Laboratory diagnostics of liver and gastrointestinal diseases

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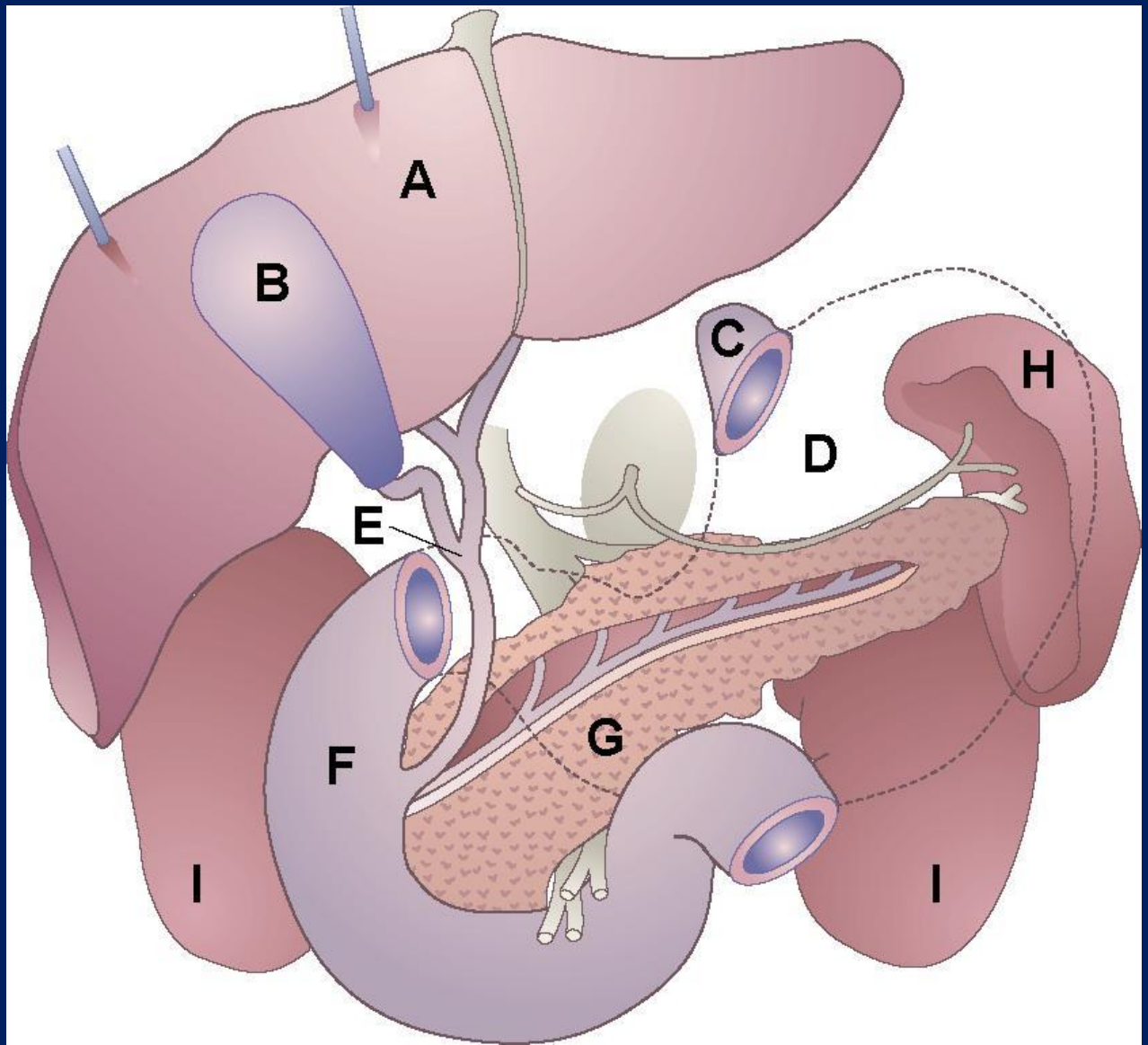
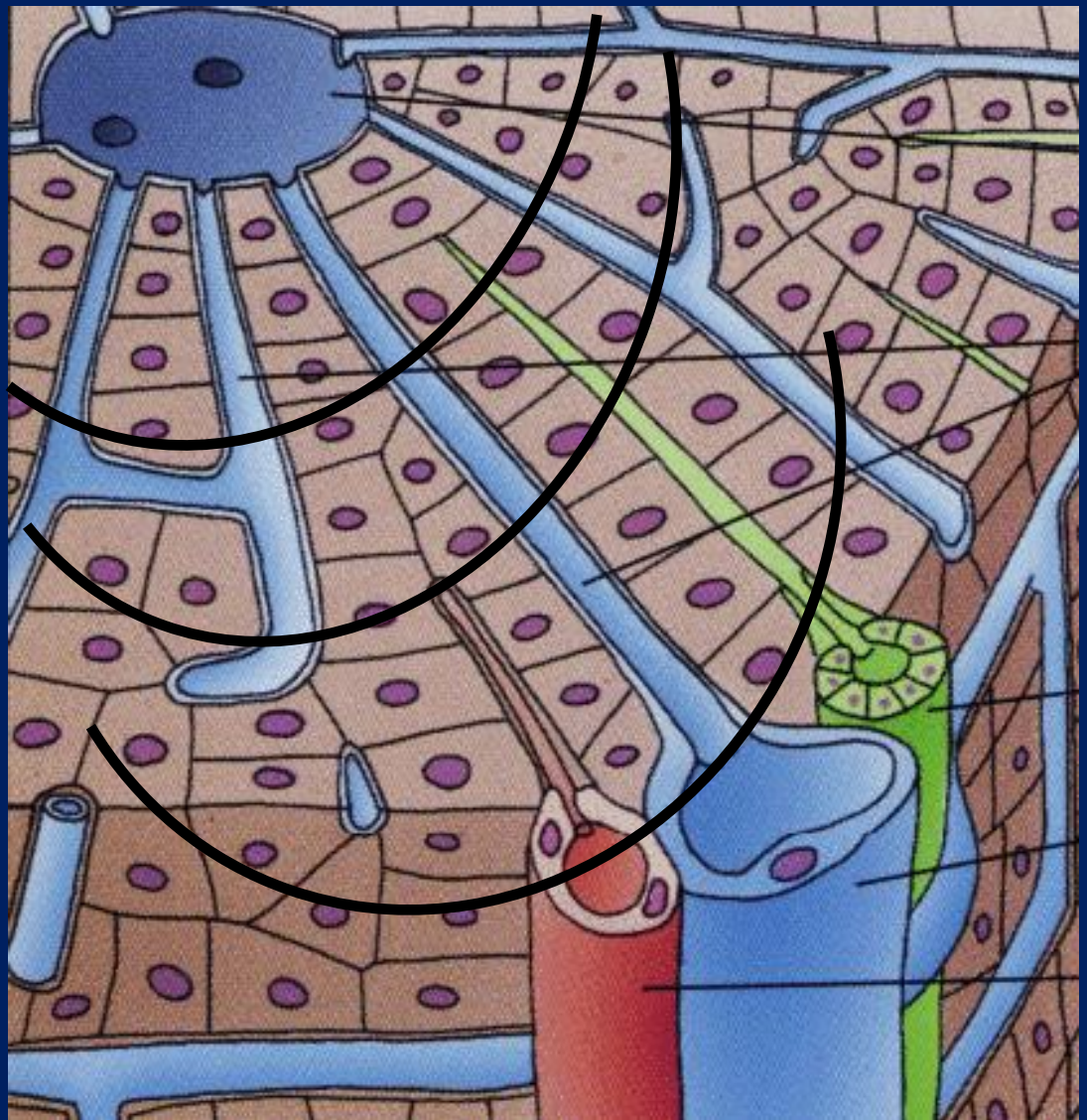
Anatomical position of major digestive organs



