Nucleic Acids

11th lect. of medical chemistry

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Introduction

Nucleic acids were first isolated by Friedrich Miescher in 1869.

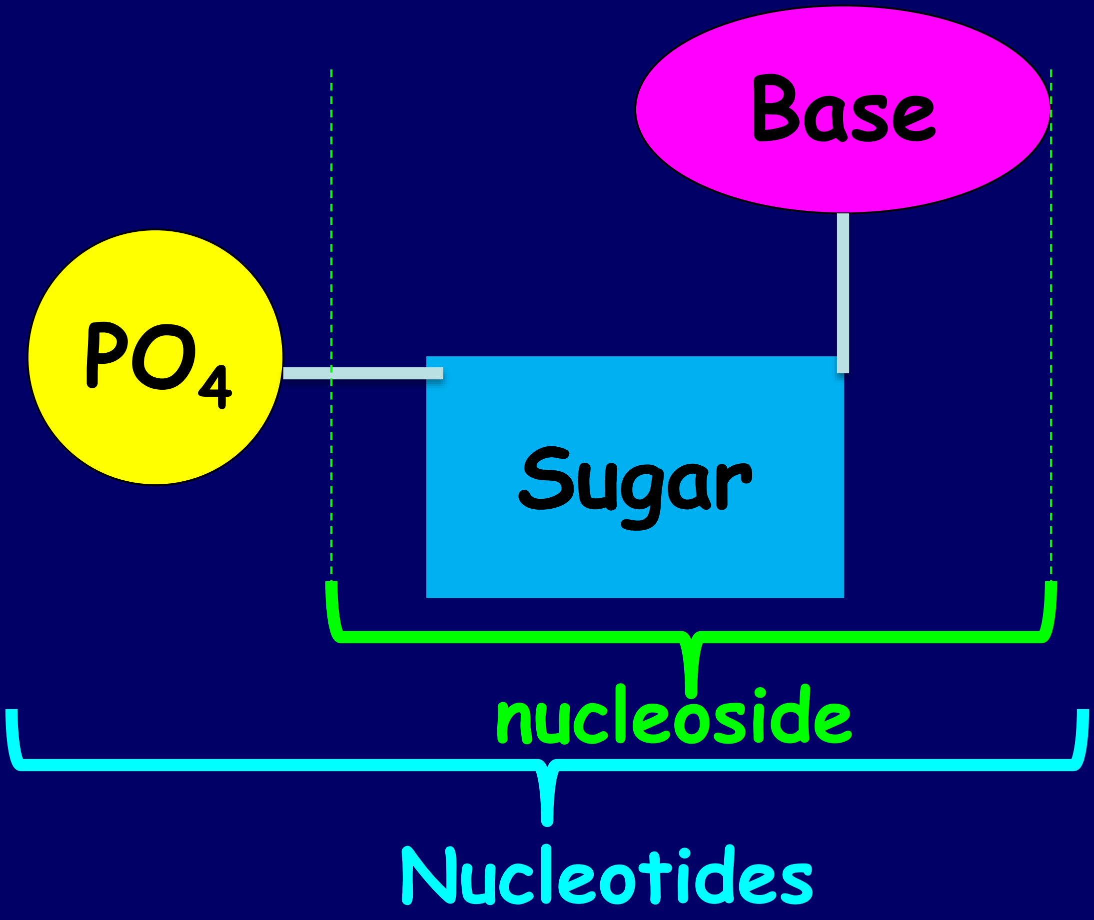
Nucleic acids are the third class of biopolymers (polysaccharides and proteins being the others)

Large molecules consisting of long chains of monomers called nucleotides.

Nucleic acids are molecules that store information for cellular growth and reproduction

Nucleotides

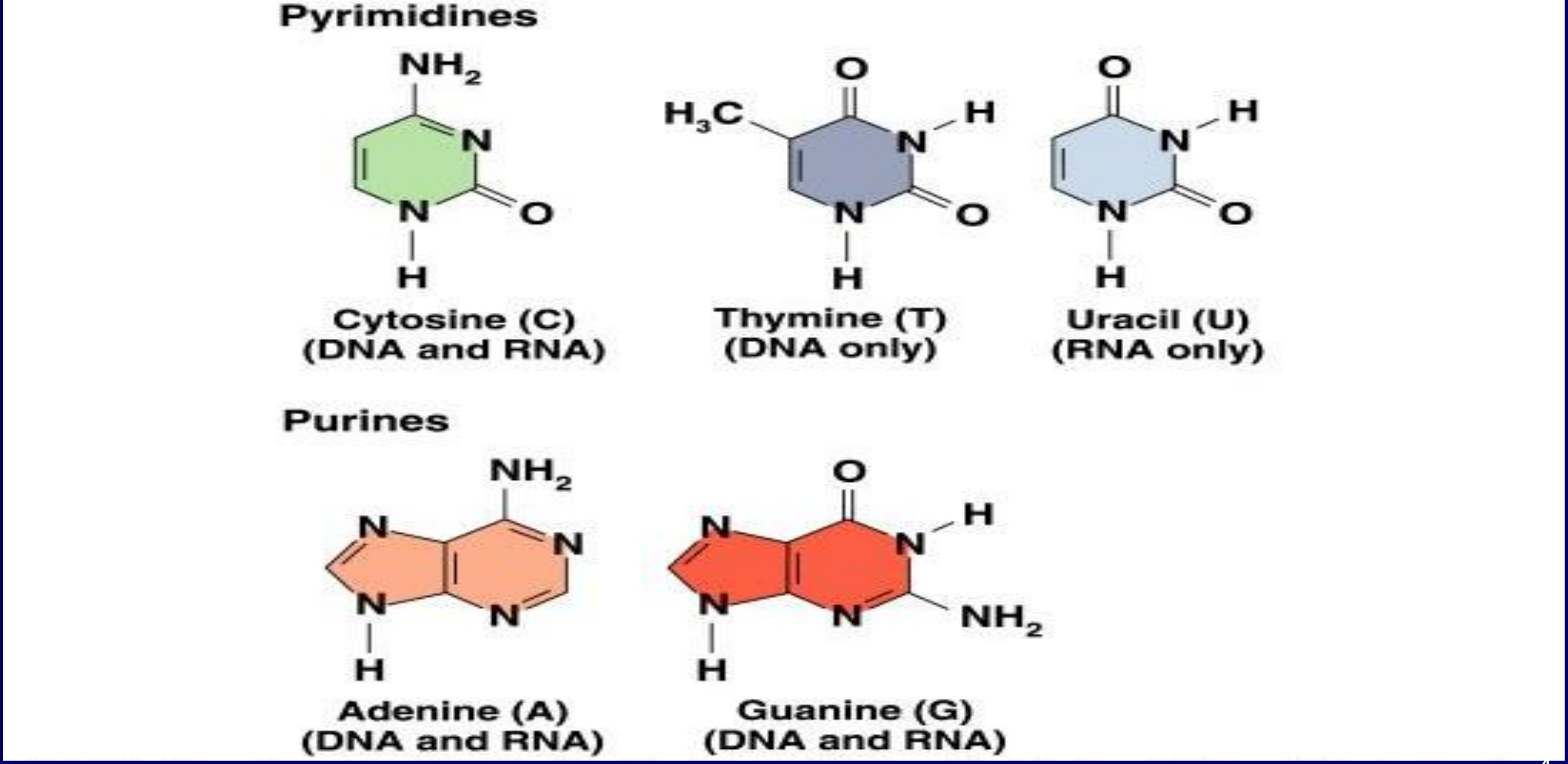
A **nucleotide** consists of a nitrogenous base ,pentose sugar and phosphate group



Nitrogen-Containing Bases

The nitrogen bases in nucleotides consist of two types:

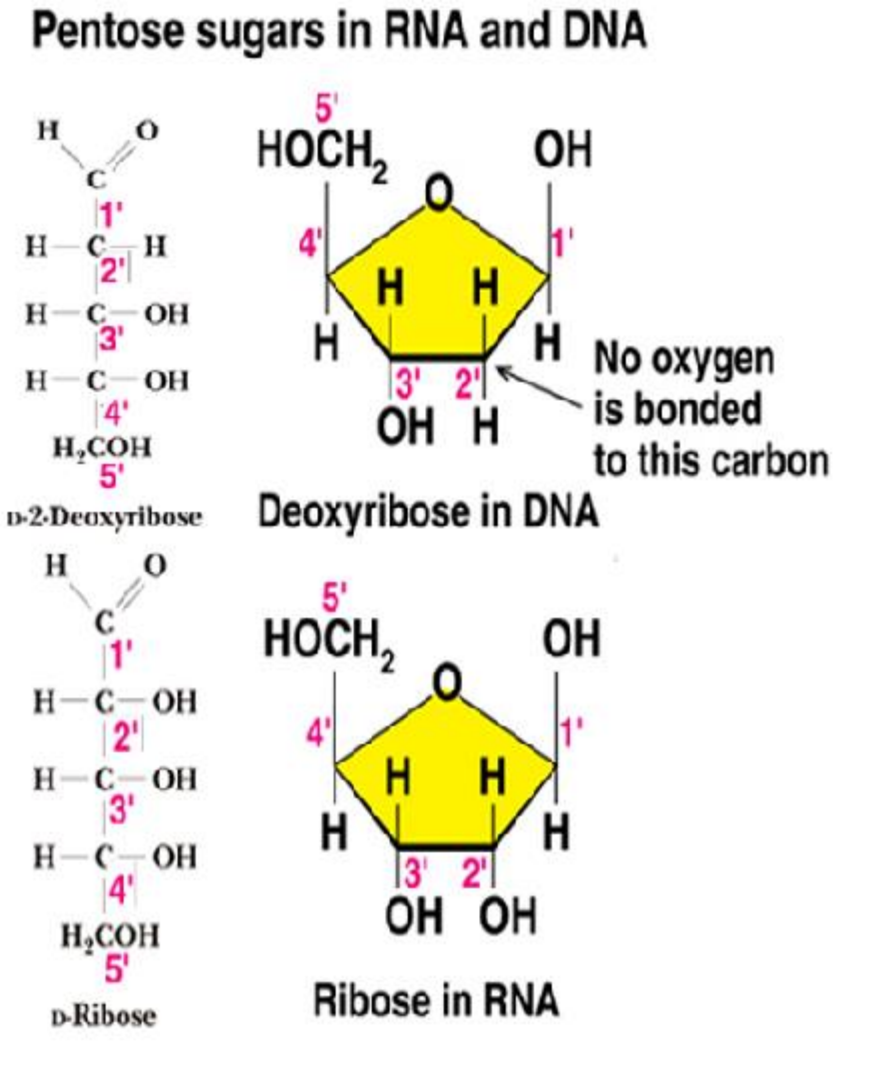
1. **purines:** adenine (A) and guanine (G).
2. **pyrimidines:** cytosine (C), thymine (T) and uracil (U).



Pentose Sugars

There are two related **pentose sugars**:-

1. RNA contains **ribose**
2. DNA contains **deoxyribose**



Nucleosides

A nucleoside consists of a nitrogen base linked by a glycosidic bond to C1′ of a ribose or deoxyribose.

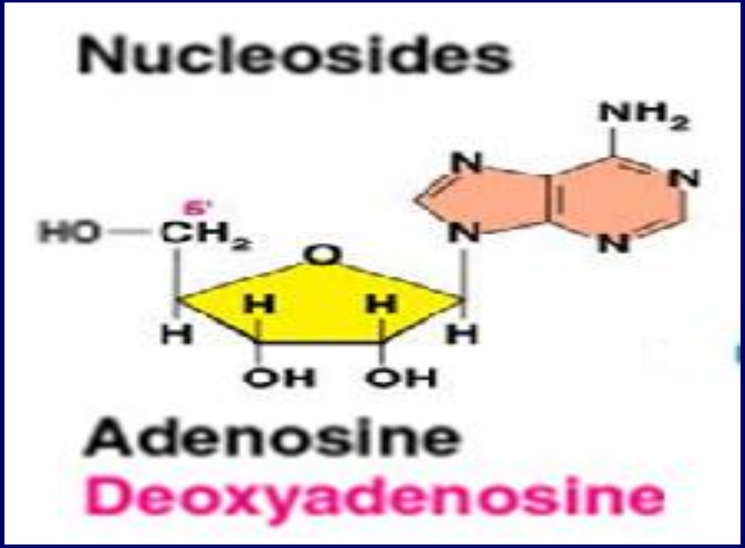
Nucleosides are named by changing the nitrogen base ending to *-osine* for purines and *–idine* for pyrimidines

