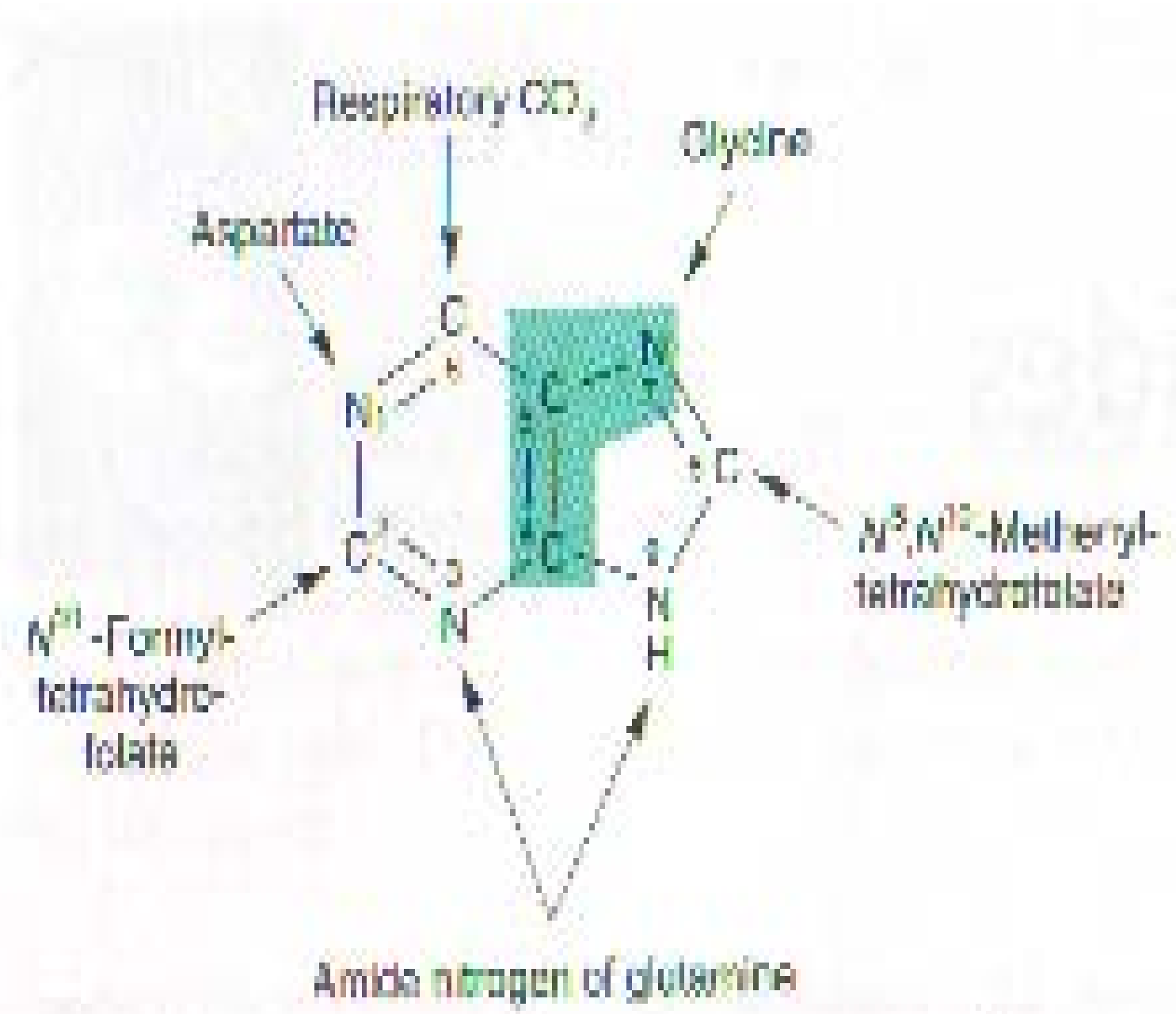
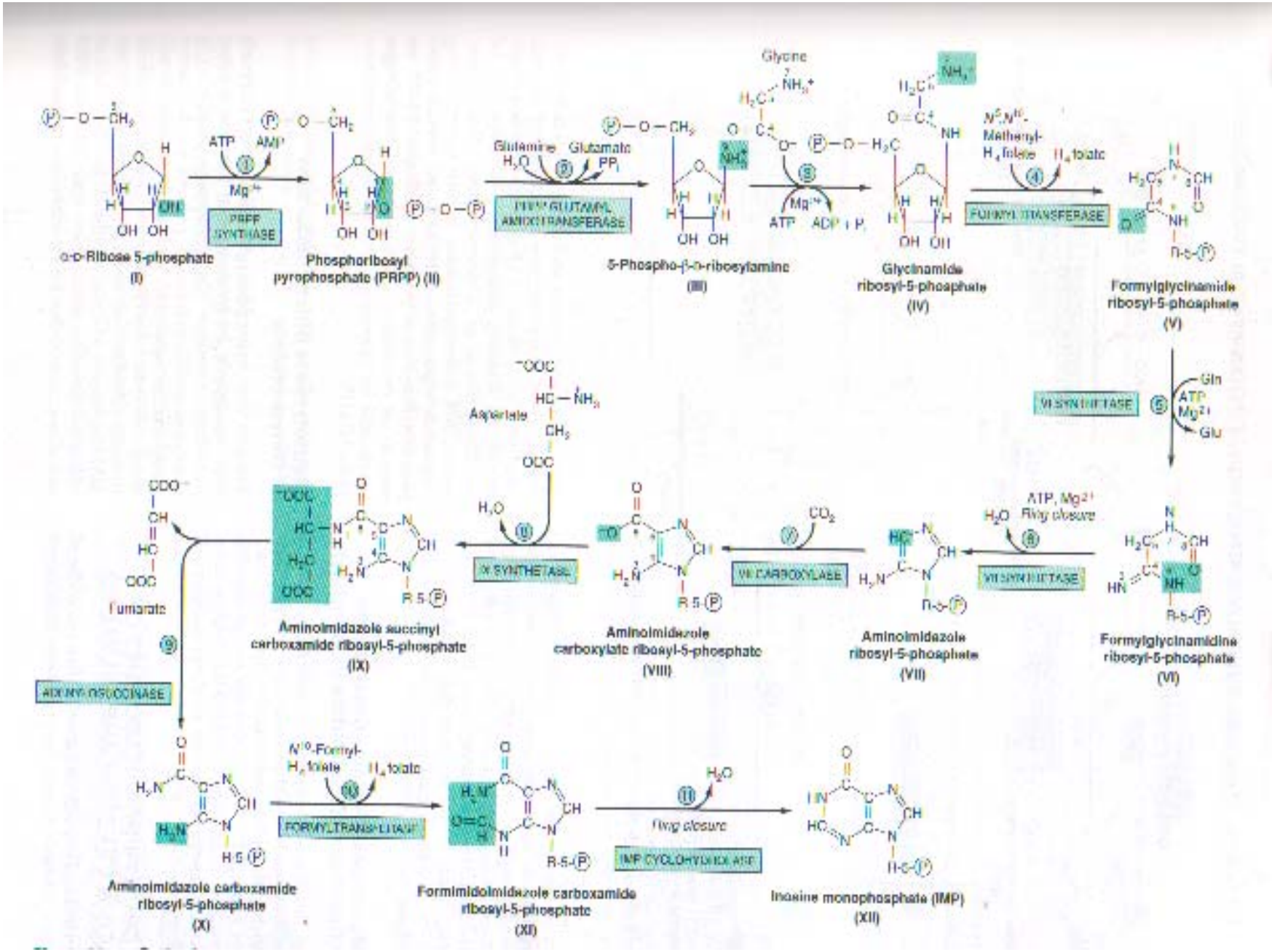
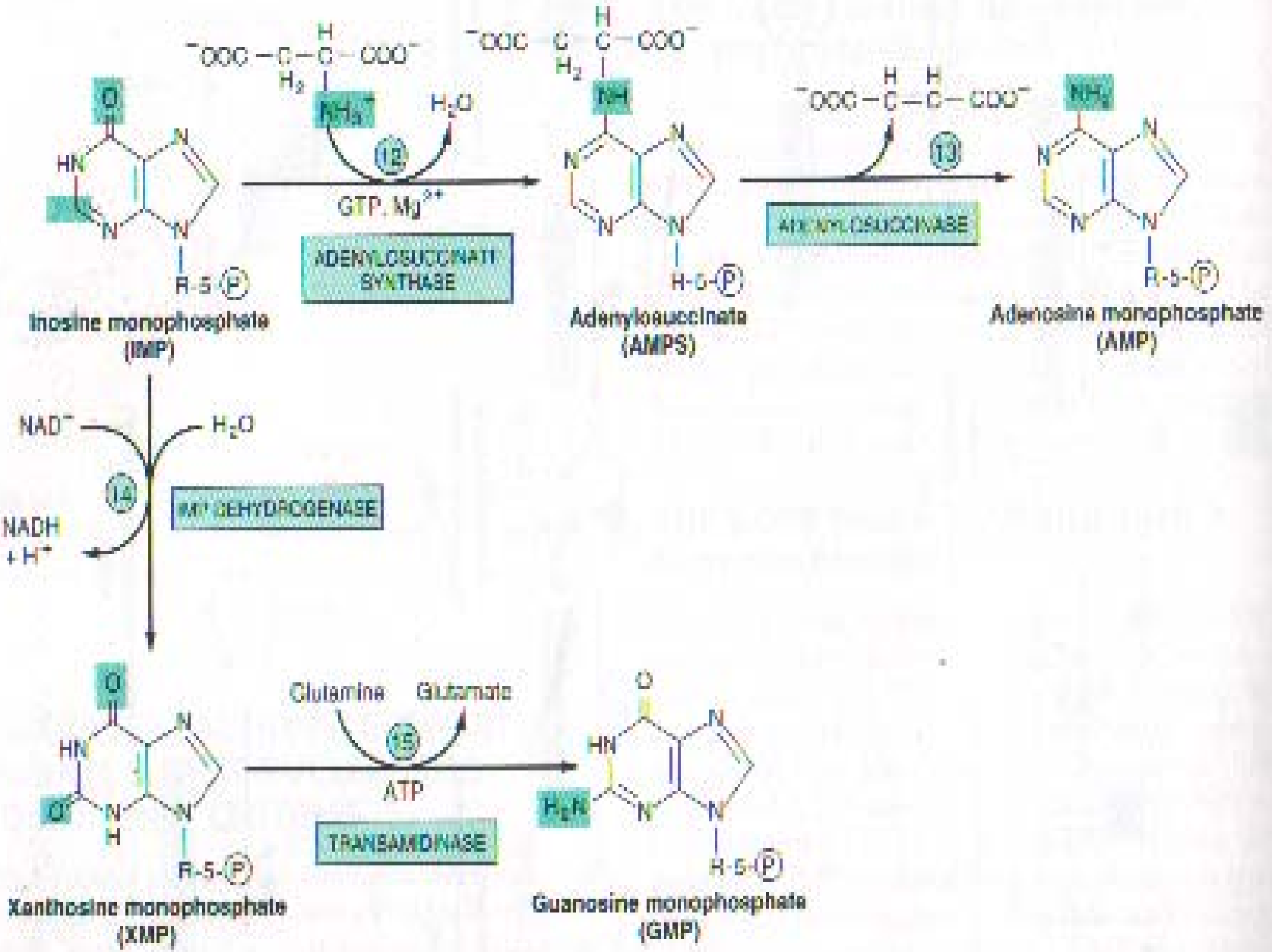
PURINE & PYRIMIDINE METABOLISM

