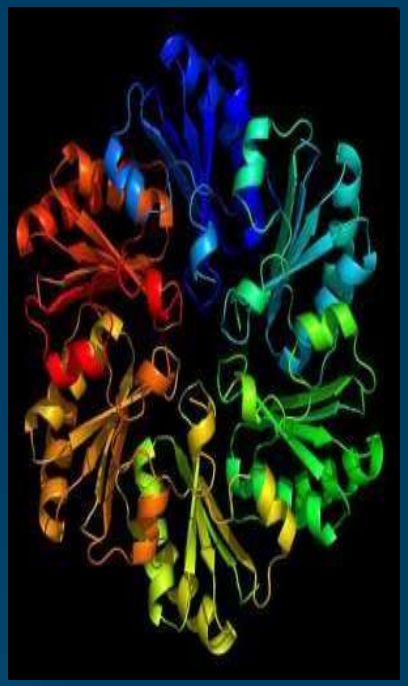
PURINE & PYRIMIDINE METABOLISM & DISORDERS



FUNCTIONS OF NUCLEOTIDES

- Polymerize to make DNA and RNA
- Energy currency of the cell e.g. ATP, GTP
- Act as carriers of active intermediates in various metabolic pathways e.g. UDP-glucose in glycogen synthesis, SAM
- Component of coenzymes e.g. FAD, NADH, NADPH
- Act as 2nd messengers e.g. cAMP and cGMP
- Allosteric regulation of various metabolic pathways e.g. ATP inhibits PFK-1

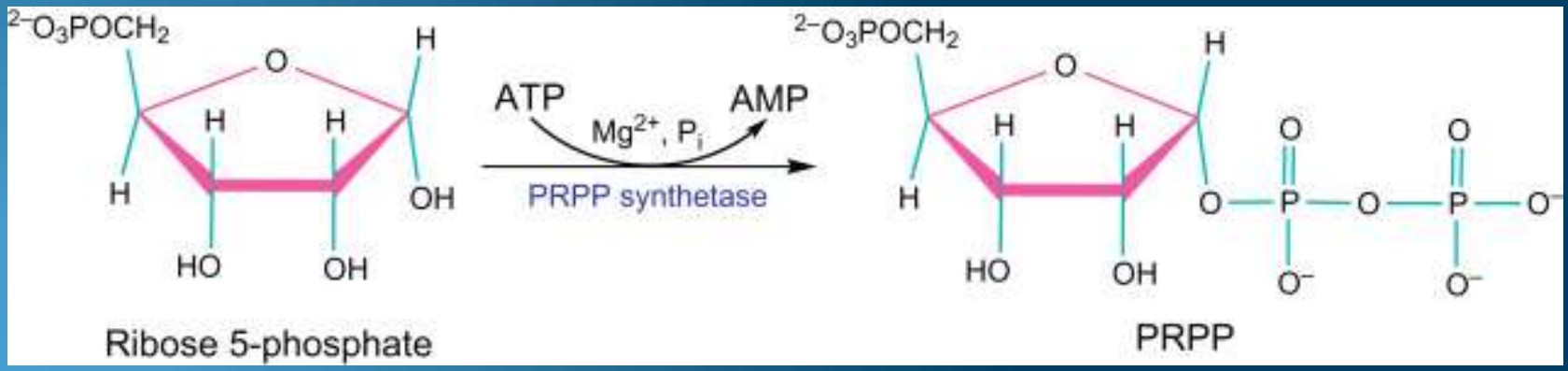
There are two pathways leading to nucleotides

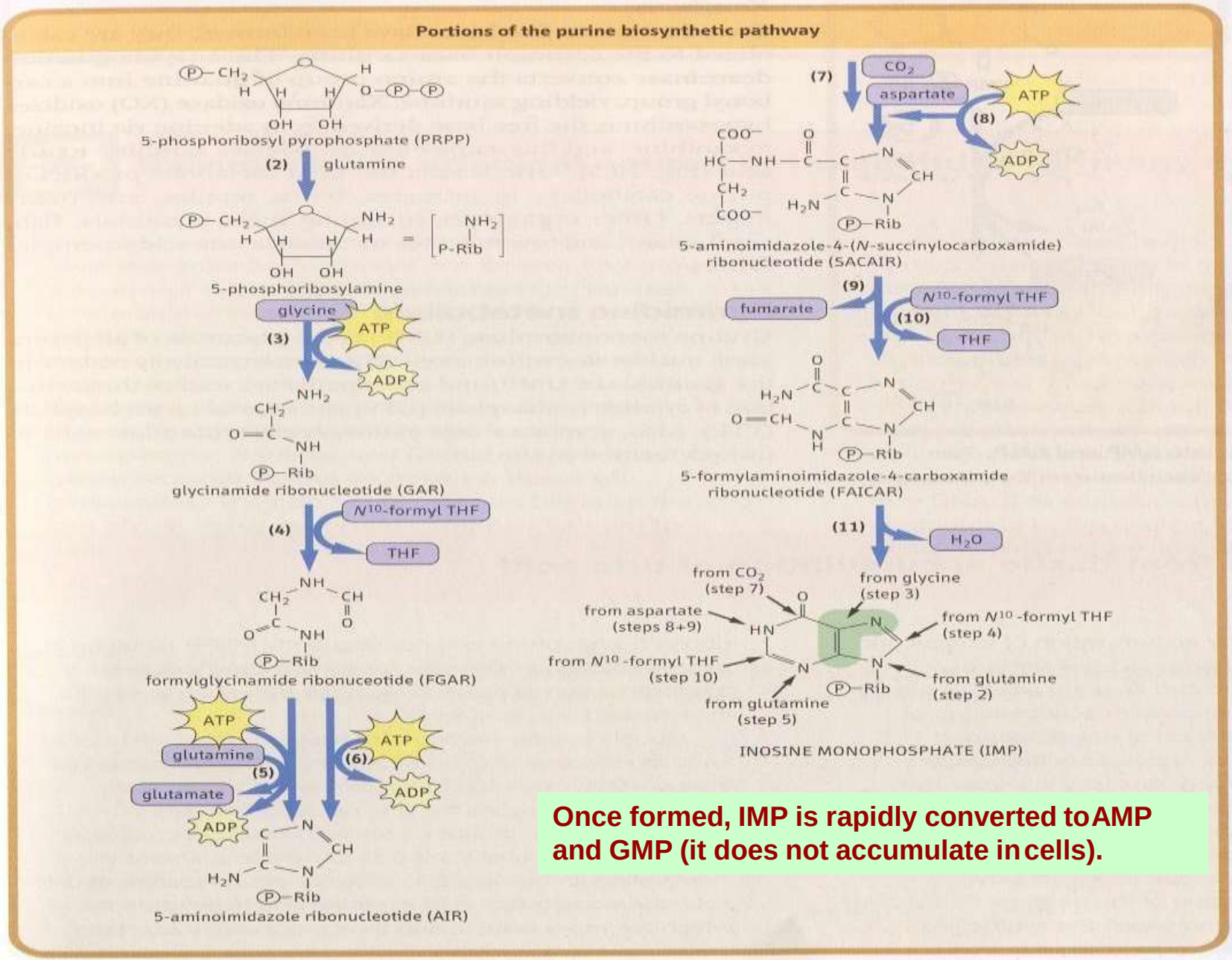
- **De novo synthesis**: The synthesis of nucleotides begins with their metabolic precursors: ***amino acids, ribose-5-phosphate, CO_2, and one-carbon units***.
- **Salvage pathways:** The synthesis of nucleotide **by recycle the free bases or nucleosides** released from nucleic acid breakdown.

De novo synthesis of purines:

- Occur in **the cytosol** of the cell
- Starts by conversion of ribose 5- phosphate to PRPP

By the enzyme PRPP synthase then formation of 5-phosphoribosylamine by PRPP glutamyl amidotransferase , then condensation reactions of glycine , aspartate, glutamine, Co2 and folate to form IMP





Once formed, IMP is rapidly converted to AMP and GMP (it does not accumulate in cells).

Regulation

1- Availability of PRPP

2- PRPP synthetase is feedback regulated by AMP, ADP, GMP and GDP.

3- Activity of PRPP glutamyl amidotranferse is feedback Regulated by GMP and AMP.

Inhibitors of purine synthsis

-they are toxic

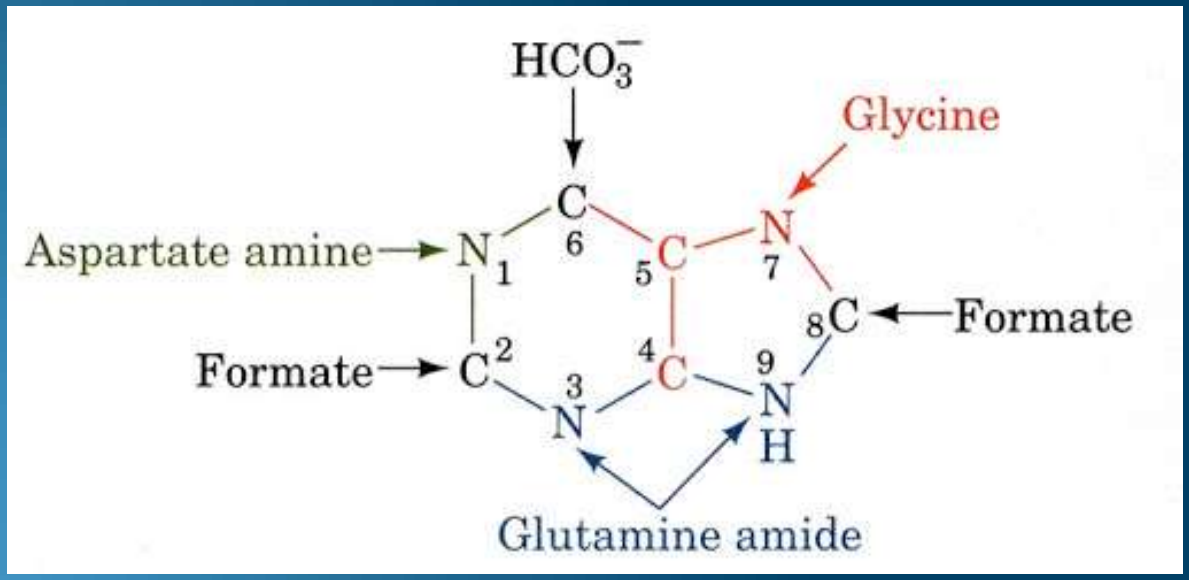
-Examples:

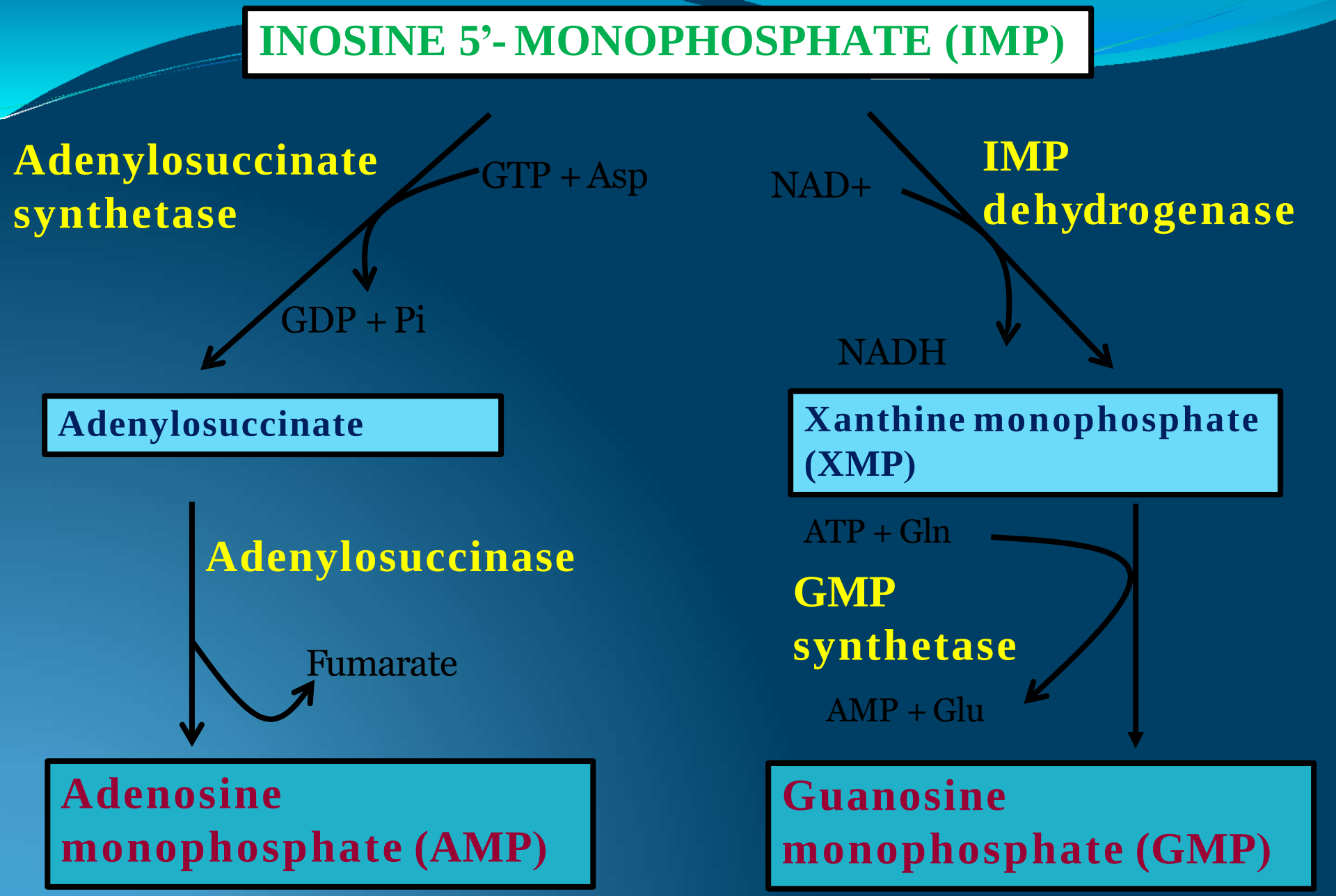
1- Azaseine : glutamine analogue

2-Trimethoprim, methotrxate: folic acid analogues

IMP Synthesis - Significance

- IMP = serves as a precursor for synthesis of all other purine nucleotides such as adenine and guanosine monophosphate (AMP & GMP)and ATP.




INOSINE 5'- MONOPHOSPHATE (IMP)
Adenylosuccinate synthetase
GTP + Asp
GDP + Pi
Adenylosuccinate
Adenylosuccinase
Fumarate
Adenosine monophosphate (AMP)
NAD+
IMP dehydrogenase
NADH
Xanthine monophosphate (XMP)
ATP + Gln
GMP synthetase
AMP + Glu
Guanosine monophosphate (GMP)

Salvage Pathways for Purine Synthesis

Purine bases created by degradation of RNA and DNA and intermediate of purines synthesis can be directly converted to the corresponding nucleotides.

The significant of salvage pathway

1 Save fuel

2Some tissues and organs such as brain and bone marrow are only capable of synthesizing nucleotides by Salvage pathways

Broken down endogenous nucleotides = salvage pathways.

Purine salvage pathways us one of two enzymes.

Adenine phosphoribosyltransferase (APRT).

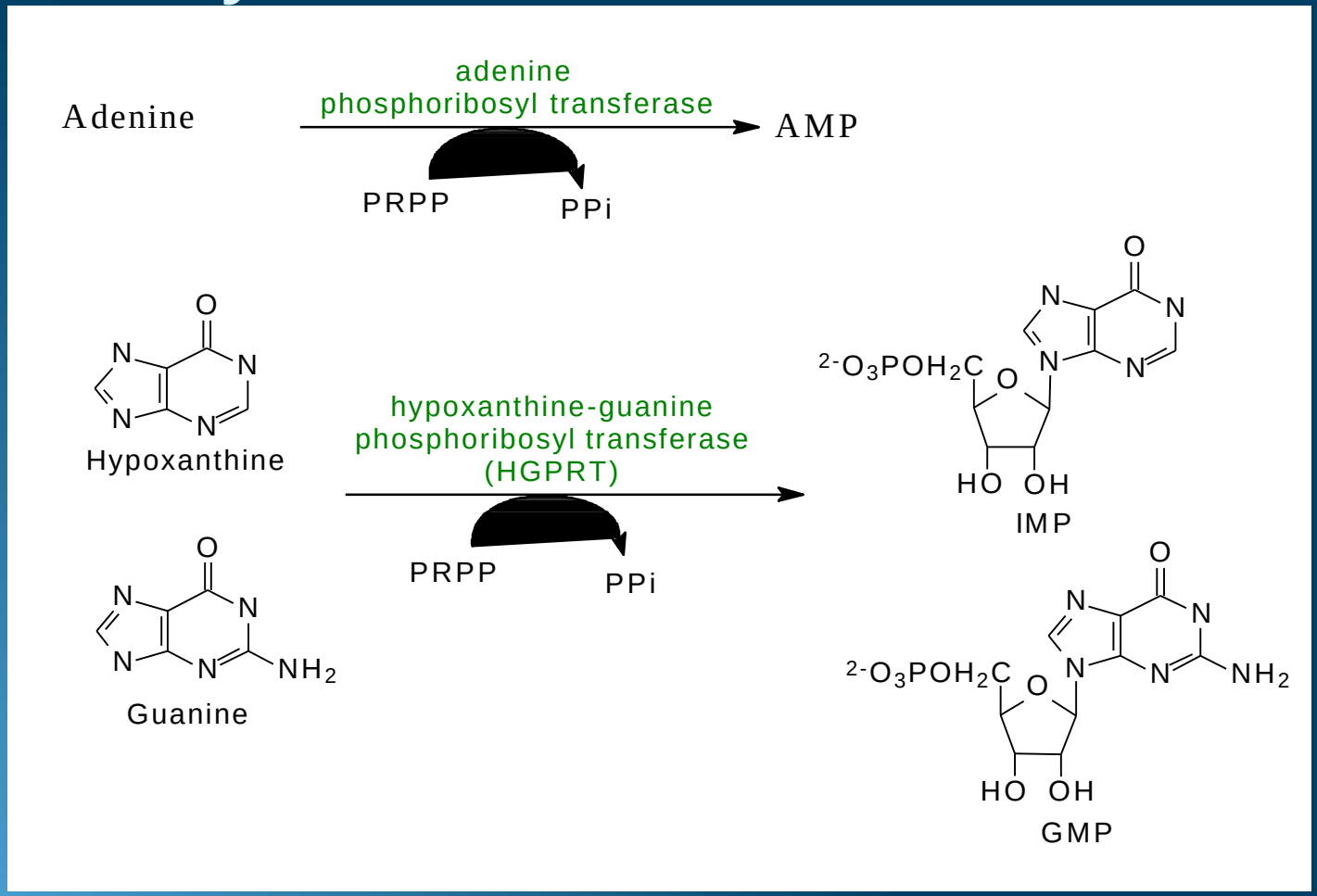
Converts free adenine to AMP

Hypoxanthine-guanine phosphoribosultransferase (HGPRT).

