Quadrant II – Transcript and Related Materials

Programme: Bachelor of Science (Third Year)

Subject: Botany

Paper Code: BOC 108

Paper Title: Cytogenetics and plant breeding

Unit: VII

Module Name: Mutagens- Chemical

Module No: 35

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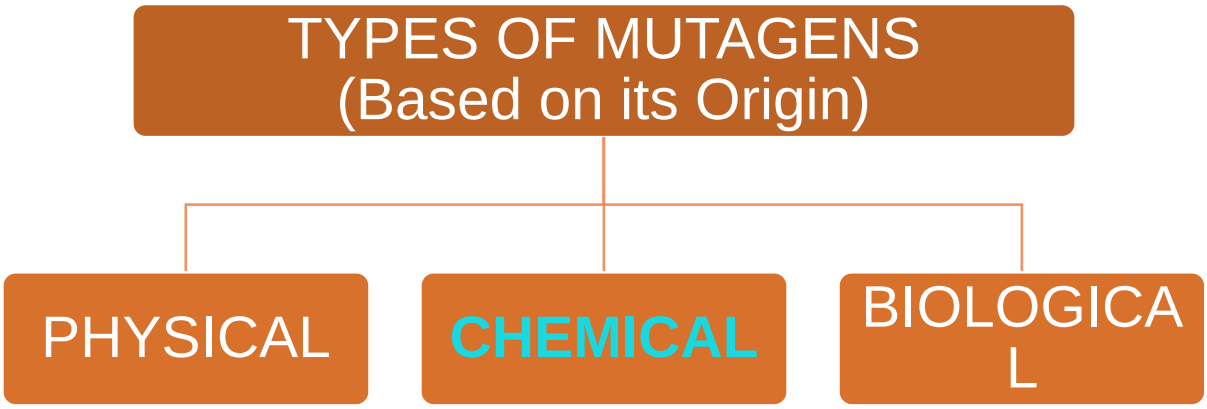
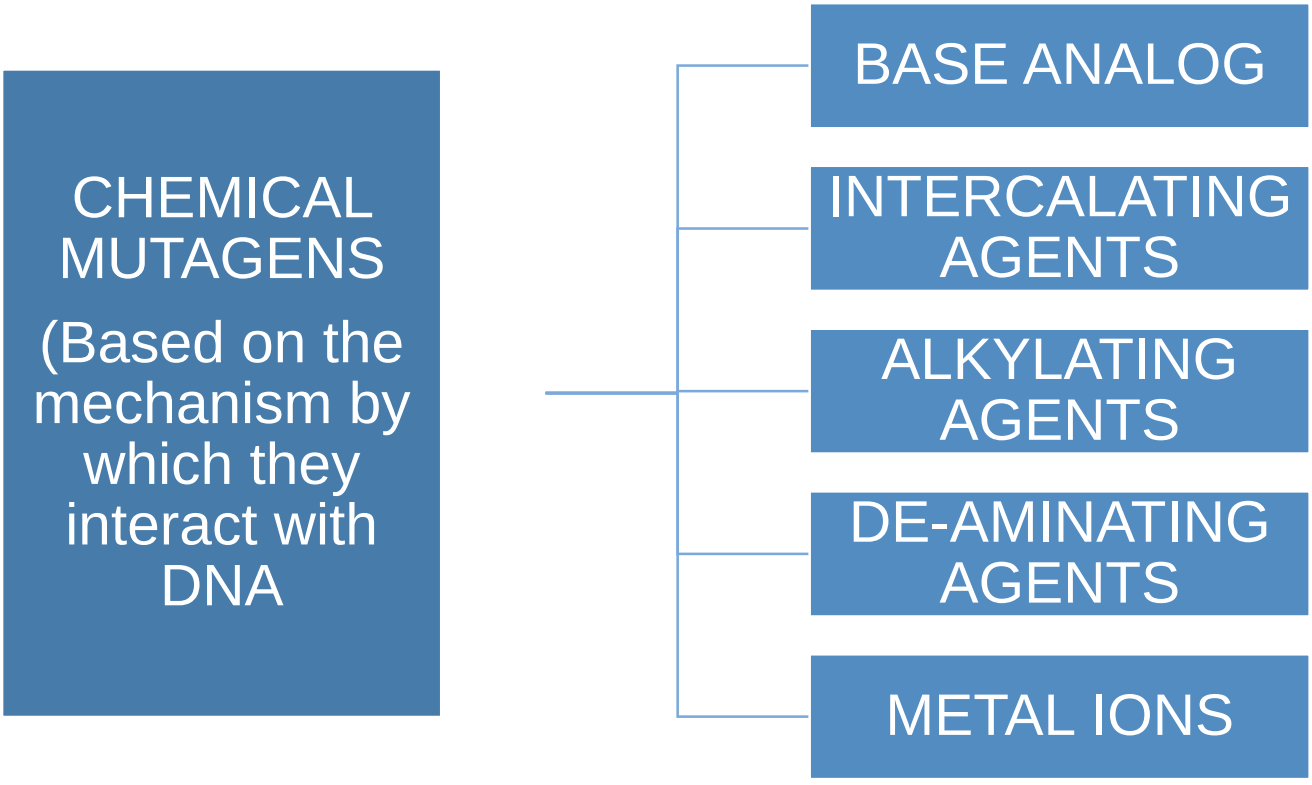
Notes

