Purine degradation & Gout (Musculoskeletal Block)

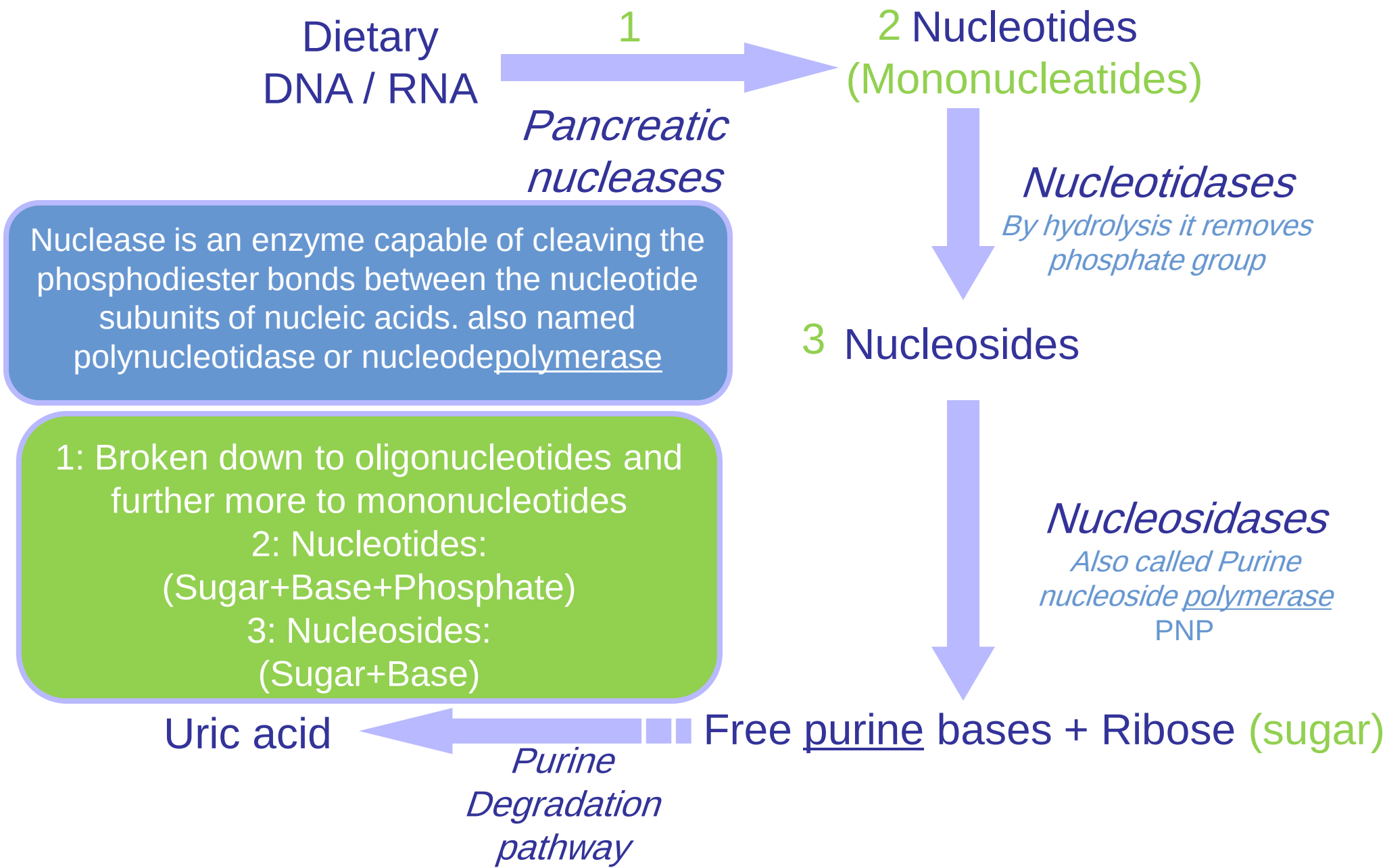
1 Lecture

Dr. Sumbul Fatma

- **Purine degradation pathway**
- **Fate of uric acid in humans**
- **Gout and hyperuricemia:**
  - **Biochemistry**
  - **Types**
  - **Treatment**

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
1
Pancreatic
nucleases
2 Nucleotides
(Mononucleatides)
Nucleotidases
By hydrolysis it removes
phosphate group
Nuclease is an enzyme capable of cleaving the phosphodiester bonds between the nucleotide subunits of nucleic acids. also named polynucleotidase or nucleodepolymerase
3 Nucleosides
1: Broken down to oligonucleotides and further more to mononucleotides
2: Nucleotides:
(Sugar+Base+Phosphate)
3: Nucleosides:
(Sugar+Base)
Nucleosidases
Also called Purine
nucleoside polymerase
PNP
Uric acid
Free purine bases + Ribose (sugar)
Purine
Degradation
pathway

