

## Chapter 3: Metabolism

**Because of the complexity of the study of metabolism, only the following basics of metabolism will be covered from Chapter 3 and will be clarified and discussed in class:**

1. The two laws of bioenergetics.
2. The way that foodstuffs such as fats and carbohydrates represent energy—covalent bonds contain energy (put there by photosynthesis in many cases) which is liberated for use by the body when broken down via metabolism (actually catabolism).
3. All chemical reactions (including those in the body) proceed in the direction that results in the release of free energy. Such reactions are termed “exergonic” reactions.
4. Metabolism can be divided into “catabolism” (breaking down) and “anabolism” (building up). Most of what we deal with in the chapter on metabolism is catabolism. Anabolic metabolism is mostly related to the growth process or creating larger molecules from smaller ones (such as building proteins from amino acids).
5. ATP is the way that the body stores energy for direct use by the cells to perform functions that require energy (such as muscle contraction).
6. The amount of ATP in the cell is very limited (perhaps enough for a second or so of all out contraction in a muscle cell).
7. There must be ATP available to continue cell function—nothing else can be used directly for energy-requiring functions.
8. ATP (adenosine triphosphate or an adenosine molecule with three phosphates— $\text{PO}_4$ —attached to it) contains two high energy bonds. However, only one of these can be used directly to provide energy. ATP breaks down to ADP (adenosine diphosphate) which still has a high energy bond left. Two ADPs can get together to produce an ATP and an AMP (adenosine monophosphate).
9. In addition to ATP, there is also a second high energy phosphate compound present in the cell, called creatine phosphate (CrP or in many texts CR, but never referred to orally by these abbreviations!). CrP cannot be used directly for energy (as ATP can), but can be used indirectly to resynthesize (reform) ADP into ATP.
10. There is a much greater quantity of CrP in the cell than there is ATP (perhaps enough for 5-10 seconds of maximal exertion). CrP can therefore quickly resynthesize ADP into ATP to keep the cell operating for up to 10 seconds without any foodstuff supplied energy.
11. Foodstuffs can be broken down to provide almost unlimited energy for the cell, but there are constraints on this production. It takes time to get them going, thus for a while at the beginning of exercise the cell may have to get by on its stored energy resources (ATP and CrP). However, once fat and/or carbohydrate metabolism gets cranked up and going, the ATP and CrP can be resynthesized for reuse.
12. ATP, while in very limited supply in the cell, can be used over and over. To reuse it, it must be resynthesized. The ways that ATP can be resynthesized include: ADP (ADP + ADP yields ATP + AMP), CrP (ADP + CrP yields ATP + Cr), anaerobic glycolysis (using glucose), aerobic metabolism/TCA cycle (using fats or CHO)
13. While three foodstuffs (carbohydrates, fats, proteins) can provide energy for the body's needs, protein (P+ as an abbreviation) generally does not contribute in a great way to the energy needs of the body. Instead, it is reserved for anabolic purposes,

such as producing new body structures (including muscle, cell membranes, enzymes, and many other things).

14. This leaves two foodstuffs to be used for energy production (carbohydrates and fats). Fortunately, for simplicity of learning, the body converts all complex carbohydrates (starches) into the three monosaccharides (glucose, fructose, galactose) and then isomerizes all of these into glucose. Therefore only metabolism of glucose has to be dealt with!
15. Carbohydrate (glucose) metabolism has advantages and disadvantages compared to fat metabolism. A major advantage is that glucose can be broken down anaerobically (that is, without the involvement of oxygen), which makes it possible for the cell to produce energy for resynthesizing ADP to ATP in times when oxygen is in short supply (such as during heavy exercise, when the body is incapable of delivering sufficient oxygen to the working muscle cells).
16. This breaking down of glucose without oxygen is termed “anaerobic glycolysis” (anaerobic = without oxygen, glycol, as in glycogen which is nothing more than stored glucose, and lysis = to break down, hence, the breaking down of glucose without oxygen).
17. Anaerobic glycolysis (think of it as “glucolysis” even though there is no such word!) is a way of producing energy from foodstuffs (carbohydrates, in this case) without the need for oxygen. This process is valuable at the beginning of exercise, before adequate oxygen delivery can catch up with demand, as well as during heavy exercise, when the person’s maximal oxygen uptake is inadequate to meet demands.
18. Anaerobic glycolysis can provide energy for resynthesizing ADP to ATP without oxygen, which is a tremendous capability to have. Unfortunately there are limitations to the body’s ability to produce energy in this manner. A major limitation is that the amount of glucose in cells (and in the body as a whole) is very limited, especially when compared to fat.
19. The cell stores carbohydrate as glycogen, which is simply a long chain of glucose molecules loosely bonded together. When necessary, glucose molecules can be separated from the glycogen chain to provide molecules for metabolism. Glycogen is a complex carbohydrate (few complex CHOs are found in animals). NOTE: Glycogen is found in two major places in the body: In muscle cells and in liver cells. Because 40% of the average body is made up of muscle, muscle glycogen quantity is greater than for the liver, although the liver has the greatest concentration of glycogen.
20. The amount of glycogen in the typical muscle cell is good for perhaps one minute of maximal exertion (actually “supermaximal” since maximal is considered the aerobic limit!). Obviously, the body cannot call upon anaerobic glycolysis to provide energy for very long. There have to be alternative ways of producing energy from other fuels!
21. Not only is the amount of glucose (or glycogen) limited, but another problem arises when the cell attempts to provide large amounts of energy via anaerobic glycolysis when oxygen is in short supply: Without the availability of oxygen, the end product of anaerobic glycolysis is lactic acid (a.k.a., lactate), which, as its name indicates, is an acid, and acid creates problems for metabolism which occurs only within a very narrow limit of pH.

