7. Making and storing fat and retrieving it to supply energy

7.1 Fat is the major storage form of fuel

Fat is required for human life. In chapter 5 we noted that the amount of glycogen that is stored in the body is limited. You can survive, perhaps, for only about one day on stored glycogen. With fat, you can survive for weeks. Eating more and more will make you fatter and fatter as fat accumulates in the cells of the adipose tissues. Although fat is stored mainly in adipose tissue, most cells that contain mitochondria also have fat globules in them. You may ask why does the body not simply store glycogen – why bother storing fat? It would make studying metabolism easier! But, a pound of fat has about twice the calories as glycogen. If you have 20 pounds of excess fat, to store the same amount of calories as glycogen would require 40 pounds.

Most tissues can use fat to make ATP. Metabolism of fat always requires O\textsubscript{2} and fatty acids are degraded to form CO\textsubscript{2} in the mitochondria. CO\textsubscript{2} is removed from the body by breathing, and it ultimately goes to the atmosphere.

Two types of cells are notable in that they do not use fat as a fuel. Red blood cells (RBC’s) have no mitochondria and consequently RBC’S do not use fat. Brain has mitochondria but it does not use fat for energy. The reason for this is that fat in circulating blood does not cross the specialized capillaries of the brain (these capillaries are called the blood brain barrier). We learned before that brain uses glucose for fuel. However, as we will discuss in this chapter, under long term fasting, the brain switches fuel from glucose to ketoacid compounds. Liver makes ketoacids from fat, and so only under non-feeding conditions, does the brain indirectly uses fat.

Fat is triglyceride. It has three fatty acids attached to glycerol. Liver is the main organ for making fat, although the pathway for fatty acid synthesis is present in liver, brain, kidney, mammary gland, adipose tissue and others. Fat is made in the liver from excess carbohydrates, which includes sugar and flour and from excess proteins.

Fat from food also directly contribute to fat stores. Ingested fat goes from the intestine into the lymph system and then into the circulating blood. Ingested fat is carried in the blood in particles called chylomicrons. Many tissues can use the circulating fat, but if these tissues have no need for ATP they do not use fat from the diet and fat is taken into adipose tissue for storage. The transport of fat, and the relationship of fat and cholesterol to manifestations of atherosclerosis (heart disease, stroke), is an important health concern that will be discussed in the next chapter.

7.2. Making fat and retrieving fatty acids from the fat stores

Fat is made when excess food is eaten. Stored fat is used for energy when food is lacking. In Figures 1-3, GB is used to illustrate three stages of making and using fat.
Phase 1. Fat synthesis: AcetylCoA is made into fatty acids in the cytoplasm. Fatty acid synthesis requires NADPH. The “pentose phosphate shunt” pathway supplies NADPH. The pentose phosphate shunt is a simple pathway, but it is involved in diverse other pathways and important diseases (Chapter 9). Glycolysis makes 3 C compounds from glucose and pyruvate dehydrogenase takes 3 C to 2 C, i.e., acetylCoA. Fatty acids are made from acetyl-CoA, and they are assembled into triglycerides (i.e., fat) in the cytoplasm of liver cells.

Phase 2. Fat breakdown: Triglycerides are broken down into fatty acids and glycerol. Fatty acids are bound to the protein albumin when they are transported in the blood. In the tissues using fatty acids for fuel, the fatty acids are broken down to form acetylCoA in mitochondria using the β-oxidation pathway. The acetyl group gets broken down to H₂O and CO₂ using the citric acid cycle and oxidative phosphorylation (Chapter 4). Many ATP molecules are formed.

Phase 3. Ketoacids: Ketoacids are made from AcetylCoA from fat during long-term starvation. The liver makes ketoacids but does not use ketoacids for fuel. All organs with mitochondria – except the liver – are able to use ketoacids for fuel.

7.3 Phase 1. Fat synthesis

Fat is made in the liver from excess carbohydrates and amino acids. Figure 7.4 gives an overview of what happens when sugar is converted into fatty acid.
You notice two differences between glucose and fatty acid. Glucose has equal number of O’s and C’s. Fatty acids have fewer O’s and more H’s. Sugars usually have 6 C’s whereas fatty acids usually have 16 to 18 C’s. So, to make fatty acids, O must be eliminated and the molecule must be made longer.

7.3.1 Carbohydrates can be converted into fatty acids

Here is what we have learned before: carbohydrates get broken to three C compounds in the cytoplasm and then to two C, acetyl CoA, in the mitochondria. In the mitochondria acetyl CoA gets broken down to CO$_2$ with the formation of ATP. We know in general terms how acetyl CoA break-down in the mitochondria is regulated: when the cell uses up ATP, ADP is formed. ADP stimulates the electron-transport chain and NADH goes to NAD. High NAD stimulates the reactions in the Citric acid cycle that uses up acetyl-CoA. This is shown in Figure 7.5.

When more acetyl-CoA is made than is needed to make ATP (when you are eating excess carbohydrate), liver converts acetylCoA into fatty acid. Figure 7.6 shows the pathways going from glucose to fatty acid.
Figure 7.6
Flow of carbons from sugar when sugar is in excess. Sugar gets made into acetyl CoA, which is made into fatty acids and then fat.

In this picture, you see that glucose gets chopped into three C compound, pyruvate, by the glycolysis pathway in the cytoplasm. Then CO$_2$ is removed from pyruvate and the two C compound, acetyl CoA is formed in the mitochondria. The acetyl CoA leaves the mitochondria and it is made into acyl CoA, and then assembled into triglyceride, i.e. fat.

Acetyl CoA does not directly leave the mitochondria, however. Here is a more expanded view of fatty acid synthesis for what happens to the C's.

Acetyl CoA combines with a four C compound to form a six C compound; this compound is citric acid, and in the TCA cycle, the two C's get converted to CO$_2$. When ATP is not required, the reactions of the citric acid cycle slow down, and citric acid concentration builds up. It then crosses the mitochondrial membrane. The six C compound, citric acid, splits into four C and two C compounds. The two C compound is the familiar compound, acetyl CoA. The 4 C compound goes back into the mitochondria, and is part of the citric acid cycle.

Acetyl CoA hooks onto another acetyl CoA to form a four C compound, acetoacetyl CoA.
Acetoacetyl CoA is now 4 C’s long. It still contains an oxygen atom that must be gotten rid of. NADPH adds H’s to it, and H₂O is removed in a series of steps. NADPH is like NADH, except that NADPH has an extra phosphate group.

