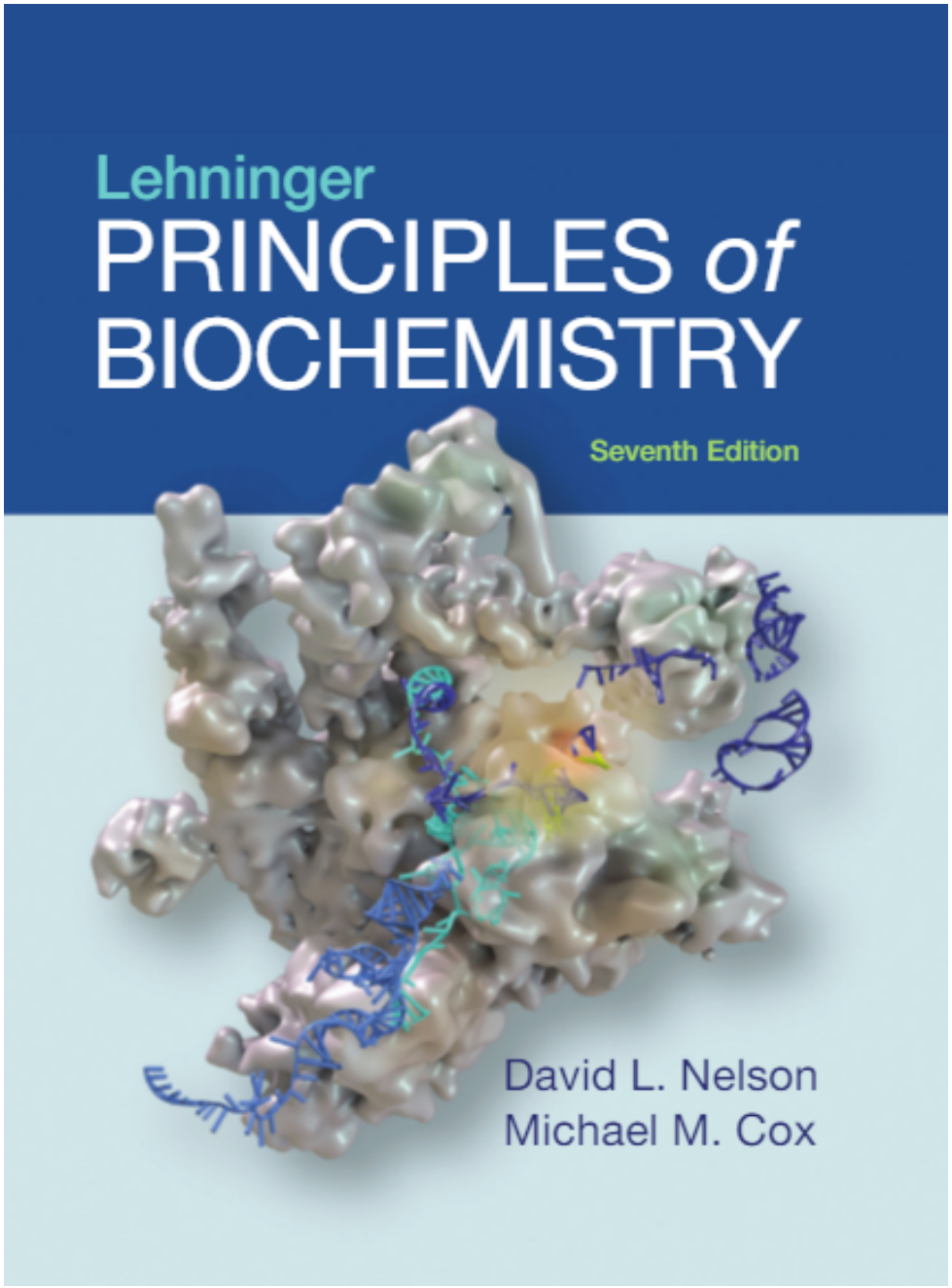
18| Amino Acid Oxidation and the Production of Urea



CHAPTER 18
Amino Acid Oxidation and the Production of Urea

Learning goals:

- How proteins are digested in animals
- How amino acids are oxidized for energy in animals
- How urea is made and excreted

The Use of Amino Acids as Fuel Varies Greatly by Organism

- About 90% of energy needs of carnivores can be met by amino acids immediately after a meal.
- Microorganisms scavenge amino acids from their environment for fuel when needed.
- Only a small fraction of energy needs of herbivores are met by amino acids.
- Plants do not use amino acids as a fuel source but can degrade amino acids to form other metabolites.

Metabolic Circumstances of Amino Acid Oxidation

- Leftover amino acids from normal protein turnover (e.g., proteolysis and regeneration of proteins)
- Dietary amino acids that exceed body's protein synthesis needs
- Proteins in the body can be broken down to supply amino acids for energy when carbohydrates are scarce (starvation, diabetes mellitus).

Dietary Proteins Are Enzymatically Hydrolyzed into Amino Acids

- Pepsin cuts protein into peptides in the stomach.
- Trypsin and chymotrypsin cut proteins and larger peptides into smaller peptides in the small intestine.
- Aminopeptidase and carboxypeptidases A and B degrade peptides into amino acids in the small intestine.

Dietary Protein Is Enzymatically Degraded Through the Digestive Tract

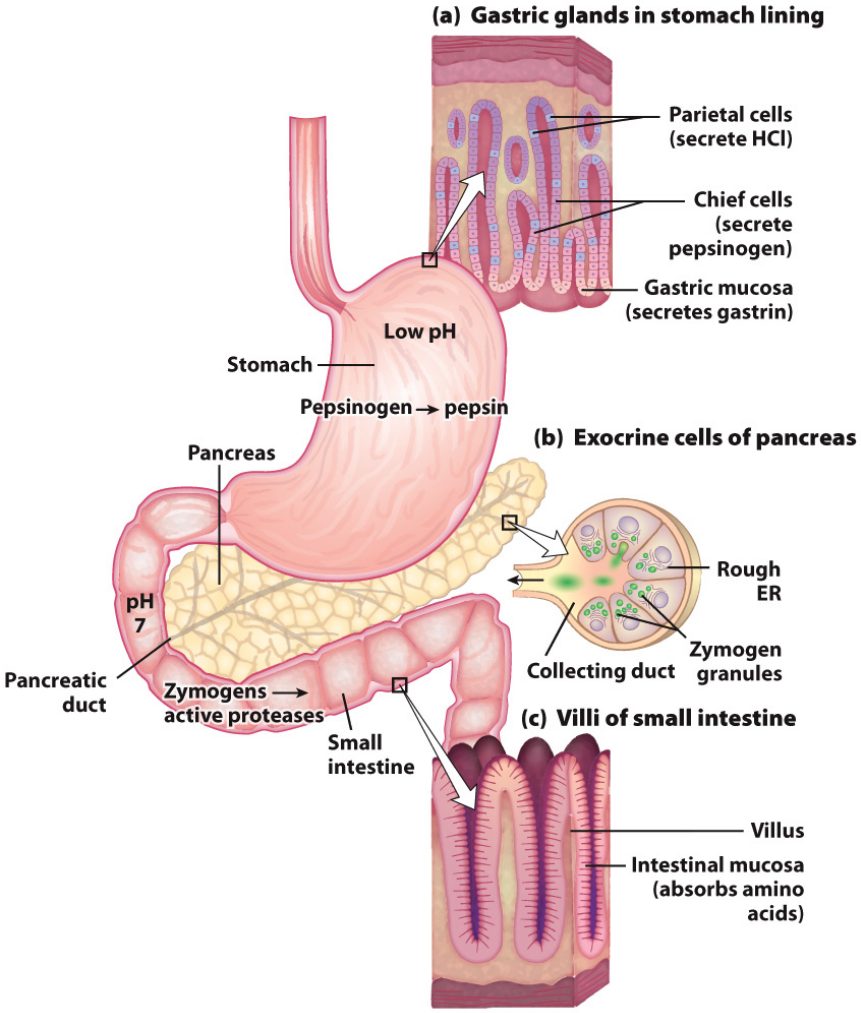


Figure 18-3
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Overview of Amino Acid Catabolism

Once broken down to amino acid, all types of protein are treated the same way dependent on the organism's energy needs:

1. Recycled into new proteins
2. Oxidized for energy
   - removal of amino group (urea cycle)
   - entry into central metabolism (glycolysis, citric acid cycle)

Overview of Amino Acid Catabolism

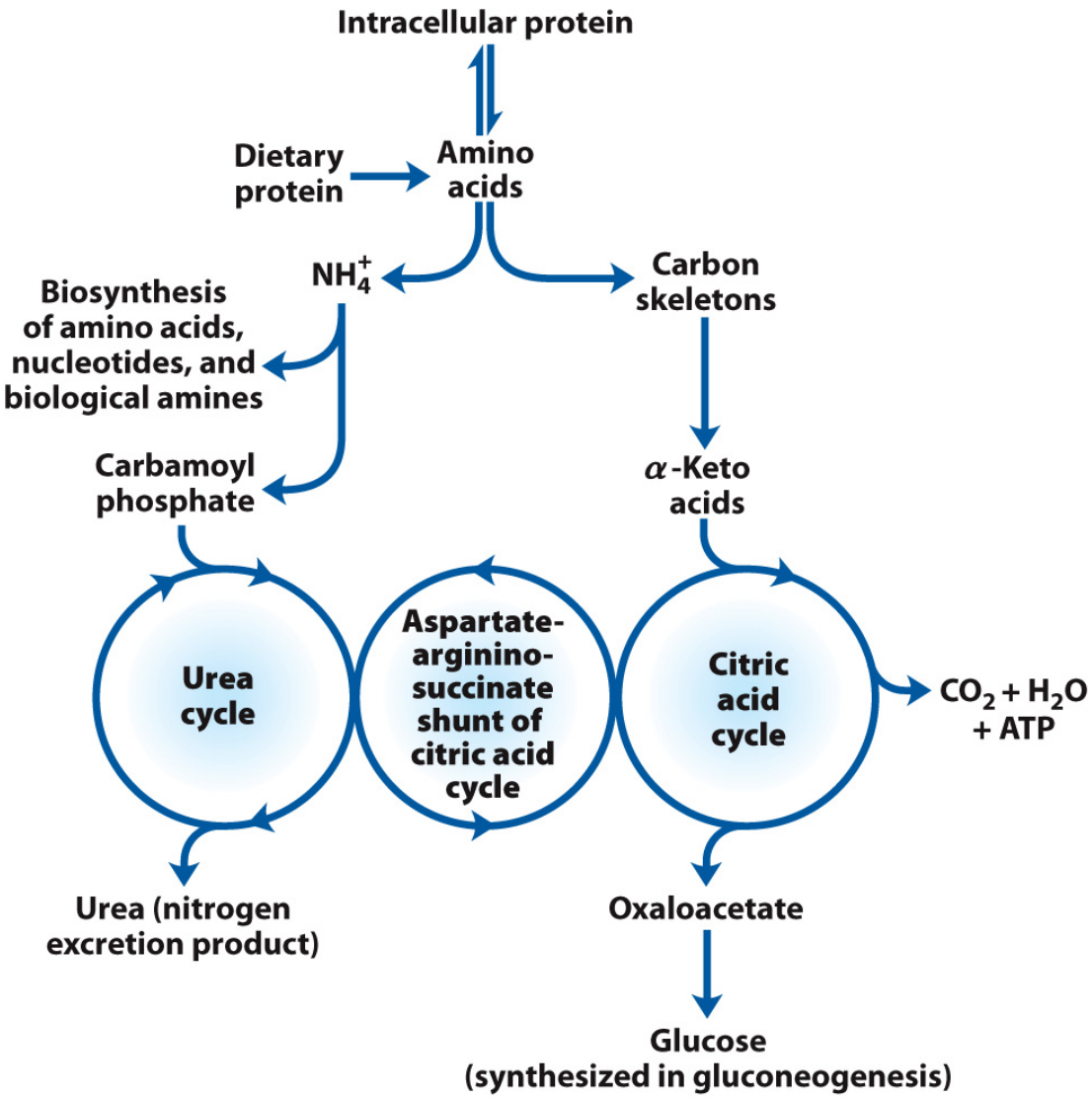

Figure 18-1
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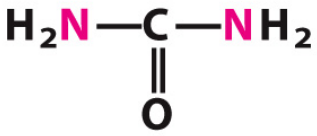
Fates of Nitrogen in Organisms

- Plants conserve almost all the nitrogen.
- Many aquatic vertebrates release ammonia to their environment.
  - passive diffusion from epithelial cells
  - active transport via gills
- Many terrestrial vertebrates and sharks excrete nitrogen in the form of urea.
  - Urea is far less toxic that ammonia.
  - Urea has very high solubility.
- Some animals such as birds and reptiles excrete nitrogen as uric acid.
  - Uric acid is rather insoluble.
  - Excretion as paste allows the animals to conserve water.
- Humans and great apes excrete both urea (from amino acids) and uric acid (from purines).