Microscopic structure of liver



Zones in the ultrastructure of liver

- 3 zones with altering nutritional and oxygen supply due to portal circulation
- Different metabolism
- Different intracellular enzyme composition
- Result: the location of the injury will determine the extracellularly measured parameter levels

Major functions of the liver

- **Synthesis: plasma proteins, carbohydrates, coagulation factors, lipids, urea, bile, etc.**
- **Storage: carbohydrates, iron**
- **„Detoxification”**
- **Biotransformation: endogenous metabolites, exogenous compounds (e.g. drugs)**
- **Phagocytosis: senescent RBCs, other compounds**

Classification of liver diseases

- **Congenital (bilirubin metabolism)**
- **Acquired - inflammation (hepatitis)**

  bacterial

  viral

  toxic (drug, alcohol)

  - bile flow disorders (mechanic, autoimmune?)
- **Acute and chronic processes**

Markers of acute viral hepatitis

- Prothrombin activity
- Iron, transferrin
- Transaminases, LDH
- Bilirubin (conjugated and unconjugated)
- Pseudo-cholinesterase
- Blood picture
- Urinary bilirubin and UBG
- Detection of virus particles (PCR)

Alcoholic hepatitis: the doses

Risk for the development of ALD.

Time to develop ALD = to amount of alcohol consumed

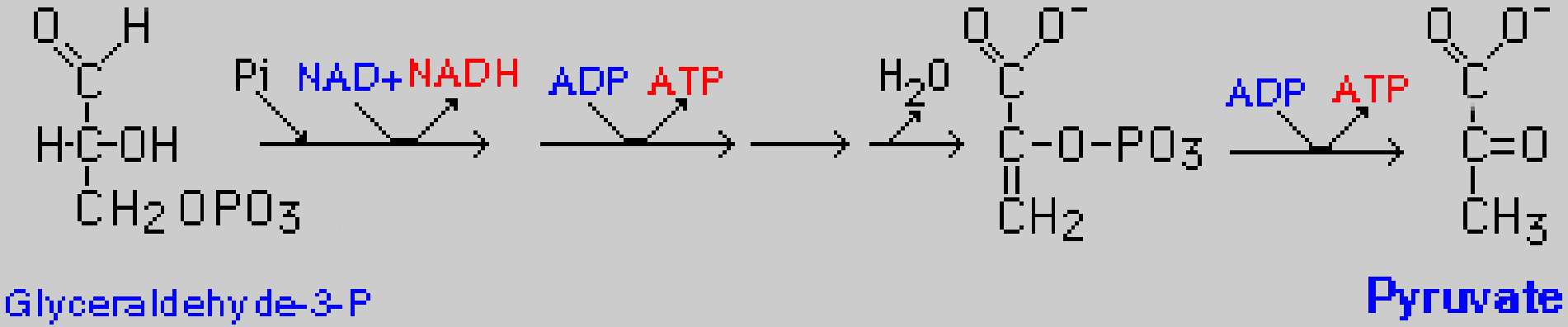
- Men : 60-80 gm/day for 10 years
- Women : 20-40 gm/day for 10 years

Alcoholic cirrhosis , develops ONLY in 10 to 20% of those who are chronically heavy drinkers.

Chronic alcoholic hepatitis

- Total protein, albumin
- Protein electrophoresis
- Immunoglobulins
- Blood picture (MCV)
- Acid-base balance, lactate, uric acid, ammonia
- Bilirubin, triglycerides, cholesterol (HDL)
- Gamma GT, alkaline phosphatase
- AFP
- (Pseudo-cholinesterase, coagulation parameters)

Utilization of NAD during glycolysis



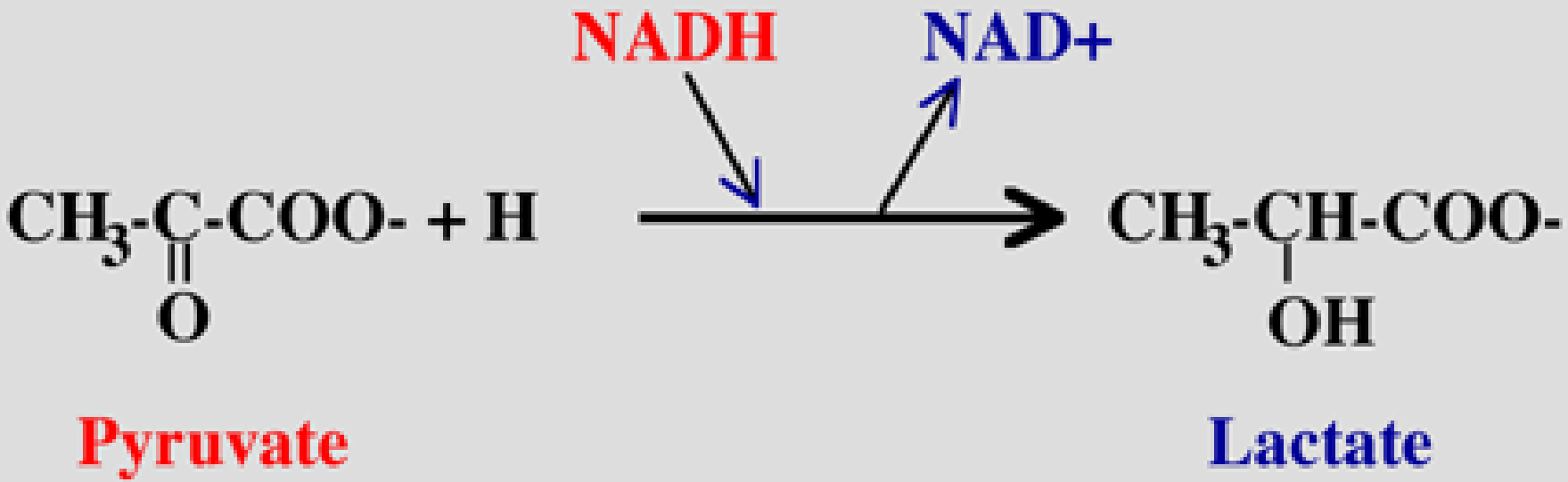
Consumption of NAD when metabolizing ethanol

