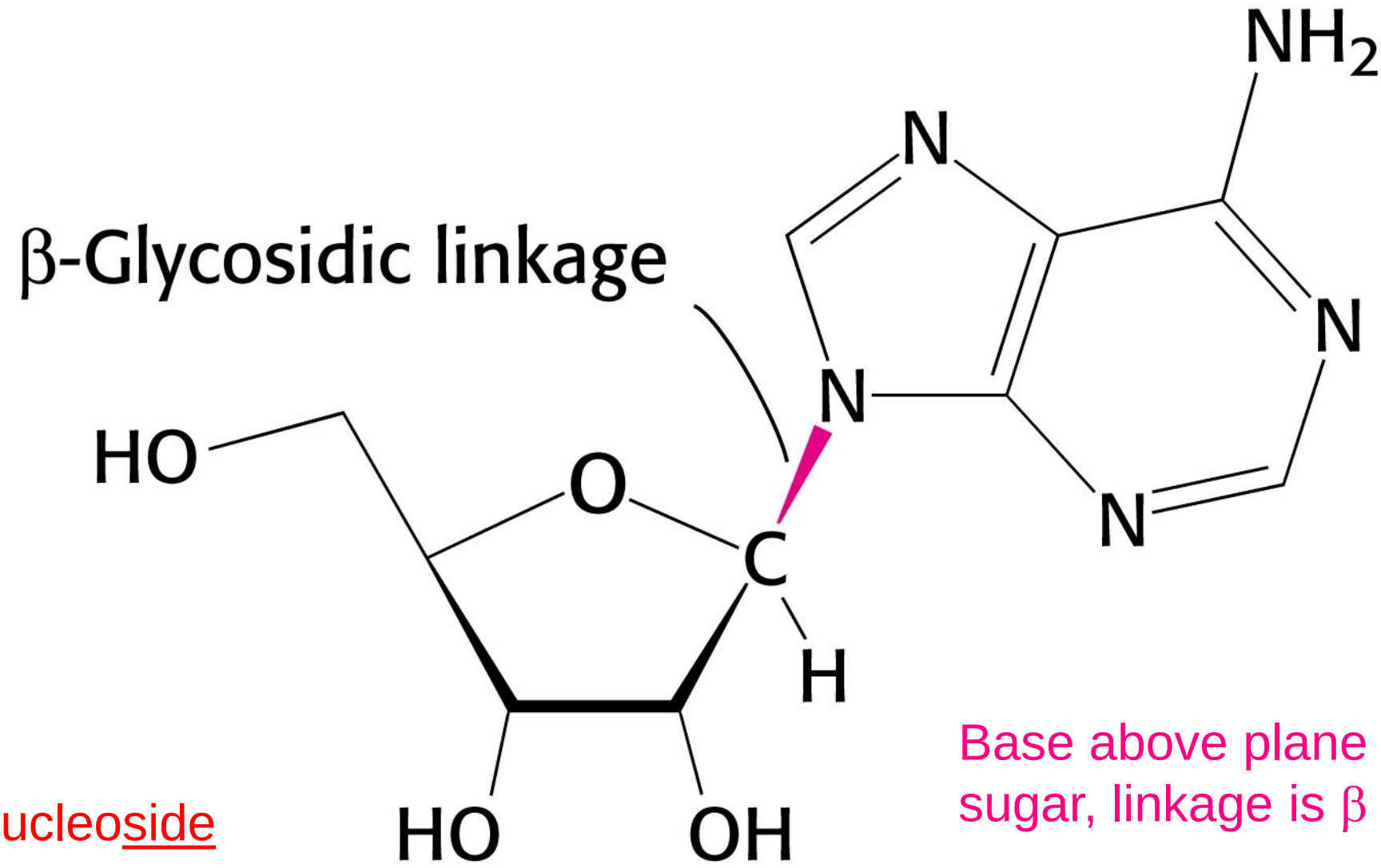
2. The nucleic acid metabolism disorders of purine and pyrimidine. Hyperuricemia, orotacidurie, therapy.

Sugar - base linkage



Base above plane of sugar, linkage is β

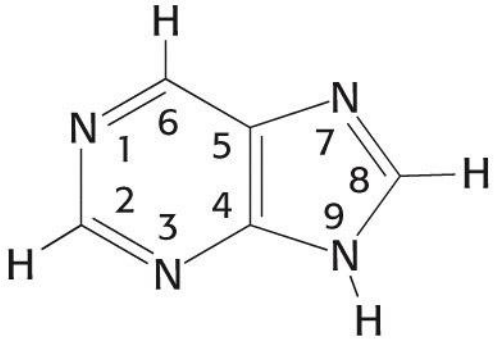
Nucleoside

RNA: adenosine, guanosine, cytidine, & uridine

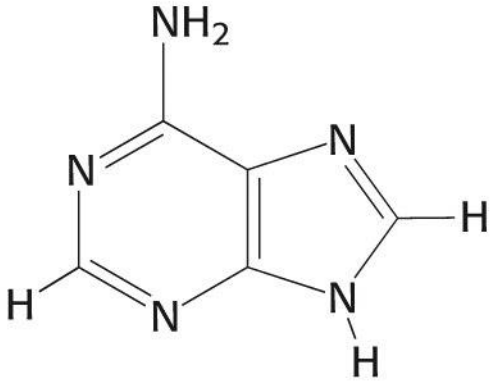
DNA: deoxyadenosine, deoxyguanosine, deoxycytidine, & thymidine

Purines & Pyrimidines

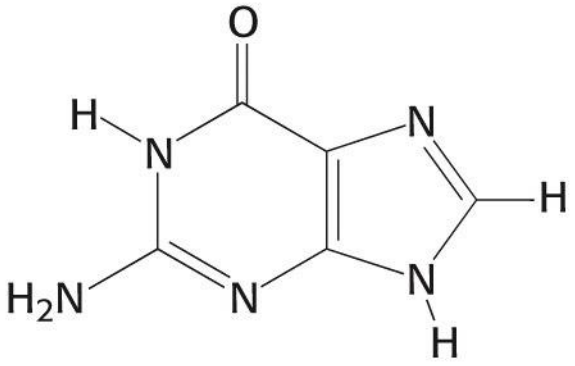
PURINES



Purine

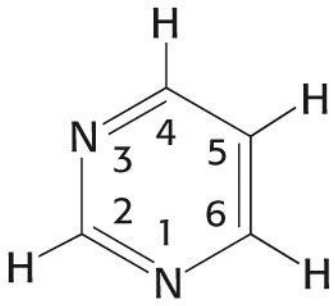


Adenine

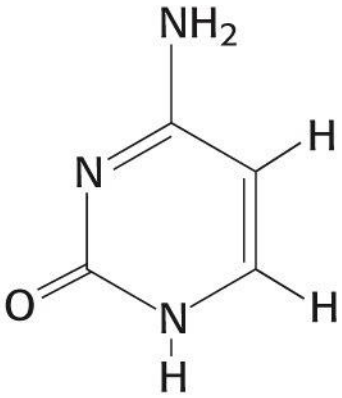


Guanine

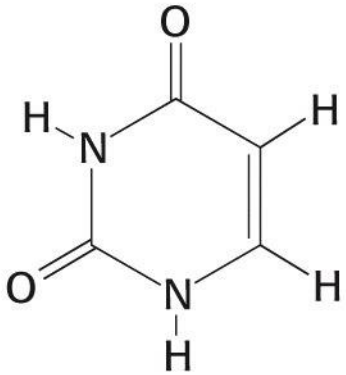
PYRIMIDINES



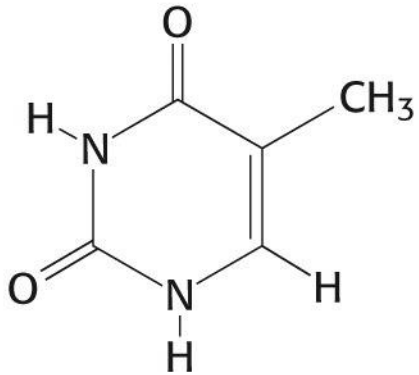
Pyrimidine



Cytosine



Uracil



Thymine

Note: ring atom #s

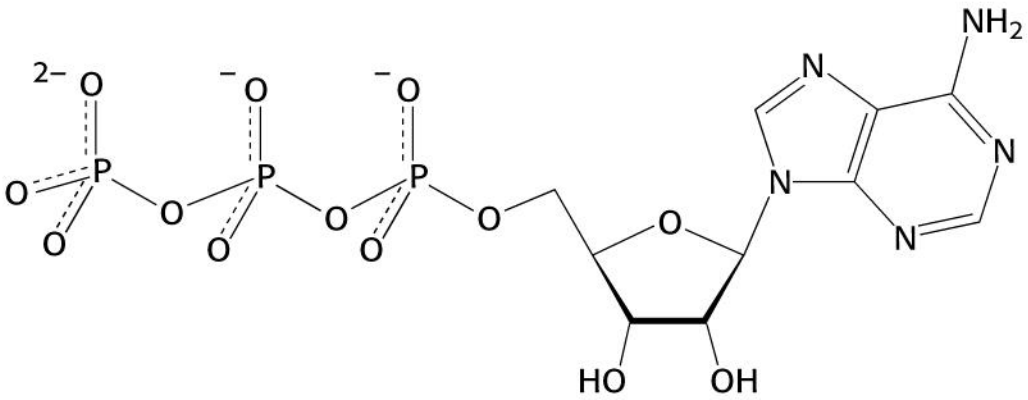
RNA

DNA

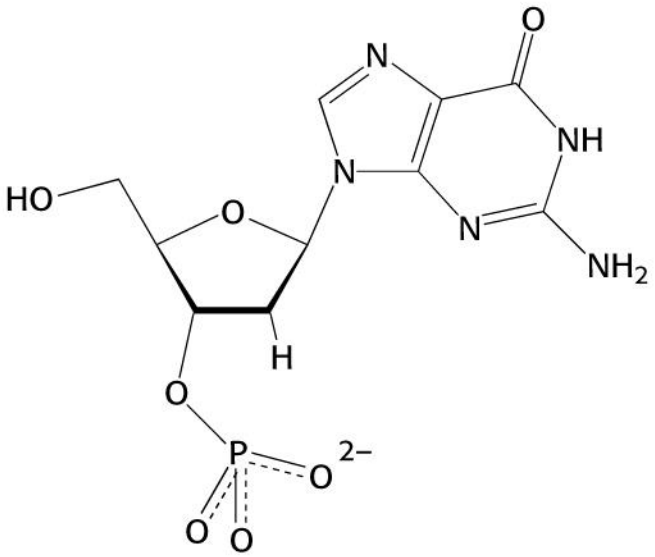
Nucleotides: monomeric units of nucleic acids

Adenosine 5’-triphosphate

Deoxyguanosine
3’ monophosphate



5′-ATP



3′-dGMP

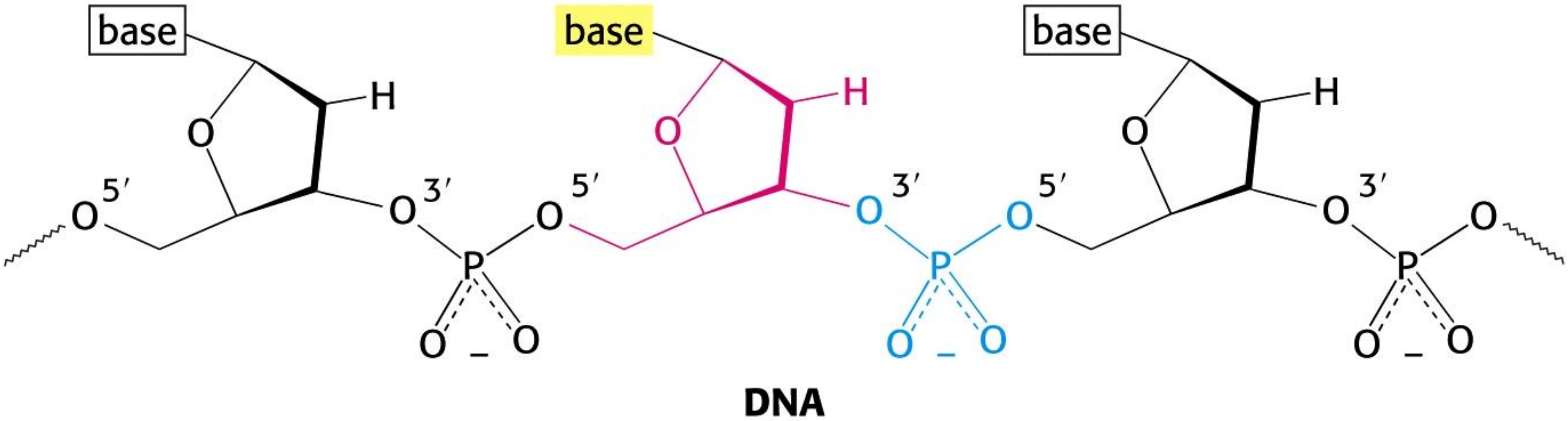
5’ nucleotide - most common

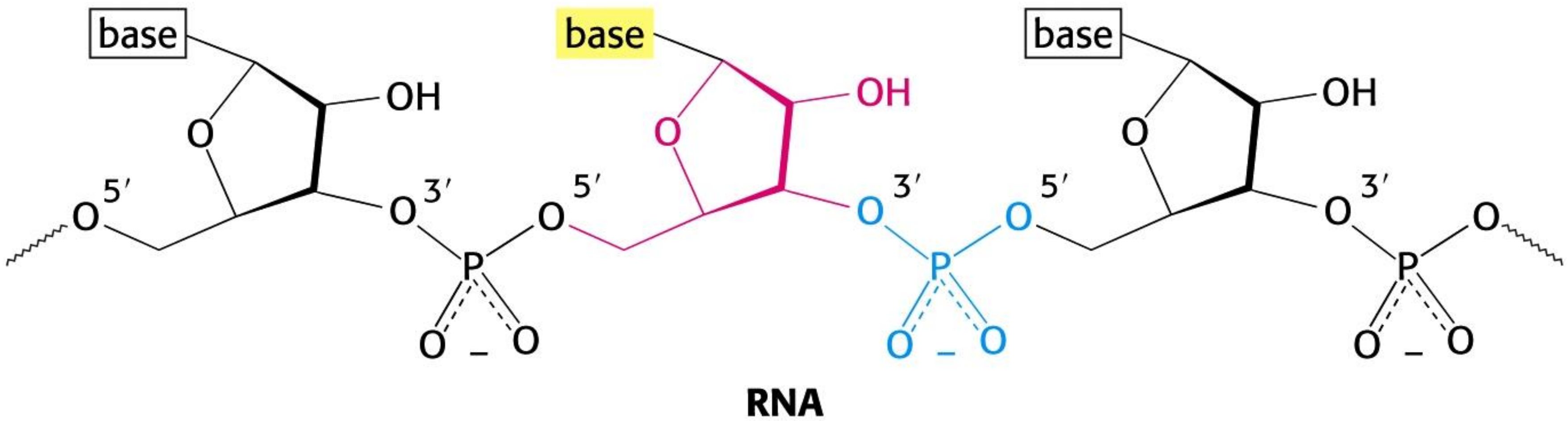
3’ nucleotide

Nucleotide: nucleoside joined to one or more phosphate groups by an ester linkage

Backbone of DNA & RNA

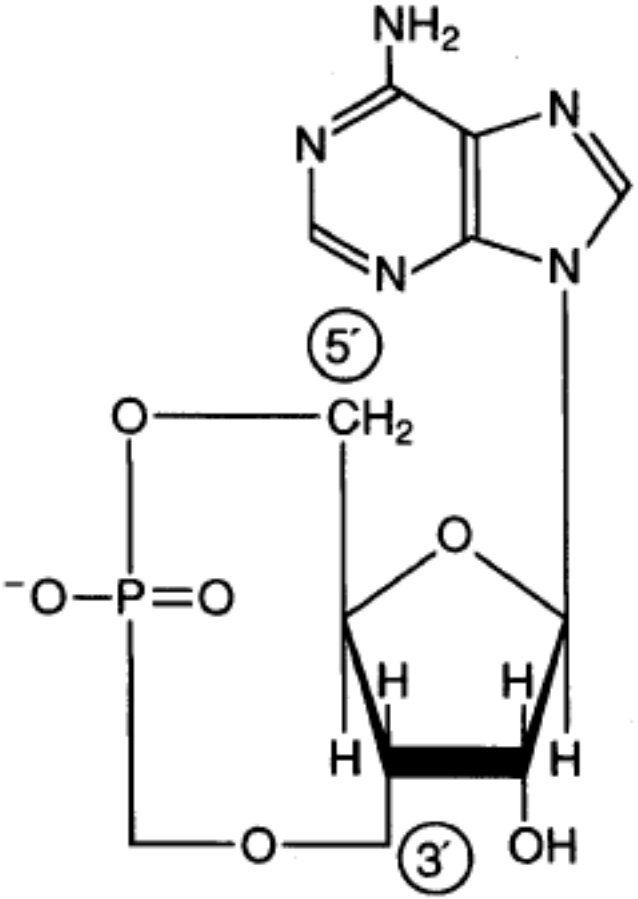
3'-to-5' phosphodiester linkages





Sugar, red. Phosphate, blue

Role of nucleotides



- Information carriers (DNA/RNA)
- Universal source of energy (ATP 30 kJ/mol)
- Second messengers: cGMP a cAMP
- Coenzymes and group transfer

http://www.benbest.com/health/cycAMP.gif

Biosynthesis of purine and pyrimidine nucleotides

• all cells needs ribonucleosides, deoxyribonucleosides and their phosphates

• not esencial (2 biosynthetic pathways)

• **purine and pyrimidine** basis **from food** are not used for biosynthesis, cleved for catabolism (pancreatic endonucleases)

• **biosynthesis purine and pyrimidine** basis (2 pathways):

•1. de novo 2. salvage pathway

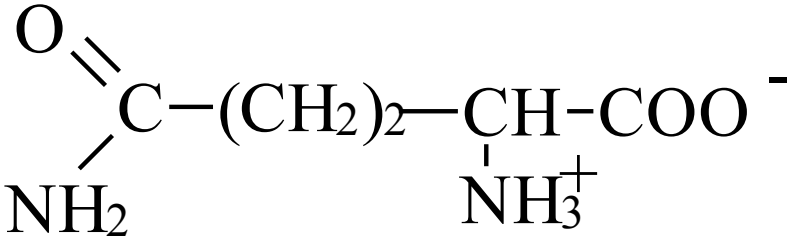
• location :- liver

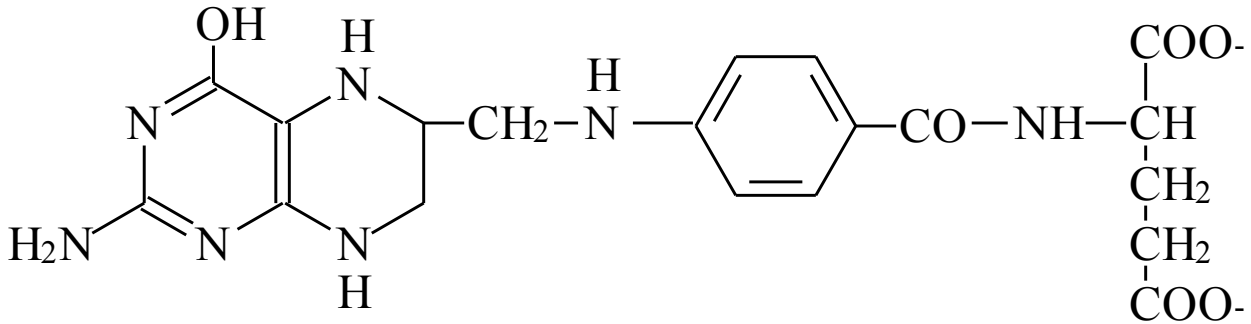
• needs: sugar (PPRP), AA(glycine, glutamine, aspartate),
. coenzyme: **tetrahydrofolate**

