Molecular Biology (5)

DNA mutations

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Resources

- This lecture
- Cooper, pp.232-243
- *http://www.ncbi.nlm.nih.gov/books/NBK21897/*
- *https://www.ncbi.nlm.nih.gov/books/NBK21936/*

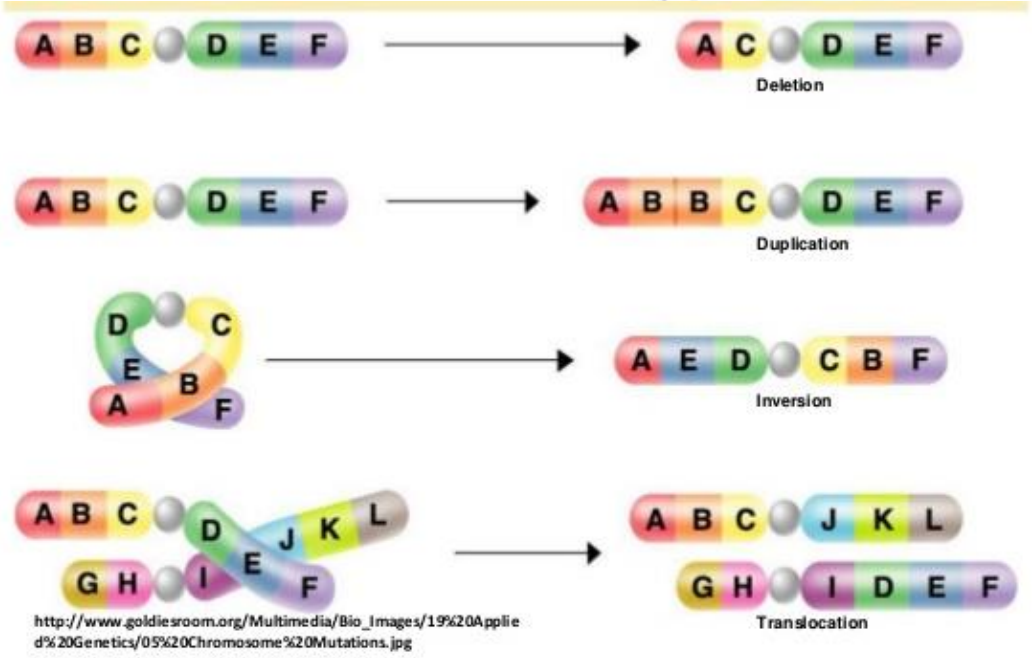
What are mutations?

- A mutation is a heritable alteration or change in the genetic material.
  - Somatic mutation occur in somatic cells and are not transmitted.
  - Germ-line mutation occur in gametes and are heritable.

- The damaging effect of mutations is different
  - Micromutation that involve small regions of the DNA
  - Macromutations that involve the chromosomes as a whole.

Types of micromutations

- Translocations, that bring different regions of gene segments together
- Deletions of a few nucleotides to long stretches of DNA,
- Insertions and duplications of nucleotides or long stretches of DNA
- Inversion of DNA segments



http://www.goldiesroom.org/Multimedia/Bio_Images/19%20Applied%20Genetics/05%20Chromosome%20Mutations.jpg

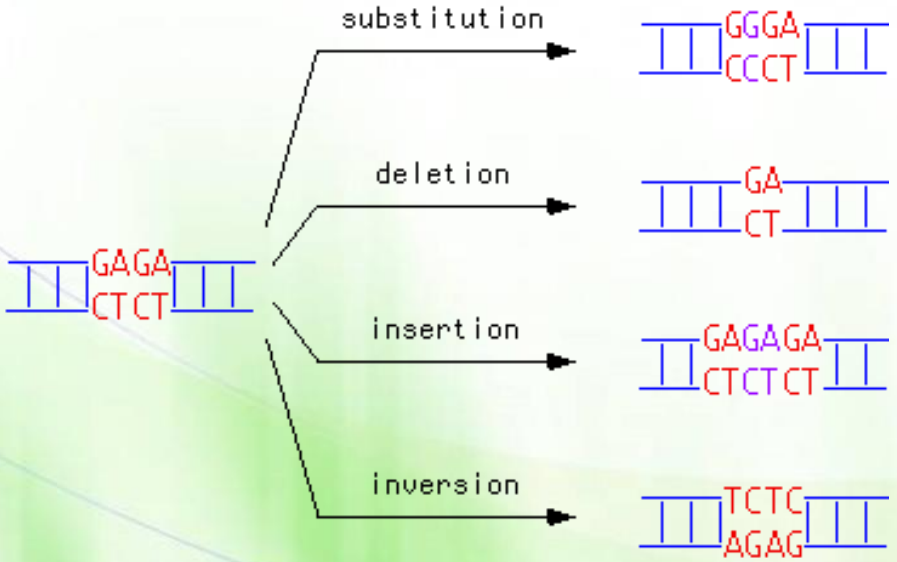
Causes of DNA mutations

- DNA mutations can arise spontaneously or induced.

