# Nucleotide metabolism

# Roles of nuclotides

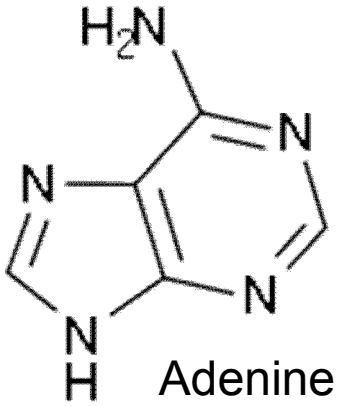
- energy storage (central role of ATP)
- nucleotide units for RNA, DNA synthesis
- components of cofactors (NAD, FAD)
- intracellular second messengers (cAMP, cGMP)
- synthesis of activated intermediates (UDP - glucose, CDP - choline,
- CDP - diacylglycerol, GDP - mannose)
- allosteric effectors

# General characteristics of nucleotides

- Lactam-lactim tautomerism
- In physiological condition the lactam form is oftener
- Low water solubility is characterictic for purine nucleotides (xanthine, guanine, uric-acid) → on acidic pH it is even worse (!!! gout)
- Sythesis and degradation is different in tissues → possible therapic solutions (tumor therapy)
- Structure: nucleobase + five-carbon sugar + phosphate

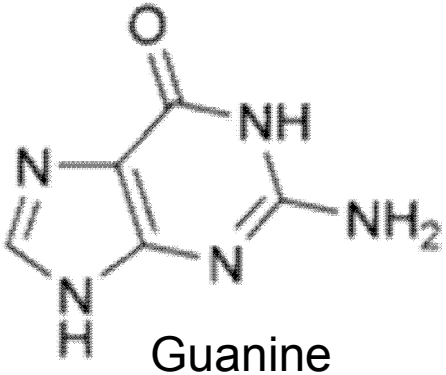
# Genesis of mononucleotides

- de novo sythesis: from amino acids, C1-parts, $CO_2$, ribose, phosphate
- From nucleotides absorbed and degradated in the gastrointestinalis system – they don't discover the nucleotide needs
- From degradation in tissues by nucleosidase



