16

Mechanisms of Genetic Variation

16.1 Mutations

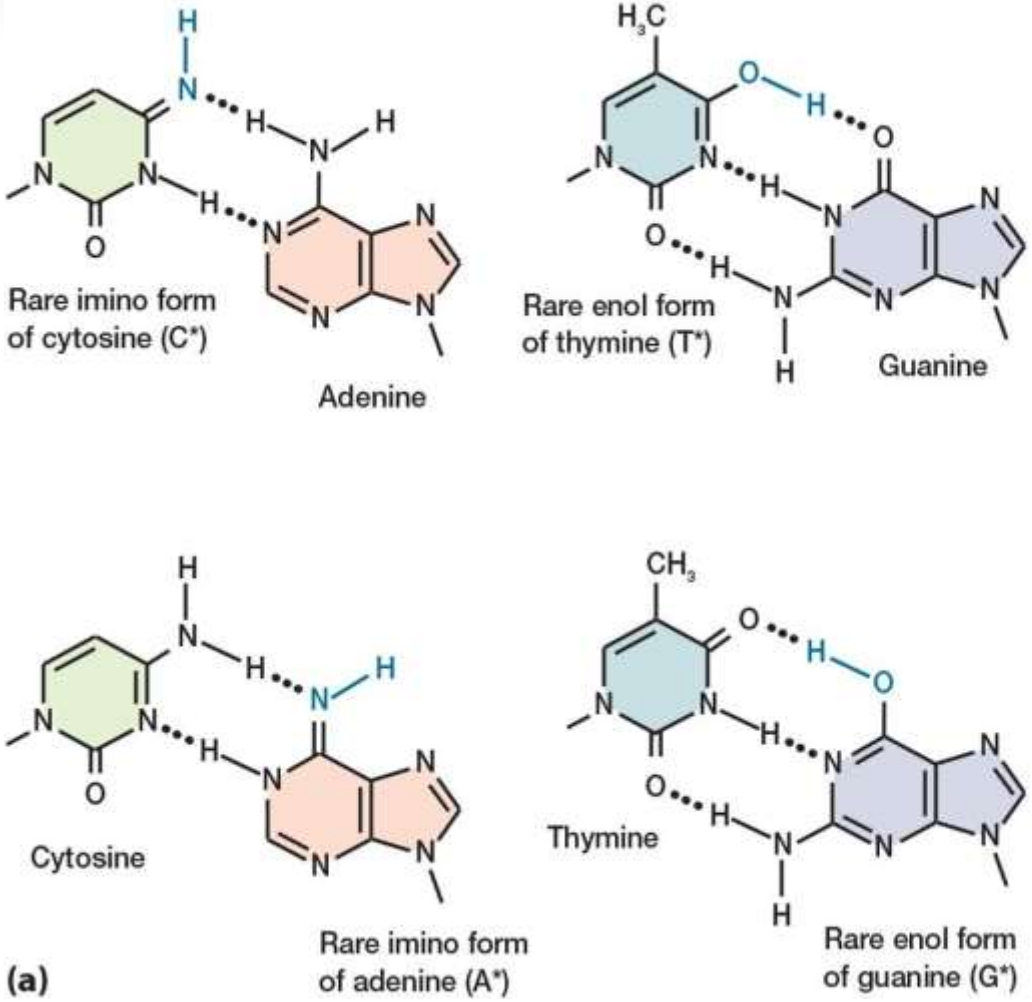
1. Distinguish spontaneous from induced mutations, and list the most common ways each arises
2. Construct a table, concept map, or picture to summarize how base analogues, DNA-modifying agents, and intercalating agents cause mutations
3. Discuss the possible effects of mutations