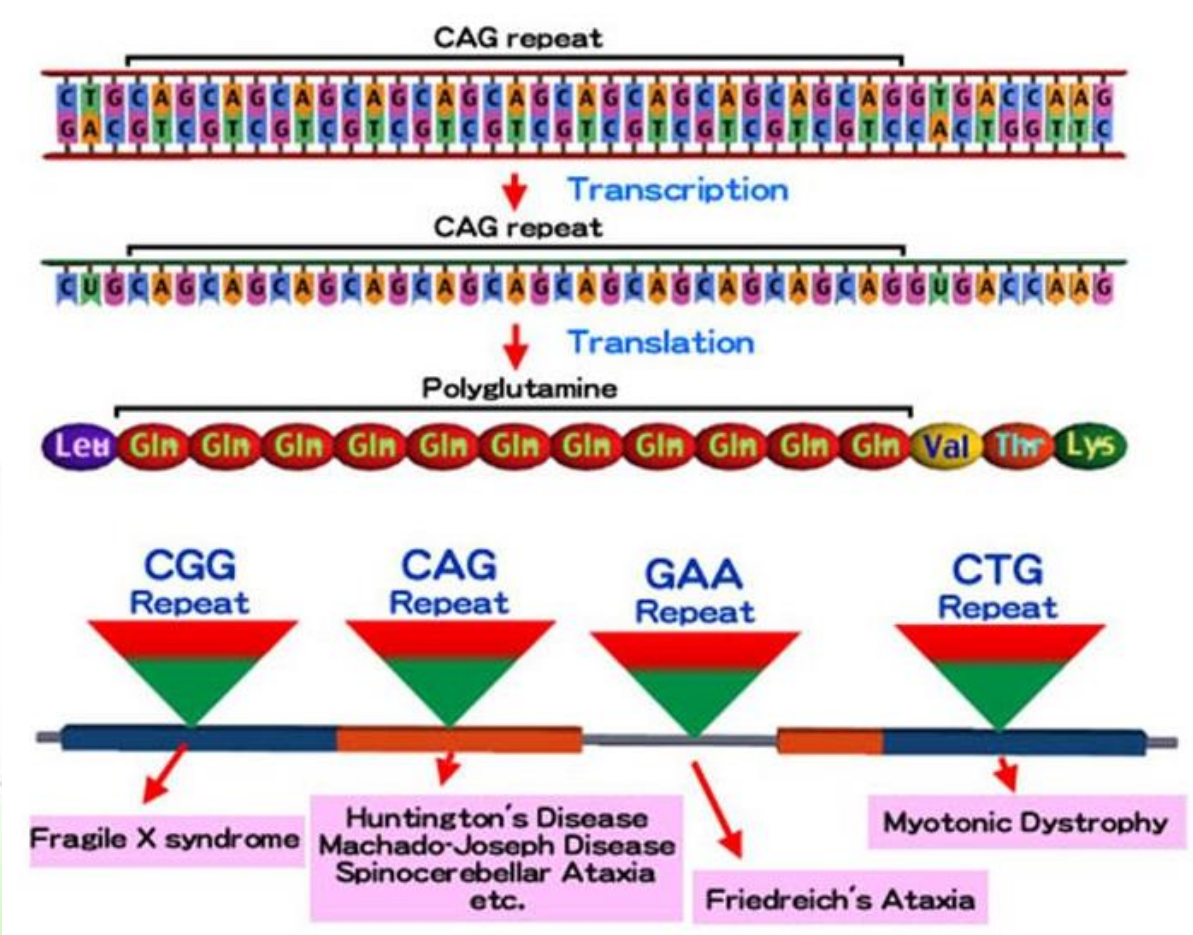
- Spontaneous mutations are naturally occurring mutations and arise in all cells.
  - They arise from a variety of sources, including errors in DNA replication and spontaneous lesions
- Induced mutations are produced when an organism is exposed to a mutagenic agent, or mutagen.
  - Some mutagens are carcinogens (cancer-causing)
    - Ionizing radiation

Sources of errors of DNA replication

- Base substitution: a result of mispairing (A-C or G-T) (most common).
- Inversion
- Insertion and deletion mutations
  - These mutations often occur at **repeated sequences**.
  - Large deletions may result in partial or whole gene deletion.
  - Large insertions may result in gene duplication.



