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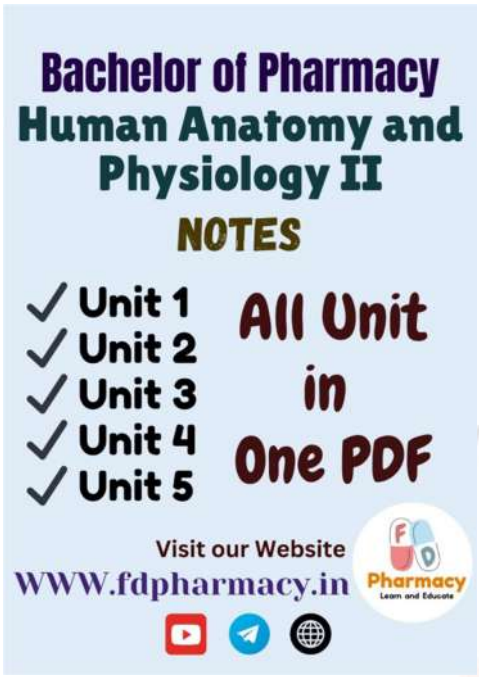
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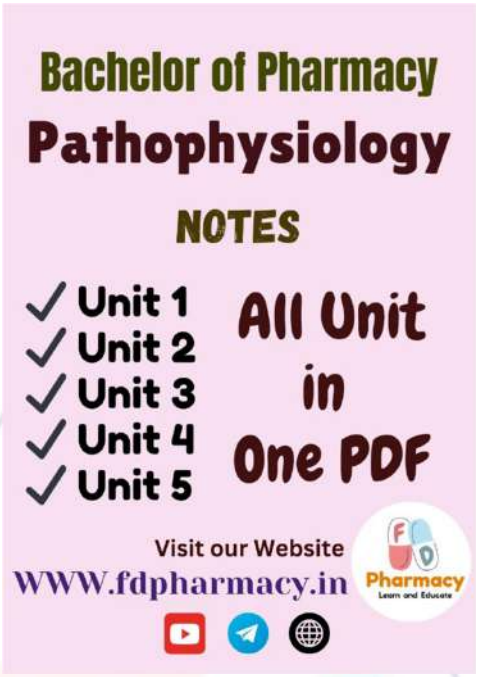
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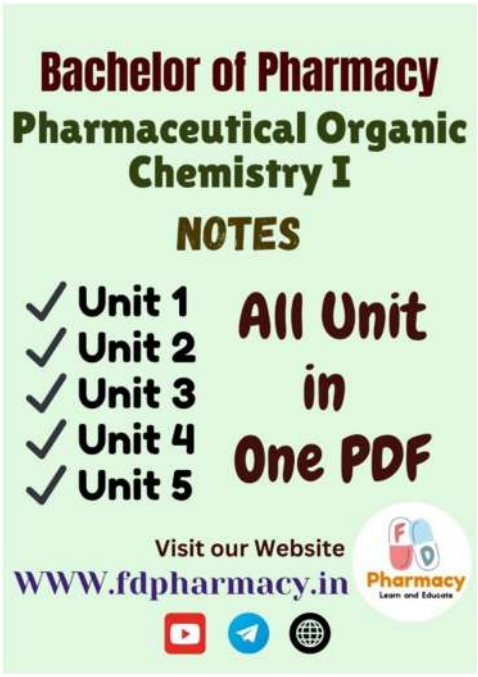
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BIOCHEMISTRY

UNIT 4

TOPIC :

- **Nucleic acid metabolism and genetic information transfer**
  Biosynthesis of purine and pyrimidine nucleotides
  Catabolism of purine nucleotides and Hyperuricemia and Gout disease
  Organization of mammalian genome
  Structure of DNA and RNA and their functions
  DNA replication (semi conservative model)
  Transcription or RNA synthesis
  Genetic code, Translation or Protein synthesis and inhibitors

Nucleic acid metabolism and genetic information transfer

Biosynthesis of purine nucleotides:

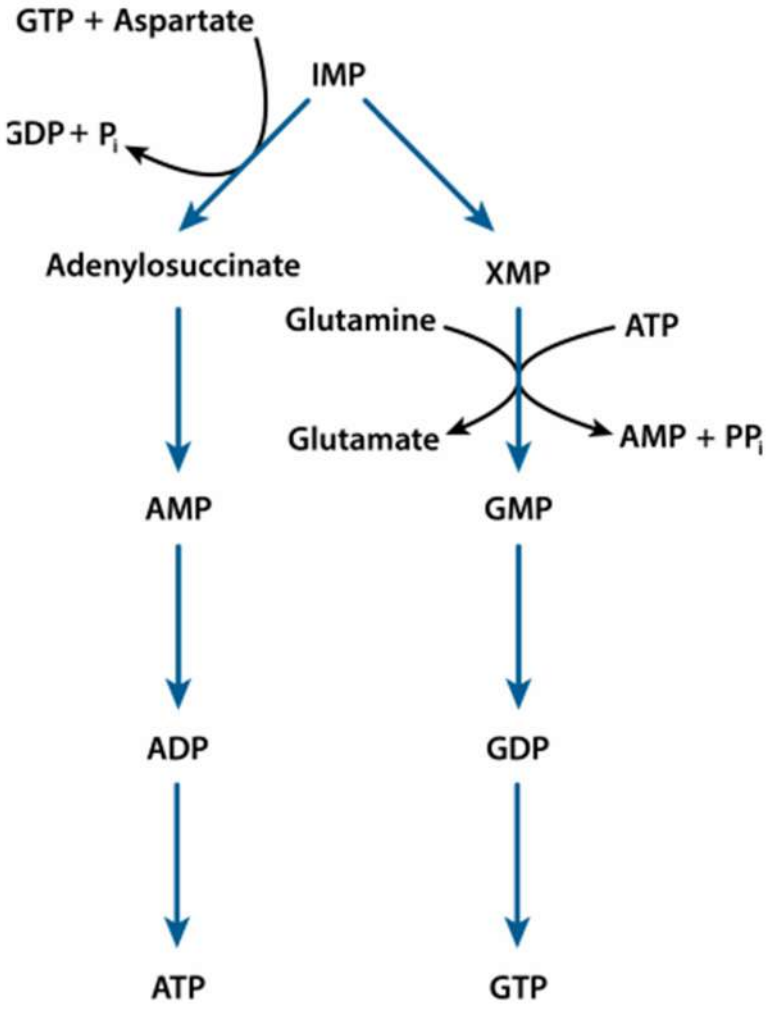
→ It is the de novo synthesis by which a new purine ring is synthesized along with the nucleotide that attaches to the ribose sugar generated by HMP pathway.

→ D-ribose-5-phosphate serves as the starting material for stepwise synthesis of the purine ring.

→ The first biosynthesized purine product after 11 step is Inosine-5'-monophosphate (See figure on next page). IMP worked as precursor for various purine base.

→ It occurs in the liver.

→ In this whole reaction 6 ATP is utilized.



Biosynthesis of purine nucleotides

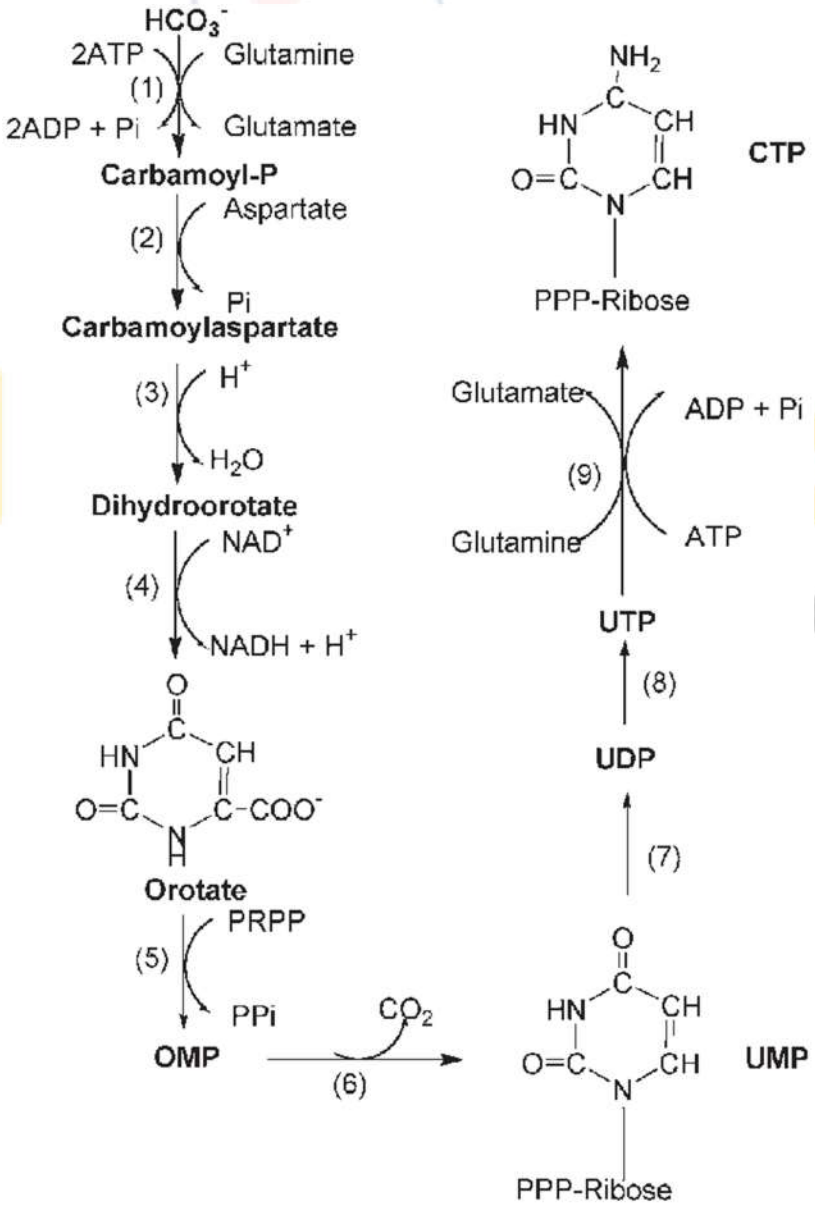
→ Pyrimidine nucleotide biosynthesis takes place with six membered pyrimidine ring synthesis followed by attachement to ribose phosphate in 8 step.

