# Mutazioni Geniche

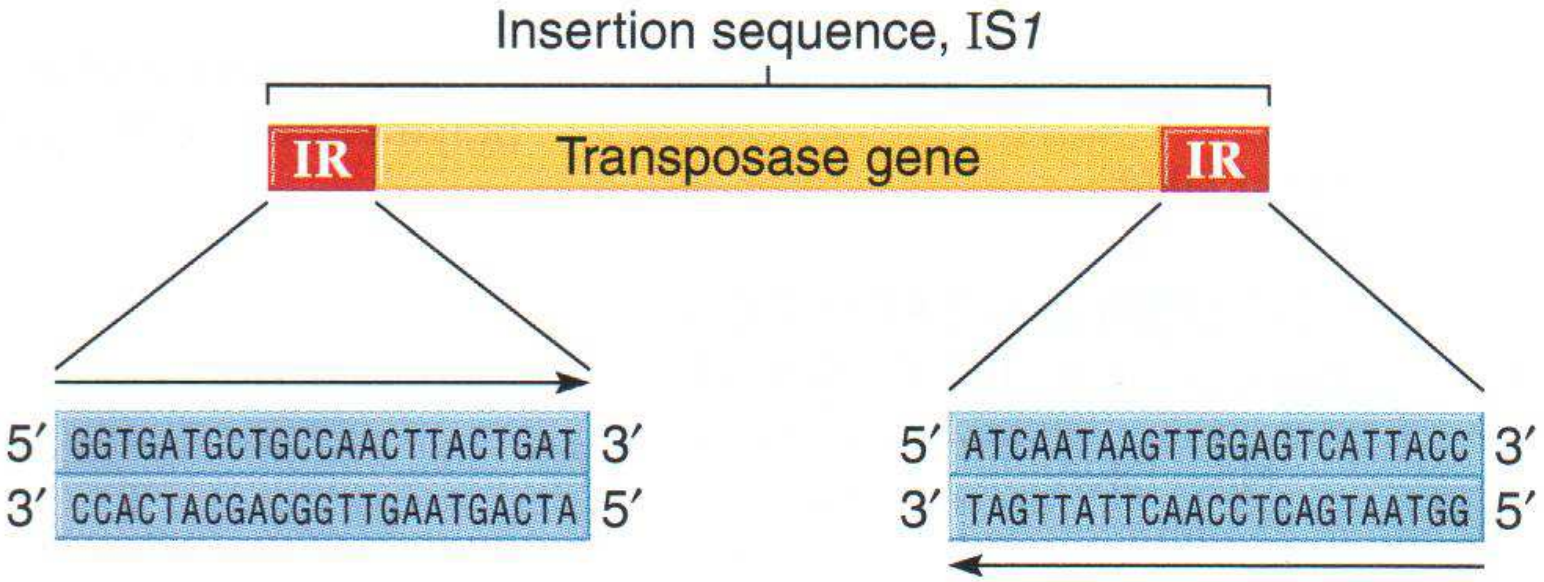
La trasposizione è una forma di ricombinazione genetica che sposta certe sequenze di DNA da un sito ad un altro.

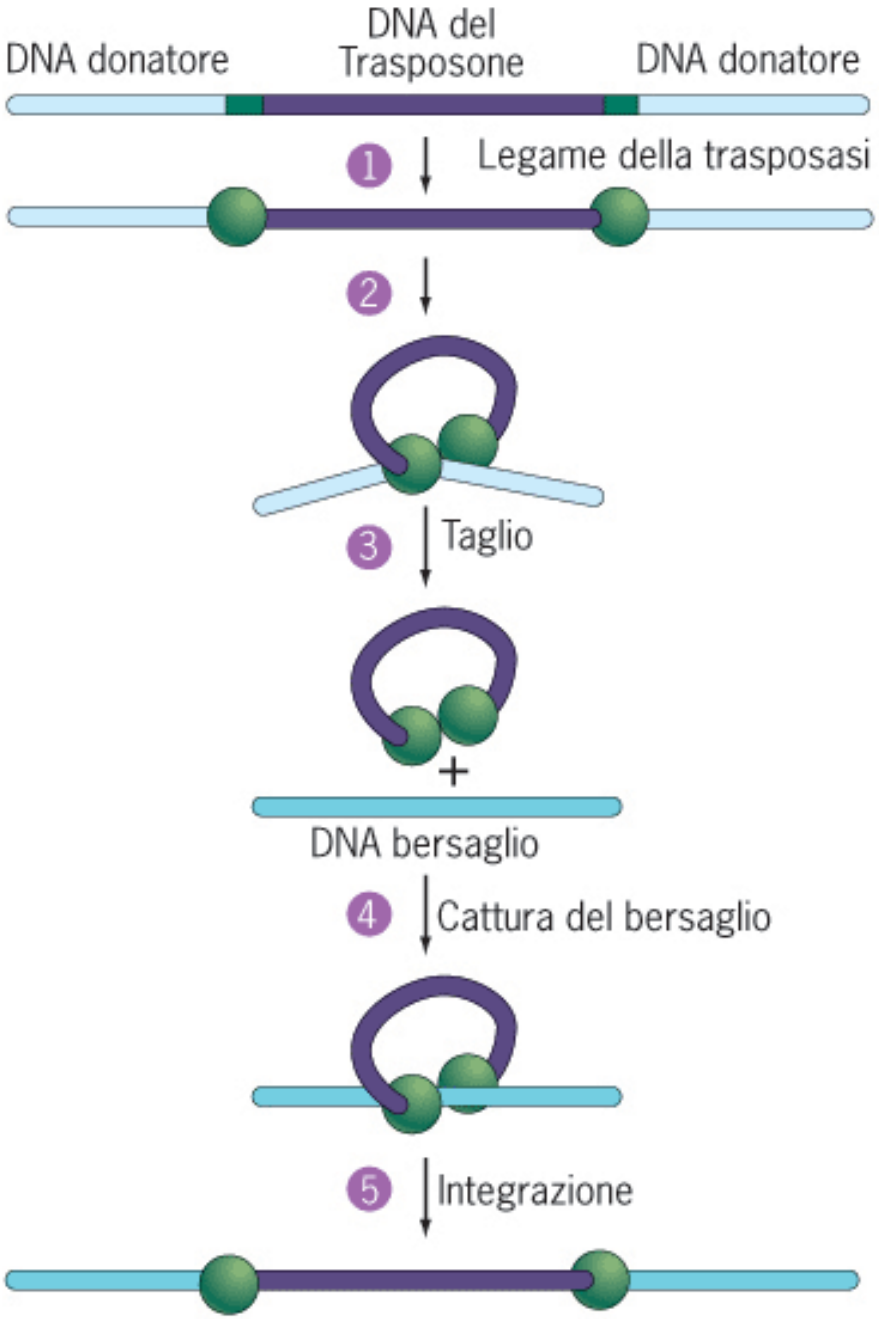
Tali elementi mobili sono detti elementi trasponibili o **trasposoni**.

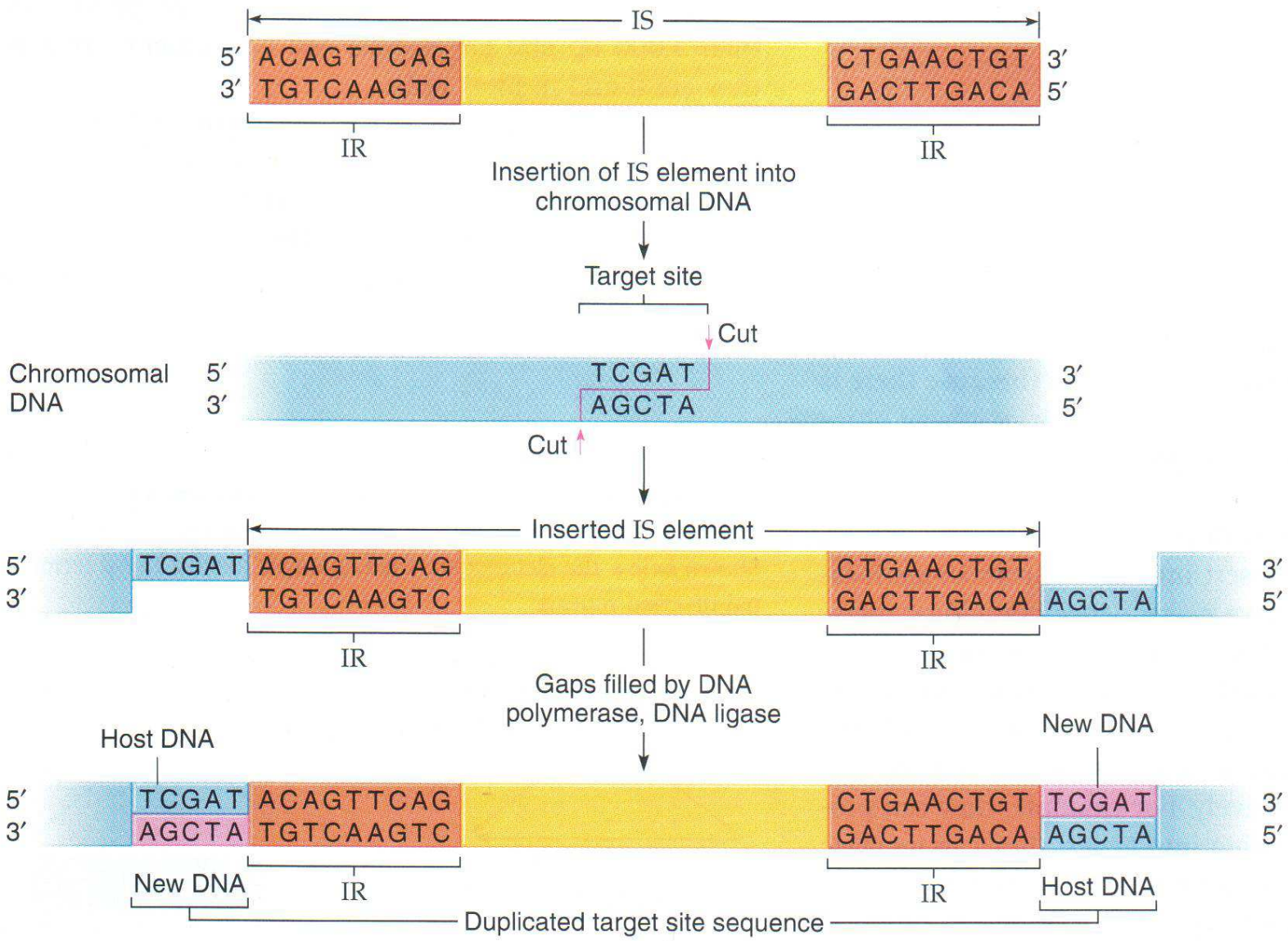
La trasposizione può avvenire con oppure senza la duplicazione dell’elemento mobile.

