Chapter 15 Lecture Notes: Metabolism

Educational Goals
1. Define the terms metabolism, metabolic pathway, catabolism, and anabolism.
2. Understand how ATP is formed from ADP and inorganic phosphate (P), and vice versa.
3. Understand how Coenzyme-A is used to transfer acyl groups.
4. Understand the roles of the NAD+/NADH and FAD/FADH₂ coenzymes in the transfer of electrons. Identify the oxidized and reduced form of each of these pairs.
5. Understand the differences between linear, circular, and spiral metabolic pathways and give an example of each.
6. Name the products formed during the digestion of polysaccharides, triglycerides, and proteins, and know the part(s) of the digestive track where each occurs.
7. Identify the initial reactant and final products of glycolysis, and understand how this pathway is controlled.
8. Understand and compare glycolysis and gluconeogenesis pathways.
9. Know the fate of pyruvate under aerobic and anaerobic conditions.
10. Define the terms hyperglycemic and hypoglycemic.
11. Understand how the body controls blood glucose concentration by the release of insulin or glucagon into the bloodstream.
12. Understand and compare glycogenesis and glycogenolysis. Understand how these processes are involved in maintaining normal blood glucose concentration.
13. Understand and compare type I, type II, and gestational diabetes.
14. Identify the initial reactant and final products of the citric acid cycle; understand how this pathway is controlled.
15. Understand how the oxidation of coenzymes during oxidative phosphorylation is used to produce ATP.
16. Compare the malate-aspartate shuttle and the glycerol 3-phosphate shuttle and understand their significance in affecting the amount of ATP that can be produced from glucose.
17. Predict how many ATP are formed when acetyl-CoA undergoes stages 3 and 4 of catabolism.
18. Describe the catabolism of triglycerides, the β-oxidation spiral, and how β-oxidation differs from fatty acid anabolism (biosynthesis).
19. Given the structure of a fatty acid, predict how many ATP are formed when it undergoes the β-oxidation spiral.
20. Understand and compare lipolysis and fatty acid synthesis.
21. Explain the biological origins of ketosis and ketoacidosis.
22. Understand how transamination and oxidative deamination are involved in the catabolism of amino acids.
23. Given the structure of an amino acid and α-ketoglutarate, predict the products of a transamination reaction.
24. Explain how quaternary ammonium groups (-NH₃⁺) are removed from amino acids and eliminated from the body.
An Overview of Metabolism

___________ is defined as the entire set of life-sustaining chemical reactions that occur in organisms.

- These reactions number in the thousands and include reactions such as those responsible for getting energy from food, processing and removal of waste, building up muscles, growth, photosynthesis in plants, cell division, and reproduction.

The entire set of metabolic reactions is organized into smaller sets of sequential reactions called metabolic _____________.

The species produced in the various reactions of a metabolic pathway are sometimes referred to as _____________.

Many of the reactions in metabolic pathways require enzymes; therefore organisms can control (accelerate or suppress) metabolic pathways, according to their current needs, by upregulating, downregulating, inhibiting, or activating one or more of the enzymes involved in the pathway.

Metabolic pathways can usually be classified as catabolic (catabolism) or anabolic (anabolism).

- **Catabolic pathways** involve the _____________ of larger organic compounds into smaller compounds.

- **Anabolic pathways** involve _____________ ____ of larger organic compounds from smaller ones.

In this chapter, you will learn about the pathways that are involved in the metabolism of carbohydrates, proteins, and fats.

- An ultimate goal of these reactions is to convert the chemical potential energy contained in food into chemical potential energy in the form of _____________.

The Coenzymes Involved in Metabolism

A coenzyme is a species that must bind to an enzyme in order for the enzyme to function.

- In most cases, a coenzyme is actually one of the substrates (reactants) in the catalyzed reaction.
- The reason that certain substrates are also referred to as coenzymes is that these substrates are common substrates in many different enzymatic reactions in which they donate electrons, atoms, or groups of atoms to other substrates, or accept electrons, atoms or groups of atoms from other substrates.
- The five group-transfer coenzymes that are central to the metabolism of food, along with the species each transfers are listed in the table on the right.

<table>
<thead>
<tr>
<th>Coenzyme</th>
<th>Species that is Transferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADP/ATP</td>
<td>phosphoryl group = [O-P-O]</td>
</tr>
<tr>
<td>NAD+/NADH</td>
<td>hydride ion (H+) or electrons</td>
</tr>
<tr>
<td>FAD/FADH₂</td>
<td>hydride ion (H+) or electrons</td>
</tr>
<tr>
<td>coenzyme A</td>
<td>acyl group = [R-C]</td>
</tr>
<tr>
<td>coenzyme Q</td>
<td>hydride ion (H+) or electrons</td>
</tr>
</tbody>
</table>
Phosphoryl Group-Transfer Coenzymes: ATP and ADP

ATP and ADP are classified as coenzymes because they are involved in the transfer of \( \text{PO}_3^- \) groups (PO₃⁻) in many different enzymatically catalyzed reactions.

- When a compound gains/accepts a phosphoryl group in a reaction, we say that the compound became “phosphorylated.”
- When a compound loses/donates a phosphoryl group in a reaction, we say that it was “dephosphorylated.”

ATP and ADP are interconverted by the transfer of a phosphoryl group, as shown below.

- Adding a phosphoryl group to ADP \( \text{requires} \) energy.
- Removing a phosphoryl group from ATP \( \text{requires} \) energy.

ATP is often formed by the reaction of ADP with hydrogen phosphate (HPO₄²⁻) and an H⁺ ion, as shown below.

Biological literature refers to hydrogen phosphate as “__________phosphate” (abbreviated as Pᵢ).

Another way that organisms convert ADP to ATP is by the reaction of ADP with an \( \text{organic molecule that contains a phosphoryl group} \). In this case, a phosphoryl group is transferred \( \text{from} \) the organic molecule to ADP, as shown in the chemical equation below.

You will see hydrogen ions (H⁺) as reactants in many of the reactions in this chapter. Because these reactions occur in aqueous solutions, H⁺ is readily available from H₂O, and can also come from H₃O⁺ or the acid forms of other species that are present.
Energy is released from ATP when it is converted to ADP. This energy is used by organisms to drive energy-requiring reactions or physical processes that would otherwise not occur spontaneously. One way that energy can be released from ATP is by reacting it with H₂O to form ADP, inorganic phosphate, and an H⁺ ion. Although this reaction is spontaneous (ΔG is negative), the reaction rate is quite slow, therefore organisms employ enzymes in order for the reaction to proceed at a useful rate. The chemical equation for this reaction is shown below.

\[
\text{H}_2\text{O} + \text{ATP} \rightleftharpoons \text{ADP} + \text{inorganic phosphate} + \text{H}^+ \]

\[\Delta G = -7300 \text{ Joules per mole of ATP}\]

Note that H⁺ is produced in this reaction. You will see H⁺ ions as products in many of the reactions in this chapter. Keep in mind that the H⁺ ions that are produced in aqueous solutions do not remain solvated as isolated ions; they quickly react with water to form H₃O⁺. Alternatively, H⁺ can react with OH⁻ or the base form of another species that is present.

Another way that organisms extract energy from ATP is to “energize” organic compounds by transferring a phosphoryl group directly to the compound. In this reaction, ATP is dephosphorylated and an organic compound is phosphorylated, as shown in the reaction below:

\[
\text{ATP} + \text{organic compound} \rightleftharpoons \text{ADP} + \text{phosphorylated organic compound} + \text{H}^+ \]

Chemical potential energy released by the conversion of ATP to ADP is transferred to the phosphorylated organic product.

- It is for this reason that we say “the organic compound is energized” in the reaction.

Example:

In this particular reaction, the reverse reaction occurs so slowly that it is negligible.

- In such cases, we refer to the reaction as an “____________________reaction.”

When writing a chemical equation for an irreversible reaction, only a forward (left to right) arrow is used, as shown above.

