

Nucleotide Metabolism: The Breakdown

By lyobosa lyare
MD 2

Question

A patient with a high cell turnover malignancy develops hyperuricemia. Which pathway is directly responsible for the excess uric acid?

- A. Pyrimidine degradation pathway
- B. Purine degradation pathway
- C. De novo purine synthesis pathway
- D. Purine salvage pathway
- E. Ribose phosphate metabolism pathway



Question

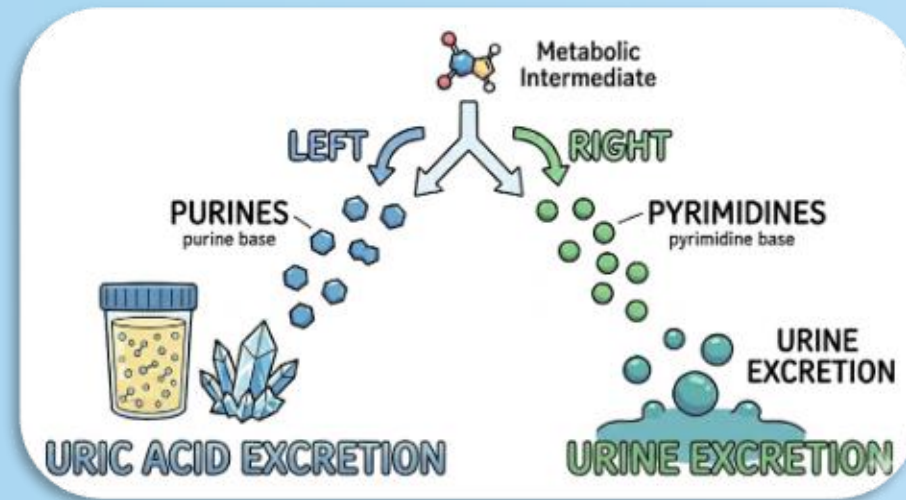
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How the body breaks down DNA and RNA

Purines end in **uric acid**. Pyrimidines become **soluble products**



Purines are **URIC ACID**, **Pyrimidines** are **PISS**

Why Do We Break Down Nucleotides?


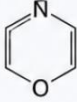
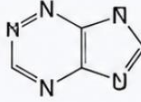







- Turn old nucleotides into waste
- Recycle usable components
 - Prevent toxic buildup