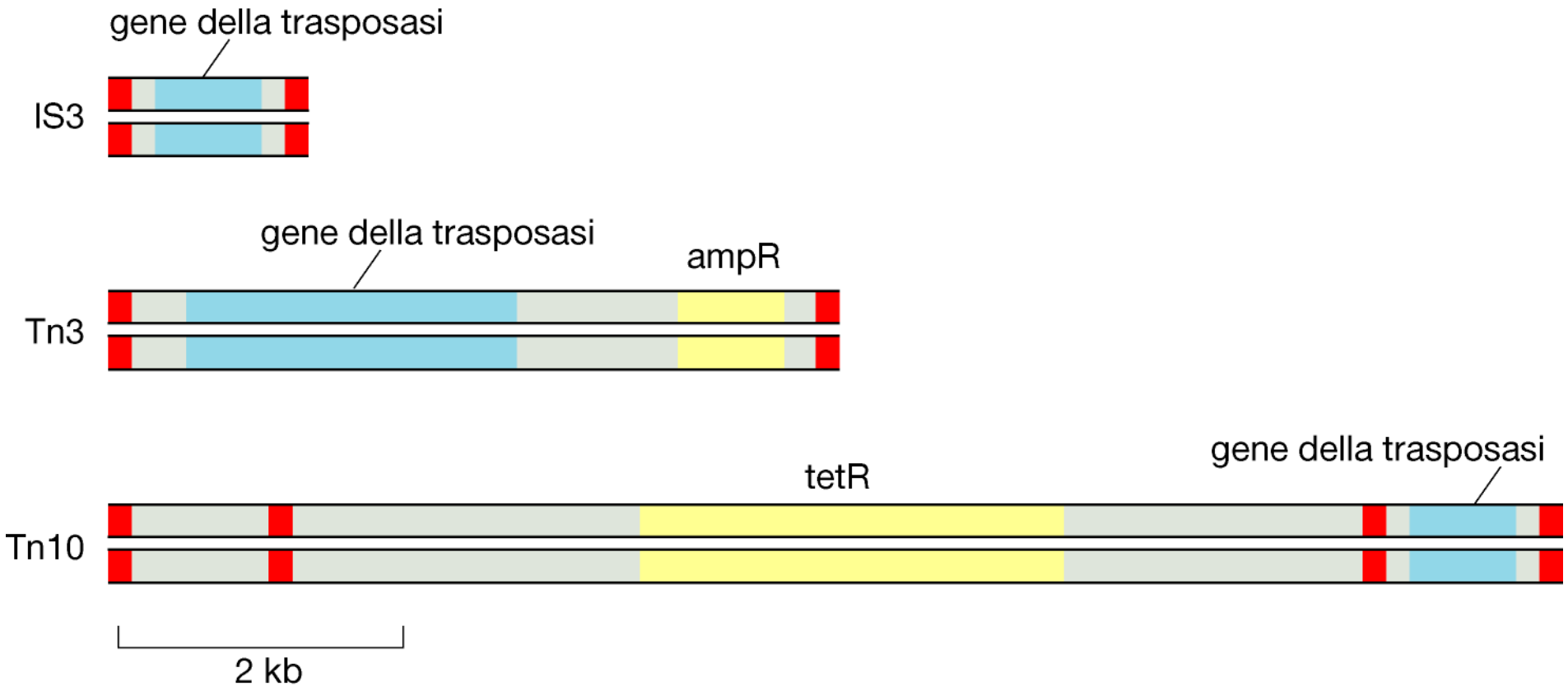
## Figure 20.1

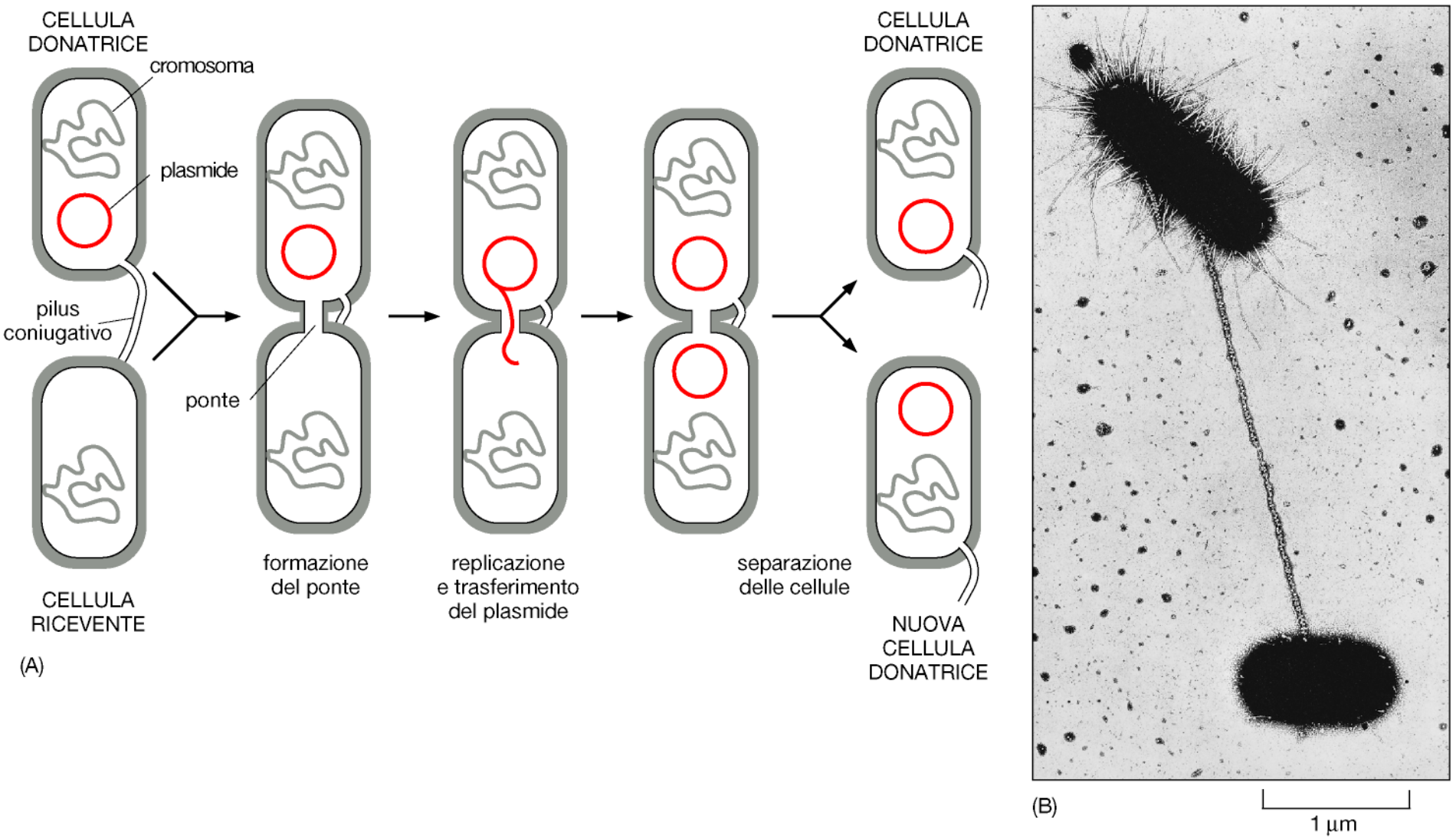
**The insertion sequence (IS) transposable element IS*1*.** The 768-bp IS element has inverted repeat (IR) sequences at the ends. Shown below the element are the sequences for the 23-bp terminal inverted repeats.




DNA donatore
DNA del Trasposone
DNA donatore
1
Legame della trasposasi
2
3
Taglio
+
DNA bersaglio
4
Cattura del bersaglio
5
Integrazione


IS
5′ ACAGTTCAG
3′ TGTCAAGTC
CTGAACTGT 3′
GACTTGACA 5′
IR
IR
Insertion of IS element into chromosomal DNA
Target site
Cut
Chromosomal DNA
5′
3′
TCGAT
AGCTA
3′
5′
Cut
Inserted IS element
5′
3′
TCGAT
ACAGTTCAG
TGTCAAGTC
CTGAACTGT
GACTTGACA
AGCTA
3′
5′
IR
IR
Gaps filled by DNA polymerase, DNA ligase
Host DNA
New DNA
5′
3′
TCGAT
AGCTA
ACAGTTCAG
TGTCAAGTC
CTGAACTGT
GACTTGACA
TCGAT
AGCTA
3′
5′
New DNA
IR
IR
Host DNA
Duplicated target site sequence


gene della trasposasi
IS3
gene della trasposasi
ampR
Tn3
tetR
gene della trasposasi
Tn10
2 kb


CELLULA DONATRICE
cromosoma
plasmide
pilus coniugativo
CELLULA RICEVENTE
ponte
formazione del ponte
replicazione e trasferimento del plasmide
separazione delle cellule
CELLULA DONATRICE
NUOVA CELLULA DONATRICE
(A)
(B)
1 µm

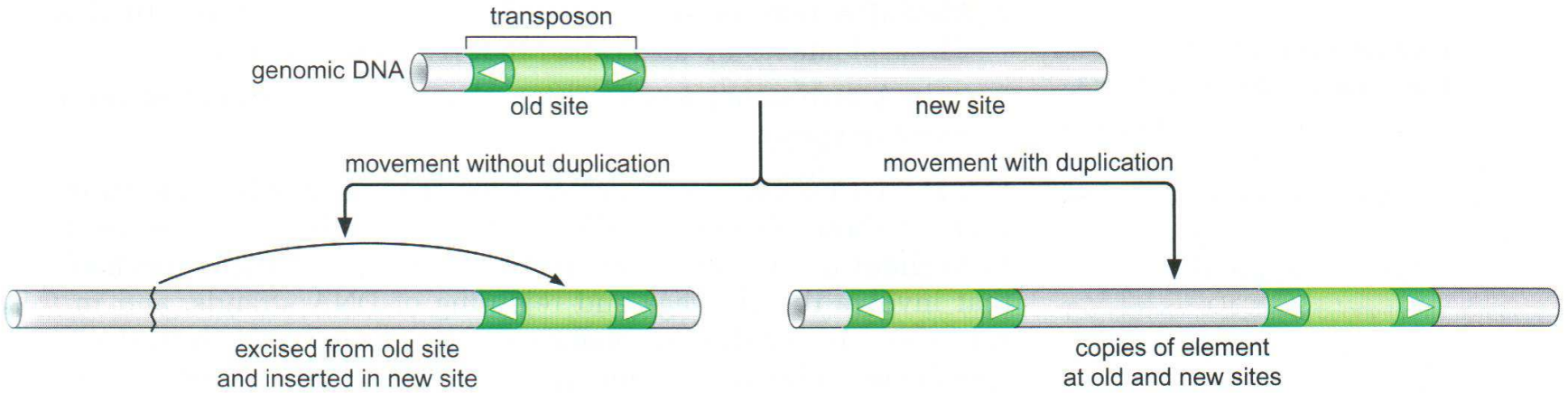
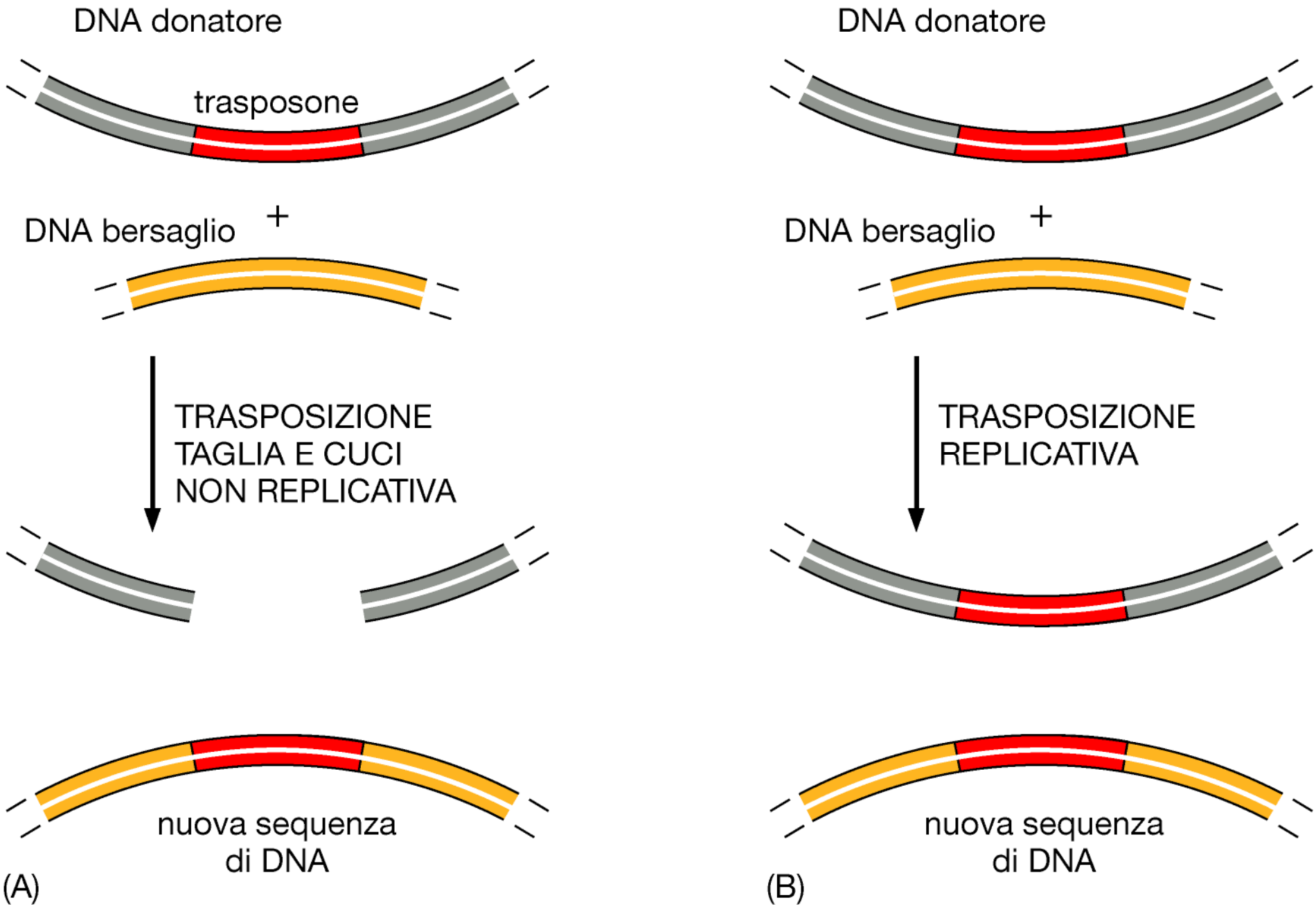


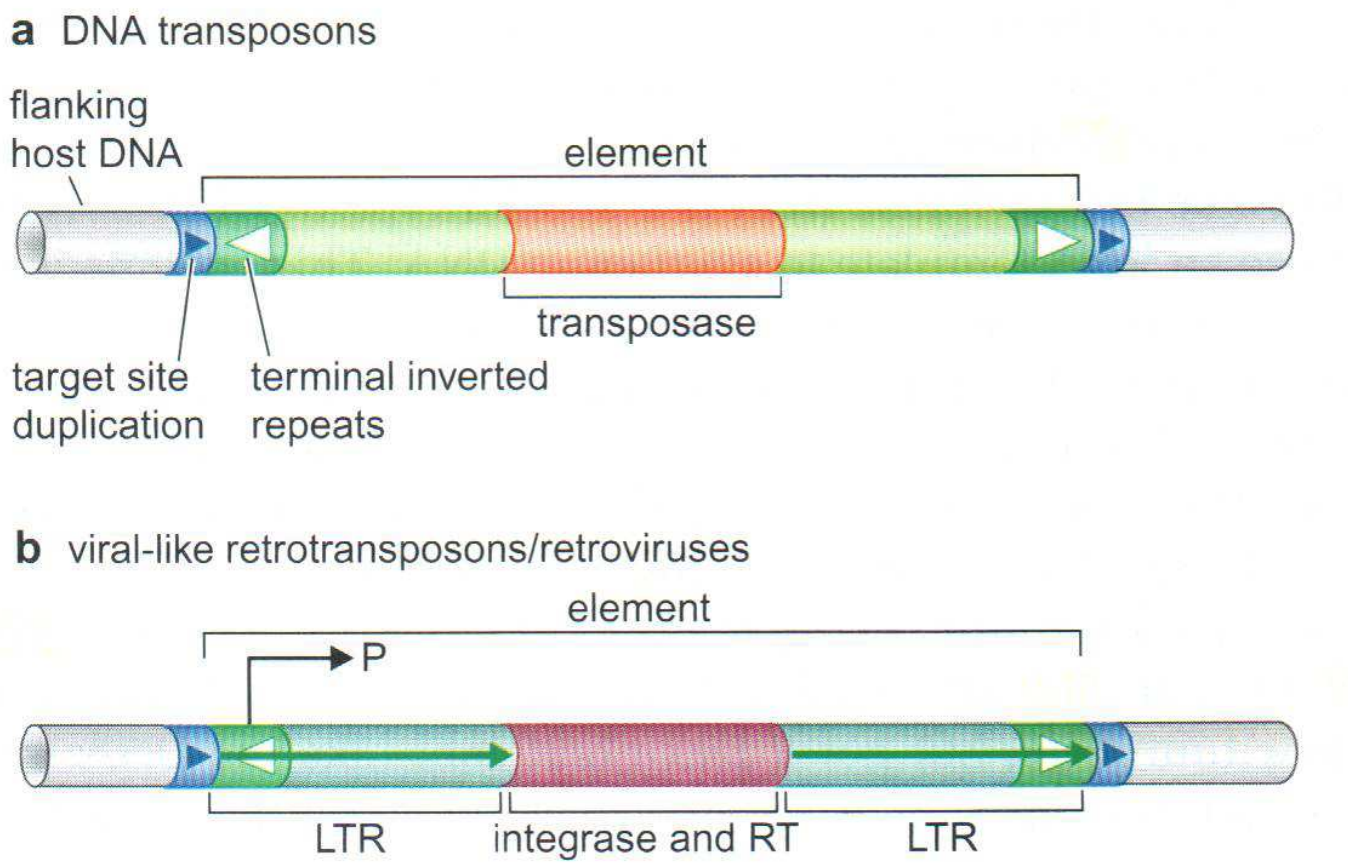

**FIGURE 11-17 Transposition of a mobile genetic element to a new site in the host DNA.**
Recombination, in some cases, involves excision of the transposon from the old DNA location (left). In other cases, one copy of the transposon stays at the old location and another copy is inserted into the new DNA site (right).