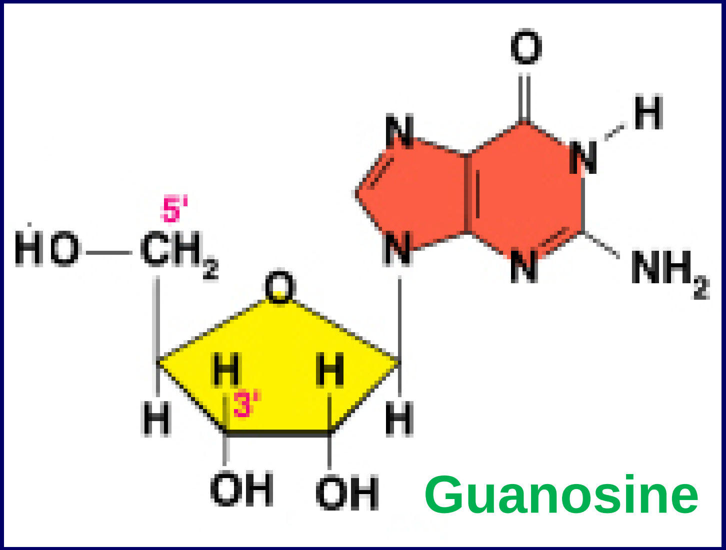
Nucleosides in DNA

Base	Sugar	Nucleoside
Adenine (A)	Deoxyribose	Adenosine
Guanine (G)	Deoxyribose	Guanosine
Cytosine (C)	Deoxyribose	Cytidine
Thymine (T)	Deoxyribose	Thymidine

Nucleosides in RNA

Base	Sugar	Nucleoside
Adenine (A)	ribose	Adenosine
Guanine (G)	ribose	Guanosine
Cytosine (C)	ribose	Cytidine
Uracil (U)	ribose	Uridine

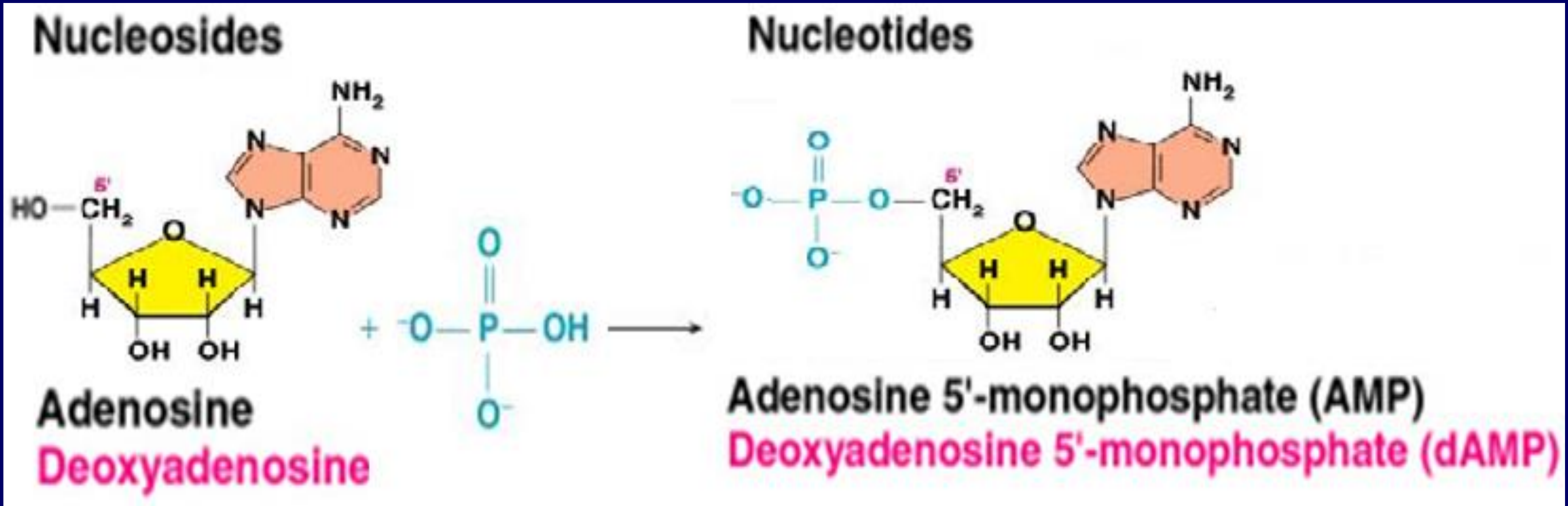


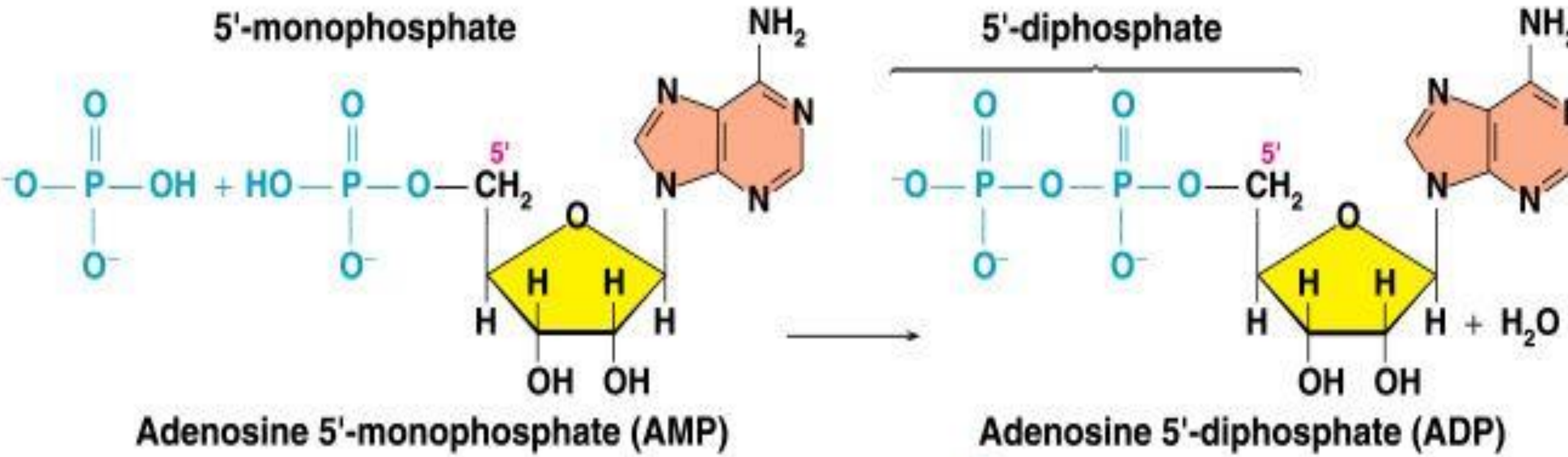


Nucleotides

A nucleotide is a nucleoside that forms a phosphate ester with the C5′ OH group of ribose or deoxyribose.

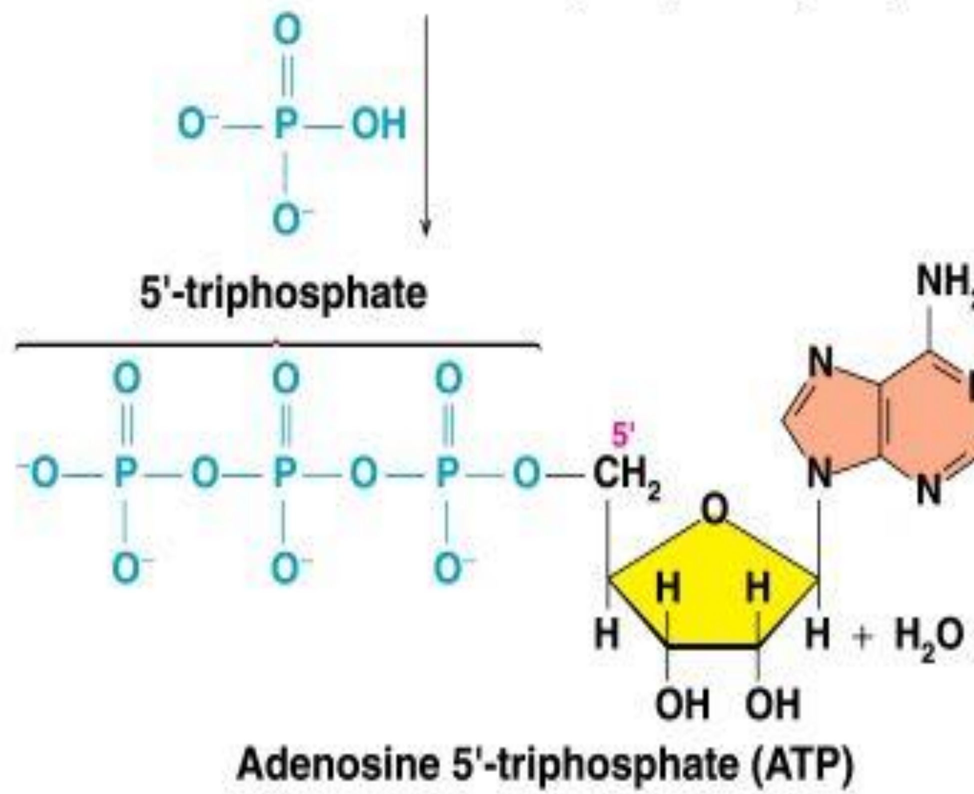
Nucleotides are named using the name of the nucleoside followed by *5′-monophosphate.*





Additional phosphate groups can be added to the nucleoside 5'-monophosphates to form diphosphates and triphosphates.

ATP is the major energy source for cellular activity



Phosphodiesters

The chemical linkage between nucleotide units in nucleic acids is a ***phosphodiester***, which connects the 5′-hydroxyl group of one nucleotide to the 3′-hydroxyl group of the next nucleotide.

The nucleotides in nucleic acids are joined by phosphodiester bonds.

phosphodiester formed by Polymerase and Ligase activities

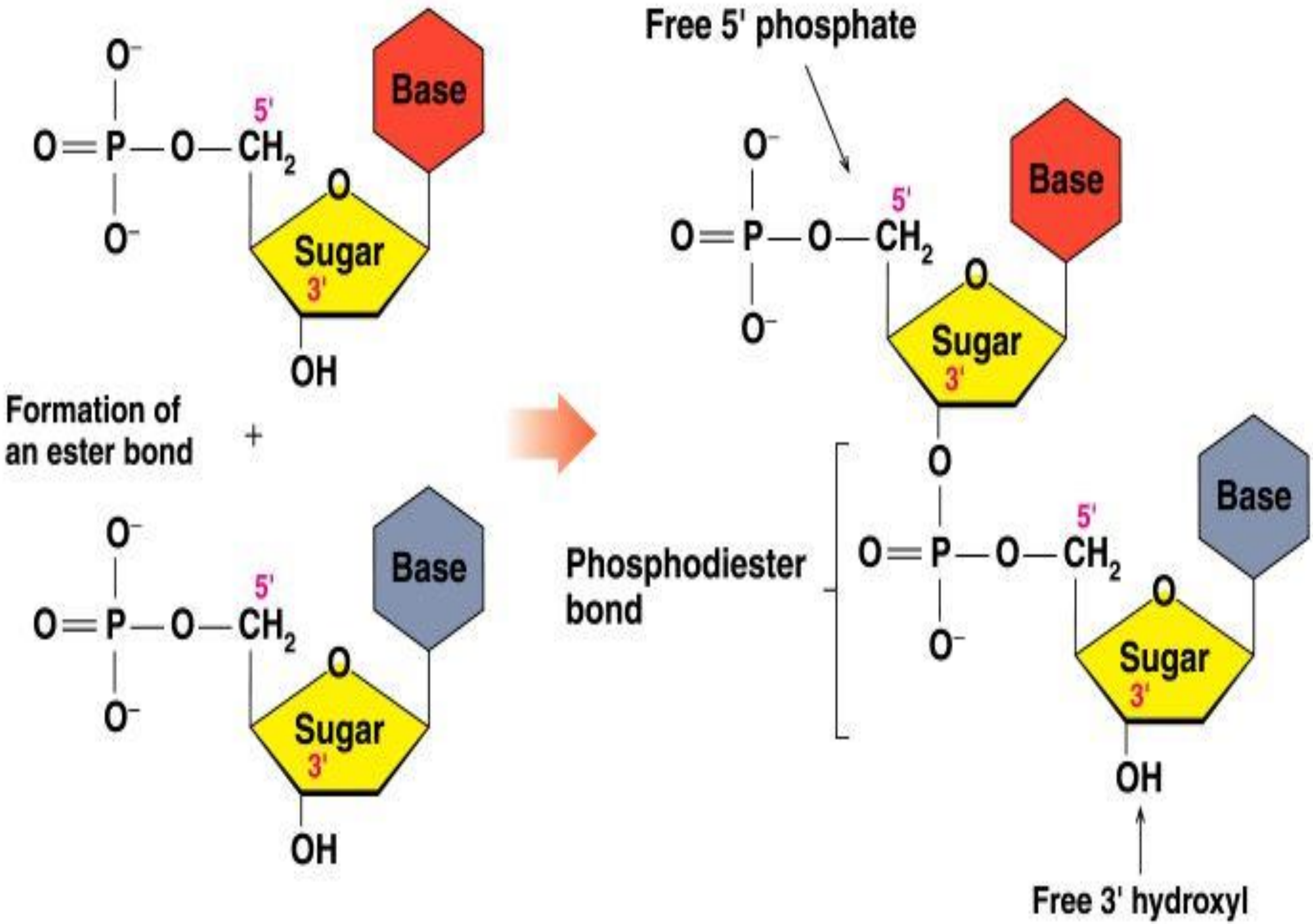
Two nucleotides joined by a phosphodiester linkage gives a dinucleotide.

