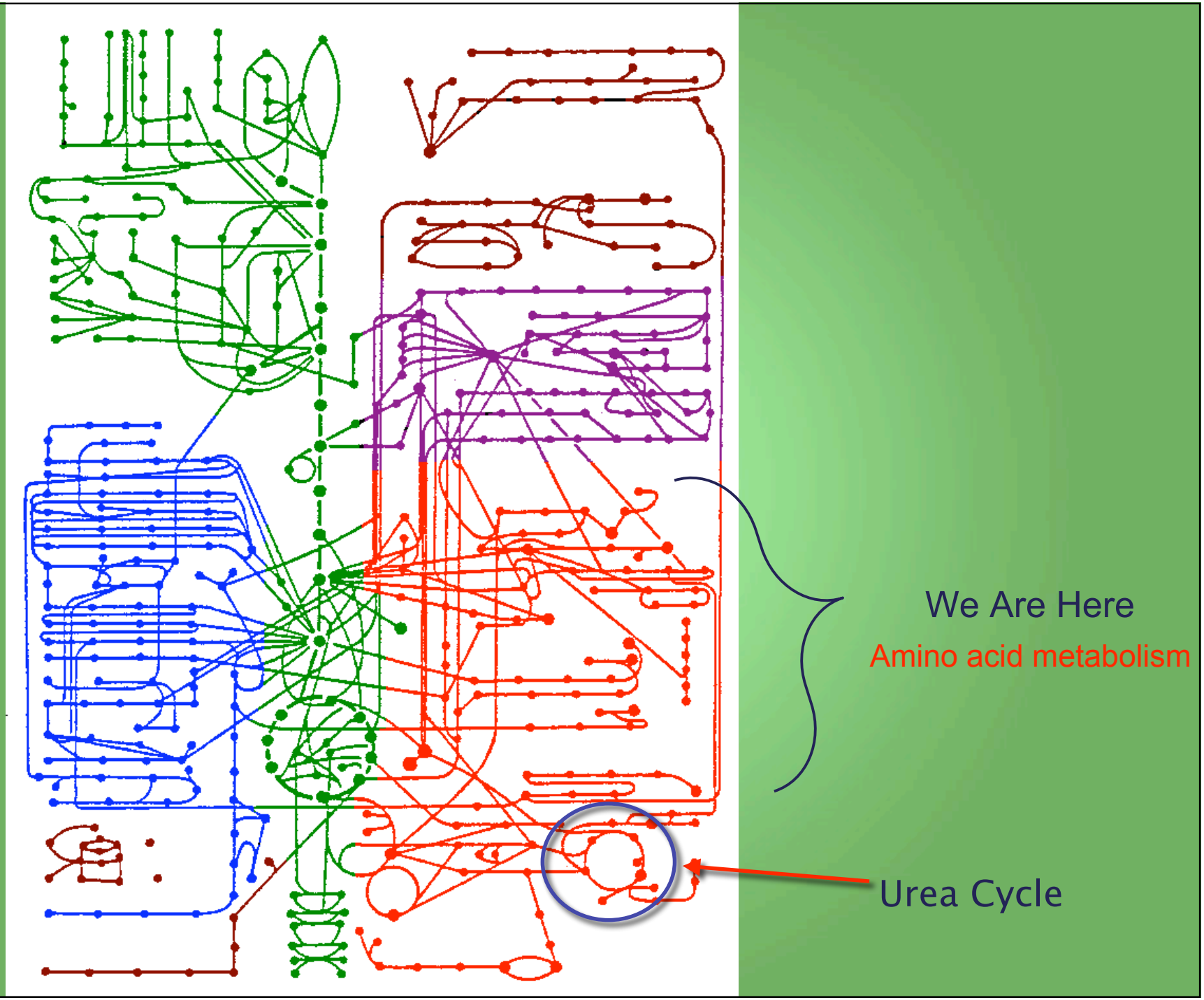
Protein Turnover and Amino Acid Catabolism

Chem 454: Biochemistry II
University of Wisconsin-Eau Claire


We Are Here
Amino acid metabolism
Urea Cycle

Introduction

- Proteins are degraded into amino acids.
- Protein turnover is tightly regulated.
- First step in protein degradation is the removal of the nitrogen
- Ammonium ion is converted to urea in most mammals.
- Carbon atoms are converted to other major metabolic intermediates.
- Inborn errors in metabolism

Introduction

Amino acids used for synthesizing proteins are obtained by degrading other proteins

- Proteins destined for degradation are labeled with *ubiquitin*.
- Polyubiquinated proteins are degraded by *proteosomes*.

Amino acids are also a source of nitrogen for other biomolecules.

Introduction

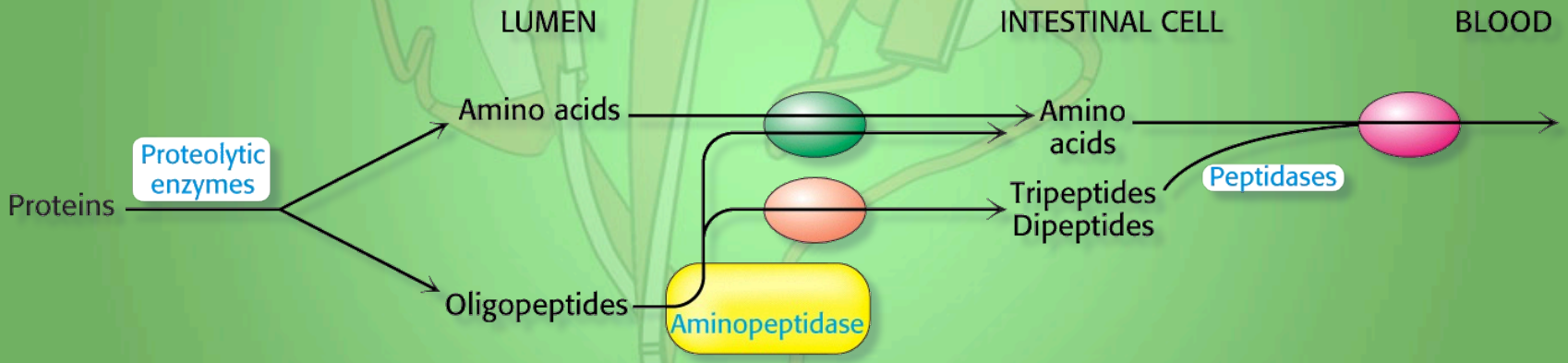
- Excess amino acids cannot be stored.
- Surplus amino acids are used for fuel.
  - Carbon skeleton is converted to
    - Acetyl-CoA
    - Acetoacetyl-CoA
    - Pyruvate
    - Citric acid cycle intermediate
  - The amino group nitrogen is converted to urea and excreted.
- Glucose, fatty acids and ketone bodies can be formed from amino acids.

1. Protein Degradation

- Dietary proteins are a vital source of amino acids.
- Discarded cellular proteins are another source of amino acids.

1.1 Dietary Protein Degradation

Dietary proteins are hydrolyzed to amino acids and absorbed into the bloodstream.



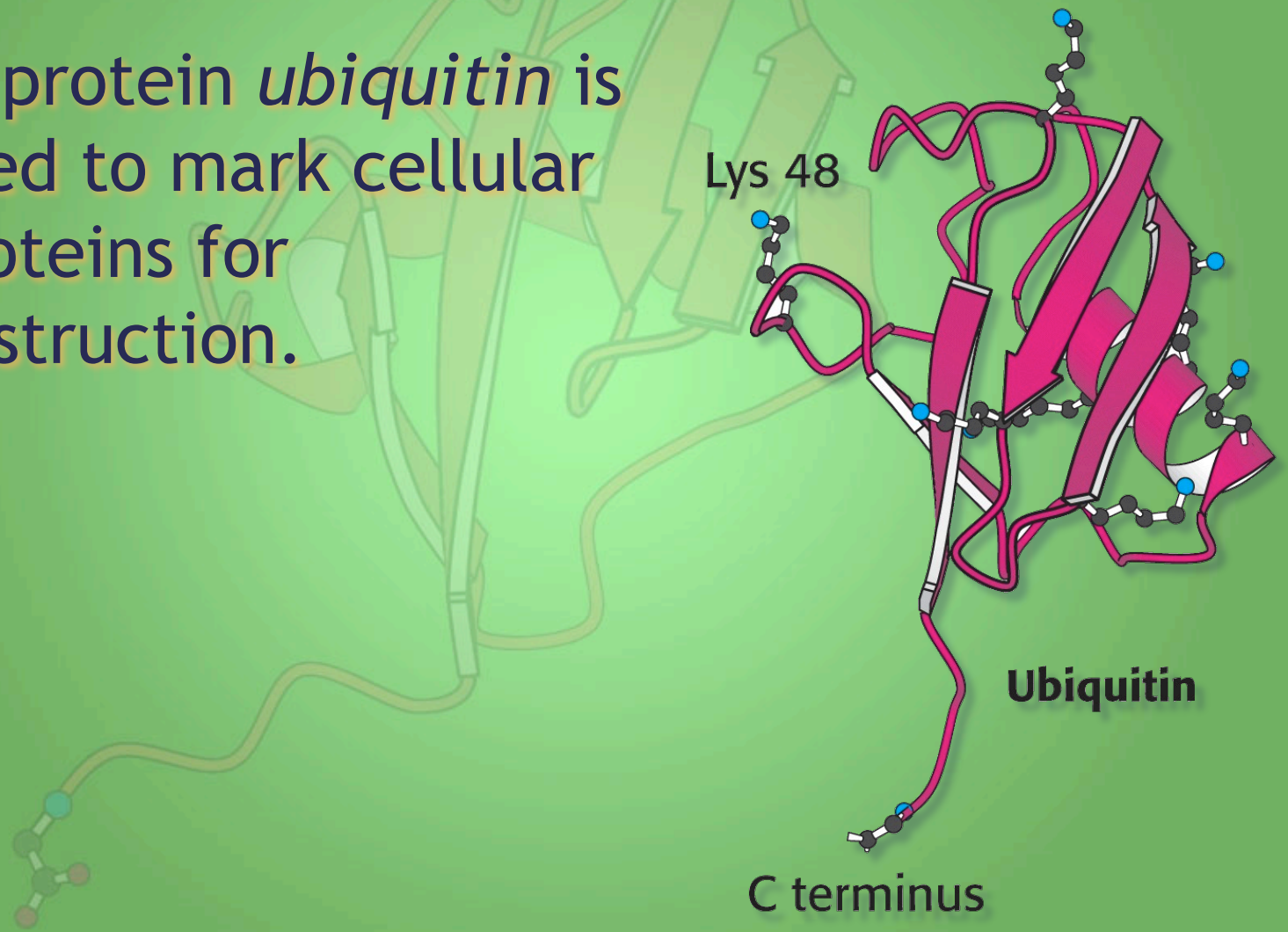
1.2 Cellular Protein Degradation

Cellular proteins are degraded at different rates.

- Ornithine decarboxylase has a half-life of 11 minutes.
- Hemoglobin lasts as long as a red blood cell.
- ϒ-Crystallin (eye lens protein) lasts as long as the organism does.

2. Regulation of Protein Turnover

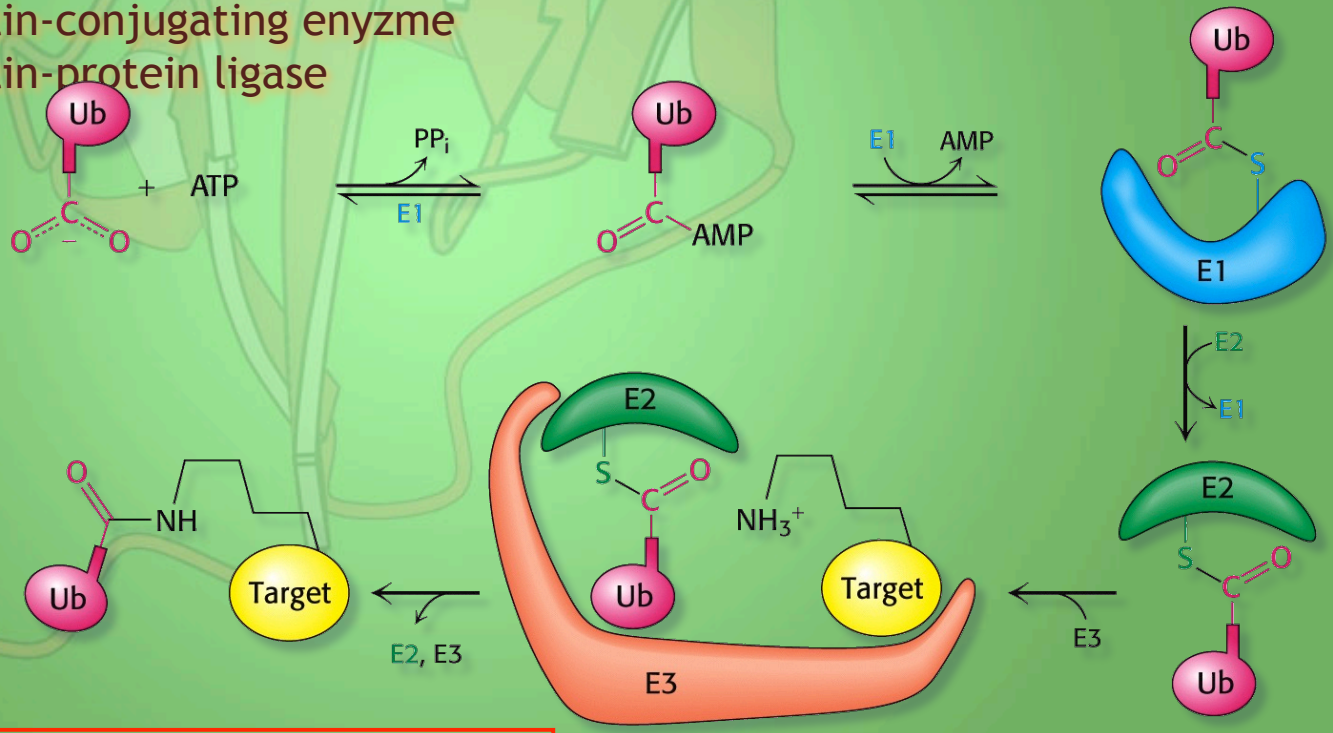
The protein *ubiquitin* is used to mark cellular proteins for destruction.



2.1 Ubiquitin

Ubiquitin is activated and attached to proteins using a group of three enzymes

- E1 - Ubiquitin activating enzyme
- E2 - Ubiquitin-conjugating enyzme
- E3 - Ubiquitin-protein ligase



The human papilloma virus encodes for an E3 protein which targets the p53 tumor suppressor protein in its host. 90% of the cervical cancers are associtated with this type of activity.

