

Nucleic acid metabolism and Genetic information transfer

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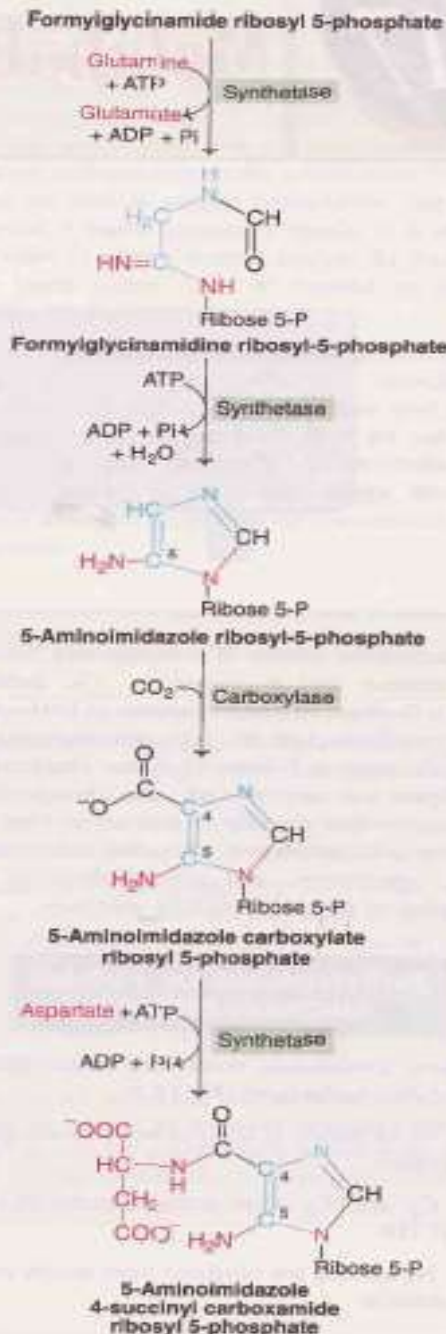
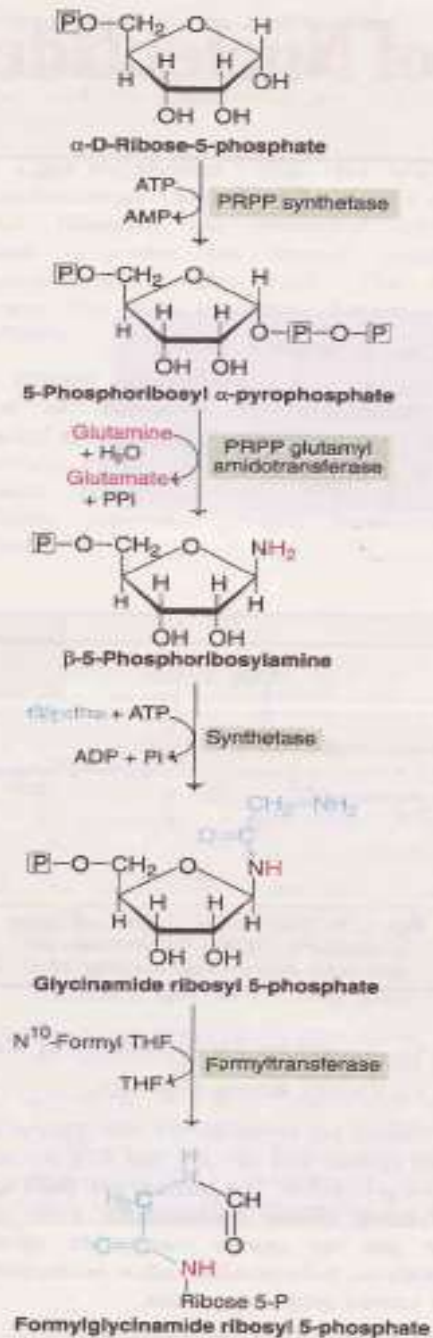
CONTENTS

- Biosynthesis of purine and pyrimidine nucleotides
- Catabolism of purine nucleotides and Hyperuricemia and Gout disease
- Organization of mammalian genome
- Structure of DNA and RNA and their functions
- DNA replication (semi conservative model)
- Transcription or RNA synthesis
- Genetic code
- Translation or Protein synthesis and inhibitors

