10. Delivering oxygen

10.1 Oxygen is continually needed

We started the discussion of metabolism with this equation:

\[
\text{Food + O}_2 \quad \text{(from air)} \rightarrow \text{CO}_2 + \text{H}_2\text{O} + \text{energy}
\]

To obtain energy we need food and O\(_2\). So far, we have been talking what happens to food – C, H, O and N. The food part is explained through these basic concepts: foods are composed of fats, carbohydrates and protein, and the metabolism in each organ of the body depends upon its energy needs. But, as we study deeper, food metabolism becomes more complicated. Why is this? First of all, we eat so many things. Therefore, metabolism must be flexible. Second, we store fats, carbohydrates and proteins. Mechanisms are needed to both store fuel and retrieve it from storage when needed. Third, we do so many things. The mobilization of food from storage depends on activity, food intake and stress level and it depends upon the cooperation of all the organs of the body.

Unlike the metabolism of food, the other part of metabolism is easy. We use O\(_2\) – and nothing else – to convert the C’s and H’s in food to CO\(_2\) and H\(_2\)O. O\(_2\) is used in the mitochondria and it is essential for producing ATP. We do not store vast supplies of O\(_2\), so we need to breathe air containing O\(_2\) at all times.

The body uses interesting, intricate means to insure the delivery of O\(_2\) to all tissues. Two protein molecules, involved in O\(_2\) transport, are myoglobin and hemoglobin. Hemoglobin is in red blood cells (RBC’s) and it makes blood red. O\(_2\) binds to hemoglobin in the lungs and releases O\(_2\) in capillaries. When O\(_2\) is released in the capillary, O\(_2\) molecules diffuse across the capillary wall and across the cell membrane, and go through the cell to the mitochondria where they are used. Aerobic muscle cells contain myoglobin. Myoglobin binds O\(_2\) and gives a small extra amount of O\(_2\) reserve for the muscle cells. Myoglobin is also red, and it gives aerobic muscles a red or brownish color.

Special properties of myoglobin and hemoglobin ensure that O\(_2\) is delivered to tissue where it is needed. Myoglobin binds O\(_2\) in a simple manner: the more O\(_2\) around, the more O\(_2\) is bound to myoglobin until all myoglobin molecules have O\(_2\) bound to them. Hemoglobin, on the other hand, is more complicated. It binds O\(_2\) tighter in the lung where O\(_2\) is high, and less tightly in the tissue, where O\(_2\) is low. Both taking in O\(_2\) in the lung and release of O\(_2\) in the tissue is achieved by this means. Two pathways, the glycolytic pathway and the citric acid cycle, indirectly play a role in assisting the binding and release of O\(_2\) from hemoglobin.

10.2 First the big picture on how O\(_2\) is transported to tissue

Oxygen, O\(_2\), surrounds us in the atmosphere. Oxygen comprises 20% of the atmosphere. It is at the surface of every part of the body. We might think that we could use this oxygen – that we would not need to breathe. But, O\(_2\) is not very soluble in water and we are made up of mostly water. Only very little O\(_2\) diffuses through the skin. Lungs, heart, blood vessels and blood are all needed to deliver O\(_2\) to tissue.
Figure 10.1. Picture of capillary and two cells that do not contain myoglobin.

Red blood cells (RBC) are red, and contain hemoglobin. Blood plasma is indicated by yellow, and plasma contains glucose, amino acids, fatty acids, lipoproteins. O$_2$ is released from hemoglobin, and O$_2$ diffuses through the capillary wall into the cell, and into the mitochondria.

When GB is skateboarding or mountain climbing, GB.'s muscles need more ATP and to make ATP in the mitochondria O$_2$ is needed. There is a sensor for O$_2$ in the carotid artery. When O$_2$ in the blood gets low and CO$_2$ produced from metabolism gets high, a signal gets sent from chemical sensors in the carotid artery and aorta to the area of the brain that controls breathing rate. GB begins to breathe faster and the heart beats faster. More O$_2$ is delivered to the tissue as the blood circulates through the body faster. This is a short-term, immediate response to the acute need for O$_2$.

Long term response of the body also occurs when O$_2$ in the blood is low. Specialized cells in the kidney sense low O$_2$ and excrete the hormone erythropoietin. Erythropoietin stimulates the production of red blood cells (RBC’s) in the bone marrow. More RBC’s are made. After a person loses blood, blood RBC’s and hemoglobin will be restored by the stimulus of erythropoietin. When RBC’s are initially made they have a nucleus. RBC’s with a nucleus are called reticulocytes. Within a few days of circulating in the blood, they lose the nucleus. Since nuclei have DNA, which has the information for protein synthesis, mature RBC’s without a nucleus cannot make protein. As they get older, the cells suffer damage and finally after about 120 days the spleen removes old RBC’s. In normal blood, about 1 – 2 % of RBC’s are reticulocytes, the new RBC’s with a nucleus.

Under conditions of chronic, long-term O$_2$ deprivation, more capillaries form. This can happen when living for a long time at high altitudes and some people living at high altitude in the Andes have this condition. Formation of more capillaries may also occur in people who are suffering from a weakened heart. The complexion of these patients may appear red due to more capillaries in their tissue.

Breathing faster, increasing blood circulation and making more hemoglobin along with more RBC’s are some ways that O$_2$ delivery to tissue is regulated. But the molecules myoglobin and hemoglobin, both of which carry O$_2$, need to be examined to understand how O$_2$ is delivered.

10.3 Myoglobin in muscle cells
Myoglobin binds O\textsubscript{2} in red muscle, which are dependent upon mitochondria to give ATP. Myoglobin serves as a small store of O\textsubscript{2} in this tissue and gives red meat its color. Figure 2 shows a picture of the capillary, and a mitochondrial-rich red muscle cell. The inset is a picture of myoglobin.

**Figure 10.2.**

Picture of a capillary and muscle cell that contains myoglobin.

Red muscle cells contain myoglobin. The blow-up shows a picture of myoglobin. Green shows the part that is made up of amino acids. An iron atom resides within a heme group where the arrow is pointing. Oxygen binds to iron. The symbol for iron is Fe.

Iron (Fe) is in the center of myoglobin. O\textsubscript{2} binds to the iron atom. When O\textsubscript{2} concentration is high, more myoglobin will bind O\textsubscript{2}. For those of you who like equations\textsuperscript{1}, here is the equation that describes this:

\[
\frac{[\text{myoglobin with bound O}_2]}{[\text{Total myoglobin}]} = \frac{[O_2]}{K_m + [O_2]}
\]

This equation is explained as follows. First, everything inside brackets [ ] refers to concentration. So [O\textsubscript{2}] says how much O\textsubscript{2} there is in a given volume. (Chemists usually use the units of moles in a liter. But you can say pounds in a quart too). When there is no O\textsubscript{2}, then [O\textsubscript{2}] equals zero and there will be no O\textsubscript{2} bound to myoglobin. Therefore, the value of the left side of the equation is zero too. \(K_m\) is a constant that tells you the concentration when half of the myoglobin has O\textsubscript{2} bound to it. You can see that when [O\textsubscript{2}] equals \(K_m\), the value of the right hand side of the equation is 0.5. When O\textsubscript{2} levels are very high, then the left hand part of the equation is 1, telling you that all myoglobin molecules have O\textsubscript{2} bound to them.

