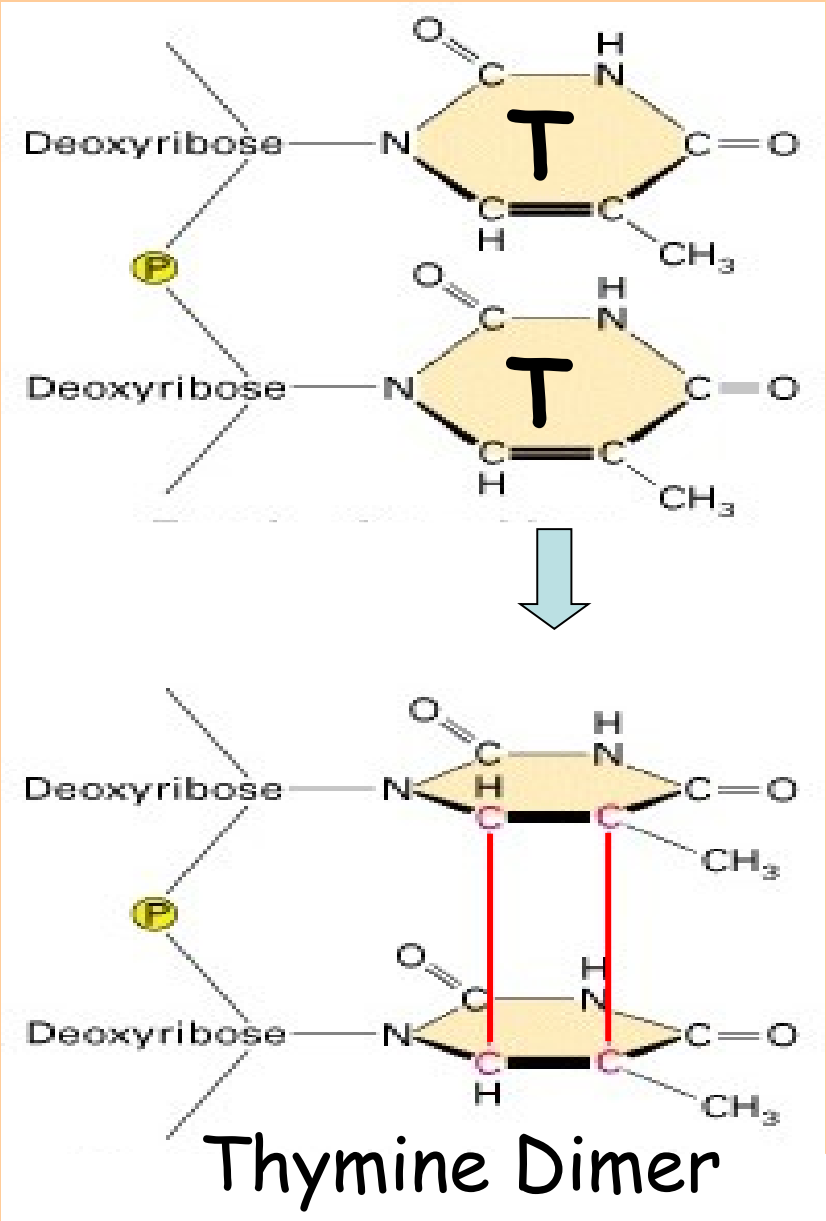
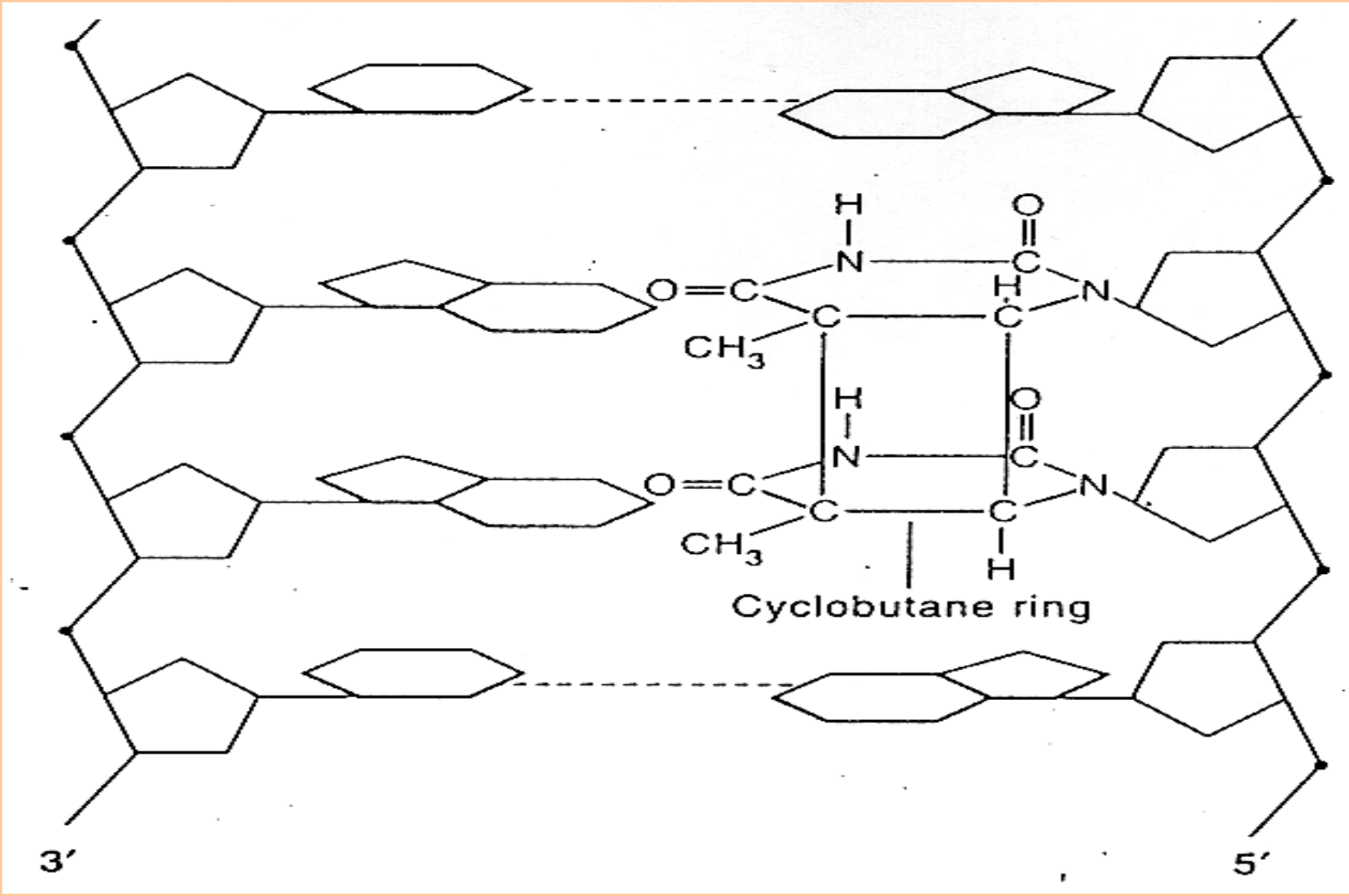
Some notes on causation of skin cancers

- **Ultraviolet Light Damage and DNA Repair**
- Ultraviolet (UV) light is an agent that causes damage to DNA.
- Absorption of UV light by DNA causes adjacent pyrimidine bases to become covalently linked to form a pyrimidine dimer.