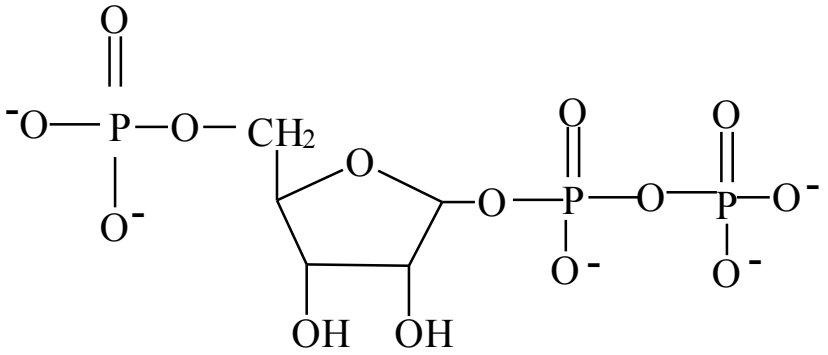
• synthesis of purine and pyrimidine nucleotides are coordinated

Precursore molecules for purine and pyrimidine nucleotides

- 3 main compounds:
- 1) **tetrahydrofolate**
- 2) **glutamine**
- 3) **PRPP – 5-phosphoribosyl-1-pyrophosphate**



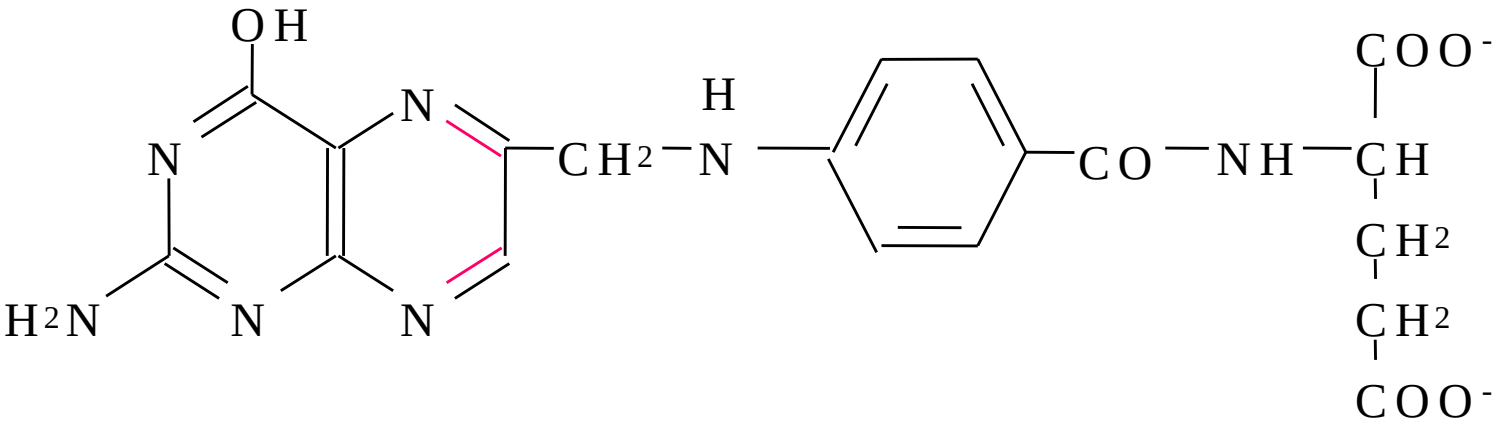




Importance of folic acid for biosynthesis of NA bases

Green leafy vegetables, liver, whole grains, yeast, k

Folate



Used form in human is tetrahydrofolate

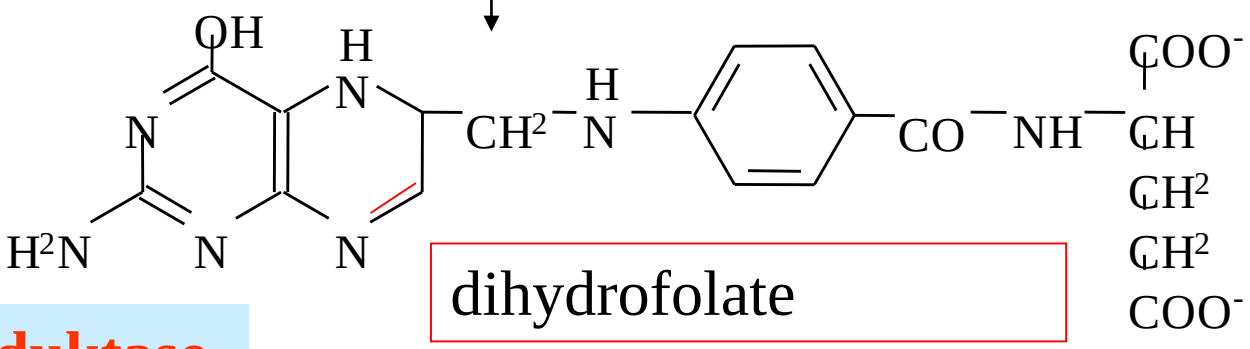
Formation of tetrahydrofolate

folate

NADPH + H+

NADP +

DEHYDOGENATION

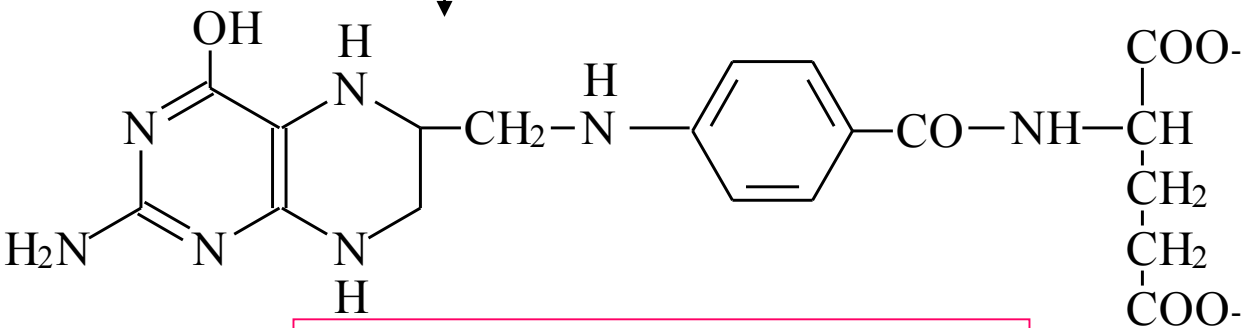


dihydrofolate

(dihydro)folatereduktase

NADPH + H+

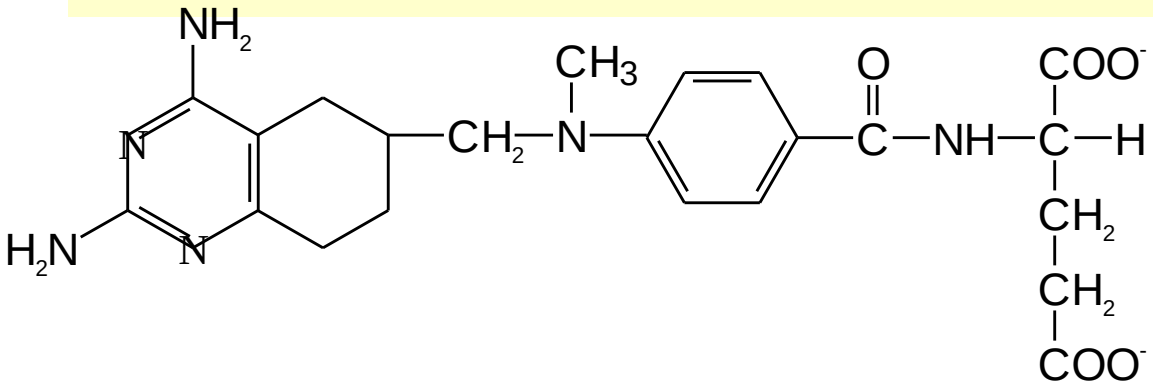
NADP +



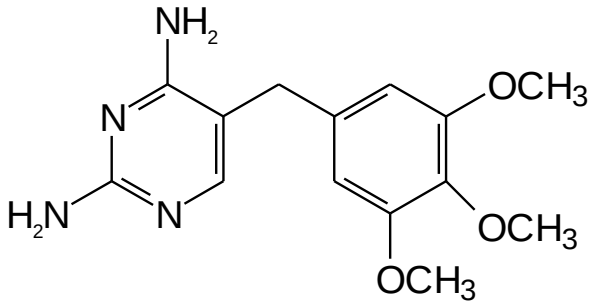
tetrahydrofolate

Inhibitors (dihydro)folatereductase:

Methotrexate (anticancer agent)



Trimethoprim (bacteriostaticum)



Dihydrofolate reductase - an objective antitumor therapy.

Dihydrofolate reductase was the first enzyme for which focused antitumor therapy.

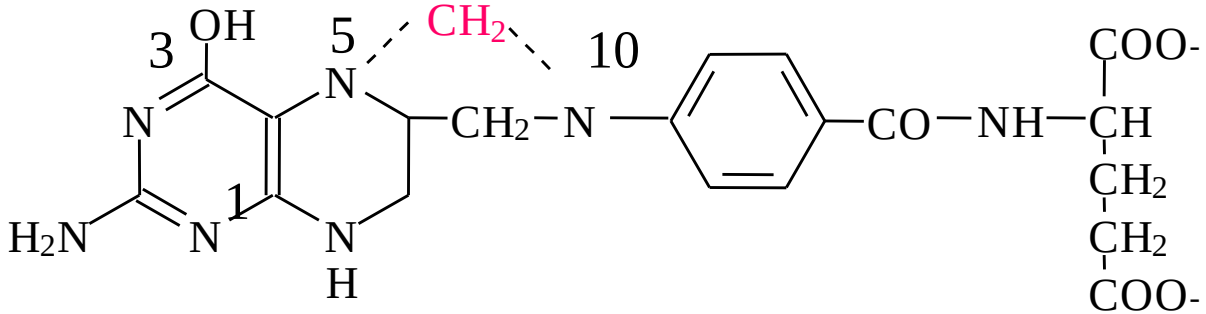
The first-used inhibitor was **aminopterin**.

It binds to the enzyme 1000 times tighter than folate, acts as a competitive inhibitor.
Currently used **methotrexate** and similar derivatives.

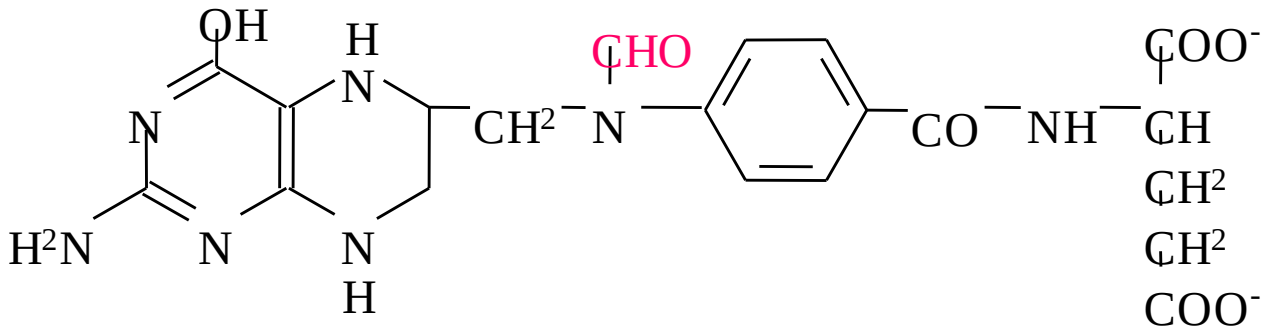
All drugs which affect the synthesis of purines and pyrimidines, deplete rapidly dividing cells - but not only cancer cells but also cells in the bone marrow and GI tract cells such as hair follicles.

Using of tetrahydrofolate

N-5,N-10- methylen H_4F – synthesis of thymin

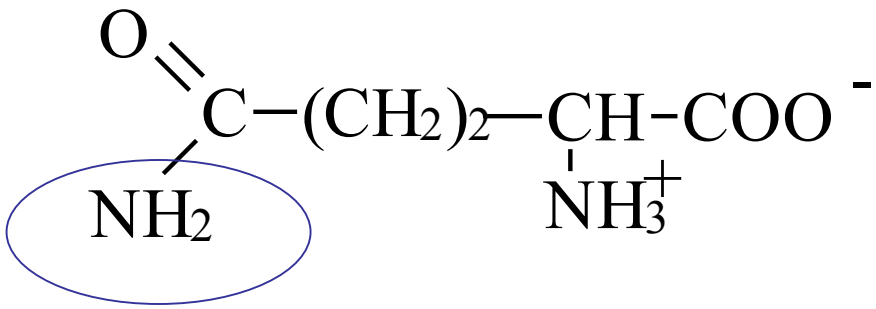


N-10-formyl H_4F – synthesis of purins

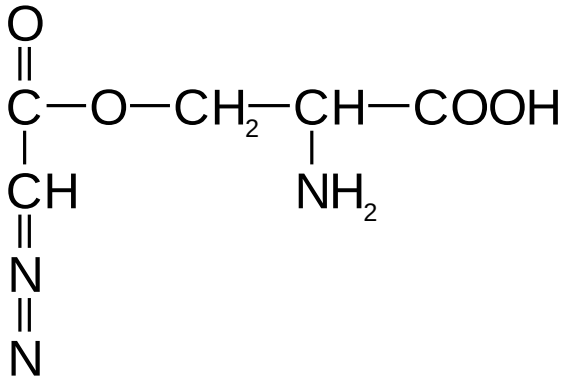


Importance of glutamin for purine and pyrimidine biosynthesis

- Donor of aminogroup



Glutamine antagonists inhibits synthesis of purines and pyrimidines



azaserin

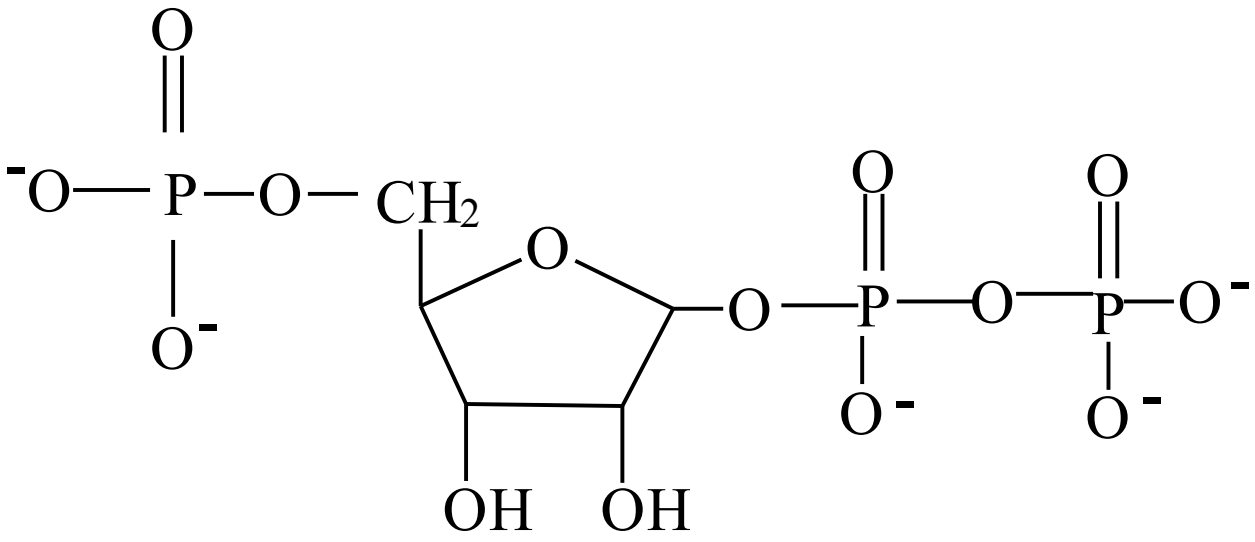
PRPP - phosphoribosylphyridoxalphosphate

Necessary for synthesis:

Purine nucleotides

Pyrimidine nucleotides

NAD^+, $NADP^+$

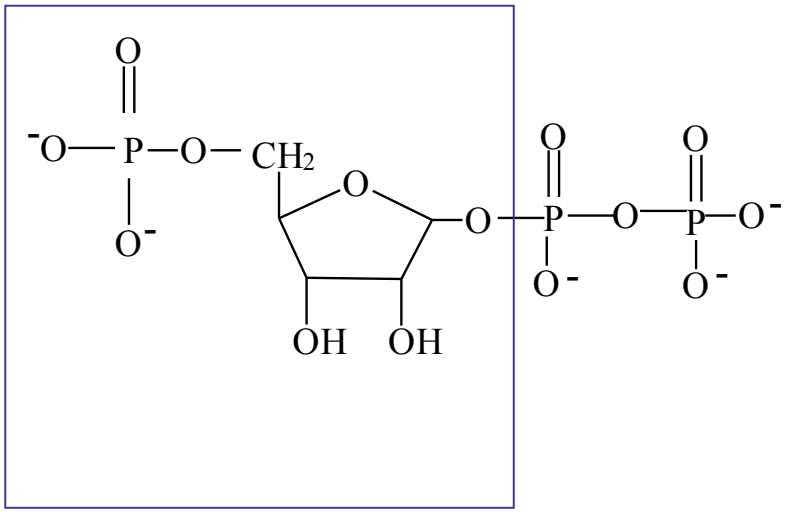


Synthesis of PRPP

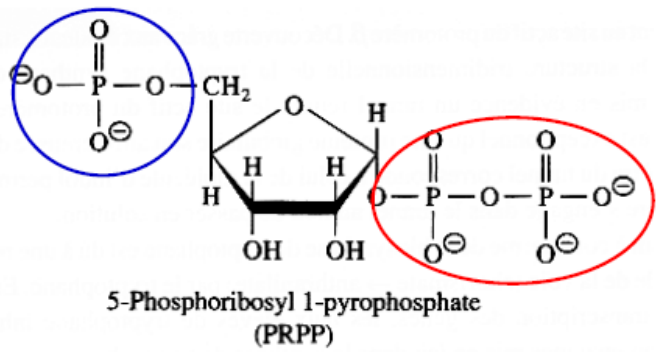
PRPP-synthetase

ribose-5-phosphate (pentose cycle), activeted penthose

Ribosa-5P + ATP → PRPP + AMP



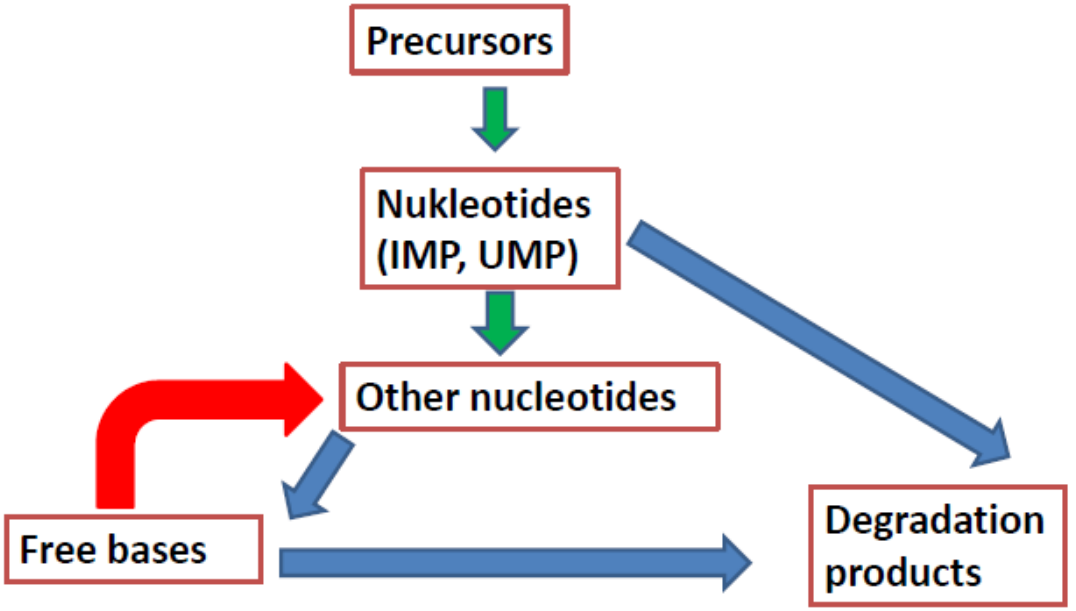
PRPP = 5-fosforibosylpyrofosfate



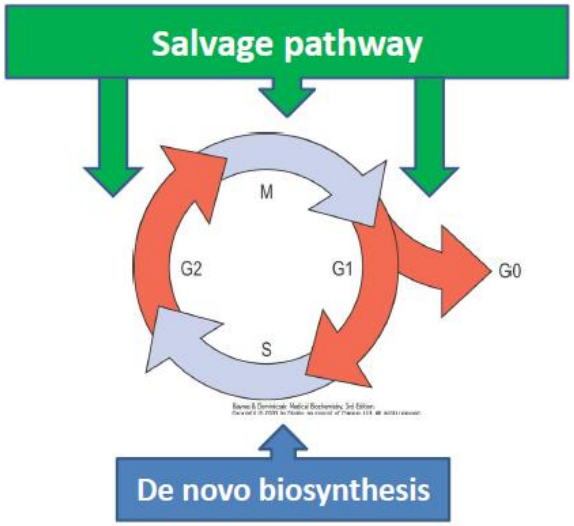
- Purines: first step in IMP synthesis
- Pyrimidines: last steps in UMP synthesis
- P/P: salvage pathway

http://ead.univ-angers.fr/~jaspard/Page2/COURS/2N2NH3aaetUree/2Figures/9AAaromatiques/8PRPP.gif

Synthesis and degradation of P/P



Cell cycle and P/P synthesis



TEST

Metabolism of purines and pyrimidines

	purines	pyrimidines
PRPP	1st step	Last steps
product	IMP	UMP
localization	cytoplasm	cytoplasm + 1 enzyme in mitochondria
Degradation products	Uric acid, ammonia	CO_2, NH_4, β-Alanine, β-Aminoisobutyrate

Differences in purine and pyrimidine synthesis

Synthesis - *puzzle* – one part to others.

Diffrence in the beginning :

–purines : first PRPP and than is form base

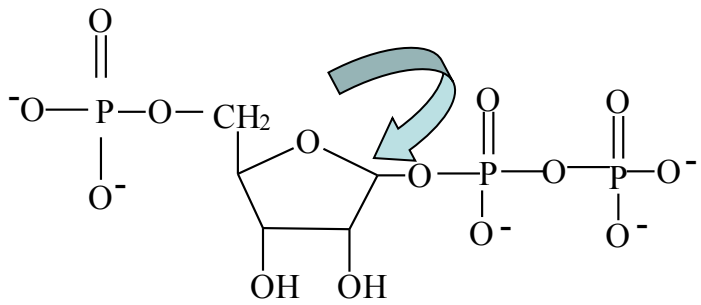
- Pyrimidines : first base and than ribosa-5-P from PRPP.

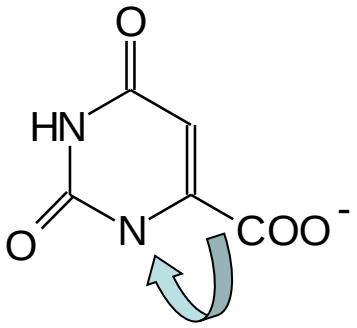
Purins

First PRPP…

Pyrimidins

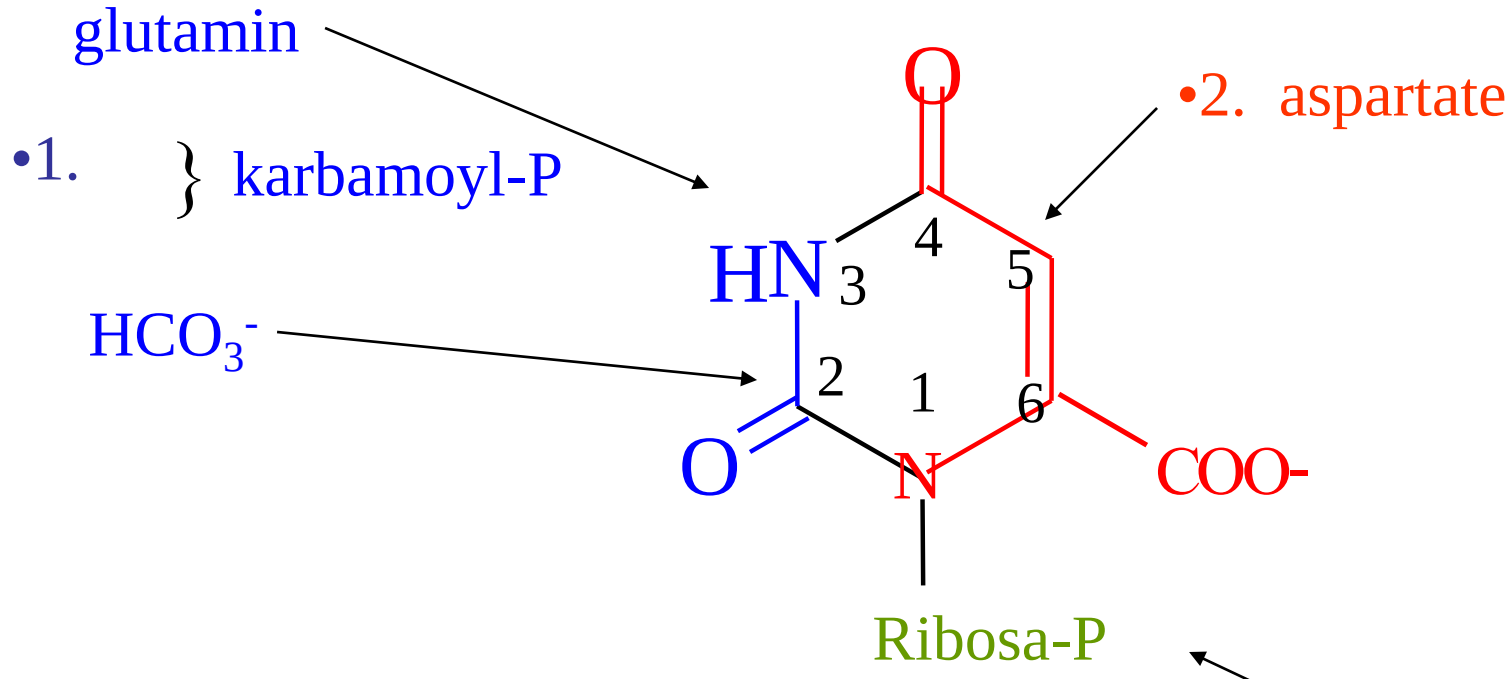
First heterocycle ribose-P from PRPP





1) BIOSYNTESIS of PYRIMIDINS

Origin of atoms in pyrimidines



Orotidinmono-P

Decarboxylation – uridin mono-P

BIOSYNTESIS OF PYRIMIDINS

- **syntesis of karbamoyl -P**

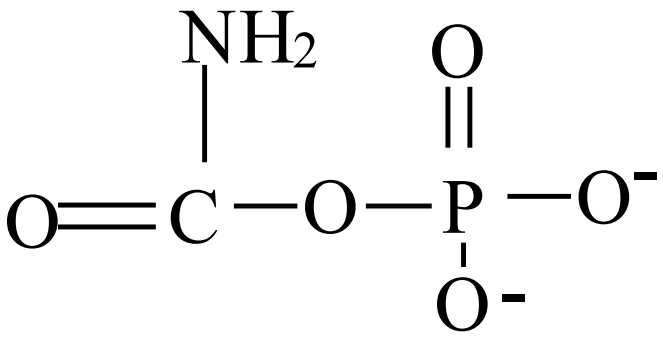
CYTOPLASM

Karbamoyl-P-synthetase

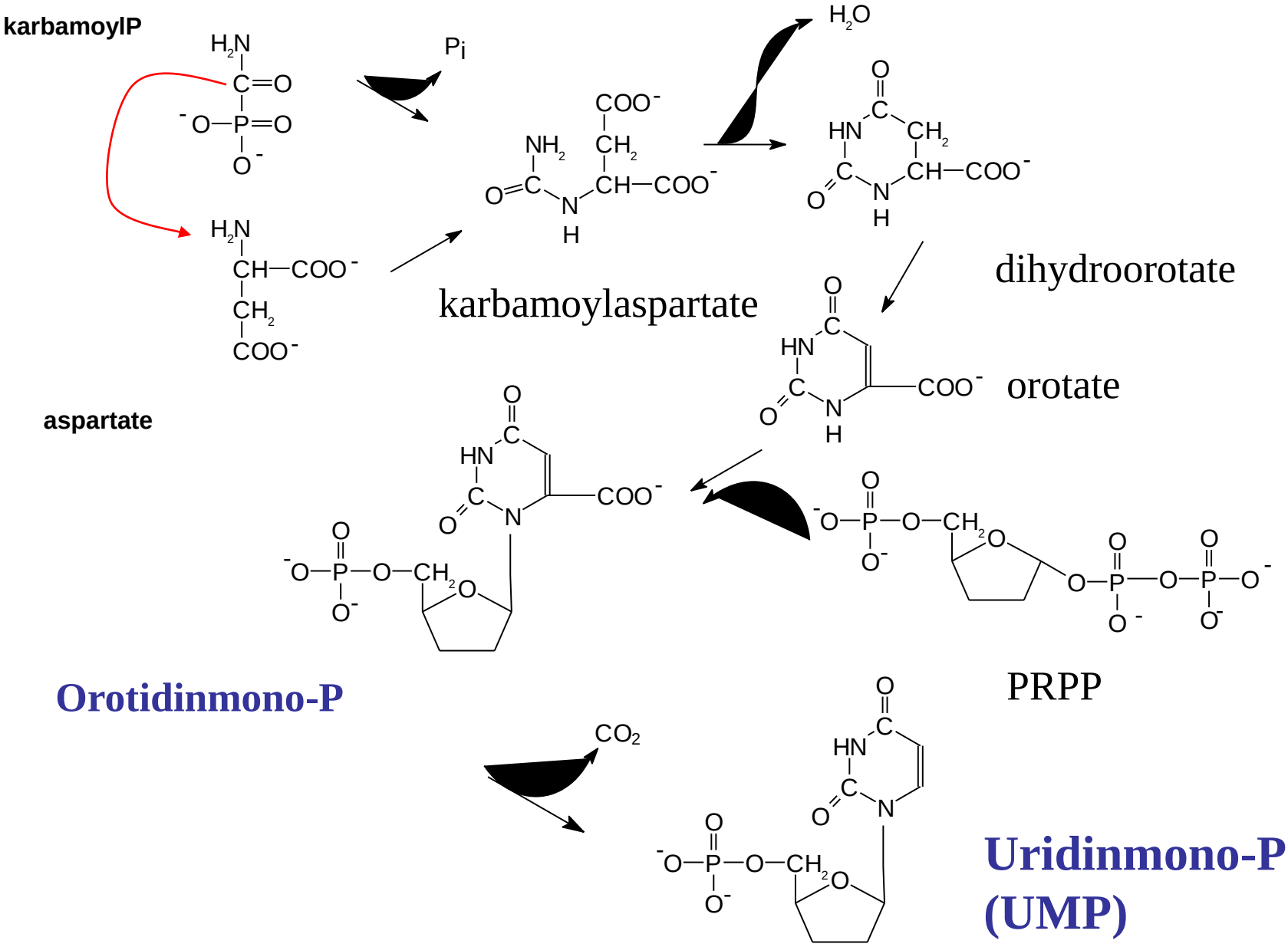
-energy, enzym **karbamoylphosphatesynthetase II**
Inhibition by UTP („inhibition by product“) and **aktivation by ATP**.

- 1 Glutamine + 2 ATP + HCO_3^-

$\rightarrow$ karbamoyl-P + glutamate + 2 ADP + P_i

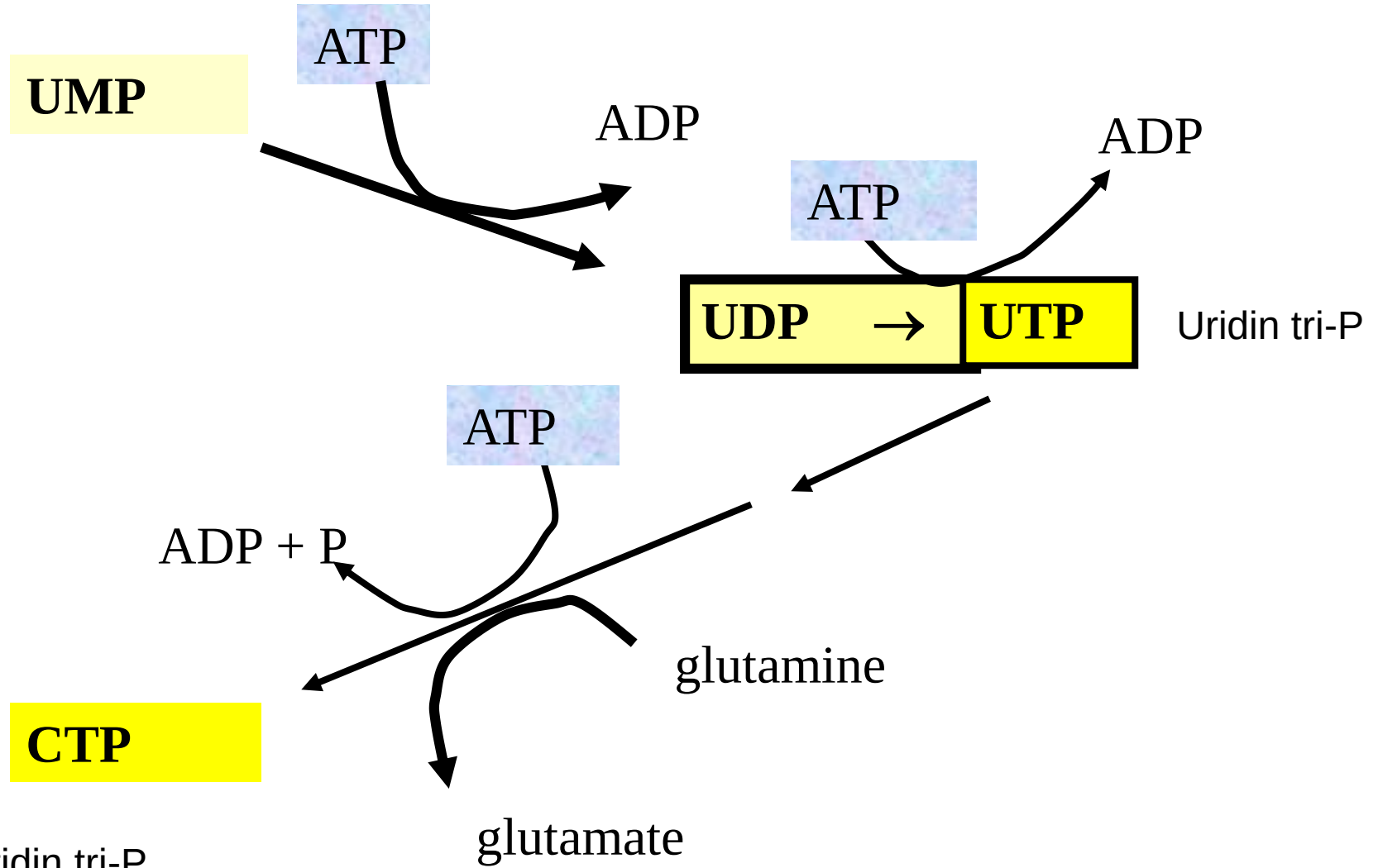


BIOSYNTESIS OF PYRIMIDINS



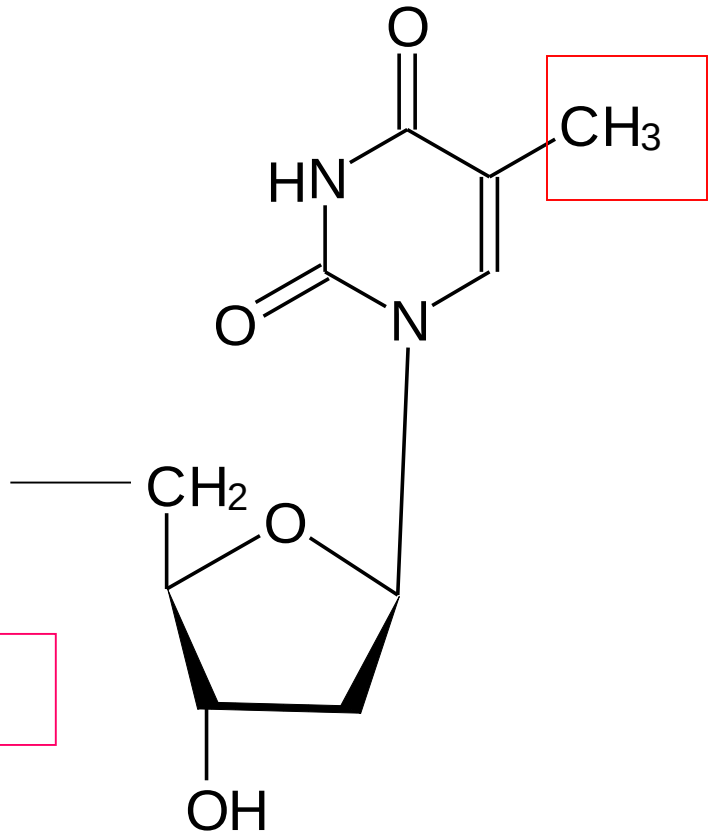
BIOSYNTESIS OF PYRIMIDINS

Biosyntesis of UTP and CTP



dTMP (methylation)

