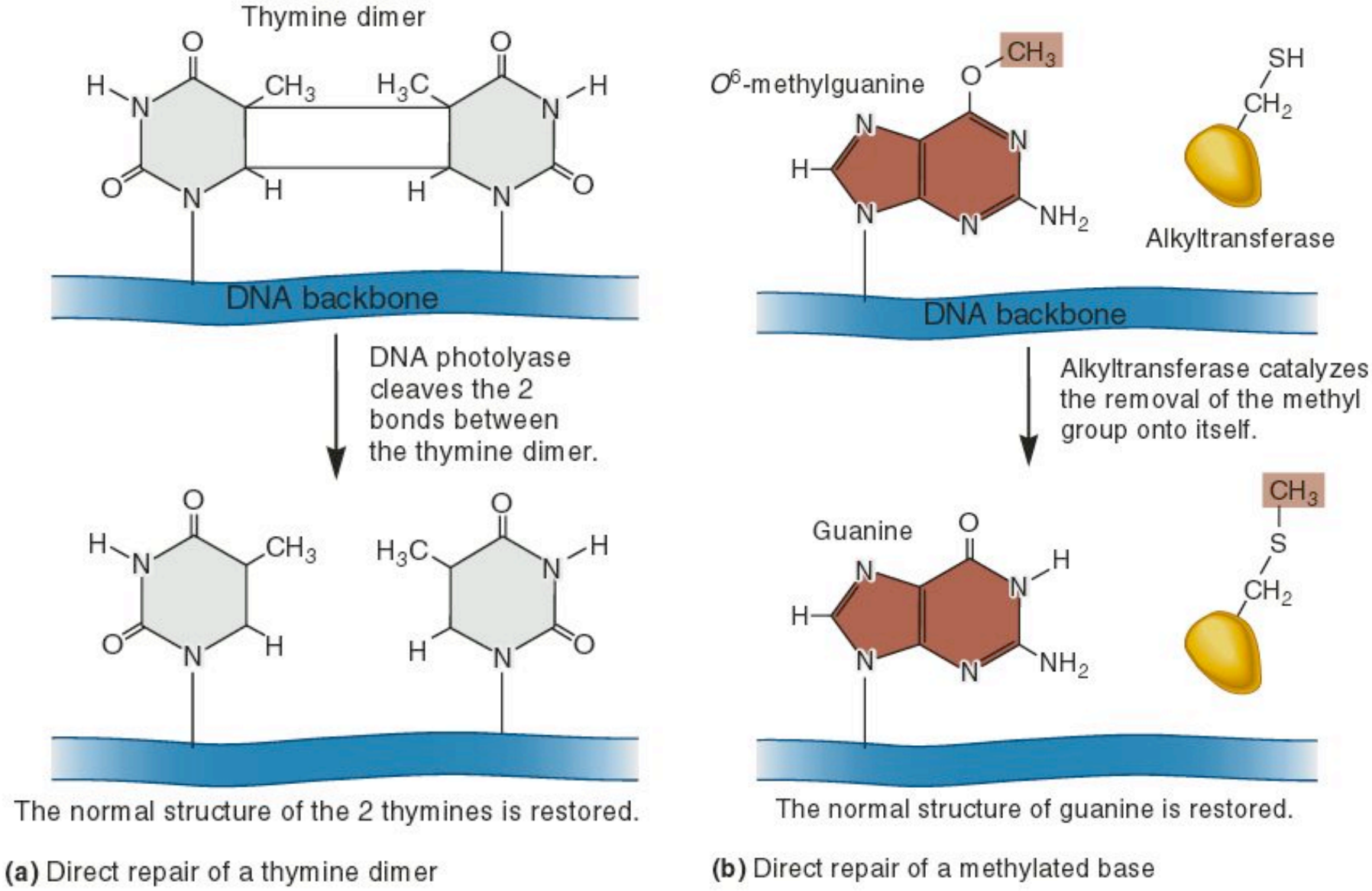
DNA Repair

- Since many mutations are deleterious, DNA repair systems are vital to the survival of all organisms
  - Living cells contain several DNA repair systems that can fix different type of DNA alterations
- DNA repair mechanisms fall into 2 categories
  - Repair of damaged bases
  - Repair of incorrectly basepaired bases during replication
- In most cases, DNA repair is a multi-step process
  - 1. An irregularity in DNA structure is detected
  - 2. The abnormal DNA is removed
  - 3. Normal DNA is synthesized

