

## Blood Lipids

### Chylomicrons

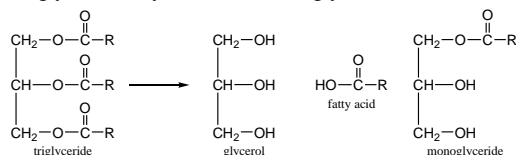
- The smaller molecules that are produced, along with cholesterol, are absorbed into cells of the intestinal mucosa (the innermost layer of the gastrointestinal wall), where resynthesis of the triglycerides and phosphoglycerides occurs.
- For transport within the aqueous environment of lymph and blood, water-insoluble triglycerides, phosphoglycerides, and cholesterol are complexed with proteins to form lipoprotein aggregates called **chylomicrons**. These aggregates can pass into the lymph system and then into the bloodstream.
- Chylomicrons are modified by the liver into smaller lipoprotein particles, the form in which most lipids are transported to various parts of the body by the bloodstream.

### Introduction

- In this chapter, we will discuss the storage, degradation, and synthesis of lipids and amino acids, and the relationships between the metabolism of amino acids, lipids, and carbohydrates.
- Triglycerides** (fats and oils) are important dietary sources of energy. Fat also functions as a major form of energy storage (9 Cal/g).
  - Because it is water-insoluble, fat can be stored in larger quantities than carbohydrates.
  - Carbohydrate reserves are depleted after about 1 day without food, but stored fat can provide needed calories for 30-40 days.
- Amino acids** are the building blocks for proteins, they provide C and N for the synthesis of other biomolecules, and they are also sources of energy (4 Cal/g).

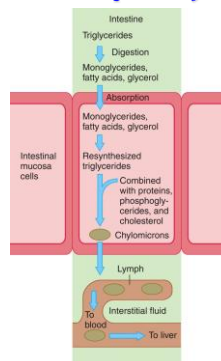
### Digestion of Triglycerides

- During digestion, triglycerides are hydrolyzed to glycerol, fatty acids, and monoglycerides:



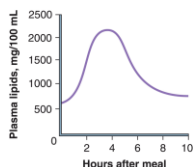
- Phosphoglycerides are also hydrolyzed to their component substances (glycerol, fatty acids, phosphate groups, and aminoalcohols).

### Digestion and Absorption of Triglycerides



### Plasma Lipid Levels

- The behavior of blood lipids parallels that of blood sugar.
  - The concentration of plasma lipids increases after a meal, and returns to normal as a result of storage in fat depots and oxidation to provide energy.
  - The concentration of plasma lipids rises within 2 hours after a meal, peaks after 4-6 hours, then drops to normal levels.



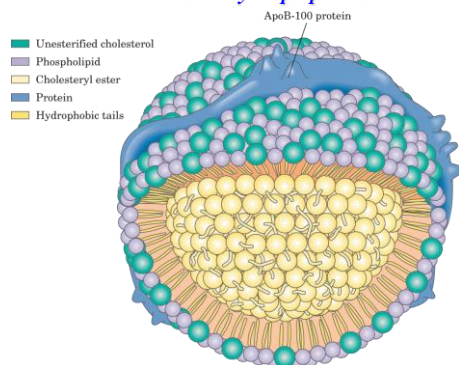
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### Classifying Lipoproteins by Density

- Lipoproteins may be classified by **density**. Because lipids are less dense than proteins, increasing the lipid concentration makes the lipoprotein less dense.
  - Chylomicrons** carry triglycerides from the intestines to the liver, skeletal muscle, and adipose tissue.
  - Very-low-density lipoproteins (VLDL)** carry newly synthesized triglycerides from the liver to adipose tissue.
  - Low-density lipoproteins (LDL)** carry cholesterol from the liver to cells of the body (“bad cholesterol”).
  - High-density lipoproteins (HDL)** collect cholesterol from the body’s tissues, and bring it back to the liver (“good cholesterol”).