$$C_2H_2OH + NAD \rightarrow CH_3\text{-}CHO + NADH$$

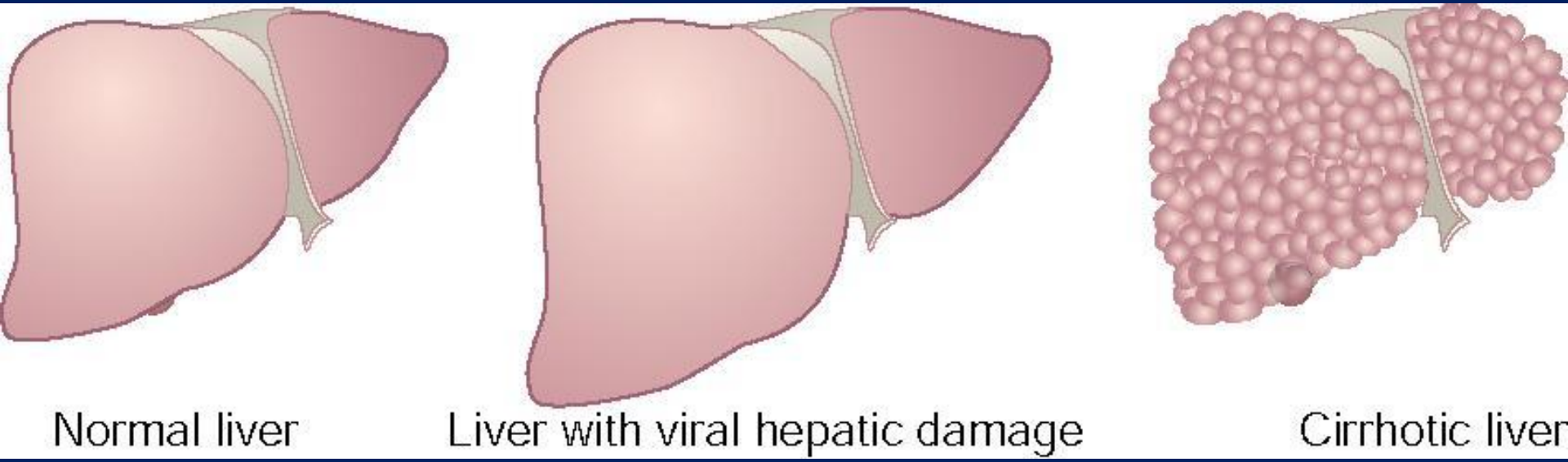
(ethanol) (acetylaldehyde)

- **Acetaldehyde (toxic) excess**
- **↑ NADH: ↓ citrate cycle, ↓ gluconeogenesis, ↑ free fatty acids, ↑ lactate production**
- **H+: facilitates fatty acid synthesis**
- **Fatty liver, hyperlipidemia (triglycerides), ↑ lactate, (attack of gout)**

Lactate production in the absence of NAD



Macroscopic picture of the liver in acute and chronic injury



„Liver function” tests

- **Key enzymes: ALT, ASAT, LDH, ALP, gammaGT**
- **Bilirubin metabolism:**
  - **prehepatic icterus**
  - **hepatic icterus**
  - **posthepatic icterus**
- **Urine testing: UBG, bilirubin**

Digestive system

- Digestive enzymes: great excess! – isoenzymes
- Oral cavity: protective effects of saliva
- Stomach: vitamin B_{12}, iron absorption
- Pancreas: like a secured bomb, anti-proteases in circulation, carbohydrate metabolism
- Small intestine: bile, maldigestion, malabsorption, intolerances, bacterial flora
- Large intestine: carcinogenesis

Diseases of the intestines

- **Malabsorption: absorption probes**
  serum Ca, retinol bining protein (RBP), transferrin, prealbumin (transthyretin)
- **Autoimmune illnesses: anti-gliadine antibodies (gluten sensitivity)**
- **Crohn's disease, colitis ulcerosa**
- **Electrolyte, energy, metabolite, vitamin, trace element supplementation!**

Purine metabolism and gout

Based partially on:

Gihan E-H Gawish, MSc, PhD

Ass. Professor

Molecular Genetics and Clinical Biochemistry

KSU

Purine-rich foods

- Animal proteins (e.g. calf meat)
- Fish (sardines in oil)
- Theobromine (cocoa)
- Yeast (brewer's)
- Alcohol (not itself but induces synthesis)

Purine metabolism (Overview)