Biochemical literature often uses an alternative chemical equation format. For example, the reaction shown above is often written as:
Electron-Transfer Coenzymes and Their Role as Oxidizing and Reducing Agents

Oxidation-reduction reactions, which involve the transfer of one or more electrons, are quite common in organisms. Many of these reactions involve the transfer of an electron by way of the hydride ion \((H^-)\).

A **reduction** occurs when a ____________ ion forms a bond with an organic compound.

- The transfer of a hydride ion is a reduction because of hydride’s “extra” electron. For example, aldehydes or ketones are **reduced** when a **hydride ion** forms a bond with them.

\[
\begin{align*}
\text{H}^+ & \quad \text{an H}^+ \text{ from the solution} \\
\text{R} & \quad \text{C} \quad \text{C} \quad \text{R'} & \quad \text{R} & \quad \text{C} \quad \text{C} \quad \text{R'} \\
\text{H}^- & \quad \text{a hydride ion} & \quad \text{H}^- & \quad \text{OH} \\
\text{a ketone} & \quad \text{an alcohol} & 
\end{align*}
\]

An ____________ occurs when a **hydride ion** \((H^-)\) and an \(H^+\) ion are **removed** from an organic compound.

- For example, \(2^\circ\) alcohols can be **oxidized** to ketones, as shown in the chemical equation below.

\[
\begin{align*}
\text{R} & \quad \text{OH} \\
\text{CH} & \quad \text{R'} & \quad \text{R} & \quad \text{C} \quad \text{R'} + \text{H}^- + \text{H}^+ \\\n\text{an alcohol} & \quad \text{a ketone} & 
\end{align*}
\]

- This is considered an oxidation because the hydride ion carries away the “extra” electron.

Nicotinamide adenine dinucleotide (NAD\(^+\)) and flavin adenine dinucleotide (FAD) are classified as **coenzymes** because they are common substrates, involved in the transfer of ____________, in many different enzymatically catalyzed reactions.

**Nicotinamide Adenine Dinucleotide (NAD\(^+\))**

The structural formula of NAD\(^+\) is shown on the left. NAD\(^+\) contains two nucleotide residues. One of the nucleotides has an **adenine** base, and the other contains a **nicotinamide** base.
When NAD$^+$ accepts a hydride ion from another species, it is reduced to NADH.

- It is for this reason that NADH is referred to as a reduced form of the coenzyme or a “______________ ________________.”
- The reduction of NAD$^+$ requires energy.

When NADH donates a hydride ion (to another species) it is oxidized to NAD$^+$.

- NAD$^+$ is referred to as the oxidized form of the coenzyme or an “______________ ________________.”
- Oxidation of NADH releases energy.

**Example:** The oxidation of an organic compound using NAD$^+$ as the oxidizing agent:

$$\text{HO-C} + \text{NAD}^+ \rightarrow \text{CH}_2 + \text{NAD} + \text{H}^+$$

- In this reaction, malate is oxidized and NAD$^+$ is reduced.
Flavin Adenine Dinucleotide (FAD)

When FAD accepts a hydride ion from another species (and an \( \text{H}^+ \) from solution), it is **reduced** to FADH\(_2\).
- The reduction of FAD **requires** energy.

FADH\(_2\) is **oxidized** to FAD by *donating two* electrons (and two \( \text{H}^+ \) ions) to other species.
- The oxidation of FADH\(_2\) **releases** energy.

Much like NAD\(^+\)/NADH and FAD/FADH\(_2\), **Coenzyme Q** (*not shown*), transfers electrons and hydrogen ions when it cycles between its oxidized and reduced forms.

**Acyl Group-Transfer Coenzyme: Coenzyme A**

Coenzyme A (H-CoA) is used in many metabolic reactions. Its structural formula is shown below.
Coenzyme A is classified as a coenzyme because it is involved in the transfer of an ______ group in many different enzymatically catalyzed reactions.

- An acyl group consists of a carbonyl group bonded to an organic group (R), as shown on the right.
- When coenzyme A (H-CoA) accepts an acyl group, the acyl group replaces the left-most hydrogen in the coenzyme A structure.

An acyl group that is central to the metabolism of food is the ____________ group.
- Acetyl groups are donated and accepted by coenzyme A, as shown below:

Carbohydrate Metabolism

The energy that is contained in food can be traced back to the ____________.

- Energy from sunlight is captured by plants during photosynthesis as they convert CO₂ and H₂O into glucose and O₂.
- Without energy from sunlight, the reaction of CO₂ with H₂O to produce glucose and O₂ is not spontaneous.
- The input of energy from sunlight provides the energy that is required to convert CO₂ and H₂O to glucose and O₂.
In photosynthesis, energy from the sun’s light does not vanish; it is converted to 
_________________________ within _____________.

- Plants store excess glucose as starch.

Organisms, including humans, use a series of catabolic chemical reactions to slowly _______________ carbohydrates and other food, eventually converting it back to CO₂ and H₂O.

Energy that is released in these oxidations is converted to chemical potential energy within ________.

All three classes of macronutrients in food, carbohydrates, triglycerides (fats), and proteins, are catabolized in four stages:

Stage 1: ________________________________
Stage 2: ________________________________
Stage 3: ________________________________
Stage 4: ________________________________

Stage 1: Digestion of Carbohydrates

Digestion is the process in which the body breaks down carbohydrate, protein, and triglyceride polymers into their _______________ residues.

- For example, carbohydrate polymers are converted to monosaccharides.

Digestion occurs in the digestive system.

The digestive system, sometimes referred to as the digestive track or gastrointestinal (GI) track, includes the organs that are responsible for digesting food and eliminating the undigestible components of food. The major organs of the human digestive system are shown on the right.

During the digestion of carbohydrate polymers, most oligosaccharides (2-10 monosaccharide residues) and polysaccharides (> 10 monosaccharide residues) can be broken down to _________________.

- These reactions are catalyzed by _______________ ________________.

Approximately 50% of our dietary carbohydrates are in the form of starch.

- Starch has two components, amylose and amylopectin, both of which are composed entirely of ________________ residues.
Digestion of amylose and amylopectin (starch) begins in the ____________.

Saliva contains ____________ ____________ enzymes, which catalyze the hydrolysis of some of the \( \alpha-(1\rightarrow4) \) glycosidic bonds in amylose and amylopectin.

In the hydrolysis of carbohydrates, water molecules are used to lyse (break) ____________ bonds.

An Illustrative Overview of the Digestion of Carbohydrates

Salivary amylase catalyzes the hydrolysis of amylose and amylopectin to form maltose (an \( \alpha-(1\rightarrow4) \) glucose-glucose disaccharide) and small oligosaccharides called dextrins.

Dextrins are oligosaccharides that generally contain between three and eight glucose residues.

The maltose, dextrins, and other non-starch dietary carbohydrates then pass through the stomach, where carbohydrate digestion temporarily stops because the salivary amylase is denatured by the stomach’s low pH (very acidic) environment.

Digestion continues in the small intestine with the help of more digestive enzymes.

Pancreatic amylase catalyzes the hydrolysis of dextrins to form maltose and isomaltose. Isomaltose is an \( \alpha-(1\rightarrow6) \) glucose-glucose disaccharide that comes from the branching points in amylopectin.

Maltase and isomaltase enzymes catalyze the hydrolysis of maltose and isomaltose (respectively) into glucose.
The **non starch** dietary carbohydrates, *lactose* and *sucrose*, are converted to monosaccharides with the help of *lactase* and *sucrase* enzymes, respectively.

- Lactose is hydrolyzed to galactose and glucose.
- Sucrose is hydrolyzed to fructose and glucose.

It is critical that oligosaccharides and polysaccharides be converted to monosaccharides in order for the sugars to pass through the intestine wall and into the bloodstream so that they are available to cells throughout the body.

Monosaccharides are transported into the cells by passive diffusion through transmembrane proteins.

Not all dietary carbohydrates can be digested.

- For example, cellulose cannot be digested because humans do not have a dietary enzyme capable of hydrolyzing β-(1→4) glucose-glucose glycosidic bonds. Cellulose cannot pass through the small intestine and therefore passes through the digestive track until it is excreted in feces.

