chemotherapeutic drugs and intercalating agent drugs function by damaging DNA.

**Radiation**

Gamma rays, X-rays, even UV light can interact with compounds in the cell generating free radicals which cause chemical damage to DNA.

### *3. Insertions*

The insertion of additional base pairs may lead to frameshifts depending on whether or not multiples of three base pairs are inserted. Combinations of insertions and deletions leading to a variety of outcomes are also possible.

## Causes of Mutations

### Errors in DNA Replication

On very, very rare occasions DNA polymerase will incorporate a noncomplementary base into the daughter strand. During the next round of replication the missincorporated base would lead to a mutation. This, however, is very rare as the exonuclease functions as a proofreading mechanism recognizing mismatched base pairs and excising them.

### Errors in DNA Recombination

DNA often rearranges itself by a process called recombination which proceeds via a variety of mechanisms. Occasionally DNA is lost during replication leading to a mutation.

### Chemical Damage to DNA

Many chemical mutagens, some exogenous, some man-made, some environmental, are capable of damaging DNA. Many chemotherapeutic drugs and intercalating agent drugs function by damaging DNA.

### Radiation

Gamma rays, X-rays, even UV light can interact with compounds in the cell

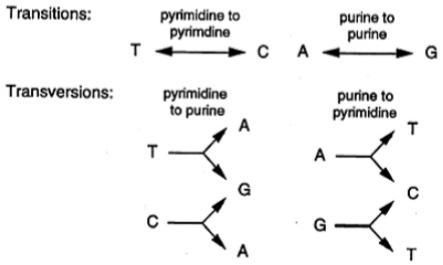
**Missence**: When base **substitution** results in the generation of a codon that specifies a different amino acid and hence leads to a different polypeptide sequence. Depending on the type of amino acid substitution the missense mutation is either conservative or nonconservative. For example if the structure and properties of the substituted amino acid are very similar to the original amino acid the mutation is said to be conservative and will most likely have little effect on the resultant proteins structure / function. If the substitution leads to an amino acid with very different structure and properties the mutation is nonconservative and will probably be deleterious (bad) for the resultant proteins structure / function (i.e. the sickle cell point mutation).

**Nonsense**: When a base **substitution** results in a stop codon ultimately truncating translation and most likely leading to a nonfunctional protein.

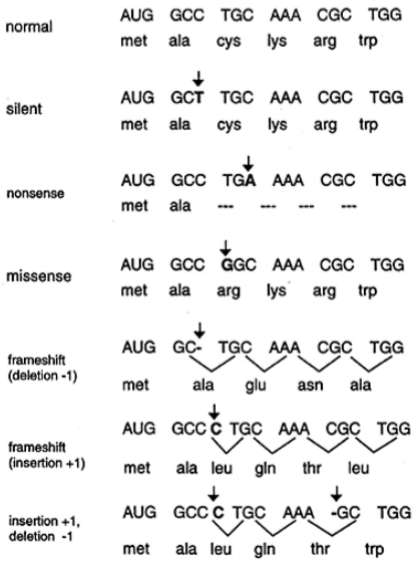
***2. Deletions***

A deletion, resulting in a frameshift, results when one or more base pairs are lost from the DNA (see Figure above). If one or two bases are deleted the translational frame is altered resulting in a garbled message and nonfunctional product. A deletion of three or more bases leave the reading frame intact. A deletion of one or more codons results in a protein missing one or more amino acids. This may be deleterious or not.

**Transversion**: when a purine is substituted for a pyrimidine or a pyrimidine replaces a purine.




Point mutations that occur in DNA sequences encoding proteins are either silent, missense or nonsense.




**Silent**: If abase **substitution** occurs in the third position of the codon there is a good chance that a synonymous codon will be generated. Thus the amino acid sequence encoded by the gene is not changed and the mutation is said to be silent.

**Missence**: When base **substitution** results in the generation of a codon that specifies a different amino acid and hence leads to a different polypeptide sequence. Depending on the type of amino acid substitution the missense mutation is either conservative or nonconservative. For example if the structure and properties of the substituted

# DNA Mutation and Repair

A mutation, which may arise during replication and/or recombination, is a permanent change in the nucleotide sequence of DNA. Damaged DNA can be mutated either by substitution, deletion or insertion of base pairs. Mutations, for the most part, are harmless except when they lead to cell death or tumor formation. Because of the lethal potential of DNA mutations cells have evolved mechanisms for repairing damaged DNA.

## Types of Mutations

There are three types of DNA Mutations: base substitutions, deletions and insertions.

### *1. Base Substitutions*

Single base **substitutions** are called point mutations, recall the point mutation Glu -----> Val which causes sickle-cell disease. Point mutations are the most common type of mutation and there are two types.

**Transition**: this occurs when a purine is substituted with another purine or when a pyrimidine is substituted with another pyrimidine.

**Transversion**: when a purine is substituted for a pyrimidine or a pyrimidine replaces a purine.