Here is what the binding of O\textsubscript{2} to myoglobin looks like:

\textsuperscript{1} This equation is also for those of you who will study Biochemistry further. The same equation describes enzyme kinetics, i.e. how the speed of an enzyme-catalyzed reaction depends upon the substance being acted upon. If you continue in studying medicine, you will see this equation and binding curve many times! In pharmacology, this equation is called the “dose response curve.” It says that at low dosage, giving higher amounts of drug produces a response. The amount of drug for 50% response is the \(K_m\). At a high dosage giving more drug gets no more response.
Figure 10.3.

Binding curve to myoglobin.
Blue line represents myoglobin with a binding affinity of 5. At 5 \([O_2]\) (shown on the x-axis) 50% of myoglobin has \(O_2\) bound to it (shown on the y-axis). The red line shows what happens if oxygen binding to myoglobin is 6 times less strong. Now the concentration of \(O_2\) must be 30 in order to get 50% of the myoglobin to be binding \(O_2\).

The curve in Figure 3 shows that as \(O_2\) concentration increases, more and more \(O_2\) gets bound to myoglobin until all the myoglobin has \(O_2\) bound to it. Looking back at the equation when \(O_2\) goes very high, the right hand side of the equation comes close to 1, and then the left hand part of the equation is 1, i.e., 100% of myoglobin has \(O_2\) bound to it. The dotted line in the graph shows the point where 50% of the myoglobin has \(O_2\) bound to it. \(K_m\) is a constant that tells you the concentration of \(O_2\) when myoglobin has 50% of the molecules with \(O_2\) bound. When you look at the equation, you will see that when \(O_2\) equals \(K_m\) then the value of the left hand side is 0.5, meaning that 50% of myoglobin has \(O_2\) bound. When myoglobin does not bind very well, the \(K_m\) value will be higher — it takes more \(O_2\) to get 50% bound.

The equation describes a general binding curve. Let us consider the red muscle cells again. When \(O_2\) is high most of the myoglobin has bound \(O_2\). When muscle contracts \(O_2\) is consumed in the mitochondria to make ATP. Suddenly the \(O_2\) concentration is lower. Then some of the \(O_2\) from myoglobin is released, giving the cells an extra bit of \(O_2\). In this way, myoglobin acts as a small store of \(O_2\).

10.4 Oxygen binding to hemoglobin

RBC’s, containing many hemoglobin molecules, are cells that are circulating in blood. Hemoglobin molecules within the cells need to pick up \(O_2\) in the lungs and release it in the capillaries.

But, for this simple function, hemoglobin has very interesting properties that differ from myoglobin. Although, hemoglobin resembles myoglobin, hemoglobin is four times bigger and it has four protein peptide chains. Each peptide chain has an iron atom in it and each iron atom can bind one \(O_2\) molecule. The inset in Figure 10.4 shows what a hemoglobin molecule looks like.
Figure 10.4.

Hemoglobin has 4 protein or polypeptide chains, shown in different colors. There are two pairs of polypeptide chains; one is called alpha chain and the other is beta chain. Hemoglobin has 4 Fe (iron) atoms; each polypeptide has one Fe atom.

Each polypeptide chain in hemoglobin is similar to one myoglobin molecule. Myoglobin can bind one O\textsubscript{2} molecule. Hemoglobin can bind four O\textsubscript{2} molecules.

With little O\textsubscript{2} around, the protein does not bind O\textsubscript{2} with high affinity. The protein is called “T” for taut or tight. The polypeptide chain wraps tightly around the iron making it hard for O\textsubscript{2} to bind. Therefore, you need a high concentration of O\textsubscript{2} for binding. Conversely, bound O\textsubscript{2} does not stay bound to hemoglobin. What is bound to hemoglobin, gets released to the tissues. By this means, the tissues, which are low in O\textsubscript{2} gets O\textsubscript{2} delivered to them.

After one or two O\textsubscript{2} molecule is bound to one or two irons, the protein changes. The polypeptide chain now wraps around looser around the iron. It wraps in a “relaxed” manner, making it easier for O\textsubscript{2} to bind. The protein conformation is now called “R” for relaxed. The result of this change is that the initial binding of O\textsubscript{2} makes it easier for hemoglobin to bind more O\textsubscript{2}. This is what happens in the lung. The hemoglobin molecule “likes” to have when there are many O\textsubscript{2} molecules around. Therefore, in the lungs, it binds O\textsubscript{2}.

The diagram on Figure 5 shows how initial binding of O\textsubscript{2} to hemoglobin makes more O\textsubscript{2} bind with stronger affinity:

Figure 10.5

At low O\textsubscript{2} concentrations, hemoglobin binds O\textsubscript{2} with low affinity.

At high O\textsubscript{2} concentrations, hemoglobin binds O\textsubscript{2} tightly, high affinity.

The final result is that the binding of O\textsubscript{2} to hemoglobin is “cooperative”. Hemoglobin binds O\textsubscript{2} tightly at high concentrations. Hemoglobin switches between a protein that binds O\textsubscript{2} loosely into one that binds O\textsubscript{2} tightly.

Without hemoglobin’s ability to change its ability to bind O\textsubscript{2}, we would not survive. In the lungs where O\textsubscript{2} concentration is high, hemoglobin binds O\textsubscript{2} tightly. All or nearly all of the Fe
molecules have \( O_2 \) bound to them. In the tissue, \( O_2 \) levels are low because mitochondria are using \( O_2 \). Then hemoglobin no longer binds \( O_2 \) tightly. It then releases the \( O_2 \) to the tissue.

The binding of \( O_2 \) to hemoglobin is said to be cooperative. When first molecule of \( O_2 \) binds it "cooperates" with the next \( O_2 \) molecule making it easier for the next one to bind. The transition from low affinity to high affinity binding is smoother than shown in Figure 10.5. Figure 10.6 shows the way \( O_2 \) binding to hemoglobin actually occurs when \( O_2 \) concentration is changed.

![Figure 10.6](image)

This is what the cooperative binding of \( O_2 \) to hemoglobin looks like.

Hemoglobin binds \( O_2 \) tightly in the lungs where \([O_2]\) is high.

In the tissue, \([O_2]\) is low and hemoglobin releases \( O_2 \) that is bound.

Hemoglobin is a wonderful molecule. It is designed to pick up \( O_2 \) in the lungs where it binds \( O_2 \) tightly. Then it releases \( O_2 \) in the tissue, where \( O_2 \) concentration is low. This means that mitochondria in all of tissue in the body are supplied with \( O_2 \).

### 10.5 Metabolism affects \( O_2 \) release from hemoglobin

The interesting hemoglobin molecule has even more tricks. Metabolism has a direct effect on \( O_2 \) release. The goal is get as much \( O_2 \) from hemoglobin to the tissue as fast as possible.

The release of \( O_2 \) from hemoglobin occurs more readily at low pH. This statement causes several questions: What is pH? When and where is pH low in the blood? What produces the change in pH?

pH is a measure of \( H^+ \) ions. Water molecules, \( H_2O \), separate to a small amount into \( H^+ \) and \( OH^- \) ions. The amount of \( H^+ \) and \( OH^- \) is small compared with the molecules of water present. \( H_2O \) is 55 M.\(^2\) In neutral water, the concentration of \( H^+ \) is 0.0000001 M and \( OH^- \) is 0.0000001 M. The pH is 7 – indicating the number of zero’s after the decimal point. When \( H^+ \) is bigger than \( OH^- \), then a substance is considered acidic. For instance, the stomach fluid is acidic; its \( H^+ \) concentration is about 0.1 M after eating. This is equivalent to a pH of 1 – only one zero after the decimal point. Lemonade is also acidic. The pH of lemonade is about 4, indicating the \( H \) concentration is 0.0001 M.