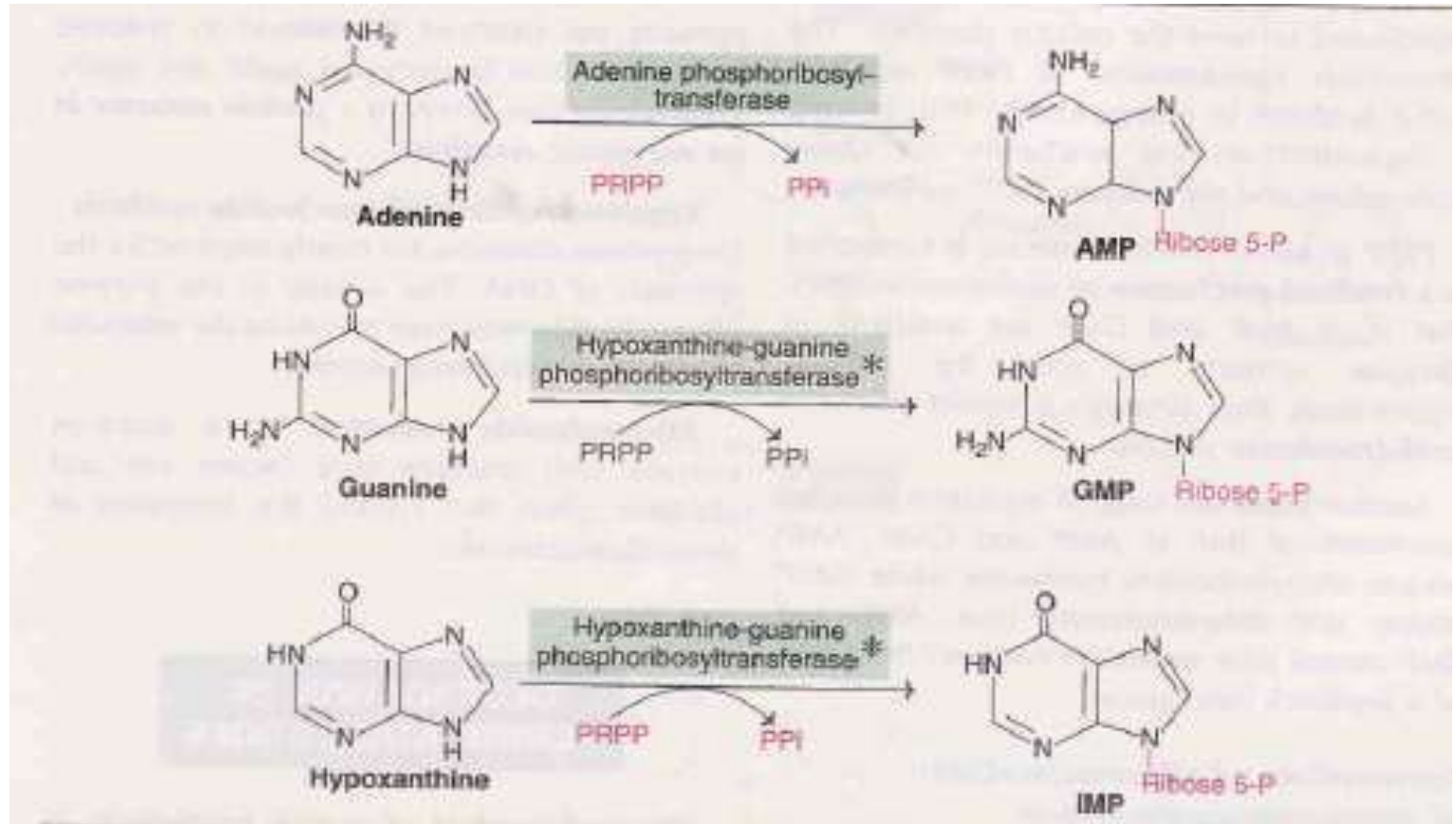
Biosynthesis of purine nucleotides

- **Ribose 5-phosphate** is the starting material for purine nucleotide synthesis.
- It reacts with ATP to form **phosphoribosyl pyrophosphate (PRPP)**.
- Glutamine transfers its amide nitrogen to PRPP and produce 5-phosphoribosyl amine by the action of enzyme **PRPP glutamyl amidotransferase**.
- Phosphoribosylamine reacts with glycine in the presence of ATP to form glycinamide ribosyl 5-phosphate (GAR).
- N₁₀-Formyl tetrahydrofolate donates the formyl group and the product formed is formylglycinamide ribosyl 5-phosphate.
- Glutamine transfers the second amido amino group to produce formyl glycinamide ribosyl 5-phosphate.

