BHARATHIDASAN UNIVERSITY

Tiruchirappalli – 620024

Tamil Nadu, India.

Programme: Biochemistry

Course Title: Intermediary Metabolism

COURSE CODE: BC201CR

Unit: 5

Nucleic acid Metabolism

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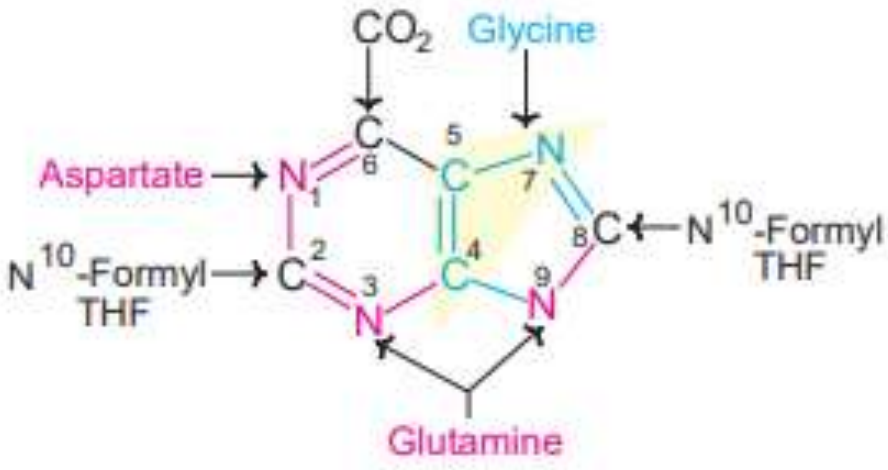
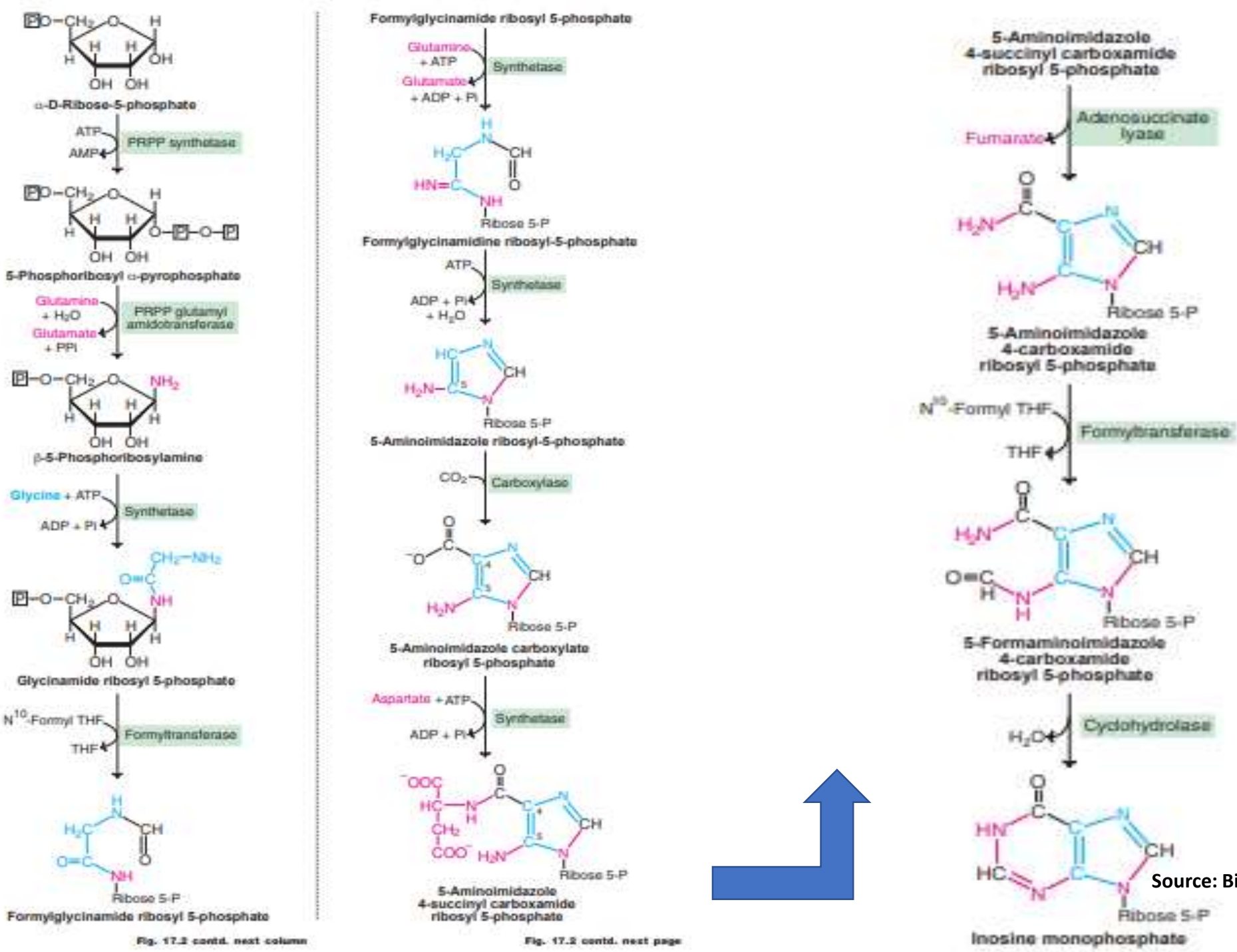
Nucleotide Biosynthesis