\(^2\) M is a symbol standing for the number of molecules in one liter. M stands for 630,000,000,000,000,000,000,000,000 molecules. Instead of writing that big number all the time, the symbol M is used. The normal glucose level in blood is 0.005 M. So the number of molecules in a liter of blood is 0.005 times that big number. Pure water is 55 M in \( H_2O \). The number of water molecules in a liter of water is 55 times that big number.
For biological fluids, the number 7 is important to know. If the number gets lower, the fluid is acidic (more H than OH). If it is higher, it is basic (more OH than H). Normal pH of blood is about 7.3. When pH goes much lower than this (meaning that H⁺ goes high) coma results. The brain does not work properly.

What changes the pH of blood in normal conditions?

It turns out that CO₂ does. CO₂ in water forms an acid. This is what happens when CO₂ is in water:

\[ \text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{H}^+ + \text{HCO}_3^- \]

CO₂ dissolves in water and forms H⁺. This is how soda pop is made; CO₂ is put into water. The water becomes acidic and has a sharp -- and refreshing -- taste. Bubbles form as the CO₂ gradually goes out of the water.

We know where in the body CO₂ is formed. It is formed by the citric acid cycle and pyruvate dehydrogenase in mitochondria. When CO₂ is formed, it diffuses out of the cell into the capillaries. There it dissolves into the blood plasma and forms H⁺ and HCO₃⁻. Blood in the capillaries become more acidic. When hemoglobin is in an acidic environment, it binds O₂ less strongly. Therefore, the metabolite CO₂ aids in making hemoglobin release O₂ near the cells producing CO₂.

In the lungs CO₂ is exhaled. Then the reverse of the reaction occurs.

\[ \text{H}^+ + \text{HCO}_3^- \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{CO}_2 + \text{H}_2\text{O} \]

Now when the lungs exhale CO₂, the pH goes up. At higher pH, hemoglobin binds O₂ tighter, and therefore more O₂ gets bound to hemoglobin in the lung.

There is another means to aid the release of O₂. As we stated, hemoglobin is in RBC’s. The glycolysis pathway of RBC’s produces ATP to maintain salt gradients. Glycolysis of RBC’s has another function. One of the intermediates of glycolysis gets converted into a chemical called 2,3 BPG (bis-phosphoglycerate). This substance binds to hemoglobin and acts to make it more likely to release O₂ in the tissue.

Figure 10.7 shows the net result of these metabolic effects on hemoglobin binding.
Figure 10.7

Binding curve for hemoglobin in the lungs and in the tissue.

Lowing pH (more H\(^+\) ions) and the presence of 2,3 BPG makes it easier for hemoglobin to release O\(_2\) in the tissues.

In the lungs, the high pH means hemoglobin binds O\(_2\) tightly, with high affinity. In the tissue, the presence of 2,3 BPG and low pH means that O\(_2\) binds to hemoglobin less tightly, and O\(_2\) is released from hemoglobin.

So, the release of O\(_2\) is influenced by metabolism of glucose in glycolysis, which makes 2,3 BPG. It is also influenced by the citric acid cycle in the mitochondria, which makes CO\(_2\).

### 10.6 Cases involving anemia

Anemia is the word that describes the condition when RBC’s and hemoglobin are low in the blood. When hemoglobin is low, O\(_2\) delivery to tissues will be less. When a patient has low hemoglobin, the question is why. Whenever something is low, there are two possibilities: Not enough is being made, or it is being removed too fast.

**Case 1. Anemia in an adult woman**

ST is a 30 year old woman. In the past three years she has had three children. A son was born 3 years ago, and 6 months ago she delivered twins. The pregnancies and delivery were normal. She complains of fatigue.

**Signs**

<table>
<thead>
<tr>
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<th>Patient</th>
<th>Normal</th>
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</thead>
<tbody>
<tr>
<td>Blood hemoglobin</td>
<td>9.1 g/dl</td>
<td>12 to 14 g/dl</td>
</tr>
<tr>
<td>reticulocytes</td>
<td>1.5%</td>
<td>1 to 2</td>
</tr>
<tr>
<td>bilirubin</td>
<td>low</td>
<td>low</td>
</tr>
</tbody>
</table>

**Discussion and treatment.** The patient has low blood hemoglobin is severely anemic. Hemoglobin contains iron. When diet is insufficient in iron, the intestine does not absorb enough iron from food. If the patient loses iron by blood loss, the patient becomes iron deficient. Without iron, the body is no longer able to make enough hemoglobin. When hemoglobin levels go to 8 g/dl or below, the physician usually recommends a blood transfusion.

Iron deficiency is a common form of anemia, especially among women of child-bearing age. Blood loss occurs during menstruation and through pregnancies. Iron deficiency is an example of the case when not enough is being made.
Iron supplements are recommended, and the patient is counseled to eat iron rich foods. In iron deficiency hemoglobin is low because not enough is made, because iron is needed for the synthesis of hemoglobin.

**Case 2: Anemia in a child.**

Symptoms: Patient, A.B., is 8 year old boy was found to be tired and unable to keep up in playing with other children. The whites of his eyes are yellow. (Yellowing is called icterus. Another name for this is jaundice).

**Signs:**

<table>
<thead>
<tr>
<th></th>
<th>Patient</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood hemoglobin</td>
<td>10.1 g/dl</td>
<td>13 to 16 g/dl</td>
</tr>
<tr>
<td>reticulocytes</td>
<td>7 %</td>
<td>1 to 2</td>
</tr>
<tr>
<td>bilirubin</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>

**Diagnosis and treatment:** This patient is suffering from hemolytic anemia. The word “lytic” means to break, and hemolytic anemia means that the RBC’s are breaking down. A clue for hemolytic anemia is the high level of reticulocytes. Reticulocytes are being formed, but the mature RBC’s are not lasting as long as is normal. Consequently, the percentage of reticulocytes in the blood is high. The other clue for this is elevated bilirubin. Bilirubin is a break-down product of hemoglobin and it is metabolized by the liver and then excreted. Bilirubin gives a yellow color to the whites of eyes and a yellow tinge to the skin, and the patient is said to have jaundice. For the patient here, the reason for bilirubin is “overproduction.” Too much is being produced. The clue for this is the high reticulocytes which are being made in response to the break-down of RBC’s.

With further enzyme tests, the physicians could determine that his patient has a defective pyruvate kinase, an enzyme of glycolysis. Pyruvate kinase is the last enzyme of glycolysis; it takes the phosphate on phosphoenolpyruvate, a 3 C intermediate of glycolysis to form ATP and pyruvate. Without enough ATP, the salt levels in the RBC’s cannot be maintained, and the RBC’s swell and are taken from circulation by the spleen. This is a genetic disease; it is a recessive disease, and so he inherited it from both his parents. There is a mutation in the portion of his DNA that makes pyruvate kinase.

A permanent cure for this patient would be gene therapy, whereby his DNA would be altered. However, although there is much work in this area, right now it is not possible to do this. The simple treatment is to give a blood transfusion when the hemoglobin becomes dangerously low. The disease is usually most noticeable in growing children during a growth spurt.

### 10.7 Anemia due to hemoglobin variants and relationship to malaria

Hemoglobin shows many variants, this is to say that people coming from different parts of the world often show slightly different kinds of hemoglobin. Many of these variants occur in malaria-infected areas. Mosquitoes transmit the organism of Plasmodium to humans where it infects red blood cells as part of its life-cycle. During history most tropical and temperate parts of the world had malaria, and at present, 225 million people contract malaria in a year, as estimated by the World Health Organization.