1. Nomenclature/nucleotide structure

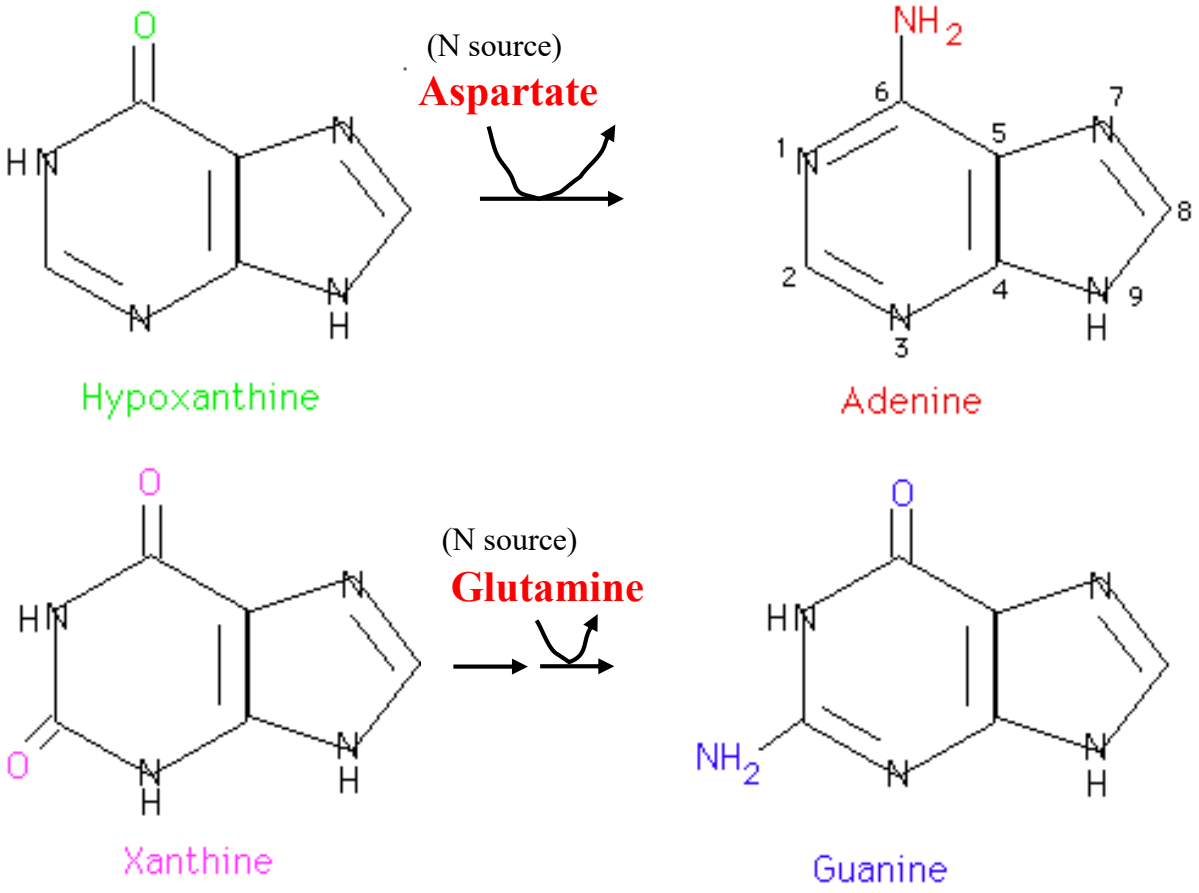
2. Extracellular Hydrolysis of Ingested Nucleic Acid

3. *De novo* synthesis pathways

4. Re-utilization pathways

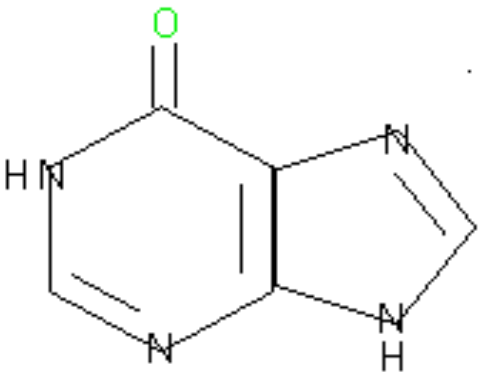
5. Metabolic diseases of purine Metabolism (Gout, Lesch-Nyhan, SCID)

Hypoxanthine is an intermediate for Adenine and Guanine

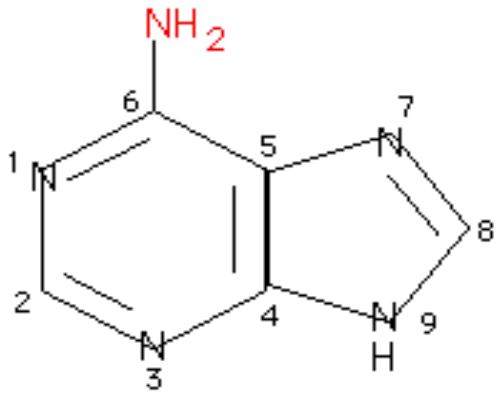


The common mechanistic them for the conversion of A and G is the conversion of a carbonyl oxygen to an amino group

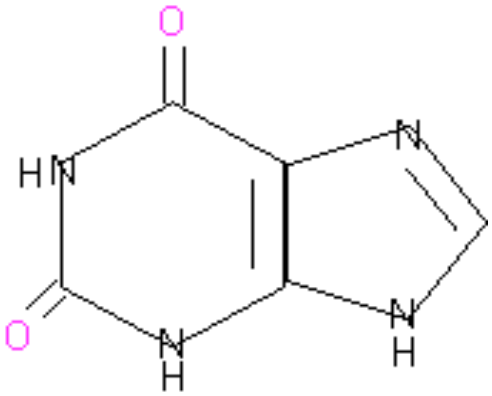
Structures of Common Purine Bases.



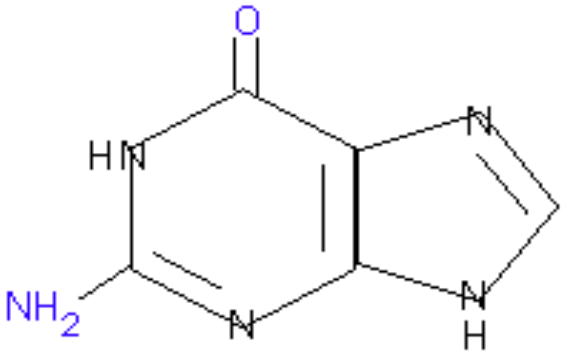
Hypoxanthine



Adenine



Xanthine



Guanine

H= 6 oxy purine
X= 2,6 dioxy purine

A= 6 amino purine
G= 2 amino, 6-oxy purine

There are two basic mechanisms to generate purines and pyrimidines

1. *DE NOVO* BIOSYNTHETIC PATHWAYS

(building the bases from simple building blocks)

2. SALVAGE PATHWAYS

(the reutilization of bases from dietary or catabolic sources)

