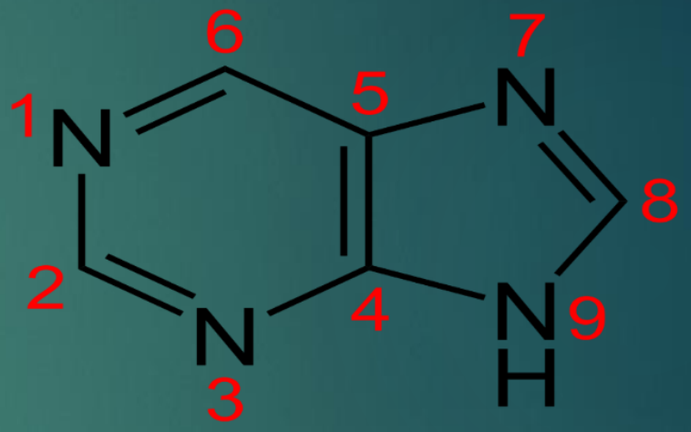
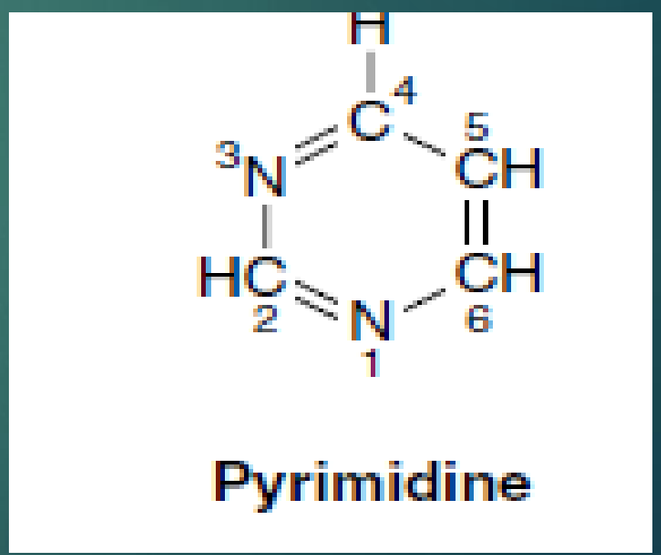
Purine and Pyrimidine Metabolism

BCH 305

PURINES AND PYRIMIDINES

Purines and pyrimidines are nitrogen-containing heterocyclic compounds whose rings contain both carbon and other elements (hetero atoms)





The Nitrogenous Bases

In DNA:
- Adenine
- Guanine
- *Thymine*
- Cytosine

In RNA:
- Adenine
- Guanine
- *Uracil*
- Cytosine

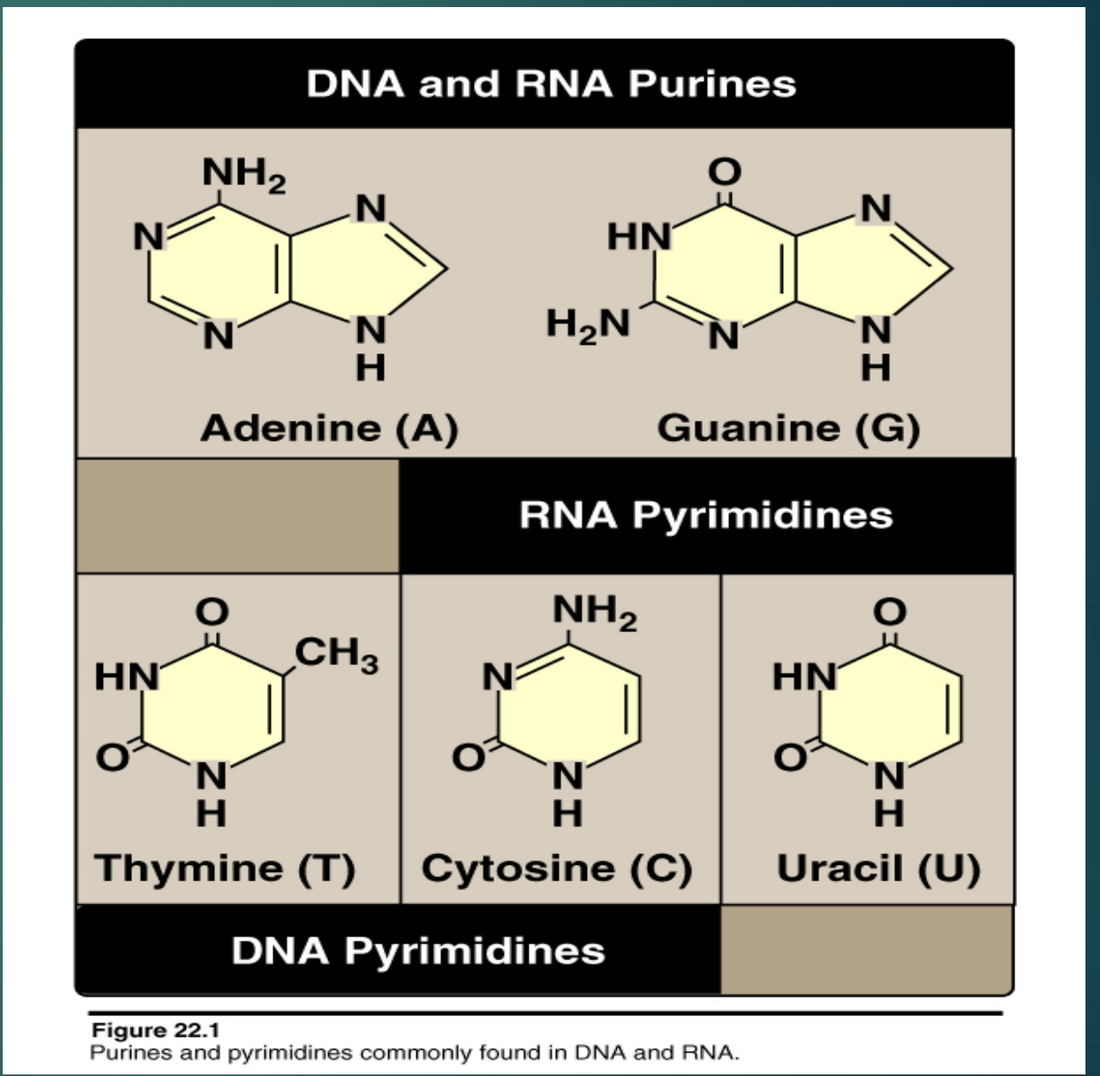


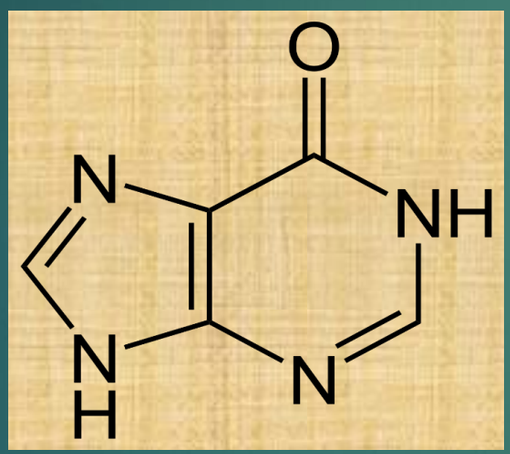
Figure 22.1
Purines and pyrimidines commonly found in DNA and RNA.

Purine chemical names

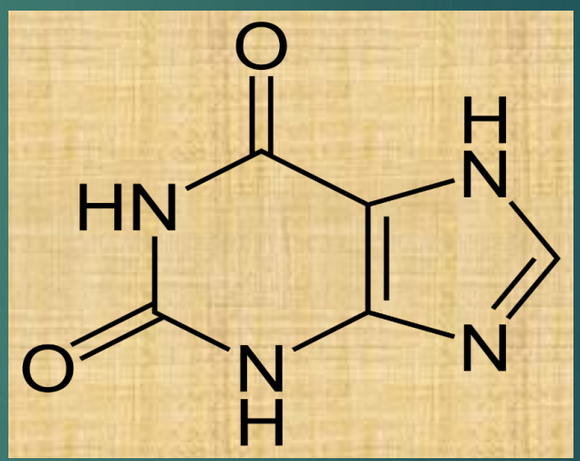
- Adenine = 6-amino purine
- Guanine = 2-amino-6-oxy purine
- Hypoxanthine = 6-oxy purine
- Xanthine = 2,6-dioxy purine
- Uracil = 2,4-dioxy pyrimidine
- Thymine = 2,4-dioxy-5-methyl pyrimidine
- Cytosine = 2-oxy-4-amino pyrimidine
- Orotic acid = 2,4-dioxy-6-carboxy pyrimidine

Important metabolic intermediates; not typically
found in either DNA or RNA.

