Chapter 6: Macronutrient & Alcohol Metabolism

Now that we have digested, taken up, absorbed, and transported the macronutrients, the next step is to learn how these macronutrients are metabolized. Alcohol is also included at the end of this chapter, even though it is not a macronutrient.

Sections:
6.1 Metabolism Basics
6.2 Carbohydrate Metabolism
6.3 Lipid Metabolism
6.4 Protein Metabolism
6.5 Alcohol Metabolism

6.1 Metabolism Basics

Metabolism consists of all the chemical processes that occur in living cells. These processes/reactions can generally be classified as either anabolic or catabolic. Anabolic means to build, catabolic means to breakdown. If you have trouble remembering the difference between the two, remember that anabolic steroids are what are used to build enormous muscle mass.

Figure 6.11 One of these two is taking anabolic steroids, which one would be your guess?

An anabolic reaction/pathway requires energy to build something. A catabolic reaction/pathway generates energy by breaking down something. This is shown in the example below of glucose and glycogen. The same is true for other macronutrients.
Figure 6.12 The breakdown of glycogen to glucose is catabolic. The glucose can then be used to produce energy. The synthesis of glycogen from glucose is anabolic and requires energy.

Anabolic and catabolic can also be used to describe conditions in the body. For instance, after a meal there is often a positive energy balance, or there is more energy and macronutrients than the body needs at that time. Thus, some energy needs to be stored and the macronutrients will be used for synthesis, such as amino acids being used for protein synthesis. However, after a fast, or a prolonged period without energy intake, the body is in negative energy balance and is considered catabolic. In this condition, macronutrients will be mobilized from their stores to be used to generate energy. For example, if prolonged enough, protein can be broken down, then the released amino acids can be broken down to be used as an energy source.

A number of the metabolic reactions either oxidize or reduce compounds. A compound that is being oxidized loses at least one electron, while a compound that is reduced gains at least one electron. To remember the difference, a mnemonic device such as OIL (oxidation is lost), RIG (reduction is gained) is helpful. Oxidation reactions and reduction reactions are “coupled” reactions, one cannot exist without the other. For example, a reduction reaction requires an electron. Where does that electron come from? It comes from an oxidation reaction. Scientists commonly refer to oxidation reactions and reduction reactions as oxidation-reduction reactions, or as redox reactions. Oxidation-reduction reactions are illustrated in the figure below.
Another way to remember oxidation versus reduction is LEO goes GER (like a lion).

Lose Elections = Oxidation

Gain Elections = Reduction (YES, gaining electrons is considered reduction)

Iron is a good example we can use to illustrate oxidation-reduction reactions. Iron commonly exists in two states (Fe$^{3+}$ or Fe$^{2+}$). It is constantly oxidized/reduced back and forth between the two states. The oxidation/reduction of iron is shown below.

Fe$^{3+}$ loses an e$^-$ → Fe$^{2+}$ (Oxidation)
Fe$^{2+}$ gains an e$^-$ → Fe$^{3+}$ (Reduction)

Interestingly, the oxidation states of iron (mentioned above) are critical to our ability to use the iron present in our diet. Fe$^{2+}$ (also known as ferrous iron) is easily absorbed in the small intestine. Fe$^{3+}$ (also known as ferric iron) is not so easily absorbed. Gastric acid (produced by the stomach) and vitamin C promote the conversion of Fe$^{3+}$ to Fe$^{2+}$ so we can maximize iron absorption in the small intestine.
However, some oxidation reduction reactions are not as easy to recognize. There are some simple rules to help you recognize less-obvious oxidation/reduction reactions that are based upon the gain or loss of oxygen or hydrogen. These are as follows:

Oxidation: gains oxygen or loses hydrogen
Reduction: loses oxygen or gains hydrogen

Remembering how this applies to hydrogen will be very helpful later in this chapter.

References

6.11 Cofactors

A number of enzymes require cofactors to function. Cofactors can be either organic or inorganic molecules that are required by enzymes to function. Many organic cofactors are vitamins or molecules derived from vitamins. Most inorganic cofactors are minerals. Cofactors can be oxidized or reduced for the enzymes to catalyze the reactions.

Two common cofactors that are derived from the B vitamins, niacin and riboflavin, are NAD (nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide), respectively.

Both of these cofactors can be reduced (remember that reduction is a process by which electrons, as part of H in this case, are gained); NAD is reduced to form NADH, while FAD is reduced to form FADH$_2$ as shown in the 2 figures below.

