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## Review on DNA Replication

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### ABSTRACT

According to the model proposed by James Watson and Francis Crick of DNA molecule consists of two long strands coiled around a common, imaginary, central axis to form double helix. DNA is genetic material of living organism and is located in the chromosomes of each cell. If every organism must produce copies of itself in order to pass on genetic information to its young before it dies. DNA replication results in one DNA molecule becoming two daughter molecules each an exact copy of the original molecule. Each new DNA molecule consists of one old strand and one new strand. If the replication method were semi-conservative, one round of replication would yield to DNA molecule that each contain one strand of parental DNA and one strand of new DNA. After replication each DNA molecule has one old and the other new strand. It shows that 50% part of the mother molecule is retained or conserved while remaining 50% part is newly constructed. Hence the process is referred to as semi-conservative replication. DNA – polymerase catalyses polymerization only in one direction that is 3'-5'. Consequently one strand replication is continuous, while on the other strand it is discontinuous.

**Keyword:** James Watson and Francis Crick model of DNA, Semi-conservative replication.

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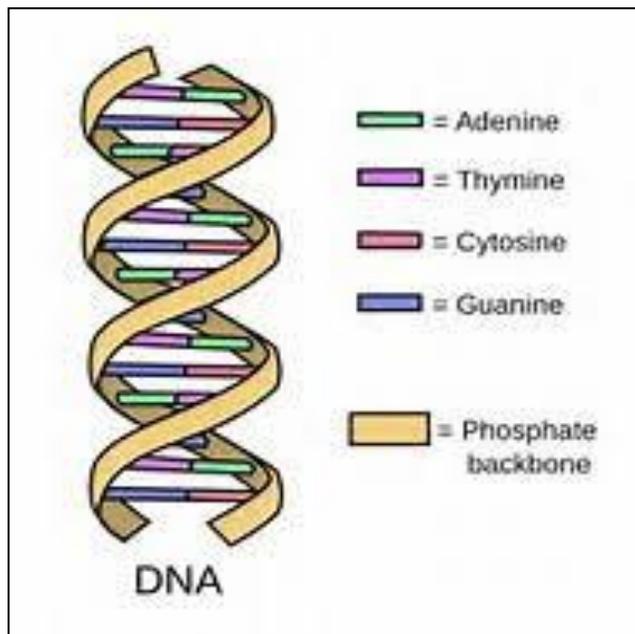
## INTRODUCTION:

DNA as genetic material of living organism the continued existence of biological species requires its genetic material to be chemically stable. DNA replication is the biological process of producing two identical replicas of DNA from one original DNA molecule. The process in which a DNA molecule produces exact copy or replica of itself is known as replication of DNA. This process occurs in all living organisms and is the basis for biological inheritance. The cell possesses the distinctive property of division, which makes replication of DNA essential DNA is made up of a double helix of two complementary strands. During replication, these strands are of its counterpart, a process referred to as semi-conservative replication separated. Each strand of the original DNA molecule then serves as a template for the production of its counterpart, a process referred to as semi-conservative replication. Cellular proofreading and error-checking mechanisms ensure near perfect fidelity for DNA replication. DNA usually exists as a double-stranded structure, with both strands coiled together to form the characteristic double-helix. Each single strand of DNA is a chain of four types of nucleotides. Nucleotides in DNA contain a deoxyribose sugar, a phosphate, and a nucleobase. The four types of nucleotide correspond to the four nucleobases adenine, cytosine, guanine, and thymine, commonly abbreviated as A, C, G and T. Adenine and guanine are purine bases, while cytosine and thymine are pyrimidines.

DNA polymerases are a family of enzymes that carry out all forms of DNA replication. DNA polymerases in general cannot initiate synthesis of new strands, but can only extend an existing DNA or RNA strand paired with a template strand. To begin synthesis, a short fragment of RNA, called a primer, must be created and paired with the template DNA strand.

