УНИВЕРСИТЕТ ЛОБАЧЕВСКОГО

Lecture 7
REGULATION OF ENZYMESACTIVITY AND METABOLIC PATHWAYS. MEDICAL IMPLEMENTATION OF ENZYMES

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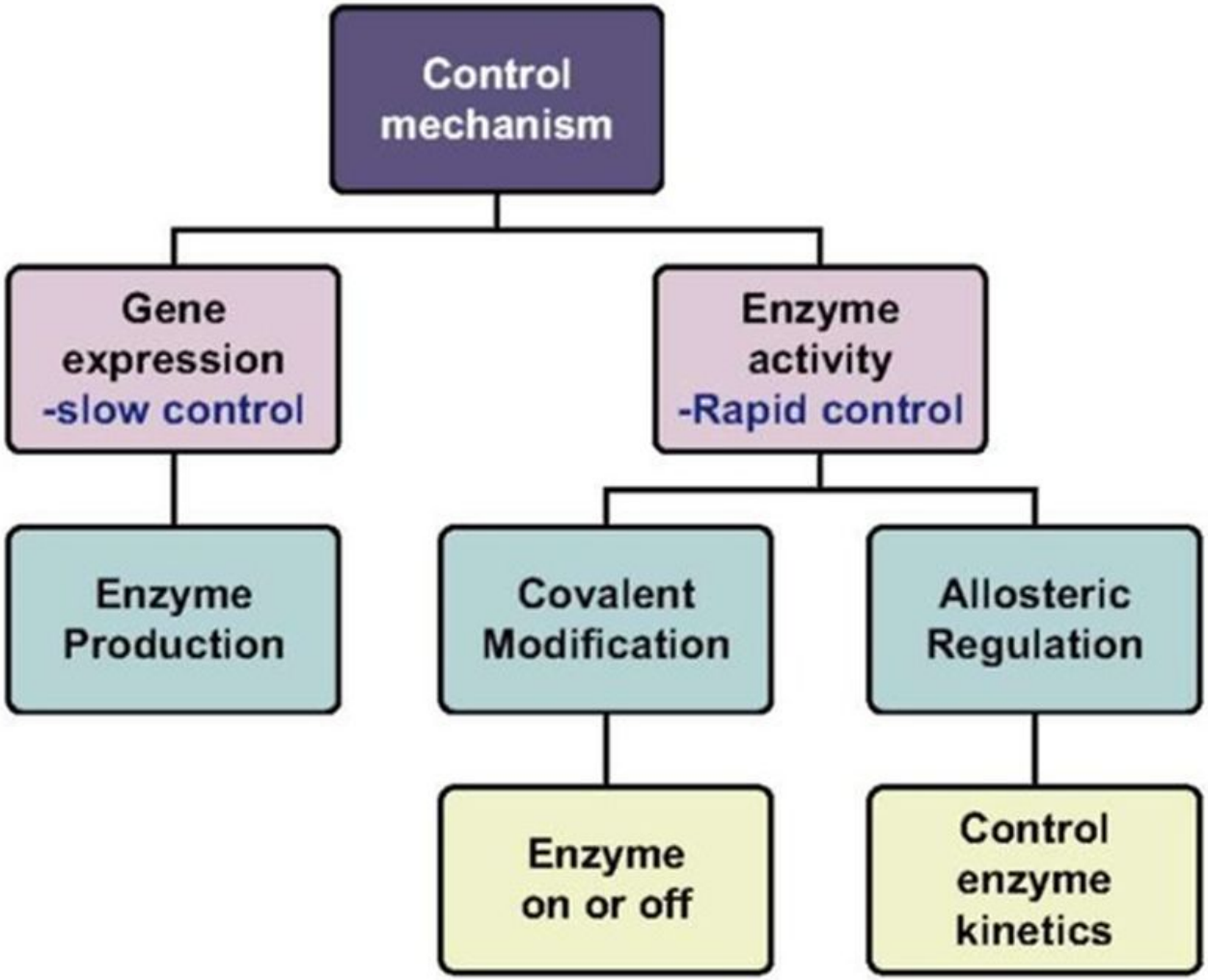
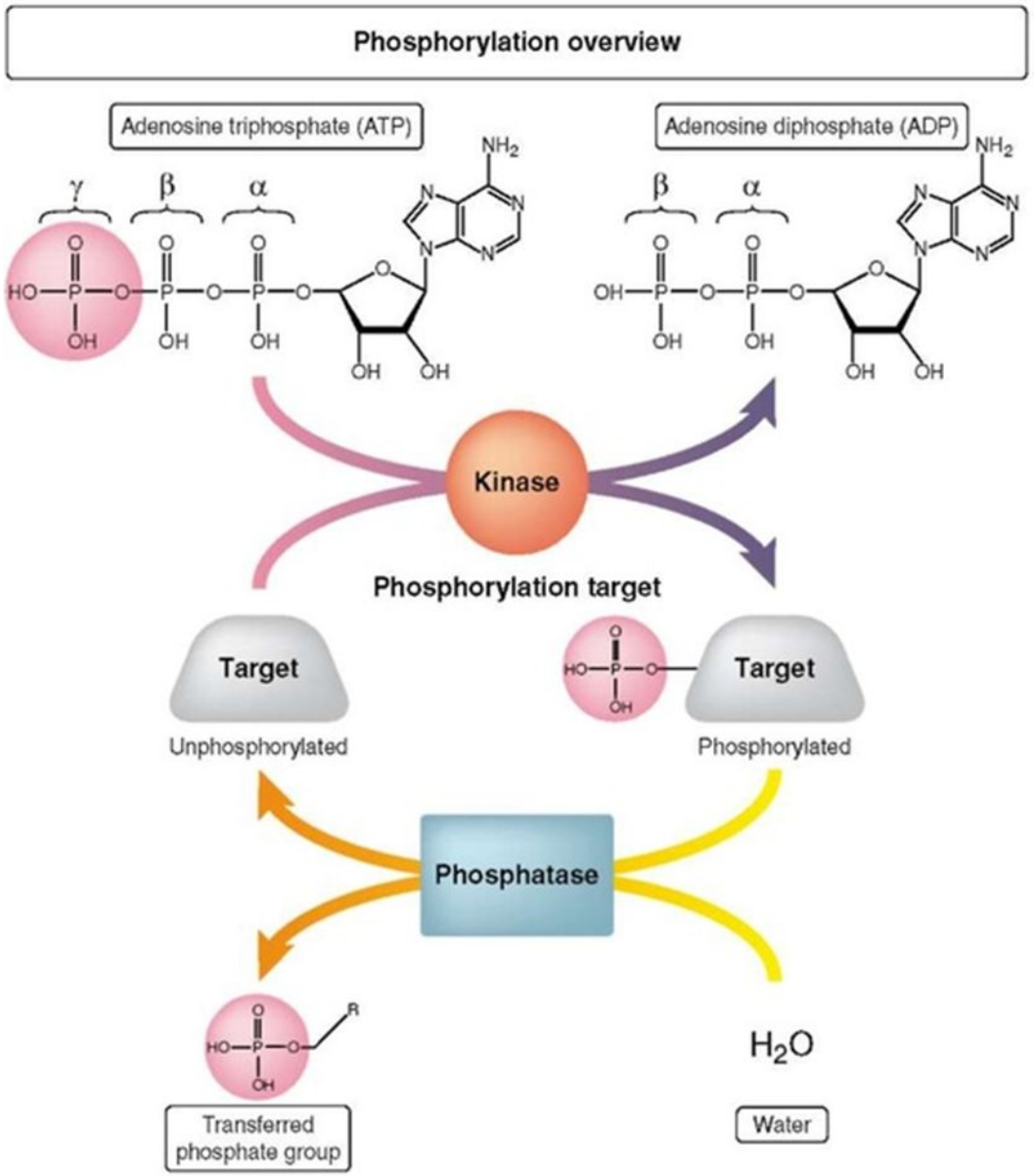
2020

