Metabolism of Purine & Pyrimidine Nucleotides

Biomedical importance

- Biosynthesis is strongly regulated to insure their production in appropriate Quantities and at times suitable to their physiologic demand.
- Genetic disease of
  Purine metabolism:

  Gout – Lecsh-Nyhan syndrome-Adenosine deaminase and purine nucleotide phosphorylase deficiency.

  Pyrimidine metabolism:

  Orotic aciduria.

Purines and Pyrimidines are dietarily nonessential

- Synthesized from amphibolic intermediates.
- Fate of Ingested nucleic acids (dietarily nonessential):

Nucleic acid →Nucleotides (Intestinal tract)

↓

Purine and Pyrimidine bases

↓

Uric acid (absorbed or excreted in urine)

- Ingested nucleotides cannot be incorporated ,Injected compounds can be incorporated.

Biosynthesis of Purine nucleotides

- Synthesis from amphibolic intermediates.
- Phosphoribosylation of purines.
- Phosphorylation of purine nucleosides.

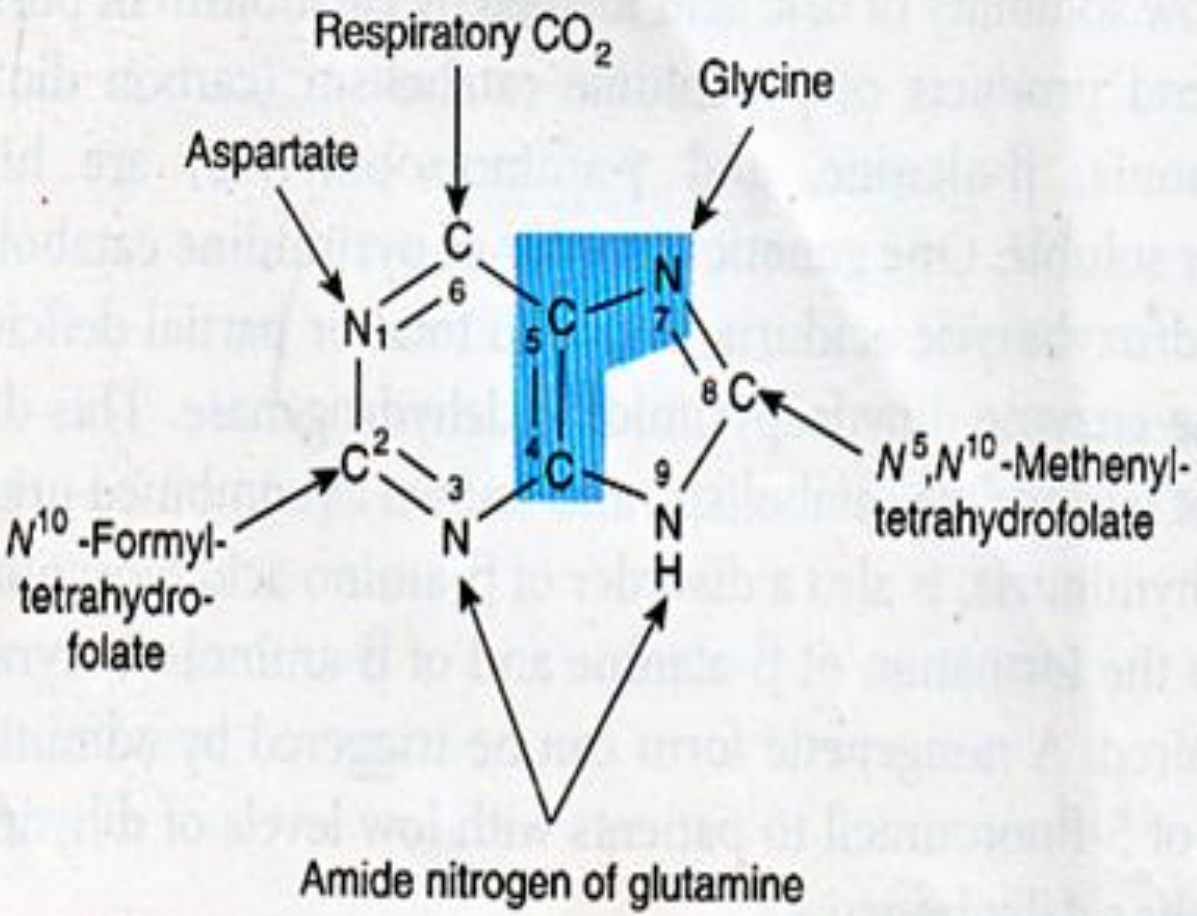


FIGURE 33–1 Sources of the nitrogen and carbon atoms of the purine ring. Atoms 4, 5, and 7 (**blue highlight**) derive from glycine.

