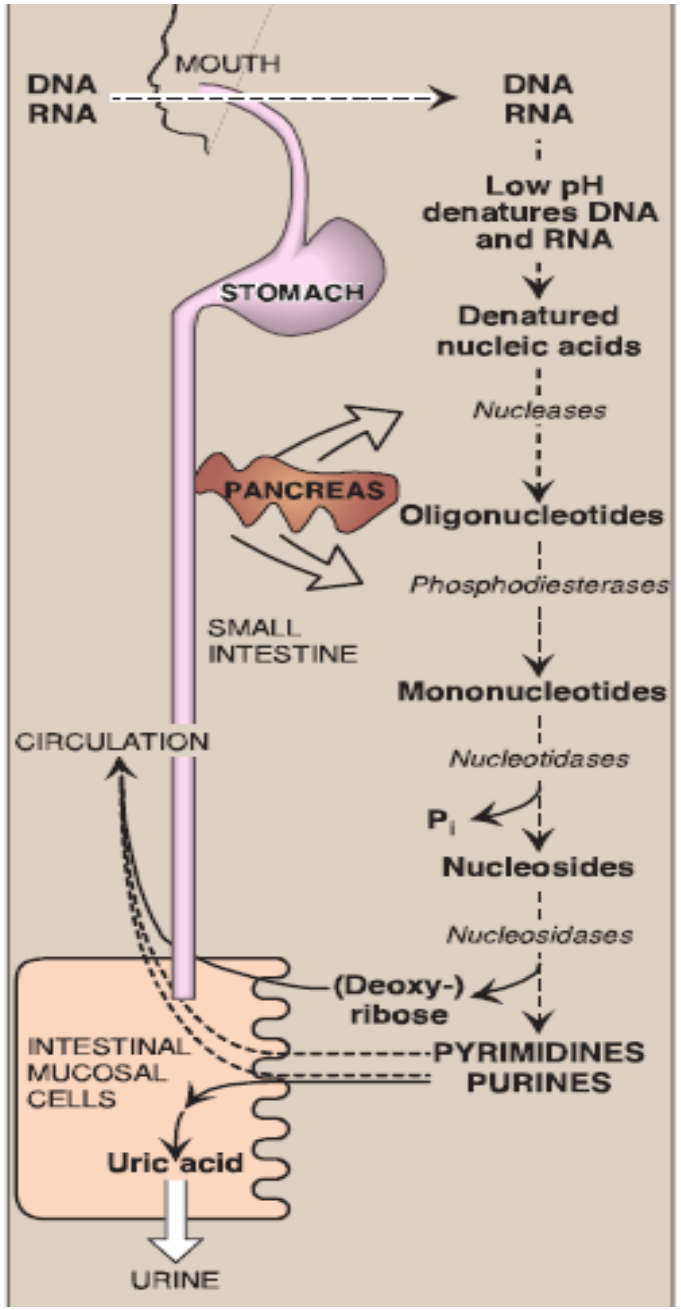
Purine Degradation & Gout

(Musculoskeletal Block)

Objectives

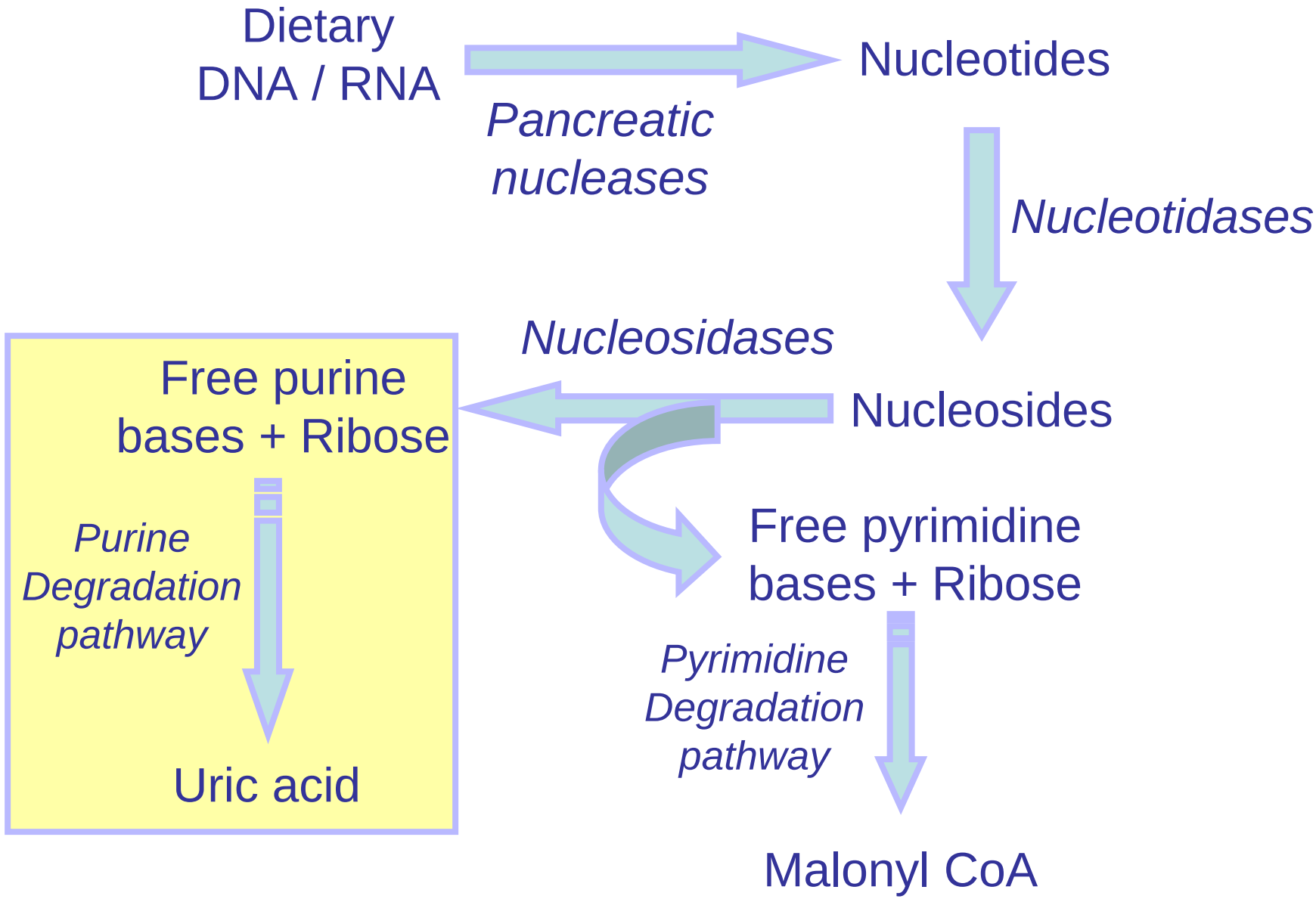
By the end of this lecture, students should be familiar with:

- Purine degradation, uric acid formation and its association with gout.
- Fate of uric acid in humans.
- Recognize the importance of uric acid in the pathogenesis of gout.
- Overview of Gout classification and treatment.


MOUTH
DNA
RNA
DNA
RNA
Low pH
denatures DNA
and RNA
STOMACH
Denatured
nucleic acids
Nucleases
PANCREAS
Oligonucleotides
Phosphodiesterases
SMALL
INTESTINE
Mononucleotides
CIRCULATION
Nucleotidases
P_i
Nucleosides
Nucleosidases
(Deoxy-)
ribose
INTESTINAL
MUCOSAL
CELLS
PYRIMIDINES
PURINES
Uric acid
URINE

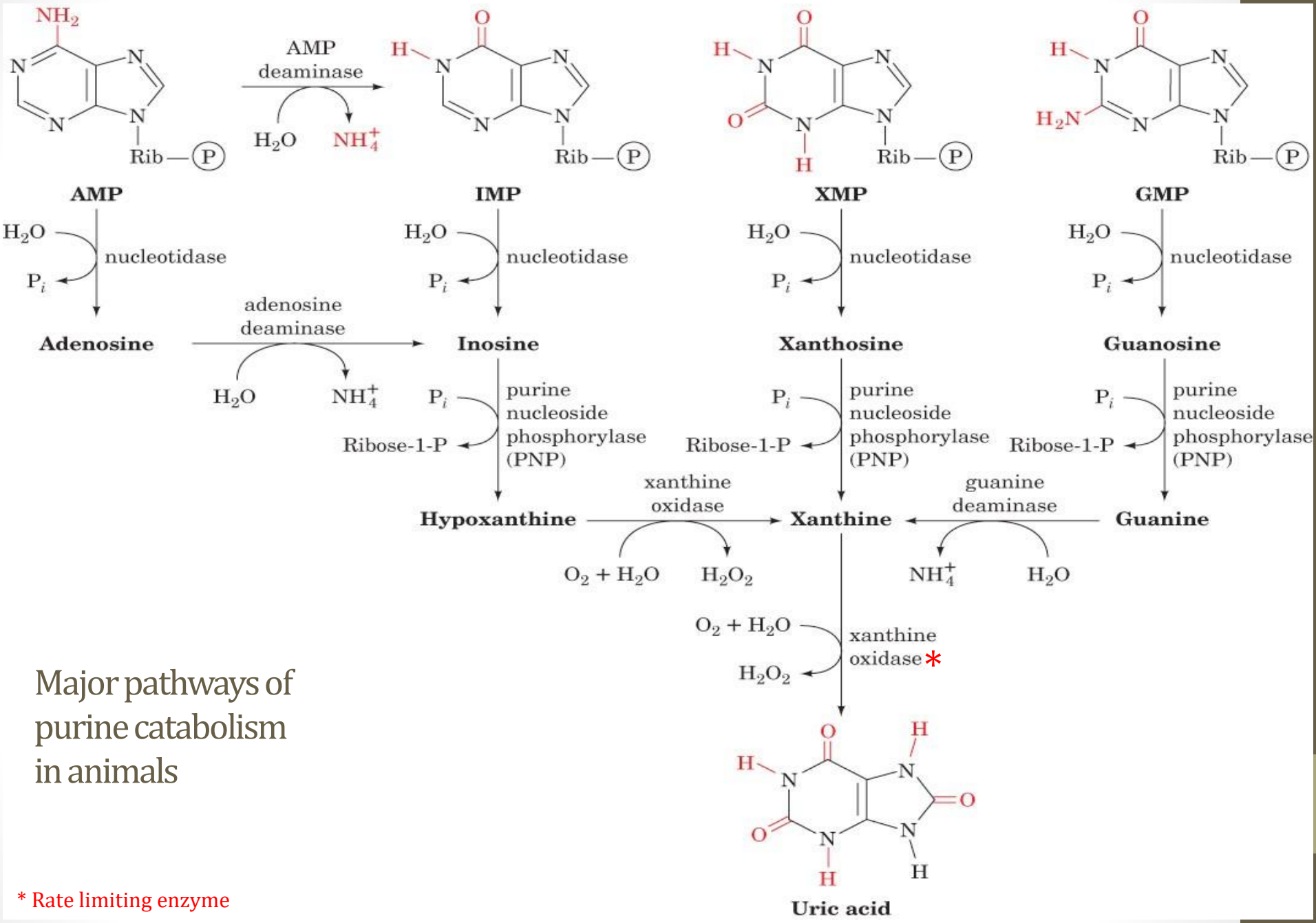
Purine degradation pathway

- The major source of dietary nucleic acids (purines and pyrimidines) is meat
- Purine and pyrimidine bases are absorbed by the intestine
- The ingested bases are mostly degraded into different products by degradation pathways
