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About the course: www.life.umd.edu/classroom/BSCI410-Liu/BSCI410/

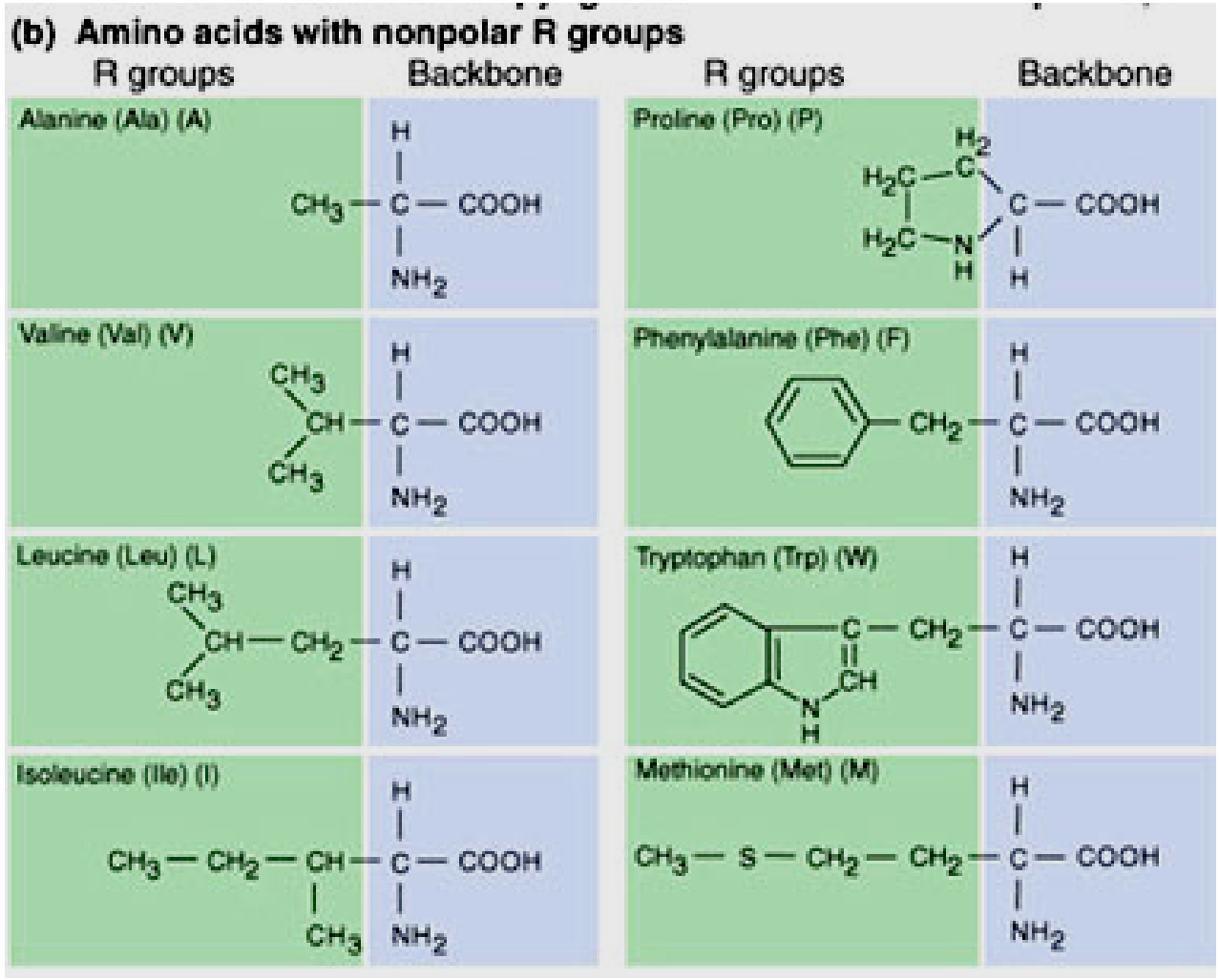
Lecture 2: Mutation and its effect

- Mutation type
- Mutational effect
- Spontaneous Mutation
- Mutagens

Read: Ch 7 p192-193; 196-198; 200-205

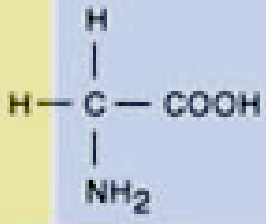
Figs: 7.2; 7.6; 7.7; 7.8; 7.12; 7.21; 7.22; 8.15; 8.16;

Fig. 7.21

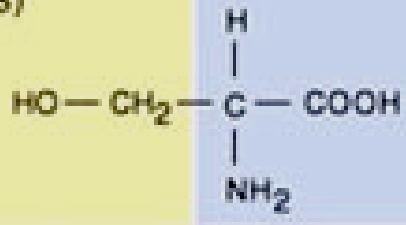

(b) Amino acids with nonpolar R groups
R groups
Backbone
R groups
Backbone
Alanine (Ala) (A)
Proline (Pro) (P)
Valine (Val) (V)
Phenylalanine (Phe) (F)
Leucine (Leu) (L)
Tryptophan (Trp) (W)
Isoleucine (Ile) (I)
Methionine (Met) (M)

Amino acids with uncharged polar R groups

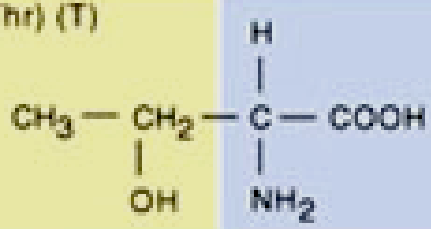
Glycine (Gly) (G)



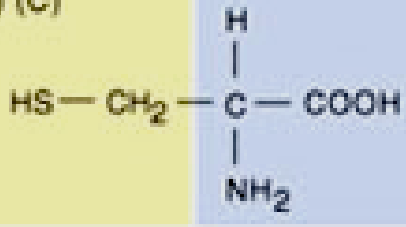
Serine (Ser) (S)



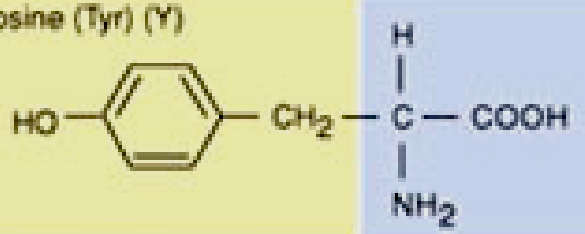
Threonine (Thr) (T)



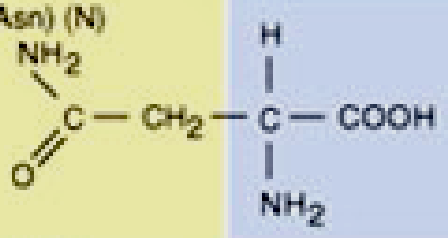
Cysteine (Cys) (C)



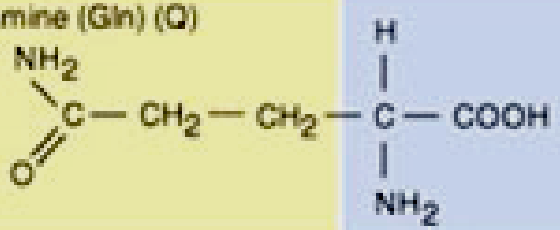
Tyrosine (Tyr) (Y)



Asparagine (Asn) (N)

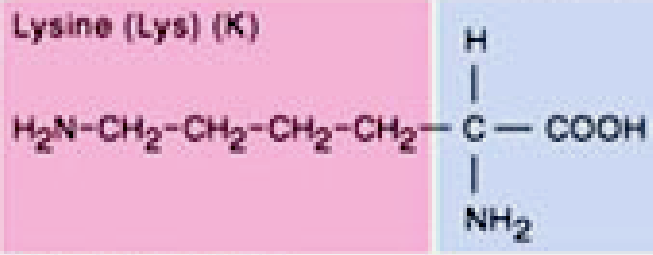


Glutamine (Gln) (Q)

