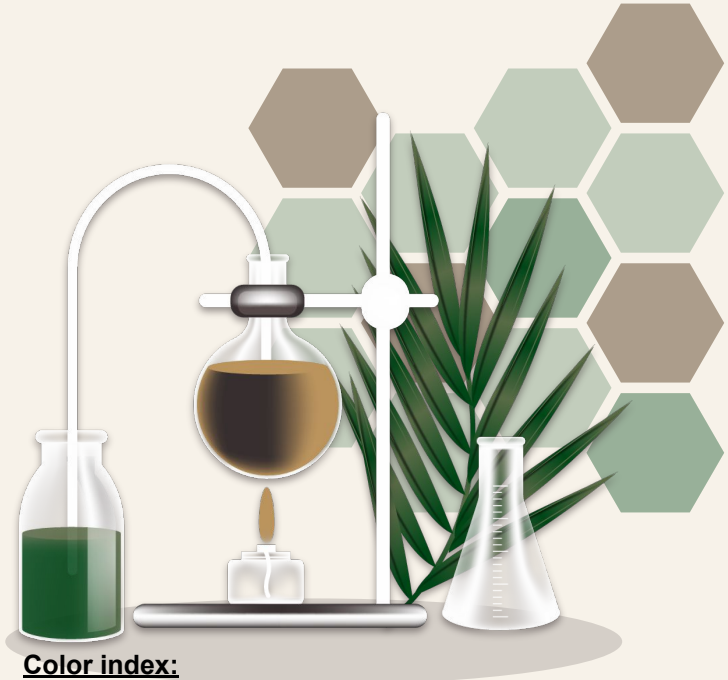
Biochemistry

Purine degradation & GOUT



Color index:
-Main text -Girls' slides -Boys' slides
-Important - Dr's notes -Extra

Editing File

Objectives:

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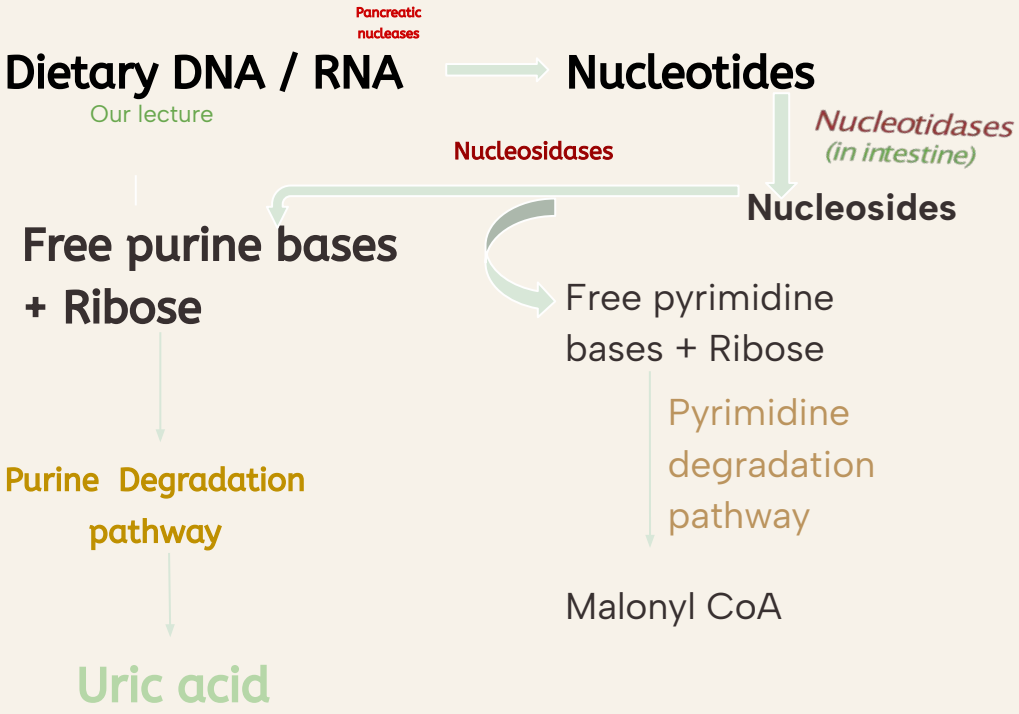
- Purine degradation, uric acid formation and its association with gout.
- Fate of uric acid in humans.
- Recognize the importance of uric acid in the pathogenesis of gout.
- Overview of Gout classification and treatment.