Damaged Bases Can Be Directly Repaired

- Called DIRECT REPAIR
- In a few cases, the covalent modifications of nucleotides can be reversed by specific enzymes
  - Photolyase can repair thymine dimers induced by UV light
    - It splits the dimers restoring the DNA to its original condition
  - O^6-alkylguanine alkyltransferase repairs alkylated bases
    - It transfers the methyl or ethyl group from the base to a cysteine side chain within the alkyltransferase protein

Direct repair of damaged bases in DNA



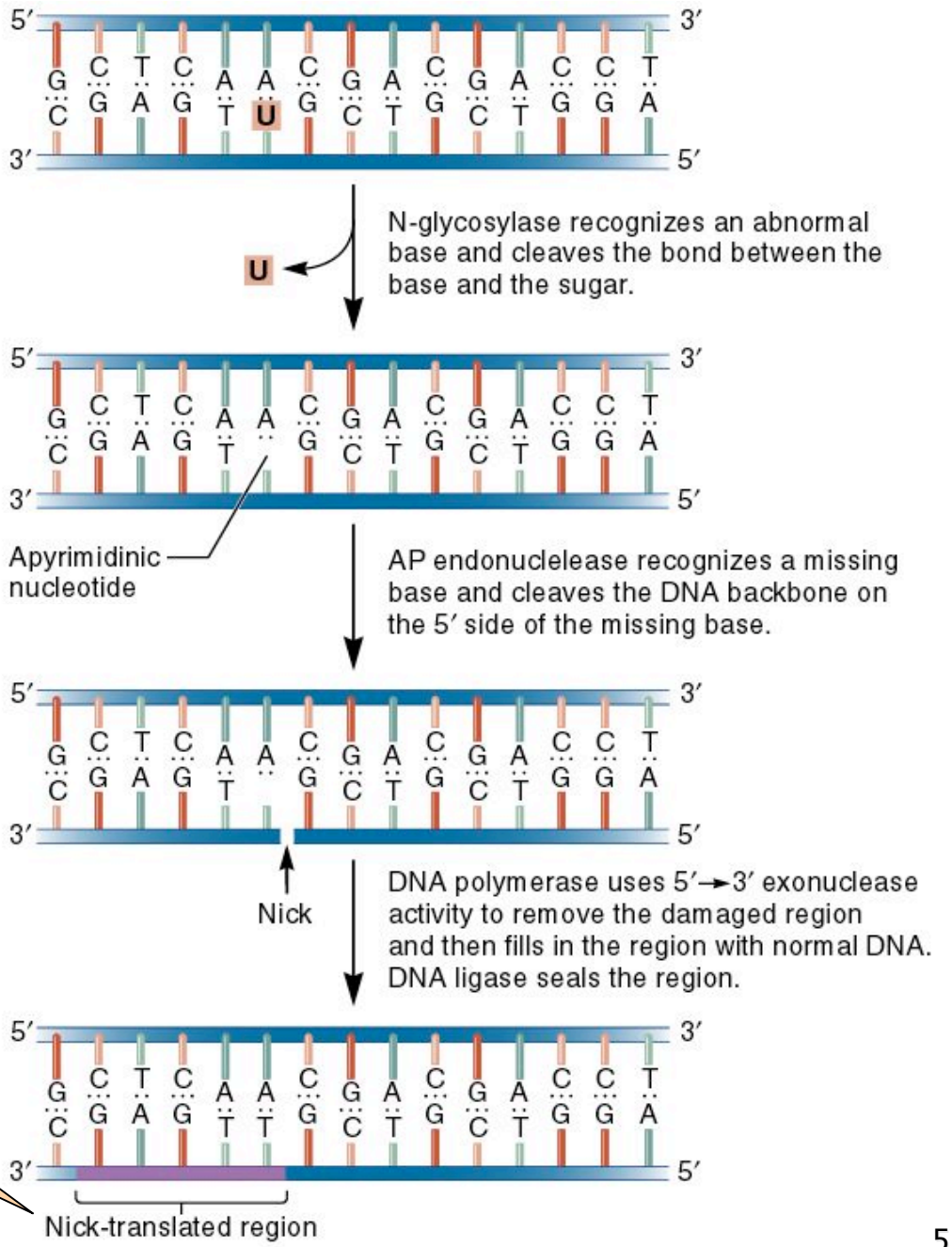
Base Excision Repair System

- Base excision repair (BER) involves a category of enzymes known as DNA-N-glycosylases
  - These enzymes can recognize a single damaged base and cleave the bond between it and the sugar in the DNA
  - Removes one base, excises several around it, and replaces with several new bases using Pol adding to 3' ends then ligase attaching to 5' end

- Depending on the species, this repair system can eliminate abnormal bases such as
  - Uracil; Thymine dimers
  - 3-methyladenine; 7-methylguanine

Base Excision Repair System

Depending on whether a purine or pyrimidine is removed, this creates an apurinic and an apyrimidinic site, respectively