Extracellular Hydrolysis of Ingested Nucleic Acid

DNA
RNA

1- Endonucleases

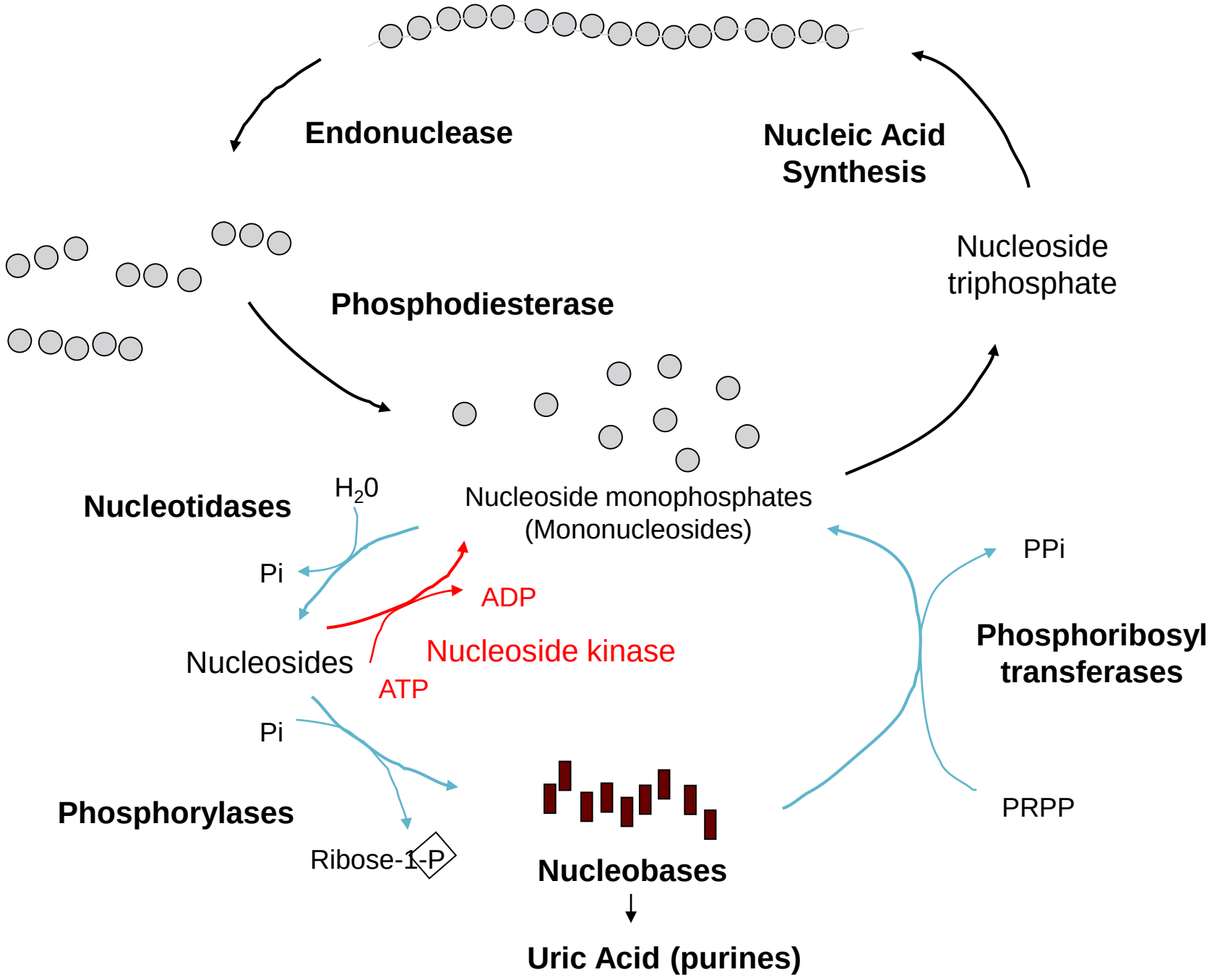
Oligonucleotides

2-Phosphodiesterase

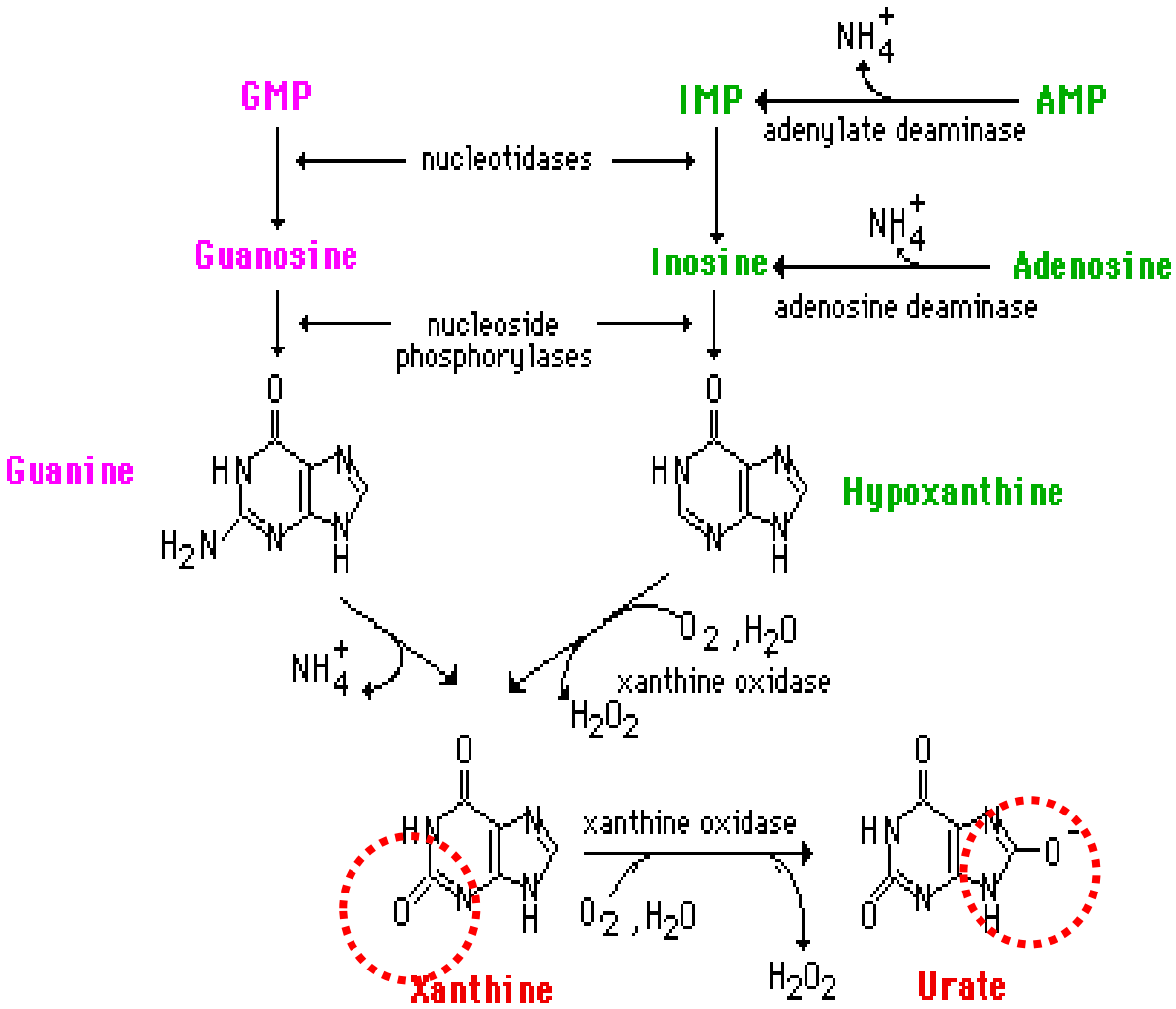
Nucleotides

3- Phosphorylase

Ribose + Free Bases


Endonuclease
Nucleic Acid Synthesis
Nucleoside triphosphate
Phosphodiesterase
Nucleotidases
H_20
Nucleoside monophosphates (Mononucleosides)
Pi
ADP
Nucleoside kinase
Nucleosides
ATP
PPi
Phosphoribosyl transferases
Pi
Phosphorylases
PRPP
