the editing file

Purine degradation and gout

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- Only in girls' slides
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Biochemistry team 438

Objectives:

Slide No. 3

1. purine degradation, uric acid formation and its association with gout.

Slide No 7

2. Fate of uric acid in humans.

Slide No. 9

3. recognize the importance of uric acid in the pathogenesis.

Slide No. 11

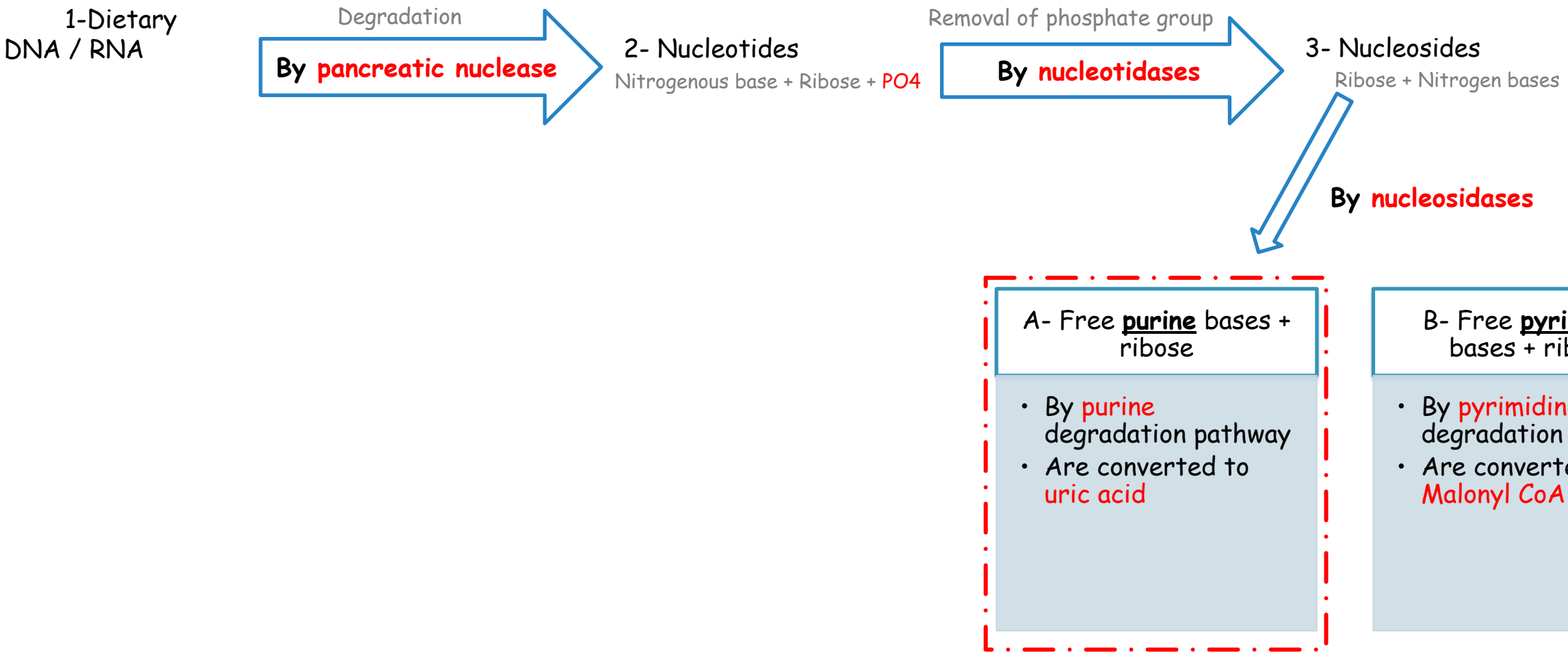
4. Overview of Gout classification and treatment.