- Nucleotide consists purine / pyrimidine base, ribose/deoxyribose and phosphates.
- Nucleoside consists purine/pyrimidine base and ribose/deoxyribose.
- Purine base contains adenine, guanine and hypoxanthine.
- Pyrimidine base contains cytosine, uracil and thymine.


Respiratory CO_2
Glycine
Aspartate
N^5,N^{10}-Methenyl-
tetrahydrofolate
N^{10}-Formyl-
tetrahydro-
folate
Amide nitrogen of glutamine


α-D-Ribose 5-phosphate
(I)
ATP
AMP
Mg++
PRPP SYNTHASE
Phosphoribosyl pyrophosphate (PRPP) (II)
Glutamine
Glutamate
PPi
PRPP GLUTAMYL AMIDOTRANSFERASE
5-Phospho-β-D-ribosylamine
(III)
Glycine
ATP
ADP + Pi
Glycinamide ribosyl-5-phosphate
(IV)
N5,N10-Methenyl-H4folate
H4folate
FORMYL TRANSFERASE
Formylglycinamide ribosyl-5-phosphate
(V)
GS SYNTHETASE
Gln
ATP
Mg2+
Glu
Formylglycinamidine ribosyl-5-phosphate
(VI)
ATP, Mg2+
H2O
Ring closure
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-H4folate
H4folate
FORMYLTRANSFERASE
Aminoimidazole carboxamide ribosyl-5-phosphate
(X)
H2O
Ring closure
IMP CYCLOHYDROLASE
Formimidoimidazole carboxamide ribosyl-5-phosphate
(XI)
Inosine monophosphate (IMP)
(XII)