Purine degradation pathway

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

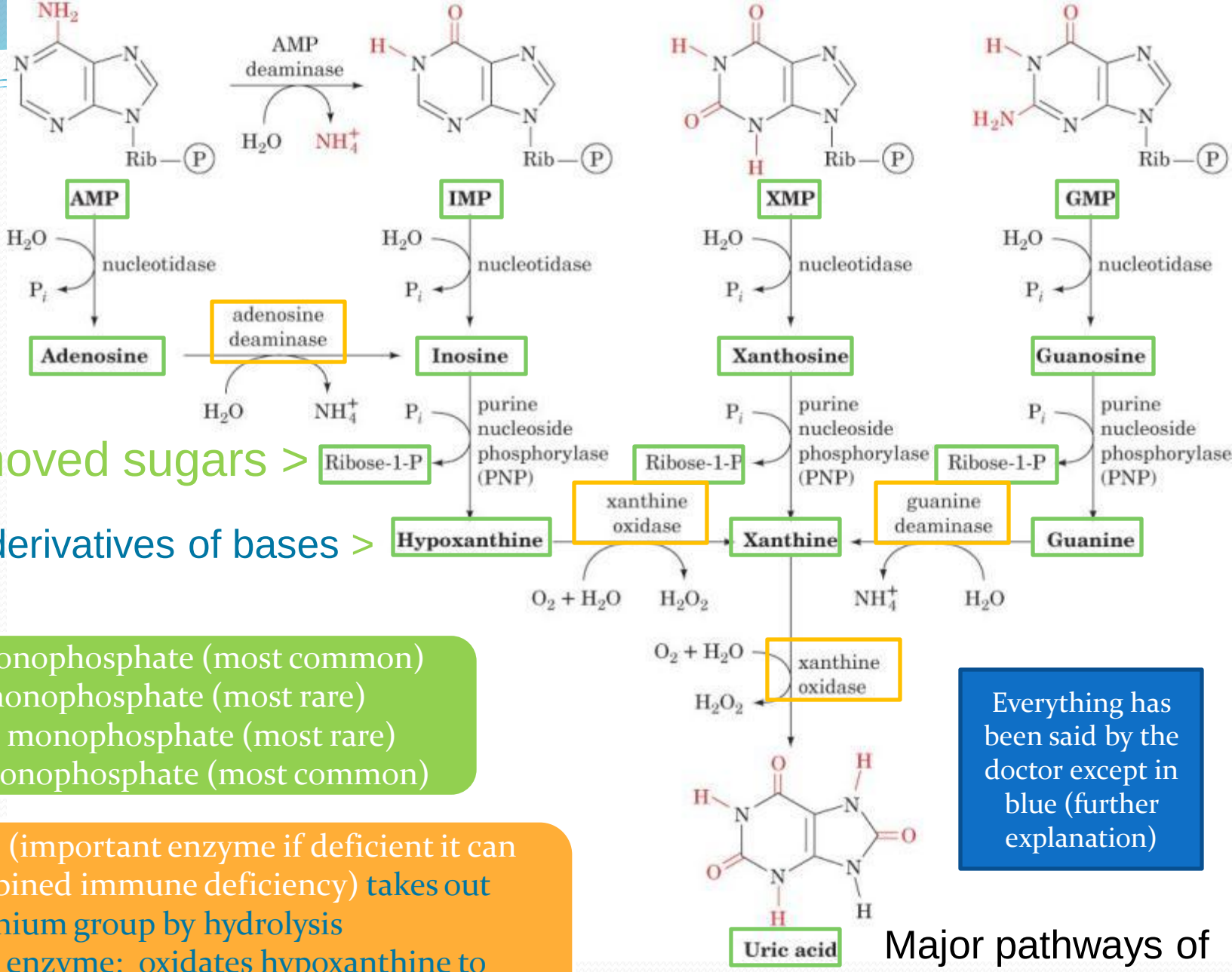
Dr.Sumbul said this slide is for your better understanding

Nucleotides >

Nucleosides >

Removed sugars >

Purine Bases or derivatives of bases >



AMP: adenosine monophosphate (most common)
IMP: inosine monophosphate (most rare)
XMP: xanthosine monophosphate (most rare)
GMP: Guanosine monophosphate (most common)

Deaminase enzyme (important enzyme if deficient it can cause severe combined immune deficiency) takes out ammonium group by hydrolysis
Xanthine oxidase enzyme: oxidates hypoxanthine to xanthine and oxidates xanthine to uric acid.