Hypoxanthine

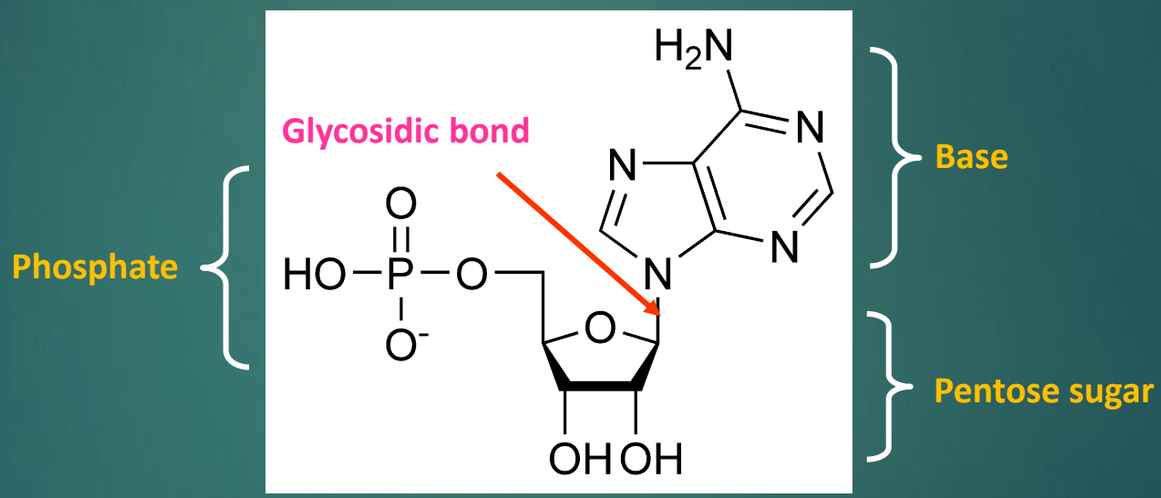


Xanthine



Nucleotides

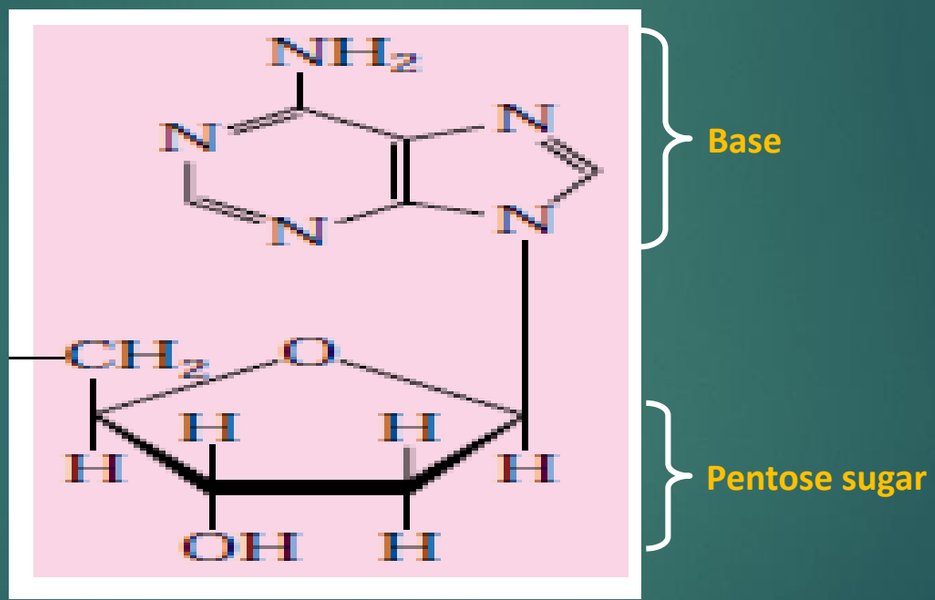
Chemical compound composed of three components: (1) heterocyclic or nitrogenous base; (2) sugar (pentose; ribose); and (3) one or more phosphate groups



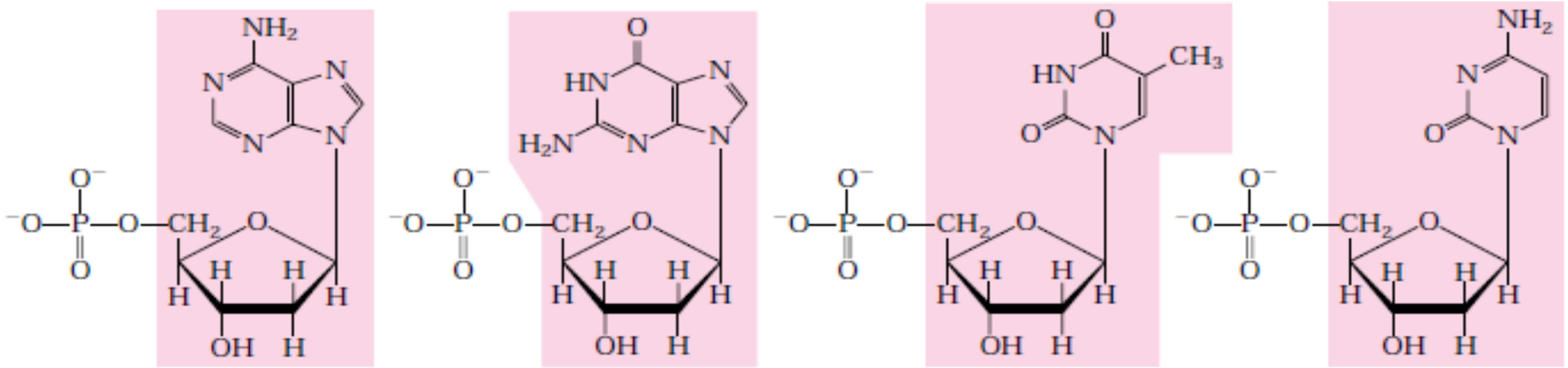
Adenosine monophosphate (AMP)

Nucleosides

Nucleosides are derivatives of purines and pyrimidines that have a sugar linked to a ring Nitrogen. The sugar can be ribose (ribonucleotides)or deoxyribose (deoxyribonucleosides).

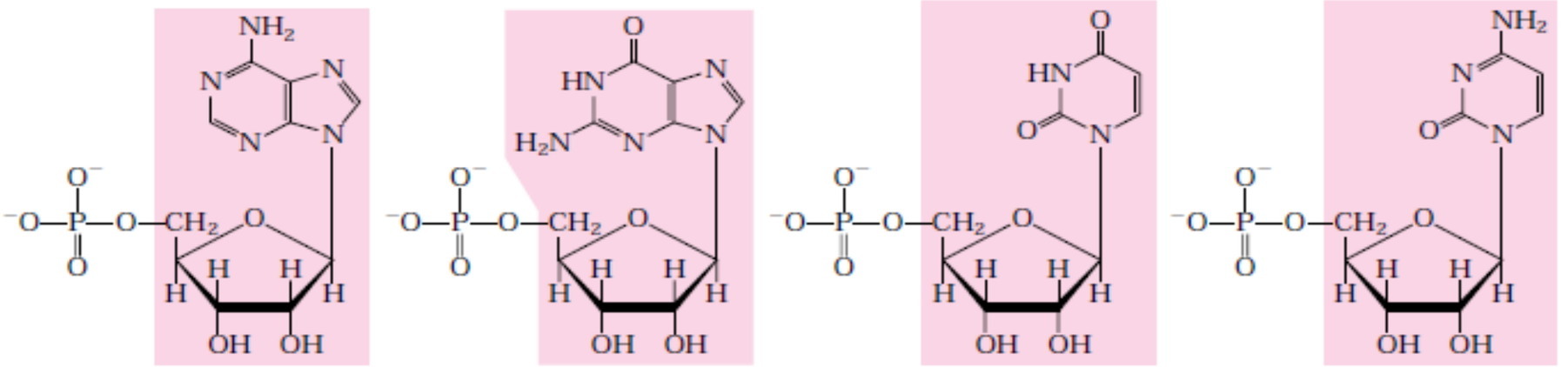


DEOXYADENOSINE



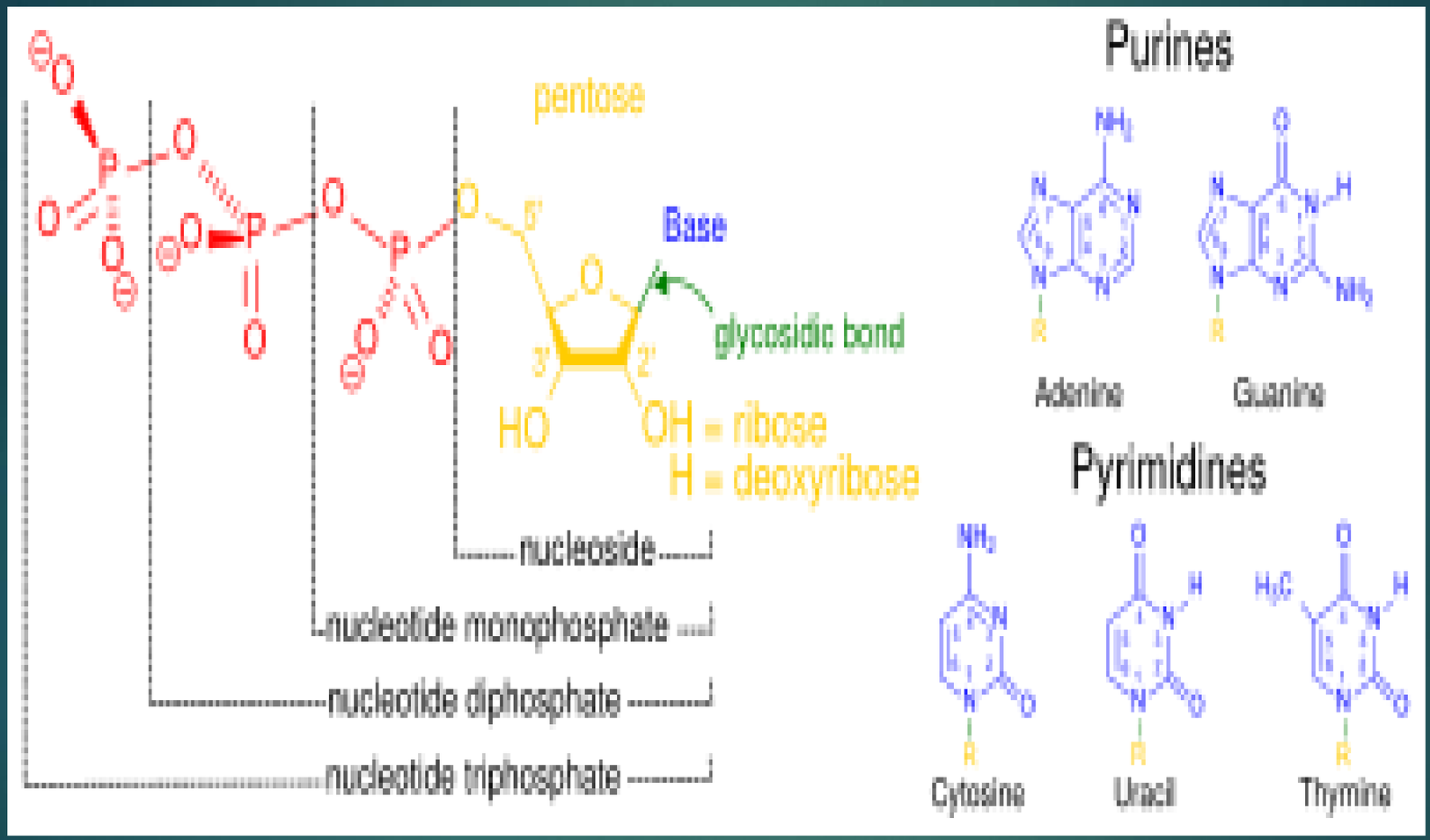
	Deoxyadenylate (deoxyadenosine 5′-monophosphate)	Deoxyguanylate (deoxyguanosine 5′-monophosphate)	Deoxythymidylate (deoxythymidine 5′-monophosphate)	Deoxycytidylate (deoxycytidine 5′-monophosphate)
Nucleotide:				
Symbols:	A, dA, dAMP	G, dG, dGMP	T, dT, dTMP	C, dC, dCMP
Nucleoside:	Deoxyadenosine	Deoxyguanosine	Deoxythymidine	Deoxycytidine