- These products are then excreted by the body


Dietary
DNA / RNA
Pancreatic
nucleases
Nucleotides
Nucleotidases
Nucleosidases
Free purine
bases + Ribose
Nucleosides
Free pyrimidine
bases + Ribose
Purine
Degradation
pathway
Uric acid
Pyrimidine
Degradation
pathway
Malonyl CoA

Purine degradation pathway

- Adenosine and guanosine (purines) are finally degraded to uric acid by:
  - Purine degradation pathway



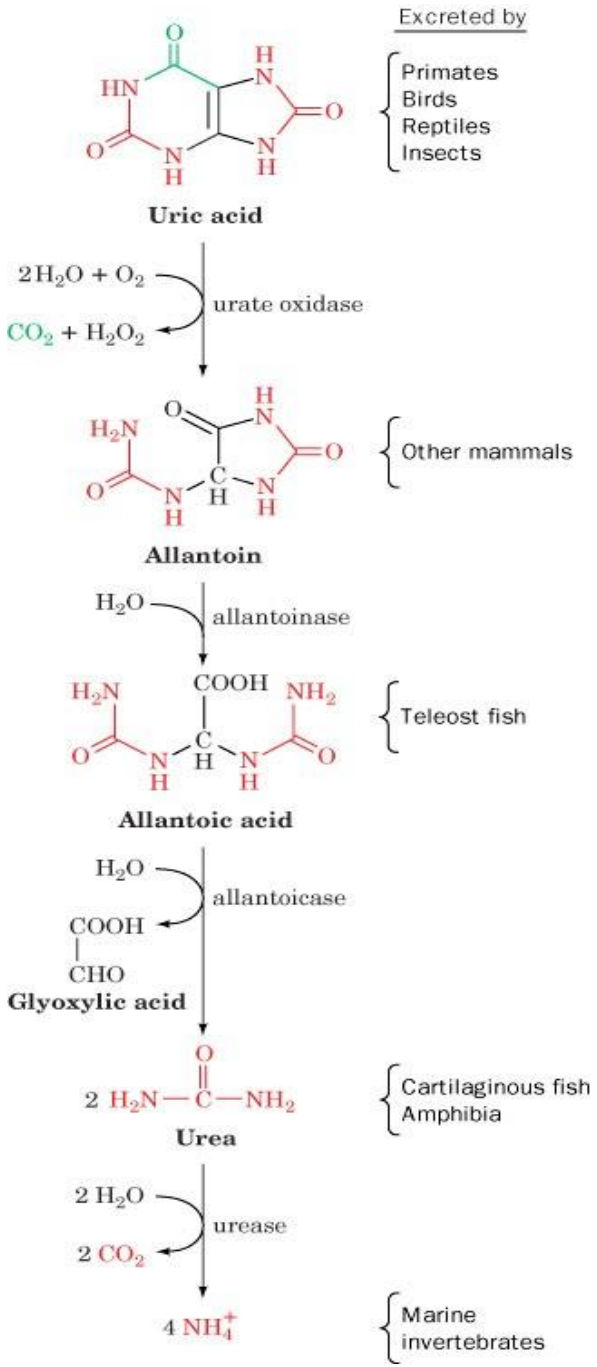
Major pathways of purine catabolism in animals

* Rate limiting enzyme

Fate of uric acid in humans

- In humans, primates, birds and reptiles the final product of purine degradation is uric acid
- Uric acid is excreted in the urine
- Some animals convert uric acid to other products:
  - Allantoin
  - Allantoic acid
  - Urea
  - Ammonia