Another acetyl CoA adds on to the four C compound, and the O atom is removed and H’s added. We now have a six C compound. The steps are repeated until 16 or 18 C’s are attached. The final product is 16 or 18 C fatty acid in the form of CoA, also called acyl CoA.

The fatty acids are attached to glycerol, and the final product, fat, is obtained.

### 7.3.2 NADPH is supplied by the pentose phosphate shunt

The C’s for fat synthesis come from glucose. It turns out that glucose also supplies the extra H’s required to make fat by supplying NADPH. NADPH is made in a pathway called the **pentose phosphate shunt**. The name “pentose phosphate shunt” arises because pentose phosphate is a product, and “shunt” is used because this pathway shunts C’s from the glycolytic pathway. (Some textbooks call this pathway the “hexose monophosphate pathway.” Glucose 6-phosphate, a hexose monophosphate, is the starting material of this pathway, hence this name). NADPH is like NADH but it has a phosphate attached to it. Enzymes that use NADPH cannot use NADH and vice versa. So the synthesis of fat is dependent upon the presence of NADPH.

The enzymes for this pathway are located in the cytoplasm of all cells. This makes sense because NADPH is used to make fat, and fat synthesis is also in the cytoplasm.

The cell uses the pentose phosphate shunt to make NADPH and ribose-5-P, a five C sugar. The production of which product depends upon the needs of the cell. 5 C sugars are used in the making of DNA and ATP, and then much ribose-5-P is used. When fat synthesis is going on, the important metabolite of the pentose phosphate shunt is NADP. The NADPH comes from the pentose shunt is involved in fat synthesis in the liver as seen in Figure 7.7.
Figure 7.7.

Glucose reacts with NADP to form phosphogluconate and NADPH. NADPH gives H's to make fat. Phosphogluconate loses CO$_2$ to form a 5C sugar, called ribose-5-P. The ribose sugar rearranges to form 3 C compounds and these ultimately make pyruvate.

So, both the C's and H's of fat come from sugar. Notice that the making of sugar is not 100% efficient in saving C's. One C is lost in the pentose phosphate shunt. And a C is also lost in going from pyruvate to acetyl CoA. No process is 100% efficient in the body. The making of fat from glucose is still advantageous because when fat is broken down so many ATP molecules are formed.

7.4 Phase 2. Fat mobilization and use

Fat from the adipose is used to make ATP in most tissues when glucose in the blood is low.

Figure 7.8 gives an overview of fat mobilization. Triglyceride, fat is stored in the adipose tissue. When insulin is low and glucogon and adrenaline is high – i.e. when a person is not eating – a protein called lipase is activated.
Fat is hydrolyzed to form fatty acids and transported bound to the protein albumin. When you are fasting, fatty acid in the blood increases. In blood work from your doctor’s office, this is called FFA, free fatty acid.

**Figure 7.9. Albumin**

Albumin is a protein in the blood serum. It binds fatty acids strongly; in the picture the green molecules are fatty acids and the blue is the polypeptide chain of albumin; many fatty acids are bound to one albumin molecule. Albumin transports fatty acids from adipose to cells that use fat for energy. Most cells use fatty acids from albumin, but the brain does not, since fatty acids bound to albumin do not pass through the blood brain barrier.

Fatty acid gets taken into a cell. Fatty acid then gets broken down to acetyl CoA, and then to CO$_2$ in the mitochondria. The steps are given in Chapter 4. Many molecules of ATP are formed.

In some tissues, fat oxidation is occurring at all times. The heart primarily uses fatty acids for fuel. So while fat may be being made in the liver, the heart is oxidizing fat to CO$_2$ and H$_2$O.

### 7.5 Phase 3. Long term fasting and the use of ketoacids.

We are now going back to our patient, GB. We are considering his metabolism under starvation conditions. He has not eaten for several days.

In short-term fasting, proteins from muscle and other tissue are converted into glucose by the liver and used by the brain. In long-term starvation, the body has the means to turn down the use of protein and to turn up the use of fat. It does it by making ketoacids from acetyl CoA. This is good! The metabolism of fat gives more calories than protein; this is to say fat metabolism produces more ATP. Because proteins are used for important functions in the body, it is beneficial to spare the use of proteins for fuel.
During long-term starvation, fatty acids are transported to the liver, and acetyl CoA builds up. The two ketoacids that are produced by the liver are acetylacetic acid and β-hydroxybutyric acid, shown here:\(^1\)

Ketoacids are made in the mitochondria of the liver only.\(^2\) Cortisol stimulates the enzymes that make ketoacids in the liver. After synthesis, acetoacetate and β-hydroxybutyrate go into the bloodstream. Most tissues, including heart, skeletal muscle and brain use them for fuel. Liver does not use them for fuel because the enzymes to break them down are not found in the liver. RBC’s do not use them for fuel, because they are metabolized to CO\(_2\) and O\(_2\) in mitochondria, and RBC’s do not have mitochondria.

The enzymes that break down ketoacids in tissues other than liver increase during starvation. These enzymes are stimulated by cortisol. The ketoacids get broken down to acetyl CoA. Acetyl CoA gets broken down to CO\(_2\) in the citric acid cycle and ATP is made by oxidative phosphorylation.

Notice that the liver is again the “good guy”; it makes keto-acids for use in other tissues but it itself does not use them. The production of keto-acids reduces the brain’s reliance on sugar, which comes from protein during starvation. If you turn back to Figure 6.3, you notice that the amount of glucose made by the liver decreases during long-term fasting. The brain is now using keto-acids for fuel, and so less glucose is needed for the brain to survive. Since glucose is made from protein, the use of keto-acids for fuel spares the use of protein.

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\(^1\) Many texts call these compounds “ketone bodies”. Acetylacetate is a keto-acid and β-hydroxybutyrate is a hydroxy acid. Since these two acids interconvert we shall lump both into the term “keto-acids” for simplification. We do not use the word “body”, since this is not a term used in organic chemistry.

\(^2\) There is an exception. A few amino acids are converted to keto-acids in muscle.
To emphasize, the brain uses glucose as its main fuel, but during starvation it relies upon the use of acetylacetate and β-hydroxybutyrate, the ketoacids. These are 4 C compounds made from fat using acetyl CoA. During this time, the enzymes of the brain also change. Transporters for the ketoacids appear, and the enzymes to break-down ketoacids into acetylCoA appear. Even though the metabolism of the brain has changed, it retains its cognitive functions.