Adenine

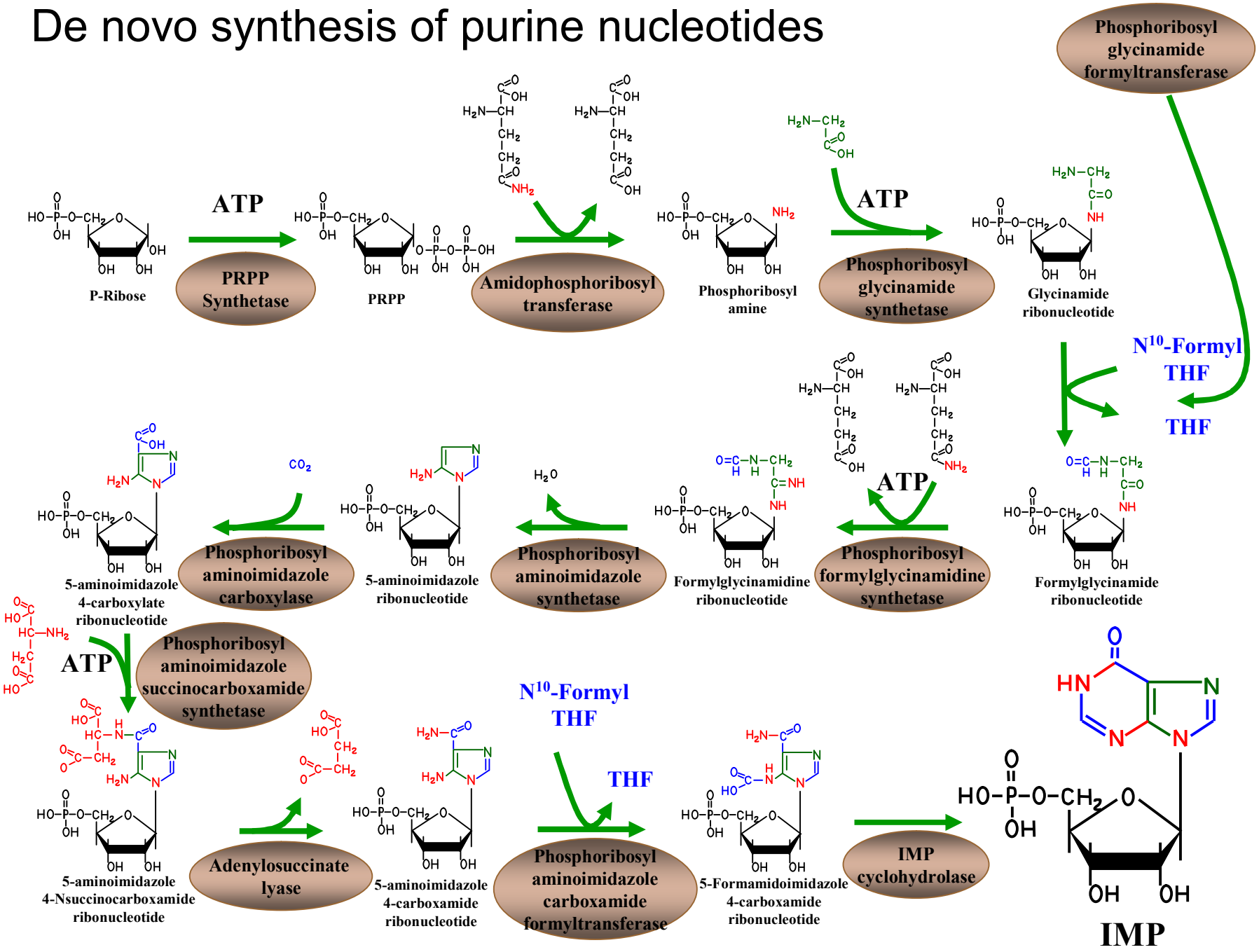
# Purine nucleotides



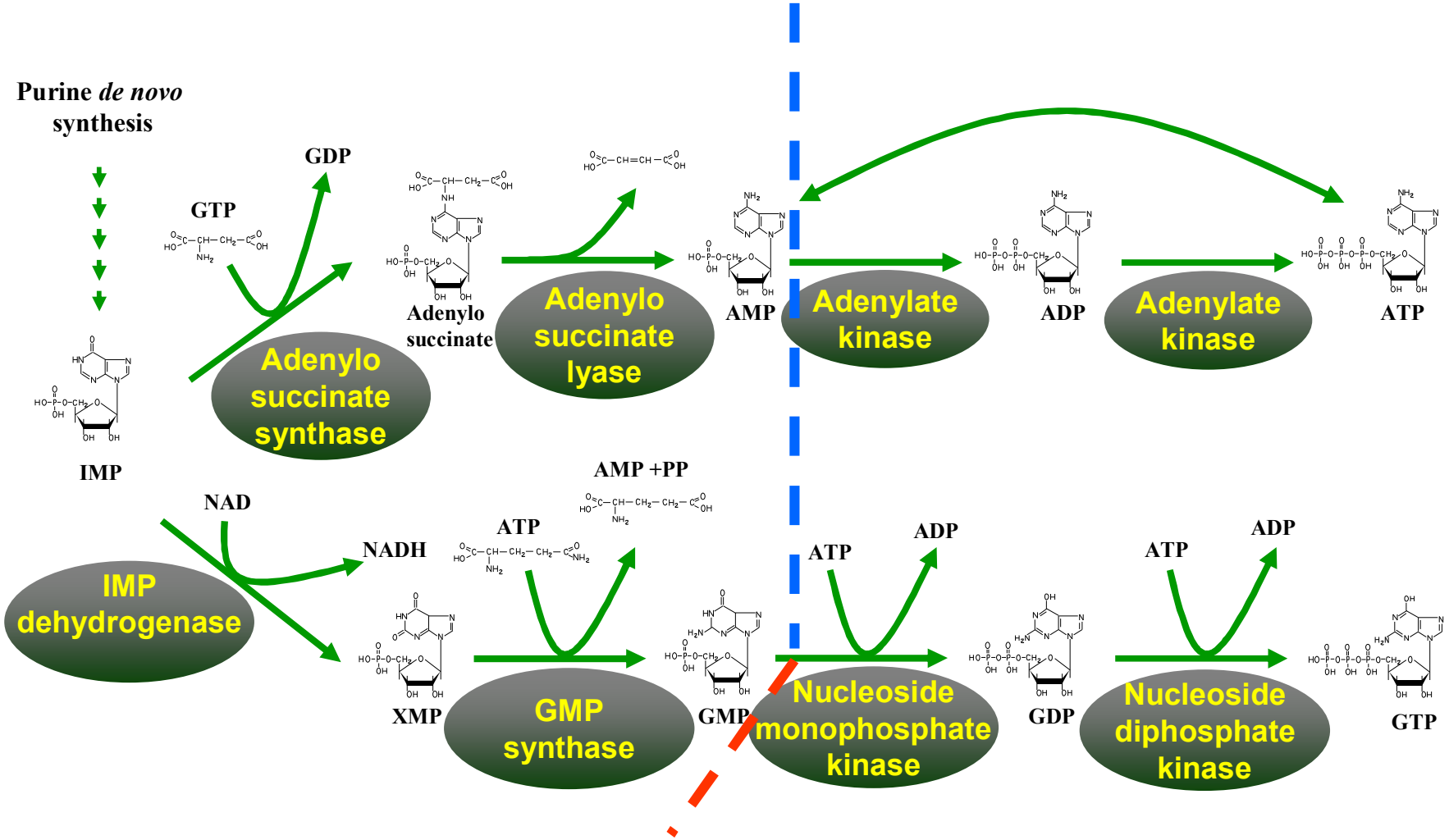
Guanine

- Purine nucleotides: adenine, guanine
- Synthesis: ribose → IMP (PRPP-sythase) → ATP and GTP formation
