Amino Acid Degradation

K,W

- Intermediates of the central metabolic pathway
- Some amino acids result in more than one intermediate.
- Ketogenic amino acids can be converted to ketone bodies.

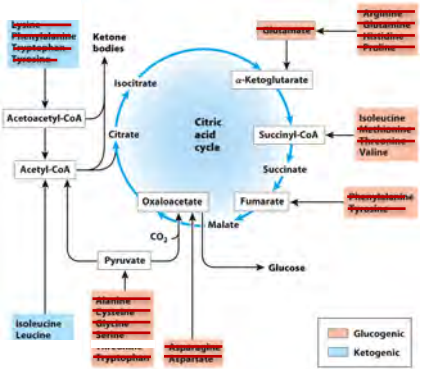
Seven to Acetyl-CoA	Leu, Ile, *Thr*, Lys, Phe, Tyr, Trp

- Glucogenic amino acids can be converted to glucose.

Six to pyruvate[1]	Ala, Cys, Gly, Ser, *Thr*, Trp
Five to α-ketoglutarate[2]	Arg, Glu, Gln, His, Pro
Four to succinyl-CoA	Ile, Met, **Thr**, Val
Two to fumarate[3]	Phe, Tyr
Two to oxaloacetate[4]	Asp, Asn

[1]Pyruvate family
[2]Glu family
[3]Aromatic family
[4]Trans-/de-aminase family

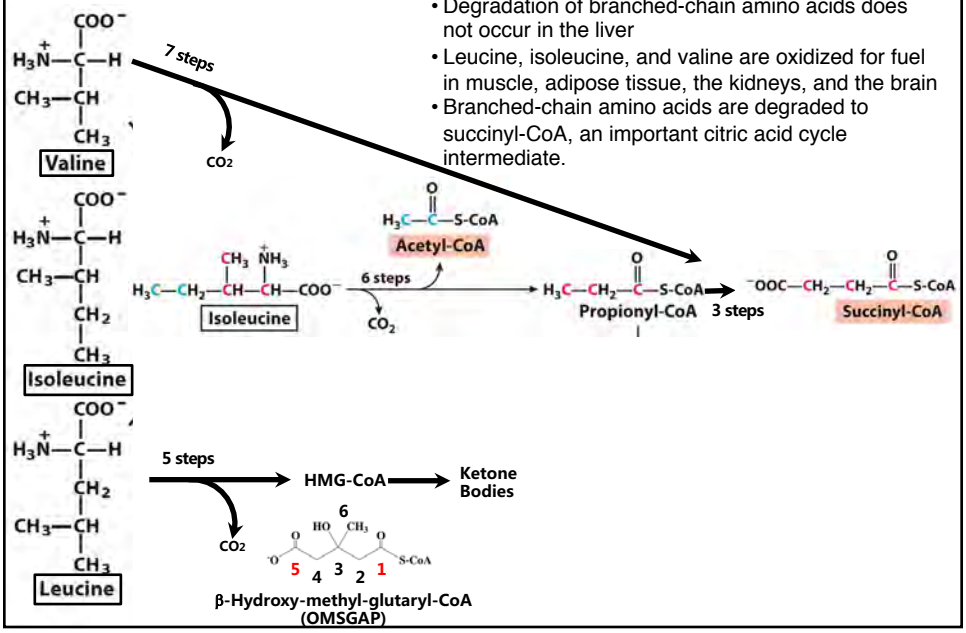
1.Transaminase/Deaminase Family
2.Glu Family
3.Pyruvate Family
4.α–ketobutyric Family
5.Aromatic Family
6.α–ketoadipic Family
7.Branched-chain Family