Triplet repeat disease



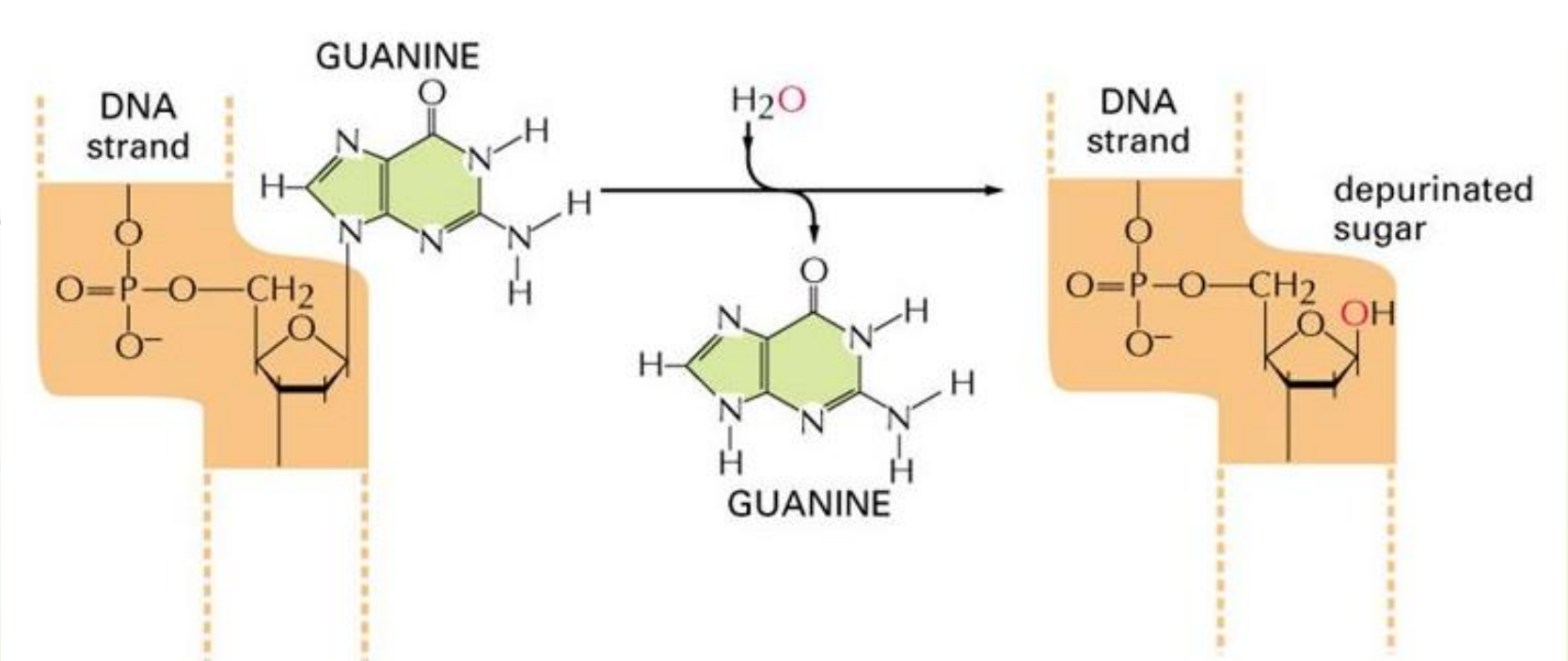
Kearns-Sayre syndrome (a mitochondrial encephalomyopathy) results form d**eletion of a three-base-pair repeat.**

Spontaneous lesions

- Spontaneous lesions are naturally occurring type of DNA damage that can generate mutations
  - Depurination
  - Deamination
  - Oxidatively damaged bases