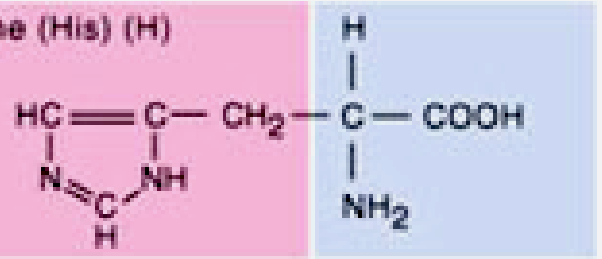


Amino acids with basic R groups

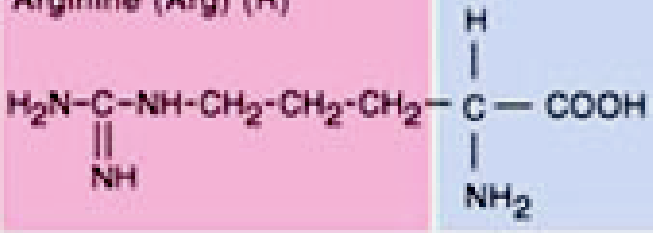
Lysine (Lys) (K)



Histidine (His) (H)

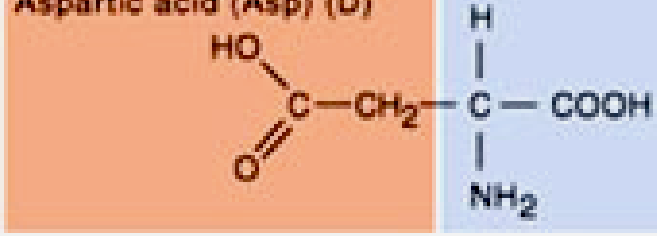


Arginine (Arg) (R)

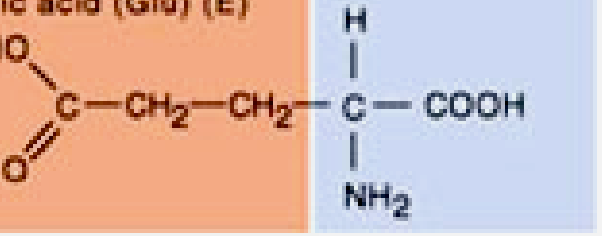


Amino acids with acidic R groups

Aspartic acid (Asp) (D)



Glutamic acid (Glu) (E)



Mutations

1. Substitution-1 base --> one of the three other bases

Transition: purine --> purine or pyrimidine --> pyrimidine
A--> G or G--> A T--> C or C--> T

Transvertion: purine --> pyrimidine or *vice versa*
A--> T, C; G -->T,C; T-->A, G; C-->A,G

causes missense, nonsense, silent, neutral or

splicing mutational effects

2. Deletion or insertion-often causes frameshift mutation

3. Chromosomal rearrangement
inversion or translocation can change multiple genes

Effects of point mutations

tyrosine TAT, TAC

TAT -> CAT	tyr -> his	missense
TAT -> TAA	tyr -> stop	nonsense
TAT -> TTT	tyr -> phe	neutral in many cases
TAT -> TAC	tyr-> tyr	silent

Fig. 7.22

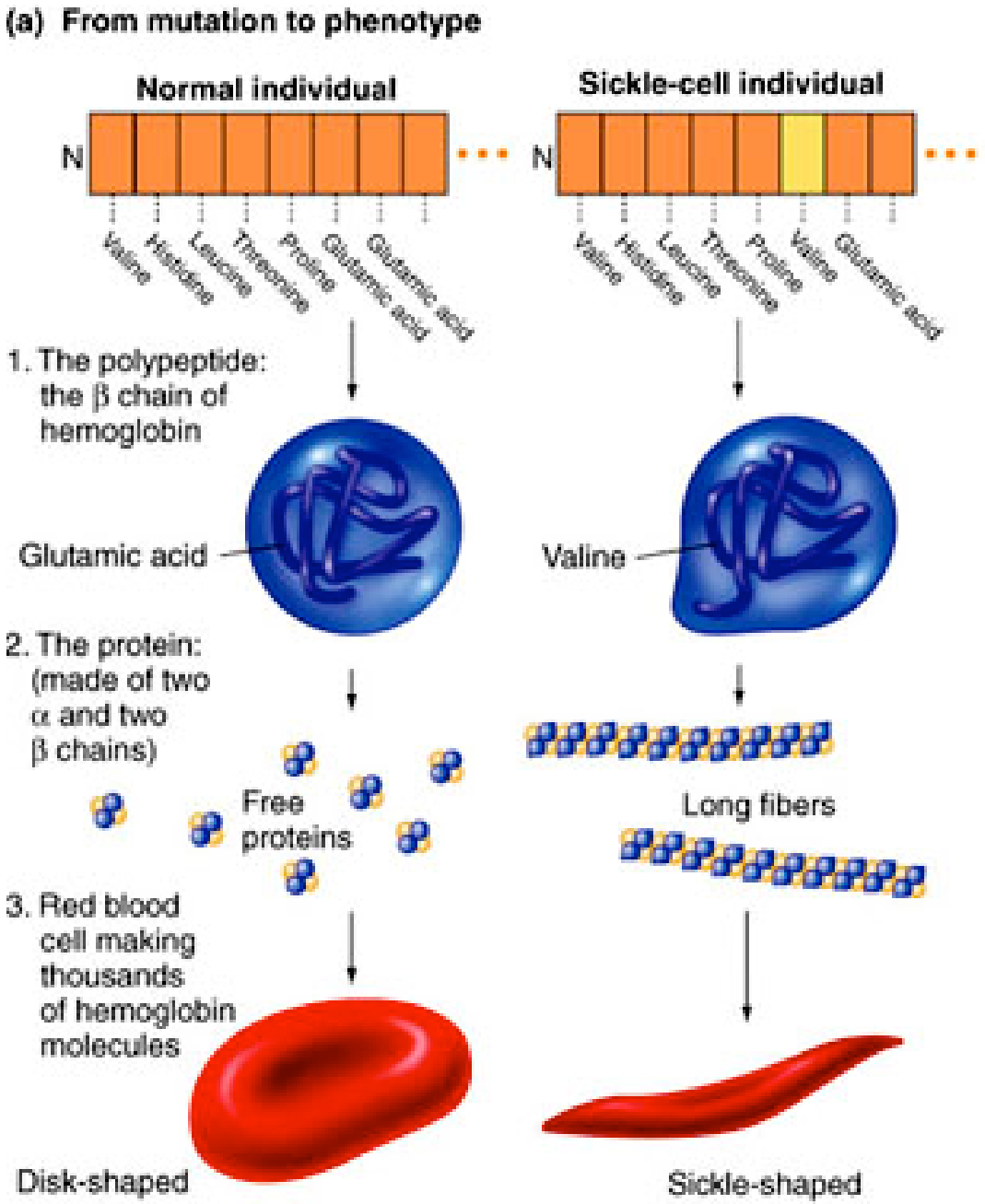

(a) From mutation to phenotype
Normal individual
Sickle-cell individual
N
N
Valine
Histidine
Leucine
Threonine
Proline
Glutamic acid
Glutamic acid
Valine
Histidine
Leucine
Threonine
Proline
Valine
Glutamic acid
1. The polypeptide: the β chain of hemoglobin
Glutamic acid
Valine
2. The protein: (made of two α and two β chains)
Free proteins
Long fibers
3. Red blood cell making thousands of hemoglobin molecules
Disk-shaped
Sickle-shaped

Fig. 8.15

Splicing removes introns from a primary transcript.

