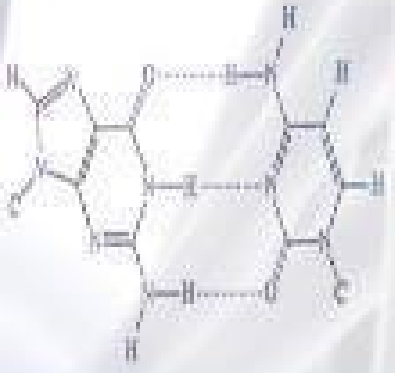
Medical Committee
The University of Jordan

SLIDE SHEET

SLIDE : 23

DR.NAME: Dr. Nayef

Biochemistry



Majida Al-Foqaraa'

NUCLEOTIDE METABOLISM

Nucleotides are essential :-

- DNA + RNA — protein synthesis
- Energy currency
- Carriers & activated intermediates
- Components & essential cofactors: CoA, FAD, NAD^+, $NADP^+$
- Regulatory compounds cAMP, ATP, cGMP

Synthesis :-

I → **De novo synthesis**

II → **Salvage pathway :-**

III → Degradation of Nucleotides (DNA & RNA) in G.I.T → bases & nucleoside (little only) → blood
→ Uric acid

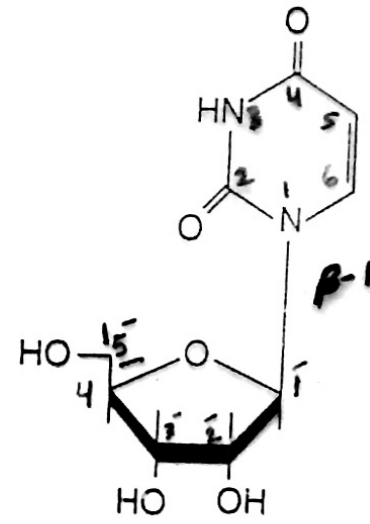
Pyrimidine Nucleosides

- major Pyrimidine nucleotides are those of Uracil & cytosine, thymine.

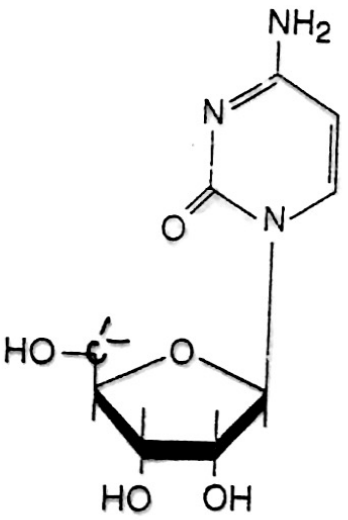
β-N-Glycosidic bond
- Stable to Alkali
- stable to Acid treatment
- 60% PCA +100°C release bases

Nucleotides (more polar) more soluble than nucleosides & free bases

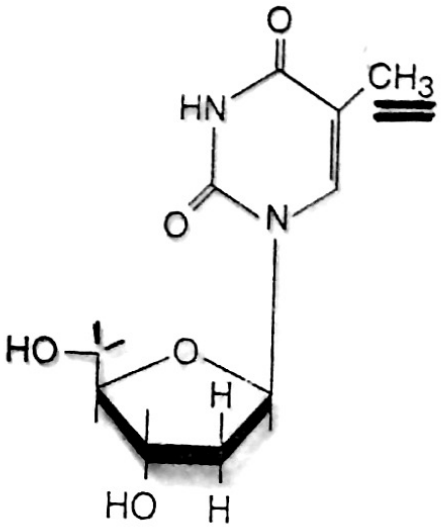
Nucleosides are more stable than free bases



Uridine

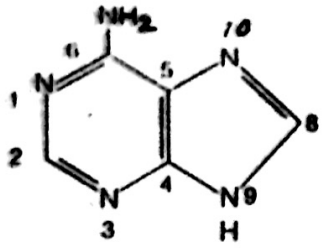


Cytidine

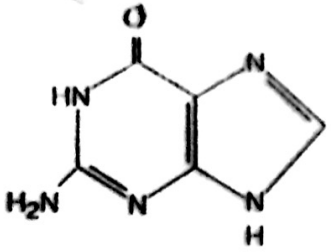


Thymidine

Chemistry of Nucleotides:-

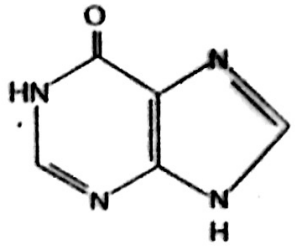


Adenine

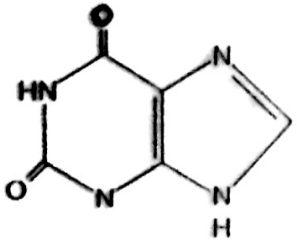


Guanine

3 major

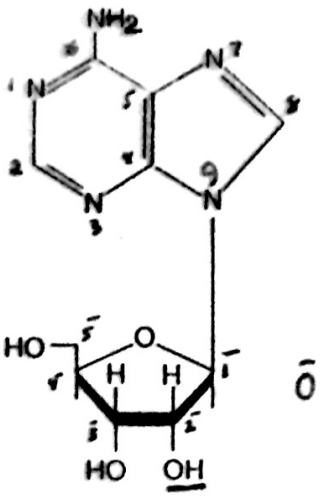


Hypoxanthine

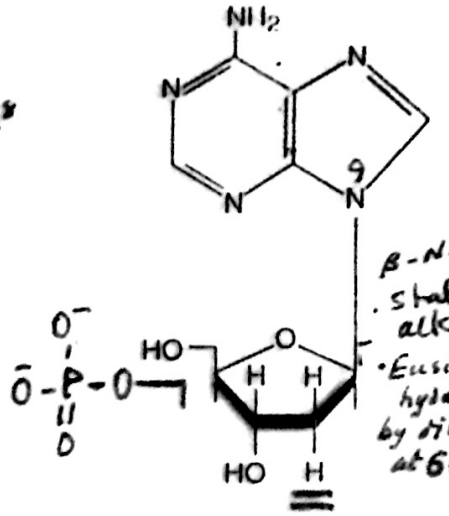


Xanthine

FIGURE 12.1
Purine bases.



Adenosine



Deoxyadenosine

β-N-Glycosidic
· Stable to alkali
· Easily hydrolyzed by dil. acid at 60°C + above

FIGURE 12.2
Adenosine and deoxyadenosine.

