

# Mutagenic agents

Microbiology VI

# Mutagens

- A **mutagen** is a substance or agent that causes DNA impairment that results in the alteration of the DNA sequence.
- The alteration of the DNA sequence is known as **mutation**.
- Any agent causing mutation is called mutagen.
- Mutagens can be:
  - physical mutagens
  - chemical mutagens, or
  - biological mutagens.
- The ability of a substance to induce the alterations in the base pairs of DNA or mutation is known as **mutagenicity**.

## Types of Mutagens

### Radiation



UV  
(from sunlight)



X-rays  
(medical uses)



Carcinogens  
(e.g. cigarettes)



Processed foods  
& preservatives



Cosmetics &  
cleaning products



Viruses  
(e.g. HPV)



Bacteria  
(e.g. *Helicobacter*)

- A mutagen alters the specific pattern and sequence of the nucleic acid bases in the DNA resulting in the change in the protein transcribed from it.
- Though these changes may be inheritable or non-inheritable depending on their occurrence in somatic cells or germline cells.
- Some of the common **examples** of mutagens are:
  - UV light
  - X-rays
  - reactive oxygen species (ROS)
  - alkylating agents
  - base analogs,
  - Transposons , *etc.*

## Physical agents:

- **Ionizing radiations** such as X-rays, gamma rays and alpha particles cause DNA breakage and other damages.
- The most common lab sources include cobalt-60 and cesium-137.

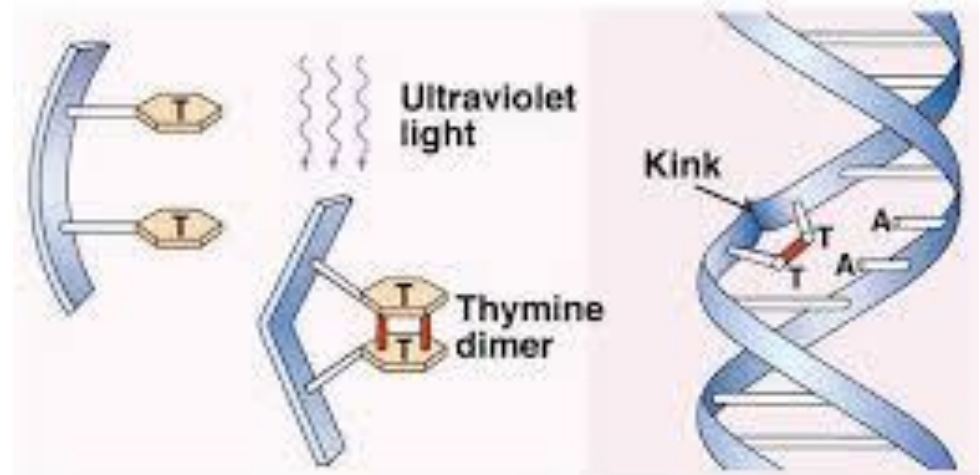
Ionizing radiations cause **breaks** in polysugar phosphate backbone of DNA

- This causes chromosomal mutations such as break, deletion, addition, inversion and translocation.

- **Ultraviolet radiations** with wavelength above 260 nm are absorbed strongly by bases
- It produces **pyrimidine dimers** which can cause **error in replication** if left uncorrected.
- **Radioactive decay** such as  $^{14}\text{C}$  in DNA which decays into nitrogen.

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## Pyrimidine Dimer



## Temperature


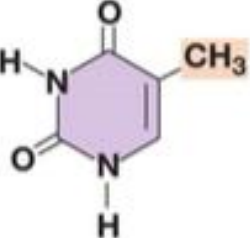
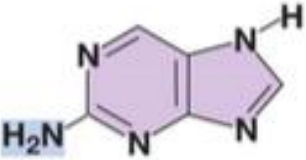
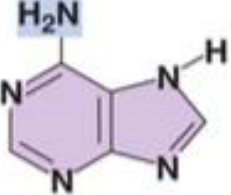
- The rate of all chemical reactions are influenced by temperature.
- It is reported that the rate of mutation is increased due to increase in temperature.
- For example, an increase of 10°C temperature increases the mutation rate two or three fold.
- Temperature probably affects both thermal stability of DNA and the rate of reaction of other substances with DNA.

## Chemical Agents

- Many chemical substances have been responsible to increase the mutability of genes.
- Some of the known chemical mutagens include:
- **Reactive oxygen species (ROS):**
- Such as:
  - superoxide
  - hydroxyl radicals
  - hydrogen peroxide
- large number of these highly reactive species are generated by normal cellular processes.