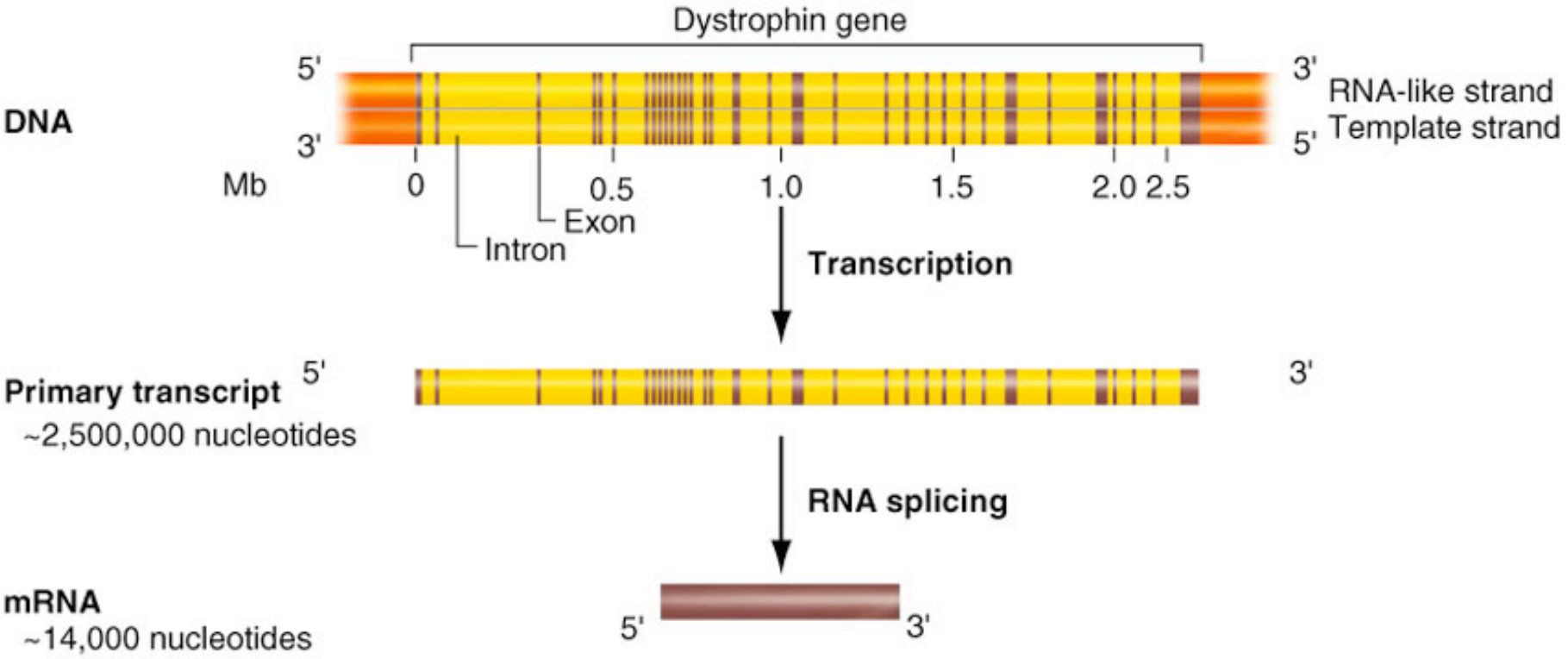
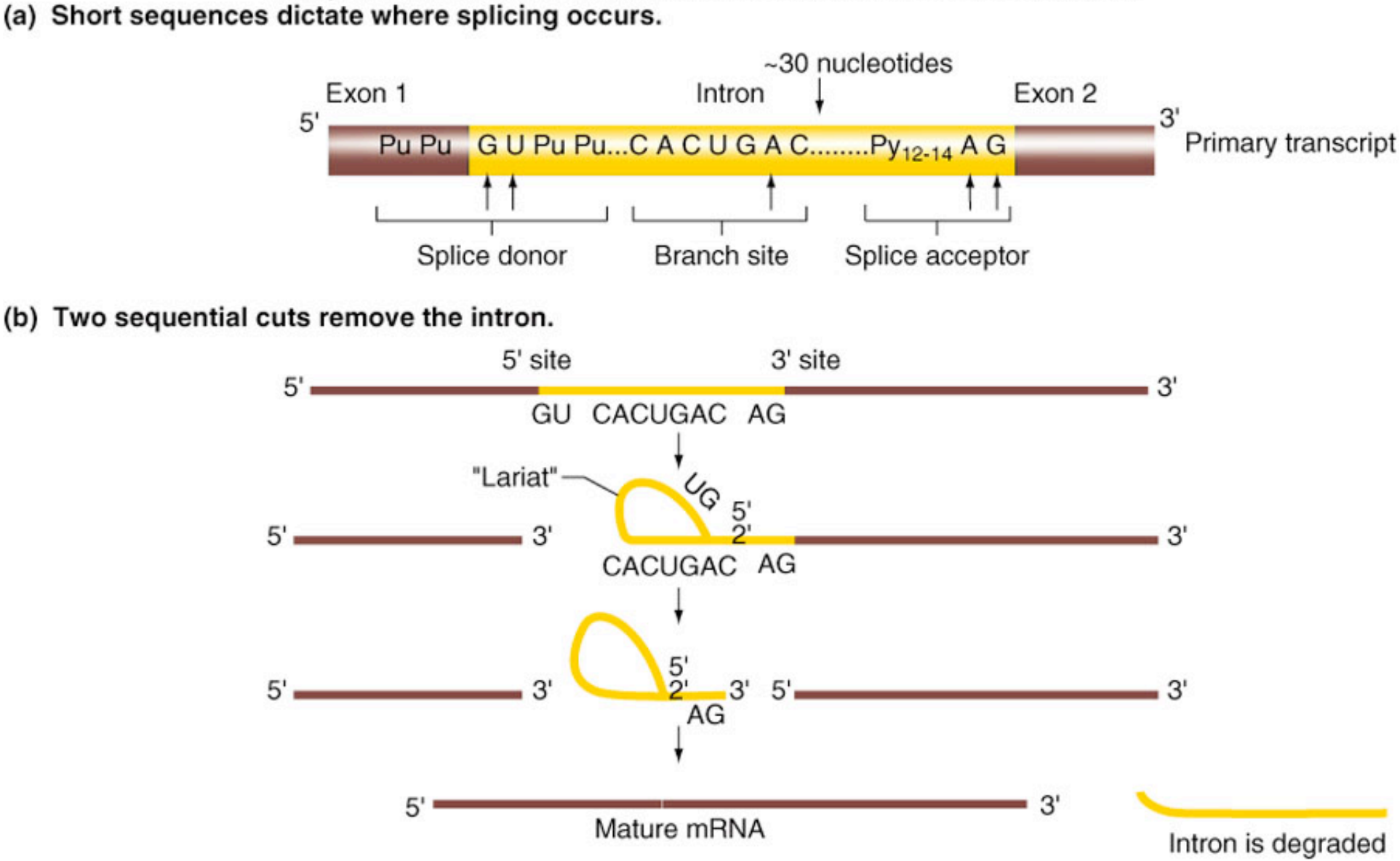
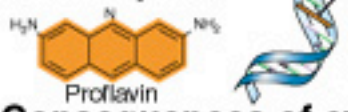


Fig. 8.16



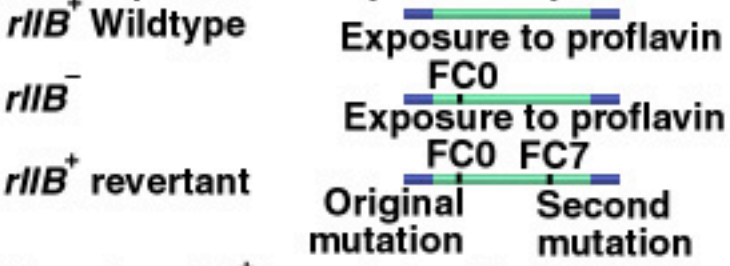
Frameshift mutations

(a) The mutagen proflavin can insert between two base pairs



Molecule of proflavin inserted between stacked base pairs

(b.1) Consequences of exposure to proflavin

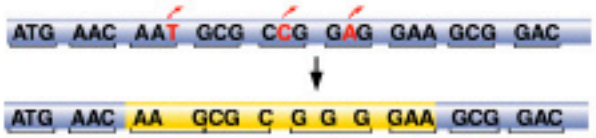


(b.2) Crossing *rIIB*$^+$ revertant with wildtype yields *rIIB*$^-$ recombinants

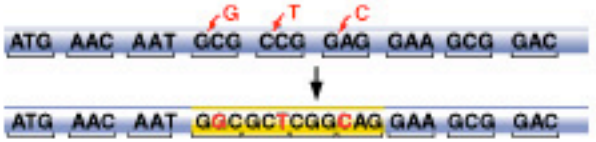
(c) Different sets of mutations generate either a mutant or a normal phenotype

