Chapter 12

Chromosomal Rearrangements and Changes in Chromosome Number

Sections to study

12.1 Rearrangements of chromosomal DNA

12.2 The effects of rearrangements

12.3 Transposable genetic elements

12.4 Aberrations in chromosome number: Aneuploidy

12.5 Variation in number of chromosome sets: Euploidy

12.6 Genome reconstructing and evolution

Two types of events that reshape genomes

- Chromosomal rearrangements
  - Rearrangements of DNA sequences within one or more chromosomes.
- Changes in chromosome number
  - Losses or gains of chromosomes or sets of chromosomes.

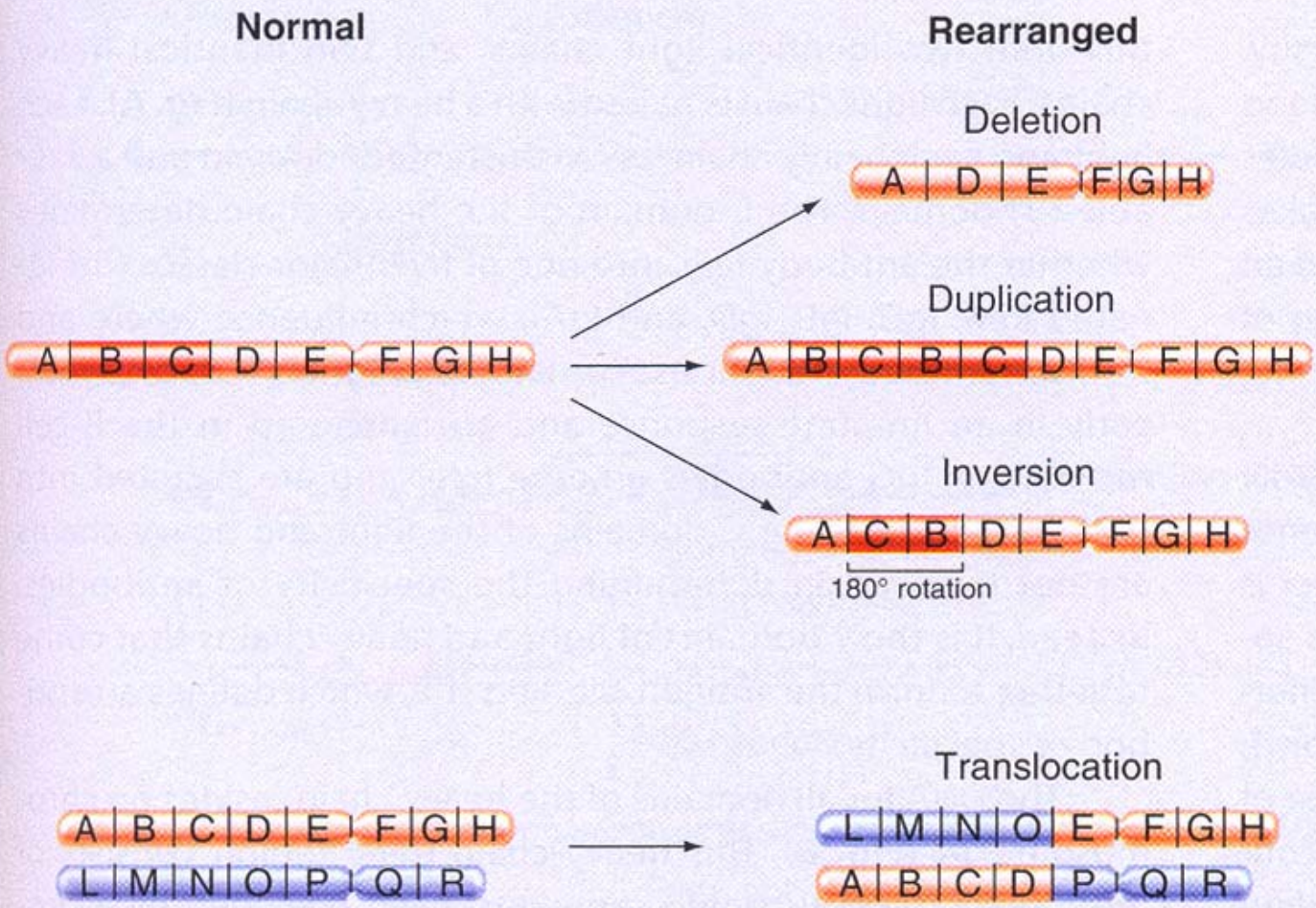
Significance:

- Forces that drive the evolution of new species
  - Chromosome rearrangement
  - Genome duplication

12.1 Rearrangements of chromosomal DNA

TABLE 12.1 Major Classes of Chromosomal Rearrangements

Letters represent large chromosomal regions. Different (nonhomologous) chromosomes are indicated as *red* and *blue*.



Chromosome breakage and subsequent DNA repair can result in all classes of chromosomal rearrangements.

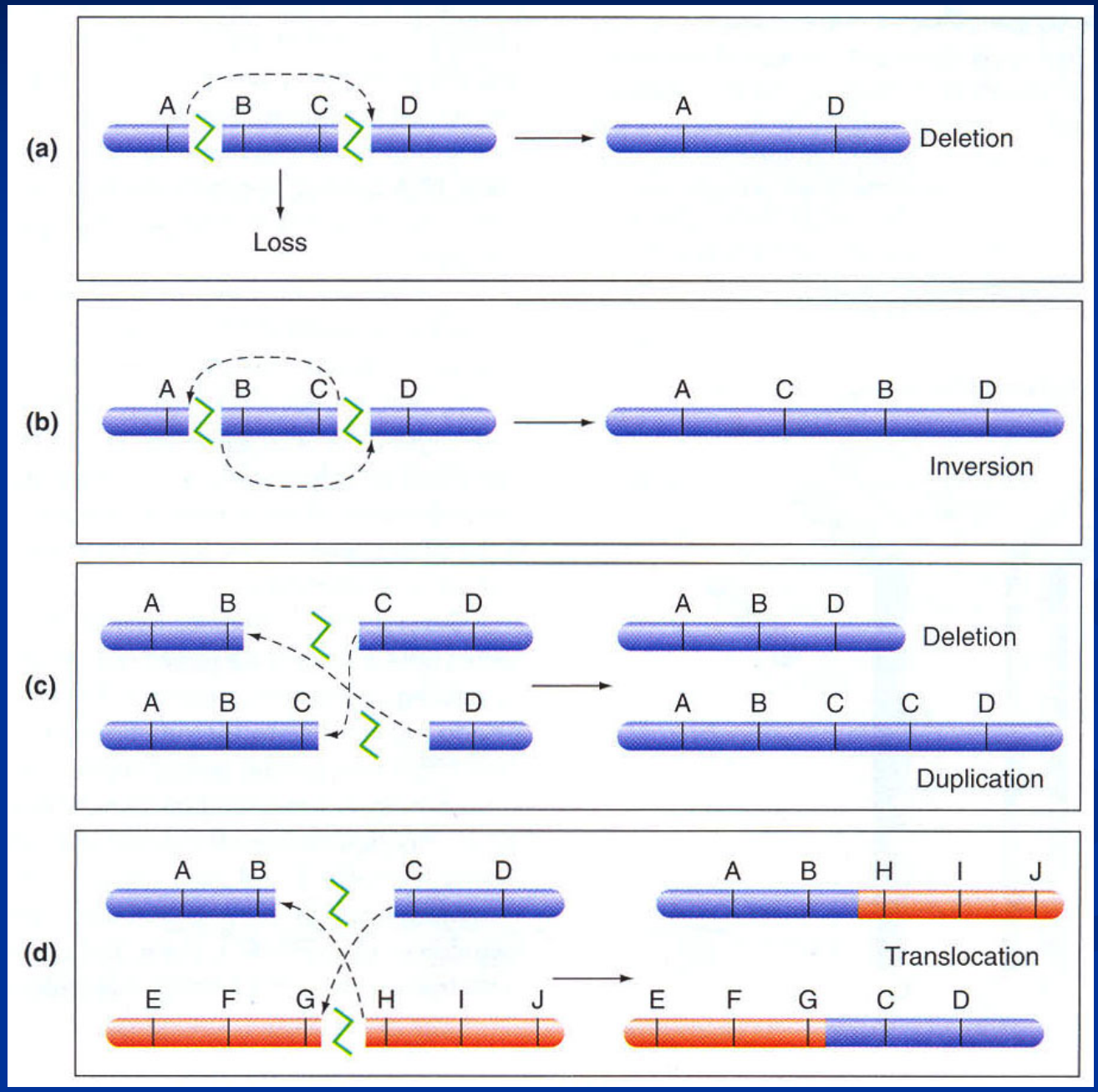


Fig 12.2

Aberrant crossing-over at repeated sequences can also produce rearrangements.

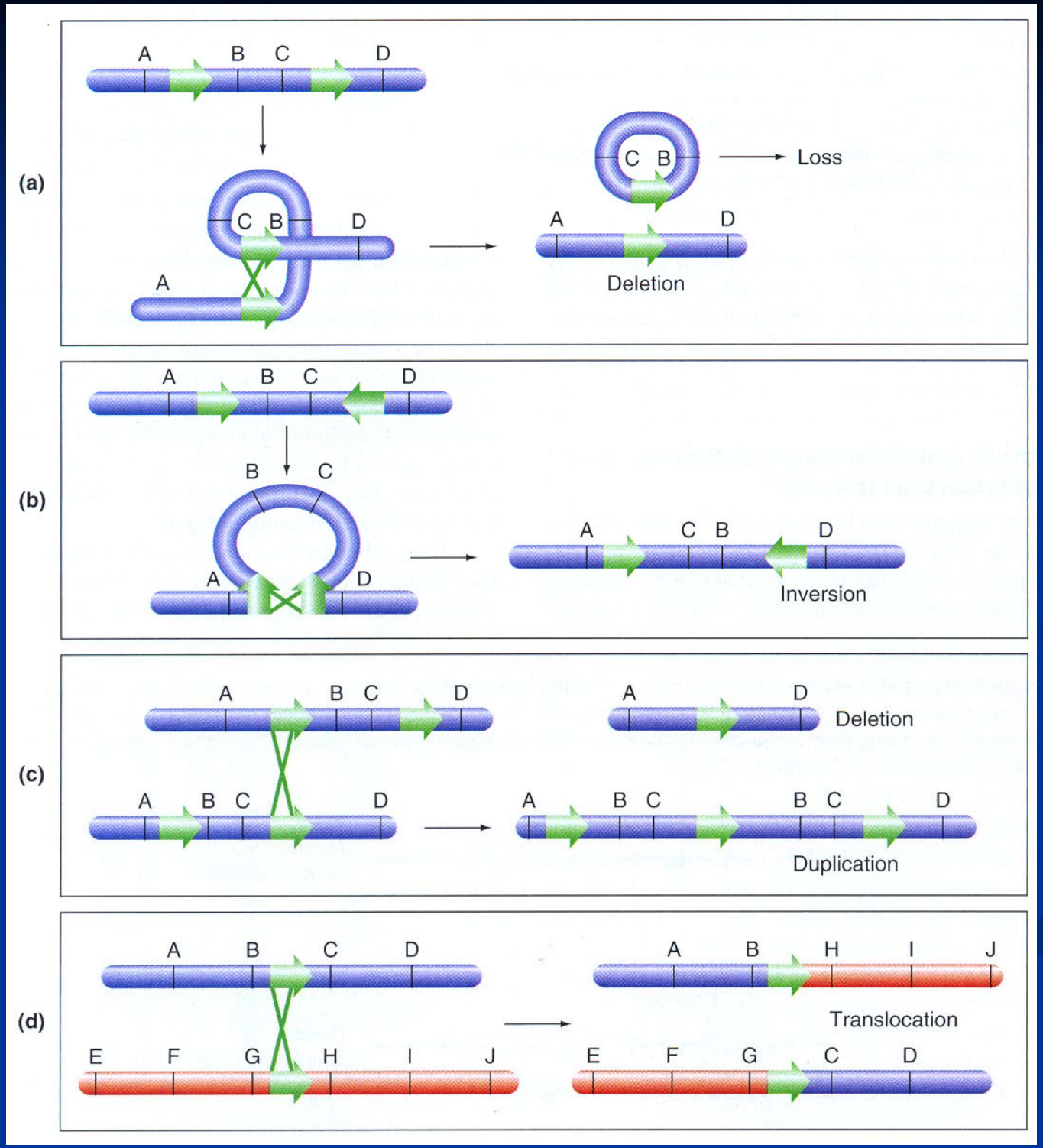


Fig 12.3

A variety of methods can detect chromosomal rearrangements

- Fluorescent *in situ* hybridization (FISH)
- PCR

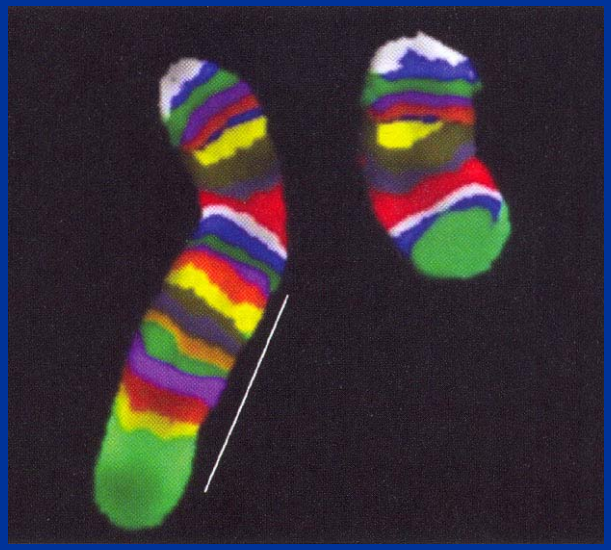
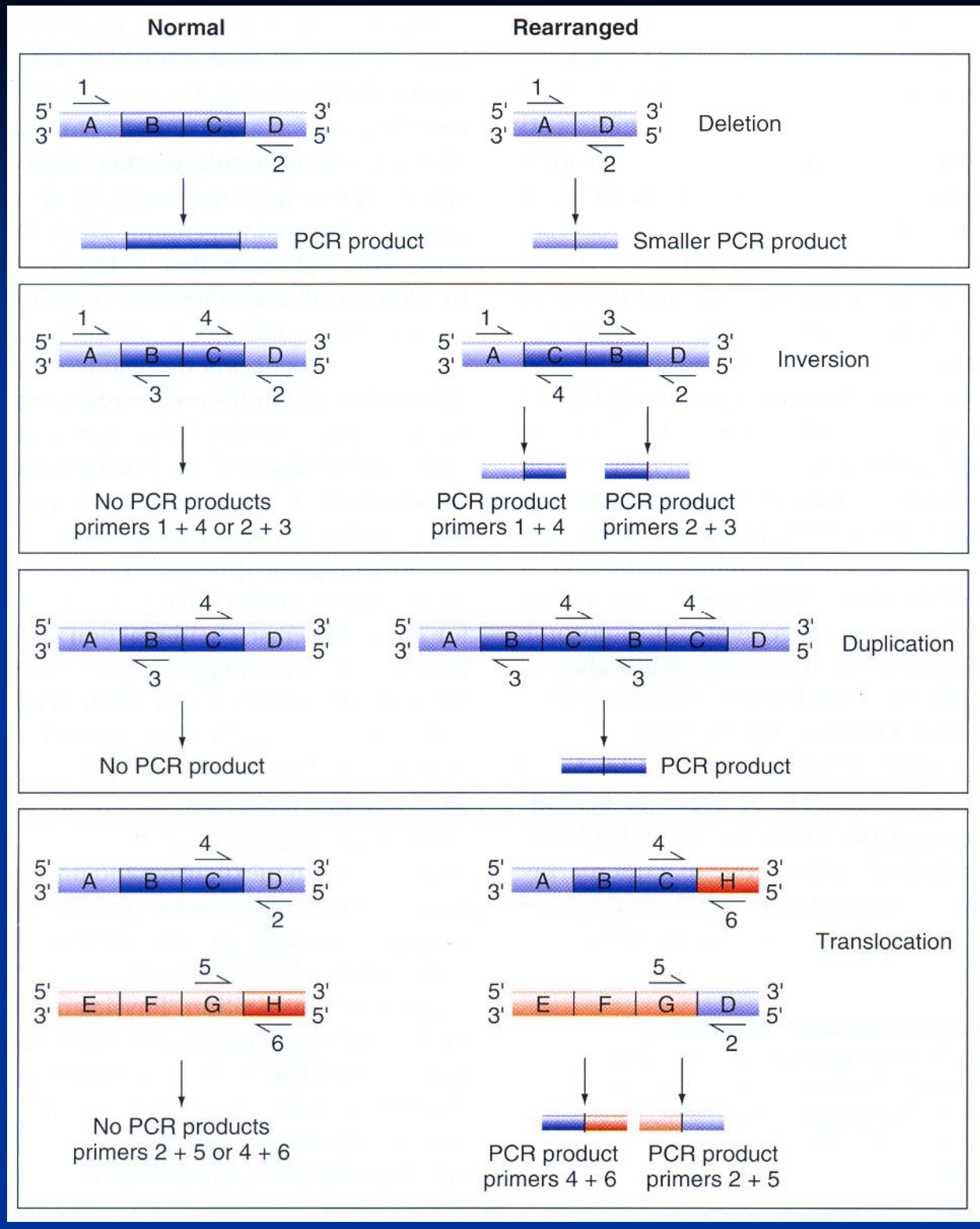
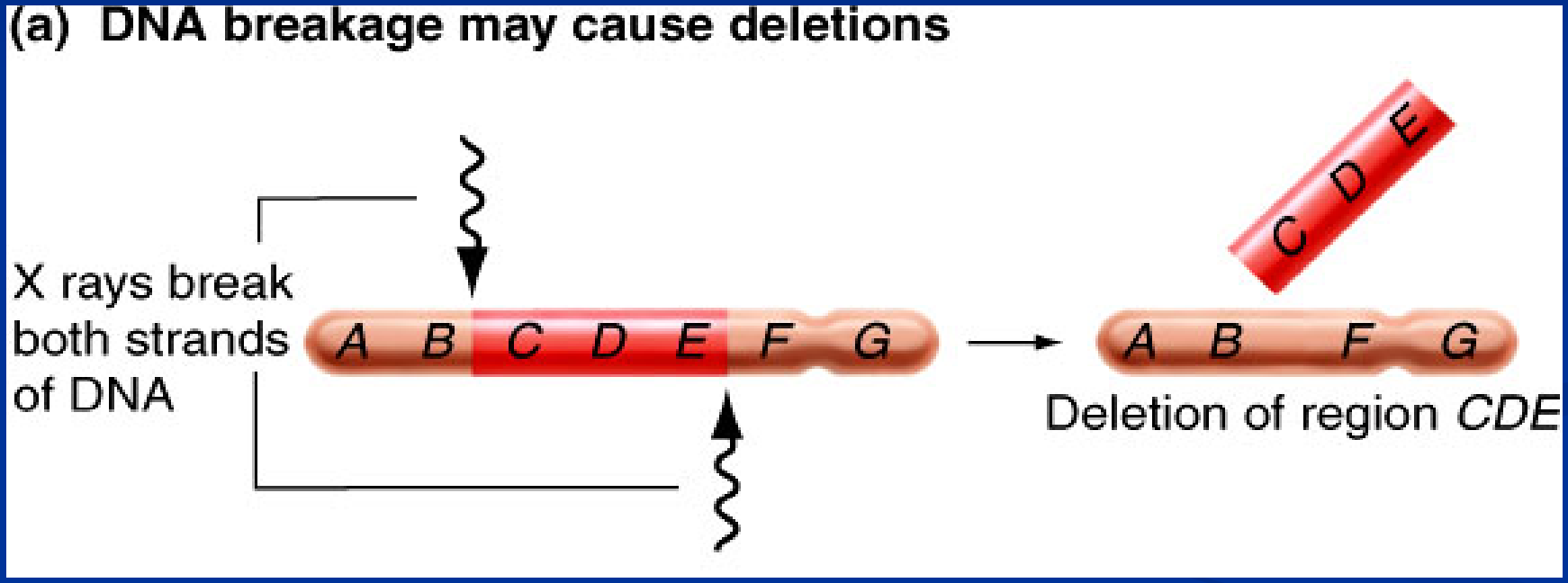


Fig. 12.5



12.2 The effects of rearrangements

1. Deletions remove DNA from the genome.



Deletions may have phenotypic consequences

- **Homozygosity** for a deletion is often, but not always, lethal.
- **Heterozygosity** for a deletion is often detrimental. Even small deletions can be harmful.
  - **Haploinsufficiency**: Half of the normal gene dosage does not produce enough protein product for a normal phenotype.
  - Vulnerability to mutation that inactivate the remaining copy of a gene. For example, RB^{-}/RB^{+}

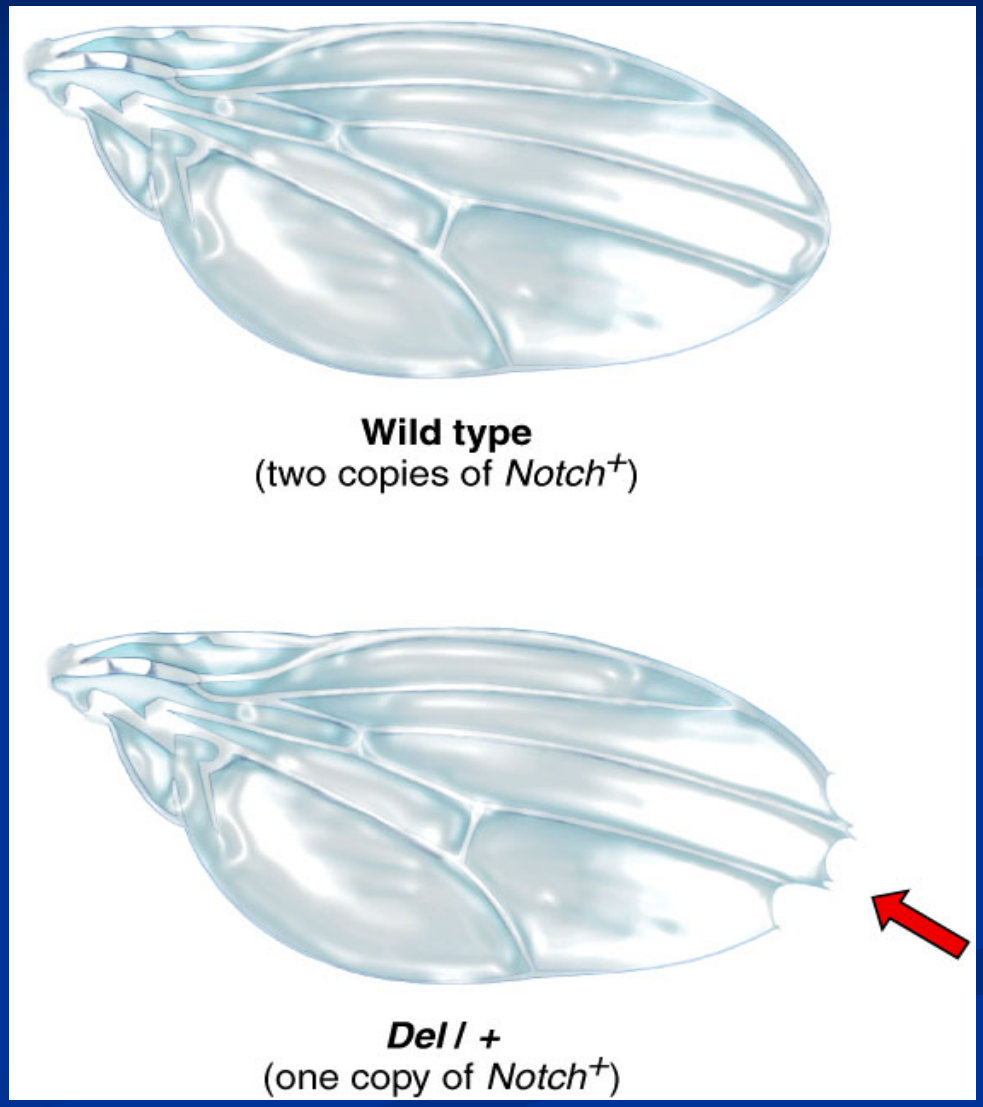


Fig. 12.9

Deletions in heterozygotes can "uncover" genes

- **Pseudodominance** – A deletion uncovers the phenotype of a recessive mutation.

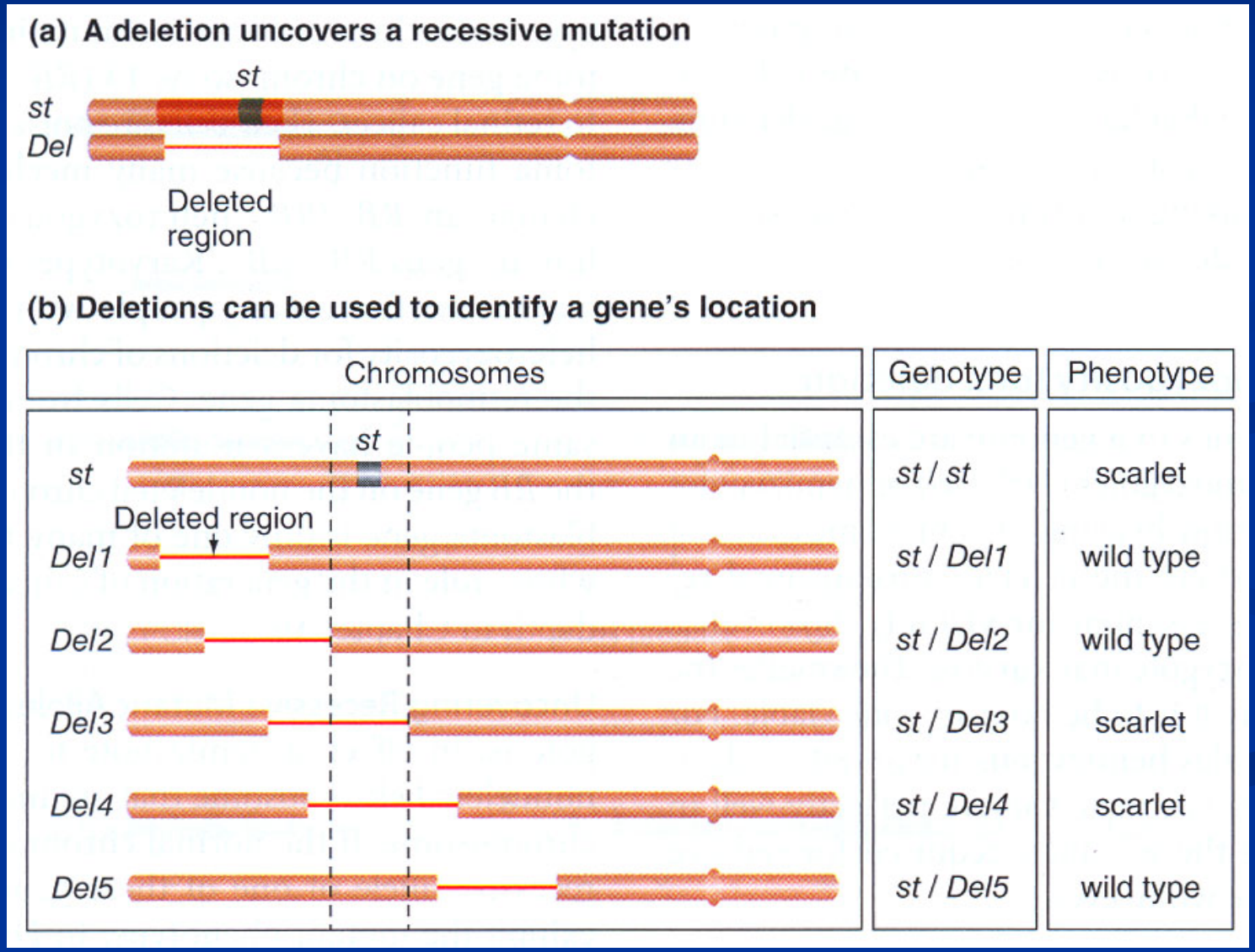
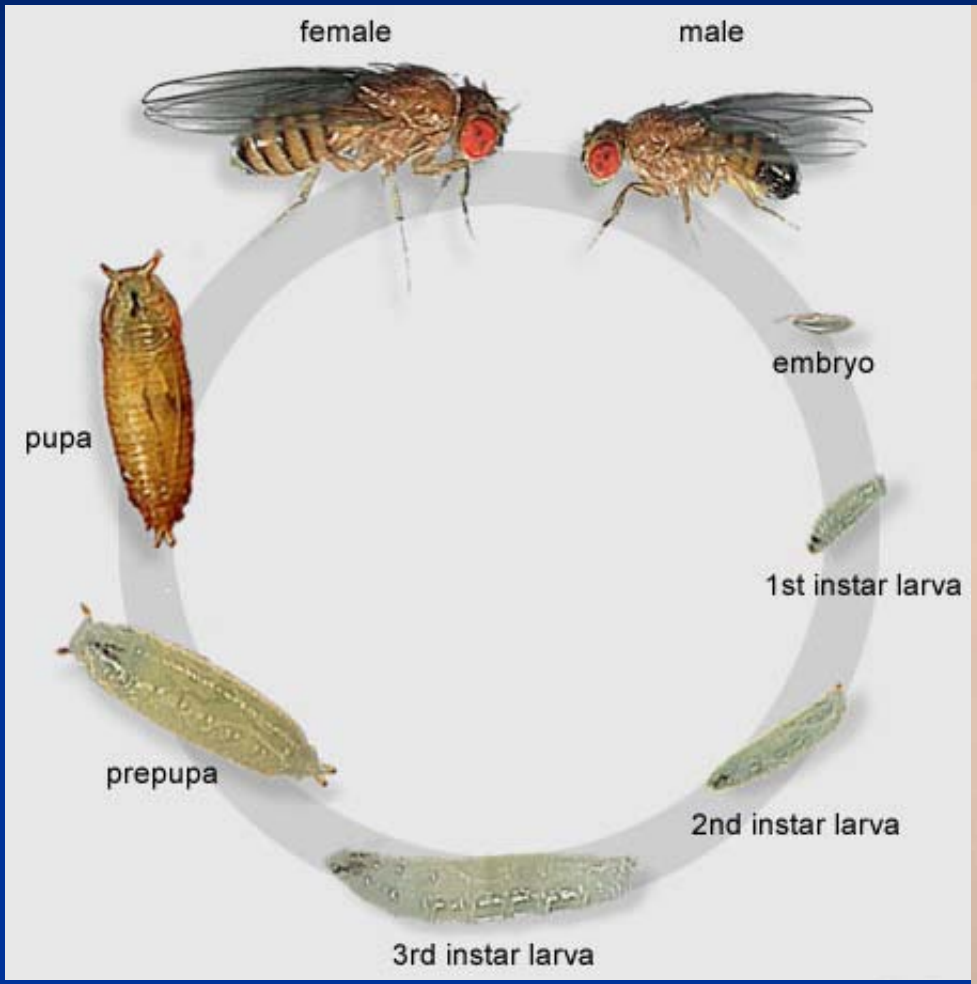