Everything has been said by the doctor except in blue (further explanation)

Major pathways of purine catabolism in animals

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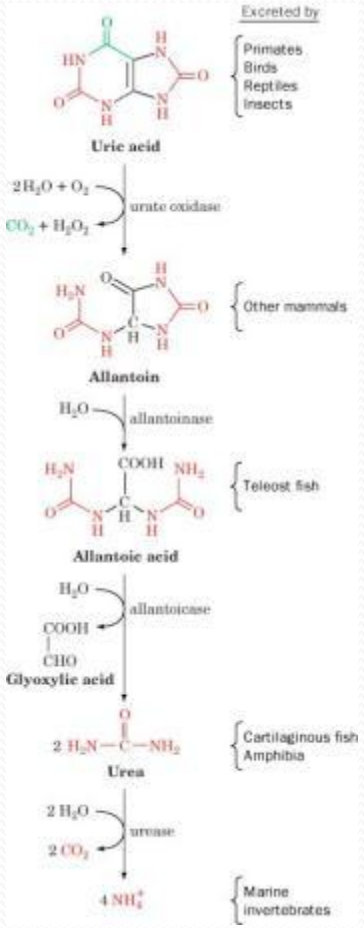
Fate of uric acid in humans

- 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: (because they have the enzymes that humans lack that enables them to convert uric acid to other products)
  - Allantoin
  - Allantoic acid
  - Urea
  - Ammonia

Degradation of uric acid to ammonia in some animals

You don't need to know the enzymes just know the products from previous slide

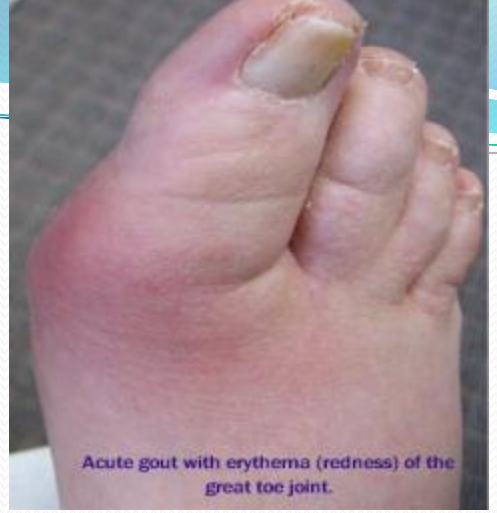


Fate of uric acid in humans

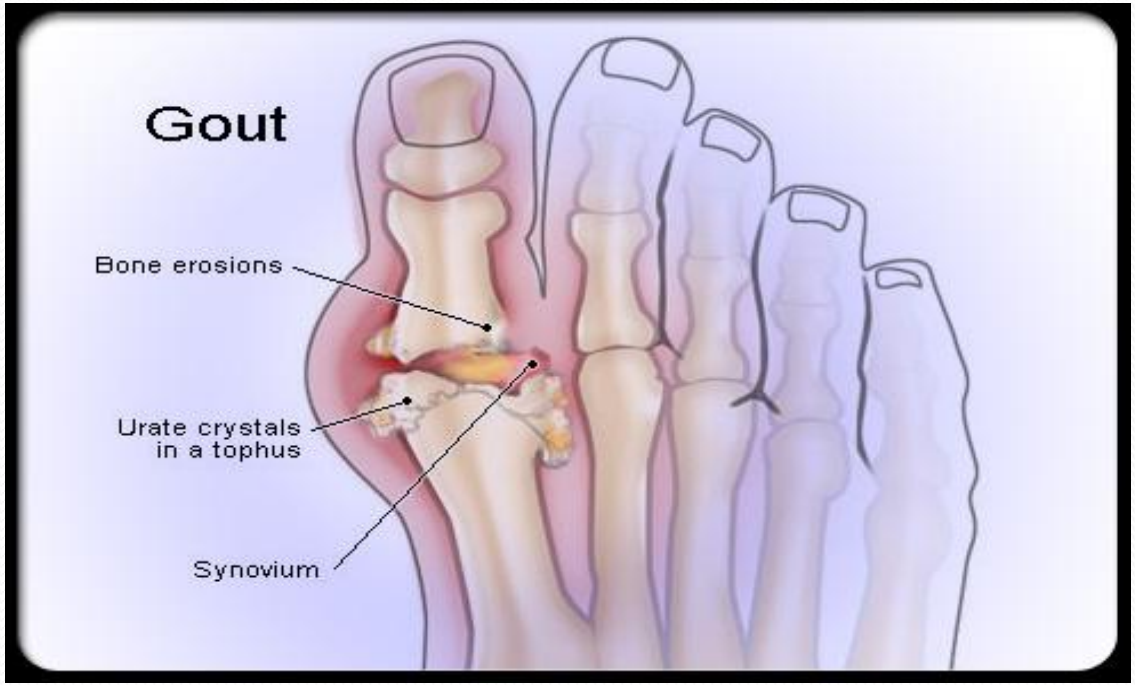
- Uric acid is less soluble in water
- Reptiles, insects and birds excrete uric acid as a paste of crystals to save water
- Humans excrete uric acid in urine
- Humans are ureotelic: excrete excess nitrogen as urea.
- Reptiles insects and birds are Uricotelic: produces uric acid (solid urea) as a result of deamination

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
- Hyperuricemia is not a disease. It is a condition of elevated uric acid in the blood. It can be referred as a disease once it shows symptoms or causes other diseases such as gout.



Usually the first to get affected is the big toe (the extremities in general) deposits of uric acid develop in the extremities where the pH factor and a lower body temperature are present. Since uric acid is highly insoluble, a pH factor of 7.4 and above and also a lower body temperature will increase the risk factor.