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

Purine degradation pathway

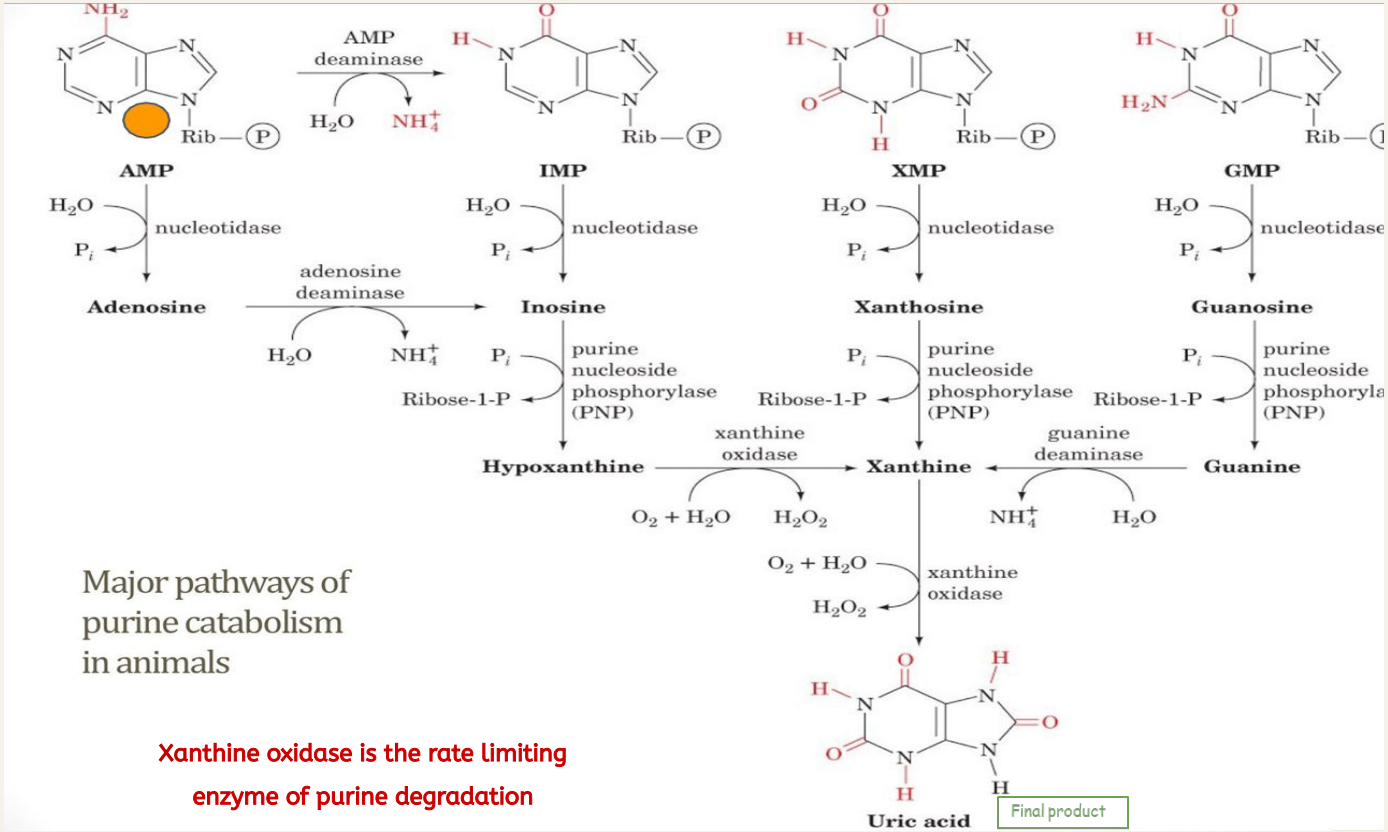


Adenosine and guanosine (purines) are finally degraded to uric acid by:

- Purine degradation pathway

You have to know each enzyme and its function

Major pathways of purine catabolism in animals



Xanthine oxidase is the rate limiting enzyme of purine degradation

Nucleotidase: Remove the **phosphate** group

PNP: Remove the **sugar** group

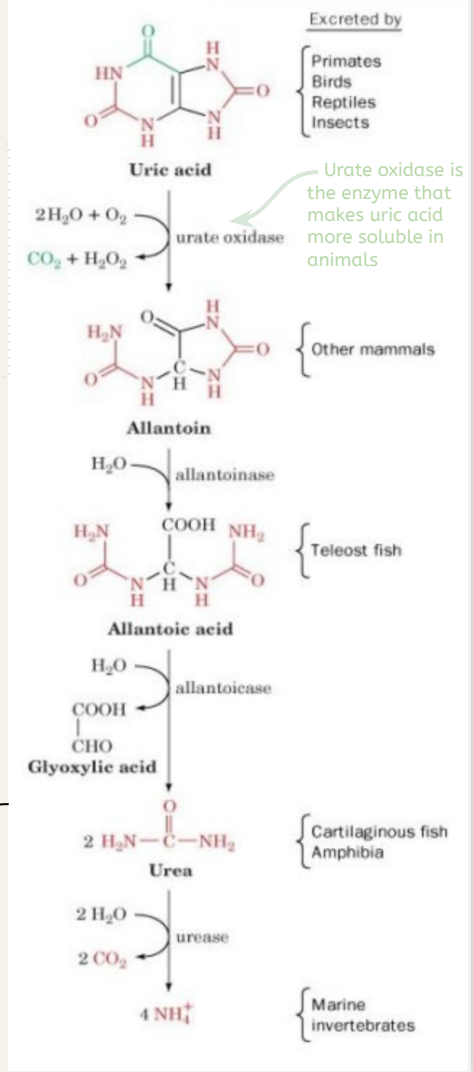
deaminase: Remove the **amine** group

Enzyme	Examples	function
Deaminase	AMP Deaminase	AMP → IMP
	Adenosine Deaminase	Adenosine → Inosine
	Guanine Deaminase	Guanine → Xanthine
Nucleotidase	Nucleotidase	GMP → Guanosine
		AMP → Adenosine
		IMP → Inosine
		XMP → Xanthosine
Purine Nucleoside Phosphorylase (PNP)	PNP	Inosine → Hypoxanthine
		Xanthosine → Xanthine
		Guanosine → Guanine
Xanthine oxidase	Xanthine oxidase	Hypoxanthine → Xanthine
		Xanthine → Uric acid

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:
- 1. Allantoin
- 2. Allantoic acid
- 3. Urea
- 4. Ammonia

Team441:Humans don't have urate oxidase. Therefore, they can't degradate Uric acid into Allantoin



You don't have to memorize anything here of the pathway

Fate of uric acid in humans

1. Uric acid is less soluble in water.
2. Reptiles, insects and birds excrete uric acid as a paste of crystals, to save water.
3. Humans excrete uric acid in urine.
4. Humans do not have enzymes to further degrade uric acid.
5. Excessive production of uric acid causes deposition of uric acid crystals in the joints leading to:
   - Gout
   - hyperuricemia (high level of uric acid)

Gout

Gout : is a disease due to high levels of uric acid in body fluid.
7.0 mg/dL and above

- Uric acid accumulates because of:

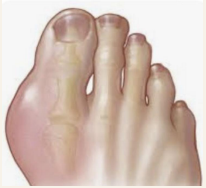
1. Overproduction (high consumption of meat)
2. Underexcretion (kidney impairment, dehydration)

Videos for more explanation

Gout symptoms

What is a symptom of gout?

Painful arthritic joint inflammation due to deposits of insoluble sodium urate crystals (especially big toe)



Sodium urate crystals accumulate in kidneys, ureter, joints leading to chronic gouty arthritis

Sodium urate crystals in urine

Affects 3 per 1000 persons

Gout

I

Inaccurately associated with overeating and drinking (Alcohol drinking)

II

Alcohol used to be contaminated with lead during manufacture and storage

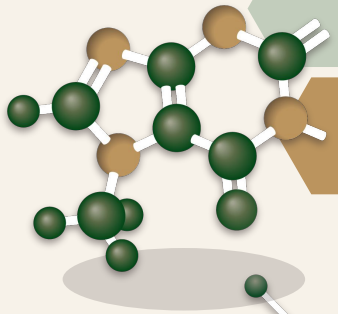
III

Lead to decrease excretion of uric acid from kidneys causing hyperuricemia and gout

IV

Excessive meat consumption increases uric acid production in some individuals

Gout causes



Two main causes

I Overproduction of uric acid

II Underexcretion of uric acid

Important slide

Causes of hyperuricemia due to increased purine biosynthesis and/or urate production