3. Removal of Nitrogen

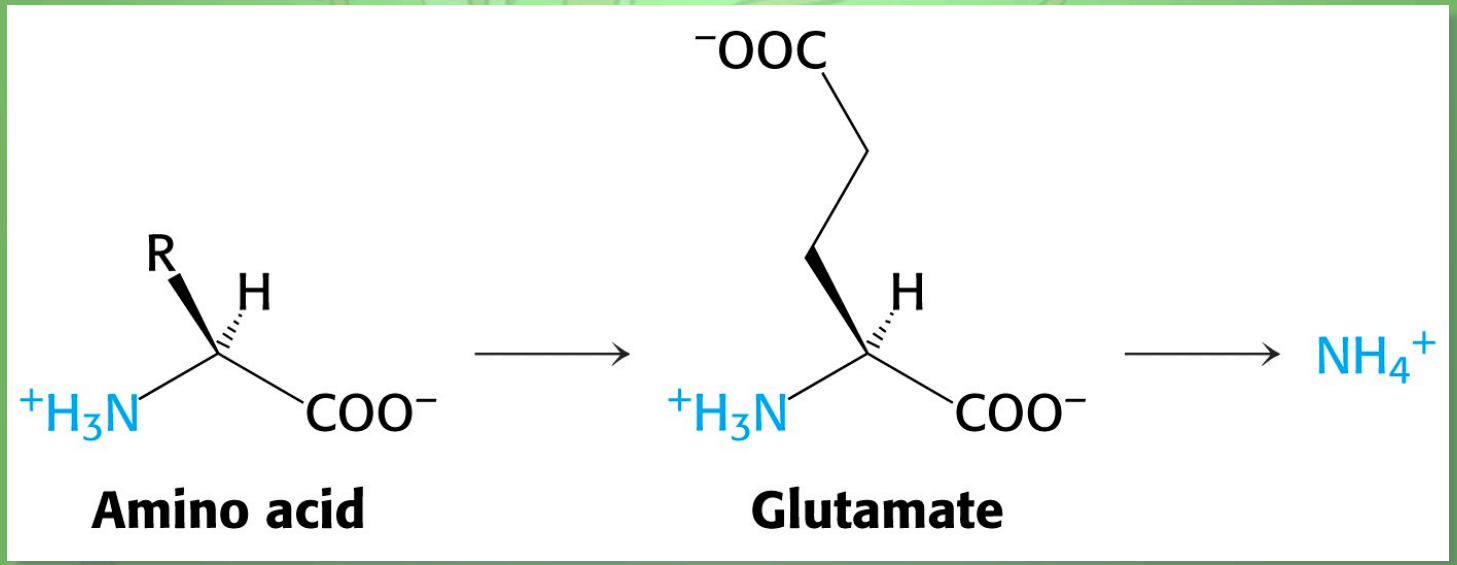
The first step in amino acid degradation is the removal of the nitrogen.

- The liver is the major site of protein degradation in mammals.

Deamination produces α-keto acids, which are degraded to other metabolic intermediates.

3.1 Conversion to Ammonium Ions

α-Amino groups are converted to ammonium ions by the oxidative deamination of glutamate



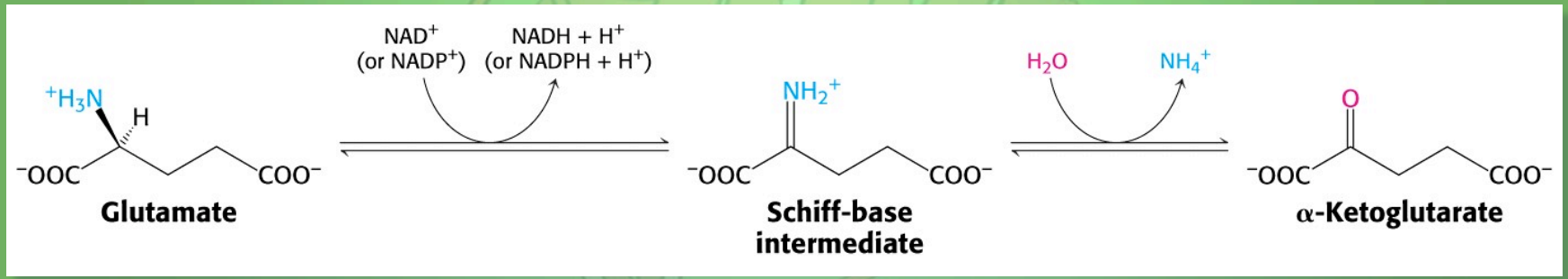
3.1 Transamination

Generally these enzyme funnel amino groups to α-ketoglutarate.

- Aspartate transaminase
- Alanine transaminase

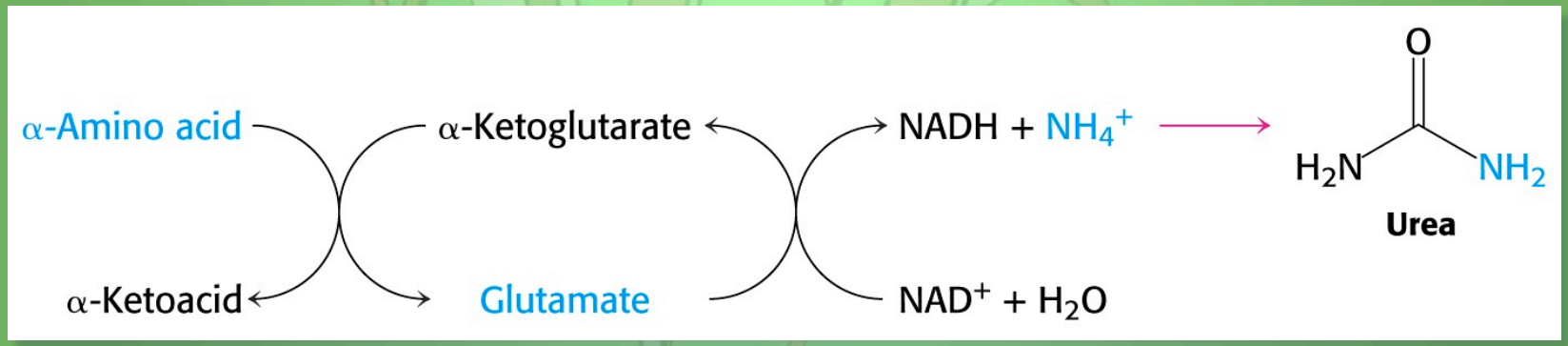
3.1 Deamination

Glutamate dehydrogenase



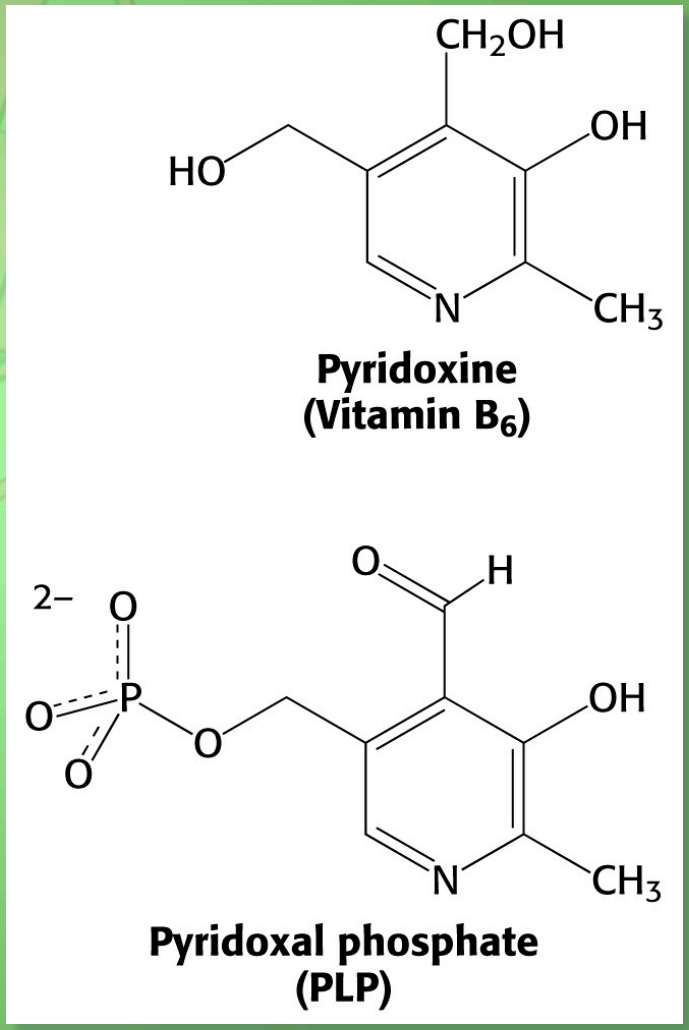
3.1 Deamination

In most terrestrial vertebrates the ammonium ion is converted to urea.



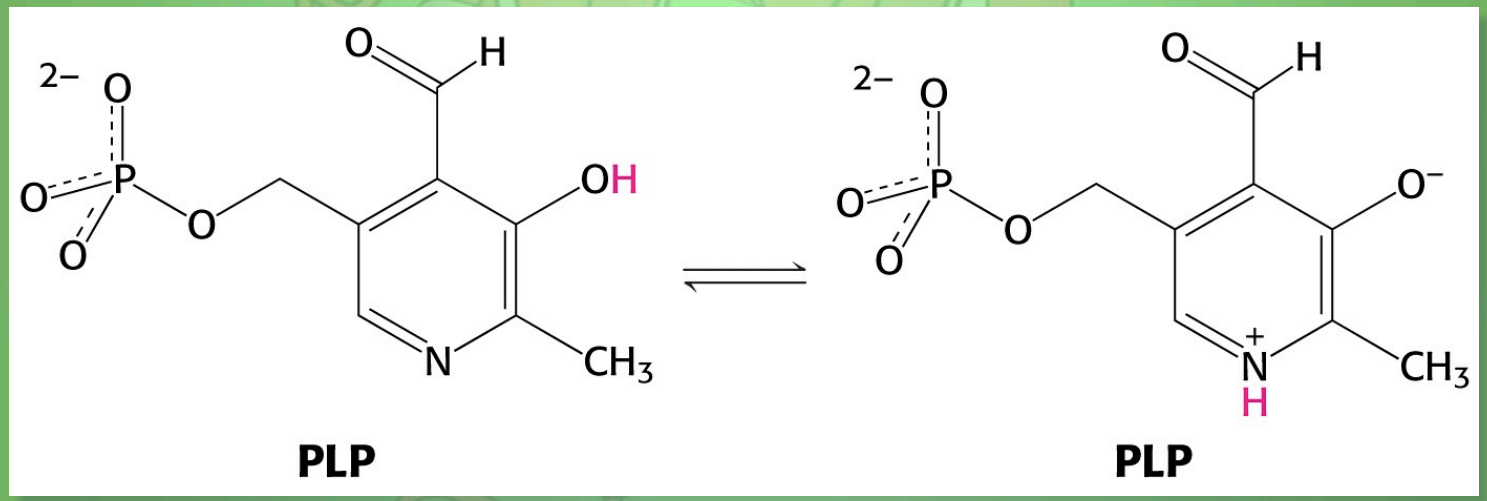
3.2 Pyridoxal Phosphate

Pyridoxal phosphate forms a Schiff-base intermediates in aminotransferase reactions.



3.2 Pyridoxyl Phosphate

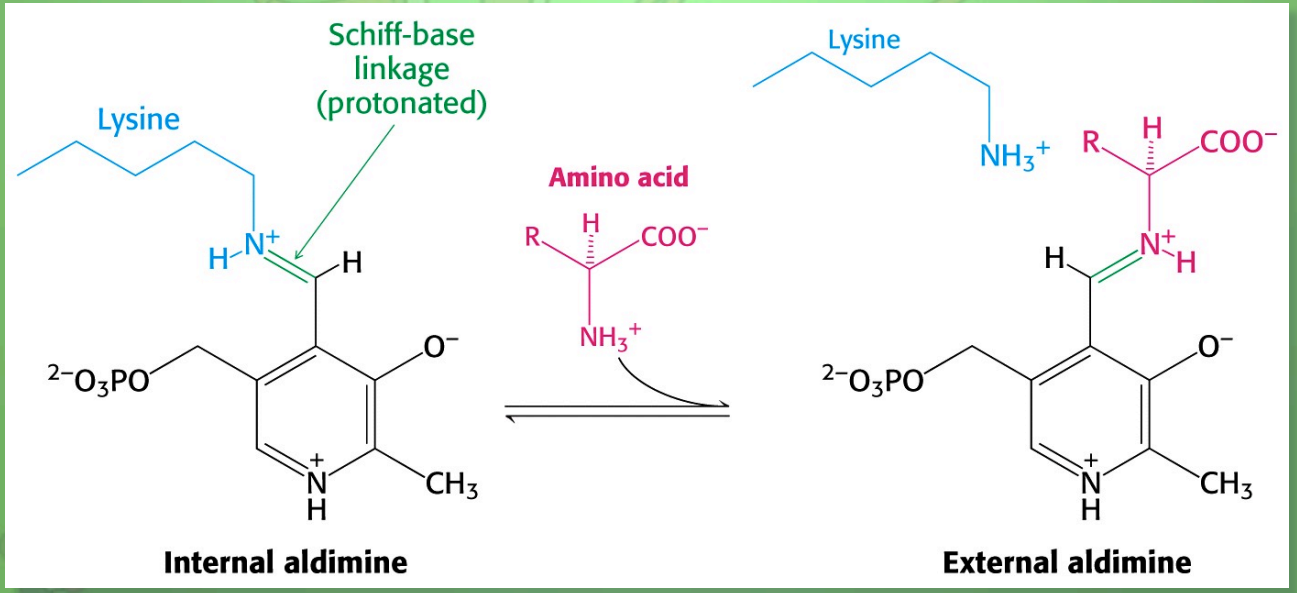
Pyridoxyl phosphate can under go acid/base tautomerization.



3.2 Pyridoxyl Phosphate

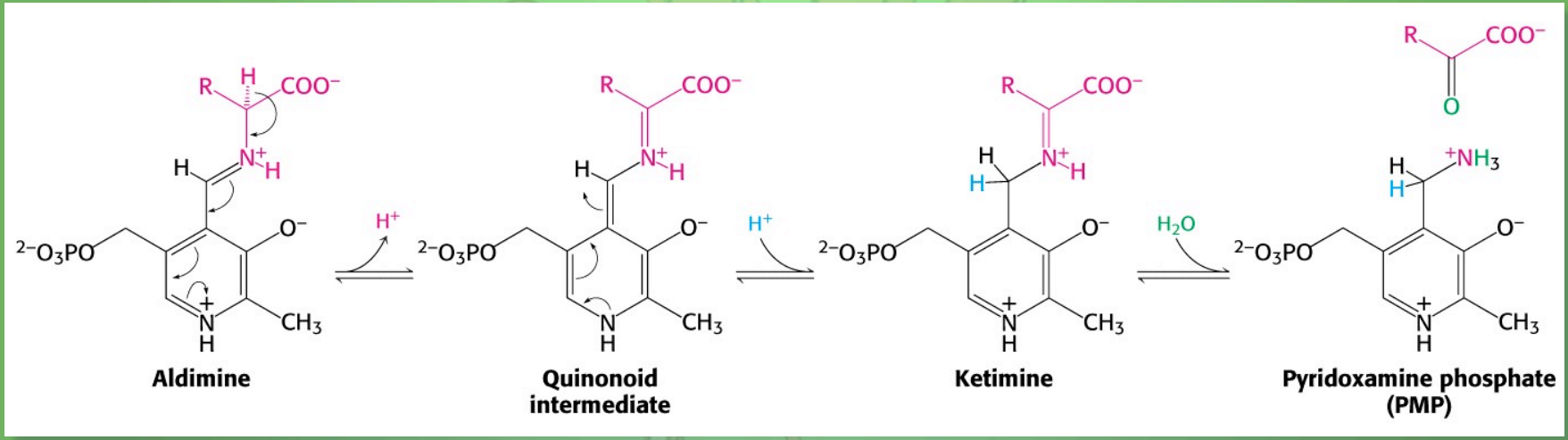
The aldehyde forms a Schiff-base with an ϵ-amino group on the enzyme.