A **mutagen** is defined as any physical or chemical substance that can change the genetic material of an organism, thereby causing a mutation



Introduction

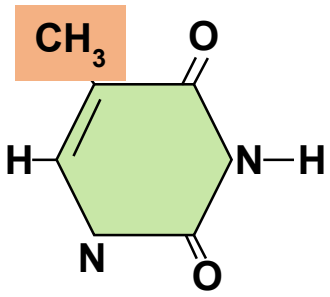
- DNA is the genetic material made up of nitrogen-containing bases (cytosine [C], guanine [G], adenine [A], or thymine [T]) that are covalently bonded with Deoxyribose sugar and a phosphate group.
- The typical pattern of nucleic acid bases encodes all the genetic information of a cell.
- A mutagen alters the specific pattern, sequence of the nucleic acid bases in the DNA resulting in the change in the protein.
- These changes may be inheritable or non-inheritable depending on their occurrence in germline cells or somatic cells respectively.
- Chemicals are actually dangerous for the entire world.
- The first mutagenic effect of the nitrogen mustard was reported by charlotte Auerbach in 1942. (Used during World war 1 & 2).
- **DEFINITION OF CHEMICAL MUTAGENS**
- Chemicals that cause mutations if cells are exposed to them in high concentration and/or prolonged periods of time.
- A substance that can alter a base that has already been incorporated into DNA and change its hydrogen bonding specificity.



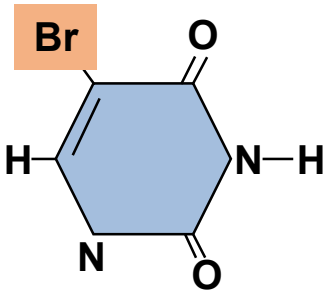
1. BASE ANALOGUE:

- These are chemicals which are structurally similar to DNA nitrogen bases- purine and pyrimidine.
- They can get incorporated into DNA at the time of replication and can cause wrong base pairing resulting in mutations.
- An incorrect base pairing results in transitions or transversions after DNA replication.
- 5-bromouracil **(5BU)** and 2- amino purine **(2AP).**
- 5BU is similar to thymine, but it has bromine
- at the C5 position, whereas thymine has CH3
- group at C5 position.
- The presence of Br in 5BU enhances its tautomeric shift from keto form to the enol form

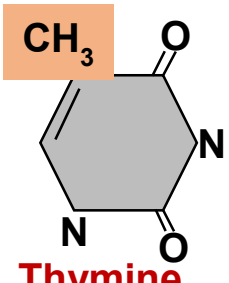
Normal nucleotide base Thymine



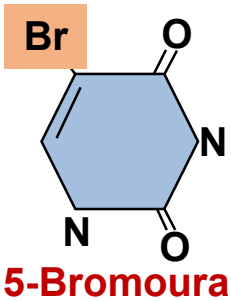
Analogue 5'-bromouracil



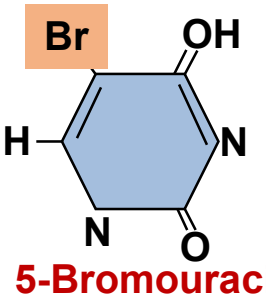
- The change or shift of H atoms from one position to another either in a purine or in a pyrimidine base is known as **tautomeric shift** and such process is known as **tautomerization**.
- The base which is produced as a result of tautomerization is known as **tautomeric form or tautomer**.