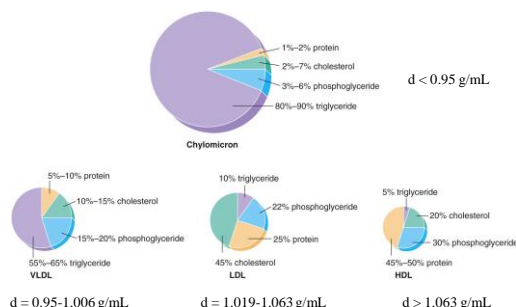
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### A Low-Density Lipoprotein



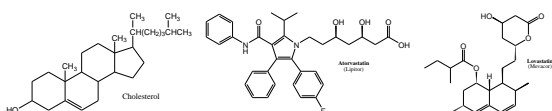
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### Composition of Lipoproteins



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### Cholesterol and LDL's



- Cholesterol is involved in the formation of cell membranes, the insulation of nerves, the synthesis of a number of hormones, and the digestion of food.
  - LDL's transport cholesterol into the wall of an artery, causing the formation of plaques (an accumulation and swelling in artery walls), and leading to atherosclerosis.
  - HDL's are able to remove cholesterol from plaques in the arteries and transport it to the liver for excretion or reuse.

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### Cholesterol and LDL's

- There are several medications which have been used to either lower the total cholesterol level in the bloodstream, or to lower the concentration of the LDL (“bad”) cholesterol levels:
  - Resin drugs** (Questran, Colestid) bind with bile acids in the digestive tract and remove them from operation; the liver synthesizes more bile acids from cholesterol, so less cholesterol available to be released into the blood from LDL.
  - Lipid**, or large doses of **niacin** reduce the production of triglycerides, which are involved in the formation of LDL; less cholesterol circulates in the blood.
  - Statins** (Mevacor, Zocor, Pravachol, Lipitor) block the synthesis of cholesterol in the liver by inhibiting HMG-CoA reductase, causing liver cells to remove cholesterol from the circulating blood; they also help the body to reabsorb cholesterol from plaque that has formed in blood vessels.

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# Fat Mobilization and Glycerol Metabolism

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## Fat Mobilization

- When cells need fatty acids for energy, the endocrine system produces several hormones, including epinephrine, which interact with **adipose tissue**, stimulating the hydrolysis of triglycerides to fatty acids and glycerol, which enter the bloodstream. This process is called **fat mobilization**.
  - In the blood, mobilized fatty acids form a lipoprotein with the plasma protein called **serum albumin**.
  - In this form, the fatty acids are transported to the tissue cells that need them.
  - The glycerol is water soluble, so it dissolves in the blood and is also transported to cells that need it.

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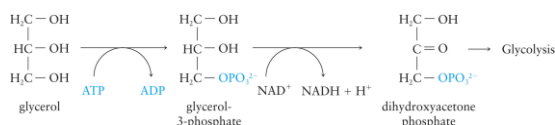
## Glycogen and Glucose Stores

- Carbohydrates from dietary sources and glycogen catabolism are used preferentially for energy production by some tissues, such as the brain and active skeletal muscles.
- Body stores of glycogen are depleted after only a few hours of fasting, which requires fatty acids stored in triglycerides to be used as energy sources.
  - Even when glycogen supplies are adequate, resting muscle and liver cells use energy from triglycerides because this conserves glycogen stores and glucose for use by brain cells and red blood cells.
    - Brain cells do not obtain nutrients from blood.
    - Red blood cells do not have mitochondria, and cannot do fatty acid oxidation.

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## Glycerol Metabolism

- The glycerol hydrolyzed from triglycerides can provide energy to cells. It is converted to dihydroxyacetone phosphate in two steps:



- Dihydroxyacetone phosphate is one of the chemical intermediates in glycolysis. It is converted to pyruvate, and thus contributes to cellular energy production.
- The pyruvate can also be converted to glucose through gluconeogenesis.

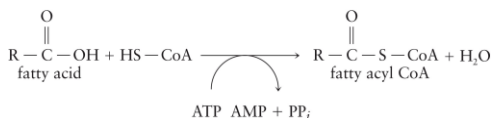
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# The Oxidation of Fatty Acids

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## The Formation of Fatty Acyl CoA

- Fatty acids that enter tissue cells cannot be oxidized to produce energy until they pass through the membrane of the mitochondria. This cannot occur until the fatty acid is converted into fatty acyl CoA by reaction with coenzyme A, with energy provided by ATP:

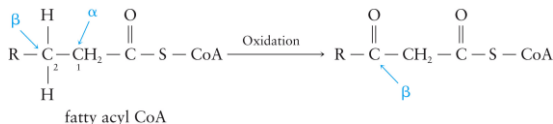


- This reaction is catalyzed by acyl CoA synthetase.
- This reaction is referred to as **activation** of the fatty acid because the fatty acyl CoA is a high-energy compound.