Inosine monophosphate
(IMP)
GTP, Mg^{2+}
ADENYLOSUCCINATE SYNTHASE
Adenylosuccinate
(AMPS)
ADENYLOSUCCINASE
Adenosine monophosphate
(AMP)
NAD^+
H_2O
NADH
$+ H^+$
IMP DEHYDROGENASE
Xanthosine monophosphate
(XMP)
Glutamine
Glutamate
ATP
TRANSAMIDINASE
Guanosine monophosphate
(GMP)

Biosynthesis of purine

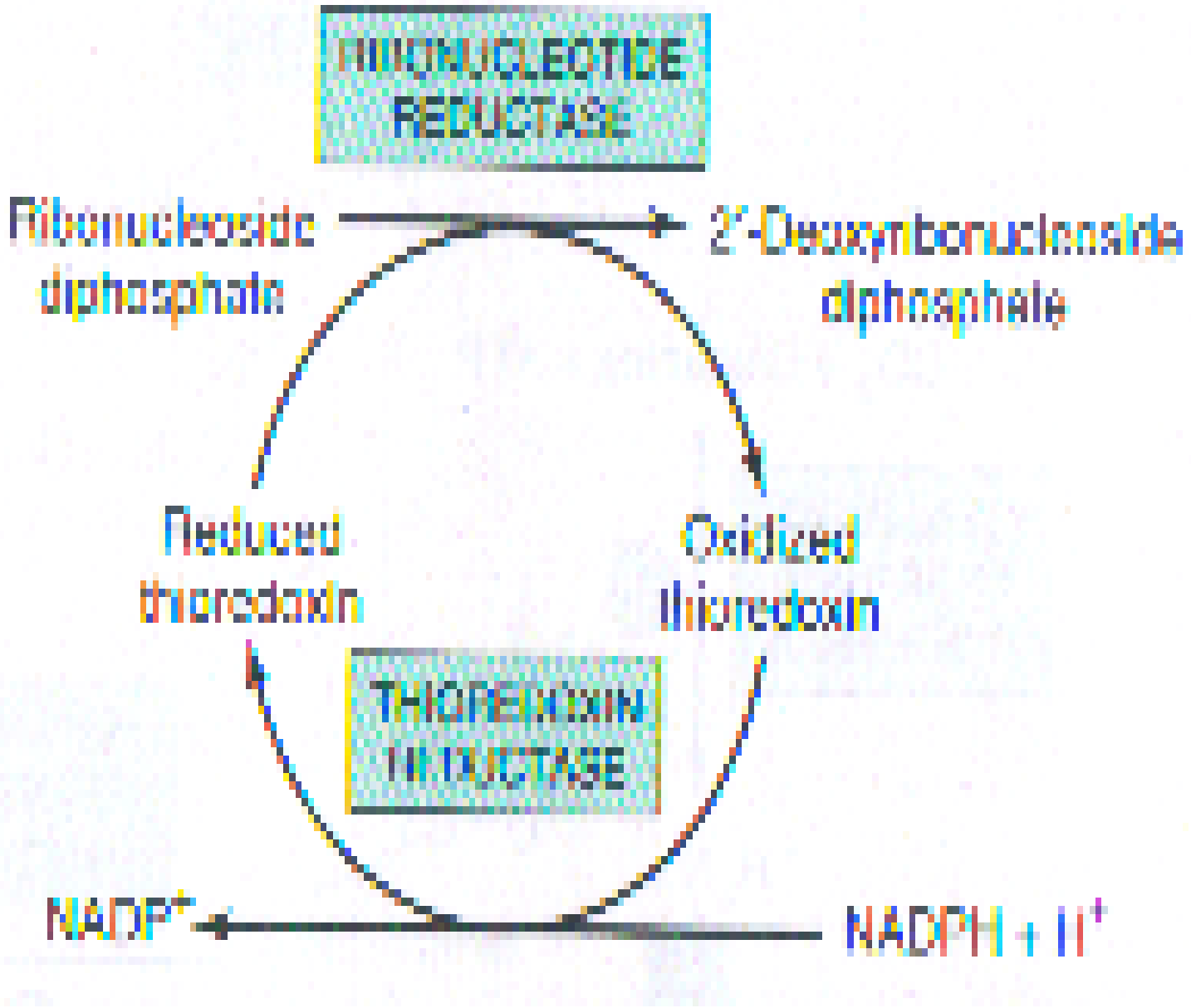
- It begins with PRPP(phosphoribosyl phosphate) synthesis and PRPP synthase. Afterwards PRPP glutamyl amidotransferase . Those 2 enzymes are the key regulatory enzymes for the purine synthesis. IMP is synthesized and could make AMP or GMP.
- It happens in almost most cells' cytosol except human brain,polymorphonuclear leukocytes and erythrocytes.

Purine salvage pathway

- Liver is the major site of synthesis.
- It contains phosphoribosylation by PRPP of free purine to form purine mononucleotide such as adenine to AMP(with APRT) and hypoxanthine / guanine to IMP/ GMP(with HGPRT).
- It contains too phosphoryl transfer from ATP to purine ribonucleoside such as adenosine kinase catalyzes adenosine to AMP.