- This Schiff-bases can be exchanged for one with the α-amino group of an amino acid



3.2 Pyridoxyl Phosphate

Transamination mechanism:

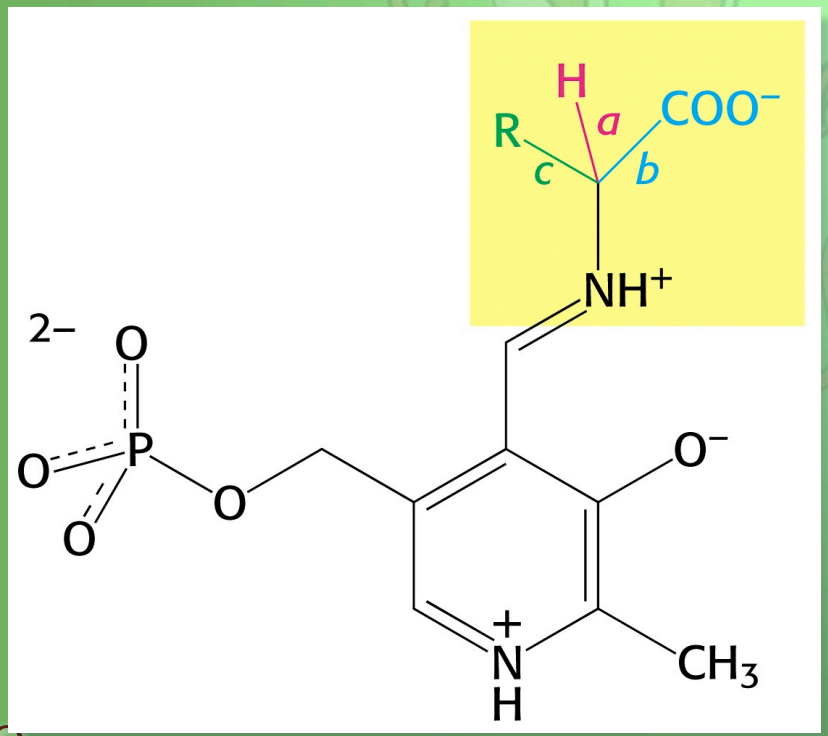


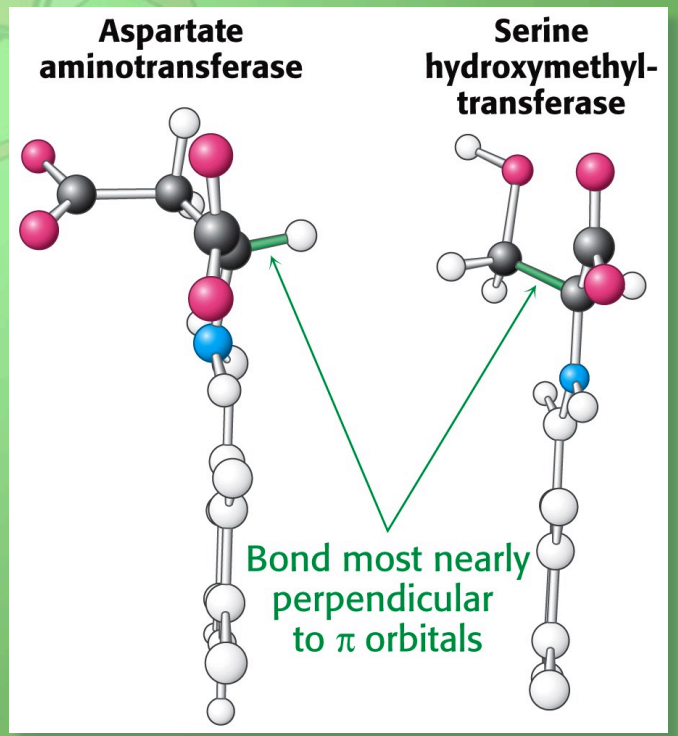
- The second half of the reaction reverses these steps with a different α-keto acid.

3.2 Pyridoxyl Phosphate

Pyridoxyl phosphate is is a very versatile cofactor

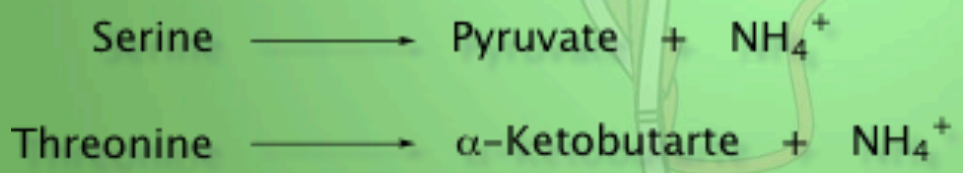
- used to make bonds to C_α susceptible to cleavage.

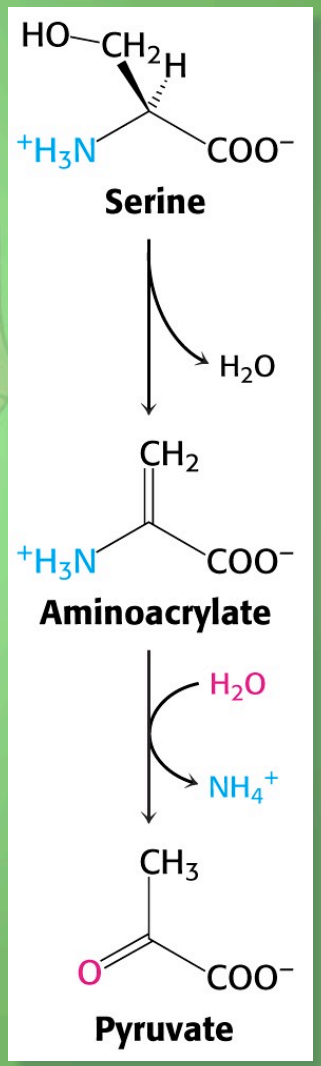




3.4 Serine and Threonine

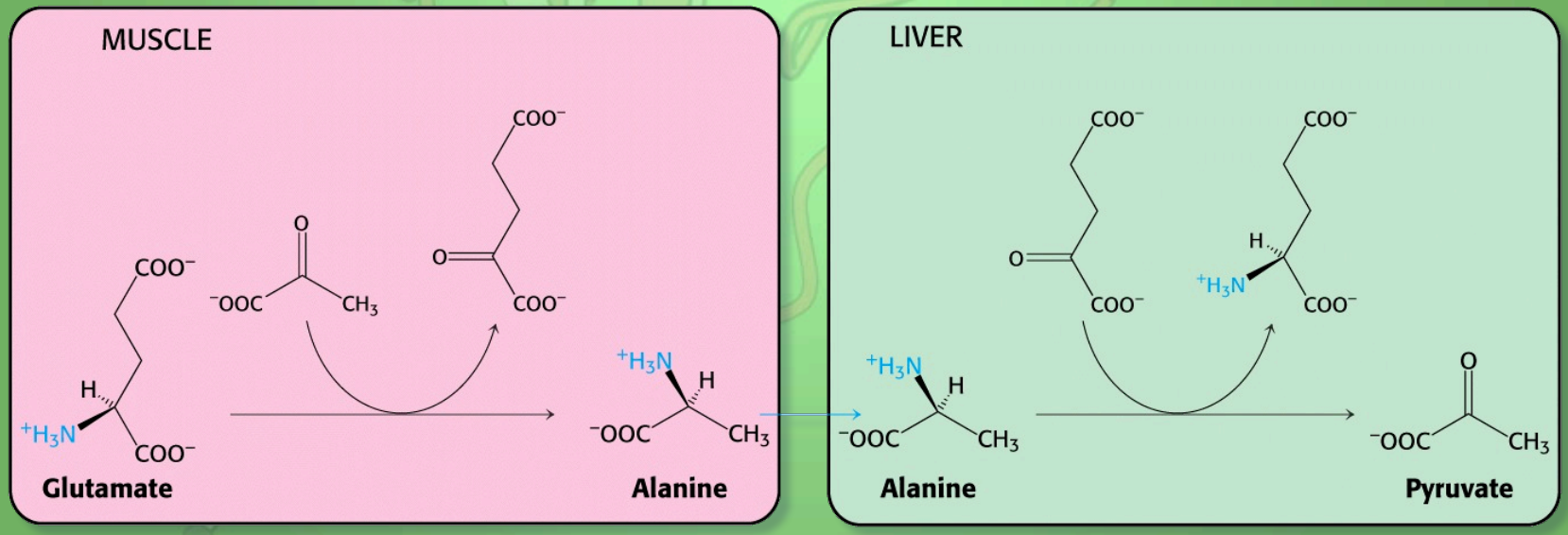
The β-hydroxy amino acids, serine and threonine, can be directly deaminated





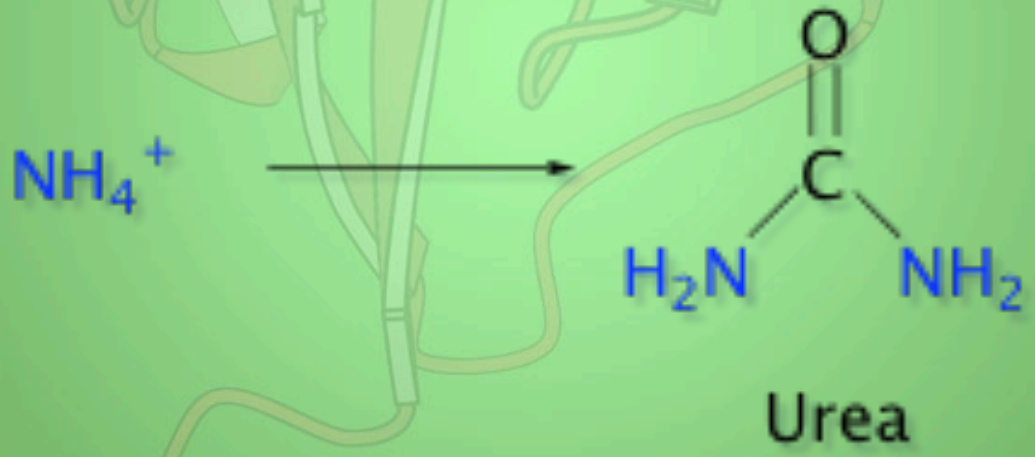
3.5 Transporting Nitrogen to Liver

- Urea is produced in the Liver
- The *alanine cycle* is used to transport nitrogen to the liver

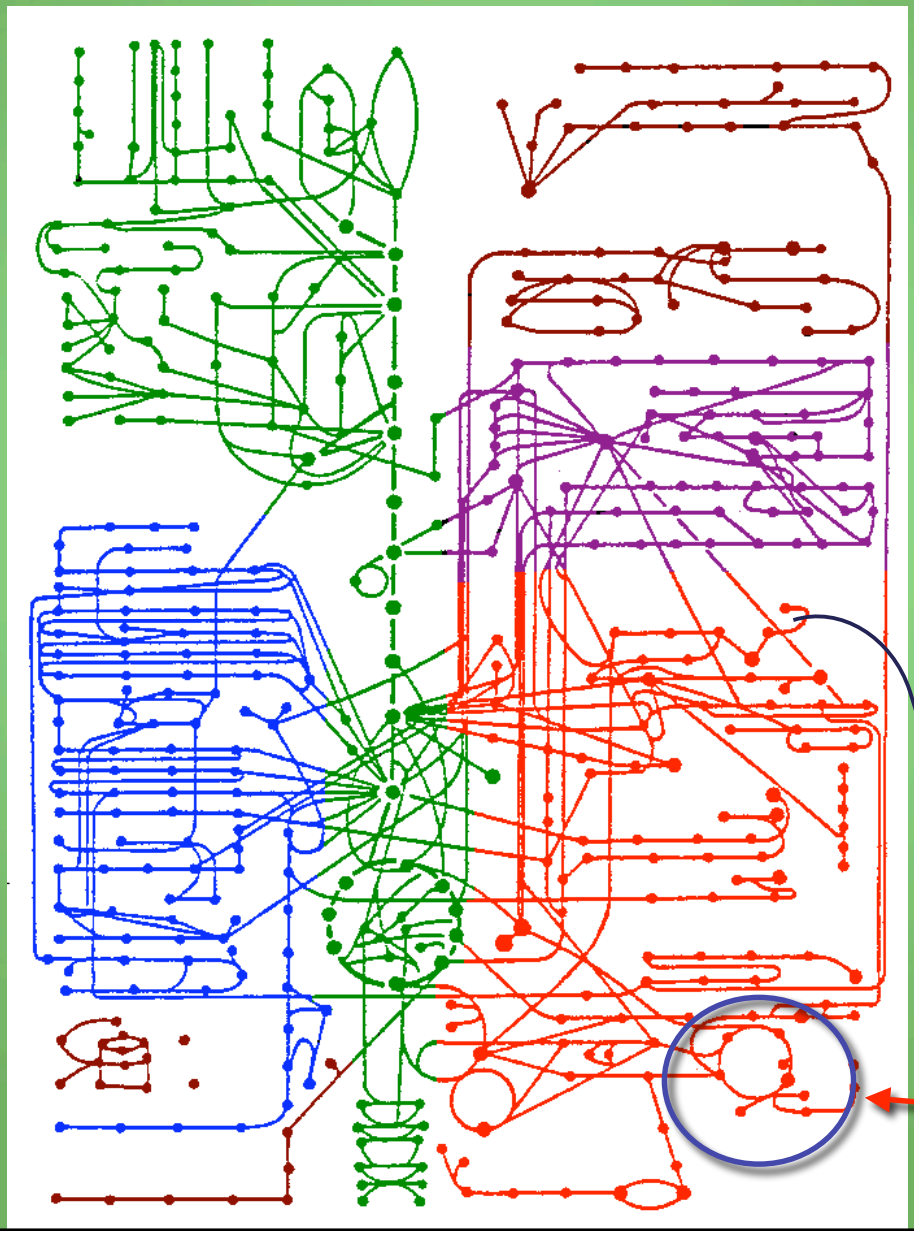


4. Ammonium Ion

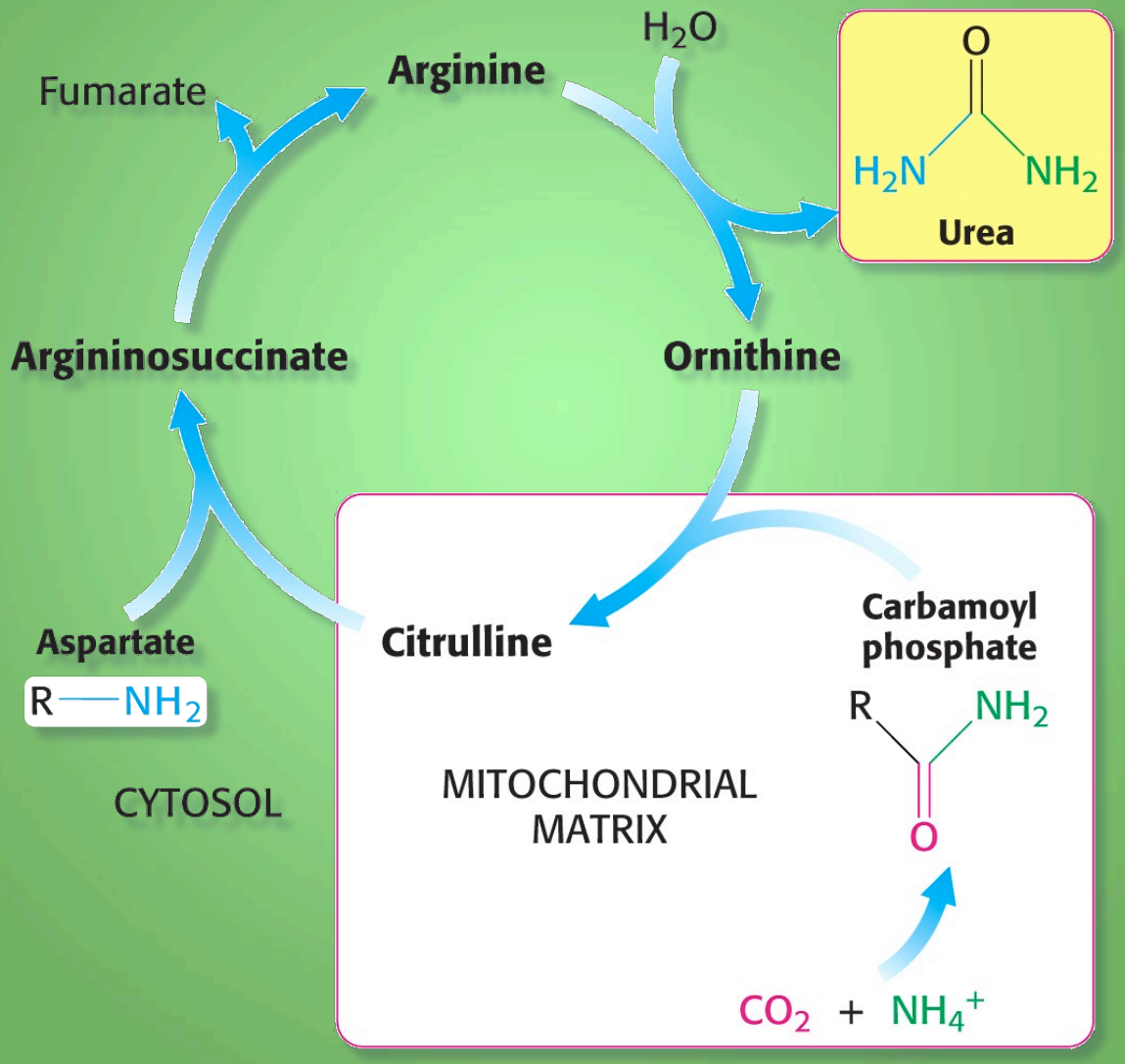
Ammonium ion is converted into urea in most terrestrial vertebrates