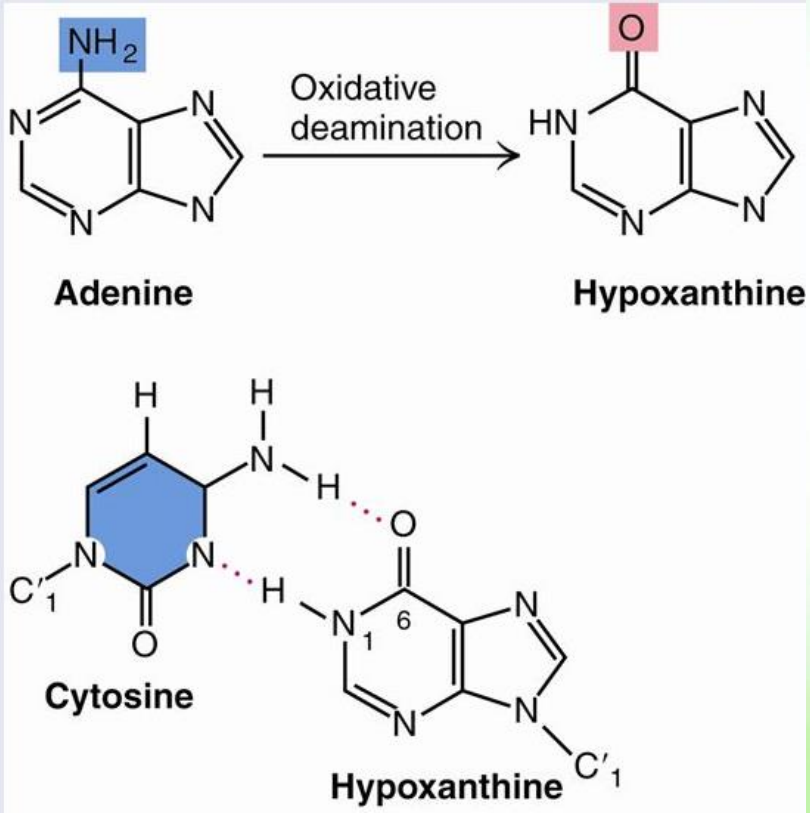
Depurination

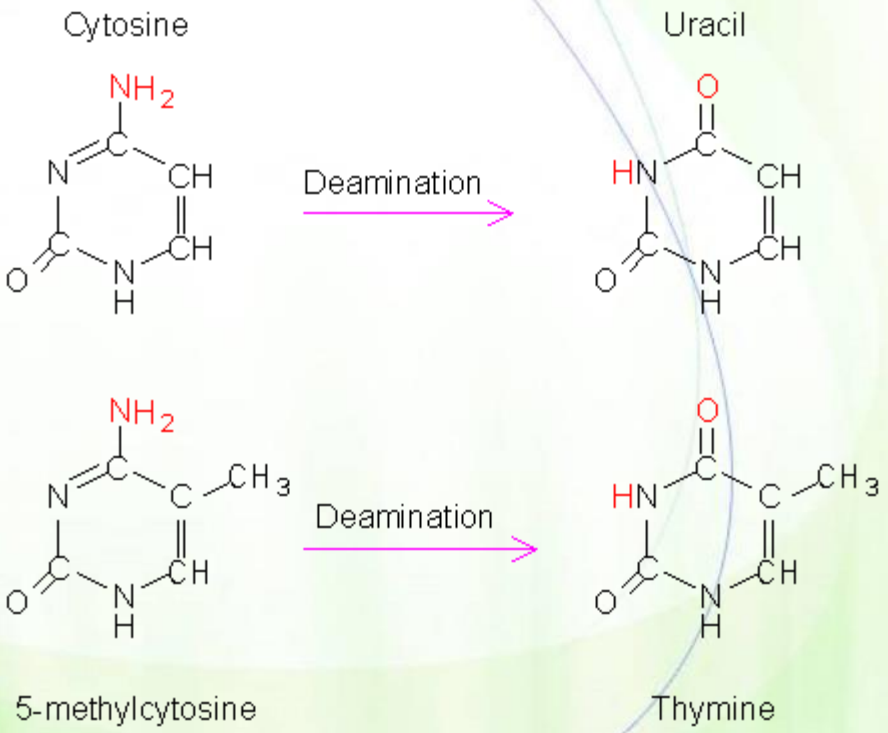
- Cleavage of the glycosidic bond between the base and deoxyribose creating apurinic sites (AP sites)
- During replication, a random base can be inserted across from an apurinic site resulting in a mutation.



Deamination

- The deamination of cytosine yields uracil.
- The deamination of methylated cytosine yields thymine.
- The deamination of adenine yields hypoxanthine.