- **Denovo synthesis Pathway:**
- In this pathway, the cell constructs purine and pyrimidine nucleotides from basic molecular building blocks: the synthesis of nucleotides from scratch, using simple precursors like amino acids, ribose-5-phosphate, CO_2, and ammonia.
- Purines (such as AMP and GMP) are synthesized starting with ribose-5-phosphate and involve several enzymatic steps.
- Pyrimidines (such as UMP, CMP, TMP) are synthesized from carbamoyl phosphate and aspartate, eventually leading to the production of nucleotide bases.
- The de novo synthesis of nucleotides is energetically expensive because it requires multiple steps, enzymes(PRPP synthetas) and ATP.
- This pathway is particularly active when cells need to rapidly generate nucleotides, for instance during cell division.
- **Salvage pathway:**
- The salvage pathway involves the recycling of pre-existing nucleotides or their bases to form new nucleotides, which is a more energy-efficient process compared to de novo synthesis.

BIOSYNTHESIS OF PURINE

- N1 of purine is derived from amino group of aspartate.
- C2 and C8 arise from formate of N10- formyl THF.
- N3 and N9 are obtained from amide group of glutamine.
- C4, C5 and N7 are contributed by glycine.
- C6 directly comes from CO2





Source: Biochemistry Satyanarayan 4th Edition

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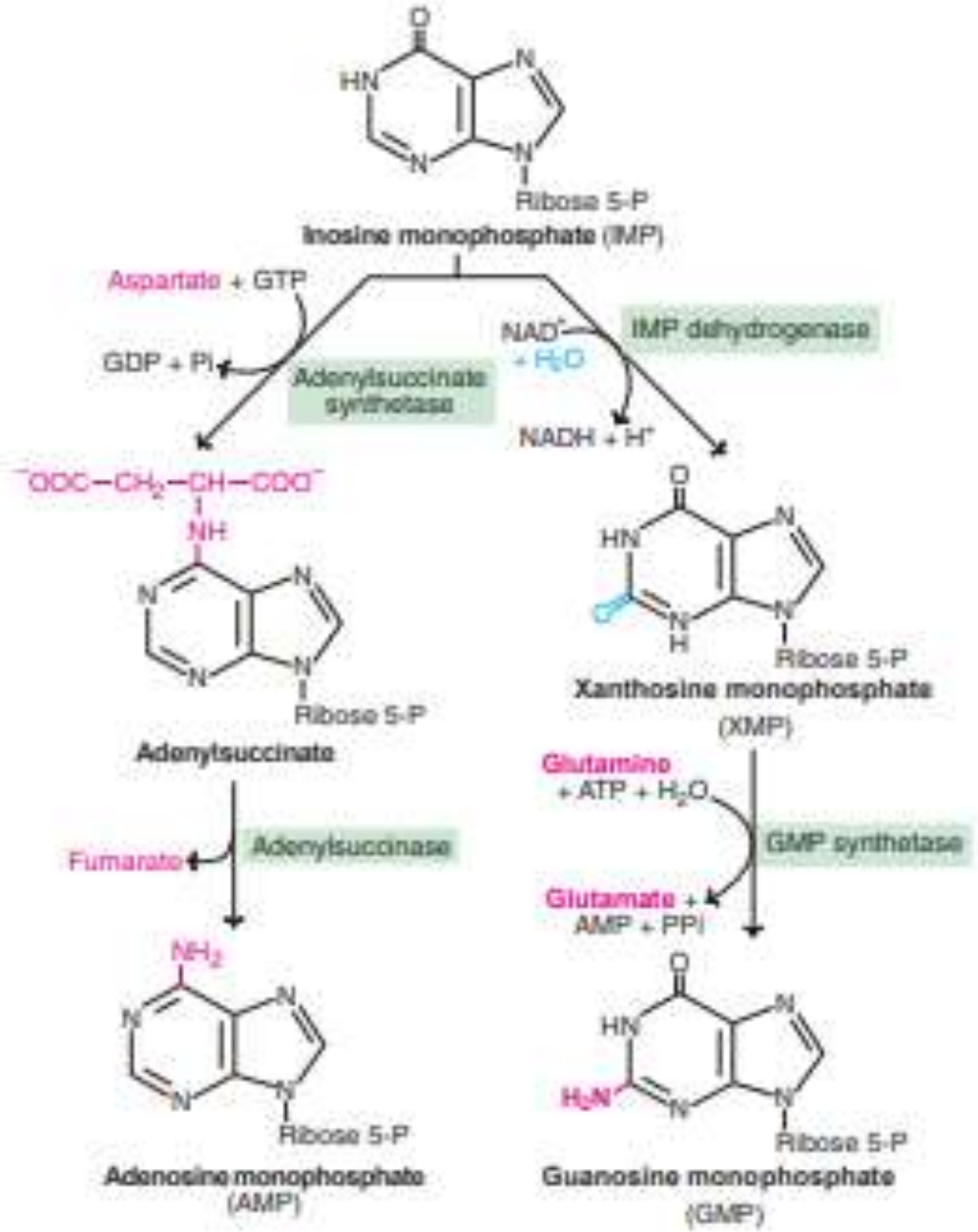
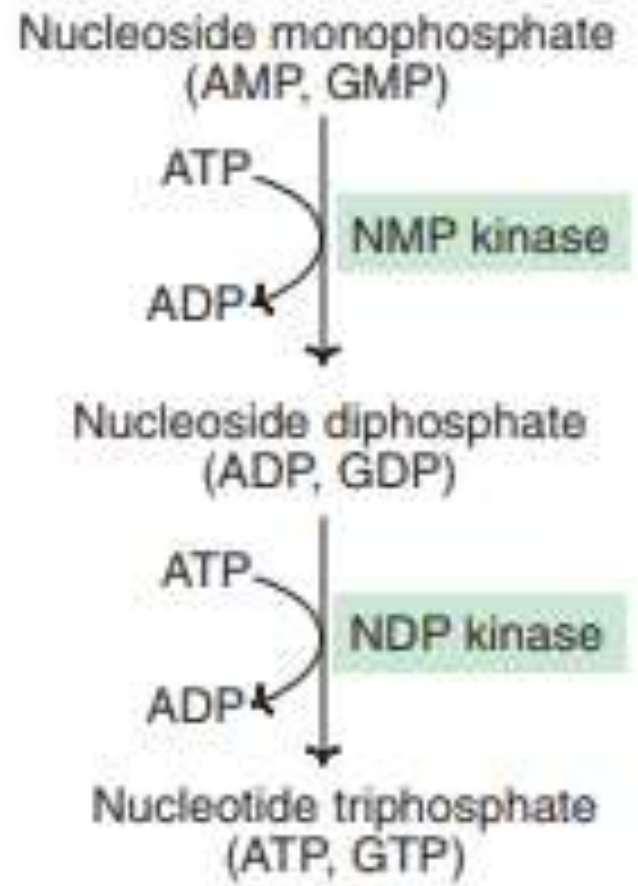
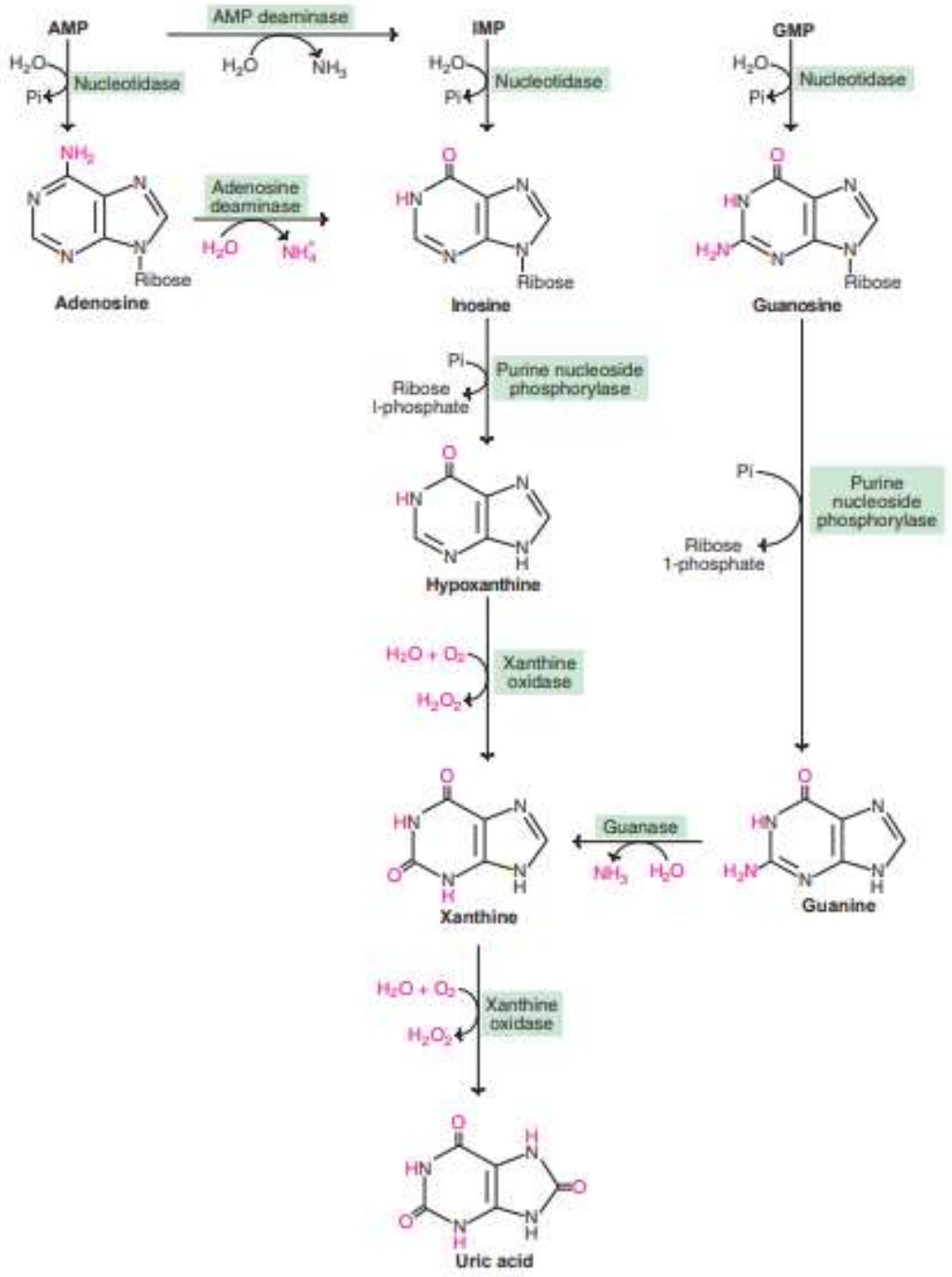




