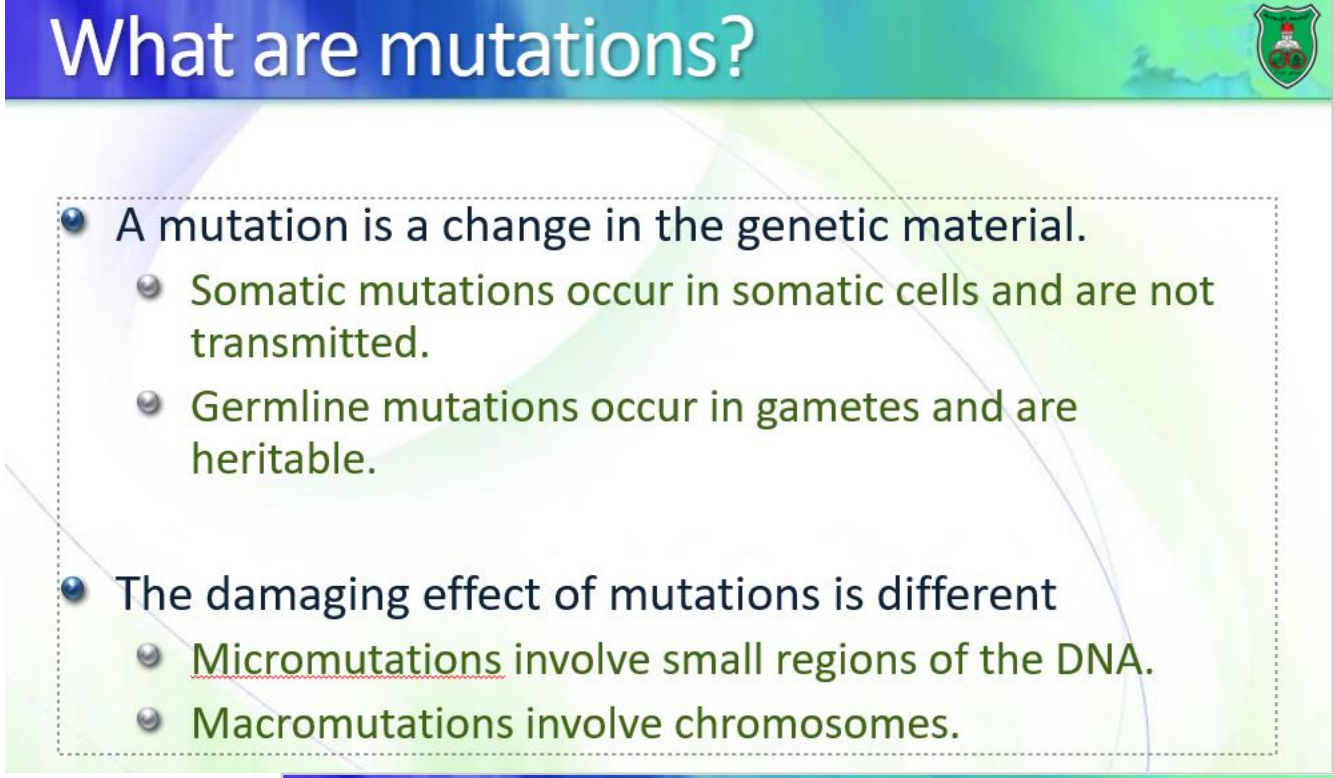
DONE BY anonymus

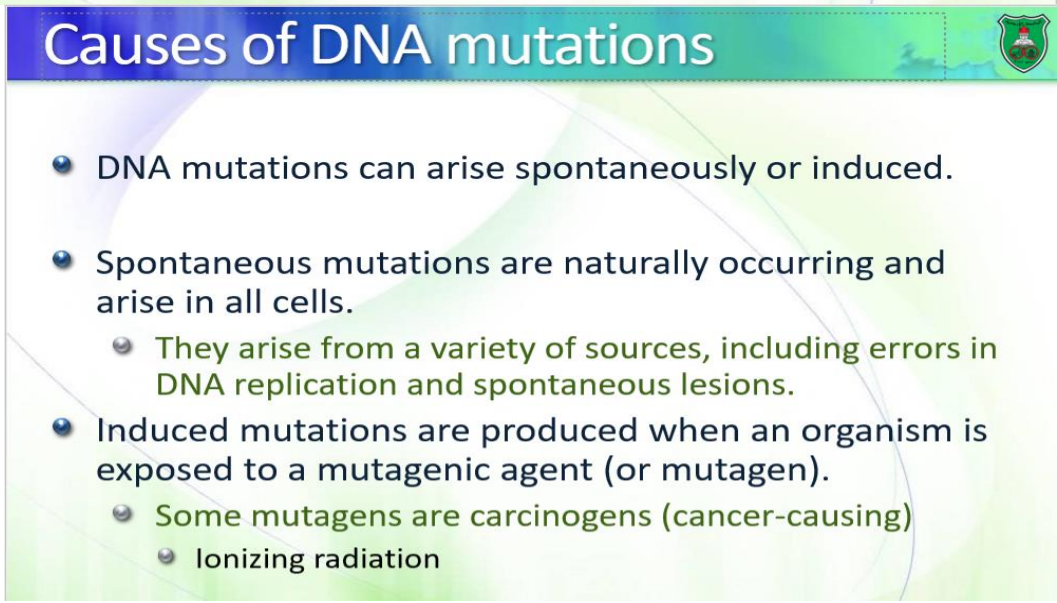
Mutations: anything that happens in the DNA
Somatic mutations any mutation that occurs in any cell other than germline cells(sperm/eggs).

-We can classify the mutations according to their size:
1- micromutations:involve changes in nucleotide or few nucleotides we can observe them using pcr.
2- macromutations: large and can be observed under the light microscope.



