* Nucleic Acids → مسؤولة عن transmitting genetic information within cells.

* Types of Nucleic Acids
  - DNA.
  - RNA.

* تعريف الـ DNA :-

هو الجزيء الذي يحمل التعليمات الوراثية الضرورية لنمو و وظائف وتكاثر جميع الكائنات الحية.

* central Dogma → flow genetic information from DNA to RNA and then to protein

→ مؤسس هذا المفهوم francis crick هو

Date: / /

structure DNA

DNA

unbranched

Polymer

→ deoxyribonucleotides (monomers)

→ phosphate (H_3PO_4)

→ Deoxyribose ($C_5H_{10}O_4$) (sugar)

→ Nitrogenous Base

Heterocyclic

aromatic

compound

→ purines

two Ring

→ Adenine (A)

→ Guanine (G)

→ pyrimidines

single Ring

→ Thymine (T)

→ Cytosin (C)

→ phosphodiester Linkages

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DNA primary structure

* حكينا انو الـ DNA بتتكون من :-

deoxyribonucleotides

ترتيب هذه الـ deoxyribonucleotides يبدأ من

(5' → 3')

مثل لما اقرأ كتاب من اليسار الى اليمين

برضة فيه عندنا الـ Base pairs (bp) :-

A (Adenine) pairs with T (thymine)

G (guanine) pairs with C (cytosine)

* هاي الـ (base pairs) تعبر عن حجم الحمض النووي (size of DNA)

more base pairs mean a large DNA molecule *

Free 5' carbon (start)

Free 3' carbon (end)

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* Genes
  - Parts of DNA that control traits (سمات)
  - usually correspond to a
    - single protein.
    - RNA.
  - in eukaryotic cells (يتكون من)
    1. Exons → coding regions that provide instruction
    2. Introns → non-coding Regions that are removed

Date: / /

* Mutations
  - is a change in the DNA sequence
  - اسبابها
    - errors in DNA replication.
    - exposure to mutagens.
    - viral infection.
  - Types
    - Germline mutations
      - occur in eggs and sperm.
      - can be passed to offspring.
    - somatic mutations
      - occure in body cells.
      - not passed to offspring

CanadianSolar

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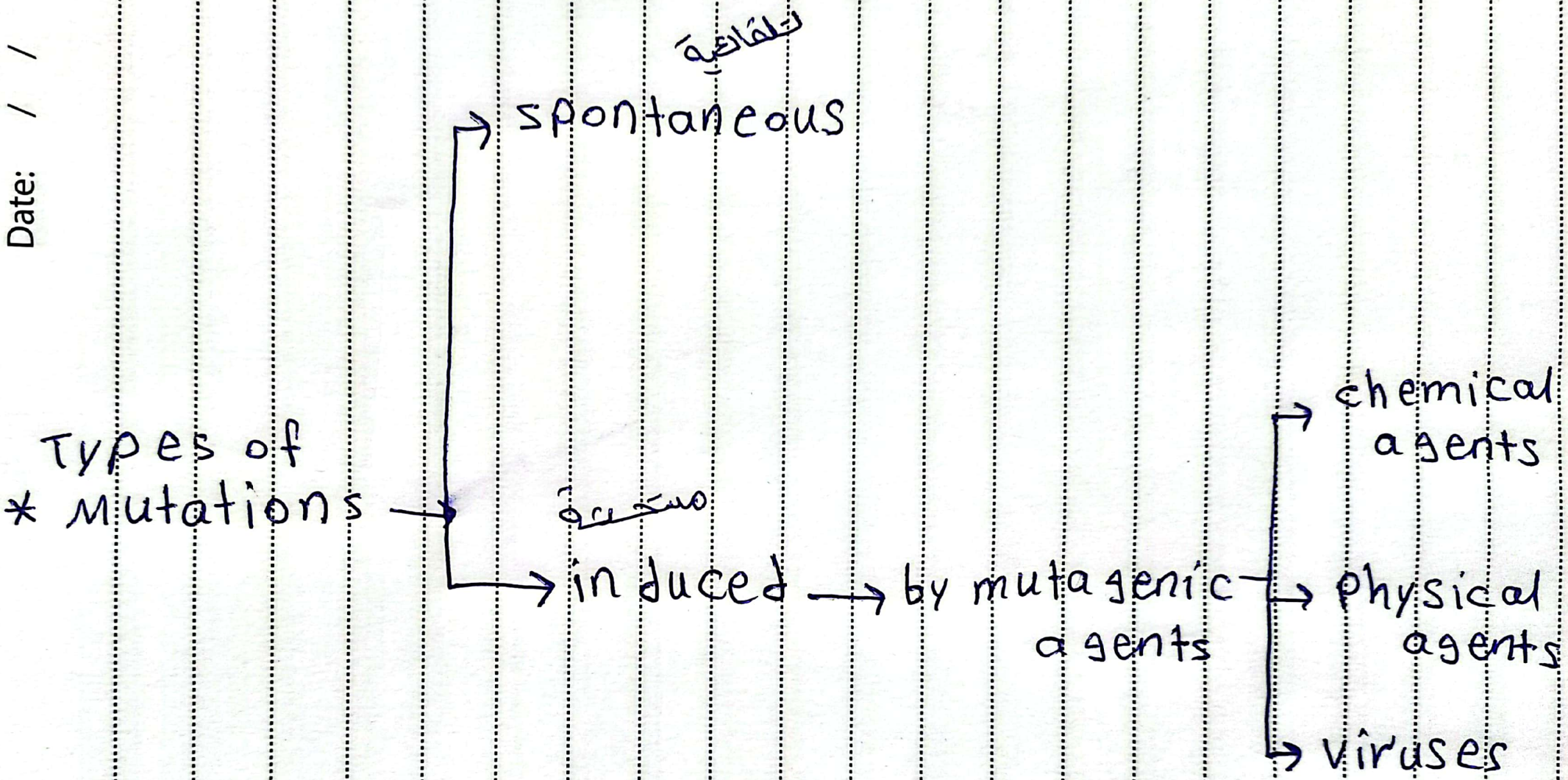