Purine degradation pathway

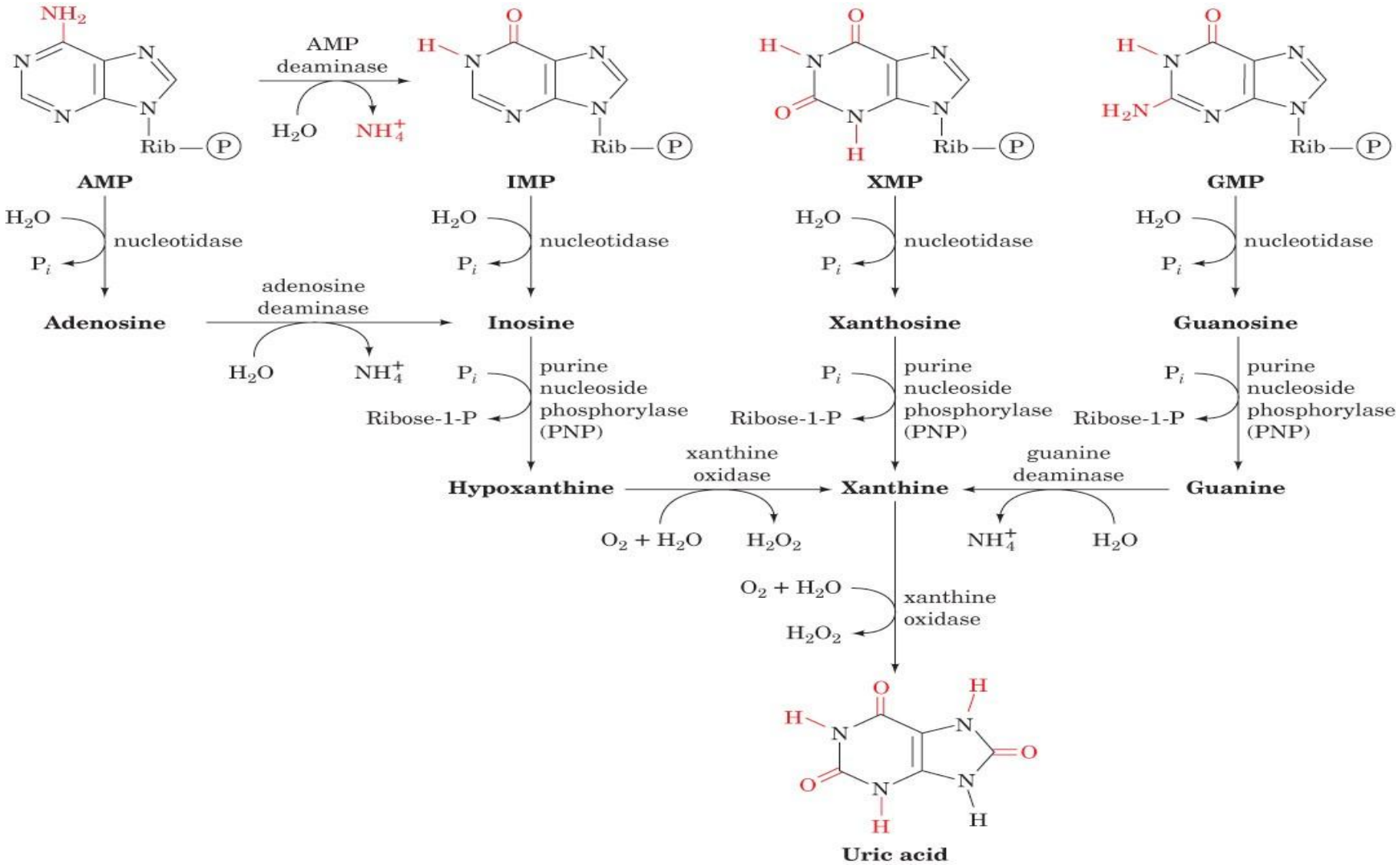
- The major source of dietary nucleic acids (purines and pyrimidines) is meat.
- Purine and pyrimidine bases are absorbed by the intestine. (small intestine)
- The ingested bases are mostly degraded into different products by degradation pathways
  - Adenosine and guanosine (purines) are finally degraded to uric acid by purine degradation pathway.
- These products are then excreted by the body

★ In cells DNA is synthesized via :
1) from primary raw materials "most of DNA"
2) Recycling pathway
3) from food (dietary nucleic acids) "small amount of DNA"

Purine degradation pathway



Major pathway of purine catabolism in animals



Purine degradation enzymes

substrate:	1. AMP 2. Gunaine 3. Adenosine	1. IMP 2. XMP 3. GMP	1. Inosine 2. Xanthosine 3. Guanosine	1. hypoxanthine 2. Xanthine
enzyme:	Deaminase	Nucleotidase	purine nucleoside phosphorylase (PNP)	Xanthine oxidase
mechanism:	a. Remove amino group b. Add carbon	remove Phosphate group	remove ribose sugar (delete the prefix sine)	oxidation
product:	1. IMP 2. Xanthine 3. Inosine	1. Inosine 2. Xanthosine 3. Guanosine	1. Hypoxanthine 2. Xanthine 3. Guanine	1. Xanthine 2. Uric acid