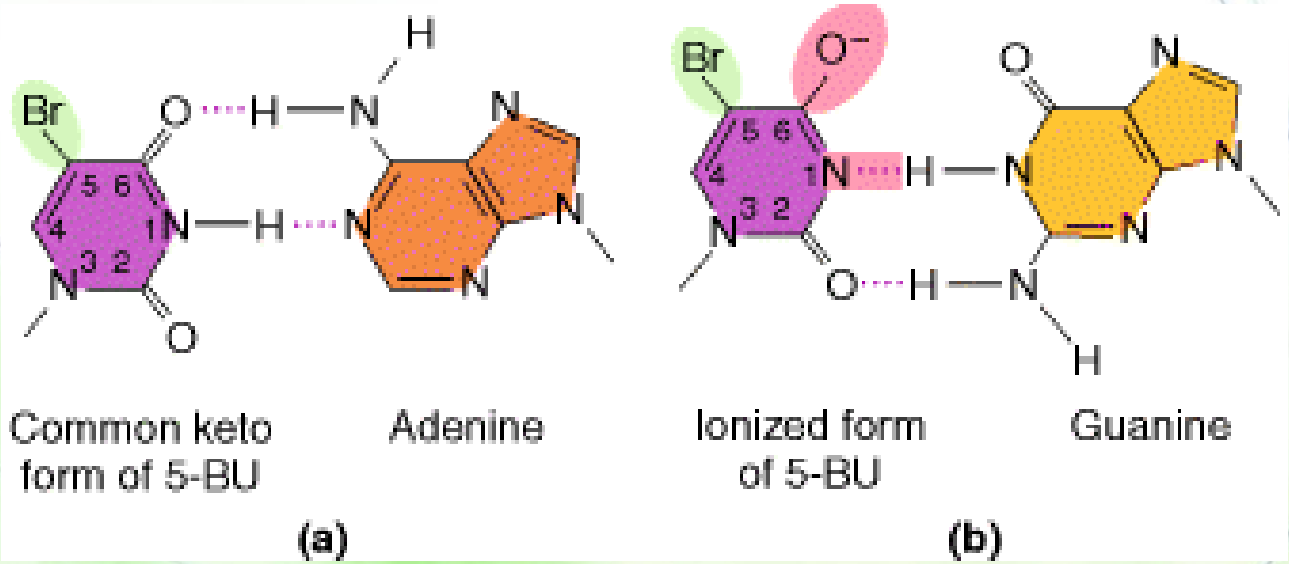
Induced mutations

Mechanisms of mutagenesis

- Mutagens induce mutations by at least three different mechanisms:
  - Add a base analog during DNA replication
  - Alter an existing base causing mispairing (alkylation)
  - Damage a base disabling pairing with any base

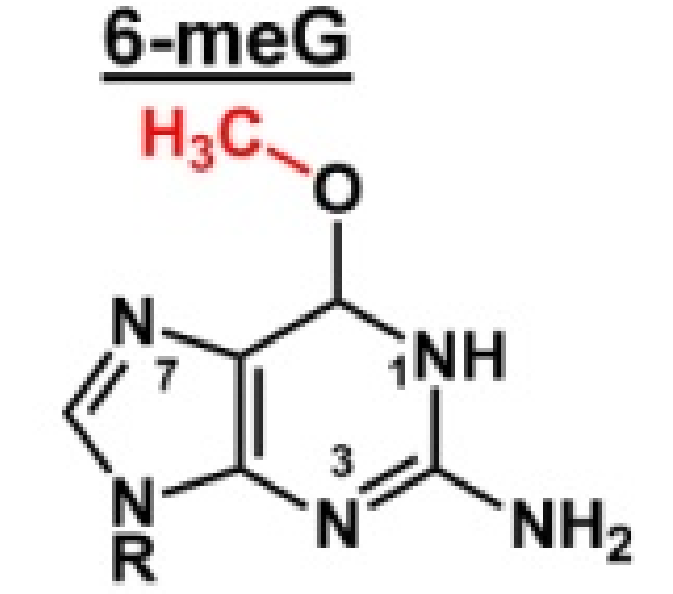
Incorporation of base analogs

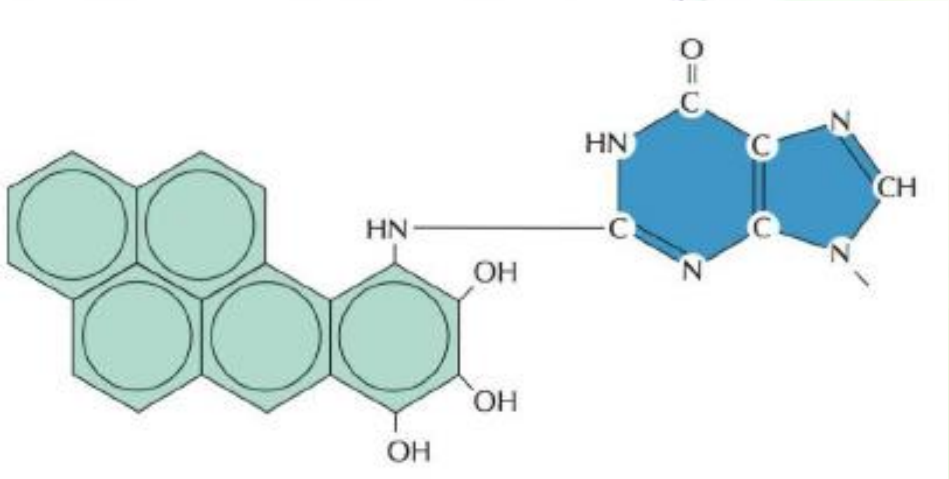
- Base analogs have similar structure to normal nucleotides and are incorporated into DNA during replication.
- 5-bromouracil (5-BU), an analog of thymine, pairs with adenine, but, when ionized, it pairs with guanine.



