INTRODUCTION

- The term mutation refers to a heritable change in the genetic material
- Mutations provide allelic variations
  - On the positive side, mutations are the foundation for evolutionary change
  - On the negative side, mutations are the cause of many diseases
- Since mutations can be quite harmful, organisms have developed ways to repair damaged DNA

Mutations are the ultimate source of all genetic change

- **Gene mutation**:
- mutational events (changes in the DNA sequence) that take place within individual genes.
- These changes may or may not result in altering the spatial or functional state of the protein or the level of activity or specificity of the protein.

- **Chromosome mutation**:
- mutational events that affect the entire chromosome or large pieces of the chromosome.
- These affects will mainly result in gene dosage defects.

Random vs Adaptive Mutation

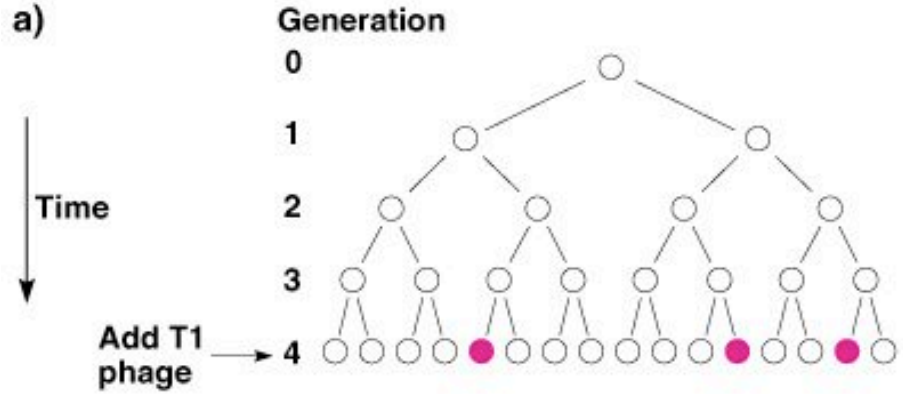
- Does mutation cause random variation leading to adaptation, or does the environment induces heritable adaptations?????
  - Lamarckism is the doctrine of inheritance of acquired characteristics.
  - The random mutation doctrine says that sometimes chance changes happen to be adaptive, thus altering phenotype by changing a protein (Figure 15.1).
  - The observation that phage T1–resistant *E. coli* arise could be interpreted to support either of these theories.

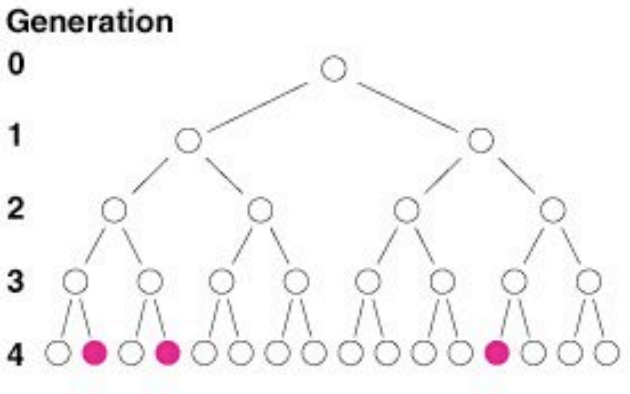
Random vs Adaptive Mutation

- An *E. coli* population that started from one cell would show different patterns of T1 resistance depending on which model is correct.
  - The adaptive theory says that cells are induced to become resistant to T1 when it is added.
    - Therefore, the proportion of resistant cells would be the same for all cultures with the same genetic background.
  - The mutation theory says that random events confer resistance to T1, whether the phage is present or not.
    - Cultures will therefore show different numbers of T1–resistant cells, depending on when the resistance mutation(s) occurred.

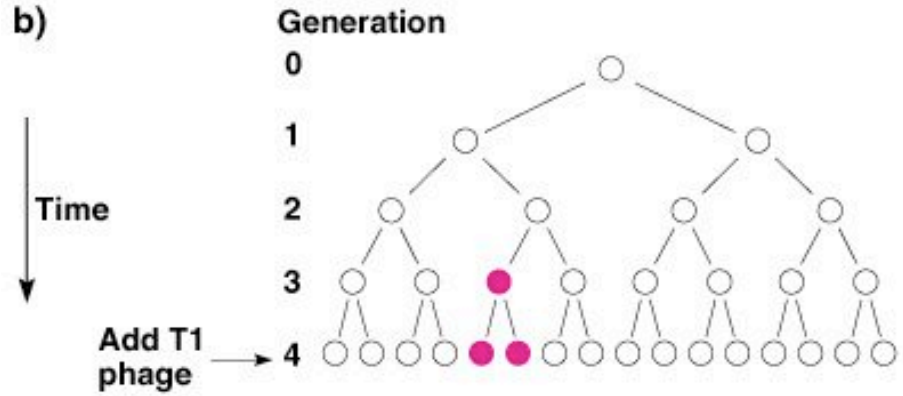
Fig. 15.1
Representation of a dividing population of T1 phage-sensitive wild-type *E. coli*