Three nucleotides joined by two phosphodiester linkages gives a trinucleotide, etc.

A polynucleotide of about 50 or fewer nucleotides is called an *oligonucleotide.*

Nucleic acid sequences are written from left to right, from the 5′-end to the 3′-end.

Nucleic acids are negatively charged.

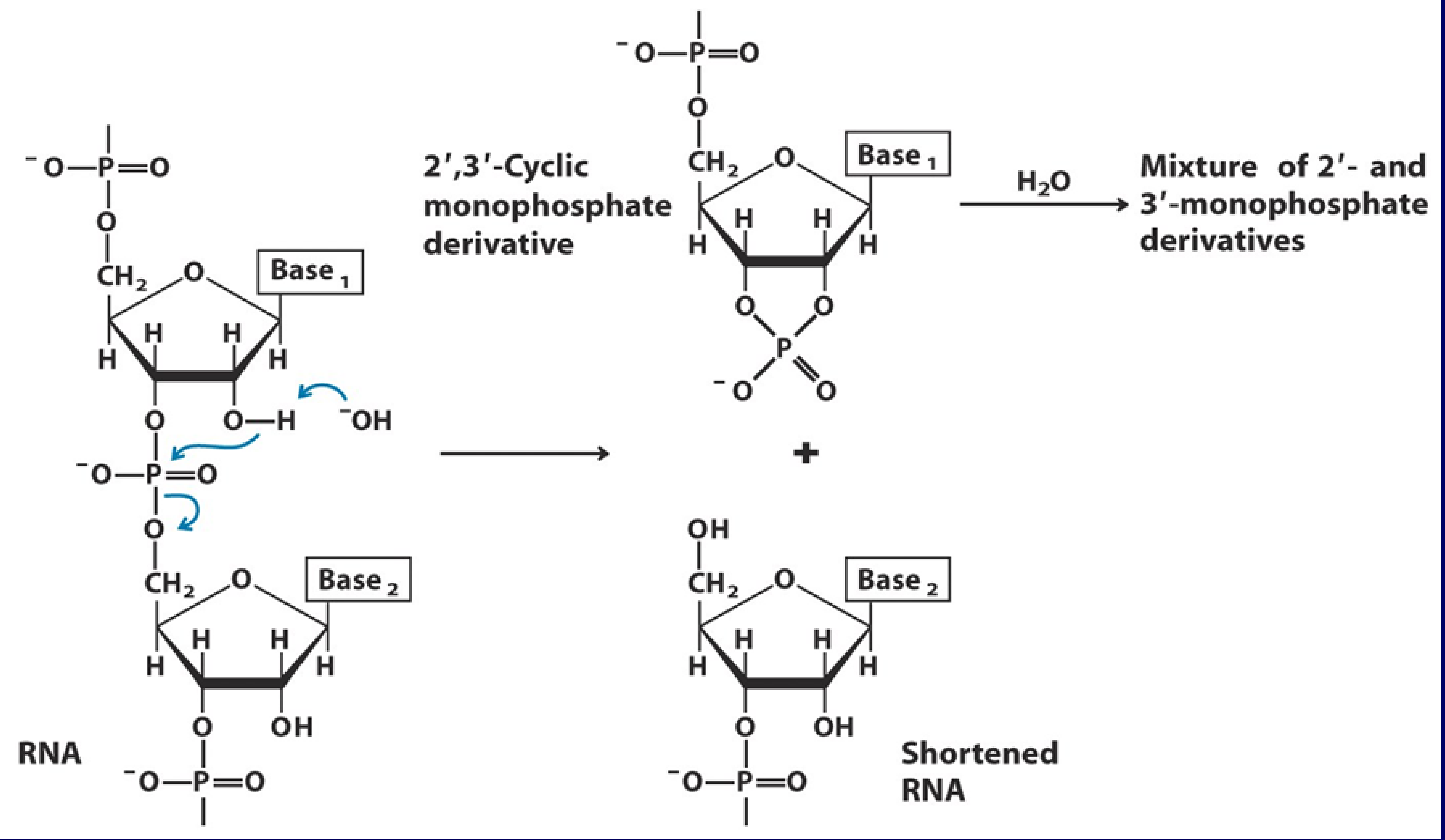

O⁻
O=P—O—CH2
5'
O⁻
Base
O
Sugar
3'
OH
Formation of
an ester bond
+
O⁻
O=P—O—CH2
5'
O⁻
Base
O
Sugar
3'
OH
Free 5' phosphate
O⁻
O=P—O—CH2
5'
O⁻
Base
O
Sugar
3'
O
Phosphodiester
bond
O=P—O—CH2
5'
O⁻
Base
O
Sugar
3'
OH
Free 3' hydroxyl

Functions of Nucleotides

1. Nucleoside 5'-triphosphates are carriers of energy
2. Bases serve as recognition units
3. Cyclic nucleotides are signal molecules and regulators of cellular metabolism and reproduction
4. ATP is central to energy metabolism
5. GTP drives protein synthesis
6. CTP drives lipid synthesis
7. UTP drives carbohydrate metabolism

Cyclic nucleotides

Hydrolysis of RNA under alkaline conditions



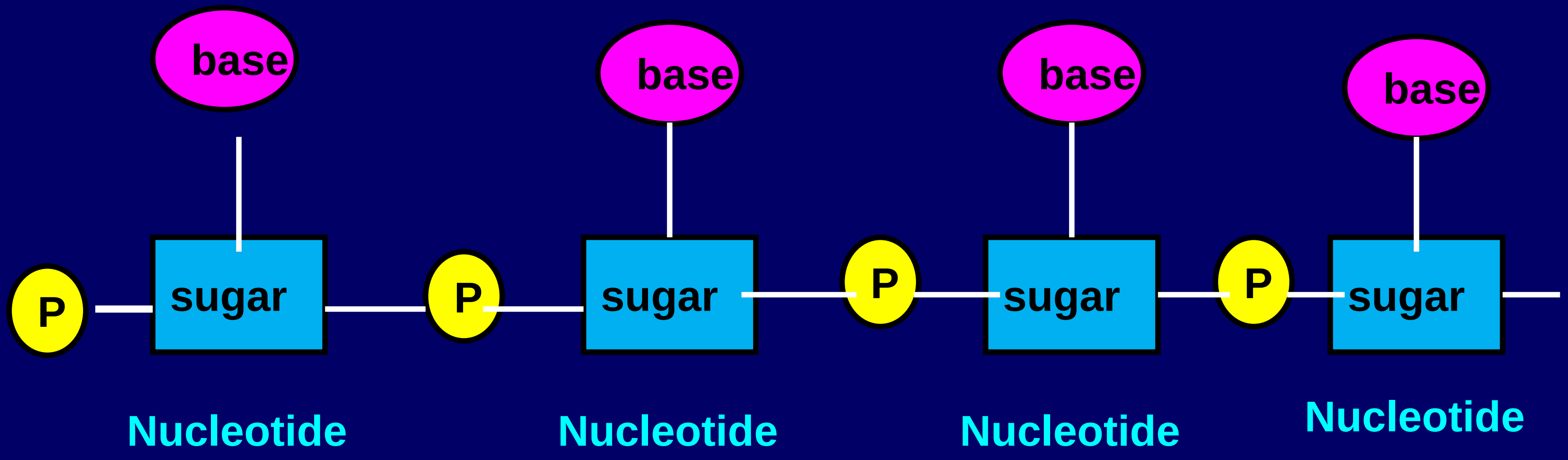
Nucleic Acids

Nucleic acids were first isolated by Friedrich Miescher in 1869.

Polymers of at least four nucleotides.

The nucleotides are all orientated in the same direction.

Linked 3' to 5' by phosphodiester bridges



Structure of Nucleic

primary structure

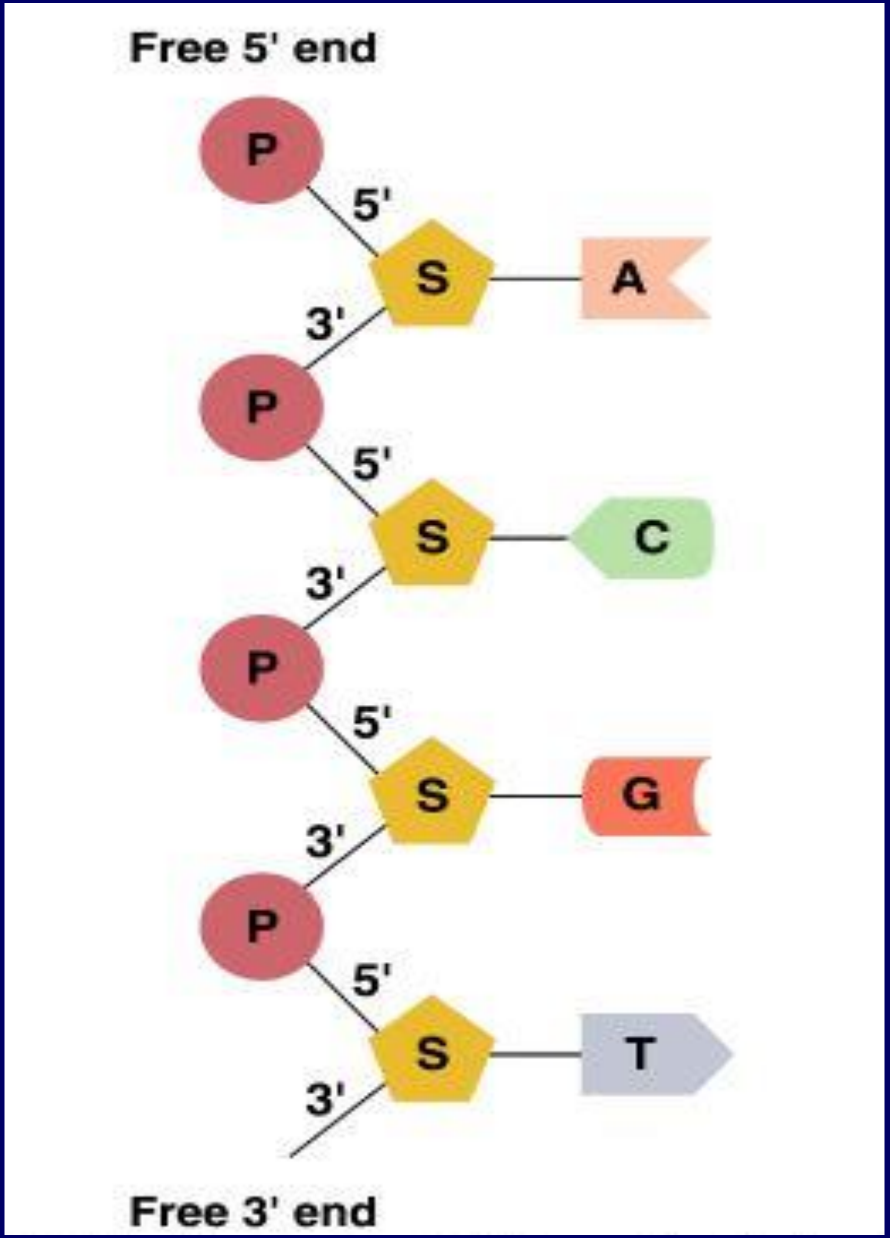
The **primary structure** of a nucleic acid is the nucleotide sequence.

The nucleotides in nucleic acids are joined by 3'- 5' phosphodiester bonds.

