

Purine and Pyrimidine Metabolism

Dr Zunjarrao G Badade,
Professor of Biochemistry,
MGM Medical College, Navi Mumbai

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- Introduction to Nucleotide formation and degradation.
- Biosynthesis of purine nucleotides and its regulation
- Catabolism of purine nucleotides and disorders associated with purine nucleotide metabolism
- Laboratory results of analytes associated with gout and Lesch Nyhan syndrome
- De novo synthesis of pyrimidine nucleotides
- De novo catabolism of pyrimidine nucleotides, and disorders of pyrimidine nucleotide metabolism
- Enzymes of the nucleotide biosynthesis that are inhibited by anticancer drugs

- Purine and pyrimidine are dietary nonessential components.
- Dietary nucleic acids and nucleotides do not provide essential constituents for the biosynthesis of endogenous nucleic acids.
- Dietary purine and pyrimidine are neither converted to nucleotides nor incorporated into nucleic acids.
- Purine bases are oxidized to uric acid and pyrimidine bases are oxidized to CO_2 and ammonia, which are subsequently excreted in the urine

Nucleotide Needs



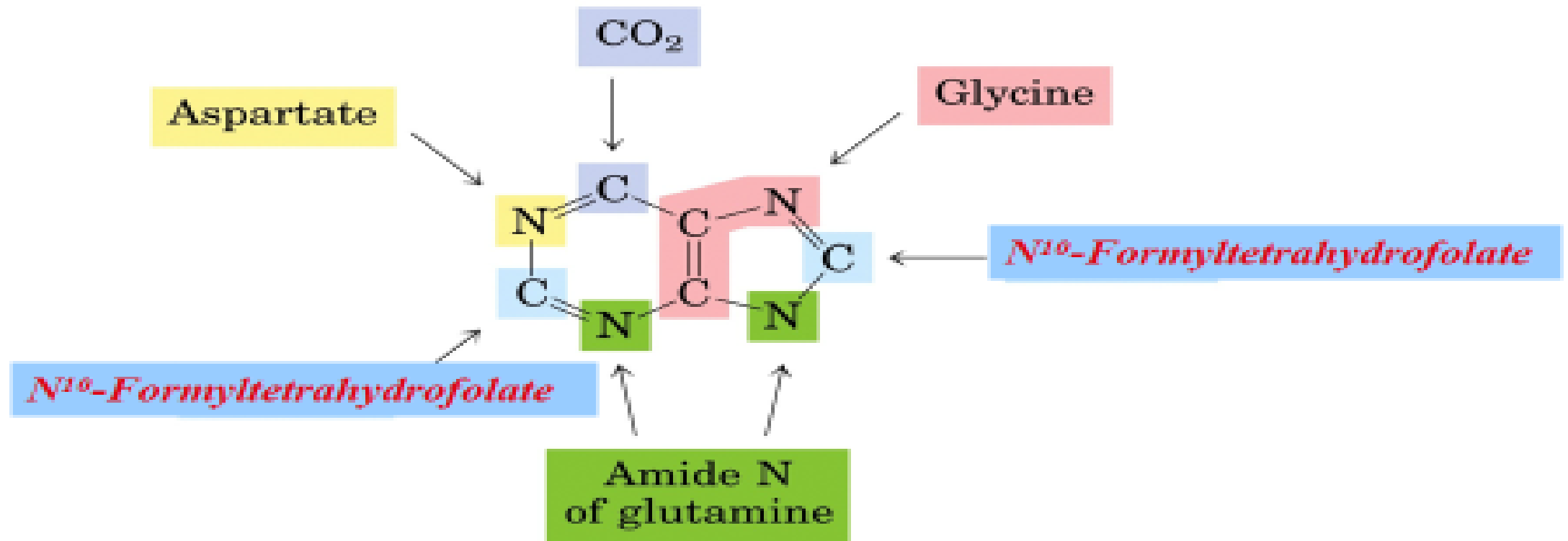
- DNA synthesis
- RNA synthesis
- Energy Currency like
 - ↳ **ATP**
- Secondary messenger
 - ↳ **C-AMP, C-GMP**
- Intermediate in metabolisms = Co-Enzyme
 - ↳ **NAD, NADP, FAD, AMP, ATP**

Source of Nucleotide



- Denovo Synthesis of Nucleotide
- Salvage Pathway (Normal cell turnover)
- Diet

Element sources of purine bases



First, synthesis Inosine-5'-Monophosphate, IMP

BIOSYNTHESIS OF PURINE NUCLEOTIDES

The two purine nucleotides of nucleic acids are:

1. Adenosine monophosphate, AMP
2. Guanosine monophosphate, GMP

Purine nucleotides can be synthesized by two pathways:

1. De novo pathway
2. Salvage pathway



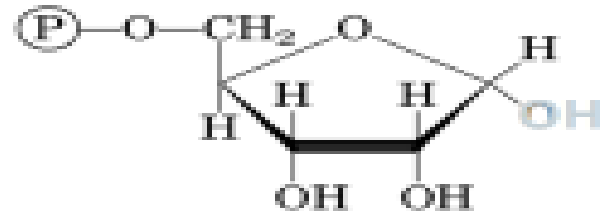
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Prof ZG Badade, Biochem Dept, MGM Medical College, Navi

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De Novo Biosynthesis Of Purine Nucleotides

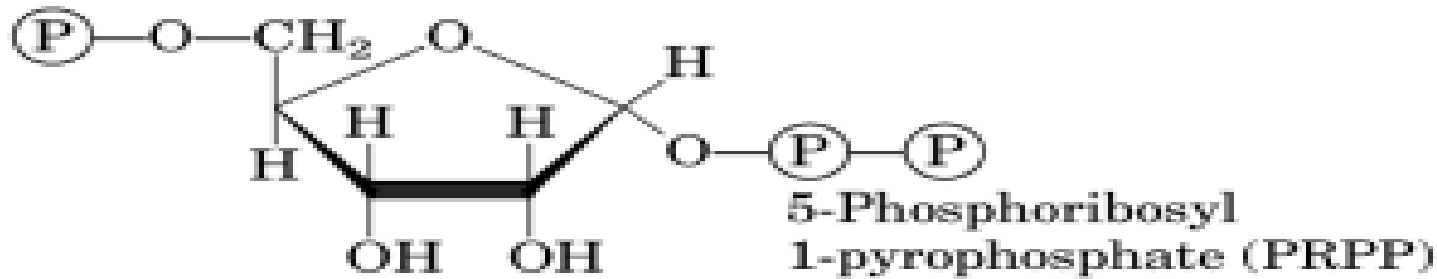
- In de novo pathway, the purine ring formed from variety, of precursors is assembled on **ribose-5-phosphate**.
- Precursors for the De Novo Synthesis of Purine
 - Glycine provides C4, C5 and N7
 - Aspartate provides N1
 - Glutamine provides N3 and N9
 - Tetrahydrofolate derivatives furnish C2 and C8
 - Carbon dioxide provides C6.



Step 1

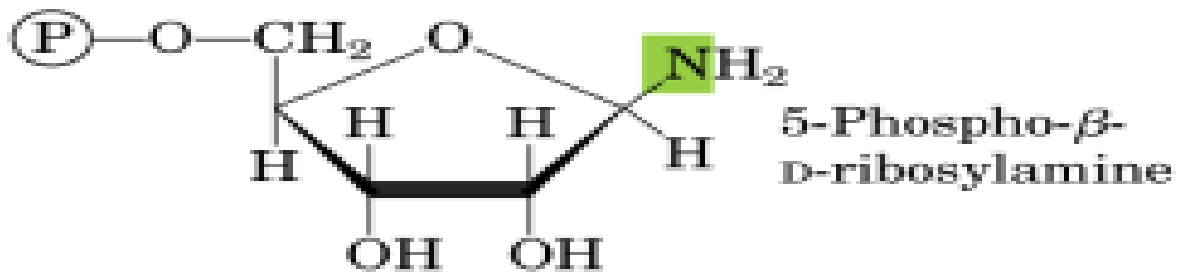


PRPP Synthetase



Step 2:

Gln:PRPP amidotransferase

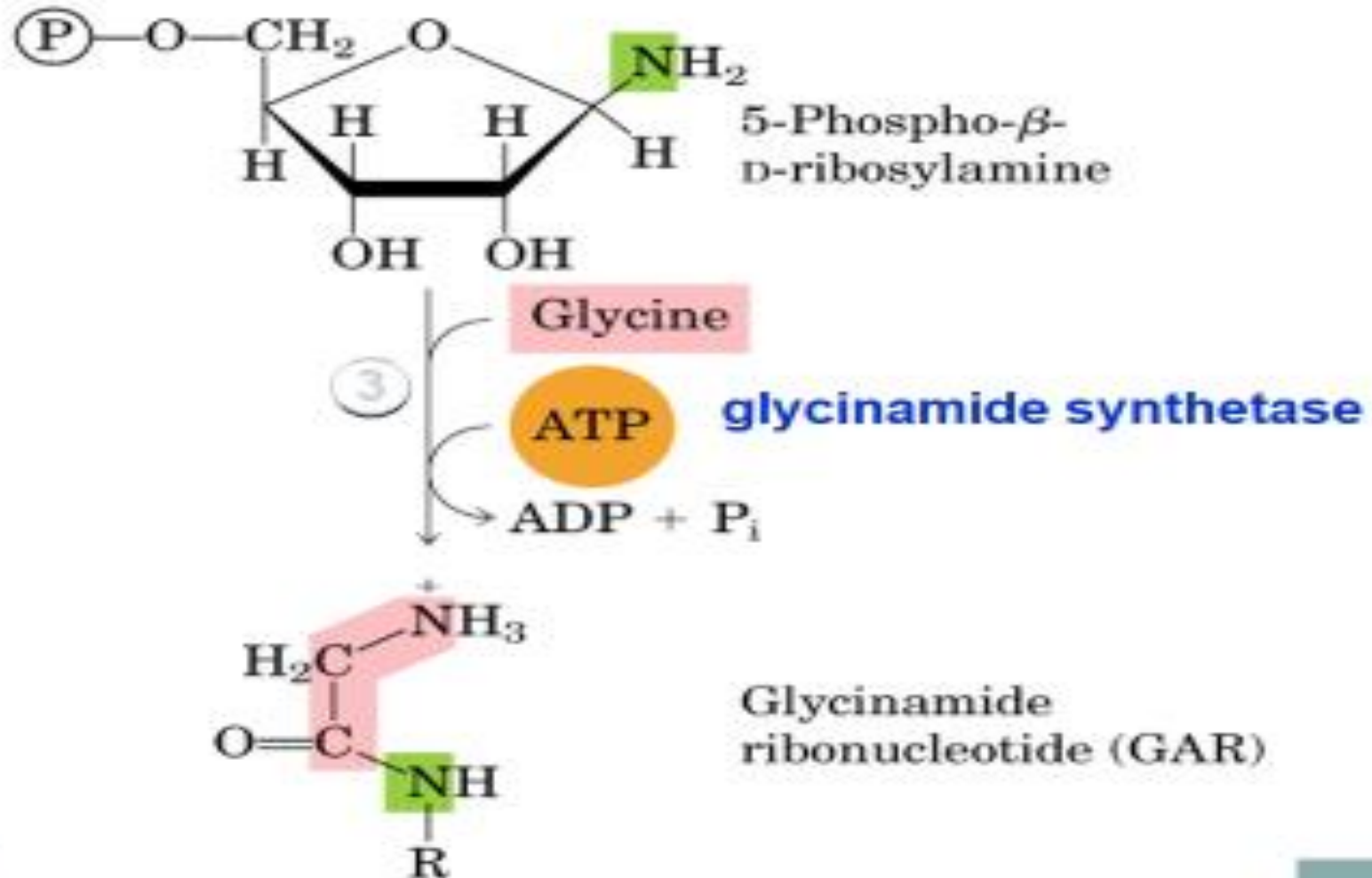


Synthesis of IMP (“Parent” purine nucleotide)

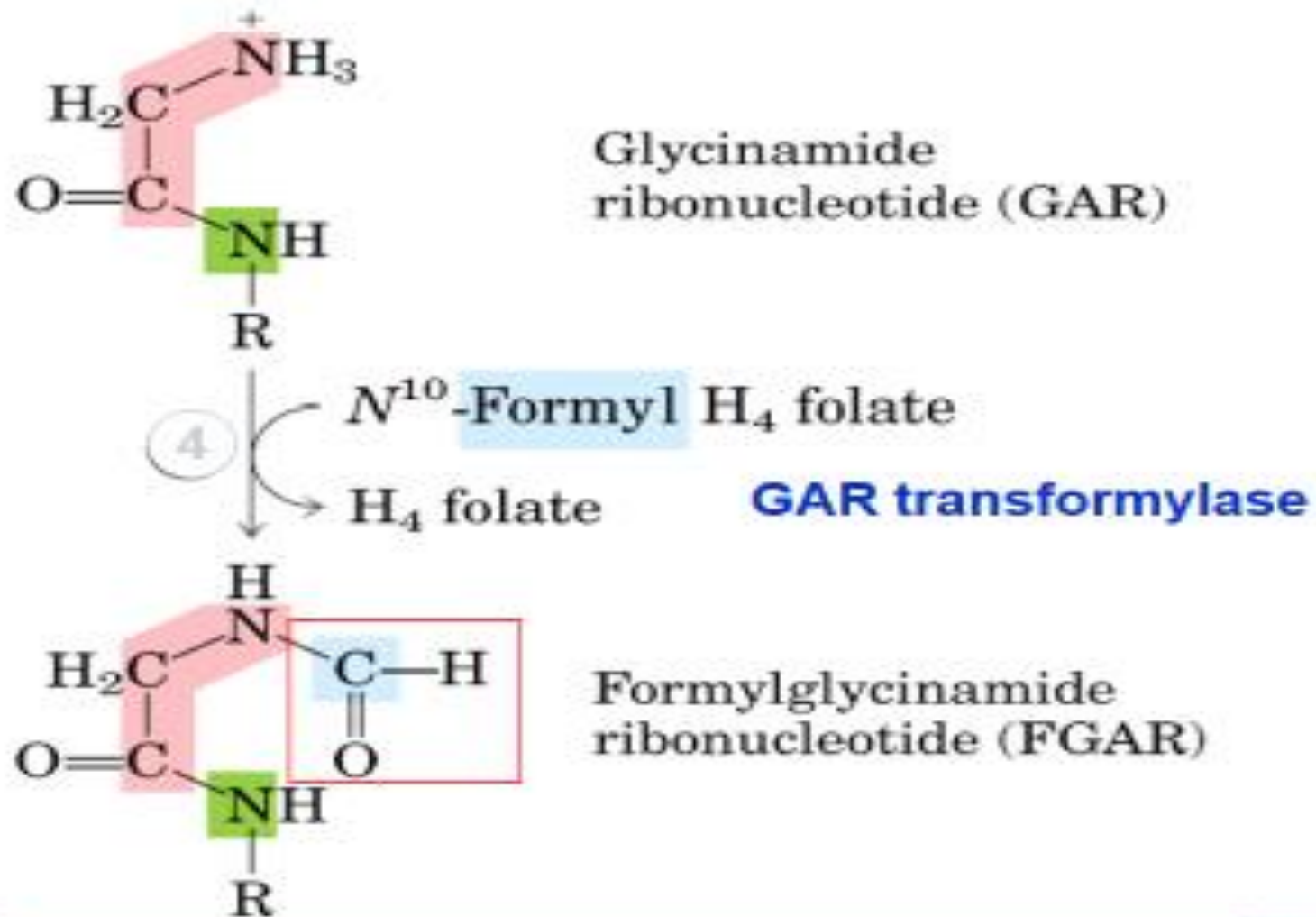


- **Next nine steps** in purine nucleotide biosynthesis leading to the synthesis of **IMP** (whose base is hypoxanthine).
- Requires
 - **four ATP.**
 - **N¹⁰-formyltetrahydrofolate.**
 - **Aspartate.**
 - **Glycine**

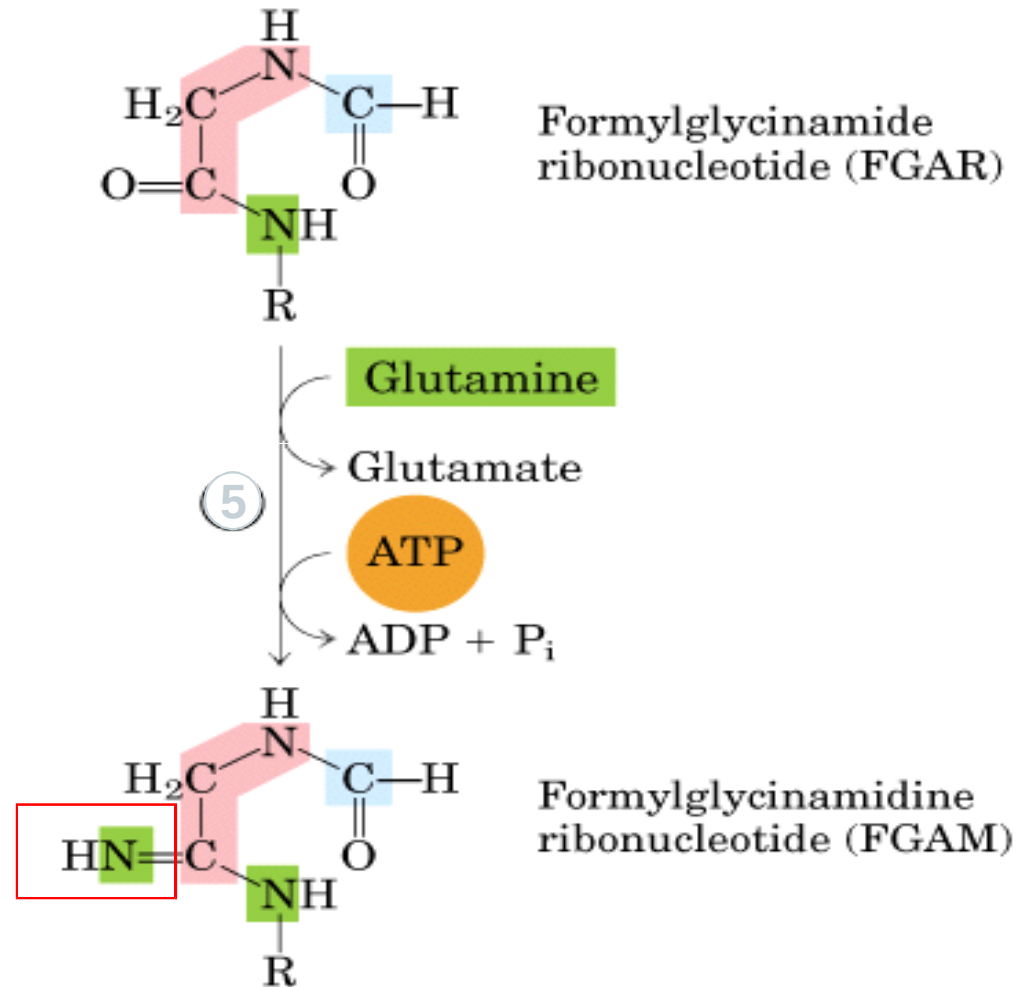
Step 3: acquisition of purine atoms C4, C5, and N7