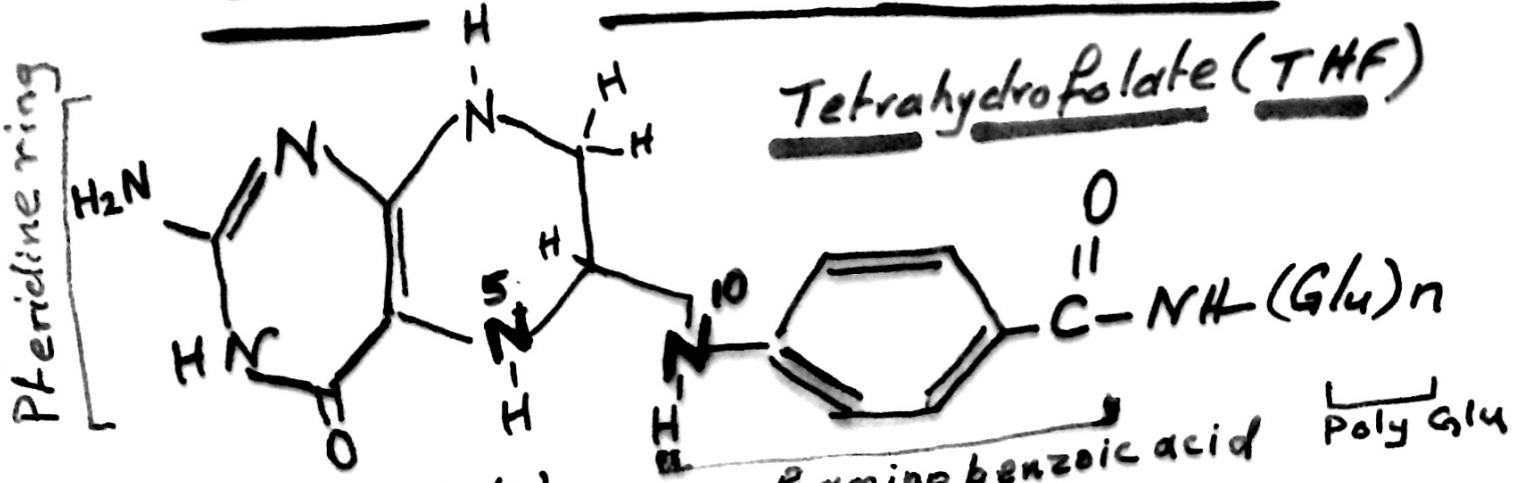
Nucleotides

- Di & tri-phosphates more than mono-, nucleosides & free bases
- ATP is found highest
- Conc. varies with cell type.
- Ribo nucleotides > Deoxy-

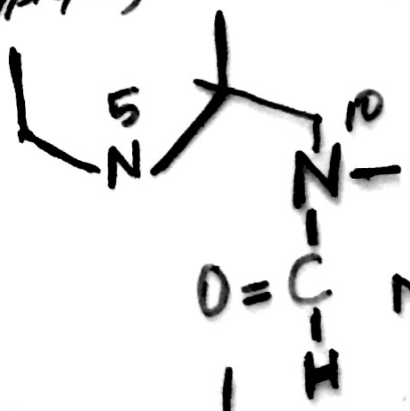
Absorption of light in U.V. at 260nm
Purine derivatives have stronger absorption than pyrimidine derivatives

One-Carbon Unit Carried by THF

Tetrahydrofolate (THF)

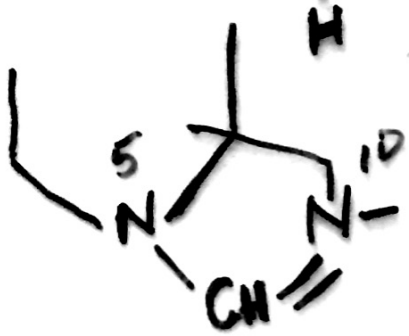


Formate (from tryptophan) + THF → Purines



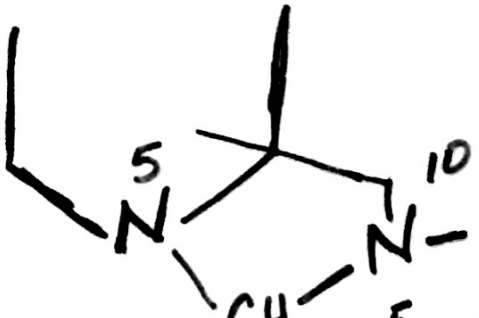
N^{10}-Formyl-THF

Histidine + THF →



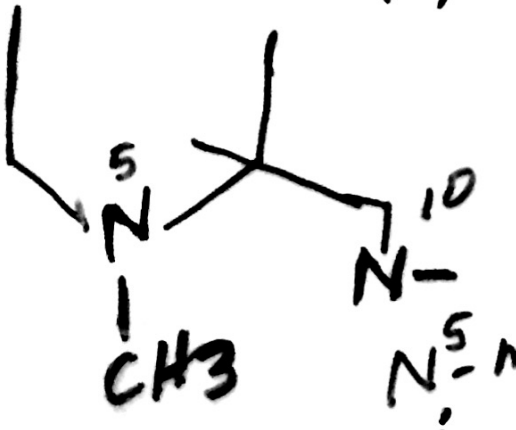
N^5, N^{10}-methenyl-THF

Glycine
Serine
+
THF



→ TMP (from dUMP)