The sequence is read from the free 5'-end using the letters of the bases

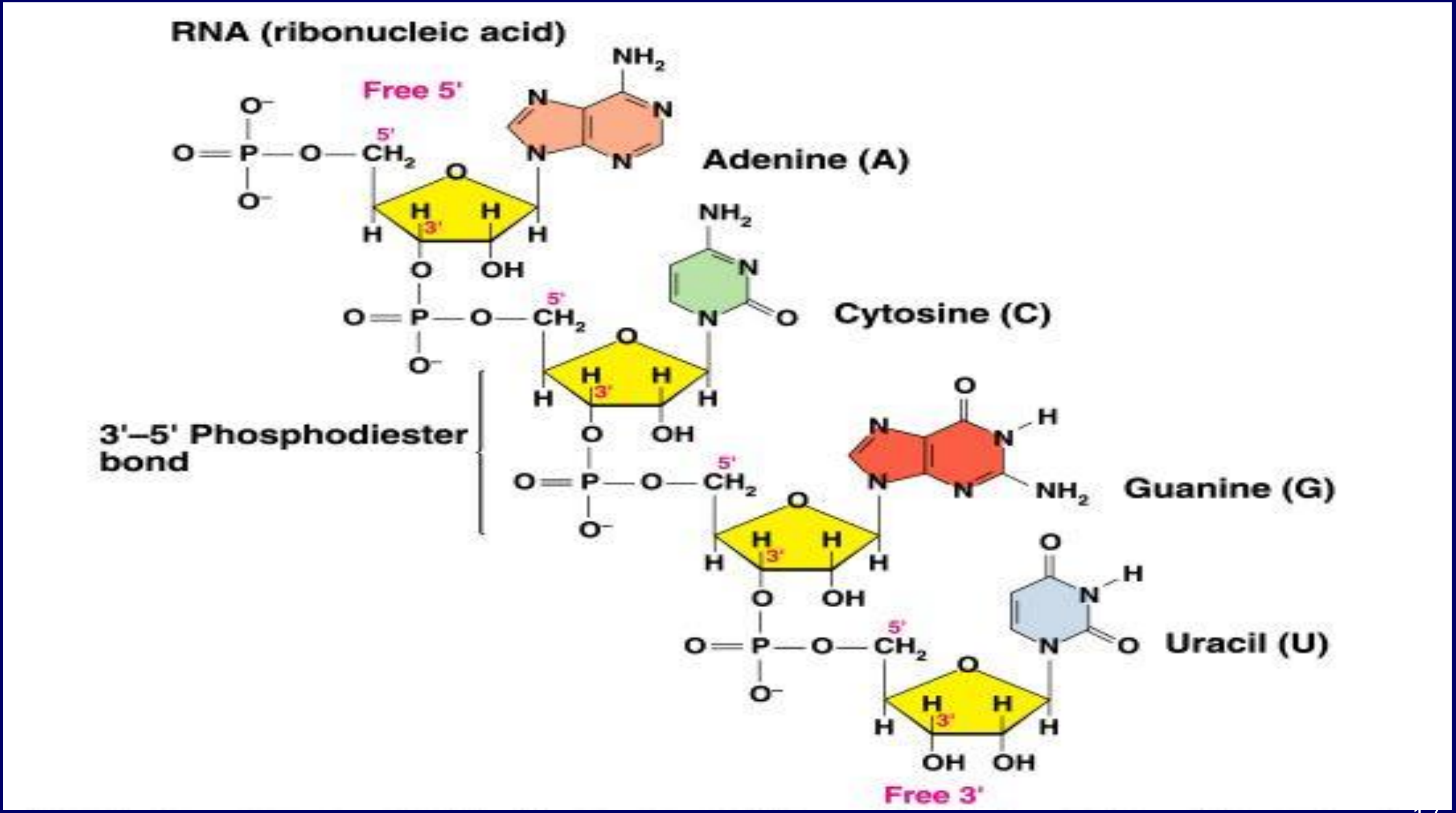
This example reads:

5'—A—C—G—T—3'



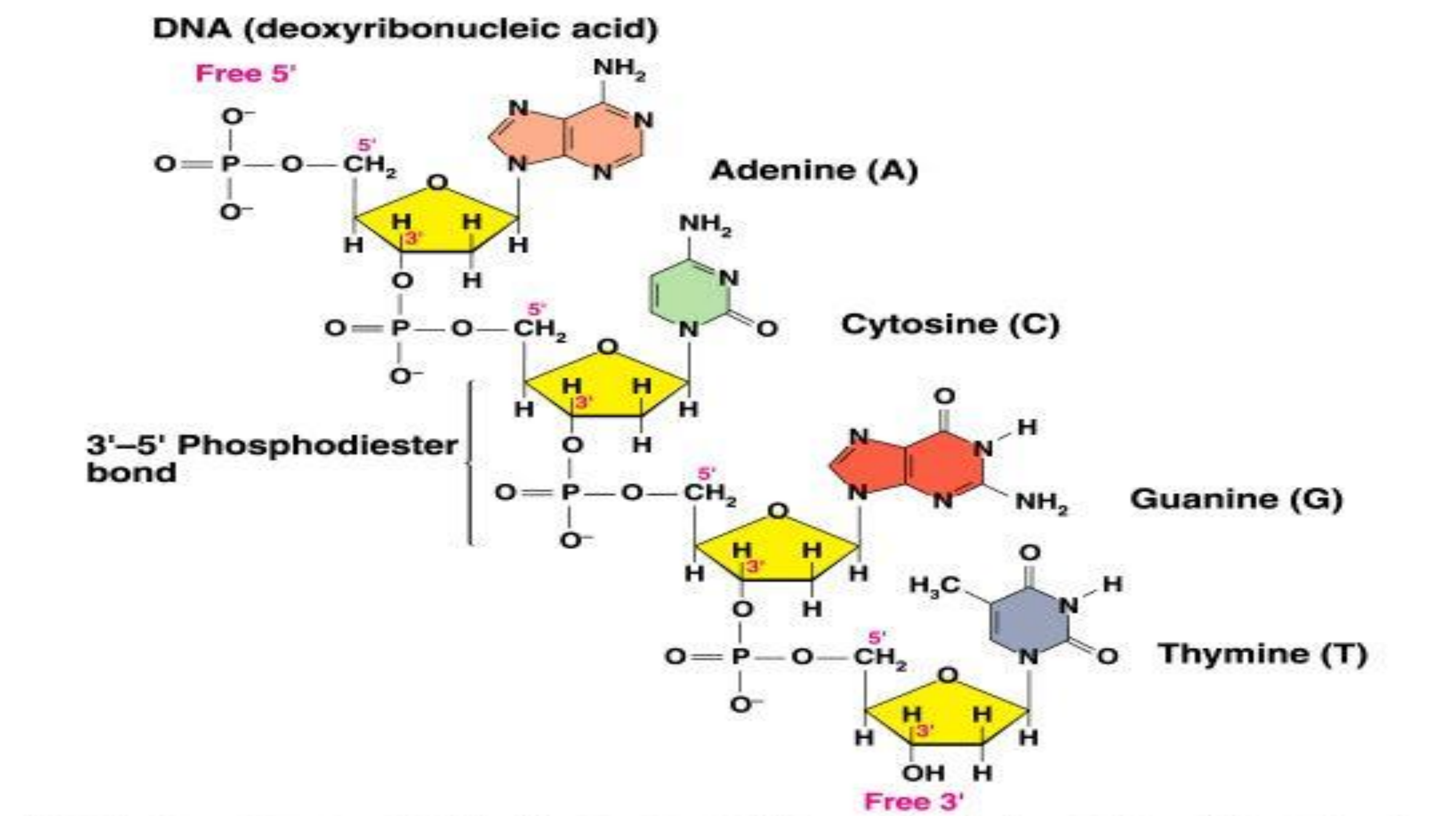
Example of RNA Primary Structure

In RNA, A, C, G, and U are linked by 3′-5′ ester bonds between ribose and phosphate



Example of DNA Primary Structure

In DNA, A, C, G, and T are linked by 3′-5′ ester bonds between deoxyribose and phosphate



Secondary Structure

In DNA there are two strands of nucleotides that wind together in a **double helix.**

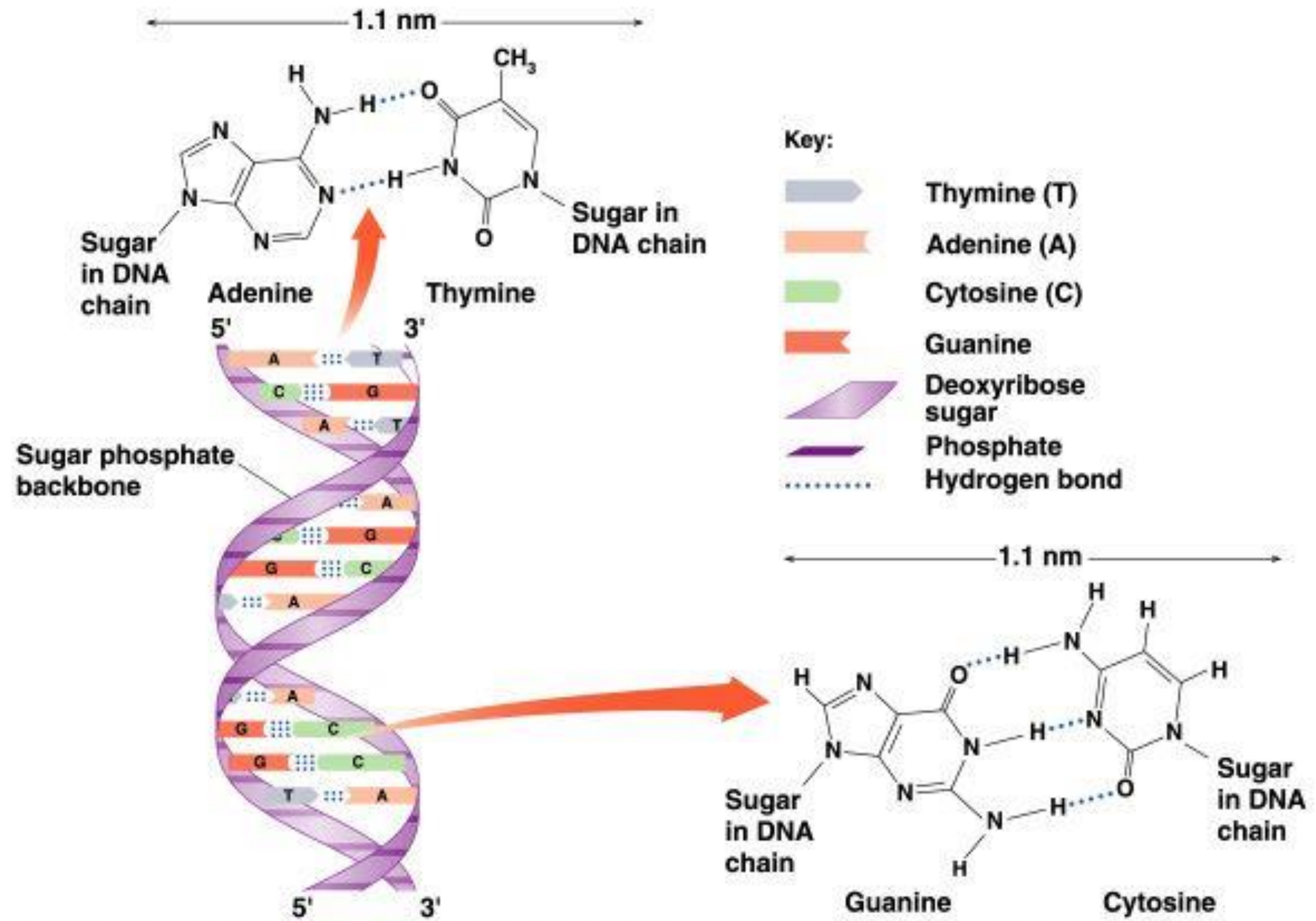
- ✓The strands run in opposite directions
- ✓The bases are arranged in step-like pairs
- ✓The **base pairs** are held together by hydrogen bonding

The pairing of the bases from the two strands is very specific.

The **complimentary base pairs** are **A-T** and **G-C**

- ➢Two hydrogen bonds form between A and T
- ➢Three hydrogen bonds form between G and C

Each pair consists of a purine and a pyrimidine, so they are the same width, keeping the two strands at equal distances from each other


1.1 nm
CH3
H
N
H
O
N
N
H
N
N
N
N
O
Sugar in DNA chain
Sugar in DNA chain
Adenine
Thymine
5'
3'
A
T
C
G
A
T
Sugar phosphate backbone
A
G
G
C
A
A
G
C
G
C
T
A
5'
3'
Key:
Thymine (T)
Adenine (A)
Cytosine (C)
Guanine
Deoxyribose sugar
Phosphate
Hydrogen bond
1.1 nm
H
H
H
H
N
O
H
N
N
N
H
N
N
N
N
H
O
H
N
Sugar in DNA chain
Sugar in DNA chain
Guanine
Cytosine

Tertiary Structure of DNA: Supercoils

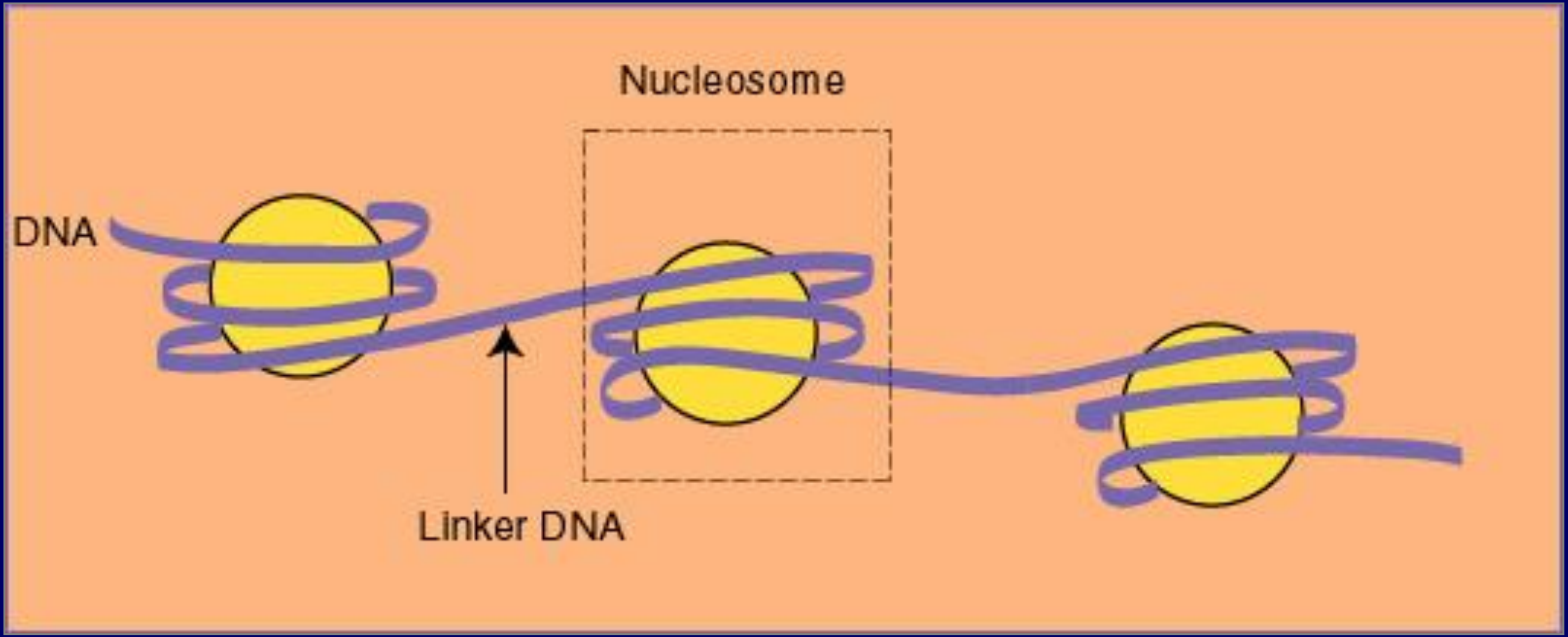
A strand of DNA is too long (about 3 cm in length) to fit inside a cell unless it is coiled.