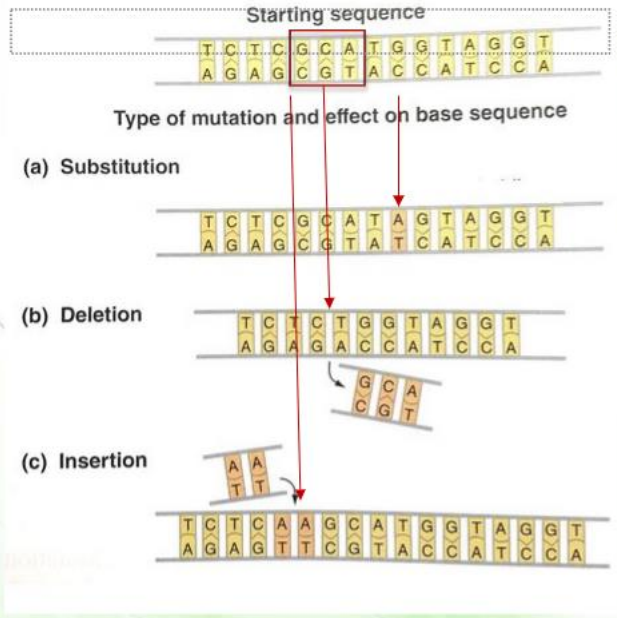
Also We can classify DNA mutations in how they happen:
1-spontaneous: they just happen because of DNA replication mistakes or just happen from bad luck or something inside the cell like reactive oxygen species hitting the chromosome.

2-Induced: from external factors that cause mutations and these are called mutagenic agent or mutagen
Some are carcinogens examples of them:
Ionizing radiation like UV light or sunlight or Xray.



-Macromutations occur at the level of chromosome
-It can be a duplication of a whole region of the chromosome it occurs at the same chromosome. LOOK AT A
-Deletions removal of a whole region of the chromosome region B for ex. Figure B
-Inversion of DNA segments exchanging the location between segments in the same chromosome. C
-Translocation involves 2 chromosomes exchanging segments between them. D

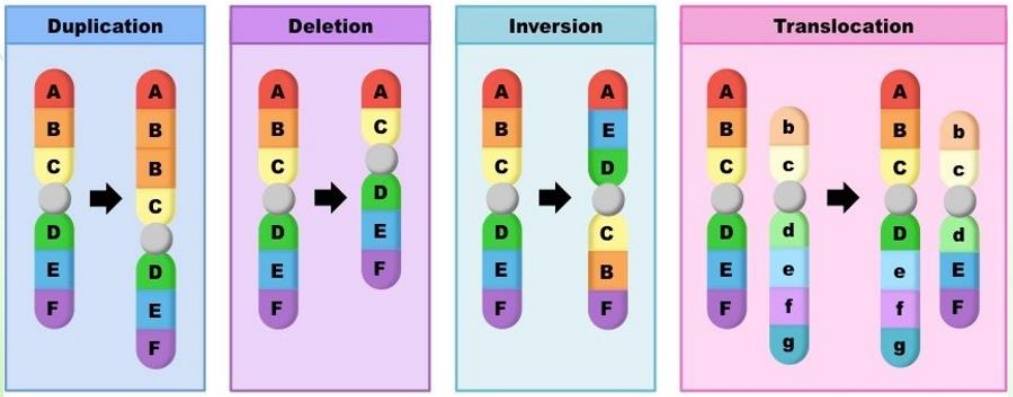
Types of micromutations

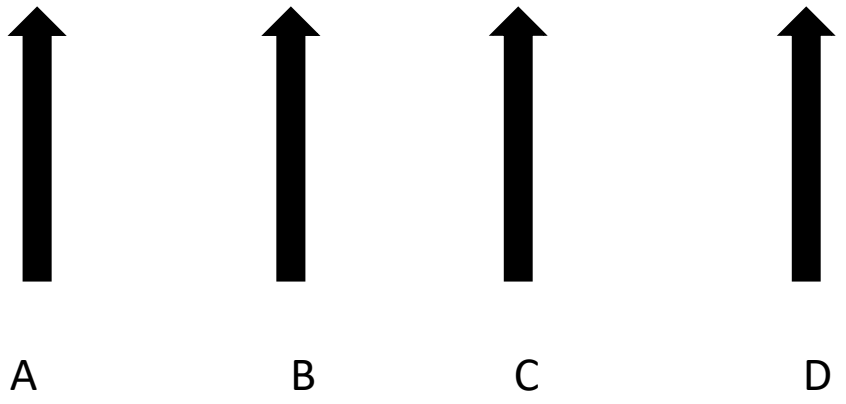


- Point mutations
  - The most common and include substitutions, insertion, and deletion
- Deletions or insertions of a few nucleotides to long stretches of DNA

