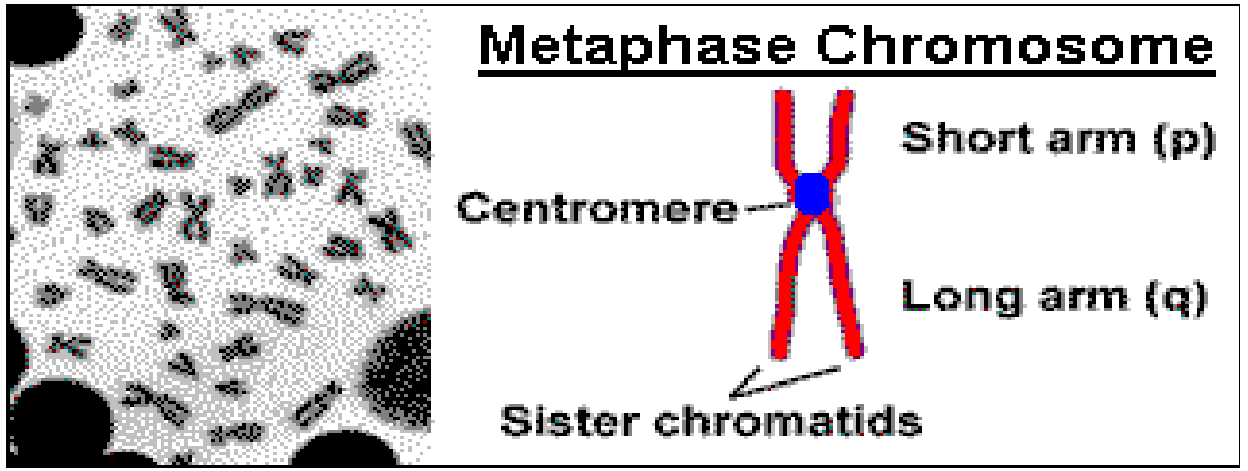
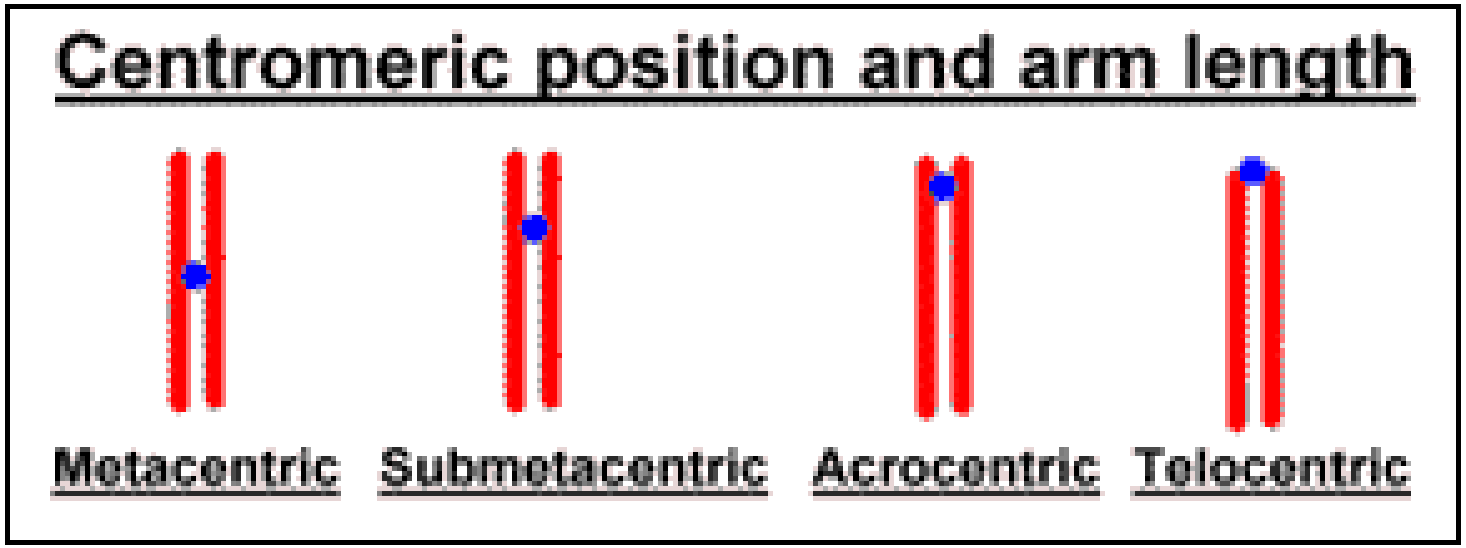
X

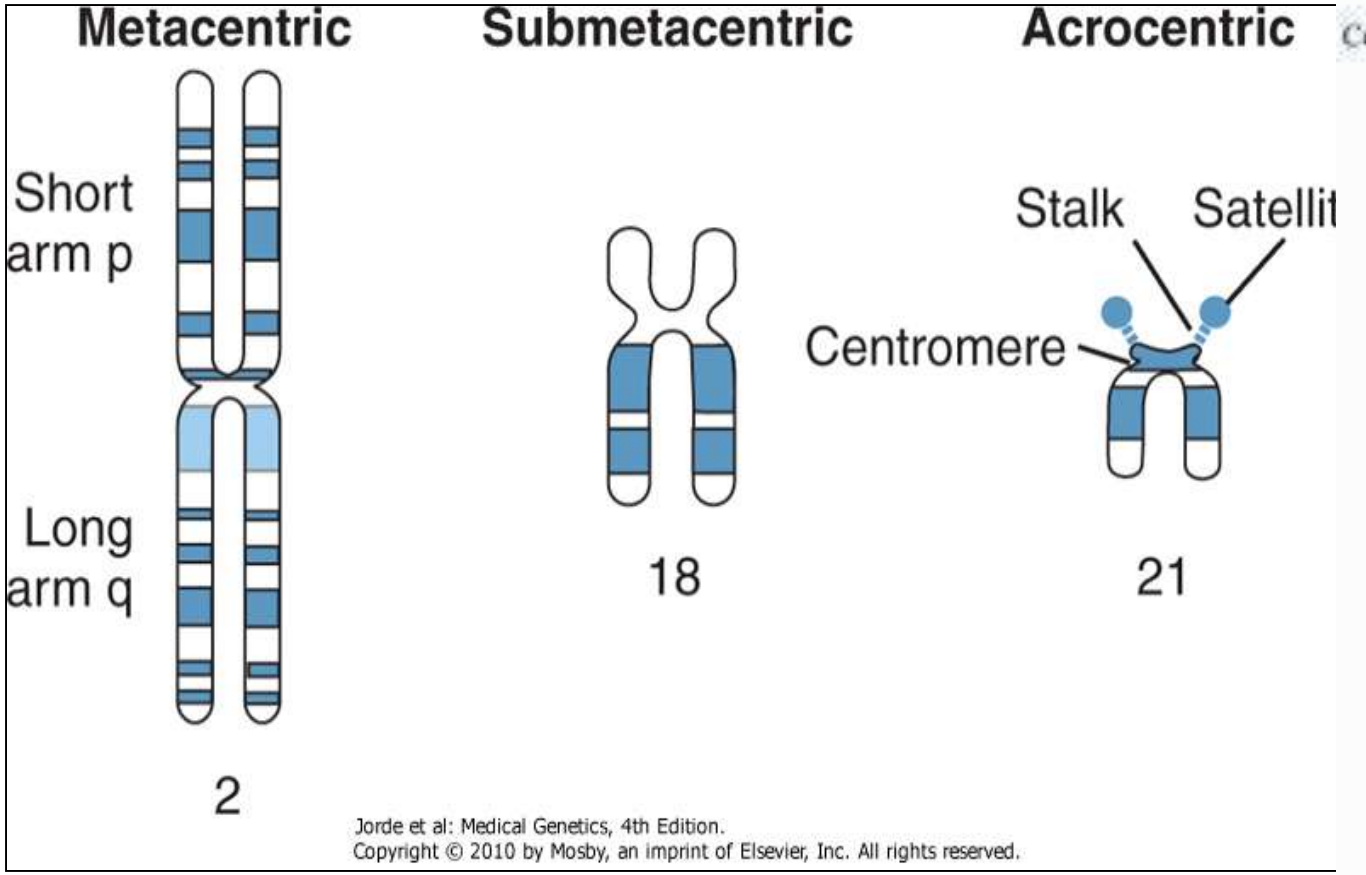
Nomenclature of chromosomes

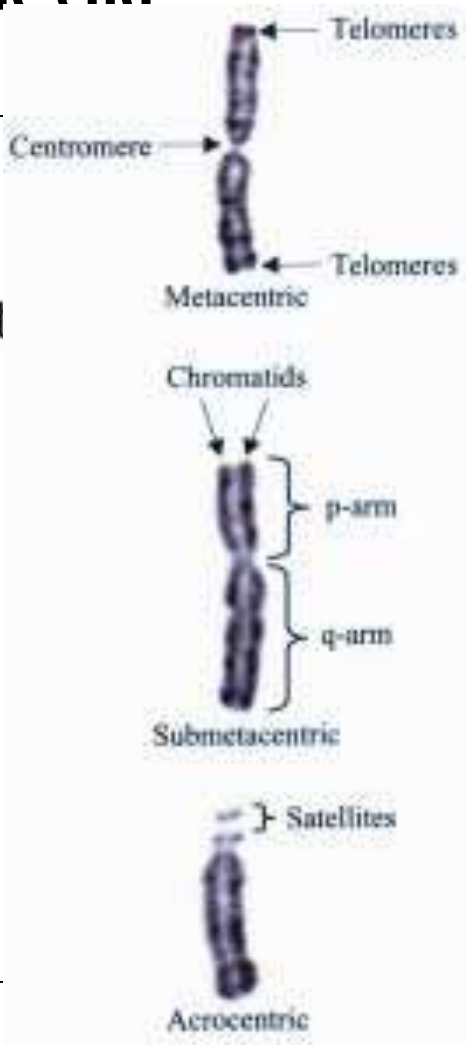




Chromosome Shape

Metacentric- centromere is located in the middle of chromosome
Submetacentric- centromere is displaced from the center
Acrocentric – centromere is placed near the end



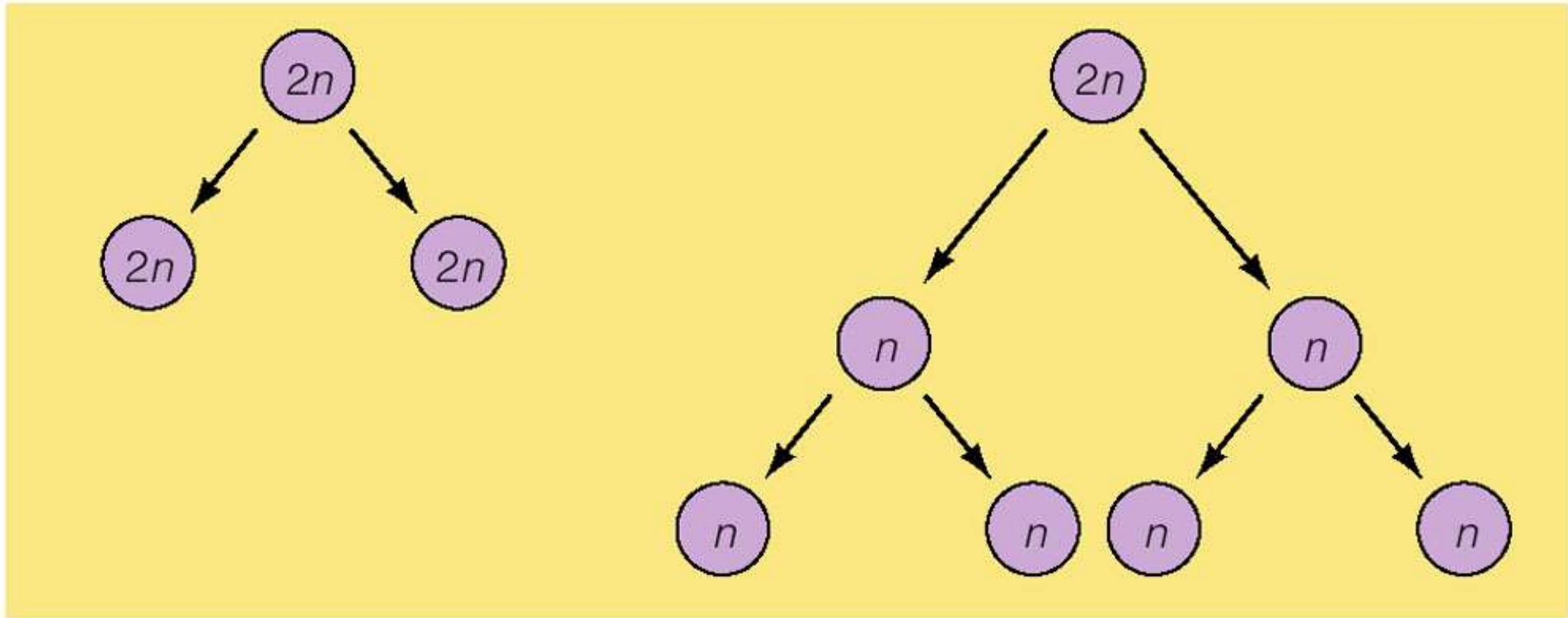


Human chromosomes

- 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)

Mitosis

Meiosis



Interphase

- **Gap 1** (G1)– many cytoplasmic organelles are constructed; RNA, protein and other molecules are synthesized; cell almost doubles in size
- **Synthesis** (S)– DNA is replicated and chromosomes duplicate, forming 2 sister chromatids attached at the centromere
- **Gap 2** (G2)– more cell growth; mitochondria divide; spindle precursors form

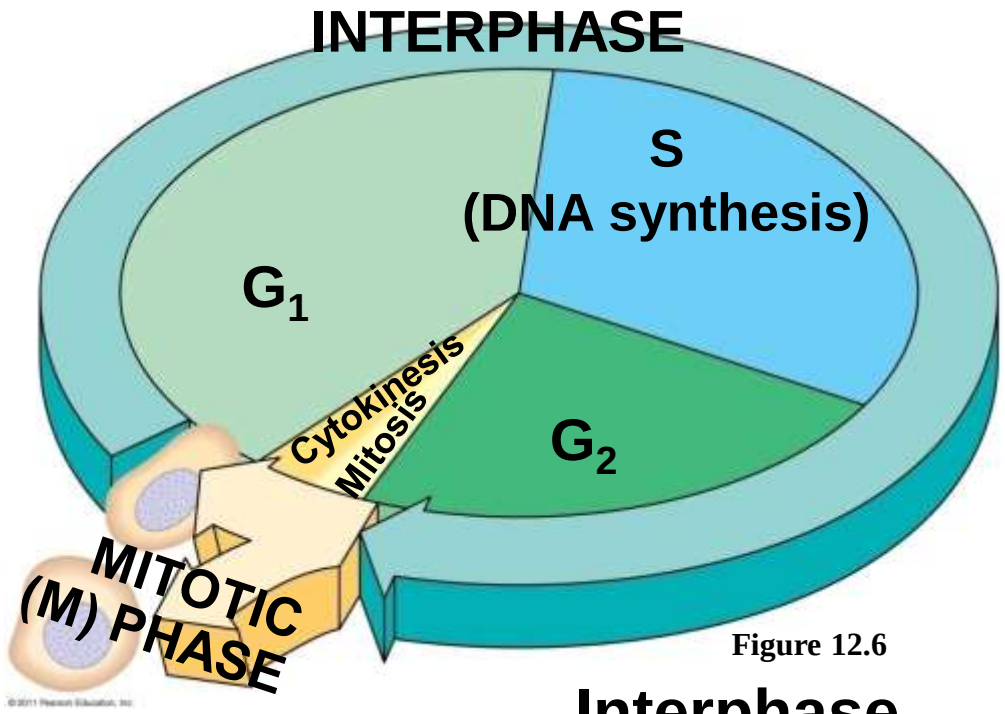


Figure 12.6

Interphase
18-24 hours

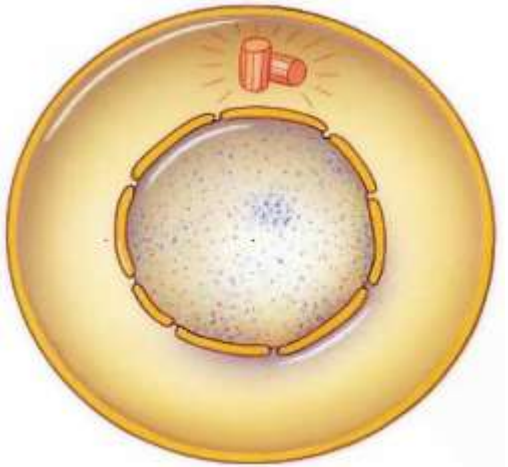
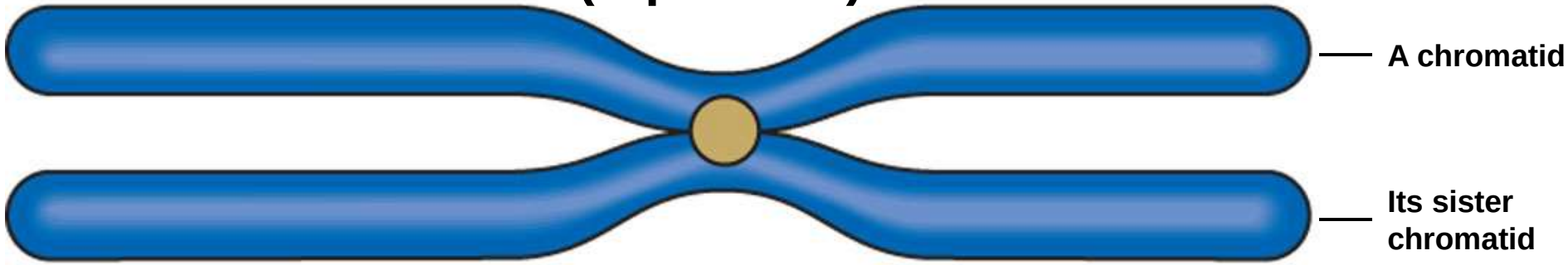
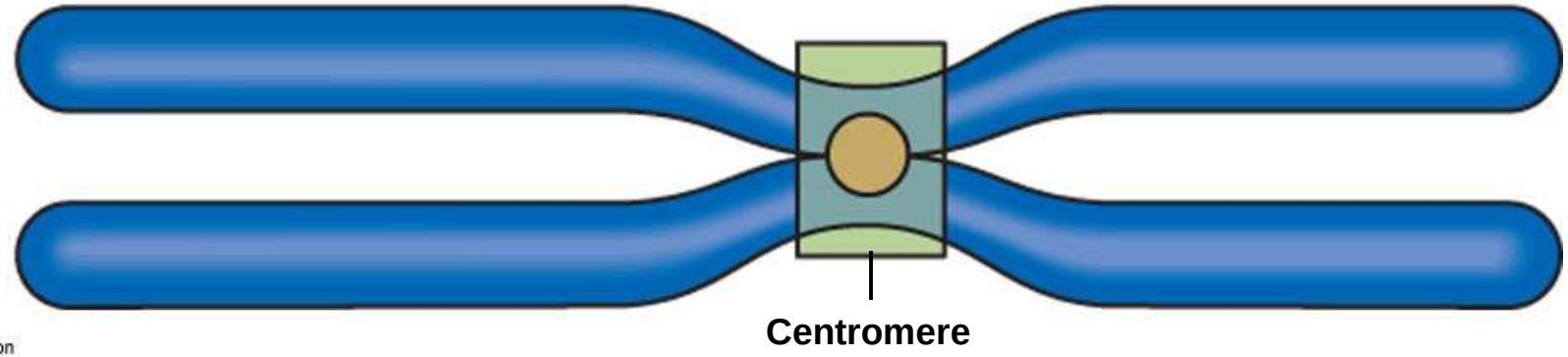


Fig. 2.8a

One chromosome (unreplicated)

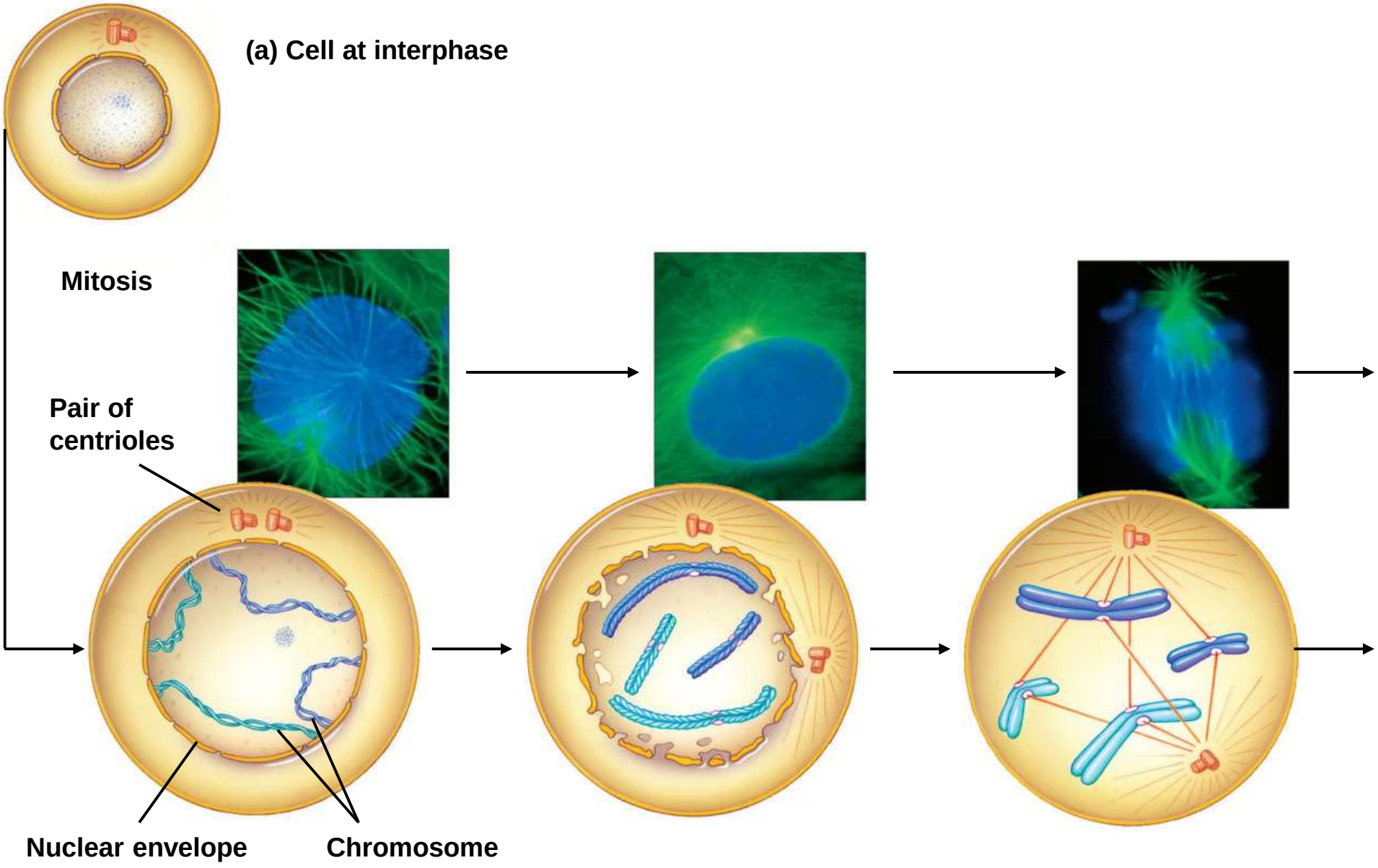
One chromosome (replicated)



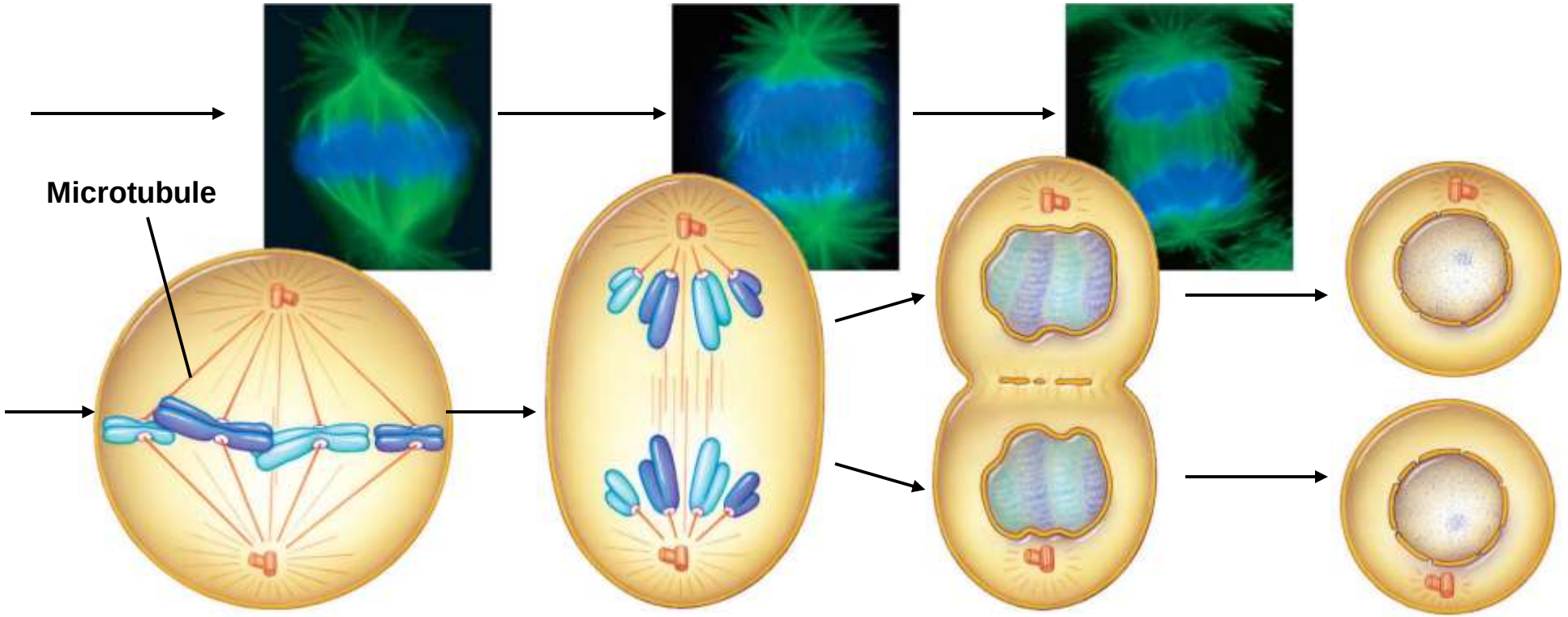


Mitosis

- Produces identical daughter cells
  - (46 chromosomes)
- It must be accurate for cells to function properly
- Continuous process but divided into distinct steps:
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase


(a) Cell at interphase
Mitosis
Pair of centrioles
Nuclear envelope
Chromosome
(b) Early Prophase
(c) Late Prophase
(d) Transition to Metaphase

Stepped Art


Microtubule
(e) Metaphase
(f) Anaphase
(g) Telophase
(h) Interphase

Stepped Art

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

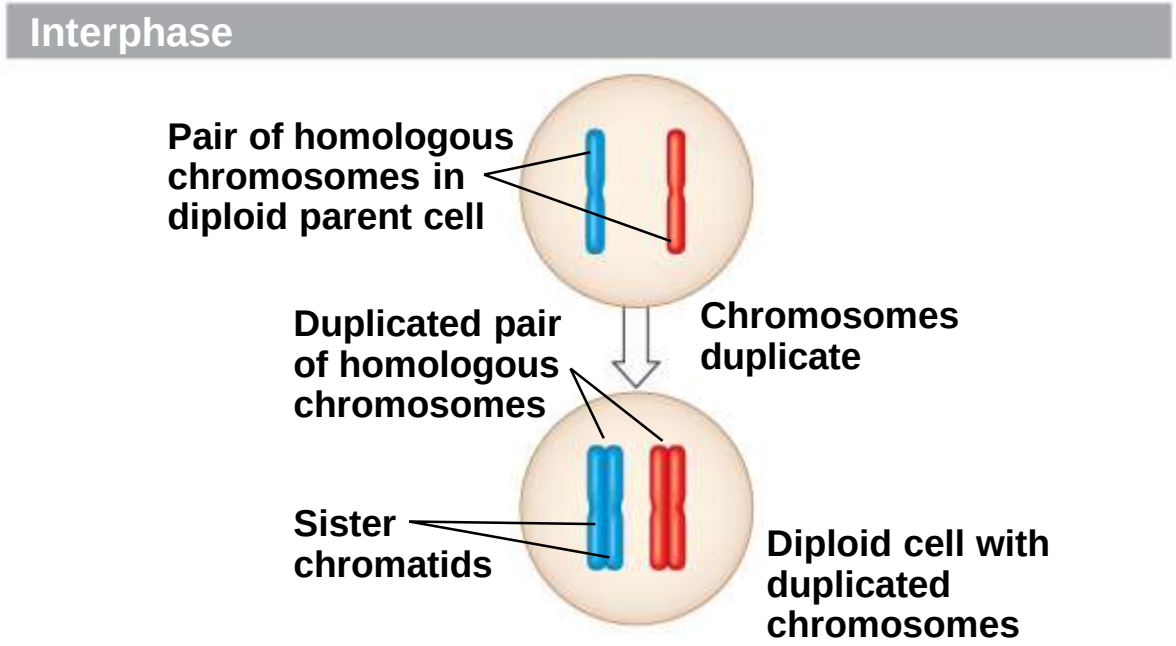


Figure 13.7-2

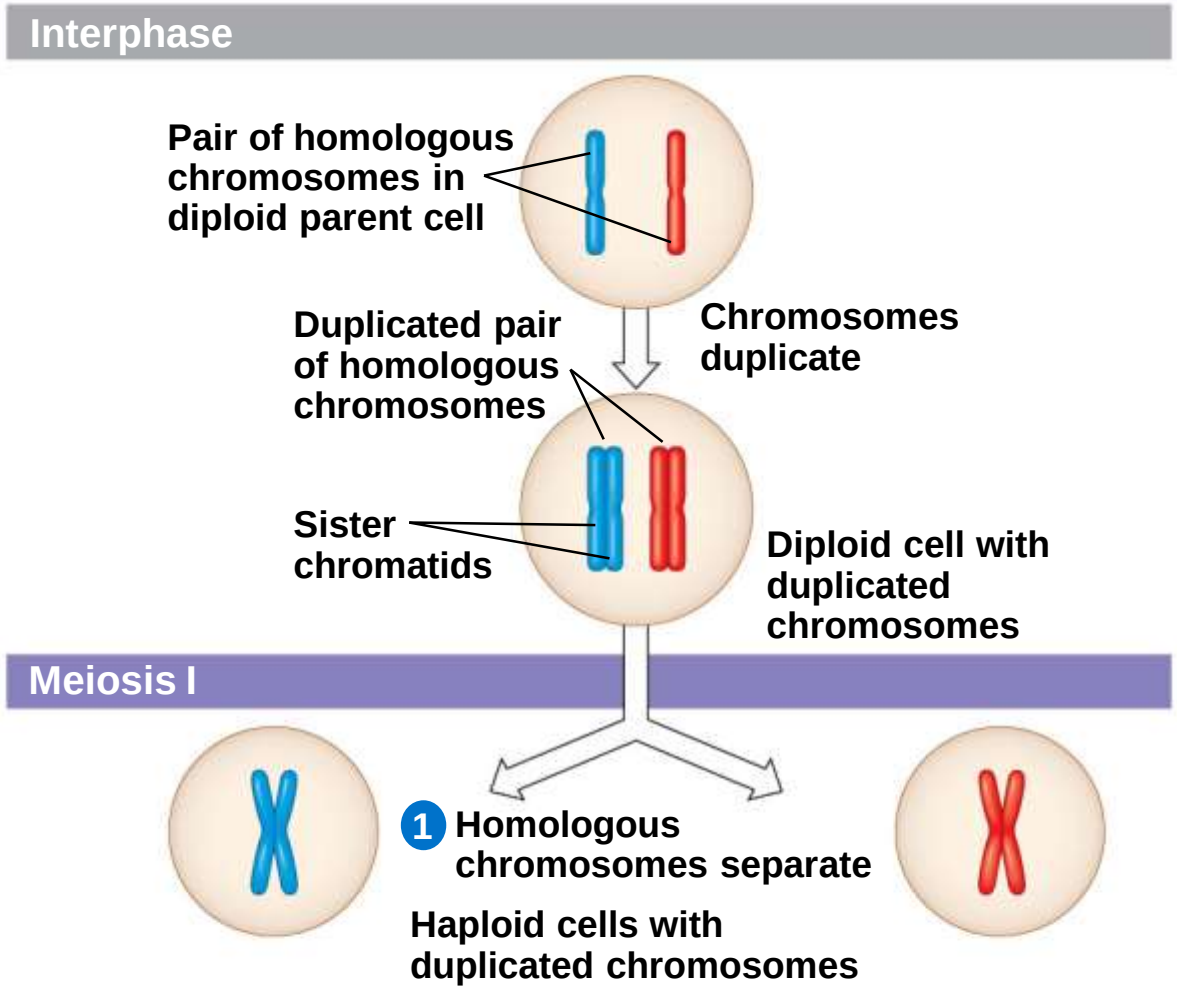
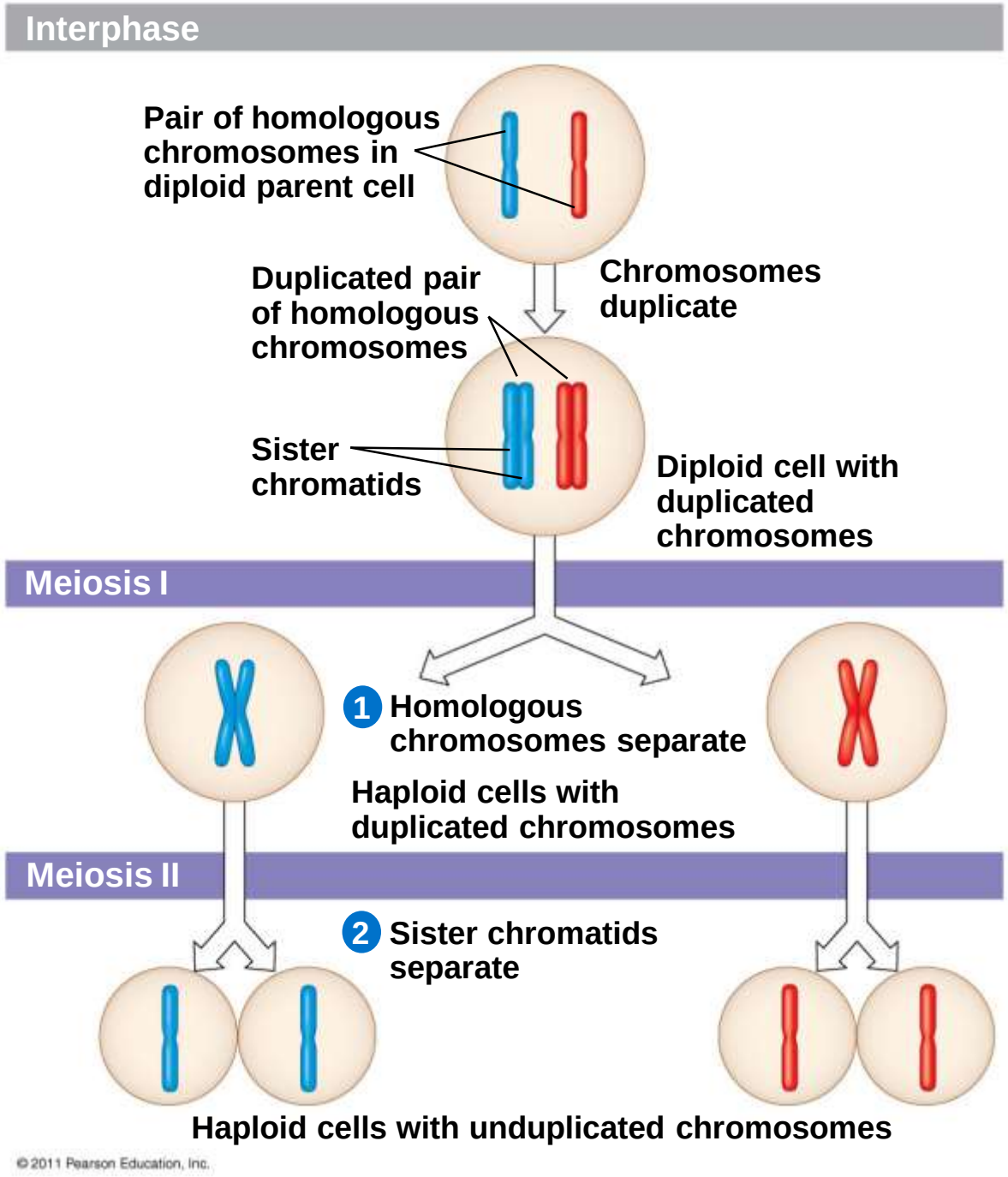
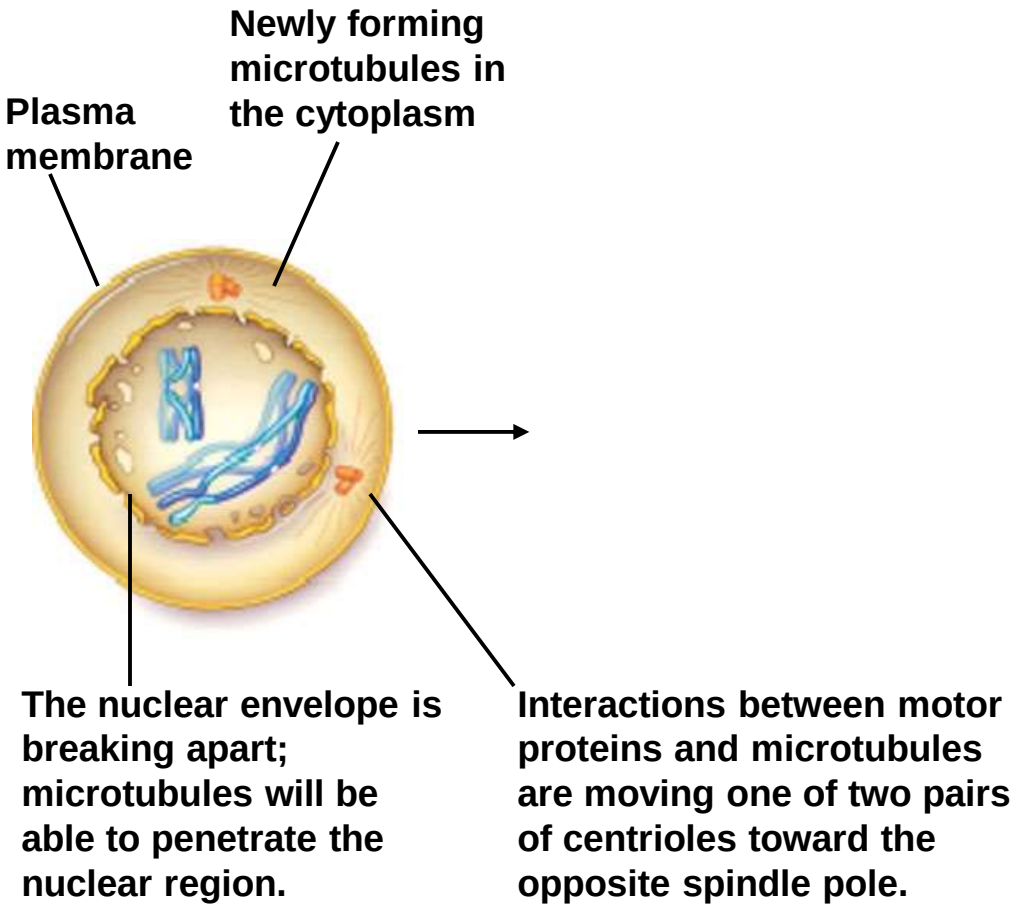


Figure 13.7-3



Meiosis I



(a) Prophase I

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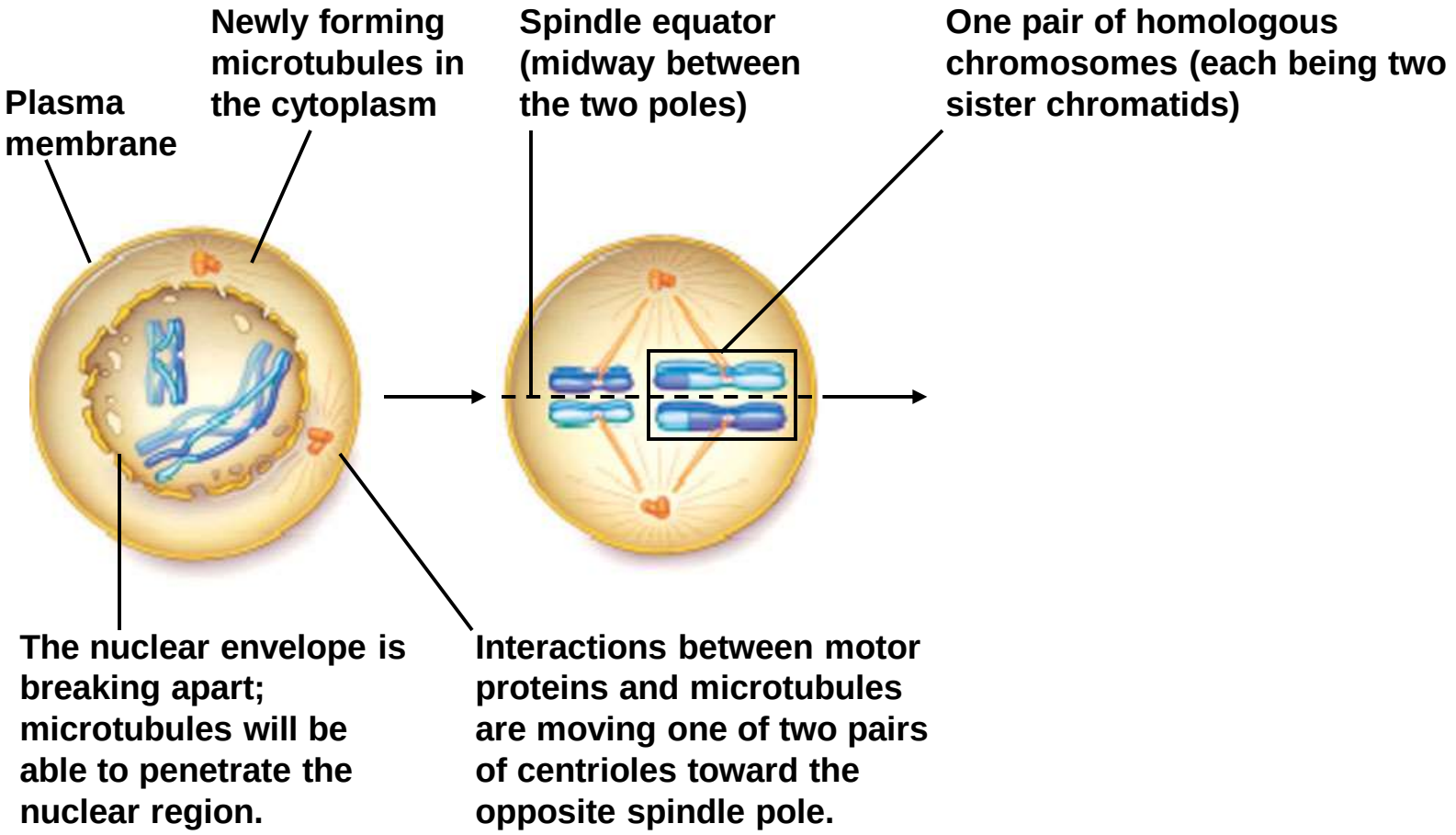
Meiosis I



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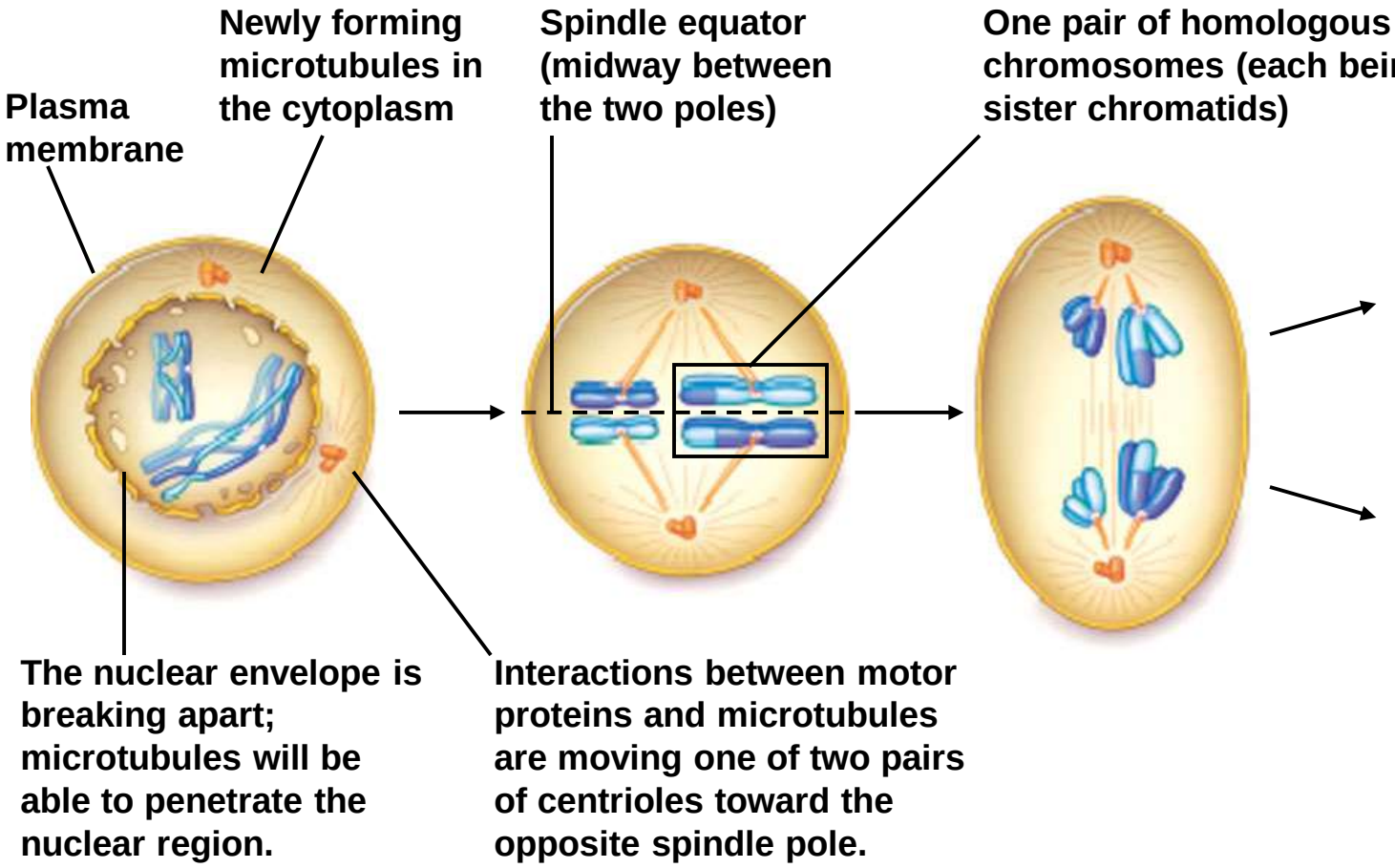
Meiosis I