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3 Jaundice, due to high bilirubin, is sometimes seen in premature babies. The reason that these babies have high bilirubin is that their livers are not developed enough to remove the bilirubin.
Peoples living in malarial areas (now wet areas of the tropics and subtropics) have developed some resistance to malaria. In the past chapter, we mentioned a variant in the enzyme glucose-6-phosphate dehydrogenase. This variant enzyme is found in populations living near the Mediterranean, and it is thought to help in by making red blood cells fragile. When RBC’s are infected with the parasite, a strain is put on the RBC’s. Fragile RBC’s lyse, i.e. break open, and the parasite is destroyed. Therefore, fragility in RBC’s gives an advantage in resistance to malaria.

Variants of hemoglobin also give resistance to malaria. Hemoglobin molecules are very densely packed in the red blood cell – so dense that the hemoglobin molecules are nearly touching. One variant of hemoglobin is called sickle cell hemoglobin. In this disease, one amino acid on one chain of the hemoglobin is altered. This makes the hemoglobin molecule “sticky” and it binds to another hemoglobin molecule and so on, finally making a big fiber of hemoglobin molecules. This fiber distorts the RBC’s. It is not so easy for distorted RBC’s to go through capillaries. The RBC’s tend to lyse and the life cycle of the parasite is interrupted. The sickle cell trait is common in sub-Saharan Africa.

Another variant of hemoglobin occurs when the chains of hemoglobin are not in the usual ratio. In most people hemoglobin is composed of two alpha chains and two beta chains. When more alpha chains are made than beta chains – or vice versa – a condition called thalessemia results. Hemoglobin with an unusual ratio of alpha to beta chains is less stable than hemoglobin with the usual 1:1 ratio. One type of thalessemia is found in people with origins in Southeast Asia and another type is found in people from the Mediterranean region.

Glucose-6 phosphate dehydrogenase, sickle cell hemoglobin and thalessemia diseases are inherited. A gene is inherited from both the father and mother. When a person is heterozygous, meaning that only one gene for the particular condition is present, the anemia is mild or even not noticeable. When the person is homozygous, meaning that the gene has been inherited from both father and mother, the anemia’s are more pronounced.
11. Engine trouble: Diabetes and the homeostasis of glucose

11.1 Diabetes

One theme of this book on energy production has been the requirement of the brain to be supplied with glucose. The level of glucose in blood plasma is under tight homeostasis. The word homeostasis means that the level of glucose is regulated so that its level is approximately constant. When glucose gets high, the hormone insulin stimulates the pathways that remove glucose from the blood and converts glucose to storage forms of energy, namely glycogen and fat. When glucose is low, the hormones glucagon, epinephrine and cortisol stimulate the production of glucose so that the glucose blood level is stable. The production of keto-acids is stimulated during long-term starvation.

Diabetes is a disease where the regulation of sugar level in the blood is impaired. The manifestations of diabetes involve all the metabolic pathways. The National Institutes of Health estimates that diabetes affects 25.8 million people in the U.S. population. Nearly everyone in the U.S. either has the disease or has a friend or relative with the disease. Diabetes is a disease affecting the whole world. Research published in The Lancet estimated that 350 million people worldwide have diabetes, and that global diabetes rates doubled from 1980 to 2008.

Diabetes has various classifications. In Type I, or juvenile diabetes, pancreatic beta cells are destroyed, most likely by an infection or by an autoimmune response. They can no longer secrete enough insulin. In Type II diabetes the cells that have receptors to insulin become less sensitive to insulin. The beta cells respond by secreting more insulin, but ultimately they are overwhelmed.

By considering what happens when insulin is not present, we can review what we learned about metabolism.

11.2 Bringing glucose levels down: GB after feasting

We are going back to our patient, GB. Again GB eats a big piece of cake, and this time GB eats ice cream too. The sugar in his blood goes up. In response to high glucose levels, the pancreas secretes insulin. The ice cream supplies GB with protein too. High amino acids in the blood obtained from the protein meal also stimulate the release of insulin.
Figure 11.1

The pancreas secretes insulin when sugar in the blood rises. Insulin stimulates the transport of glucose into the muscle and liver. It also stimulates the making of protein and glycogen in both tissues. In liver, insulin stimulates the making of fatty acid.

Insulin stimulates all the pathways which remove glucose from the blood and which stores the C’s supplied by carbohydrates and proteins. The general picture of insulin response in Figure 2 indicates that glycogen synthesis is enhanced, proteins are made in the muscles and other cells, fat is made in the liver, and fat is transported to the other tissues, especially to the adipose tissue.

Figure 11.2

Liver and adipose after high sugar and high protein meal

11.3 Blood glucose levels of GB when fasting

Now we look at what happens when GB is not eating. Because the fuel comes from different sources and the source of fuel depends upon length of fasting and the energy requirements, a single hormone is not sufficient to release stored food. Three hormones are important during this nutritional period: glucagon, cortisol and adrenaline. Figure 3 shows the location where the three hormones are made. The three hormones stimulate the release of energy stores. Fuel comes from stored glycogen and fat and from protein.
Three hormones, glucagon, adrenalin and cortisone control the release of energy stores.

Figure 4 shows the pathways that are stimulated by adrenalin, glucagon and cortisol.

Figure 11.4. Mobilizing fuel during starvation conditions
The liver cell is shown in blue; blood plasma is yellow.
1. Receptors on the liver membrane bind adrenaline and glucagon. These receptors induce
an enzyme called protein phosphorylase. This enzyme puts a phosphate on key enzymes that serve to mobilize fuel stores.

2. Glucagon stimulates enzymes that phosphorylate the enzymes that break down glycogen to form glucose-6-phosphate. This hormone plays a role in maintaining glucose levels during an overnight fast. The last step is breaking glucose-6-phosphate to glucose by the enzyme glucose-6-phosphase. This enzyme is only found in the liver.

3. Protein from muscle is broken down, in stimulation from cortisol. The major amino acid produced is alanine. Alanine gets converted into pyruvate in the liver; pyruvate is converted to glucose-6-phosphate by gluconeogenesis. The last step is breaking glucose-6-phosphate to glucose by the enzyme glucose-6-phosphase.

4. Low insulin stimulates the lipase in fat cells. The lipase transforms triglyceride to free fatty acids. The free fatty acid gets transformed into acetyl CoA. The synthesis of enzyme HMGCoA synthetase is induced by cortisol. HMGCoA synthetase catalyzes the synthesis of acetoacetate, a ketoacid. This enzyme is found in the liver.

GB does not eat for a long time, say, several days. Yet GB is healthy and alert. Under these conditions fatty acids are being used to make ketoacids. The transporters in the brain are altered and the brain uses ketoacids for fuel. Muscle also can use ketoacids for fuel. Muscles are broken down less rapidly than during beginning starvation; since ketoacids are used instead of glucose, there is less need for alanine to make glucose.

Figure 11.5.
During long-term starvation, ketoacids, made from fat in the liver, are used by the brain for fuel.

11.4 Case: what happens when a patient does not have insulin

Case: Coma in a student. A 20 year-old college student, XY, is admitted into the emergency room at 2:00 AM in a coma. He attended a football game in the evening, and then he went to a disco with a group of friends. His arm bracelet indicates that he has diabetes. His breath has a fruity odor. His skin is shriveled and dry. It does not “bounce” back when pinched into a fold.