Excretory Forms of Nitrogen

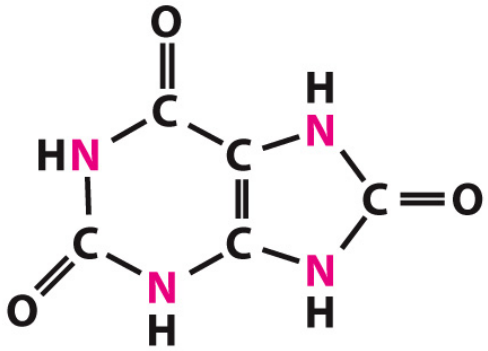
Ammonia (as ammonium ion)



Urea

Ammonotelic animals: most aquatic vertebrates, such as bony fishes and the larvae of amphibia

Ureotelic animals: many terrestrial vertebrates; also sharks



Uric acid

Uricotelic animals: birds, reptiles

Figure 18-2b
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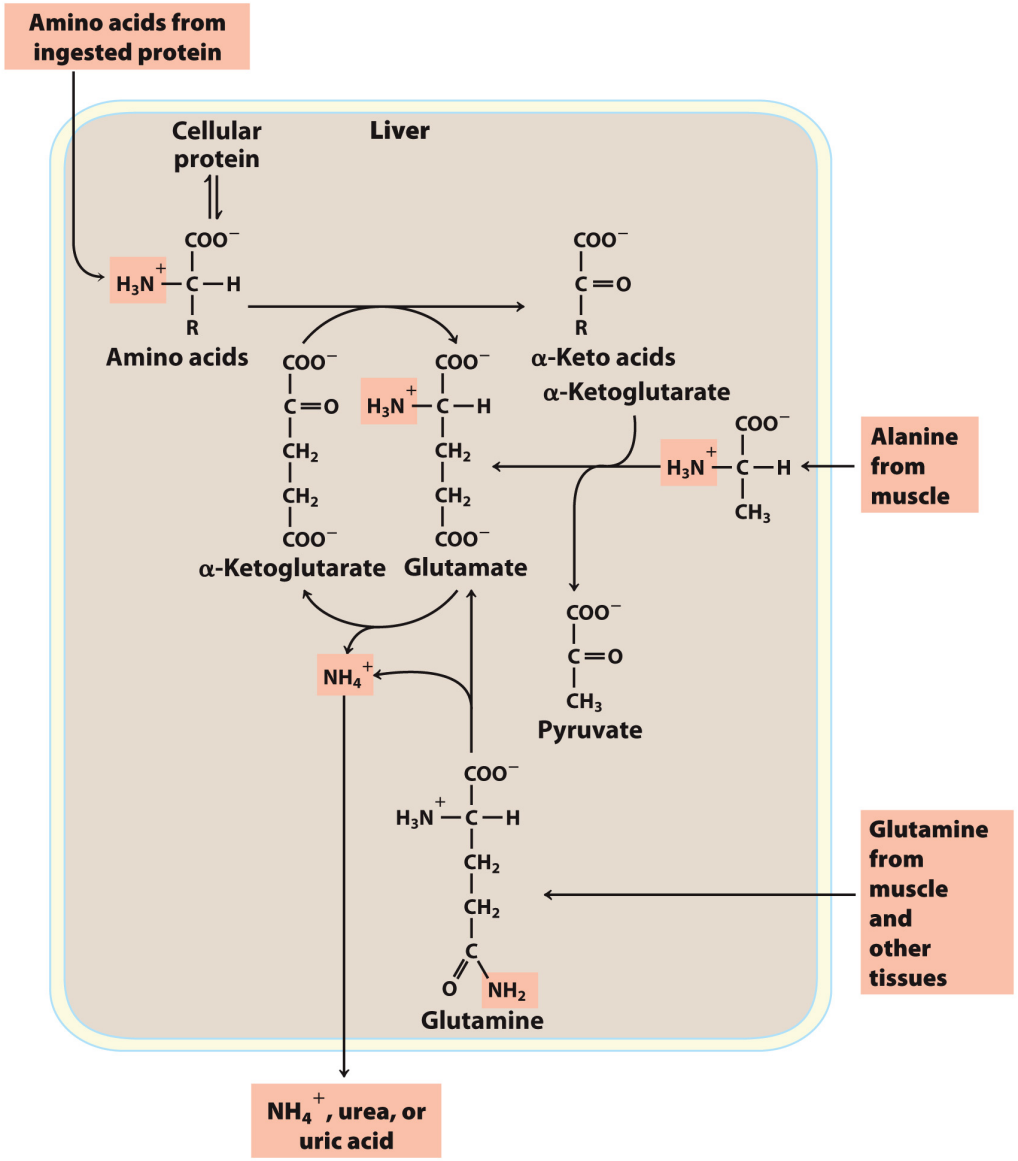
Step 1: Removal of the Amino Group



- Release of free ammonia is toxic.
- Ammonia is captured by a series of transaminations.
- Transaminations allow transfer of an amine to a common metabolite (e.g., α-ketoglutarate) and generate a traffickable amino acid (e.g., glutamate).

Figure 18-2a
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Enzymatic Transamination

- Catalyzed by aminotransferases
- Uses the pyridoxal phosphate cofactor
- Typically, α-ketoglutarate accepts amino groups.
  - Transfer of one amine to α-ketoglutarate results in synthesis of glutamate (e.g., transamination).
  - Transfer of a second amine results in synthesis of glutamine (e.g., glutamine synthetase).
- L-Glutamine acts as a temporary storage of nitrogen.
- L-Glutamine can donate the amino group when needed for amino acid biosynthesis.

Enzymatic Transamination to Glutamate

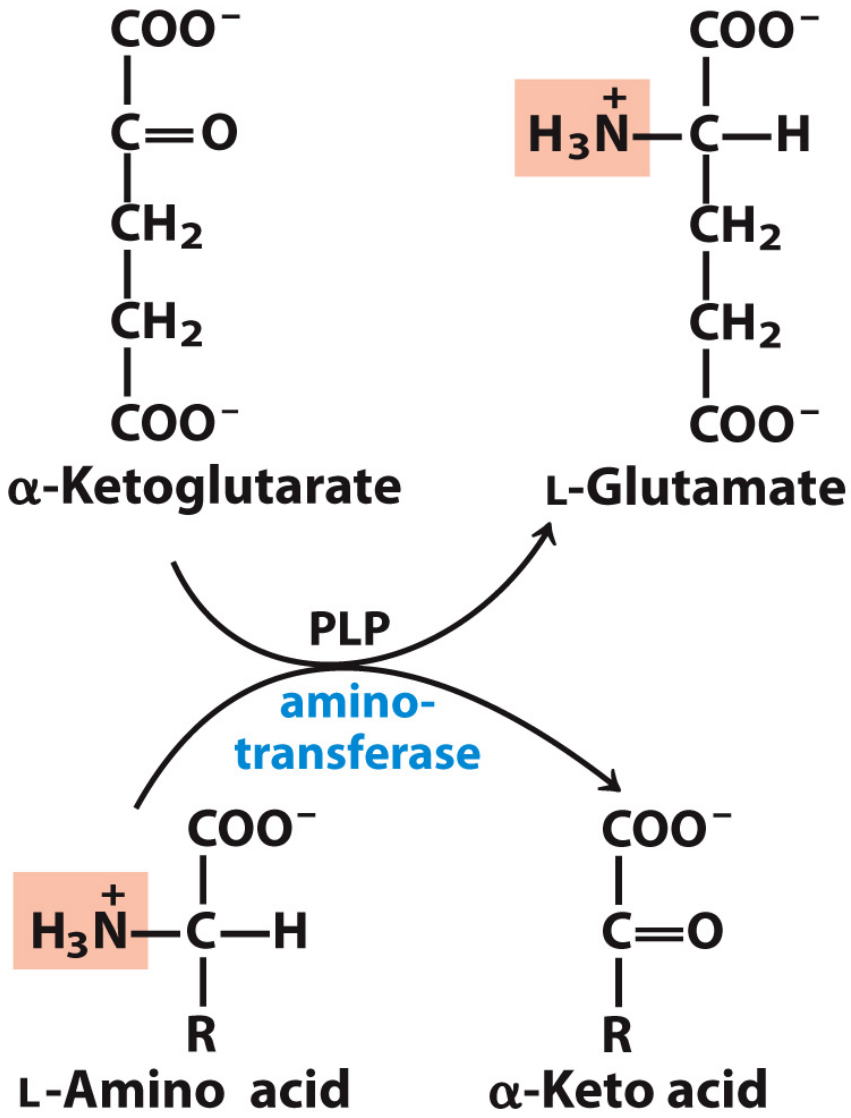

Figure 18-4
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Ammonia Is Safely Transported in the Bloodstream as Glutamine

Excess glutamine is processed in the intestines, kidneys, and liver.

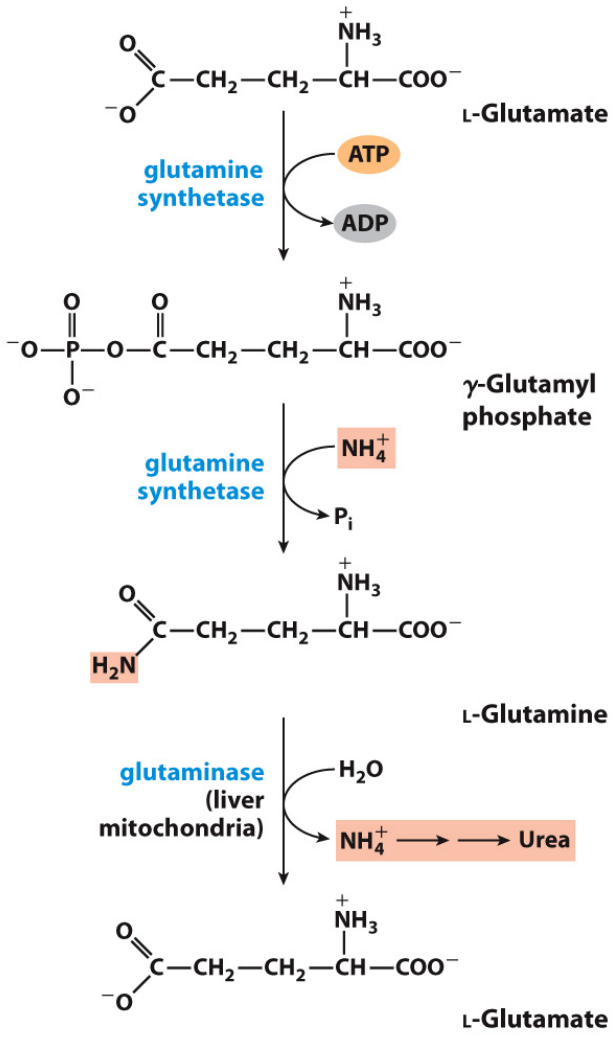

Figure 18-8
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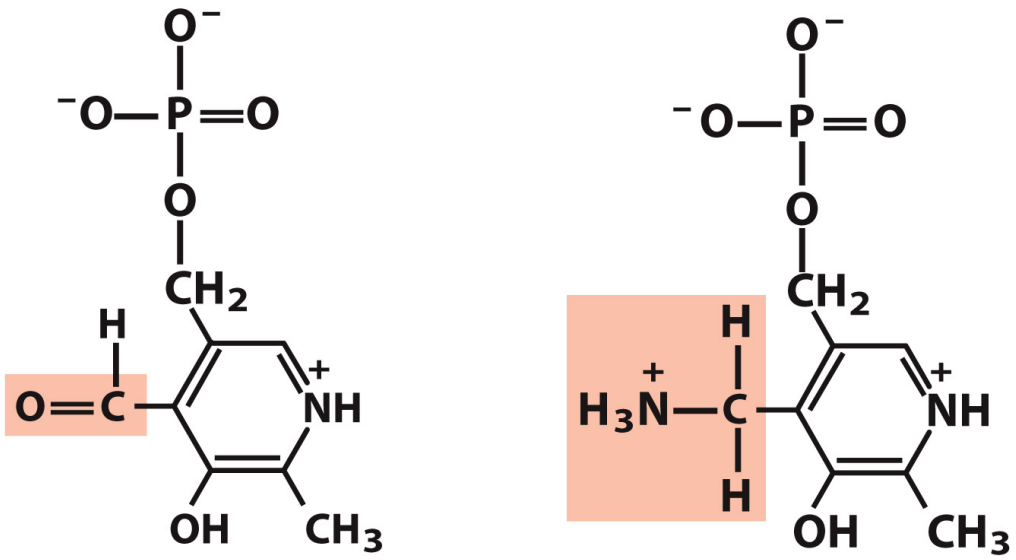
Structure of Pyridoxal Phosphate and Pyridoxamine Phosphate

- Intermediate, enzyme-bound carrier of amino groups
- Aldehyde form can react reversibly with amino groups.
- Aminated form can react reversibly with carbonyl groups.



Pyridoxal phosphate (PLP)

Pyridoxamine phosphate

Figure 18-5a
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Pyridoxal Phosphate Is Covalently Linked to the Enzyme in the Resting Enzyme

- By an internal aldimine
- The linkage is made via a nucleophilic attack of the amino group of an active-site lysine.