N^5, N^{10}-methylene-THF

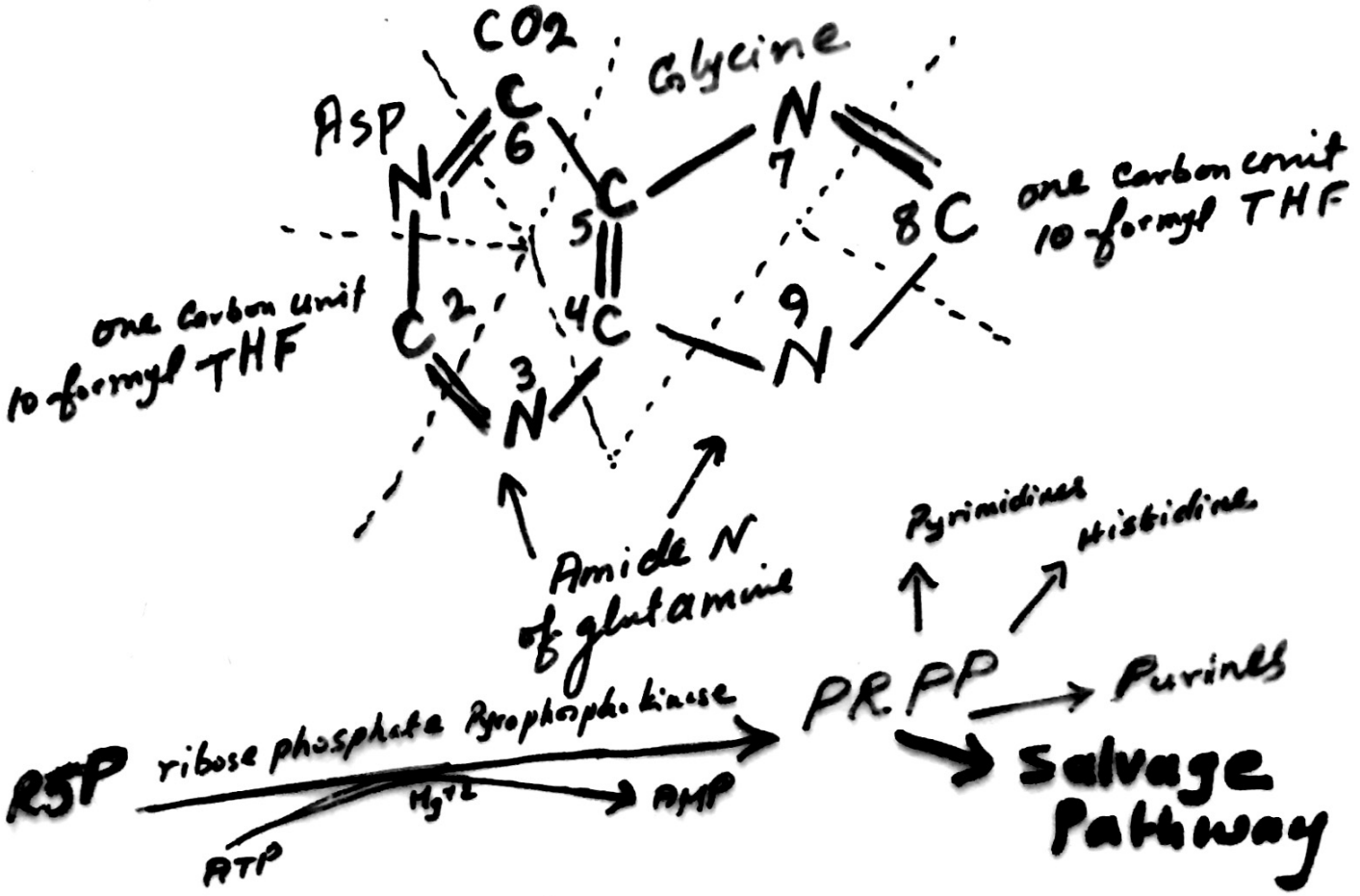


→ Methionine (from homocysteine)

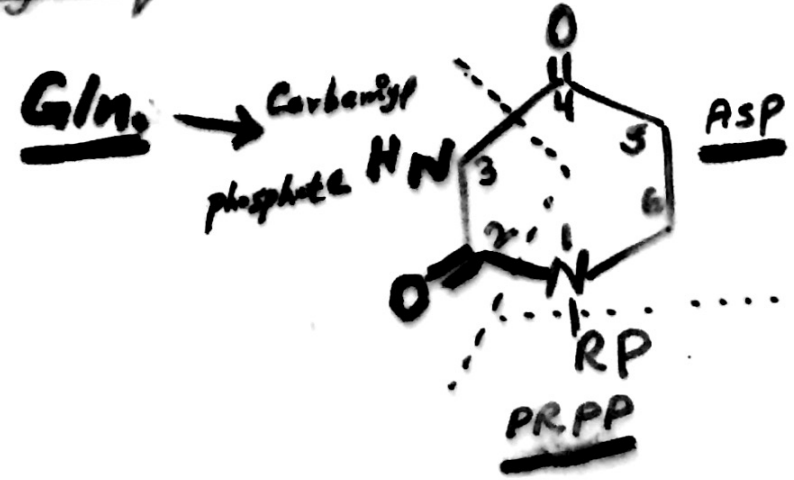
N^5-methyl-THF

De Novo Synthesis of Purines

→ Origin of the ring atoms of purines

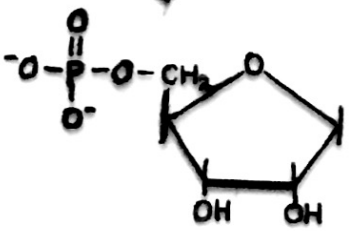


→ Origin of the ring atoms of Pyrimidine



Purine Biosynthesis

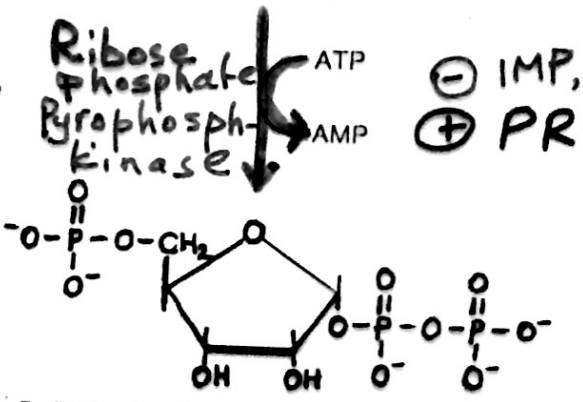
- Synthesis of PRPP



Riboso 5-phosphate

Source of ribose moiety for

- Purine Nucleotides ←
- Pyrimidine " ←
- Salvage Pathway ←

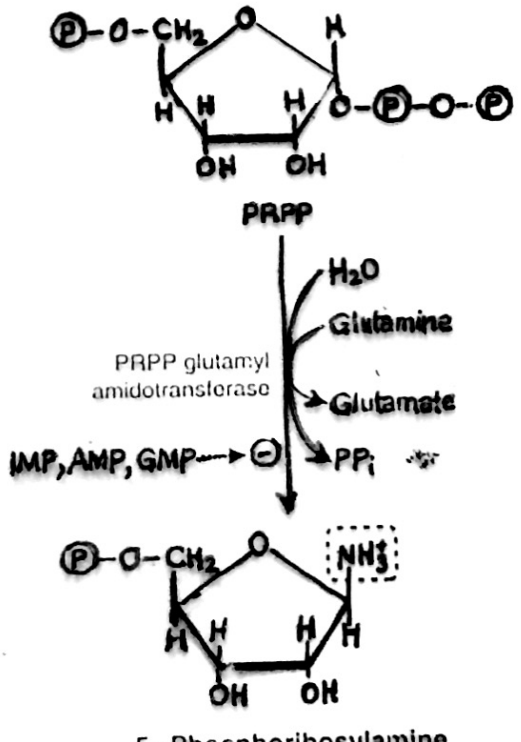


⊖ IMP, AMP & GMP
⊕ PRPP

5-Phosphoribosyl 1-pyrophosphate (PRPP)

