An Overview of Metabolism•

I. Introduction:

A. Up to now we have considered how motion is generated. We have seen that two important processes, the crossbridge cycle and Ca^{++} pumping require ATP and we have learned what will happen if the [ATP] gets too low. But we have not learned how ATP is generated. That will be our task in the next week or so.

B. The material we are about to cover is central to much of exercise physiology. More than anything except muscle function itself, it is the performance of the processes that generate ATP, the wastes these processes produce, and the demands these processes put on the body for fuels, oxygen, and waste removal that constrain (limit) exercise. It is vital that you understand how these processes work.

C. **<u>Attention:</u>** I must emphasize that it is important to be familiar with all that has come before in the course. Likewise, it is important that you <u>learn</u> the new material as fast as we cover it. Increasingly you will be asked to think about how the whole system (first cells then organs and finally the entire body works -- remember our discussion of the role of hierarchy and integration in biology from the start of the course). If you recall little and if you only think of isolated processes you will have no real understanding of how your body really works in exercise. Please get and stay current now or you will truly be left behind.

D. **<u>Definitions</u>**:

1. **<u>Metabolism</u>**: the sum of all chemical reactions in the body. As such it is all encompassing and difficult to measure. But we will see that there are ways to estimate it accurately. They will involve the measurement of heat production (since most reactions release heat -- thus the more reactions that occur, the more heat that is released per unit time) or some means of measuring processes that produce energy for other reactions. More about this later. In any case, <u>metabolism is the sum of two processes</u>:

2. **<u>Catabolism</u>**: Processes that breakdown energy rich compounds (usually large and complex molecules) to yield energy. The term metabolism, interestingly, is also often used as a synonym for catabolism.

(a) We will see that catabolic pathways are organized systems of enzymes that remove energy from certain molecules ("fuels") and briefly <u>conserve</u> some of the energy in compounds such as ATP. More about this in a moment.

(b) There are two general biochemical process that make up the catabolic processes:

(1) <u>Anaerobic Glycolysis</u>: the <u>breakdown of 6C sugars without the benefit of oxyge</u>n to yield some useful energy (in the form of newly

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synthesized ATP) with lactic acid and heat as waste products. This occurs in the sarcoplasm.

(2) Aerobic Metabolism: The breakdown using oxygen of either carbohydrates, fats, or proteins to yield energy conserved in the form of ATP -- with waste products of CO_2 , water, heat, and certain other substances when protein or fat is used as a fuel. These processes take place mainly in the mitochondria.

(b) Catabolic processes are spontaneous (of course they still require enzymes to run at a high rate). They release energy and create entropy. Catabolic processes provide the energy to drive non-spontaneous processes. We will also refer to catabolic processes as **SUPPLY PROCESSES** since they supply the body with energy in a usable form.

3. Anabolism and Movement**:** These are different except for the fact that both are **non-spontaneous** processes. In other words, none of these will happen unless they are driven by some other process that is spontaneous -- some process that yields lots of energy. What makes these processes non-spontaneous is that both involve storing significant amounts of energy (they also release energy, but more about this later).

(a) **Anabolism**: processes that take simple, often energy poor compounds and build up complex, energy rich compounds. You are certainly familiar with this term from the idea of anabolic drugs. These drugs supposedly cause the body to increase the synthesis of muscle proteins. Recall that proteins are made of simpler compounds -- amino acids. Energy is used to put the correct amino acids together to yield a large complex compound such as the protein myosin. Thus, protein synthesis is an example of anabolism. Likewise, the production of the complex molecule glycogen (see below) from glucose requires energy -- glycogen synthesis is also anabolic as is the production of fatty acids and fats from simple precursors. All of the processes in our bodies that involve growth and storage are at their hearts anabolic. All are driven by catabolic processes.

