# Metabolism of nucleotides

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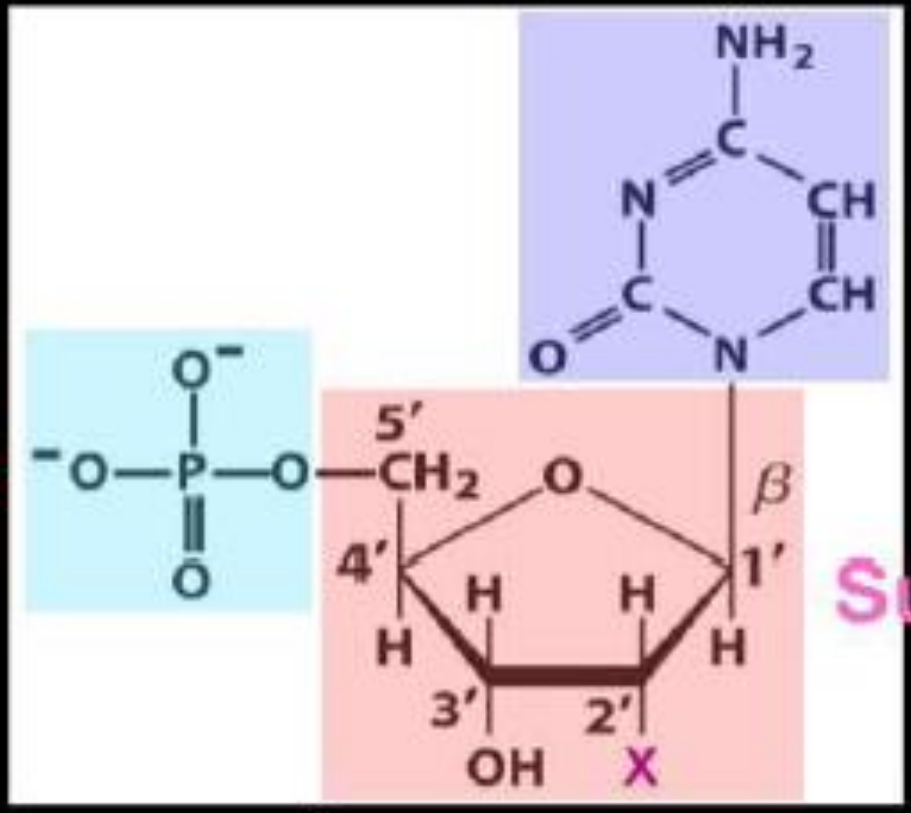
# Overview of questions:

1. Digestion of nucleic acids in the gastrointestinal tract. Degradation of nucleic acids in tissues.
2. Degradation of purine and pyrimidine nucleotides.
3. Biosynthesis of purine nucleotides: synthesis of phosphoribosylamine, origin of atoms in the purine ring.
4. Inosinic acid as a precursor for synthesis of adenylic and guanylic acids. Regulation of biosynthesis of purine nucleotides.
5. Biosynthesis of pyrimidine nucleotides. Regulation of biosynthesis of pyrimidine nucleotides.
6. Synthesis of deoxyribonucleotides. Synthesis of thymidylic acid.
7. Re-utilization of nucleosides and nitrogenous bases for synthesis of nucleotides.
8. Disorders of metabolism of nucleotides: xanthinuria, orotaciduria, gout.




X=H: **DNA**
X=OH: **RNA**

**Nucleoside**

**Nucleotide**

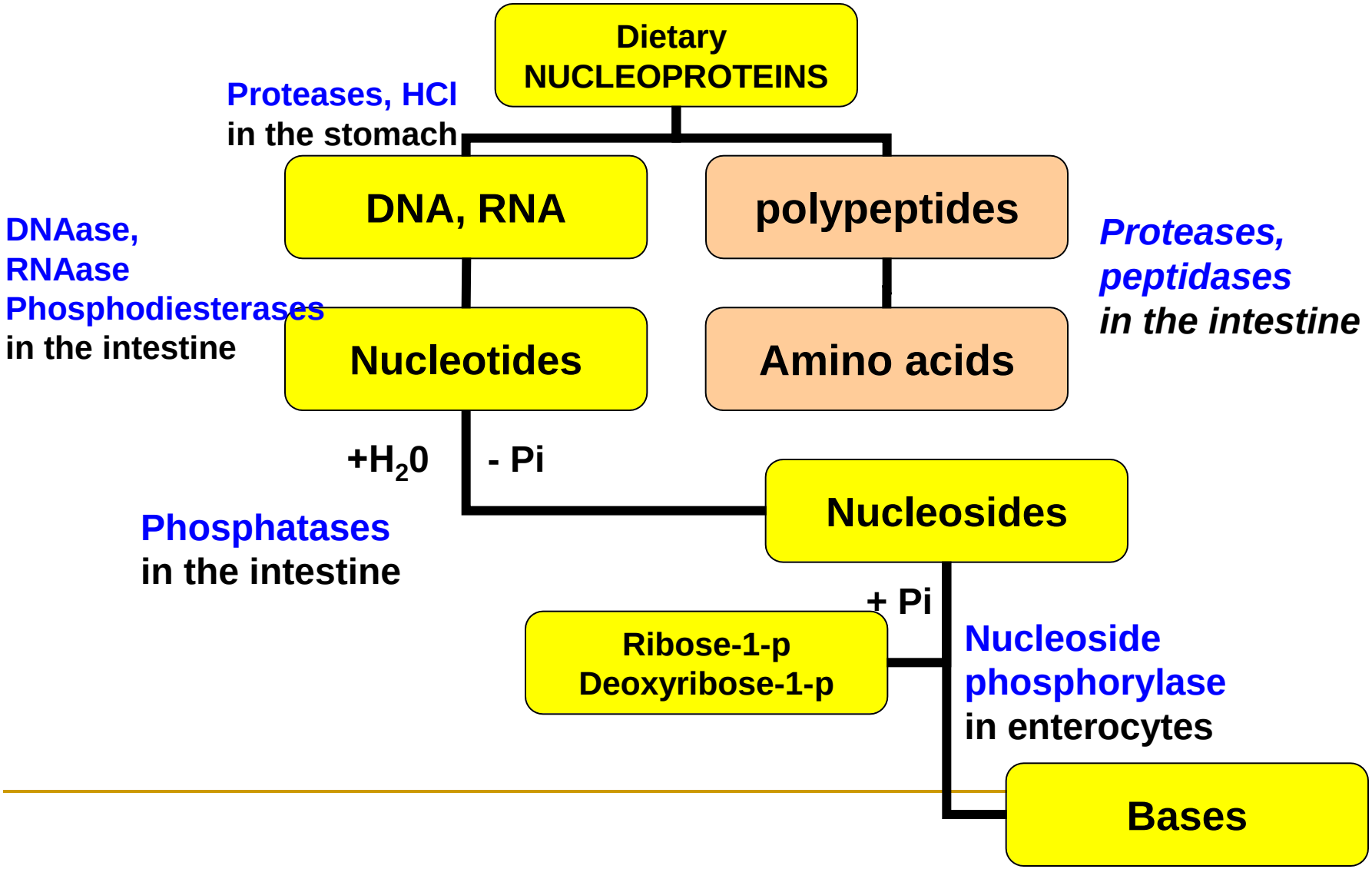
# Names of nucleosides and nucleotides for memorizing (DNA)

| *Nitrogenous base* | *Nucleoside* | *Nucleotide* |
|---|---|---|
| ***Purines:*** | | |
| **Adenine** | **Deoxy-Adenosine** | **dAMP, deoxy-Adenosine monophosphate, d-Adenylic acid** |
| **Guanine** | **Deoxy-Guanosine** | **dGMP, deoxy-Guanosine monophosphate, d-Guanylic acid** |
| ***Pyrimidines*** | | |
| **Cytosine** | **Deoxy-Cytidine** | **dCMP, deoxy-Cytidine monophosphate, cytidylic acid** |
| **Thymine** | **Thymidine** | **TMP, thymidine monophosphate, thymidylic acid** |

# Names of nucleosides and nucleotides for memorizing (RNA)

| *Nitrogenous base* | *Nucleoside* | *Nucleotide* |
|---|---|---|
| ***Purines:*** | | |
| **Adenine** | **Adenosine** | **AMP, adenosine monophosphate, adenylic acid** |
| **Guanine** | **Guanosine** | **GMP, guanosine monophosphate, guanylic acid** |
| ***Pyrimidines*** | | |
| **Cytosine** | **Cytidine** | **CMP, cytidine monophosphate, cytidylic acid** |
| **Uracil** | **Uridine** | **UMP, uridine monophosphate, uridylic acid** |