**Stage 2: Acetyl-Coenzyme A Production**

When glucose enters a cell, it can then undergo stages 2, 3, and 4 of catabolism.

In stage 2 of carbohydrate catabolism, *glucose* is converted into *acetyl-coenzyme A*, CO₂, and H₂O.

This process begins with a **catabolic pathway** called ____________.

**Glycolysis** is a series of ______ sequential reactions that ultimately converts one glucose molecule to two pyruvate ions and two H₂O molecules.

**NOTE:** I want to minimize any possible student anxiety by informing you that is not my intention for you to memorize these reactions, the names of the intermediates, or the names of the enzymes that are involved.

The **reactions of glycolysis**:
Notice that one glyceraldehyde 3-phosphate is produced in reaction 4 and a second glyceraldehyde 3-phosphate is produced in reaction 5. Therefore, each of the subsequent reactions in the pathway will occur twice for each molecule of glucose that undergoes glycolysis.

It is for this reason the reactants and products in the chemical equations that follow have a stoichiometric coefficient of “2.”

Reaction 6) In this reaction, glyceraldehyde 3-phosphate is oxidized. An oxidation cannot occur without a reduction. In this case, NAD$^+$ is reduced to NADH. This occurs when a hydride ion (H$^-$) is transferred from glyceraldehyde 3-phosphate’s carbonyl carbon to NAD$^+$. The reduction of NAD$^+$ to NADH requires energy, that energy comes from glyceraldehyde 3-phosphate.

The energy that is acquired by NADH can later be used to convert ADP to ATP.

- You will learn how that happens when I discuss stage 4 of metabolism.
The reactions of glycolysis result in a net gain of two ATP and two NADH.

When there is a sufficiently high concentration of ATP, pyruvate, or other pathway products, then the rate of glycolysis can be slowed down. If the ATP concentration becomes low, then glycolysis can be accelerated. The rate of the glycolysis pathway is controlled by enzyme inhibitors and enzyme activators of the enzymes involved in the irreversible reactions (1, 3, and 10).

- For example, ATP and phosphoenolpyruvate (the product of reaction 9) act as inhibitors of the phosphofructokinase enzyme that catalyzes reaction 3.
Summary of Glycolysis

The chemical equation for the overall glycolysis pathway is:

\[
glucose + 2 \text{ADP} + 2 \text{P}_i + 2 \text{NAD}^+ \rightleftharpoons 2 \text{pyruvate ions} + 2 \text{ATP} + 2 \text{NADH} + 2 \text{H}_2\text{O} + 2 \text{H}^+ \]

The ten reactions of glycolysis result in a net gain of ________ ATP and ________ NADH.

Not all of the energy from glucose is transferred to the ATP and NADH formed in glycolysis.

- Some energy was lost as heat during the reactions, however, most of glucose’s chemical potential energy remains in the two pyruvate ions.

Glycolysis is characterized as a ____________ metabolic pathway.

- A linear metabolic pathway is a series of reactions that are not repeated.

Understanding Check:

a. How many ATP are produced when six glucose molecules undergo glycolysis?

b. How many NADH are produced when six glucose molecules undergo glycolysis?

Before we take a look at the fate of the pyruvate that is produced in glycolysis, let’s consider how non glucose monosaccharides are metabolized.

The Entry of Non Glucose Monosaccharides into Glycolysis

Although glucose is the major product of carbohydrate digestion, it is not the only monosaccharide that is produced.

Other monosaccharides can be catabolized when they are converted to ____________ in the glycolysis pathway.

- For example, fructose, galactose, and mannose monosaccharides are produced in carbohydrate digestion and can be converted to the glycolysis intermediates as shown on the right.
The Fate of Pyruvate

The fate of the pyruvate that is produced by aerobic organisms (organisms that require O\textsubscript{2} to grow), such as humans and most other organisms, depends on the availability of ____________ in cells.

During strenuous physical activity, the oxygen in muscle cells becomes depleted (anaerobic condition).

- When this occurs, the pyruvate that is made in glycolysis remains in the cytoplasm and is converted (reduced) to ____________, as shown in the reaction below.

\[
\begin{array}{c}
\text{pyruvate} \\
\text{H}^+ \text{ (from solution)}
\end{array}
\xrightarrow{\text{lactate dehydrogenase}}
\begin{array}{c}
\text{NADH} \\
\text{NAD}^+
\end{array}
\xrightarrow{\text{OH}}
\begin{array}{c}
lactate
\end{array}
\]

The presence of lactate in a muscle causes the muscle to tire and feel sore.

Lactate is released by muscle cells into the circulatory system and then taken up by ____________ cells. **In the liver, lactate can be cycled back to pyruvate.**

After lactate is transformed back to pyruvate, it can be converted to glucose and stored for future use.

The conversion of non carbohydrate species to glucose is called ____________.

- The conversion of lactate and pyruvate to glucose is an example of gluconeogenesis.

The **gluconeogenesis** and **glycolysis** pathways share many reactions. The differences occur at the three irreversible glycolysis reactions (reactions 1, 3, and 10), as shown in the figure on the left.

Gluconeogenesis does not use reaction 10 of glycolysis, and it uses different enzymes in order to enable the reverse of reactions 1 and 3 of glycolysis.

Gluconeogenesis takes place primarily in the liver.

In the figure above, **glycolysis** proceeds in the downward direction, and **gluconeogenesis** proceeds in the upward direction.
When oxygen is present (___________ conditions), much more energy can be derived from pyruvate.

Under aerobic conditions, pyruvate passes from the cytoplasm into the _______________ and is then converted to acetyl-coenzyme A and CO₂ (as shown in the equation below).

\[
\begin{align*}
\text{pyruvate} & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ quasi
Stage 3: The Citric Acid Cycle

The citric acid cycle is also referred to as the Krebs Cycle because it was H. A. Krebs who, in 1937, discovered these reactions and recognized their significance in energy-transfer reactions.

NOTE: you do not need to memorize these reactions, the names of the intermediates, or the names of the enzymes that are involved.

The citric acid cycle is characterized as a ________________ metabolic pathway.

- A circular pathway is a repeating series of reactions in which the final product is _______ an initial reactant.

- In the first reaction, acetyl-coenzyme A (acetyl-CoA) reacts with oxaloacetate. In the citric acid cycle, oxaloacetate is not only a reactant in the first reaction; it is also the product of the last reaction.
Acetyl-CoA brings two carbons in its acetyl group (these carbons are shown in red font in the video).

When one acetyl-CoA is completely processed in the citric acid cycle, ______NADH, ______FADH₂, ______ ATP, and two CO₂ molecules are produced.

In this process, energy that was originally contained in acetyl-CoA is converted to chemical potential energy within NADH, FADH₂ and ATP.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Type of Reaction</th>
<th>Enzyme</th>
<th>Energy Transferred to</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>acetyl group transfer</td>
<td>citrate synthase</td>
<td>An acetyl group is transferred to oxaloacetate.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>isomerization</td>
<td>aconitase</td>
<td>The product and reactant are constitutional isomers.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>oxidation/reduction and decarboxylation</td>
<td>isocitrate dehydrogenase</td>
<td>NADH</td>
<td>This reaction is irreversible. \textit{Isocitrate} is decarboxylated and its hydroxyl group is oxidized to a carbonyl group. A hydrate ion (H₂⁻) is transferred from \textit{isocitrate} to \textit{NAD⁺}, thereby reducing \textit{NAD⁺} to NADH. This reaction is the body's main regulation point for the citric acid cycle. When cells are &quot;energy rich,&quot; ATP and NADH concentrations are high. ATP and NADH inhibit the \textit{isocitrate dehydrogenase} enzyme. When energy is in demand, ADP and NAD⁺ concentrations are high. ADP and NAD⁺ activate \textit{isocitrate dehydrogenase}.</td>
</tr>
<tr>
<td>4</td>
<td>oxidation/reduction and decarboxylation</td>
<td>(\alpha)-ketoglutarate dehydrogenase</td>
<td>NADH</td>
<td>This irreversible process has multiple steps (not shown). Two electrons are transferred from (\alpha)-ketoglutarate to an intermediate species. Ultimately, the two electrons and a H⁺ ion are transferred from an intermediate to \textit{NAD⁺} to form NADH.</td>
</tr>
<tr>
<td>5</td>
<td>acyl group transfer and phosphorylation</td>
<td>succinyl-CoA synthase</td>
<td>ATP</td>
<td>Humans have a \textit{succinyl-CoA synthase} enzyme that produces GTP (guanosine triphosphate). Energy in GTP is used to produce an ATP. We have another \textit{succinyl-CoA synthase} enzyme that produces ATP directly.</td>
</tr>
<tr>
<td>6</td>
<td>oxidation/reduction</td>
<td>succinate dehydrogenase</td>
<td>FADH₂</td>
<td>-CH₂-CH₂⁻ is oxidized to -CH=CH⁻. FAD is reduced to FADH₂. The FAD/FADH₂ coenzyme is permanently bound to the succinate dehydrogenase enzyme.</td>
</tr>
<tr>
<td>7</td>
<td>hydration</td>
<td>fumarase</td>
<td>Hydration of an alkene.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>oxidation/reduction</td>
<td>malate dehydrogenase</td>
<td>NADH</td>
<td>Malate's 2⁺ alcohol is oxidized to a ketone. NAD⁺ is reduced to NADH.</td>
</tr>
</tbody>
</table>