7.6 An additional pathway: Very long chain fatty acids

The fat that we and most animals and plants store is made from 16 and 18 C’s fatty acids. But we eat many things and a small portion of the fat that we eat has more than 18 C’s. There are enzymes in the lysosome that have a specialized way to process very long chain fatty acids.

Figure 7.12
Processing fatty acids with 20 or more C’s.

The long chain fatty acids are broken down to acetyl CoA and six C acyl CoA. The six C acyl CoA can lose the CoA, and six C carboxylic acid is lost to the blood plasma, and excreted into the urine. Some of the six C acyl carboxylic acid is converted by enzymes in the endoplasmic reticulum to make it have two carboxyl groups on it – one on each end. This compound, a dicarboxylic acid, is excreted into the urine.

The net effect of the enzymes of the lysosome and the endoplasmic reticulum is called “detoxification”. These enzymes act to change many substances that we eat. The lysosome breaks the substance down, and the endoplasmic reticulum puts carboxyl or sugar groups on the compound to make it more soluble. Then these substances go into the blood stream, and they are excreted in the urine.

Enzymes within the lysosomes break down long chain fatty acids and other fatty acid compounds with unusual composition. When an enzyme is defective in the lysosomes, these unusual fatty acids and fat accumulate and cause havoc to the health of the patient.

7.7 Importance of unsaturated fatty acids

Many of diseases of lysosomes involve neurological symptoms. Lipids form the core of membranes. You remember that K⁺ salt is inside cells and Na⁺ salt is outside, and that this is essential for nerve function. When the lipids are not of normal composition, this salt distribution across the membrane is disrupted. Diseases of lysosomes include Tay-Sachs, Pompe, and Gaucher diseases.
The reason that a defect in the metabolism of fatty acids causes problems in processes involving membranes is that membranes are composed of fat-like substances. One of the major components of membranes is lecithin (Chapter 3). Biological membranes are composed of lecithin plus many other compounds similar to lecithin. Instead of the “choline” part, there may be a compound resembling an amino acid or sugar. When the head group is sugar, the compound is called a glycolipid. Glycolipids are found in high amounts in nerve cells. Membranes have different lipids within them. Unsaturated lipids are fluid, and they keep the center, hydrophobic part, flexible. We cannot make lipids that have many unsaturated double bonds, and we must get them from our diet. Some dieticians recommend eating fish oils, high in unsaturated fatty acids, to ensure that we get enough unsaturated fatty acids.

7.8 Concluding comments

Excess dietary carbohydrate and protein are converted into fat for storage. During long-term starvation, fat is converted into keto-acids. The brain uses keto-acids for fuel.

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3 Unsaturated fatty acids are also precursors for prostaglandins, hormones that are important in immunity.
8. Fat and cholesterol transport

8.1 Fat and cholesterol are transported in specialized particles

Sugars and amino acids dissolve in water. To transport glucose and amino acids from the liver to another tissue, the substance dissolves in the water of blood, and the heart pumps the blood to all tissues. Fat does not dissolve in water, as you know if you try to dissolve cooking oil in water. Fat is transported in the blood, but the body needs a different system to get the fat into the blood. Fat is incorporated in specialized particles in the blood called lipoproteins. Lipoproteins are small particles in blood that contain protein, fat and cholesterol.

Some fat comes from the diet and this fat is transported in the blood using one kind of lipoprotein, called chylomicrons. Other fats are made in the liver when excess sugar or protein is eaten. Another group of lipoproteins transport this fat. The important lipoprotein in this group is called low-density lipoprotein, or LDL. Some of the proteins in chylomicrons and LDL are the same. Finally, there is a particle called high-density lipoprotein, or HDL, aids in transfer of the proteins between the particles and in removing cholesterol from tissues.

All lipoproteins contain cholesterol. Hence, we need to talk about cholesterol and fat together. This chapter will describe how fat and cholesterol is transported from the intestine from food and between organs. As always, we are describing what happens in humans – the way that fat and cholesterol are transported is quite different in other animals.

The transport of fat and cholesterol in the blood has major health considerations. People who have high amounts of LDL are more likely to have cardiovascular diseases such as heart attack or stroke. People who have high amounts of HDL have lower risk for these diseases. When your doctor tells how much cholesterol is in your blood, you will be told that LDL is “lousy” or “bad” cholesterol. HDL is “healthy” or “good” cholesterol. The doctor may tell you that if the ratio of LDL to HDL is low, that this is a healthy indication.

8.2 Cholesterol: friend or foe?

Most people are aware that high cholesterol in the blood can lead to heart attacks and strokes. We talk about our cholesterol levels at parties. Cholesterol seems to be a bad guy! But is it?

What is cholesterol? The structure of cholesterol is shown below. Remember that whenever there is a bend in the structure, the bend represents a C, with associated H’s. You see that cholesterol is mostly made up of C’s and H’s. Since it is made up of mostly C’s and H’s it is hydrophobic and does not dissolve in water.
Our bodies make cholesterol. Liver synthesizes most of the body’s cholesterol, but all our cells that have mitochondria (that basically means all cells except red blood cells) are able to make cholesterol. Cholesterol is made from acetyl (2 carbon) groups.

We also get cholesterol from animal products in diet. Cholesterol is high in animal fat and in dairy foods and eggs. Dairy products and egg yolks are foods that are intended to nourish the young of mammals and birds. The enzymes that make cholesterol are not always developed in the young. It makes sense that the food given to the young would have cholesterol. In fact, some pediatricians recommend that children be given whole milk, which contains cholesterol, rather than skim milk, to drink until they are about five years old. By this time, the child’s liver enzymes are developed to make enough to supply the needs of cholesterol.

We do not get cholesterol from plant foods since plants do not make cholesterol. Plants have related molecules (called sitosterol and lanosterol).

We absolutely require cholesterol. No person in the world is living that is known to have no cholesterol – this would not be compatible with human life. There are very rare diseases in which the cholesterol transport from the liver to other tissues is impaired. These patients are very sick.