Fate of Uric Acid in Humans

- In humans, primates, birds and reptiles the final product of purine degradation is uric acid.
  - ★ Primates are creatures of one biological order that includes monkeys, apes, the latter of which includes humans)

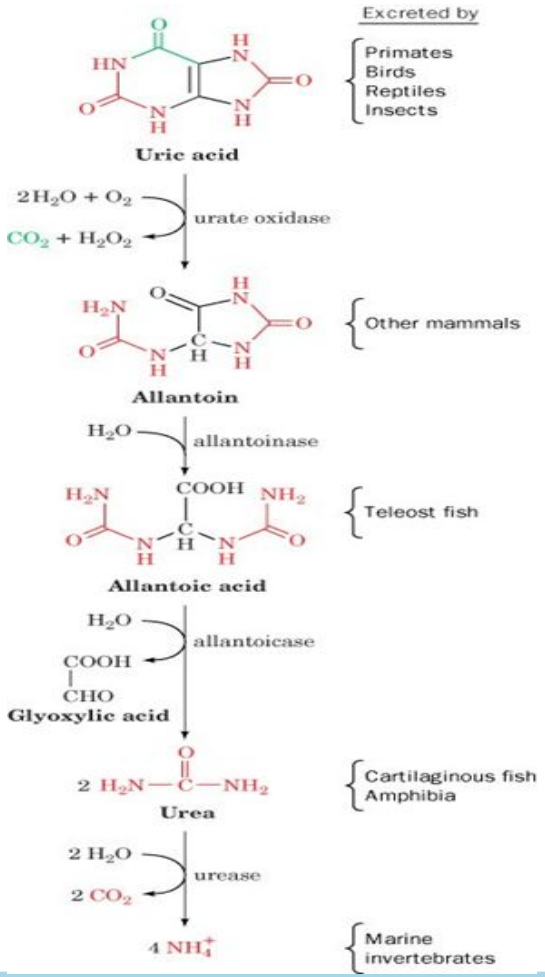
➔ Uric acid is excreted in the urine.

- Some animals convert uric acid to other products:
  - ★ humans lack the enzyme urate oxidase "its genes are available but nonfunctional", which can convert the product to allantoin that can be easily excreted in urine, instead uric acid is excreted as it is and has a chance when accumulating to be crystallized which causes gout and kidney stones.

  - Allantoin
  - Allantoic acid
  - Urea
  - Ammonia

(you don't have to know this pathway)

Degradation of uric acid to ammonia in some animals

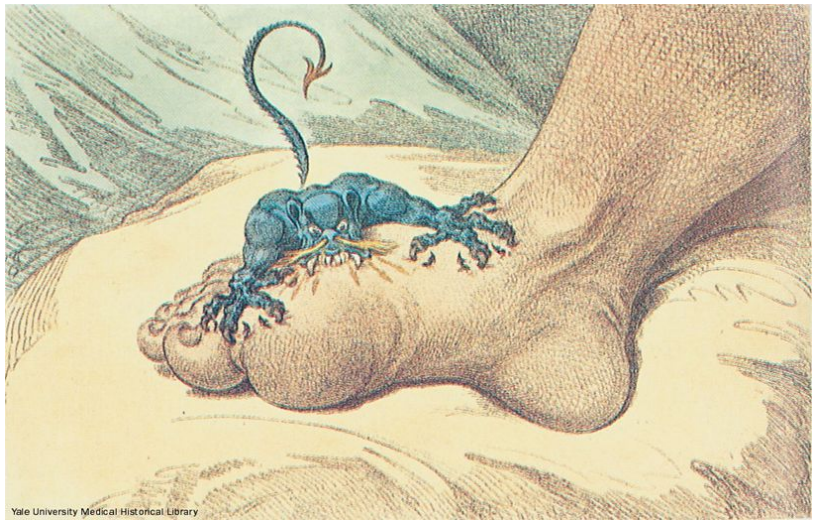


Fate of Uric Acid in Human

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

- Humans do not have enzymes to further degrade uric acid
- Humans excrete uric acid in urine

- Excessive production of uric acid causes deposition of uric acid crystals in the joints (mainly) leading to:
  - Gout
  - Hyperuricemia