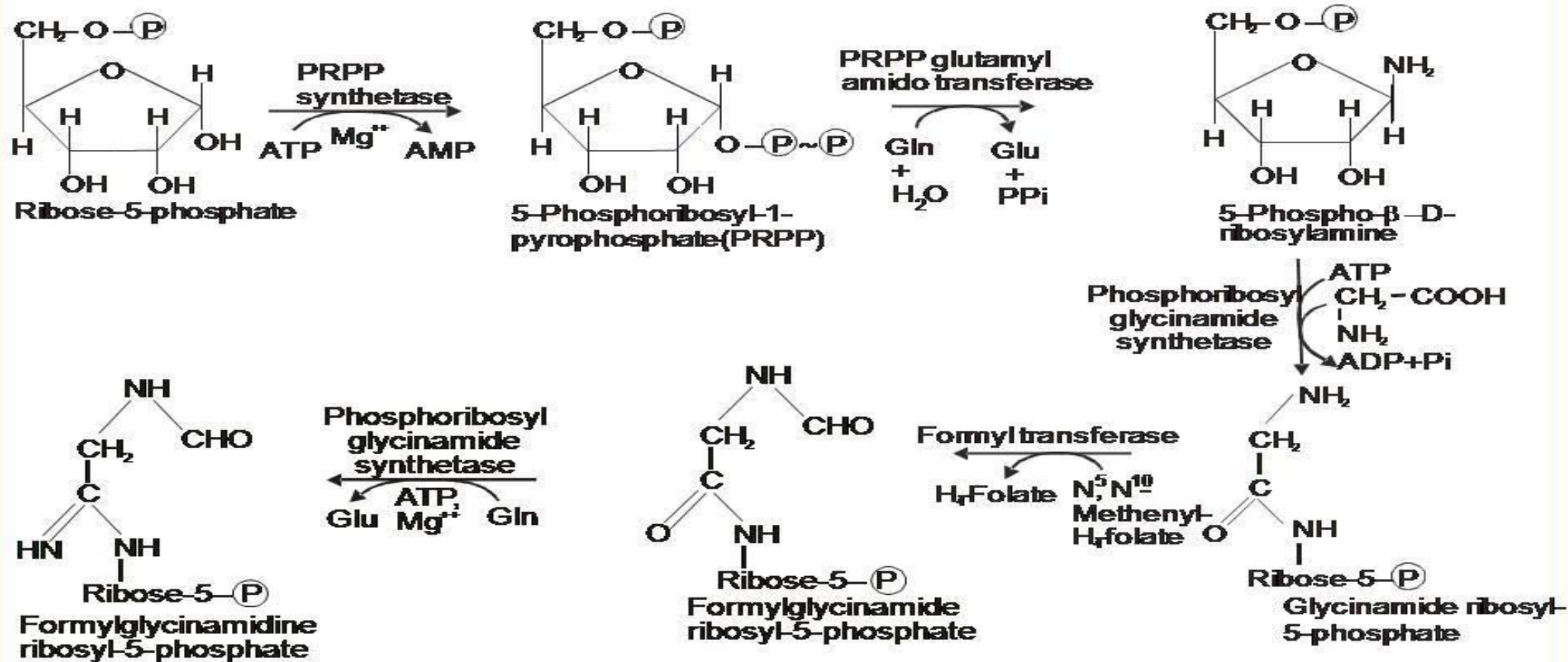


•Step 4: acquisition of purine atom C8



Step 5: acquisition of purine atom N3

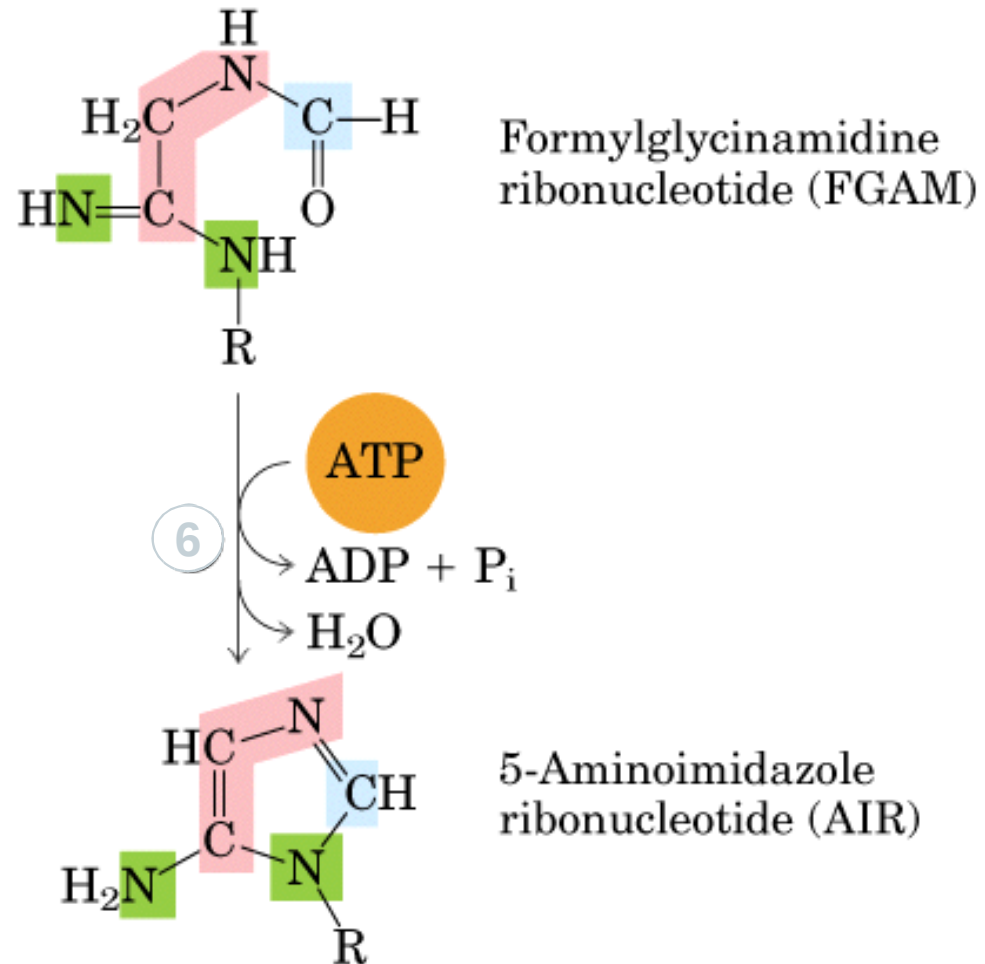




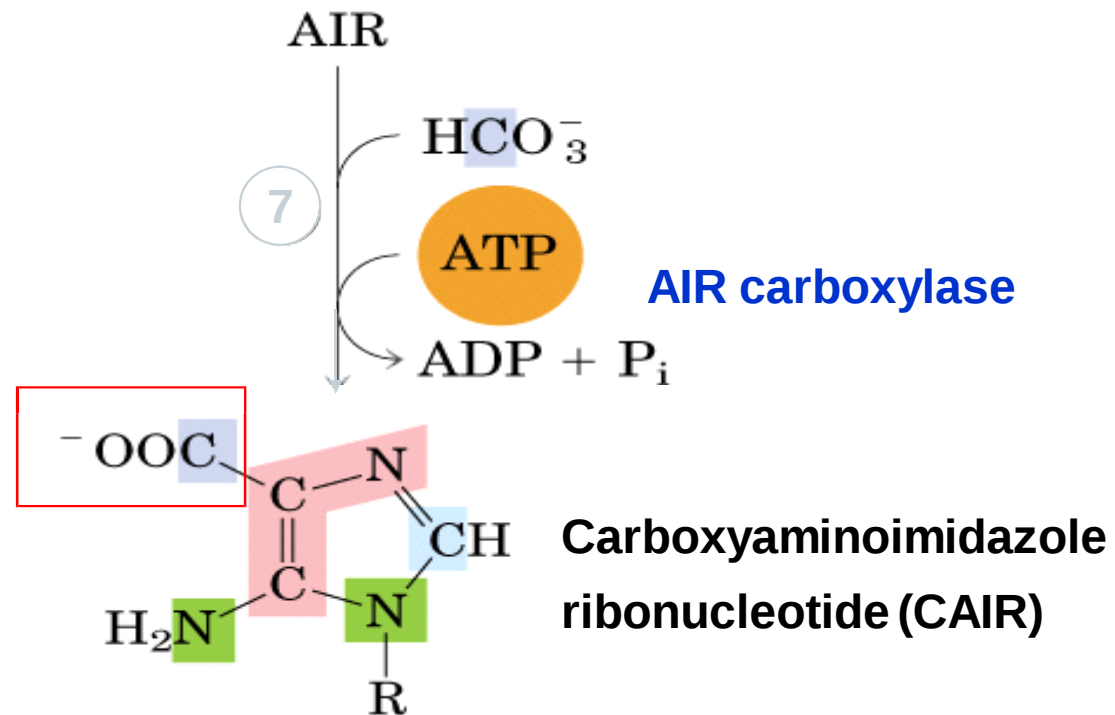
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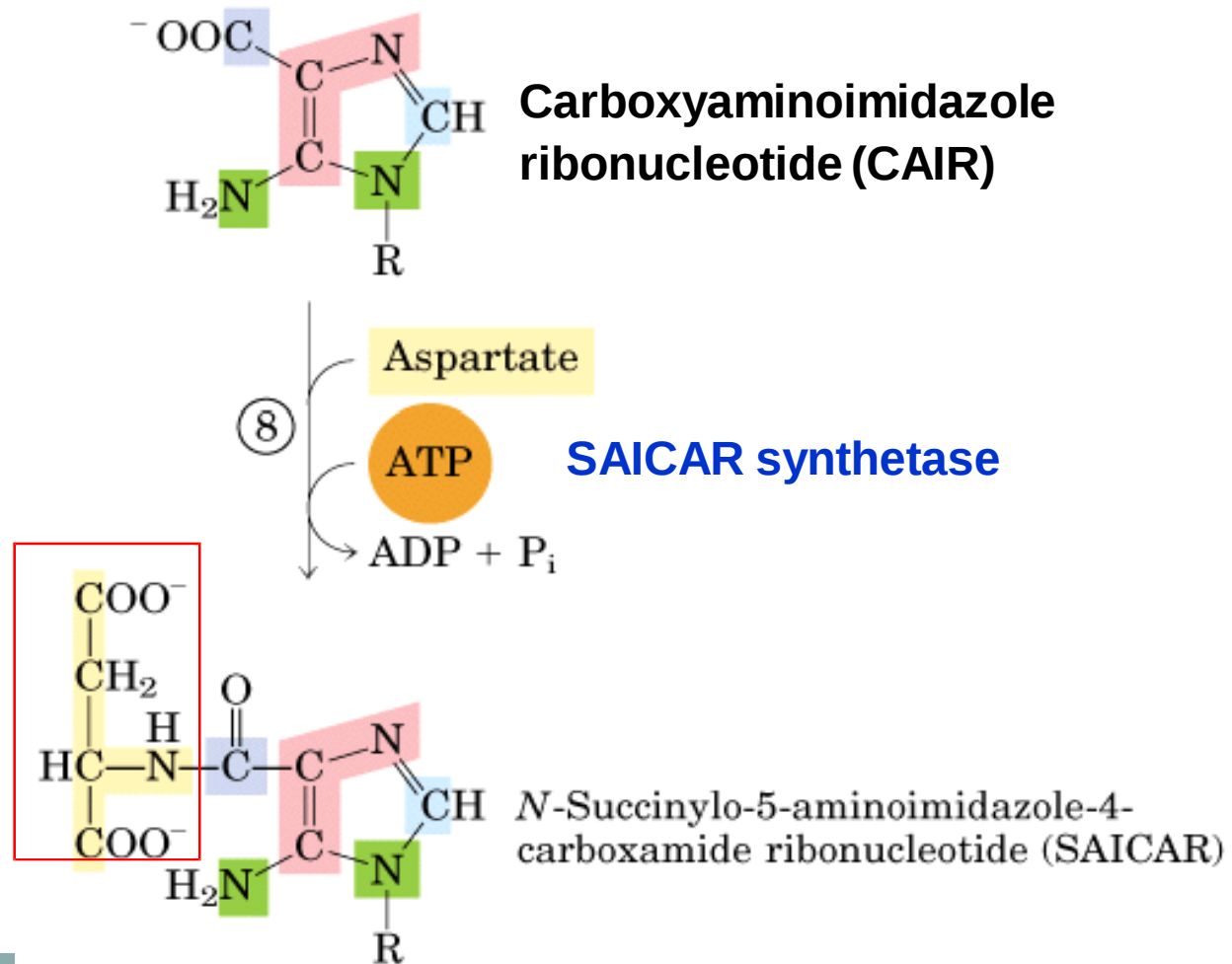
•Step 6: closing of the imidazole ring



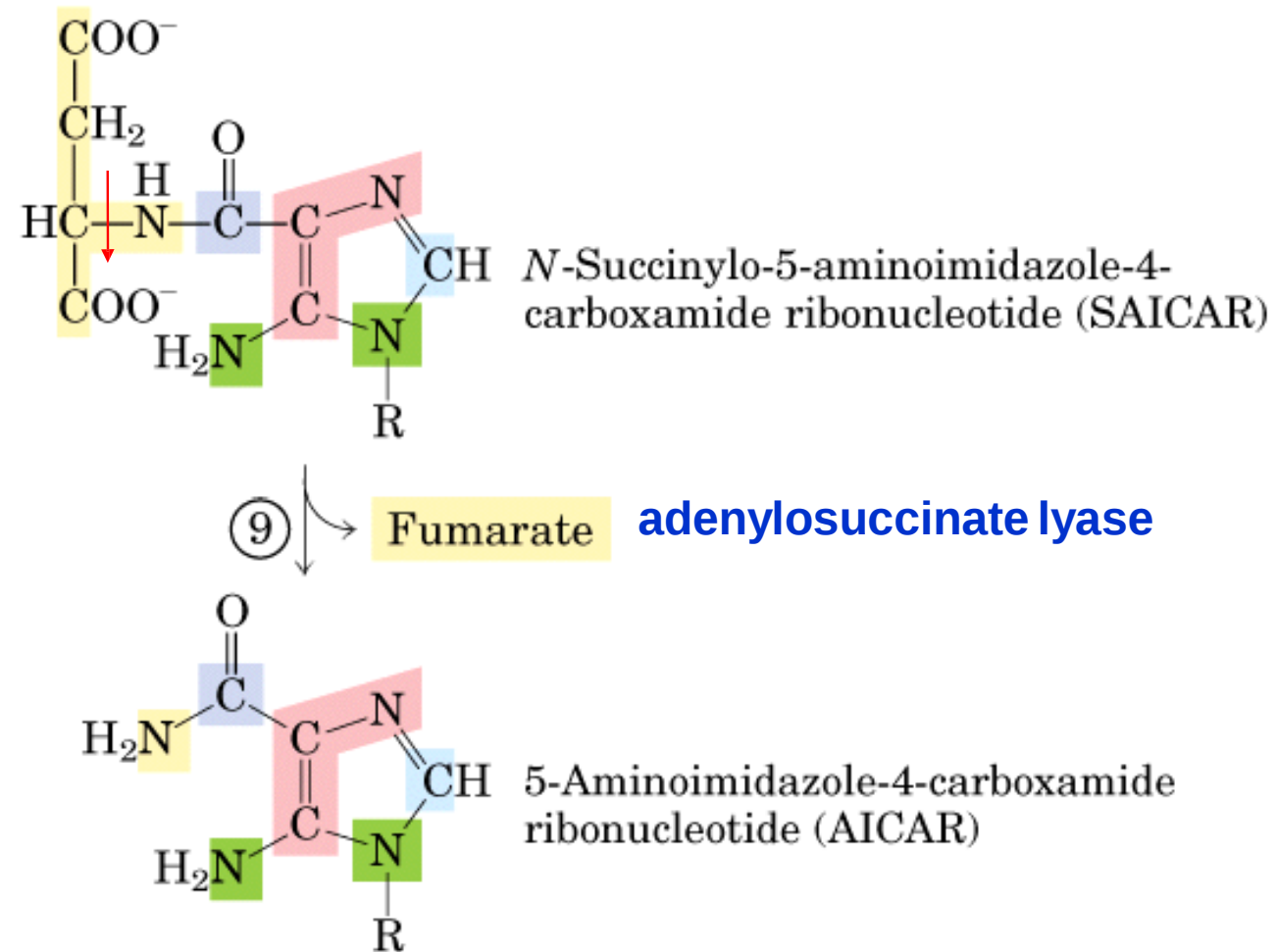
Step 7: acquisition of C6



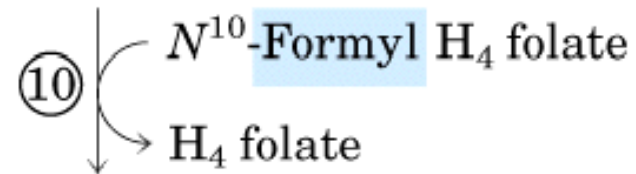
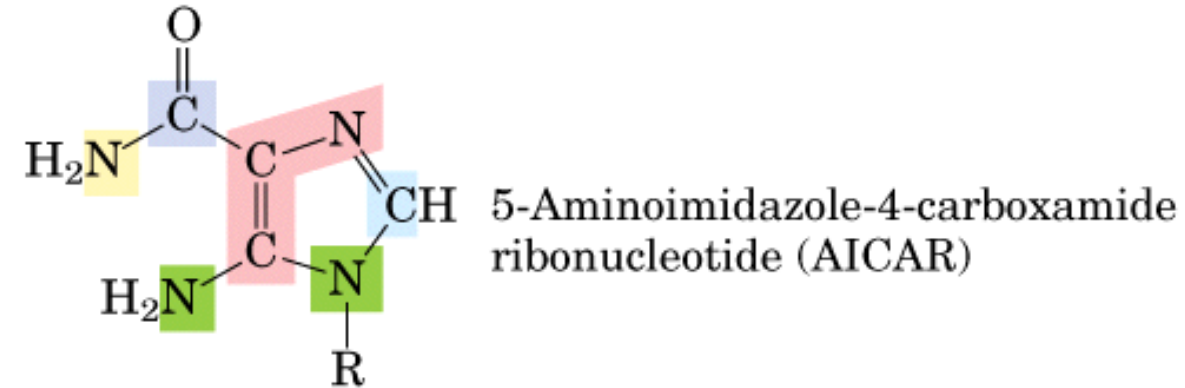
Step 8: acquisition of N1