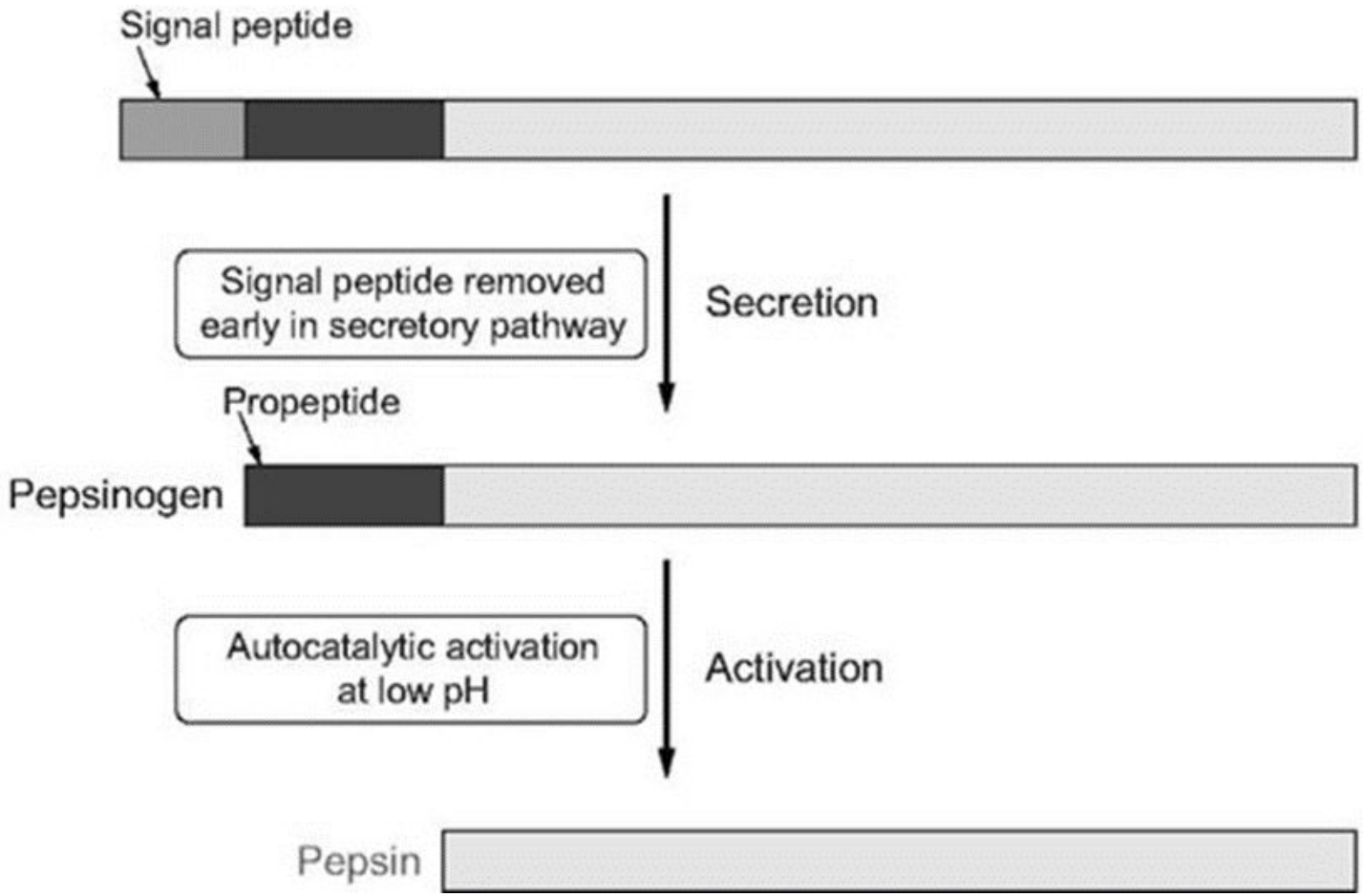
Ways of regulation of enzymatic activity