Thymine



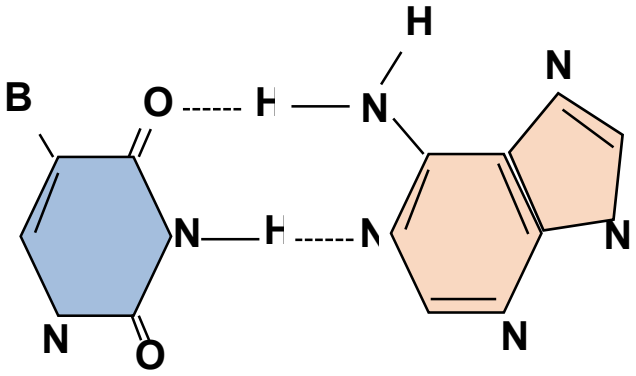
5-Bromouracil (keto form)



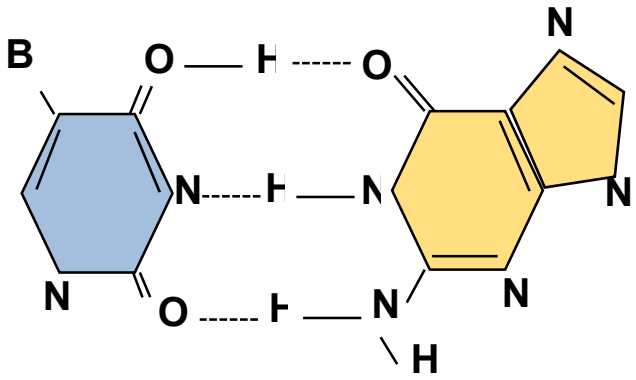
5-Bromouracil (enol form)

The pairing of adenine and 5-bromouracil.

The bromouracil replaces the adenine and pairs with the guanine during replication.