The Gout, a cartoon by James Gilroy (1799)

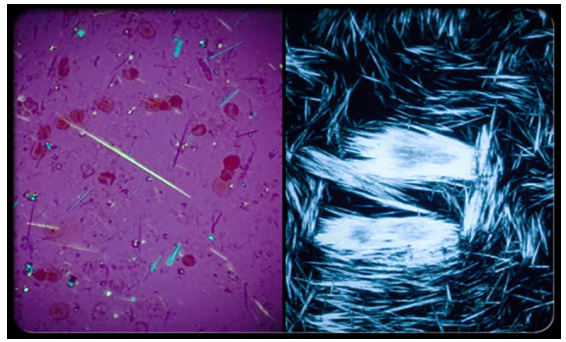
NOTE

★ hyperuricemia is a condition in which the concentration of uric acid is increased in the serum due to overproduction/underexcretion, and it is the most common predisposing factor for gout **but does not necessarily lead to it**, some individuals may have gout with normal uric acid levels and some may have high uric acid levels and not have gout

Objective 3: recognize the importance of uric acid in the pathogenesis.

Gout

Sodium urate crystals in urine



★ Overview:

- It's a disease due to high uric acid in body fluids
- Painful arthritic joint inflammation due to deposits of insoluble sodium urate crystals (especially big toe)
-
- Affects 3 per 1000 persons

★ Pathogenesis:

Overproduction or Underexcretion of uric acid → **uric acid accumulation in body fluids** → **deposits of insoluble sodium urate crystals** → **When Sodium urate crystals accumulate in organs** → **chronic gouty arthritis**

★ Hyperuricemia does not necessarily cause Gout

7.0 mg/dL and above

- joints (first target
- kidney
- ureter

Gout

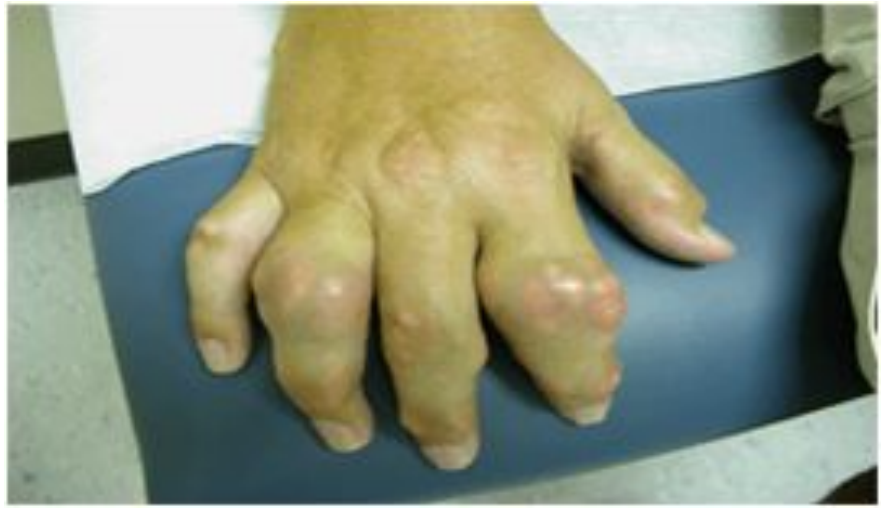
★ Causes:

- 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

➔ 2 main Causes:

Overproduction of uric acid

Underexcretion of uric acid



Swollen joints (tophi)

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) this will inhibit the salvage pathway (bio synthetic pathway of uridine) **"recycling of uric acid"** so it will channel the nucleosides to the other pathway which is making Uric acid.	Overproduction of uric acid
Secondary Gout (10% of cases)	
Associated with increase nucleic acid turnover – e,g. Leukaemia Excessive breakdown of RBCs —> Breakdown of their nucleic acids —> Purine degradation —> Production of Uric acid	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