IMP is synthesized from amphibolic intermediates

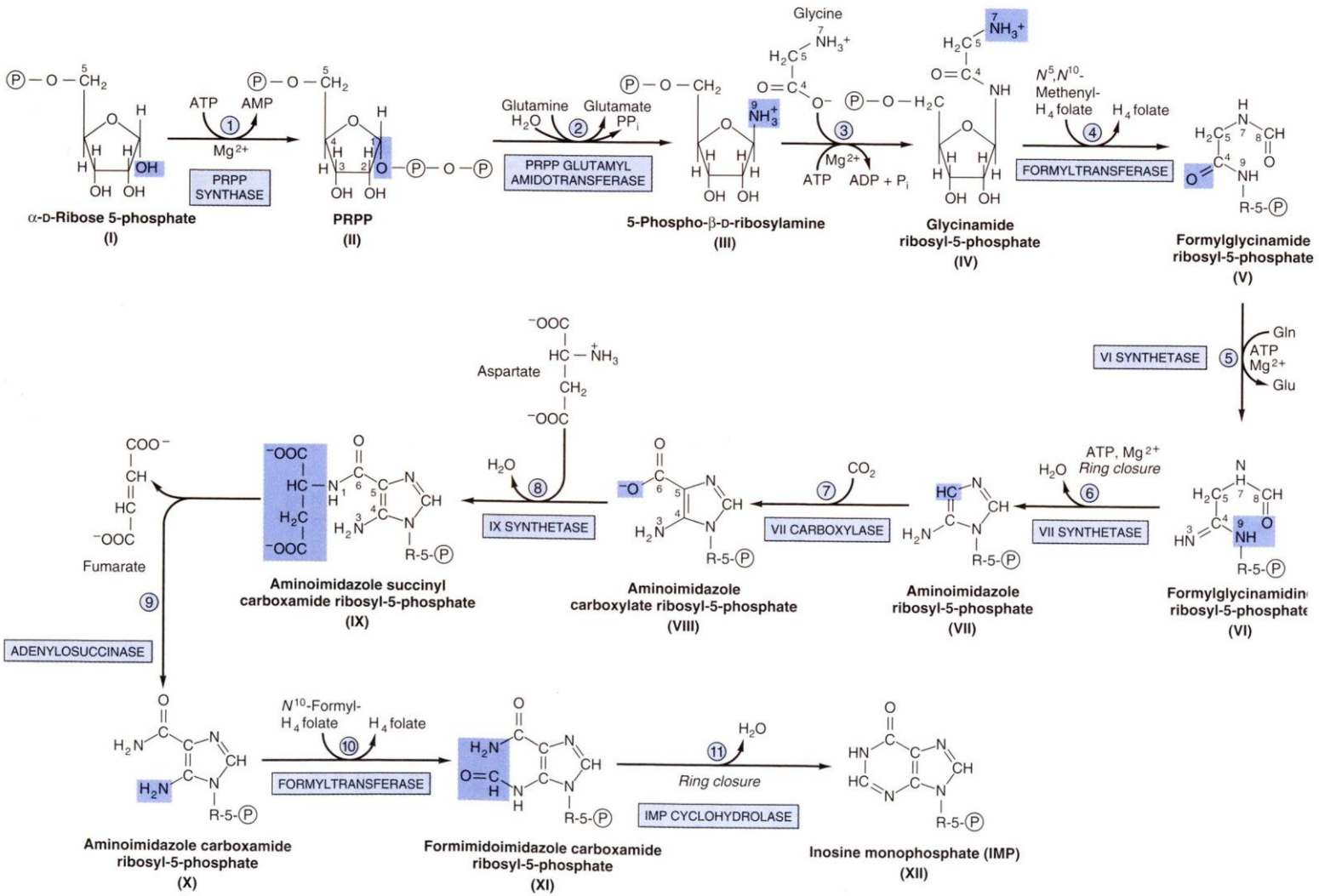


Figure 34–2. Purine biosynthesis from ribose 5-phosphate and ATP. See text for explanations. (Ⓟ, PO_3^{2-} or PO_4^-.)