Fig. 12.6

Polytene chromosomes (多线染色体) in *Drosophila* salivary glands can be used to map deletions



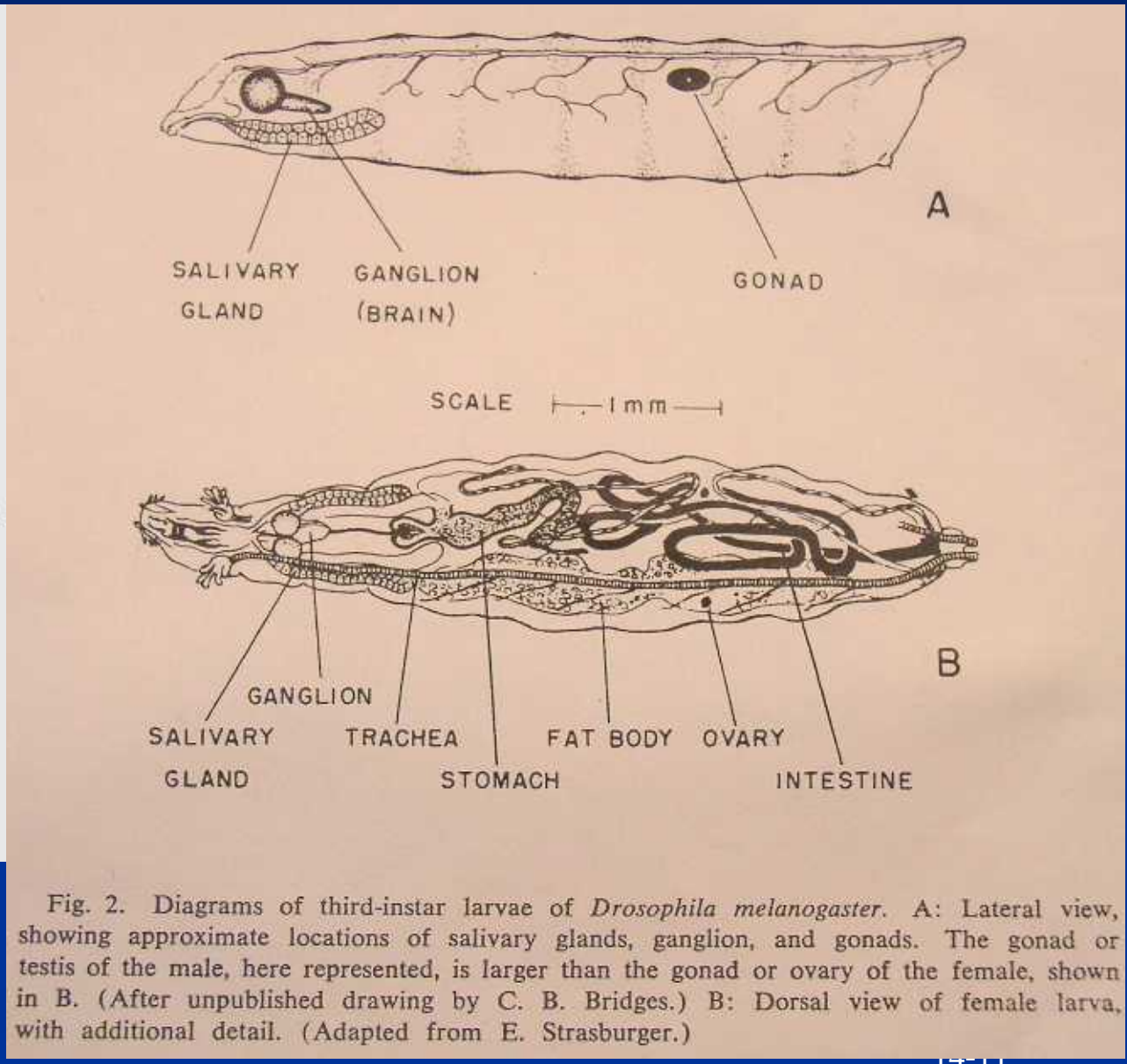
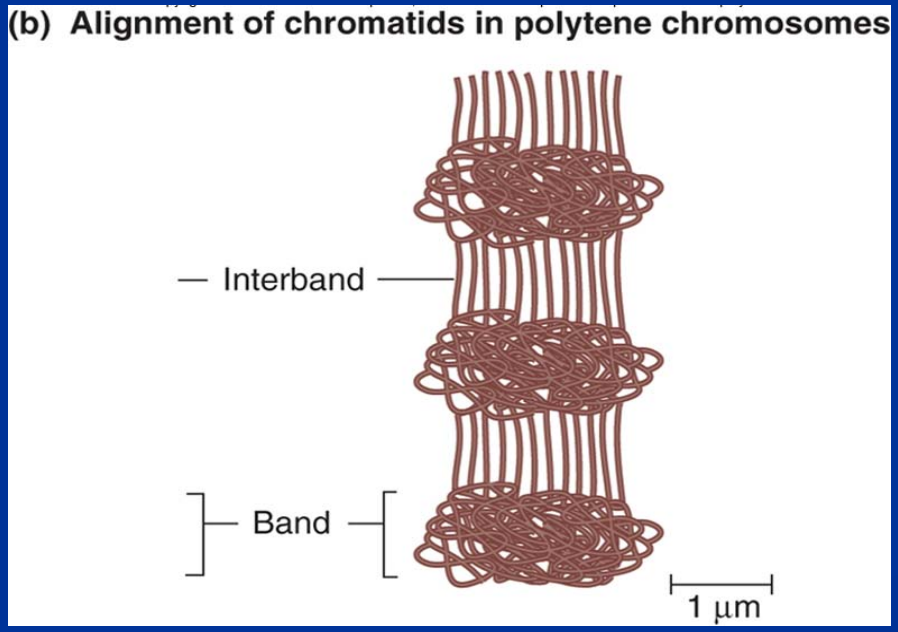
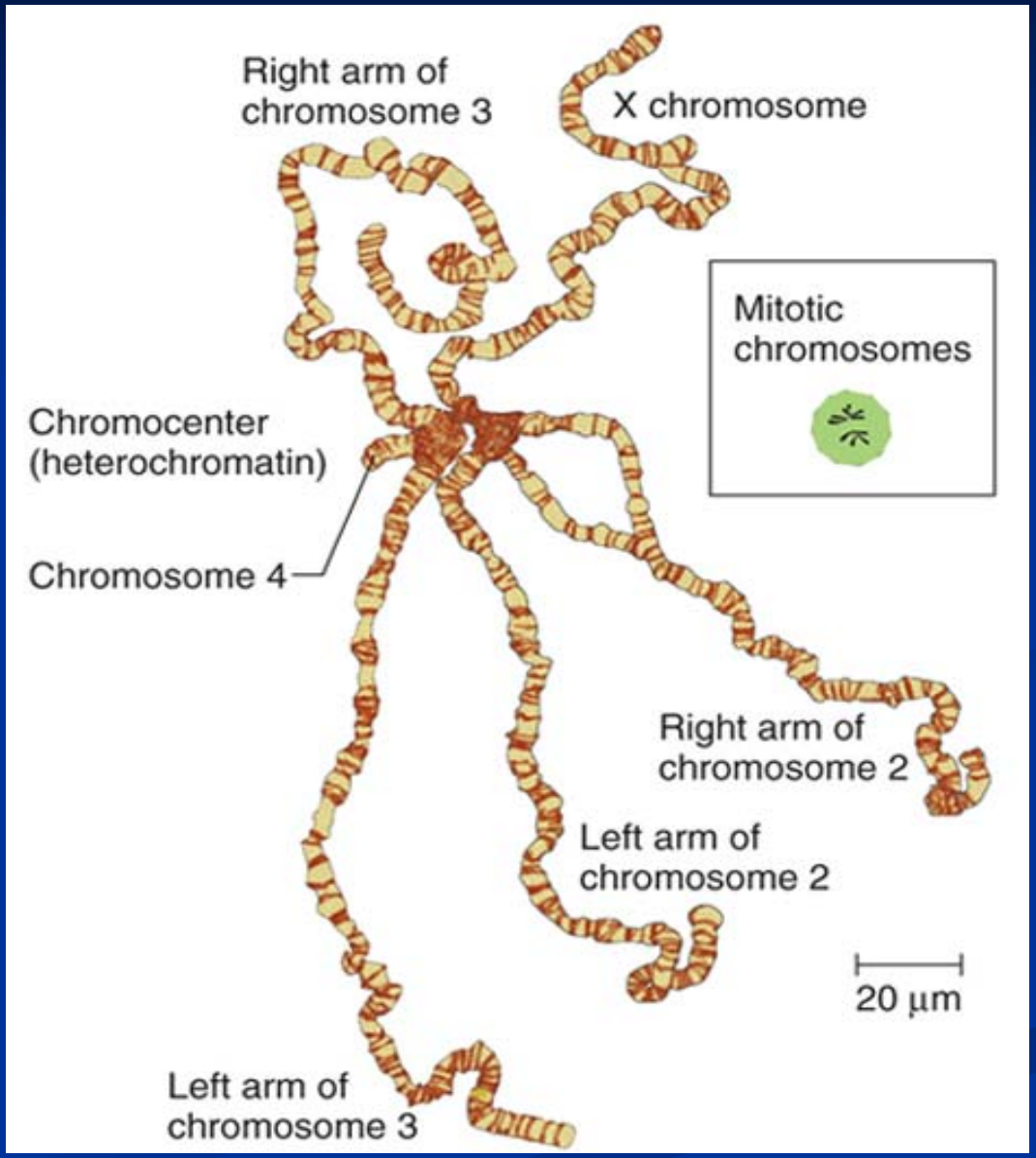


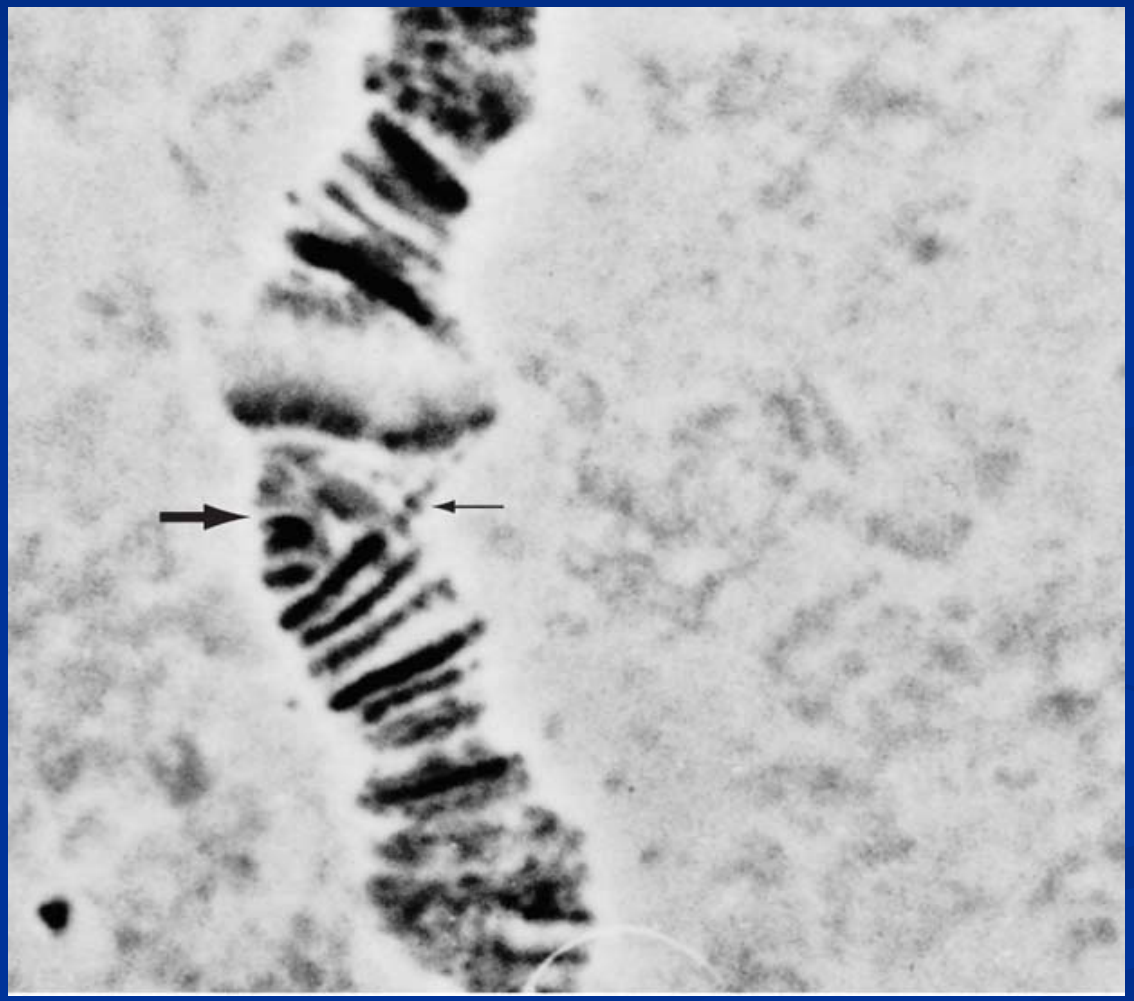
Fig. 2. Diagrams of third-instar larvae of *Drosophila melanogaster*. A: Lateral view, showing approximate locations of salivary glands, ganglion, and gonads. The gonad or testis of the male, here represented, is larger than the gonad or ovary of the female, shown in B. (After unpublished drawing by C. B. Bridges.) B: Dorsal view of female larva, with additional detail. (Adapted from E. Strasburger.)

- Interphase chromosomes replicate 10 times.
  - Each chromosome consists of 2^{10} (1024) double helices.
- Reproducible bands provide detailed physical guide to gene mapping.
  - Total of about 5000 bands ranging from 3 kb to 150 kb.



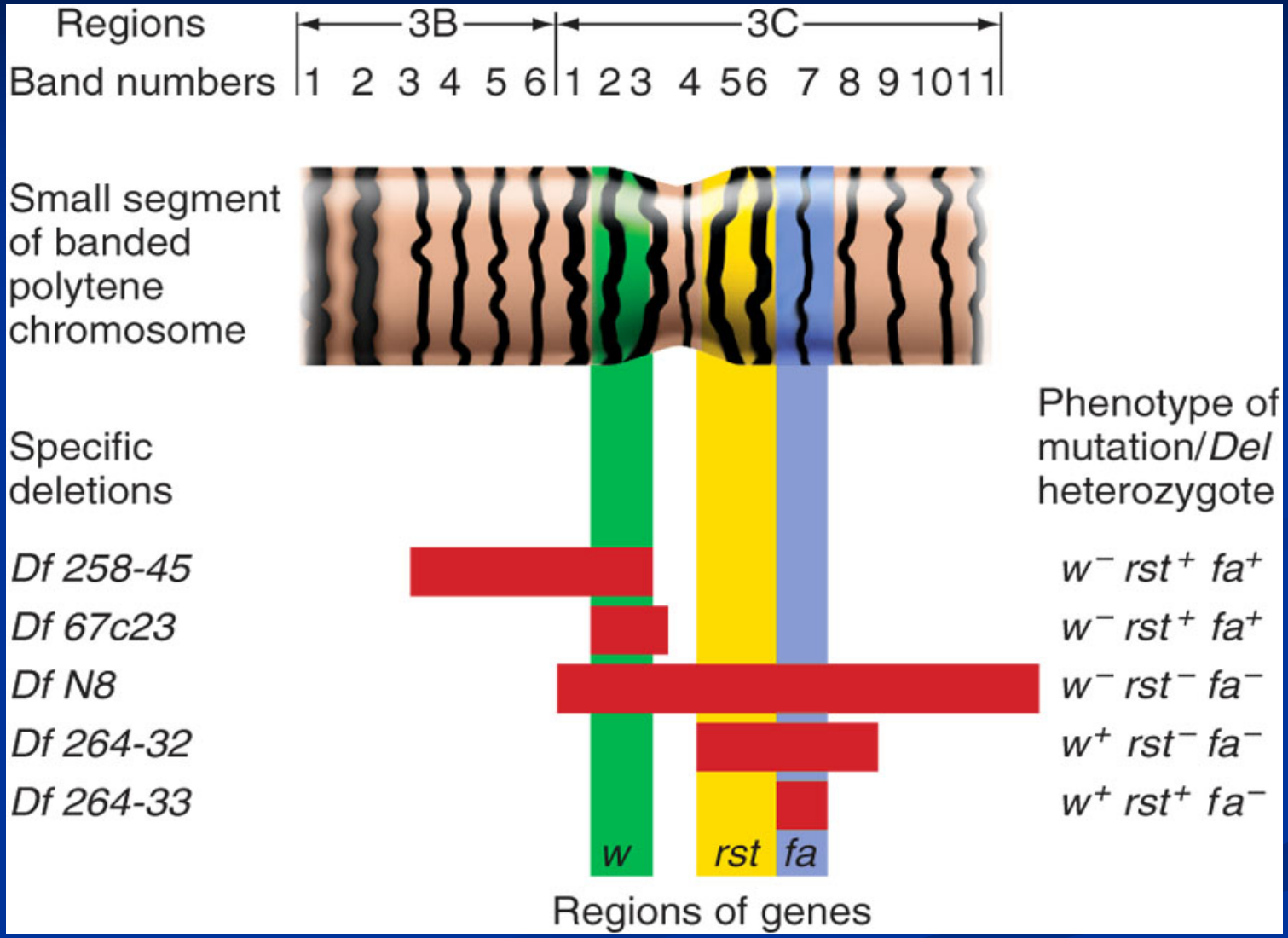


- ***Drosophila*** **deletion heterozygotes form visible deletion loops in the paired polytene chromosomes**



Deletions can be used to locate genes

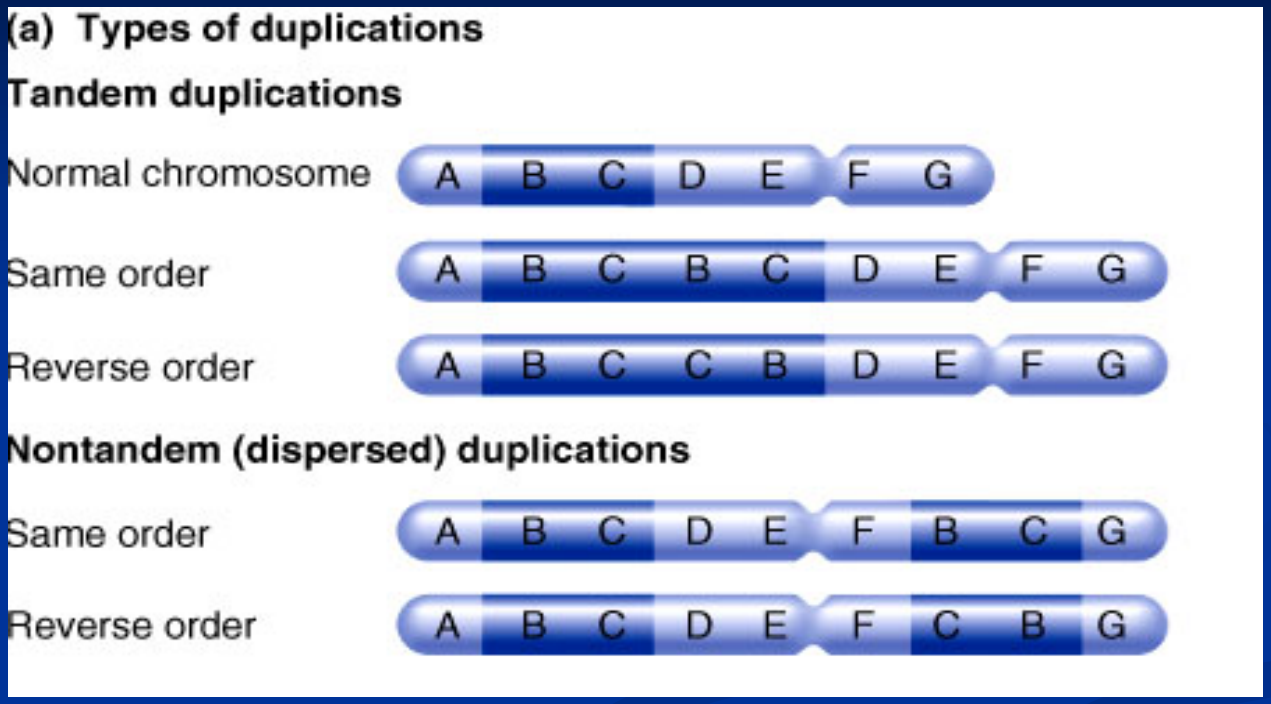
- Deletions to assign genes to bands on *Drosophila* polytene chromosomes.
- Complementation tests crossing deletion mutants with mutant genes of interests.
- Deletion heterozygote reveals chromosomal location of mutant gene.



Drosophila white **(w^+),** ***roughest*** **(rst^+), and** ***facet*** **(fa^+) genes on the X chromosome**

2. Duplications chromosomes have extra copies of some genes

Duplications add material to the genome.



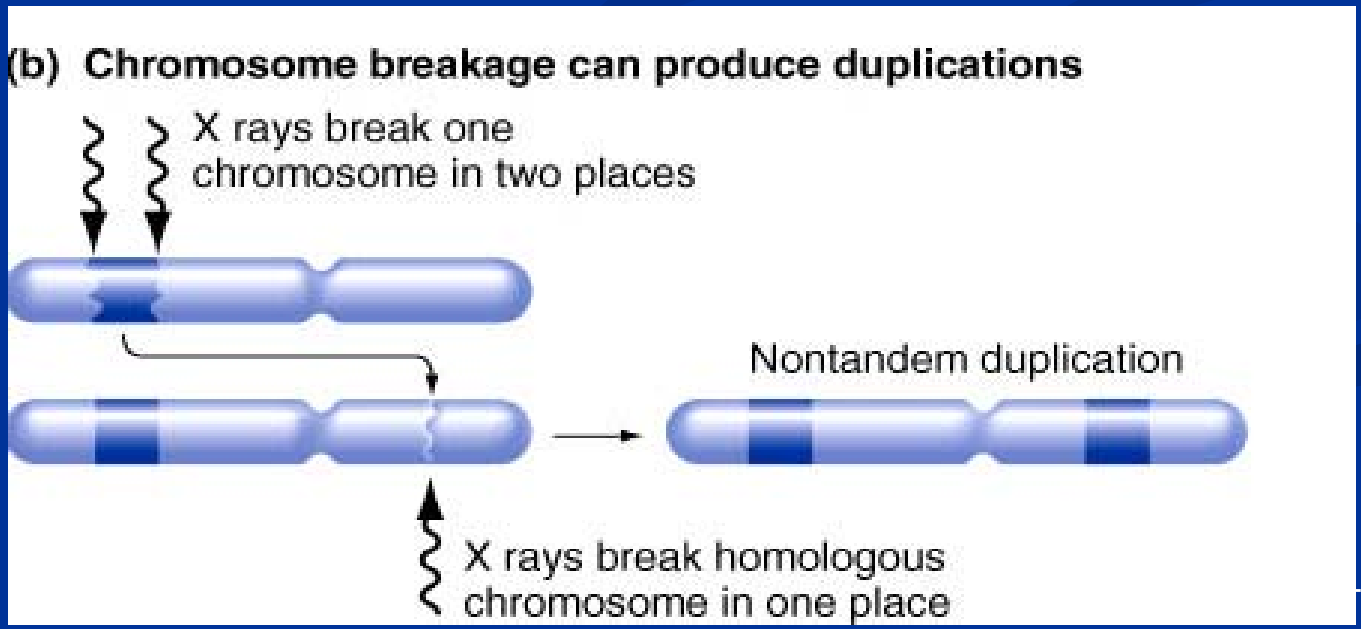
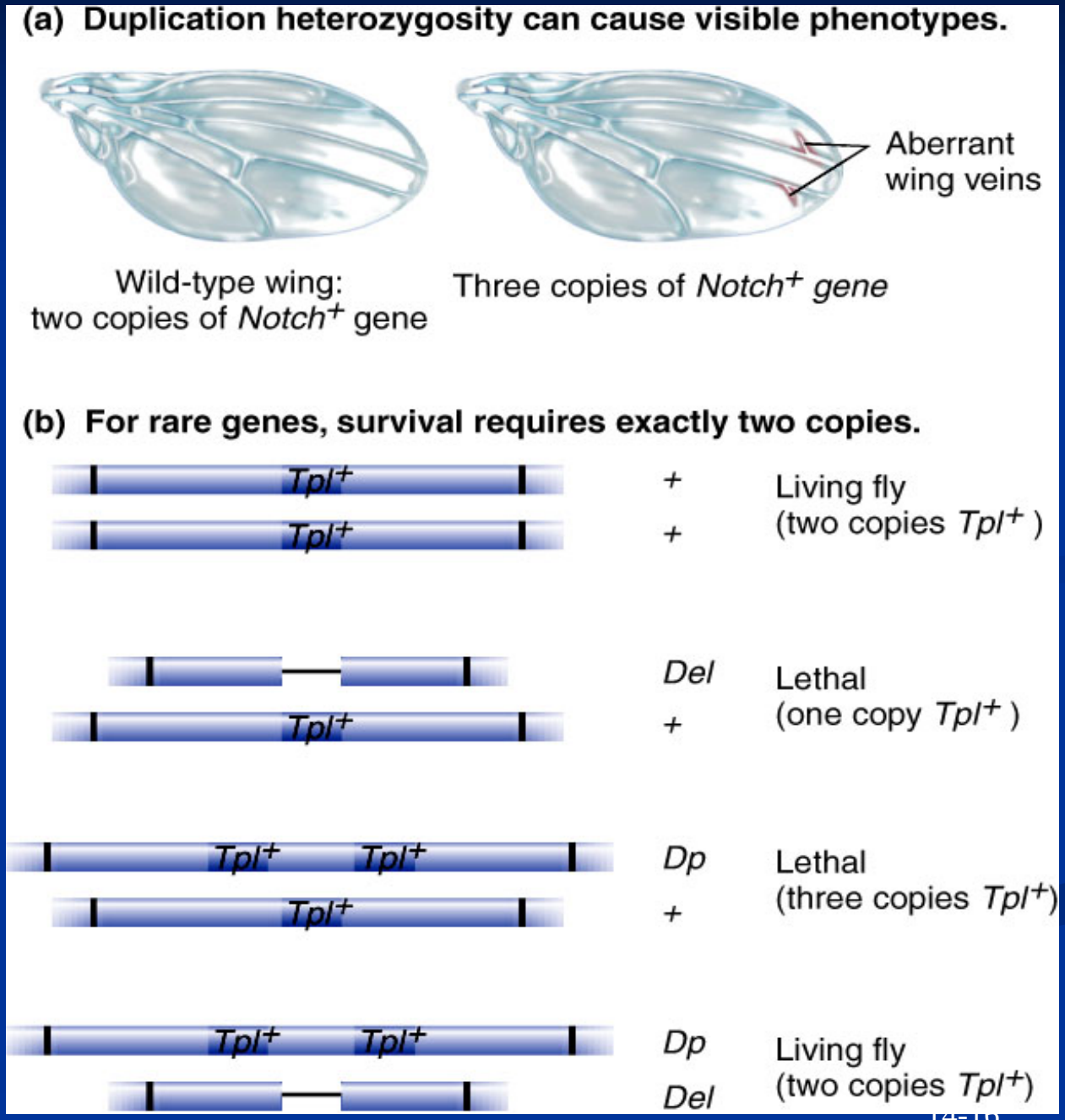