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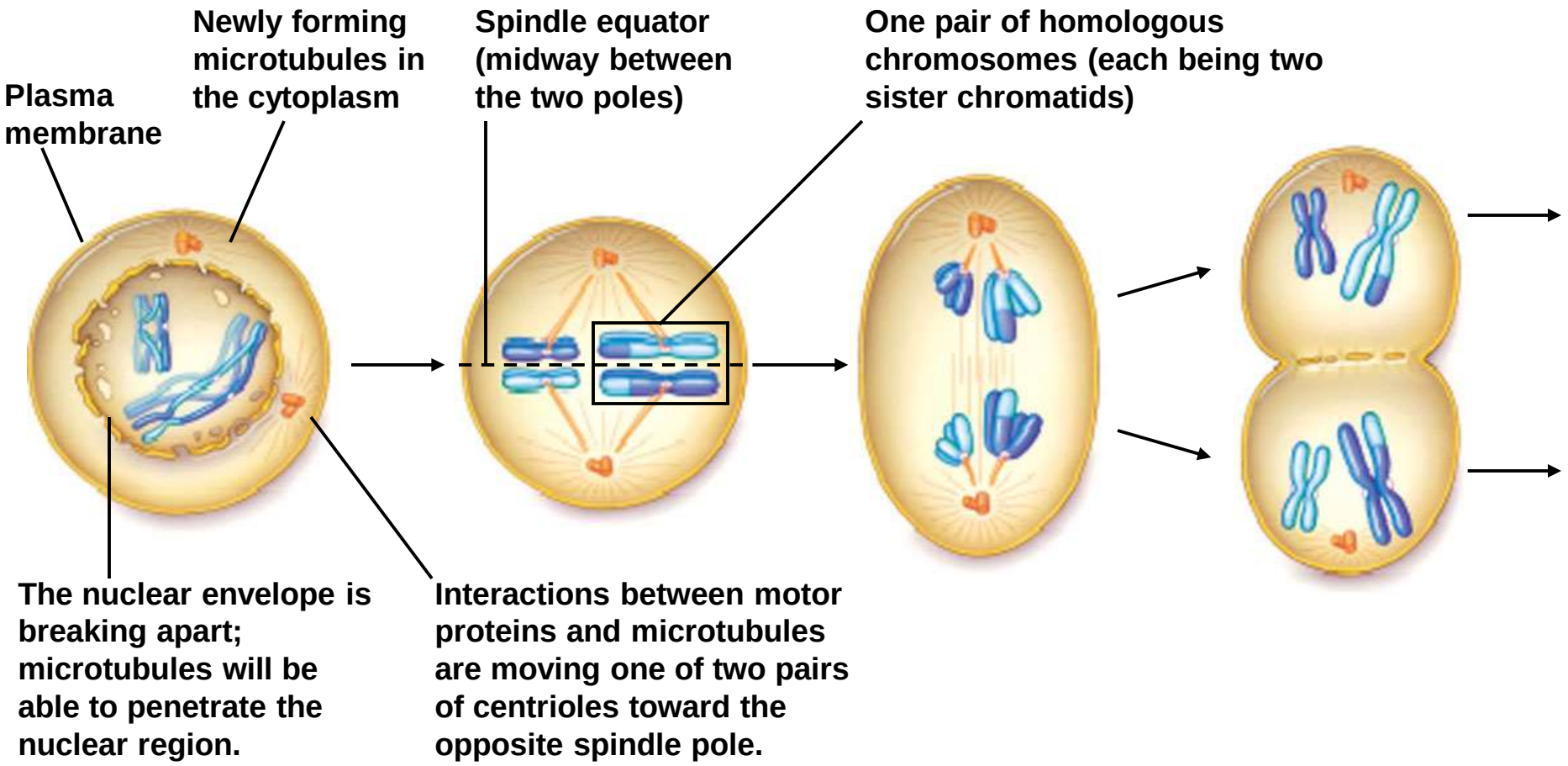
Meiosis I



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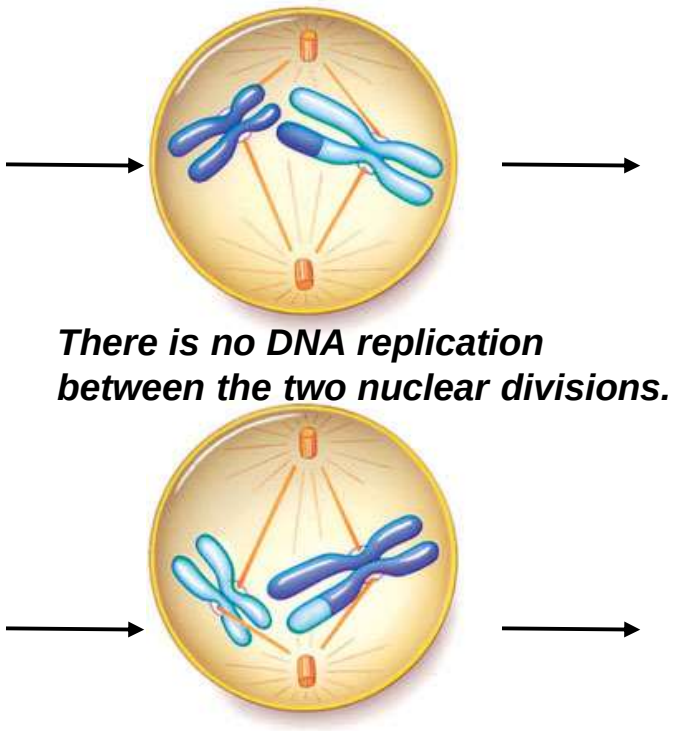
Meiosis II

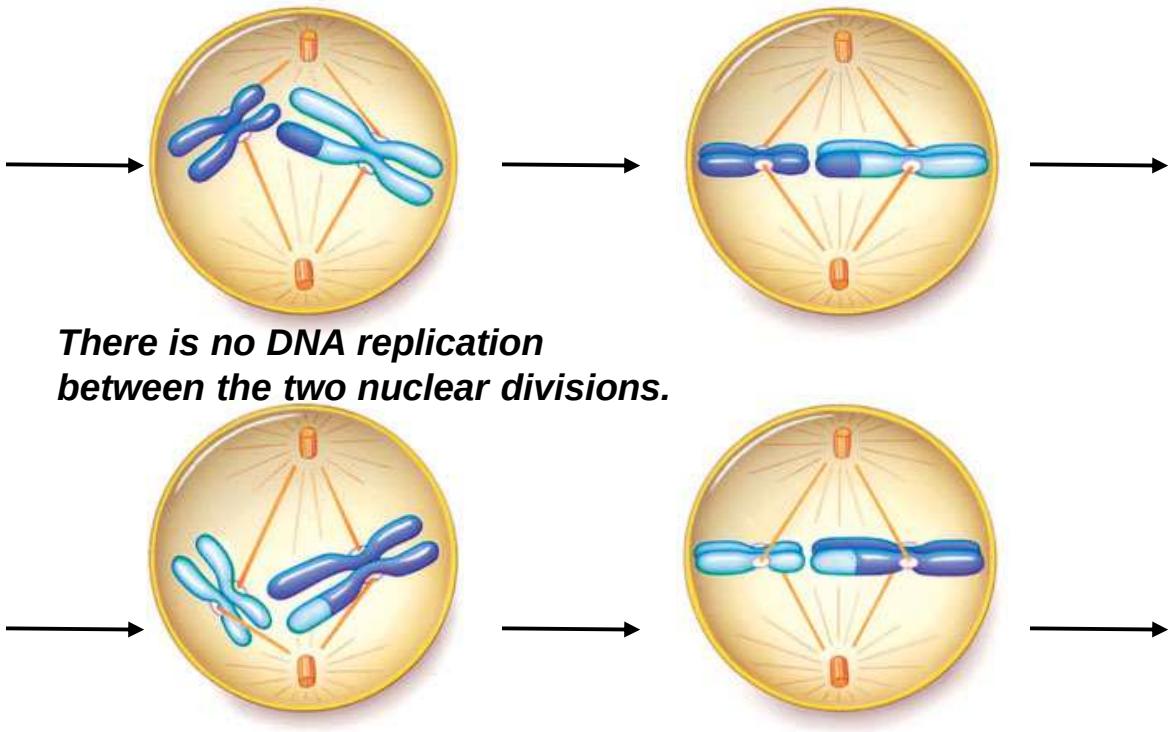


There is no DNA replication between the two nuclear divisions.

(e) Prophase II

Stepped Art

Meiosis II



There is no DNA replication between the two nuclear divisions.

(e) Prophase II **(f) Metaphase II**

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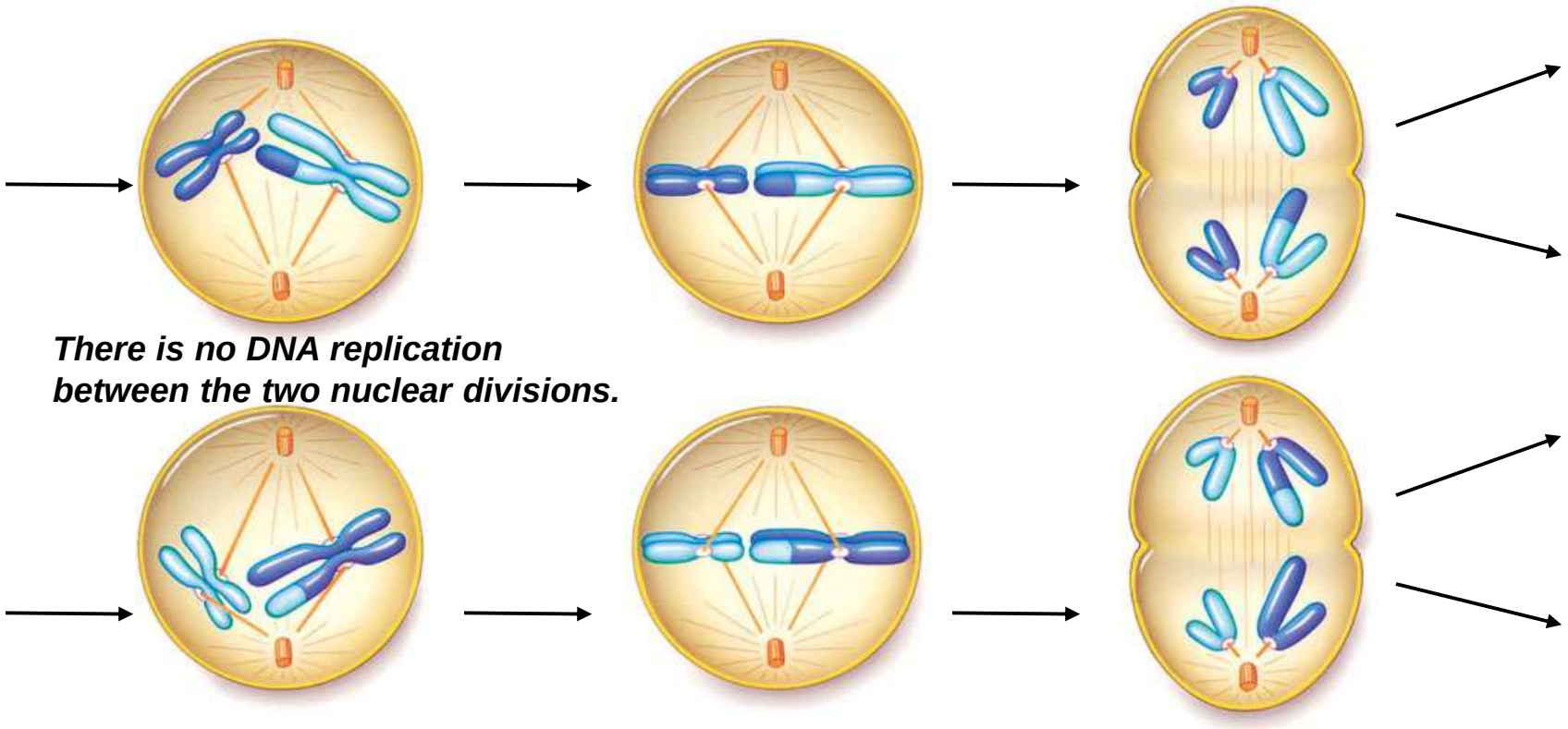
Meiosis II



There is no DNA replication between the two nuclear divisions.

(e) Prophase II **(f) Metaphase II** **(g) Anaphase II**

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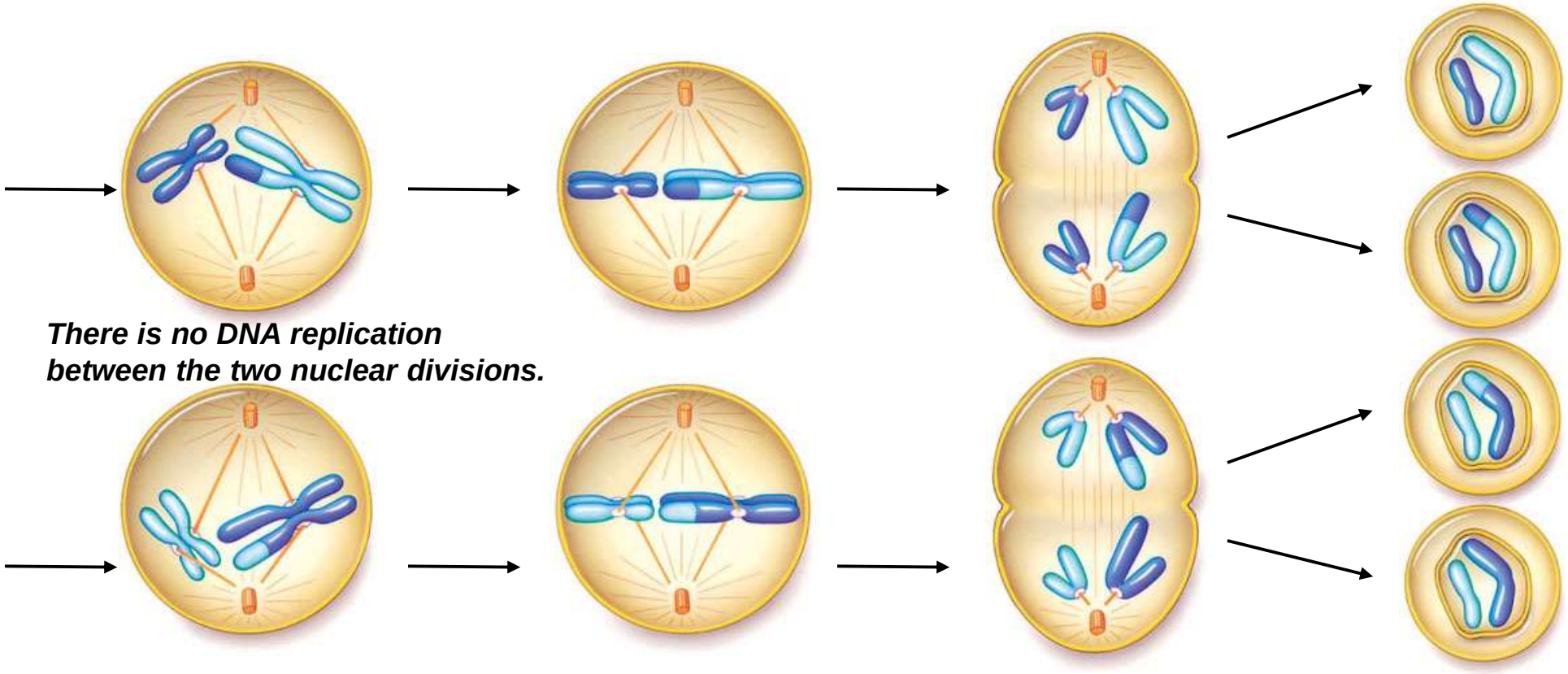
Meiosis II



There is no DNA replication between the two nuclear divisions.

(e) Prophase II **(f) Metaphase II** **(g) Anaphase II** **(h) Telophase II**

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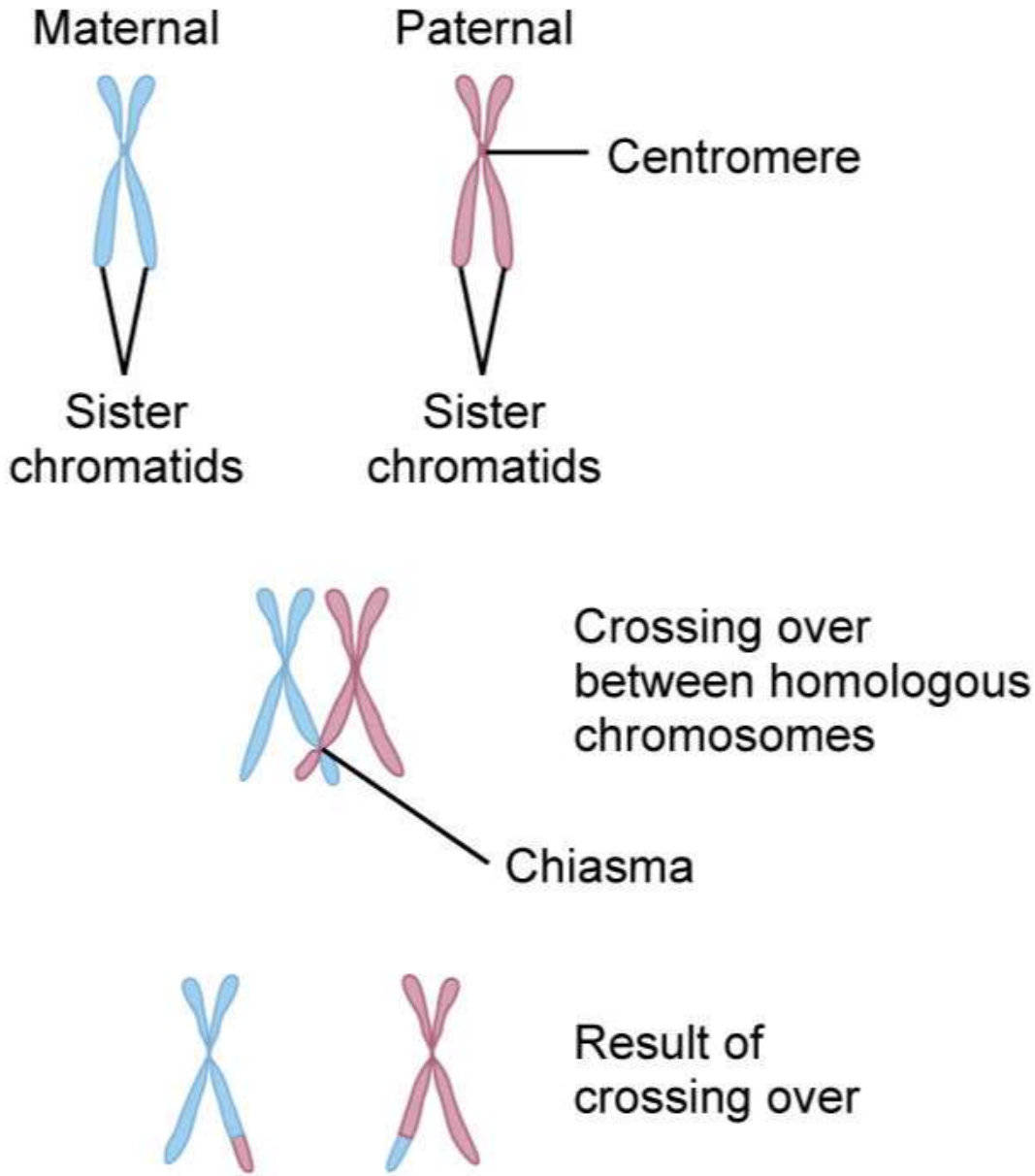
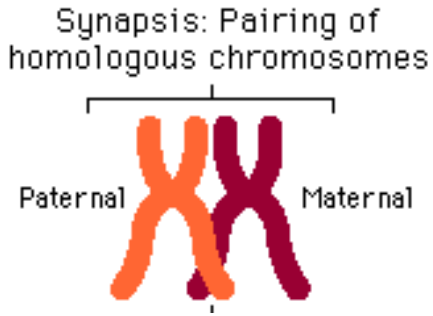
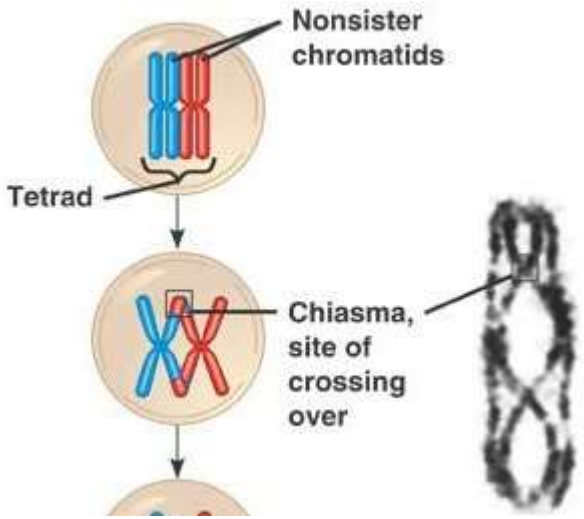
Homologous chromosomes

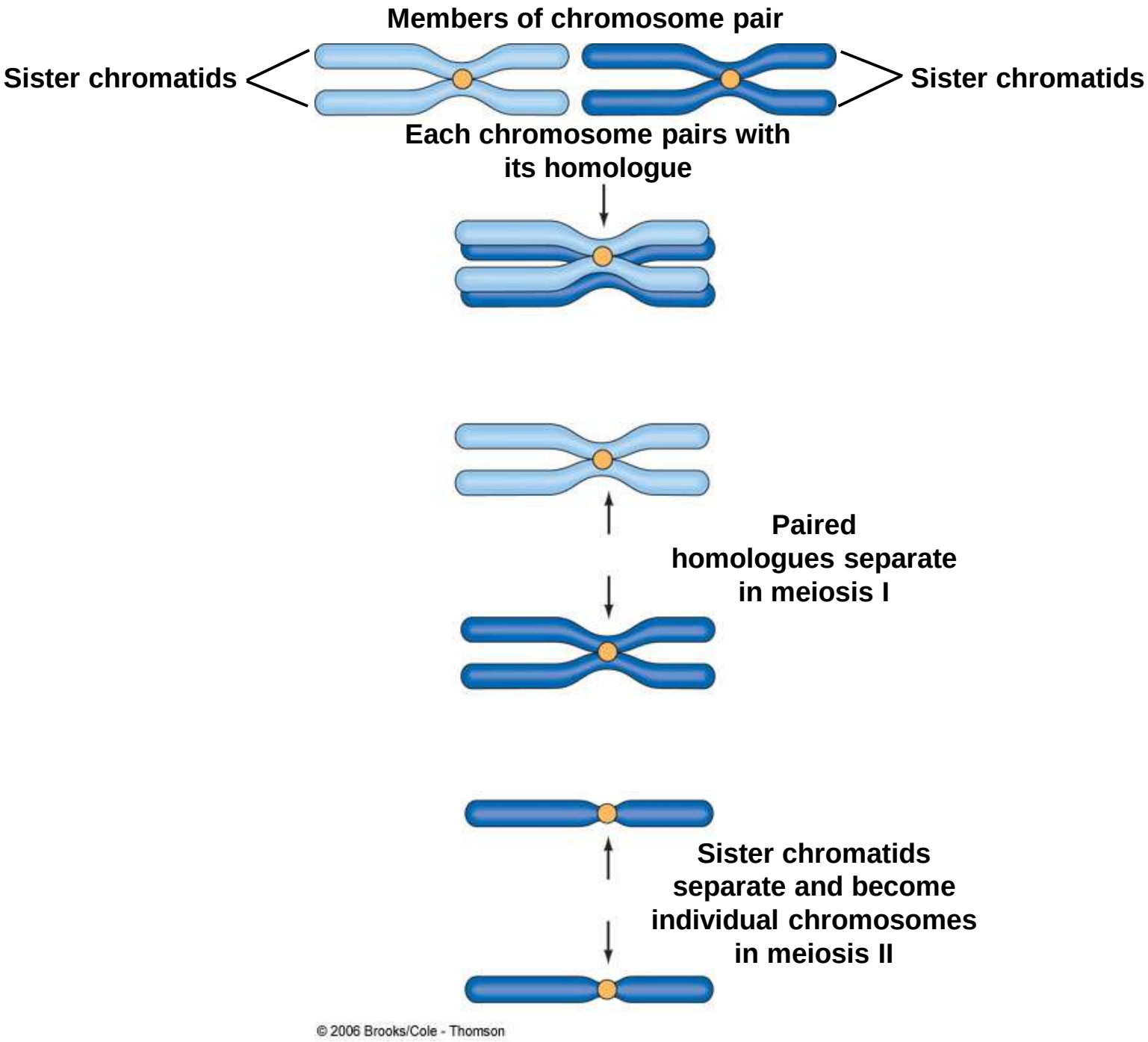


Prophase I

- Leptotene
  - Replicated chromosomes align and begin to condense
- 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**)
  - **Crossing over** occurs (recombination at **chiasmata**)
- Diplotene
  - Homologous chromosomes separate some but remain bound at chiasmata
    - usually 2 chiasmata/chromosome, more frequent in females)
- Diakinesis
  - Further chromosome condensation; tetrads viable



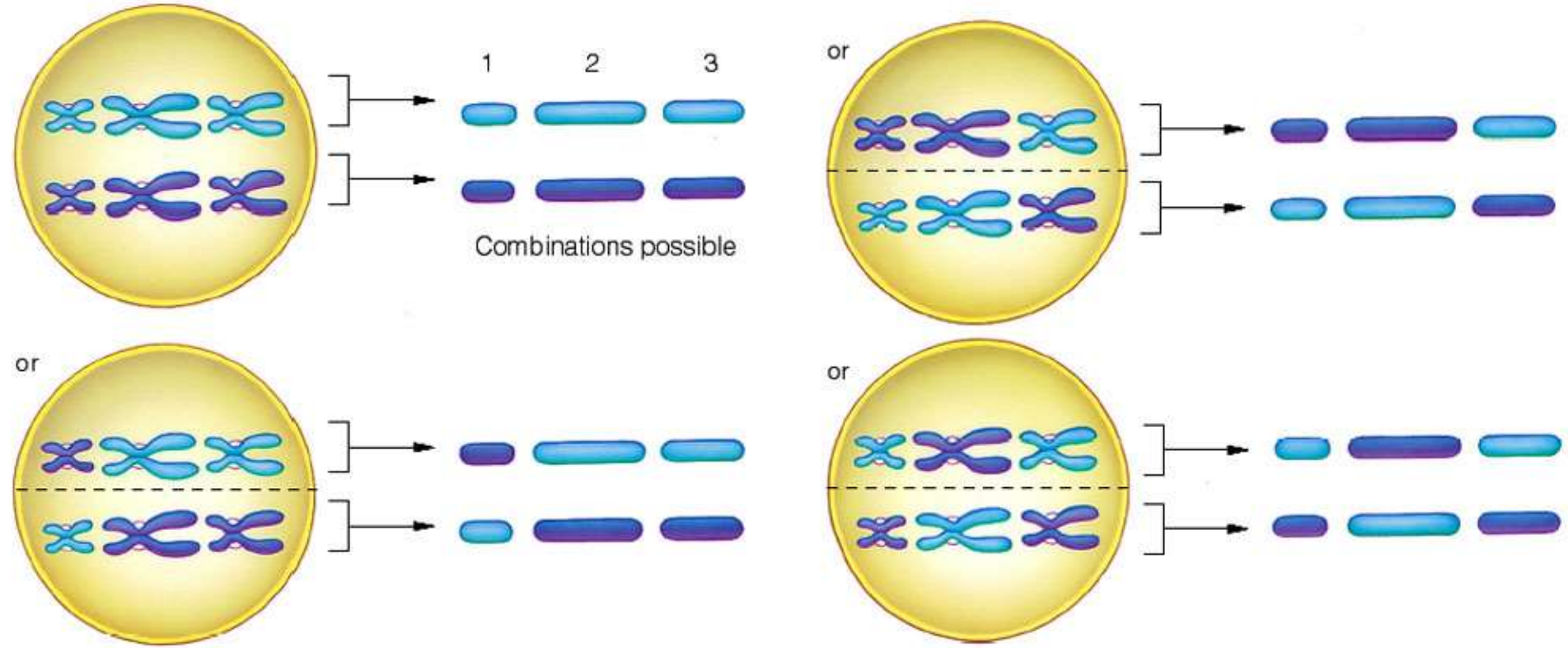




Genetic consequences of meiosis

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

Chromosome combinations: independent assortment



Knowledge of chromosomes is important in many areas of clinical medicine and research.

In humans, approximately 0.6-1% of all liveborns have a chromosomal abnormality.

chromosomal aberrations are noted in:

(1) 20%-27% of individuals having sex reversal or pubertal anomalies;

(2) 33% to 67% of spontaneous miscarriages;

(3) 2% to 5% of couples having a history of multiple miscarriages;

(4) the majority of cells from leukemia samples or solid tumors.

Why Study Human Chromosomes?

Morbidity/Mortality	Estimate of Cases with Cytogenetic Abnormality
Early embryonic death in unrecognized pregnancies	?? 33-67%
Recognized embryonic and fetal deaths (≥ 5 weeks)	About 30% total; rate varies from 50% at 8-11 weeks to 5% in stillbirths (≥ 28 weeks)
Infant and childhood deaths	5-7%
Birth defects	4-8%
Congenital heart defects	13%
Sex reversal/pubertal anomalies	20-27%
Multiple miscarriages in couples	2-5%
Neoplasms	20-80+%

Research Uses for Cytogenetic Evaluation

- **Localization of DNA onto a chromosome(s)**
- **Determination of genomic complement**
- **Characterization of genetic change(s)**
- **Recognition of chromosomal changes following treatment(s) or *in vitro* culturing**

Tissues for Chromosome Studies

- **Peripheral blood (lymphocytes)**
- **Bone marrow**
- **Chorionic villi biopsy**
- **Amniotic fluid cells**
- **Skin or organ biopsy**

- A karyogram is photograph ora diagram of an ordered arrangement of chromosomes from cells that are placed in a standard order (generally by length; chromosome 1 is longest and 22 shortest).

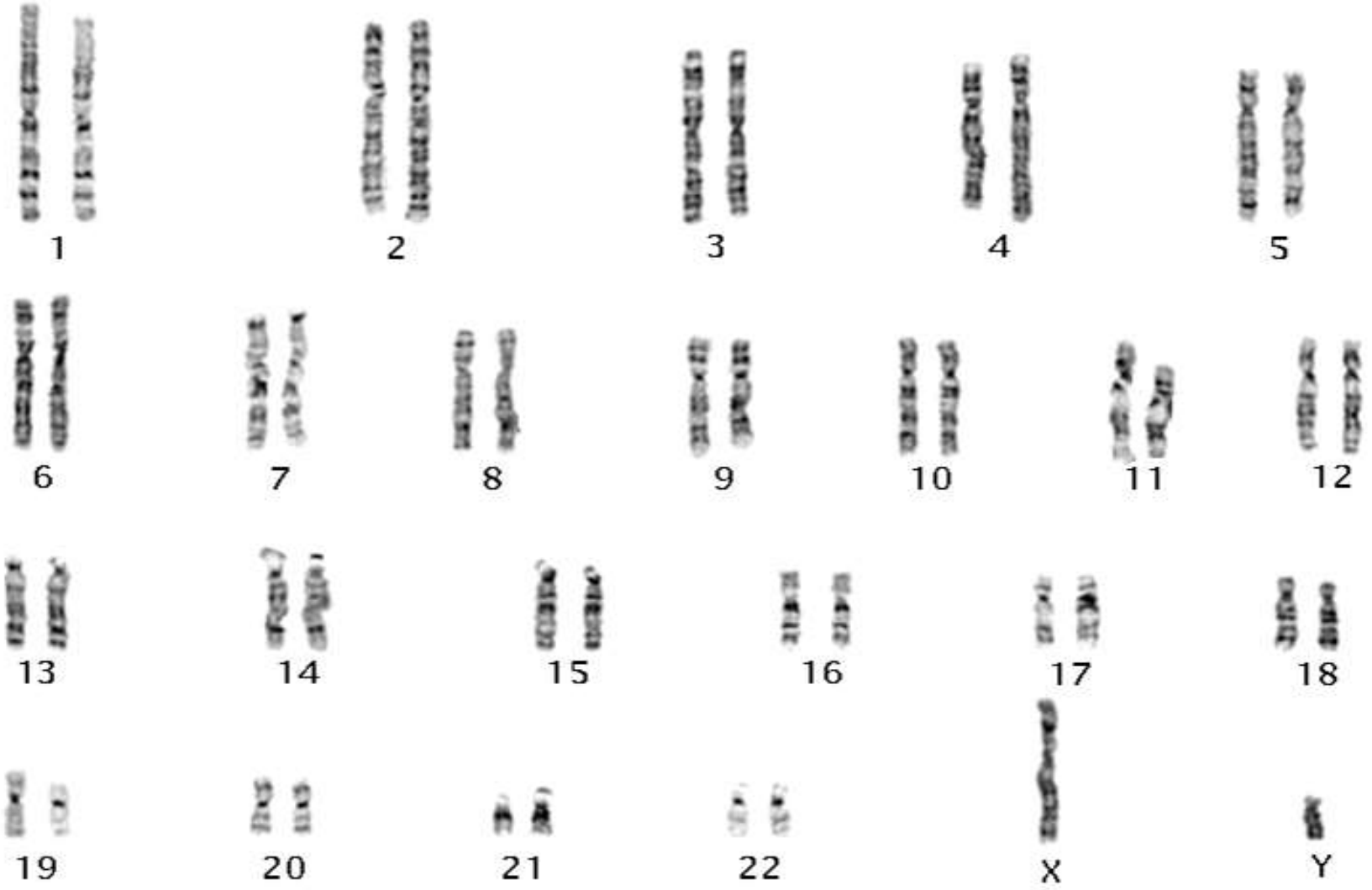
- Once a computer image of the chromosomes from a dividing cell is obtained, the chromosomes are arranged as homologous pairs.

- Each homologous pair of chromosomes consists of one maternally and one paternally inherited chromosome.

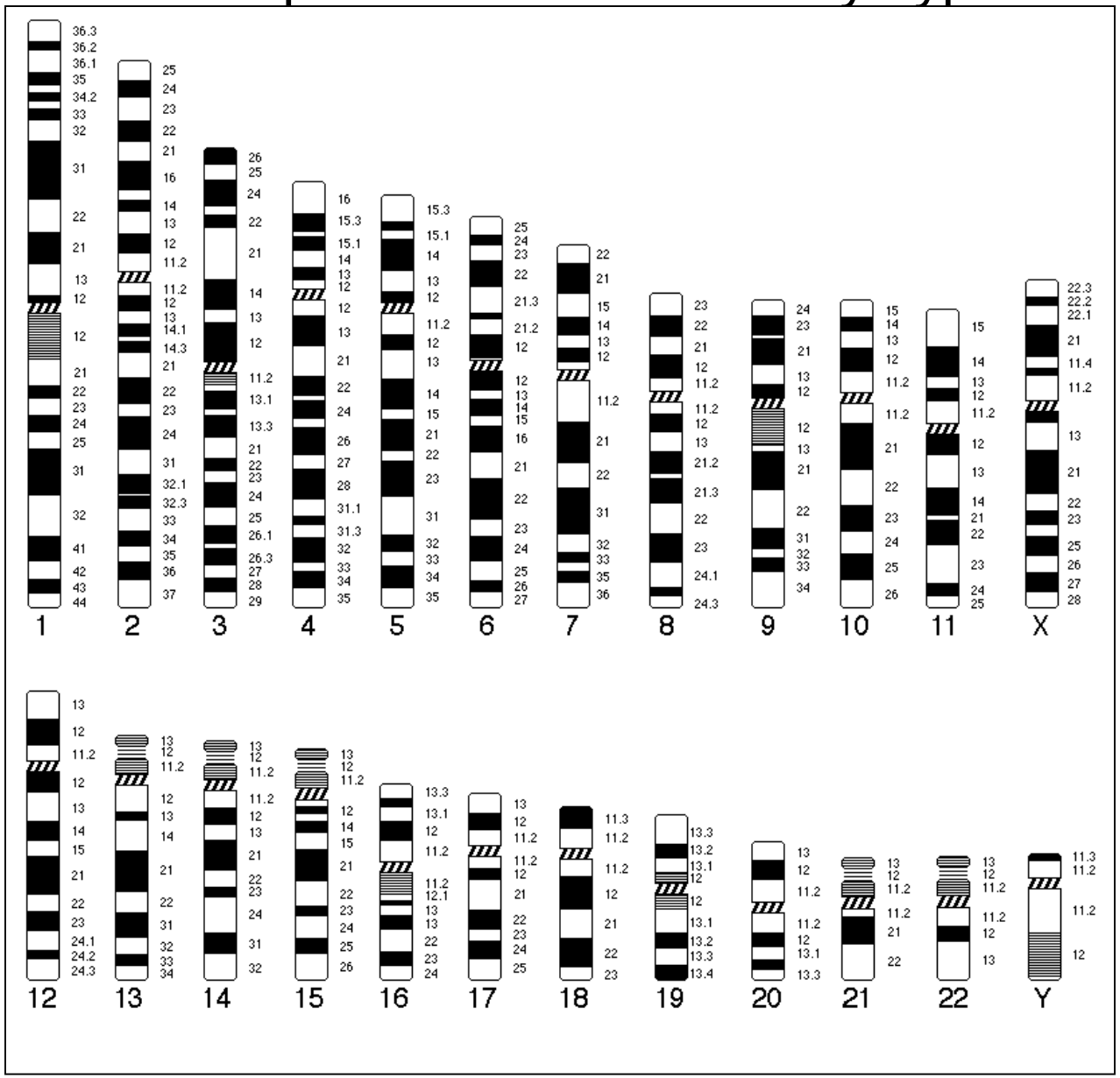
- The normal diploid chromosome number for humans is 46.

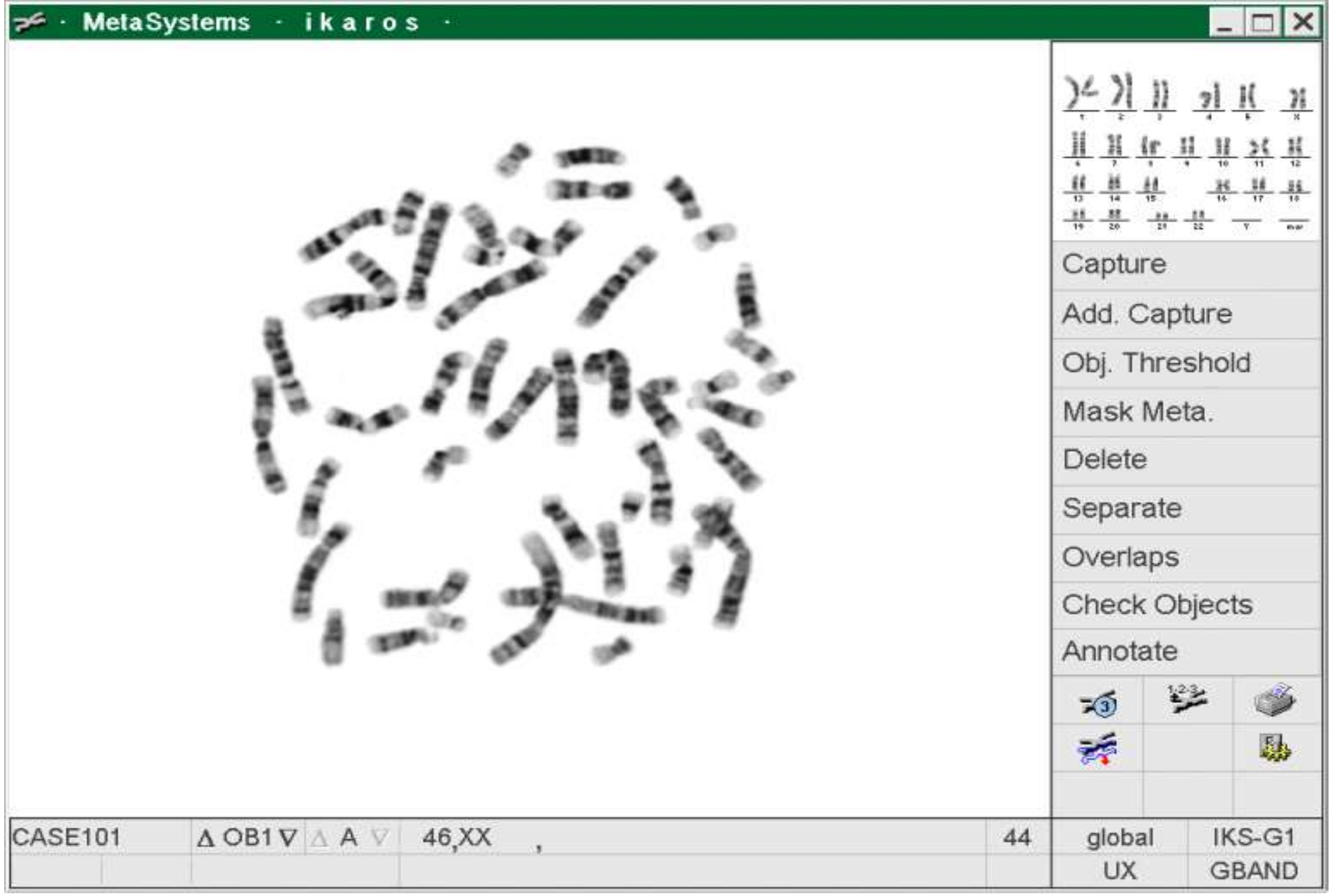
Karyogram is also called Karyotype

<u>Karyogram</u> – An ordered arrangement of the chromosomes from a cell placed in a standard sequence (generally by length).



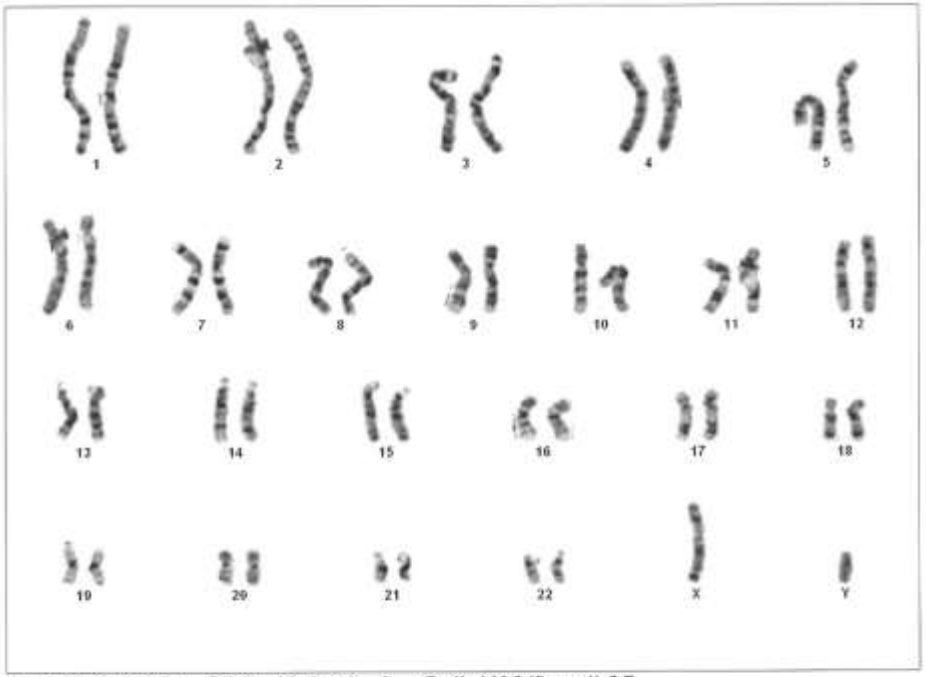
The ideogram of a chromosomal complement is a diagrammatic representation of the karyotype.