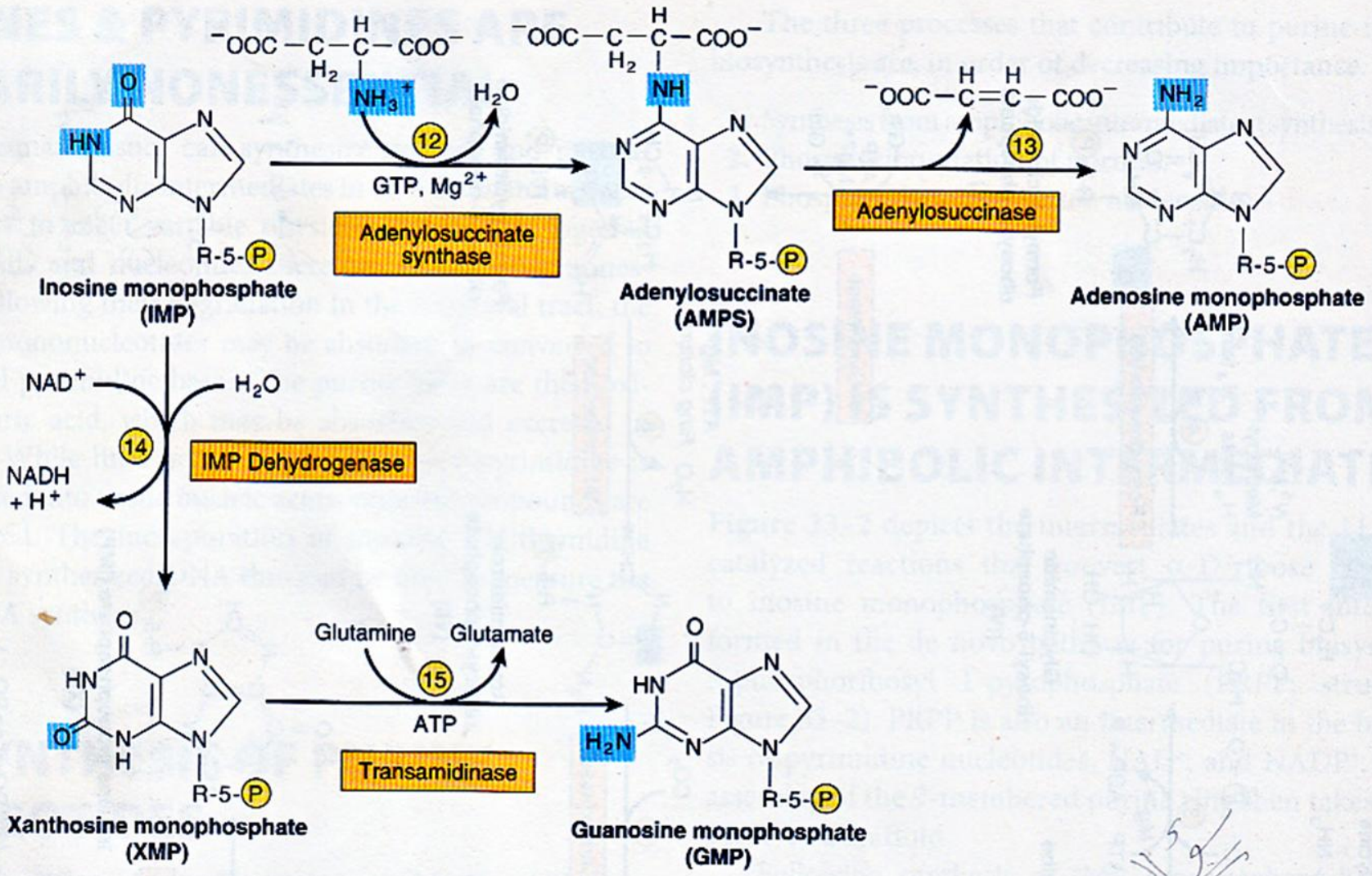


FIGURE 33–3 Conversion of IMP to AMP and GMP.