- 5-aminoimidazole ribosyl 5-phosphate is formed in an ATP dependent reaction.
- Addition of CO₂ occurs to yield aminoimidazole carboxylate ribosyl 5-phosphate.
- Aspartate condenses with aminoimidazole carboxylate ribosyl 5-phosphate to form aminoimidazole 4-succinyl carboxamide ribosyl 5-phosphate.
- **Adenosuccinate lyase** cleaves off fumarate to form aminoimidazole 4-carboxamide ribosyl 5-phosphate.
- N₁₀-Formyl tetrahydrofolate donates a one-carbon moiety to produce formaminoimidazole 4-carboxamide ribosyl 5-phosphate.
- The final reaction catalysed by **cyclohydrolase** leads to ring closure with an elimination of water molecule.
- The product obtained is **inosine monophosphate(IMP)**, the parent purine nucleotide from which other purine nucleotides can be synthesized.

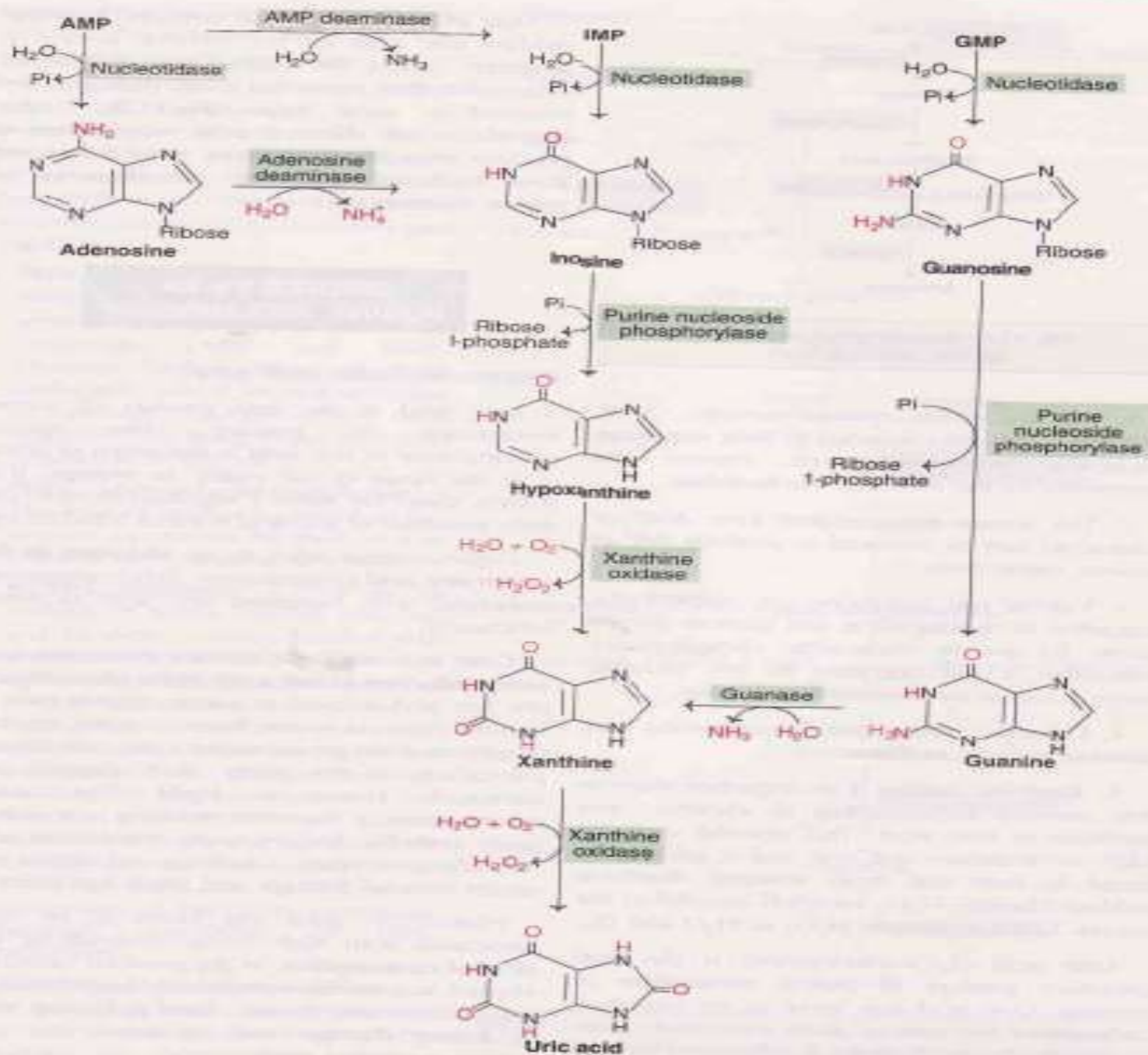


- The purines can be directly converted to the corresponding nucleotides, and this process is known as **salvage pathway**.
- **Adenine phosphoribosyl transferase** catalyses the formation of AMP from adenine.
- **Hypoxanthine-guanine phosphoribosyl transferase (HGPRT)** converts guanine and hypoxanthine, respectively, to GMP and IMP.



Degradation of purine nucleotides


- The end product of purine metabolism in humans is **uric acid**.
- The nucleotide monophosphates (**AMP, IMP and GMP**) are converted to their respective nucleoside forms (adenosine, inosine and guanosine) by the action of **nucleotidase**.
- The amino group, either from AMP or adenosine, can be removed to produce IMP or inosine, respectively.
- **Inosine** and **guanosine** are respectively, converted to **hypoxanthine** and **guanine** by **purine nucleoside phosphorylase**.
- Adenosine is not degraded by this enzyme, hence it has to be converted to inosine.