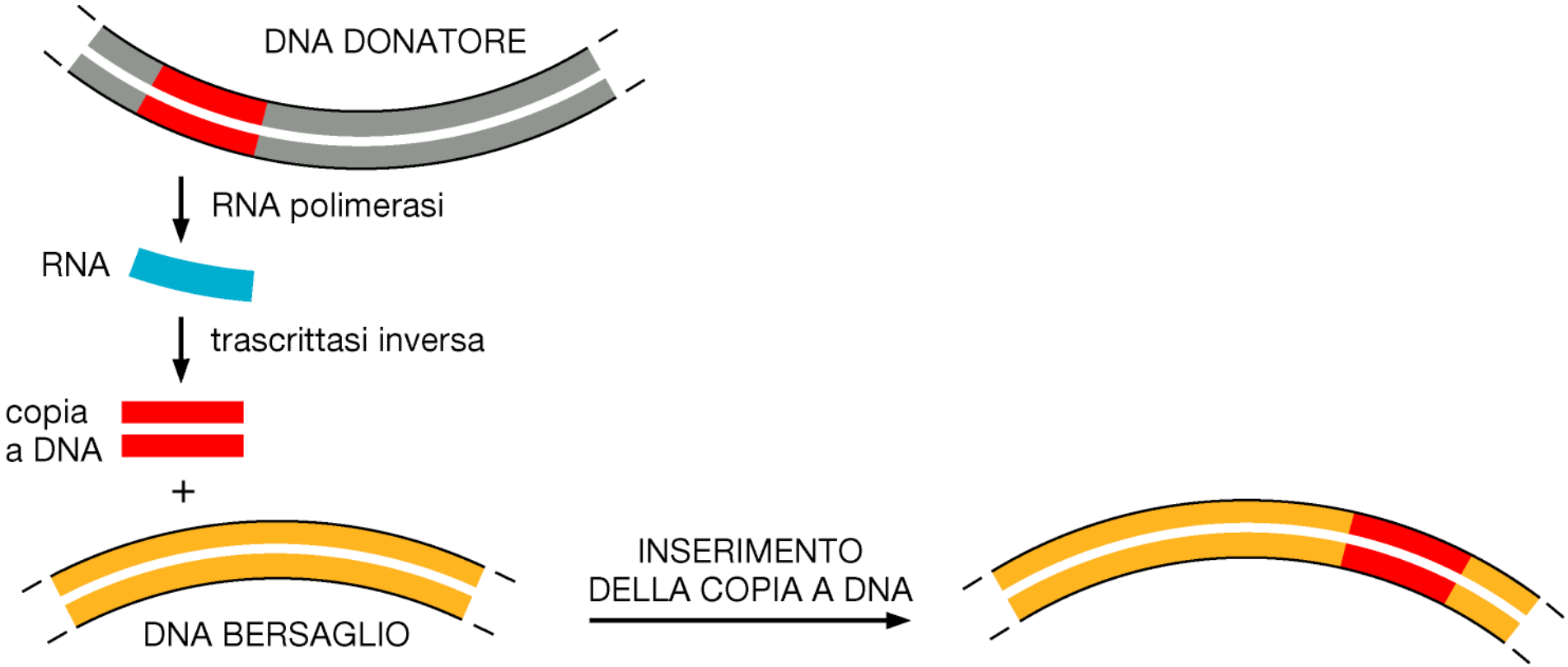

DNA donatore
trasposone
DNA bersaglio
+
TRASPOSIZIONE
TAGLIA E CUCI
NON REPLICATIVA
nuova sequenza
di DNA
(A)
DNA donatore
DNA bersaglio
+
TRASPOSIZIONE
REPLICATIVA
nuova sequenza
di DNA
(B)

I trasposoni non mostrano selettività per il sito di inserzione.

I trasposoni possono inserirsi all’interno di sequenze codificanti di un gene, abolendone la funzione.

I trasposoni possono inserirsi all’interno di sequenze di regolazione di un gene, modificandone l’espressione.


a DNA transposons
flanking
host DNA
element
transposase
target site
duplication
terminal inverted
repeats
b viral-like retrotransposons/retroviruses
element
P
LTR
integrase and RT
LTR


DNA DONATORE
RNA polimerasi
RNA
trascrittasi inversa
copia
a DNA
+
DNA BERSAGLIO
INSERIMENTO
DELLA COPIA A DNA

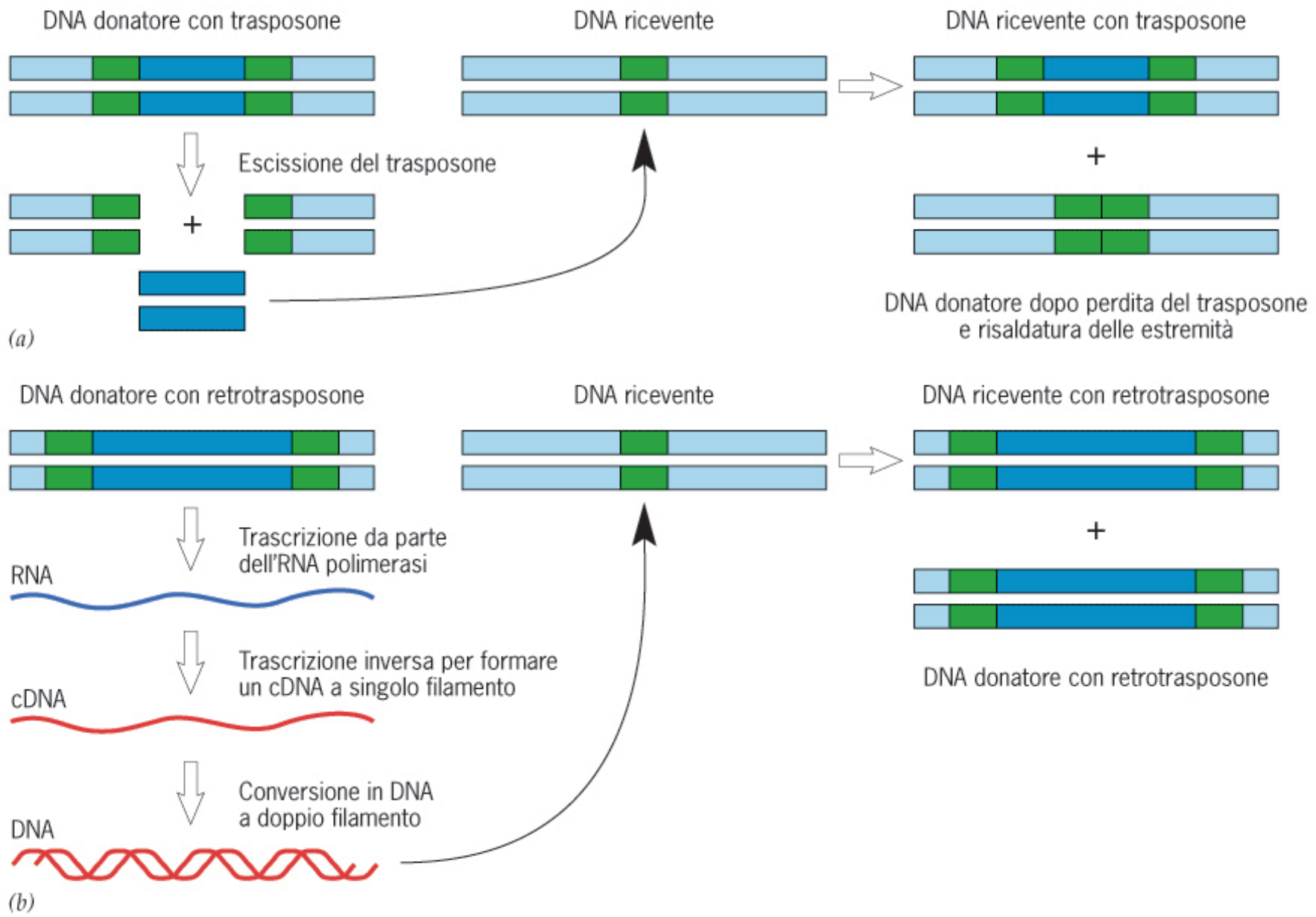
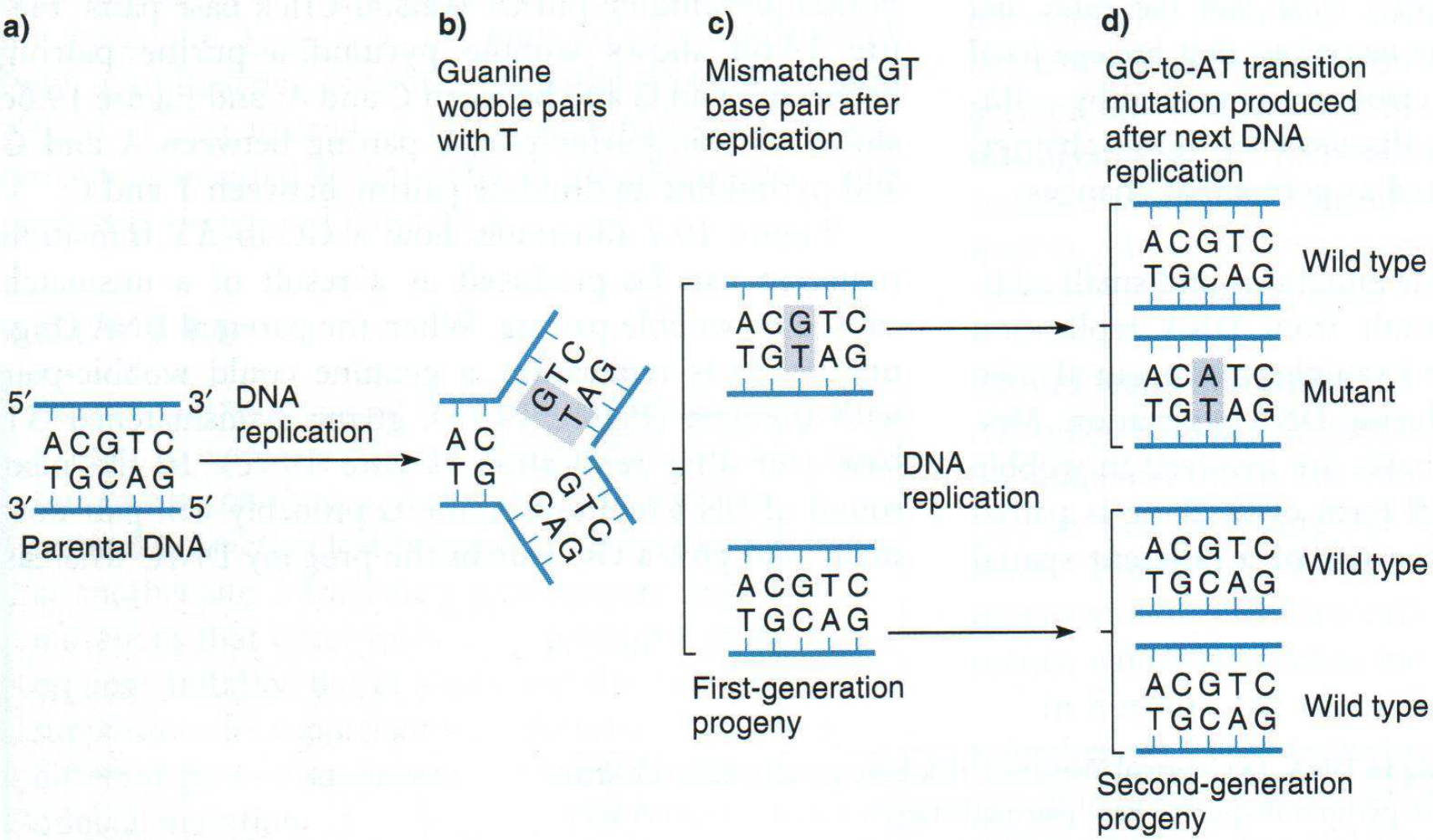
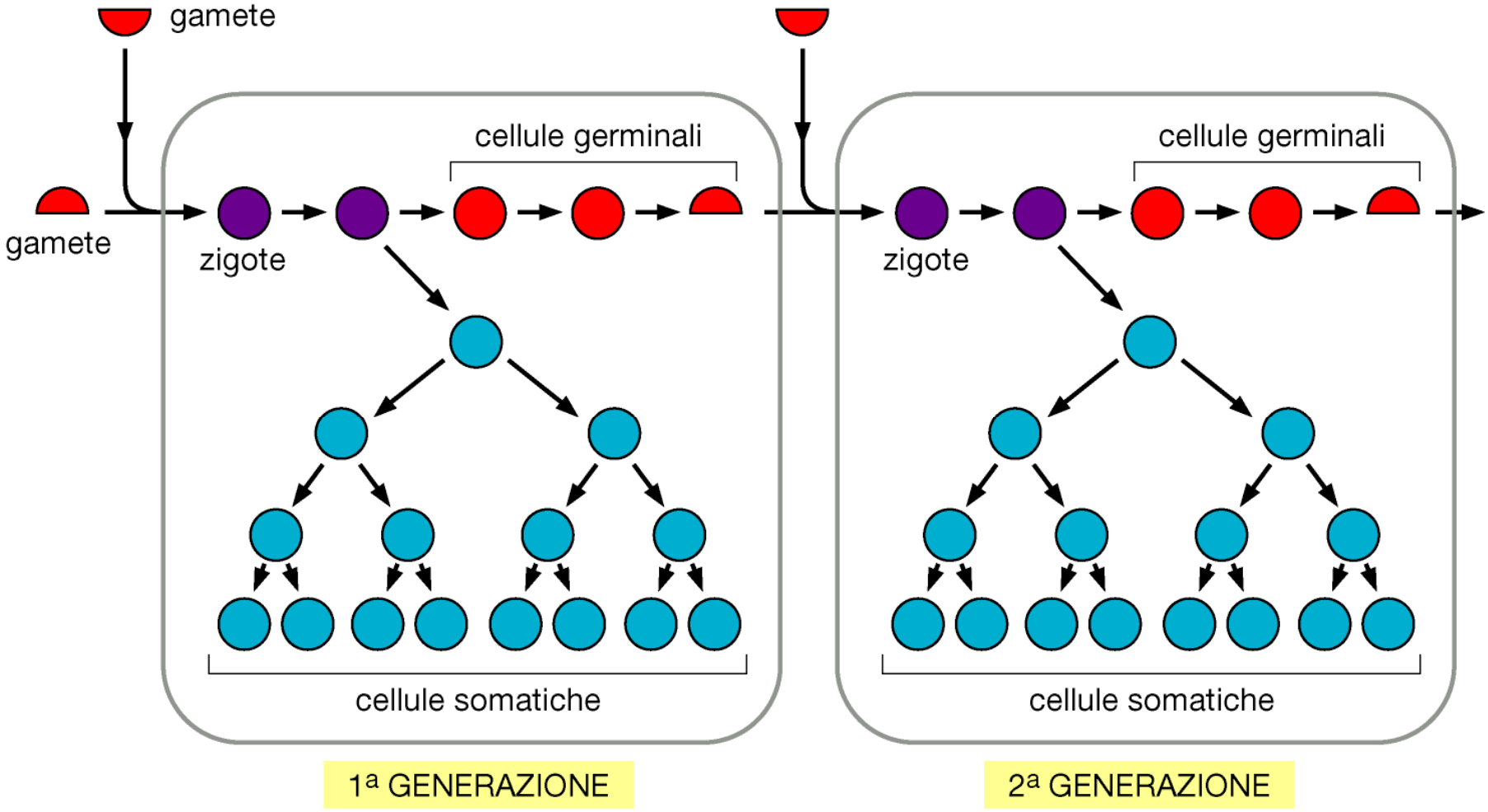
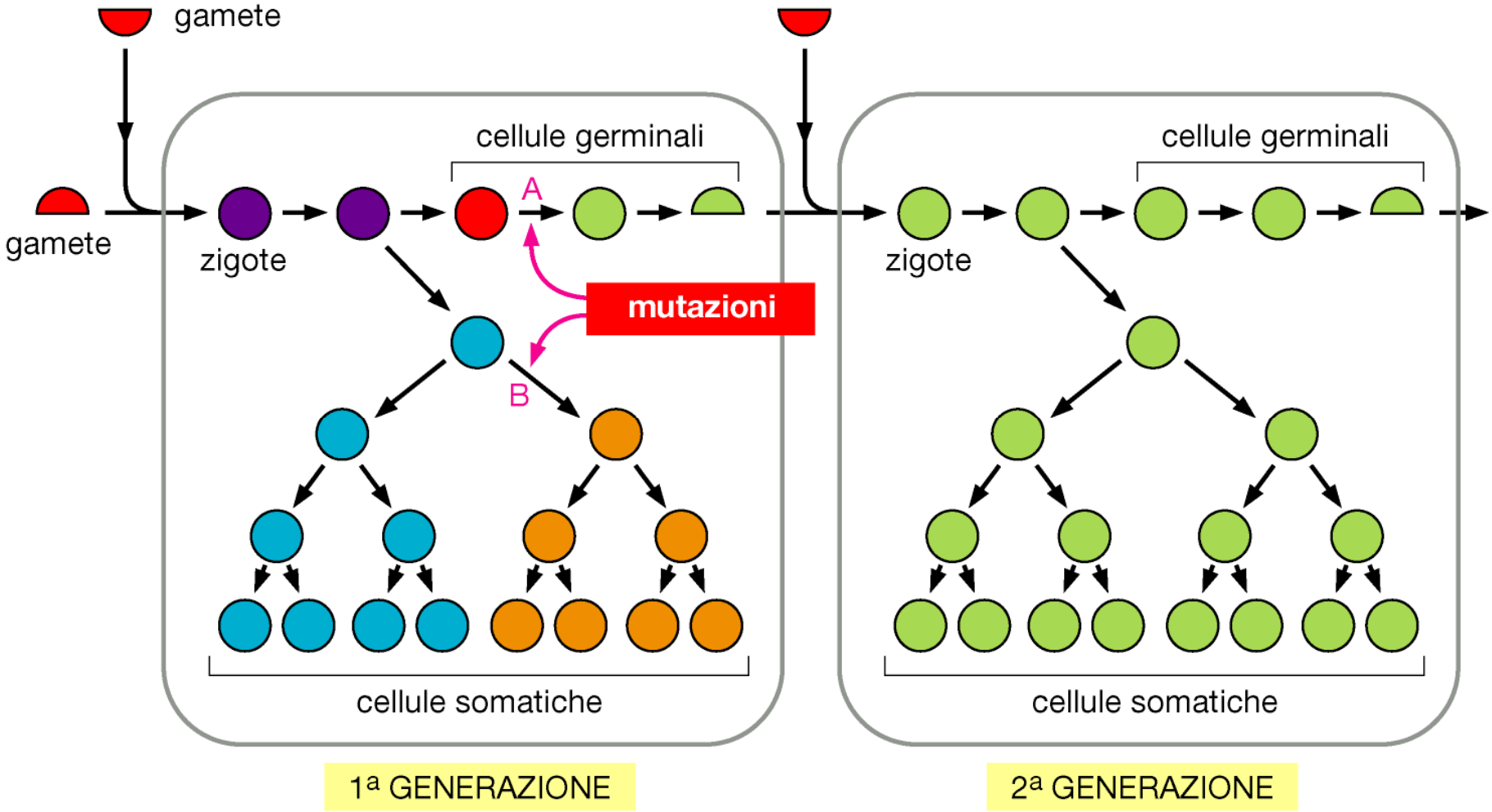

