# MUTATION

One of characters of genetic material means error in it which affects expression & replication.

**Classification of mutation:**

1-According to origin:

Spontaneous mutation - Induced mutation

2- According to cell type:

Somatic mutation - Gametic mutation

3- According to type of change:

Substitutional mutation - Frame shift mutation

## 1. According to origin

**a. Spontaneous Mutations:**

Arising from nature due to: effect of natural elements as cosmic rays, radioactive minerals, chemical & thermal element. Random error in genetic material by incorrect base inserted & rarely by DNA polymerase.

Occur with average 1\100 million ($10^{-8}$) cell divisions (higher in Drosophila and humans, i.e. 1/1,000,000 to 1/100,000 ($10^{-6}$ to $10^{-5}$) mutations per gamete formed).

**b. Induced Mutations:**

Arising due to artificial factor: abnormal environmental factor as ionizing radiation (X-ray) & non ionizing radiation (UV & heat). Also chemical mutagens cause it.

## 2. According to cell type

**a. Somatic mutations:**

Occur during replication of DNA in somatic cells. It not transmitted to future generations.

N.B: mutation in single cell in a tissue may not impair the organism, even if it is harmful (except cancer cell)

**b. Gametic Mutations**:

Occur in gametic cell. Transmitted to offspring so more important than somatic mutations.

Type of mutant allele determines its effect: Dominant autosomal mutations will be expressed phenotypically in the first generation. Recessive autosomal mutations may go unnoticed (because of heterozygosity) for many generations until 2 recessive allele exist. Sex-linked recessive mutations in heterogametic female expressed in hemizygous male offspring.

## 3. According to type of change

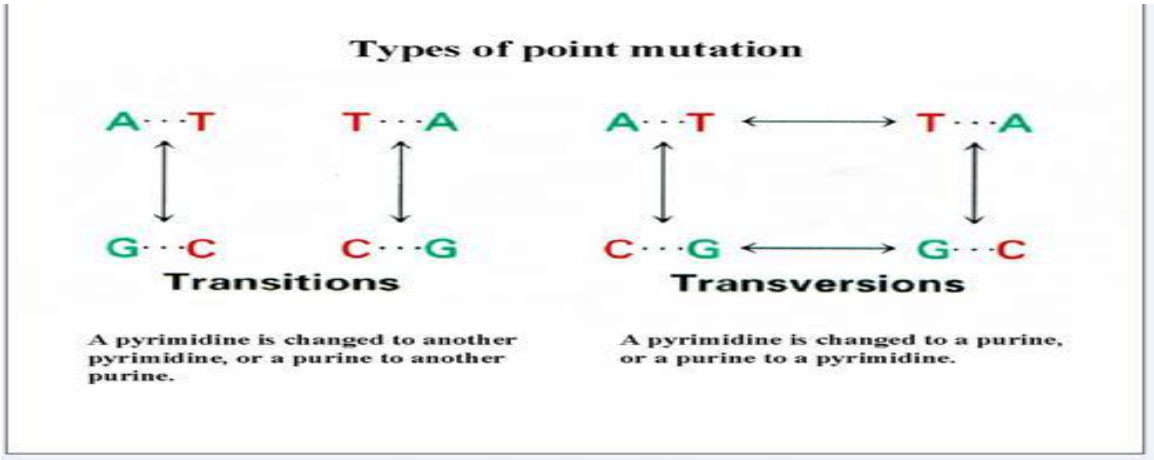
### a. Substitutional Mutation:

Substitution of a single nucleotide (point mutation) leads to change the nucleotide; changing one amino acid into another result in change in protein (missense mutation).

Types:

Transition: if pyrimidine replaces pyrimidine or purine replaces purine.