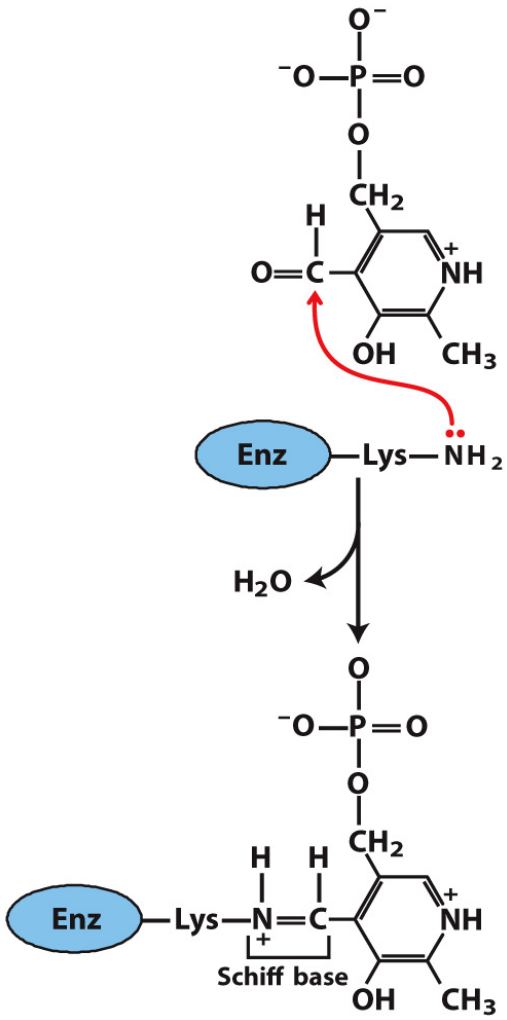

Figure 18-5b
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Internal Aldimine in Aminotransferases

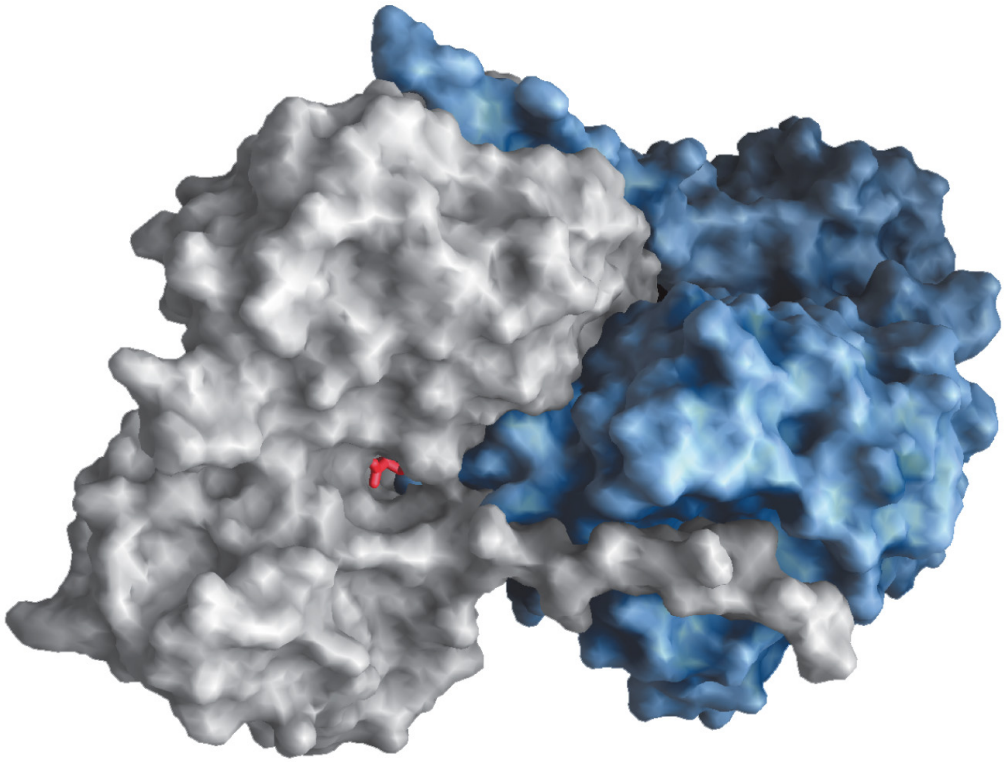

Figure 18-5c
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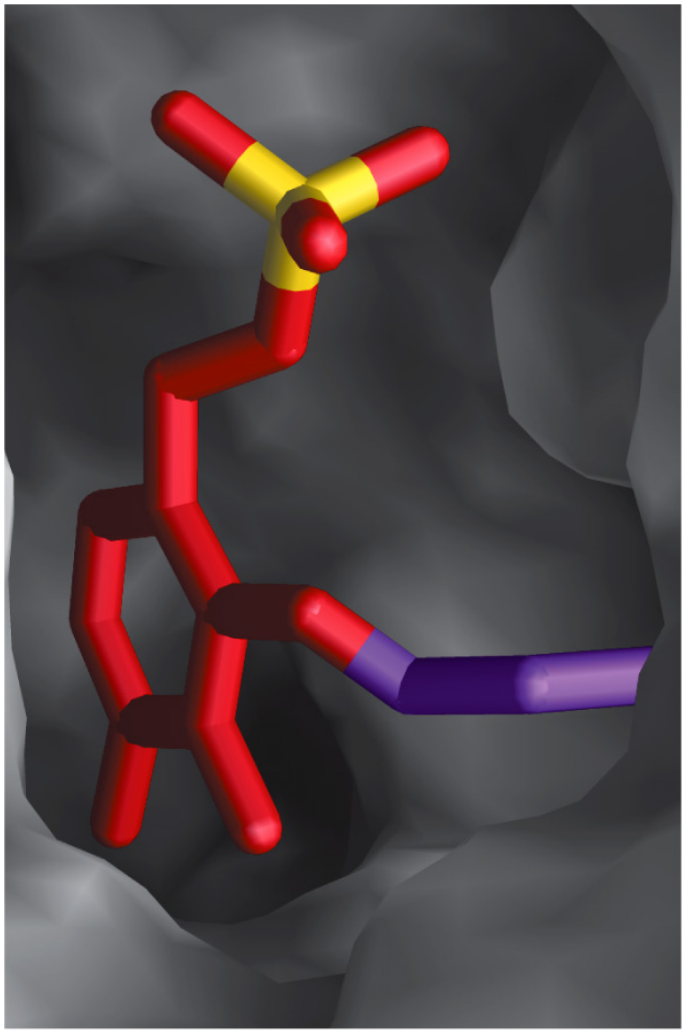

(d)

Figure 18-5de
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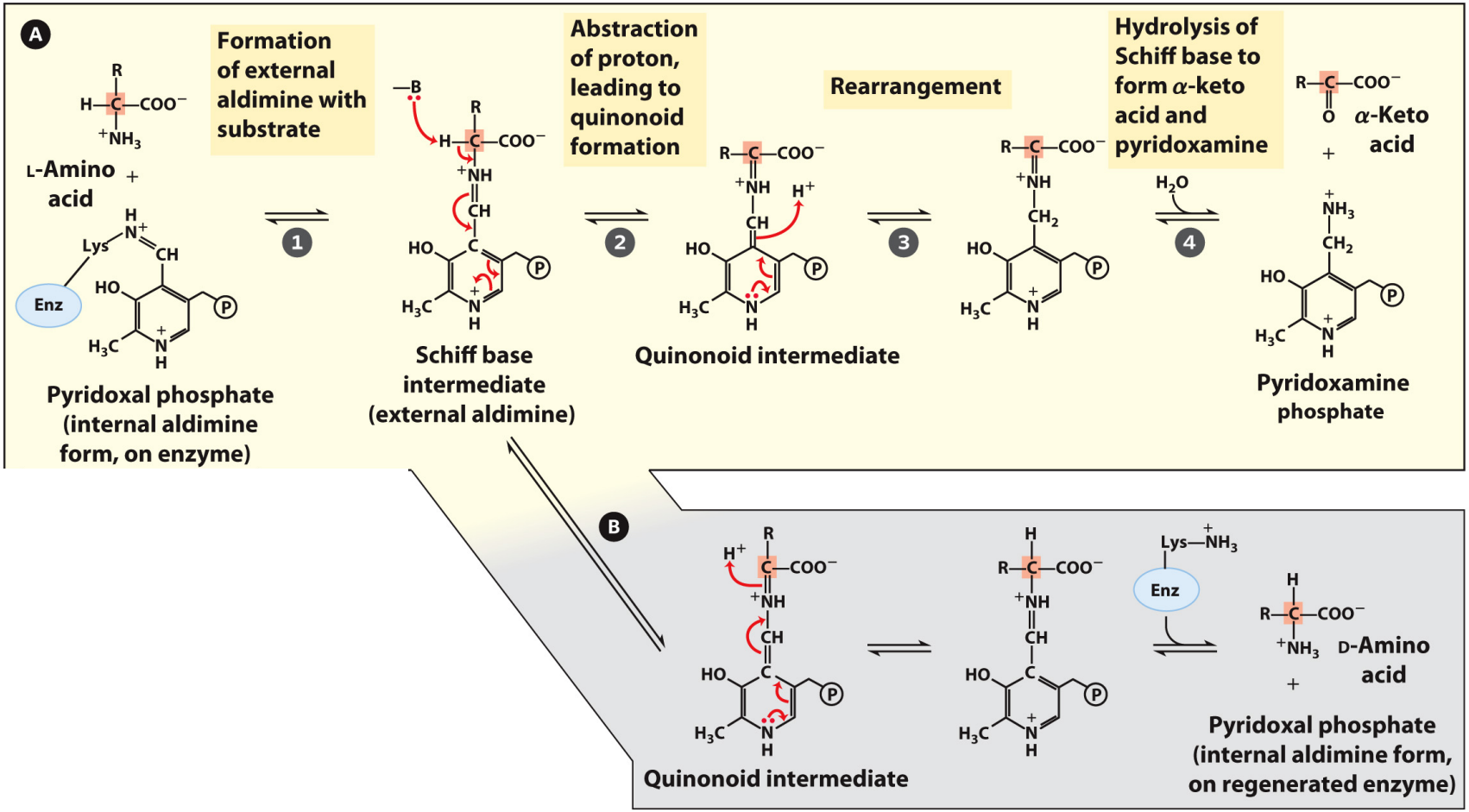
PLP Also Catalyzes Racemization of Amino Acids

Deamination



Racemization

PLP Also Catalyzes Decarboxylation of Amino Acids

Deamination

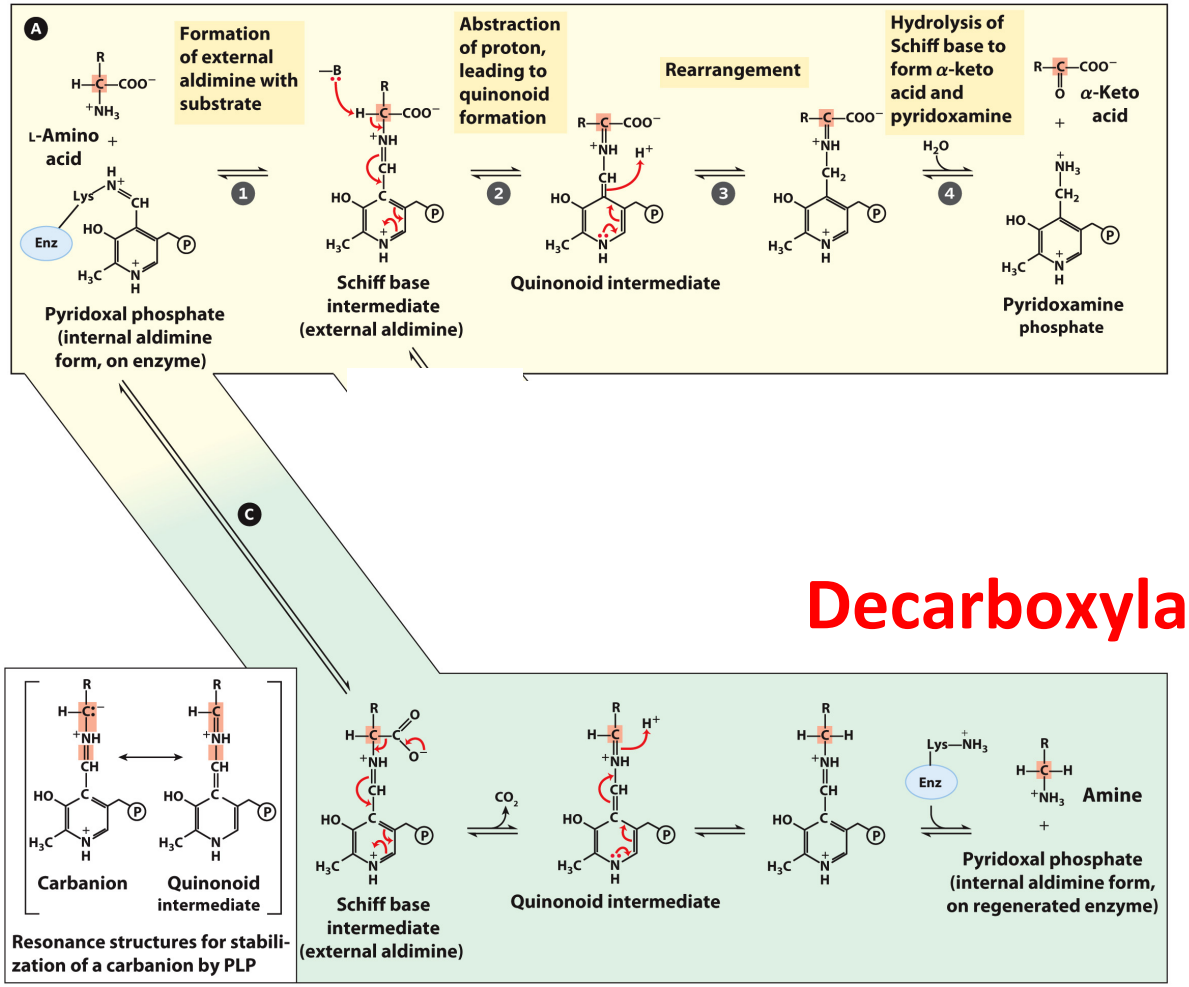


Figure 18-6
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Ammonia Collected in Glutamate Is Removed by Glutamate Dehydrogenase

- Oxidative deamination occurs within mitochondrial matrix.
- Can use either NAD^+ or $NADP^+$ as electron acceptor
- Ammonia is processed into urea for excretion.
- Pathway for ammonia excretion; transdeamination = transamination + oxidative deamination

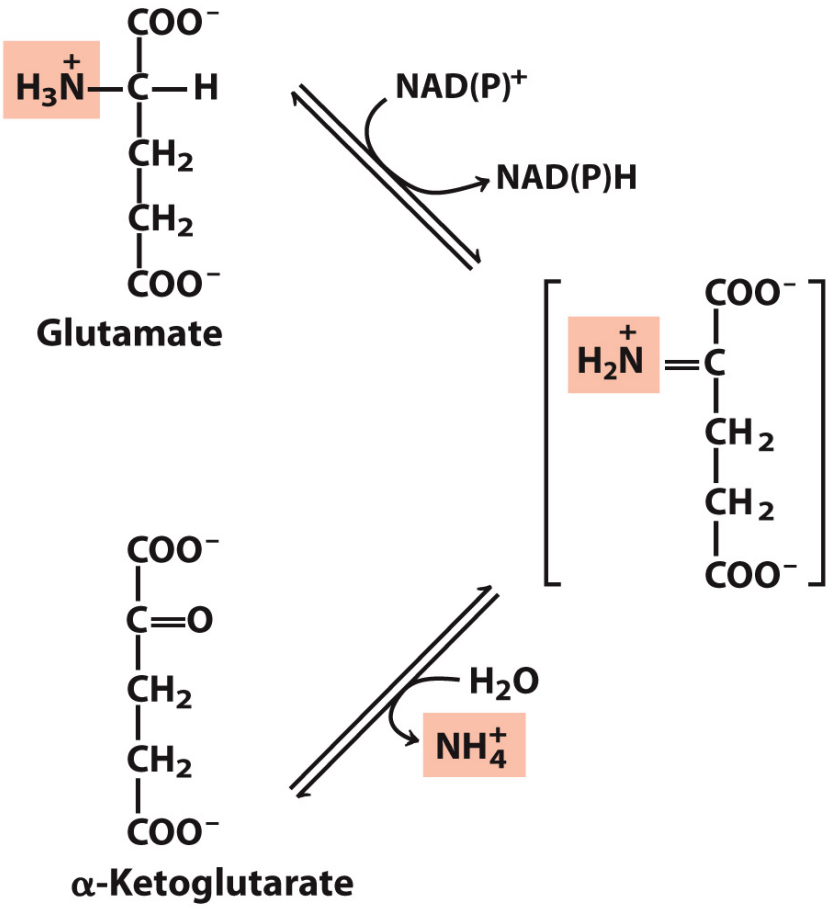

Figure 18-7
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The Glucose-Alanine Cycle