![NAD and FAD Reduction](image)

Figure 6.111 The reduction of NAD (left) to form NADH (right)³
NADH and FADH$_2$ are molecules that are critical to our cells’ ability to process the energized electrons obtained through the catabolism (digestion) of food molecules, like glucose. The energized electrons, which are highly reactive and potentially destructive, are temporarily managed by NADH and FADH$_2$ until they can be processed by the Electron Transport Chain step of Cellular Respiration (see Section 6.26 below).

An example of a mineral that serves as a cofactor is Fe$^{2+}$ for proline and lysyl hydroxylases. Proline and lysine are two amino acids that must be hydroxylated (the addition of an OH group) in order to be used as building blocks for collagen, perhaps the most important structural protein in the body. We will discuss later in detail why vitamin C (ascorbic acid) is needed to reduce iron to Fe$^{2+}$ so that it can serve as a cofactor for proline and lysyl hydroxylases.

References & Links
6.21 Monosaccharide Metabolism

Galactose and fructose metabolism is a logical place to begin looking at carbohydrate metabolism, before shifting focus to the cell’s preferred monosaccharide, glucose. Once absorbed in the small intestine (Chapter 4), these monosaccharides are transported to the liver via the hepatic portal system. The figure below shows that galactose and fructose are phosphorylated (have a phosphate added to them) in the liver (a hepatocyte is a liver cell).

Galactose and fructose are transported into the hepatocyte and phosphorylated by specific enzymes. Galactose is phosphorylated by galactokinase, and fructose is phosphorylated by fructose-1-phosphate. The resulting monophosphate derivatives can then be used in metabolic pathways. Glucose, on the other hand, is transported into the hepatocyte via GLUT2 and phosphorylated by glucokinase.

As shown above, galactose is phosphorylated in the cells of the liver, resulting in a molecule called galactose-1-phosphate. Galactose-1-phosphate is converted to glucose-1-phosphate, before finally being converted to glucose-6-phosphate. As shown below, glucose 6-phosphate can then be used in either glycolysis (the breakdown of glucose for energy) or glycogenesis (the production of glycogen for storage), depending on the person's current energy state.
Fructose
Unlike galactose, fructose cannot be used to form glucose 6-phosphate. Instead, fructose-1-phosphate is cleaved in the liver to form glyceraldehyde 3-phosphate, an intermediate in the process of glycolysis (see Section 6.23 below).

The Importance of Glucose-6-Phosphate
Within hepatocytes or myocytes (muscle cells), glucose-6-phosphate can be used either for glycogenesis (glycogen synthesis) or glycolysis (breakdown of glucose for energy production). If the person is in an anabolic state (e.g. after a meal), they will use glucose-6-phosphate for storage. If they are in a catabolic state (e.g. fasted), they will use it for energy production.

References & Links
6.22 Glycogenesis & Glycogenolysis

As discussed earlier, glycogen is the stored form of glucose in humans. If a person is in an anabolic state, such as after consuming a meal, most glucose-6-phosphate within the myocytes (muscle cells) or hepatocytes (liver cells) is going to be stored as glycogen.

Glycogen is mainly stored in the liver and the muscle. It makes up ~6% of the weight of the liver, but only ~1% of muscle weight. However, since we have far more muscle mass in our body, there is 3-4 times more glycogen stored in muscle than in the liver. This is of great practical importance since glycogen is an importance source of energy for muscle contraction. We have limited glycogen storage capacity in the liver. Thus, after a high-carbohydrate meal, our glycogen stores will reach capacity fairly quickly. After glycogen stores are filled, glucose will have to be metabolized in different ways for it to be stored in a different form, often as fat.

Glycogenesis

The synthesis of glycogen from glucose is a process known as glycogenesis. You will remember that glucose can be converted to glucose-6-phosphate (see Figure 6.211). If glucose storage (as glycogen) is required at any given time, the glucose-6-phosphate is converted to glucose-1-phosphate and then converted to glycogen (Figure 6.222).

Glycogenolysis

The process of liberating glucose from glycogen is known as glycogenolysis. This process is essentially the opposite of glycogenesis. Glycogen is hydrolyzed and the individual glucose molecules are phosphorylated (converted into glucose-6-phosphate) through the action of an
enzyme called glycogen phosphorylase as shown below\(^3\).

![Glycogen Phosphorylase](image)

**Figure 6.223 Glycogenolysis**

**References & Links**

### 6.23 Glycolysis

If a person is in a catabolic state (in need of energy) such as during fasting, most glucose-6-phosphate will be used for glycolysis.