Cholesterol has important functions in our body:

1. Cholesterol is found in membranes that surround the cell. During development of a baby, the nerves in the brain get covered with membranes called the myelin sheath. Myelin sheath is composed of layers of membranes that are composed of mainly a glycolipid and cholesterol. If a child does not have enough cholesterol, the brain will not develop normally. For the most part, cholesterol is not found in membranes inside of the cell. For instance, mitochondrial membranes do not have cholesterol.
2. Cholesterol is needed to transport fat in the blood stream. All types of lipoproteins contain cholesterol.
3. Cholesterol is used to form vitamin D. Vitamin D regulates calcium levels in the body. Vitamin D is made in our skin in response to light; hence cells in the skin makes it when we are outside in the sunshine. Vitamin D stimulates pumps for Ca++ absorption in the intestine. In the kidney, Ca++ is lost, but vitamin D stimulates pumps to take Ca++ back into the blood. Without vitamin D, therefore, not enough Ca is absorbed from the diet, plus, Ca++ in the blood is lost in the urine.
4. The precursor to make cholesterol is also used to make coenzyme Q. Coenzyme Q is found in mitochondria. Mitochondria need coenzyme Q in order to use oxygen and make ATP.
5. Cholesterol is a precursor for bile acids. Bile acids aid in the digestion of fat.
6. Cholesterol is used to make the steroid hormones. Steroid hormones include the sex hormones. Testosterone in males and estrogen in females regulate sex characteristics. Another steroid hormone is cortisol. This hormone is one of many that regulate metabolism.

And this final interesting fact about cholesterol: although we make it and get it from our diet, and we use it in important ways, we do not get calories from it. It is made from 2 C units using enzymes in our cells, but we do not have the enzymes to break it down to acetyl CoA. Consequently, it is not converted to CO₂ and H₂O in the mitochondria. And mitochondria make no ATP from it – no energy, i.e. calories, for the cell.
So right now we have a gigantic idea. Cholesterol is good – we absolutely need it! And we don’t get calories from it! Why not eat a lot of cholesterol and stay healthy and slim? The story is more complicated. Too much cholesterol causes many problems. To understand why, we need to know how cholesterol is transported in the body and how the body gets rid of excess cholesterol.

**8.3 Fat and cholesterol get into the body in the intestine**

Figure 8.1 shows a meal that is high in cholesterol, cholesterol esters and fat. You remember that fat is triglyceride, composed of three fatty acids that are attached to the three OH groups of the glycerol molecule. Cholesterol has one OH (hydroxy) group and a fatty acid can also attach to fatty acid. Then it is called cholesterol ester. Diet will contain both cholesterol esters and cholesterol. Figure 8.1 shows what happens to the fat and cholesterol after a meal.

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**Figure 8.1.**

**Step 1.** Fat and cholesterol from the diet gets emulsified by bile acids in the intestine. Bile acids are themselves made from cholesterol.

**Step 2.** Fat and cholesterol gets packaged into chylomicrons. The bile acids are recyled by being taken up again by the intestine and returned to the gall bladder. Some are lost in the feces.

**Step 3.** Chylomicrons pass into the lymph system and then into the blood.

**Step 4.** Adipose (fat tissue) and other tissues take the triglyceride from the chylomicrons. The chylomicron particle gradually becomes smaller, until it is the chylomicron remnant, rich in cholesterol.

**Step 5.** The liver takes in the remnant.

Step 1. When we eat fat, cholesterol and cholesterol esters these water insoluble molecules get “emulsified” by bile acids. This is the same process that cleans clothes in the washing machine. The soap in the washing machine or the bile acids in the intestine break up globules of fat to smaller particles. One of the most common bile acid is cholic acid that itself is made from cholesterol. This is the structure of cholic acid.
You see that it looks like cholesterol but has more OH groups on it. The process of emulsification occurs in the intestine. Bile acids, made from cholesterol by the liver, are stored in the gall bladder. They are secreted into the intestine, and they break up fat into particles that are suspended in water. An analogous process breaks up fat in your frying pan when you clean it with dishwashing detergent.

Step 2. The intestine transfers fat and cholesterol across the intestinal wall. In cells called enterocytes, fat and cholesterol are assembled into a particle called the chylomicron. Chylomicrons contain fat, cholesterol and cholesterol esters and they are held together by specialized proteins called apoproteins. These proteins are named apoA, apoB, apoC and apoE (Figure 8.2).

Some of the bile acid molecules are reabsorbed to be used again, and some are lost in the feces. The loss of bile acids during digestion results in less cholesterol in the body. This is an important way to reduce the amount of cholesterol in the body.

Step 3. The chylomicron goes from the enterocyte into the lymph system. From the lymph it goes to the subclavian vein, where the fat goes into the general blood circulation. Fat soluble vitamins, such as vitamin A and D, also enter the body through this system. They get distributed to the various tissues, initially by-passing the enzymes in the liver that would remove them by “detoxification” described briefly in the last chapter.

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4 You notice that the treatment of fat by digestion is quite different from protein and carbohydrates. Proteins are broken down to amino acids and carbohydrates are broken to single sugars in the intestine. The portal vein transports these to the liver. The liver transforms the sugars and amino acids, and then they get into the general circulation.
Figure 8.2

Fat and cholesterol from the diet gets packaged into particles that get transferred to the left subclavian vein. This vein connects eventually to the superior vena cava vein, which brings blood to the heart. The heart pumps the blood into the general circulation.

(Doctors always refer to left and right relative to the patient. So although the left subclavian vein on the picture is on the right, it would be on the left on the patient.)

Step 4. After eating a big meal of fat, your blood plasma appears milky from chylomicrons. The adipose cells (i.e. our fat) recognize the proteins E and B-48 on the chylomicrons, and the chylomicrons transiently bind to the cells. During this process the triglyceride within the chylomicron is transferred to adipose and other tissues. Gradually, over a period of hours, the chylomicrons become depleted of fat, and then the particle is called chylomicron remnant.

Figure 8.3

Proteins of chylomicrons are shown as magenta spheres, phospholipids are represented by blue circles with tails. Triglycerides and cholesterol are represented by yellow and orange, respectively.

During circulation triglycerides are transferred to adipose tissue (Step 4). The particle loses apoC. It is now called chylomicron remnant.

Step 5. The remnant retains most of the cholesterol. The liver recognizes the proteins on the chylomicron particle and it engulfs it (this is called endocytosis), and the cholesterol from the diet becomes part of the pool of cholesterol in the liver.

If you have ever had your blood cholesterol tested, you will remember that you needed to fast before the test. The reason for fasting is to test cholesterol made in your body and not the transient high levels of cholesterol due to a Big Mac you might have just eaten. So,
testing is carried out after all the chylomicrons arising from eating have disappeared from circulation. This takes several hours, and usually you are instructed not to eat overnight.