Nick replication would be a more accurate term

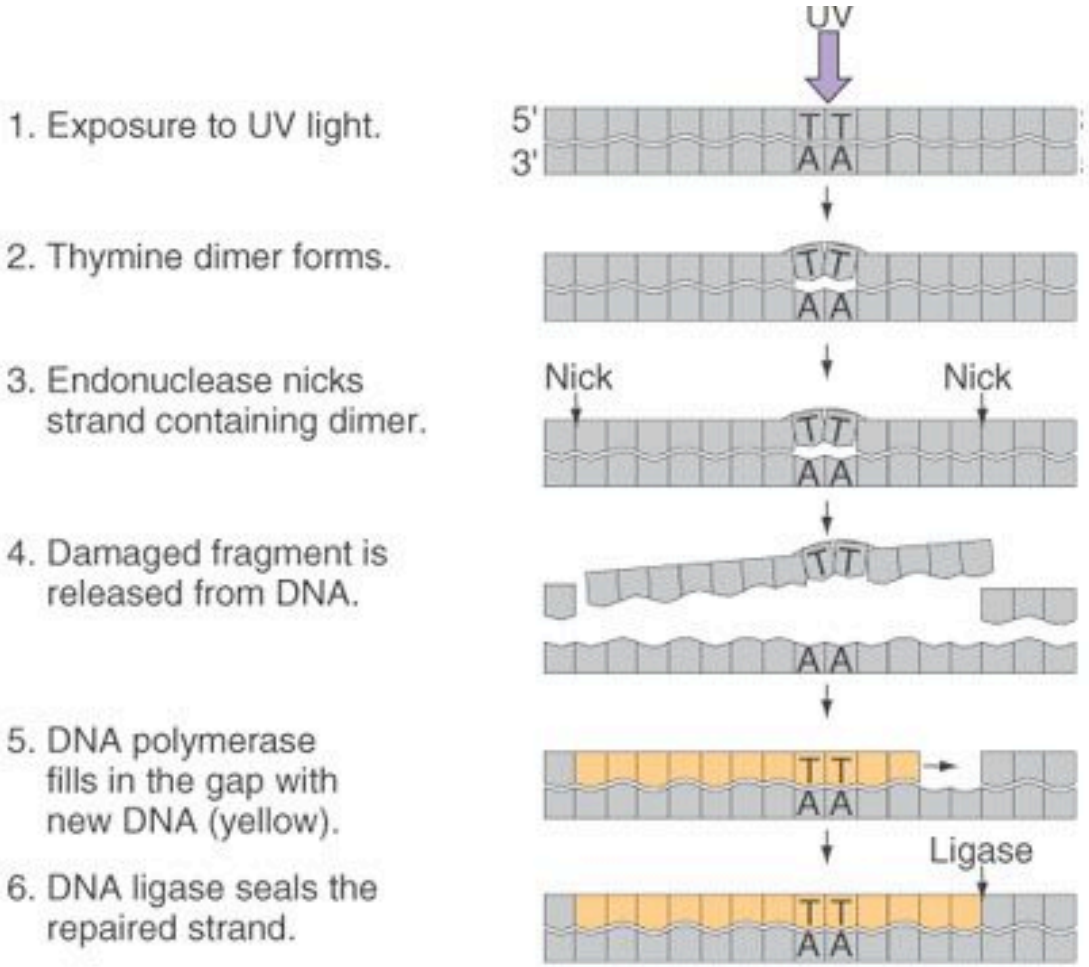
Nucleotide Excision Repair System

- An important general process for DNA repair is nucleotide excision repair (NER)
  - Nicks DNA around damaged base and removes region
  - Then fills in with Pol on 3'ends, and attaches 5' end with ligase

- This type of system can repair many types of DNA damage, including