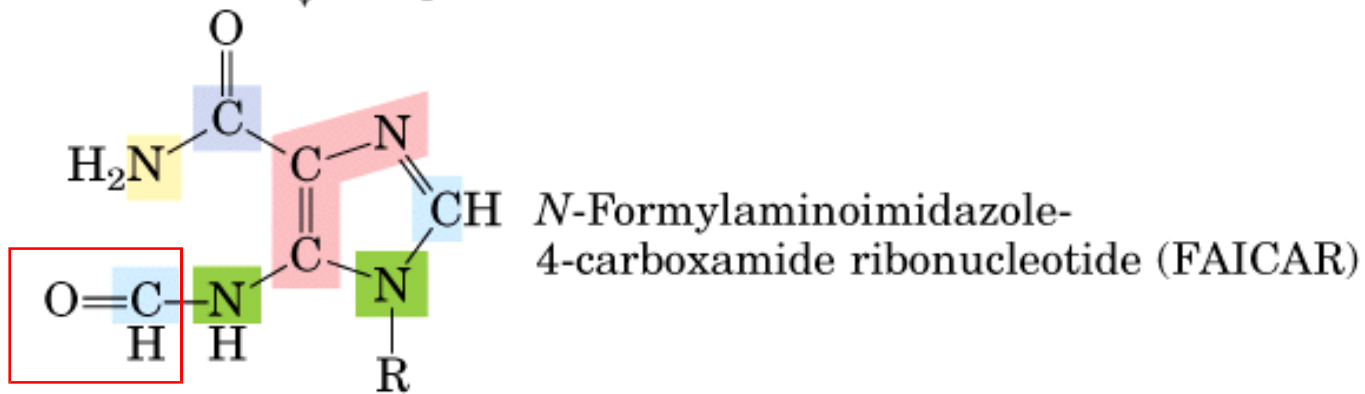
Step 9: elimination of fumarate



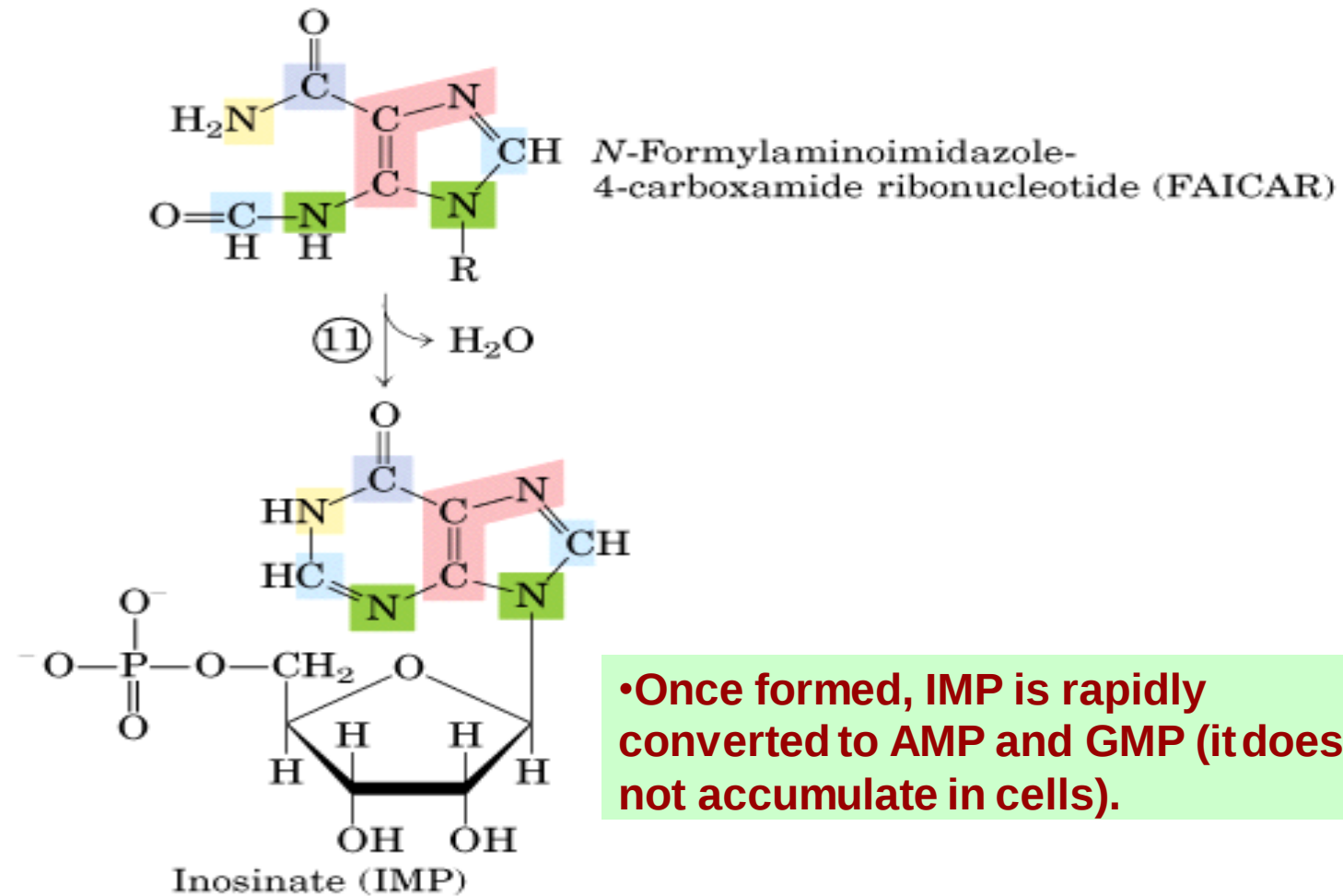
Step 10: acquisition of C2

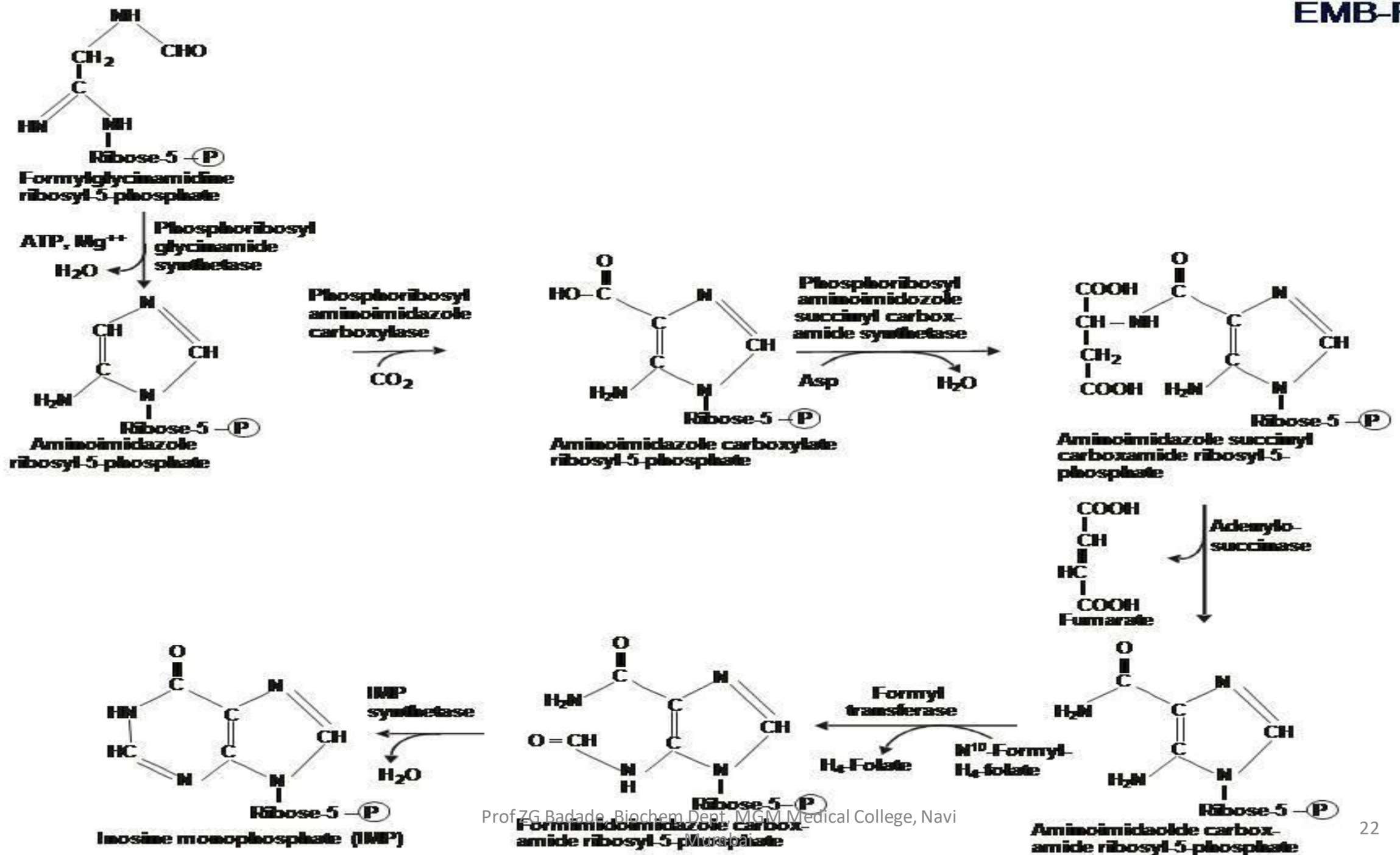


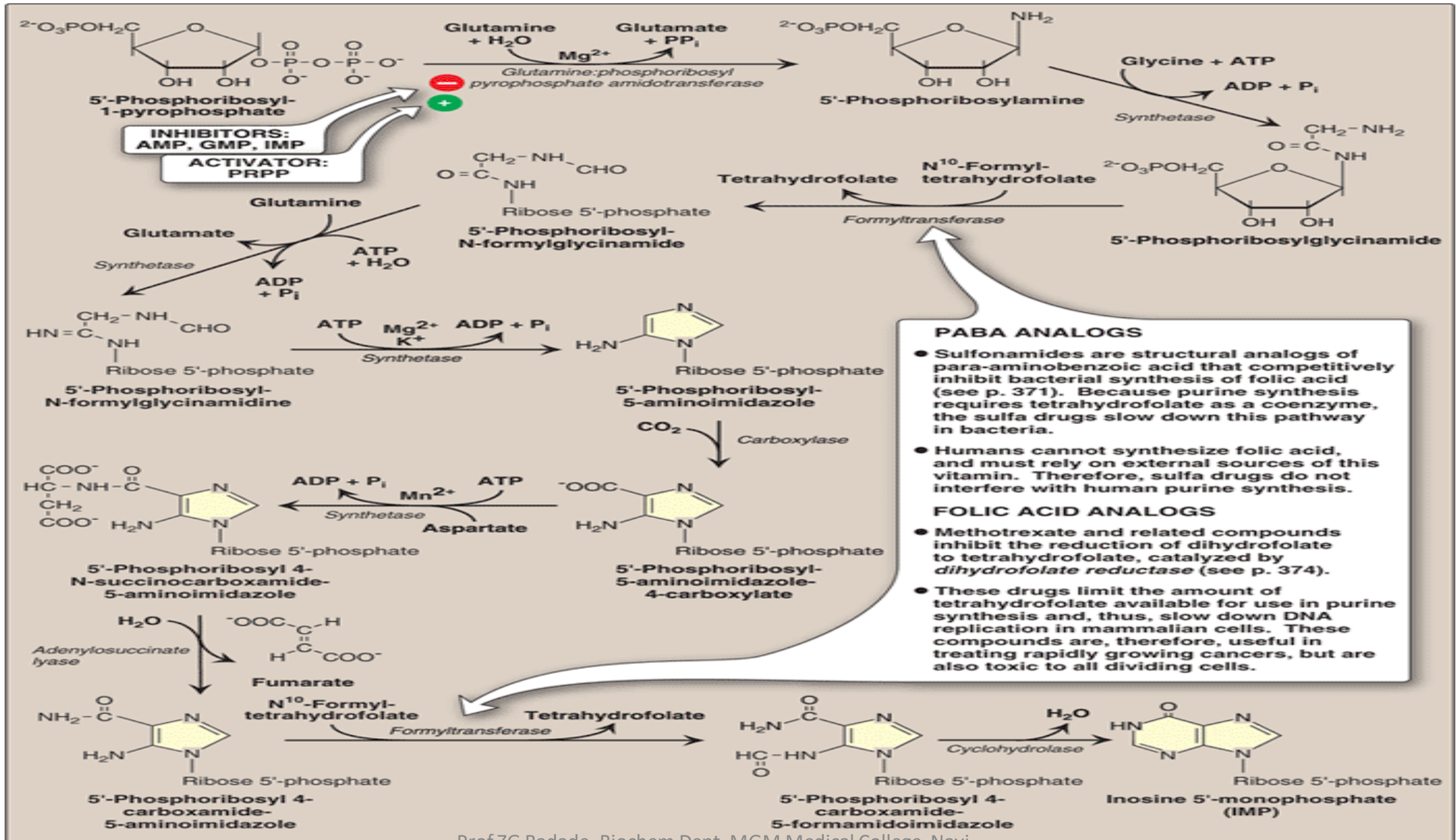
AICAR transformylase



Step 11: ring closure to form IMP



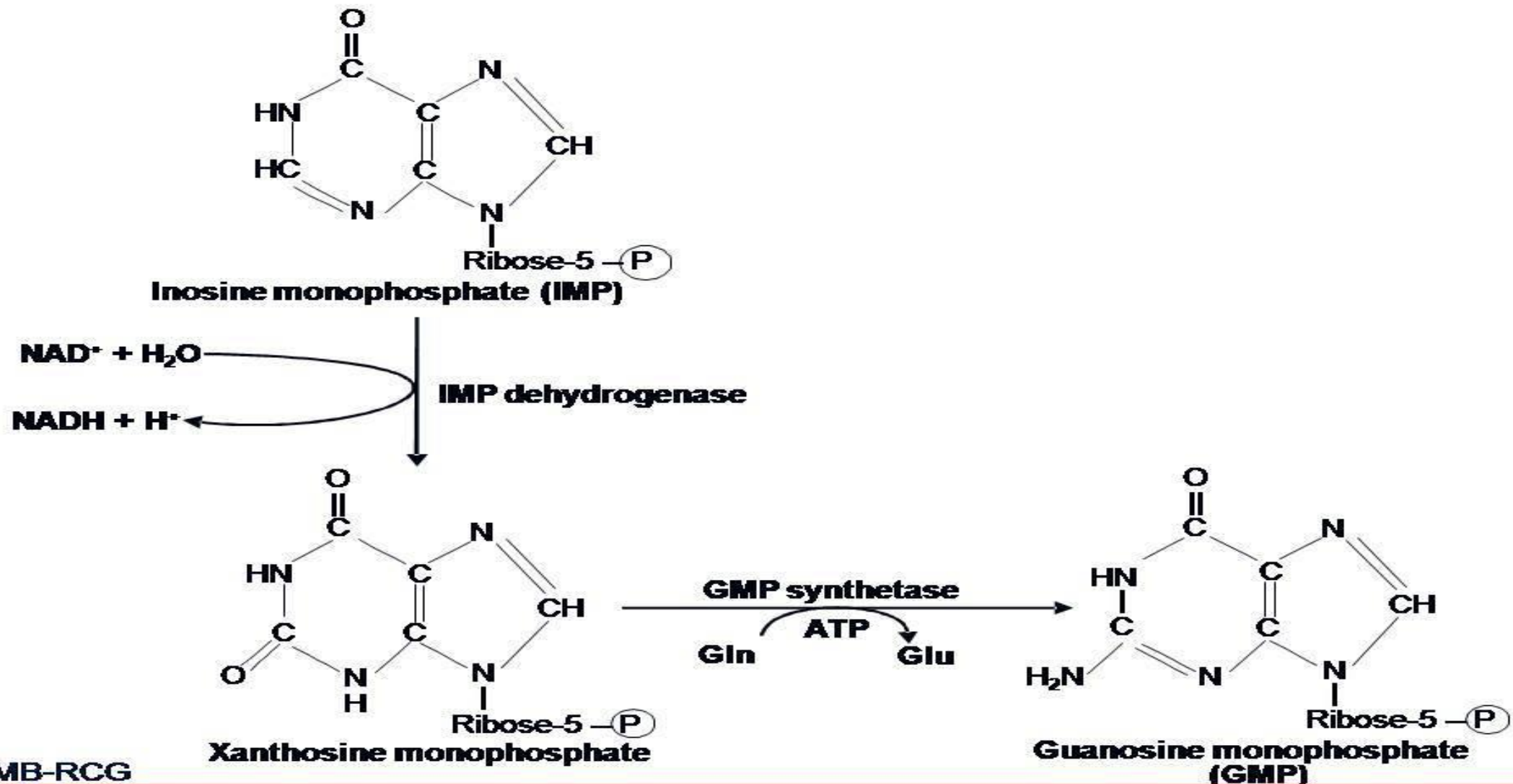




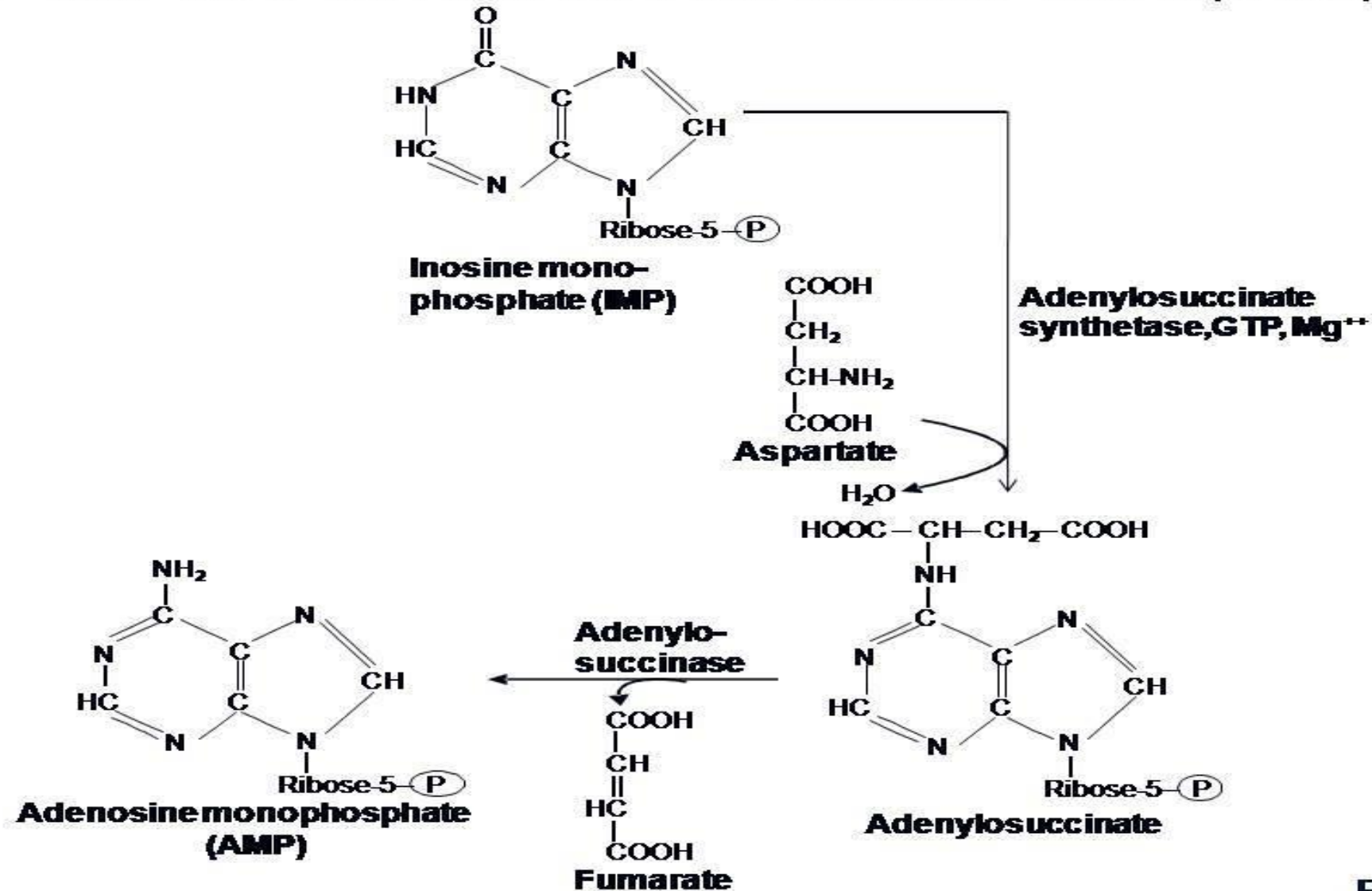
Inhibitors of Purine Synthesis

- **Sulfonamides** (antibiotic) = PABA analogs)
- **Trimethoprim**
- = Folate analogs
 - = Selective inhibition of bacterial dihydrofolate reductase.
- **Methotrexate (chemotherapy)** = Folic acid analogs
 - ℞ Inhibitors of human purine synthesis
 - ℞ **Inhibit Rapidly replication cell.**
 - ℞ **Bone marrow suppression.**
 - ℞ **Nause – Vomiting – Gastritis – Ulcer**
 - ℞ **Hair loss.**

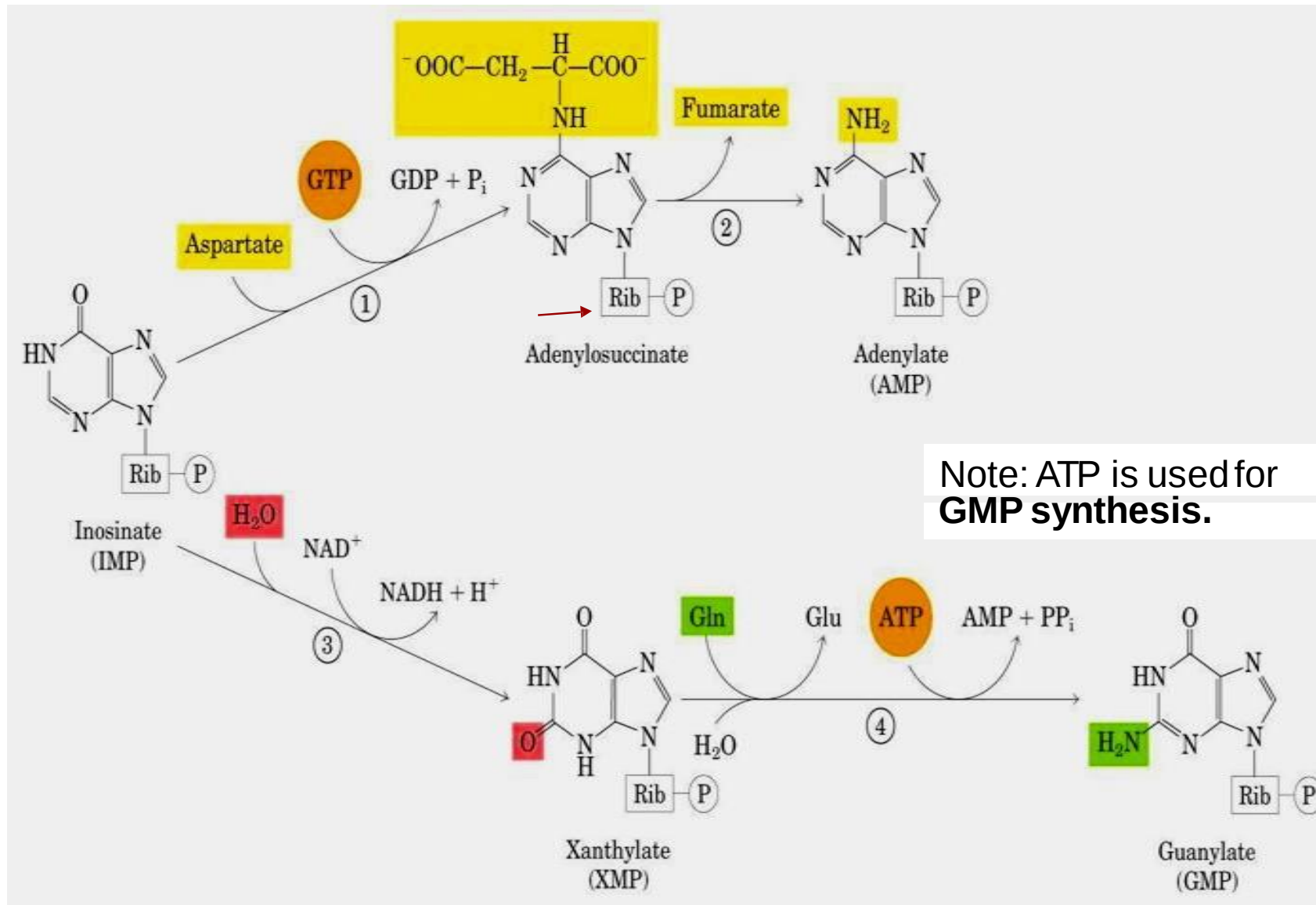
GMP can be formed from inosine monophosphate



AMP can also be formed from inosine monophosphate

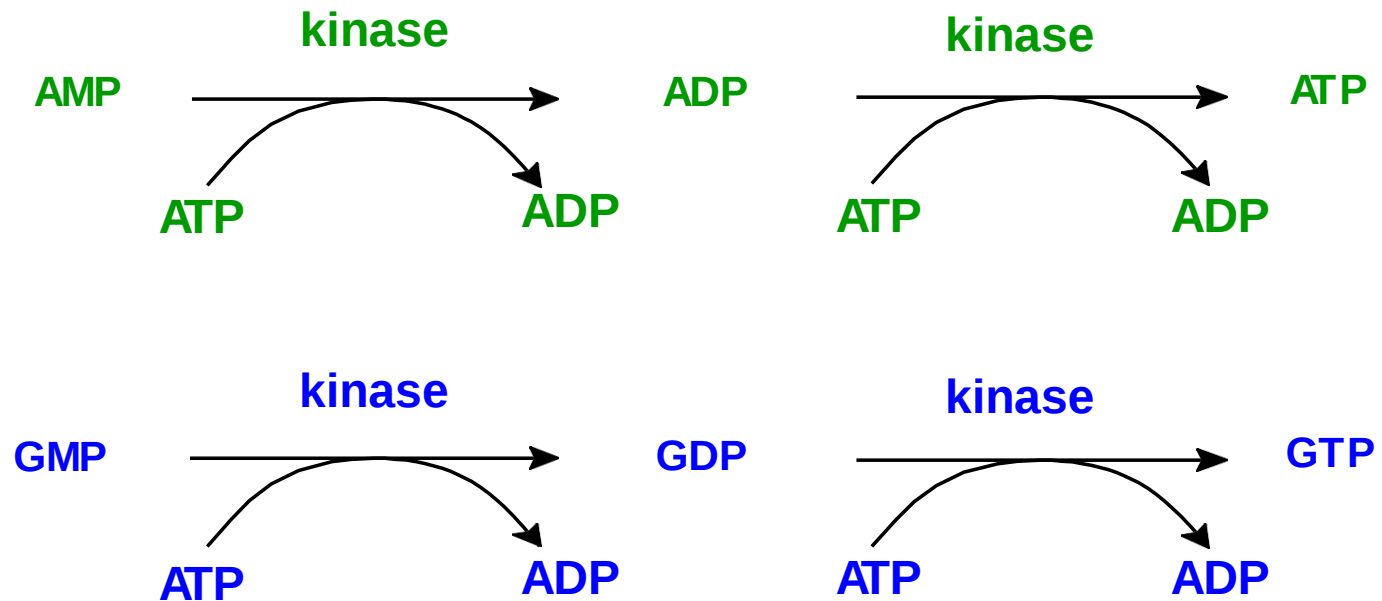


EMB-RCG

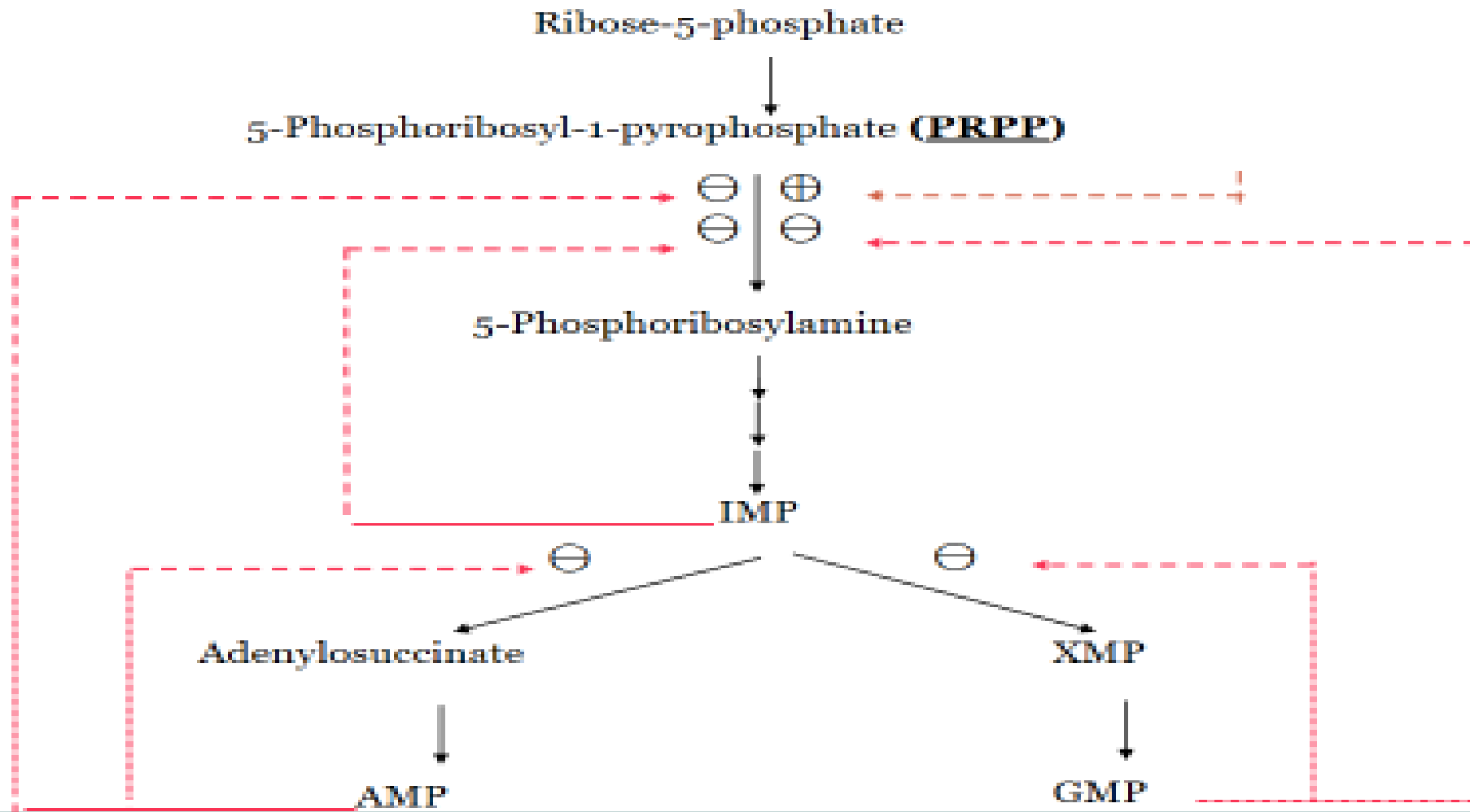


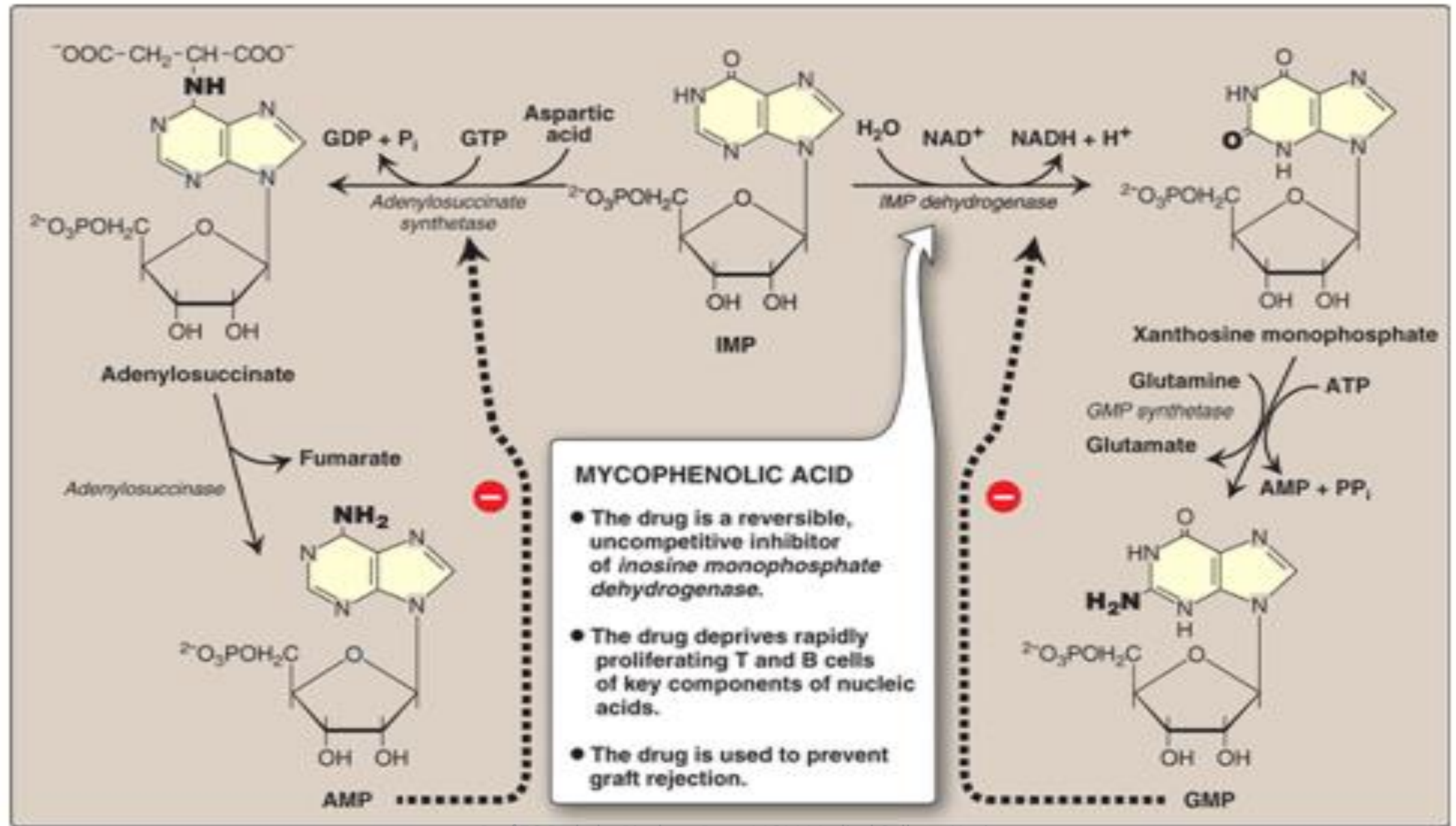
IMP is the precursor for both AMP and GMP.