- Regulation of synthesis (when there are enough end product, synthesis is unnecessary): AMP, GMP, IMP – feedback effect, regulation of PRPP-sythase and PRPP-amidotransferase enzymes, AMP and GMP synthesis regulation

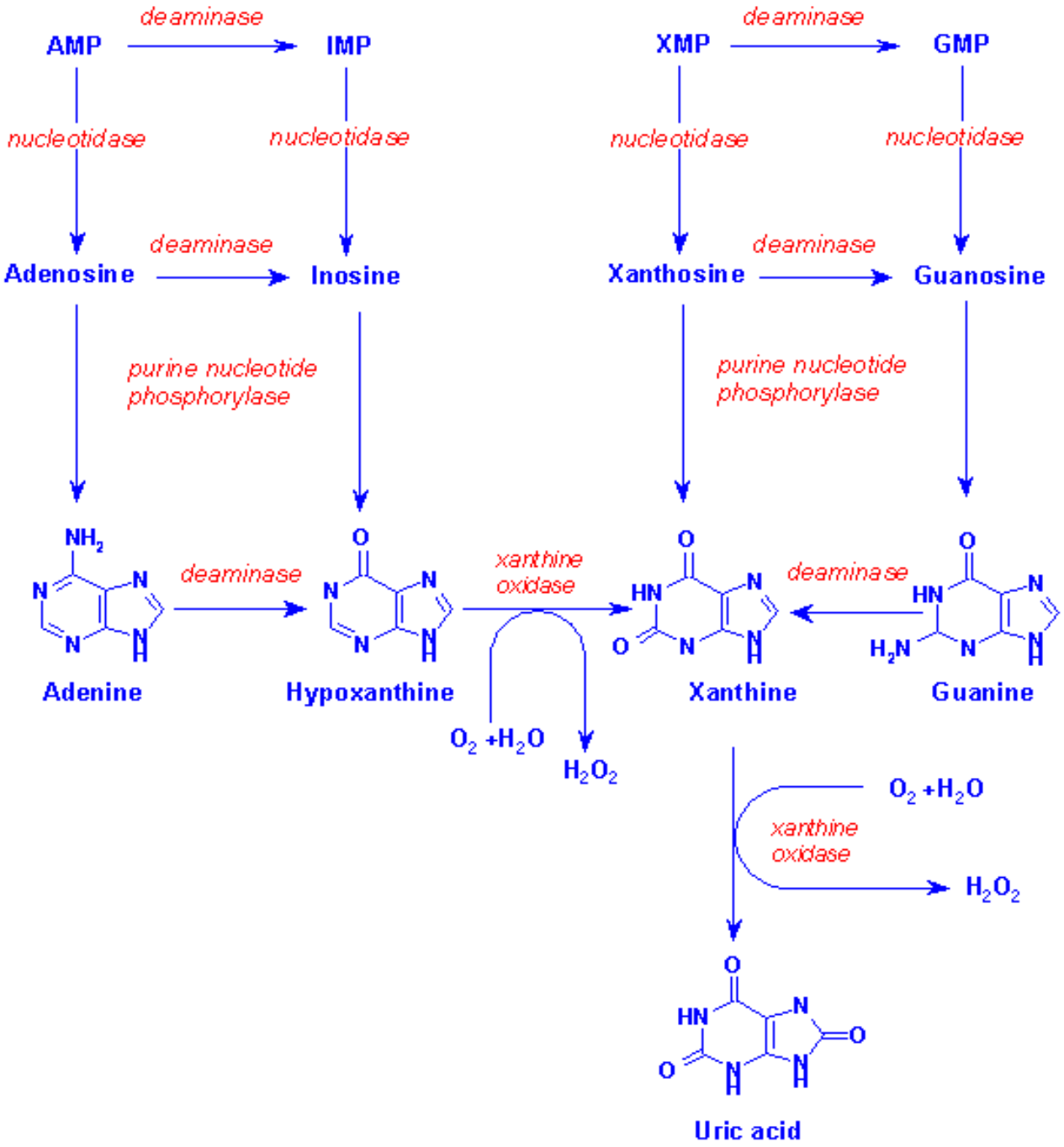
# De novo synthesis of purine nucleotides