→ The synthesis begins with combined CO_2 and NH_3 and Pyrimidine ring is formed first.

→ Formation of cytosolic carbamoyl phosphate is a regulatory step.

→ This biosynthesis occurs in cytoplasm.

→ Carbamoyl phosphate is used in urea synthesis which is made in the mitochondrion.



Catabolism of Purine Nucleotides

- Breakdown of adenine and guanine bases from DNA, RNA, ATP, GTP into final excretory product uric acid (in humans and higher primates).

Major Sites:

- Liver
- Small intestine
- Other extrahepatic tissues (less actively)

Step-by-Step Pathway of Purine Catabolism

A. From AMP to Uric Acid **(Adenine Pathway)**

1. **AMP → Inosine**
   - Enzyme: **AMP deaminase** (or via 5'-nucleotidase → adenosine → inosine by **adenosine deaminase**)
2. **Inosine → Hypoxanthine**
   - Enzyme: **Purine nucleoside phosphorylase (PNP)**
3. **Hypoxanthine → Xanthine**
   - Enzyme: **Xanthine oxidase**
4. **Xanthine → Uric Acid**
   - Enzyme: **Xanthine oxidase**

B. From GMP to Uric Acid **(Guanine Pathway)**

1. **GMP → Guanosine**
   - Enzyme: **5'-nucleotidase**
2. **Guanosine → Guanine**
   - Enzyme: **Purine nucleoside phosphorylase (PNP)**
3. **Guanine → Xanthine**
   - Enzyme: **Guanase**
4. **Xanthine → Uric Acid**
   - Enzyme: **Xanthine oxidase**

Final Product in Humans:

- **Uric acid**, which is excreted in **urine**
- In many other animals, **uricase** converts uric acid to **allantoin** (more soluble), but **humans lack uricase**

Hyperuricemia

Hyperuricemia is a condition characterized by **elevated levels of uric acid in the blood**.

- **Normal serum uric acid levels**:
  - **Men**: 3.4 – 7.0 mg/dL
  - **Women**: 2.4 – 6.0 mg/dL
- **Hyperuricemia**:
  - **> 7 mg/dL in men**
  - **> 6 mg/dL in women**

Uric acid is the **end product of purine metabolism** in humans, and is normally excreted by the **kidneys**.

Causes of Hyperuricemia

A. Overproduction of Uric Acid

- High **cell turnover** (e.g., leukemia, lymphoma)
- High-purine diet (organ meats, red meat, seafood)
- **Enzyme defects** (e.g., PRPP synthetase overactivity, **Lesch-Nyhan syndrome**)
- Excess alcohol consumption
- **De novo purine synthesis** increased

B. Decreased Excretion of Uric Acid

- **Chronic kidney disease** or reduced GFR
- Dehydration

- Drugs (thiazide diuretics, loop diuretics, low-dose aspirin, cyclosporine)
- Lactic acidosis, ketoacidosis
- Lead nephropathy

Types of Hyperuricemia

Type	Mechanism	Common Examples
Primary	Genetic or metabolic defects	Lesch-Nyhan syndrome, PRPP overactivity
Secondary	Due to other conditions	Renal failure, tumor lysis syndrome, drugs
Transient	Temporary, due to diet or stress	After intense exercise, fasting

Treatment: uricosuric drug (e.g. probenecid, allopurinol) and NSAID drugs.

Gout

→ A form of arthritis characterised by severe pain, redness and tenderness in joints.
→ Pain and inflammation occur when too much uric acid crystallises and deposits in the joints.

Type :

a) acute gout which is also known as gout attack.

b) Chronic gout attacks are caused by the deposition of urate in various joints in body.

Symptoms of gout include severe pain, redness and swelling in joints, often the big toe. Attacks can come suddenly, often at night.