Thymine dimer formation by UV light

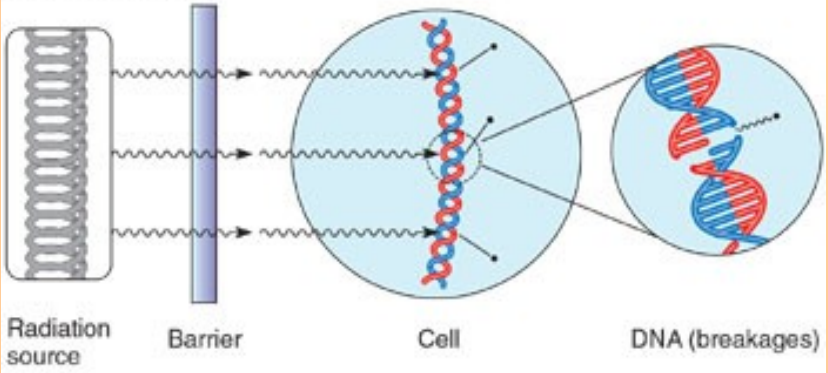


4. Radiation

1. Ionizing radiation – deep penetrating power, breaks DNA,
   - gamma rays, X-rays, cathode rays
   - used to sterilize medical supplies & food products
1. Nonionizing radiation – little penetrating power to sterilize air, water & solid surfaces
   - uv light creates thymine pyrmidines, which interfere with replication

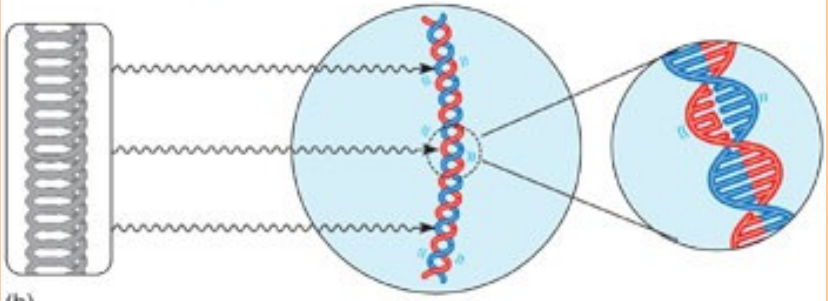
Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.

Ionizing Radiation

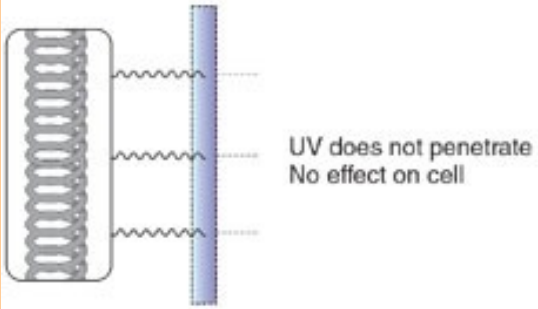


(a)

Nonionizing Radiation

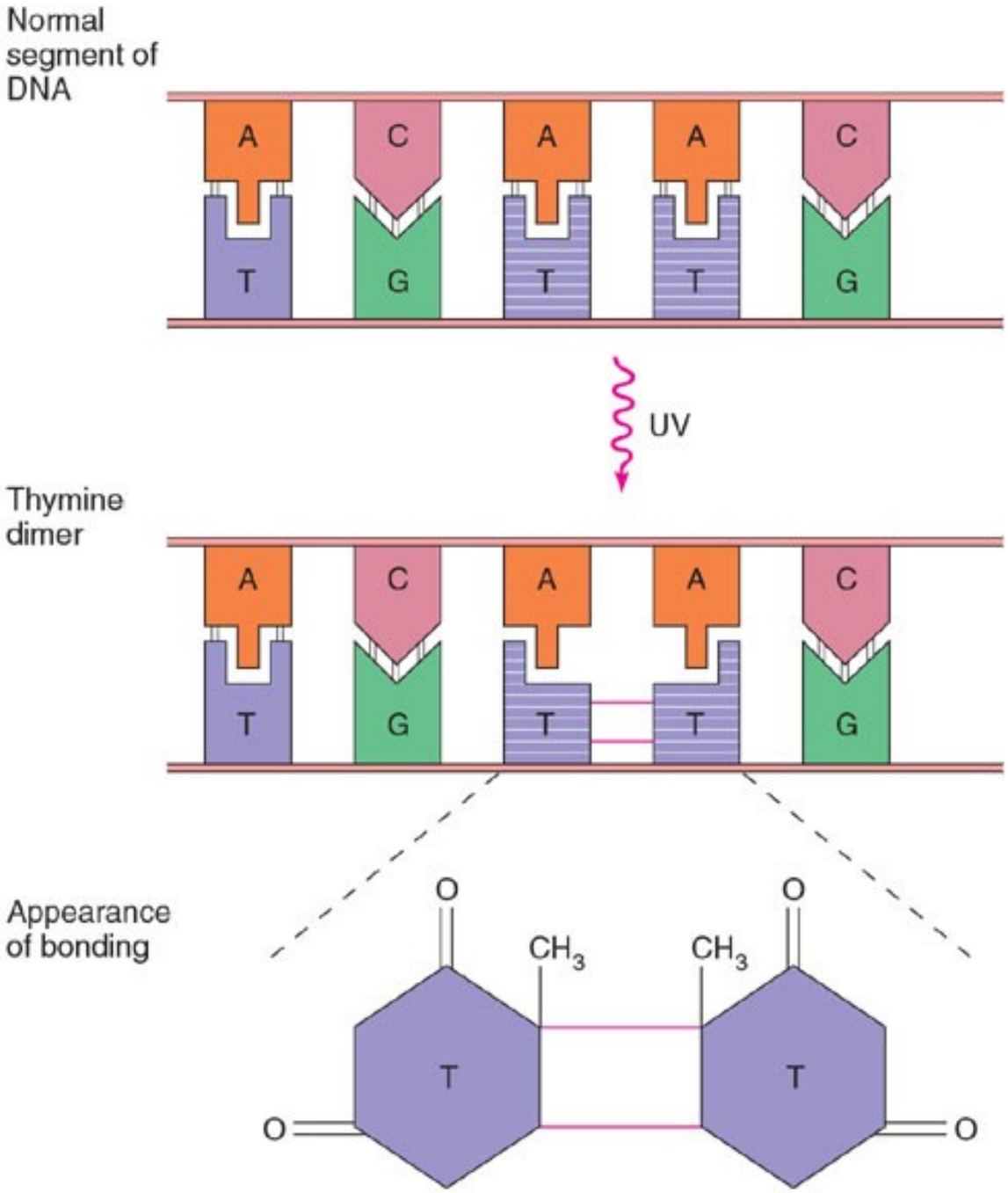


(b)



(c)

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



- As a result of pyrimidine dimer formation, there is no hydrogen bonding between these pyrimidine molecules and the complementary bases on the other DNA strand.
- This stretch of DNA cannot be replicated or transcribed!
- Organisms have mechanisms to repair ultraviolet light damage, but such processes can make a mistake.
- When the UV damage repair system makes an error and causes a change in the nucleotide sequence of the DNA, mutations, and disease occur

- In medicine, the pyrimidine dimerization reaction is used to advantage in hospitals where germicidal (UV) light is used to kill bacteria in the air and on environmental surfaces, such as in a vacant operating room.
- This cell death is caused by pyrimidine dimer formation on a massive scale. The repair systems of the bacteria are overwhelmed, and the cells die.
- The same type of pyrimidine dimer formation can occur in human cells as well. Lying out in the sun all day to acquire a fashionable tan exposes the skin to large amounts of UV light.
- This damages the skin by formation of many pyrimidine dimers. Exposure to high levels of UV from sunlight or tanning booths has been linked to a rising incidence of skin cancer in human populations.

