

DNA Repair

- DNA repair mechanisms reduce the mutation rate (in humans) by over 1000 fold.

Lesions in DNA repair systems increase the mutation rate and increase ones predisposition to cancer

Table 5–2 Some Inherited Syndromes with Defects in DNA Repair

NAME	PHENOTYPE	ENZYME OR PROCESS AFFECTED
MSH2, 3, 6, MLH1, PMS2	colon cancer	mismatch repair
Xeroderma pigmentosum (XP) groups A–G	skin cancer, UV sensitivity, neurological abnormalities	nucleotide excision–repair
XP variant	UV sensitivity, skin cancer	translesion synthesis by DNA polymerase η
Ataxia telangiectasia (AT)	leukemia, lymphoma, γ-ray sensitivity, genome instability	ATM protein, a protein kinase activated by double-strand breaks
BRCA2	breast, ovarian, and prostate cancer	repair by homologous recombination
Werner syndrome	premature aging, cancer at several sites, genome instability	accessory 3'-exonuclease and DNA helicase
Bloom syndrome	cancer at several sites, stunted growth, genome instability	accessory DNA helicase for replication
Fanconi anemia groups A–G	congenital abnormalities, leukemia, genome instability	DNA interstrand cross-link repair
46 BR patient	hypersensitivity to DNA-damaging agents, genome instability	DNA ligase I

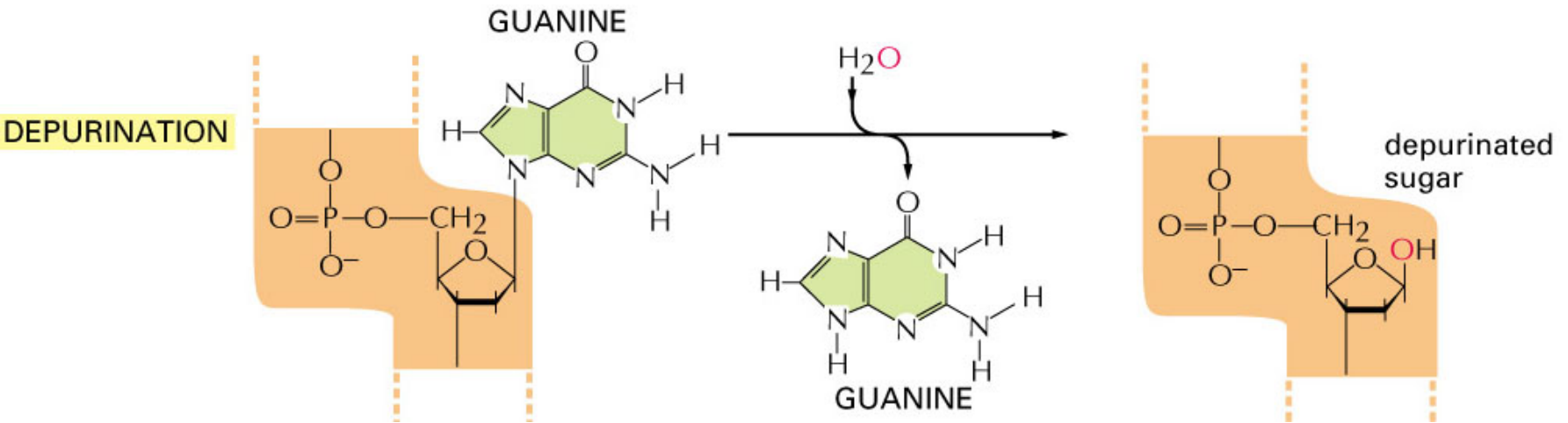
Table 5-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

The major causes of DNA damage include

- Depurination
- Deamination
- UV radiation
- Ionizing radiation (gamma rays, X rays)
- Mutagenic chemicals (like EMS)