Treatment:

→ During an acute attack, anti-inflammatory medication (NSAIDs) can help to relieve
→ pain and shorten the duration of the attack. Patients with chronic gout can use behavioural
→ modification such as diet, exercise and decreased intake of alcohol to help minimise the
→ frequency of attacks. Additionally, patients with chronic gout are often put on medication to
→ reduce uric acid levels.

Organization of mammalian genome

- The genome of an organism refers to the complete set of hereditary information encoded in its DNA, or RNA in the case of some viruses.
- It includes both the genes (that code for proteins or functional RNA) and the non-coding sequences that play structural or regulatory roles.
- In humans, the genome is organized across 23 pairs of chromosomes within the cell nucleus, along with a small circular genome present in the mitochondria.
- Chromosomes act as the primary storage structures for genetic material.

Structure of DNA (Deoxyribonucleic Acid)

→ DNA is the molecule that carries genetic instructions used in the growth, development, functioning, and reproduction of all known living organisms and many viruses. Its structure was discovered by James Watson and Francis Crick in 1953, based on X-ray diffraction data from Rosalind Franklin.

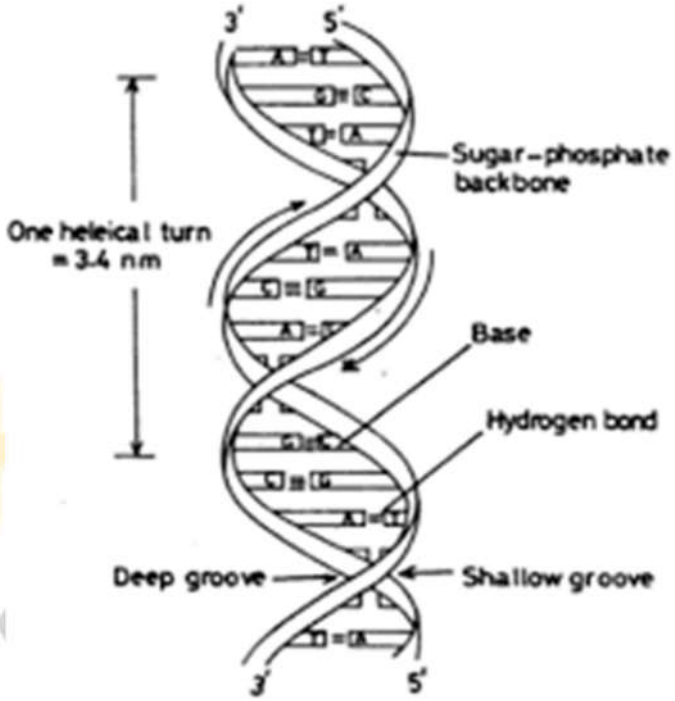
Basic Components of DNA

DNA is a **polymer of nucleotides**, and each nucleotide has three components:

1. **Nitrogenous base** (4 types):
   - **Purines**: Adenine (A), Guanine (G) – double-ring structures
   - **Pyrimidines**: Cytosine (C), Thymine (T) – single-ring structures
2. **Pentose sugar**:
   - Deoxyribose (a 5-carbon sugar without an oxygen atom at carbon 2')
3. **Phosphate group**:
   - Links the sugar of one nucleotide to the sugar of the next via **phosphodiester bonds**

Watson and Crick model of DNA

- DNA as an acidic substance present in the nucleus was first identified by Frederich Meischer in 1869. He named it as 'nucleon'. Due to technical limitations in isolating such a long polymer intact the elucidation of structure of DNA remained elusive for a long period of time.
- It was only in 1953 that James Watson and Francis Crick proposed the very simple but famous double helix model for the structure of DNA.
- The main opposition was base pairing between the two strands of polynucleotide chains



Watson and Crick Model of DNA Molecule

The salient features of double helix structure of DNA are as follows

- It is made up of two polynucleotide chains.
- The two chains have antiparallel polarity if one has polarities and the second chain must have polarity.

- The base into strands is paired through hydrogen bond forming base pairs. Adenine forms to hydrogen bonds with thymine from opposite strands and vice versa.
- Similarly guanine forms three H bonds with cytosine. As a result, purine comes opposite to pyrimidine.
- Because of this approximate a uniform distance between the two strengths of The Helix occurs.
- The two chains are called in a right-handed fashion. Pitch of the helix is and there are roughly 10bp in each turn.
- The plane of one base pair is stacked over the other in a double helix. This confirms stability of the helical structure.