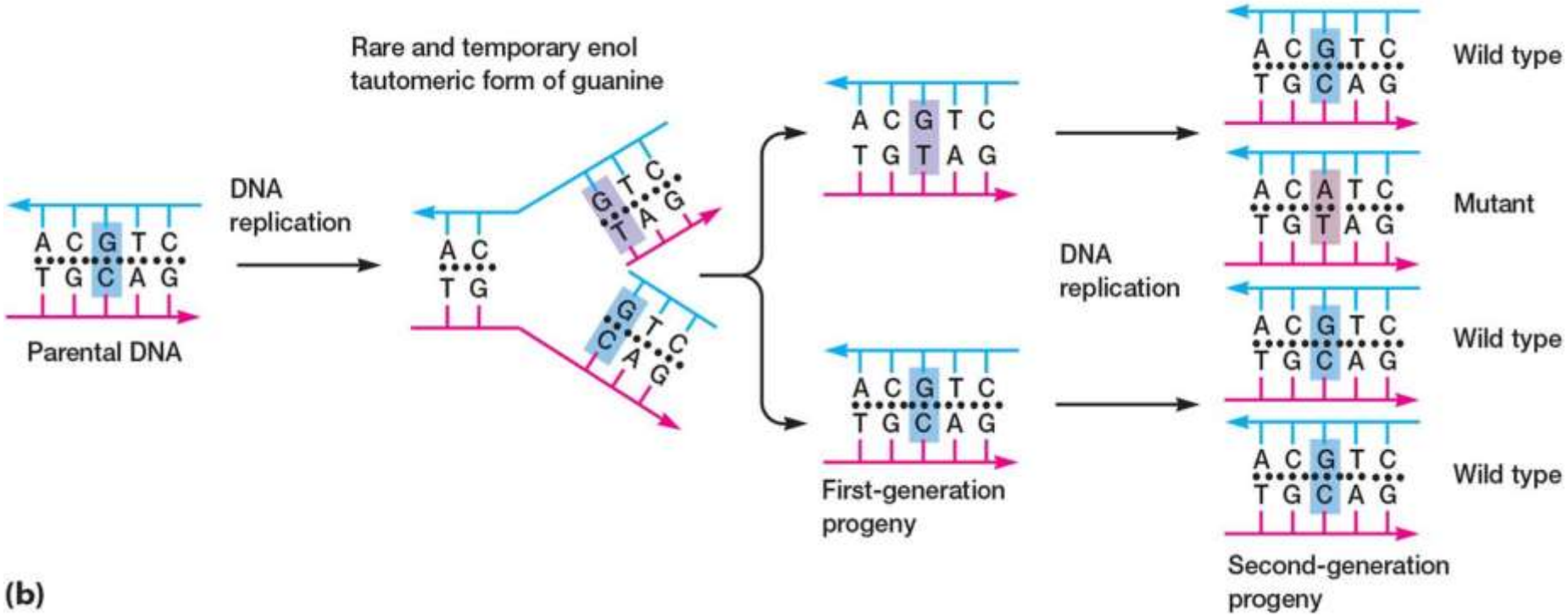
Mutations: Their Chemical Basis and Effects

- Stable, **heritable(موروثة) changes in sequence of bases in DNA**
  - **point mutations most common**
    - from alteration of single pairs of nucleotide
    - from the **addition** or **deletion** of nucleotide pairs
  - **larger mutations are less common**
    - **insertions, deletions, inversions, duplication, and translocations of nucleotide sequences**
- Mutations can be **spontaneous** or **induced**

Spontaneous Mutations

- **Arise without exposure to external agents**
- **May result from errors in DNA replication**
  - due to base tautomerization resulting in transition and transversion mutations
  - **due to insertion or deletion of nucleotides**
- May also result from the action of mobile genetic elements such as transposons