  - Thymine dimers and chemically modified bases

- NER is found in all eukaryotes and prokaryotes
  - However, its molecular mechanism is better understood in prokaryotes

DNA REPAIR of damaged base:
Nucleotide Excision Repair fixes errors created by mutagens

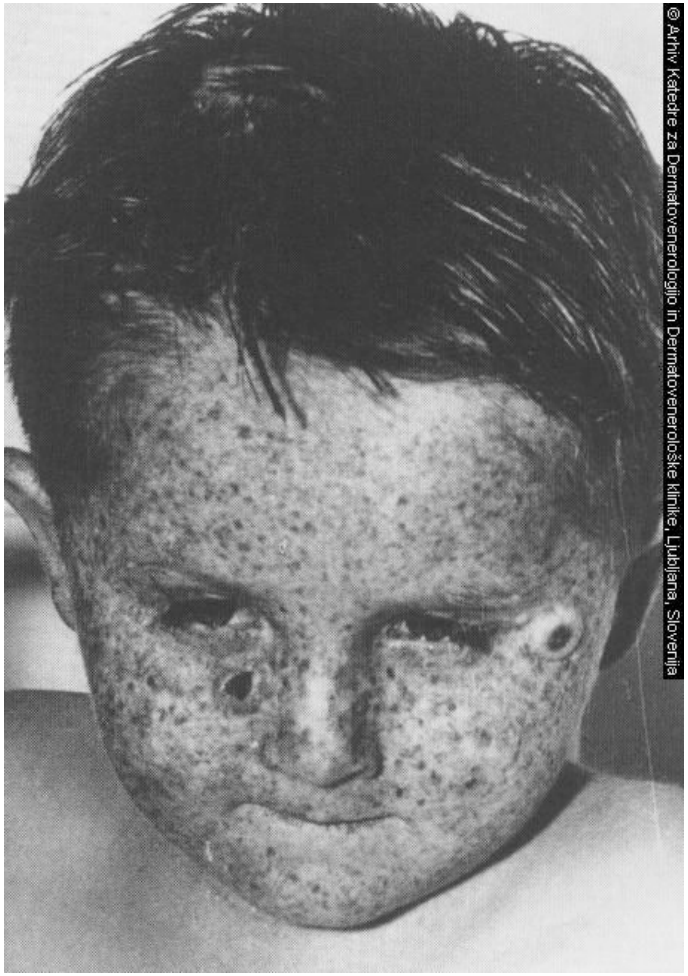


- Excision repair enzymes release damaged regions of DNA.
- Single strand released
- Repair is then completed by DNA polymerase and DNA ligase