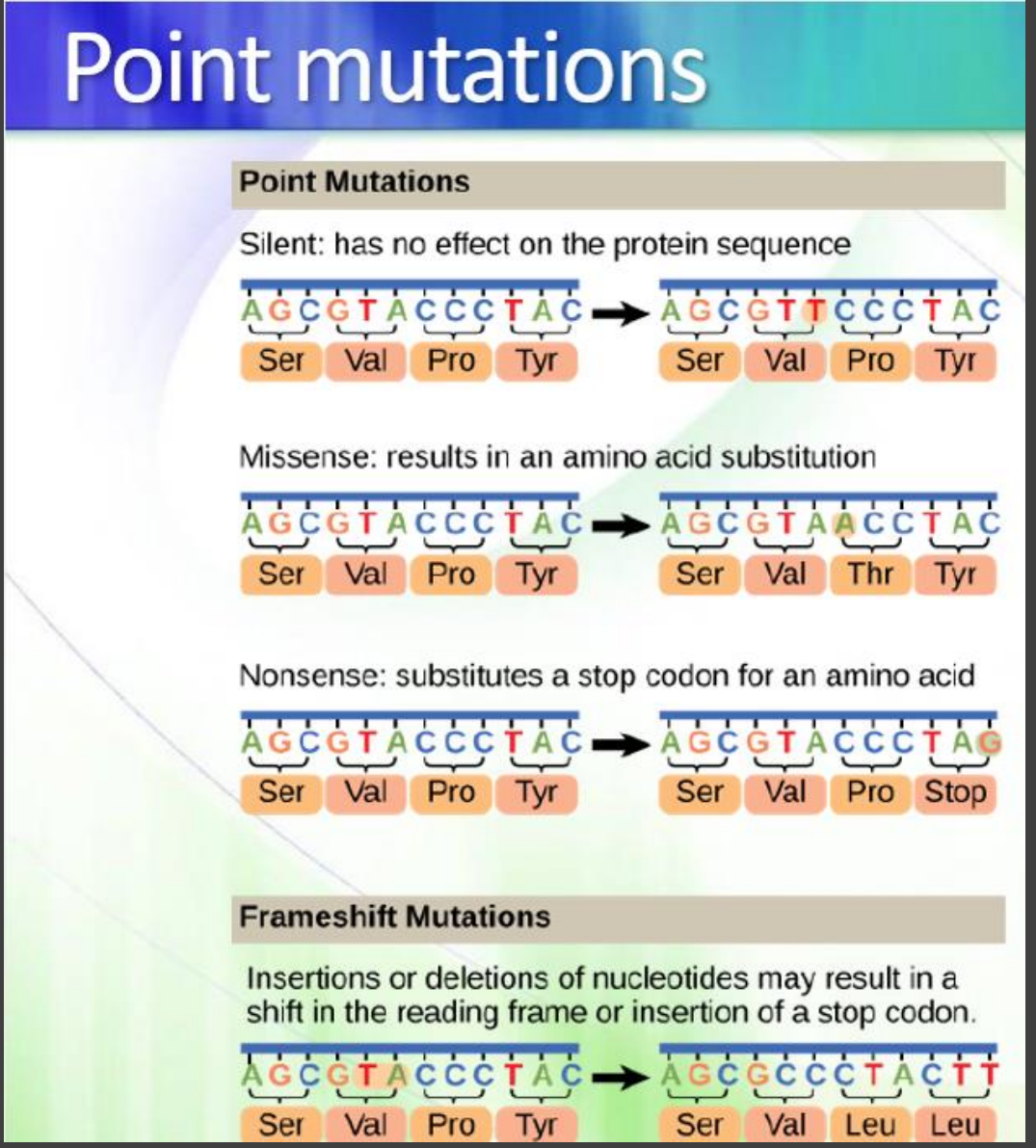
Macromutations

- Translocations
- Inversion of DNA segments
- Duplications
- Deletions





A B C D



- There are different types of micromutations like point mutation
- Point mutation:a mutation affecting only one or very few nucleotides in a gene sequence
- For example you can change a pair of nulceotides like you change A in one of the strands of course it's complementary sequence will change
- So instead of having A/T you will have for example G/C
- Or you can have deletion or insertion of nucleotides they can be of removing or adding one or more nucleotides.
- Now point mutation types:

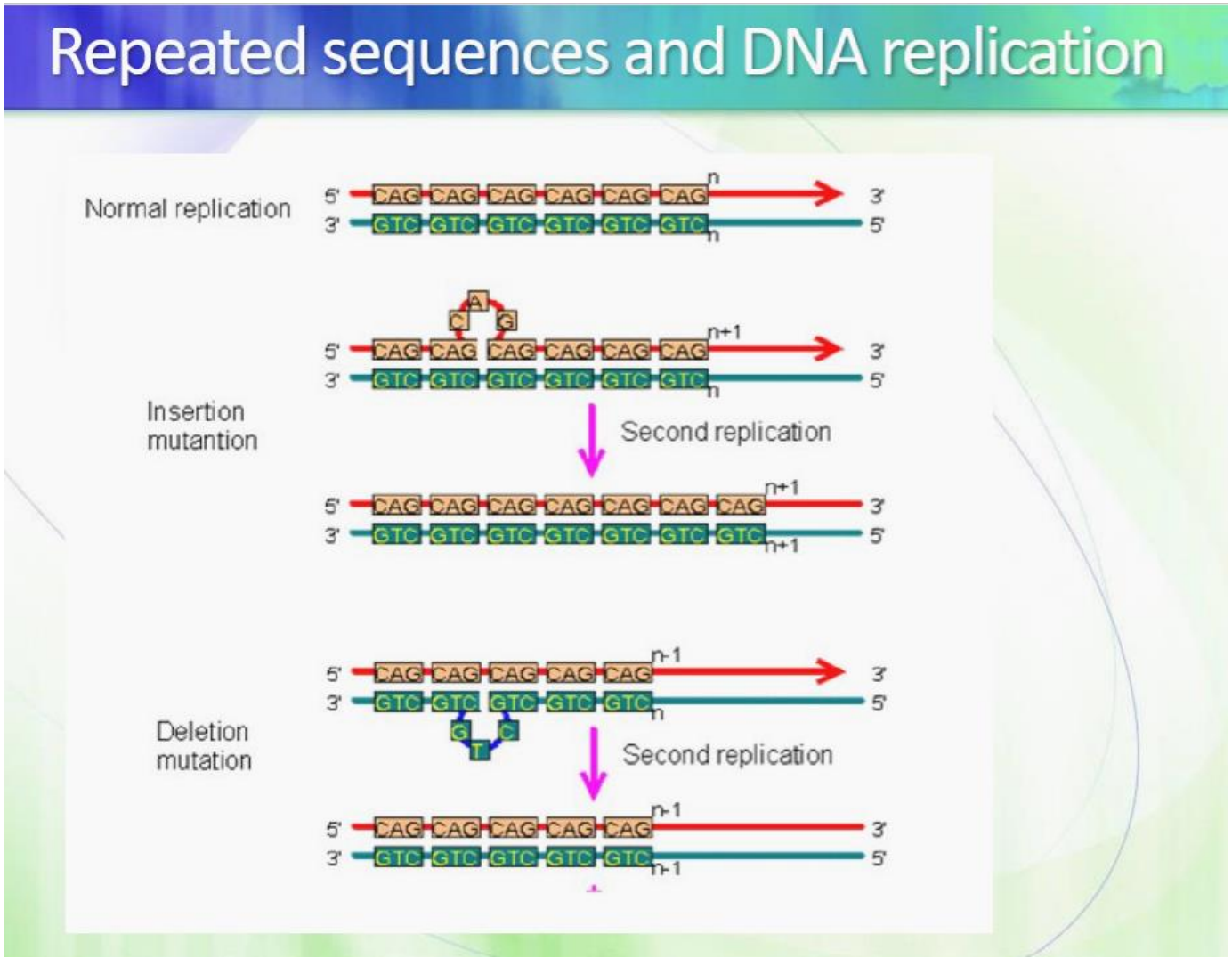
1-Silent mutation there is no change in the amino acid sequence of the polypeptide or a protein usually this change occurs in the third position of the nucleotide we said before that codons consist of 3 nucleotides and there is a flexible binding in the 3rd position wobble base pairing and the doctor said usually usually silent mutation has no effect.

