Disorders of metabolism
1. purine and pyrimidine
2. porphyria
3. ketogenesis/ketolysis
4. Biochemistry of starvation

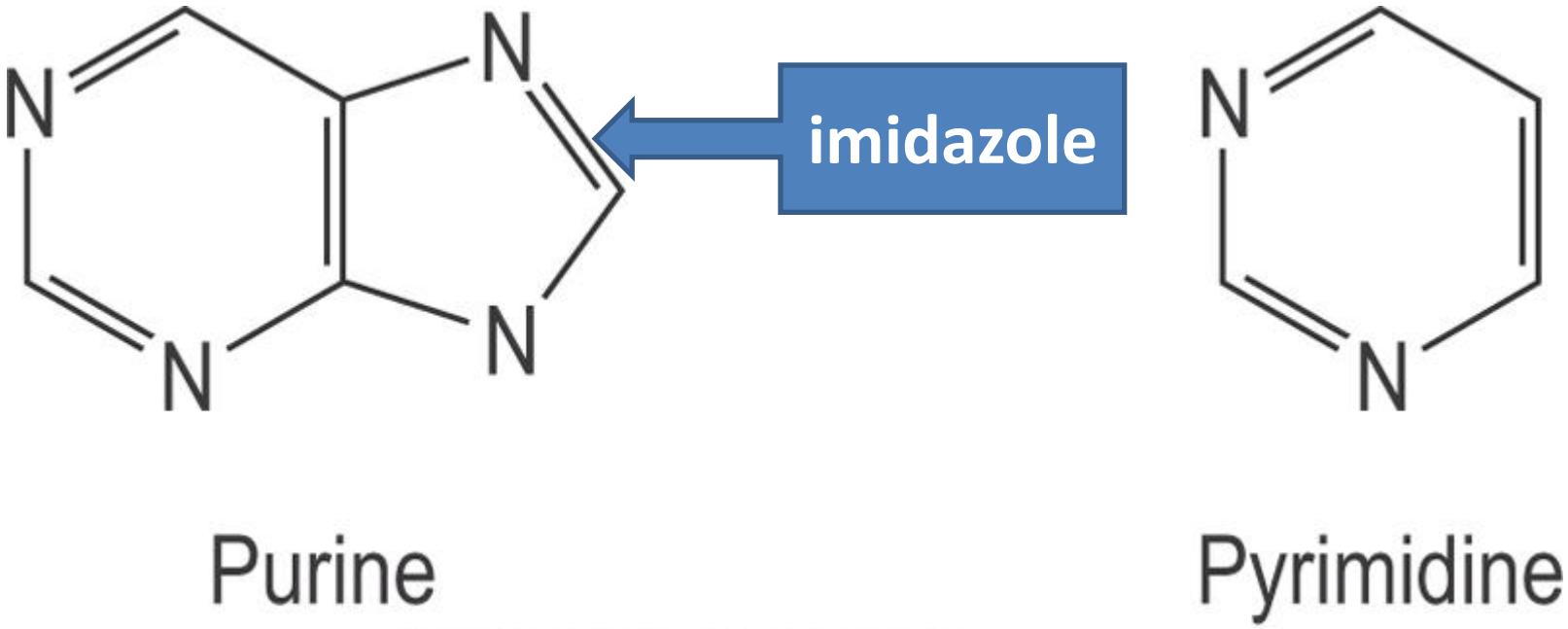
Pavel Jesina

Exam questions

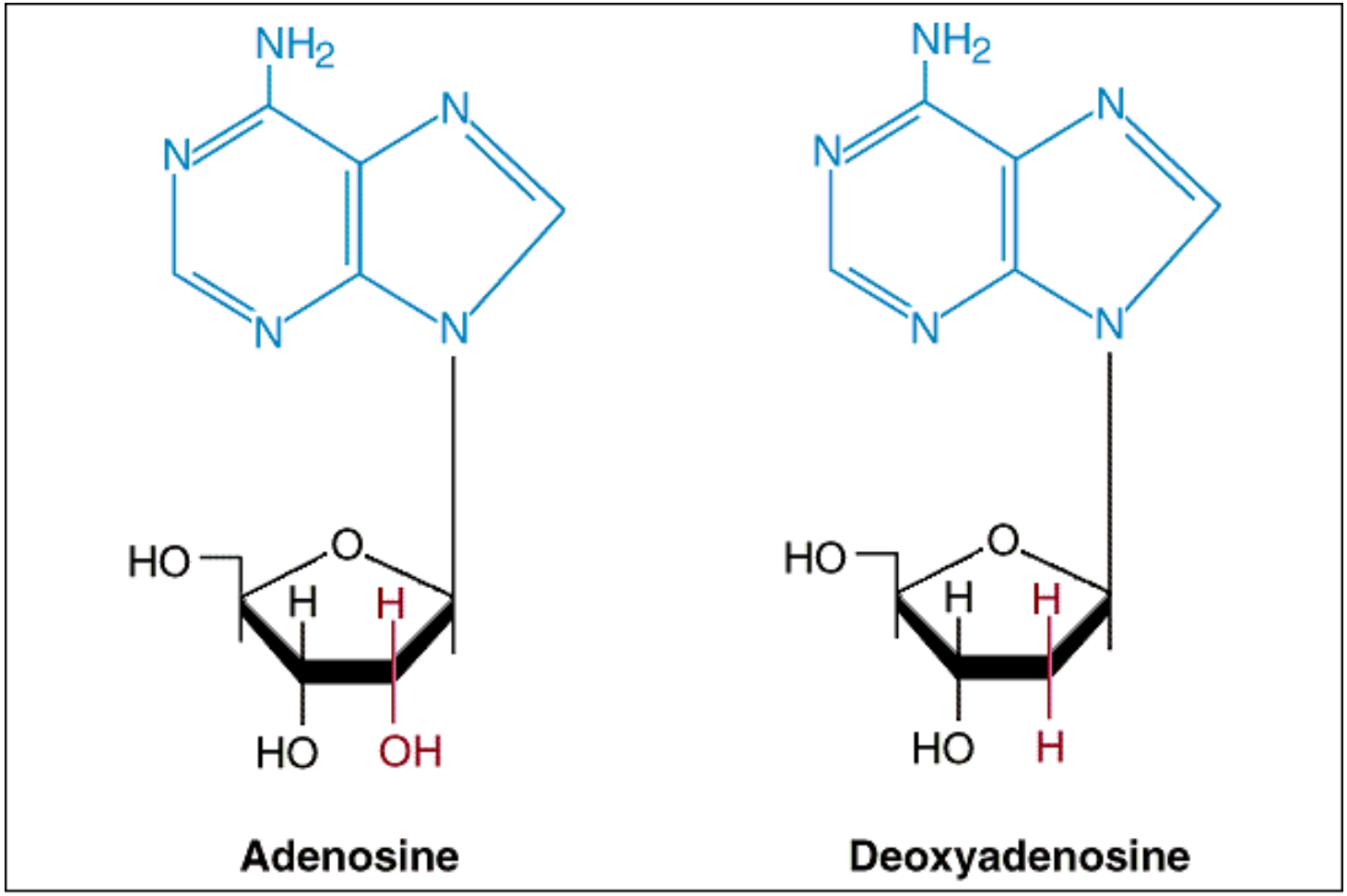
- Disorders of uric acid metabolism
- Disorders of purines/pyrimidines metabolism
- Hepatic porphyrias
- Cutaneous porphyrias
- Disorders of ketogenesis and ketolysis;

  Biochemistry of starvation

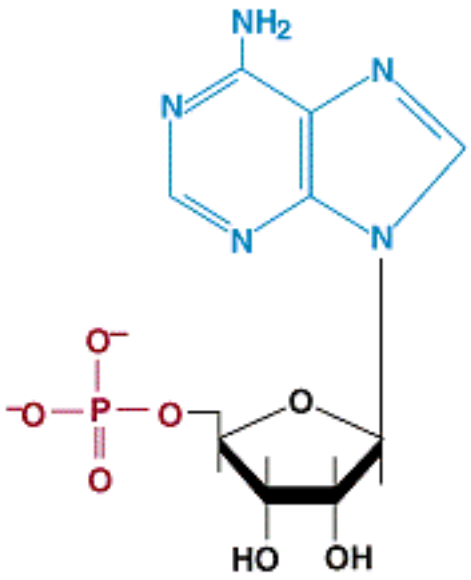
Nucleic bases



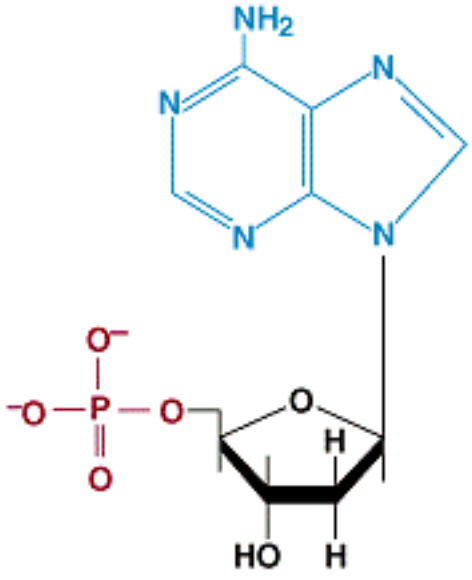
Nukleosides



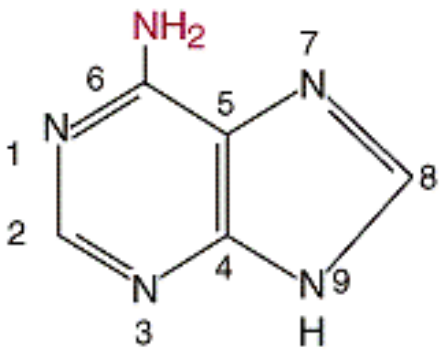
Nukleotides



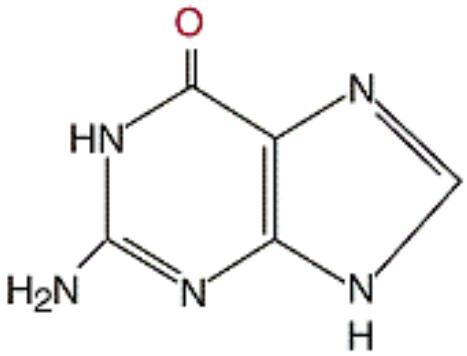
Adenosine 5'-monophosphate (AMP)



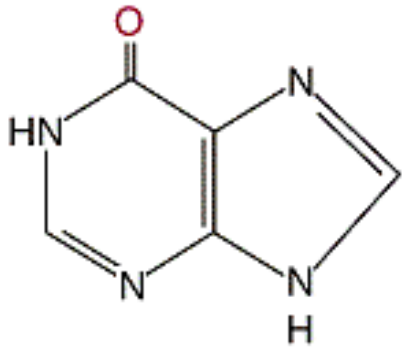
Deoxyadenosine 5'-monophosphate (dAMP)



Adenine

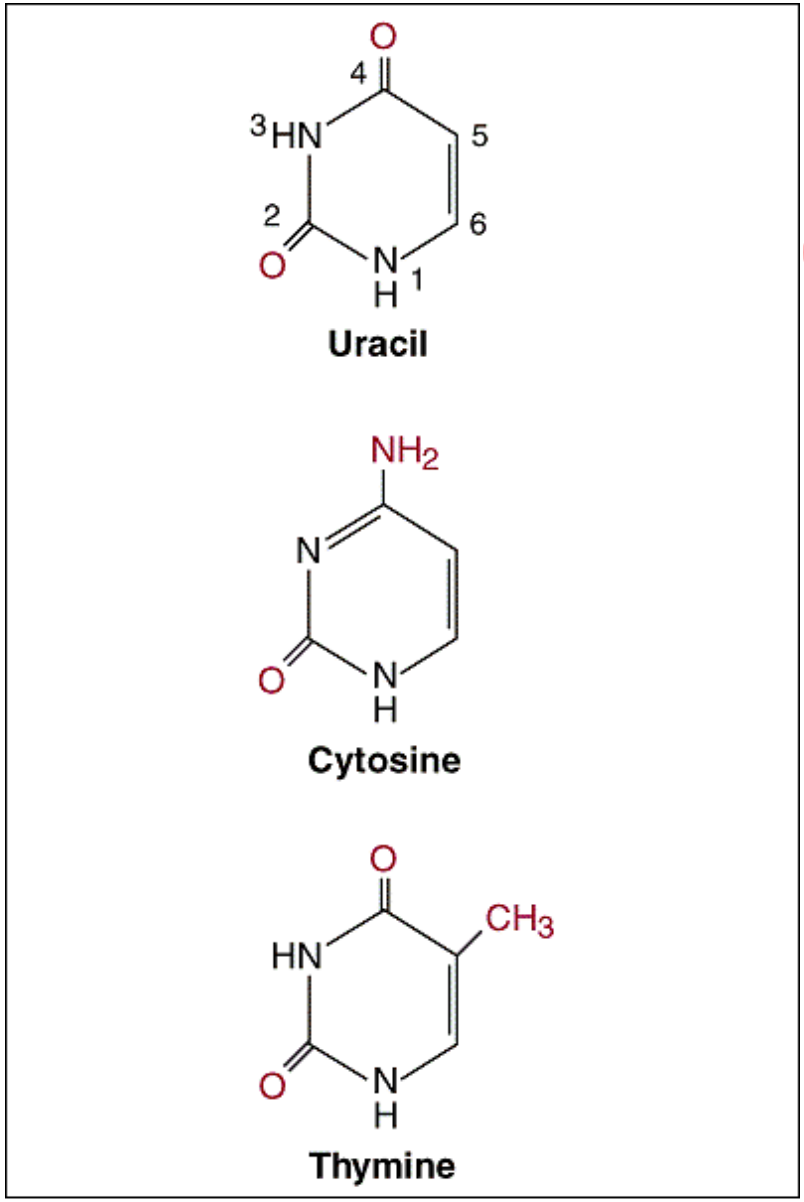


Guanine



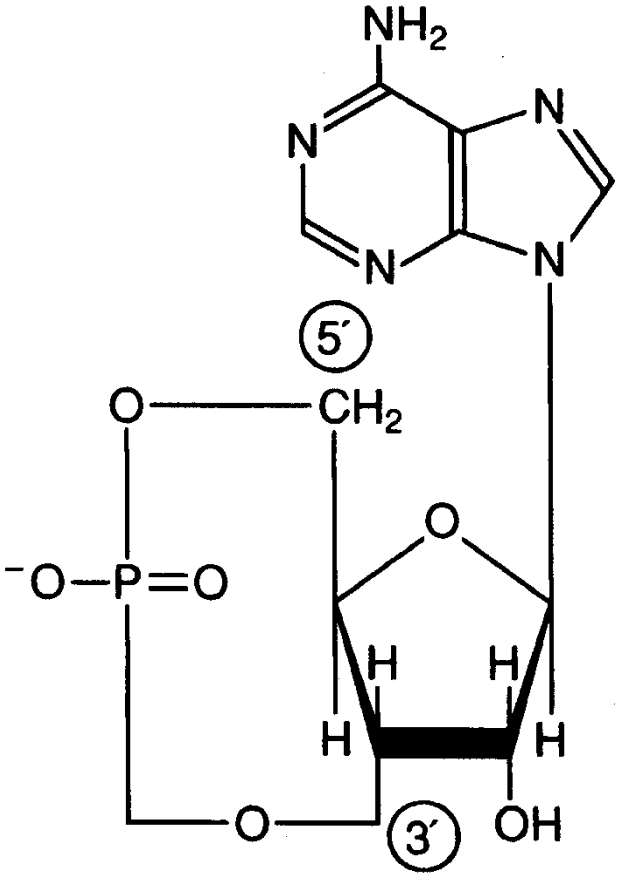
Hypoxanthine

Inosine!!!!!



Uridine!!!!!!!

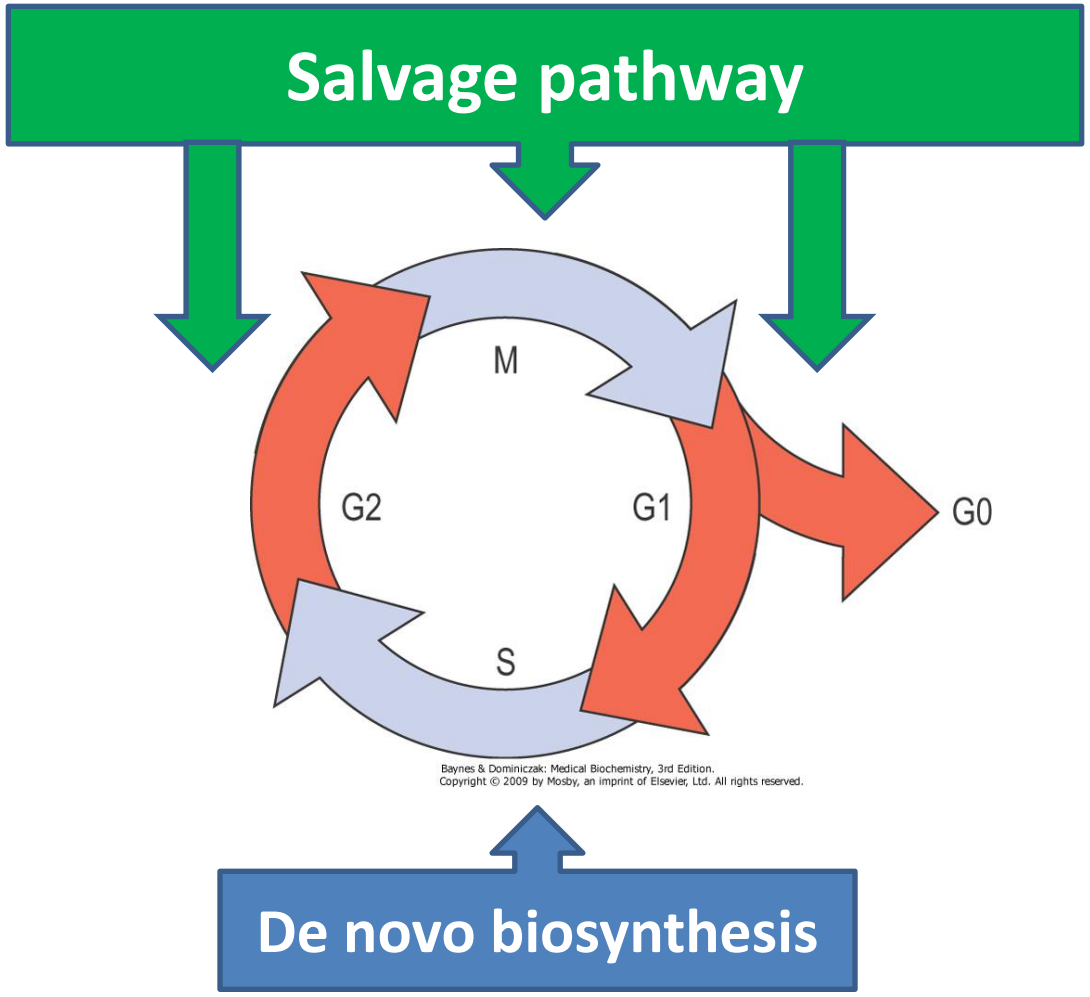
Role of nucleotides



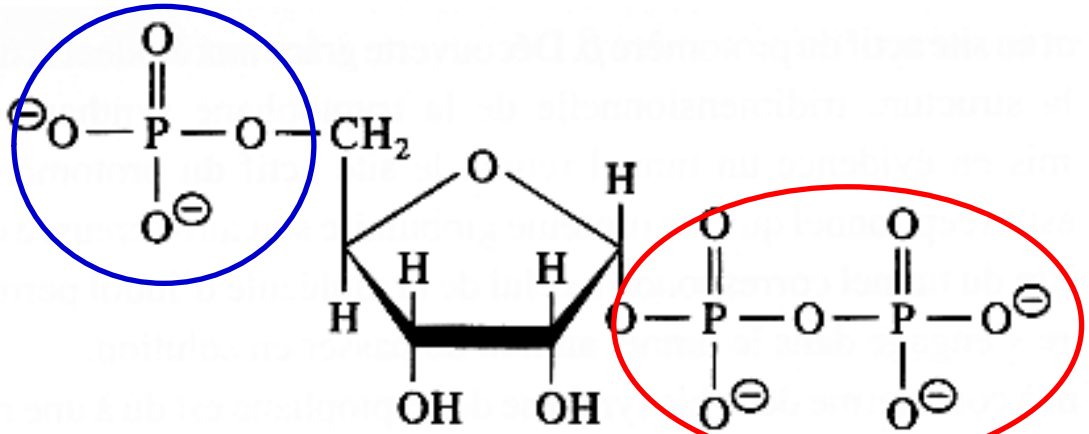
- Information carriers (DNA/RNA)
- Universal source of energy (ATP 30 kJ/mol)
- Second messengers: cGMP a cAMP
- Coenzymes and group transfer (e.g.AdoMet)

