Chapter 4

The Chromosome Theory of Inheritance

Sections to study

4.1 Chromosomes: The carriers of genes

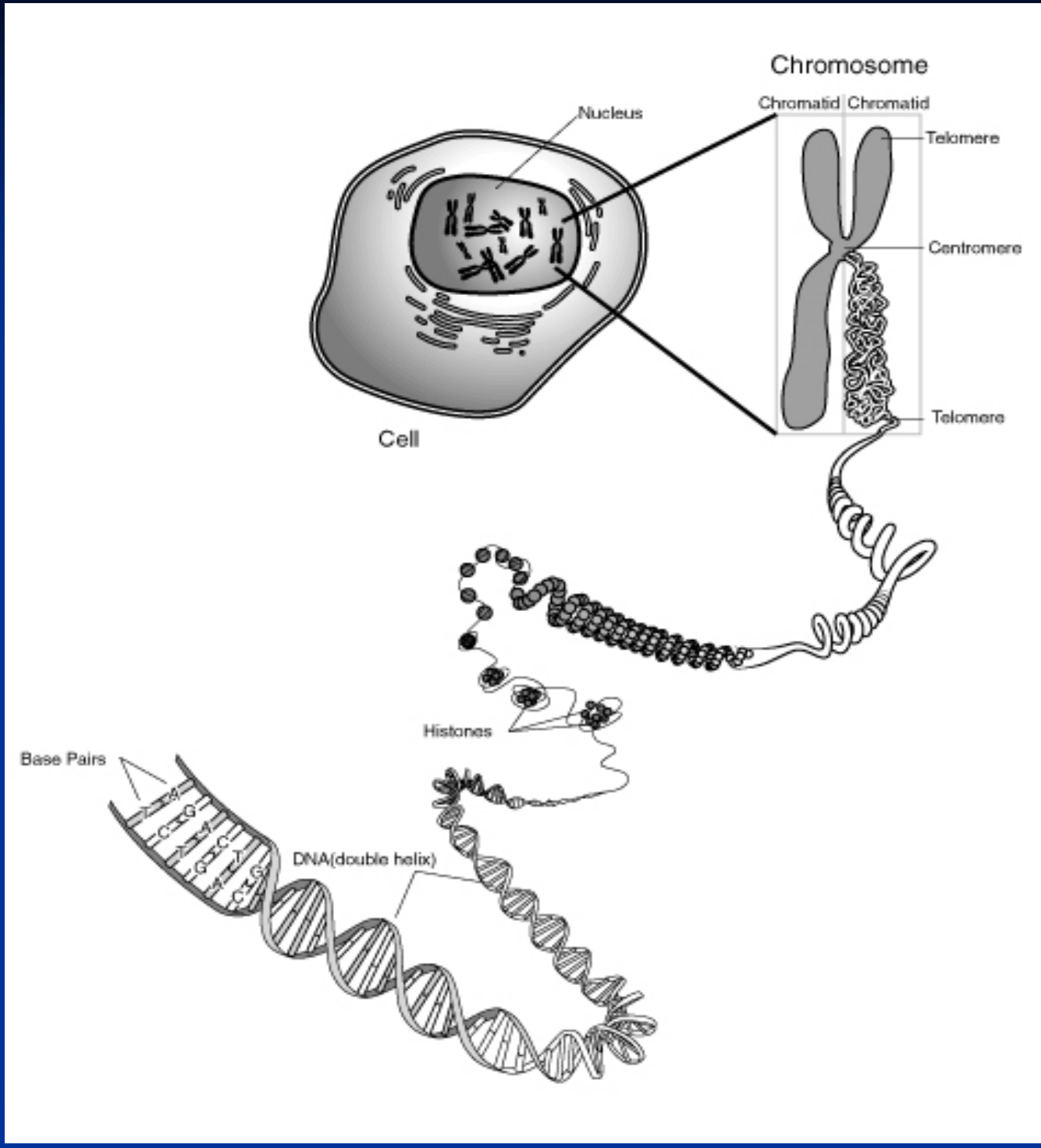
4.2 Mitosis: Cell division that preserves chromosome number

4.3 Meiosis: Cell division that halve chromosome number

4.4 Gametogenesis

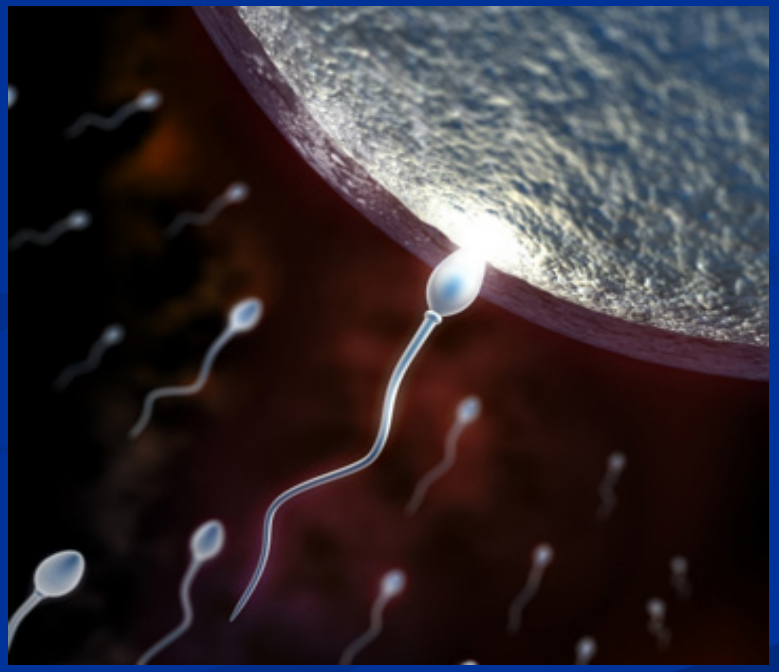
4.5 Validation of the chromosome theory

4.1 Chromosomes: The carriers of genes



- 1667 – Anton van Leeuwenhoek
  - Semen contains spermatozoa (“sperm animals”)
  - Hypothesized that sperm may enter egg to achieve fertilization.

- 1854-1874 – confirmation of fertilization through union of eggs and sperms
  - Observed fertilization in frogs and sea urchins using microscopy.
  - The nuclei are the only elements contributed equally by sperms and eggs.



Evidence that genes reside in chromosomes

- 1880s – innovations in microscopy and staining techniques identified thread-like structures: **chromosomes** ("colored bodies").

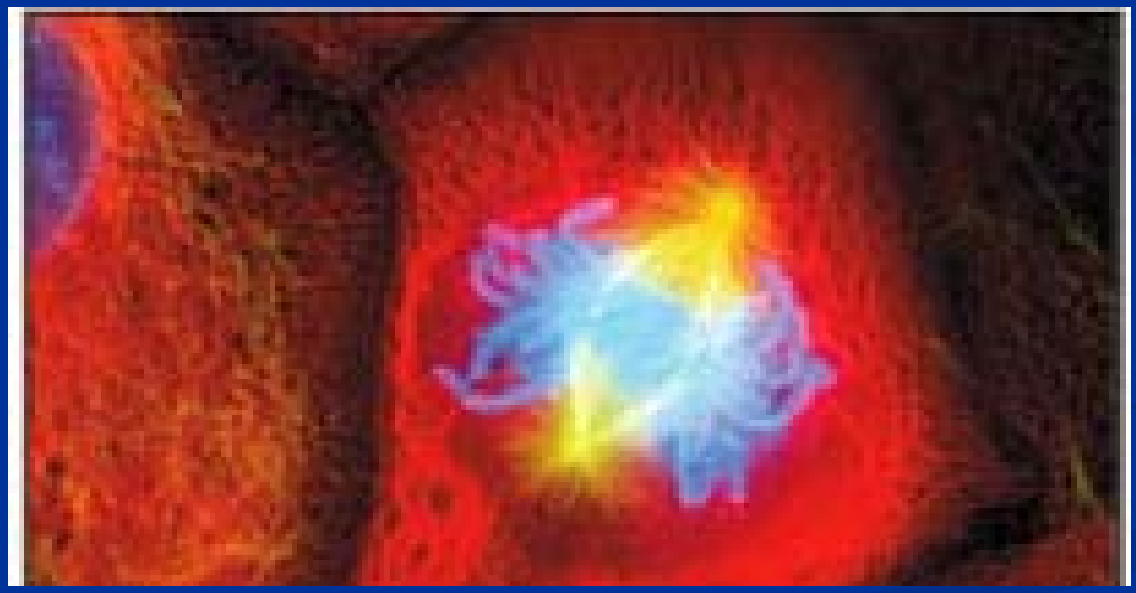


Fig. 4.8

- **Tracking the movement of chromosomes during cell division.**
  - **Somatic cells undergo mitosis – one type of nuclear division that results in two daughter cells containing same number and type of chromosomes as parent cells.**
  - **Germ cells undergo meiosis – one type of nuclear division that results in daughter cells containing half the number of chromosomes as the parents.**

Haploid vs diploid cells

- Gamete contains one-half the number of chromosomes as the zygote.
  - **Haploid** – cells that carry only a single chromosome set
  - **Diploid** – cells that carry two matching chromosome sets
  - ***n*** – the number of chromosomes in a haploid cell
  - ***2n*** – the number of chromosomes in a diploid cell
- At fertilization, haploid gametes produce diploid zygotes.

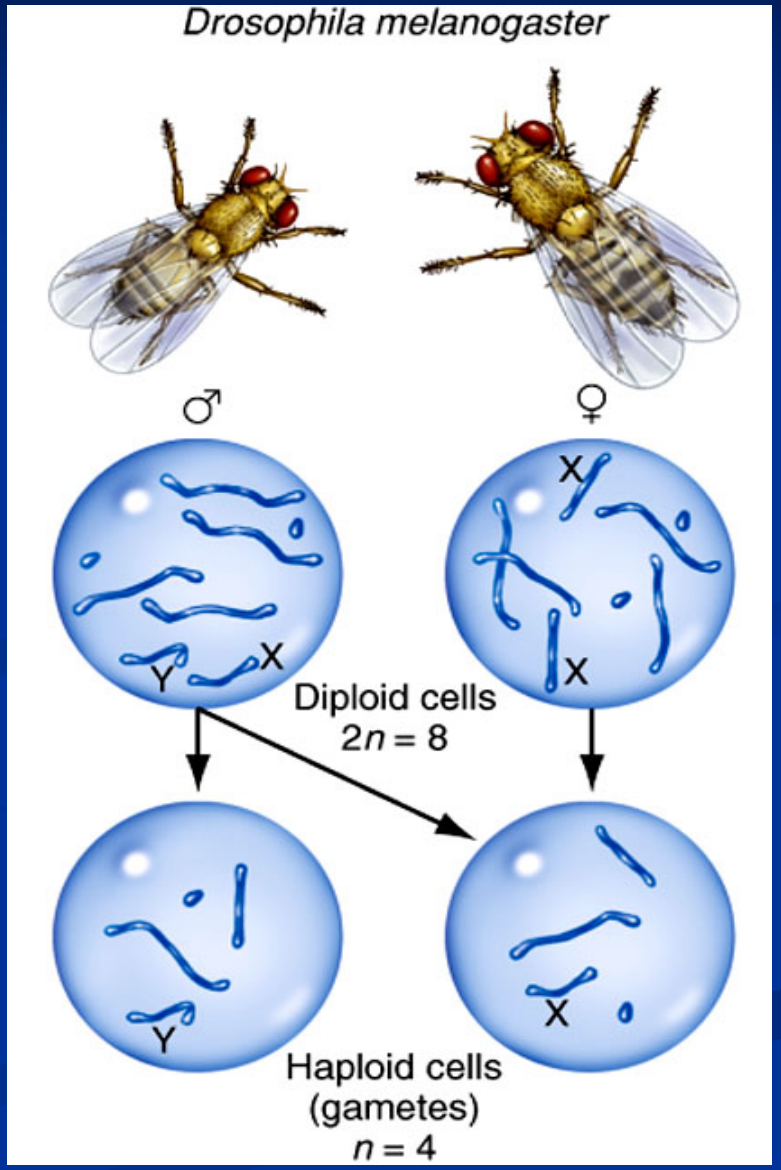


Fig. 4.2

The number and shape of chromosomes vary from species to species

Organism	*n*	*2n*
Drosophila melanogaster	4	8
Drosophila obscura	5	10
Drosophila virilus	6	12
Peas	7	14
Macaroni wheat	14	28
Giant sequoia trees	11	22
Goldfish	47	94
Dogs	39	78
Humans	23	46

Anatomy of a chromosome

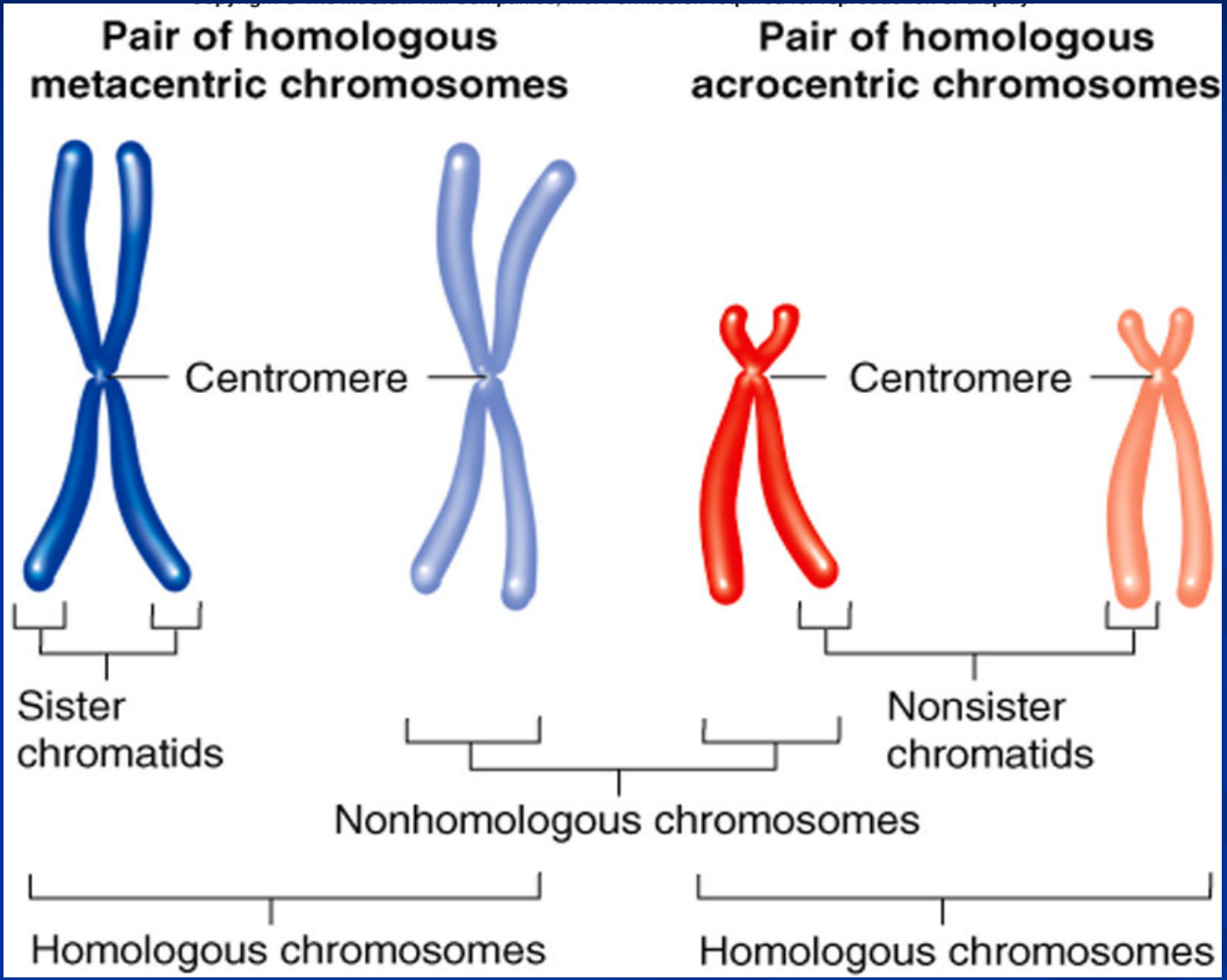
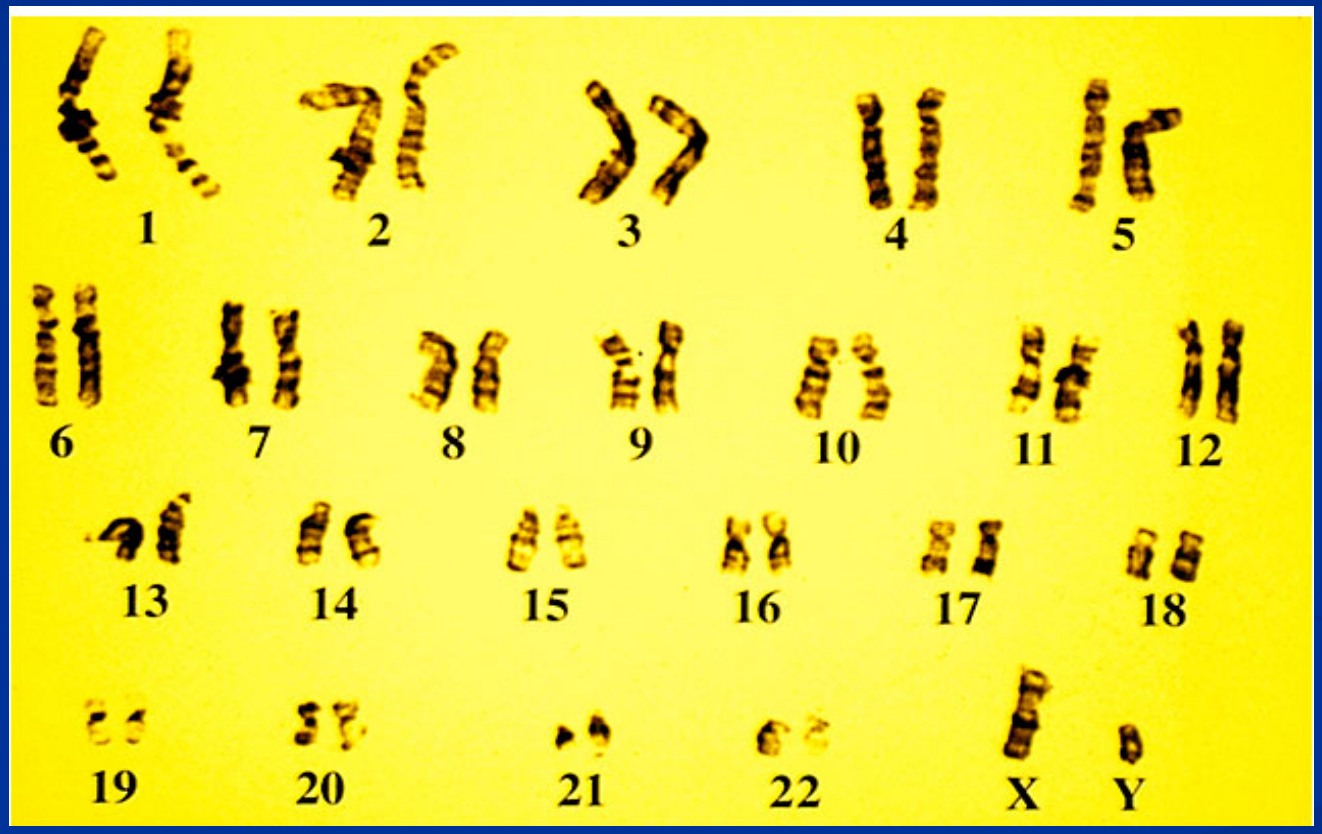


Fig. 4.3

Homologous chromosomes (homologs)

- Each pair matches in size, shape, and banding pattern.
- Contain the same set of genes.
- Genes may carry different alleles.
- Nonhomologous chromosomes carry completely unrelated sets of genes.

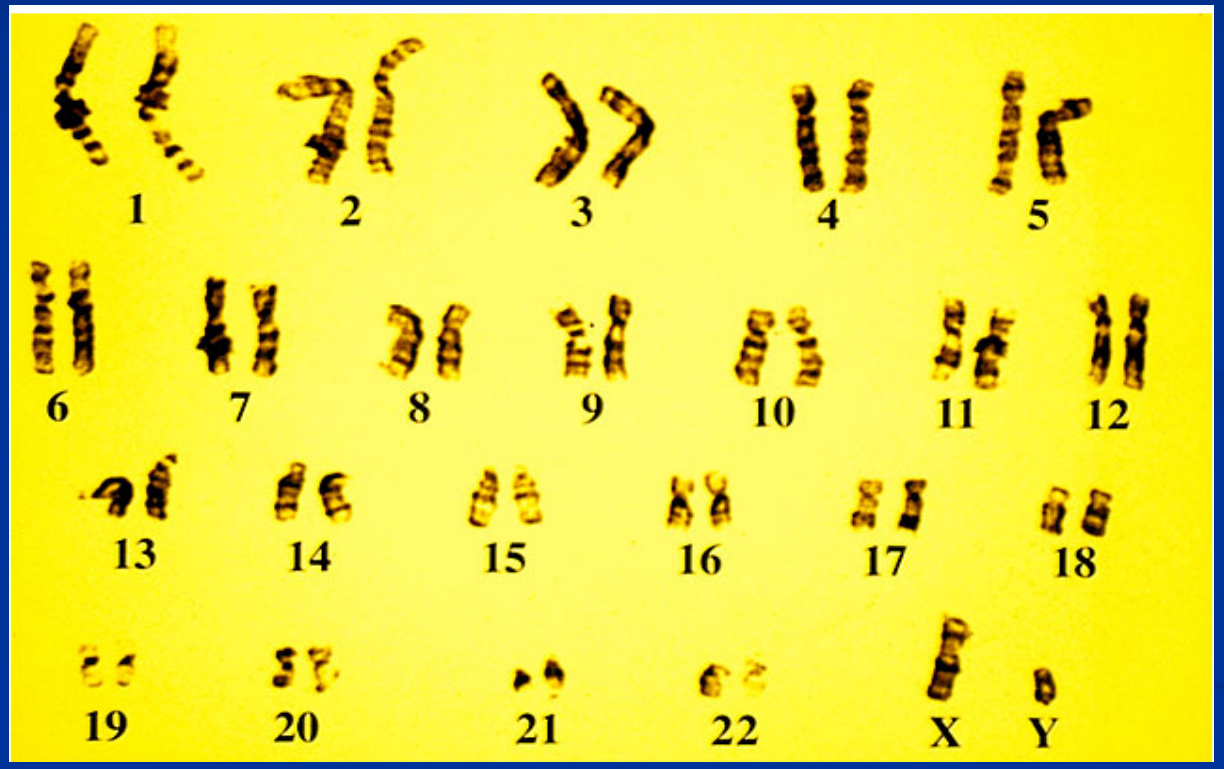
Karyotype: The visual description of the complete set of chromosomes in one cell of an organism.