Nucleotide Excision Repair Removes Damaged DNA Segments

- Several human diseases have been shown to involve inherited defects in genes involved in NER
  - These include xeroderma pigmentosum (XP) and Cockayne syndrome (CS)
    - A common characteristic of both syndromes is an increased sensitivity to sunlight
  - Xeroderma pigmentosum can be caused by defects in seven different NER genes

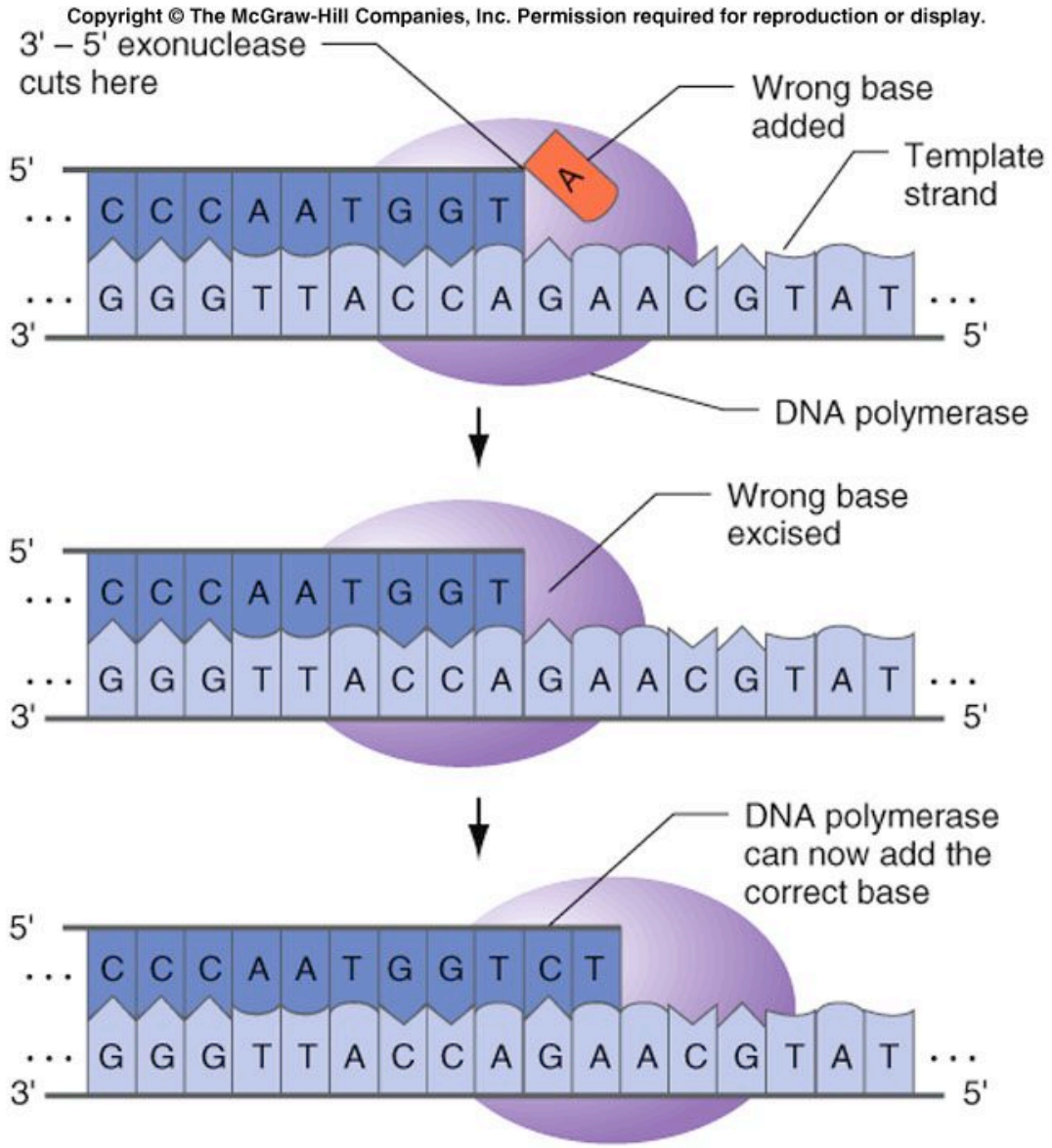
Skin lesions of Xeroderma Pigmentosum



Mistakes during replication alter genetic information

- Errors during replication are exceedingly rare, less than once in 10^9 base pairs
- Proofreading enzymes correct errors made during replication
  - DNA polymerase has 3′ – 5′ exonuclease activity which recognizes mismatched bases and excises them
  - If errors slip through proofreading:
    - In bacteria, methyl-directed mismatch repair finds these errors on newly synthesized strands and corrects them
    - In euks, mismatch repair finds these errors on newly synthesized strands and corrects them

DNA polymerase proofreading

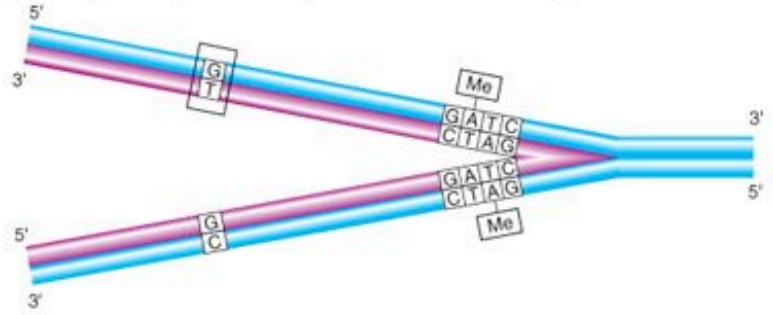


Mismatch Repair System