Depurination

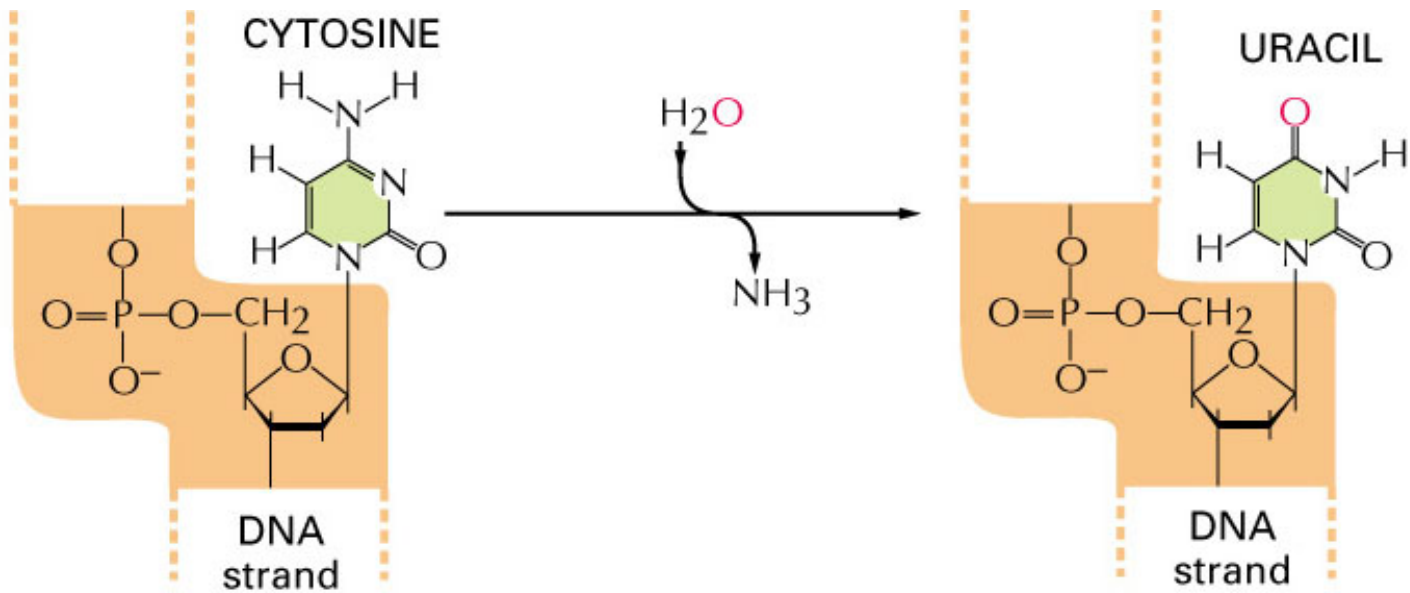
- Loss of a purine (A or G) base
- Caused by thermal fluctuations
- Frequency in humans: 5000/cell/day



Deamination

- Loss of an amine group converts a cytosine to uracil
- Caused by thermal fluctuations
- Frequency in humans: 100/cell/day

DEAMINATION



Ultraviolet Light

- Forms thymine dimers, in which adjacent thymine bases become covalently bonded to each other.