2-Missense: sense like logic/ missense wrong logic

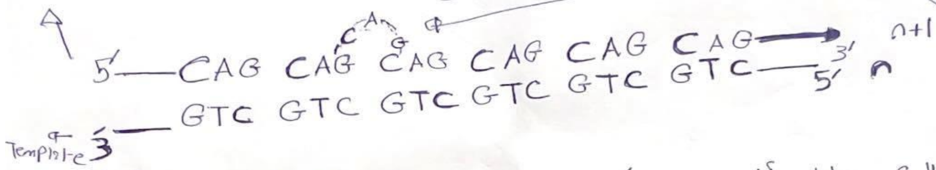
3-Nonsense:means no logic at all so simply it means the change of one codon to a stop codon which results in incomplete polypeptide and shorter than normal we call it truncated "cut" protein.

4-Another type of point mutation is frame shift mutation
Every codon can be imagined to exist in a frame so the deletion of 2 nucleotides for example will result in shifting the nucleotides sequence and that results in changing every amino acid occurs after this mutation and we will have a different protein
You can imagine different types of frame shift mutations so for ex. The insertion of 1 nucleotide.
-note here the strands shown are the coding strands the ones complementary to the template strand

- -however the case is different for addition or deletion of 3 nucleotides a whole codon
- So if you inserted 3 nuleotides between 2 frames (codons) you will have an additional codon in between them new amino acid or if you deleted a codon you will have one less amino acid in the resulting polypeptide
- But if the insertion is within a frame you will have a different polypeptide.
- -DNA replication is quite accurate but mutations can take place (insertions and deletions) usually when there are repeats.
- Explanation in the next page.



* خلاصة الموضوع أنو ال polymerase بكون يشتغل بشكل طبيعي يعني خاف؟ وبكل بساطة
بقرأ فبشوف مثلا GTC مكررة 20 مرة تخيل وصل الدور 20 هو لازم يضيف
CAG بس هو بيضفي مع حاله insertion of CAG / or deletions فرجع يحكي طب أنا كم ضفت 20 ولا ؟ *
إذا قال ضفت 20 مش حيرجع يضيف ال b
newly synthesized فبصير عنا نقص
بصير زيادة إذا فكر أنو ضاف أقل



* الدكتور قال أنو بسبب يكون في وحدة من ال strands فيها مثلا
10 و الثانية 8 أنو DNA dynamic متحرك الزيادة إلي بتطلع
من ال newly synthesized رح تطلع لفوق فلما يصير جولة أخرى من
ال replication رح ينقرأ هاي الزيادة فرح يأدي لزيادة في
آخر strand فبنتج two strands عنهم زيادة في واحد n+1

* أو ممكن يصير حذف بحيث يكون في ال Template زيادة
على ال new strand

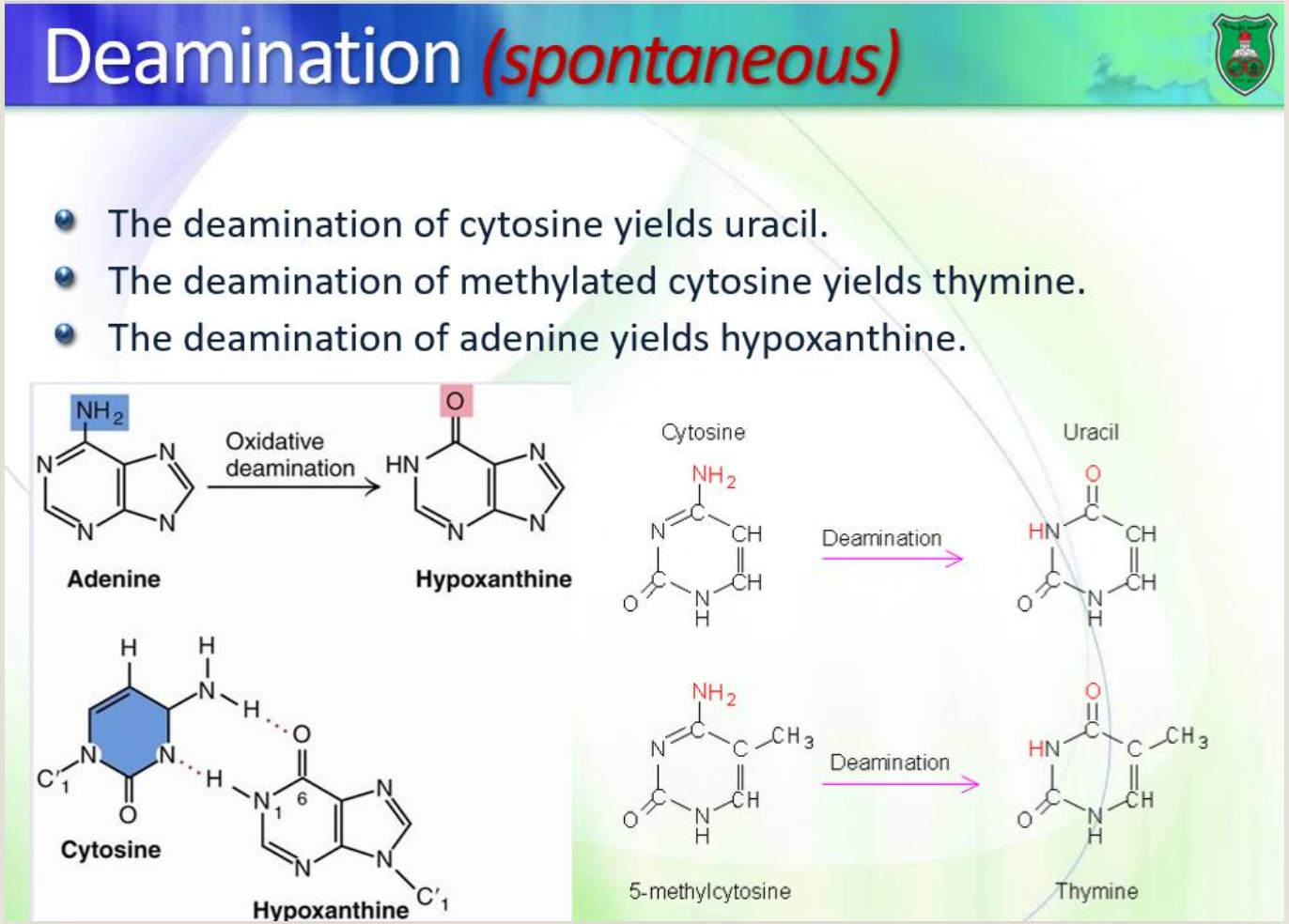
فلما يصير جولة ثانية من ال replication يعني لما
نستعمل ال strands رح ينتج عندي 1/2
من ال two strands → n-1