Here are the lab tests of XY’s blood:

<table>
<thead>
<tr>
<th></th>
<th>patient</th>
<th>normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood glucose</td>
<td>66 mM</td>
<td>4.5 -5.0 mM</td>
</tr>
</tbody>
</table>
11.5 Questions regarding diagnosis and treatment of patient XY

What two hormonal sets could cause a coma?  When a known diabetic patient is in coma, there must be a differential diagnosis as to the cause of coma. Too much insulin can reduce blood sugar to levels where the brain can no longer function. Too little or no insulin can raise the blood sugar levels to very high levels, stimulate keto-acid production, and result in death. In the case of patient XY, the level of insulin was so low that it could not be detected.

Is the patient in a coma because his brain is not getting enough glucose?  No. Glucose transport into the brain does not require insulin. The patient has very high levels of glucose in the blood and in brain.

Is the patient in a coma because the blood pH is low?  Low pH will cause coma. Low pH means that the blood has more H⁺ ions, i.e. the blood becomes acidic. pH is defined as the negative of the log of H⁺ concentration. This means that pH 6 has 10 times higher H⁺ concentration than pH 7, and pH 5 has 10 times higher than pH 6 and 100 times higher than pH 7.

The answer to this question is yes. The pH of the patient’s blood is dangerously low.

What metabolites cause the low pH?  Acetoacetate and β-OH-butyrate originate from carboxy acids. Here is what happens to acetoacetic acid in water:

Acetocetic acid loses H⁺ and becomes acetoacetate. The same happens with β-OH-butyrate. Both contribute to the increase in the H⁺ concentration in the blood and the lower pH.

What pathway or pathways produce bicarbonate (HCO₃⁻)?  Pyruvate dehydrogenase and the reactions of the citric acid cycle both produce CO₂. In water CO₂ becomes bicarbonate. The reaction is:

\[
\text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+
\]

Why is bicarbonate (HCO₃⁻) concentration low in the blood of patient XY?  When something is low, we always think: “Is it being produced at a lower amount, or is it taken away faster?”  In the case of patient XY, CO₂ is being taken away.
faster than for the control. High H\(^+\) ions force the reaction to go to the left. More CO\(_2\) is lost in the lungs.

**Why are fatty acids high?** Low insulin stimulates the release of fatty acids from the adipose tissue. The fatty acids are transported in the blood to the liver bound to albumin.

**What accounts for the fruity breath of the patient?** Ketoacids smell fruity. (Ketoacids are chemically similar to the compounds found in finger nail polish remover, which is how they smell to me). They are being made from fatty acids in liver.

**What pathways lead to high ketoacids?** First, low insulin and high glucagon causes a breakdown in fat in the adipose tissue. The fat gets broken down to fatty acids and glycerol. Fatty acids go into the liver and they get broken to acetyl CoA by \(\beta\)-oxidation. Acetyl CoA gets transformed into ketoacids by ketoacid synthesis pathway.

**How do the levels of ketoacids in the diabetic patient compare with the level of ketoacids in GB during long-term fasting (Chapter 7)?** The levels of ketoacids in blood during long-term fasting is about 7 to 8 mM – much lower than in our patient, XY. During fasting, there is still a low level of insulin. The insulin prevents the ketoacids to go to higher levels. The pH of the blood does not drop during long-term fasting.

**What does the skin condition tell you about the patient?** The patient is dehydrated. Kidney removes some of the glucose from the blood, and the patient's urine will test positive for glucose. In the transport of glucose to the urine, water is also transferred. A patient who has high glucose experiences thirst, but still gets dehydrated because he has frequent urination.

**What do you do for treatment?** The primary problem is that XY does not have insulin. Insulin is absolutely required for human metabolism. The patient needs to be given insulin. For immediate treatment, the patient's blood has a low pH. Intravenous (IV) infusion of bicarbonate (HCO\(_3\)^-) would raise the pH. The patient is also severely dehydrated, and needs fluid in general. As a result of dehydration, the patient's electrolytes (Na, K) in the blood are disturbed. He would have lost Na (sodium) and K (potassium), and if just water were given by IV, the Na and K in his blood plasma would be too low. The physician is especially concerned about the loss of K, since low K can cause heart beating to become irregular.

Now we think about the long-term treatment of the patient

**XY carries a syringe of glucagon. He is advised to use it if he ever over-doses with insulin, and his blood glucose drops. Why would a large does of glucagon raise XY’s blood sugar?** High insulin is a stimulus to store glycogen. Glucagon is the stimulus to break down glycogen to glucose. When the patient is given a pharmacological dose (meaning a dose that is much higher than normally found), then glucagon stimulates the breakdown of glycogen in the
liver to form glucose. This glucose goes into the blood stream and raises the blood glucose.

**Does muscle glycogen contribute to blood glucose after giving a large does of glucagon?** No, for two reasons. Muscle does not have glucose phosphatase, so it can never produce glucose from glucose-6-phosphate. Also, muscle does not have glucagon receptors.

**Diabetic patients are advised to keep weight within normal levels. Why would eating excess carbohydrate lead to an increase in cholesterol?** Excess carbohydrate is made into fat by the liver. Fat molecules are packaged into a lipoprotein particle, called LDL (low density lipoprotein) that goes into the blood and transports fat to the adipose tissue. This particle requires cholesterol to be intact. The liver makes cholesterol in order to make the LDL particle. Therefore, eating excess carbohydrate leads to increased cholesterol in the blood. Some physicians recommend the use of statins to reduce cholesterol levels in diabetic patients.

12. GB’s engine

**12.1 Recap**

We go back to our patient and, by now, our dear friend, GB. During metabolism, his body converts carbohydrates, fat and proteins to CO$_2$ and H$_2$O, coinciding with making ATP from ADP. At all times, ATP provides energy for most everything that occurs in cells.

After GB eats birthday cake, the cake’s sugar is transferred from the gastro-intestinal tract to GB’s blood. Blood glucose level rises, and the hormone insulin levels rise. Ingested glucose supplies fuel for the brain and other tissues during this phase of eating. Insulin stimulates the removal of glucose from blood, resulting in the conversion of glucose 3 C compounds, pyruvate and lactate, in the cytoplasm by the glycolysis pathway. More ATP is produced when the 3 C compound is converted to a 2 C compound and then to CO$_2$ and H$_2$O in the mitochondria (the pathways are pyruvate dehydrogenase, citric acid cycle and oxidative phosphorylation). Insulin also stimulates the storage of glucose as glycogen in muscle and liver. Excess glucose is transformed by the liver to make fat, and fat is stored in the adipose tissue. This removal of glucose from blood allows the blood glucose levels to return to normal levels.

In our story of GB, we noticed that after eating cake, he did not eat for quite a time. Initially, glucose is released to blood from liver glycogen under the influence of the hormone glucagon, and the brain uses this blood glucose for fuel. Muscle also has glycogen, but this glycogen is used for fuel by muscle. Muscle and liver glycogen release from storage are stimulated by the hormone epinephrine. During skateboarding muscle glycogen was broken in the cytoplasm to form lactate and ATP. As GB slowly walked home, lactate in his blood was converted to 2C compound, acetate (in the form of acetyl CoA). Acetyl CoA is converted to CO$_2$ and H$_2$O in the muscle mitochondria, concomitant with the formation of ATP.
GB continued not to eat, and he went to sleep without eating. During this time blood glucose is made from amino acids. To make glucose from amino acids requires ATP, and the energy for making ATP comes from metabolizing fat to CO$_2$ and H$_2$O in the liver. Indeed, most tissues, except for brain and red blood cells, use fat to make ATP. The heart muscle uses fat at all times. To use fat as a fuel, and to completely oxidize glucose and amino acids to CO$_2$ and H$_2$O, O$_2$ from the atmosphere must be supplied. Within a few minutes of not breathing ATP levels in cells are depleted, and death occurs.