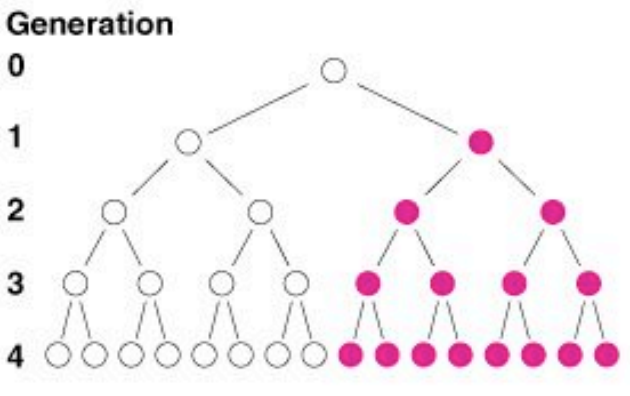
Adaptive





Random





Mutation vs. Adaptation

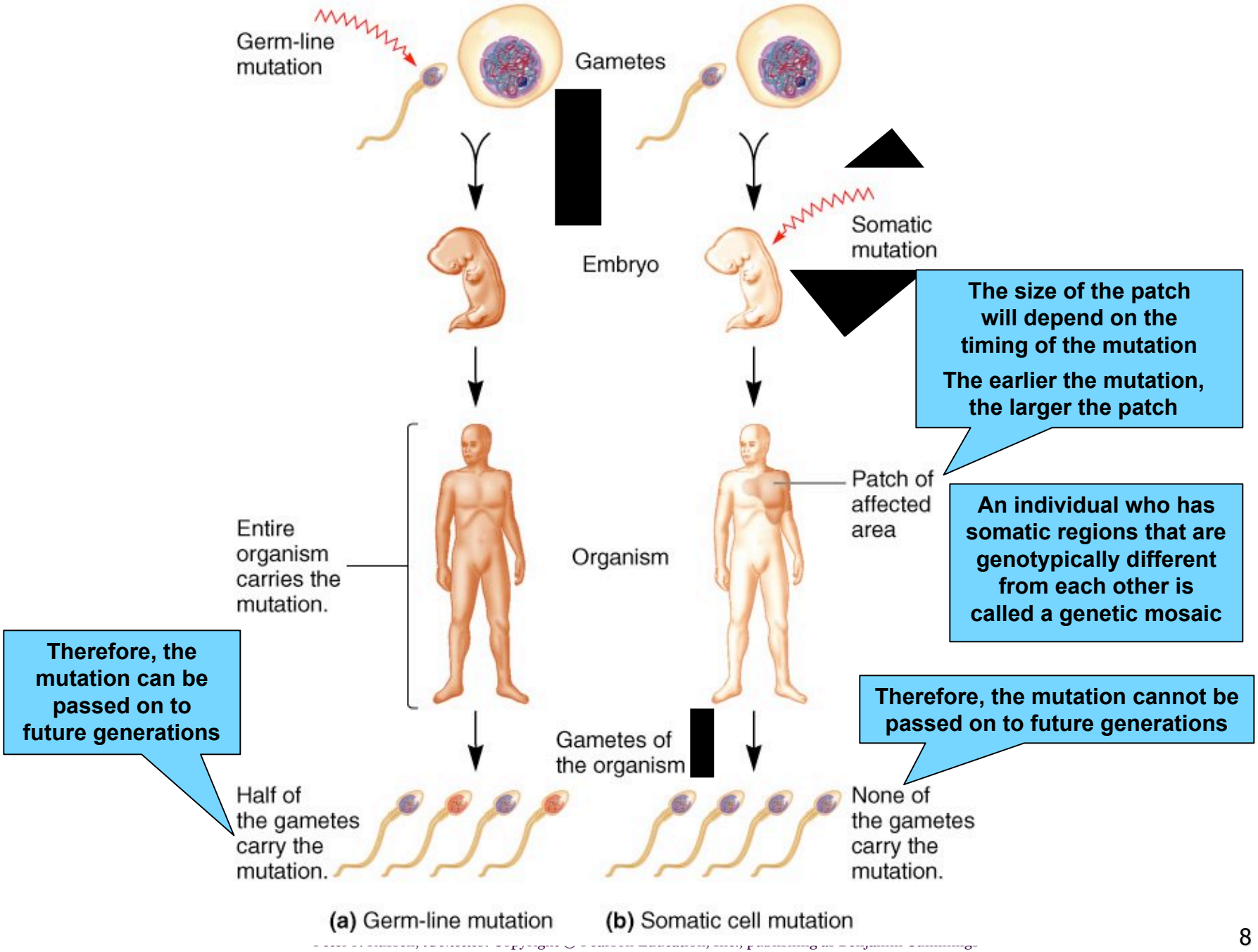
- Results:

  Luria and Delbrück observed fluctuating numbers of resistant bacteria from *E. coli* cultures

  – indicating that the random mutation model is correct.

Mutations Defined

- A mutation is a change in a DNA base pair or a chromosome.
  1. Somatic mutations affect only the individual in which they arise.
  2. Germ-line mutations alter gametes, affecting the next generation.


Germ-line mutation
Gametes
Somatic mutation
Embryo
The size of the patch will depend on the timing of the mutation
The earlier the mutation, the larger the patch
Patch of affected area
An individual who has somatic regions that are genotypically different from each other is called a genetic mosaic
Entire organism carries the mutation.
Organism
Therefore, the mutation can be passed on to future generations
Therefore, the mutation cannot be passed on to future generations
Gametes of the organism
Half of the gametes carry the mutation.
None of the gametes carry the mutation.
(a) Germ-line mutation
(b) Somatic cell mutation