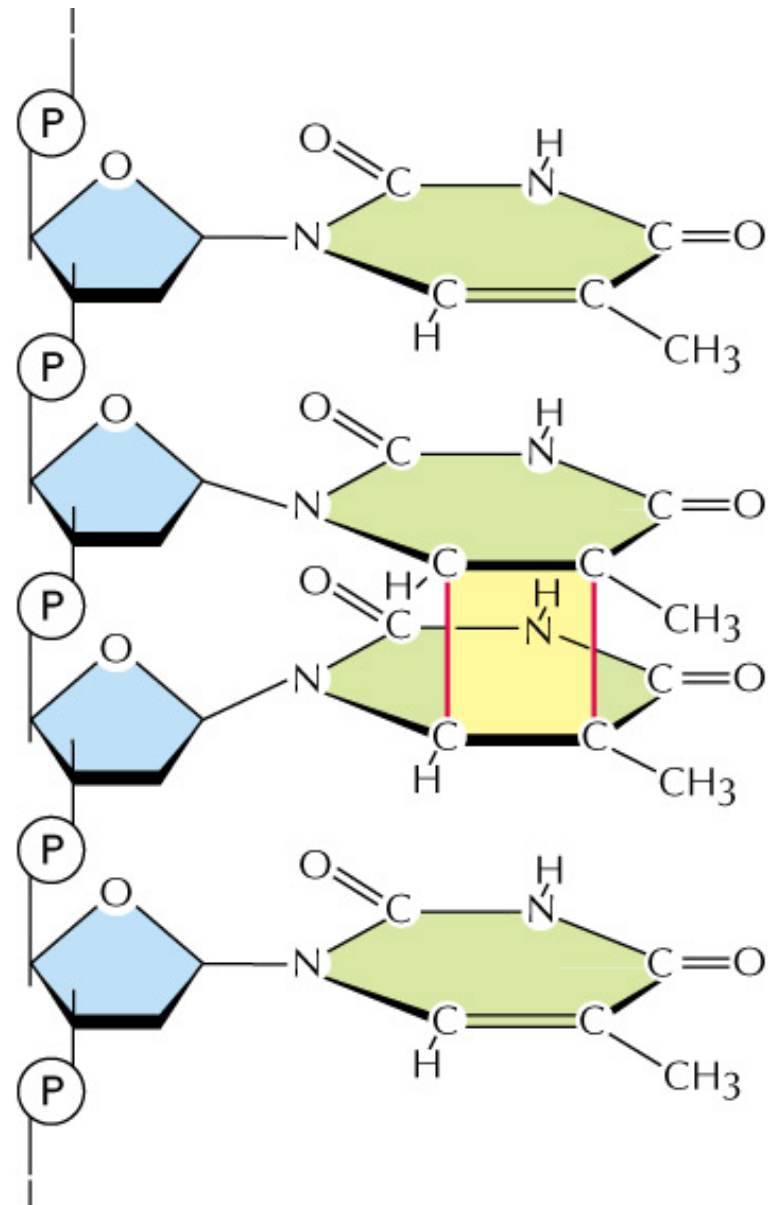


Figure 5-48. Molecular Biology of the Cell, 4th Edition.

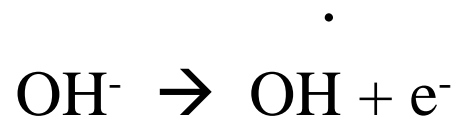
Ionizing radiation forms free radicals that induce breaks in DNA

- Free radicals (molecules with unpaired electrons) include:

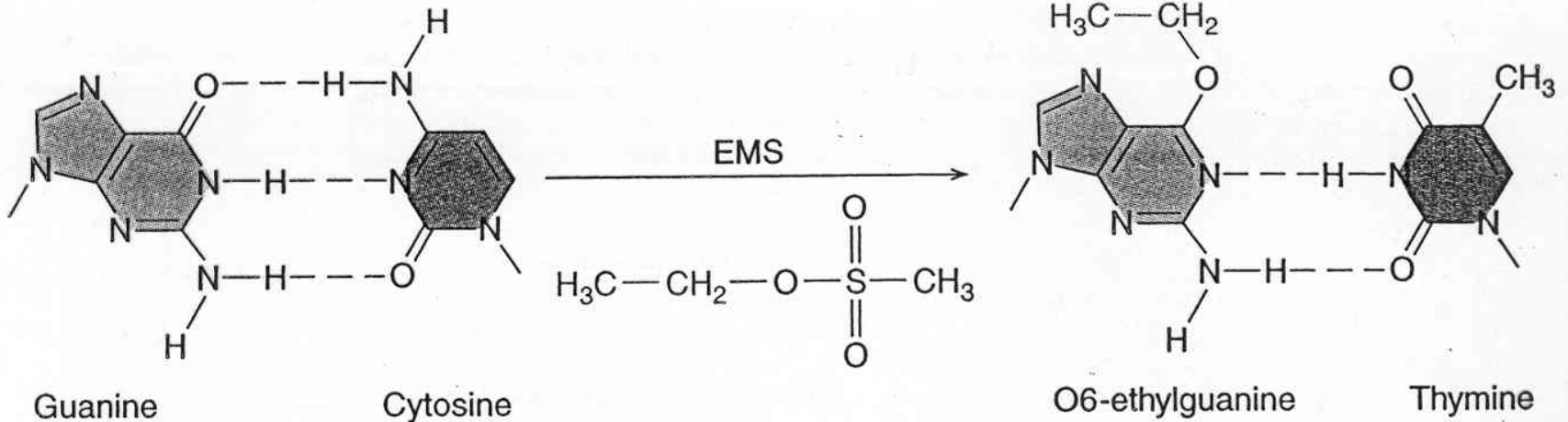
- Superoxide radical



- Hydroxyl radical



Ethylmethane Sulfonate (EMS) causes mutations by altering the chemistry of guanine nucleotides



