NUCLEOTIDES CHEMISTRY (BI 6.2)

Nucleotides are central to maintenance and propagation of life

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Think-Pair-Share

- Biomedical importance of nucleotides

NUCLEOTIDES

Precursors of the nucleic acids

The storage and the transfer of genetic information.

Precursor of ATP

Components of important co-enzymes like NAD+ and FAD, and metabolic regulators such as cAMP and cGMP.

Composition of Nucleotides

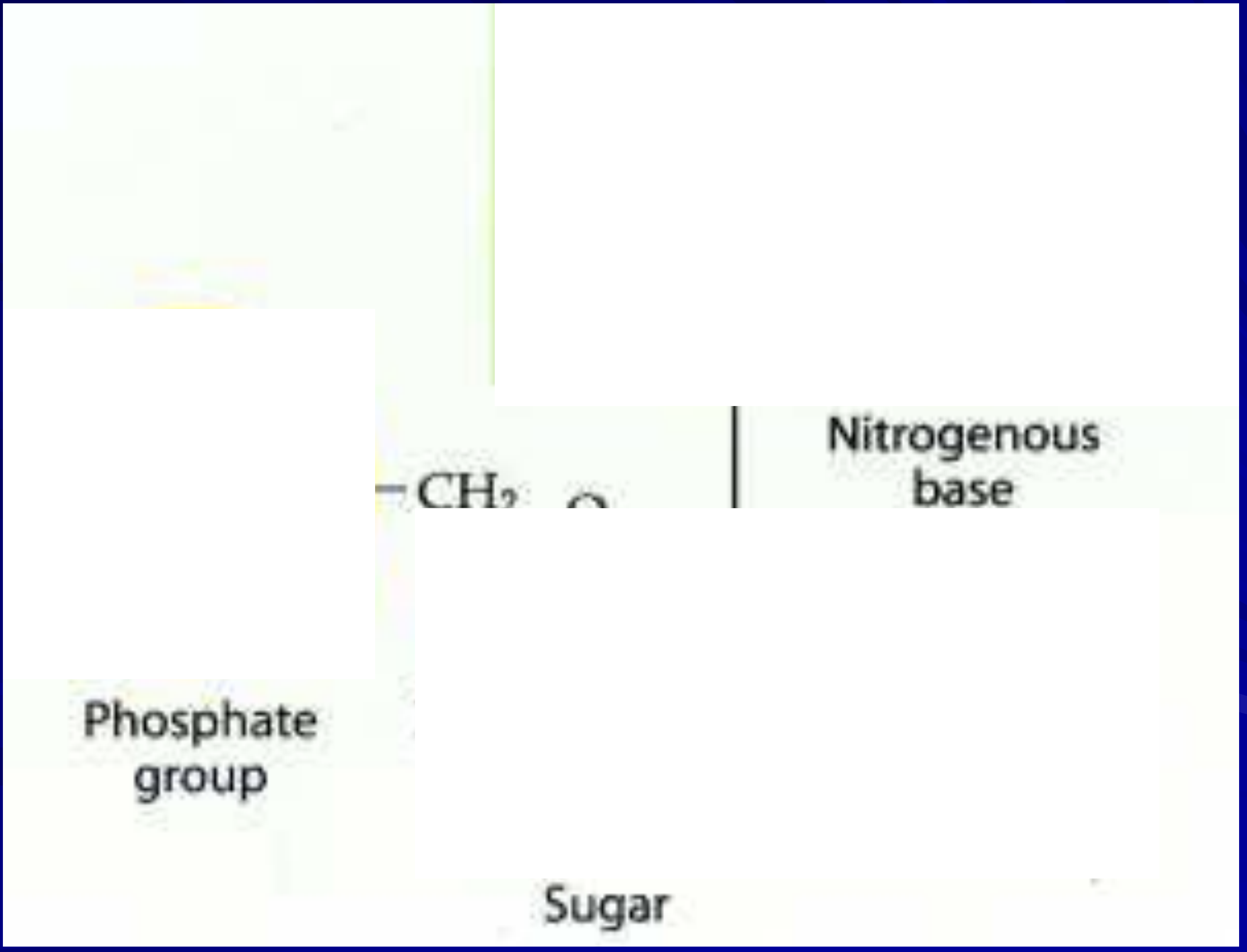
- A nucleotide is made up of 3 components:

a. Nitrogenous base, (a purine or a pyrimidine)

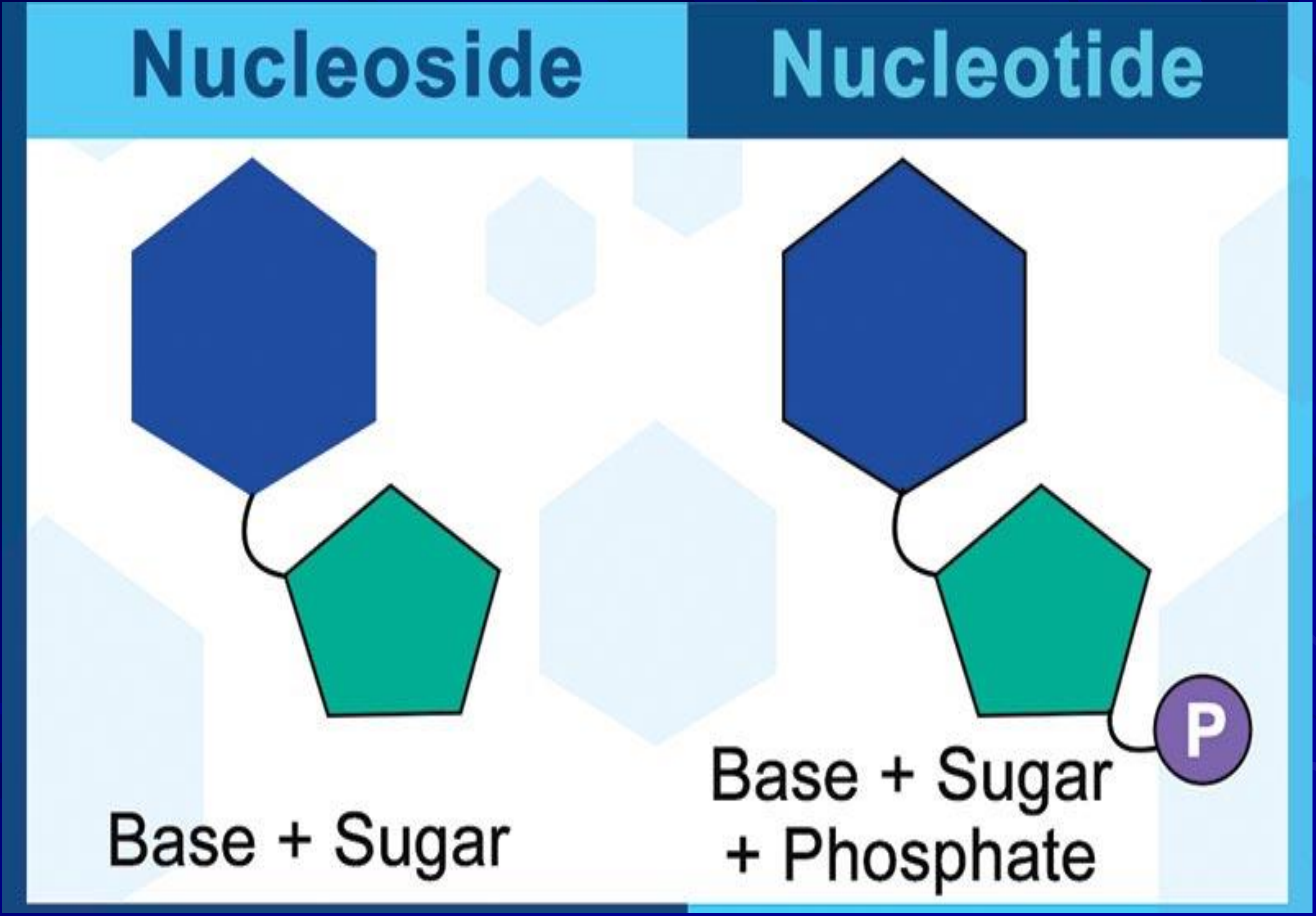
b. Pentose sugar,either ribose or deoxyribose;

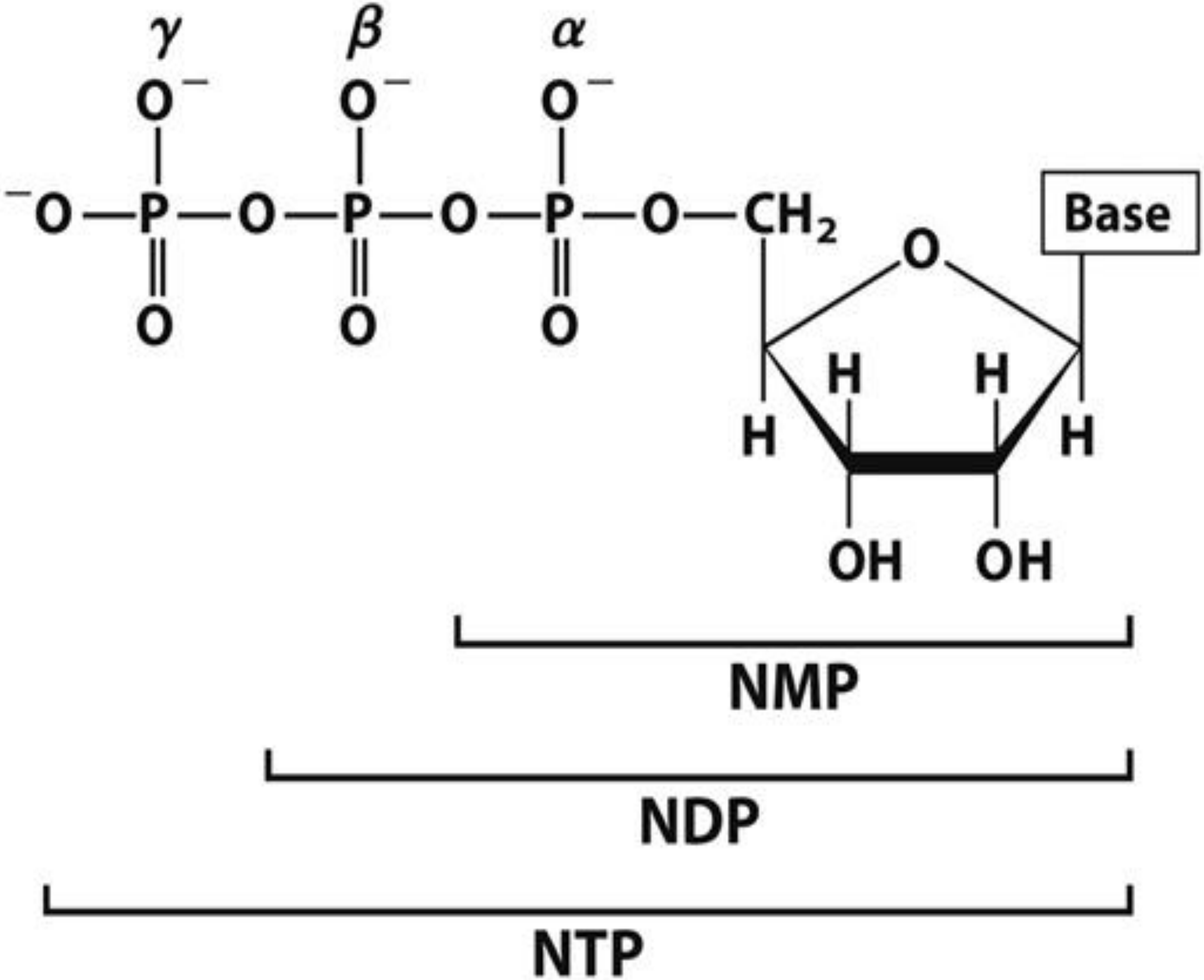
c. Phosphate groups esterified to the sugar

Composition of Nucleotides



- When Base + Pentose sugar → **nucleoside**
- When the nucleoside is esterified to a phosphate group, it is called **nucleotide or nucleoside monophosphate.**
- When a second phosphate gets esterified to the existing phosphate group, a **nucleoside diphosphate** is generated.
- The attachment of the 3rd phosphate group results in the formation of a **nucleoside triphosphate** .
- The nucleic acids (DNA and RNA) are polymers of nucleosides monophosphates.


Nucleoside
Nucleotide
P
Base + Sugar
Base + Sugar
+ Phosphate


γ
β
α
Base
NMP
NDP
NTP

BASES

- Two types of bases:

1. Purines are fused five- and six-membered rings

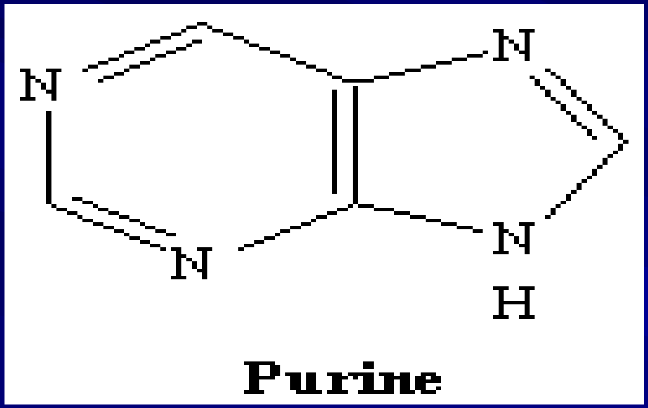
Adenine	A	DNA	RNA
Guanine	G	DNA	RNA

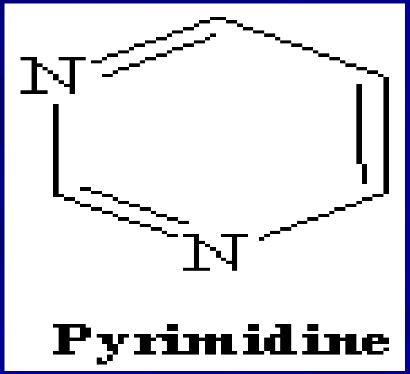
2. Pyrimidines are six-membered rings

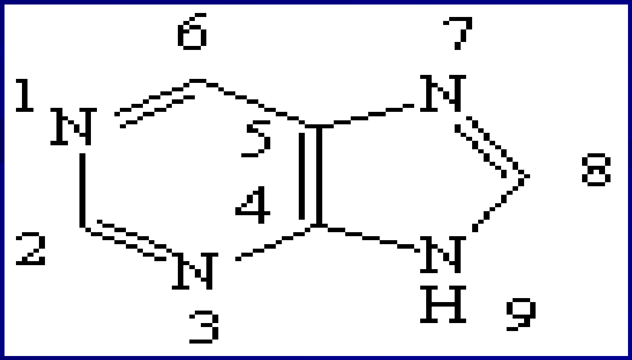
Cytosine	C	DNA	RNA
Thymine	T	DNA	
Uracil	U		RNA

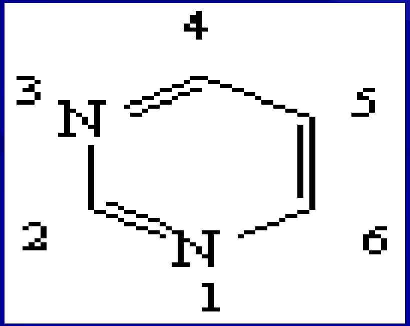
Nitrogenous Bases

- Planar, aromatic, and heterocyclic
- Derived from purine or pyrimidine



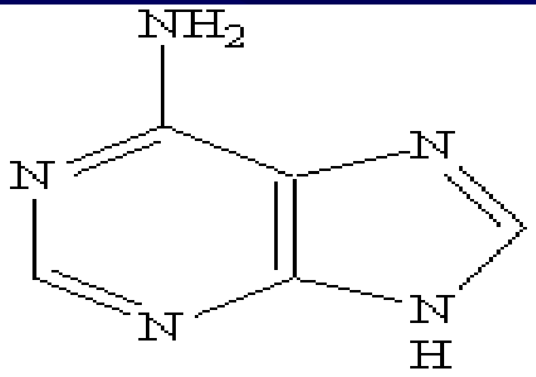




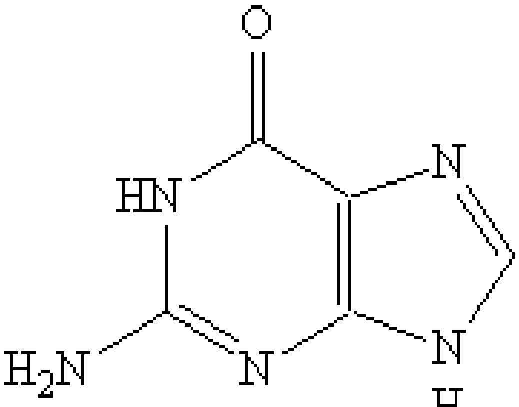


Nucleic Acid Bases

Purines

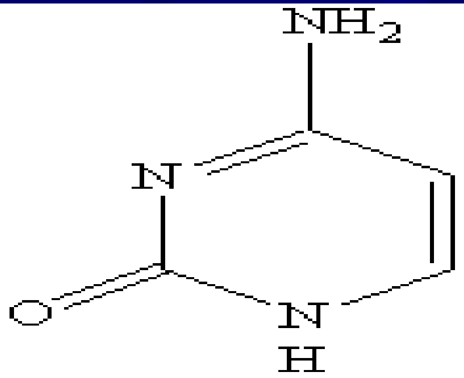


Adenine (A)

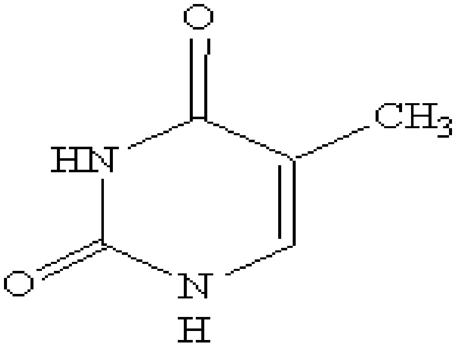


Guanine (G)