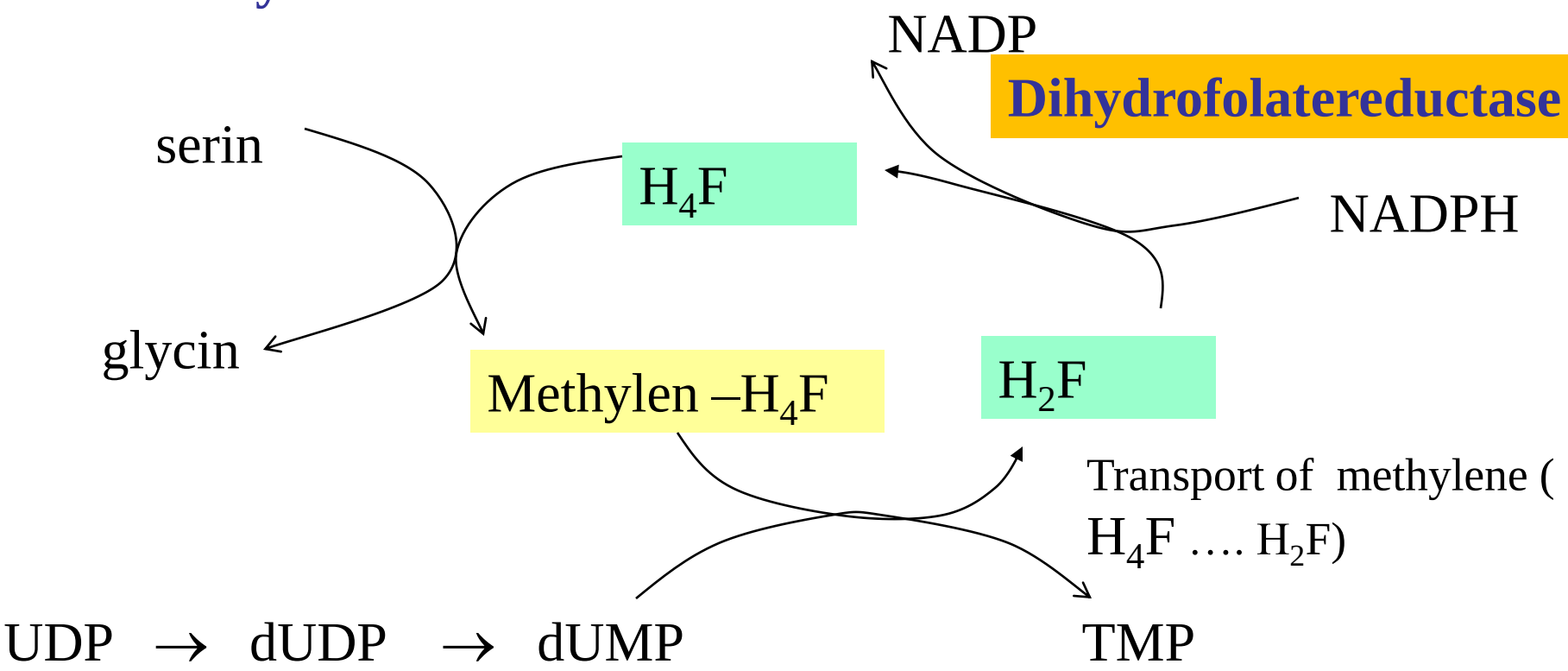
Deoxythymidintri-P



Methylation- H_4F

Methylen group in H_4F is reduced to methyl dUMP

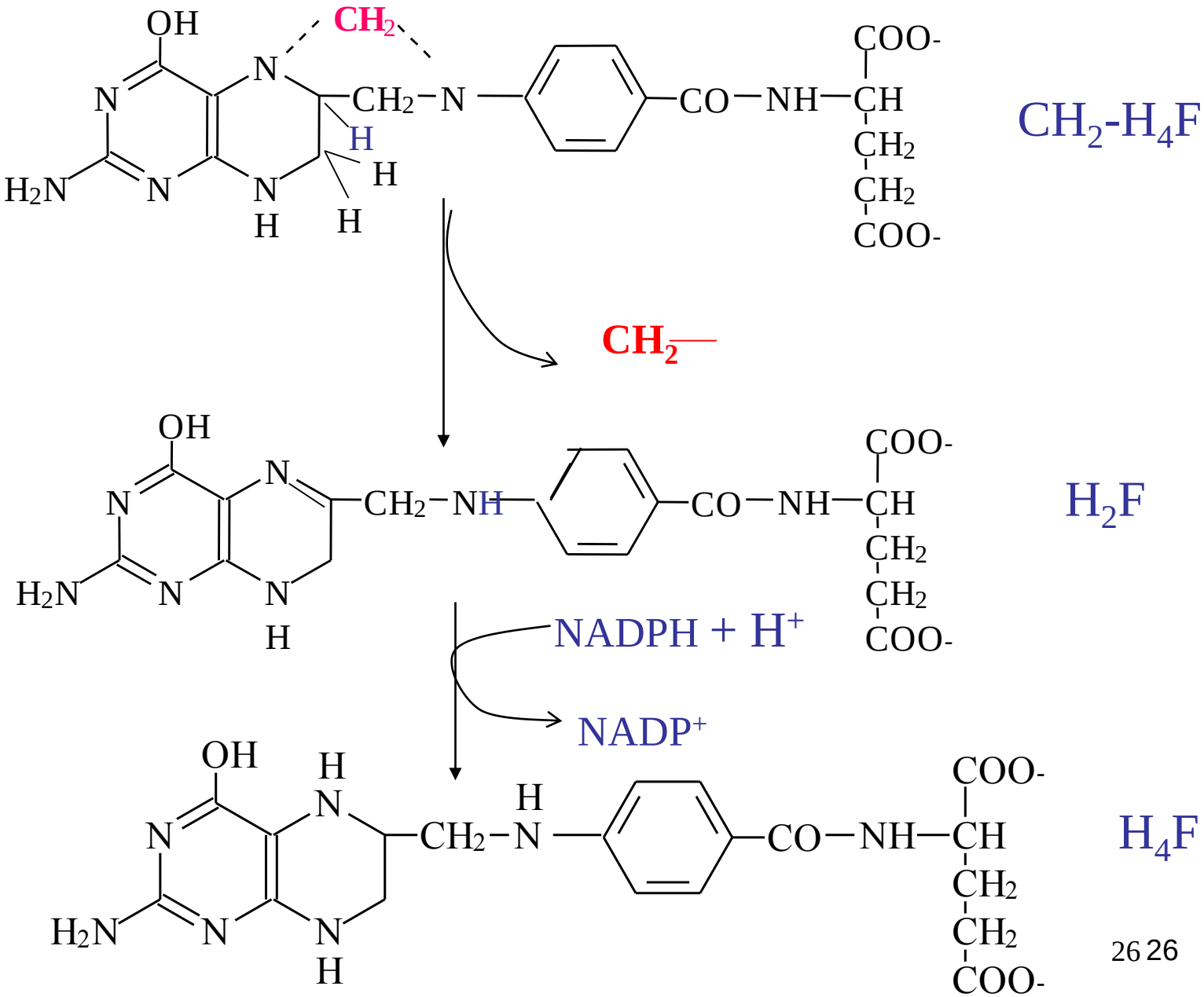
Synthesis of TMP



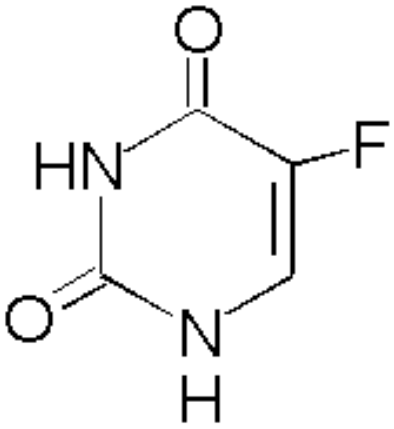
Thymidylatesynthase

(enzym dependent on folate)

Anticancer drugs


CH2
CH2-H4F
CH2
H2F
NADPH + H+
NADP+
H4F

thymidylate synthase



5-fluorouracil

The administration of fluorouracil

↓

organism conversion to
5-fluorodeoxyuridine monophosphate

↓

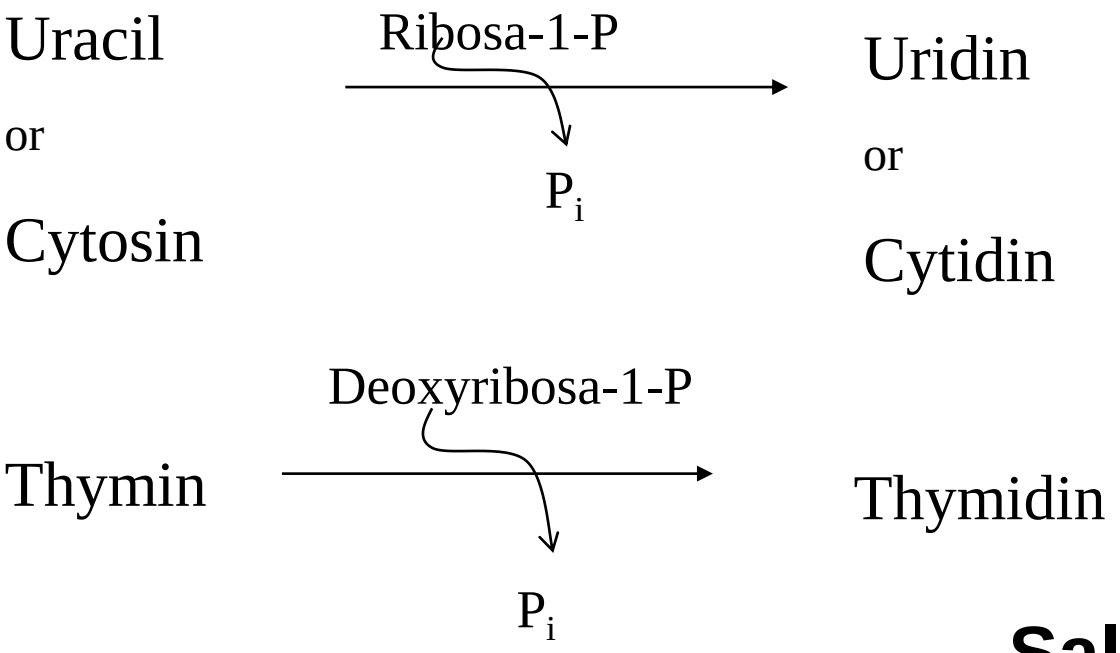
Competitive inhibition
thymidylatesynthasy

Thymidylate
synthase because it is blocked by a competitive inhibitor, which in effect prevents dTMP, resulting in a slowdown (disabling) of cell division.

The cytostatic effect of a drug

2. Synthesis of pyrimidins by *salvage pathway*

1. nucleosides



2. Kinase - phosphorylation

Salvage pathway – extrahepatal tissues

- thymidin + ATP → TMP + ADP
- cytidin + ATP → CMP + ADP
- deoxycytidin + ATP → dCMP + ADP
- uridin + ATP → UMP + ADP

Regulation of biosyntesis of pyrimidins

❑ **Allosteric:**

- Karbamoyl-P-synthetase:
  inhibition by UTP, purins nucleotides,

  activation by PRPP

❑ dependence on cell cycle

KarbamoylP-synthetase in S phase is more sensitive to activation by PRPP

Degradation of pyrimidins nucleotides

TEST

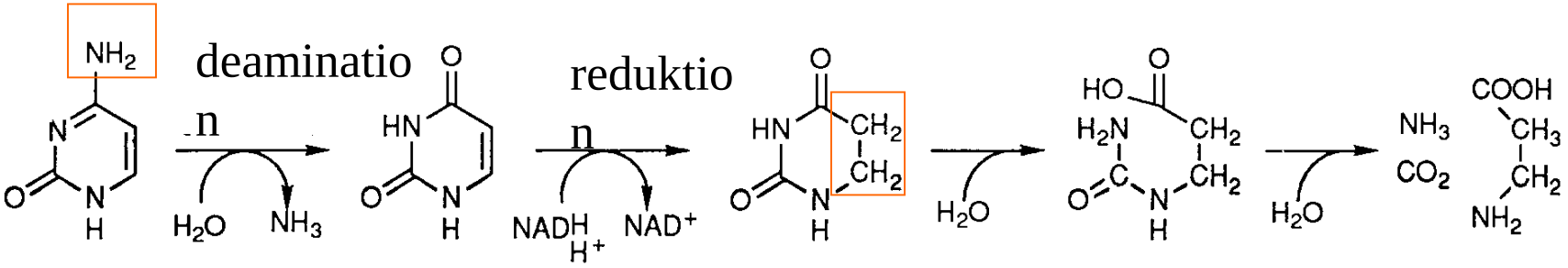
Pyrimidins – to the simple compounds – in urine
Pyrimidine base, we are able in our body break down into simpler components
STEPS:

a) Release of P
b) Release of sugar
c) Degradation of pyrimidine base

End products of cleavege of pyrimidines:

NH_3, CO_2, β-alanin, (β -aminoisobutyrate)

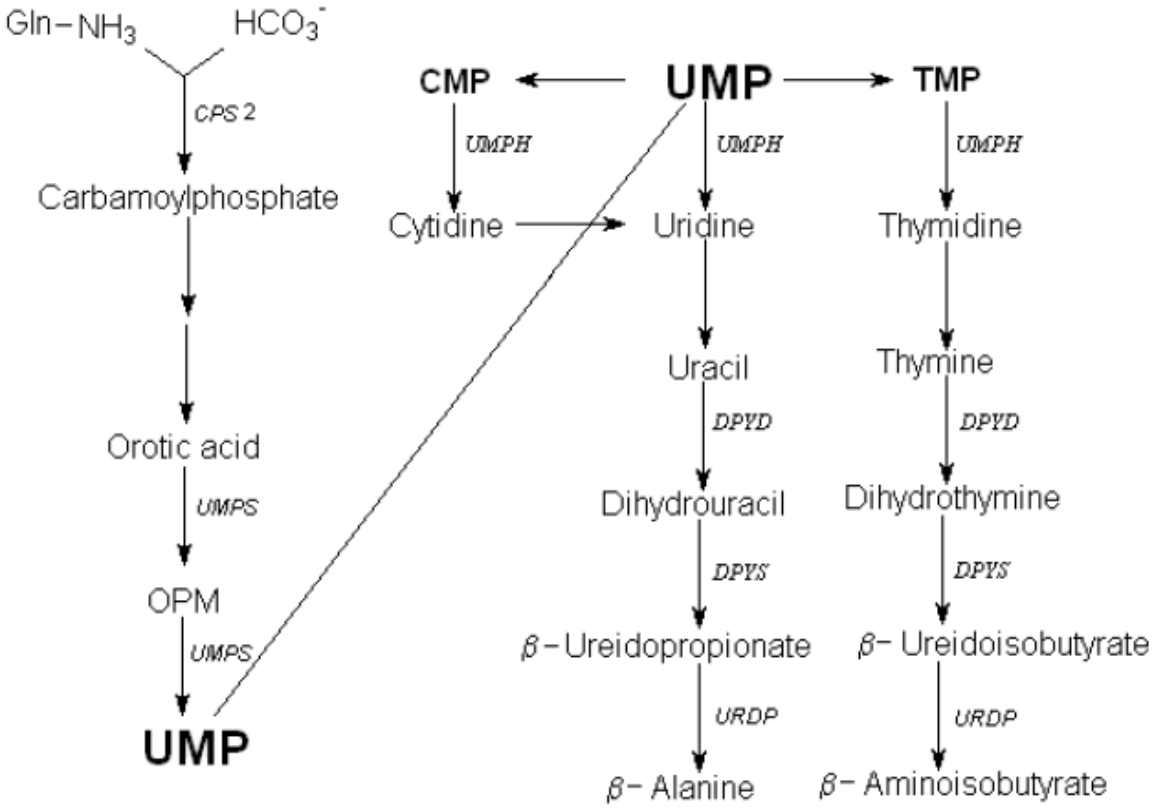
Soluble metabolist – excretion by urine



β-alanin

β-aminoisobutyrate

Inherited metabolic disorder of pyrimidine metabolism

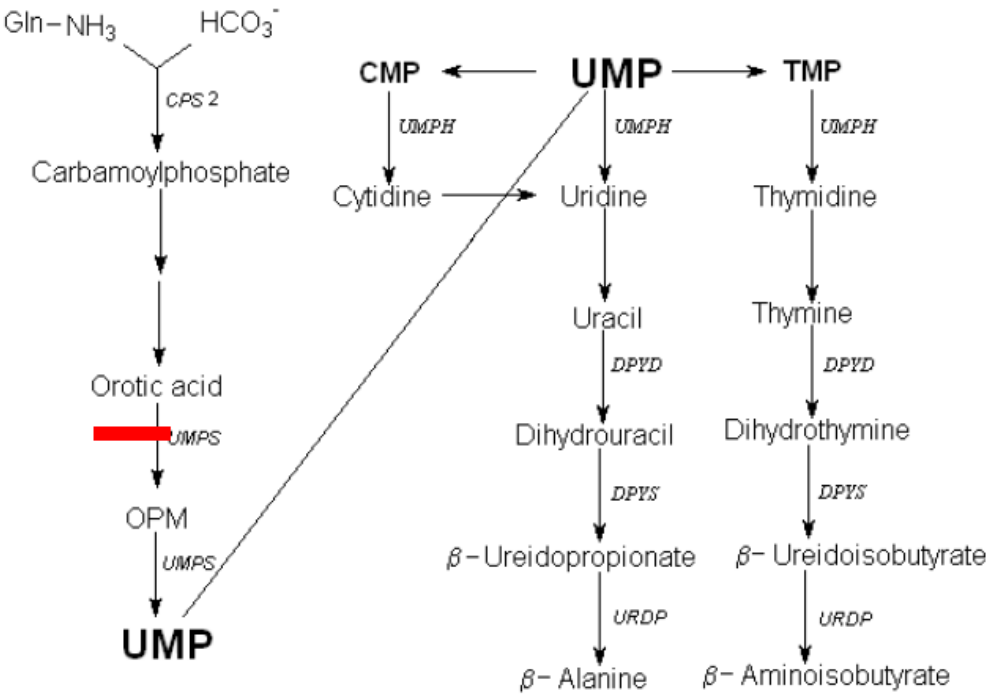


- **Orotic aciduria (UMP synthase deficiency)**
- **Dihydropyriminidase deficiency**
- **Thymidine phosphorylase deficiency MNGIE**

Inherited metabolic disorder of pyrimidine metabolism

1. uridine 5'-monophosphate synthase deficiency (orotic aciduria)