(a) Deoxyribonucleotides

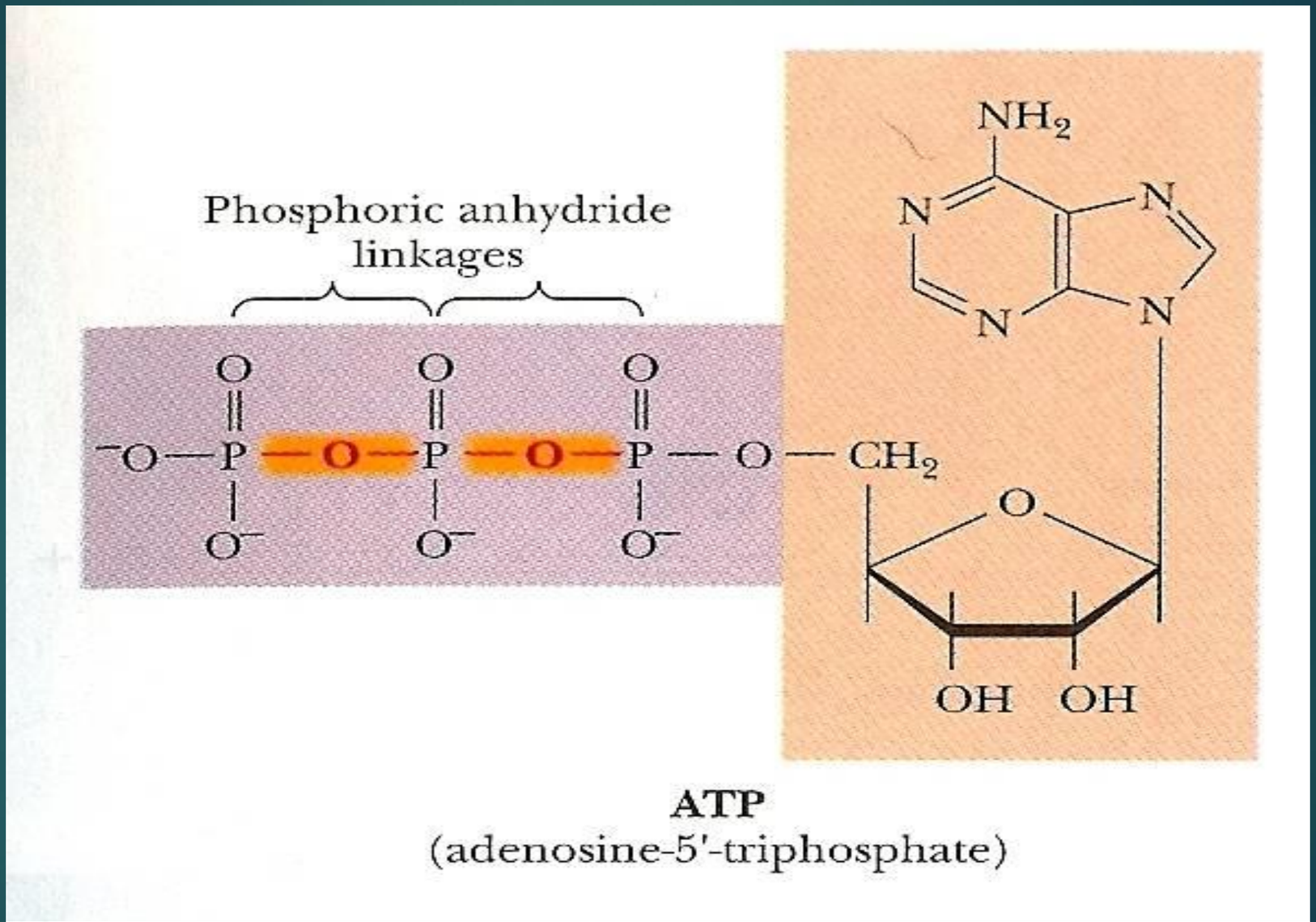


	Adenylate (adenosine 5′-monophosphate)	Guanylate (guanosine 5′-monophosphate)	Uridylate (uridine 5′-monophosphate)	Cytidylate (cytidine 5′-monophosphate)
Nucleotide:				
Symbols:	A, AMP	G, GMP	U, UMP	C, CMP
Nucleoside:	Adenosine	Guanosine	Uridine	Cytidine

(b) Ribonucleotides

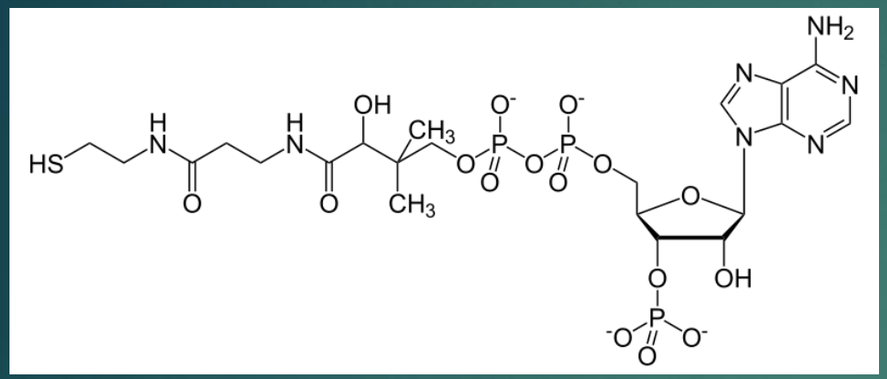

pentose
Base
glycosidic bond
HO
OH = ribose
H = deoxyribose
nucleoside
nucleotide monophosphate
nucleotide diphosphate
nucleotide triphosphate
Purines
Adenine
Guanine
Pyrimidines
Cytosine
Uracil
Thymine

Energy Currency

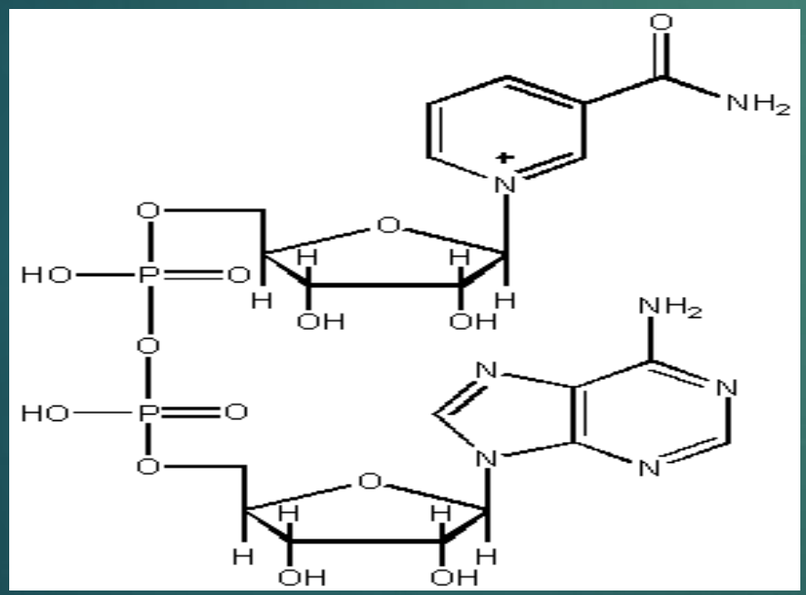


ATP
(adenosine-5'-triphosphate)

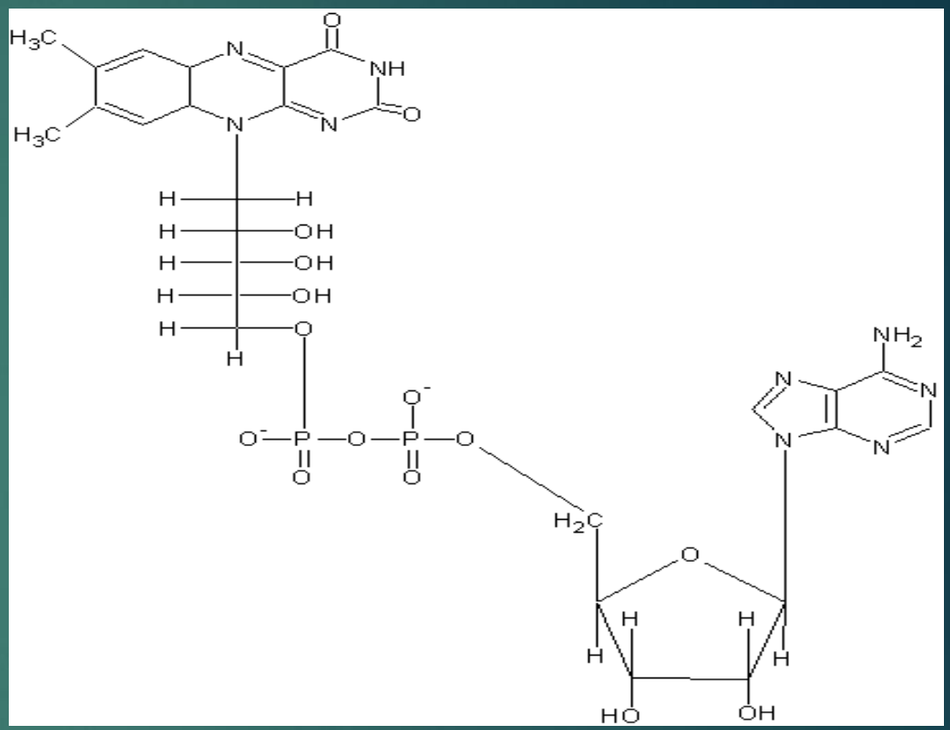
Structural Components of:



Coenzyme A

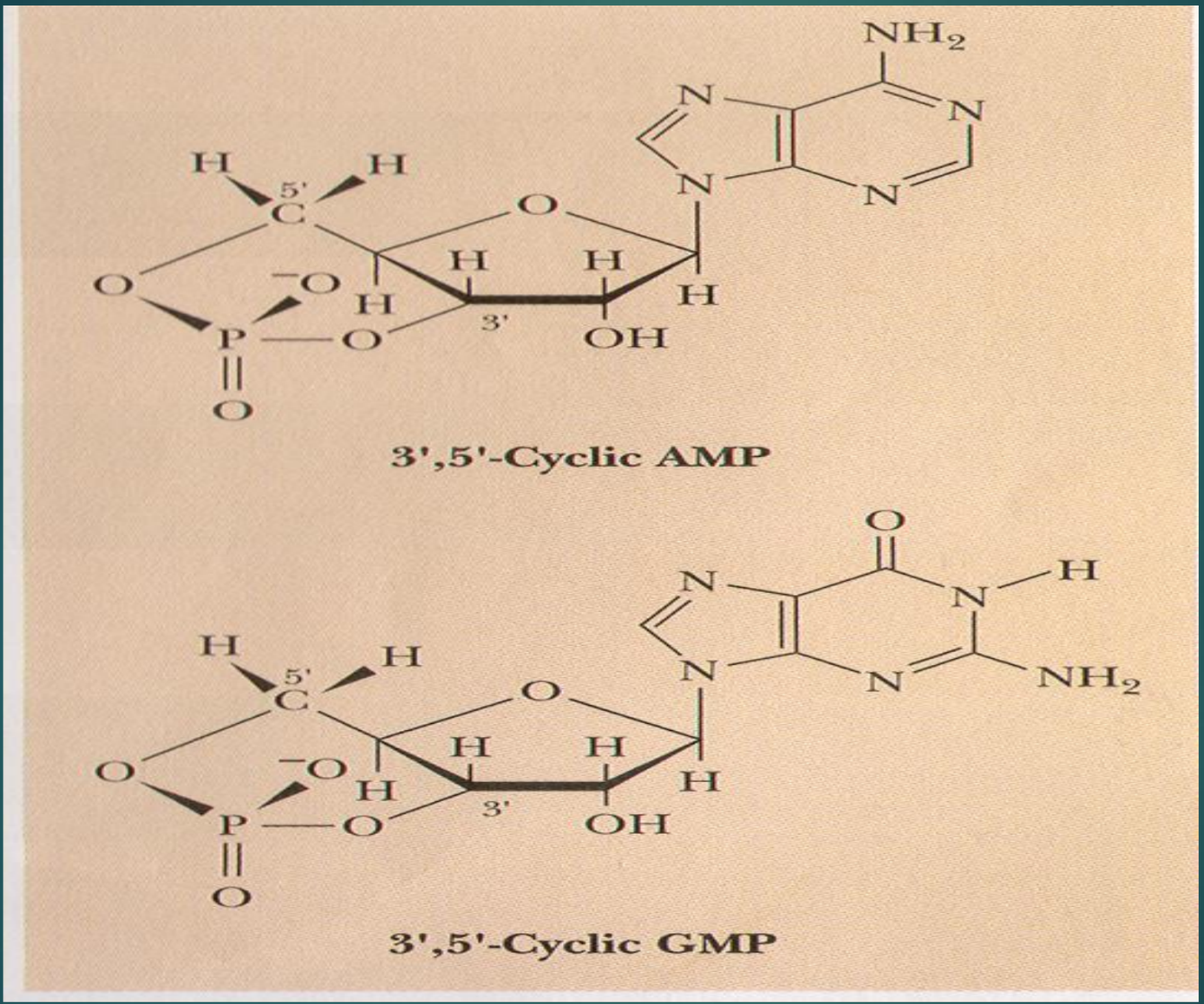


NAD(P)+



Flavin adenine dinucleotide (FAD)

Signaling Molecules

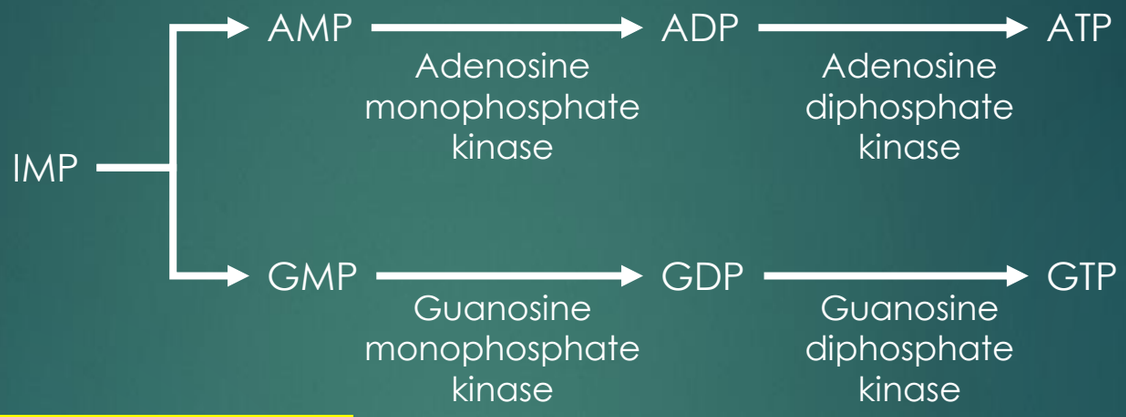


Purine synthesis

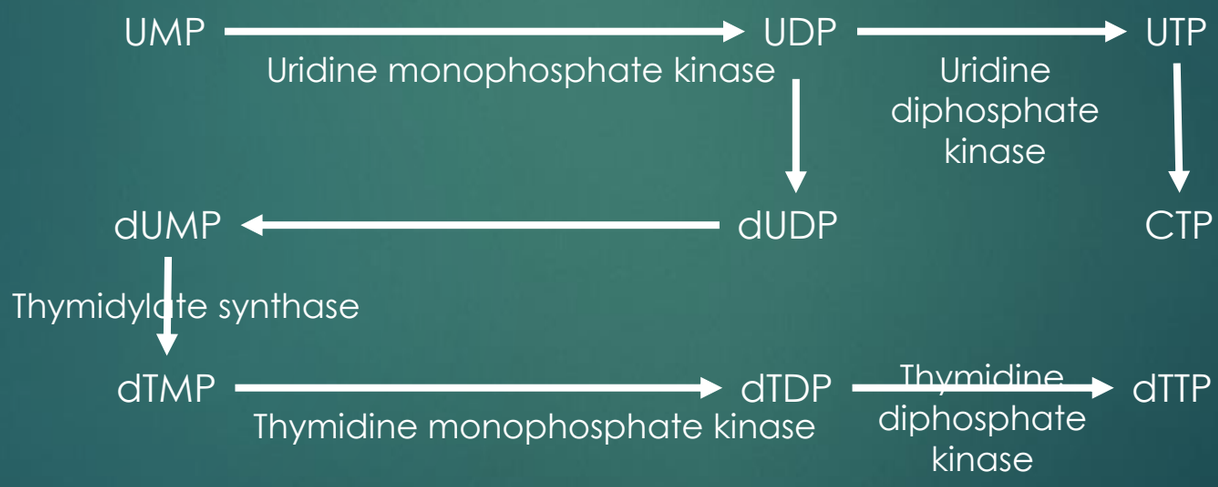
Purine Synthesis

- Two ways:
  - ***De Novo* Pathway**: means from scratch; nucleotide bases are produced from simpler compounds
    - Purines: base is synthesized in segments, in order, directly onto the ribose structure
    - Pyrimidines: base is synthesized first and then assembled onto the ribose structure
  - **Salvage Pathway**: "a process whereby a metabolite is reutilized for biosynthesis of a compound from which the metabolite was derived"