Gout

- Gout is a disease due to high levels of uric acid in body fluids
- 7.0 mg/dL and above (normal: 2.5-5 mg/dL)
- Uric acid accumulates because of:
  - Overproduction or
  - Underexcretion
- Gout used to be called the disease of the rich because the rich would always drink alcohol and eat plenty of meat - famous people who had gout were Benjamin Franklin and Isaac Newton

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 consumption increases uric acid production in some individuals

Lead = رصاص

Gout

Two main causes:

- Overproduction of uric acid
- Underexcretion of uric acid

Primary Gout

- Due to overproduction of uric acid
- Genetic abnormality in the enzymes of purine degradation
- Excessive production and degradation of purine bases (adenine, guanine, hypoxa nthine, inosine)

- Primary always means that it is idiopathic (unknown cause)
- Secondary has a known cause.

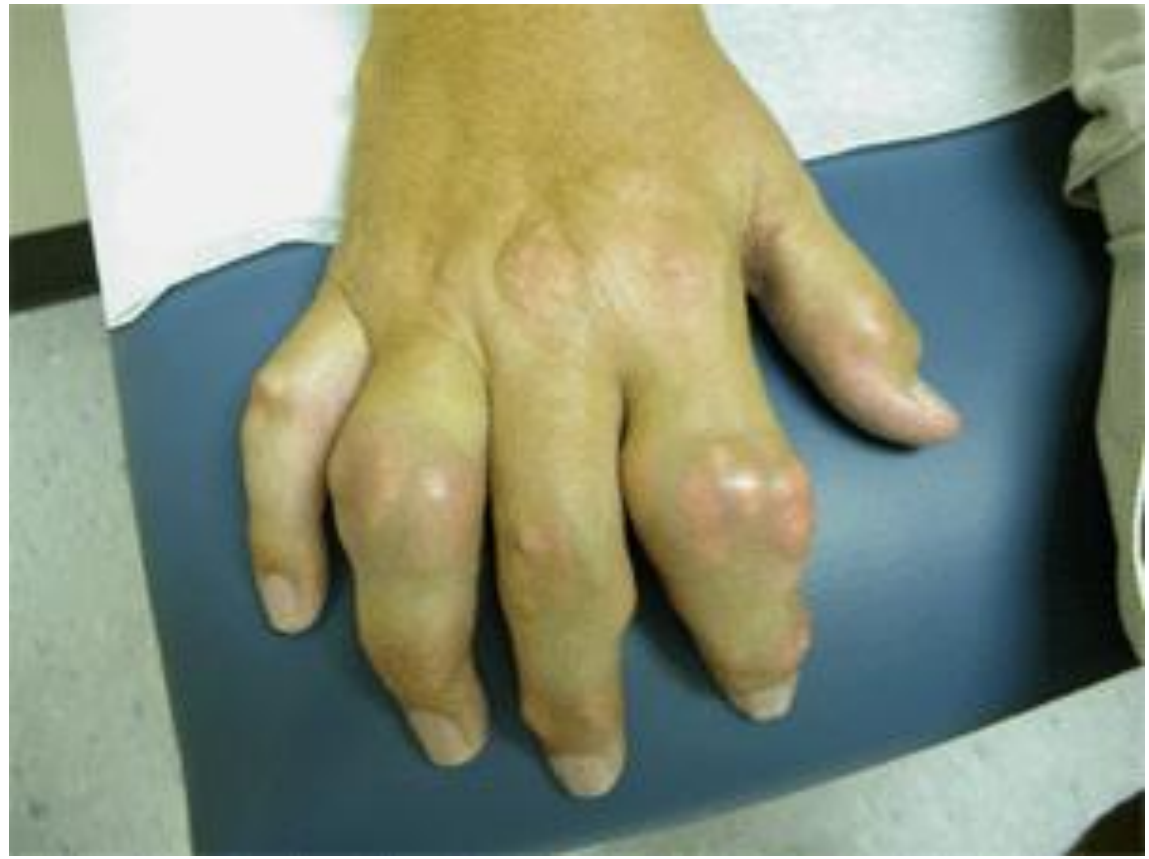
Secondary hyperuricemia

- A variety of disorders and lifestyles cause secondary hyperuricemia
- Underexcretion of uric acid cause: due to chronic renal disease
- Chemotherapy cause: due to excessive tissue (including purine) turnover after chemotherapy destroyed the tissue trying to kill malignant cells
- Excessive consumption of purine-rich foods such as meat cause: purine in meat
- Excessive alcohol intake cause: lead in alcohol which decreases excretion of uric acid from kidneys