4. The Urea Cycle:reminder



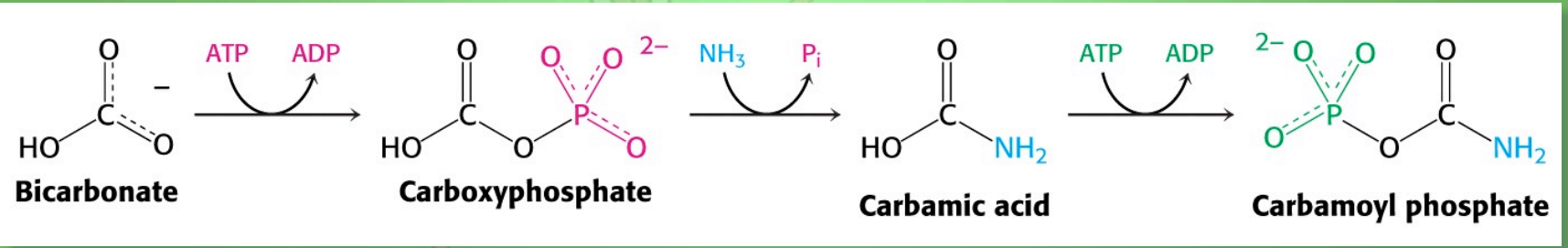
4. The Urea Cycle



4.1 Formation of Carbamoyl Phosphate

Carbamoyl synthetase

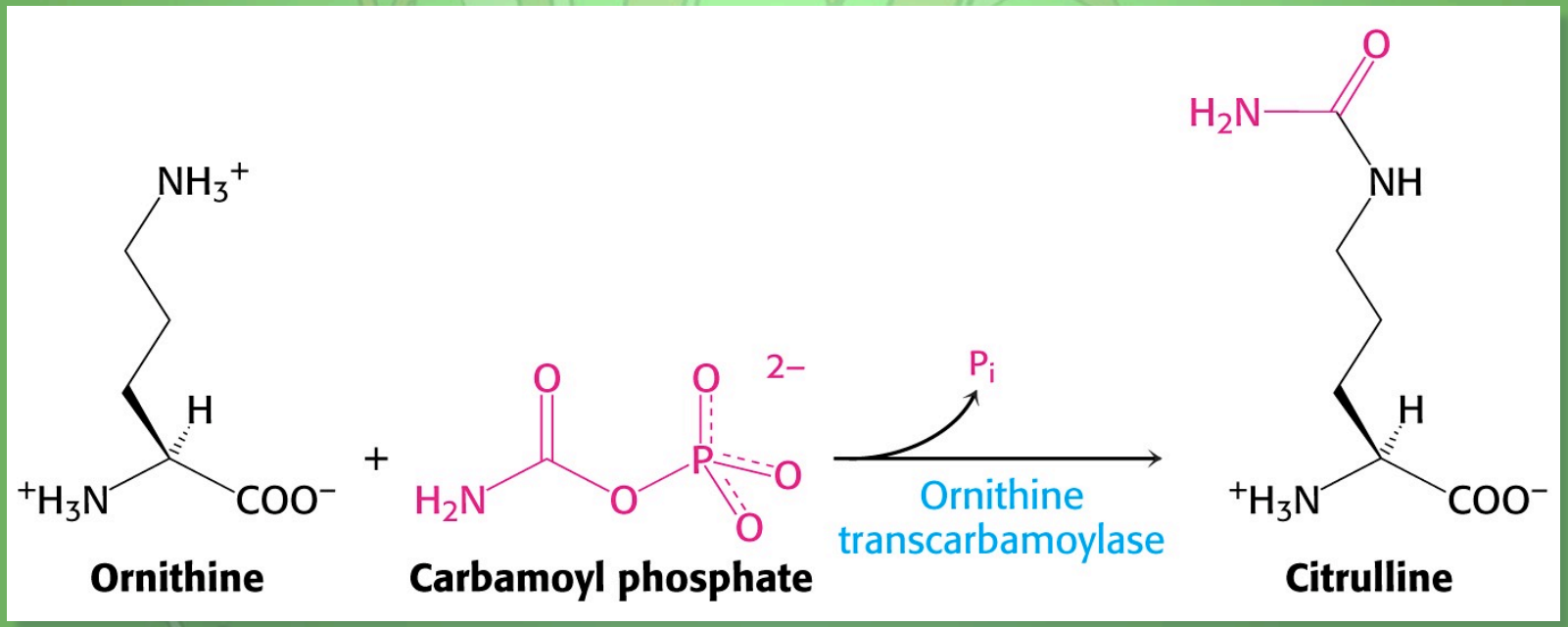
- Free NH4 reacts with HCO3 to form carbamoyl phosophate.
- Reaction is driven by the hydrolysis of two molecules of ATP



4.1 Formation of Citrulline

Ornithine transcarbamoylase

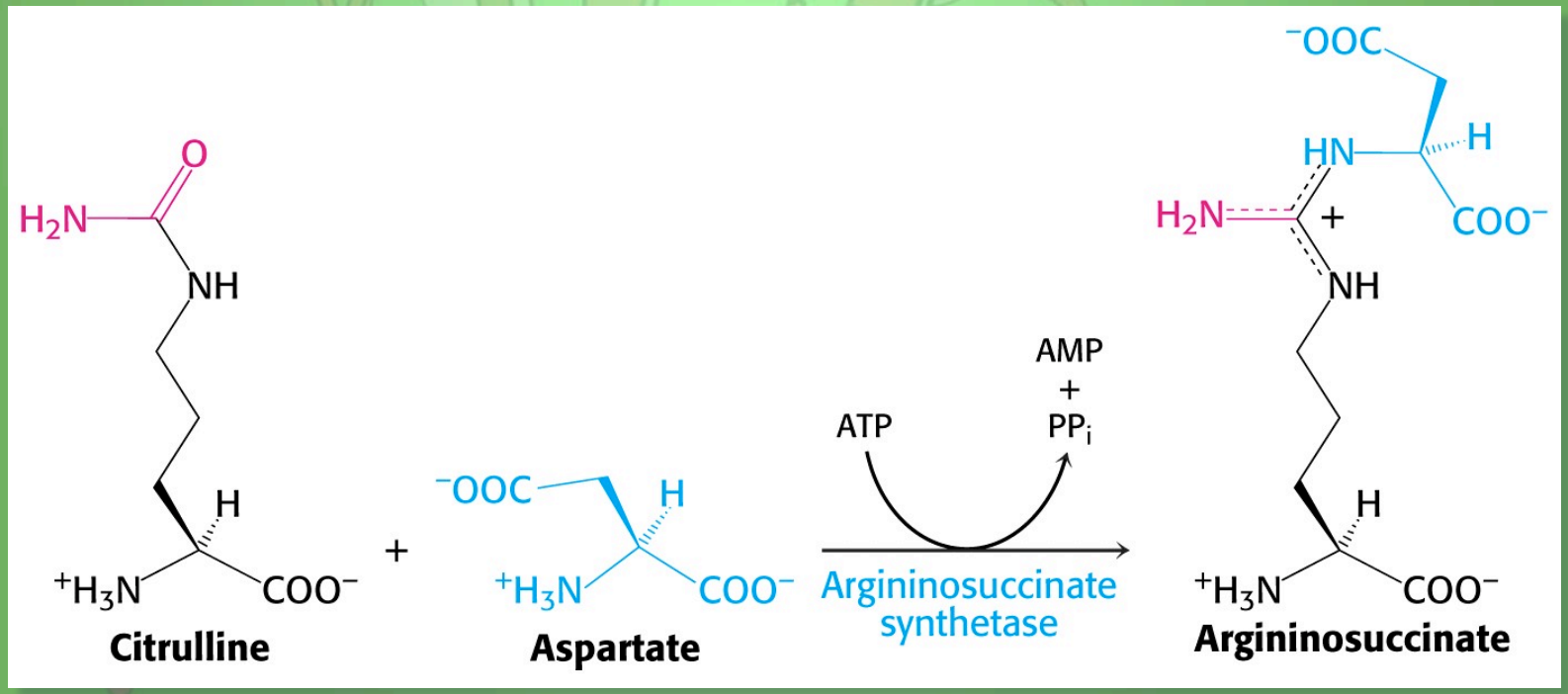
- Citrulline is formed from transfer of the carbamoyl group to the γ–amino group of ornithine.



4.1 Formation of Arginosuccinate

Condensation of citrulline with aspartate to form arginosuccinate

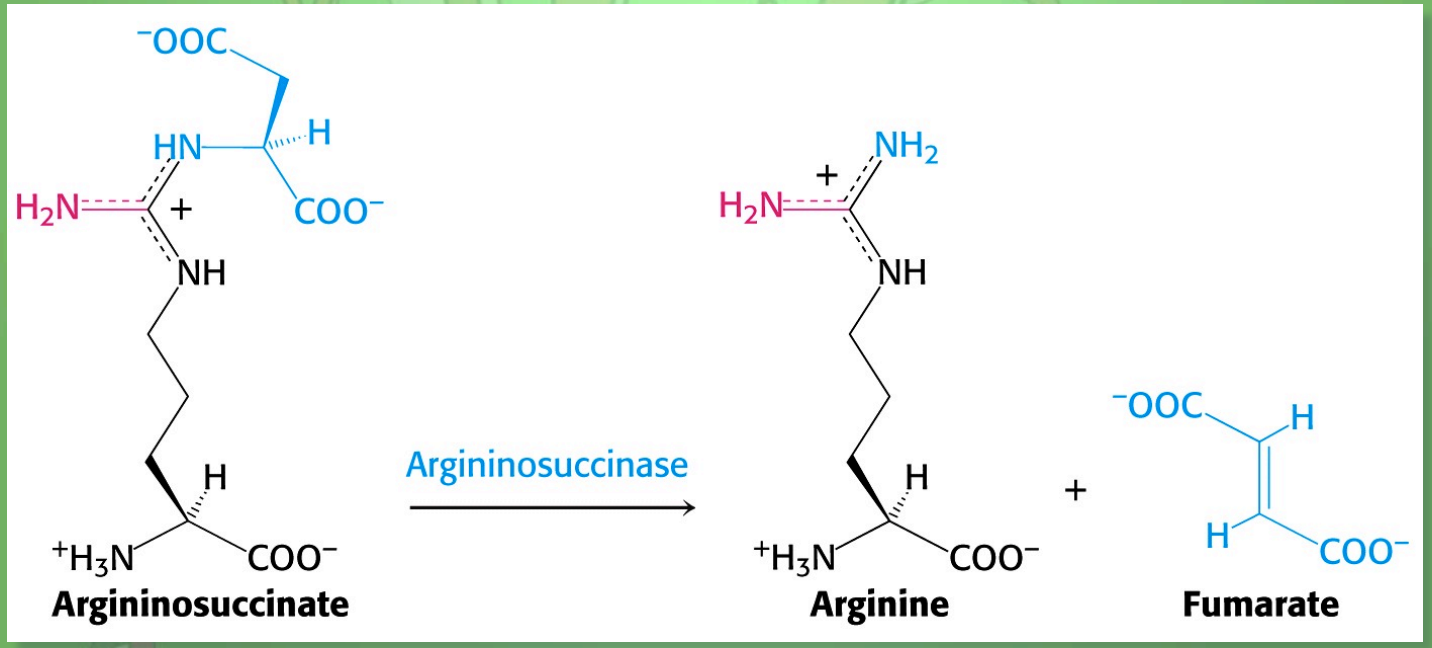
- Two equivalent of ATP are required.



4.1 Formation of Arginine and Fumarate

Arginosuccinase

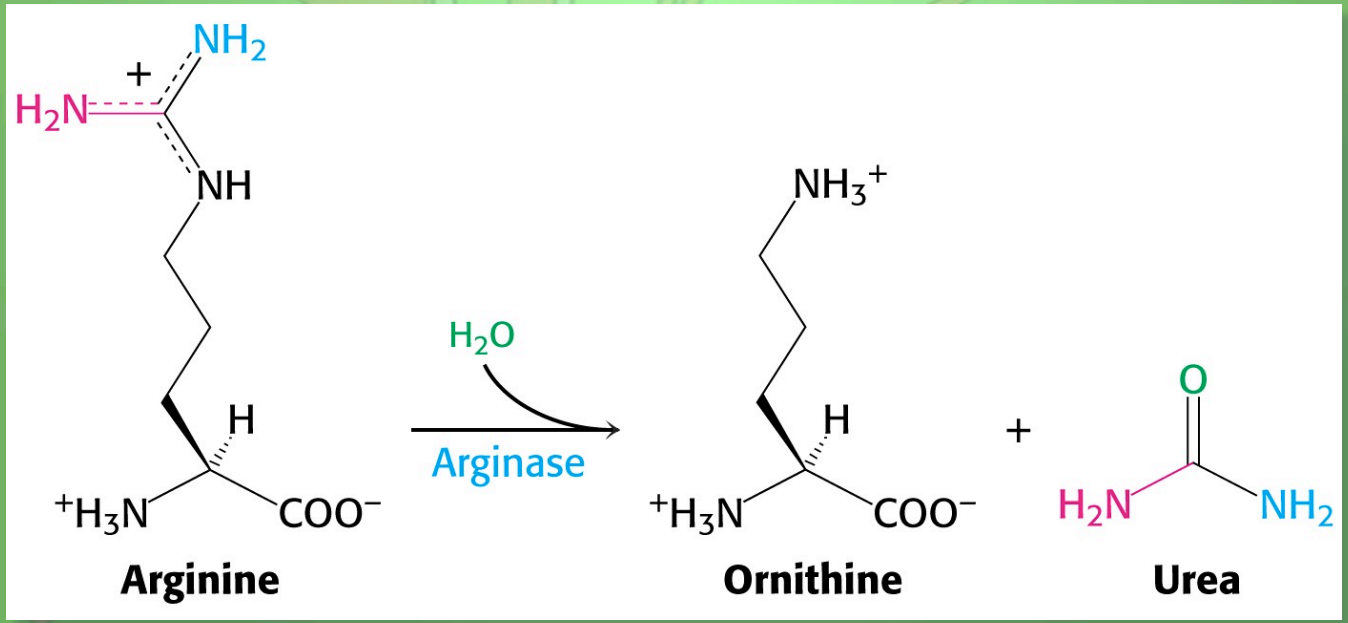
- Cleaves arginosuccinate to form arginine and fumarate