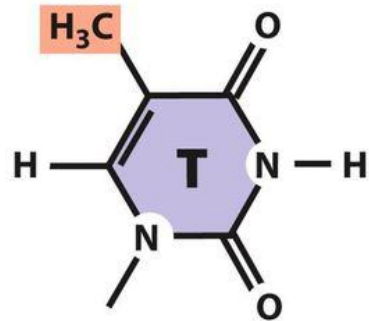


- **Base analogs:**
- These agents possess structural similarities to the bases i.e., purines and pyrimidines.
- Ex: **5-Bromouracil (5-BU)** and aminopurine.
- Due to structural similarities of these agents with the DNA bases, base analogs get incorporated in the DNA structure during the process of replication.
- **Aminopurine** is similar to **adenine** and can form a base pair with C or T (though base pairing with C is rare).

Analog	Substitutes for
 <p data-bbox="765 654 993 689">5-Bromouracil</p> <p data-bbox="653 696 697 732">(a)</p>	 <p data-bbox="1199 654 1338 689">Thymine</p>
 <p data-bbox="765 1072 993 1108">2-Aminopurine</p> <p data-bbox="653 1115 697 1150">(b)</p>	 <p data-bbox="1209 1072 1338 1108">Adenine</p>

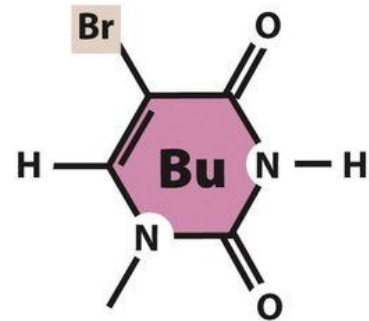
- **5-Bromouracil** exhibits tautomeric forms.
- Each of the tautomeric combines with different base pairs.
- **Keto form** of the 5-bromouracil replaces **thymine** in the DNA and forms a pair with the **adenine** in the DNA
- **Enol forms** a complementary base pair with **guanine**.
- 5-Bromo uracil thereby results in a point mutation.
- Thus, 5-Bromouracil changes base pair from A-T to G-C or from a G-C to an A-T.

## Normal base



## Thymine

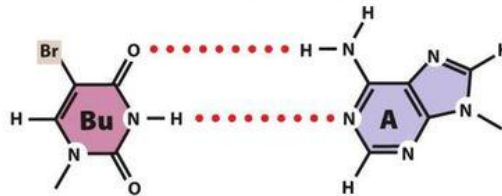
## Base analog



## 5-Bromouracil

Figure 18.16a  
Genetics: A Conceptual Approach, Fifth Edition  
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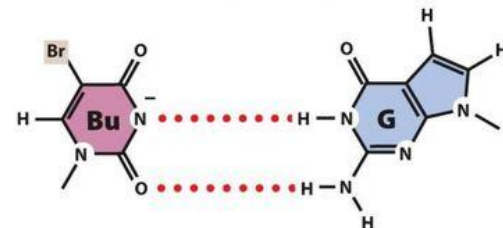
### Normal pairing