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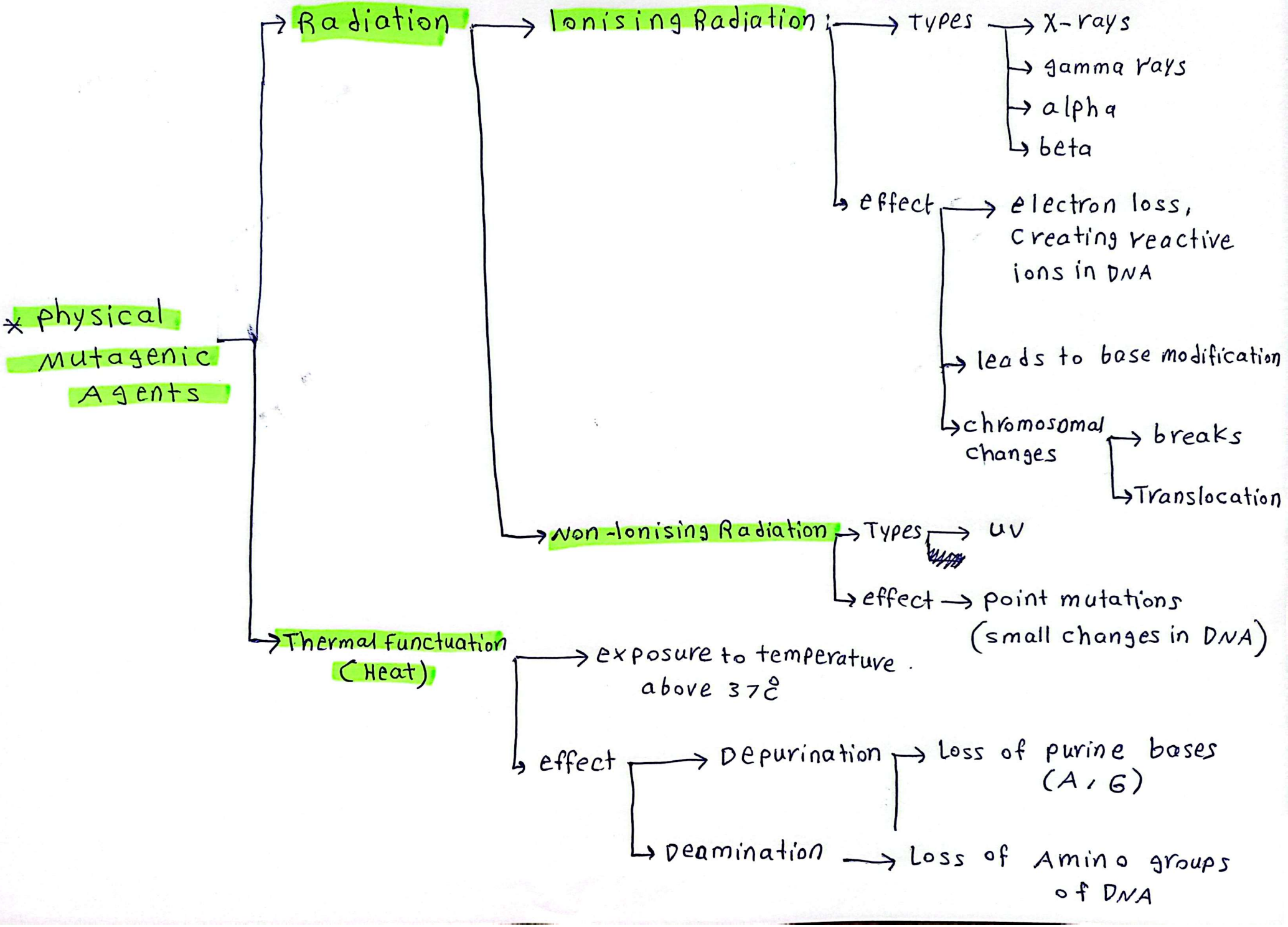
* Chemical Mutagenic Agents