Ribose-1-P
Nucleobases
Uric Acid (purines)

Purines in humans are degraded to Urate



Important points:

1. Nucleotides are constantly undergoing turnover!

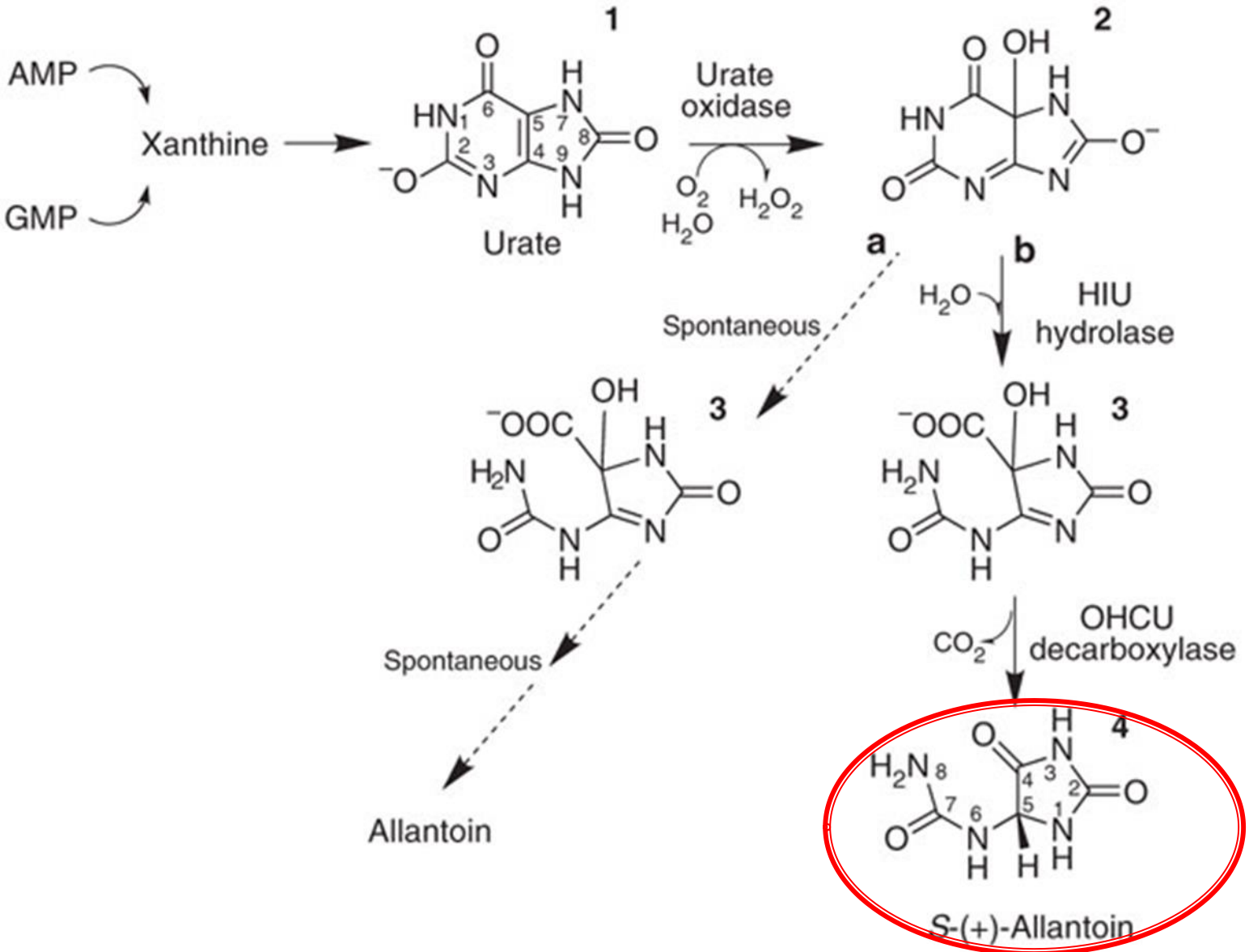
2. There are many enzymes involved;

- **Nucleotidases**
- **Nucleoside phosphorylases**
- **Deaminases**
- **Xanthine oxidases**

3. the final common intermediate in humans is Urate, which is excreted.

4. there are several metabolic disorders resulting from defects in purine catabolism.