4. ADP, ATP, GDP and GTP biosynthesis



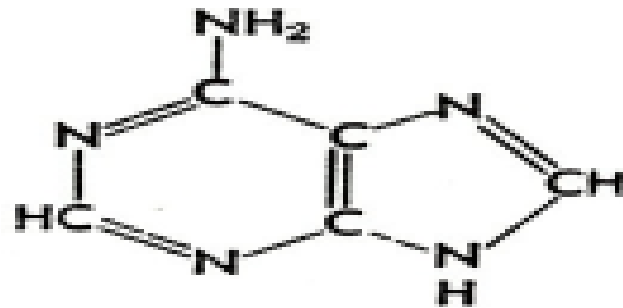
Summary of Regulation





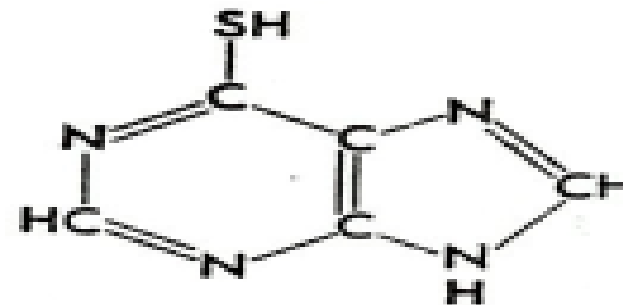
Inhibition of Purine Biosynthesis by the Antitumor Agent

Metabolite

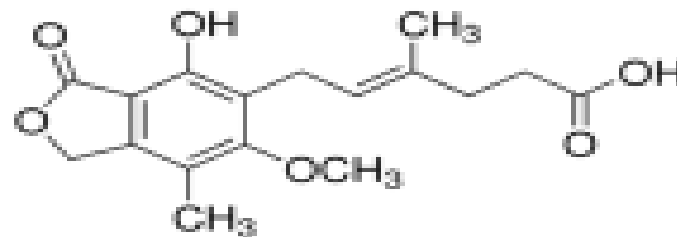


Adenine

Antimetabolite



6-Mercaptopurine



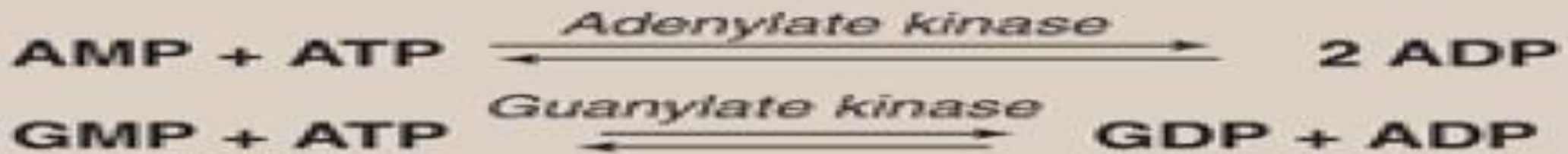
Mycophenolic acid

Conversion of ?MP = ?DP and ?TP

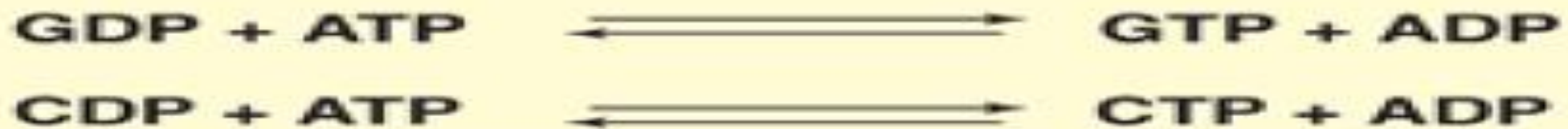


- Adenylate kinase = active in liver and muscle.
- Nucleoside diphosphate kinase = broad specificity.

Base-specific nucleoside monophosphate kinases



Nucleoside diphosphate kinase



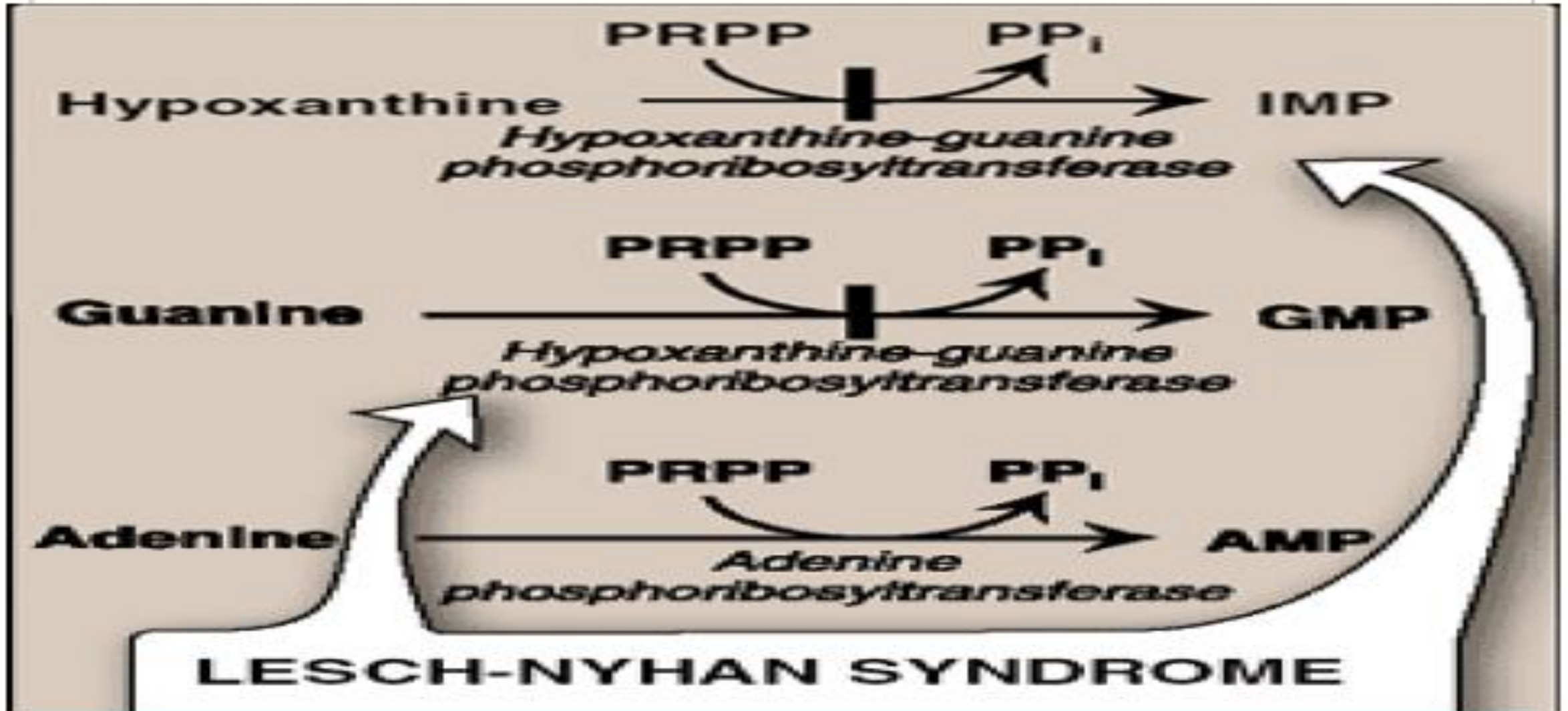
Synthesis Of Purine Nucleotides By Salvage Pathway

- The pathway involved in the conversion of free purines to nucleotides is called salvage pathway. It consists of a single reaction
- Free purine bases (adenine, guanine and hypoxanthine) are formed in cells during the metabolic degradation of nucleic acids and nucleotides which are salvaged and used over again to remake purine nucleotides.

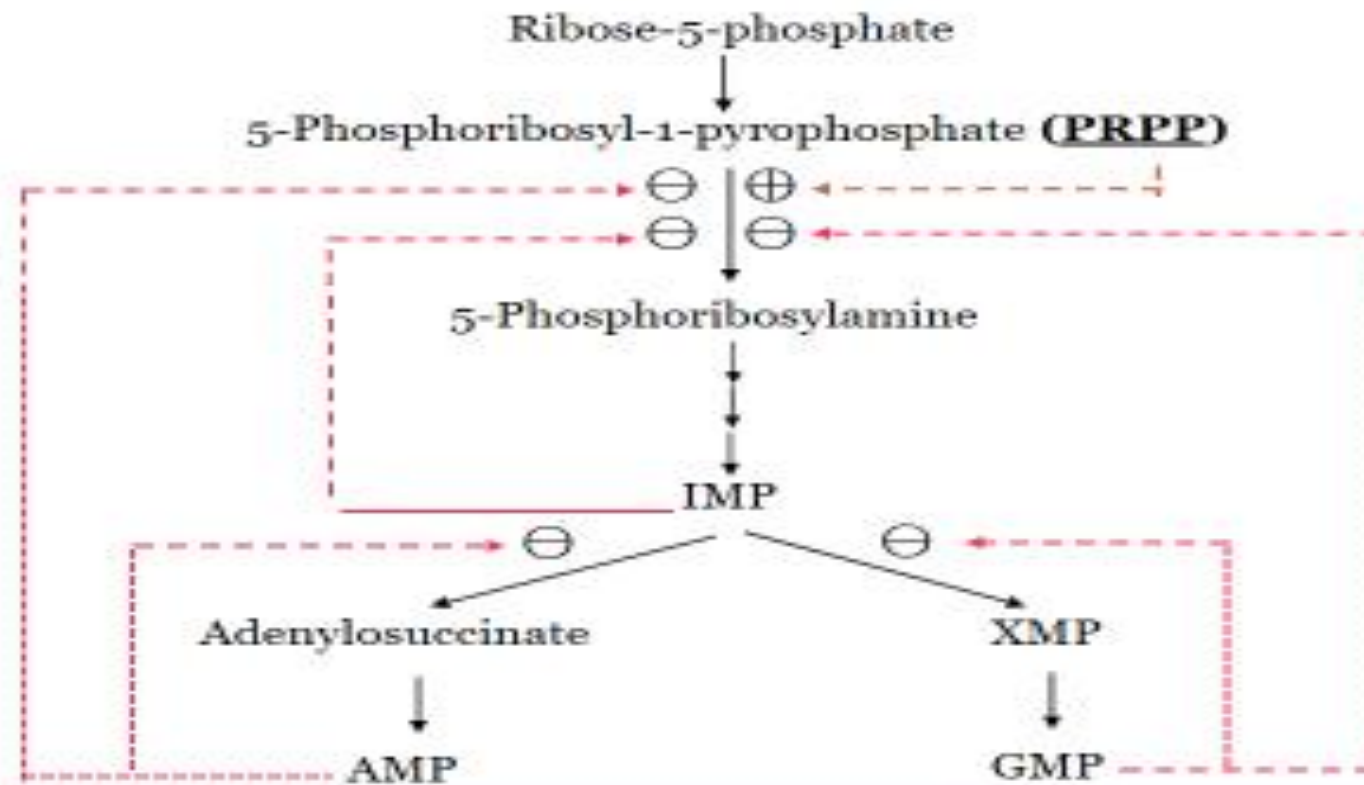
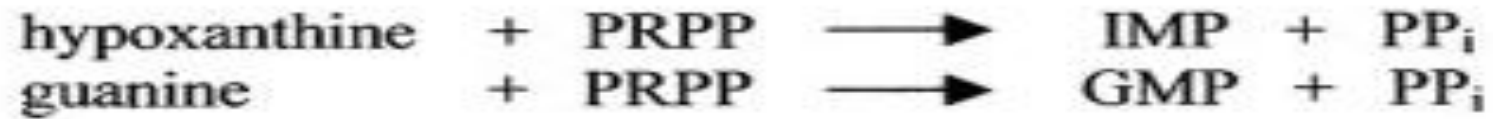
Salvage Pathway

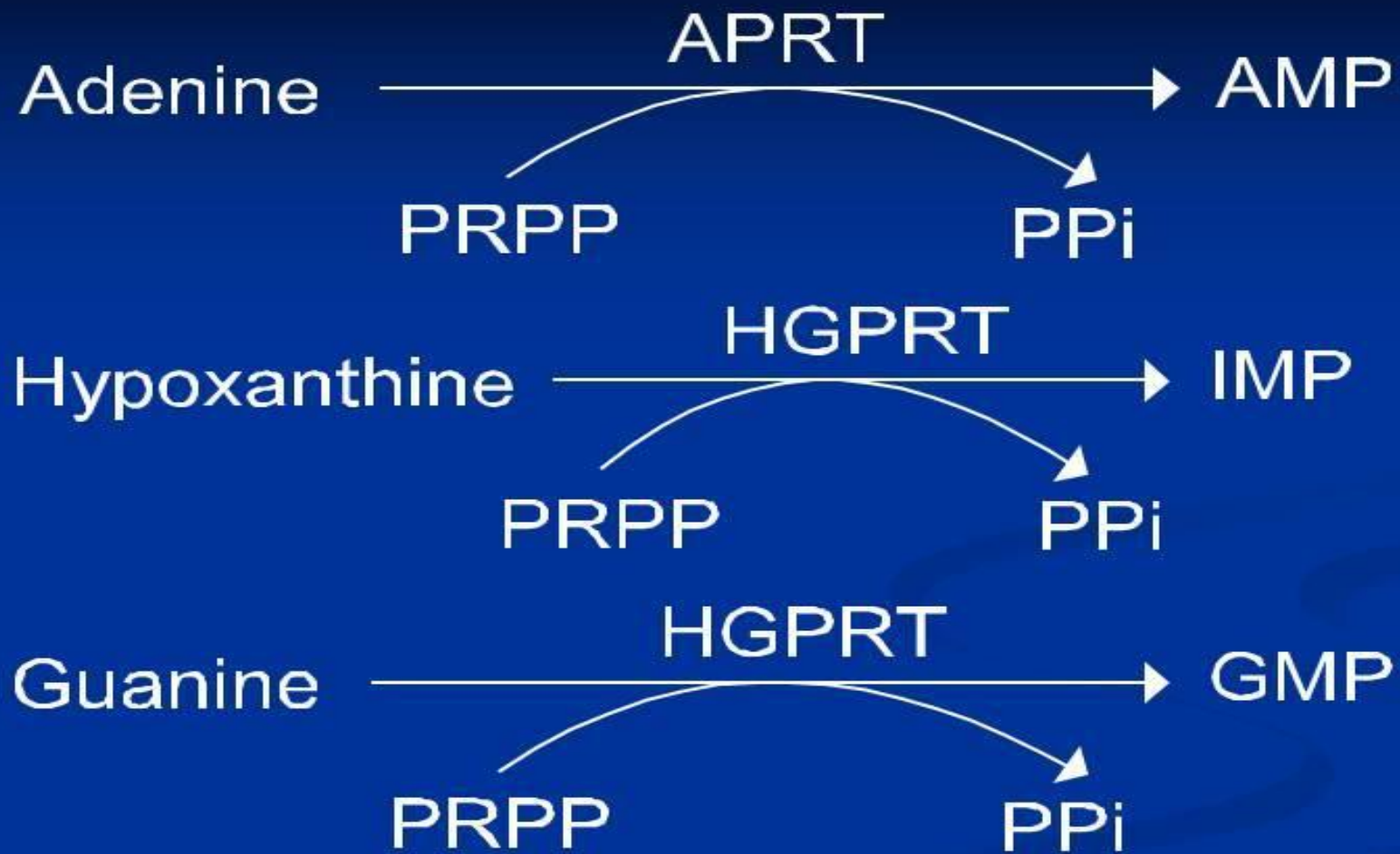
- Sources of NTP
 - ↳ from denovo synthesis
 - ↳ from the **diet**.
 - ↳ from normal **cellular turnover**.
- *HGPRT (Hypoxanthine Guanine Phosphoribosyl Transferase)*

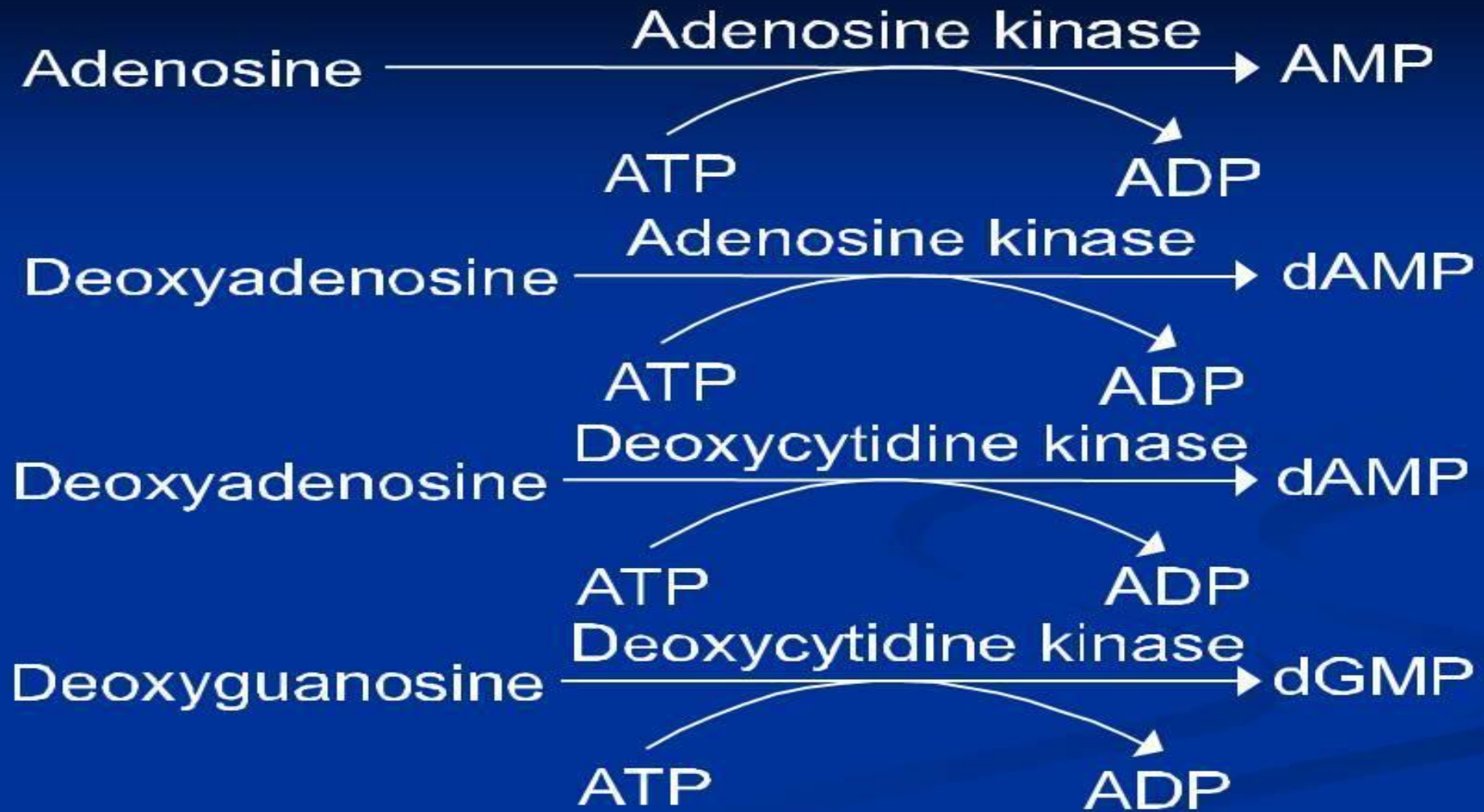
Salvage Pathway



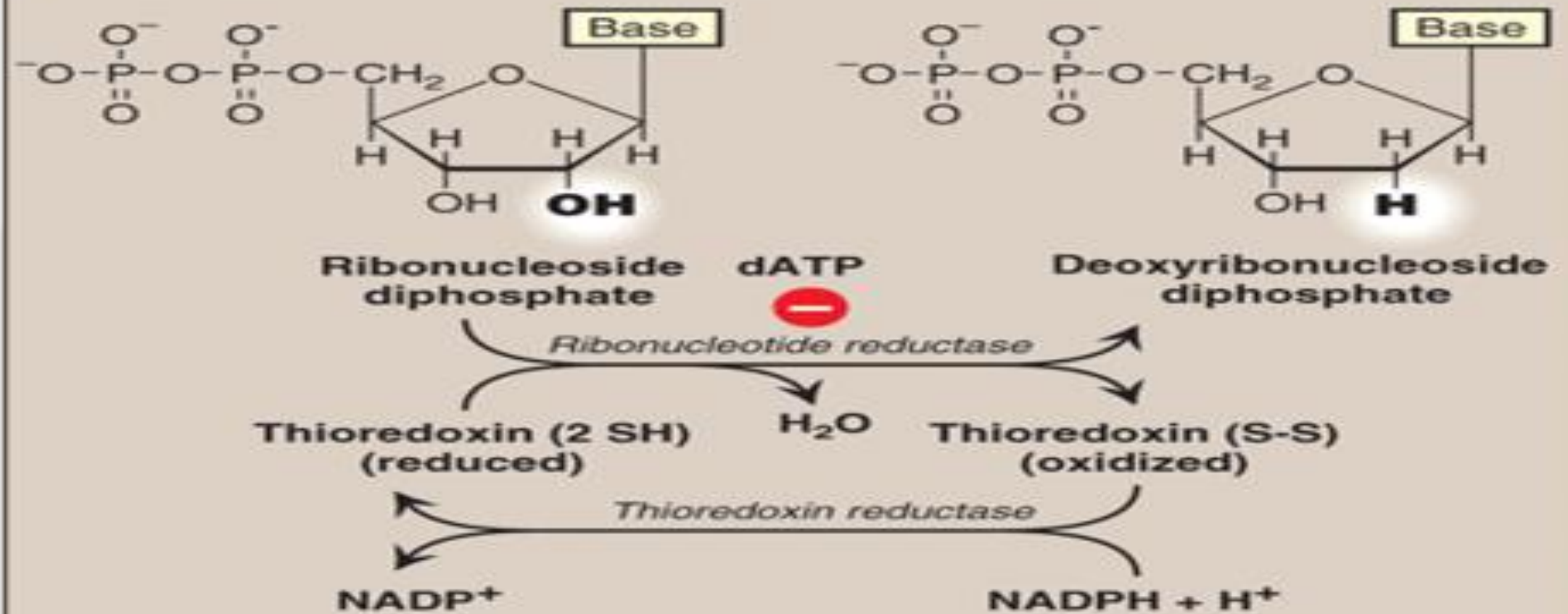
Enzyme: Hypoxanthine-guanine phosphoribosyltransferase (HGPRase)







Synthesis of Deoxyribonucleotides



Regulation of Deoxyribonucleotides



- Thioredoxin contains two cysteine residues separated by two amino acids in the peptide chain
- **dATP**
 - **Allosteric inhibit enzyme**
 - **Inhibit reduction of all four nucleoside diphosphates.**
- **dATP increase = in Adenosine deaminase deficiency**
- This effectively prevents DNA synthesis
- **Hydroxyurea** destroys the free radical required for enzyme activity of ribonucleotide reductase
- Used in Cancer treatment.
- E.g. Chronic Myelogenous Leukemia.