- **Consequences of Defects in DNA Repair => disease!**
- **The human repair system for pyrimidine dimers is quite complex, requiring at least five enzymes.**
- **The first step in repair of the pyrimidine dimer is the cleavage of the sugar-phosphate backbone of the DNA near the site of the damage.**
- **The enzyme that performs this is called a repair endonuclease. (**NER)
- **If the gene encoding this enzyme is defective, pyrimidine dimers cannot be repaired.**
- **The accumulation of mutations combined with a simultaneous decrease in the efficiency of DNA repair mechanisms leads to an increased incidence of cancer.**
- **For example, a mutation in the repair endonuclease gene, or in other genes in the repair pathway, results in the genetic skin disorder called xeroderma pigmentosum.**
- **People who suffer from xeroderma pigmentosum are extremely sensitive to the ultraviolet rays of sunlight and develop multiple skin cancers, usually before the age of twenty.**

The discovery of NER

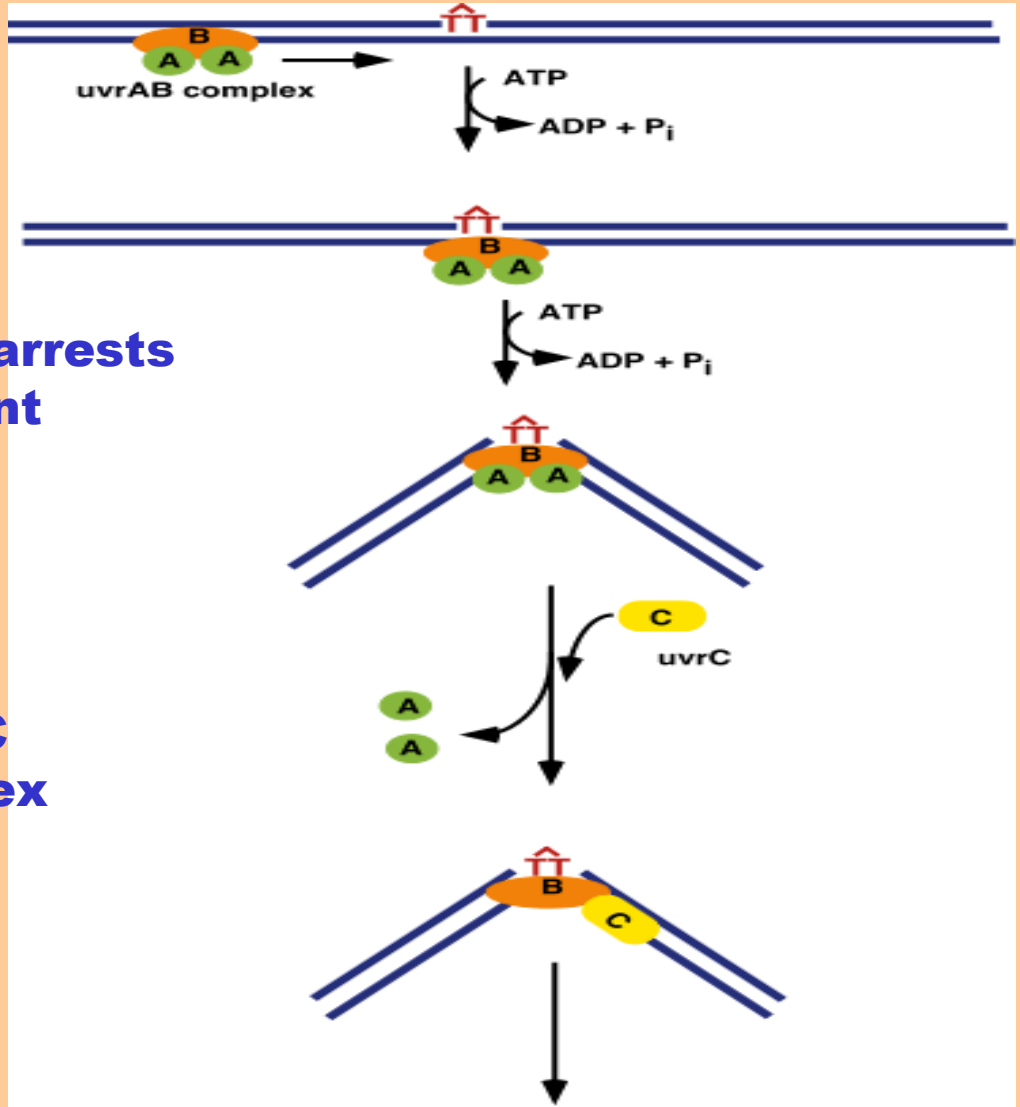
- Setlow found three mutations in E. coli that rendered the cells sensitive to UV damage.
- The genes were named UvrA, UvrB and UvrC for UV resistance.
- Using cell-free extracts, Sancar determined the mechanism of uvrABC which has been refined over the years.

The process of uvrABC excision of DNA damage is called nucleotide excision repair.