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

Cell cycle and P/P synthesis



PRPP = 5-fosforibosylpyrofosfate

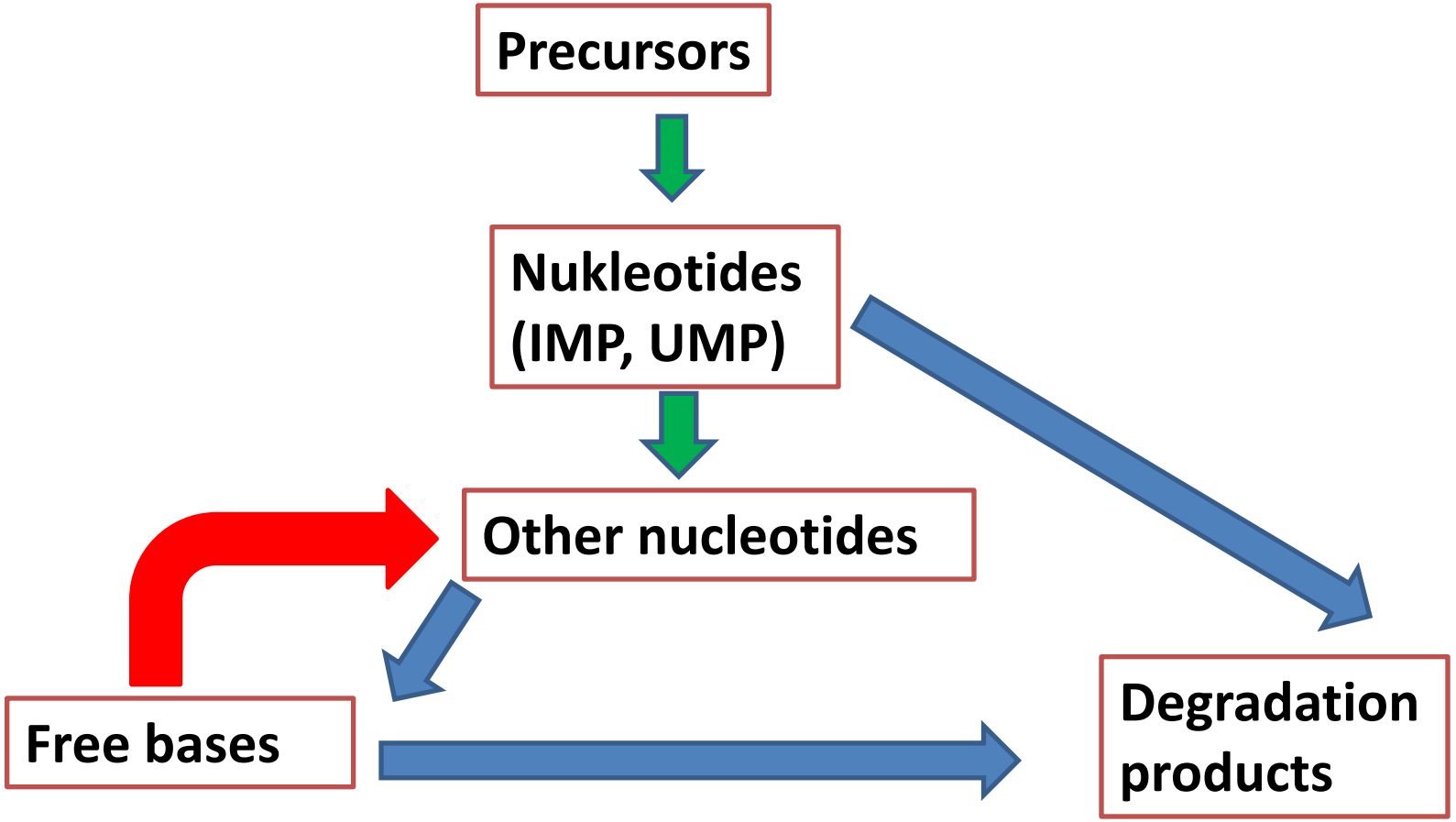


5-Phosphoribosyl 1-pyrophosphate
(PRPP)

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

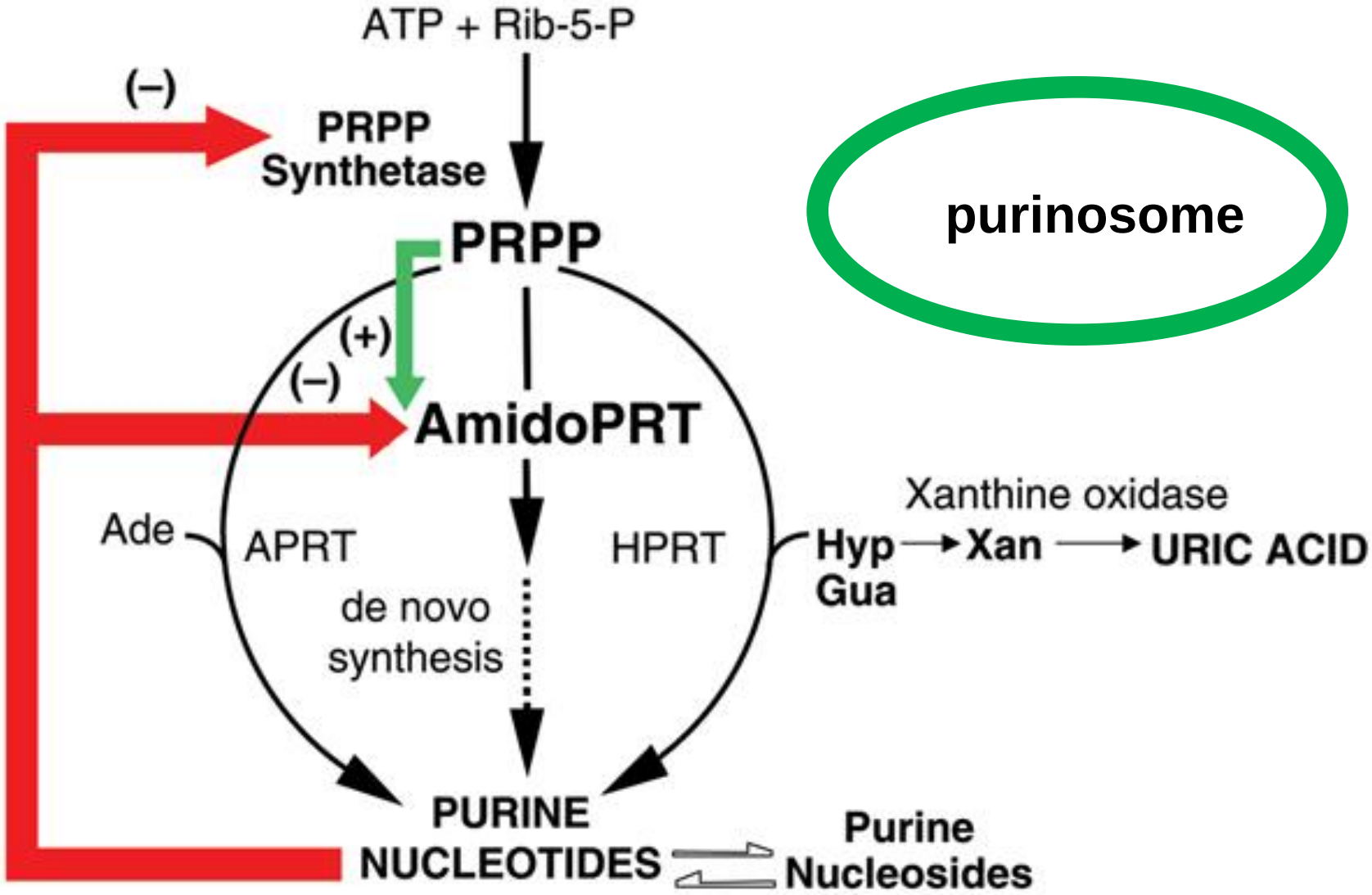
http://ead.univ-angers.fr/~jaspard/Page2/COURS/2N2NH3aaetUree/2Figures/9AAaromatiques/8PRPP.gif

Synthesis and degradation of P/P

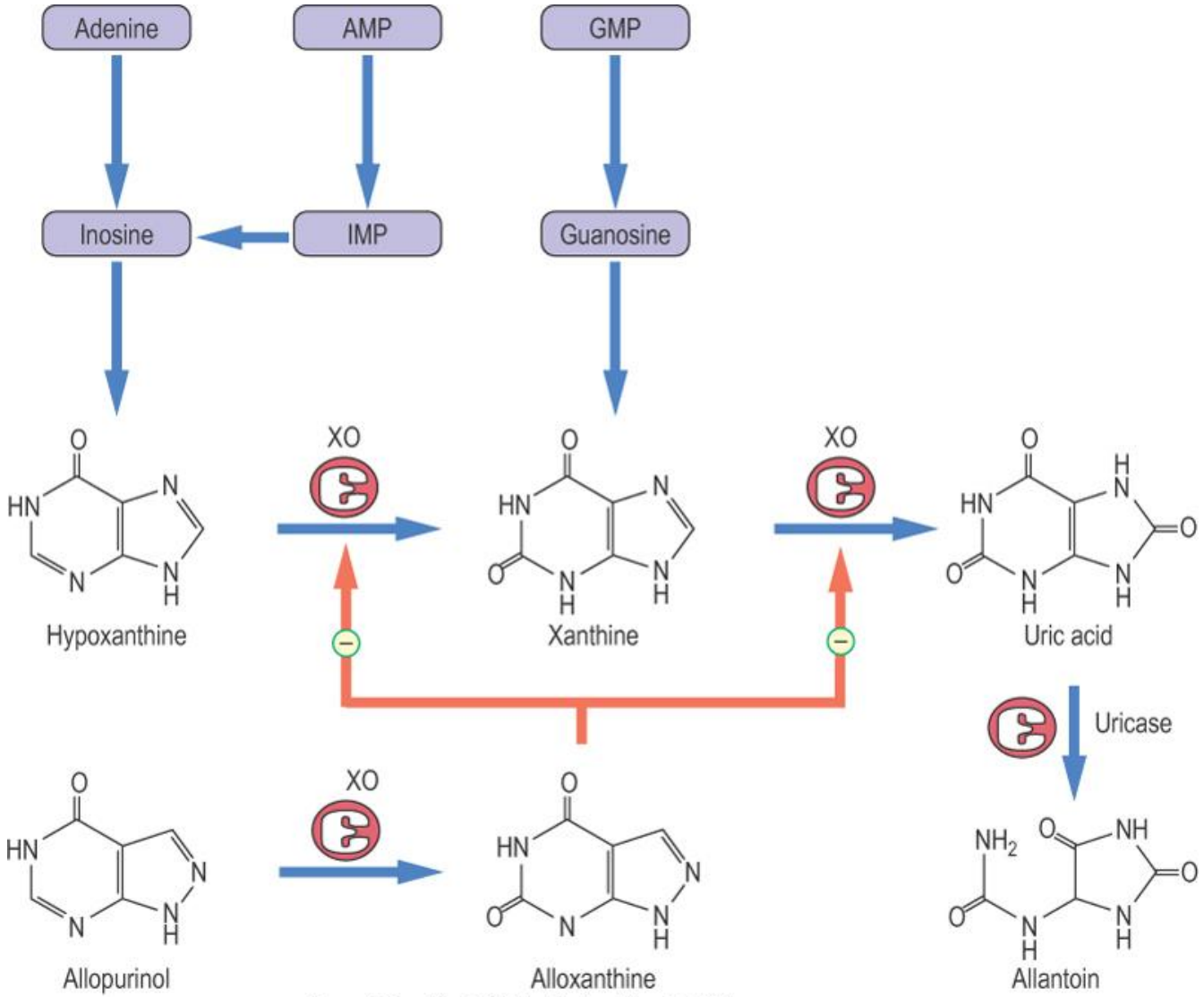


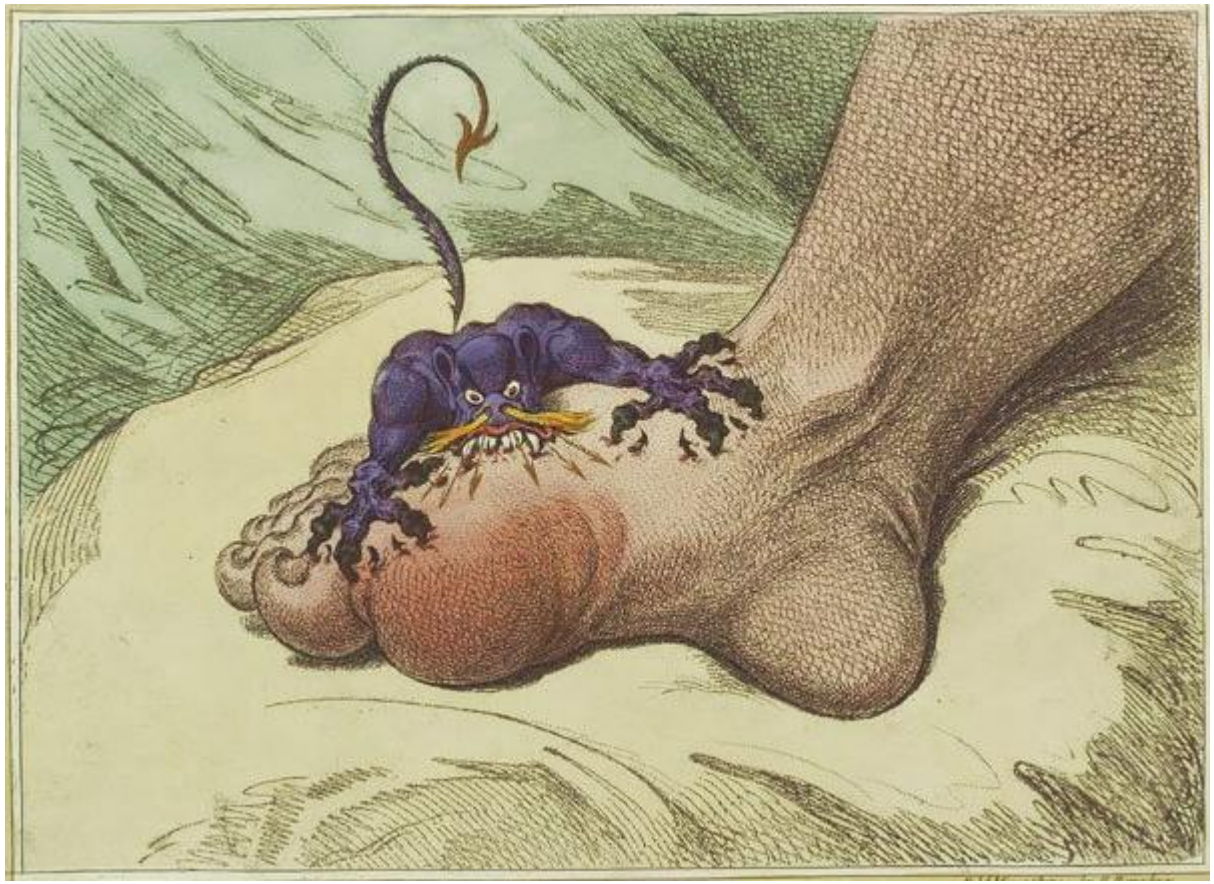
Metabolism of purines and pyrimidines

	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

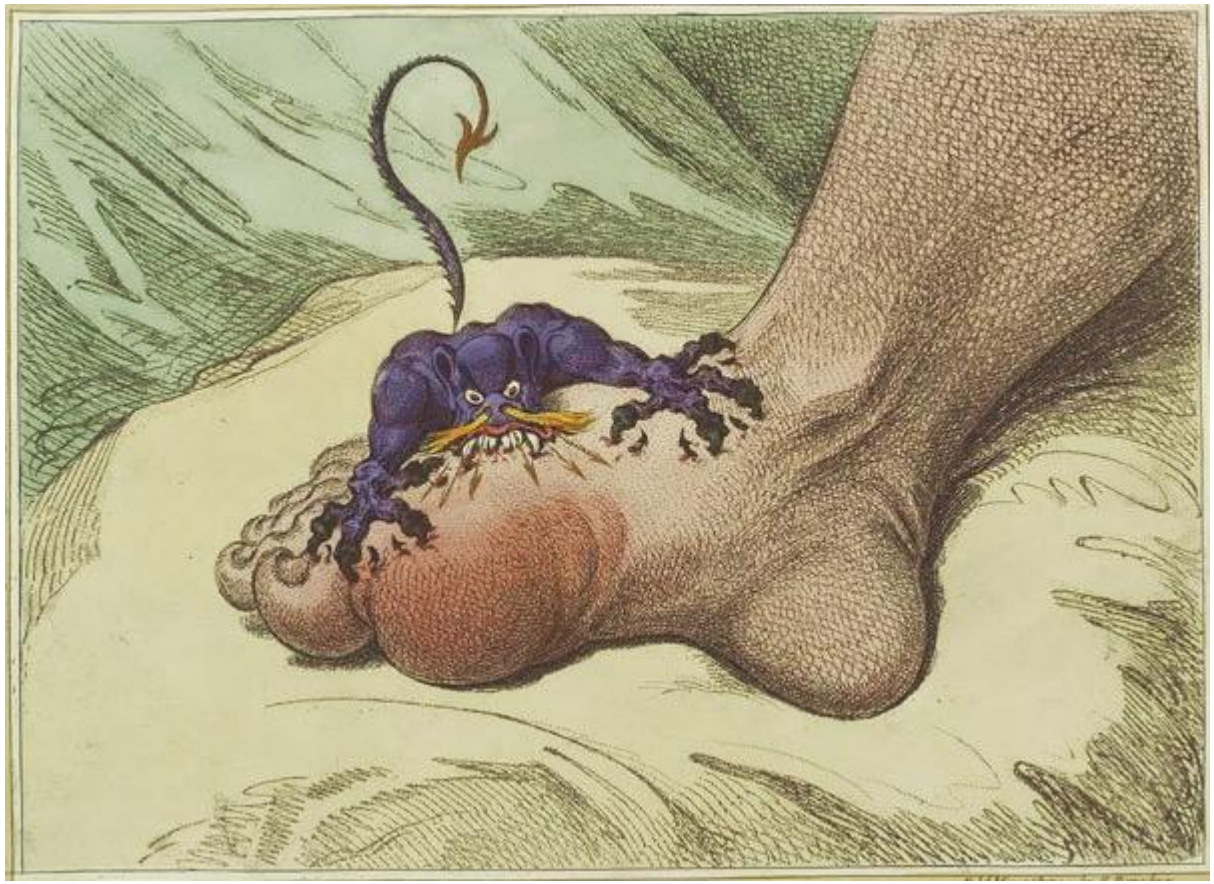


http://arthritis-research.com/content/figures/ar1909-2.gif





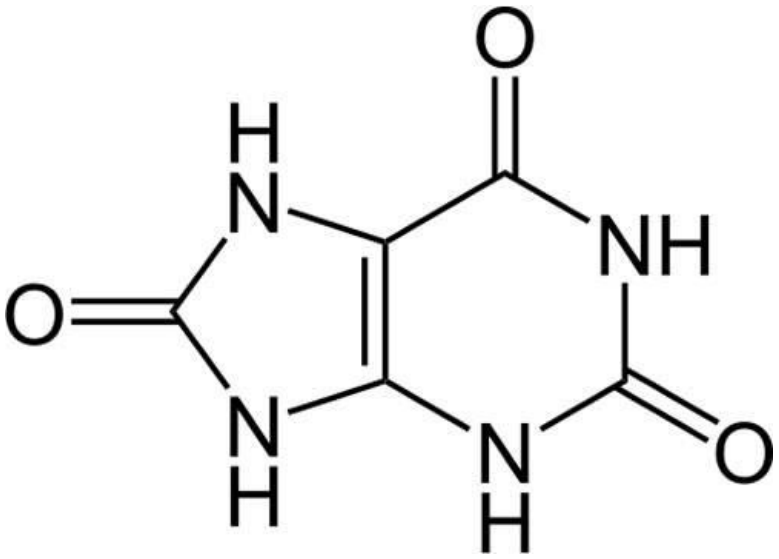
http://scienceblogs.com/moleculeoftheday/images/gout-cartoon.jpg