- Base Analogues
  - Isomers of nitrogenous bases that differ in functional group position.
  - Example
    - 5- Bromouracil:- Replaces thymine in DNA
    - 2- Aminopurine:- Replaces Adenine in DNA
  - Made of Action → incorporated into DNA during replication instead of the correct base.
- Intercalating Agents
  - flat molecules that slip between DNA base pairs
  - cause base pairs to separate, leading to insertions or deletions during DNA replication & changing reading pattern.
  - Example
    - Acridine (orange)
    - Benzopyrene
    - Ethidium Bromide
    - Proflavine

Date:

* Chemical Mutagenic Agents :→ Modification of Nitrogenous Bases

- Remove Groups from nitrogenous Bases :-
  - Nitrous Acid :→ Removes amino group from bases
- Add Groups of Nitrogenous Bases :-
  - Mustard gas :→ Add methyl or ethyl groups to bases



* Viral mutagenic Agents → oncogenic viruses (linked to cancer)

- DNA viruses
  - Polyomavirus
  - Adenovirus
  - Hepatitis B
  - Herpesvirus - EBV
  - papillomavirus
  - ① produce proteins that interfere with cell regulation
  - ② inactivate tumor suppressor genes ; such as:
    - ① p53 :→ A protein that prevents damaged cells from growth
    - ② Retinoblastoma (Rb) protein: → regulates cell growth
  - ③ uncontrolled cell growth + genomic instability + potential for tumor formation.
- RNA virus → Retroviruses

insert near oncogenes potentially changing gene function and leading to cancer.

* Types of Mutations

① According to production method:
- Spontaneous mutations.
- Induced mutations → by mutagenic agents.

② According to Affected Genetic material
- 1 Structural chromosomal mutations → Affect fragments of chromosomes
  - Types
    - Translocation
    - Duplication
    - Inversions
    - Insertions
    - Delation
- 2 Gene mutations → May or may not cause a change in the reading pattern of genes
  - Types
    - 1 substitutions ← Replacement of one nucleotide for another, potentially Leading to a change in the amino acid
      - 2 synonymous substitutions ← no change in the amino acid
    - 3 insertions ← Generally cause a change in the reading frame.
    - 4 Deletions ← Generally cause a change in the reading frame.

* Types of mutations

3 According to effect
- 1 silent mutations : change in nucleotide sequence does not result in an amino acid change in the protein.
- 2 Missense mutations → cause a change of one amino acid to another.
- 3 Nonsense mutations → change from a coding codon to a stop codon

4 According to Affected cells
- 1 somatic mutations
  - Located in the DNA of somatic cells
  - Typically occur in tumor cells and may be associated with tumor aggressiveness or therapy response.
- 2 Germline mutations
  - originate in germline cells and can be passed on to descendants
  - present in all cells of the individual's body and may predispose the carrier to cancer

*DNA Replication

- Duplication of the DNA molecule before cell division.
- carried out by a series of enzymes.
- occurs in the 5′ to 3′ direction.
- Leading strand and Legging strand.
- Replication fork: → The point where the two strands are split.
- Key Enzymes
  - **DNA Helicase**
    - unwinds the DNA double helix.
    - Acts like a zipper slider.
    - Break the hydrogen bonds holding the two strands together.
  - **DNA Polymerase**
    - synthesizes new DNA
    - matches exposed bases with complementary nucleotides.
    - can only synthesize DNA in (5′→3′) direction (nucleotides can only be added to the 3′OH).
  - **Primase**
    - Lays down RNA primers
    - to allow DNA Polymerase to initiate replication.
  - **Ligase** ← Joins Okazaki fragments on the Lagging strand.