Significance of Salvage Pathway

1. **HGPRTase** channels hypoxanthine and guanine back into DNA synthesis. **Failure of this enzyme** results:

- Increased uric acid, a purine breakdown product.
- The de novo pathway is stimulated due to an excess of PRPP (phosphoribosyl-pyrophosphate).

2. **Salvage pathway provides purine nucleotides for tissues**, incapable of their biosynthesis by de novo pathway. For example,

- **Human brain** has low level of PRPP amidotransferase and therefore **depends in part on salvage pathways**.
- **Erythrocytes and polymorphonuclear leukocytes** cannot synthesize 5-phosphoribosylamine and therefore utilize exogenous purines to form nucleotides.

Purine Degradation

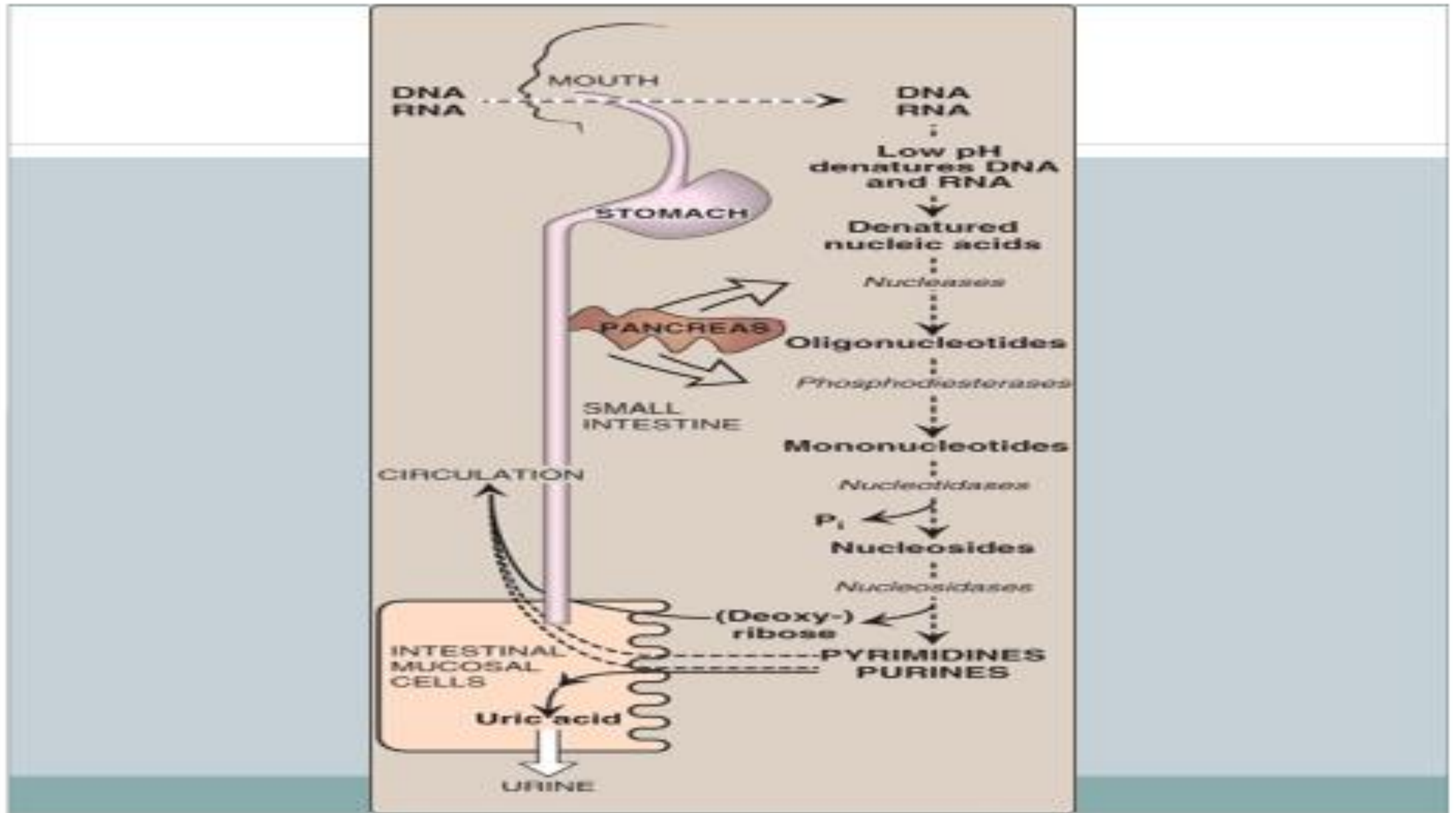


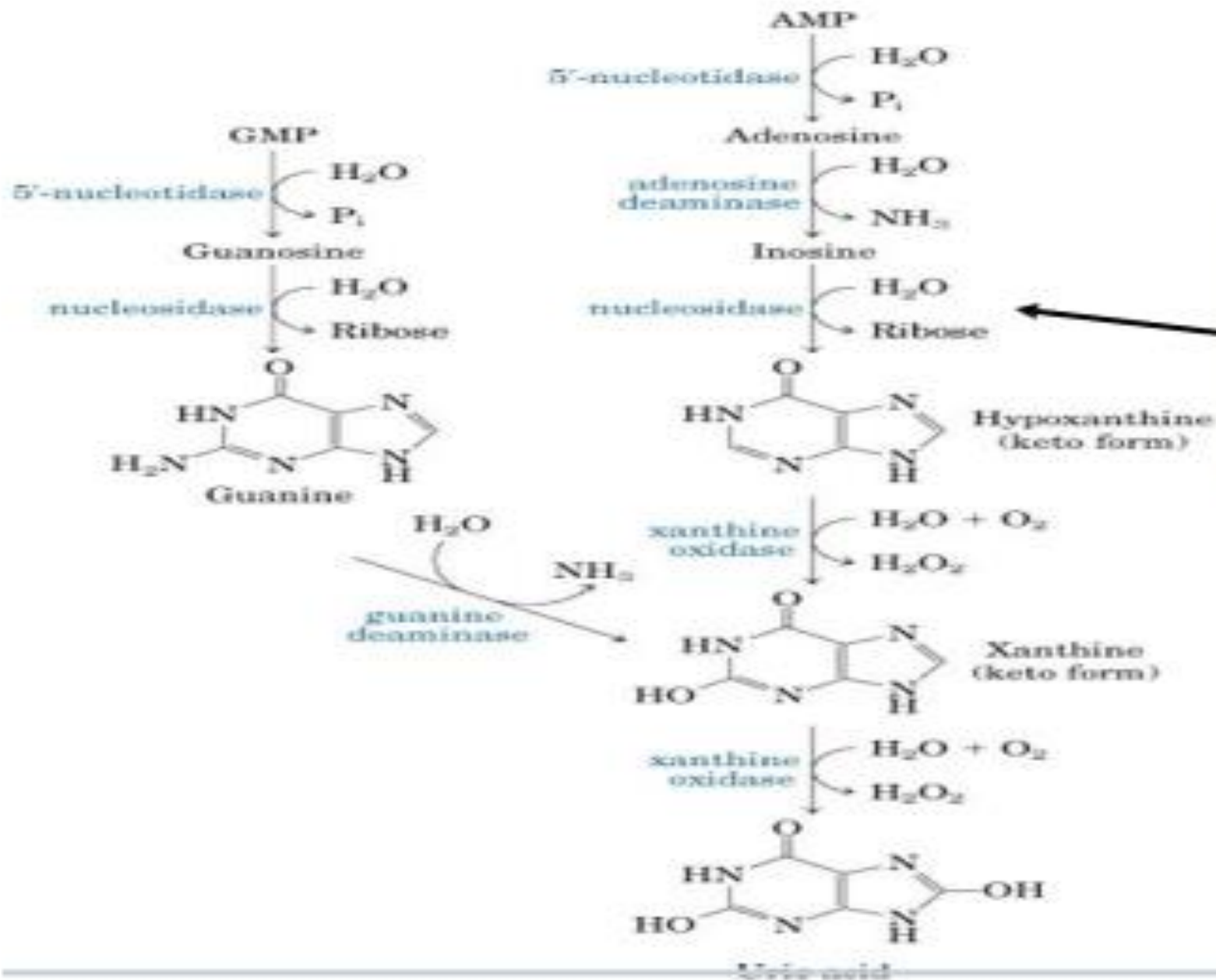
- Occurs in the small intestine
- Pancreatic enzymes hydrolyzes the nucleotides to nucleosides and free bases.
- Inside cells, **Purine nucleotides = Uric acid.**
- In Mammals & Some organism
 - ℞ **Uric acid = Allantoin.**
 - ℞ **Uric acid = Urea / Ammonia.**
- Humans excrete about 0.6 g uric acid every 24 hours.

Degradation of Dietary Nucleotide



- Pancrease Release
 - Ribonucleases and Deoxyribonucleases
 - hydrolyze RNA and DNA to Oligonucleotides.
 - Pancreatic phosphodiesterases
 - Oligonucleotides to 3'- and 5'-mononucleotides.
 - Nucleotidases
 - Removes phosphate = Nucleosides
 - Nucleosides = Free bases.
- Purines and pyrimidines are not used for synthesis of tissue nucleic acids.
- Dietary purines = Uric acid





The enzyme “nucleotidase” is also known as purine nucleotide phosphorylase (PNP)

CATABOLISM OF PURINE NUCLEOTIDES

- The end product of purines (adenine and guanine) is **uric acid**
- The pathway for the degradation of AMP includes an extra step because adenosine is not a substrate for nucleoside phosphorylase.
- In the extra step, adenosine is deaminated to inosine, which is a substrate for nucleoside phosphorylase.
- A healthy adult human excretes **uric acid** at a rate of about **0.6 g/24 hour**

DISORDERS OF PURINE CATABOLISM

- The catabolism of the purines, adenine and guanine produces uric acid. At physiological pH, uric acid is mostly ionized and present in plasma as sodium urate.
- The normal blood serum level of uric acid is 4 to 7 mg per 100 ml
- An elevated serum urate concentration is known as hyperuricemia.

The causes of hyperuricemia

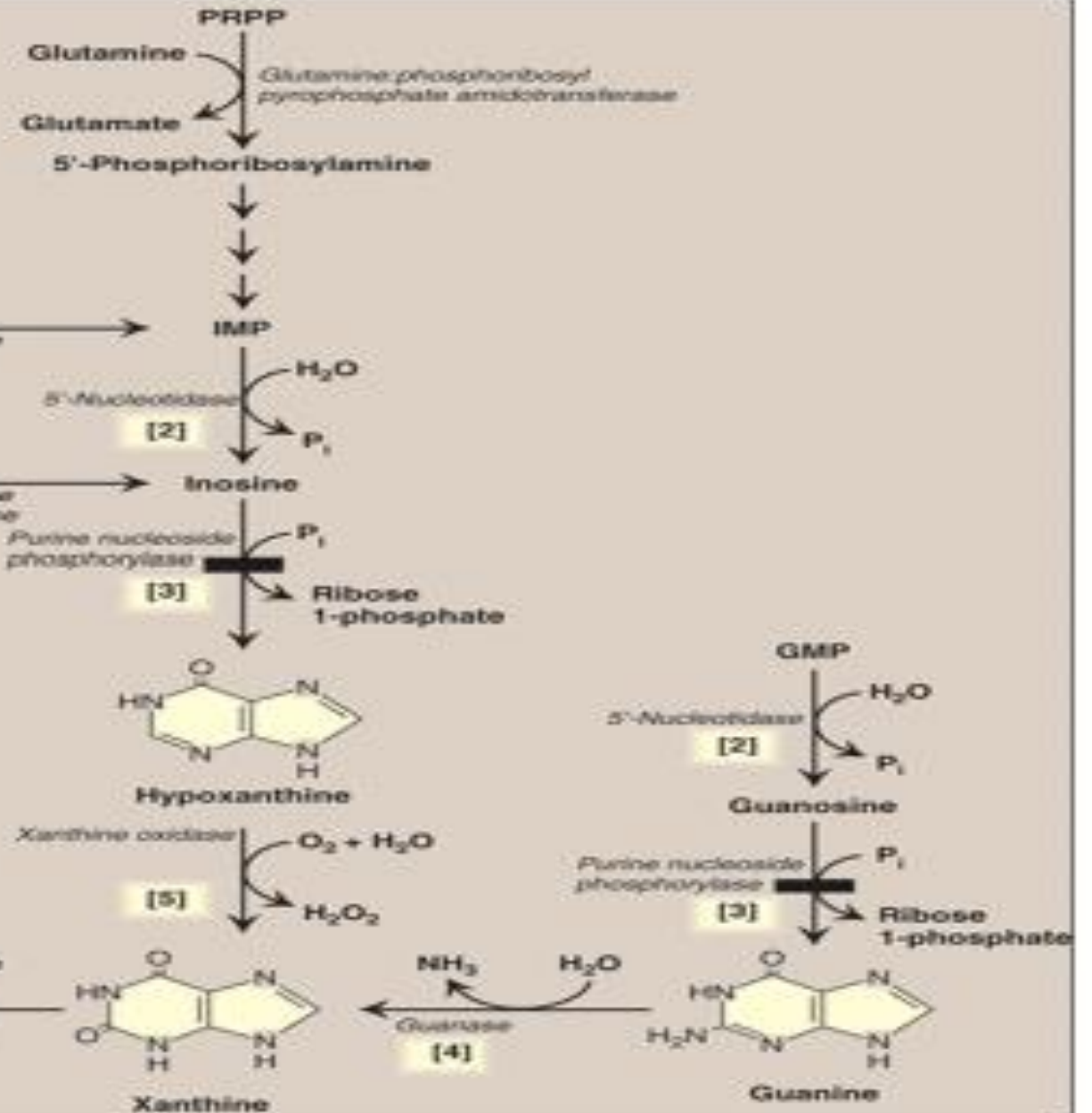
Uric acid and urate are relatively insoluble molecules which readily precipitate out of aqueous solutions such as **urine or synovial fluid**. The consequence of this is the condition, **gout**.

Formation of uric acid, depends on the rate of:

- **De novo synthesis of purines**
- The **metabolism of endogenous DNA, RNA** and other purine containing molecule such as **ATP**
- The **breakdown of dietary nucleic acids**

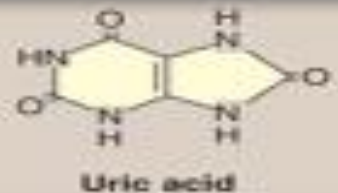
ADENOSINE DEAMINASE (ADA) DEFICIENCY

- This deficiency causes a type of severe combined immunodeficiency (SCID), involving T-cell and B-cell depletion (lymphocytopenia).
- Untreated ADA-deficient children usually die before two years of age from overwhelming infection.



GOUT

- This disorder is characterized by hyperuricemia with recurrent attacks of acute arthritic joint inflammation, caused by deposition of monosodium urate crystals.
- In gout, the hyperuricemia results primarily from the underexcretion of uric acid. Overproduction of uric acid is less common, and known causes involve certain inborn errors of metabolism or increased availability of purines.
- Treatment with allopurinol inhibits xanthine oxidase, resulting in an accumulation of hypoxanthine and xanthine—compounds more soluble than uric acid.



GOUT



- Accumulation of **Monosodium Urate crystals** in synovial fluid
- Inflammation in surrounding area = **Acute Arthritis**.
- At 30 °C & in acidic pH solubility is lower.
- Deposited in cooler areas of body.
- **Tophi** = **Mass** of monosodium urate crystals
- Deposited in the soft tissues
- Deposition of uric acid crystals in the urinary tract.
- Stone damage to kidney

Uric acid is excreted in two ways:

- Via the kidney: The majority of uric acid is excreted via the kidney
- Via the gut: Smaller amount of urate is excreted into the gut, where it is broken down by bacteria. This process is called uricolysis.

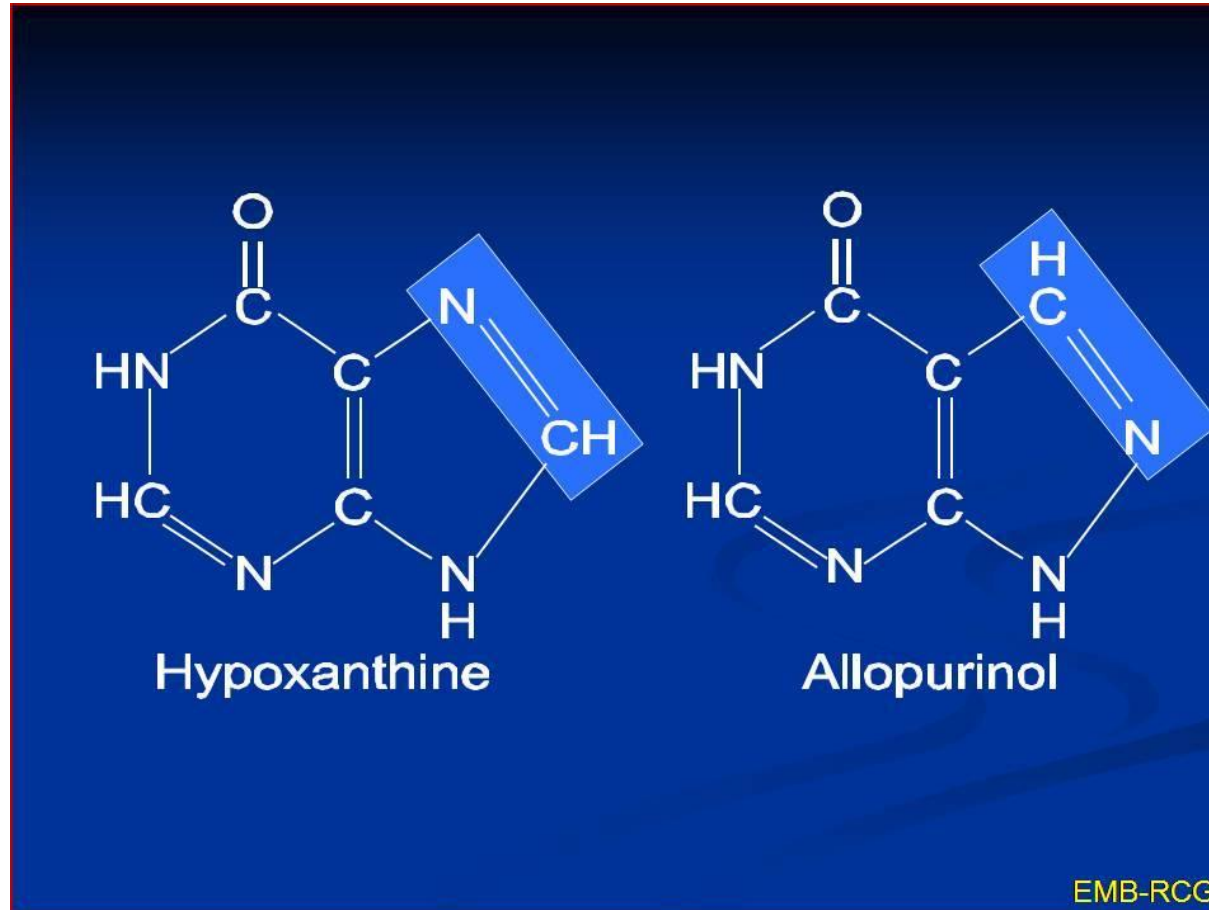
Gout

- Gout is a metabolic disorder associated with an elevated level of uric acid in the serum.
- The increased serum uric acid is due to either increased formation of uric acid or its decreased renal excretion.
- Whatever be the cause, gout is associated with hyperuricemia but hyperuricemia is not always associated with gout.

URIC ACID



- Serum Uric acid = 2-5 mg/dl in females
= 3-7 mg/dl in males.
- Elevated uric acid = hyperuricaemia ($> 7\text{mg/dl}$)
- The manifestation are due to low solubility of uric acid in water.



Classification of gout

Gout is classified into two broad types:

1. Primary gout
2. Secondary gout

Primary gout

- Primary gout is an inborn error of metabolism due to overproduction of uric acid.
- In primary gout, increased level of uric acid is associated with increased synthesis of purine nucleotides
 - Increased synthesis of purine nucleotides is caused by defective enzymes of purine nucleotide biosynthesis, such as:
PRPP synthetase, PRPP glutamyl amidotransferase, HGPRTase

Symptoms of primary gout

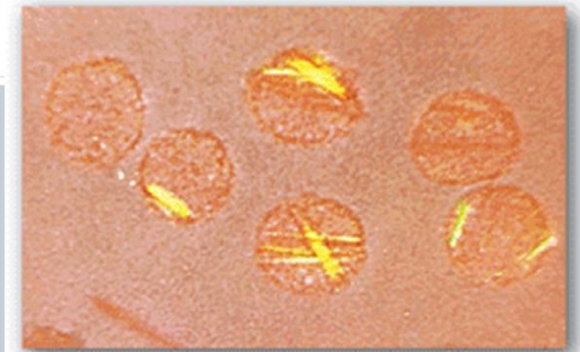
- Elevated concentration of uric acid in the blood and tissues.
- The joints become inflamed, painful, and arthritic due to abnormal deposition of sodium urate crystals.
- Patients with primary gout often show deposition of urate as tophi (clusters of urate crystals) in soft tissues that affects the joints and leads to painful arthritis.
- The kidneys are also affected, since excess urate is also deposited in the kidney tubules and leads to renal failure.