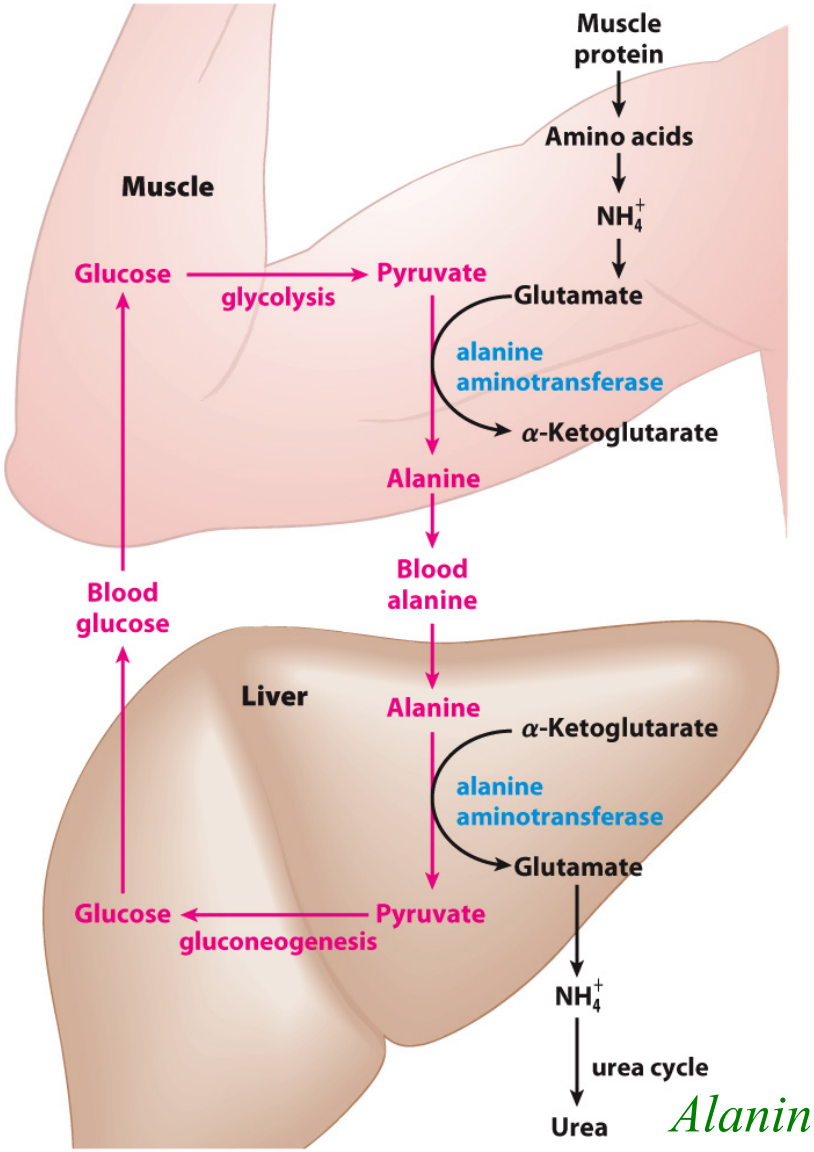

Figure 18-9
Lehninger Principles of Biochemistry, Seventh Edition

- Vigorously working muscles operate nearly anaerobically and rely on glycolysis for energy.
- Glycolysis yields pyruvate.
  – If not eliminated, lactic acid will build up.
- This pyruvate can be converted to alanine for transport into the liver.

Alanine is a carrier of ammonia and the carbon skeleton of pyruvate from skeletal muscle to liver.

Excess Glutamate Is Metabolized in the Mitochondria of Hepatocytes

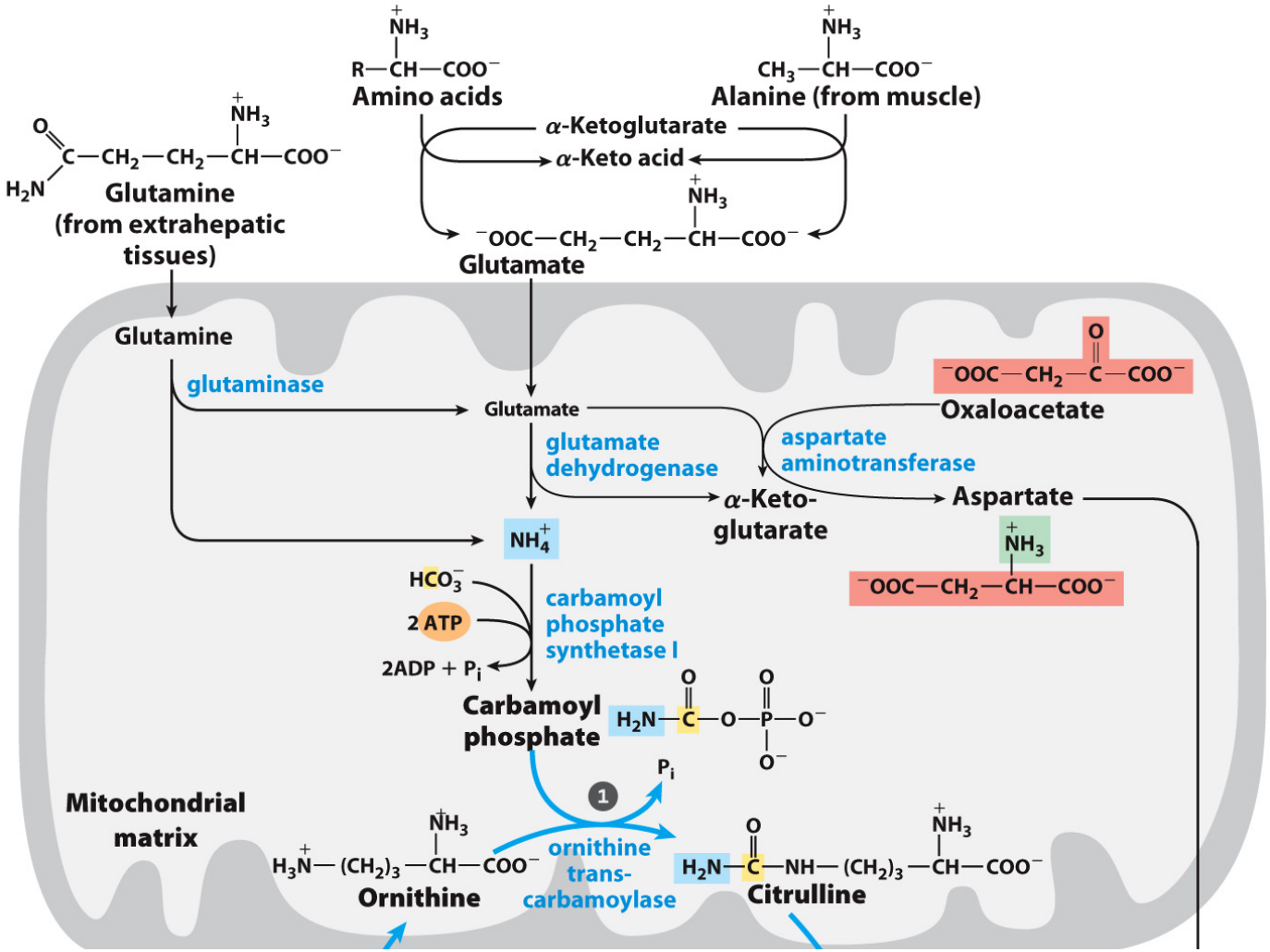

Figure 18-10
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Ammonia Is Recaptured via Synthesis of Carbamoyl Phosphate

- The first nitrogen-acquiring reaction of the urea cycle

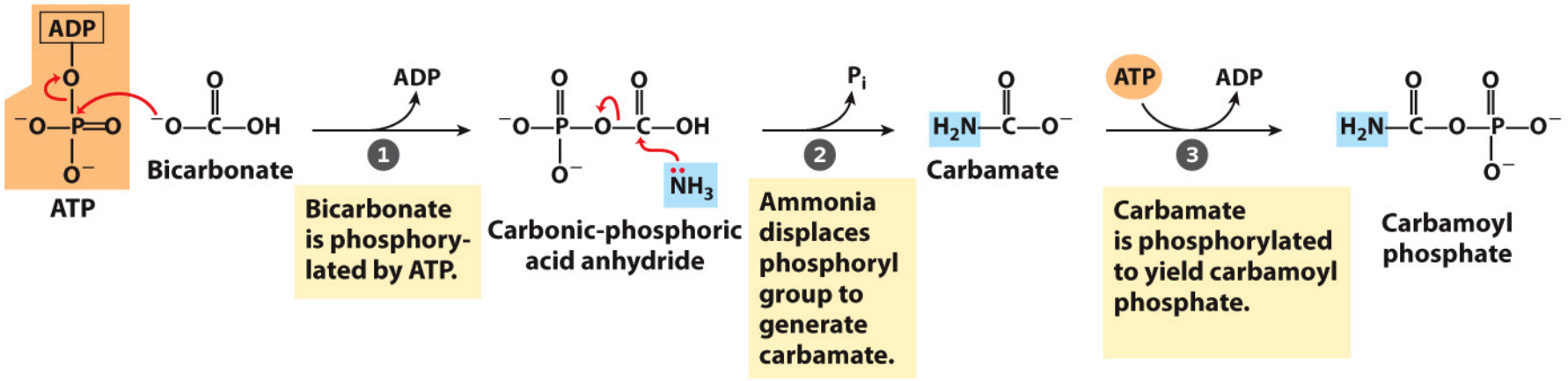

Figure 18-11a
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Nitrogen From Carbamoyl Phosphate Enters the Urea Cycle

- The majority of reactions within the urea cycle occur within the cytosol.
- In order to move to the cytosol, **carbamoyl phosphate must condense with ornithine to create citrullene**. This reaction releases the phosphate of carbamoyl phosphate into the mitochondrial matrix. **Citrullene** can then be transported to the cytosol.

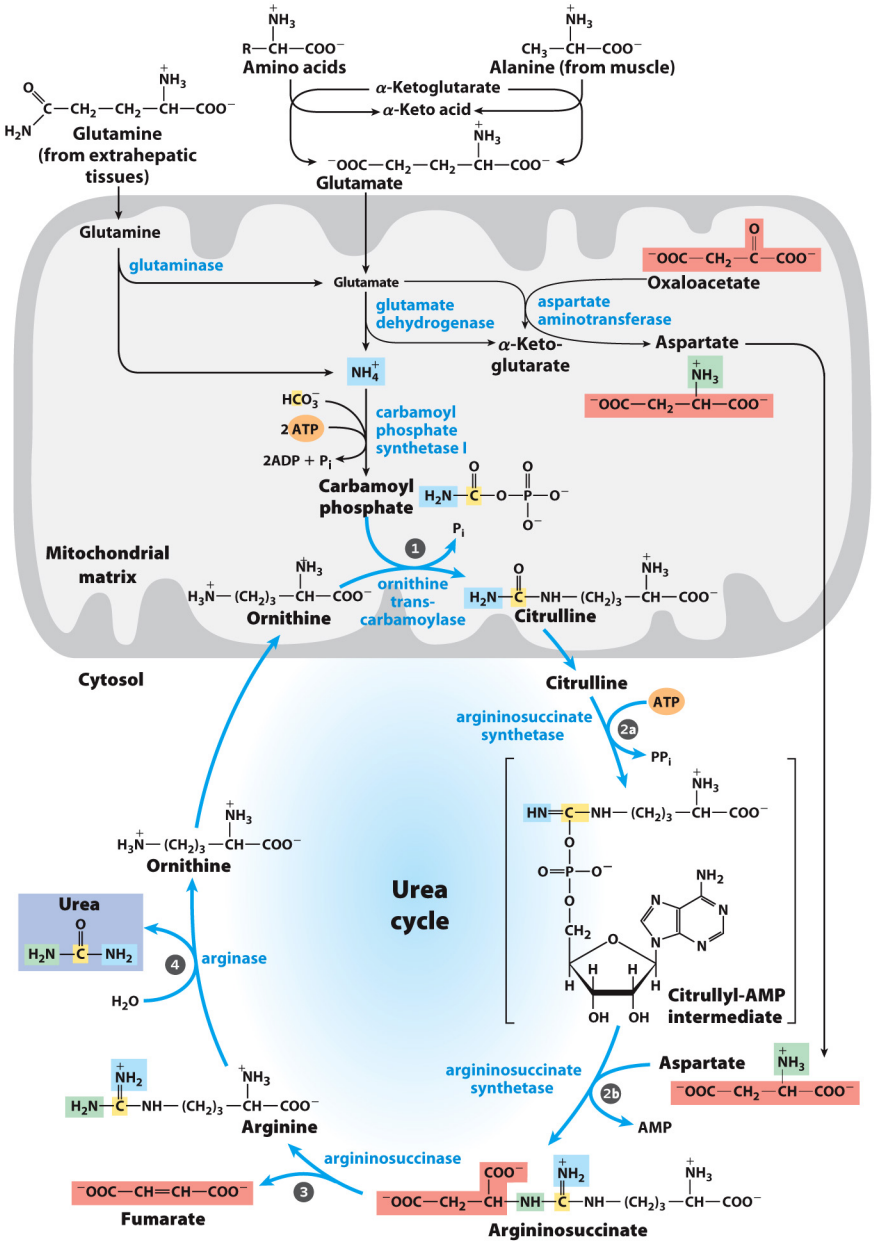

Figure 18-10
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The Reactions in the Urea Cycle