Karyotype of a human male

Fig 4.4

Karyotypes can be produced by cutting micrograph images of stained chromosomes and arranging them in matched pairs of decreasing size.



Autosomes – chromosomes in matching pairs
Sex chromosomes - unmatched chromosomes

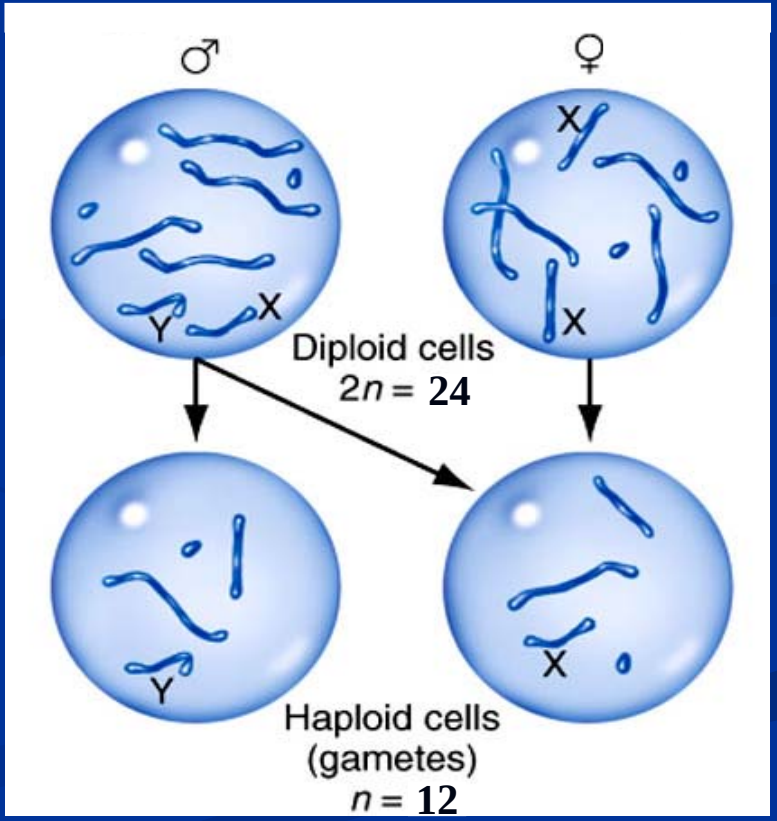
Fig 4.4

Chromosomes carry information for determining trait

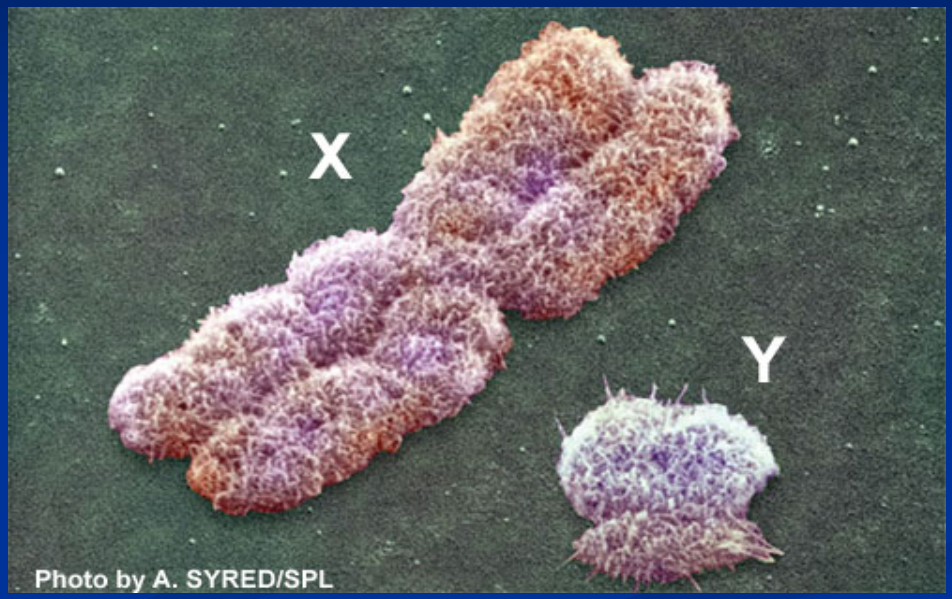
- In many species, one pair of chromosome determines an individual's sex.
- **Walter Sutton** studied chromosome dynamics during spermatogenesis in great lubber grasshopper.

Walter S. Sutton
(1877-1916)

- Prior to meiosis, precursor cells in the testes contain 24 chromosomes: 11 matched pairs (**autosomes**) and 2 unmatched chromosomes X and Y (**sex chromosomes**).
- Sperms contain 11 chromosomes and X or Y in equal numbers.
- After fertilization
  - Cells with XX were females.
  - Cells with XY were males.
- **Conclusion:** X and Y chromosomes determine sex.



- **Sex chromosomes**
  - Provide basis for sex determination
  - One sex has matching pair.
  - The other sex has one of each type of chromosome.



Human X and Y chromosome

Fig. 4.6 a

Sex determination in humans

- Children receive only an X chromosome from mother but X or Y from father.
- Male: Female ratio is 1:1.
  - Caucasian 1.06; African-American 1.025; Korea 1.15 (1969 census data)

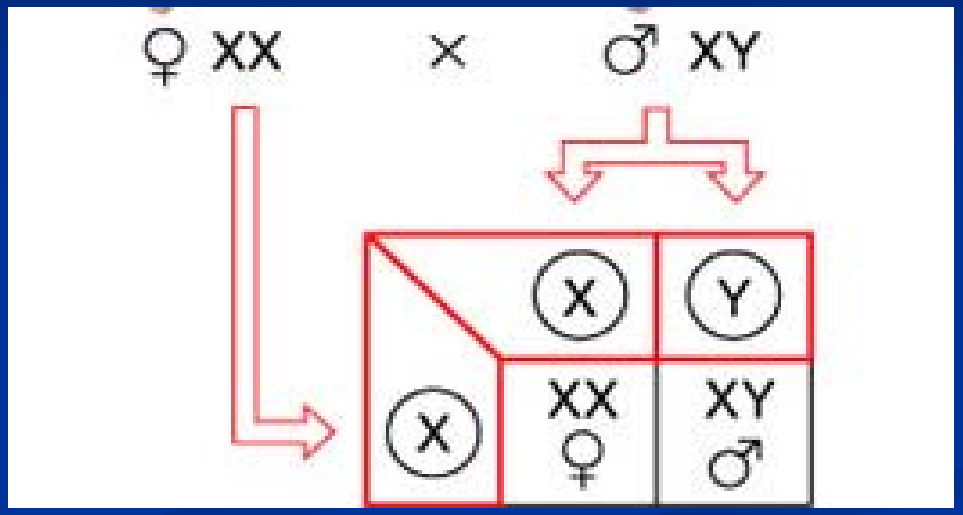
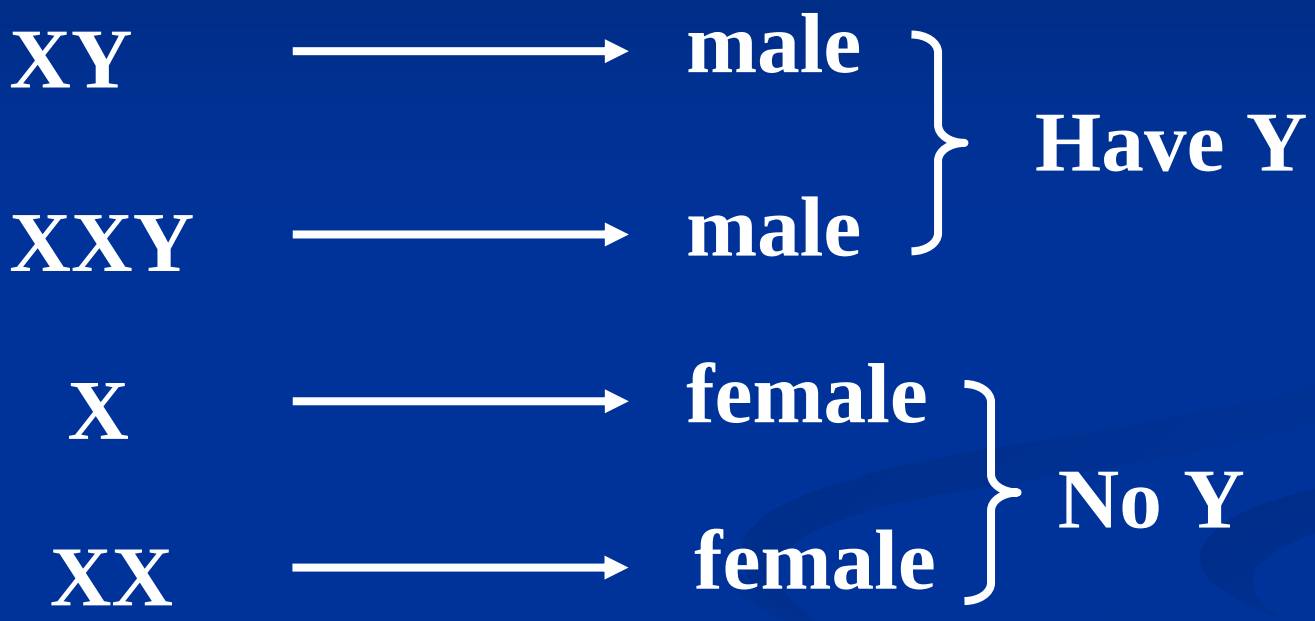


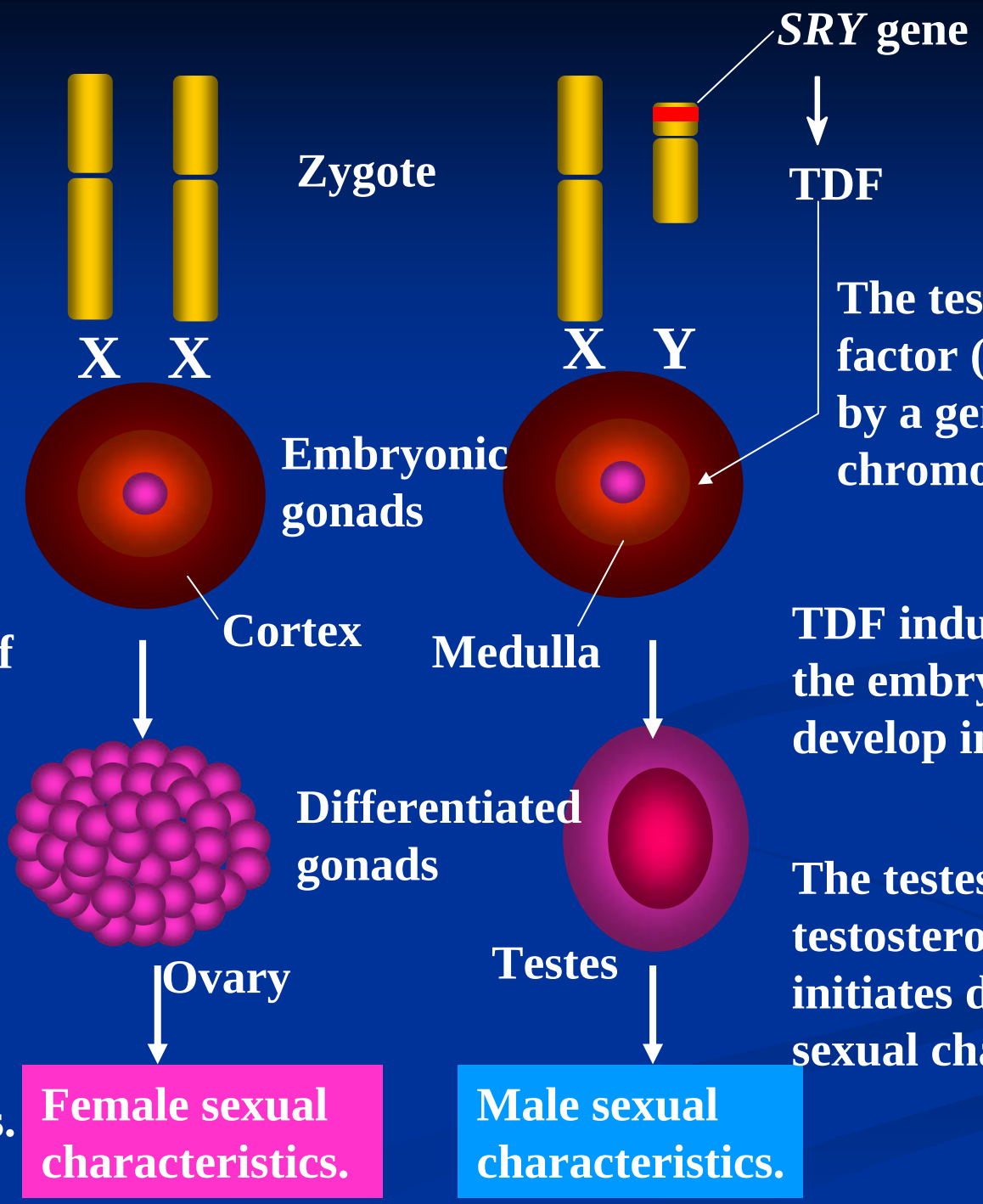
Fig. 4.6 b

Role of X and Y chromosomes in human sex determination



Conclusion:

Y chromosome determines maleness.



In the absence of a Y chromosome, no TDF is produced

The testis-determining factor (TDF) is produced by a gene on the Y chromosome.

The lack of TDF allows the cortex of the embryonic gonads to develop into ovaries.

TDF induces the medulla of the embryonic gonads to develop into testes.

In the absence of testosterone, the embryo develops female characteristics.

The testes produce testosterone, a hormone that initiates development of male sexual characteristics.

People carry abnormal number of sex chromosomes are not rare

Chromosomes	Syndrome	Frequency at birth
Sex chromosomes, females		
XO, monosomic	Turner	1/5000
XXX, trisomic		1/700
XXXX, tetrasomic		
XXXXX, pentasomic		
Sex chromosomes, males		
XYY, trisomic	Normal	1/10,000
XXYY, tetrasomic	Klinefelter	1/500
XXXY, tetrasomic		
XXXXY, pentasomic		
XXXXXY, hexasomic		

About 0.4% of all babies born have a detectable chromosomal abnormality that generates a detrimental phenotype.

Variation between species in how chromosomes determine an individual's sex

Chromosomes	Females	Males	Organism
XX-XY	XX	XY	Mammals, *Drosophila*
XX-XO	XX	XO	Moths, *C.elegans*
ZZ-ZW	ZW	ZZ	Birds, Butterflies

Table 4.2

In fruit flies, the ratio of X chromosomes to autosomes determines sex.

TABLE 4.1 Sex Determination in Fruit Flies and Humans

	Complement of Sex Chromosomes						
	XXX	XX	XXY	XO	XY	XYY	OY
Drosophila	Dies	Normal female	Normal female	Sterile male	Normal male	Normal male	Dies
Humans	Nearly normal female	Normal female	Klinefelter male (sterile); tall, thin	Turner female (sterile); webbed neck	Normal male	Normal or nearly normal male	Dies

Humans can tolerate extra X chromosomes better than *Drosophila* (compare the fate of XXX individuals). Complete absence of an X chromosome is lethal to both fruit flies and humans because this chromosome carries essential genes not found on other chromosomes. Additional Y chromosomes have little effect in either species.

4.2 Mitosis: Cell division that preserves chromosome number

- **Cell cycle** – The repeating pattern of cell growth and division.
  - Alternates between interphase and mitosis

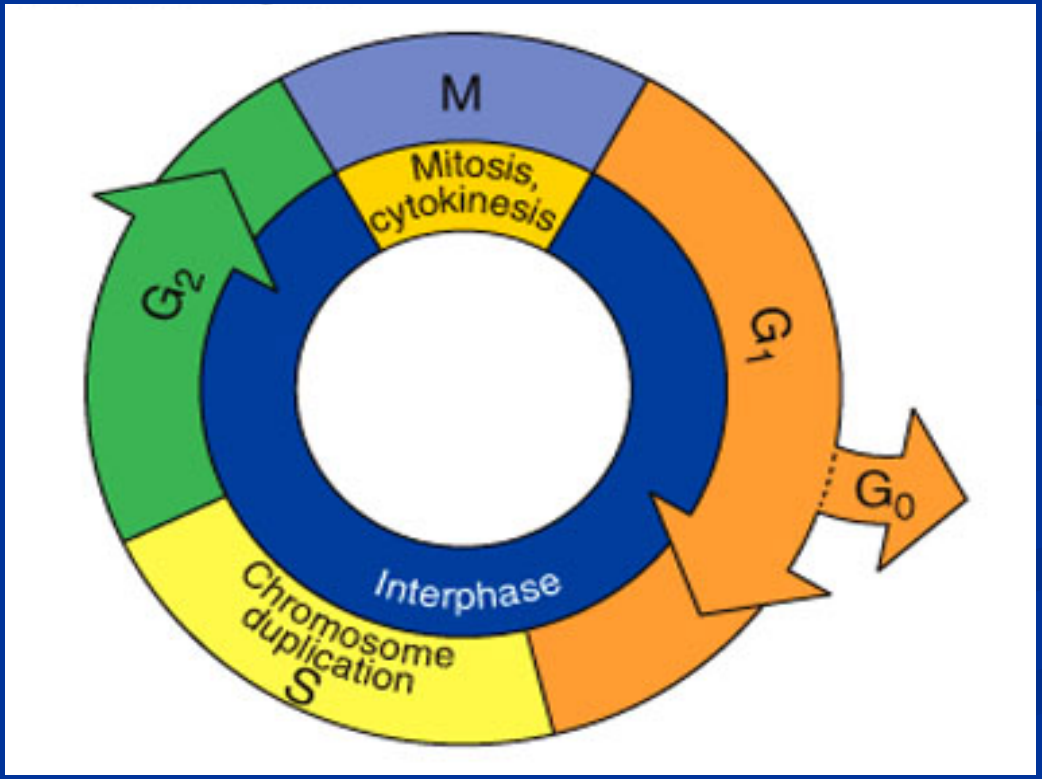
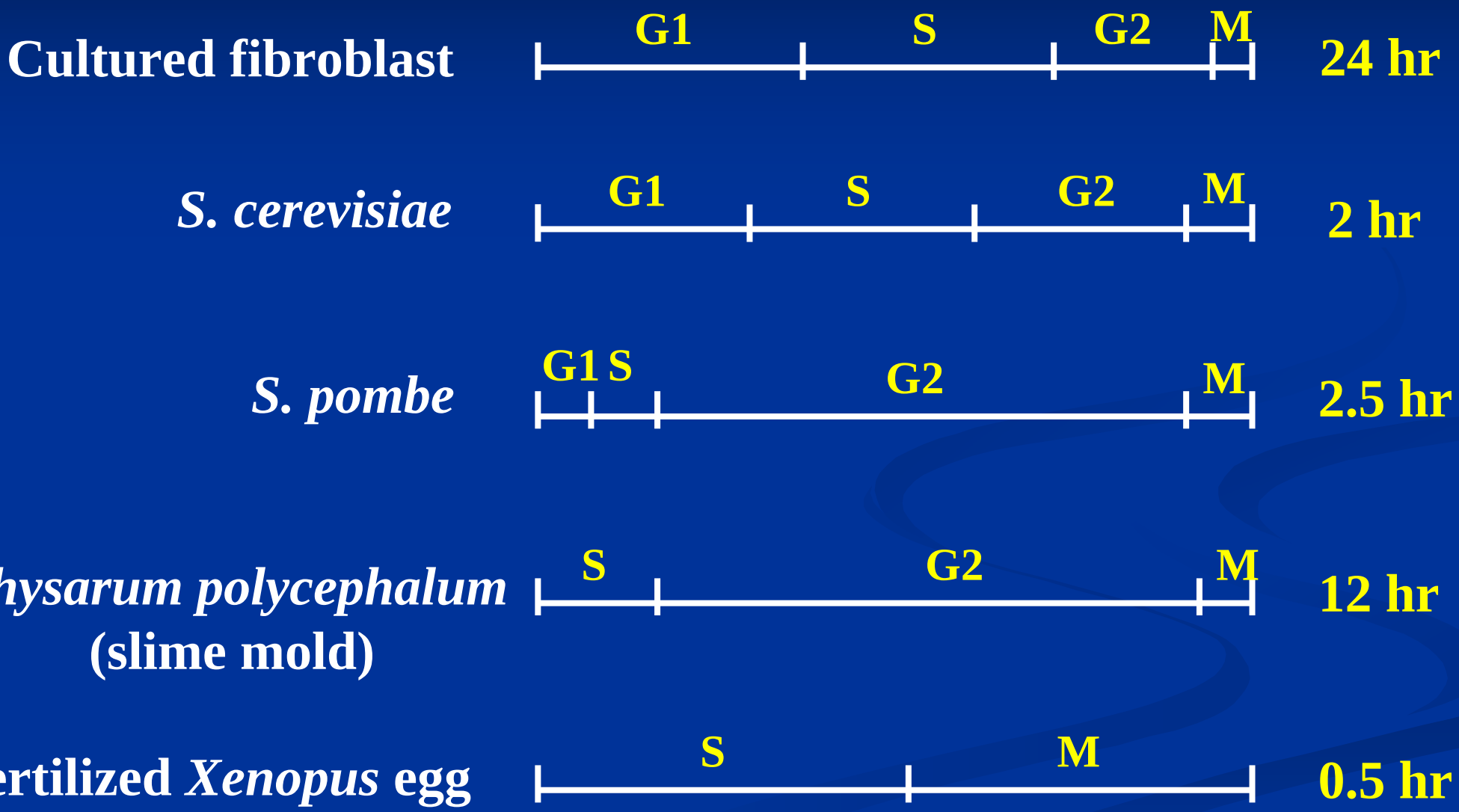


Fig. 4.7a

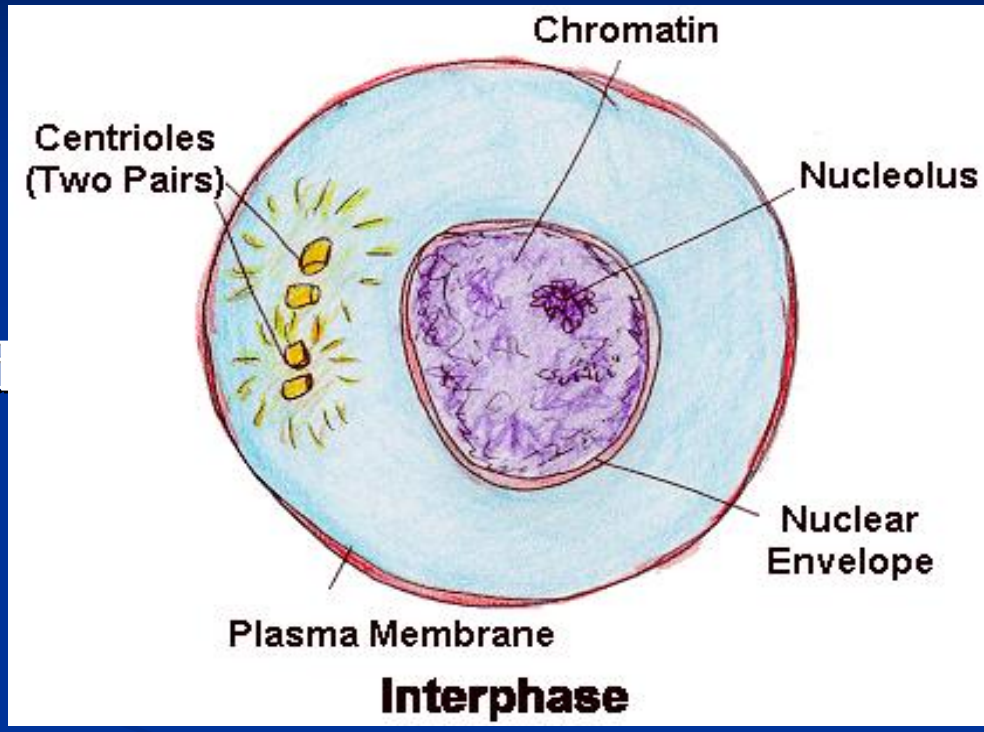
- **Interphase**: Period of cell cycle between divisions. Cells grow and replicate chromosomes
  - **G1** – gap phase – birth of cell to onset of chromosome replication/cell growth
  - **S** – synthesis phase – duplication of DNA
  - **G2** – gap phase – end of chromosome replication to onset of mitosis
- **Mitosis**: The division of the nucleus.
  - Prophase
  - Metaphase
  - Anaphase
  - Telophase
- **Cytokinesis**: The division of the cytoplasm.