Gout = athritis urica

http://scienceblogs.com/moleculeoftheday/images/gout-cartoon.jpg

Uric acid

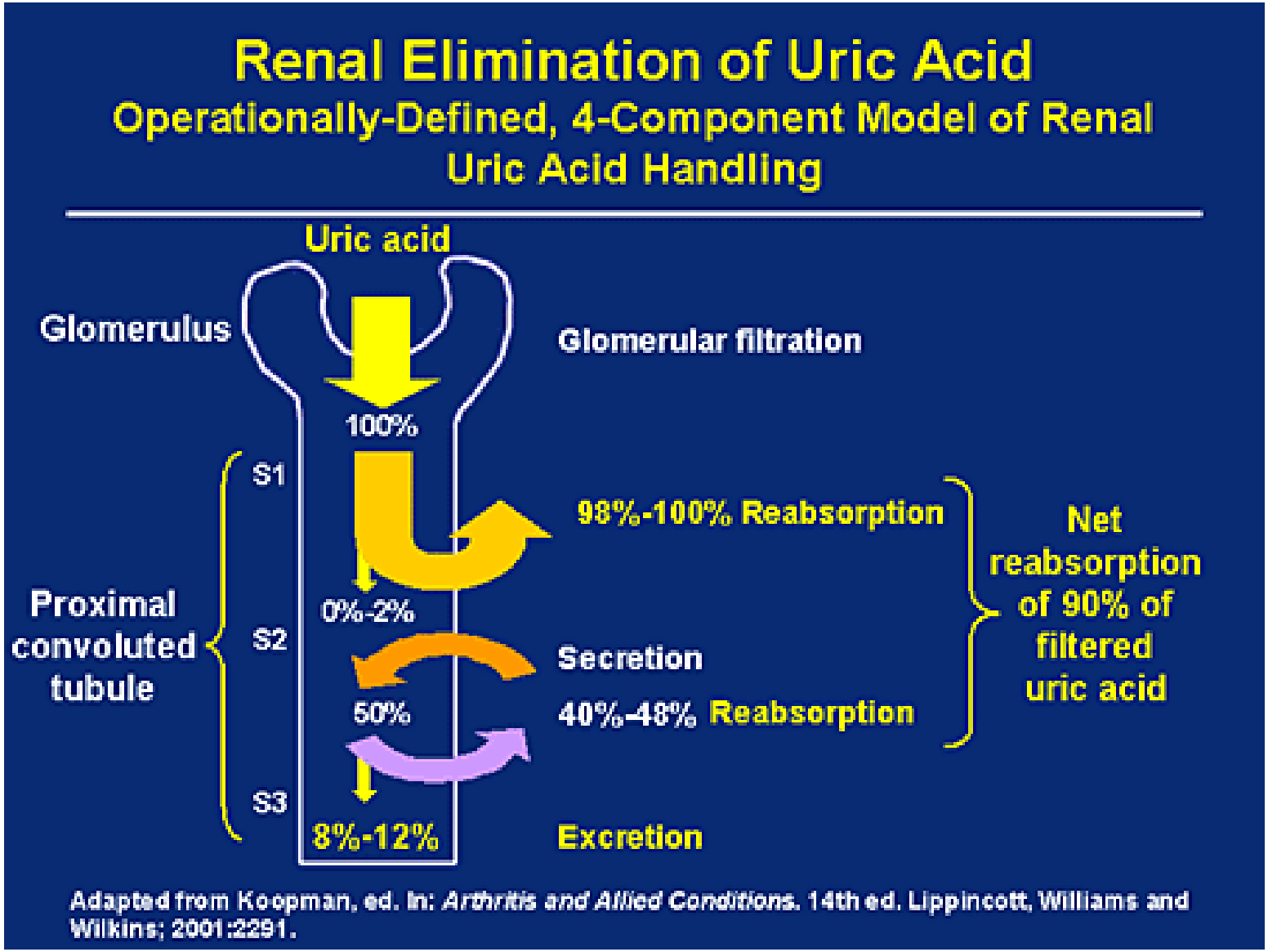


- Trioxopurine
- Keto/enol
- Physiological pH: monosodium urate
- Limited solubility
- Free radical scaveneger

http://0.tqn.com/d/chemistry/1/0/M/R/1/Uric_acid.jpg

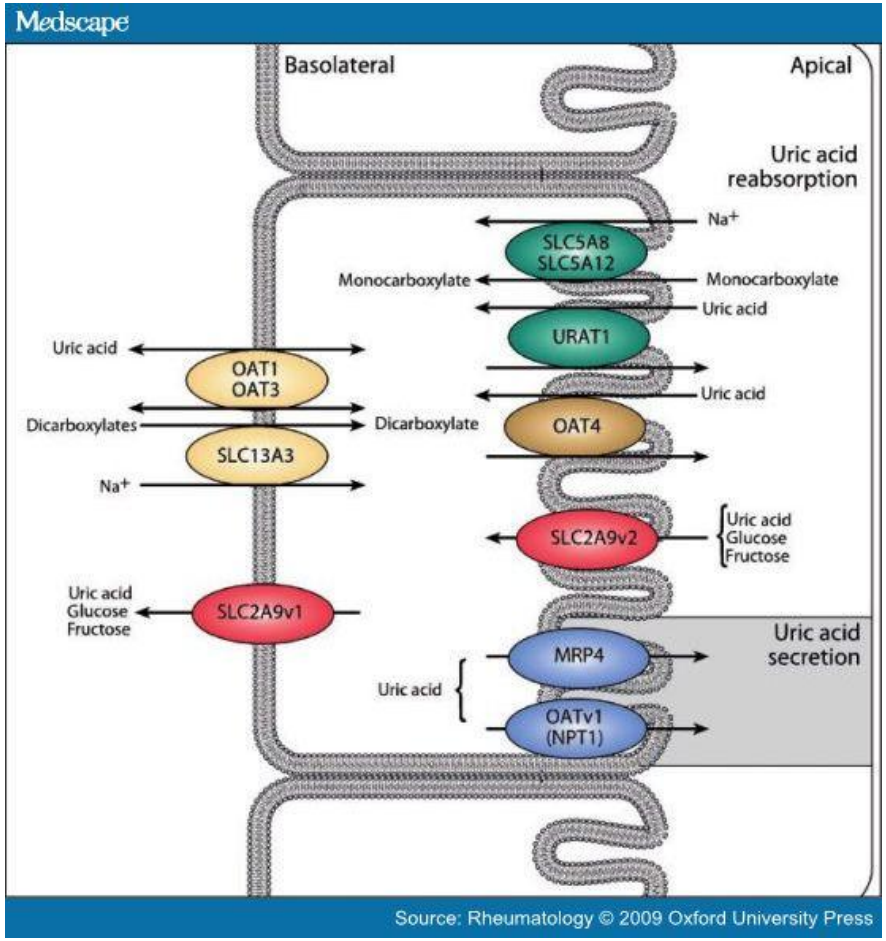
Urinary concrements-uric acid

http://img.medscape.com/pi/emed/ckb/pediatrics_general/980683-983759-669.jpg



http://img.medscape.com/slide/migrated/editorial/cmecircle/2006/4933/images/edwards/slide006.gif

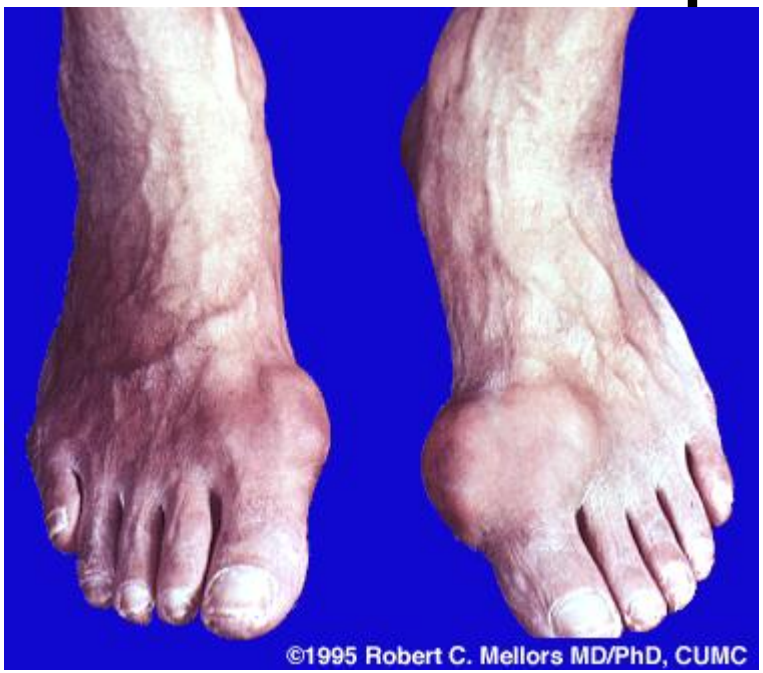
Renal reabsorption and secretion

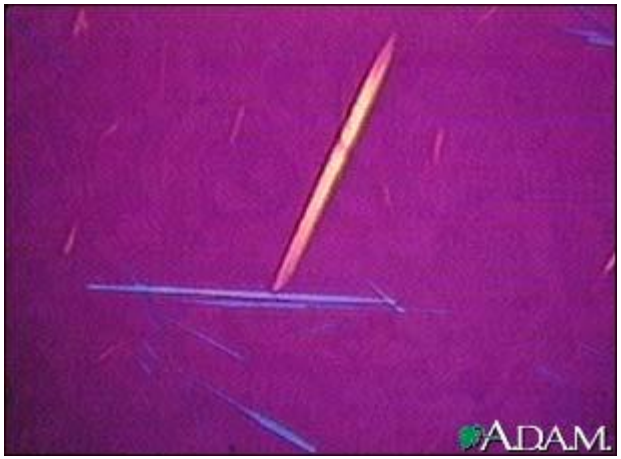


- Elevated uric acid in blood
- Low excretion fraction of uric acid
- Normal purine and pyrimidine profile

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

Familiar juvenile hyperuricaemic nefropathy (FJHN)





- juvenile onset of hyperuricaemia, gouty arthritis, nephrolithiasis and progressive renal failure
- Inheritance - AD

Inherited metabolic disorders of purine metabolism

PPRP synthase superactivity

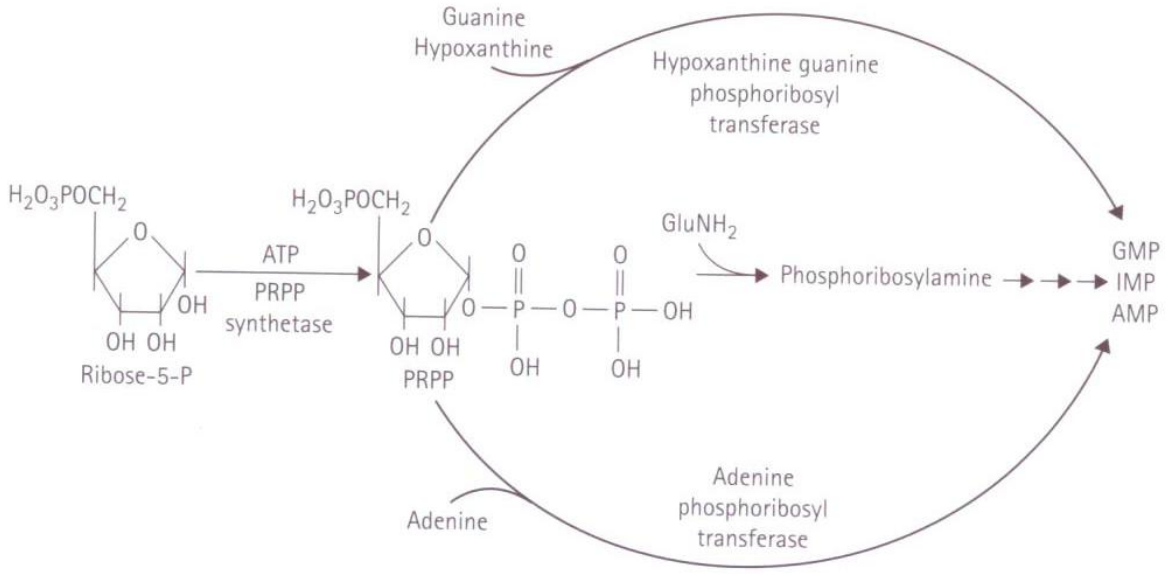


Figure 67.1 *PRPP synthetase. The role of the product PRPP is central in the interrelation of purines and their nucleotides.*

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

PPRP synthase superactivity

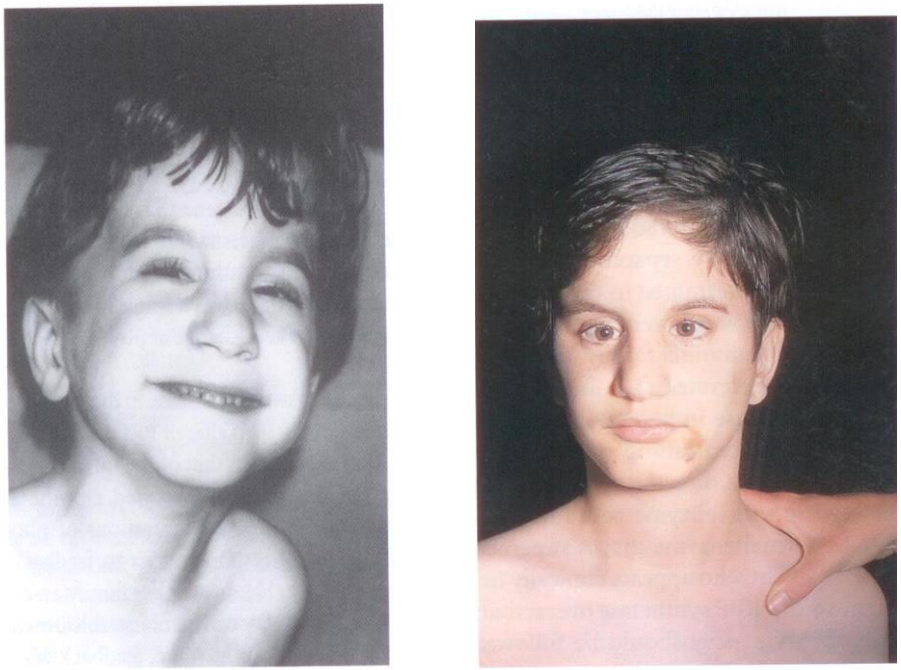
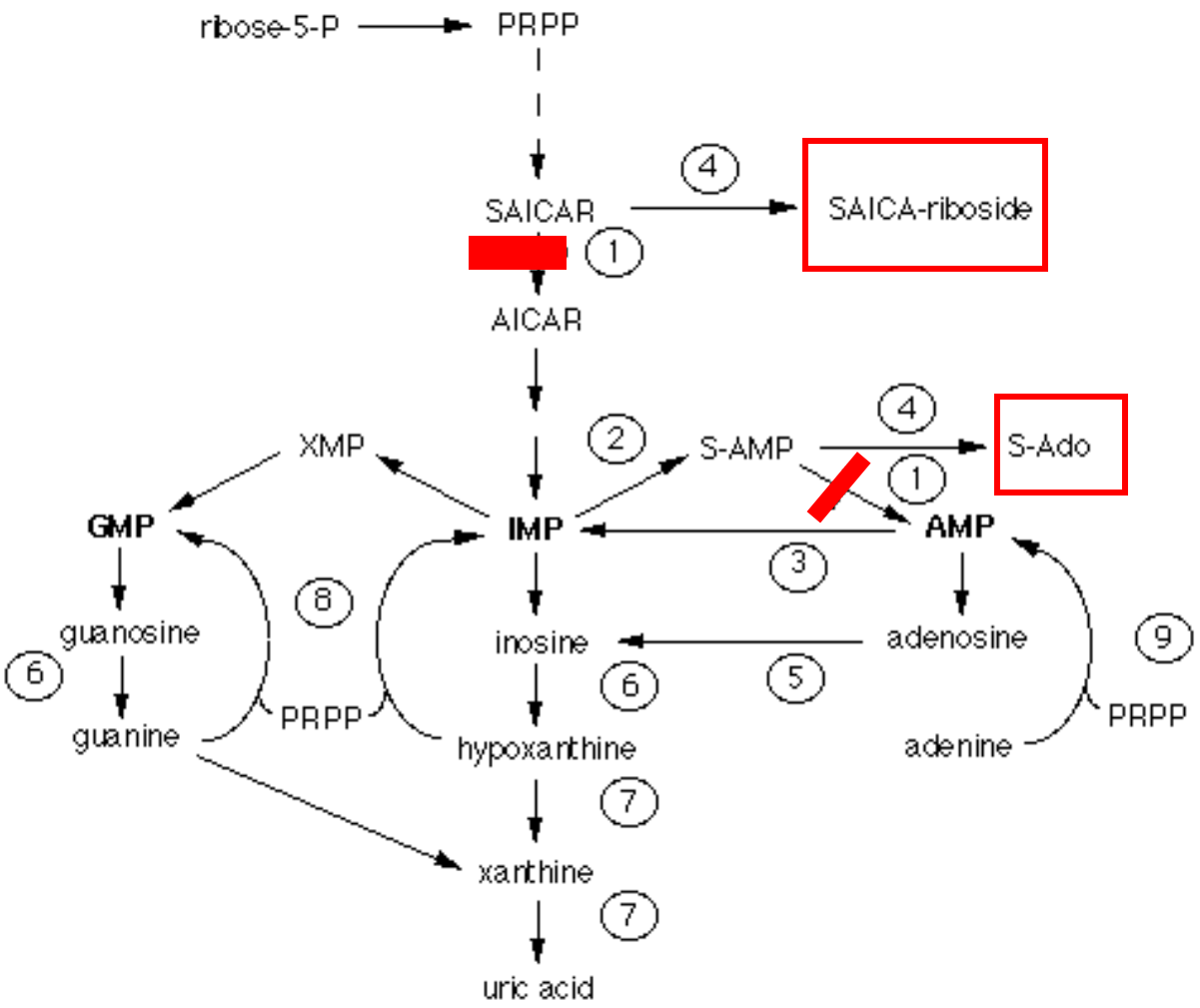


Figure 67.2 *S.M., a 3-year-old with an abnormal PRPP synthetase. The odd grimace was characteristic. (Reprinted with permission from the* Journal of Pediatrics *[5]).* *S.M., at 14 years-of-age.*

- 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

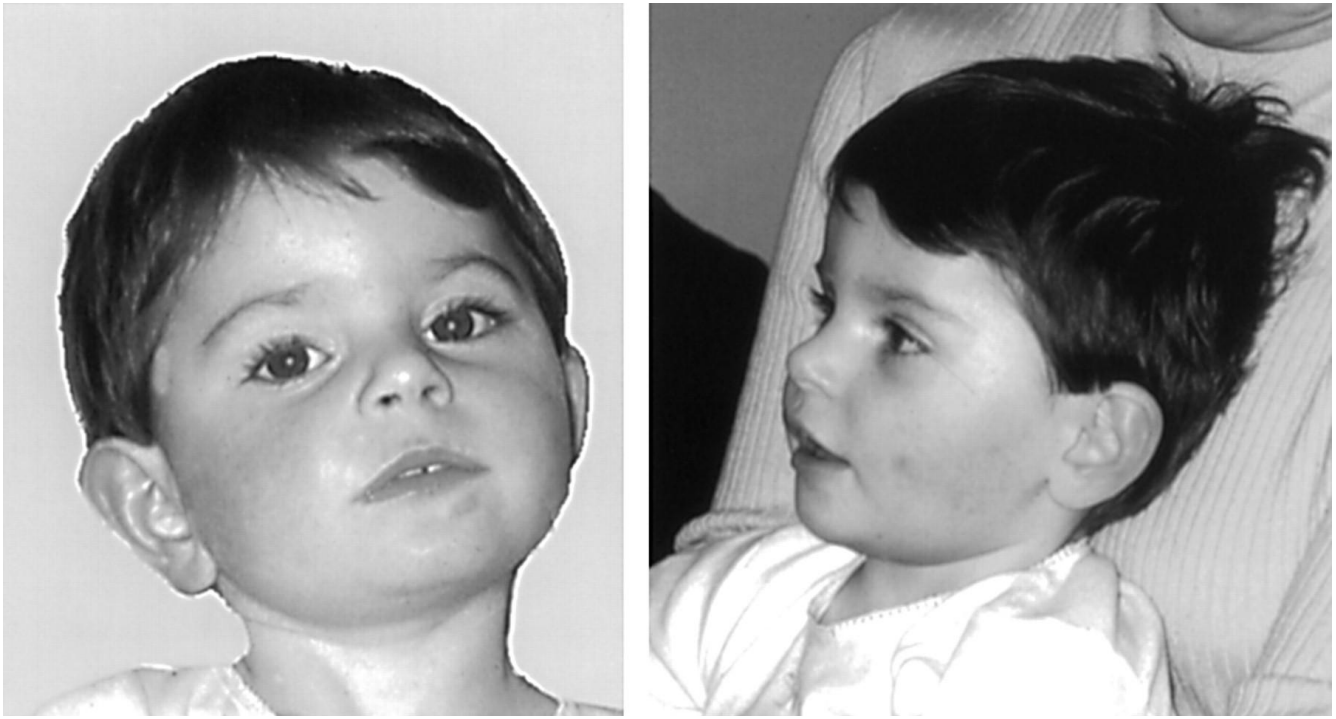
Adenylosuccinate lyase deficiency (ADSL)



ADSL deficiency

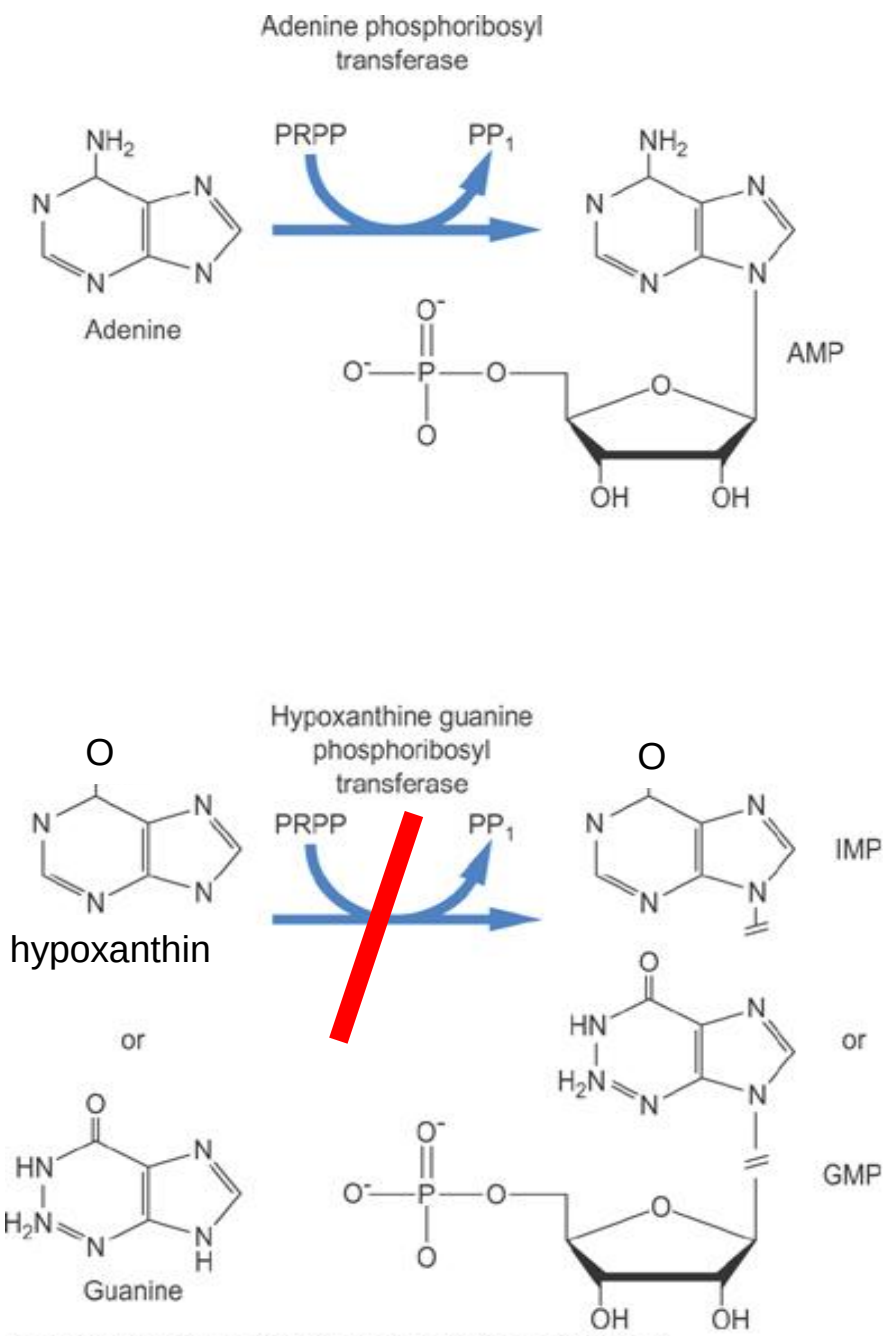
- AR inheritance
- SAICAR toxic for neurons (impaired utilization of glucose), S-Ado may be protective
- Uncertain role of purine depletion (not confirmed)
- Variable neurological findings (neonatal epilepsy,encephalopathy, stereotypic movement, ataxia, PMR, seizures, hypotonia)
- Autistic like behaviour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