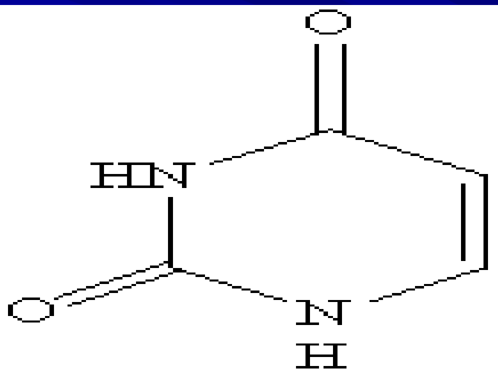
Pyrimidines



Cytosine (C)



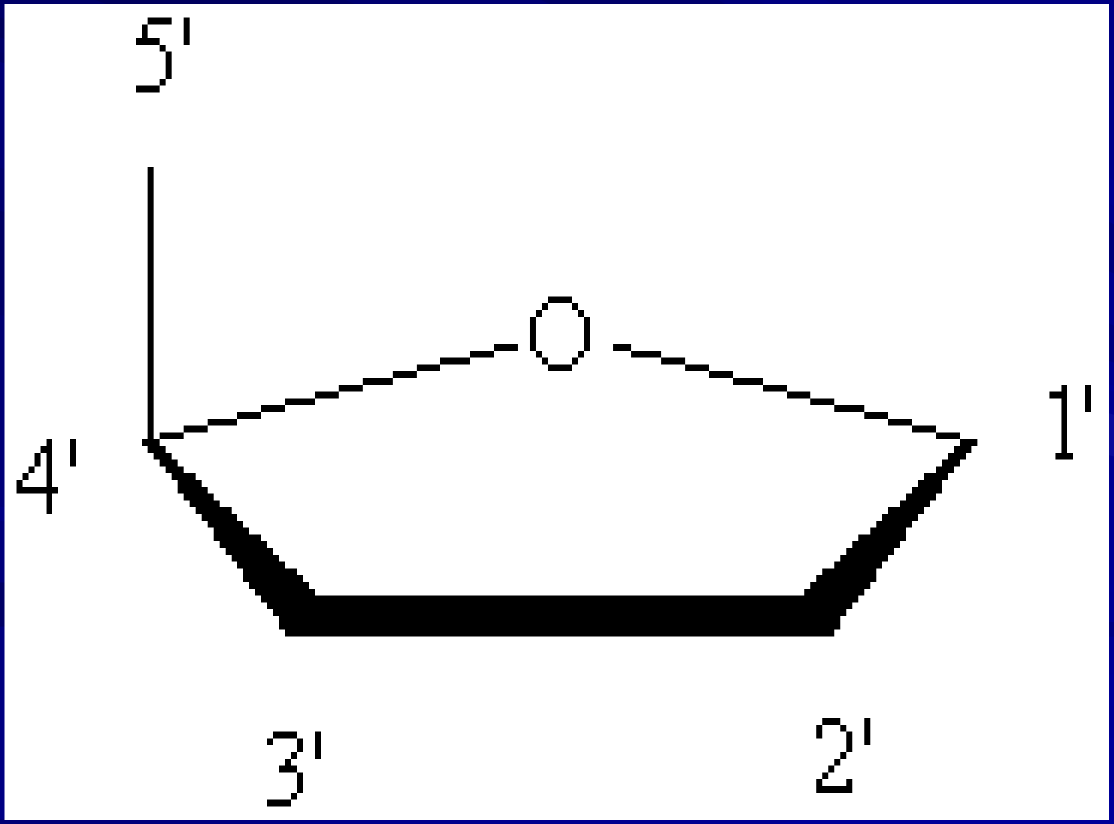
Thymine (T)
(5-methyluracil)

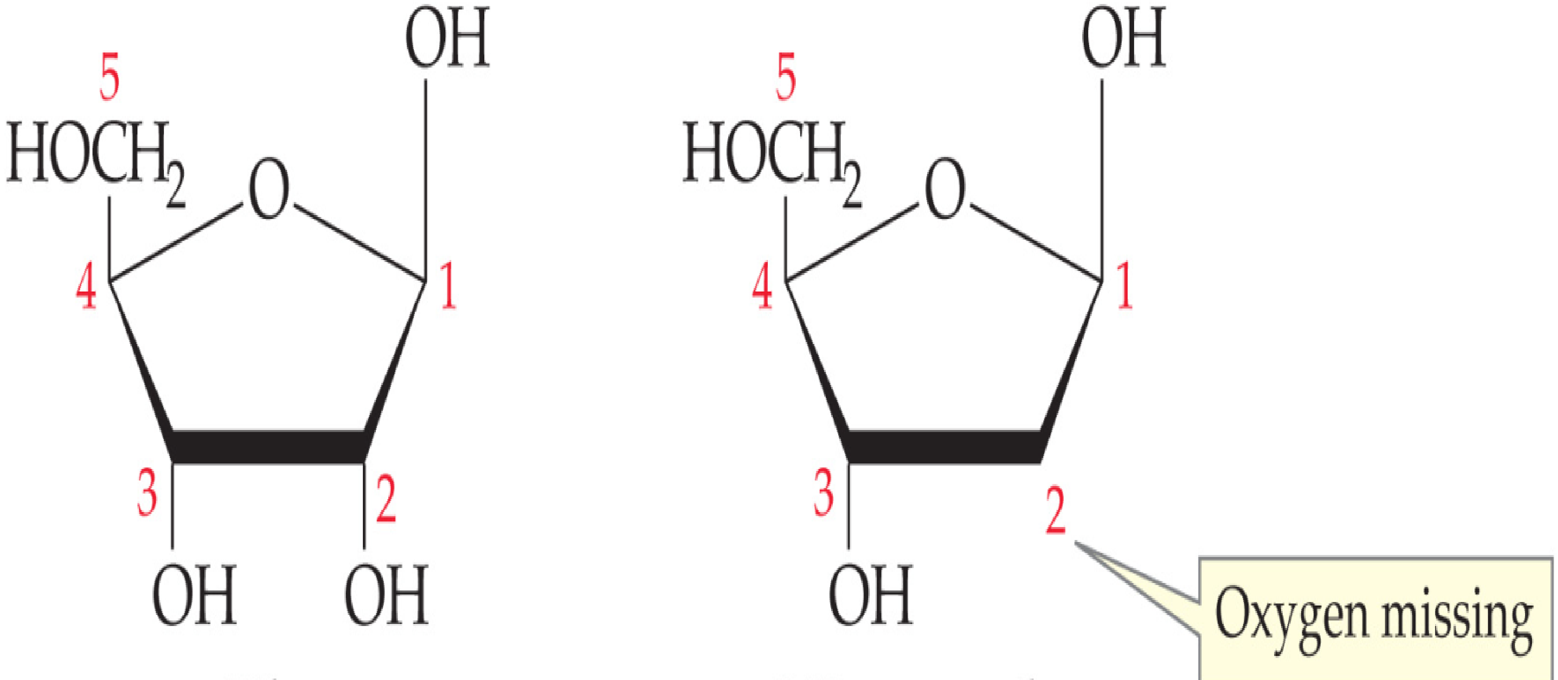


Uracil (U)

Sugars

- Pentoses (5-C sugars)
- Numbering of sugars is “primed”





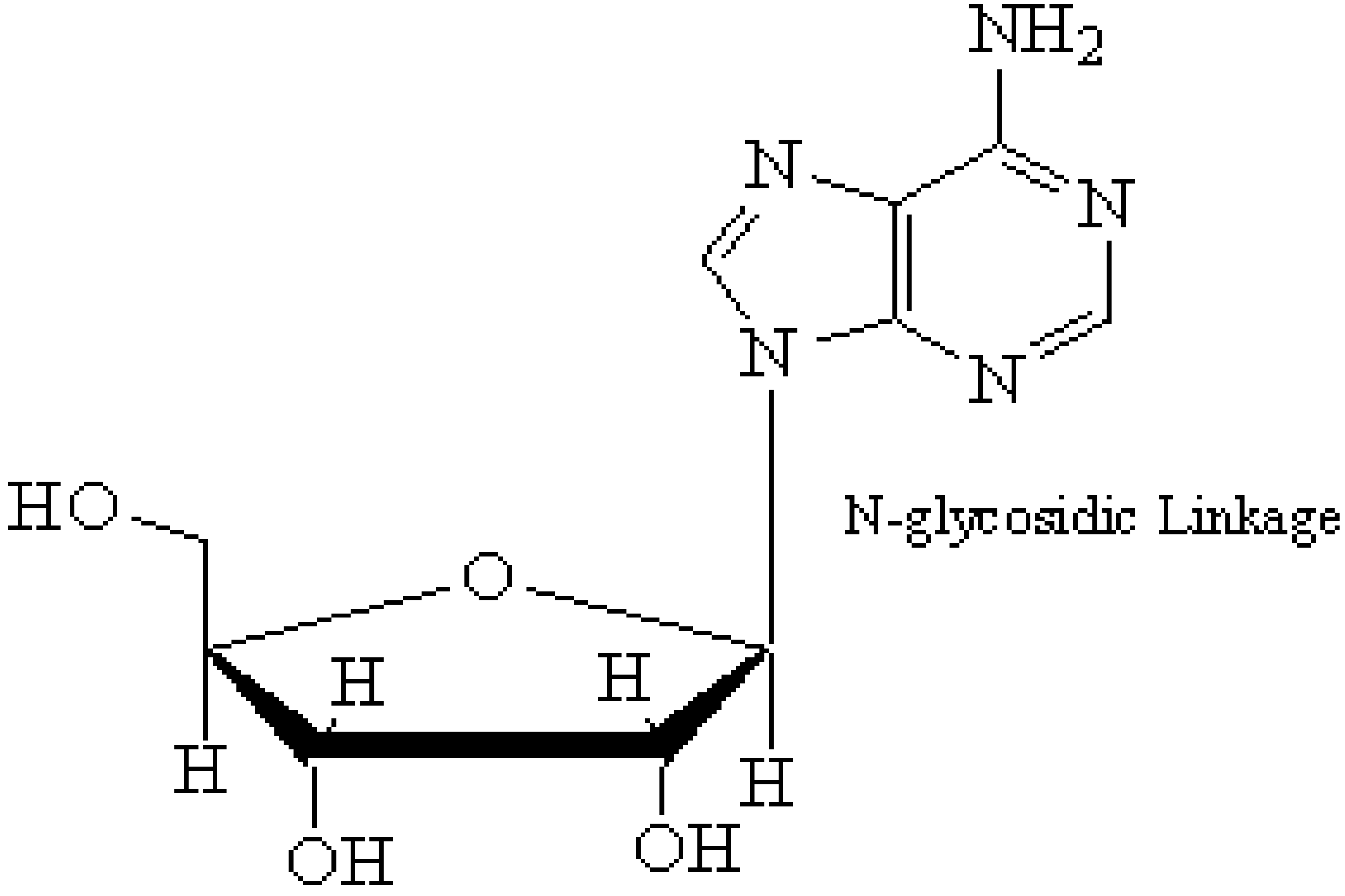
D-Ribose
(in RNA)

2-Deoxy-D-ribose
(in DNA)

Nucleosides

- Result from linking one of the sugars with a purine or pyrimidine base through an **beta-N-glycosidic linkage**
  - Purines bond to the C1’ carbon of the sugar at their N9 atoms
  - Pyrimidines bond to the C1’ carbon of the sugar at their N1 atoms

Nucleosides



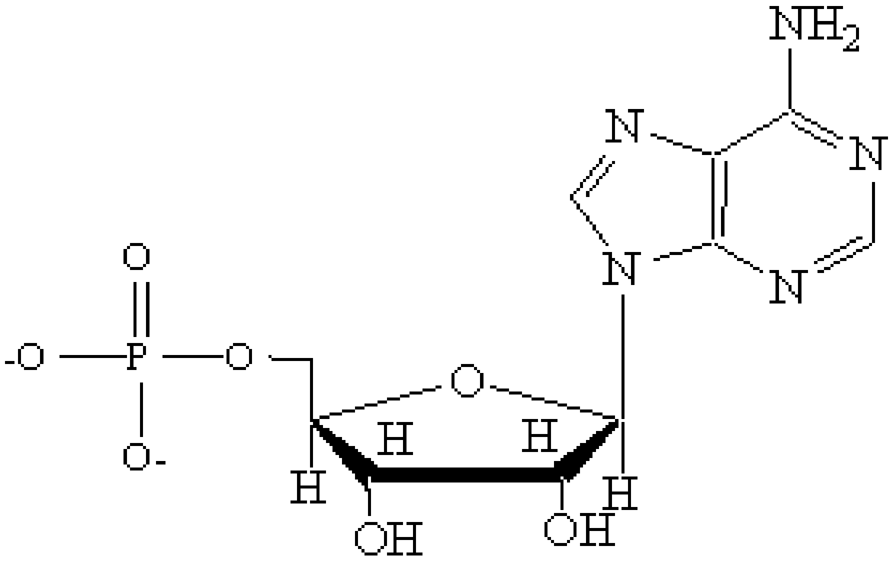
Adenosine

Naming Conventions

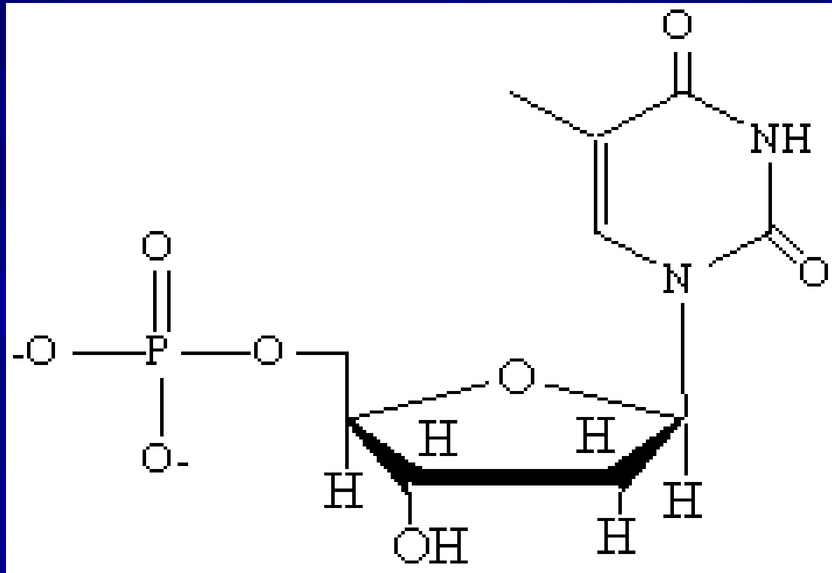
- **Nucleosides:**
  - Purine nucleosides end in **"-sine"**
    - **Adenosine, Guanosine**
  - Pyrimidine nucleosides end in **"-dine"**
    - **Thymidine, Cytidine, Uridine**
- **Nucleotides:**
  - Start with the nucleoside name from above and add "mono-", "di-", or "triphosphate"
    - Adenosine Monophosphate, Cytidine Triphosphate, Deoxythymidine Diphosphate

Nucleotides

- Result from linking one or more phosphates with a nucleoside onto the 5’ end of the molecule through esterification



Adenosine Monophosphate (AMP)
(a ribonucleotide)



2'-Deoxythymidine Monophosphate
(a deoxyribonucleotide)

Abbreviations of ribonucleoside 5′-phosphates			
Base	Mono-	Di-	Tri-
Adenine	AMP	ADP	ATP
Guanine	GMP	GDP	GTP
Cytosine	CMP	CDP	CTP
Uracil	UMP	UDP	UTP

Abbreviations of deoxyribonucleoside 5′-phosphates			
Base	Mono-	Di-	Tri-
Adenine	dAMP	dADP	dATP
Guanine	dGMP	dGDP	dGTP
Cytosine	dCMP	dCDP	dCTP
Thymine	dTMP	dTDP	dTTP

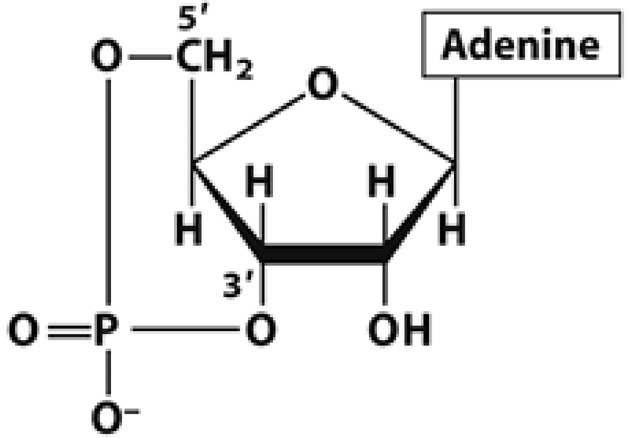
Nucleotides of Biological Importance

- ***Classification:***

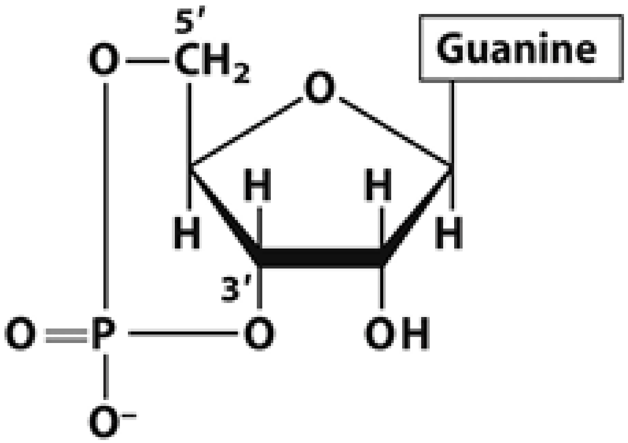
1. **Adenosine nucleotides:** ATP, ADP, AMP, cAMP.
2. **Guanosine nucleotides:** GTP, GDP, GMP, cGMP.
3. **Uridine nucleotides:** UTP, UDP, UMP.
4. **Cytidine nucleotides:** CTP, CDP, CMP.