# Digestion of nucleic acids in the gastrointestinal tract

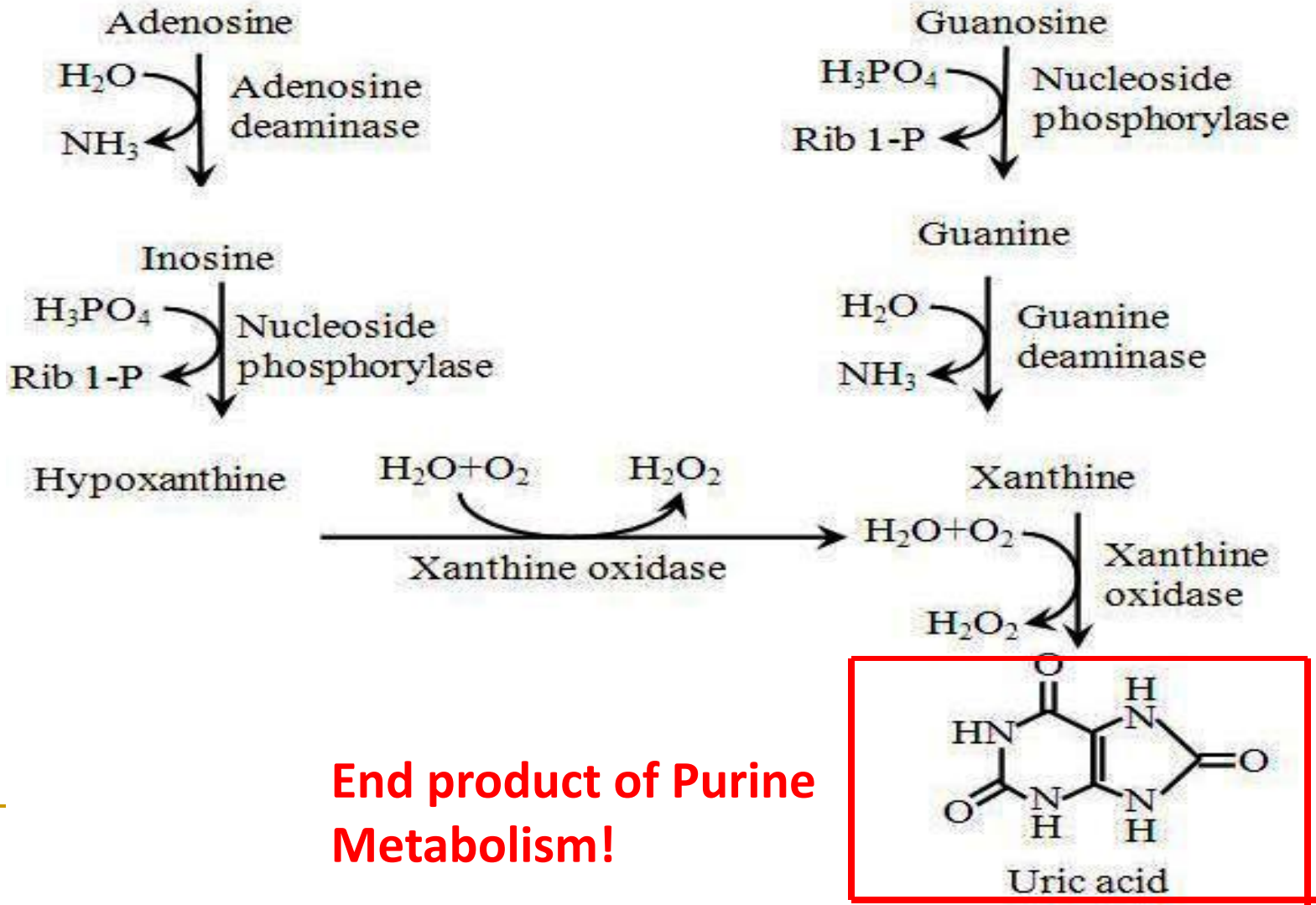


| | |
|---|---|
| **In the stomach** | **Degradation of NUCLEOPROTEINS by gastric enzymes and HCl to POLYPEPTIDES and NUCLEIC ACIDS.** |
| **In the small intestine** | **▪Pancreatic DNAses and RNAses break down nucleic acids to polynucleotides.**<br>**▪Phosphodiesterase of the intestinal mucosa completes hydrolysis of nucleic acids to mononucleotides.**<br>**▪Mononucleotides are hydrolytically cleaved by non-specific acidic and alkaline phosphatases to form nucleosides and phosphate.**<br>**▪Polypeptides are cleaved to free amino acids** |
| **Enterocytes** | **Nucleosides are absorbed into enterocytes and cleaved by nucleoside phosphorylases to bases and ribose-1-P or deoxyribose-1-p** |

# Digestion of nucleic acids in tissues by lysosomal enzymes

- **Is similar to as in the GIT.**
- **Nucleic acids are degraded by following enzymes:**
  - **ENDONUCLEASES catalyze hydrolytic cleavage of inner phosphodiester bonds of DNA or RNA to produce oligonucleotides.**
  - **EXONUCLEASES catalyze hydrolytic removal of terminal mononucleotides from DNA or RNA molecule.**
  - **DEOXYRIBONUCLEASES I and II catalyze cleavage of phosphodiester bonds within one and both of DNA strands.**
  - **RIBONUCLEASES (RNASES) catalyze cleavage of phosphodiester bonds within RNA.**
  - **RESTRICTASES catalyze cleavage of DNA at strictly defined regions of the DNA molecule exhibiting a palindromic structure (the same read forth and back, e.g. "madam").**
  - **POLYNUCLEOTIDE PHOSPHORYLASE catalyzes phosphorolytic breakdown of RNA by adding inorganic phosphate to a mononucleotide cleaved from RNA to produce ribonucleoside diphosphate (RDP):**
  - **DNA-GLYCOSIDASES (N-GLYCOSIDASES). They catalyze hydrolysis of modified nitrogenous bases in a DNA molecule. DNA-glycosidases play an important role in the repair of DNA.**
- **NUCLEOSIDES undergo hydrolysis to form PENTOSE SUGAR and a BASE**

# DEGRADATION OF PURINE NUCLEOTIDES in tissues




**End product of Purine Metabolism!**

# Clinical significance of uric acid

- **Blood:** 140-340 mkmol/l (female)
- 200-415 mkmol/l (male)
- **Urine:** 1.6-6.47 mmol/day

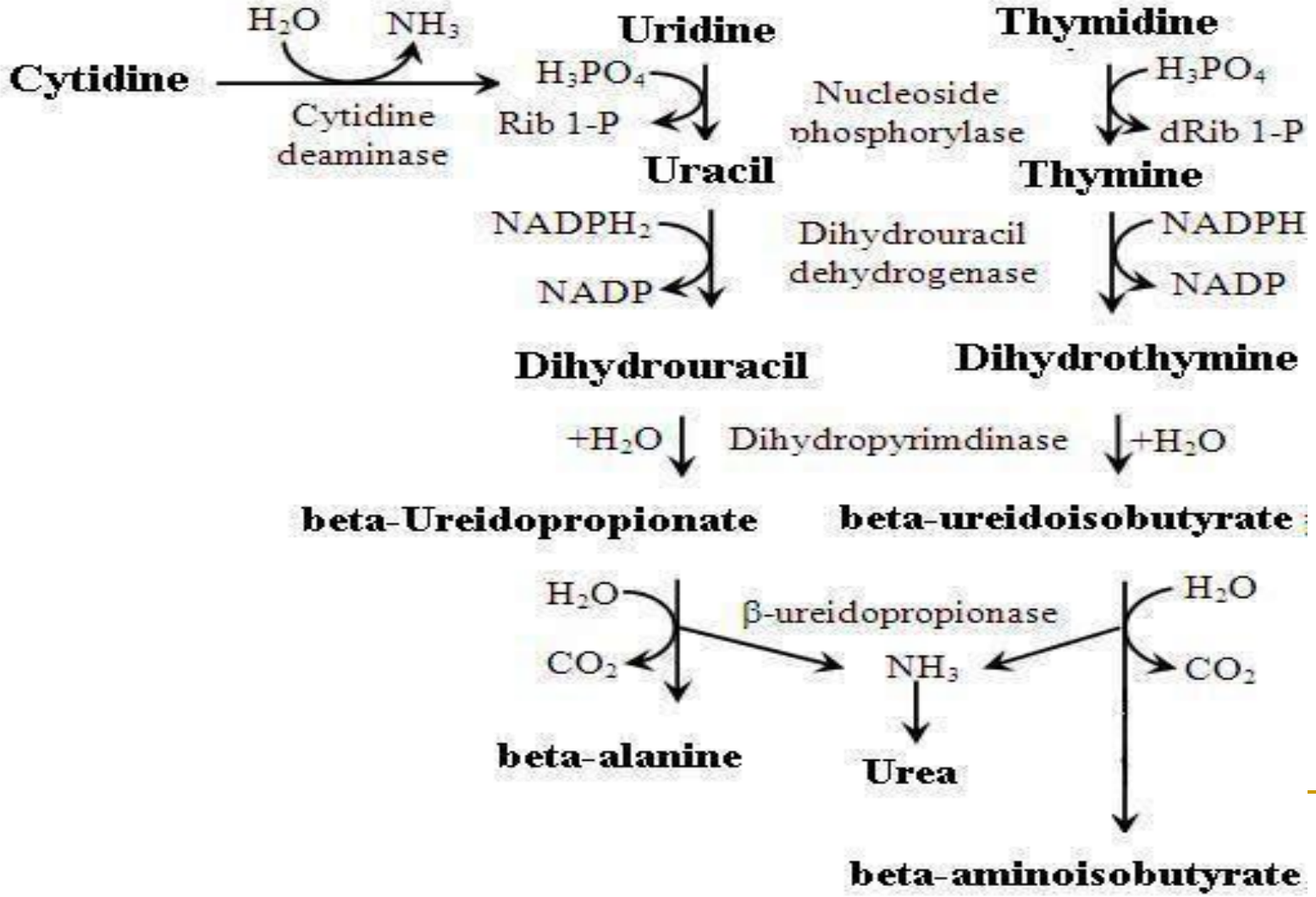
## Hyperuricemia:

- High purine diet
- gout,
- increased nuclear breakdown (e.g. in chemotherapy of cancer)
- renal diseases

## Hypouricemia:

- Low purine diet
- Fanconi syndrome
- Wilson's disease
- Syndrome of inappropriate antidiuretic hormone (SIADH) secretion

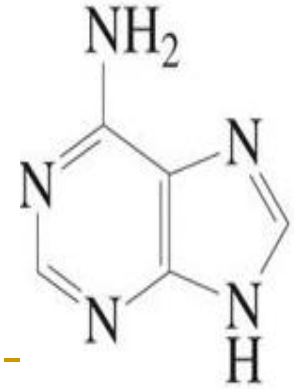
# DEGRADATION OF PYRIMIDINE NUCLEOTIDES



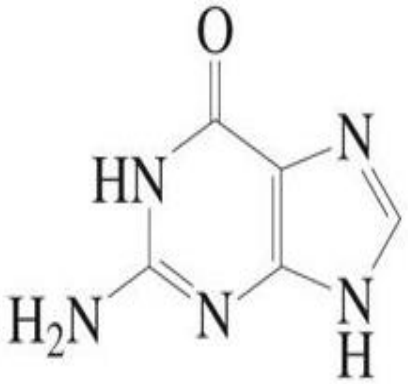
# Synthesis of purine and pyrimidine nucleotides


purine

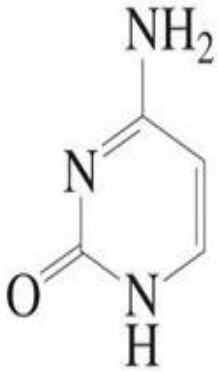

pyrimidine



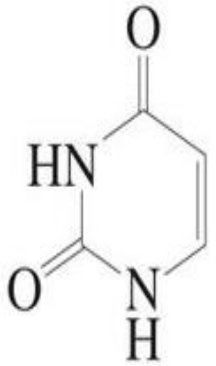

adenine



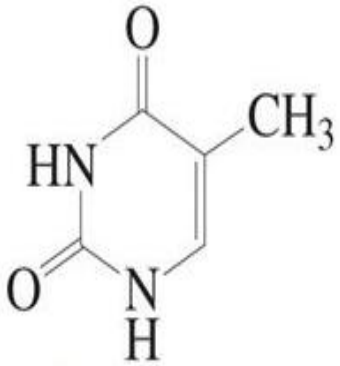

guanine




cytosine




uracil




thymine

# 2 ways of the synthesis of nucleotides in the cells

- **De novo synthesis** from simple compounds:

  ribose-5-phosphate, PRPP, amino acids, $CO_2$, ATP, etc.

  prevails in most of cells

- **Salvage pathways** or re-synthesis from bases and nucleosides, released from natural degradation of nucleic acids.

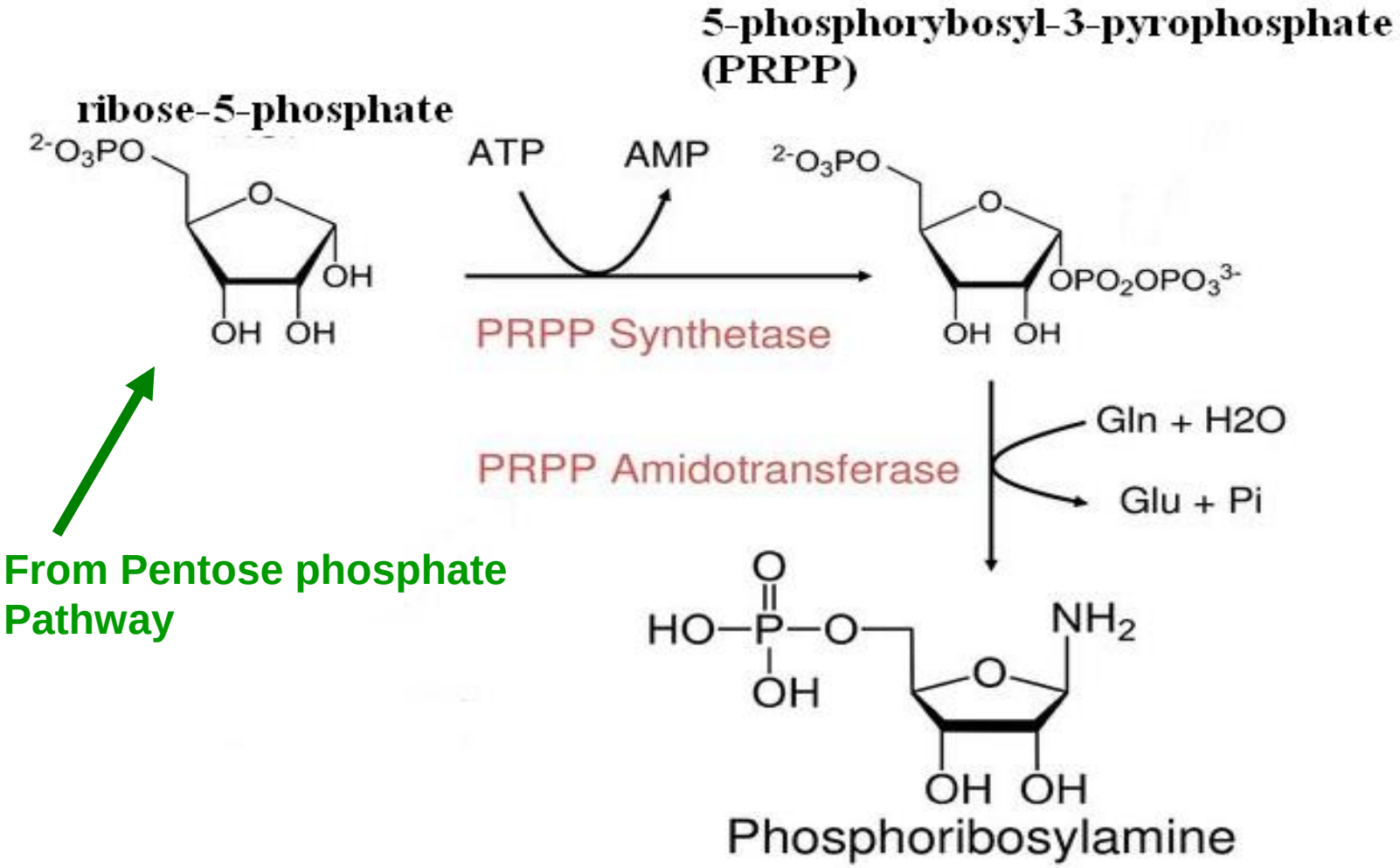
  only 10% of all nucleotides produced

# Synthesis of phosphoribosylamine (de novo)

- **Purine nucleotides are biologically synthesized in the cytoplasm from ribose-5-phosphate, a product of the pentose phosphate pathway.**

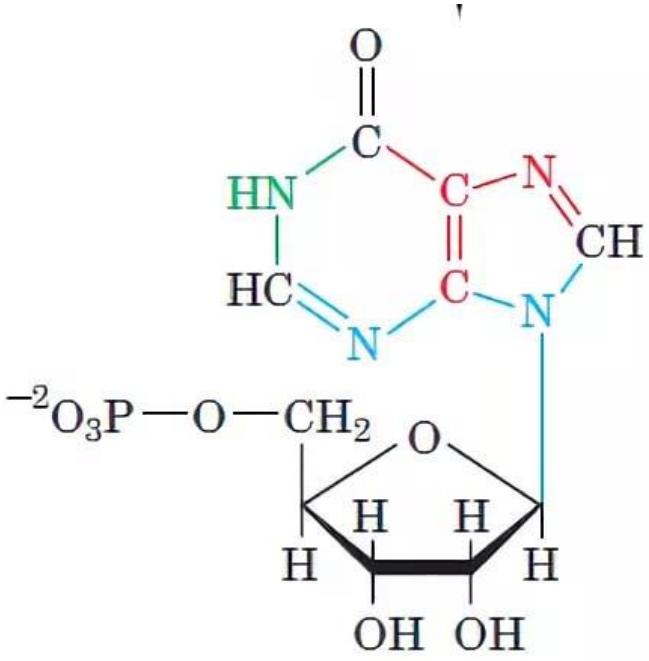
- **Both adenine and guanine are derived from the nucleotide inosine monophosphate (IMP), which is the first compound in the pathway to have a completely formed purine ring system.**