Random coiling would reduce accessibility to critical regions.

Efficient coiling of DNA is accomplished with the aid of proteins called ***histones***.

Histones are proteins rich in basic amino acids such as lysine and arginine.

Histones are positively charged at biological pH. DNA is negatively charged.
DNA winds around histone proteins to form nucleosomes.



Each nucleosome contains one and three-quarters turns of coil = 146 base pairs.
Linker contains about 50 base pairs.

Storage of DNA

In **eukaryotic cells** (animals, plants, fungi) DNA is stored in the **nucleus**, which is separated from the rest of the cell by a semipermeable membrane.

The DNA is only organized into **chromosomes** during cell replication.

Between replications, the DNA is stored in a compact ball called **chromatin**, and is wrapped around proteins called **histones** to form **nucleosomes**

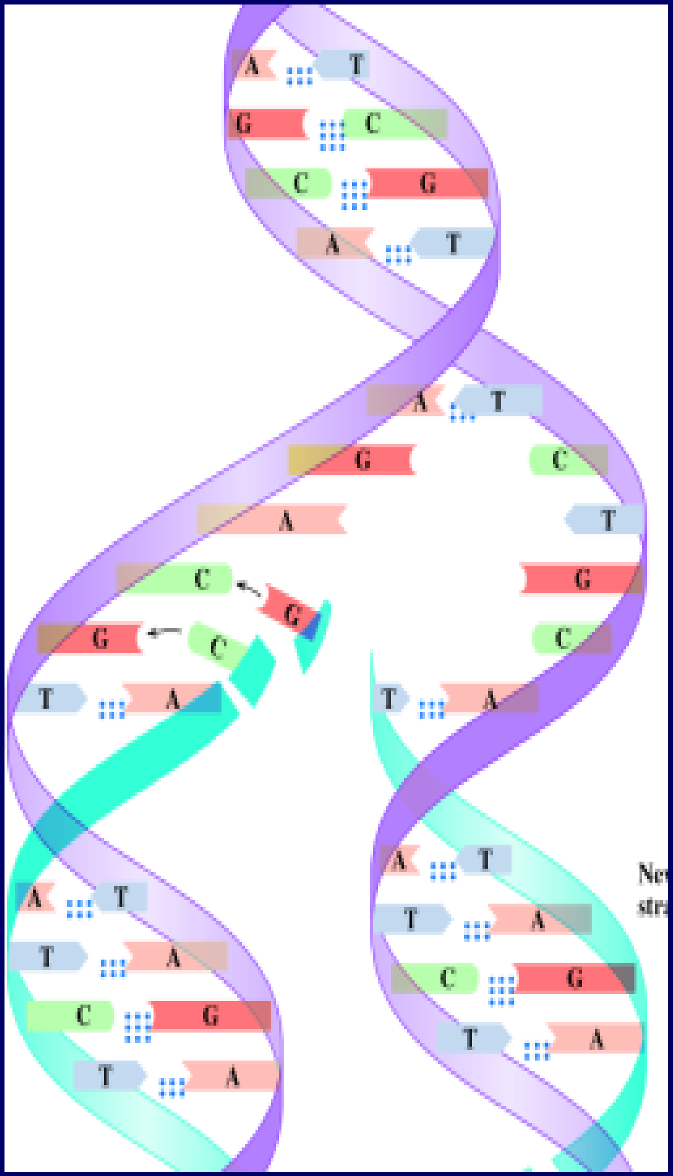
DNA Replication

When a eukaryotic cell divides, the process is called **mitosis.**

- the cell splits into two identical daughter cells
- the DNA must be replicated so that each daughter cell has a copy

DNA replication involves several processes:

1. First, the DNA must be unwound, separating the two strands.



2. The single strands then act as templates for synthesis of the new strands, which are complimentary in sequence
3. Bases are added one at a time until two new DNA strands that exactly duplicate the original DNA are produced

The process is called **semi-conservative replication** because one strand of each daughter DNA comes from the parent DNA and one strand is new

The energy for the synthesis comes from hydrolysis of phosphate groups as the phosphodiester bonds form between the bases.

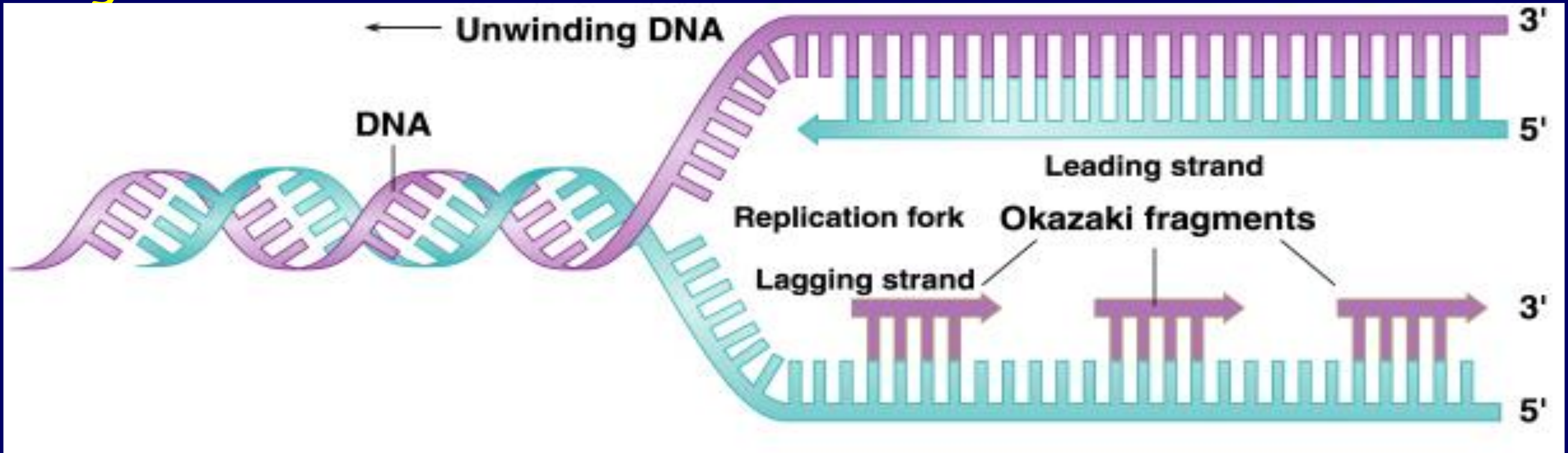
Direction of Replication

The enzyme **helicase** unwinds several sections of parent DNA.

At each open DNA section, called a **replication fork**, DNA *polymerase* catalyzes the formation of 5′-3′ester bonds of the **leading strand**

The **lagging strand**, which grows in the 3′-5′ direction, is synthesized in short sections called **Okazaki fragments.**

The Okazaki fragments are joined by DNA *ligase* to give a single 3′-5′ DNA strand



Ribonucleic acid RNA

Ribonucleic acid (RNA) is formed by condensation of nucleotides.

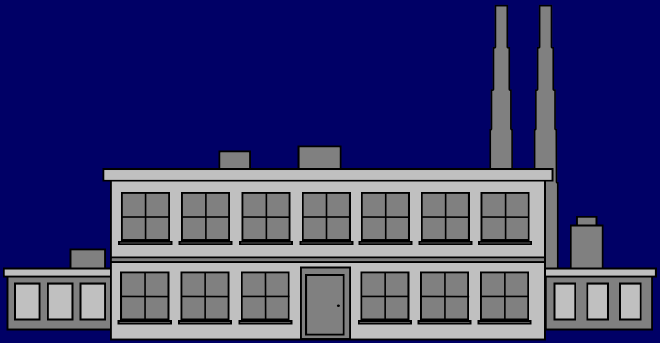
- RNA is a long, unbranched macromolecule
- May contain 70 to several thousand nucleotides.
- RNA molecule is usually single stranded.

RNA contains adenine (A), guanine (G), cytosine (C) and uracial (U)..

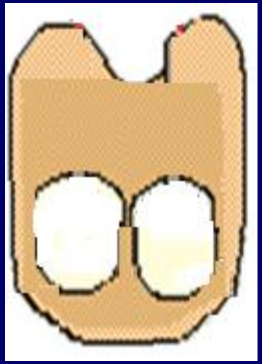
Classification of (RNA)

According to the function of RNA, it can be classified as:

1. Ribosomal (rRNA)

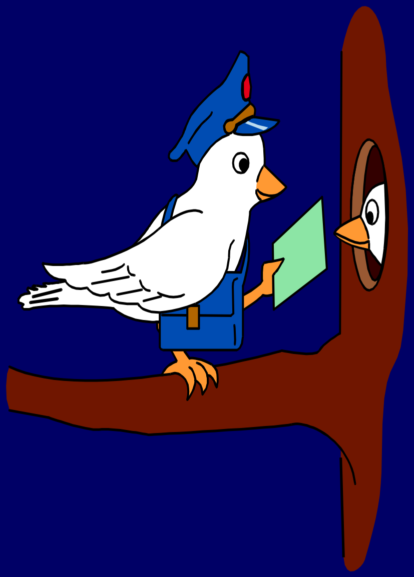


- Found in ribosomes.
- Essential for protein synthesis in all living organisms
- Consist of ribosomal DNA (65%) and proteins (35%).
- Have two subunits,



2. Messenger (mRNA)

Molecule in cells that carries genetic codes from the DNA in the nucleus to the sites of protein synthesis in the cytoplasm (the ribosomes).



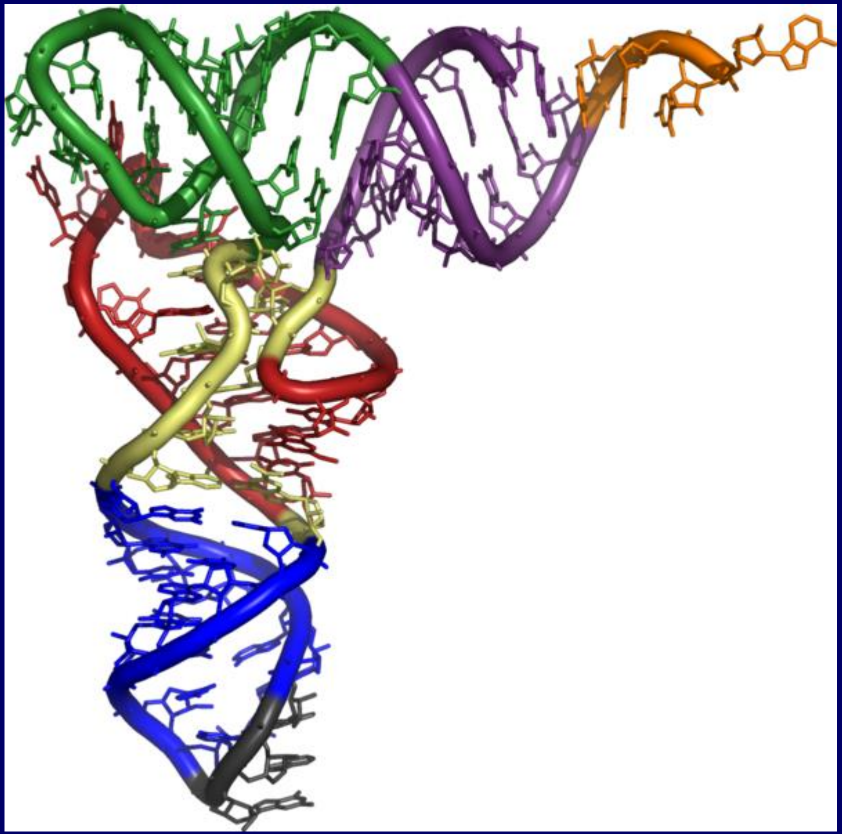
3. Transfer (tRNA)