uvrA is a ATP-helicase that moves along the DNA looking for damage

When DNA damage is encountered the complex arrests at the site. The DNA is bent

uvrA is released and uvrC is recruited to the complex

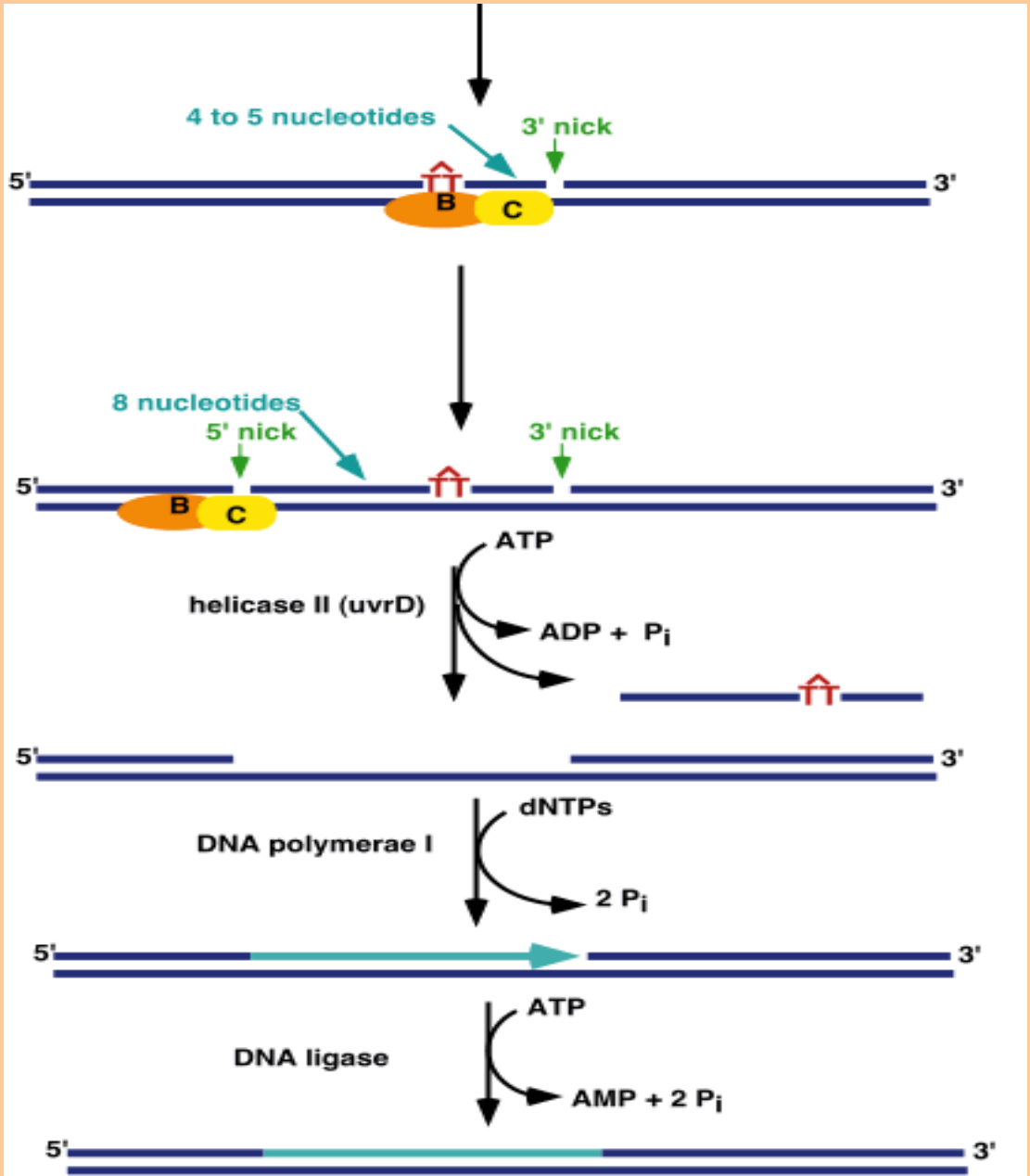


NER in E. coli continued

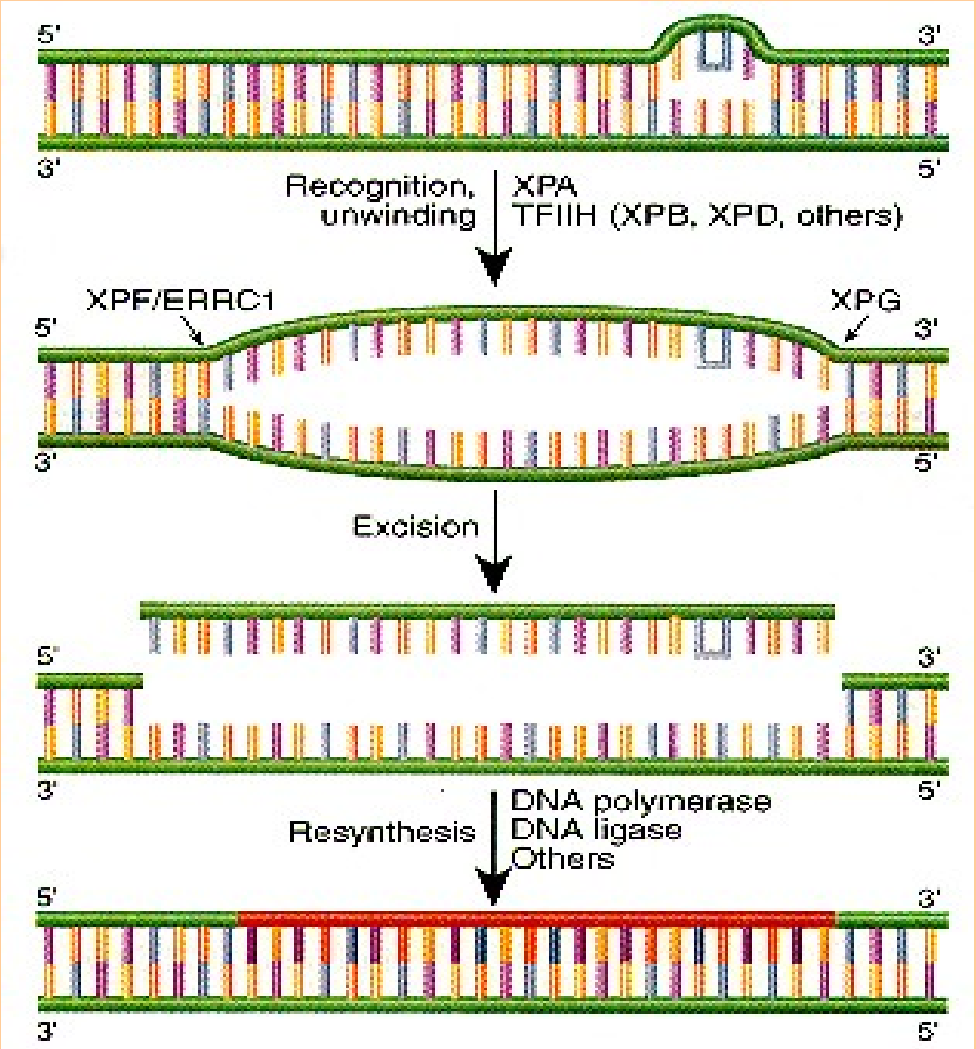
two single strand nicks are placed to the 3' side of the dimer (4 to 5 nucleotides) and to the 5' side of the dimer (8 nucleotides)

helicase II (uvrD) unwinds 12 - 13 b fragment containing the dimer, ATP hydrolysis required