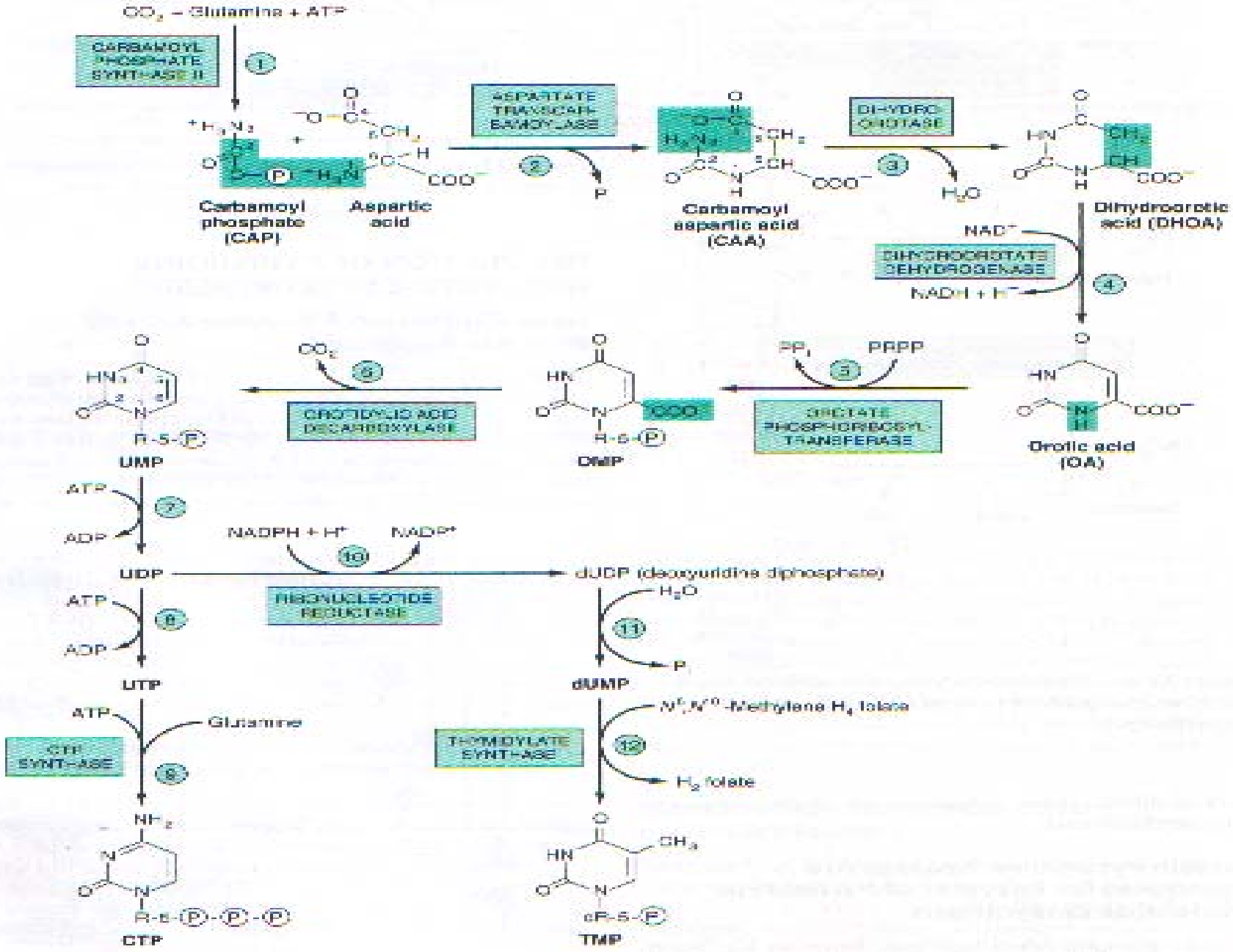
Reduction of ribonucleoside diphosphate to deoxyribonucleoside diphosphate.

- The enzyme is ribonucleotide reductase complex and active only when cells are activelyly synthesizing DNA. It requires thioredoxin, thioredoxin reductase and NADPH.


RIBONUCLEOTIDE REDUCTASE
Ribonucleoside diphosphate
2'-Deoxyribonucleoside diphosphate
Reduced thioredoxin
Oxidized thioredoxin
THIOREDOXIN REDUCTASE
NADP+
NADPH + H+

Pyrimidine synthesis

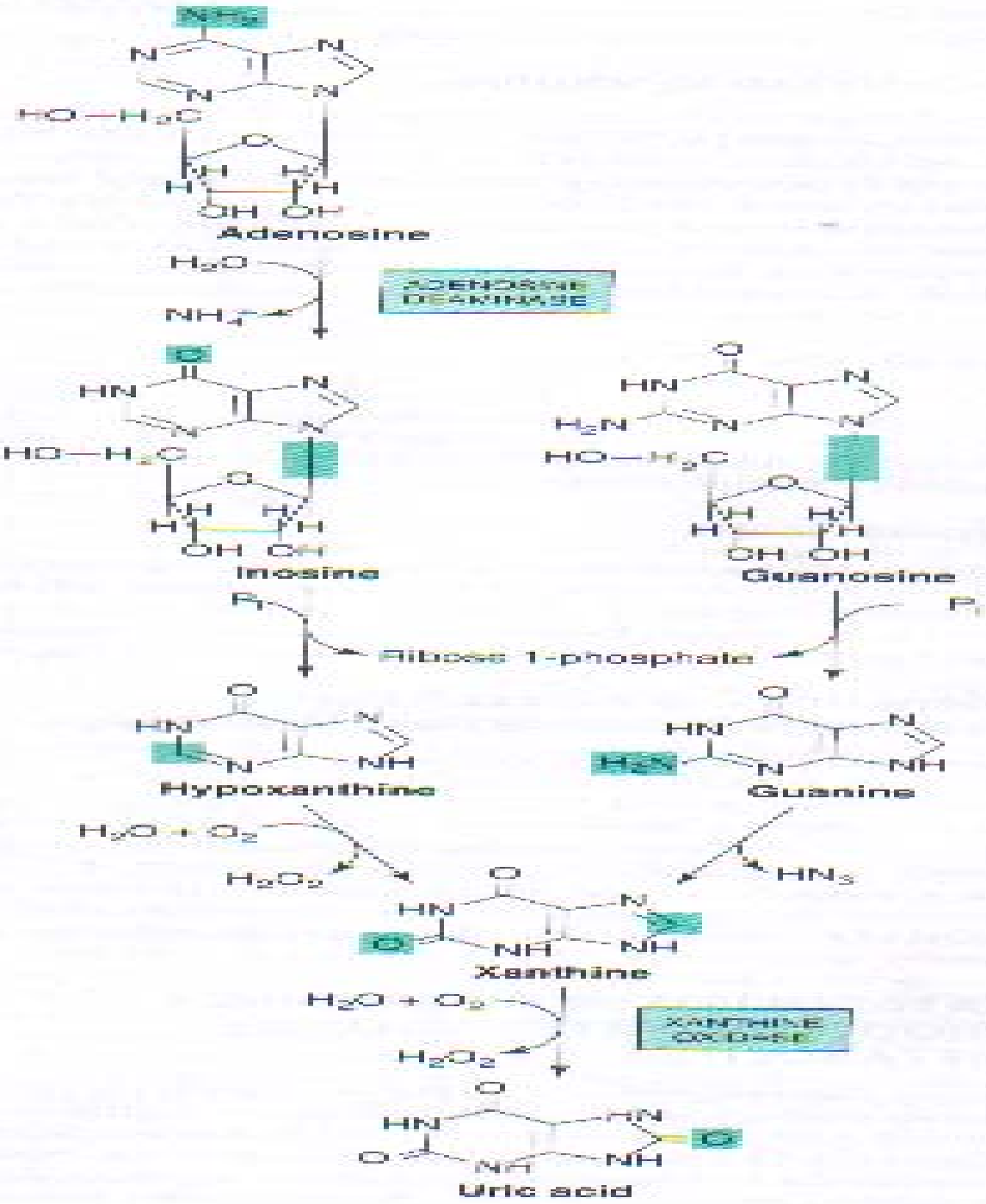
- It starts with carbamoyl phosphate with carbamoyl phosphate synthase II (in cytosol).
- PRPP will involve later in synthesis.
- Salvage pathway is not that important such as OPRT.