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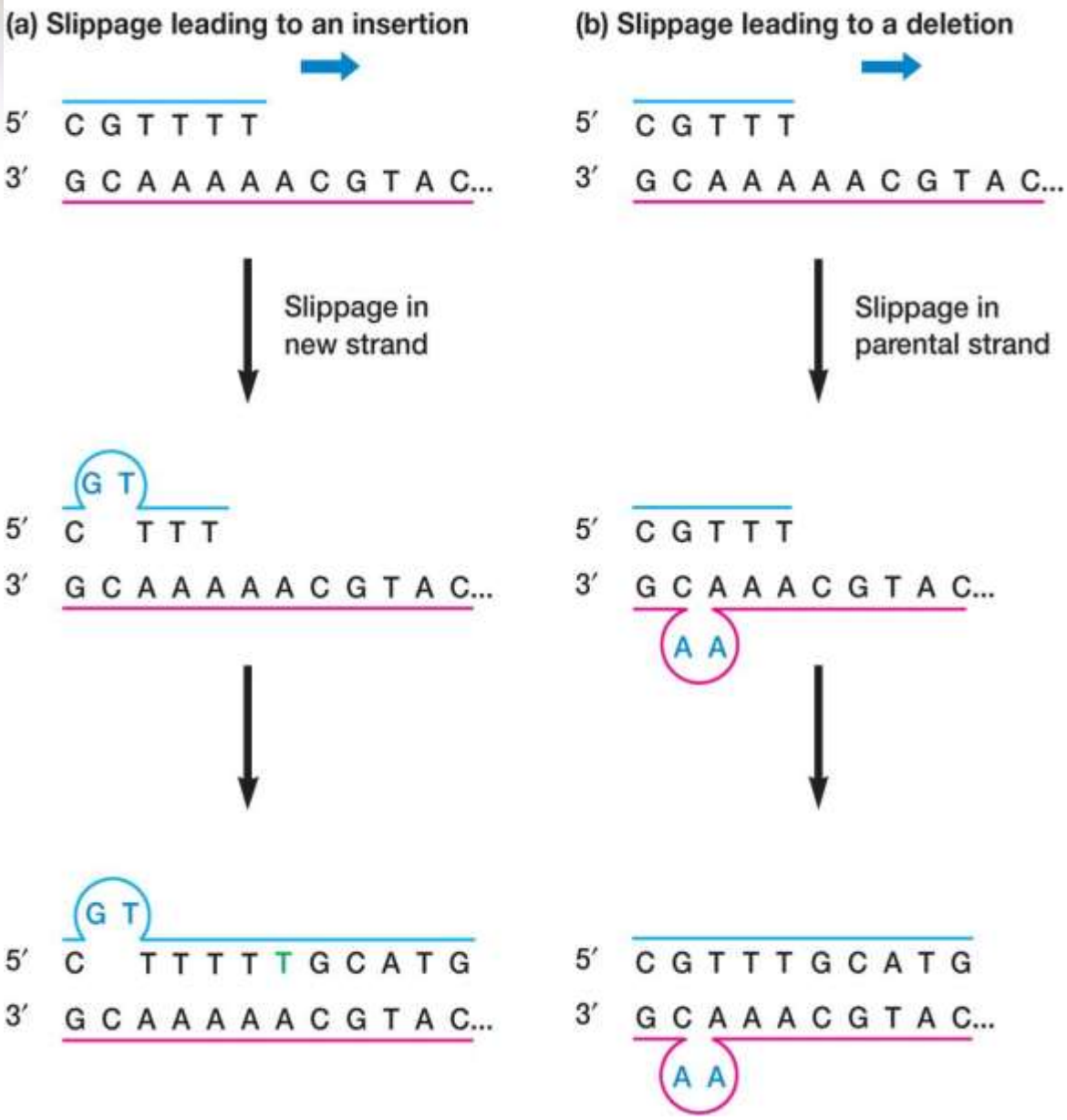