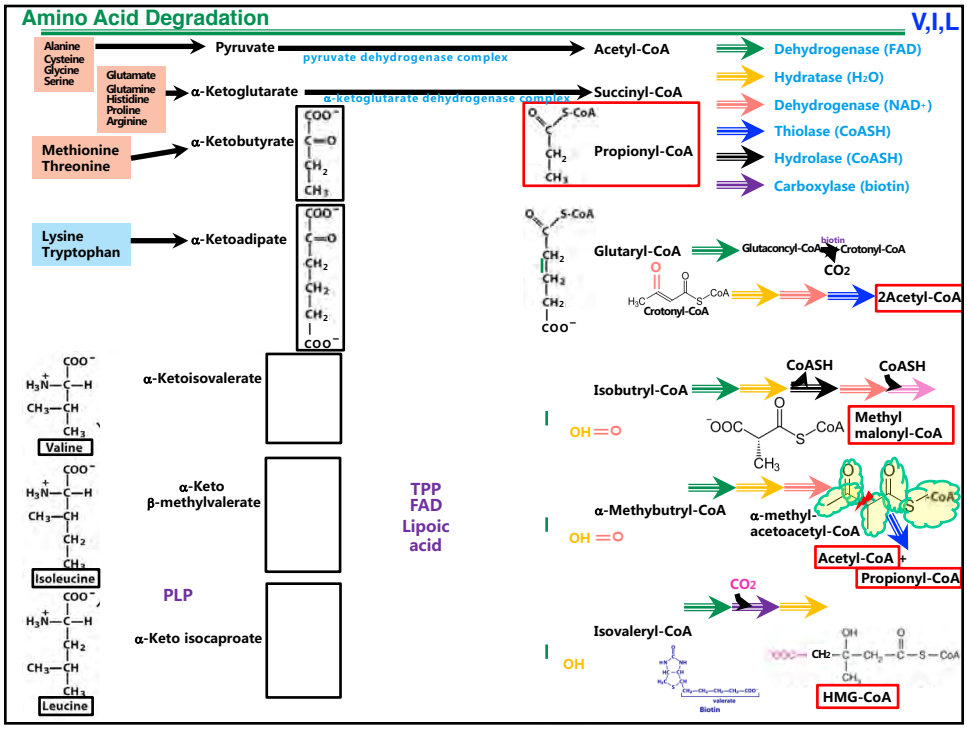


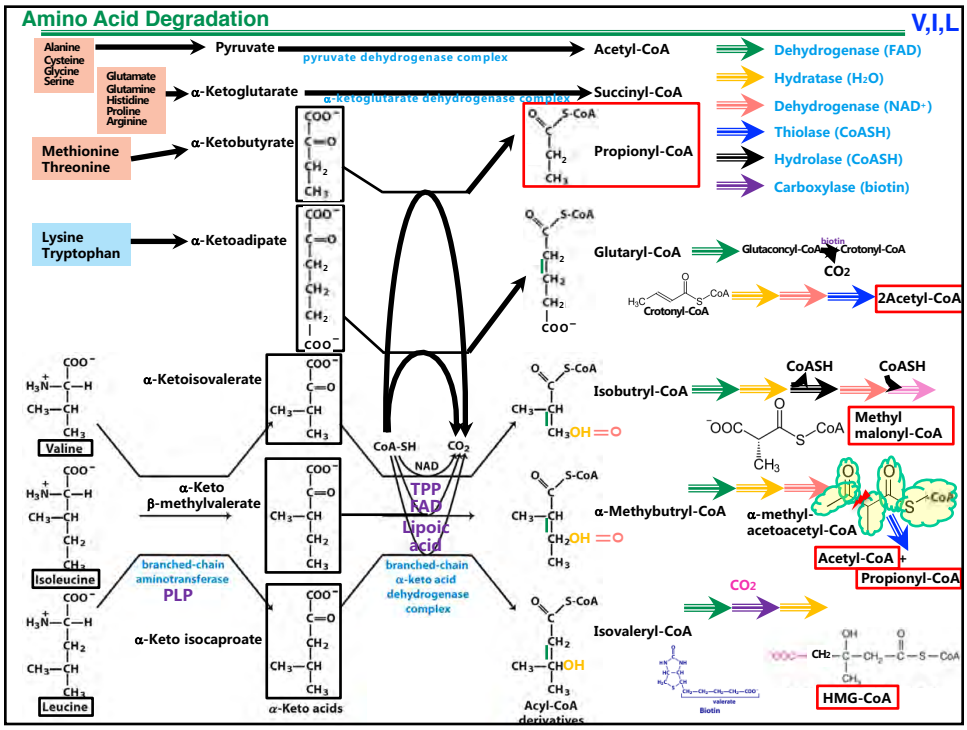
Amino Acid Degradation

V,I,L

- Degradation of branched-chain amino acids does not occur in the liver
- Leucine, isoleucine, and valine are oxidized for fuel in muscle, adipose tissue, the kidneys, and the brain
- Branched-chain amino acids are degraded to succinyl-CoA, an important citric acid cycle intermediate.




Amino Acid Degradation
V,I,L
Alanine
Cysteine
Glycine
Serine
Pyruvate
pyruvate dehydrogenase complex
Acetyl-CoA
Glutamate
Glutamine
Histidine
Proline
Arginine
α-Ketoglutarate
α-ketoglutarate dehydrogenase complex
Succinyl-CoA
Methionine
Threonine
α-Ketobutyrate
Propionyl-CoA
Lysine
Tryptophan
α-Ketoadipate
Glutaryl-CoA
Glutaconcyl-CoA
Crotonyl-CoA
CO2
Crotonyl-CoA
2Acetyl-CoA
Valine
α-Ketoisovalerate
Isobutyryl-CoA
CoASH
CoASH
Methyl malonyl-CoA
Isoleucine
α-Keto β-methylvalerate
α-Methybutyryl-CoA
α-methyl-acetoacetyl-CoA
Acetyl-CoA +
Propionyl-CoA
TPP
FAD
Lipoic acid
PLP
Leucine
α-Keto isocaproate
CO2
Isovaleryl-CoA
HMG-CoA
Biotin
Dehydrogenase (FAD)
Hydratase (H2O)
Dehydrogenase (NAD+)
Thiolase (CoASH)
Hydrolase (CoASH)
Carboxylase (biotin)