Conversion of IMP to AMP and GMP

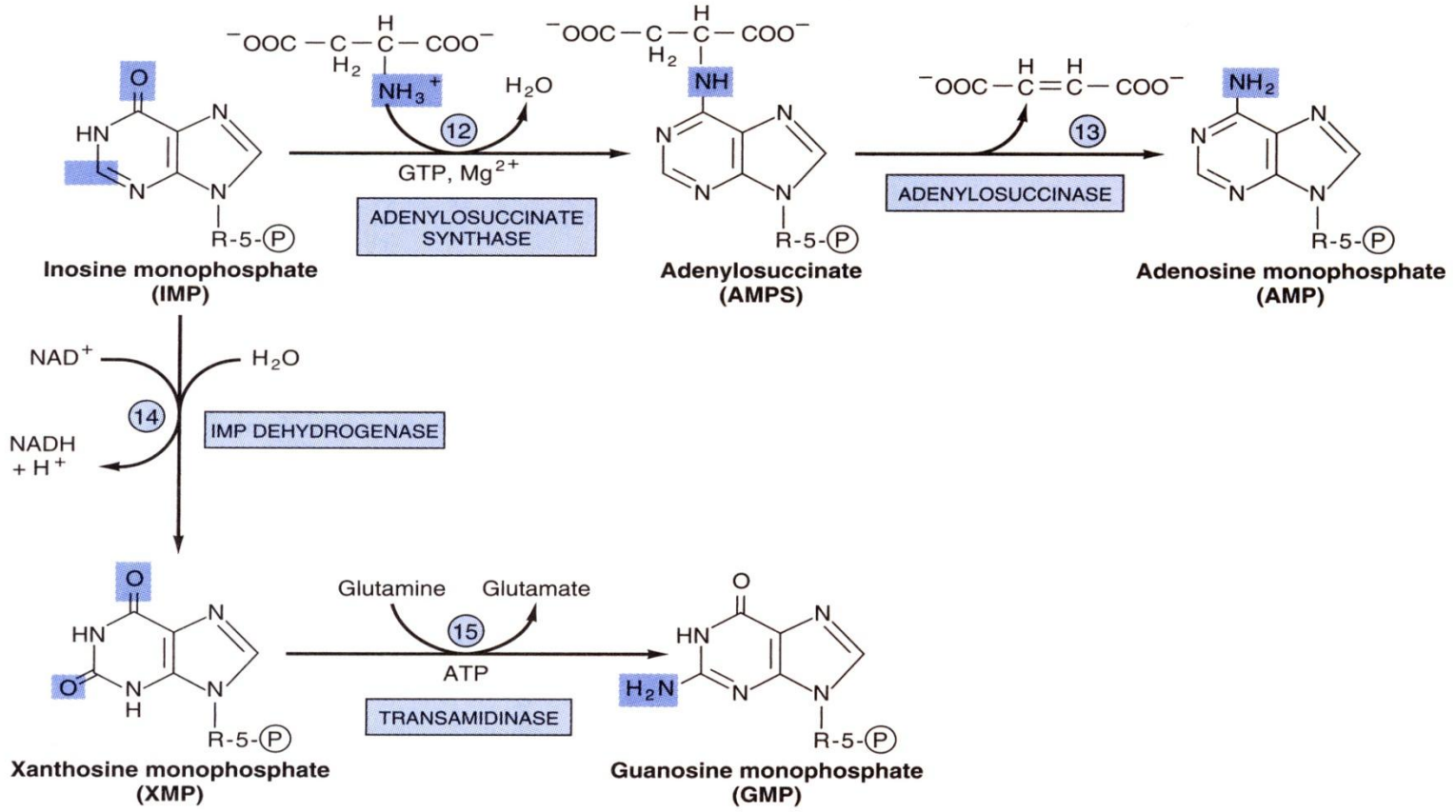


Figure 34–3. Conversion of IMP to AMP and GMP.

Intermediates and precursors of purine biosynthesis:

- Ribose 5 phosphate -CO_2
- ATP -Aspartate
- Glutamine
- Glycine
- N5,N10 methenyl H4Folate
- N10Formyl H4 Folate

Precursors for conversion of IMP to AMP:

Aspartate

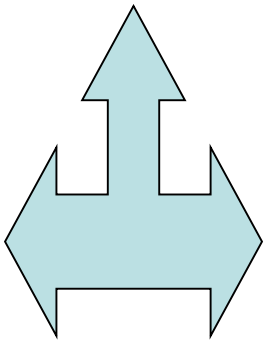
Precursors for conversion of IMP to GMP:

NAD – Glutamine.

Ribose 5 phosphate

↓

IMP



AMP

GMP

Purine synthesis from Ribose 5 Phosphate and ATP

- Importance of TetrahydroFolate
- Anti Folate drugs and Glutamine Analogs are used in cancer chemotherapy.

Salvage reactions convert Purines and their Nucleosides to Mononucleotides

PosphoRibosylation of PurinesandPhosphorylation of Purine Nucleosides are called Salvation Reactions

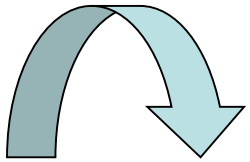
1.PhosphoRibosylation of Purines:

- The Enzyme Ribosyl Transferase catalyses

  Adenine → AMP

  Hypoxanthine → IMP

  Guanine → GMP



PR-PP PPi

2-Phosphorylation of a Purine Ribonucleoside by ATP→Purine Ribonucleotide+ADP

- The Enzyme Adenosine Kinase catalyzes:

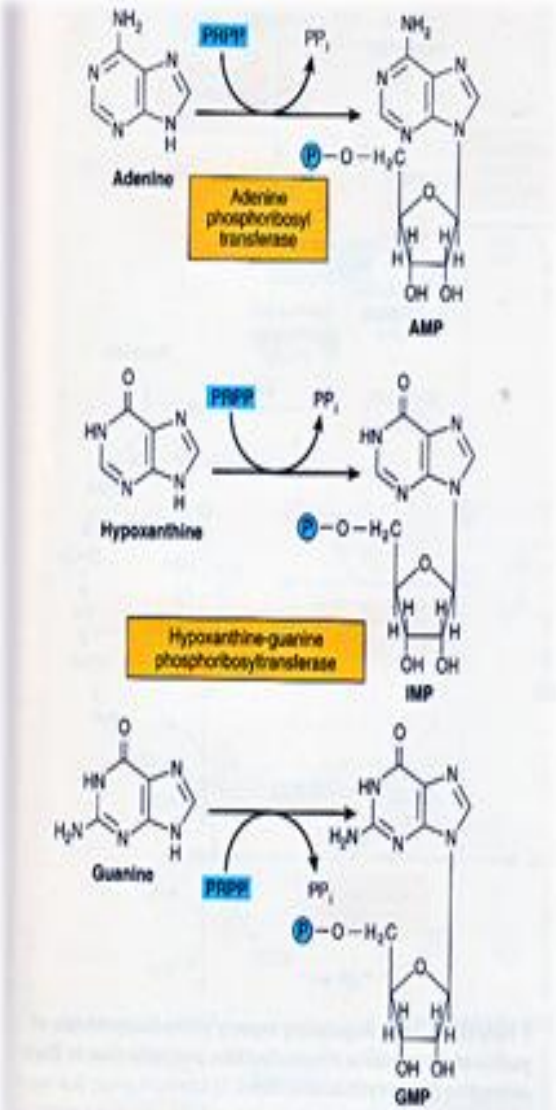
  Adenosine → AMP

  d‘Adenosine→d‘AMP

- the Enzyme deoxy Cytidine Kinase catalyzes:

  d`Cytidine →d`CMP

  2`deoxyGuanosine →dGMP



IGURE 33–4 Phosphoribosylation of adenine, hypoxanthine, d guanine to form AMP, IMP, and GMP, respectively.

..

Where And **Why** Does Salvage Reaction occur:

Where? In the **liver**….it provides Purine and Purine Nucleosides for Salvage reactions.

Why? To Provide Nucleotides for tissues incapable of synthesizing them.

Examples:

Human brain-Erythrocytes-Polymorphonuclear Leukocytes.

Hepatic Purine Biosynthesis is stringently regulated

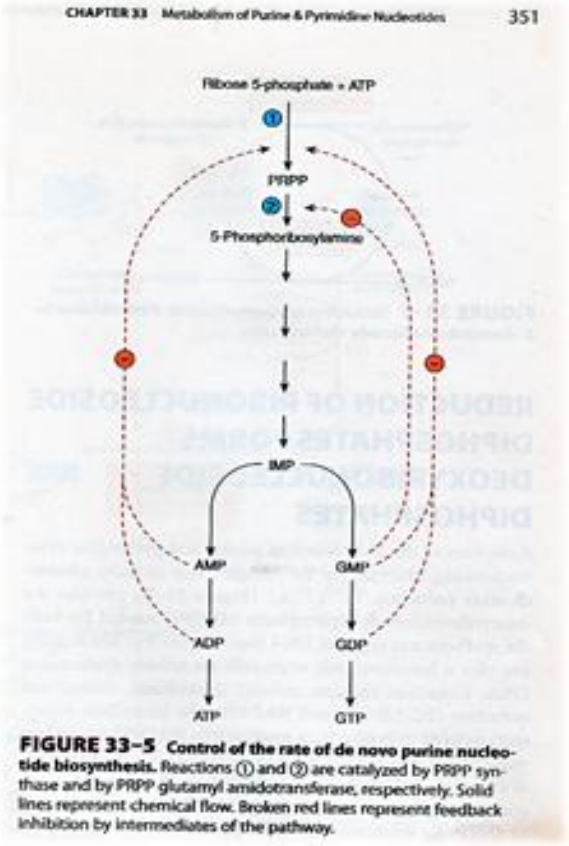


FIGURE 33–5 Control of the rate of de novo purine nucleotide biosynthesis. Reactions ① and ② are catalyzed by PRPP synthase and by PRPP glutamyl amidotransferase, respectively. Solid lines represent chemical flow. Broken red lines represent feedback inhibition by intermediates of the pathway.

AMP &GMP Feedback Regulate their Formation from IMP

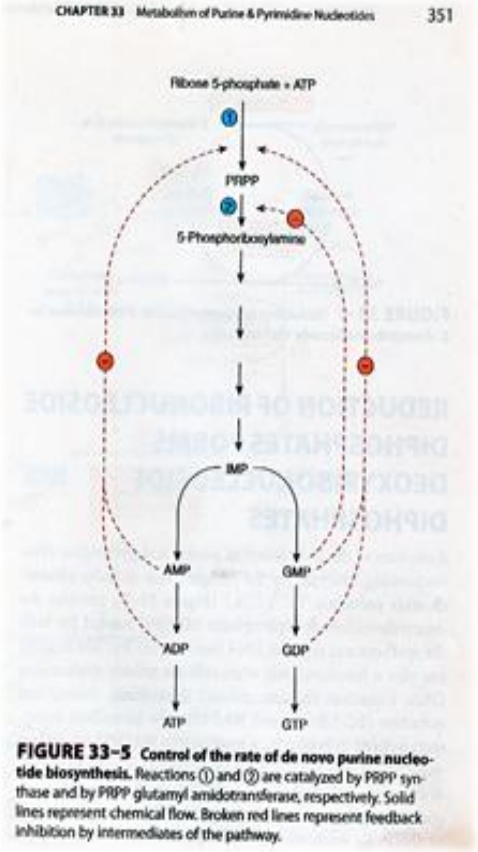


FIGURE 33–5 Control of the rate of de novo purine nucleotide biosynthesis. Reactions ① and ② are catalyzed by PRPP synthase and by PRPP glutamyl amidotransferase, respectively. Solid lines represent chemical flow. Broken red lines represent feedback inhibition by intermediates of the pathway.