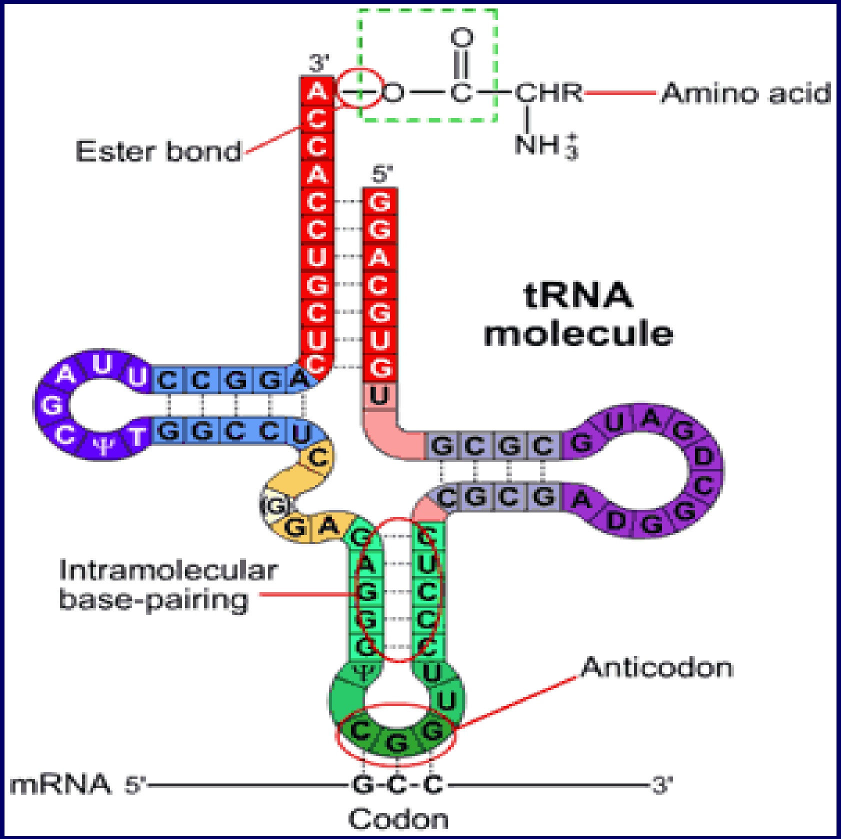
- Translates the genetic code from the messenger RNA and brings specific amino acids to the ribosome for protein synthesis
- Each amino acid is recognized by one or more specific tRNA
- tRNA has a tertiary structure that is L-shaped
- One end attaches to the amino acid and the other binds to the mRNA by a 3-base complimentary sequence

There are 20 different tRNAs, one for each amino acid.

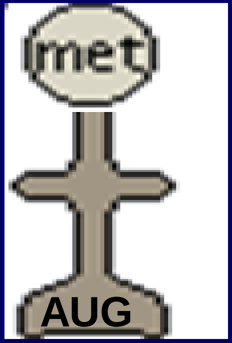
Each tRNA consists of sets of three bases (triplet) at its 3' end.

A particular amino acid is attached to the tRNA by an ester linkage involving the carboxyl group of the amino acid and the 3' oxygen of the tRNA hydroxyl group.





Will referee to in protein biosynthesis as



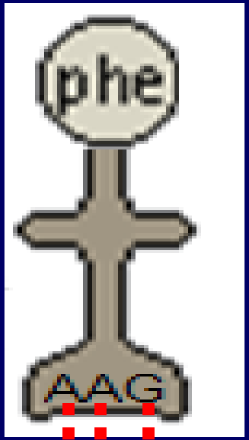
Example—Phenylalanine transfer RNA

One of the mRNA codons for phenylalanine is:

5' ⟵ UUC ⟶ 3'

The complementary sequence in tRNA is called the *anticodon*.

3' ⟵ AAG ⟶ 5'



5' ⟵ UUC ⟶ 3'

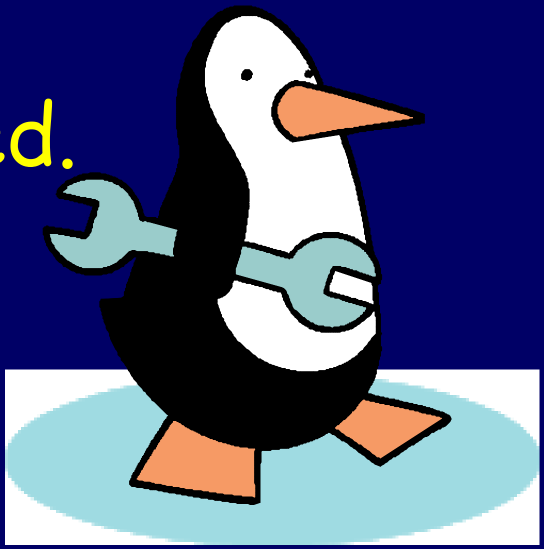
Protein Biosynthesis

"The Central Dogma" Francis Crick, 1957

"DNA makes RNA makes protein."

Three kinds of RNA are involved.

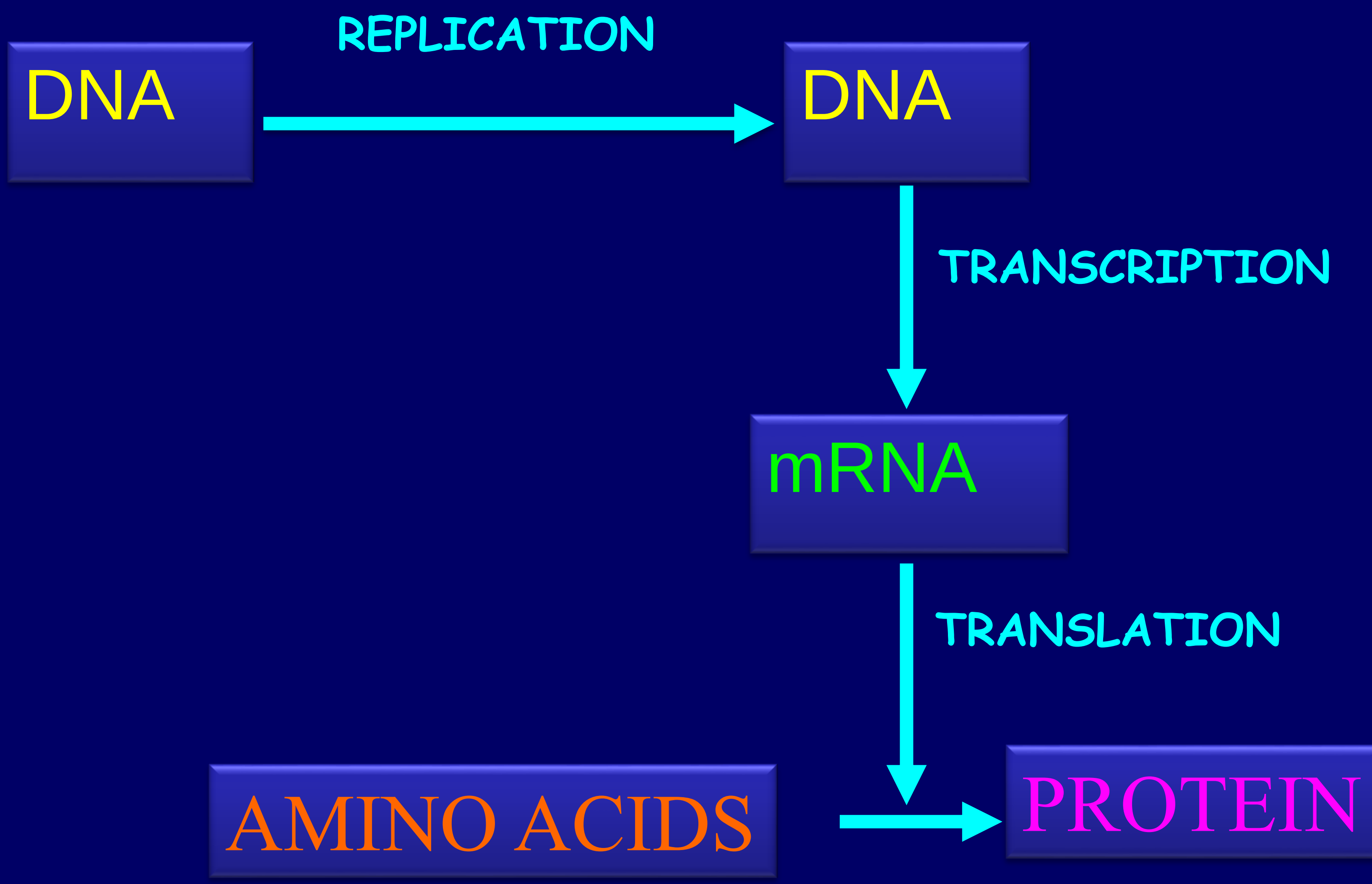
1. messenger RNA (mRNA)
2. transfer RNA (tRNA)
3. ribosomal RNA (rRNA)



There are two main stages.

1. transcription
2. translation

Protein Biosynthesis



1. Transcription

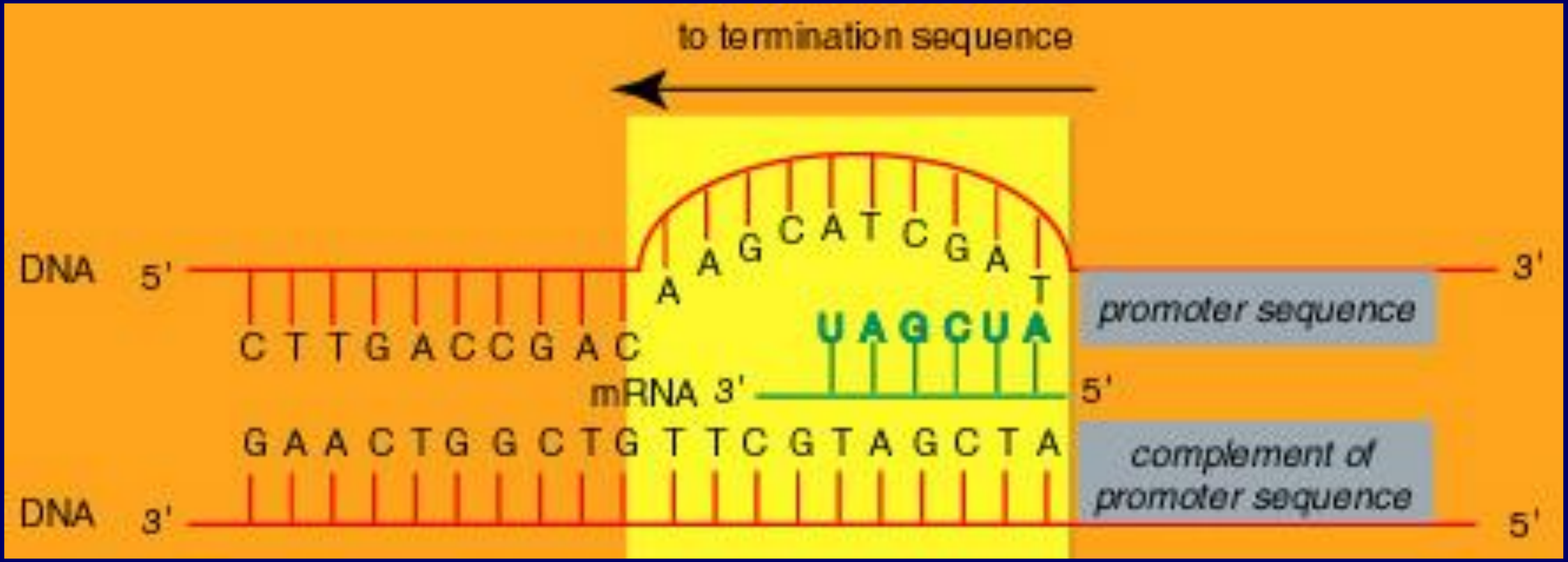
In transcription, a strand of DNA acts as a template upon which a complementary RNA is biosynthesized.

This complementary RNA is *messenger RNA* (mRNA).

Mechanism of transcription resembles mechanism of DNA replication.

Transcription begins at the 5' end of DNA and is catalyzed by the enzyme *RNA polymerase*.

Only a section of about 10 base pairs in the DNA is unwound at a time.
Nucleotides complementary to the DNA are added to form mRNA.



2. Translation

- The genetic code consists of 64 triplets of nucleotides. These triplets are called **codons**.
- With three exceptions each codon encodes for one of the 20 amino acids used in the synthesis of proteins.
- most of the amino acids being encoded by more than one codon.
- The genetic code can be expressed as either RNA codons or DNA codons
- RNA codons occur in messenger RNA (**mRNA**) and are the codons that are actually "read" during the synthesis of polypeptides (the process called **translation**).

	U	C	A	G	
U	UUU Phe UUC Phe UUA Leu UUG Leu	UCU Ser UCC Ser UCA Ser UCG Ser	UAU Tyr UAC Tyr UAA Stop UAG Stop	UGU Cys UGC Cys UGA Stop UCG Trp	U C A G
C					U C A G
A					U C A G
G					U C A G

First letter

Second letter

Third letter

	U	C	A	G	
	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
U	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UCG Trp	G
	CUU Leu	CCU Pro	CAU His	CGU Arg	U
C	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CCG Arg	G
	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
A	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	ACG Arg	G
	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
G	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GCG Gly	G

UAA, UGA, and UAG are "stop" codons that signal the end of the polypeptide chain.