(b) **Movement**: When we move, it is often against gravity or even when with gravity it usually involves the need to control the effects of gravity (exception -- a fall). Thus, movement is a decidedly non-spontaneous process. We have already seen that it requires large amounts of energy from ATP (a sure sign of a non-spontaneous process). We should also see that in all cases movement involves storing or at least using potential energy. Consider this example. When you climb something, the energy you use moves your body further away from the earth. You are actively working against gravity. However, some of the energy you used can be gotten back, albeit in a different form than the chemical energy you used to make the climb. Once you have completed the climb, you can jump back to where you started -- the energy to move you back is stored in your new position. It is lost as heat and perhaps sound when you fall. Another way of demonstrating that you have stored energy is the fact that you could use your position and fall to do work on something else. For instance, if someone else is standing on a teeter totter and you fall from a height onto the other end, some of the energy you stored prior to jumping will be transferred to the other person and cause them to vault. In a similar manner, if you move from one place to another, even if no energy is stored, it still took a large amount of energy to make the move. You cannot run from Worcester to Boston without using energy anymore than a car could drive there without using energy from gas. Thus movement shares many features in common with anabolism, especially with regard to energy requirements.

(c) We will lump all non-spontaneous processes (anabolism and movement) together into what we will call **DEMAND PROCESSES**. What they demand is energy.

4. **Linking Supply and Demand -- ATP as an Energy "Currency"**:

(a) We have already learned that ATP is a compound that can transfer energy to many processes that require energy. Examples include to myosin to run the crossbridge cycle and to the Ca^{++} pump to move Ca^{++} into the SR. There are many more examples. In fact, so many processes that require energy use ATP or one of several compounds closely akin to it (*e.g.* **UTP, GTP**) that we call it (ATP) the "**universal energy currency of the cell**". The term is a bit of a stretch since there are other energy currencies (*e.g.,* NADH (see next lectures)) and many reactions that require energy do not use ATP as its source. Nevertheless, so many movement-related and anabolic reactions require ATP that the "universal energy currency" designation is a useful generalization.
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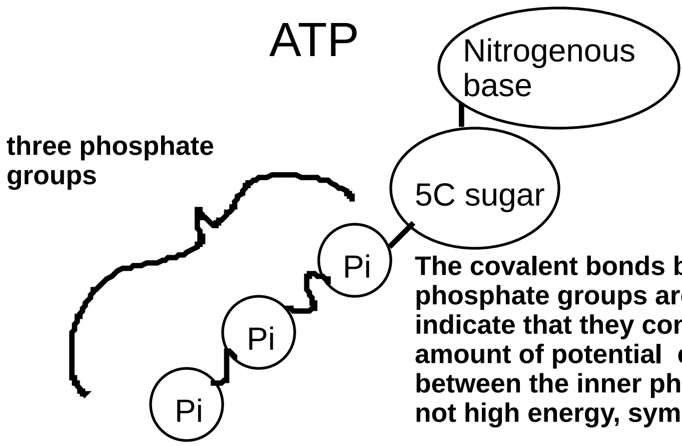
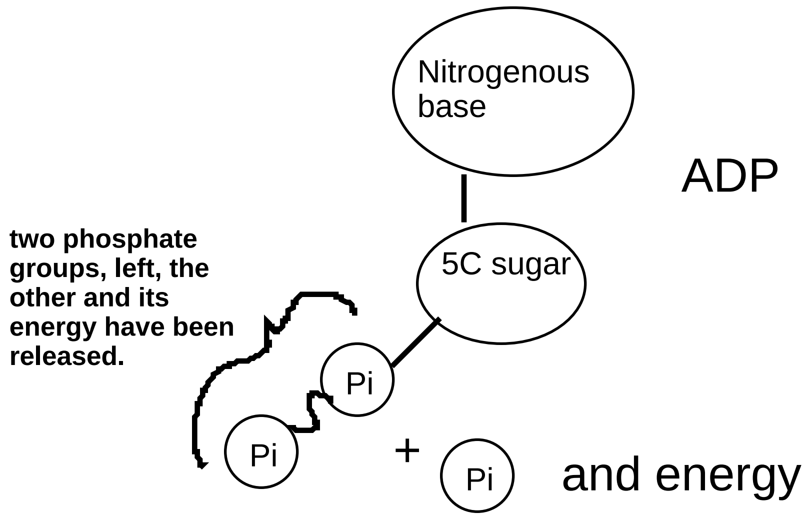
One note -- we will see that even within the "supply", catabolic processes, there are occasionally reactions that require ATP.