Converts hypoxanthine to IMP

Converts guanine to GMP

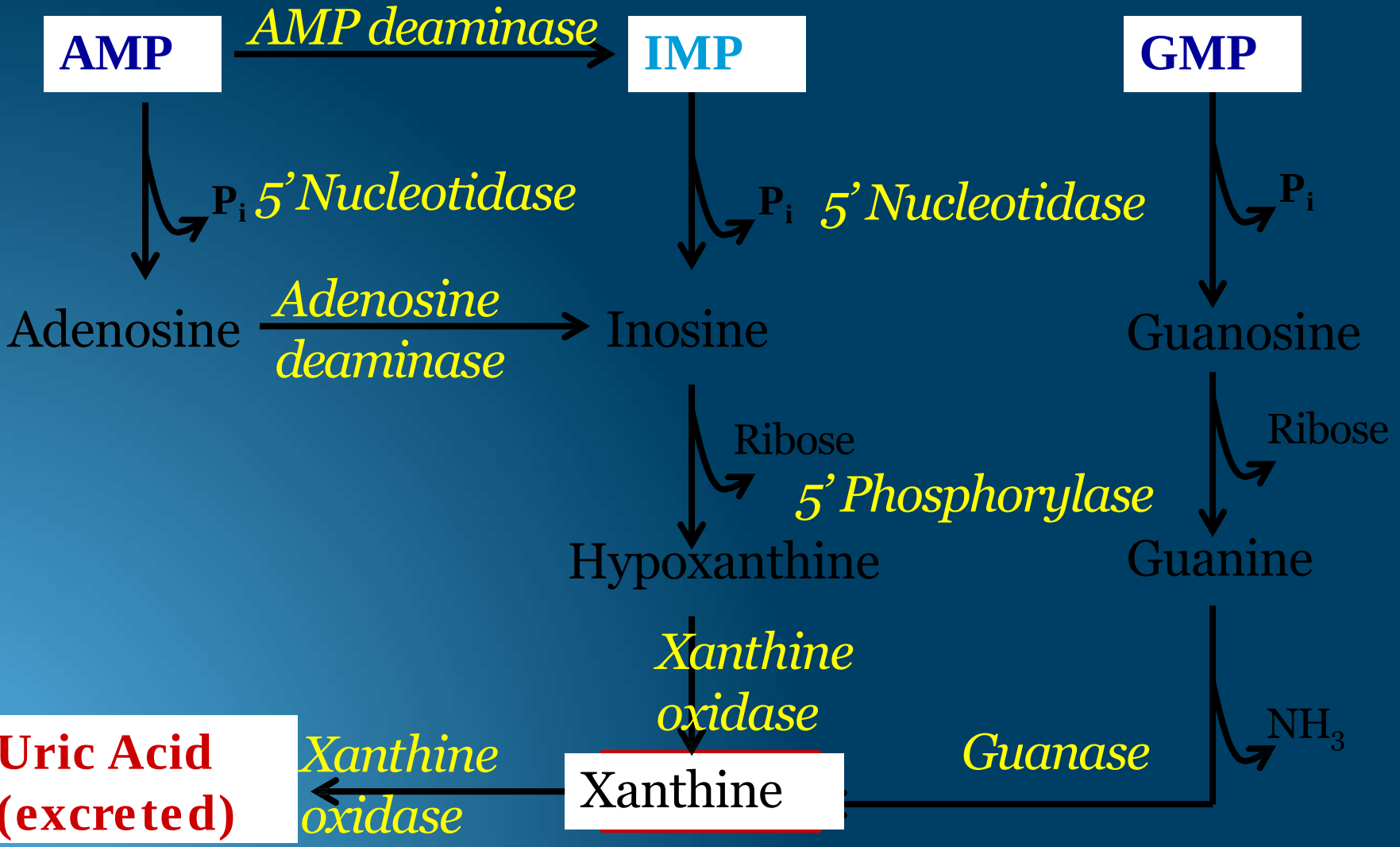
Purine Salvage Pathway



Absence of activity of HGPRT leads to Lesch-Nyhan syndrome.

DEGRADATION OF PURINE NUCLEOTIDES

IMP is the precursor for both AMP and GMP



DISEASES ASSOCIATED WITH DEFECTS IN PURINE METABOLISM

- HYPERURICEMIA
- GOUT
- LESCH-NYHAN SYNDROME
- KIDNEY STONES
- SEVERE COMBINED IMMUNODEFECIENCY (SCID)

HYPERURICEMIA

Characterized by plasma urate (uric acid) level greater than 7.0 mg/dL

Normal plasma levels

Females = 2.4-6 mg/dL

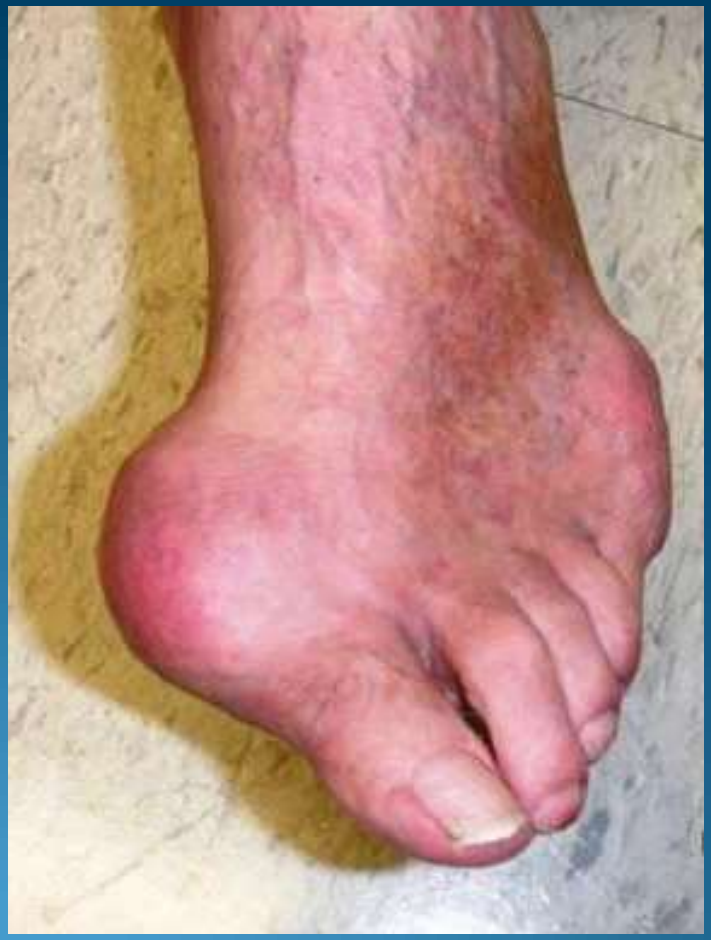
Males = 3.4-7 mg/dL

HYPERURICEMIA

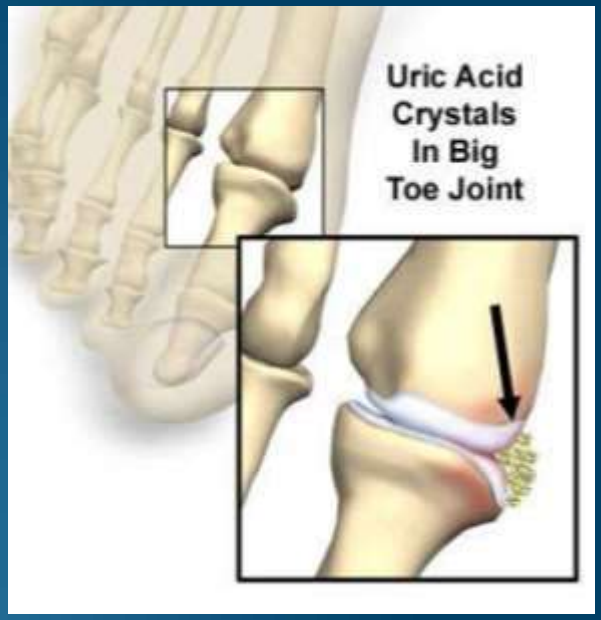
- **Primary Hyperuricemia**: an innate defect in purine metabolism and/or uric acid excretion

- **Secondary Hyperuricemia**: increased availability of purines due to medications/ medical conditions or through diet.

GOUT



Gout is caused by precipitation of sodium urate crystals in the joints resulting in inflammation and pain.



Progression of Hyperuricemia to Gout

Stage 1: Asymptomatic hyperuricemia. At a serum urate concentration greater than 6.8 mg/dL, urate crystals may start to deposit in the joints. No evidence that treatment is required.

Stages 2 : Acute gout. If sufficient urate deposits develop around joints, and if the local environment or some trauma triggers the release of crystals into the joint space, an inflammatory response occurs. These flares can be self-resolving but are likely to recur.

Stage 3 : Intercritical periods. These are the intervals between attacks. During these periods, crystals may still be present at a low level in the synovial tissue and fluid, resulting in future attacks.

Stage 4 : Advanced gout. If crystal deposits continue to accumulate, patients may develop chronically stiff, swollen joints and tophi. This advanced stage of gout is relatively uncommon generally avoidable with therapy.

GOUT - Causes

- **Underexcretion of uric acid**
- **Diet rich in purines/alcohol; deficient in dairy products**
- **Increased purine degradation**
- **Increased PRPP Synthetase activity**

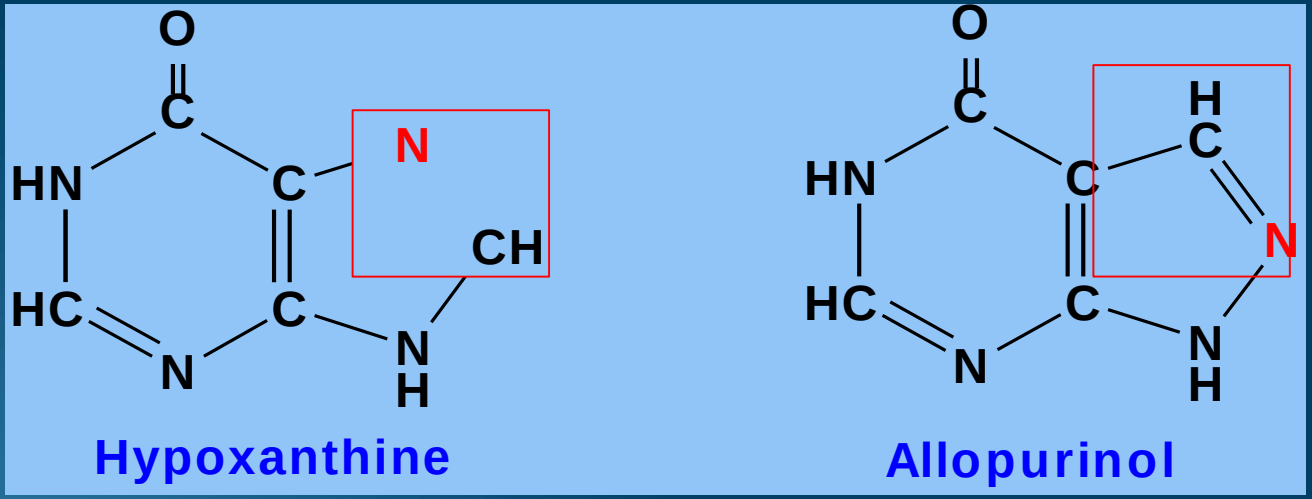
  overproduction of PRPP = increased purine synthesis = increased purine degradation = increased uric acid production
- **Decreased/partial HGPRT activity**