DNA polymerase I fills in the gap dNTPs required



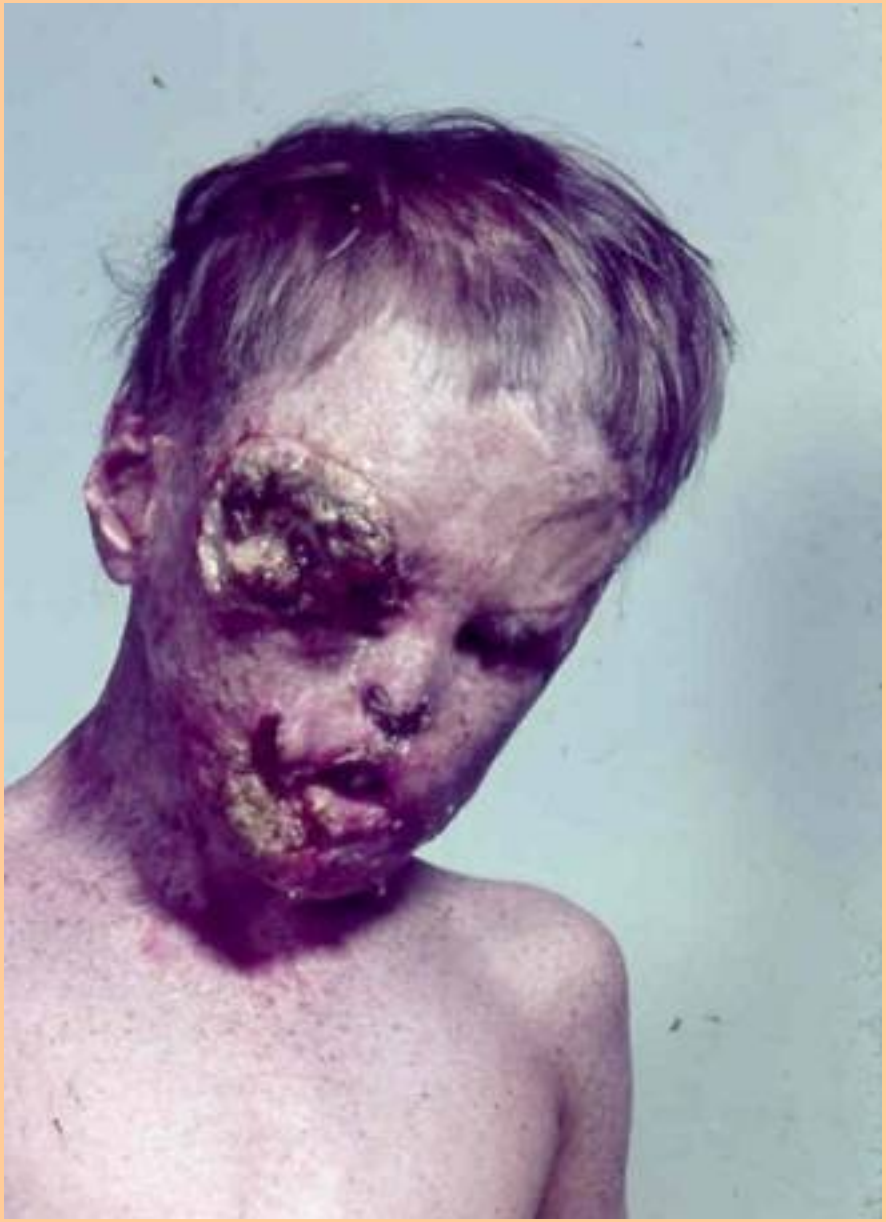
Nucleotide Excision Repair

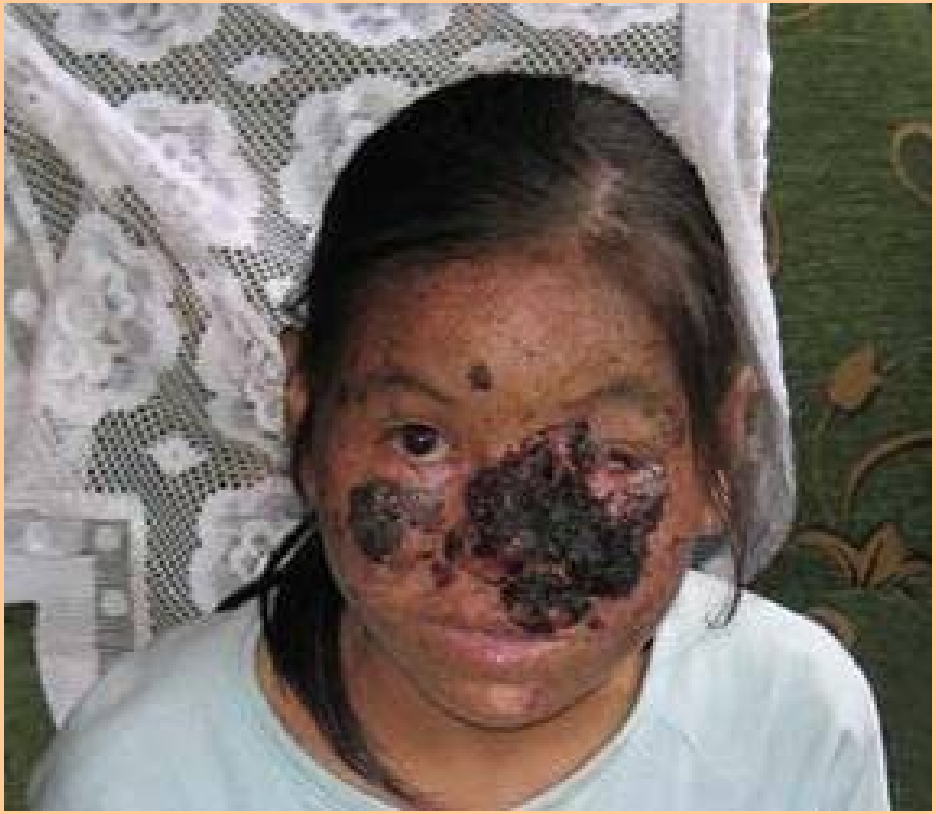


Cutting it out. In excision repair, the nucleases XPF/ERRC1 and XPG clip out about 30 nucleotides in all.

- Many cancers (eg XP) are caused by defective repair of DNA
- **Such cancers are caused by mutations in genes associated with growth control.**
- **Defects in DNA-repair systems are expected to increase the overall frequency of mutations and, hence, the likelihood of a cancer-causing mutation.**

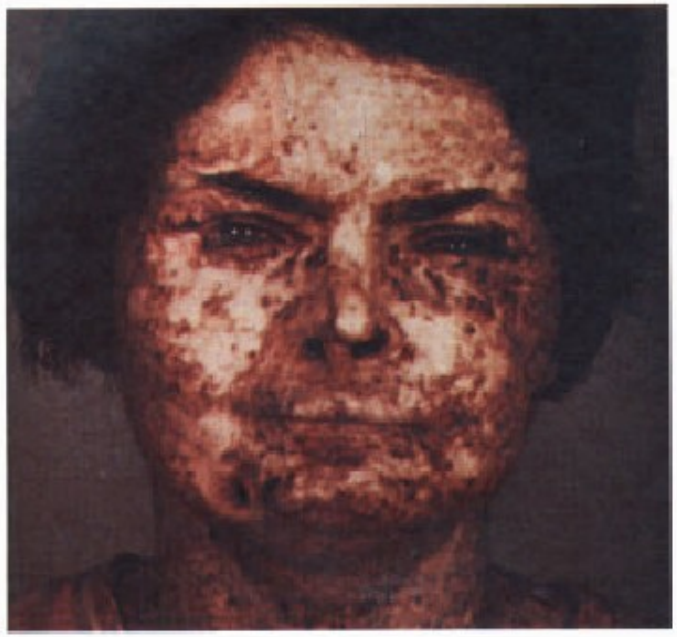
Xeroderma Pigmentosum - a Disease that is due to Defective Repair of DNA