Mutations Defined

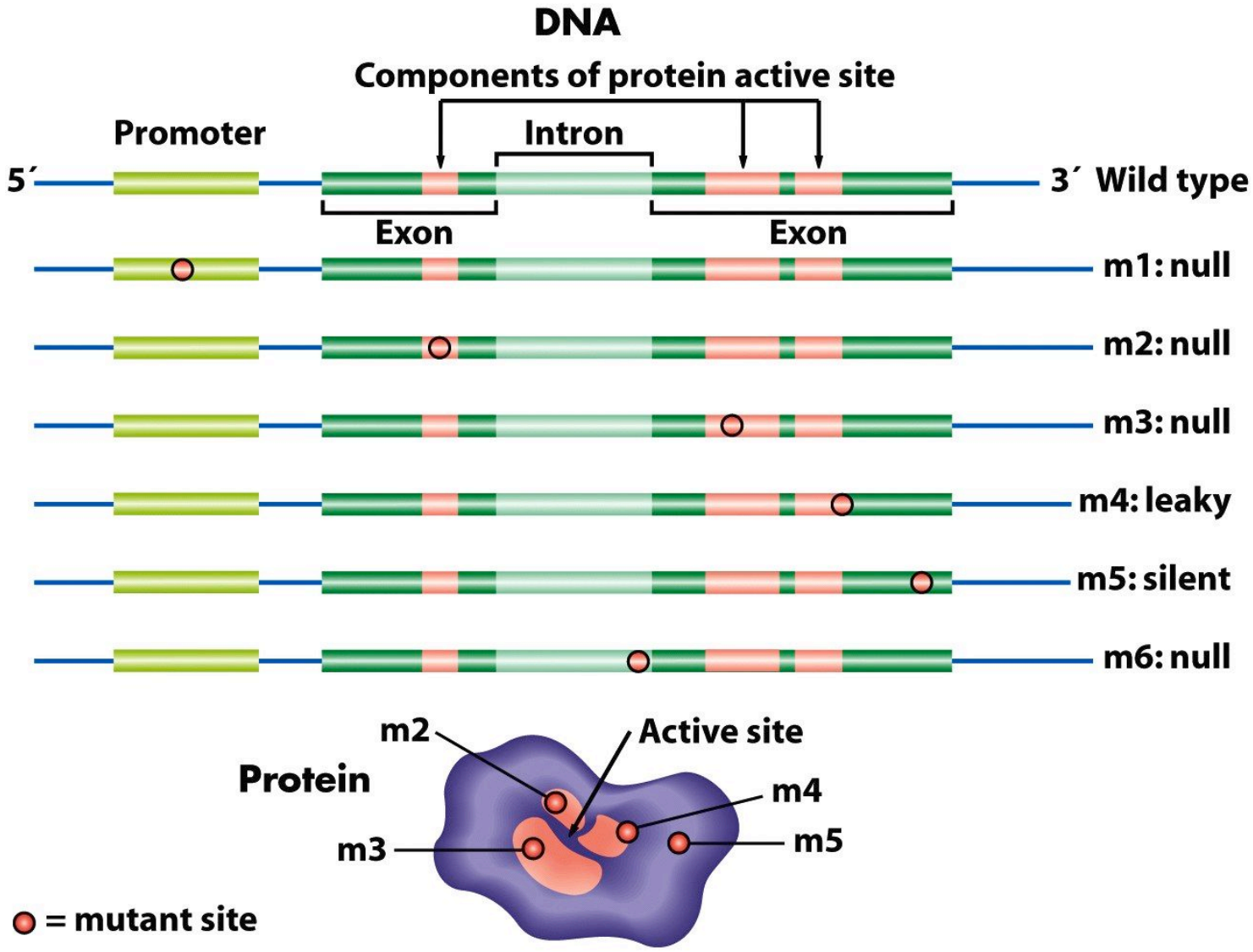
- Mutations are quantified in two different ways:
  - Mutation rate is the probability of a particular kind of mutation as a function of time

    (e.g., number per gene per generation).

  - Mutation frequency is the number of times a particular mutation occurs in proportion to the number of cells or individuals in a population

    (e.g., number per 100,000 organisms).

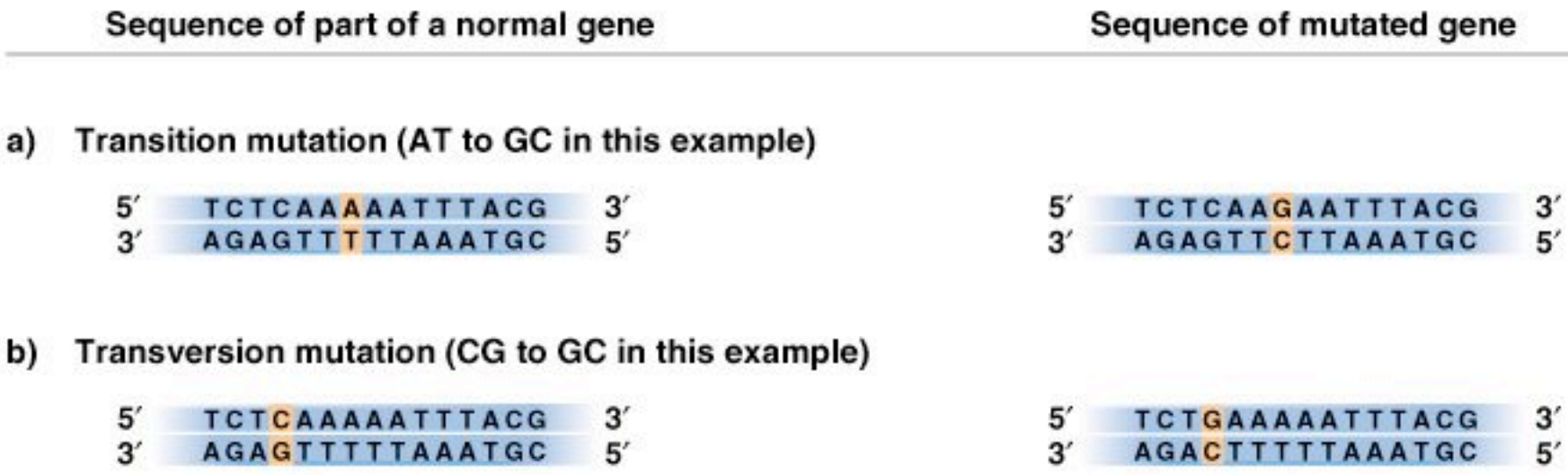
Not All Nucleotide Changes Result in Changes in Protein Activity