(b) The structure of ATP and related compounds are very similar. All consist of a 5 C sugar, something called a nitrogenous base (adenine and guanine are two examples you might remember from other science courses) and three phosphates. The only part of this structure that is important to us are the outer two phosphates:



The covalent bonds between the outer two phosphate groups are shown as squiggly" lines to indicate that they contain a particularly large amount of potential energy. The attachment between the inner phosphate and the 5C sugar is not high energy, symbolized by a straight line.

(c) ATP and related compounds all release energy by losing one (or sometimes two) phosphate groups. Here is the result of the most common type of this process where a single phosphate is lost yielding ADP, Pi and a certain amount of energy (about 7 Kcal per mol of ATP broken to ADP):



(d) Thus, ATP is the higher energy version and ADP the lower energy version.

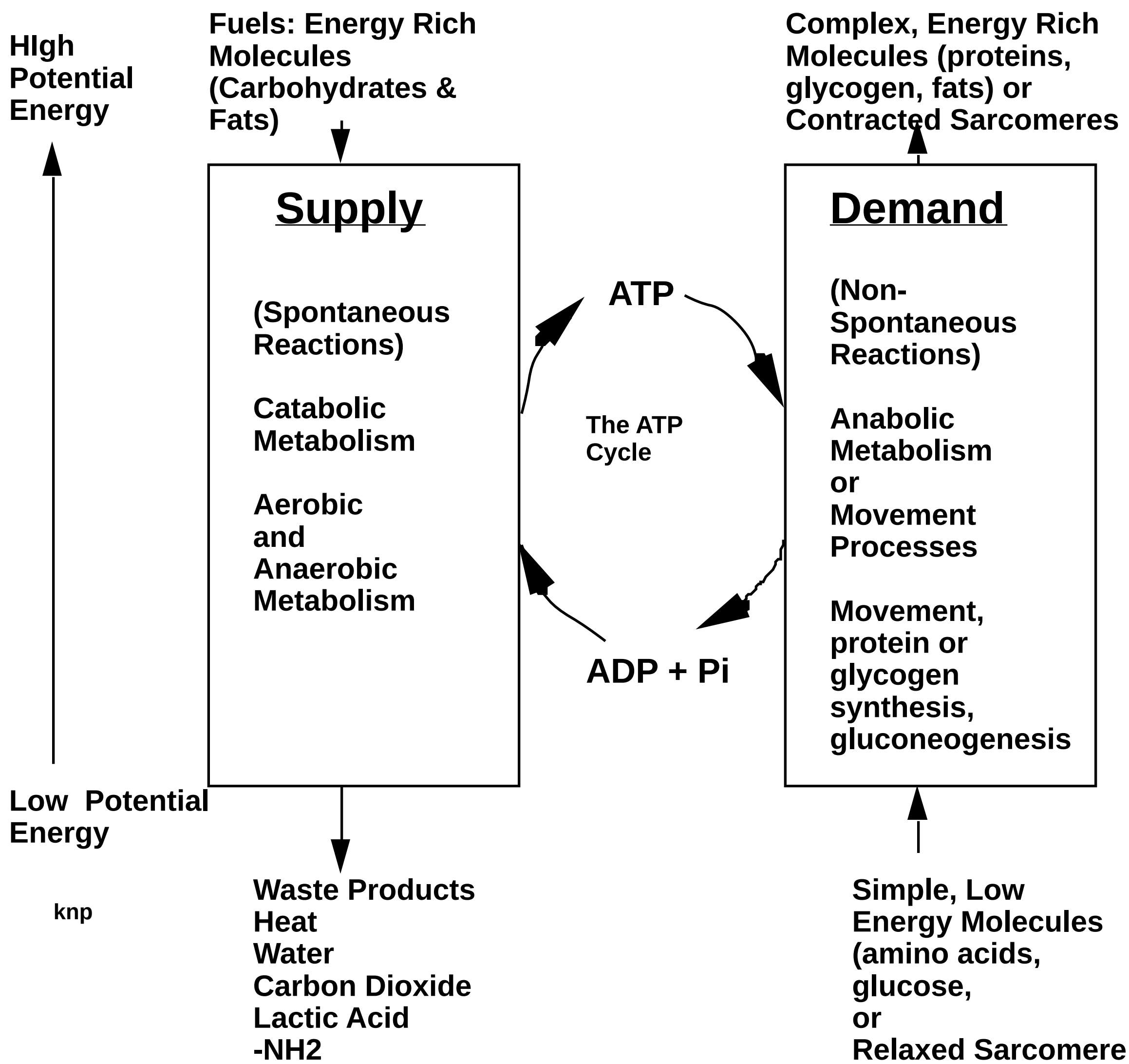
(1) <u>Processes that need energy may be able to get it from ATP</u>. When the energy is transferred to the process that requires it, the ATP loses its outer phosphate (called Pi -- inorganic phosphate -- the same stuff that is your bones with Ca^{++}) and becomes ADP.