DNA donatore con trasposone
DNA ricevente
DNA ricevente con trasposone
Escissione del trasposone
+
+
DNA donatore dopo perdita del trasposone
e risaldatura delle estremità
(a)
DNA donatore con retrotrasposone
DNA ricevente
DNA ricevente con retrotrasposone
Trascrizione da parte
dell'RNA polimerasi
RNA
+
Trascrizione inversa per formare
un cDNA a singolo filamento
cDNA
Conversione in DNA
a doppio filamento
DNA
DNA donatore con retrotrasposone
(b)

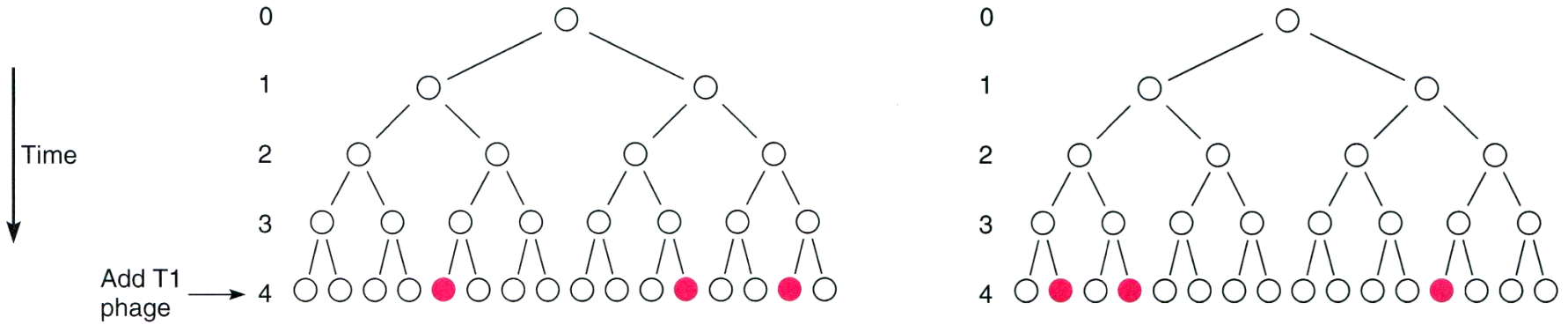
**Figure 19.7**

**Production of a mutation as a result of a mismatch caused by wobble base pairing.** The details are explained in the text.

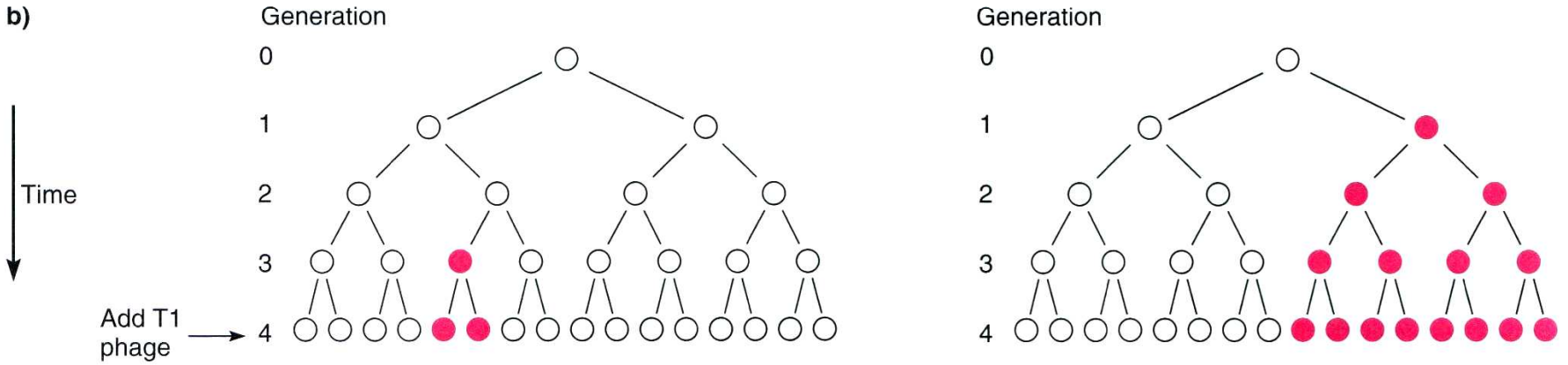



gamete
gamete
zigote
cellule germinali
cellule somatiche
zigote
cellule germinali
cellule somatiche
1ª GENERAZIONE
2ª GENERAZIONE


gamete
gamete
zigote
cellule germinali
A
mutazioni
B
cellule somatiche
1ª GENERAZIONE
zigote
cellule germinali
cellule somatiche
2ª GENERAZIONE


Time
Add T1
phage
0
1
2
3
4

**b)**

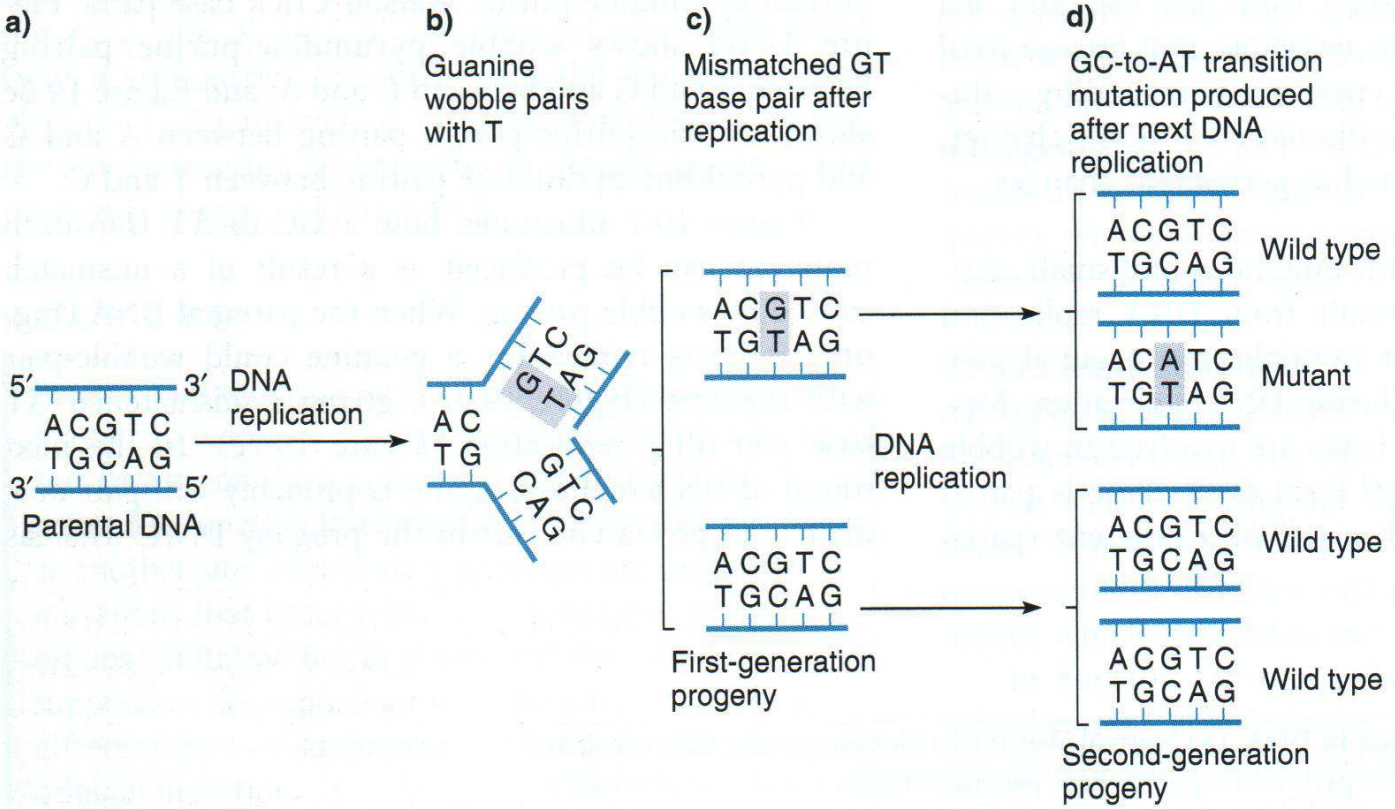

Generation
Time
Add T1
phage
0
1
2
3
4
Generation
0
1
2
3
4

# Meccanismi di Riparo

# delle Mutazioni

**Figure 19.7**

**Production of a mutation as a result of a mismatch caused by wobble base pairing.** The details are explained in the text.