Proflavin-induced mutations (+) insertion (–) deletion	Phenotype
– or +	Mutant
– – or + +	Mutant
– – – – or – – – – –	Mutant
– +	Wildtype
– – – or – – – – – – or + + + or + + + + + +	Wildtype

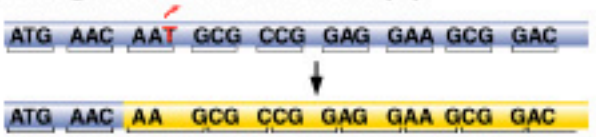
(d) Three single base deletions (– – –)



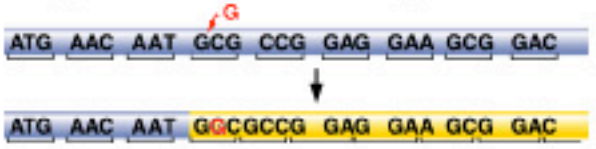
Three single base insertions (+ + +)



(e) Single base deletion (–)

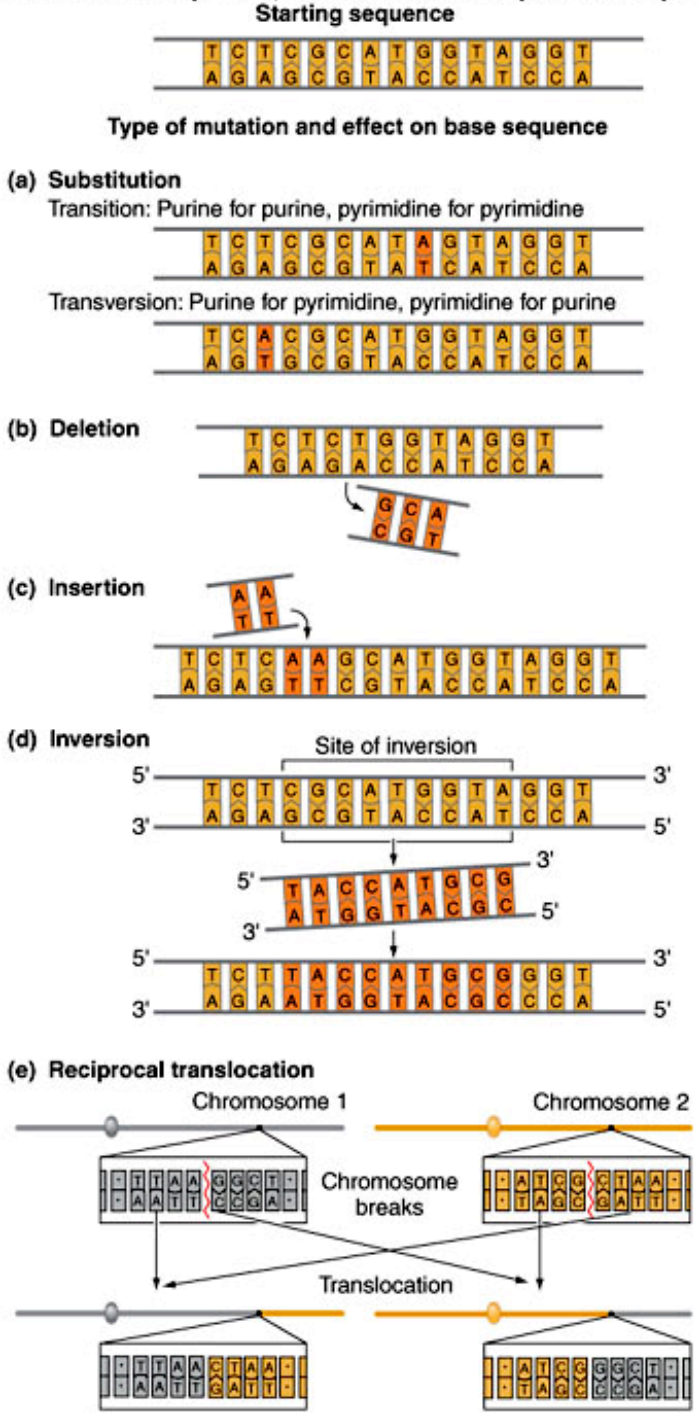


Single base insertion (+)



correct triplet
incorrect triplet

Fig. 7.2



Spontaneous mutations

Spontaneous mutation is rare: 2-12X 10^{-6} (per generation per gene)

Spontaneous mutations can be caused by

a. mistakes made during DNA replication (error rate 10^{-9})

b. environmrntal effect:

UV light: thymidine dimer

X-ray: break sugar-phosphate DNA back bone

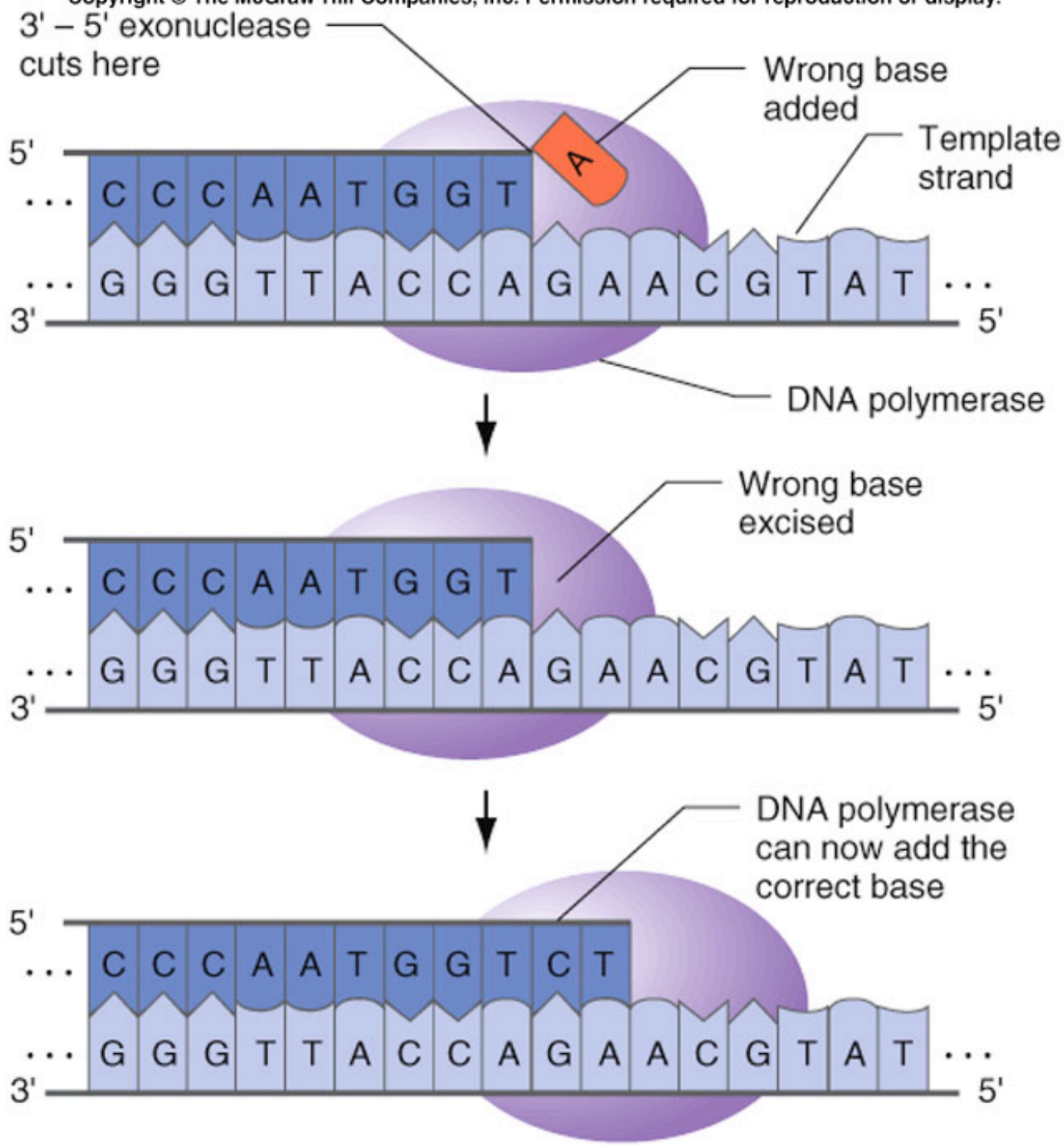
Oxidative damages: G --> 8-oxodG (pair with A)