Facial dysmorfia in ADSL deficiency



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

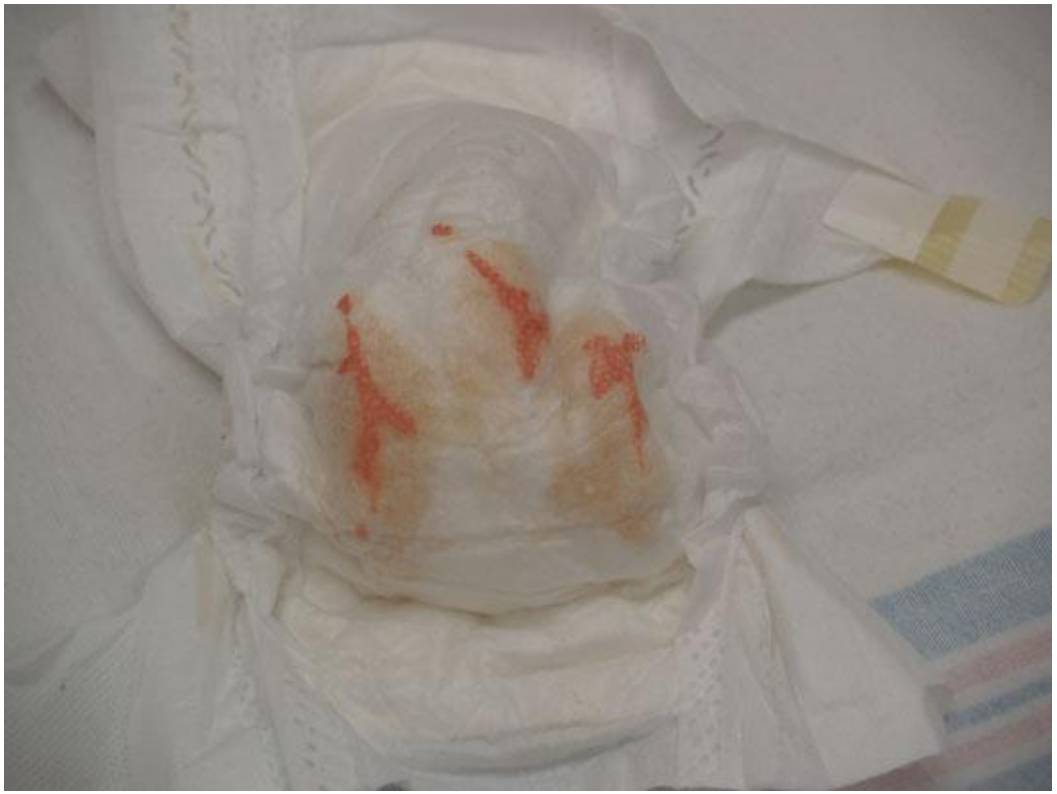
brachycephaly, prominent metopic sutures, small nose with anteverted nostrils, long, smooth philtrum, and thin upper lip.



HGPRT deficiency

- 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- diapers



http://newborns.stanford.edu/images/urates2.jpg

http://www.dent.ucla.edu/pic/visitors/teethloss/images/PreFig9.jpg

Deficit HGPRT-urate tophus

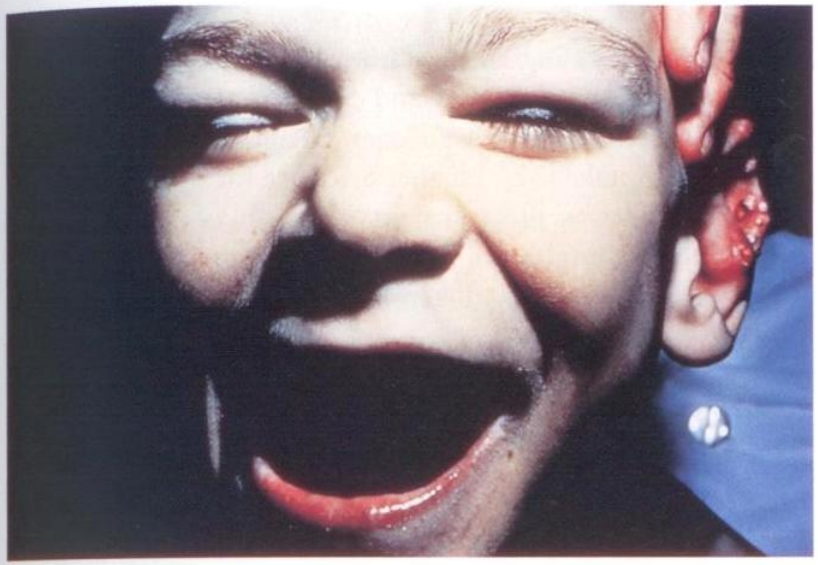
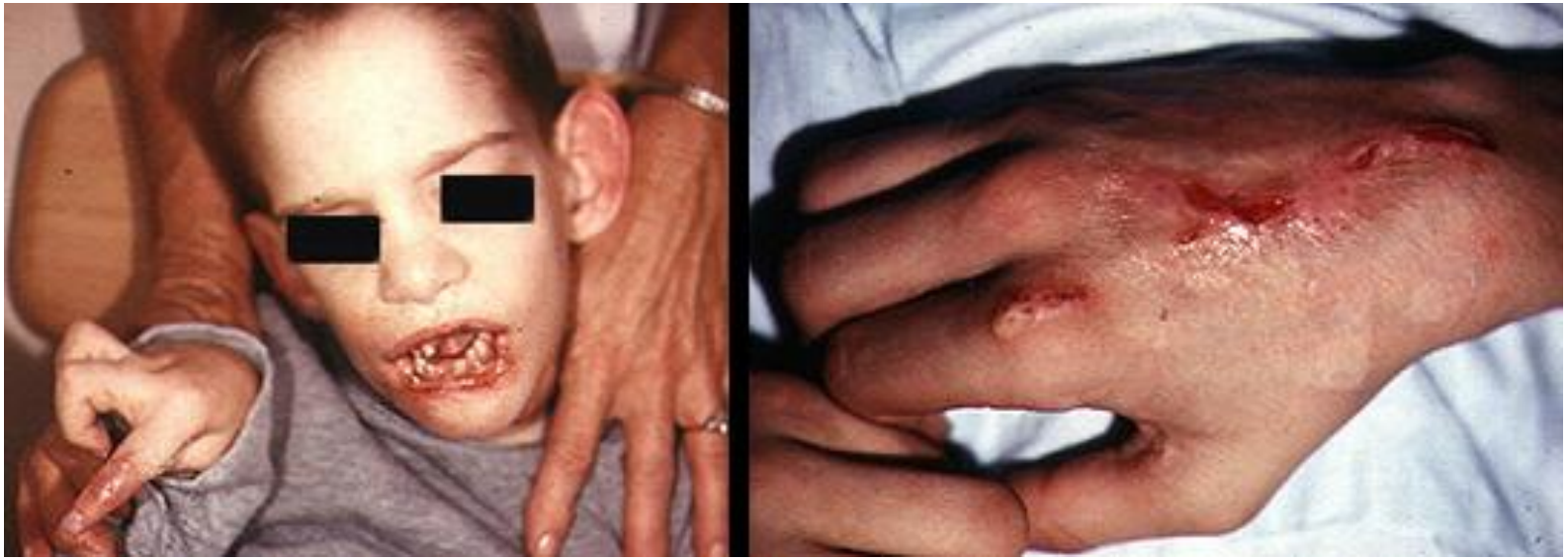


Figure 65.10 *A 17-year-old boy with prominent tophaceous deposits in the ears. The violaceous inflammatory reaction is unusual around tophi. It subsided following treatment with colchicine.*

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

HGPRT deficiency



http://newborns.stanford.edu/images/urates2.jpg

http://www.dent.ucla.edu/pic/visitors/teethloss/images/PreFig9.jpg

HGPRT deficiency

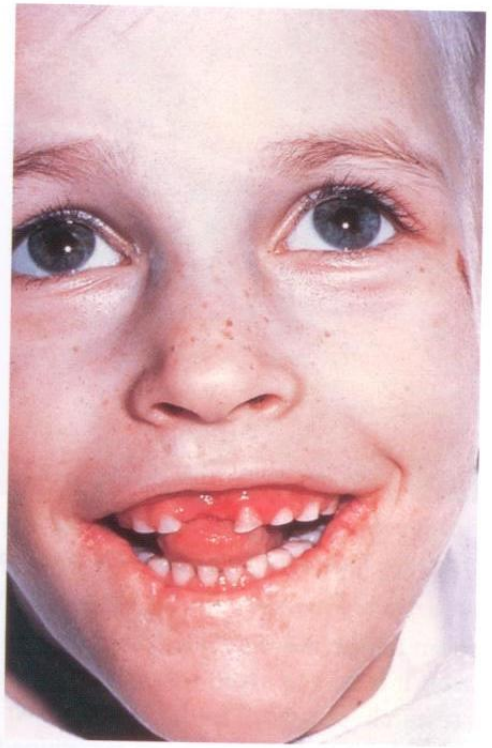


Figure 65.4 *M.J. The degree of the mutilation of the lip is relatively mild.*

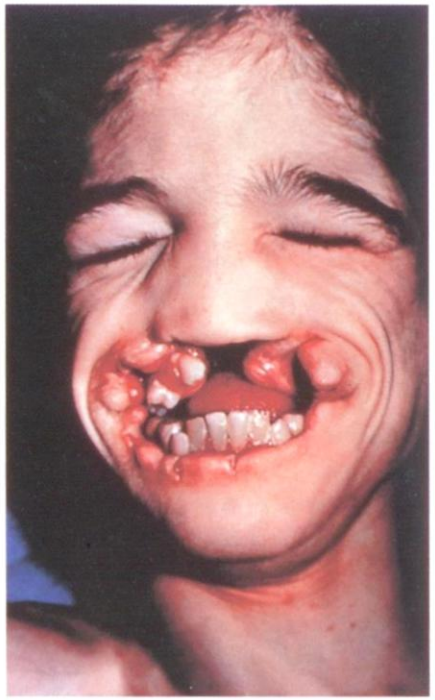


Figure 65.5 *J.J., a 14-year-old boy, illustrating an extreme degree of mutilation around the face.*

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

HGPRT deficiency

Figure 65.19 *A.A., rear view walking illustrating the dragging of his toes.*

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

HGPRT activity in fibroblasts

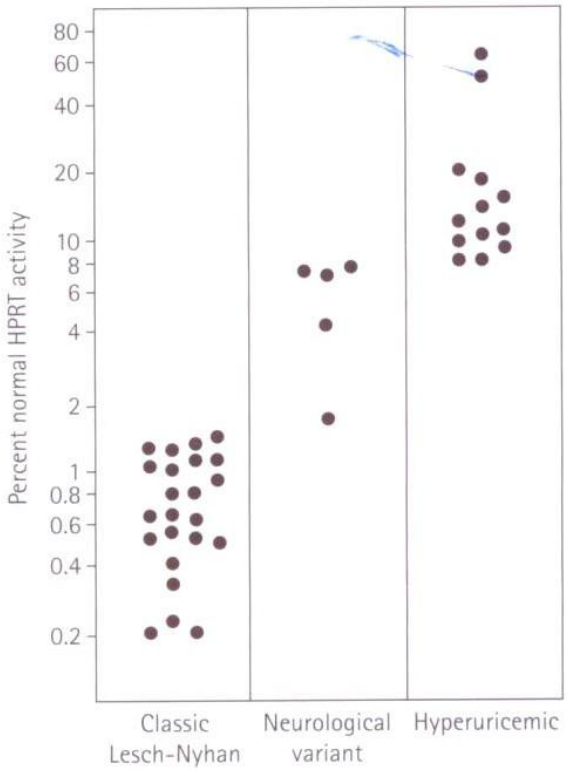


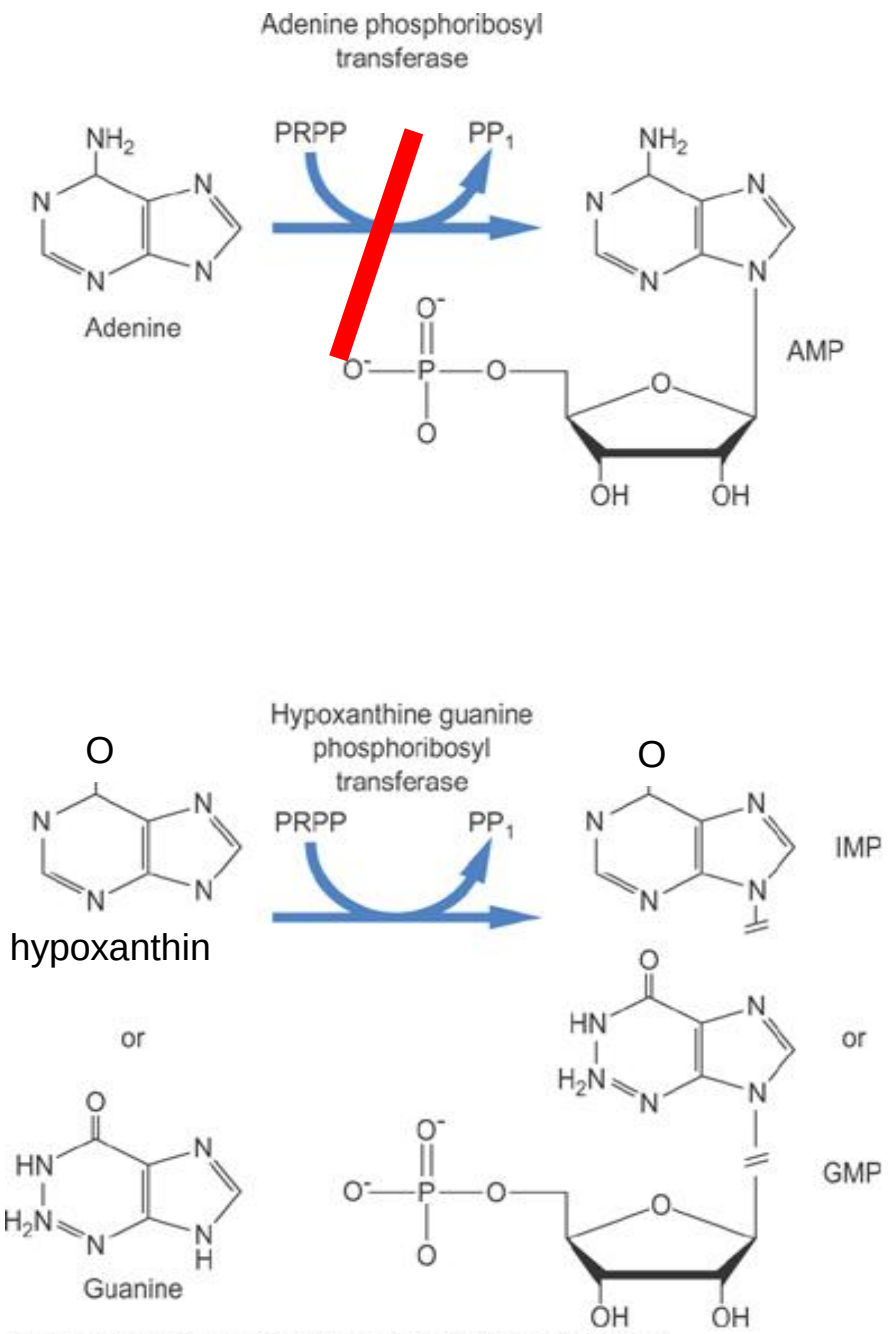
Figure 65.21 *Activity of HPRT in intact fibroblasts. The level of enzyme activity was roughly inversely proportional to the degree of clinical severity. Actually, the values fell into three groups, correlated with phenotype: the Lesch-Nyhan; the neurologic variant, and the classic partial variant.*

Lesch-Nyhan syndrome < 1.5%

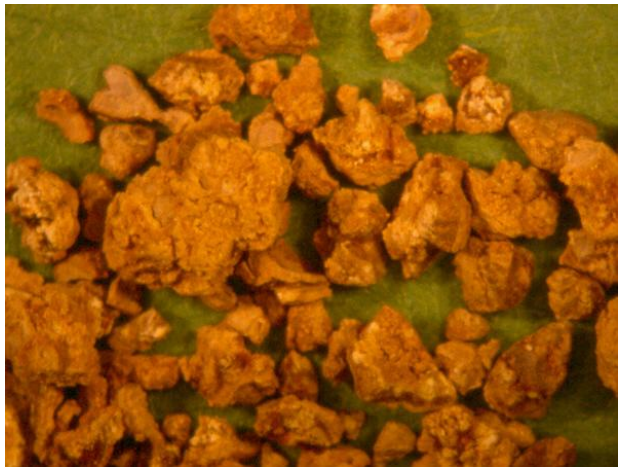
Kelly-Seegmiller syndrome 1.5 – 8%

HPRT-related hyperuricaemia > 8%

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



APRT deficiency



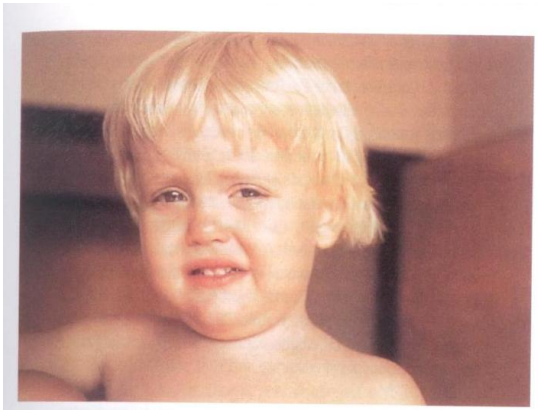


Figure 66.2 *An 18-month-old with APRT deficiency who began passing stones at birth. At last report he was a young, fit 24-year-old. (Illustration was kindly provided by Dr. H. Anne Simmonds of the United Medical and Dental Schools, University of London.)*

- 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

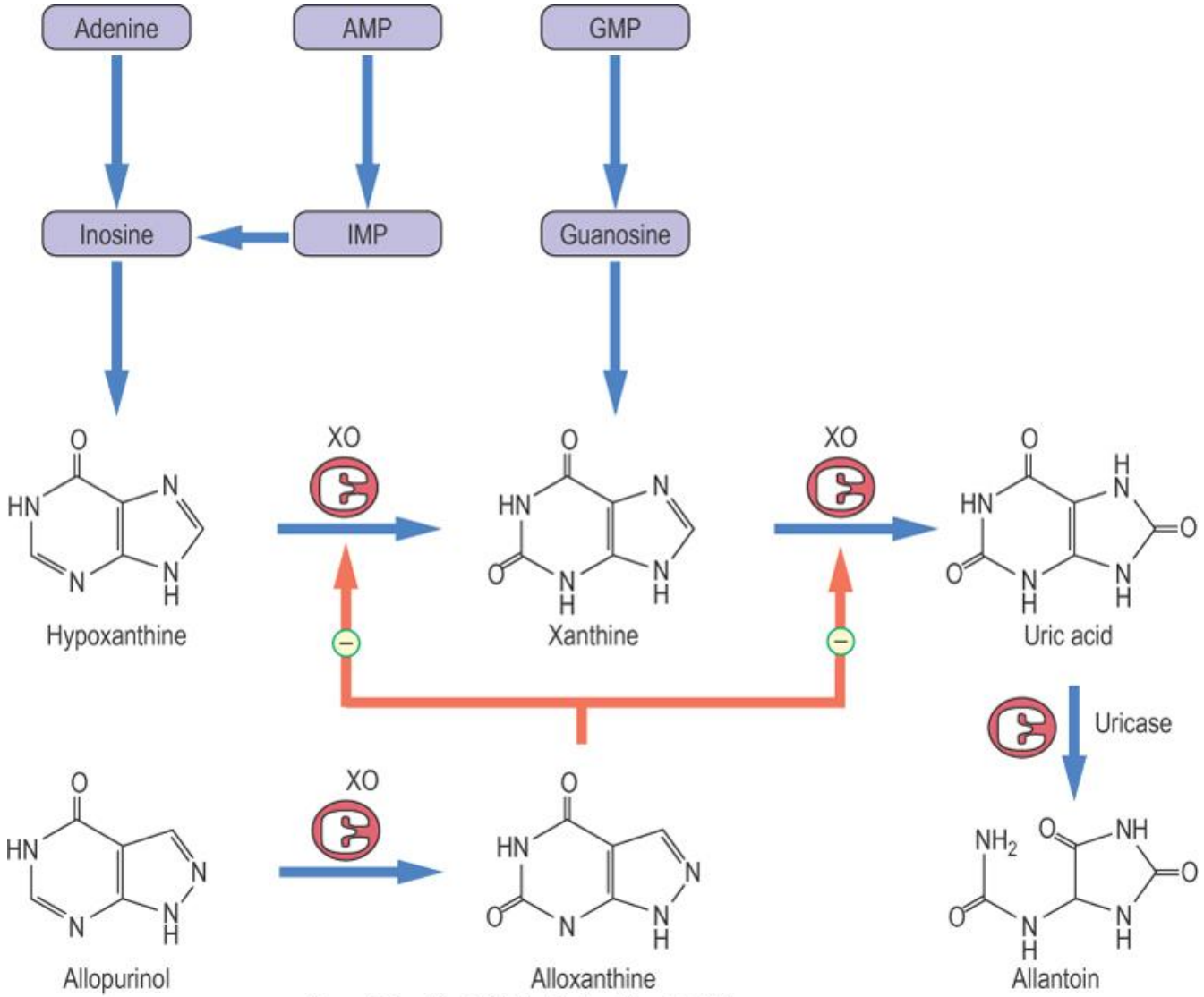
William N Nyhan, Bruce A Barshop, Pinar T Ozand (eds). Atlas of metabolic diseases, 2nd edition. London: Hodder Arnold, 2005