In very long term fasting, fat is made into ketoacids by liver. Most tissues use ketoacids for fuel, however, the liver, which makes ketoacids, does not. Ketoacids are especially important fuel for the brain during starvation. When the brain uses ketoacids it uses less glucose. Since during starvation, glucose is made from the amino acids of proteins, the use of ketoacids spares the breakdown of protein. Since proteins all have functions, the use of less glucose ensures that GB can survive longer. But during starvation some protein continuously breaks down. Eventually, enough protein is lost so muscles can no longer function. With loss of muscle breathing ceases, and with the loss of heart muscle, the heart can no longer pump blood.

Food that GB has eaten, allows him to think great thoughts and do amazing athletic feats. Seamlessly, fuel is used from the diet or from storage, with an intricate cooperation of the organs of his body, working together to utilize food and maintain life.
13. Questions for discussion

13.1 The future?

On every page of this book, there are intriguing unanswered questions that are worthy of further research. Even if you do not become a scientist, it is fun to choose an unanswered question for a “hobby” and then to follow it in the literature over the years. It is surprising to learn the twists and turns that will come out.

Here are some possible areas to follow.

1. **How does well-being affect metabolism and health?** Neurons undoubtedly interact with metabolic pathways. In case of muscle contraction, much is known. A nerve impulse triggers Ca++ release from the endoplasmic reticulum. This causes myosin and actin to interact, and ATP to be hydrolyzed to ADP during the muscle contraction. For other pathways, connections between “mind-body” are less well understood. A wise friend told me that development in this important area is hindered because people who know neuro-anatomy do not know metabolism and vice versa.

2. **What is the relationship between consciousness and metabolism?** We, and not engines, are conscious. How does memory work? It is known that proteins are synthesized when long-term memories are being stored in the brain. How do we retrieve memories? How do we make conclusions from our memories? The study of brain metabolism is an active field. Brain uses amino acids to make neurotransmitters. The brain is made of a variety of cells, and these cells interact. It appears that astrocytes use glucose to make lactate by glycolysis, and this lactate can be used by neurons.

3. **How is temperature regulated in the body?** Body temperature is very finely regulated, and if the temperature changes by a small amount, the person is sick. How is temperature regulated? What molecules sense temperature in the skin? What sensor in the brain is the temperature regulated?

Some things are known about temperature regulation. There is a special organ that serves to generate fat called brown fat. Brown fat is a tissue that is rich in mitochondria and in fat and this organ is innervated. Babies have a lot of brown fat, and as we age we have less. Brown fat can be seen under the skin of salmon, and the next time you eat a salmon steak you can look for it. (However, please do not gross out your dinner partner by dissecting the fish in the five-star restaurant where you are dining).

If indeed brown fat serves to generate heat, how is temperature sensed? We know how visible light is sensed. A protein molecule, called rhodopsin located in membranes in the retina of the eye, is the light sensor. This molecule contains retinal as a cofactor. Retinal is derived from b-carotene, known as vitamin A, that makes carrots yellow. (Vitamin A can also be found in animal products, such as milk, where the animal has eaten plans containing β-carotene). Retinal has double bonds, and in response to light one of the bonds undergoes a cis to trans conversion (Double bonds and cis/trans configurations of fatty acids were described in Chapter 2). The cis to trans conversion causes a change in the structure of the rhodopsin molecule and allows current to go across the membrane. This is the electrical stimulation for the brain to perceive light.
Is something like that happening in heat sensing? Shrimp that live around hot water vents deep in the ocean have a modified rhodopsin molecule in their backs. This molecule absorbs infrared light, i.e. heat, and presumably signals the shrimp when things are getting too hot. Do we have a modified rhodopsin molecule in our skin that allows us to sense heat, i.e. infrared light?

There is a very rare condition when a baby is born who cannot sense heat or pain. This baby does not cry in adverse conditions – not warning the parents when the baby needs help. Consequently, babies born with this condition often have a short life span.

4. What is relationship between genetics and metabolism?

This question is another big one. The sequence of the human genome is largely completed. But at this time, this knowledge does not seem to have produced many practical applications. We know that there are many variants to the proteins in humans. We gave some examples in Chapter 8 in talking about cholesterol, in Chapter 9 in talking about repair of free radicals, and Chapter 10, when talking about hemoglobin. Variants occur in every enzyme in the body, and so every one of us is unique. Will knowledge of a person’s unique proteins enable one to tailor diet and medicine for optimal health for the individual?

5. What is the long-term effect of diet and exercise?

DNA in chromosomes determines the kinds of proteins that our bodies make and proteins regulate all reactions in the body. We inherit DNA from our parents. It was once thought that our DNA from our parents is immutable – what we inherit is what we have. However is now recognized that DNA gets changed during our lifetime. One way it gets changed is by putting a methyl group on it. The study of changes in DNA is a developing “hot” area of research called “epigenetics”. These changes are inheritable to the offspring. What causes changes in DNA, how do these changes affect our health, and even the health of our children?
13.2 Questions for review

1. Why do trainers recommend a cool-down period after strenuous exercise? What happens to lactic acid that is in the muscle after strenuous exercise?

During strenuous exercise, not enough \( O_2 \) is delivered to the mitochondria to maintain ATP levels through the citric acid cycle and oxidative phosphorylation (Chapter 4). The muscle cells then rely on glycolysis, which does not use \( O_2 \). The end product of glycolysis is lactate, an acid. If the athlete uses the same muscles by repeating the same motion, but at a slow rate during a cool-down period after strenuous exercise, enough \( O_2 \) is delivered to the muscle’s mitochondria to make ATP. Then the muscle converts the lactate back to pyruvate, and pyruvate is removed in the mitochondria (pyruvate dehydrogenase and citric acid cycle in Chapter 4). By this means lactate is removed from muscle. If the athlete suddenly stops vigorous exercise, the lactate gradually leaks from the muscle to blood, but the muscles may feel a bit sore in the meantime. Lactate is taken from blood by liver. Liver can use it to make glucose, or liver can converted lactate to \( CO_2 \) and \( H_2O \) in the citric acid cycle and oxidative phosphorylation.

2. Why does the brain always need fuel? What fuel does the brain need at most times?

The brain needs fuel constantly to maintain the levels of ions in its cells (\( K^+ \) inside and \( Na^+ \) outside).

The brain uses glucose as fuel most of the time. The brain uses ketoacids during long-term starvation. (Under some conditions the brain uses amino acids. We did not discuss this).

3. What happens to glucose in the brain?

Glucose gets converted to pyruvate and lactate by glycolysis and then gets converted by the brain to \( H_2O \) and \( CO_2 \) in the mitochondria using pyruvate dehydrogenase, the citric acid cycle and oxidative phosphorylation.

4. Where does glucose for the brain come from after eating and during short term fast?

The brain uses glucose that is in the blood plasma for fuel. Carbohydrates from eating enter the blood stream from the gastrointestinal tract immediately after eating. After this source is depleted, the liver releases glucose into the blood from its store of glycogen.

5. Where is glucose for the brain obtained during an intermediate term fast? What organ makes glucose under these conditions? Where do the C’s for glucose synthesis come from?

