

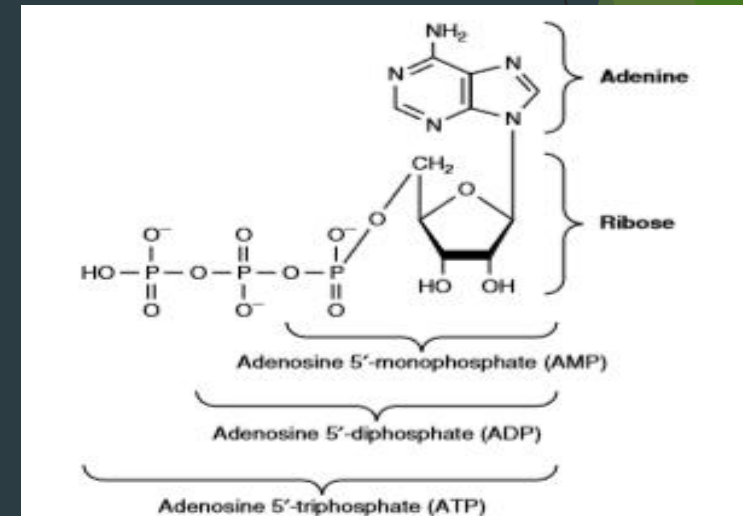
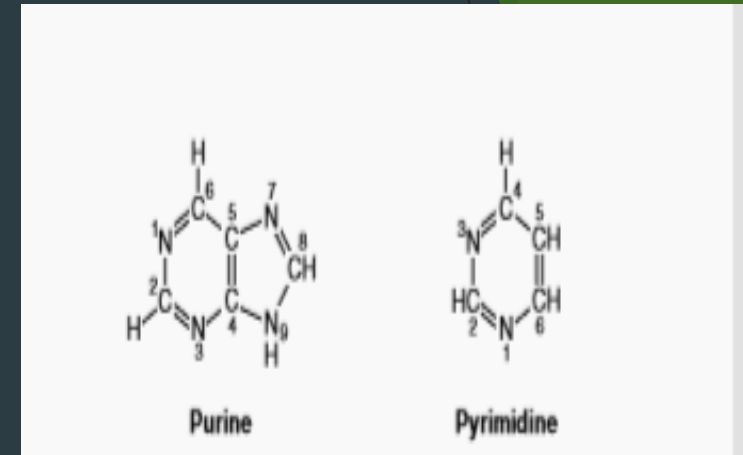
# Nucleotide Metabolism

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# Introduction

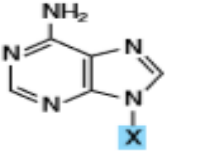
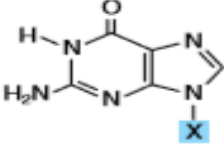
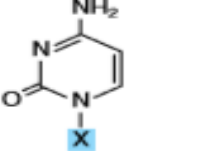
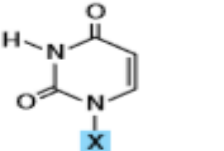
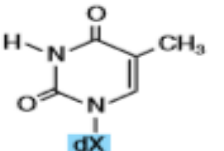
- ▶ Purines and pyrimidines are nitrogen-containing heterocycles, cyclic compounds whose rings contain both carbon and other elements.
- ▶ Nucleosides are derivatives of purines and pyrimidines that have a sugar linked to a ring nitrogen.
- ▶ Nucleotides are nucleosides with a phosphoryl group esterified to a hydroxyl group of the sugar.



# Bases, Nucleosides and Nucleotides

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

# Bases, Nucleosides and Nucleotides

Base Formula	Base X = H	Nucleoside X = Ribose or Deoxyribose	Nucleotide, Where X = Ribose Phosphate
	Adenine A	Adenosine A	Adenosine monophosphate AMP
	Guanine G	Guanosine G	Guanosine monophosphate GMP
	Cytosine C	Cytidine C	Cytidine monophosphate CMP
	Uracil U	Uridine U	Uridine monophosphate UMP
	Thymine T	Thymidine T	Thymidine monophosphate TMP

- Ingested nucleic acids and nucleotides, which are dietarily nonessential, are degraded in the intestinal tract to mononucleotides, which may be absorbed or converted to purine and pyrimidine bases.