### **The discovery of DNA structure:**

In 1953, James Watson and Francis Crick proposed DNA structure based on X-ray crystallographic studies provided by Maurice Wilkins and Rosalind Franklin. [1]



**Figure 1: Structure of DNA**

### DNA's Building Blocks:

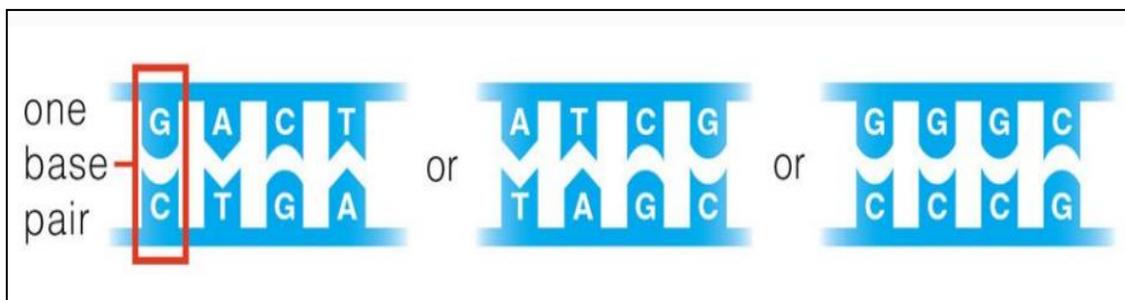
Nucleotide:

The two DNA strands are called polynucleotides since they are composed of simpler monomer units called nucleotides. [2][3]

DNA consists of four nucleotide building blocks

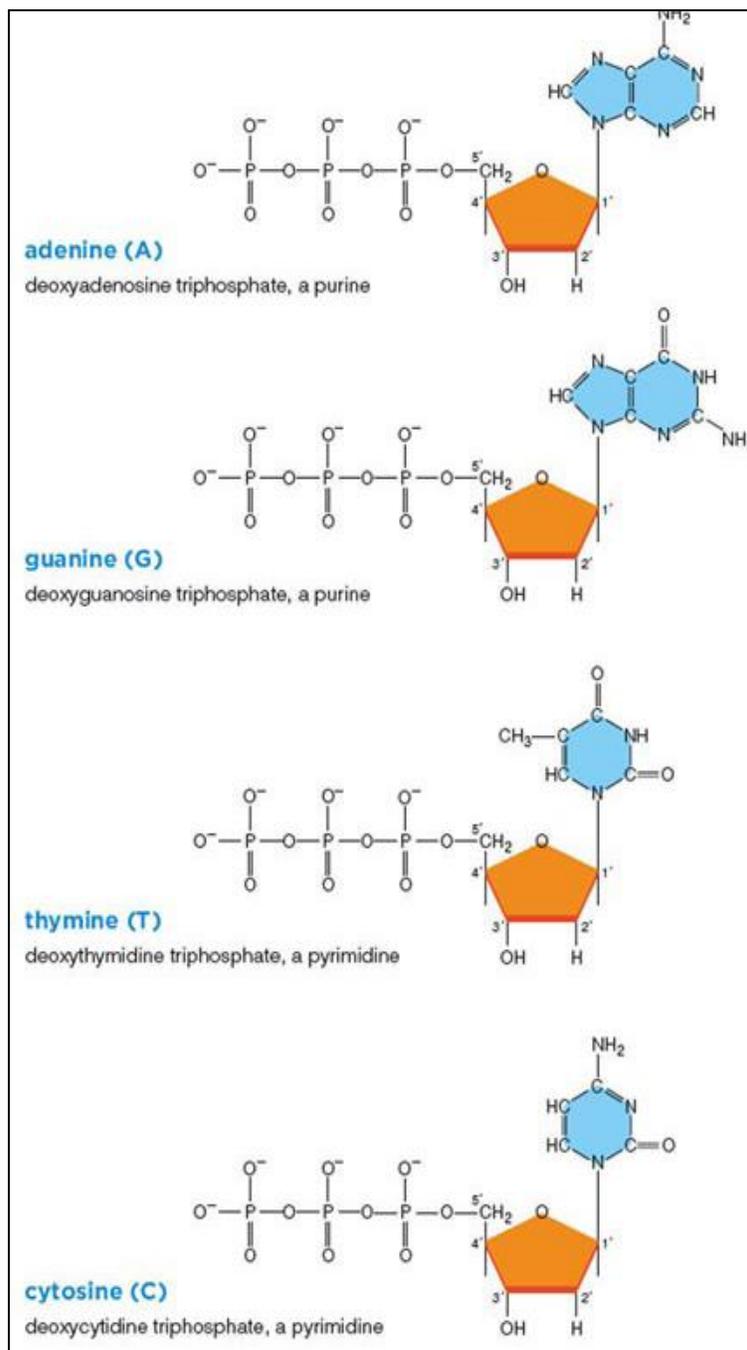
Two pyrimidines thymine and cytosine

Two purines adenine and guanine.