Important functions

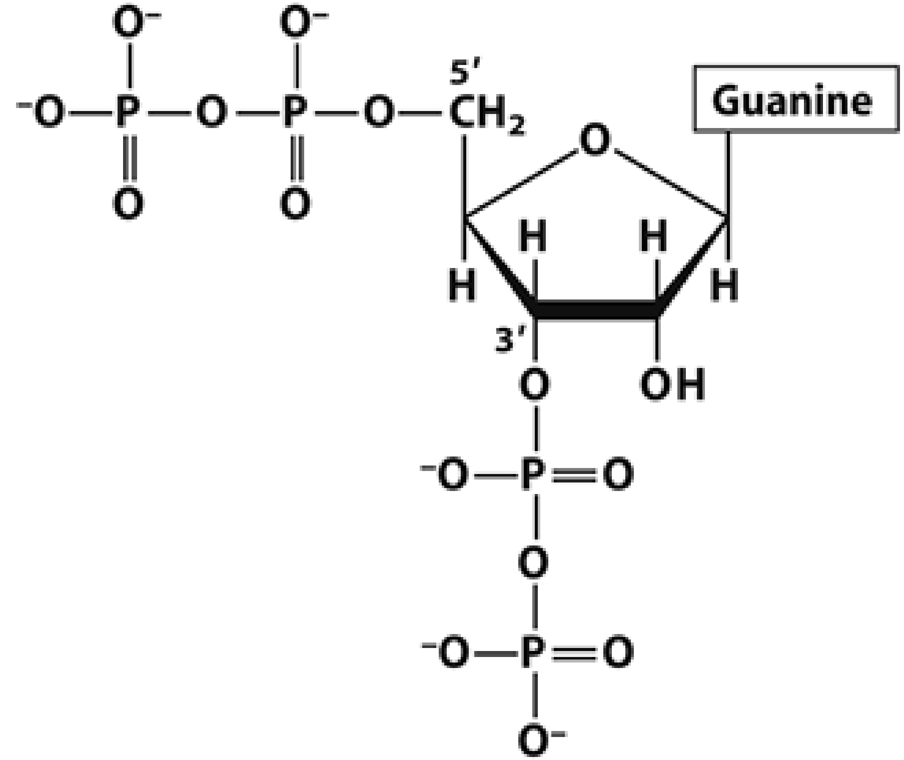
- ATP, GTP, CTP, and UTP (NTPs) → **energy metabolism and activation of metabolites**.
- cAMP, cGMP (Cyclic nucleotides) → **Second messengers**
- Phosphoadenosine-5-phosphosulfate (PAPS) is known as **"active sulfate"** and acts as a donor of sulfate in sulfation reactions.
- S-Adenosylmethionine (SAM) is the active form of methionine, which serves as the major methyl donor in **transmethylation** reactions



Adenosine 3′,5′-cyclic monophosphate
(cyclic AMP; cAMP)



Guanosine 3′,5′-cyclic monophosphate
(cyclic GMP; cGMP)



Guanosine 5′-diphosphate, 3′-diphosphate
(guanosine tetraphosphate)
(ppGpp)

Important functions

- Synthetic analogues of normally occurring nucleotides → treatment of cancer, as immunosuppression agents and antiviral drugs.
- E.g.

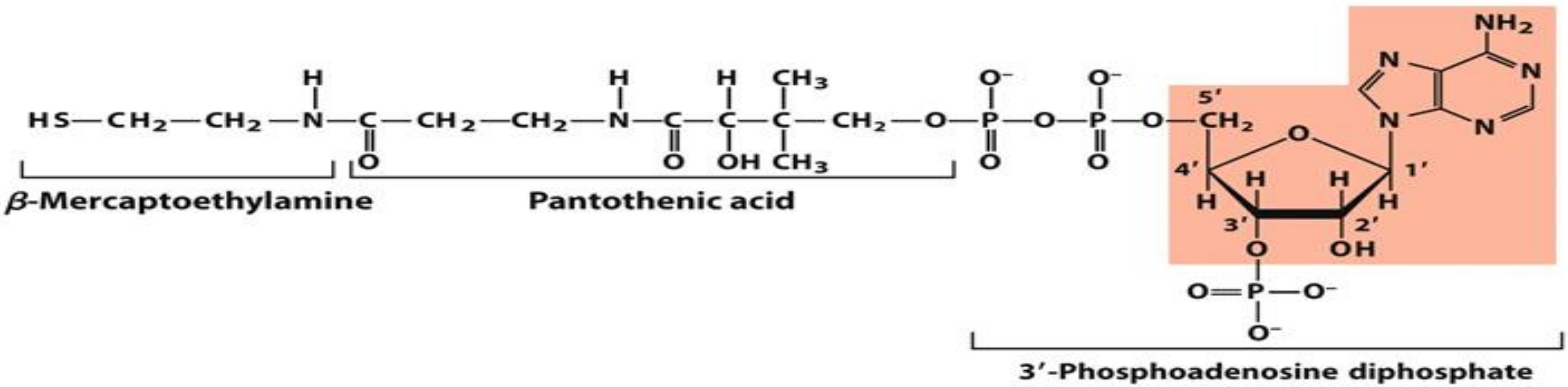
- 5-Fluorouracil→ Anti-cancer
- Azathioprine→ Immunosuppressant
- Zidovudine → Anti-HIV

Important functions

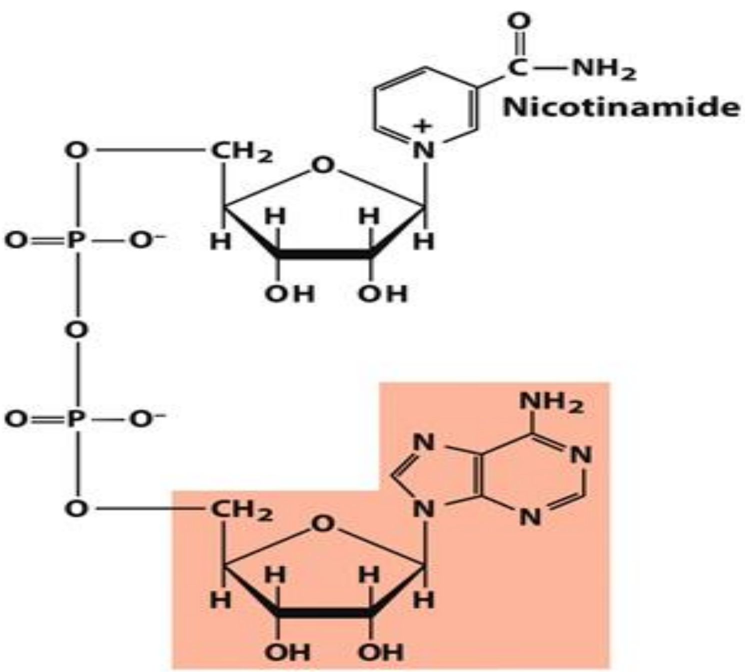
- **Nucleoside sugars** are activated precursors which are used in **biosynthetic reactions**.
- For example:
- UDP-glucose → **glycogen synthesis**
- UDP-galactose → **ceramides**
- CTP-choline → **phospholipid synthesis**

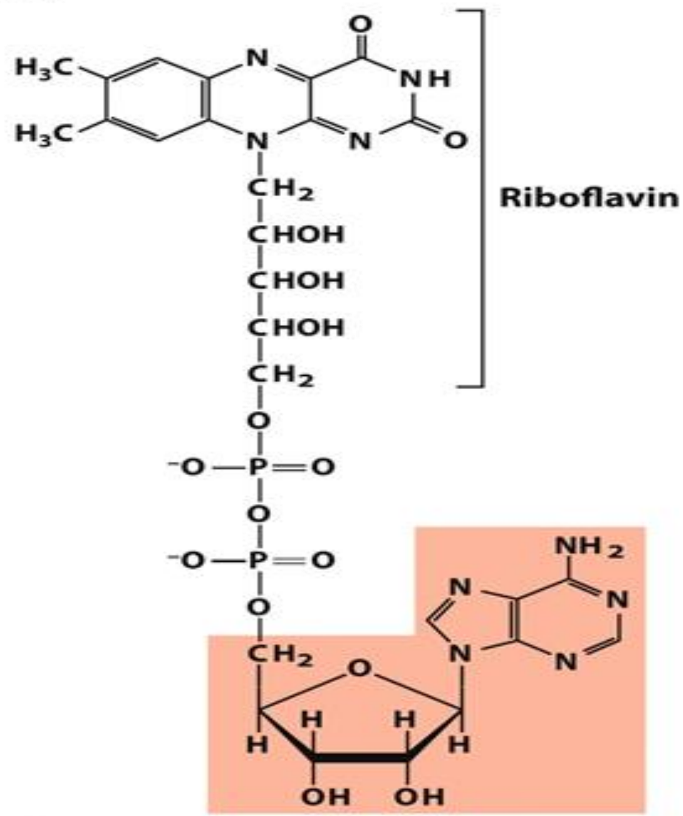
Important functions

- Nucleotides as essential components in Coenzymes, NAD+, FAD and Coenzyme A



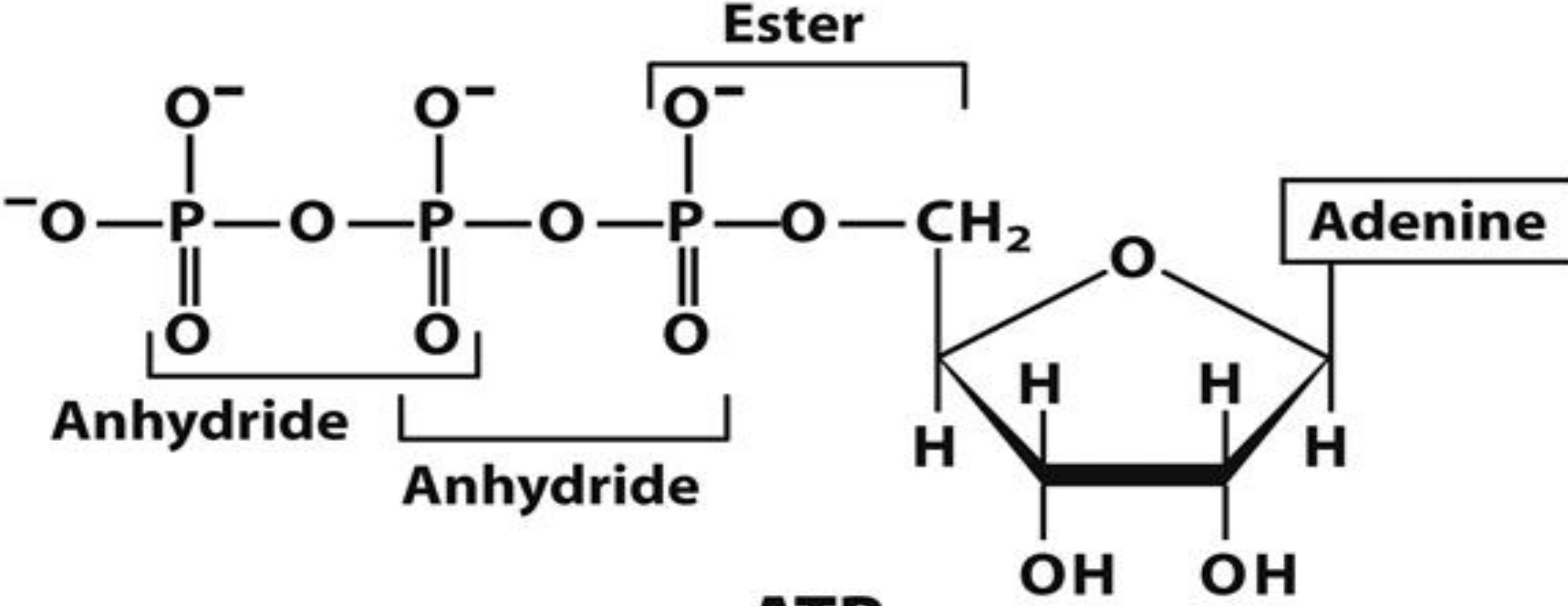
Coenzyme A





Nicotinamide adenine dinucleotide (NAD^+) **Flavin adenine dinucleotide (FAD)**

ATP



ATP

Functions of ATP

- Muscle contraction and nerve conduction.
- Active transport across membranes
- Many anabolic reactions require ATP.
- Activation of metabolites→ Phosphorylation
- Synthesis of cAMP
- Synthesis of Active methionine and active sulfate

CCES

1. Nucleosides are called

A. Beta-D-Glycoside

B. N-Glycosides

C. O-Glycosides

D. Phosphoryl glycoside

2. Pyrimidines bond to the C1’ carbon of the sugar at their……atom

A. N6
B. N3
C. N1
D. N5

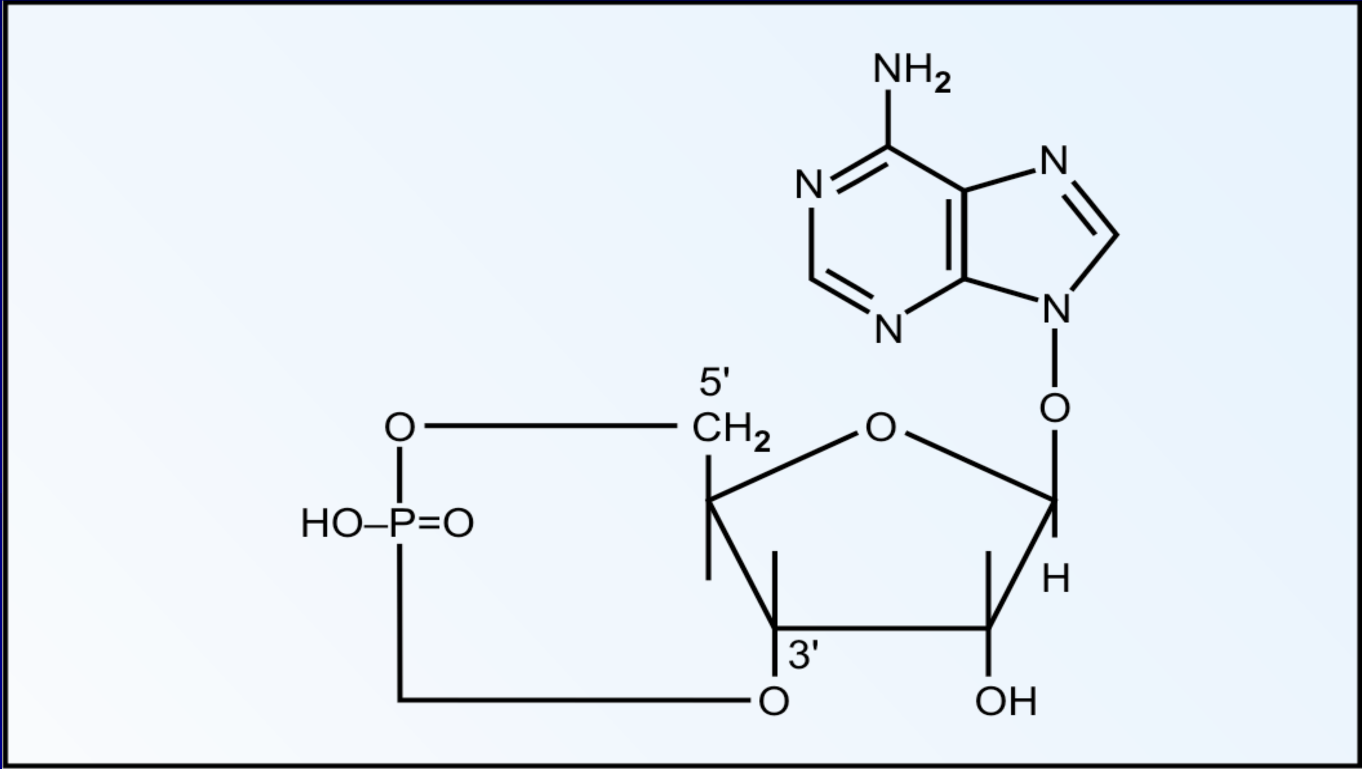
3. Identify structure

A. Cyclic nucleotide

B. Nucleotide

C. Nucleotide monophosphate

D. Nucleoside



4. **All are nucleosides except**

A. Adenosine
B. Thymidine
C. Uracil
D. Guanosine

5. **Primary PO_4 acceptor in oxidative phosphorylation is**

A. Guanosine nucleotide

B. Cytidine nucleotide

C. Adenosine nucleotide

D. Uridine nucleotide

Adenosine nucleotides

1. **Adenosine tri-phosphate (ATP):**

- Storage battery of tissues
- Two of the three phosphate residues are high energy '**phosphates (~P)**' and on hydrolysis each releases energy that is utilized for 'endergonic reactions'.
- **ATP is an important source of energy** for muscle contraction, transmission of nerve impulses, transport of nutrients across the cell membranes, motility of spermatozoa.

- Formation of '**active methionine**'→ methylation reactions.
- It donates phosphates for a variety of phosphotransferase reactions
- Formation of active sulphate which is necessary for incorporation of SO_4 in compounds like formation of **chondroitin SO_4**.
- 'In vivo' ATP is converted to ADP, AMP and cAMP which have important role to play in biochemical processes.