Reduction ofRibonucleoside Diphosphate forms DeoxyRibonucleoside DiPhosphates

- The Enzyme responsible is: **Ribonucleotide Reductase complex**

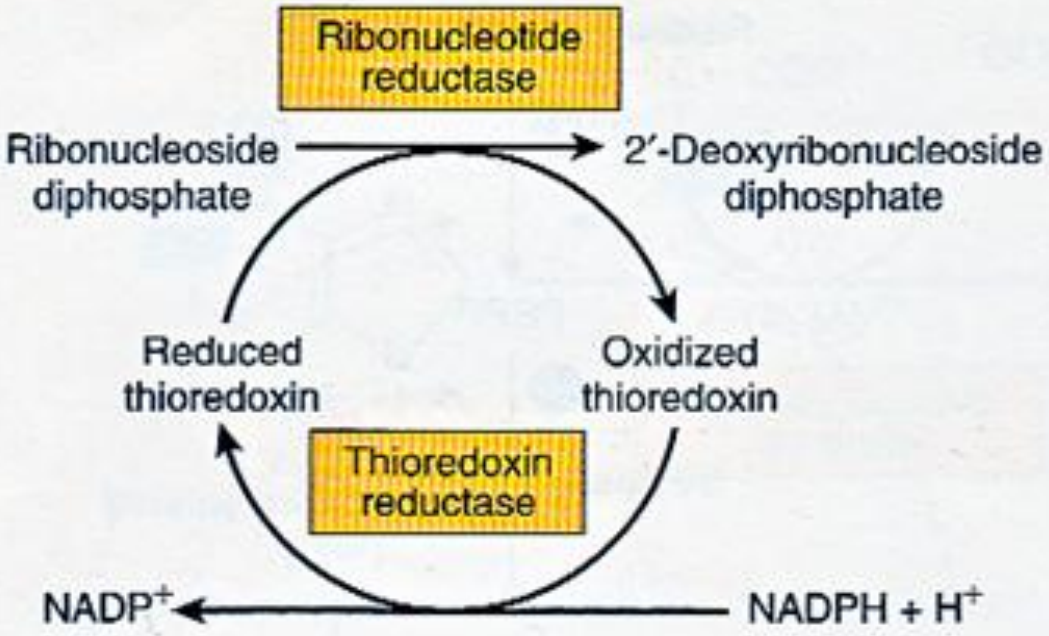
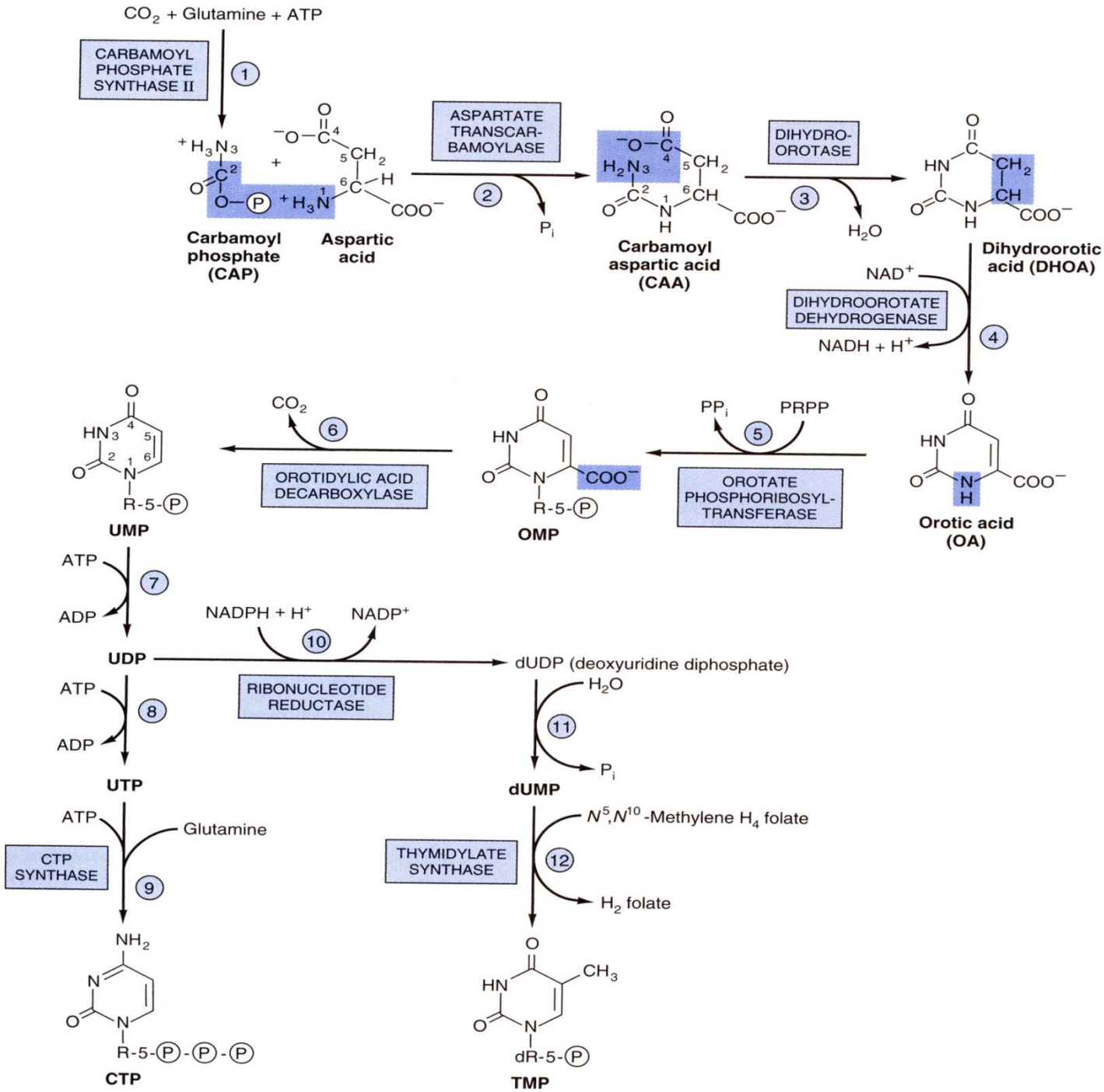