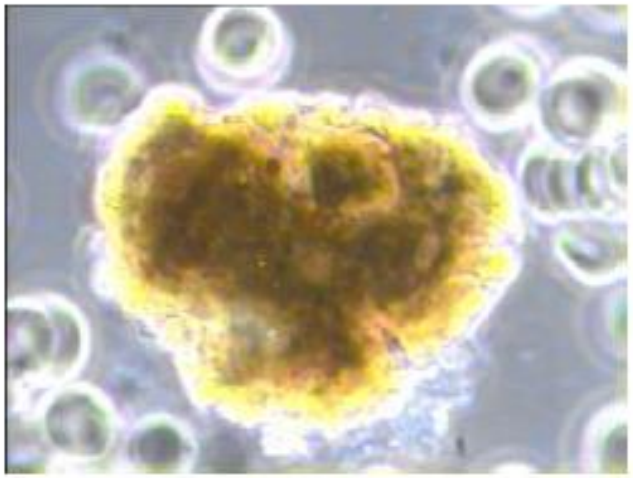
TEST



This gene encodes a **uridine 5'-monophosphate synthase**. The encoded protein is a bifunctional enzyme that catalyzes the final two steps of the de novo pyrimidine biosynthetic pathway. The first reaction is carried out by the N-terminal enzyme **orotate phosphoribosyltransferase** which converts orotic acid to orotidine-5'-monophosphate. The terminal reaction is carried out by the C-terminal enzyme OMP decarboxylase which converts orotidine-5'-monophosphate to uridine monophosphate**. Defects in this gene are the cause of hereditary orotic aciduria.**

TEST

Orotic aciduria



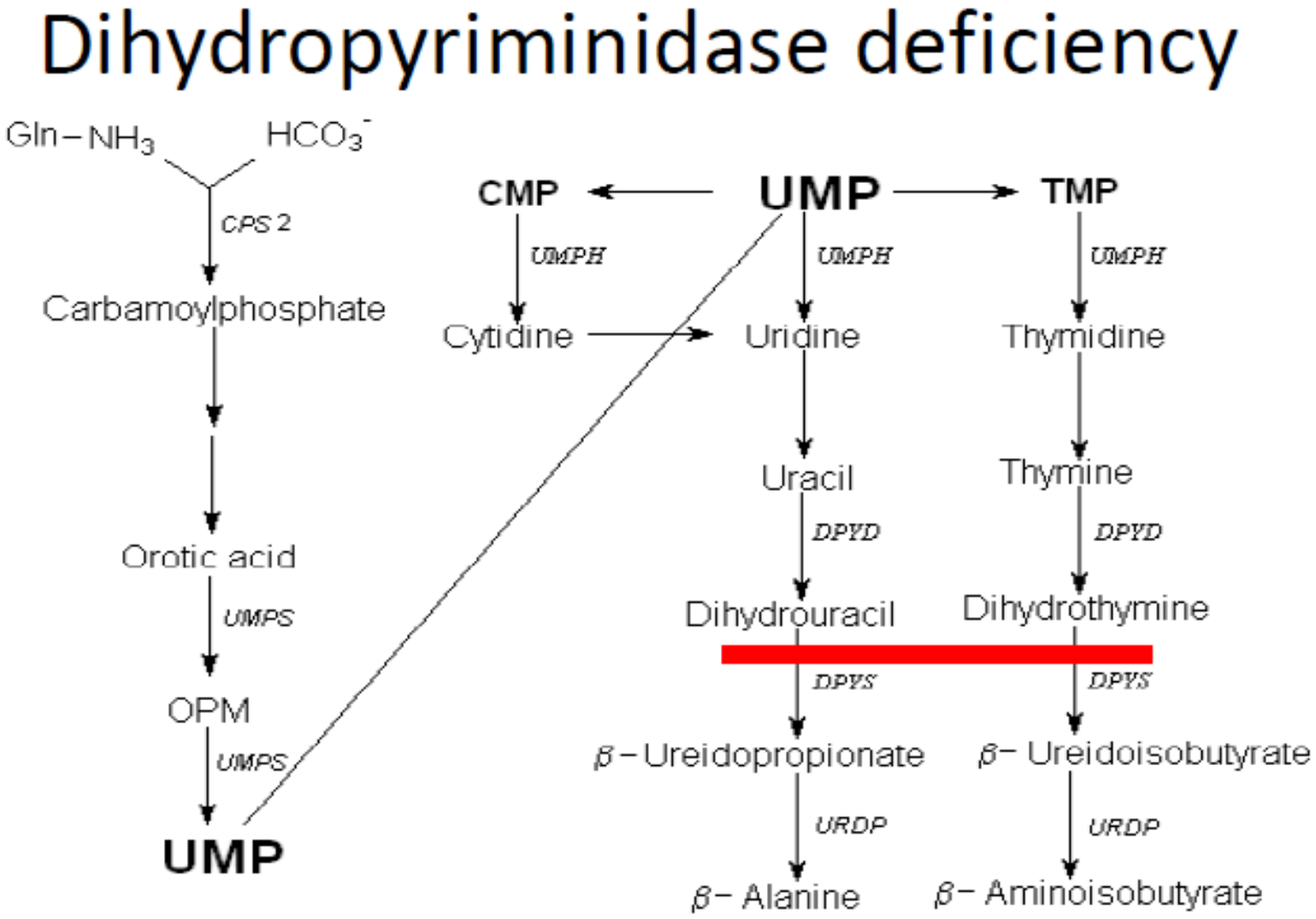
UMP synthase
uridine 5'-monophosphate synthase

- UMP synthase deficiency
- Overproduction of orotic acid - crystalluria (lithiasis is rare)
- Decreased production of pyrimidines—abnormal hematopoesis-megaloblastic anemia—PMR, FTT
- Treatment: uridine (kinase converts to UMP)

http://www.prohealthdynamics.com/images/orotic_and_sulphuric_acid_ojrx.jpg

Inherited metabolic disorder of pyrimidine metabolism

- **2. Dihydropyriminidase deficiency**



Inherited metabolic disorder of pyrimidine metabolism

- **2. Dihydropyriminidase deficiency**

DPD deficiency

(Dihydropyrimidine dehydrogenase)

Neurotrophic keratitits

- Complete deficiency
  - Childhood onset
  - PMR, hypertonus, autism
  - Mikrocephaly, dysmorphy
  - No treatment known
- Partial deficiency
  - % of common population
  - Toxicity of 5-fluorouracil (neutropenia,stomatitis, neurological symptoms)

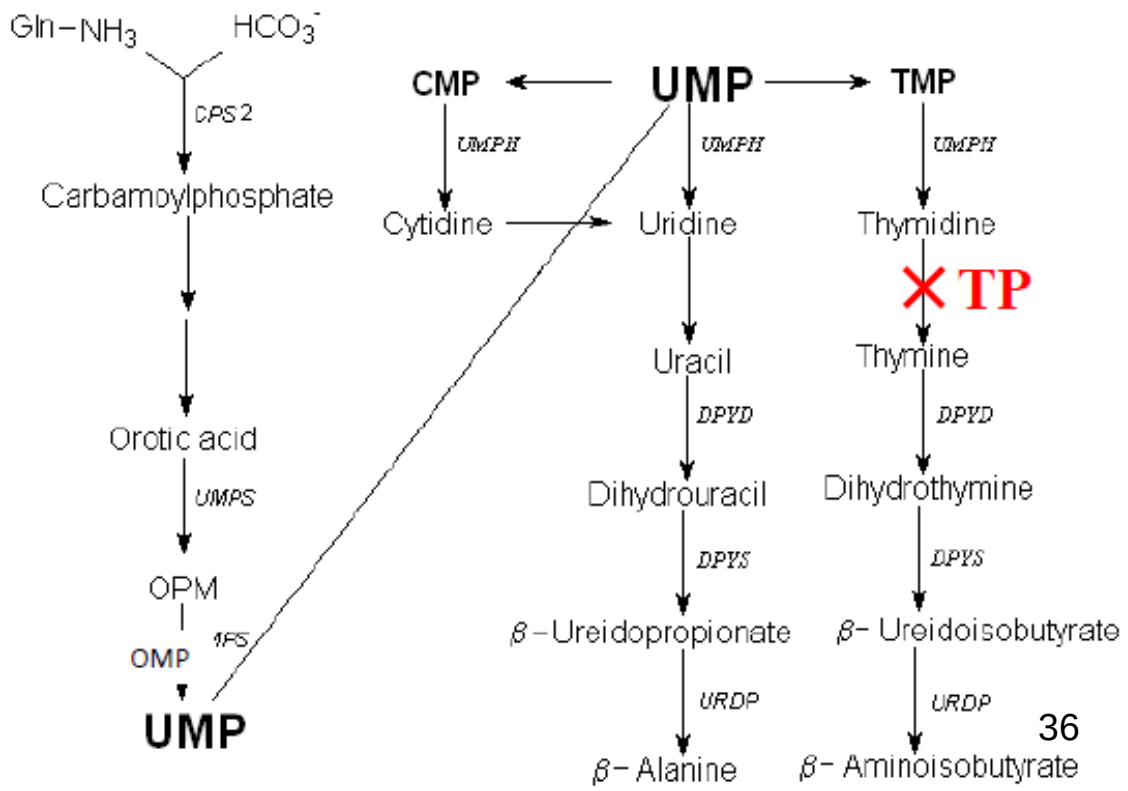
Dihydropyrimidinase (DHP) is the second enzyme in the catabolism of 5-fluorouracil (5FU), and it has been suggested that patients with a deficiency of this enzyme are at risk from developing severe 5FU-associated toxicity.

http://www.ijo.in/articles/2008/56/4/images/IndianJOphthalmol_2008_56_4_336_41422_1.jpg

Inherited metabolic disorder of pyrimidine metabolism

- 3. thymidine phosphorylase deficiency
- mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome

Deficiency of the cytosolic enzyme thymidine phosphorylase (TP) causes a multisystem disorder called mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome. Clinical symptoms are gastrointestinal dysfunction, muscle involvement and neurological deterioration.



- 3. thymidine phosphorylase deficiency
- mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome

Mitochondrial neurogastrointestinal encephalopathy syndrome (MNGIE)

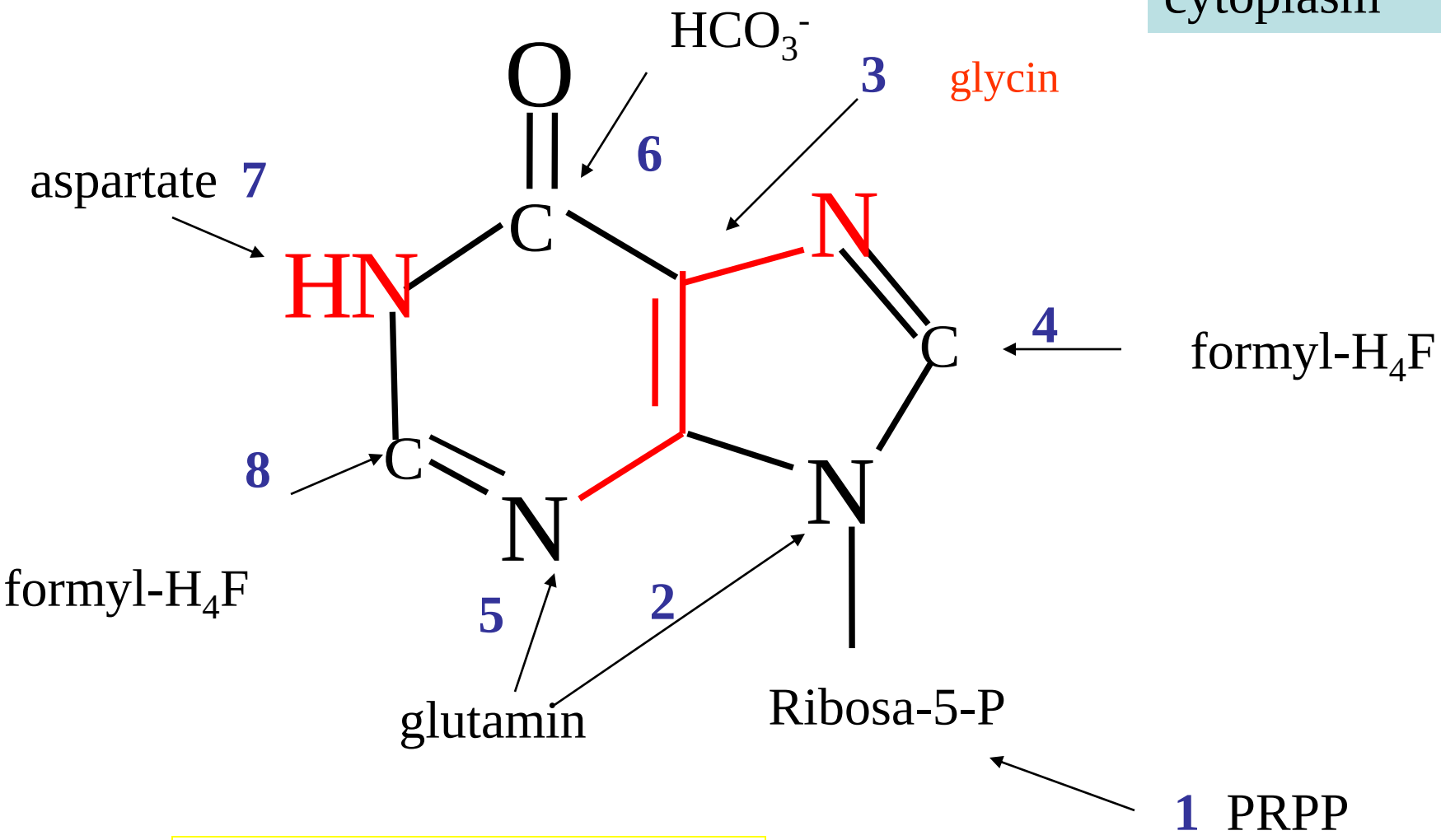
- Mitochondrial DNA depletion syndrome
- Start in 1st to 5th decade (60% pacients before 20 y)
- Progressive GIT dysmotility (vomiting, dysfagia, reflux, diarhoe/obstipation)
- Progressive cachexia
- Neurological abnormalities-demylinization of peripheral nerves, parestesias, hypacusis, ptosis
- leukoencephalopathy

Biosyntesis of purins

(multienzym complex)

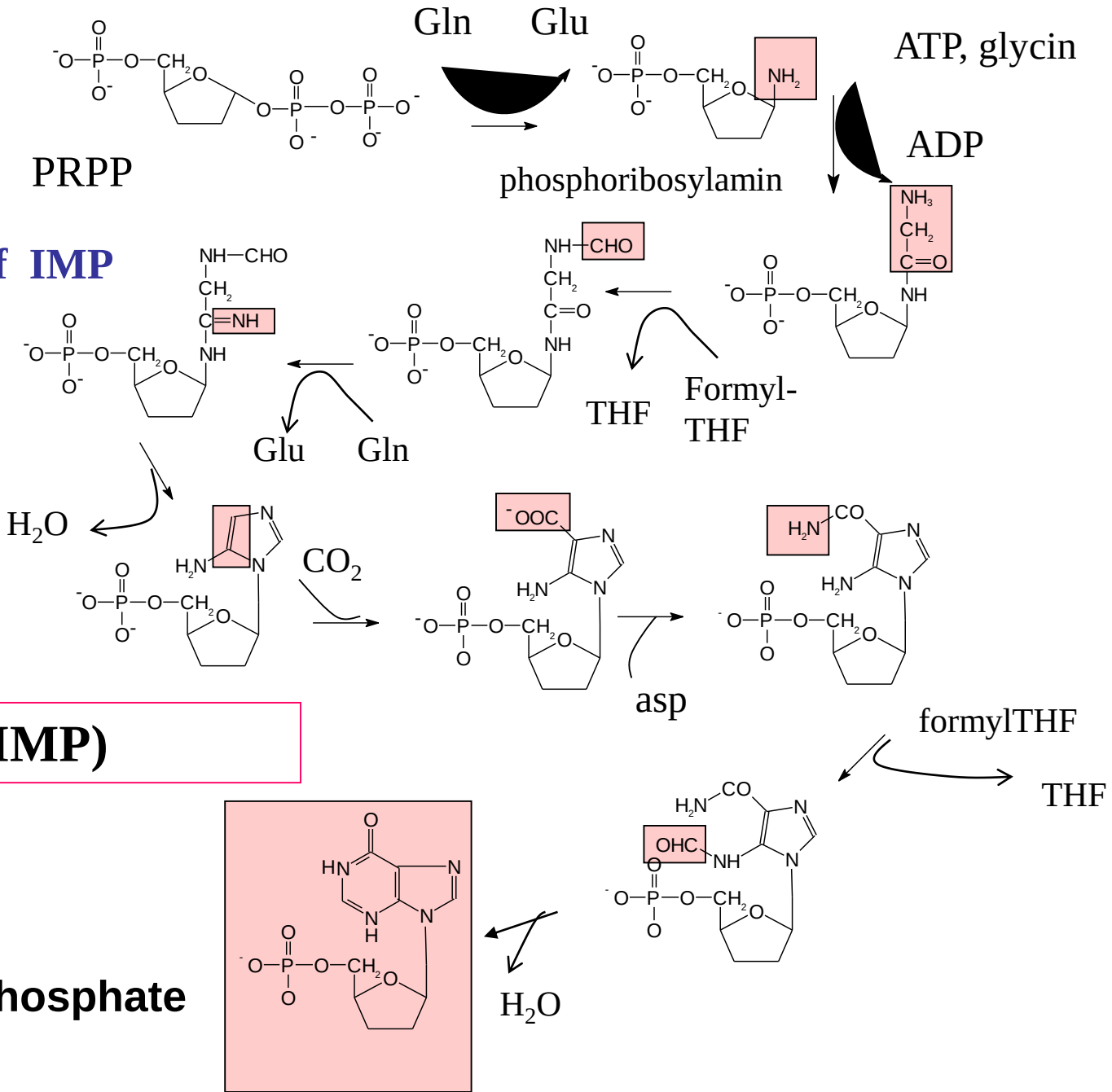
liver

cytoplasm



Inosin-5-P (IMP)