Cell cycle duration in various cell types



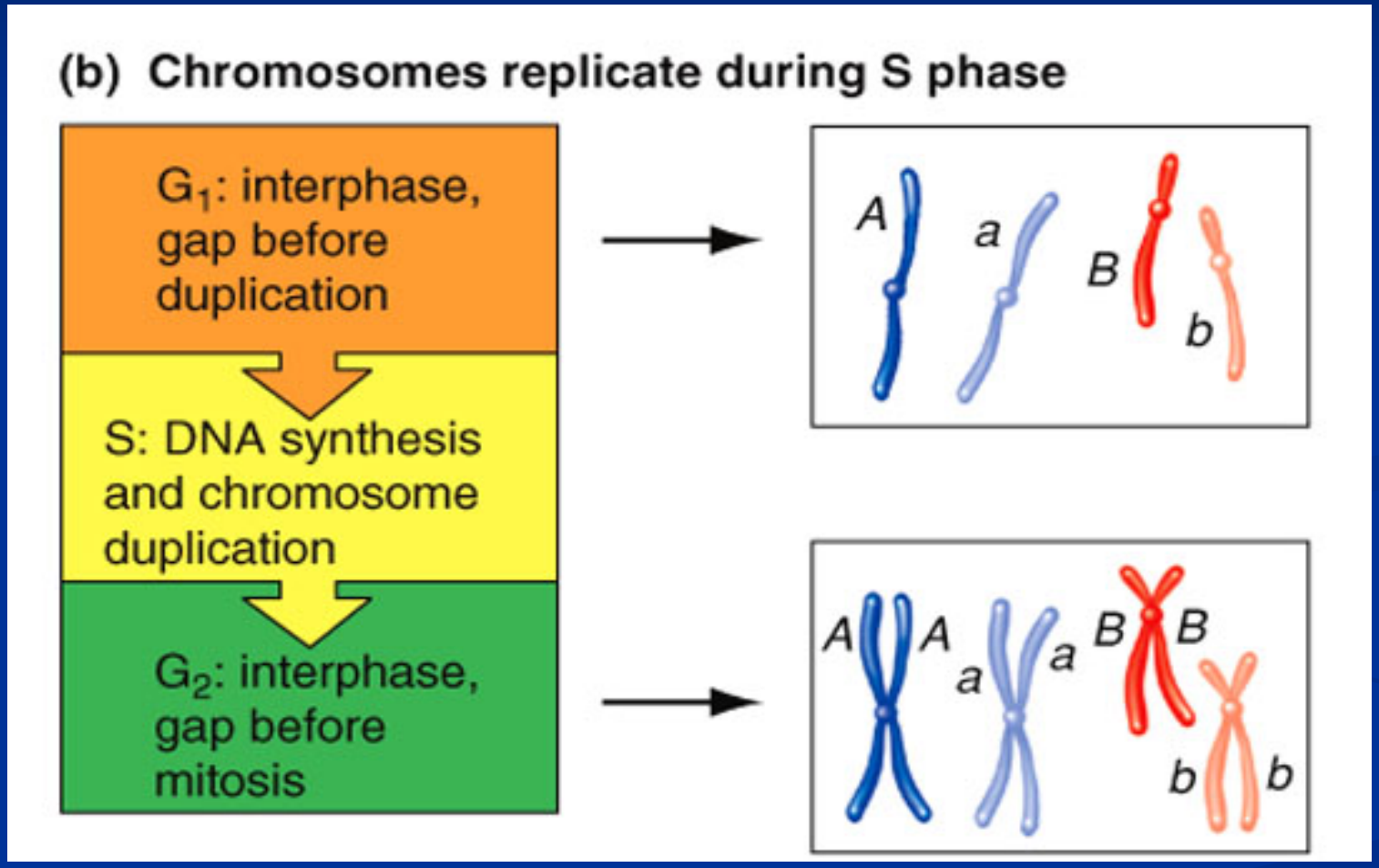
Interphase

- Outside of nucleus
  - Formation of microtubules radiating out into cytoplasm crucial for interphase processes
    - **Centrosome** – organizing center for microtubules located near nuclear envelope
    - **Centrioles** – pair of small darkly stained bodies at center of centrosome in animals (not found in plants)



- Within nucleus
  - G1, S, and G2 phase –chromosome replication

Chromosome replication during S phase



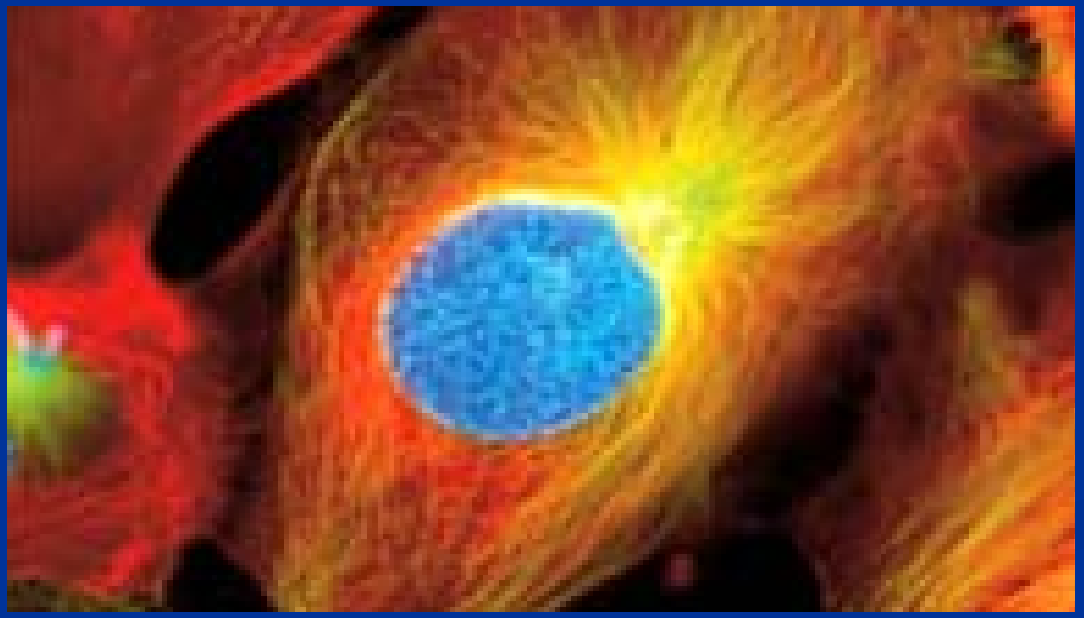
Synthesis of chromosomes

Note the formation of sister chromatids

Fig. 4.7 b

Mitosis – Sister chromatids separate

- Prophase – chromosomes condense
  - Inside nucleus
    - Chromosomes condense into structures suitable for replication.
    - Nucleoli begin to break down and disappear.
  - Outside nucleus
    - Centrosomes which replicated during interphase move apart and migrate to opposite ends of the nucleus.
    - Interphase microtubules disappear and are replaced by microtubules that rapidly grow from and contract back to centrosomal organizing centers.



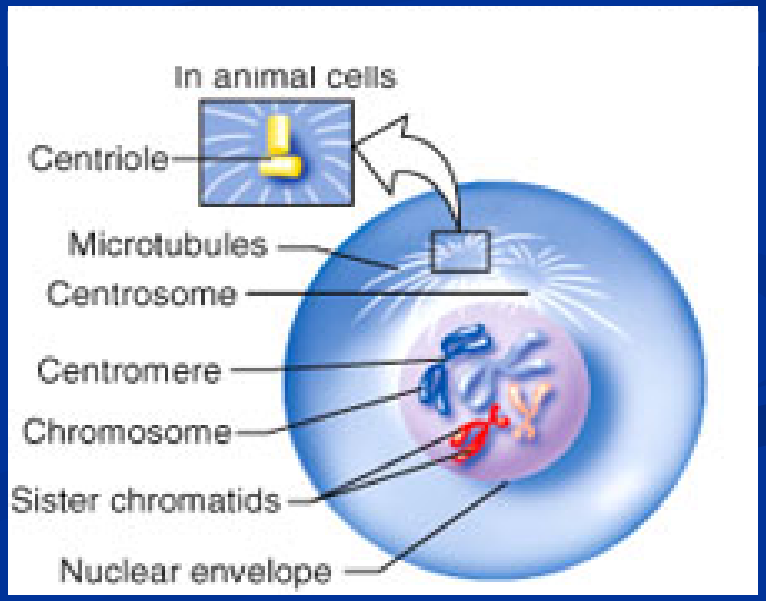
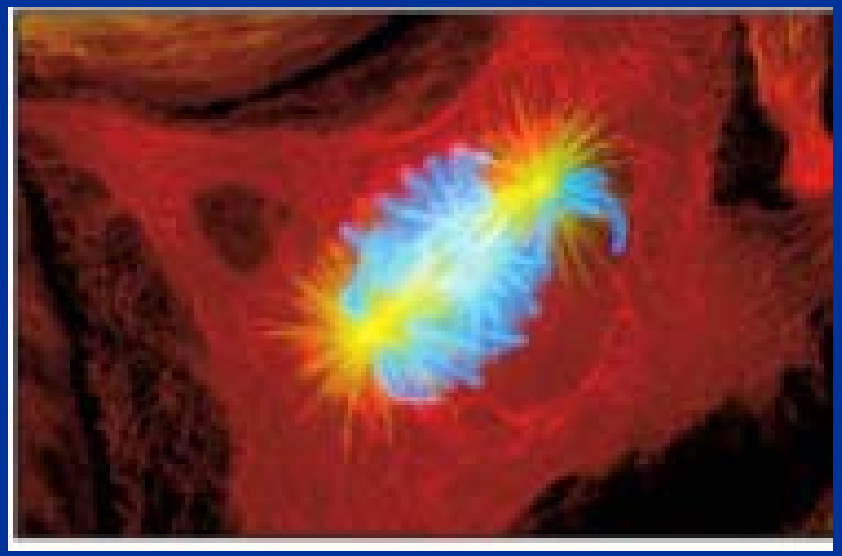


Fig. 4.8 a

- **Prometaphase**
  - Nuclear envelope breaks down
  - Microtubules invade nucleus
  - Chromosomes attach to microtubules through kinetochore
  - Mitotic spindle – composed of three types of microtubules
    - Kinetochore microtubules – centrosome to kinetochore
    - Polar microtubules – centrosome to middle of cell
    - Astral microtubules – centrosome to cell's periphery



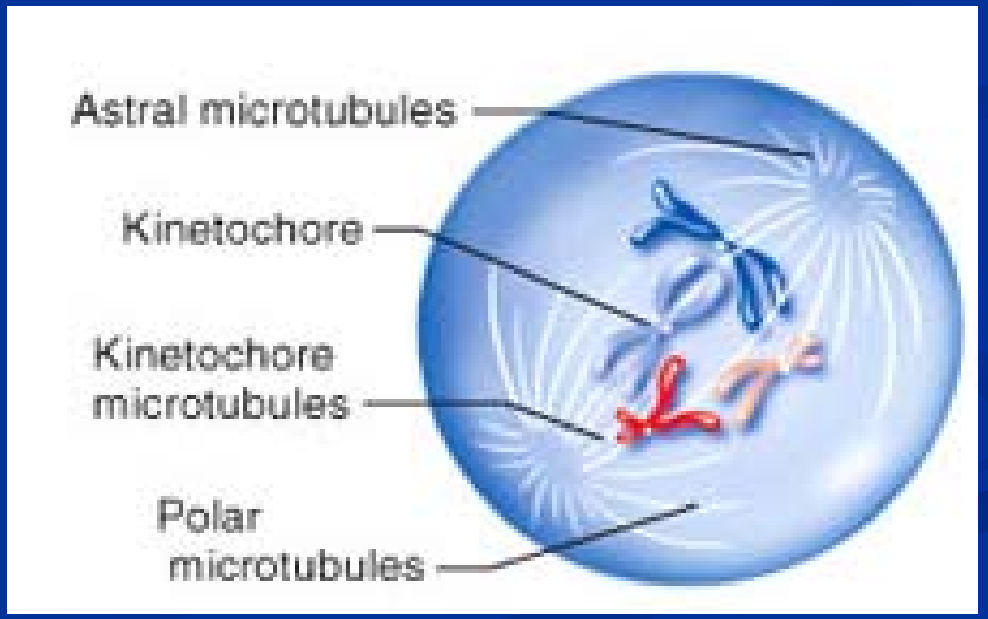
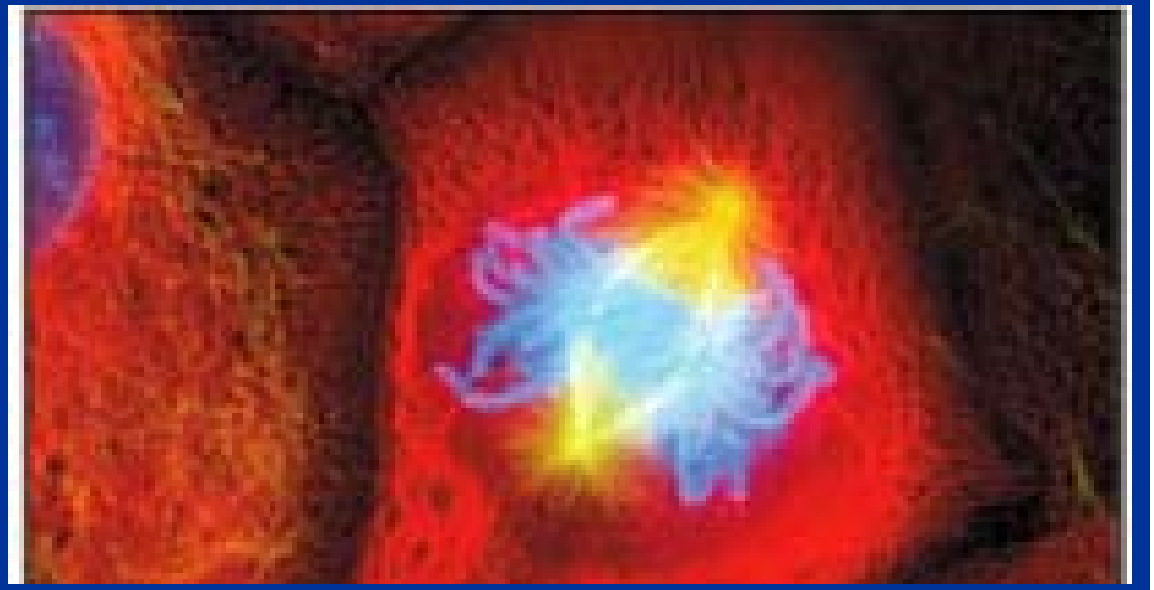


Fig. 4.8b

- **Metaphase – middle stage**
  - **Chromosomes move towards imaginary equator called metaphase plate**



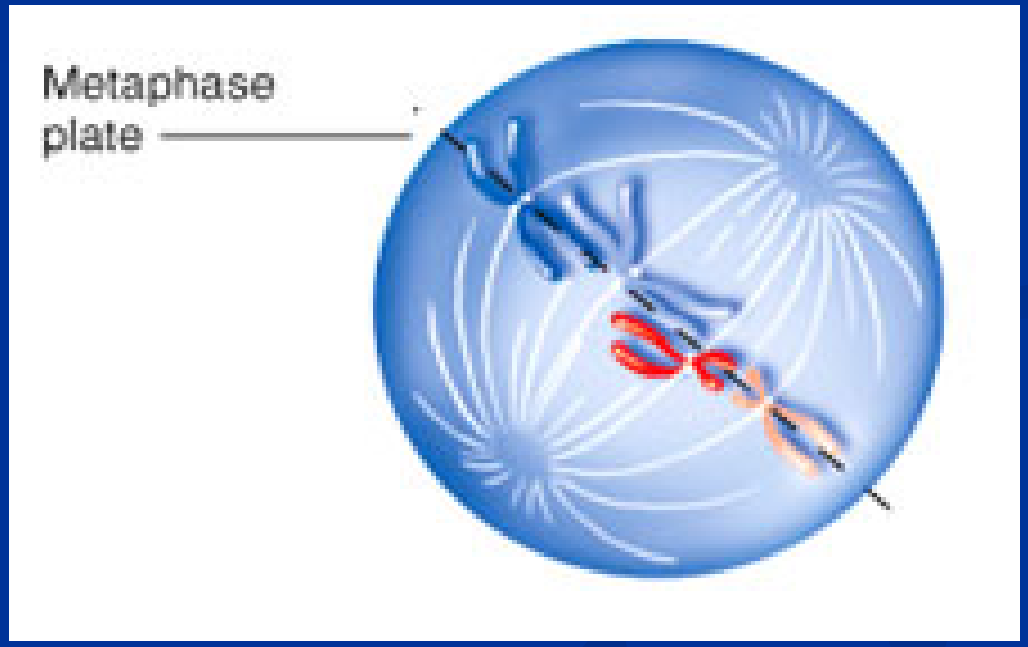
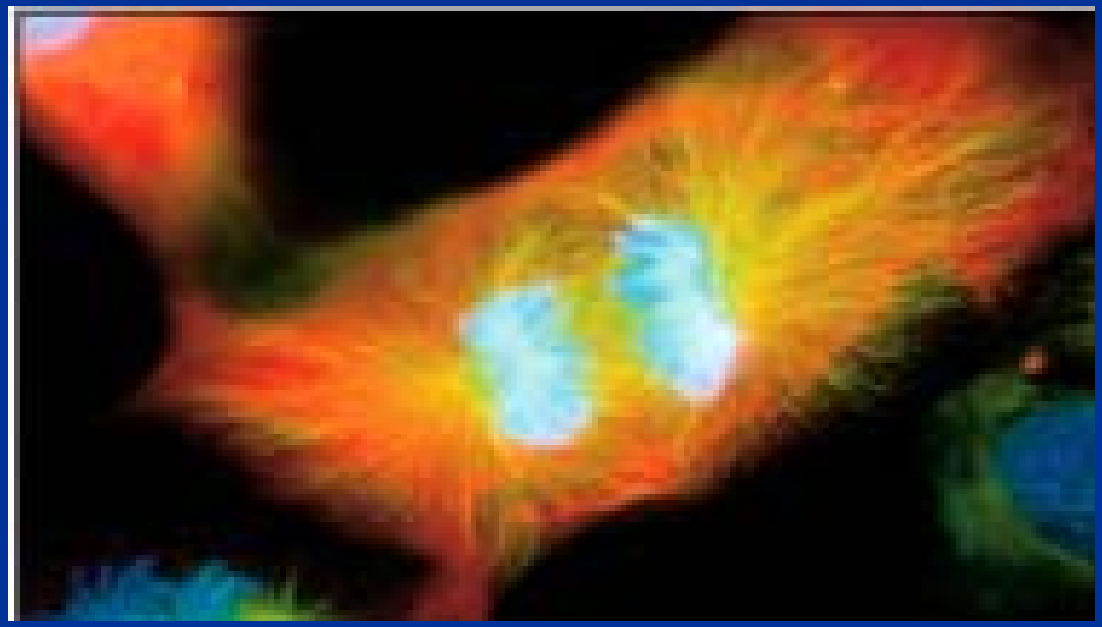


Fig. 4.8 c

- **Anaphase**
  - **Separation of sister chromatids allows each chromatid to be pulled towards spindle pole connected to by kinetochore microtubule.**



