Disorders of metabolism of purines and pyrimidines

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Disorders of metabolism of purines and pyrimidines

- **Inborn / since early childhood**
  - **Simple heredibility**
- **Acquired**
  - **Usually complicated heredibility**
  - **Influences of environment**

Disorders of metabolism of purines and pyrimidines

PURINES

Lesch-Nyhan syndrome

- **Hyperuricemia from overproduction**
- **Urate concrements**
- **Automutilation**

- **Defective hypoxanthin-guanin phosphoribosyl transferase**
  - **Leads to increased PRPP and overproduction of purines**

Von Gierke disease

- **Hyperuricemia from overproduction**
- **DefectiveG6PDH**
- **Excess of G6P stimulates production of PRPP**
- **Lactic acidosis decreases elimination of urates**

Defect of adenosine deaminase

- Poor conversion od A to I
- Accumulation of dATP & dGTP inhibits ribonucleotide reductase
  - Lack of DNA precursors
- **Immuno-deficiency** (SCID = severe combined immunodeficiency disease)

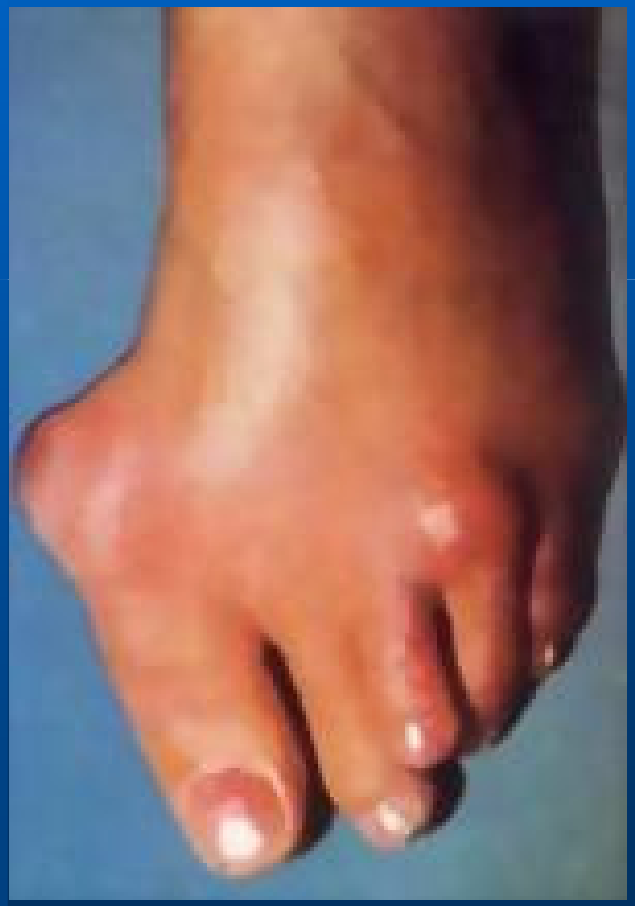
Podagra

- **Why is uric acid an acid?**
- **Under which conditions is uric acid soluble?**
- **How is it eliminated by kidneys?**

Podagra

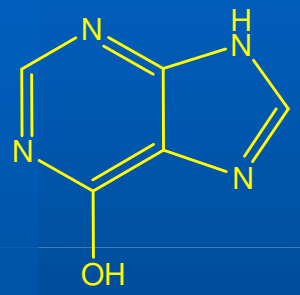
- **Overproduction of purine bases**
  - **Increased production of PRPP**
  - **Decreased activity of HGPRT**
    - **PRPP not spent**
    - **Less IMP & GMP → increased production of PRPP**
- **Cell lysis**
- **Disorders of elimination of urate**

Podagra



http://www.zdravcentra.cz/img/informacni_systemy/41da64aea6ef1_small.jpg

Podagra



hypoxanthin

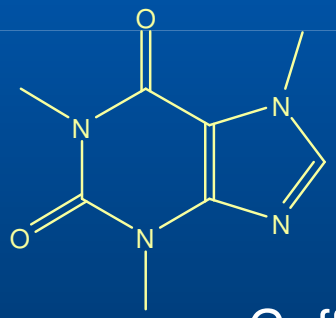
Xanthin oxidase

Uric acid

allopurinol

alloxanthin
Remains covalently
bound to
xanthin oxidase

Purines



Caffein

Disorders of metabolism of purines and pyrimidines

PYRIMIDINES

Disorders of metabolism of pyrimidines

- **Derivatives of pyrimidines are well soluble**
- **Usually not clinically significant**