Specific mispairing

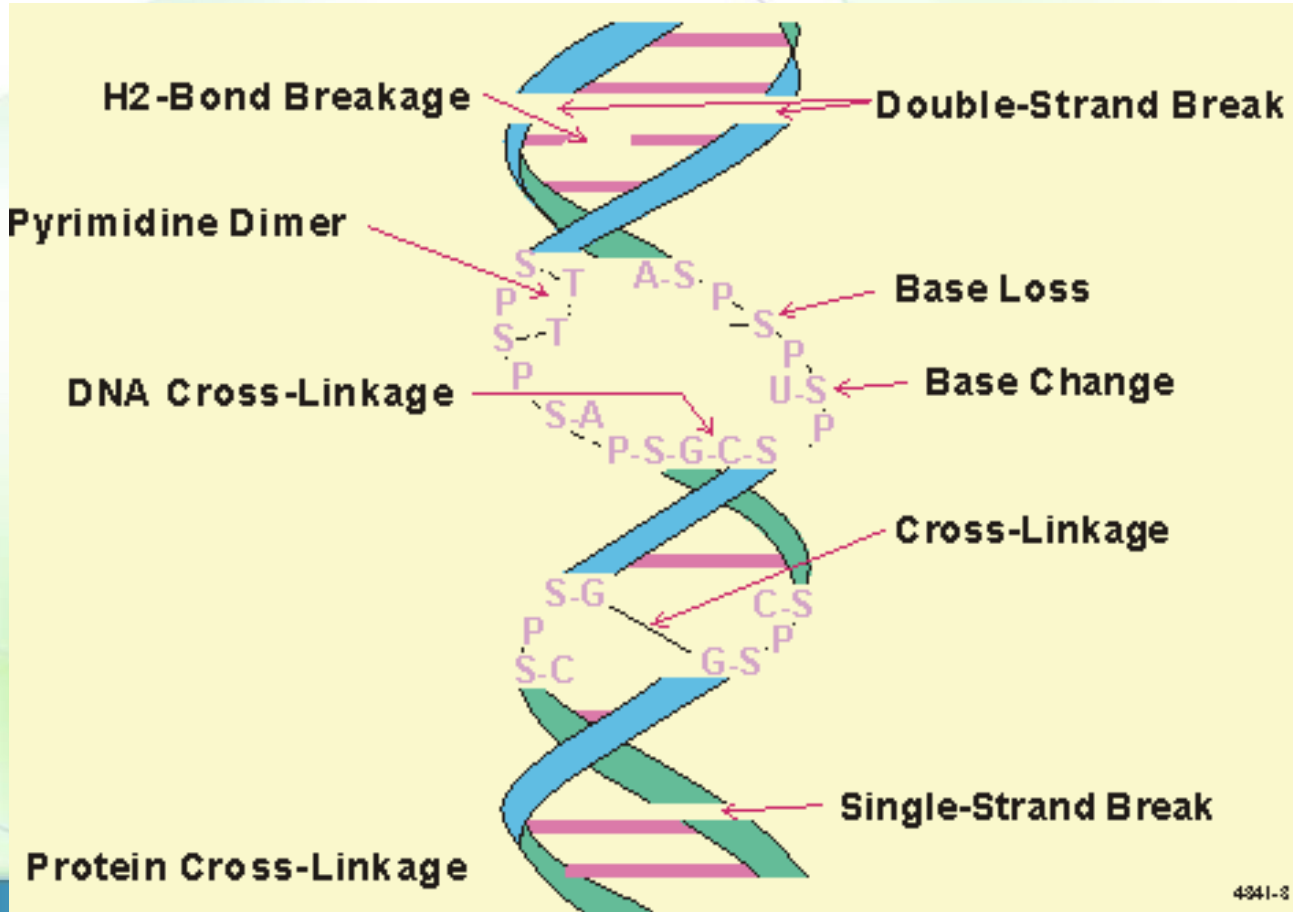
- Bases existing in DNA can be altered causing mispairing.
  - Alkylating agents can transfer methyl group to guanine forming 6-methylguanine, which pairs with thymine.
  - Addition of large chemical adducts by carcinogens.