Amino Acid Degradation
V,I,L
Alanine
Cysteine
Glycine
Serine
Pyruvate
pyruvate dehydrogenase complex
Acetyl-CoA
Glutamate
Glutamine
Histidine
Proline
Arginine
α-Ketoglutarate
α-ketoglutarate dehydrogenase complex
Succinyl-CoA
Methionine
Threonine
α-Ketobutyrate
Propionyl-CoA
Lysine
Tryptophan
α-Ketoadipate
Glutaryl-CoA
Glutaconcyl-CoA
Crotonyl-CoA
CO2
Crotonyl-CoA
2Acetyl-CoA
Valine
α-Ketoisovalerate
Isobutyryl-CoA
CoASH
CoASH
Methyl malonyl-CoA
CoA-SH
CO2
NAD
Isoleucine
α-Keto β-methylvalerate
α-Methybutyryl-CoA
α-methyl-acetoacetyl-CoA
Acetyl-CoA +
Propionyl-CoA
TPP
FAD
Lipoic acid
branched-chain aminotransferase
PLP
branched-chain α-keto acid dehydrogenase complex
Leucine
α-Keto isocaproate
CO2
Isovaleryl-CoA
α-Keto acids
Acyl-CoA derivatives
HMG-CoA
Biotin
Dehydrogenase (FAD)
Hydratase (H2O)
Dehydrogenase (NAD+)
Thiolase (CoASH)
Hydrolase (CoASH)
Carboxylase (biotin)

Amino Acid Degradation

V,I,L

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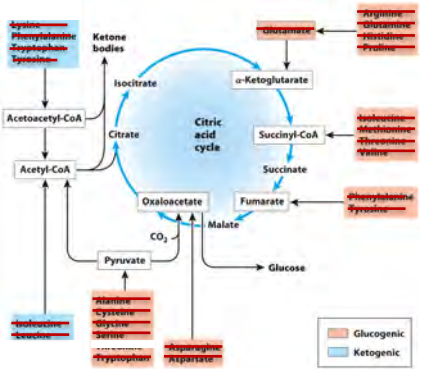
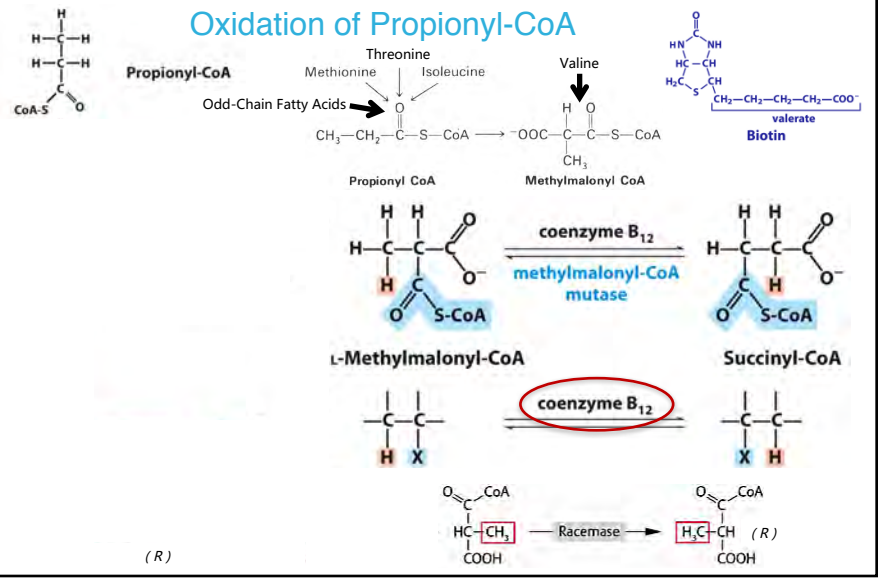
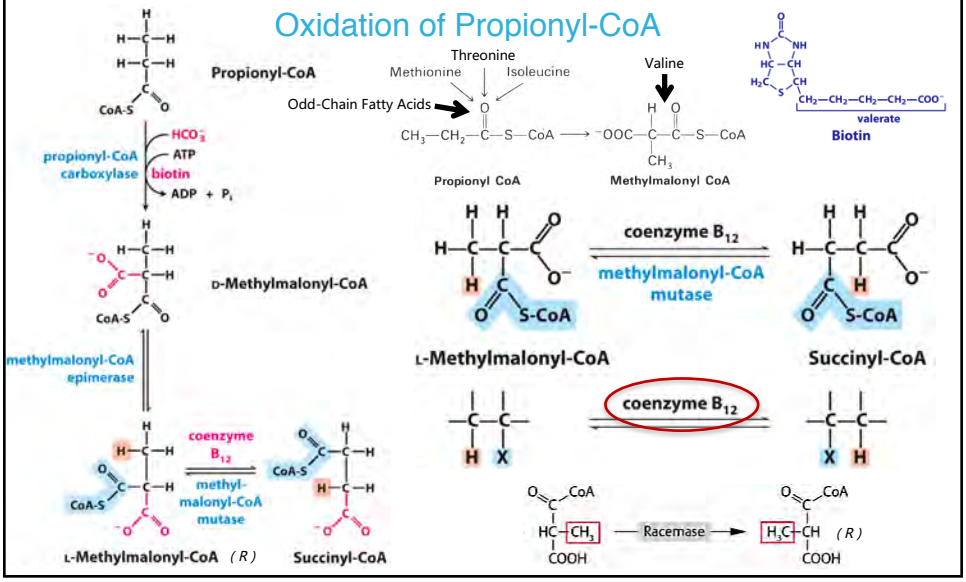