# 2 reactions of the synthesis of phosphoribosylamine



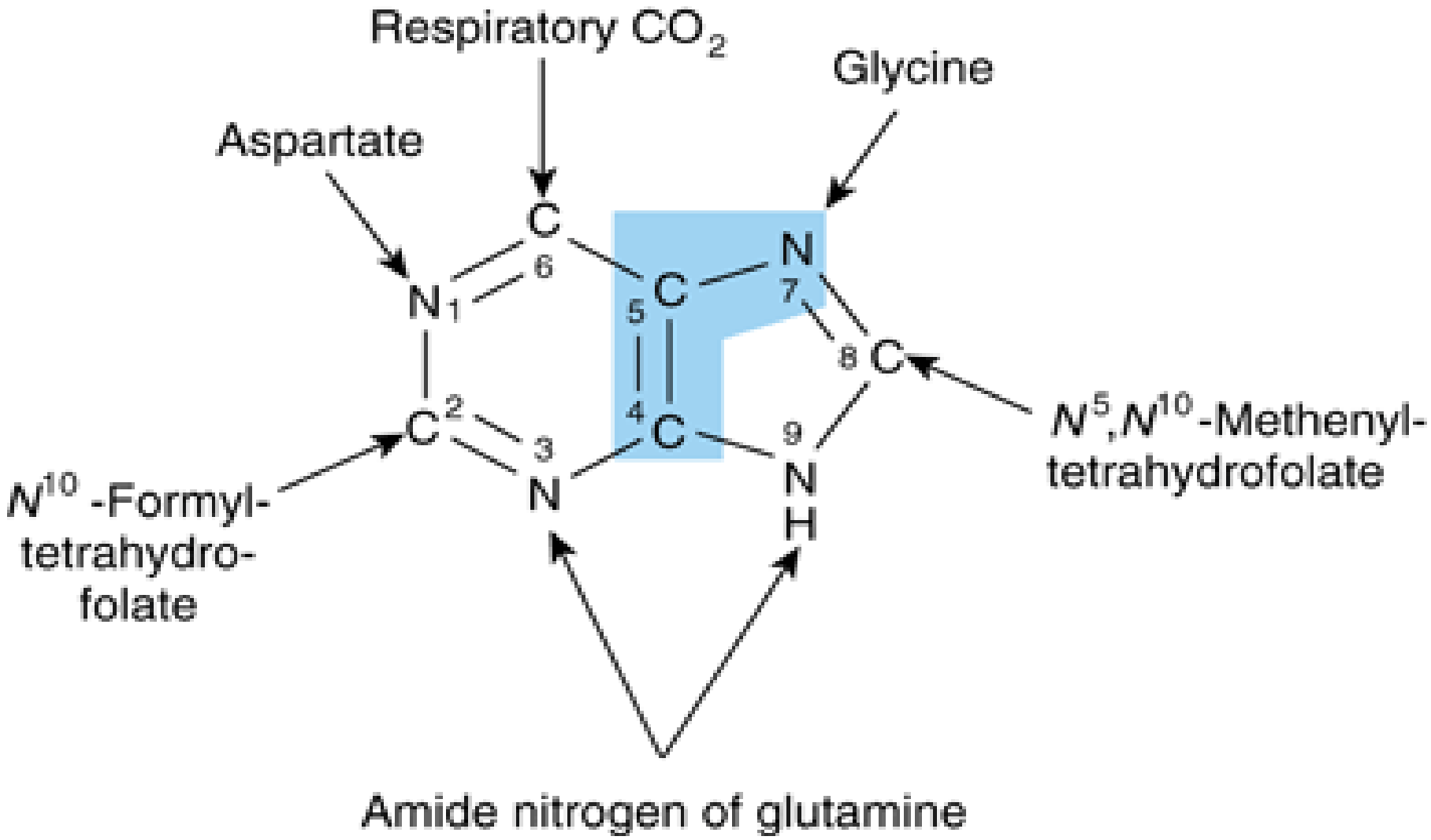

From Pentose phosphate Pathway

- **In the next 9 reactions amino group from 5'-hosphoribosylamine is used for building up the purine ring of inosine monophosphate (IMP, inosinic acid).**
- **These reactions utilize glycine, $CO_2$, aspartate, $N^5$,$N^{10}$-methenyl-tetrahydrofolate, $N^{10}$-formyl-tetrahydrofolate, and glutamine.**

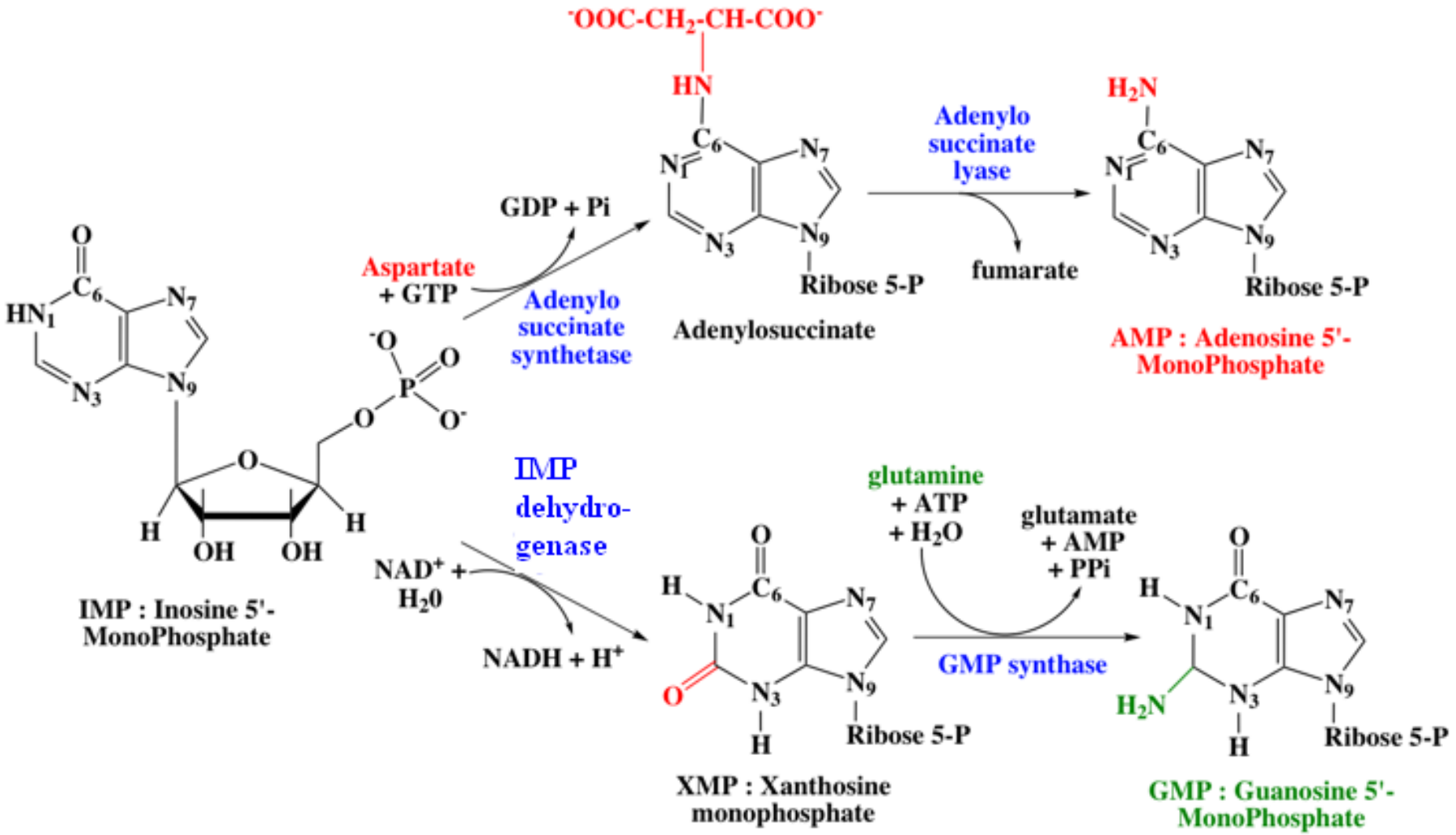



Inosine monophosphate (IMP)