Unrepaired base changes cause permanent point mutations such as deletions and substitutions

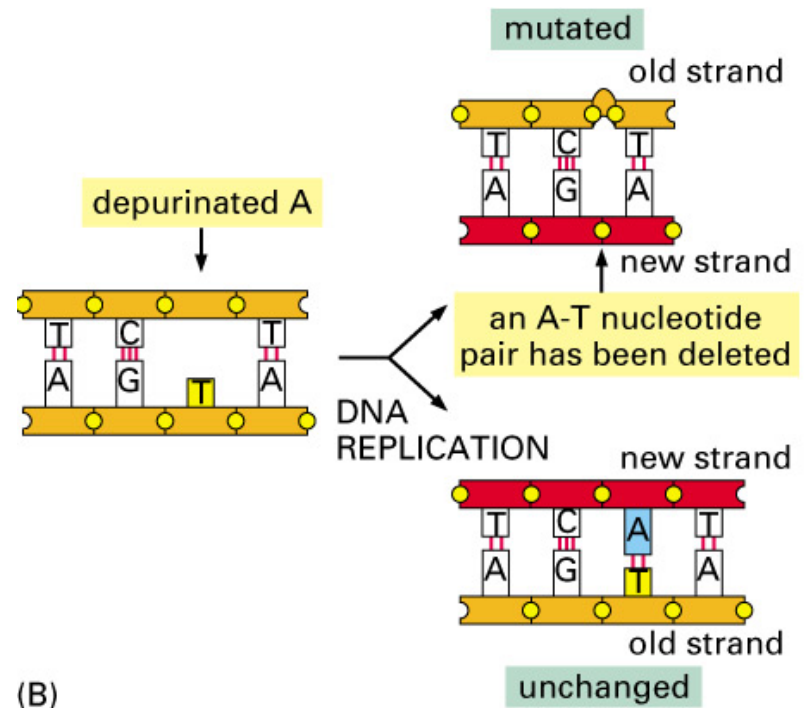
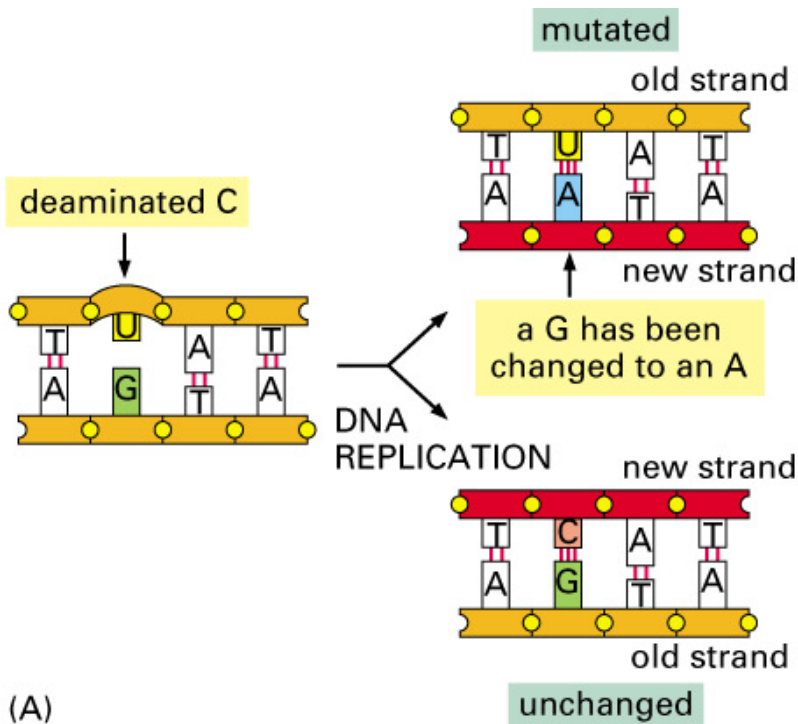


Figure 5-49 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

Figure 5-49 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

The DNA double helix is readily repaired because it has 2 strands. When one strand is mutated, the other can be used as a template to fix the error.