8.4. Plants have sterols but the intestine excretes them.

Plants have sterols that are related to cholesterol but are not exactly the same. Fat and sterols from plants are emulsified by the intestine, and transported across the intestine. The fats from plants become part of the chylomicron, and the triglycerides get stored in the adipose tissue. But plant sterols are immediately transported back out into the intestine and they are excreted in the feces. They are transported back into the intestine by proteins called ABC proteins. This process involves ATP and a variety of proteins: ABC stands for ATP Binding Cassette. Because the ABC proteins transport plant sterols back into the intestine, plants do not contribute to the body’s pool of cholesterol (Figure 8.4).

Figure 8.4
Fate of plant sterols.

Plant fats are emulsified just as animal fats are. The plant sterols get taken in the intestine wall, but then they are transported back across the intestine wall by the ABC transporters. The plant sterols are excreted in the feces. Plant fat gets made into chylomicrons.

8.5 Fat and cholesterol made in the liver are transported by lipoproteins called LDL and VLDL

You know that when you eat too many sweets your adipose tissue increases -- you get fat. Triglycerides are made mainly in the liver. We now come to how triglycerides and cholesterol that are made in the liver are transported to other tissues. Like fat from food that is transported on a lipoprotein particle (namely the chylomicron), fat made in the liver is exported from the liver by a lipoprotein particle. The particle is Very Low Density Lipoprotein, or VLDL. It is low density because it is mainly composed of fat and fat floats to the top. (The reason that cream floats to the top of milk is the same: cream is rich in lipoproteins).

VLDL circulates through the blood and gradually triglycerides are removed from it as fat goes into adipose tissue. It gradually gets smaller and smaller and finally becomes a
particle called low-density lipoprotein, or LDL. Since triglyceride has been removed, the cholesterol in LDL is high relative to the amount of triglyceride.

For the liver to make VLDL, cholesterol is required. When the liver is making fat, it also makes more cholesterol in order to make VLDL. This is why if you have high cholesterol and are overweight from eating too much carbohydrates and proteins, your physician may recommend that you lose weight. When you are no longer making fat from sugar, you will also not be making so much cholesterol.

**Figure 8.5**

VLDL particles carry triglycerides and cholesterol to adipose and to other tissues. As the triglyceride is depleted, the particle gets smaller (indicated by IDL, intermediate density lipoprotein) and finally becomes LDL, low density lipoprotein. LDL is rich in cholesterol. Some of the cholesterol can get oxidized. These LDL particles are taken into scavenger cells, on the vascular cells. They form foam cells and lead to atherosclerosis (heart disease and stroke). The liver takes in most LDL particles.

### 8.5.1. Why are LDL and VLDL called the “lousy” and “very lousy” lipoproteins?

LDL stands for “low density lipoprotein”, but you can also consider that it as “lousy” lipoprotein. This is because it contains the “bad” cholesterol. The reason it is called bad is that there is a correlation between high levels of LDL and vascular diseases. Most doctors consider that if you have high levels of these lousy LDL’s you are at increased risk for heart attack and stroke, and the doctor will recommend medicine to reduce the levels of LDL.

High levels of LDL’s lead to the formation of plaque, and foam cells in the arteries. As cholesterol circulates through O₂ – rich blood, some of the cholesterol reacts with O₂. The by-product formed – oxy-cholesterol – is thought to trigger an immune response. This makes foam cells grow. Blood is no longer able to flow through the artery.

### 8.5.2. HDL - the “Happy” or “Healthy” lipoprotein

In rough terms, the function of VLDL is to move triglycerides and cholesterol to adipose and other tissues. There is another particle in the blood whose function is to move cholesterol from tissues to the liver. HDL, standing for “high-density lipoprotein”, is the transport particle. In simple terms, its function is to remove cholesterol from the outlying tissues and deliver it to the liver. It has a protein, called apoA. The liver recognizes the apo A protein, and it endocytoses HDL, thereby removing cholesterol from the circulation. In the liver the cholesterol from HDL becomes part of the cholesterol pool in the liver.
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Figure 8.6

HDL takes cholesterol from outlying tissues and brings it to the liver.

Liver makes most of the body’s cholesterol. When cholesterol and cholesterol esters get high within the liver, the enzymes that are needed to produce cholesterol are reduced, and the overall liver production of cholesterol goes down. When cholesterol levels within the liver are low, then the enzymes that make cholesterol go up.

It seems that HDL also serves to transfer the apoproteins between the lipoproteins. There are some families that have very high cholesterol, and have no incidence of atherosclerosis or heart disease. But, for most people, high LDL and low HDL is an indication of likelihood of disease, but exceptions indicate that we do not know the whole story.

8.6. How to keep LDL (“lousy” cholesterol) low and HDL, (“healthy” lipoprotein) high

If cholesterol from LDL in the blood is too high, there is an increase risk of heart disease and stroke, as we mentioned before. So, based upon our knowledge of cholesterol transport what are we to do?

An obvious first step is to lower the amount of cholesterol that we eat. Plants do not contain cholesterol and a diet high in plants will aid in reducing cholesterol.

Another recommendation for people who are overweight is to decrease the intake of food, especially carbohydrates. Extra carbohydrates are converted into triglyceride (fat) in the liver. This fat is transported in the LDL particles to other tissue. For LDL particles to be formed, cholesterol is needed, and therefore the liver makes cholesterol for this purpose.

Another approach is to get rid of cholesterol already in the body. How can we do this? Products of cholesterol are the bile acids. Some of the bile acids are reabsorbed in the intestine, but the rest are excreted in the feces. There are resins that hinder the reabsorption of cholesterol and bile acids by the intestine. Such compounds occur naturally in some foods. Oats contain a substance that prevents reabsorption of the cholic acids. Cereals containing oat grain, such as oatmeal and oat containing cereals, such as Cheerios, are advertised as being “heart healthy”. Indeed, clinical studies showed that eating such food helps reduce cholesterol levels.

A breakfast that may aid in reducing cholesterol is shown on Figure 8.7. Oatmeal, bananas and peanuts contain no cholesterol, and oatmeal helps to reduce cholesterol. Oats contain a substance that reduces the reabsorption of cholesterol and bile acids back from the intestine back to the liver.
While efforts based upon diet may help to reduce LDL in some patients, they may not be enough in other patients. Another step would be to give the patient a drug that would either reduce LDL or increase HDL.

Statins are drugs that are widely used to reduce cholesterol. They reduce the synthesis of the critical enzyme on the pathway of cholesterol synthesis. And they also induce receptors for LDL in the liver, so that LDL in blood is taken into the liver. This reduces the amount of cholesterol in blood. Furthermore, as more LDL gets taken into the liver, the overall cholesterol inside the liver gets goes up. This reduces the amount of cholesterol made by liver.