Biosyntesis of purins



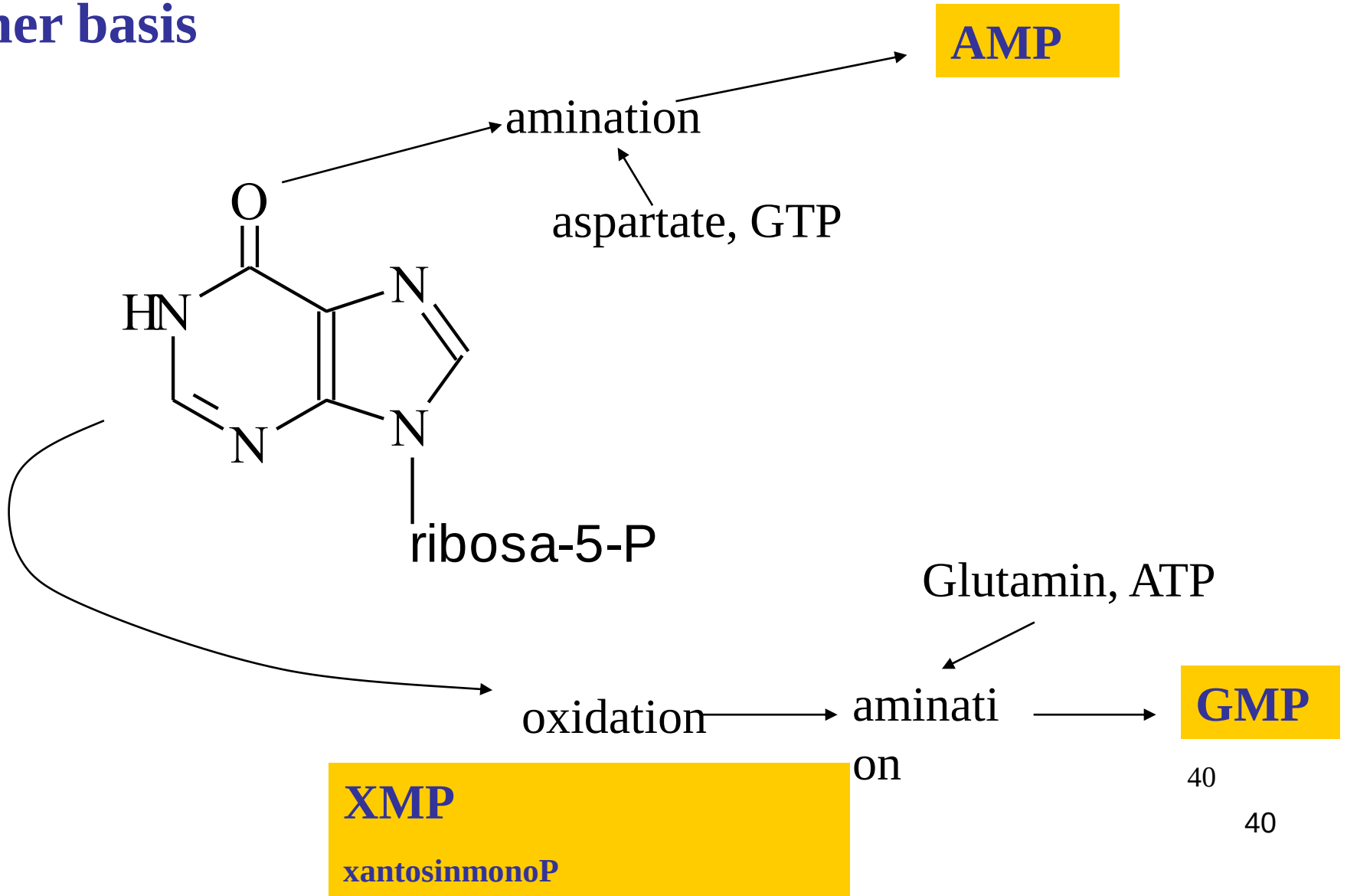
Biosyntesis of IMP

Inosin-5-P (IMP)

inosinmonophosphate

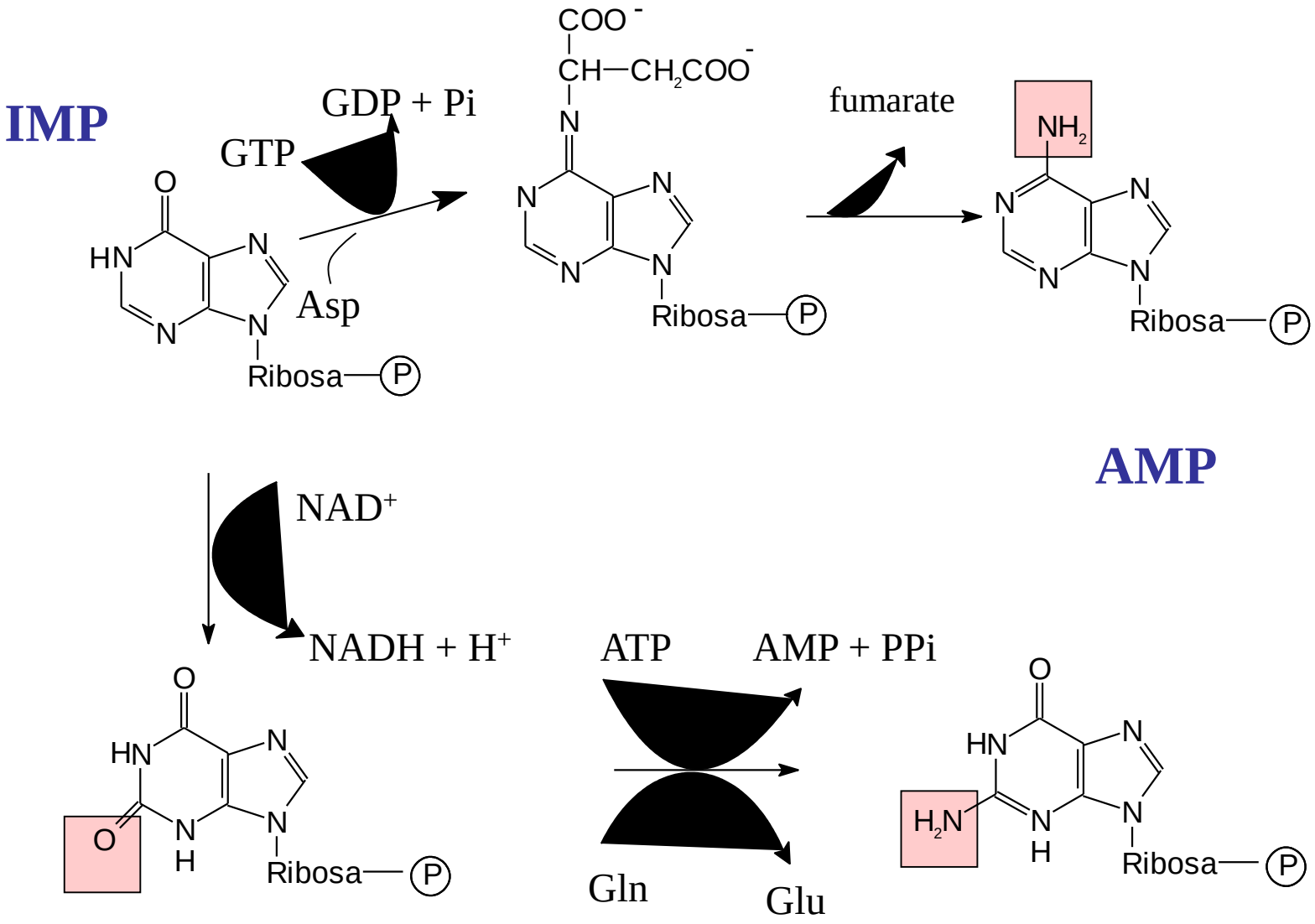
Biosyntesis of purins

Inosin-5-P (IMP)-Initial substance for synthesis of other basis



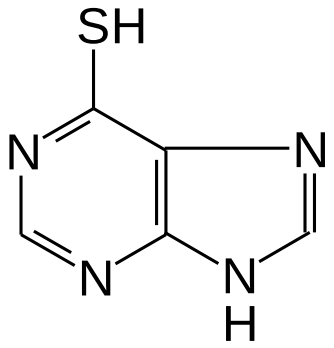
40

Syntesis of AMP a GM



Inhibitors of syntesis of purins (cytostatics)

- inhibitors **dihydrofolate reductase**
- analogy glutamin (azaserin)
- 6-merkaptopurin- inhibition of change IMP to AMP and GMP



merkaptopurin

Syntesis of purins by salvage pathway

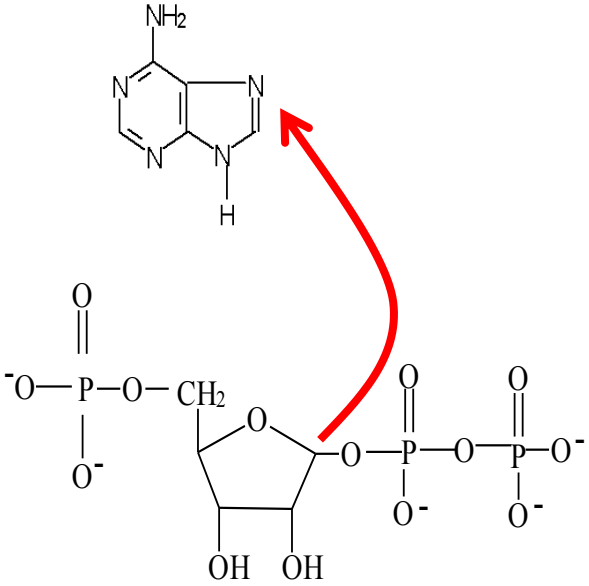
Extrahepatal tissue

phosphoribosyltransferase

Purin + PRPP → purinnukleotidmonoP + PP

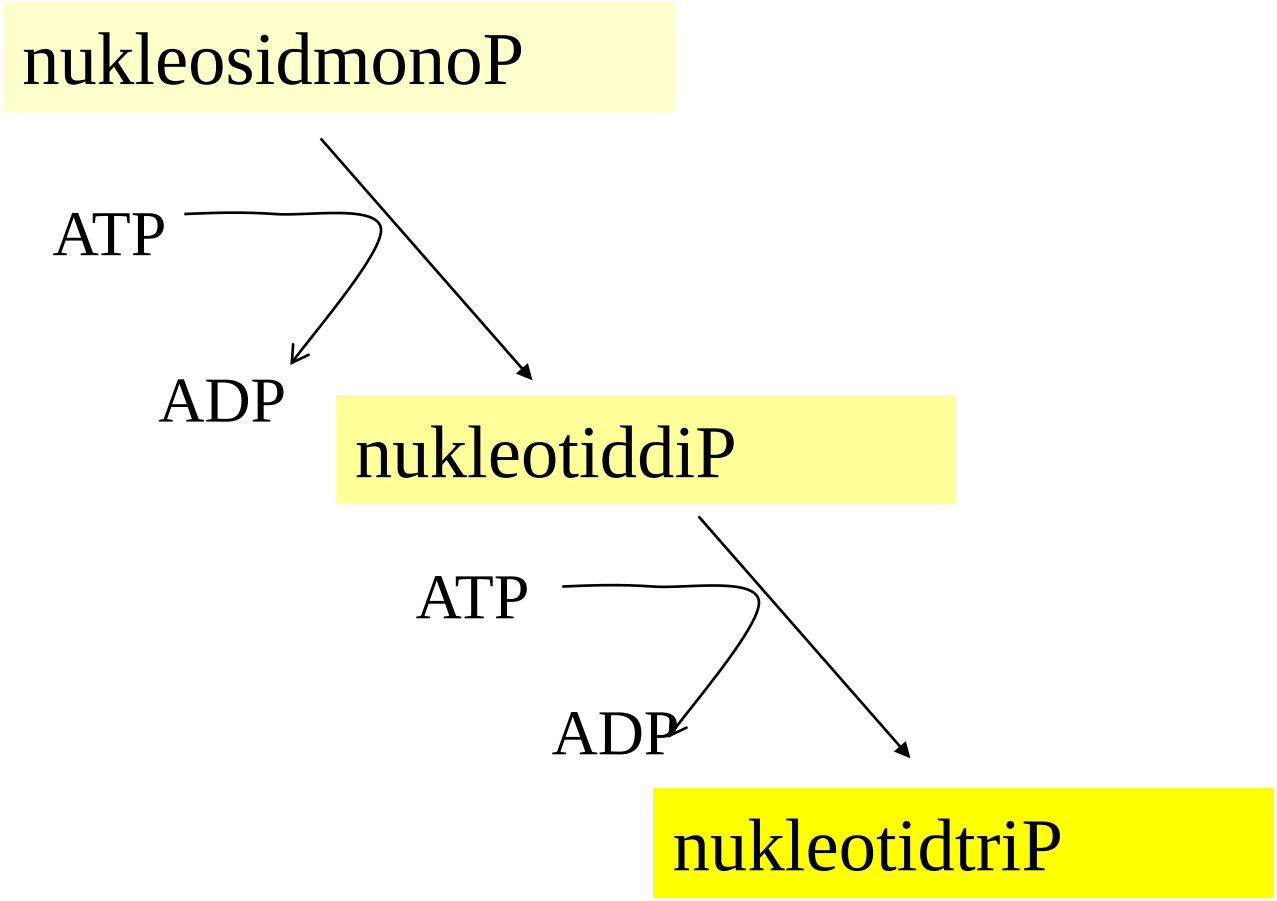
Recyclation of purins

phosphoribosyltransferase



AMP
adeninphosphoribosyltransfera
se

Syntesis of nukleotiddiP and triP



Regulation of biosyntesis of purins

1.

- concentration of PRPP

Speed of use

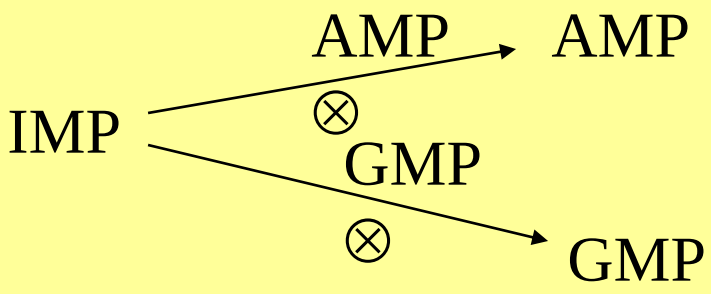
Speed of synthesis

Speed of degradation

2.

- inhibice PRPP-glutamylamidotransferase by AMP and GMP (end products)

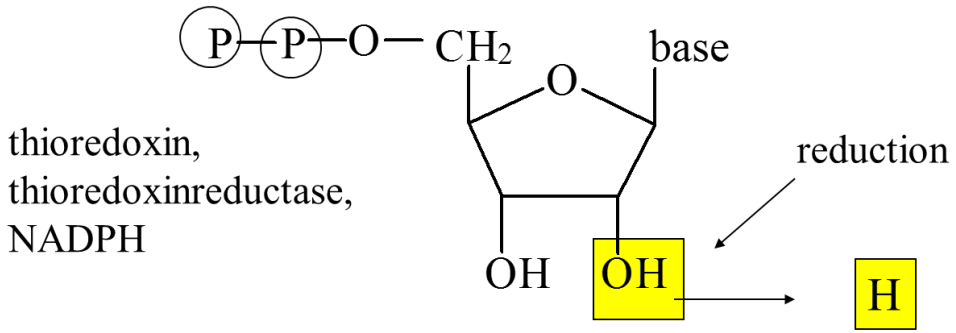
3.



Nucleotiddiphosphate → deoxynucleotiddiphosphate

2-deoxyribonucleotides

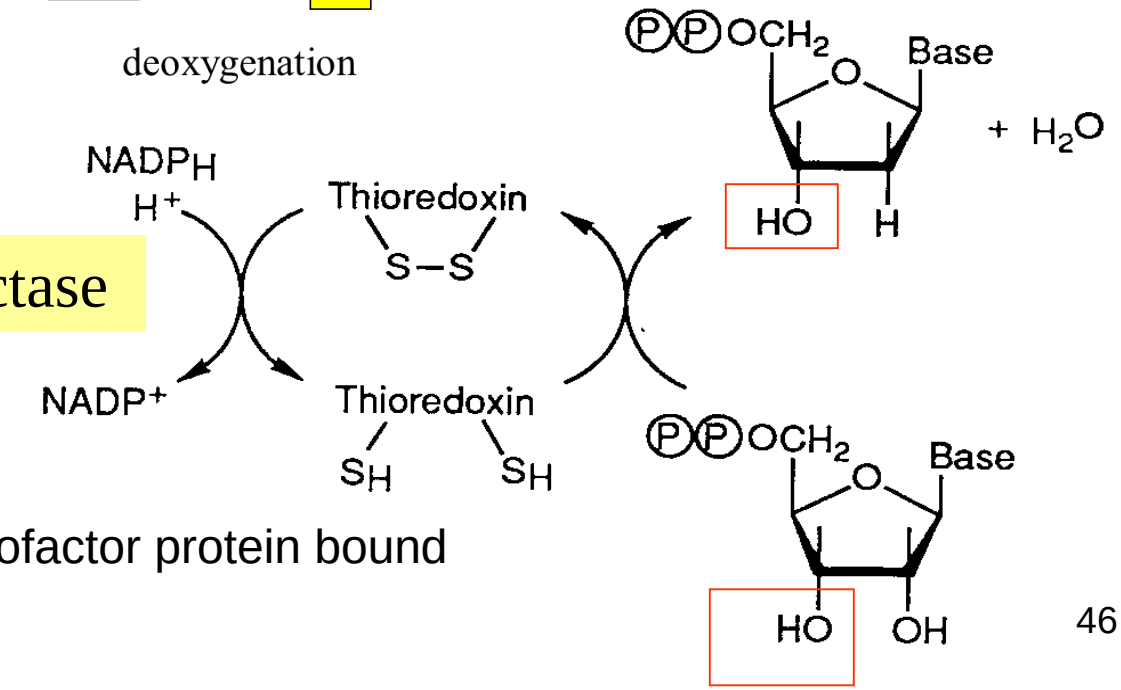
NucleotiddiP → 2-deoxynucleotiddiP



Thioredoxinreductase - Se

deoxygenation

ribonucleotidreductase



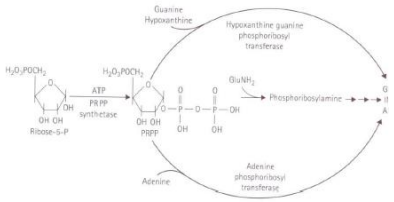
cofactor protein bound

TEST

Inherited metabolic disorder of pyrimidine/purine metabolism

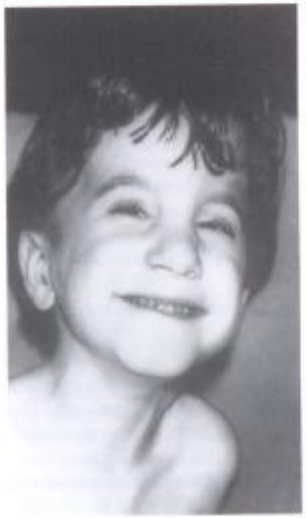
- 4. PPRP synthase superactivity

PPRP synthase supera



William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

PPRP synthase superactivity



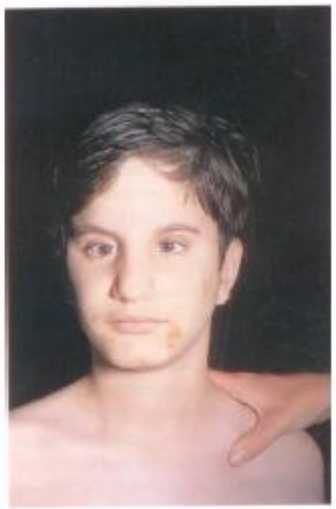


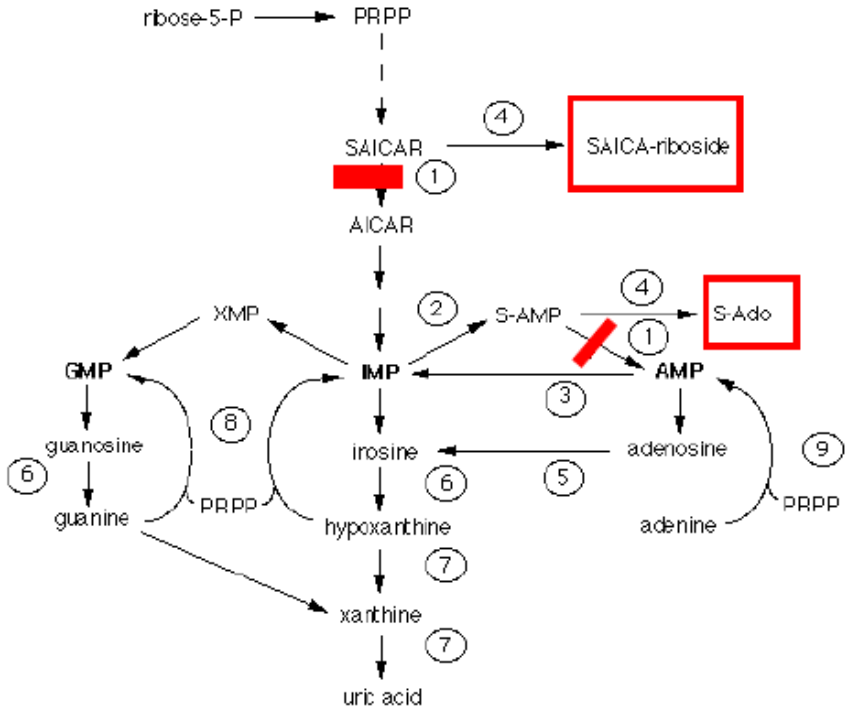
Figure 67.2 S.M., a 3-year-old with an abnormal PRPP synthetase. S.M., at 14 years-of-age. The odd grimace was characteristic. (Reprinted with permission from the Journal of Pediatrics [5]).