Amino Acid Degradation Meets Fatty Acid Degradation

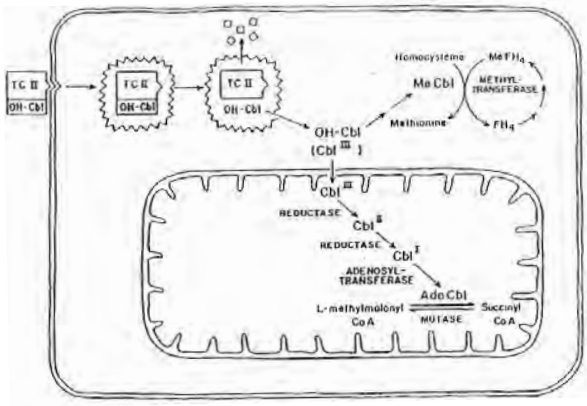


Amino Acid Degradation Meets Fatty Acid Degradation



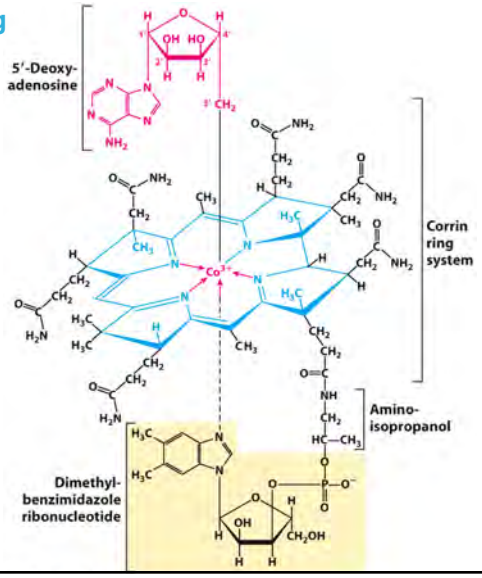
Amino Acid Degradation Meets Fatty Acid Degradation