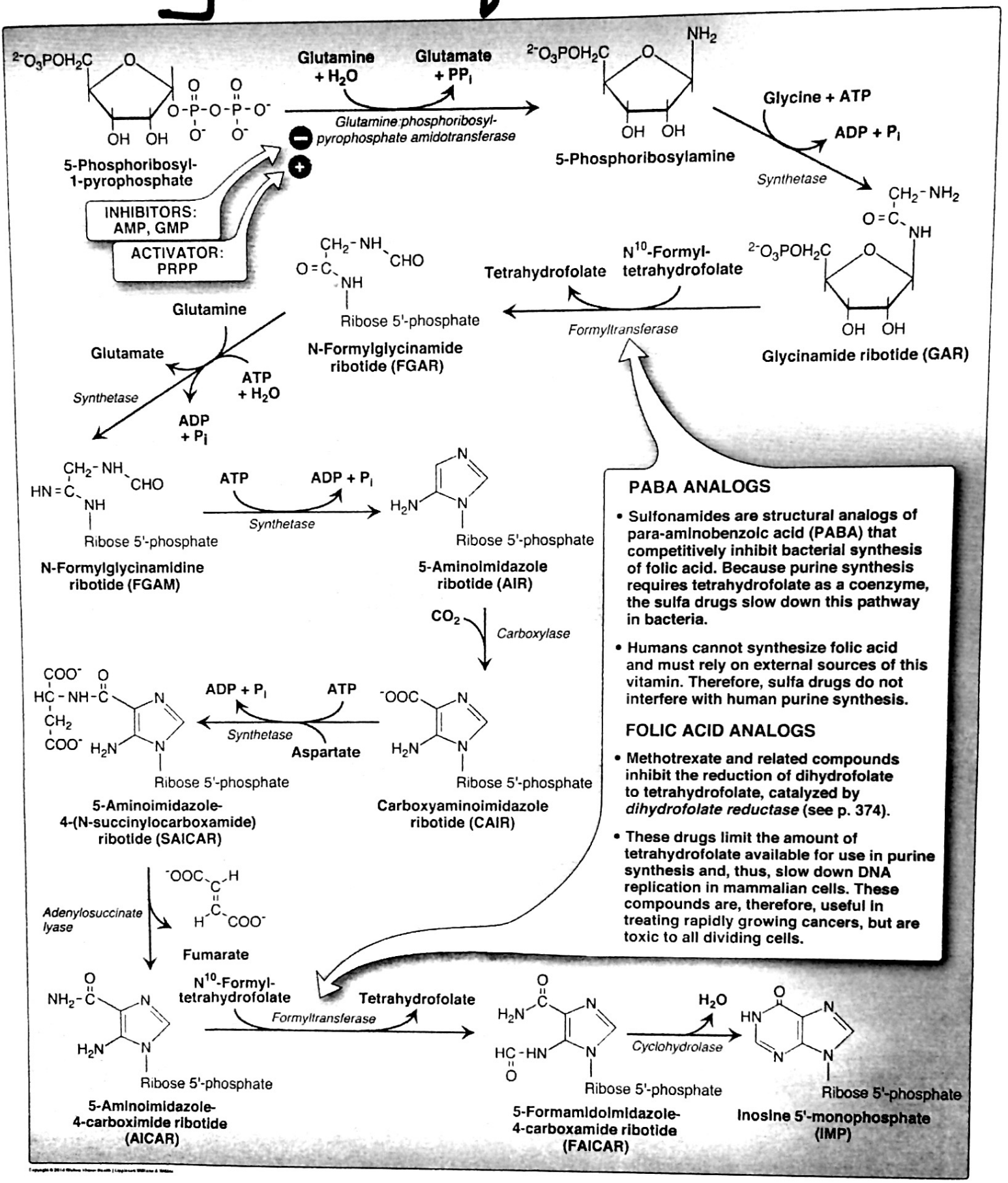
activated ribose

- First step in Purine biosynthesis



5-Phosphoribosylamine

Synthesis of Purine Nucleotides



PABA ANALOGS

- **Sulfonamides are structural analogs of para-aminobenzoic acid (PABA) that competitively inhibit bacterial synthesis of folic acid. Because purine synthesis requires tetrahydrofolate as a coenzyme, the sulfa drugs slow down this pathway in bacteria.**
- **Humans cannot synthesize folic acid and must rely on external sources of this vitamin. Therefore, sulfa drugs do not interfere with human purine synthesis.**

FOLIC ACID ANALOGS

- **Methotrexate and related compounds inhibit the reduction of dihydrofolate to tetrahydrofolate, catalyzed by *dihydrofolate reductase* (see p. 374).**
- **These drugs limit the amount of tetrahydrofolate available for use in purine synthesis and, thus, slow down DNA replication in mammalian cells. These compounds are, therefore, useful in treating rapidly growing cancers, but are toxic to all dividing cells.**

Nucleoside & Nucleotide Kinases

de novo synthesis → NMP

I Endogenous Nucleosides → (nucleoside kinase; ATP → ADP) → NMP

Exogenous [Adenosine the only Purine nucleoside is salvaged]

} kinase shows high specificity toward base & sugar

II Nucleoside monophosphate kinase

(d) NMP + ATP ⇌ (NMK) (d) NDP + ADP

specific toward base but not sugar
Four different kinases

e.g. ATP + AMP ⇌ 2 ADP (A.K.)

Adenylate kinase

III Nucleoside diphosphate kinase

$N_2DP + \underbrace{N_1TP}_{ATP} \underset{NDK}{\rightleftharpoons} N_2TP + N_1DP$

Present in high conc.
Non-specific toward base & sugar
10–100 fold > active than NMK

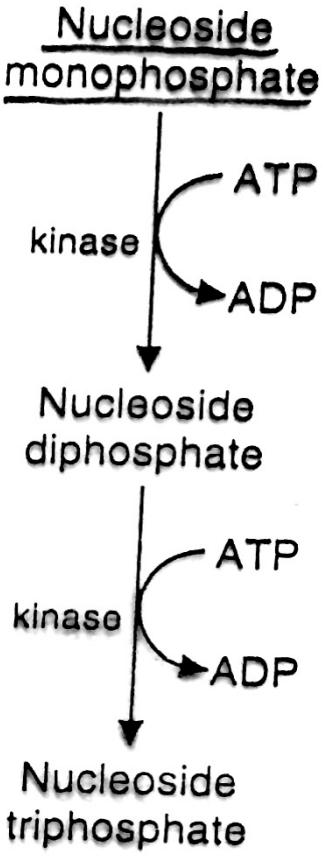


Fig. 41.18. Phosphorylation of nucleosides.