Fig. 12.8

Duplications can affect phenotype

- **Novel phenotypes**
  - **More gene copies.**
  - **Genes next to duplication displaced to new environment altering expression.**

Drosophila Triplolethal (Tpl^+) locus



Unequal crossing over between duplications increases or decreases gene copy number

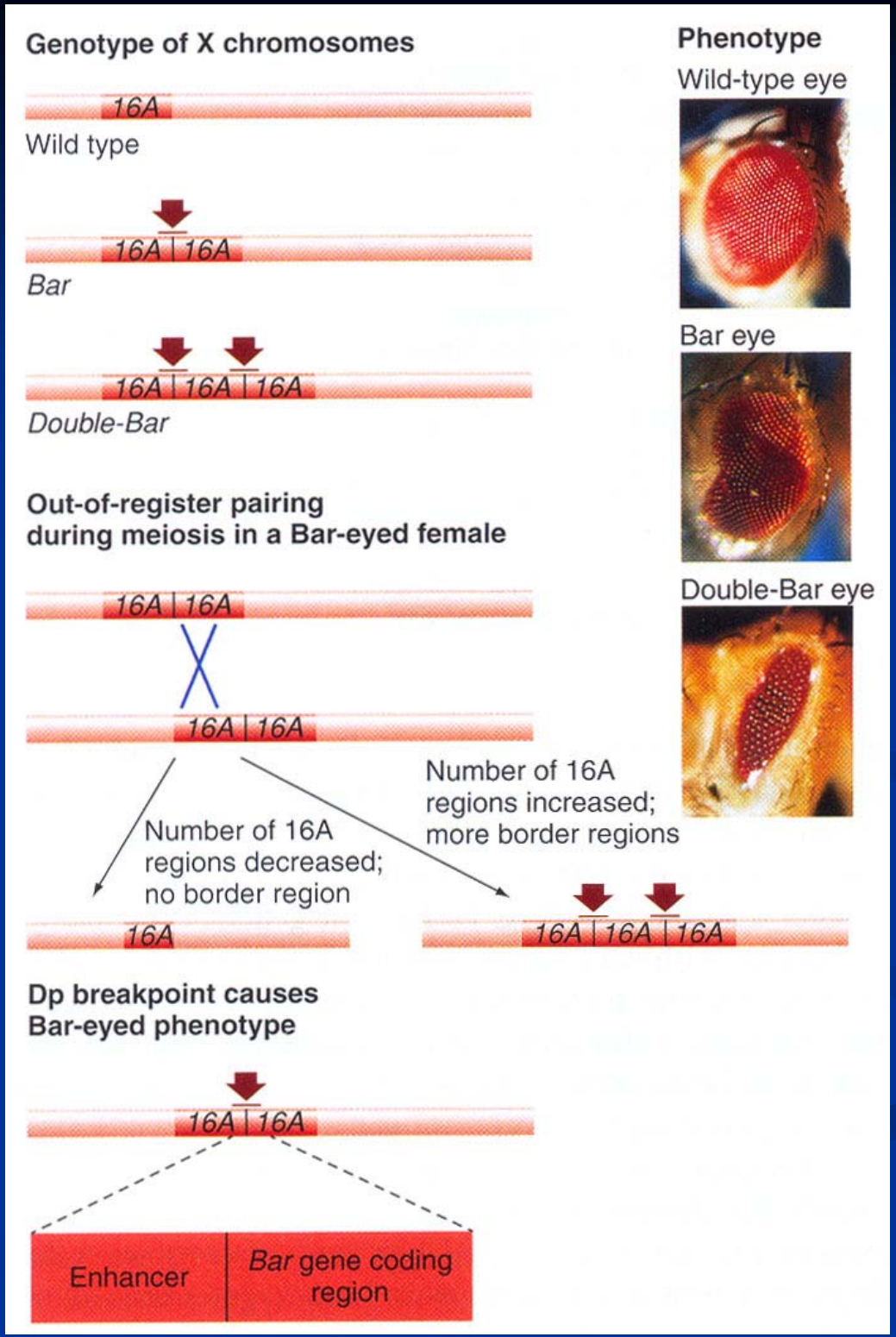


Fig. 12.10

3. Inversions reorganize the DNA sequence of a chromosome

- Produced by half rotation of chromosomal regions after double-stranded break.
- Also by rare crossover between related genes in opposite orientation or transposition.

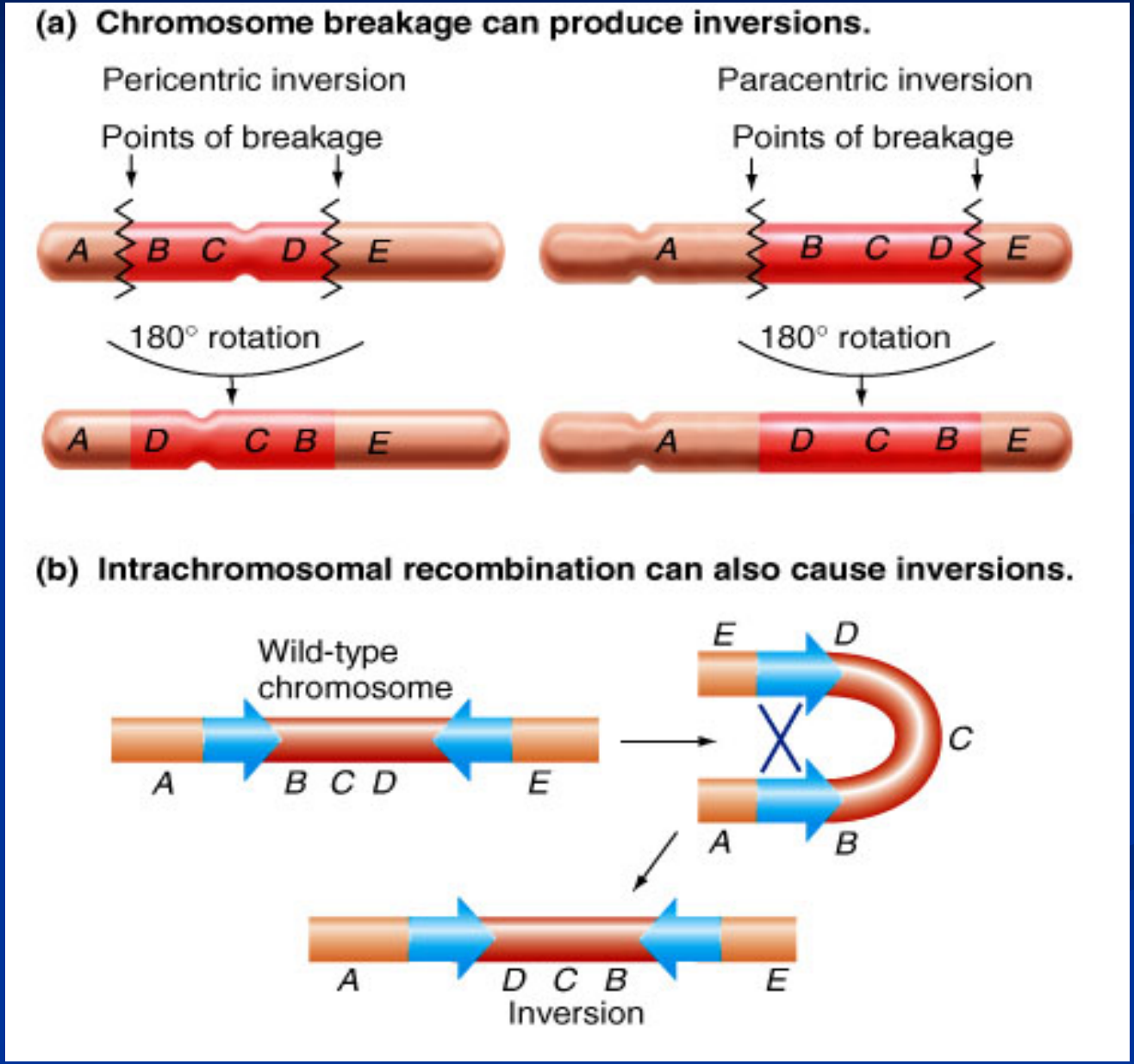
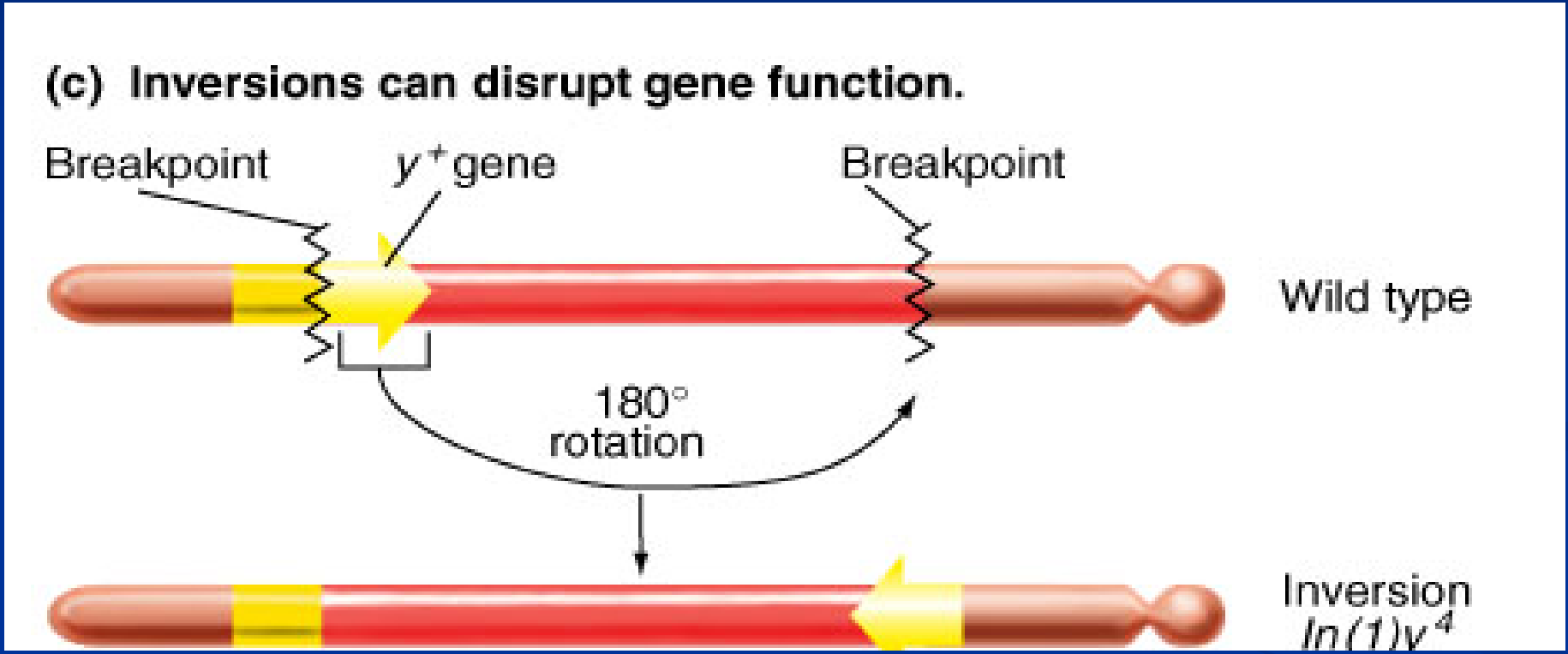


Fig. 12.11

An inversion can affect phenotype if it disrupts a gene

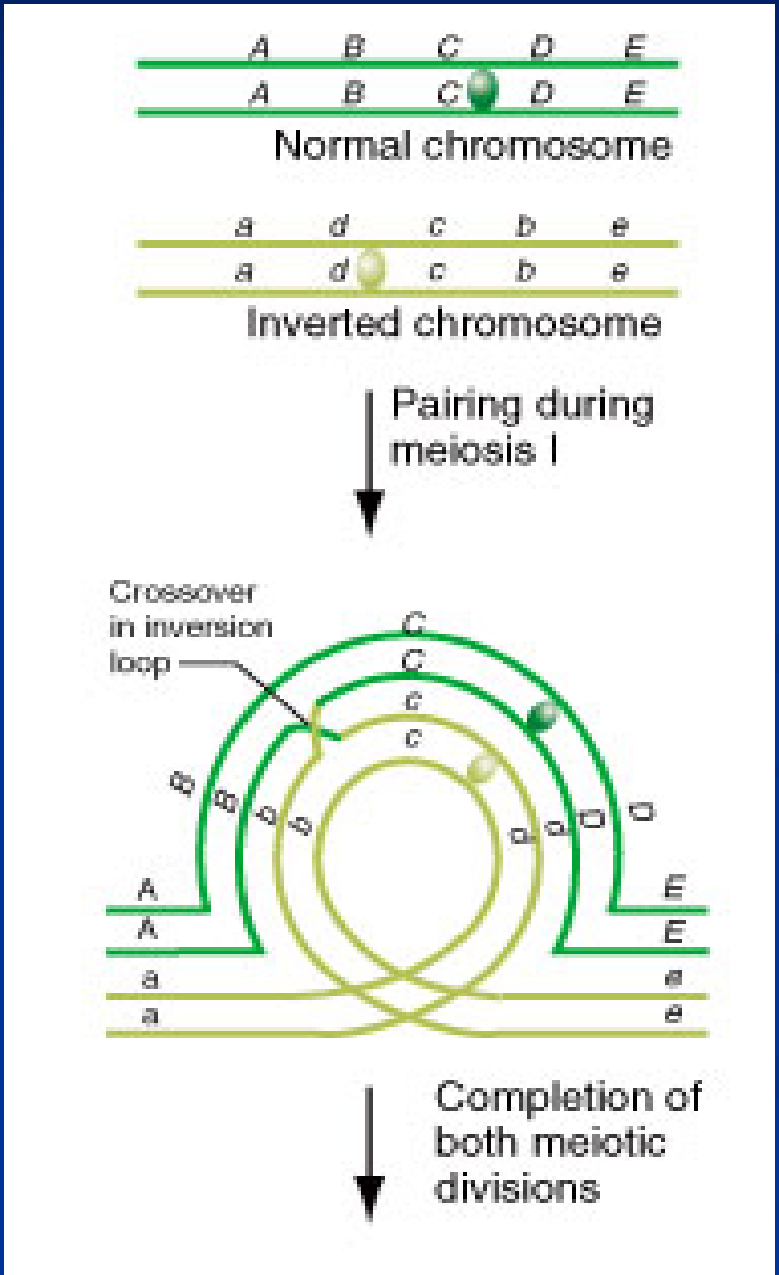


Drosophila yellow (y^+) gene

Fig. 12.12

Inversion heterozygotes produce few, if any, recombinant progeny

Pericentric inversion heterozygote



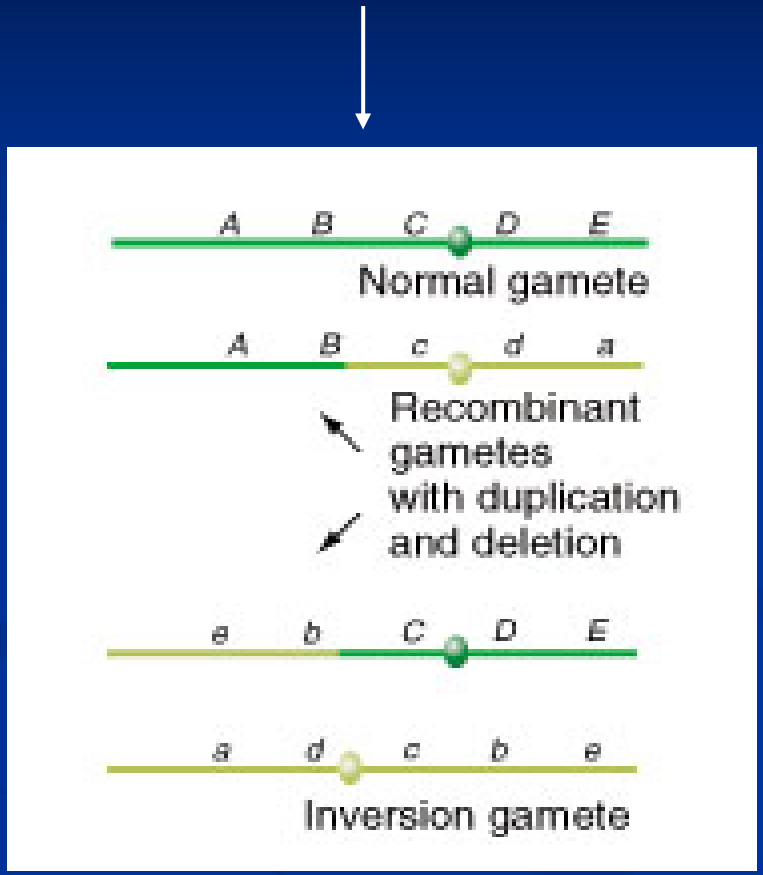


Fig. 12.14

Paracentric inversion heterozygote

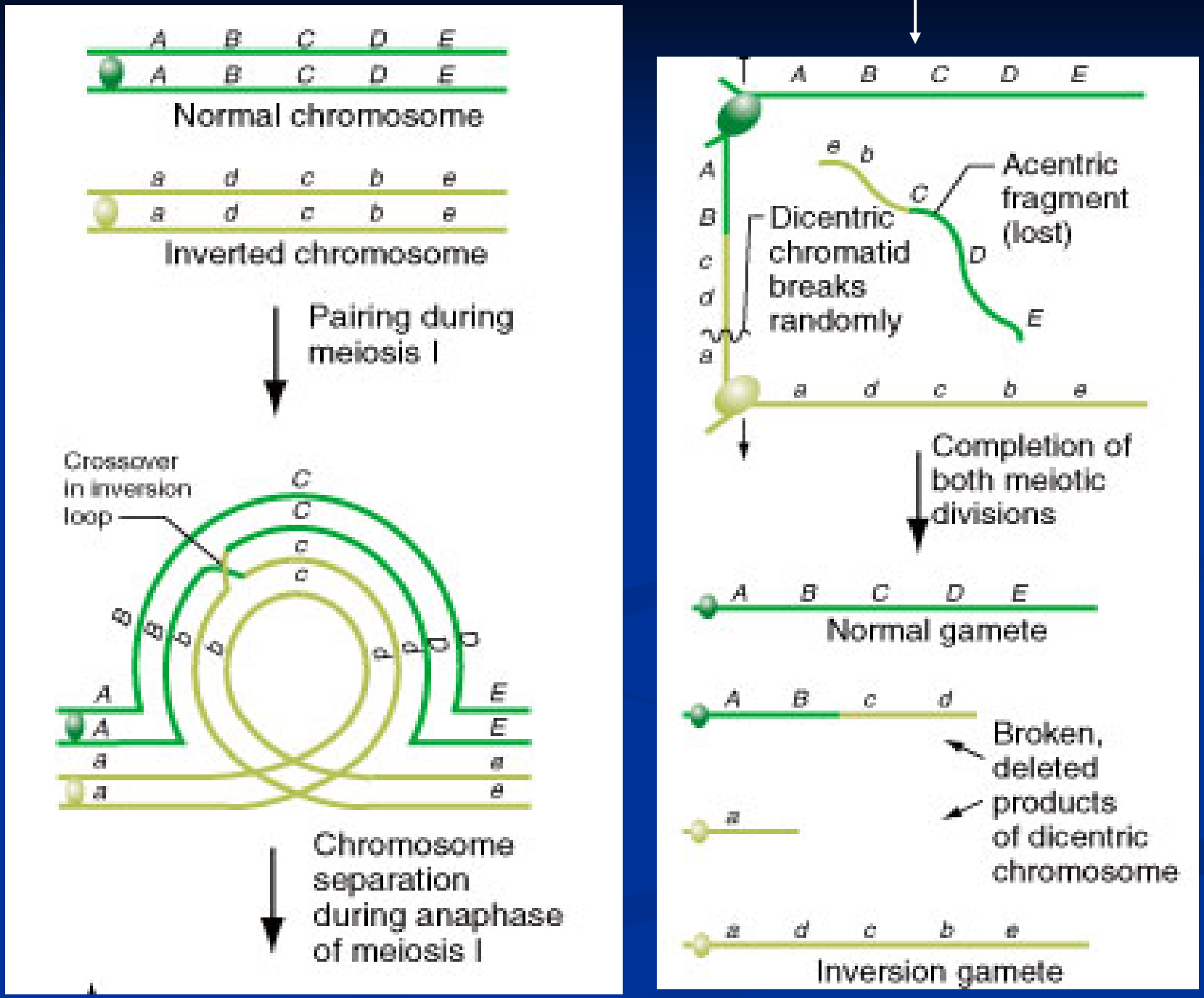


Fig. 12.14

Balancer chromosomes are useful tools for genetic analysis

- **Balancer chromosomes**
  - Carry multiple overlapping **inversions** that prevent recombination with normal chromosome.
  - Carry a **dominant marker** that produces a visible phenotype.

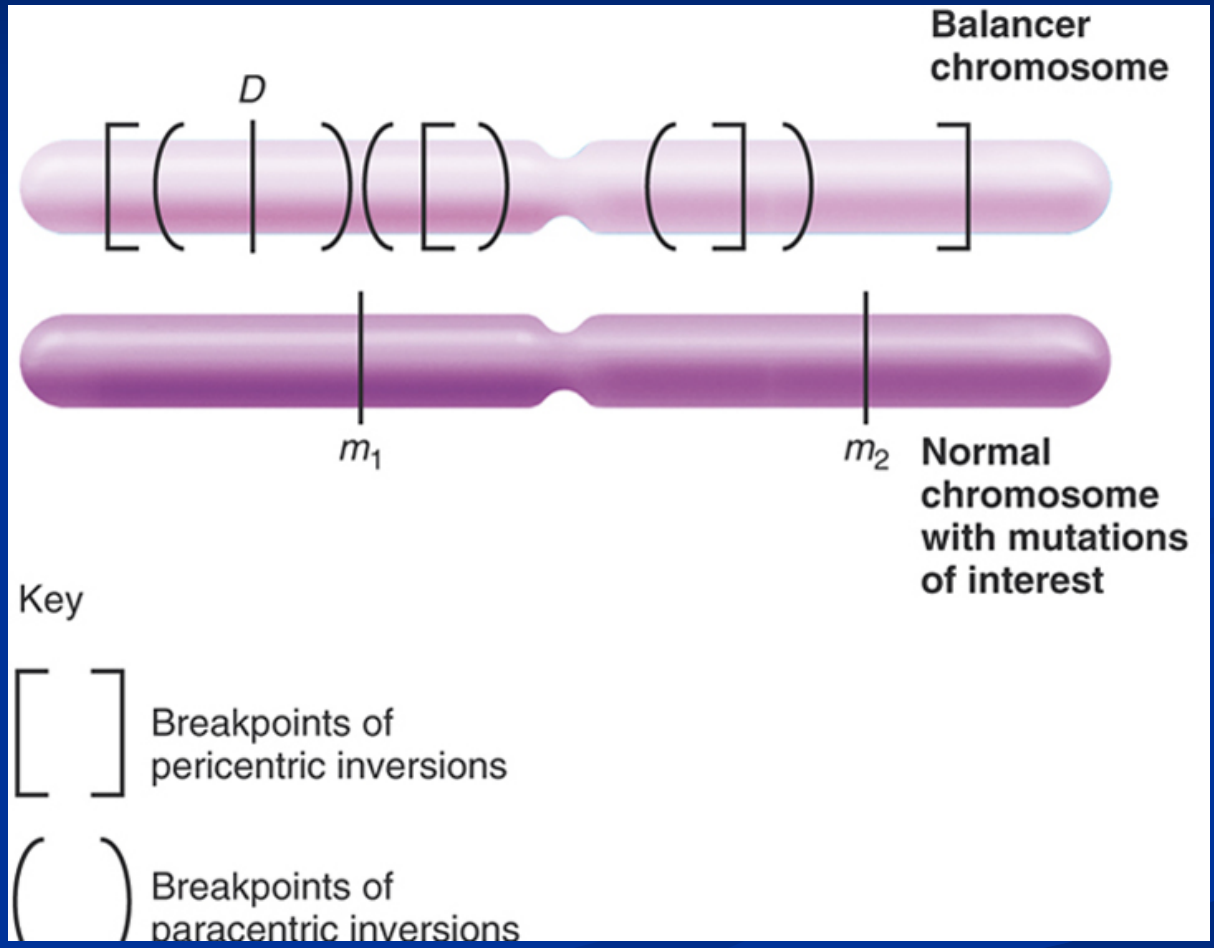
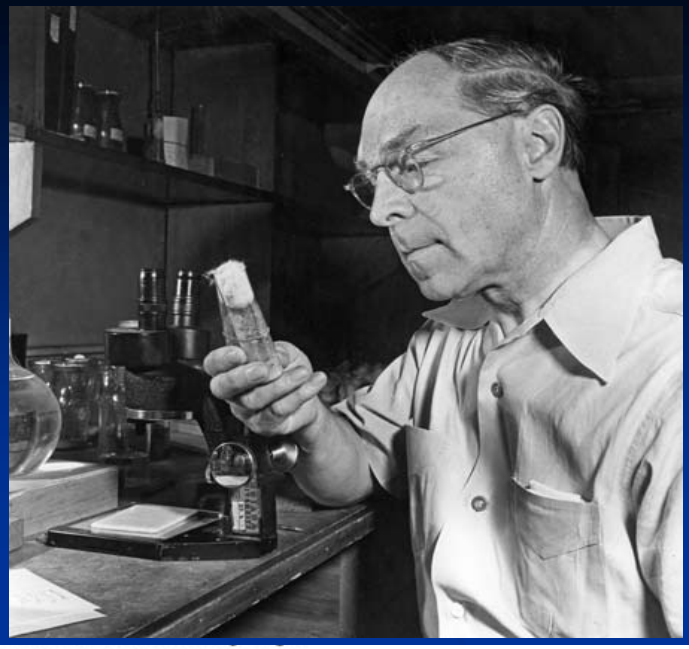