!["fork in the road" for glucose-6-phosphate](image)

**Figure 6.231 The "fork in the road" for glucose-6-phosphate**
**Glycolysis** is the breaking down of one glucose molecule (6 carbons) into two pyruvate molecules (3 carbons). During the process, a net of two ATPs and two NADHs are also produced. The Figure 6.232 below shows the steps of glycolysis. Do not get overwhelmed, you will not have to learn every step. We will break it down into smaller sections and highlight the important intermediates, but I do want you to see how glucoses progresses through the various intermediate molecules before becoming pyruvate.

![Glycolysis Diagram](image)

Figure 6.232 Glycolysis 1

The following animation, using ball-and-stick models, allows you to control the 3 steps of glycolysis.

**Required Web Links**

Glycolysis Animation

**3 steps of Glycolysis**

1. Energy investment step - 2 ATP are added to the 6-carbon glucose molecule resulting in one 6-carbon molecule of fructose 1,6-bisphosphate.
2. Glucose Split - The 6-carbon fructose 1,6-bisphosphate molecule is split into two 3-carbon molecules of glyceraldehyde 3-phosphate.

3. Energy harvesting step – The two molecules of glyceraldehyde 3-phosphate are eventually converted to two 3-carbon molecules of pyruvate resulting in a total “harvest” of 2 NADH and 4 ATPs (1 NADH and 2 ATPs are produced from each glyceraldehyde 3-phosphate.)
Thus, from a molecule of glucose, the harvesting step produces a total of four ATPs and two NADHs. Remember that in Step 1 we had to “invest” two molecules of ATP to get the process started. Therefore, the net output from one molecule of glucose is two ATPs and two NADHs. You will remember that NADH is a molecule that is used to manage energized electrons. In this case, the splitting of the glucose molecule releases two energized electrons, which are then managed by two NADH molecules. These energized electrons will ultimately be processed by the Electron Transport Chain to generate ATP in the process of Cellular Respiration.

The figure below shows the stages of glycolysis, as well as the transition reaction, citric acid cycle, and electron transport chain that are utilized by cells to produce energy. They are also the focus of the next 3 sections. Again, you’re not going to have to memorize each step. This is just to give you an overview of the entire process.
6.24 Transition Reaction

If a person is in a catabolic state, or needs energy, how the pyruvate molecules produced in glycolysis will be used depends on whether adequate oxygen levels are present. If oxygen levels are adequate (aerobic conditions), pyruvate moves from the cytoplasm, into the mitochondria, and then undergoes the transition reaction. If oxygen levels are not adequate (anaerobic conditions), pyruvate will remain in the cytoplasm to be used to produce lactate. We are going to focus on the aerobic pathway for now. We will address what happens under anaerobic conditions in the anaerobic respiration section.
The transition reaction (sometimes called the transition step) is the transition between glycolysis and the citric acid cycle. It also represents a transition in location from the cytoplasm to the mitochondrion. The transition reaction converts pyruvate molecule (3 carbons) into acetyl CoA molecules (2 carbons), producing carbon dioxide (CO$_2$) and NADH as shown below. The figure below shows the transition reaction with CoA and NAD entering, and acetyl-CoA, CO$_2$, and NADH being produced.

The acetyl is combined with coenzyme A (CoA) to form acetyl-CoA. The structure of CoA is shown below. You can think of coenzyme A as an acetyl manager...a molecule that will deliver the 2-carbon acetyl group into the citric acid cycle (see Section 6.25).
In summary, the transition reaction converts each 3-carbon pyruvate into a 2-carbon acetyl group, which is then managed by coenzyme A. The transition reaction also generates CO$_2$ (a waste product), and NADH (a reduced molecule, contains energized electrons that will be processed by electron transport chain to make ATP).

References & Links

6.25 The Citric Acid Cycle

Acetyl-CoA is a central point in metabolism, meaning there are a number of ways that it can be used. We’re going to continue to consider its use in an aerobic, catabolic state (need energy). Under these conditions, acetyl-CoA will enter the citric acid cycle (a.k.a. Krebs Cycle, TCA Cycle). The following figure shows the citric acid cycle. In the top left you will notice the acetyl-CoA we just produced.

Figure 6.251 The citric acid cycle$^1$
The **citric acid cycle** begins by acetyl-CoA (2 carbons) combining with oxaloacetate (4 carbons) to form citrate (a.k.a. citric acid, 6 carbons). Coenzyme A is removed as part of this reaction leaving a single acetyl group to continue through the cycle. A series of transformations occur as the acetyl group is processed, creating a series of intermediates known as keto acids, until oxaloacetate is eventually reformed. During these intermediate steps, the acetyl group that was created during the formation of citrate is broken down and NADH, FADH$_2$, CO$_2$, and ATP are produced.