Mutations : Substitution

- one base is replaced by one of the other three bases
  - Transition -
    - purine-purine and pyrimidine-pyrimidine
    - Only one choice
    - C to T or G to A and vice versa
  - Transversion -
    - purine-pyrimidine
    - Two choices
    - C or T to G or A; and vice versa
- Also known as a Point Mutation (single base pair change)
- Which occurs more often?
  - Transition

Fig. 15.3a-d Types of base-pair substitution mutations



What Point Mutations/Base Substitutions Do to the Protein

- Mutations in the coding sequence of a structural gene can have various effects on the polypeptide
  - Silent mutations are those base substitutions that do not alter the amino acid sequence of the polypeptide
    - Due to the degeneracy of the genetic code
  - Missense mutations are those base substitutions in which an amino acid change does occur
    - Example: Hemoglobin in sickle-cell anemia
    - NOTE: If the substituted amino acids have similar chemistry, the mutation is said to be neutral
  - Nonsense mutations are those base substitutions that change a normal codon to a termination codon

Fig. 14.3 Types of base-pair substitution mutations

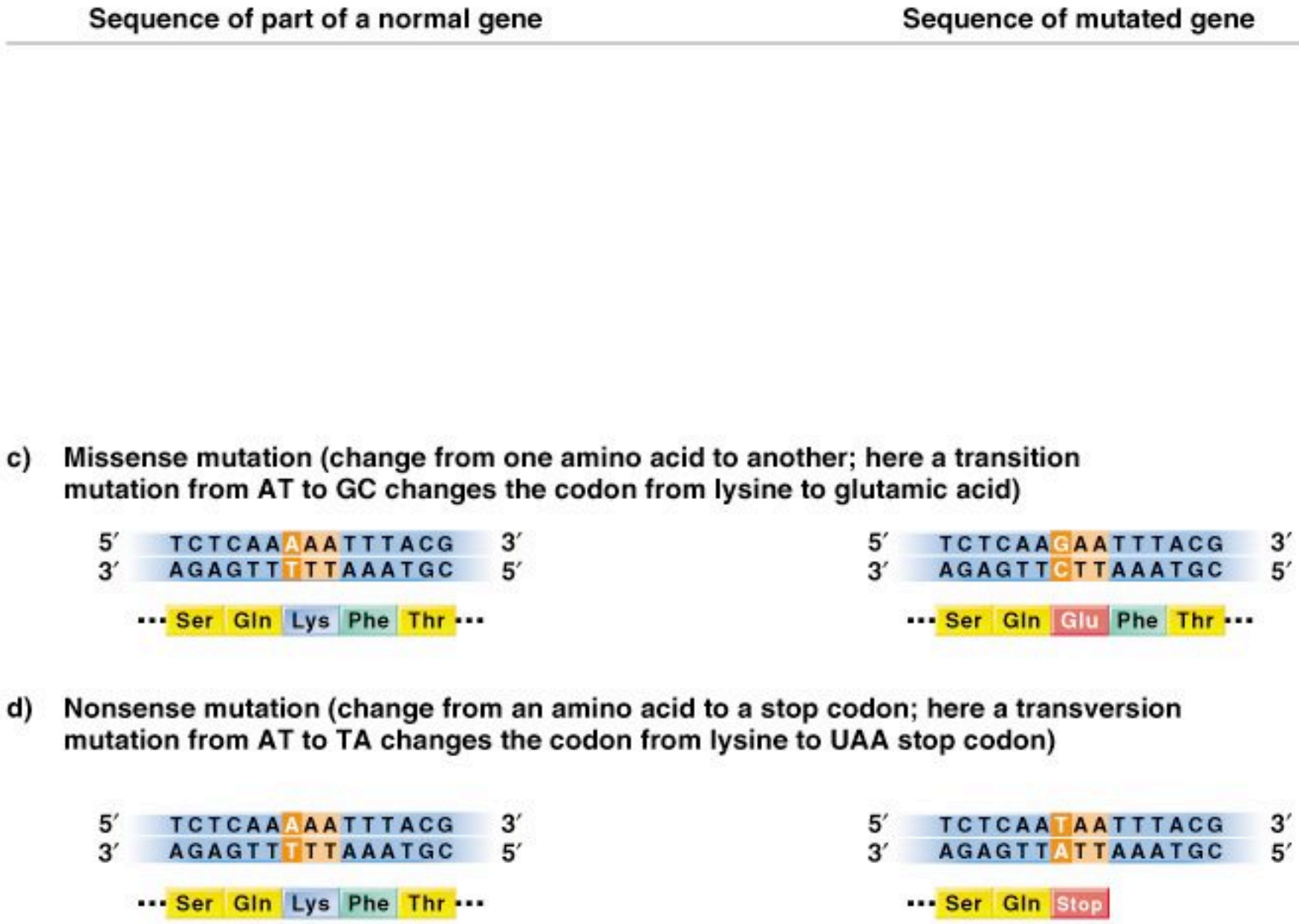


Fig. 15.4 A nonsense mutation and its effect on translation

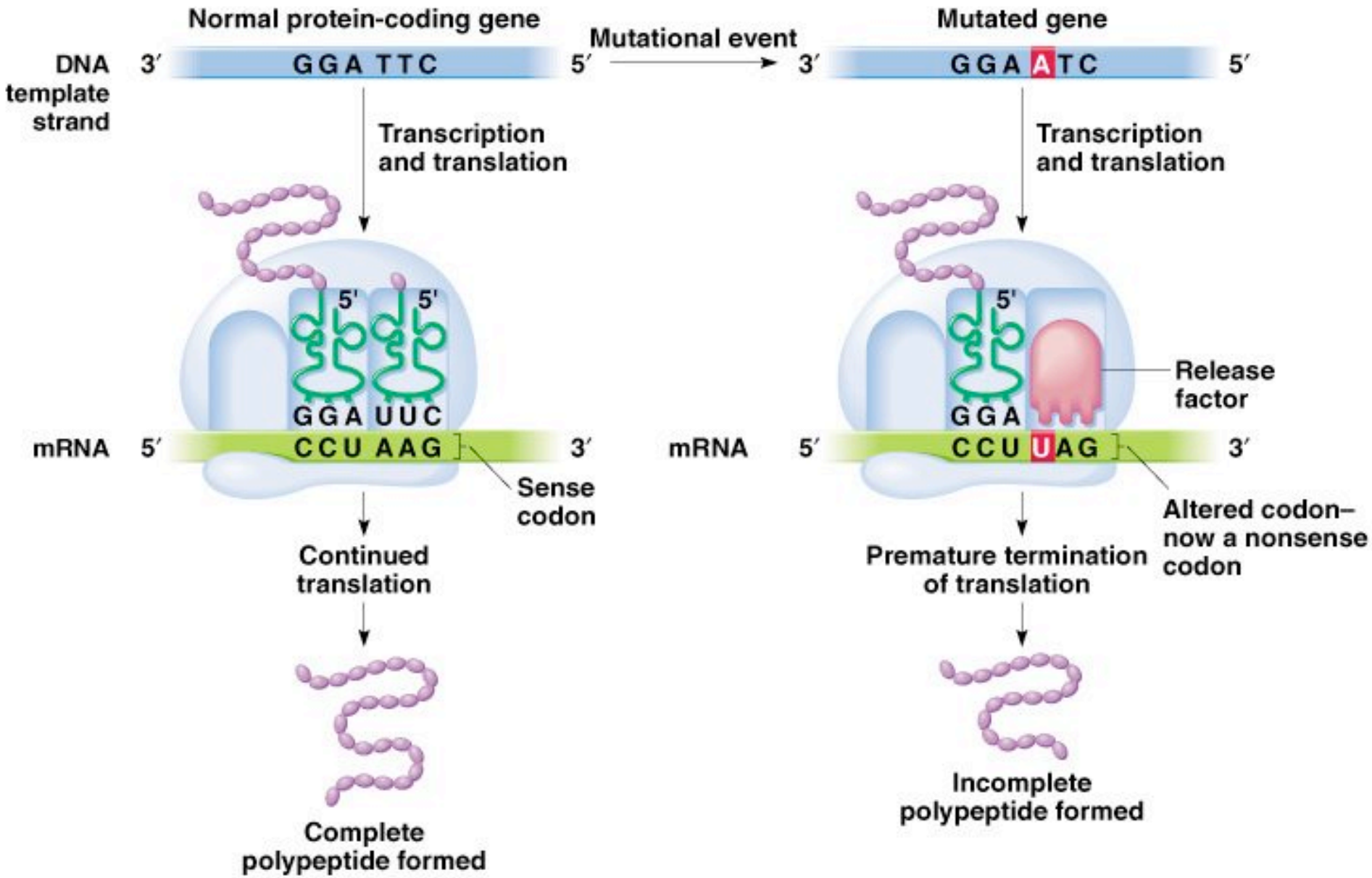
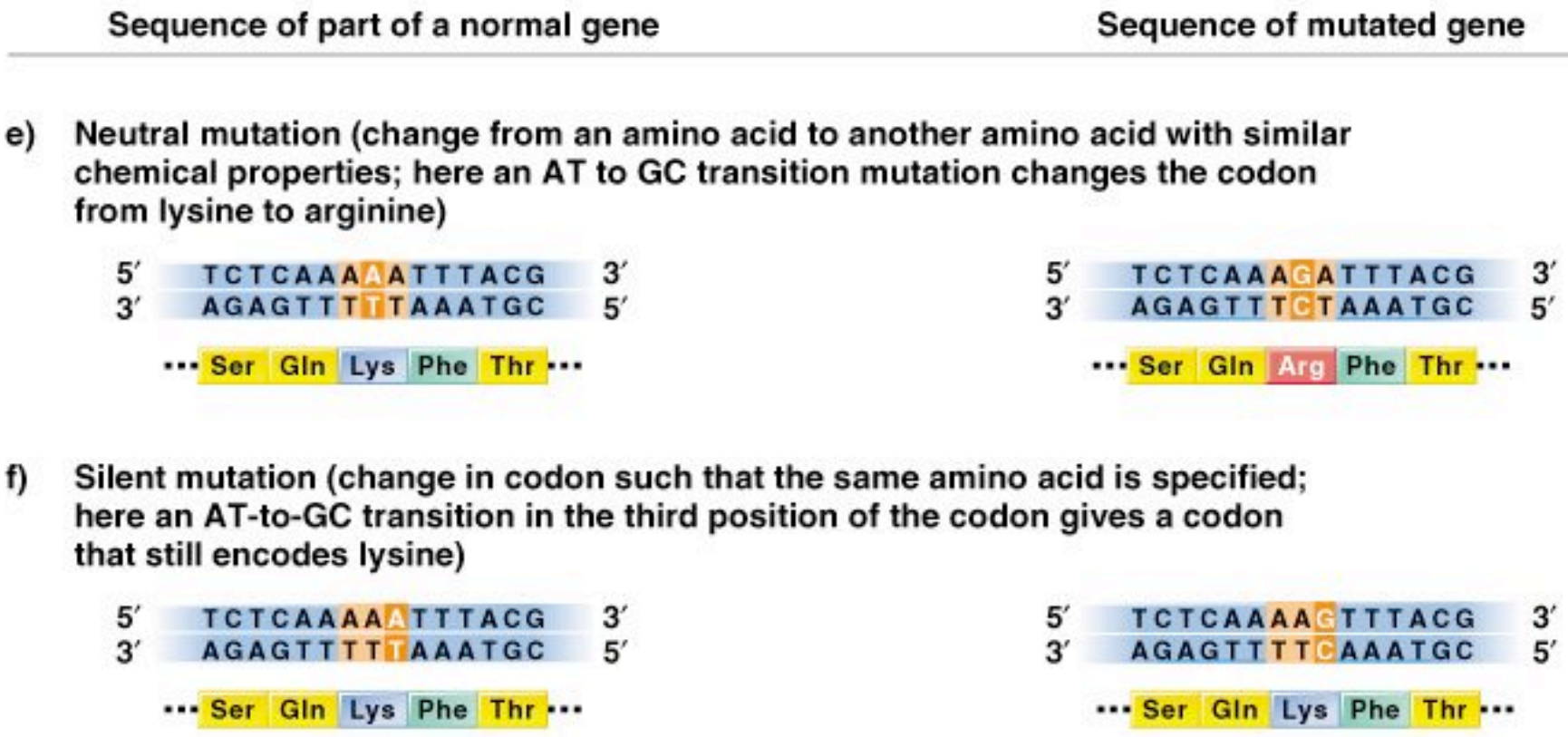