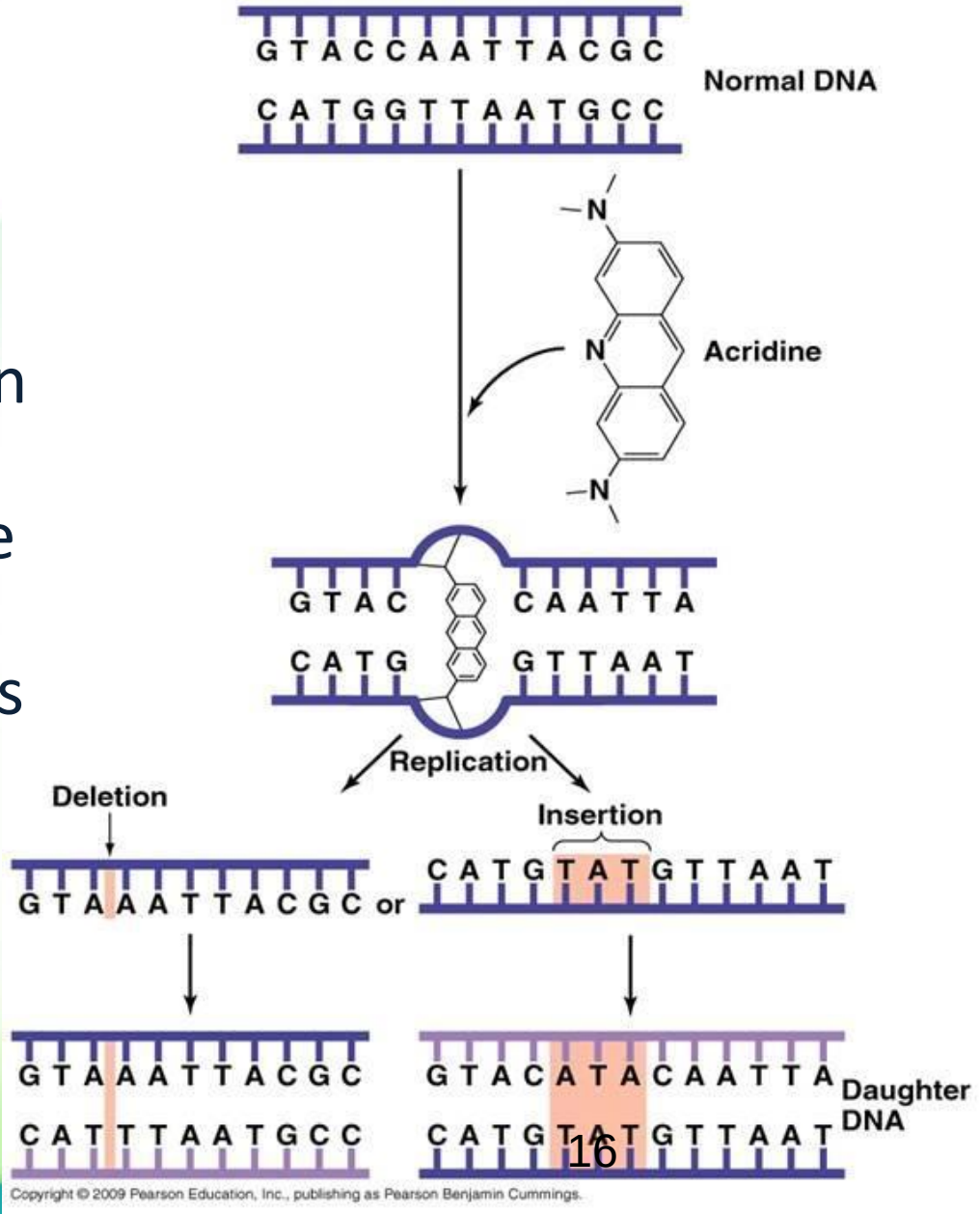
Ionizing radiation

- Ionizing radiation results in the formation of ionized and excited molecules that can cause damage to DNA including
  - Creation of AP sites (apurinic or apyrimidinic sites)
  - Base damage
  - Strand breaks