I sistemi di riparo possono:

- Riparare **direttamente** la lesione
- **Rimuovere** la lesione e poi riparare

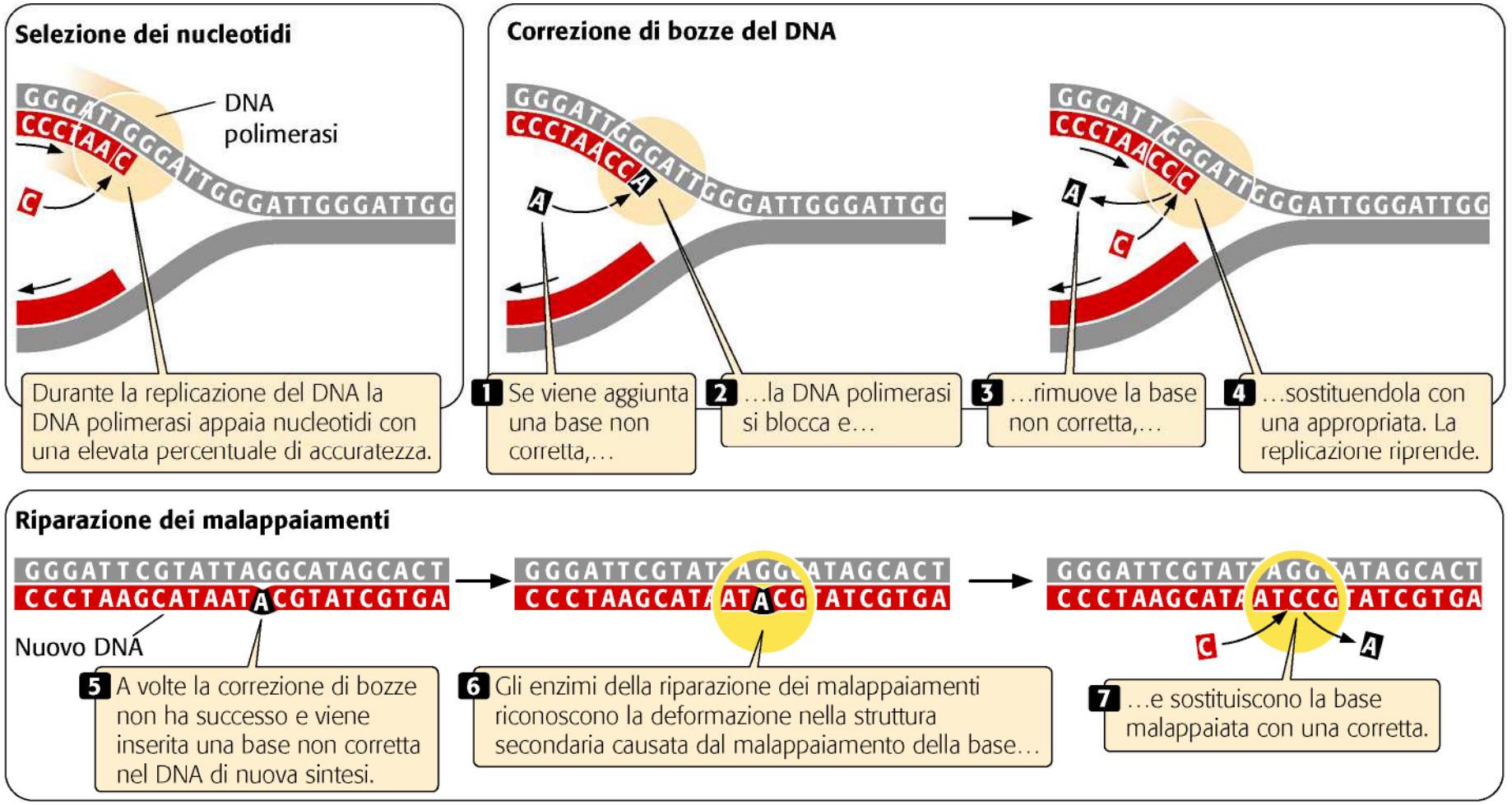
In entrambi i casi la catena danneggiata viene riparata da meccanismi che leggono l'informazione inalterata presente nella catena intatta

# Correzione diretta della mutazione

- Attività proofreading della DNA polimerasi

  Il gene *mut*D in *E. coli* codifica per la subunità ε della DNA polimerasi III. Mutanti *mut*D sono difettivi per l'attività esonucleasica 3' → 5*'.*

  **Geni mutatori**.




**Conclusione:** L'elevata accuratezza della replicazione del DNA è assicurata da svariati meccanismi.

**Table 9.1** **Comparison of the Structural and Functional Characteristics of the *E. coli* DNA Polymerases I, II, and III**

| DNA Polymerase | Polymerization: 5'→3' | Exonuclease: 3'→5' | Exonuclease: 5'→3' | Molecular Weight (daltons) | Molecules per Cell (approximately) | Structural Genes |
|---|---|---|---|---|---|---|
| I | Yes | Yes | Yes | 103,000 | 400 | *polA* |
| II | Yes | Yes | No | 90,000 | ? | *polB* |
| III | Yes | Yes | No | Core of 130,000, 27,500, and 10,000 subunits; 7 other subunits[a] | 10–20 | *dnaE*, *dnaQ*, and *holE* for core |

[a]Polymerase III consists of a catalytic core of α (alpha: 130,000 Da; *dnaE*), ε (epsilon: 27,500 Da; *dnaQ*; responsible for 3'→5' exonuclease activity), and θ (theta: 10,000 Da; *holE*), and 7 other subunits: τ (tau: 71,000 Da; *dnaX*), γ (gamma: 47,500 Da; *dnaX*), δ (delta: 35,000 Da; *holA*), δ' (delta prime: 33,000 Da; *holB*), χ (chi: 15,000 Da; *holC*), ψ (psi: 12,000 Da; *holD*), and β (beta: 40,600 Da; *dnaN*).

# Correzione diretta della mutazione

- Riparo dei dimeri di timina

  Foto-riattivazione. I dimeri di timina sono risolti per attivazione dell'enzima **fotoliasi** (gene *phr*). Mutanti *phr* sono difettivi nell'attività di riparo.

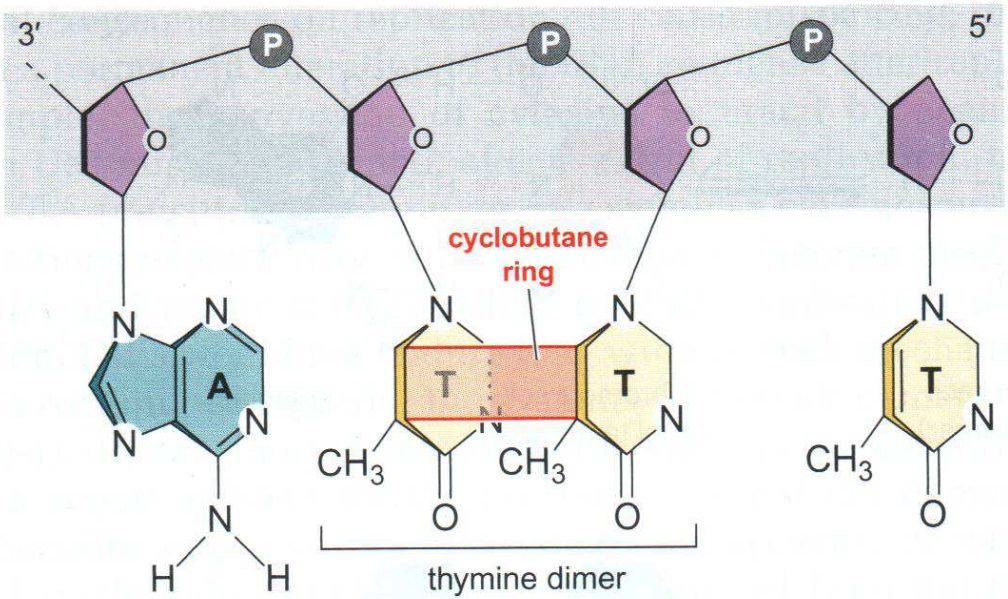



**FIGURE 9-9 Thymine dimer.** UV induces the formation of a cyclobutane ring between adjacent thymines.

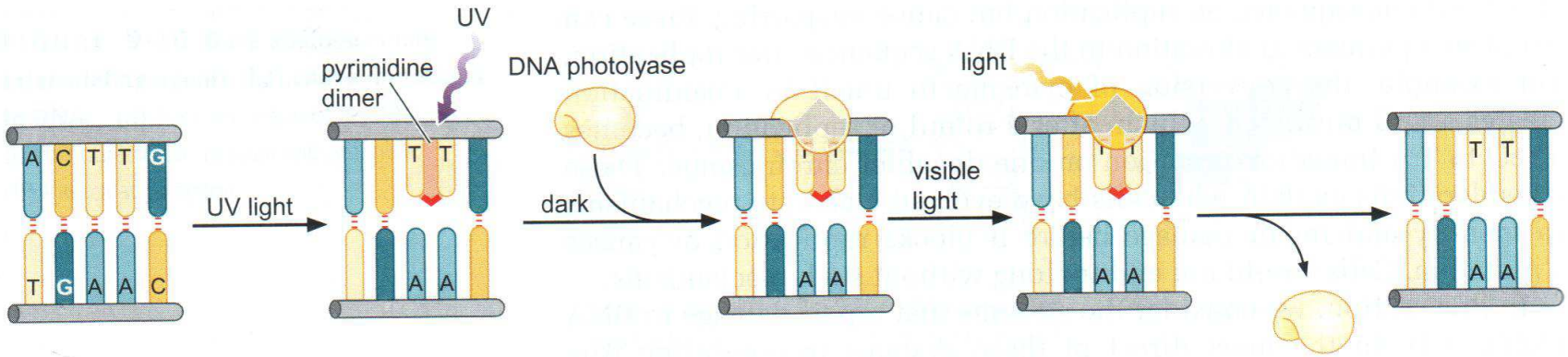
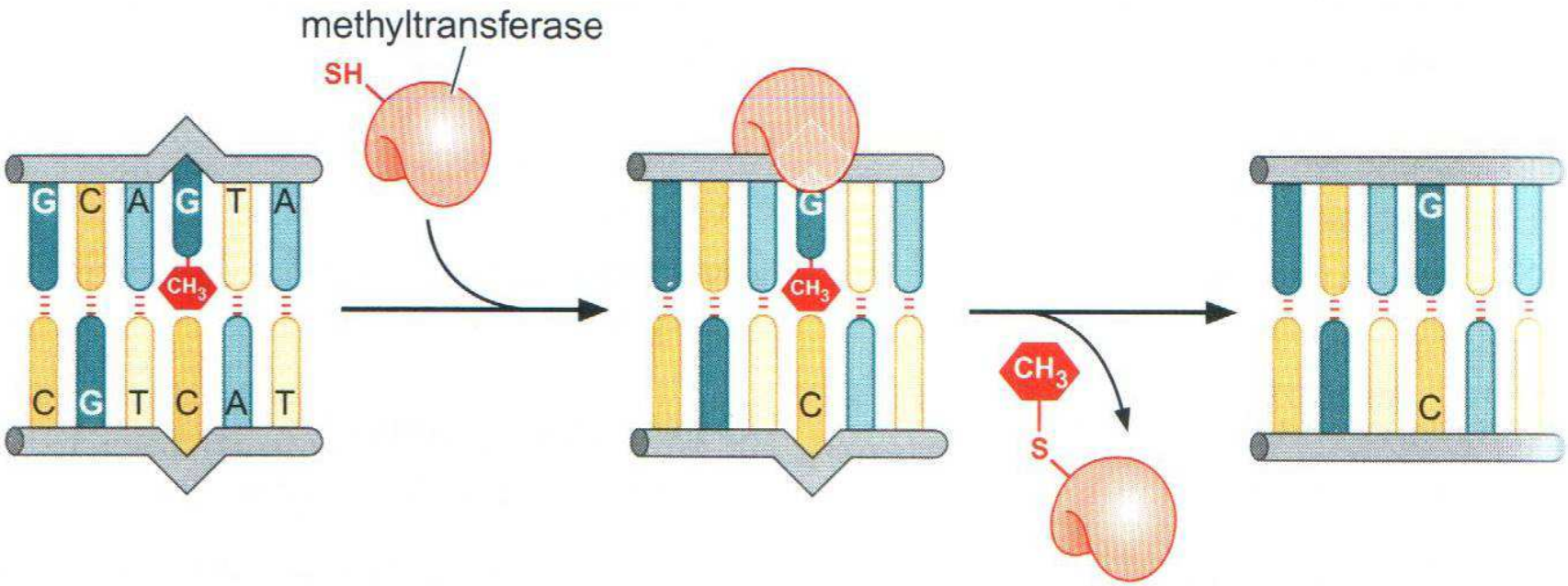



**FIGURE 9-11 Photoreactivation.** UV irradiation causes formation of thymine dimers. Upon exposure to light, DNA photolyase breaks the ring formed between the dimers to restore the two thymine residues.