Summary of the Citric Acid Cycle

The overall chemical equation for the \textit{citric acid cycle} metabolic pathway is:

\[
\text{acetyl-CoA} + 3 \text{NAD}^+ + \text{FAD} + \text{ADP} + \text{P}_i + 2 \text{H}_2\text{O} \rightleftharpoons 2 \text{CO}_2 + 3 \text{NADH} + \text{FADH}_2 + \text{ATP} + \text{H-CoA} + 3 \text{H}^+
\]

Potential energy from an acetyl-CoA that undergoes the citric acid cycle is converted to potential energy in \textit{three} NADH, \textit{one} FADH₂, and \textit{one} ATP. Some energy is lost as heat.

The CO₂ produced in the \textit{citric acid cycle} and in \textit{stage 2} of metabolism, is one of the end-products of food metabolism.

- CO₂ is the most-oxidized form of carbon in organic compounds, and therefore has a very low energy content.
- Energy that was present in the food and food metabolites that contained these carbons has been extracted in the catabolism process.
Stage 4: Oxidative Phosphorylation

Glycolysis occurs in the ________________ of the cell.

The reactions of the citric acid cycle occur in the ________________.

A mitochondrion consists of an ________ membrane bilayer and an ________ membrane bilayer.

The region between the outer and inner membranes is called the ________________ _________.

The region within the inner membrane is called the ________________.

Pyruvate oxidation/decarboxylation and the reactions of the citric acid cycle occur in the matrix region.

The pyruvate that is produced in glycolysis is able to pass from the cytoplasm, through both the inner and outer mitochondrial membranes, into the matrix region.

The next stage of carbohydrate catabolism, oxidative phosphorylation (stage 4), requires that ________ be located within the mitochondrial matrix.

- Since pyruvate oxidation/decarboxylation and the reactions of the citric acid cycle occur in the mitochondrial matrix, the NADH created in those processes can immediately undergo oxidative phosphorylation.

- The NADH that is produced by glycolysis is able to pass through the outer mitochondrial membrane and enter the intermembrane space; however, it is not able to pass through the inner mitochondrial membrane to enter the matrix region.
  
  o In order for the energy from these NADH to be utilized, they must be processed through an “NADH __________.”

Understanding Check: Calculate the net gain of NADH, FADH$_2$, and ATP from one glucose molecule that undergoes the first three stages of catabolism.

- Keep in mind that glycolysis produces **two** pyruvate ions, which results in the production of two acetyl-CoA.
The two most important NADH shuttles are the **malate-aspartate shuttle** and the **glycerol 3-phosphate shuttle**.

- The **malate-aspartate shuttle** works by oxidizing the NADH to NAD$^+$ in the intermembrane space, then transferring the electrons through the inner mitochondrial matrix to an NAD$^+$ that is **inside the matrix**, thereby producing an NADH that can undergo oxidative phosphorylation.

- In the **glycerol 3-phosphate shuttle**, NADH is oxidized in the intermembrane space by transferring electrons to an inner mitochondrial membrane-bound FAD, *thereby producing an FADH$_2$* that can undergo oxidative phosphorylation.

---

**Example Problem:** From one glucose molecule, determine how many NADH and FADH$_2$ would be available for *oxidative phosphorylation* (stage 4 of metabolism). Assume that both NADH formed in glycolysis use the **malate-aspartate shuttle**.

**Solution:** Start this problem with the amount of NADH and FADH$_2$ that are formed *from one glucose* molecule in stages 1 to 3 of glucose catabolism. In the previous **UNDERSTANDING CHECK** problem (chapter 15, part 5), you found that 10 NADH, and 2 FADH$_2$ are produced from one glucose molecule.

---

The **two NADH** that are produced in *glycolysis* cannot pass through the inner mitochondrial membrane and enter the matrix region where oxidative phosphorylation takes place. Therefore, it is necessary that “NADH shuttles” be used. In the **malate-aspartate shuttle**, each NADH produced in *glycolysis* results in one NADH that can undergo oxidative phosphorylation. In this case, there would be **10 NADH** and **2 FADH$_2$** available for oxidative phosphorylation.
The primary goal of food catabolism is the production of ATP.

At this point in my narrative of carbohydrate catabolism:
- Only four ATP have been produced from one glucose so far.
- Most of the chemical potential energy that has been extracted from glucose is still in the form of ________ ________ (NADH and FADH$_2$).

In stage 4 of catabolism (oxidative phosphorylation), chemical potential energy contained in the reduced coenzymes is ______________ to ATP.

Oxidative phosphorylation is the process in which _________ from NADH or FADH$_2$ are transferred, through a series of electron transfer intermediates, to dissolved oxygen (O$_2$) in order to provide the energy required to produce ATP.

In this process, ADP and an inorganic phosphate (P$_i$) are converted to ATP.

The formation of ATP from ADP and P$_i$ would not occur spontaneously without the input of energy that is provided when electrons are transferred to O$_2$.

Because of the availability of H$^+$ in solution (from H$_2$O, H$_3$O$^+$, or the acid form of any other species present), when electrons are transferred to oxygen, the following reaction occurs:

$$O_2 + 4H^+ + 4 \text{ electrons} \rightarrow 2H_2O$$

In the reaction above, O$_2$ is ______________; it gains electrons

O$_2$ is the final _____________ of electrons in food catabolism.

**You try one:** From one glucose molecule, determine how many NADH and FADH$_2$ would be available for oxidative phosphorylation (stage 4 of metabolism). Assume that both NADH formed in glycolysis use the glycerol 3-phosphate shuttle.
The energy released by the transfer of electrons from NADH or FADH\textsubscript{2}, through the electron transfer intermediates, to O\textsubscript{2} is not immediately used to drive the production of ATP.

Instead, this energy is used to move hydrogen ions from a region of lower hydrogen ion concentration (the mitochondrial matrix) to a region of higher hydrogen ion concentration (the intermembrane space).

By doing so, the energy that is released by the transfer of electrons is converted to ______________ potential energy:

- Physically, this is very similar to “charging” a battery

Oxidative phosphorylation does not happen in exactly the same way for NADH as it does for FADH\textsubscript{2}.

**Electron Transfers and Hydrogen Ion Transport From NADH Oxidation**

The process begins with the ______________ of NADH in the matrix region.

The electrons that are released in the oxidation of NADH are sequentially passed between electron transfer intermediates (shaded green) along the path that is indicated by the dashed red curve.

- Two of the electron transfer intermediates, *coenzyme Q* (CoQ) and *cytochrome C* (Cyt c), are quite mobile.
- The other electron transfer intermediates are *transmembrane proteins complexes* (labeled I, III, and IV).
In order for the electrons to “move through” these protein complexes, they are transferred within the complexes by sequential oxidations and reductions of neighboring prosthetic groups or cofactors (not shown in the figure).