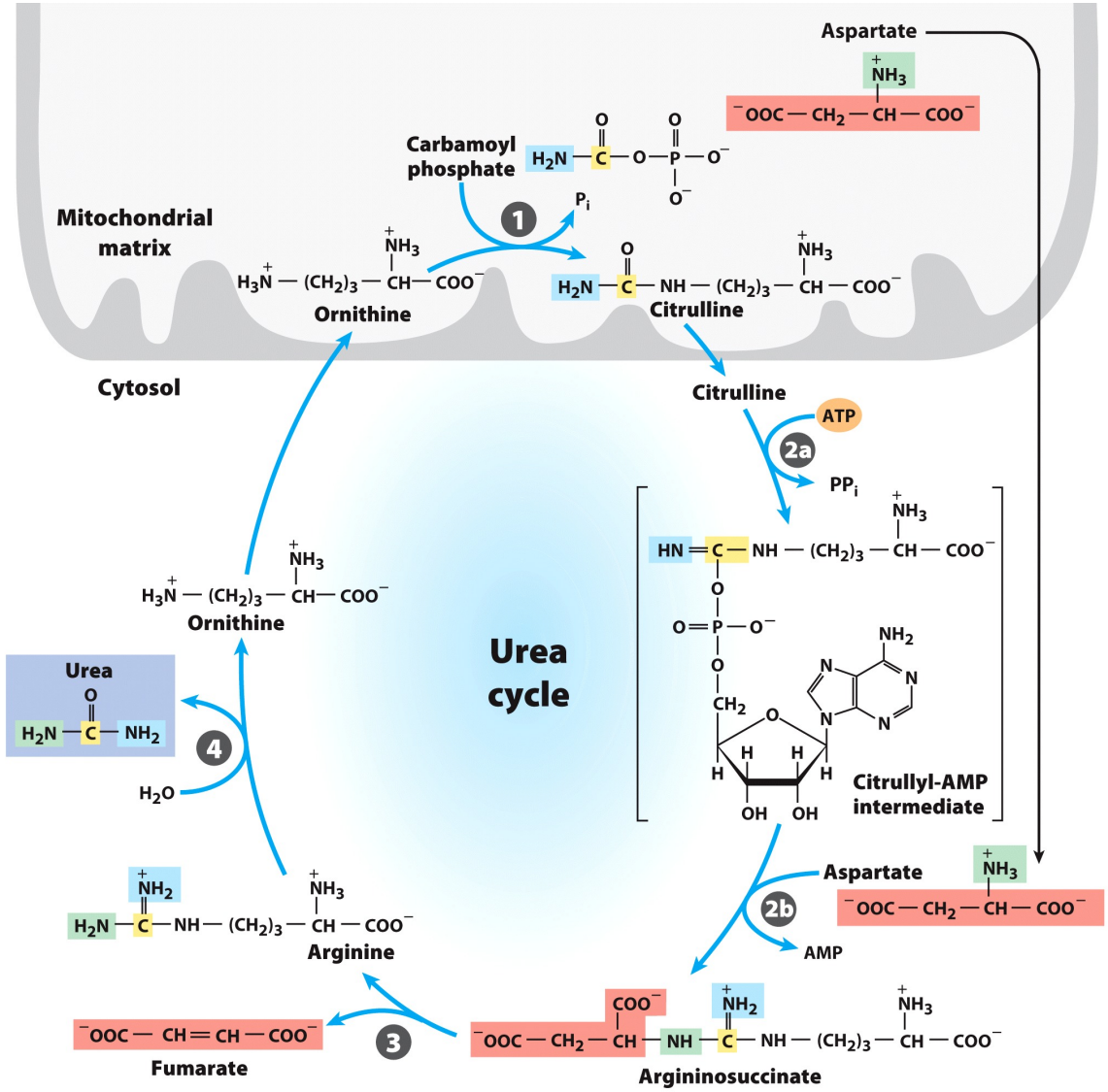

Figure 18-10 part 2
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Entry of Aspartate into the Urea Cycle

This is the second nitrogen-acquiring reaction.

In the cytosol, citrullene reacts with ATP to produce citrullyl-AMP.

AMP acts as a good leaving group, as aspartate attracts the imide carbon to produce argininosuccinate.

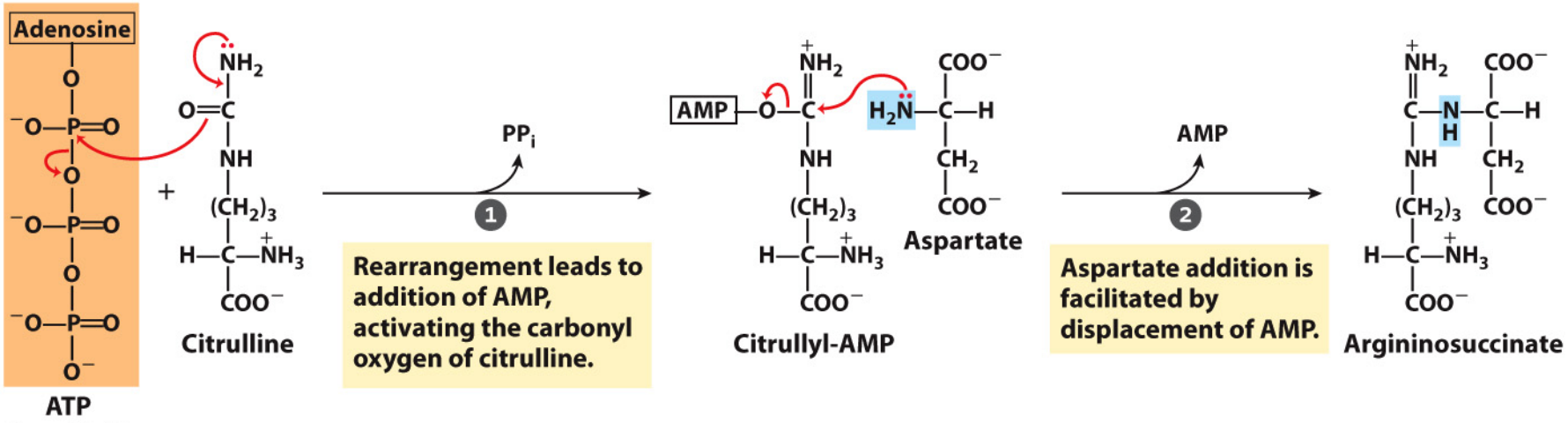

Figure 18-11b

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Release of Urea and Regeneration of Ornithine

- Argininosuccinase cleaves fumarate from argininosuccinate, resulting in arginine.
- Arginine can also enter the urea cycle at this point.
- Arginase cleaves both nitrogens added in the urea cycle from arginine, resulting in free urea.
- Ornithine is able to serve as a substrate for the next round of the cycle.

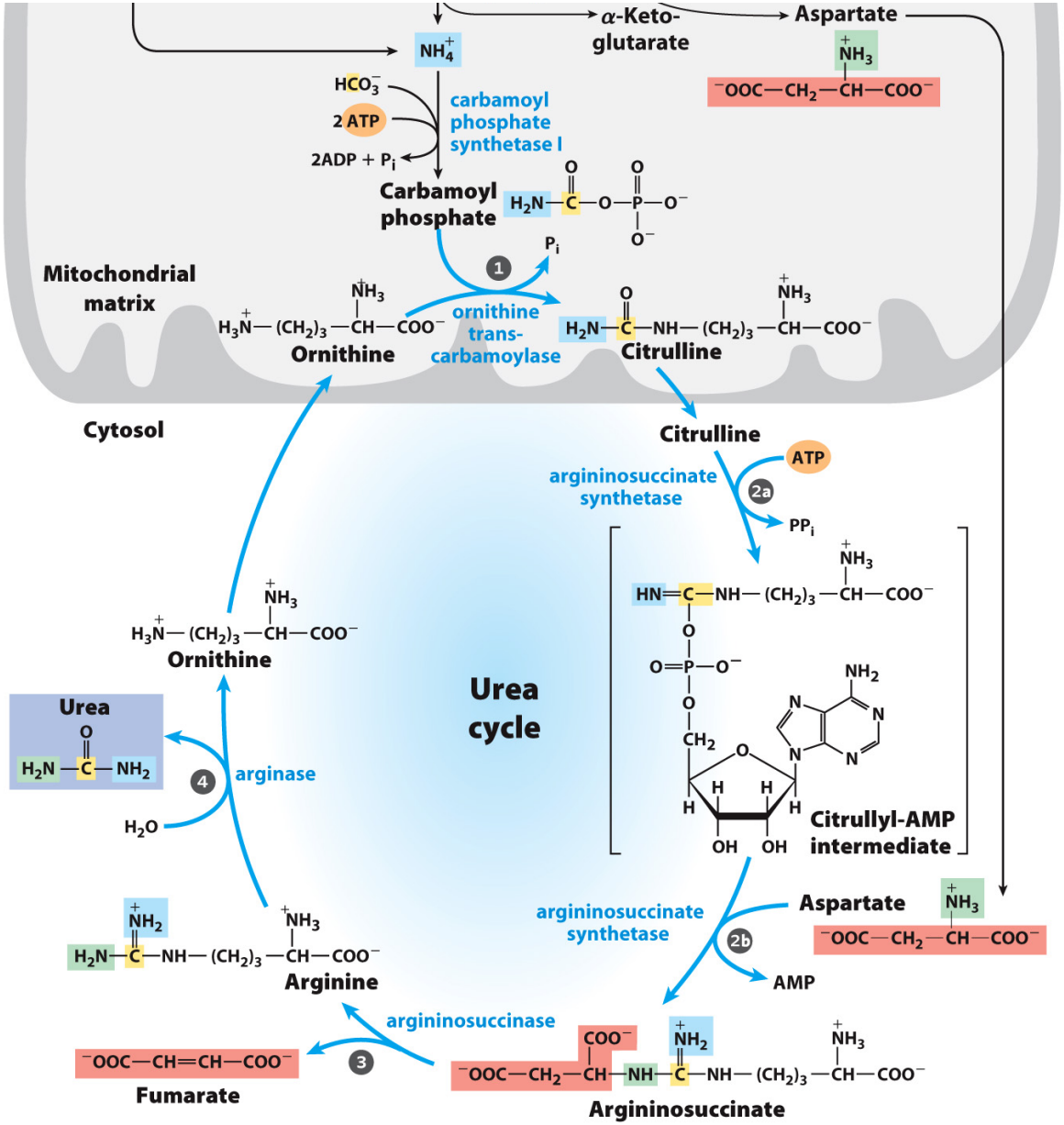

Figure 18-10
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Aspartate–Arginosuccinate Shunt Links Urea Cycle and Citric Acid Cycle

The "Krebs bicycle"

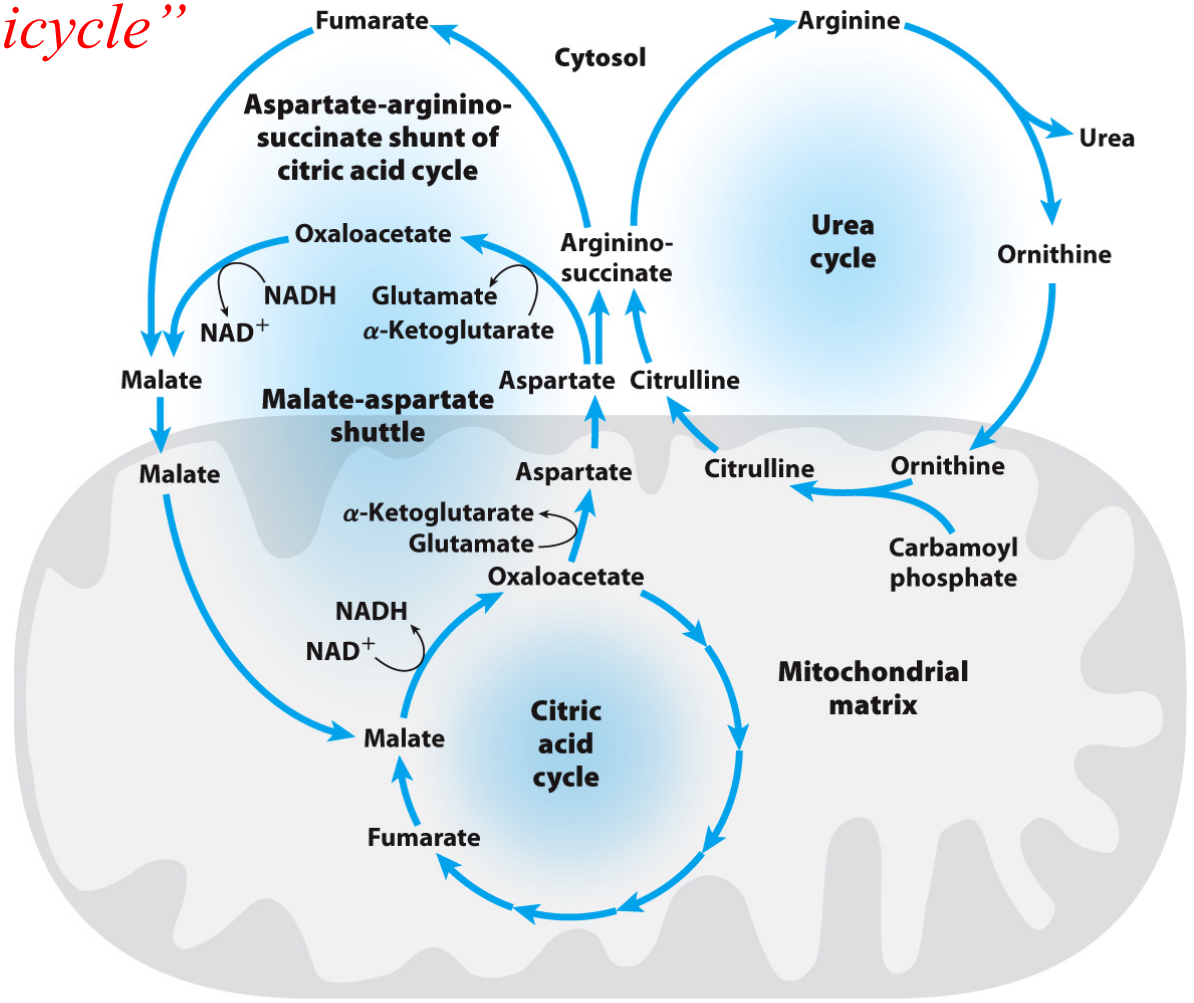

Figure 18-12
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Regulation of the Urea Cycle