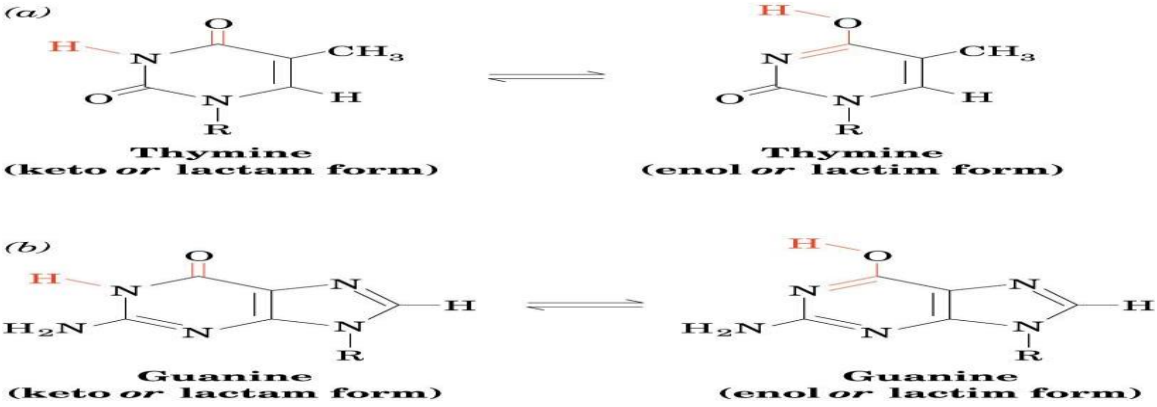
Transversion if purine and a pyrimidine are interchanged.




### Tautomeric forms:

Presence of several chemical forms of purines and pyrimidine's suggested by Watson and Crick. Caused by only a single proton shift in the molecule result in base pairing changes or mutations. It involve: change of keto group (O=) in thymine and guanine to enol group (OH) or change of amino group (NH2) in cytosine and adenine to imino group (NH).

The changed tautomer is capable of hydrogen bonding with a normally non complementary base during replication result in A-T pair is replaced by a G-C pair, or vice versa.




**b. Frameshift Mutation:**

Insertion or deletion of nucleotides lead to change in frame read downstream to mutation result in incorrect protein (nonsense mutation).

For example, an insertion of an extra G between nucleotides 6 and 7 would give:

⇩

**AUG UAU CCA UAU CCA UAG**

**fMet Tyr Pro Tyr Pro Term**

⇩

**AUG UAU GCC AUA UCC AUA**

**fMet Tyr Ala Ile Ser Ile**

# Mutagens

Mutagens are agents which cause a direct or indirect change in the base sequence of DNA.

Change can occur by: Insertion of one or more extra bases during replication & not removed or insertion of tautomeric form of a base. Deletion of one or more bases during replication. Chemical alteration of inserted base (change of base pairing)

**Types of Mutagens:**

A- Chemical mutagen.

B-Radiation mutagen.

## A. Chemical Mutagens

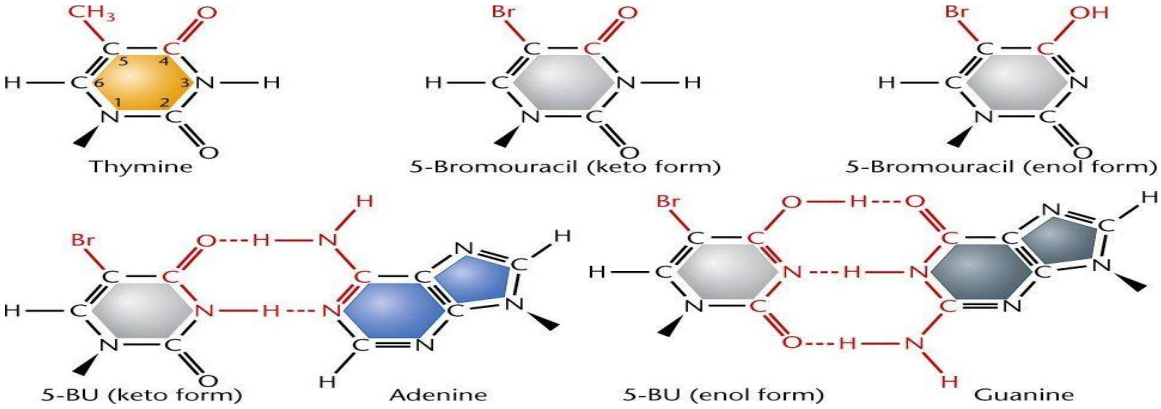
### A.1.BaseAnalogues:

They are substitutes of purines or pyrimidine's during DNA synthesis, it include:

1. halogenated derivatives of uracil (methyl group in C-5 of pyrimidine ring in Thymine replaced with bromide, chloride, and iodide) as in 5-bromouracil, 5-chlorouracil and 5- iodouracil.

2. Analogue of Adenine (2-amino purine).

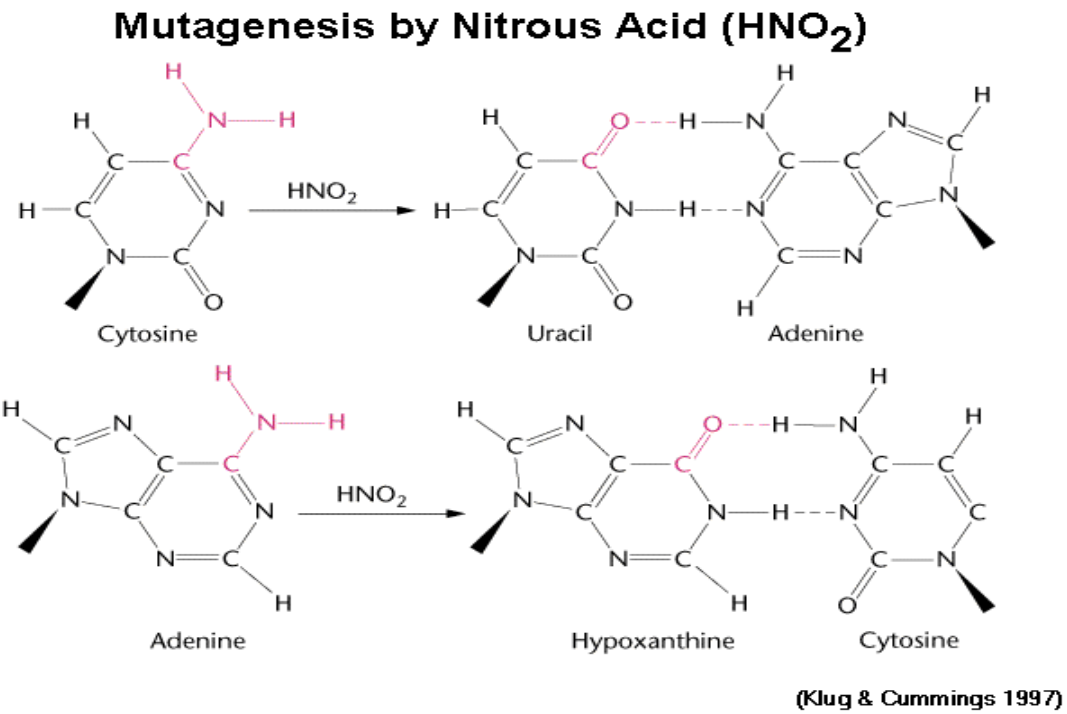
Presence of (Br) increases probability of tautomeric shift, if (5-BU) incorporated into DNA in place of (T) & occur tautomeric shift (A-T to G-C transition).




**A.2. Nitrous Acid**:

Oxidation of deaminating purines and pyrimidine's lead to conversion of the amino group (NH2) of cytosine and adenine to a keto group (O=) result in change in base pairing.