The movement of electrons through the protein complexes releases energy (analogous to water being released from a dam).

This energy is used by the complexes to ________ ________ hydrogen ions from a region of ________ hydrogen ion concentration (the mitochondrial matrix) to a region of ________ hydrogen ion concentration (the intermembrane space), as indicated in the figure by the arrows in the figure on the previous page.

Electrons are ultimately transferred to, and thereby reduce O\textsubscript{2}.

**Electron Transfers and Hydrogen Ion Transport from FADH\textsubscript{2} Oxidation**

FADH\textsubscript{2} is produced in _____________ of the citric acid cycle.

- The enzyme that catalyzes this reaction is part of an electron transfer intermediate called complex II.

In oxidative phosphorylation, FADH\textsubscript{2} is oxidized and its electrons are sequentially passed between electron transfer intermediates, along the path that is indicated by the dashed curve, and then finally transferred to O\textsubscript{2}.

The movement of electrons through protein complexes III and IV releases energy.

This energy is used by these complexes to actively transport hydrogen ions through the inner mitochondrial membrane into the intermembrane space.
Summary of the Oxidation of NADH and FADH$_2$ During Oxidative Phosphorylation

When NADH and FADH$_2$ are oxidized, their electrons are transferred, through intermediates, to O$_2$. As electrons move through complexes I, III, and IV, energy is released. This energy is used by the complexes to actively transport hydrogen ions from a region of lower hydrogen ion concentration (the mitochondrial matrix) to a region of higher hydrogen ion concentration (the intermembrane space).

In doing so, the energy from NADH and FADH$_2$ (that was originally in food) is converted to electrochemical energy within mitochondria.

This part of oxidative phosphorylation is often referred to as _______________ ________________.

The electron transfer intermediates (shaded green in the previous figures) that are involved in electron transport are sometimes called “the electron transport chain."

Next, you will learn how electrochemical energy within mitochondria is used to drive the production of ATP.

ATP Production in Oxidative Phosphorylation

When there are unequal concentrations of a species on opposite sides of a membrane, we say that a “concentration ________________” exists.

The creation of electrochemical potential energy in the form of an H$^+$ concentration gradient was like charging a battery.

As with any dissolved species, hydrogen ions will ________________ diffuse from areas of high concentration to areas of low concentration.

- It is lower in energy for the hydrogen ions to be in the matrix region (low concentration) than it is for them to be in the intermembrane space (higher concentration).

The only path between these regions in which hydrogen ions can passively diffuse is through the _______________ enzyme, as illustrated below.

Much like electrical current passing through an electric motor does work, the passing of hydrogen ion current through an ATP synthase does work.

- This work is done by forcing the enzyme to change its shape and thereby supply the energy needed to form a bond between an inorganic phosphate (P$_i$) and ADP, to produce ATP.

The ATP synthase enzyme not only catalyzes the reaction for the synthesis of ATP, it also plays a role in delivering the energy needed to make ATP synthesis occur spontaneously.
The number of ATP that can be produced from NADH or FADH$_2$ depends on the cell and its current conditions.

The latest research indicates that, on average,
one NADH produces about _______ ATP, and
one FADH$_2$ produces about _______ ATP.

Let’s calculate how many ATP can be produced from the catabolism of one glucose molecule.

- For this calculation, we will assume that each NADH produces 2.5 ATP, and each FADH$_2$ produces 1.5 ATP, and that NADH produced in glycolysis use the malate-aspartate shuttle.

Solution:

Stage 2: In glycolysis, glucose is converted to two pyruvate ions. In this process, two NADH and two ATP are formed. The two NADH undergo the malate aspartate shuttle and result in the formation of two NADH within the mitochondrial matrix.

The pyruvate ions can diffuse past both mitochondrial membranes, and enter the matrix region. There, the pyruvate ions undergo an oxidation/decarboxylation reaction. In this process, two NADH and two acetyl-CoA are formed.

Stage 3: In the citric acid cycle, the two acetyl-CoA produce a total of six NADH, two FADH$_2$, and two ATP.

Stage 4: In oxidative phosphorylation, the ten NADH and two FADH$_2$ produced in stages 2 and 3 are oxidized in order to produce ATP.

This gives total of 32 ATP, as shown in the illustration below.
Summary of Carbohydrate Catabolism

In the four stages of carbohydrate catabolism, chemical potential energy in carbohydrates is converted to chemical potential energy in ATP, a substance that can be used immediately by all cells to do cellular work.

The carbon, hydrogen, and oxygen atoms in carbohydrates, along with the oxygen we inhale, are converted to \( \text{H}_2\text{O} \) and \( \text{CO}_2 \).

Regulation of Blood Glucose Concentration

It is important for human blood glucose concentration (sometimes called blood sugar level) to remain within a “normal” range.

- The normal range of glucose concentration in the blood is about 80 to 110 mg per dL of blood.

Long term effects of having higher than normal blood glucose concentration (__________) can include damage to kidneys, the neurological system, the cardiovascular system, eyes, feet, and legs.

Between meals or during starvation, blood glucose levels fall below the normal range (__________).

- This can result in confusion, loss of coordination, difficulties in speaking, a loss of consciousness, seizures, and even death. Symptoms can come on quite quickly and include hunger, shaking, sweating, and weakness.

In the “fed” state, which occurs soon after a meal when blood glucose levels are high, liver and muscle cells (primarily) take in extra glucose and store it in the form of ____________.

- The chemical structure of glycogen is very similar to that of amylopectin; the only exception is that glycogen branches more frequently. For a review of glycogen and amylopectin structures, see chapter 12, section 6.

- The conversion of glucose to glycogen is called ____________.

- Glycogenesis is an anabolic pathway in which glucose residues, with the help of enzymes, are connected to each other through glycosidic bonds to form glycogen.

In the “fasting state,” which occurs several hours after a meal, blood glucose levels become low, and glycogen is converted back to glucose in a process called ____________.

- Glycogenolysis occurs primarily in liver and muscle cells.

- It is the opposite of glycogenesis. In glycogenolysis, the glycosidic bonds between glucose residues are hydrolyzed.

Understanding Check: Calculate how many ATP can be produced from the catabolism of one glucose molecule when the two NADH from glycolysis use the glycerol 3-phosphate shuttle.

- Assume that each NADH that undergoes oxidative phosphorylation produces 2.5 ATP, and each FADH\(_2\) produces 1.5 ATP.
Roles of Glycogenesis and Glycogenolysis in the Regulation of Blood Glucose Concentration

The body regulates blood glucose levels by releasing hormones that result in the production of compounds that inhibit and activate key enzymes in the glycogenesis and glycogenolysis pathways.

In response to increased blood glucose concentration (in the fed state), the pancreas releases a protein hormone called ____________ into the blood stream.

- When insulin binds to liver and muscle cell receptors, it triggers a series of events that result in the activation of an enzyme in the glycogenesis pathway and the inhibition of an enzyme in the glycogenolysis pathway.
  - Accelerating glycogenesis will result in decreasing the blood glucose concentration by increasing the rate of the conversion of glucose to glycogen.
  - Suppressing glycogenolysis helps in maintaining normal blood glucose concentration as the conversion of glycogen to glucose is inhibited.

- Another way that insulin is involved in lowering blood glucose concentration is by initiating a process that increases facilitated diffusion of glucose from the bloodstream into all cell types.

In response to decreased blood sugar levels (in the “fasting state”), the pancreas releases a protein hormone called ______________ into the blood stream.

- Glucagon has the ______________ effect of insulin on liver cells; it accelerates glycogenolysis and suppresses glycogenesis.
  - Accelerating glycogenolysis will result in increasing the blood glucose concentration as glucose produced during glycogenolysis is transported from liver cells into the bloodstream.
  - Suppressing glycogenolysis helps in maintaining normal blood glucose concentration by suppressing the conversion of glucose to glycogen.