(2) <u>To reattach the phosphate takes a large amount of energy</u>. <u>Some of this energy is stored in the regenerated molecule of ATP</u>. The <u>energy needed to re-attach the Pi</u> (and the energy that is stored in the newly attached phosphate) normally <u>comes from catabolic reactions</u>.

(3) Thus ATP is made from ADP and Pi using the energy released in catabolic processes, and the ATP is broken down to ADP and Pi with the release of energy in anabolic and movement processes. We call this constant cycling back and forth the <u>**ATP cycle**</u>.

(4) Recall that there is only a small total amount of ATP and ADP in a cell. Thus, each molecule is constantly going through the ATP cycle. The <u>**greater the rate the cell is using energy (for instance, when a muscle cell contracts), the greater the speed of the ATP cycle and for that matter, the greater the speed of the catabolic reactions that help to drive the ATP cycle.**</u>

D. Let's look at the overall process. The following diagram summarizes the demand and supply sides and the ways that they are linked together via the ATP cycle:



II. About Fuels and Wastes

A. Fuels:

1. **Carbohydrates**

(a) these are the most **preferred fuels in muscle fibers**.

(b) All carbs. have the **general formula $(CH_2O)_n$**. This means that the proportions are always 1 carbon to 2 hydrogens to 1 oxygen.

(1) The subscript **n** refers to how many carbons and therefore oxygens and hydrogens are present.

(2) For example, most carbohydrates are based on simple **hexose** or 6C sugars. There are two 6C sugars we commonly use -- **glucose** and **fructose** (both constituents of a more complex sugar, **sucrose** (table sugar)).

(3) Both glucose and fructose have the proportion formula $C_6H_{12}O_6$. They differ in the exact way the molecules are organized.

These different arrangements that have the same chemical formula are called **<u>isomers</u>**. These differences in arrangement result in slightly different properties (for example, fructose seems sweeter to us) but in other ways the molecules are the same. For instance, they have the same amount of stored energy. Moreover, they can be easily converted back and forth with no significant energy cost. Here are the structures (there is no reason to learn them):

Glucose

```
   H - C == O
       |
  H - C -OH
       |
OH - C - H
       |
  H - C -OH
       |
  H - C -OH
       |
  H - C -OH
       |
       H
```

Fructose

```
          H
          |
OH - C - H
          |
          C == O
          |
OH - C - H
          |
  H - C -OH
          |
  H - C -OH
          |
  H - C -OH
          |
          H
```

(4) Our bodies normally work with glucose or derivatives of it (for instance glucose with phosphate attached -- see next class). So, our bodies tend to convert any fructose we eat (and we eat a lot of it in fruits and vegetables) into glucose.

(c) There is one problem with glucose, however. The problem is that **<u>storing glucose as glucose causes problems</u>**. These problems have to do with **osmosis**.

(1) <u>Osmosis</u> will be covered in a bit more detail later. For the moment, realize that <u>whenever there are two solutions of different concentrations that are separated by a membrane (for example the blood and the sarcoplasm separated by the sarcolemma), water will tend to flow from the area where there is a lot of dissolved stuff to the area where there is less</u>.