Liver makes glucose, using amino acids that mostly come from muscle proteins. The liver releases glucose to blood, and the brain uses this glucose for fuel. To make glucose from amino acids requires ATP. ATP is generated by the conversion of fatty acids to \( CO_2 \).
6. During extended fast, what fuel does the brain use?

The brain uses ketoacids in addition to some glucose. The liver makes ketoacids from fat. All tissues except liver and RBC’s use ketoacids for fuel. Only the liver makes ketoacids from fat.

7. Many vitamins are cofactors for enzymes. What are cofactors?

Cofactors are molecules that participate in a enzymatic reaction. They remain within the cell and cycle from one form to another. NAD/NADH, flavin, and ATP/ADP are examples of cofactors. Our bodies make adenosine part of ATP and ADP, so no vitamin is needed. Parts of NAD and flavin are not made in our bodies. We need this from our diet. These molecules are defined as vitamins.

8. Enzymes in what pathways require vitamin B₃ i.e., nicotinic acid? Do you need it every day or every few days? Or can you go for a long time without it?

Nicotinic acid is used to make NADH, NAD, NADP and NADPH. Pathways that break down glucose (glycolysis, pyruvate dehydrogenase and make glucose (gluconeogenesis) require these cofactors.

Nicotinic acid is not stored for a long time in the body. Excess nicotinic acid is lost in the urine. So ideally you should have this vitamin everyday or every few days.

9. Where is the vitamin flavin used in the body? Why do you need it every day or every few days?

Flavin is used in oxidative phosphorylation and the citric acid cycle. It is also used in reactions that detoxify substances. We did not cover these reactions.

Flavin is not stored in the body. It is lost in the urine. We should have this vitamin every day.

10. Where is vitamin B₁₂ used? What vitamin is required along with vitamin B₁₂? What groups of people should have supplements of vitamin B₁₂? Can you go for a long time without it?

Vitamin B₁₂ is used in the metabolism of some amino acids. It is needed to make lecithin, a major component of membranes. Another vitamin, folic acid, is required along with vitamin B₁₂ for 1 C metabolism.

Folic acid is obtained from leafy vegetables. Vitamin B₁₂ is obtained from meat and animal products. The animals themselves do not make vitamin B₁₂ but obtain it from microorganisms. Vitamin B₁₂ is stored in the body, and so a deficiency can take time to develop.

Several groups of people are in danger of developing vitamin B₁₂ deficiency. Strict vegetarians, who eschew all animal products, make up one group. People who have stomach or intestinal surgery are another, since both organs are needed for vitamin B₁₂ absorption. Finally, the elderly may lose the ability of vitamin B₁₂, and they may become deficient. Since dementia occurs in vitamin B₁₂ deficiency, the type of dementia may be misdiagnosed as arising from another age-related dementia.
11. **What is “beer belly?” Why does it occur?**

Triglyceride, i.e. fat, is stored in specialized tissue called adipose. But fat can accumulate in many cells. When fat accumulates in liver, the liver can become very large, and people call this a “beer belly.” A person with a beer belly will sometimes have very thin chest, arms and legs, as most of the body fat has been deposited in the liver.

The interesting question is why does the fat accumulate in the liver. When insulin is low, and glucose is high, triglyceride in the adipose is hydrolyzed to produce fatty acids, which are transported to the liver. If the liver cannot use the fatty acids, then they are reesterified (fatty acids combine with glycerol) to form triglyceride.

12. **What disease occurs when insulin is lacking?**

Diabetes is a disease that is characterized by high blood sugar. In type I diabetes, the pancreatic beta cells no longer secrete insulin. This causes a raise in blood sugar. In type II diabetes, cells lose their receptors for insulin. Sugar levels rise because insulin is not effective.

13. **Which pathways are influenced by insulin?**

The pathways that remove glucose from blood, and convert glucose into storage forms are all stimulated by insulin. Insulin affects many processes in the body. Insulin stimulates the transport of glucose into cells, the conversion of glucose to glycogen, the conversion of glucose to lactate and pyruvate in glycolysis, the conversion of acetyl CoA to fatty acids and the storage of fat in adipose tissue.

14. **Does muscle use fat during anaerobic exercise?**

The oxidation of fatty acid to CO$_2$ and H$_2$O requires O$_2$. If O$_2$ is depleted in muscle, then glycolysis, using glucose obtained from muscle glycogen, is the source of ATP. Glycolysis does not require O$_2$. So anaerobic exercise does not directly use fat. However, to restore glycogen after exercise is over, ATP is required. This ATP usually comes from the oxidation of fat. Also, eating carbohydrates after exercise will restore glycogen. These carbohydrates will not be used to make fat, so indirectly, fat stores will be reduced by anaerobic exercise.

15. **What is trans-fat? Why might trans-fat be dangerous?** An unsaturated fatty acid has one or more bonds in which C bonds doubly to another C. Here is an unsaturated fatty acid:

![Unsaturated Fatty Acid](image)

The position of the two H's bound to the two C's is important. When the H's are on the same side they are said to be in the cis position. When they are on the opposite sides they are called in the trans position. Here is a trans fatty acid:

![Trans Fatty Acid](image)

Most fats in nature are on the cis position.
Fat that enters the body goes into chylomicrons and the chylomicrons circulate throughout the body. The thought is that some of trans fatty acids can be incorporated into membranes. Since, they are not normally found in membranes, some scientists think that they will alter the characteristics of various cell membranes.

16. **What is the definition of “organic” in chemistry?**

Organic refers to compounds containing carbon. This is one of many words in the English language that have different meanings in different contexts! Fat, carbohydrate and proteins are all considered organic compounds because they all contain C.

17. **What is a cation? How do you pronounce “cation?”** A molecule has an equal number of protons (positively charged groups) and electrons (negatively charged particles) and it is not charged. An ion is charged; it has either gained or lost an electron. A cation has lost an electron, and then the positive charges are greater than the negative charges. An example is salt, NaCl. NaCl has no charge. But in solution, the Na part has one fewer electron and the Cl has one more electron, and the Na is positively charged; it is a cation. The chloride part has an extra charge and it is negative, an anion.

In chemistry, syllables are strung together without changing the accent. So the root word is ion, pronounced “i on” or “eye on”. The addition of cat indicates that the ion is positively charged. Therefore, it is pronounced “cat’ eye on” not “ca-tion”. Anion is pronounced “an’ eye on”. Not really necessary to know the pronunciation, except that you appear more knowledgeable when you use the right pronunciation!

18. **What is GM food? Is it dangerous to eat genetically modified (GM) food?** Adding a gene to its DNA alters a food-producing plant. Therefore, the plant makes a protein that the original plant did not. This protein ideally aids in resistance to disease, drought, freezing or another property that would increase the food production or taste of the food. Since proteins are digested to amino acids in the G.I. tract, this additional protein found in the food is unlikely to be harmful to eat. Whether GM foods might be harmful to the environment is another issue.

19. **This statement comes from the web: eating denatured protein is dangerous. Is this statement correct?** Proteins get broken down to amino acids in the intestine. Denatured proteins will no longer function as enzymes. Consider the green bean. A freshly picked green bean contains mitochondria, the glycolytic pathway enzymes and most of the enzymes that we discussed. It also has enzymes that make chlorophyll and allow for photosynthesis. These enzymes can be isolated, and they can carry out the same reactions in the test tube that they do in the cells of the green bean. When the bean is cooked, the proteins change their shapes, and they are no longer active as enzymes. Once, they are cooked, they stay denatured. Cooked bean tastes different from a raw bean. Another common example of protein denaturation occurs with cooking an egg. Cooking denatures its protein, and once the protein is denatured, it does not become un-cooked.