* ملاحظة الزيادة والنقصان تكون على ال DNA strand الجديدة الناتجة
من أول replication لأنها هي التي يشتغل عليها ال polymerase و N عدد الكودونات

- -**Deamination** (an example of a certain mutation)(spontaneous).
- Spontaneous mutation so they naturally occur within cells normally without any external effect.
- so we have deamination reaction and deamination means removal of amino group.
- For example;* you have an adenine that can be deaminated so resulting in a change in this amino group into ketone group and that will result in different molecule named hypoxanthine so that means there would be differences in base pairing because A pairs with T SO if hypoxanthine exists in the DNA and this DNA is replicated the DNA polymerase will read this hypoxanthine as a guanine and place cytosine which is complementary to it (instead of having AT pairing we would have a GC pairing) so that results in mutation.
- -BUT How can DNA polymerase do that (normally read a G) ,why wouldn't it add something else rather than G or why wouldn't it stop DNA replication ? the reason is cells don't like to die (because if the cell stops DNA replication it would die) so since hypoxanithine looks like a G so it pairs with C and continues in the DNA replication. Also, we can have deamination of cytosine ,and this deamination converts cytosine to uracil (uracil in DNA!!!) SO when the DNA polymerase reads DNA and synthesizes a new DNA during replication it sees a U and would pair it with A !SO we would have UA pairs instead of CG pairs and then this U can be removed and replaced by a T (FINAL RESULT :having TA pairing).

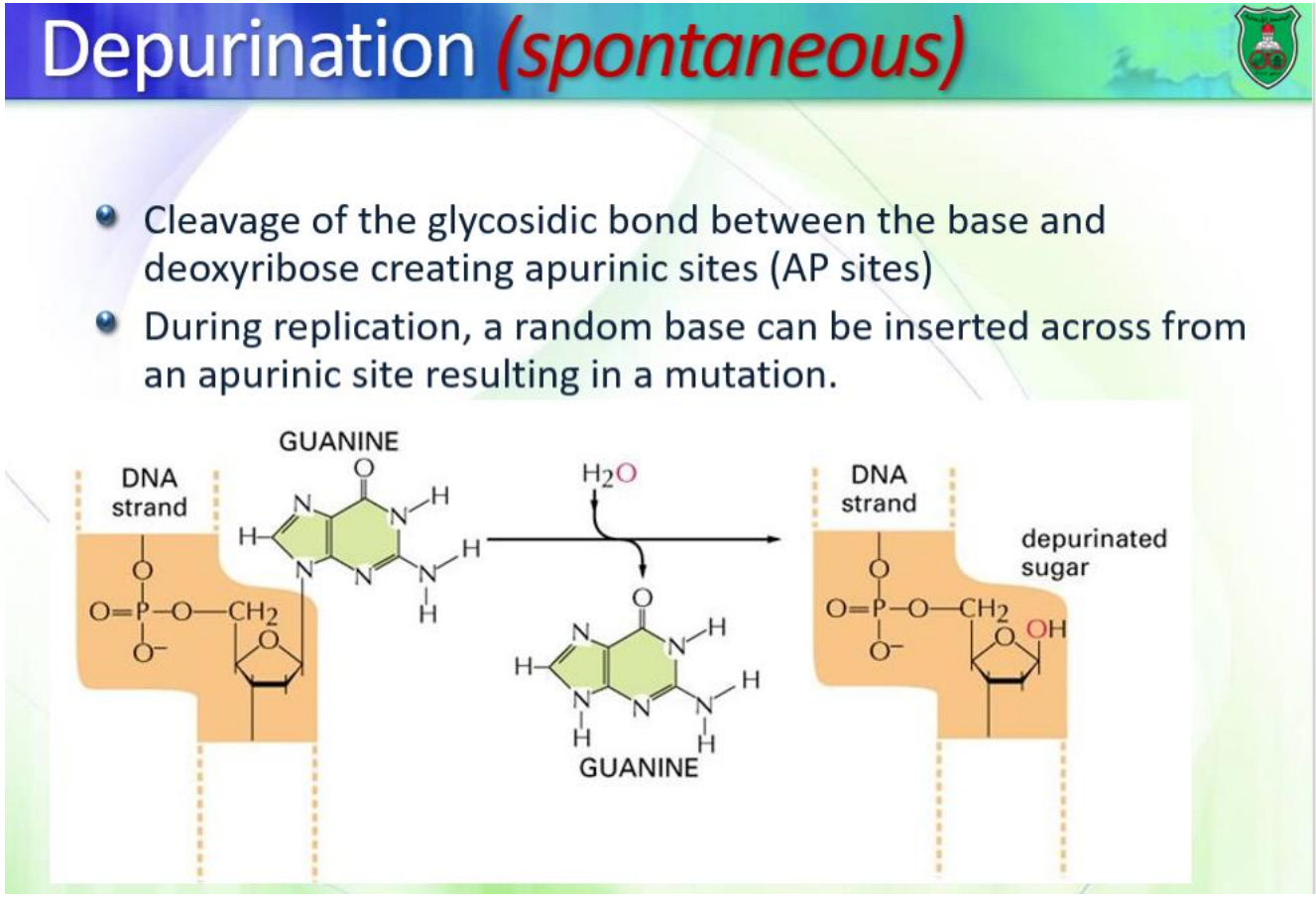
-notes:

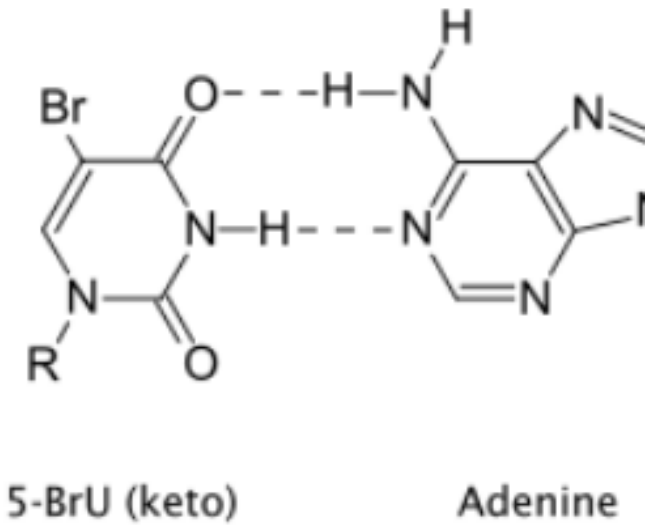
Hypoxanthine acts as G

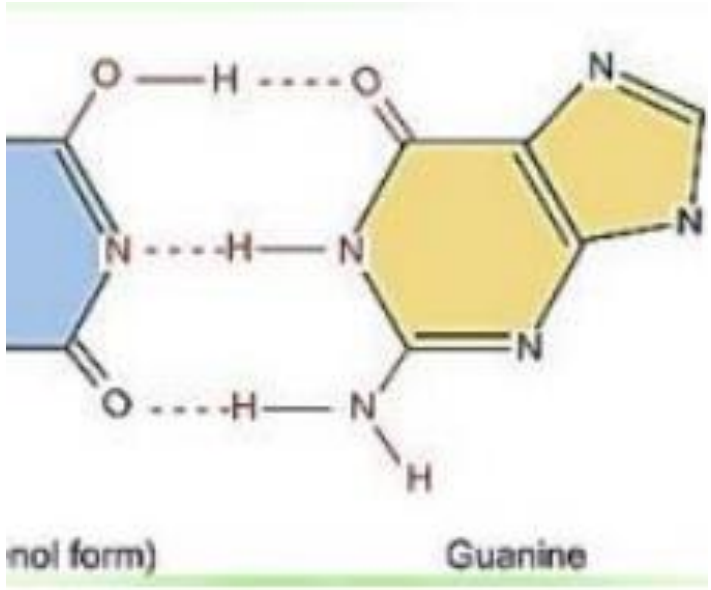


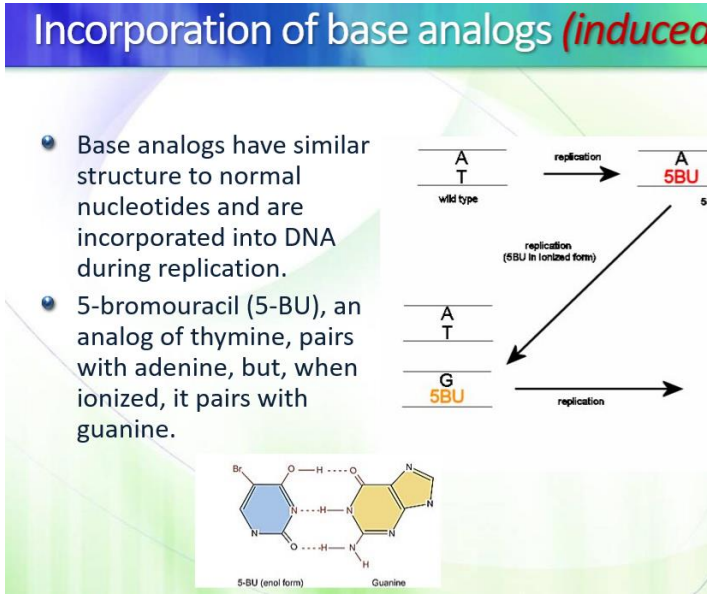
REMEMBER: when we are talking about DNA modification and that cytosine can be methylated in promoter region So if methylcytosine is deamminated that would result in converting it to T and again when DNA polymerase reads a T there is no problem in it and simply puts an A opposite to it (instead of CG we would have TA).

❖Depurination “spontaneous”.
-depurination means; removal of a purine.
-cleavage of the glycosidic bond between base (guanine) and dexoyribose (sugar)creating apurinic sites (AP sites) and then during replication as DNA read that site and see that it has no base so what it does !? it will insert anything (random base pair can be inserted) ,hopping that DNA can be repaired later on .