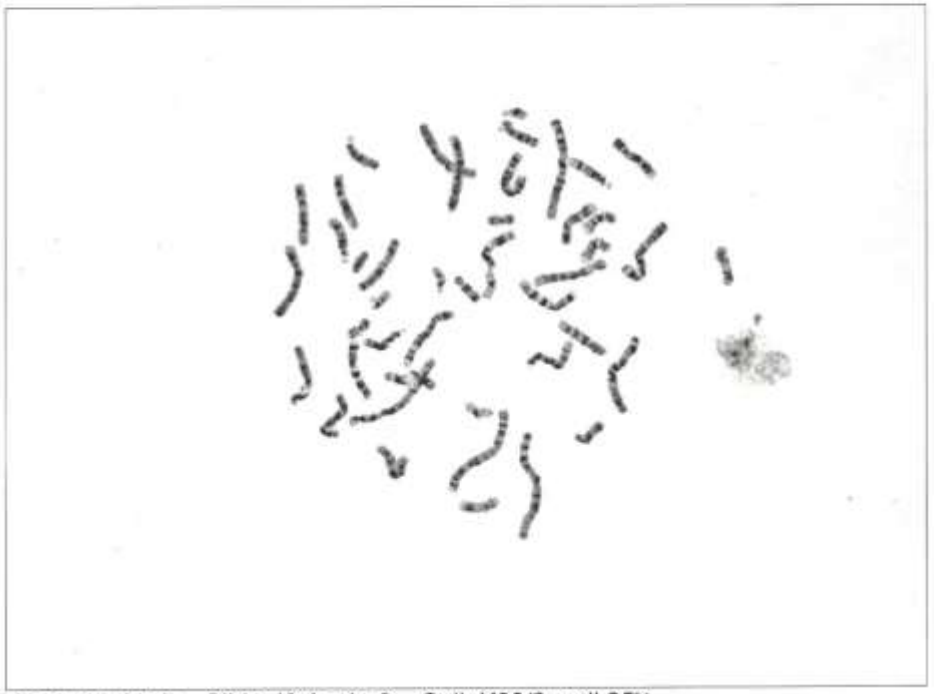


Metaphase chromosomes

- A karyotype is the number and appearance of chromosomes in the nucleus.
- The chromosomal complement for a normal female is indicated as : 46,XX
- The chromosomal complement for a normal male is indicated as : 46,XY
- To be examined by chromosome analysis for clinical purposes, cells must be capable of proliferation in culture. The most accessible cells that meet this requirement are white blood cells, specifically T lymphocytes.



Case: 12-Azab Slide: I3 Azab_3 Cell: K32/3_cell 95

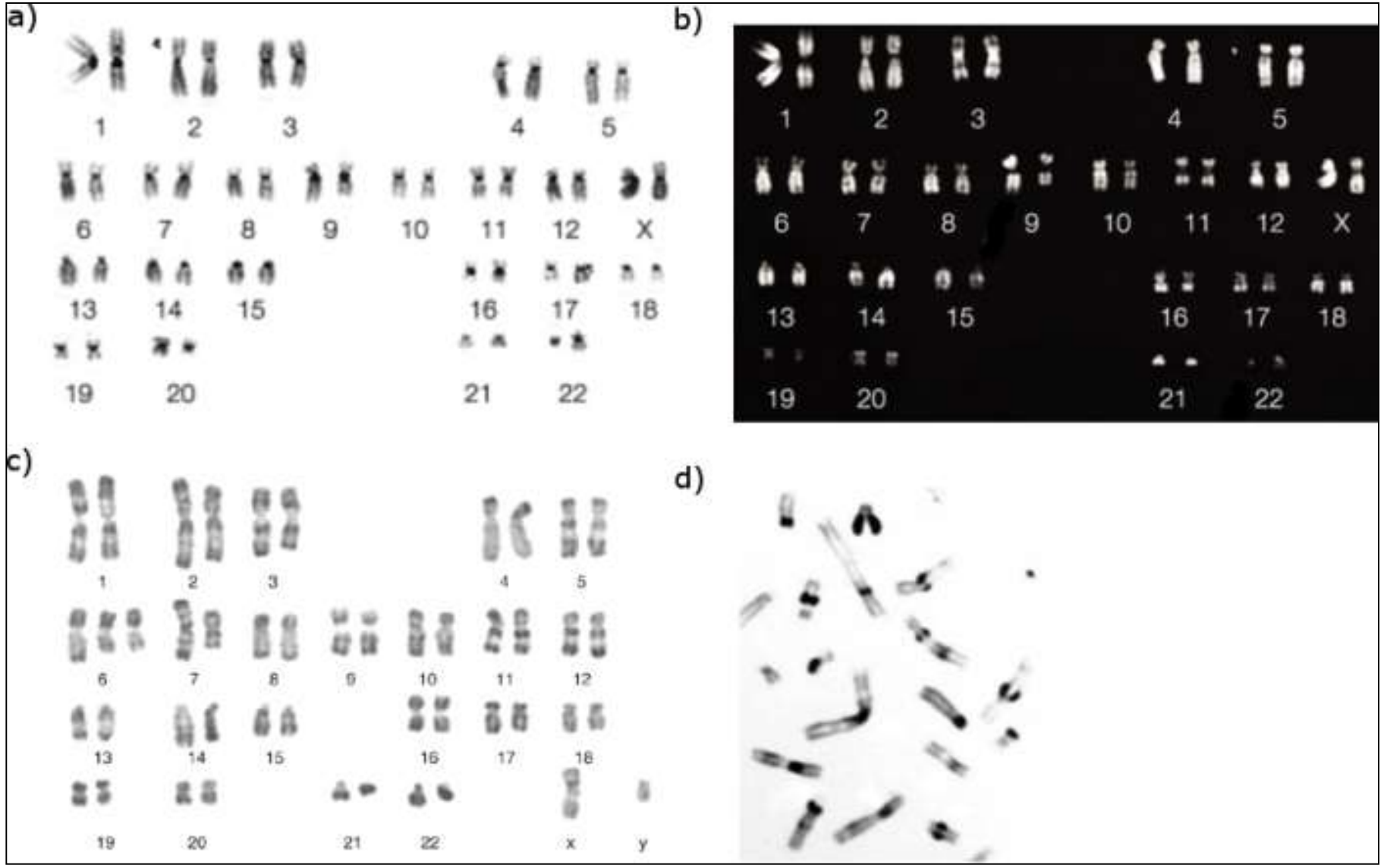

Case: 12-Azab Slide: I3 Azab_3 Cell: K32/3_cell 95³

Types of banding

- G-banding
- R-banding
- C-banding
- Q-banding
- T-banding
- Silver staining

G-banding

Q-banding



R-banding

C-banding

G-banding (GTG)

- heterochromatic regions, which tend to be AT-rich DNA and relatively gene-poor, stain more darkly The **light** regions tend to be **euchromatic**, **GC rich**.
- less condensed chromatin—which tends to be GC-rich and more transcriptionally active—incorporates less Giemsa stain, and these regions appear as light bands
- This method will normally produce 300-400 bands among the 23 pairs of human chromosomes.
- Measured in DNA terms, a G-band represents several million to 10 million base pairs of DNA, a stretch long enough to contain hundreds of genes.
- metaphase chromosomes are first treated briefly with trypsin, an enzyme that degrades proteins, before the chromosomes are stained with Giemsa. Trypsin partially digests some of the chromosomal proteins, thereby relaxing the chromatin structure and allowing the Giemsa dye access to the DNA.

R-banding

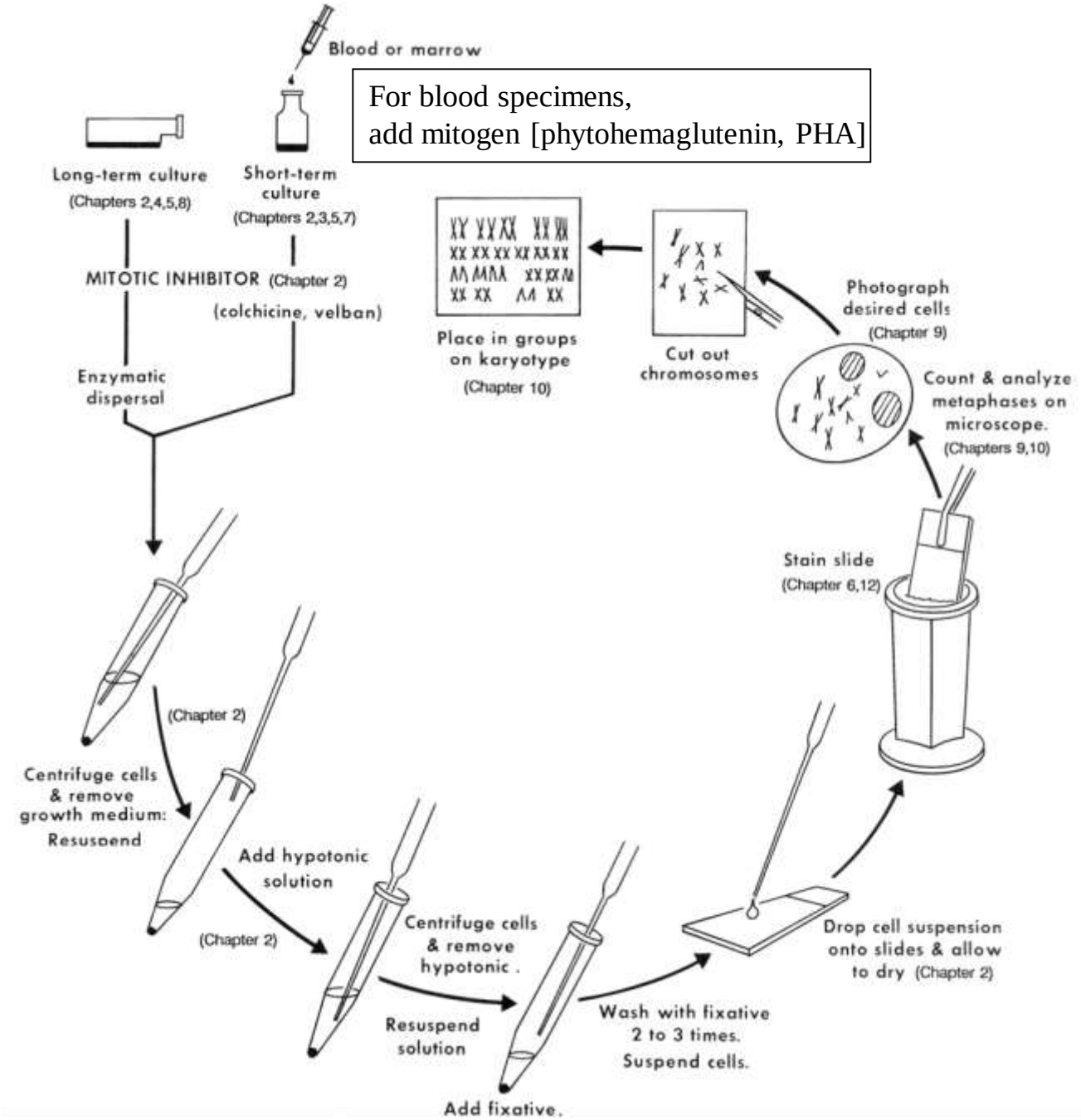
- is the reverse of G-banding (the R stands for "reverse"). The dark regions are euchromatic (guanine-cytosine rich regions). The bright regions are heterochromatic (thymine-adenine rich regions)

- provide critical details about gene-rich regions that are located near the telomeres
- often used together with G-banding on human karyotype to determine whether there are deletions.

- the chromosomes are heated before Giemsa stain is applied. The heat treatment is thought to preferentially melt the DNA helix in the AT-rich regions that usually bind Giemsa stain most strongly, leaving only the comparatively GC-rich regions to take up the stain. R-banding

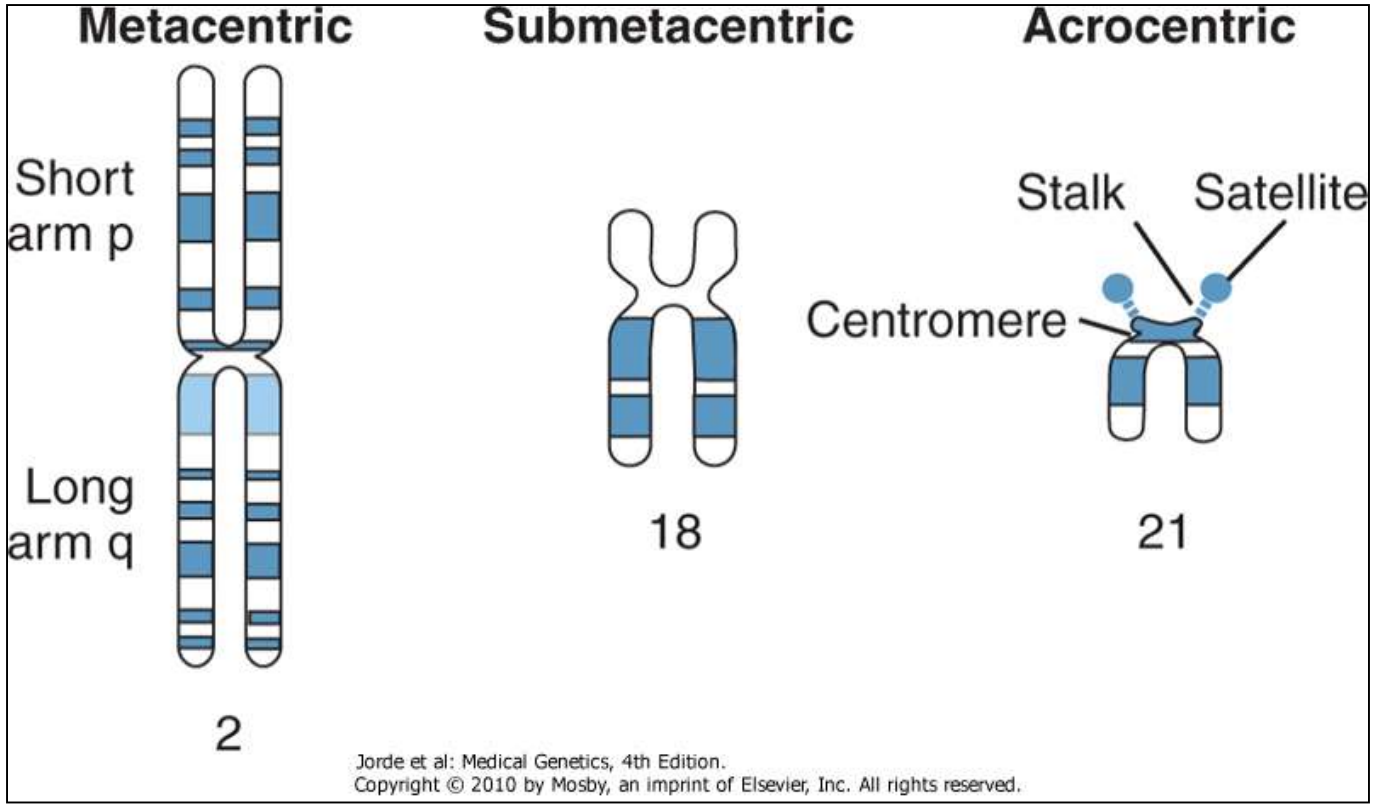
Primary Steps for Culture Establishment and Harvest of Specimens

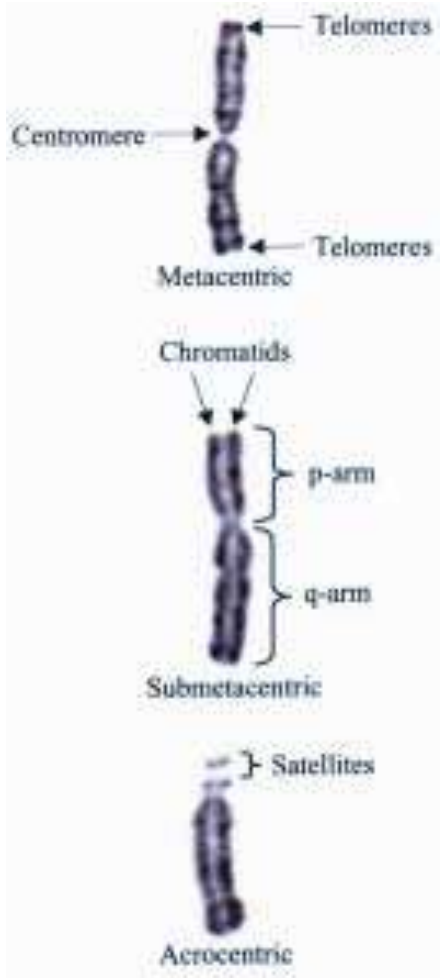
- **Add Mitogen (when needed)**
- **Hypotonic Swelling**
- **Fixation**
- **Analysis**



Chromosome Shape

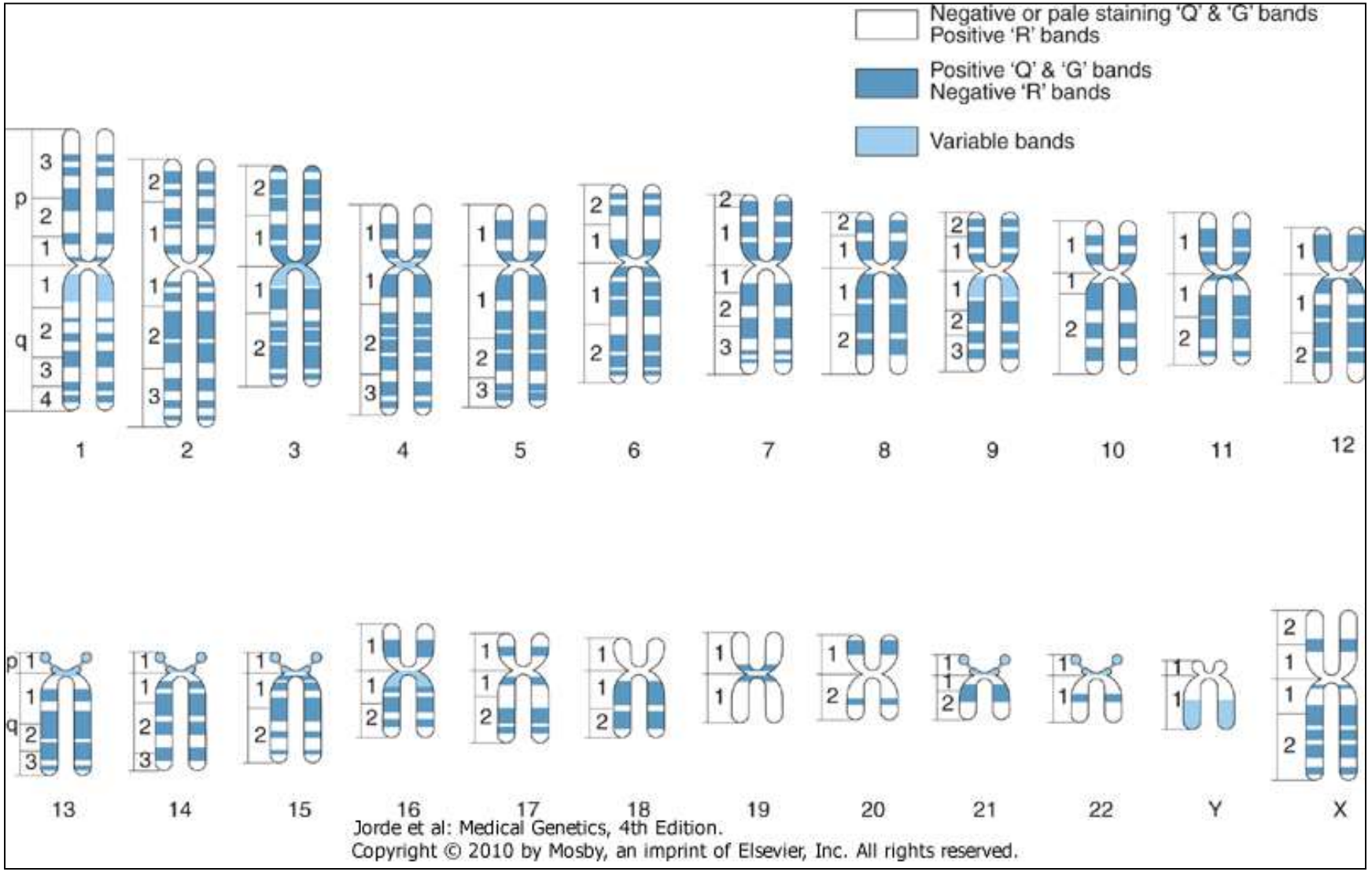
Metacentric- centromere is located in the middle of chromosome
Submetacentric- centromere is displaced from the center
Acrocentric – centromere is placed near the end





Human Chromosome Ideogram

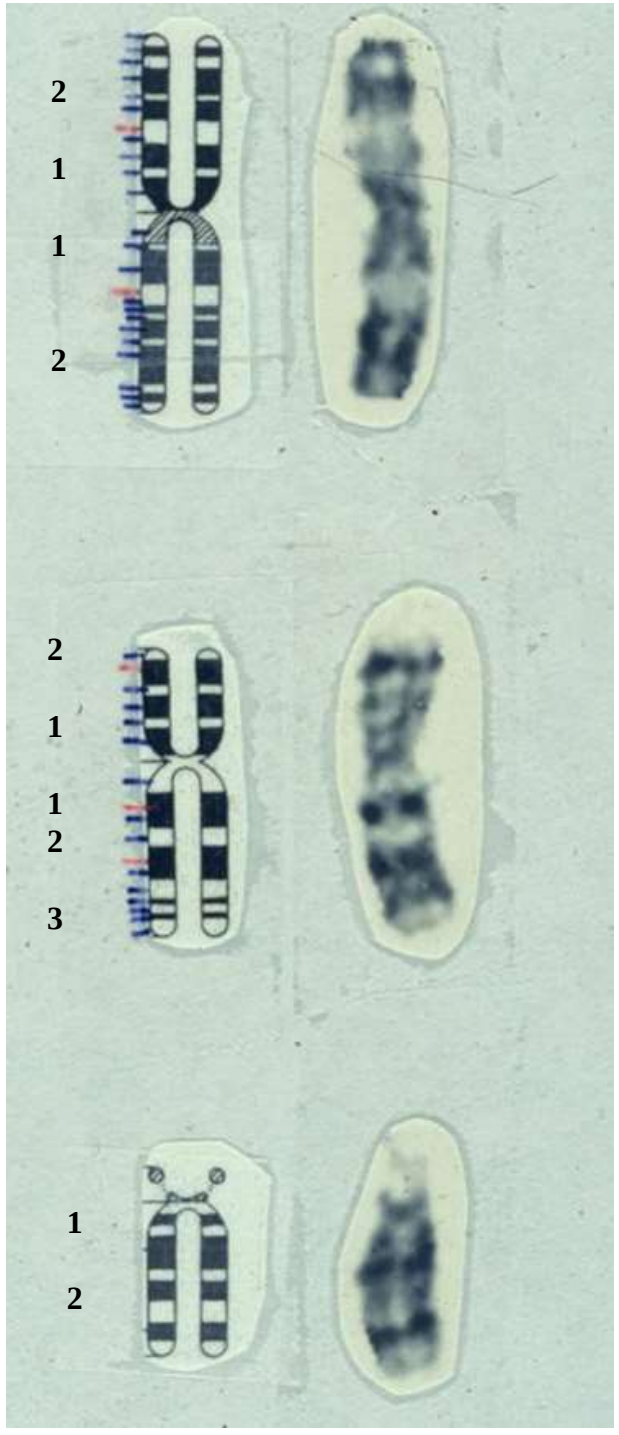
<u>Ideogram</u>- A diagrammatic representation of a karyotype

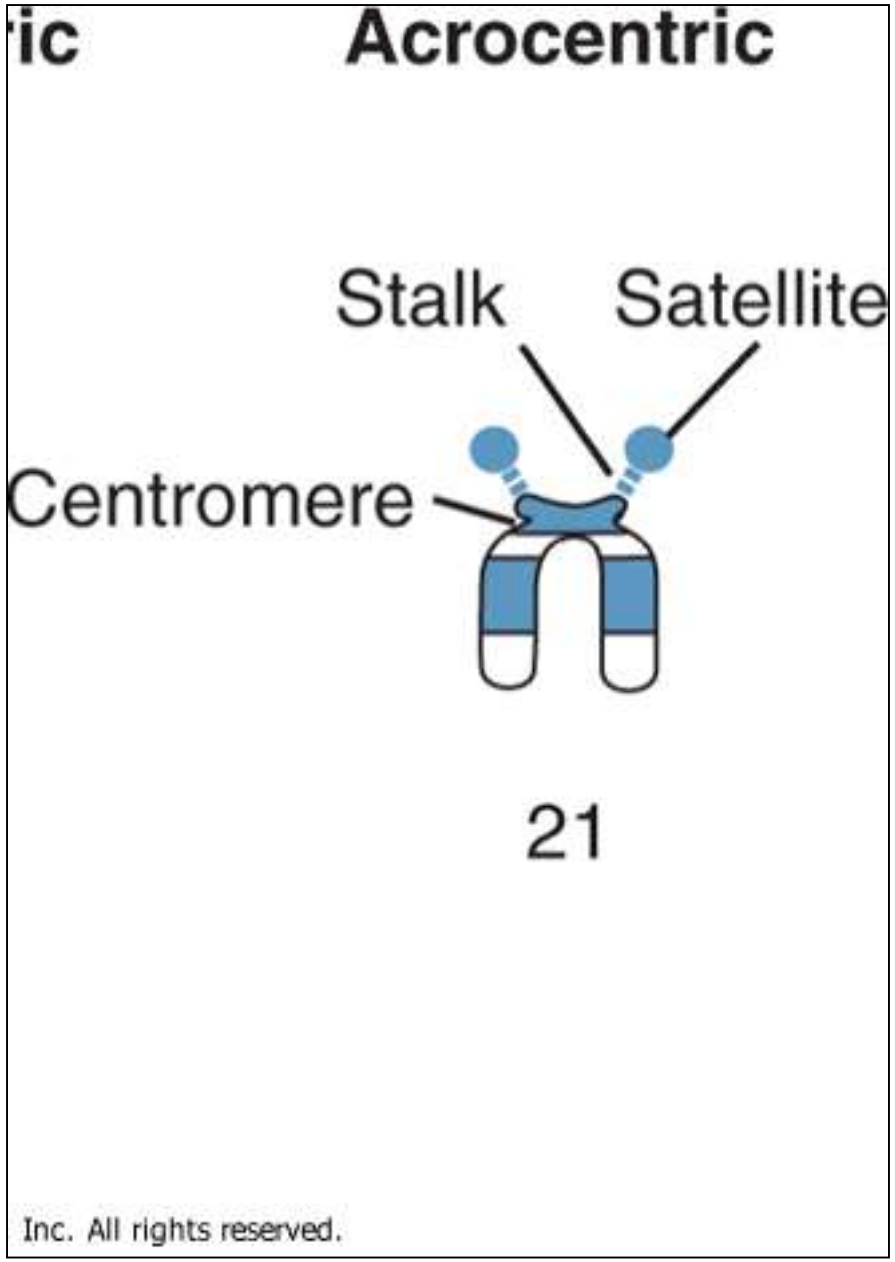


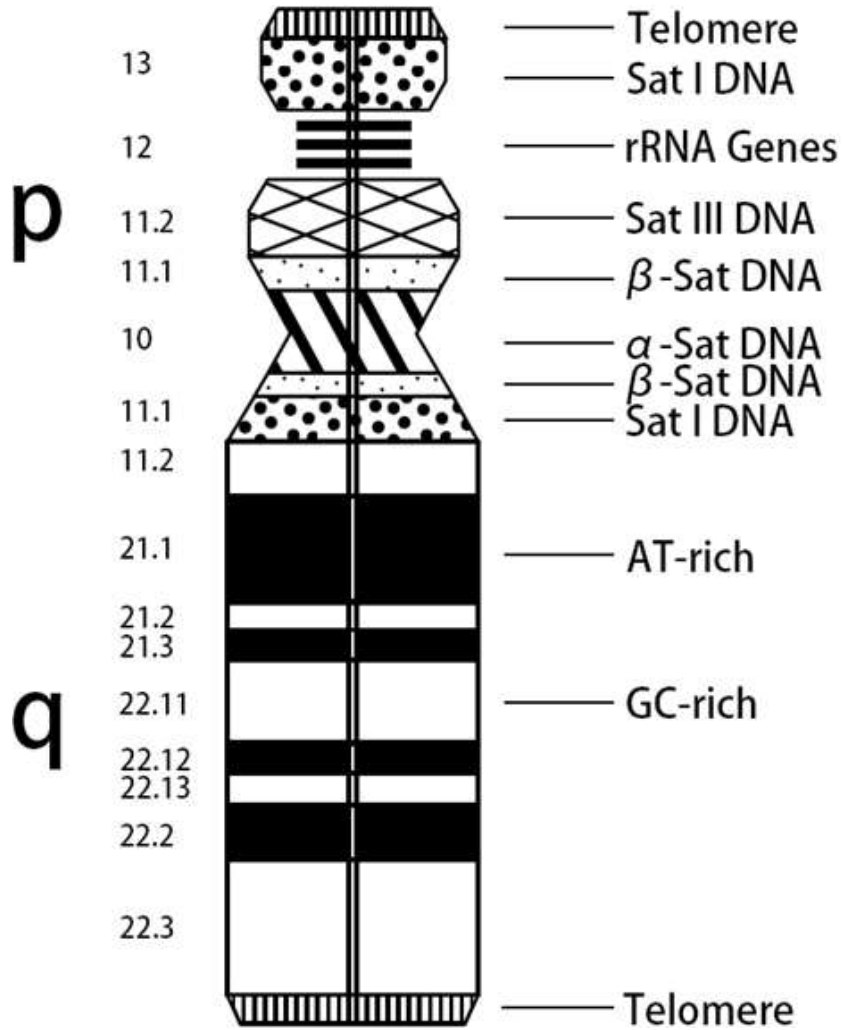
Chromosome 3
p: 2 regions
q: 2 regions

Chromosome 7
p: 2 regions
q: 3 regions

Chromosome 14
p: 1 region
q: 2 regions

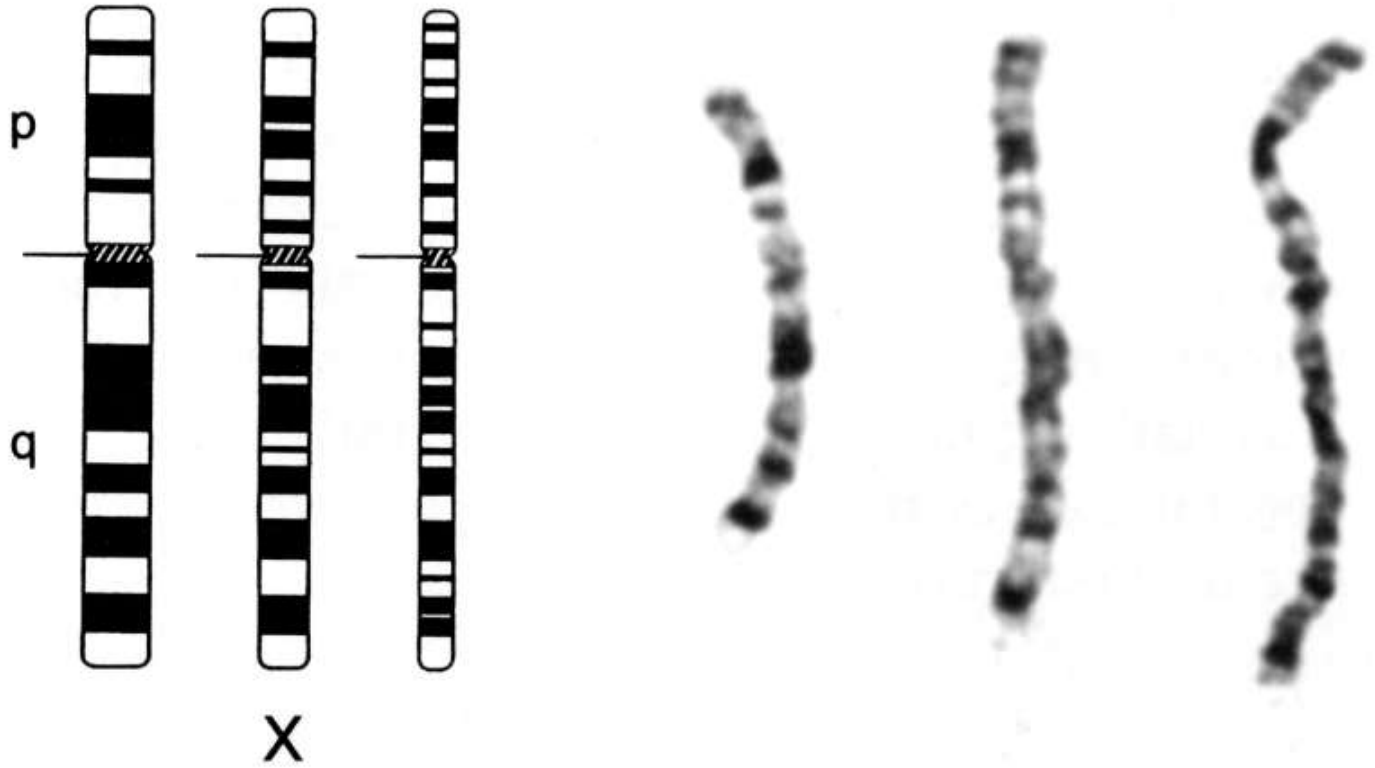



ic
Acrocentric
Stalk
Satellite
Centromere
21
Inc. All rights reserved.


p
q
13
12
11.2
11.1
10
11.1
11.2
21.1
21.2
21.3
22.11
22.12
22.13
22.2
22.3
Telomere
Sat I DNA
rRNA Genes
Sat III DNA
β-Sat DNA
α-Sat DNA
β-Sat DNA
Sat I DNA
AT-rich
GC-rich
Telomere

High Resolution Banding

High-resolution banding involves the staining of chromosomes during prophase or prometaphase, before they reach maximal condensation.
Because prophase and prometaphase chromosomes are more extended than metaphase chromosomes, the number of bands observable for all chromosomes increases from about 300 to 450 to as many as 800 per haploid set. This allows the detection of less obvious abnormalities usually not seen with conventional banding.



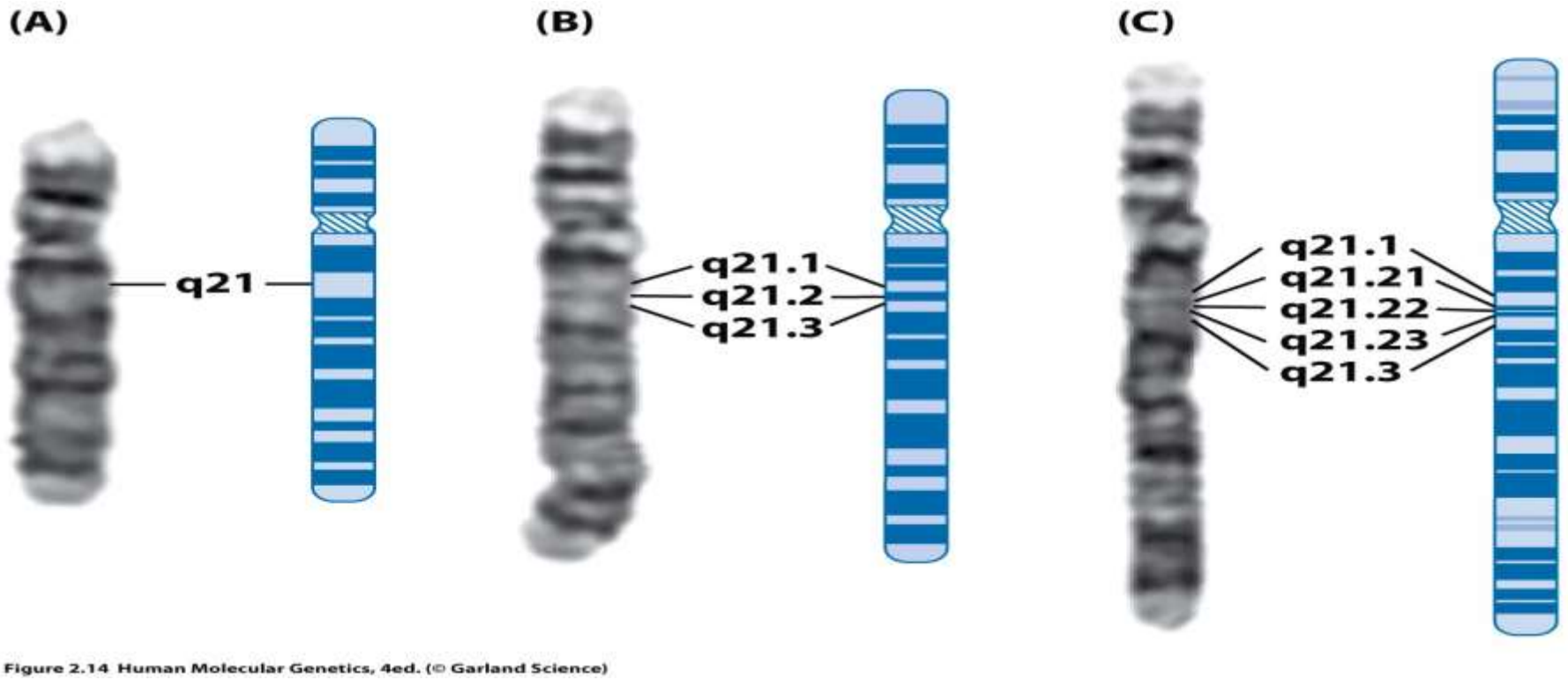


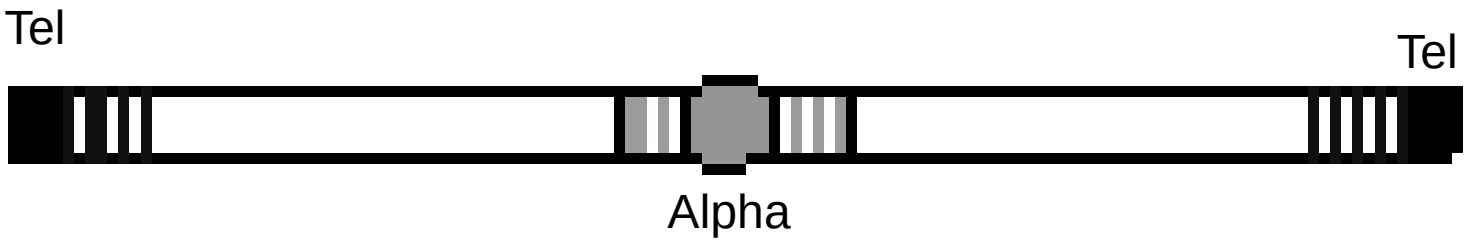
Figure 2.14 Different chromosome banding resolutions can resolve bands, sub-bands, and sub-sub-bands.

G-banding patterns for human chromosome 4 (with accompanying ideogram at the right) are shown at increasing levels of resolution. The levels correspond approximately to (A) 400, (B) 550, and (C) 850 bands per haploid set, allowing the visual subdivision of bands into sub-bands and sub-subbands as the resolution increases. [Adapted from Cross & Wolstenholme (2001). Human Cytogenetics: Constitutional Analysis, 3rd ed. (DE Rooney, ed.). With permission of Oxford University Press.]

Components of Chromosomes: Centromeres, Telomeres/Sub-telomeres

Structures of chromosomes:

Centromere
Telomere
Sub-telomere



171-bp monomers

Pericentromeric region**

Unique chromosome-specific DNA

(TTAGGG)n

Subtelomeric region*

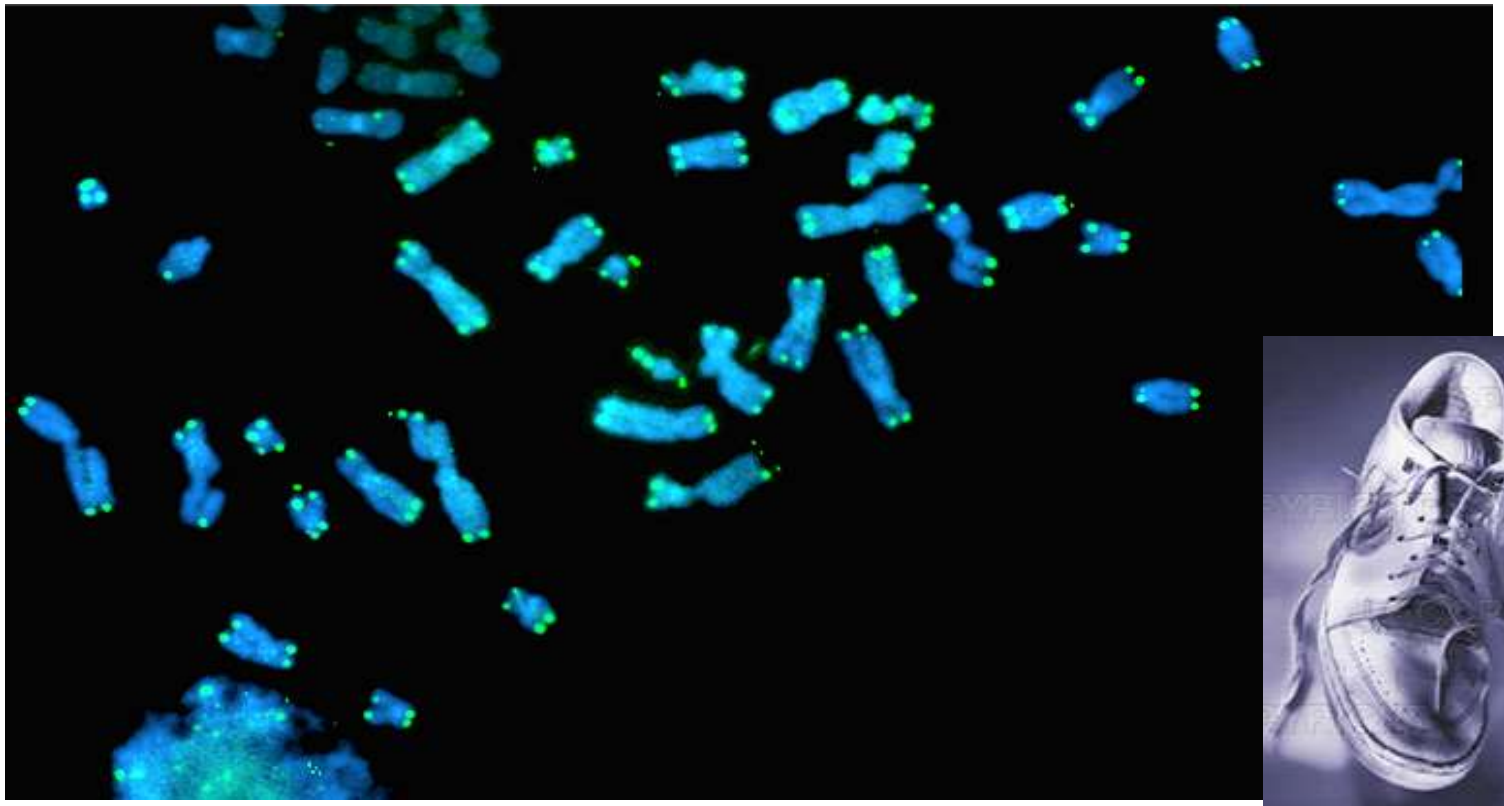
***Highly polymorphic; implicated in location of "hotspots for structural chromosomal abnormalities**

Centromere

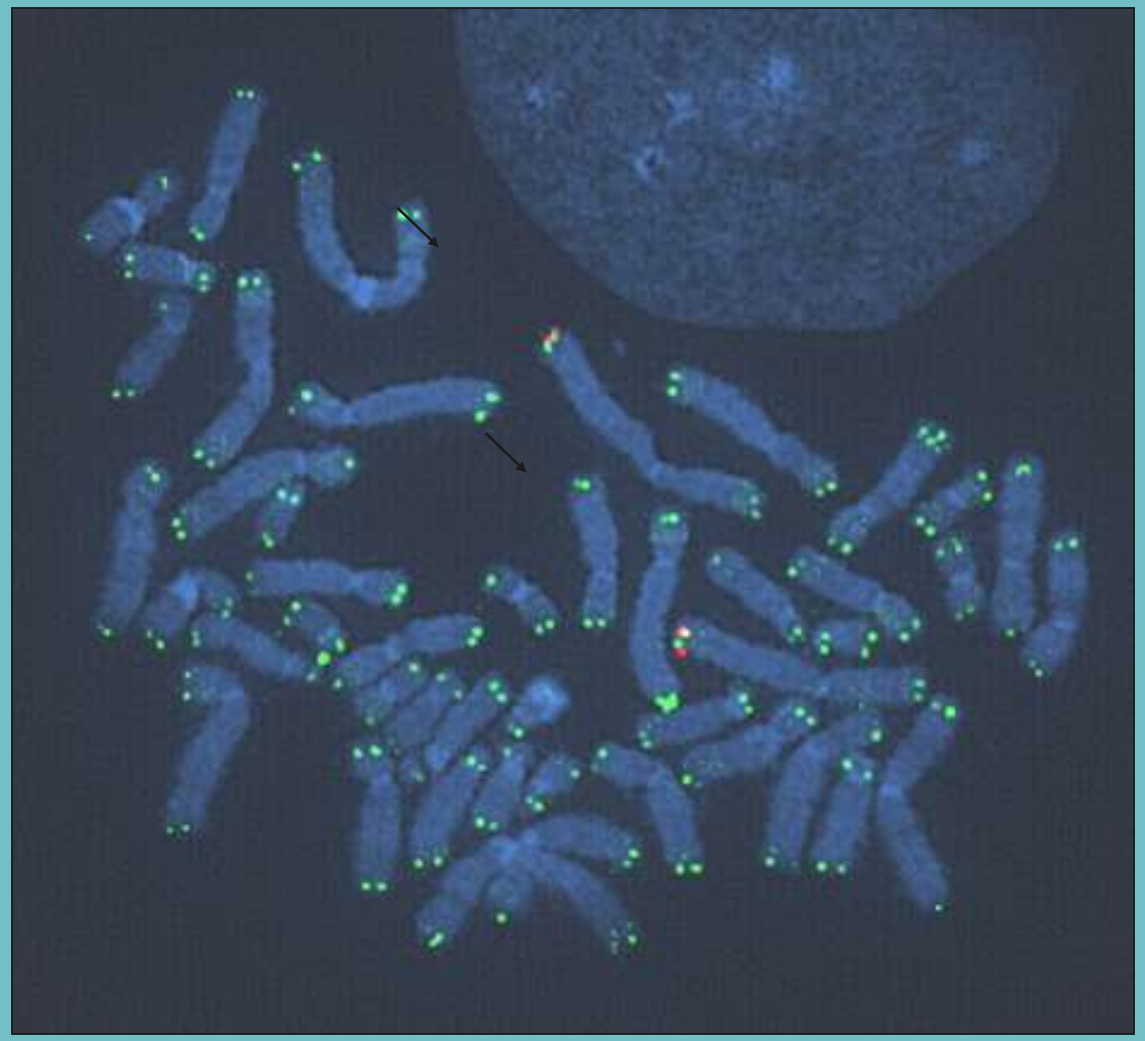
The genetic locus required for chromosome segregation; contains DNA and proteins on which the kinetochore is formed.