- Glucagon also increases blood glucose concentration by accelerating gluconeogenesis (the production of glucose from non carbohydrate species).

Diabetes

Diabetes Mellitus (DM), commonly referred to as diabetes, is a disease caused by chronic ________________.

There are three types of diabetes mellitus: type I, type II, and gestational diabetes.

- In diabetes type I, also called insulin-dependent diabetes, the pancreas produces too little __________. This can be a result of genetic disease, viral infection, or damage to the pancreas. Diabetes type I can be treated with insulin injections. Individuals must use a glucometer to frequently measure the concentration of glucose in their blood, and then inject insulin when elevated glucose levels are observed. Because diabetes type I often begins in childhood, it is sometimes referred to as __________ diabetes.
• Diabetes type II, also called insulin-____________ diabetes, occurs when sufficient insulin is produced, however the insulin receptors are unable to respond appropriately. About 90% of diabetes cases are type II. This type of diabetes can be even more difficult to manage than type I diabetes because it does not respond to insulin injections. Diabetes type II occurs after childhood and is therefore sometimes referred to as __________-onset diabetes.

• Gestational diabetes occurs during __________ in individuals without a previous diagnosis of diabetes. It is thought to be caused by pregnancy-related factors that affect insulin receptors. It is usually manageable with special diets and exercise; however, some individuals require antidiabetic drugs.

Triglyceride Metabolism

Dietary triglycerides, regardless of whether they came from plant or animal sources, are often referred to as __________.

When triglycerides are catabolized, their chemical potential energy is converted to chemical potential energy in ATP.

• This process begins with the digestion of triglycerides.
• Triglycerides are also used in the formation of phospholipids and glycolipids, and as cellular signaling compounds.

The body can store significant amounts of triglycerides, mostly in __________ cells (also called fat cells).

Digestion of Triglycerides

In order for triglycerides to pass through the intestine wall so that they can be used by the body, they must first undergo partial hydrolysis to produce __________ and ___________.

Triglycerides are first hydrolyzed to ________________, then to _____________________.

Each one of these reactions produces a fatty acid (as shown below).

This is referred to as “____________ hydrolysis” because one of the fatty acid residues remains bound to carbon number 2 of glycerol in the monoglyceride.
Triglyceride digestion begins in the __________ where lingual lipase catalyzes the partial hydrolysis of a very small percentage of triglycerides.

The majority of dietary triglycerides are digested in the __________ __________.

Large hydrophobic (insoluble) globules, that are composed mostly of triglycerides and a small amount of diglycerides, monoglycerides, and fatty acids, enter the small intestine. In the small intestine, bile salts disassemble these large hydrophobic globules and emulsify them into small micelles.

When emulsified by bile salts, the ester bonds of the glycerides are oriented toward the surface of the micelle. This enables pancreatic lipase to catalyze the partial hydrolysis of emulsified triglycerides and diglycerides to produce fatty acids and monoglycerides.

The fatty acids and monoglycerides that are formed inside the intestine can pass into the walls of the intestine. After being absorbed into the intestine walls, the fatty acids and monoglycerides are then re-assembled back into triglycerides.

Since lymph, blood, and intercellular fluids are aqueous mixtures, and triglycerides are hydrophobic, the triglycerides must be emulsified in order to be transported throughout the body. This is done by chylomicrons. Chylomicrons are small lipoproteins that are composed of a core that contains emulsified triglycerides (and some cholesterol and hydrophobic vitamins) surrounded by a lipid monolayer.

Triglycerides are emulsified in chylomicrons while in the wall of the intestine. The chylomicrons are then transferred into the lymph system, and then into the bloodstream. Triglycerides are released by the chylomicrons, and once again hydrolyzed to monoglycerides and fatty acids upon the inner surface of blood vessels. This occurs primarily at blood vessels located in adipose (fat) tissue and muscles. The monoglycerides and fatty acids can enter cells, where they are, once again, reassembled to triglycerides.
Adipose (fat) cells are the major repository for triglycerides; their primary function is to ____________ triglycerides.

Peripheral (other) cells/tissues can access this stored energy, as needed, when adipose cells completely hydrolyze the triglycerides to fatty acids and glycerol in a process called ________________.

The fatty acids are released from the adipose cells into the blood, and carried by serum albumin protein to other cells.

These fatty acids can then be ________________ to produce ATP.

**Catabolism of Fatty Acids**

Fatty acids are catabolized in order to convert their potential energy into potential energy in NADH, FADH₂, and acetyl-CoA.

The first reaction in the catabolism of fatty acids is called ________________.

- In this reaction, the _________ group of a fatty acid is transferred to coenzyme A.

![Diagram](image)

The fatty acid is converted to a __________ ________________.

This reaction does not occur spontaneously without the external energy input provided from the hydrolysis of two inorganic phosphates from ATP.

- In this case, ATP is converted to AMP and two inorganic phosphate (P) ions.

The *activation* reaction is necessary in order for the acyl group from fatty acids to pass through the inner mitochondrial membrane and enter the matrix, where the subsequent reactions of fatty acid catabolism occur.
When fatty acyl-CoA enters the *mitochondrial matrix*, it undergoes a catabolic pathway called _______ - ____________ (*β*-oxidation).

In *β*-oxidation, a fatty acyl-CoA, goes through a *repeated* series of *four* reactions, *each time* losing two of its ____________.

The carbon that is *next to* a fatty acyl’s carbonyl group is designated as the “*α*-carbon,” and the carbon that is two carbons away from the carbonyl group is designated as the “*β*-carbon.”

In reaction 1 of *β*-oxidation, the *α*- and *β*-carbons are ____________ (they lose hydrogens and electrons).
* The hydrogens and electrons are transferred to FAD to produce FADH₂.

In reaction 2 the double bond between the *α*- and *β*-carbons is *hydrated*.

In reaction 3, the hydroxyl group on the *β*-carbon is oxidized.
* In this oxidation, a hydrogen and electron are transferred to NAD⁺, reducing it to NADH.

In reaction 4, the bond between the *α*- and *β*-carbon is broken.
* A hydrogen forms a bond to what was formerly the *α*-carbon, *thereby* producing acetyl-CoA.
* The *acyl group*, containing what was formerly the *β*-carbon, is transferred to coenzyme A, thereby forming a ____________ fatty acyl-CoA.

The *new* fatty acyl-CoA is _________ *carbons shorter* than the original one.

The *new* fatty acyl-CoA can undergo the *β*-oxidation reactions.
For example, an eight-carbon fatty acyl-CoA will undergo three cycles of the \( \beta \)-oxidation reactions.

When the original fatty acyl-CoA undergoes the \( \beta \)-oxidation reactions series, one acetyl-CoA, one NADH, and one FADH\(_2\) are produced. A new fatty acyl-CoA is also produced. Each successive (new) fatty acyl-CoA undergoes the series of four reactions to produce more acetyl-CoA, NADH, and FADH\(_2\).

The acyl group’s length is decreased by two carbons with each successive \( \beta \)-oxidation reaction series. When the fatty acyl-CoA contains ________ carbons, then it will undergo the reaction series one final time.

- In the final cycle, reaction 4 produces two acetyl-CoA.

If “N” equals the number of carbons that are contained in a fatty acyl-CoA, then it will undergo \([(N/2) - 1]\) \( \beta \)-oxidation cycles. \( \beta \)-oxidation is classified a “__________” metabolic pathway.

- A spiral pathway is a metabolic pathway in which a series of repeated reactions is used to break down (or build up) a compound.

Understanding Check: How many cycles of the \( \beta \)-oxidation spiral will occur for a twelve-carbon fatty acyl-CoA?

Understanding Check: For the twelve-carbon fatty acyl-CoA in the previous problem:

- How many acetyl-CoA are produced after all of the \( \beta \)-oxidation cycles?
- How many NADH are produced after all of the \( \beta \)-oxidation cycles?
- How many FADH\(_2\) are produced after all of the \( \beta \)-oxidation cycles?

ATP Production from Fatty Acids

As was the case for carbohydrate catabolism, the catabolism of triglycerides converts potential energy in food into the form of chemical potential energy that is most useful in cells - ATP.