CO2 + Glutamine + ATP
CARBAMOYL PHOSPHATE SYNTHASE II
1
Carbamoyl phosphate (CAP)
Aspartic acid
ASPARTATE TRANSCARBAMOYLASE
2
P
Carbamoyl aspartic acid (CAA)
DIHYDROOROTASE
3
H2O
Dihydroorotic acid (DHOA)
NAD+
DIHYDROOROTATE DEHYDROGENASE
NADH + H+
4
Orotic acid (OA)
PP
PRPP
5
OROTATE PHOSPHORIBOSYL TRANSFERASE
OMP
CO2
6
OROTIDYLIC ACID DECARBOXYLASE
UMP
ATP
ADP
7
UDP
NADPH + H+
NADP+
10
RIBONUCLEOTIDE REDUCTASE
dUDP (deoxyuridine diphosphate)
H2O
11
dUMP
ATP
ADP
8
UTP
ATP
Glutamine
CTP SYNTHASE
9
CTP
N5,N10-Methylene H4 folate
THYMIDYLATE SYNTHASE
12
H2 folate
TMP

- Purine and pyrimidine biosynthesis are coordinately regulated through PRPP.
- In purine synthesis is regulated through the first and second enzymes.
- In pyrimidine synthesis, carbamoyl phosphate synthase II is inhibited by UTP and purine nucleotides, but activated by PRPP. Aspartate transcarbamoylase inhibited by CTP but activated by ATP.

Purine Catabolism

- Purines are catabolized to xanthine and uric acid in human.Uric acid then is secreted in urine.
- Gout is an arthritis that has hyperuricemia.
- Lesch-Nyhan syndrome and Von Gierke disease are disorder of this purine catabolism.


Adenosine
H_2O
NH_4^+
ADENOSINE DEAMINASE
Inosine
Guanosine
P_i
Ribose 1-phosphate
Hypoxanthine
Guanine
$H_2O + O_2$
H_2O_2
HN_3
Xanthine
$H_2O + O_2$
H_2O_2
XANTHINE OXIDASE
Uric acid

Pyrimidine catabolism

- Pyrimidines are catabolized to β-alanine and β-aminoisobutyrate then secreted in urine.