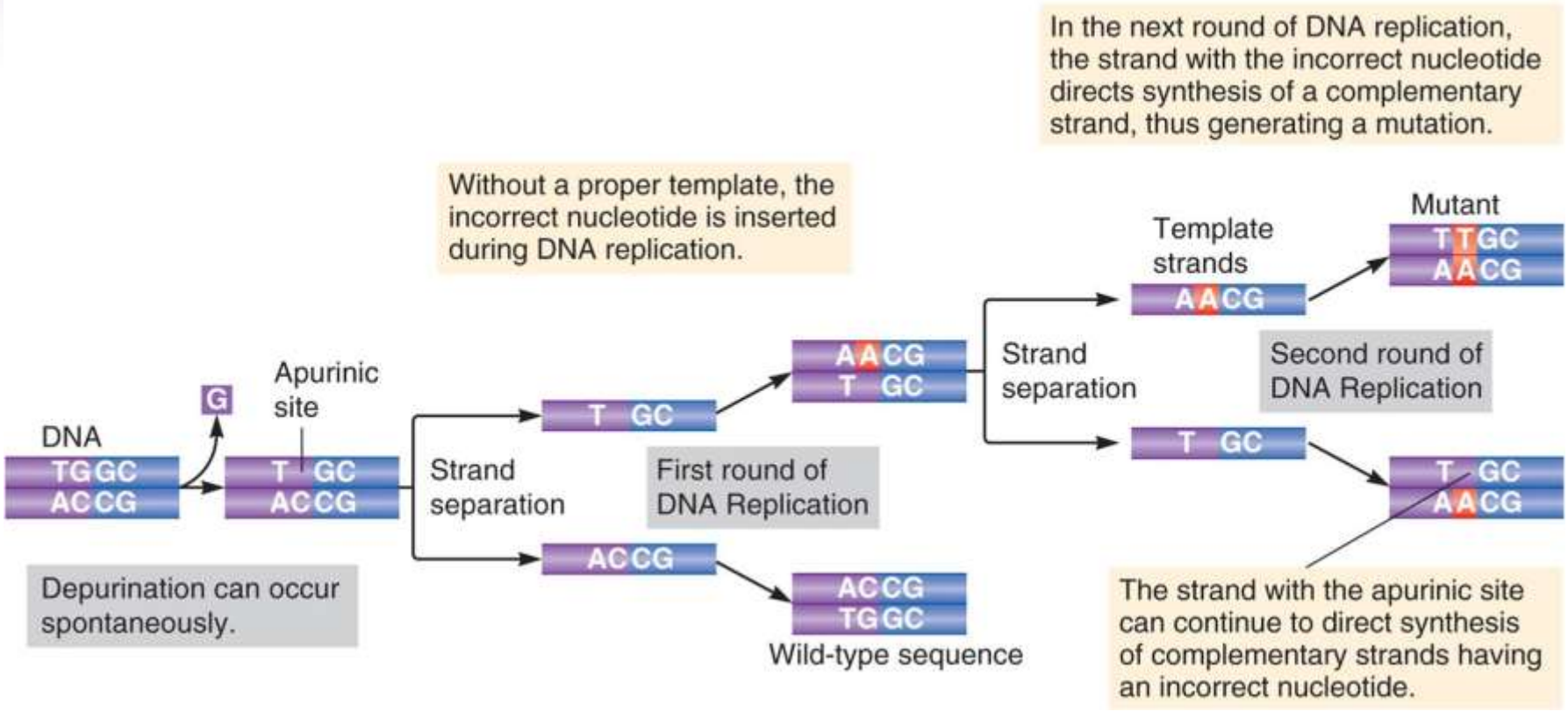

Induced Mutations

- **Caused by agents that directly damage DNA**
  - **base analogs**
    - **structurally similar to normal bases**
    - mistakes occur when they are incorporated into growing polynucleotide chain
  - **DNA modifying agents**
    - **alter a base causing it to mispair**
  - **intercalating agents**
    - **Distort(شوه) DNA to induce single nucleotide pair insertions and deletions**