- Carbamoyl phosphate synthase I is activated by *N*-acetylglutamate.
- Formed by *N*-acetylglutamate synthase
  - when glutatmate and acetyl-CoA concentrations are high
  - activated by arginine
- Expression of urea cycle enzymes increases when needed.
  - high-protein diet
  - starvation, when protein is being broken down for energy

Regulation of the Urea Cycle

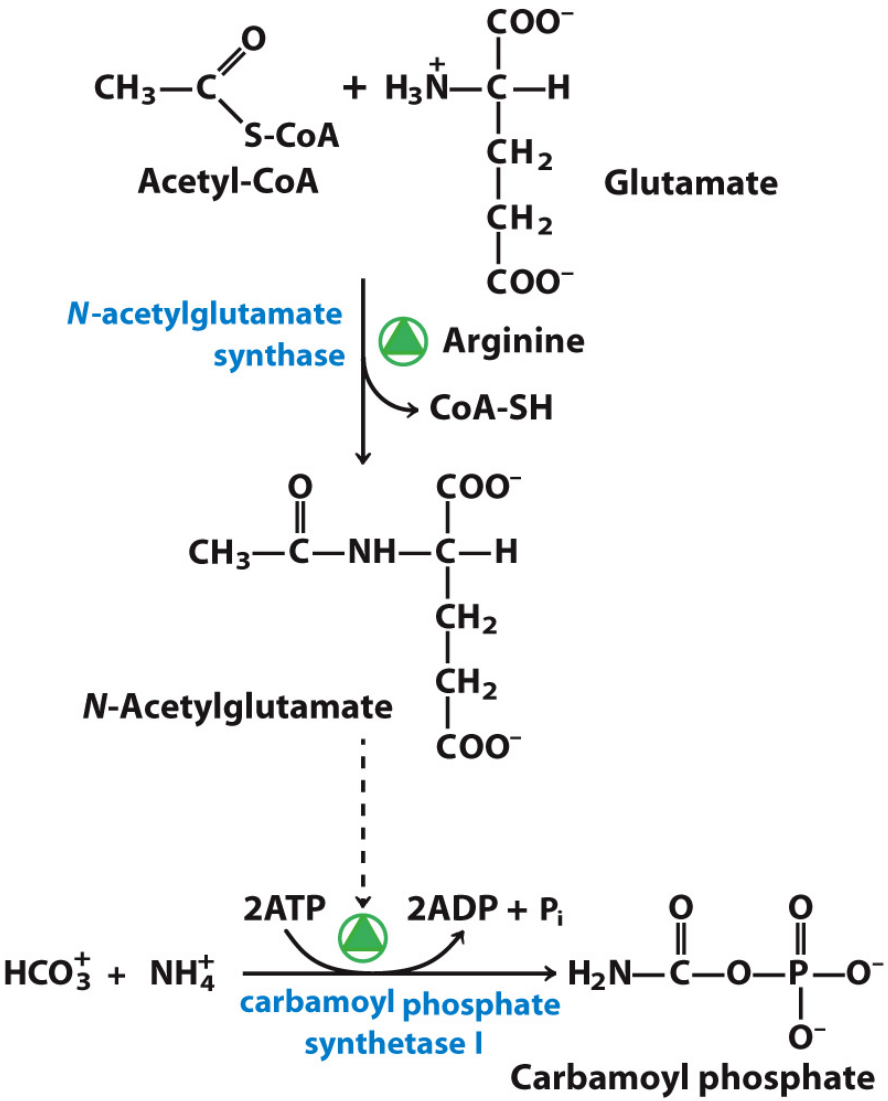

Figure 18-13
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Essential vs. Nonessential and Conditionally Essential Amino Acids

- **Essential amino acids** must be obtained as dietary protein.
- **Nonessential amino acids** are easily made from *central metabolites*.
- Consumption of a variety of foods supplies all the essential amino acids.

TABLE 18-1 Nonessential and Essential Amino Acids for Humans and the Albino Rat

Nonessential	Conditionally essential[a]	Essential
Alanine	Arginine	Histidine
Asparagine	Cysteine	Isoleucine
Aspartate	Glutamine	Leucine
Glutamate	Glycine	Lysine
Serine	Proline	Methionine
	Tyrosine	Phenylalanine
		Threonine
		Tryptophan
		Valine

[a]Required to some degree in young, growing animals and/or sometimes during illness.

End Products of Amino Acid Degradation

- 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	Ala, Cys, Gly, Ser, Thr, Trp	*Potentially ketogenic*
Five to α-ketoglutarate	Arg, Glu, Gln, His, Pro	
Four to succinyl-CoA	Ile, Met, Thr, Val	
Two to fumarate	Phe, Tyr	
Two to oxaloacetate	Asp, Asn	

Only two amino acids, leucine and lysine, are exclusively ketogenic.

Summary of Amino Acid Catabolism

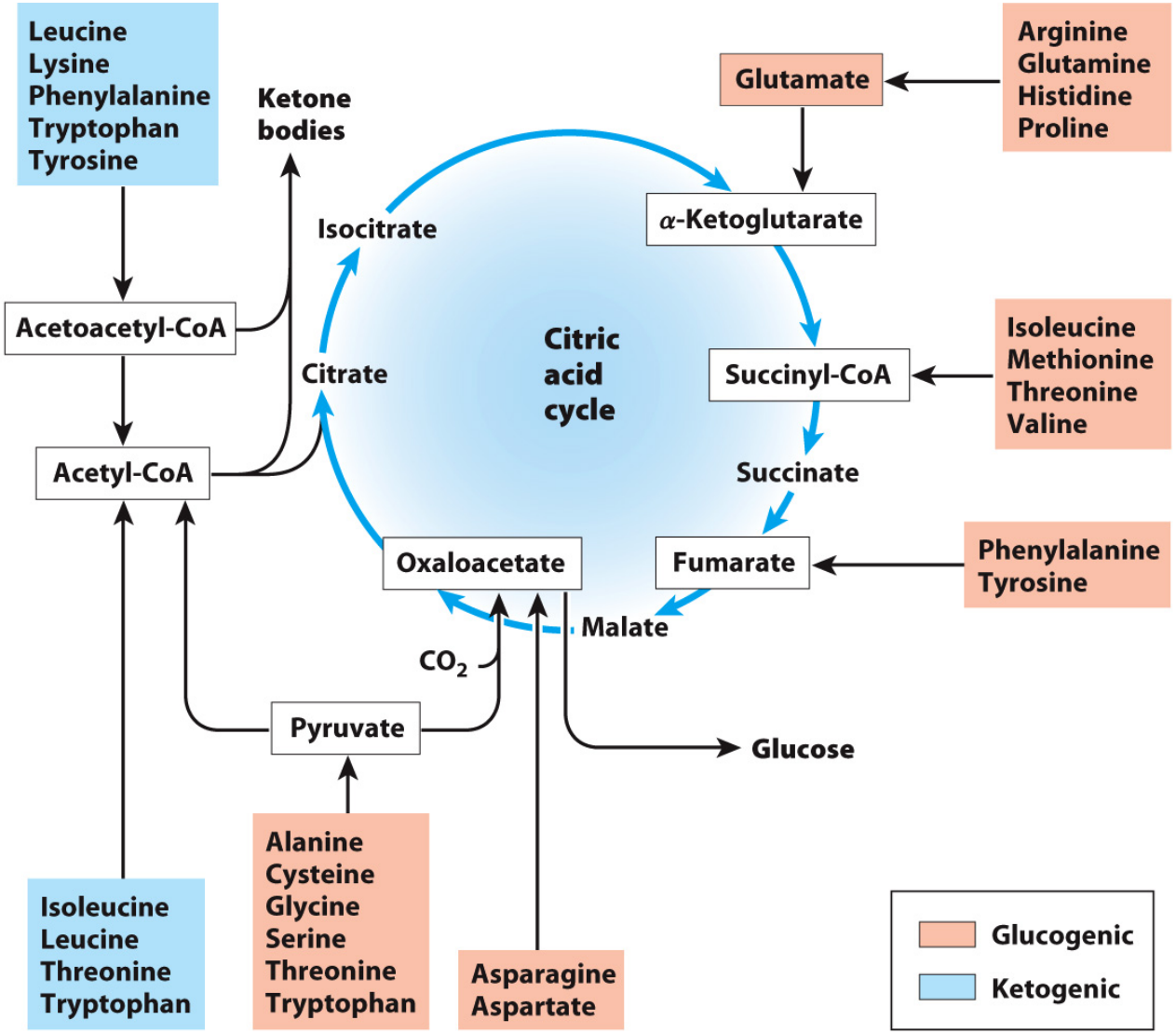

Figure 18-15

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Degradation of Ketogenic Amino Acids

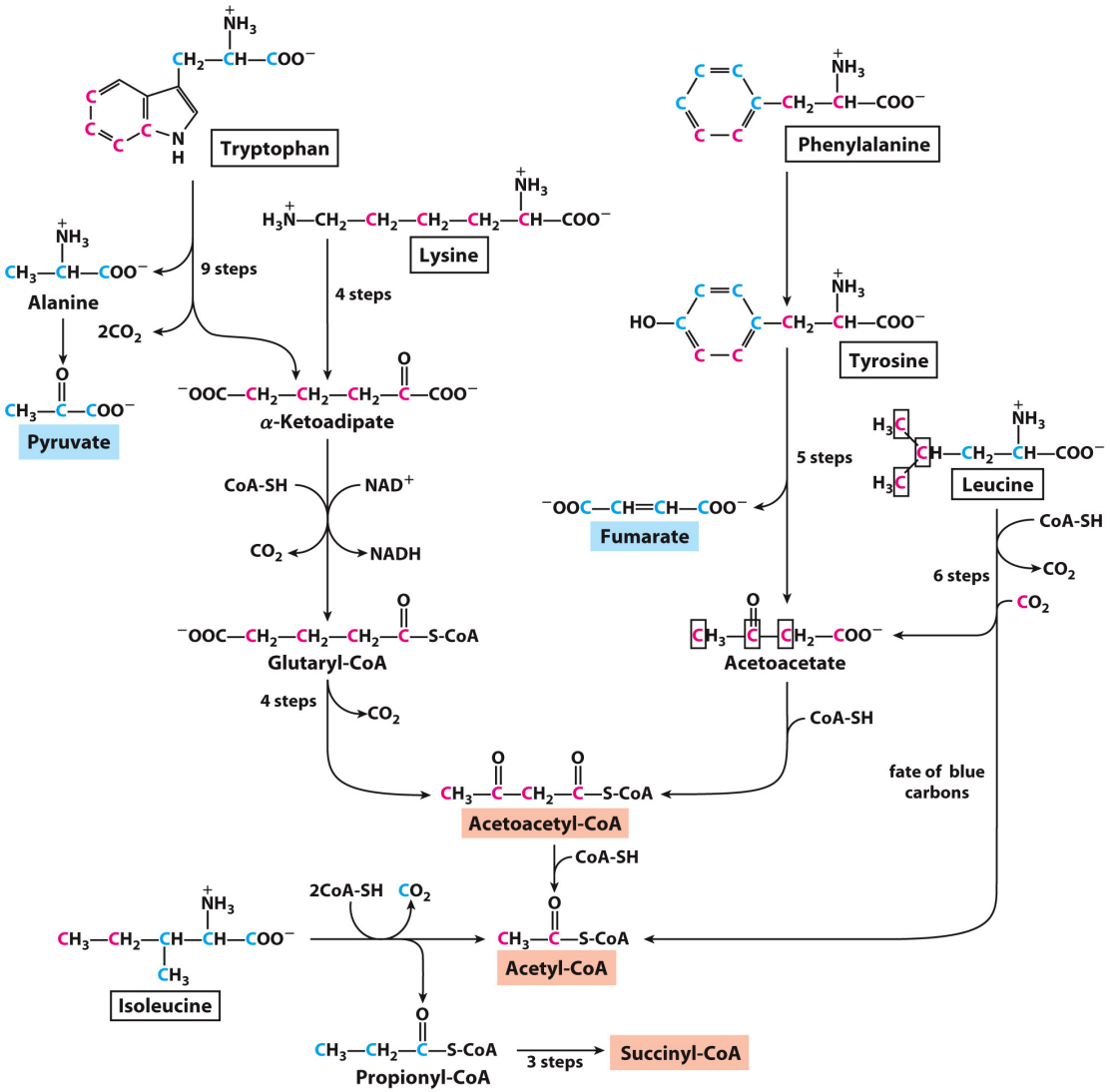

Figure 18-21
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Degradation Intermediates of Tryptophan Are to Synthesize Other Molecules