Tophi



Inflamed tophaceous gout. Three inflamed tophi over the proximal interphalangeal joints in a patient with chronic tophaceous gout. Several of the lesions ruptured spontaneously over the next three days, exuding a pasty material composed of urate crystals and inflammatory cells but no organisms. The inflammation largely subsided over one week after the administration of a nonsteroidal antiinflammatory drug. Courtesy of Michael A Becker, MD.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2790440/>



- Synovial Fluid Examination in microscope
- Light microscopy = Presence of needle-shaped monosodium urate crystals

Primary hyperuricaemia



- **Over activity of 5-phosphoribosyl amido transferase**
- **Over activity of PRPP synthase activity**
 - ▢ Increased $V_{\max}$ & lower K_m for ribose 5-phosphate
- **Deficiency of enzymes of salvage pathway**
 - ▢ Lesch-Nyhan syndrome
 - ▢ increased availability of PRPP.
- **Glucose-6-phosphatase deficiency**
 - ▢ Von Gierke disease
- **Glutathione reductase variant**

Secondary gout

Secondary gout results from a variety of diseases that cause an:

- elevated destruction of cells which occurs in cancers (leukemia, polycythaemia), psoriasis and hyper catabolic states (starvation, trauma, etc.).
- Decreased elimination of uric acid which occurs in chronic renal disease due to reduced glomerular filtrate rate.
- Glucose-6-phosphatase deficiency

Secondary Hyperuricaemia



Increased production of uric acid

- leukemias, lymphomas, polycythemias
- Radiotherapy
- Chemotherapy
- Raised rate of catabolism in starvation

Reduced excretion of uric acid

- Renal failure
- Lactic acidosis
- Ketoacidosis
- Thiazide diuretics (inhibit secretion of uric acid)

Treatment of gout

- Gout can be treated by a combination of nutritional therapy and drug therapy.
- Foods especially rich in nucleotides and nucleic acids such as liver or coffee and tea, which contain the purines caffeine and theobromine are withheld from the diet. Restriction in intake of alcohol is also advised.
- Use of the drug allopurinol, which inhibits xanthine oxidase competitively

Clinical features



- **Gouty attacks** may be precipitated by high purine and high intake of alcohol.
- **Alcohol** leads to accumulation of lactic acid.
- **Metatarsophalangeal joints.**
- Extremely painful.
- Synovial fluid will bifringent **urate crystals.**
- (**Tophi**) = Chronic cases uric acid deposited in joints.
- Deposition of urate crystal in renal = **urolithiasis & renal damage.**

Treatment



- **In Acute attack**
 - **Colchicine**
 - **Prednisone**
 - **Indomethacin.**
- **Uricosuric agents = Probenoside**
- **Reduce urate production**
- **Allopurinol & Febuxostat,**
- Allopurinol is analogue of hypoxanthine.
- Xanthine and hypoxanthine are more soluble & so are excreted more easily.

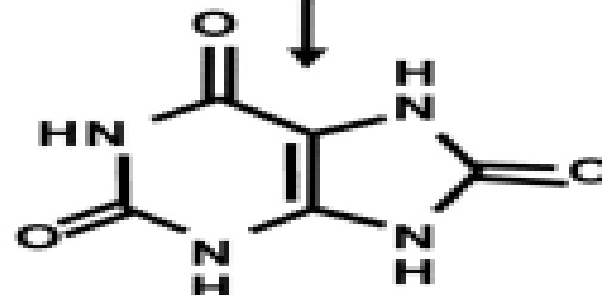
Recombinant Urate Oxidase Resburicase (Fasturtec)

Purine catabolism

Xanthine

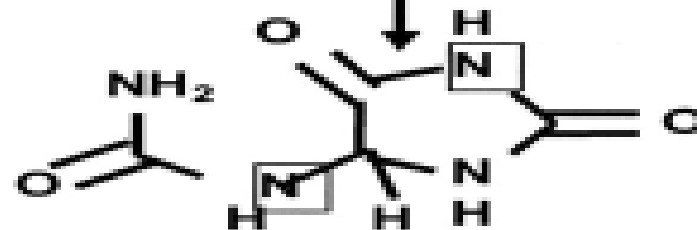
Xanthine Oxidase

└─ Allopurinol

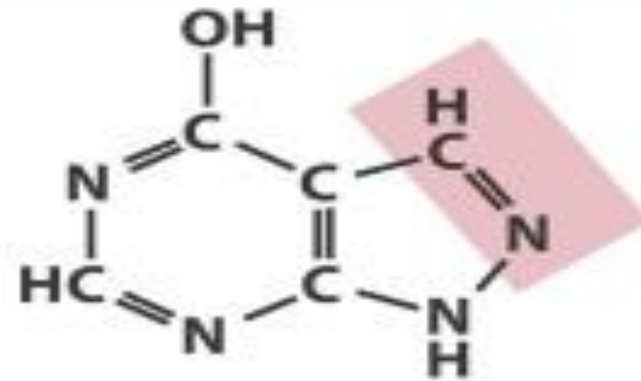


URIC ACID
(Urinary excretion)

URATE OXIDASE

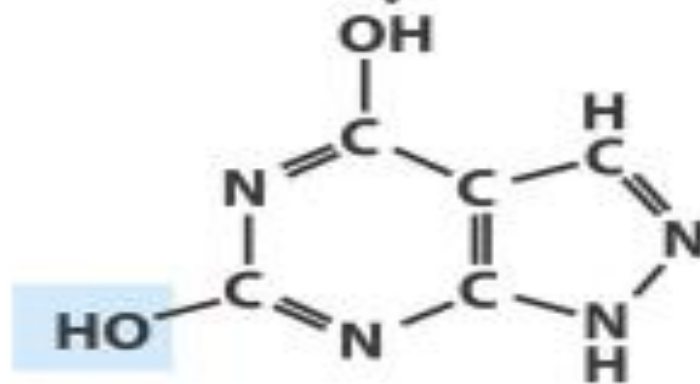


ALLANTOIN
(urinary excretion)

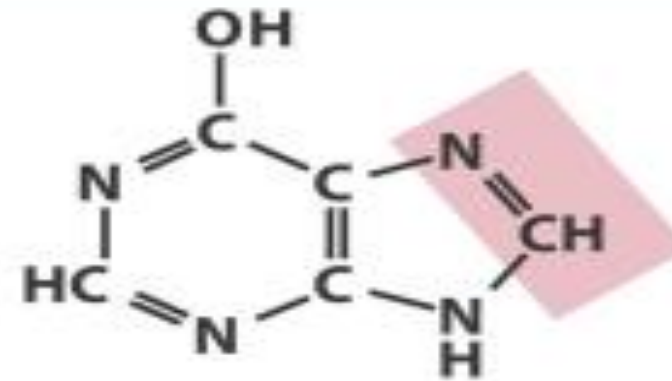


Allopurinol

xanthine
oxidase



Oxypurinol



**Hypoxanthine
(enol form)**

Excess uric acid causes
gout, treated with
allopurinol, inhibitor of
xanthine oxidase

Lesch-Nyhan Syndrome

- Inherited X-linked recessive disorder, that affects only males.
- It is caused by a complete deficiency of HGPRTase, an enzyme which is involved in purine salvage pathway
- In the absence of HGPRTase, the salvage pathway is inoperative and purines cannot be reconverted to nucleotides; instead they are degraded to uric acid.
- The genetic lack of HGPRTase causes an overproduction of PRPP, which stimulates purine biosynthesis.
- Because of increased purine synthesis, the degradation product uric acid also increases.
- This results in increased concentration of uric acid in plasma and urine and gout like damage to tissue.

Symptoms

The symptoms include:

- Hyperuricemia
- Gout
- Urinary tract stones
- The neurological symptoms or mental retardation
- Spasticity (resistance to the passive movement of a limb)
- Self-mutilation (self painful, destructive behavior of biting of fingers and lips).

Treatment

- Allopurinol reduces uric acid formation but does not alleviate the neurologic symptoms.
- This syndrome is potential target for gene therapy

Severe Combined Immunodeficiency

- Severe combined immunodeficiency (SCID) is an immunological disorder.
- The loss of adenosine deaminase (ADA) activity results in severe combined immunodeficiency (SCID).
- ADA is an enzyme involved in degradation of AMP. Person with SCID have severe recurring infections, often leading to death at an early age.
- SCID is characterized by loss of T-cells and B-cells which is essential to the immune response.
- SCID is often called the, “bubble boy disease”, because its treatment may include complete isolation of the patient in sterile “bubble” environment.

Treatment

- **Bone marrow transplants** from a matched donor to replace the hematopoietic stem cells those mature into B and T lymphocytes.
- **Enzyme replacement therapy**, requiring once or twice per week **intramuscular injection of active ADA**, is effective, but the therapeutic benefit declines after 8 to 10 years and complication arise, including malignancies.
- Permanent cure requires **replacing the defective gene** with a functional one in bone marrow cells.
- **Adenosine deaminase deficiency** was one of the first targets of human gene therapy trials in 1990.
- **Gene therapy** is rapidly becoming a viable path for long term restoration of immune function for these patients.

Adenosine deaminase (ADA) deficiency



- ADA is expressed in the cytosol of all cells
- **Lymphocytes** have the **highest** activity of this enzyme.
- Accumulation of adenosine
- Increase Adenosine =
= Increase Ribonucleotide or Deoxyribonucleotide
= **Increase dATP** levels.
- Ribonucleotide reductase is inhibited
- **Inhibit production of all deoxyribose**-containing nucleotides.
- Decrease dGTP, dCTP, dTTP production



- DNA formation during cell division inhibited.
- Severe combined immunodeficiency disease
- Involving a decrease in both T cells and B cells.
- Treatment
 - Bone marrow replacement
 - Enzyme replacement therapy
 - Gene Therapy.
- Without treatment, children die by the age of two years.

Laboratory Results Of Analytes Associated With Gout And Lesch Nyhan Syndrome

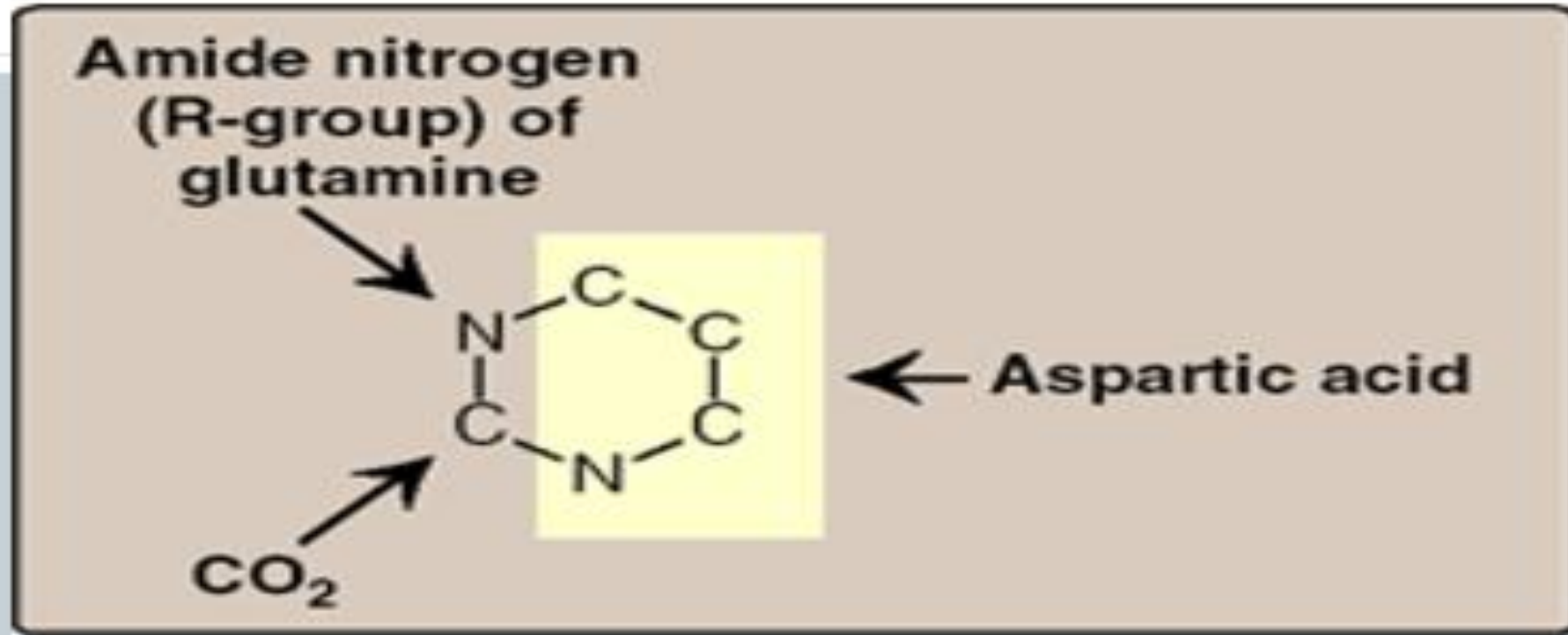
The use of **biochemical testing** for the detection of **gout**

1. Blood tests
2. Synovial Fluid Examination
3. Urinalysis

The use of **biochemical testing** for the detection of **Lesch Nyhan syndrome (LNS)**

1. Overproduction of uric acid
2. Activity of the HGPRTase enzyme
3. The urate to creatinine concentration ratio
4. Molecular Genetic testing (called as Diagnostic triad for LNS)

Pyrimidine Synthesis



- Purine synthesis = Constructed on a pre-existing ribose 5-phosphate.
- Pyrimidine Synthesis = Before attached to ribose 5-phosphate.

Two Main Domain of Pyrimidine Synthesis



1. Carbamoyl Phosphate Synthetase (CPS) II

- a. CPS II
- b. Aspartate transcarbamoylase
- c. Dihydroorotase

2. UMA Synthase

- a. Orotidylate decarboxylase
- b. Orotate phosphoribosyltransferase

Synthesis of Carbamoyl phosphate



- Carbamoyl phosphate synthetase (CPS) II.
 - ✦ Multifunctional polypeptide
 - ✦ **Three different catalytic domains** of a ~~single~~ polypeptide chain.
 - ✦ CPS II, Aspartate transcarbamoylase & Dihydroorotase
- Glutamine and CO_2 , catalyzed by
- CPS II
 - ✦ **Inhibited by UTP (the end product)**
 - ✦ **Activated by ATP and PRPP.**

De Novo Biosynthesis Of Pyrimidine Nucleotides

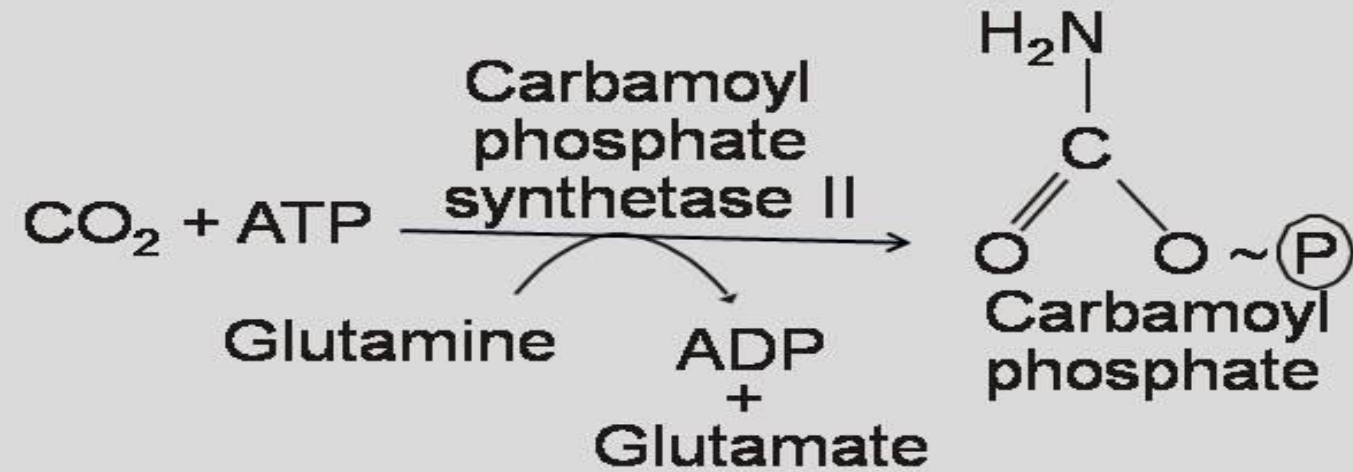
➤ The **pyrimidine nucleotides** are:

1. Cytidine monophosphate CMP
2. Uridine monophosphate UMP
3. Thymidine monophosphate TMP.

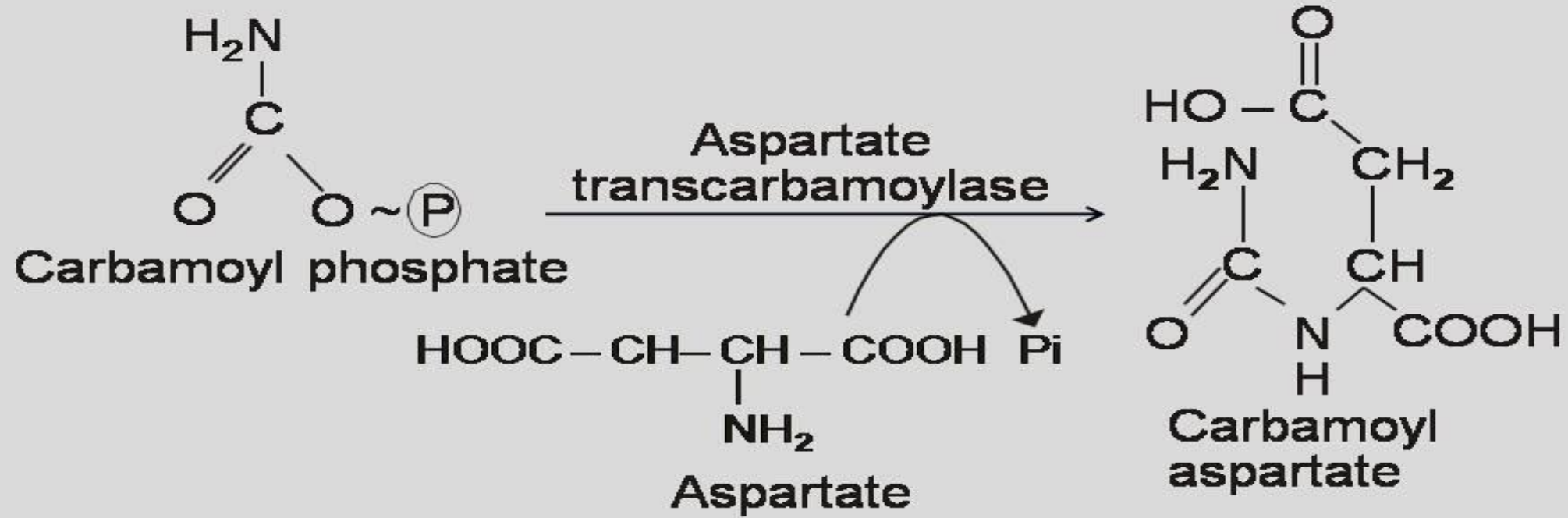
➤ Unlike the synthesis of purine nucleotide, six membered pyrimidine ring is made first and then attached to ribose phosphate, which is donated by PRPP.

Precursors for the De Novo Synthesis of Pyrimidine

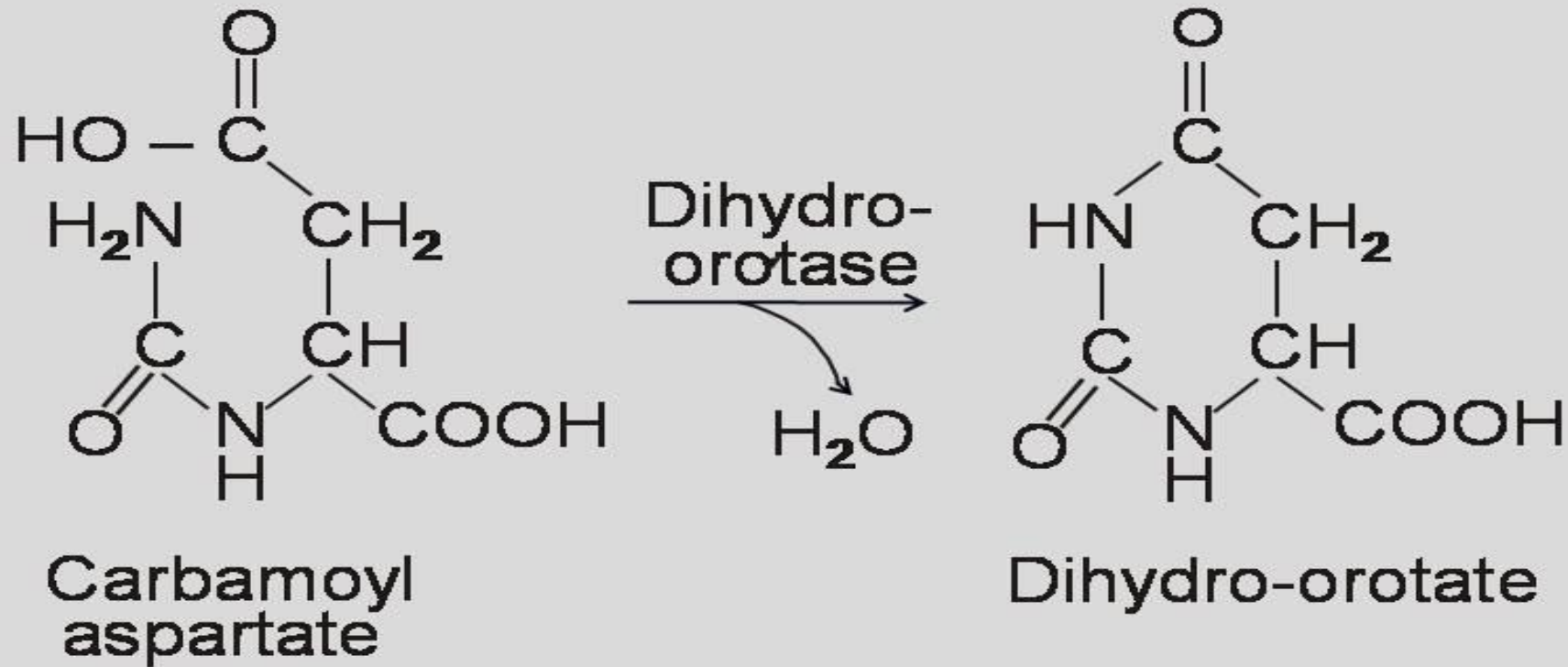
1. Glutamine provides N3
2. Aspartic acid furnishes C4, C5, C6 and N1
3. Carbon dioxide provides C2.