FIGURE 33–7 **Reduction of ribonucleoside diphosphates to 2′-deoxyribonucleoside diphosphates.**

Biosynthesis of Pyrimidine Nucleotides

- The main enzyme is Carbamoyl Phosphate Synthase II (A cytosolic enzyme.
- Carbamoyl phosphate synthase I is Mitochondrial enzyme involved in Urea cycle.
- The main precursors for synthesis are:Glutamine,ATP,CO_2,PRPP,N5 N10Methylene H4 Folate(for TMP only).


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
$NADPH + H^+$
$NADP^+$
10
RIBONUCLEOTIDE REDUCTASE
dUDP (deoxyuridine diphosphate)
ATP
ADP
8
UTP
H_2O
11
P_i
dUMP
ATP
Glutamine
CTP SYNTHASE
9
CTP
N^5,N^{10}-Methylene H_4 folate
THYMIDYLATE SYNTHASE
12
H_2 folate
TMP

The DeoxyRibonucleosides of Uracil and Cytosine Are Salvaged

- Uridine Ribonucleoside

  Cytidine Ribonucleoside

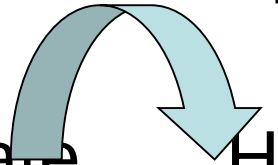
  Thymidine deoxyribonucleoside

  Deoxy Citidine

All converted to their Nucleotides Tri Phosphate by the enzyme ATP dependent phosphoryl Transferase (Kinases).

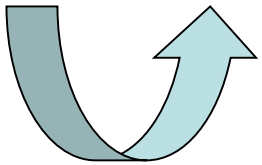
Methotrexate blocks Reduction of Dihydrofolate

- dUMP → TMP



H4Folate H2 Folate

H2 Folate H4 Folate



dihydrofolate Reductase

Methotrexate inhibits diHydroFolate Reductase

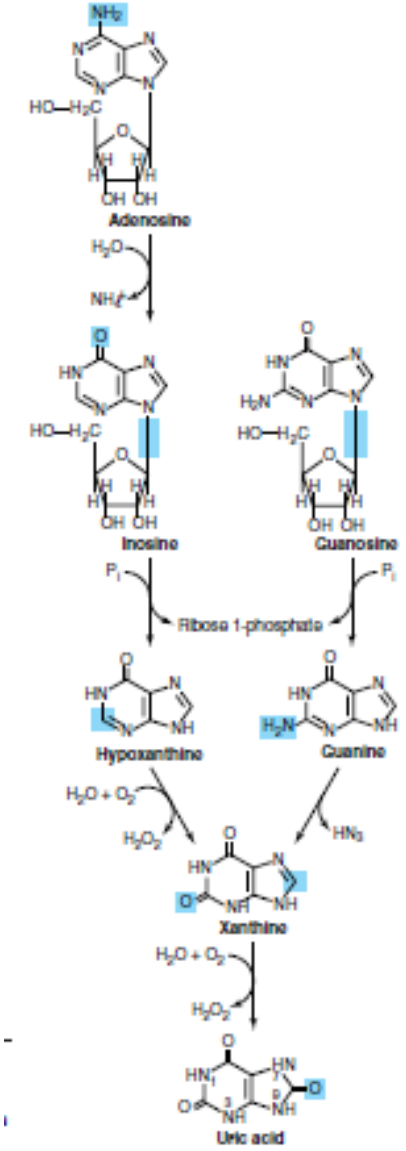
Regulation of Pyrimidine Nucleotide Biosynthesis

- Gene Expression & Enzyme activity both are regulated
- Purine &Pyrimidine Nucleotide Biosynthesis Are Coordinately Regulated

Catabolism of Purines

- Humans catabolize Purines to Uric Acid
- In Mammals other than higher primates There exists an enzyme **Uricase** converts Uric Acid → Allantoin.
- Humans lack Uricase.