In summary, the Citric Acid Cycle processes each 2-carbon acetyl group from the transition reaction. The acetyl group is delivered by coenzyme A, and is progressively broken down, resulting in the production of carbon dioxide (a waste product), ATP, and NADH and FADH$_2$ (reduced molecules that contain energized electrons that will be processed by the Electron Transport Chain to make ATP).

The first video and the animation do a good job of explaining and illustrating how the cycle works. The second video is an entertaining rap about the cycle.

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**Required Web Links**

**Video:** [Citric acid cycle (0:44)](http://www.youtube.com/watch?v=hw5nWB0xN0Y)

Citric acid cycle animation

**Video:** [TCA (Kreb's) Cycle Rap (3:01)](http://www.youtube.com/watch?v=aMBIs_Iw0kE)

---

Through glycolysis, the transition reaction, and the citric acid cycle, multiple NADH and FADH$_2$ molecules are produced. Under aerobic conditions, these molecules will enter the electron transport chain to be used to generate energy through oxidative phosphorylation as described in the next section.

**References & Links**


**Link**


**Video**

Citric acid cycle - [http://www.youtube.com/watch?v=hw5nWB0xN0Y](http://www.youtube.com/watch?v=hw5nWB0xN0Y)

TCA (Kreb's) Cycle Rap - [http://www.youtube.com/watch?v=aMBIs_Iw0kE](http://www.youtube.com/watch?v=aMBIs_Iw0kE)
The electron transport chain is located on the inner membrane of the mitochondria, as shown below.

The electron transport chain contains a number of electron carriers. These carriers take the electrons from NADH and FADH$_2$, pass them down the chain of complexes and electron carriers, and ultimately produce ATP. More specifically, the electron transport chain takes the energy from the electrons on NADH and FADH$_2$ to pump protons (H$^+$) into the intermembrane space. This creates a proton gradient between the intermembrane space (high) and the matrix (low) of the mitochondria. The protons will then move back out through the enzyme ATP synthase from high to low concentration. This is similar to how a person rides up a motorized ski-lift (the proton pump) only to use gravity (high to low concentration) to come back down the hill. ATP synthase uses the energy of the moving protons to synthesize ATP (think of a hydroelectric dam using moving water to generate electricity.) Oxygen is required for this process because it serves as the final electron acceptor, forming water. Collectively this process is known as
oxidative phosphorylation. The following figure and animation do a nice job of illustrating how the electron transport chain functions.

![Figure 6.262 Location of the electron transport chain in the mitochondria](image)

The electron transport chain generates 3 ATP for each NADH processed and 2 ATP for each FADH$_2$ processed. We can assess each of the catabolic steps of aerobic cellular respiration (steps that actually deconstruct the molecule of glucose) in terms of the number of NADH and FADH$_2$ molecules produced. For one molecule of glucose, the preceding pathways produce:

- **Glycolysis:** 2 NADH
- **Transition Reaction:** 2 NADH
- **Citric Acid Cycle:** 6 NADH, 2 FADH$_2$

**Total:** 10 NADH, 2 FADH$_2$

Note: some textbooks will use 2.5/1.5 ATP for NADH/FADH$_2$ instead of the 3/2 we are using here. This is due to the fact that the actual total varies from organism to organism, and even
from one round to the next within the same organism. For simplicity’s sake, we will stick with 3/2 here.

In the following section (Section 6.27), we will compute exactly how many ATP can be generated from the aerobic breakdown of a single molecule of glucose.

The first video does a nice job of illustrating and reviewing the electron transport chain. The second video is a great rap video explaining the steps of glucose oxidation.

**Required Web Links**

- Video: Electron Transport (1:43)
- Video: Oxidate it or Love it/Electron to the Next One (3:23)

**References & Links**


**Link**

ETC Animation - [http://www.science.smith.edu/departments/Biology/Bio231/etc.html](http://www.science.smith.edu/departments/Biology/Bio231/etc.html)

**Videos**

- Oxidate it or Love it/Electron to the Next One - [http://www.youtube.com/watch?v=VCpNk92uswY&feature=response_watch](http://www.youtube.com/watch?v=VCpNk92uswY&feature=response_watch)

### 6.27 Aerobic Glucose Metabolism Totals

The table below shows the ATP generated from one molecule of glucose in the different metabolic pathways. As you look at Table 6.271 below, be sure to recognize that the ATP produced through Electron Transport is generated through the processing of the NADH and FADH\(_2\) summarized in the previous section.