Secondary hyperuricemia

- Hyperuricemia does not always cause gout

But gout is ALWAYS accompanied with hyperuricemia :D

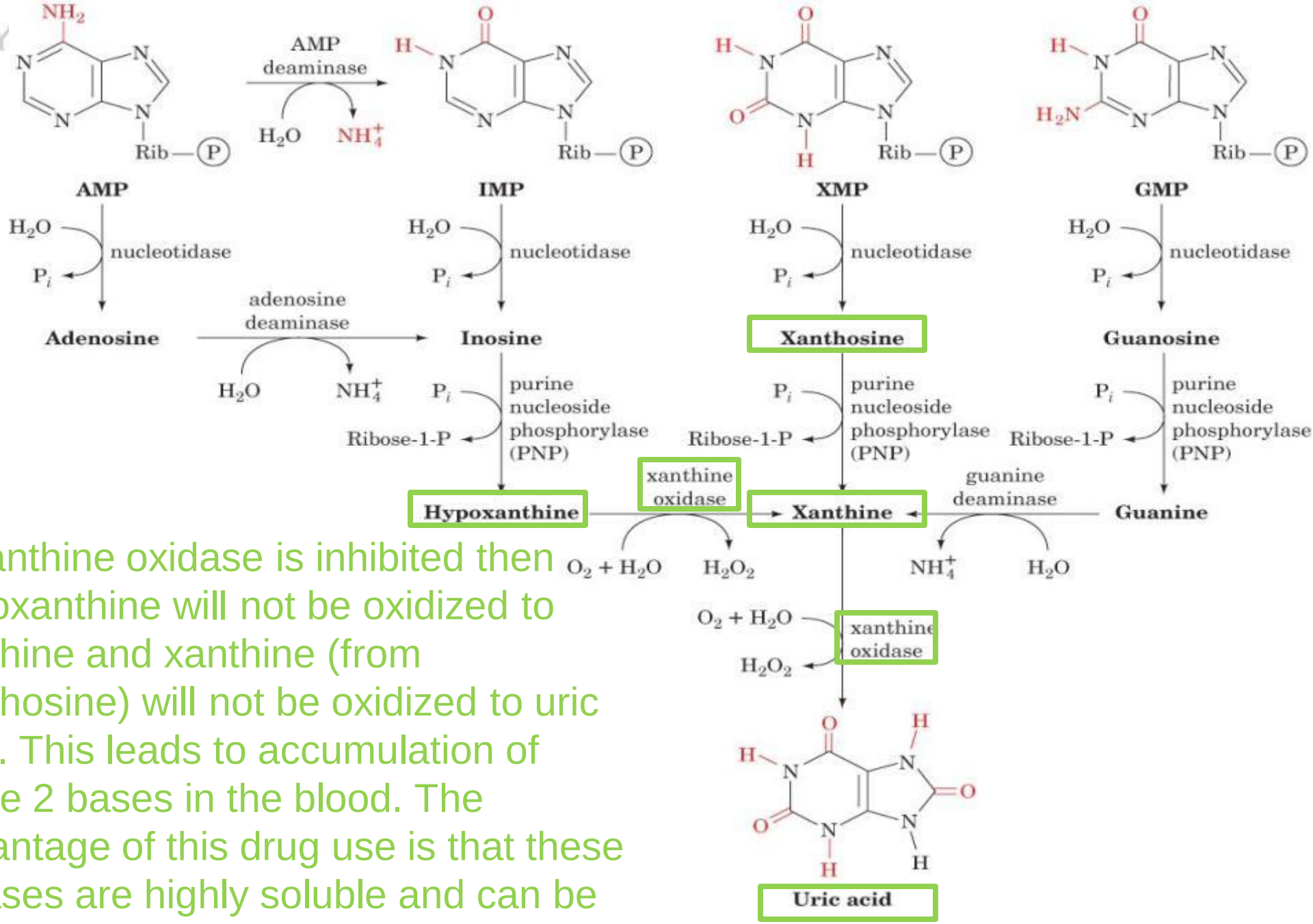


Crystals accumulate in the synovial fluid first then progress to around the joints
These are called: tophi –singular tophus-
What happens is that leukocytes gather by chemotaxis because of the inflammation and try to phagocytose the crystals but burst and send out cytokines and enzymes which have further inflammatory effects

Treatment

- Reduce pain and inflammation (analgesics, antiinflammatory drugs)
- Increase uric acid excretion (uricosuric agents)
- Reduce uric acid production
  - Allopurinol (xanthine oxidase competitive inhibitor)