# Origin of atoms in a purine ring



# Synthesis of AMP and GMP from IMP

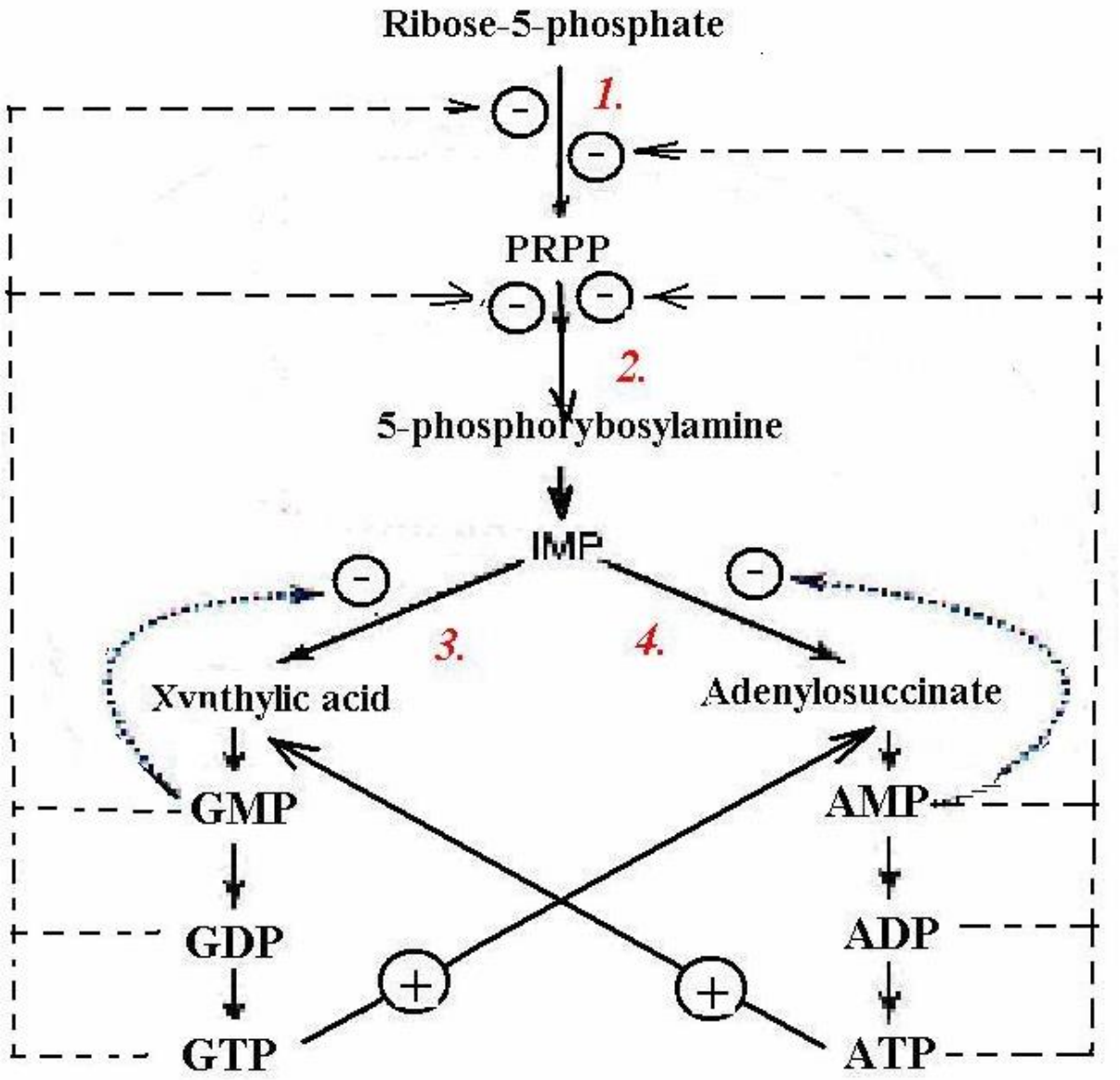


# Synthesis of ATP and GTP by phosphoryl kinases

- AMP + ATP ↔ ADP + ADP
- ADP + ATP ↔ ATP + ADP

- GMP + ATP ↔ GDP + ADP
- GDP + ATP ↔ GTP + ADP

# Regulation of purine synthesis

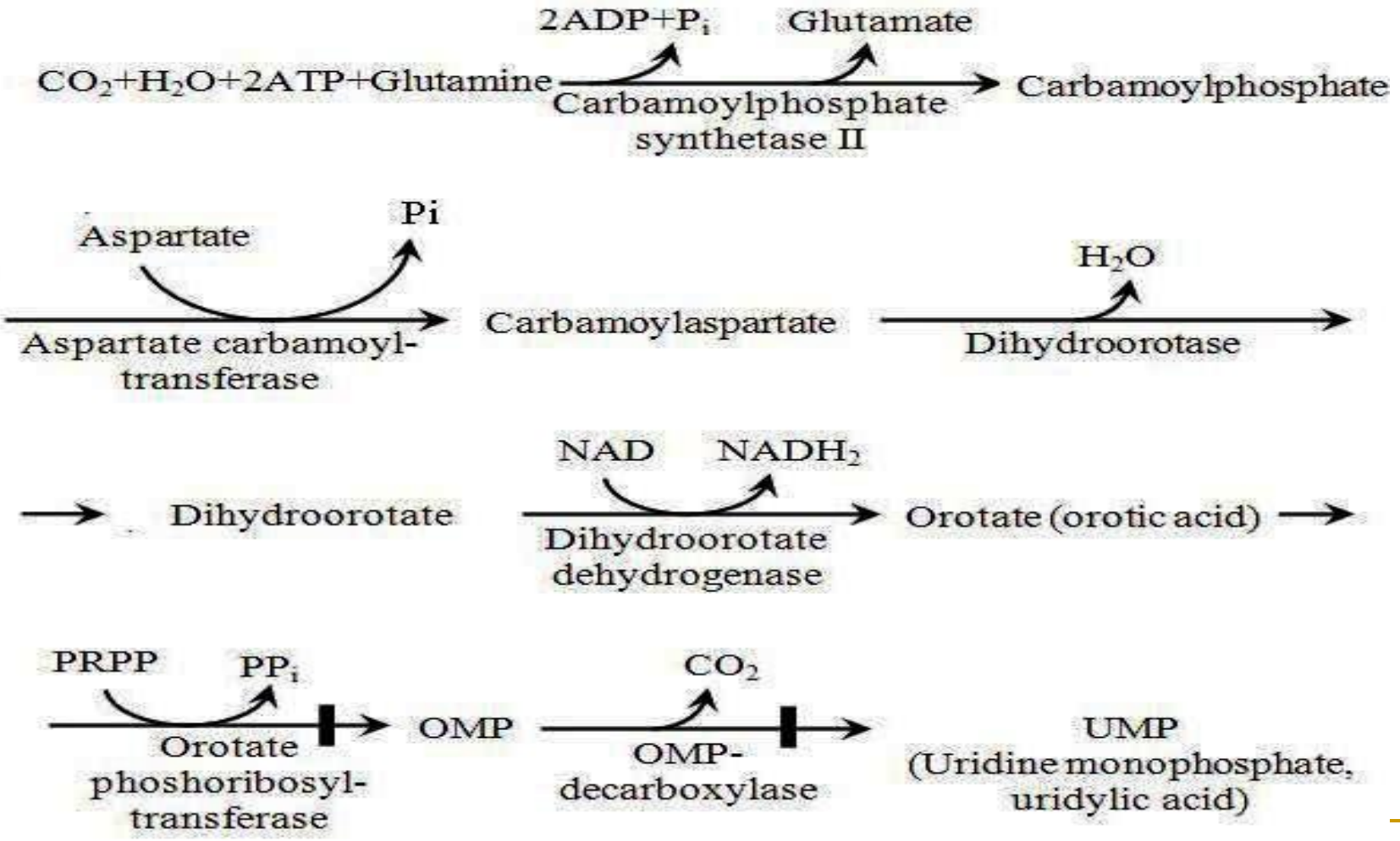



- ***PRPP-synthetase (1)*** ***and*** ***phosphoribosyl amidotransferase (2)*** ***are inhibited by the excessive amounts of ATP, ADP, AMP, GTP, GDP, and GMP.***
- ***Both AMP and GMP inhibit their own formation by the feedback inhibition of adenylosuccinate synthetase (4) and IMP dehydrogenase (3), respectively.***
- ***GTP activates the synthesis of AMP***
- ***ATP activates the synthesis of GMP***