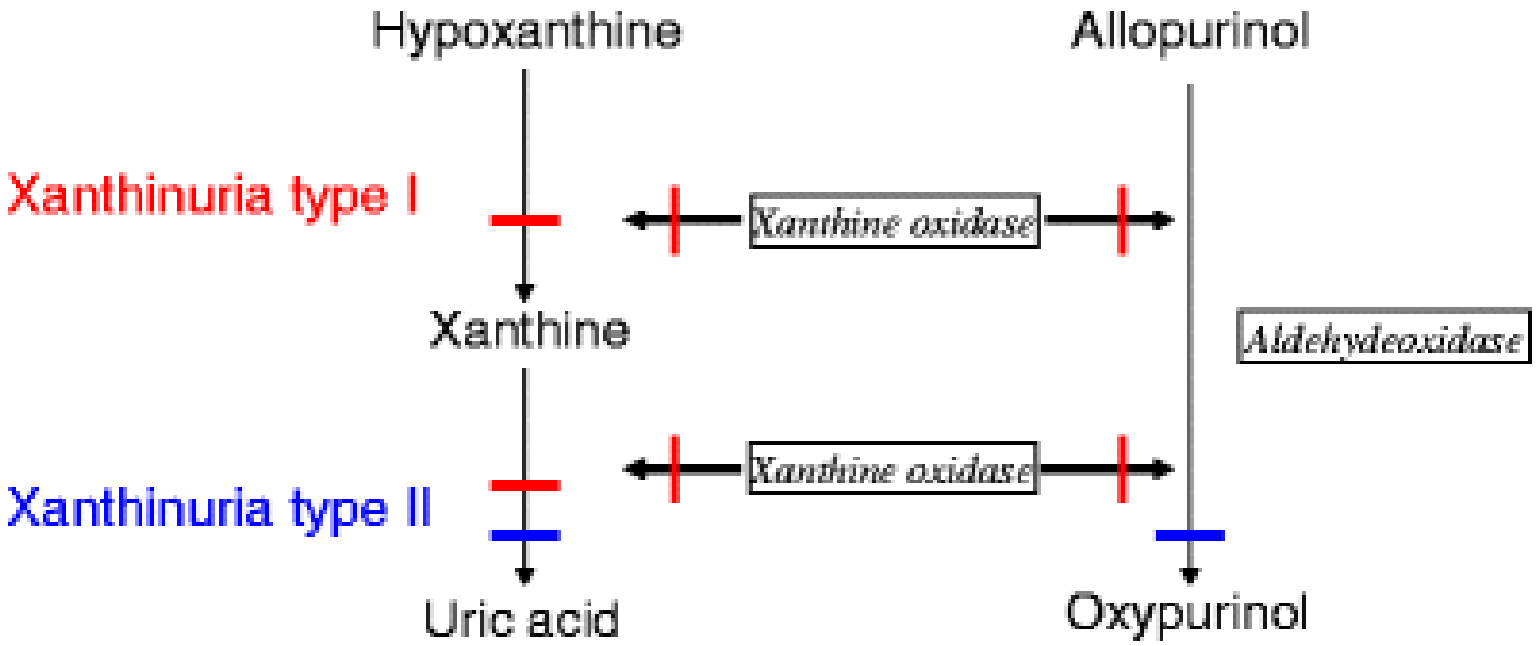
http://www.herringlab.com/photos/2/55-2,8-dihydroxyadenine97-P3.jpg

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

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

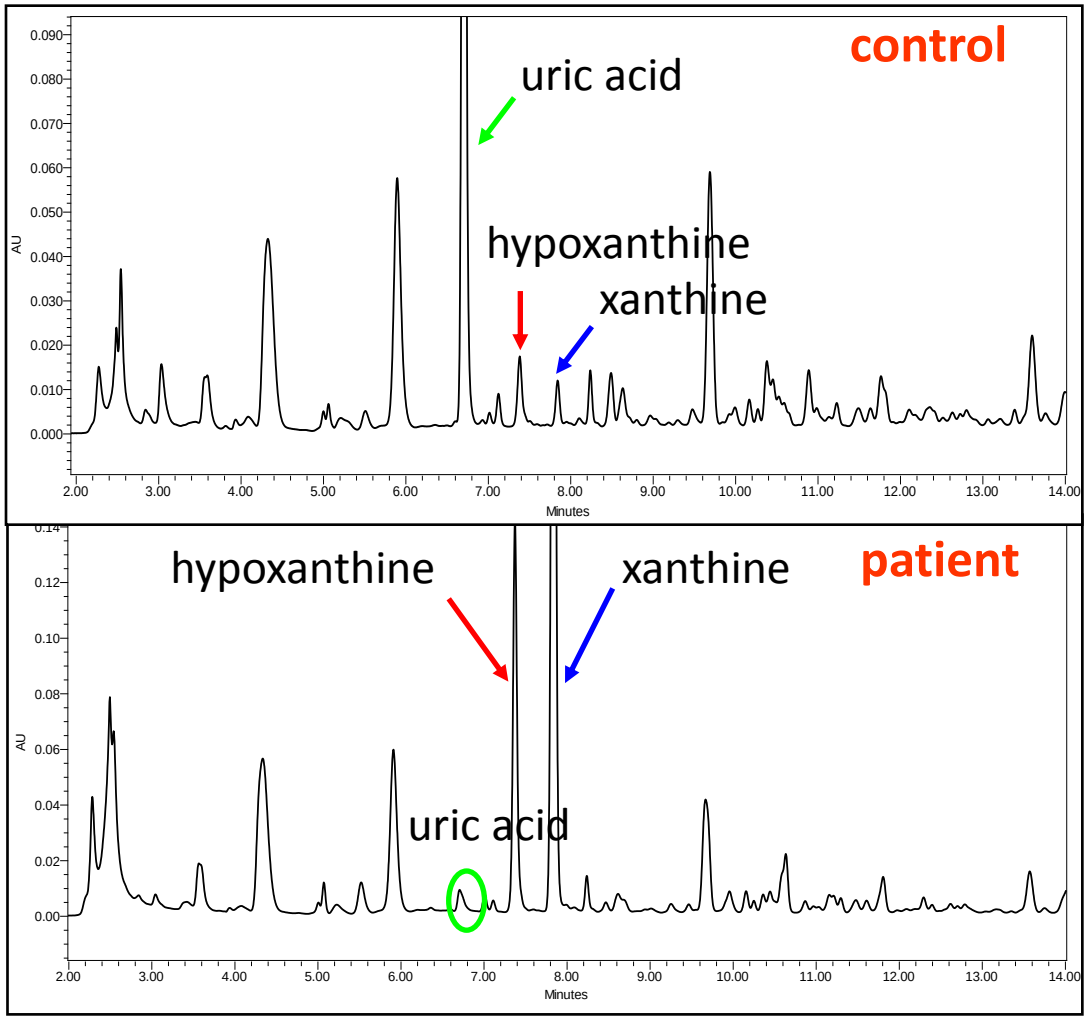




Arikyants N. et al. Pediatr Nephrol 2007

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.

Zapůjčeno laskavostí Dr.B.Stibůrkové



HPLC chromatogram močových P/P

Zapůjčeno laskavostí Dr.B.Stibůrkové

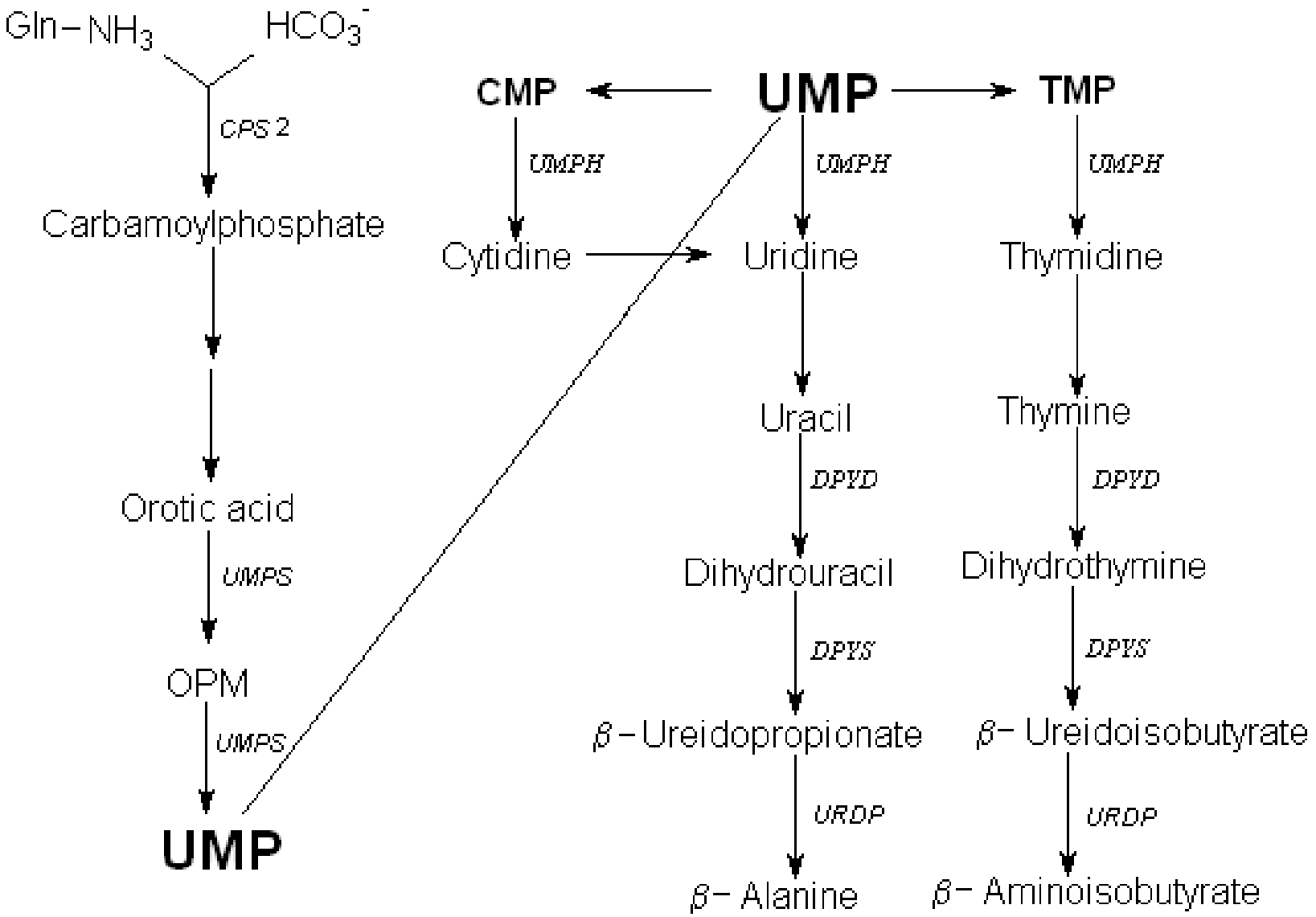
Xanthinuria

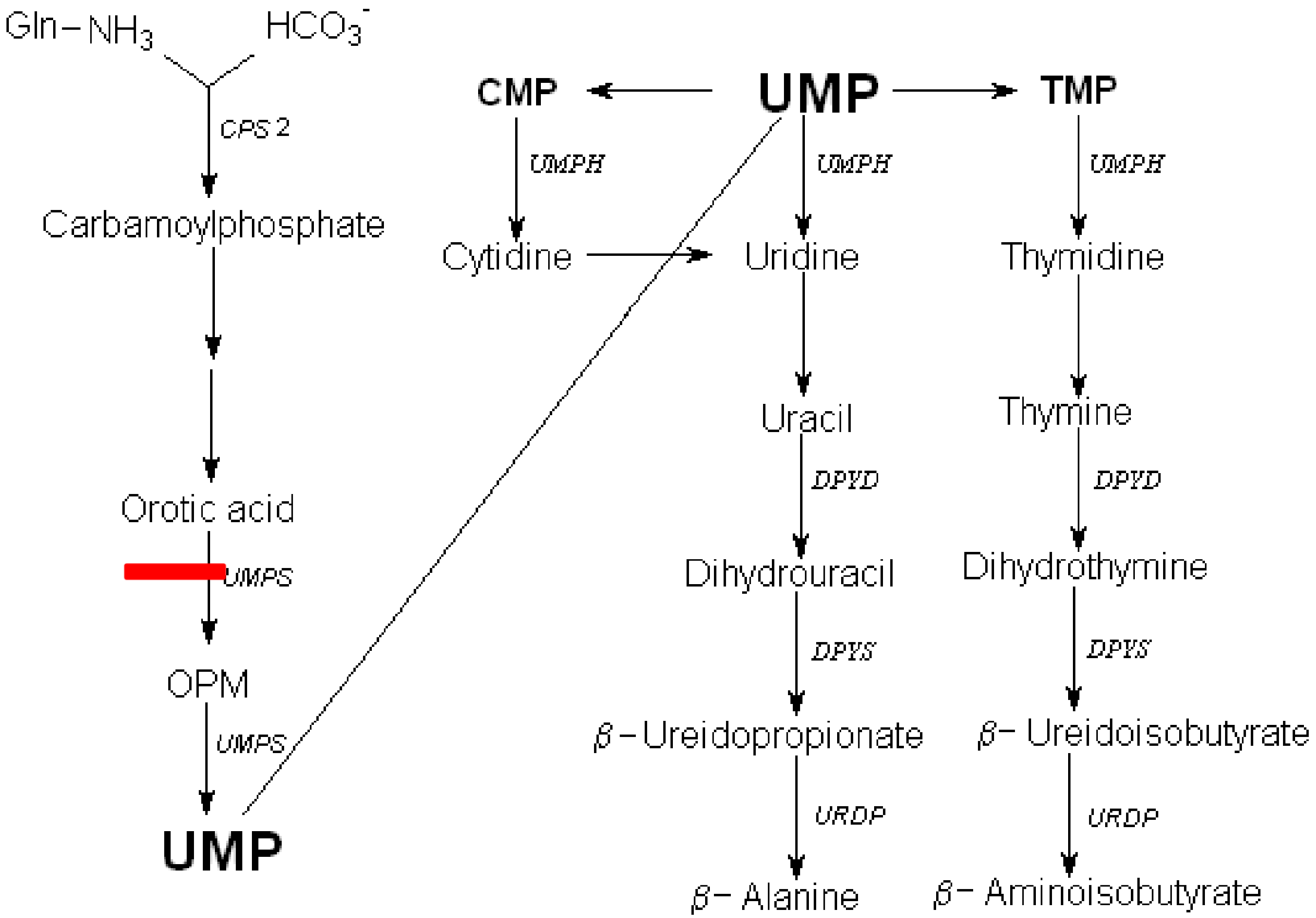
- Isolated XO deficiency
- Urolithiasis and occasionally myopathy due to xanthin crystalls, arthropathy
- 50% asymptomatic
- S and U- uric acid decreased!!!!!
- Treatment: fluid intake

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

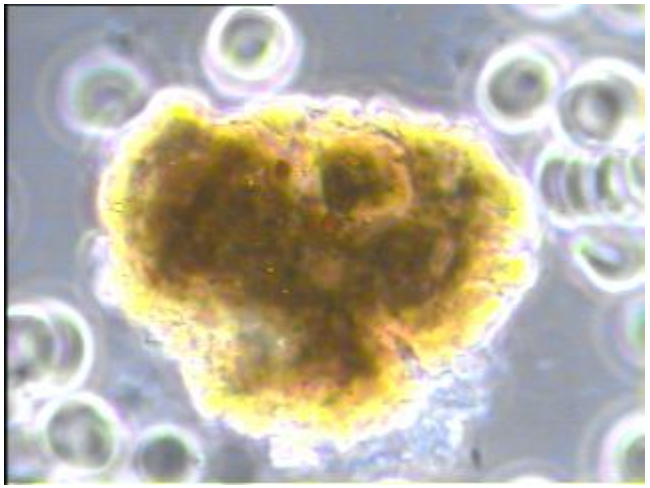
http://www.tamilspider.com/attachments/Resources/3322-71129-xanthine.jpg

Inherited metabolic disorders of pyrimidine metabolism


Gln – NH3
HCO3-
CPS 2
Carbamoylphosphate
Orotic acid
UMPS
OPM
UMPS
UMP
CMP
UMP
TMP
UMPH
UMPH
UMPH
Cytidine
Uridine
Thymidine
Uracil
Thymine
DPYD
DPYD
Dihydrouracil
Dihydrothymine
DPYS
DPYS
β – Ureidopropionate
β – Ureidoisobutyrate
URDP
URDP
β – Alanine
β – Aminoisobutyrate

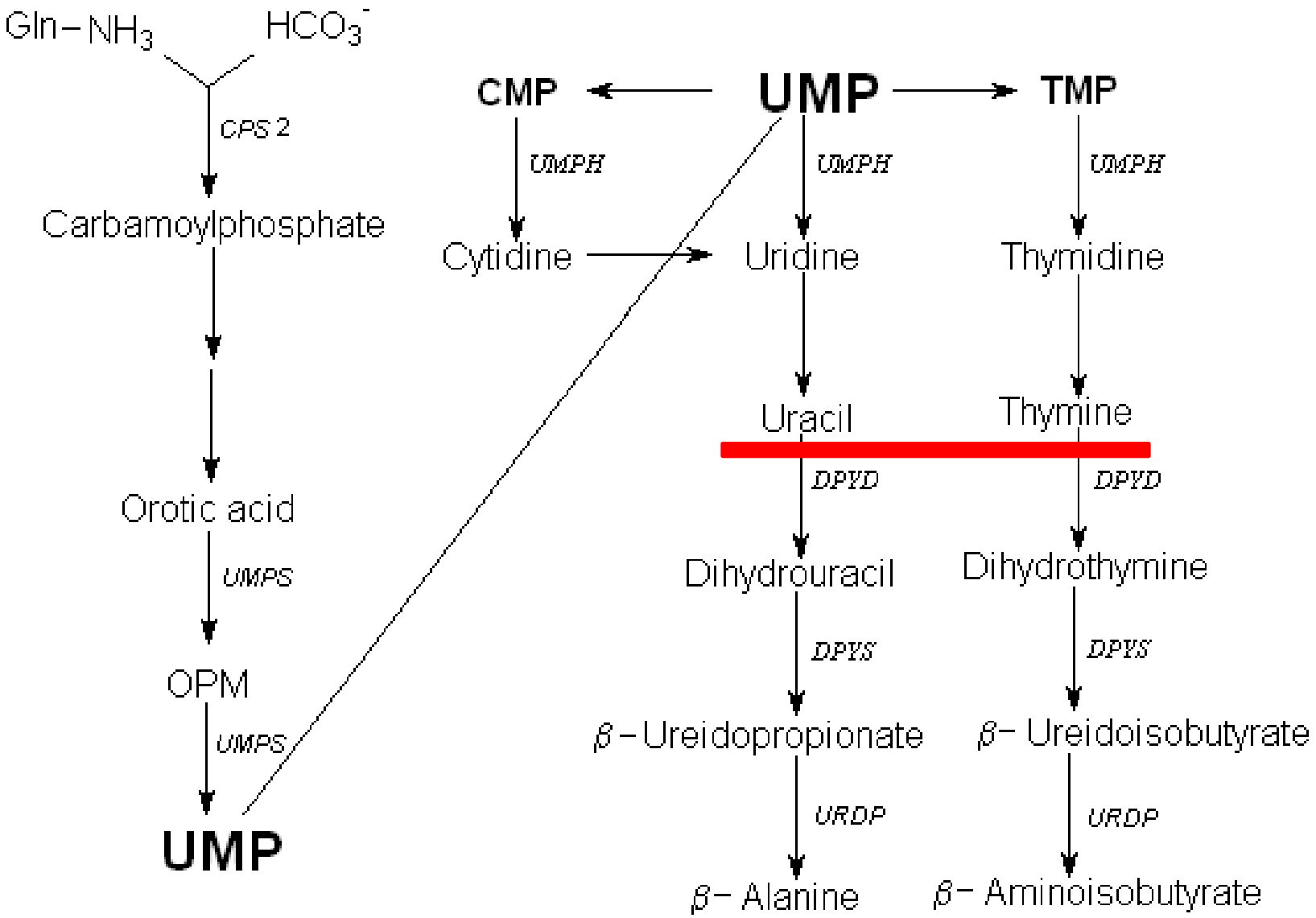

Gln – NH3
HCO3-
CPS 2
Carbamoylphosphate
Orotic acid
UMPS
OPM
UMPS
UMP
CMP
UMP
TMP
UMPH
UMPH
UMPH
Cytidine
Uridine
Thymidine
Uracil
Thymine
DPYD
DPYD
Dihydrouracil
Dihydrothymine
DPYS
DPYS
β – Ureidopropionate
β – Ureidoisobutyrate
URDP
URDP
β – Alanine
β – Aminoisobutyrate