- DNA Repair Mechanisms in *E. coli* include:
 - Nucleotide Excision Repair
 - Strand-directed Mismatch Repair

Draw these mechanisms from the Blackboard

Definitions

- Homologous
 - 2 pieces of DNA or RNA are homologous if they have the same nucleotide sequence.
 - 5'GGATTC3' is homologous to 5'GGATTC3'
- Complementary
 - 2 pieces of single stranded DNA or RNA are complementary if they can base-pair with one another
 - 5'GGATTC3' is complementary to 3'CCTAAG5'

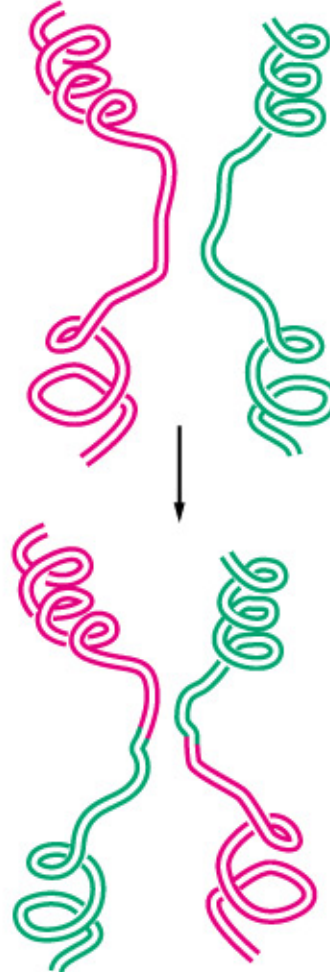
Genetic Recombination

- The rearrangement of large segments of DNA
- There are 2 basic mechanisms
 - Homologous recombination
 - Non-homologous recombination

Homologous recombination

- Two DNA helices swap DNA at positions that are perfectly homologous.
- Observed in all organisms.
- It is the basis of “crossing-over” in meiosis.