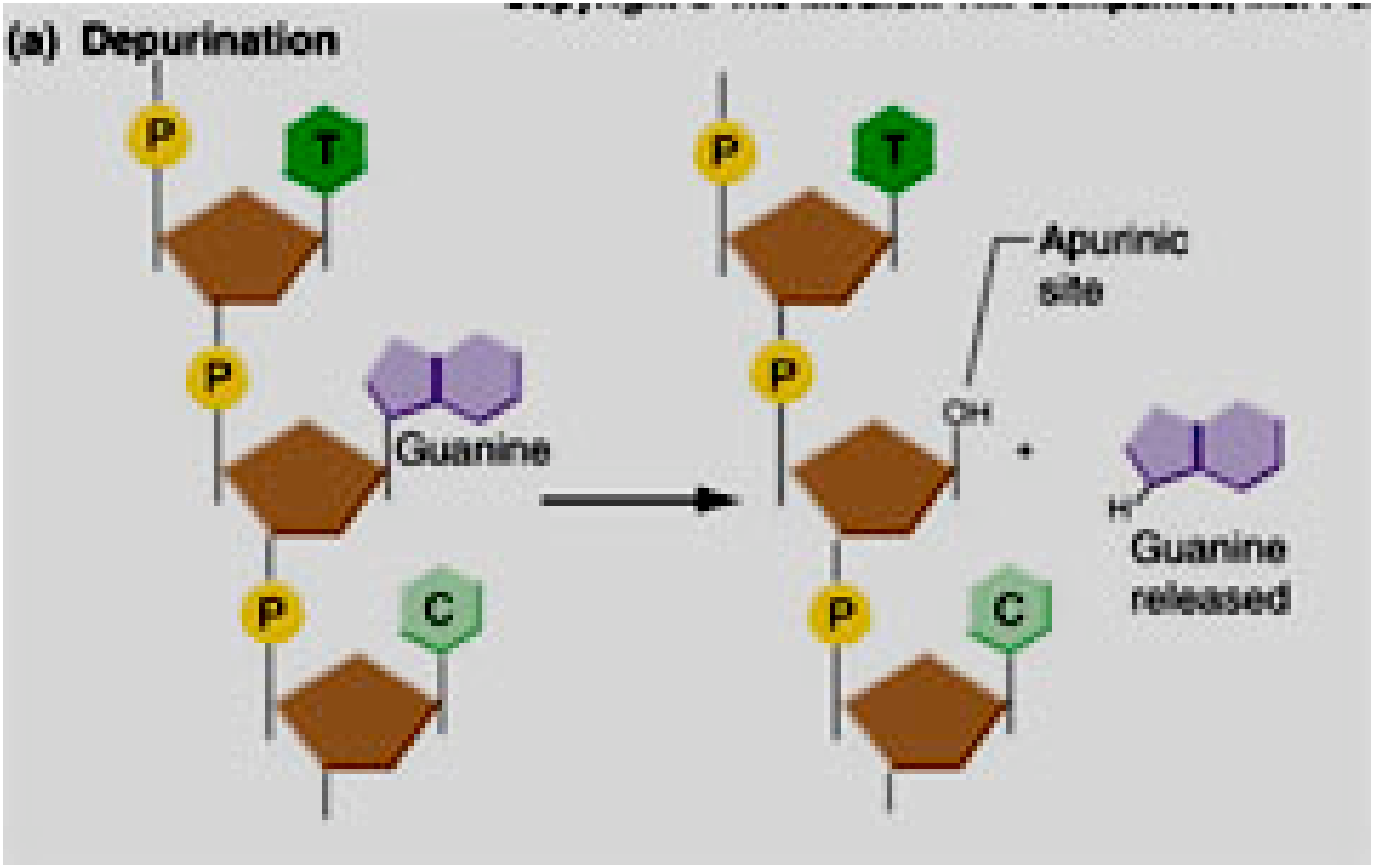
c. chemical changes (hydrolysis):