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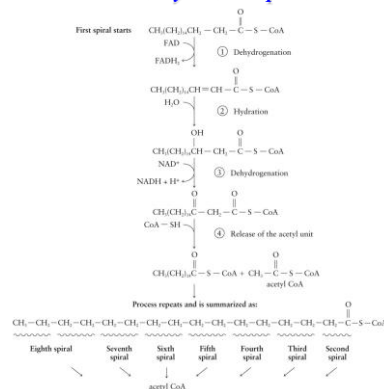
### *β-Oxidation: The Fatty Acid Spiral*

- The fatty acyl CoA molecules that enter the mitochondria then undergo a catabolic process called **β-oxidation**, in which the second (beta) carbon away from the carbonyl group of the fatty acyl CoA molecule is oxidized to a ketone:



- There are four reactions in this pathway. The fatty acyl CoA from the 18-carbon fatty acid stearic acid will be used as an example:

### *The Fatty Acid Spiral*

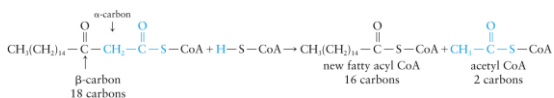


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### *The Fatty Acid Spiral*

- In the final step of β-oxidation (Step 4), the bond between the α- and β-carbons is broken by reaction with coenzyme A. A new fatty acyl CoA is formed, which is two carbons shorter than the original molecule, and a unit of acetyl CoA is released:

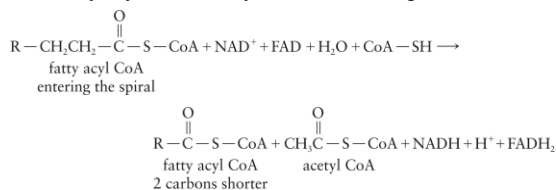


- The new fatty acyl compound enters the β-oxidation process at Step 1, and the process is repeated.
- With every pass through the “fatty acid spiral,” the chain is shortened by two carbons, until the fatty acyl CoA is completely degraded into acetyl CoA units.

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### *The Fatty Acid Spiral*

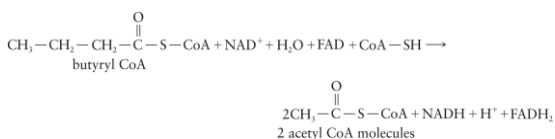
- Every run through the spiral produces one molecule each of acetyl CoA, NADH, and FADH<sub>2</sub>, until the fatty acyl CoA is only four carbons long:



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### *The Fatty Acid Spiral*

- In the last spiral, the four-carbon chain of butyryl CoA passes through the β-oxidation sequence, and produces one FADH<sub>2</sub>, one NADH, and two acetyl CoA's:



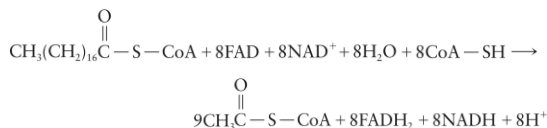
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### *The Fatty Acid Spiral*

- The complete conversion of a fatty acyl CoA to two carbon fragments of acetyl CoA always produces one more molecule of acetyl CoA than of FADH<sub>2</sub> or NADH.

– Thus, the breakdown of 18-C stearic acid requires 8 passes through the spiral, and produces 9 acetyl CoA's, but only 8 FADH<sub>2</sub>'s and 8 NADH's.