# ATP and GTP formation from IMP

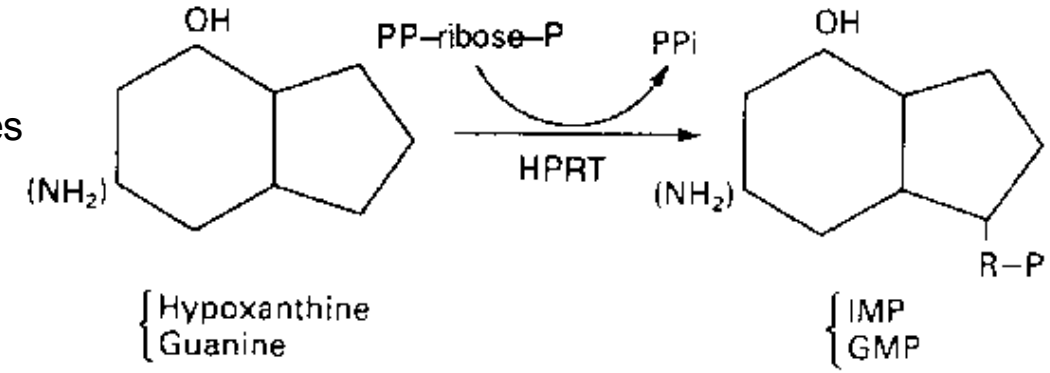


# Degradation of purin bases

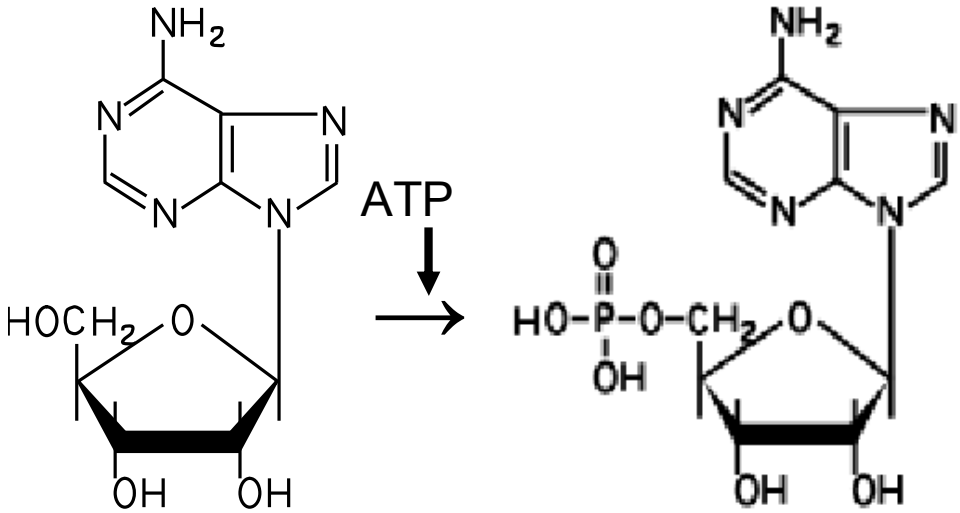


# Salvage mechanisms

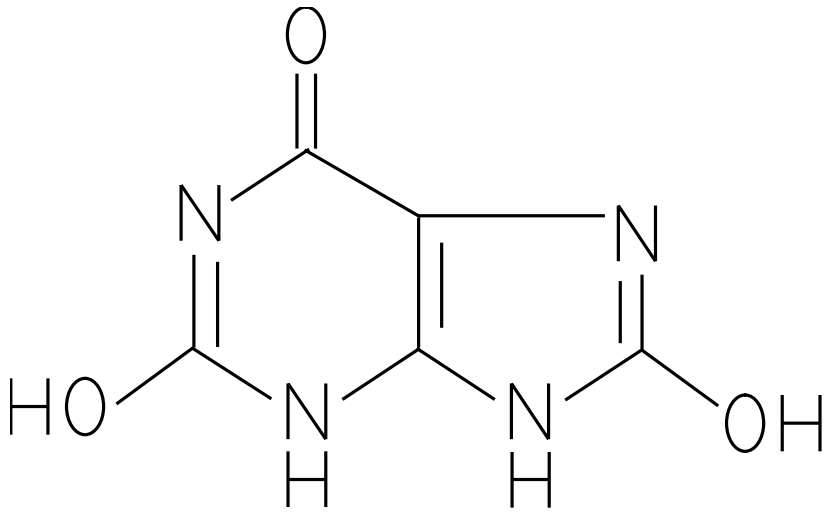
1.
A purinebases and nucleosides can transform to mononucleotides, purinebases will be recycled.
(Enzymes: adenine-phosphoribosile transferase, HGPRT.)
It is characteristic for the polimorfonuclear cells.
Salvage mechanisms inactivate de novo nucleotide synthesis.