- **Guanine** undergoes deamination by **guanase** to form **xanthine**.
- **Xanthine oxidase** converts hypoxanthine to xanthine, and xanthine to uric acid.



Disorders of purine metabolism

Hyperuricemia and gout:

- **Hyperuricemia** refers to an elevation in the serum uric acid concentration.
- This is sometimes associated with increased uric acid excretion (uricosuria).
- **Gout** is a metabolic disease associated with overproduction of uric acid.
- In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, particularly in the joints.
- Such deposits are commonly known as tophi.
- This causes inflammation in the joints resulting in a painful gouty arthritis.
- Sodium urate and/or uric acid may also precipitate in kidneys and ureters that results in renal damage and stone formation

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- Gout was found to be often associated with high living, over-eating and alcohol consumption.
 - Gout is of two **types-primary and secondary**.
 - **Primary gout** is an inborn error of metabolism due to overproduction of uric acid. This is mostly related to increased synthesis of purine nucleotide.
 - **Secondary gout** is due to various diseases causing increased synthesis or decreased excretion of uric acid.
 - The drug of choice for the treatment of primary gout is **allopurinol**.
 - Besides the drug therapy, restriction in dietary intake of purines and alcohol is advised.
 - Consumption of plenty of water will also be useful.
 - The anti-inflammatory drug colchicine is used for the treatment of gouty arthritis.
 - Other antiinflammatory drugs-such as phenylbutazone, indomethacin , oxyphenbutazone, corticosteroids are also useful.