Orotic aciduria



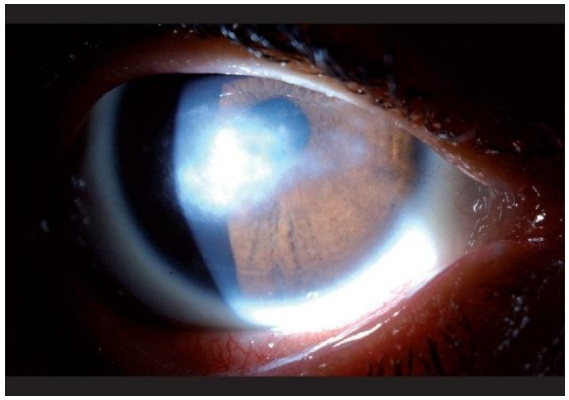
- UMP synthase deficiency
- Overproduction of orotic acid - crystalluria (lithiasis is rare)
- Decreased production of pyrimidines—abnormal hematopoesis-megaloblastic anemia—PMR, FTT
- Treatment: uridine (kinase converts to UMP)

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


Gln – NH3
HCO3-
CPS 2
Carbamoylphosphate
Orotic acid
UMPS
OPM
UMPS
UMP
CMP
UMP
TMP
UMPH
UMPH
UMPH
Cytidine
Uridine
Thymidine
Uracil
Thymine
DPYD
DPYD
Dihydrouracil
Dihydrothymine
DPYS
DPYS
β – Ureidopropionate
β – Ureidoisobutyrate
URDP
URDP
β – Alanine
β – Aminoisobutyrate

DPD deficiency

(Dihydropyrimidine dehydrogenase)

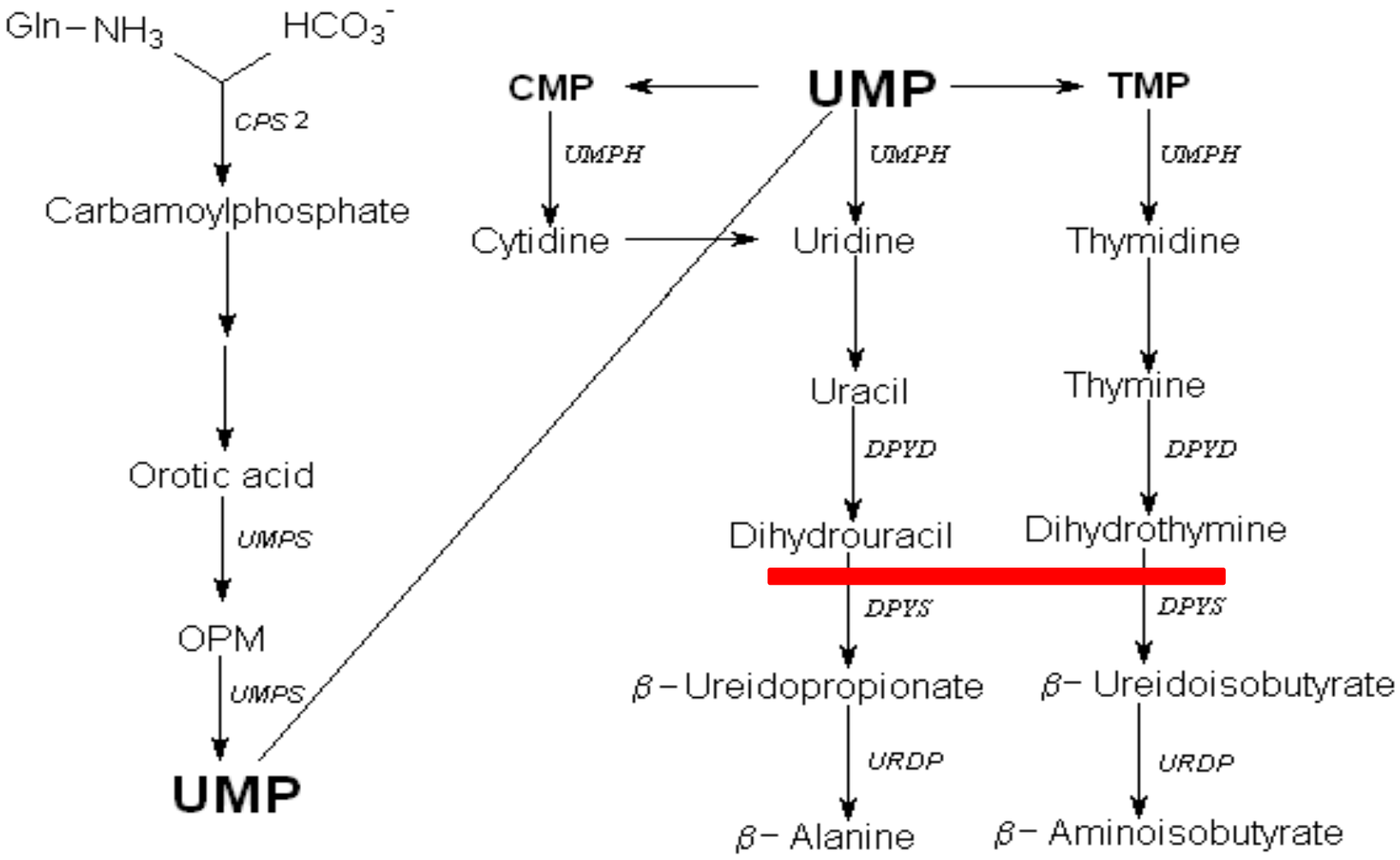


Neurotrophic keratitits

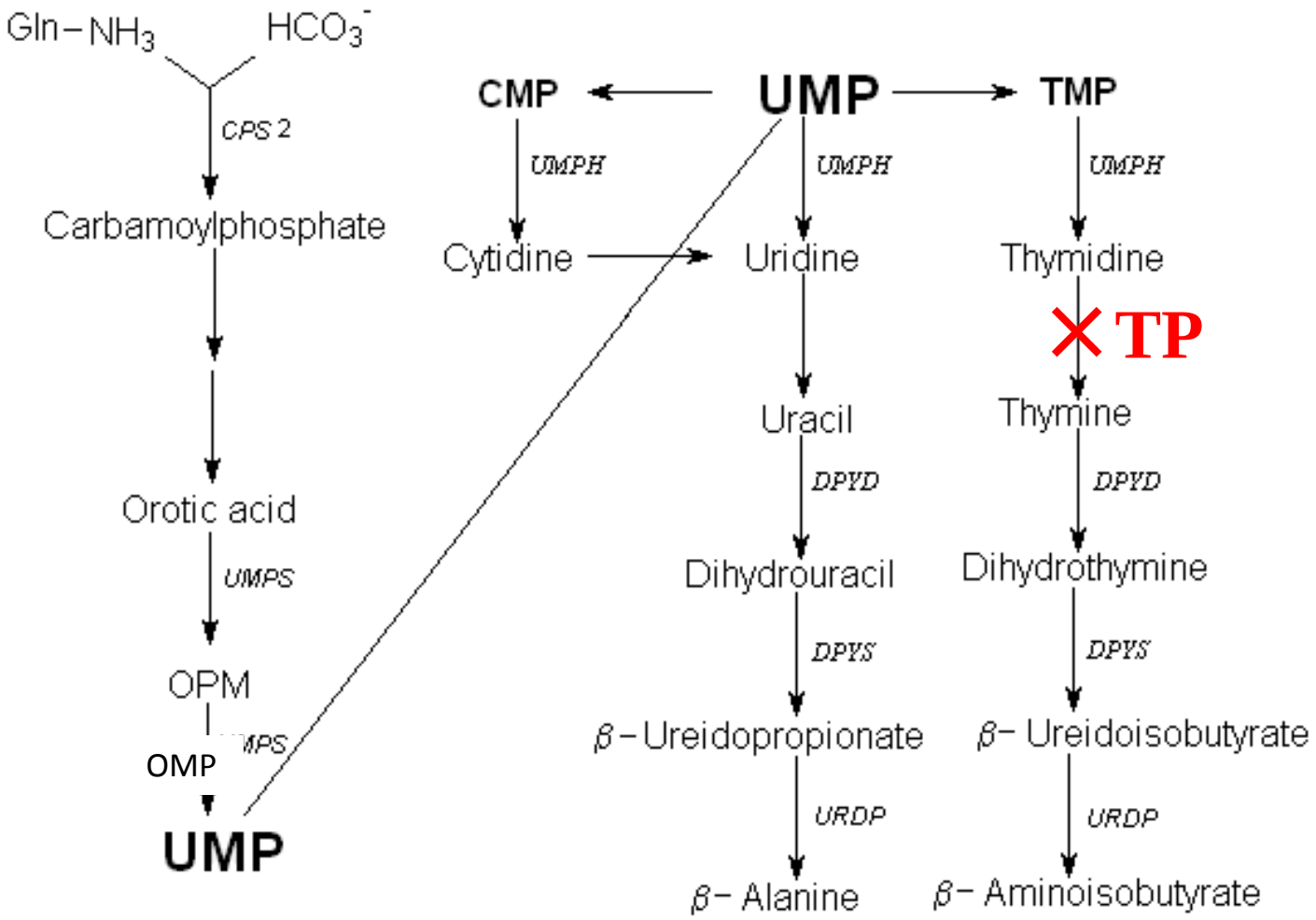
- Complete deficiency
  - Childhood onset
  - PMR, hypertonus, autism
  - Mikrocephaly, dysmorphy
  - No treatment known
- Partial deficiency
  - % of common population
  - Toxicity of 5-fluorouracil (neutropenia,stomatitis, neurological symptoms)

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

Dihydropyriminidase deficiency



Thymidine phosphorylase deficiency



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

Porphyrias, werewolves and vampires

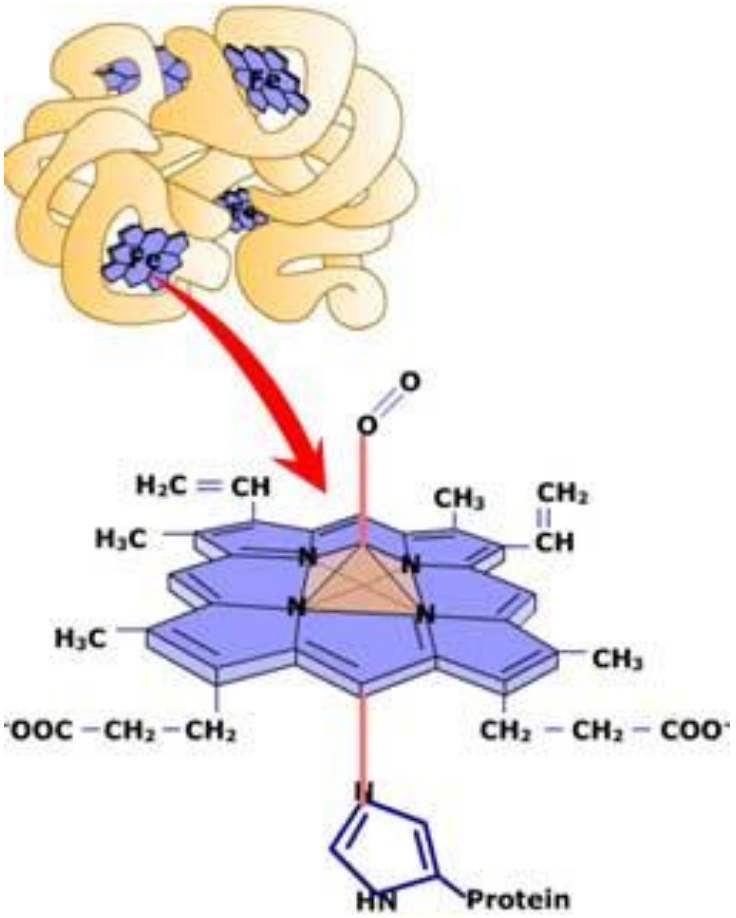
http://devoid.blogs.heraldtribune.com/files/2009/10/werewolf.jpg

http://th01.deviantart.com/fs21/300W/f/2007/258/a/5/Vampire_Caitlin_Deadly_Beauty_by_VampHunter777.jpg

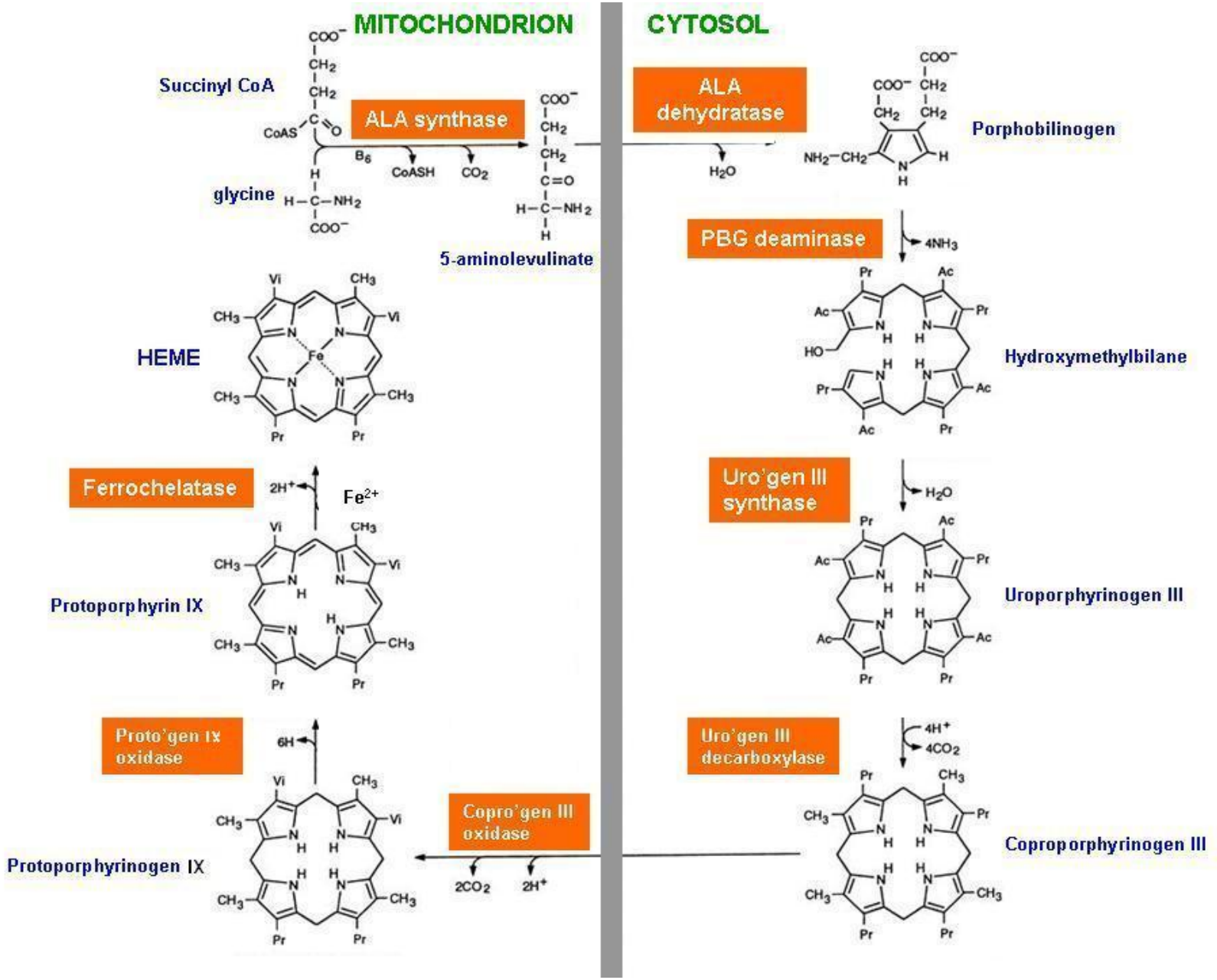
Hemoproteins-examples

- Hemoglobine/myoglobine- O_2 transport (Fe^{2+})
- Catalase-conversion of hydrogen peroxide to water and oyygen
- Cytochromes
  - Transfer of electrones in respiratory chain ($Fe^{2+} \leftrightarrow Fe^{3+}$)
  - NOS
- Cystathionine beta-synthase-structural role

Heme-structure



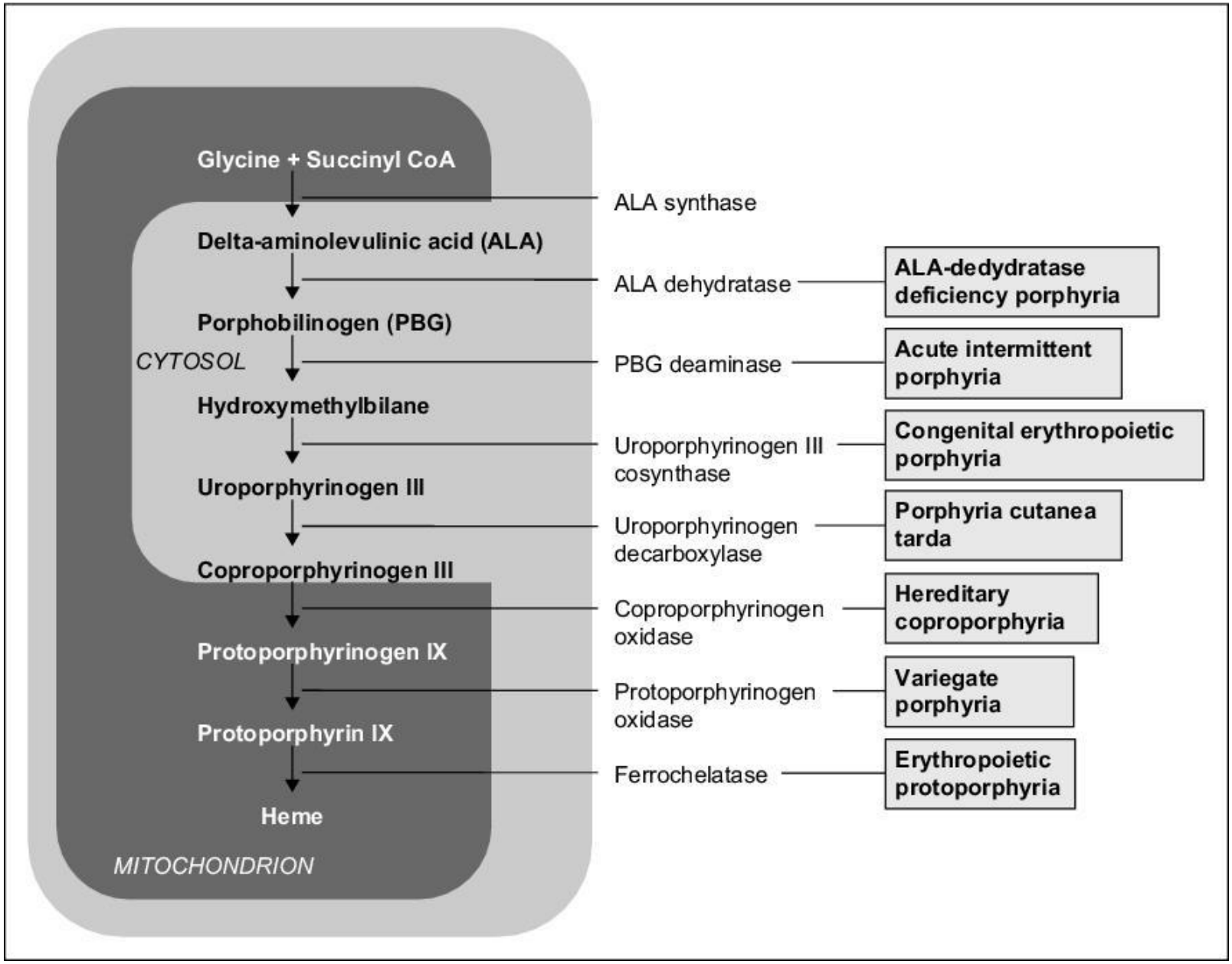
http://www.home-air-purifier-expert.com/images/heme.jpg