Fig. 12.15

Hermann Muller's experiment on X-ray's mutagenic effect



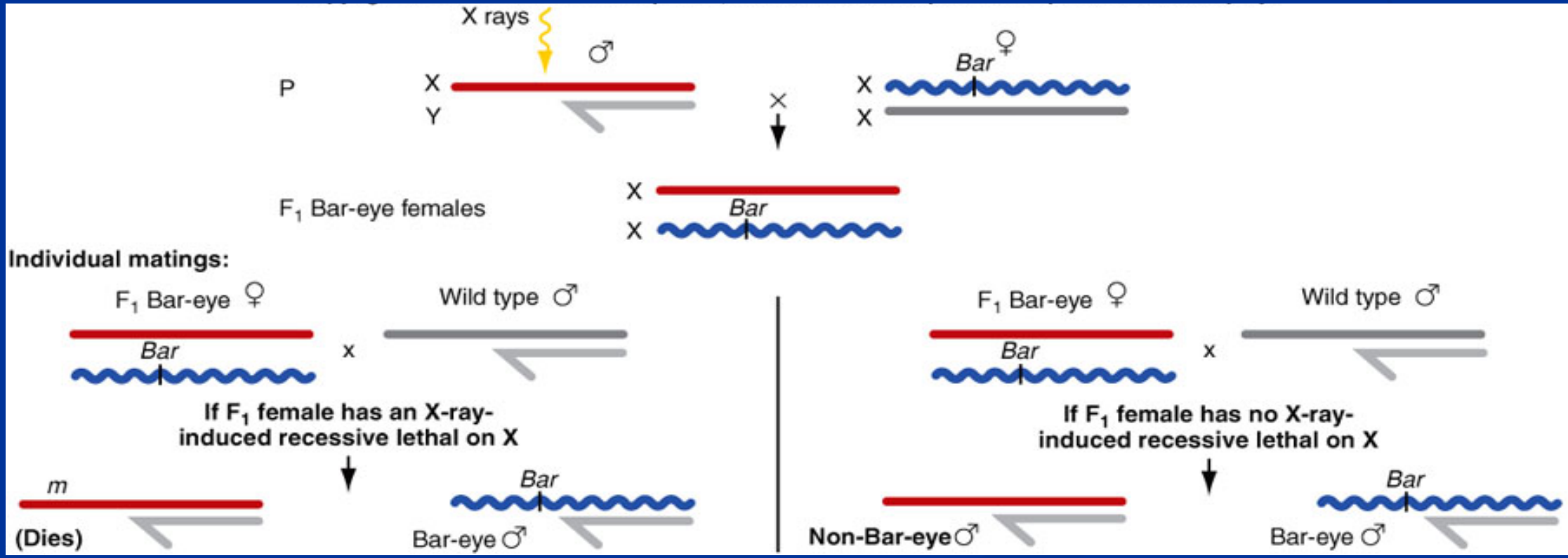
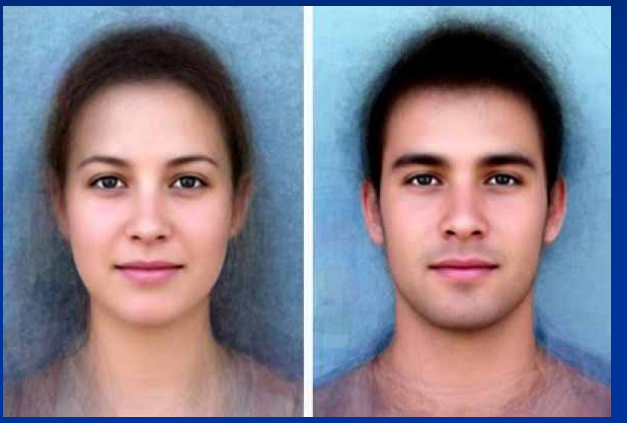
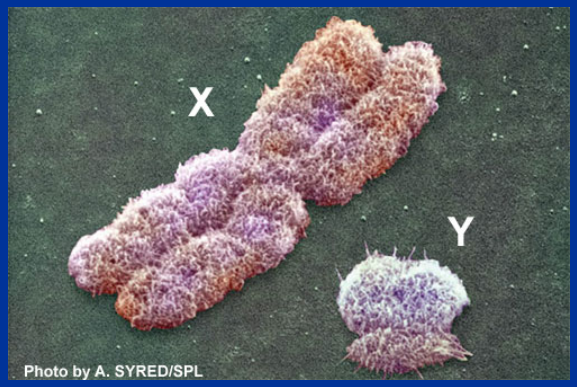
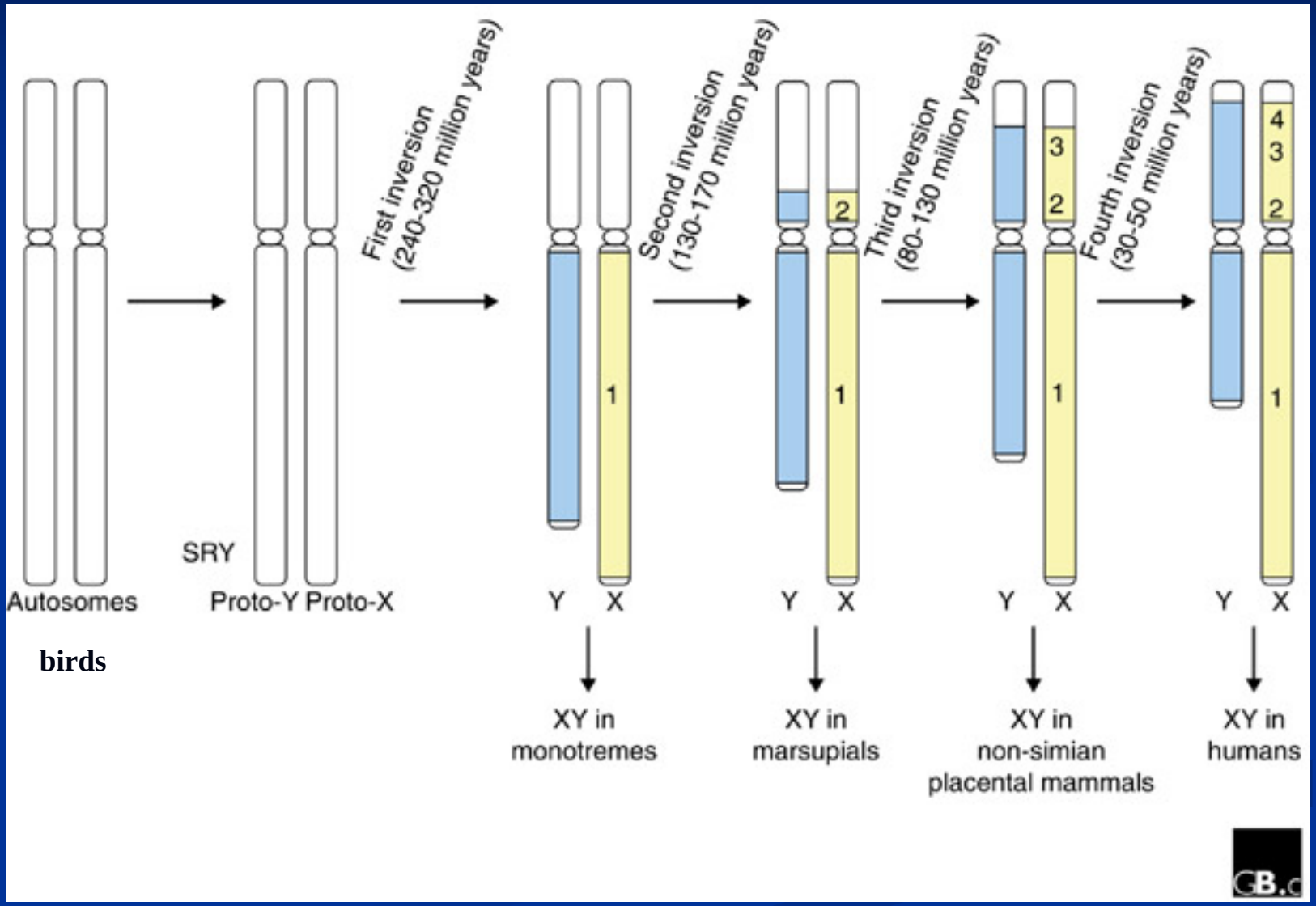


Fig. 7.13

The evolution of the human Y chromosome

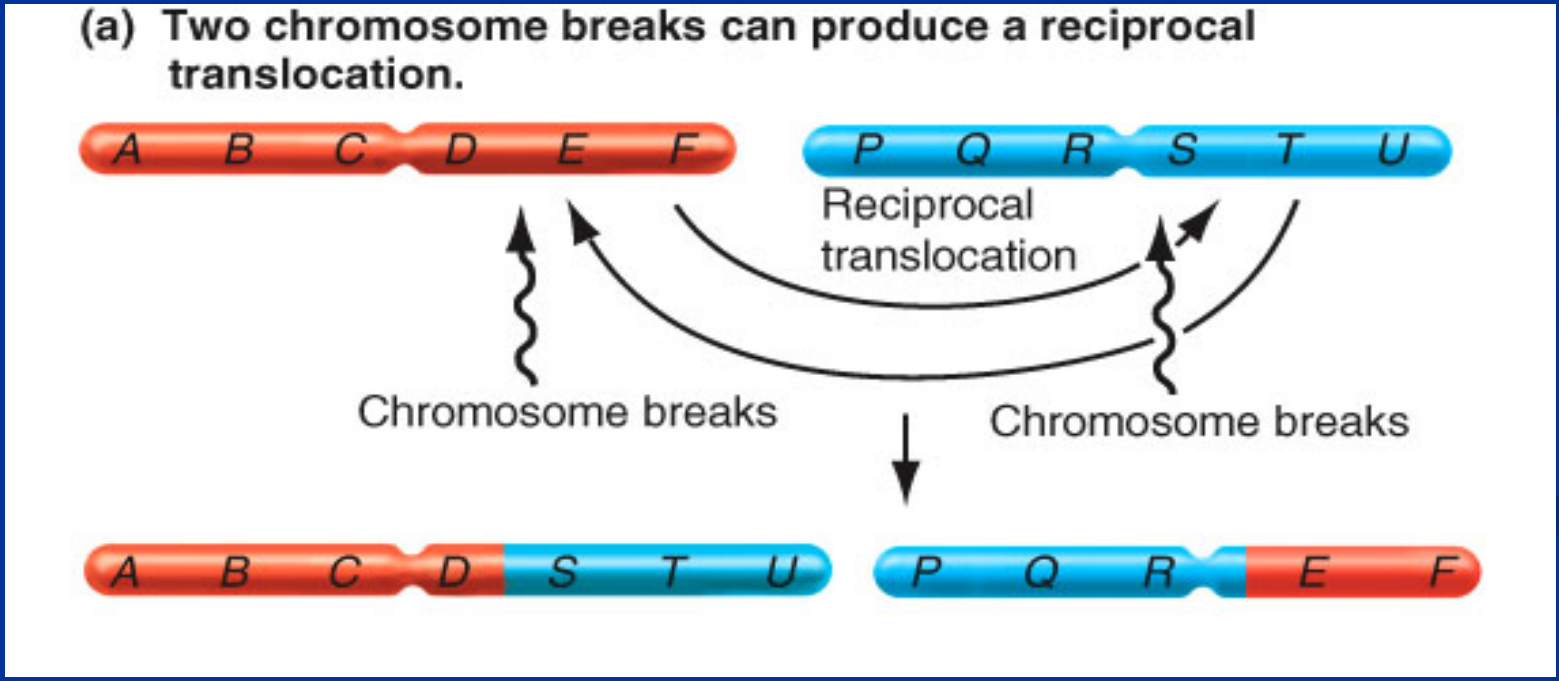




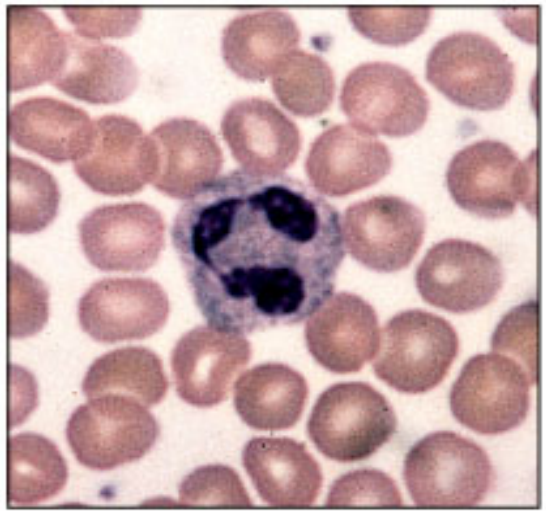


4. Translocations attach part of one chromosome to another chromosome

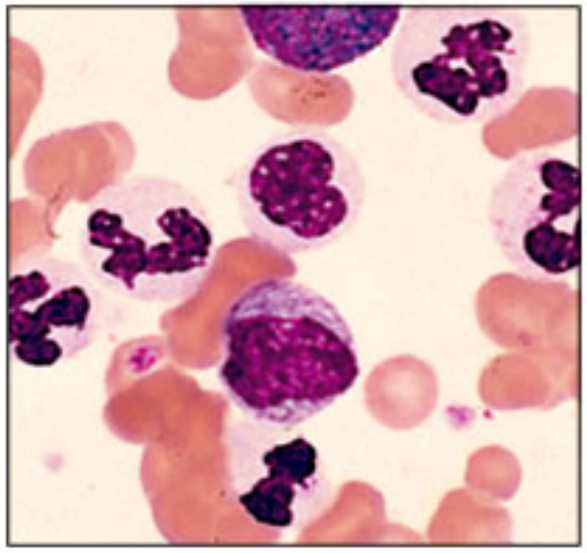
- **Translocation** – part of one chromosome becomes attached to nonhomologous chromosome.
  - ~ 1 of every 500 humans is heterozygous for some kind of translocation.
- **Reciprocal translocation** – two different parts of chromosomes switch places.



A reciprocal translocation helps cause chronic myelogenous leukemia (CML 慢性粒细胞白血病)



Normal



Leukemic

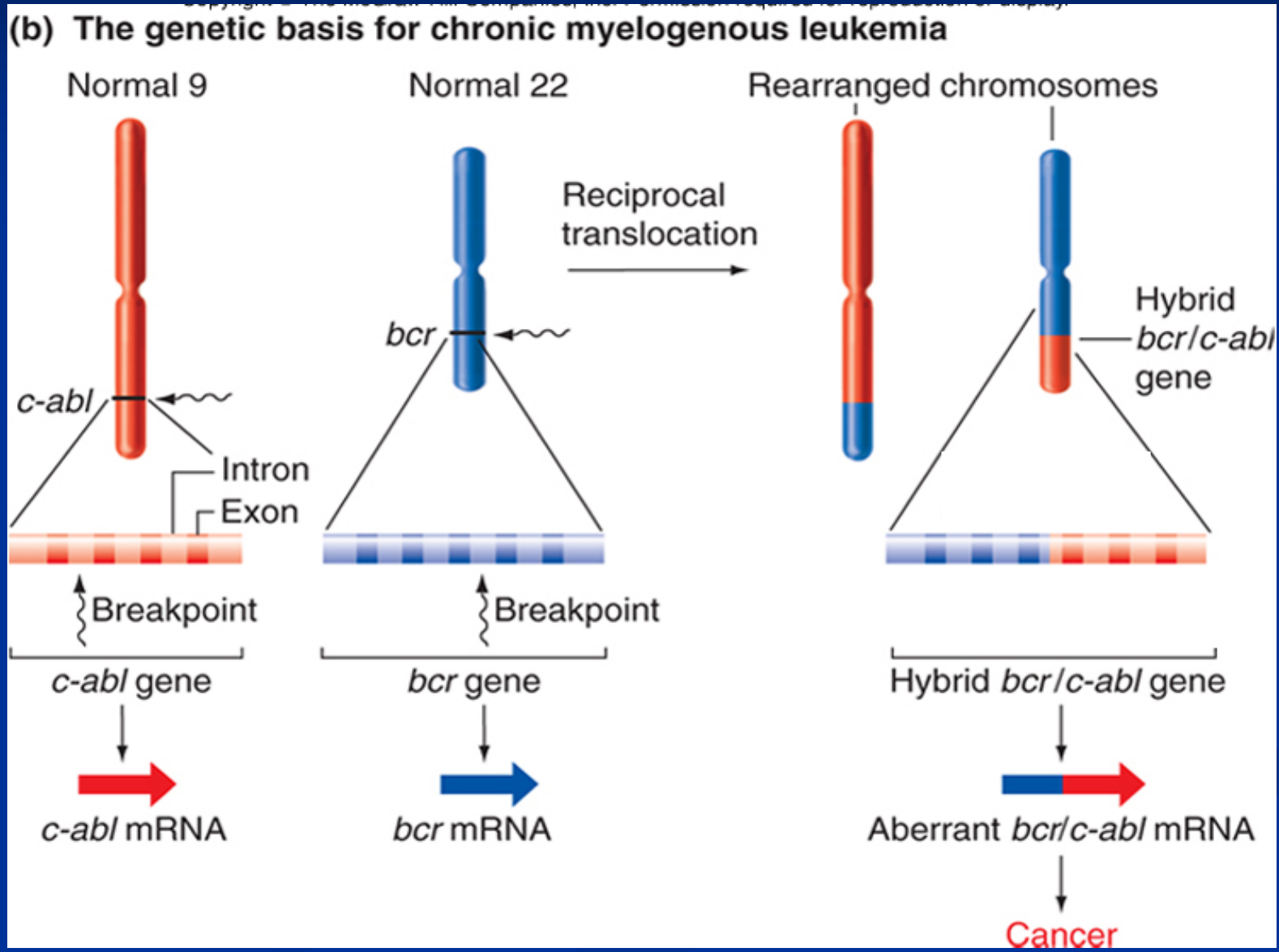
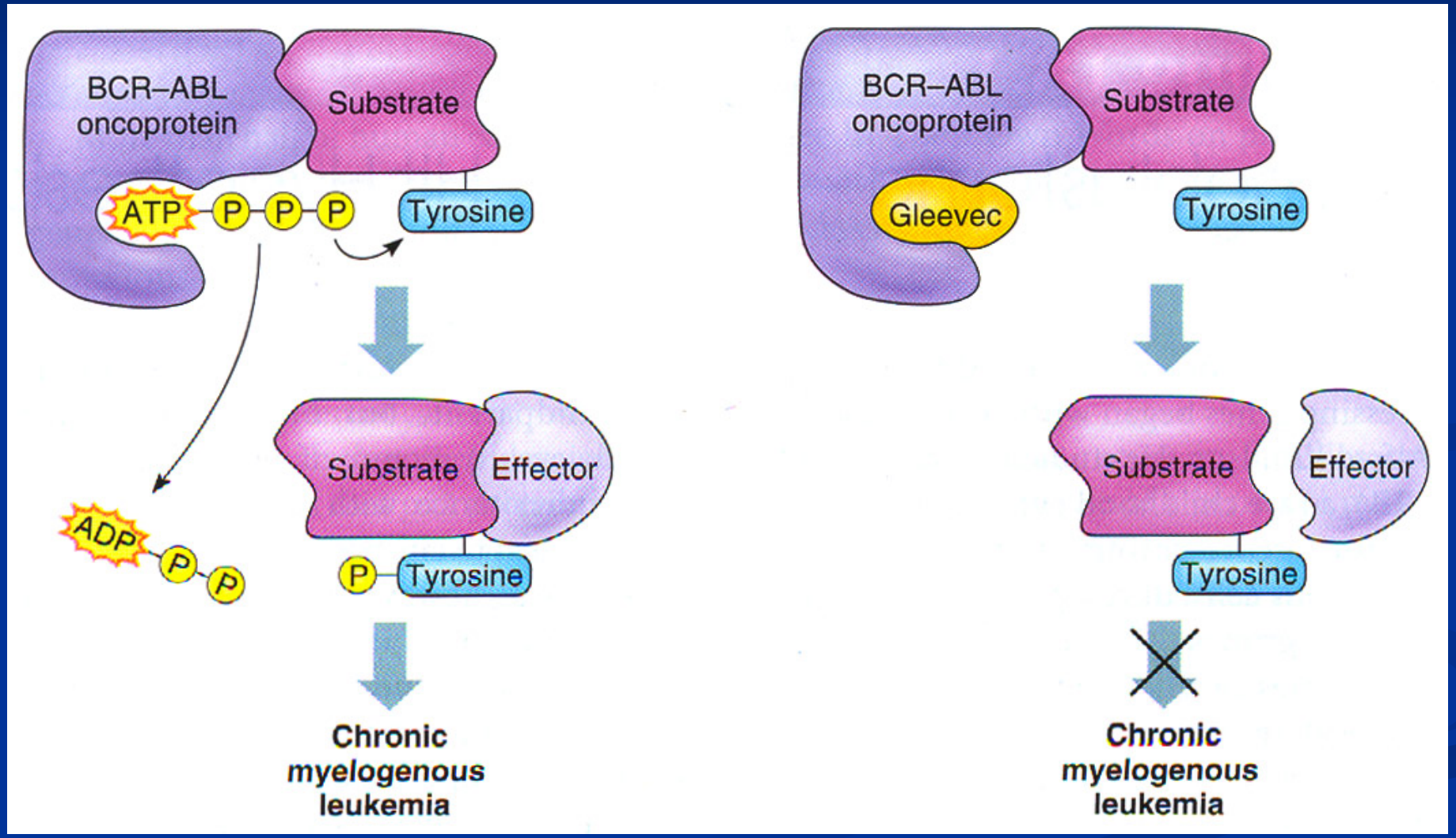


Fig. 12.16

How Gleevec treats chronic myelogenous leukemia?

(格列卫，瑞士诺华Novartis制药公司)



Robertsonian translocations can reshape genomes and contribute to evolution

- Reciprocal exchange between two acrocentric chromosomes generate a large metacentric chromosome and a small chromosome.
- Will reduce chromosome number if the small chromosome is lost.

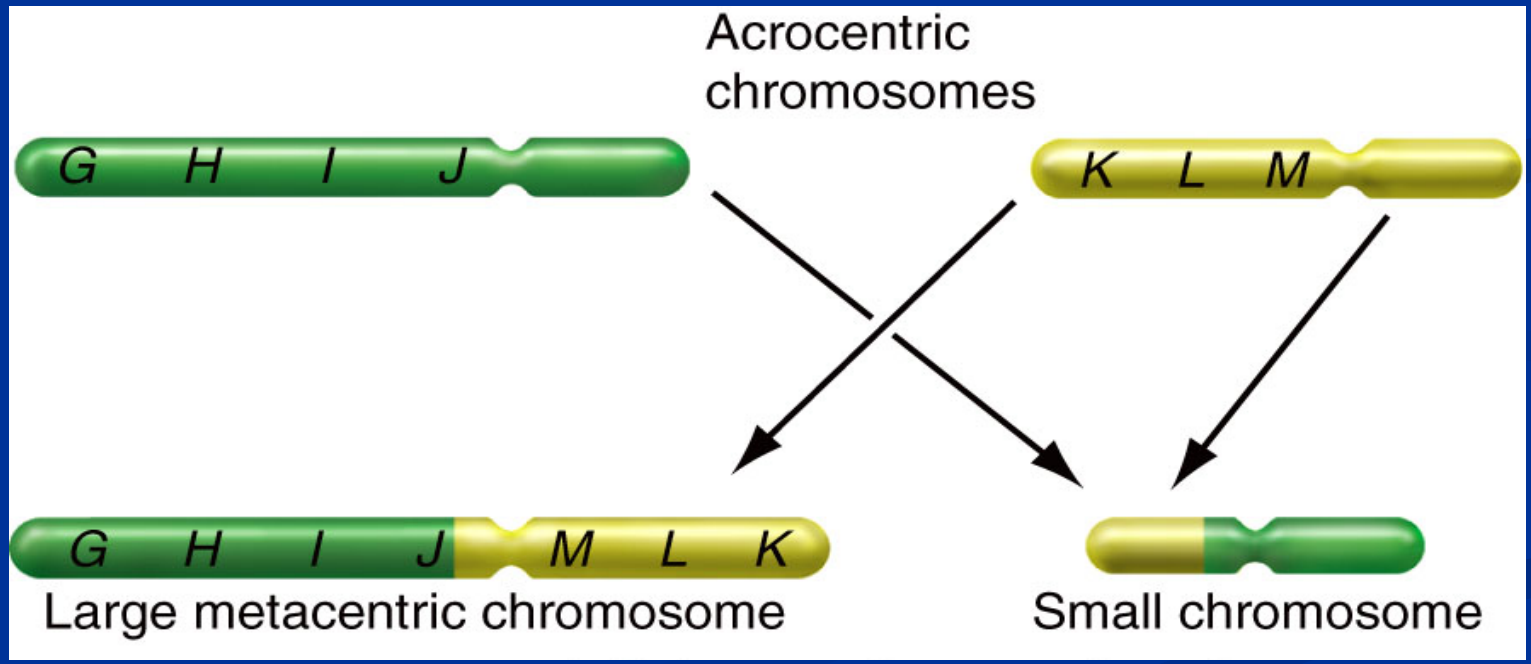


Fig. 12.18

Rapid chromosomal rearrangement in house mice on the island of Madeira

- **Robertsonian translocations** generate different populations of mice with 2*n*=24, 2*n*=22 chromosomes. (2*n*=40 for common house mice)
- Populations are close to becoming two species after colonizing the island only 600 years ago.