Notice that the vast majority of ATP is generated by the electron transport chain. Remember that this is an aerobic process and oxygen is the final electron acceptor. Oxygen is the key to the rich energy return of 38 ATP per molecule of glucose. If there were no oxygen, there would be no final electron acceptor. If there were no final electron acceptor, there would be no electron transport chain. If there were no electron transport chain, it would not be possible to process NADH and FADH\(_2\). In the next section, we will see what happens if there is a limited supply of oxygen in our cells.
Table. 6.271 ATP generated from one molecule of glucose.

<table>
<thead>
<tr>
<th>Metabolic Pathway</th>
<th>ATP Generated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolysis</td>
<td>2</td>
</tr>
<tr>
<td>Transition Reaction</td>
<td>0</td>
</tr>
<tr>
<td>Citric Acid Cycle</td>
<td>2</td>
</tr>
<tr>
<td>Electron Transport Chain</td>
<td>30 (from 10 NADH)</td>
</tr>
<tr>
<td></td>
<td>4 (from 2 FADH₂)</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
</tr>
</tbody>
</table>

No References

6.28 Anaerobic Respiration

Conditions without oxygen are referred to as anaerobic. In this case, the pyruvate will be converted to lactate in the cytoplasm of the cell as shown below.

Figure 6.281 Pyruvate fork in the road, what happens depends on whether it is aerobic or anaerobic respiration¹

What happens if oxygen isn't available to serve as the final electron acceptor? As shown in the following video, the ETC becomes backed up with electrons and can't accept any more from NADH and FADH₂.
This leads to a problem in glycolysis because NAD are limited and it is needed to accept electrons, as shown below. Without the electron transport chain functioning, once all NAD molecules have been reduced to NADH, glycolysis cannot continue to produce ATP from glucose.

Figure 6.282 Why NAD needs to be regenerated under anaerobic conditions

Thus, there is a workaround to regenerate NAD by converting pyruvate (pyruvic acid) to lactate (lactic acid) as shown below.

Figure 6.283. The conversion of pyruvic acid to lactic acid regenerates NAD

However, anaerobic respiration only produces 2 ATP from one molecule of glucose, compared to the 38 ATP from one molecule of glucose we saw with aerobic respiration. The biggest producers of lactate are muscle cells under oxygen stress (lacking adequate oxygen). During periods of intense activity, we might not be able to supply our muscle cells with sufficient oxygen to support the aerobic breakdown of glucose. At that point, our muscle cells are forced
to breakdown glucose in the absence of oxygen (which is essentially a process of glycolysis), which results in a limited amount of ATP and lactate (lactic acid). The lactate is generated because the conversion of pyruvate to lactate allows us to recycle NAD. The lactate produced, while technically a waste product, is still a metabolically valuable commodity. Through what is known as the Cori cycle, lactate produced in the muscle can be sent to the liver. In the liver, through a process known as gluconeogenesis, glucose can be regenerated and sent back to the muscle to be used again for anaerobic respiration forming a cycle as shown below.

![The Cori cycle](https://commons.wikimedia.org/wiki/File:CoriCycle-noLang.svg#/media/File:CoriCycle-eng.svg)

Figure 6.284 The Cori cycle

It is worth noting that the Cori cycle also functions during times of limited glucose (like fasting) to spare glucose by not completely oxidizing it.

**References & Links**


**Video**

What happens when your run out of oxygen? -
[http://www.youtube.com/watch?v=StXlo1W3Gvg](http://www.youtube.com/watch?v=StXlo1W3Gvg)
6.3 Lipid Metabolism Pathways

Five lipid metabolic pathways/processes will be covered in the following subsections:

6.31 Lipolysis (Triglyceride Breakdown)
-Breakdown of triglycerides to glycerol and free fatty acids.

6.32 Fatty Acid Oxidation (Beta-Oxidation)
-Breakdown of fatty acids to acetyl-CoA

6.33 De Novo Lipogenesis (Fatty Acid & Triglyceride Synthesis)
-Synthesis of fatty acids from acetyl-CoA and esterification into triglycerides

6.34 Ketogenesis (Ketone Body Synthesis)
-Synthesis of ketone bodies from acetyl-CoA

6.35 Cholesterol Synthesis

6.31 Lipolysis (Triglyceride Breakdown)

Lipolysis is the cleavage of triglycerides to glycerol and fatty acids, as shown below.