Fig. 7.3e-g Types of base-pair substitution mutations



Point Mutations: Deletions & Insertions

- Deletions and insertions can change the reading frame of the mRNA downstream of the mutation, resulting in a frameshift mutation.
  - When the reading frame is shifted, incorrect amino acids are usually incorporated.
  - Frameshifts may bring stop codons into the reading frame, creating a shortened protein.
  - Frameshifts may also result in read-through of stop codons, resulting in a longer protein.
  - Frameshift mutations result from insertions or deletions when the number of affected base pairs is not divisible by three.

The Reading Frame & Shifts

- The reading frame (ORF) of a gene is similar to the reading frame of a sentence, there is only one correct way to read it!
  - The sun was hot but the old man was not

- If we insert a new letter (base) into the sentence, we shift the reading frame:
  - ATh esu nwa sho tbu tth eol dma nwa sno t

- As you can see, this results in a nonsensical sentence, and will result in the formation of a nonsensical RNA message in cells.

The Reading Frame & Shifts

Sequence of part of a normal gene **Sequence of mutated gene**

g) Frameshift mutation (addition or deletion of one or a few base pairs leads to a change in reading frame; here the insertion of a GC base pair scrambles the message after glutamine)

Point Mutations: Phenotypic Effect

- Point mutations are divided into two classes based on their effect on phenotype:

1. Forward mutations change the genotype from wild type to mutant.
2. Reverse mutations (reversions or back mutations) change the genotype from mutant to wild type or partially wild type.
   - A reversion to the wild-type amino acid in the affected protein is a true reversion.
   - A reversion to some other amino acid that fully or partly restores protein function is a partial reversion.

Spontaneous and Induced Mutations

- Spontaneous are more frequent than induced mutations

- Spontaneous
  - DNA Replication Errors
  - Spontaneous chemical changes

- Induced
  - Physical Mutagens
    - X-ray Irradiation
    - UV Irradiation
  - Chemical Mutagens