2. Adenosine diphosphate (ADP):

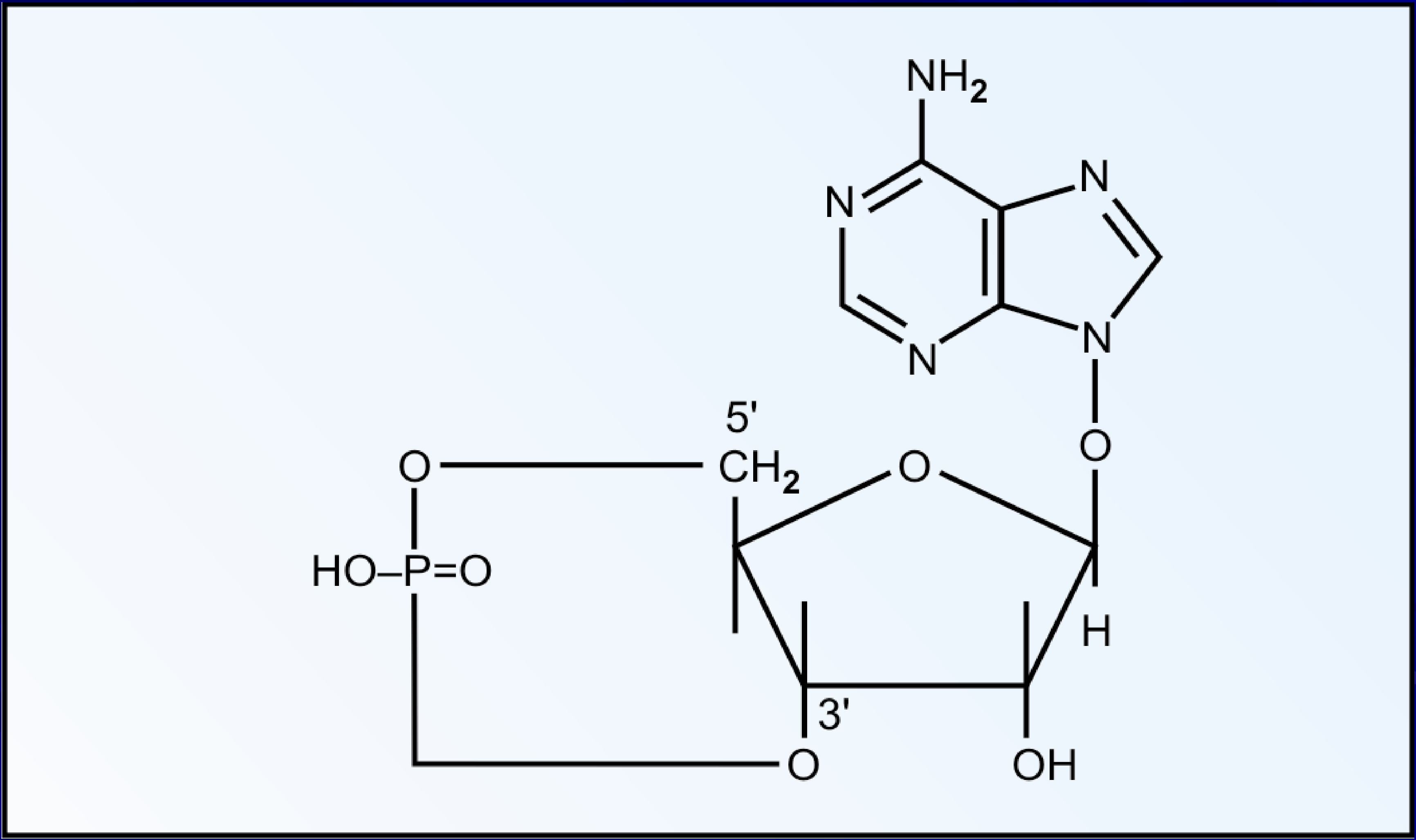
- Acts as a primary PO_4 acceptor in oxidative phosphorylation.
- Thus plays an important role in **cellular respiration and muscle contraction.**
- It activates enzyme glutamate dehydrogenase required for de-amination reaction in liver to produce ammonia.

3. Adenosine monophosphate (AMP):

- It acts as an activator of several enzymes in tissues.
- In glycolytic pathway, the enzyme phosphofructokinase is inhibited by ATP but the inhibition is reversed by AMP.
- In resting muscle, AMP is formed from ADP, by the enzyme adenylate kinase reaction.
- The AMP produced activates the phosphorylase enzyme of muscle and increases the breakdown of glycogen.

4. Cyclic AMP:

- Chemically, it is **3', 5'-adenosine monophosphate.**



- It is synthesized in the tissues from ATP.
- It is a mediator of hormone action by acting as a **second messenger.**
- It modulates both transcription and translation in protein biosynthesis.
- It also regulates permeability of cell membranes to water, sodium, potassium and calcium.

Guanosine nucleotide

Guanosine triphosphate (GTP):

- It is a Guanosine analogue of ATP which is involved in important metabolic reactions like

1. The oxidation of succinyl CoA in the citric acid cycle.
2. Required for protein synthesis.
3. Necessary for production of cAMP.
4. Role in Rhodopsin cycle.
5. Role in gluconeogenesis.
6. Required in purine synthesis.

Uridine nucleotides

- **UDP- glucose---** glucose donor in glycogen synthesis.
- **UDP-galactose, UDP-glucoronate, UDP-N-acetylgalactosamine** act as sugar donors for biosynthesis of glycoproteins & proteoglycans

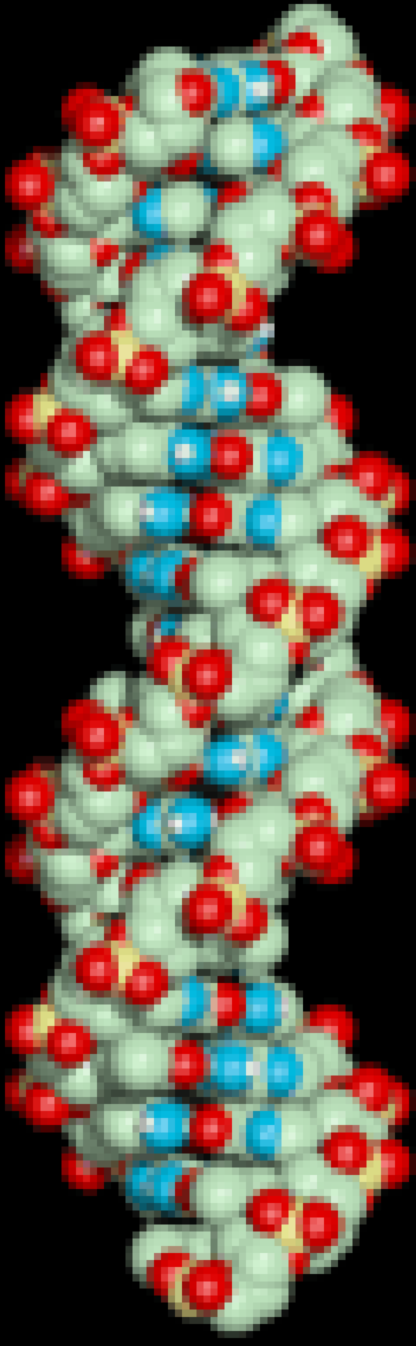
Cytidine nucleotides

- These are **CTP, CDP and CMP.**
- CDP- choline, CDP- glycerol, CDP- ethanolamine are involved in the **biosynthesis of phospholipids.**
- CMP- sialic acid is present in salivary glands and involved in synthesis of salivary mucin.

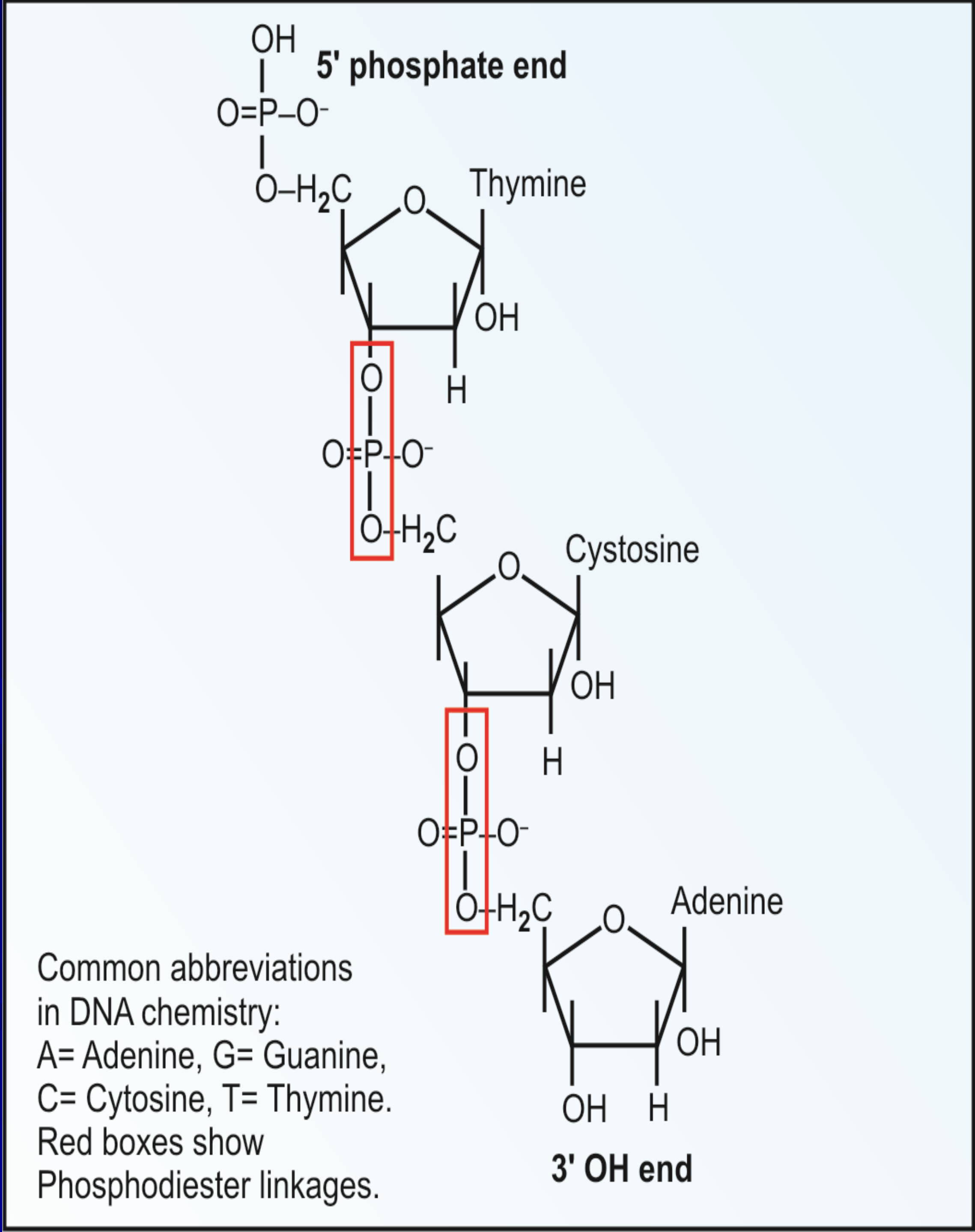
Coenzymes

- Many coenzymes are nucleotide derivatives e.g. **NAD, NADP, FAD, coenzyme- A.**

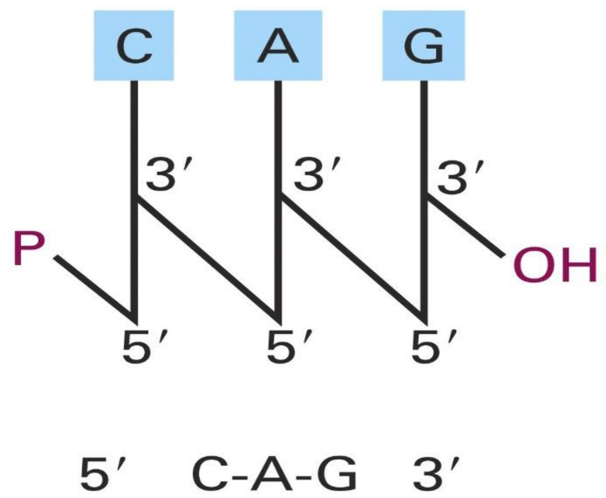
DNA

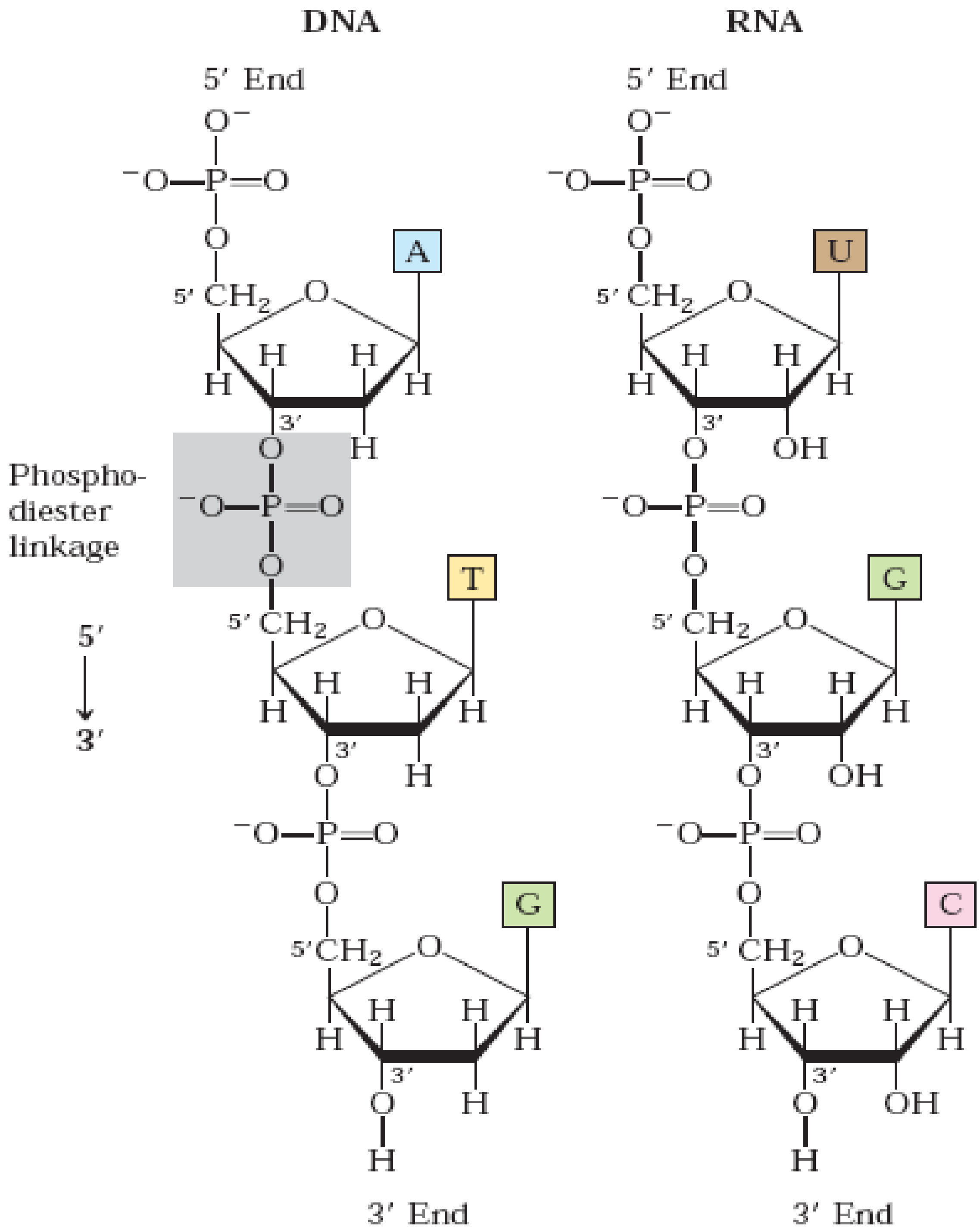


- Composed of ATGC.
- Combined through 3’ to 5’ **phosphodiester bonds** to polymerize into a long chain.