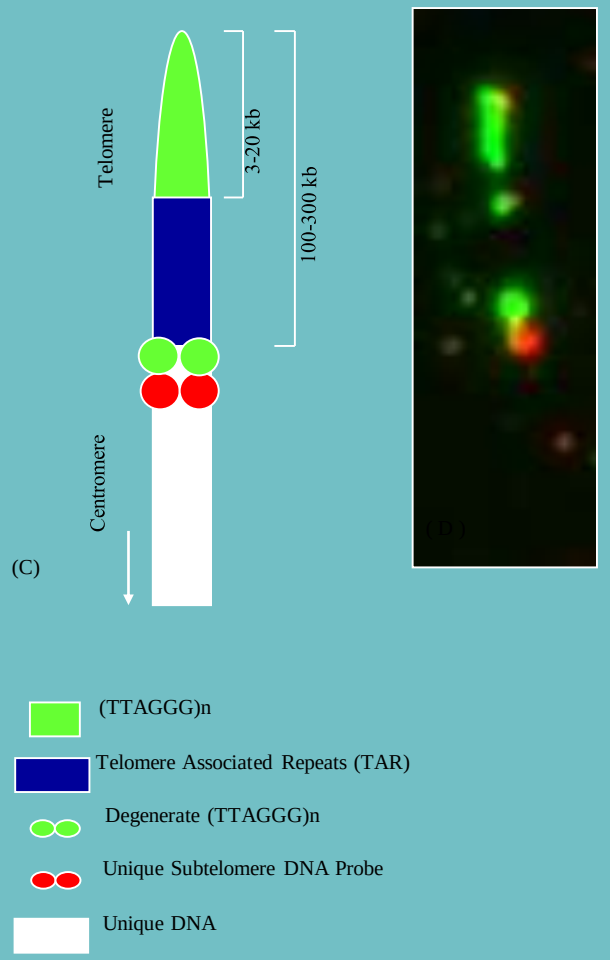
Telomere $(TTAGGG)_n$

A specialized structure at the ends of eukaryotyic chromosomes. Maintain chromosomal integrity by preventing end-to-end fusion of chromosomes.



Human Sub-telomeric Regions





There is some sequence homology between subtelomeres

Nondisjunction

Failure of:

(1) chromosome pair to disjoin during MI or

(2) chromatids to separate in MII or mitosis.

Abnormal Chromosome Number

- In **nondisjunction**, pairs of homologous chromosomes do not separate normally during meiosis
- As a result, one gamete receives two of the same type of chromosome, and another gamete receives no copy

Figure 15.13-1

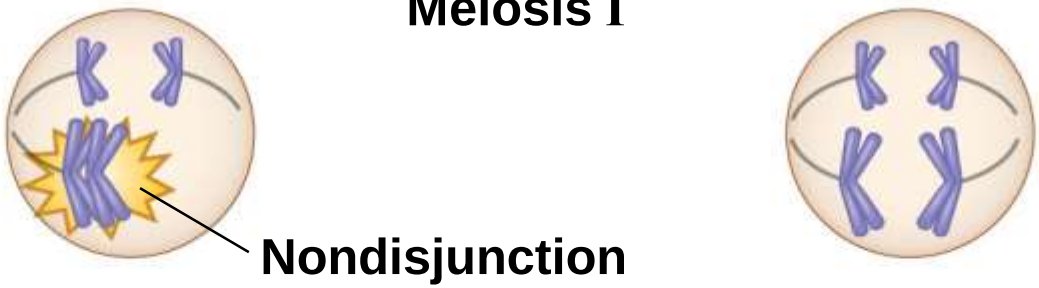


Figure 15.13-2

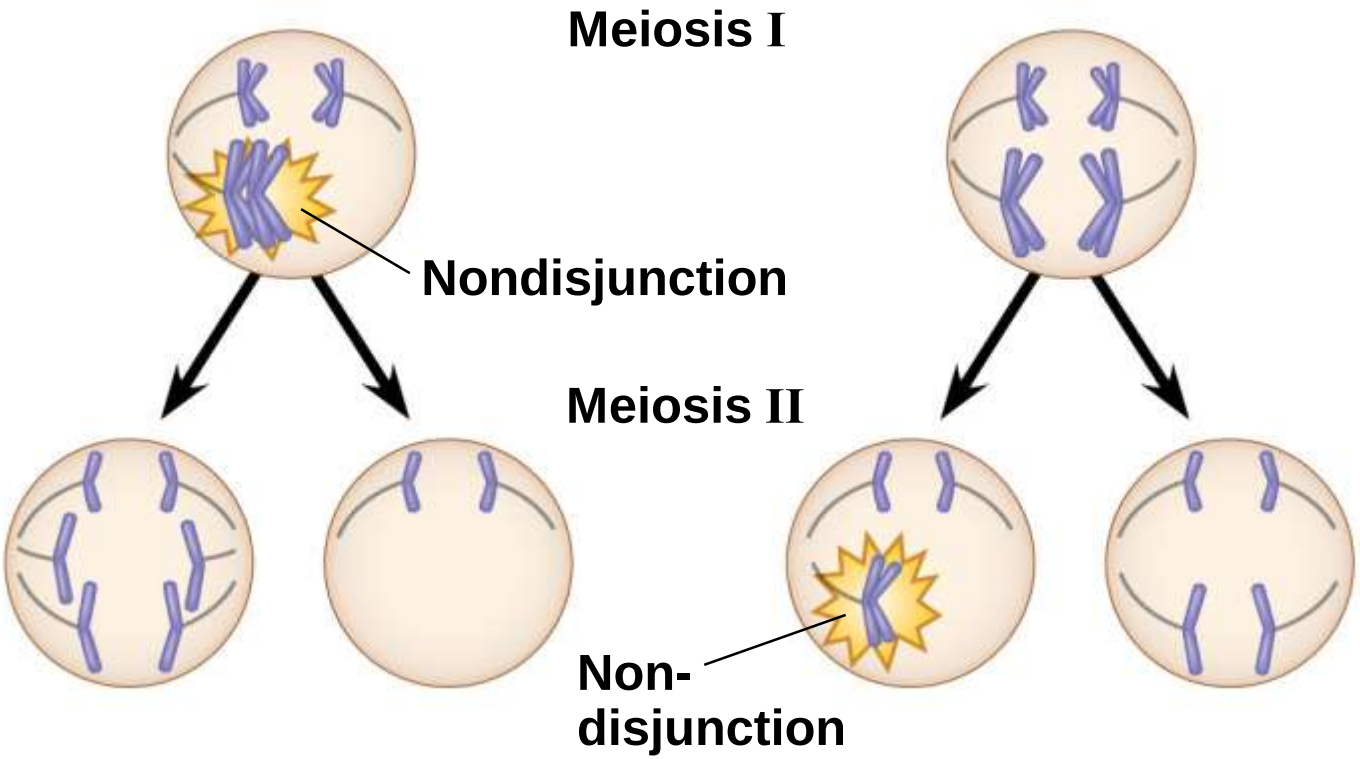
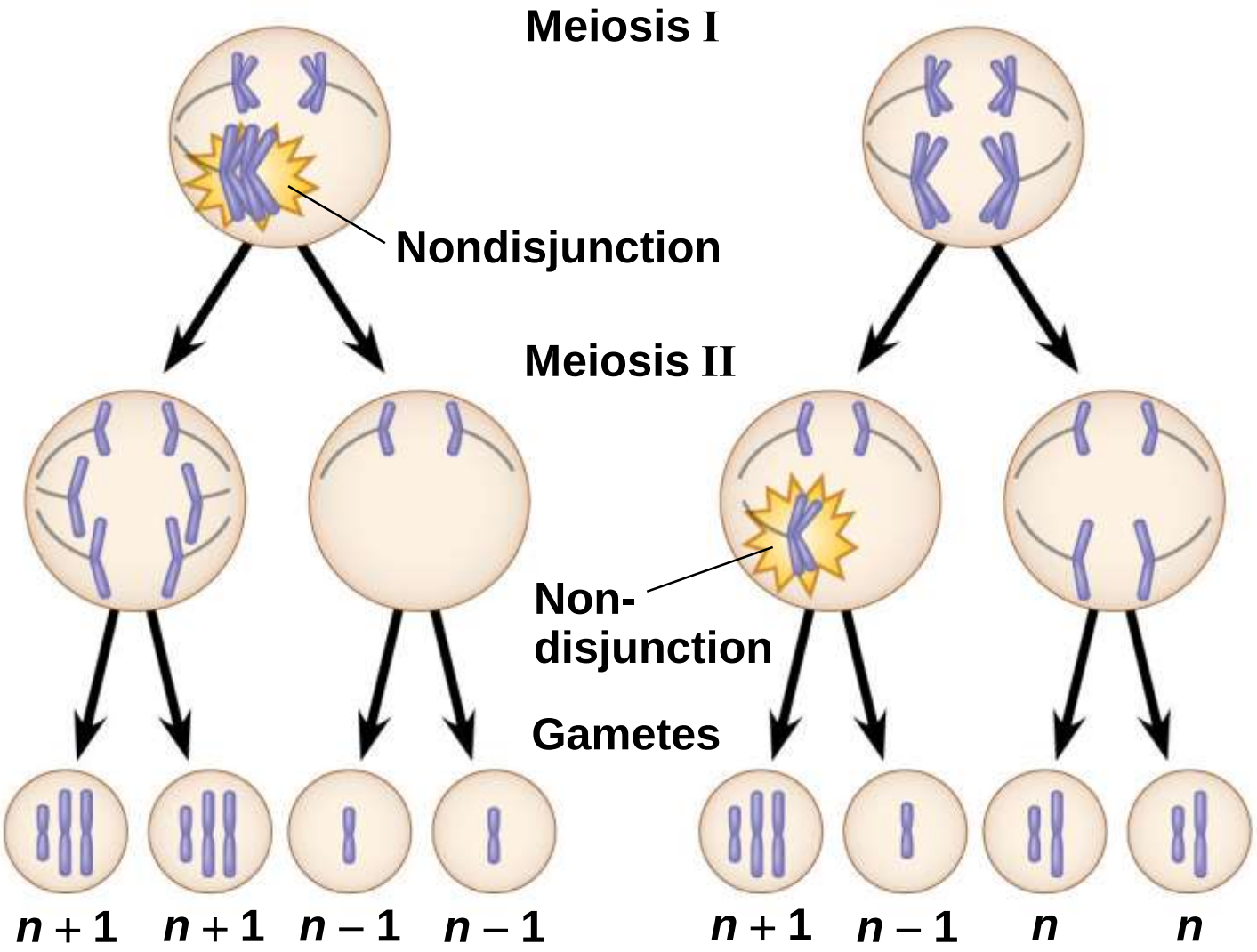
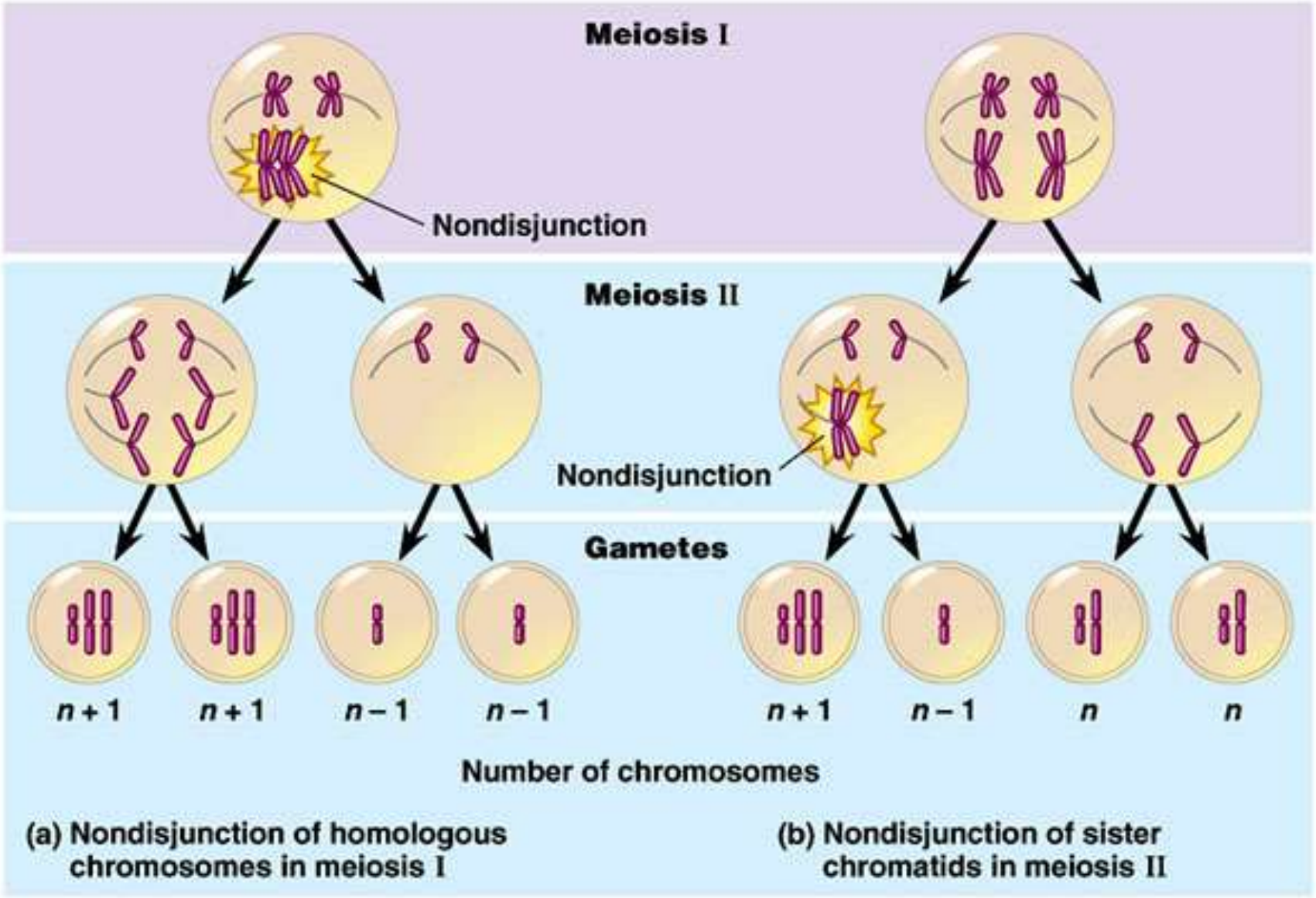


Figure 15.13-3



(a) Nondisjunction of homologous chromosomes in meiosis I

(b) Nondisjunction of sister chromatids in meiosis II



- **Aneuploidy** results from the fertilization of gametes in which nondisjunction occurred
- Offspring with this condition have an abnormal number of a particular chromosome

- A **monosomic** zygote has only one copy of a particular chromosome
- A **trisomic** zygote has three copies of a particular chromosome

Trisomy

Additional (3 rather than 2) chromosome.

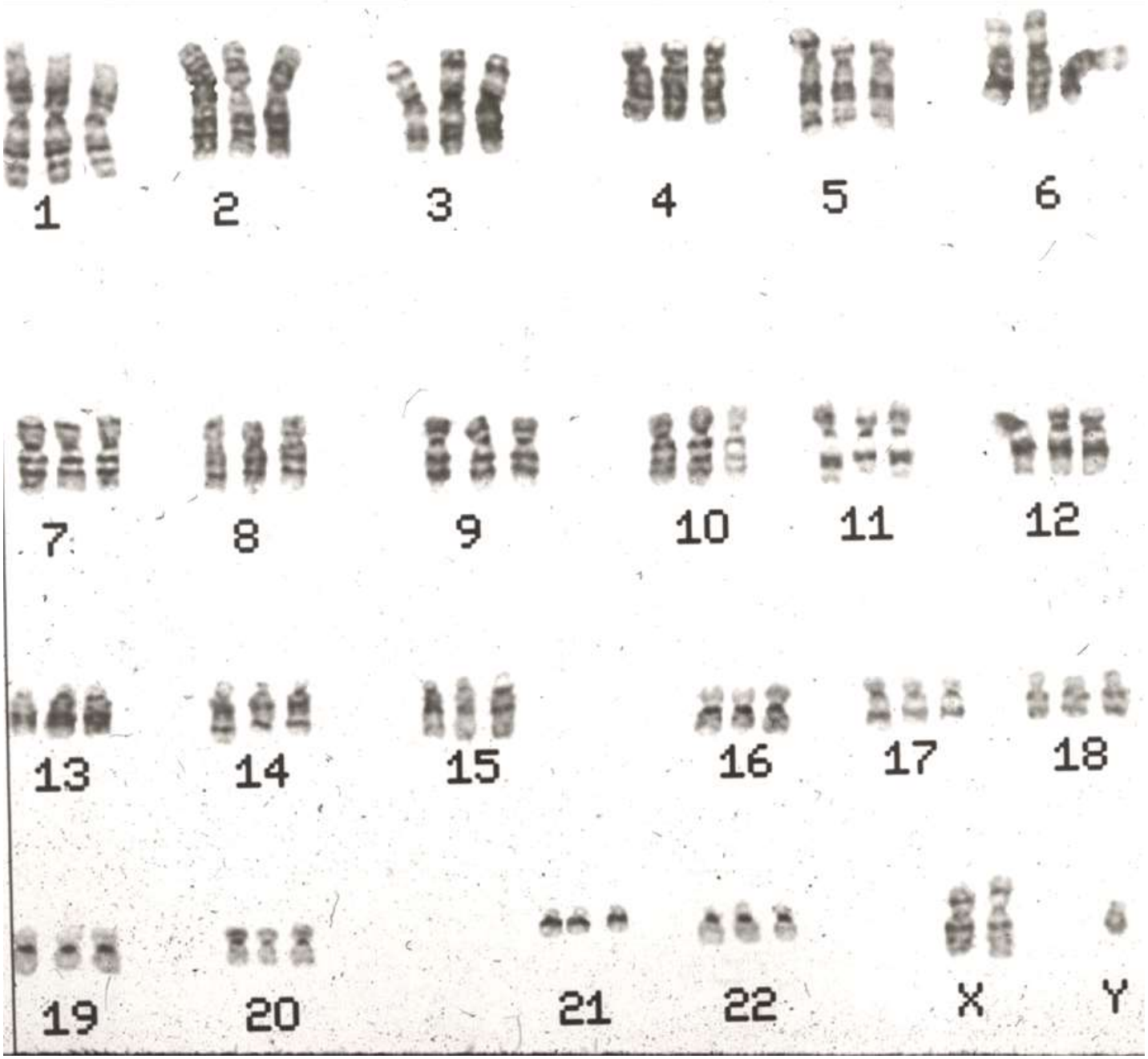
Monosomy

One chromosome of a pair missing.

- **Polyploidy** is a condition in which an organism has more than two complete sets of chromosomes
  - Triploidy (3*n*) is three sets of chromosomes
  - Tetraploidy (4*n*) is four sets of chromosomes
- Polyploidy is common in plants, but not animals
- Polyploids are more normal in appearance than aneuploids

Euploid - any chromosome number that is an exact multiple of the number of chromosomes in a normal haploid gamete (n). Most somatic cells are diploid (2N).

haploid (1 set), diploid (2 sets), triploid (3 sets), tetraploid (4 sets)



Triploidy
69,XXY

Alterations of Chromosome Structure

- Breakage of a chromosome can lead to four types of changes in chromosome structure
  - **Deletion** removes a chromosomal segment
  - **Duplication** repeats a segment
  - **Inversion** reverses orientation of a segment within a chromosome
  - **Translocation** moves a segment from one chromosome to another

Figure 15.14a

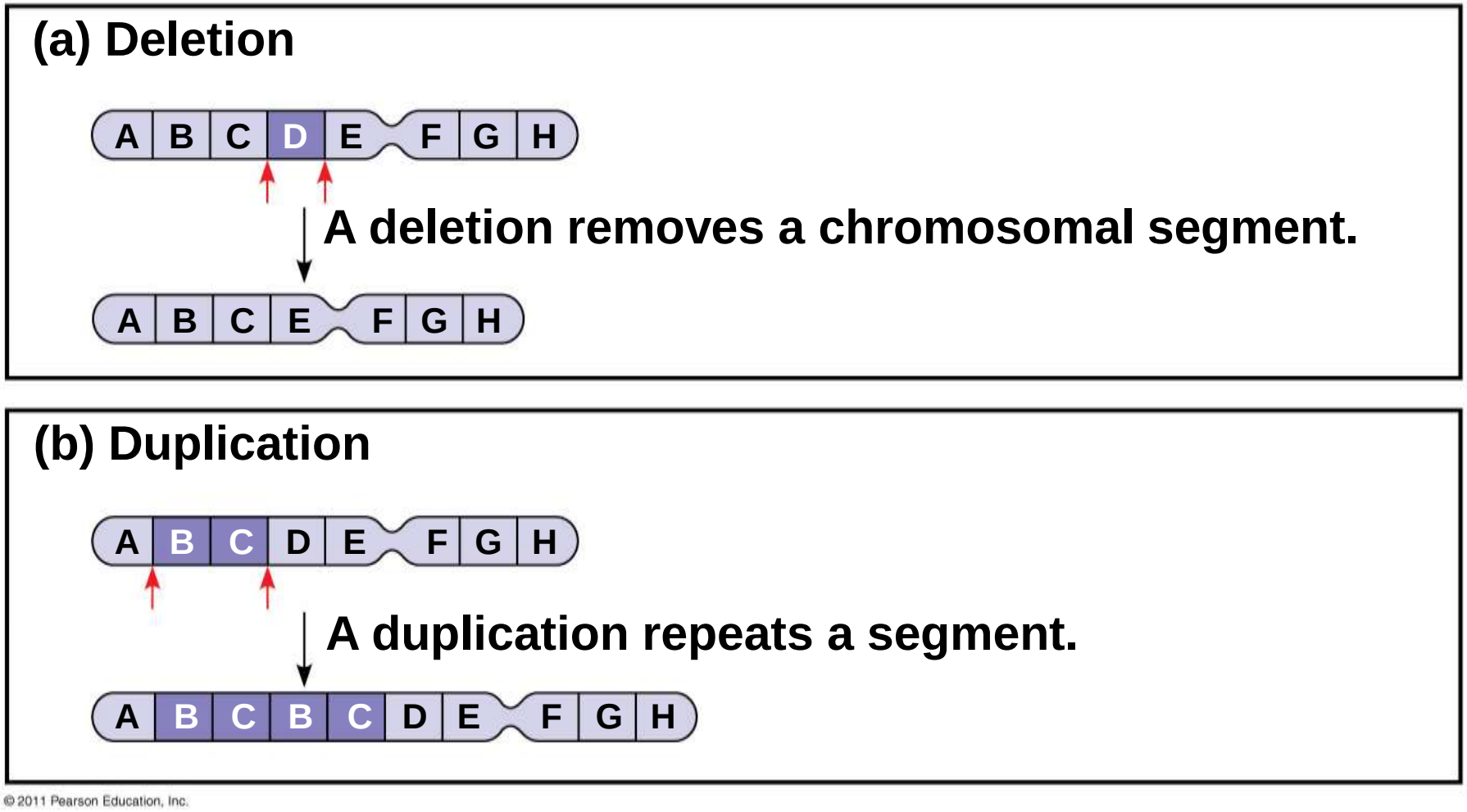
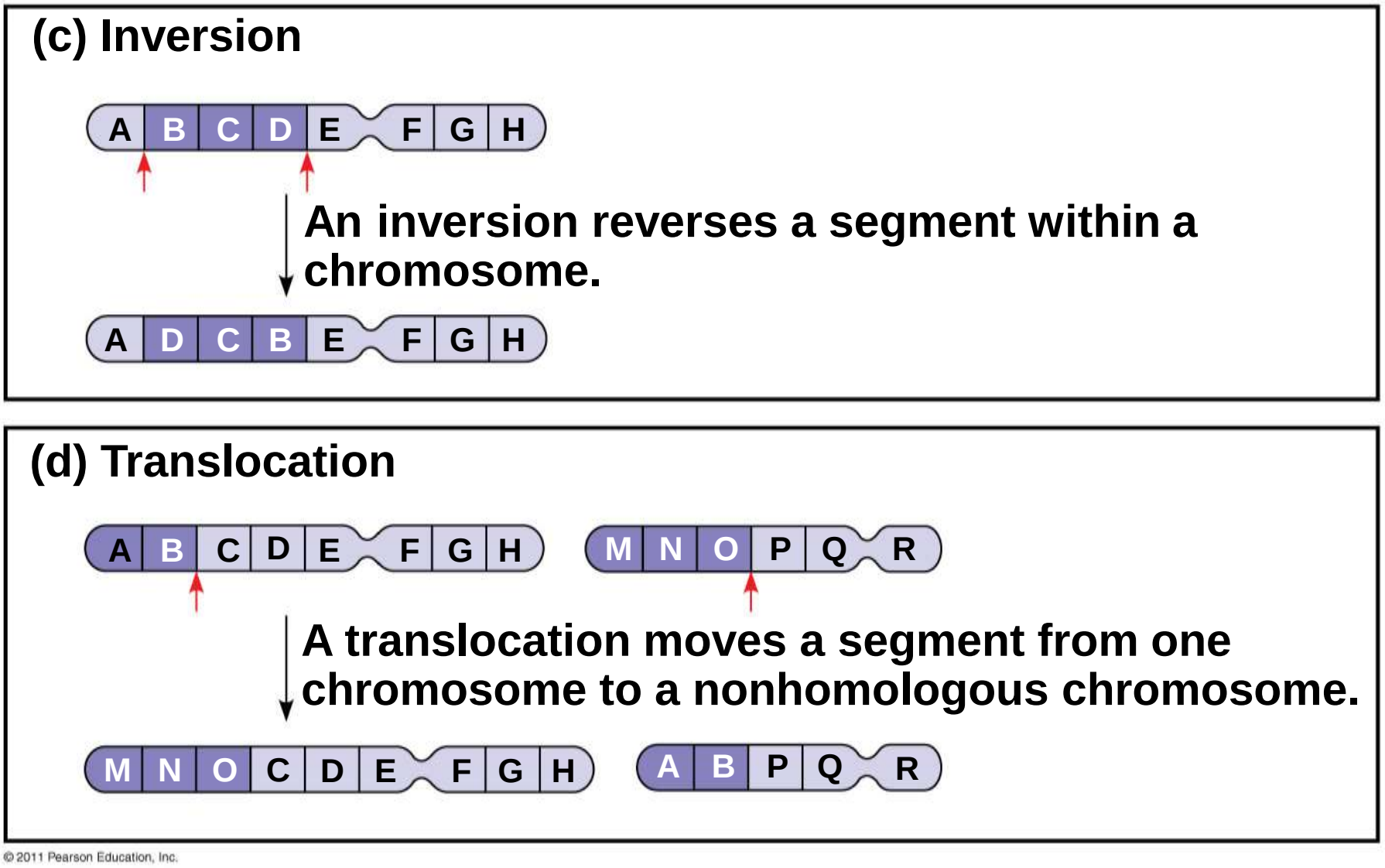


Figure 15.14b



Human Disorders Due to Chromosomal Alterations

- Alterations of chromosome number and structure are associated with some serious disorders
- Some types of aneuploidy appear to upset the genetic balance less than others, resulting in individuals surviving to birth and beyond
- These surviving individuals have a set of symptoms, or syndrome, characteristic of the type of aneuploidy

Incidence of Chromosomal Abnormalities in Newborns

Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 newborns)	
(Sex chromosomes and autosomes)	
Balanced rearrangements	
Robertsonian	1/1000
Other (reciprocal and others)	1/885
Unbalanced rearrangements	1/17,000
All Chromosome Abnormalities	
Autosomal disorders and unbalanced rearrangements	1/230
Balanced rearrangements	1/500
Total	1/154

Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

Down Syndrome (Trisomy 21)

- **Down syndrome** is an aneuploid condition that results from three copies of chromosome 21
- It affects about one out of every 700 children born in the United States
- The frequency of Down syndrome increases with the age of the mother, a correlation that has not been explained

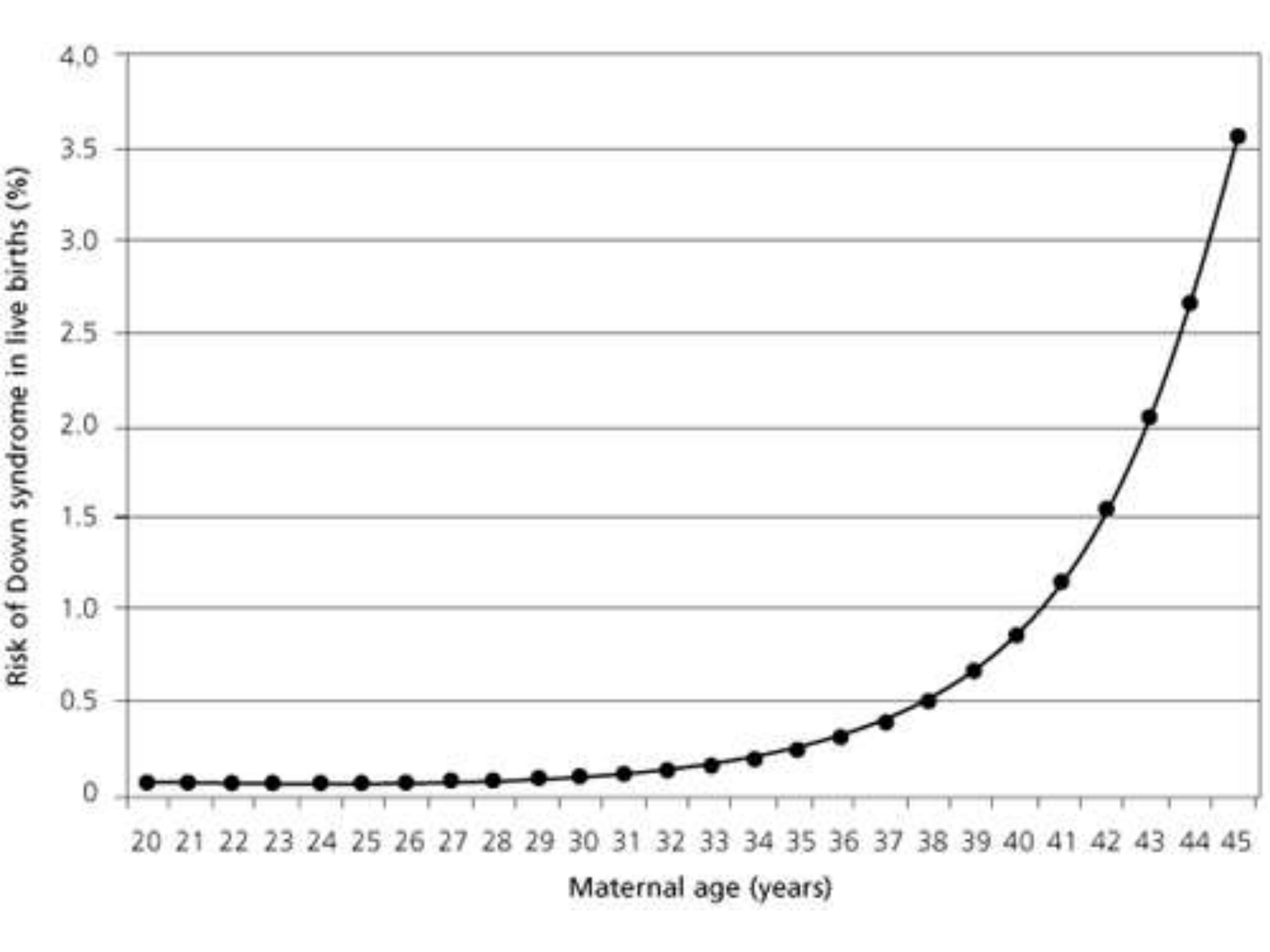
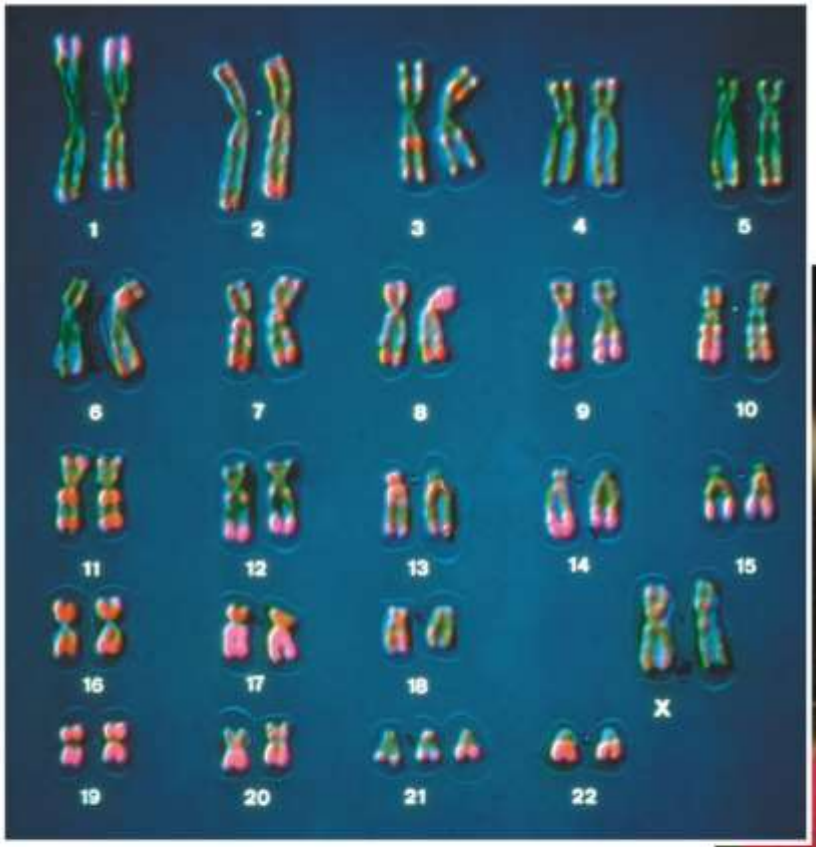
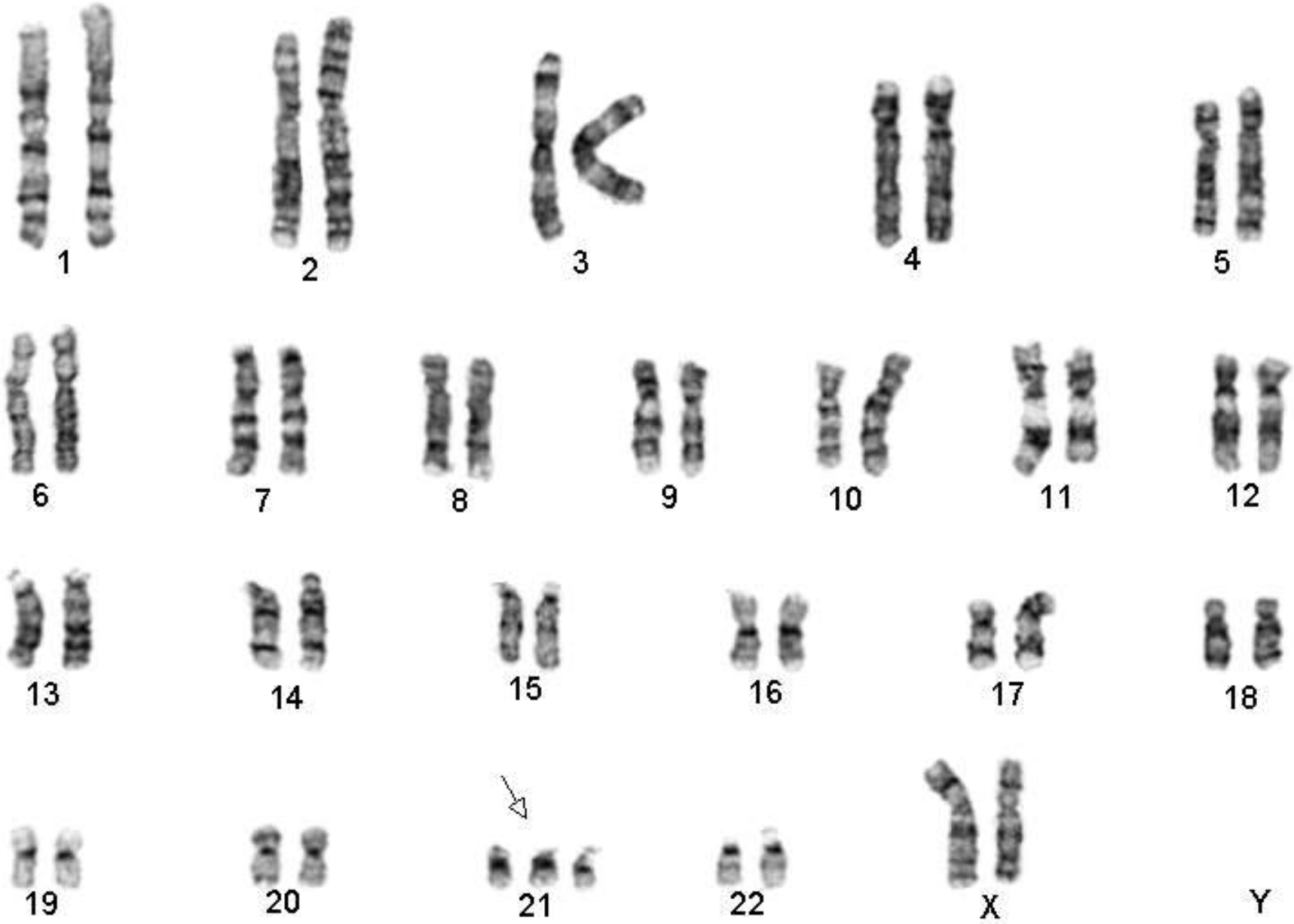
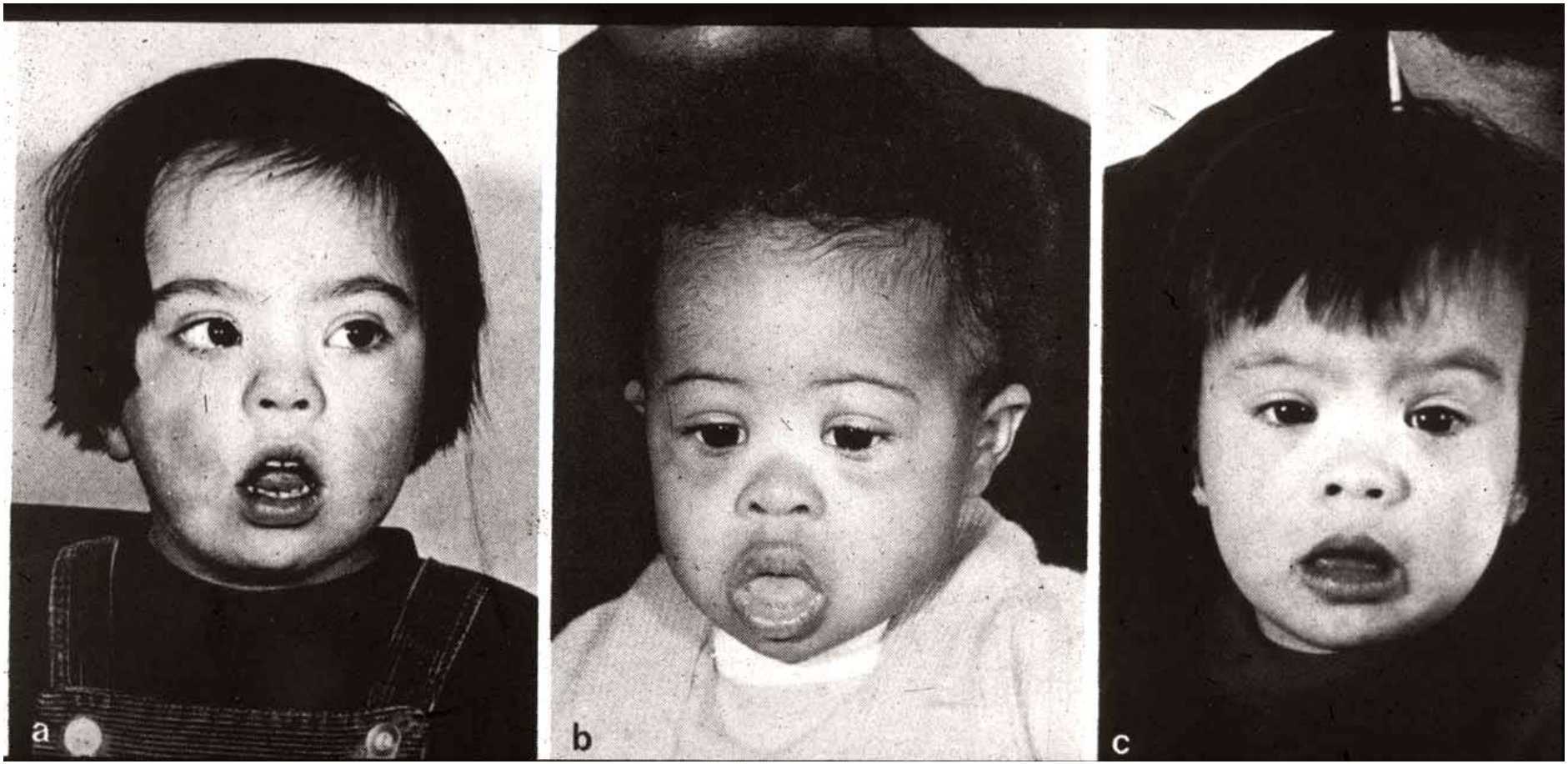

4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Risk of Down syndrome in live births (%)
20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45
Maternal age (years)

Figure 15.15



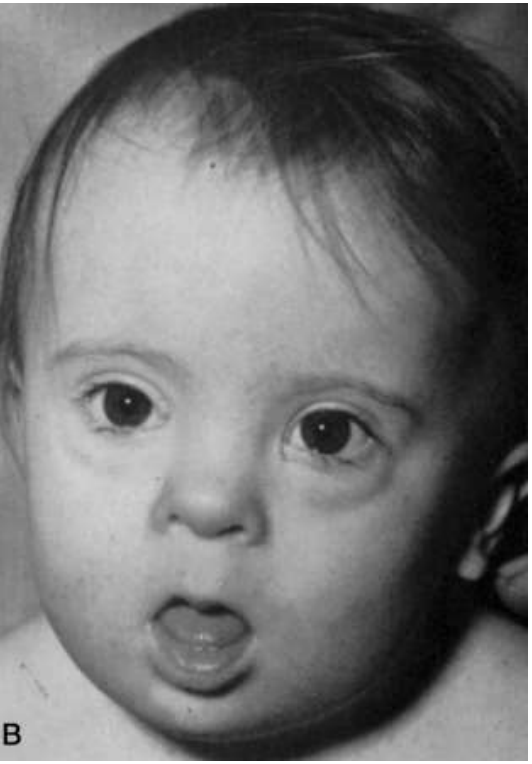
Most common numerical abnormality in liveborns is Trisomy 21 (Down syndrome)

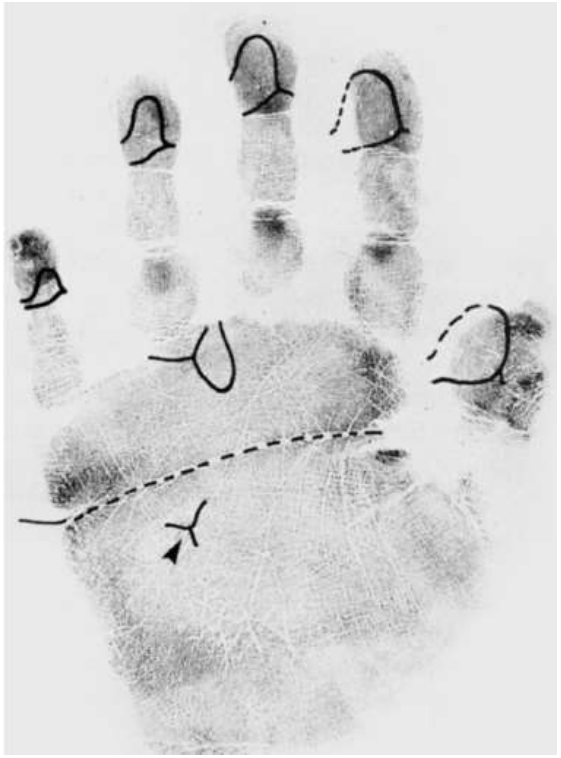




Male:Female Ratio - 3:2

Down Syndrome



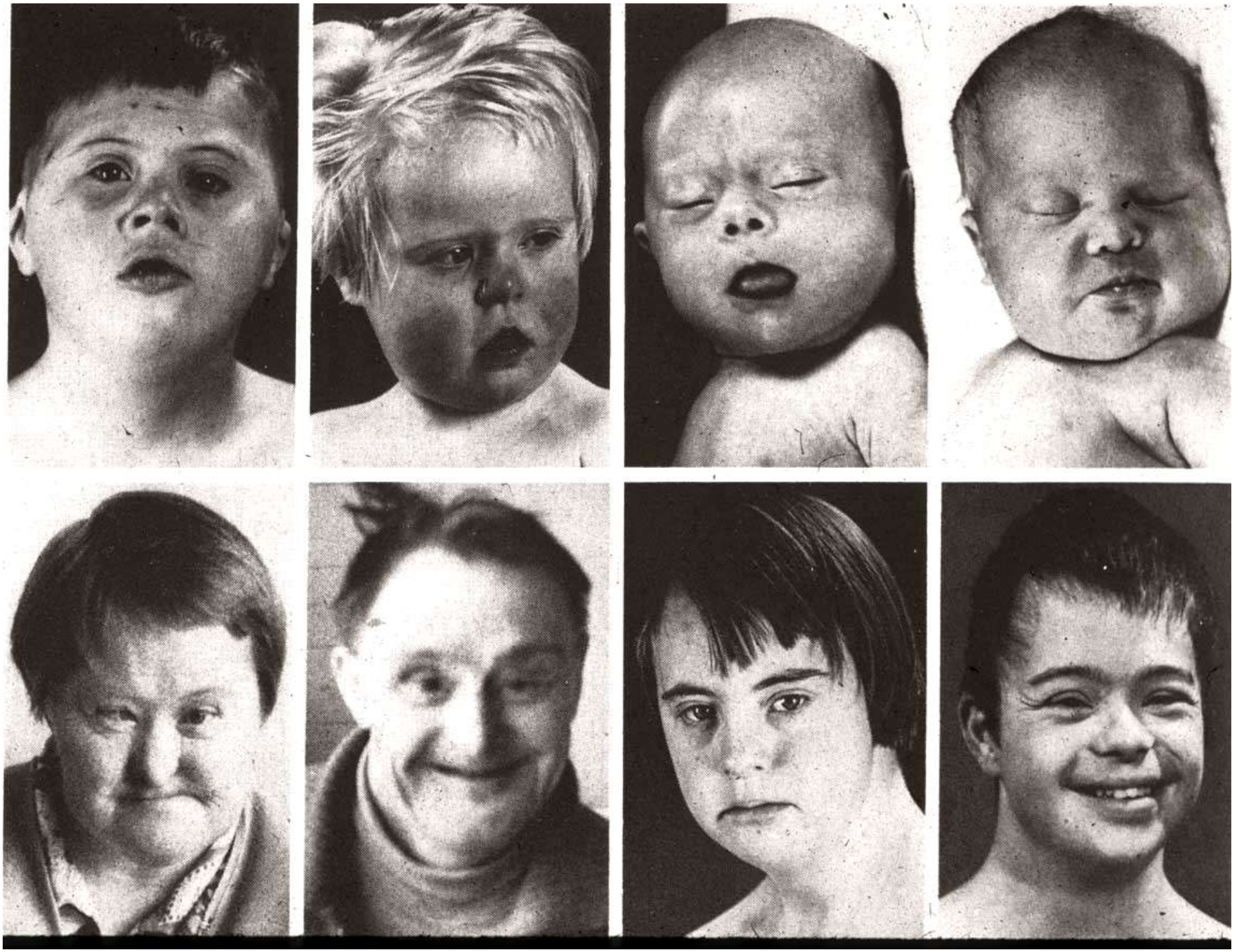


Mental retardation (IQ 25-50)
*Low nasal bridge (90%)
*Hypotonia (80%)
*Up slanting palpebral fissures (80%)
Small, low-set ears (60%)
*Congenital heart disease (30%-50%)**

*Epicanthic folds
Protruding tongue
Intestinal problems
Gap between first and second toes
15-fold increase in risk for leukemia
*Simian line (transverse crease) (45%)

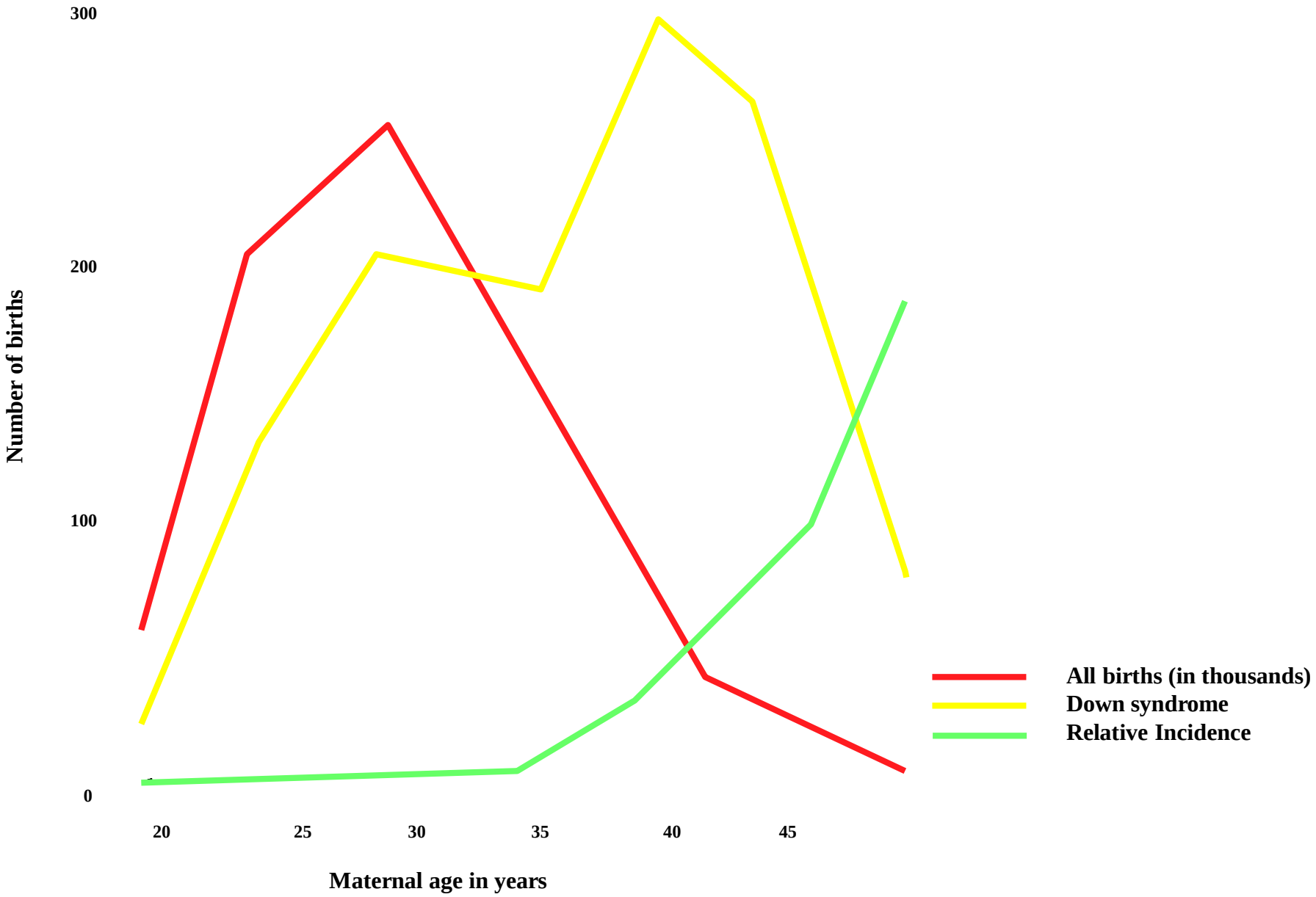
These features are easily recognized at birth.