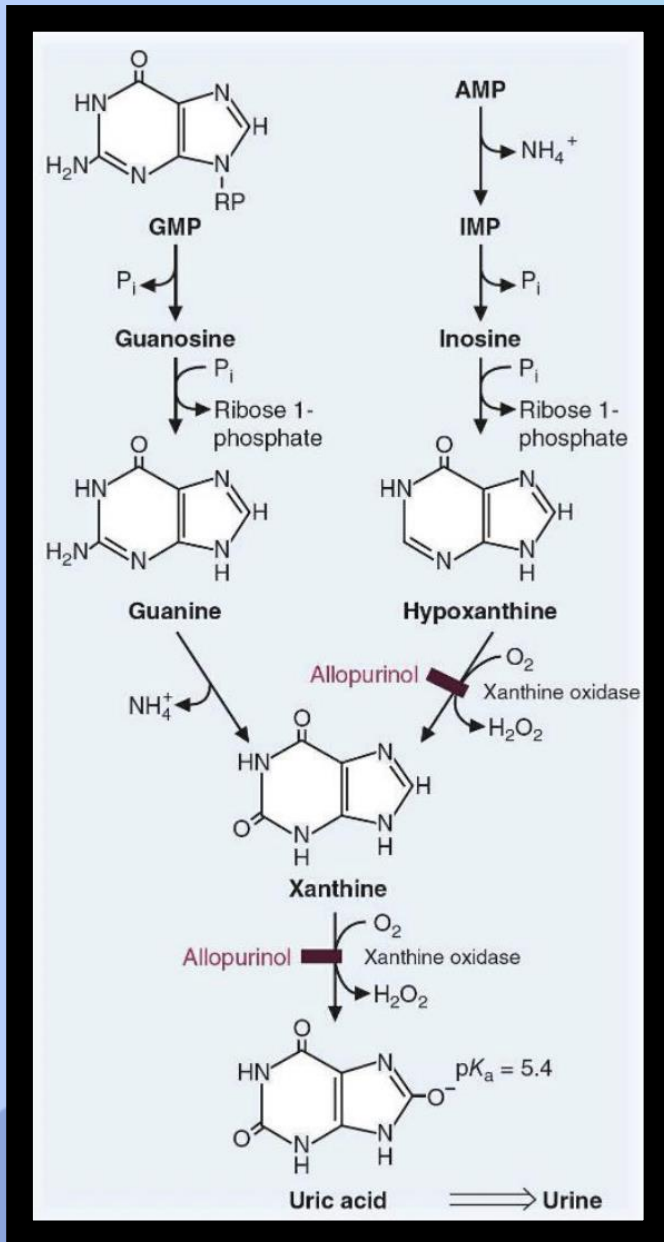
NOTE

DNA/RNA → *Nucleotides* → *Nucleosides* → *Bases* → *Waste*

PURINES and PYRIMIDINES

Feature	Pyrimidines	Purines
 Structure	Single-ring structure (6-membered ring) 	Double-ring structure (6-membered + 5-membered ring) 
 Bases	Cytosine (C) Thymine (T) Uracil (U)	Adenine (A) Guanine (G)
 Found in	DNA: C, T RNA: C, U	DNA: A, G RNA: A, G
 Biosynthesis	De novo synthesis of ring first, then attached to PRPP	PRPP + amino acids → ring assembled on PRPP
 Degradation	Broken down to β-alanine, β-aminoisobutyrate, CO ₂ , NH ₃	Broken down to uric acid (final product in humans)
 End product (excretion)	Water-soluble → easily excreted (β-alanine derivatives)	Uric acid → less soluble → excreted by kidneys
 Energy cost (of synthesis)	Lower (ring made first)	Higher (ring built stepwise on PRPP)
 Examples of nucleotides	CMP, UMP, TMP	AMP, GMP

Purines: ring stays intact → uric acid



PURINE DEGRADATION OVERVIEW

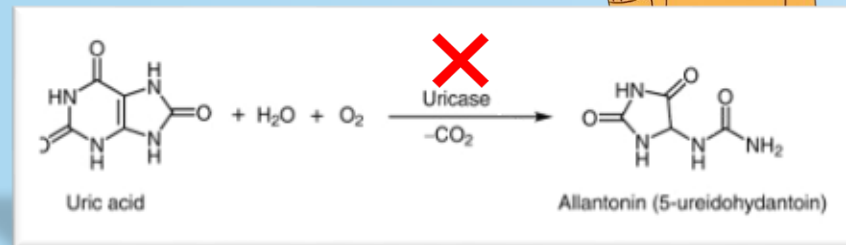
Degradation pathways:

AMP → IMP → inosine → hypoxanthine → xanthine → uric acid

GMP → guanosine → guanine → xanthine → uric acid

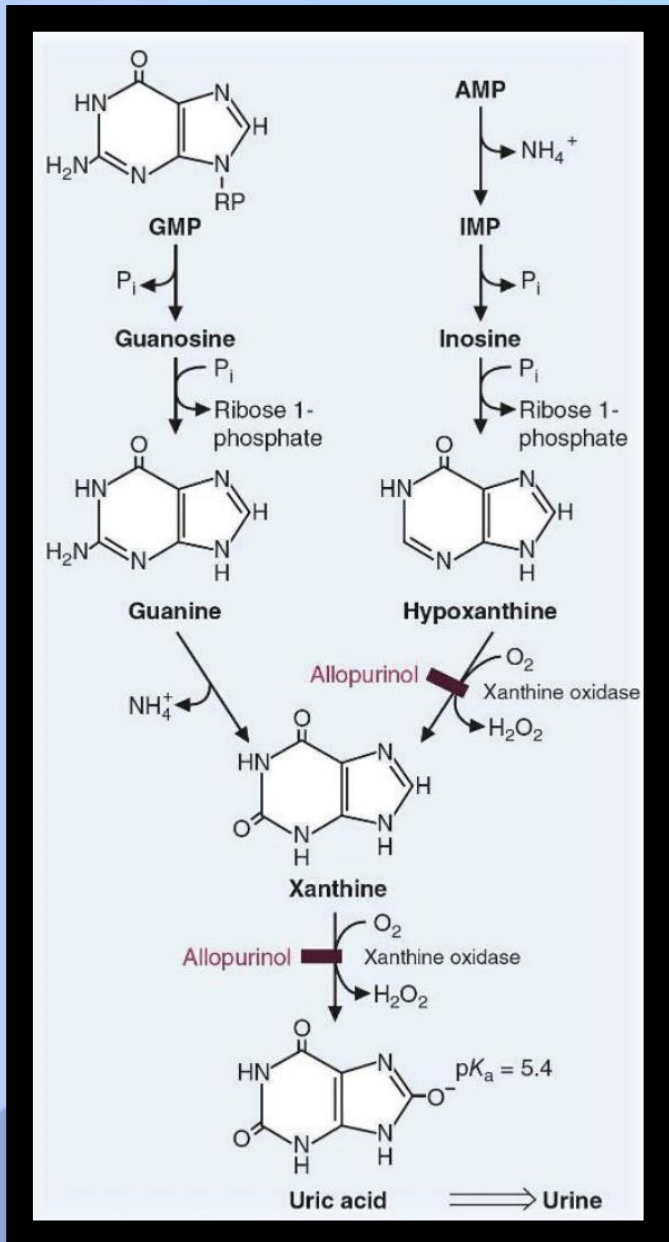


Humans lack uricase while animals have it



AMP is **IMPINO HIPPO** → X → URINE
GMP is **GUANO** → X → URINE

PURINE DEGRADATION OVERVIEW

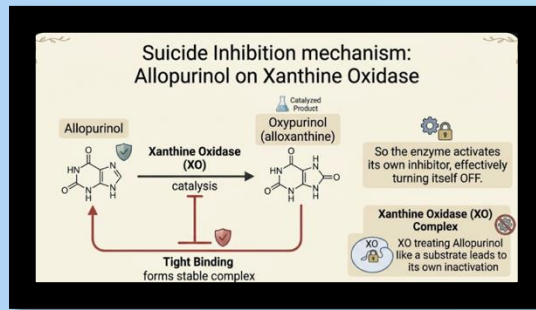
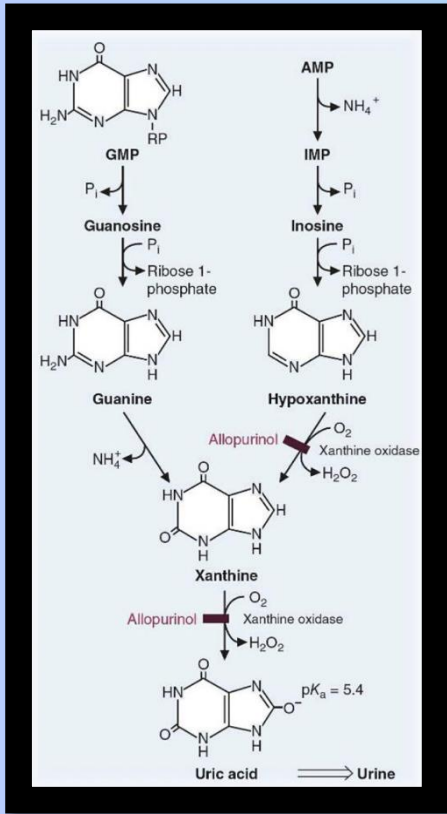


Degradation pathways:

AMP → **IMP** → **inosine** → **hypoxanthine** → **xanthine** → **uric acid**

GMP → **guanosine** → **guanine** → **xanthine** → **uric acid**



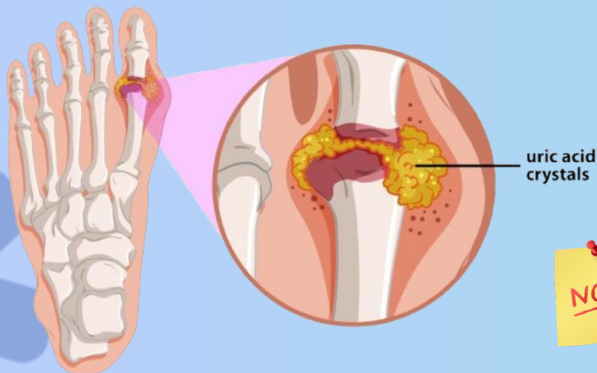


Gout



Painful form of inflammatory arthritis

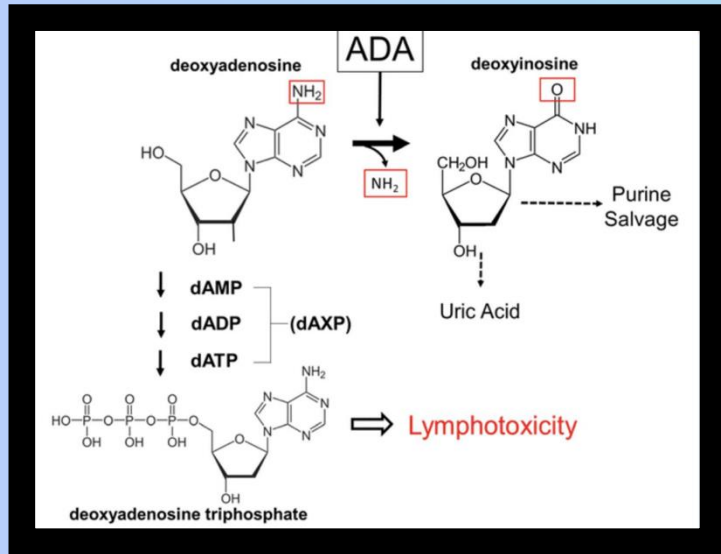
- Increased levels of uric acid in blood (hyperuricemia)
- Due to overproduction (10%) or underexcretion (90%) of uric acid
- Deposits of monosodium urate (MSU) crystals in joints causing an inflammatory response
- Treated with **Allopurinol (hypoxanthine analogue)** which inhibits Xanthine oxidase → decreased uric acid production



In acute attacks use NSAIDs, colchicine, or steroids to reduce inflammation

**What if the immune system
never really switches on
after birth?**

Severe Combined Immunodeficiency (SCID)



SCID MECHANISM

Adenosine deaminase (ADA) deficiency

ADA catalyzes:

- Adenosine → Inosine
- Deoxyadenosine → Deoxyinosine



Deoxyadenosine (dA) and deoxyadenosine triphosphate (dATP) accumulate →

lymphotoxicity

- T cells + B cells are both deficient
- Increased susceptibility to **infections**

PYRIMIDINE DEGRADATION

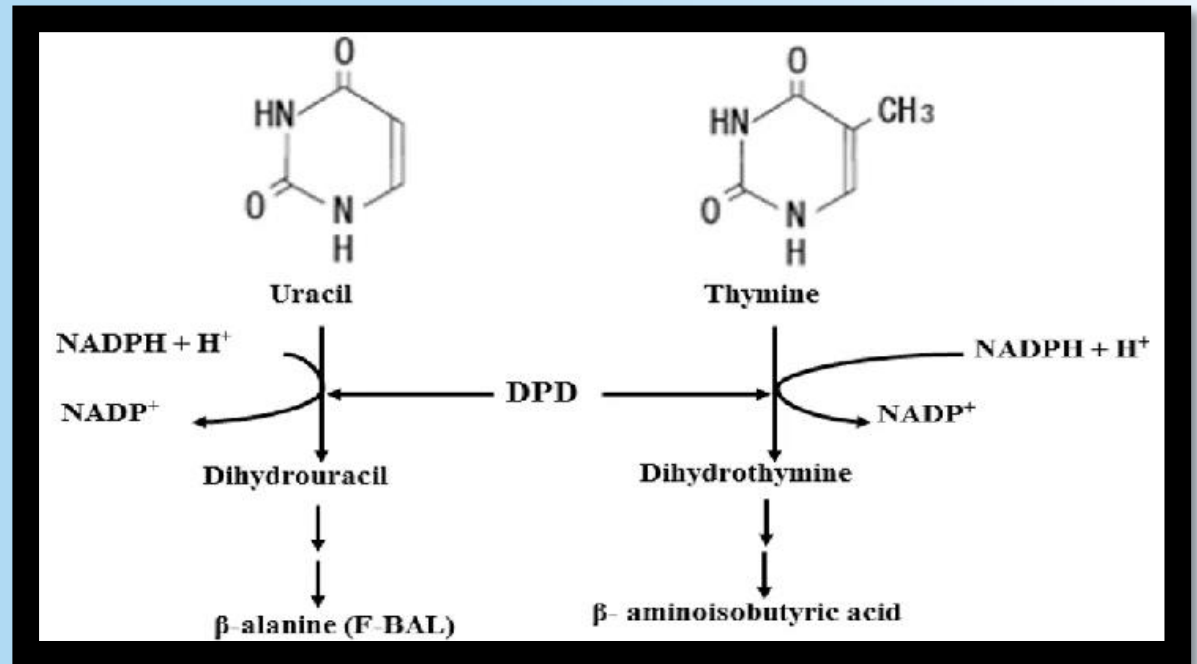
Pyrimidines: ring opens → water-soluble products