Degradation of uric acid to ammonia in some animals

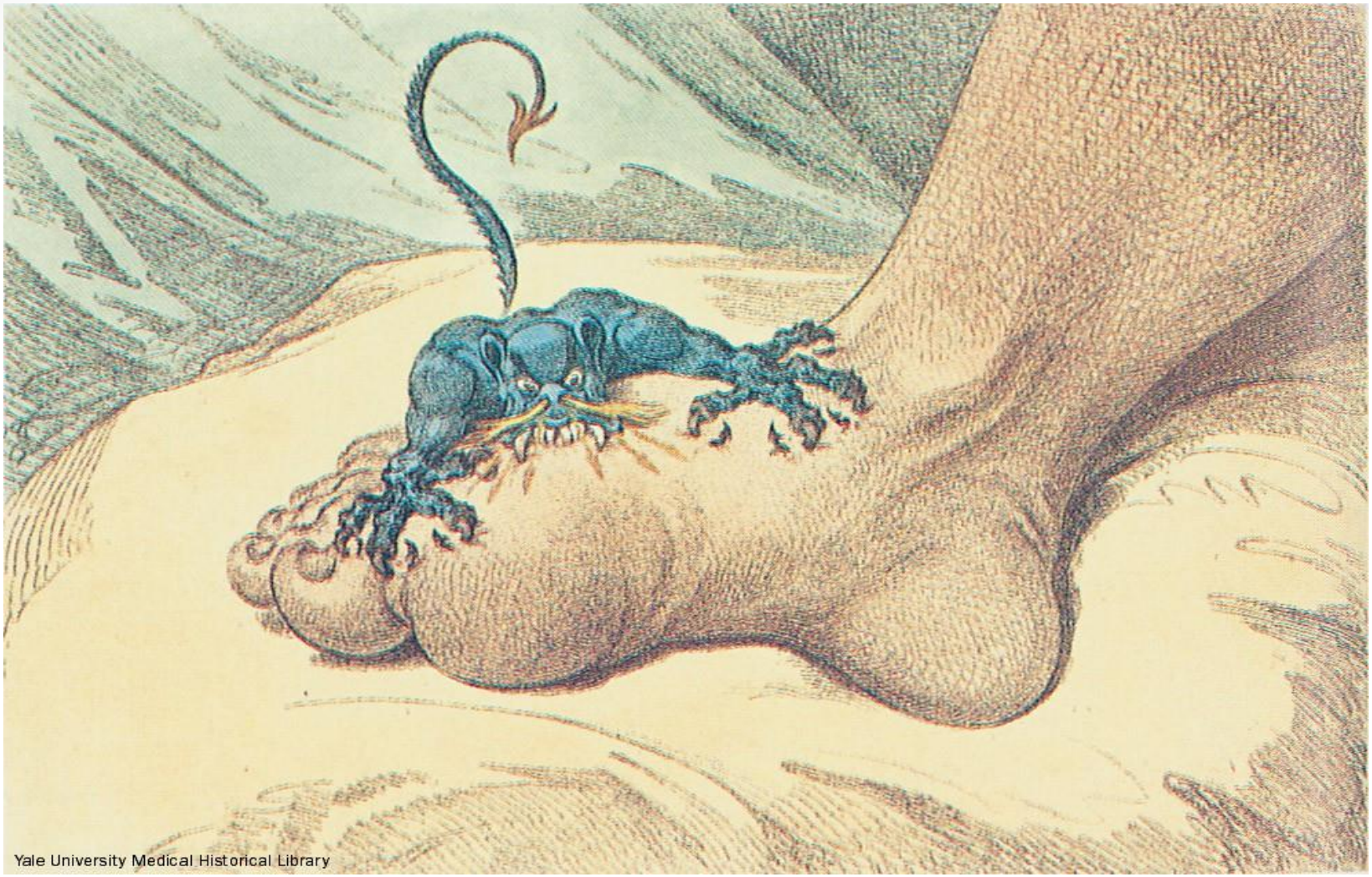


Fate of uric acid in humans

- Uric acid is less soluble in water
- Reptiles, insects and birds excrete uric acid as a paste of crystals
- To save water
- Humans excrete uric acid in urine

Fate of uric acid in humans

- Humans do not have enzymes to further degrade uric acid
- Excessive production of uric acid causes deposition of uric acid crystals in the joints leading to:
  - Gout
  - Hyperuricemia



The Gout, a cartoon by James Gilroy (1799)