**Figure 2: DNA nucleotides**

The four bases found in DNA are adenine (A), cytosine (C), guanine (G) and thymine (T). These four bases are attached to the sugar-phosphate to form the complete nucleotide, as shown for adenosine monophosphate. Adenine pairs with thymine and guanine pairs with cytosine. It was represented by A-T base pairs and G-C base pairs. [4][5]

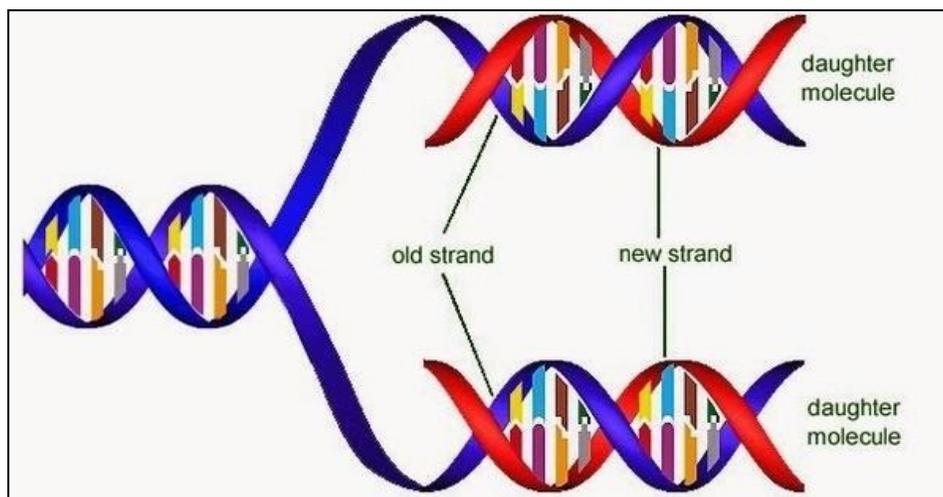


**Figure 3: Nucleotide building blocks**

### Semi-conservative replication of DNA:

The process in which a DNA molecule produces exact copy or replication of itself is known as replication of DNA.

Each strand of a DNA double helix is a template for synthesis of a complementary strand of DNA. One template builds DNA continuously; the other builds DNA discontinuously, in segments. Each new DNA molecule consists of one old strand and one new strand. [6]



**Figure 4: Semi-conservative replication of DNA**

### Enzymes of DNA replication:

DNA helicase:

Breaks hydrogen bonds between DNA stands

DNA polymerase:

Joins free nucleotides into a new stands of DNA

DNA ligase:

Joins DNA segments on discontinuous stand.

(Keyword: DNA helicase, DNA polymerase, DNA ligase)

At the replication fork, many replication enzymes assemble on the DNA into a complex molecular machine called the replisome. The following is a list of major DNA replication enzymes that participate in the replisome: [7]

Enzyme	Function in DNA replication
DNA Helicase	Also known as helix destabilizing enzyme. Helicase separates the two strands of DNA at the Replication Fork behind the topoisomerase.
DNA Polymerase	The enzyme responsible for catalyzing the addition of nucleotide substrates to DNA in the 5' to 3' direction during DNA replication. Also performs proof-reading and error correction. There exist many different types of DNA Polymerase, each of which performs different functions in different types of cells.
DNA clamp	A protein which prevents elongating DNA polymerases from dissociating from the DNA parent strand.
Single-Strand Binding (SSB) Proteins	Bind to ssDNA and prevent the DNA double helix from re-annealing after DNA helicase unwinds it, thus maintaining the strand separation, and facilitating the synthesis of the nascent strand.

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Topoisomerase	Relaxes the DNA from its super-coiled nature.
DNA Gyrase	Relieves strain of unwinding by DNA helicase; this is a specific type of topoisomerase
DNA Ligase	Re-anneals the semi-conservative strands and joins Okazaki Fragments of the lagging strand.
Primase	Provides a starting point of RNA (or DNA) for DNA polymerase to begin synthesis of the new DNA strand.
Telomerase	Lengthens telomeric DNA by adding repetitive nucleotide sequences to the ends of eukaryotic chromosomes. This allows germ cells and stem cells to avoid the Hayflick limit on cell division. [8]