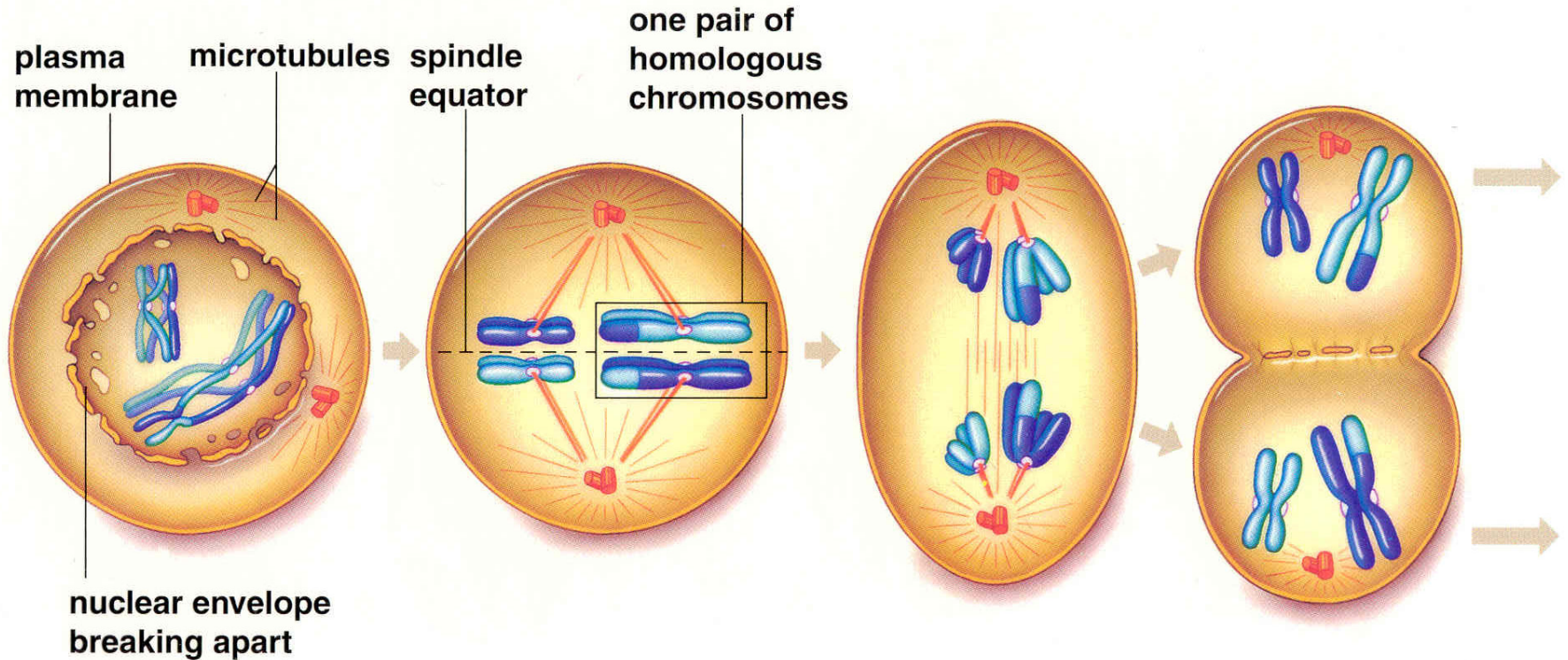
two homologous DNA double helices



two DNA molecules that have crossed over

Crossing over in Meiosis

Meiosis I



Prophase I

Metaphase I

Anaphase I

Telophase I

Homologous Recombination

(This slide will not be on the exam)