*HGPRT: Hypoxanthine-Guanine Phosphribosyl Transferase

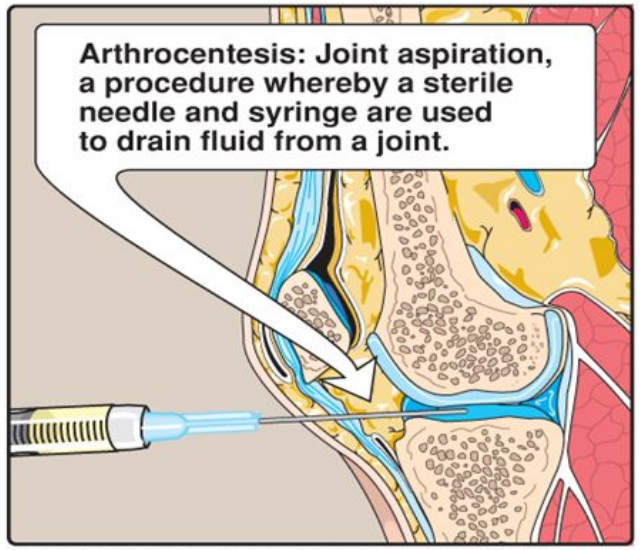
Important slide

Gout

★ 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. Sensitive & Specific for gout



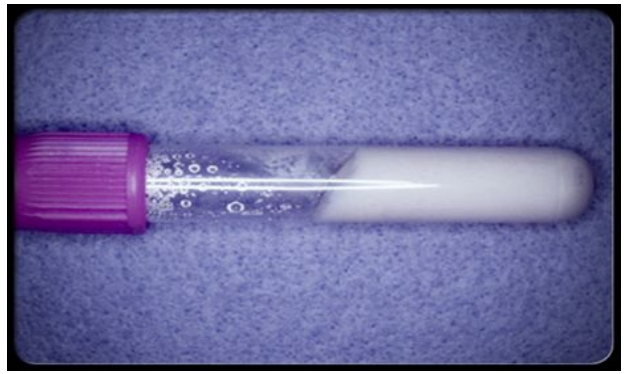
❑ Blood test

It uses to measure :

- the levels of uric acid
- CPC , EBC "to detect inflammation"
- Sensitive for hyperurithimia

❑ Urine test

to see the crystals



★ Abnormal synovial fluid
★ Normal: clear yellowish fluid

NOTES

★ high level of uric acid in the blood test means that the patient at high risk of gout or he already have it
★ Joint fluid test is only used on patient with affected joint

★ Treatment:

❑ To reduce pain and inflammation :

- Analgesic
- anti-inflammatory drugs

❑ To increase uric acid excretion :

- Uricoseric agents.

★ Used in cases of renal problems for example.

❑ To reduce uric acid production:

- Allopurinol (Xanthine oxidase inhibitor)

★ a competitive inhibitor of this enzyme.

★ can be used in cases of overproduction.

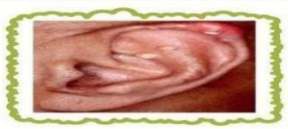
Take home message

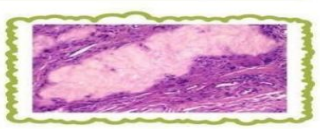
- The biochemical causes that contribute to the development of gout and hyperuricemia are defects in purine degradation pathway and impaired excretion of uric acid.
- Hyperuricemia does not always cause gout.

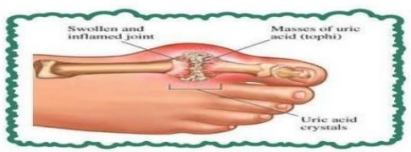
thanks to 437 pathology teamwork

Goat

- *Definition*: Monosodium urate crystals precipitate from supersaturated body fluids and induce an acute inflammatory reaction
- *Etiology*: Caused by excessive amounts of uric acid
- *Marked by*:
  - Recurrent episode of acute arthritis
  - Formation of large crystalline aggregates called **tophi**
- *Risk factors*:
  - Obesity
  - Excess alcohol intake
  - Consumption of Purine-rich foods
  - Diabetes
  - The metabolic syndrome
  - Renal failure
- *Types*:
  - 90% Primary
    - Enzyme defects - Unknown (85-90% of cases)
      - Overproduction of uric acid, normal or increased excretion
      - Underexcretion of uric acid with normal production
    - Known enzyme defect - e.g. partial HGPRT deficiency (rare) — Overproduction of uric acid
  - 10% Secondary
    - Associated with increased nucleic acid turnover - e.g. leukemia's — Overproduction of uric acid with increased urinary excretion
    - Chronic renal disease — Reduced excretion of uric acid with normal production
    - Inborn errors of metabolism — Overproduction of uric acid with increased urinary excretion e.g. complete HGPRT deficiency (Lesch-Nyhan syndrome)
- *Morphology*:
  - Acute arthritis
    - Characterized by a dense neutrophilic infiltrate permeating the synovium & synovial fluid
    - Long, slender, needle-shaped monosodium urate crystals
  - Chronic tophaceous arthritis
    - Repetitive precipitation of urate crystals during acute attacks
    - The synovium becomes hyperplastic, fibrotic & thickened by inflammatory cells
  - Tophi
    - Pathognomonic for goat
    - Appear in the articular cartilage of joints & soft tissues (ear lobes & nasal cartilage
    - Formed by
      - large aggregations of urate crystals
      - intense inflammatory reaction of lymphocytes
      - macrophages
      - foreign-body giant cells