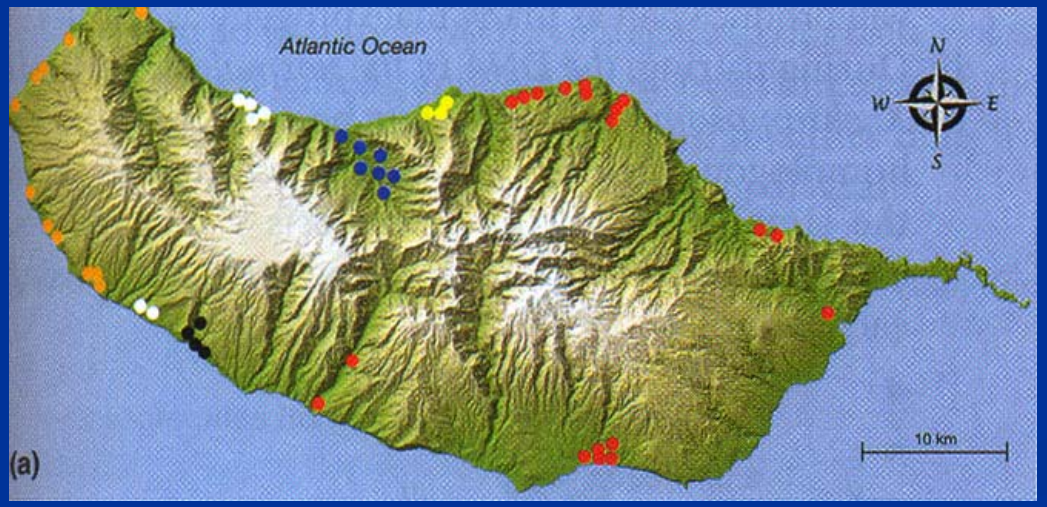
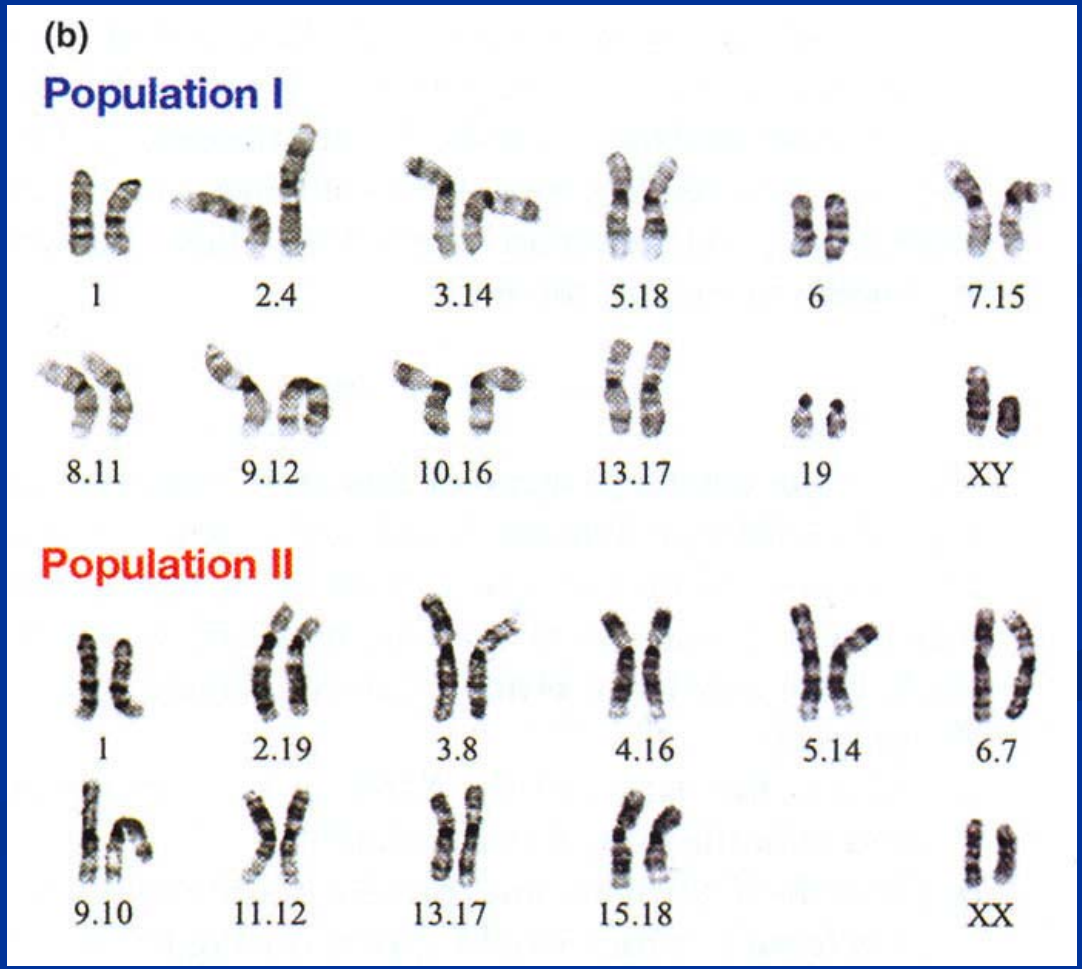
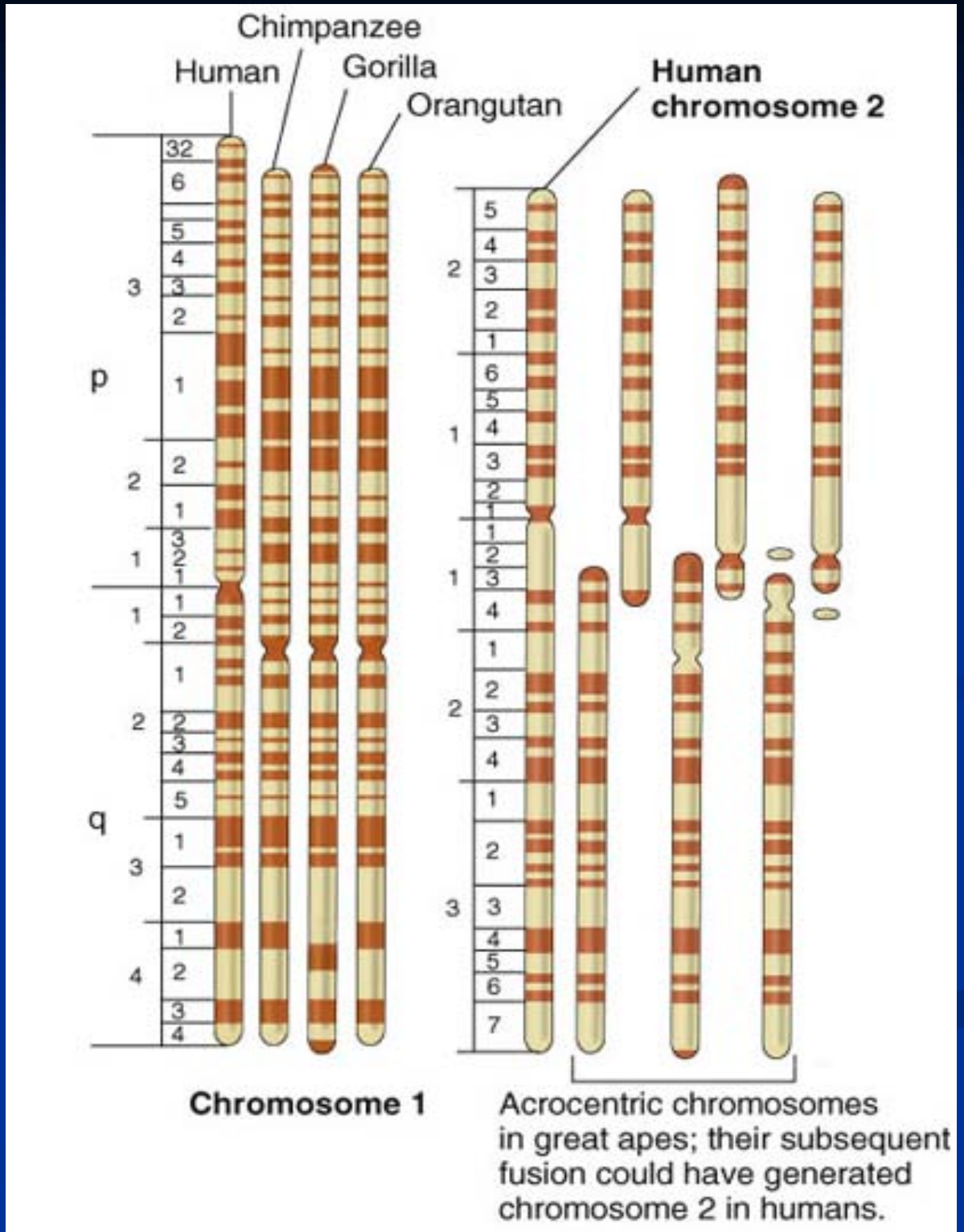
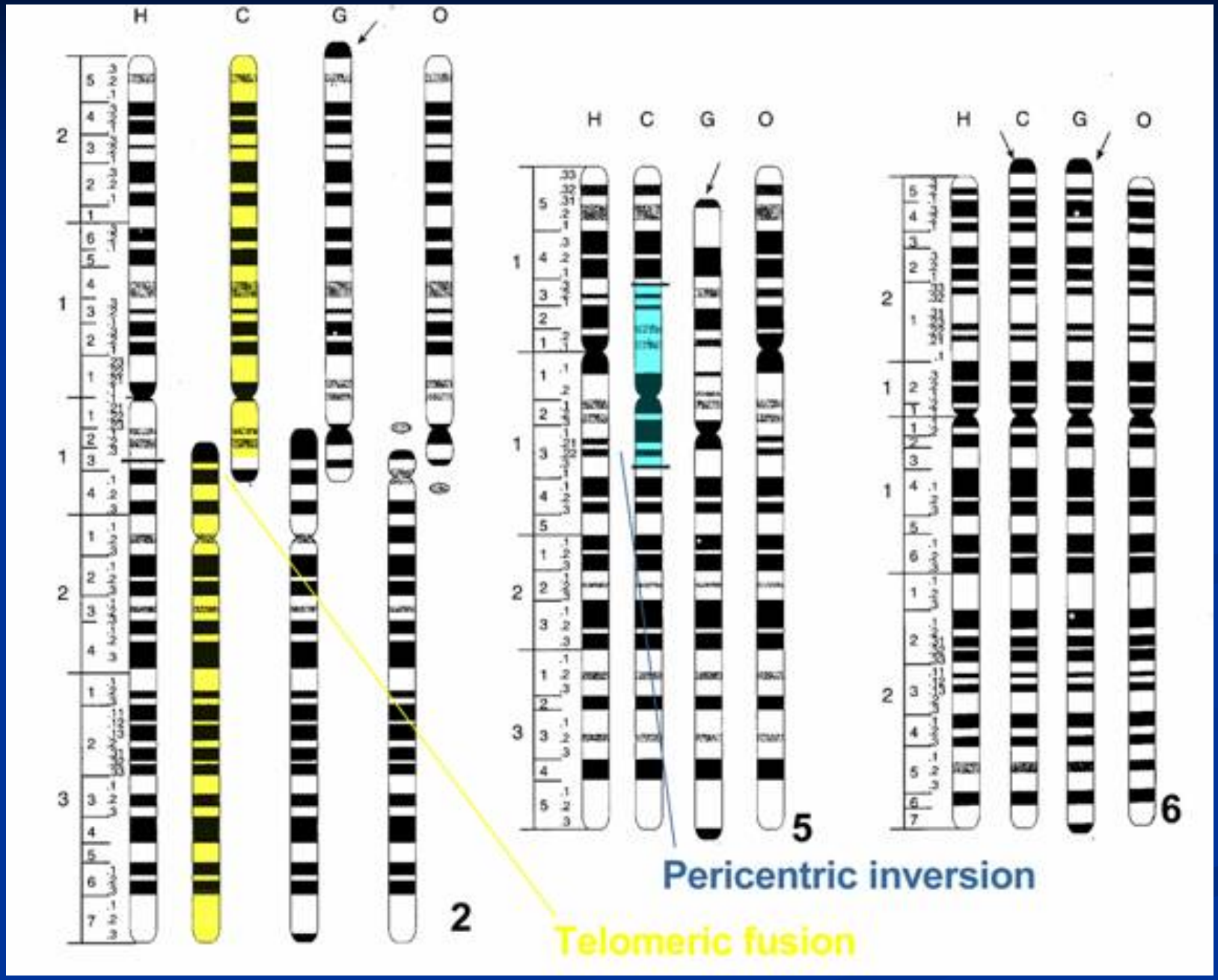


Fig 12.37



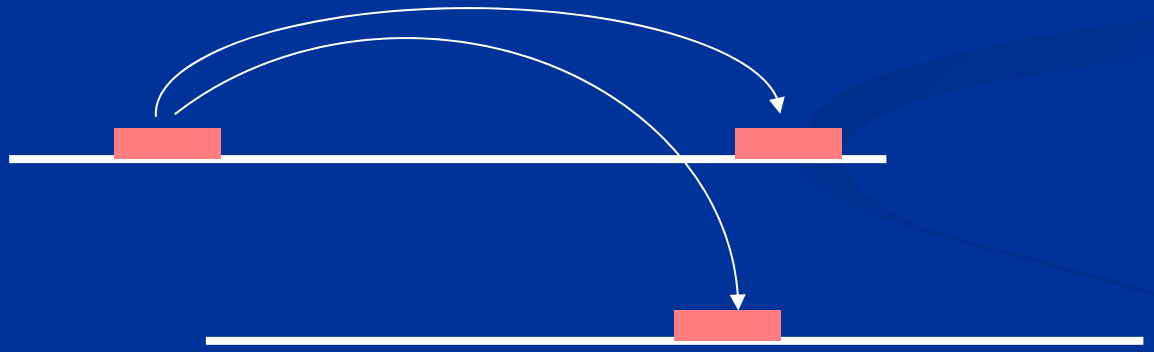
The human chromosome 2 may be generated through a Robertsonian translocation




H
C
G
O
2
H
C
G
O
5
H
C
G
O
6
Pericentric inversion
Telomeric fusion

12.3 Transposable genetic elements

- **Transposable element**: DNA segment that is able to move from one place to another in the genome.
- **Transposition**: The movement of transposable elements from one place to another in the genome.



- **Found in all organisms. Selfish DNA carrying only information to self-perpetuate.**
  - **Marcus Rhoades in 1930s and Barbara McClintock in 1950s found transposable elements in corn.**

Barbara McClintock

The Nobel Prize in Physiology or Medicine 1983 was awarded to her for her discovery of mobile genetic elements.

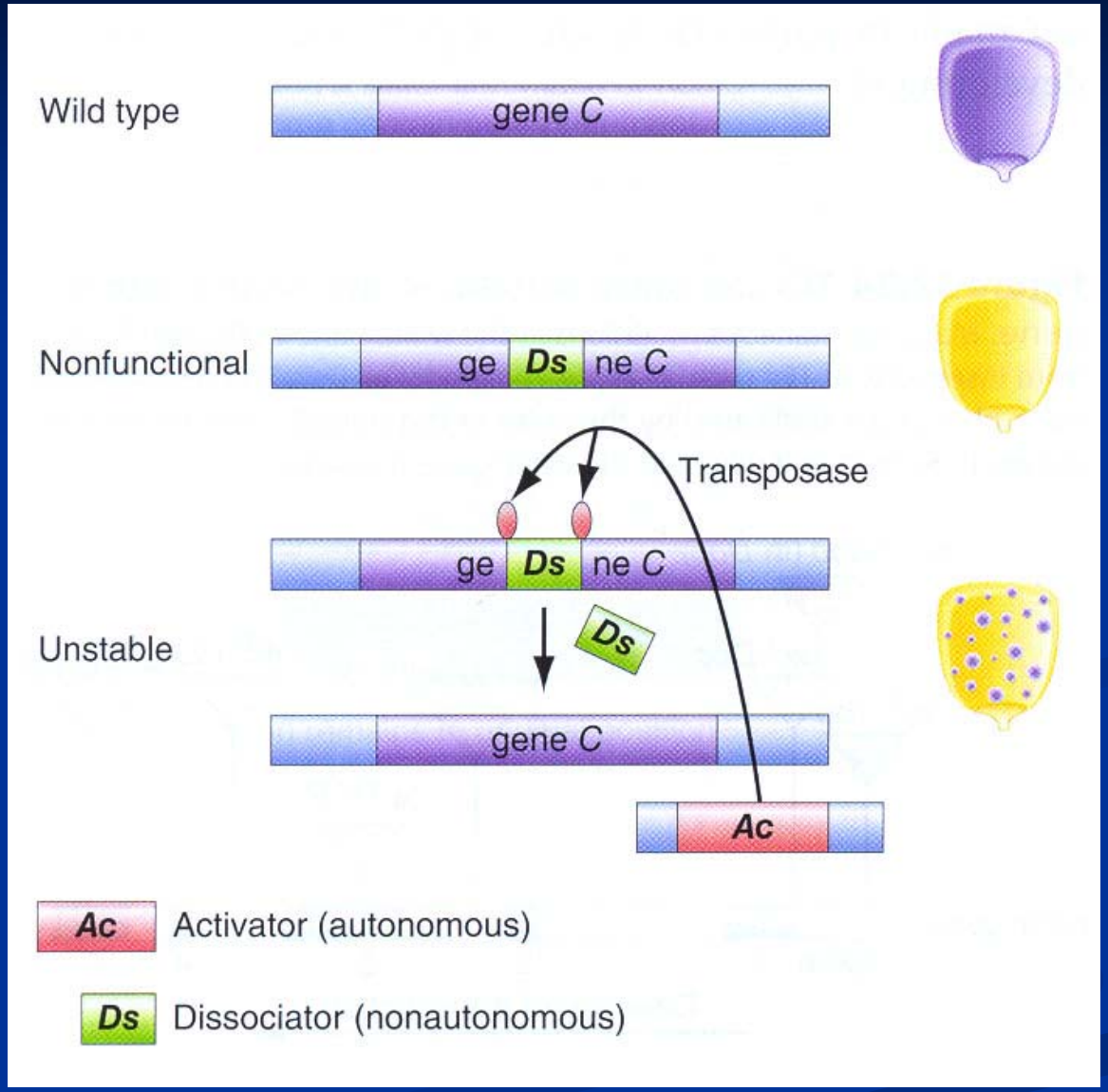


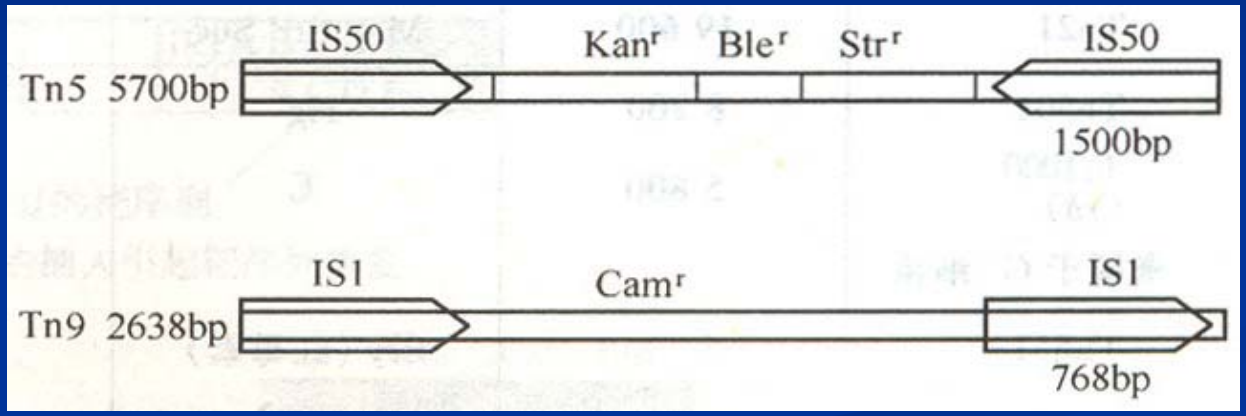
Fig. 12.20, 12.25

Transposable elements can be divided into several types

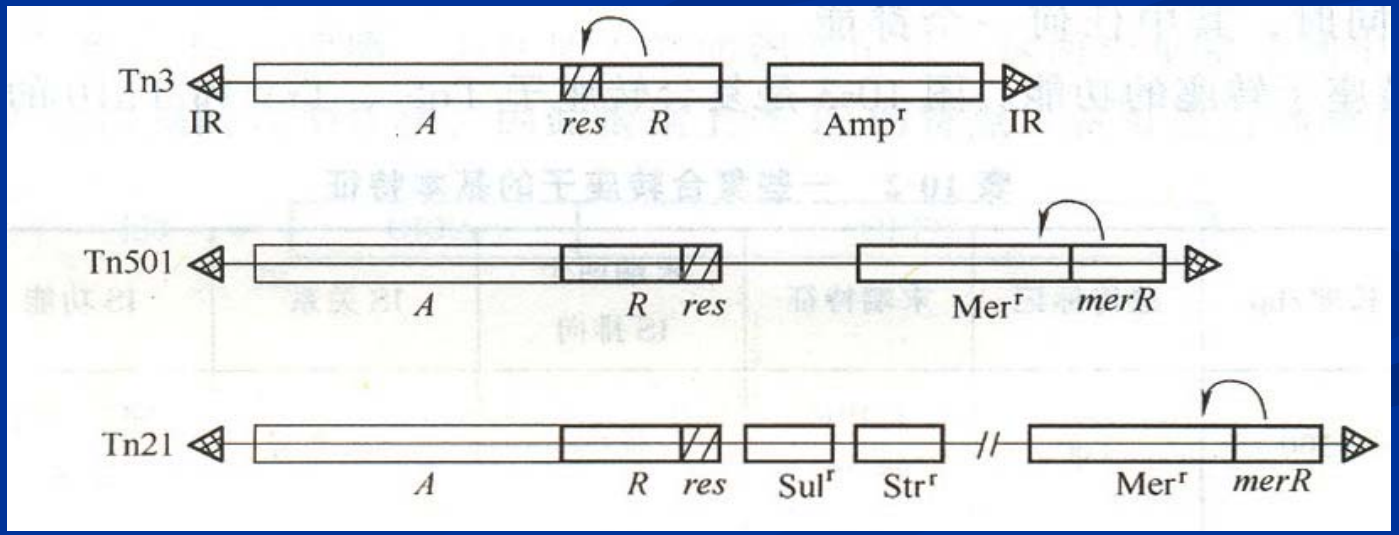
- **Insertion sequence** (IS)
- **Transposon** (Tn): Transposable elements that move from one place to another in the genome without an RNA intermediate.
- **Retroposon**: One type of transposable elements that transpose via reverse transcription of an RNA intermediate.

Insertion sequence

Composite transposon



Complex transposon



Transposons encode transposase enzymes that catalyze events of transposition

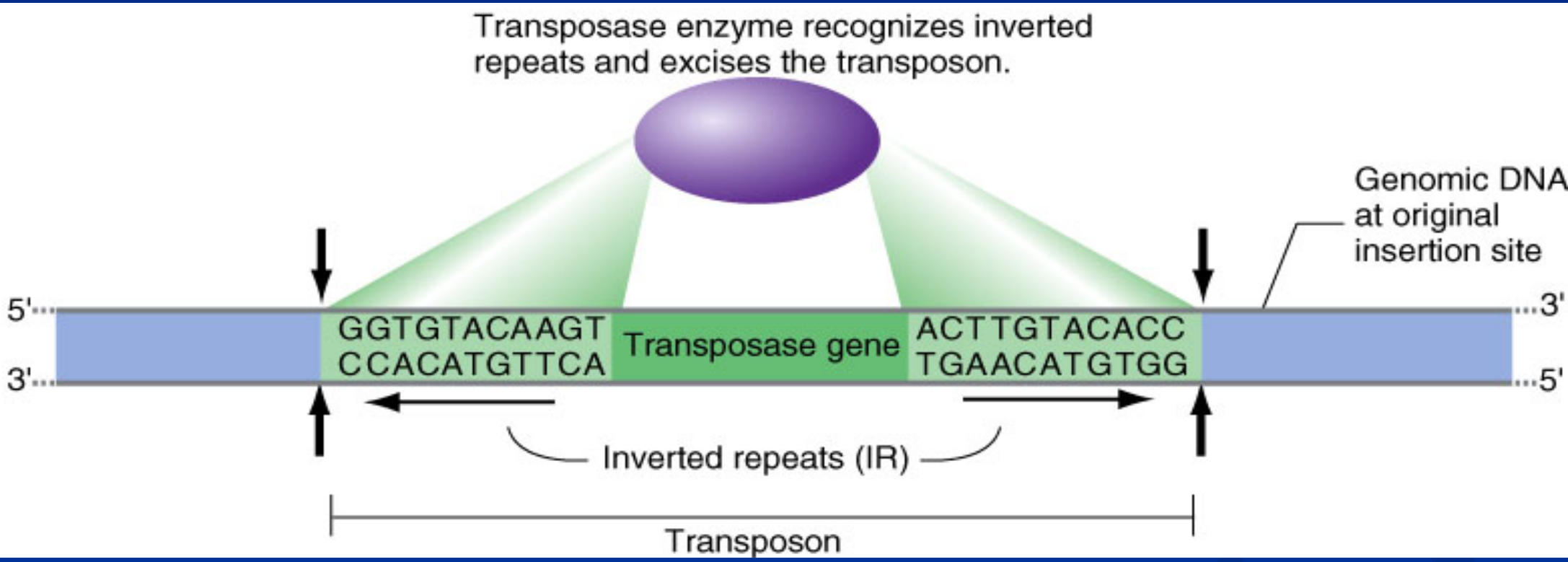
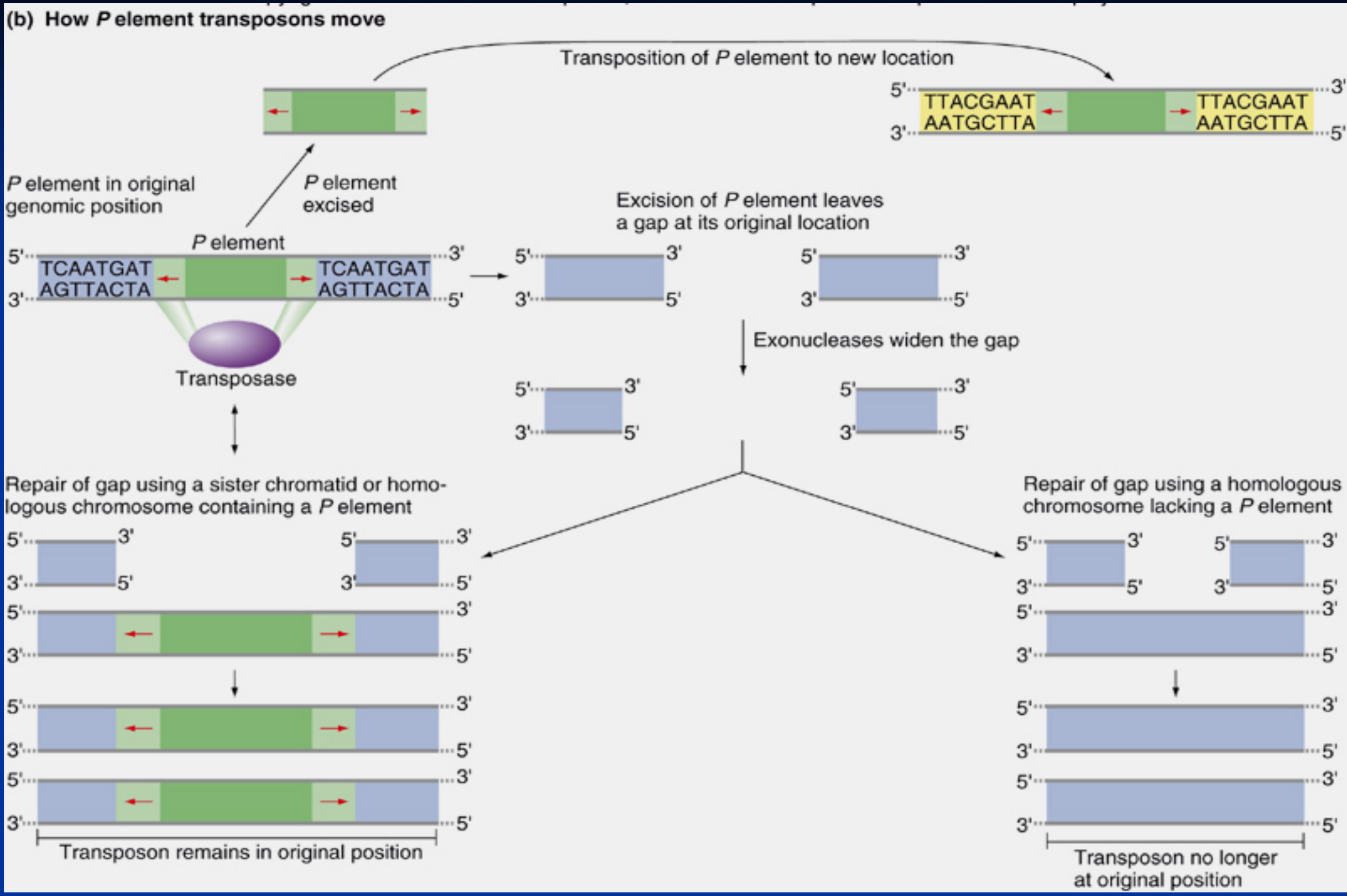


Fig. 12.23


(b) How P element transposons move
Transposition of P element to new location
5'
TTACGAAT
AATGCTTA
3'
TTACGAAT
AATGCTTA
P element in original genomic position
P element excised
P element
TCAATGAT
AGTTACTA
TCAATGAT
AGTTACTA
Transposase
Excision of P element leaves a gap at its original location
Exonucleases widen the gap
Repair of gap using a sister chromatid or homologous chromosome containing a P element
Transposon remains in original position
Repair of gap using a homologous chromosome lacking a P element
Transposon no longer at original position

Retroposons generate an RNA that encodes a reverse transcriptase-like enzyme

- Two types
  - **Poly-A tail** at 3' end of RNA-like DNA strand
  - **Long terminal repeat** (LTRs) oriented in same direction on either end of element

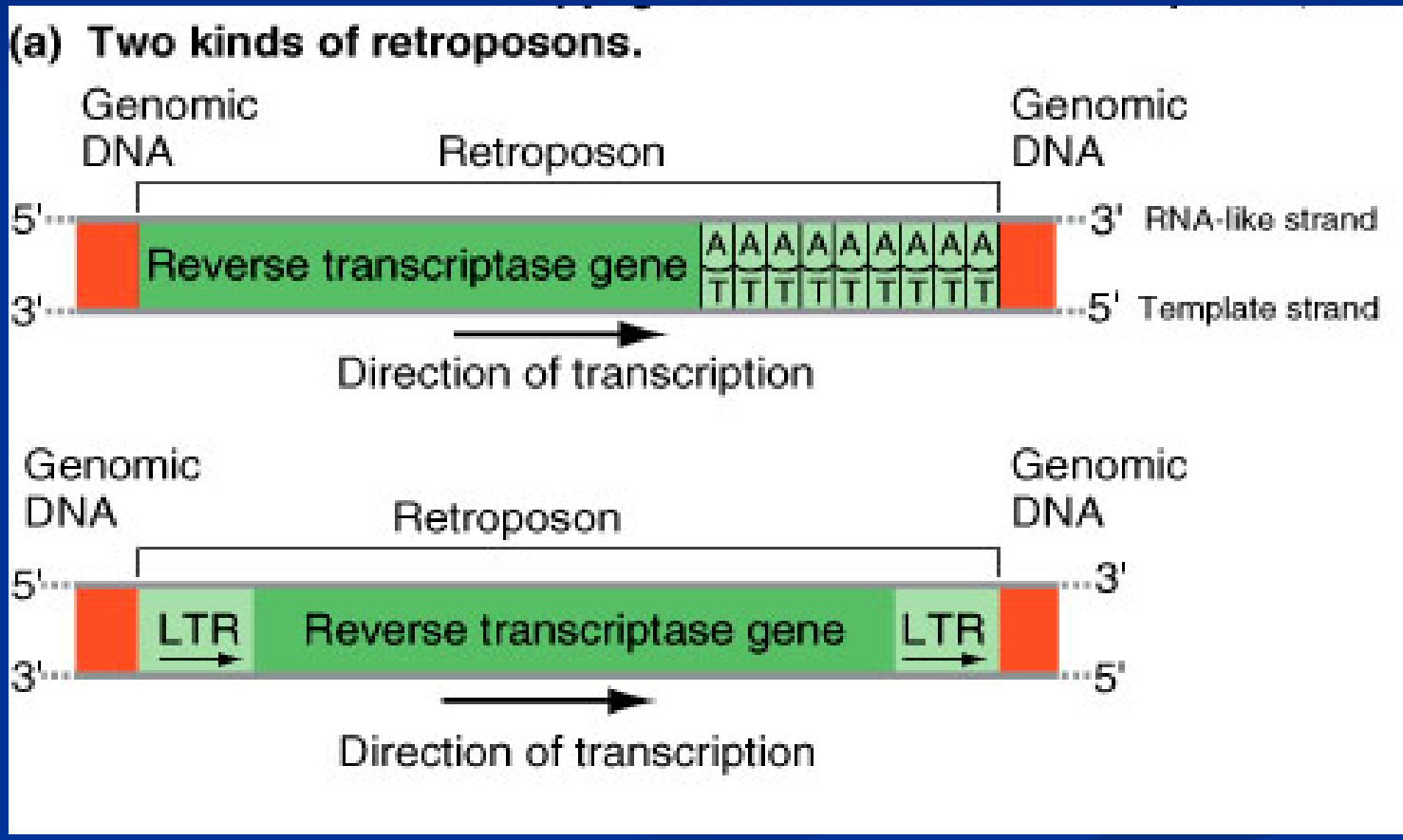
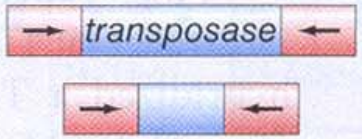


TABLE 12.2 Transposable Elements in the Human Genome

LINES and SINES are poly-A type retrotransposons: LINES encode an RNA-binding protein and reverse transcriptase (the *ORF1* and *pol* genes) that enable their mobilization after pol II transcription, while SINES, derived from pol III transcripts (such as tRNAs), rely on the LINE-encoded proteins to move after transcription by pol III. HERVs are LTR-type retrotransposons that, in addition to a *pol* gene, can include *gag* and *env* genes encoding retroviral coat proteins. DNA transposons in other organisms move due to the action of transposase enzyme on the inverted repeats at the ends of the transposon. Because of mutations in the genes they carry or in the end sequences needed for transposition, only a few LINEs and SINEs in the human genome are able to move; the HERVs and DNA transposons in the human genome are immobile relics.