- X-linked diseases
- Increased activity (activating mutation)
- Hyperuricemia, gout
- Neurological impairment (unclear)
- Deafness
- PMR, autismic-like behaviour

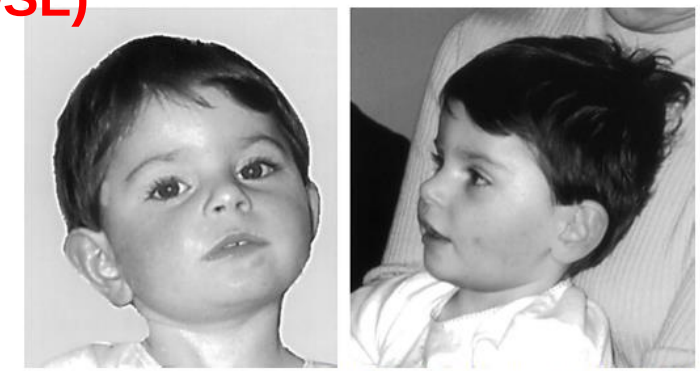
William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

Inherited metabolic disorder of purine metabolism

- **1.Adenylosuccinate lyase deficiency (ADSL)**



Facial dysmorfia in ADSL deficiency



Holder-Espinasse M et al. J Med Genet 2002;39:440-442

brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, long, smooth philtrum, and thin upper lip.

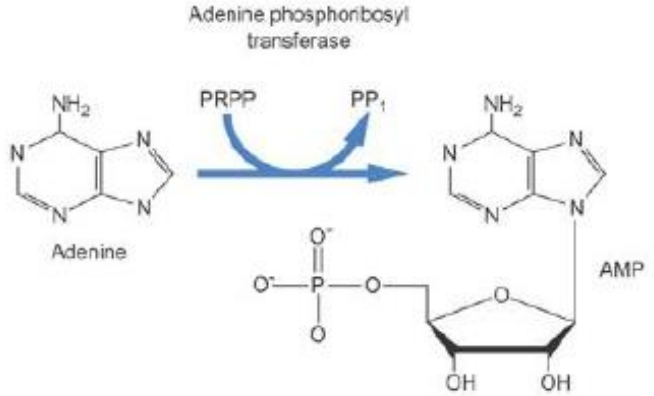
ADSL deficiency

- AR inheritance
- SAICAR toxic for neurons (impaired utilization of glucose), S-Ado may be protective
- Uncertain role of purine depletion (not confirmed)
- Variable neurological findings (neonatal epilepsy,encephalopathy, stereotypic movement, ataxia, PMR, seizures, hypotonia)
- Autistic like behaviour
- Facial dysmorphy in some patients
- Treatment unknown

TEST

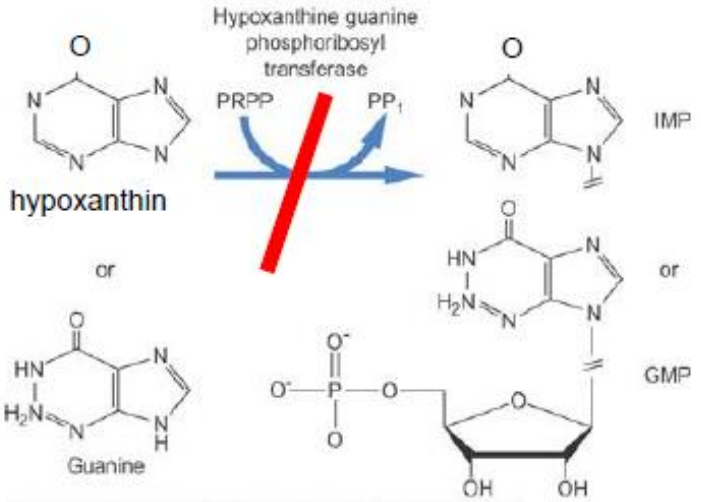
Inherited metabolic disorder of purine metabolism

- **1. HGPRT deficiency**



TEST

- X-linked disease
- Various forms: Lesch-Nyhan syndrome, partial deficiency (Kelly-Seegmiller syndrome)
- Hyperuricemia (the only treatable feature of disease)
- Neurological abnormalities: automutilation, aggresivity, PMR, seizures, gait disturbances
- Various theories for neurological anormalities incl. purines depletion, possibly secondary dopamin synthesis defect (decreased DOPA-decarboxylase)



HGPRT deficiency

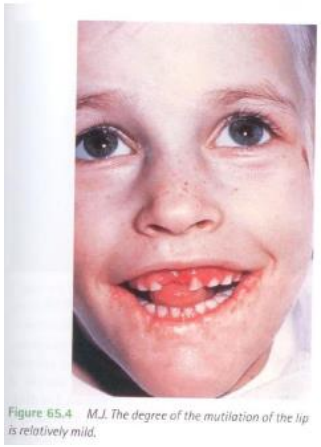


Figure 65.4 M.J. The degree of the mutilation of the lip is relatively mild.

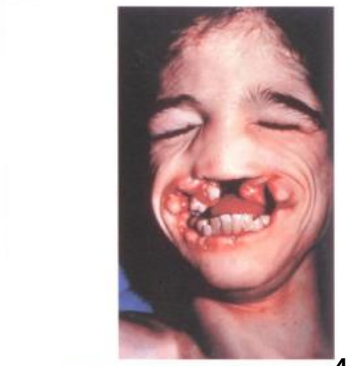
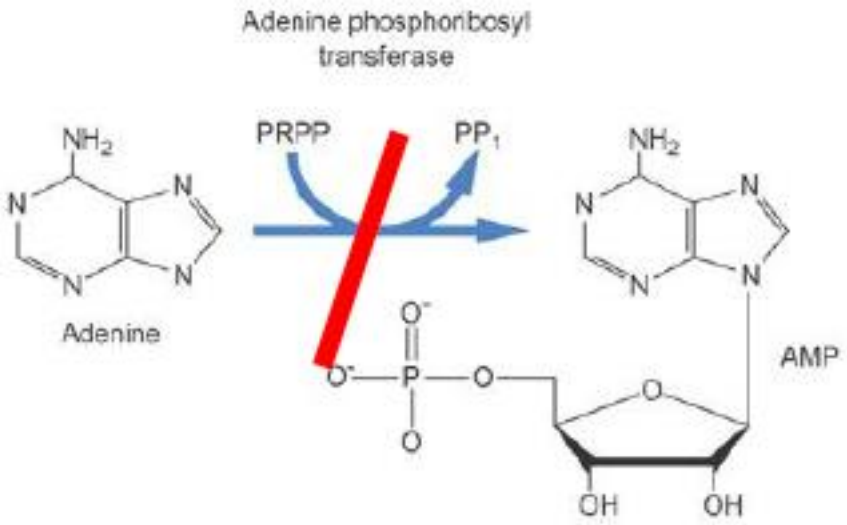


Figure 65.5 J.J., a 14-year-old boy, illustrating an extreme degree of mutilation around the face.

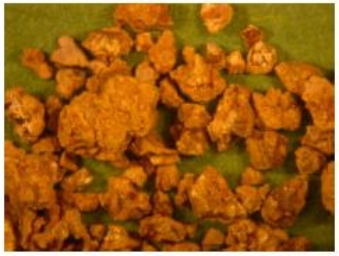
Inherited metabolic disorder of purine metabolism

- **2. Adenine phosphoryl transferase**
- **deficiency**

Adenine phosphoryl transferase



APRT deficiency



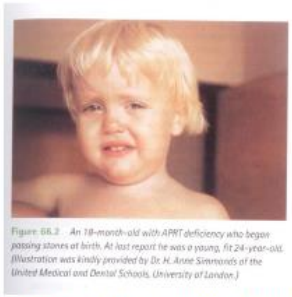


Figure. 68.2 . An 18-month-old with APRT deficiency who began passing stones at birth. At last report he was a young, fit 24-year-old. (Illustration was kindly provided by Dr. H. Anne Simmonds of the United Medical and Dental Schools, University of London.)

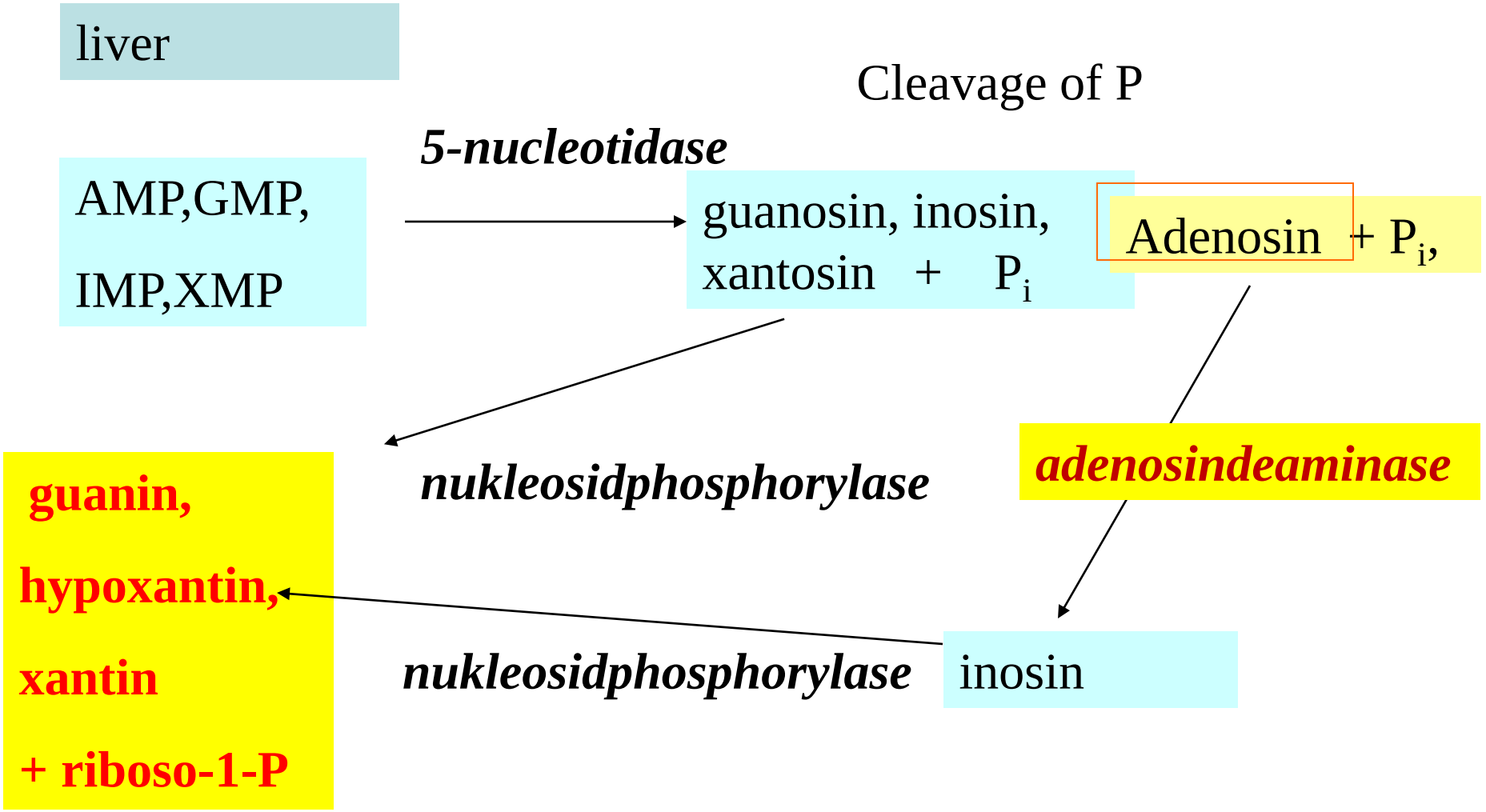
- Production of 2,8-dihydroxyadeninu
- Very low solubility: 3 mg/L (vs. uric acid 150 mg/L)
- Crystalluria (spots on diaper); renal colic, dysuria, acute renal failure
- Treatment: allopurinol, dietary restriction, high fluid intake

William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

http://www.herringlab.com/photos/2/55-2,8-dihydroxyadenine97-P3.jpg

TEST

Degradation of purines



Inherited metabolic disorder of purine metabolism

- **3. adenosine deaminase deficiency**

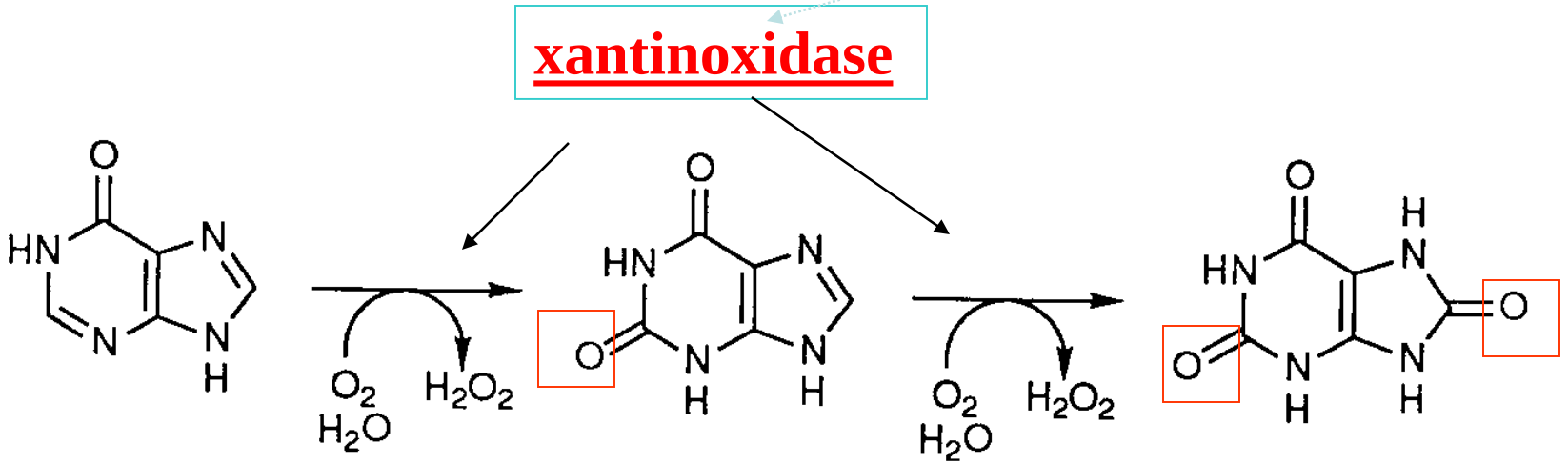
Enzyme deficiency leads to the accumulation of toxic deoxyadenosine, which affects immunocompetent cells
One of the causes of severe combined immunodeficiency (severe combined immunodeficiency disease-SCID).

ADA – adenosine deaminase deficiency

- SCID – severe combined immunodeficiency
- Failure to thrive, progressive neurological symptoms (movement disoders, spasticity)
- Lymphopenia, hypogammaglobulinaemia
- Elevated adenosine
- Therapy – bone marrow transplantation
  - enzyme replacement therapy
  - gene therapy

Degradation of purins

Inhibition by allopurinolem



hypoxantin

xantin

Uric acids

guanase

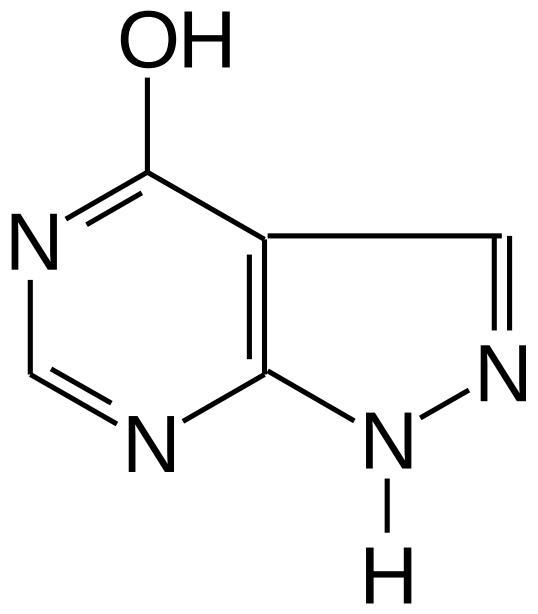
guanin

end metabolit primate, ….. (400-600 mg /den)

Xanthine Oxidase

- A homodimeric protein
- Contains electron transfer proteins
  - FAD
  - Mo-pterin complex in +4 or +6 state
  - Two 2Fe-2S clusters
- Transfers electrons to $O_2 \rightarrow H_2O_2$
  - H_2O_2 is toxic
  - Disproportionated to H_2O and O_2 by catalase

Allopurinol – competitive inhibitor of xantinoxidase

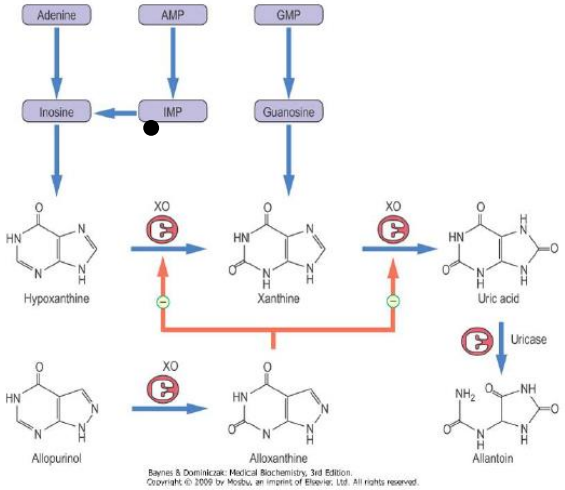


Gout: allopurinol inhibits the oxidation of hypoxanthine to xanthine

hypoxanthine is more soluble and more readily excreted

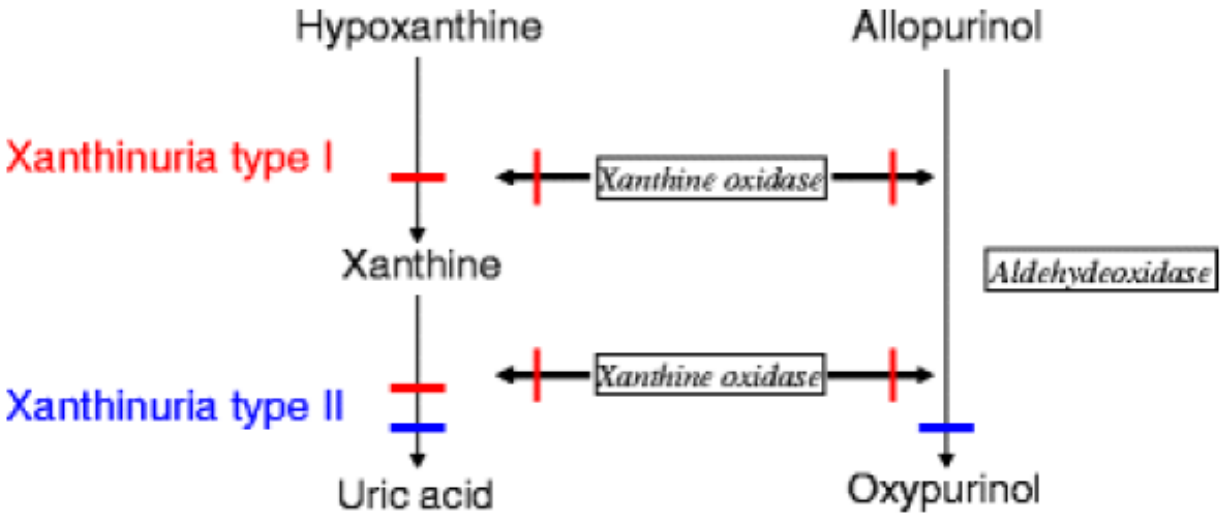
Allopurinol (structural analog of hypoxanthine) is converted to the xanthine oxypurinol
(= alloxanthin), which binds tightly to the enzyme and prevents its further catalytic activity.
Allopurinol is the " suicide " inhibitor of xanthine oxidase , reduces the concentration of uric
acid in the blood and thus the other fluids (eg . synovial) ; amount of secreted urate
decreases excretion rises somewhat better soluble hypoxanthine and xanthine . moreover
final metabolite is not a single product but three , so decreasing the risk of excess constants
solubility that would be the case for one of the final product .