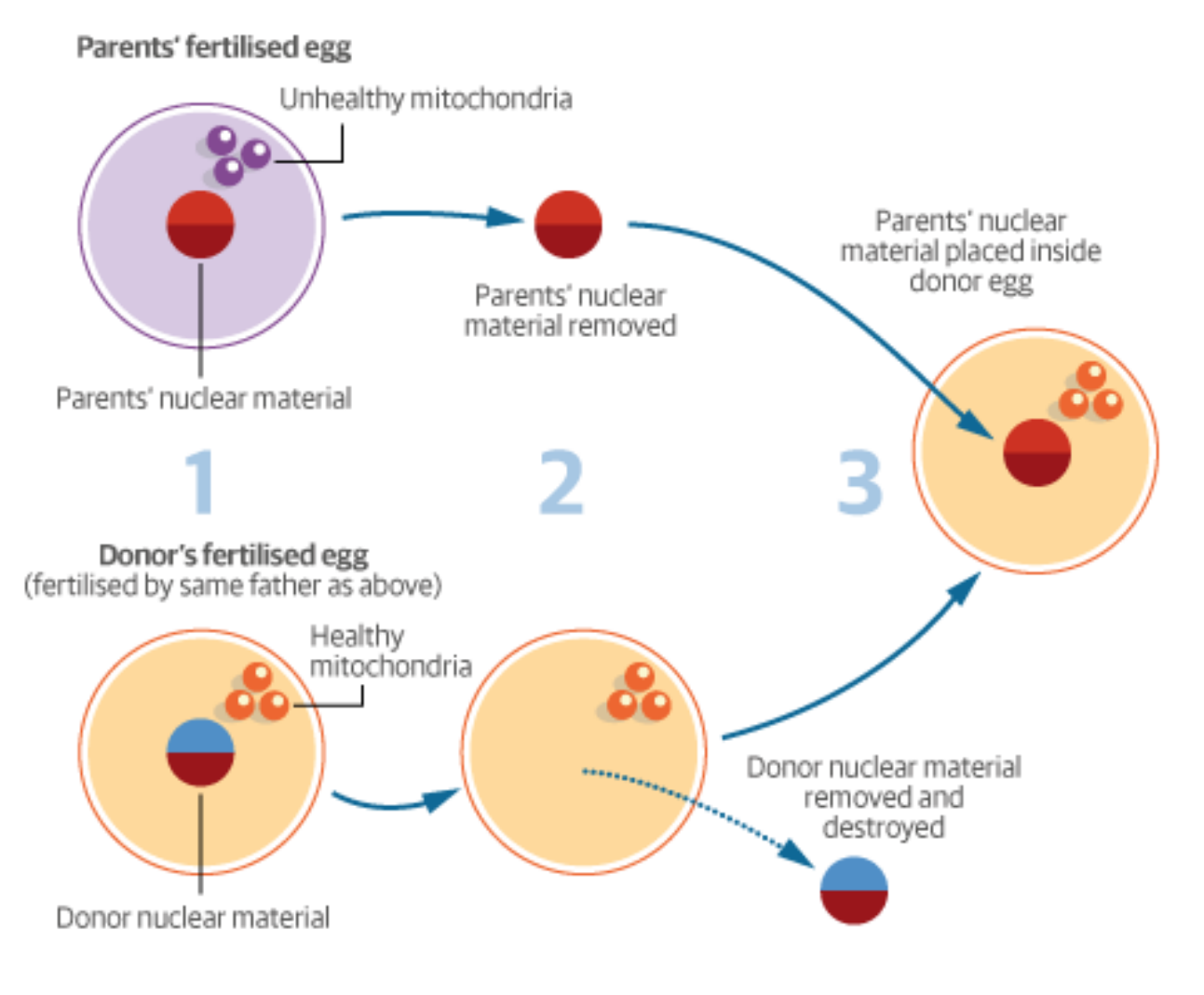
Intercalating agents

- The intercalating agents such as proflavin and ethidium bromide are planar molecules that can insert themselves (intercalate) between the bases and cause single-nucleotide-pair insertions or deletions.



Controversial issue

Three-parent babies



https://www.theguardian.com/science/2015/feb/02/three-parent-babies-explained

Not secure | nationalpost.com/news/world/jordanian-couple-has-baby-using-three-parent-genetic-engineering-but-its-actually-abou

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*The **British**-developed technique was performed in **Mexico** by a **Chinese-American** physician who worked in New York*

Jordanian couple has baby using 'three parent' genetic engineering — but it's actually about 2.001 parents

The Jordanian newborn represents the first successful birth in a new wave of "three parent" techniques, although the procedure is illegal in most countries

This Jordanian newborn represents the first successful birth in a new wave of “three parent” techniques — ones that are more sophisticated, and that will likely stick around much longer.