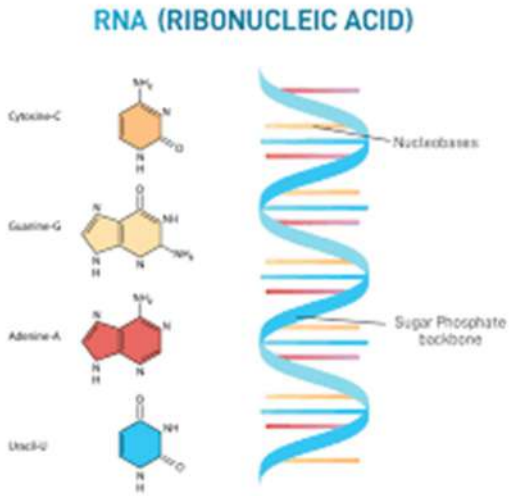
Biological Functions of DNA

- ✓ DNA (Deoxyribonucleic Acid) is the hereditary material found in almost all living organisms. It holds the instructions necessary for an organism's growth, development, reproduction, and cellular function. Genes are small segments of DNA, usually ranging from 250 to 2 million base pairs, and each gene typically codes for a polypeptide or protein.
- ✓ A sequence of three nitrogenous bases (called a codon) corresponds to one specific amino acid. These amino acids join together to form polypeptide chains, which further fold into secondary, tertiary, and quaternary structures to become functional proteins. Since every organism possesses thousands of genes, DNA enables the production of a wide variety of proteins, which are essential for both structure and function in living cells.
- ✓ Apart from storing and transmitting genetic information, DNA is involved in the following biological functions:
- ✓ Replication process: Transferring the genetic information from one cell to its daughters and from one generation to the next and equal distribution of DNA during the cell division

- ✓ Mutations: The changes which occur in the DNA sequences
- ✓ Transcription
- ✓ Cellular Metabolism
- ✓ DNA Fingerprinting
- ✓ Gene Therapy

Structure of RNA

- Ribonucleic Acid RNA is a long unbranched macromolecule consisting of nucleotides joined by $3^{|}$ to $5^{|}$ Phosphodiester bonds.
- RNA is a single stand dose not contain regions of double helical structure.
- RNA contain ribose sugar instead of 2-deoxyribose that present in DNA.
- The Structure of RNA Molecule was described by Robert William Holley in 1965.
- It contain four major bases such as
  - Purine base : Adenine & Guanine
  - Pyrimidine base : Cytosine & Uracil
- RNA Pairs
  - Adenine with Uracil
  - Cytosine with Guanine



Types of RNA / Function

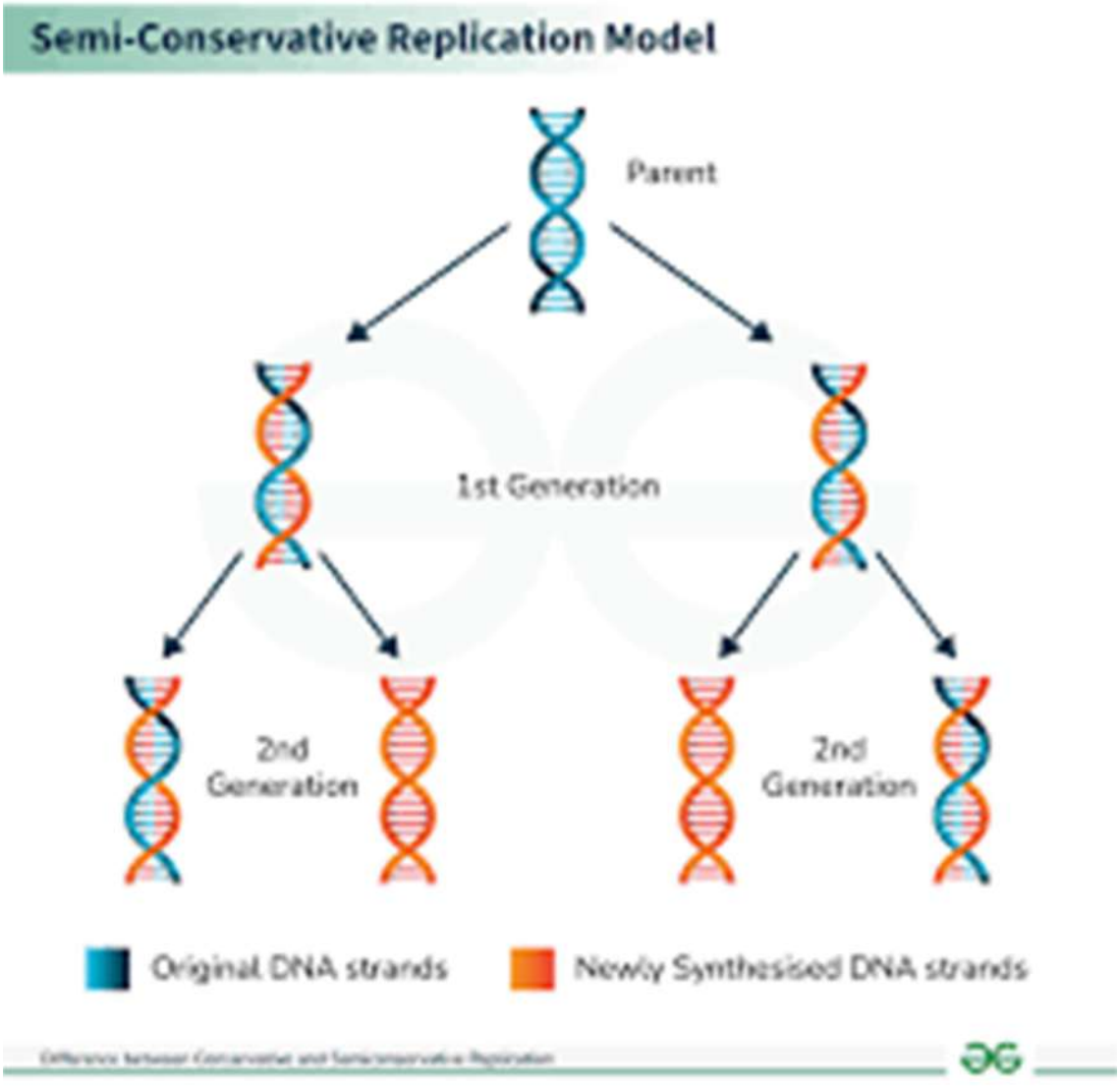
- ✓ **mRNA :** It takes genetic massages from DNA and help in protein synthesis.
- ✓ **t-RNA :** It transfer amino acids to the codes information of mRNA.
- ✓ **r-RNA (ribose RNA) :** It play an important role in protein synthesis.