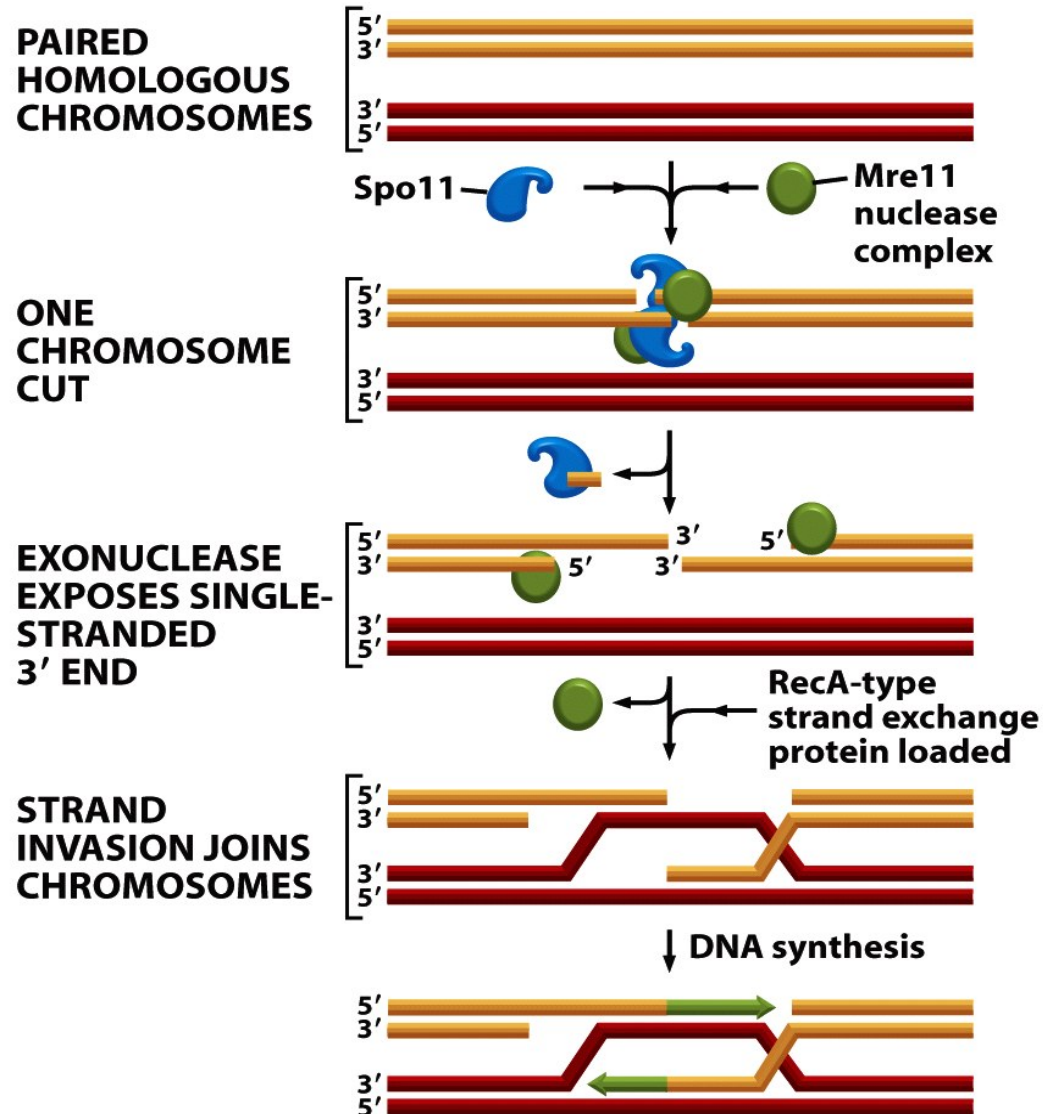


Figure 5-64 part 1 of 2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

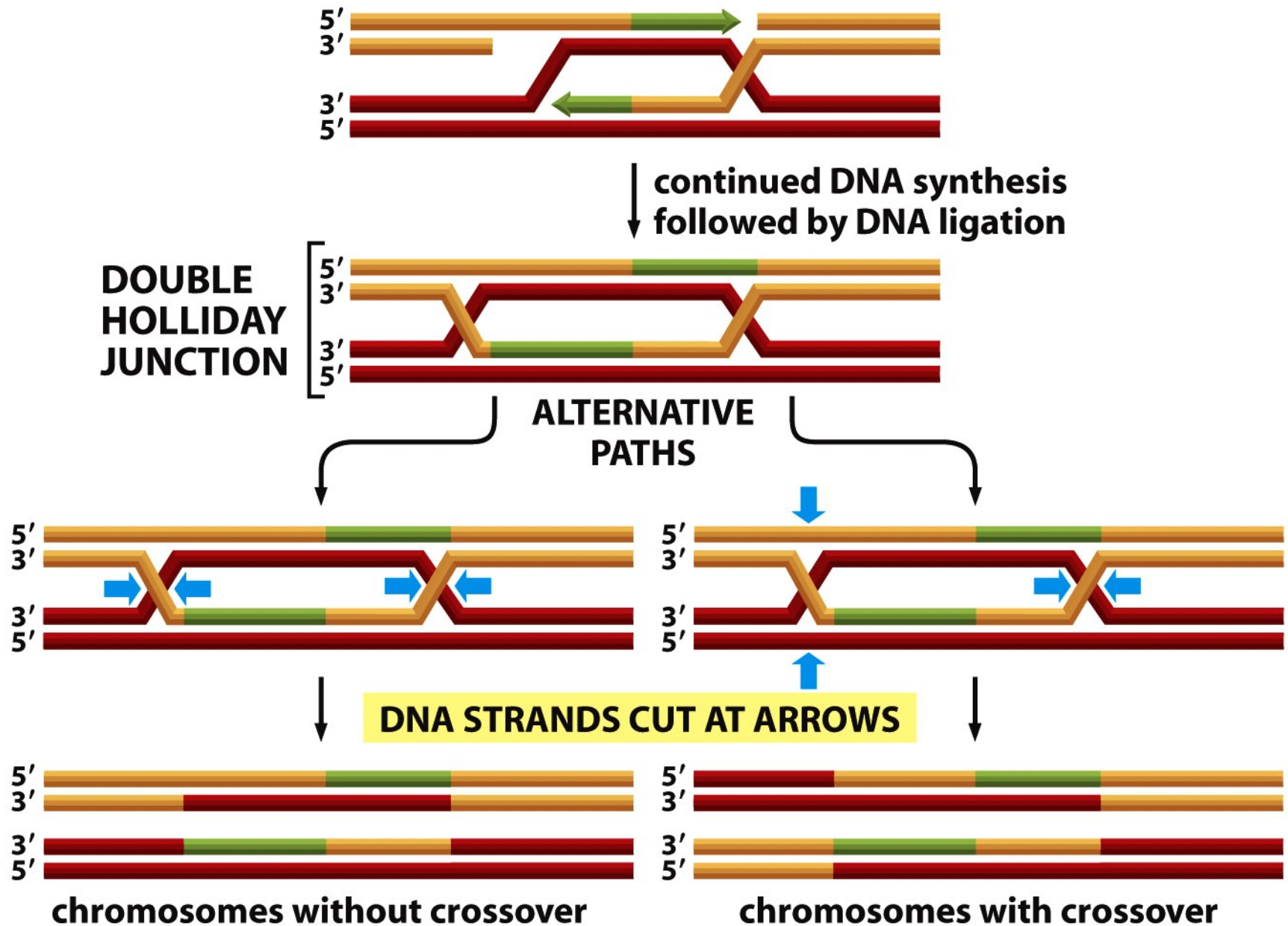


Figure 5-64 part 2 of 2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Non-Homologous Recombination

- Mobile genetic elements (transposons and viruses) integrate into random sites within a chromosome.

Transposons

- Transposons encode a transposase enzyme and have DNA sequence repeats (in red) required for movement.