# Metabolism

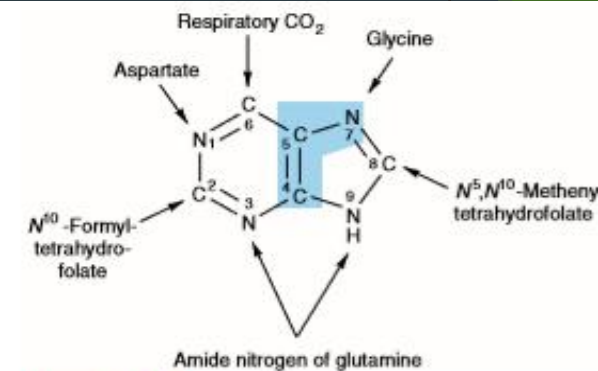
Metabolism is broadly divided into two categories:

- 1 . Catabolism : The degradative processes concerned with the breakdown of complex molecules to simpler ones, with a concomitant release of energy.
2. Anabolism : The biosynthetic reactions involving the formation of complex molecules from simple precursors

# Process involved in nucleotides biosynthesis

These are, in order of decreasing importance

- (1) Synthesis from amphibolic intermediates (synthesis de novo).
- (2) Phosphoribosylation of purines
- (3) Phosphorylation of purine nucleosides.



**Figure 34-1.** Sources of the nitrogen and carbon atoms of the purine ring. Atoms 4, 5, and 7 (shaded) derive from glycine.

# Biosynthesis of purine nucleotides

- ▶ Conversion of purines, their ribonucleosides, and their deoxyribonucleosides to mononucleotides involves so called “salvage reaction.
- ▶ Liver is the major site for purine nucleotide synthesis.
- ▶ Erythrocytes, polymorphonuclear leukocytes and brain cannot produce purines.
- ▶ Folic acid is essential for the synthesis of purine nucleotides. Folic (methotrexate) are employed to control cancer.