- Net reaction:



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### The Energy from Fatty Acids

#### How much energy do we get from a fatty acid?

- The activation of stearic acid by coenzyme A to form stearoyl CoA comes from the hydrolysis of 2 ATP's (total=-2 ATP's).
- As a stearoyl CoA molecule (18 C's) passes through the  $\beta$ -oxidation spiral, 9 acetyl CoA's, 8 FADH<sub>2</sub>'s, and 8 NADH's are produced.
  - Acetyl CoA can enter the citric acid cycle / electron transport chain and form 10 ATP's (total=9x10=90 ATP's)
  - Each FADH<sub>2</sub> yields 1.5 ATP's (total=8x1.5=12 ATP's), and each NADH yields 2.5 ATP's (total=8x2.5= 20).
- Thus, from one 18-C stearic acid molecule, 120 molecules of ATP are formed.**

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### The Energy from Fatty Acids

**Table 24.1** Energy Produced by the Oxidation of Stearic Acid

Oxidation Product or Step	ATP/Unit	Total ATP
Activation step		-2
9 acetyl CoA	10	90
8 FADH <sub>2</sub>	1.5	12
8 (NADH + H <sup>+</sup> )	2.5	20
Total ATP from the 18-carbon fatty acid		120

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### An Energy Comparison: Fatty Acids vs. Glucose

- Stearic acid (18 C's) vs. Glucose (6 C's):
  - The complete oxidation of a single glucose molecule produces 32 ATP's.
  - Since three glucose molecules have 18 C's (3x6=18), three glucose molecules would produce 96 ATP's.
  - A stearic acid molecule (also 18C's) produces 120 ATP's.
  - On the basis of an equal number of carbons, lipids are nearly 25% more efficient than carbohydrates as energy-storage systems.

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### An Energy Comparison: Fatty Acids vs. Glucose

- Stearic acid (18 C's) vs. Glucose (6 C's):
  - On a mass basis, one mole of stearic acid weighs 284 g, and yields 120 mol of ATP.
  - Three moles of glucose weighs 540 g and yields 96 mol of ATP.
  - On this basis, 284 g of glucose would produce 50 mol of ATP.
  - On an equal-mass basis, lipids contain more than twice the energy of carbohydrates.
- This is partially because lipids, which are primarily hydrocarbons, are a more reduced form of the fuel, while glucose, which contains a lot of OH groups, is already partially oxidized.

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## Ketone Bodies

### Changes Caused by Fasting

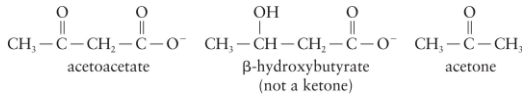
- Under normal conditions, most acetyl CoA produced during fatty acid metabolism is processed through the citric acid cycle.
- During fasting, the balance between carbohydrate and fatty acid metabolism is lost, and fatty acids become the body's primary energy source.
  - Because minimal amounts of cellular glucose are available, the level of glycolysis decreases, and a reduced amount of oxaloacetate is synthesized.
  - Oxaloacetate is also used for gluconeogenesis to a greater extent as the cells make their own glucose.
  - The lack of oxaloacetate reduces the activity of the citric acid cycle, and acetyl CoA produced by fatty acid oxidation builds up faster than it can be processed by the citric acid cycle.

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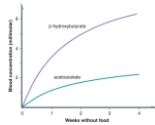
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### Ketone Bodies

- As the concentration of acetyl CoA builds up, the excess is converted in the liver to the **ketone bodies** acetoacetate, b-hydroxybutyrate, and acetone.



- These ketone bodies are carried by the blood to body tissues, mainly the brain, heart, and skeletal muscles, where they may be oxidized to meet energy needs.
- Under normal conditions, the concentration of ketone bodies in the blood averages 0.5 mg/100 mL.



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### Diabetes and Ketosis

- Diabetes mellitus** also produces an imbalance in carbohydrate and lipid metabolism. Even though blood glucose reaches hyperglycemic levels, a deficiency of insulin prevents the glucose from entering tissue cells in sufficient amounts to meet cellular energy needs.
  - This results in an increase in fatty acid metabolism, and the excessive production of acetyl CoA, and a substantial increase in the level of ketone bodies in the blood of untreated diabetics.
- A concentration of ketone bodies higher than 20 mg / 100 mL of blood is called **ketonemia** (“ketones in the blood”).