Element	Structure	Length (kb)	Number	Genome fraction
Retrotransposons				
LINEs		6-8	1,000,000	20%
SINEs		<0.3	2,000,000	13%
HERVs		1-11	600,000	8%
DNA transposons				
		2-3	400,000	3%
		Total	4,000,000	44%

How do retroposons move?

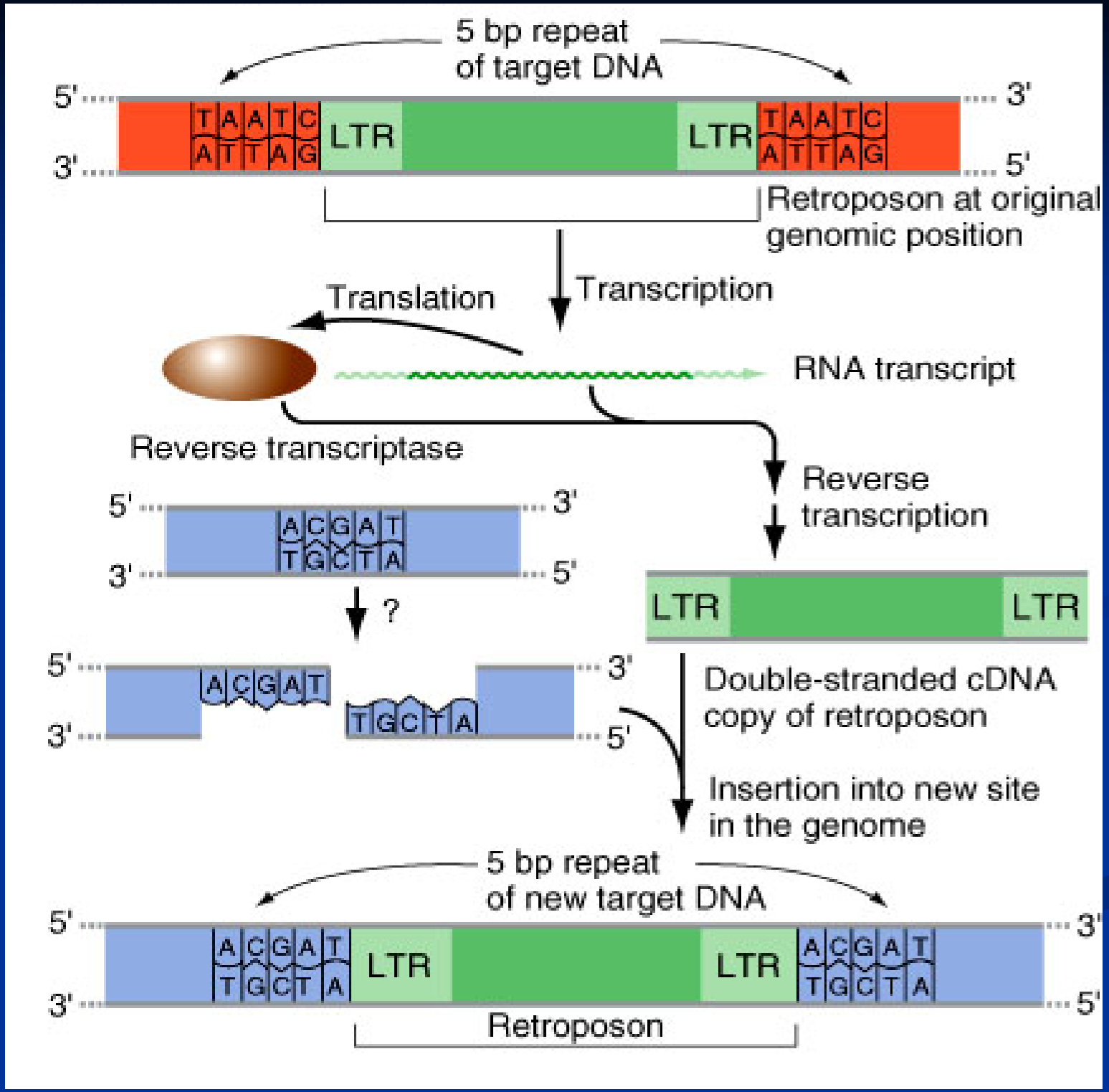


Fig. 12.22

(b) Retroposons move via RNA intermediates.

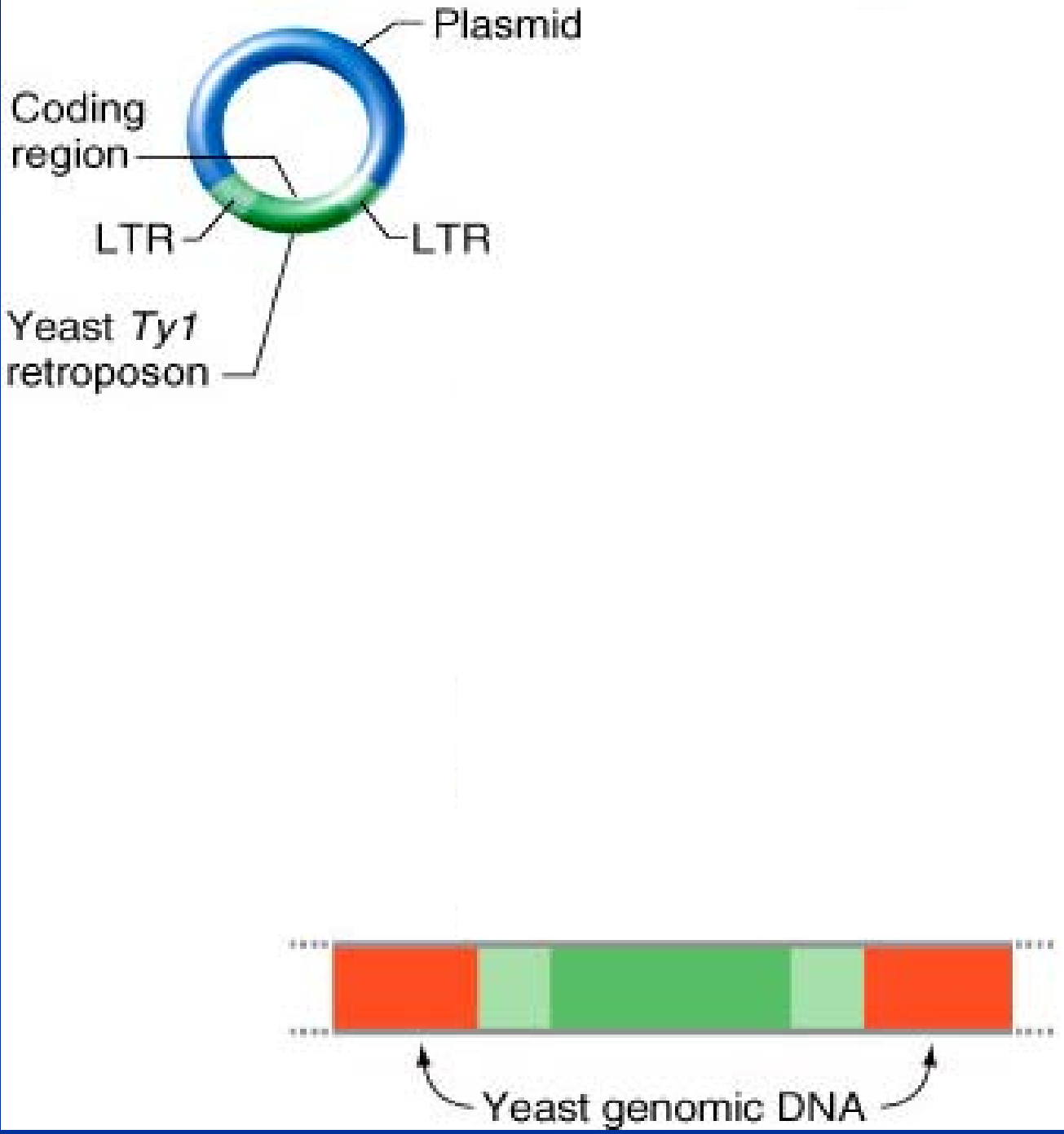


Fig. 12.21

Genomes often contain defective copies of transposable elements

- **Autonomous transposable elements** – Able to move by themselves.
- **Nonautonomous transposable elements** – Some deletions generate defective TEs that can not move on their own, but require the activity of non-deleted copies of same type of TE for movement.
  - A deletion removes one of the inverted repeats at one end of a transposon, e.g. most SINEs and LINEs.
  - A deletion removes the promoter needed for the transcription of a retroposon.

TEs can generate mutations in adjacent genes

Many spontaneous mutations in the *white* gene of *Drosophila* arise from insertions of TEs such as P, copia, roo, or Doc.

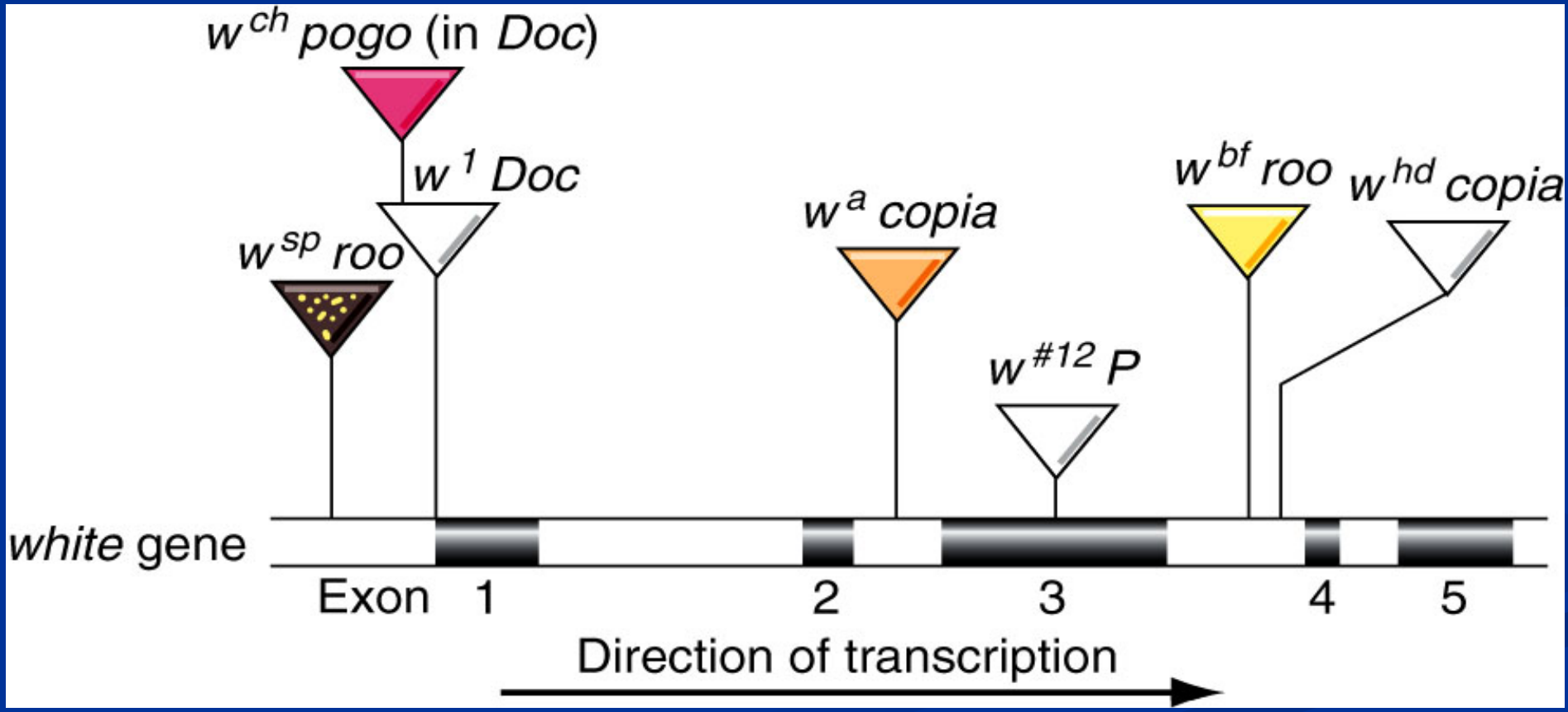
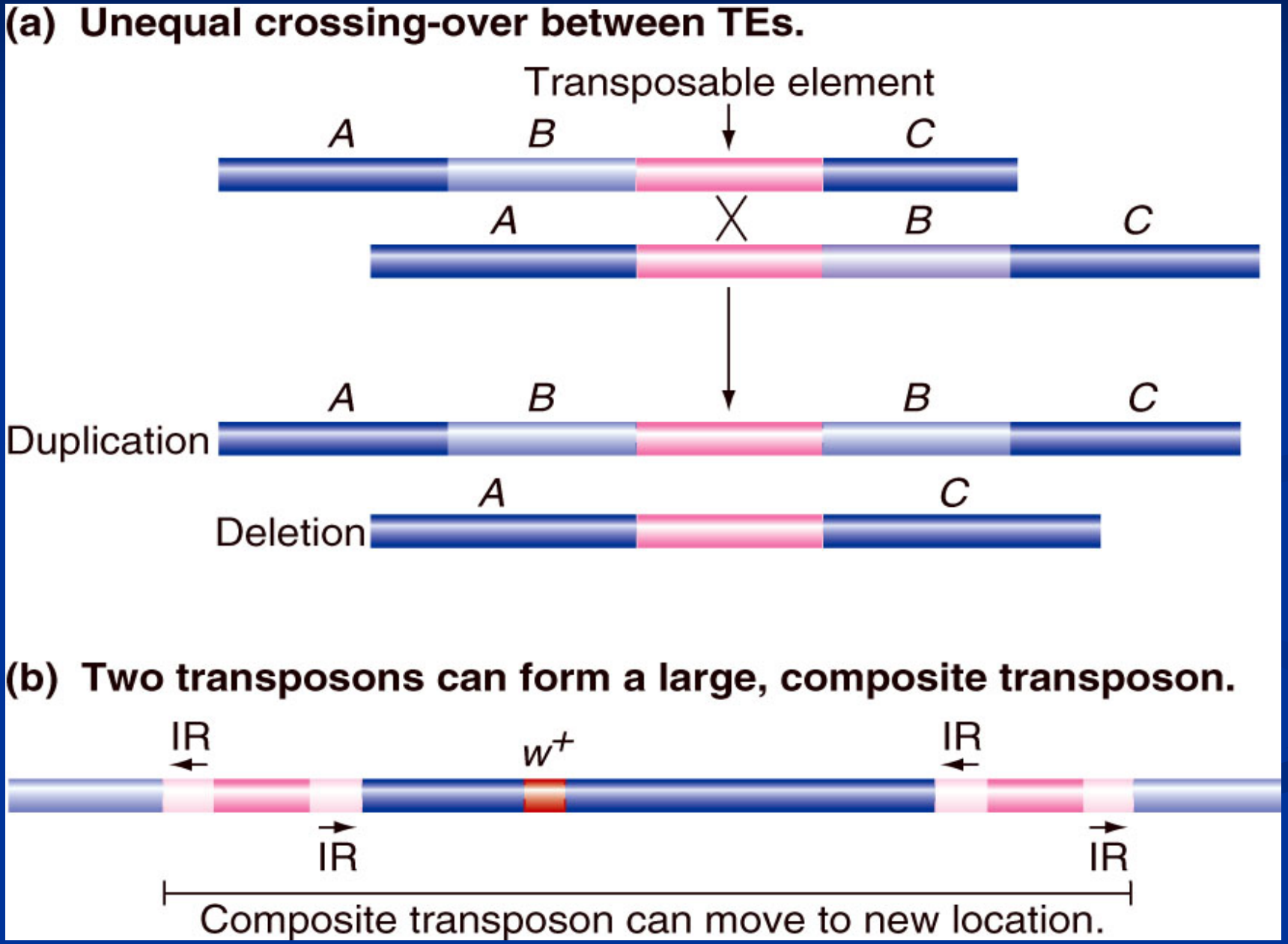


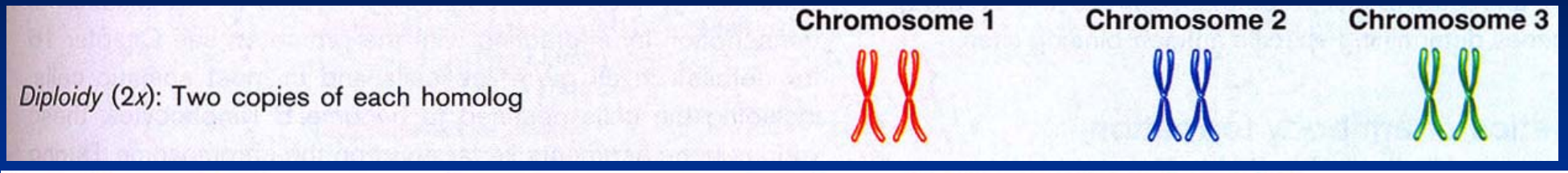
Fig. 12.24

TEs can generate chromosomal rearrangements and relocate genes



12.4 Aberrations in chromosome number: Aneuploidy

- **Diploid – carry two complete sets of chromosomes as those present in the gametes.**



(a) Bacteria

(b) Dolphin

(c) Plants

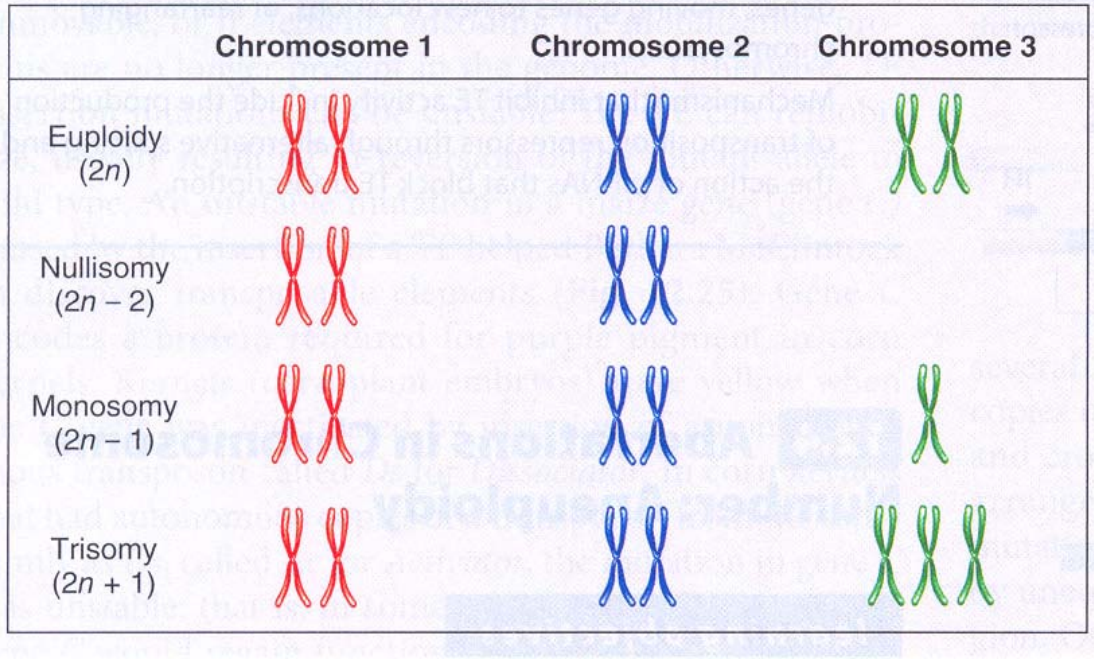
(d) Mouse

(e) Humans

Aneuploid (非整倍体):
An individual whose chromosome number is not an exact multiple of the haploid number (*n*) for the species.

- **Monosomic (单体): Individual lacking one chromosome from the diploid number (2*n*-1) for the species.**
- **Trisomic (三体): Individual having one extra chromosome in addition to the normal diploid set (2*n*+1) of the species.**
- **Tetrasomic (四体): Individual having two extra chromosomes in addition to the normal diploid set (2*n*+2) of the species.**

TABLE 12.3 Different Kinds of Aneuploidy in a Normally Diploid Organism



In this theoretical organism, $n = 3$.

Aneuploidy is harmful to humans

- Monosomies usually lethal
- Trisomies – highly deleterious

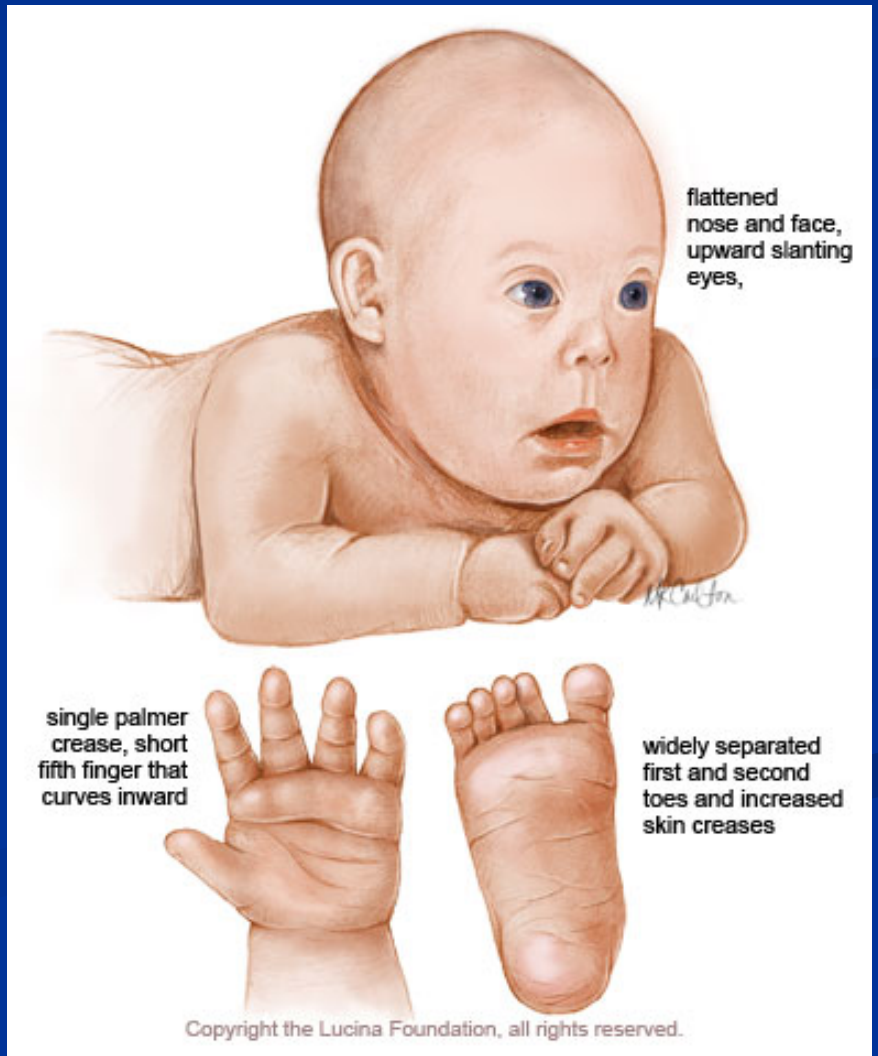
TABLE 12.4 Aneuploidy in the Human Population

Chromosomes	Syndrome	Frequency at Birth
Autosomes		
Trisomic 21	Down	1/700
Trisomic 13	Patau	1/5000
Trisomic 18	Edwards	1/10,000
Sex chromosomes, females		
XO, monosomic	Turner	1/5000
XXX, trisomic XXXX, tetrasomic XXXXX, pentasomic		1/700
Sex chromosomes, males		
XYY, trisomic	Normal	1/10,000
XXY, trisomic XXYY, tetrasomic XXXY, tetrasomic XXXXY, pentasomic XXXXXY, hexasomic	Klinefelter	1/500

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

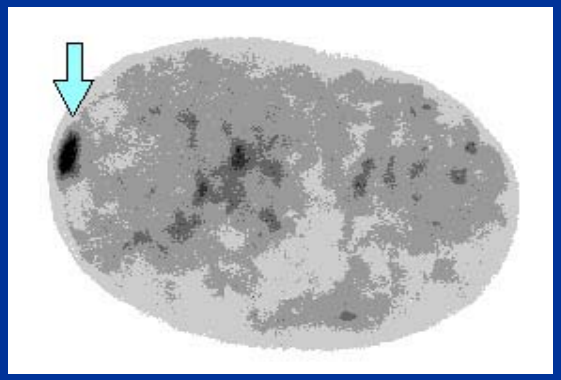
Down syndrome (DS)

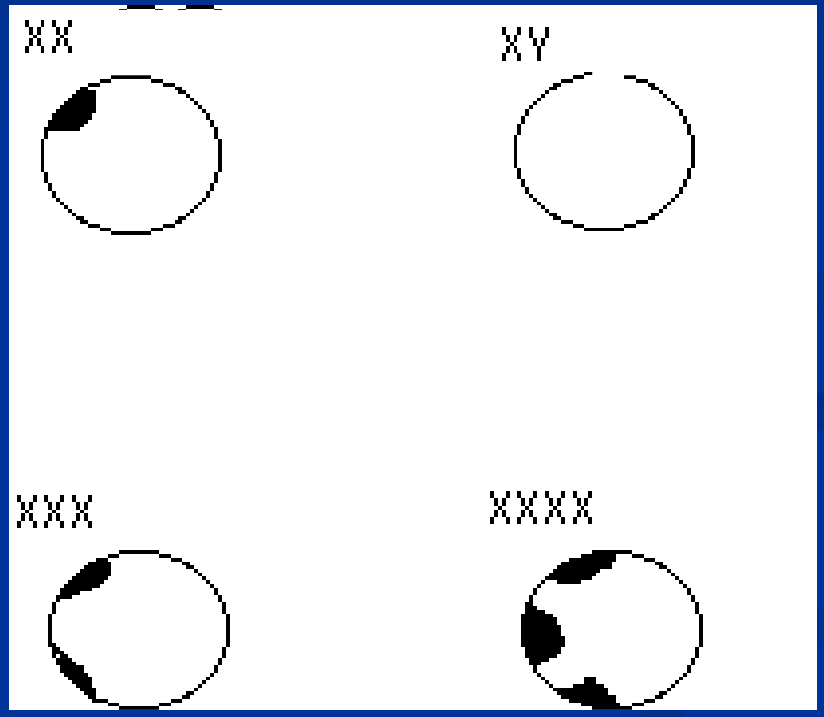
- First described by British physician John L. Down in 1866.
- Trisomy 21, 1 in 700 occurrence at birth in the U.S.
  - Mental retardation, slow growth, atypical fingerprints
  - Male infertility



Humans can tolerate X chromosome aneuploidy because X inactivation compensates for dosage

Barr body





Several genes near the centromere and telomere can escape X chromosome inactivation

- **XO women** (Turner syndrome, short) and **XXY men** (Klinefelter syndrome, tall and long-limbed) usually display skeletal abnormalities.
  - Due at least in part to abnormal dosage of the 30 **PAR genes** in somatic cells.
  - One PAR gene, ***SHOX*** (*short stature homeobox*), encodes a protein important for bone development.