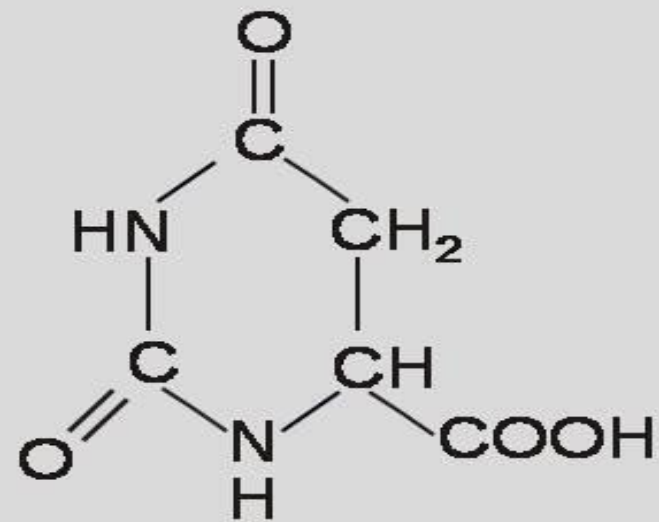
Synthesis of carbamoyl phosphate from carbon dioxide, ATP and glutamine



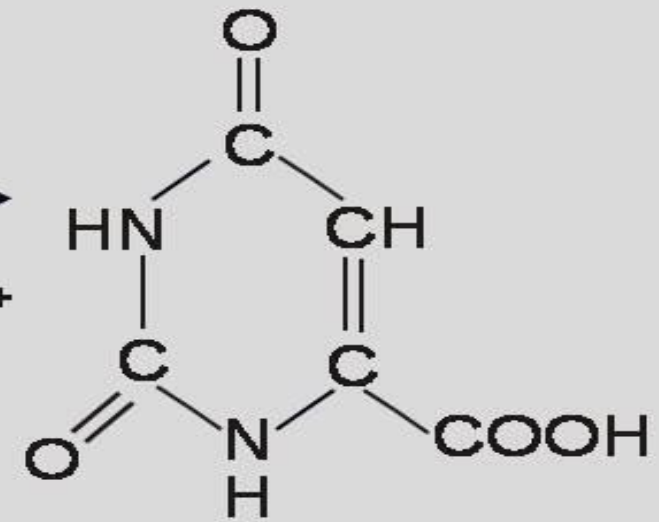
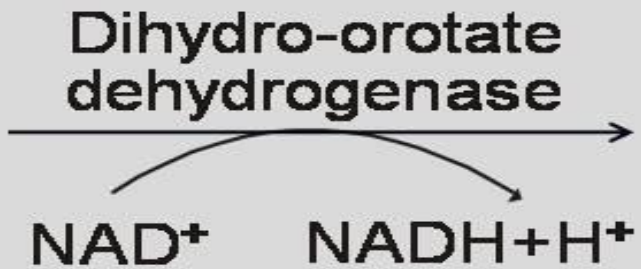
Carbamoyl group transferred to aspartate



Ring closure forms dihydro-orotate

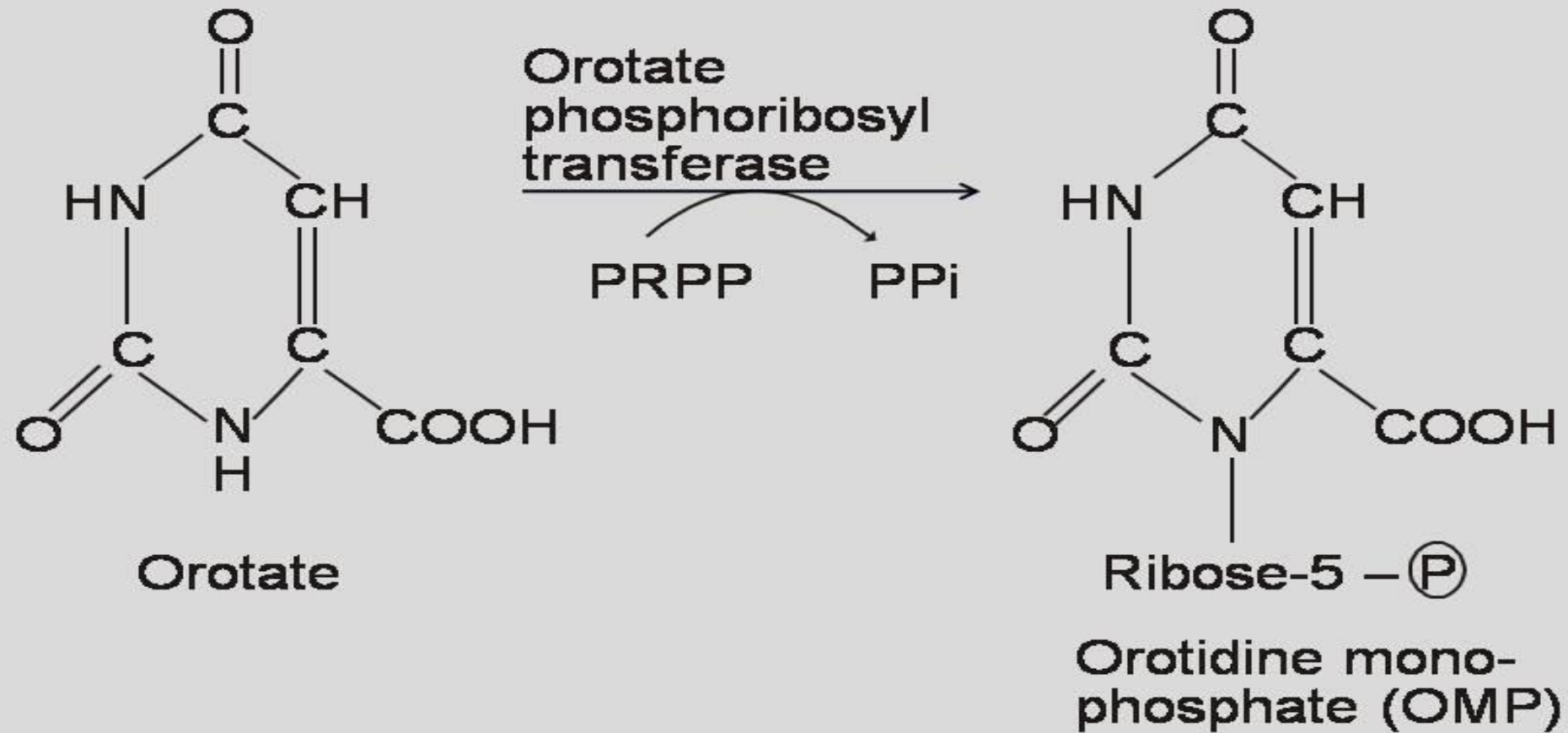


Dihydro-orotate

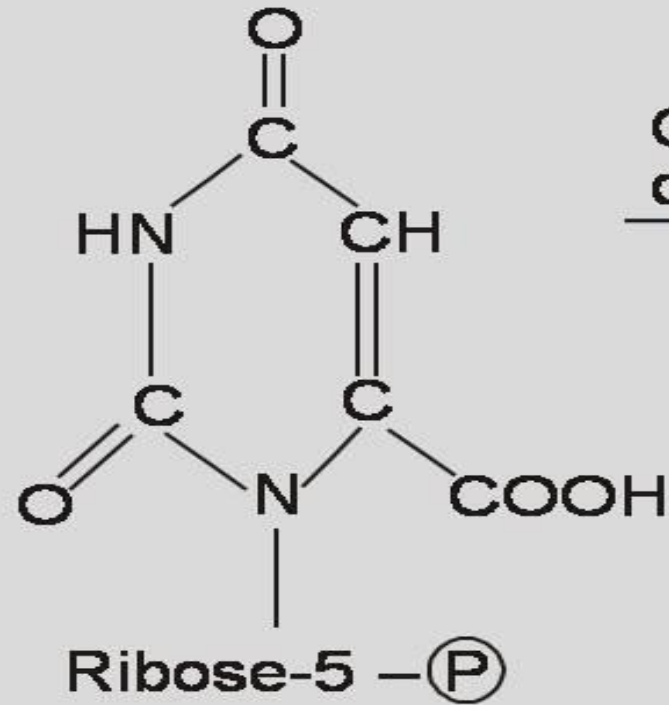


Orotate

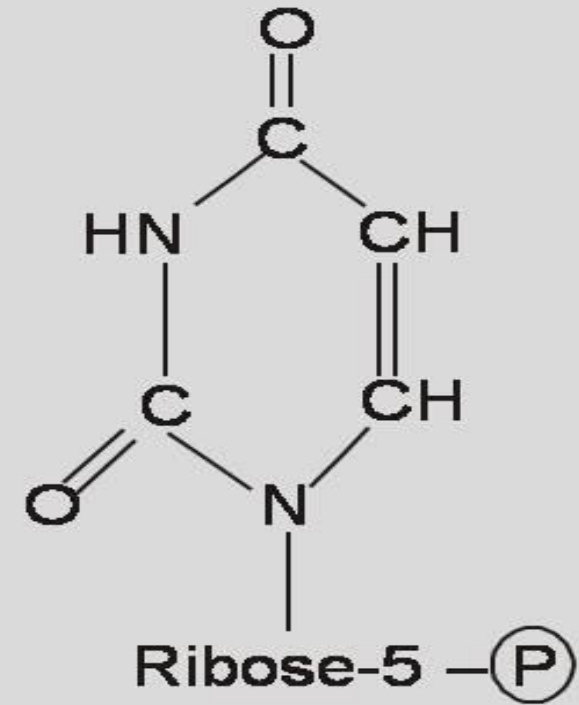
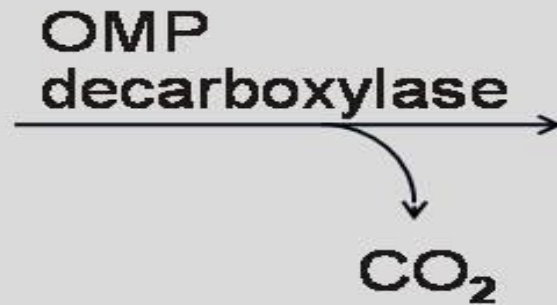
Dihydro-orotate oxidised to orotate



Phosphoribosyl group added to orotate



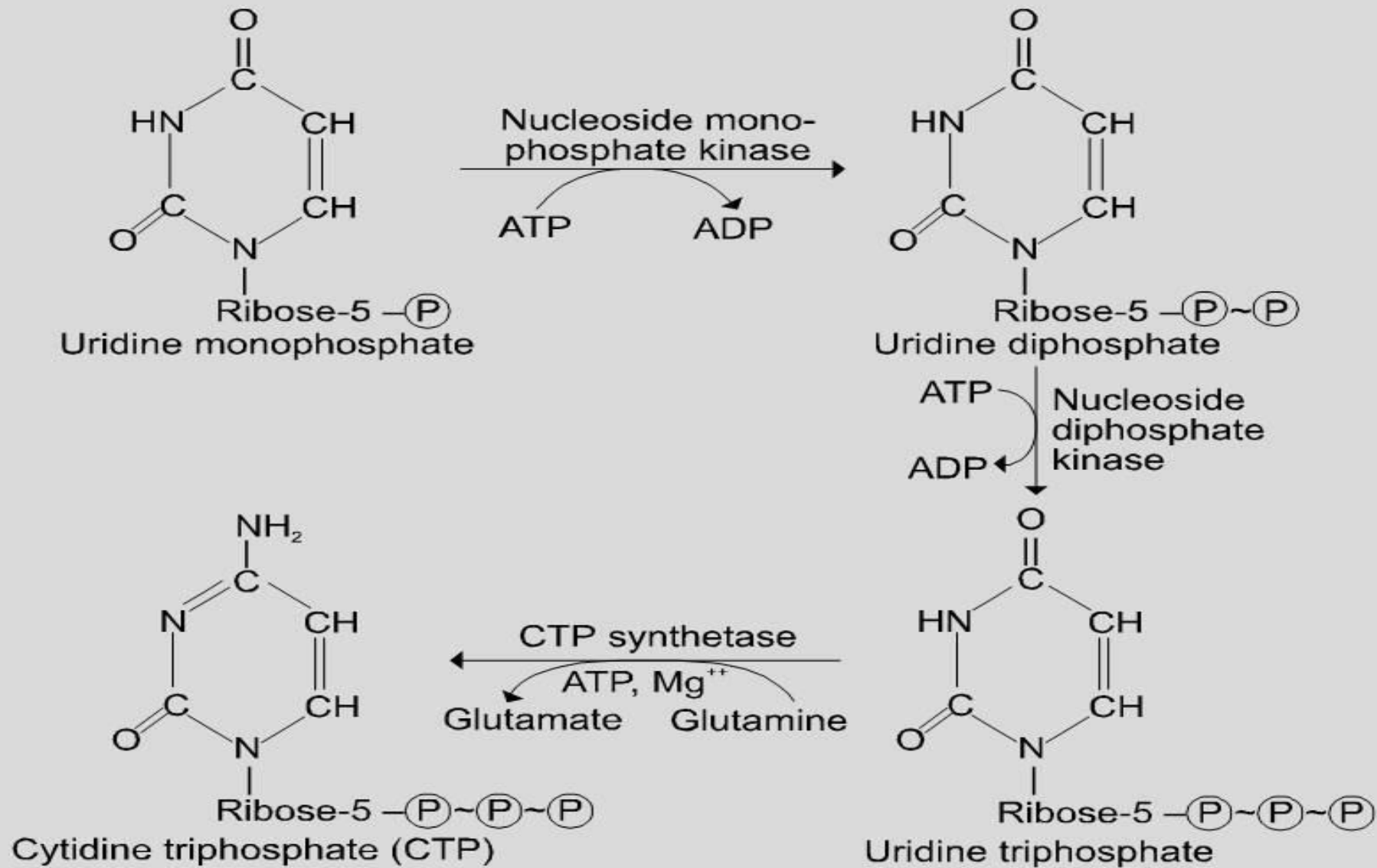
Orotidine mono-phosphate (OMP)



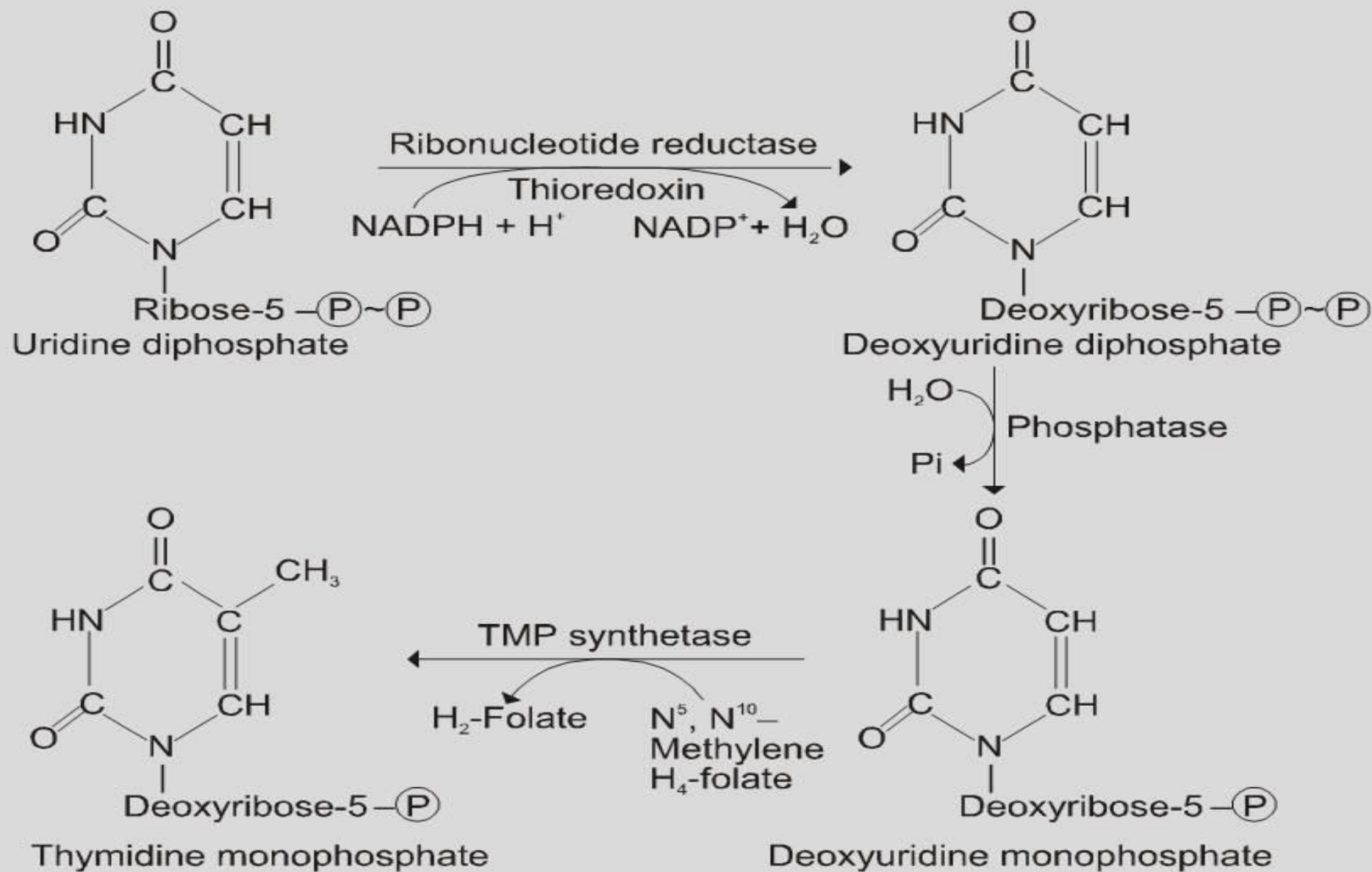
Uridine mono-phosphate (UMP)

OMP decarboxylated to UMP

From **Essentials of Medical Biochemistry** by R.C. Gupta



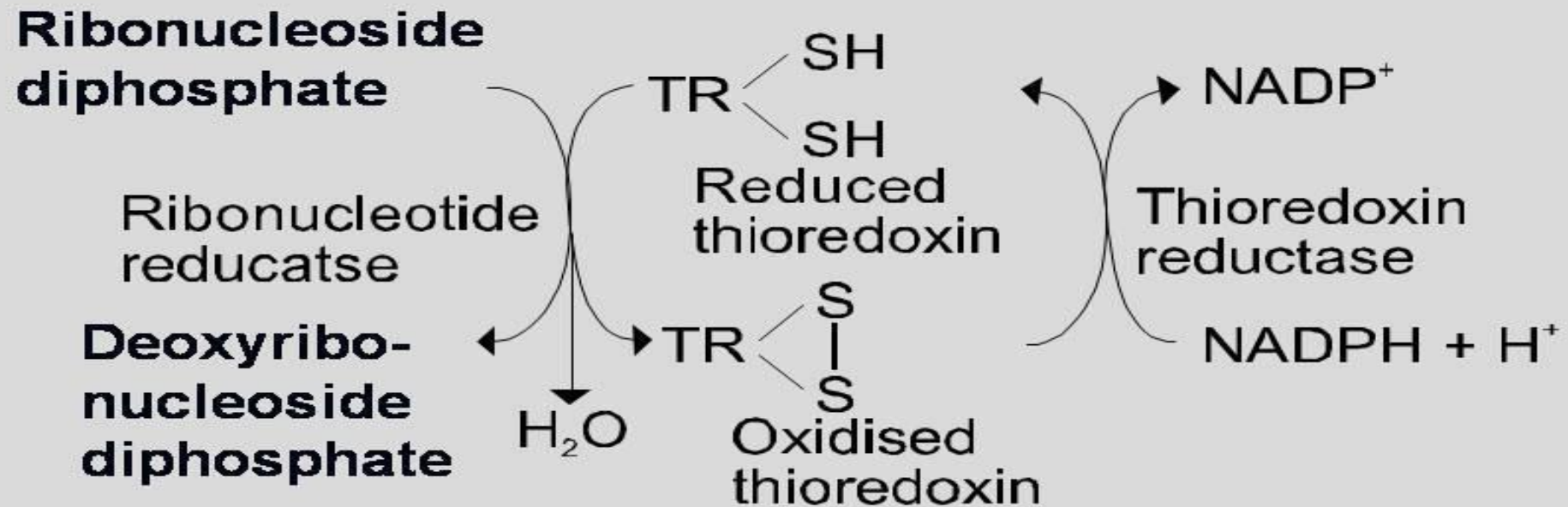
From Essentials of Medical Biochemistry by R.C. Gupta



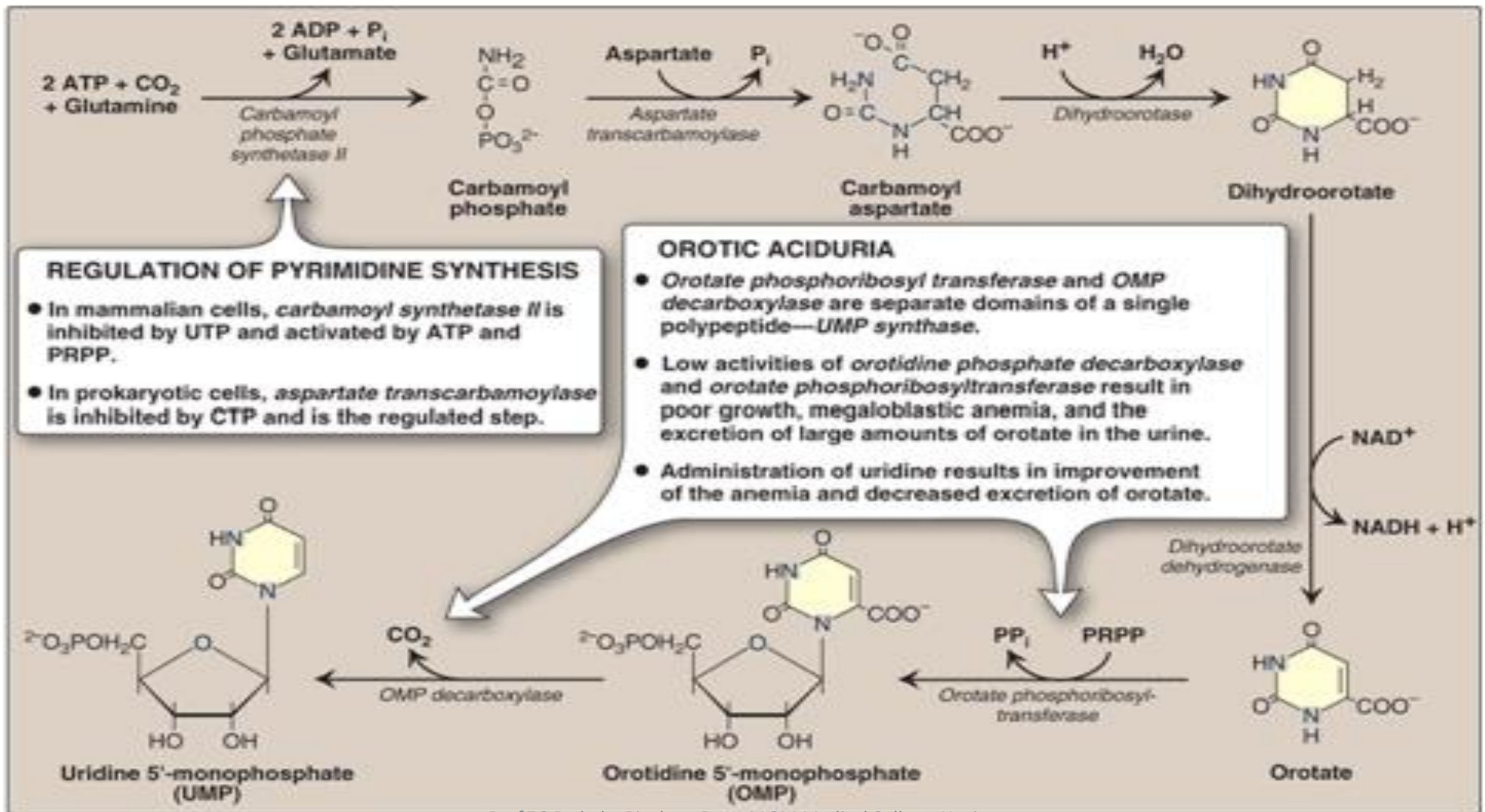
From **Essentials of Medical Biochemistry** by **R.C. Gupta**

Prof ZG Badade, Biochem Dept, MGM Medical College, Navi

Mumbai



From **Essentials of Medical Biochemistry** by R.C. Gupta



Formation of a Pyrimidine nucleotide



- PRPP is again the ribose 5-phosphate donor.
- Both purine and pyrimidine synthesis thus require glutamine, aspartic acid, and PRPP as essential precursors.
- **UMP synthase = domains of a single polypeptide chain**
 - ▢ Orotidylate decarboxylase
 - ▢ Orotate phosphoribosyltransferase