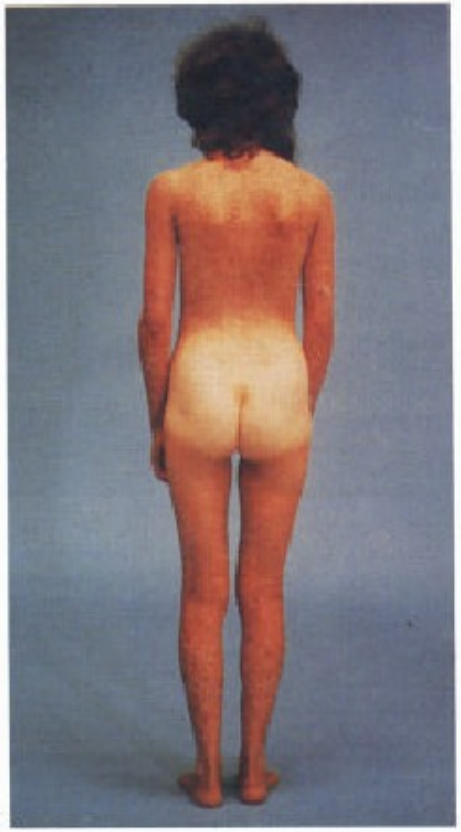


Xeroderma pigmentosum

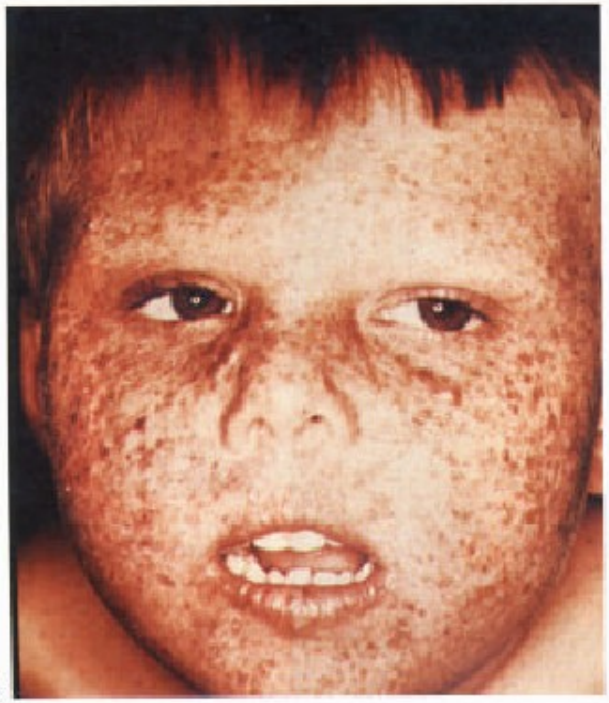

(c) University Erlangen,
Department of Dermatology
Phone: (+49) 9131 - 85 - 2727



A



B



C

D

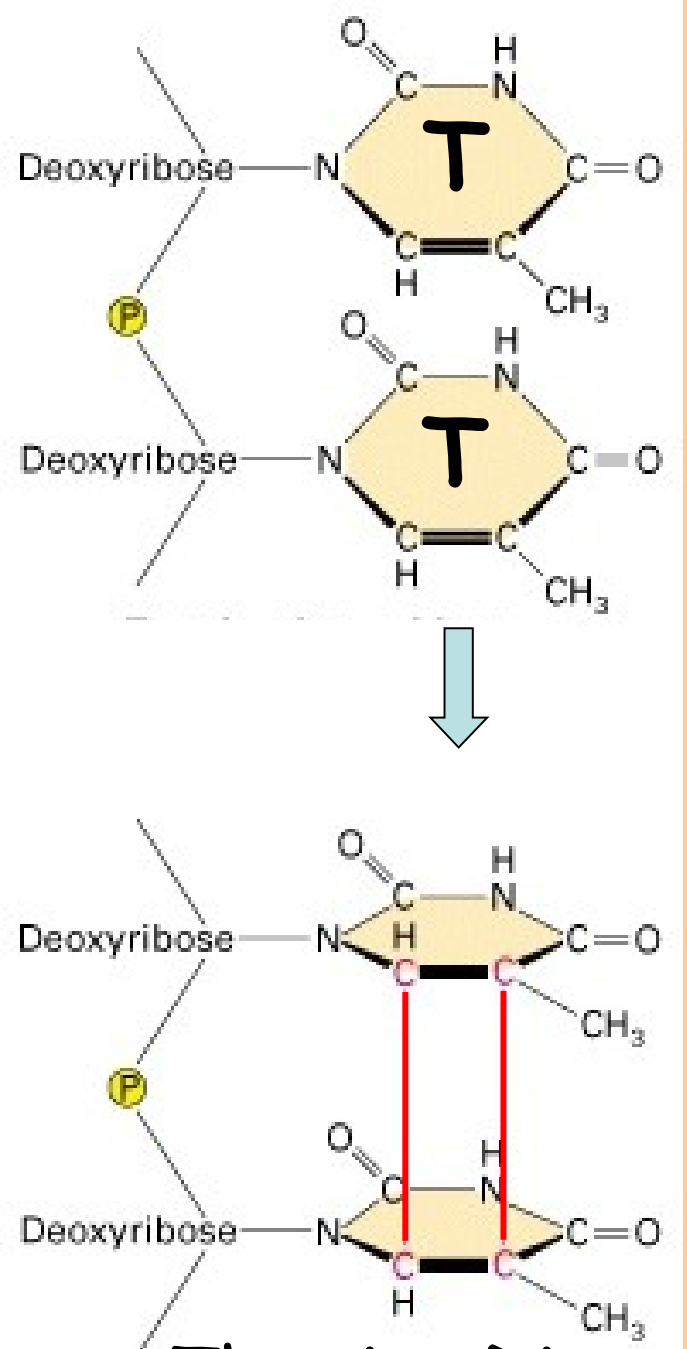
Xeroderma pigmentosum (XP), the first disease recognized to be caused by defective DNA repair, **is a rare inherited human skin disease, that is genetically transmitted as an autosomal recessive trait, in which the mechanisms for repair of DNA subsequent to damage by UV irradiation are defective.**

- **This arises because of mutations in the genes encoding components of the nucleotide excision pathway of repair. i.e it is associated with failure of nucleotide excision repair system (NER).**
- **This predisposes the patient to pigmented lesions on areas of the skin after even short exposure to the sun and an elevated incidence of skin cancer.**

- **Xeroderma pigmentosum seems to involve the repair of damaged DNA, particularly thymine dimers as the inherited defect.**
- If UV damage is not repaired, mutations in DNA will result and may cause cancer.
- Patients with xeroderma pigmentosum often suffer from a variety of skin cancers from an early age.
- It has been estimated that patients with xeroderma pigmentosum have a 1000-fold greater chance of developing skin cancer than do normal individuals.