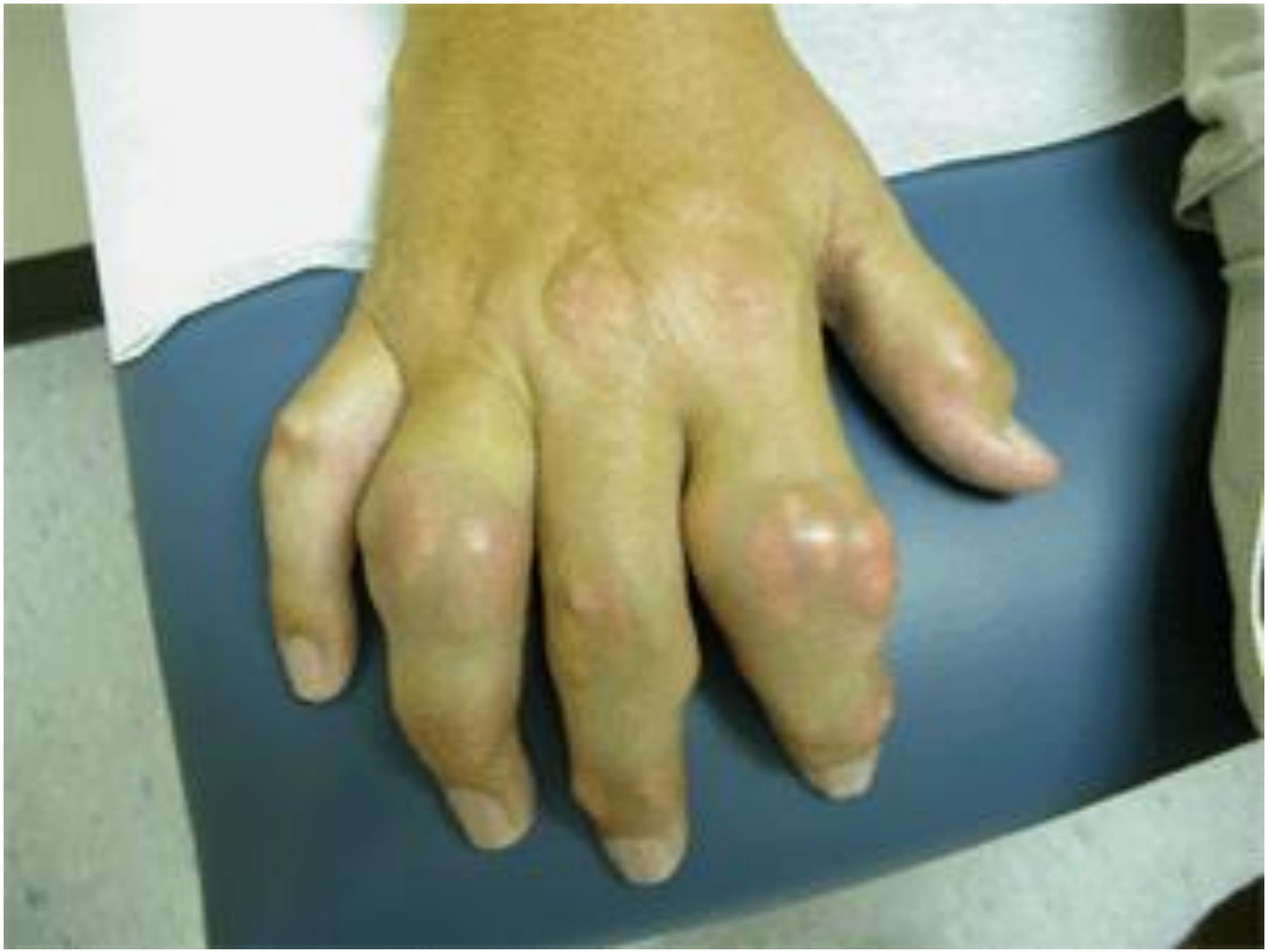
Gout

- Gout is a disease due to high levels of uric acid in body fluids
- 7.0 mg/dL and above
- Uric acid accumulates because of:
  - Overproduction or
  - Underexcretion

Gout

- Painful arthritic joint inflammation due to deposits of insoluble sodium urate crystals (especially big toe)
- Affects 3 per 1000 persons
- Sodium urate crystals accumulate in kidneys, ureter, joints leading to chronic gouty arthritis

Sodium urate crystals in urine



Gout

- Inaccurately associated with overeating and drinking
- Alcohol used to be contaminated with lead during manufacture and storage
- Lead decreases excretion of uric acid from kidneys causing hyperuricemia and gout
- Excessive meat comsumption increases uric acid production in some individuals

Gout

- Two main causes
- Overproduction of uric acid
- Underexcretion of uric acid

Classification of Gout

Clinical Category	Metabolic defect
Primary Gout (90% of cases)	
Enzyme defects-Unknown (85% to 90% of cases)	❑ **Overproduction of uric acid** -Normal excretion (Majority) -Increased excretion (Minority) ❑ **Underexcretion of uric acid with normal production**
Known enzyme defects – e.g., Partial HGPRT deficiency (rare)	**Overproduction of uric acid**
Secondary Gout (10% of cases)	
Associated with increase nucleic acid turnover – e,g. Leukaemia	**Overproduction of uric acid with increase urinary excretion**
Chronic renal disease	**Reduced excretion of uric acid with normal production**
Inborn errors of metabolism – e.g complete HGPRT deficiency (Lesch-nyhan syndrome)	**Overproduction of uric acid with increased urinary excretion**

Hypoxanthine-guanine phosphoribosyltransferase (HGPRT)