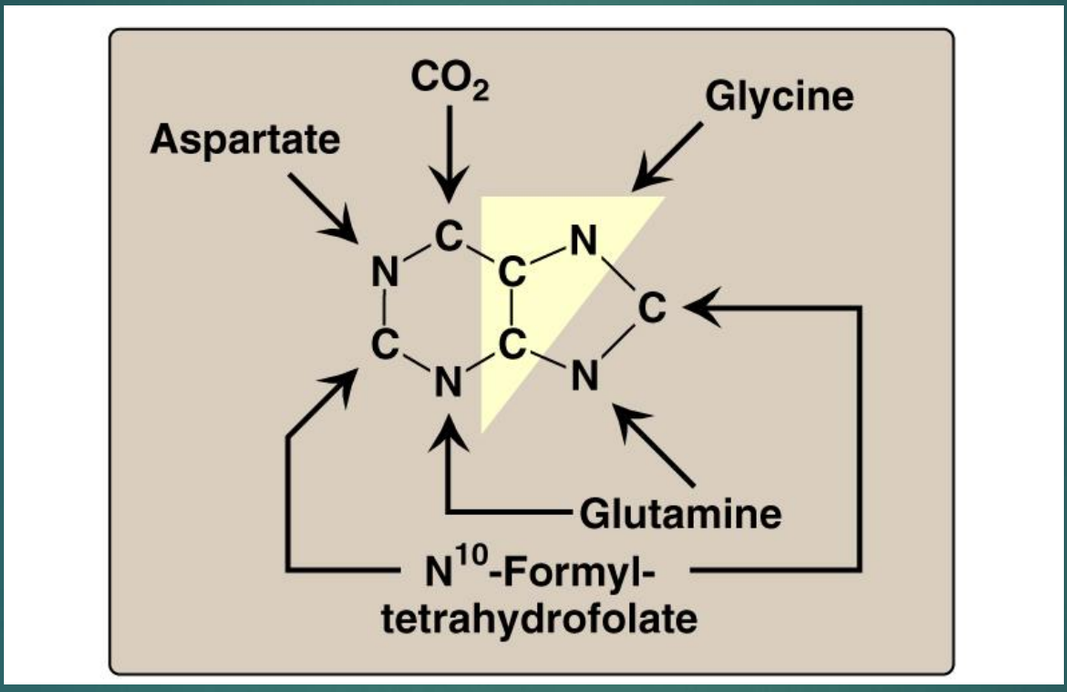
De novo purine synthesis



De novo pyrimidine synthesis



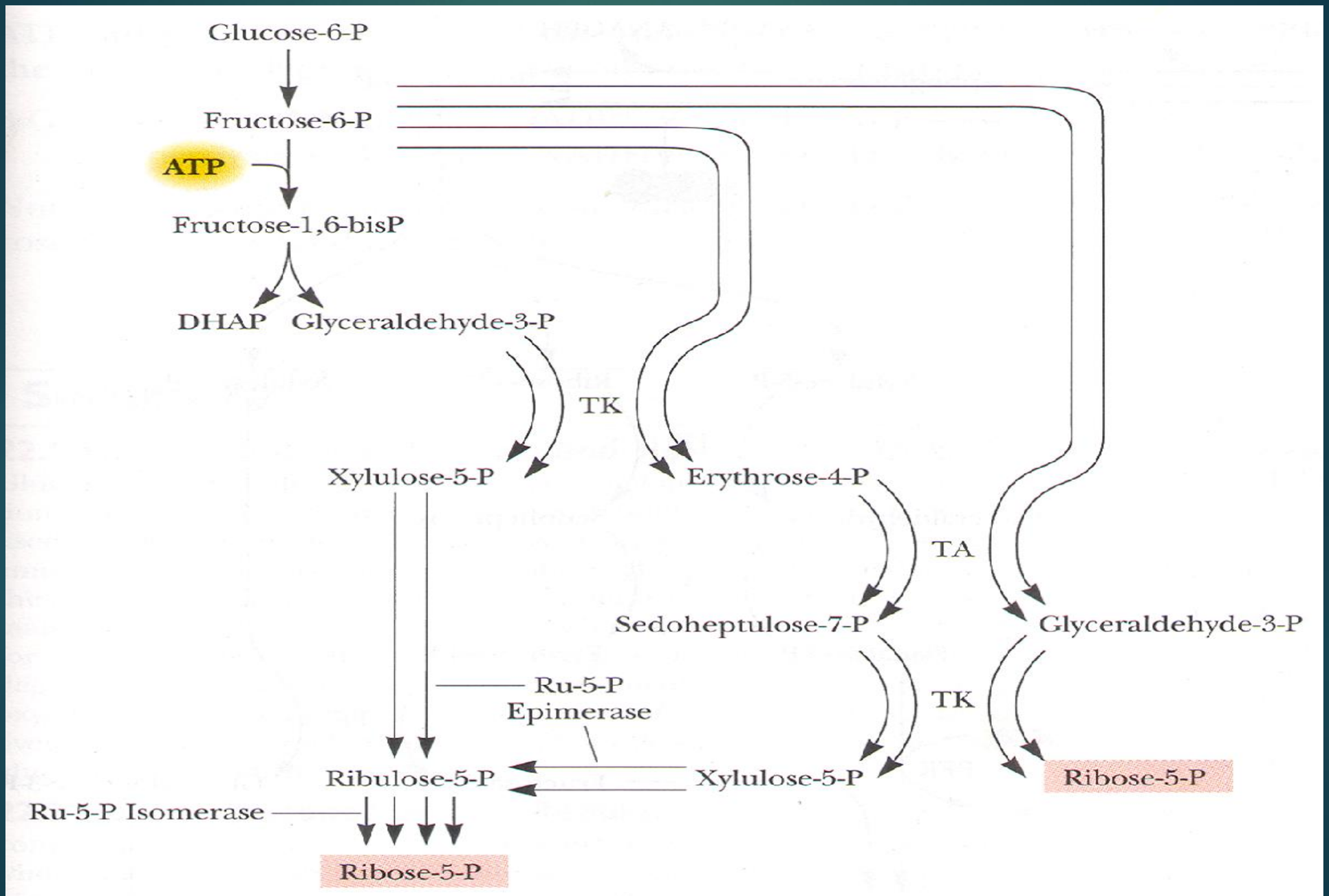
De novo purine synthesis



De novo purine synthesis

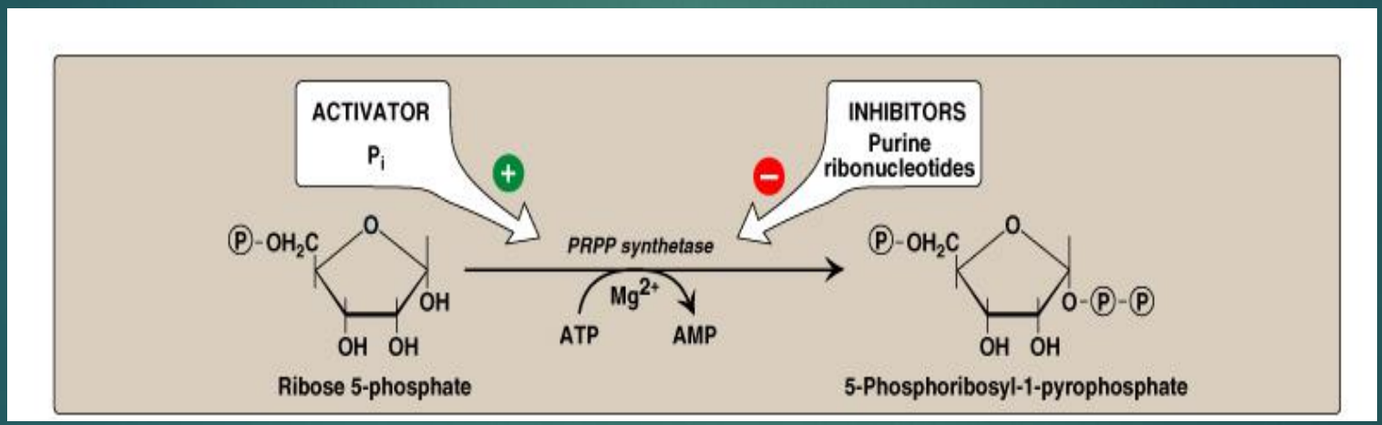
- Purine ring: synthesized by a series of 12 reactions; carbon and nitrogen atoms added to a pre-formed ribose-5-phosphate.
- Ribose-5-phosphate: Hexose MonoPhosphate Pathway.
- In humans: enzymes found in the cytoplasm of the cell.