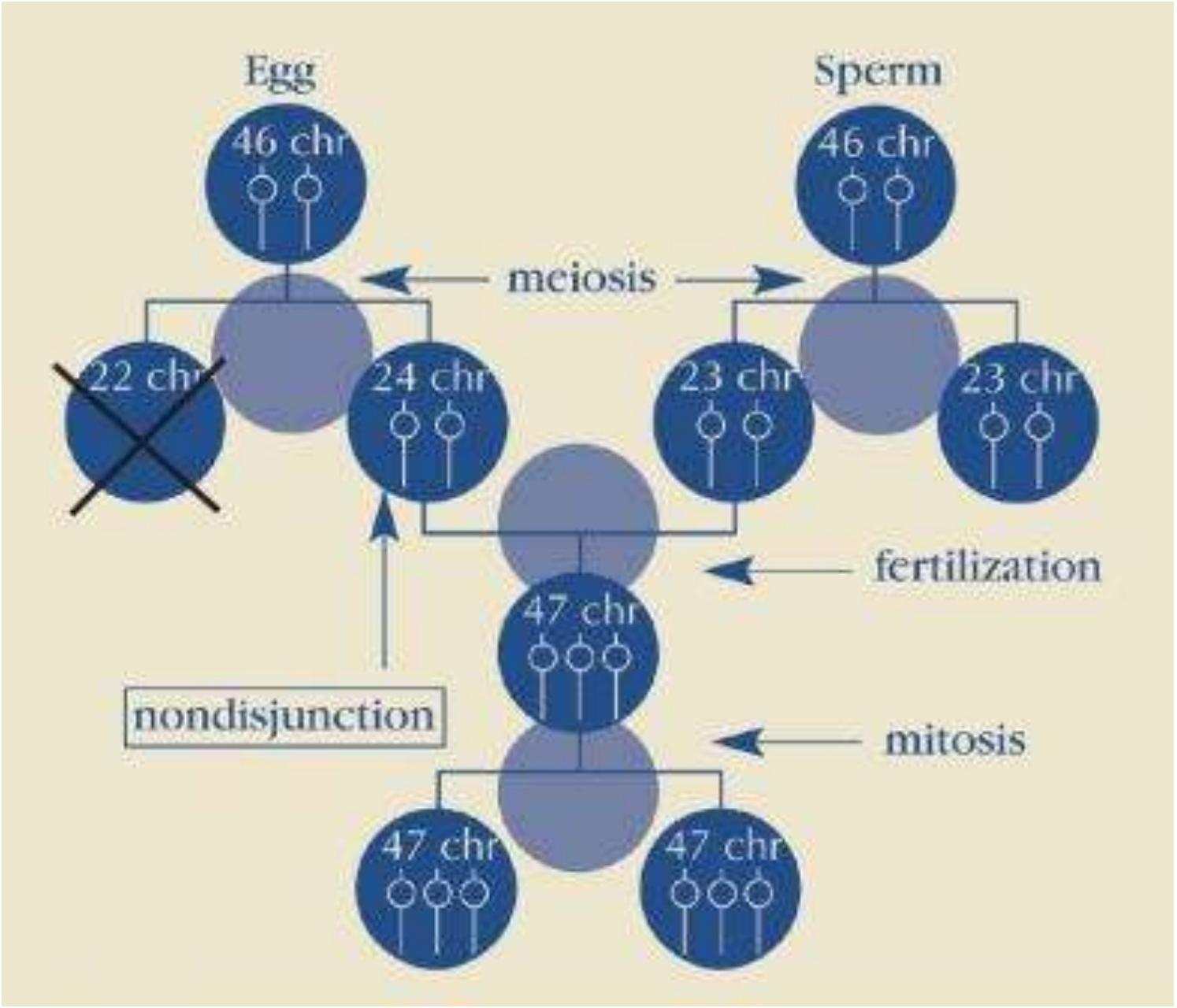
**The congenital heart problems noted in people having Down syndrome include ventricular septal defect (VSD) and arterioventricular defects (AV) canal. Approximately 40% with congenital heart disease die during the first year.

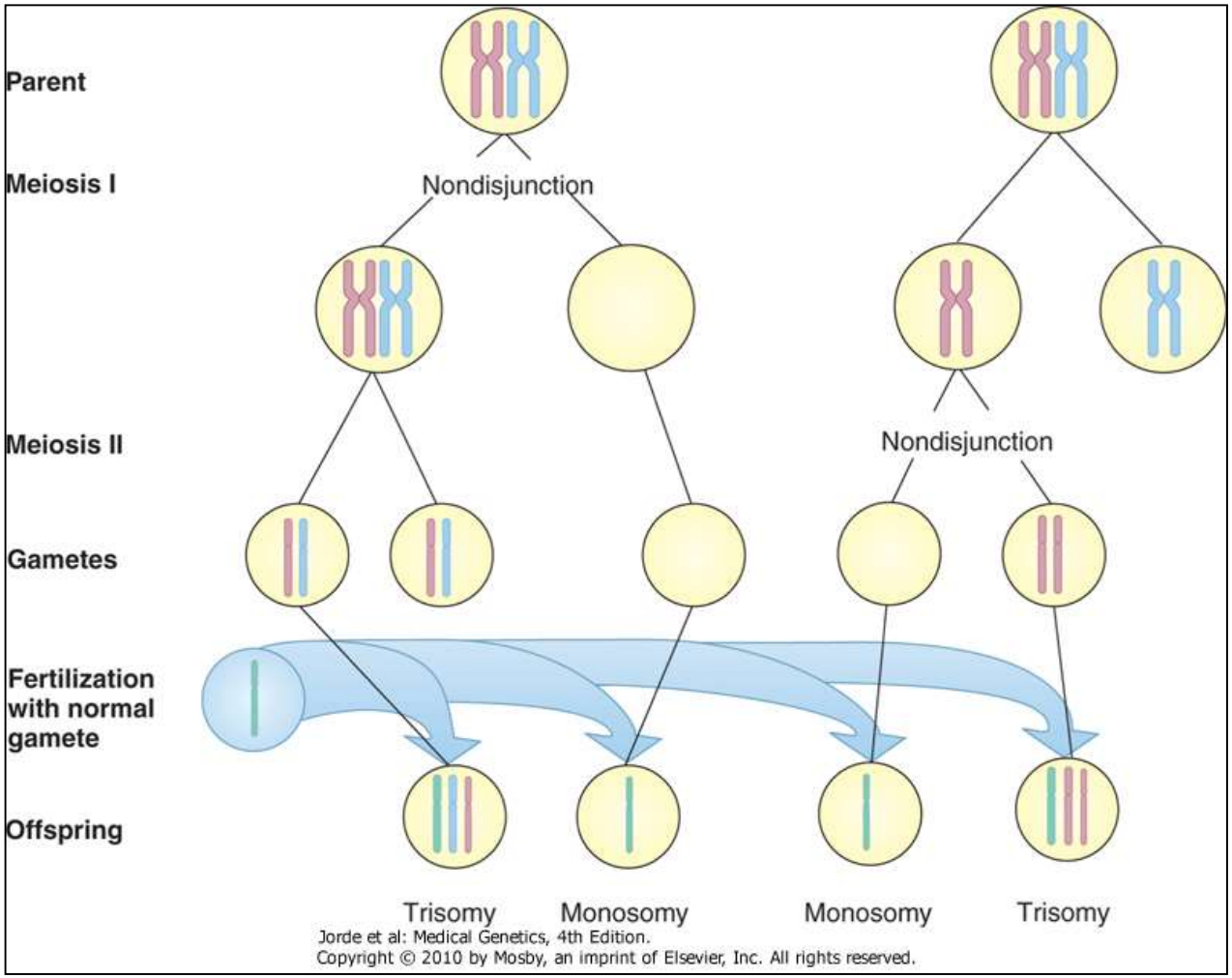


1 in 770 babies

Maternal Age and Nondisjunction




Egg
Sperm
46 chr
46 chr
meiosis
22 chr
24 chr
23 chr
23 chr
fertilization
47 chr
nondisjunction
mitosis
47 chr
47 chr

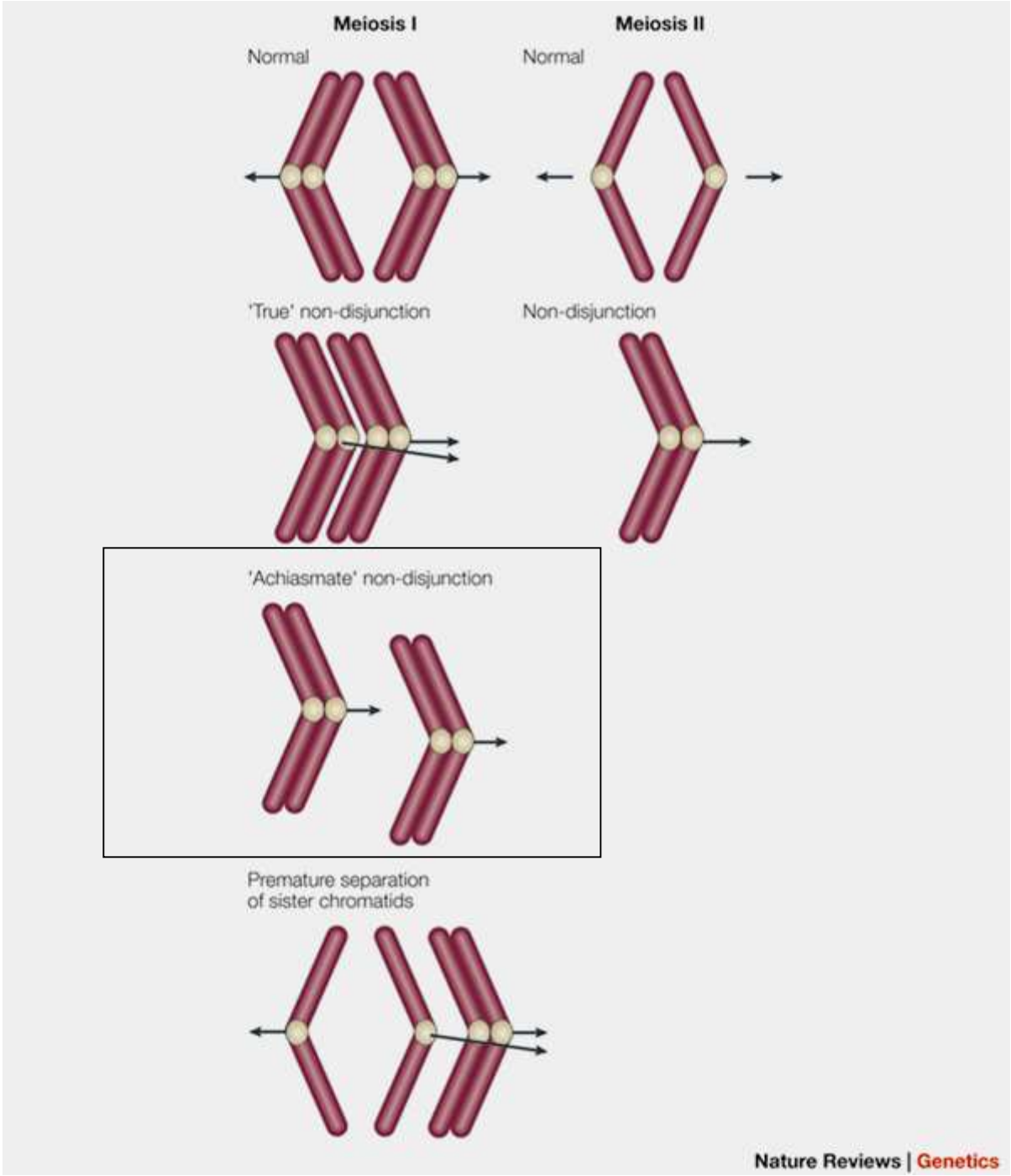


Trisomy 21

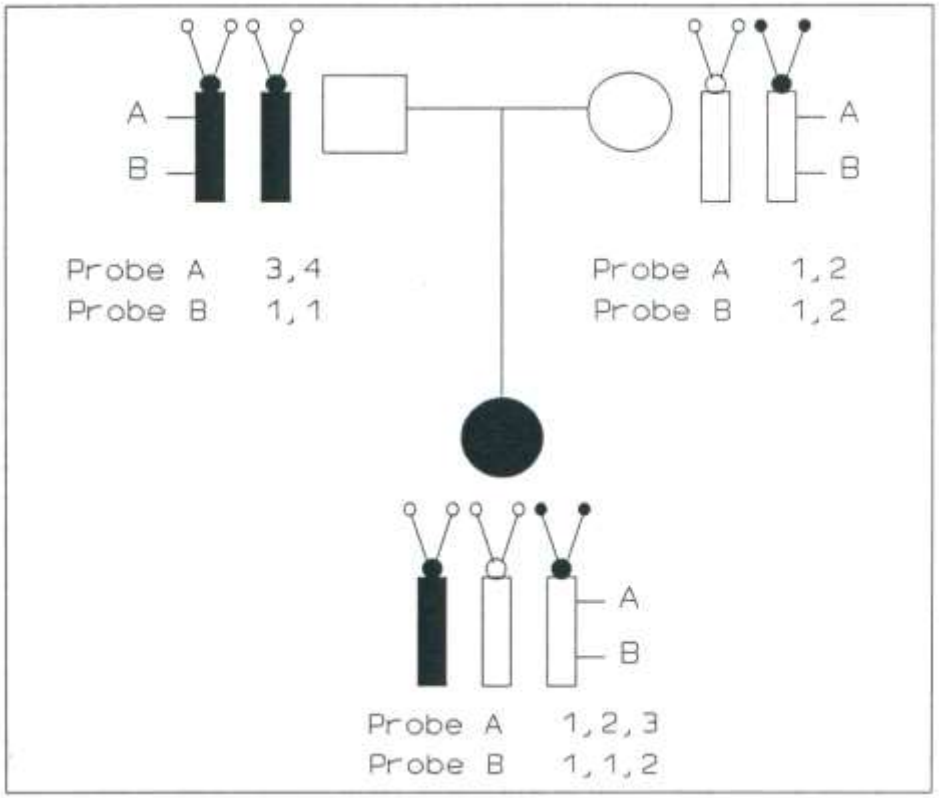
Maternal Errors: 94% of cases
- **MI 64%**
- **MII 19%**
- **Indeterminate 11%**

Paternal Errors: 4.5% of cases
- **MI 1%**
- **MII 3.5%**

Unknown: 1.5%


Meiosis I
Meiosis II
Normal
Normal
'True' non-disjunction
Non-disjunction
'Achiasmate' non-disjunction
Premature separation
of sister chromatids

Causal Factors in Nondisjunction

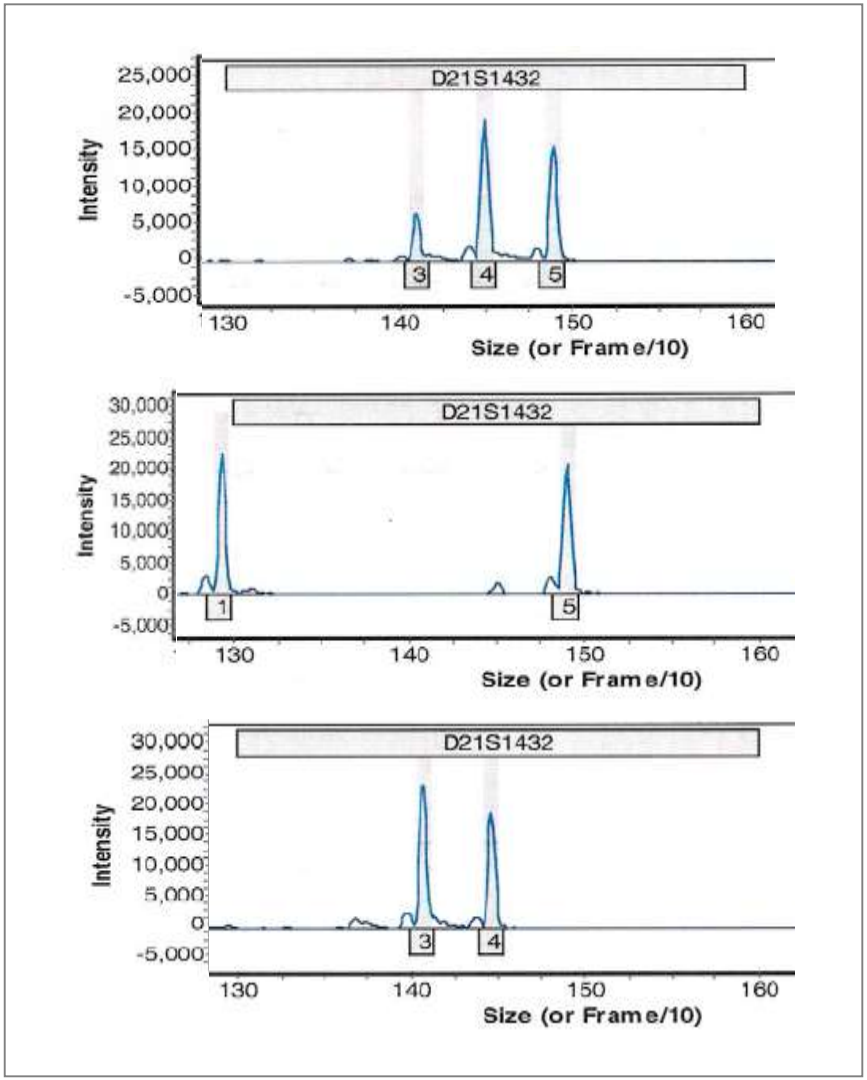


Evaluate the Origin of the Extra Chromosome Using Polymorphic Markers

Proband

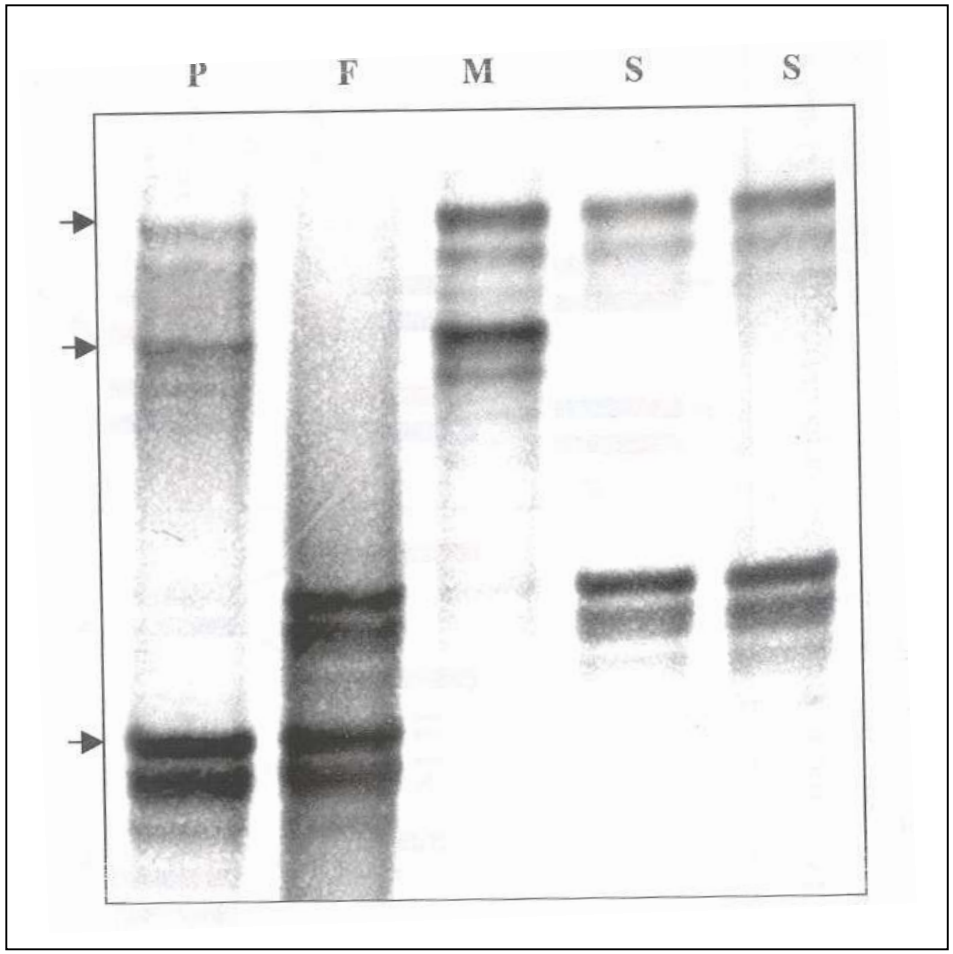
Father

Mother



D21S1432 Tetranucleotide STRP

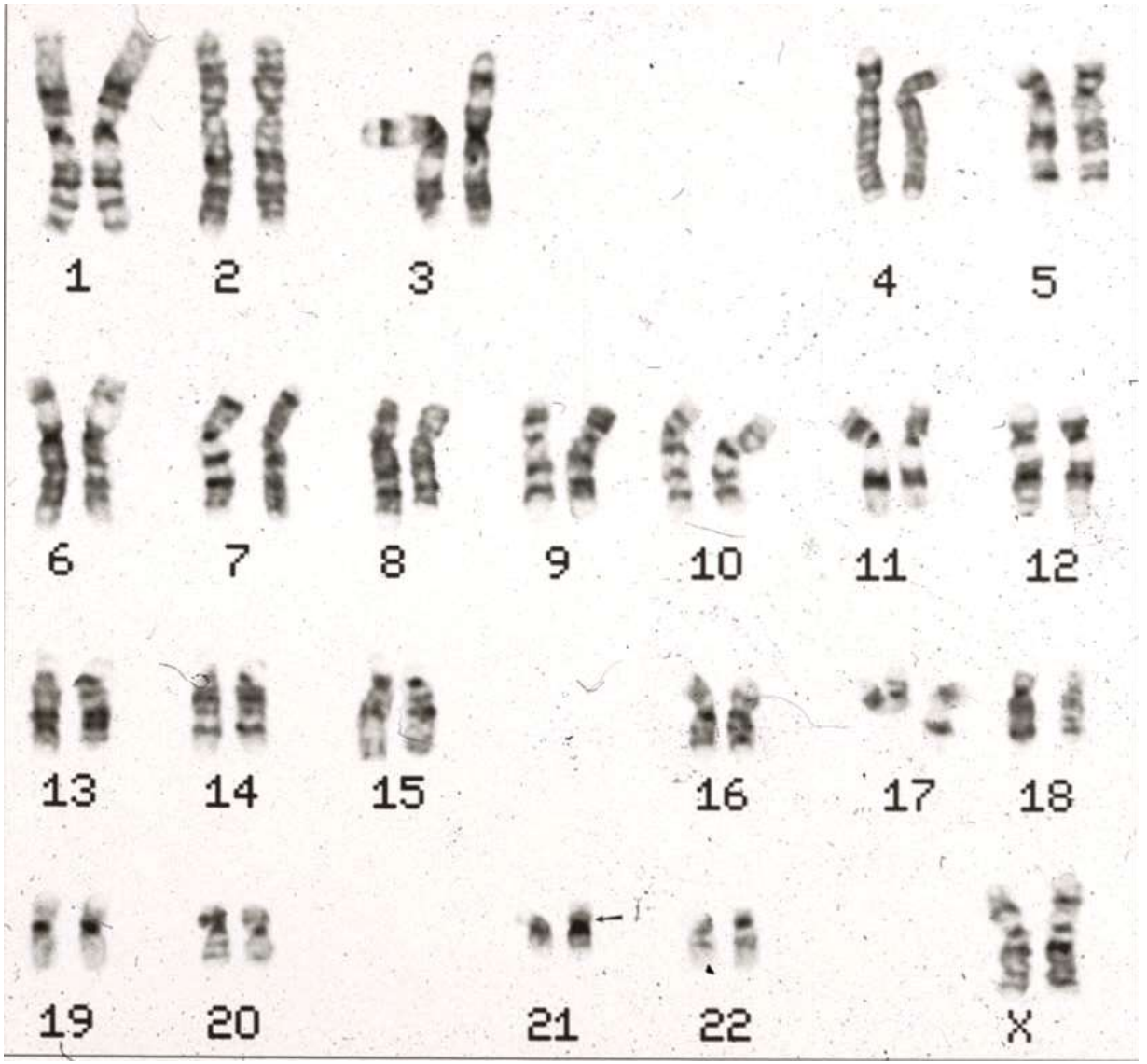
DNA markers can be used to determine the parental origin of the extra chromosome in trisomic individuals

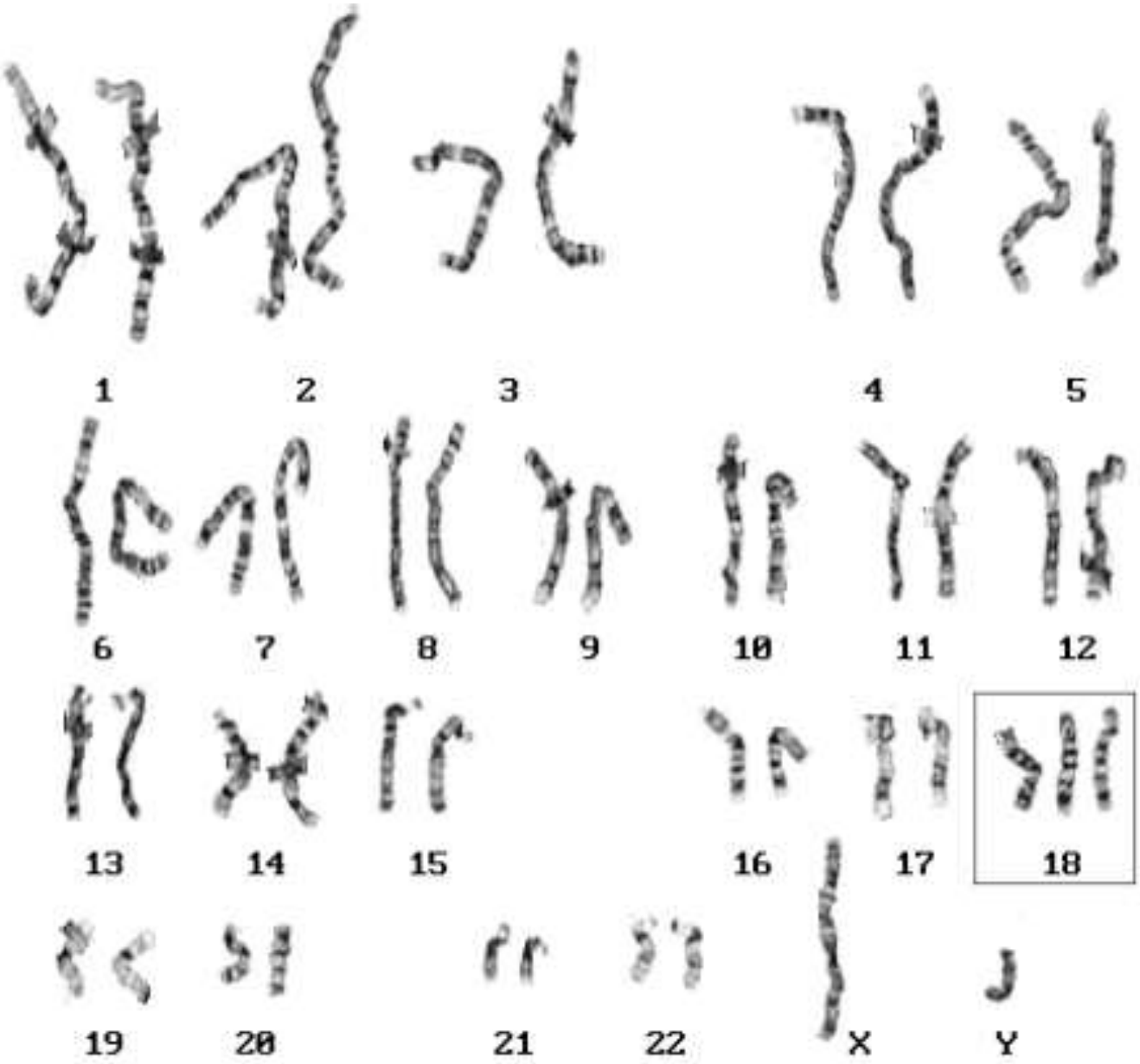


Trisomy	*n*	Maternal		Paternal		PZM (%)
		MI (%)	MII (%)	MI (%)	MII (%)	
Acrocentrics						
13	74	56.6	33.9	2.7	5.4	1.4
14	26	36.5	36.5	0.0	19.2	7.7
15	34	76.3	9.0	0.0	14.7	0.0
21	782	69.6	23.6	1.7	2.3	2.7
22	130	86.4	10.0	1.8	0.0	1.8
Non-acrocentrics						
2	18	53.4	13.3	27.8	0.0	5.6
7	14	17.2	25.7	0.0	0.0	57.1
8	12	50.0	50.0	0.0	0.0	50.0
16	104	100	0.0	0.0	0.0	0.0
18	150	33.3	58.7	0.0	0.0	8.0

[a]Adapted from Hall *et al.* (6). MI, meiosis I; MII, meiosis II; PZM, post-zygotic mitotic.

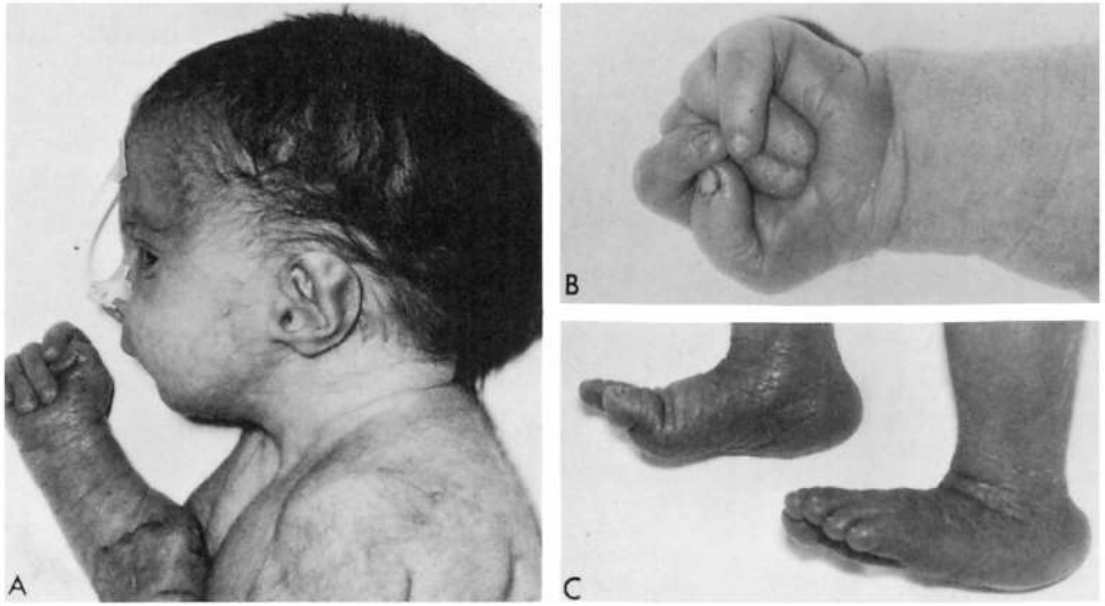
Partial Trisomy 21 (21q)





Karyotype: 47,XY,+18

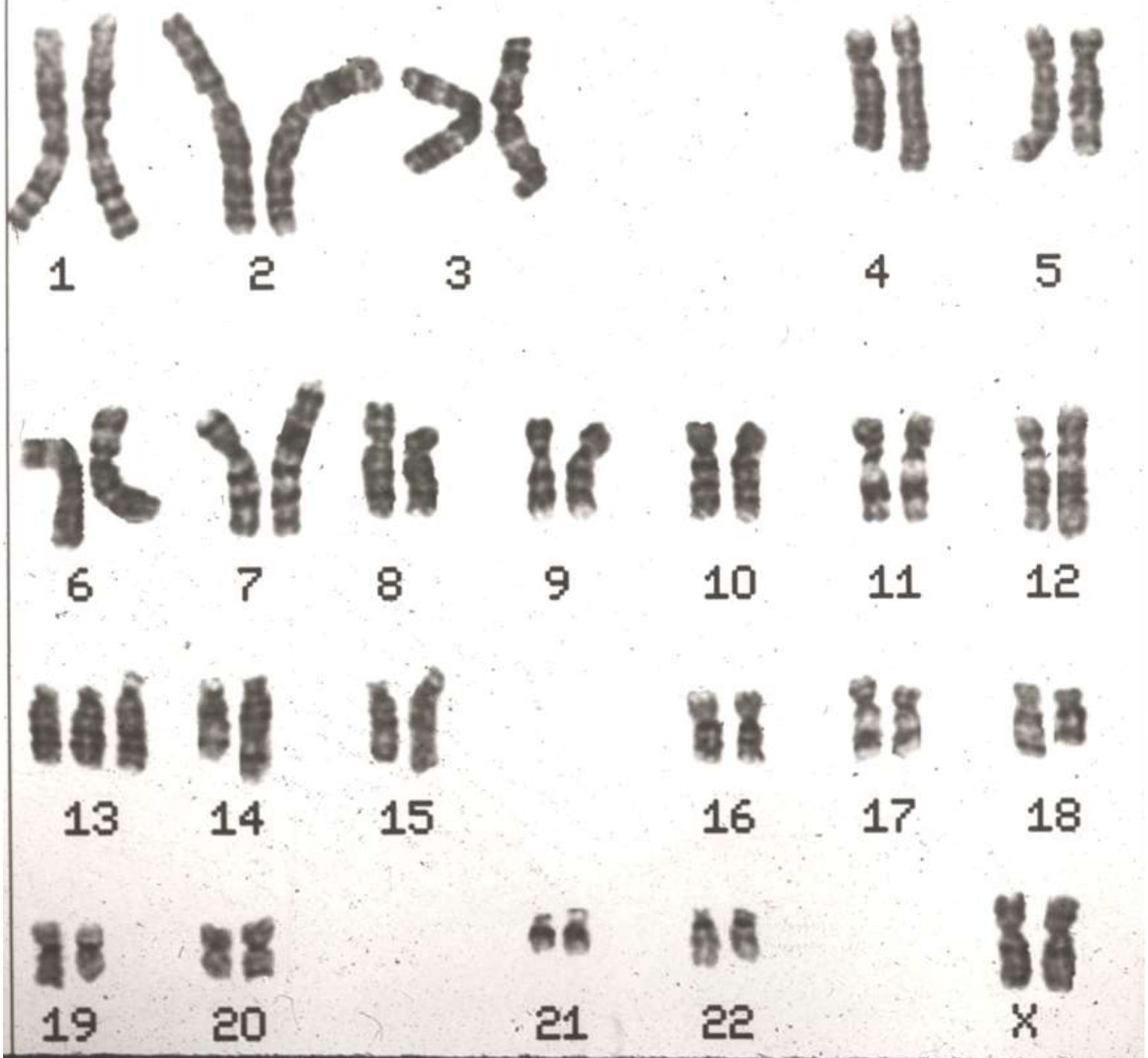
Trisomy 18 (Edward syndrome)



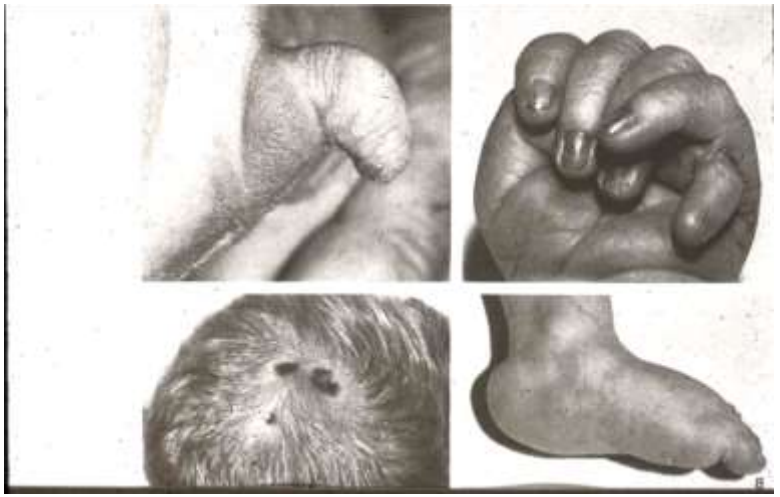
Findings:

CHD (95%)
Failure to thrive (FTT)
Mental retardation
Growth retardation
Hypertonia
Prominent Occiput

Low-set, malformed ears
Short sternum
Intestinal Abnormalities
Unusual hand position
Rocker bottom feet