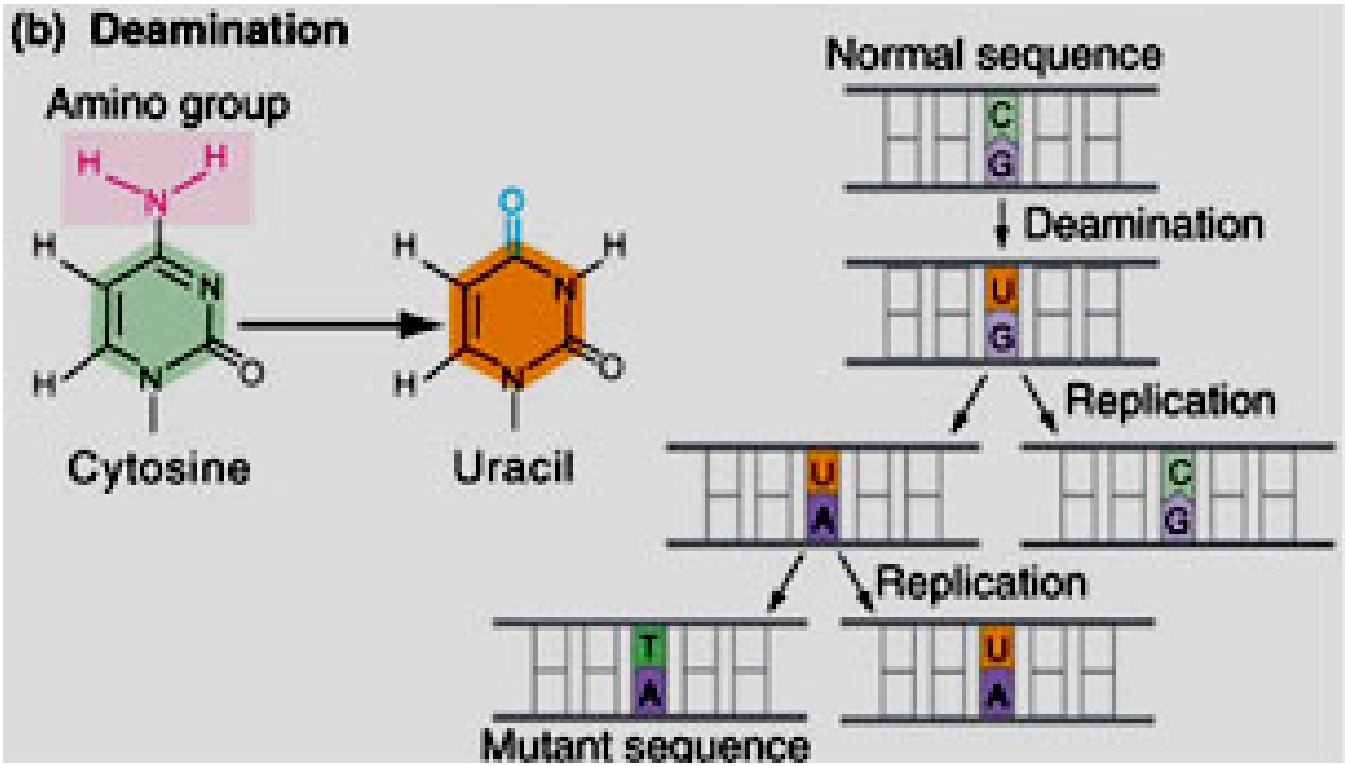
depurination; A,G --> O

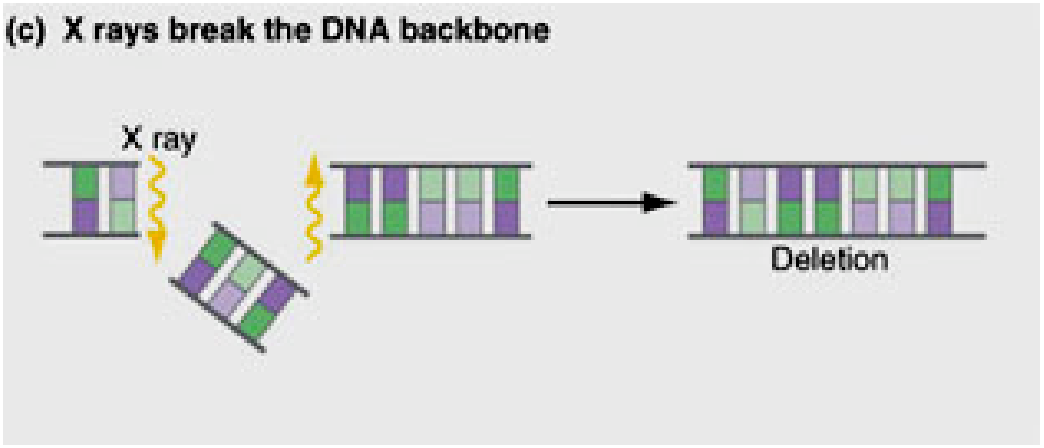
deamination: C--> U

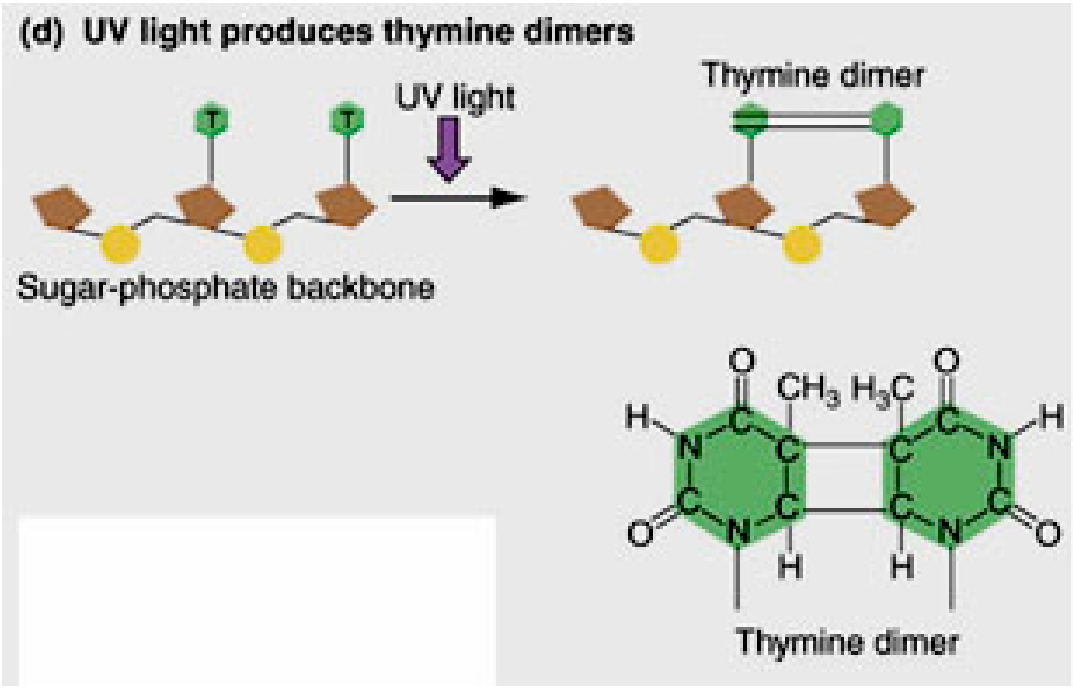
Fig. 7.8




(a) Depurination
P
T
P
Guanine
P
C
P
T
P
Apurinic site
OH
+
H
Guanine released
P
C


(b) Deamination
Amino group
Cytosine
Uracil
Normal sequence
Deamination
Replication
Replication
Mutant sequence


(c) X rays break the DNA backbone
X ray
Deletion


(d) UV light produces thymine dimers
UV light
Thymine dimer
Sugar-phosphate backbone
Thymine dimer