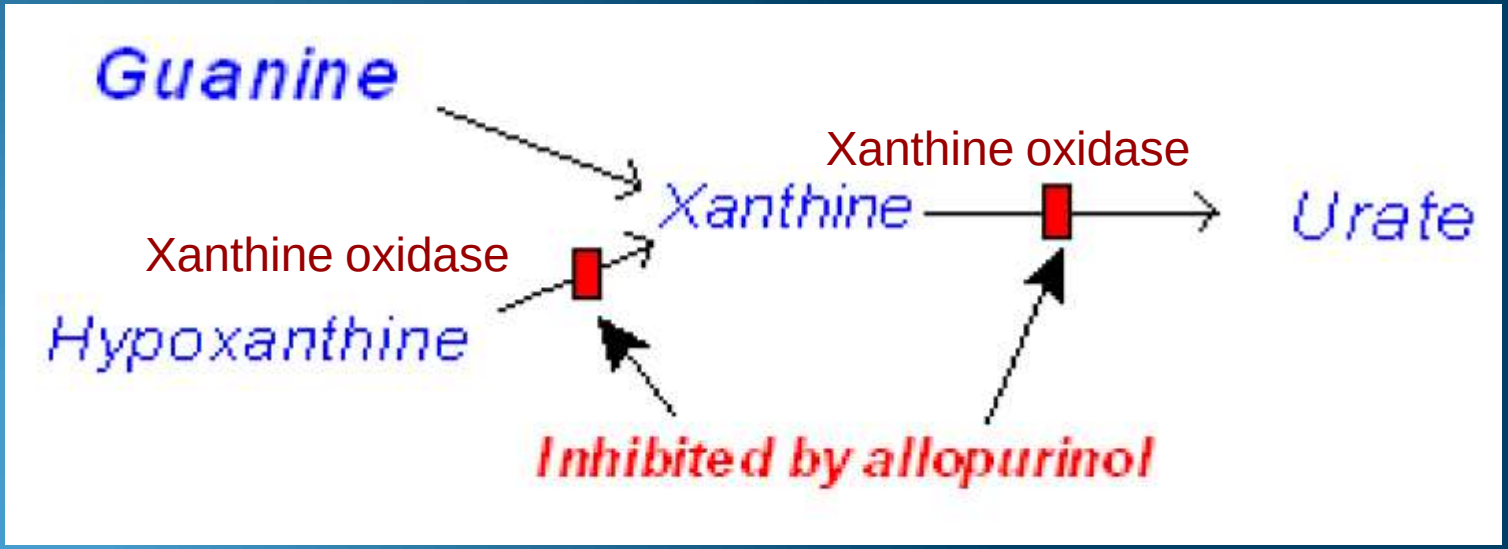
  1) Deficiency of HGPRT = increased HX and G
  2) Deficiency of HGPRT = accumulation of PRPP = increased purine synthesis = increased uric acid levels
  3) Deficiency of HGPRT = decreased IMP and GMP = decreased inhibitors for purine synthesis

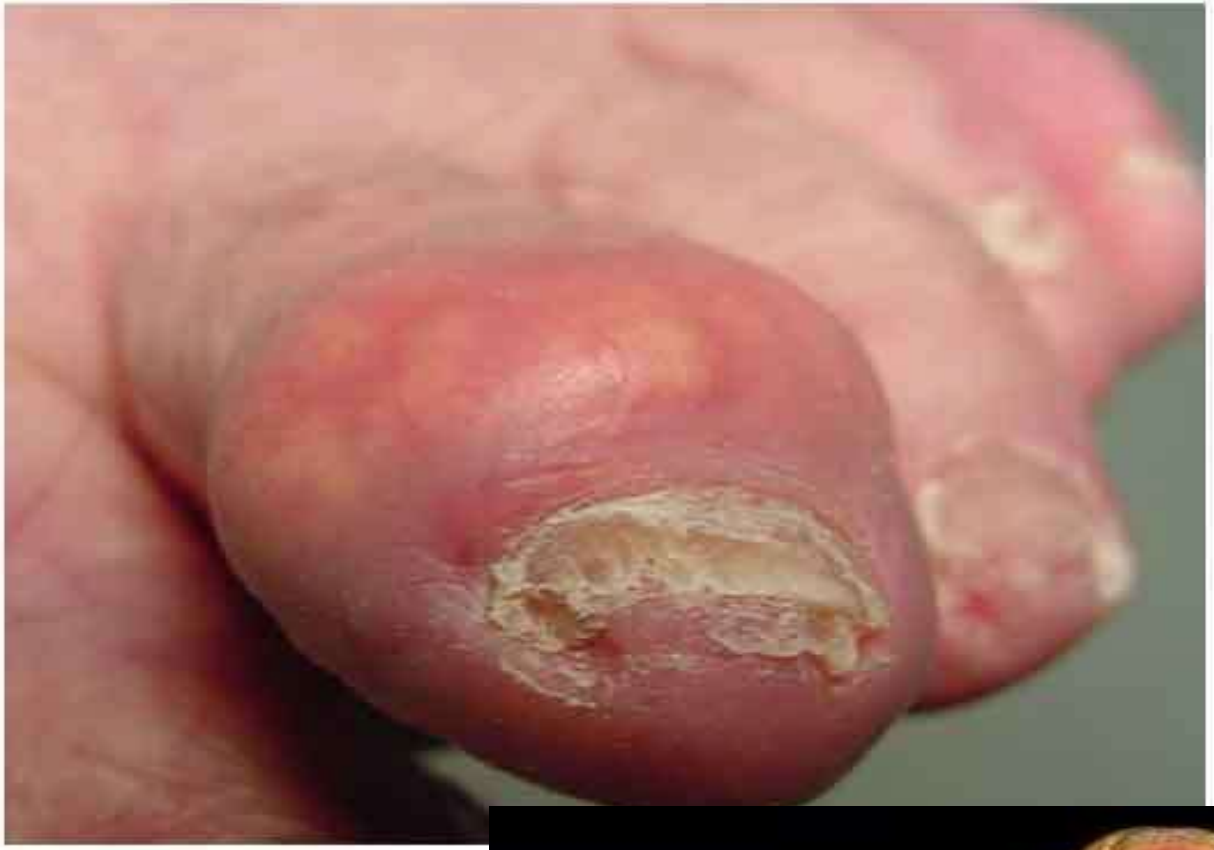
GOUT - Treatment

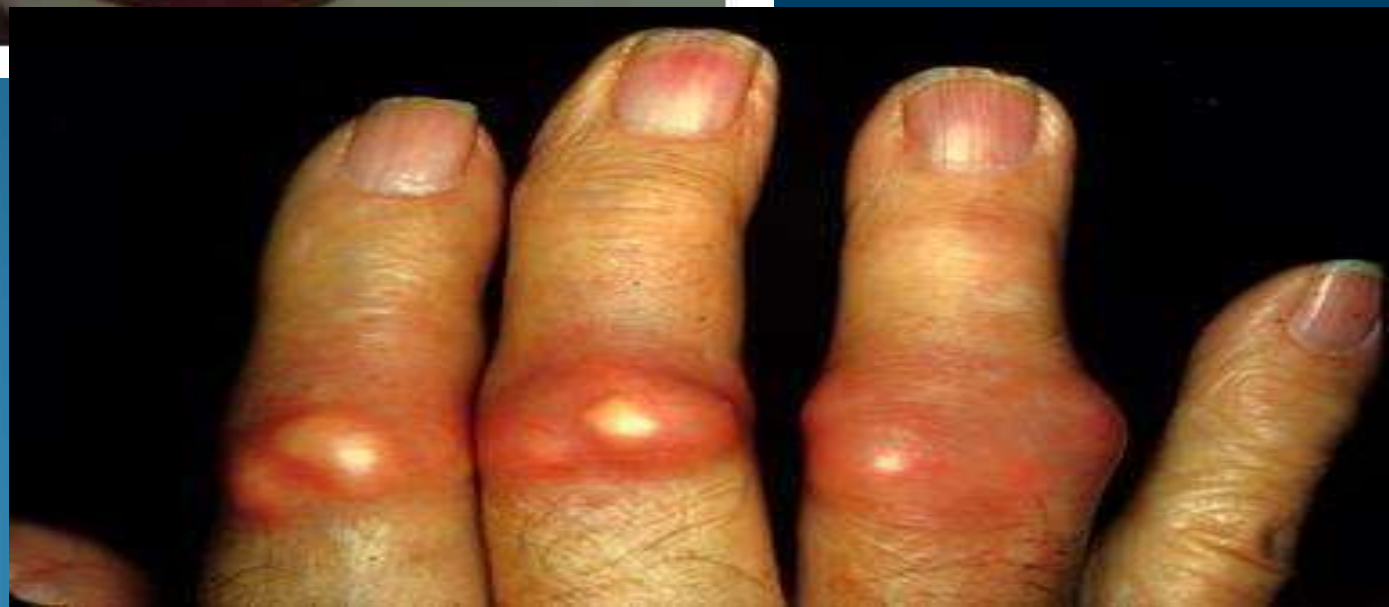
- **Colchicine** –reduces inflammation
- **Allopurinol** – inhibits uric acid synthesis
- **Low purine diet - Foods that are high in purine include:**
  - Red meat and organ meats (eg. liver)
  - Yeasts and yeast extracts (eg. beer and alcoholic beverages)
  - Asparagus, spinach, beans, peas, lentils, oatmeal, cauliflower and mushrooms
- **Avoid caffeine and alcohol**
- **Keep hydrated**