Because \( \beta \)-oxidation occurs in the mitochondrial matrix, each acetyl-CoA that is produced can undergo the reactions of the citric acid cycle to produce an ATP, three NADH, and one FADH\(_2\).
More ATP is produced when the NADH and FADH$_2$ formed in the $\beta$-oxidation cycles, along with the NADH and FADH$_2$ formed in the citric acid cycle, undergo oxidative phosphorylation.

Let’s consider how many ATP are produced from the catabolism of a typical fatty acid, myristate, which contains 14 carbon atoms (assume that oxidative phosphorylation produces, on average, 2.5 ATP per NADH and 1.5 ATP per FADH$_2$).

First, myristate is activated to produce a 14-carbon fatty acyl-CoA. The activation consumes one ATP. The net gain of ATP from can be calculated as shown in the illustration below.

Each of the first five cycles of the $\beta$-oxidation spiral produces one acetyl-CoA, one NADH, and one FADH$_2$. The final cycle of the spiral produces two acetyl-CoA, one NADH, and one FADH$_2$. The acetyl-CoA are processed through the citric acid cycle, producing ATP and more reduced coenzymes. The NADH and FADH$_2$ formed in $\beta$-oxidation and the NADH, and FADH$_2$ formed in the citric acid cycle undergo oxidative phosphorylation. Since one ATP was consumed in the activation reaction, it is subtracted when calculating the net gain of ATP. $\beta$-oxidation of myristate, on average, results in a net gain of 93 ATP.
Catabolism of Unsaturated Fatty Acids

Unsaturated fatty acids (derived from unsaturated fat) have double bonds in their hydrocarbon tails. Depending on the location of these double bonds, extra steps may be required to transform the double bonds in order to produce fatty acyl-CoA that can undergo β-oxidation.

Ketone Bodies

Catabolism of large quantities of triglycerides will result in high concentrations of acetyl-CoA. Acetyl-CoA that is produced in excess of the amount that can be metabolized in the citric acid cycle results in a high concentration of acetyl-CoA in the mitochondrial matrix.

When this occurs, acetyl-CoA reacts with other acetyl-CoA to produce the three compounds that are referred to as ______________ ____________.

This process is referred to as ______________.

Ketone bodies are water-soluble, therefore easily dispersed from the liver to other parts of the body. Most cells, with liver cells being the notable exception, are capable of converting ketone bodies back into acetyl-CoA, and then metabolizing it in the citric acid cycle. Converting ketone bodies back to acetyl-CoA is the reverse of ketogenesis (different enzymes are involved). Some cell types rely on ketone bodies for ATP production more than others. Heart muscles and the renal cortex use ketone bodies more readily than glucose. The brain’s primary energy source is glucose, but it is unable to store glucose and does not allow fatty acid salts (or amino acids) to enter. In the case of starvation, when there is very little glucose present, the brain gets 75% of its energy from ketone bodies.

**Understanding Check:** What is the net gain in ATP for β-oxidation of a twelve-carbon fatty acid? Assume that oxidative phosphorylation produces, on average, 2.5 ATP per NADH and 1.5 ATP per FADH₂.

Remember to subtract one ATP to account for the ATP that was consumed in the activation step.
When individuals diet, they begin to metabolize the triglycerides that are stored in fat cells. This leads to **ketogenesis**.

In cases of starvation, poorly treated diabetes, and conditions related to alcoholic binge drinking, the cells cannot get glucose and extremely high rates of fatty acid salt catabolism results in dangerous, and even fatal levels of ketone bodies.

- **β-hydroxybutyric acid** and **acetoacetic acid** (the acid forms of **β-hydroxybutyrate** and acetoacetate, respectively) have significant acid strength.
- Their production results in a higher concentration of H.O{\textsuperscript{+}}, which can overcome the blood’s buffering capacity.
- When this occurs, the blood becomes acidic.

When blood pH is less than the normal range (7.35-7.45), the condition is called ____________.

- **Acidosis** can result in tissue dysfunctions and is especially damaging to the central nervous system.
- When **acidosis** is caused by excess **ketone bodies**, the condition is called ________________.

### Fatty Acid Anabolism

Fatty acids are **produced** by a **spiral metabolic pathway** that operates in the **opposite** direction as **β-oxidation**; it builds-up fatty acyl-CoA by a repeating series of reactions that **add** acetyl-CoA to a growing fatty acyl-CoA structure.

This **anabolic** process of synthesizing fatty acids from acetyl-CoA is called **fatty acid** ________________.

Fatty acid synthesis occurs primarily in adipose and liver cells.

The body can synthesize almost all of the fatty acids it needs **except for linoleic and linolenic acid**.

- Linoleic and linolenic acid can **only** be obtained through dietary triglycerides, and are therefore classified as **essential fatty acids**.

### Protein Metabolism

When **dietary proteins** are digested, they are converted to **amino acids**. The **amino acids** are then used in various metabolic pathways.

- In an **anabolic** process, they are used to build proteins and peptides according to the body’s needs. You learned about this process in chapter 14 when I discussed how proteins are synthesized in the **translation** process.
- **Amino acids** are also used as nitrogen sources for the biosynthesis of other amino acids and other nitrogen-containing compounds, such as nucleotide bases.

Amino acids that are ingested in excess of what is needed for these biosynthesis needs are catabolized to produce **ATP**.
Digestion of Proteins

In the digestion process, dietary proteins are converted to **amino acids** by the **hydrolysis** of their ______________  ______________.

When a peptide bond is hydrolyzed, the peptide bond is broken and an oxygen is added to the carbonyl carbon and two hydrogens to the nitrogen.

Protein digestion begins in the __________ and continues in the **small intestine**.

In the stomach, an acidic environment and proteolytic enzymes (primarily **pepsin**) catalyze the hydrolysis of proteins to **amino acids** and **oligopeptides**.

As these species move through the small intestine and enter the intestinal cells, the oligopeptides are further hydrolyzed to amino acids. This is done with the help of dietary enzymes called **peptidases**.

The amino acids are released from the intestinal cells into the bloodstream, and then transported to other cells.

**Understanding Check:** Draw the structural formulas of the three amino acids that are produced when all of the peptide bonds in the tripeptide shown below are hydrolyzed.
Catabolism of Amino Acids

Some of the amino acids produced in digestion are used for the synthesis of **proteins**, the synthesis of **other amino acids**, and the synthesis of **other nitrogen-containing compounds**.

Amino acids that are ingested in surplus of these biosynthesis needs are ____________ as fuel for the production of **ATP**.

This is done by transforming them into intermediate metabolites that can be converted to ____________, __________, __________, or undergo the ___________ ___________.

The entry points of amino acids into the various metabolic pathways are indicated in the figure below.

I do not expect students to memorize this table; however, there are a couple of important concepts that I want you to know:

1) Amino acids can be converted to pyruvate, acetyl-**CoA**, acetoacetyl-**CoA**, or some citric acid cycle intermediates. These compounds are then converted to glucose, ketone bodies, or undergo the citric acid cycle.

2) All **twenty common amino acids** can be converted into either pyruvate, acetyl-**CoA**, acetoacetyl-**CoA**, or a citric acid cycle intermediate.
   - The details of how the twenty common amino acids are converted into the metabolic intermediates are far beyond the scope of this course.
   - What is important to understand is that these conversions involve one or both of two important amino acid reactions: __________ and __________.

---

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   - The details of how the twenty common amino acids are converted into the metabolic intermediates are far beyond the scope of this course.
   - What is important to understand is that these conversions involve one or both of two important amino acid reactions: __________ and __________.
Transamination

Transamination involves the ____________ of a quaternary ammonium group (NH₃⁺).

The NH₃⁺ that is bound to the α-carbon of an amino acid is transferred to an α-keto acid.

- An α-keto acid is a carboxylic acid that has a carbonyl group (C = O) at the α-carbon.

In a transamination reaction, an amino acid and an α-keto acid are converted to a **new** amino acid and a **new** α-keto acid. The general form of the transamination reaction is shown below.