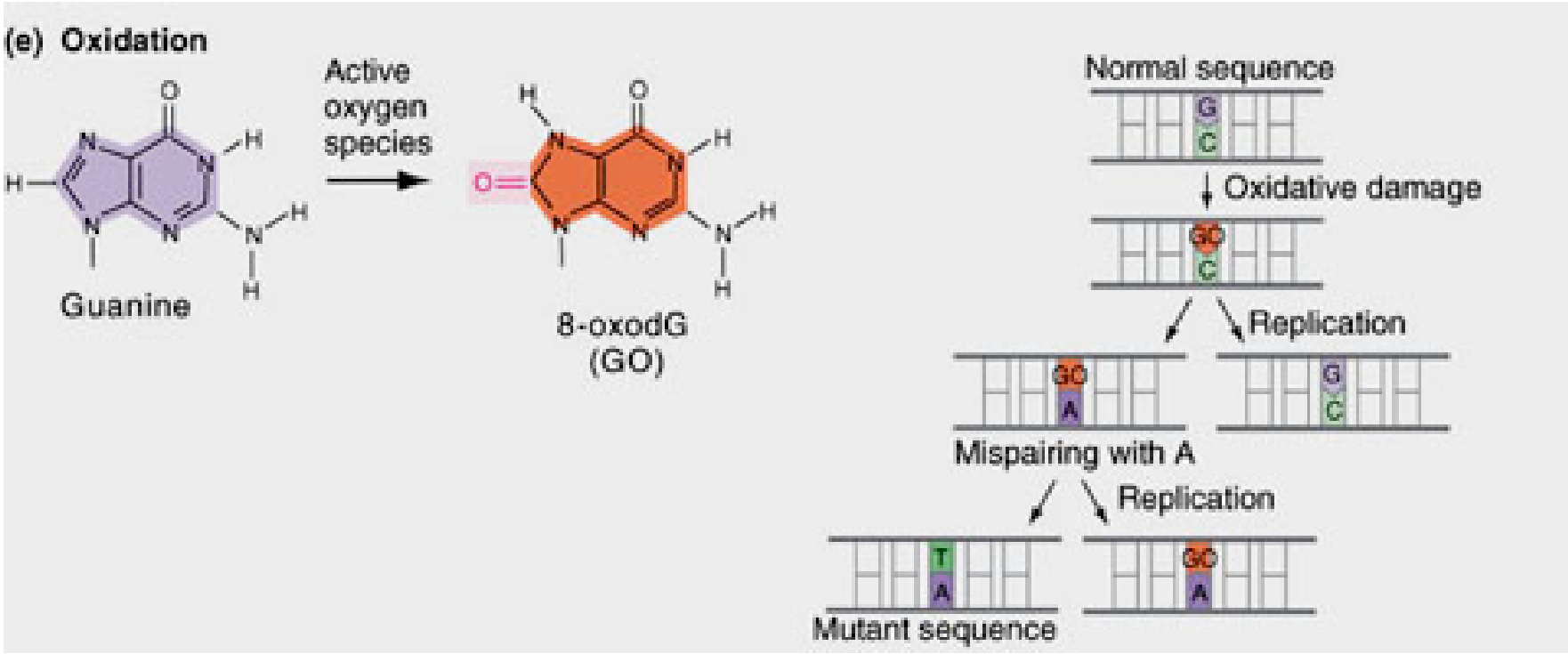
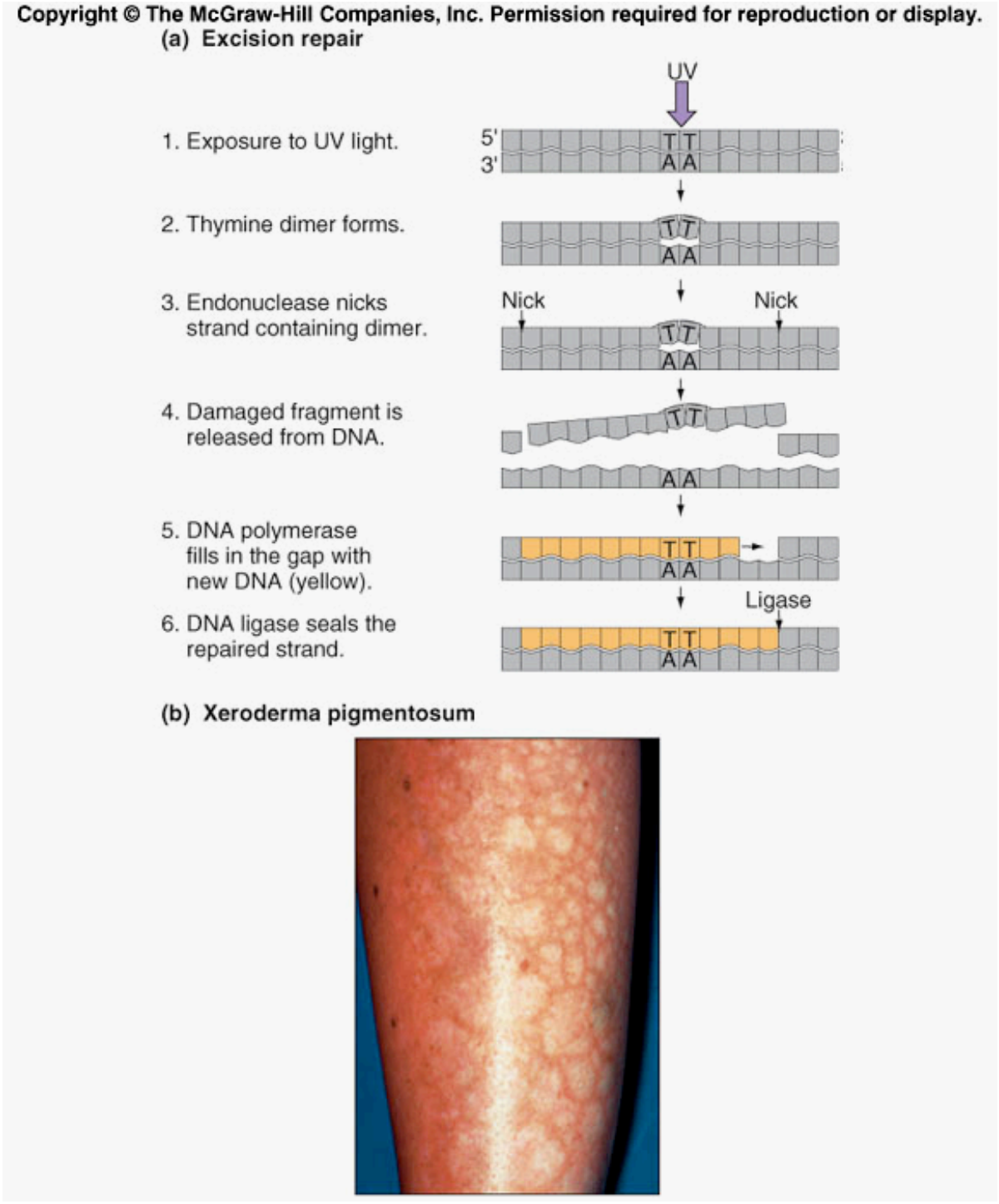

(e) Oxidation
Active
oxygen
species
Guanine
8-oxodG
(GO)
Normal sequence
Oxidative damage
Replication
Mispairing with A
Replication
Mutant sequence

Fig. 7.7



Mutagens

Mutagen treatment greatly increases the mutation rate

Exposure to X-ray, UV light

Chemical treatment: base analogs 5'-bromouracil (=T or rarely C)

hydroxylating agent (add OH-group to C)

alkylating agent such as EMS (ethylmethane sulfonate)

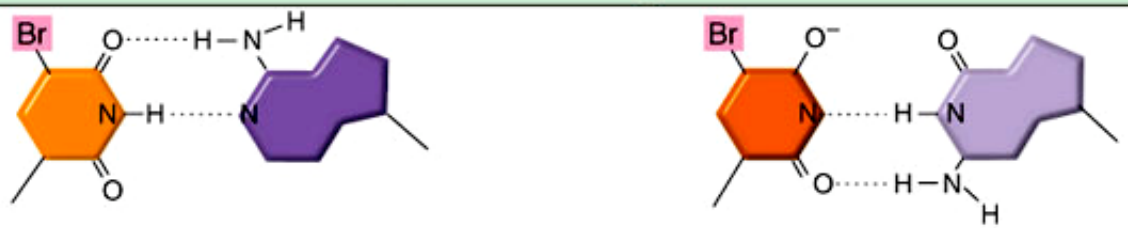
deaminating agent such as nitrous acid

intercalating agent such as Acridine Orange

Transposons that insert into a gene and disrupt the normal reading frame

Chemical Mutagens

Fig. 7.12a1

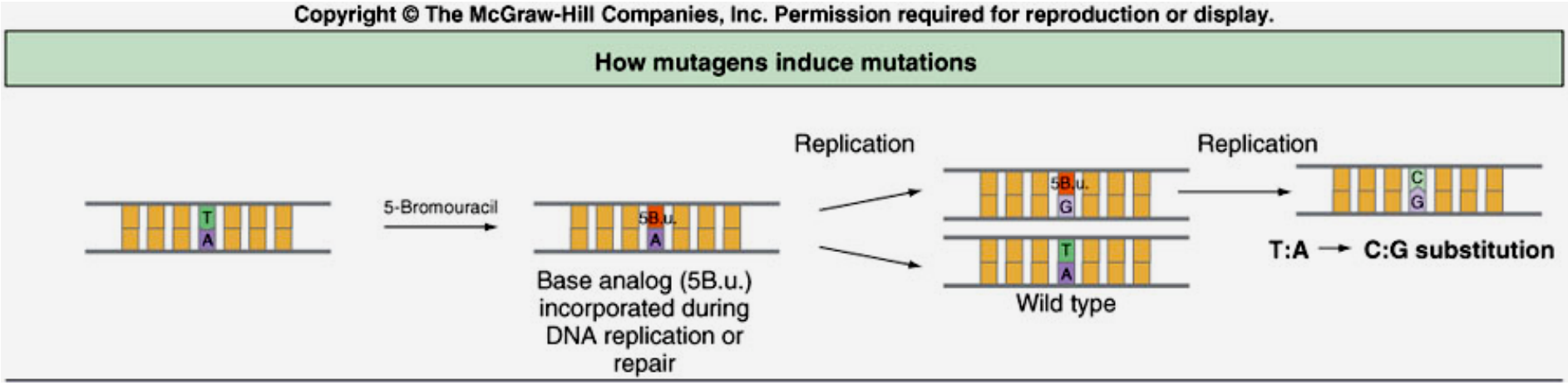
Type of mutagen	Chemical action of mutagen
(a) Replace a base: Base analogs have a chemical structure almost identical to that of a DNA base.	

5-Bromouracil–normal state, behaves like thymine — Adenine

5-Bromouracil–rare state, behaves like cytosine — Guanine

5-Bromouracil: almost identical to thymine. Normally pairs with A; in transient state, pairs with G.