Cooking, putting the protein in acetic acid (making pickles) or lemon juice (ceviche or pickled herring) are ways to denature proteins of our food. These help preserve food, destroy organisms living in the food, make the food easier to digest and taste better. We
humans have been eating denatured food since our ancestors discovered the use of fire. The statement that denatured protein is dangerous is not true.

20. **Another claim from the web:** that certain vitamin pills will aid in weight loss. **Our question is:** will vitamins produce weight loss? Weight gain occurs when you take in more food than what is converted to CO$_2$ and H$_2$O. Many vitamins serve as cofactors for the enzymes used to metabolize food. Table 2, below, indicates some of these vitamins and reactions in which they are used. In Chapter 4, we indicated that riboflavin and niacin are used in reactions in glycolysis and oxidative phosphorylations – pathways that provide ATP. During dieting, gluconeogenesis occurs. Two vitamins are used as cofactors in pathways that yield the production of glucose from amino acids. Transamination converts alanine to pyruvate (3C), which ultimately is made into glucose. Transamination reactions require pyridoxal or vitamin B$_6$. Pyruvate undergoes a carboxylation reaction, and enzymes that catalyze carboxylations require biotin. Vitamins that are formulated for “weight loss” usually contain high biotin and pyridoxal. Although these vitamins are needed for gluconeogenesis, the fact is that eating these vitamins will not produce weight loss. Eating less food and exercising more will result in weight reduction.

21. **Some years ago the “alkaline diet” was popular, and it is still used today by a few people. What is an alkaline diet? Do dietary foods have a direct influence on blood pH? Is an alkaline diet beneficial?** Early on, it was recognized that food metabolism in the body and burning produces CO$_2$ and H$_2$O. When some food is burned an ash remains. Water added to this ash is alkaline; its pH is above 7. At that time in the late 19th century, it was thought that the components in food that produced the ash helped to raise blood pH.

Look back at Figure 3.1, and instead of a human cell imagine that it is a cell of broccoli. When you eat broccoli, you are eating the whole plant. Outside of the cell, the fluids are high in the ions Ca and K, and inside they are high in Mg and Na. When broccoli is burned, the ions stay in the residue as forms of salt. When water is added to the residue, the water becomes alkaline. In contrast, some of our food is made from storage fuels of plants. For instance, bread is made from flour, which is a plant’s storage form of glucose. Oils are plants’ storage form of fat. Oil and flour do not have salts. They burn completely to CO$_2$ and H$_2$O.

Ion pumps regulate ion levels in cells. Extremes in pH in blood are avoided by HCO$_3$ (bicarbonate) that forms in blood from CO$_2$ from metabolism. Eating the so-called “alkaline-rich” foods do not change pH.

Although this diet does not change pH, it may have other benefits. The diet is high in foods where you eat whole cells such as fruits and vegetables. You get vitamins from these foods. On the other hand, the diet is high in K. K is needed for heart function, but too much is bad for the heart. Some people with impaired heart function are advised to avoid high K diets.
Appendices

Appendix 1. Name and symbols of elements mentioned in this book

<table>
<thead>
<tr>
<th>Element</th>
<th>Symbol</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbon</td>
<td>C</td>
<td>All food contains carbon. It gets metabolized to ( \text{CO}_2 ), carbon dioxide</td>
</tr>
<tr>
<td>hydrogen</td>
<td>H</td>
<td>H is in all food, and is a part of water, ( \text{H}_2\text{O} ).</td>
</tr>
<tr>
<td>oxygen</td>
<td>O</td>
<td>Oxygen that we breathe is the molecule ( \text{O}_2 ).</td>
</tr>
<tr>
<td>nitrogen</td>
<td>N</td>
<td>Nitrogen is in the amino acids that make up proteins</td>
</tr>
<tr>
<td>phosphorous</td>
<td>P</td>
<td>Phosphorous combines ( \text{O}_2 ) to make phosphate. Three phosphate groups are in ATP</td>
</tr>
<tr>
<td>iron</td>
<td>Fe</td>
<td>Fe binds ( \text{O}_2 ) in hemoglobin; iron compounds are in mitochondria</td>
</tr>
<tr>
<td>sodium</td>
<td>Na</td>
<td>( \text{Na}^+ ) is a cation that is mainly outside of cells. ( \text{Na}^+ ) is an electrolyte</td>
</tr>
<tr>
<td>chlorine</td>
<td>Cl</td>
<td>( \text{Cl}^- ) is a negative electrolyte. It is an anion.</td>
</tr>
<tr>
<td>potassium</td>
<td>K</td>
<td>( \text{K}^+ ) is an electrolyte that is mainly inside of cells</td>
</tr>
<tr>
<td>calcium</td>
<td>Ca</td>
<td>Ca is used for bones and teeth; Ca is needed for muscle contraction</td>
</tr>
<tr>
<td>sulfur</td>
<td>S</td>
<td>Sulfur is in some amino acids</td>
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## Appendix 2. Vitamins, enzyme cofactor, source and deficiency disease

<table>
<thead>
<tr>
<th>Enzyme cofactor</th>
<th>Enzyme(s)</th>
<th>Source/ deficiency</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiamine, vitamin B&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Decarboxylations: Pyruvate dehydrogenase α-ketoglutarate dehydrogenase</td>
<td>Whole wheat; beri-beri is disease when thiamine is deficient (occurs when polished rice is major part of diet)</td>
<td></td>
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<tr>
<td>Thiamine</td>
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<tr>
<td>Riboflavin, Vitamin B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Succinate dehydrogenase (TCA) Fatty acyl dehydrogenase FAD/FADH</td>
<td>Milk, eggs, leafy veggies</td>
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<tr>
<td>Niacin, nicotinic acid</td>
<td>NAD/NADH; NADP/NADPH Many dehydrogenases</td>
<td>Grains, milk, liver Pellagra is deficiency disease (dermatitis, diarrhea, dementia)</td>
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<tr>
<td>Niacin</td>
<td><img src="image" alt="Niacin structure" /></td>
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<tr>
<td>Pyridoxal, vitamin B&lt;sub&gt;6&lt;/sub&gt;</td>
<td>Transamination reactions</td>
<td>Wheat, liver meats</td>
<td></td>
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<tr>
<td>Pyridoxal</td>
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<tr>
<td>Biotin</td>
<td>Carboxylation: pyruvate carboxylase</td>
<td>All foods, liver, milk Deficiency very rare</td>
<td></td>
</tr>
</tbody>
</table>
| **folic acid** | 1 C | Found in vegetables ("foliage")
Deficiency leads to megaloblastic anemia |
|---|---|---|
| **Vitamin B₁₂, cobalamine** | Synthesis of methionine from homocysteine.
Rearrangement of carbon atoms of methylmalonyl Co to succinyl CoA, making of lecithin, which is a component of membranes | Found in meat. Deficiency leads to pernicious anemia due to folate methyl trap.
Deficiency also leads to degeneration of nerves |
About the author

Jane Marie Vanderkooi went to primary school in Amherst, South Dakota and secondary school in Herman Minnesota. She obtained her B.A. degree from Central College, Pella, Iowa and her Ph.D. degree from St. Louis University in St. Louis Missouri. She is a professor of Biochemistry and Biophysics at the University of Pennsylvania in Philadelphia. She is the coauthor of about 200 papers.