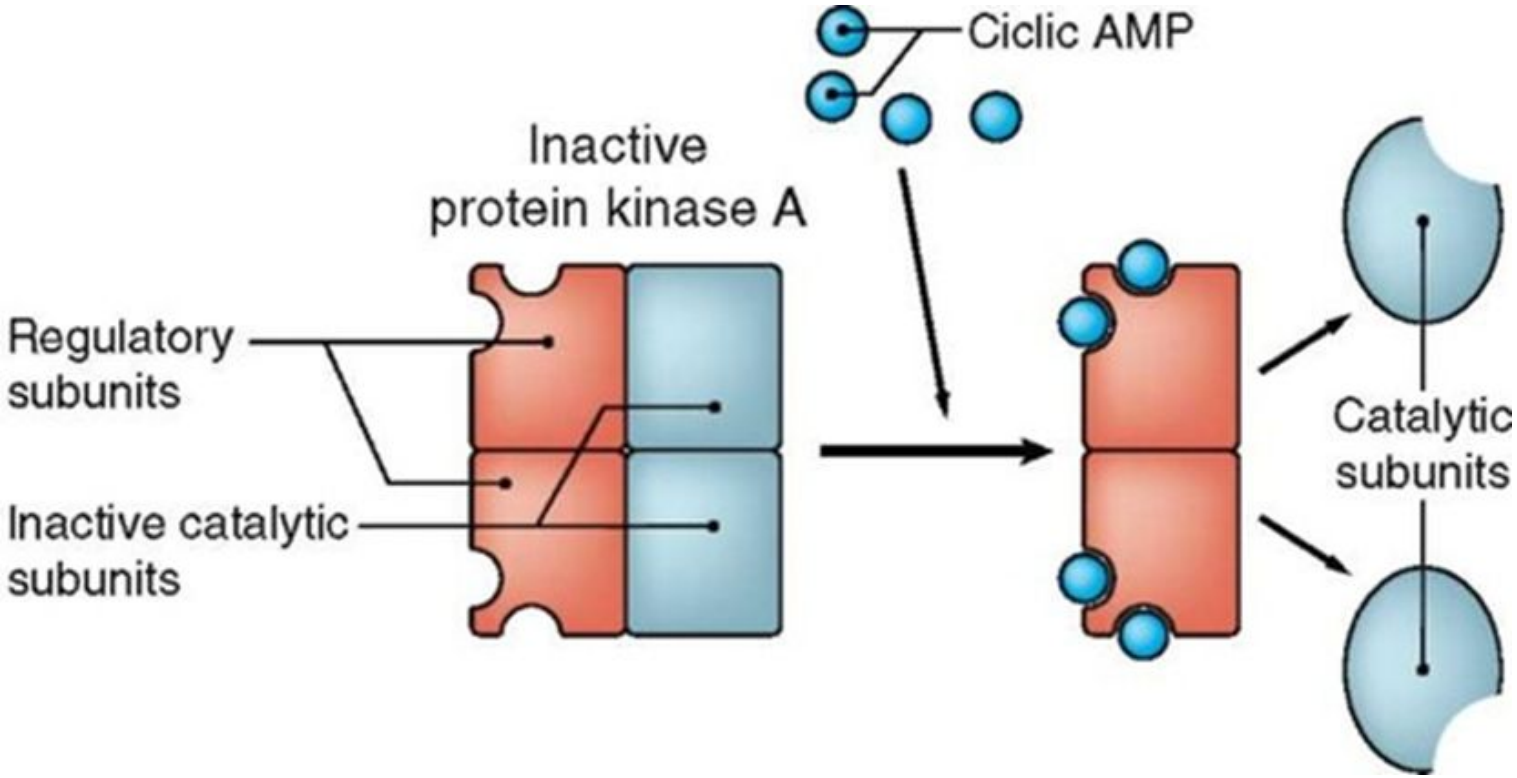
Enzymes phosphorylation/ dephosphorylation



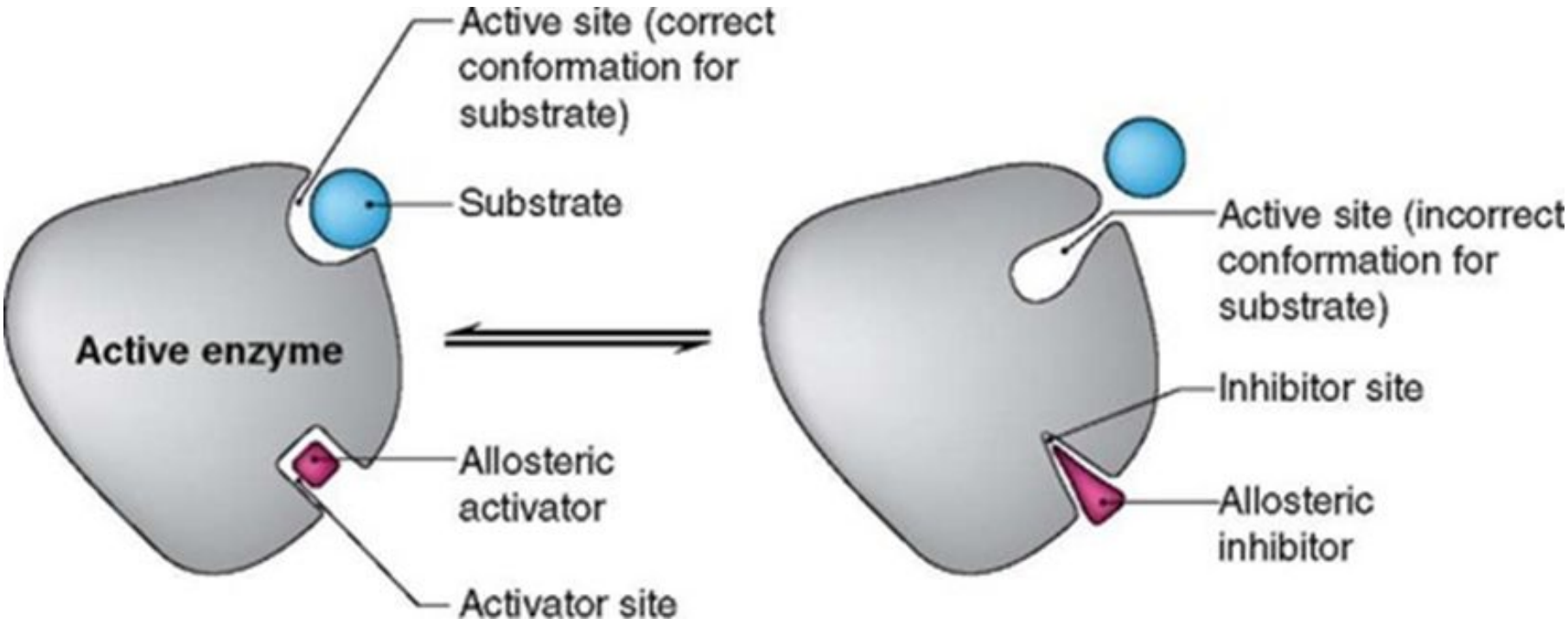
The scheme of activation of pepsinogen – partial proteolysis