4.1 Formation of Urea

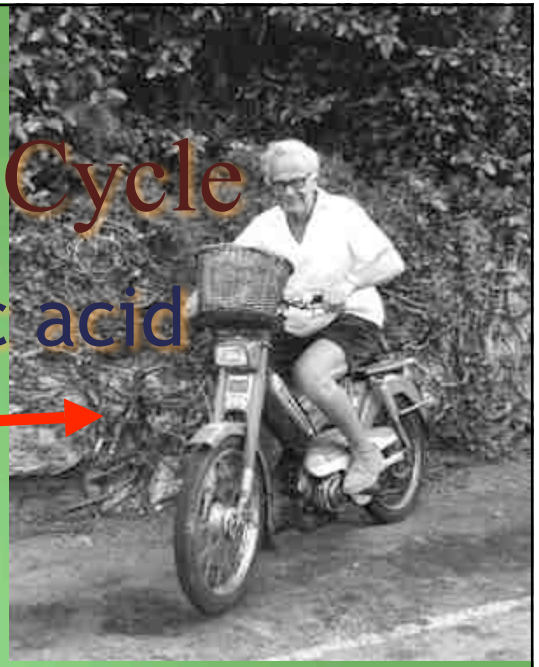
Arginase

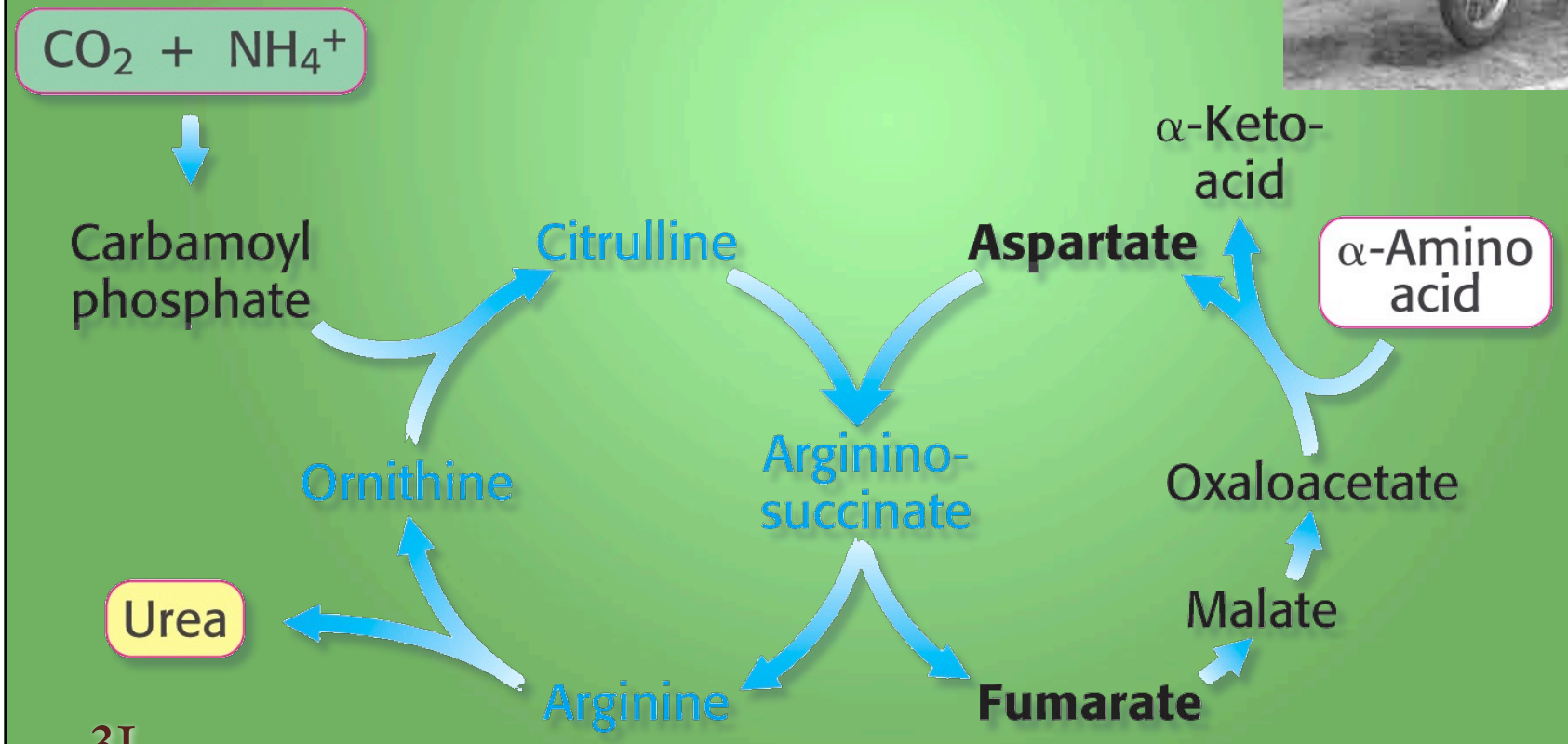
- The arginine is hydrolyzed to produce the urea and to reform the ornithine.
- The ornithine reenters the mitochondrial matrix.



4.2 Linked to Citric Acid Cycle

The urea cycle is linked to the citric acid cycle: Kreb's Bi-cycle!!





5. Carbon Atoms

The carbon atoms of degraded amino acids emerge as major metabolic intermediates.

- Degradation of the 20 amino acids funnel into 7 metabolic intermediates
  - Acetyl-CoA
  - Acetoacetyl-CoA

  Ketogenic
  - Pyruvate
  - α-Ketoglutarate
  - Succinyl-CoA
  - Fumarate
  - Oxaloloacetate

  Glucogenic

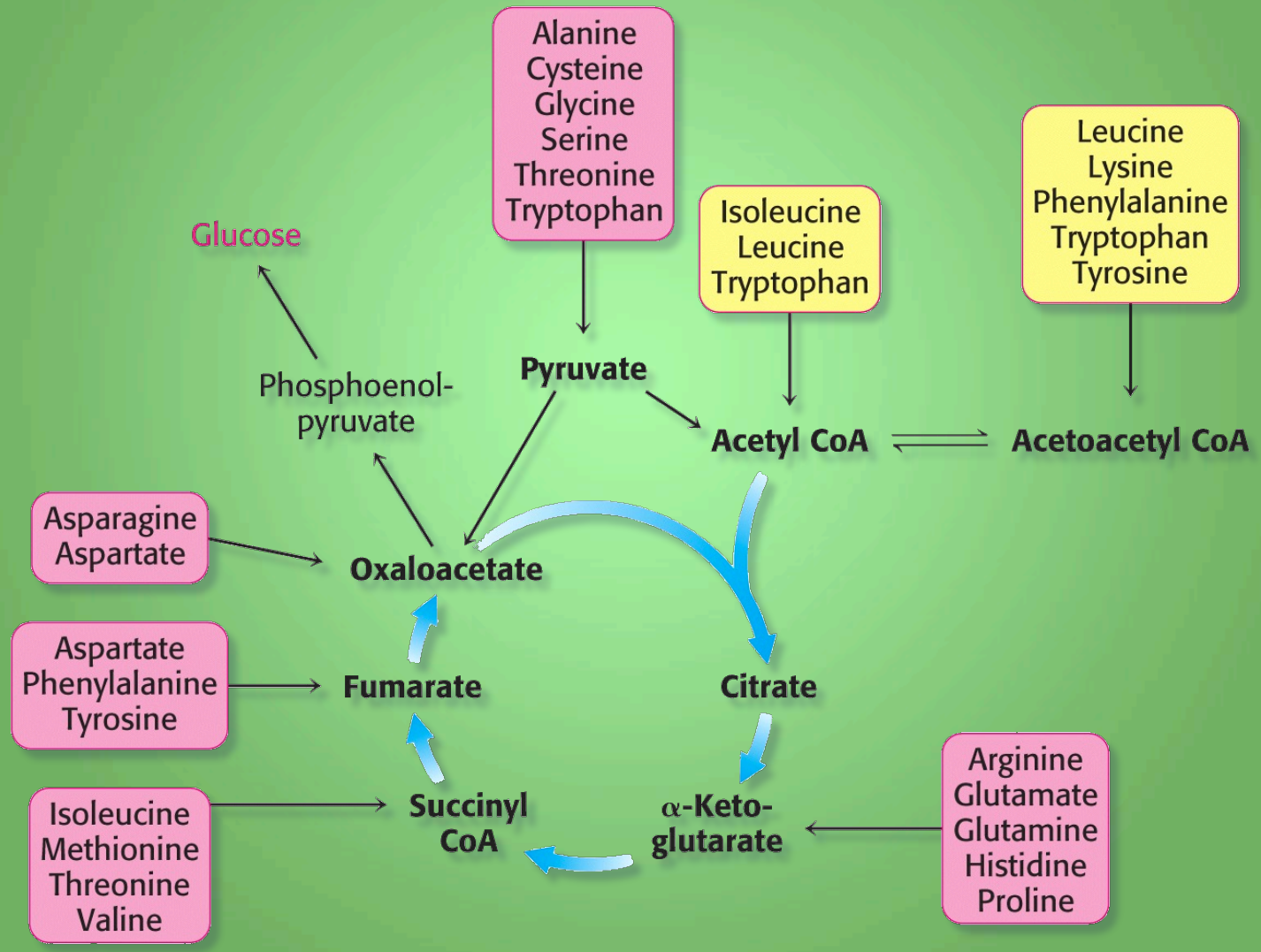
5. Carbon Atoms

Ketogenic	Glucogenic	Both
leucine	serine	isoleucine
lysine	threonine	phenylalanine
	aspartic acid	tryptophan
	glutamic acid	tyrosine
	asparagine	
	glutamine	
	glycine	
	alanine	
	valine	
	proline	
	histidine	
	arginine	
	methionine	
	cysteine	

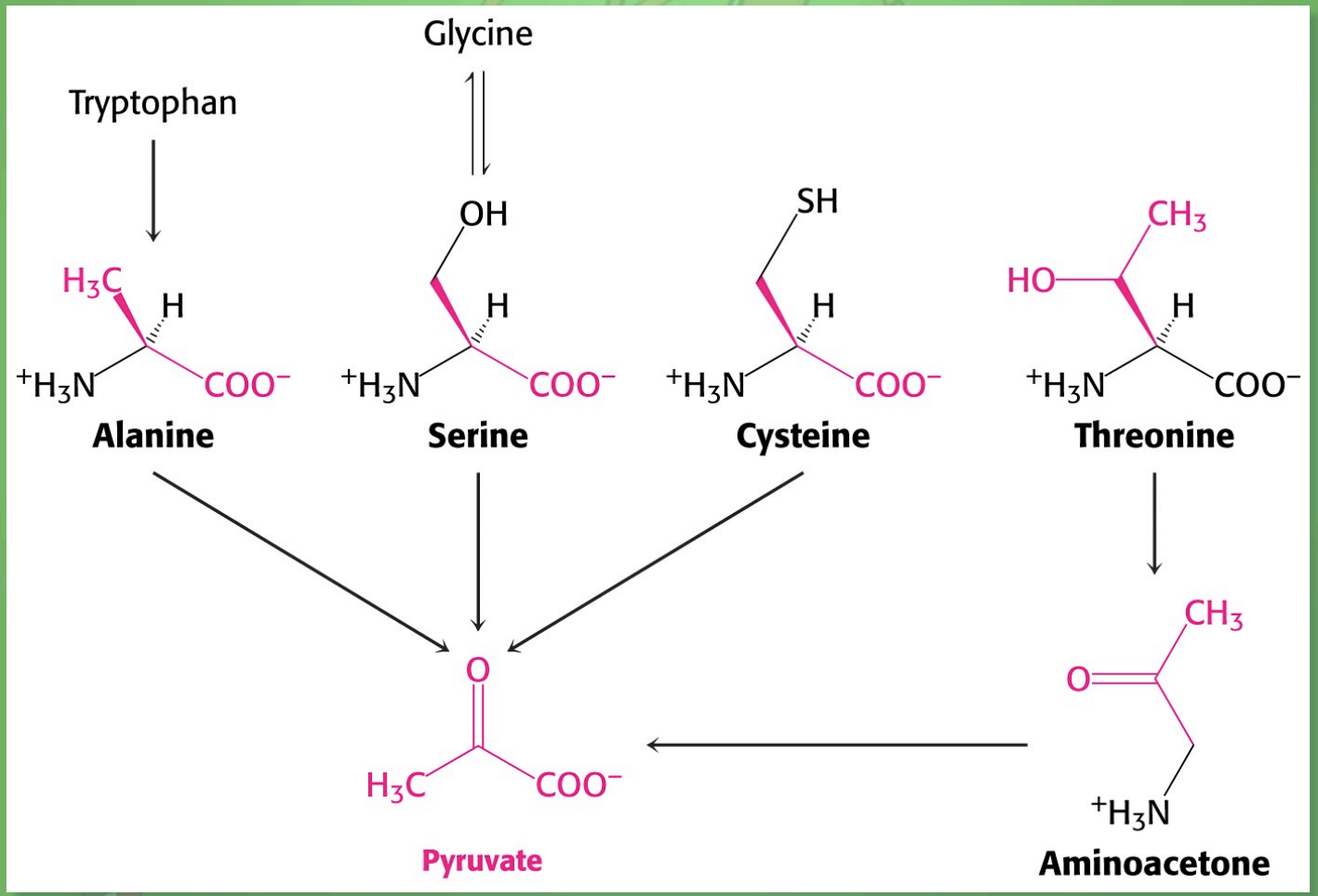
Class problem

Explain the meaning (from a biochemistry perspective) of the saying "fats burn in the flame of carbohydrates." How would proteins fit into this statement?