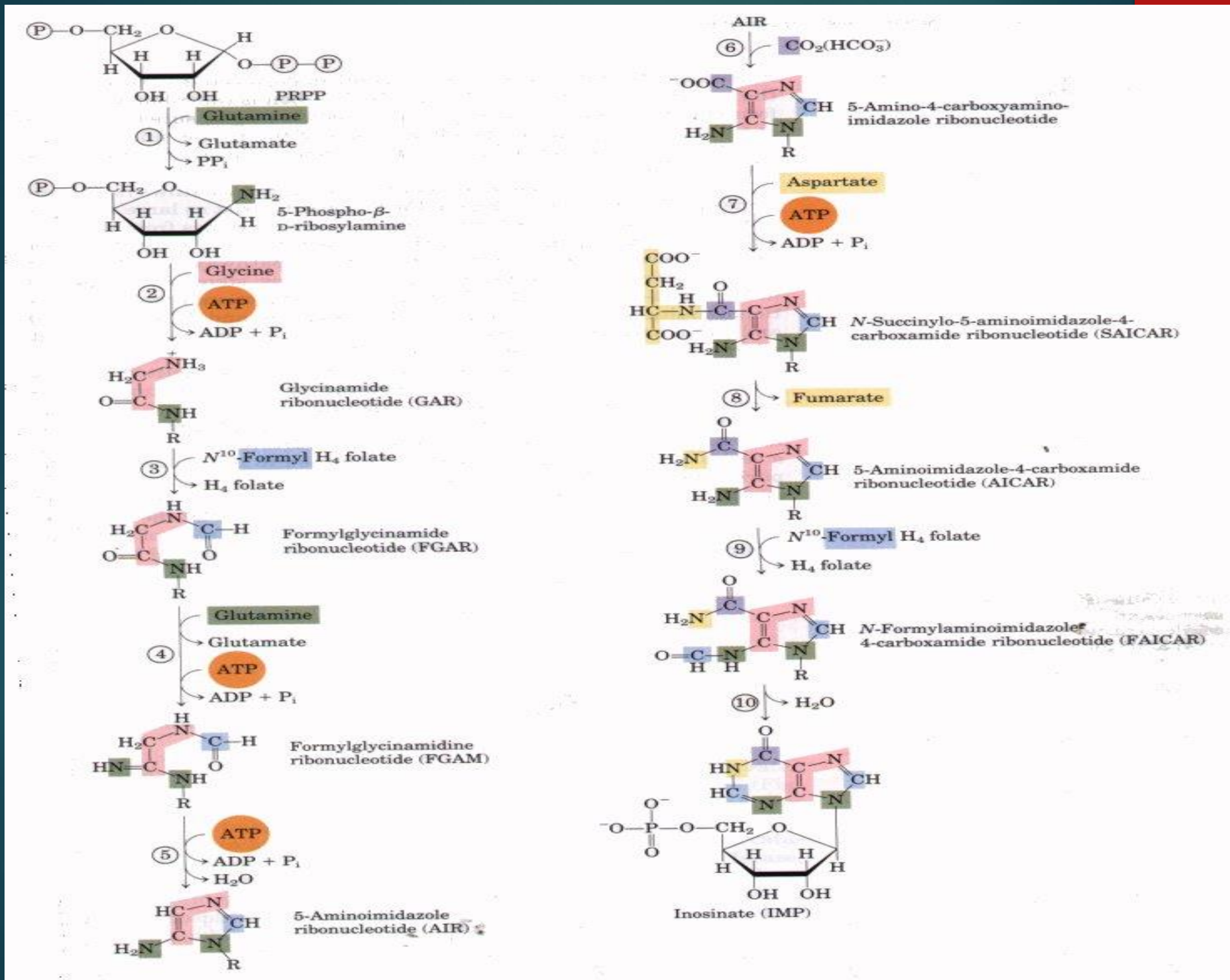
Source For Ribose-5-Phosphate

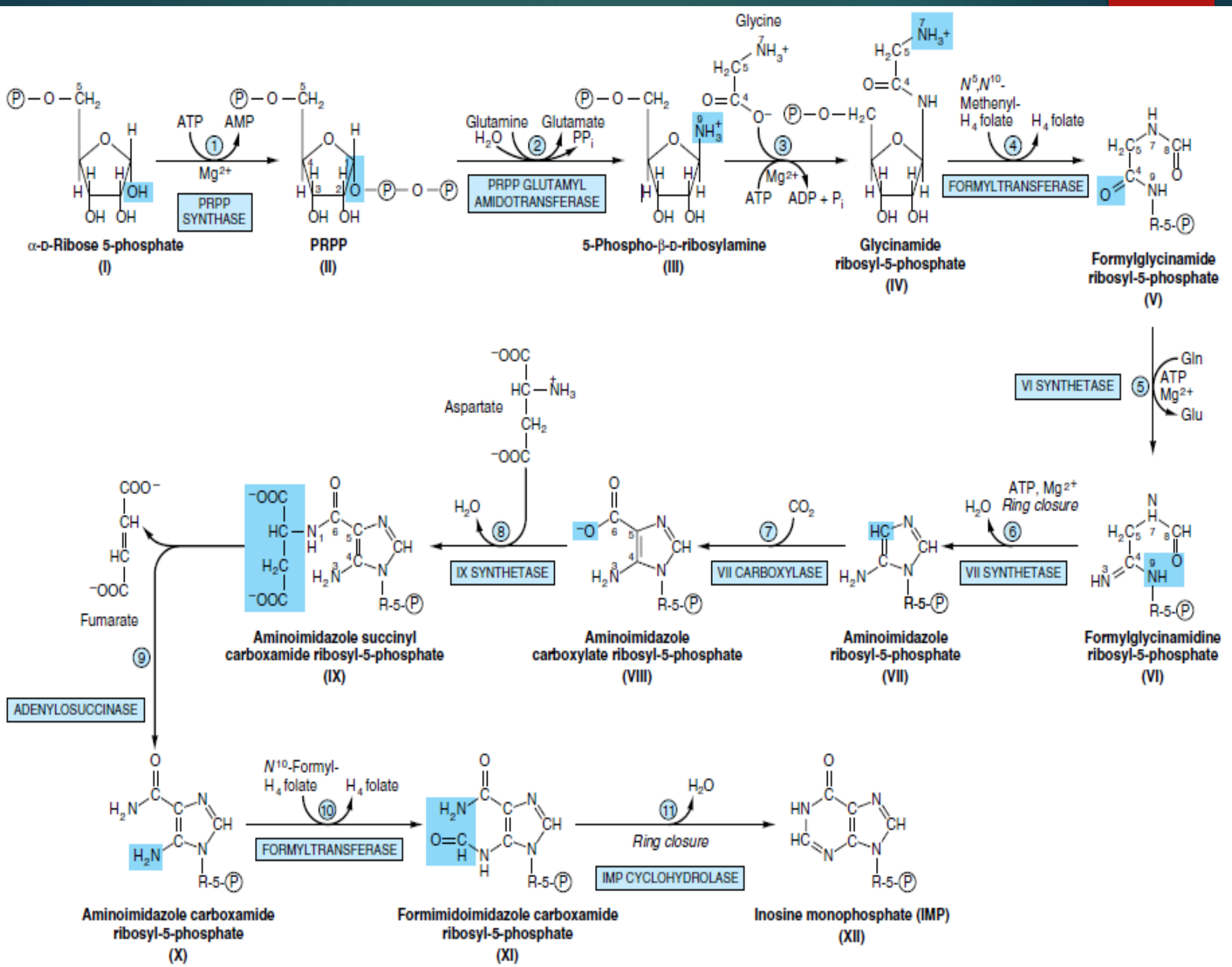


Conversion of Ribose-5-phosphate to PRPP

- Ribose: Pentose sugar; may be reduced to deoxyribose (DNA).
- 5-Phosphoribosyl-1-pyrophosphate (PRPP): also involved in pyrimidine synthesis, NAD^+, and histidine biosynthesis.




PRPP
Glutamine
Glutamate
PPi
5-Phospho-β-D-ribosylamine
Glycine
ATP
ADP + Pi
Glycinamide ribonucleotide (GAR)
N10-Formyl H4 folate
H4 folate
Formylglycinamide ribonucleotide (FGAR)
Glutamine
Glutamate
ATP
ADP + Pi
Formylglycinamidine ribonucleotide (FGAM)
ATP
ADP + Pi
H2O
5-Aminoimidazole ribonucleotide (AIR)
AIR
CO2(HCO3−)
5-Amino-4-carboxyamino-imidazole ribonucleotide
Aspartate
ATP
ADP + Pi
N-Succinylo-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)
Fumarate
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)
N10-Formyl H4 folate
H4 folate
N-Formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
H2O
Inosinate (IMP)


α-D-Ribose 5-phosphate
(I)
ATP
AMP
Mg2+
PRPP SYNTHASE
PRPP
(II)
Glutamine
H2O
Glutamate
PPi
PRPP GLUTAMYL AMIDOTRANSFERASE
Glycine
5-Phospho-β-D-ribosylamine
(III)
ATP
ADP + Pi
Glycinamide ribosyl-5-phosphate
(IV)
N5,N10-Methenyl-H4 folate
H4 folate
FORMYLTRANSFERASE
Formylglycinamide ribosyl-5-phosphate
(V)
VI SYNTHETASE
Gln
ATP
Mg2+
Glu
Formylglycinamidine ribosyl-5-phosphate
(VI)
ATP, Mg2+
Ring closure
H2O
VII SYNTHETASE
Aminoimidazole ribosyl-5-phosphate
(VII)
CO2
VII CARBOXYLASE
Aminoimidazole carboxylate ribosyl-5-phosphate
(VIII)
Aspartate
H2O
IX SYNTHETASE
Aminoimidazole succinyl carboxamide ribosyl-5-phosphate
(IX)
Fumarate
ADENYLOSUCCINASE
N10-Formyl-H4 folate
H4 folate
FORMYLTRANSFERASE
Aminoimidazole carboxamide ribosyl-5-phosphate
(X)
H2O
Ring closure
IMP CYCLOHYDROLASE
Formimidoimidazole carboxamide ribosyl-5-phosphate
(XI)
Inosine monophosphate (IMP)
(XII)

Purine Salvage Pathway

- From normal turnover of cellular nucleic acids
- Obtained from the diet
- Reutilization of adenine, hypoxanthine, and guanine
  - Two enzymes:
    - 1. Adenine phosphoribosyltransferase
    - 2. Hypoxanthine-guanine phosphoribosyltransferase

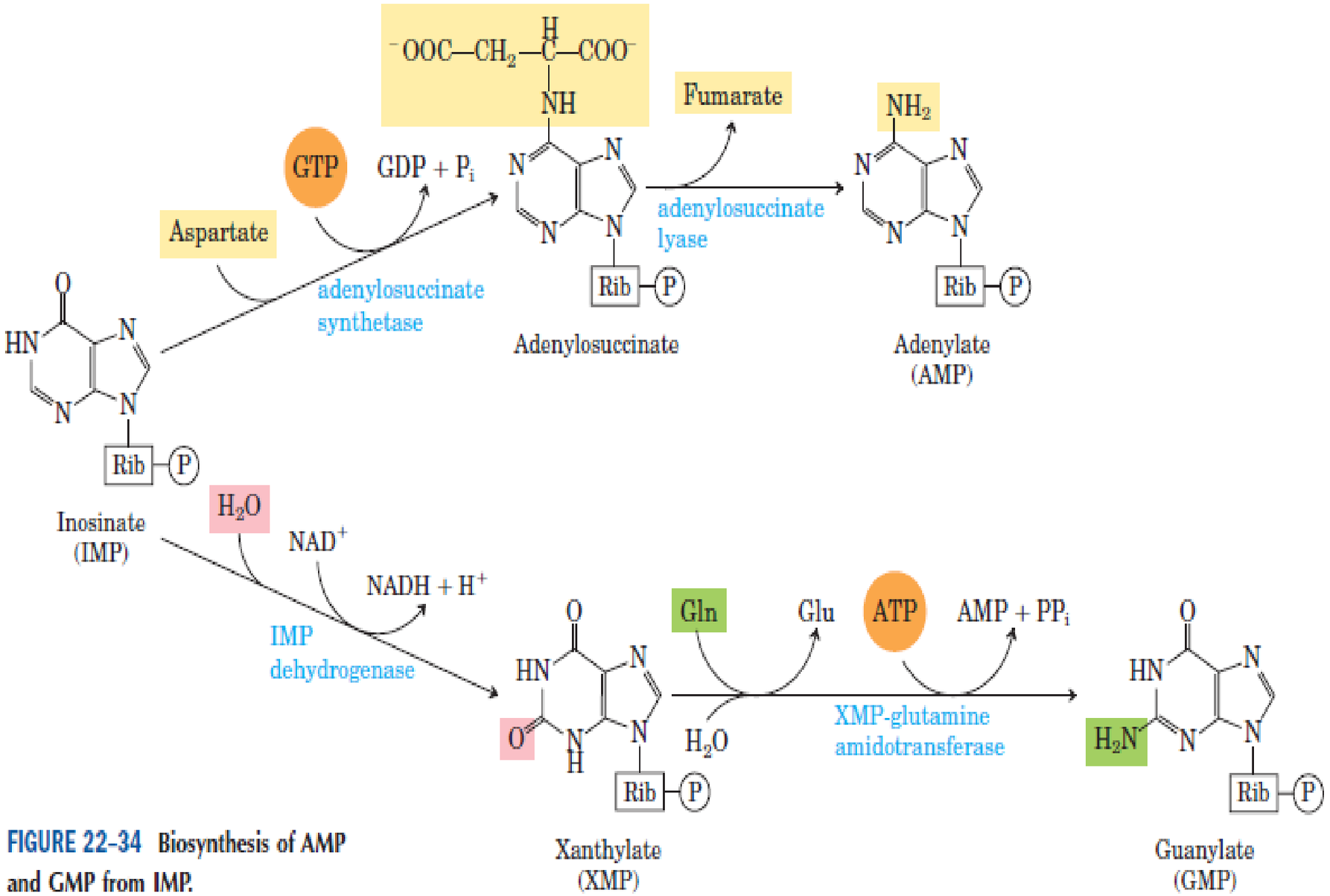
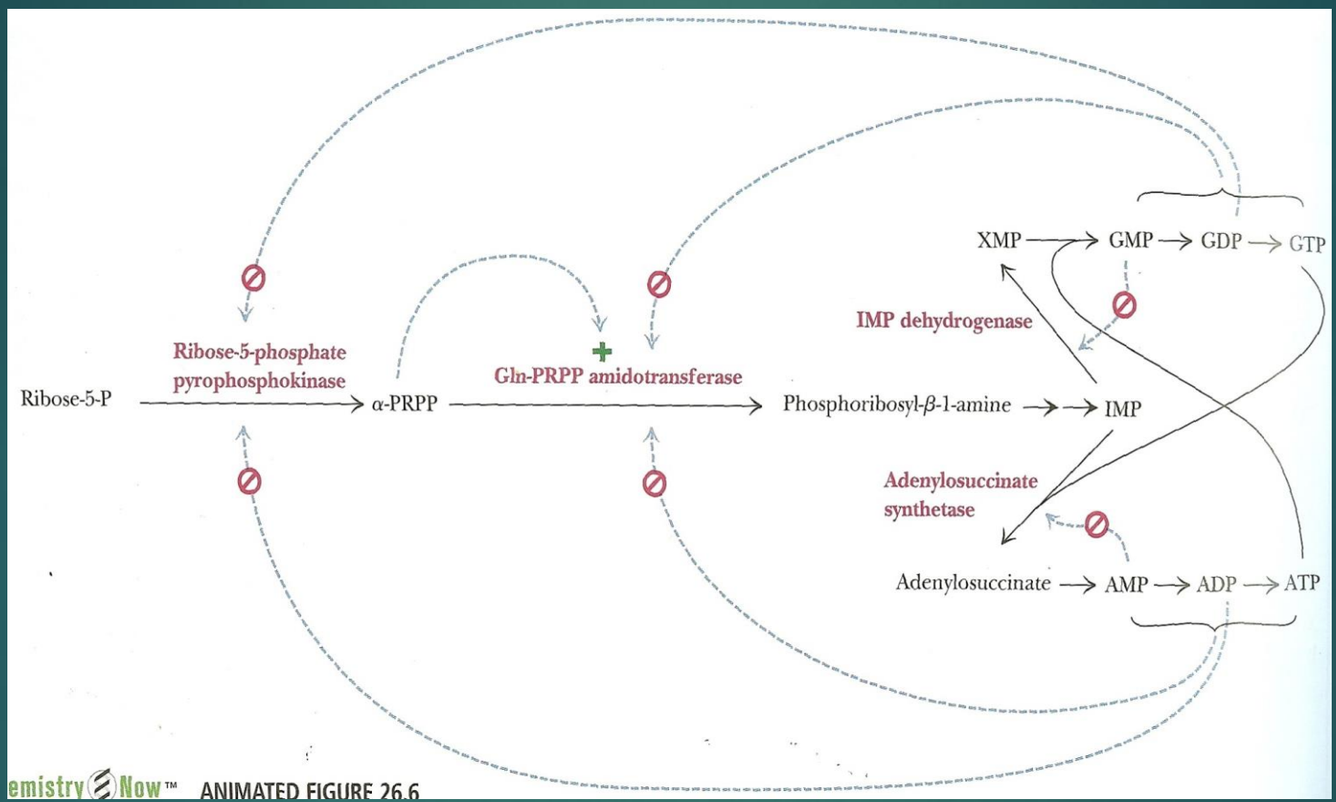


FIGURE 22-34 Biosynthesis of AMP and GMP from IMP.