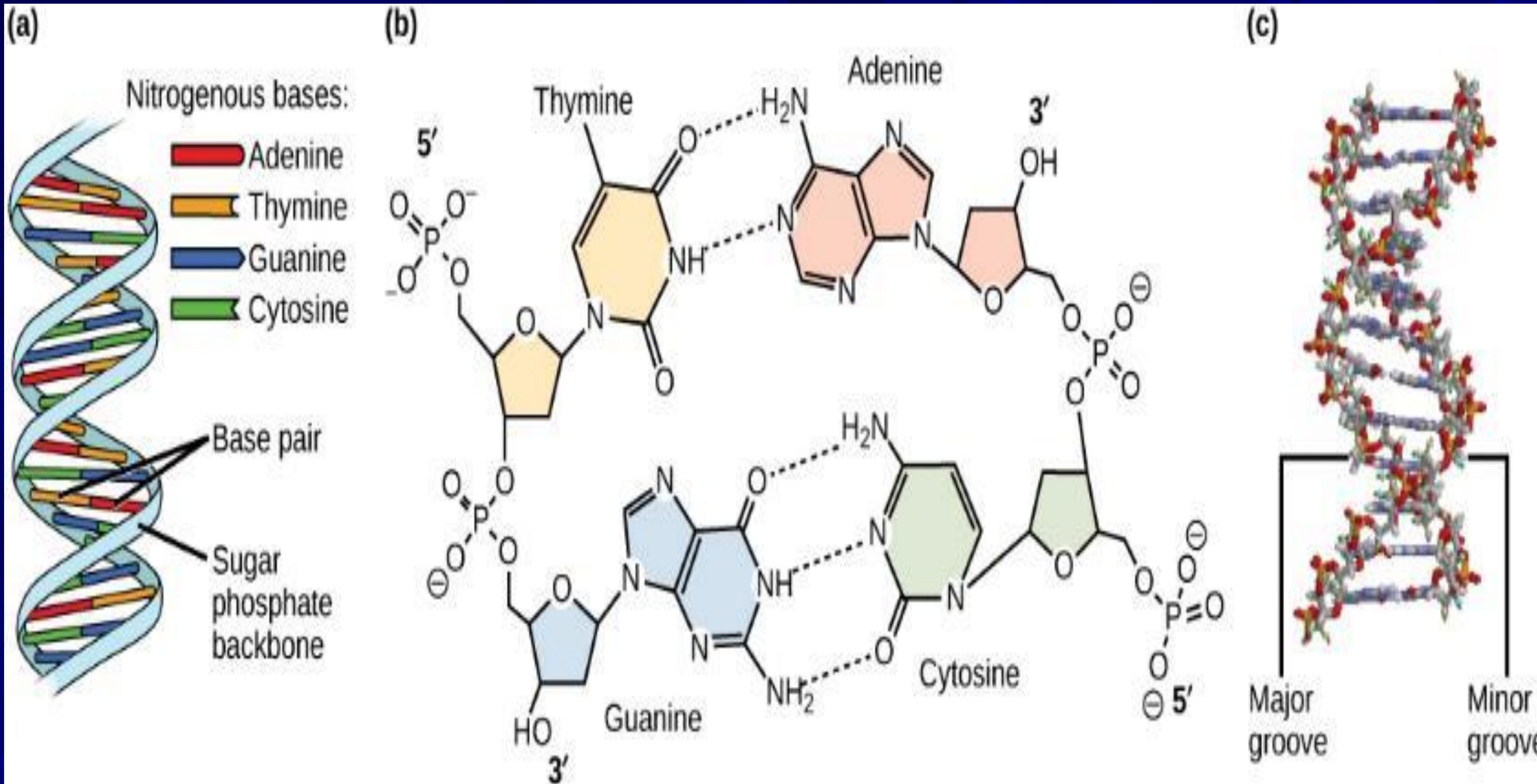
Polarity of the DNA





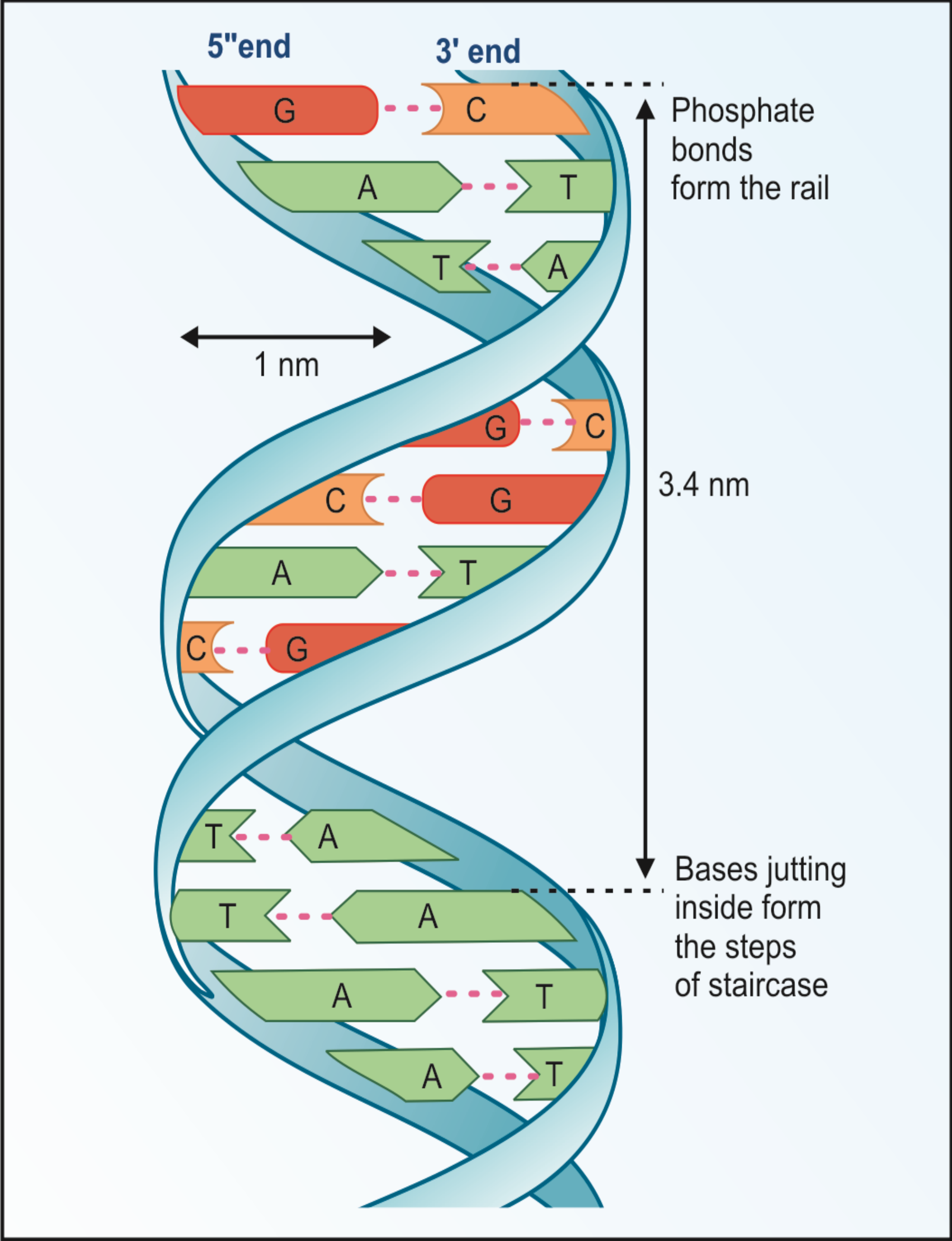
Watson – Crick Model

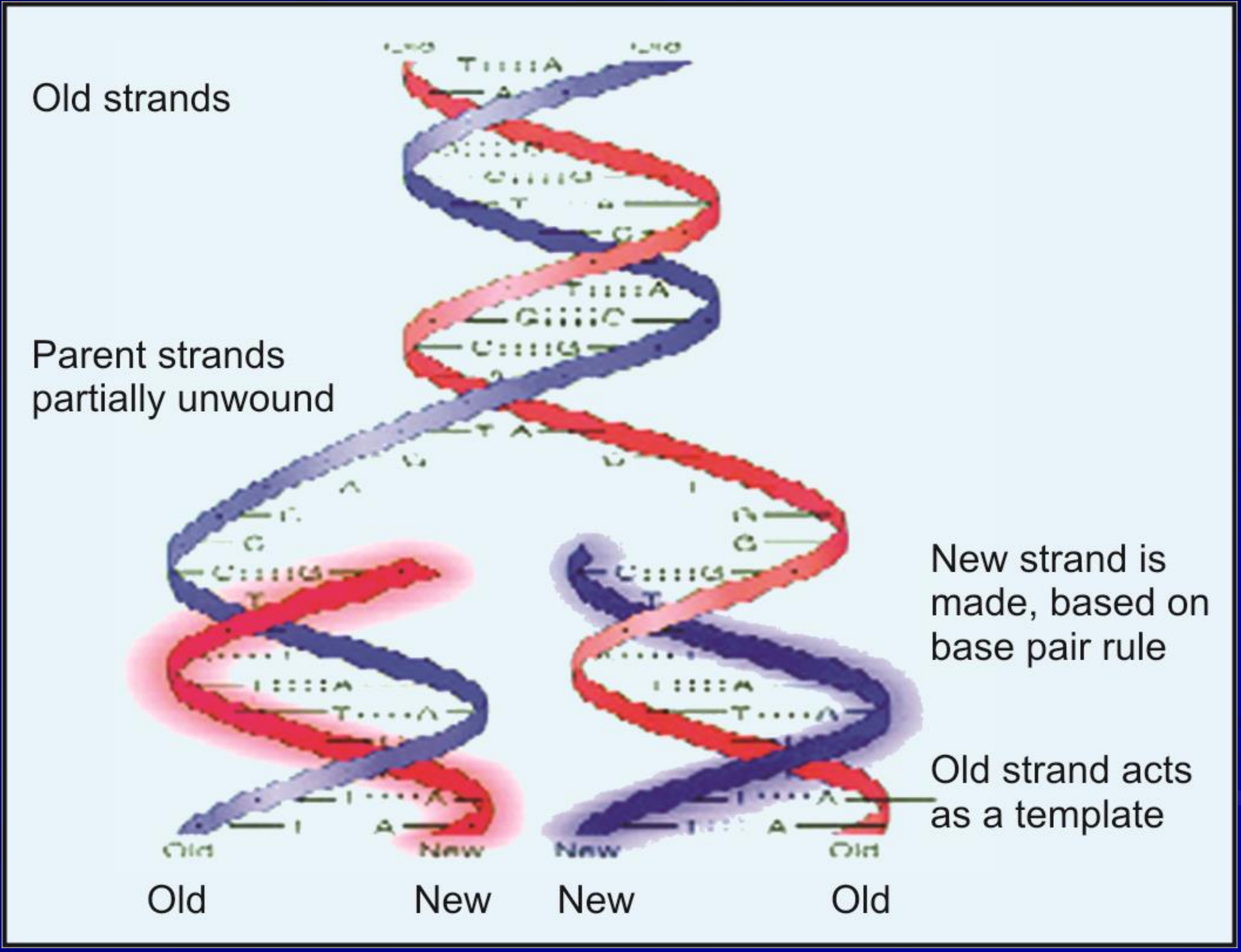
1. **Right handed double helix**
2. Always the two strands are **complementary to each other.**
3. **Antiparallel**
4. **Base pairing rule**
   - **Chargaff's rule**
5. **Hydrogen bonding**
6. **Each strand acts as a template**


(a)
Nitrogenous bases:
Adenine
Thymine
Guanine
Cytosine
Base pair
Sugar phosphate backbone
(b)
Thymine
Adenine
Guanine
Cytosine
5′
3′
3′
5′
(c)
Major groove
Minor groove

Major and Minor Groove

DNA binding proteins locate and interact with specific base sequences exposed in the grooves.




Old strands
Parent strands partially unwound
New strand is made, based on base pair rule
Old strand acts as a template
Old
New
New
Old

Structural forms of the double helix:

- ***Three major structural forms of DNA:***
- **the B form**, described by Watson and Crick in 1953.
- the **A form**
- the **Z form.**

B form

- **Right-handed helix** with
- **Ten** residues per 360° turn of the helix,
- **Chromosomal DNA** is thought to consist primarily of B-DNA.

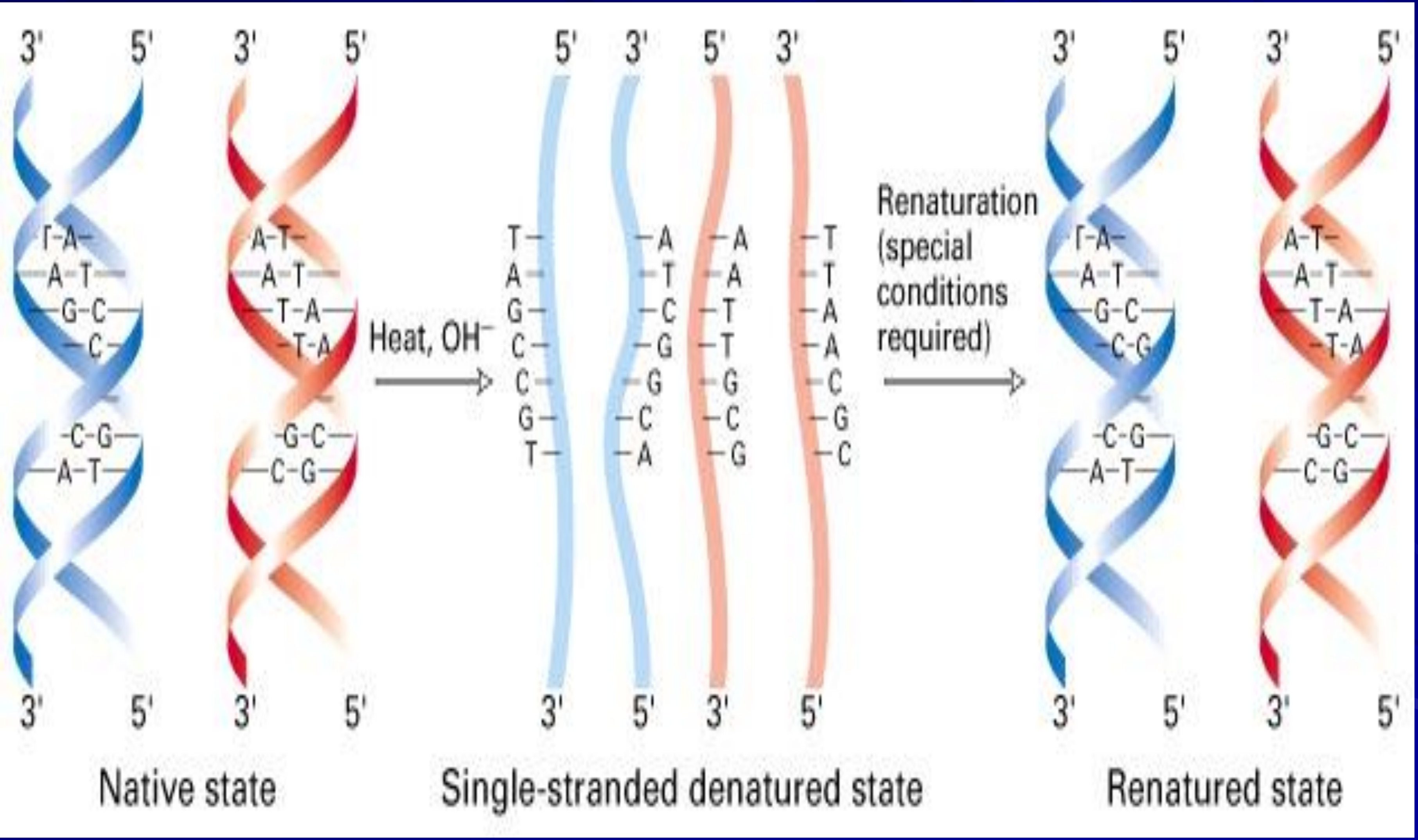
A form.

- Right-handed helix
- **Eleven base pairs per turn**
- The conformation found in **DNA–RNA hybrids** or **RNA–RNA double-stranded regions** is probably very close to the A form.

Z-DNA

- **Left-handed helix**
- **Twelve base pairs per turn** .
- Occur naturally in regions of DNA that have a sequence of **alternating purines and pyrimidines**, for example, poly GC.

Denaturation and Renaturation of DNA



Higher organization of DNA

- In higher organisms, DNA is organized inside the nucleus.
- Double stranded DNA is first wound over histones: this is called **nucleosomes.**
- Chromatin is a long stretch of DNA in association with histones.
- Chromatin is then further and further condensed to form chromosomes.

Histones and the formation of nucleosomes

- There are five classes of histones, designated **H1, H2A, H2B, H3, and H4.**
- Basic Proteins→ high content of **lysine and arginine**.
- Because of their positive charge, they form ionic bonds with negatively charged DNA.
- **Histones,** along with positively charged ions such as **Mg**$^{+2}$, help neutralize the negatively charged DNA phosphate groups.