22. Lactic acid, the end product of anaerobic glycolysis when oxygen is not available, is self-limiting. That is, the cell (and body as a whole) can tolerate only so much of it. When lactic acid is produced in a cell, it diffuses through the cell membrane and out into the interstitial fluid between the cells and eventually into the blood to be distributed throughout the body. This “permeability” of the cell membrane to lactic acid is very fortunate, for it allows the high concentration of lactic acid in the working muscle cell to be diluted by mixing it with all the body fluids. Despite this, there is still a poor tolerance for lactic acid and it can quickly build up to the point where it causes the body to have to slow down or stop exercising.
23. At the end of a maximal exercise bout (when the subject has gone as hard as they can for as long as they can!) the amount of lactic acid in the body has interfered with the metabolic machinery (by decreasing pH/increasing acidity) to the point where the subject has been forced to stop exercise (or at least greatly decrease the level). The lactic acid produced during exercise and circulating in the body must be dealt with, usually during recovery.
24. Before dealing with the topic of lactic acid removal, it is first necessary to have an understanding of where lactic acid comes from in the first place. When we talk about anaerobic glycolysis there is sometimes the assumption that it is undesirable because of the lactic acid it produces. Not so!! Actually, anaerobic glycolysis doesn’t always produce lactic acid.
25. At the end of a rather complicated series of reactions (see the simplified metabolic schematic provided in class) glucose goes from its original “hexose” or six carbon form to two “triose” or three carbon molecules, with the final triose being pyruvic acid or “pyruvate.” During this process of becoming two pyruvate molecules, the original glucose molecule gives off four hydrogen ions (two for each pyruvate formed). Since hydrogen ions are nasty little buggers when it comes to maintaining cell pH (pH=negative log of the hydrogen ion concentration!), it is imperative that hydrogen ions not be allowed to drift off into the cytoplasm (cellular fluid) unencumbered.
26. Thus the need for NAD! NAD (you don’t really want to know what it stands for!) is a “co-enzyme” specifically for the purpose of providing a “holding tank” for H<sup>+</sup>. As what will eventually become pyruvate moves through the chemical steps, whenever hydrogen ions are released, NAD quickly comes to the rescue and attaches to them forming NADH<sub>2</sub> or NAD<sub>2</sub>H or just NADH (depending upon the textbook). Attaching the H<sup>+</sup> to NAD effectively neutralizes the H<sup>+</sup> and protects the environment of the cell from adverse changes in pH.
27. So far, so good. However, there is a problem! There is a very limited supply of NAD to pick up H<sup>+</sup> so it doesn’t take long to run out of NAD. Without available NAD the H<sup>+</sup> might simply be turned loose to affect pH but this can’t be allowed. So there has to be a way to free up NADH by getting rid of its H<sup>+</sup>. Actually there are two ways—one when sufficient oxygen is available and one when insufficient oxygen is available.
28. First the way when not enough oxygen is available. In this case, pyruvate (same thing as pyruvic acid) that was just formed and in the process gave off two H<sup>+</sup> to NAD to form NADH, simply reaccepts the H<sup>+</sup> to become lactic acid! What is lactic acid? Nothing more than pyruvic acid with an additional two hydrogens.