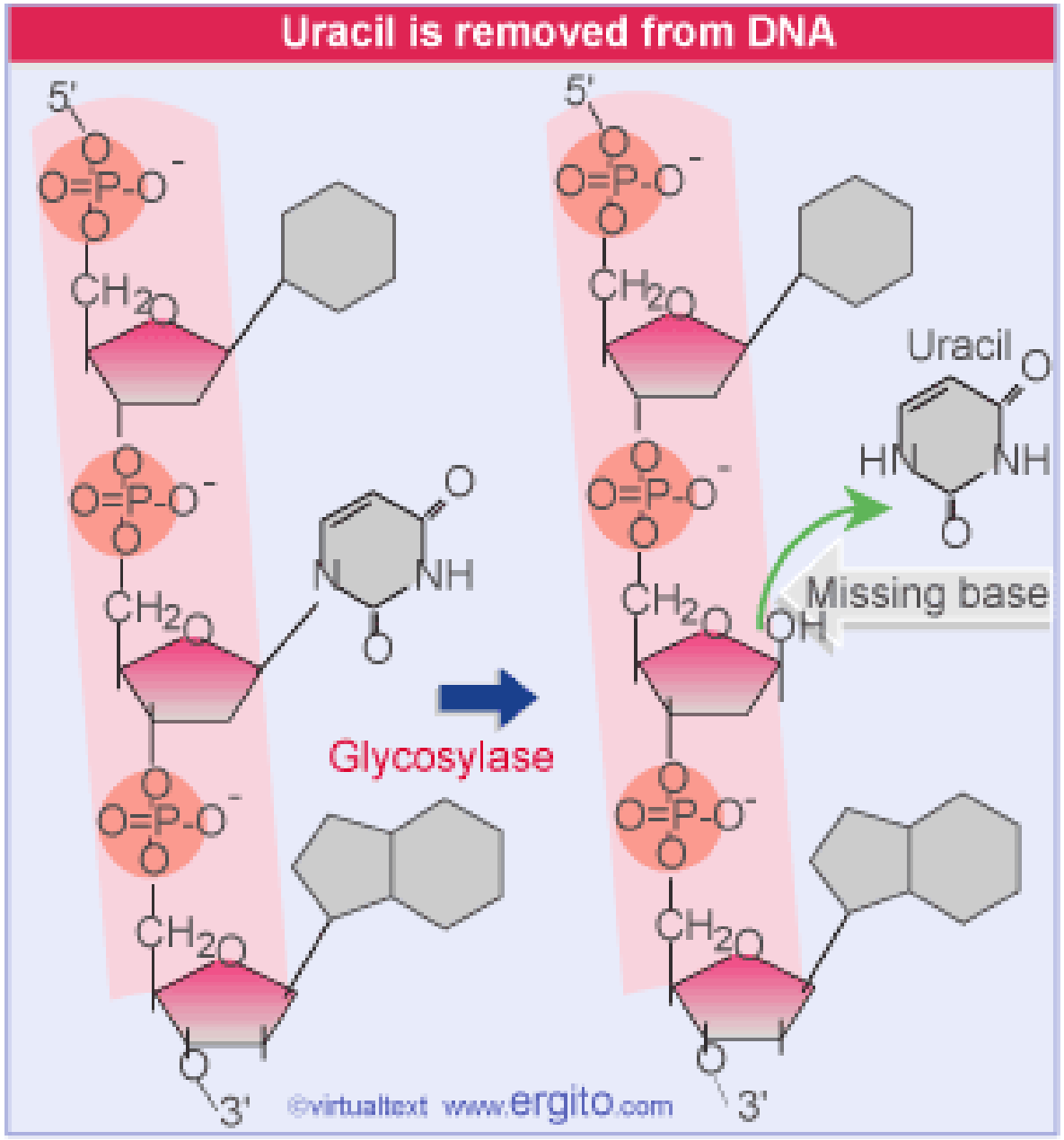

methyltransferase
SH
G C A G T A
C G T C A T
CH3
G
C
CH3
CH3
S
G
C

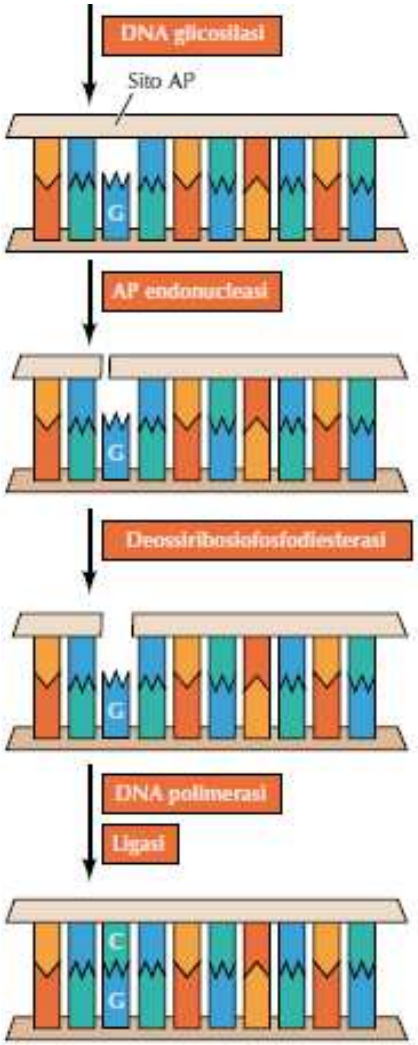
# Correzione dopo excisione

- Base Excision Repair

Si basa sull’azione di enzimi noti come **glicosidasi**.

Esistono diverse glicosidasi con diversa specificità, es: uracile glicosidasi


Uracil is removed from DNA
5'
O=P-O
CH2
N
NH
Glycosylase
Uracil
HN
NH
Missing base
OH
3'
©virtualtext www.ergito.com


DNA glicosilasi
Sito AP
G
AP endonucleasi
G
Deossiribosiofosfodiesterasi
G
DNA polimerasi
Ligasi
C
G

# Correzione dopo excisione

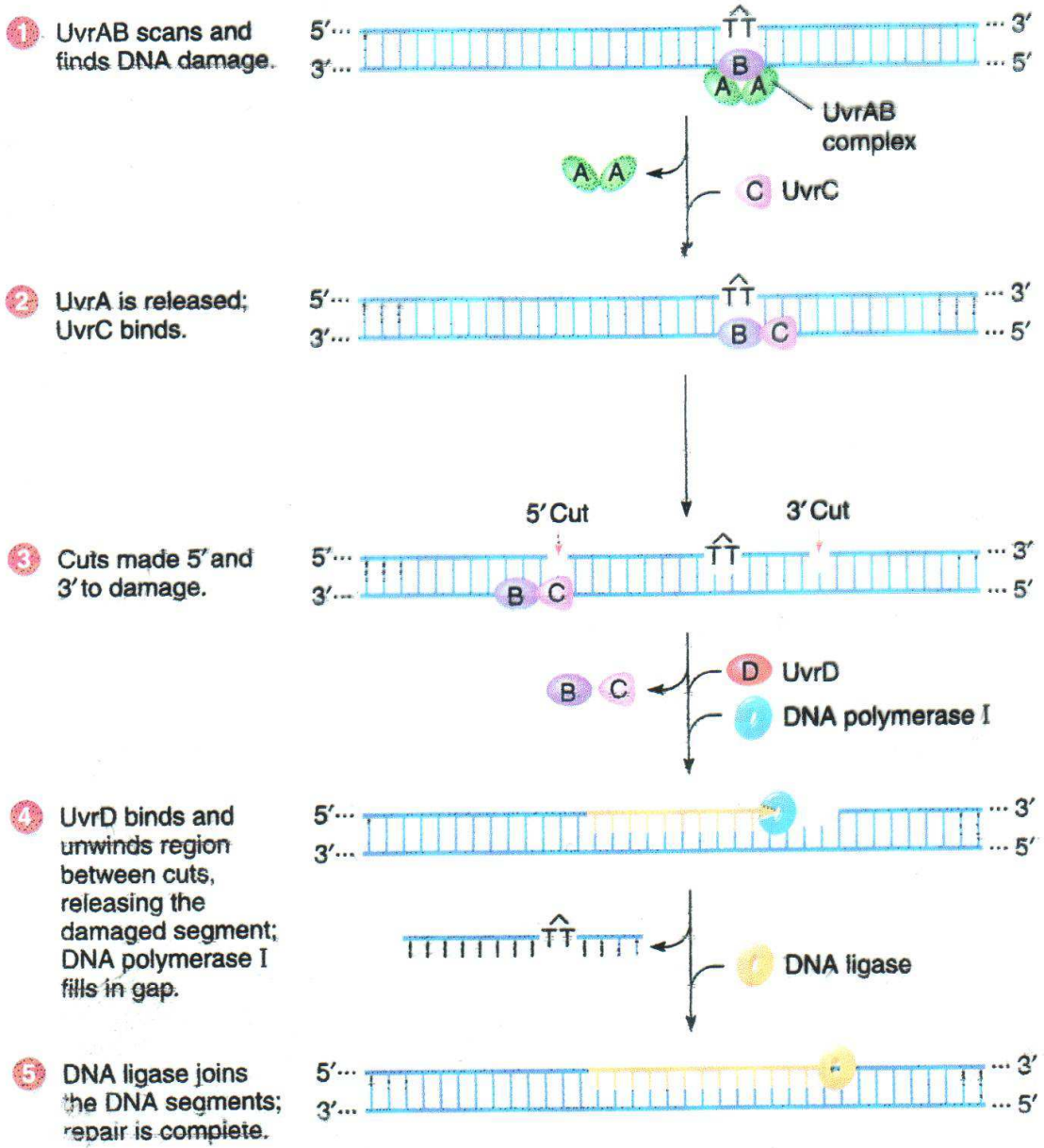
- Sistema NER (Nucleotide Excision Repair)

  In *E. coli* è regolato dai geni *uvr*A, *uvr*B, *uvr*C, *uvr*D.

  Tale tipo di sistema si trova in un gran numero di organismi diversi.

Figure 19.15

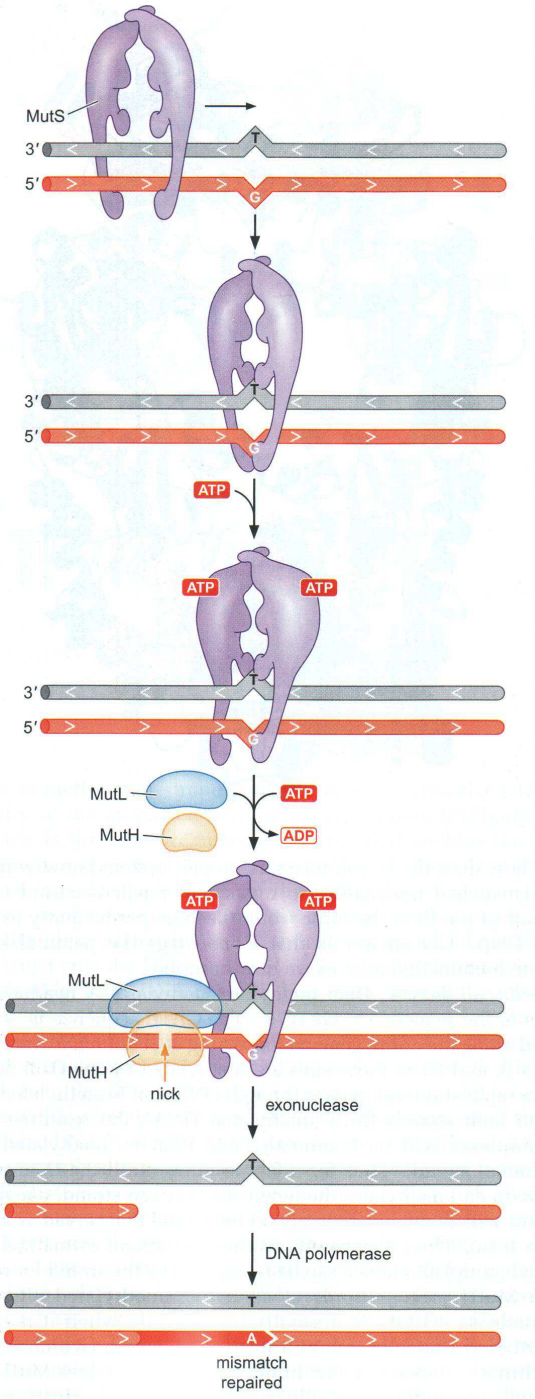
**Nucleotide excision repair (NER) of pyrimidine dimer and other damage-induced distortions of DNA.**

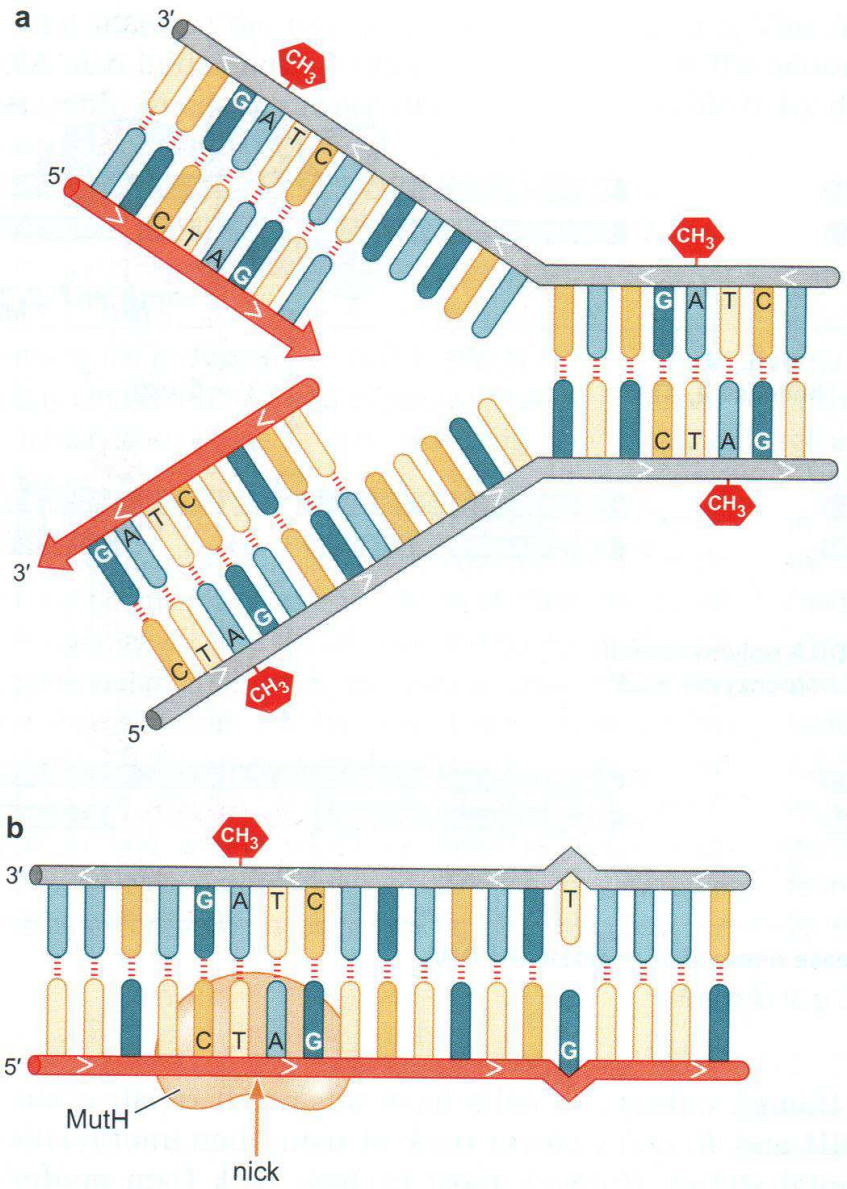


# Correzione dopo excisione

- Riparo dei mismatch

  In *E.coli* è regolato dai geni *mut*S, *mut*L, *mut*H. Tale sistema è presente anche in eucarioti.