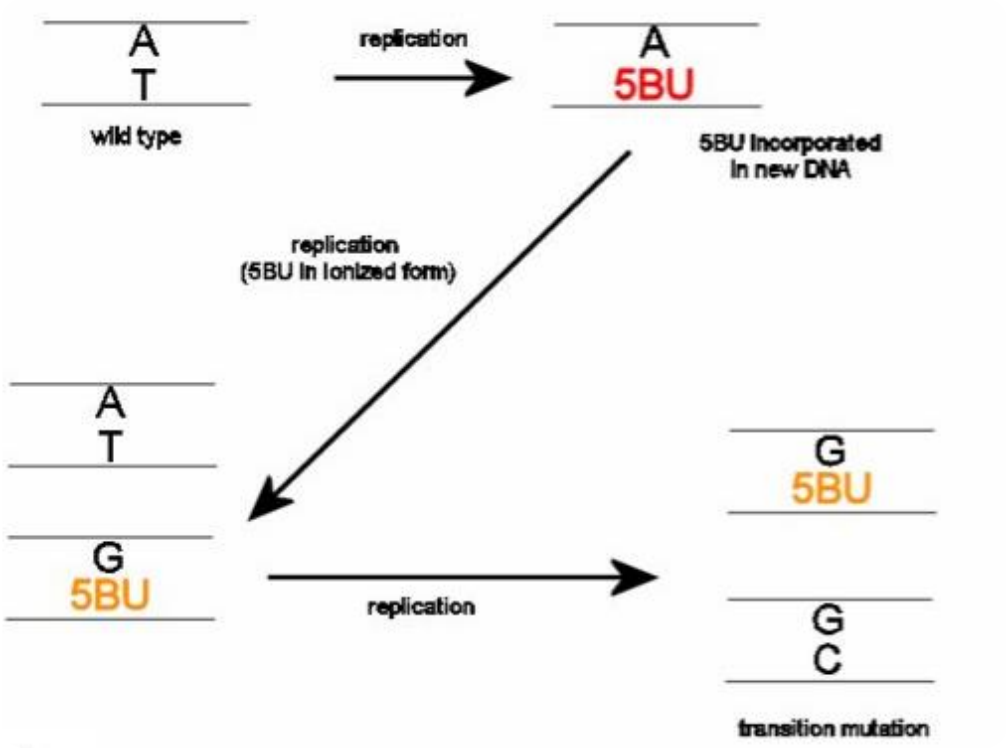








- ❖Incorporation of base analogs “induced”
- -Base analogs have similar structure to normal nucleotides and are incorporated into DNA during replication.
- -5-bromouracil (5-BU), an analog of thymine, pairs with adenine, but, when ionized, it pairs with guanine (because it looks like cytosine)
- -5-bromouracil (5BU) IF inserted into DNA by mistake by (DNA polymerase for example), so if you have an AT and during a DNA replication and 5BU is inserted into DNA ,since it looks like a T , what happens is that A it gets place in the DNA and the 5BU would pair with A.
- -If this 5BU is ionized and found in it’s ionized form which is complementary to guanine if we have a round of replication the upper strand (A) would be normal. But the other (lower) strand would pair with G because ionized form of 5BU looks like a C (please notice the difference between these 2 pictures look to the carbon alongside brome carefully).



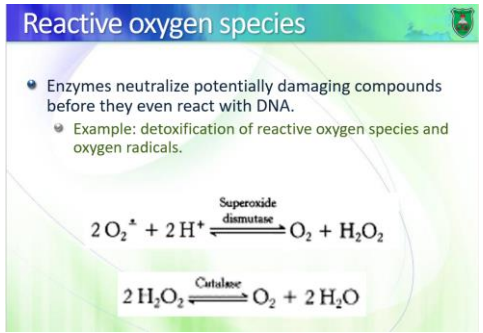
- And if we have again another round of replication what happens is that G would be read normally ,but 5BU would pair with G so finally ! we have a change from AT into GC.
- NOTE:This means that 5BU can be present in DNA either opposite A OR G
- 5BU normal form -→ looks like T.
- 5BU Ionized form -→ looks like C.

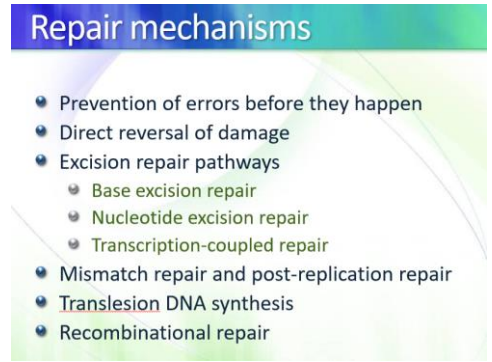
- -The result of this is that during a subsequent round of replication a different base is aligned opposite the 5-BrU residue. Further rounds of replication 'fix' the change by incorporating a normal nitrogen base into the complementary strand.
- *Thus 5-BrU induces a point mutation via base substitution. This base pair will change from an A-T to a G-C or from a GC to an A-T after a number of replication cycles, depending on whether 5-BrU is within the DNA molecule or is an incoming base when it is ionized.

- *WILD TYPE: means normal because when the scientists first studied the genetics in fruit fly they basically looked wild (the normal type was known as wild type) so the normal sequence of DNA was called a wild type.

- Repair mechanism
- -Types of repair mechanism:
- 1-Preventing of errors before they happen.
- There is a protective mechanism within our cells that prevents errors before they happen.
- -first anything harmful inside the cell is removed right away ,and an example of this:
- -Reactive oxygen species molecules that are oxygen but they are hyper active ,example; radicals “free oxygen radical” ,these free oxygen radicals are missing an electron.
- Like
- 1- O2° which is known as superoxide and this superoxide is so hyper active it misses an electron and it can attack any molecule inside a cell and steal an electron from these molecules so it get relaxed (become stable) but at the same time the other molecule that gets oxidized is damaged.
- So imagine that this superoxide to attack DNA so this DNA will be damaged . Also these radicals can attack lipids in membrane and the membrane will be damaged and that cell dies by the way.
- 2-H2O2 (HYDROGEN PEROXIDE) ,also reactive molecule and can be removed enzymatically by an enzyme known as catalase. Whereas superoxide can be removed by superoxide dismutase

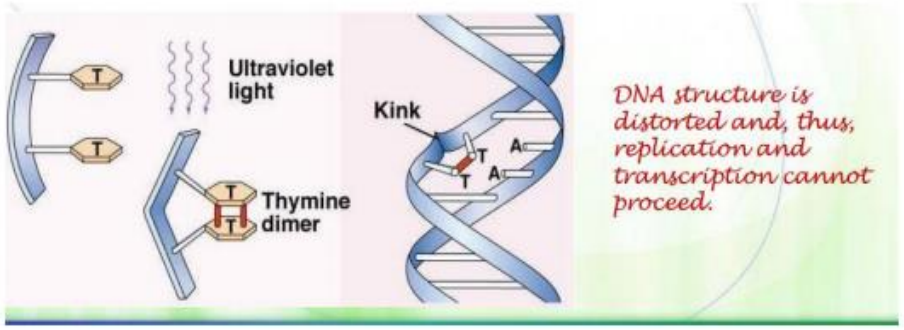
⇨Enzymes neutralize potentially damaging compounds before they even react with DNA (detoxification of reactive oxygen species and oxygen radicals).





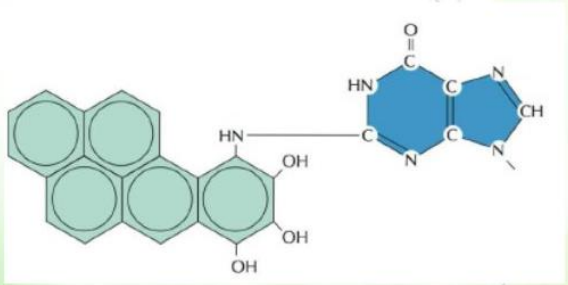
❖Repair mechanism
-Types of repair mechanism:
1-Preventing of errors before they happen.
2-Direct reversal of damage.
Those are the types we will talk about in this sheet