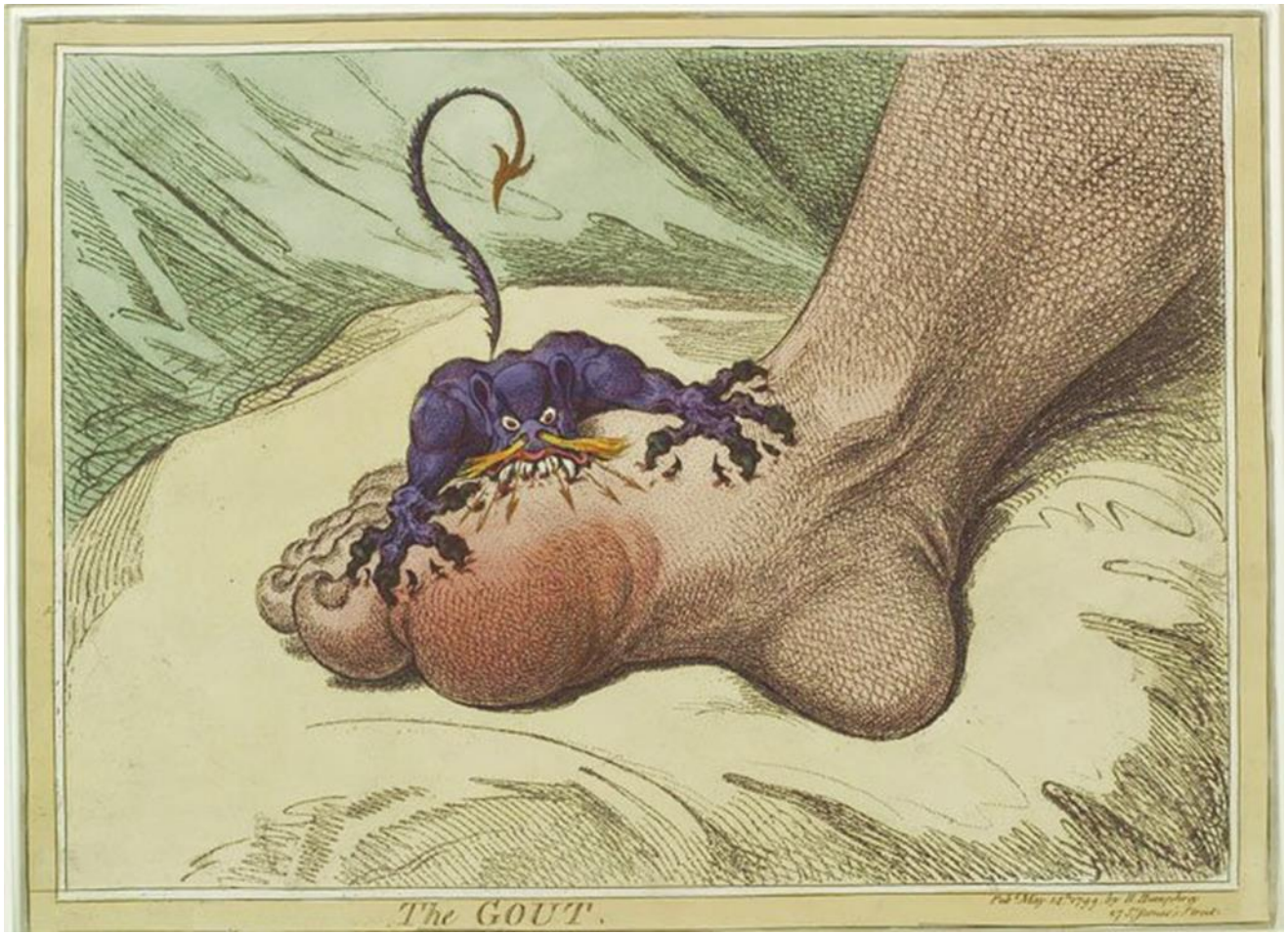
Urate is degraded to allantoin



Disorders of Purine Metabolism:

Disorder	Defect	Comments
Gout	PRPP synthase/ HGPRT	Hyperuricemia
Lesch Nyhan syndrome	lack of HGPRT	Hyperuricemia
SCID	ADA	High levels of dAMP
von Gierke's disease	glucose -6-PTPase	Hyperuricemia