2.
Purin ribonucleosides (adenosine, guanosine) are phosphorilated by ATP→ AMP, GMP is formed. (Kinase activates this step.)
Erythrocytes, brain immun cells can't do de novo purne synthesis. → Exogene nucleoside uptake.



# Uric acid




- solubility is decreased
- when uric acid level increases, it deposes in organism
- keto-enol tautomerism
- advantage: antioxidant
- (in other mammal it is degraded by urokinase, allantion is formed, which has a good water solubility)

# Hyperuricaemia (abnormally high level of uric acid in the blood), gout

Primary:

1. Idiopathic
2. Enzyme defects: -HGPRTdeficiency
   -ribose-P-diphosphokinase ↑
   -adenophosphoribosil-transferase ↓
3. Decreased renal excretion of uric acid

Secundary:

<u>Increased purin katabolism and turnover</u>

1.Myeloproliferative disorders
2.Lymphoproliferative disorders
3. Carcinoma and sarcoma
4. Chronic hemolitic anemia
5. Citotoxic drugs
6. Psoriasis

<u>Decreased renal excretion of uric acid</u>

1. Intrinsic renal disease
2. Functional disorders of tubular transport:

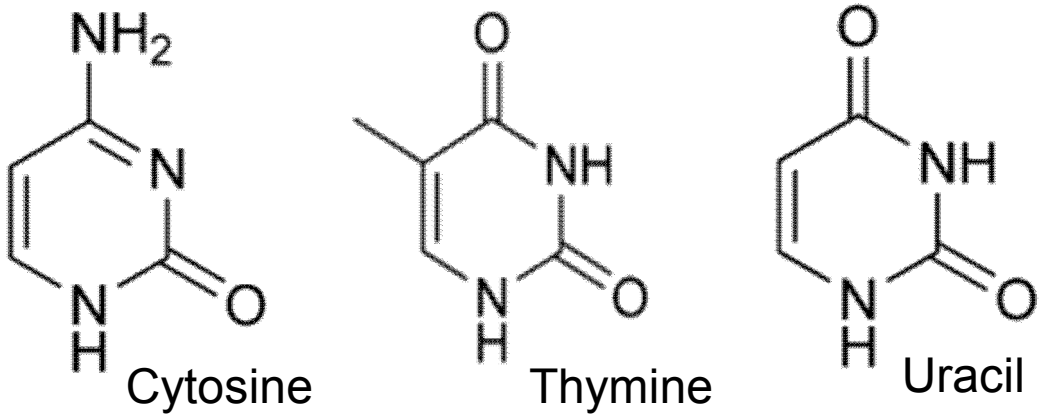
   drugs, increased lactate level, hyperketoacidaemia, diabetes insipidus, Bartter-sydrome

→ Urate crystals deposite in joints (tophus formation – gout), in kidneys (kidney stone).

Sympthoms are getting worse on purine-rich diet, in excessive cell damage.