5BU –Keto Adenin



5BU –Enol Guanin

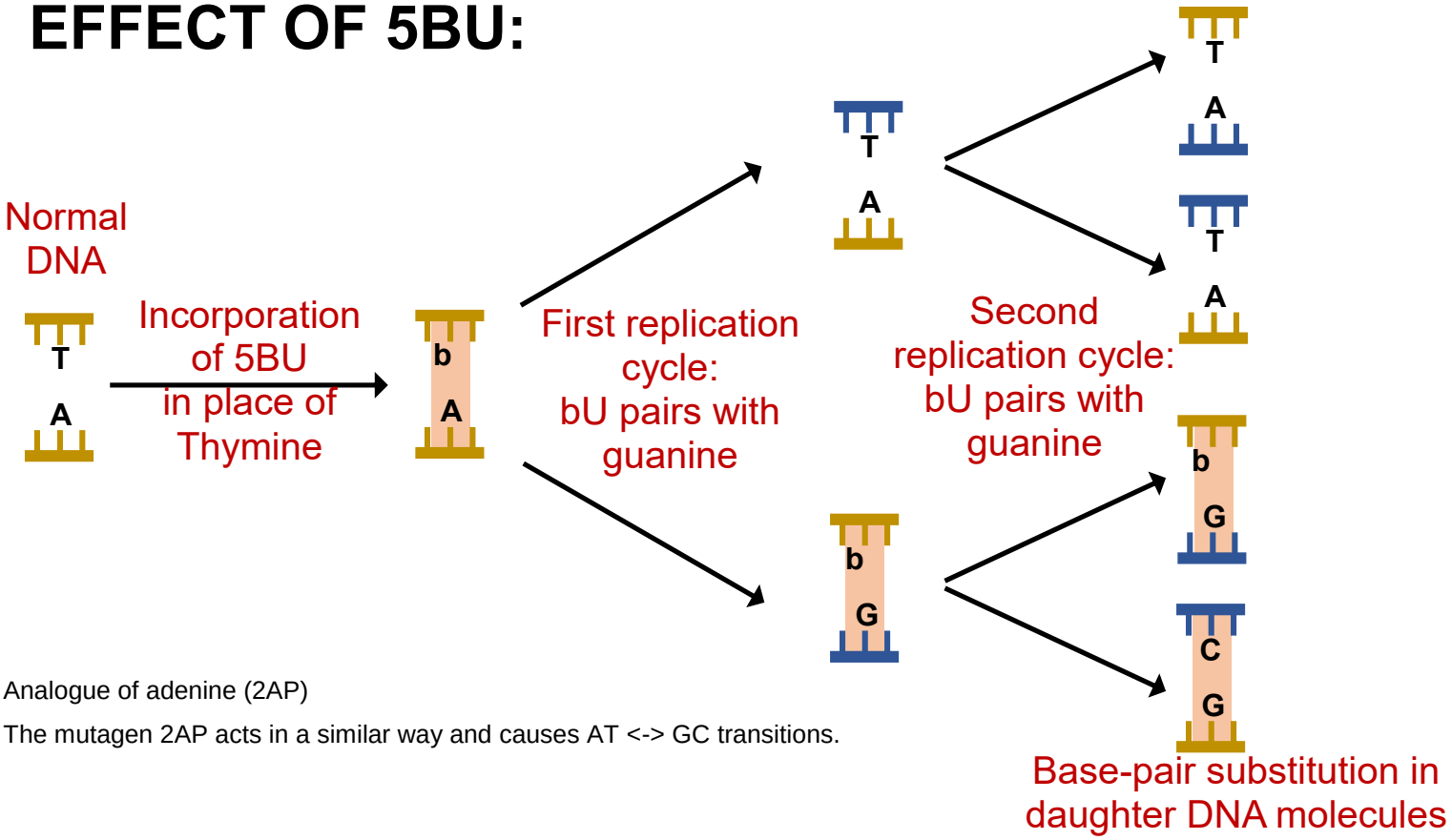
- The keto form is a usual and more stable form, while enol form is a rare and less stable or short lived form.

Mechanism

- Due to tautomerization, the amino group (-NH2) of cytosine and adenine is converted into imino group (-NH).
- Similarly keto group (C = 0) of thymine and guanine is changed to enol group (-OH).
- 5BU is similar to thymine, therefore, it pairs with adenine (in place of thymine).
- A tautomer of 5BU will pair with guanine rather than with adenine.

- Since the tautomeric form is short-lived, it will change to keto form at the time of DNA replication which will pair with adenine in place of guanine.
- In this way it results in AT GC and GC —> AT transitions.
- Thus the TA base pair is replaced by the GC base pair at the end of the replication and this happens because of the tautomeric shift of 5-BU from ‘enol’ to ‘keto’ form.

EFFECT OF 5BU:



Analogue of adenine (2AP)

The mutagen 2AP acts in a similar way and causes AT <-> GC transitions.