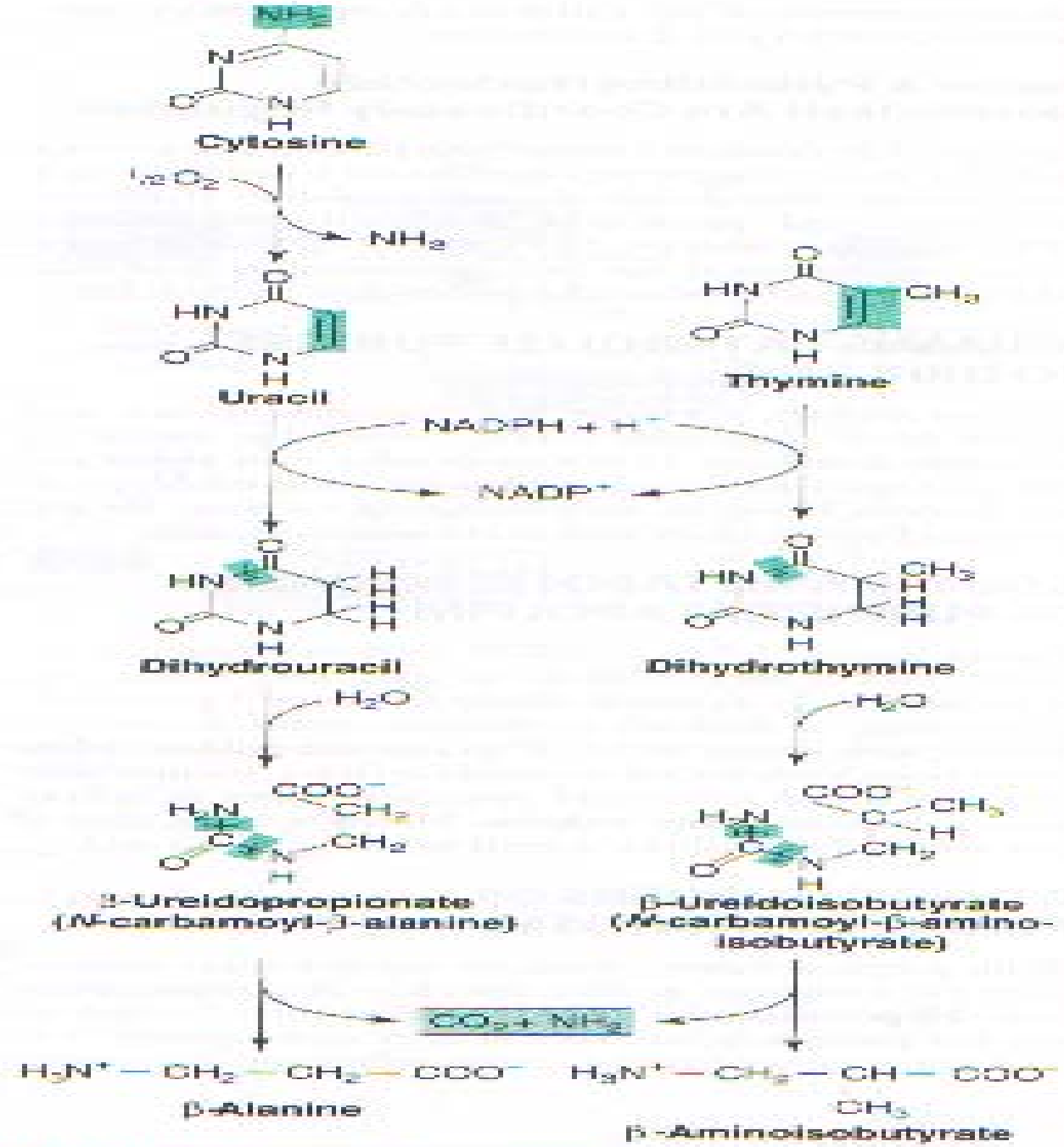
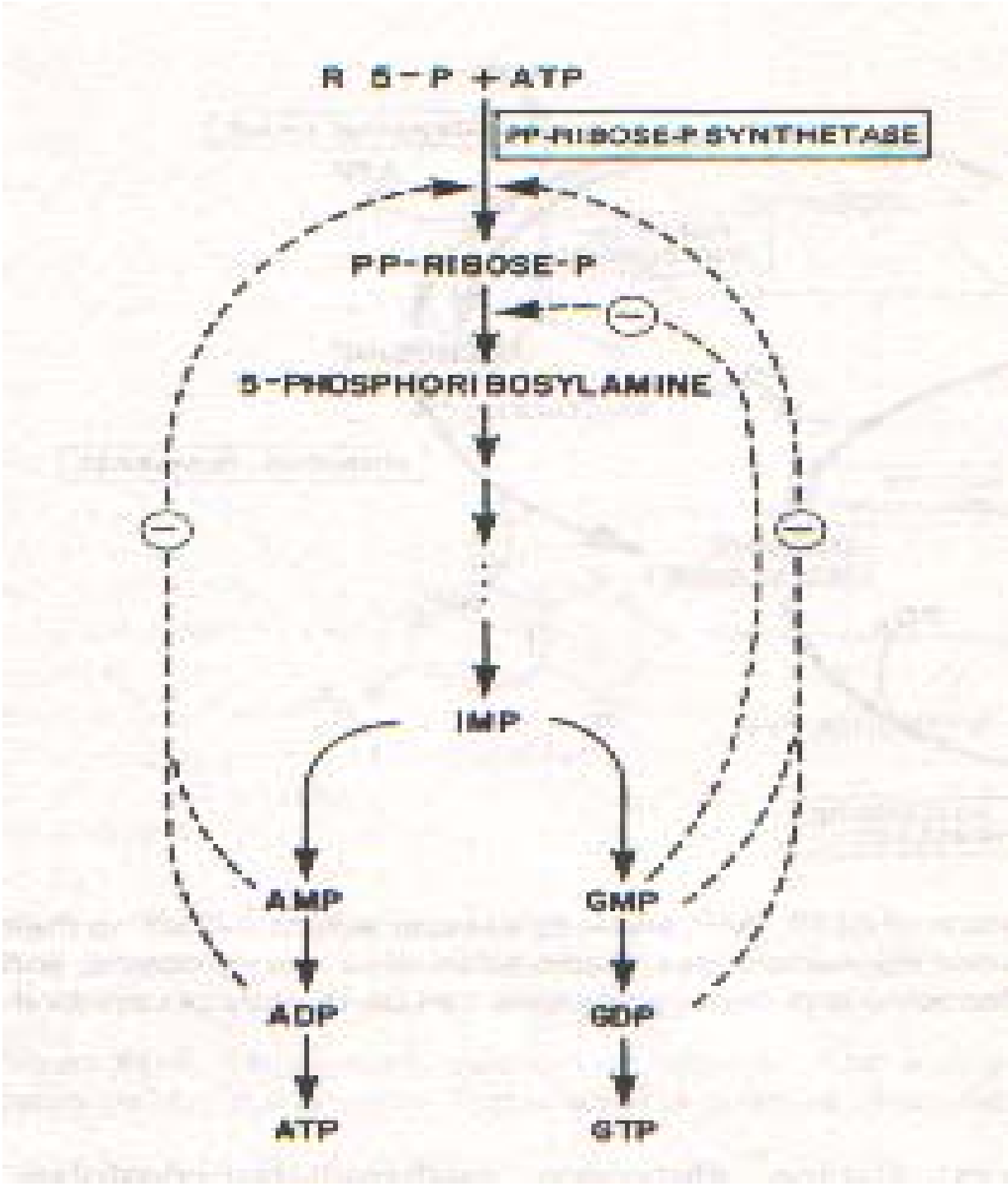
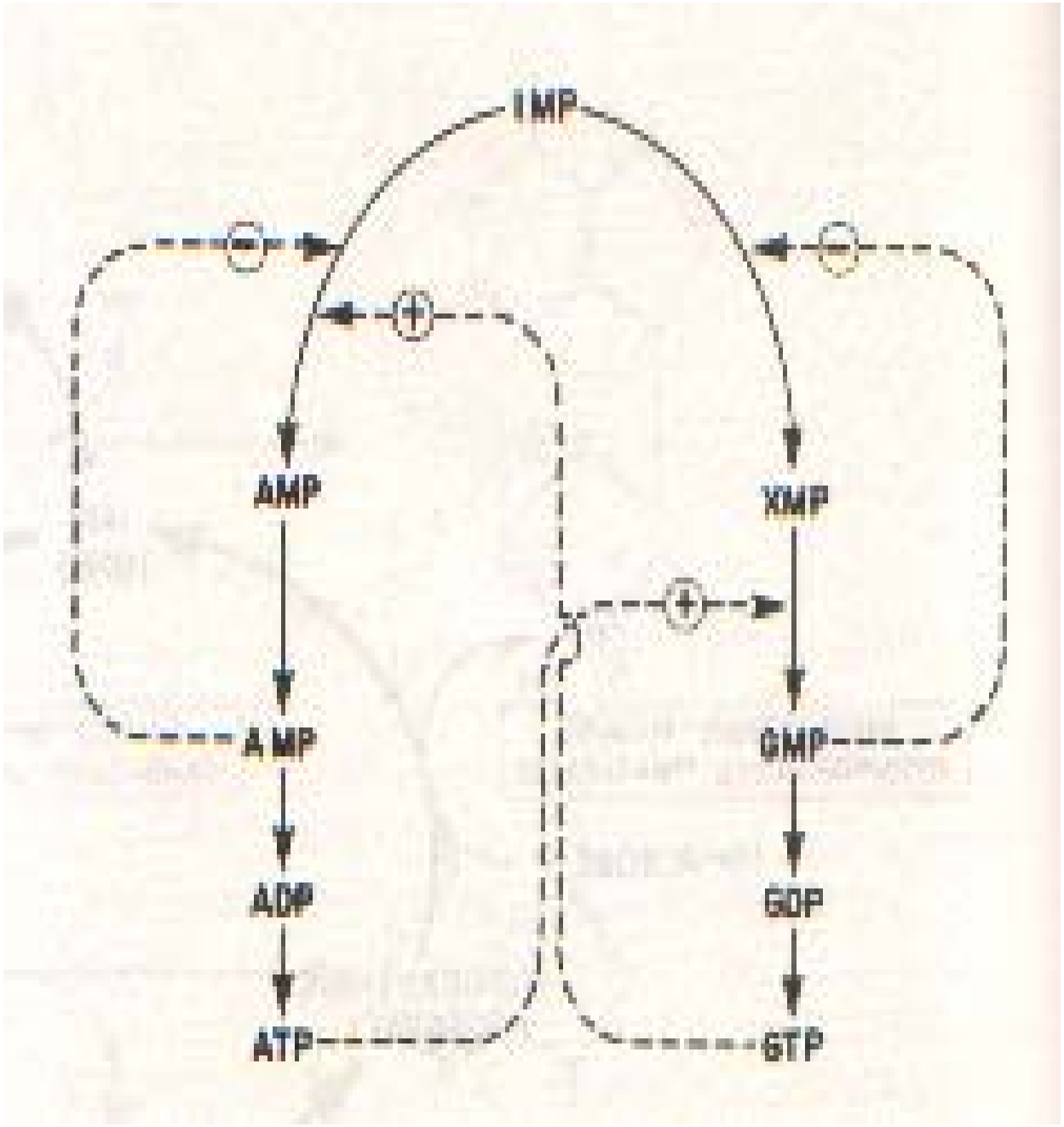
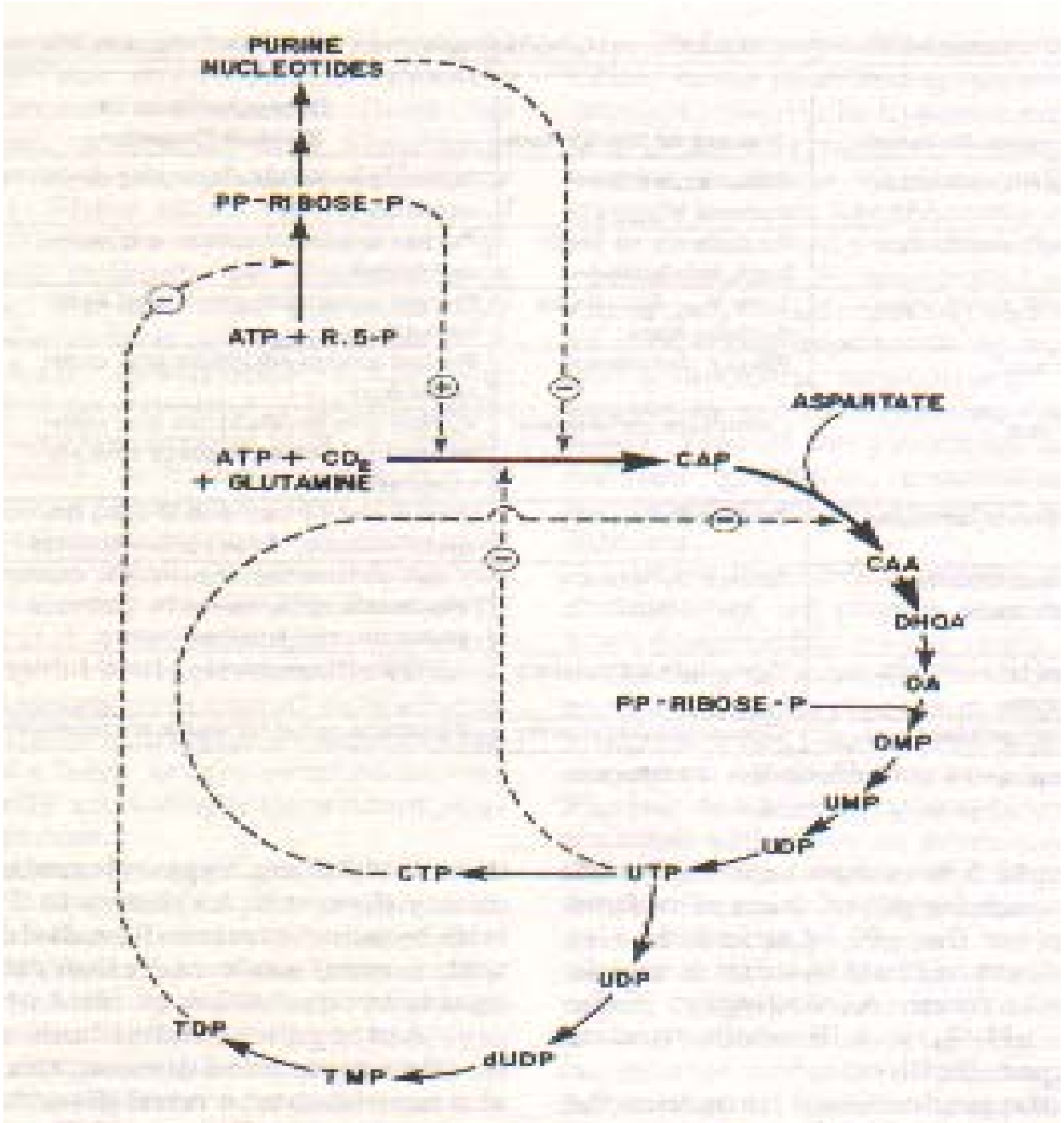
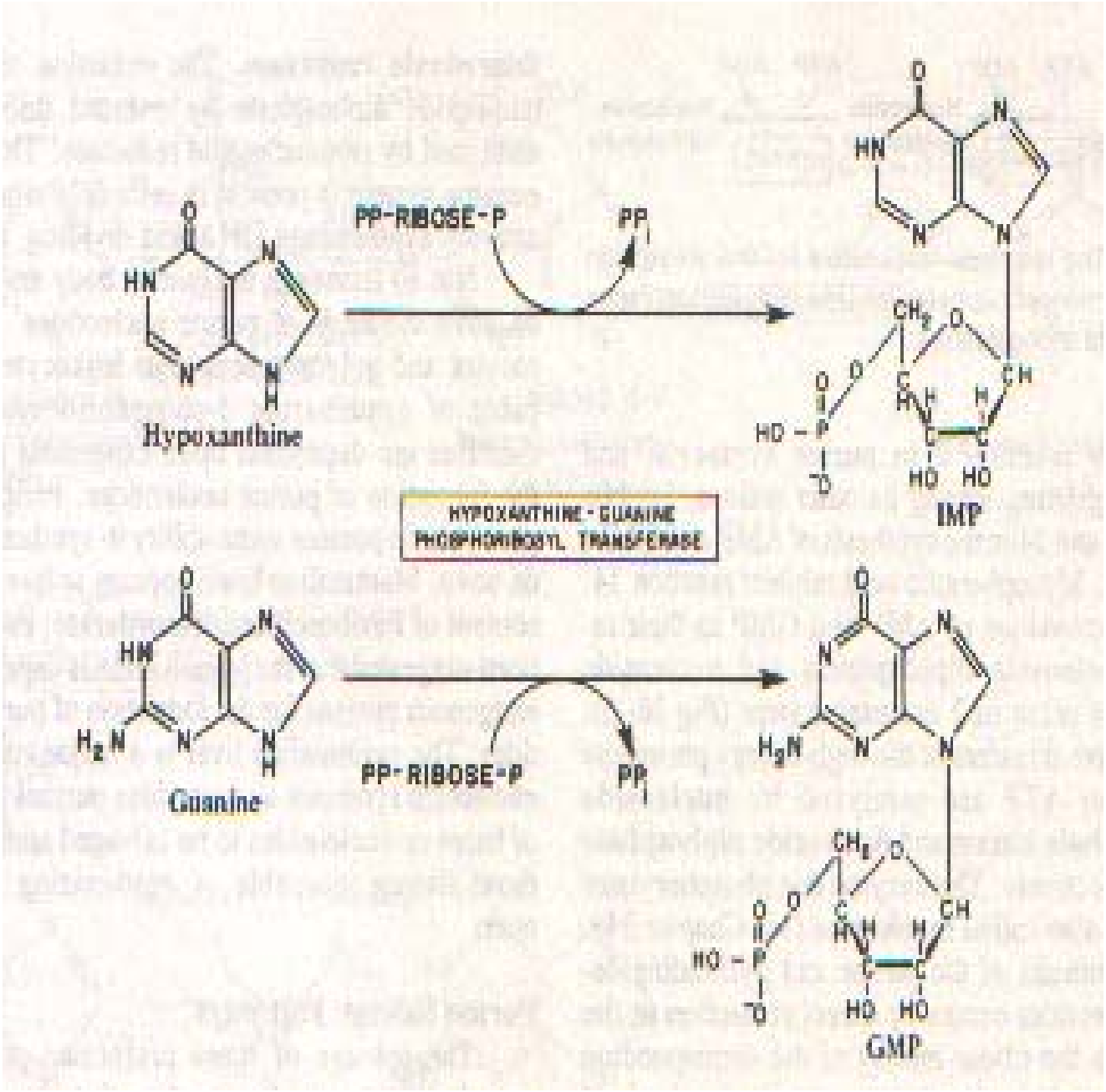