In transamination reactions, the NH₃⁺ from an amino acid is _usually_ transferred to α-ketoglutarate (an α-keto acid).

**Example:**

In this reaction, alanine is converted to pyruvate.

Another example of a transamination reaction is the conversion of aspartic acid to oxaloacetate, as shown below.

In transamination reactions, α-ketoglutarate is converted to glutamic acid. We will now take a look at how glutamic acid is recycled back to α-ketoglutarate in the oxidative deamination reaction.
In oxidative deamination, a quaternary ammonium group (-\(\text{NH}_3^+\)) is \underline{__________} from glutamic acid, thereby producing an ammonium ion (\(\text{NH}_4^+\)) and \(\alpha\)-ketoglutarate.

\[
\begin{align*}
\text{NH}_3^+ & \quad \text{C}^\alpha \quad \text{C} \quad \text{O}^- \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{O}^- &
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{O} & \quad \text{NAD}^+ & \quad \text{NADH} + \text{H}^+ \\
\text{NH}_4^+ & \quad \text{O}^- & \quad \text{C}^\alpha \quad \text{C} \\
\text{CH}_2 & \quad \text{CH}_2 \\
\text{O}^- &
\end{align*}
\]

In addition to the removal of a quaternary ammonium group, glutamic acid’s \(\alpha\)-carbon is oxidized (gains an oxygen \textit{and} loses a hydrogen). This oxidation is accompanied by the reduction of \(\text{NAD}^+\).

The \(\alpha\)-ketoglutarate that is produced in the reaction is now free to accept a \underline{__________} quaternary ammonium group from another amino acid in a \textit{transamination reaction}, as illustrated below.

The free ammonium ions (\(\text{NH}_4^+\)) that are produced in oxidative deamination are \textit{toxic} at elevated concentrations. Humans and most other terrestrial vertebrates are capable of converting the ammonium ions to \underline{__________}.

- This occurs in a series of reactions called the \textit{urea cycle}.

Urea is filtered, by the \underline{__________}, into the urinary track and then removed from the body during urination. Kidney disease can result in the build up of dangerous amounts of urea.

In cases of \textit{end-stage renal (kidney) failure}, safe blood urea levels are exceeded, and patients must undergo \underline{__________} treatments.

Dialysis involves artificial methods of urea removal. The most common of these is called \textit{hemodialysis}. Hemodialysis takes several hours and is usually done multiple times per week. This process is not only time-consuming, but far from ideal because of many complications and side effects. Bedside nocturnal dialyzers are now available.

In otherwise healthy patients with kidney failure, kidney transplants are possible. Kidney donations are fairly common since most humans have two kidneys, and one kidney is usually sufficient to eliminate urea.
Summary of Metabolism

The body is able to build proteins, carbohydrates, and triglycerides from smaller organic compounds in anabolic processes.

- Anabolic processes generally require the input of external energy.
- This energy often comes from chemical potential energy in ATP.

The body is able to break down proteins, carbohydrates, and triglycerides into smaller organic compounds in catabolic processes.

- Catabolic processes typically release energy.
- This energy is often used by the body to produce ATP.

The metabolic strategy behind the production of ATP is that ATP is an energy source that can be instantaneously used by organisms to do cellular work and to provide the energy required for life-sustaining reactions that would otherwise not occur spontaneously.

The metabolic strategies of catabolism and anabolism are summarized in the illustration below.
Catabolism

The catabolism of food is summarized in the image below:

In the four stages of food catabolism, chemical potential energy in food is converted to chemical potential energy in ATP, NADH, and FADH₂.

- The NADH and FADH₂ can then be converted to electrochemical energy in the form of a hydrogen ion gradient.
- The electrochemical potential in this gradient is used to drive the production of ATP.
The *catabolic processes* discussed in this chapter are digestion, glycolysis, pyruvate oxidation/decarboxylation, the citric acid cycle, glycogenolysis, lipolysis, β-oxidation, and oxidative deamination.

These *catabolic processes* are listed and briefly described in the table below.

### The Catabolic Processes in Chapter 15

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>digestion</td>
<td><em>Carbohydrates</em> are hydrolyzed to <em>monosaccharides</em>. <em>Triglycerides</em> are “partially” hydrolyzed to <em>fatty acid salts</em> and <em>monoglyceride</em>. <em>Proteins</em> are hydrolyzed to <em>amino acids</em>.</td>
<td></td>
</tr>
<tr>
<td>glycolysis</td>
<td>A <em>linear metabolic pathway</em> in which glucose is converted into two pyruvate ions.</td>
<td>High concentrations of <em>ATP</em>, <em>pyruvate</em>, or other pathway products suppress this process.</td>
</tr>
<tr>
<td>pyruvate oxidation/</td>
<td><em>Pyruvate</em> is oxidized and decarboxylated to produce <em>acetyl-CoA</em>.</td>
<td></td>
</tr>
<tr>
<td>decarboxylation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>citric acid cycle</td>
<td>A <em>circular metabolic pathway</em> in which <em>acetyl-CoA</em> is metabolized to produce <em>ATP</em>, <em>NADH</em>, and <em>FADH₂</em>.</td>
<td>Low blood glucose and glucagon accelerate this process. High blood glucose and insulin suppress this process.</td>
</tr>
<tr>
<td>glycogenolysis</td>
<td><em>Glycogen</em> is converted to <em>glucose</em>. Glycogenolysis occurs primarily in <em>liver</em> and <em>muscle</em> cells. Liver cells will release the glucose into the bloodstream so that it can be taken in by other types of cells.</td>
<td></td>
</tr>
<tr>
<td>β-oxidation</td>
<td>A <em>spiral metabolic pathway</em> in which fatty acids are converted to <em>acetyl-CoA</em>, <em>NADH</em> and <em>FADH₂</em>.</td>
<td></td>
</tr>
<tr>
<td>lipolysis</td>
<td><em>Triglycerides</em> that are stored primarily in adipose (fat) cells and muscle cells are broken down into <em>fatty acids</em> and <em>glycerol</em>. Liver cells can release the fatty acids and glycerol into the bloodstream so that they can be taken in by other types of cells.</td>
<td></td>
</tr>
<tr>
<td>oxidative deamination</td>
<td>A <em>quaternary ammonium group</em> (-NH₄⁺) is removed from <em>glutamic acid</em>, thereby producing ammonium (NH₄⁺) and α-ketoglutarate.</td>
<td></td>
</tr>
</tbody>
</table>
Anabolism

The *anabolic processes* discussed in this chapter are gluconeogenesis, glycogenesis, fatty acid synthesis, and protein synthesis.

These *anabolic processes* are listed and briefly described in the table below.

<table>
<thead>
<tr>
<th>Name</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>gluconeogenesis</td>
<td>The conversion of <em>non-carbohydrate species into glucose</em>. This process is similar to the reverse of glycolysis. Gluconeogenesis occurs primarily in the liver. It increases blood glucose levels because liver cells can release the glucose that is produced into the bloodstream.</td>
<td>Low blood glucose and glucagon accelerate this process.</td>
</tr>
<tr>
<td>glycogenesis</td>
<td><em>Glucose is converted to glycogen.</em> Glycogenesis occurs primarily in liver and muscle cells. Glycogenesis lowers blood glucose levels because glucose is taken up by liver and muscle cells and then converted to glycogen.</td>
<td>High blood glucose and insulin accelerate this process. Low blood glucose and glucagon suppress this process.</td>
</tr>
<tr>
<td>fatty acid synthesis</td>
<td>Fatty acids are produced by a spiral pathway that works in the opposite direction of β-oxidation; it builds up fatty acyl-CoA by a repeating series of reactions that add acetyl-CoA to a growing fatty acyl-CoA structure. Fatty acid synthesis occurs primarily in adipose and liver cells.</td>
<td></td>
</tr>
<tr>
<td>protein synthesis</td>
<td><em>Amino acids are converted to proteins.</em></td>
<td>This process was mentioned briefly in this chapter; however, it was <em>thoroughly discussed chapter 14.</em></td>
</tr>
</tbody>
</table>