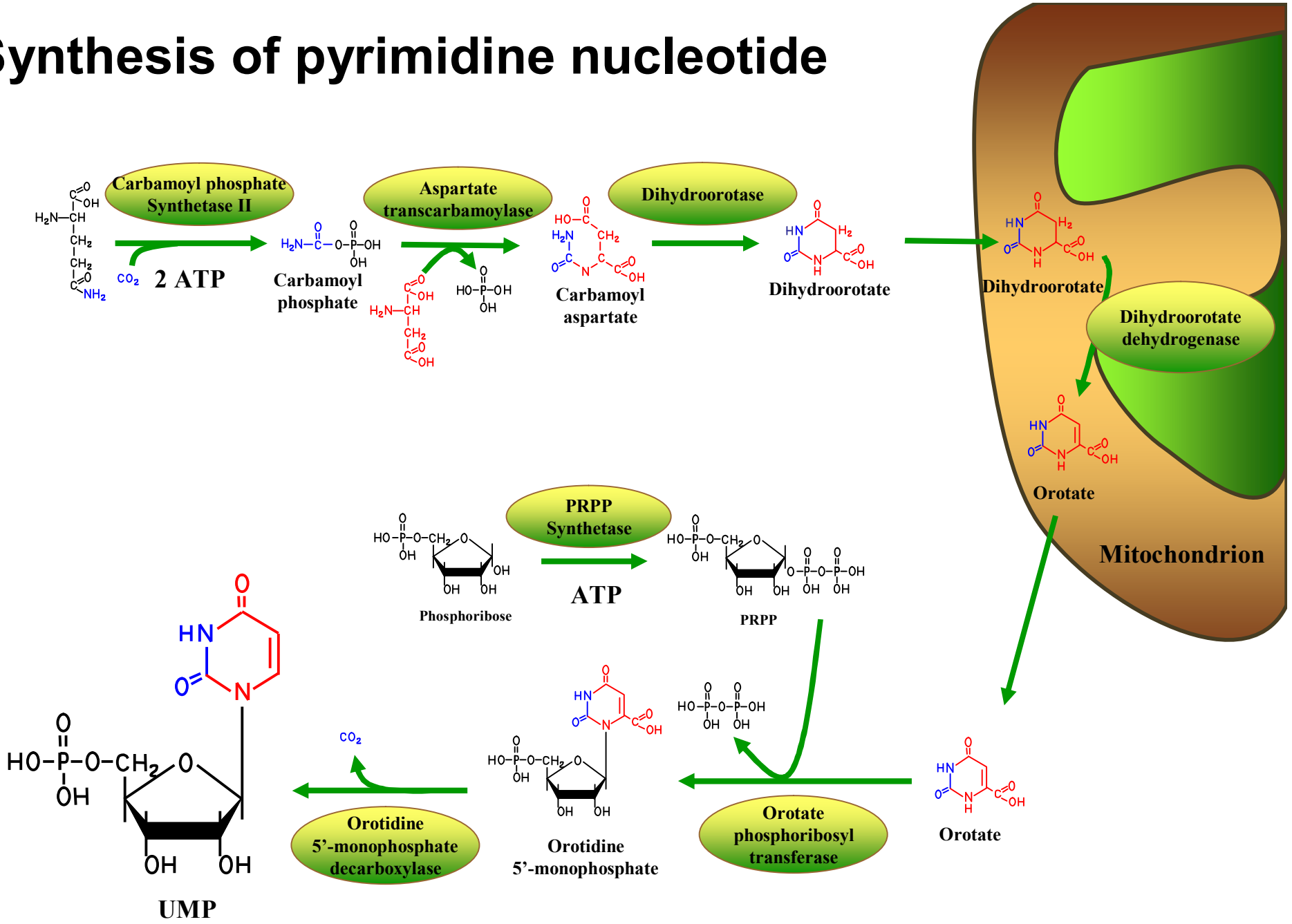
Therapy: allopurinol → inhibits the xanthineoxidase → inhibits the last step of uric acid synthesis and the de novo purine synthesis.