Source: Biochemistry Satyanarayan 4th Edition

DEGRADATION OF PURINE

- The end product of purine metabolism in humans is uric acid. The sequence of reactions in purine nucleotide degradation is given in



Source: Biochemistry Satyanarayan 4th Edition

REGULATION OF PURINE BIOSYTHESIS

- The purine nucleotide synthesis is well coordinated to meet the cellular demands.
- The intracellular concentration of PRPP regulates purine synthesis to a large extent
- This, in turn, is dependent on the availability of ribose 5-phosphate and the enzyme PRPP synthetase.
- PRPP glutamyl amidotransferase is controlled by a feedback mechanism by purine nucleotides.
- Another important stage of regulation is in the conversion of IMP to AMP and GMP.
- AMP inhibits adenylsuccinate synthetase while GMP inhibits IMP dehydrogenase. Thus, AMP and GMP control their respective synthesis from IMP by a feedback mechanism.

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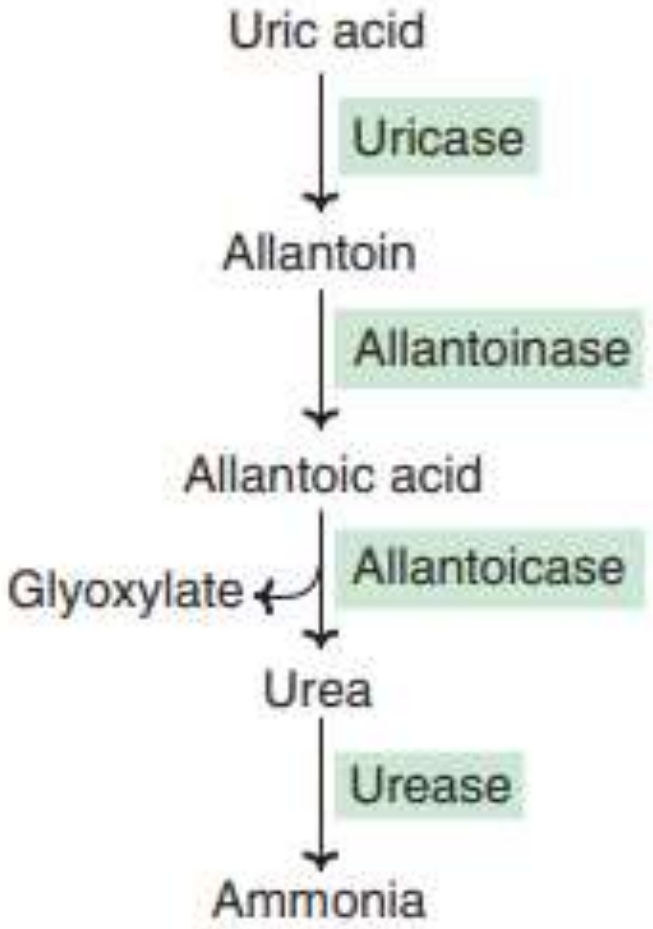


Source: Biochemistry Satyanarayan 4th Edition

DISORDERS OF PURINE METABOLISM

- 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. At the physiological pH, uric acid is found in a more soluble form as sodium urate. In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, particularly in the joints
- Primary gout : It is an inborn error of metabolism due to overproduction of uric acid. This is mostly related to increased synthesis of purine nucleotides

Pyrimidine metabolism

- Pyrimidine metabolism is a complex network of enzymatic pathways that synthesizes and breaks down nucleotides, the building blocks of DNA and RNA. Pyrimidine metabolism is important for cell proliferation, survival, and genetic integrity:

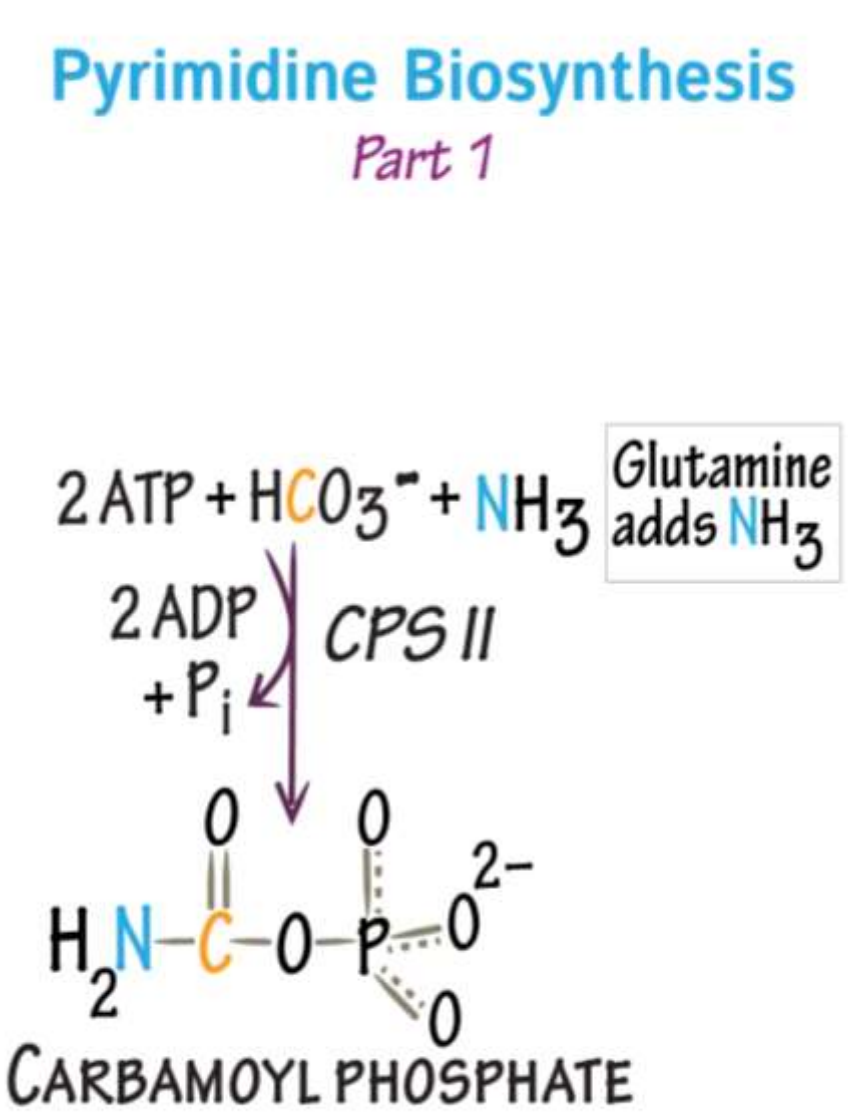
Function:

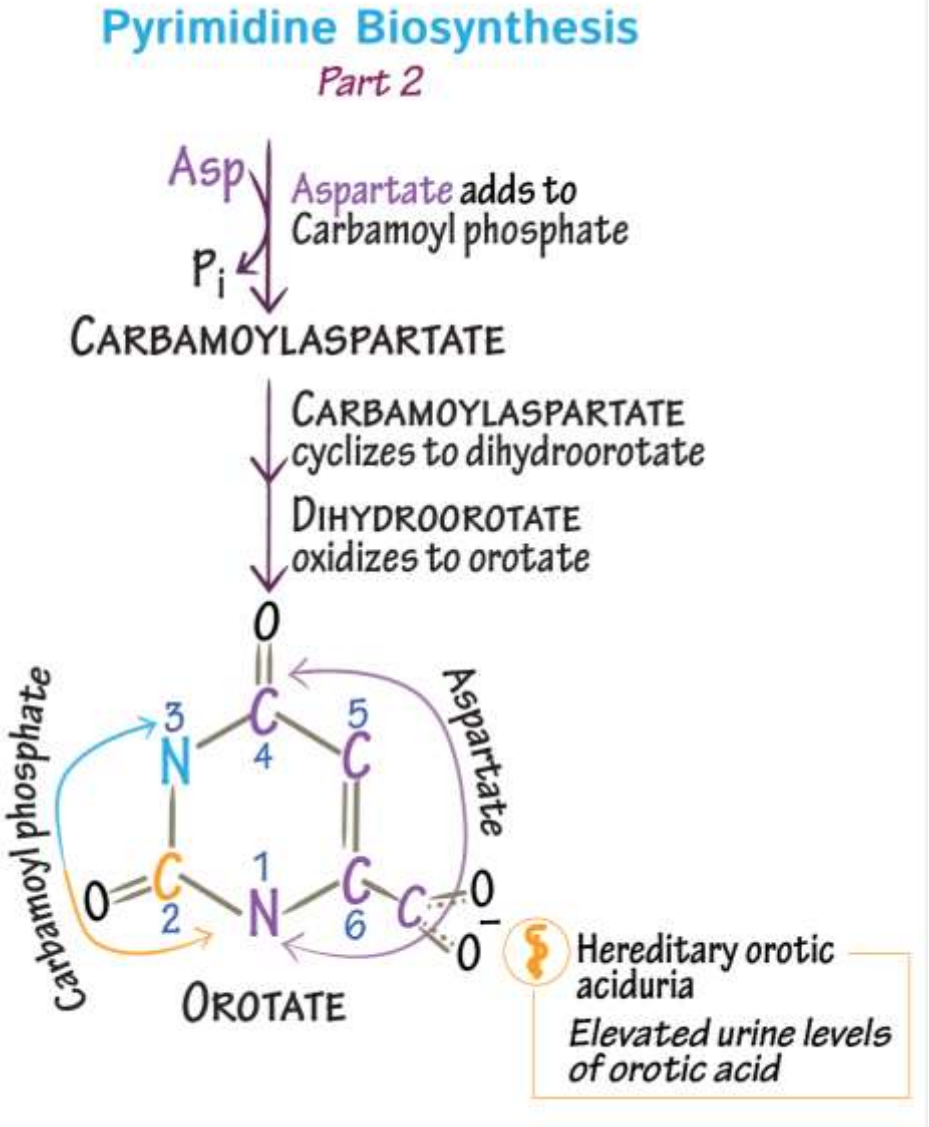
- Pyrimidines are structural components of key molecules that participate in many cellular functions, including the synthesis of DNA, RNA, lipids, and carbohydrates.