# De novo synthesis of pyrimidine nucleotides

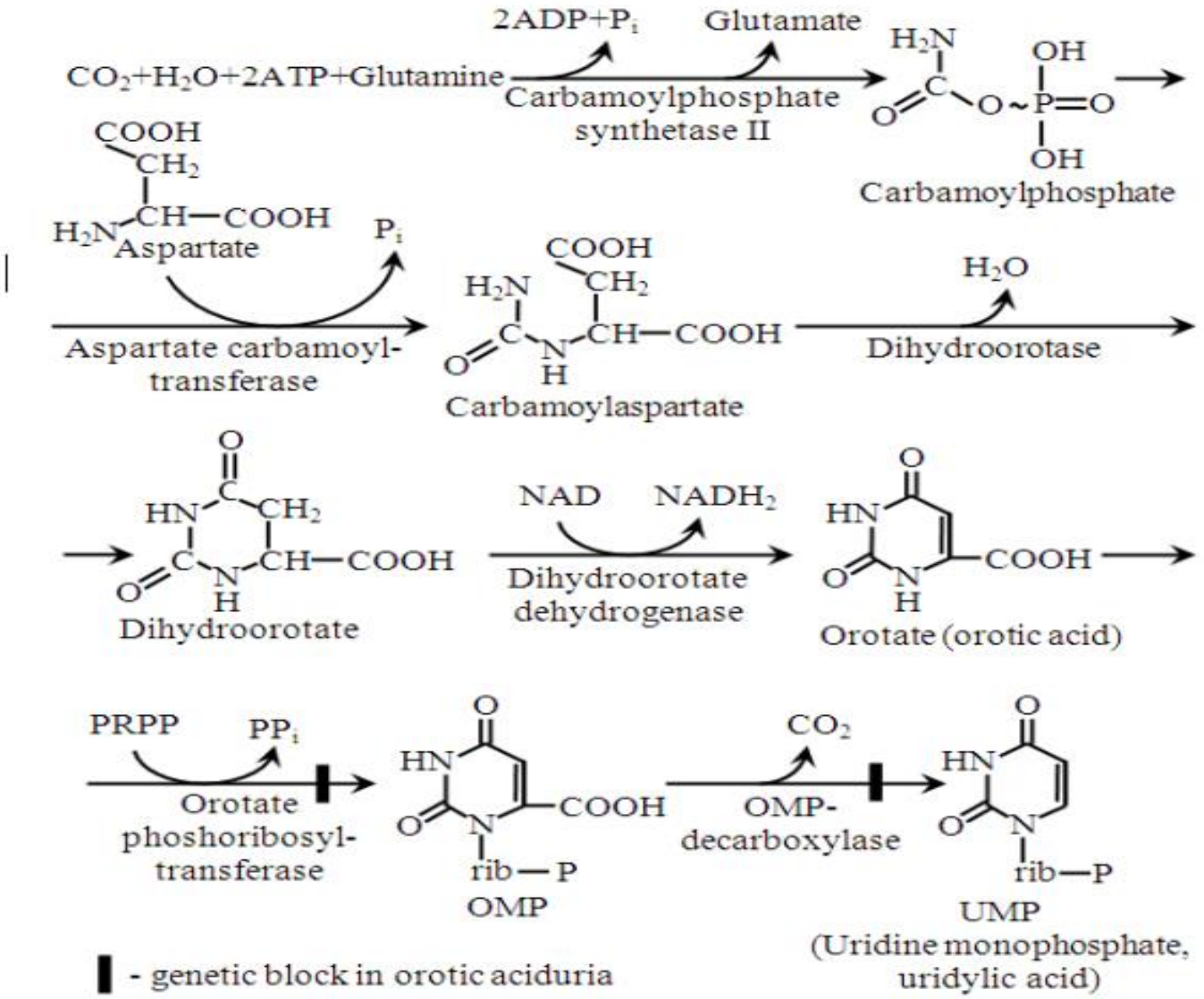
- takes place in the cytoplasm.
- The first reaction is catalyzed by carbamoylphosphate synthetase II (CPS II)
- CPS II is located in the cytoplasm, takes part in the synthesis of pyrimidine nucleotides, and uses nitrogen of glutamine to form carbamoylphosphate

# Synthesis of pyrimidine nucleotides (UMP)




▌- genetic block in orotic aciduria

# Synthesis of pyrimidine nucleotides (UMP) with structures



# Synthesis of UDP, UMP, and cytosine nucleotides

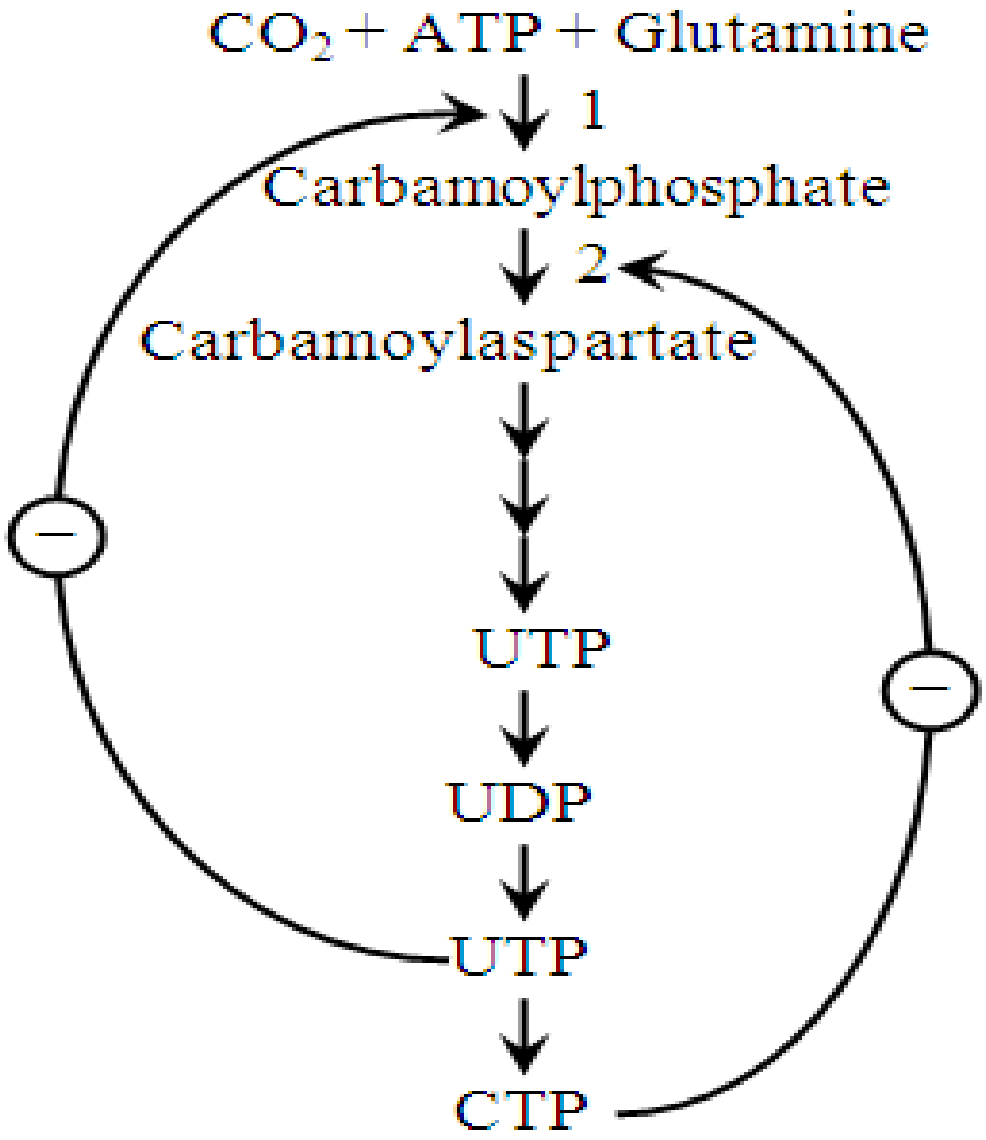
1. **Phosphoryltransferases (kinases) catalyze transfer of phosphoryl groups of the ATP molecules to UMP, and latter, to UDP:**

- **UMP + ATP ↔ UDP + ADP;**
- **UDP + ATP ↔ UTP + ADP**

2. **Cytidine triphosphate (CTP) is synthesized from UTP is the reaction, catalyzed by CTP-synthase:**

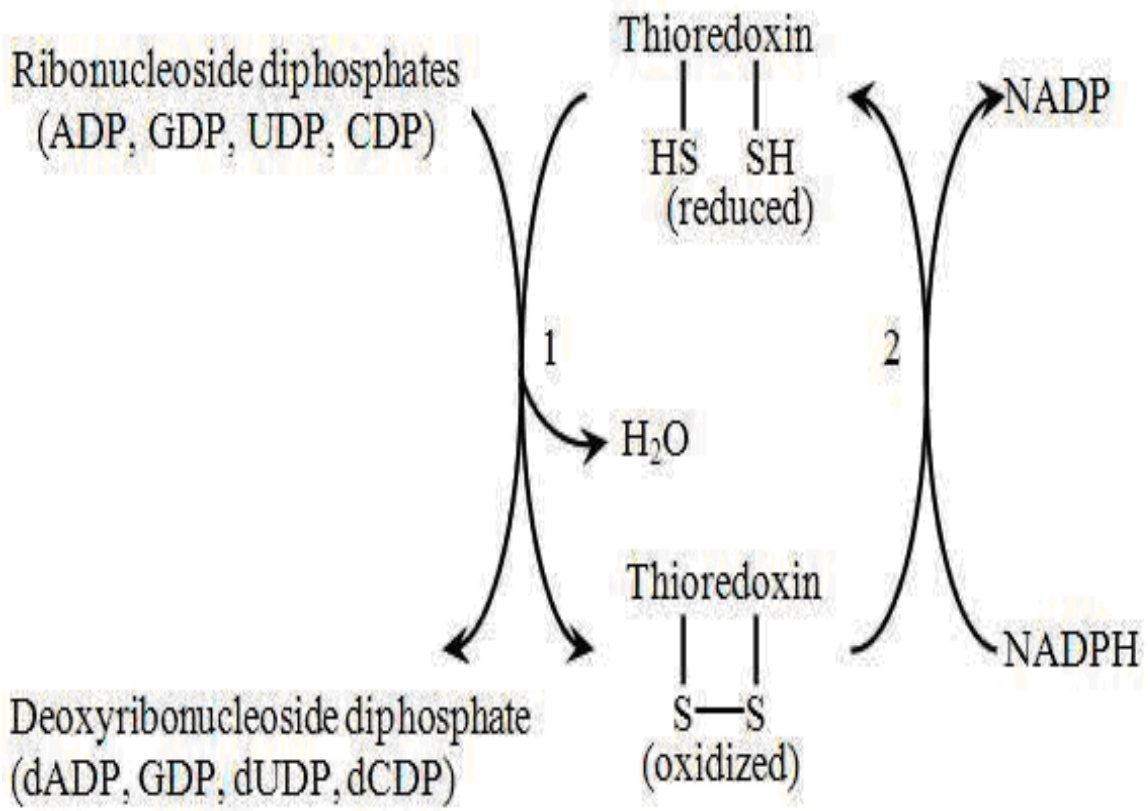
- **UTP + glutamine + ATP → CTP + glutamate + ADP + Pi**