- Transposase enzyme excises the transposon then facilitates its integration into a different chromosomal site.
- Draw the Mechanism from the Blackboard

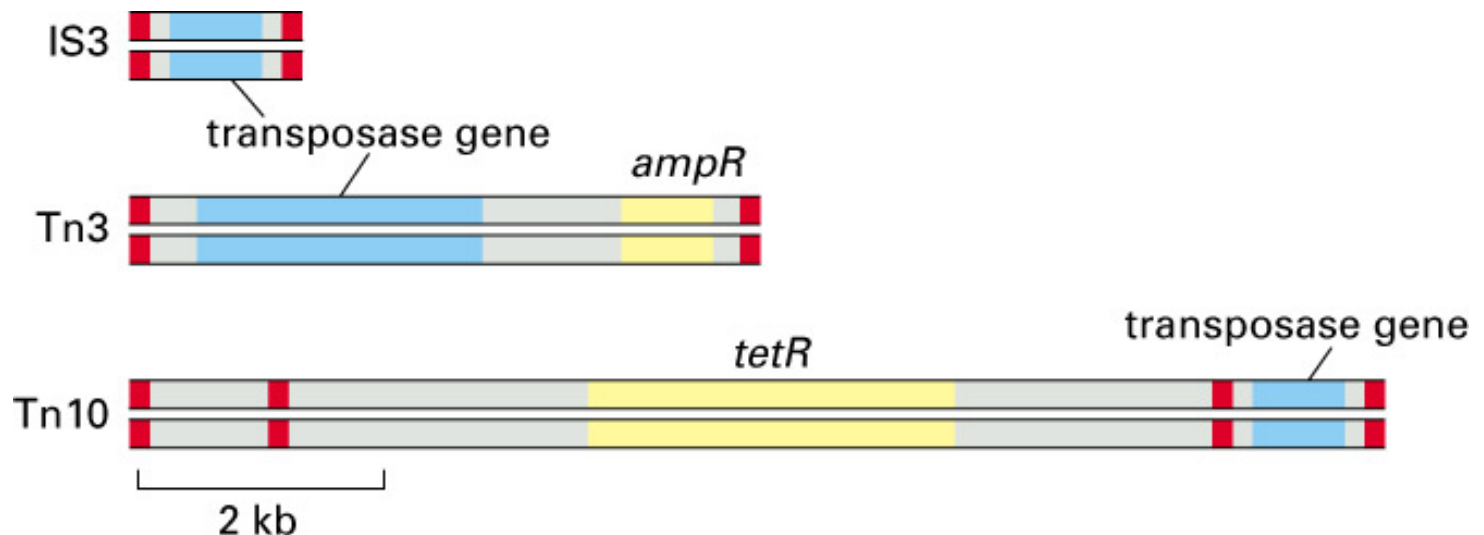


Figure 5-69. Molecular Biology of the Cell, 4th Edition.

- Retrovirus such as HIV use non-homologous recombination to integrate their genomes into the host chromosome.
- Draw this mechanism from the board.

Human Immunodeficiency Virus (HIV)