Pathways:

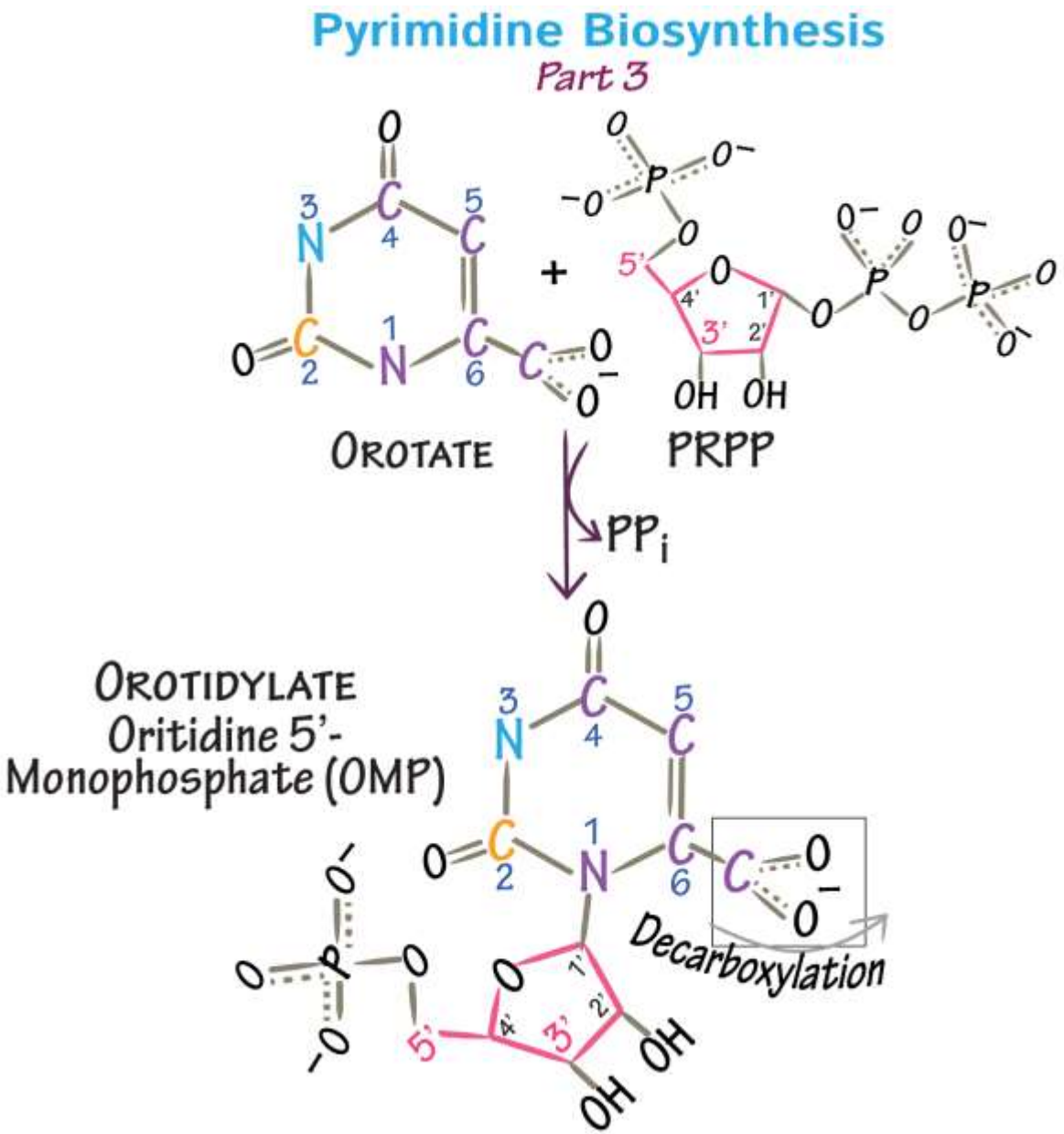
- Pyrimidine metabolism involves three pathways:
- Salvage: Uptake of circulating pyrimidines in the bloodstream
- De novo synthesis: Synthesis from amino acids and ribose precursors
- Catabolism: Degradation of excess nucleotides and nucleoside