Dissociation of protein kinase A - Protein-protein interactions

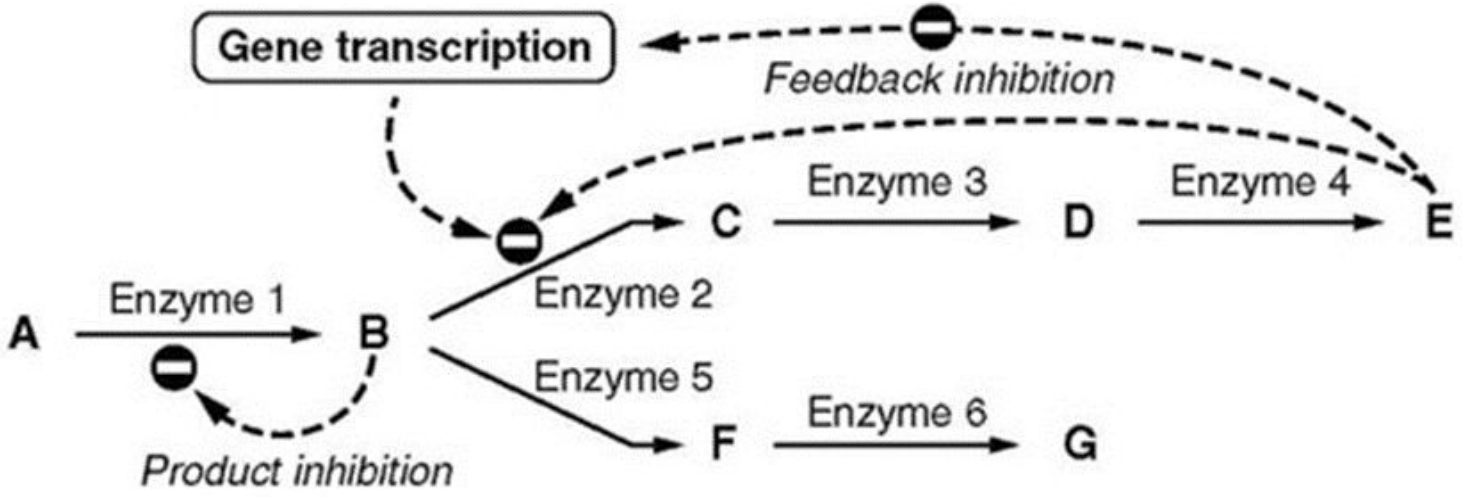


Allosteric regulation



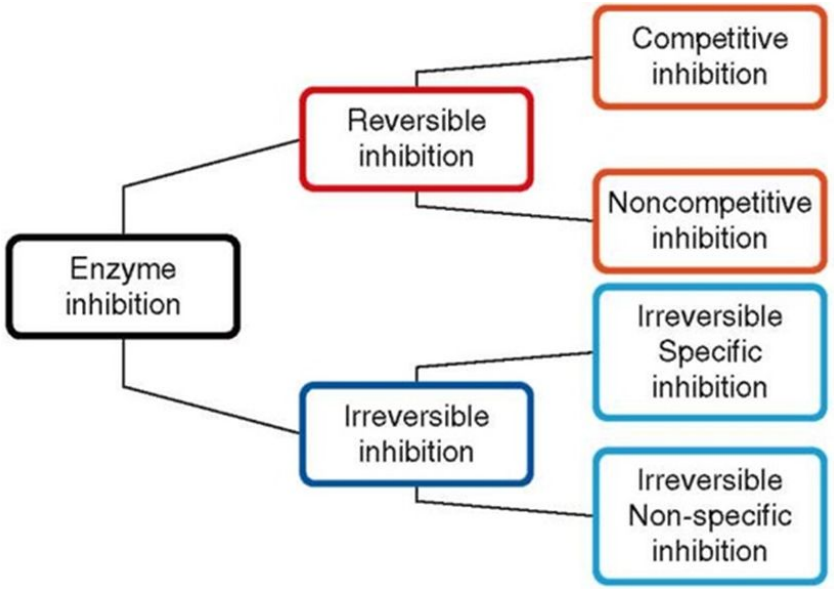
Regulation of the metabolic pathways

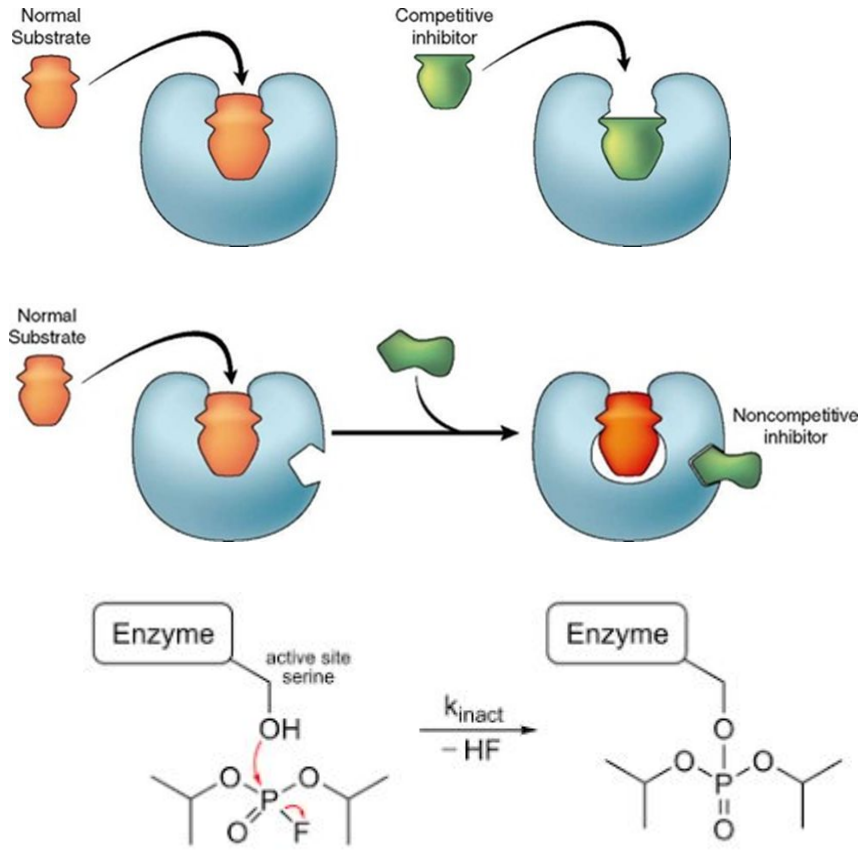
The key enzymes in the metabolic pathways usually catalyze:
► irreversible (→) or partially reversible reactions;
► the slowest reactions;
► reactions at the beginning of the metabolic pathways or in branching places of metabolic pathways.