Dihydropyrimidine dehydrogenase (DPD) is the *first and rate-limiting enzyme* in pyrimidine breakdown

Uracil → β -alanine

Thymine → β -aminoisobutyrate

Eventually breakdown to $\text{CO}_2 + \text{NH}_3$

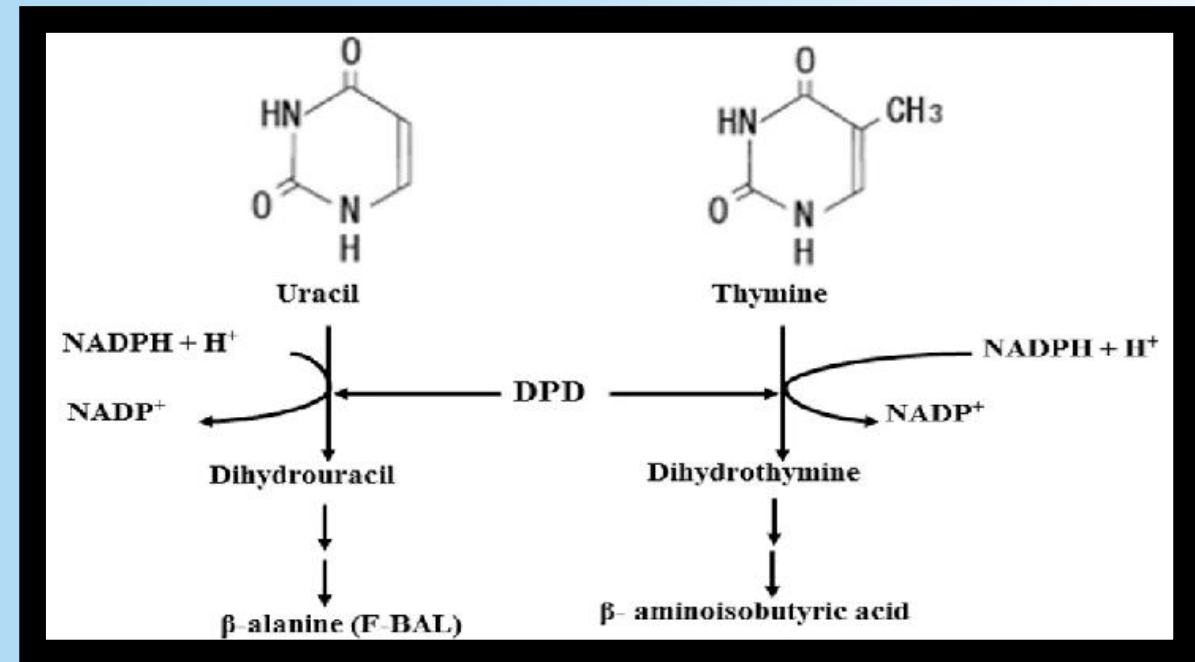


NOTE

Pyrimidine disorders are MUCH rarer than purine disorders

COMPLICATIONS OF PYRIMIDINE DEGRADATION

- **Dihydropyrimidine dehydrogenase (DPD) deficiency**
- Uracil and Thymine Accumulate in blood and urine → Generally mild baseline metabolic buildup
- 5-fluorouracil (5-FU) - (Broken down by DPD)
- A chemotherapy drug that is a pyrimidine analogue that mimics uracil
- 5-FU is NOT broken down → drug accumulates to toxic levels → even standard doses become overdoses