  > Next slide to understand

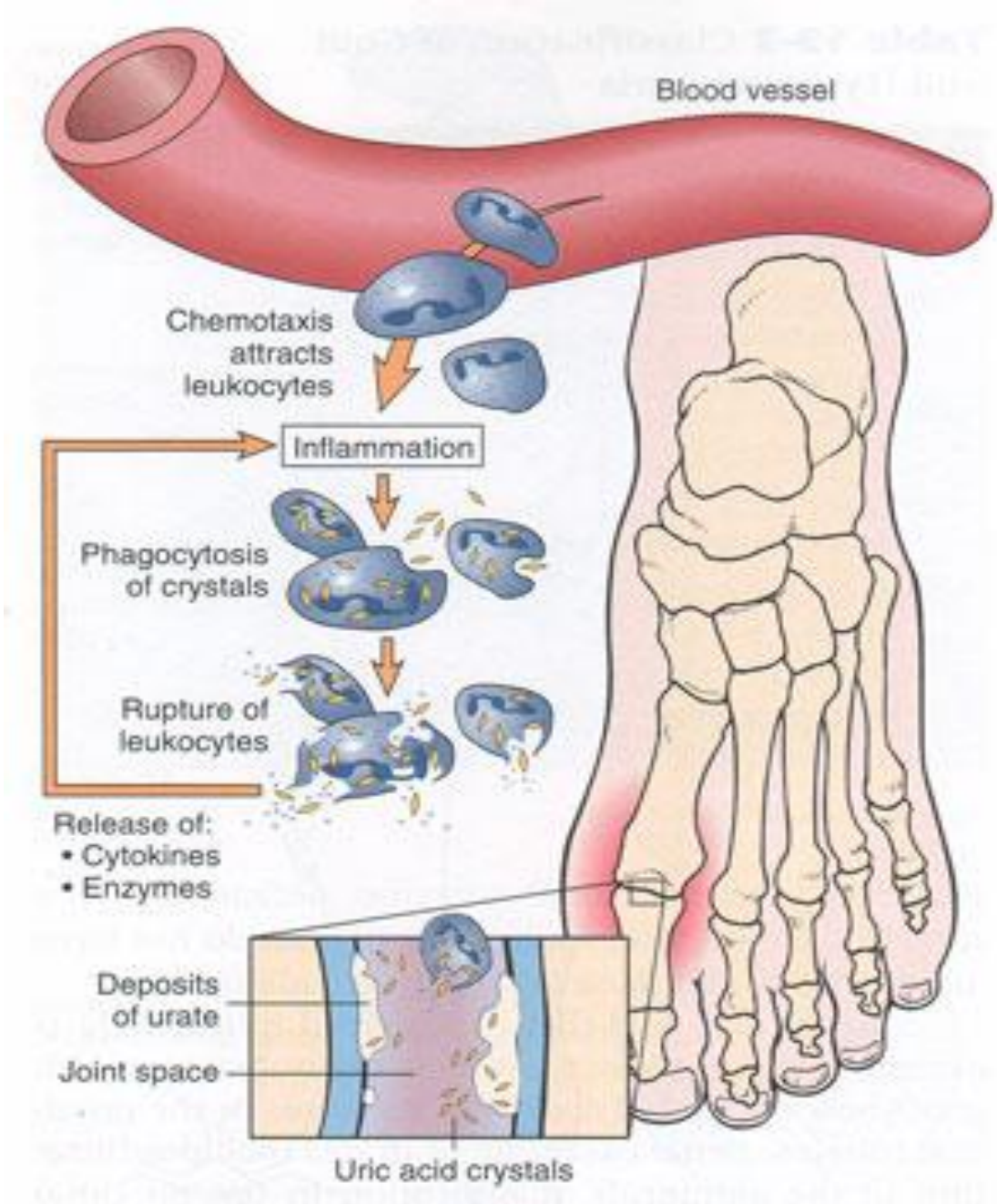


If Xanthine oxidase is inhibited then hypoxanthine will not be oxidized to xanthine and xanthine (from xanthosine) will not be oxidized to uric acid. This leads to accumulation of these 2 bases in the blood. The advantage of this drug use is that these 2 bases are highly soluble and can be readily excreted in the urine :D woho!