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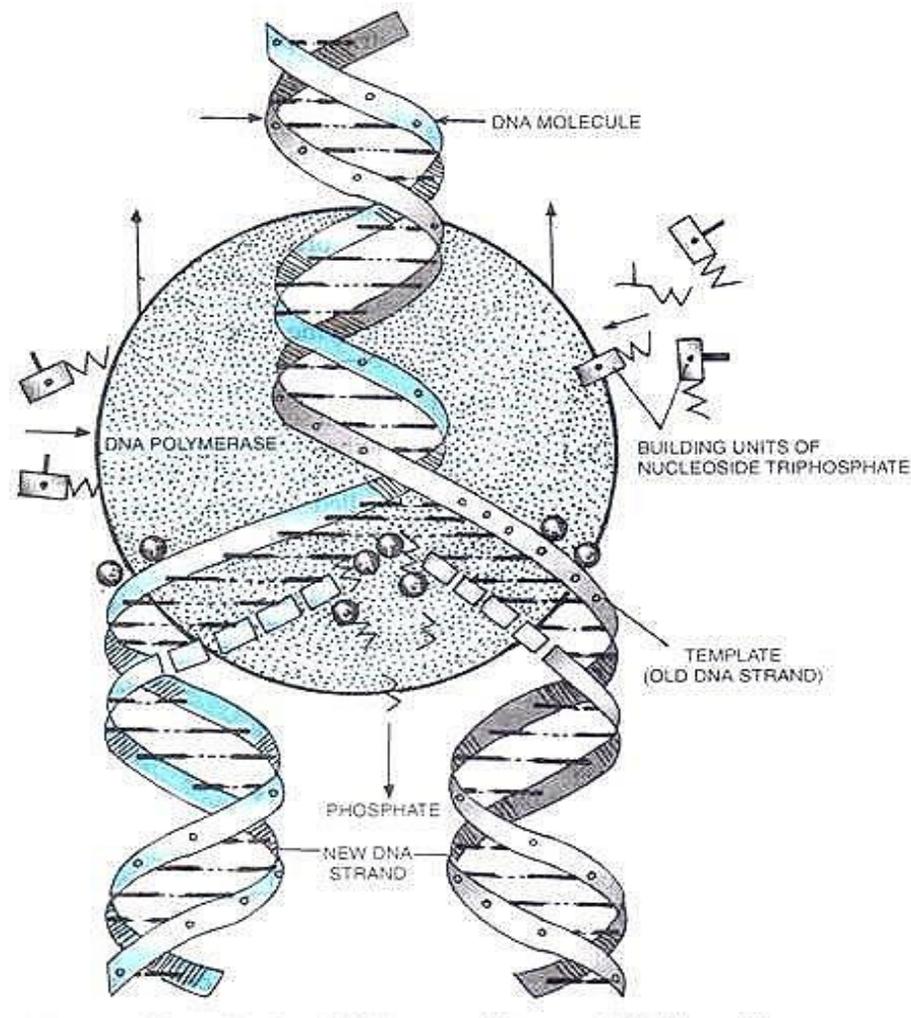
### **Mechanism of DNA replication:**

In molecular biology, **DNA replication** is the biological process of producing two identical replicas of DNA from one original DNA molecule. This process occurs in all living organisms and is the basis for biological inheritance. The cell possesses the distinctive property of division, which makes replication of DNA essential.

DNA is made up of a double helix of two complementary strands. During replication, these strands are separated. Each strand of the original DNA molecule then serves as a template for the production of its counterpart, a process referred to as semiconservative replication. Cellular proofreading and error-checking mechanisms ensure near perfect fidelity for DNA replication. [9][10]

In a cell, DNA replication begins at specific locations, or origins of replication, in the genome. [11] Unwinding of DNA at the origin and synthesis of new strands results in replication forks growing bi-directionally from the origin. A number of proteins are associated with the replication fork to help in the initiation and continuation of DNA synthesis. Most prominently, DNA polymerase synthesizes the new strands by adding nucleotides that complement each (template) strand. DNA replication occurs during the S-stage of interphase.

DNA replication can also be performed *in vitro* (artificially, outside a cell). DNA polymerases isolated from cells and artificial DNA primers can be used to initiate DNA synthesis at known sequences in a template DNA molecule. The polymerase chain reaction (PCR), a common laboratory technique, cyclically applies such artificial synthesis to amplify a specific target DNA fragment from a pool of DNA. DNA carries the information from parent



**Figure.5: The replication of DNA as per Watson and Crick's model**

### **1. Activation of deoxyribonucleosides:**

The four nucleosides of DNA i.e., AMP, GMP, CMP and TMP are found floating free in the nucleus. They all are activated by ATP to form deoxyribonucleoside triphosphates called ATP, GTP, CTP and TTP. Enzyme required at this step is phosphorylase and step is called phosphorylation. [12]