Only a handful of enzymes require Coenzyme B_{12}

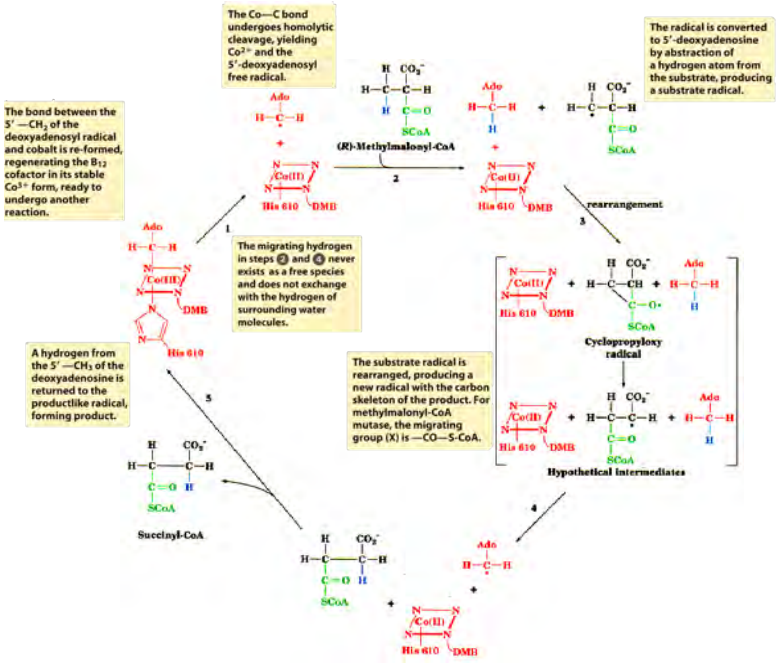


Amino Acid Degradation Meets Fatty Acid Degradation

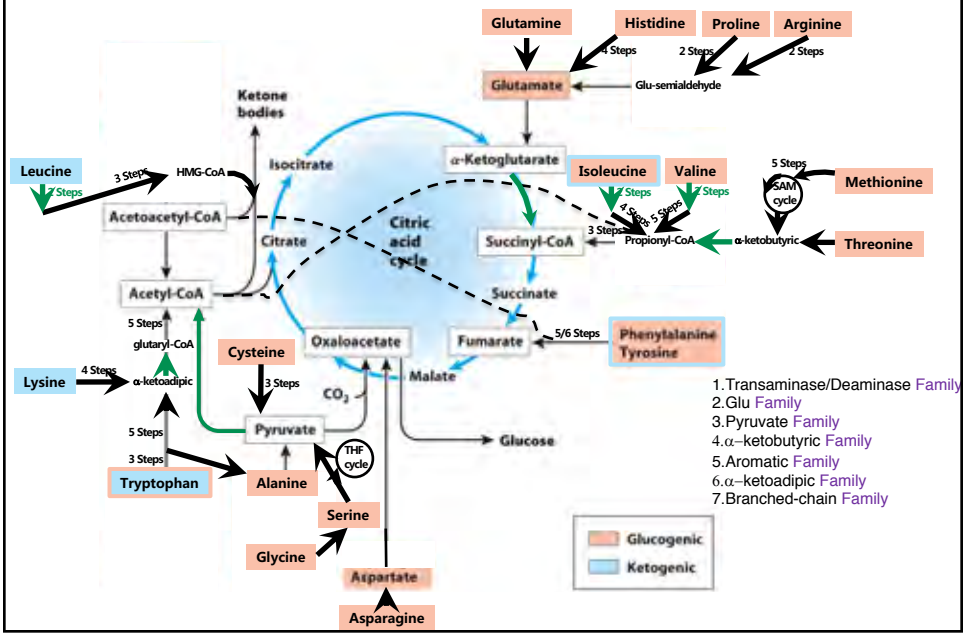
Complex Cobalt-Containing Compound: Coenzyme B_{12}



Amino Acid Degradation Meets Fatty Acid Degradation



Amino Acid Degradation: Overview



Amino Acid Degradation: Overview

TABLE 18-2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

Medical condition	Approximate incidence (per 100,000 births)	Defective process	Defective enzyme	Symptoms and effects
Albinism	<3	Melanin synthesis from tyrosine	Tyrosine 3-monooxygenase (tyrosinase)	Lack of pigmentation; white hair, pink skin
Alkaptonuria	<0.4	Tyrosine degradation	Homogentisate 1,2-dioxygenase	Dark pigment in urine; late-developing arthritis
Argininemia	<0.5	Urea synthesis	Arginase	Mental retardation
Argininosuccinic acidemia	<1.5	Urea synthesis	Argininosuccinase	Vomiting; convulsions
Carbamoyl phosphate synthetase I deficiency	<0.5	Urea synthesis	Carbamoyl phosphate synthetase I	Lethargy; convulsions; early death
Homocystinuria	<0.5	Methionine degradation	Cystathionine β-synthase	Faulty bone development; mental retardation
Maple syrup urine disease (branchedchain ketoaciduria)	<0.4	Isoleucine, leucine, and valine degradation	Branched-chain α-keto acid dehydrogenase complex	Vomiting; convulsions; mental retardation; early death
Methylmalonic acidemia	<0.5	Conversion of propionyl-CoA to succinyl-CoA	Methylmalonyl-CoA mutase	Vomiting; convulsions; mental retardation; early death
Phenylketonuria	<8	Conversion of phenylalanine to tyrosine	Phenylalanine hydroxylase	Neonatal vomiting; mental retardation

Amino Acid Degradation: Overview

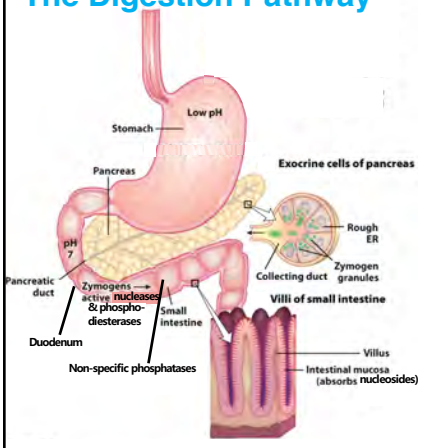
We learned that:

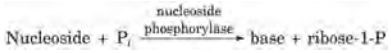
- amino acids from protein are an important energy source in carnivorous animals
- the first step of AA catabolism is transfer of the NH_3 via PLP-dependent aminotransferase usually to α-ketoglutarate to yield L-glutamate
- in most mammals, toxic ammonia is quickly recaptured into carbamoyl phosphate and passed into the urea cycle
- amino acids are degraded to pyruvate, acetyl-CoA, α-ketoglutarate, succinyl-CoA, and/or oxaloacetate
- amino acids yielding acetyl-CoA are ketogenic
- amino acids yielding other end products are glucogenic
- genetic defects in amino degradation pathways result in a number of human diseases
- amino acid catabolism is dependent on a variety of cofactors, including THF, ado-Met (SAM), Cbl, and **PLP**

Nucleotide Degradation

Nucleotide Degradation

The Digestion Pathway





- Ingestion of food always includes nucleic acids.
- As you know from BI 421, the low pH of the stomach does not affect the polymer.
- In the duodenum, zymogens are converted to nucleases and the nucleotides are converted to nucleosides by non-specific phosphatases or nucleotidases.
- Only the non-ionic nucleosides are taken up in the villi of the small intestine.
- In the cell. the first step is the release of the ribose sugar, most effectively done by a non-specific nucleoside phosphorylase to give ribose 1-phophate (Rib1P).
- Most ingested nucleic acids are degraded.

Nucleotide Degradation: Overview

Fate of Nucleic Acids:

Purine Nucleoside Phosphorylase

Nucleotides

P_i

Nucleosides

P_i → αD-Rib 1-P (or Rib) & αD-dRib 1-P (or dRib)

Bases

Purine & Pyrimidine Salvage Pathway

Oxidation

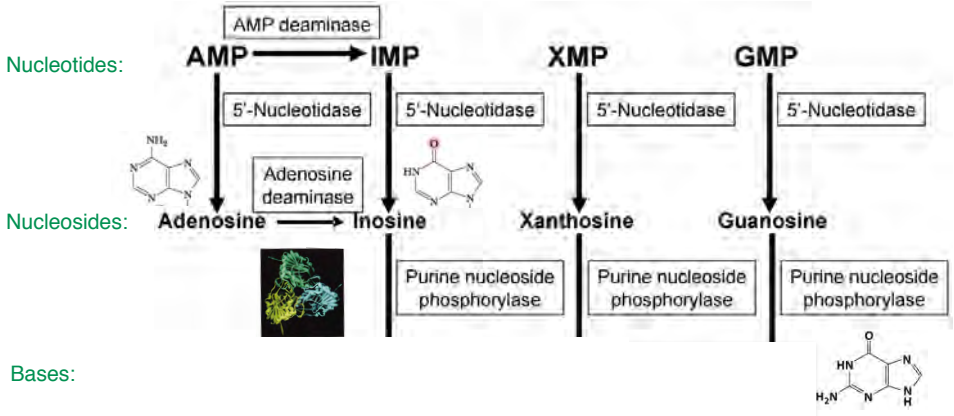
Once broken down to the nitrogenous bases they are either:

1. Salvaged for recycling into new nucleic acids (most cells; from internal, not ingested, nucleic acids).
2. Oxidized (primarily in the intestine and liver) by first converting to nucleosides, then to
   - –Uric Acid (purines)
   - –Propionyl CoA (pyrimidines)

The Salvage Pathways are in competition with the *de novo* biosynthetic pathways, and are both ANABOLISM

Nucleotide Degradation

Catabolism of Purines

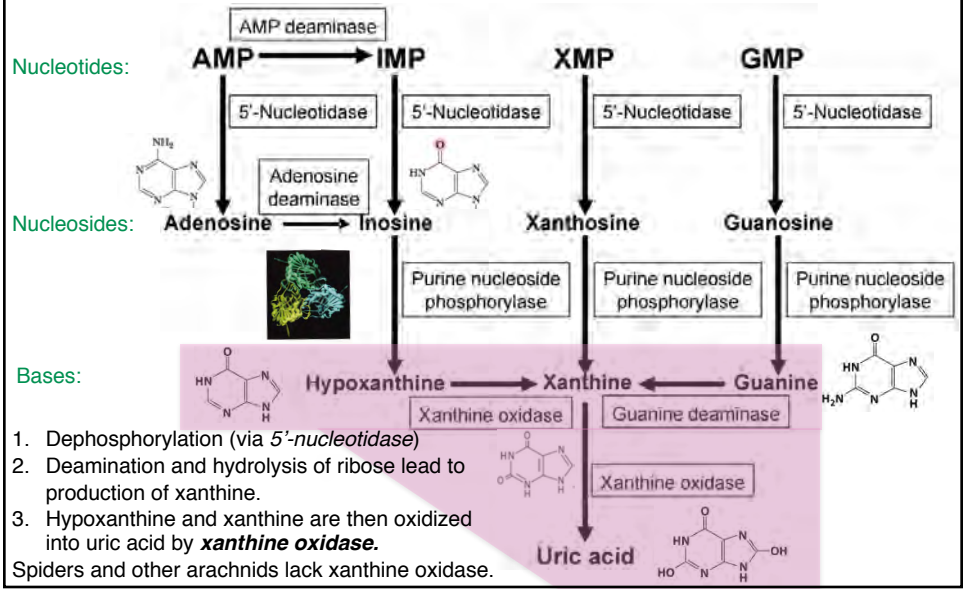


1. Dephosphorylation (via *5'-nucleotidase*)
2. Deamination and hydrolysis of ribose lead to production of xanthine.
3. Hypoxanthine and xanthine are then oxidized into uric acid by ***xanthine oxidase.***

Spiders and other arachnids lack xanthine oxidase.