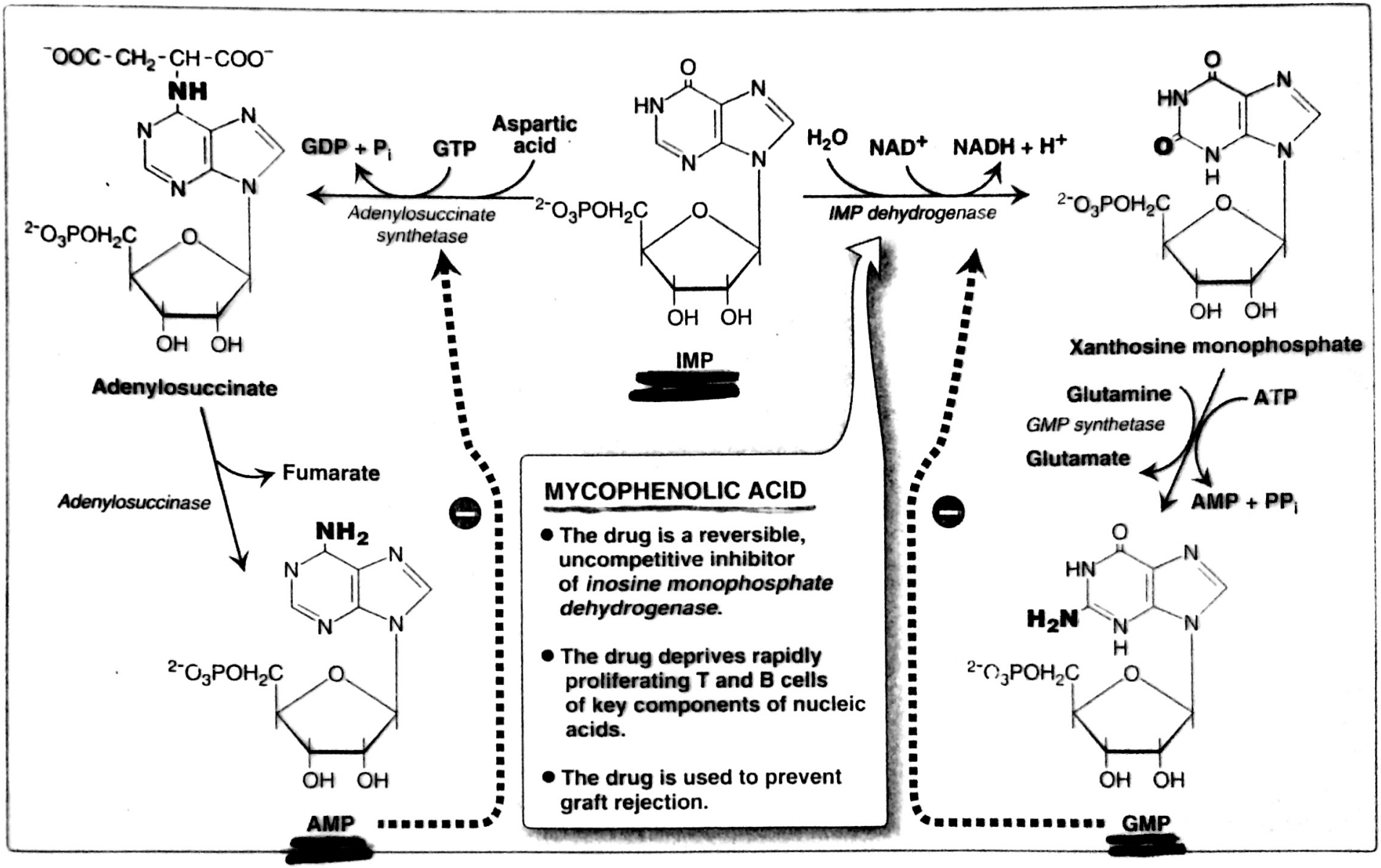
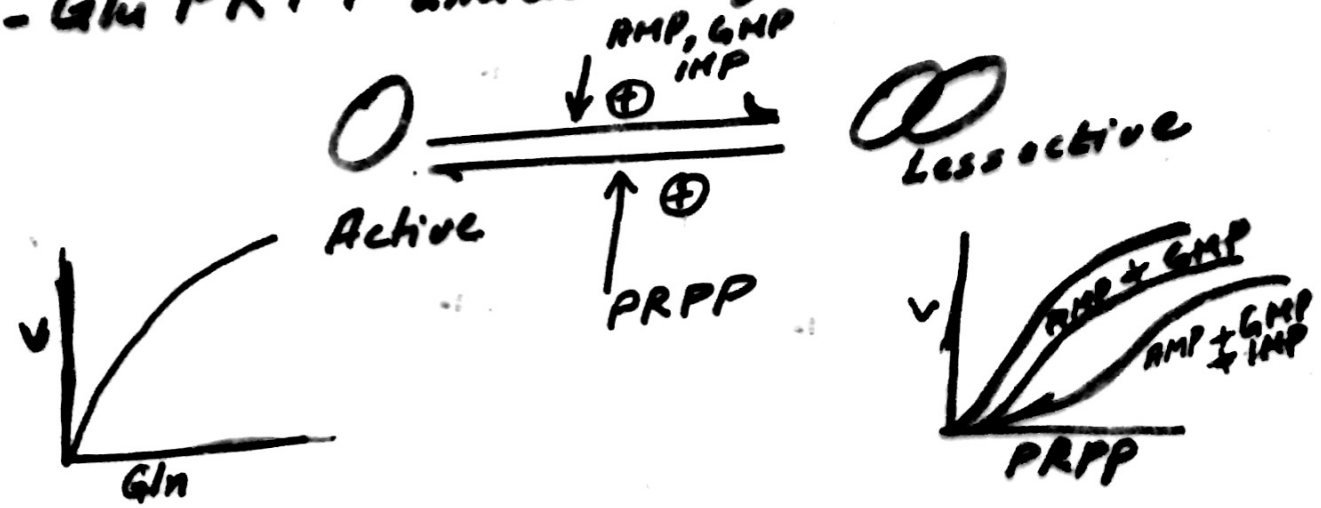
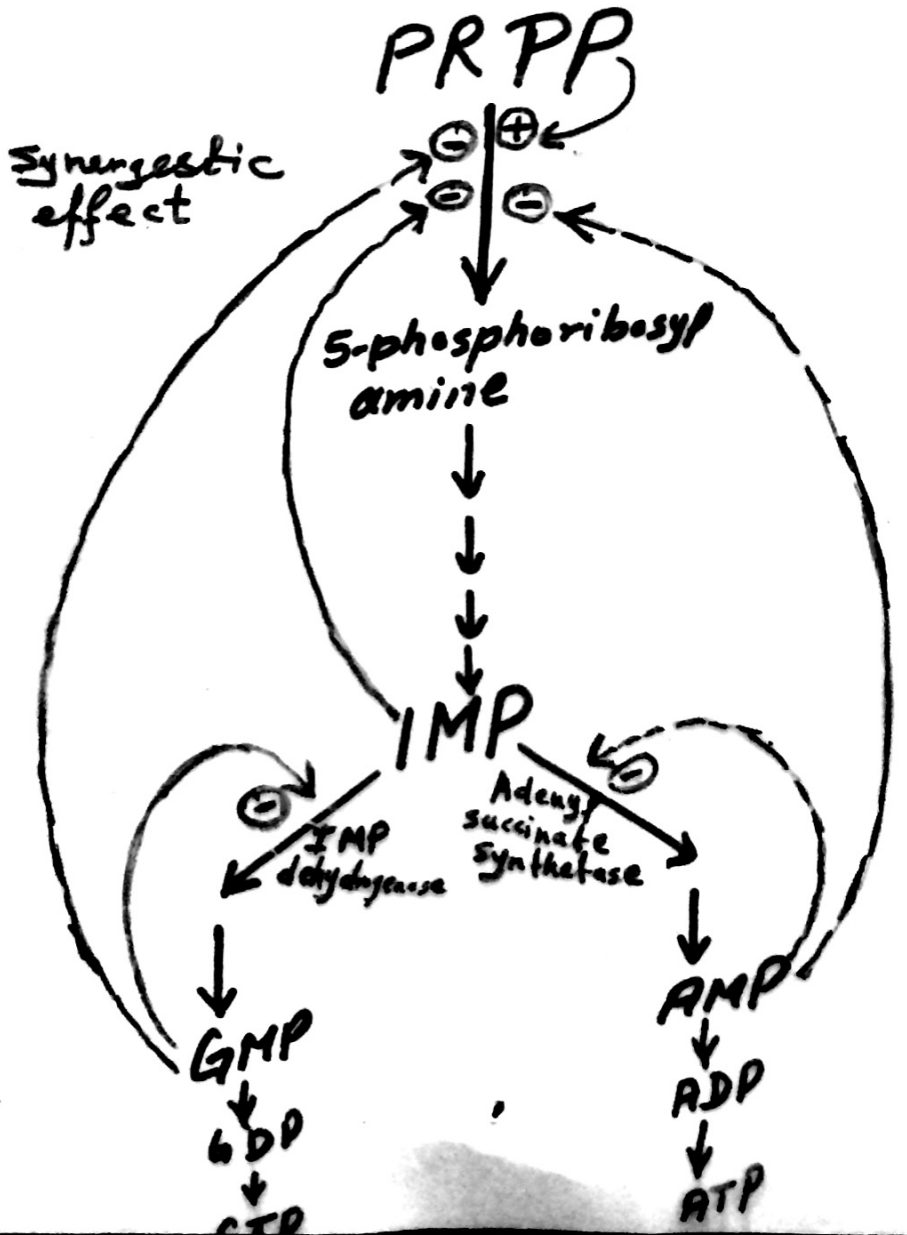