Inherited enzyme defects leading to purine overproduction (rare monogenic disorders)
Hypoxanthine-guanine phosphoribosyltransferase deficiency
Phosphoribosylpyrophosphate synthetase overactivity
Glucose-6-phosphatase deficiency (glycogen storage disease, type I)
Clinical disorders leading to purine and/or urate overproduction
Myeloproliferative disorders
Lymphoproliferative disorders
Hemolytic disorders
Psoriasis
Tissue hypoxia
Down syndrome
Glycogen storage diseases (types III, V, VII)
Drug- and diet-induced purine and/or urate overproduction
Excessive ethanol ingestion
Excessive dietary purine ingestion
Excessive fructose ingestion
Cytotoxic drugs

UpToDate

Saq:Q 3 answers

Causes of hyperuricemia due to decreased uric acid clearance

Clinical disorders
Chronic kidney disease of any form
Lead nephropathy (saturnine gout)
Effective volume depletion (eg, fluid losses, heart failure)
Diabetic or starvation ketoacidosis
Lactic acidosis
Preeclampsia
Obesity and high circulating insulin
Rare monogenic disorders causing decreased uric acid clearance
Autosomal dominant tubulointerstitial kidney disease caused by *UMOD* pathogenic variants
Glomerulocystic kidney disease
Common variants in genes encoding transporters that regulate renal or gut uric acid clearance (numerous; genes with largest reported effect are shown), not currently tested in clinical practice
SLC2A9
ABCG2
SLC17A1
SLC22A11
PDZK1
SLC16A9
SLC22A12
Drug- or diet-induced decreased uric acid clearance
Diuretics (thiazides and loop diuretics)
Cyclosporine and tacrolimus
Low-dose salicylates
Ethambutol
Pyrazinamide
Ethanol
Levodopa
Laxative abuse (alkalosis)
Salt restriction
Nicotinic acid

UpToDate

Saq:Q4 answer

Important slide

Risk factors for hyperuricemia and gout (may not be causal)

Nonmodifiable risk factors

- Age
- Sex
- Ethnicity
- Genetic variants

Modifiable risk factors

- Obesity
- Hypertension
- Hyperlipidemia
- Metabolic syndrome
- Diabetes mellitus
- Chronic kidney disease
- Dietary factors
- Alcohol
- Medications altering
- urate balance

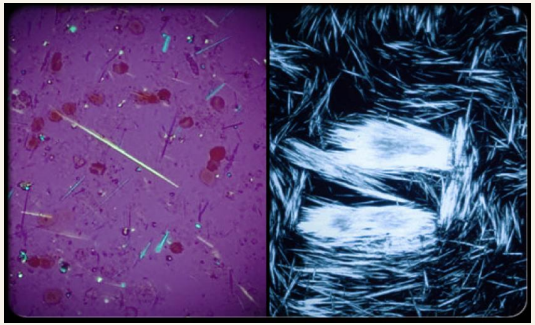
Saq:Q5 answer

Gout diagnosis

Biochemical Diagnosis

I Blood test

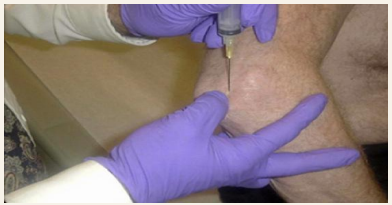
- It uses to measure the levels of uric acid.

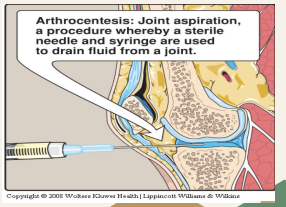


Monosodium urate crystals

II 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.





Gout 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)

Multiple choice questions

1

The drug Allopurinol inhibits which of the following enzyme?

A- Adenosine Deaminase

B- Nucleotidase

C- Xanthine Oxidase.

2

Purine and pyrimidine bases are absorbed by the?

A-Stomach

B-Intestine

C-Liver

3

What is the final product of pyrimidine degradation pathway?

A-Malonyl Coa

B-Uric acid

C-Ribose

Answers/ 1:C / 2:B / 3:A

SAQs

Question:

1- What is the major source of dietary nucleic acids (purine and pyrimidine)? And why?

Question:

2- Some animals convert uric acid to other products, name two of them?

Question:

3- What are the causes of hyperuricemia due to ((increased)) purine biosynthesis , and give me example for each one?

Question:
4- What are the causes of hyperuricemia due to ((decreased)) uric acid clearance

Question:

5-what are the risk factor for hyperuricemia and gout , and give me example for each one?

Answers of SAQs:

Q1/ Meat, because it has DNA and RNA

Q2/ Allantoin, allantoic acid, urea, ammonia

Answers of SAQs:
Q3/ slide No 13

Q4/ slide No 13

Q5/ slide No 14

Meet our Team

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