References

- Lippincott 4th Edition
- Voet & Voet

Supplementary slides

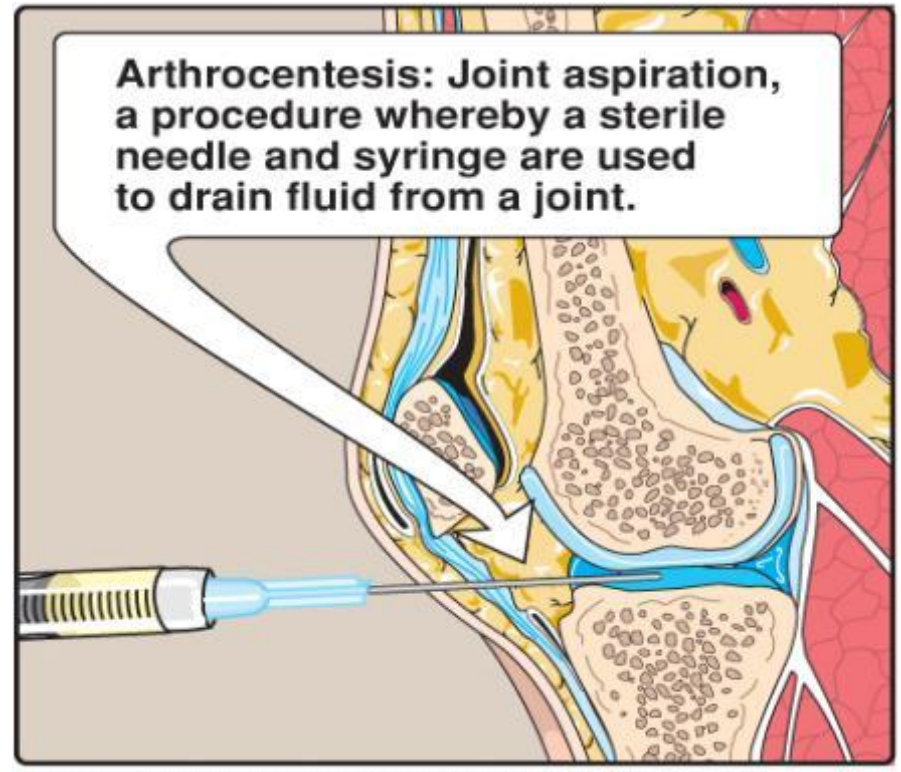

Blood vessel
Chemotaxis attracts leukocytes
Inflammation
Phagocytosis of crystals
Rupture of leukocytes
Release of:
• Cytokines
• Enzymes
Deposits of urate
Joint space
Uric acid crystals

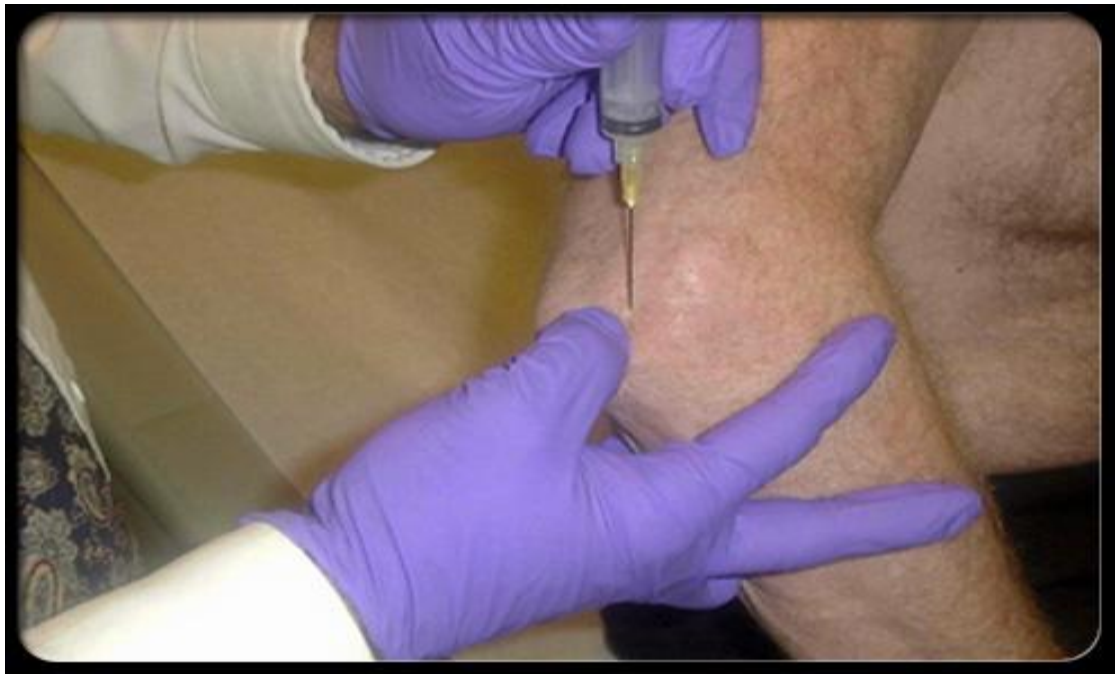
Diagnostic features

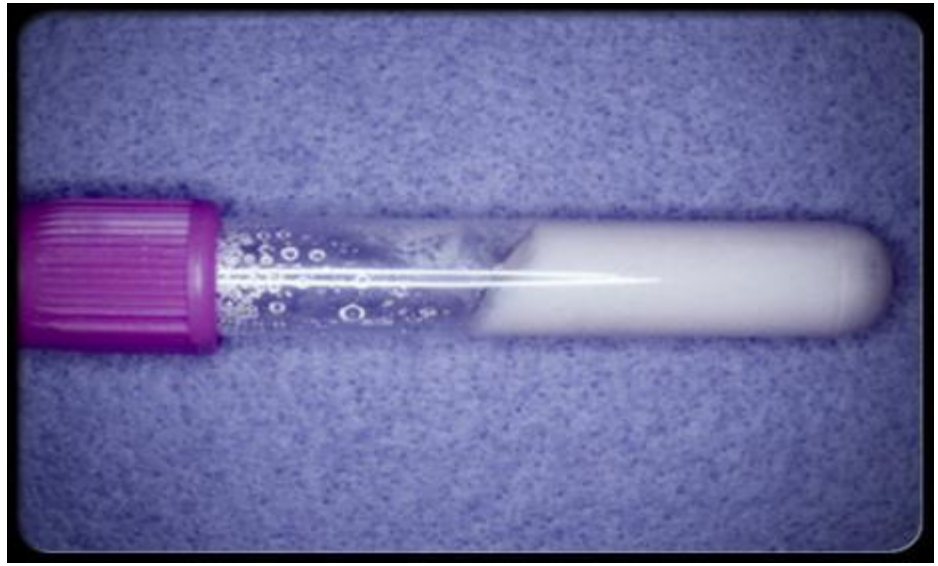
- usually affect joints in the lower extremities (95%)
- onset is fast and sudden
- pain is usually severe; joint may be swollen, red and hot
- attack may be accompanied by fever, leukocytosis and an elevated ESR