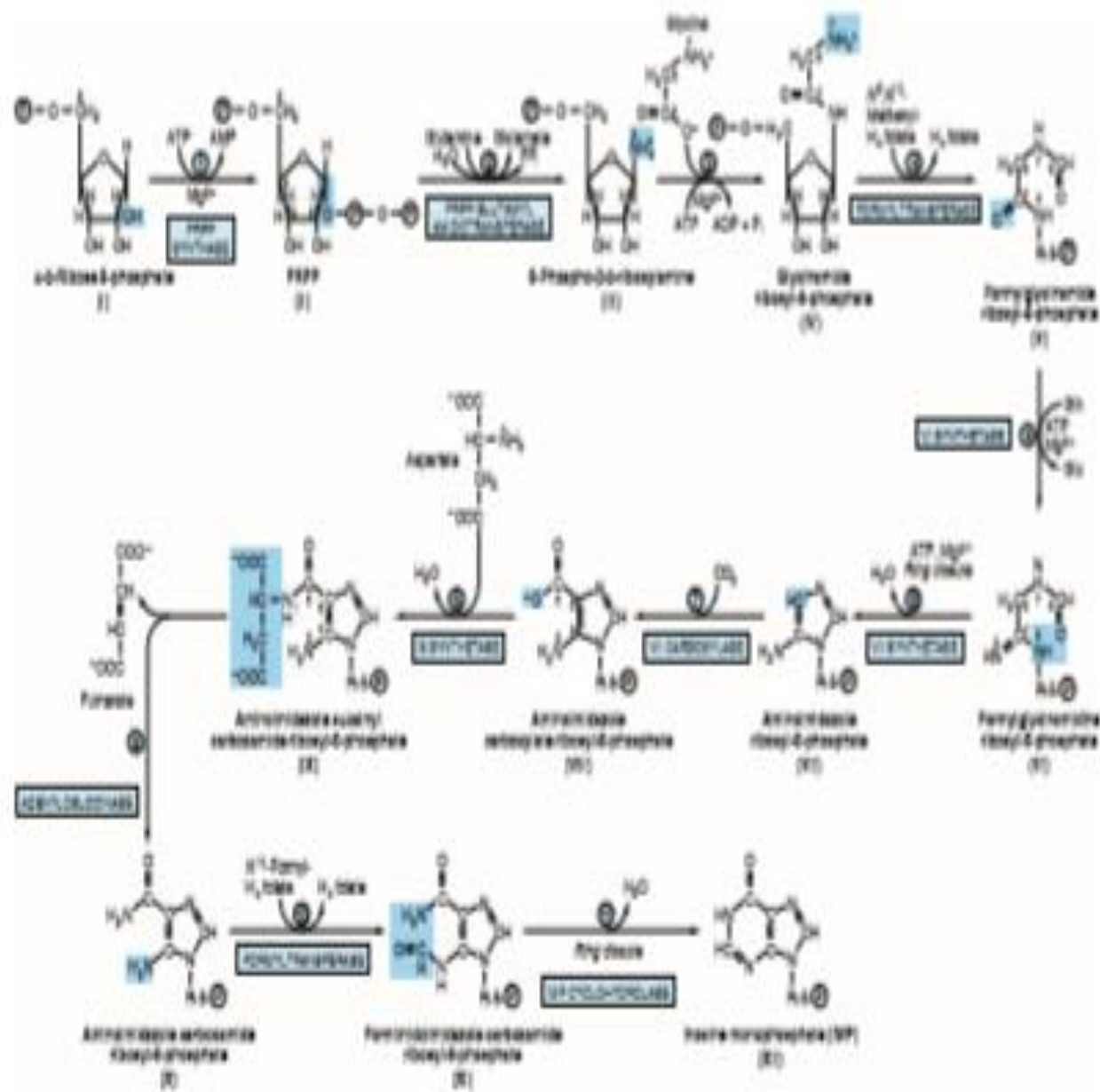


Figure 34-2. Purine biosynthesis from ribose 5-phosphate and ATP. See text for explanations. (P, PO<sub>4</sub><sup>3-</sup> or PO<sub>3</sub><sup>2-</sup>)