# Regulation of pyrimidine synthesis




- ***Carbamoylphosphate synthetase II (1) and aspartate carbamoyl transferase (2) are inhibited by UTP and CTP, respectively***

# Synthesis of deoxyribonucleotides



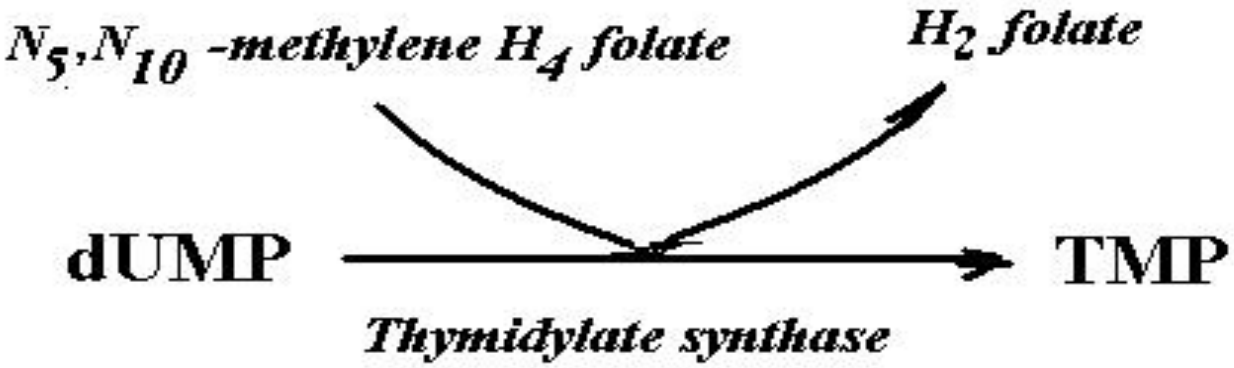

1. **The enzyme ribonucleoside diphosphate reductase (1) removes oxygen atom from 2'-OH group of ribose to form $H_2O$ with the use of two H atoms from thioredoxin.**

   **As a result, deoxyribose is formed within nucleoside diphosphate.**

2. **Reduced thioredoxin is restored in the reaction catalyzed by thioredoxin reductase (2) in the presence of NADPH.**

# Synthesis of thymidylic acid

1. **Hydrolysis of deoxy-UDP to deoxy-UMP**
   - **$dUDP + H_2O \rightarrow dUMP + Pi$**
2. **Convertion of dUMP to TMP by thymidylate synthase. N5, N10-methylene-tetrahydrofolate is the donor of $CH_3$-group.**



# RE-UTILIZATION OF NUCLEOSIDES AND NITROGENOUS BASES FOR SYNTHESIS OF NUCLEOTIDES (SALVAGE PATHWAYS)

- **A salvage pathway is a metabolic pathway in which nucleotides (purine and pyrimidine) are synthesized from intermediates in the degradative pathway for nucleotides.**
- **Salvage pathways are used to recover nucleotides from bases and nucleosides that are formed during degradation of nucleic acids.**
- **This is important in some organs because some tissues cannot synthesize nucleotides from ribose-5-phosphate (purines), and $CO_2$, $H_2O$, glutamine, etc (pyrimidines).**
- **The salvaged bases and nucleosides can then be converted back into nucleotides.**

# PURINE SALVAGE PATHWAYS

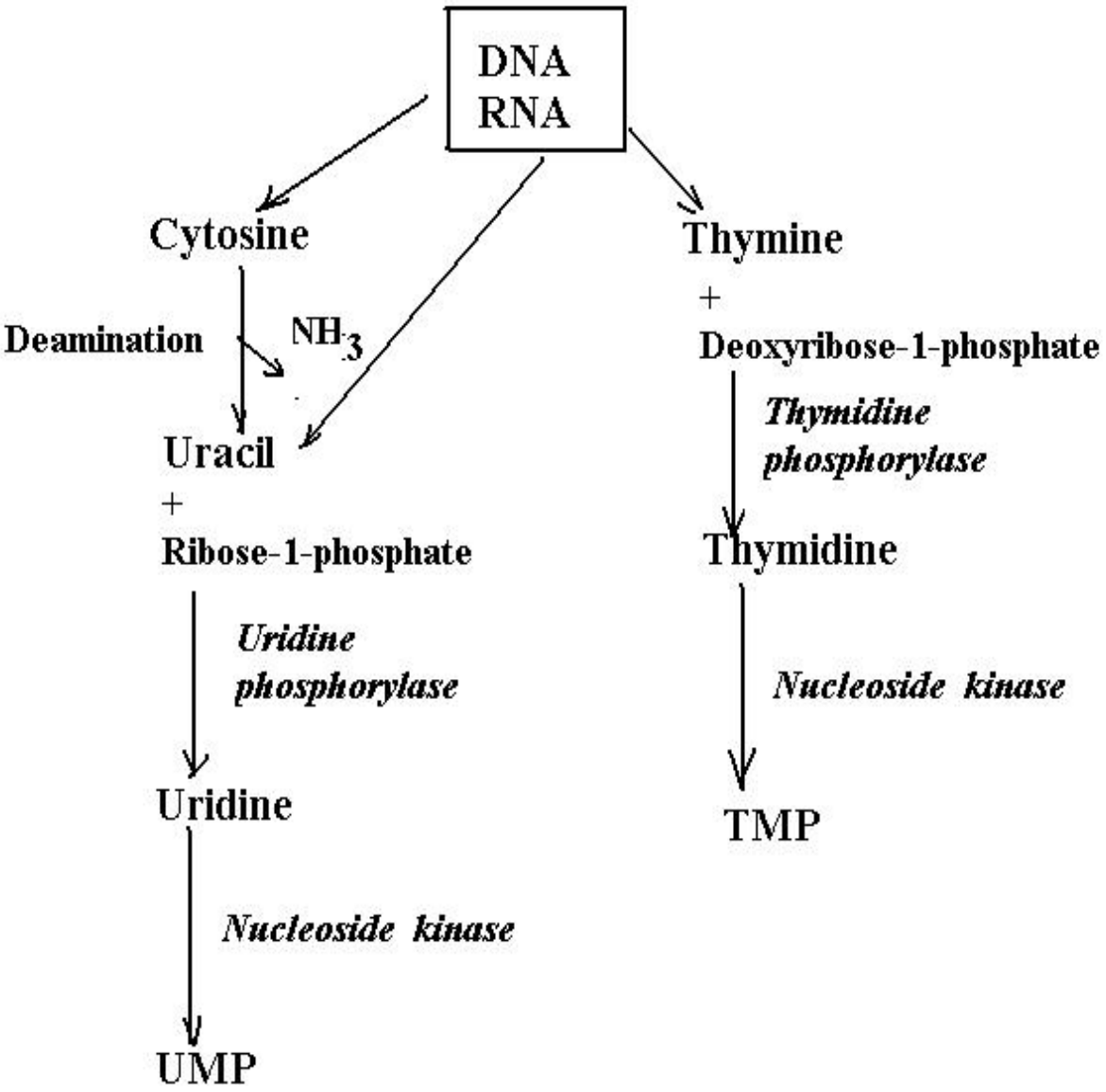
**Purine bases from turnover of cellular nucleic acids (or from food) can also be salvaged and reused in new nucleotides, using phosphoribosyl pyrophosphate (PRPP) and 2 enzymes:**

1. **ADENINE PHOSPHORIBOSYLTRANSFERASE (APRT)**
   - **Adenine + PRPP → AMP + PPi (pyrophosphate)**

2. **HYPOXANTINE-GUANINE PHOSPHORIBOSYLTRANSFERASE (HGPRT)**
   - **Guanine + PRPP → GMP + PPi**
   - **Hypoxantine + PRPP → inosine monophosphate (IMP) + PPi**