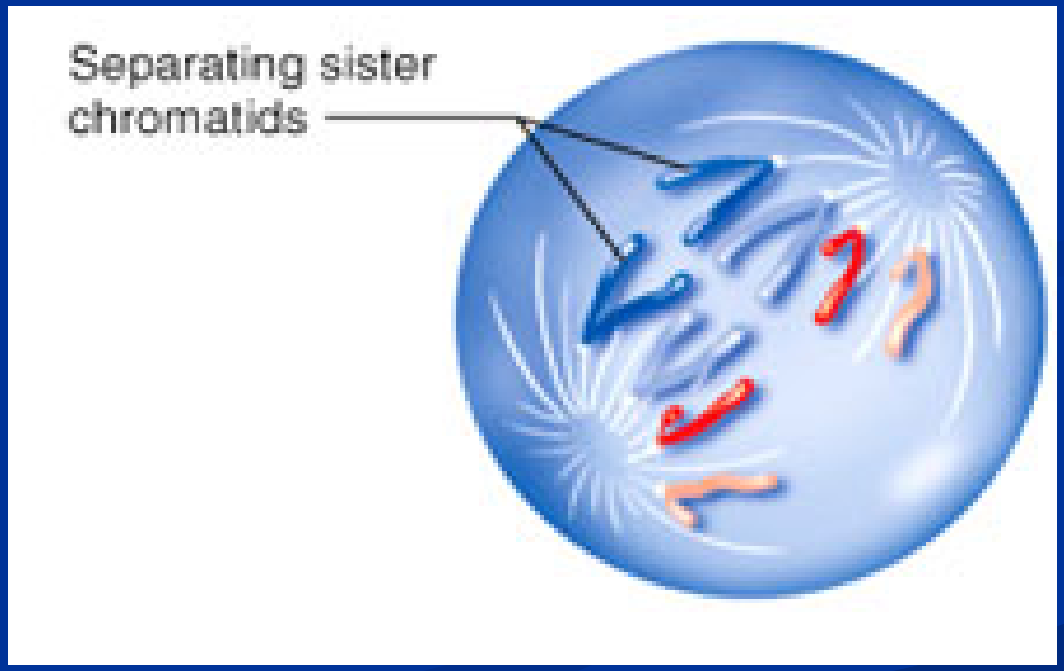
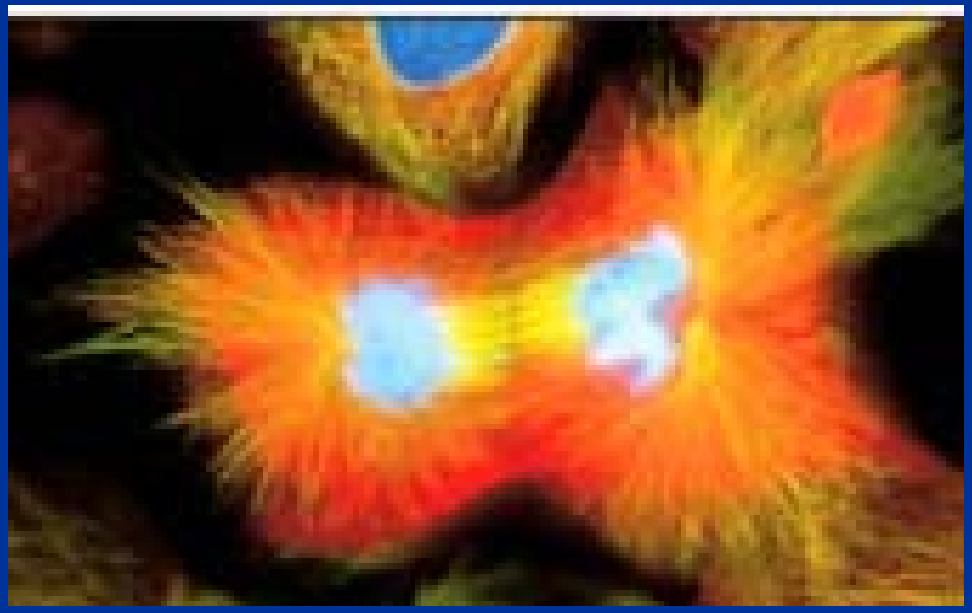


Fig. 4.8 d

- **Telophase**
  - Spindle fibers disperse
  - Nuclear envelope forms around group of chromosomes at each pole
  - One or more nucleoli reappear
  - Chromosomes decondense
  - Mitosis complete



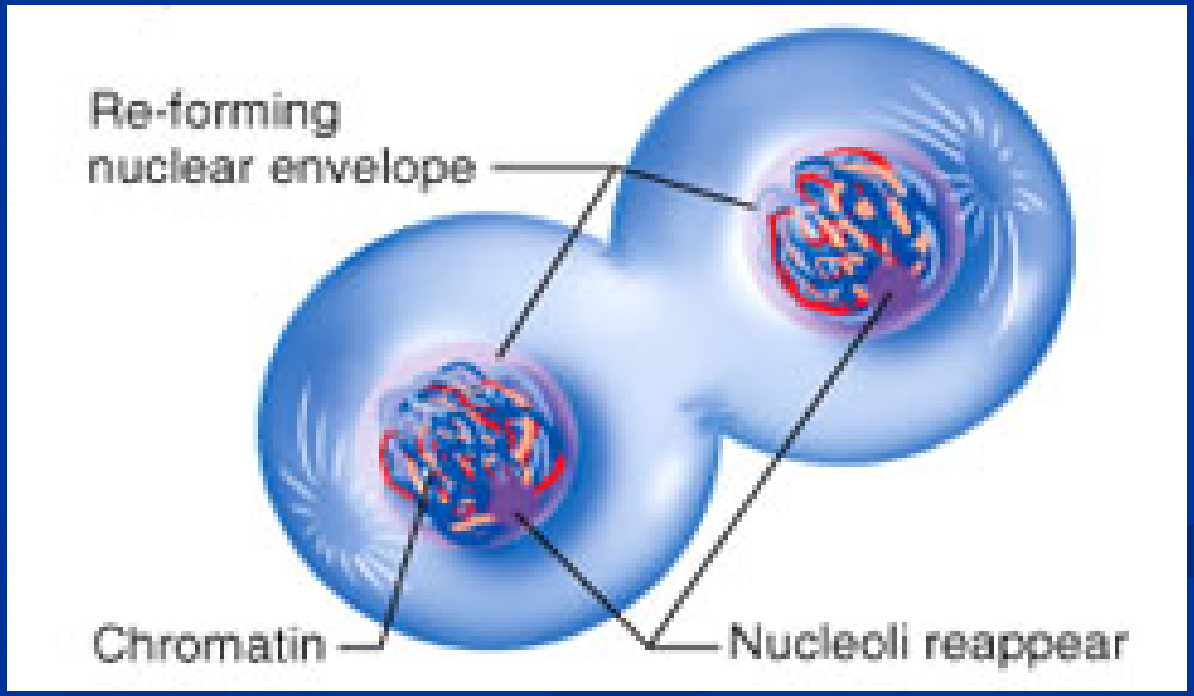
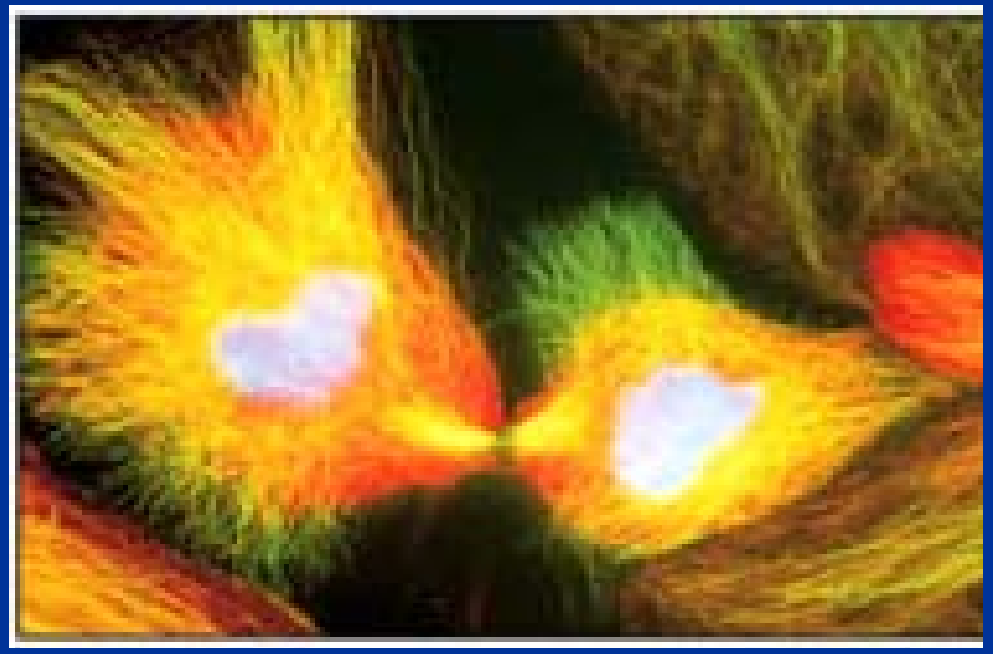


Fig. 4.8 e

- **Cytokinesis - cytoplasm divides**
  - **Starts during anaphase and ends in telophase**



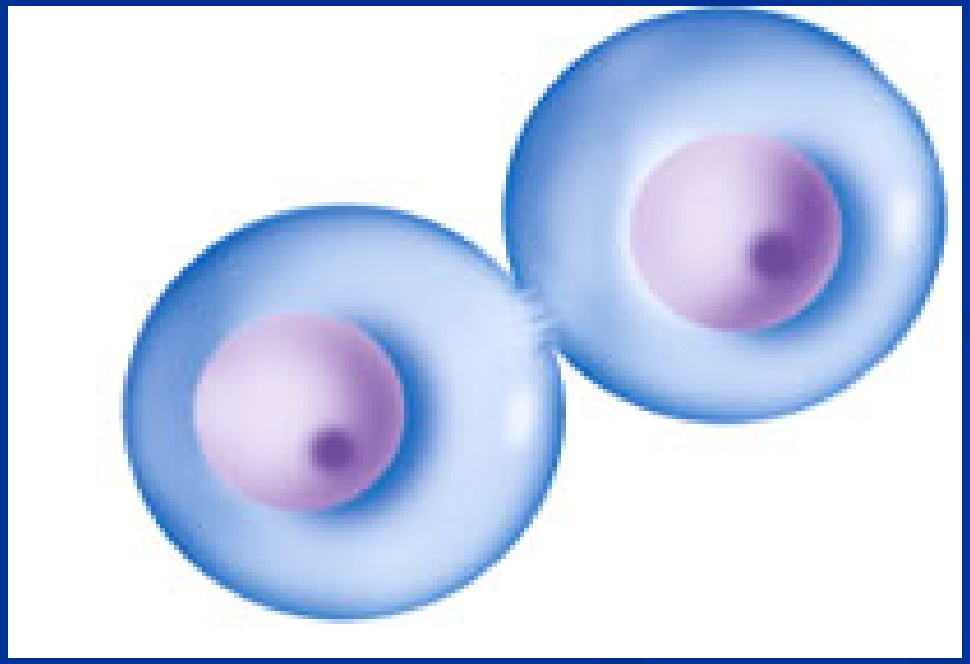


Fig. 4.8 f

Checkpoints ensure correct chromosome segregation

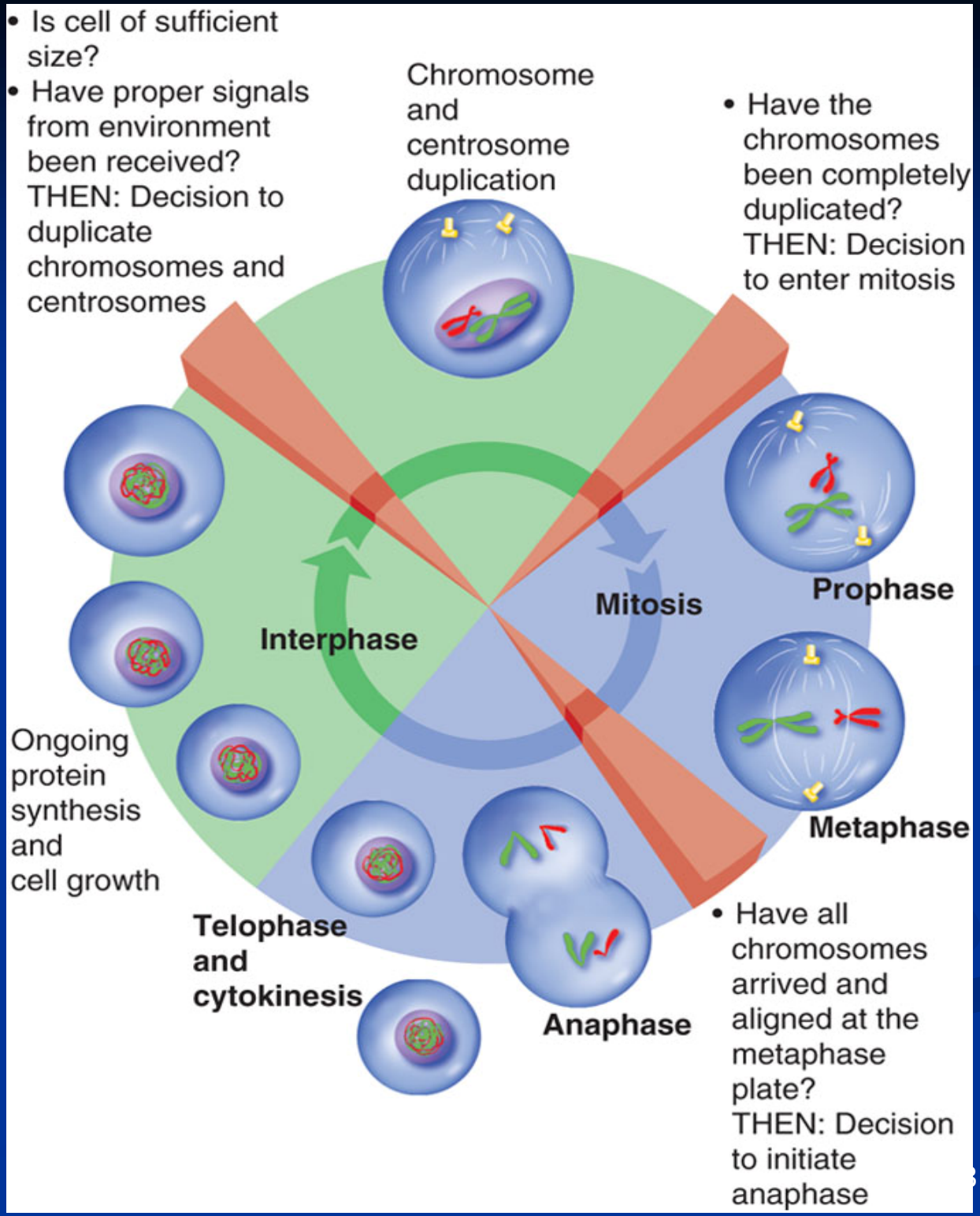


Fig. 4.11

4.3 Meiosis: Cell division that halve chromosome number

- **Somatic cells**: Cells that divide mitotically and make up vast majority of organism's tissues.
- **Germ cells**: Specialized cells for the production of gametes.
  - Arise during embryonic development in animals and floral development in plants.
  - Undergo meiosis to produce haploid gametes.
  - Gametes unite with gamete from opposite sex to produce diploid offspring.

Meiosis
Chromosomes replicate once.
Nuclei divide twice.