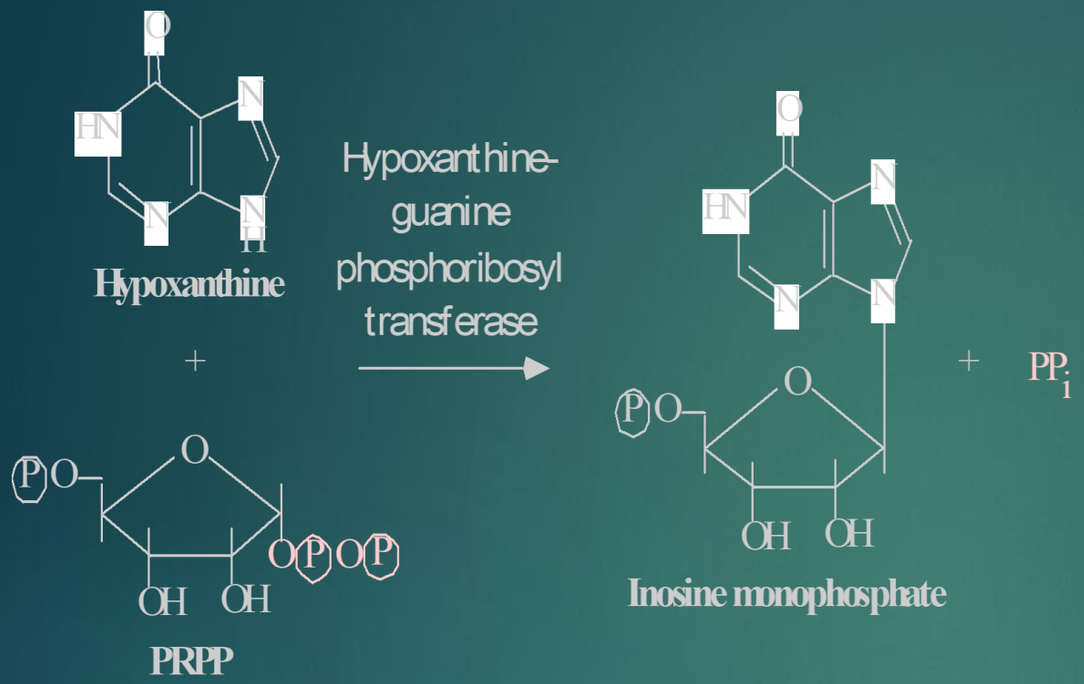
Regulation

- KEY: Feedback Inhibition
  - Purine biosynthesis: 3 sites:
    - 1) glutamine phosphoribosyl amidotransferase
    - 2) the reactions leading away from inosinate
    - 3) the reciprocal substrate relationship between GTP and ATP

Another Look at Regulation



Lesch-Nyhan Syndrome



- Build up of hypoxanthine and guanine
- Degradation of hypoxanthine and guanine results in increased uric acid
- Excess uric acid in urine often results in orange crystals in the diaper of affected children
- Severe mental retardation
- Self-mutilation
- Involuntary movements
- Gout

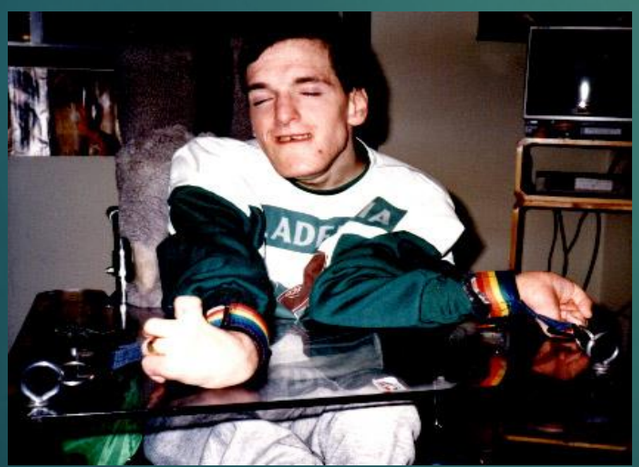
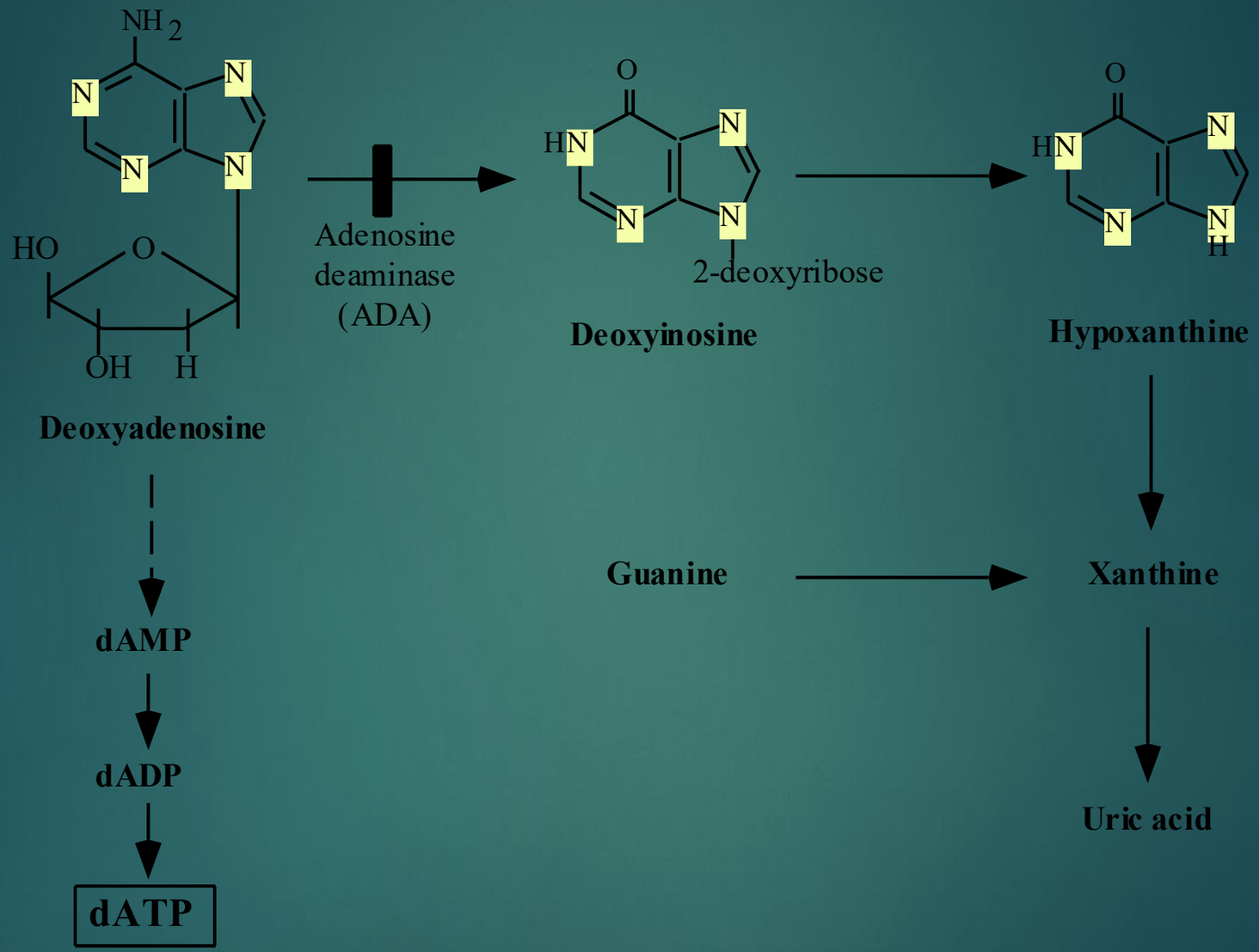
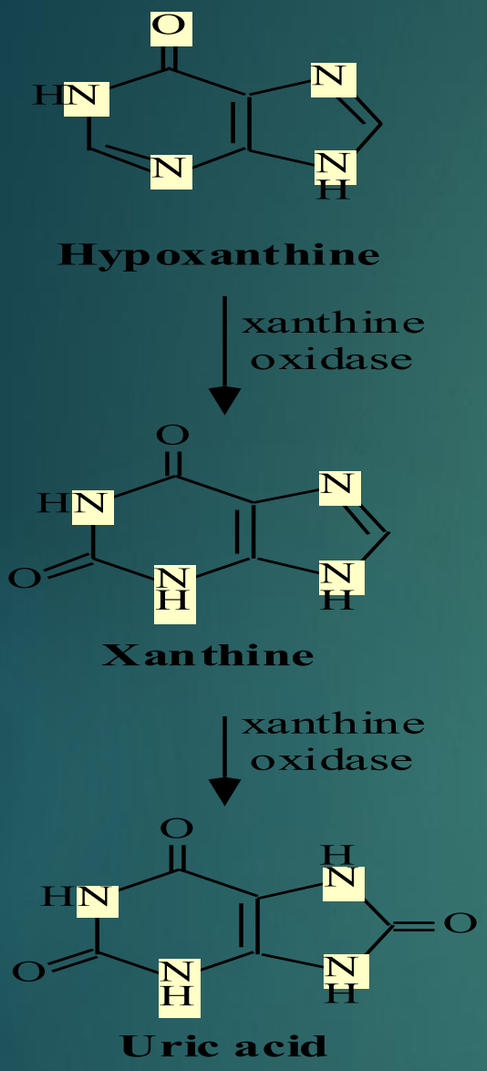


Figure 22.11
Lesions on the lips of Lesch-Nyhan patients caused by self-mutilation.