Scheme of regulation of enzyme activity by feedback inhibition

Regulation of the metabolic pathways





Clinical applications of enzymes

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- ► enzyme diagnostics;
  enzymopathology:
  - accumulation of substrate reaction. For example, phenylalanine in phenylketonuria, free bilirubin in physiological jaundice of the newborn, some fats in diseases of lysosomal accumulation (lipidosis);
  - product deficiency. For example, melanin in albinism, catecholamines in parkinsonism;
  - both features simultaneously, as in glycogenosis, accompanied by hypoglycemia with an excess of glycogen in the liver;
- ► enzyme therapy;
- ► use of enzymes in medical technology and industry (Enzyme immunoassay: *enzyme-antigen-antibody*);
- ► use of enzyme inhibitors:
  - natural and artificial poisons
  - insecticides
  - herbicides
  - disinfectants such as triclosan
  - chemotherapy:
    - competitive inhibitors (Sulfonamides)
    - competition at the active site (treatment of methanol intoxication)
    - irreversible inhibition (nonsteroidal anti-inflammatory drugs –aspirin)
    - Anti-cancer drugs (Methotrexate – analogue of folic acid)

Principle serum enzymes used in clinical diagnosis

Serum Enzyme	Major Diagnostic Use
Aminotransferases **Aspartate aminotransferase** **Alanine aminotransferase**	Myocardial infarction Viral hepatitis
Amylase	Acute pancreatitis
Ceruloplasmin	Hepatolepticular degeneration
Creatine kinase	Muscle disorders and myocardial infarction
r-Glutamyl transpeptidase	Various liver diseases
Lactate dehydrogenase (isozymes)	Myocardial infarction
Lipase	Acute pancreatitis
Phosphatase, acid	Metastatic carcinoma of the prostate
Phosphatase, alkaline (isozymes)	Various bone disorders, obstructive liver diseases

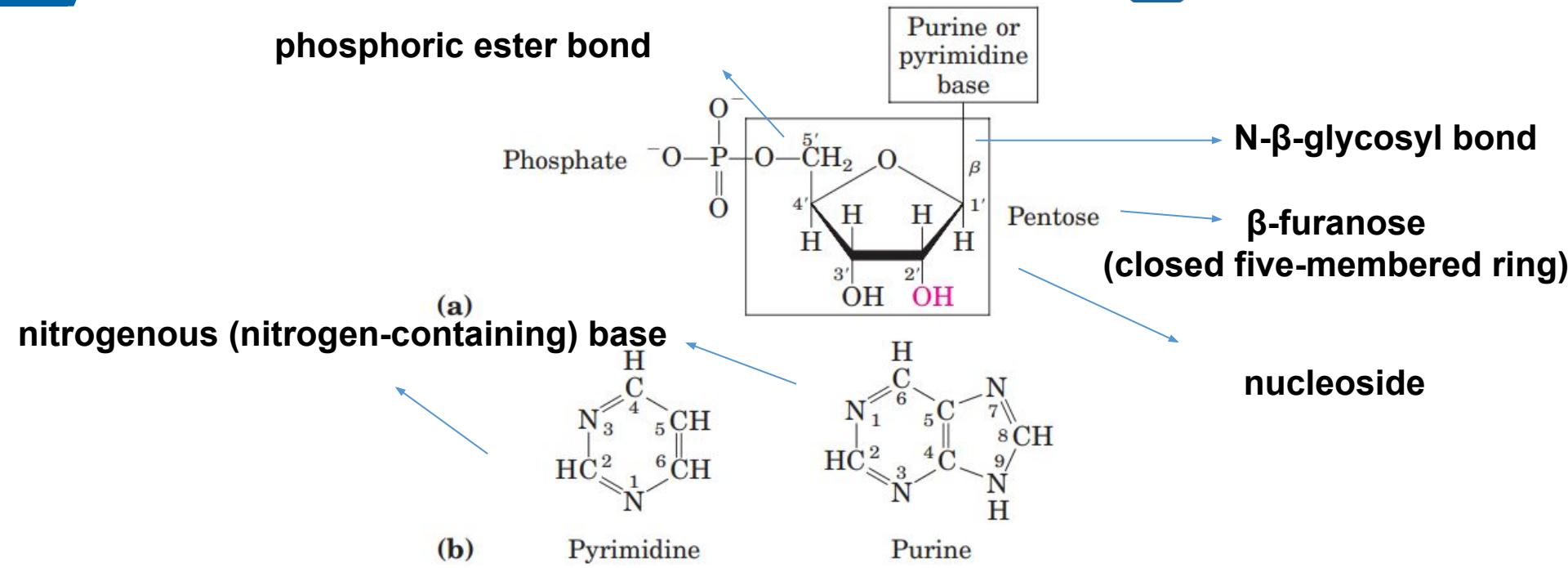
Introduction to nucleic acids

Role of nucleotides:
-the energy currency in metabolic transactions (ATP, GTP),
-the essential chemical participants in signals transduction paths of hormones and other extracellular stimuli in the of cells
-the structural components of enzyme cofactors and metabolic intermediates
-the molecular repositories of genetic information.

Gene is a segment of a DNA molecule that contains the information required for the synthesis of a functional biological product, whether protein or RNA.

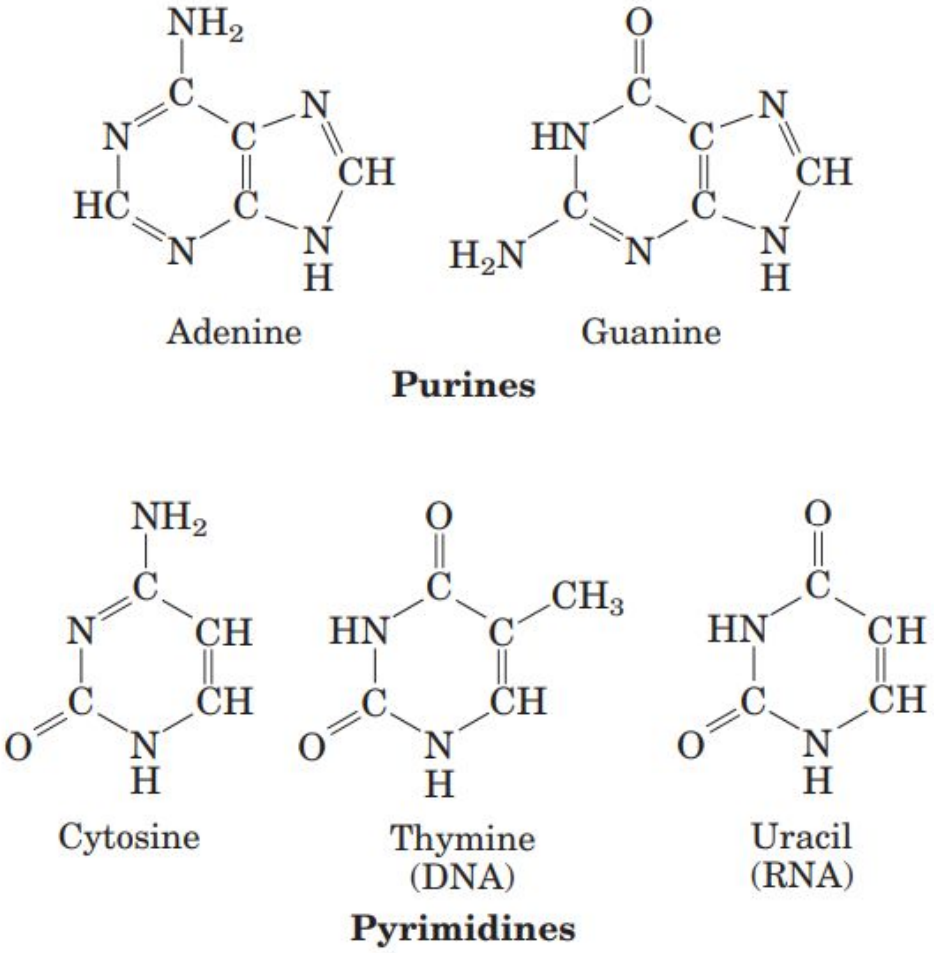
Ribosomal RNAs (rRNAs) are components of ribosomes
Messenger RNAs (mRNAs) are intermediaries, carrying genetic information from one or a few genes to a ribosome
Transfer RNAs (tRNAs) are adapter molecules that faithfully translate the information in mRNA into a specific sequence of amino acids.