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### Diabetes and Ketosis

- At a level of about 70 mg/100 mL of blood, the renal threshold for ketone bodies is exceeded, and ketone bodies are excreted in the urine, resulting in **ketonuria** (“ketones in the urine”).
- Acetone levels in the blood can reach levels so high that it is expelled through the lungs, producing **acetone breath**.
- When ketonemia, ketonuria, and acetone breath exist simultaneously, the condition is called **ketosis**.

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### Ketoacidosis

- Two of the ketone bodies are acids, and their accumulation in the blood results in a particular **acidosis** (low blood pH) called **ketoacidosis**.
  - If this condition is uncontrolled, the person becomes severely dehydrated because the kidneys excrete excessive amounts of water in response to low blood pH.
  - Prolonged ketoacidosis leads to general debilitation, coma, or death.
- Patients suffering from diabetes-related ketosis are usually given insulin as a first step in treatment. The insulin restores normal glucose metabolism and reduces the rate of formation of ketone bodies.
- Acid-base balance can be resorted by the intravenous administration of sodium bicarbonate.

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## Fatty Acid Synthesis

### Fatty Acid Synthetase System

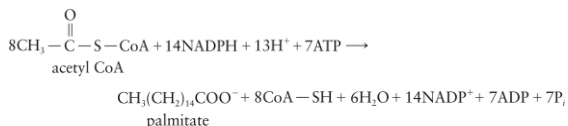
- Excess nutrients are converted to fatty acids, and then to body fat. The process for fatty acid synthesis is separate from that of fatty acid degradation, and occurs in the cytoplasm rather than in the mitochondria.
  - In both processes, the reactions occur in two-C fragments from acetyl CoA.
- Acetyl CoA is generated in the mitochondria, and transported to the cytoplasm for fatty acid synthesis in the form of citrate (Step 1 of the citric acid cycle).
- Fatty acid synthesis occurs in a complex series of reactions catalyzed by an complex called the **fatty acid synthetase system**. This system consists of six enzymes and a protein called the acyl carrier protein (ACP), to which all intermediate are attached.

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### The Synthesis of Palmitic Acid

- The reaction shown below for the synthesis of palmitic acid from acetyl CoA requires a large input of energy in the form of 7 ATP's and 14 NADPH's (a phosphate derivative of NADH):



- Fatty acids are incorporated into triglycerides and stored in the form of fat in **adipose tissues**.
- This large input of energy is stored in the synthesized fatty acids, and is one of the reasons it is difficult to lose excess weight due to fat.

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### Fatty Acids and the Liver

- The liver is the most important organ involved in fatty acid and triglyceride synthesis. It is able to modify body fats by lengthening or shortening the chain, or saturating or unsaturating the chain.
  - The only fatty acids that cannot be synthesized by the body are those that are polyunsaturated
  - Linoleic and linolenic acids from the diet can be converted to other polyunsaturated fatty acids.
- The human body can convert glucose to fatty acids, but cannot convert fatty acids to glucose.
  - Humans have no enzyme that catalyzes the conversion of acetyl CoA to pyruvate, which is required for gluconeogenesis.
  - Plants, and some bacteria do possess such enzymes.

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## Amino Acid Metabolism

### The Amino Acid Pool

- The most important function of amino acids (about 75% of amino acid utilization) is to provide building blocks for the synthesis of proteins in the body.
- The maintenance of body proteins must occur constantly because tissue proteins break down from normal wear and tear, from injuries, and from diseases.
- The amino acids that are used in this maintenance come from the **amino acid pool** of the body. These amino acids can come from:
  - proteins that are eaten and hydrolyzed during digestion
  - the body's own degraded tissues
  - the synthesis in the liver of certain amino acids.

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### Protein Turnover and Half-Life

- The process in which body proteins are continuously hydrolyzed and resynthesized is called **protein turnover**.
  - The **turnover rate**, or life expectancy, of body proteins is a measure of how fast they are broken down and resynthesized, expressed as a half-life.
    - The half-life of liver proteins is about 10 days: over a 10-day period, half the proteins in the liver are hydrolyzed to amino acids and replaced.
  - Plasma proteins = 10 days
  - Hemoglobin = 120 days
  - Muscle protein = 180 days
  - Collagen = as high as 1000 days
  - Enzyme and polypeptide hormones = as short as a few minutes. (Insulin = 7-10 minutes)

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### Other Compounds from Amino Acids

- The frequent turnover of proteins allows the body to continually renew important molecules and respond to changing needs.
- There is also a constant draw on the amino acid pool for the synthesis of other N-containing biomolecules, such as the bases in DNA and RNA, the heme in hemoglobin and myoglobin, the aminoalcohols in phospholipids, and neurotransmitters.