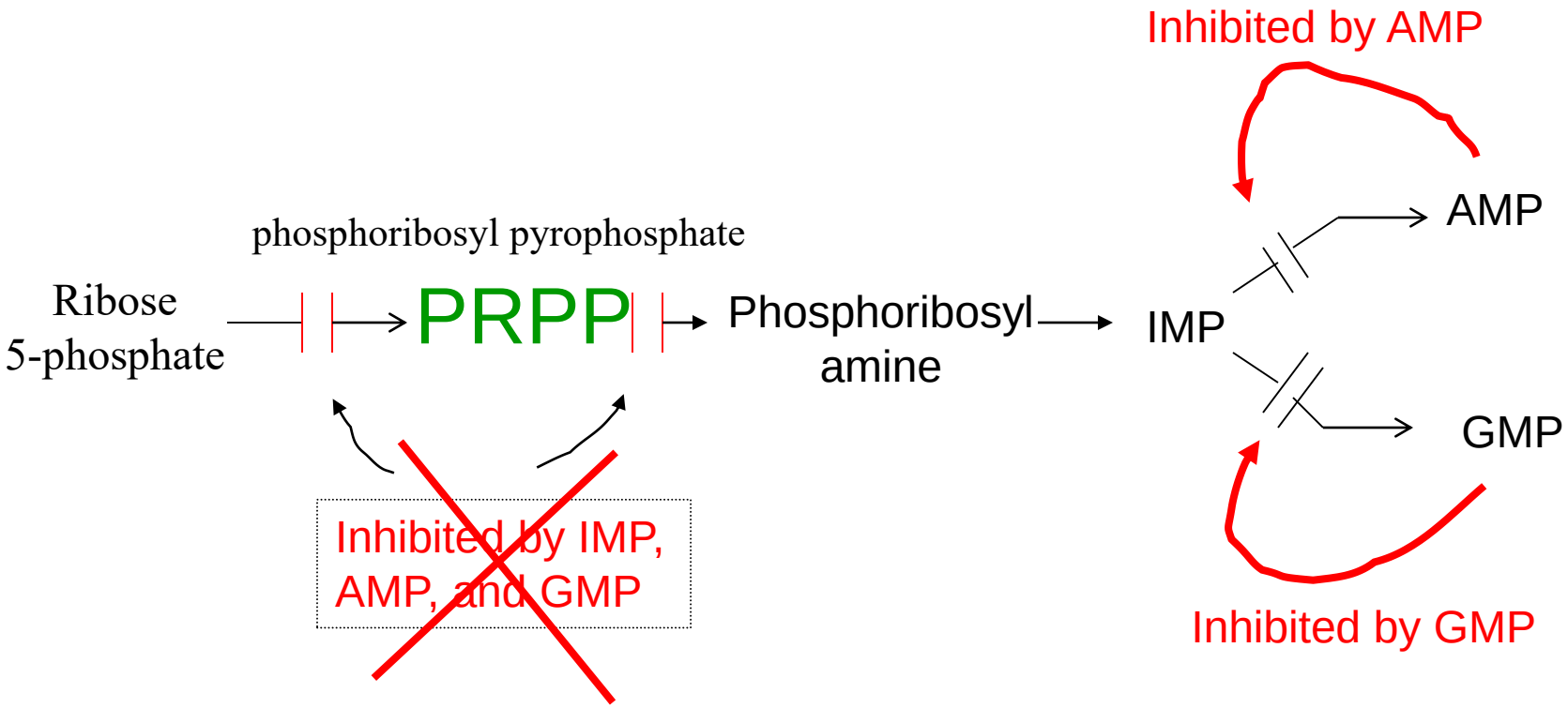
Gout



GOUT

- a disorder associated with abnormal amounts of urates in the body
- **early stage:** recurring acute non-articular arthritis
- **late stage**: chronic deforming polyarthritis and eventual renal complication
- disease with rich history dating back to ancient Greece

What happens in gout?

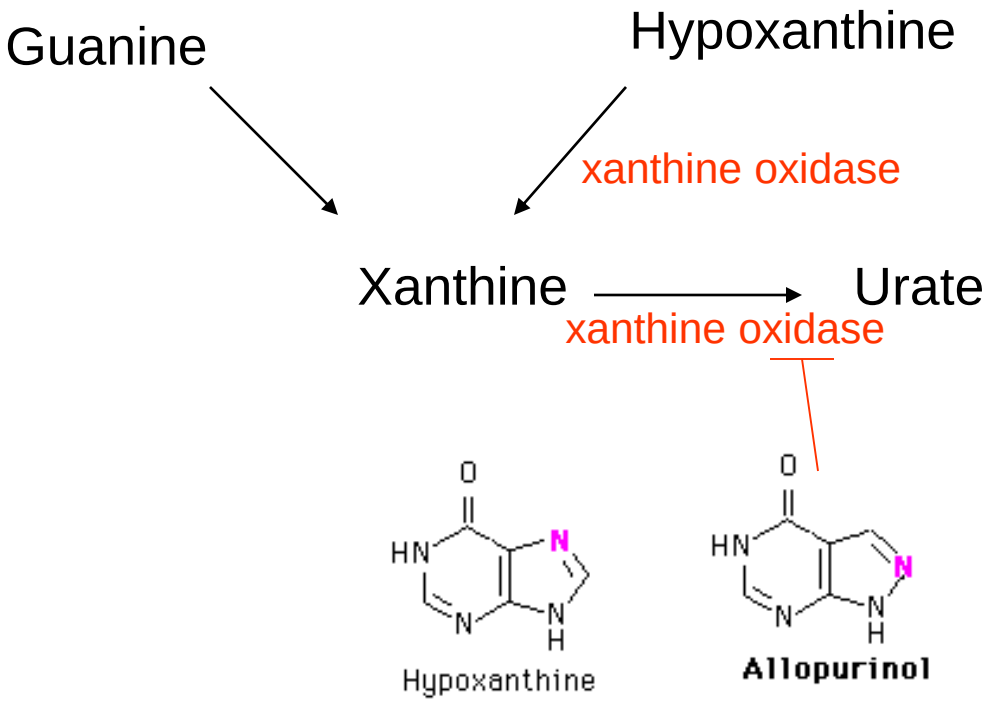


1. Negative regulation of PRPP Synthetase & PRPP Amidotransferase is lost
2. PRPP levels are increased because of defects in salvage pathways

Therefore, there is net increase in biosynthetic/degradation pathways!!

GOUT (Gouty Arthritis): A defect of purine metabolism

Serum Uric Acid Levels (mg/dl)	Incidence of Gout (% of cases)
>9.0	~10%
7-9	0.5-3.5%
<7.0	0.1%



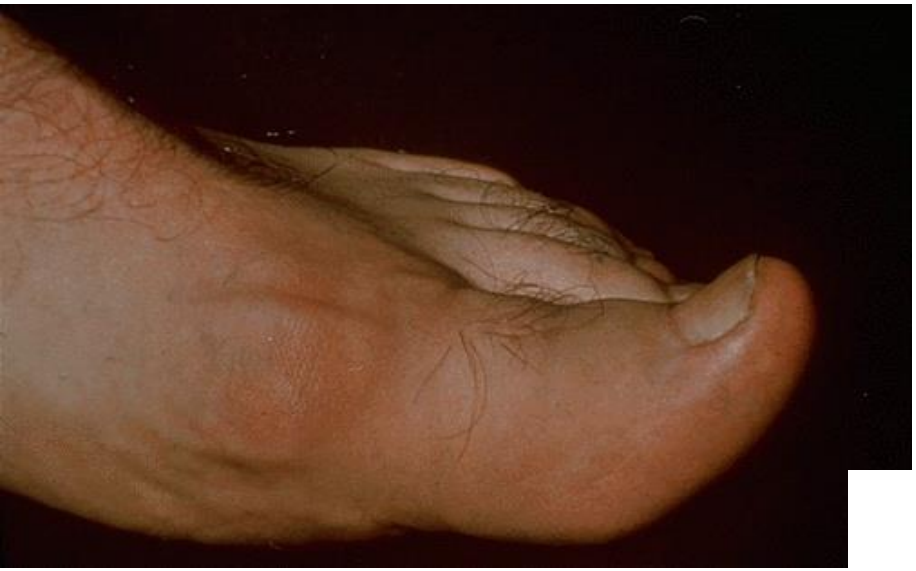
Allopurinol:

a. decrease urate
b. increase xanthine & hypoxanthine
c. decrease PRPP

Gout

- prevails mainly in adult males
- rarely encountered in premenopausal women
- symptoms are caused by deposition of crystals of monosodium urate monohydrate (can be seen under polarized light)
- usually affect joints in the lower extremities (the big toe is the classic site)

Gout



Sodium Urate Crystals

How to prevent gout?

- Diet poor in nucleotides (fruits, vegetables)
- Sufficient fluid intake
- Avoidance of excess alcohol (dehydration, acidosis)
- Physical exercise (microcirculation)

How to treat gout?

- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Colchicine
- Corticosteroids

- Xanthine oxidase inhibitors
- Probenecid (kidney excretion)

Iatrogenic gout, complications

- Chemotherapy
- Tumor lysis syndrome
- Extreme catabolism without fluid intake
- Renal stones!