The precursor in the pathway for making cholesterol is also used to make CoQ, a substance required in mitochondria. Since statins inhibit the production of the precursor of both cholesterol and CoQ, there is a danger that the CoQ levels will become too low. If this happens, muscle weakness will result, since muscles require the ATP’s that are produced by mitochondria. The physician will monitor her patient for any muscle weakness, and recommend reducing the dosage of statins or perhaps using CoQ supplements, if needed.

Other drugs that increase the production of HDL are available. The physician may recommend a combination of drugs.

8.7. Summary

Lipoproteins in the blood transport fat and cholesterol. Chylomicrons transport fat and cholesterol from food in the diet. LDL (low density lipoprotein) transports fats made in the liver. HDL (high density lipoprotein) is the third major lipoprotein. High HDL and low LDL are associated with low risk of heart disease and stroke. The opposite is also true: low HDL and high LDL indicates an increased risk of heart disease and stroke.
9. Repair of the engine

9.1. All motors need repair

Sometimes you may lose a hubcap from your car. The battery may wear out. Or you may have a fender-bender. You can repair the car by buying a new hubcap or battery or by knocking out dents in the fender.

Materials from cells sometimes go astray or become damaged too. The theme of this chapter is how the cell replaces and salvages some materials and repairs others.

We are constantly being bombarded with dangerous substances, and even things that we need, can turn out to cause harm. We need O\textsubscript{2} and light to survive, for example. But both are also dangerous. Vitamin D is formed when light interacts with our skin, and so light is beneficial. But too much light causes damage to DNA. Since DNA ultimately determines what proteins are made, when DNA is damaged, the regulation of protein synthesis can be impaired. This can lead to skin cancer. The same is true for O\textsubscript{2}. We need O\textsubscript{2} at all times but O\textsubscript{2} can also form reactive species that can destroy proteins and DNA.

Every time that we breathe, and every time we are in light, reactive compounds are formed. For the most part, these compounds do not kill cells, because cells have mechanisms that restore damaged and lost molecules.

The pentose phosphate shunt pathway is a player in protecting our cells. The pentose phosphate shunt is tied in to the making of fatty acids by providing NADPH used in making fat (Chapter 8). Proteins are sometimes damaged, and the pentose phosphate shunt aids in recovery of damaged protein. It does this by making NADPH, which is used for repair. We will also mention the importance of anti-oxidants in the diet. These compounds are also used to restore damaged molecules.

9.2 Protein damage in red blood cells is repaired by the pentose phosphate shunt

The purpose of red blood cells is to transport oxygen, O\textsubscript{2}, from the lungs to the tissue. Red blood cells do not consume O\textsubscript{2} as they have no mitochondria and O\textsubscript{2} is required for oxidative phosphorylation. Consequently, the concentration of O\textsubscript{2} is higher in red blood cells than in other tissues.

Nucleic acid molecules such as DNA and RNA and protein molecules are fragile. Chemical reactions can destroy them. There are many reactions that can cause tissue damage. One type of these reactions is caused by what is called “reactive oxygen species”, ROS.

ROS are toxic products of oxygen. One is the familiar hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) used to bleach hair. It does this by chemically destroying the pigment in hair. There are also other ROS’s. Many of these are free radical species. In a free radical species the rules of chemical bonding (for instance one rule is that O has two bonds and C has four bonds) no longer hold. Free radical species are very reactive and can wreck havoc on proteins. Fire is an example of a free radical chemical reaction. Left alone, fire will rage until all the fuel is consumed. It is not good to have many free radical species in the body.
Several of the 20 amino acids that make up proteins contain sulfur, and these amino acids are susceptible to damage by ROS. One of these is cysteine, a 3 C amino acid like alanine. The structure of cysteine is:

\[
\begin{align*}
&\text{H-S} \\
&\text{H} \\
&\text{C} \underline{\text{C}} \underline{\text{C}} \\
&\text{H} \\
&\text{O-H}
\end{align*}
\]

The symbol for sulfur is S. In proteins, the -SH group is called a sulfhydryl group. SH groups in proteins are usually on the surface of the protein and exposed to the surrounding water.

The SH group is required for the proper function of many enzymes, but the –SH group is very reactive to ROS. When –SH reacts with ROS where the H from S is removed from -SH a free radical species forms.

In the cell, two cysteine amino acids that are free radicals hook on to each other, forming a dimer (dimer means being composed of two single molecules or groups. The single molecule is called monomer). The dimer is called cystine and this is what it is:

This reaction also occurs in proteins that contain cysteine. In the figure below, part of a peptide containing cysteine is shown. A whole peptide chain in a protein is much bigger than the peptide shown and the red blob illustrates the rest of the protein peptide chain.

| Figure 9.1A | This is a hypothetical protein that has two cysteine amino acids |
| Figure 9.1B | When the cysteine –SH group has an H removed, the free radical –S` is formed. Now two molecules can join. The two protein molecules are no longer attached to each other. They can form attachments with other protein molecules, and a big mess results. |

When proteins contain more than one cysteine, then the reactive free radical SH group can react with another. Cysteine, the SH form of the amino acid, is found in most proteins within cells. These proteins are functional only when the cysteine is in the SH form. In contrast, cystine, the dimeric form of cysteine that has –S-S-, is found in proteins found outside of...
cells. For instance, in the hormone insulin, an extracellular protein found in the blood plasma, the form is cystine.

### 9.3 How to keep proteins within cells in the SH form

Within cells, the pentose-phosphate shunt pathway keeps the amino acid in the cysteine form for proteins within cells. Since we always need $O_2$, ROS are always present and, at all times, there must be a way to repair proteins with damaged SH groups.

One could imagine that the damaged protein could be repaired using a specialized “repair” enzyme. But there are many proteins in the cell, and each type of protein would need its own repair enzyme. Instead, a small compound called glutathione repairs all SH groups. Glutathione is composed of three amino acids that we have seen before: glutamic acid, cysteine and glycine. Figure 9.2 shows that glutathione attacks S-S bonds by adding H atoms. In so doing, it becomes a S free radical, which reacts with another S free radical to form glutathione disulfide.

![Figure 9.2](image)

**Figure 9.2**

The cell has a high level of glutathione. Glutathione transform S-S to SH. The protein will no longer be aggregated.

This molecule repairs the free radical S groups, but in turn it gets transformed to a S-free radical molecule. Then NADPH, from the pentose phosphate shunt pathway, repairs glutathione, using just one enzyme, called glutathione reductase. Notice the “trick” that the cell uses. There are many reactive species reactive species made. To repair these many species, one compound, glutathione is used. Then a single enzyme system using NADPH restores the glutathione.