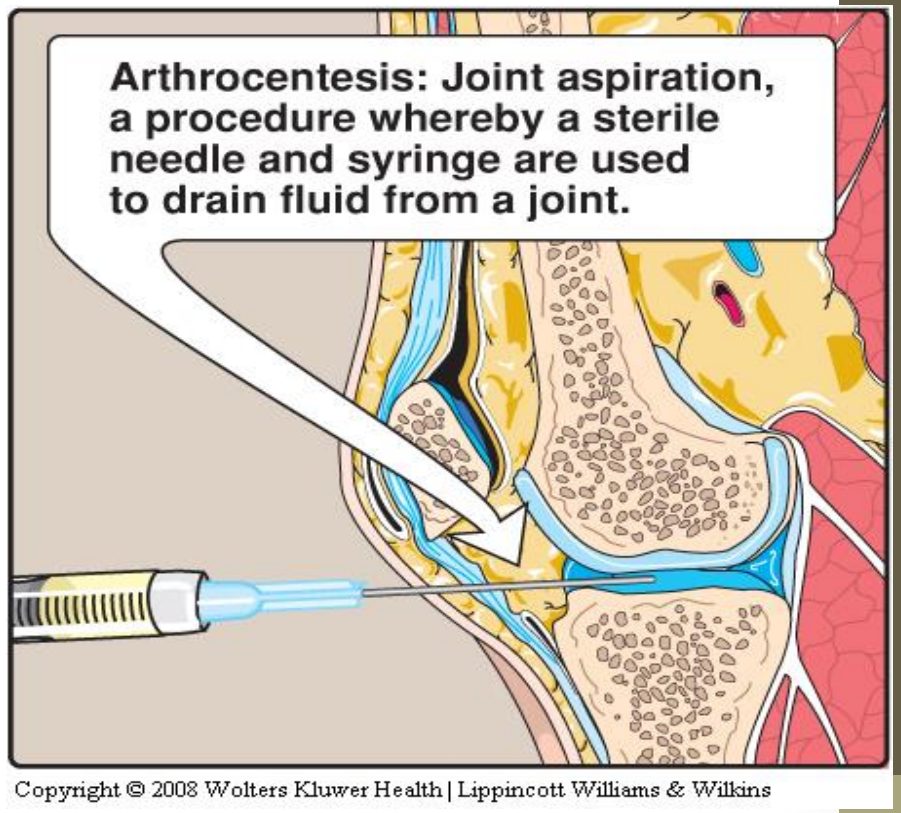
Biochemical Diagnosis

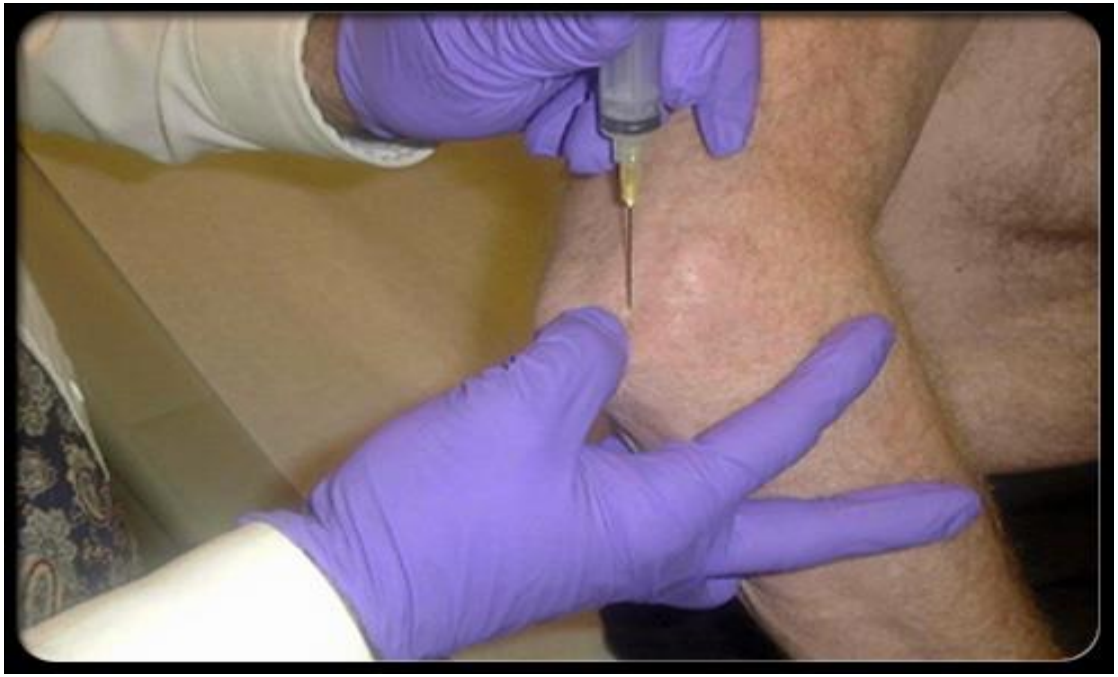
- **Joint fluid test**

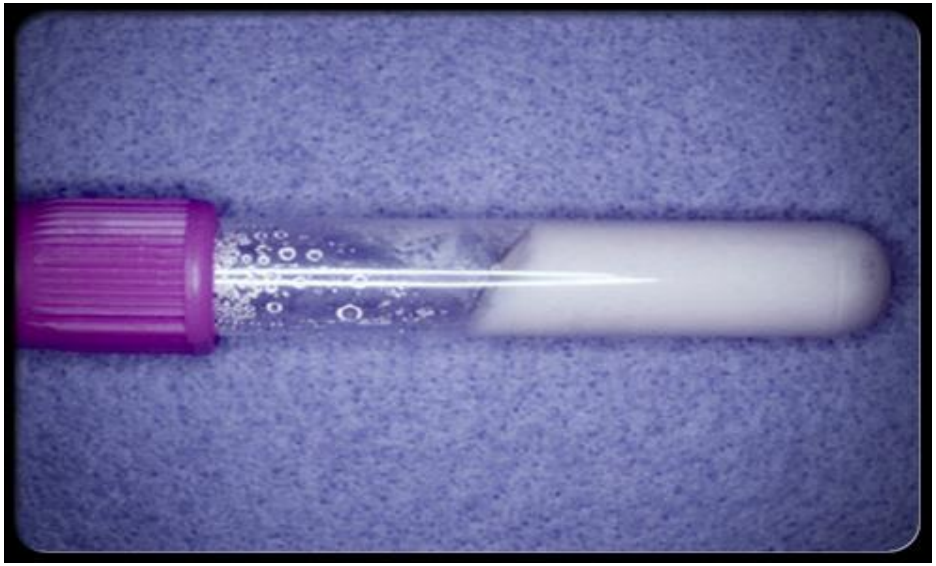
The definitive diagnosis of gout requires aspiration and examination of synovial fluid