	U	C	A	G	
U			UAA Stop UAG Stop	UGA Stop	U C A G
C					U C A G
A	AUU Ile AUC Ile AUA Ile AUG Met	ACU Thr ACC Thr ACA Thr ACG Thr	AAU Asn AAC Asn AAA Lys AAG Lys	AGU Ser AGC Ser AGA Arg ACG Arg	U C A G
G					U C A G

AUG is the "start" codon. Biosynthesis of all proteins begins with methionine as the first amino acid. This methionine is eventually removed after protein synthesis is complete.

Protein Biosynthesis

1. Translation

Initiation of protein synthesis

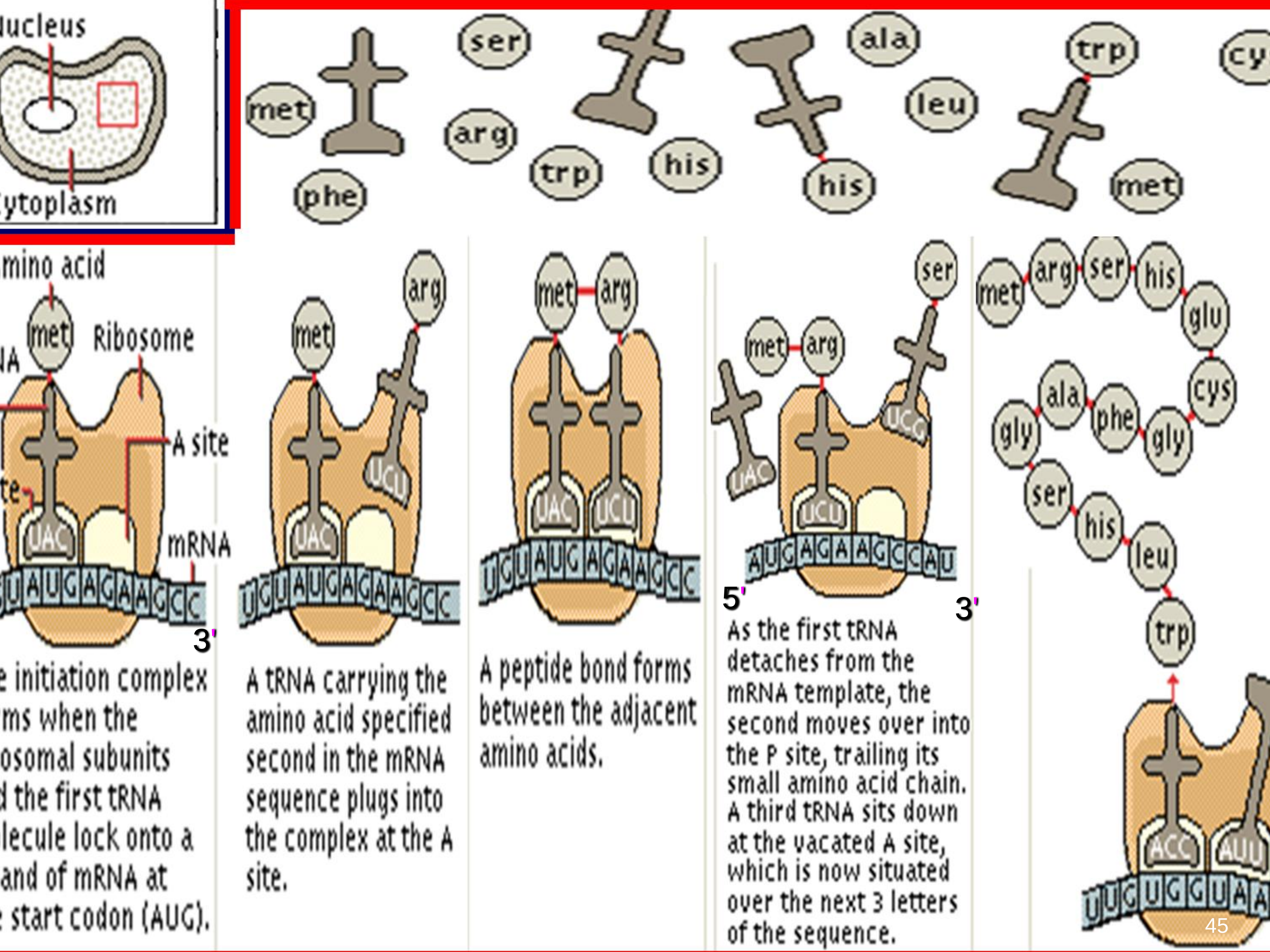
1. A mRNA attaches to a ribosome.
2. mRNA is read in its 5'-3' direction begins at the start codon AUG. with methionine.
3. The second codon attaches to a tRNA with the next amino acid.
4. A peptide bond forms between the adjacent amino acids at the first and second codons.
5. mRNA Ends at stop codon (UAA, UAG, or UGA)

3. Translocation

1. The first tRNA detaches from the ribosome.
2. The ribosome shifts to the adjacent the second codon on the mRNA.
3. A new tRNA/amino acid attaches to the open binding site.
4. A peptide bond forms and that tRNA detaches.
5. The ribosome shifts down the mRNA to read next codon.

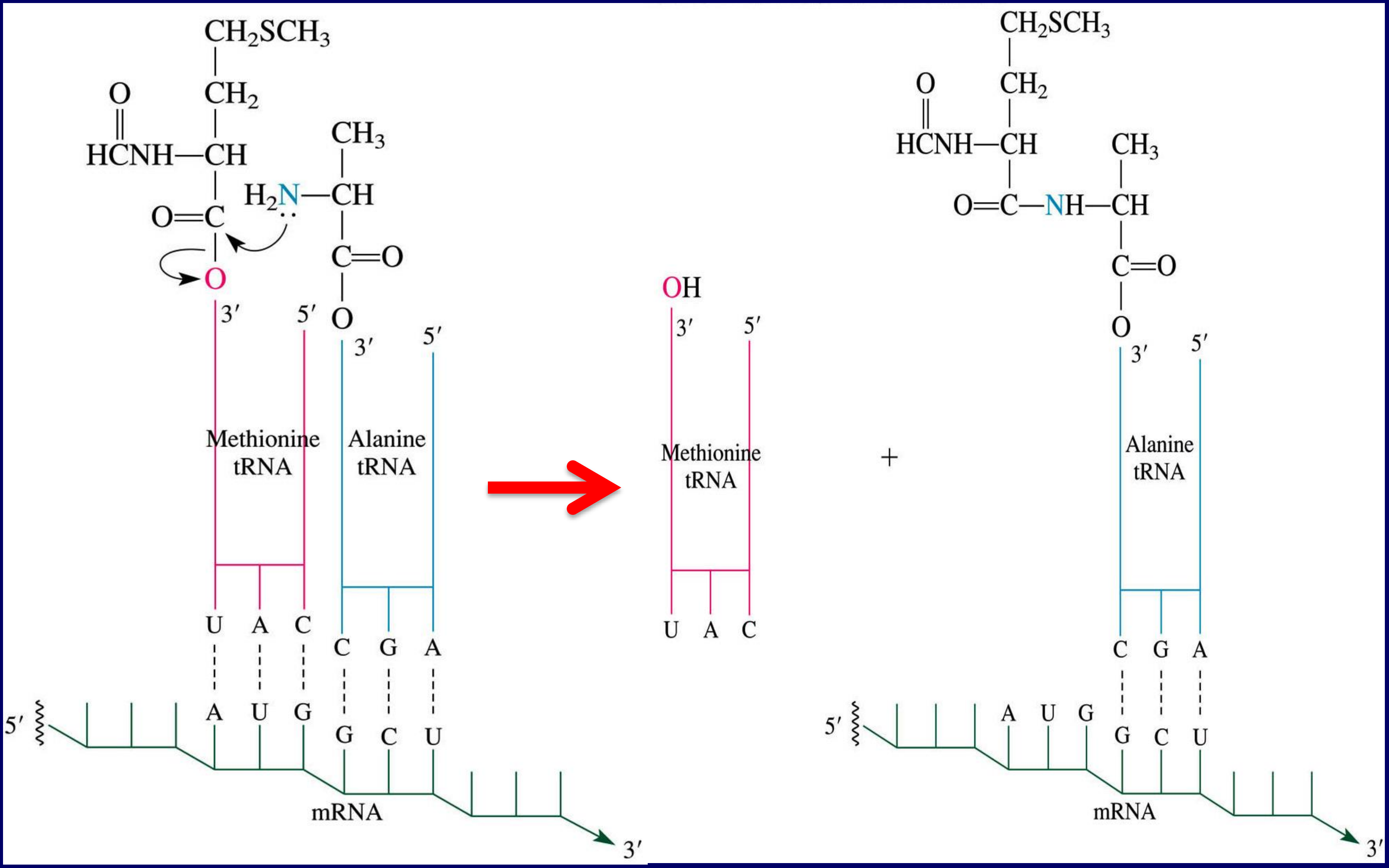
3. Termination step

- All the amino acids are linked.
- The ribosome reaches a “stop” codon: UGA, UAA, or UAG.
- There is no tRNA with an anticodon for the “stop” codons.
- The polypeptide detaches from the ribosome.



Nucleus
Cytoplasm
met
ser
arg
trp
phe
his
ala
leu
trp
cy
his
met
mino acid
met
Ribosome
A site
mRNA
UAC
UGUAUGAGAAGCC
3'
e initiation complex
ms when the
osomal subunits
d the first tRNA
lecule lock onto a
and of mRNA at
e start codon (AUG).
met
arg
UCU
UAC
UGUAUGAGAAGCC
A tRNA carrying the
amino acid specified
second in the mRNA
sequence plugs into
the complex at the A
site.
met
arg
UAC
UCU
UGUAUGAGAAGCC
A peptide bond forms
between the adjacent
amino acids.
ser
met
arg
UAC
UCU
UCG
AUGAGAAGCCAU
5'
3'
As the first tRNA
detaches from the
mRNA template, the
second moves over into
the P site, trailing its
small amino acid chain.
A third tRNA sits down
at the vacated A site,
which is now situated
over the next 3 letters
of the sequence.
met
arg
ser
his
glu
cys
gly
phe
ala
gly
ser
his
leu
trp
ACC
AUU
UUGUGGUAA

Translation/ Formation of peptied pond



DNA Profiling

DNA sequencing involves determining the nucleotide sequence in DNA.

The nucleotide sequence in regions of DNA that code for proteins varies little from one individual to another, because the proteins are the same.

Most of the nucleotides in DNA are in "noncoding" regions and vary significantly among individuals.

Enzymatic cleavage of DNA give a mixture of polynucleotides that can be separated by electrophoresis to give a "profile" characteristic of a single individual.

When a sample of DNA is too small to be sequenced or profiled, the *polymerase chain reaction* (PCR) is used to make copies ("amplify") portions of it.

Genetic Mutations

A **mutation** can:-

Alter the nucleotide sequence in DNA.

Result from mutagens such as radiation and chemicals.

Produce one or more incorrect codons in mRNA.

Produce a protein containing one or more incorrect amino acids.

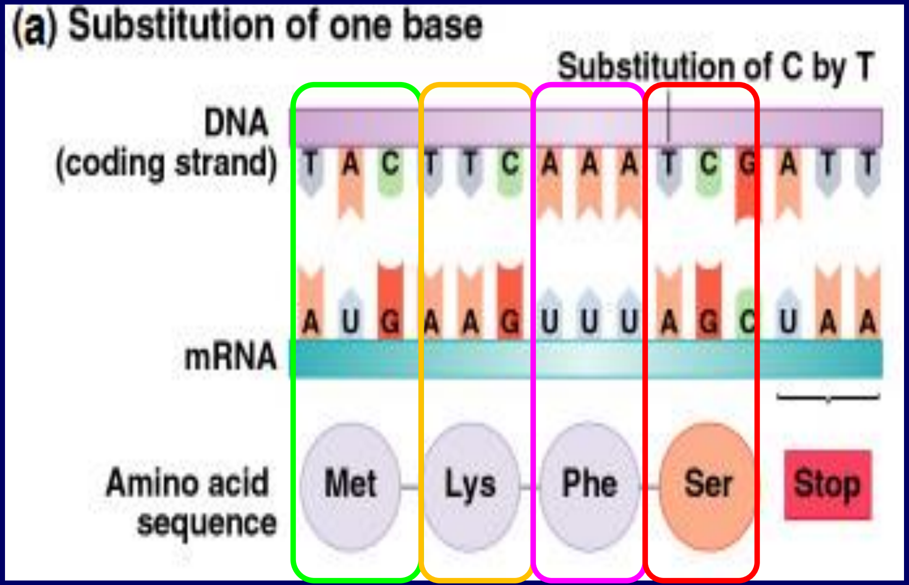
Produce defective proteins and enzymes.