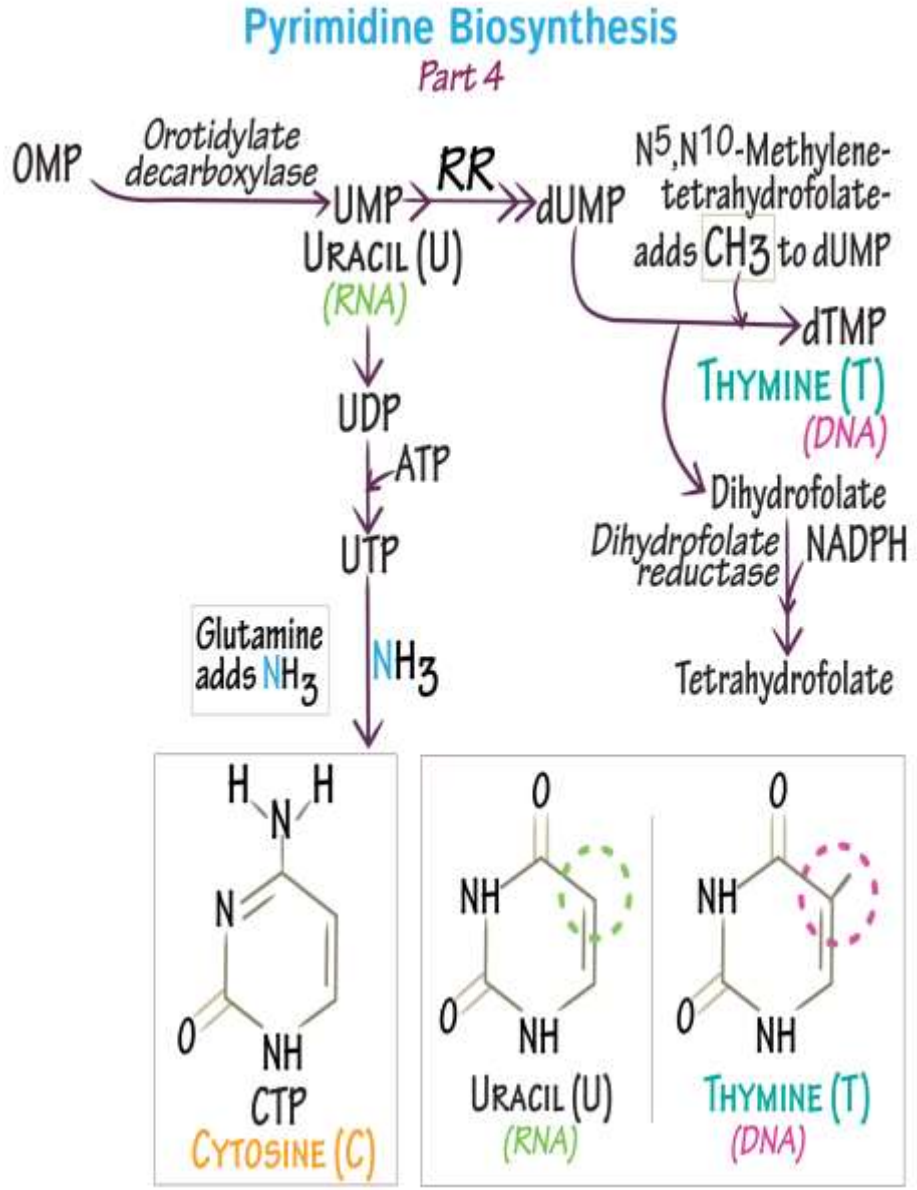
Pyrimidine Biosynthesis





Source:https://ditki.com/course/biochemistry/glossary/biochemical-pathway/pyrimidine-biosynthesis





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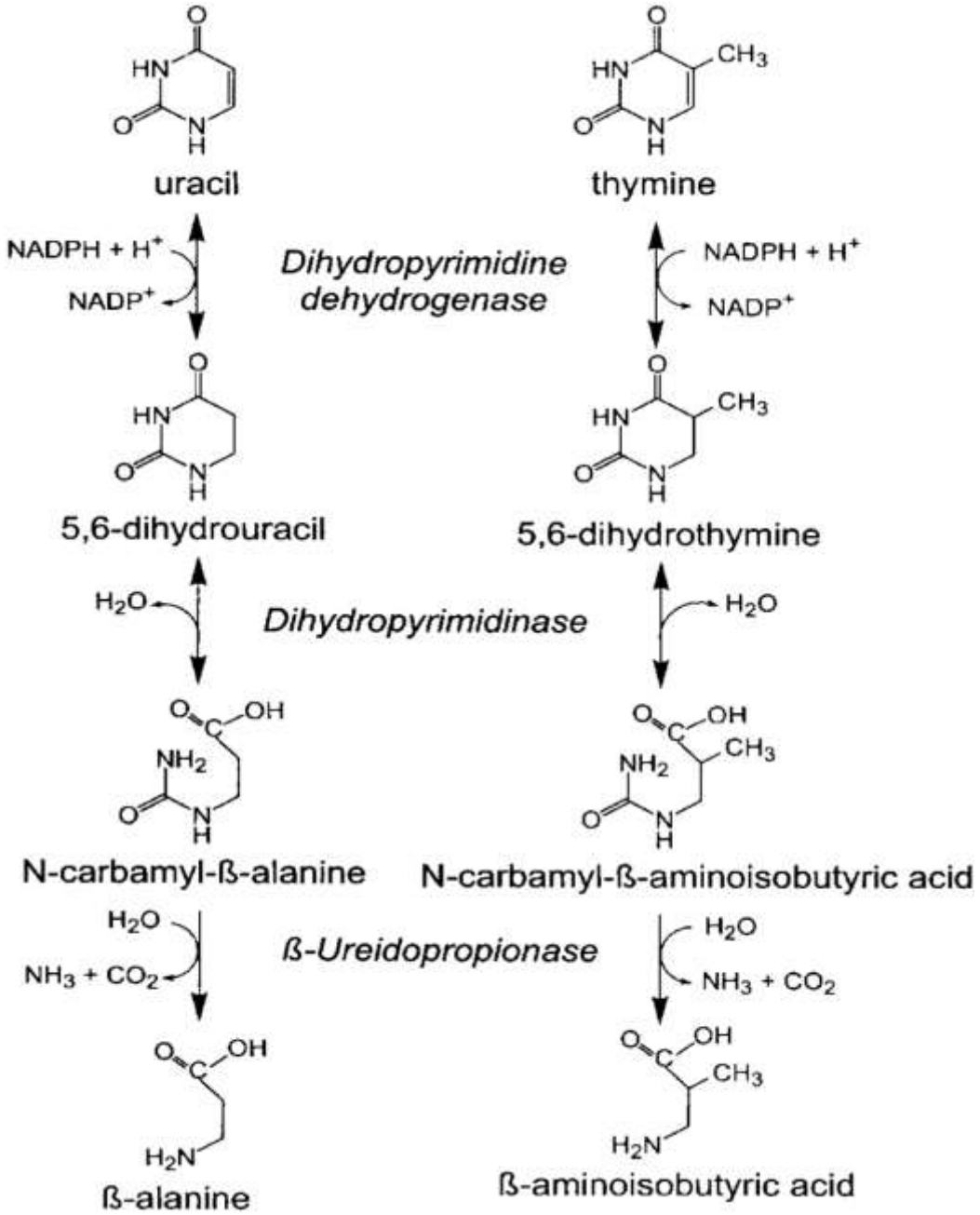
Degradation of Pyrimidine Metabolism