Structure of nucleotides

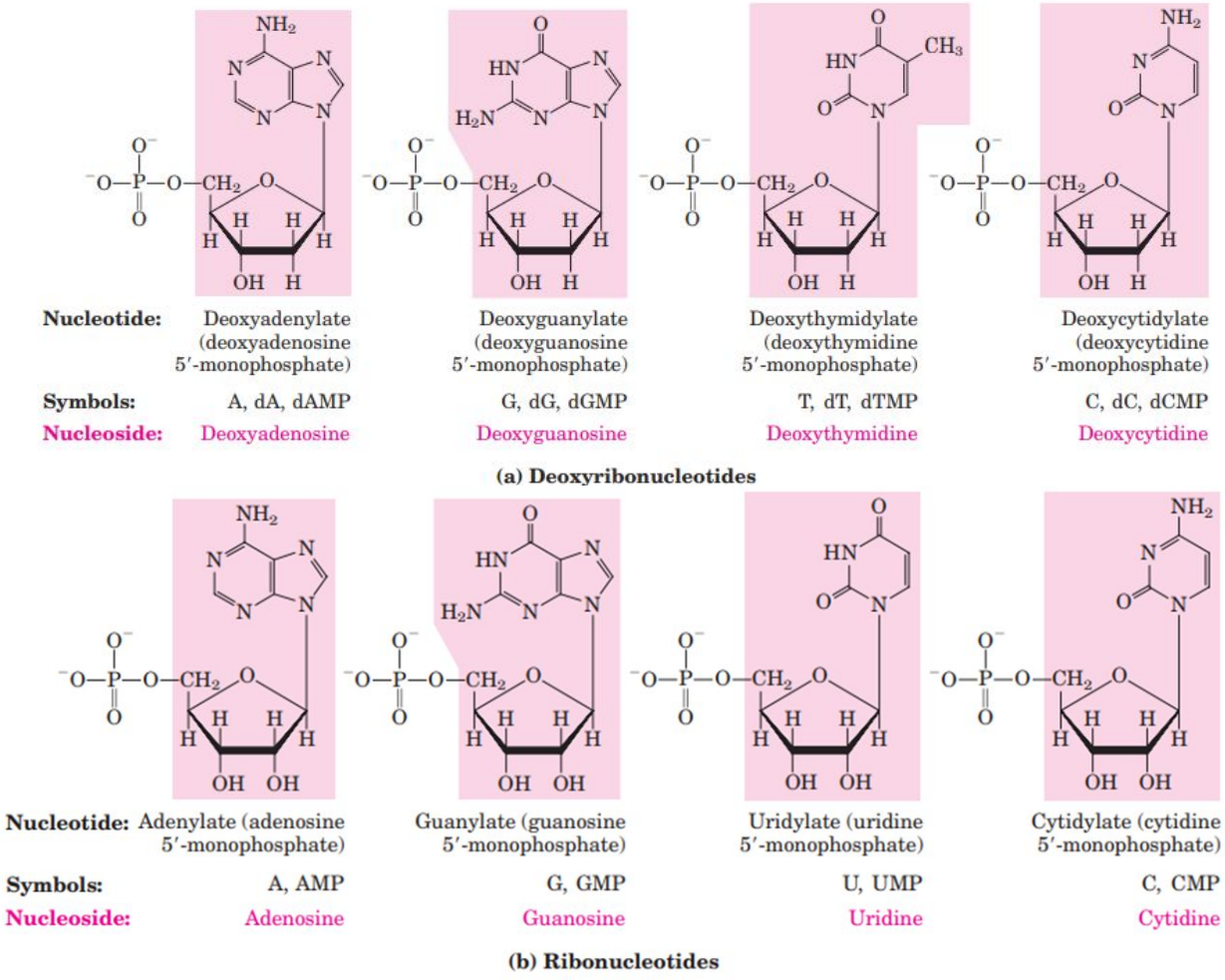


Base	Nucleoside	Nucleotide	Nucleic acid
Purines			
Adenine	Adenosine Deoxyadenosine	Adenylate Deoxyadenylate	RNA DNA
Guanine	Guanosine Deoxyguanosine	Guanylate Deoxyguanylate	RNA DNA
Pyrimidines			
Cytosine	Cytidine Deoxycytidine	Cytidylate Deoxycytidylate	RNA DNA
Thymine	Thymidine or deoxythymidine	Thymidylate or deoxythymidylate	DNA
Uracil	Uridine	Uridylate	RNA