Figure 22.8
Conversion of IMP to AMP and GMP showing feedback inhibition.

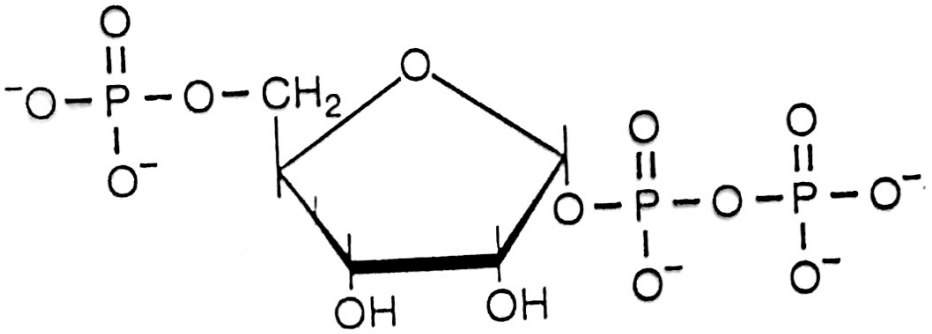
- Purine Nucleotide Synthesis is Highly Regulated:-

- Glu PRPP amidotransferase is rate-limiting



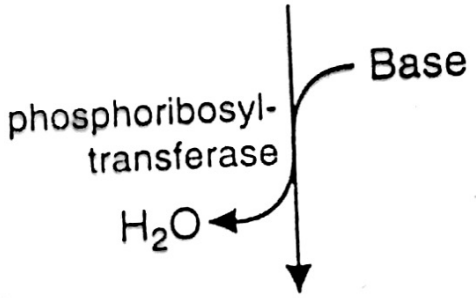


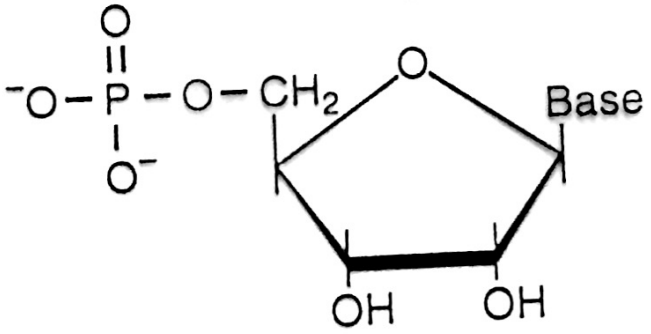
Salvage of the Bases



5-Phosphoribosyl 1-pyrophosphate (PRPP)

HGPRT
APRT





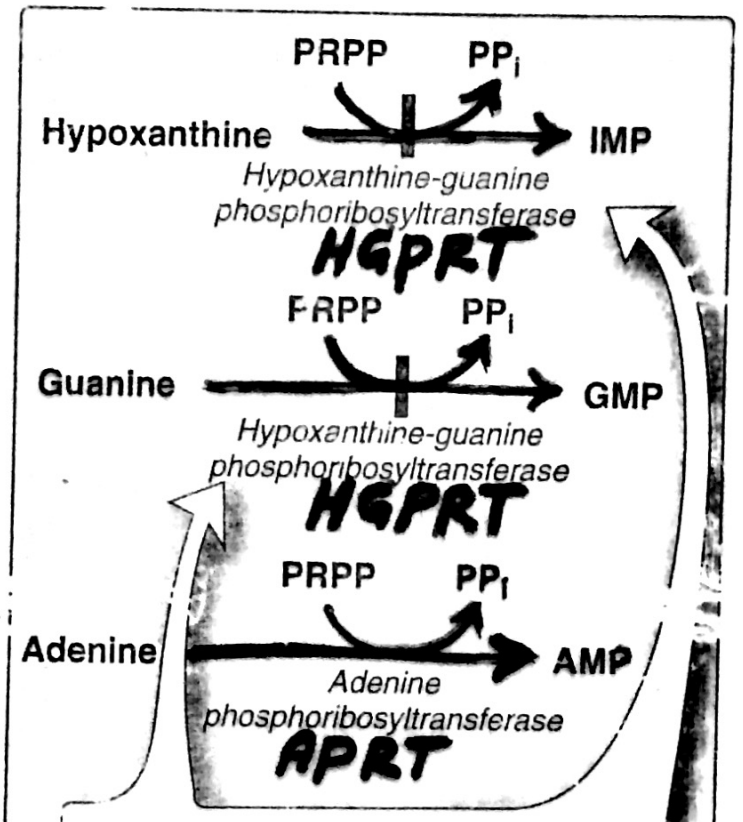
Nucleotide

- Most of the de novo synthesis of bases & nucleotides in liver and to some extent in brain, neutrophils & other cells of Immune System