5. Carbon Atoms



5.1 Pyruvate Entry Point



5.2 Oxaloacetate Entry Point

Aspartate

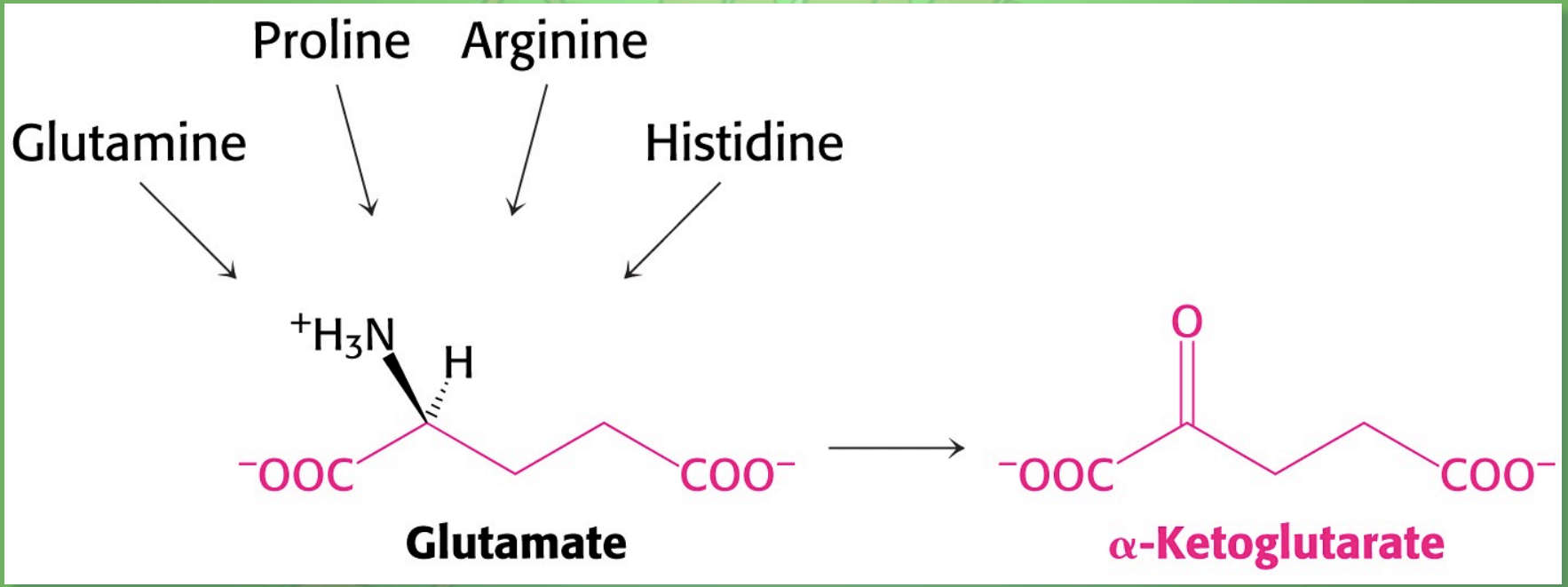
- Transamination to oxaloacetate

Asparagine

- Hydrolysis to Aspartate + NH_4^+
- Transmination to oxaloacetate

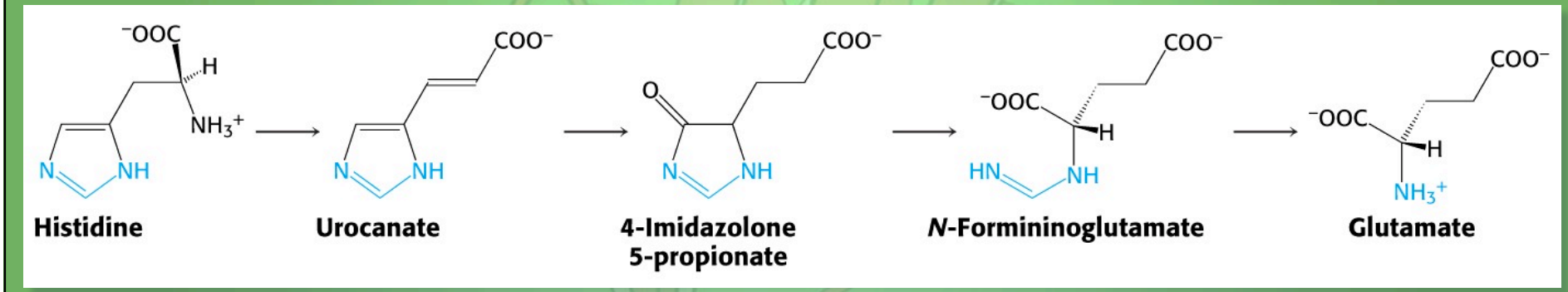
5.3 α–Ketoglutarate Entry Point

Five carbon amino acids



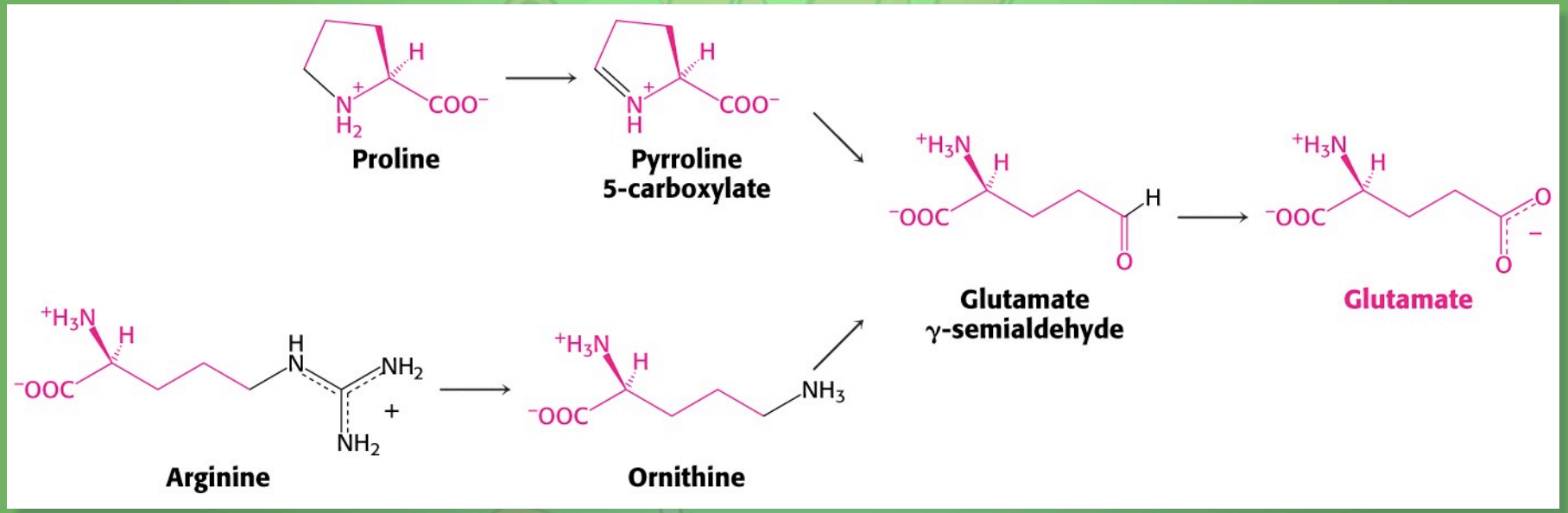
5.3 α–Ketoglutarate Entry Point

Histidine



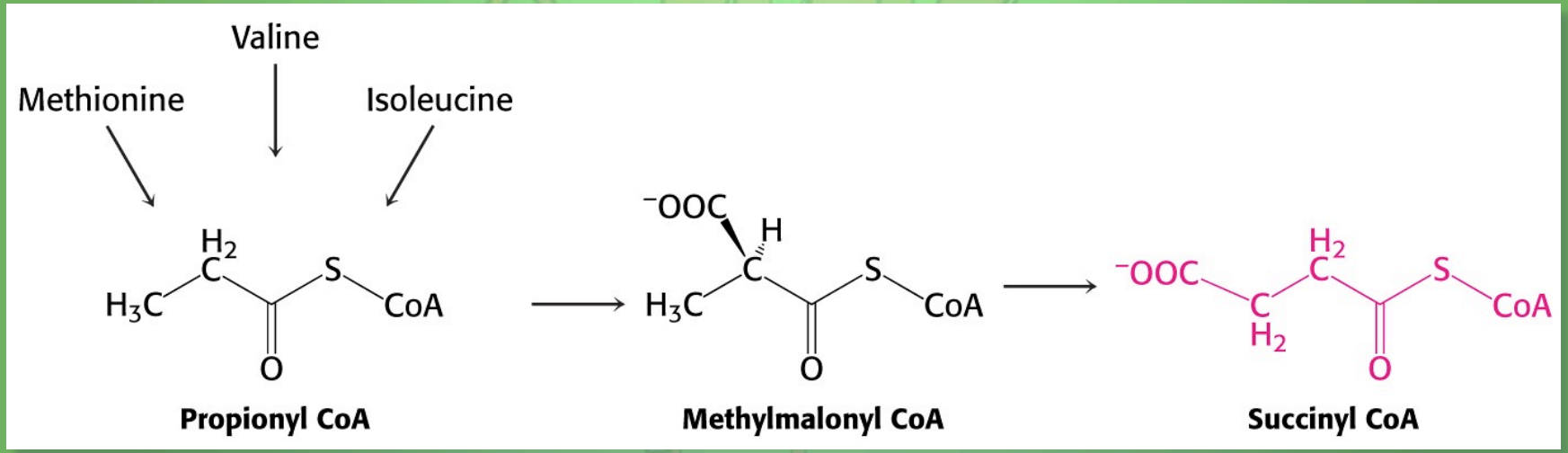
5.3 α–Ketoglutarate Entry Point

Proline and Arginine



5.4 Succinyl–CoA Entry Point

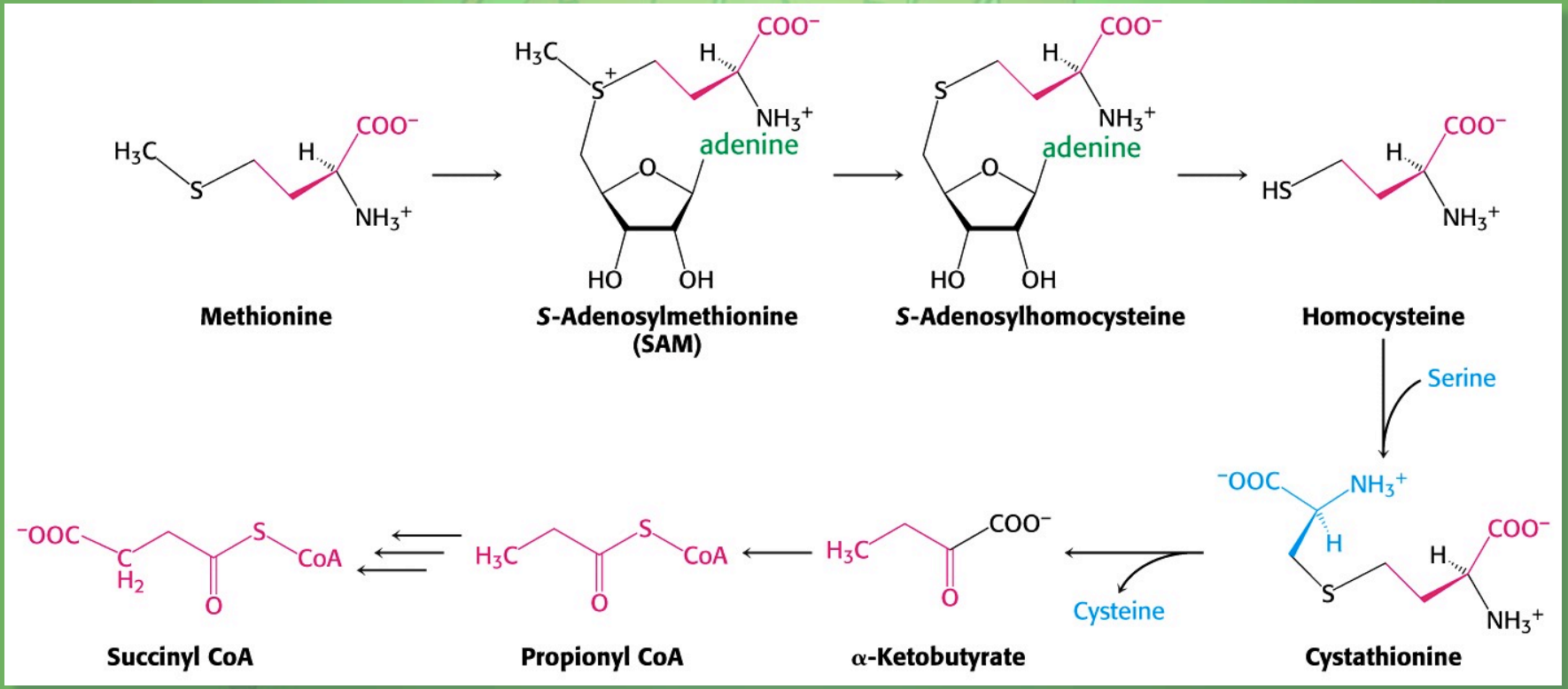
Methionine, Valine & Isoleucine



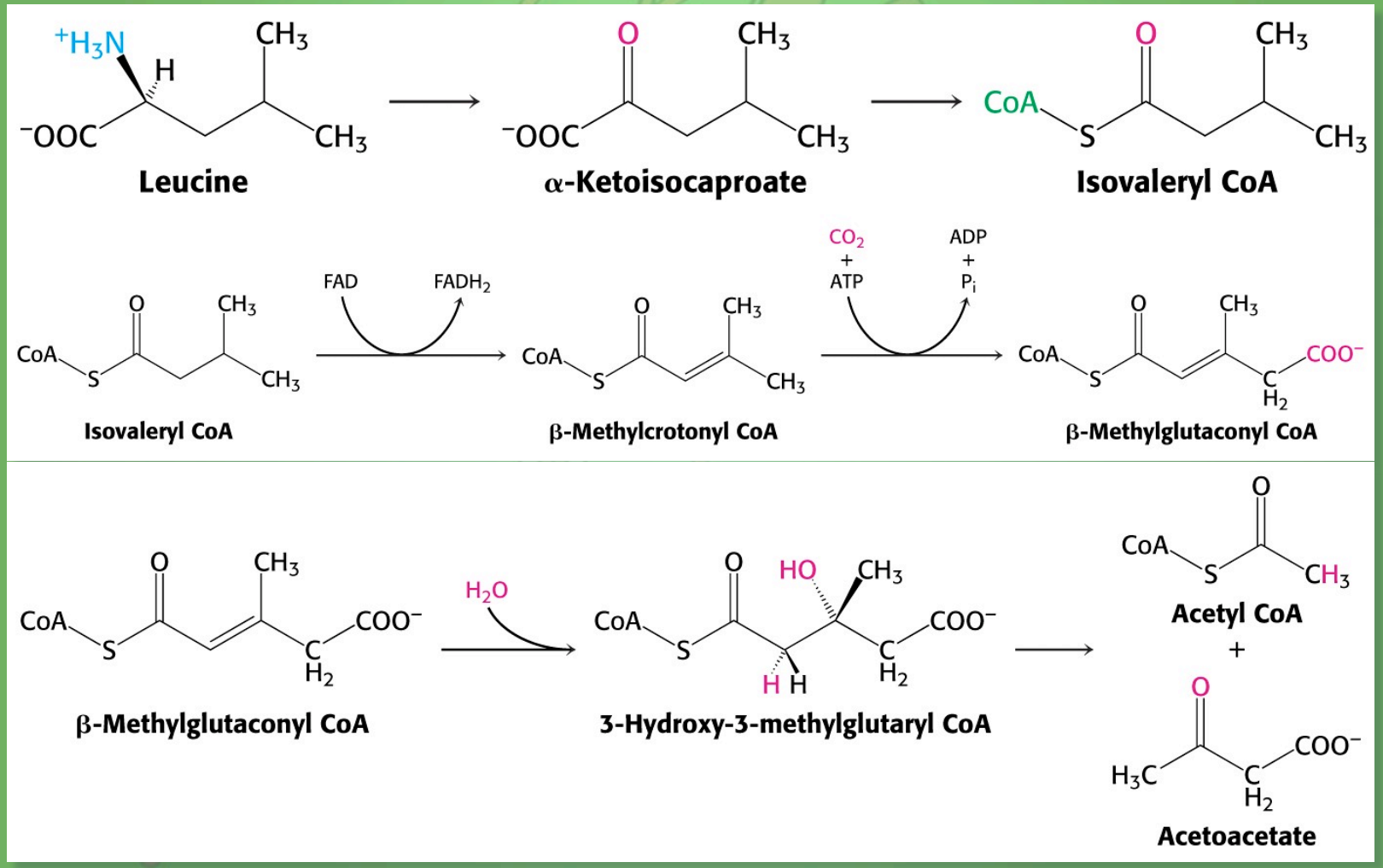
5.4 Succinyl–CoA Entry Point

Methionine

- Forms S-Adenosylmethionine