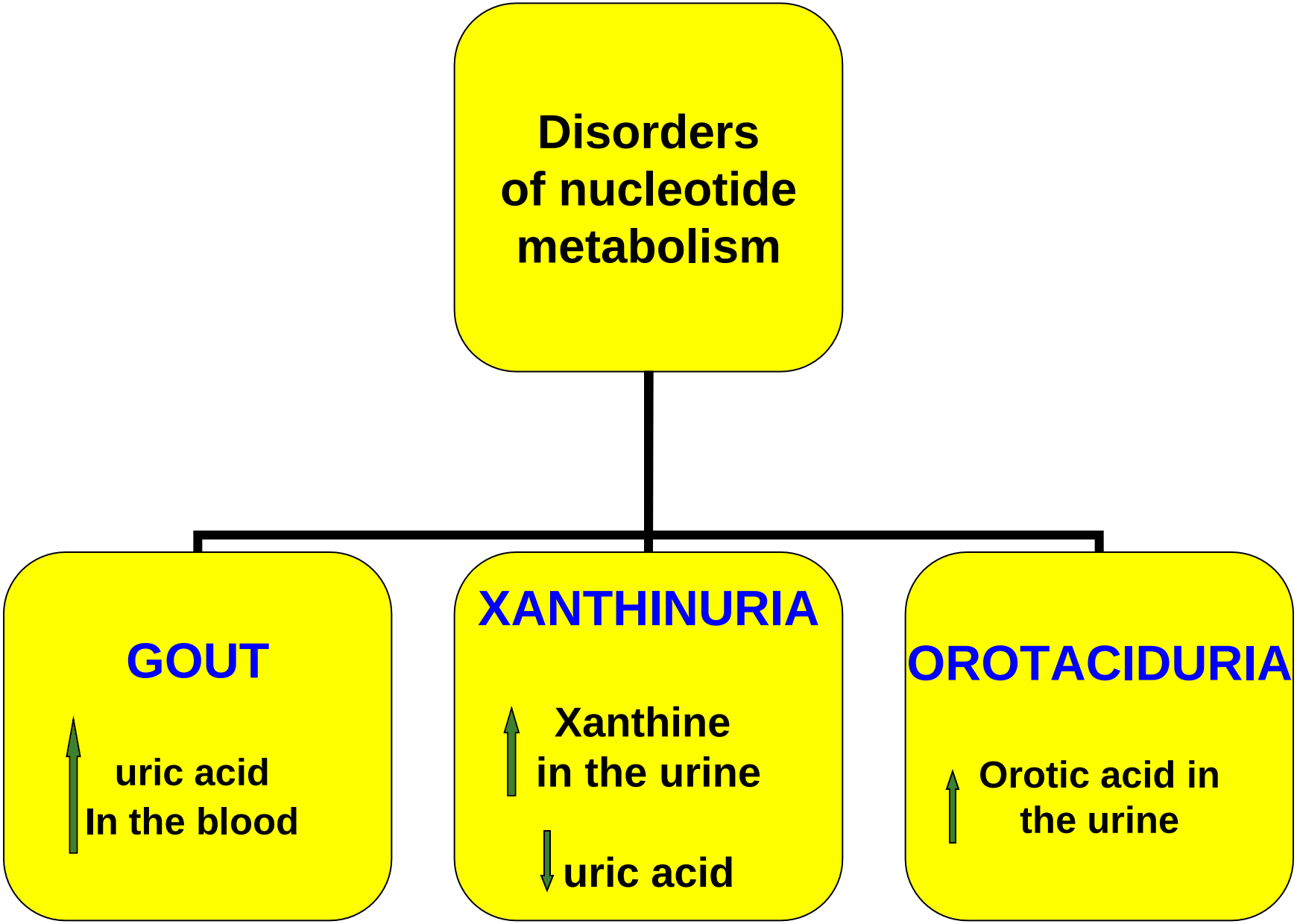
**After that IMP may be converted to the either GMP, or AMP, as described above.**

# PYRIMIDINE SALVAGE PATHWAYS



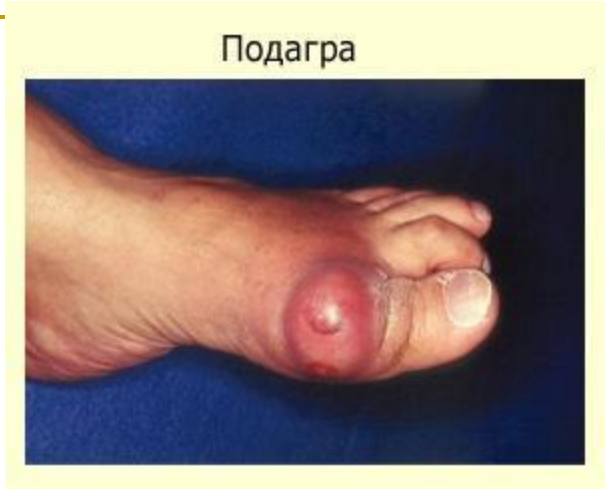

- **Pyrimidine bases from turnover of cellular nucleic acids (or from food) are reused in new nucleotides, using ribose-1-phosphate (or deoxyribose-1-phosphate) and pyrimidine-nucleoside phosphorylases.**

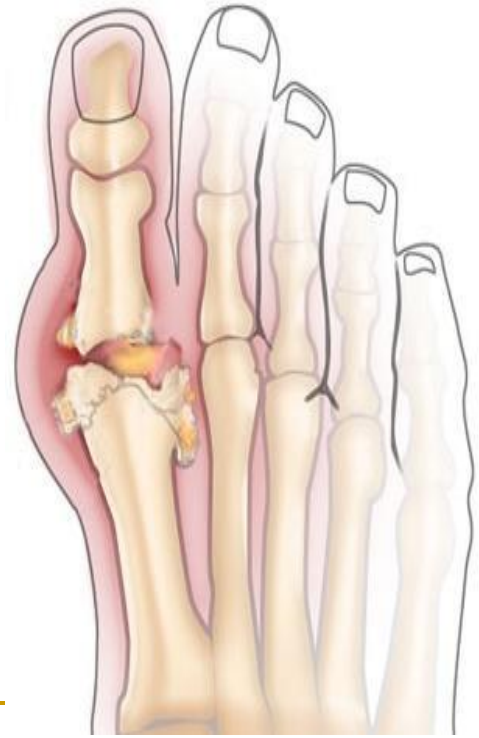
- **After that nucleoside kinases phosphorylate these nucleosides into UMP and TMP, respectively.**


Disorders of nucleotide metabolism
GOUT
uric acid In the blood
XANTHINURIA
Xanthine in the urine
uric acid
OROTACIDURIA
Orotic acid in the urine

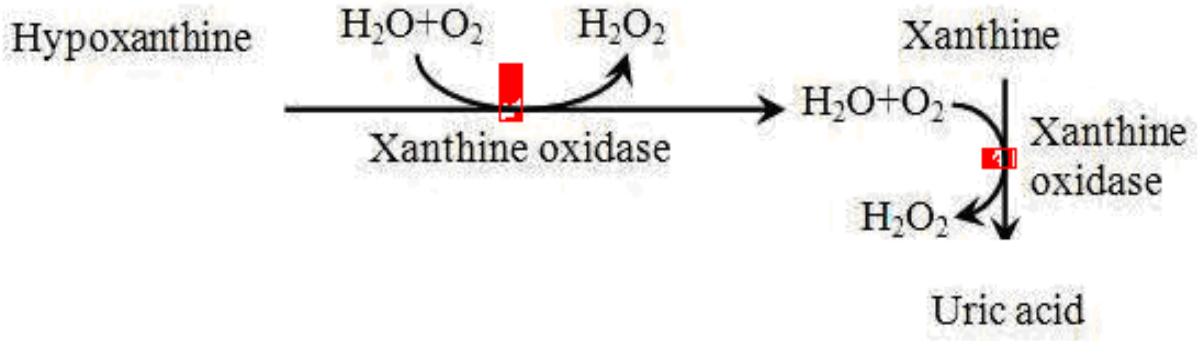
# Gout

- Is a form of inflammatory arthritis characterized by recurrent attacks of a red, tender, hot, and swollen joint.
- HYPERURICEMIA because of elevated production of URIC ACID.
- Uric acid and its salts (urates) may precipitate to form needle-shaped sodium urate crystals which are deposited in joints (tophi).
- Tophi cause deformity of joints and impair their function.
- Increased excretion of uric acid may cause uric acid crystals to be deposited in the collecting tubules of kidney and lower urinary tract, leading to stone formation (urolithiasis).



# Xantinuria




- is a rare genetic disorder caused by inherited deficiency of xanthine oxidase.
- decreased production of uric acid (hypouricemia)
- increased excretion of hypoxanthine and xanthine.
  - Type I xanthinuria can be caused by a deficiency of the enzyme converting xanthine to uric acid.
  - Type II xanthinuria is caused by lack of one or two other enzymes in addition to xanthine oxidase.

- Sufferers have unusually high concentrations of xanthine in their blood and urine, which can lead to health problems such as renal failure and XANTHINE LITHIASIS , one of the rarest types of kidney stones.

# Orotaciduria or Orotic Aciduaria

- **hereditary disease resulting in inability of the body to synthesize pyrimidines.**
- **is caused by the deficiency of Uridine monophosphate synthase (UMPS), which is a bifunctional protein that includes the enzyme activities of OROTATE PYROPHOSPHORYL-TRANSFERASE and OROTIDYLIC DECARBOXYLASE.**
- **excessive excretion of OROTIC ACID in urine because of the inability to convert orotic acid to UMP.**
- **It causes megaloblastic anemia and may be associated with mental and physical developmental de**