MutS
3′
5′
T
G
ATP
ATP
ATP
MutL
MutH
ATP
ADP
MutL
MutH
nick
exonuclease
DNA polymerase
A
mismatch
repaired


a
3′
5′
CH3
G A T C
C T A G
CH3
G A T C
C T A G
CH3
3′
G A T C
C T A G
CH3
5′
b
CH3
3′
G A T C
T
C T A G
G
5′
MutH
nick

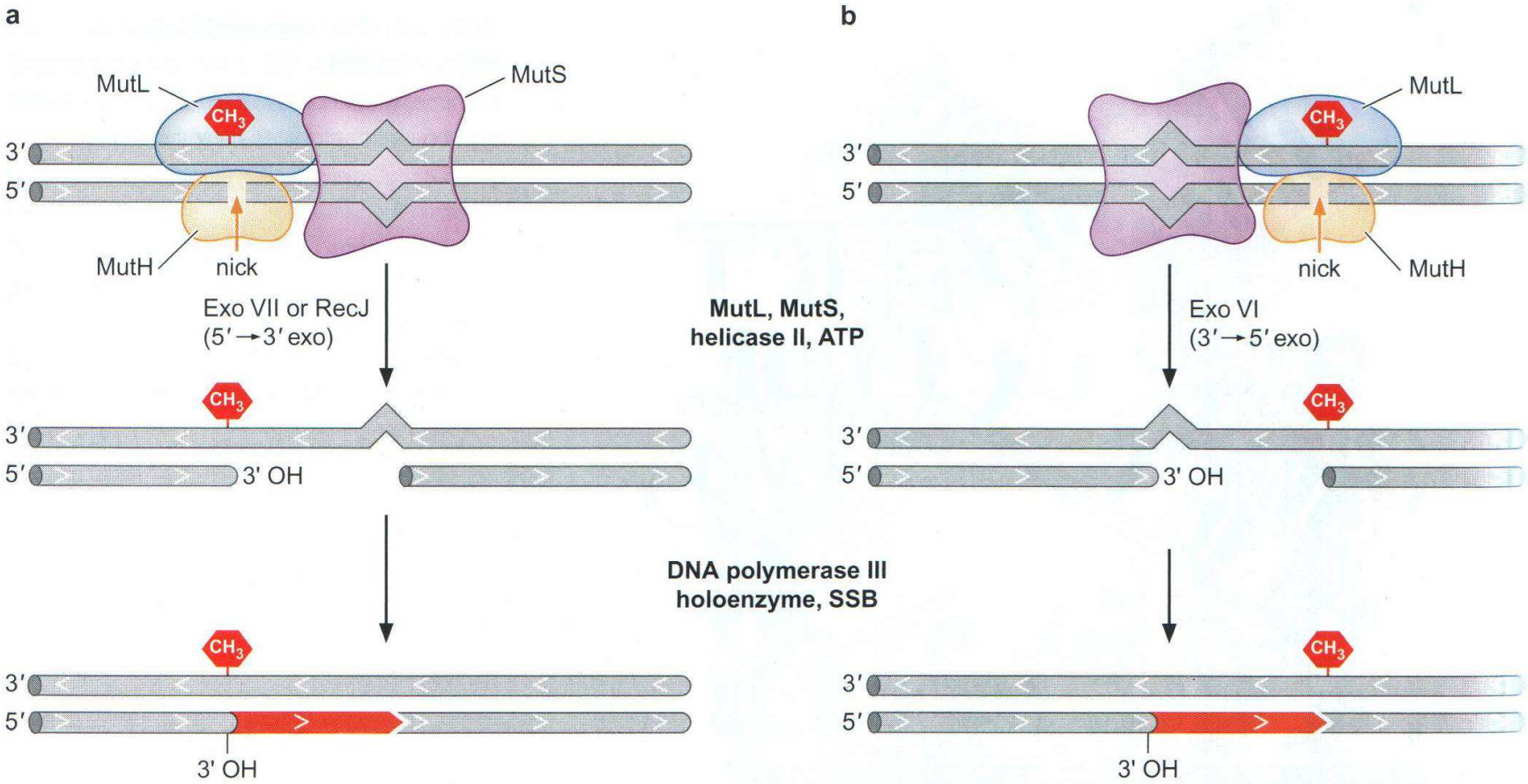



**FIGURE 9-6 Directionality in mismatch repair: exonuclease removal of mismatched DNA.**
(a) Unmethylated GATC is 5′ of mutation. (b) Unmethylated GATC is 3′ of mutation.

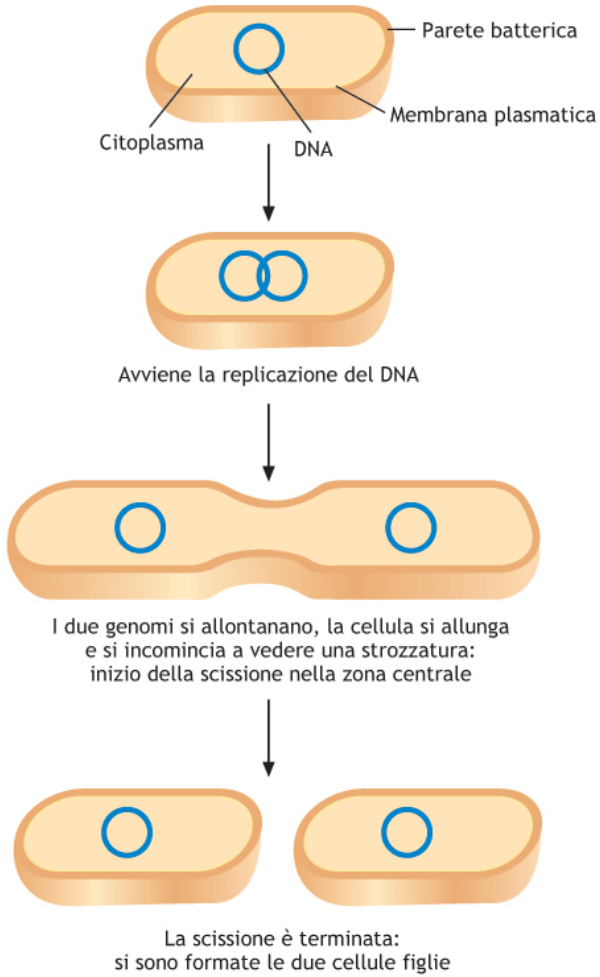
**TABLE 9-1 DNA Repair Systems**

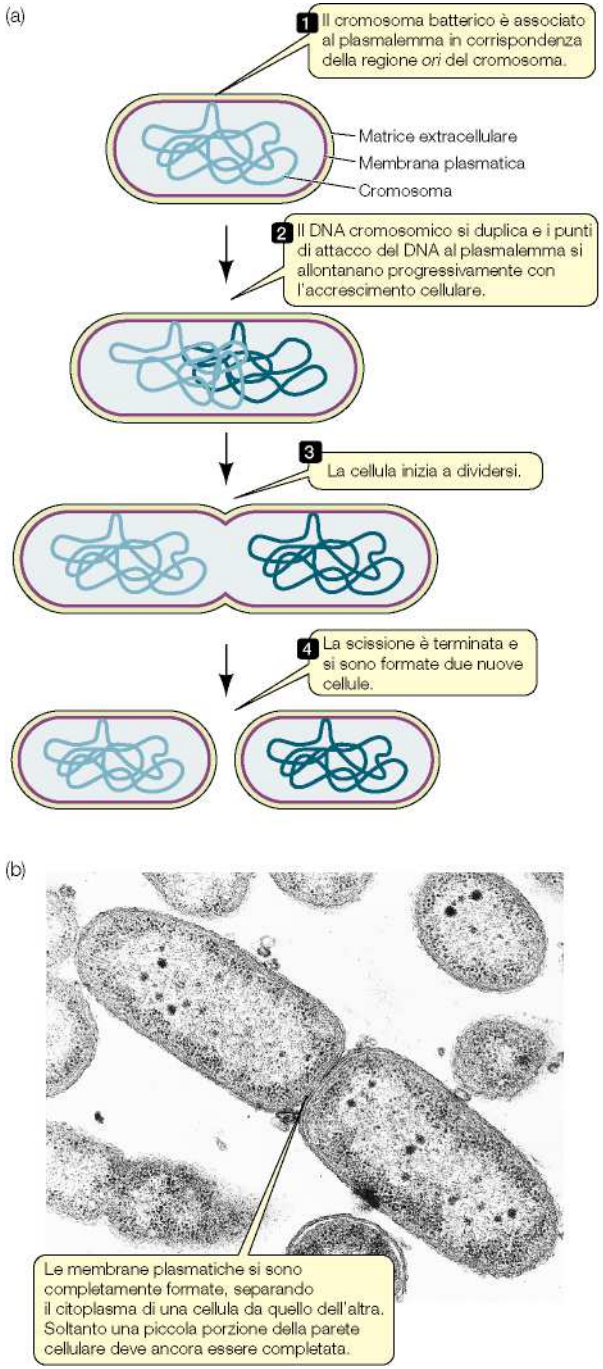
| Type | Damage | Enzyme |
|---|---|---|
| Mismatch repair | Replication errors | MutS, MutL, and MutH in *E. coli*<br>MSH, MLH, and PMS in humans |
| Photoreactivation | Pyrimidine dimers | DNA photolyase |
| Base excision repair | Damaged base | DNA glycosylase |
| Nucleotide excision repair | Pyrimidine dimer<br>Bulky adduct on base | UvrA, UvrB, UvrC, and UvrD in *E. coli*<br>XPC, XPA, XPD, ERCCI-XPF, and XPG in humans |
| Double-strand break repair | Double-strand breaks | RecA and RecBCD in *E. coli* |
| Translesion DNA synthesis | Pyrimidine dimer or apurinic site | Y-family DNA polymerases, such as UmuC in *E. coli* |

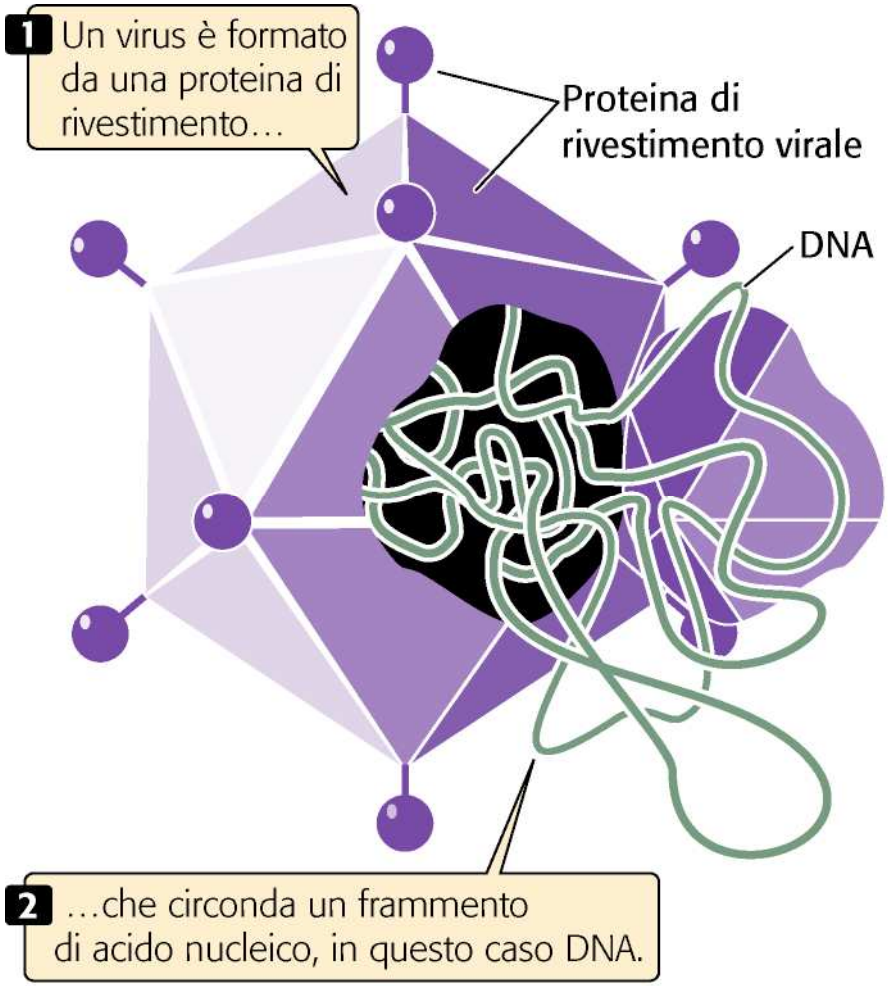
**Table 19.1** Some Examples of Naturally Occurring Human Cell Mutants That Are Defective in DNA Replication or Repair