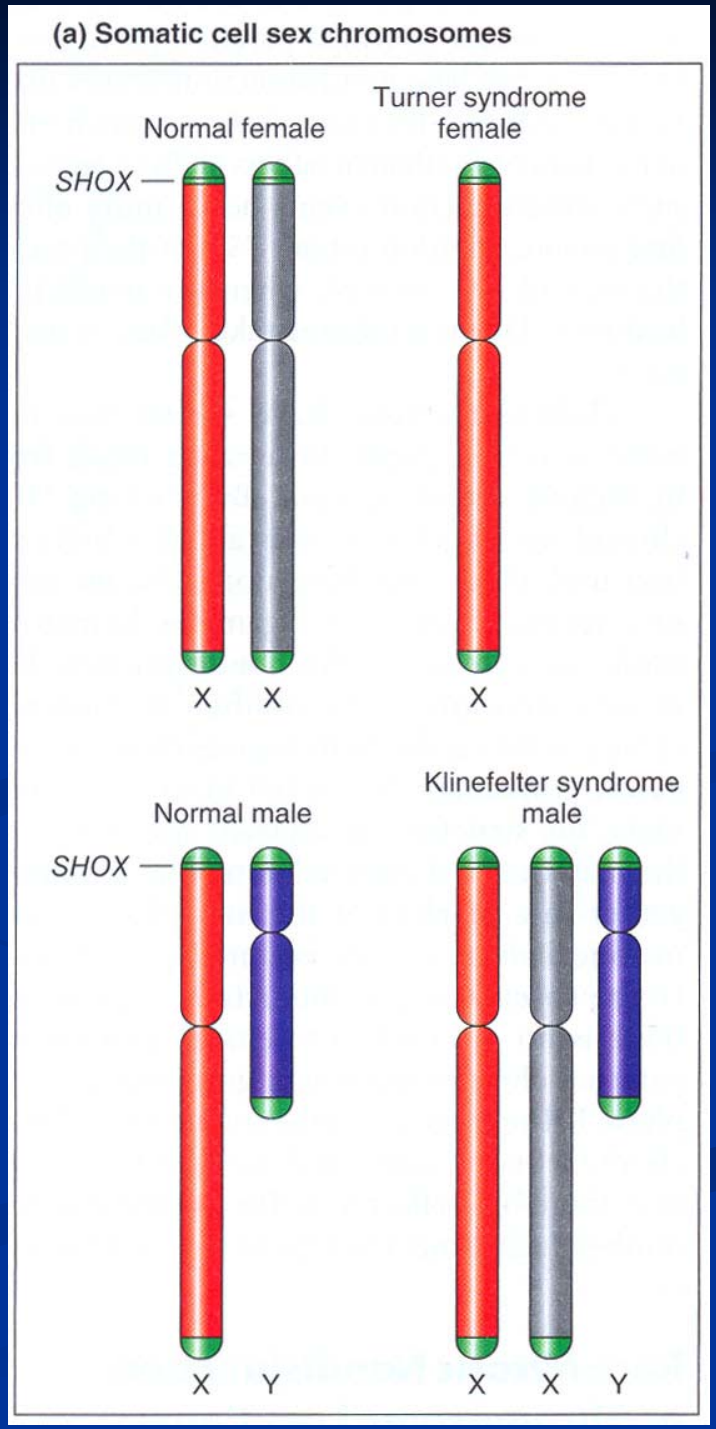


Fig. 12.28a

- **XO women** are usually infertile.
  - Due to defects in **X chromosome reactivation** in oogonia.
  - XO women have only one X chromosome and may undergo defective oogenesis.
- **XXY men** are usually infertile.
  - Due to defects in **X chromosome reactivation** in spermatogonia.
  - Two XX chromosomes cause defective sperm production.

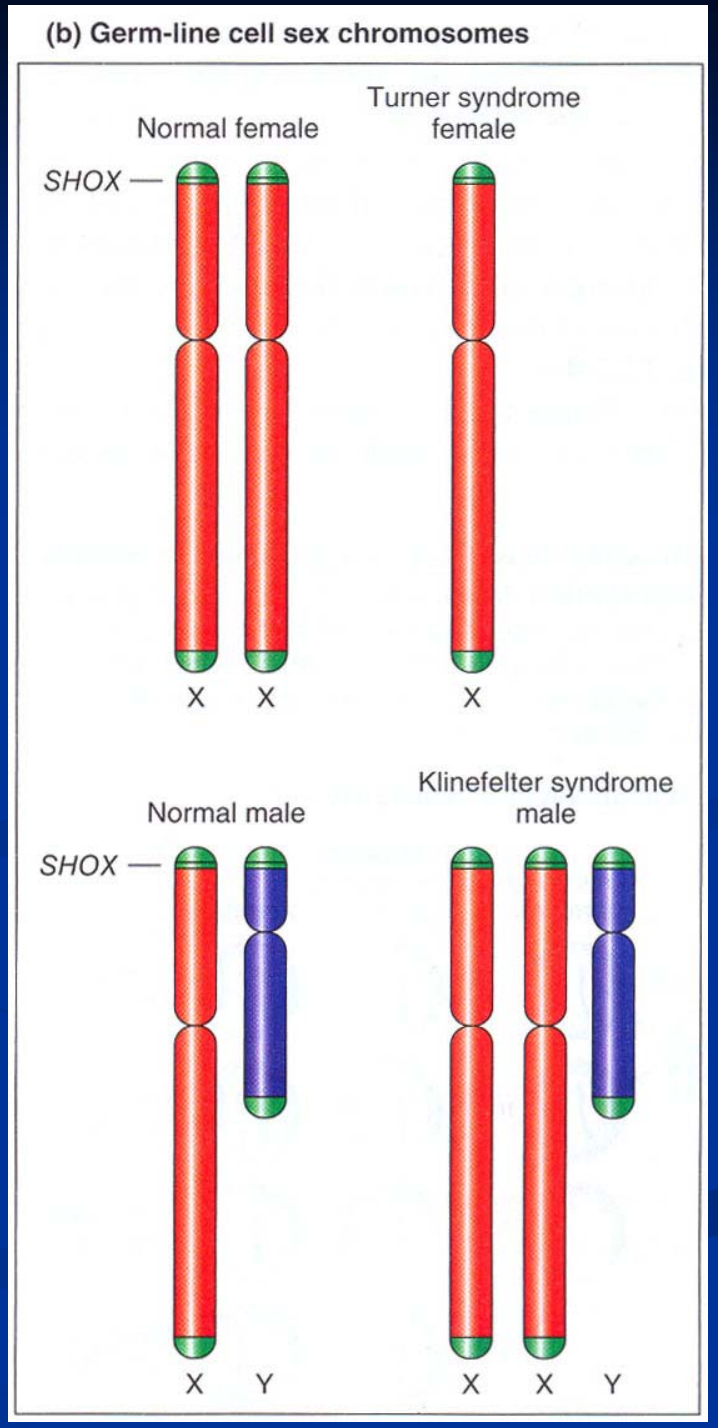


Fig. 12.28b

Aneuploidy results from meiotic nondisjunction

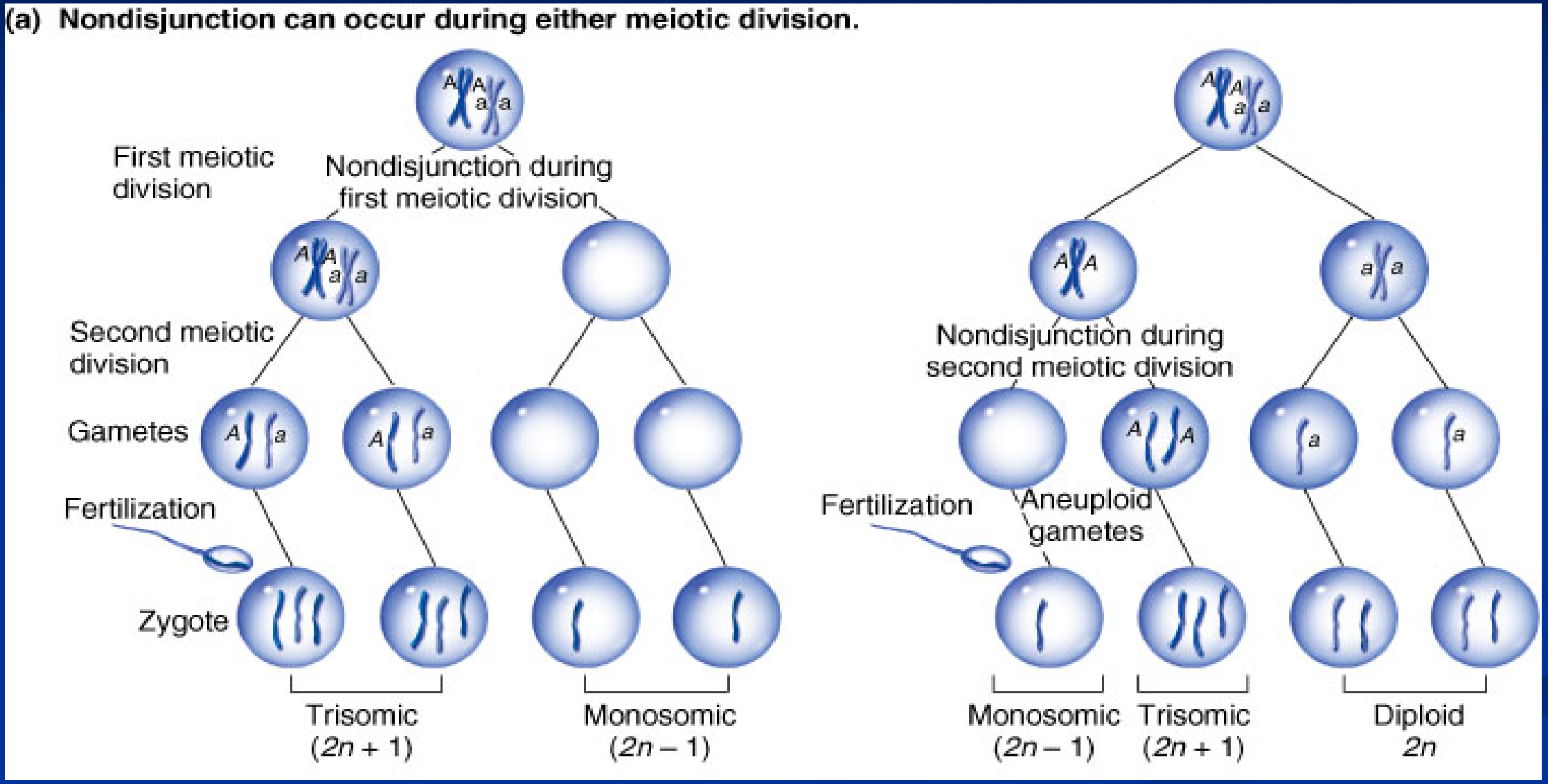
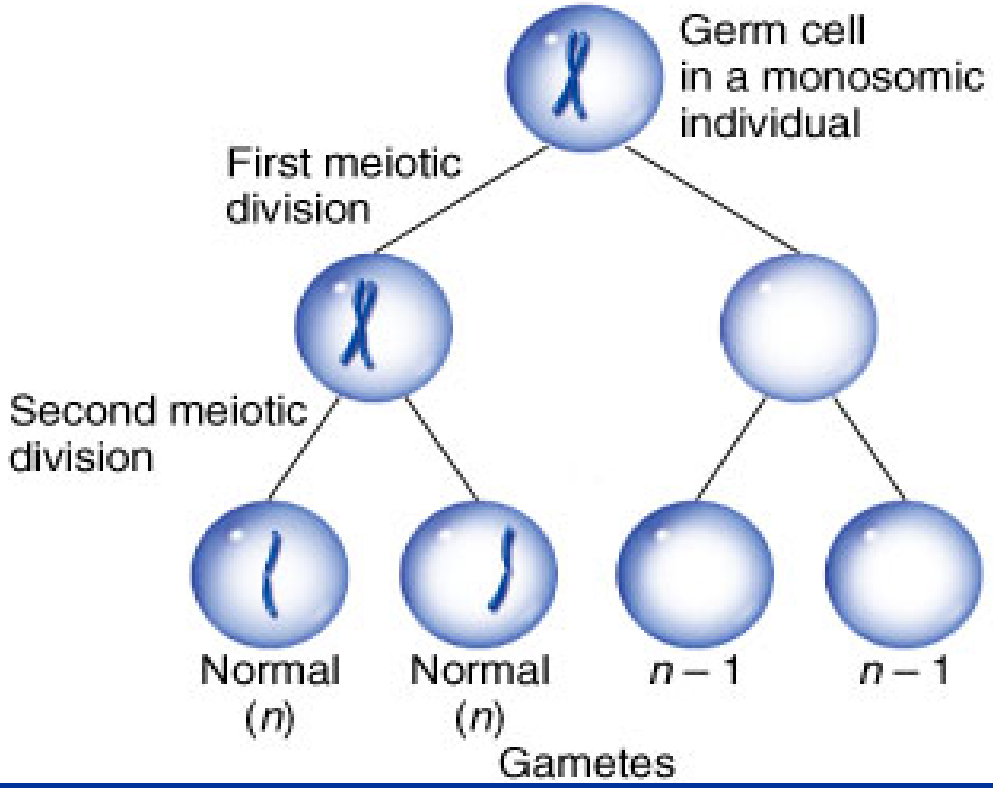


Fig. 12.29

(b) Aneuploids beget aneuploid progeny.



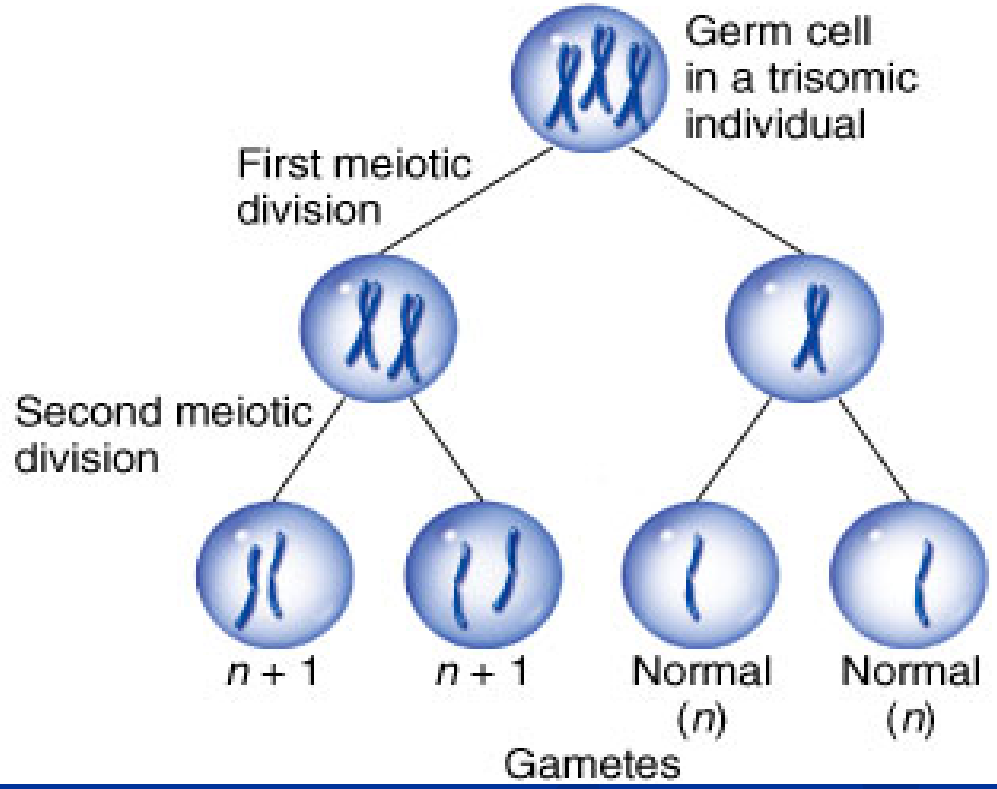


Fig. 12.29

Mistakes during mitosis can produce clones of aneuploid cells

- **Mitotic nondisjunction**
  - Failure of two sister chromatids to separate during mitotic anaphase
  - Generates reciprocal trisomic and monosomic daughter cells
- **Chromosome loss**
  - Produces one monosomic and one diploid daughter cell

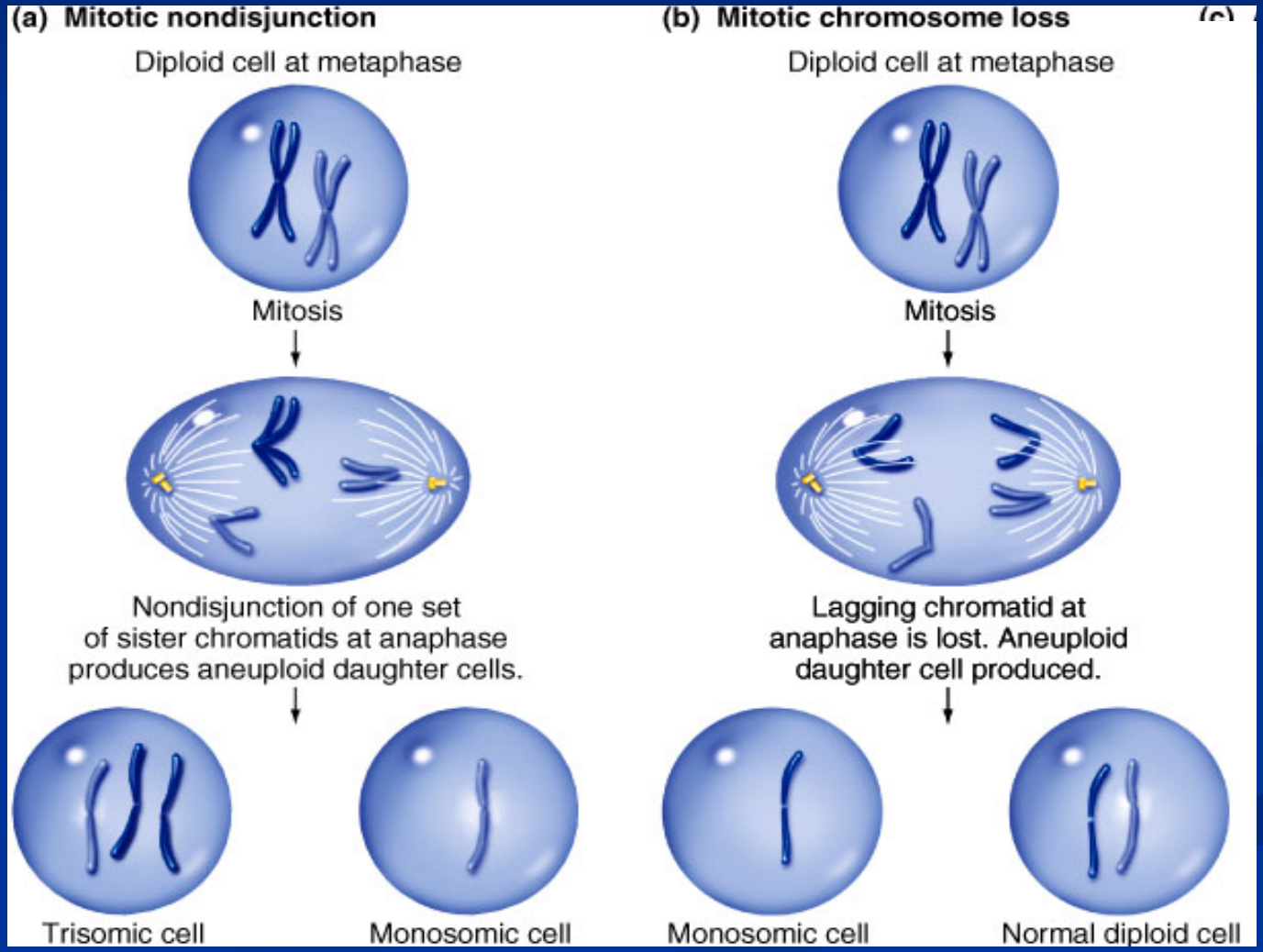


Fig. 12.30

- **Aneuploid mosaics – aneuploid and normal tissues lie side-by-side.**
  - **Aneuploids give rise to aneuploid clones.**

Gynandromorph

- **A rare genetic mosaic with both male and female tissue on the same body, usually in equal amounts.**
- **Results from losing one X chromosome during first mitotic division of a *Drosophila* female zygote.**

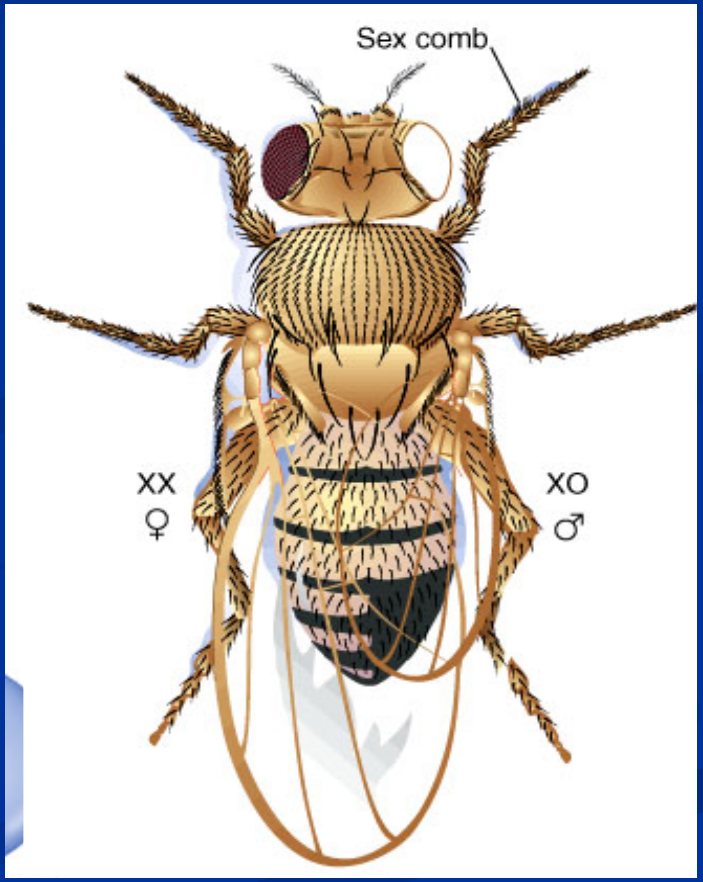
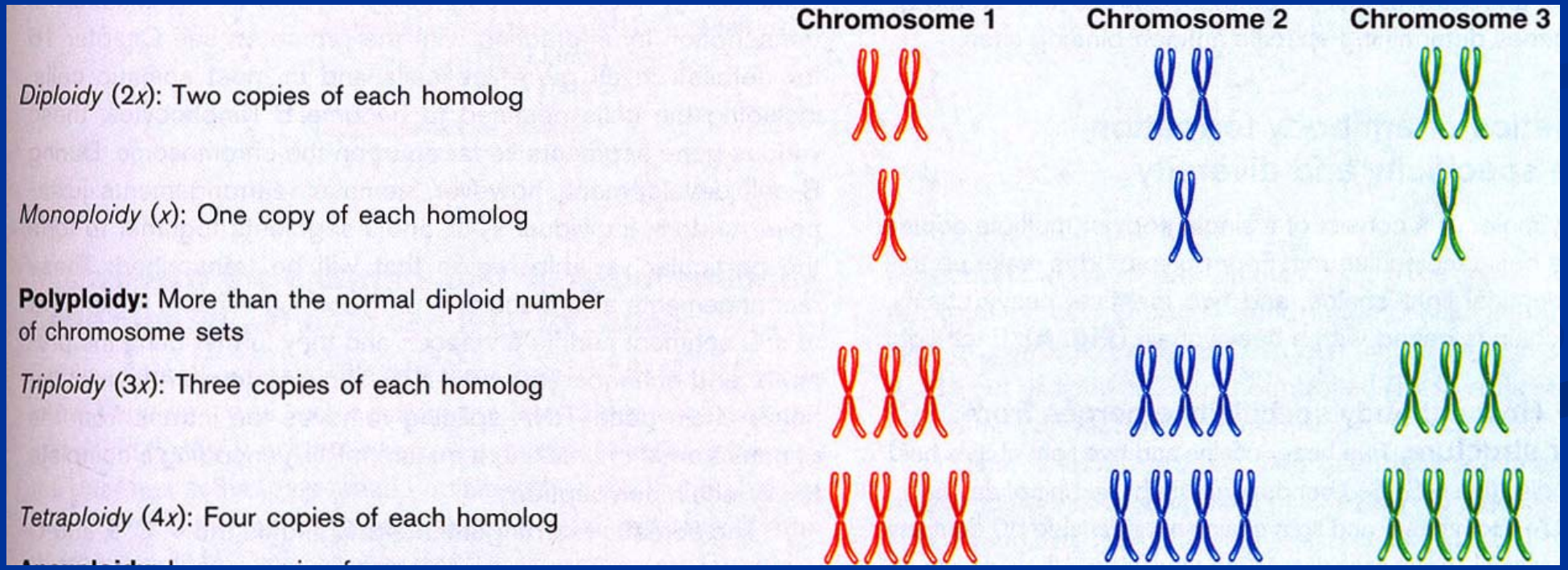


Fig. 12.30

12.5 Variation in number of chromosome sets: Euploidy

- **Euploid (整倍体) : An individual that carries complete sets of chromosomes.**
- **Monoploid (haploid)– carry only a single set of unpaired chromosomes.**
- **Polyploid – carry three or more complete sets of chromosomes.**



In animals, monoploid and polyploid are rare

Monoploids

- Males in some species of ants, bees, and wasps.
  - Developed from unfertilized eggs.
  - Males produce gametes through a modified meiosis, which ensures that all the chromosomes are distributed into one cell, the gamete.
- Certain species of fish and lizards.

Polyploids

- Goldfishes (tetraploid), earthworms (hermaphrodite).
- Triploid and tetraploid female *Drosophila*.

In plants, polyploids are common

- "*x*" indicates basic chromosome number - the number of different chromosomes that make up a single complete set.
- "*n*" indicates the number of chromosomes in the gametes.

Diploid species: $n = x$

Polyploid species: $n \neq x$

Bread wheat, $x = 7$.

The plant (hexaploid) has $2n = 6x = 42$ chromosomes.

Its gametes (triploid) has $n = 3x = 21$ chromosomes.