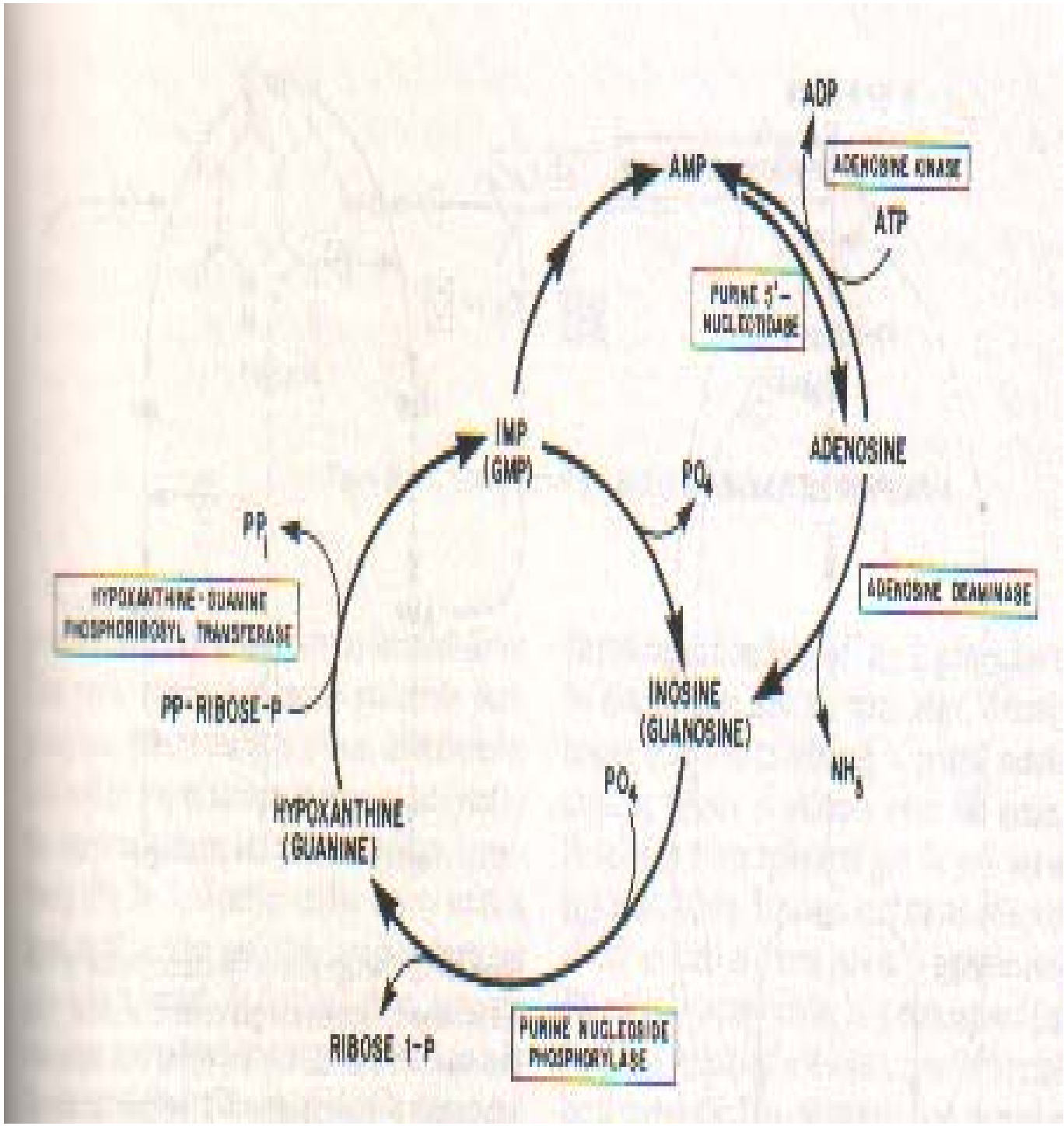
Figure 33–9. Catabolism of pyrimidines.