### **2. Origin or Initiation point:**

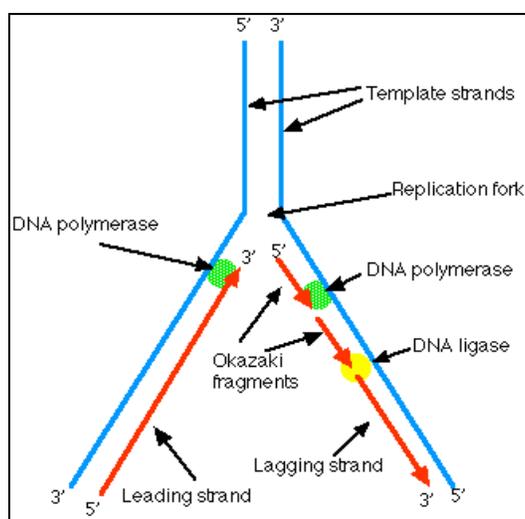
At which place of DNA molecule replication should start? From a particular point unwinding of DNA molecule starts. This specific point is called initiation point. For identifying the initiation point on DNA molecule specific initiator proteins are needed. In viruses and prokaryotes like bacteria, there may be only one origin of replication. In eukaryotes with large DNA molecule, there may be many initiation points (origin) of replication which finally merge with one another. [12]

### **3. Unwinding of DNA strand:**

After the activation of initiator proteins the strands of DNA are free from each other but not separated. This separation of the strands is done by DNA –unwinding protein i.e. helicase enzyme (also called rep proteins). Now the DNA molecule appears as inverted ‘Y ‘–shaped structure called replication fork. The separated strands are prevented from coiling by SSBP (Single strand DNA binding protein) or helix destabilizing protein.

The DNA double helix unwinds and uncoils into single strands of DNA by breakdown of weak hydrogen bonds. Unwinding of helix is helped by enzyme helicases. Enzymes called topoisomerases cut and rejoin one strand of DNA helping the separation of DNA helix.

If two highly inter-wined ropes are pulled apart by applying force, the two strands of ropes automatically inter-wine as soon as application of force is stopped. And if one of the strands of inter-wined rope is cut, tension is relieved and two strands fail to come together. [12]



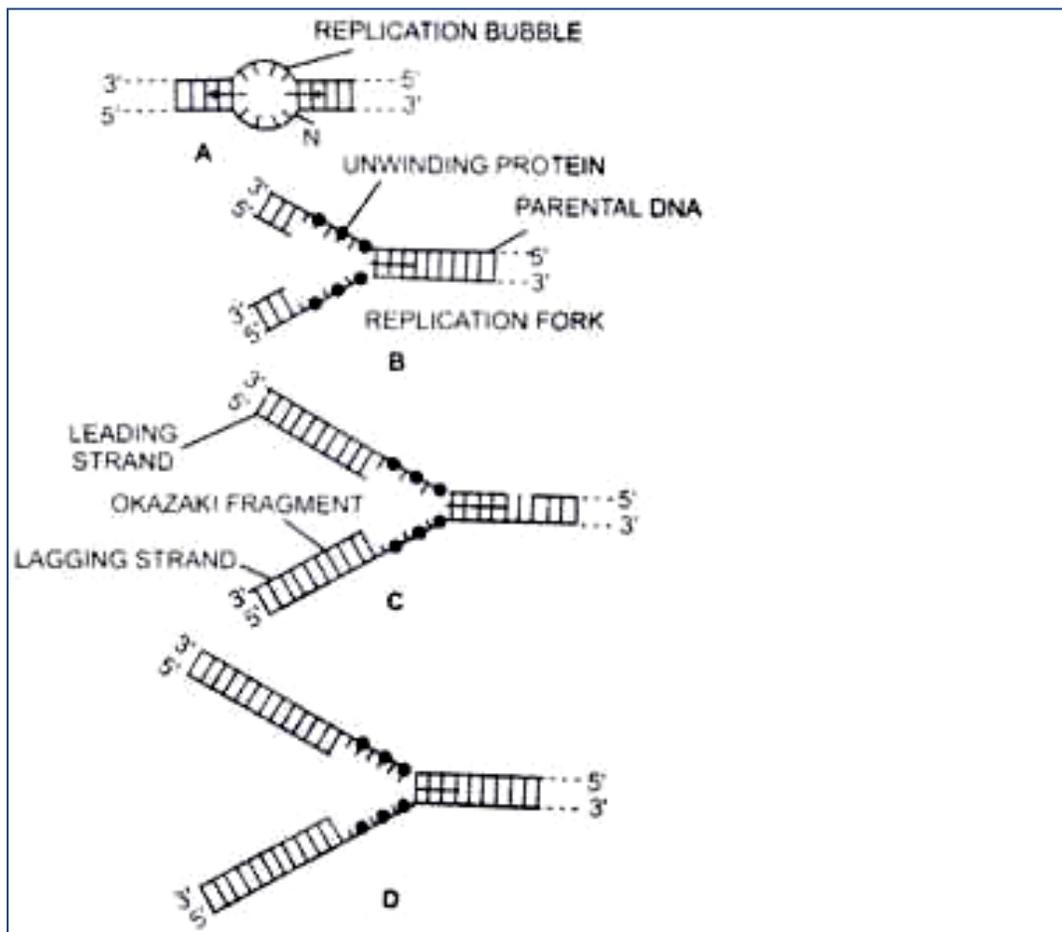
**Figure.6: DNA Replication fork (diagrammatic)**