Table 16.1 Examples of Mutagens

Mutagen	Effect(s) on DNA Structure
Chemical	
5-Bromouracil	Base analogue
2-Aminopurine	Base analogue
Ethyl methanesulfonate	Alkylating agent
Hydroxylamine	Hydroxylates cytosine
Nitrogen mustard	Alkylating agent
Nitrous oxide	Deaminates bases
Proflavin	Intercalating agent
Acridine orange	Intercalating agent
Physical	
UV light	Promotes pyrimidine dimer formation
X rays	Cause base deletions, single-strand nicks, cross-linking, and chromosomal breaks

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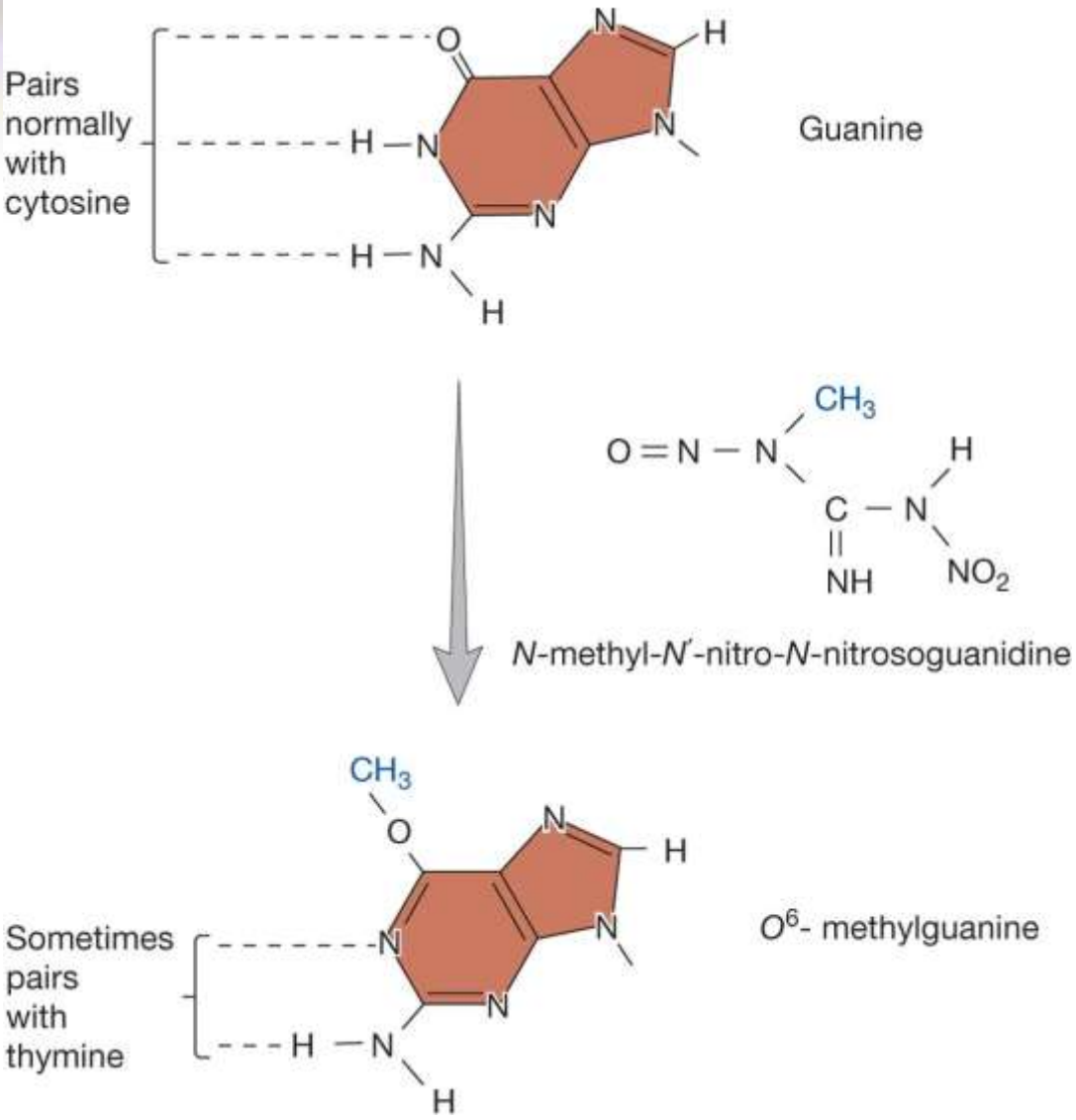