nucleotides → nucleoside → bases → Blood → Other tissues

Bases + PRPP —salvage→ nucleotides

Disorder of purines salvage pathway



LESCH-NYHAN SYNDROME

- This is an X-linked, recessive, inherited disorder associated with a virtually complete deficiency of *hypoxanthine-guanine phosphoribosyltransferase* and, therefore, the inability to salvage hypoxanthine or guanine.
- The enzyme deficiency results in increased levels of PRPP and decreased IMP and GMP, causing increased de novo purine synthesis.
- This results in the excessive production of uric acid, plus characteristic neurologic features, including self-mutilation and involuntary movements.

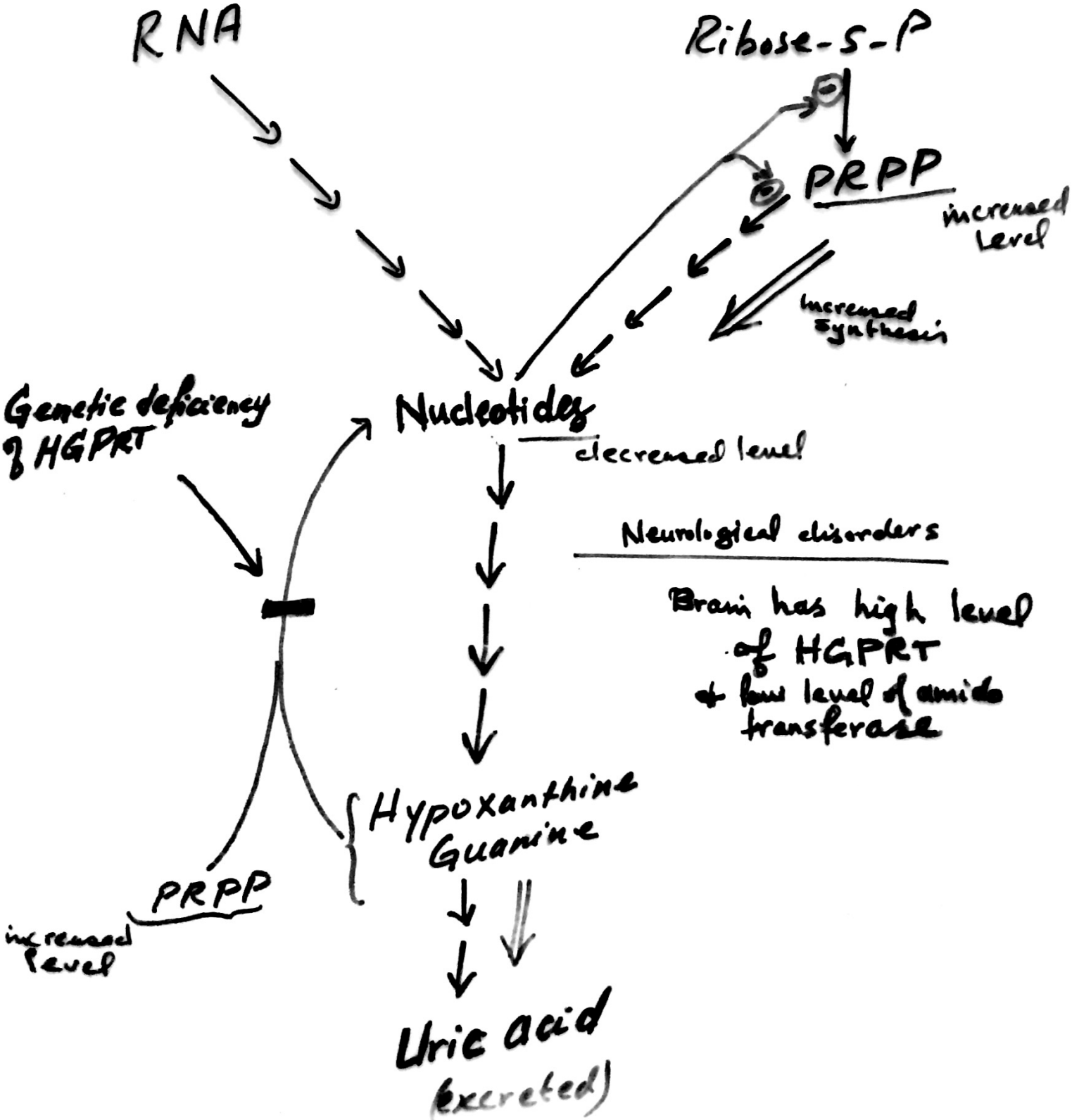
Hyperuricemia:
→ uric acid stones in kidneys (urolithiasis)
→ deposition of urate crystals in the joints (gouty arthritis) and in soft tissues

→ motor dysfunction
cognitive deficits
behavioral disturbances
e.g. self mutilation
involuntary movements