- *Clinical features*:
  - Most common affected site: first metatarsophalangeal joint
  - Swollen, red & very painful
  - Renal manifestation of goat appears as renal colic, associated with passage of gravel & stones

MCQs

Q1: what is the substrate for xanthine oxidase ?			
A) Xanthine	B) Hypoxanthine	C) AMP	D) Both A&B
Q2: the conversion of Adenosine to Inosine is done by which of the following enzymes ?			
A) PNP	B) ADA	C) nucleotidase	D) Adenosine oxidase
Q3: Most of the cases of gout are ..			
A)Secondary	B) Primary	C) chronic	D) HGPRT deficiency
Q4: The major source of purines in the diet is ...			
A) Meat	B) Vegetables	C) Both A and B	D) None of the above
Q5: what's the deficient enzyme in humans that further metabolizes uric acid to a more water-soluble molecule ?			
A) allantoin primase	B) urate oxidase	C) PNP	D) Deaminase
Q6:Gout is usually preceded by hyperuricemia but you can have gout without any increase in Uric acid in the blood			
A)T	B)F		
Q7:If a patient with chronic renal disease has increased amount of uric acid (was found to have hyperuricemia) what's the most likely cause of it:			
A) Overproduction with increased excretion of uric acid	B) Overproduction with normal excretion of uric acid	C) Normal production with decreased excretion of uric acid	D) arthritis
Q8: the final product of purine degradation in humans is:			
A)Allantoin	B)Allantoic acid	C)Ammonia	D) Uric acid

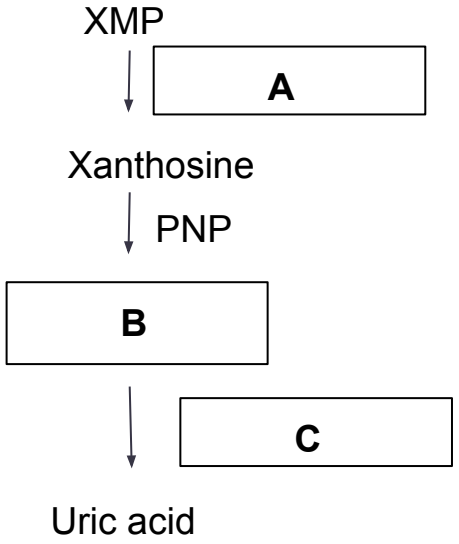
Answer key:

1) D
2) B
3) B
4) A
5) B
6) A
7) C
8) D

SAQs

Q1: identify A, B and C

A: Nucleotidase
B: Xanthine
C: Xanthine oxidase



Q2:Excessive production of uric acid causes deposition of uric acid crystals in the joints leading to?

Gout

Q3: Gout is caused by

Overproduction or Underexcretion of uric acid

Q4: What's the biochemical Diagnosis & The name of the Drug used to treat Gout

1-Joint fluid test 2-blood test

The drug is Allopurinol

❖ Team leaders:

Deema Almaziad **Raed Alojairi**

❖ Girls team:

- ➔ **Abeer Alkhodair**
- ➔ **Alwateeen albalawi**
- ➔ **Shahd Alsalamh**
- Reem Alqarni
- Taif Alotaibi
- Noura almazrou
- Lina alosaimi
- Nouran Arnous
- Ajeed Alrashoud
- Elaf Almusahel
- Noura Alturki
- Nouf Alhumaidhi

❖ Boys team:

- ➔ **Nayef alsaber**
- ➔ **Rakan alfaifi**
- ➔ **Mohabbad alqarni**
- Saad Dammas
- Omar alghamidi
- Alkaseem Binobaid

★ The harder the conflict, the more glorious the triumph.

438 BIOCHEMISTRY TEAM

➢ Contact us:

@Biochemistry438

Biochemistryteam438@gmail.com