![Figure 6.311 Lipolysis](image)

Figure 6.311 Lipolysis
There are two primary lipolysis enzymes:

1. Lipoprotein lipase (LPL)
2. Hormone-sensitive lipase (HSL)

Despite performing the same function, the enzymes are primarily active for seemingly opposite reasons. In the anabolic state, LPL on the lining of blood vessels cleaves lipoprotein triglycerides into fatty acids so that they can be taken up into adipocytes (fat cells) for storage as triglycerides, or myocytes (muscle cells) where they are primarily used for energy production. This action of LPL on lipoproteins is shown in Figures 6.312 & 6.313.

Figure 6.312 Lipoprotein lipase cleaves fatty acids from the chylomicron, forming a chylomicron remnant.

Figure 6.313 Lipoprotein lipase cleaves triglycerides from VLDL and IDL, forming subsequent lipoproteins (IDL and LDL) that contain less triglyceride.
HSL is an important enzyme in adipose tissue, which is a major storage site of triglycerides in the body. HSL activity is increased by glucagon and epinephrine ("fight or flight" hormone), and decreased by insulin. Thus, during hypoglycemia (such as during a fast; a catabolic state), or a "fight or flight" response, triglycerides in the adipocytes (fat cells) are cleaved, releasing fatty acids into circulation that then bind with the transport protein albumin that carry them to muscle cells for use as an energy source. Thus, HSL is important for mobilizing fatty acids so they can be used to produce energy. The figure below shows how fatty acids can be taken up and used by tissues such as the muscle for energy production.

![Muscle Cell](image)

Figure 6.314 Hormone-sensitive lipase

We are not going to focus on glycerol (the other product of triglyceride breakdown), but it does have two metabolic fates.

1. It can be broken down in glycolysis
2. It can be used to synthesize glucose (gluconeogenesis)

![Glycerol](image)

Figure 6.315 Metabolic fates of glycerol
6.33 De novo Lipogenesis (Fatty Acid Synthesis)

De novo in Latin means "from the beginning." Thus, de novo lipogenesis is the synthesis of fatty acids, beginning with acetyl-CoA. You will remember that acetyl-CoA is the product of the transition reaction that is the starting point of the citric acid cycle. We had mentioned earlier (in Section 6.25) that “Acetyl-CoA is a central point in metabolism.” Acetyl-CoA moves out of the mitochondria, where it is subsequently combined with additional acetyl-CoA molecules to form palmitate, a 16-carbon fatty acid\(^1\). The palmitate produced can be used as a component in the production of triglycerides (fat) for storage.

![Fatty acid synthesis diagram](image)

Figure 6.331 Fatty acid synthesis\(^2\)

References

6.34 Ketone Body Synthesis

In cases where there is not enough glucose available for the brain (very low carbohydrate diets, starvation), the liver can use acetyl-CoA to synthesize ketone bodies (ketogenesis). The
structures of the three ketone bodies; acetone, acetoacetic acid, and beta-hydroxybutyric acid, are shown below.

![Ketone Bodies](http://en.wikipedia.org/wiki/File:Ketone_bodies.png)

Figure 6.341 The three ketone bodies, from top to bottom (acetone, acetoacetic acid, and beta-hydroxybutyric acid)

After they are synthesized in the liver, ketone bodies are released into circulation where they can travel to the brain. The brain converts the ketone bodies to acetyl-CoA that can then enter the citric acid cycle for ATP production, as shown below.

![Ketone Body Metabolism](http://commons.wikimedia.org/wiki/File:Liver.svg)

Figure 6.342 The production, release, use, or exhalation of ketone bodies

If there are high levels of ketones secreted, it results in a condition known as ketosis or ketoacidosis. The high level of ketones in the blood decreases the blood’s pH, meaning it becomes more acidic. It is debatable whether mild ketoacidosis (as seen with ketogenic and Atkin’s diets) is harmful, but severe ketoacidosis can be lethal. One symptom of this condition is fruity or sweet-smelling breath, which is due to increased acetone exhalation.

**References & Links**
6.35 Cholesterol Synthesis

Acetyl-CoA is also used to synthesize cholesterol. As shown below, there are a large number of reactions and enzymes involved in cholesterol synthesis. You will not have to memorize all these steps, but it does illustrate the complexity of this process.

Simplifying this, acetyl-CoA is converted to acetoacetil-CoA (4 carbons) before forming 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA is converted to mevalonate by the enzyme HMG-CoA reductase. This enzyme is important because it is the rate-limiting enzyme in cholesterol synthesis.
A rate-limiting enzyme is like a bottleneck in a highway, as shown below, that determines the flow of traffic past it. Traffic is limited in how fast it can flow due to the emergency vehicle (rate-limiting enzyme) slowing it down.