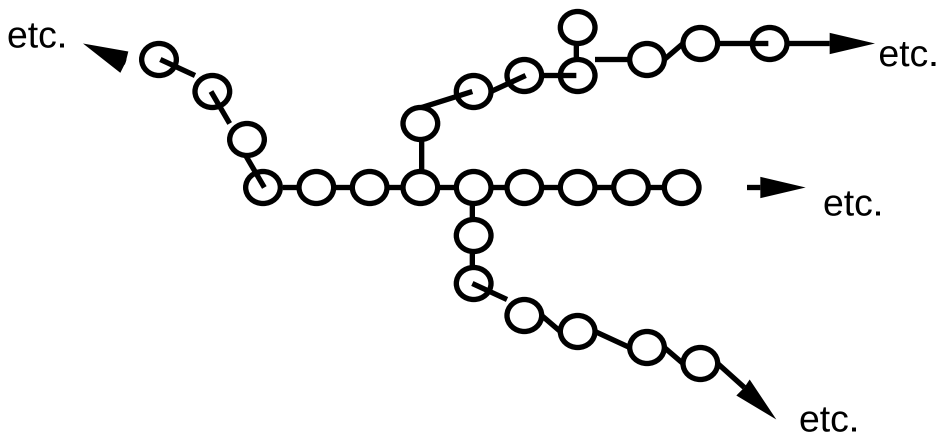
(2) Let's see how this affects cells.

(i) Suppose that a cell tries to concentrate a lot of glucose inside of it. The result will be that the overall concentration of dissolved stuff increases (since the cell has put more glucose (dissolved stuff) in than was there before).

(ii) The result is that water will tend to enter the cell from the blood and the cell will swell and perhaps even burst!

(3) So, glucose cannot be stored in large amounts in any tissue. (One other example of this -- even though your blood is the main means to move glucose around, the concentration cannot get too high (when it is too high you have the disease called diabetes). In all of your blood the amount of glucose is about 3.5 grams -- this is about equal to what is in a bag of sugar you'd use to sweeten coffee or tea!)

(d) To get around the problem just covered, the body stores glucose as a starch called **glycogen**. Glycogen is an indefinitely large molecule that is a branched polymer of glucose. Think of each of the circles below as glucose molecules and the lines between them as covalent bonds that hold them together:



The individual chains are made longer by adding glucose to the ends whenever it is present in higher than normal amounts. To add the glucose, energy is required in the form of UTP, a high energy molecule that works very much like ATP. The reaction is:

Glycogen synthetase
Glucose + UTP + Glycogen Chain ----------------------------->
Longer Glycogen Chain + UDP + Pi

Notice that this is an example of an **anabolic reaction**. Energy (from the ATP-like UTP) is being used to make a more complex, energy rich compound (the larger glycogen chain) from simpler, smaller compounds (the smaller glycogen molecule and the glucose).

You need not learn the last reaction but you should be able to recognize a reaction like it as being anabolic in nature and you should see the role of energy from ATP or similar substances in making these compounds. Try to relate all of this back to the overview graph on page 5 of these notes.

(e) the glycogen gets around the osmosis problem since all of the glucose incorporated into glycogen is not in solution! Instead it is a big starch grain somewhere inside the cell. This is kind of like a piece of spaghetti in water. The spaghetti is starch (like glycogen, entirely made of glucose) but it is not dissolved in the water. Thus, adding spaghetti to water does not increase the concentration of dissolved substances in the water and making glycogen in a cell does not contribute to the concentration of dissolved substances in the cell.

(f) One other comment about glycogen. It is **found mainly** in two parts of your body -- the **muscles and liver**. The amounts present in both places change according to when and what you ate last. We will later see that there are certain techniques an athlete can use to increase the amount of glycogen in the body; this has use in certain types of athletic events.

(g) Energy and carbohydrates.

(1) If we **completely burn any carbohydrate with oxygen** so that all we get is water and CO_2 , then we liberate about **4.2 Kcal of energy for each gram** of carbohydrate burned. This figure is worth remembering.