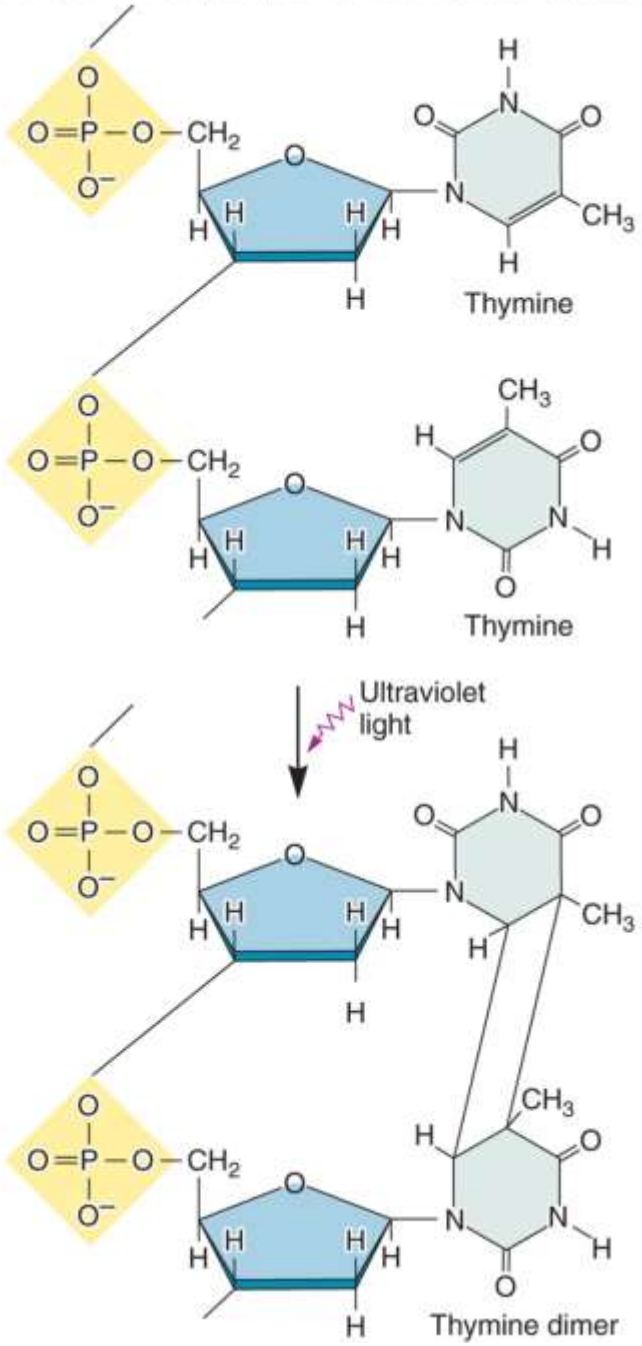

Effects of Mutations

- **Wild type**
  - most prevalent(الأكثر انتشاراً) form of gene
- **Forward mutation**
  - wild type → mutant form
- **Reversion mutation**
  - mutant phenotype → wild type phenotype
    - **suppressor mutation**
      - occurs when the second mutation is at a different site than the original mutation