2. INTERCALATING AGENTS:

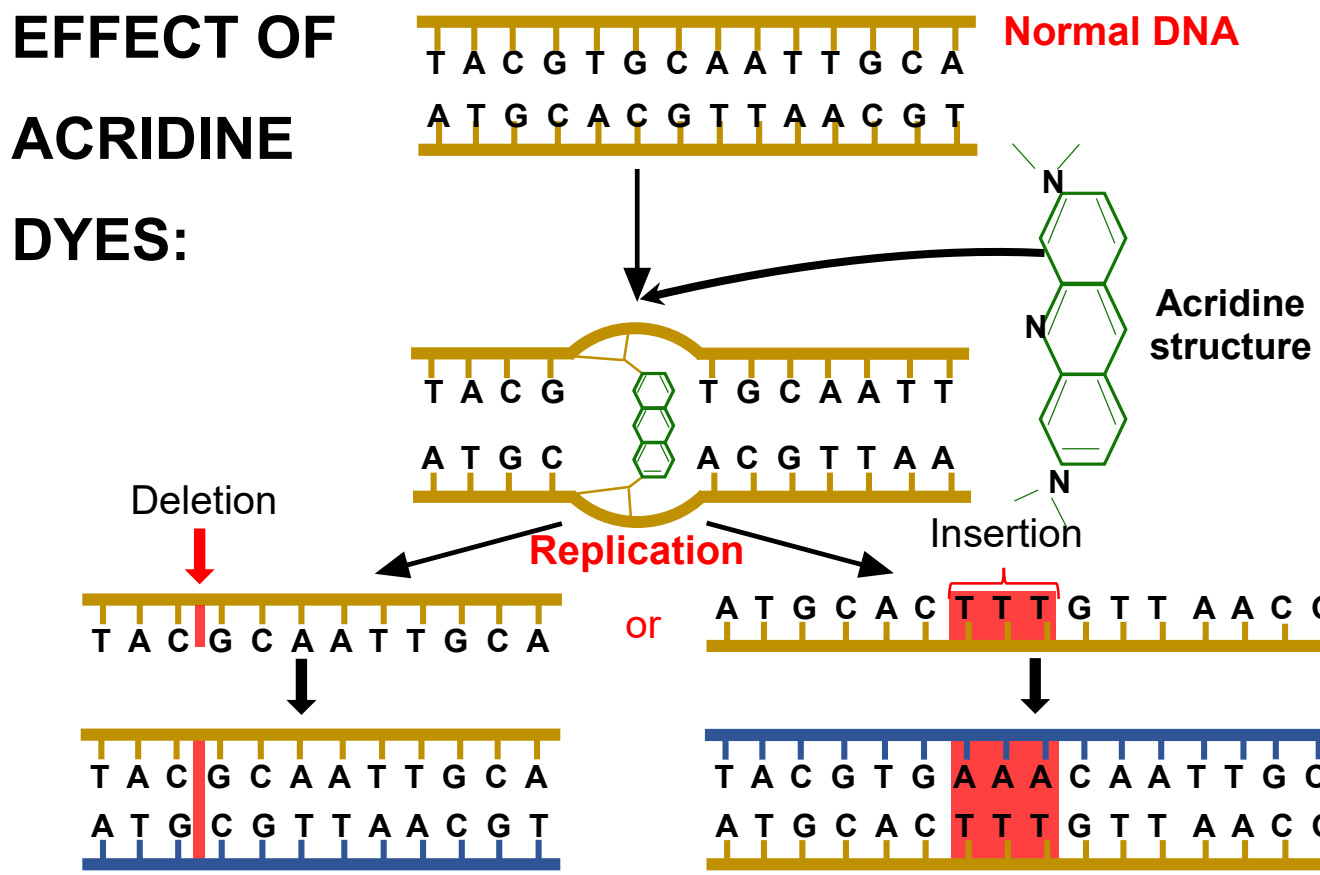
- The chemical molecule intercalate in between two base pair in Double stranded DNA helix and hence disrupt the structure of DNA at that position.
- If it is incorporated during the replication, it can cause **frameshift** mutation. It may also block transcription.
- Examples; Acridine orange, ethidium bromide, proflavin, benzopyrene, acridine yellow, acriflavin.

MECHANISM:-

- All are flat, multiple ring molecules which interact with bases of DNA and insert between them.
- This insertion causes a **"stretching"** of the DNA duplex and the DNA polymerase is **"fooled"** into inserting an extra base opposite an intercalated molecule.
- The result is that intercalating agents cause frameshift.

ACRIDINE DYES:

- Acridine dyes get inserted between two base pairs of DNA and lead to addition or deletion of single or few base pairs when DNA replicates. Thus, they cause frameshift mutations and for this reason acridine dyes are also known as **frameshift mutagens.**
- Proflavin is generally used for induction of mutation in bacteriophages and acriflavin in bacteria and higher organisms.



3. ALKYLATING AGENTS:

- They induce mutations especially transitions and transversions by adding an alkyl group (either ethyl or methyl) at various positions in nitrogen bases of DNA.
- The agents induce base-pairing errors by increasing ionization and produces gaps in the DNA strand.
- Examples:- Ethyl Methane Sulphonate (EMS) , Methyl Methane Sulphonate (MMS) ,Ethylene sulphonate, Mustard or Sulphur gas AT-GC transition and GC-AT transition.