Rate-limiting enzymes limit the rate at which a metabolic pathway proceeds. The pharmaceutical industry has taken advantage of this knowledge to lower people's LDL ("bad" cholesterol) levels with drugs known as statins. These drugs inhibit HMG-CoA reductase and thus decrease cholesterol synthesis. Less cholesterol leads to lower LDL levels, and hopefully a lower risk of cardiovascular disease.
The brand names of some common statins approved for use in the US include:

- Lipitor
- Lescol
- Crestor
- Zocor
- Livalo

The body synthesizes approximately 1 gram of cholesterol a day, whereas it is recommended that we consume less than 0.3 gram a day. A number of tissues synthesize cholesterol, with the liver accounting for ~20% of synthesis. The intestine is believed to be the most active among the other tissues that are responsible for the other 80% of cholesterol synthesis.

References & Links

6.4 Protein Metabolism

Section 2.22 described how proteins are synthesized. Thus, this section will focus on how proteins and amino acids are broken down. There are four protein metabolic pathways that will be covered in this section:

**Transamination** – transfer of an amino group from one amino acid to another

**Deamination** – removal of an amino group, normally from an amino acid.

**Gluconeogenesis** – synthesis of glucose from a non-carbohydrate source.

**Protein Turnover/Degradation** – liberation of amino acids from proteins.

Subsections:
6.41 Transamination, Deamination, & Ammonia Removal as Urea
6.42 Gluconeogenesis
6.43 Protein Turnover/Degradation
Amino acids are important metabolic resources for our cells. The first step in making an amino acid useful is deamination, the removal of its amino group (-NH₂). Once the amino group has been removed, what remains is a 2-carbon keto acid with a side chain. The keto acid is the valuable component of the amino acid in that it can be used as a foundation for the construction of a new amino acid (transamination below), it can be used as the foundation for the construction of ketone bodies (ketogenesis below), and it can be used as a starting point for the construction of glucose (gluconeogenesis below). As we shall see below, not all amino acids are the same in terms of what can be done with them after an event of deamination. We will also determine that deamination has a possible negative consequence (hyperammonemia).

Transamination

Transamination is the transfer of an amino group from an amino acid to a keto acid (amino acid without an amino group), thus creating a new amino acid and keto acid as shown below.

Figure 6.411 Generic transamination reaction where the top keto acid is converted to an amino acid, while the bottom amino acid is converted to a keto acid¹

Keto acids and/or carbon skeletons are what remains after amino acids have had their nitrogen group removed by deamination or transamination. Transamination is used to synthesize nonessential amino acids.
Deamination
Deamination is the removal of the amino group as ammonia (NH₃), as shown below.

\[
\text{NH}_2 \quad \xrightarrow{\text{+ H}_2\text{O}} \quad \text{O} \quad \xrightarrow{- \text{NH}_3} \quad \text{O} \\
\text{Cytosine} \quad \text{Uracil}
\]

Figure 6.412 Deamination of cytosine to uracil (nucleotides, not amino acids)²

The potential problem with deamination is that too much ammonia is toxic, causing a condition known as hyperammonemia. The symptoms of this condition are shown in the following figure.

![Symptoms of Hyperammonemia](image)

Figure 6.413 Symptoms of Hyperammonemia³

Our body has a method to safely package ammonia in a less toxic form to be excreted. This safer compound is urea, which is produced by the liver using 2 molecules of ammonia (NH₃) and 1 molecule of carbon dioxide (CO₂). Most urea is then secreted from the liver and incorporated into urine in the kidney to be excreted from the body, as shown in Figure 6.414.
Figure 6.414 Production of urea helps to safely remove ammonia from the body.

References
5. http://upload.wikimedia.org/wikipedia/commons/b/b0/Kidney_section.jpg

6.42 Gluconeogenesis

Gluconeogenesis is the synthesis of glucose from non-carbohydrate sources. Certain amino acids can be used for this process, which is the reason that this section is included here instead of the carbohydrate metabolism section. Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround, as shown below. Remember oxaloacetate is also an intermediate in the citric acid cycle.

Figure 6.421 Gluconeogenesis is glycolysis in reverse with an oxaloacetate workaround.
Not all amino acids can be used for gluconeogenesis. The ones that can be used are termed **glucogenic**, and can be converted to either pyruvate or a citric acid cycle intermediate. Other amino acids can only be converted to either acetyl-CoA or acetoacetyl-CoA, which cannot be used for gluconeogenesis. However, acetyl-CoA or acetoacetyl-CoA can be used for ketogenesis to synthesize the ketone bodies, acetone and acetoacetate. Thus, these amino acids are instead termed **ketogenic**.