DNA Replication (Semi-Conservative Model)

- DNA replication is the biological process by which a cell copies its DNA before cell division (mitosis or meiosis). It ensures that each daughter cell receives an exact copy of the DNA.

Semi-Conservative Model of Replication

- The semi-conservative model of DNA replication was proposed by Watson and Crick and experimentally proven by Meselson and Stahl in 1958. According to this model:
- Each new DNA molecule consists of one original (parental) strand and one newly synthesized strand.



Steps of DNA Replication

1. *Initiation*

- Replication begins at specific regions called origin of replication.
- Helicase enzyme unwinds the double helix by breaking hydrogen bonds between base pairs.
- This forms a replication fork – a Y-shaped structure with two separated DNA strands.

2. *Formation of RNA Primer*

- Primase, an RNA polymerase enzyme, synthesizes a short RNA primer to provide a starting point for DNA synthesis.
- DNA polymerase can only add nucleotides to an existing strand; it cannot start on its own.

3. *Elongation*

- DNA polymerase III adds free nucleotides (dATP, dTTP, dGTP, dCTP) to the 3′ end of the primer using the parental strand as a template.
- It follows the base pairing rule:
  - A with T
  - G with C
- One strand is synthesized continuously (called the leading strand).
- The other strand is synthesized in short fragments called Okazaki fragments (called the lagging strand).

4. *Joining of Fragments*

- DNA polymerase I removes RNA primers and replaces them with DNA nucleotides.
- DNA ligase joins the Okazaki fragments by forming phosphodiester bonds, completing the lagging strand.

5. *Termination*

- When the replication is complete, two identical DNA molecules are formed.
- Each new DNA molecule contains:
  - One parental (old) strand
  - One new strand

  →This confirms the semi-conservative nature of replication.

Transcription (RNA Synthesis)

Transcription is the biological process in which the genetic information stored in the DNA is copied into RNA. It is the first step of gene expression and occurs in the nucleus of eukaryotic cells and in the cytoplasm of prokaryotes.

In transcription, a specific segment of DNA (gene) is used as a template to synthesize a complementary strand of RNA.