29. If you think about this, it may raise the question: If lactic acid is bad, why would we want to form it from pyruvate by adding the extra H<sup>+</sup>? A simple answer is that basically it is much better to form lactic acid which, being an acid, dissociates (loses) some of its H<sup>+</sup>, rather than turning loose all the H<sup>+</sup> from NADH or from the breakdown of “triose” into pyruvic acid (which would wreak havoc on pH, comparatively speaking).
30. Another question: Why is it necessary to do something with the H<sup>+</sup>, why not just let all the NADs become NADH? If this were to happen, then the metabolism of glucose to pyruvic acid would have to stop (since H<sup>+</sup> can't be dumped freely into the cytoplasm). If we quit forming pyruvic acid, we quit producing energy—which is the purpose of metabolism in the first place. Without the energy from anaerobic glycolysis, high intensity exercise would not be possible. Not an option!
31. So one method of disposing of the extra H<sup>+</sup> is to form lactic acid from pyruvic acid, thus freeing up the NAD to continue to bring more glucose down to pyruvic/lactic acid. In this way the energy production process can continue, at least as long as we can tolerate the lactic acid that is being produced by the process and distributed throughout the body by the blood.
32. The second way to deal with pyruvic acid and the H<sup>+</sup> given to NAD to form NADH is to involve oxygen and the aerobic phase of metabolism. If oxygen is available (and it always is to some extent), some, if not all, of the pyruvic acid that is formed (and the NADH that was also formed in the process) will be put into the aerobic cycle and associated pathways to be converted to the harmless end products of carbon dioxide and water. With oxygen available, two H<sup>+</sup> can be attached to an oxygen atom to form H<sub>2</sub>O. In this way an extremely hazardous product (H<sup>+</sup>) can be converted into a harmless, indeed necessary, end product! Likewise, carbon (not nearly so problematic as H<sup>+</sup>) can be eliminated from the body by combining it with oxygen to form CO<sub>2</sub> which is carried to the lungs by the blood and exhaled.
33. The process of removing lactic acid during recovery (actually of reconvertng it back to glucose or glycogen) involves both the muscles and the liver and is called the Cori cycle. The Cori cycle works like this: Muscle glycogen → muscle glucose → muscle pyruvic acid → muscle lactic acid → blood lactic acid → liver lactic acid → liver pyruvic acid → liver glucose → liver glycogen → (perhaps much later) liver glucose → blood glucose → muscle glucose → muscle glycogen (which is where we started!). This process of reconvertng lactic acid to glucose or glycogen is called gluconeogenesis or literally “the creating of new glucose (or glycogen).”
34. So what is the function of oxygen in metabolism? This element that is essential for life, that must be provided in adequate amounts just to sustain life? It is nothing but a garbage collector! However, never underestimate the importance of garbage collection, especially in large cities! When sanitation workers go on strike the entire city shuts down as the refuse with its stench and disease potential mounts! Garbage collection is equally important in the body.
35. What has thus far been referred to as “aerobic metabolism” is more scientifically called by other names: The Krebs cycle or the TCA (tricarboxylic acid) cycle. In addition there are “associated pathways” that include the electron transport chain (ETC) where oxygen is actually combined with the H<sup>+</sup> to form water and large amounts of the “aerobic” energy is manufactured by “oxidative phosphorylation.”