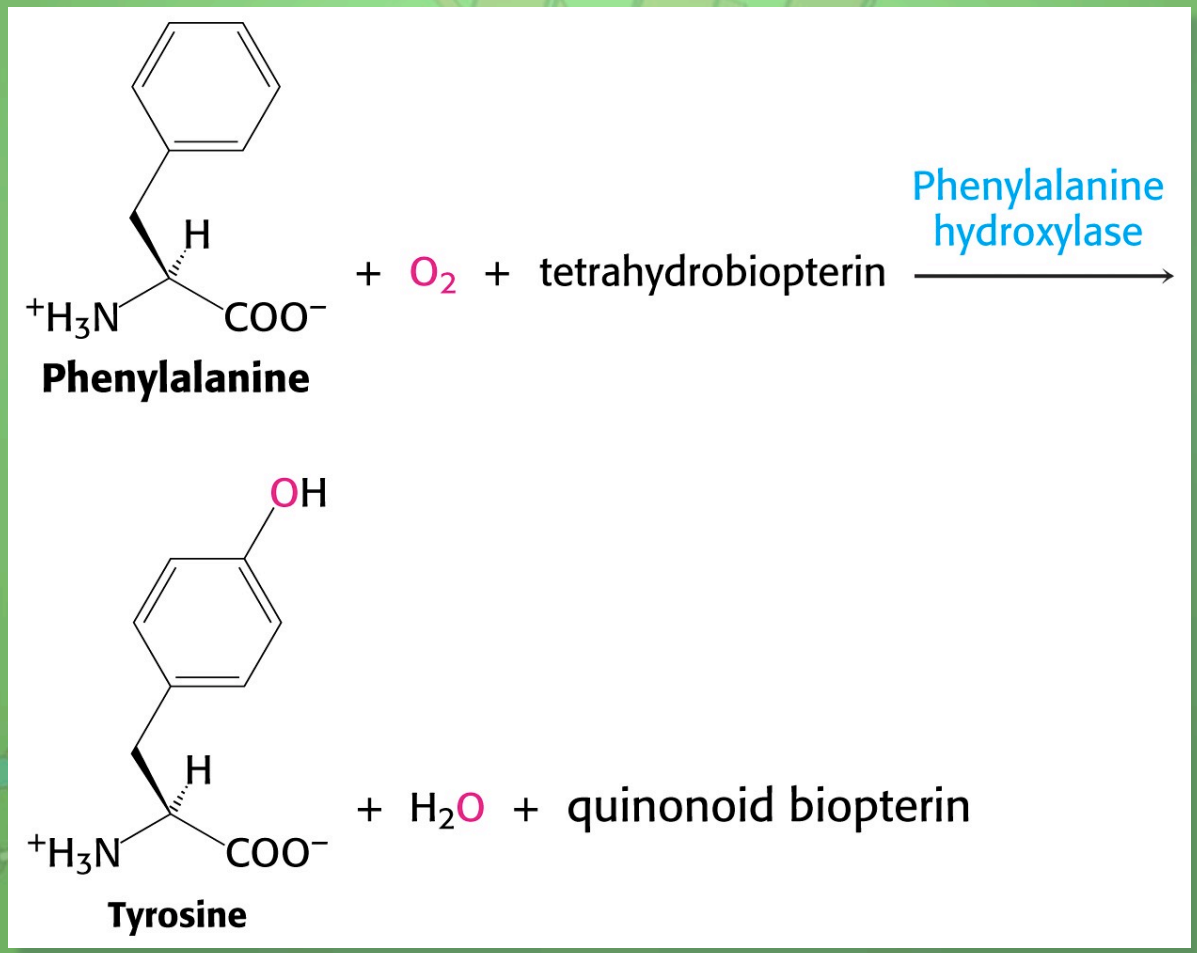


5.6 Branched-chained Amino Acids



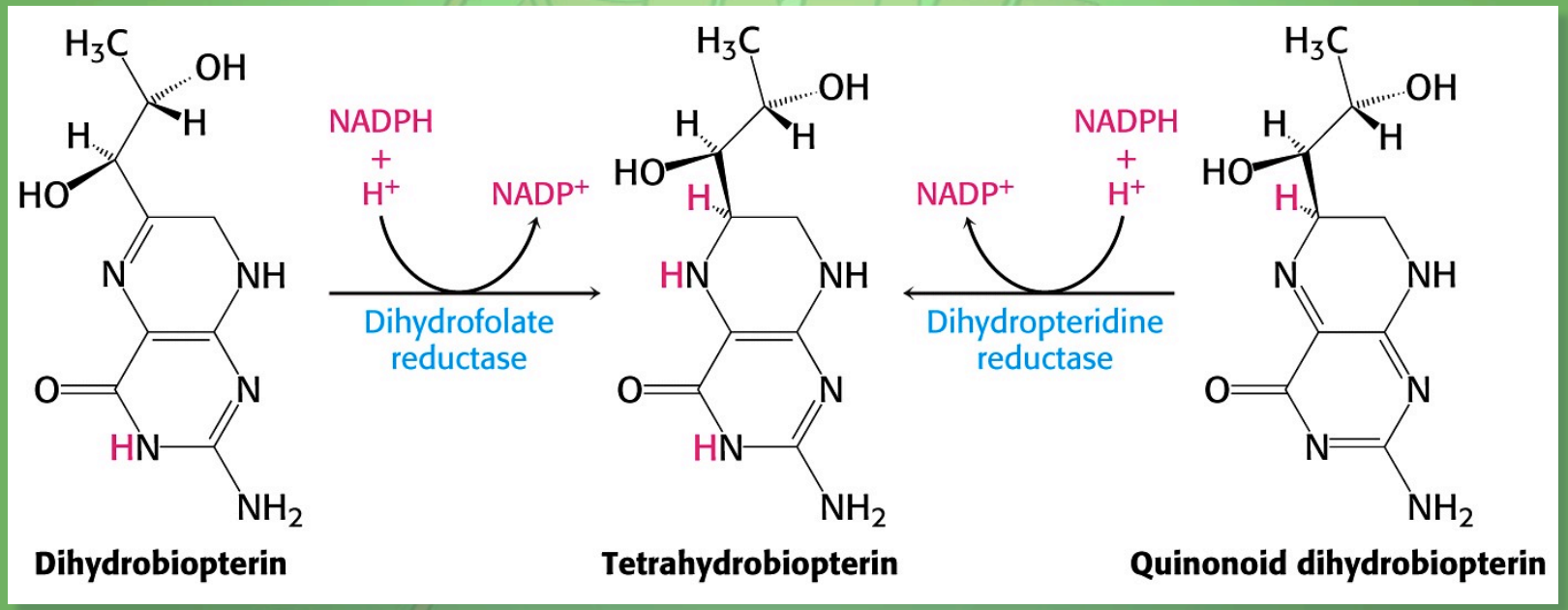
5.7 Aromatic Amino Acids

Phenylalanine



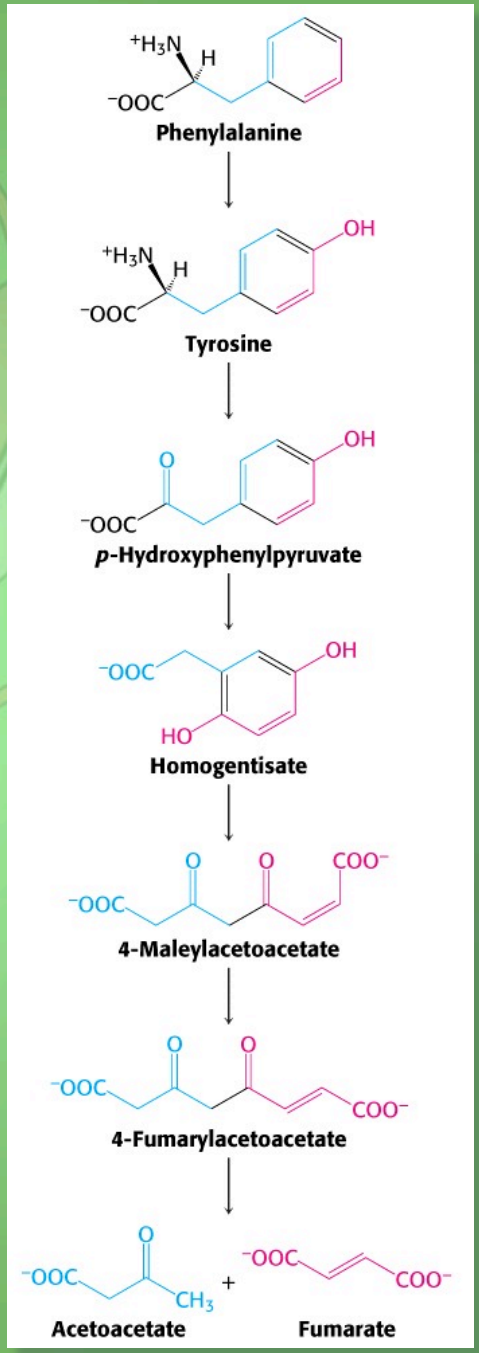
5.7 Aromatic Amino Acids

Tetrahydrobiopterin - electron carrier



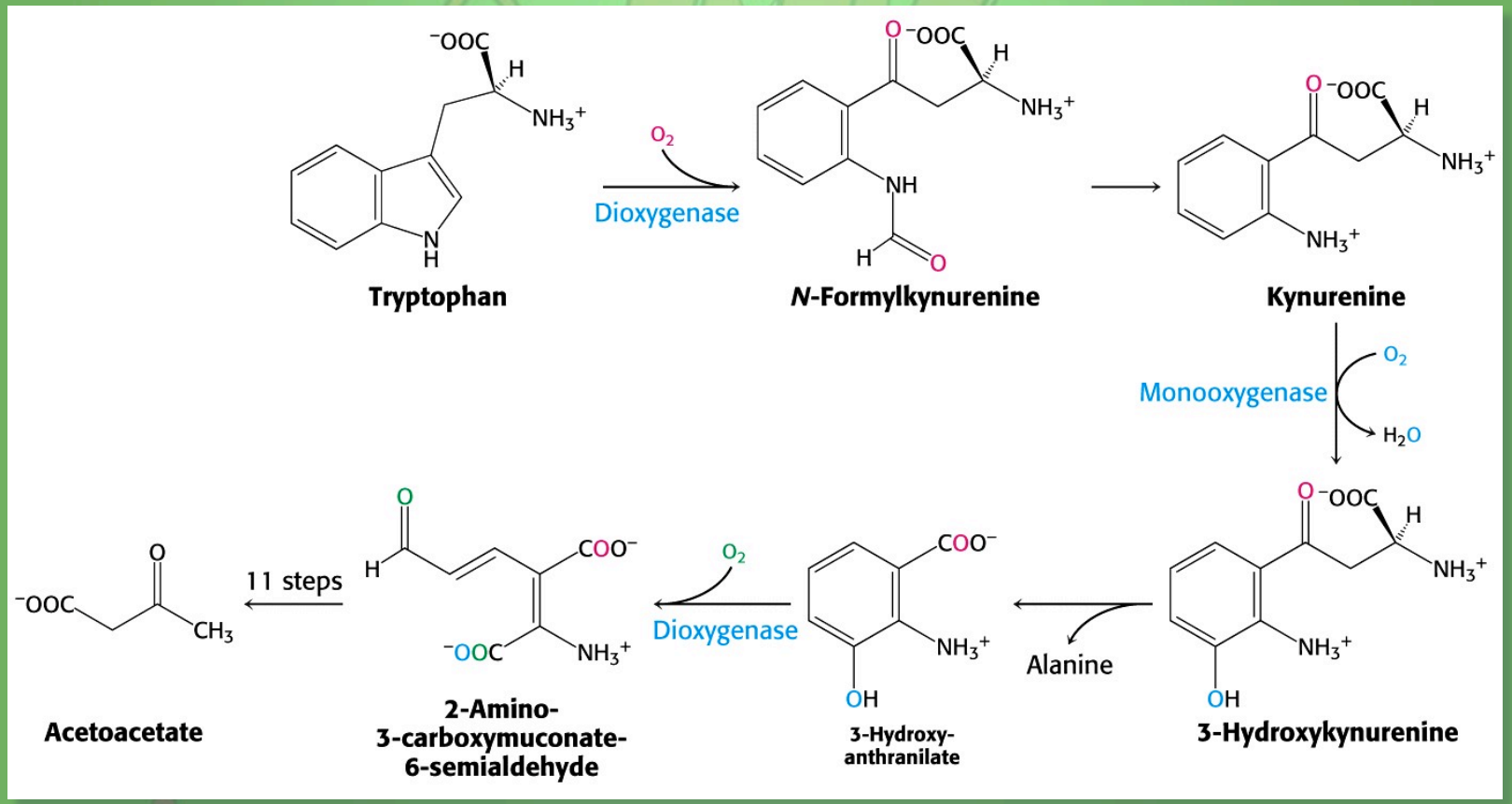
5.7 Aromatic Amino Acids

Phenylalanine & Tyrosine



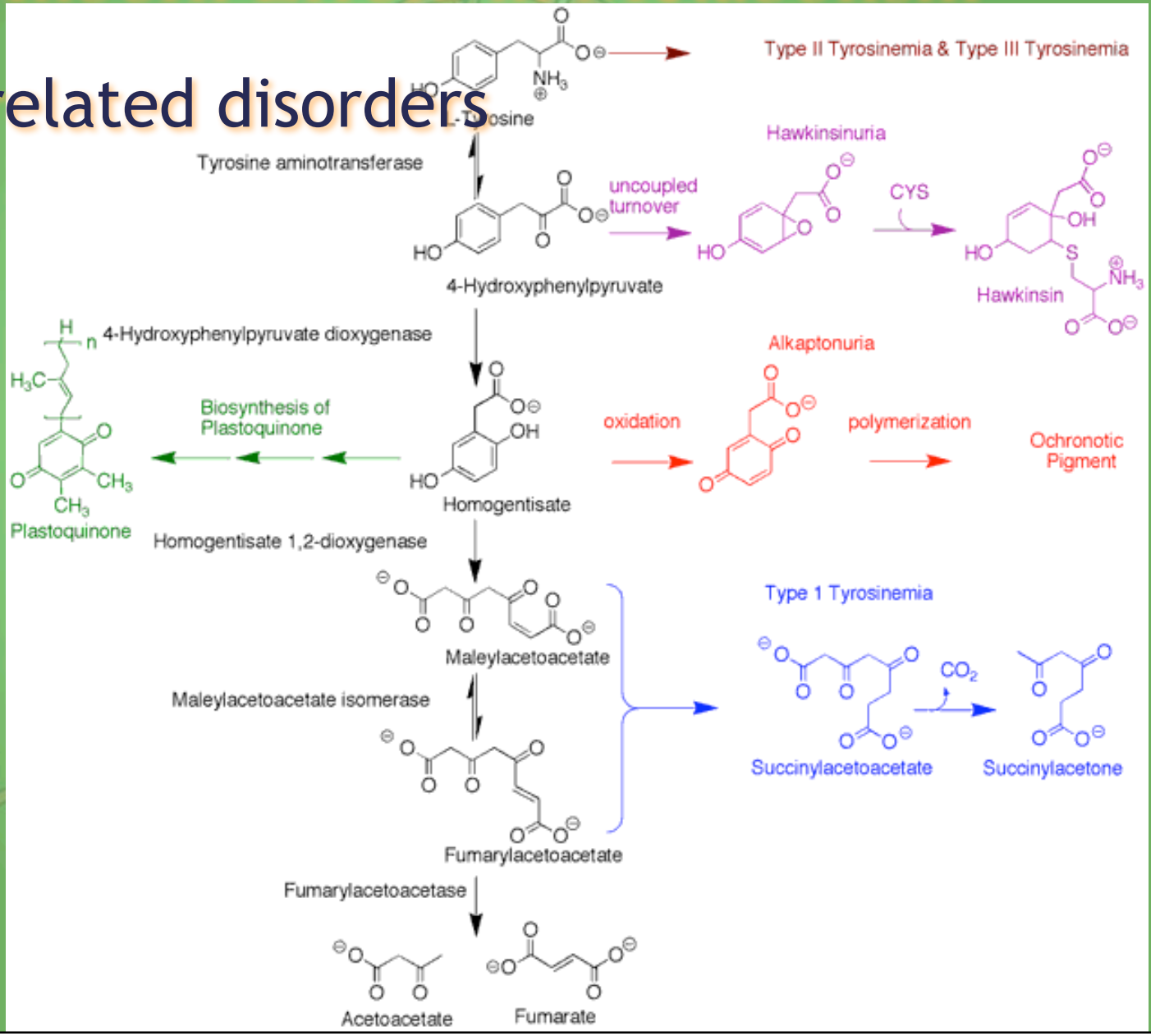
5.7 Aromatic Amino Acids

Tryptophan



6. Inborn Errors in Metabolism

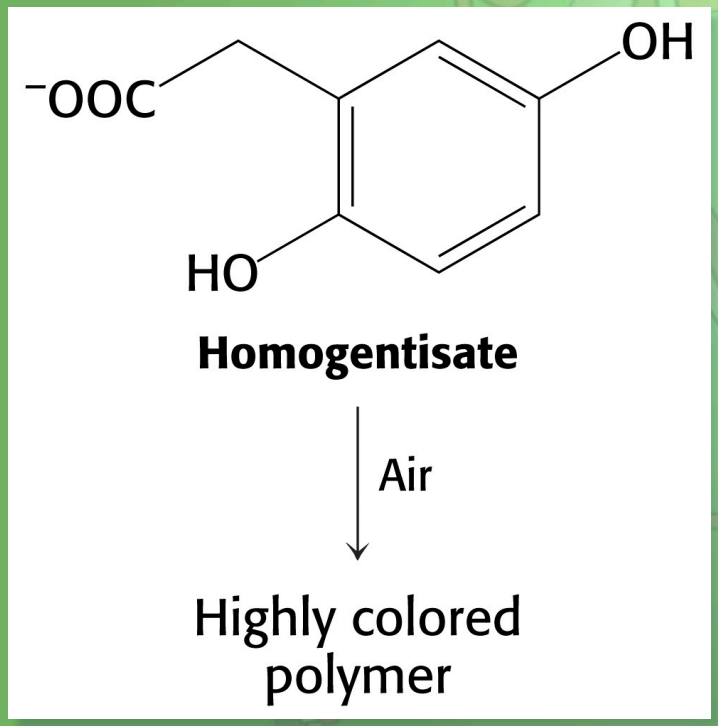
Tyrosine related disorders



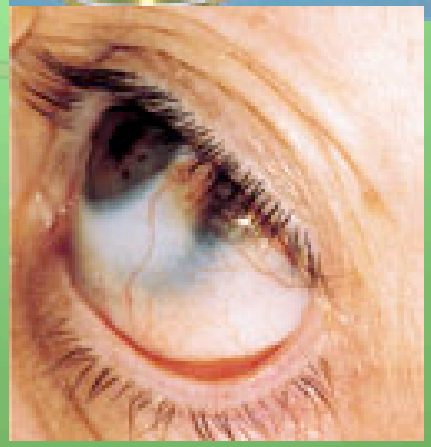
6. Inborn Errors in Metabolism

Alcaptonuria

- Absence of homogentisate oxidase activity
  http://www.emedicine.com/ped/topic64.htm