Nucleotide Degradation

Catabolism of Purines



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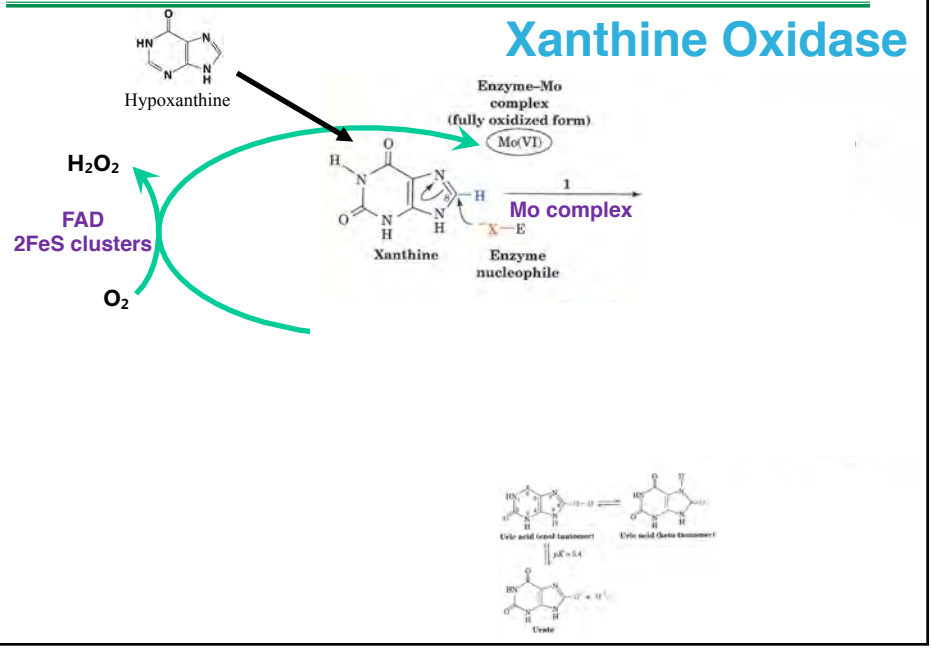
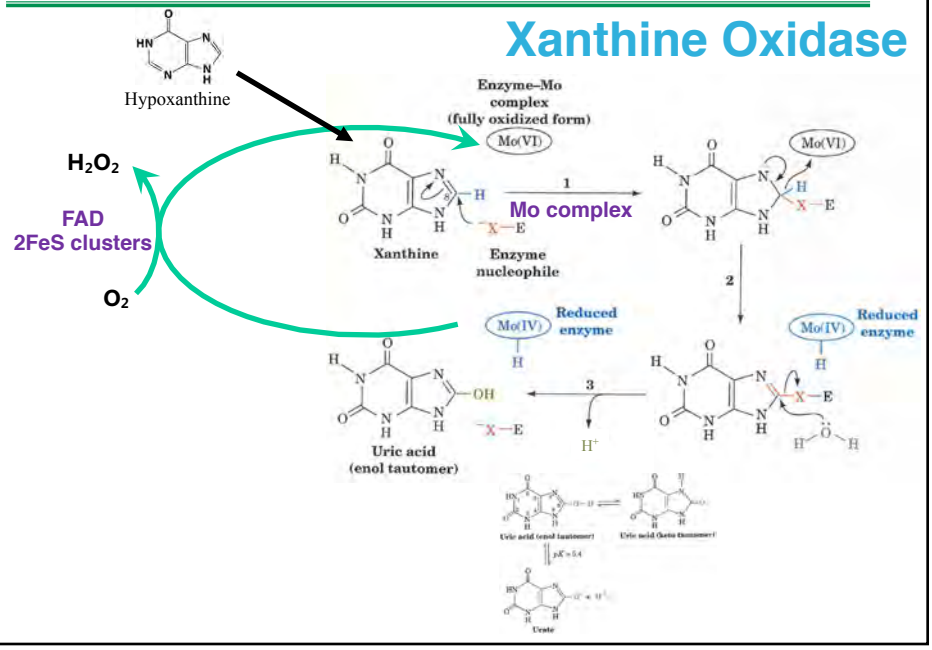
Nucleotide Degradation