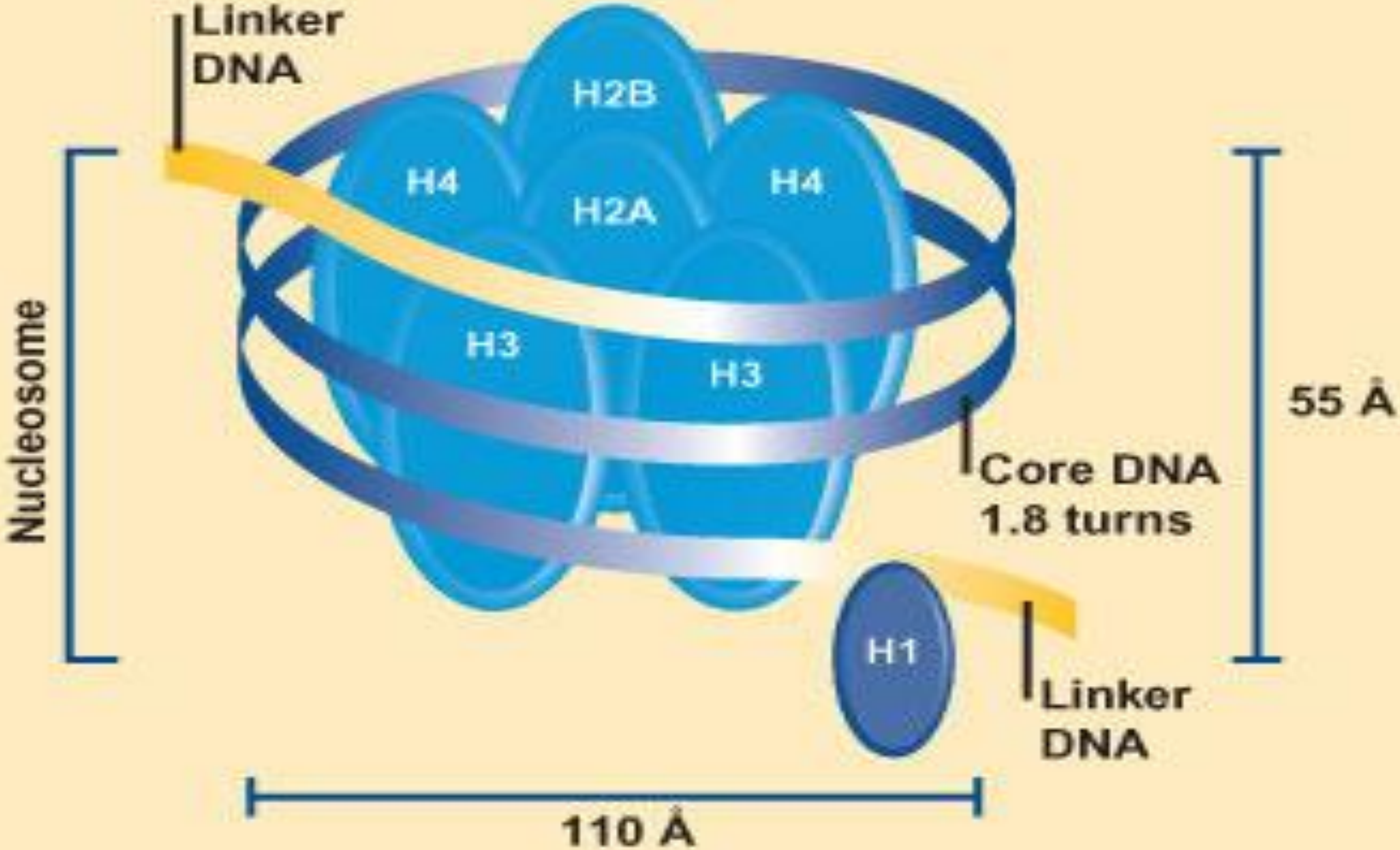
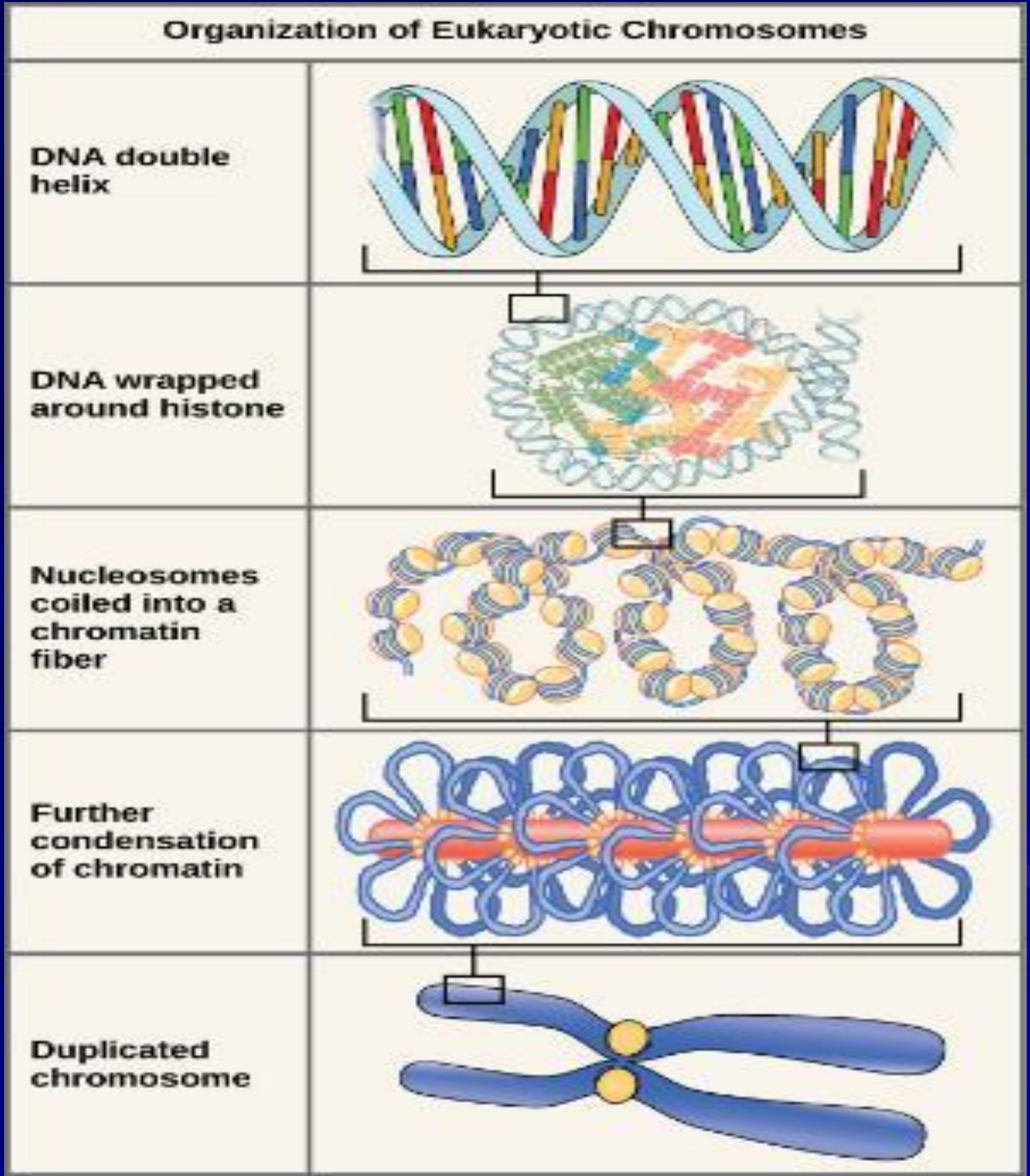
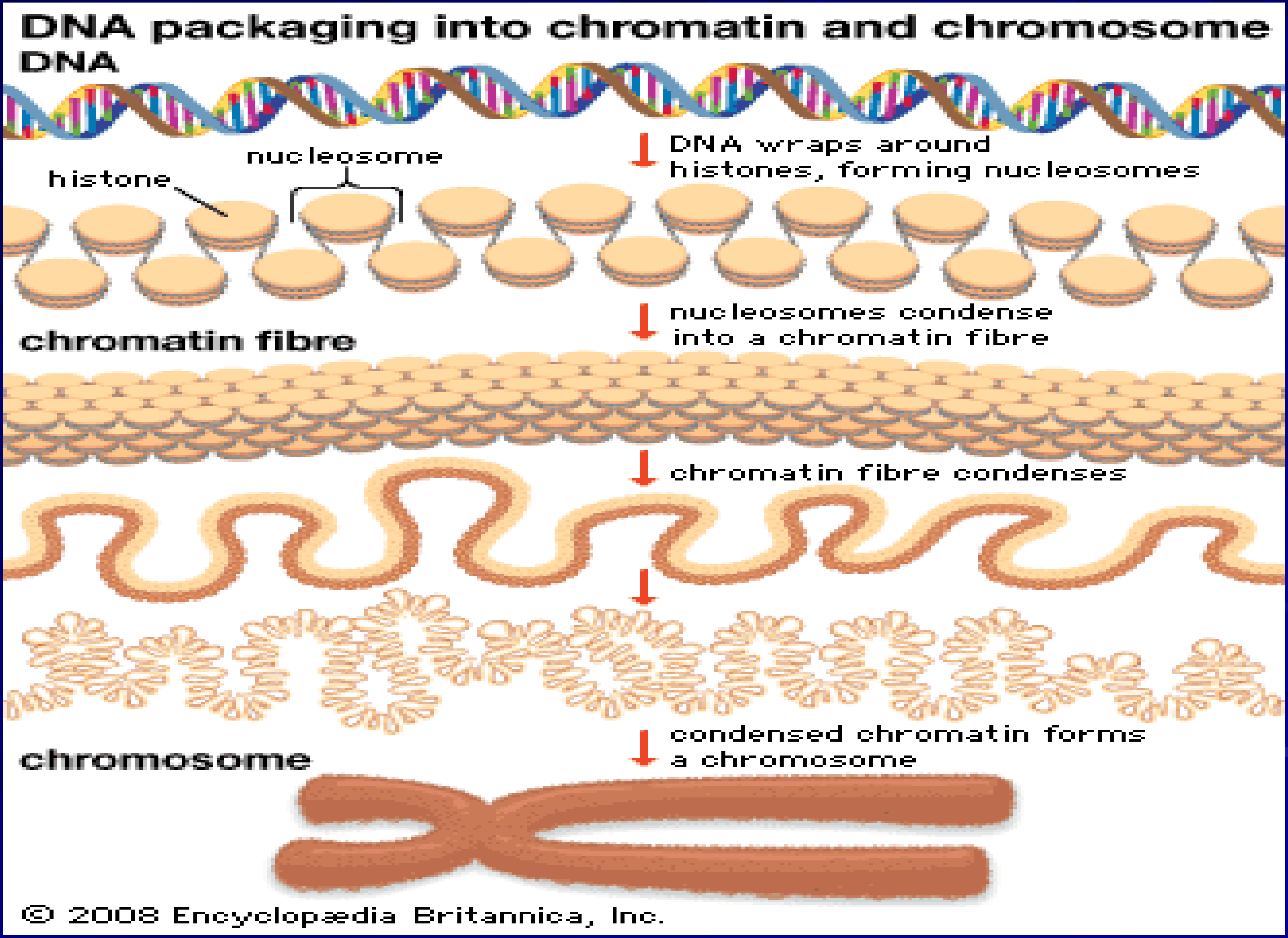


Figure 1. Nucleosomal structure.


Organization of Eukaryotic Chromosomes
DNA double helix
DNA wrapped around histone
Nucleosomes coiled into a chromatin fiber
Further condensation of chromatin
Duplicated chromosome


DNA packaging into chromatin and chromosome
DNA
DNA wraps around
histones, forming nucleosomes
nucleosome
histone
nucleosomes condense
into a chromatin fibre
chromatin fibre
chromatin fibre condenses
condensed chromatin forms
a chromosome
chromosome
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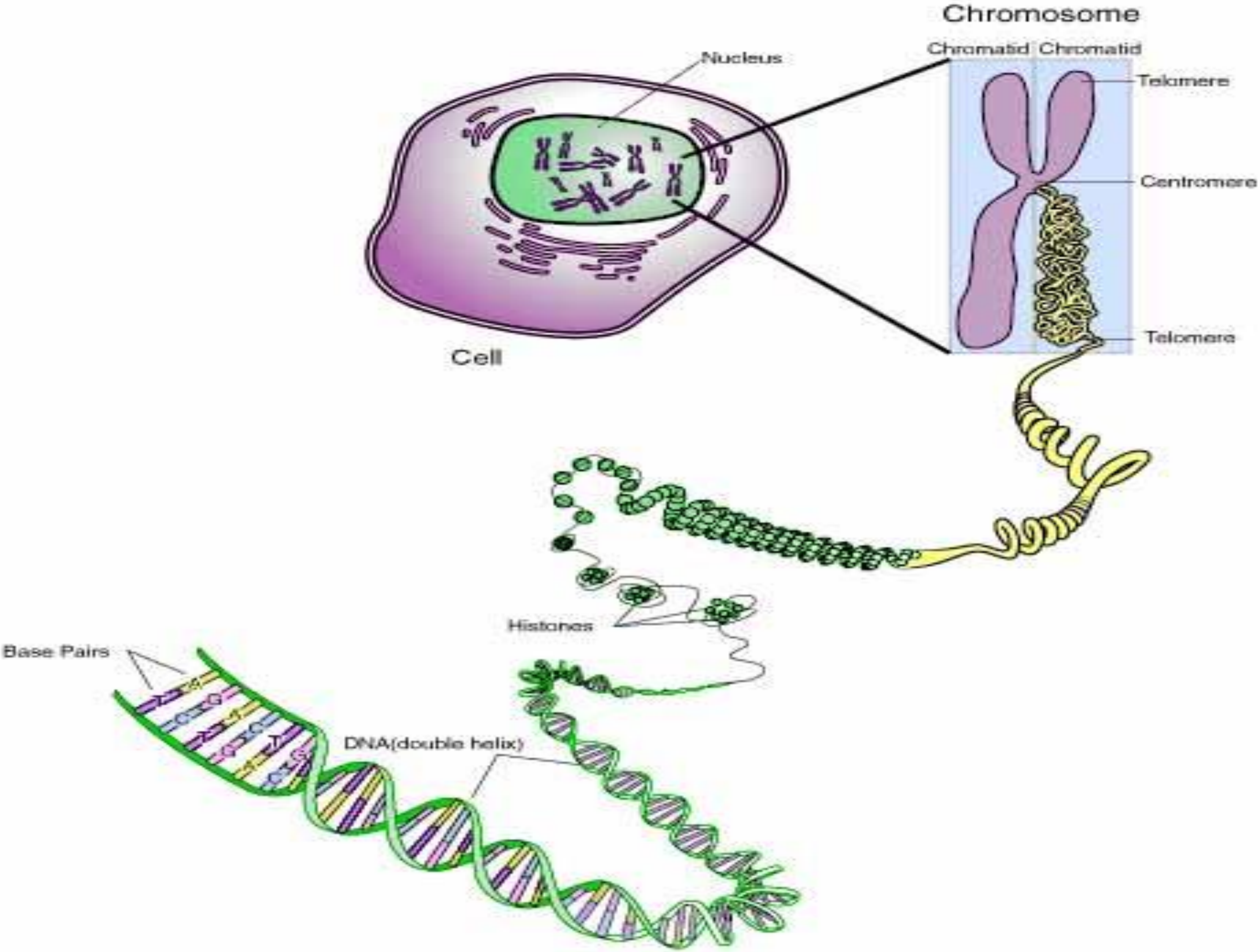

Chromosome
Chromatid
Chromatid
Nucleus
Telomere
Centromere
Telomere
Cell
Histones
Base Pairs
DNA(double helix)