In addition to ketogenic amino acids, fatty acids also cannot be used to synthesize glucose. The transition reaction is a one-way reaction, meaning that acetyl-CoA cannot be converted back to pyruvate. As a result, fatty acids can't be used to synthesize glucose, because their oxidation produces acetyl-CoA. This acetyl-CoA enters the citric acid cycle and the carbons from it will eventually be completely oxidized and given off as CO$_2$. It is important to remember that while the fatty acids from a triglyceride cannot be used to generate glucose, that the glycerol portion of the triglyceride (Figure 6.315).

**References**

### 6.43 Protein Turnover/Degradation

Proteins serve a number of functions in the body, but what happens they have completed their lifespan? They are recycled.

![Recycling symbol](https://via.placeholder.com/150)

**Figure 6.431 Recycling symbol**

Proteins are broken down to amino acids that can be used to synthesize new proteins. Two of the main systems of protein degradation are:

1. Ubiquitin-proteasome degradation
2. Lysosome degradation
1. Ubiquitin-Proteasome Degradation

Proteins that are damaged or abnormal are tagged with the protein ubiquitin. There are multiple protein subunits involved in the process (E1-E3), but the net result is the production of a protein (substrate) with a ubiquitin tail, as shown below.

This protein then moves to the proteasome for degradation. Think of the proteasome like a garbage disposal. The ubiquitinated "trash" protein is inserted into the garbage disposal where it is broken down into its component parts (primarily amino acids). The following video illustrates this process nicely.

![Figure 6.432 Ubiquitination of a protein (substrate)](image)

2. Lysosome Degradation

The lysosomes are organelles that are found in cells. They contain a number of proteases (enzymes that breakdown proteins) that degrade proteins, similar to how proteins are digested in our own GI tracts.

References & Links

Video
Proteasome Degradation - https://www.youtube.com/watch?v=w2Qd6v-4Ilc
6.5 Alcohol Metabolism

The other energy source is alcohol. The alcohol we consume contains two carbons and is known as ethanol.

Figure 6.51 Structure of ethanol

Ethanol is passively absorbed by simple diffusion into the enterocytes. Ethanol metabolism occurs primarily in the liver, but 10-30% is estimated to occur in the stomach. For the average person, the liver can metabolize the amount of ethanol in one drink (1/2 ounce) per hour. There are three ways that alcohol is metabolized in the body.

1. **Catalase** – an enzyme that we will cover again in the antioxidants section. Catalase is estimated to metabolize less than 2% of ethanol, so it is not shown below or discussed further here.

2. **Alcohol dehydrogenase (ADH)** – This is the major ethanol-metabolizing enzyme that converts ethanol and NAD to acetaldehyde and NADH, respectively. Aldehyde dehydrogenase (ALDH) uses NAD, CoA, and acetaldehyde to create acetyl-CoA and to produce another NADH. The action of ADH is shown in the figure below.

Figure 6.52 Ethanol Metabolism
3. Microsomal ethanol oxidizing system (MEOS) - When a person consumes a large amount of alcohol, the MEOS is the overflow pathway that metabolizes ethanol to acetaldehyde. It is estimated that the MEOS metabolizes 20% of consumed ethanol\(^3\), and it differs from ADH in that it uses ATP to convert reduced NADPH + H\(^+\) to NADP\(^+\). The action of the MEOS is also shown in the Figure 6.52 above.

At high intakes, or with repeated exposure, there is increased synthesis of MEOS enzymes resulting in more efficient metabolism, also known as increased tolerance. However, ADH levels do not increase based on alcohol exposure. MEOS also metabolizes a variety of other compounds (drugs, fatty acids, steroids), and alcohol competes with these compounds for the enzyme's action. This can cause the metabolism of drugs to slow and potentially reach harmful levels in the body\(^3\).

It should be noted that females have lower stomach ADH activity and body H\(_2\)O concentrations. As a result, a larger proportion of ethanol reaches circulation, thus, in general, females have a lower tolerance for alcohol. Additionally, approximately 36% of East Asians (Japanese, Chinese, and Koreans) have an inherited deficiency in the enzyme ALDH (aldehyde dehydrogenase). This leads to buildup of acetaldehyde and undesirable symptoms such as: flushing, dizziness, nausea, and headaches\(^2\). The following short video explains what happens when the MEOS system gets involved in alcohol metabolism.

**Required Web Link**

Video: MEOS Overflow Pathway

**References & Links**


**Video**

MEOS Overflow Pathway - [http://nutrition.jbpub.com/resources/animations.cfm?id=20&debug=0](http://nutrition.jbpub.com/resources/animations.cfm?id=20&debug=0)