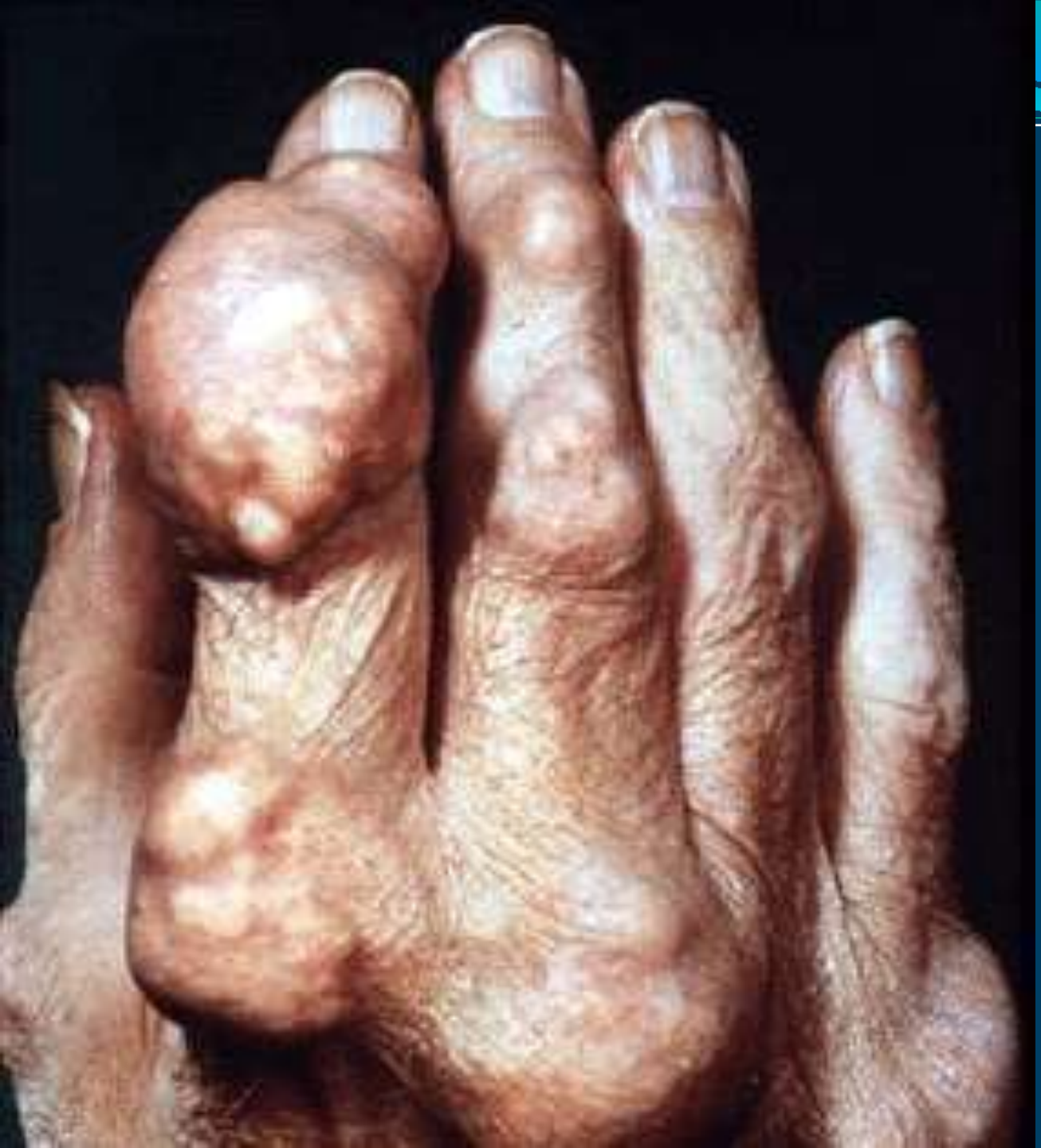
Allopurinol – a suicide inhibitor used to treat Gout







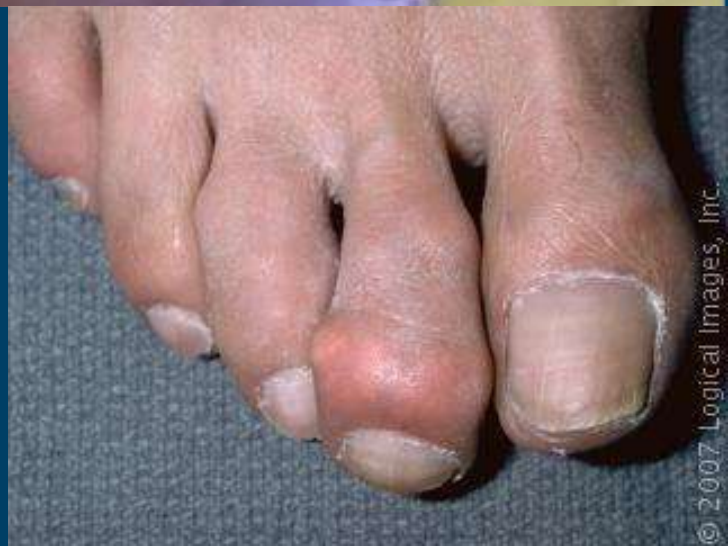


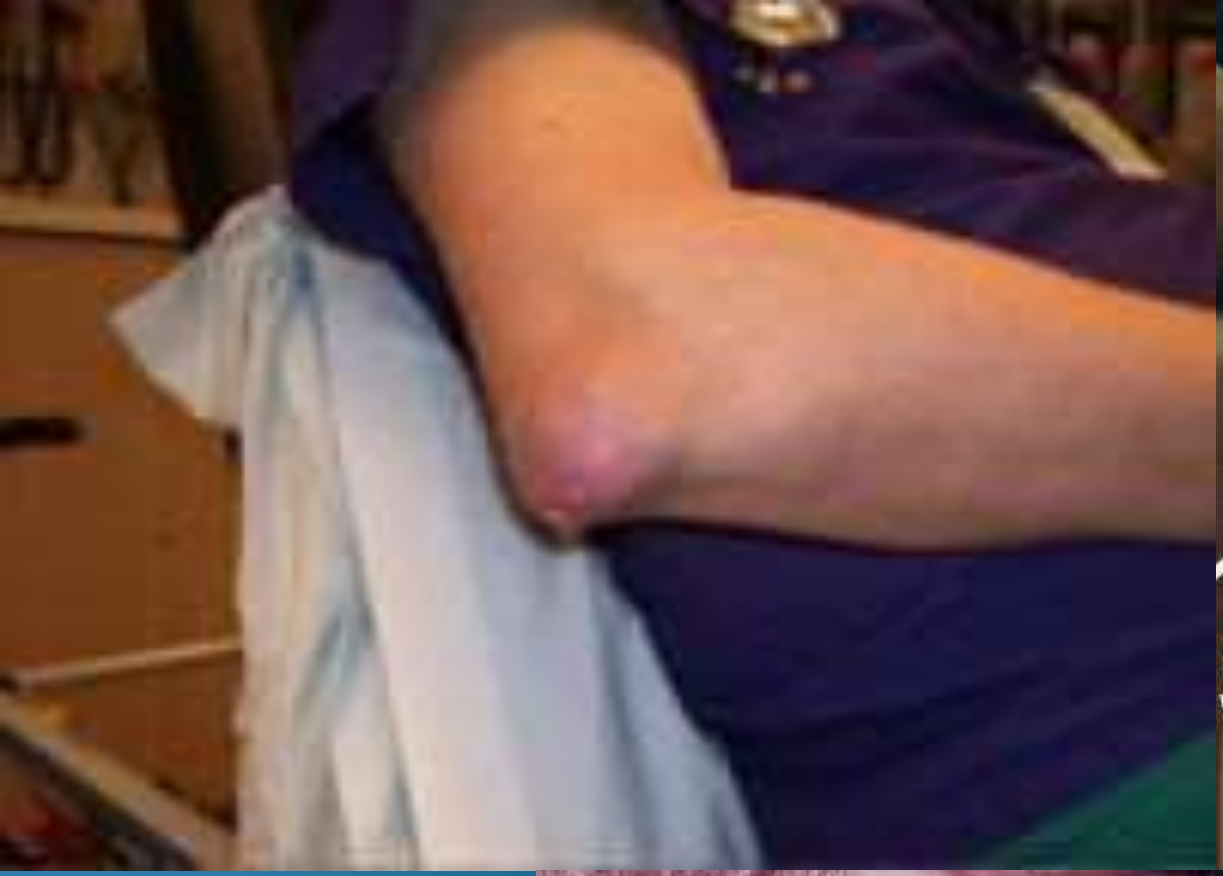


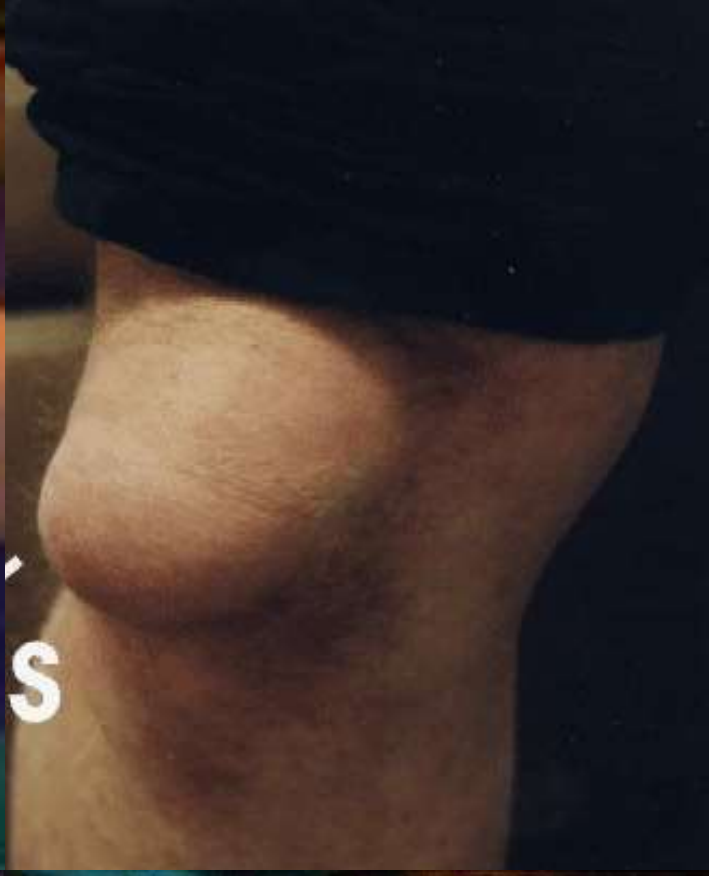
Gout:

accumula-tion of uric acid salts in joints

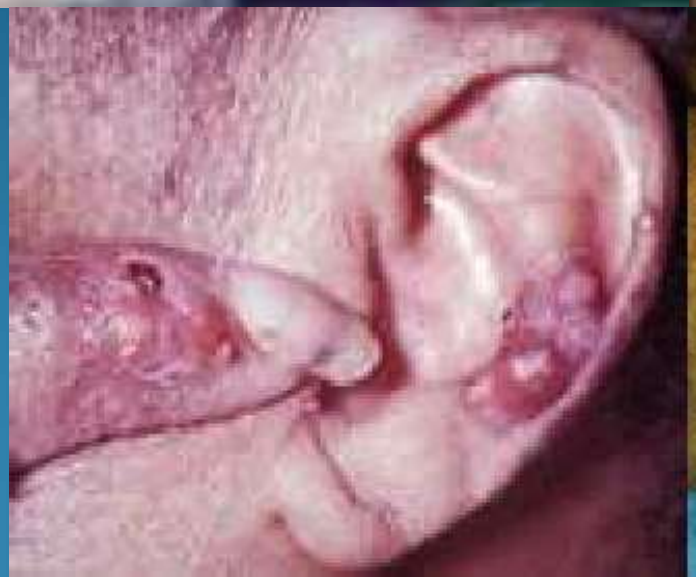
Gout: accumulation of uric acid salts in joints

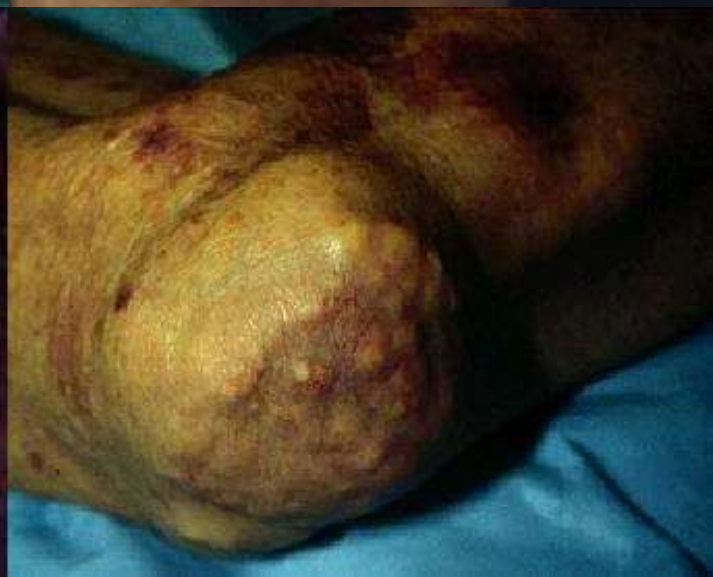






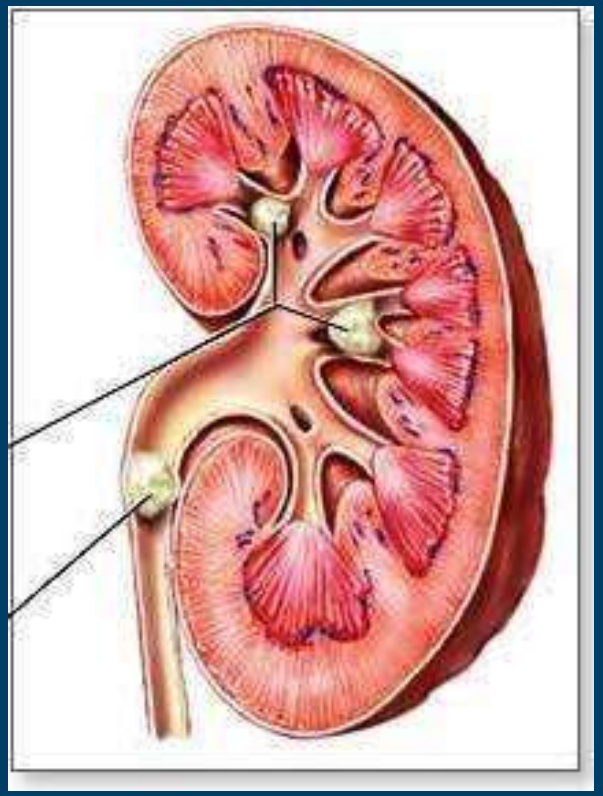
Gout: *tophuses* – accumulation of uric acid salts in cartilages, under skin.