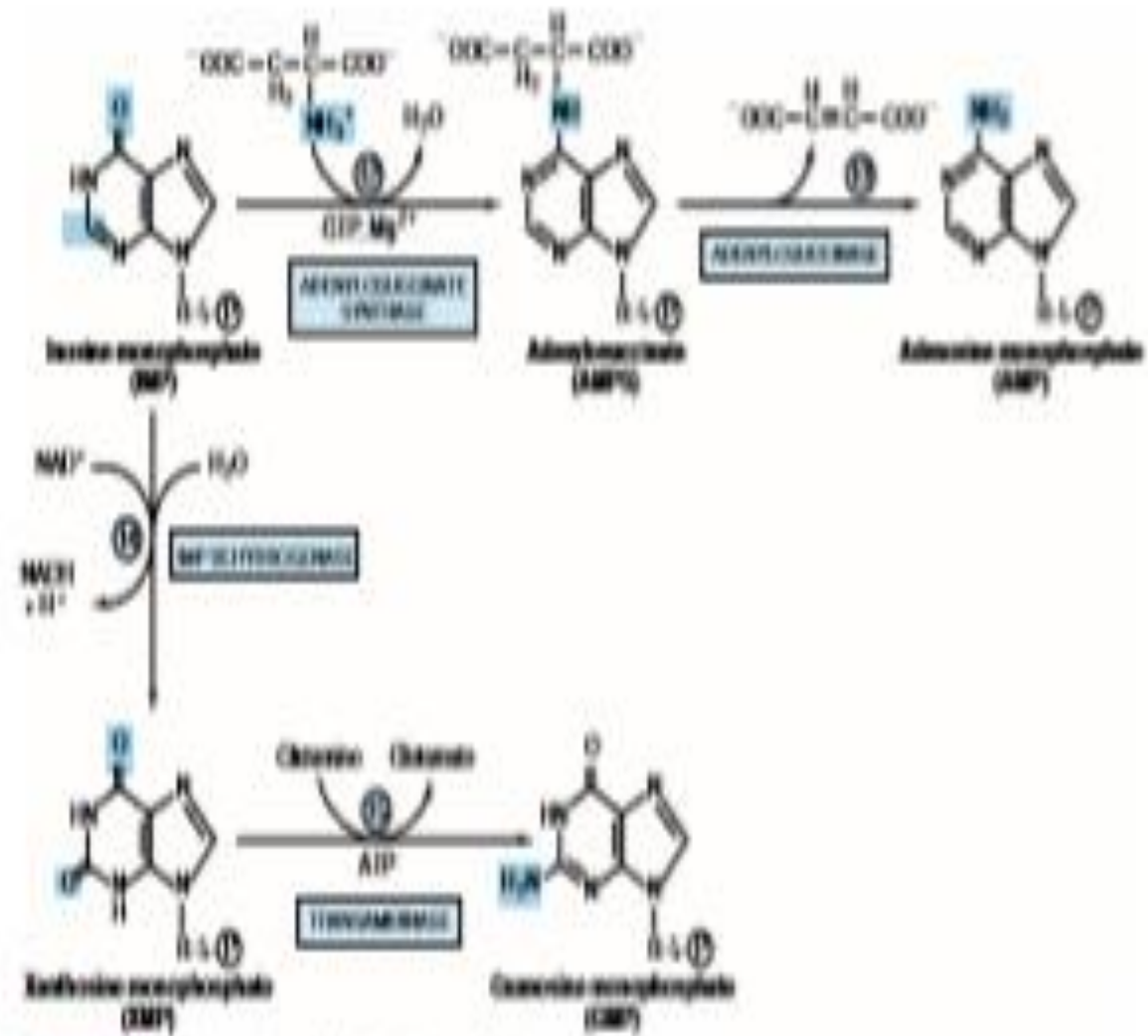


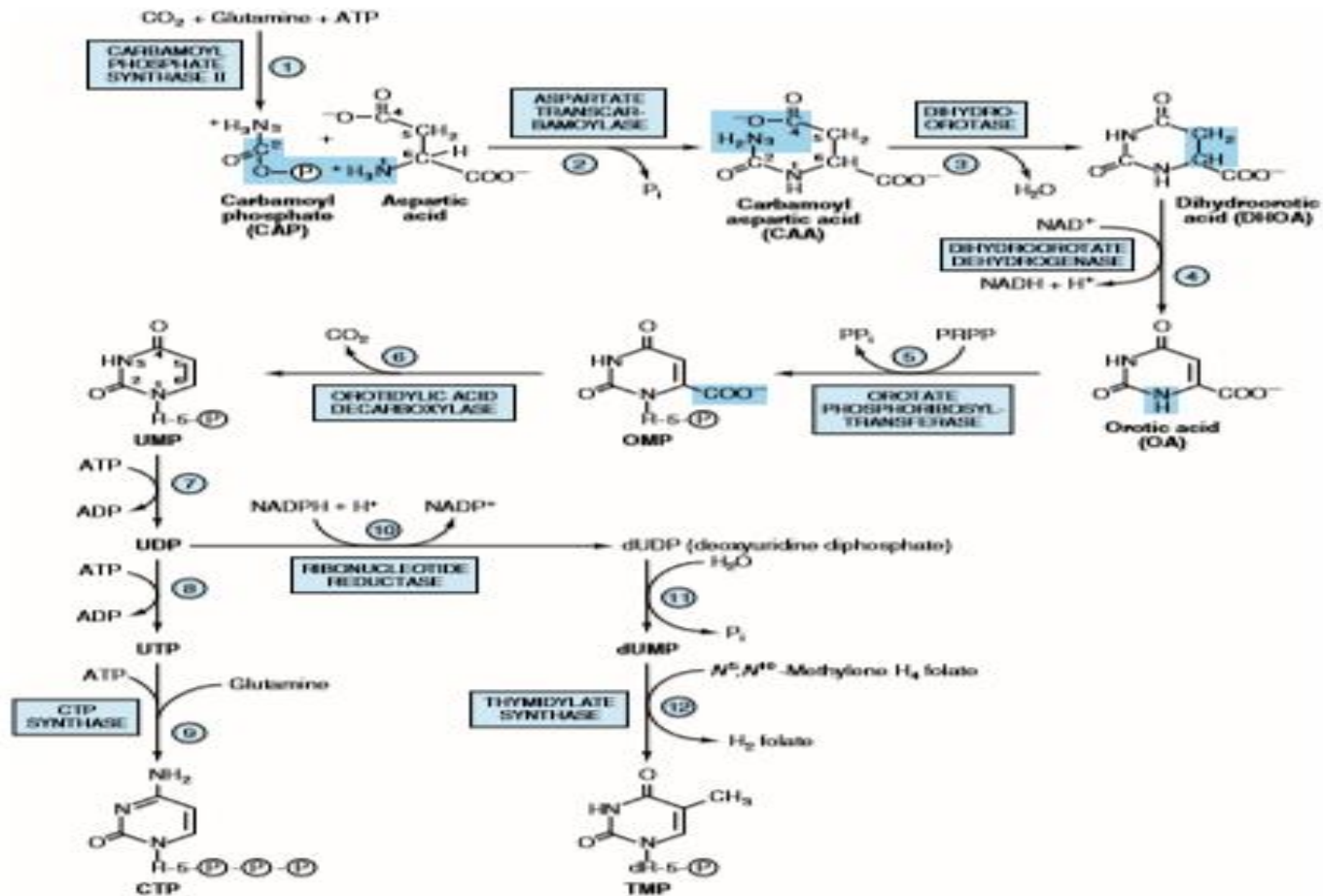
Figure 34-3. Conversion of IMP to AMP and GMP.