Major purine and pyrimidine bases of nucleic acids



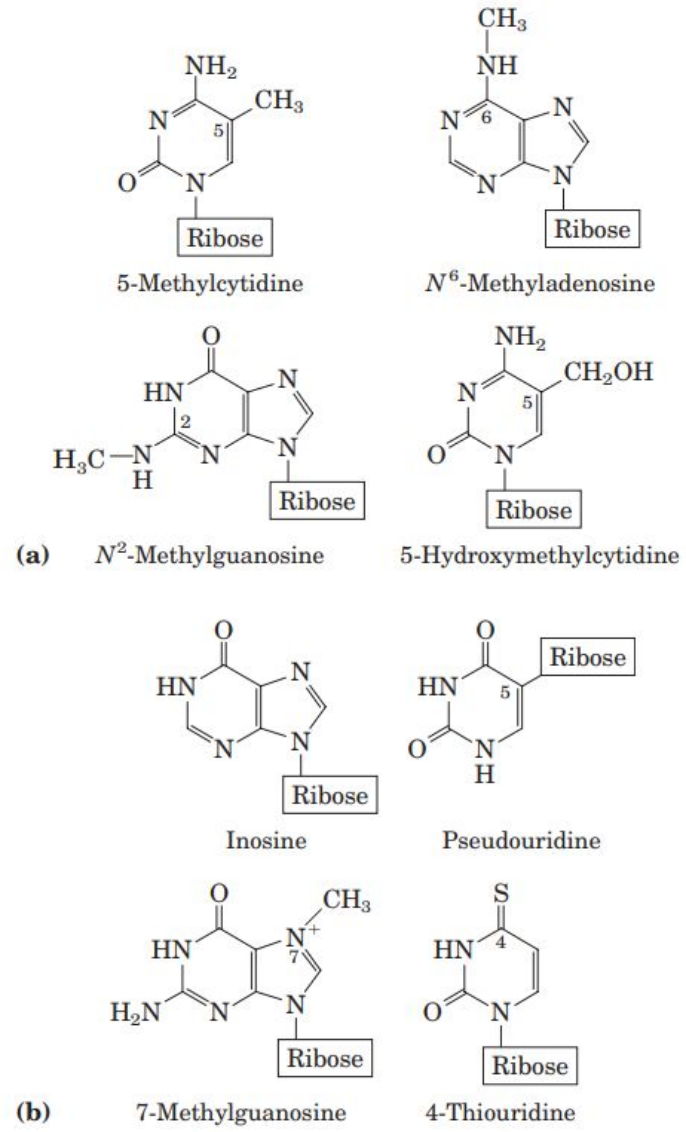
Deoxyribonucleotides and ribonucleotides of nucleic acids



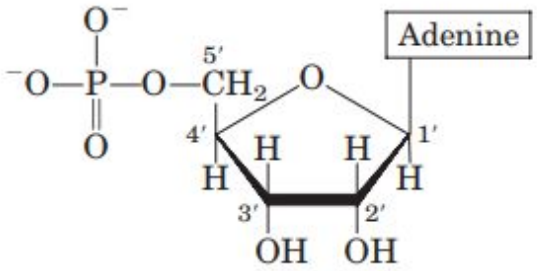
The nucleotide units of DNA (a) are usually symbolized as A, G, T, and C, sometimes as dA, dG, dT, and dC; those of RNA (b) as A, G, U, and C..

In their free form the deoxyribonucleotides are commonly abbreviated dAMP, dGMP, dTMP, and dCMP; the ribonucleotides, AMP, GMP, UMP, and CMP.

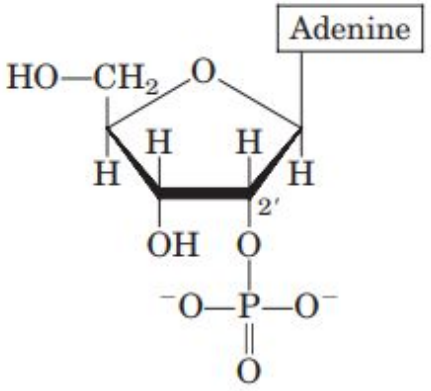
Some minor purine and pyrimidine bases



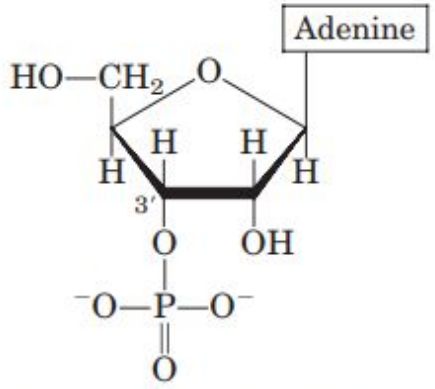
Some adenosine monophosphates



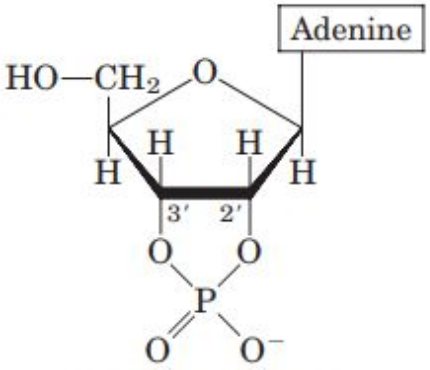
Adenosine 5′-monophosphate



Adenosine 2′-monophosphate



Adenosine 3′-monophosphate



Adenosine 2′,3′-cyclic monophosphate

3,5-cyclic monophosphate (cAMP)
guanosine 3,5-cyclic monophosphate (cGMP)