from an affected joint (or material from a tophus) using polarized light microscopy to confirm the presence of needle-shaped monosodium urate crystals.

- **Blood test**

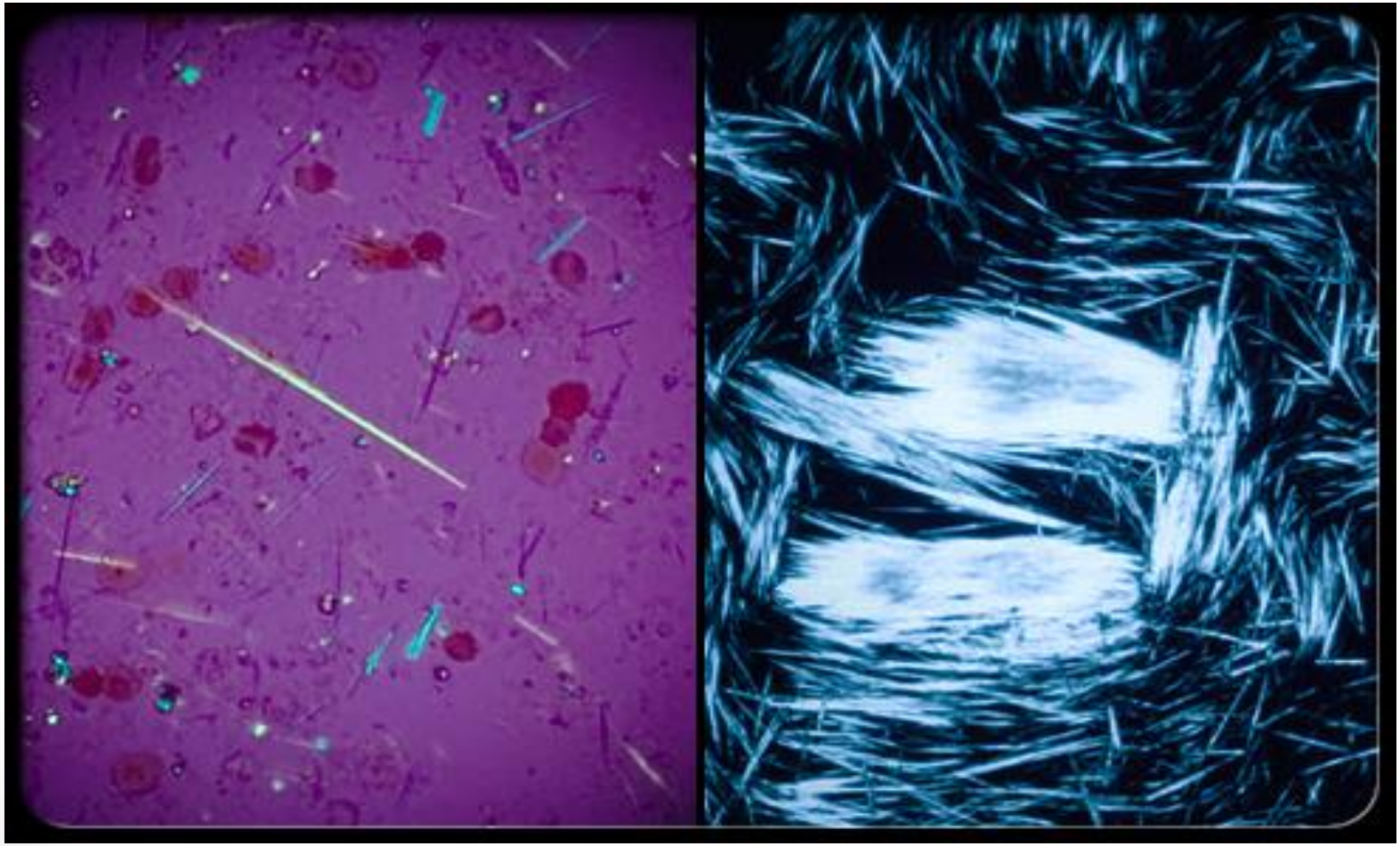
It uses to measure the levels of uric acid