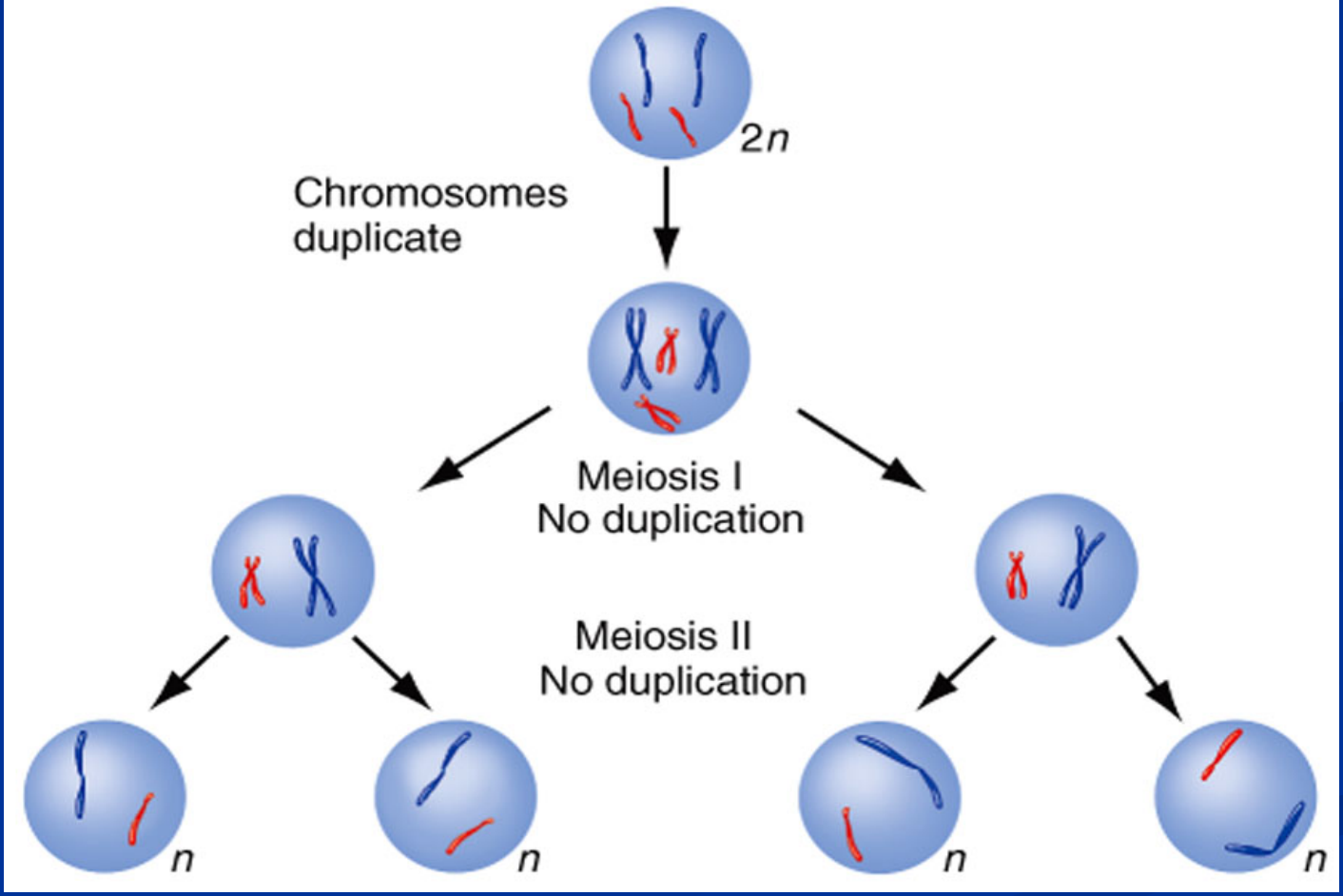


Fig. 4.12

Meiosis – Prophase I

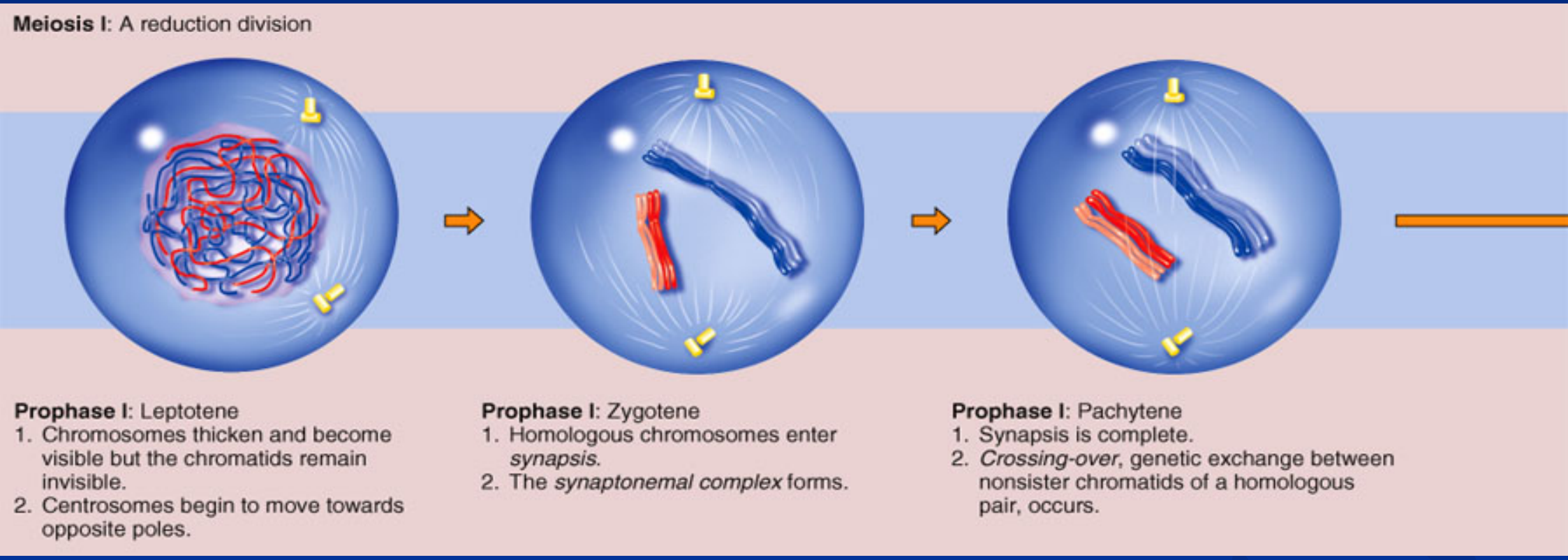


Figure 4.13

Meiosis – Prophase I continued

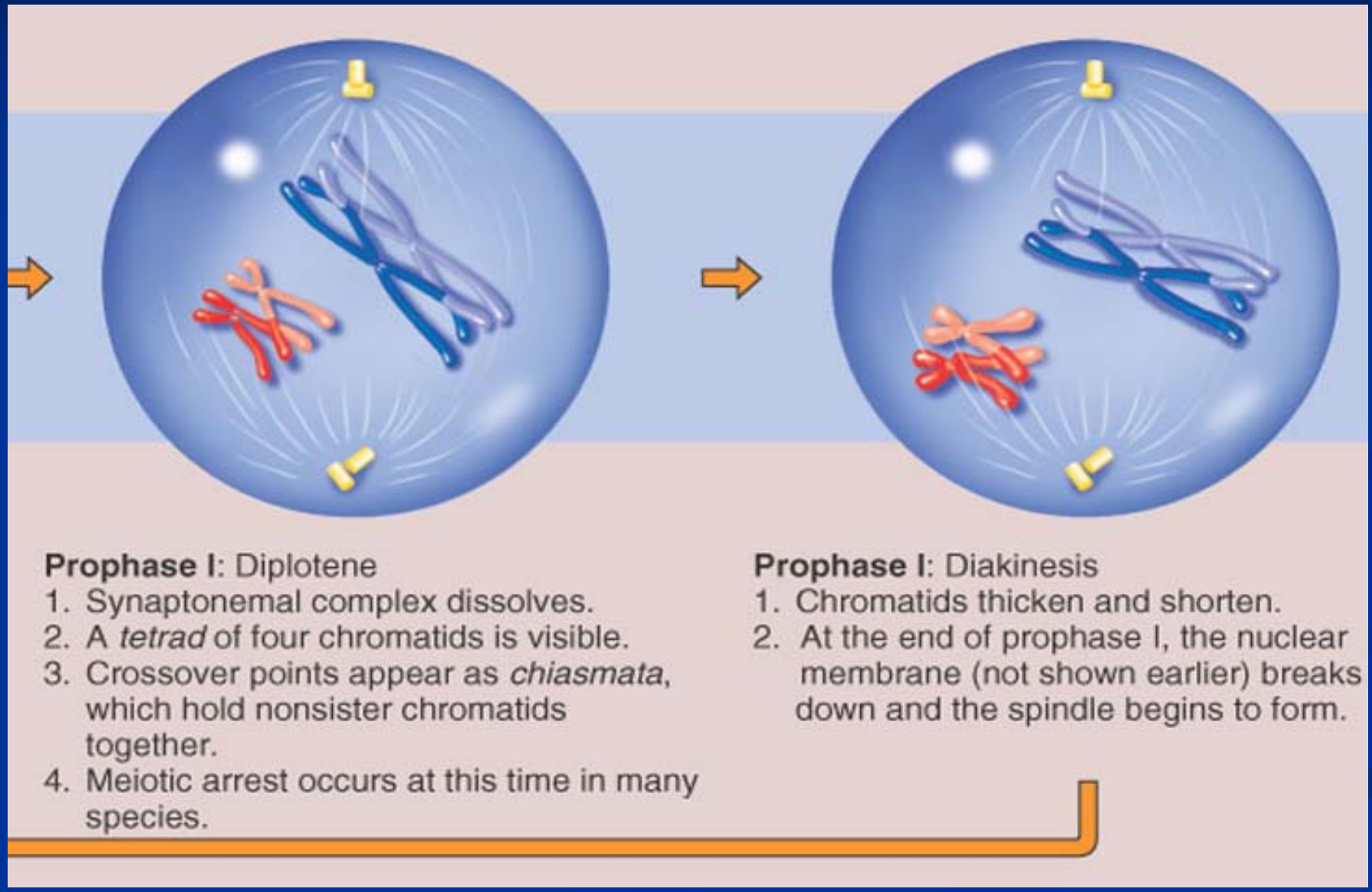
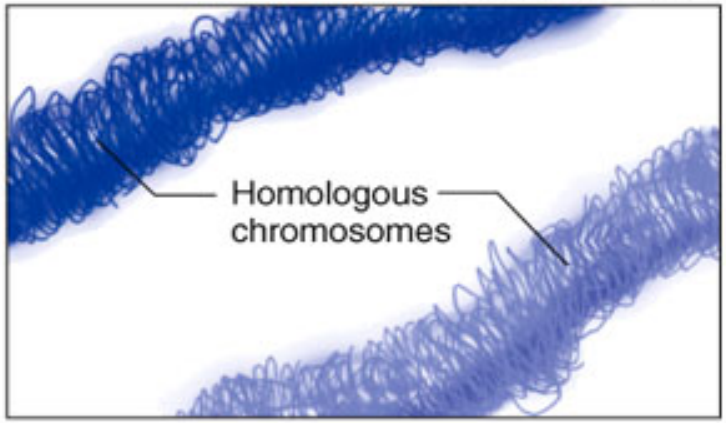
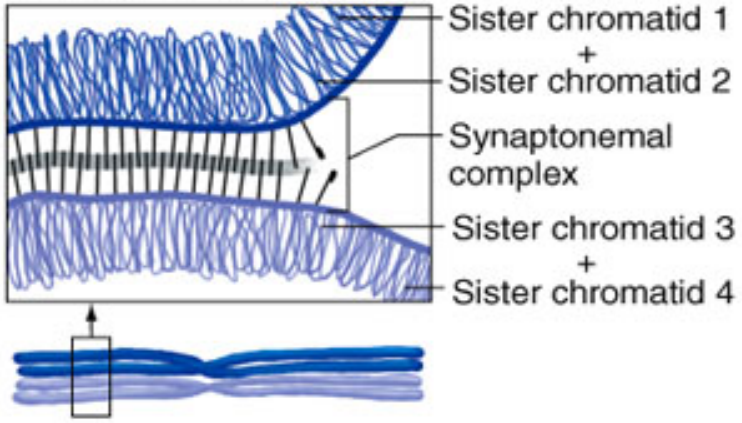


Figure 4.13

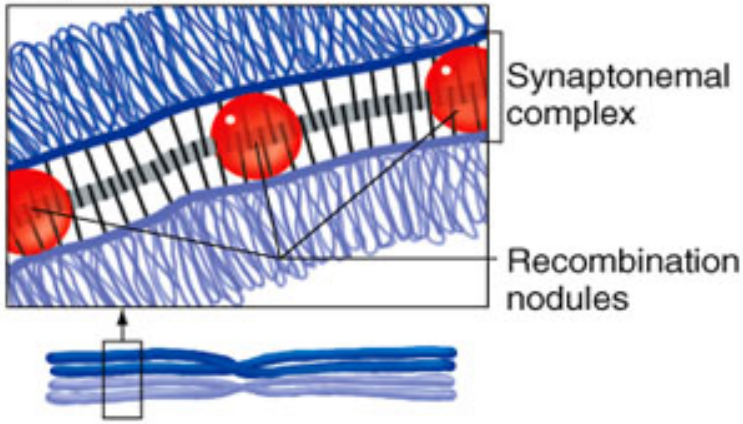
Crossing over during prophase produces recombined chromosomes



(a) **Leptotene:** Threadlike chromosomes begin to condense and thicken, becoming visible as discrete structures. Although the chromosomes have duplicated, the sister chromatids of each chromosome are not yet visible in the microscope.

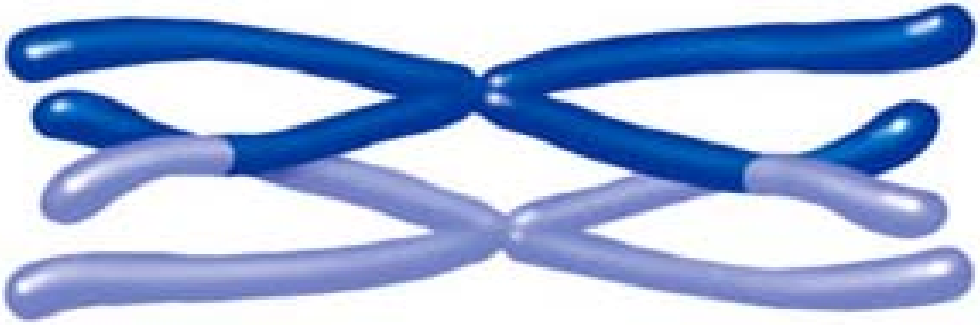


(b) **Zygotene:** Chromosomes are clearly visible and begin active pairing with homologous chromosomes along the synaptonemal complex to form a bivalent, or tetrad.

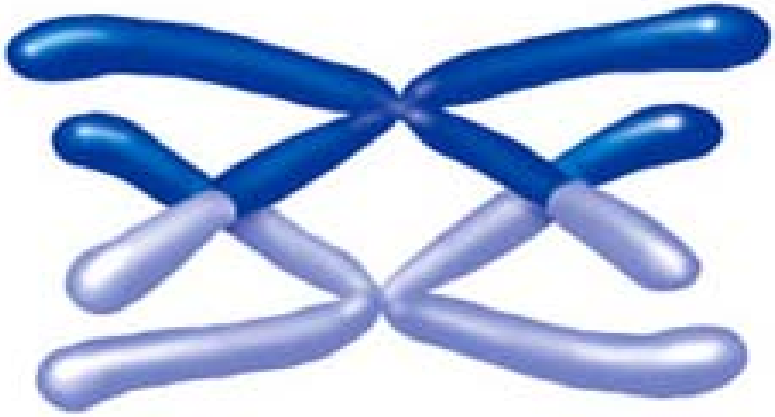


(c) **Pachytene:** Full synapsis of homologues. Recombination nodules appear along the synaptonemal complex.

Fig. 4.14 a-c



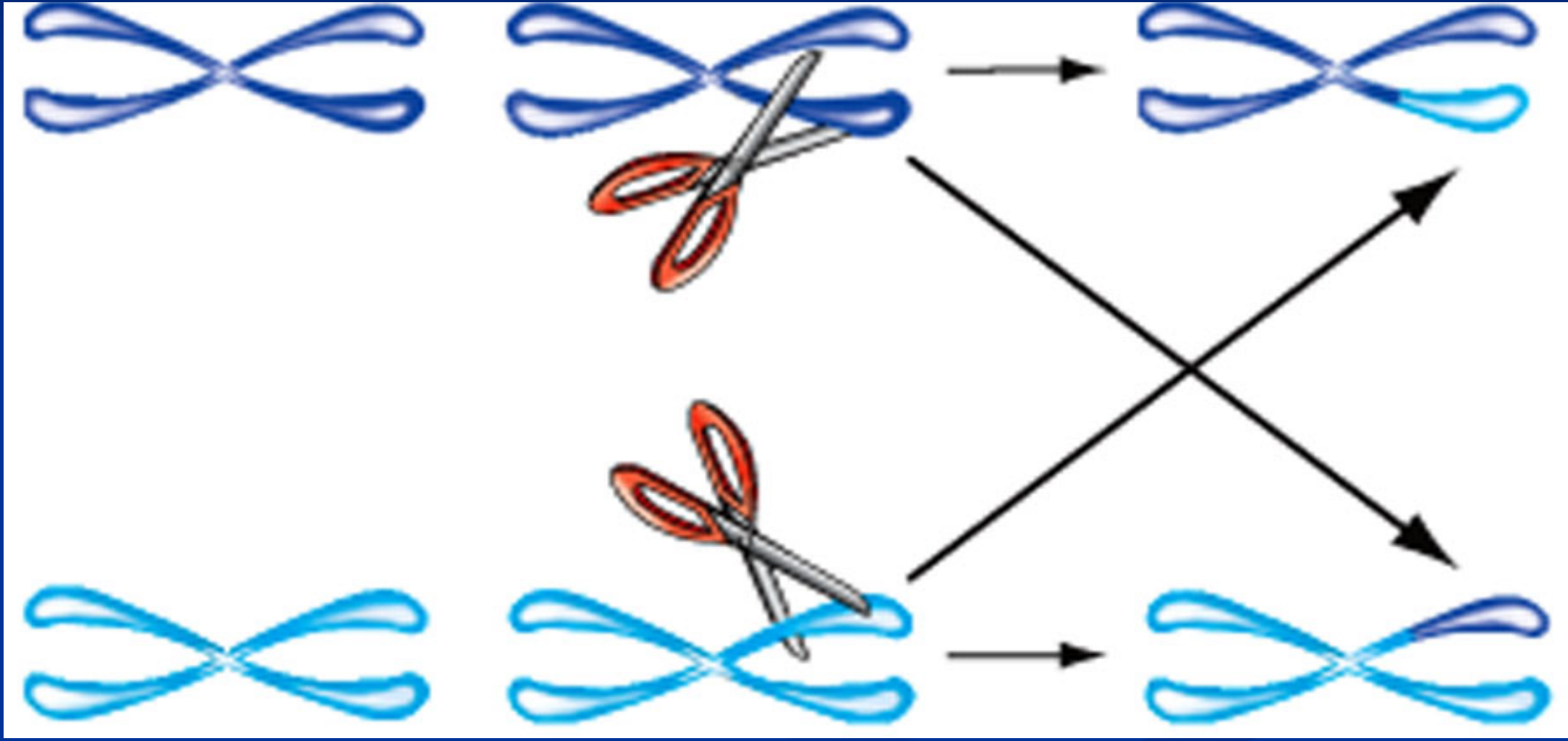
(d) **Diplotene:** Bivalent appears to pull apart slightly but remains connected at crossover sites, called chiasmata.



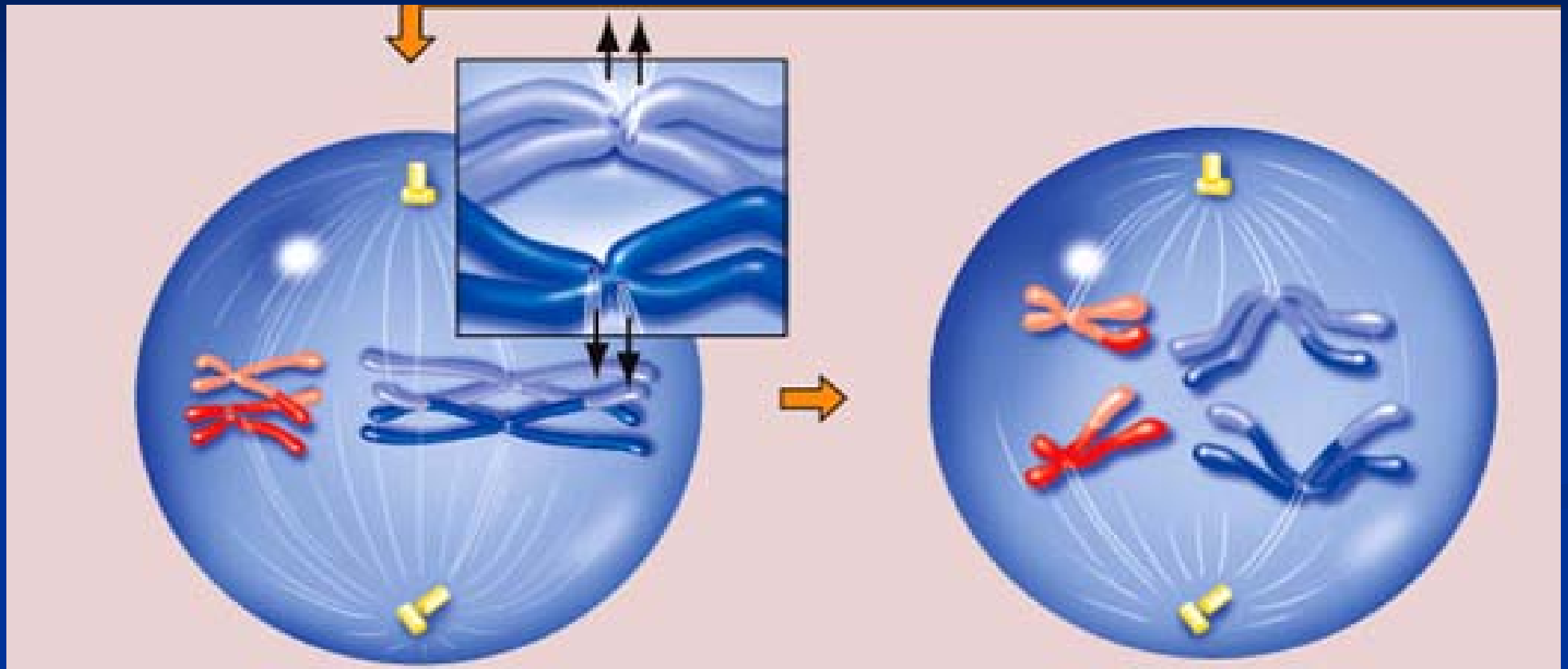
(e) **Diakinesis:** Further condensation of chromatids. Nonsister chromatids that have exchanged parts by crossing-over remain closely associated at chiasmata.

Fig. 4.14 d, e

How crossing over produces recombined gametes?



Meiosis I – Metaphase and Anaphase



Metaphase I

1. Tetrads line up along the *metaphase plate*.
2. Each chromosome of a homologous pair attaches to fibers from opposite poles.
3. Sister chromatids attach to fibers from the same pole.

Anaphase I

1. The centromere does not divide.
2. The chiasmata migrate off chromatid ends.
3. Homologous chromosomes move to opposite poles.