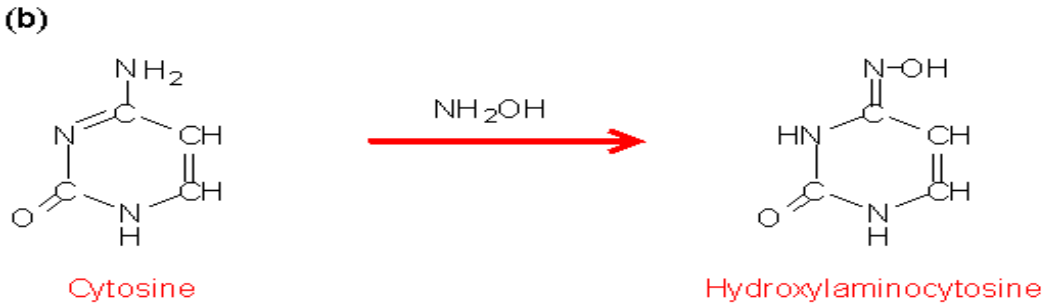
Cytosine change to uracil pairs with adenine instead of guanine (G-C to A-T transition); Adenine change to hypoxanthine pairs with cytosine instead of thymine (A-T to G-C transition).




(Klug & Cummings 1997)

## A.3. Hydroxylamine (NH2OH):

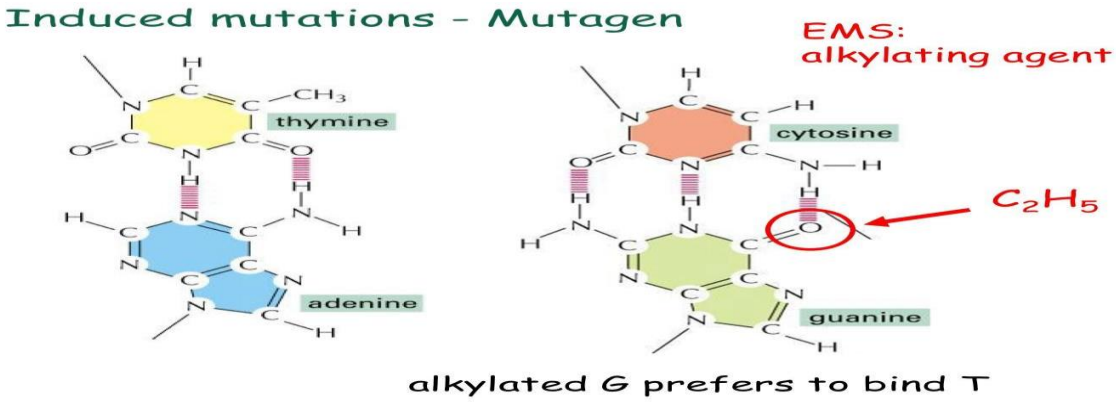
Reacts specifically with cytosine by adding a hydroxyl group (OH) to its amino group change it to hydroxyl amino cytosine, undergo tautomeric shift pair with adenine instead of guanine (G-C to A-T transition).




## A.4. Alkylating Agents:

As mustard gases cause alkylation by donating an alkyl group such as CH3- or Ch3-Ch2- to amino or keto groups in nucleotides.

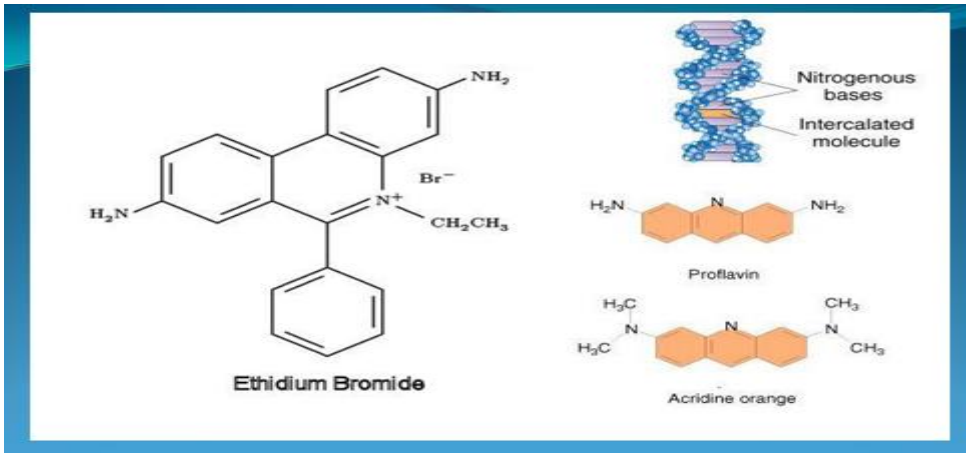
e.g.: ethyl methane sulphonate (EMS) alkylates keto group at C-6 of guanine make it pair with Thymine instead of Cytosine (G-C to A-T transition); and keto group at C-4 of thymine make it pair with Guanine instead of Adenine (A-T to G-C transition).