# Biosynthesis Of Pyrimidine Nucleotides

- ▶ The catalyst for the initial reaction is cytosolic carbamoyl phosphate synthase II, a different enzyme from the mitochondrial carbamoyl phosphate synthase I of urea synthesis .
- ▶ Compartmentation thus provides two independent pools of carbamoyl phosphate. PRPP, an early participant in purine nucleotide synthesis, is a much later participant in pyrimidine biosynthesis.
- ▶ Mammalian cells reutilize few free pyrimidines, “salvage reactions” convert the ribonucleosides uridine and cytidine and the deoxyribonucleosides thymidine and deoxycytidine to their respective nucleotides.

- ▶ ATP dependent phosphoryltransferases (kinases) catalyze the phosphorylation of the nucleoside diphosphates 2'-deoxycytidine, 2'-deoxyguanosine, and 2'-deoxyadenosine to their corresponding nucleoside triphosphates.
- ▶ In addition, orotate phosphoribosyltransferase, an enzyme of pyrimidine nucleotide synthesis, salvages orotic acid by converting it to orotidine monophosphate (OMP).
- ▶ Antifolate drugs and glutamine analogs inhibit purine biosynthesis.

# The biosynthetic pathway for pyrimidine nucleotides



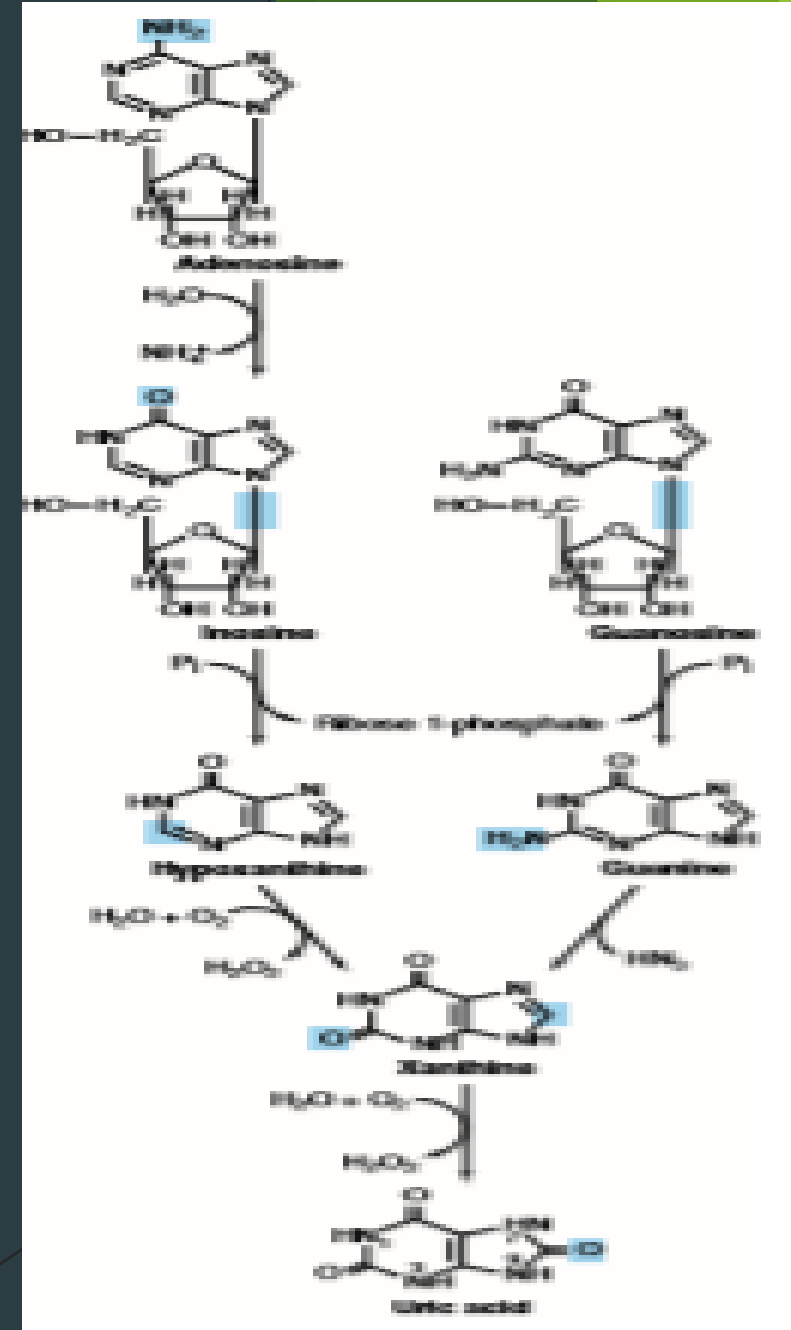
# Catabolism of purines

Humans convert adenosine and guanosine to uric acid.

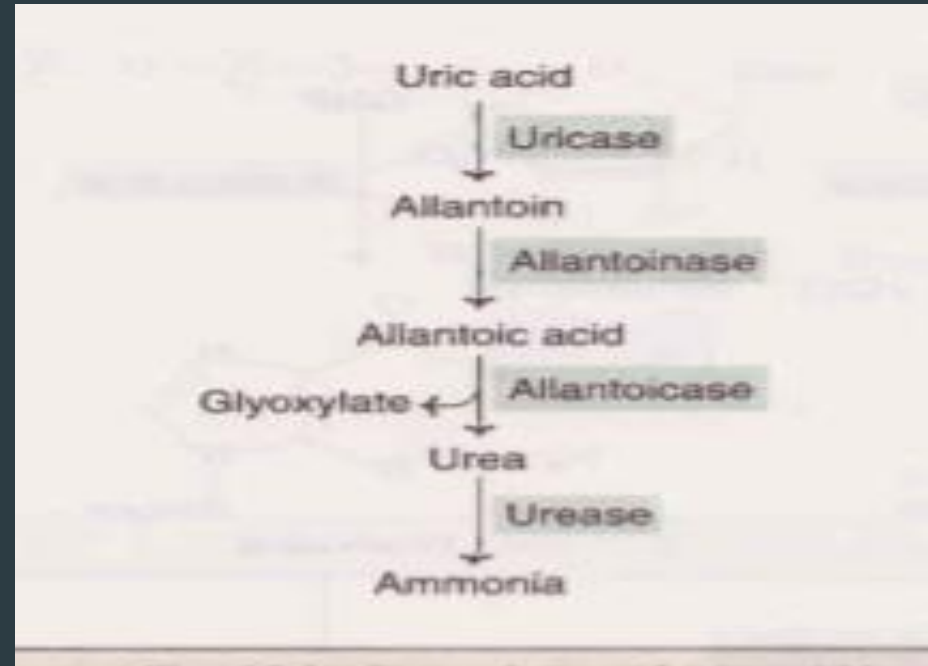
Adenosine is first converted to inosine by adenosine deaminase.

In mammals other than higher primates, uricase converts uric acid to the watersoluble product allantoin.

Since humans lack uricase, the end product of purine catabolism in humans is uric acid.