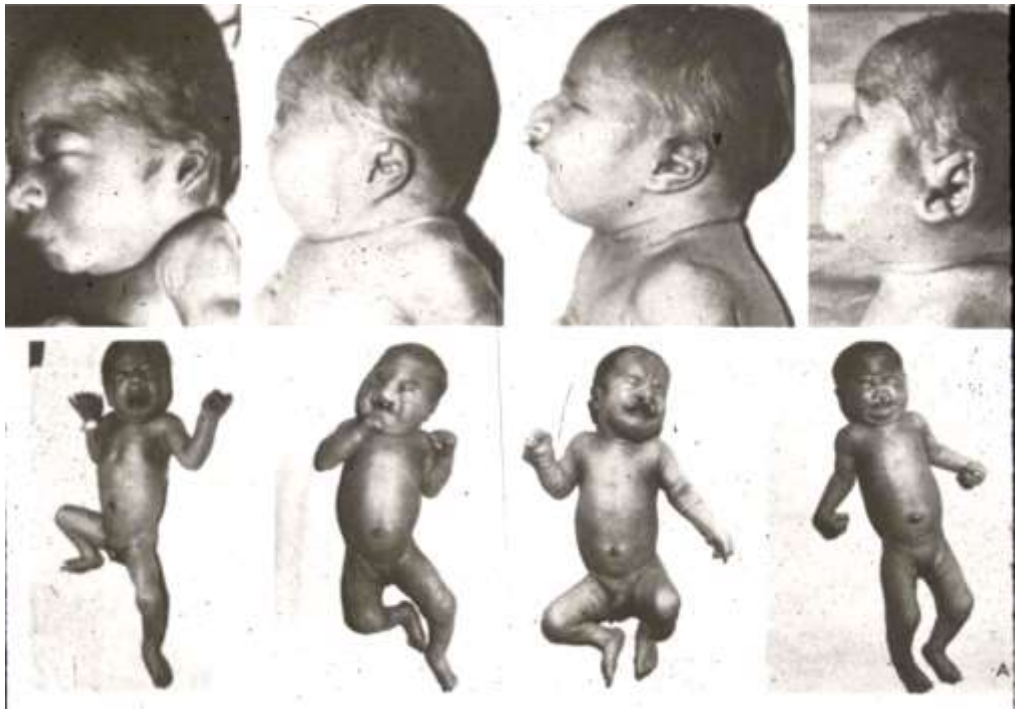

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X

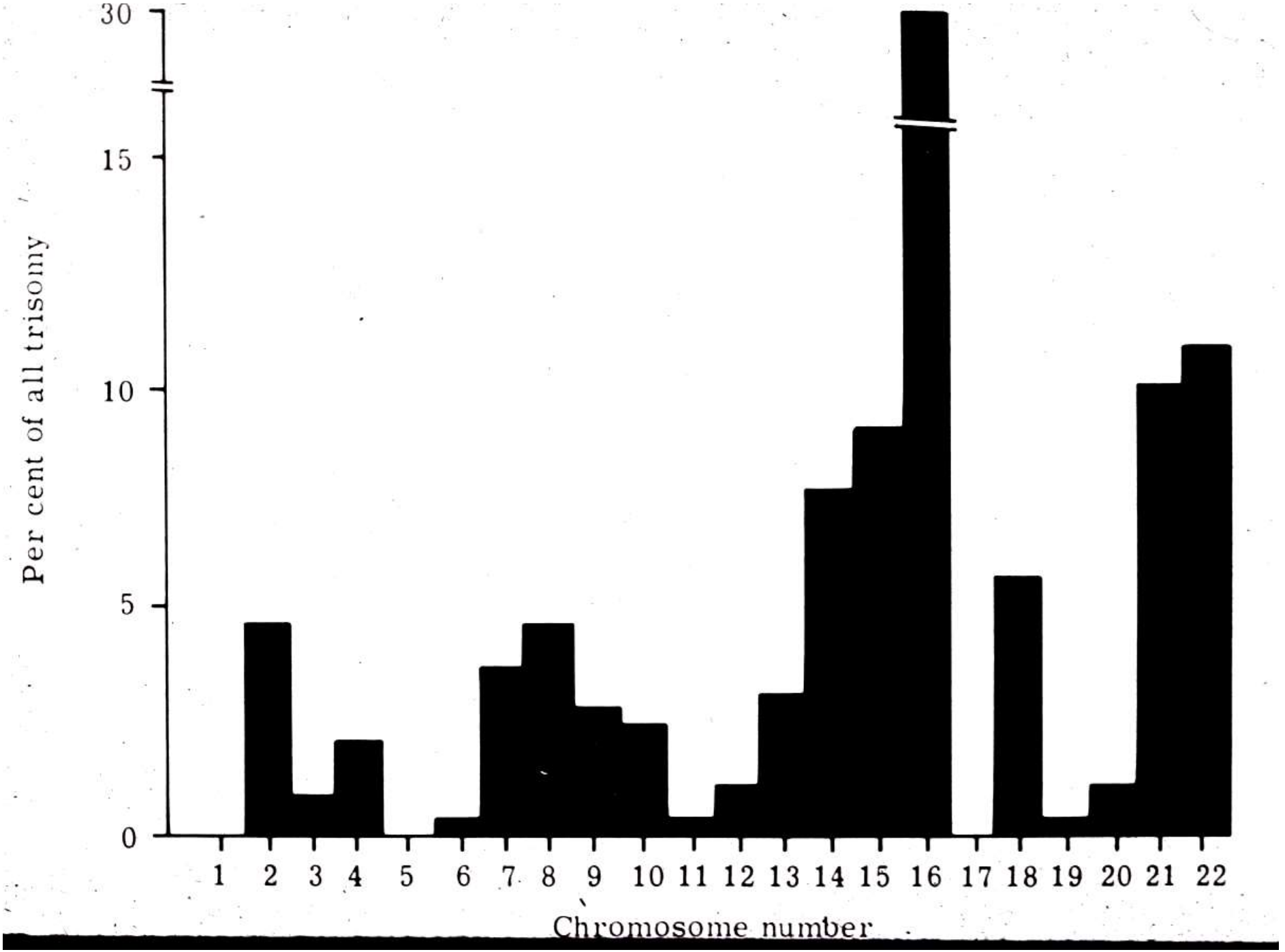
Trisomy 13
(Patau syndrome)



Findings:

CHD (85%)
Mental retardation
Hyper- or hypotonia
Scalp defects
Microcephaly
Small eyes
Low-set, malformed ears
Cleft lip/palate
Polydactyly and syndactyly
Polycystic kidneys
Rocker-bottom feet




30
15
10
5
0
Per cent of all trisomy
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosome number

Aneuploidy of Sex Chromosomes

- Nondisjunction of sex chromosomes produces a variety of aneuploid conditions
- **Klinefelter syndrome** is the result of an extra chromosome in a male, producing XXY individuals
- Monosomy X, called ***Turner syndrome***, produces X0 females, who are sterile; it is the **only** known viable monosomy in humans

Incidence of Chromosomal Abnormalities in Newborns

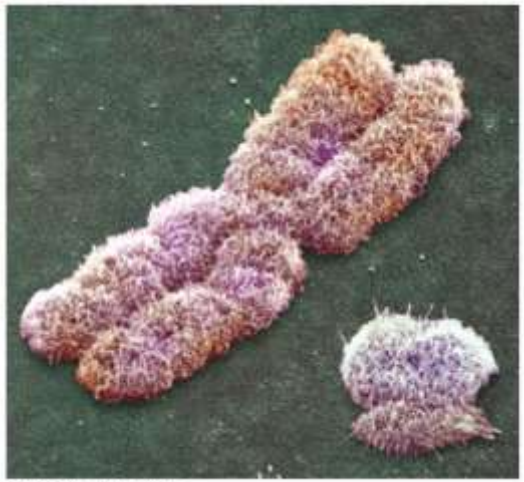
Type of Abnormality	Prevalence at Birth
Sex Chromosome Aneuploidy	
Males (43,612 newborns)	
47,XXY	1/1000
47,XYY	1/1000
Females (24,547 newborns)	
45,X	1/5000
47,XXX	1/1000
Autosomal Aneuploidy (68,159 newborns)	
Trisomy 21	1/800
Trisomy 18	1/6000
Trisomy 13	1/10,000
Structural Abnormalities (68,159 newborns)	
(Sex chromosomes and autosomes)	
Balanced rearrangements	
Robertsonian	1/1000
Other (reciprocal and others)	1/885
Unbalanced rearrangements	1/17,000
All Chromosome Abnormalities	
Autosomal disorders and unbalanced rearrangements	1/230
Balanced rearrangements	1/500
Total	1/154

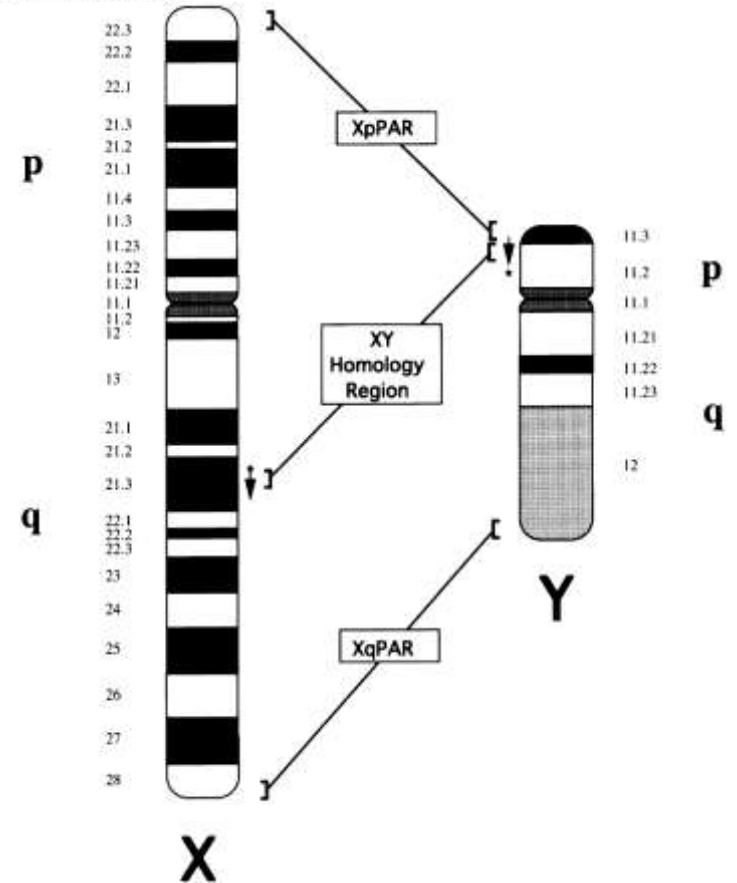
Data from Hsu LYF (1998) Prenatal diagnosis of chromosomal abnormalities through amniocentesis. In Milunsky A (ed.), *Genetic Disorders and the Fetus*, 4th edition, Johns Hopkins University Press, Baltimore, pp. 179-248.

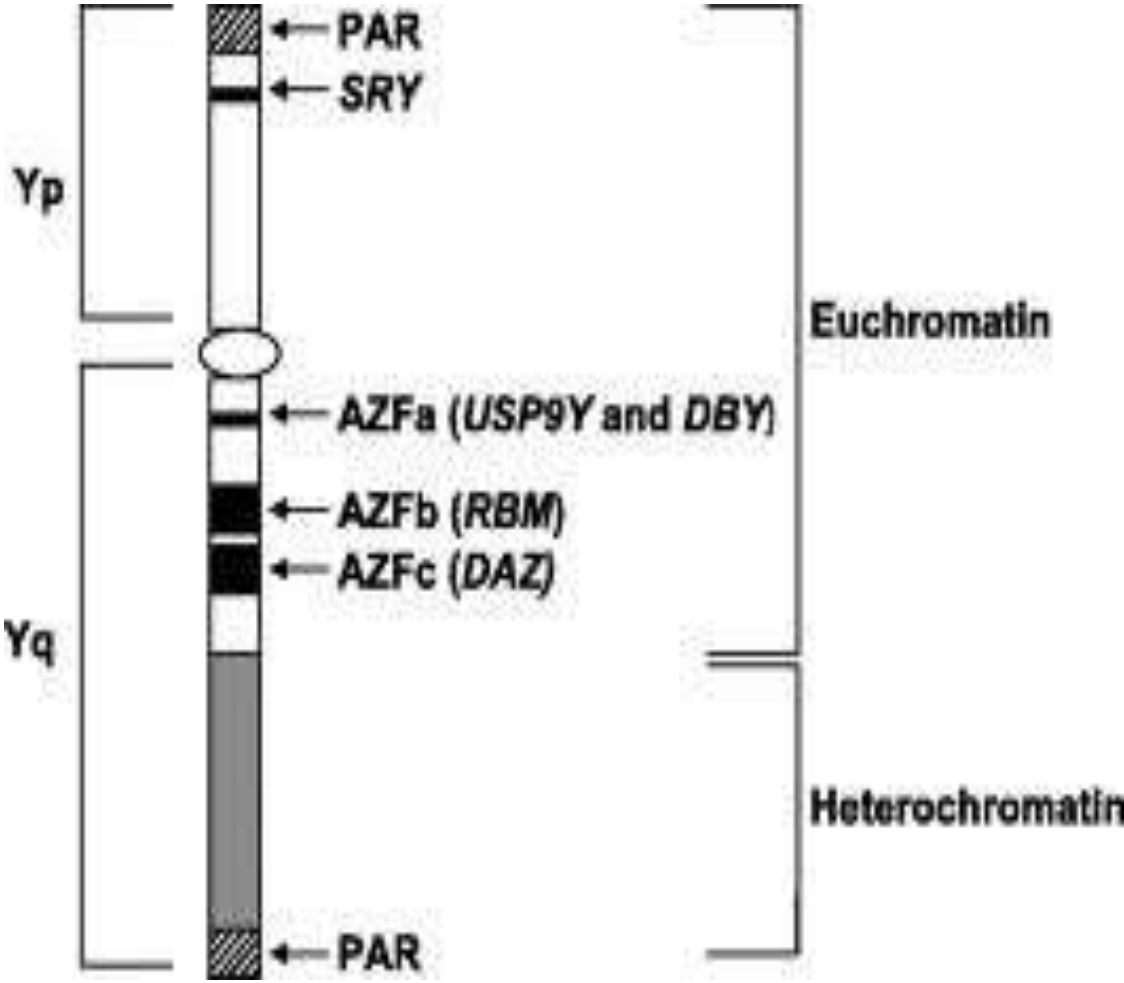
The Chromosomal Basis of Sex

- In humans and other mammals, there are two varieties of sex chromosomes: a larger X chromosome and a smaller Y chromosome
- Only the **ends of the Y** chromosome have regions that are **homologous** with corresponding regions of the X chromosome
- The ***SRY*** gene on the Y chromosome codes for a protein that **directs the development of male anatomical features**

Figure 15.5



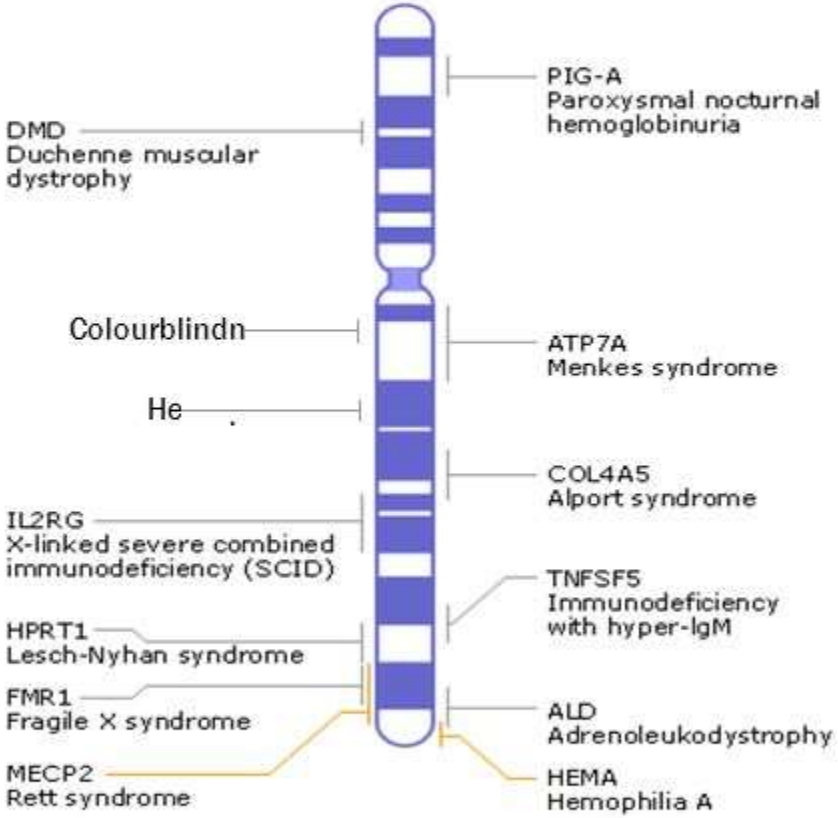




SRY (Sex-determining region Y)

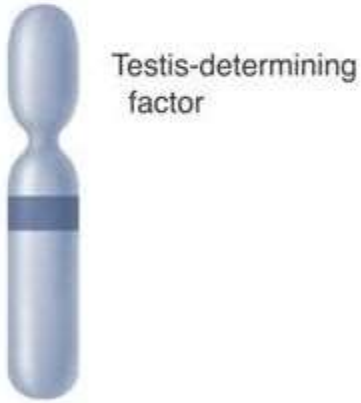
Sex Chromosomes

X chromosome



900-1600 genes

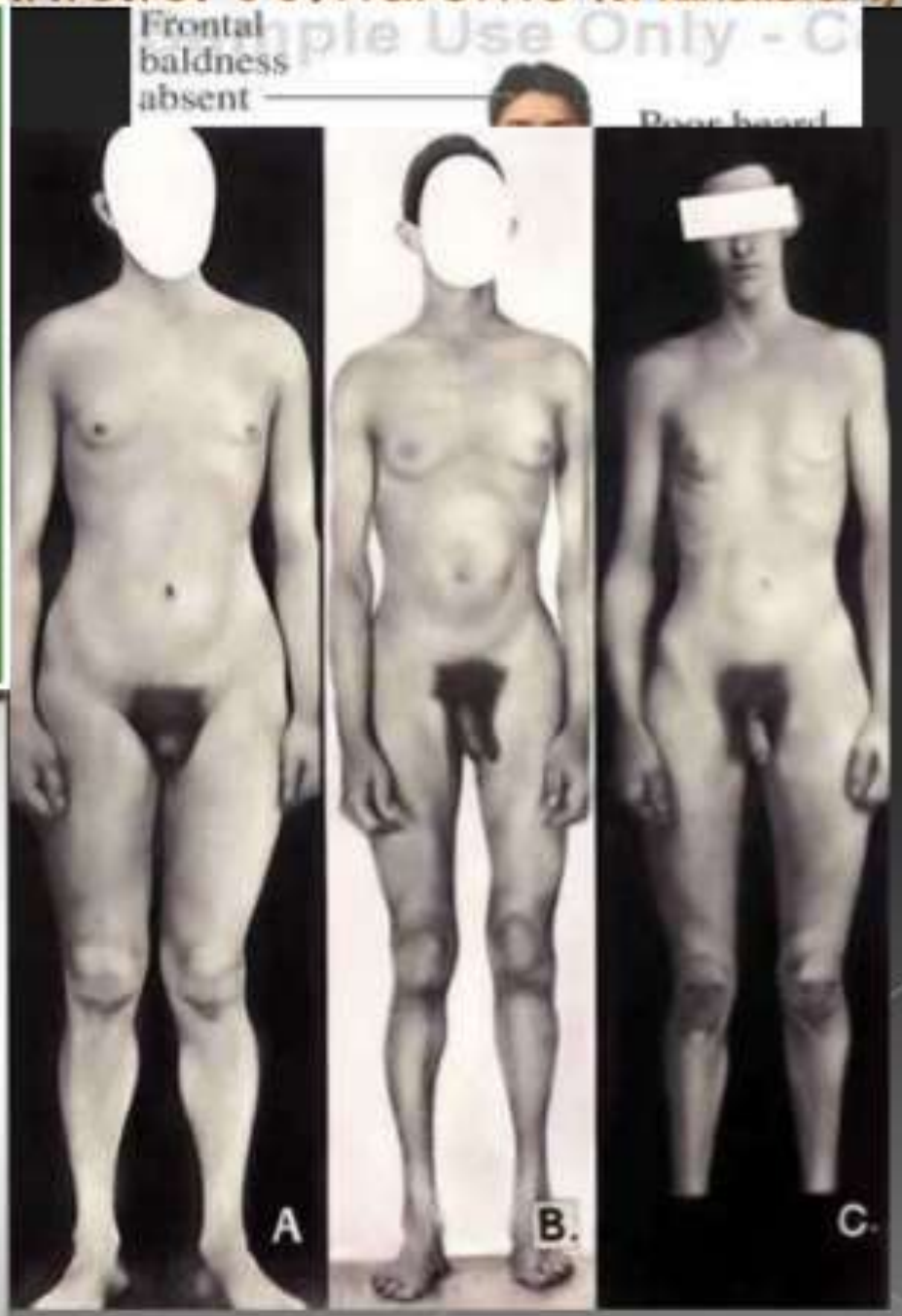
Y chromosome

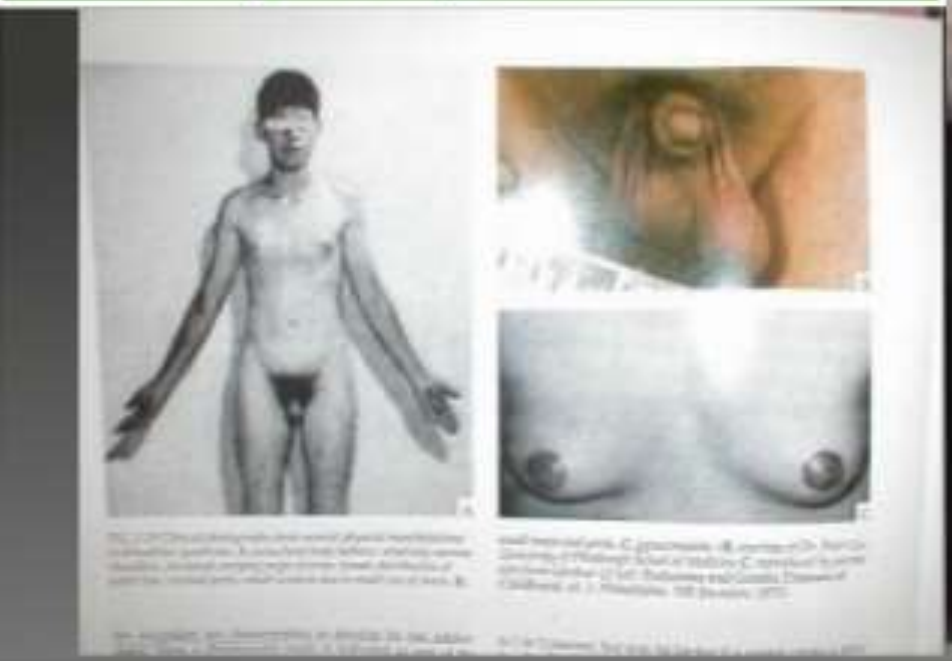


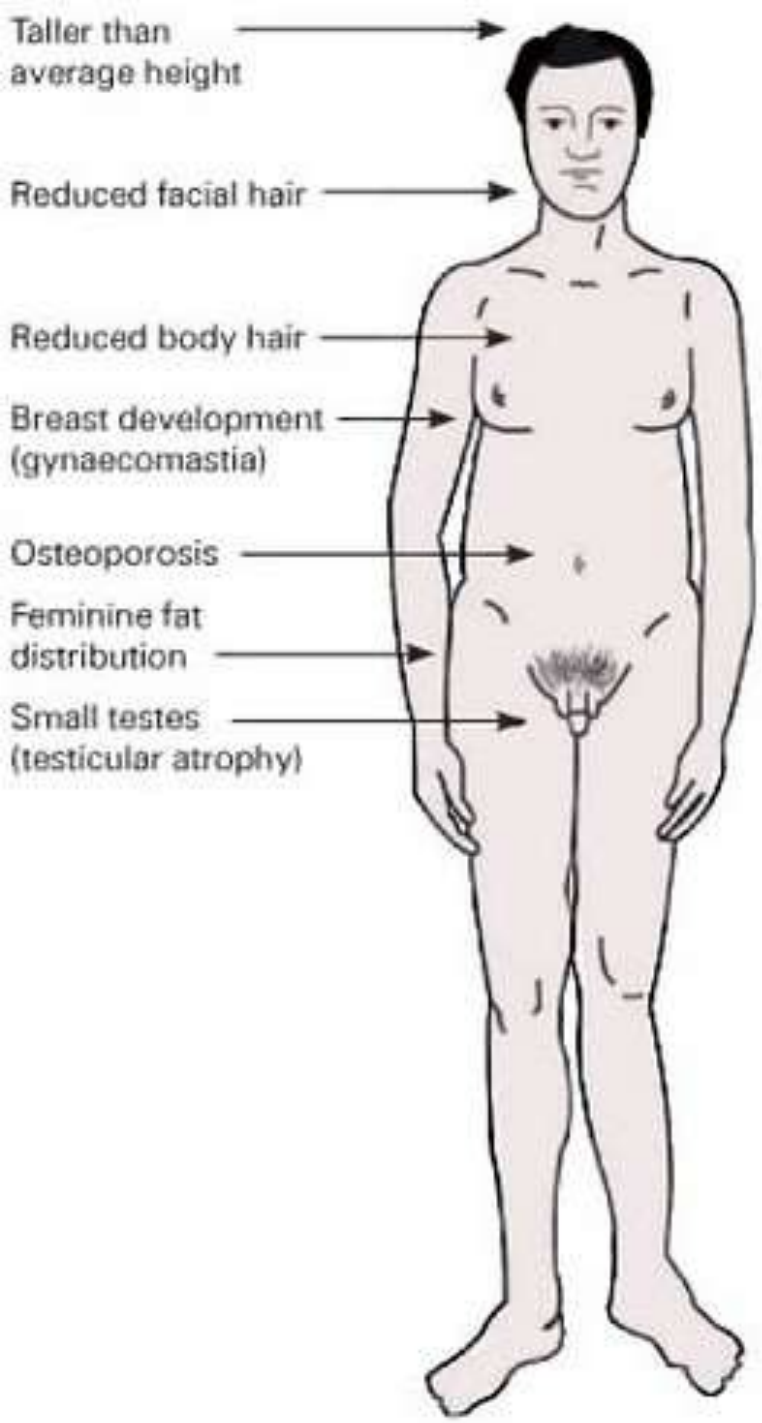
70-200 genes

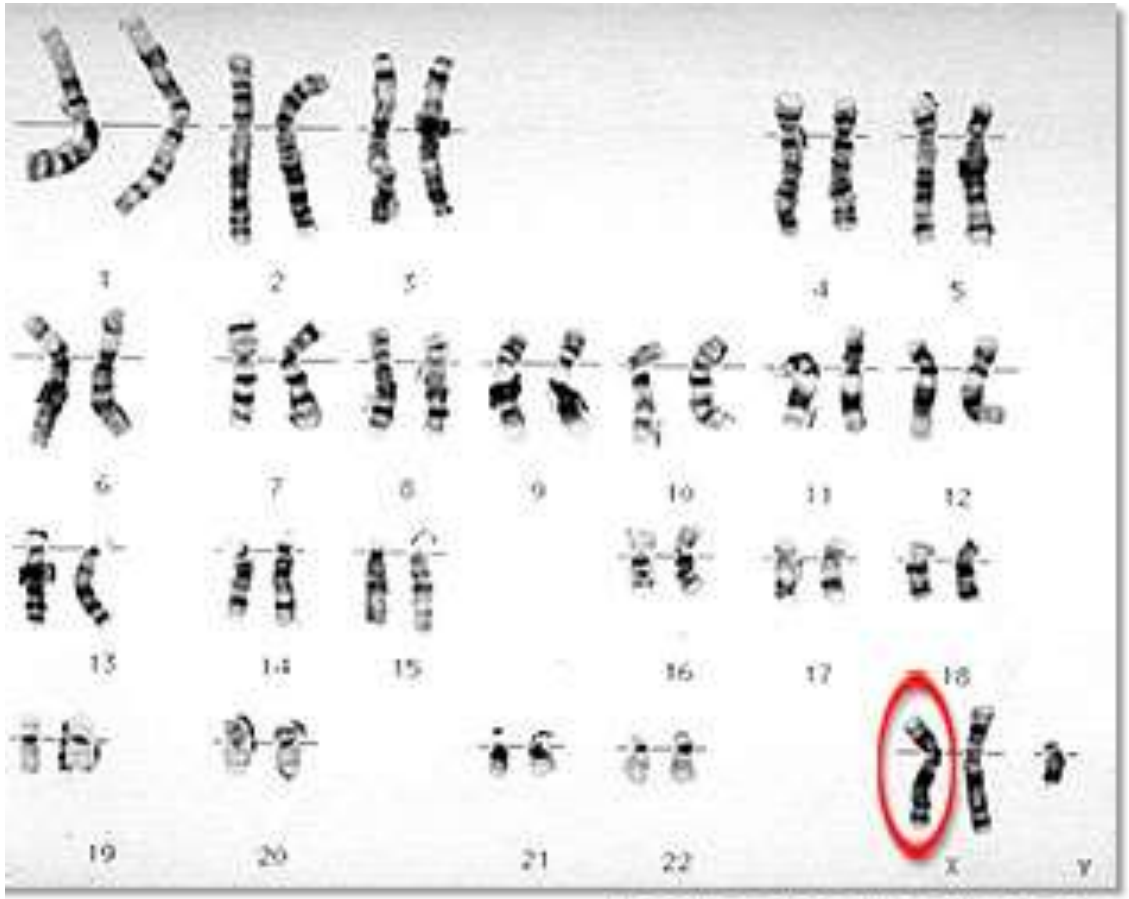
Kleinfelter's syndrome (or Klinefleter's)

- Males with some development of breast tissue normally seen in females.
- Little body hair is present, and such person are typically tall, have small testes.
- Infertility results from absent sperm.
- Evidence of mental retardation may or may not be present.









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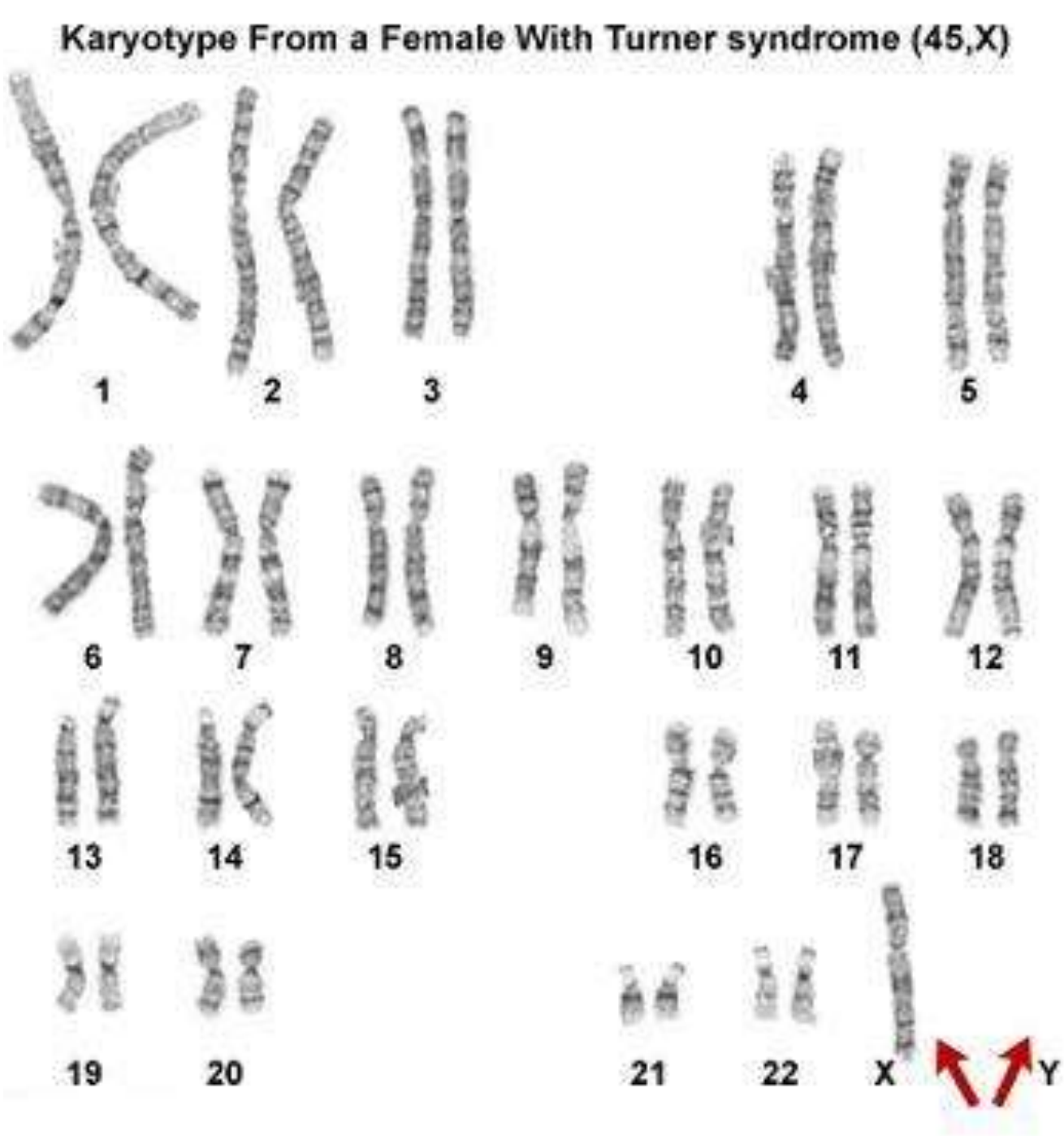
Oral manifestations

- **Maxillary and mandibular prognathism.**
- **(mandibular prognathism being more common).**
- **Permanent tooth crowns larger than usual and taurodontism**


Karyotype From a Female With Turner syndrome (45,X)
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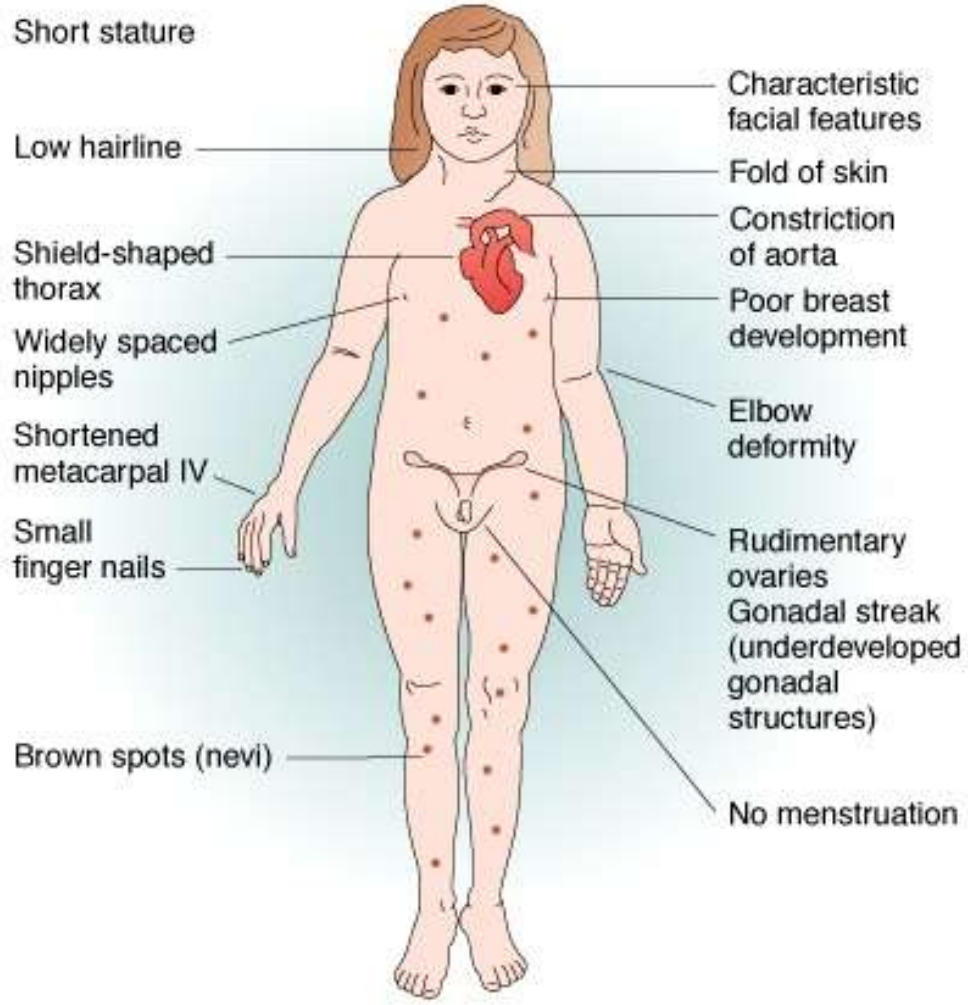
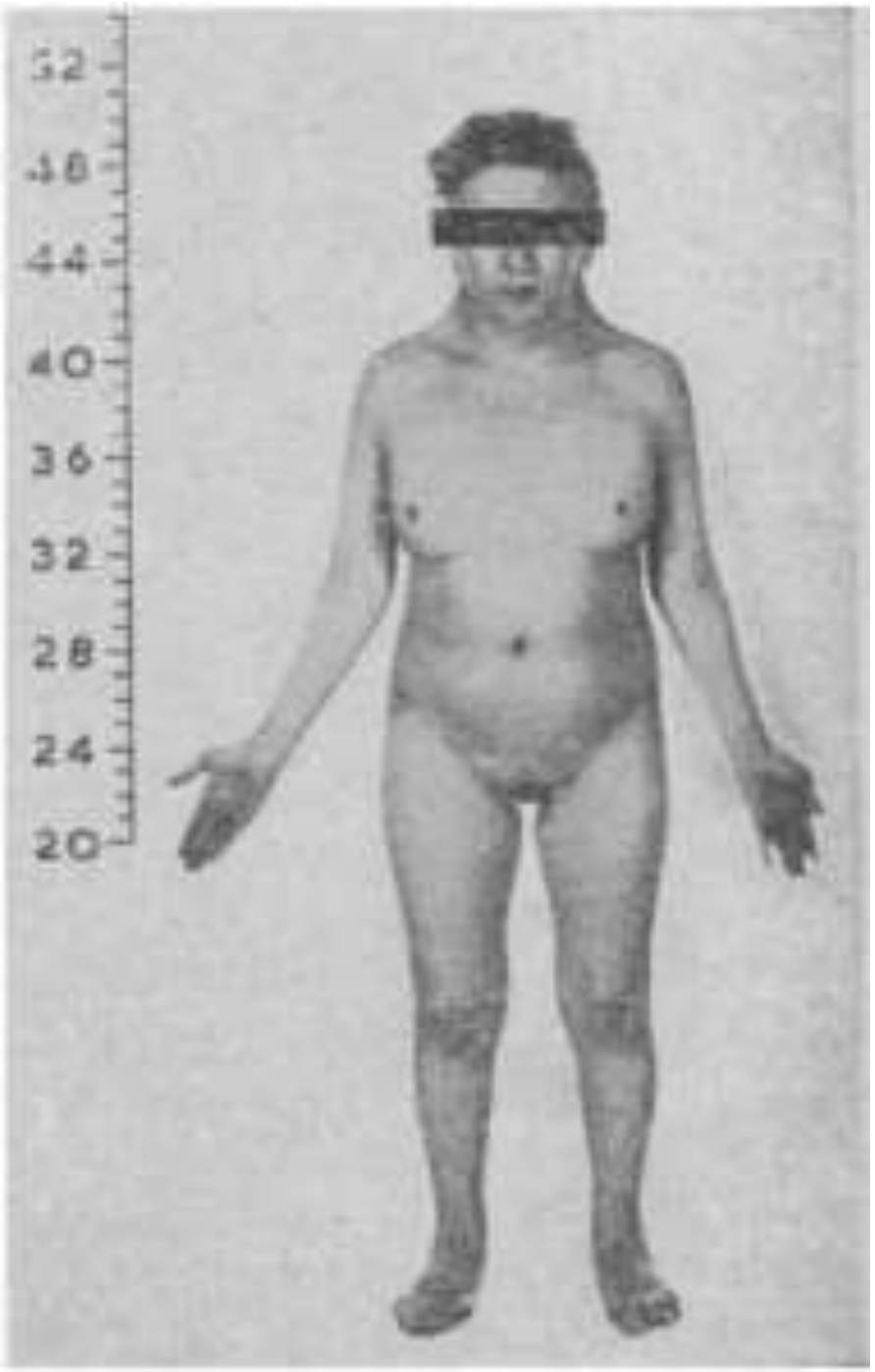

Short stature
Low hairline
Shield-shaped thorax
Widely spaced nipples
Shortened metacarpal IV
Small finger nails
Brown spots (nevi)
Characteristic facial features
Fold of skin
Constriction of aorta
Poor breast development
Elbow deformity
Rudimentary ovaries
Gonadal streak (underdeveloped gonadal structures)
No menstruation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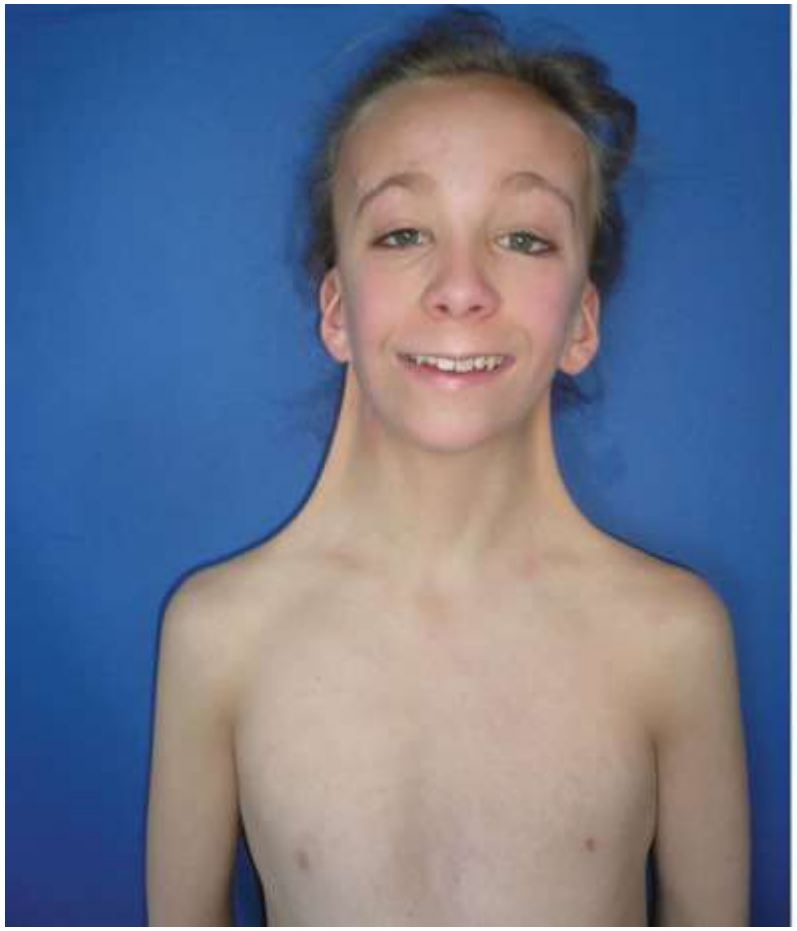
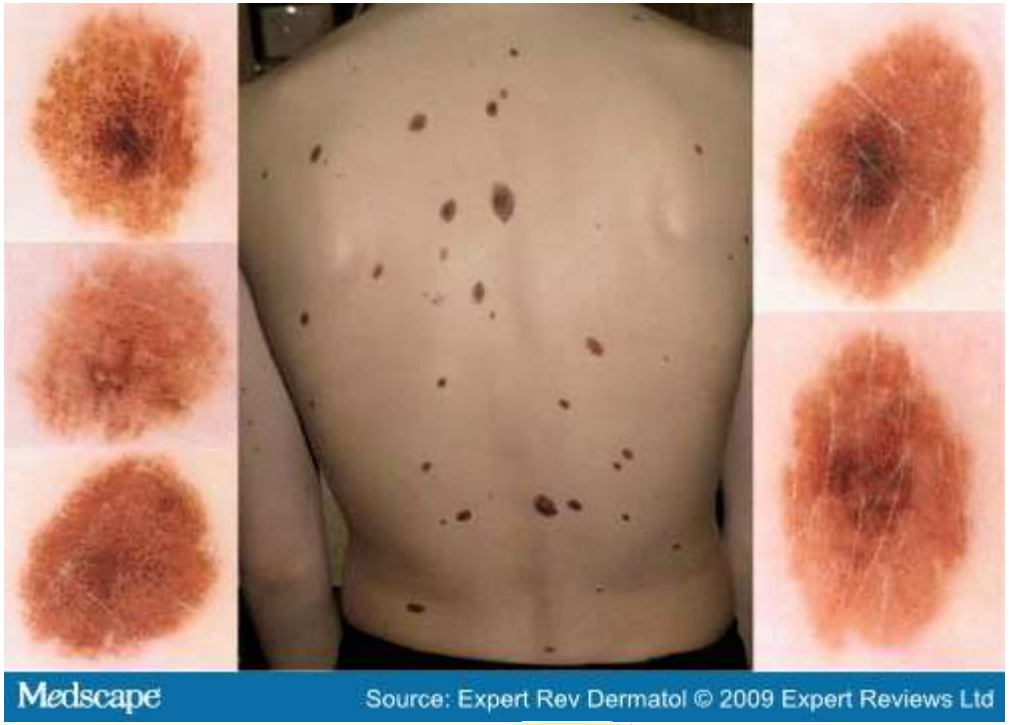
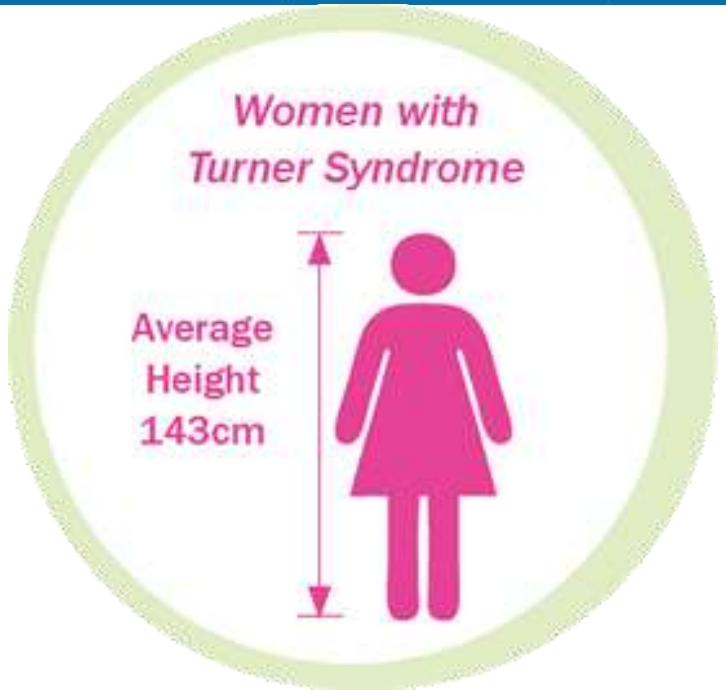
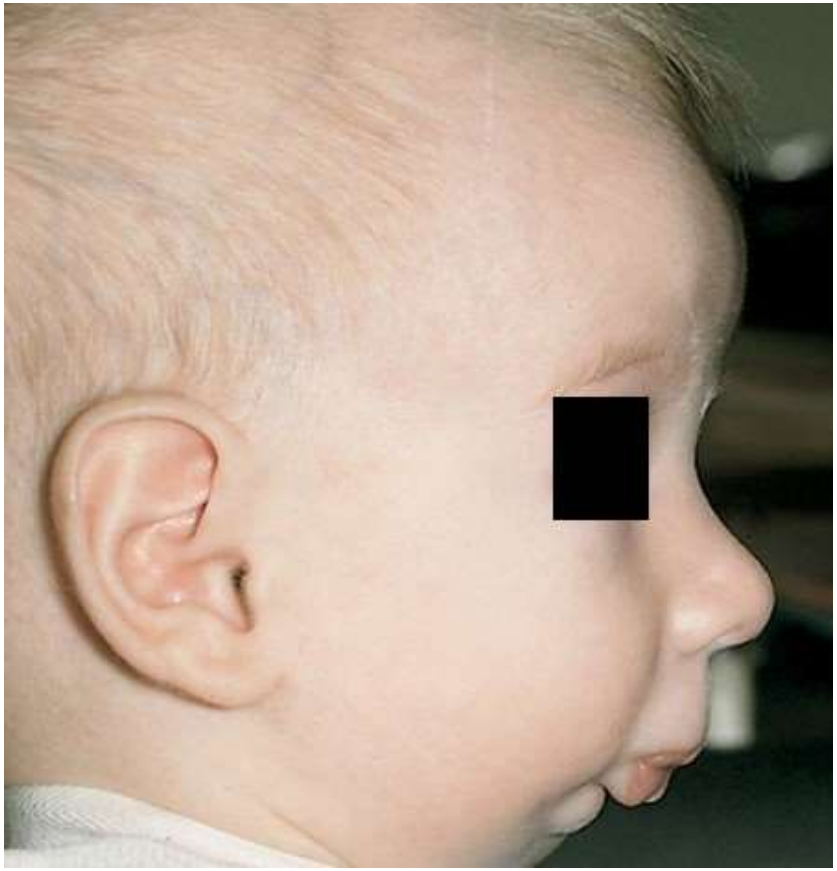