OTHER EXAMPLES OF ALKYLATING AGENTS

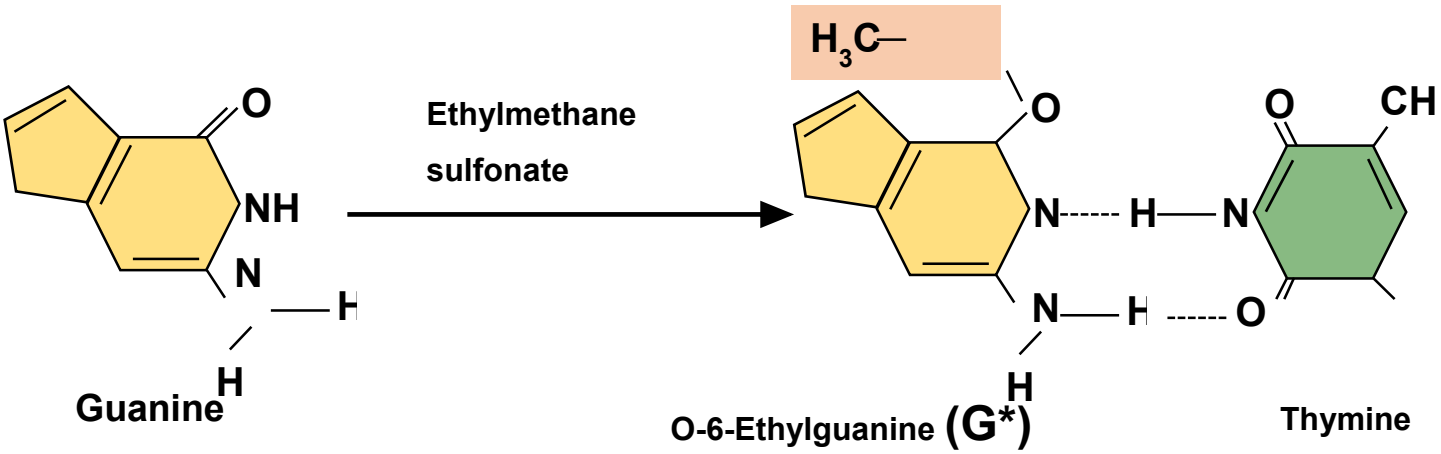
- Ethylnitrosourea, mustard gas, vinyl chloride, Methylhydrazine , Temozolomide, Dacarbazine, Busulfan, Thio-TEPA, Carmustine, lomustine, Dimethyl sulfate , Ethyl ethane sulphate.

NOTE

- “When nitrities (food preservatives) added to smoked meat, it forms nitrosamine like mutagen that can break DNA or creates DNA cross-linking.”
- The alkylated purine bases are removed by the phenomenon called depurination, although depurination is not mutagenic and can be repaired by the DNA repair pathway.
- The effect of alkylating agents resembles those of ionizing radiations, they are also known as **radiomimetic chemicals.**
- Alkylating agents can cause various large and small deformations of base structure resulting in base pair transitions and transversions.

ALKYLATING AGENTS:

Add ethyl (CH_2 CH_3) or methyl (CH_3) groups



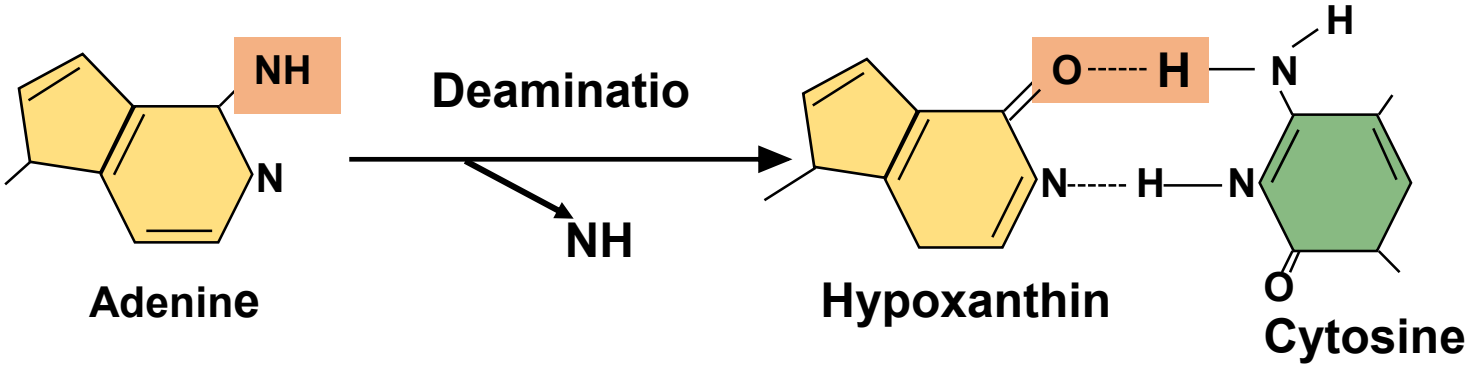
EMS adds an ethyl group to guanine or thymine. Modified G pairs with T above, and modified T pairs with G.

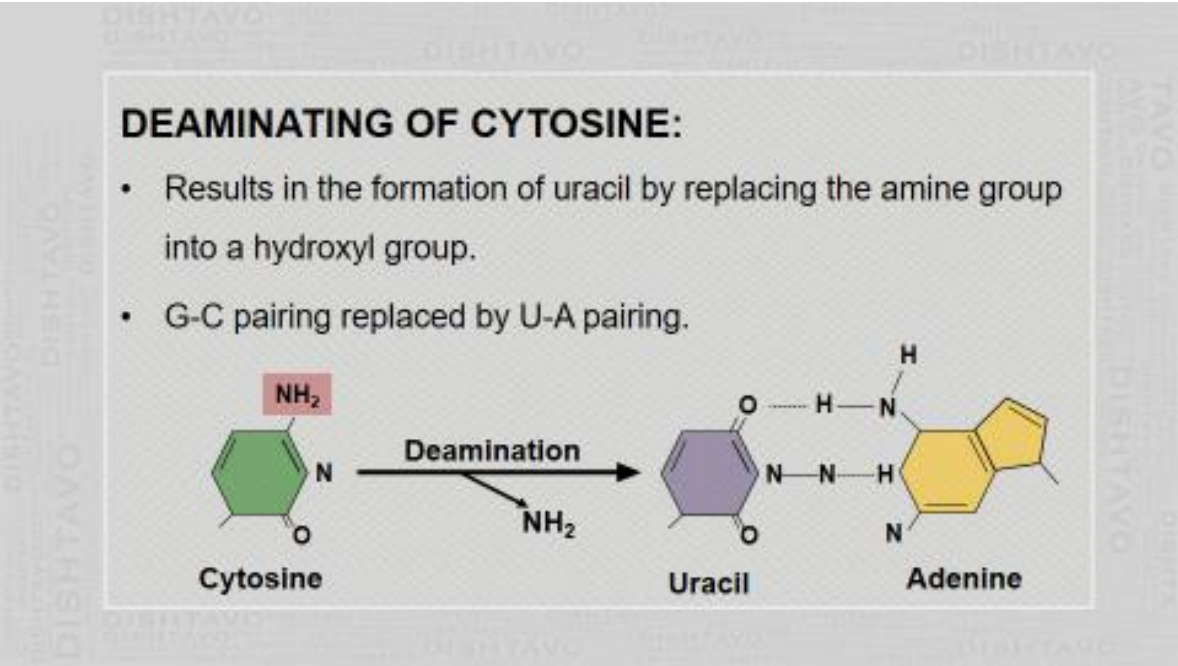
4. DEAMINATING AGENTS:

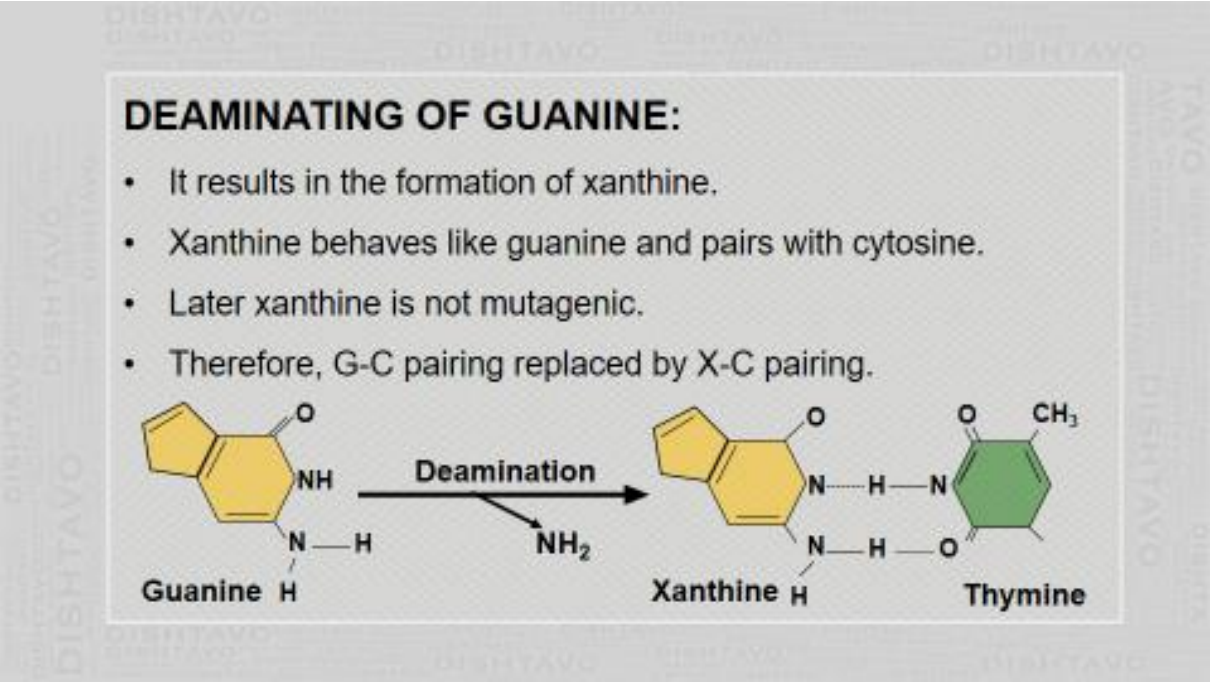
- Deamination is the removal of amino group from a molecule.
- Chemicals after incorporation into DNA change the specificity of H-bonding.
- Examples:- Deamination of adenine, Deamination of guanine, Deamination of cytosine, Hydrazine & Nitrous oxide.

DEAMINATING OF ADENINE:

- It results in the formation of hypoxanthine.
- It paired with cytosine instead of thymine.
- Replacing A-T pairing by G-C pairing.







- **Nitrous Oxide (HNO_2):**

Nitrous oxide converts the amino group of bases into keto group through oxidative deamination. The order of frequency of deamination (removal of amino group) is adenine > cytosine > guanine.

- **Hydroxylamine (NH_2OH):**

It hydroxylates the C4 nitrogen of cytosine and converts into a modified base via deamination which causes to base pairs like thymine. Therefore, GC pairs are changed into AT pairs.

4. METAL IONS:

- Metal ions also dangerous to our DNA as it acts in varieties of different ways.
- They work by producing ROS (reactive oxygen species), hindering the DNA repair pathway, cause DNA hypermethylation or may directly damages the DNA.
- Example:- Nickel, chromium, cobalt, cadmium, arsenic, chromium and iron.

Group of Mutagen	Name of Chemical	Mode of Action
1. Base Analogues	5 Bromouracil 2 Amino Purine	AT GC Transitions
2. Intercalating Agents	Acridine Dyes (Acriflavin , Proflavin)	Deletion, addition and frameshift.
3. Alkylating Agents	EMS , MMS , EES & EI	AT GC Transitions GC AT Transitions
4. Deaminating Agents	Hydrazine & Nitrous oxide.	AT GC Transitions GC AT Transitions
5. Metal Ions	Ni, Cr, Co, Cd, Ar, and Fe.	ROS damage DNA