NADPH is formed in the cytoplasm by the pentose-phosphate shunt. The pentose-phosphate shunt is indicated in blue:
Figure 9.3

ROS stands for Reactive Oxygen Species. The black part of the figure shows glycolysis. The pentose-phosphate shunt is shown in blue.

ROS damages protein by causing cysteines to bind to other cysteine residues. This makes the proteins aggregate. Glutathione restores the cysteine. Glutathione itself forms a bond with another glutathione molecules in the process. NADPH restores the glutathione.

Glucose-6-phosphate is obtained glucose from the breakdown of glycogen or coming in from the blood. The products of glycolysis are pyruvate and lactate, which, for red blood cells, go back into the blood and ultimately get metabolized by the liver. But not all of the glucose-6-phosphate goes to pyruvate. When NADP levels are high some glucose-6-phosphate reacts with NADP to form NADPH and ultimately ribose-5-P. The first enzyme in this pathway is called glucose-6-phosphate dehydrogenase. This enzyme is inhibited when NADPH is high. This means that the enzyme does not work, and most of the glucose-6-phosphate is metabolized through glycolysis. But when NADPH is transformed into NADP in the repair of S groups, then the enzyme is active. Glucose-6-phosphate is transformed into phosphogluconate and NADPH is formed.

9.4 Pentose phosphate shunt in disease

When proteins within the cell aggregate inappropriately, they no longer act in the way that they should. Disease occurs. The first case describes a disease that affects primarily the red blood cells. Hemoglobin is densely packed in RBC's. When the SH are damaged, hemoglobin molecules will bind to each other.

Case 1 (Milner et al., Blood 43, 271-276 (1974): A 39 year-old male, H. I., entered a hospital for an unrelated condition. During examination while in the hospital it was observed that his skin and the sclera (whites of eyes) had a yellow tinge. The relevant laboratory results are below:

<table>
<thead>
<tr>
<th></th>
<th>patient</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, g/dl</td>
<td>12</td>
<td>13-15</td>
</tr>
<tr>
<td>Reticulocyte count, %</td>
<td>25</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td>Total bilirubin, mg/dl</td>
<td>3.9</td>
<td>0.2-1.2</td>
</tr>
<tr>
<td>Appearance of red blood cells</td>
<td>Heinz bodies</td>
<td>No Heinz bodies</td>
</tr>
</tbody>
</table>
The physicians were alerted to a possible problem for H. I. by the yellow color of his skin and sclera, and this suggests a problem called jaundice, which means bilirubin is high. Indeed, testing showed that bilirubin in his blood is high. Bilirubin is a break-down product of heme. Heme is the substance that binds O\textsubscript{2} in hemoglobin. Bilirubin can be high because too much is produced or not enough is removed. Some new-born babies have high bilirubin, leading to jaundice (also yellow skin and sclera). This can occur in premature babies because the liver is sometimes not developed enough to contain the enzymes that break-down bilirubin and lead to bilirubin excretion. For the baby, high bilirubin is due to under-consumption. The body produces the normal amount of bilirubin, but the level is high because it is not removed fast enough.

H.I. is not a new-born baby, but we can still ask whether there may be a problem with bilirubin removal. However, the observation of high reticulocytes is another clue. Reticulocytes are young red blood cells. They have a nucleus that can be seen under a microscope. As the cells mature, they lose the nucleus; mature red blood cells have no nucleus.

The observation of elevated reticulocytes is characteristic of a hemolytic anemia. This occurs because the red blood cells do not last for their usual 120 days, but are lysed, i.e., they break open. Therefore, the percentage of young cells in the blood increases. When red blood cells are reduced, a hormone called erythropoietin is produced that stimulates the production of new red blood cells. The high reticulocytes suggest that red blood cells are broken down but H.I. does not become severely anemic because the synthesis of new red blood cells compensates.

The red blood cells appeared abnormal under the microscope. They had dark enclosures. These features are called "Heinz bodies". They are aggregated hemoglobin molecules. (Think of dried up catsup around a catsup bottle, and you have a way to remember what Heinz bodies are)!

Discussion, diagnosis and treatment of H.I.: Red blood cells of H.I. were studied. The researchers found that the enzyme glucose-6-phosphate dehydrogenase was defective in H.I. so production of NADPH was reduced. This resulted in the Heinz bodies in the RBC's, and led to fragility of the RBC's.

Glucose-6-phosphatase dehydrogenase (G6PD) deficiency is a common disease-producing enzymopathy (a disease produced by abnormal enzyme) in humans. One amino acid of G6PH in H.I has been changed to another one. H.I. has a mild form of the disease. Reactive ROS increase with severe infection, and with some drugs including antimalarial drugs. A substance in fava beans also produce ROS's. In these cases, the patient may have a hemolytic attack. The patient should be advised not to use certain drugs or eat fava beans. In case of a hemolytic attack he can be treated by dialysis and blood transfusion.

G6PD deficiency is inherited as an X-linked disorder and it affects 400 million people worldwide. There are many variants of G6PD deficiency and that one that H.I. has is called the Manchester variant, named after the English city in which it was discovered. G6PD deficiency confers protection against malaria, which probably accounts for its high gene frequency. The variant is prevalent in people of Mediterranean origin. H.I.
came from England, and the variant is not uncommon in the British Isles. (Remember, England was once a Roman colony).

**Case 2: Cancer patient receiving radiation.** A 49 year-old female, J.K., was diagnosed with breast cancer, specifically ductal carcinoma. She was treated by surgery, followed by chemotherapy and then radiation. X-ray treatment occurred each day for 30 consecutive days. The radiologist suggested an arm exercise that exercises the pectoral muscle that was below the radiation site. What metabolic pathways would be in play with these exercises and how might that aid in repair of the muscle from the radiation damage?

**Discussion:** X-ray beams break chemical bonds forming free radical species. Within a short time these species transform SH groups in proteins to S free radicals that can react with other S free radical species to make –S–S– bonds. Exercise increases Ca levels in the muscle, and stimulates glycogen breakdown to glucose-6-phosphate. Glucose-6-phosphate is the starting compound for the pentose-phosphate shunt. When NADPH is low the enzyme that transforms glucose-6-phosphate to phosphogluconate with the production of new NADPH is stimulated. Exercise, therefore, could help to help repair the free radicals and to lessen damage to protein. This explanation is an hypothesis only, however, since there is little experimental evidence to support this.