Salvage of Pyrimidines

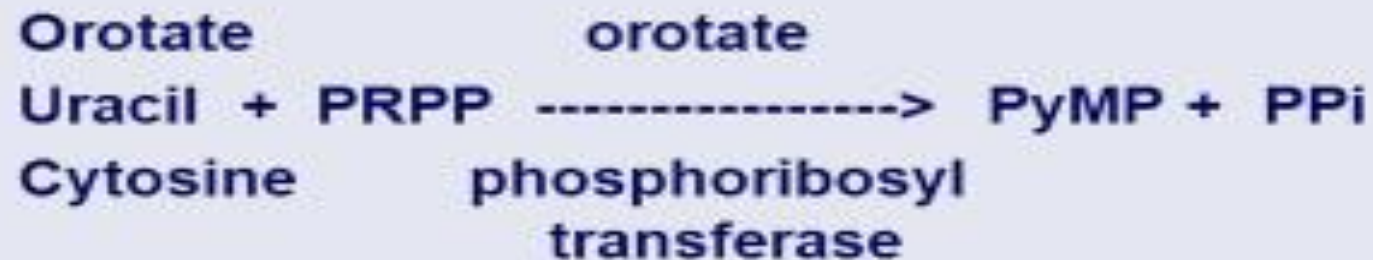
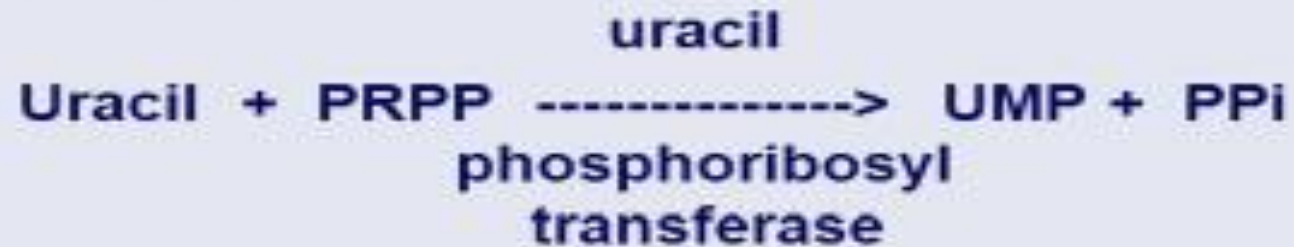


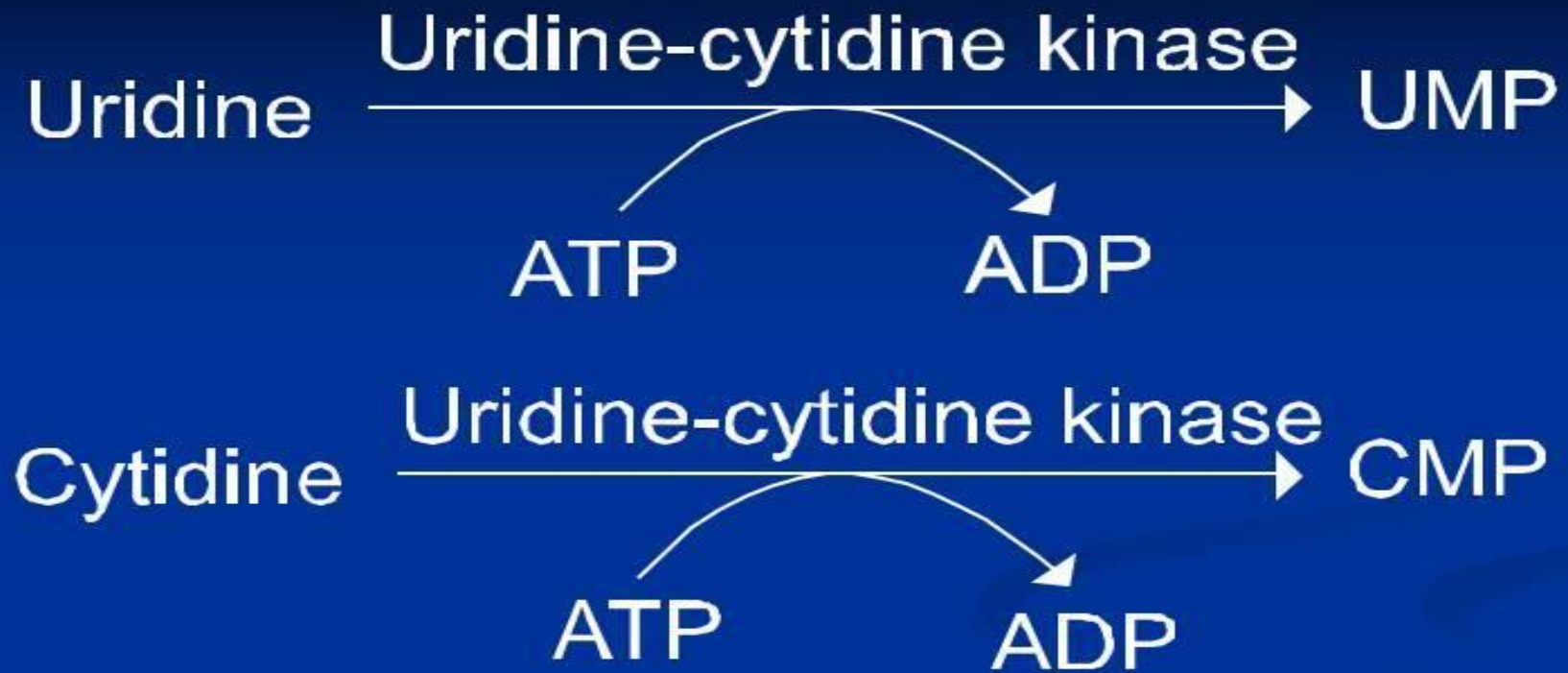
- Nucleoside kinases that utilize ATP
- Through phosphorylation of the nucleosides to nucleotides.
- The salvage of pyrimidine nucleotides is the basis for using uridine in the treatment of hereditary orotic aciduria.

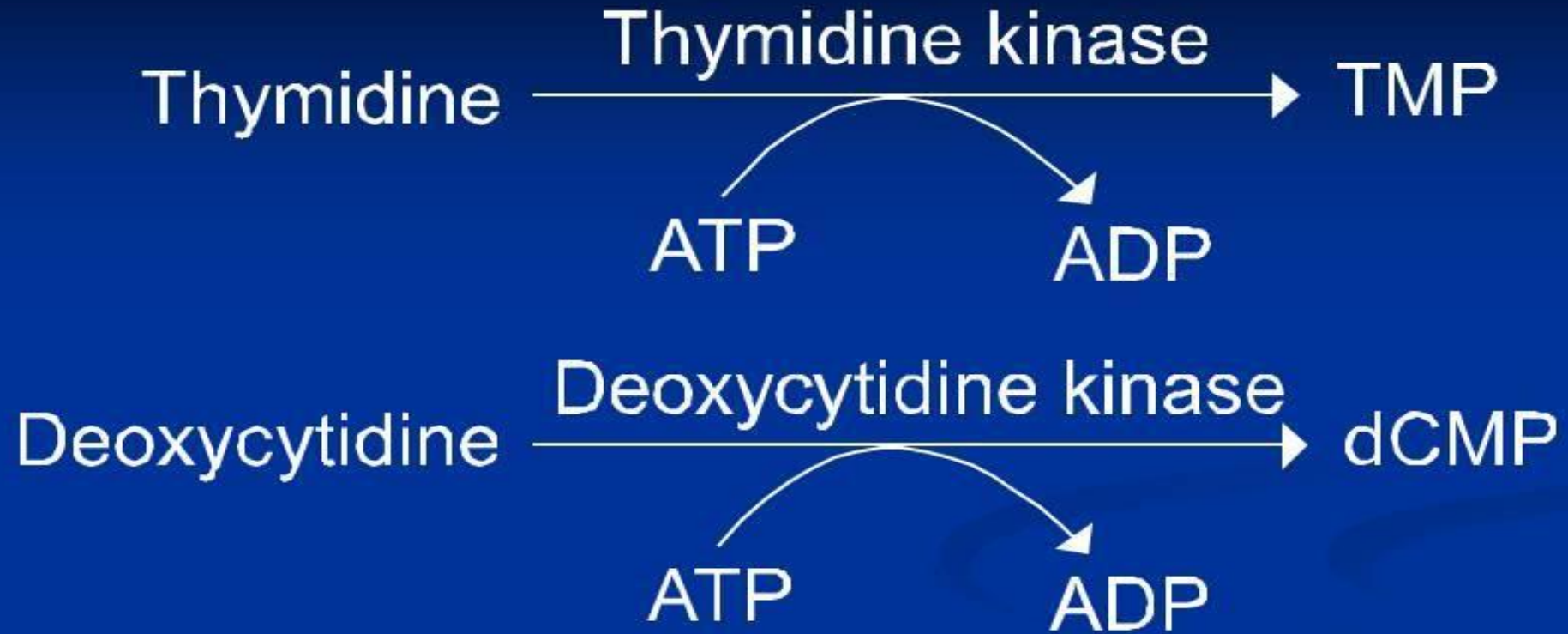
26.3 Pyrimidine Salvage Pathways

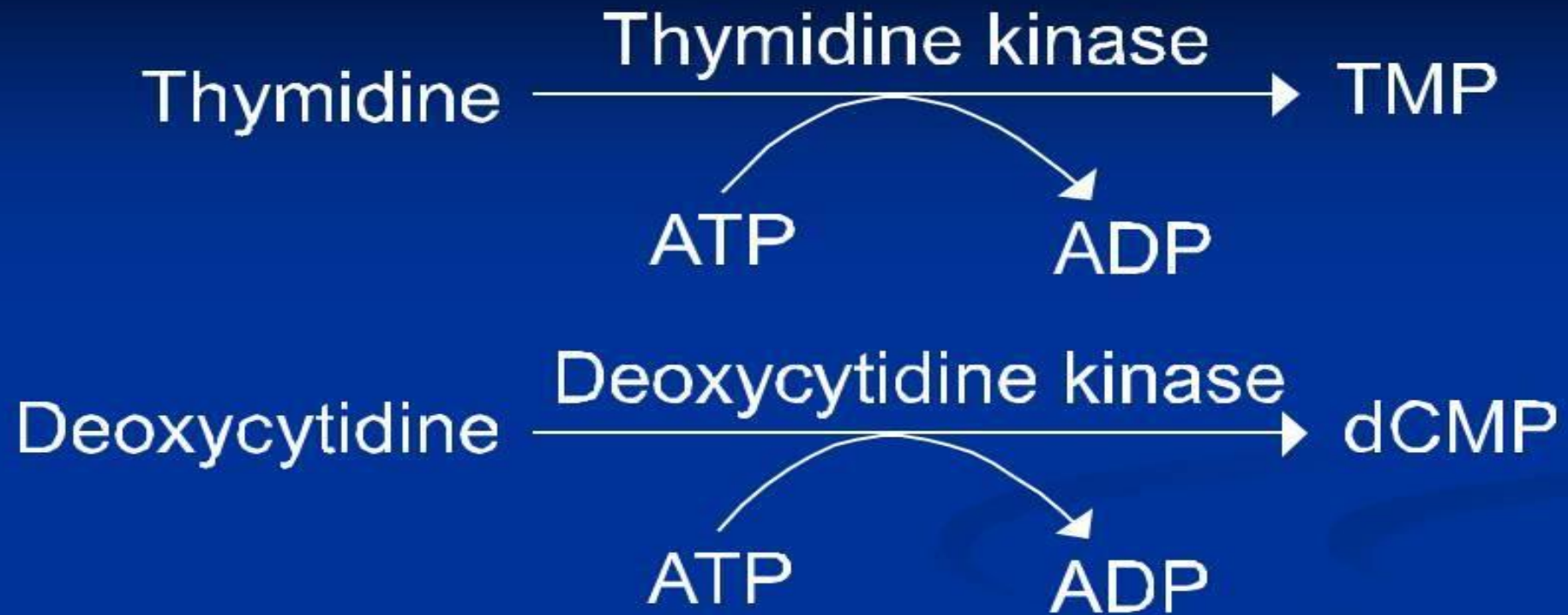


PYRIMIDINES:









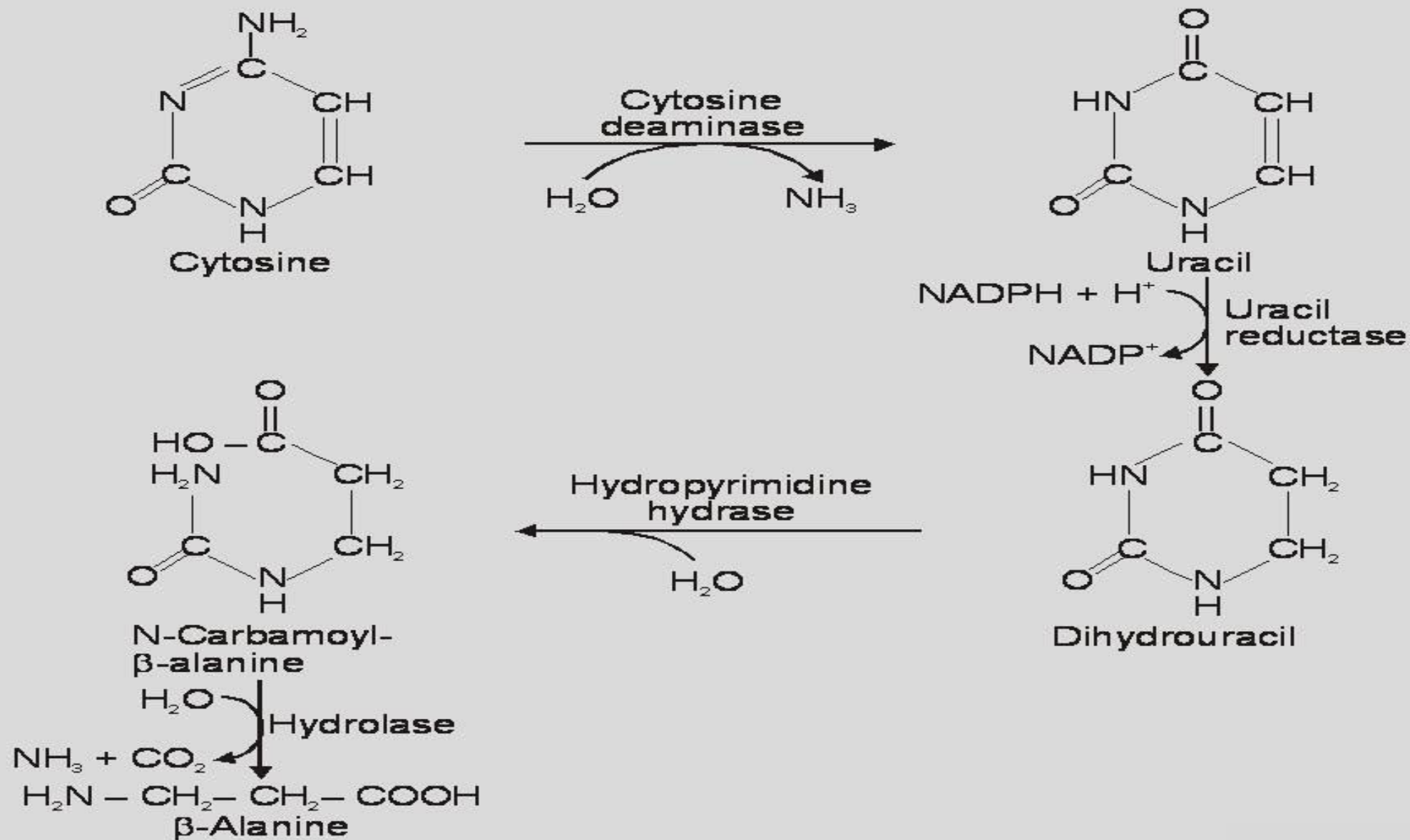
Regulation of De Novo Synthesis of Pyrimidine nucleotides

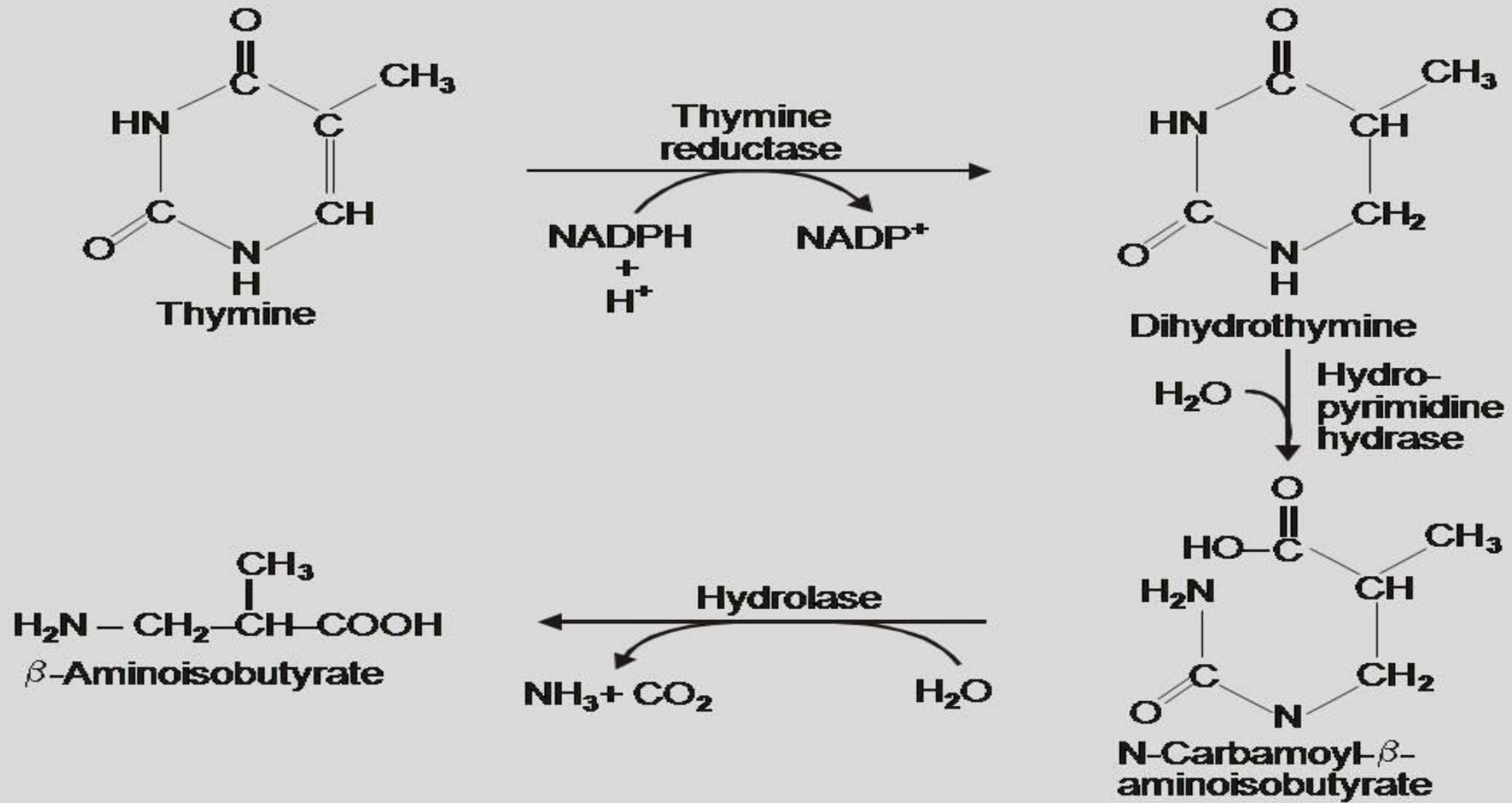
- The first two enzymes carbamoyl phosphate synthase-II and aspartate transcarbamoylase are allosteric enzymes and are regulated allosterically
- Carbamoyl phosphate synthase-II, is feed- back inhibited by UTP and activated by PRPP.
- Aspartate transcarbamoylase,, is feedback inhibited by CTP and activated by ATP.

Catabolism Of Pyrimidine Nucleotides

The end products of pyrimidine catabolism are highly water soluble:

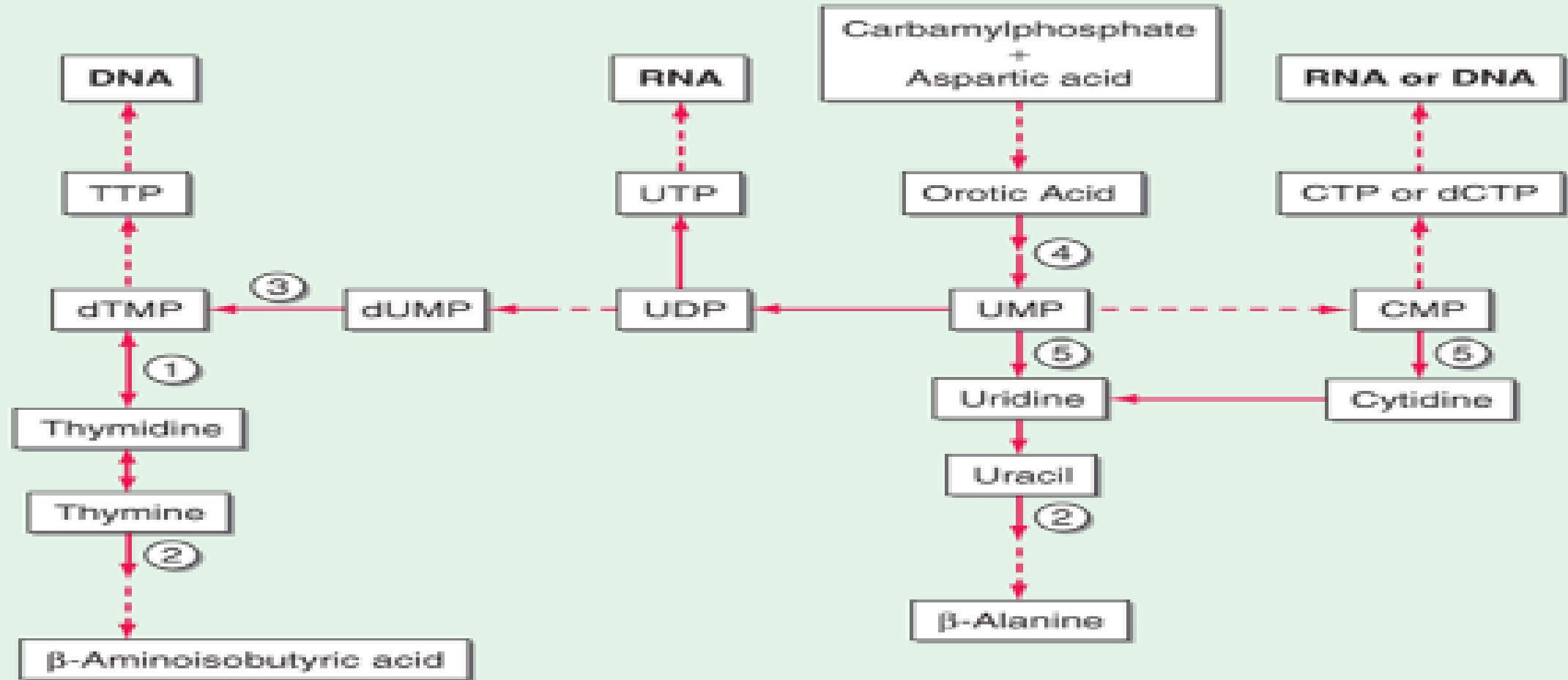
- CO₂
- NH₃
- β-alanine
- β-aminoisobutyrate
- Humans probably transaminate β-aminoisobutyrate to methylmalonate semialdehyde which is then converted to succinyl-CoA via methylmalonyl-CoA.
- β-alanine can serve as precursor of acetyl-CoA.





From Essentials of Medical Biochemistry by R.C. Gupta

Pyrimidine Degradation



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 18th Edition: www.accessmedicine.com
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Disorders Of Pyrimidine Catabolism

Since the end products of pyrimidine catabolism are highly water soluble, **overproduction of pyrimidine catabolites** is rarely associated with clinically significant abnormalities.

Disorder of Pyrimidine Synthesis

- **Orotic Aciduria**
- **Reye's syndrome**

Enzymes Of The **Nucleotide Biosynthesis** That Are Inhibited By Anticancer Drugs

Orotic aciduria



Deficiency of

UMA Synthase

Orotidylate decarboxylase

Orotate phosphoribosyltransferase

- Orotic acid in the urine.
- Megaloblastic Anaemia.
- Rx
- Uridine ????????