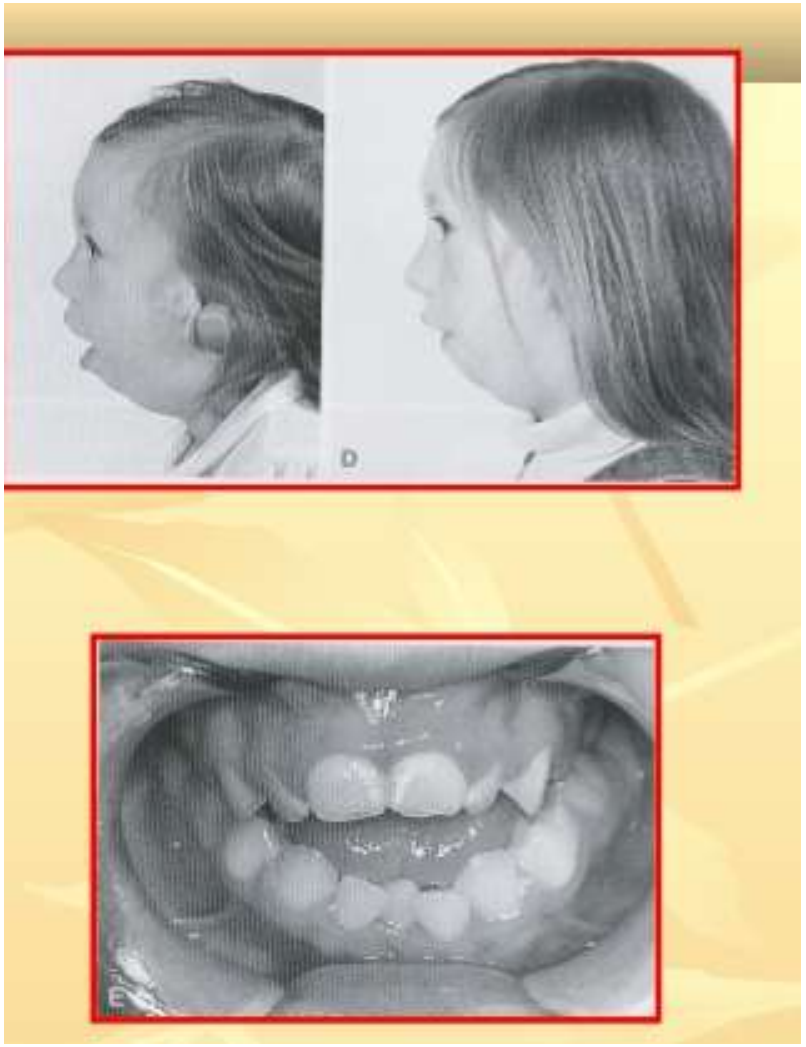

Medscape
Source: Expert Rev Dermatol © 2009 Expert Reviews Ltd


Women with
Turner Syndrome
Average
Height
143cm

Craniofacial features and Oral manifestations

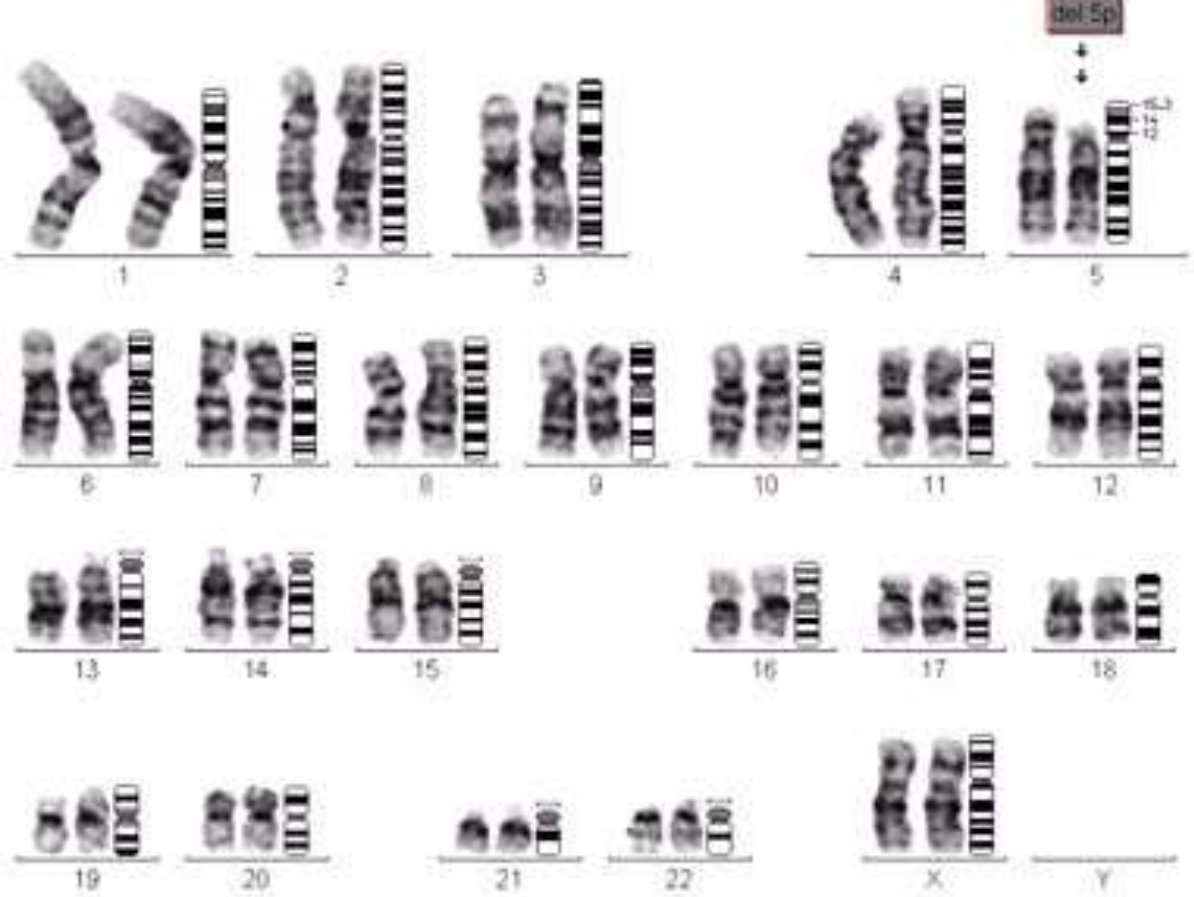
Minor dysmorphic face.
Small chin.
Curved upper lip.
Micrognathia.
Premature eruption of permanent molars
Narrow maxilla.
High arched palate.
Malocclusion




D

Disorders Caused by Structurally Altered Chromosomes

- The syndrome *cri du chat* (“cry of the cat”), results from a specific deletion in chromosome 5
- A child born with this syndrome is mentally retarded and has a catlike cry; individuals usually die in infancy or early childhood
- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes


del 5p
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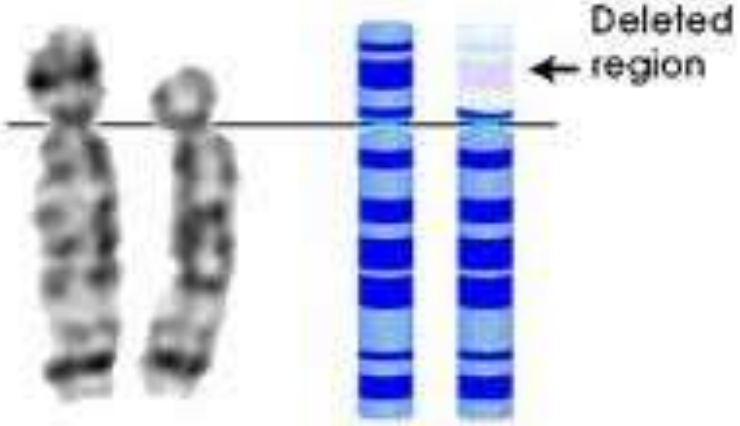

Deleted region
Cri-du-chat Chromosome 5 pair

Symptoms of cri du chat syndrome are mostly those of looks. People who have this syndrome have very distinct looks. They have:

- Small heads (microcephaly)
- Unusually round face
- Small chin
- Eyes that are very far apart
- Folds of skin over their eyes
- Small nose bridge

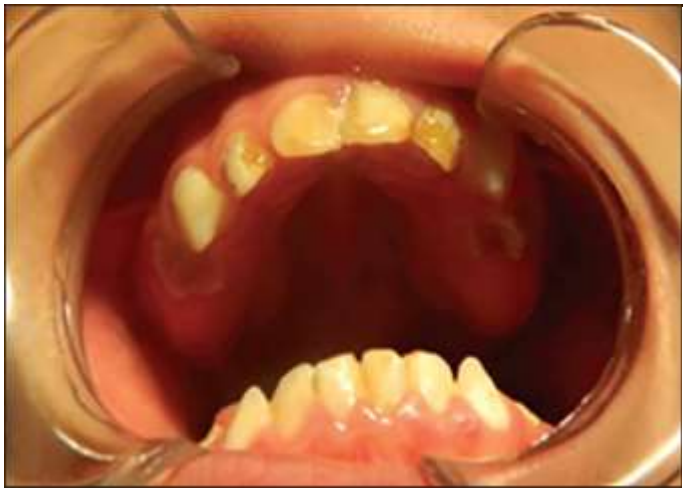
Symptoms occur inside the body also. Heart defects, muscular/skeletal problems, hearing or sight problems, and poor muscle tone are all possible. When children diagnosed with Cri Du Chat grow, they usually have difficulty walking and talking correctly. They might have behavior problems like hyperactivity and aggression. Also, some may have severe mental retardation

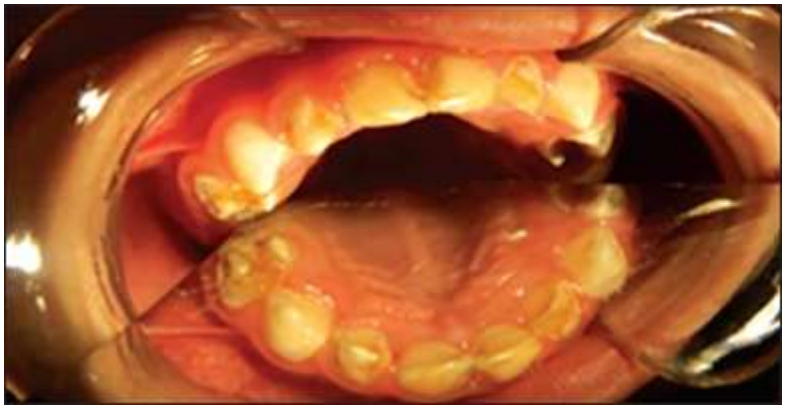
Cri-du-chat Symptoms

- Approximately 75% of the patients with cri-du-chat syndrome die within the first few months of life and about 90% before they are aged 1 year. These figures are from an older study (1978), and decreased morbidity and mortality are most likely with contemporary interventions. Survival to adulthood is possible.
- Pneumonia, aspiration pneumonia, congenital heart defects, and respiratory distress syndrome are the most common causes of death.

Craniofacial features and Oral manifestations

Microcephaly.
Broad nasal bridge.
Widely spaced eyes.
Micrognathia.
Malocclusion, especially overjet and clift lip and clift palate





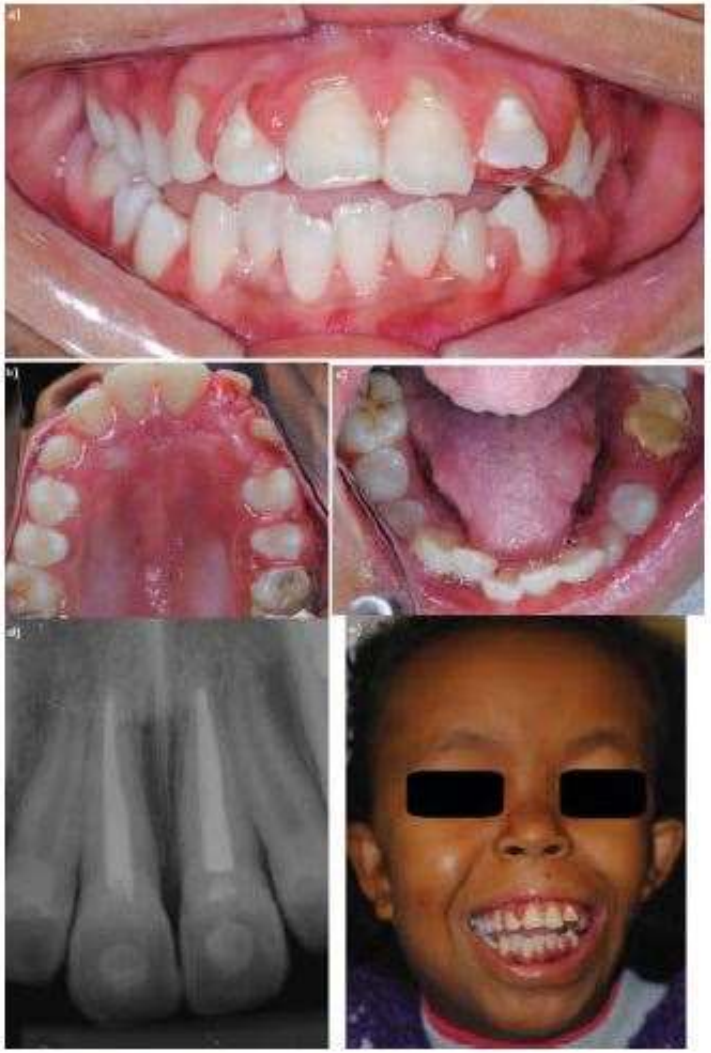


FIGURE 3 – a-c) Clinical features 1 year and 10 months after the first visit, demonstrating adequate hygiene and the correct eruption of permanent teeth; d) control periapical radiograph of both traumatized incisors obtained 17 months after final obturation; e) final facial aspect of patient.

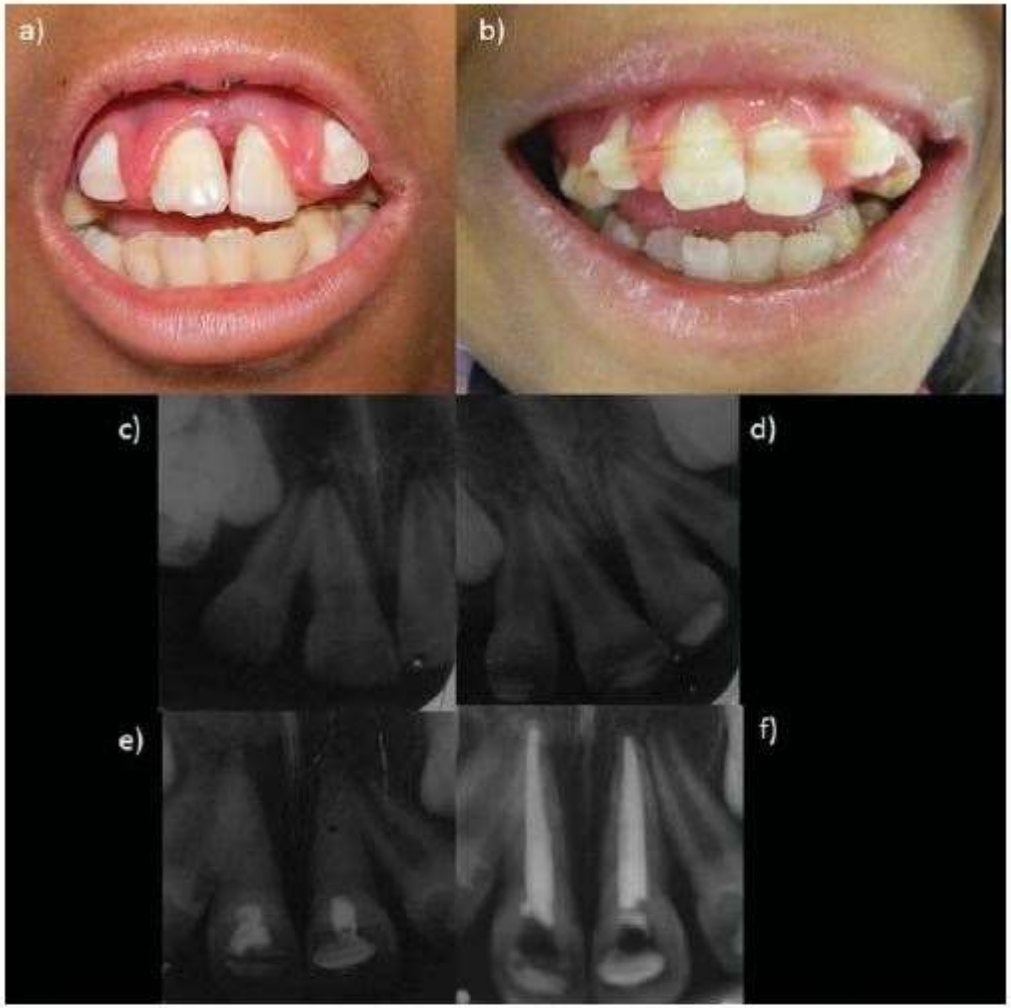


FIGURE 2 – a) Traumatized upper central incisors at first visit; b) 4 days later, with better gingival condition, a flexible splint was anchored to the primary molar to allow periodontal healing of both traumatized incisors; c) periapical radiograph obtained at first visit; d) 3 weeks later, an initial process of external root resorption in both teeth was observed; e) introduction of calcium hydroxide paste to stimulate apexification of immature teeth; f) 5 months later, successful apical barrier formation was observed, with no signs of external resorption progression and final obturation of both incisors.

Disorders Caused by Structurally Altered Chromosomes

- Certain cancers, including *chronic myelogenous leukemia* (CML), are caused by translocations of chromosomes

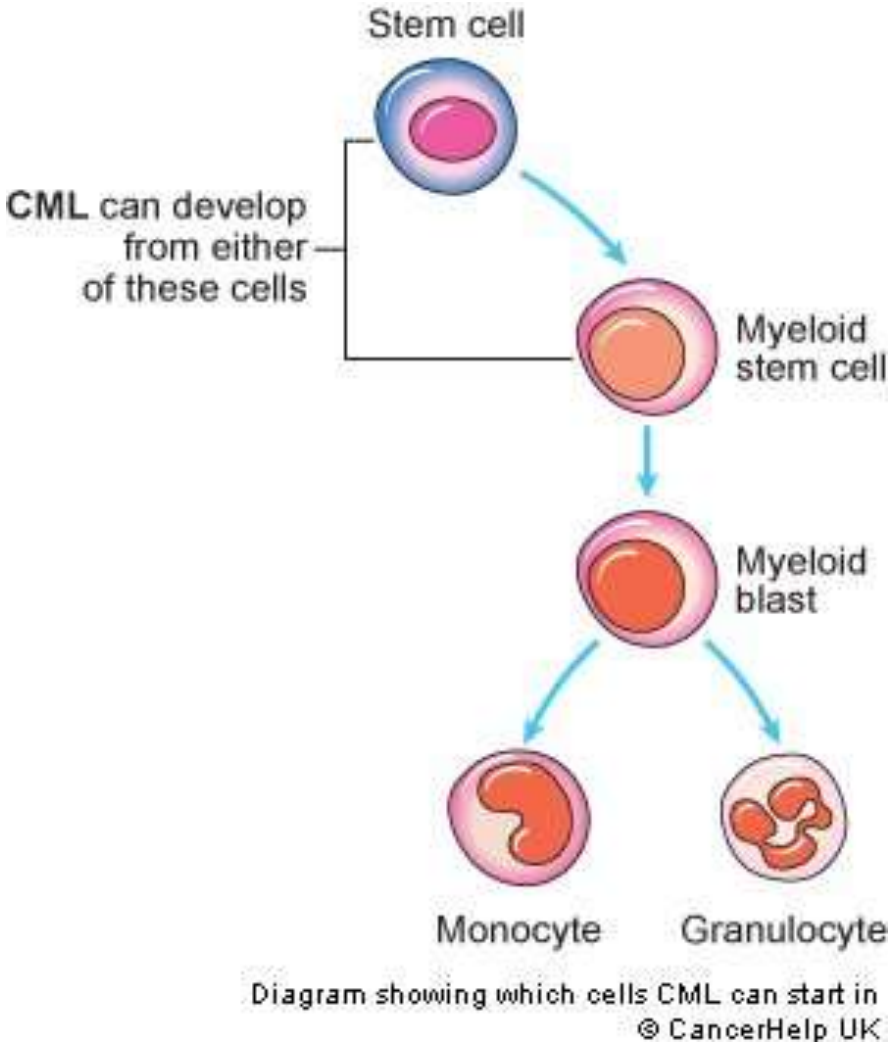
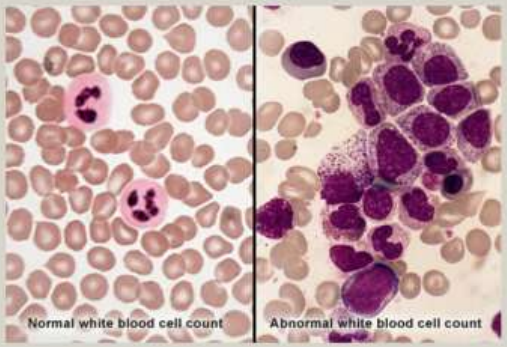


Diagram showing which cells CML can start in
© CancerHelp UK

What is leukemia?

A cancer found in the blood and bone marrow, caused by too many white blood cells in the body. The white blood cells don't let the body fight disease and prevent the body from making red blood cells and platelets.



4 types of leukemia

Acute lymphoblastic leukemia

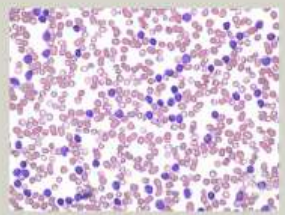
Found in lymphoid cells
Grows quickly
Common in children
6,000 cases a year

Acute myelogenous leukemia

Found in myeloid cells
Grows quickly
Common in adults and children
18,000 cases a year

Chronic lymphoblastic leukemia

Found in lymphoid cells
Grows slowly
Common in adults 55+
15,000 cases a year



Chronic myelogenous leukemia

Found in myeloid cells
Grows slowly
Common in adults
6,000 cases a year

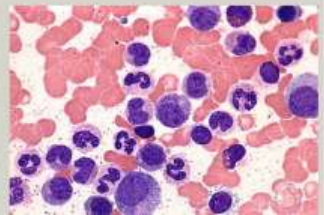
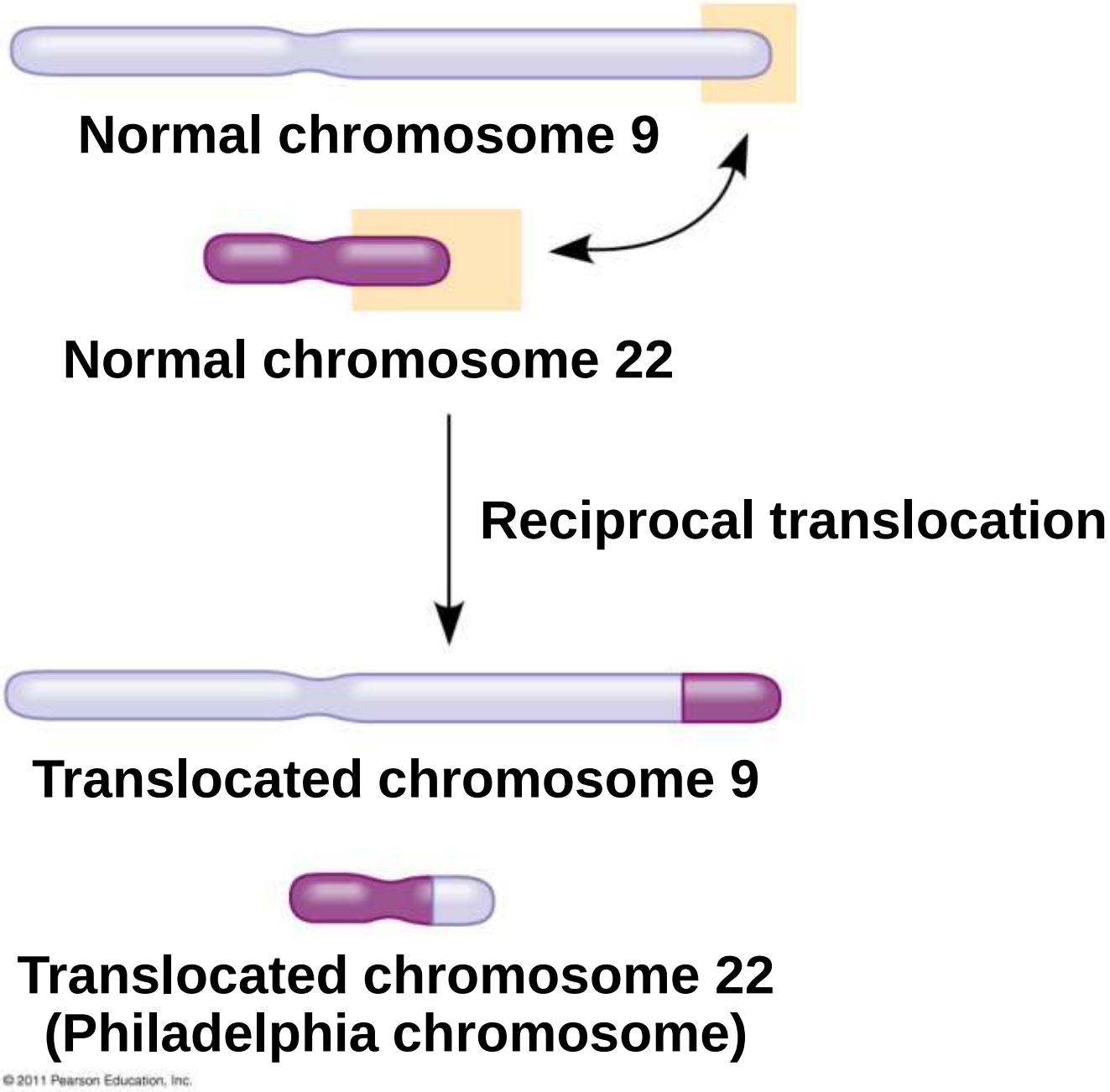
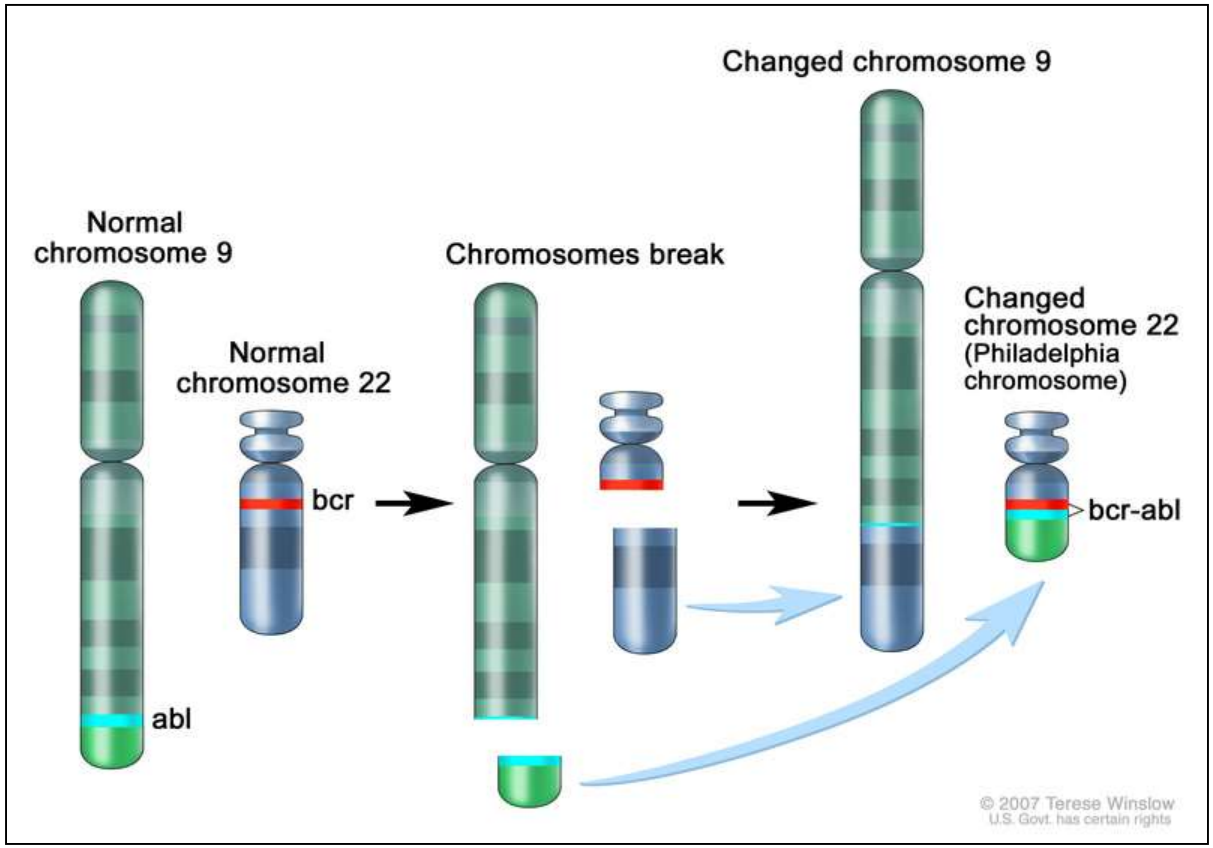
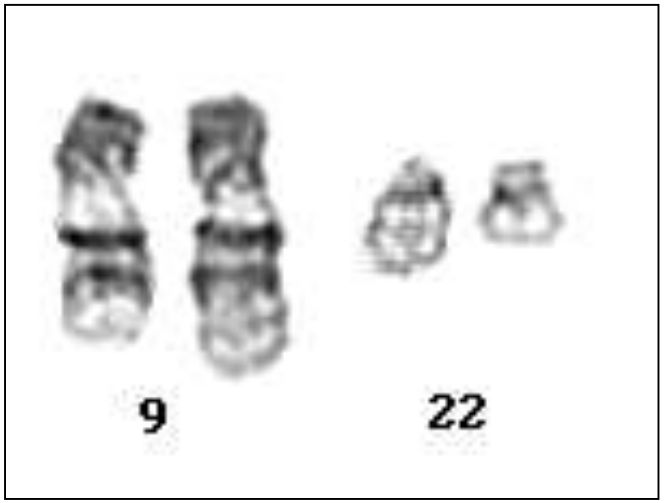


Figure 15.16







result of the translocation is the oncogenic BCR-ABL gene fusion, located on the shorter derivative 22 chromosome. This gene encodes the Bcr-abl fusion protein

The ABL tyrosine kinase activity of *BCR-Abl* is elevated relative to wild-type ABL

Abl gene expresses a membrane-associated protein, a tyrosine kinase, the BCR-Abl transcript is also translated into a tyrosine kinase. The activity of tyrosine kinases is typically controlled by other molecules, but the mutant tyrosine kinase encoded by the BCR-Abl transcript results in a protein that is "always on" or continuously activated, which results in unregulated cell division (i.e. cancer)

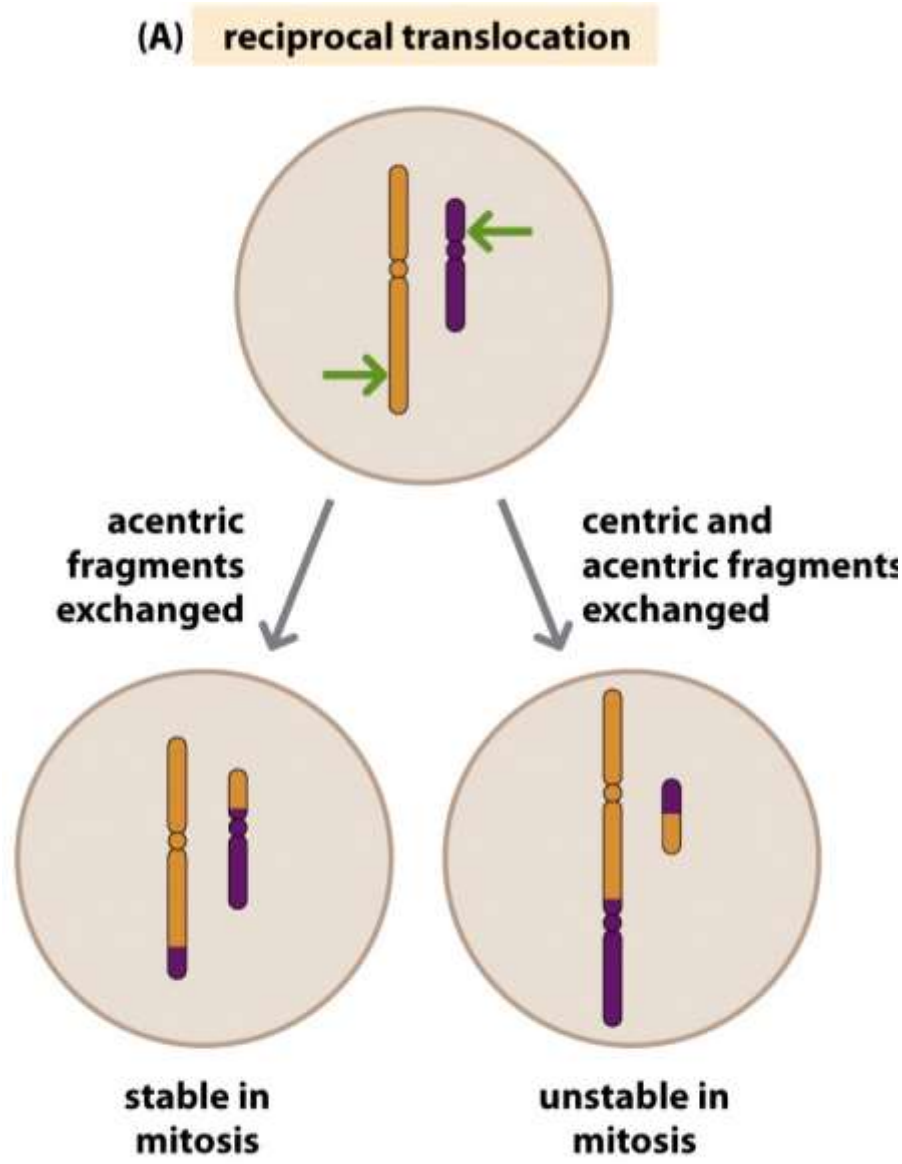
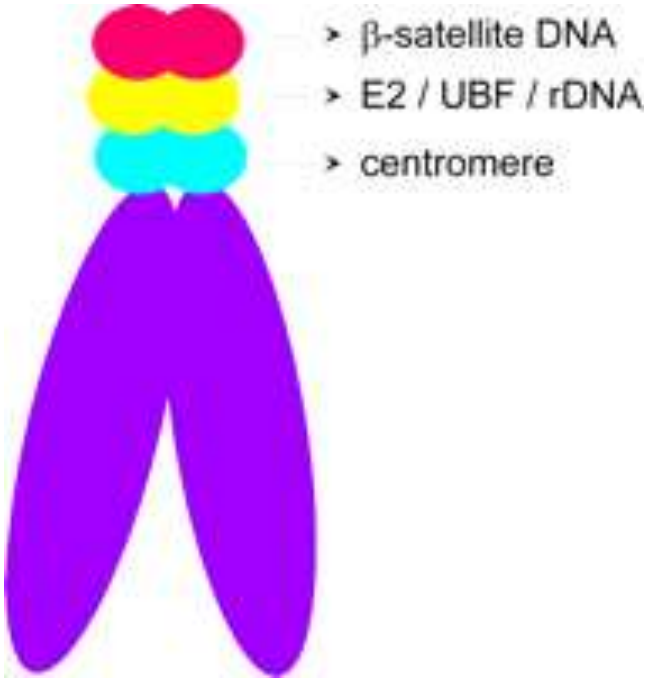


Figure 2.23 Human Molecular Genetics, 4ed. (© Garland Science)

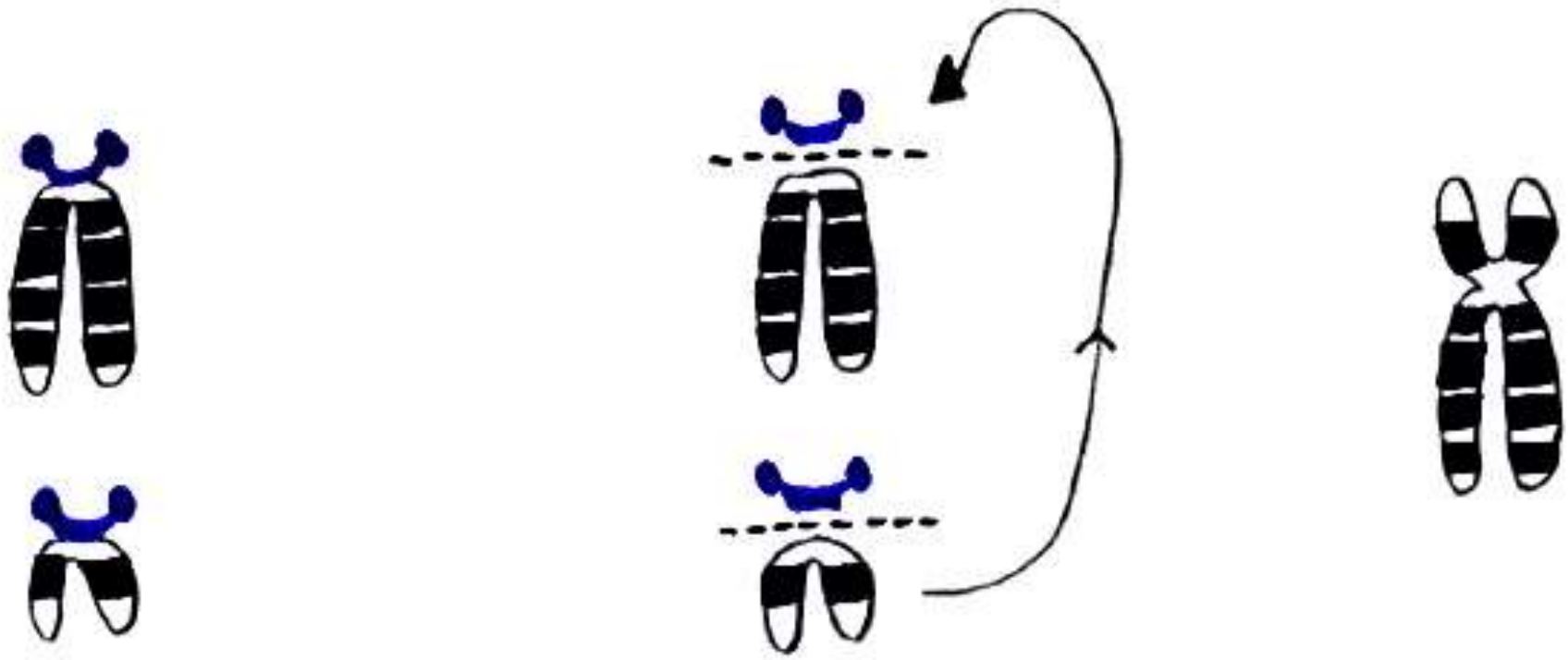
(A) Reciprocal translocation. The derivative chromosomes are stable in mitosis when one acentric fragment is exchanged for another; when a centric fragment is exchanged for an acentric fragment, unstable acentric and dicentric chromosomes are produced.

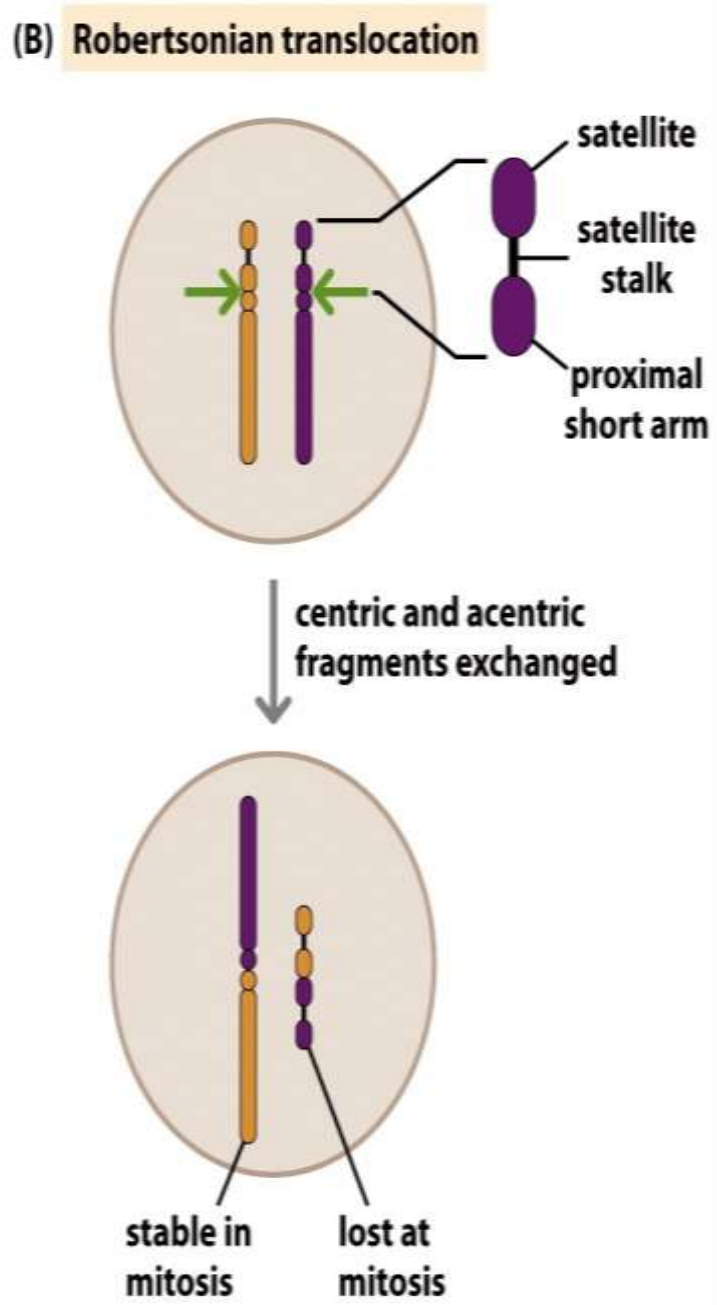
If an acentric fragment from one chromosome is exchanged for an acentric fragment from another, the products are stable in mitosis, however exchange of an acentric fragment for a centric fragment results in acentric and dicentric chromosomes that are unstable in mitosis.

- **A robertsonian translocation** is a specialized type of translocation between two of the five types of **acrocentric** chromosome in human (13,14,15,21,and 22) the short arm is very small and very similar in DNA content ,each contains **1-2Mb** of tandemly repeated rRNA genes sandwiched between two blocks of heterochromatic DNA



Robertsonian translocation
(with chromosome #14 and chromosome #21)





(B) Robertsonian translocation. This is a highly specialized reciprocal translocation in which exchange of centric and acentric fragments produces a **dicentric chromosome** that is nevertheless stable in mitosis, plus an acentric chromosome that is lost in mitosis without any effect on the phenotype. It occurs exclusively after breaks in the short arms of the human acrocentric chromosomes 13, 14, 15, 21, and 22.