Phosphodiester linkages in the covalent backbone of DNA and RNA

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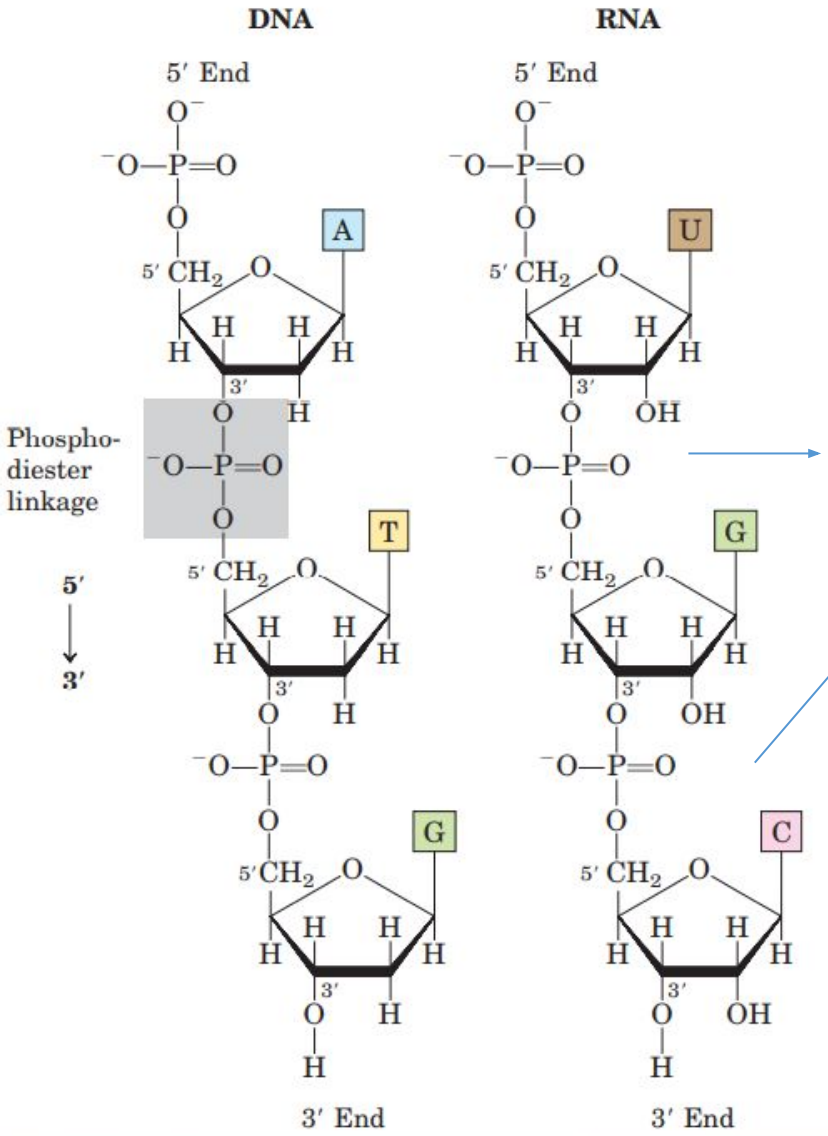
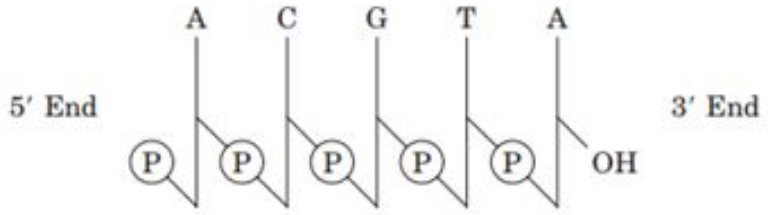
oligonucleotide



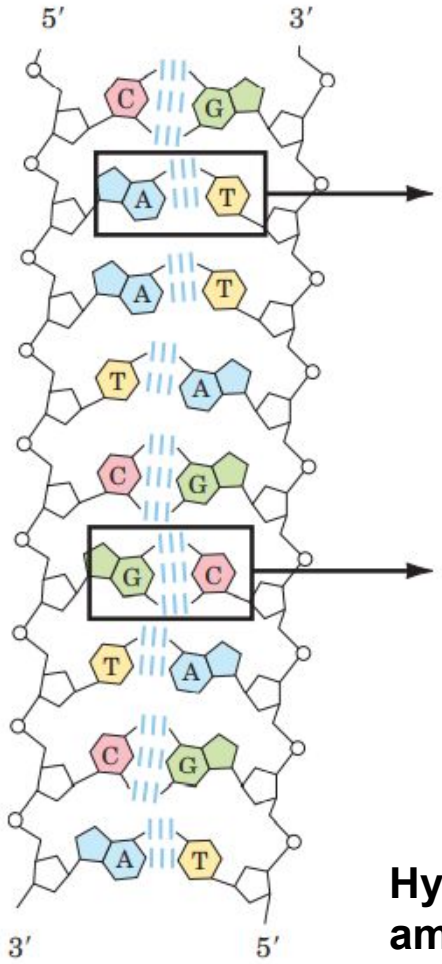
The backbone of alternating pentose and phosphate groups in both types of nucleic acid is highly polar. The 5 end of the macromolecule lacks a nucleotide at the 5 position, and the 3 end lacks a nucleotide at the 3 position.

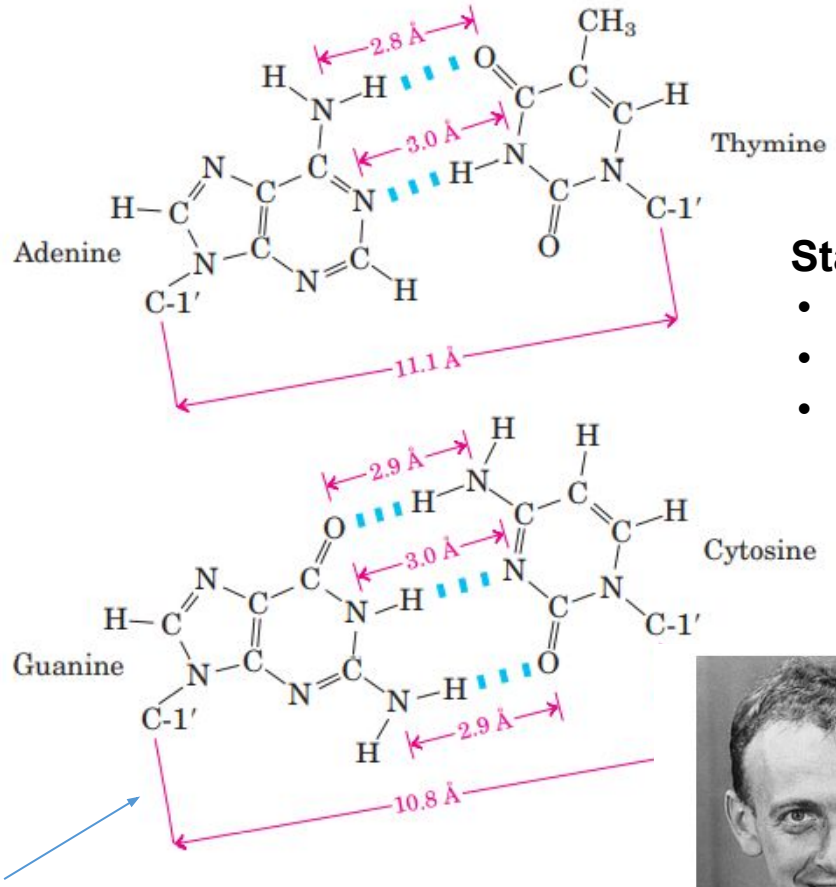
5-phosphate group of one nucleotide unit is joined to the 3-hydroxyl group of the next nucleotide, creating a <u>phosphodiester linkage</u>



Some simpler representations of this pentadeoxyribonucleotide are: pA-C-G-T-AOH, pApCpGpTpA, and pACGTA

Hydrogen-bonding patterns in the base pairs defined by Watson and Crick





Hydrogen bonds involving the amino and carbonyl groups

Stacking interactions:

- *hydrophobic*
- *van der Waals*
- *dipole-dipole interactions*

James D. Watson

Francis Crick,