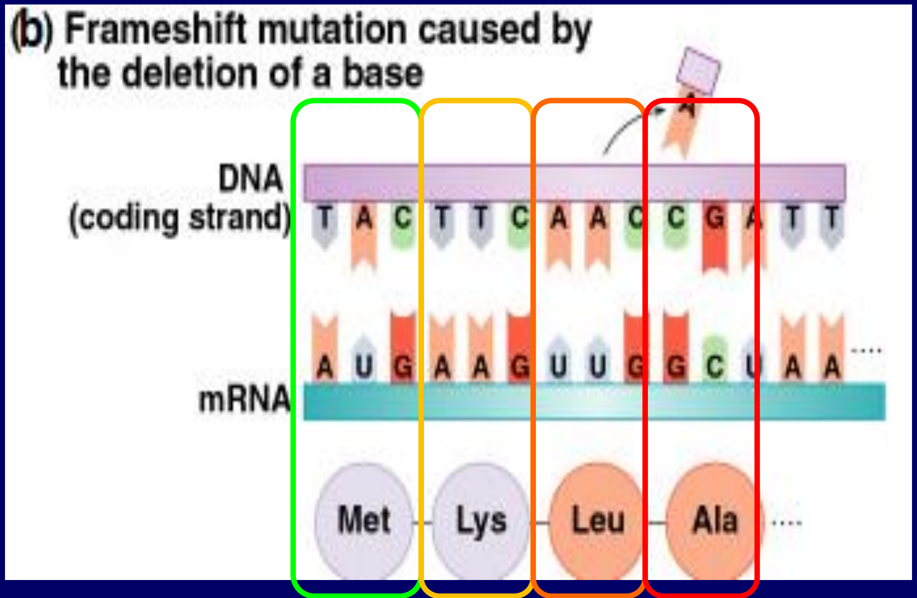
Cause genetic diseases.

Examples of Genetic Diseases

1. Galactosemia
2. Cystic fibrosis
3. Downs syndrome
4. Muscular dystrophy
5. Huntington's disease
6. Sickle-cell anemia
7. Hemophilia
8. Tay-Sachs disease

Two types of Mutation



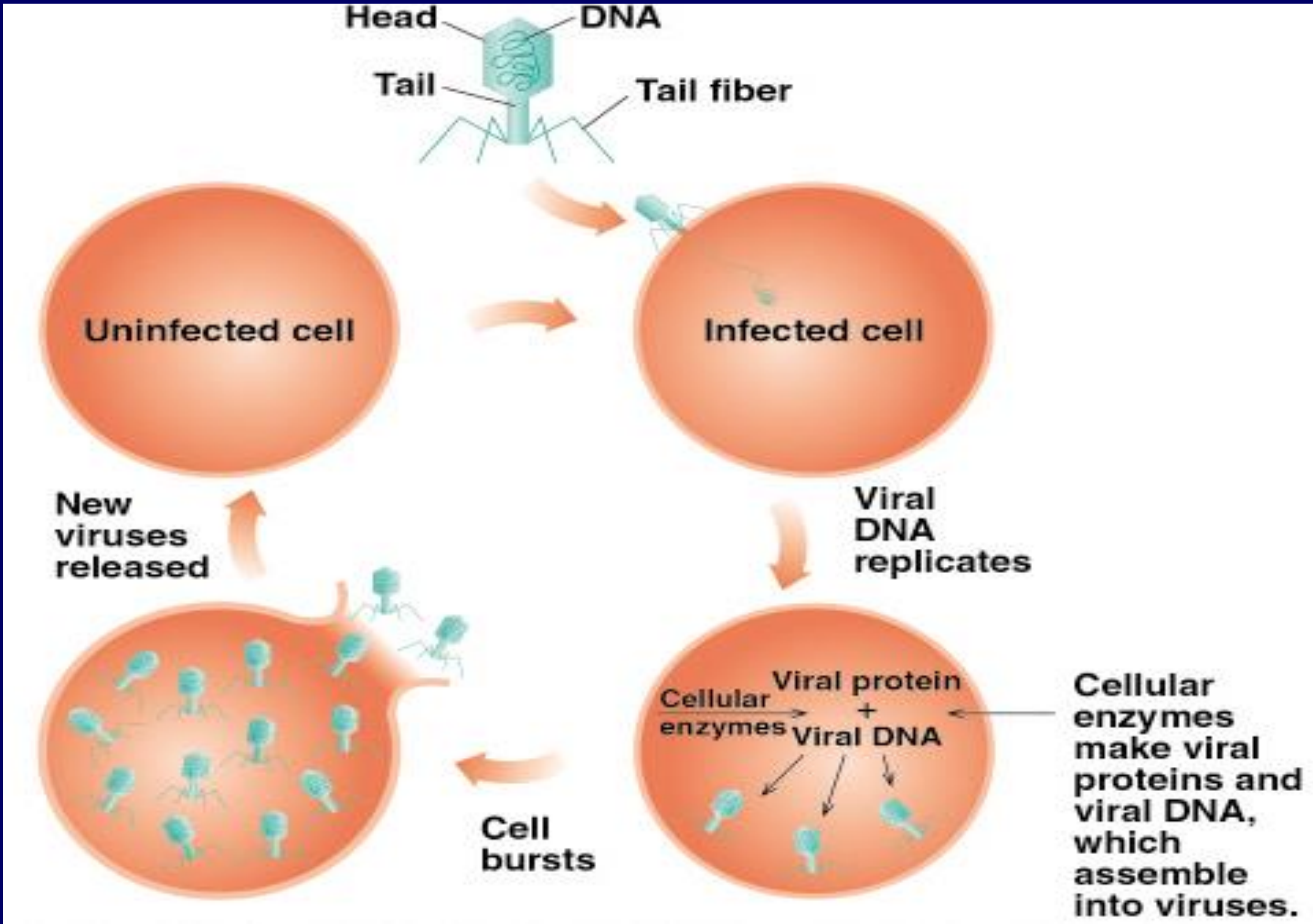


(a) Substitution of a base in DNA changes a codon in the mRNA. A different codon leads to the placement of an incorrect amino acid in the polypeptide

(b) Frame shift mutation, An extra base adds to or is deleted from the normal DNA sequence. All the codons in mRNA and amino acids are incorrect from the base change.

Viruses

- Are small particles of DNA or RNA that require a host cell to replicate.
- Cause a viral infection when the DNA or RNA enters a host cell.
- Are synthesized in the host cell from the viral RNA produced by viral DNA.


Head
DNA
Tail
Tail fiber
Uninfected cell
Infected cell
Viral DNA replicates
Viral protein
Cellular enzymes
+
Viral DNA
Cellular enzymes make viral proteins and viral DNA, which assemble into viruses.
Cell bursts
New viruses released

Reverse Transcription

In reverse transcription

A retrovirus, which contains viral RNA, but no viral DNA, enters a cell.

The viral RNA uses *reverse transcriptase* to produce a viral DNA strand.

The viral DNA strand forms a complementary DNA strand.

The new DNA uses the nucleotides and enzymes in the host cell to synthesize new virus particles.

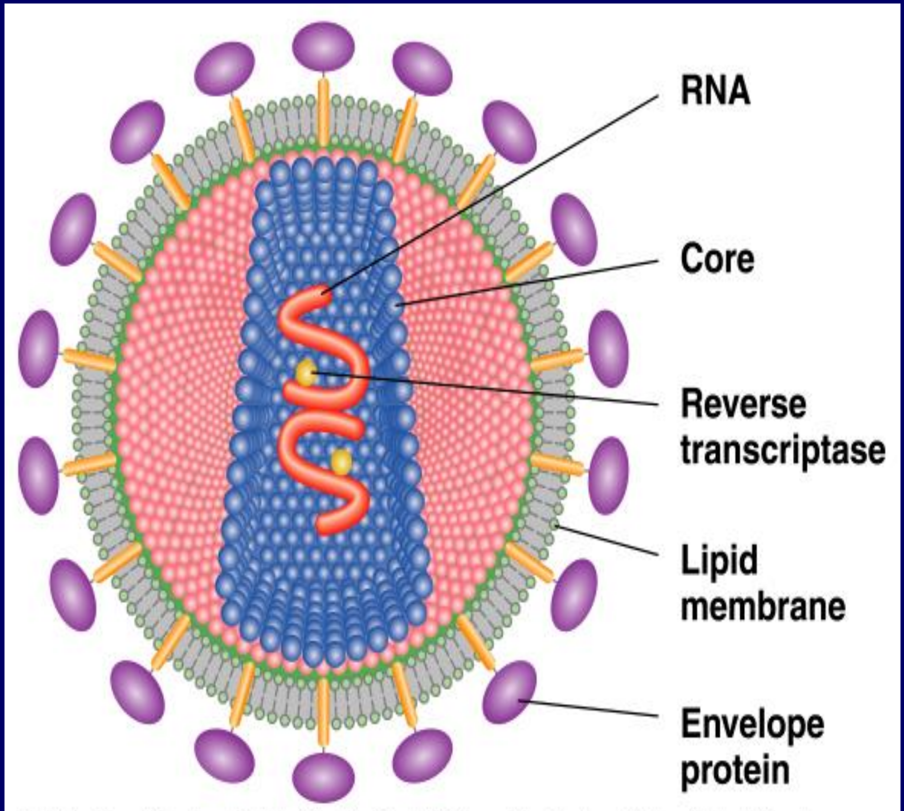
HIV Virus and AIDS

The HIV-1 virus

Is a retrovirus that infects T4 lymphocyte cells.

Decreases the T4 level and the immune system fails to destroy harmful organisms.

Causes pneumonia and skin cancer associated with AIDS

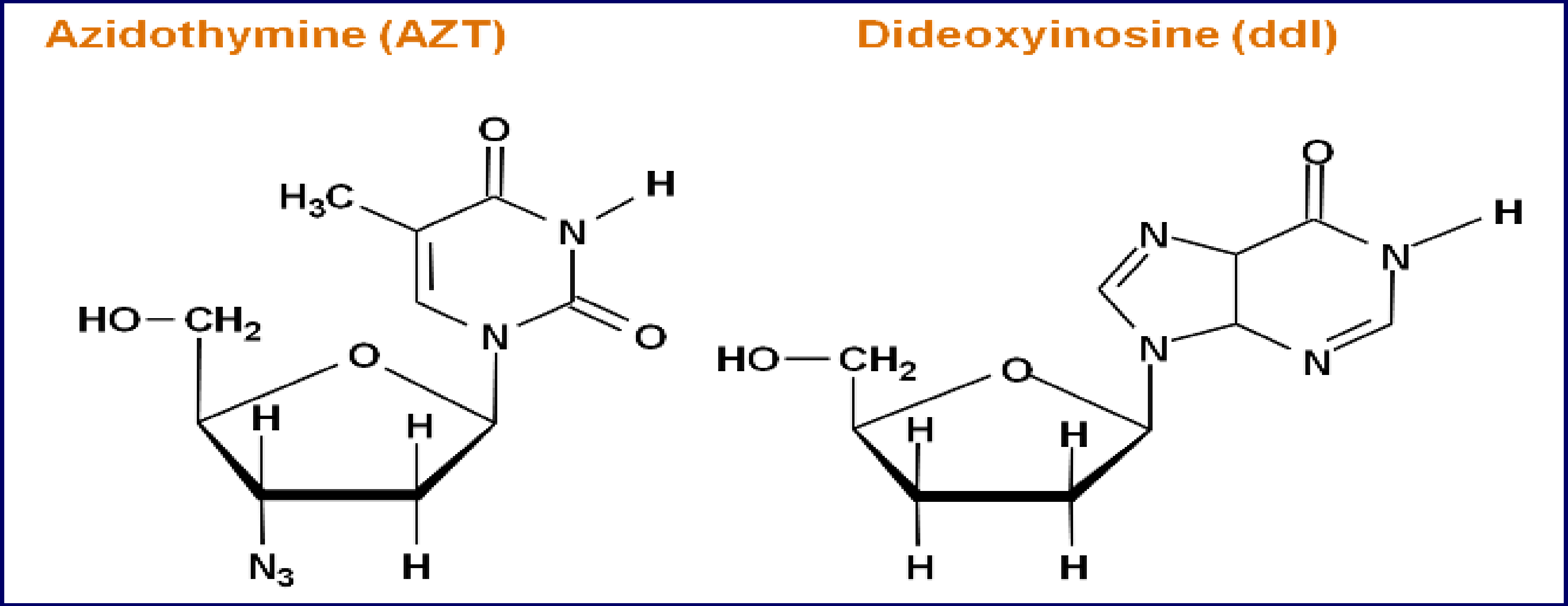


HIV virus

AIDS Treatment

One type of AIDS treatment prevents reverse transcription of the viral DNA.

When altered nucleosides such as AZT and ddI are incorporated into viral DNA, the virus is unable to replicate.



Another type of AIDS treatment involves protease inhibitors such as saquinavir, indinavir, and ritonavir.

Protease inhibitors modify the active site of the protease enzyme, which prevents the synthesis of viral proteins.

Inhibited by AZT, ddI	Inhibited by protease inhibitors
reverse transcriptase	protease

Viral RNA → Viral DNA → Viral proteins

Thank you for your attention