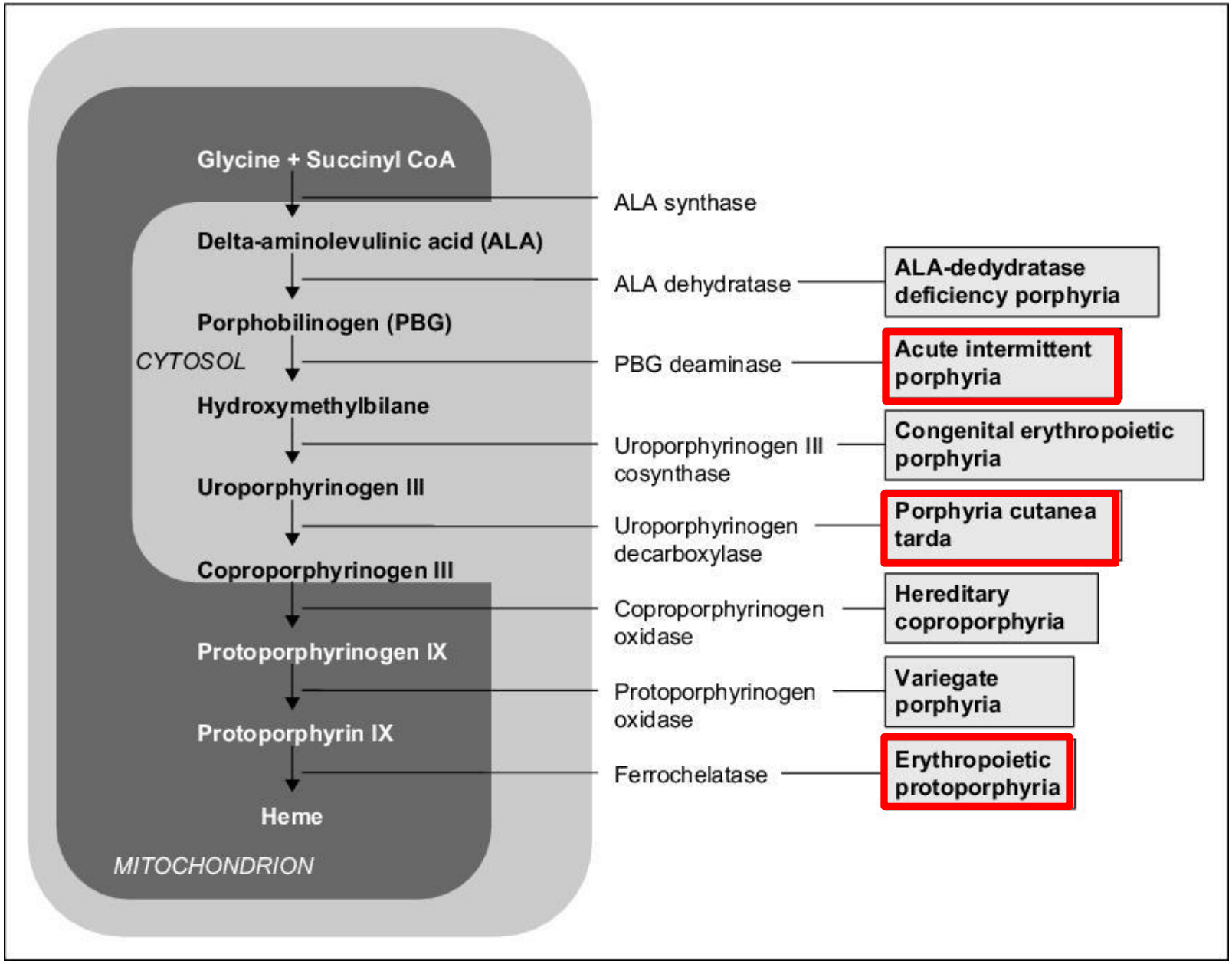
http://www.reactome.org/figures/porphyrin_biosynthesis.jpg

Porphyrias

- Often AD inheritance, some AR inheritance
- Usually onset in adulthood
- Common manifestation only after exposure (fasting, menses, drugs, sunlight)
- Classification-site of enzyme defect:
    - Liver
    - Erythropoetic
- Classification-symptoms:
    - Neurovisceral
    - Skin

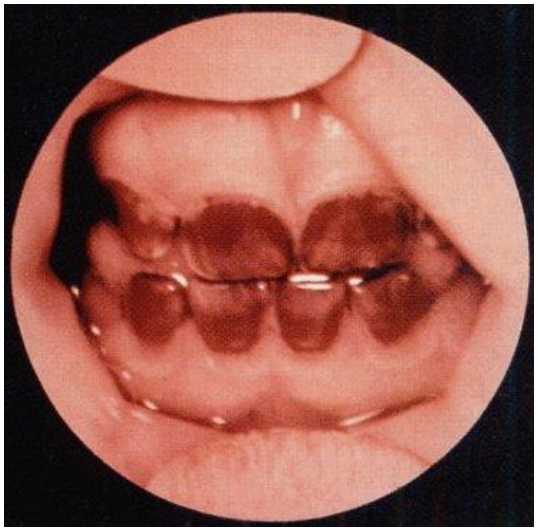


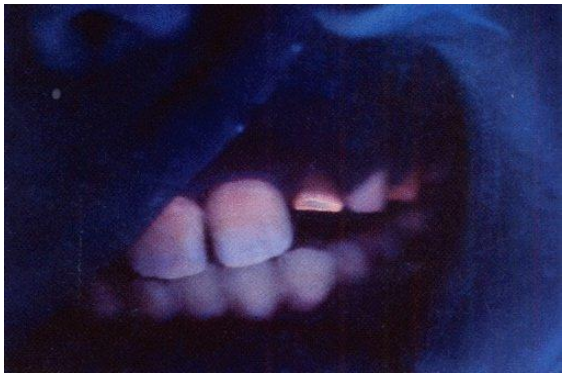
http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg



http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

How to detect porphyria by eye?

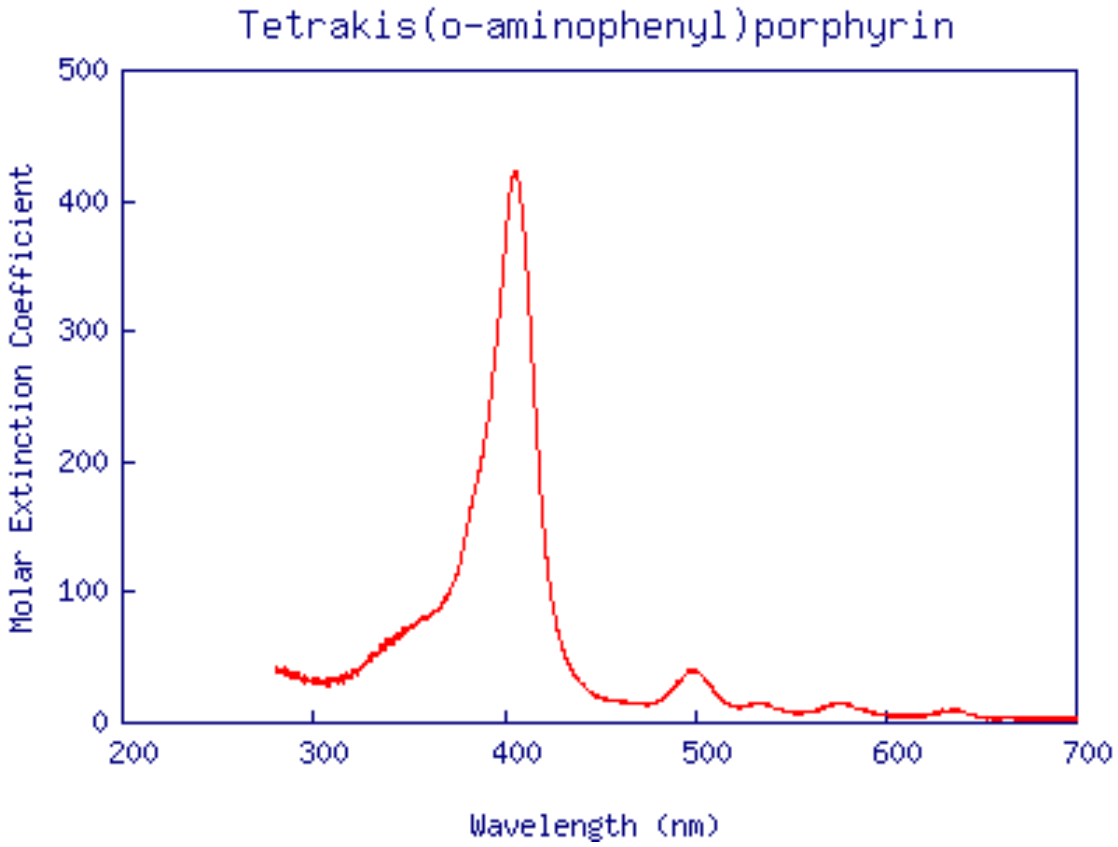




http://terrycomeau.com/Porphyria/Porphyria.htm

http://www.pathguy.com/lectures/erythrodontia.jpg

Absorption spectrum of porphyrins



Hepatic – acute - induced porphyrias

- Acute intermittent porphyria
- Porphyria variegata
- Hereditary koproporphyria
- Doose porphyria (AR)

- Inheritance - AD
- Trigger from some drugs, alcohol, hormones, hunger, ..

  like acute crisis (vomiting, acute abdomen, neurological and psychiatrical symptoms, …)

Neurological symptoms in porphyrias

- Peripheral NS
    - Increased activity of sympathicus: tachycardia, hypertension
    - Abdominal pain-nonlocalised but also colic
    - Parestesias
    - Peripheral neuropathy- muscle weaknes
- Central NS
    - Aggitation
    - Psychotic episodes
- Mechanisms: synaptic function interference (GABA vs.ALA similarity), heme depletion (NOS, Trp pyrrolase)

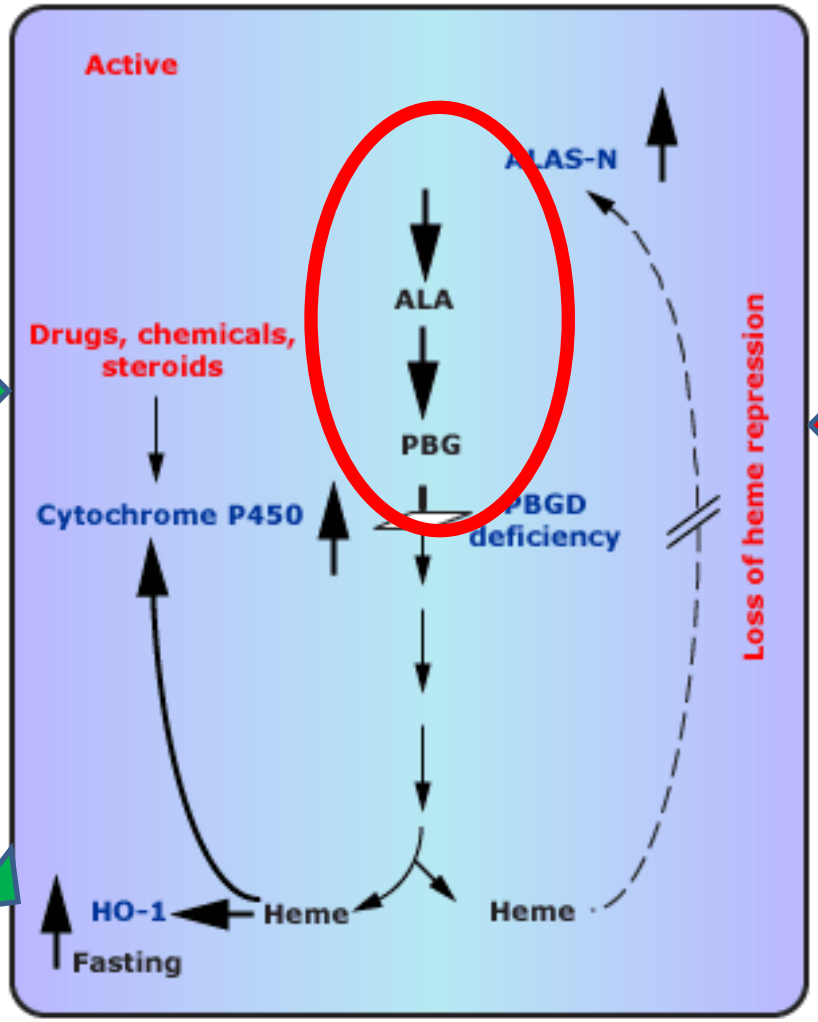
Mary Stuart-AIP?

en.wikipedia.org/wiki/Porphyria

AIP – acute intermitant porhyprias

- AD
- 20-40 years, > 2:1
- **Acute crisis** – triggers include drugs, hunger , stress, menstruation, hormones, …
  - Abdomen pain
  - Polyneuropathy
  - Psychiatric symptoms – agitation, depression
- Between crisis – asymptomatic
- Dg – porphyrins, porphobilinogen, ALA in urine

Increased need of heme synthesis



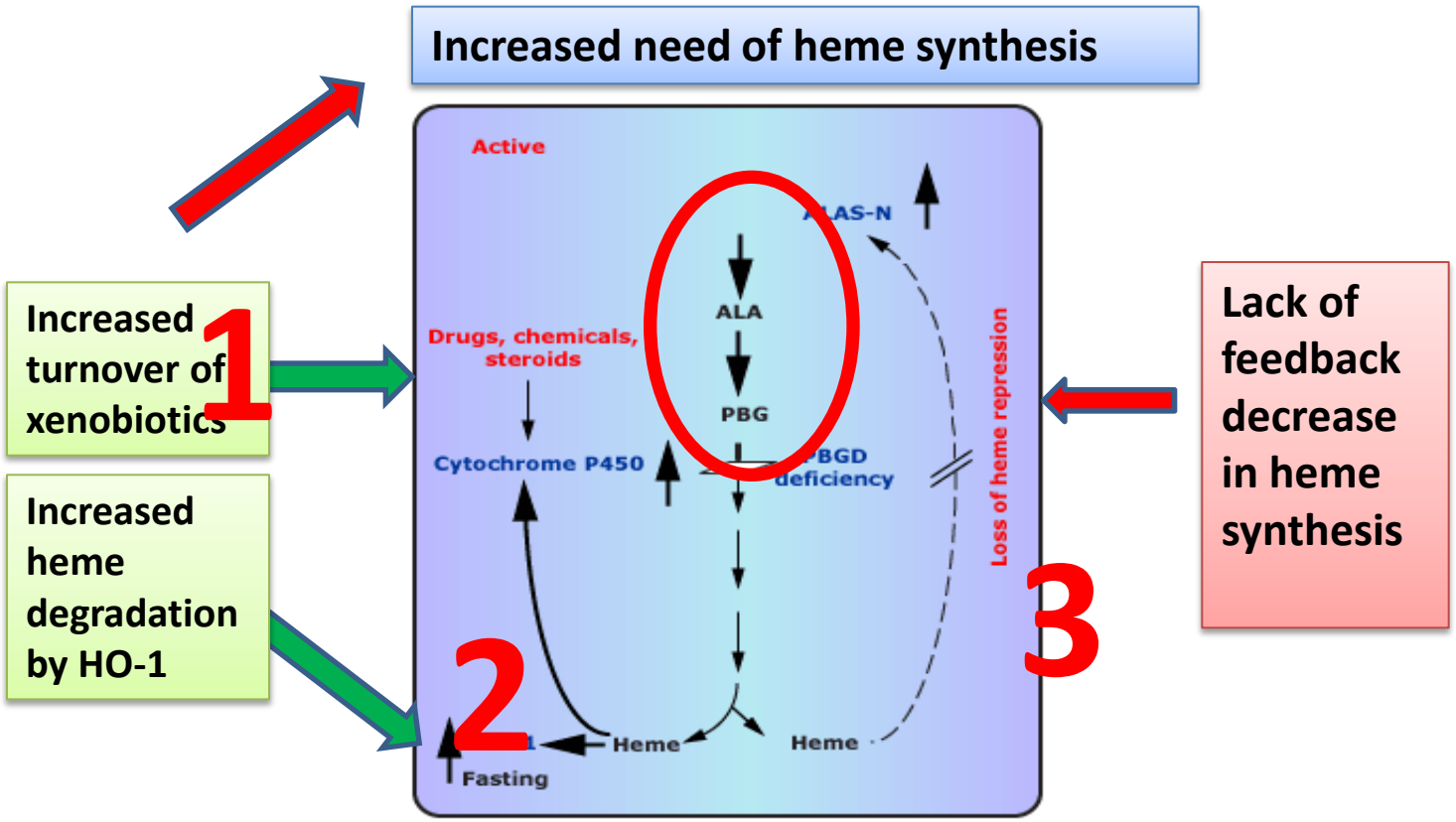
Increased turnover of xenobiotics

Increased heme degradation by HO-1

Lack of feedback decrease in heme synthesis

http://terrycomeau.com/Porphyria/Porphyria.htm

Treatment of AIP



1. Avoid of drugs, hormones, alcohol, …
2. Avoid of starvation – glucosis
3. Heme, heminarginate

Hepatic porphyrias

- Hereditary coproporphyria and Porphyria variegata
  - Very rare
  - AD
  - Abdomanal crisis, neuropsychiatric symptoms
  - Photosensitivity

- Doose disease
  - AR

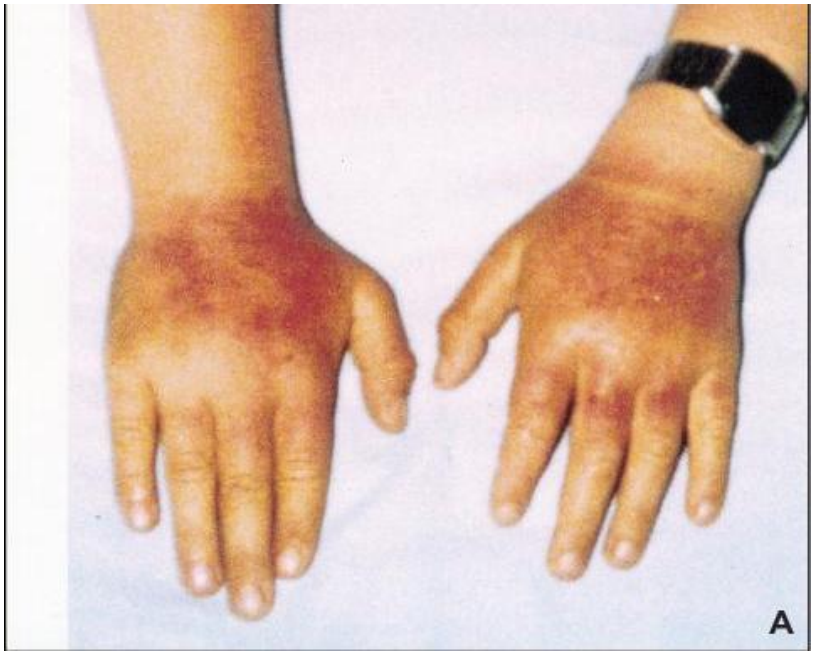
Photosensitive porphyrias

- Porphyria cutanea tarda
- Congenital erytropoietic porphyria (Gunther diseases)
- Erytropoietic protoporphyria

- Inheritance – AD (Gunther disease – AR)

- Dg – specific porphyrins in urine, blood and faeces

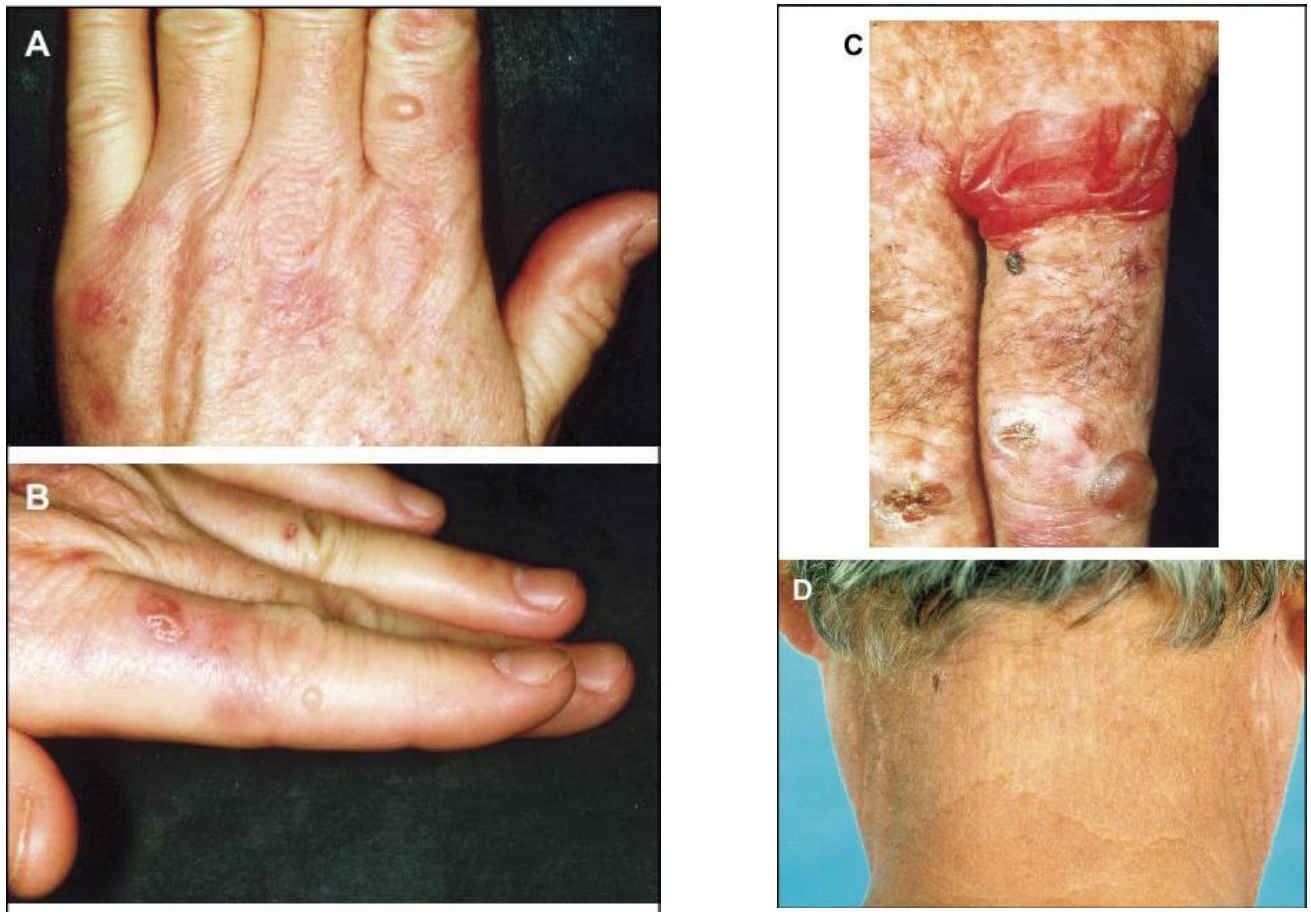
Photosensitivity in porphyrias



- Absorption in UV region
- Production of free radicals
- Development of inflammation (rush at start)

http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

PCT (porphyria cutanea tarda)