* synthesizes DNA only in the (5′ → 3′) direction
* Nucleotides can only be added to the (3′OH) end

* Leading strand
  - → synthesized continuously.
  - → DNA polymerase follows DNA helicase as it unwinds the DNA.

* Lagging strand
  - → synthesized in short burste.
  - → DNA polymerase moves away from the replication fork.
  - → composed of okazaki fragments.
  - → Fragments are joined by an enzyme to form a continuous strand.

* importance of DNA Repair :→ Essential for maintaining genome stability due to constant exposur to damage
  - UV Light.
  - chemicals.
  - replication errors.

* cells may resort to apoptosis or senescence if damage is excessive.

* Nobel prize in chemistry 2015 → Awarded to
  - Tomas Lindahl
  - paul Modrich
  - Aziz Sancar

for educidating DNA repair mechanisms

* DNA Repair Mechanisms :
  1. Base Excision Repair (BER).
  2. Nucleotide Excision Repair (NER).
  3. Mismatch Repair (MMR)
  4. Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ)

① Base Excision Repair (BER):
- → Repairs small, non-helix distorting base lesions.
- → Damaged base removal and replacement.

Process

① cytosine loses an amino group, forming uracil.

② uracil cannot pair with guanine, causing a mismatch in the DNA.

③
- → Enzyme: Glycosylase.
- → Action: Detects and removes the damaged base (uracil) from the DNA strand.

④ other enzymes remove the remaining part of the nucleotide, creating a gap in the DNA strand

⑤
- → DNA Polymerase ⟶ Fills the gap with the correct nucleotide.
- → DNA Ligase ⟶ Seals the DNA strand, restoring its integrity.

② Nucleotide Excision Repair (NER)

وظيفة → Removes bulky lesions → UV induced thymine dimers

→ Example → Xeroderm Pigmentosum (genetic disorder caused by NER defects)

→ Process

step 1 → UV radiation can cause thymine dimers to form.

step 2 → Enzyme recognizes the damage and cut the DNA strand; twelve nucleotides are removed

step 3 → DNA polymerase fills the resulting gap.

step 4 → DNA ligase seals the DNA strand, completing the repair.

③ Mismatch Repair (MMR): وظيفة → fixes replication

→ Example → Mismatch repair defects lead to lynch syndrom (hereditary cancer risk)

↓

Process

① During DNA replication, incorrect nucleotide pairings can occur.

→ Two enzymes → MutS, MutL, detect these mismatched bases on the newly synthesized DNA strand

② The enzyme MutH identifies the original template strand by its methyl groups.

→ only the original (template) strand is methylated, which allows the system to distinguish it from the newly synthesized strand.

③ MutH creates a cut near the mismatch on the un methylated, newly synthesized strand.

→ MutL and MutS recruit additional repair machinery to this site.

④ The section of DNA containing the error is removed.

⑤ → DNA polymerase fills in the gap with the correct bases.

→ DNA ligase seals the repaired segment completing the correction.

④ Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ):

HR	NHEJ
- uses sister chromatid for accurate repair of double-strand breaks. - This method is precise دقيق	- Directly ligates (→ joins) broken ends without a template. - faster but more error-prone - lead to small insertions or deletions at the repair site

* Defects in DNA Repair systems and cancer:-

→ Defects:
1. DNA repair systems prevent genomic instability.
2. congenital defects in NER lead to xeroderma pigmentosum (UV sensitivity, skin cancer).
3. MMR (mismatch repair) defects increase hereditary colon cancer risk.
4. cancer cells often have defective repair systems, Leading to instability and mutations.
5. Inhibition of remaining repair systems can be a target for cancer therapies.

→ Pharmaceutical Applications: → olaparib (PARP Inhibitor) → used to inhibit repair systems in cancer cells

* DNA Repair and Drug Development :-

- **Cancer Treatment**
  - many therapies induce DNA damage
    - radiation.
    - chemotherapy.
  - understanding repair mechanisms informs drug development to inhibit these processes.
  - Example → PARP inhibitor → for BRCA mutated cancer.
- **Targeting DNA Repair pathways**
  - Drugs blocking repair pathways enhance treatment efficacy.
  - Tumor cells with defective mismatch Repair MMR are more sensitive to immunotherapy

* Personalized Medicine and DNA Repair

- **Pharmacogenomics** → Tailors treatments based on DNA repair capacity.
- **BRCA1 and BRCA2**
  - key genes in homologous recombination.
  - Genetic mutations inform therapy selection.
  - patients with BRCA mutations are more susceptible to specific cancer and benefit from PARP inhibitor
- **Clinical Implication**

understanding DNA repair defects helps oncologists choose therapies that exploit cancer cell weaknesses.

هديل الزعبي