### 9.5 Other substances that are anti-oxidants

ROS produces free radicals when it reacts with fatty substances, DNA, RNA, proteins and other molecules. Vitamin C and vitamin E are two substances that are antioxidants. Vitamin C is involved in collagen formation. Collagen is a protein that is extracellular, and it is used for structure – it holds tissues together. Lack of vitamin C leads to the disease called scurvy, characterized by malaise, skin and gum disorders.

Vitamin E is not water soluble, and it is thought to protect the fatty acid part of membranes from oxidation. Neurological problems occur with vitamin E deficiency. β-carotene and polyphenol are other anti-oxidants that are soluble in the fatty acid part of membranes.

Clinical trials are mostly inconclusive for possible benefits of other anti-oxidant supplements. Just because something is an anti-oxidant in the test tube does not mean it will be anti-oxidant in the body. There must be enzymes in the body that will use the particular anti-oxidant molecule. But there are credible studies showing people who eat diets rich in fruits and vegetables, foods rich in antioxidants, have health benefits.

### 9.6 Salvaging adenosine

ATP is the dollar bill of metabolism. Just as money is needed to keep the economy going, the energy produced when ATP loses a phosphate to make ADP is required to keep metabolism going.

Here are the components of ATP:
Our bodies make adenosine from basic small molecules, but it is “expensive” to do so. Many ATP reactions of ATP going to ADP are required to make adenosine.

Although, ADP gets phosphorylated to cycle back to ATP, there is a gradual decline in the amount of ADP and ATP in cells. We can understand this by looking at the reactions of ATP. When there is a demand for energy ATP goes to ADP with the release of P.

\[
\text{ATP} \rightarrow \text{ADP} + P
\]

In tissues where demand is suddenly high, there is a way to get ATP from ADP. The enzyme myokinase catalyzes this reaction:

\[
2 \text{ADP} \rightarrow \text{ATP} + \text{AMP}
\]

This is an “emergency” reaction; it gives ATP when there is a sudden and large need for extra ATP to provide energy. Myokinase was first found in muscles (the preface “myo” means muscle) and but it is also found in other cells, including the nervous system.

AMP can be further degraded to for adenosine and the ribose sugar. The ribose sugar is metabolized to to 3 C units, as shown in Figure 1, and then ultimately to CO\(_2\) in the citric acid cycle.

The adenosine part is also finally degraded. Oxygen atoms are attached to it, forming the compound urate. Urate is a waste product and it is excreted into the urine.

High levels of urate is associated with disease. When urate is too high in the blood, urate crystals can form. This can lead to renal stones and to the condition called gout, where crystals of urate form in joints, especially the joints of toes. This is a painful condition.\(^5\)

To save energy required to make more adenosine, and to reduce the amount of urate excreted in the urine, the body salvages the adenine. More than 90% of the AMP broken down does not get excreted from the body, but is salvaged.

The ability to reclaim adenosine and transform it back to AMP, and then ADP and ATP is found in all tissues. Here is the pathway for breakdown and salvage.

\(^5\) Many famous people have suffered from gout, including Thomas Jefferson, Henry VIII, Benjamin Disraeli, Karl Marx and Pope Clement VIII.
AMP gets transformed to IMP, and then the ribose sugar gets taken off. The product is inosine. Inosine gets transferred into hypoxanthine. Hypoxanthine can diffuse out of the cell into the blood. But most of the hypoxanthine gets the sugar put back on it to form IMP. The sugar is a 5 C sugar, pentose, made by the phosphopentose shunt. Once the sugar is added, IMP can be transformed into AMP. AMP is phosphorylated by myokinase (above) and oxidative phosphorylation to make ATP. The liver also has these salvage enzymes, but the liver can convert hypoxanthine to urate by adding oxygen atoms. Urate formed in the liver goes into the blood, and then is excreted in the urine.

9.7 Too much urate acid: gout and kidney stones

There are several general reasons why high urate in the blood might occur. One is that too much is produced. Too much produced may be due to altered enzymes in the synthesis. It can also be due to impaired salvage pathway.

The following case is a very rare disease, in which the salvage pathway is missing.

**Case:** Patient, L.M. was a full term baby. At three months he was weak and cried excessively. He was late in sitting up and never learned to walk. At age three he began to bite his lips and fingers. He bit his fingers so much that he literally ate them and he lost the fingers on one hand. As he grew older he developed kidney stones and gout. He never learned to speak.

**Diagnosis, treatment and discussion:** This describes a patient with Lesch-Nyhan syndrome, where the salvage enzyme is lacking. All of the hypoxanthine gets transformed into urate. The neurological problems are probably related to the lack of sufficient ATP in the nerve cells, but the bizarre behavior is not understood. A drug called allopurinal partially inhibits the enzyme that forms uric acid. In this case hypoxanthine increases in the blood. Hypoxanthine is excreted in the urine. The patient’s blood will also have a mixture of hypoxanthine, xanthine and urate. A mixture also inhibits the formation of urate crystals. Allopurinal helped relieved L.M.’s gout, but did not reverse the severe neurological problems.

This disease is linked to the x chromosome, and so it is seen more in boys than in girls. Although this is a very rare disease, this disease illustrates the importance of salvaging adenosine, since without salvage the patient is very sick.

Another reason for high urate is under-secretion, i.e. the body does not properly get rid of urate. This is the more common reason, and is often seen in the elderly. As people age, the
kidney function often decreases. The kidney does not remove the urate fast enough and urate levels increase.

**Case:** L.M. is a 74 year old male. He has had high glucose in his blood, and the doctor prescribed metformin for this. He has arthritis in the knees and for 10 years he has taken aspirin to control pain. In spite of this, he drinks a six-pack of beer every day and often has a shot of whiskey in the evening. In the last two weeks his left toe became red, swollen and painful. He cannot walk on it. It is even painful to have a blanket on the toe when he is sleeping.

**Diagnosis, treatment and discussion:** Blood tests showed high urate in the blood. L.M. is drinking mainly alcohol, not water. Urate levels became high because not enough water is going through his kidney. By drinking more water, more water goes through the kidney and this helps to dilute the urate. With age kidney function deteriorates; gout is often seen in the elderly because kidney function often deteriorates with age. Some medicines also have side effects of causing kidney malfunction. L.M. has high urate acid in his blood due to underexcretion of urate.

L.M. should be encouraged to drink more water and less alcohol. The physician should examine the medicines the L.M. is taking to make sure that he is not suffering kidney impairment.