36. Anaerobic processes (from glycogen or glucose down to pyruvic acid or lactic acid) occur in the liquid matrix or “cytoplasm” (called “sarcoplasm” in muscle cells) of the cell. These processes therefore do not occur in any kind of organelle, but rather occur in the liquid portion of the cell. All required enzymes and co-enzymes are located there. Aerobic processes occur in the mitochondria (the “powerhouses” of the cell!). Aerobic training increases the number and size of the mitochondria in the trained muscle tissue.
37. Aerobic processes use the “substrates” or products of anaerobic glycolysis (actually acetyl-CoA, a two carbon molecule formed from pyruvic acid—minus a CO<sub>2</sub>—and a co-enzyme aptly named co-enzyme A). Each glucose anaerobically produces two pyruvic acids (which can become two acetyl-CoA molecules) and a small amount of energy (actually two high energy phosphate bonds or “2 ATPs”—two ADPs resynthesized to 2 ATPs).
38. Most of the available energy from the original glucose molecule is still available at the end of anaerobic glycolysis in the form of pyruvic acid/acetyl-CoA and the H<sup>+</sup> attached to NAD/NADH. To convert this available energy into ATP requires oxygen.
39. The aerobic energy yield from the original glucose molecule is 36 ATPs (in addition to the 2 ATPs produced anaerobically), thus 36 ADPs are resynthesized into 36 ATPs. However, to produce this large amount of energy, a considerable amount of oxygen is required. Only when the cardiovascular system can provide sufficient oxygen to the working muscles can this large amount of energy be produced. Obviously, since oxygen supply to the muscle is key to energy production, maximal oxygen uptake is the criterion measure of endurance performance (more oxygen = more aerobic energy, without harmful end products such as lactic acid). You must produce the energy required to perform the work. If you can produce the energy aerobically, you get lots of energy without lactic acid. If you can't deliver the oxygen to produce the energy aerobically, then you have to produce the energy anaerobically. While it is possible to do this for a while, eventually the lactic acid builds up and you have to slow down.
40. How can a trained endurance athlete run a marathon (26.2 miles) at a sub-five-minute-mile pace while most HPE majors have difficulty running at an eight-minute-mile pace for more than a couple of miles? The difference is Max V<sub>O<sub>2</sub></sub>: 70 ml/kg/min for the trained marathoner vs. 35-45 ml/kg/min for the typical major!
41. So far only glucose (CHO) has been considered metabolically and there is good reason for this—CHO is the primary foodstuff used during all short-term exercise and especially during high intensity exercise. It has already been mentioned that while CHO, fats, and P+ can be utilized metabolically for energy production, P+ generally contributes little to energy production.
42. This leaves just CHO and fat for energy production during exercise. CHO (glucose) we have seen can be used anaerobically (without oxygen) to produce some energy and to provide substrates (products) for aerobic energy production, namely acetyl-CoA and NADH. Since CHO produces pyruvic acid which may become lactic acid (if oxygen is not available) or acetyl-CoA (when oxygen is available), it stands to reason that priority will be given to forming acetyl-CoA from pyruvic acid rather than making products from fat that will result in pyruvic acid becoming lactic acid.

43. Actually acetyl-CoA can be produced from fat as well as from glucose. The process of creating acetyl-CoAs from fatty acids is called “beta oxidation.” This process involves oxidizing the “beta” carbon of a 14 to 16 carbon free fatty acid (FFA) then cleaving (breaking off—like chopping with a meat cleaver!) two carbons and the attached hydrogen and oxygen from the chain, which becomes an acetyl-CoA. In this way a single FFA can produce 7 or 8 acetyl-CoAs which may enter the TCA cycle like those produced by glucose. But, to utilize fat as acetyl-CoA in the Krebs or TCA cycle you must use extra oxygen in beta oxidation to get the acetyl-CoA, and then use the usual oxygen that the TCA cycle requires. Fat metabolism is therefore not as efficient with oxygen as glucose metabolism, thus glucose will be preferred as the fuel for exercise of all but the lightest intensity or longest duration (because glucose is very limited, while fat is abundant!).
44. Think about it: If oxygen is in short supply, why would the body waste oxygen with a “double dipping” process using fat when it could more efficiently produce energy from glucose?
45. Also: When the intensity of exercise is great enough that some of the energy required must be produced using anaerobic glycolysis (producing at least some lactic acid), does this not indicate that more pyruvic acid is being produced by anaerobic glycolysis than can be handled as acetyl-CoA in the TCA cycle? If this is the case, why would fat metabolism be used to produce more acetyl-CoA which would result in the need to produce more lactic acid? Especially since fat production of acetyl-CoA takes more oxygen than from glucose? When the intensity of exercise is high, glucose provides almost all the energy—first from anaerobic glycolysis and then by utilizing the substrates produced by anaerobic glycolysis (pyruvic acid and NADH).
46. The higher the intensity of exercise the greater the need for energy and the greater the need for oxygen. If there is not enough oxygen to handle all the pyruvic acid being produced, some of the pyruvic acid will become lactic acid. Unless intensity of exercise decreases, lactic acid will continue to mount up until eventually it causes exhaustion. During light to moderate exercise (steady state) the body is able to deliver sufficient oxygen so as to be able to take all of the pyruvic acid produced by anaerobic glycolysis into the TCA cycle as acetyl-CoA, thus none of the pyruvic acid has to be converted to lactic acid. In addition, since there is plenty of oxygen being delivered to the muscles, some of the energy can be produced through beta oxidation (or more accurately by utilizing acetyl-CoAs produced by beta oxidation). Even though more oxygen is needed to produce energy this way, this is not a problem since plenty of oxygen is available.
47. Recap: Two fuels are available to produce energy during exercise: CHO (glucose) and fat. CHO is the highest quality of fuel because it can produce energy anaerobically and when used aerobically takes less oxygen than fat metabolism. However, CHO is in short supply and can be used up quickly unless “spared” by using fat. Fat is a very abundant fuel but can only be used aerobically and takes more oxygen than CHO to produce aerobic energy. Therefore, the muscle utilizes fat as much as possible and CHO only as necessary. At rest, muscles use almost all fat metabolism to meet their minimal needs. When exercise begins (even light exercise), CHO metabolism quickly gets going to produce the needed energy. If the exercise is steady state the body will soon start to produce acetyl-CoAs via beta oxidation, thus moving away from CHO as a fuel. The longer the exercise lasts, the more fat will be