Catabolism of purine nucleotides to Uric acid



Disorders of Purine Catabolism

- **Gout:**

  A Genetic defect in PRPP Synthase causes an overproduction of Purine catabolites(Uric Acid) ,or abnormalities of renal handling of UA.
- **Lesh-Nyhan syndrome**:

  A defect in hypoxanthine –guanine phosphoribosyl Transferase (purine salvage enzyme) → overproduction of PRPP → overproduction of purine.
- **Von Geirkes Disease**:

  Deficiency of Glucose 6 phosphatase → increase in ribose 5 p → increase of PRPP.

  Hypouricemia:

  Deficiency of xanthine oxidase (converts xanthine →UA)
- **Adenosine Deaminase & Purine Nucleoside Phosphorylase Deficiency:**

  Associated with an immunodeficiency disease (accumulation of dGTP, dATP) → inhibition of Ribonucleotide Reductase → depleting cells of DNA precursors.

Catabolism of Pyrimidines

- **Catabolism produces water-soluble metabolites:**
- **Pseudouridine is excreted unchanged**

  No human enzyme catalyzes hydrolysis or phosphorylysis of pseudouridine,therefor it is excreted unchanged.

- **Overproduction of pyrimidine catabolites is only rarely associated with clinically significant abnormalities:**

  Disorders of Folate and vit B12 →deficiency of TMP.
- **Orotic aciduria:**

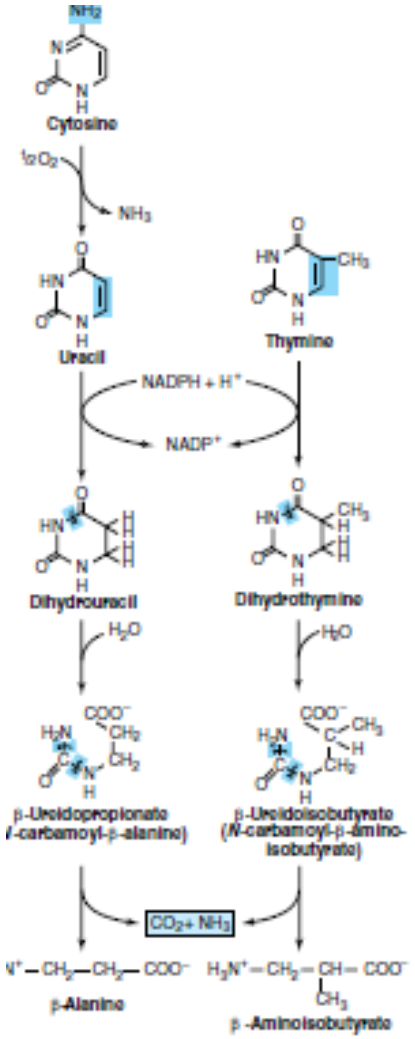
  Reye syndrome:Damaged mitichondria→unable to utilize carbamoyle phosphate →available for cytosolic overproduction of Orotic acid.

  Type I Orotic aciduria: deficiency of orotatephospho ribosyl transferase and orotidylate decarboxylase.

  Type 2 Orotic Aciduria:deficiency of Orotidylate decarboxylase.

- **Deficiency of a urea cycle Enzyme results in excretion of pyrimidine precursors:**
- **Drugs may precipitate Orotic Aciduria:**

Catabolism of pyrimidines



Catabolism of pyrimidines.

TABLE 33–1 Metabolic Disorders of Purine and Pyrimidine Metabolism

Defective Enzyme	Enzyme Catalog Number	OMIM Reference	Major Signs and Symptoms	Figure and Reaction
Purine Metabolism				
Hypoxanthine-guanine phosphoribosyl transferase	2.4.2.8	308000	Lesch-Nyhan syndrome. Uricemia, self-mutilation	33–4 ②
PRPP synthase	2.7.6.1	311860	Gout; gouty arthritis	33–2 ①
Adenosine deaminase	3.5.4.6	102700	Severely compromised immune system	33–1 ①
Purine nucleoside phosphorylase	2.4.2.1	164050	Autoimmune disorders; benign and opportunistic infections	33–11 ②
Pyrimidine Metabolism				
Dihydropyrimidine dehydrogenase	1.3.1.2	274270	Can develop toxicity to 5-fluorouracil, also a substrate for this dehydrogenase	33–12 ②
Orotate phosphoribosyl transferase and orotidylic acid decarboxylase	2.4.2.10 and 4.1.1.23	258900	Orotic acid aciduria type 1; megaloblastic anemia	33–9 ⑤ and ⑥
Orotidylic acid decarboxylase	4.1.1.23	258920	Orotic acid aciduria type 2	33–9 ⑥