# Degradation of uric acid in animals other than man



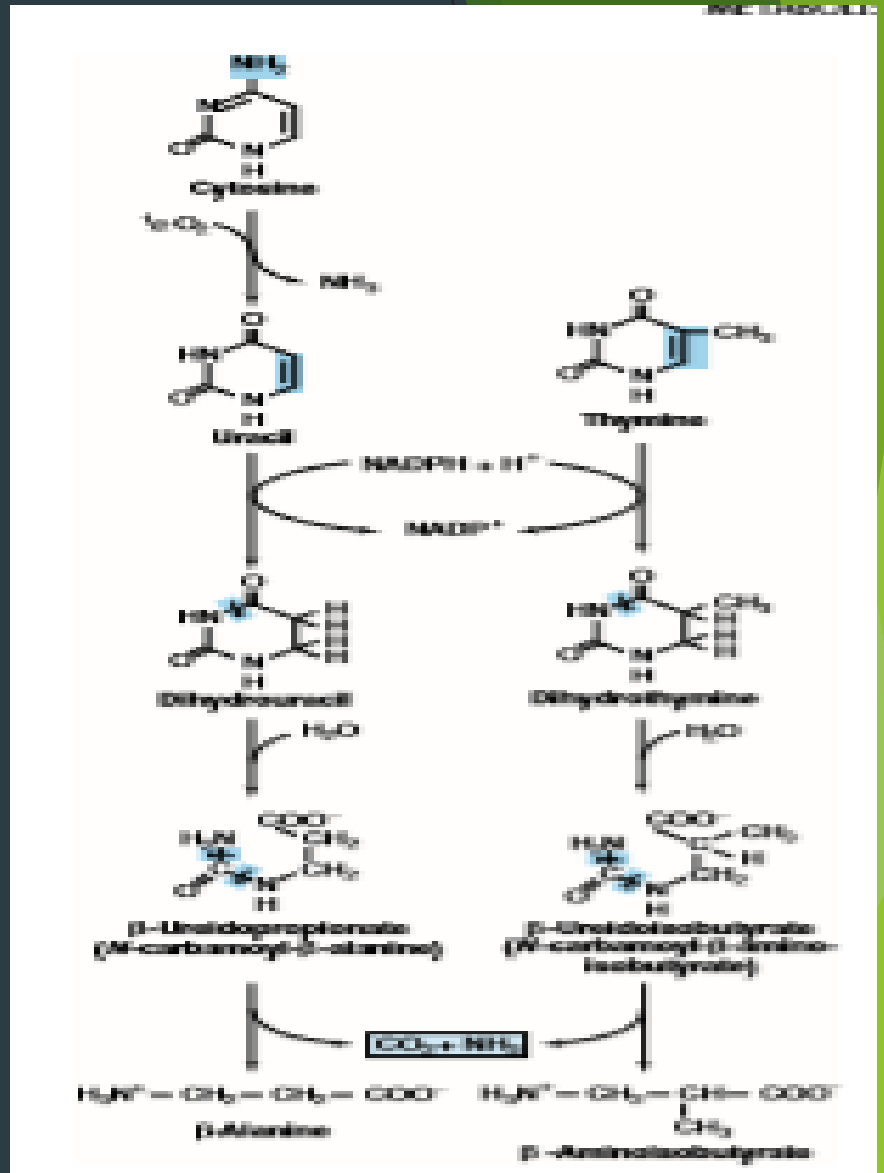
# Catabolism of pyrimidines

Pyrimidine catabolism are highly water-soluble: CO<sub>2</sub>, NH<sub>3</sub>, β-alanine, and β-aminoisobutyrate .

Excretion of β-aminoisobutyrate increases in leukemia and severe x-ray radiation exposure due to increased destruction of DNA.

Humans probably transaminate β-aminoisobutyrate to methylmalonate semialdehyde, which then forms succinyl-CoA .

Since the end products of pyrimidine catabolism are highly water-soluble, pyrimidine overproduction results in few clinical signs or symptoms.



# Conclusions

- ▶ Coordinated regulation of purine and pyrimidine nucleotide biosynthesis ensures their presence in proportions appropriate for nucleic acid biosynthesis and other metabolic needs.
- ▶ Pyrimidine nucleotides are synthesized from the precursors aspartate, glutamine and CO<sub>2</sub>, besides ribose 5-phosphate.
- ▶ Pyrimidines are degraded to amino acids, namely β alanine and β aminoisobutyrate which are then metabolized