#### **4. Synthesis of new strands (Formation of RNA primer):**

Now each separated strand acts as a template or mould for synthesis of a complementary new strand. It takes place with the help of a small RNA molecule called RNA primer. Synthesis of this RNA primer is controlled by the enzyme RNA primase. It gets attached at the 3' end of the template strand. RNA primer attracts complementary nucleotides from the surrounding nucleoplasm. It occurs under the influence of the enzyme DNA polymerase. The new complementary nucleotides are arranged on this strand to build a strand in 5'-3' direction.

The DNA directed RNA polymerase forms the RNA primer. It is comparatively easier to add on already existing small chain called primer formed from DNA template. This is accomplished by the synthesis of a short segment of RNA primer. [13]

This produces a 3' hydroxyl end on the sequence of ribonucleotides, to which deoxyribonucleotides are added. The RNA primer is ultimately removed enzymatically leaving a gap in the newly synthesized deoxyribonucleotide strand. This gap must be filled in.



**Figure:7. Steps involve in replication of DNA**

### **Leading strand:**

The leading strand is the strand of nascent DNA which is being synthesized in the same direction as the growing replication fork. A polymerase "reads" the leading strand template and adds complementary nucleotides to the nascent leading strand on a continuous basis. [14]

### **Lagging strand:**

The lagging strand is the strand of nascent DNA whose direction of synthesis is opposite to the direction of the growing replication fork. Because of its orientation, replication of the lagging strand is more complicated as compared to that of the leading strand. As a consequence, the DNA polymerase on this strand is seen to "lag behind" the other strand.

The lagging strand is synthesized in short, separated segments. On the lagging strand template, a primase "reads" the template DNA and initiates synthesis of a short complementary RNA primer.

A DNA polymerase extends the primed segments, forming Okazaki fragments. The RNA primers are then removed and replaced with DNA, and the fragments of DNA are joined together by DNA ligase.

#### **Formation of daughter DNA molecule:**

In this way for each old strand, a new complimentary strand is constructed. Simultaneously both the strands (new and old) undergo coiling and two identical daughter DNA molecules are formed at the end of the process.

After replication each DNA molecule has one old and the other new strand. It shows that 50% part of the mother molecule is retained or conserved while remaining 50% part is newly constructed. Hence the process is referred to as semi-conservative replication. [14]

#### **Types of DNA Damage:**

After DNA has been completely replicated, the daughter strand is often not a perfect copy of the parent strand it came from. Mutations during replication and damage after replication make it necessary for there to be a repair system to fix any errors in newly synthesized DNA. There are three main sources of damage to DNA.

1. Attack by water which can lead to the removal of an amine group from the base group of a nucleotide or the loss of the entire base group.
2. Chemical damage that permanently alters the structure of the DNA.
3. Radiation damage which can lead to nicks in the backbone of DNA or the formation of thymine dimers, which will be discussed later.

These different sources of damage lead to different categories of DNA damage. The damage that is caused by water attack can lead to unnatural bases. Chemical and radiation damage leads to the formation of bulky adducts to, or breaks in, the growing DNA strand. In the previous section we discussed the 3' to 5' proof-reading exonuclease that is responsible for fixing mismatches. Because it is not a perfect system, it can miss mismatched bases. As a result, a third category of DNA damage is mismatched bases.

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