Mutations in Protein Coding Genes

- **Point mutations**
  - in protein-coding genes can affect protein structure in a variety of ways
- **Are named according to if and how they change the encoded protein**
- The most common types are: **silent, missense, nonsense, and frameshift mutations**

Table 16.2 Types of Point Mutations

Type of Mutation	Change in DNA	Example
Forward Mutations		
None	None	5′-A-T-G-A-C-C-T-C-C-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Ser - Pro - Lys - Gly
Silent	Base substitution	5′-A-T-G-A-C-A-T-C-C-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Ser - Pro - Lys - Gly
Missense	Base substitution	5′-A-T-G-A-C-C-T-G-C-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Cys - Pro - Lys - Gly
Nonsense		5′-A-T-G-A-C-C-T-C-C-C-C-G-T-A-A-G-G-G-3′ Met - Thr - Ser - Pro - STOP!
Frameshift	Insertion/deletion	5′-A-T-G-A-C-C-T-C-C-G-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Ser - Ala - Glu - Arg
Reverse Mutations		
	Base substitution	5′-A-T-G-A-C-C-T-C-C forward→ A-T-G-C-C-C-T-C-C reverse→ A-T-G-A-C-C-T-C-C Met - Thr - Ser — Met - Pro - Ser — Met - Thr - Ser
	Base substitution	5′-A-T-G-A-C-C-T-C-C forward→ A-T-G-A-C-C-T-G-C reverse→ A-T-G-A-C-C-A-G-C Met - Thr - Ser — Met - Thr - Cys — Met - Thr - Ser
	Base substitution	5′-A-T-G-A-C-C-T-C-C forward→ A-T-G-C-C-C-T-C-C reverse→ A-T-G-C-T-C-T-C-C Met - Thr - Ser — Met - Pro - Ser — Met - Leu - Ser (polar amino acid) — (nonpolar amino acid) — (polar amino acid) pseudo-wild type
Suppressor Mutations		
Frameshift of opposite sign (intragenic suppressor)	Insertion/deletion	5′-A-T-G-A-C-C-T-C-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Ser - Pro - Lys - Gly ↓ Forward mutation 5′-A-T-G-A-C-C-T-C-C-G-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Ser - Ala - Glu - Arg ↓ Suppressor mutation (deletion) 5′-A-T-G-A-C-C-C-C-G-C-C-G-A-A-A-G-G-G-3′ Met - Thr - Pro - Pro - Lys - Gly
Extragenic suppressor Nonsense suppressor		Gene (e.g., for tyrosine tRNA) undergoes a mutation in its anticodon region that enables it to recognize and align with a nonsense mutation (e.g., UAG). Thus an amino acid (tyrosine) is inserted at the mutant stop codon and translation continues.
Physiological suppressor		A defect in one chemical pathway is circumvented by another mutation; for example, one that opens up another chemical pathway to the same product or one that permits more efficient uptake of a compound produced in small quantities because of the original mutation.

Point Mutations

- **Silent mutation** – change nucleoside sequence of codon – but not the encoded amino acid
- **Missense mutation** – a single base substitution that changes codon for one amino acid into codon for another amino acid
- **Nonsense mutation** – converts a sense codon to a stop codon
- **Frameshift mutation** – results from insertion or deletion of one or two base pairs in the coding region of the gene

Other Types of Mutations

- **Conditional mutations**
  - expressed only under certain environmental conditions
- **Auxotrophic mutant**
  - unable to make an essential macromolecule such an amino acid or nucleotide
    - has a conditional phenotype
    - wild-type strain from which it arose is called a prototroph

Other Types of Mutations

- **Mutations in Regulatory Sequences**
  - **conditional *lac* operon mutants**
    - many of these mutations map in the operator site and produce altered operator sequences not recognized by repressor
    - operon is always transcribed and β-galactosidase is always synthesized
- **Mutations in tRNA and rRNA genes**
  - protein synthesis is disrupted