# Pyrimidin nucleotides

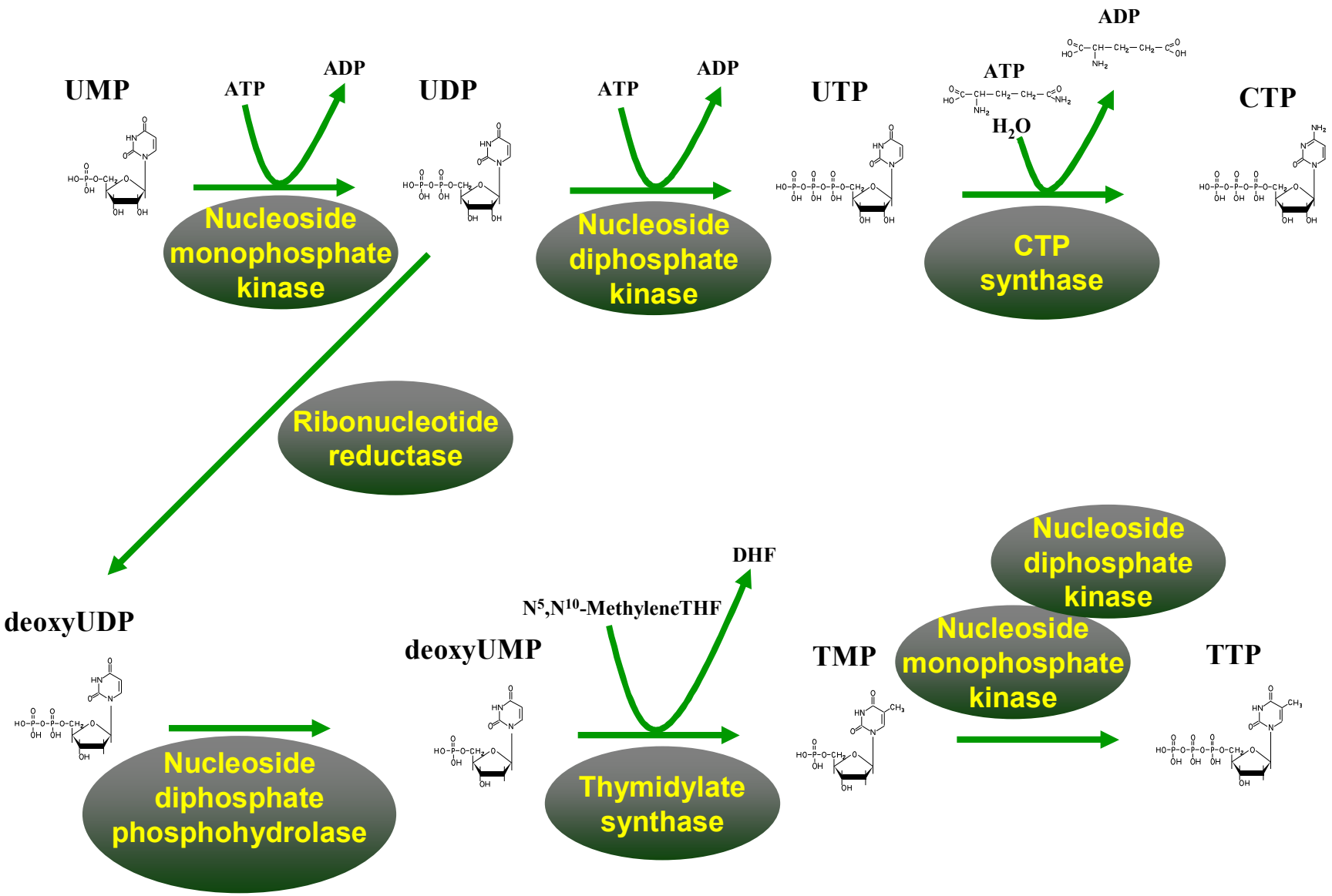



- Pyrimidine nucleotides: cytosine, thymine, uracil.
- Synthesis: Asp, Gln, CO2 + activated ribose-phosphate → dihydro-orotate → in mitochondrion orotate → UMP → UDP → UTP → CTP
  ↘ TTP
- Regulation of synthesis: UMP, UTP, CTP – feedback mechanisms, enzyme regulations

# Synthesis of pyrimidine nucleotide



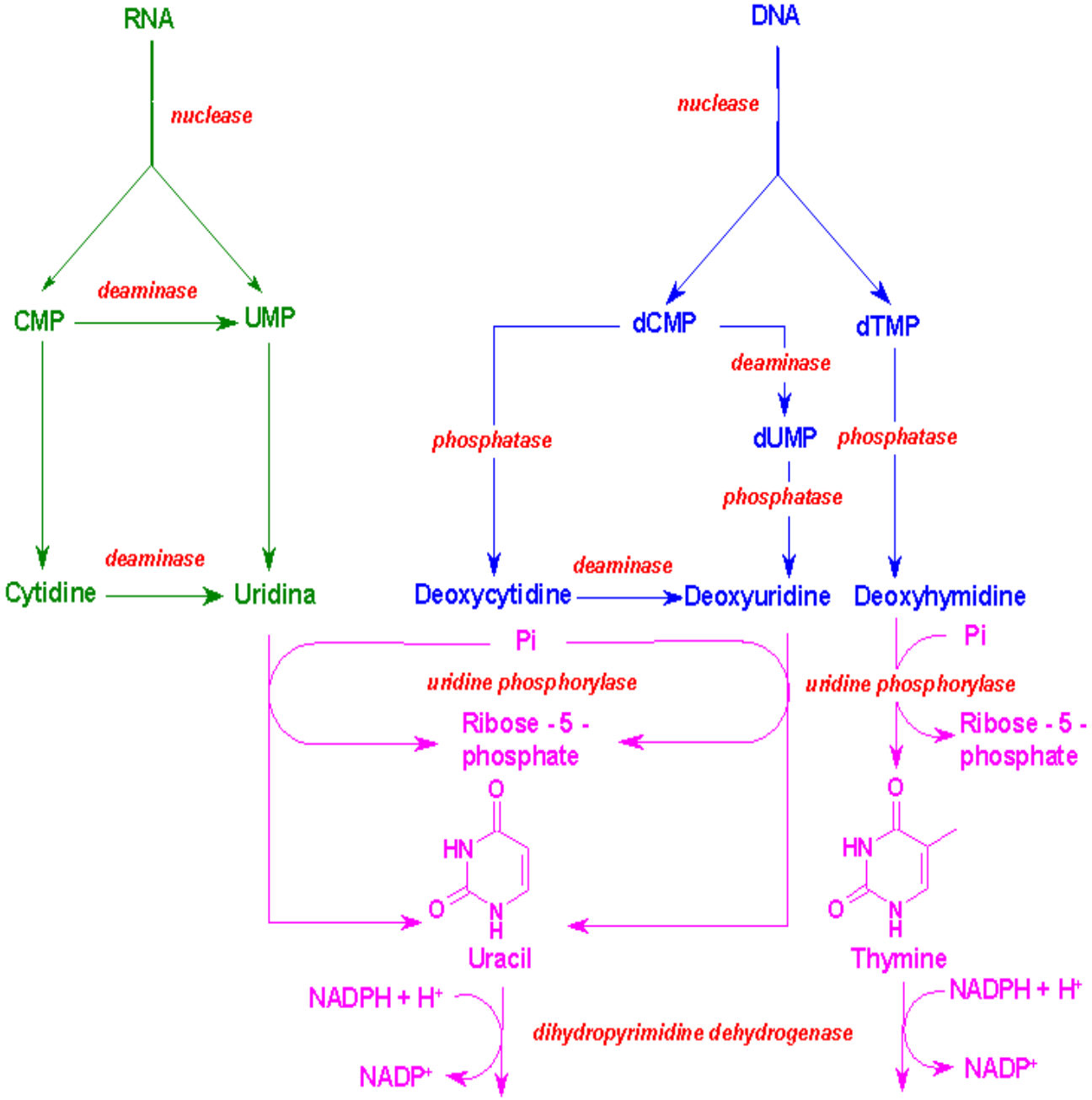
# Formation of pyrimidine nucleoside di- and tripfosphates