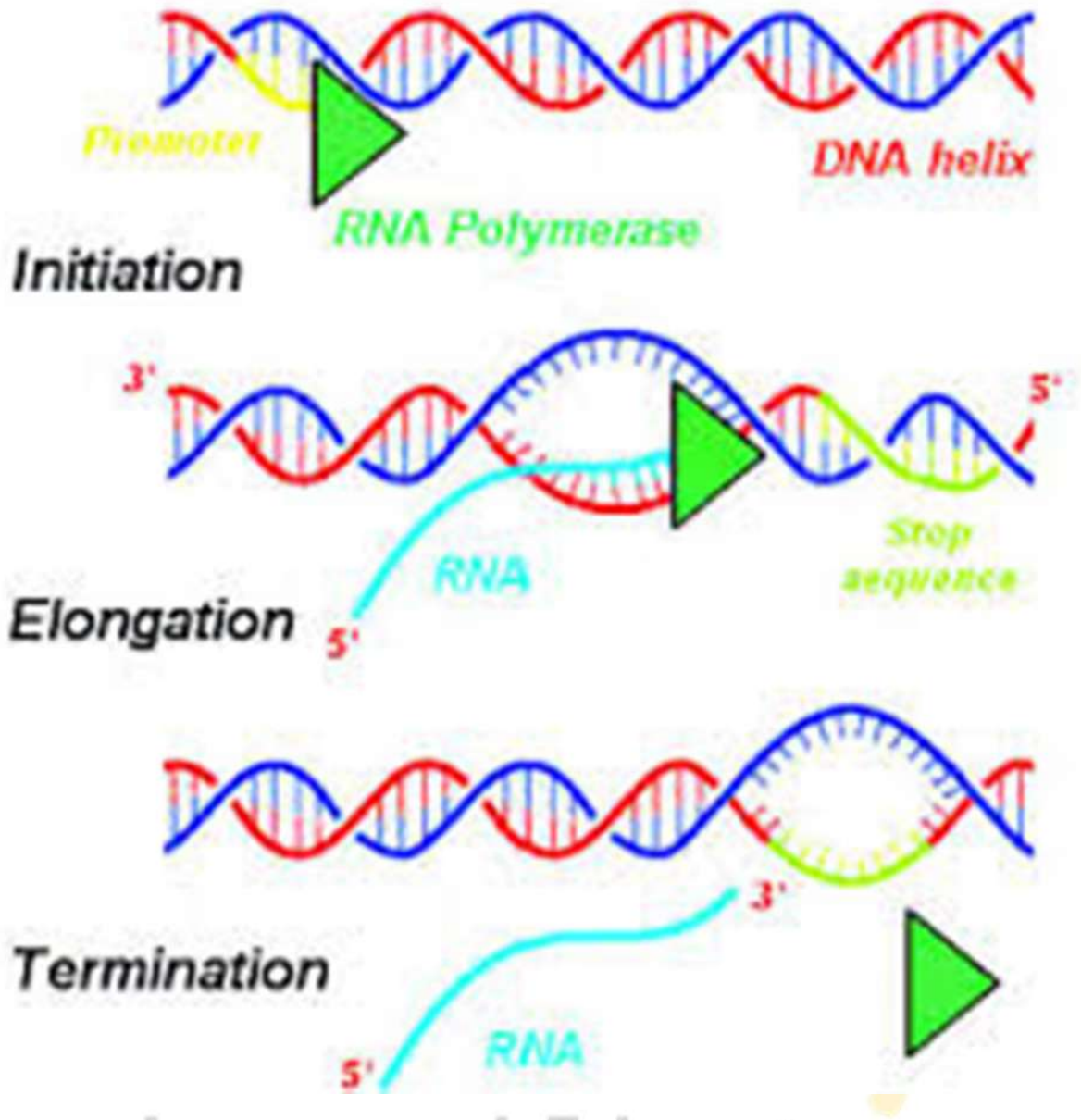
- To produce **messenger RNA (mRNA)** that carries genetic information from DNA to ribosomes.
- The mRNA is then translated into **proteins** during the process of translation.

Types of RNA Produced

During transcription, different types of RNA are synthesized:

- **mRNA** – carries the code for protein
- **tRNA** – brings amino acids during translation
- **rRNA** – forms ribosomes
- **snRNA**, **miRNA** – regulatory and processing functions

Steps of Transcription



1. Initiation

- RNA polymerase binds to a specific region on DNA called the promoter.
- Promoter contains specific sequences (like TATA box) that signal the starting point.
- The DNA strands unwind to expose the template strand.

2. Elongation

- RNA polymerase reads the template strand (3′→5′) and builds RNA in the 5′→3′ direction.
- Ribonucleotides (ATP, UTP, GTP, CTP) are added using base pairing rules:
  - A → U
  - T → A
  - G → C
  - C → G

3. Termination

- RNA polymerase reaches a terminator sequence in the DNA.
- RNA synthesis stops, and the newly formed RNA strand (primary transcript) is released.
- DNA rewinds back into its double helix form.

Genetic Code

- The genetic code is a set of instructions used by living cells to translate genetic information (stored in DNA or RNA) into proteins, which are made of amino acids.
- The genetic code consists of 64 triplets of nitrogen bases, also known as codons (e.g., AAA, AUG).
- Each codon is made up of three nucleotides (A, U, G, C in RNA; A, T, G, C in DNA).
- A codon specifies either an amino acid or a signal for starting or stopping protein synthesis.