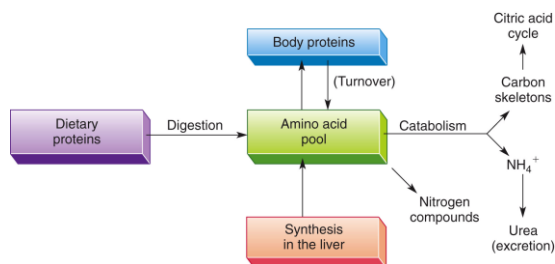
Amino Acid	Product	Function
Tyrosine	dopamine	Neurotransmitter
	norepinephrine	Neurotransmitter, hormone
	epinephrine	Hormone
	thyroxine (T3 & T4)	Hormone
	melanin	Skin pigmentation
Tryptophan	serotonin	Neurotransmitter
Histidine	histamine	Involved in allergic reactions
Serine	ethanolamine	Required in cephalin synthesis
Cysteine	taurine	A compound of bile salts

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### Amino Acid Metabolic Pathways

- Amino acids in excess of immediate body requirements cannot be stored for later use.
  - The N atoms are converted to either ammonium ions, urea, or uric acid (depending on the organism), and excreted.
  - Their carbon skeletons are converted to pyruvate, acetyl CoA, or one of the intermediates in the citric acid cycle and used for energy production, the synthesis of glucose through gluconeogenesis, or conversion to triglycerides.

### Amino Acid Metabolic Pathways



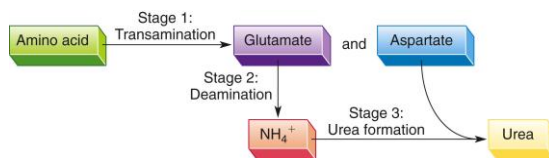
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## Amino Acid Catabolism: The Fate of the Nitrogen Atoms

### The Fate of Nitrogen Atoms

- The N atoms in amino acids are either excreted or used to synthesize other N-containing compounds. There are three stages in nitrogen catabolism:
  - Stage 1: Transamination
  - Stage 2: Deamination
  - Stage 3: Urea Formation

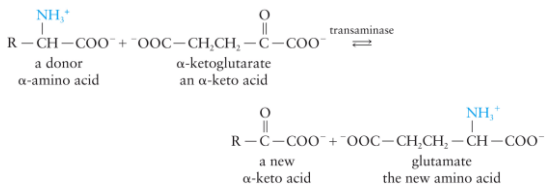


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### Stage 1: Transamination

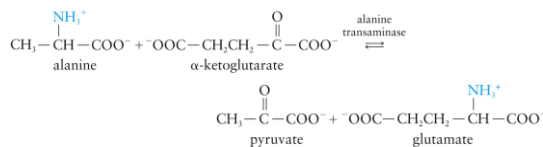
- In the tissues, amino groups freely move from one amino acid to another, under the influence of enzymes called **amino transferases** or **trans aminases**. A key reaction for amino acids undergoing catabolism is a transamination involving the transfer of amino groups to  $\alpha$ -ketoglutarate. The carbon skeleton of the amino acid remains behind as an  $\alpha$ -keto acid:



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### Stage 1: Transamination

- Specific example:

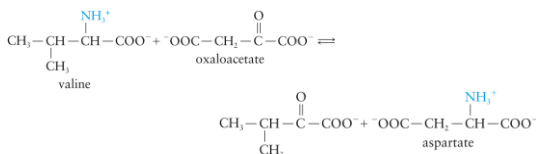


- The net effect of this reaction is to exchange the  $\text{NH}_3^+$  on the amino acid with a =O.

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### Stage 1: Transamination

- Another important example of transamination is the production of aspartate, which is used in Stage 3, urea formation, from the transfer of an amino to oxaloacetate:



- This process is an important method for the biosynthesis of the nonessential amino acids glutamate and aspartate from a variety of other amino acids.