# Degradation of pyrimidine nucleotides

- During degradation CO2, NH3, β-alanine → coA is formed
- UMP, CMP → uridine, citidine → uracile → dihydrouracile → N-carbamil- β-alanin dihydropyrimidinase) → CO2, NH3, β-alanine → coA
- dihydropyrimidinase defect: thymidine level increases in blood, appeares in urine, causes epileptic seizures. Gout doesn't appears, pyrimidine intermediers are water soluble.
- salvage mechanisms

# Degradation of pyrimidine bases



# Deoxynucleotides

- They are formed by ribonucleotide-reductase komplex
- It is active in fissiparous cells
- The OH-group of the 2. C-atom of ribose will be reducated, H2O will be formed
- Just nukleoside-diphosphate is substrate for this enzyme
- It is a multicomponent enzymesysthem: ribonucleotide reductase (SH protein), tioredoxine (cofactor)
- SH-groups become oxydated (S-S)
- In eucaryotes glutathion-reductase, in procaryotes thyoredoxin-reductase rereducates the cofactor

# Influential drugs of nucleotide biosynthesis

- Aim: to inhibit baneful cell proliferationsokat (e.g.: in tumors, in viral infections, in autoimmun diseases)
- They have also side effects on hemopoetic cells, on immunsystem cells, on gamete and enterocytes
- Folate-, purine- és pyrimidine antagonists or analogues.

## AMINOPTERIN, METHOTREXATE:

-tetrahidrofolate analogues

-due to the competitive inhibition of dihydrofolate-reductase no N5,N10-metyl-THF is formed

-dUMP will not be metylated to dTMP

## SULFONAMIDES:

-analogues of p-amino-benzoeacid (PABA) in folate

-it reduces/inhibits the folate sythesis of bacteria, the nucleotide sythesis of them is also hampered

-it was the first antibacterial drug

## 6-MERCAPTOPURINE:

-analogue of the hipoxanthine structure

-it is phosphoribosilated by the HGPRT, and so instead of insin acid tioinosin acid is formed,which doesn't transforms to adenilate and guanilate

## CITOSINE-ARABINOSIDE:

-it is an antimetabolite, interferes with citosine

-instead of ribose arabinoside is the sugar component

-after phosphorillation it becomes analogue of dCTP, so it inhibits DNS synthesis

## 5-FLUOROURACILE:

-by kinases it is formed to F-dUMP

-F-dUMP binds kovalent to timidilate sythnase (suicide enzyme)

## NUKLEOSIDE ANALOGUES:

-they are the best antiviral drugs (Zovirax®)

-the viral thymidine-kinase is the substrate

-the products inhibit the DNA-polymerates