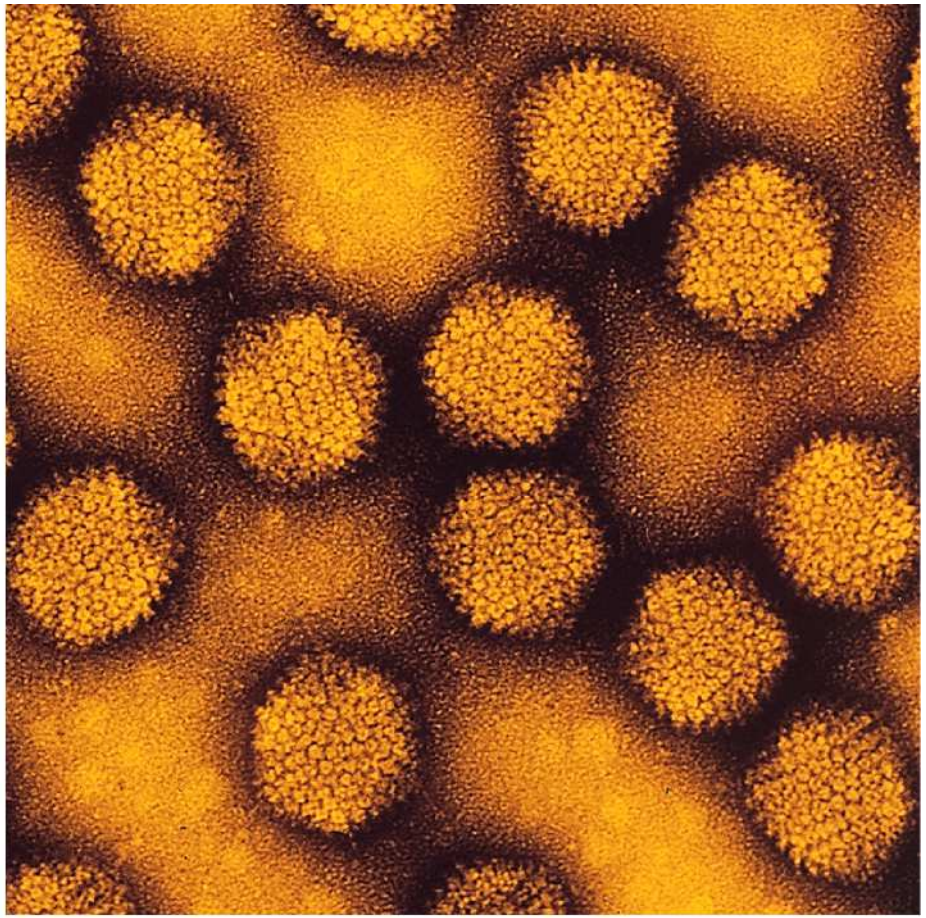
| Disease and Mode of Inheritance | Symptoms | Functions Affected | Chromosome Location[a] |
|---|---|---|---|
| Xeroderma pigmentosum (XP) —autosomal recessive | Sensitivity to sunlight with skin freckling and cancerous growths on skin; lethal at early age as a result of the malignancies | Repair of DNA damaged by UV irradiation or chemicals | 9q34.1 |
| Ataxia-telangiectasia (AT) —autosomal recessive | Muscle coordination defect; propensity for respiratory infection; progressive spinal muscular atrophy in significant proportion of patients in second or third decade of life; marked hypersensitivity to ionizing radiation; cancer prone; high frequency of chromosome breaks leading to translocations and inversions | Repair replication of DNA | 11q22.3 |
| Fanconi anemia (FA) —autosomal recessive | Aplastic anemia[b]; pigmentary changes in skin; malformations of heart, kidney, and limbs; leukemia is a fatal complication; genital abnormalities common in males; spontaneous chromosome breakage | Repair replication of DNA, UV-induced pyrimidine dimers, and chemical adducts not excised from DNA; a repair exonuclease, DNA ligase, and transport of DNA repair enzymes have been hypothesized to be defective in patients with FA | 16q24.3 |
| Bloom syndrome (BS) —autosomal recessive | Pre- and postnatal growth deficiency; sun-sensitive skin disorder; predisposition to malignancies; chromosome instability; diabetes mellitus often develops in second or third decade of life | Elongation of DNA chains intermediate in replication; candidate gene is homologous to *E. coli* helicase Q | 15q26.1 |
| Cockayne syndrome (CS) —autosomal recessive | Dwarfism; precociously senile appearance; optic atrophy; deafness; sensitivity to sunlight; mental retardation; disproportionately long limbs; knee contractures produce bowlegged appearance; early death | Precise molecular defect is unknown, but may involve transcription-coupled repair | 5 |
| Hereditary nonpolyposis colon cancer (HNPCC) —autosomal dominant | Inherited predisposition to non-polyp-forming colorectal cancer | Defect in mismatch repair develops when the remaining wild-type allele of the inherited mutant allele becomes mutated; homozygosity for mutations in any one of four genes (*hMSH2*, *hMLH1*, *hPMS1*, and *hPMS2*, known as mutator genes) has been shown to give rise to HNPCC | 2p22-p21 |

# La Divisione Cellulare

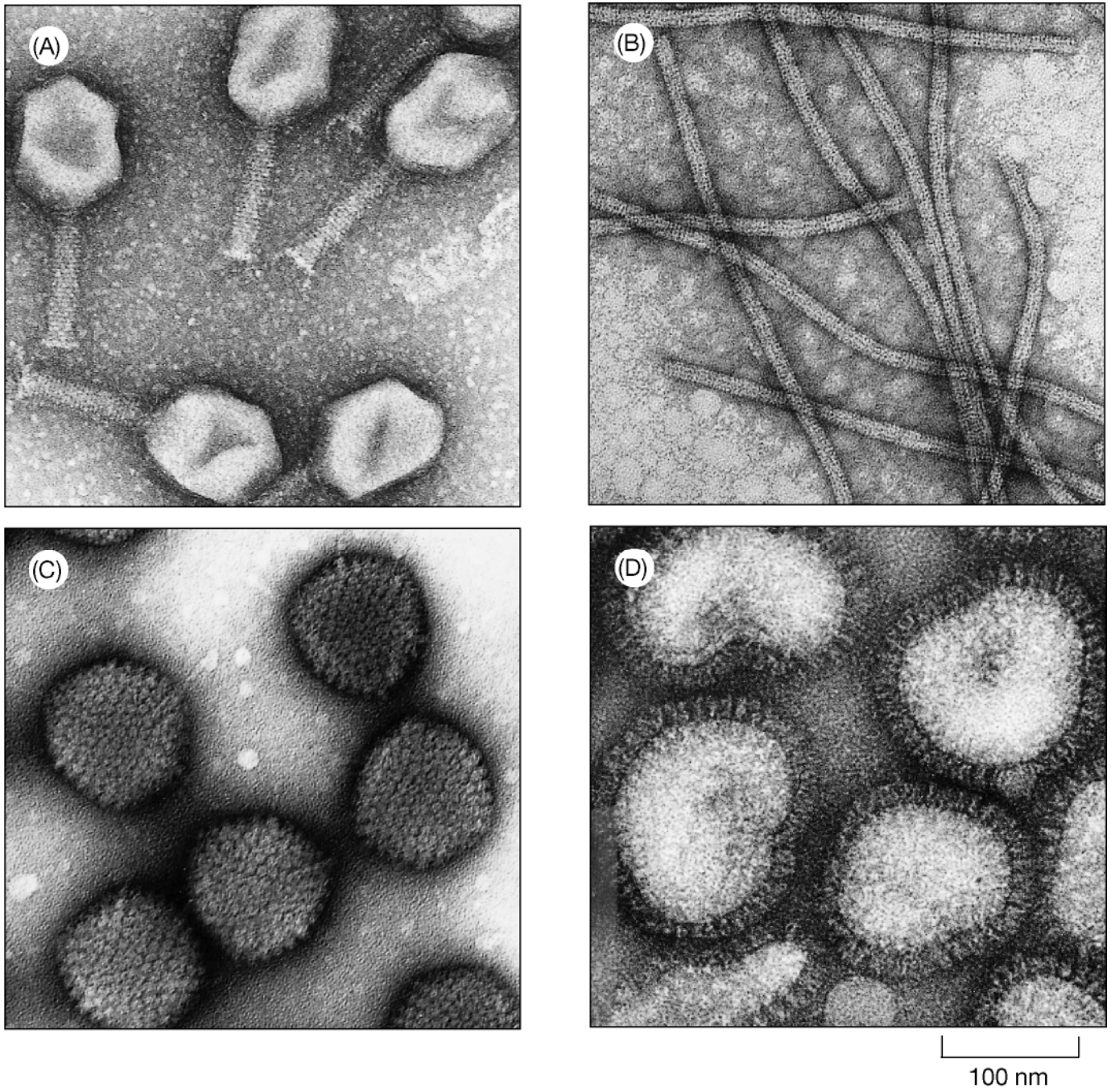

Parete batterica
Membrana plasmatica
Citoplasma
DNA
Avviene la replicazione del DNA
I due genomi si allontanano, la cellula si allunga
e si incomincia a vedere una strozzatura:
inizio della scissione nella zona centrale
La scissione è terminata:
si sono formate le due cellule figlie


(a)
1 Il cromosoma batterico è associato al plasmalemma in corrispondenza della regione *ori* del cromosoma.
Matrice extracellulare
Membrana plasmatica
Cromosoma
2 Il DNA cromosomico si duplica e i punti di attacco del DNA al plasmalemma si allontanano progressivamente con l'accrescimento cellulare.
3 La cellula inizia a dividersi.
4 La scissione è terminata e si sono formate due nuove cellule.
(b)
Le membrane plasmatiche si sono completamente formate, separando il citoplasma di una cellula da quello dell'altra. Soltanto una piccola porzione della parete cellulare deve ancora essere completata.


1 Un virus è formato da una proteina di rivestimento…
Proteina di rivestimento virale
DNA
2 …che circonda un frammento di acido nucleico, in questo caso DNA.



Adenovirus


(A)
(B)
(C)
(D)
100 nm

RNA monofilamento

DNA monofilamento

DNA circolare
a filamento doppio

RNA a filamento doppio

DNA circolare
monofilamento

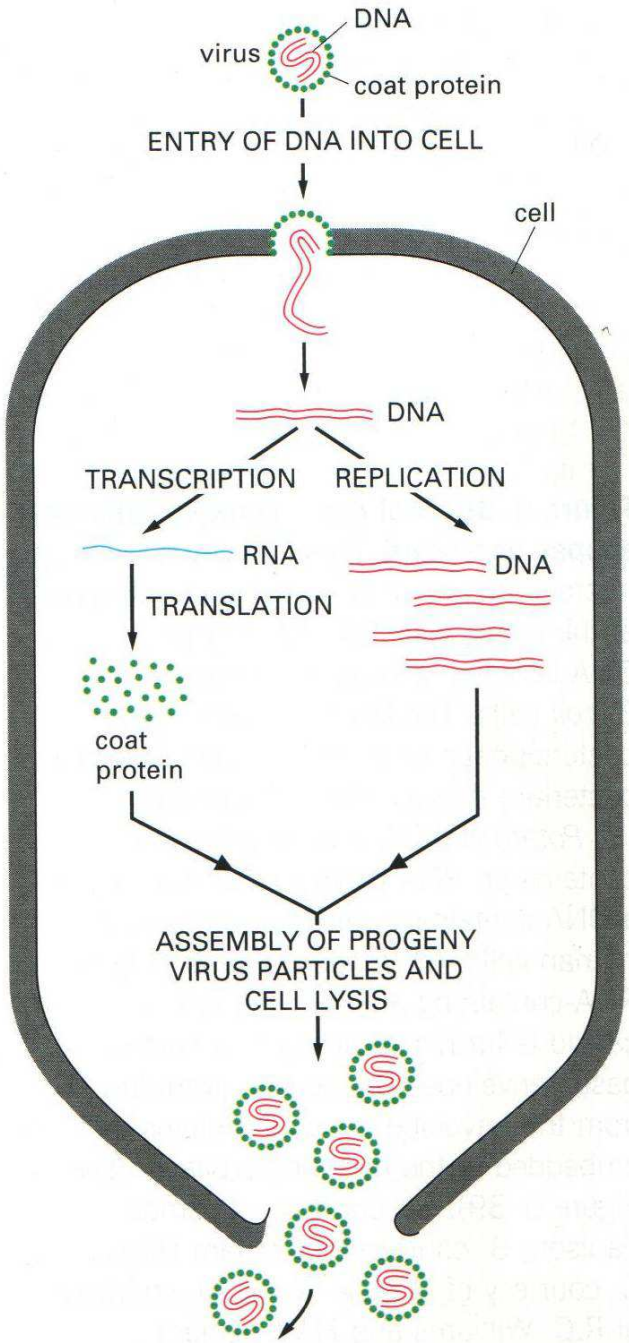
DNA a filamento doppio

DNA a filamento doppio
con terminali chiusi covalentemente

DNA a filamento doppio
con proteina terminale
legata covalentemente

**Table 6–2 Viruses That Cause Human Disease**

| VIRUS | GENOME TYPE | DISEASE |
|---|---|---|
| Herpes simplex virus | double-stranded DNA | recurrent cold sores |
| Epstein-Barr virus (EBV) | double-stranded DNA | infectious mononucleosis |
| Varicella-zoster virus | double-stranded DNA | chicken pox and shingles |
| Smallpox virus | double-stranded DNA | smallpox |
| Hepatitis B virus | part single-, part double-stranded DNA | serum hepatitis |
| Human immuno-deficiency virus (HIV) | single-stranded RNA | acquired immunodeficiency syndrome (AIDS) |
| Influenza virus type A | single-stranded RNA | respiratory disease (flu) |
| Poliovirus | single-stranded RNA | infantile paralysis |
| Rhinovirus | single-stranded RNA | common cold |
| Hepatitis A virus | single-stranded RNA | infectious hepatitis |
| Hepatitis C virus | single-stranded RNA | non-A, non-B type hepatitis |
| Yellow fever virus | single-stranded RNA | yellow fever |
| Rabies virus | single-stranded RNA | rabies |
| Mumps virus | single-stranded RNA | mumps |
| Measles virus | single-stranded RNA | measles |


DNA
virus
coat protein
ENTRY OF DNA INTO CELL
cell
DNA
TRANSCRIPTION
REPLICATION
RNA
DNA
TRANSLATION
coat
protein
ASSEMBLY OF PROGENY
VIRUS PARTICLES AND
CELL LYSIS