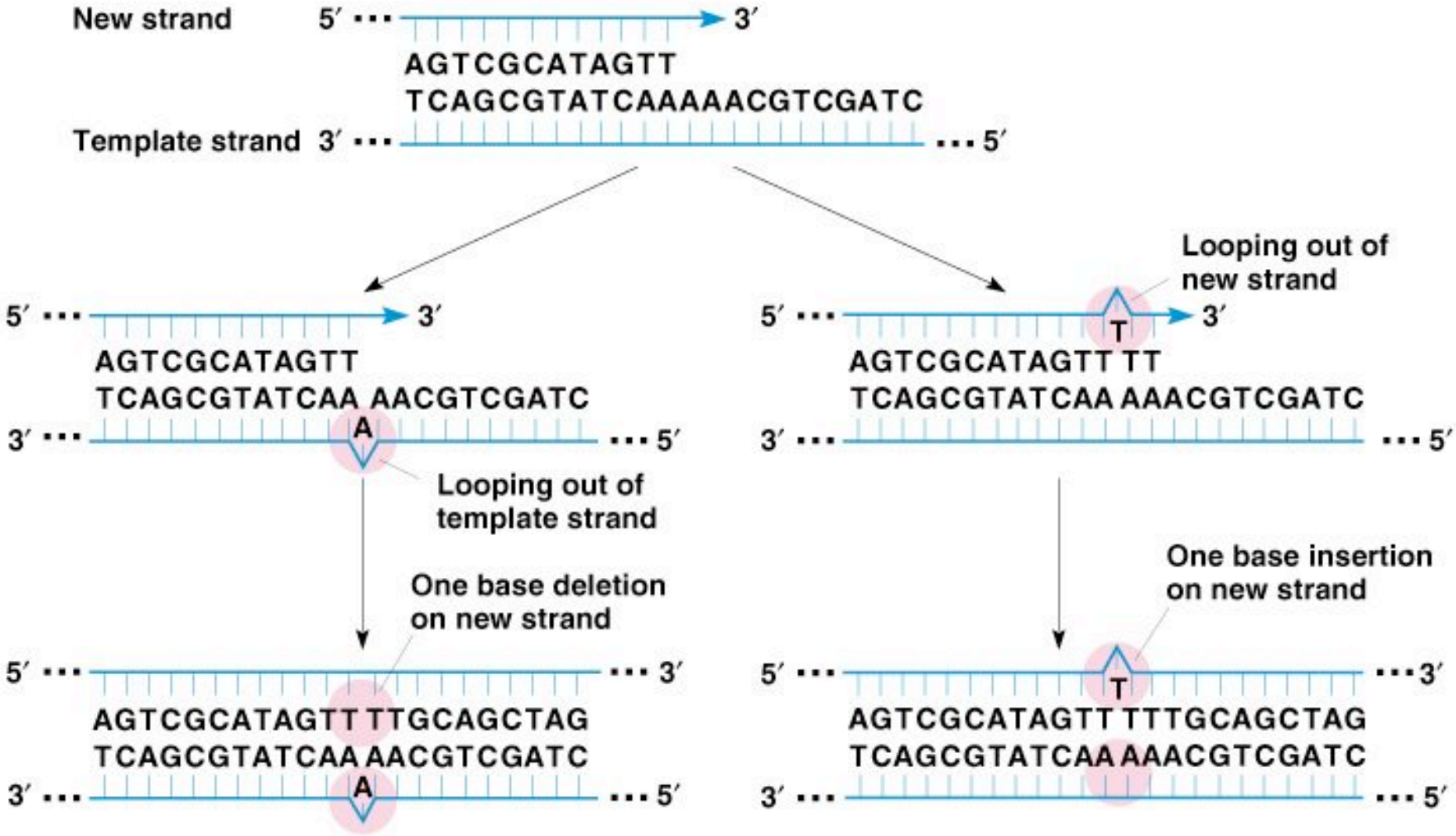
DNA Replication Errors

- can be either point mutations
- or small insertions or deletions.
- bases can form incorrect base pairs when the bases undergo a spontaneous chemical mutatin within the cell.
  - This can allow a G to base pair with a T, and a C to pair with an A.
  - GT base pairs are targets for correction by proofreading during replication, and by other repair systems.
  - Only mismatches uncorrected before the next round of replication lead to mutations

DNA Replication Errors

- Additions and deletions can occur spontaneously during replication (Figure 15.8).
  - DNA loops out from the template strand
    - generally in a run of the same base.
  - DNA polymerase skips the looped-out bases
    - creating a deletion mutation.
  - If DNA polymerase adds untemplated base(s)
    - new DNA looping occurs, resulting in additional mutation.
  - Insertions and deletions in structural genes generate frameshift mutations
    - if they are not in multiples of three.

Fig. 15.8 Spontaneous generation of addition and deletion mutants by DNA looping-out errors during replication