Monoploid plants carry a single copy of each chromosome and are usually infertile

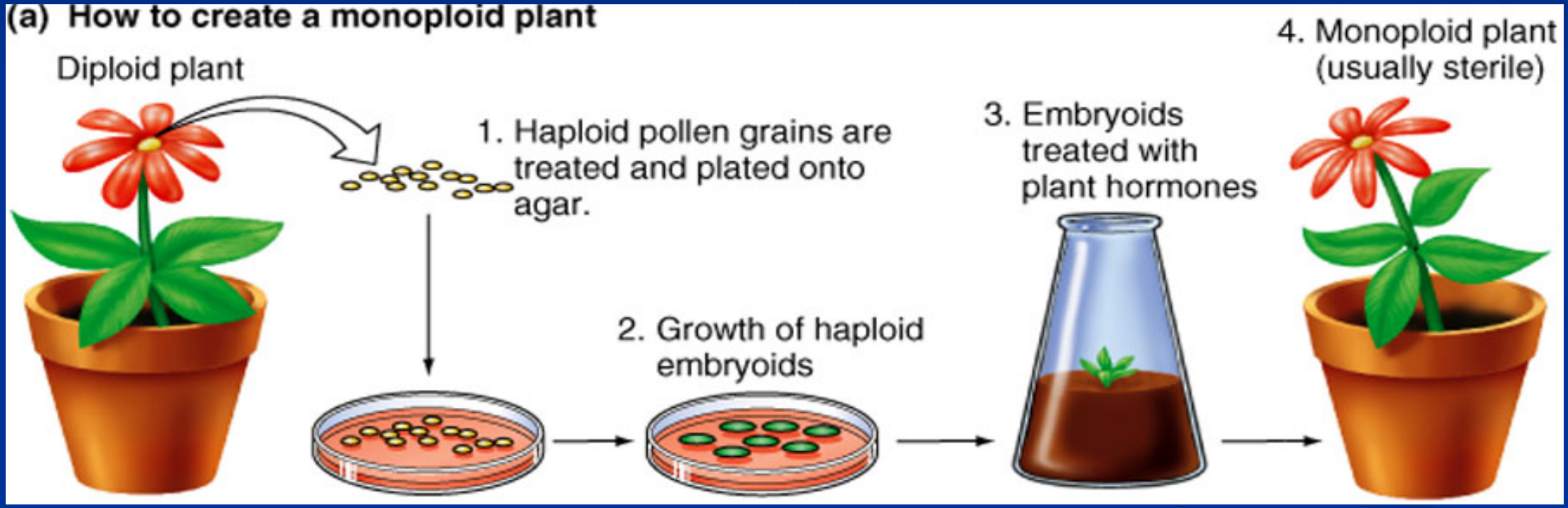


Fig. 12.31

- **Monoploid plants have many uses:**
  - **Visualize recessive traits directly**
  - **Introduction of mutations into individual cells**
  - **Select for desirable phenotypes (herbicide resistance)**

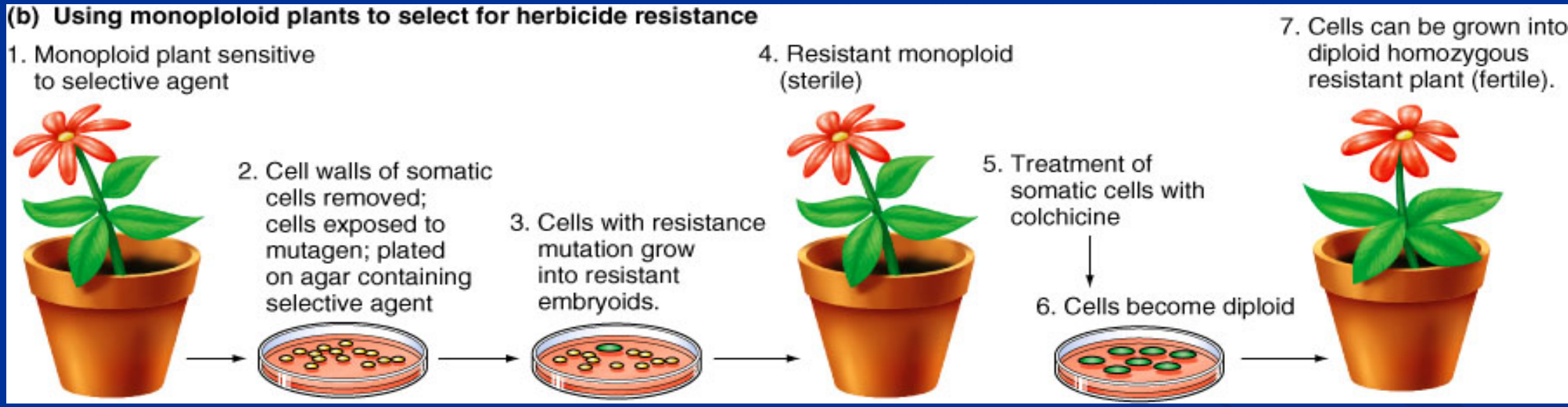


Fig. 12.31

Treatment with colchicine (秋水仙素) converts monoploid cells that express desired phenotypes to homozygous diploid

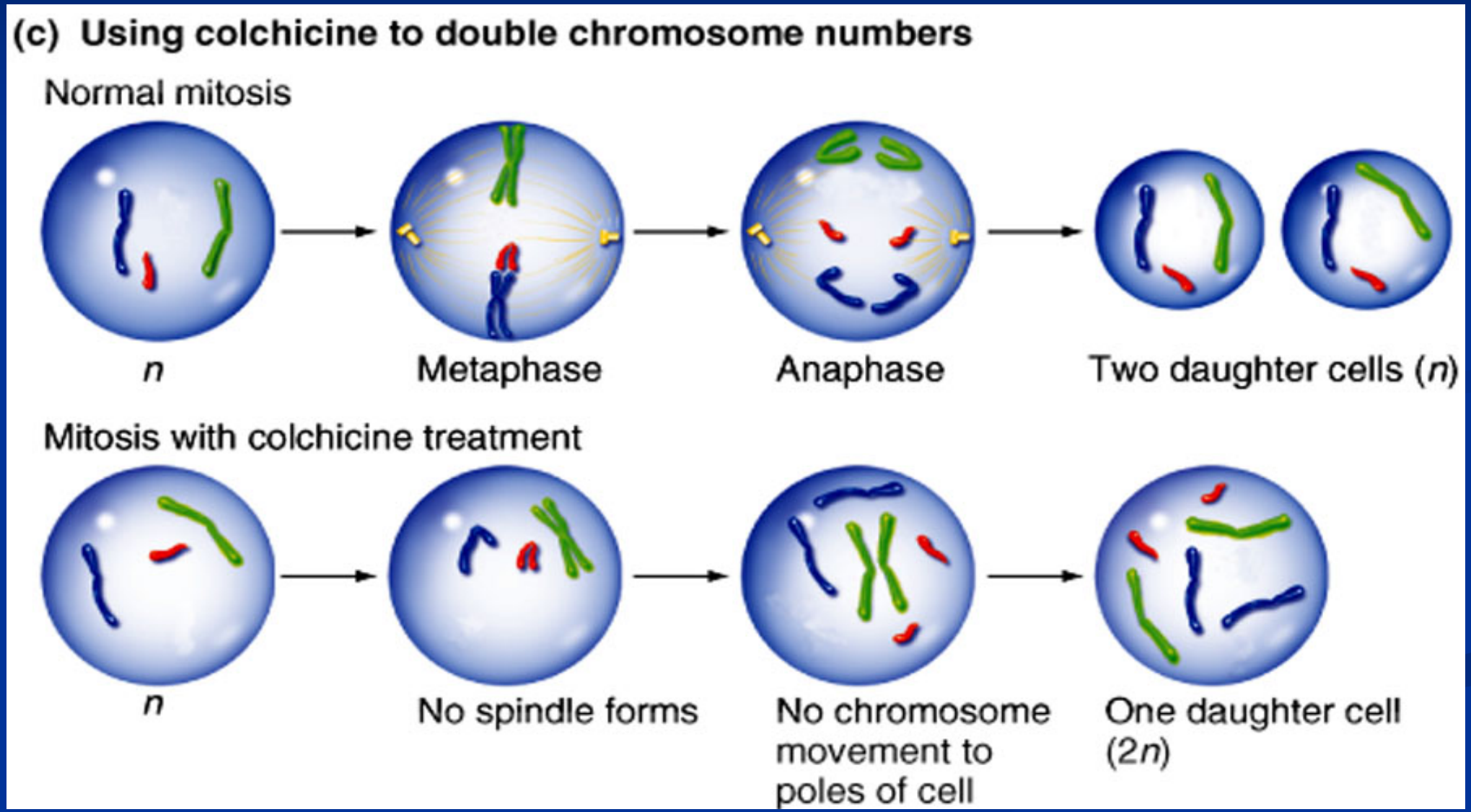
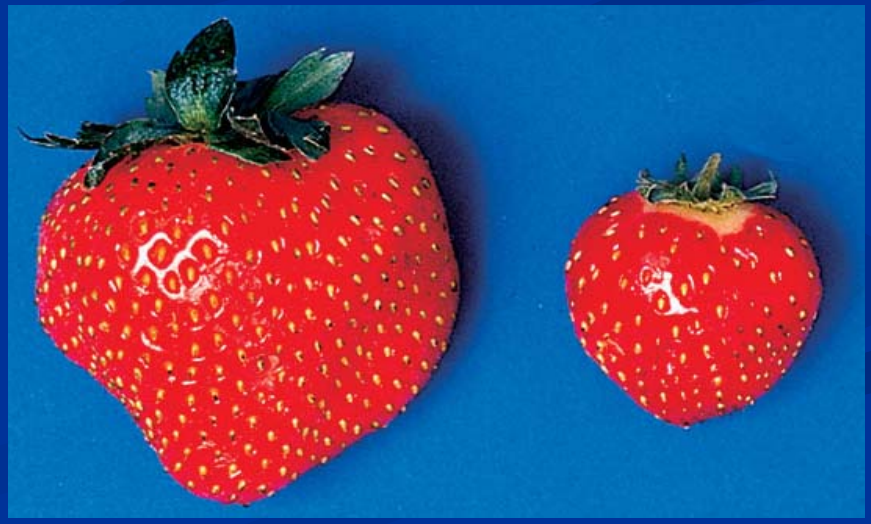


Fig. 12.31

Polyploidy has accompanied the evolution of many cultivated plants

- 1/3 of known flowering plants are polyploid.
- Polyploidy often increases plant size and vigor.
- Often selected for agricultural cultivation
  - Triploid – banana
  - Tetraploids – peanut, alfalfa, coffee, MacIntosh apple, Barlett pear
  - Octaploid - strawberry



Octaploid Diploid

Fig. 12.34

Tetraploids:

- Arise from failure of chromosomes to separate into two daughter cells during mitosis in diploid germ cells.
- In plants, tetraploid can be genetrated by colchicine treatment.
- Tetraploids are often source of new species.

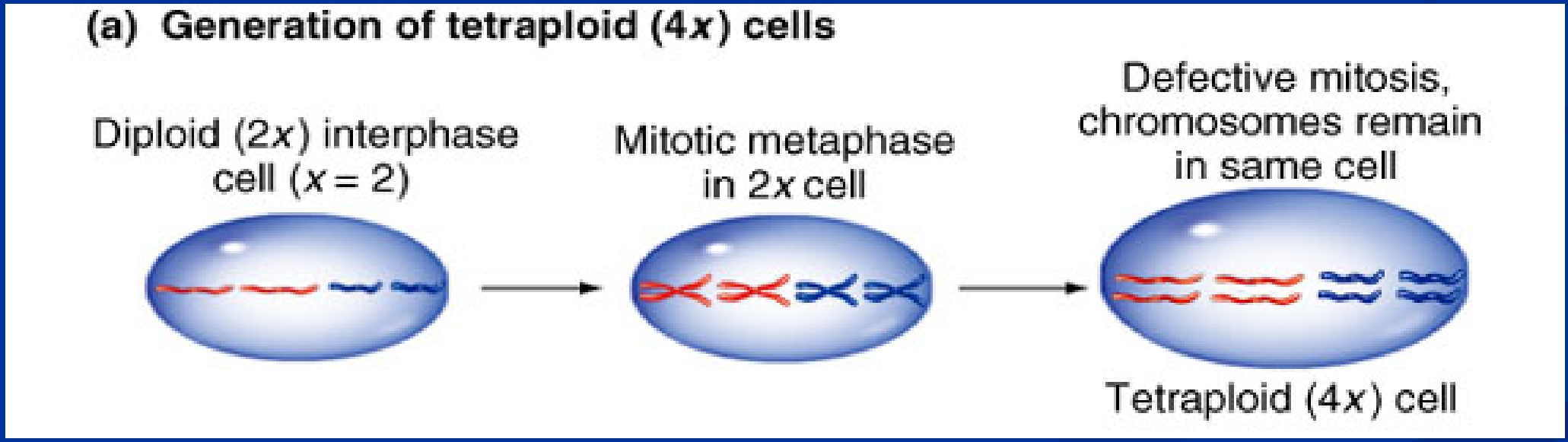
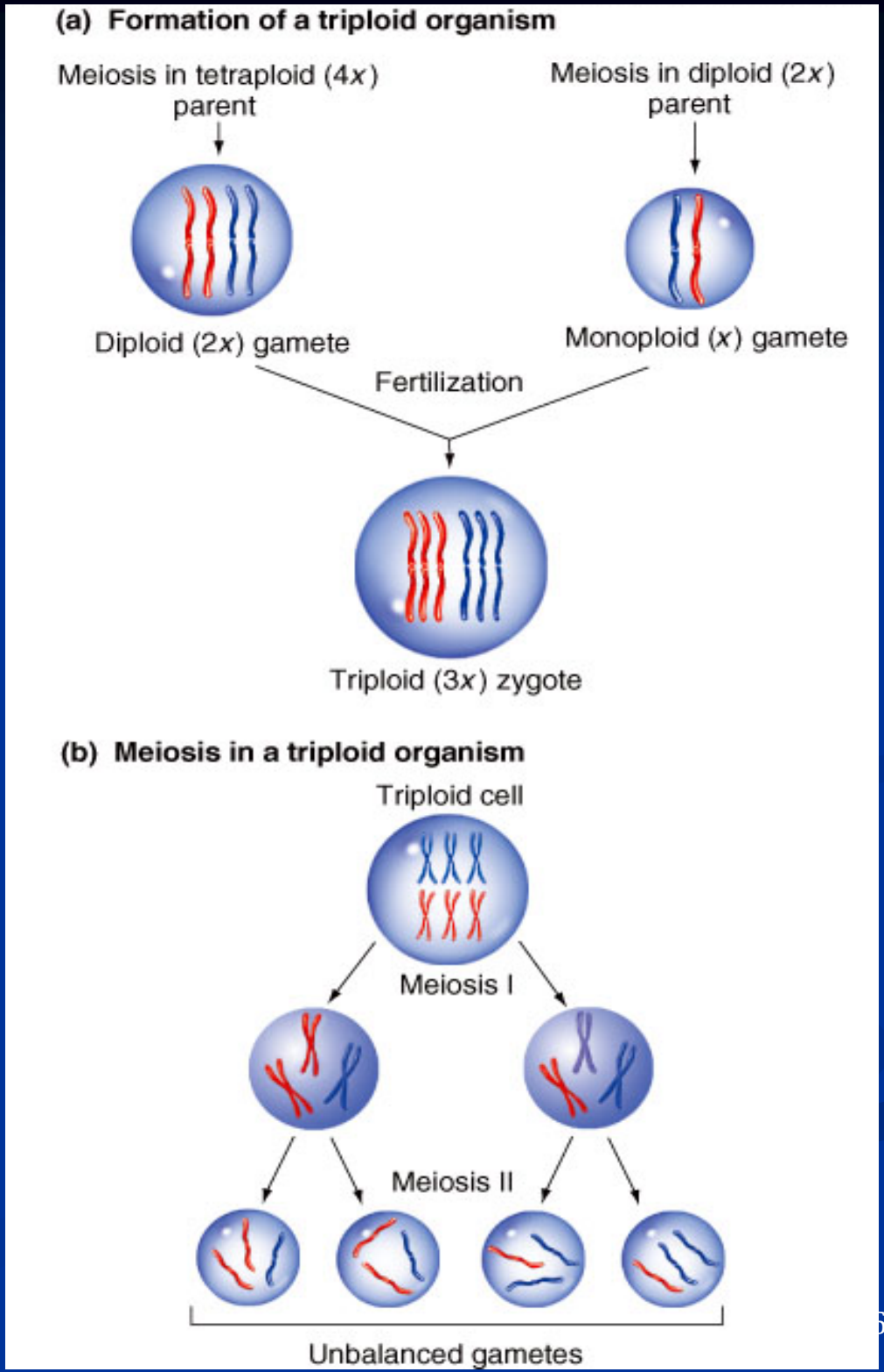


Fig 12.33

Triploids:

- Result from union of monoploid and diploid gametes
- Almost always sterile.
- Meiosis produces unbalanced gametes.



The creation of seedless watermelon, a triploid

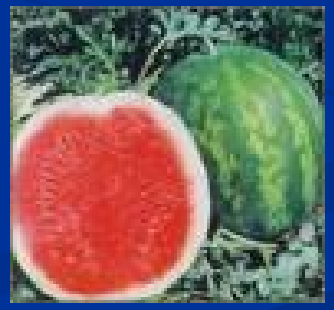
Diploid (2n=22)

Diploid (2n=22) pollen

Tetraploid (4n=44) egg

F1 hybrid (3n=33), a sterile triploid

Pollinate with normal pollen



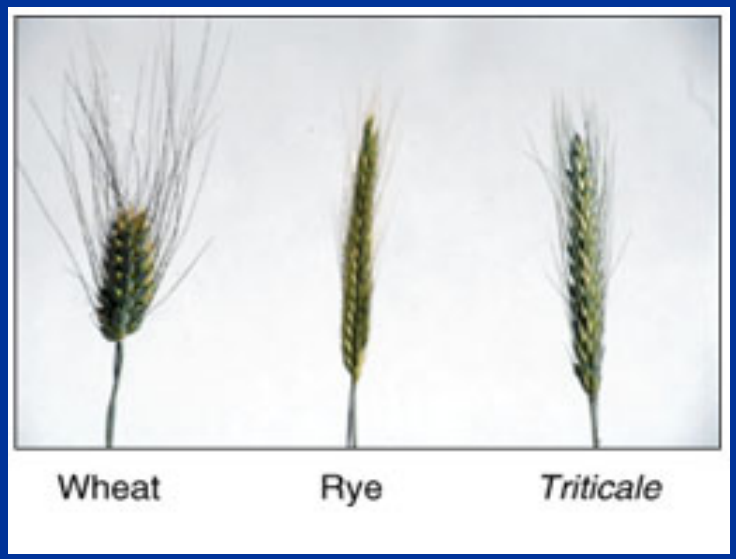
"Seedless" fruit

Some polyploids have agriculturally desirable traits derived from two species

- **Allopolyploid** (异源多倍体) – Polyploid hybrids in which the chromosome sets come from two or more distinct, though related, species.
  - Nearly all allopolyploids are infertile.
- **Amphidiploid** (双二倍体) – Organism produced by two diploid parental species. They contain two diploid genomes, each one derived from a different parent.
  - Arise from chromosomal doubling in germ cells.

The creation of *Triticale*

- Cross between tetraploid wheat and diploid rye produce a new crop with desirable traits.



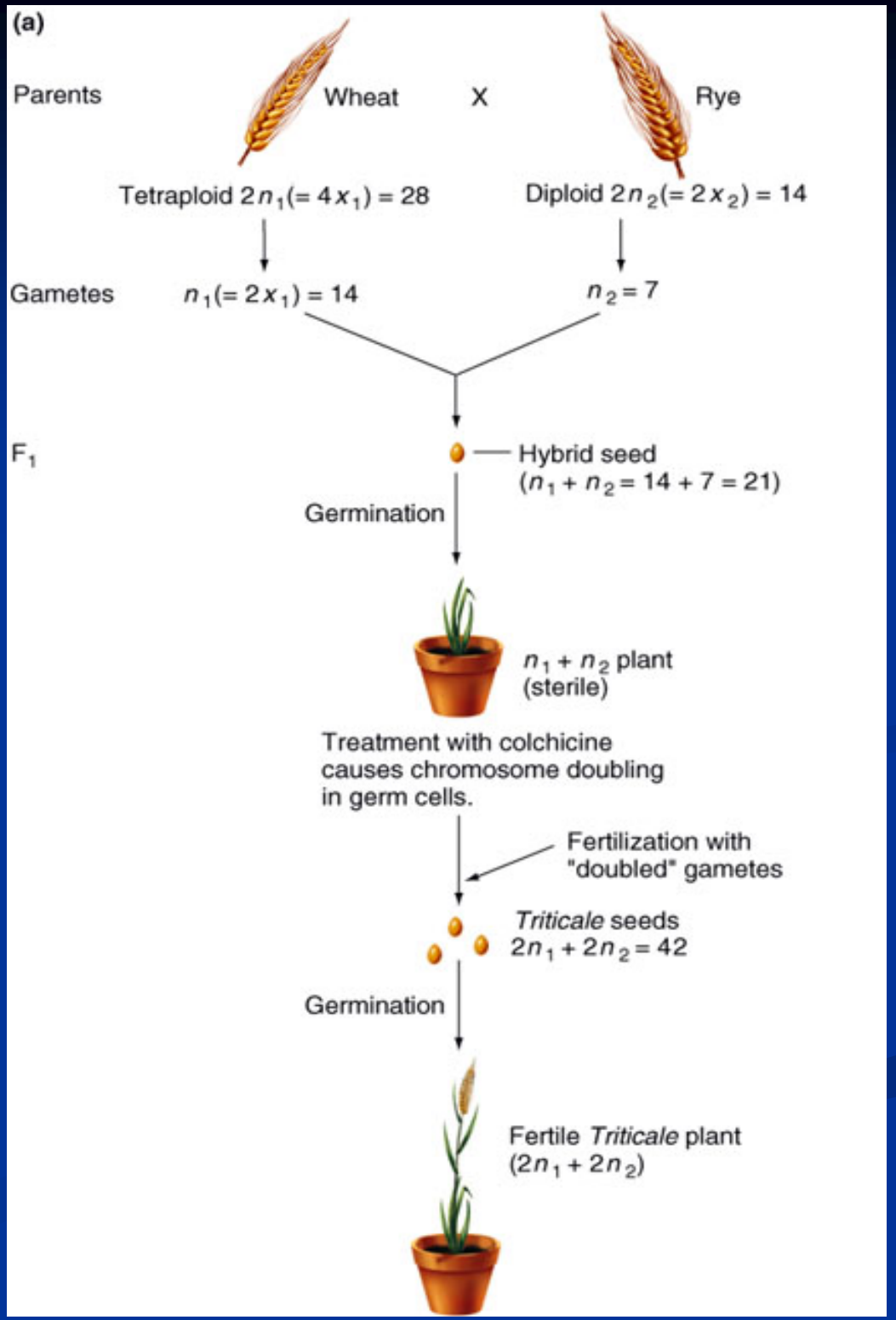


Fig. 12.35

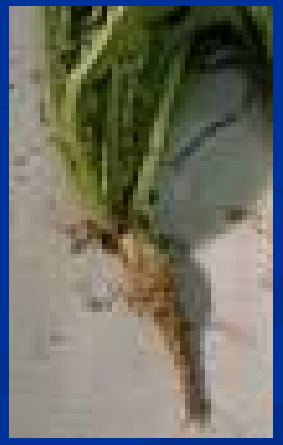
The creation of *Raphanobrassica*

- Georgi Karpechenko, a Russian cytologist, in 1927.
- Cross between cabbage *Brassica oleracea* and radish *Raphanus sativus*.

Brassica (2n1=18) *Raphanus* (2n2=18)

F1 hybrid (2n1+2n2=18), sterile

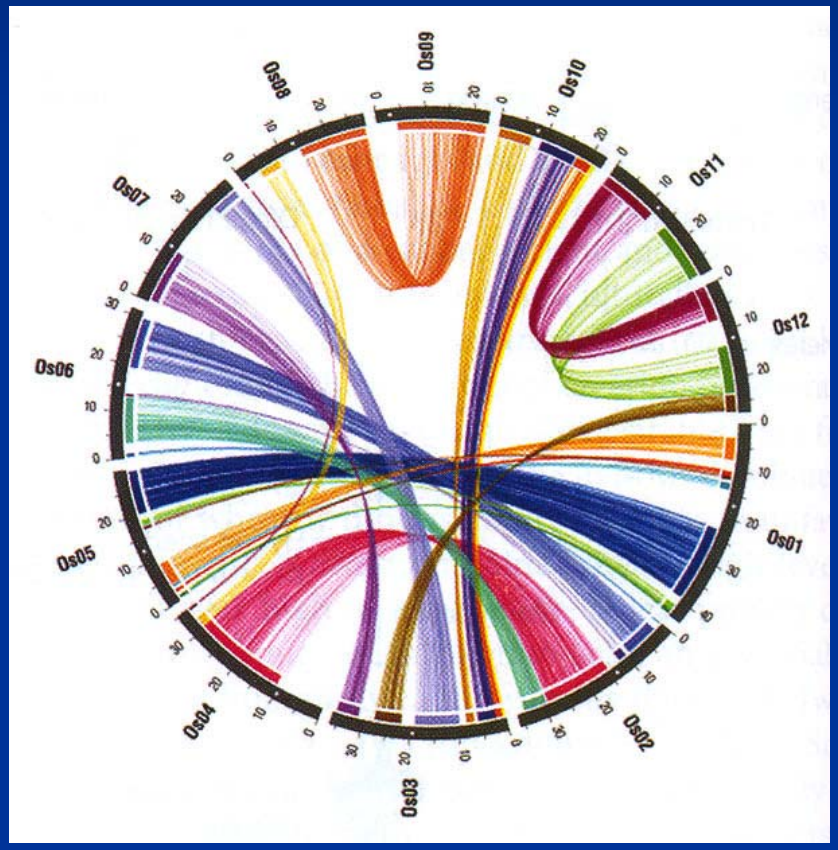
Colchicine treatment



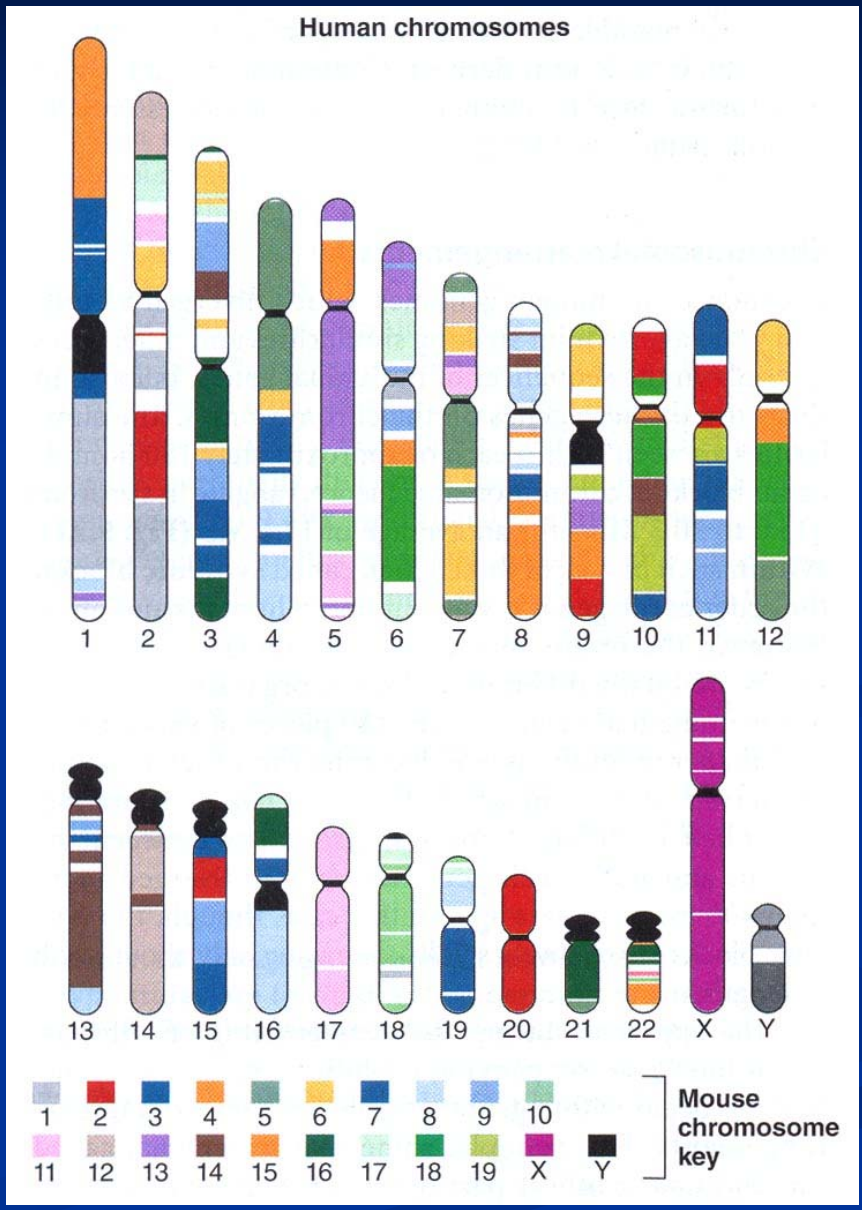
Raphanobrassica (2n1+2n2=36), fertile

12.6 Genome restructuring and evolution

- Genome duplication
- Chromosomal rearrangements



Genome duplication in ancient common ancestor of all cereal grasses (5 chr). Rice genome (12 chr) shows duplicated regions.



Comparison of human and mouse genomes reveals chromosomal rearrangements.

Fig. 12.36, 9.21

Rapid chromosomal rearrangement in house mice on the island of Madeira

- **Robertsonian translocations** generate different populations of mice with 2*n*=24, 2*n*=22 chromosomes. (2*n*=40 for common house mice)
- Populations are close to becoming two species after colonizing the island only 600 years ago.

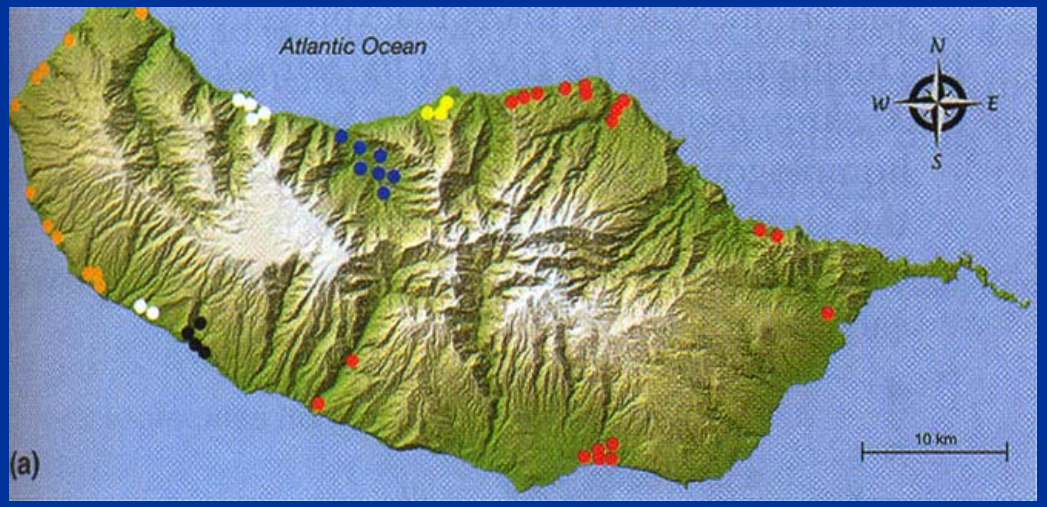


Fig 12.37