Figure 4.13

Meiosis – Telophase I and Interkinesis

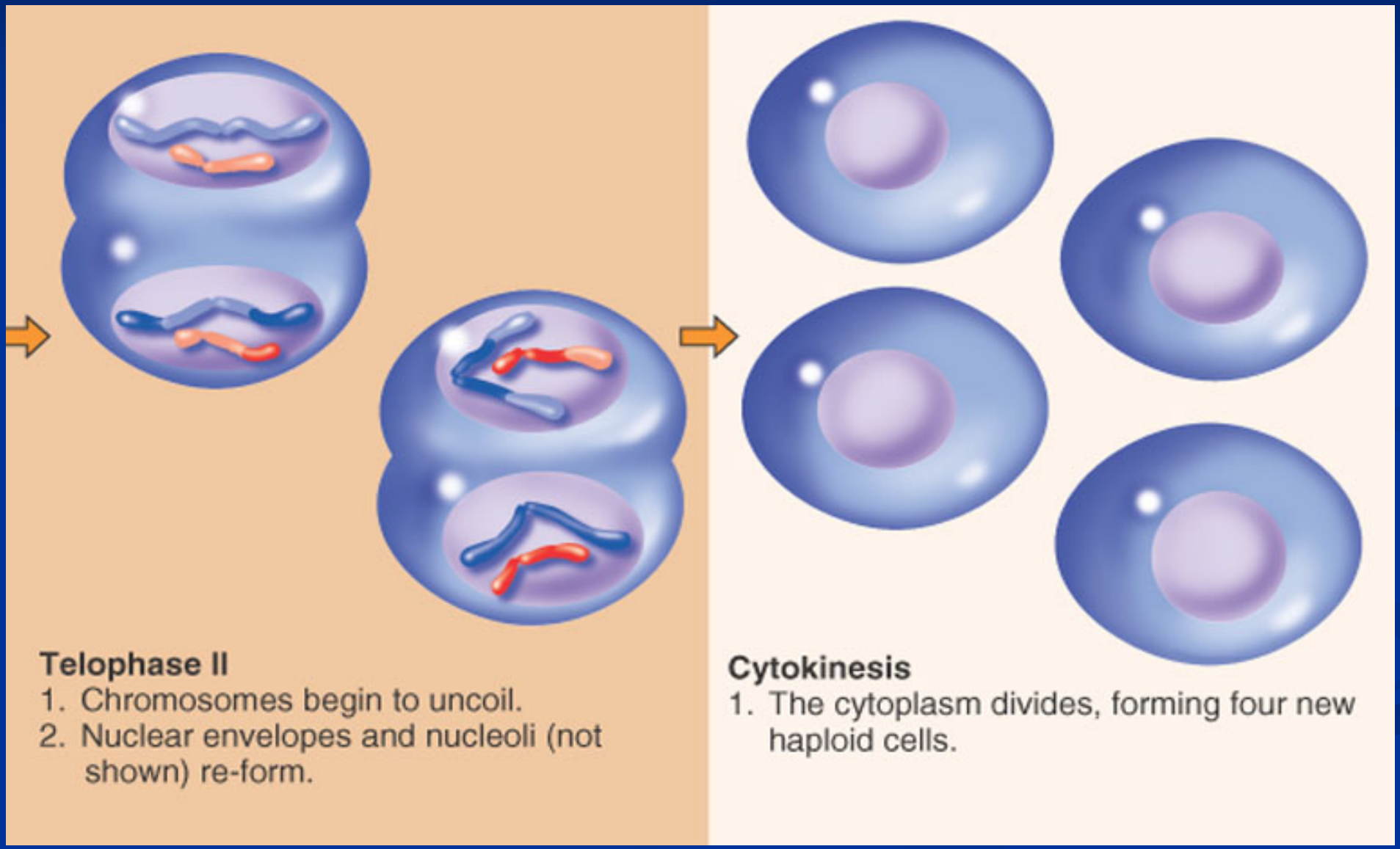


Figure 4.13

Meiosis – Prophase II and Metaphase II

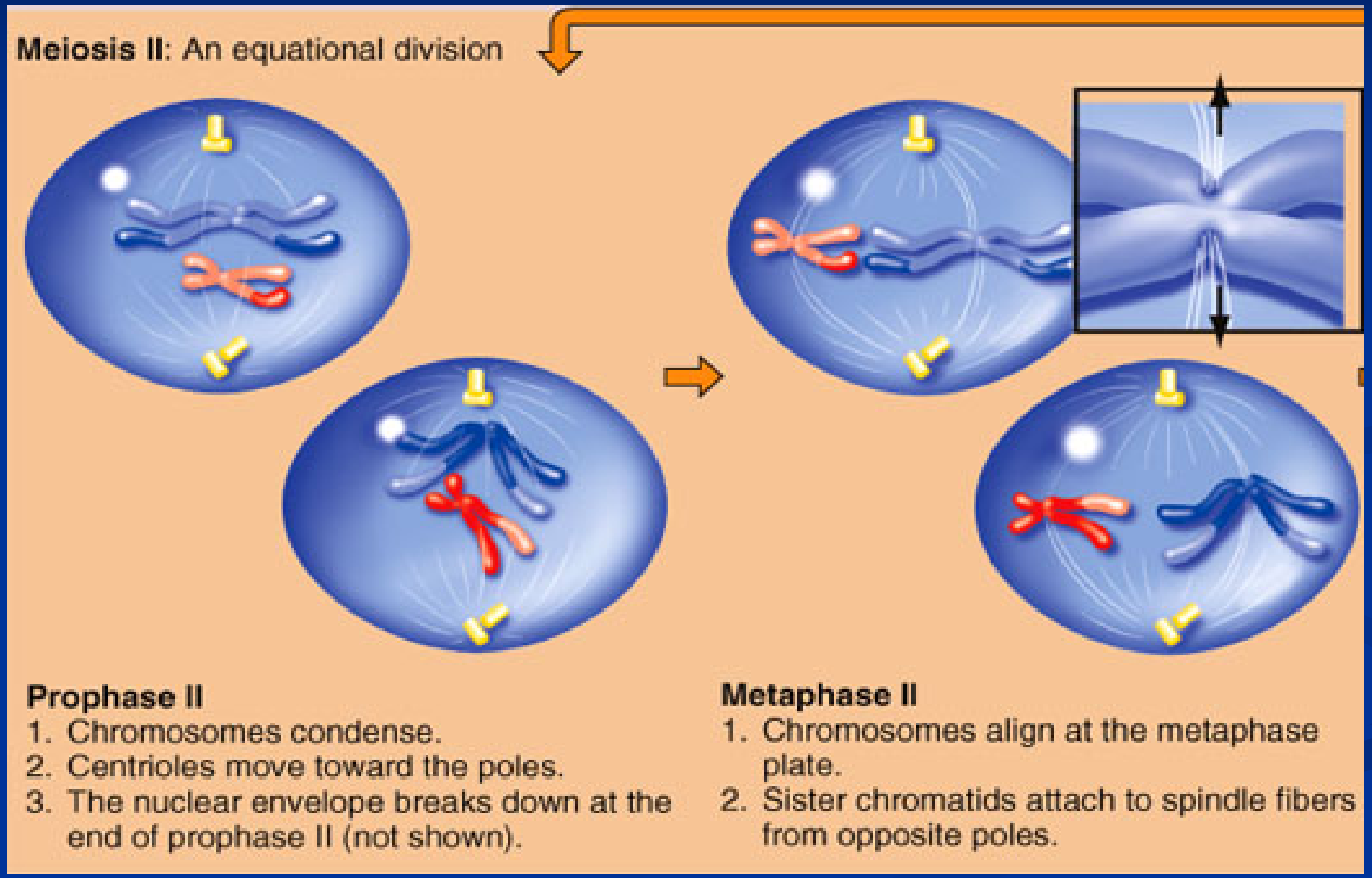
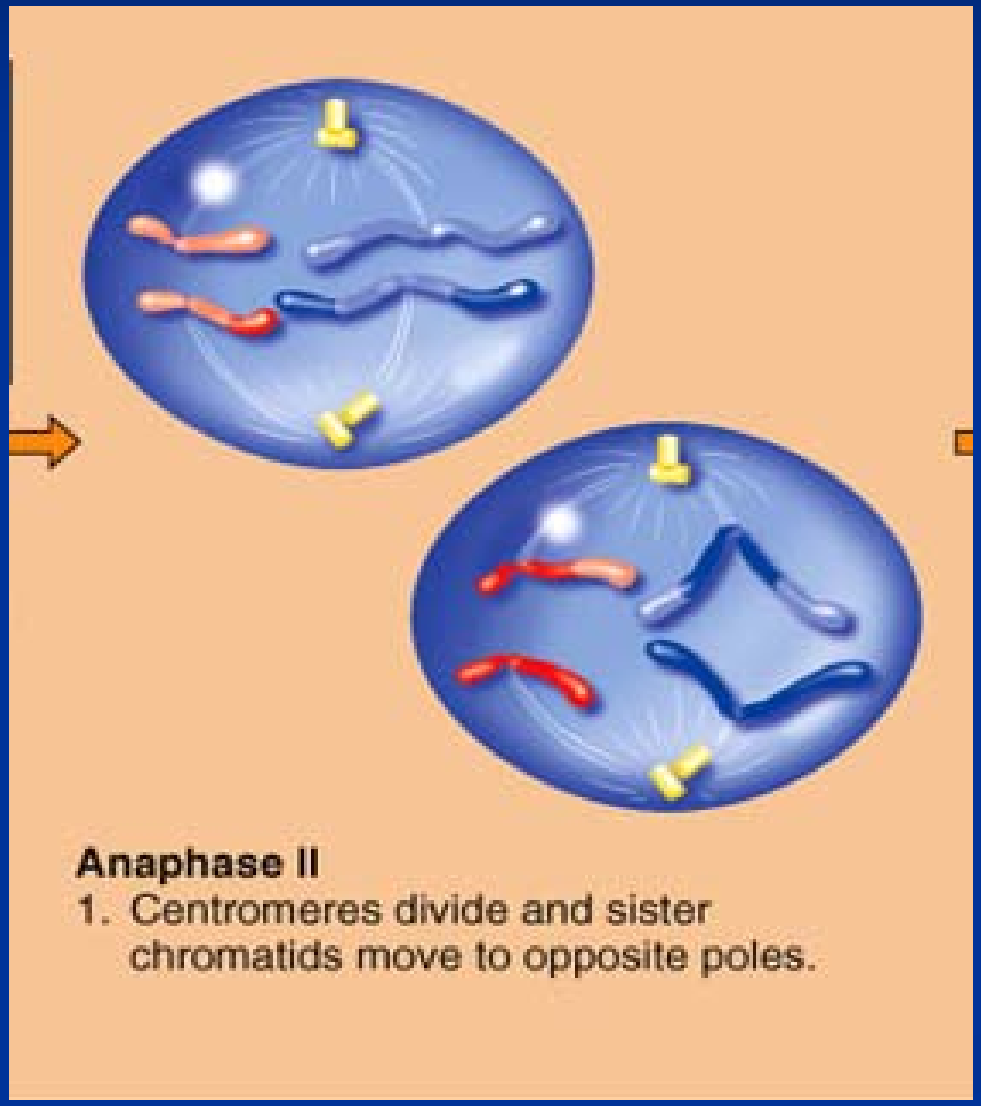
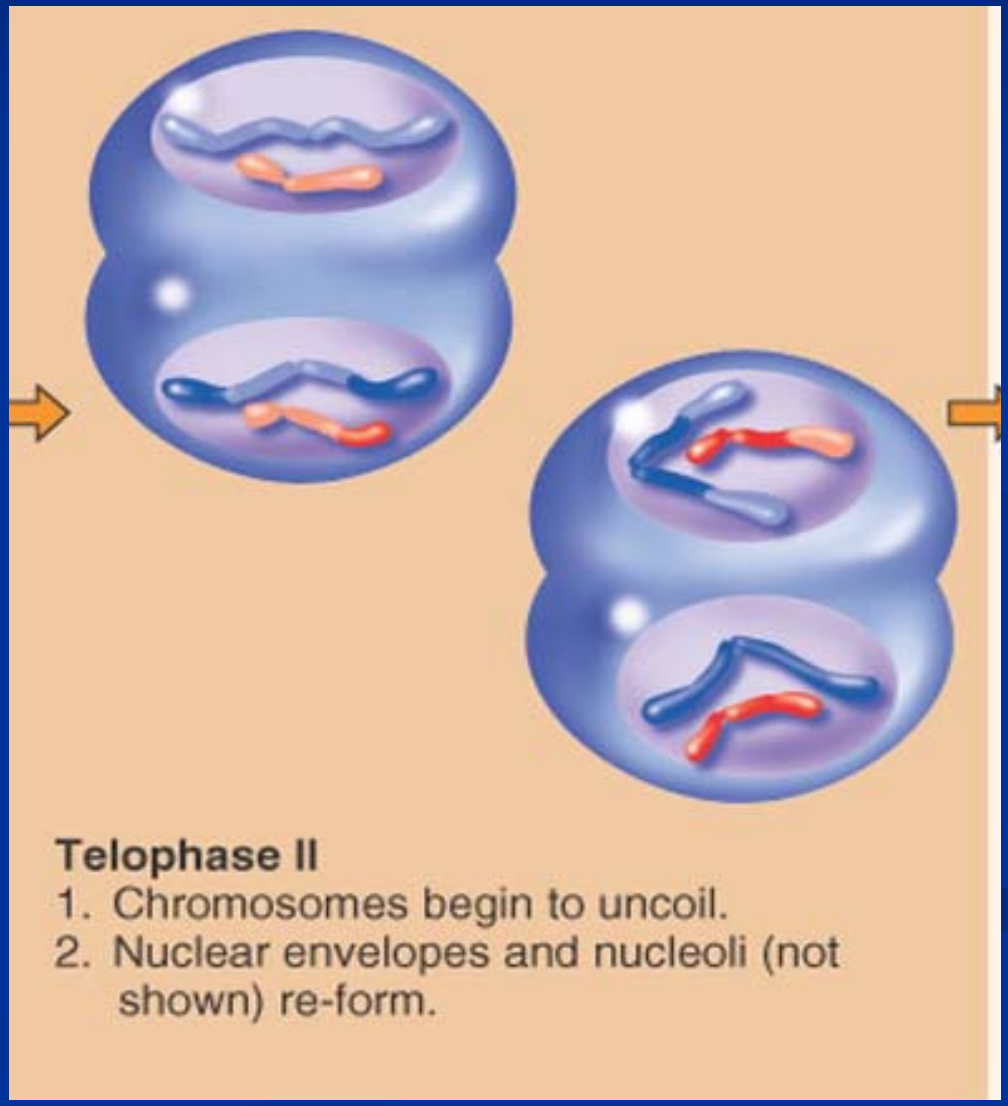


Figure 4.13

Meiosis – Anaphase II and Telophase II



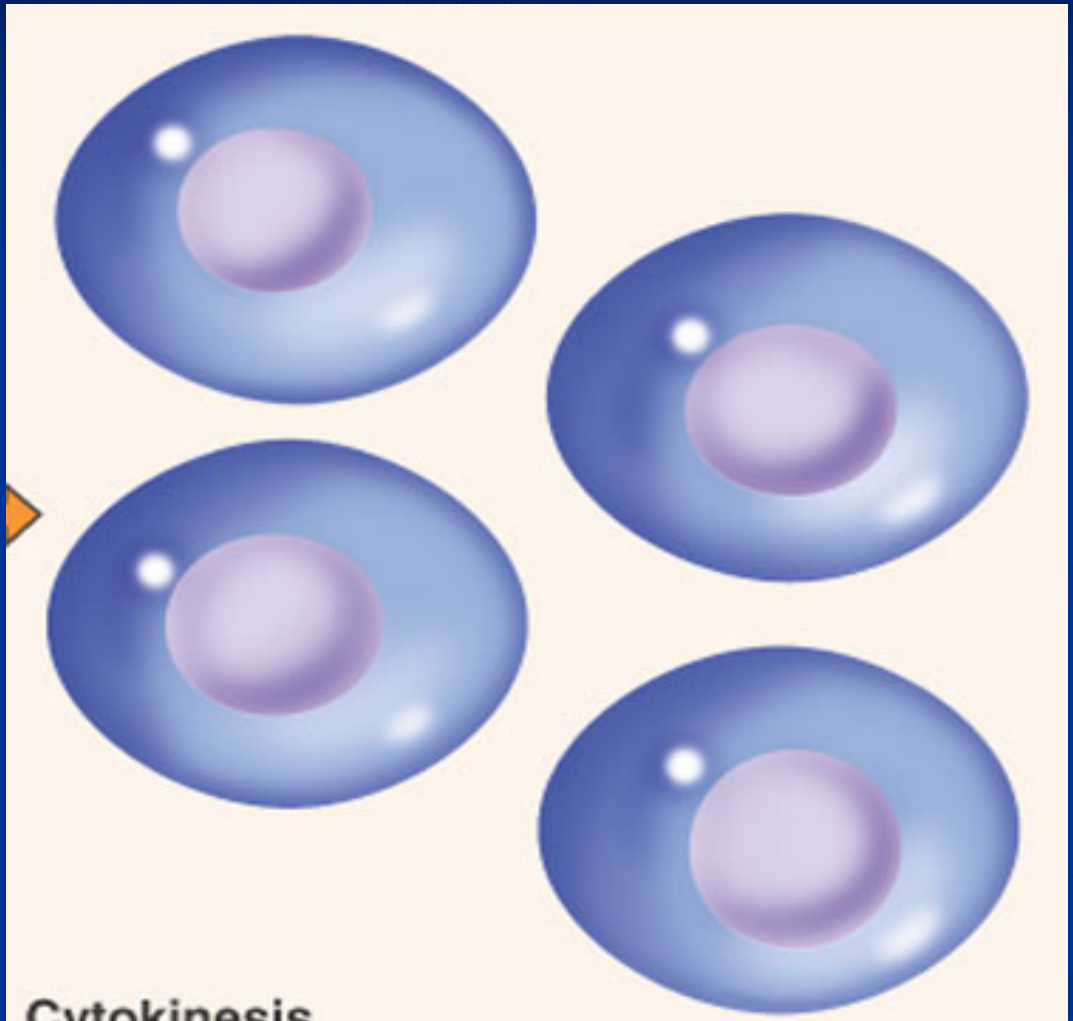
Anaphase II
1. Centromeres divide and sister chromatids move to opposite poles.



Telophase II
1. Chromosomes begin to uncoil.
2. Nuclear envelopes and nucleoli (not shown) re-form.

Figure 4.13

Meiosis - Cytokinesis



Cytokinesis

1. The cytoplasm divides, forming four new haploid cells.

Fig. 4.13

Meiosis contributes to genetic diversity in two ways

- Independent assortment of nonhomologous chromosomes creates different combinations of alleles among chromosomes.
- Crossing-over between homologous chromosomes creates different combinations of alleles within each chromosome.

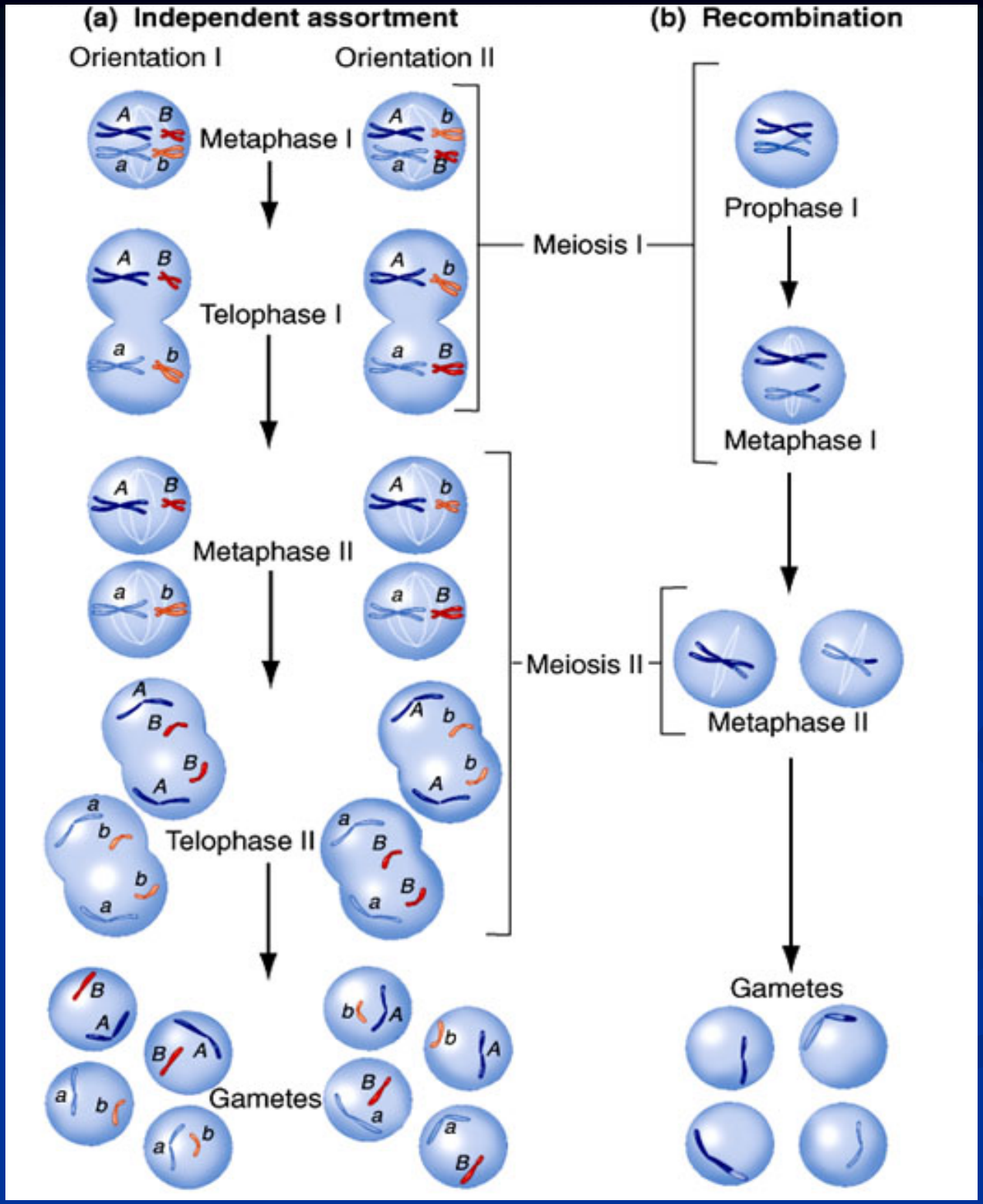

(a) Independent assortment
(b) Recombination
Orientation I
Orientation II
Metaphase I
Telophase I
Meiosis I
Prophase I
Metaphase I
Metaphase II
Meiosis II
Metaphase II
Telophase II
Gametes
Gametes

Fig. 4.16

4.4 Gametogenesis

- **Oogenesis** – egg formation in human females.
  - Diploid germ cells called oogonia multiply by mitosis to produce primary oocytes.
  - Primary oocytes undergo meiosis I to produce one secondary oocyte and one small polar body (which arrests development).
  - Secondary oocyte undergoes meiosis II to produce one ovum and one small polar body.
  - Polar bodies disintegrate leaving one large functional gamete.

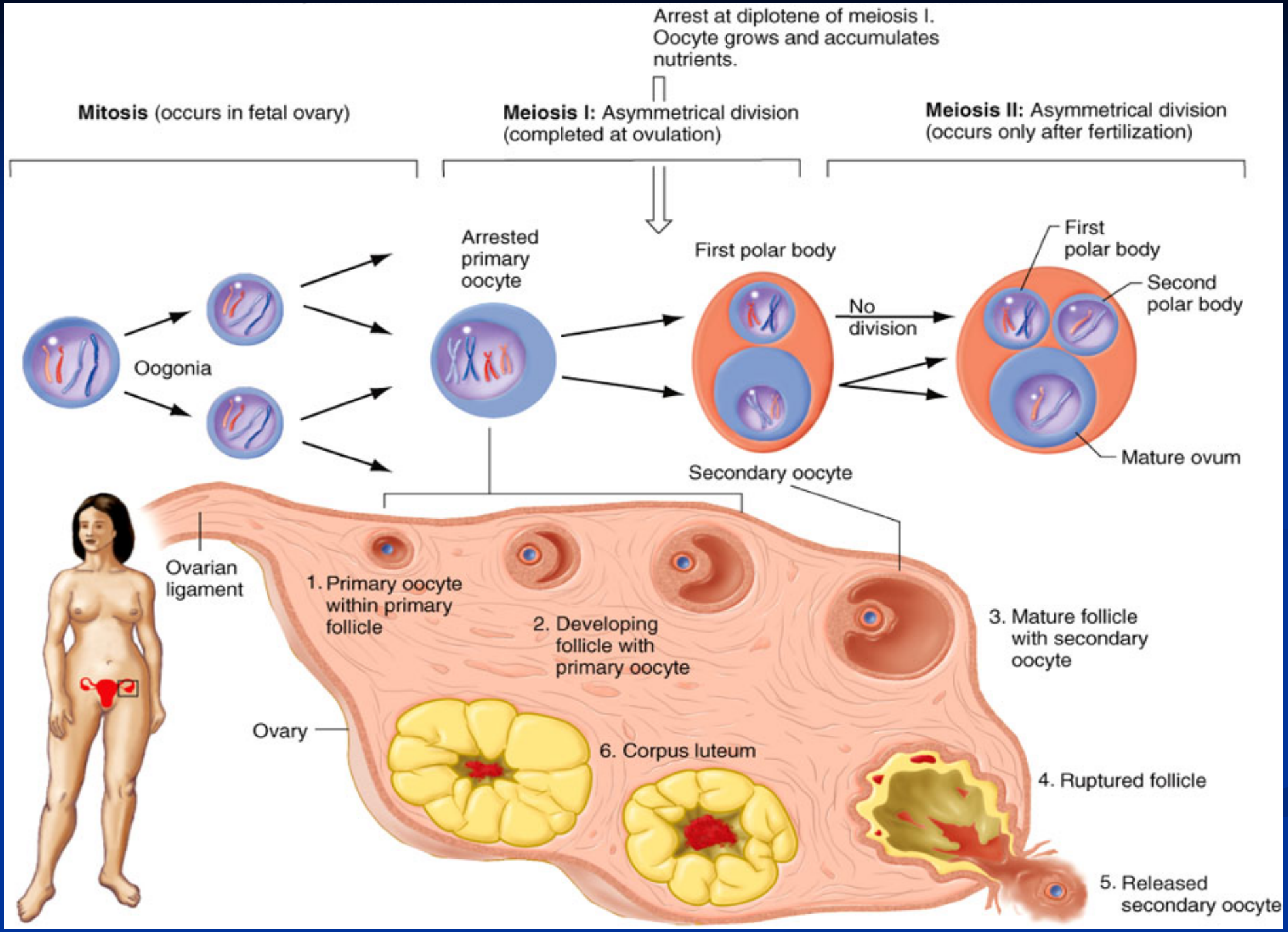

Arrest at diplotene of meiosis I.
Oocyte grows and accumulates nutrients.
Mitosis (occurs in fetal ovary)
Meiosis I: Asymmetrical division (completed at ovulation)
Meiosis II: Asymmetrical division (occurs only after fertilization)
Oogonia
Arrested primary oocyte
First polar body
No division
First polar body
Second polar body
Mature ovum
Secondary oocyte
Ovarian ligament
1. Primary oocyte within primary follicle
2. Developing follicle with primary oocyte
3. Mature follicle with secondary oocyte
Ovary
6. Corpus luteum
4. Ruptured follicle
5. Released secondary oocyte

Fig 4.17

- **Spermatogenesis** – sperm formation in human males.
  - Begins in male testes in germ cells called spermatogonia.
  - Mitosis produces diploid primary spermatocytes.
  - Meiosis I produces two secondary spermatocytes per cell.
  - Meiosis II produces four equivalent spermatids.
  - Spermatids mature into functional sperm.