- Fragility, erosions, secondary infections, crusts, blisters, scarrind alopecia, hyperpigmentation, …

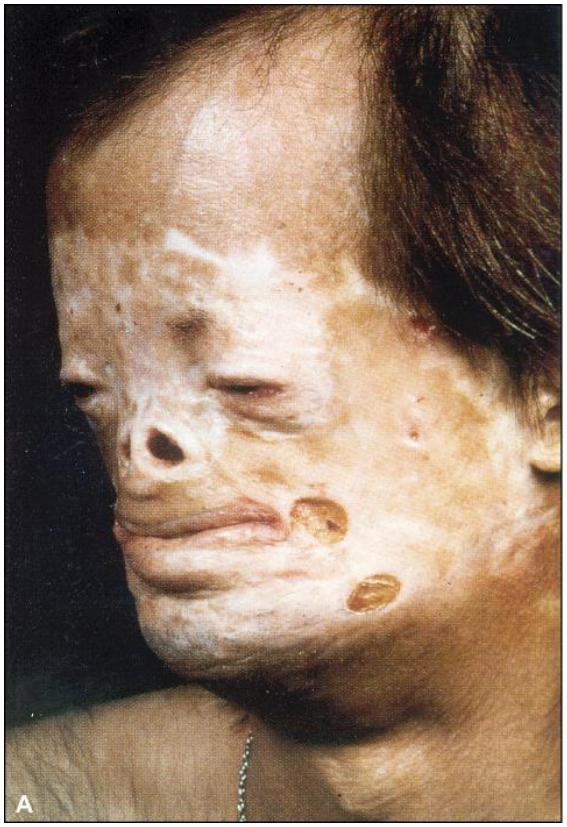
http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

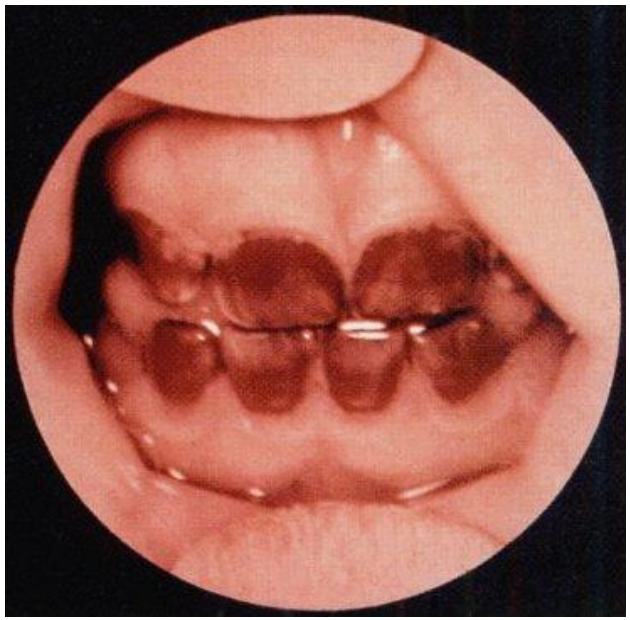
PCT (porphyria cutanea tarda)

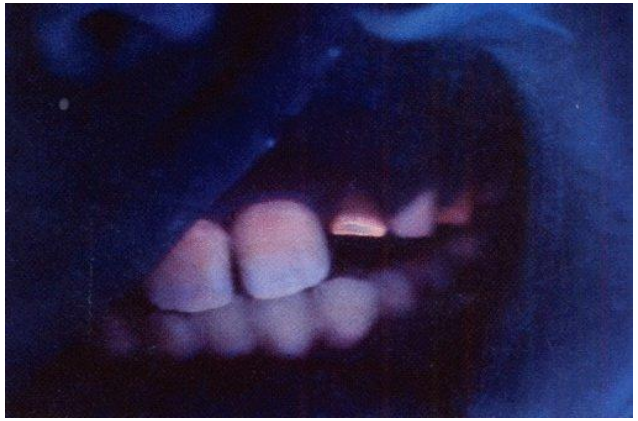
- AD; most frequent 1:5000
- No neurological symptoms
- Risk factors – alcohol, oestrogens, hepatatis C, haemochromatosis
- Th – phlebotomy, chlorochine (depletion of porphyrines from liver)

http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

CEP(congenital erythropetic porphyria)







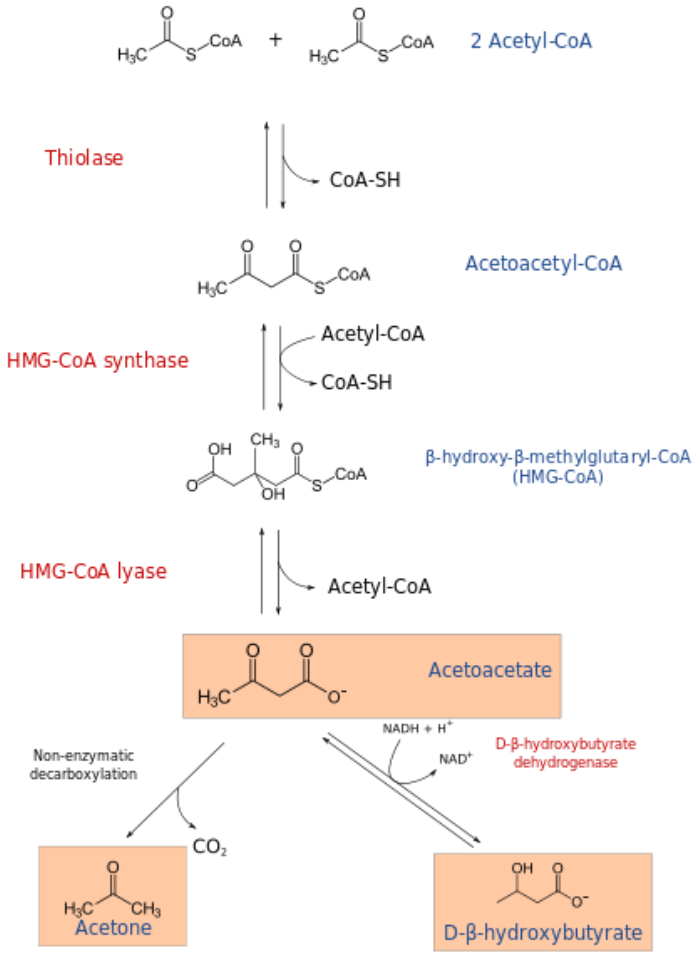
http://www.pathguy.com/lectures/erythrodontia.jpg

http://www.jle.com/en/revues/medecine/ejd/e-docs/00/04/18/FB/texte_alt_jleejd00203_gr1.jpg

Erythropoietic protoporphyria

- AD defect of ferrochelatase – accumulation in bone marrow, skin and liver
- Early onset in childhood
- Photosensitivity and erythrodontia
- Hemolysis and liver abnormalities- ca hepatis
- Neurological abnormalities rarely
- Therapy: transfusion, beta-caroten, transplant

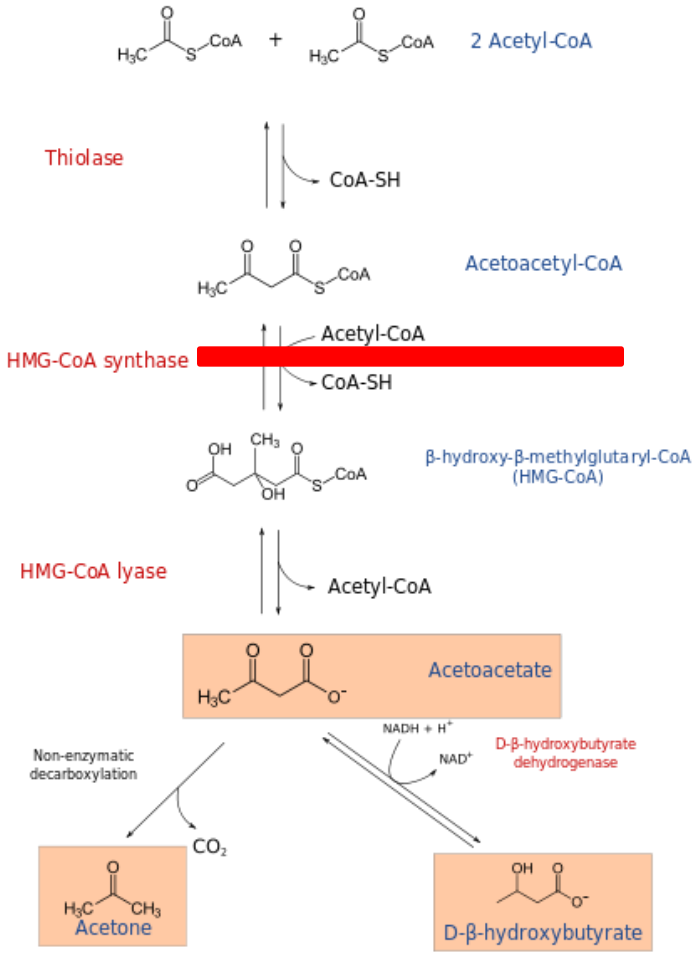
Ketogenesis



http://www.wikipedia.org

- in liver
- Ketones – brain, heart

Ketogenesis



http://www.wikipedia.org

- in liver
- Ketones – brain, heart

HMG-CoA synthase deficiency

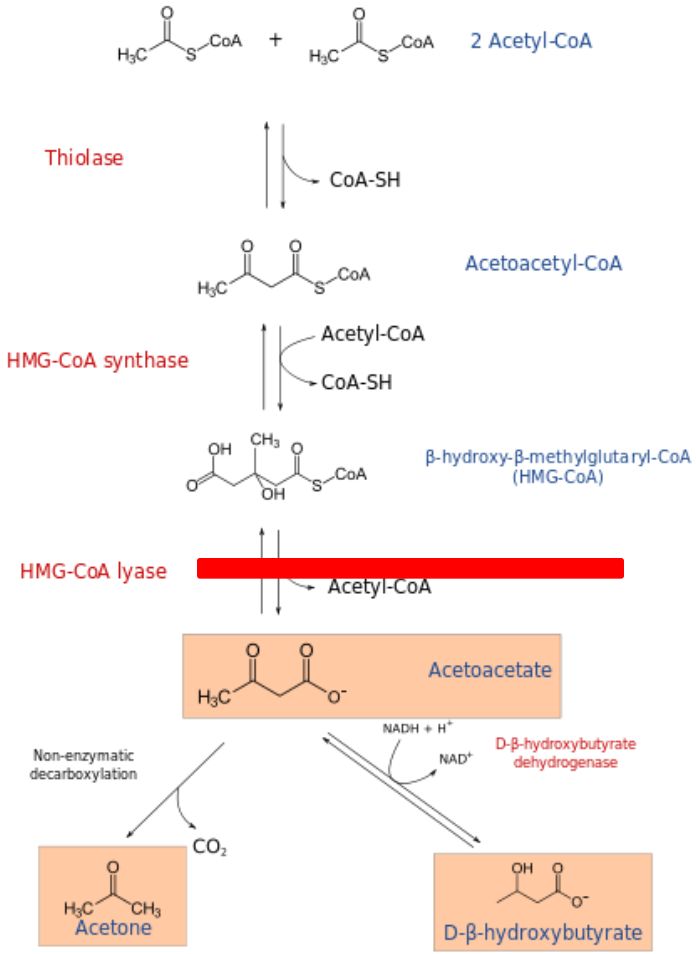
Acute hypoketotic hypoglycaemia

Metabolic acidosis

Therapy – avoid fasting

frequent meals (sugar)

Ketogenesis



http://www.wikipedia.org

- in liver
- Ketones – brain, heart

HMG-CoA lyase deficiency

Acute hypoketotic hypoglycaemia

Metabolic acidosis

Reye-like epizodes

Hepatopathy

Therapy – avoid fasting

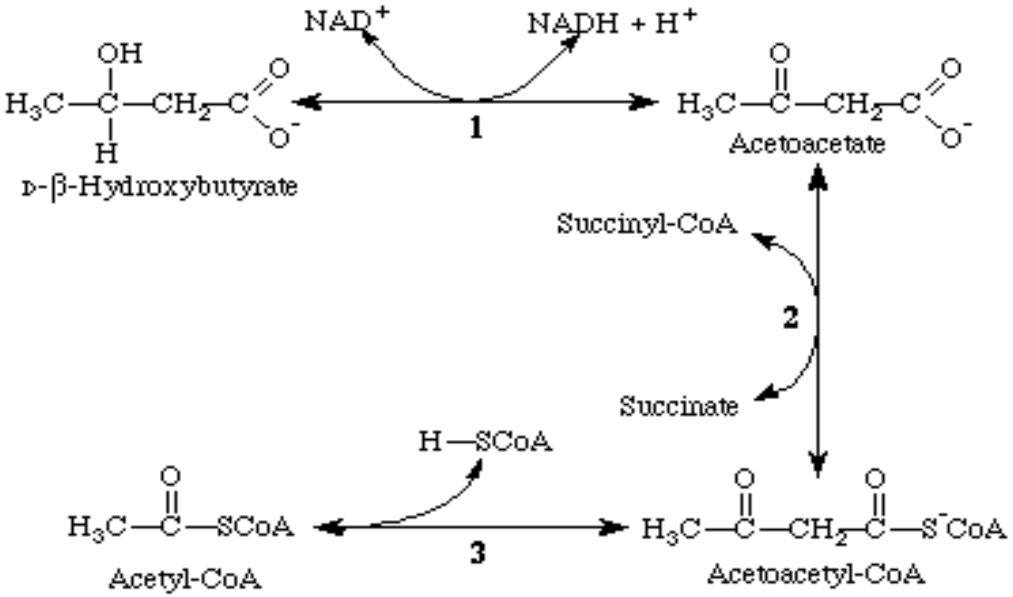
frequent meals (sugar)

low fat diet

protein restriction

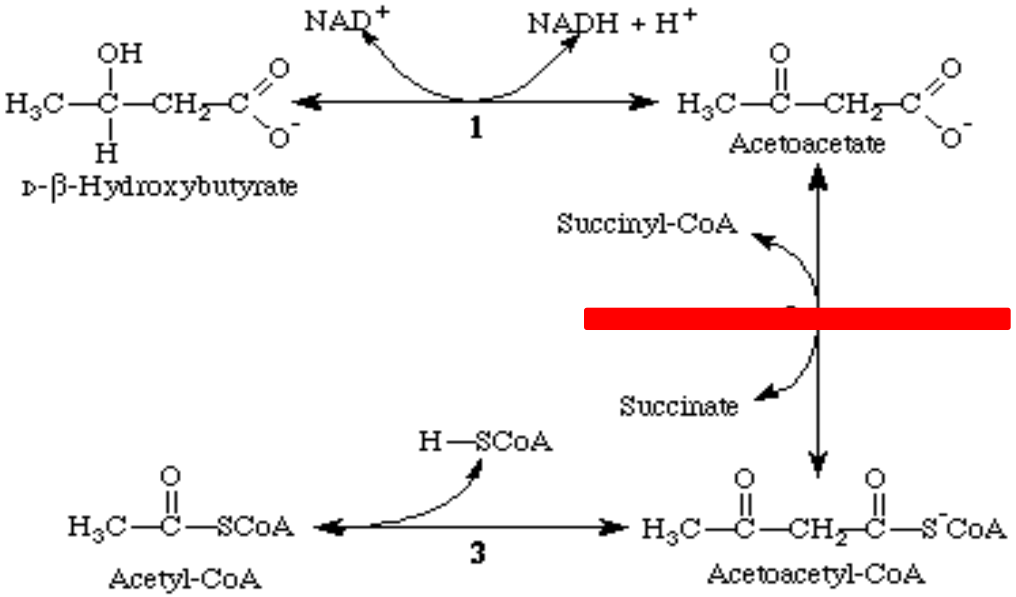
Ketolysis

- extrahepatic
- Ketones – brain, heart



Ketolysis

- extrahepatic
- Ketones – brain, heart



SCOT (succinyl-CoA.3-oxoacid-Coa transferase)

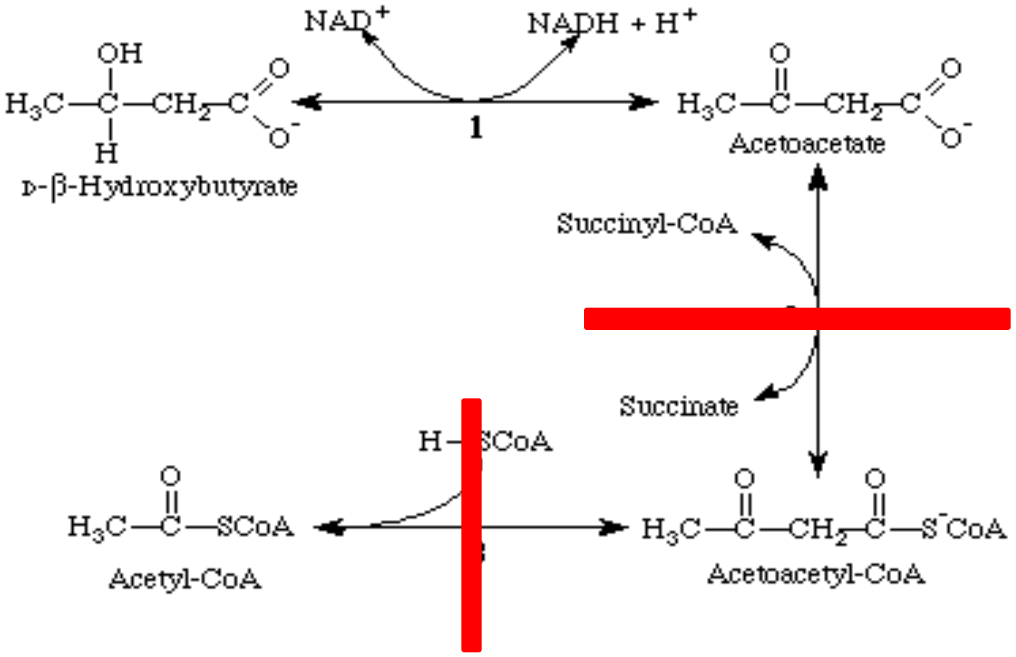
Severe ketoacidosis

Hyperketotic hypoglycaemia

coma, hypotonia

Ketolysis

- extrahepatic
- Ketones – brain, heart



SCOT (succinyl-CoA.3-oxoacid-Coa transferase)

3-oxothiolase deficiency

Ketoacidosis

Hyperketotic hypoglycaemia

Reye-like; coma, hypotony

Therapy – low protein

(proteins induce ketogenesis; Ile)

- sugar rich diet

Pathobiochemistry of fasting/starvation

- Fasting – after nutrient reabsorbation to starvation

  ↑ glucosis in blood -> ↑ insuline and ↓ glucagon ->

  glycolysis, lipogenesis, glycogenesis, proteosynthesis

- Starvation - 3 phasis –

  phase early gluconeogenetic

  phase of adaptation

  terminal phase – catabolism, critical

Pathobiochemistry of fasting/starvation

Early gluconeogenetic phase –

- normoglycaemia
- **glycogen degradation** in liver
- **gluconeogenesis** in liver

  Cori cycle; Alanine cycle

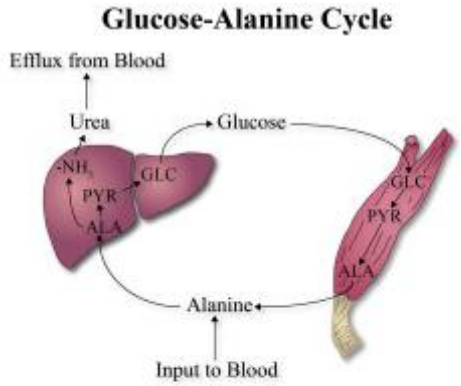
  BCAA in muscle and Gln (GIT, kidney)
- lipolysis – hormone sens.lipase

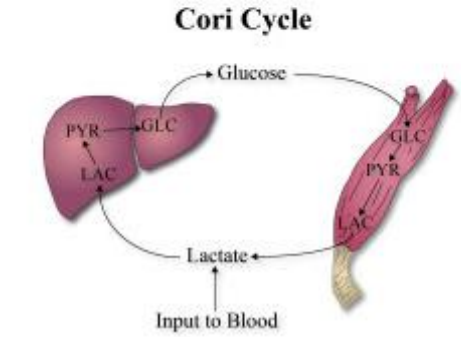
  ↑ glucagon, adrenalin; ↓ insuline

  glycerol in liver

  beta oxidation of FFA in muscle,

  myocard, liver and kidney





Pathobiochemistry of fasting/starvation

Phase of adaptation – 3rd day to some weeks

- glycogen pool is limited – no glycogen degradation
- decreased gluconeogenesis

  glucose from glycerol, limited pool of lactate, pyruvate, alanine
- **increased beta oxidation FFA** - energy
- **ketogenesis** (in liver) **and ketolysis** (in brain, muscle, myocard)
- protein sparing phase

Pathobiochemistry of fasting/starvation

Terminal phase – after 7-8 weeks

- no fat pool; no glycogen pool
- Activation of proteocatabolism –
    - muscle loss – weight loss
    - imunite reaction inhibition
    - Coagulapathy
    - decreased tissue reparation
    - ….
    - death

Thank you