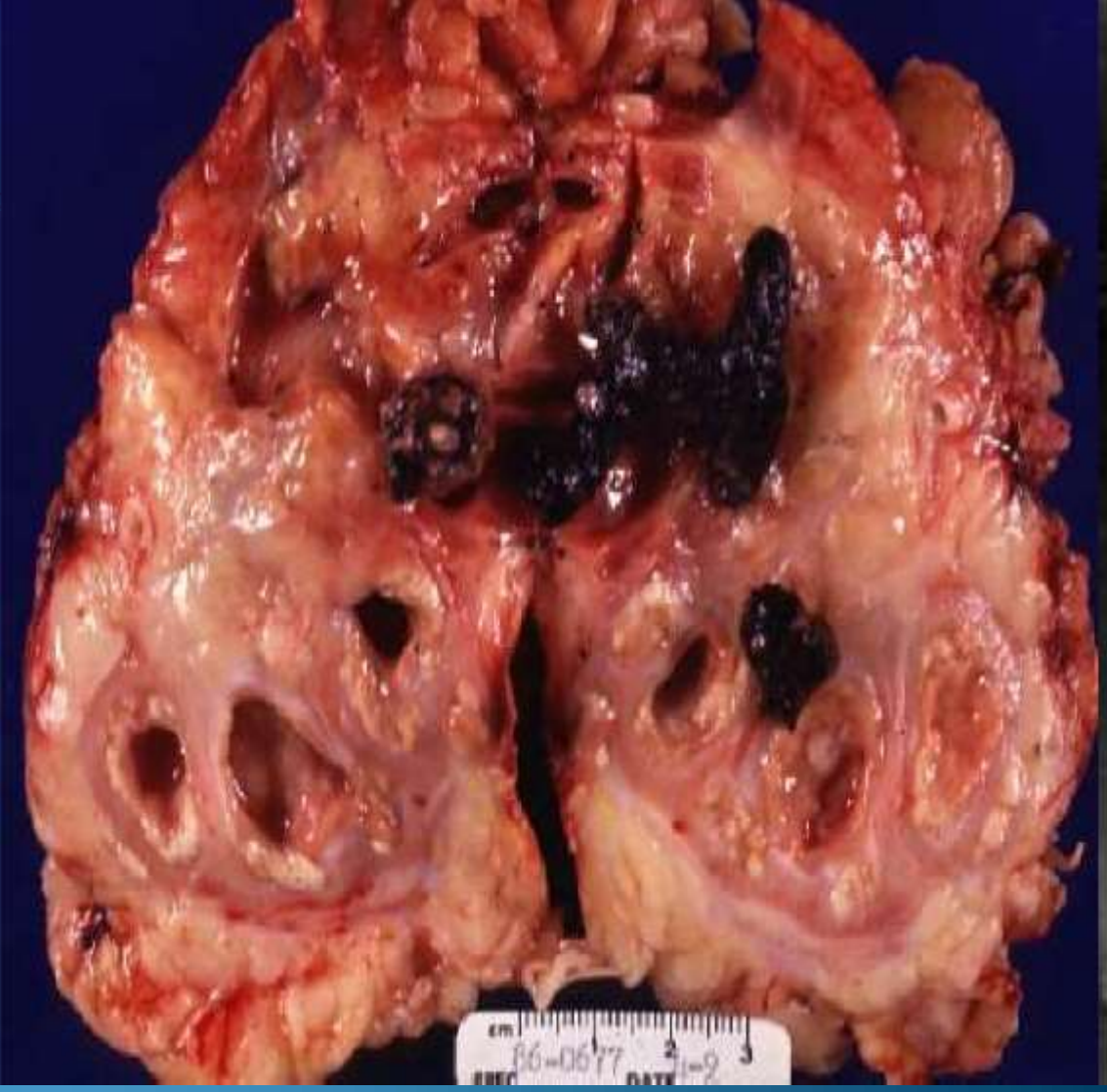


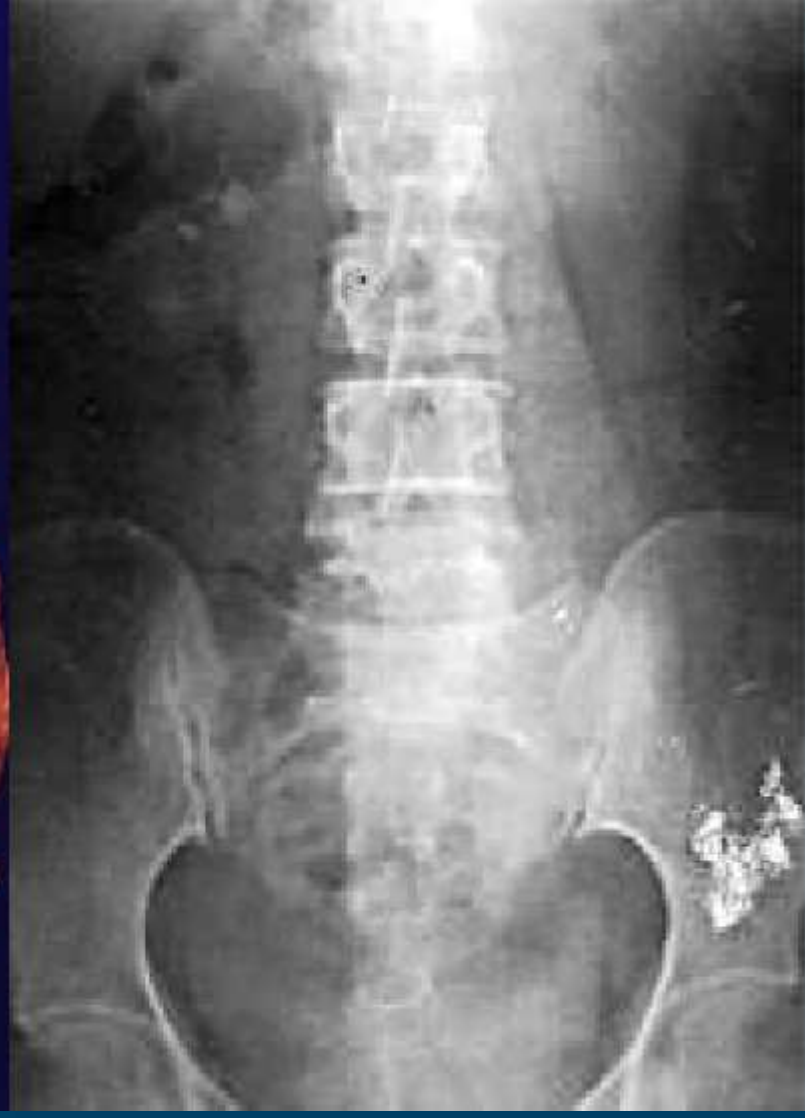


KIDNEY STONES

When uric acid is present in high concentrations in the blood, it may precipitate as a salt in the kidneys. The salt can form stones, which can in turn cause pain, infection, and kidney damage.





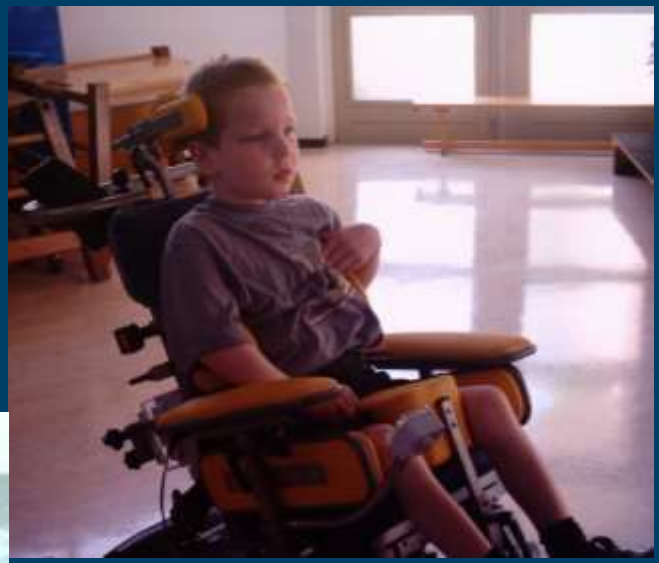


Gout: kidney stones.

Lesch-Nyhan Syndrom: **is a inherited disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase. LNS is present at birth in baby boys.**

Hypoxanthine and guanine are not used in the salvage pathway of purine nucleotides synthesis.

Hypoxanthine and guanine are not utilizied repeatedly but converted into uric acid.



Symptoms:

- **severe gout**

-severe mental and physical problems

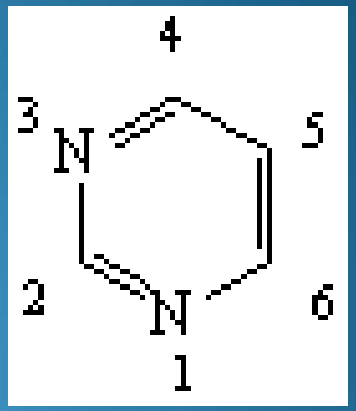
- self-mutilating behaviors

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

- Adenosine deaminase deficiency
- Accumulation of dATP = inhibition of ribonucleotide reductase =B and T cells unable to divide

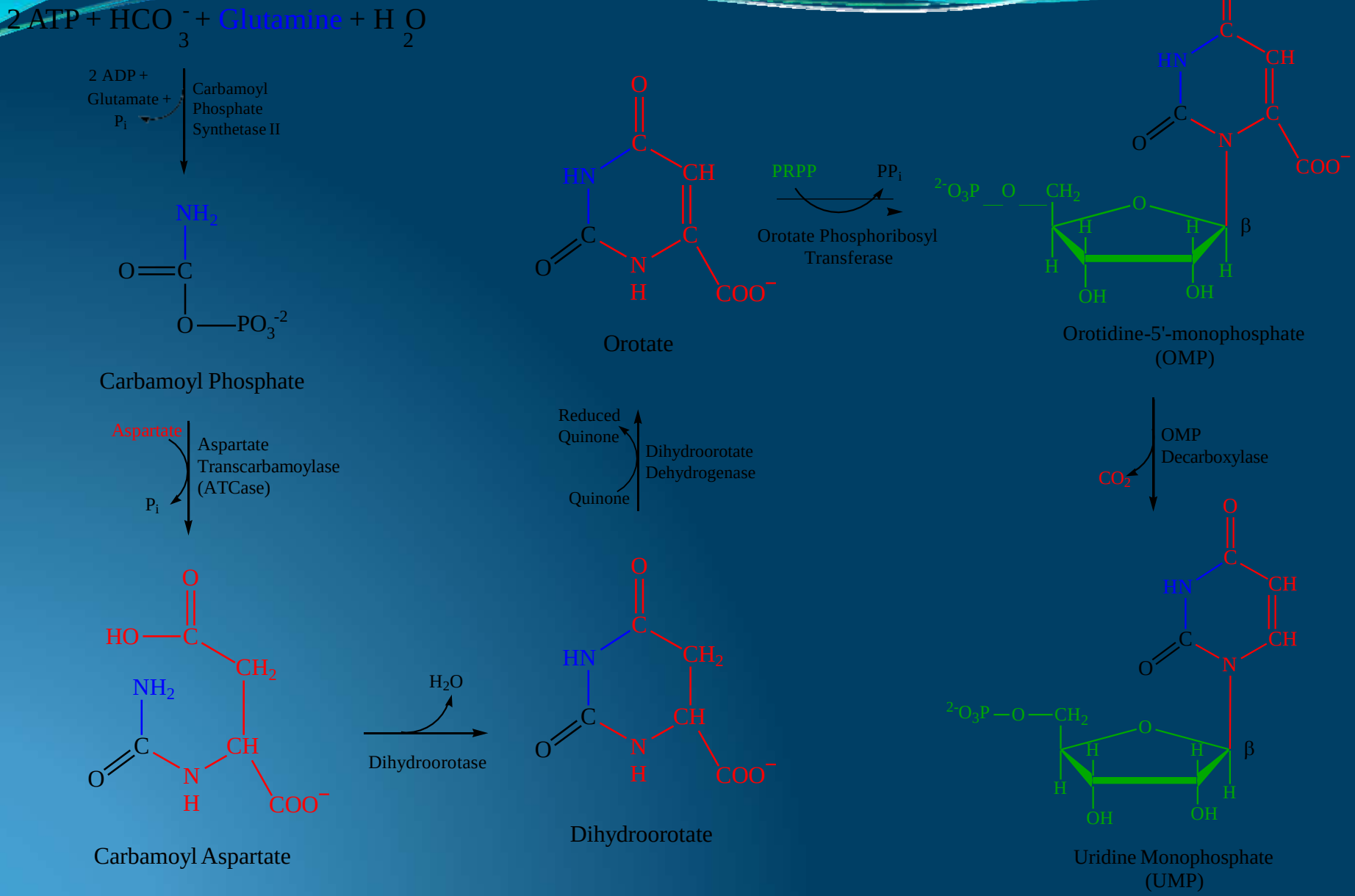
Pyrimidine Ribonucleotide Synthesis

- Uridine Monophosphate (UMP) is synthesized first
  - CTP is synthesized from UMP
- Pyrimidine ring synthesis completed first; then attached to ribose-5-phosphate