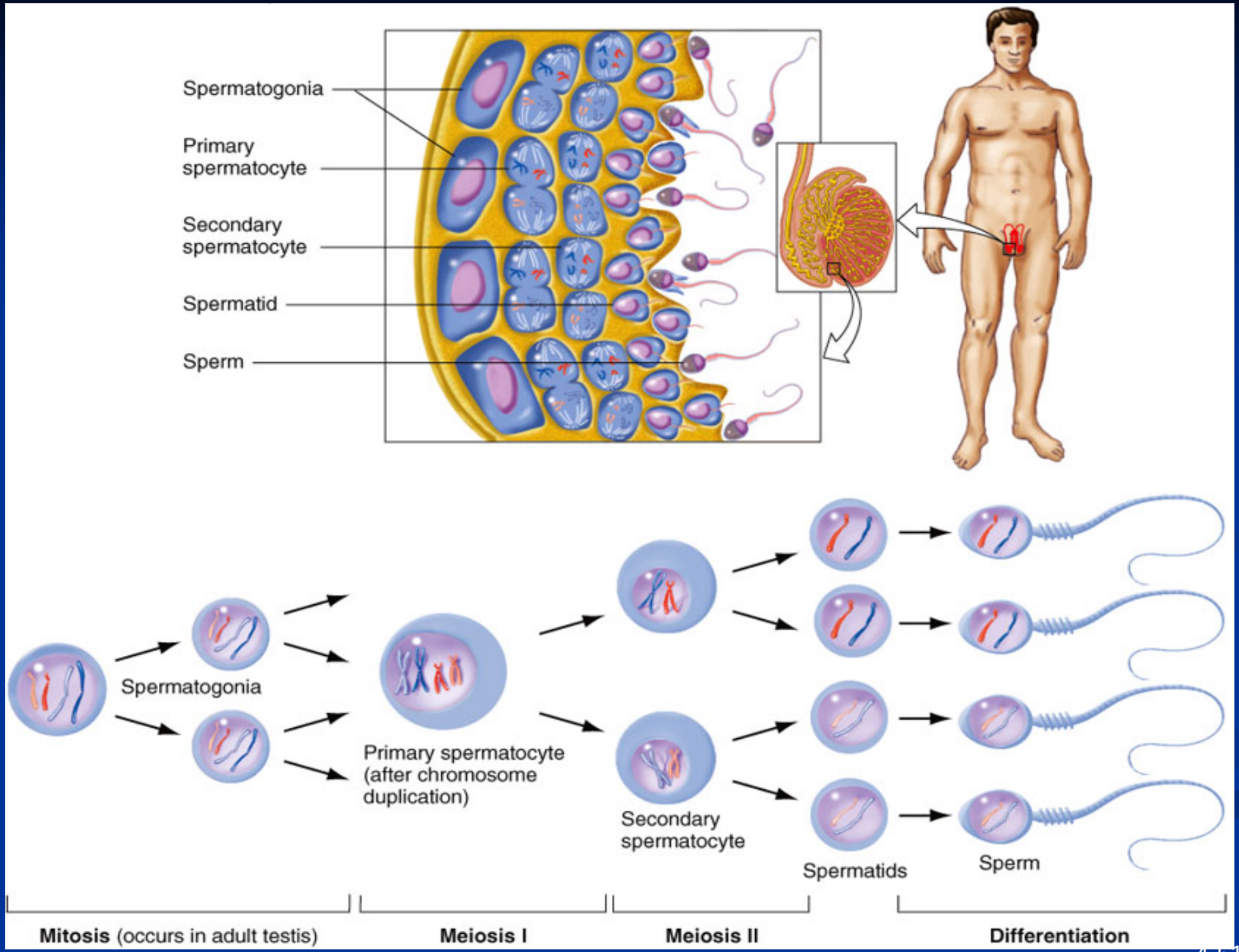

Spermatogonia
Primary spermatocyte
Secondary spermatocyte
Spermatid
Sperm
Spermatogonia
Primary spermatocyte (after chromosome duplication)
Secondary spermatocyte
Spermatids
Sperm
Mitosis (occurs in adult testis)
Meiosis I
Meiosis II
Differentiation

Fig. 4.18

4.5 Validation of the chromosome theory

- Also called **the Boveri-Sutton chromosome theory**.
  - **Theodor Boveri** described the segregation of chromosomes in sea urchin in 1902-1904.
  - **Walter Sutton** reported the behavior of chromosome segregation in grasshopper in 1902-1903.

Theodor Boveri
(1862-1915)

Walter S. Sutton
(1877-1916)

- **“*Chromosome movements parallel the behavior of Mendel’s genes. Chromosomes are likely to carry the genetic material*.”**
- **Confirmed in the following 15 years through studies on the fruit fly *Drosophila melanogaster*.**
- **The theory transformed the concept of a gene from an abstract particle to a physical reality.**

The chromosome theory correlates Mendel's laws with chromosome behavior during meiosis

Chromosome Behavior

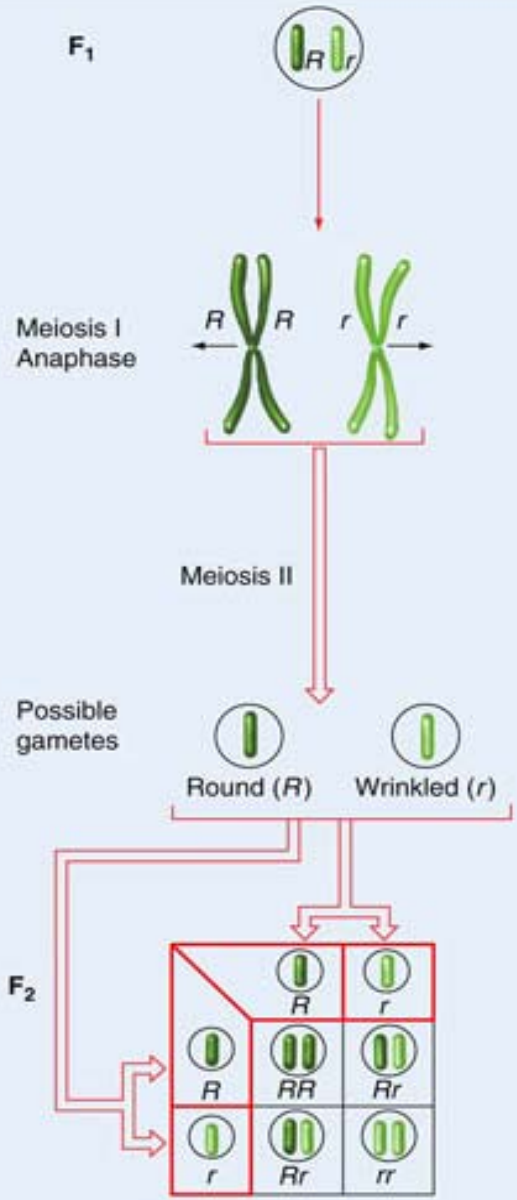
- Each cell contains two copies of each chromosome
- Chromosome complements appear unchanged during transmission from parent to offspring.
- Homologous chromosomes pair and then separate to different gametes.
- Maternal and paternal copies of chromosome pairs separate without regard to the assortment of other homologous chromosome pairs.
- At fertilization an egg's set of chromosomes unite with randomly encountered sperm's chromosomes.
- In all cells derived from a fertilized egg, one half of chromosomes are of materna

Behavior of genes

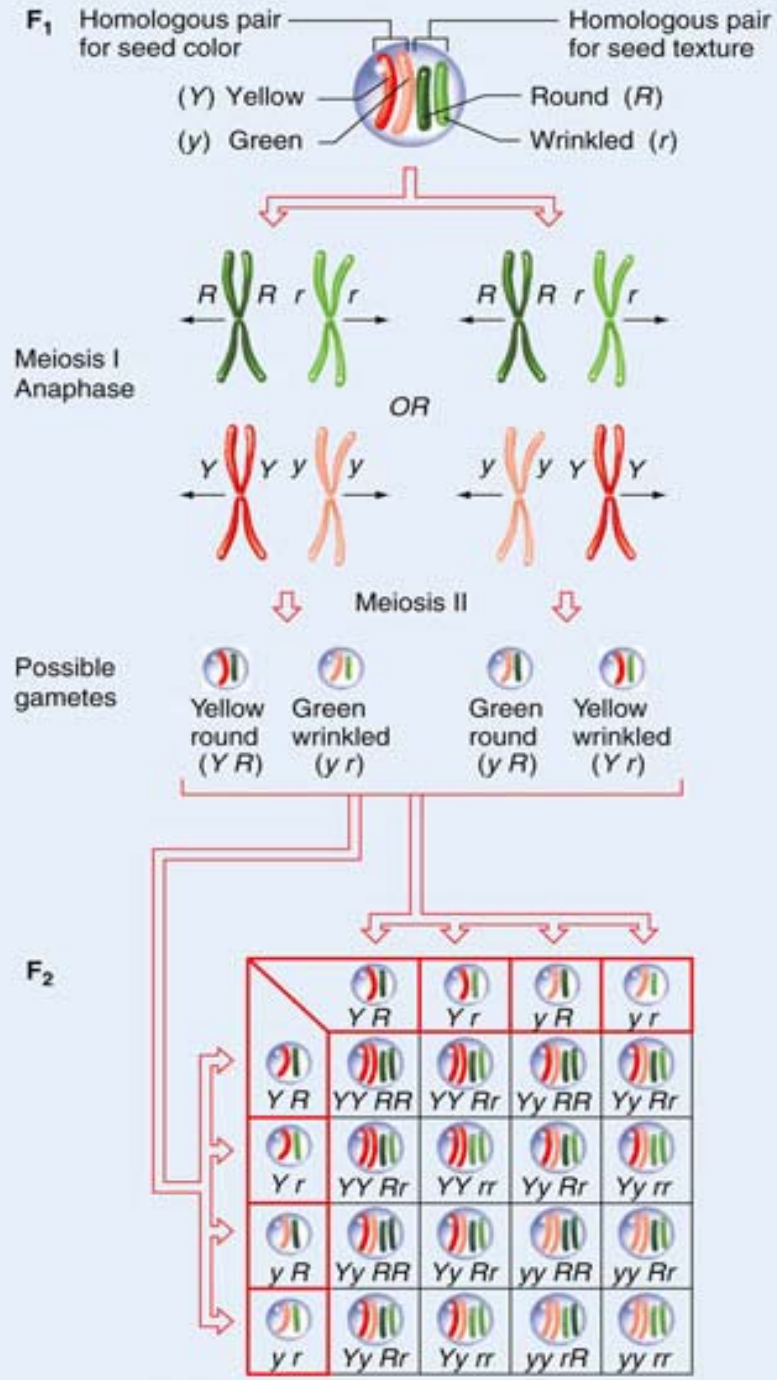
- Each cell contains two copies of each gene.
- Genes appear unchanged during transmission from parent to offspring.
- Alternative alleles segregate to different gametes.
- Alternative alleles of unrelated genes assort independently.
- Alleles obtained from one parent unite at random with those from another parent.
- In all cells derived from a fertilized gamete, one half of genes are of maternal origin, and half are paternal.

TABLE 4.4 How the Chromosome Theory of Inheritance Explains Mendel's Laws

(a) The Law of Segregation



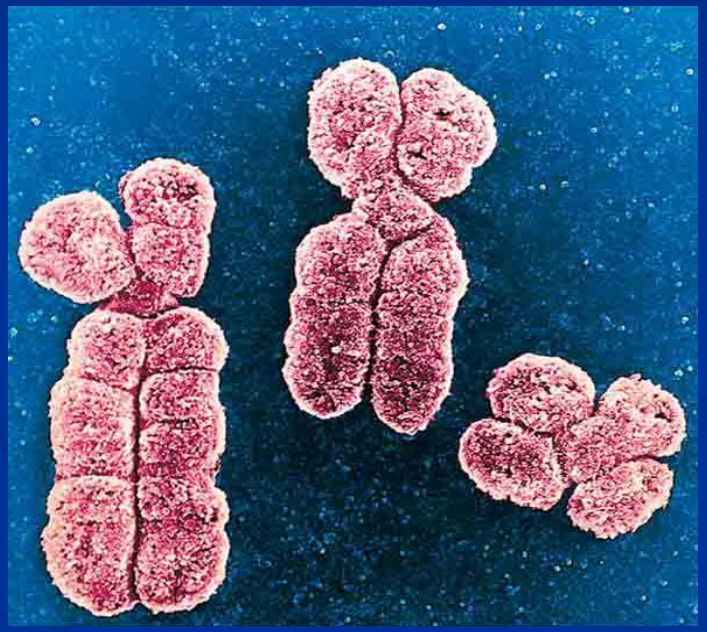
(b) The Law of Independent Assortment



Recall that Mendel's law of segregation was based on the results obtained by the self-fertilization of F_1 hybrid peas for traits such as pea shape. Sutton assumed that in the hybrids, the allele for round-seeded peas (*R*) is found on one chromosome, and the allele for wrinkled peas (*r*) is on the homologous chromosome. The pairing between the two homologous chromosomes during prophase through metaphase of meiosis I

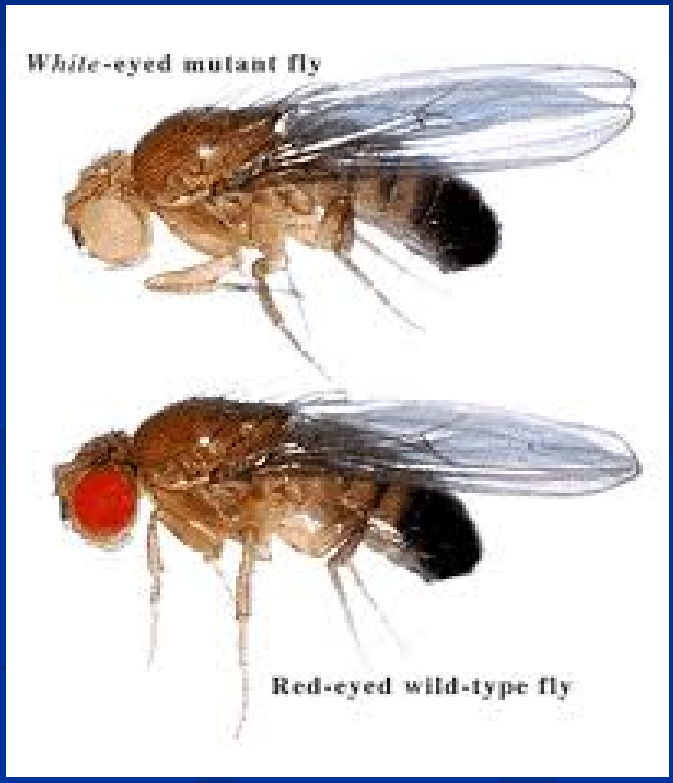
Specific traits are transmitted with specific chromosomes

- A test of the chromosome theory
  - If genes are on specific chromosomes, traits determined by the gene should be transmitted with the chromosome.
  - **Thomas H. Morgan**'s experiments demonstrate the transmission of traits with chromosomes.

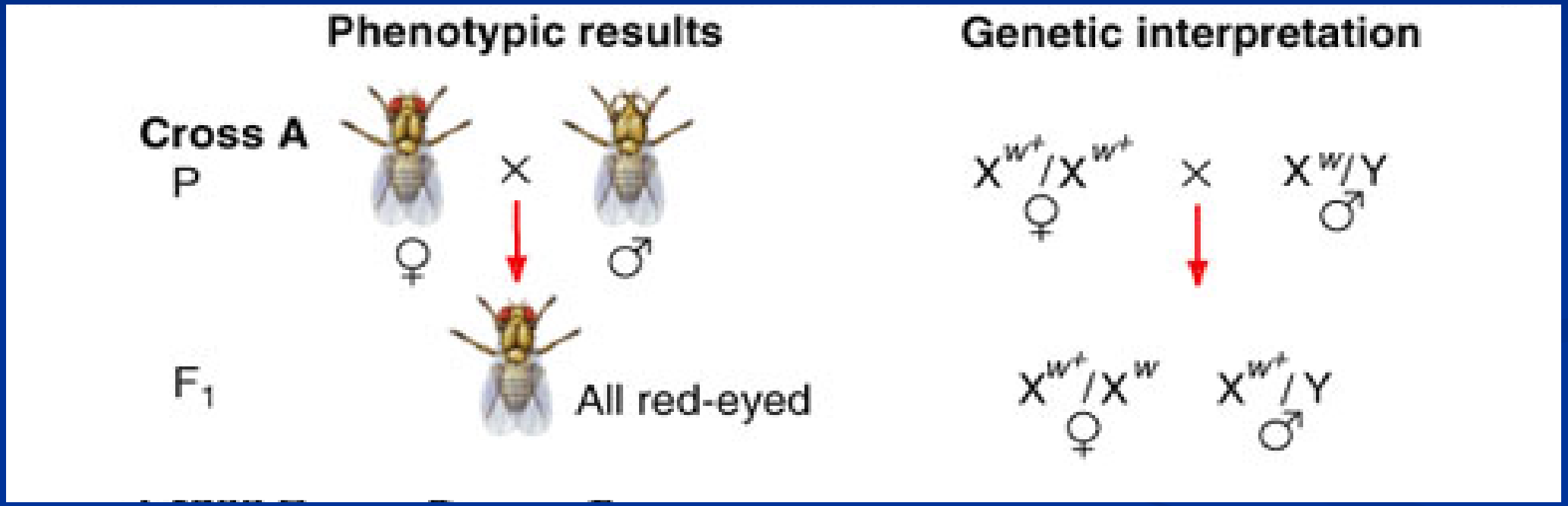


Human chromosomes

- In May, 1910, **Thomas H. Morgan** discovered a white-eyed male fruit fly *Drosophila melanogaster*.

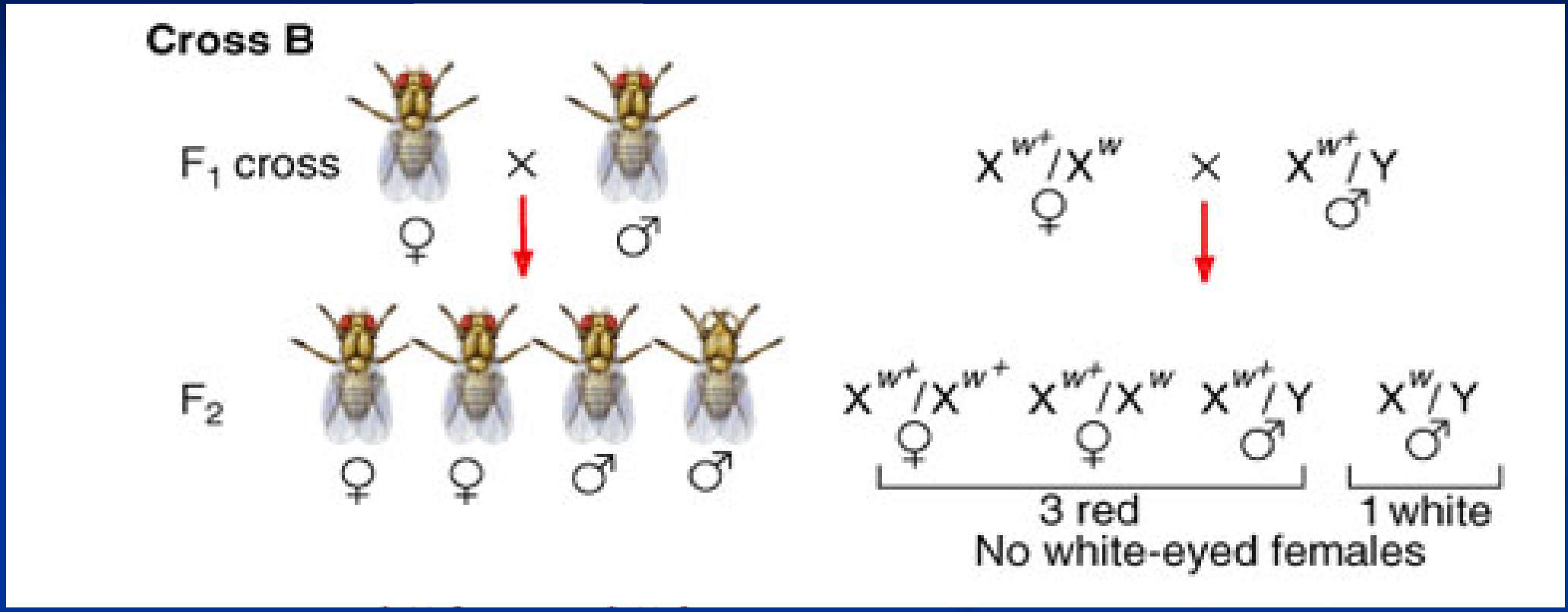


Crisscross inheritance of the white gene demonstrates X-linkage



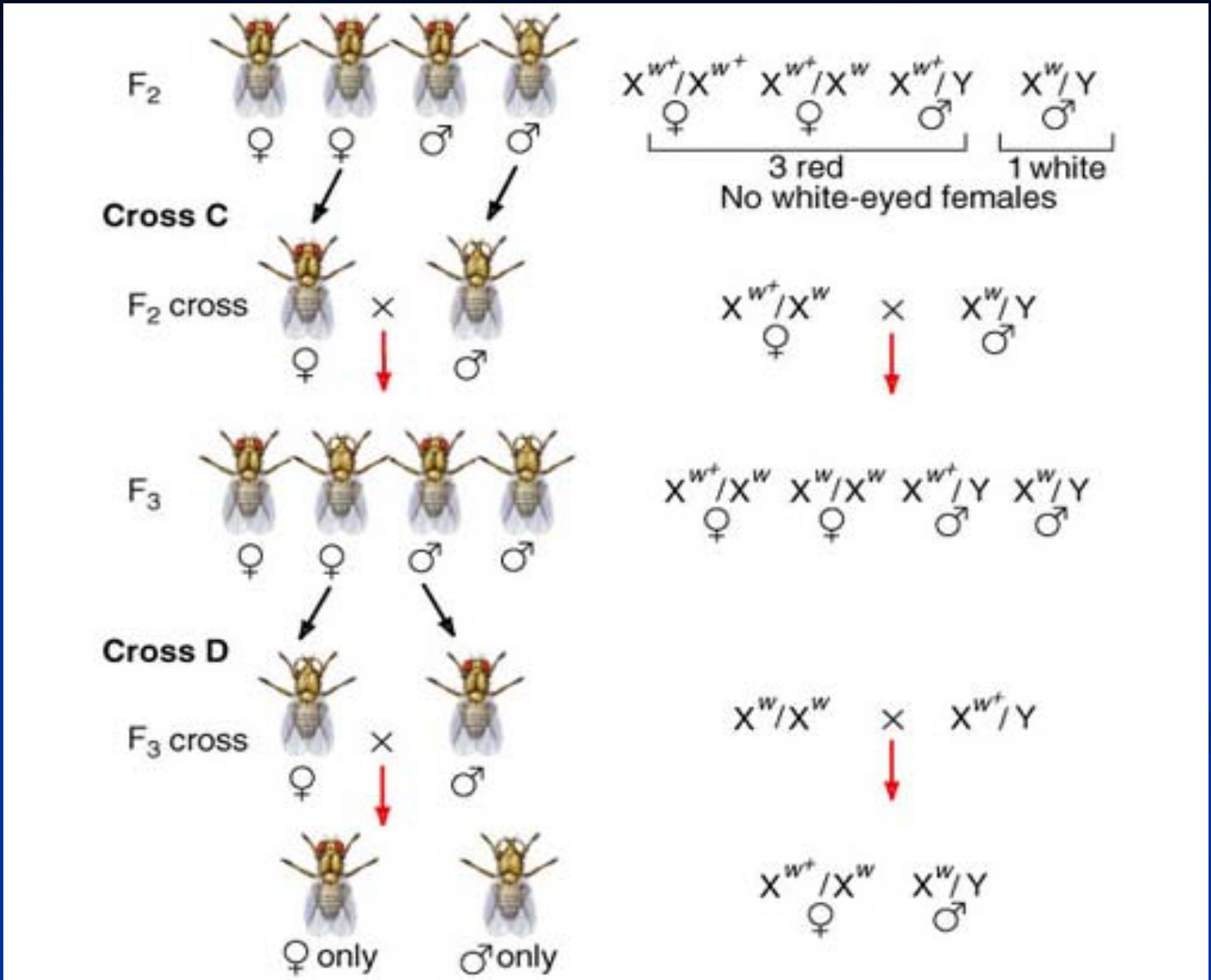
w^+: red eyes, wild-type
w: white eyes
X: X chromosome
Y: Y chromosome

Fig. 4.19



***w*⁺: red eyes, wild-type**
***w*: white eyes**
X: X chromosome
Y: Y chromosome

Fig. 4.19



Conclusion: white eye mutation is on the X chromosome.