**A.5. Acridine Dyes:**

As proflavine and acridine orange intercalate or wedge between purines and pyrimidine of intact DNA. Intercalation before replication leads to insertion of an extra base during replication (insertion mutation); while intercalation during replication lead to base will be missed (deletion mutation).

N.B: Both are considered Frame shift mutations.




## B. Radiation Mutation

All radiation can be mutagenic, energy varies inversely with wavelength. Non ionizing have long wave length (low energy) so not strong to penetrate tissue affect surface tissue e.g: heat & UV. Ionizing radiation has short wave length (high energy) strong enough to penetrate deeply into tissue causing ionization of molecule along their path e.g: X-ray & gamma ray.

### B.1. Non-ionizing radiation:

### B.1.a. Heat:

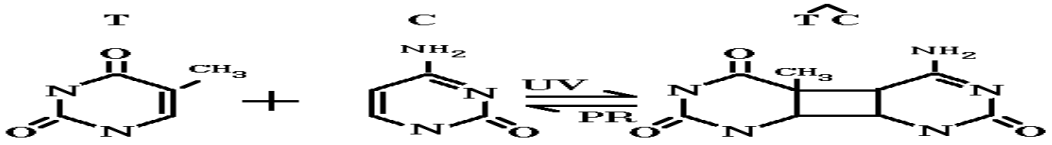
It causes deamination of cytosine to form uracil, as does nitrous acid, causing C-G to T-A transition. It also causes transversions from G-C to C-G by some unknown mechanism.

Over 100 heat-induced mutations occur in human cell each day, but the majority of it repaired by one of the DNA repair mechanism.

**B.1.b. Ultraviolet Radiation (UV):**

The major effect of UV light is on pyrimidines, leading to the formation of pyrimidine dimers. It form chemical bonds between two adjacent pyrimidine molecules (between two adjacent thymine) leading to thymine dimers. Dimerized bases cannot form hydrogen bonds with the complementary purines on the opposite DNA strand inhibits normal replication and transcription prevents the transmission of the altered genome from parent to offspring.

N.B: The inhibitory effect of UV seems to be responsible for the killing effects of this radiation on microorganisms.




• Human skin disorder called xeroderma pigmentosum (XP) is caused by an autosomal recessive gene, and is associated with abnormal pigmentation of the skin. Exposure of patients to sunlight results in malignant growth of the skin. More than one gene responsible for

this condition, which is due to failure of one of the DNA repair mechanisms which in normal people repair the dimers.

**B.2. Ionizing Radiation:**

High energy rays at high speed transform stable molecules to free radicals and electrically charged reactive ions which directly or indirectly affect the genetic material altering purines and pyrimidine's in DNA resulting in point mutations; also capable of breaking chromosomes resulting in a variety of aberrations.

Experiments on the effect of X-rays on Drosophila shown that there is linear relationship between X-ray dose level and the frequency of mutation. Acute radiation (single large dose) more mutagenic; such as X- rays or nuclear explosion can cause leukemia. While chronic radiation (same dose divided into smaller exposure) is less mutagenic like natural or background radiation (cosmic rays).