urine

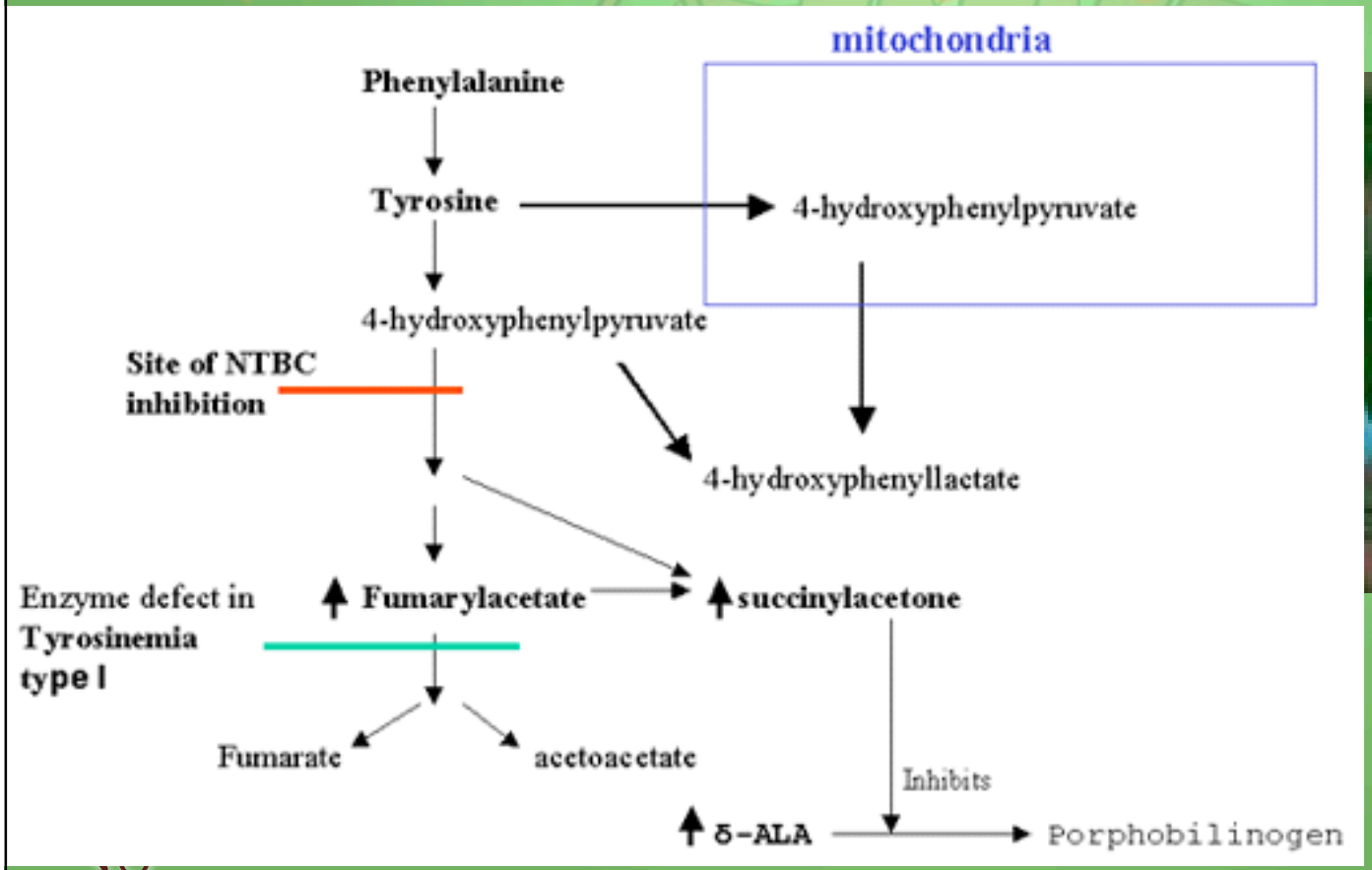


sclera

6. Inborn Errors in Metabolism

Tyrosinemia

- Absence of activity of fumarylacetoacetase
  http://www.childrenshospital.org/newenglandconsortium/NBS/d

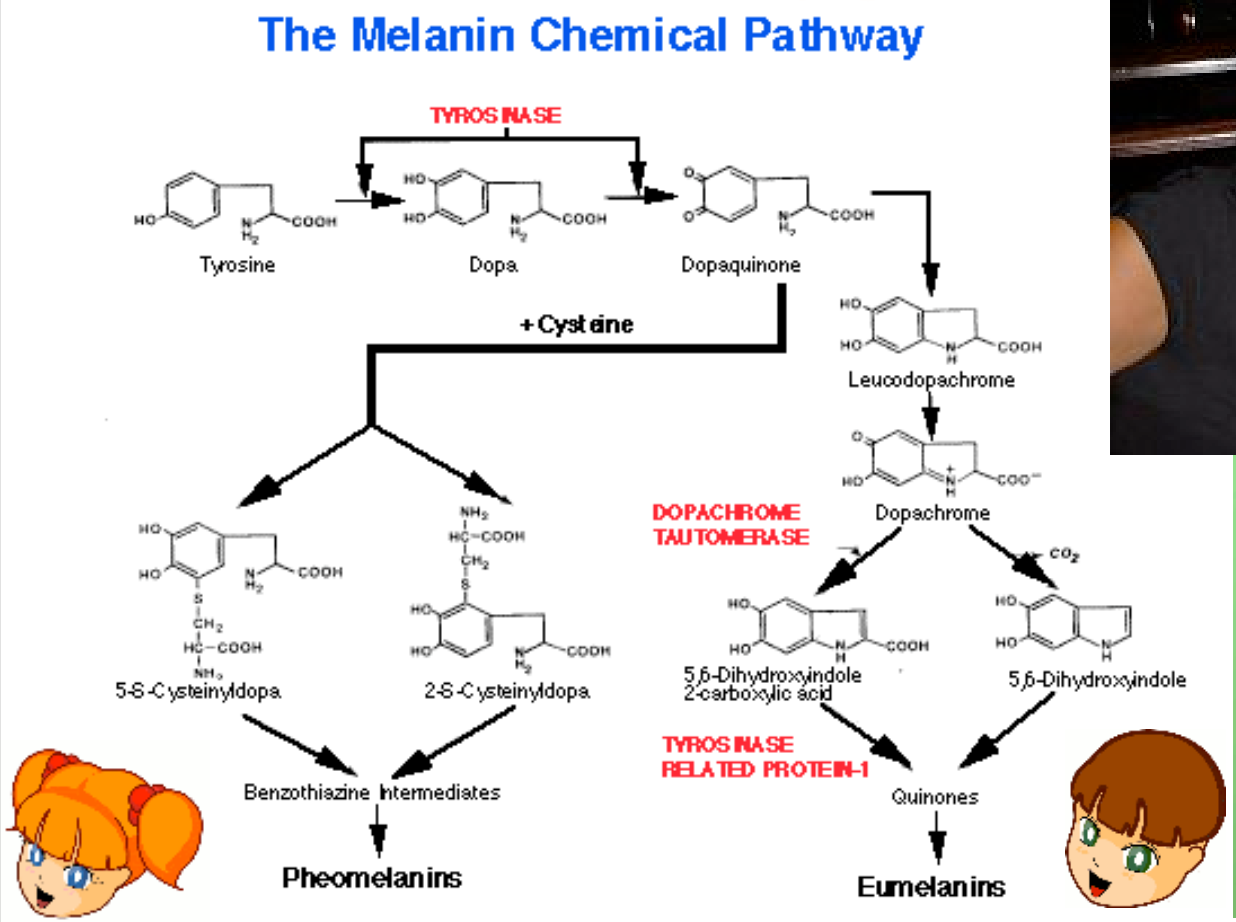


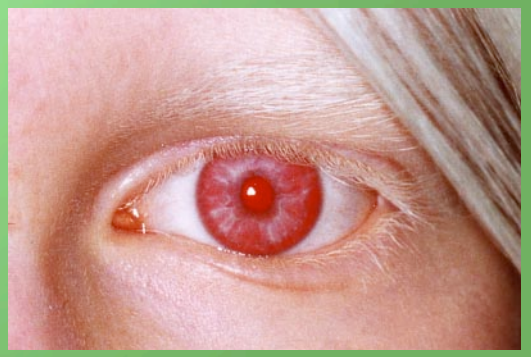
http://www.myspecialdiet.com/Shop/Search.aspx?t=department&i=14

6. Inborn Errors in Metabolism

Albinism

- Absence of melanin pigment





http://home.clara.net/knowlton/family/Albinism/bianca.htm

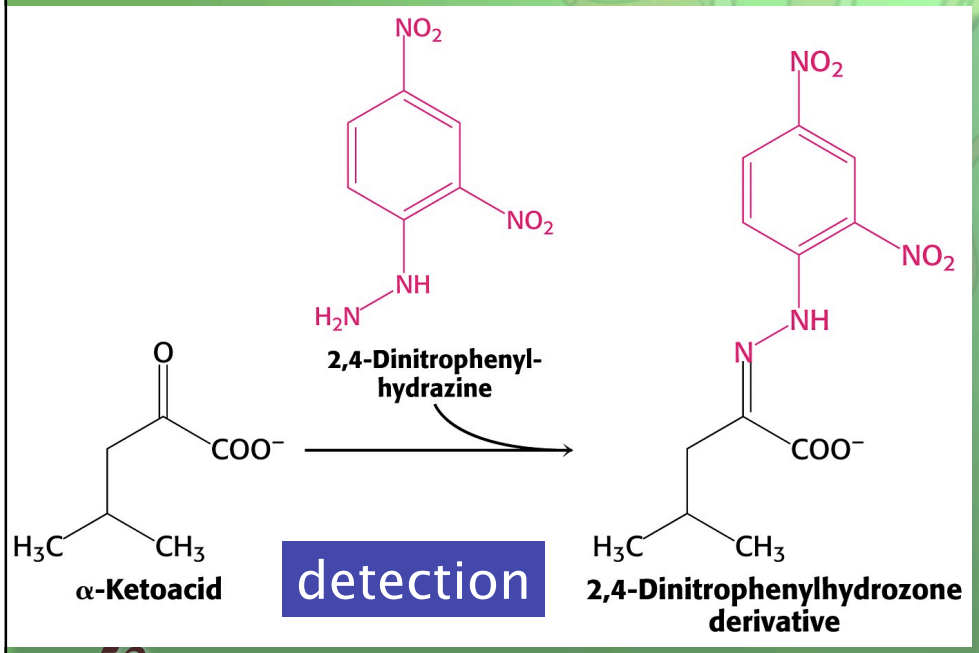
http://www.nlm.nih.gov/medlineplus/ency/article/001166.htm

6. Inborn Errors in Metabolism

http://www.nlm.nih.gov/medlineplus/ency/article/000373.htm

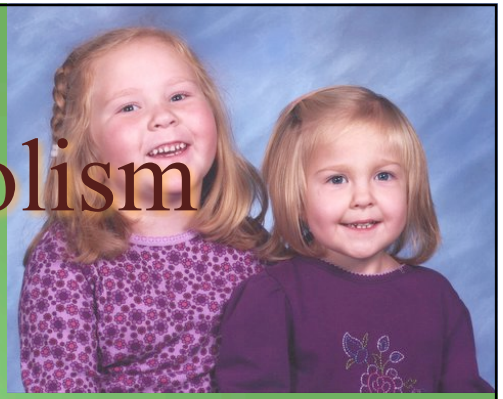
Maple syrup urine disease

- Lack of branch-chain dehydrogenase activity
- Leads to elevation of α-keto banched-chain acids (branched-chain keto aciduria)



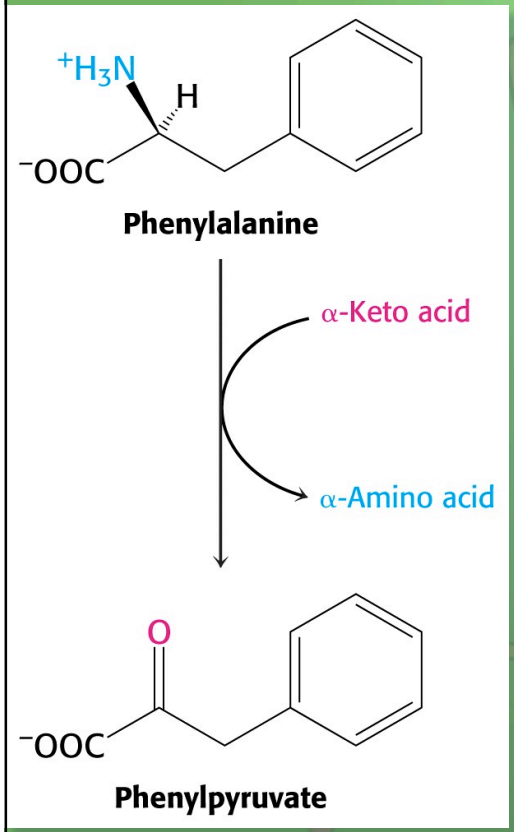
An isoleucine-, leucine- and valine-free unflavored powder

6. Inborn Errors in Metabolism



Phenylketonuria

- Absence of phenylalanine hydroxylase activity



http://www.nlm.nih.gov/medlineplus/ency/article/001166.htm

6. Inborn Errors in Metabolism

TABLE 23.3 Inborn errors of amino acid metabolism

Disease	Enzyme deficiency	Symptoms
Citrullinema	Arginosuccinate lyase	Lethergy, siezures, reduced muscle tension
Tyrosinemia	Various enzymes of tyrosine degradation	Weakness, self-mutilation, liver damage, mental retardation
Albinism	Tyrosinase	Absence of pigmentation
Homocystinuria	Cystathionine β-synthase	Scoliosis, muscle weakness, mental retardation, thin blond hair
Hyperlysinemia	α-Aminoadipic semialdehyde dehydrogenase	Seizures, mental retardation, lack of muscle tone, ataxia