CCES

1. Polarity of DNA is considered from

A. 3’→ 5’

B. 3’→ 3’

C. 5’→ 3’

D. 5’→ 5’

2. Chargaff's rule states

A. Purines=Purines
B. Pyrimidines=Purines
C. Pyrimidines=Pyrimidines
D. A+T=C+G

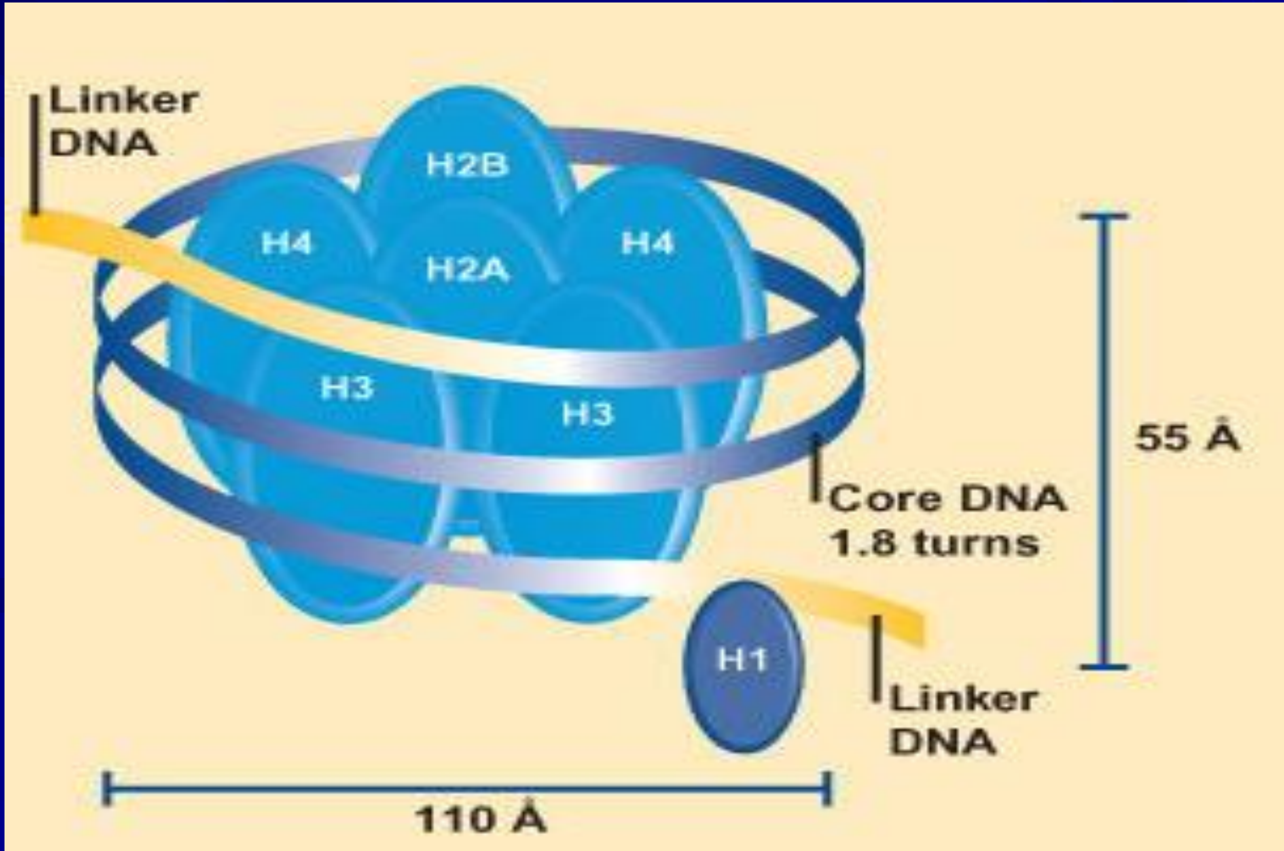
3. Identify structure

A. Histones

B. Chromatid

C. Histone core

D. Nucleosome



4. **DNA–RNA hybrids are**

A. A-form DNA

B. Z-form DNA

C. B-form DNA

D. Circular DNA

5. **In sample of DNA has 10% G, what is the % of T?**

A. 30% T
B. 40% T
C. 50 % T
D. 10% T

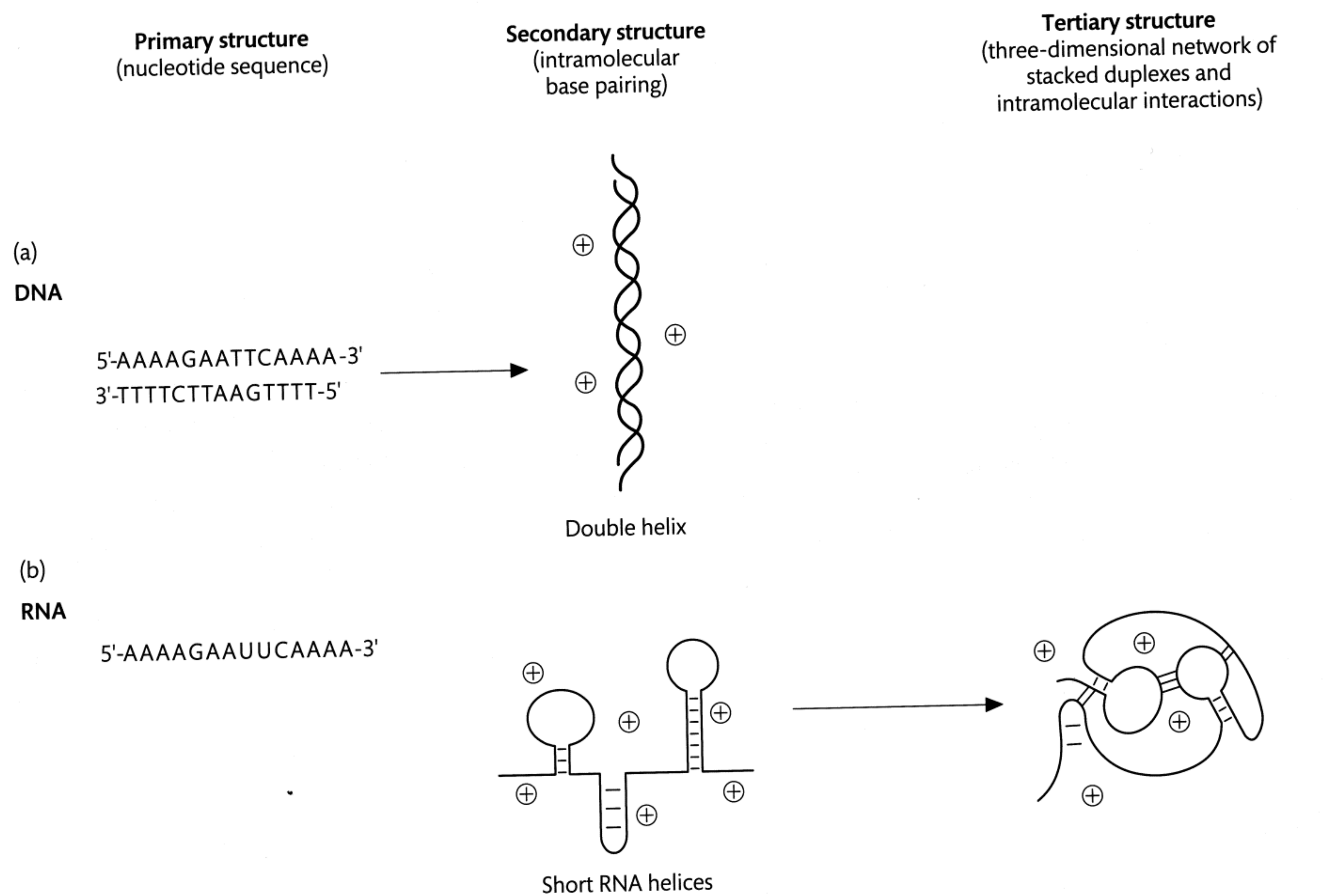
RNA

RNA

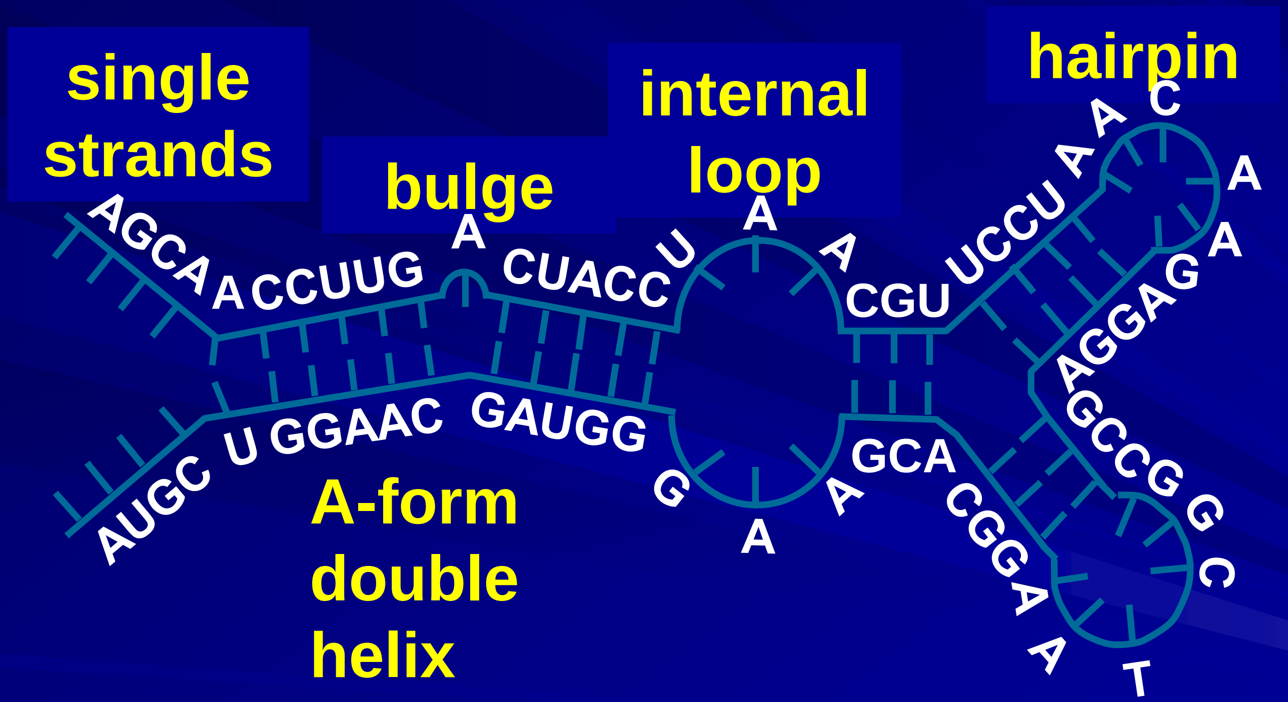
- 50% in Ribosomes and endoplasmic reticulum
- 25% in cytoplasm
- 15% in mitochondria
- 10% in nucleus.
- ***Cellular RNAs are of 5 types***:

1. Messenger RNA (mRNA)
2. Heterogenous nuclear RNA (hnRNA)
3. Transfer RNA (tRNA)
4. Ribosomal RNA (rRNA)
5. Small nuclear RNA (snRNA)

RNA vs DNA Structure

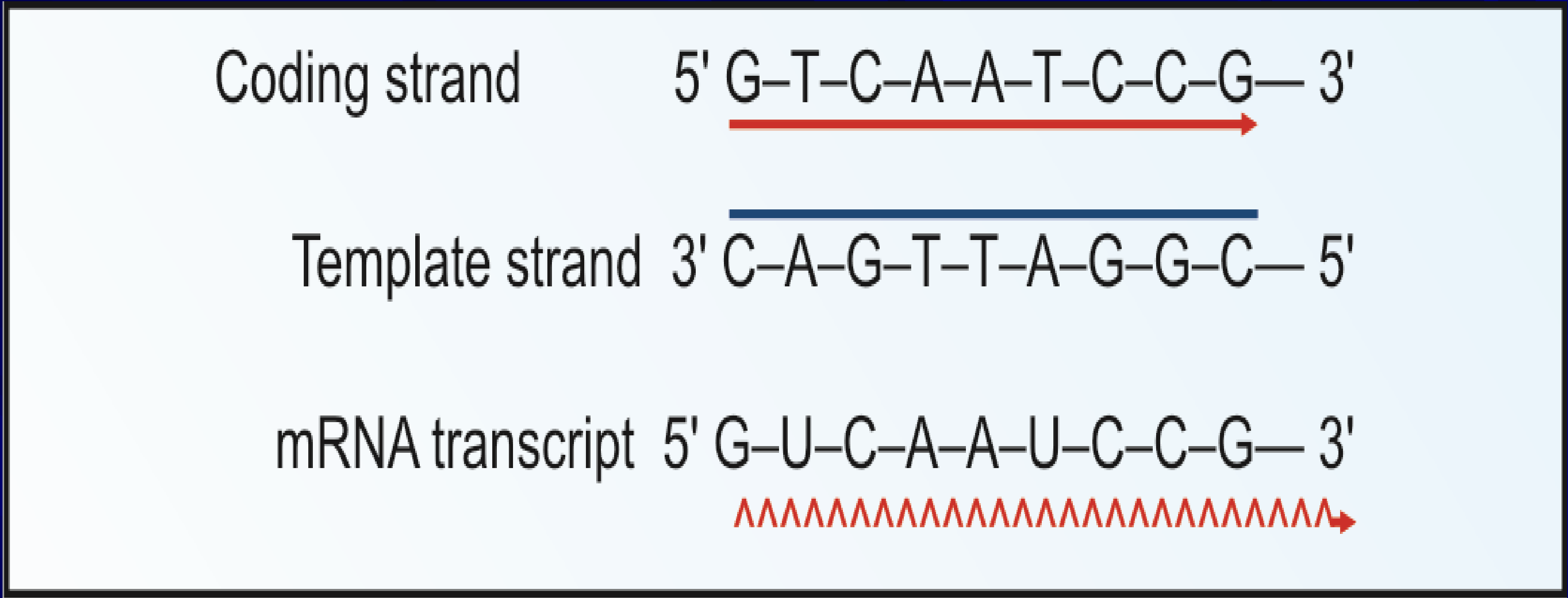


Most RNA molecules consist of a single strand that folds back on itself to form double-helical regions



Messenger RNA

- It acts as a messenger of the information from the gene in **DNA to** the protein synthesizing machinery in **cytoplasm**.
- The template strand of DNA is transcribed into a **single stranded mRNA**.
- The mRNA is a **complementary copy** of the template strand of DNA .
- **Uracil** will be incorporated in RNA

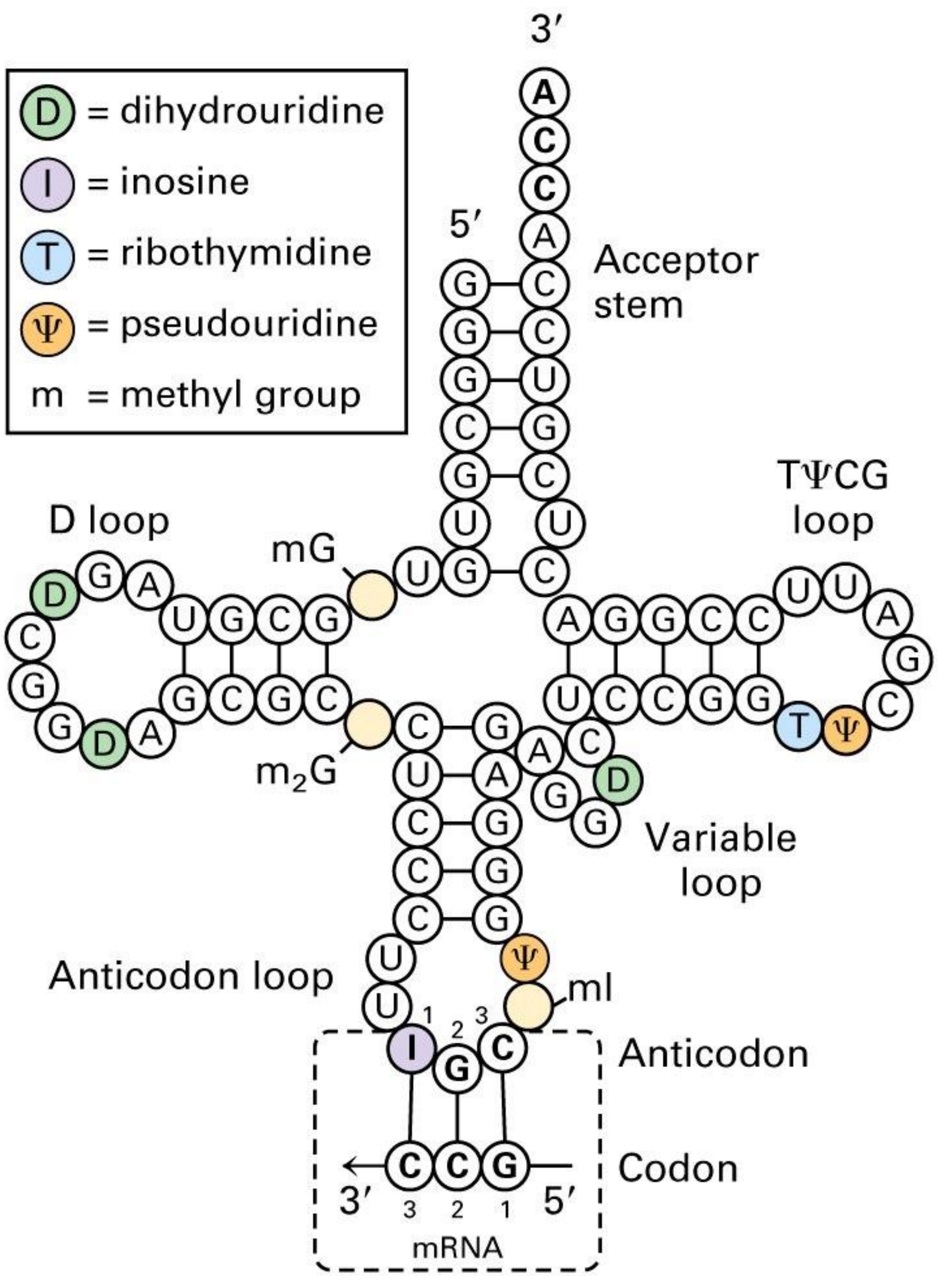


- The mRNA formed and released from the DNA template is known as the **primary transcript.**
- It is also known as **heteronuclear mRNA or hnRNA.**

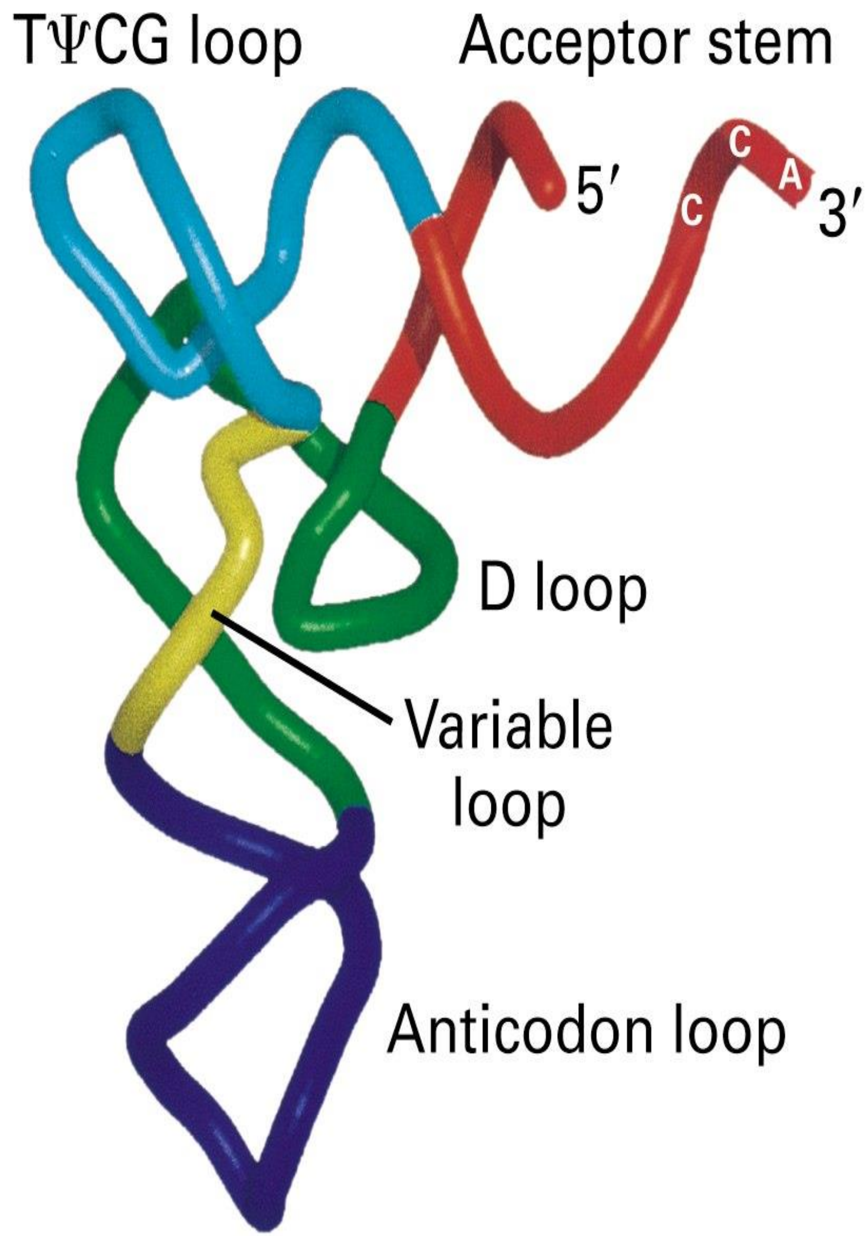
Transfer RNA (tRNA)

- They transfer amino acids from cytoplasm to the ribosomal protein synthesizing machinery
- Since they are easily soluble , they are also referred to as **soluble RNA** or **sRNA**.