Fig. 4.19

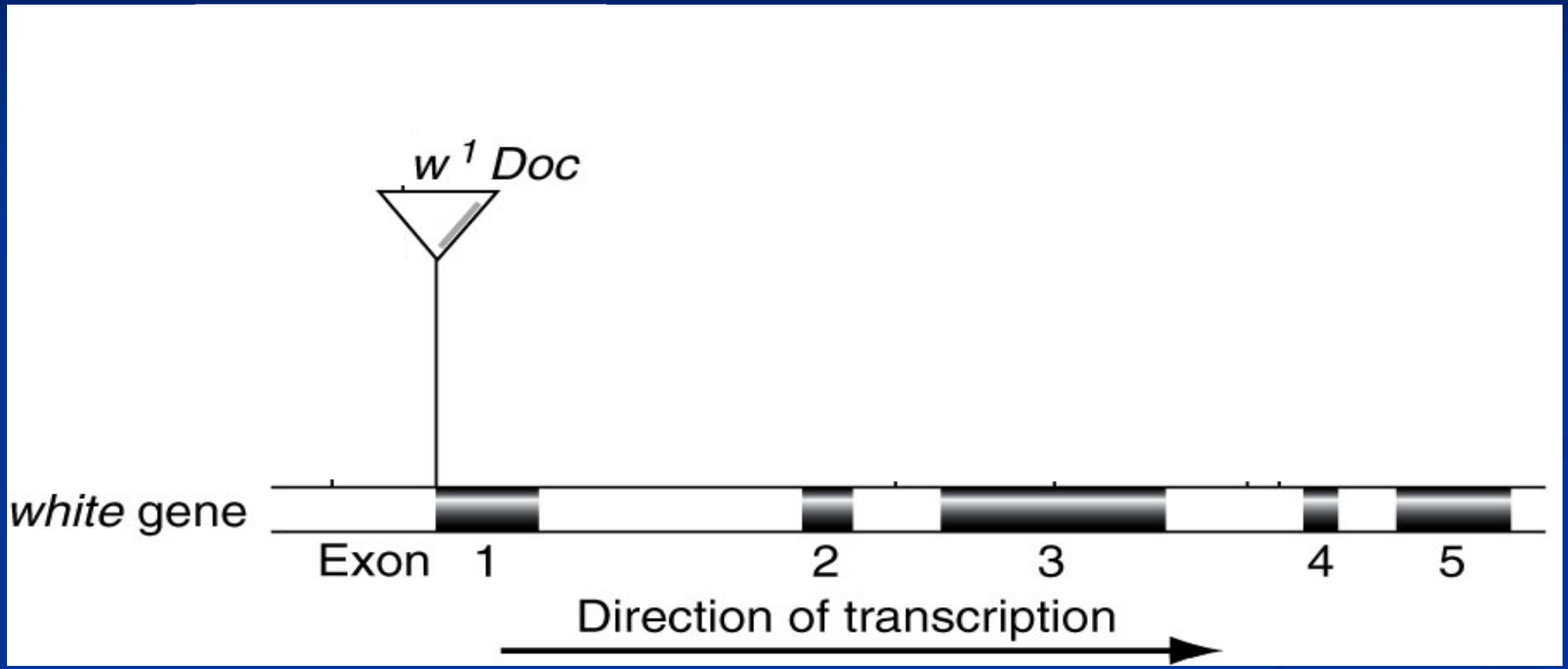
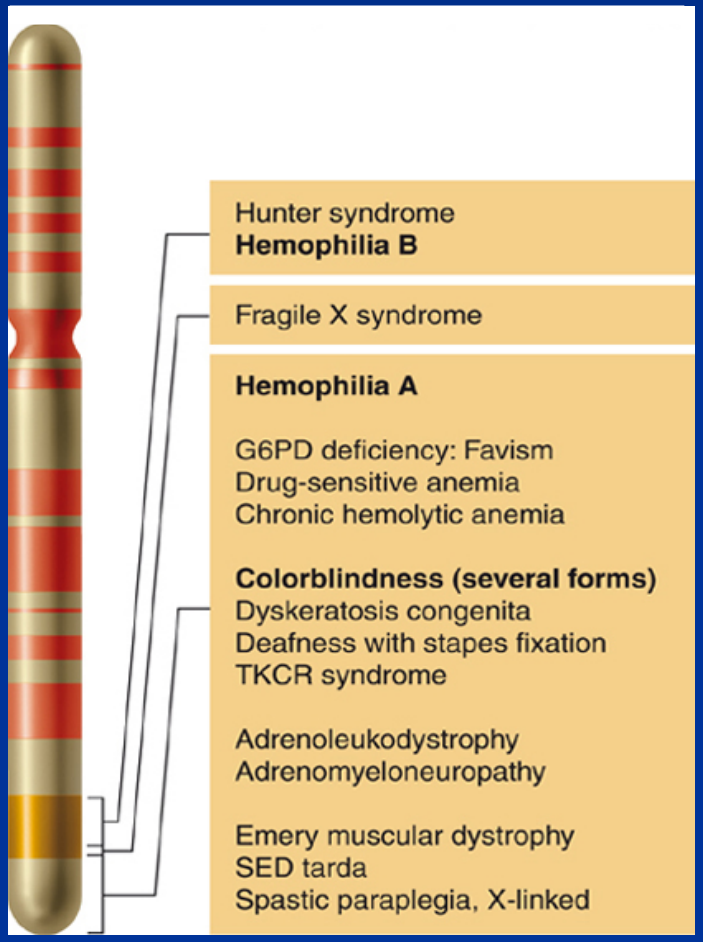
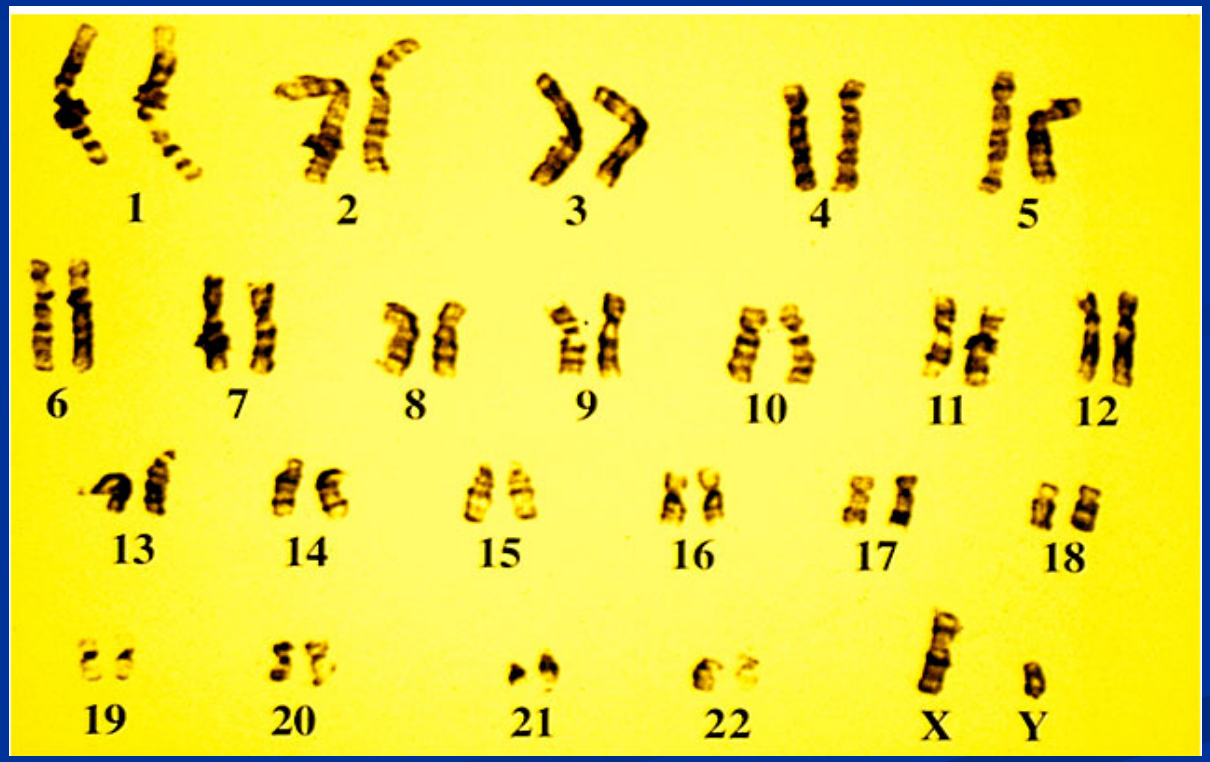


Fig. 13.28

T. H. Morgan's experiments on sex-linked inheritance of a gene demonstrate the transmission of traits with chromosomes.



Human X chromosome



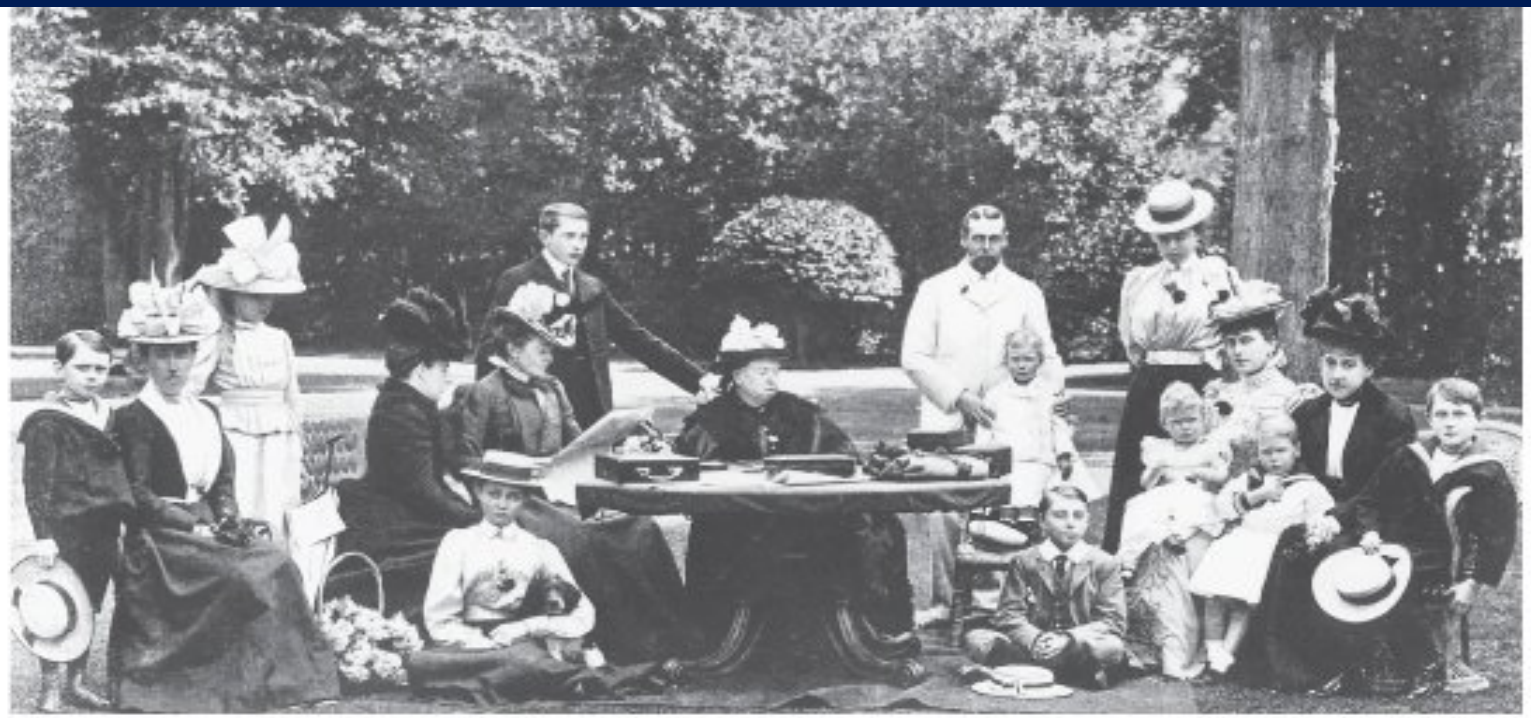
Human male karyotype

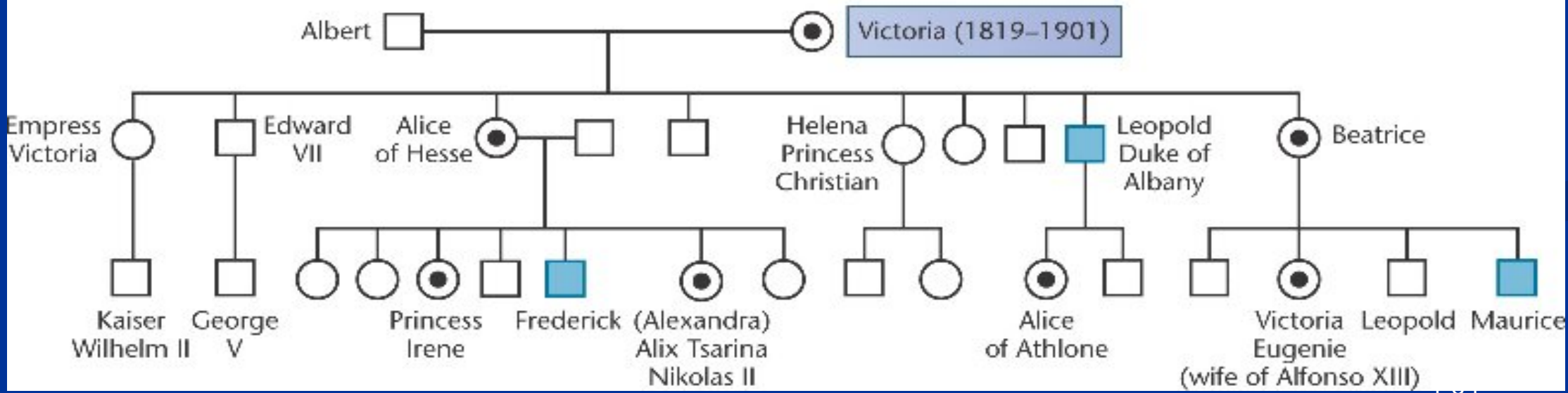
X-linked recessive trait in humans

Hemophilia:

- **Bleeders disease**, the blood failed to clot properly when there is a wound.
  - **Hemophilia A** (factor VIII deficiency)
  - **Hemophilia B** (factor IX deficiency), 1 in 25,000 males (3,300 people in US), less common than hemophilia A.

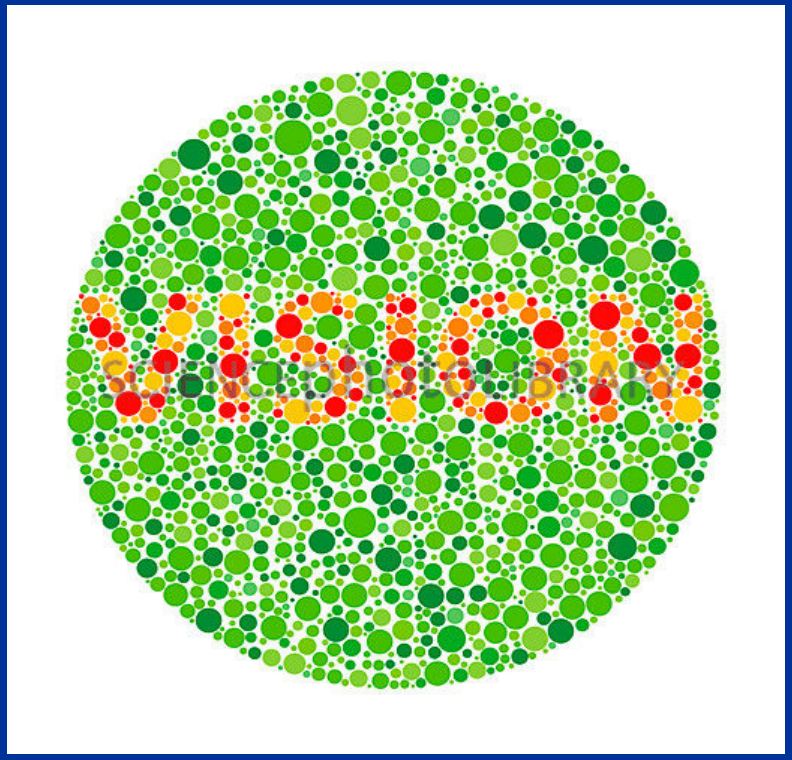
Hemophilia in the British royal family

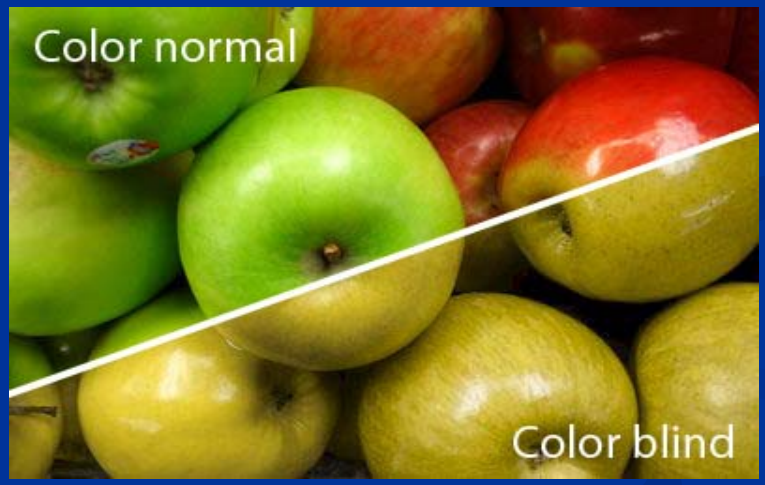




Red-green colorblindness:

- 8% male, 0.44% female, among Western Europeans in Europe and North America.
- In 1911, Edmund B. Wilson believed the gene is on X chromosome.





X-linked dominant trait in humans

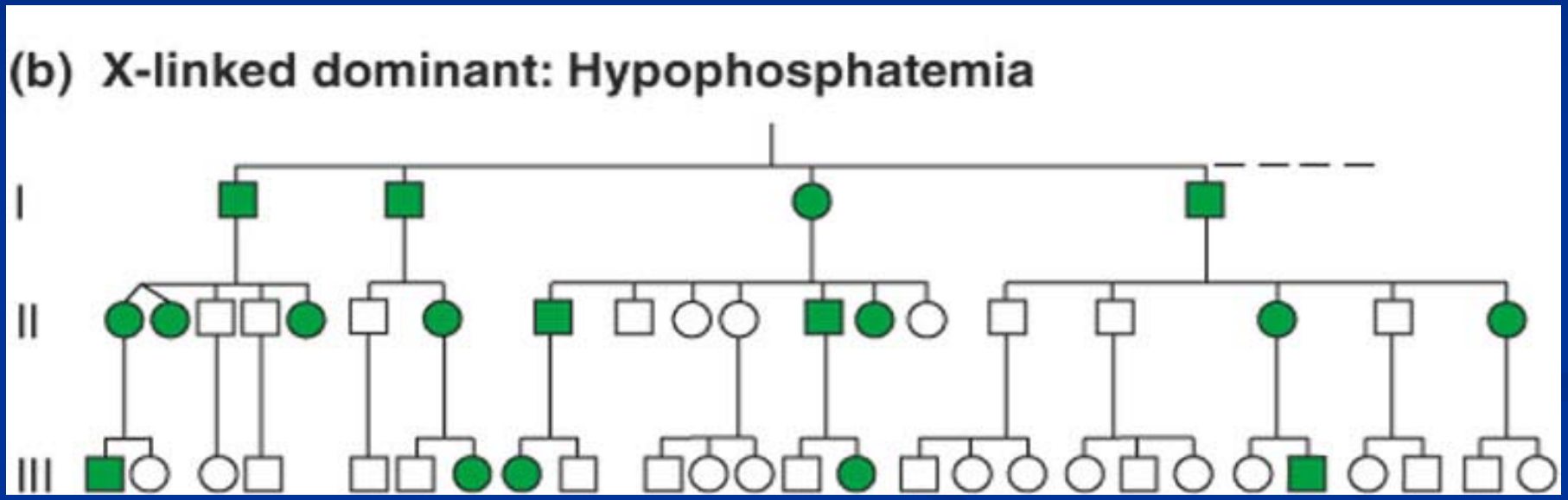


Fig. 4.22 b

TABLE 4.5 Pedigree Patterns Suggesting Sex-Linked Inheritance

X-Linked Recessive Trait

1. The trait appears in more males than females since a female must receive two copies of the rare defective allele to display the phenotype, whereas a hemizygous male with only one copy will show it.
2. The mutation will never pass from father to son because sons receive only a Y chromosome from their father.
3. An affected male passes the X-linked mutation to all his daughters, who are thus unaffected carriers. One-half of the sons of these carrier females will inherit the defective allele and thus the trait.
4. The trait often skips a generation as the mutation passes from grandfather through a carrier daughter to grandson.
5. The trait can appear in successive generations when a sister of an affected male is a carrier. If she is, one-half her sons will be affected.
6. With the rare affected female, all her sons will be affected and all her daughters will be carriers.

X-Linked Dominant Trait

1. More females than males show the aberrant trait.
2. The trait is seen in every generation because it is dominant.
3. All the daughters but none of the sons of an affected male will be affected. This criterion is the most useful for distinguishing an X-linked dominant trait from an autosomal dominant trait.
4. One-half the sons and one-half the daughters of an affected female will be affected.

Y-Linked Inheritance

1. The trait is seen only in males.
2. All male descendants of an affected man will exhibit the trait.
3. Not only do females not exhibit the trait, they also cannot transmit it.