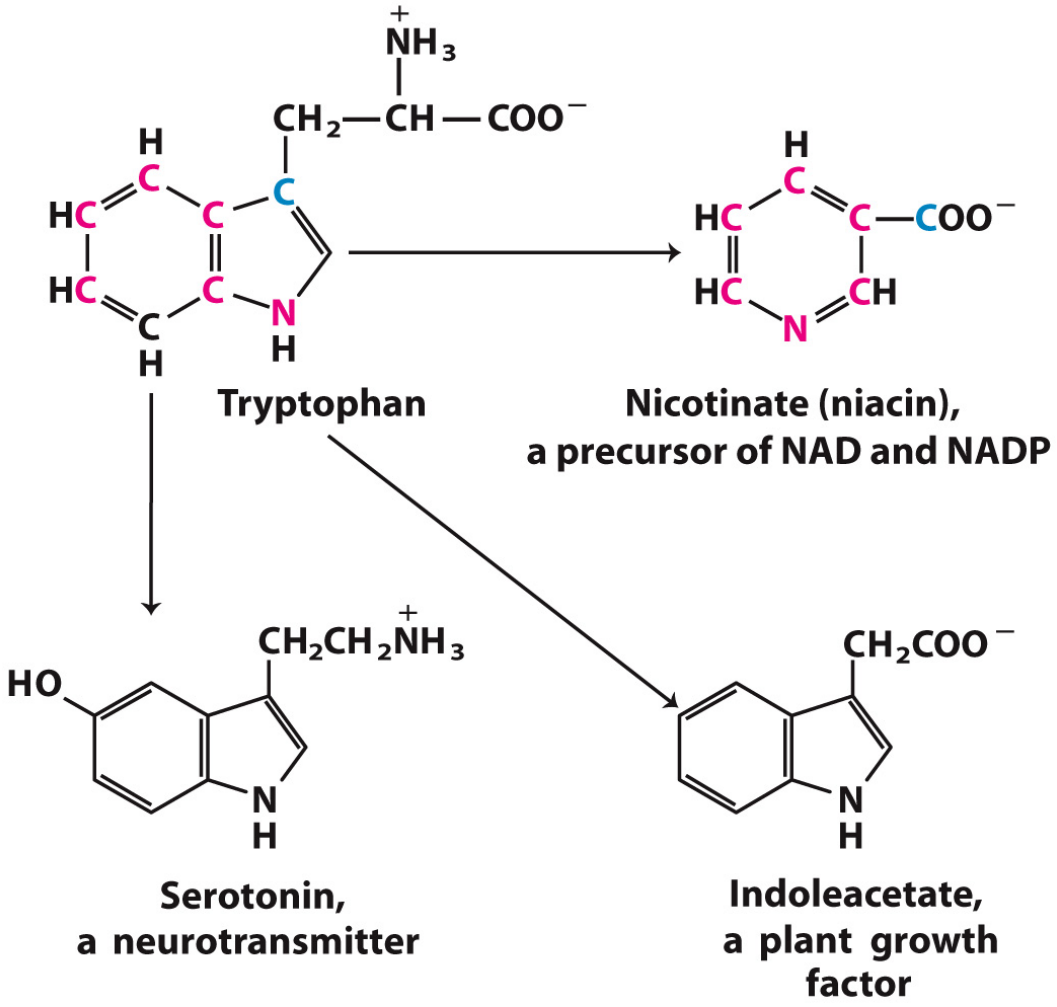

Figure 18-22
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Genetic Defects in Many Steps of Phe Degradation Lead to Disease

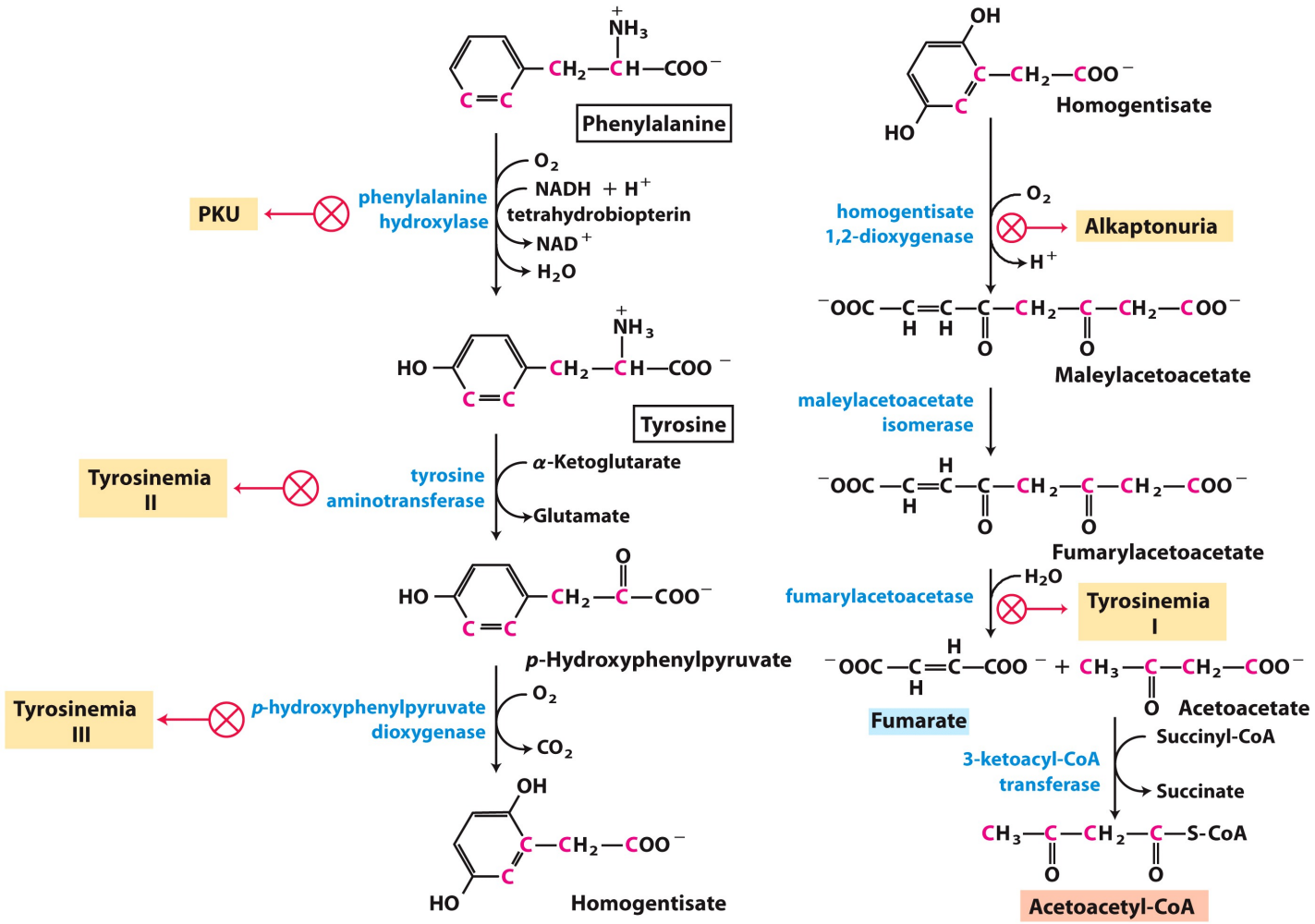

Figure 18-23
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Phenylketonuria Is Caused by a Defect in the First Step of Phe Degradation

- A buildup of phenylalanine and phenylpyruvate
- Impairs neurological development leading to intellectual deficits
- Controlled by limiting dietary intake of Phe

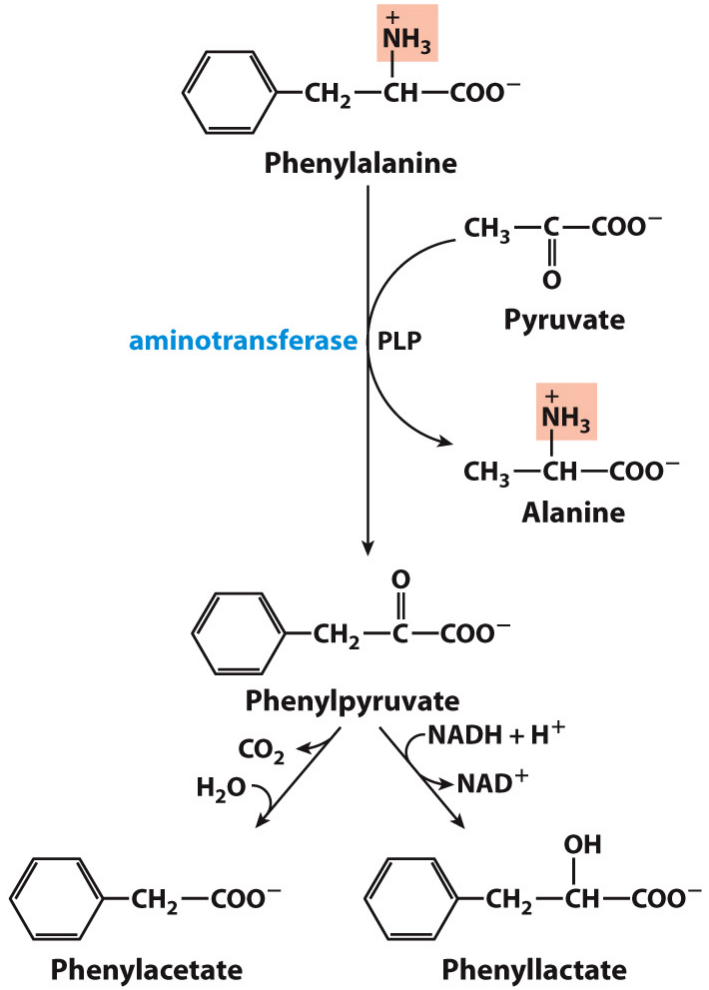

Figure 18-25
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Degradation of Amino Acids to Pyruvate