Fig. 7.12a2


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
How mutagens induce mutations
T
A
5-Bromouracil
5B.u.
A
Base analog (5B.u.) incorporated during DNA replication or repair
Replication
5B.u.
G
T
A
Wild type
Replication
C
G
T:A → C:G substitution

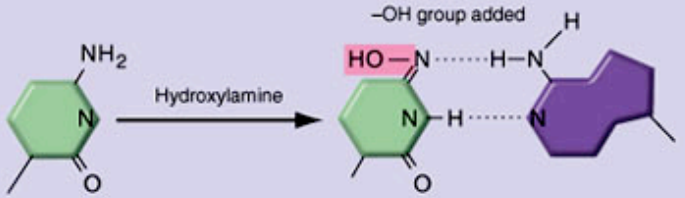
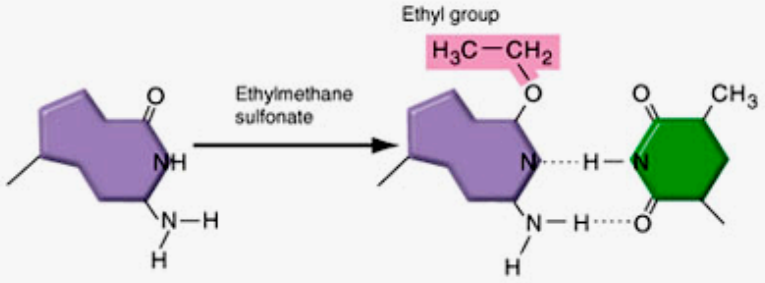
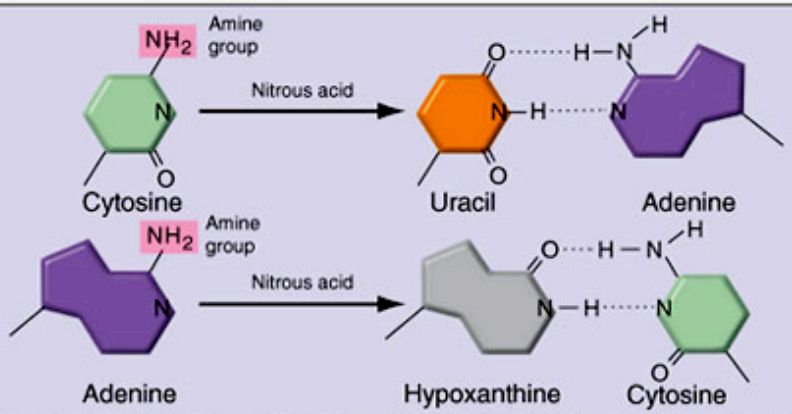
Type of mutagen	Chemical action of mutagen
(b) Alter base structure and properties: *Hydroxylating agents*: add a hydroxyl (–OH) group	 Hydroxylamine adds –OH to cytosine; with the –OH, hydroxylated C now pairs with A instead of G.
Alkylating agents: add ethyl (–CH_2–CH_3) or methyl (–CH_3) groups	 Ethylmethane sulfonate adds an ethyl group to guanine or thymine. Modified G pairs with T above, and modified T pairs with G (not shown).
Deaminating agents: remove amine (–NH_2) groups	 Nitrous acid modifies cytosine to uracil, which pairs with A instead of G; modifies adenine to hypoxanthine, a base that pairs with C instead of T.

Fig. 7.12b1

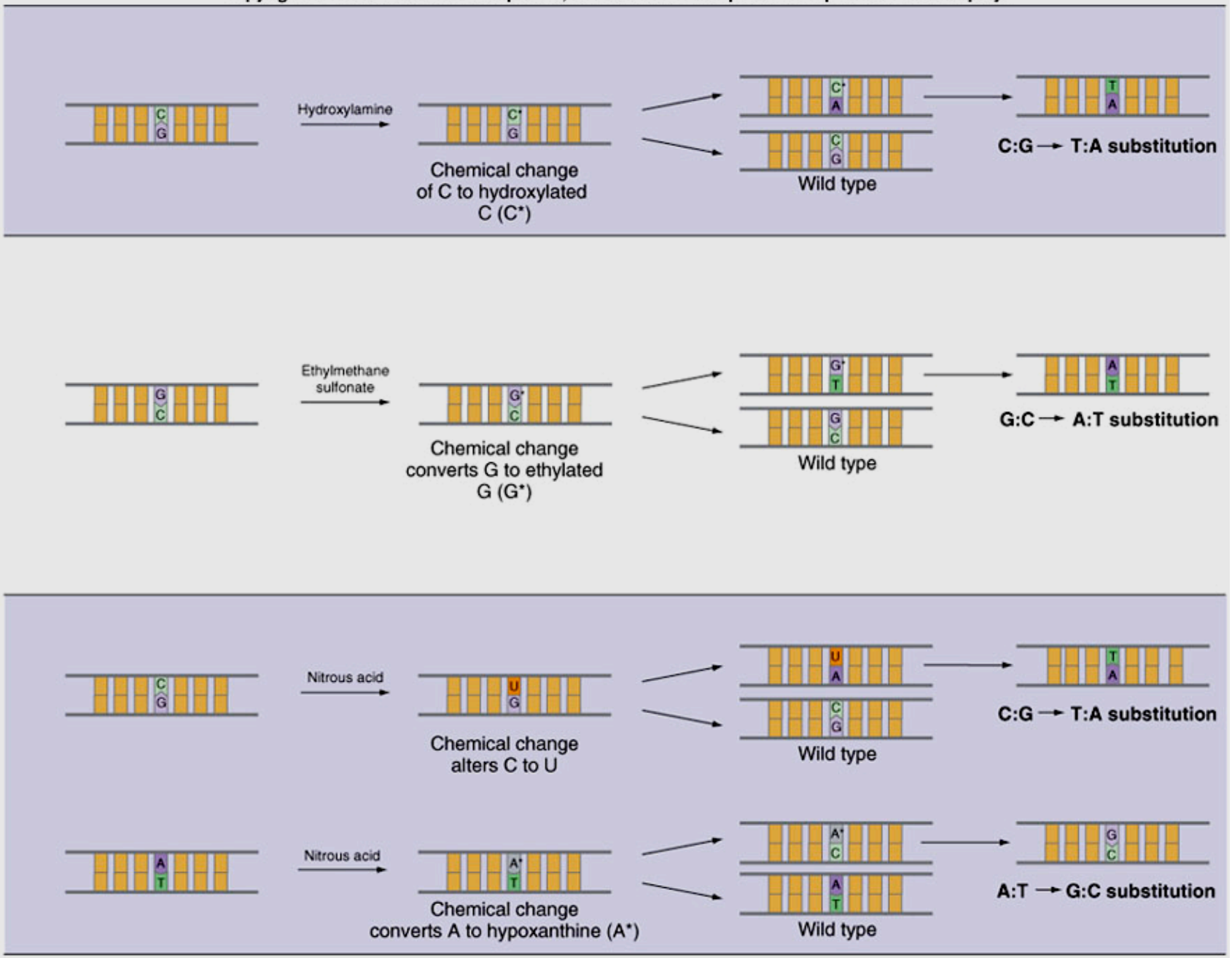


Fig. 7.12c1

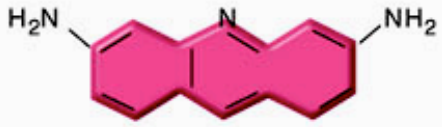
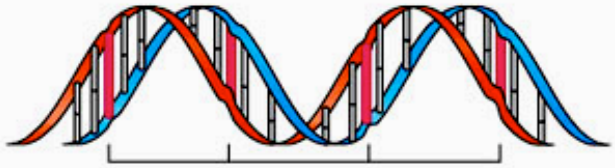
Type of mutagen	Chemical action of mutagen
(c) Insert between bases: Intercalating agents	 Proflavin  Intercalated proflavin molecules Proflavin intercalates into the double helix. This disrupts DNA metabolism, eventually resulting in deletion or addition of a base pair.

Fig. 7.12c2