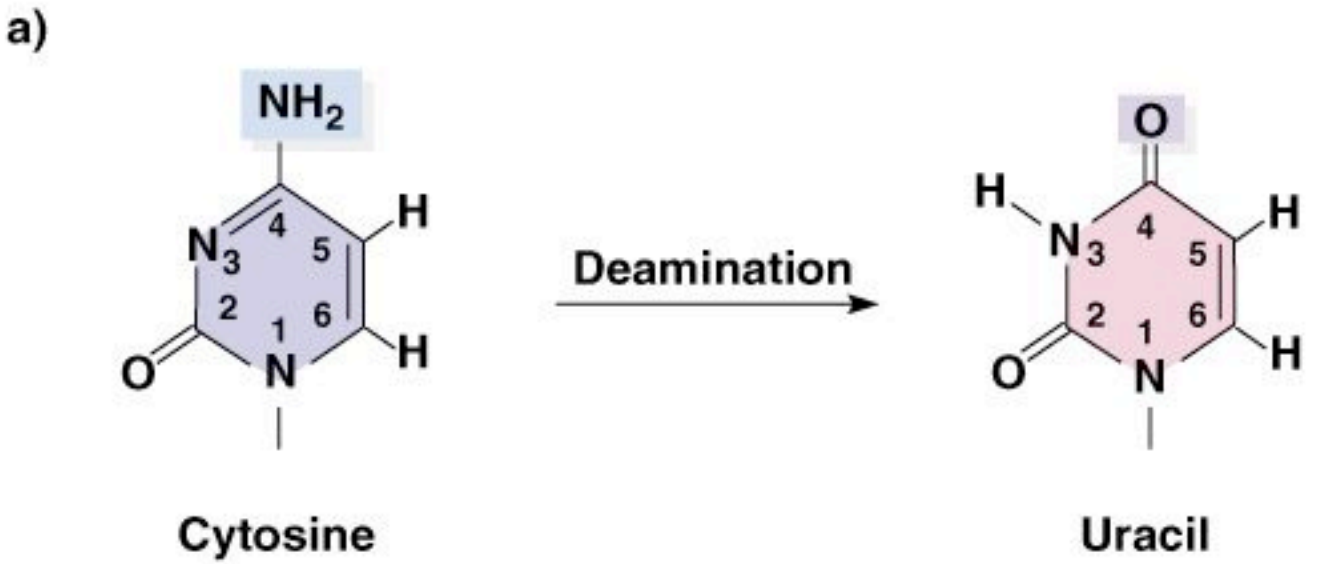


Spontaneous Chemical Changes

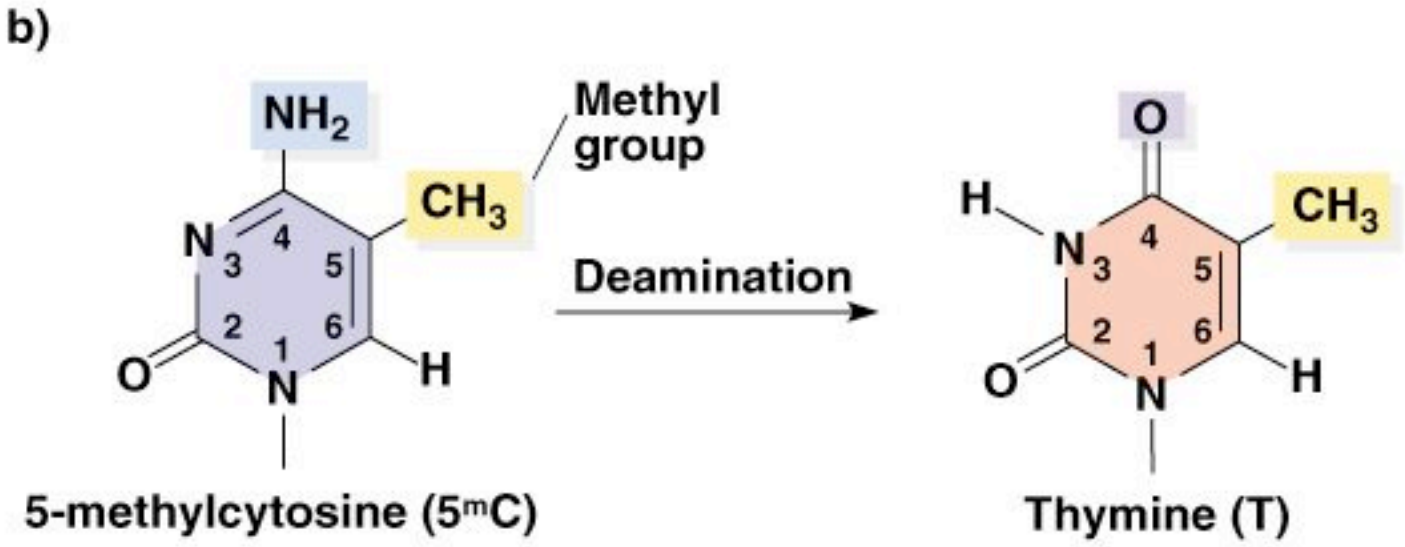
- can lead to incorrect base pairing during replication, or worse, an interruption of replication.
- include depurination and deamination of particular bases

Fig. 15.9

Deamination of cytosine to uracil



Deamination of 5-methylcytosine to thymin3-



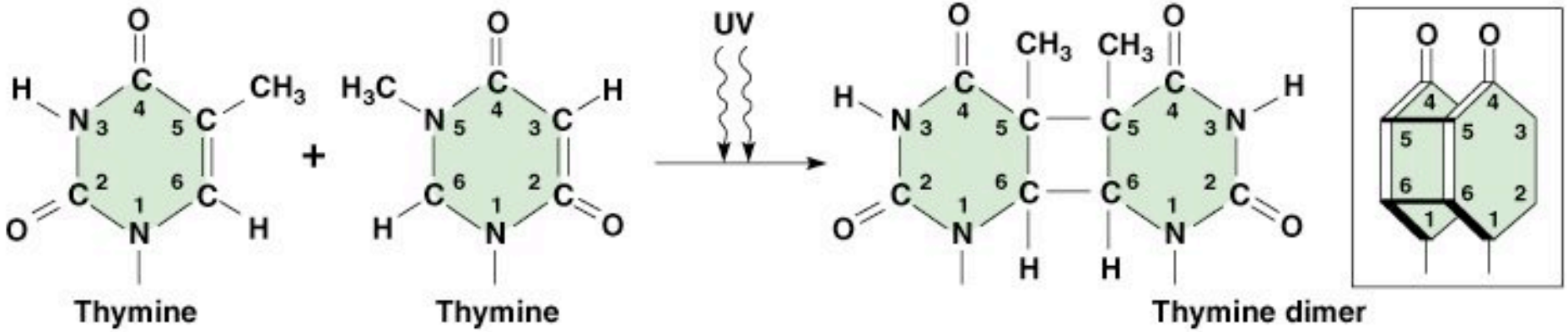
X-ray Radiation

- X-rays are an example of ionizing radiation
- penetrates tissue and collides with molecules
  - knocking electrons out of orbits and creating ions.
    - Ions can break covalent bonds, including those in the DNA sugar-phosphate backbone.
    - Ionizing radiation is the leading cause of human gross chromosomal mutations.
    - Ionizing radiation has a cumulative effect.

UV Radiation

- Ultraviolet (UV) causes photochemical changes in the DNA.
  - UV is not energetic enough to induce ionization.
- UV has lower-energy wavelengths than do X-rays
  - has limited penetrating power to skin only
- A common effect of UV radiation is the formation of dimers between adjacent pyrimidines, commonly thymines
  - designated T^T) (Figure 15.10).
  - Any pyrimidine dimer can cause problems during DNA replication.
  - Most pyrimidine dimers are repaired because they produce a bulge in the DNA helix.
  - If enough are unrepaired, cell death may result.

Fig. 15.10
Production of thymine dimers by ultraviolet light irradiation



Chemical Mutagens

- A wide variety of chemicals exist in our environment, and many can have mutagenic effects that can lead to genetic diseases and cancer. Examples include:
  - Drugs
  - Cosmetics
  - Food additives
  - Pesticides
  - Industrial compounds
  - Chemical warfare agents such as mustard gas

Chemical Mutagens:

- Base modifiers covalently modify the structure of a nucleotide
  - For example, nitrous acid, replaces amino groups with keto groups ($-NH_2$ to $=O$)
    - Examples: Nitrogen mustards and ethyl methanesulfonate (EMS)

- Intercalating agents contain flat planar structures that intercalate themselves into the double helix
  - This distorts the helical structure
  - At replication, a template that contains an intercalated agent will cause insertion of a random extra base.
  - The base-pair addition is complete after another round of replication, during which the intercalating agent is lost.
    - Examples:
      - Ethidium Bromide
      - SYBR Safe

Homework Problems

- Chapter 15

- #1, 2, 3, 5, 9, 11, 14,

- DON'T forget to take the online QUIZ A
- DON'T forget to submit the online iActivity
  - "Overview A"