Biosynthesis of pyrimidine nucleotides

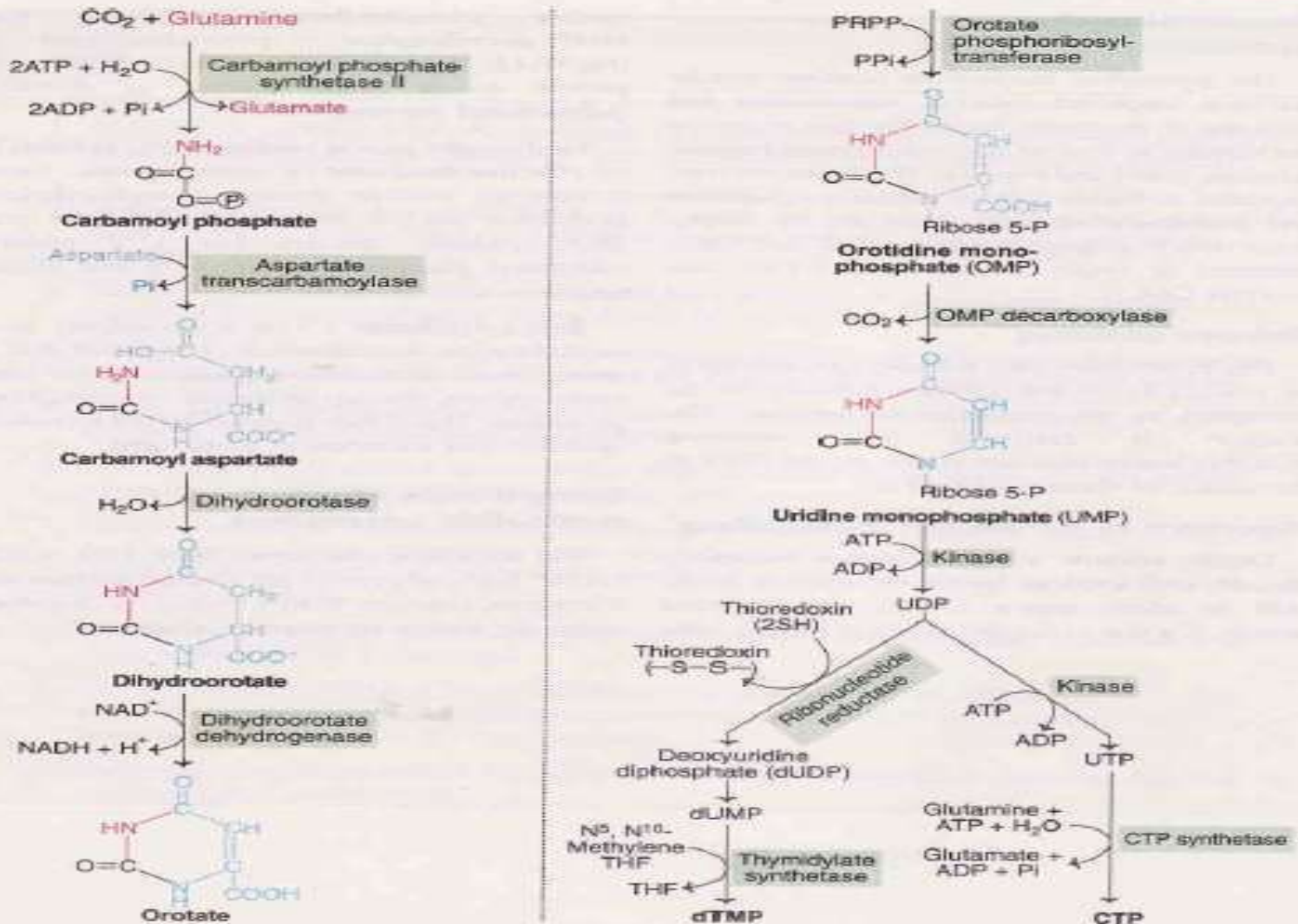


Fig. 17.12 contd. next column

Fig. 17.12 : Metabolic pathway for the synthesis of pyrimidine nucleotides.

- Glutamine transfers its amido nitrogen to CO_2 catalysed by **carbamoyl phosphate synthetase II** to produce carbamoyl phosphate.
- Carbamoyl phosphate condenses with aspartate to form carbamoyl aspartate. This reaction is catalysed by **aspartate transcarbamoylase**.
- **Dihydroorotase** catalyses the pyrimidine ring closure with a loss of H_2O .
- Orotate is formed by NAD^+ dependent dehydrogenation.
- Ribose-5-phosphate is added to orotate to produce orotidine monophosphate (OMP). This reaction is catalysed by **orotate phosphoribosyltransferase**.
- OMP undergoes decarboxylation to uridine mono-phosphate (UMP)
- By an ATP-dependent **kinase** reaction, UMP is converted to UDP which serves as a precursor for the synthesis of dUMP, dTMP, UTP and CTP..