- If proofreading fails, the methyl-directed mismatch repair system comes to the rescue
- This repair system is found in all species
- In humans, mutations in the system are associated with particular types of cancer
- Methyl-directed mismatch repair recognizes mismatched base pairs, excises the incorrect bases, and then carries out repair synthesis.

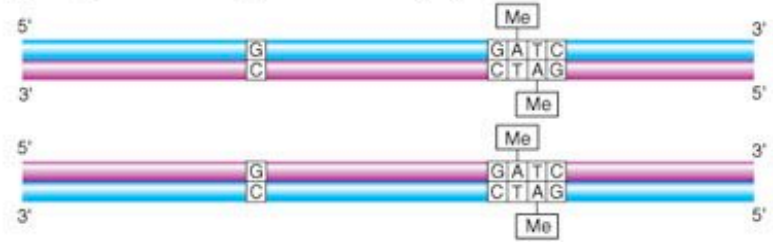
(a) Parental strands are marked with methyl groups.

(b) Enzyme system recognizes mismatch in replicated DNA.



(c) DNA on unmarked new strand is excised.

(d) Repair and methylation of newly synthesized DNA strand.



Methyl-directed mismatch repair in Prokaryotes

Mismatch Repair in Eukaryotes

- Eukaryotes also have mismatch repair, but it is not clear how old and new DNA strands are identified.
  - Four genes are involved in humans, *hMSH2* and *hMLH1, hPMS1,* and *hPMS2*
  - All of these are mutator genes
  - mutation in any one of them confers hereditary predisposition to hereditary nonpolyposis colon cancer

A question

1. What are the major types of DNA damage repaired by each of the following pathways: (a) photoreversal, (b) base excision repair, (c) nucleotide excision repair, and (d) mismatch repair?