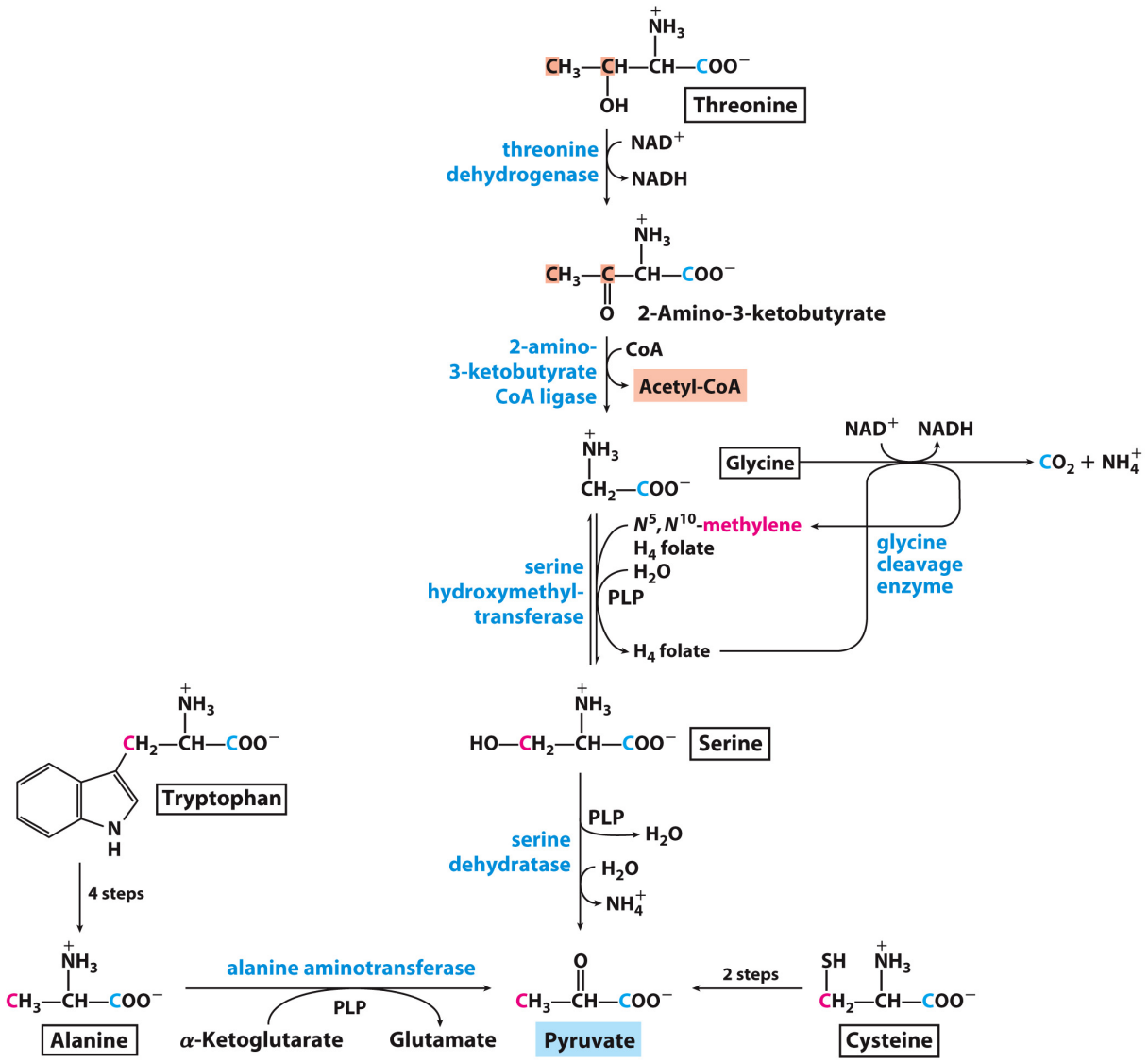

Figure 18-19

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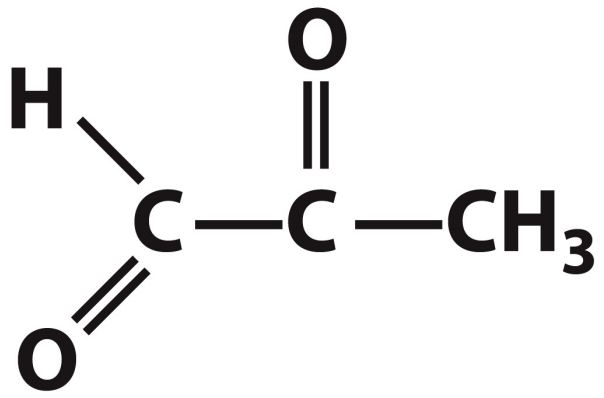
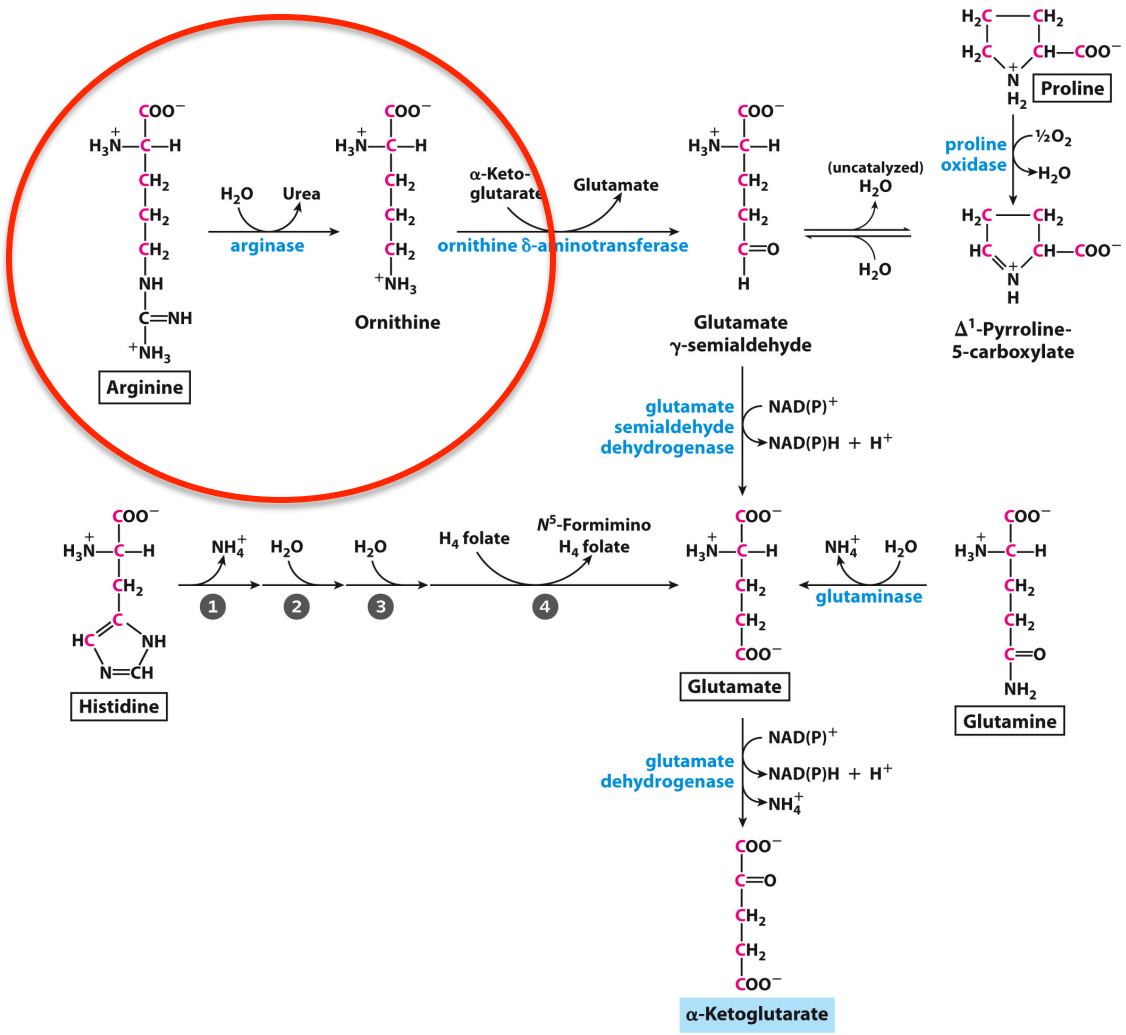
Degradation of Glycine

- Pathway #1: hydroxylation to serine → pyruvate
- Pathway #2: glycine cleavage enzyme
  - apparently major pathway in mammals
  - separation of three central atoms
  - releases CO_2 and NH_3
  - methylene group is transferred to THF
- Pathway #3: D-amino oxidase
  - relatively minor pathway
  - ultimately oxidized to oxalate
  - major component of kidney stones



Methylglyoxal

Degradation of Amino Acids to α-Ketoglutarate



Proline, arginine, histidine, and glutamine are all converted to glutamate. Glutamate is deaminated to α-ketoglutarate.

Arginine degradation is part of the urea cycle.

Figure 18-26
Lehninger Principles of Biochemistry, Seventh Edition

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

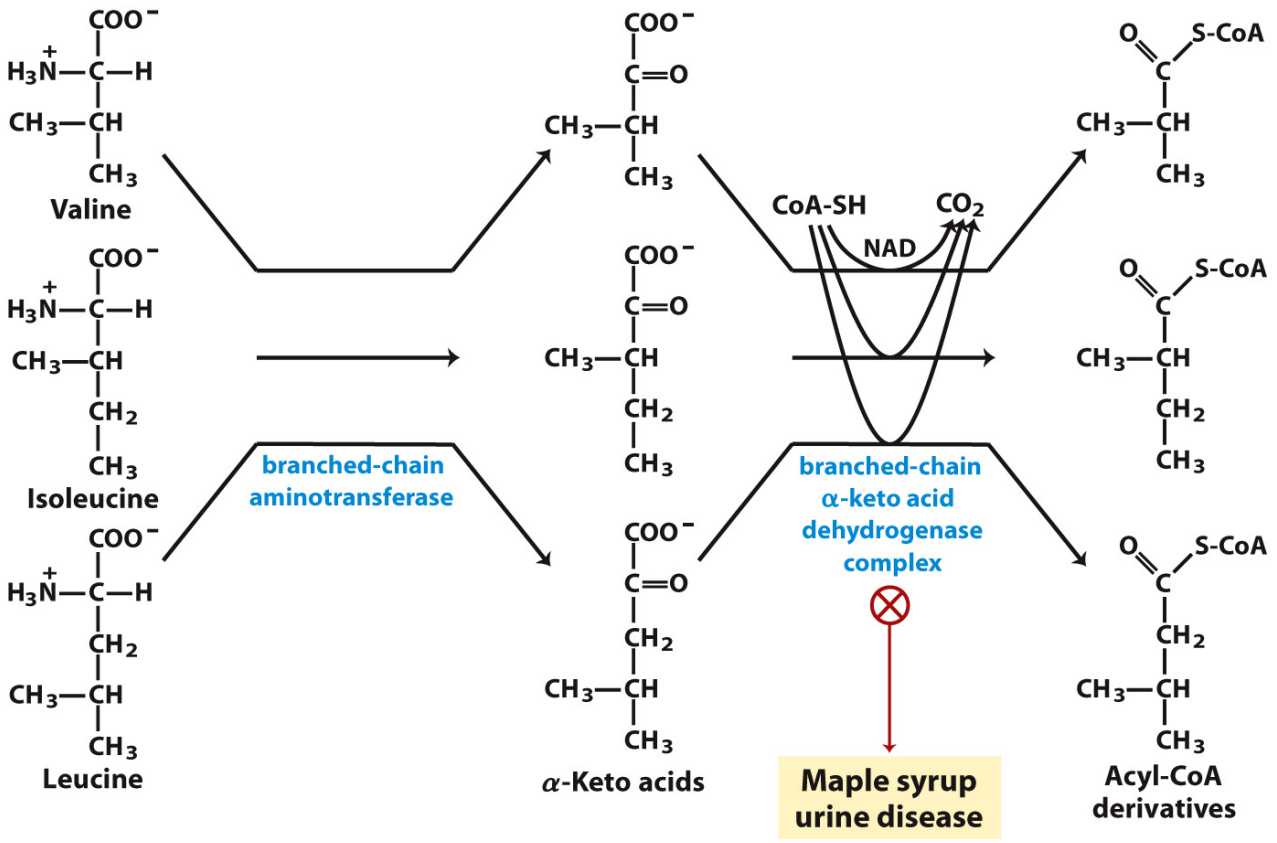


Figure 18-28
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Degradation of Branched-Chain Amino Acids Does Not Occur in the Liver

Branched-chain amino acids are degraded to succinyl-CoA, an important citric acid cycle intermediate.

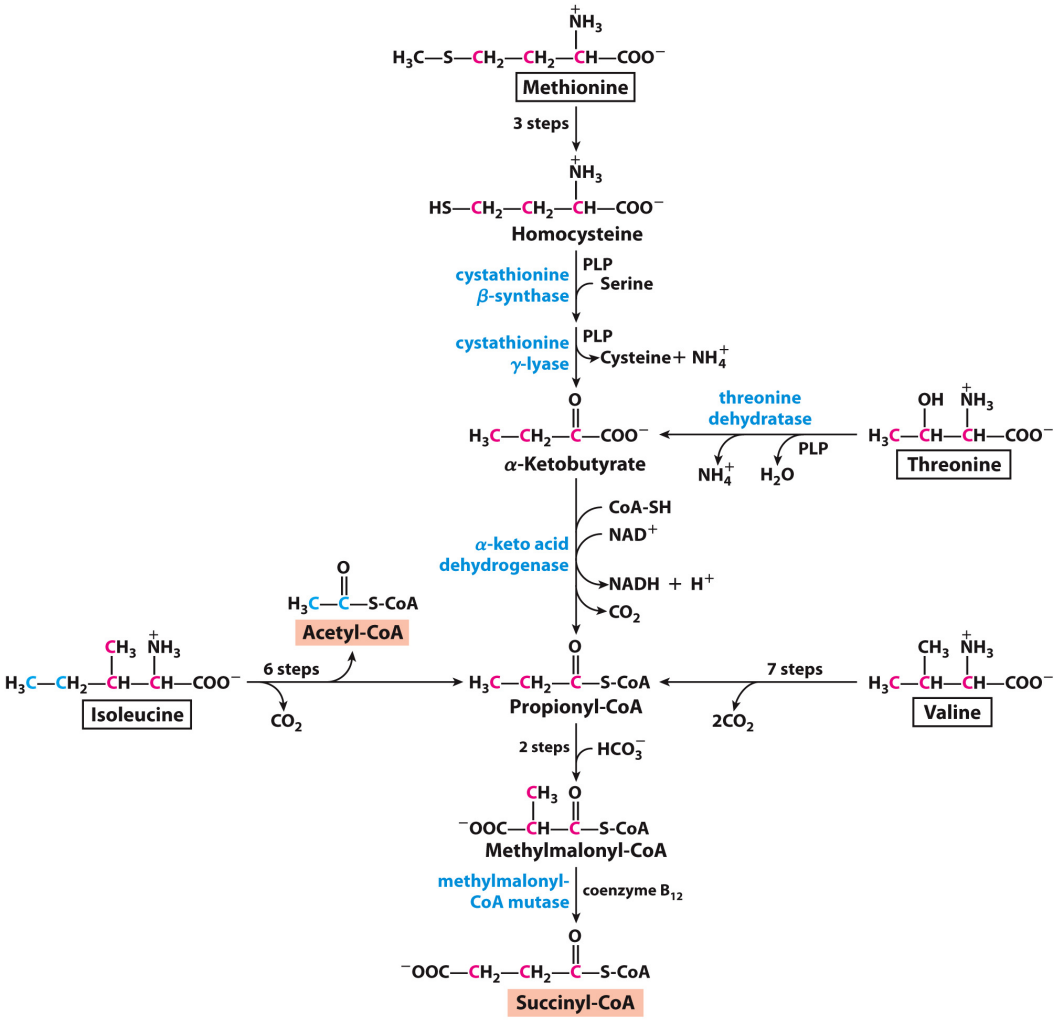

Figure 18-27
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The case of wrong diagnosis: Patricia Stallings

- https://www.youtube.com/watch?v=5lL0qJgIOQE
- Box 18-2

Degradation of Asn and Asp to Oxaloacetate

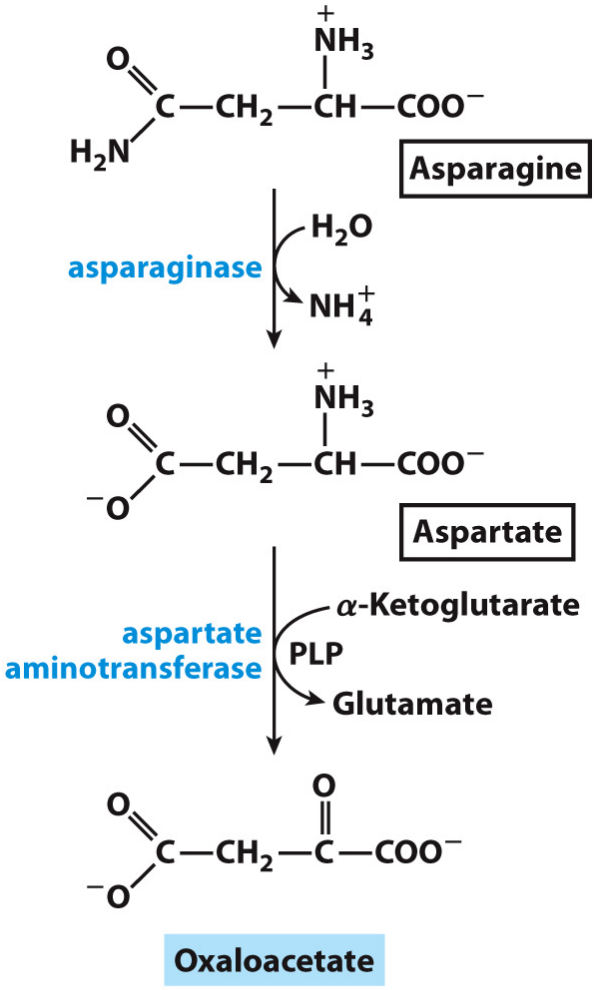

Figure 18-29
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TABLE 18-2 Some Human Genetic Disorders Affecting Amino Acid Catabolism

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

Chapter 18: Summary

In this chapter, 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