Xanthine Oxidase



Nucleotide Degradation

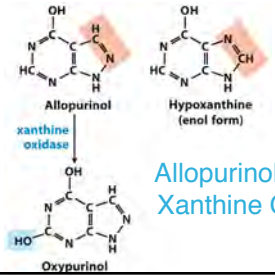
Xanthine Oxidase



Nucleotide Degradation

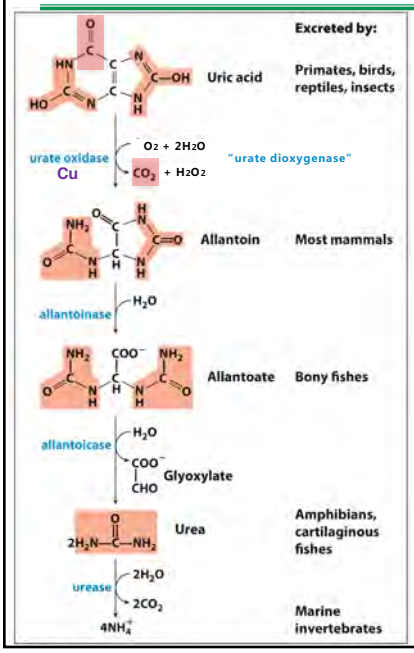
Excess Uric Acid causes Gout

- Painful joints (often in toes) due to deposits of sodium urate crystals
- Primarily affects males
- May involve genetic under-excretion of urate and/or may involve overconsumption of fructose
- Treated with avoidance of purine-rich foods (seafood, liver) or avoidance of fructose
- Also treated with xanthine oxidase inhibitor **allopurinol**



Allopurinol Inhibits Xanthine Oxidase

Nucleotide Degradation



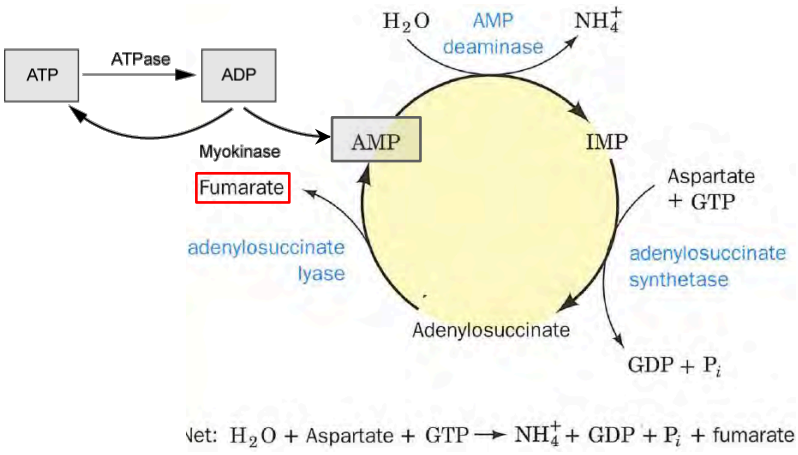
- Degree of further oxidation of uric acid is organism dependent.
- Birds and insects don't excrete amino-acid nitrogen as urea, but as uric acid to conserve water.

Conversion of Uric Acid to Allantoin, Allantoate, and Urea

Nucleotide Degradation

In muscle

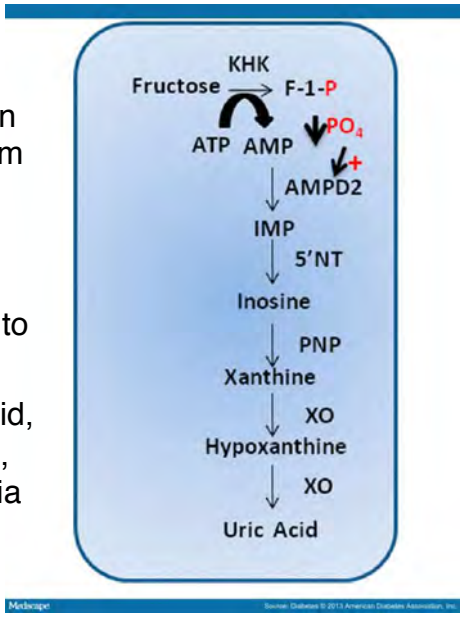
Purine Nucleotide Cycle



Nucleotide Degradation

Hyperuricemia

- The interesting connection between sugar metabolism and nitrogen metabolism
- What is even more interesting is that this metabolism is connected to fat metabolism as well
- The production of Uric Acid, by unknown mechanisms, converts liver mitochondria to fatty acid synthesis.



Nucleotide Degradation

Catabolism of Pyrimidines

- Leads to NH_4^+ and urea
- T is degraded to succinyl-CoA.
- U & C is degraded to acetyl-CoA