### 5-Bromouracil

### Adenine

### Mispairing

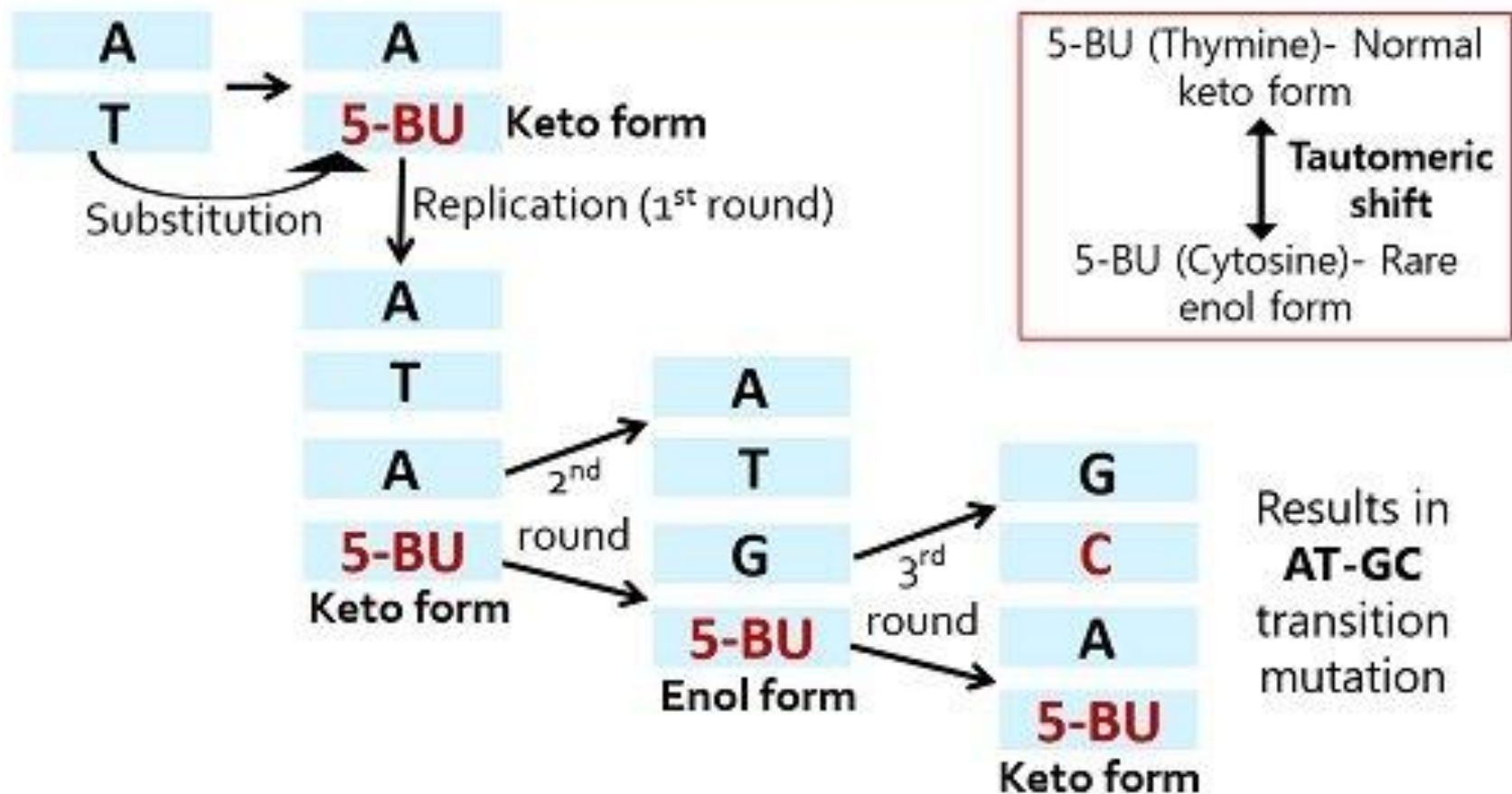


### 5-Bromouracil (ionized)

### Guanine

Figure 18.16b  
Genetics: A Conceptual Approach, Fifth Edition  
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## Mechanism of Base Analog Mutation by 5-Bromouracil



- **Intercalating agents.**
- Intercalating agents are the molecules that have a hydrophobic heterocyclic ring structure and resemble the ring structure of base pairs.
- These agents place themselves in the DNA helix, which eventually interferes with the replication, translation, and transcription resulting in mutation, most commonly frameshift mutation.
- **Ex:** Ethidium bromide, proflavine, acridine orange, actinomycin D, or daunorubicin, etc.
- Amongst these, Daunorubicin along with Epirubicin, Epirubicin, and Mitoxantrone are some of the common anti-cancer or antineoplastic drugs.