Source:https://www.researchgate.net/figure/Catabolic-pathway-of-the-pyrimidines-uracil-and-thymine_fig1_8330442

Regulation of Pyrimidine Metabolism:

Pyrimidine metabolism is tightly regulated to ensure balanced nucleotide levels for DNA and RNA synthesis. Key regulatory mechanisms include:

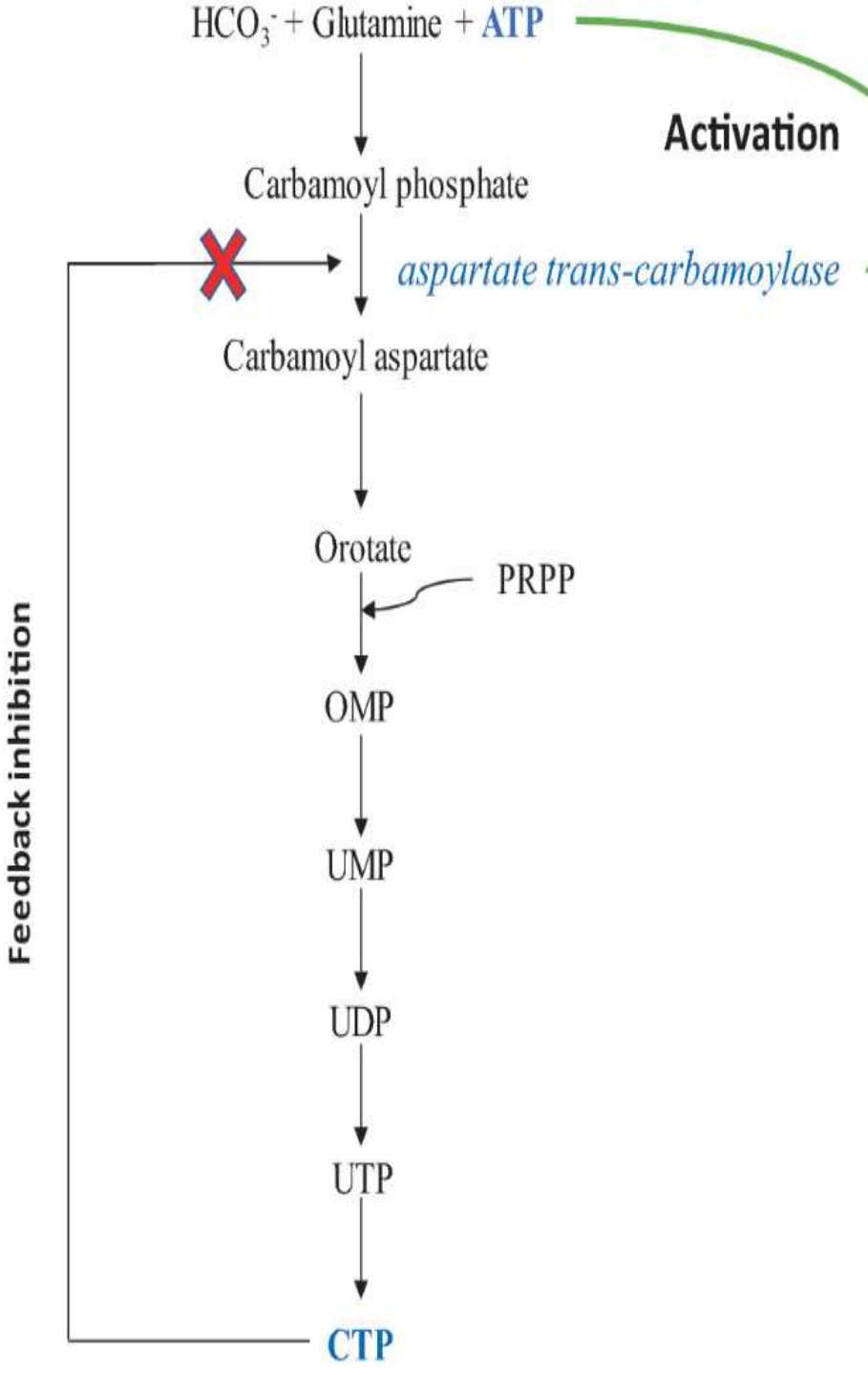
1. Feedback Inhibition:

- Carbamoyl phosphate synthetase II (CPS II), the first enzyme in pyrimidine biosynthesis, is inhibited by UTP and CTP (end products), preventing overproduction of pyrimidines.
- Thymidine kinase (TK) and uracil phosphoribosyltransferase (UPRT) are inhibited by their product nucleotides, dTMP and UMP, respectively.
- CMP synthetase is inhibited by CMP(its product).

2. Activation by Intermediates:

- PRPP (phosphoribosyl pyrophosphate) activates CPS II and other enzymes in the de novo pathway.
- ATP activates CPS II during periods of rapid cell growth and DNA synthesis.

Source:*https://link.springer.com/chapter/10.1007/978-981-16-0723-3_19*



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3. Cell Cycle Regulation:

- Pyrimidine metabolism is upregulated during the S-phase of the cell cycle when DNA replication occurs, increasing demand for nucleotides.

4. Nutrient Availability:

- Availability of glutamine and CO_2 regulates CPS II, while PRPP availability governs nucleotide synthesis.

This complex regulation ensures nucleotide homeostasis and supports cell growth, division, and repair.