- **What causes the genetic disease xeroderma pigmentosum?**

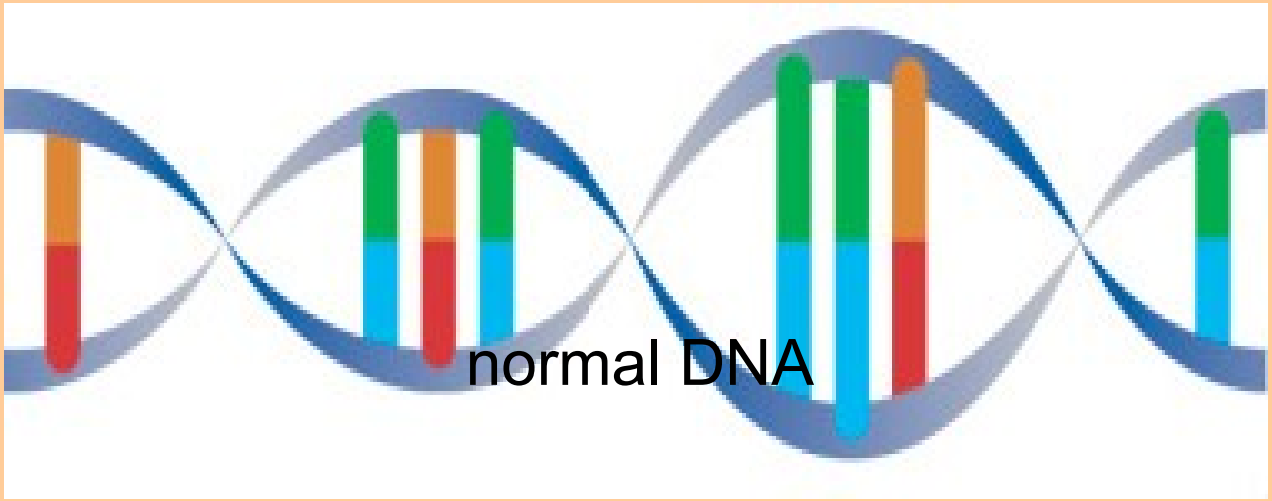
- Ionizing radiation and UV light are carcinogenic agents that can **cause the formation of pyrimidine dimers by the covalent linkage of adjacent pyrimidine bases.**