Orotic aciduria

- **Rey‘s syndrome**
  - **Damage to mitochondria, disability do metabolise carbamoylphosphate**
  - **Excess of carbamoylphosphate stimulates production of orotate**
- **Type I and Type II**
  - **Disorders of conversion of OMP to UMP**
  - **I: both orotate phosphoribosyl transferase and orotidylate decarboxylase**
  - **II: orotidylate decarboxylase only**

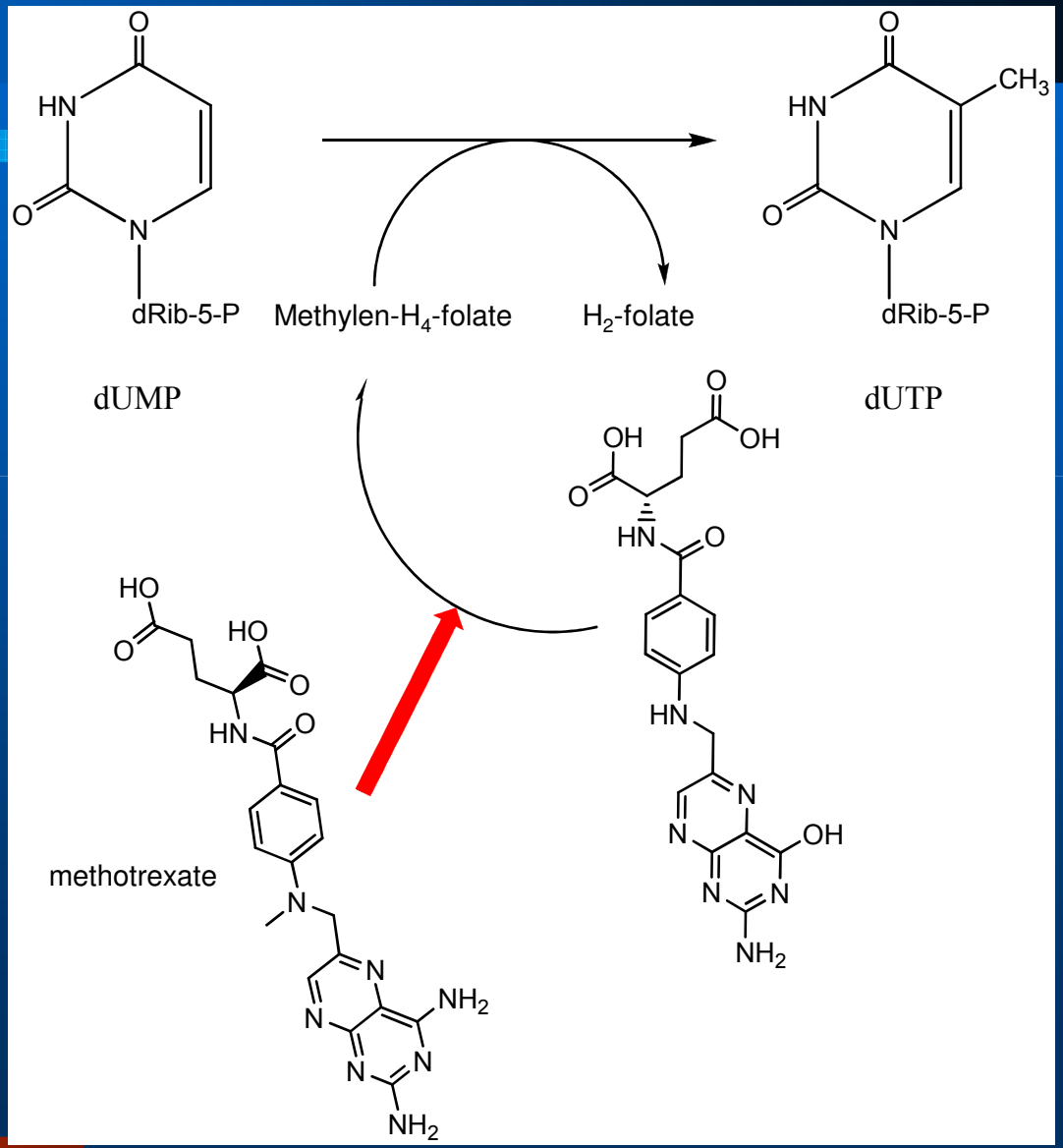
Defects of ureasynthesis

- **Defect of mitochondrial ornithin transcarbamoyltransferase**
- **Excess of carbamophosphate stimulates production of pyrimidinesMild orotic aciduria**

Methotrexat

- **Inhibits dihydrofolate reductase**
  - **Blocks reduction of dihydrofolate to tetrahydrofolate**
  - **Tetrahydrofolate is essential for synthesis of TMP**

Methotrexate



Other chemotherapeutics

- **Purine analogs**
  - **Mercaptopurine**
- **Pyrimidine analogs**
  - **Fluorouracil**
  - **Cytosinarabinoside**