N_1, C_4, C_5, C_6 : Aspartate
C_2 : HCO_3^-
N_3 : Glutamine amide Nitrogen

Pyrimidine Synthesis

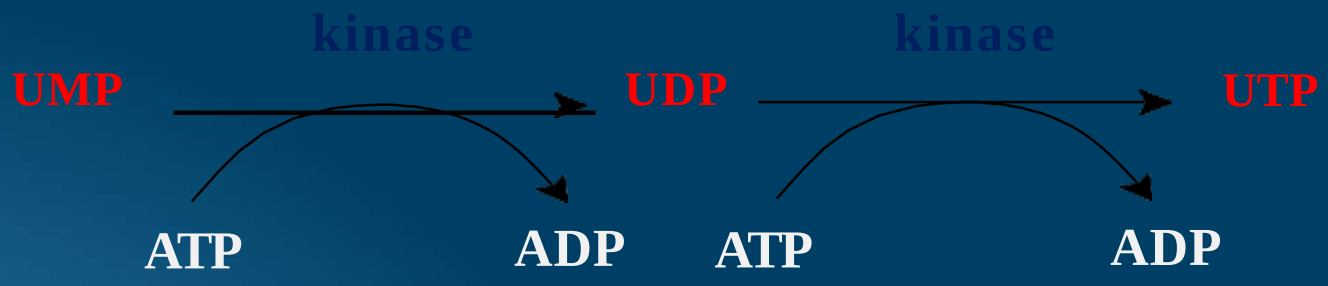


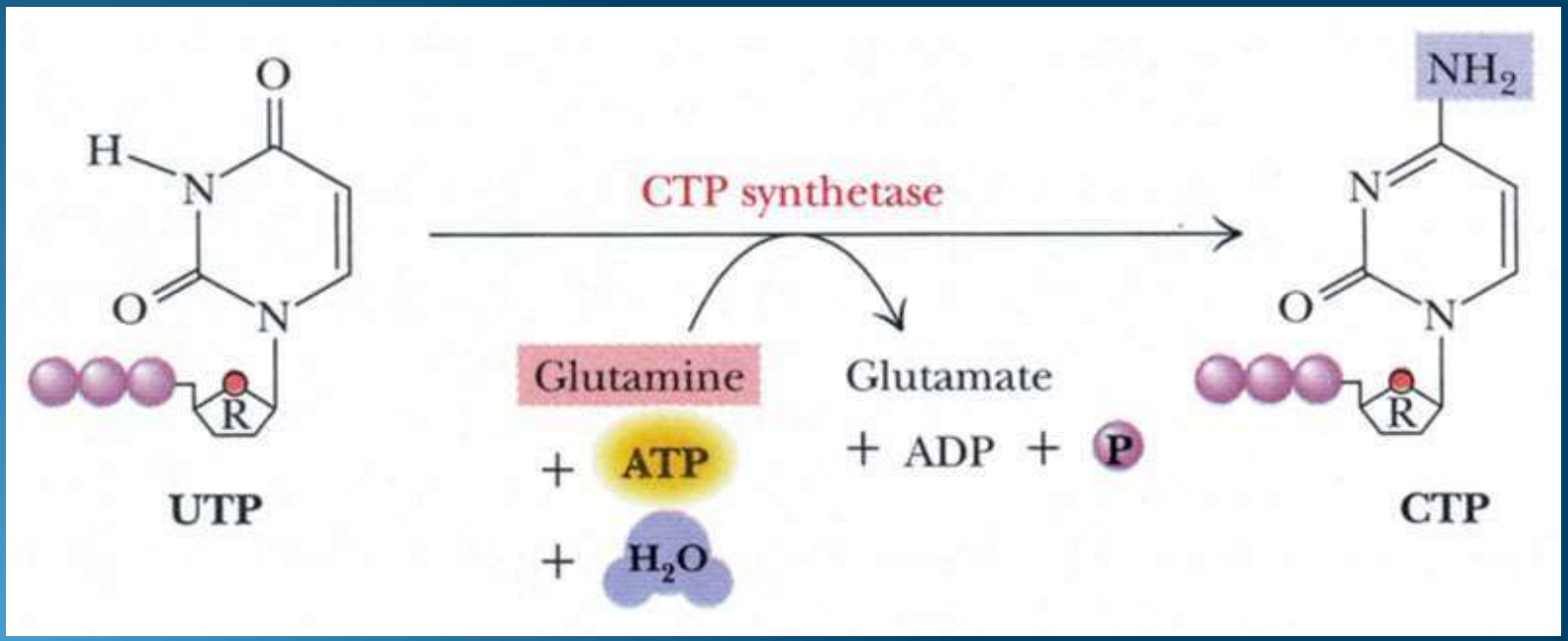
UMP → UTP and CTP

- Nucleoside monophosphate kinase catalyzes transfer of P_i to UMP to form UDP; nucleoside diphosphate kinase catalyzes transfer of P_i from ATP to UDP to form UTP

- CTP formed from UTP via CTP Synthetase driven by ATP hydrolysis
  - Glutamine provides amide nitrogen for C_4 in animals

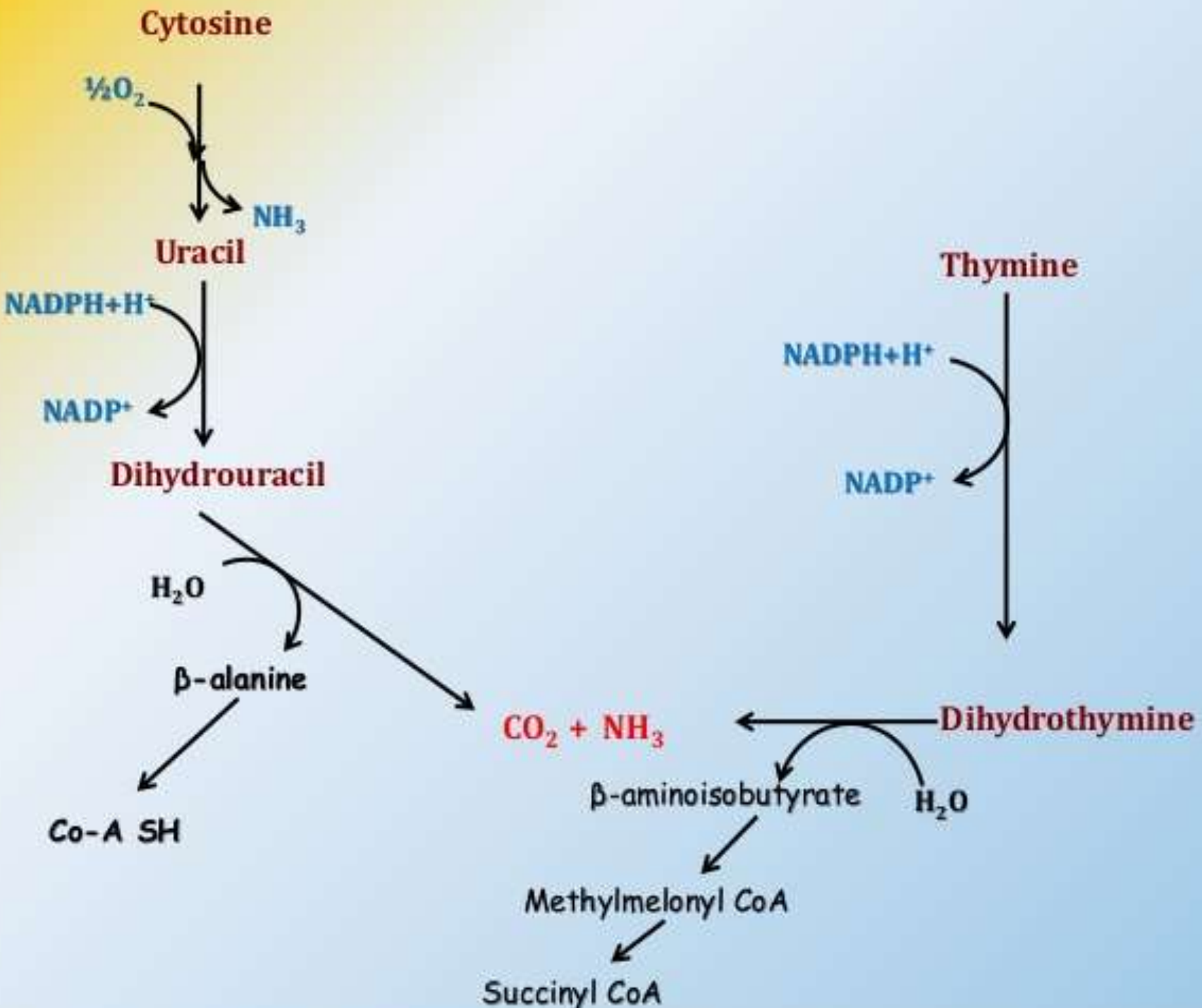
UTP and CTPbiosynthesis





Degradation of Pyrimidines

- CMP and UMP degraded to bases similarly to purines by
  - Dephosphorylation
  - Deamination
  - Glycosidic bond cleavage
- Uracil reduced in liver, forming β-alanine
  - Converted to malonyl-CoA → fatty acid synthesis for energy metabolism


Cytosine
½O2
NH3
Uracil
NADPH+H+
NADP+
Dihydrouracil
H2O
β-alanine
Co-A SH
CO2 + NH3
Thymine
NADPH+H+
NADP+
Dihydrothymine
β-aminoisobutyrate
H2O
Methylmelonyl CoA
Succinyl CoA

OROTACIDURIA

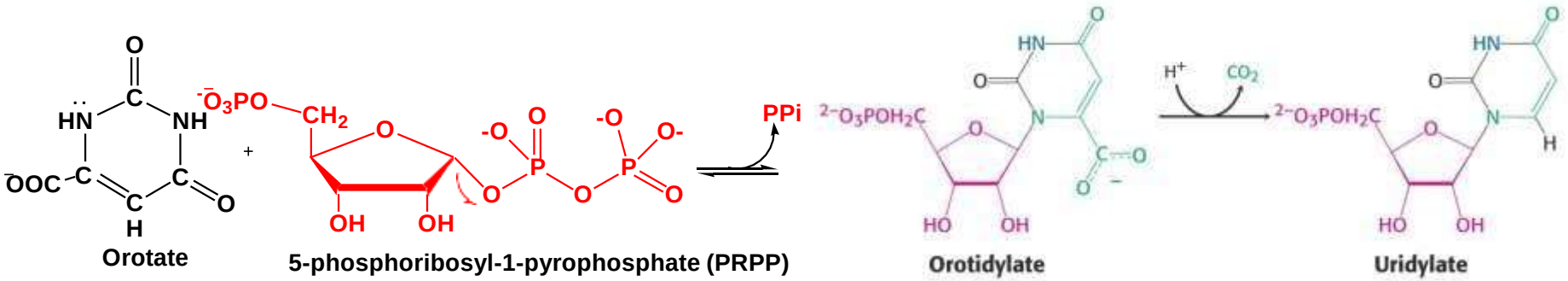
inherited disorder of pyrimidine synthesis caused by a deficiency of the enzyme of *orotate-phosphoribosyltransferase* and *decarboxylase*.

Symptoms:

–excess of orotic acid and its excretion with urine (1.0-1.5 g)

-mental and physical retardation

-megaloblastic anemia



– **Treatment: patients are fed uridine**

U → UMP → UDP → UTP

UTP inhibits carbamoyl phosphate synthase II, preventing the biosynthesis and accumulation of orotic acid