Types of Codons:

1. **RNA Codons**
   - Found in **mRNA**, used during **translation.**
2. **DNA Codons**
   - Found in **DNA**, and are **transcribed into RNA codons.**

Classification of Codons:

1. **Sense Codons**
   - These codons **code for amino acids.**
   - There are **61 sense codons** for **20 amino acids.**
   - Example: **AAA** codes for **Lysine.**
2. **Signal Codons**
   - These codons act as **signals** in protein synthesis:
     - **Start Codon: AUG** (codes for Methionine and signals the beginning of translation)
     - **Stop Codons: UAA, UAG, UGA** (in RNA) and **TAA, TAG, TGA** (in DNA)

Applications of the Genetic Code:

1. ATG (AUG) is the start codon – signals the beginning of protein synthesis.
2. TAG, TGA, TAA are stop codons – signal the end of translation.
3. Start codon tells the ribosome where to begin adding amino acids.
4. Stop codon tells the ribosome where to stop, ending the protein chain.

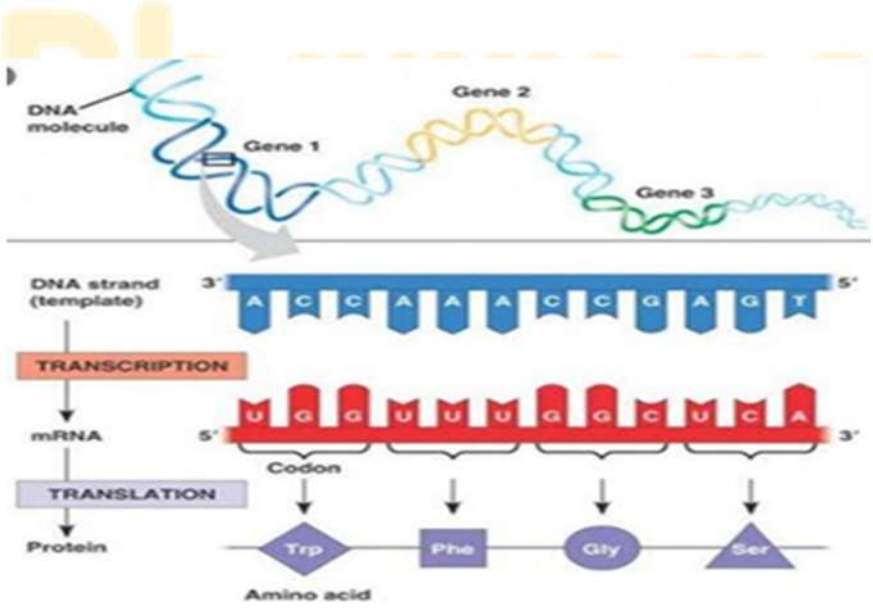
Translation (Protein Synthesis)

- Translation is the second step of gene expression, in which the genetic code on mRNA is decoded to synthesize a specific protein (polypeptide chain).
- It takes place in the cytoplasm, at the ribosome.

Major Components Involved in Translation

1. **mRNA (Messenger RNA)** – Carries codons from DNA.
2. **tRNA (Transfer RNA)** – Brings specific amino acids and matches codons using its anticodon.
3. **rRNA (Ribosomal RNA)** – Combines with proteins to form **ribosomes** (site of translation).
4. **Amino acids** – Building blocks of proteins.
5. **Enzymes & Factors** – Aminoacyl-tRNA synthetase, initiation/elongation/release factors.

Steps of Translation



1. **Activation of Amino Acids**

- Each amino acid is attached to its specific tRNA by the enzyme aminoacyl-tRNA synthetase.
- This forms an aminoacyl-tRNA complex.

2. ***Initiation***

- The small ribosomal subunit binds to the mRNA near the start codon (AUG).
- Initiator tRNA carrying methionine binds to AUG.
- The large ribosomal subunit then attaches, forming a complete ribosome.
- Ribosome has three sites:
  - A site (Aminoacyl) – Entry for new tRNA
  - P site (Peptidyl) – Holds tRNA with growing peptide
  - E site (Exit) – Where empty tRNA leaves

3. ***Elongation***

- A new aminoacyl-tRNA enters the A site.
- A peptide bond forms between the amino acid in the P site and the new one in the A site.
- The ribosome shifts (translocates) to the next codon.
- The tRNA in the P site moves to E site and exits; A site is ready for the next tRNA.

4. ***Termination***

- When a stop codon (UAA, UAG, UGA) is reached, release factors bind to the ribosome.
- The completed polypeptide chain is released.
- Ribosomal subunits detach, ending translation.

Inhibitors of Translation or Protein synthesis

- ✓ Protein synthesis inhibitors are a substance that stops or slows the growth of prokaryotic and eukaryotic cells at ribosomal level.
- ✓ Inhibitors of both prokaryotic and eukaryotic protein synthesis: Edeine, Fusidic acid, Tetracycline
- ✓ Inhibitors specific for prokaryotes (only in bacterial cell): Chloramphenicol, Colicin E3, Erythromycin, Streptomycin.
- ✓ Inhibitors specific for eukaryotes: anisomysin, Pactamicin,