Inherited metabolic disorder of purine metabolism



- **4. Xanthinuria**

lack of enzyme, xantin oxidase

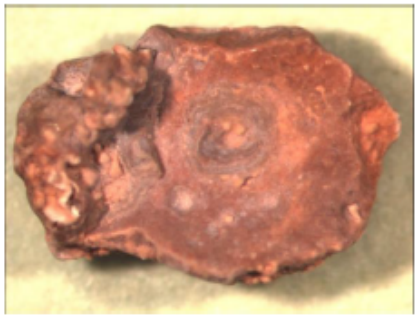


Arikyants N. et al. Pediatr Nephrol 2007

In **type I**, the isolated XO deficiency leads to a block in UA production and accumulation of xanthine and hypoxanthine whereas the conversion of allopurinol to oxypurinol is unaffected. In **type II** the combined deficiency of the XO and AO complex impairs the production of UA and oxypurinol.

TEST

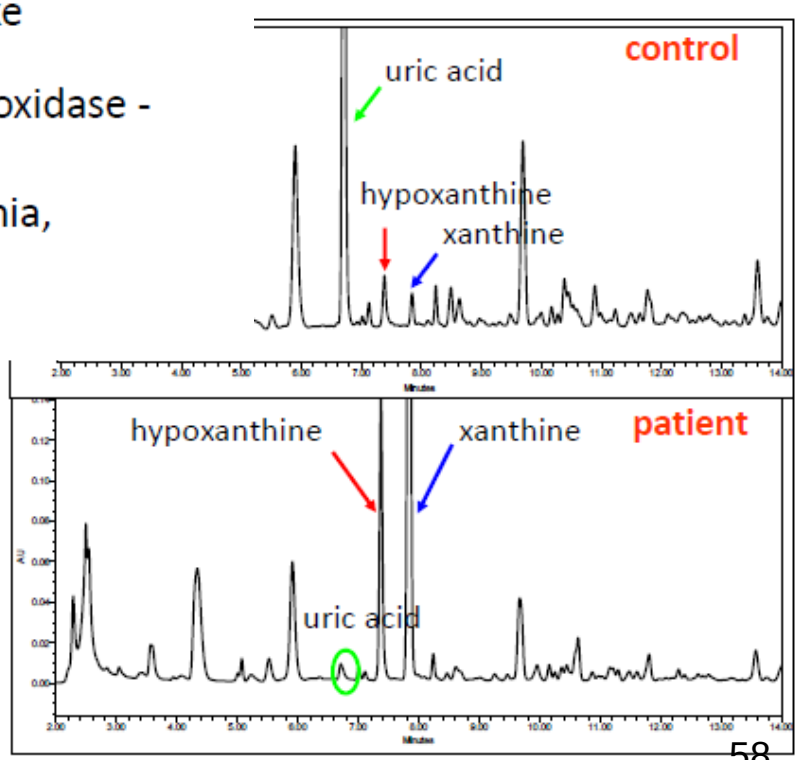
Xanthinuria



- Isolated XO deficiency
- Urolithiasis and occasionally myopathy due to xanthin crystalls, arthropathy
- 50% asymptomatic
- S and U- uric acid decreased!!!!!
- Treatment: fluid intake

Molybdene is cofactor for XO and also for sulphite oxidase - combined XO/SO deficiency (neonatal neurological abnormalities – epilepsy, encephalopathy, hypertonia, death in early childhood)

http://www.tamilspider.com/attachments/Resources/3322-71129-xanthine.jpg



HPLC chromatogram močových P/P

Inherited metabolic disorder of purine metabolism

- **5. Gout**
- **enzyme deficiency HGPRT**
- **enzyme deficiency glucose-6-phosphatase**
- **increased enzyme activity PRPPsynthetase**

GOUT (hyperuricemia)

increasing of production and decreasing of excretion of uric acid

- defect in salwa pathway

⟶ (deficit hypoxantin-guaninphosphoribosyltransferase) (HGPRT)

hypoxantin + PRPP ⊗ IMP + PP ⟶

- decrease of clearance in kidney

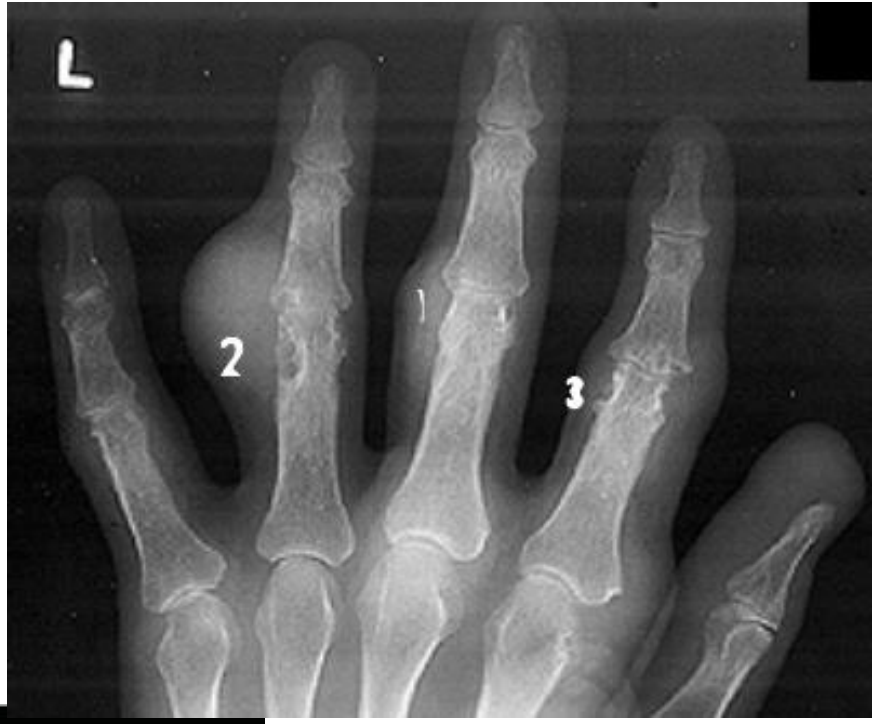
⇩

Keeping of crystals of UA in tissue

Gout

- **Impaired excretion or overproduction of uric acid**
- Uric acid crystals precipitate into joints (Gouty Arthritis), kidneys, ureters (stones)
- Lead impairs uric acid excretion – lead poisoning from pewter drinking goblets
  - Fall of Roman Empire?
- **Xanthine oxidase** inhibitors inhibit production of uric acid, and treat gout
- **Allopurinol treatment** – hypoxanthine analog that binds to Xanthine Oxidase to decrease uric acid production

Disorder	Defect	Nature of Defect	Comments
Gout	PRPP synthetase	increased enzyme activity	hyperuricemia
Gout	HGPRT[a]	enzyme deficiency	hyperuricemia
Gout	glucose-6-phosphatase	enzyme deficiency	hyperuricemia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2
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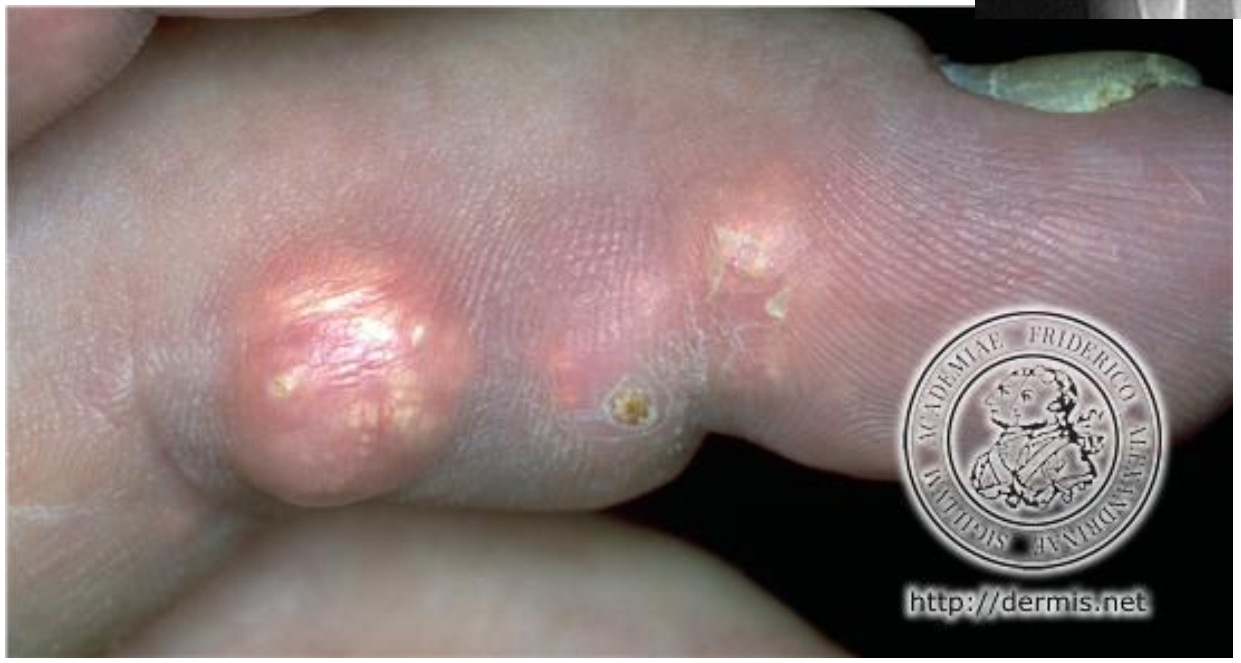
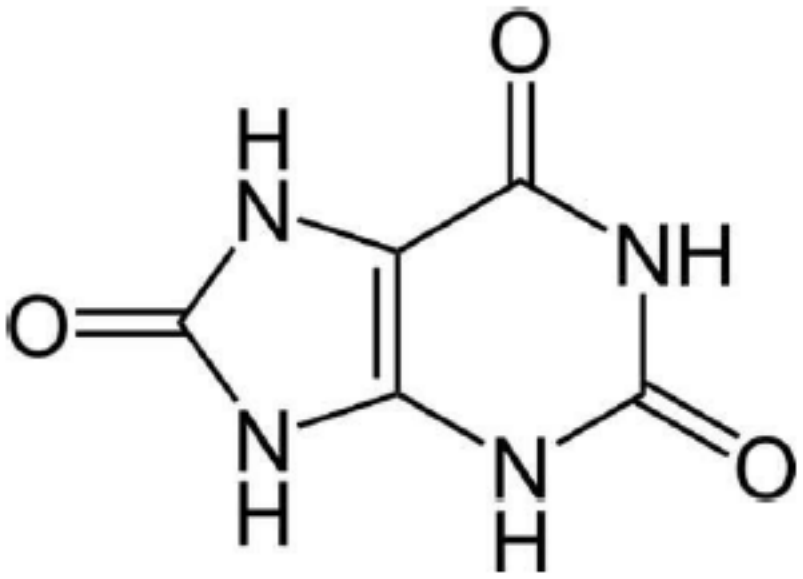
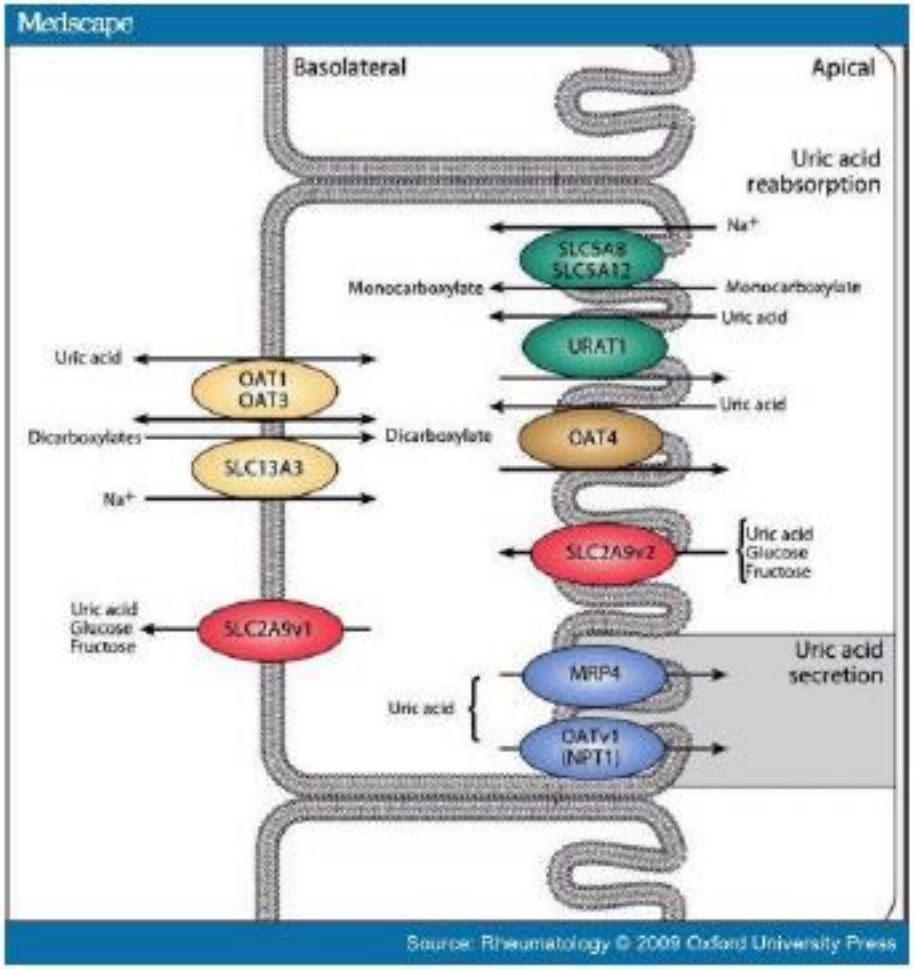

http://dermis.net

Uric acid



- Trioxopurine
- Keto/enol
- Physiological pH: monosodium urate
- Limited solubility
- Free radical scaveneger

Renal reabsorption and secretion



- Elevated uric acid in blood
- Low excretion fraction of uric acid
- Normal purine and pyrimidine profile

http://img.medscape.com/article/705/178/705178-fig1.jpg

Hyperuricemia is an abnormally high level of uric acid in the blood. In the pH conditions of body fluid, uric acid exists largely as urate, the ion form.[1][2] The amount of urate in the body depends on the balance between the amount of purines eaten in food, the amount of urate synthesised within the body (e.g., through cell turnover), and the amount of urate that is excreted in urine or through the gastrointestinal tract.[2] In humans, the upper end of the normal range is 360 μmol/L (6 mg/dL) for women and 400 μmol/L (6.8 mg/dL) for men.

Inherited metabolic disorders of purine metabolism

Lesch-Nyhan syndrome	HGPRT	lack of enzyme	see above

6. Lesch-Nyhan Syndrome

TEST

- A defect in production or activity of HGPRT
  - Causes increased level of Hypoxanthine and Guanine (→↑ in degradation to uric acid)
- Also,PRPP accumulates
  - stimulates production of purine nucleotides (and thereby increases their degradation)
- Causes gout-like symptoms, but also neurological symptoms → spasticity, aggressiveness, self-mutilation
- First neuropsychiatric abnormality that was attributed to a single enzyme

Lesch–Nyhan syndrome (**LNS**),

also known as **Nyhan's syndrome**, **Kelley-Seegmiller syndrome**, and **juvenile gout**,[1] is a rare inherited disorder caused by a deficiency of the enzyme **hypoxanthine-guanine phosphoribosyltransferase (HGPRT),** produced by mutations in the HPRT gene located on the X chromosome. LNS affects about one in 380,000 live births.[2] The disorder was first recognized and clinically characterized by medical student Michael Lesch and his mentor, pediatrician William Nyhan, who published their findings in 1964.[3]
The HGPRT deficiency causes a build-up of uric acid in all body fluids. This results in both hyperuricemia and hyperuricosuria, associated with severe gout and kidney problems.

Inherited metabolic disorders of purine metabolism

Disorder	Defect	Nature of Defect	Comments
Gout	PRPP synthetase	increased enzyme activity	hyperuricemia
Gout	HGPRT[a]	enzyme deficiency	hyperuricemia
Gout	glucose-6-phosphatase	enzyme deficiency	hyperuricemia
Lesch-Nyhan syndrome	HGPRT	lack of enzyme	see above
SCID	ADA[b]	lack of enzyme	see above
Immunodeficiency	PNP[c]	lack of enzyme	see above
Renal lithiasis	APRT[d]	lack of enzyme	2,8-dihydroxyadenine, renal lithiasis
Xanthinuria	Xanthine oxidase	lack of enzyme	hypouricemia and xanthine renal lithiasis
von Gierke disease	Glucose-6-phosphatase	enzyme deficiency	see above

[a] hypoxanthine-guanine phosphoribosyltransferase
[b] adenosine deaminase
[c] purine nucleotide phosphorylase

d adenosine phosphoribosyltransferase

TEST