Adenosine Deaminase Deficiency:





Gout: deposition of urate crystals in joints, "tophi" in cooler periphery

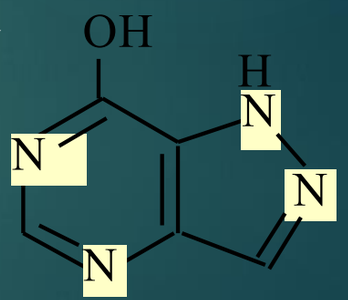
Hyperuricemia can be caused by:

Accelerated degradation of purines:

- Accelerated synthesis of purines
- Increased dietary intake of purines

Impaired renal clearance of uric acid

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:



Allopurinol

The hands of a patient with a long history of gout, including high serum urate levels

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Purine Biosynthesis Summary:

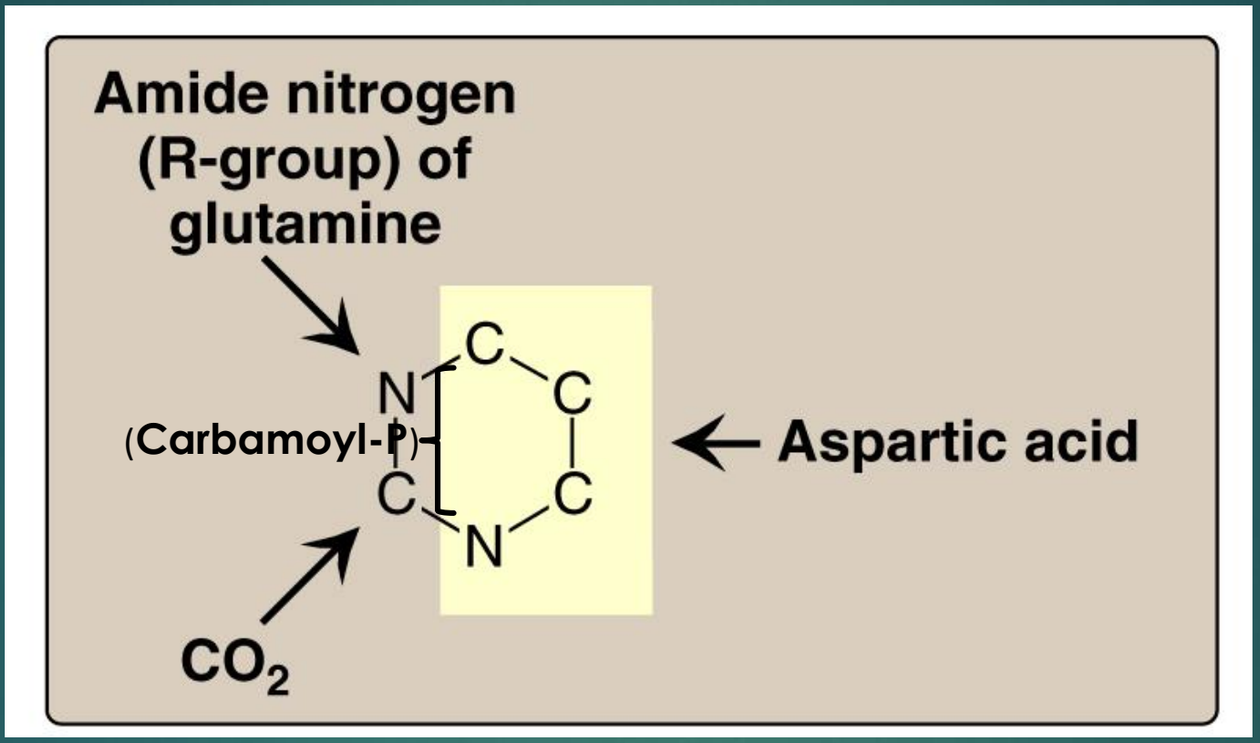
1. Sulfonamides inhibit purine synthesis in bacteria by interfering with folate synthesis.
2. Methotrexate inhibits dihydrofolate reductase.
3. IMP, end product of *de novo* purine synthesis.
4. AMP, GMP, and IMP inhibit; PRPP is an activator.
5. Rate limiting step of the pathway and source of atoms for the purine ring.
6. Requires 4 ATP molecules.

Pyrimidine synthesis

Pyrimidine Synthesis

- Pyrimidine ring: completely synthesized, then attached to a ribose-5-phosphate donated by PRPP

- Source of carbons and nitrogens less diverse than purines.

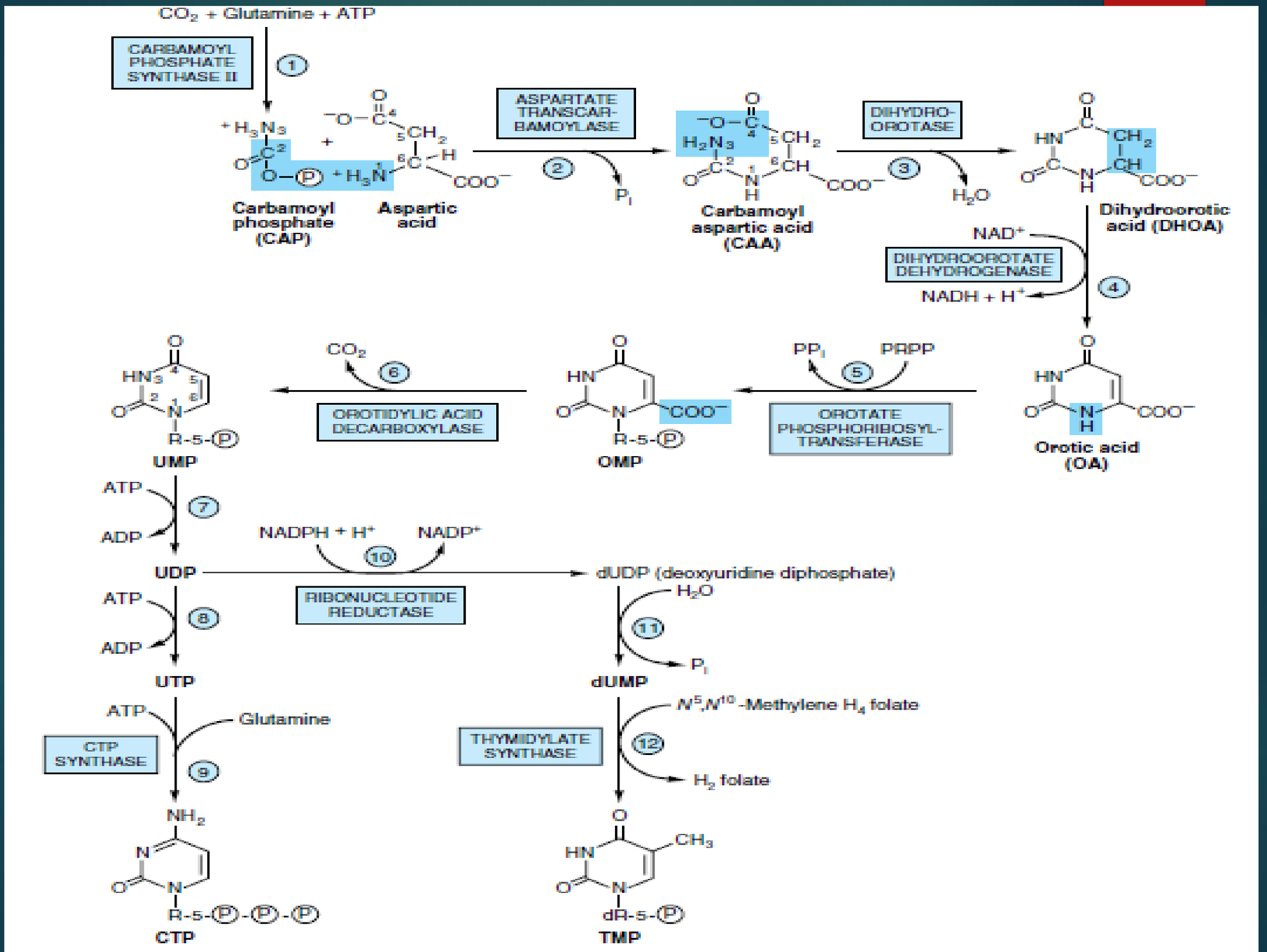

Amide nitrogen
(R-group) of
glutamine
(Carbamoyl-P)
Aspartic acid
CO_2

Pyrimidine synthesis

- Carbamoyl-phosphate synthetase II, Aspartate transcarbamoylase, Dihydroorotase, i.e. the ***CAD Complex*** (in mammals); located on the outer face of the inner mitochondrial membrane.

- Orotate phosphoribosyltransferase and Orotidylate decarboxylase, i.e., the

  UMP Synthase


CO_2 + Glutamine + ATP
CARBAMOYL PHOSPHATE SYNTHASE II
1
Carbamoyl phosphate (CAP)
Aspartic acid
ASPARTATE TRANSCAR-BAMOYLASE
2
P_i
Carbamoyl aspartic acid (CAA)
DIHYDRO-OROTASE
3
H_2O
Dihydroorotic acid (DHOA)
NAD^+
DIHYDROOROTATE DEHYDROGENASE
$NADH + H^+$
4
Orotic acid (OA)
PP_i
PRPP
5
OROTATE PHOSPHORIBOSYL-TRANSFERASE
OMP
CO_2
6
OROTIDYLIC ACID DECARBOXYLASE
UMP
ATP
ADP
7
UDP
8
UTP
ATP
Glutamine
CTP SYNTHASE
9
CTP
$NADPH + H^+$
$NADP^+$
10
RIBONUCLEOTIDE REDUCTASE
dUDP (deoxyuridine diphosphate)
H_2O
11
P_i
dUMP
N^5,N^{10}-Methylene H_4 folate
THYMIDYLATE SYNTHASE
12
H_2 folate
TMP

Regulation

- KEY: Feedback Inhibition
  - Pyrimidine Biosynthesis
    - In bacteria: **Aspartate Transcarbamoylase**
    - In both prokaryotes and eukaryotes: **Carbamoyl phosphate synthetase**

Pyrimidine Biosynthesis summary

1. CPSII, aspartate transcarbamoylase, and dihydroorotase are three enzymatic functions in one protein.
2. Orotate phosphoribosyltransferase and OMP decarboxylase are two enzymatic functions in one protein; deficiency = Orotic Aciduria.
3. Orotate, 1st pyrimidine base made, then attached to a PRPP.

Basis for Deoxyribonucleotide synthesis

- High [ATP]
  - plenty of energy, make DNA
  - activation of ribonucleotide reductase is active (ON)
- ATP
  - in specificity site S favors CDP or UDP in catalytic site C → [dCDP] and [dUDP] ↑
- dCDP and dUDP become metabolized to dTTP
- [dTTP]↑, occupies specificity site favoring GDP in catalytic site; [dGP]↑ → [dGTP]↑
- [dGTP]↑,occupies specificity site, favors ADP in catalytic site, [dADP]↑ → replace ATP in activity site and turn enzyme off