→ Increased Purine synthesis

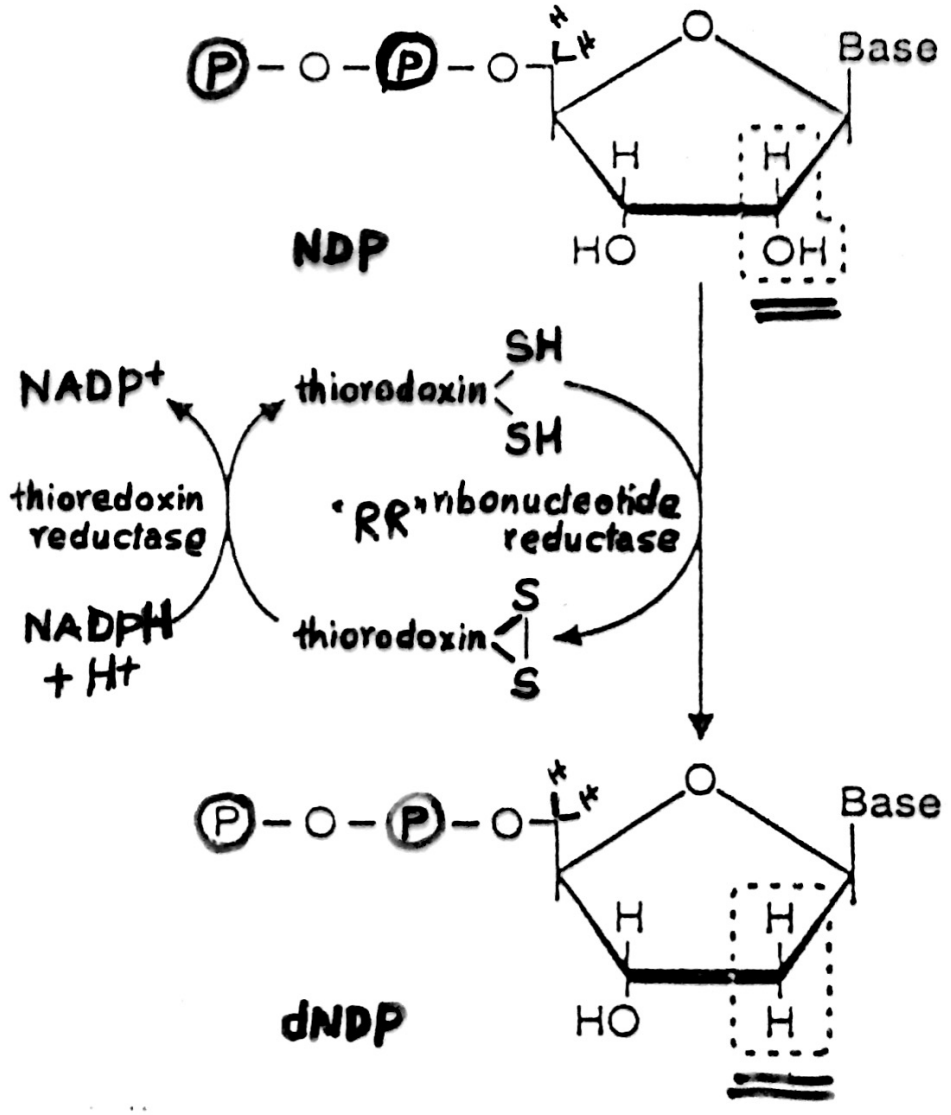
→ Increased Uric acid (Gout)

Mechanism of Increased Uric acid production and de novo synthesis of purine nucleotides in deficiency of HGPRT



Reduction of Ribose → deoxy Ribose

Synthesis of Deoxyribonucleotides:



Regulation of RR

→ balanced supply of d NDP

→ two Identical B_1 + two Identical B_2 subunits

→ One Single active site

→ two regulatory site

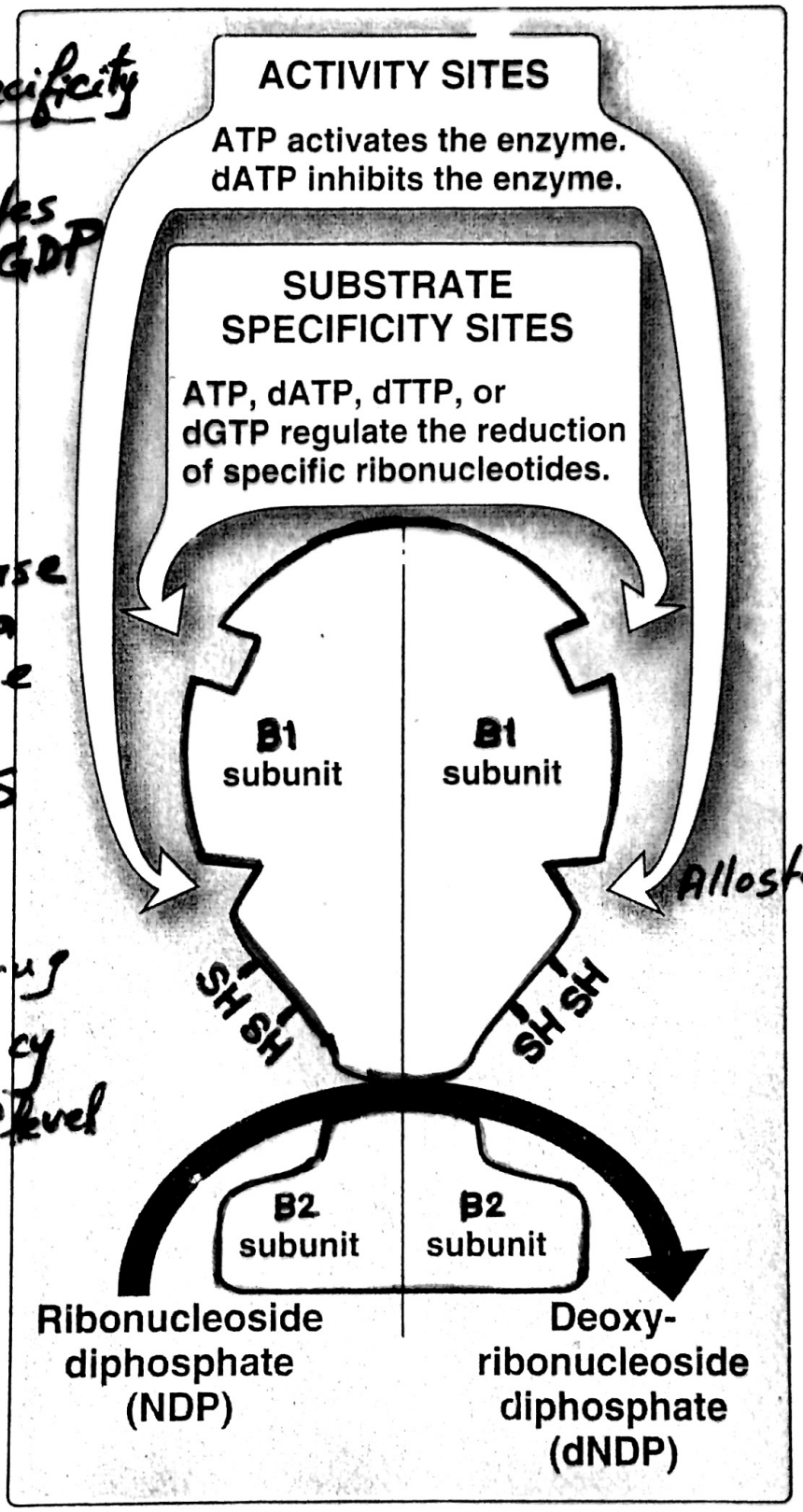
- Activity site dATP↓ ATP↑
- substrate specificity site

Substrate Specificity

e.g.
dTTP activates reduction of GDP

Hydroxy urea
- inhibit RRase by destroying required free radical
- treating HbS disease by increasing HbF level
- Anticancer drug

ADA deficiency → ↑dATP level



Allosteric sites

Figure 22.13
Regulation of *ribonucleotide reductase*.