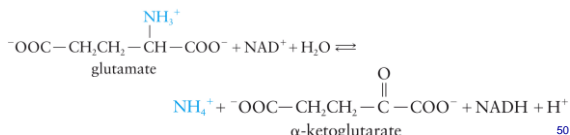
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### Stage 2: Deamination

- This phase of amino acid catabolism uses the glutamate produced in Stage 1. The enzyme glutamate dehydrogenase catalyzes the removal of the amino group as an ammonium ion and regenerates  $\alpha$ -ketoglutarate, which can participate in transamination again.

– This reaction is the principal source of  $\text{NH}_4^+$  in humans.

– Because the deamination results in the oxidation of glutamate, it is called **oxidative deamination**.



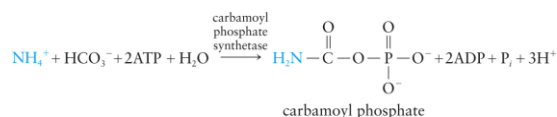
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### Stage 2: Deamination

- The NADH produced in this stage enters the electron transport chain and eventually produces 2.5 ATP molecules.
- Other amino acids can be catabolized by oxidative deamination in the liver by enzymes called **amino acid oxidases**.

### Stage 3: Urea Formation

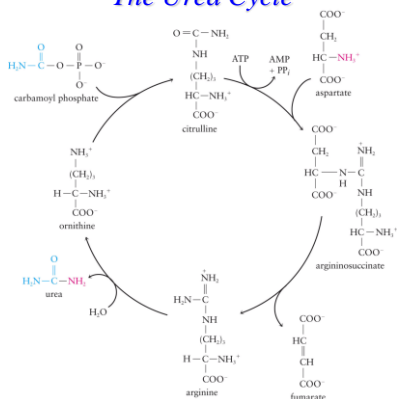
- The ammonium ions released by the glutamate dehydrogenase in Step 2 are toxic, and must be prevented from accumulating. In the **urea cycle**, which only occurs in the liver,  $\text{NH}_4^+$  is converted to urea, which is less toxic, and can be allowed to concentrate until it is excreted in urine.
- The urea cycle process  $\text{NH}_4^+$  in the form of carbamoyl phosphate, the fuel for the urea cycle. This compound is synthesized in the mitochondria from  $\text{NH}_4^+$  and  $\text{HCO}_3^-$ :



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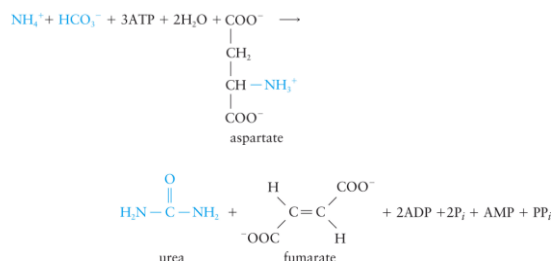
### The Urea Cycle



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### Stage 3: Urea Formation

- The net reaction for carbamoyl phosphate formation and the urea cycle is:



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*Stage 3: Urea Formation*

- After urea is formed, it diffuses out of liver cells and into the blood. It is then filtered out by the kidneys, and excreted in the urine.
- Normal urine from an adult usually contains about 23-30 g of urea daily, although this varies with the protein content of the diet.
- The direct excretion of  $\text{NH}_4^+$  accounts for a small but important amount of the total urinary nitrogen.
- The excretion of ammonium along with acidic ions is a mechanism that helps the kidneys to control the acid-base balance of body fluids.

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## Amino Acid Catabolism: The Fate of the Carbon Skeleton