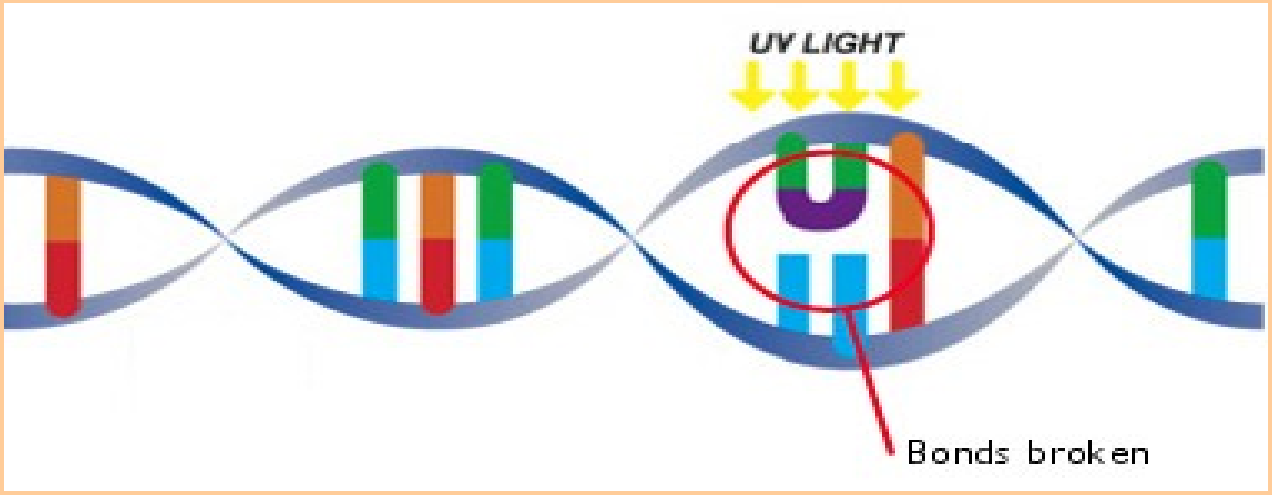


Thymine Dimer

5′--CCGAAttCAG--3′
3′--GGCTTAAGTC--5′

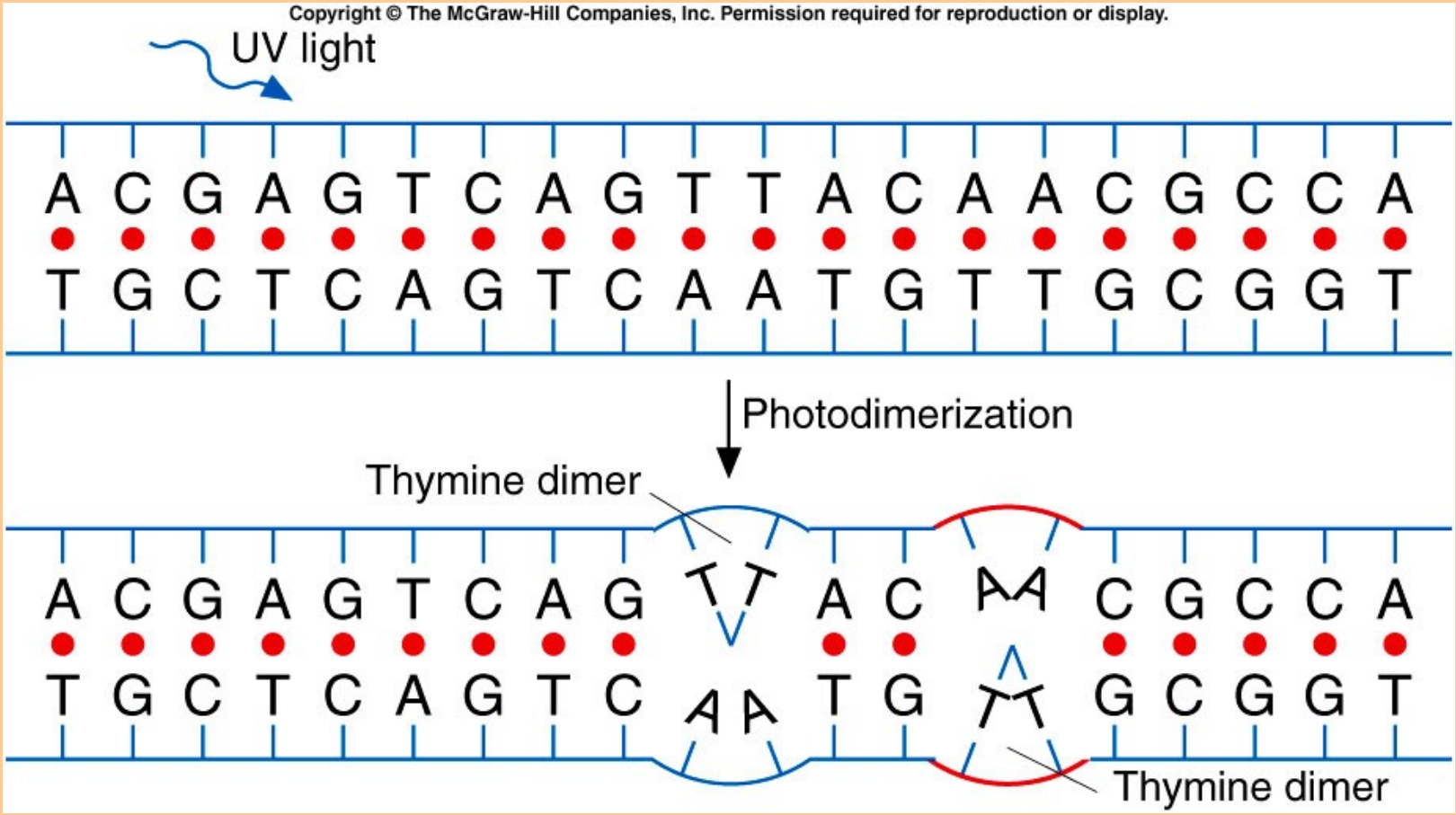
UV Radiation, Pyrimidine dimers





DNA with pyrimidine dimers

UV Damage


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
UV light
A C G A G T C A G T T A C A A C G C C A
T G C T C A G T C A A T G T T G C G G T
Photodimerization
Thymine dimer
A C G A G T C A G T T A C A A C G C C A
T G C T C A G T C A A T G T T G C G G T
Thymine dimer

- **Why are people who suffer from xeroderma pigmentosum prone to cancer?**
- Normally one of two repair pathways usually fix such problems.
- There are 2 types of NER:
- ~Global Genome (GG-NER)
- ~Transcription coupled (TC-NER)
- But if these repair pathways become overwhelmed, or defected such that they are unable to repair DNA damaged by UV radiation, this inability can lead to xeroderma pigmentosum.
- People who suffer from this genetic skin disorder are very sensitive to UV light and develop multiple skin cancers, such as squamous cell carcinoma, melanoma.

- The major damage inflicted on DNA by UV irradiation is the formation of thymine dimers, where covalent bonds are formed between carbons 5 and 5 and 6 and 6 of adjacent intrachain thymine residues. Other types of damage can also occur.

- Pyrimidine dimers can be formed in the skin cells of humans exposed to unfiltered sunlight, because ultraviolet light produces pyrimidine dimers in human DNA.
- In normal fibroblasts, half the pyrimidine dimers produced by ultraviolet radiation are excised in less than 24 hours.
- However, studies of skin fibroblasts from patients with xeroderma have revealed a biochemical defect in one form of this disease that disables their cells from repairing the damaged DNA, resulting in extensive accumulation of mutations and, consequently, skin cancers.
- In contrast, to normal persons, almost no dimers are excised in this time interval in fibroblasts derived from patients with xeroderma pigmentosum.

- **The results of these studies show that xeroderma pigmentosum can be produced by a defect in the exonuclease that hydrolyzes the DNA backbone near a pyrimidine dimer.**
- **The most common form of this disease is caused by the absence of the U V-specific endonuclease (see Figure 30.23).**
- **Cells cultured from patients xeroderma pigmentosum exhibit low activity for the nucleotide excision-repair process**.
- The drastic clinical consequences of this enzymatic defect emphasize the critical importance of DNA-repair processes.
- The disease can also be caused by mutations in eight other genes for DNA repair which attests to the complexity of repair processes.

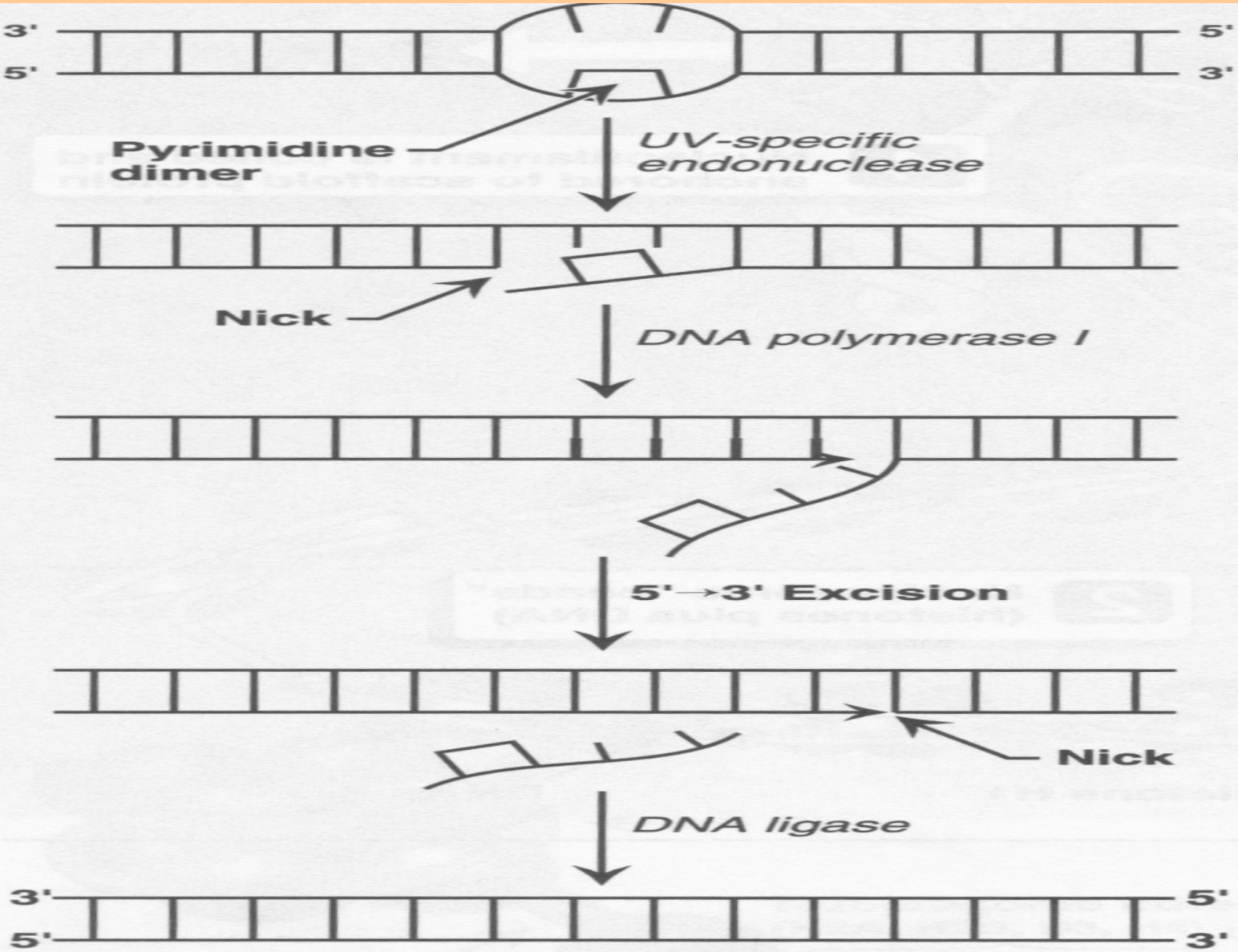


Figure 30.23
Excision repair of pyrimidine dimers in DNA.

This slide summarizes the mechanisms involved in the disease