The short arm of the acrocentric chromosomes consists of three regions: a proximal heterochromatic region (composed of highly repetitive noncoding DNA), a distal heterochromatic region (called a chromosome satellite), and a thin connecting region of euchromatin (the satellite stalk) composed of tandem rRNA genes. Breaks that occur close to the centromere can result in a dicentric chromosome in which the **two centromeres** are so **close** that they can function as a **single centromere**. The loss of the small acentric fragment has no phenotypic consequences because the only genes lost are rRNA genes that are also present in large copy number on the other acrocentric chromosomes

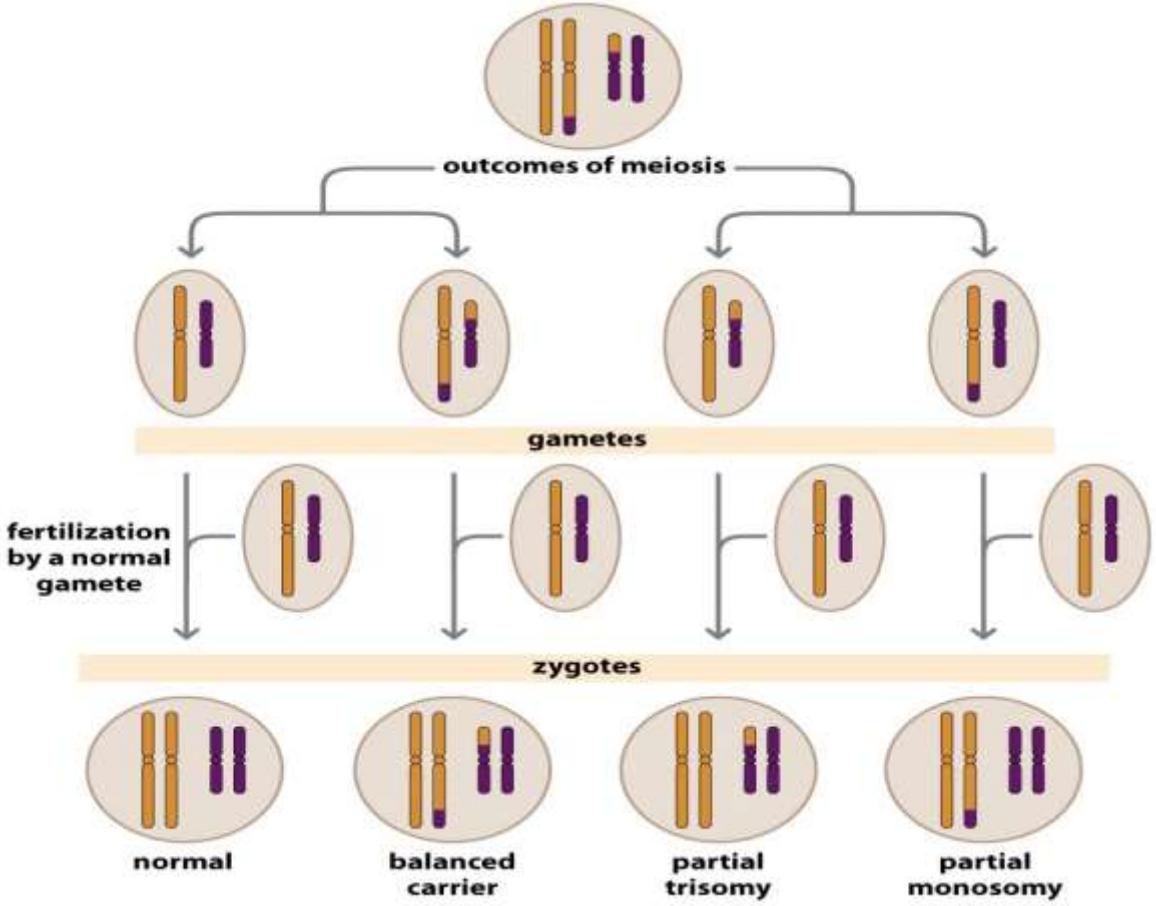


Figure 2.24 Possible outcomes of meiosis in a carrier of a balanced reciprocal translocation. Other modes of segregation are also possible, for example 3:1 segregation.

The relative frequency of each possible gamete is not readily predicted.

The risk of a carrier having a child with each of the possible outcomes depends on its frequency in the gametes and also on the likelihood of a conceptus with that abnormality developing to term.

➢A carrier of a balanced Robertsonian translocation can produce gametes that after fertilization give rise to an entirely normal child ,a phenotypically normal balanced carrier , or a conceptus with full trisomy or full monosomy for one of the chromosomes involved

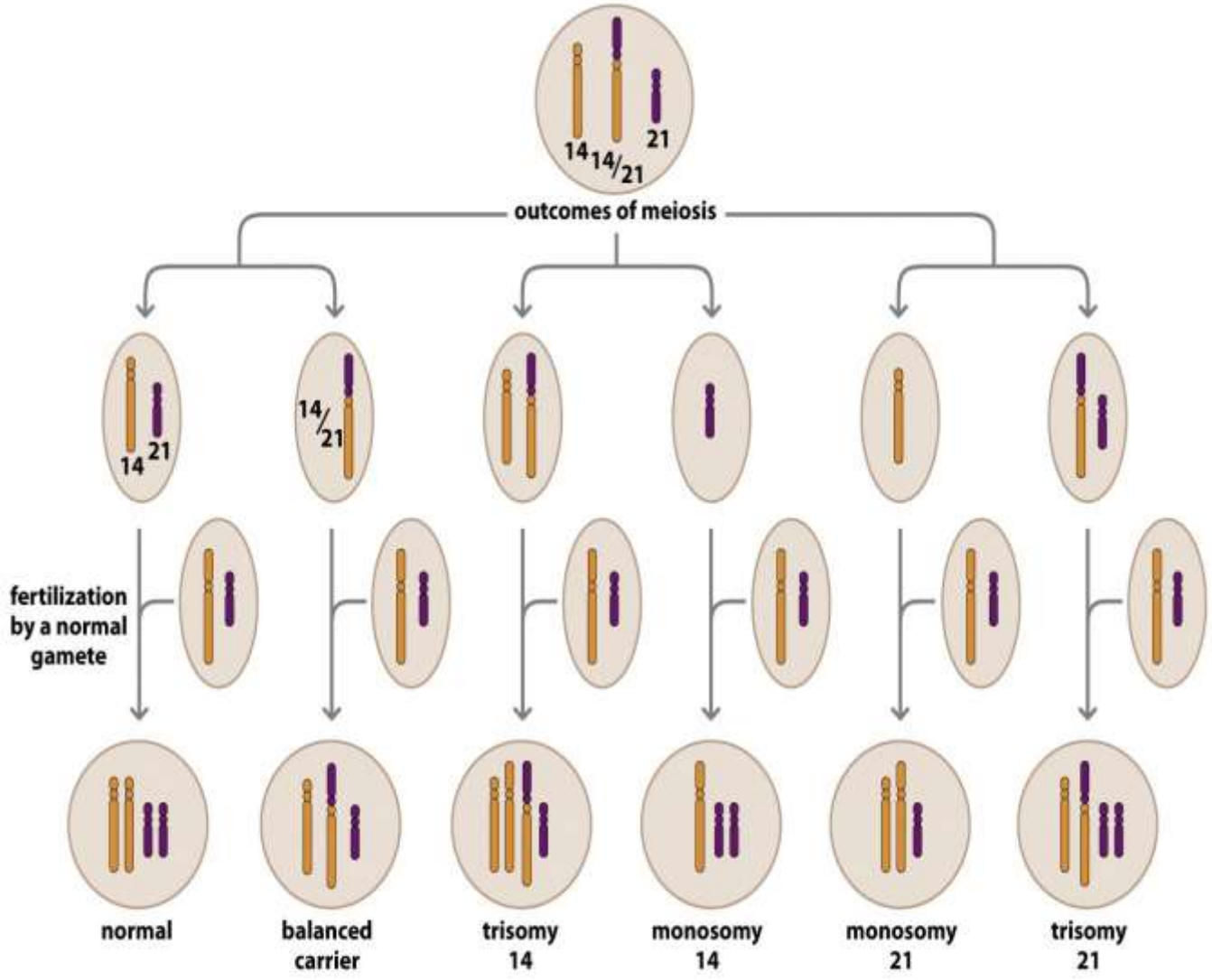


Figure 2.25 Possible outcomes of meiosis in a carrier of a Robertsonian translocation.
Carriers are asymptomatic but often produce unbalanced gametes that can result in a monosomic or trisomic zygote. The two monosomic zygotes and the trisomy 14 zygote in this example would not be expected to develop to term.

Figure 2.25 Human Molecular Genetics, 4ed. (© Garland Science)

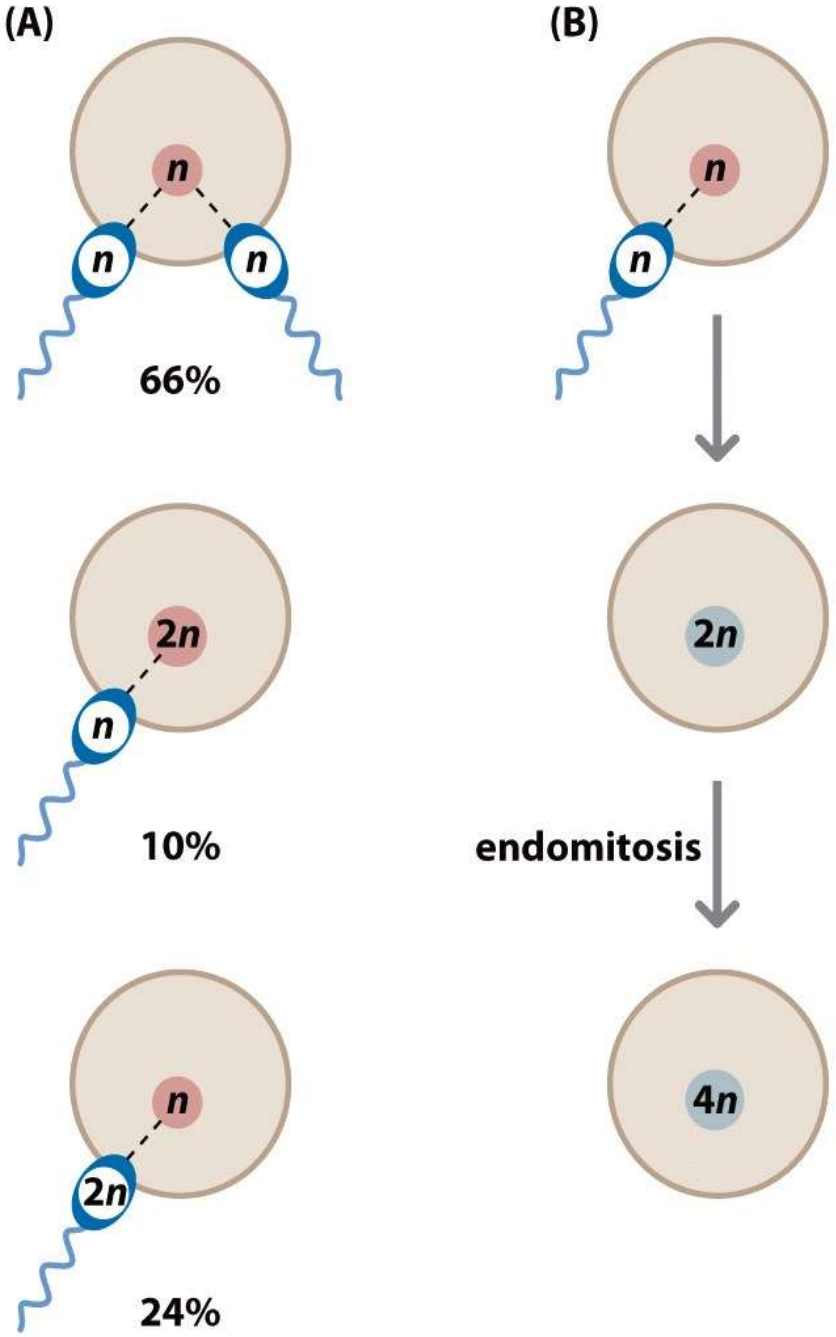


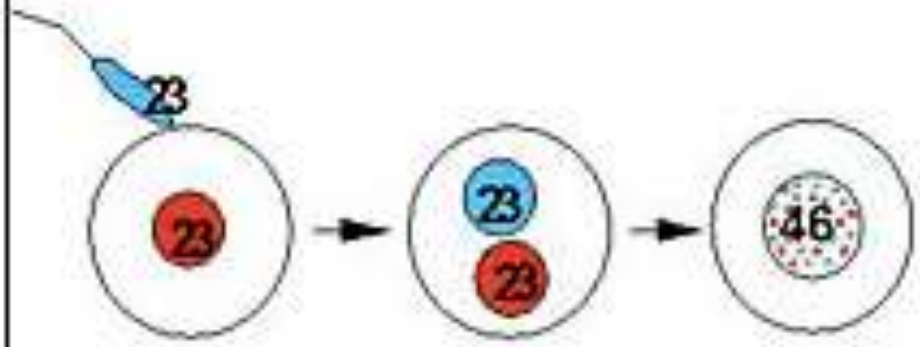
Figure 2.21 Human Molecular Genetics, 4ed. (© Garland Science)

Origins of triploidy and tetraploidy.

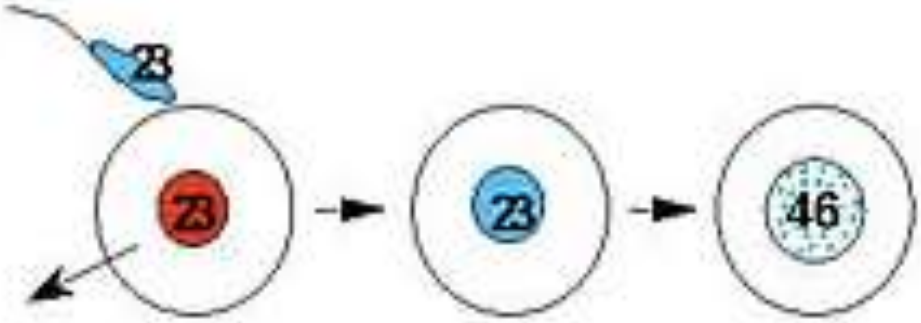
(A) Origins of human triploidy. **Dispermy** is the principal cause, accounting for 66% of cases. Triploidy is also caused by **diploid gametes** that arise by occasional faults in meiosis; fertilization of a diploid ovum and fertilization by a diploid sperm account for 10% and 24% of cases, respectively.

(B) **Tetraploidy** involves normal fertilization and fusion of gametes to give a normal zygote. Subsequently, however, tetraploidy arises by endomitosis when DNA replicates without subsequent cell division.

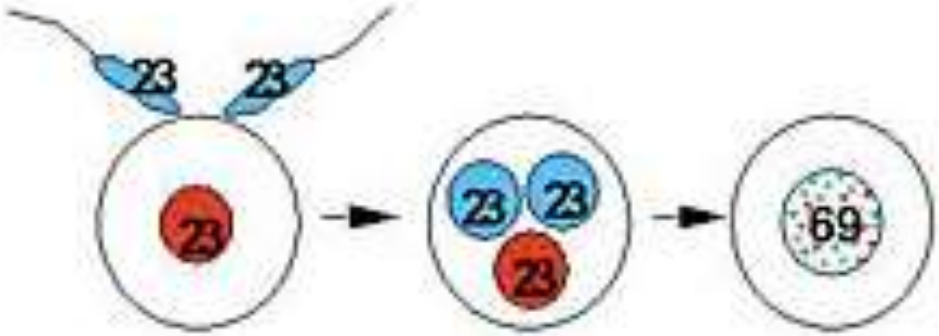
Genetic status in normal conception and molar pregnancy



- **Normal conception**
- 2 sets of genes
- 1 paternal
- 1 maternal
- Viable foetus



- **Complete Mole**
- 2 sets of paternal genes
- no maternal genes
- No foetus



- **Partial mole**
- 3 sets of genes
- 1 maternal
- 2 paternal
- non-viable foetus

Triploidy is the presence of an additional haploid set of chromosomes, is the cause of 20% of spontaneous abortions, premature births and perinatal deaths.

Triploidy syndrome is a rare syndrome and is estimated to occur in about 2 per cent of conceptuses. Triploidy occurs when there is double fertilization of an ovum (dispermy). The result may be 69, XXX or 69, XXY or 69, XYY. The extra set of paternal chromosomes predisposes to formation of a partial mole, features of which may or may not be grossly or microscopically apparent.

- 69,XXX triploidy
- 69,XXY triploidy
- 69,XYY triploidy

Triploidy - stillbirth at 39 weeks (69,XXX) - note the appearance of the hands

Physiopathology

Triploidy is constituted by an extra haploid set of chromosomes for a total of 69 chromosomes in humans. A "parent-of-origin" effect has been demonstrated by analysis of cytogenetic polymorphisms of triploidy pregnancies. Two distinct phenotypes of human triploid fetuses have been recognized according to the parental origin of the extra haploid set.

The first one or triploidy of diandric type occurs when the extra haploid set of chromosomes arises from the father, the second one or triploidy of digynic type occurs when the extra haploid set of chromosomes arises from the mother. Diandric fetuses appear relatively well grown with a large placenta, while digynic fetuses show intrauterine growth retardation with a small placenta.

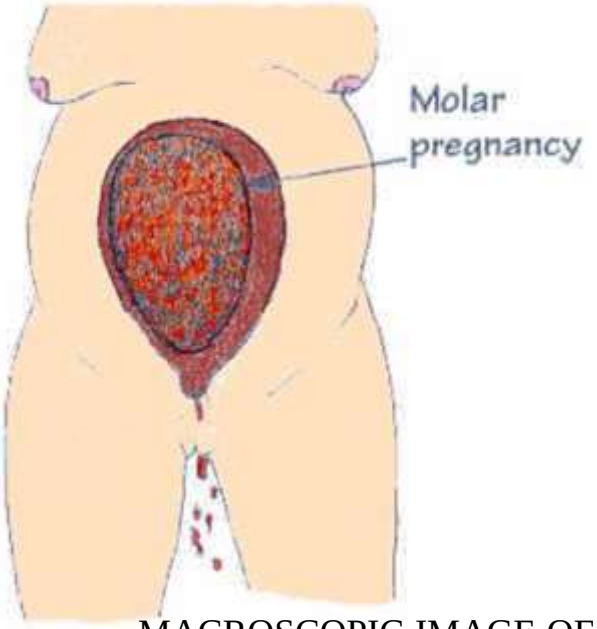
Types

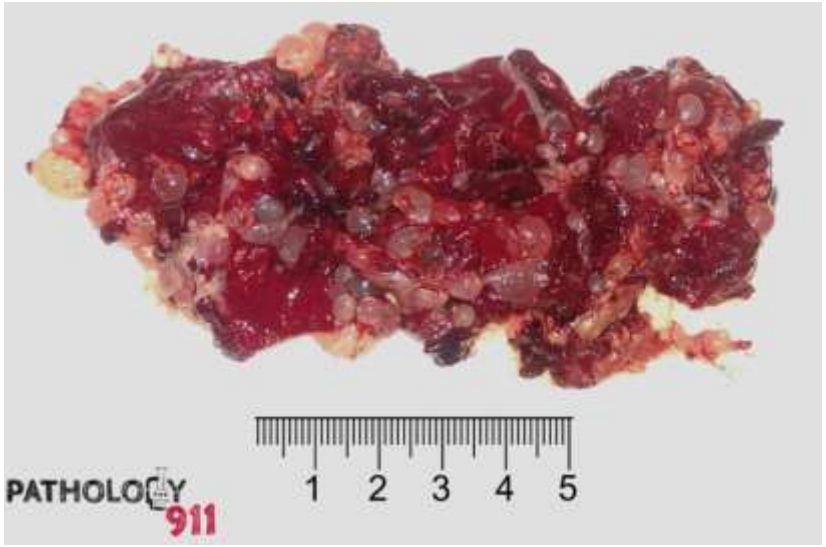
- maternal triploidy (triploidy by digyny)
- paternal triploidy (diandry or dispermy)

Synopsis

The most common clinical signs of triploidy are: severe intrauterine growth retardation, macrocephaly, total syndactyly of third and fourth fingers and CNS, heart and renal defects.

Hydatidiform mole, one of the characteristic features of pure triploidy, is found in more than 90% of cases.





MACROSCOPIC IMAGE OF A COMPLETE HYDATIDIFORM MOLE, SHOWING THE CHARACTERISTIC VESICULAR, OR ‘BUNCHES OF GRAPES’ APPEARANCE OF THE CHORIONIC VILLI.

PARTIAL MOLE

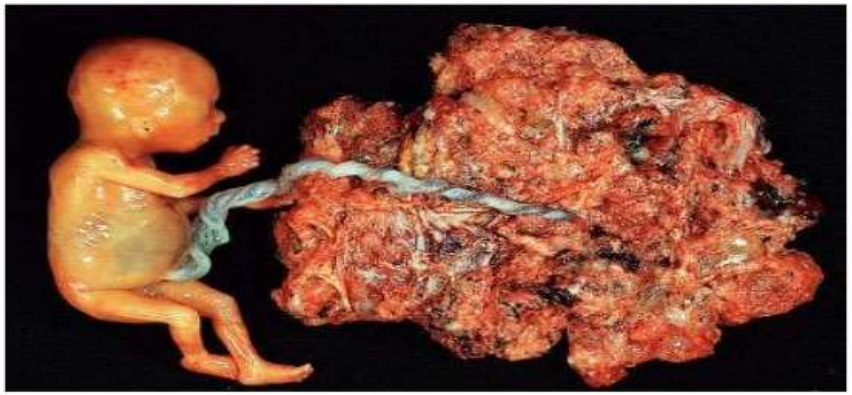
- The oocyte has an intact set of maternal DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA
- Option B: Fertilised by two sperm
- Karyotype: Triploid – 69 chromosomes (69 XXY – an extra set of paternal DNA)

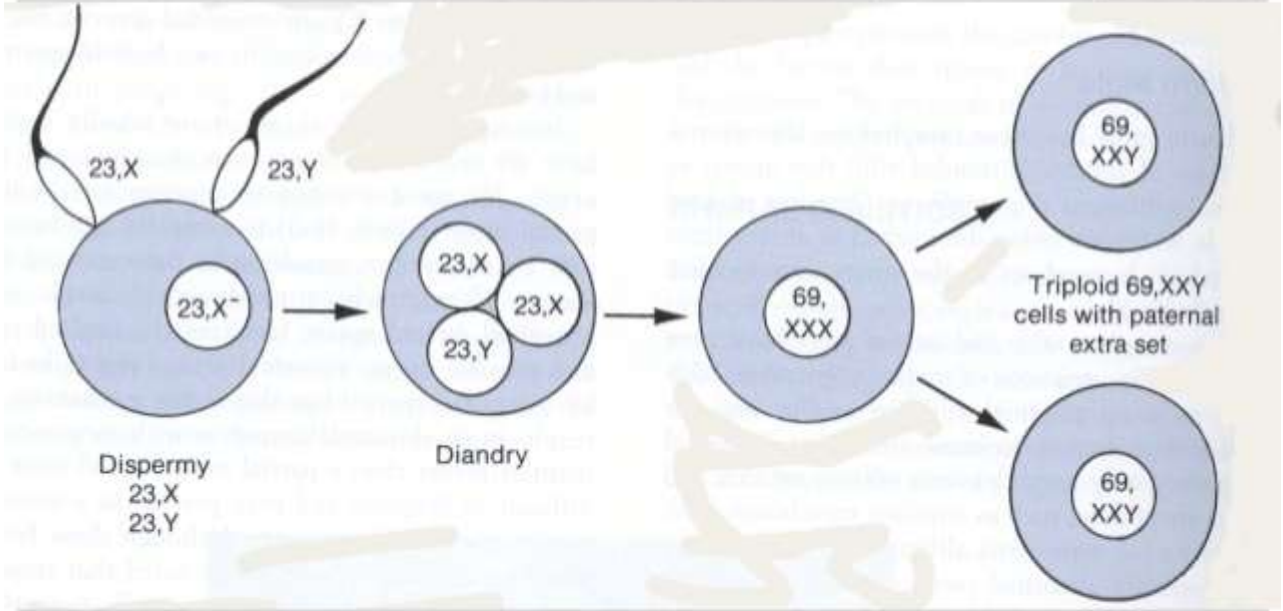
COMPLETE MOLE

- The oocyte has somehow lost its DNA – it is 'empty' of DNA
- Option A: Fertilised by one sperm – reduplicates its own DNA = *homozygous*
- Option B: Fertilised by two sperm = *heterozygous*
- Karyotype: Diploid – 46 chromosomes (46XX or 46XY – the 46YYs are not viable)

Note: (*all paternal DNA* – no maternal DNA – i.e. androgenetic)

Partial mole



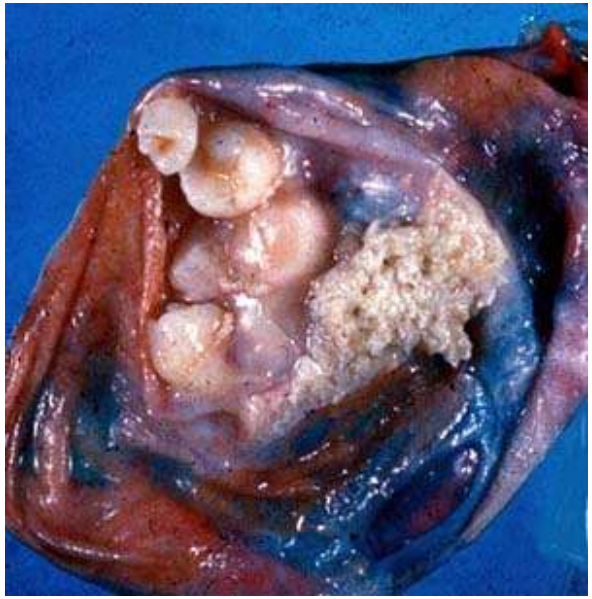


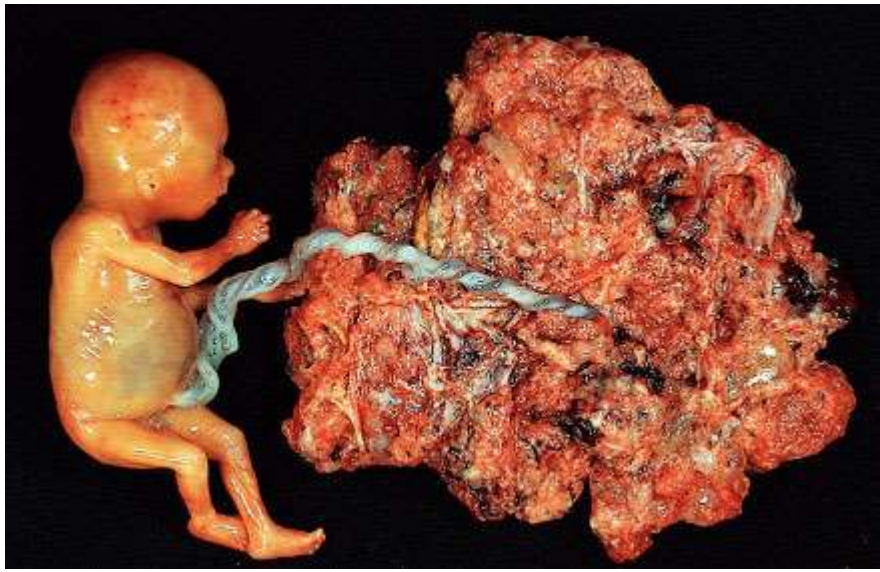
Diandric triploidy

Uniparental diploidy changes the balance between the embryo or fetus and its supporting membranes

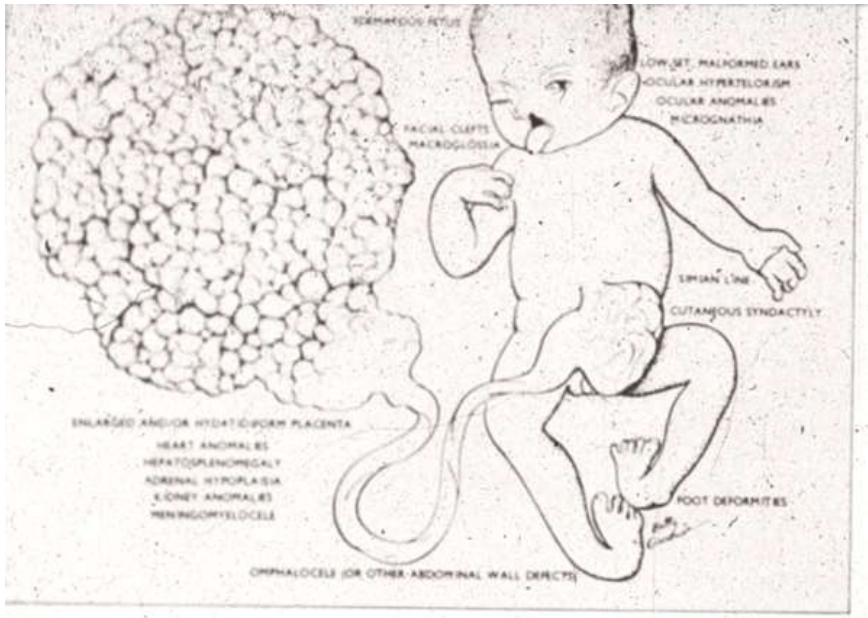
- **Paternal uniparental diploidy** produces hydatidiform moles, abnormal conspectuses that develop to show widespread hyperplasia (overgrowth)of the trophoblast but no fetal parts, they may transform into choriocarcinoma.

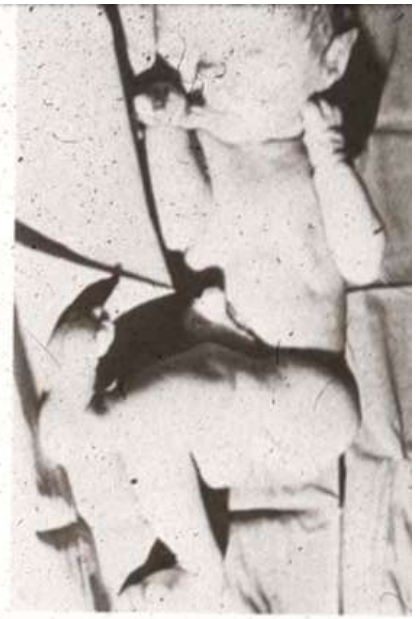
- **Maternal uniparental diploidy** results in ovarian teratomas , rare benign tumors of the ovary which consist of disorganized embryonic tissue but are lacking in vital extra-embryonic membranes.





Triploidy

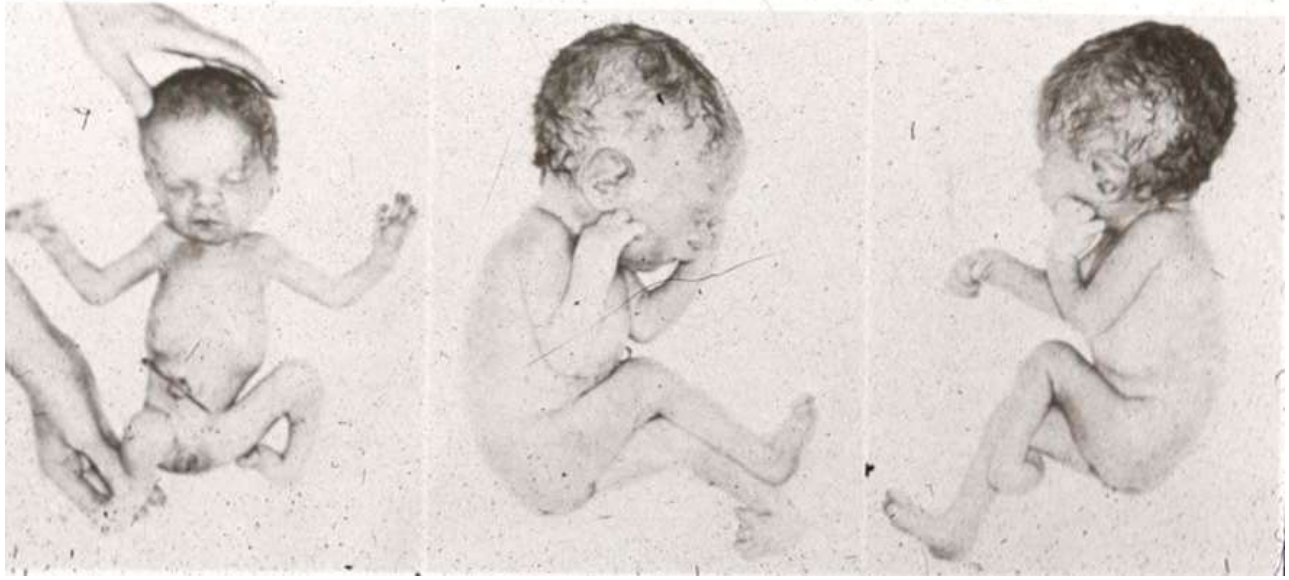




24.1

24.3

24.2



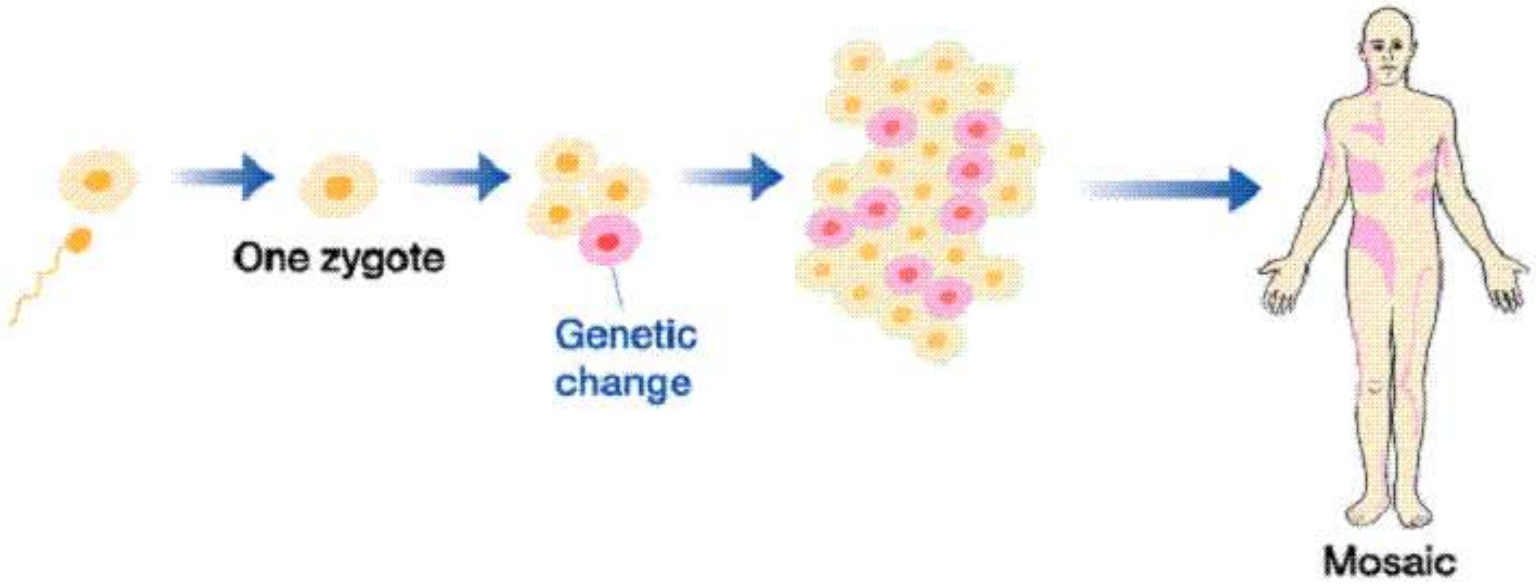
Findings:
CHD
Kidney anomalies
Low-set, malformed ears
Hypertelorism
Foot deformities
Abdominal wall defects

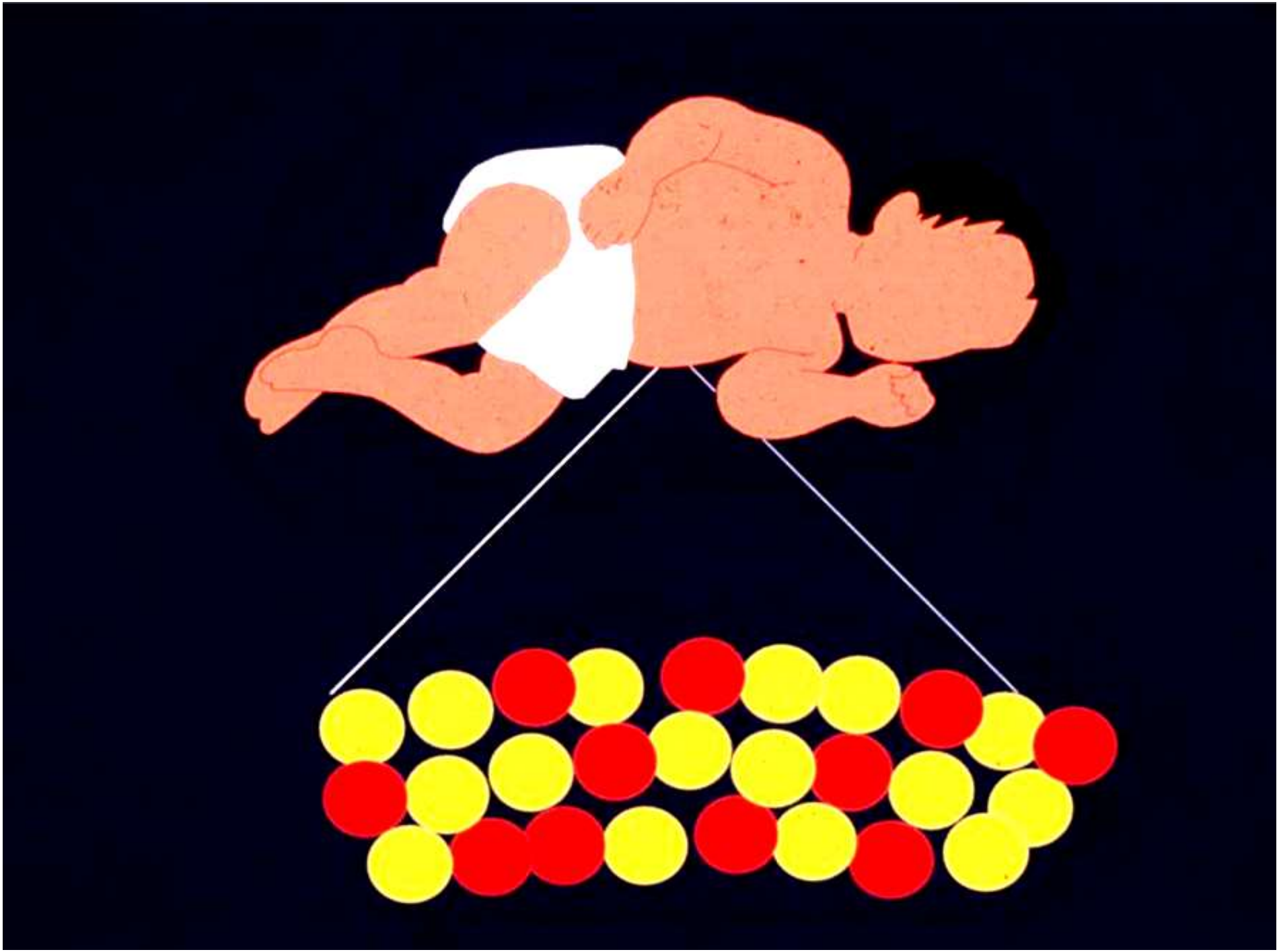
<u>Diandric</u>
Enlarged placenta
Cyst-like placenta
Well-formed fetus with or without microcephaly

<u>Digynic</u>
Macrocephaly
Severe intrauterine growth retardation

Mosaicism

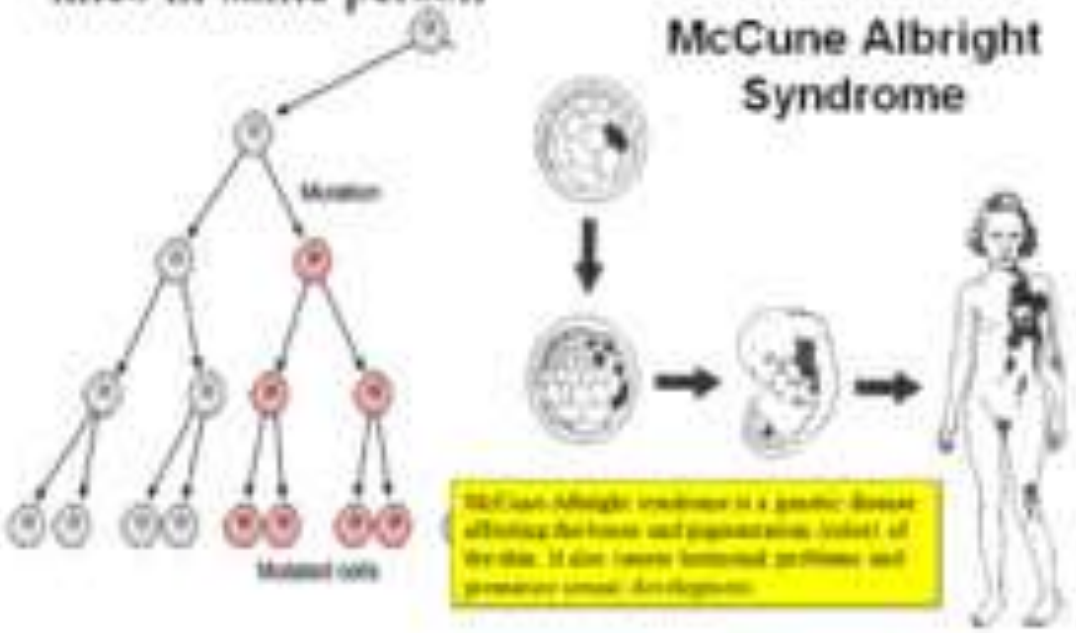
Two or more distinct cell lines from single zygote differing because of mutation or nondisjunction.

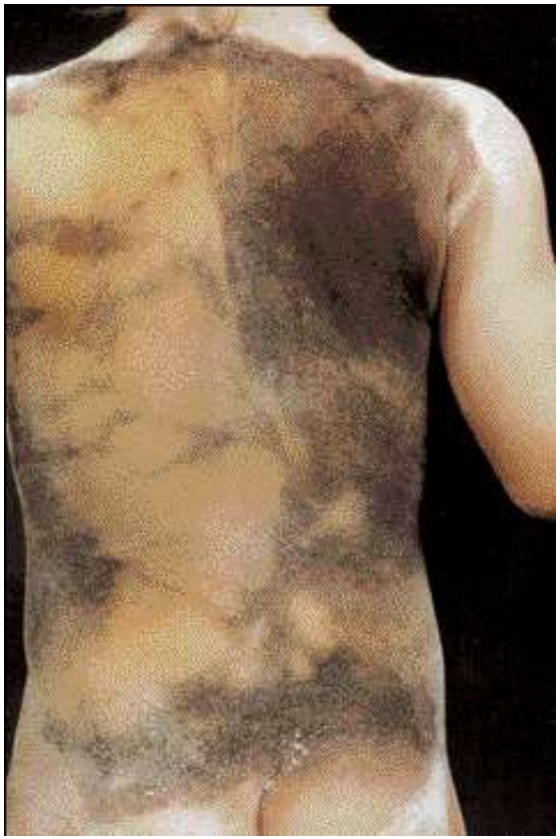

One zygote
Genetic change
Mosaic

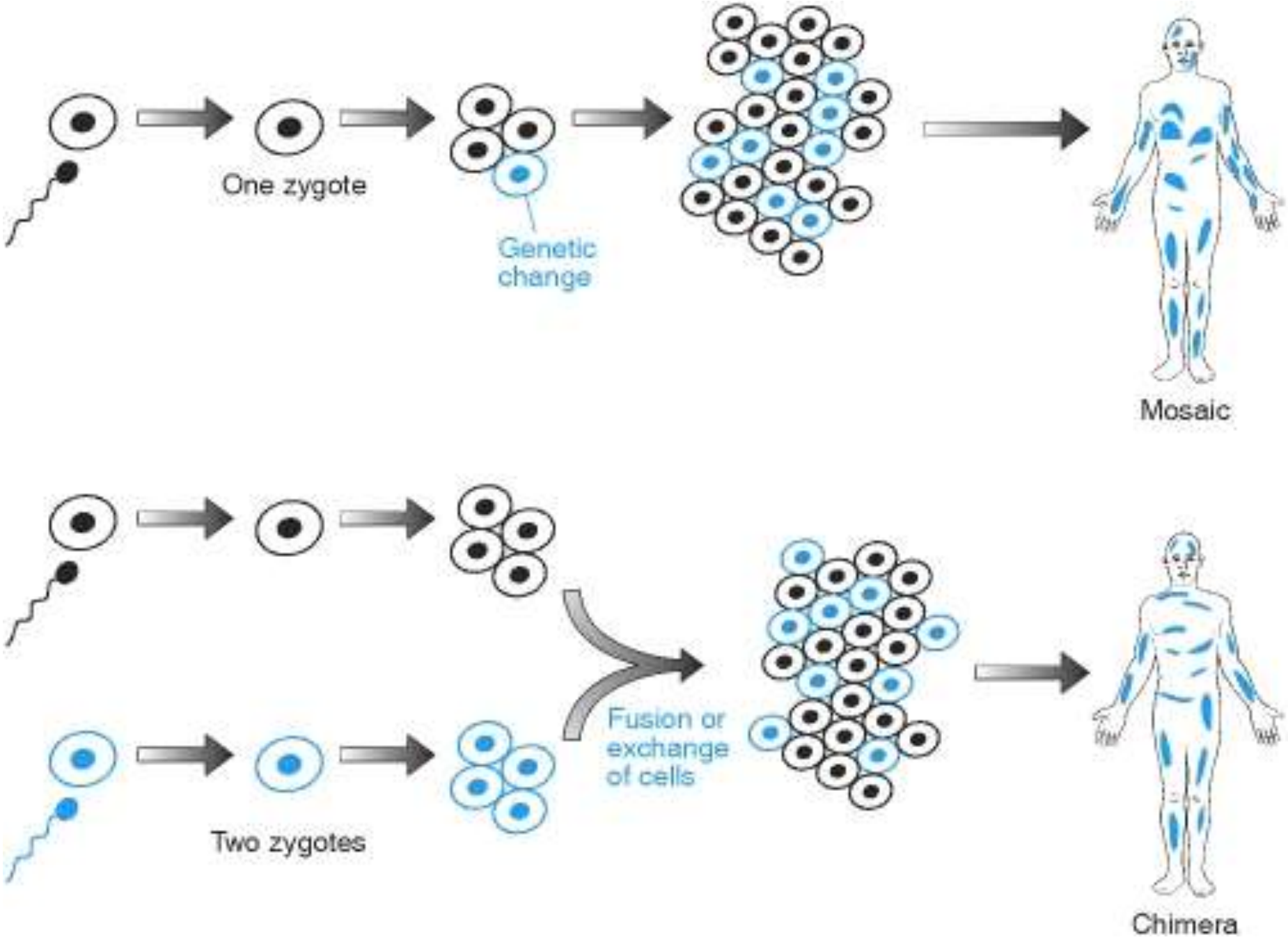


Somatic Mosaicism Gives Different Cell Lines

- *Mosaicism*: occurrence of two or more cell lines in same person






One zygote
Genetic change
Mosaic
Two zygotes
Fusion or exchange of cells
Chimera