Diagnosis

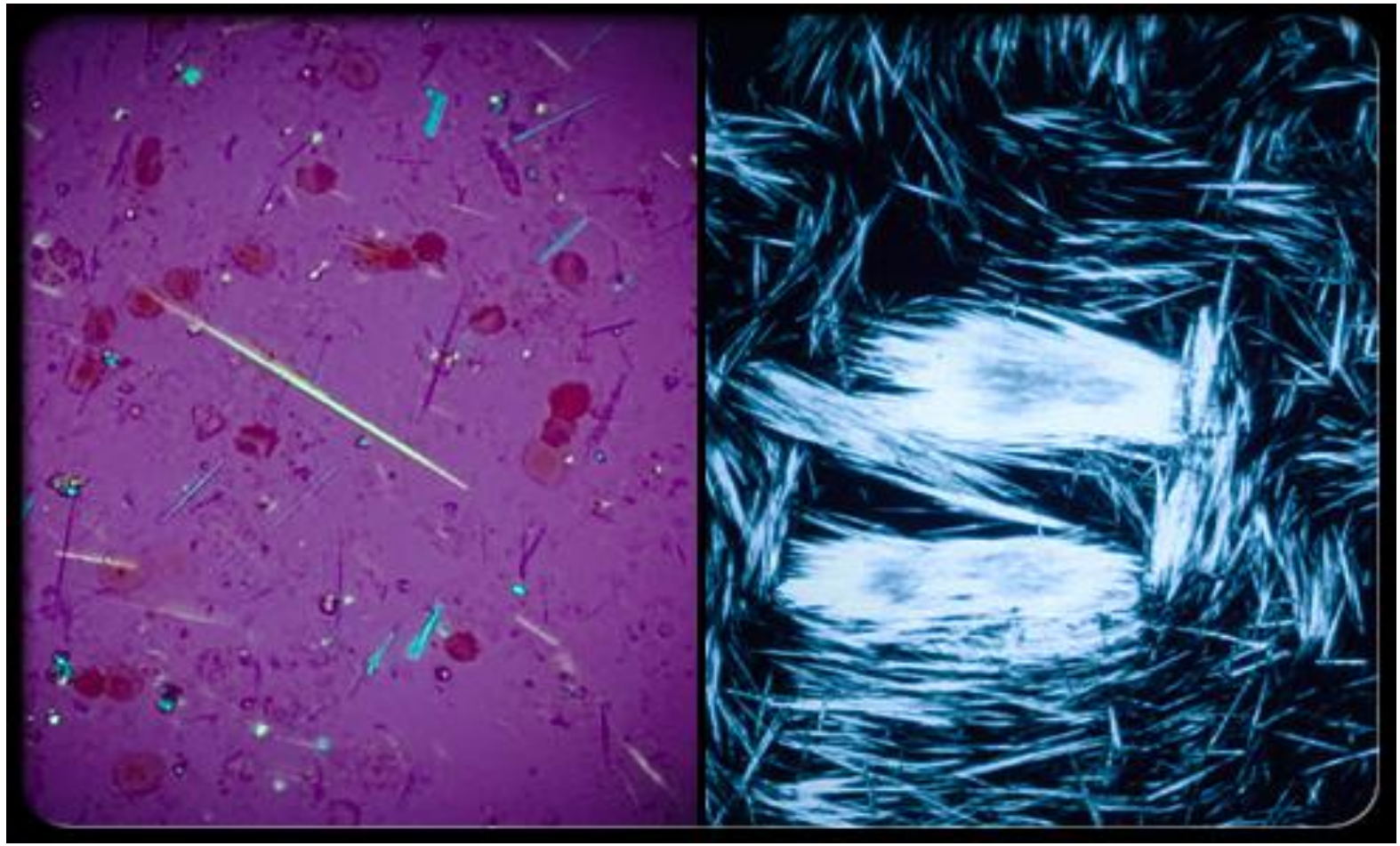
- The definitive diagnosis of gout requires aspiration and examination of synovial fluid from an affected joint (or material from a tophus) using polarized light microscopy to confirm the presence of needle-shaped monosodium urate crystals







Monosodium urate crystals



CLASSIFICATION OF THE CAUSES OF HYPERURICEMIA AND GOUT

Hyperuricemia
may be caused by:

Dietary excess

Overproduction of urate

Undersecretion of urate

Gout
may be:

Primary
Most are undersecretors, a few are overproducers

Secondary
Undersecretion:
eg. renal failure, diuretic therapy

Overproduction:
eg. myeloproliferative diseases

After chemotherapy