Secondary structure



Tertiary structure

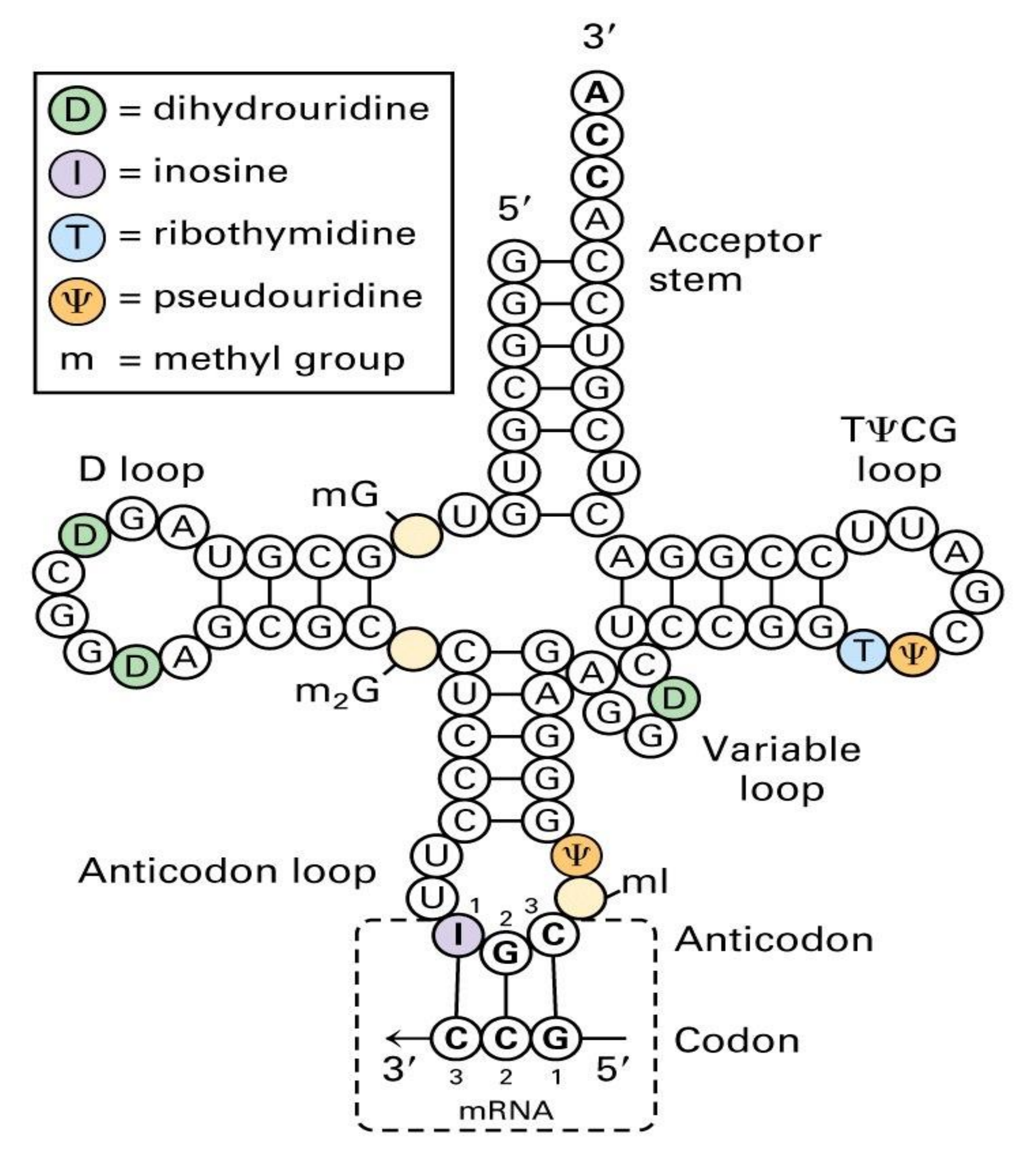


Acceptor Arm at 3' end

Anticodon Arm

DHU Arm

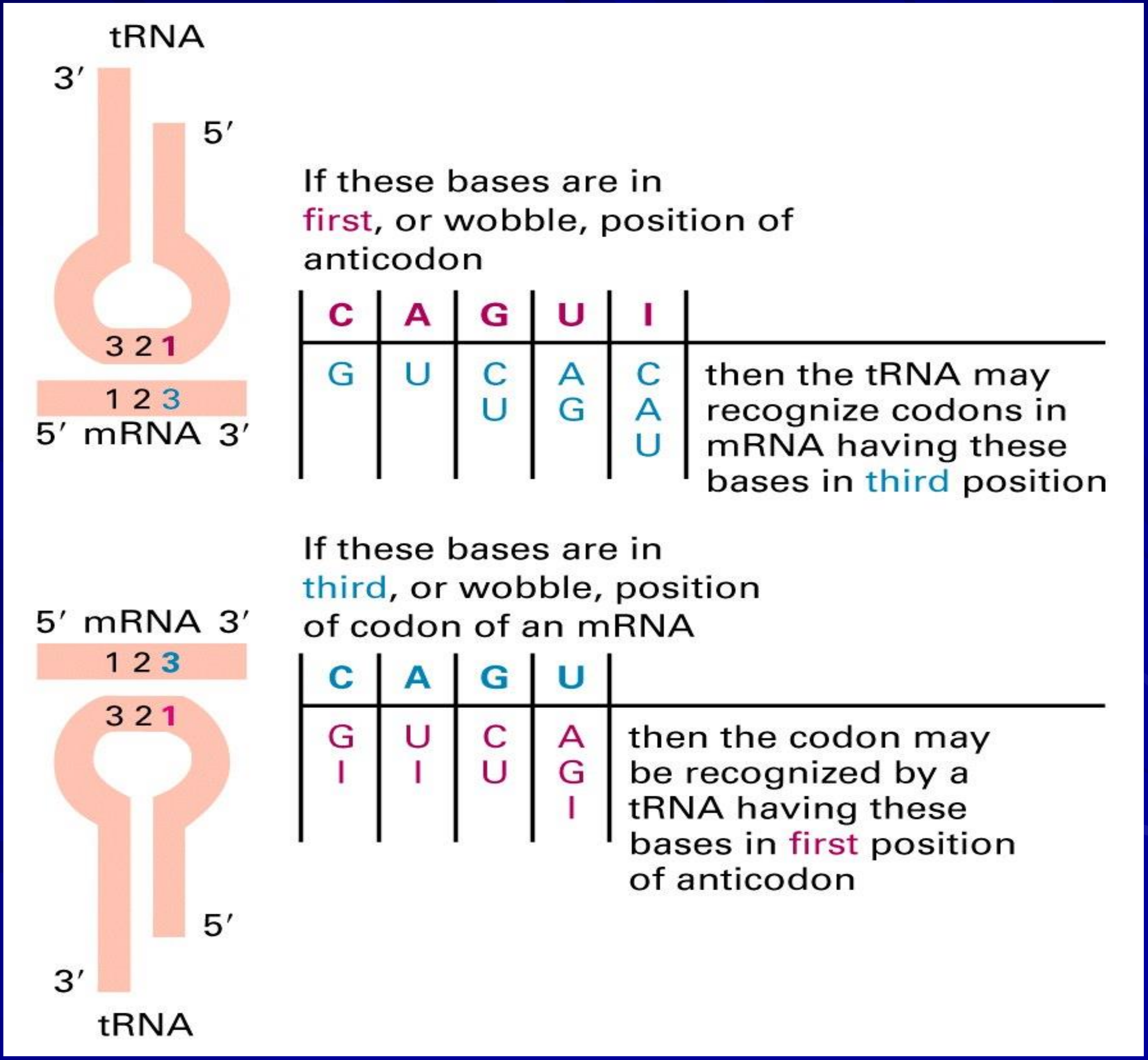
Pseudouridine Arm



Codon-anticodon Base Pairing

Wobble base pairing reduces the number of tRNA genes

It also helps protect against mutations

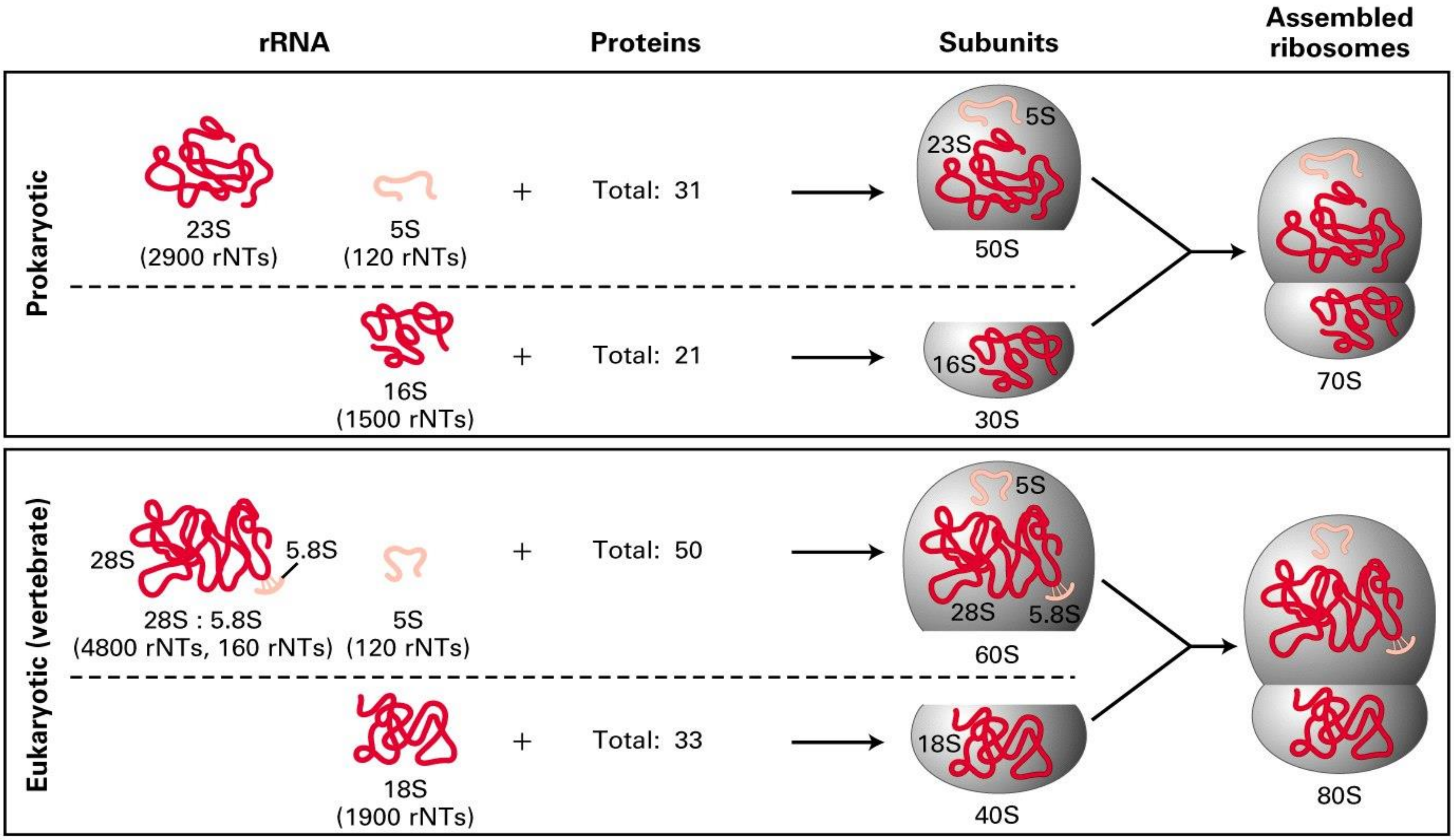


rRNA (Ribosomal RNA)

- rRNAs are found in association with several proteins as components of the ribosomes—the complex structures that serve as the sites for protein synthesis.
- Three distinct size 23S, 16S, and 5S in prokaryotic cells.
- 28S, 18S, 5.8S, and 5S In the eukaryotic cytosol.
- **"S" = Svedberg unit** which is related to the molecular weight and shape of the compound.
- Some rRNA function as catalysts in protein synthesis, termed as **"Ribozyme".**

RNA-protein supramolecular complexes

Although proteins outnumber rRNAs, rRNAs comprise **60%** of the ribosomal mass.



Small nuclear RNAs (snRNA)

- Their size ranges from **90-300 nucleotides**.
- They are named as **U1-7**.
- The U stands for the **uracil rich** nature
- They take part in the formation of **spliceosomes**.
- They complex with specific proteins, to form small nuclear ribonucleoprotein particles **(snRNPs)**.it is pronounced as "**snurps**".

Comparing DNA & RNA

	DNA	RNA
Sugar is deoxyribose	√	
Sugar is ribose		√
Adenine base is present	√	√
Cytosine base is present	√	√

Comparing DNA & RNA

	DNA	RNA
Guanine base is present	√	√
Thymine base is present	√	
Uracil base is present		√
Shape is double helix	√	

Comparing DNA & RNA

	DNA	RNA
Shape is single stranded		√
Located in nucleus	√	√
Located in cytoplasm		√
Stores genetic information	√	

Comparing DNA & RNA

	DNA	RNA
Functions in protein synthesis	√	√
Composed of nucleotides	√	√
Template for synthesis of proteins	√	
Transcribes the Template		√
More than one type		√

CCES

1. DNA helps in synthesis of

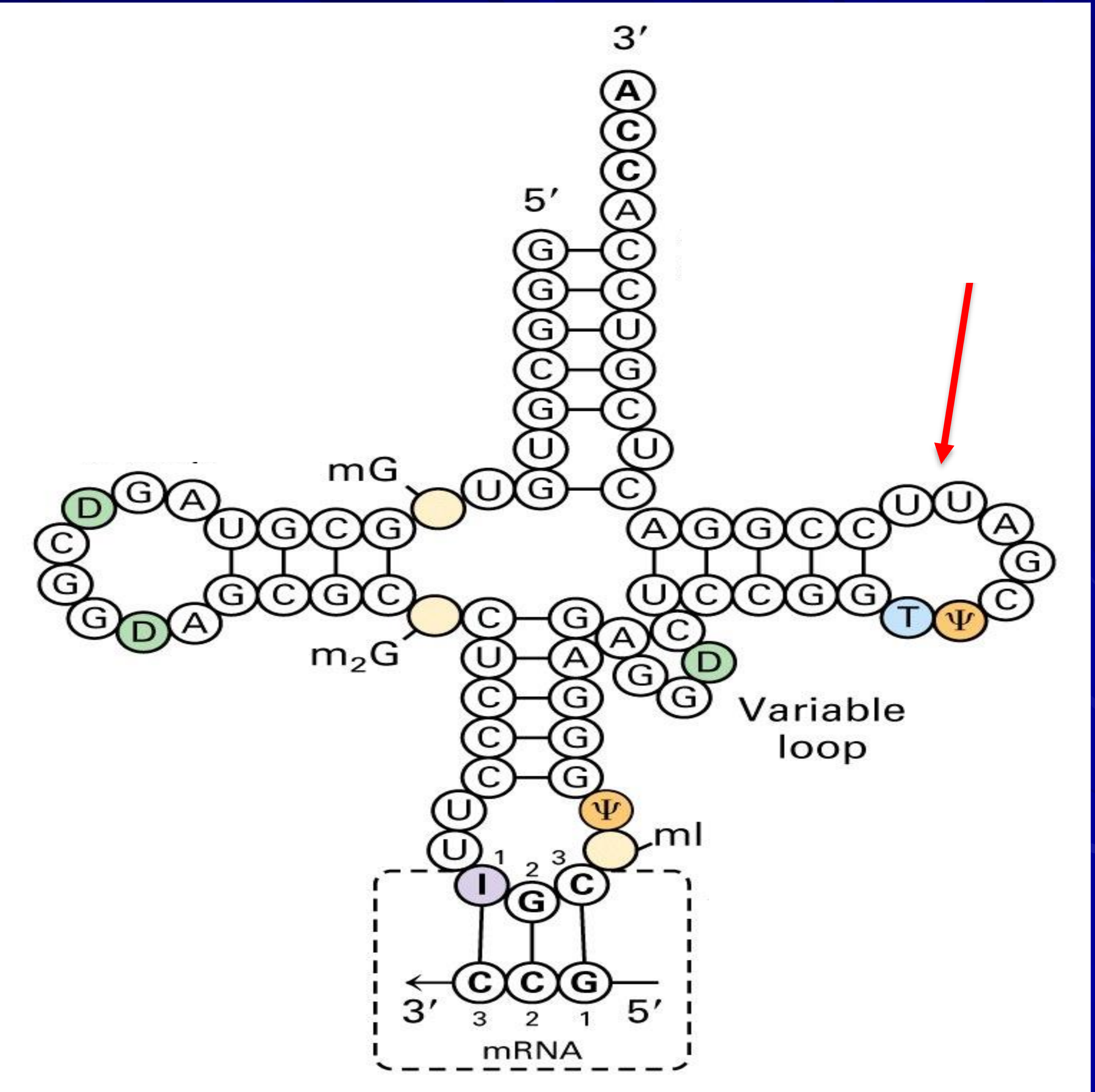
A. mRNA
B. tRNA
C. rRNA
D. All of the above

2. **Wobble position is**

A. 3rd position of the codon and 1st position of the anticodon
B. 3rd position of the anticodon and 1st position of the codon
C. 1st position of the codon and 3rd position of the anticodon
D. None of the above

3. Identify arm (arrowed) of tRNA

A. Acceptor
B. DHU
C. Psi (Ψ)
D. Short



4. **Primary transcript is called**

A. mRNA

B. hnRNA

C. tRNA

D. Matured mRNA

5. **Base paring is observed in**

A. dsDNA

B. dsRNA

C. mRNA

D. Both A & B