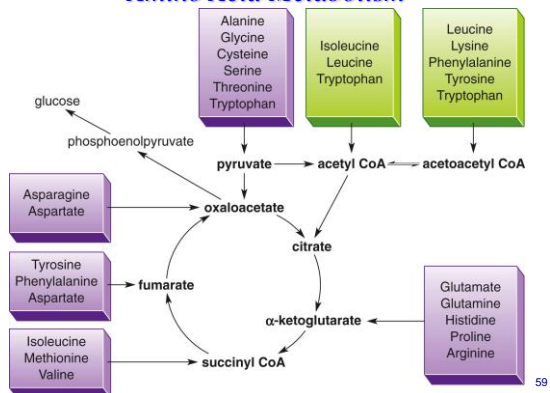
*The Fate of the Carbon Skeleton*

- After the amino group is removed by transamination or oxidative deamination, the remaining amino acid carbon skeleton undergoes catabolism and is converted into one of several products.
- After the amino group is gone, the skeletons of all 20 amino acids are degraded into either pyruvate, acetyl CoA, acetoacetyl CoA (which is degraded to acetyl CoA), or various substances that are intermediates in the citric acid cycle.
- All these degraded forms of the carbon skeletons are a part of or can enter the citric acid cycle, and thus may be very important in the production of energy.

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*Amino Acid Metabolism*



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*Glucogenic and Ketogenic Amino Acids*

- There are two types of amino acid carbon skeletons:
  - **Glucogenic amino acids** have a carbon skeleton that can be metabolically converted to pyruvate or an intermediate of the citric acid cycle. These amino acids can be used to make glucose.
  - **Ketogenic amino acids** have a carbon skeleton that can be metabolically converted to acetyl CoA or acetoacetyl CoA. They cannot be converted into glucose, but can be used to make ketone bodies and fatty acids.
- After glycogen stores are used up, glucogenic amino acids can be used to synthesize glucose. The amino acids come from hydrolysis of proteins from body tissues, primarily muscle. The body can meet its energy needs for only a limited time by sacrificing proteins.

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# Amino Acid Biosynthesis

## Essential and Nonessential Amino Acids

- The liver produces most of the amino acids that the body can synthesize. Amino acids that can be made in the amounts needed by the body are called **nonessential amino acids**, because they do not need to be obtained from the diet.
- The **essential amino acids** cannot be made in large enough amounts, and must be obtained from the diet.

**Table 24.3** Essential and Nonessential Amino Acids

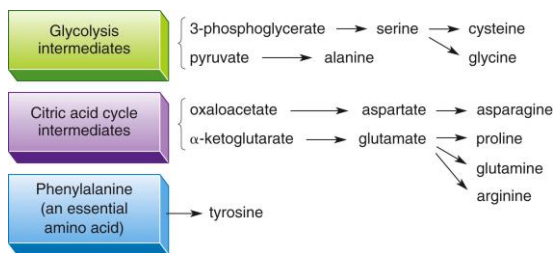
Essential	Nonessential	Essential	Nonessential
Histidine	Alanine	Threonine	Glutamine
Isoleucine	Arginine	Tryptophan	Glycine
Leucine	Asparagine	Valine	Proline
Lysine	Aspartate		Serine
Methionine	Cysteine		Tyrosine
Phenylalanine	Glutamate		

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## Biosynthesis of Nonessential Amino Acids

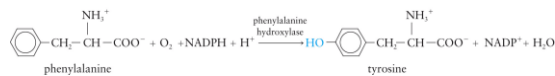
- The key starting materials for the synthesis of 10 nonessential amino acids are intermediates in glycolysis and the citric acid cycle:



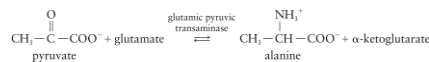
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## Biosynthesis of Nonessential Amino Acids

- Tyrosine is produced from the essential amino acid phenylalanine:



- Three nonessential amino acids (glutamate, alanine, and aspartate) are synthesized from α-keto acids via transamination:

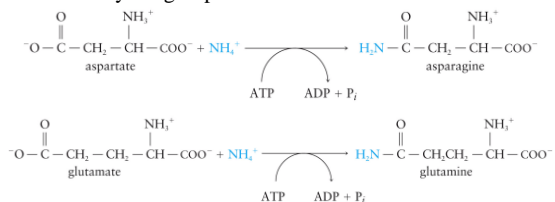


- The transaminases adjust the relative proportions of amino acids to meet the needs of the body, since most of our diets do not contain amino acids in the exact proportions needed by the body

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## Biosynthesis of Nonessential Amino Acids

- Asparagine and glutamine are formed from aspartate and glutamate by reaction of the side-chain carboxylate groups with ammonium ions:



- The synthesis of arginine, cysteine, glycine, proline, and serine are considerably more complex.

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