2-direct reversal of damage:
-Lets say that harmful thing happen and damage takes place inside the cell
So How do cells handle such damage? How do they repair it?
-A type of a common mutation that takes place inside cells is : pyrimidine dimer since we are all exposed to sunlight and sunlight is basically UV light and it really damages the DNA and what happens is that when UV light hits DNA this results in the formation of a covalent interaction between two adjacent pyrimidines leading to the formation of structures known as cyclobutene pyrimidine dimers, and commonly between two thymine (50-100 reactions per second), a lot of mutations take place but these mutations are repaired and they are repaired in different mechanisms in humans and in bacteria “we will talk about humans later on”.
-but in bacteria we have an enzyme known as photolyase (photolyase doesn’t exist in humans) : which does simple reversion of pyrimidine dimers or thymine dimer so these covalent interactions are removed .
-This product is a mutagenic photodimer so during DNA replication and during transcription enzymes can not proceed they can not synthesize DNA or RNA and that results in killing cells or results in production of mutations.
-so within one strand if we have two adjacent TT and UV light hits DNA these Ts would have formation of covalent interactions between these Ts resulting in the formation of cyclobutane



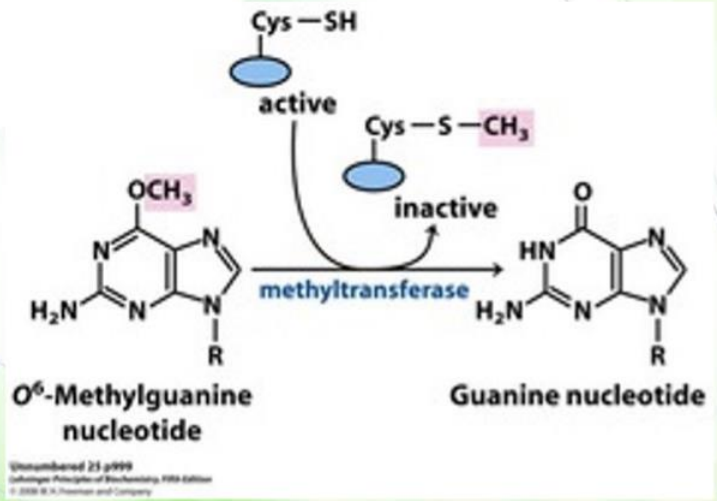
Specific mispairing

- Bases existing in DNA can be altered causing mispairing.
  - Alkylating agents can transfer methyl group to guanine forming 6-methylguanine, which pairs with thymine.
  - Addition of large chemical adducts by carcinogens.

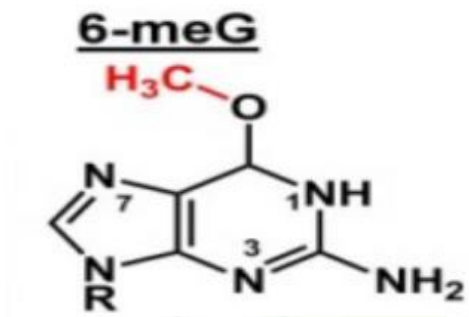


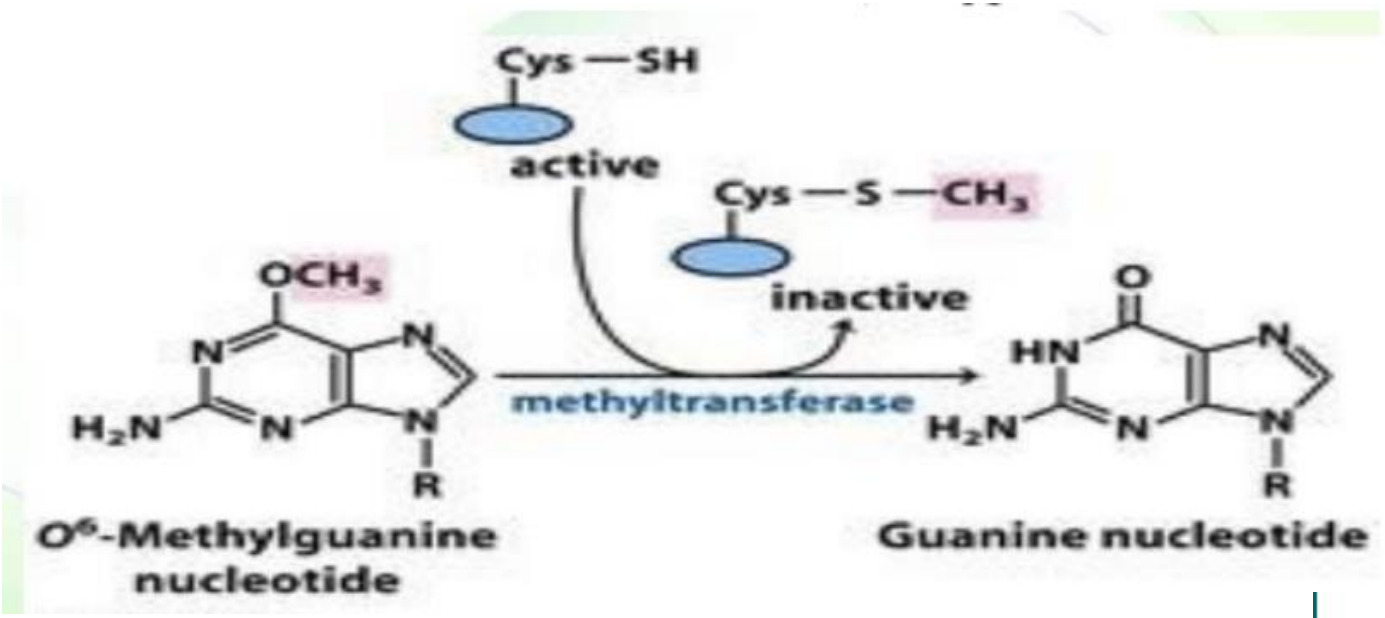
Repair of O^6-methylguanine

- This is done via O^6-methylguanine methyltransferase.



-we can have modification of nucleotides and that causes mispairing during DNA replication so you can have addition of an alkyl group (like methyl) to carbon number 6 in guanine forming 6-methylguanine (6-meG) which mispairs with thymine so instead of having GC we would have meG pairing with T and if we have replication that results in formation of one strand pair of AT so at result we will have a change of GC to AT.





*it can be repaired enzymatically by an enzyme called methylguanine methyltransferase this enzyme will remove the additional alkyl group which is in this case methyl

-NOTE: few types of damaged DNA are repaired in this way.

-Or addition of large objects (large group of molecule as you can see in the picture) to DNA and this is considered mutagenic and it can be carcinogenic as well.