R 5-P + ATP
PP-RIBOSE-P SYNTHETASE
PP-RIBOSE-P
5-PHOSPHORIBOSYLAMINE
IMP
AMP
GMP
ADP
GDP
ATP
GTP


IMP
AMP
XMP
AMP
GMP
ADP
GDP
ATP
GTP


PURINE NUCLEOTIDES
PP-RIBOSE-P
ATP + R.5-P
ATP + CO_2 + GLUTAMINE
CAP
ASPARTATE
CAA
DHOA
OA
PP-RIBOSE-P
OMP
UMP
UDP
CTP
UTP
UDP
dUDP
TMP
TDP


Hypoxanthine
PP-RIBOSE-P
PP
IMP
HYPOXANTHINE - GUANINE
PHOSPHORIBOSYL TRANSFERASE
Guanine
PP-RIBOSE-P
PP
GMP


ADP
AMP
ADENOSINE KINASE
ATP
PURINE 5'-
NUCLEOTIDASE
IMP
(GMP)
ADENOSINE
PO4
PPi
HYPOXANTHINE - GUANINE
PHOSPHORIBOSYL TRANSFERASE
ADENOSINE DEAMINASE
PP-RIBOSE-P
INOSINE
(GUANOSINE)
NH3
PO4
HYPOXANTHINE
(GUANINE)
RIBOSE 1-P
PURINE NUCLEOSIDE
PHOSPHORYLASE