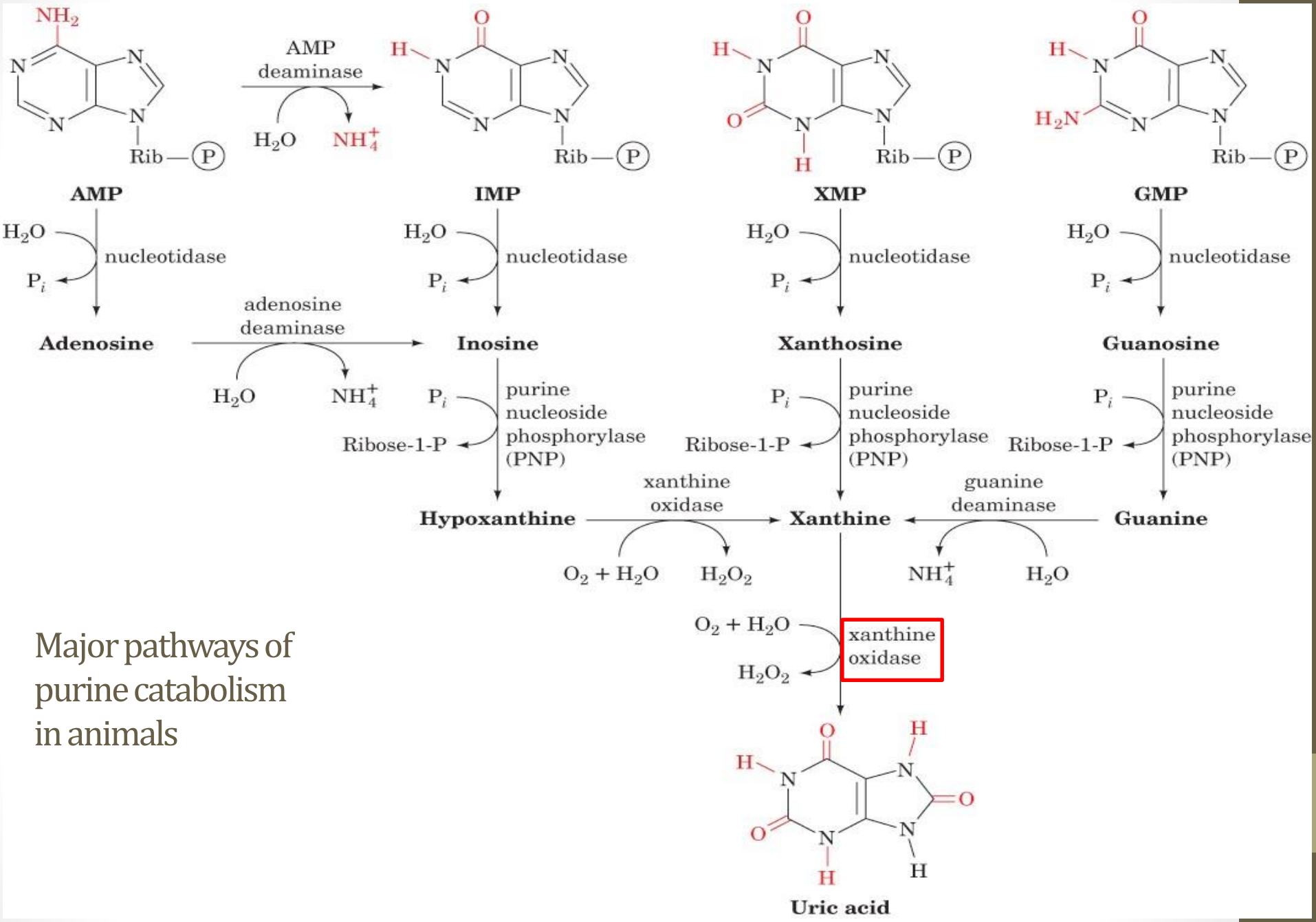
Monosodium urate crystals



Treatment

- To reduce pain and inflammation (analgesics, anti-inflammatory drugs)
- To increase uric acid excretion (uricosuric agents)
- To reduce uric acid production

  Allopurinol (xanthine oxidase inhibitor)



Major pathways of purine catabolism in animals

Take home message

- **The biochemical causes that contribute to the development of gout and hyperuricemia are defects in purine degradation pathway and impaired excretion of uric acid.**

- **Hyperuricemia does not always cause gout.**