QUICK RECAP

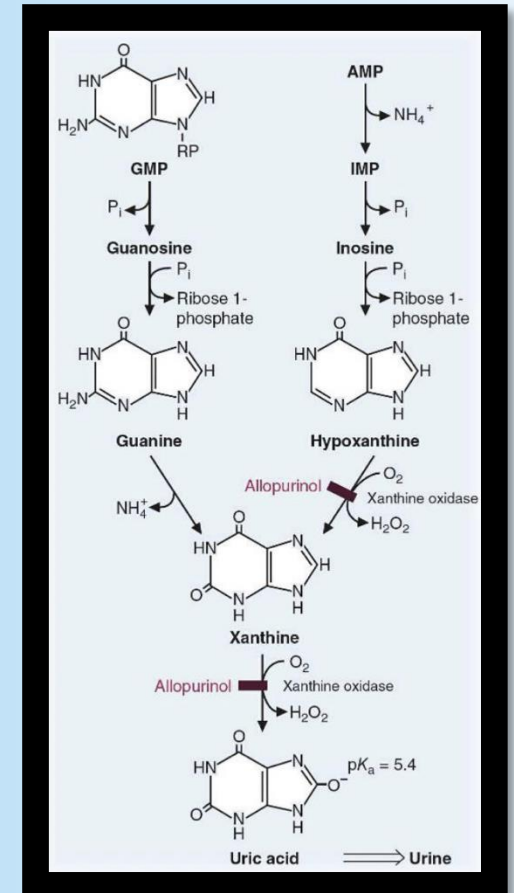


A patient treated with allopurinol develops increased urinary excretion of hypoxanthine and xanthine. Which property of these molecules explains the therapeutic benefit?

- A. They inhibit neutrophil chemotaxis
- B. They are more water-soluble than uric acid
- C. They suppress de novo purine synthesis directly
- D. They activate renal urate transporters
- E. They are not filtered by the glomerulus

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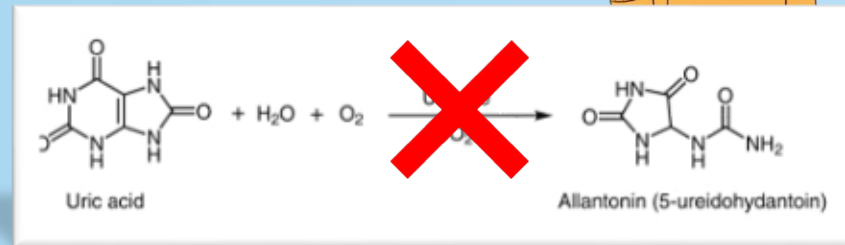


The major biochemical reason humans are predisposed to gout compared with many other mammals is the absence of:

- A. GPRT
- B. APRT
- C. Uricase
- D. ADA
- E. CPS II

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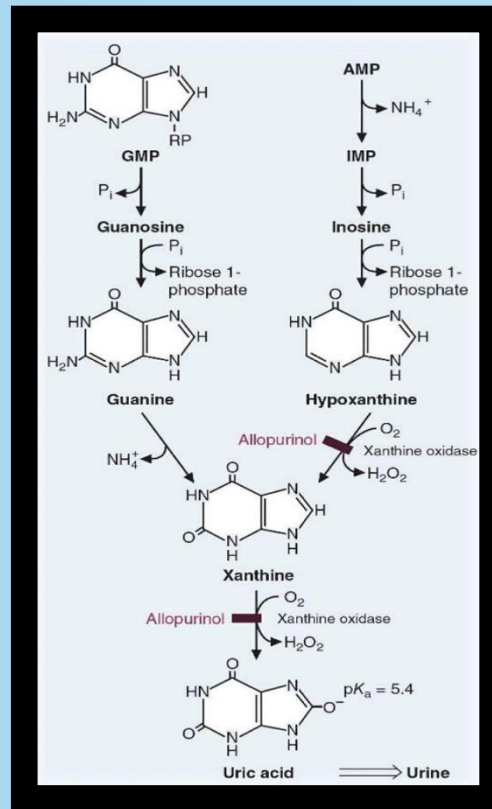


A patient with recurrent gout is treated with allopurinol. Which metabolite is most likely to increase?

- A. Uric acid
- B. dATP
- C. Xanthine
- D. PRPP
- E. Orotic acid

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If the salvage pathway fails, what do you think happens to purines instead?

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Expected: degraded to uric acid

Would HGPRT deficiency decrease or increase de novo purine synthesis?

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Expected: Increase

That's All For Now. Study Hard!

~~Party Hard!~~

Do your best!

THE END