# Effect of Intercalating agents on DNA:

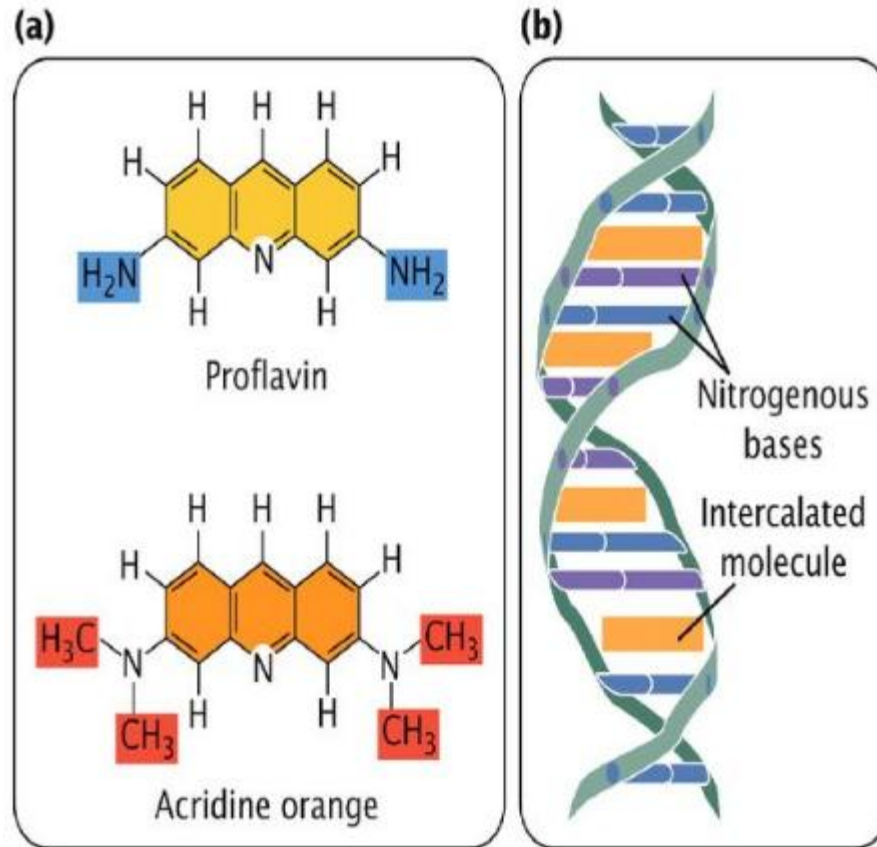
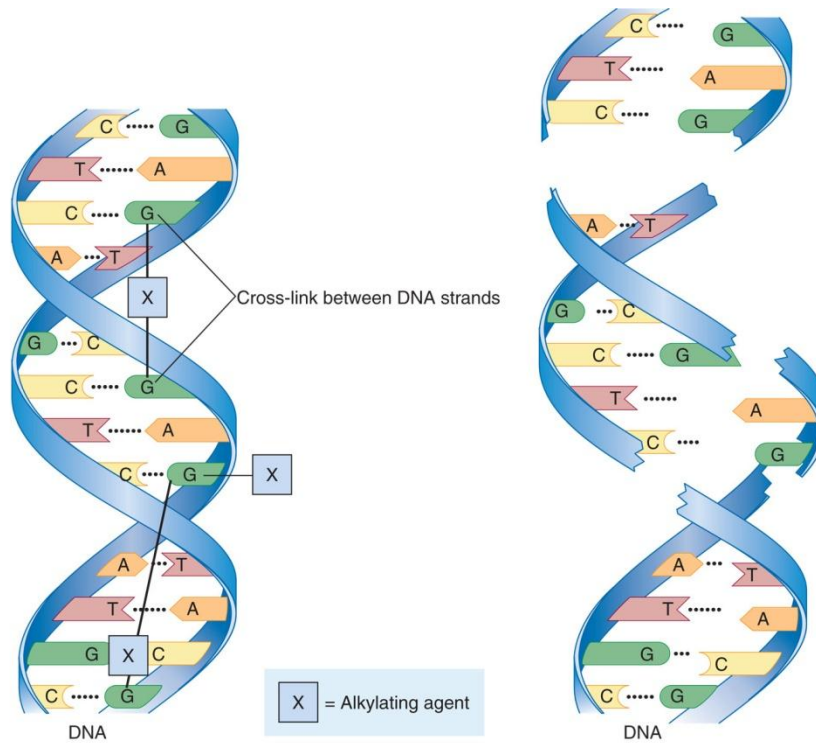


Fig. 17-22 *Genetics, Second Edition* © 2005 W.H. Freeman and Company

- **Alkylating agents.**
- These agents induce alkyl groups in DNA resulting in DNA damage.
- The introduction of the alkyl groups increases ionization that results in base-pairing errors and eventually inducing gaps in the DNA strand.
- Ex: ethylnitrosourea, mustard gas, vinyl chloride, Methylhydrazine, Busulfan, Carmustine, lomustine, Dimethyl sulfate, Temozolomide, *Dacarbazine*, Ethyl ethane sulfate, and Thio-TEPA.
- Though during the DNA repairing process, these agents can be removed from the DNA by the process of depurination. Depurination is a non-mutagenic process.





(a) Alkylation occurring during G<sub>0</sub> (resting) phase of cell cycle

(b) Strand breaks occurring when DNA replicates during S phase of cell cycle

- **Deaminating agents:**
- such as **nitrous acid** can cause transition mutations by converting cytosine to uracil.
  
- **Metal ions:**
- Mineral ions like nickel, chromium, cobalt, cadmium, arsenic, chromium and iron, generate reactive oxygen species (ROS) that cause DNA hypermethylation, thereby promoting DNA damage and hindering the DNA repair process.
  
- **Polycyclic aromatic hydrocarbon (PAH):**
- when activated to diol-epoxides can bind to DNA and form adducts.
  
- **Benzene:**
- an industrial solvent and precursor in the production of drugs, plastics, synthetic rubber and dyes.

- **Nitrosamines:**
- are an important group of mutagens found in tobacco
- may also be formed in smoked meats and fish via the interaction of amines in food with nitrites added as preservatives.
  
- **Alkylating agents** include mustard gas and vinyl chloride.
  
- **Alkaloid:**
- from plants such as from Vinca species, may be converted by metabolic processes into the active mutagen or carcinogen.