(2) Alternately, if we completely burn 1 mol of a 6 carbon sugar such as glucose or fructose, we get:

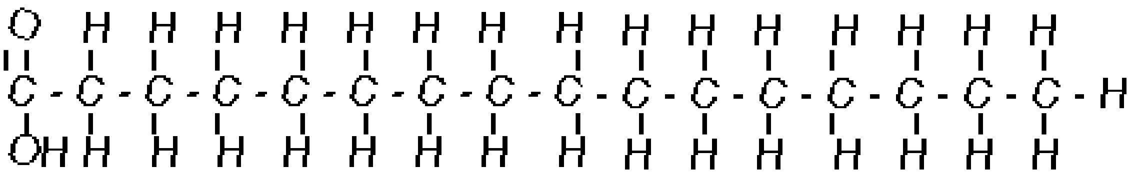
$$C_6H_{12}O_6 + 6\ O_2 \text{ ----------------> } 6\ H_2O + 6\ CO_2 + 686\ \text{Kcal}$$

(this figure is not worth remembering, but some familiarity with the above equation is useful).

Bomb Calorimetry: The way that we find the amounts of energy released when foods are burned (the so-called **caloric equivalents of the food**) is by using a device called a "bomb calorimeter". Basically it is a heavy metal container. A dried sample of the food (*e.g.* sugar) is placed inside and lots of pure oxygen is pumped in -- more than enough to totally burn the food. Then a spark ignites the food which then actually explodes. The metal container keeps the explosion contained but it heats up from the energy released by the explosion. The amount it heats up is used to calculate the amount of energy released and *voila*, we have the caloric equivalent.

2. **LIPIDS**

(a) The other main energy source, but not the one preferred by muscles, is fat which are one type of compounds more generally called lipids. Lipids are compounds made almost entirely of carbon and hydrogen. For reasons that we do not need to explore, they contain very large amounts of potential energy. One type of lipid are compounds called **sterols** like cholesterol or certain hormones (estrogen, progesterone, testosterone, aldosterone to name a few). **Fats** are primarily composed of structures called fatty acids which in part look like this:



(please excuse the wavy lines).

(b) the big things to realize about this molecule are that;

(1) it is very non-polar and therefore it will not dissolve or interact well with water. Compare this with the carbohydrates that have lots of polar groups (C-OH and C=O).

(2) It contains a very large amount of energy. In large part, this is related to the fact that it contains very little oxygen.

(c) How much energy? - if we burn **one gram of fat** completely with oxygen to water and carbon dioxide, about **9.4 Kcal** of heat are released. Notice that this is over twice the energy contained in a gram of carb. (4.2 Kcal).

(d) Fats are not as accessible to the muscles as fuel sources. They can be burned slowly under aerobic conditions (where there is plenty of oxygen). However, they are excellent long term storage molecules -- they take up less room per Kcal of energy saved than glycogen because they (i) contain twice as much energy per gram and (ii) don't bind with water the way carbohydrates such as glycogen do.

(e) Fats have at least two other functions -- fatty tissues are excellent insulators since they tend to have little water and also a small blood supply. That is why mammals and birds, unlike all other animals, tend to put fat just under the skin. Fat in this location tends to reduce heat loss. Also, some fat deposits (such as the fat around the heart and kidneys) acts as a shock absorber.

3. **Proteins**. We will not say much about proteins now except to remind ourselves that we have no true store of proteins. Body proteins are not used for energy. Instead, if broken down they are simply recycled. The amino acids are put into other proteins. The only time body proteins are normally used for energy is in the advanced stages of starvation. On the other hand, any protein that is consumed in excess of what is required is either used as fuel (its not a very good one) or it is converted into fat or carbohydrate. Again, it is neither stored nor will eating more protein increase the rate at which proteins are made (for instance eating significantly more protein (translation -- 2 or 3X the so called daily requirement) will not affect the rate at which muscles are built up during training).

B. Wastes

1. We will be concerned with the following waste materials from catabolism (demand) pathways:

(a) from anaerobic metabolism: lactic acid

(b) from aerobic metabolism: water, CO_2 , and, in some cases other compounds.

(c) from all types of metabolism -- excess heat.

2. What wastes do if they remain in cells, how they get out of cells and how the body eliminates them will be important stories for the remainder of the course.