called upon and the less CHO metabolism will be used. This is a “sparing” effect to conserve CHO, which is quite limited.

48. Recap: When a resting muscle cell begins contracting, energy is immediately required in the form of ATP. Since ATP is there, ready to go, there is no problem. However, there is only about one second’s worth of ATP in the cell, so very quickly the cell calls upon its second high energy compound CrP to begin resynthesizing ADP to ATP. There is also a third way to produce ATPs quickly and that is by changing two ADPs into one ATP and one AMP (same amount of total energy, but partly usable as ATP). These three ways to provide immediate energy for muscle contraction are together referred to as the “phosphagen system” or “phosphagens” and can provide energy for perhaps 10 seconds or so (not long!). While they are great for getting things going, the phosphagens are only there to provide energy until “real” metabolic pathways can get cranked up and start providing ATP energy from foodstuffs. After the phosphagen system, anaerobic glycolysis is the quickest way to begin producing energy. Since there are several steps that must occur before any energy is produced, it takes a while to get anaerobic glycolysis going. The slowest way to produce energy is the TCA cycle, not only because many steps must occur but also because oxygen is needed—it takes time for the body to  $\uparrow$ HR in order to  $\uparrow$ Q<sub>C</sub> and to  $\uparrow$ V<sub>E</sub>. As soon as exercise begins, ATP springs into action to provide the energy. CrP just as quickly resynthesizes the ATP. Meanwhile, the body begins the process of cranking up anaerobic glycolysis and aerobic metabolism and tells the cardiovascular and respiratory (cardiorespiratory!) systems to  $\uparrow$ oxygen to the muscles. It takes between two and four minutes to make these C-R adaptations and ready a steady state during light to moderate exercise.
49. Recap: The purpose of metabolism (catabolism!) is to meet the energy needs of the body by taking the energy contained in the covalent bonds of foodstuffs (CHO, P+, fat, and even alcohol!) and convert this energy into a usable form—ATP.
50. Phosphagens are like a battery—they store energy that is produced by “real” energy-producing mechanisms and allow their stored energy to “tide” the body over until the “real” mechanisms can get going and start producing energy from foodstuffs. Phosphagens are used only as necessary until foodstuff metabolism can “catch up.” The 10 seconds of energy available from phosphagens would be largely consumed in a 100-meter dash, especially if performed with no warm up. By the end of the dash anaerobic glycolysis would be getting going pretty good and aerobic metabolism would be just beginning to contribute energy. Little lactic acid would be produced during the event, simply because the race would not last long enough for much lactic acid to be produced.
51. In running a 400-meter race with warm up, when the gun is fired the initial energy burst out of the blocks would come from phosphagens, with anaerobic glycolysis and aerobic processes contributing some energy quickly (due to the warm up) and lactic acid will quickly begin to mount. Over the course of the spring aerobic metabolism will provide as much energy as the available oxygen will allow, but this will be far less than required, with anaerobic glycolysis (producing lactic acid) accounting for the rest. In this approximately one-minute race, a near maximal amount of lactic acid will build up and the runner will come close to reaching his/her Max V<sub>O<sub>2</sub></sub>. The greater the runner’s Max V<sub>O<sub>2</sub></sub> the less the lactic acid buildup and the more likely the runner will finish the race at nearly top sprint speed (and without the loss of coordination often seen). Also, the greater the Max V<sub>O<sub>2</sub></sub>, the faster the recovery,

again because aerobic metabolism was able to provide more energy during the run, requiring less lactic acid to be removed after the run. Warm up is very important in such races to increase the availability of both oxygen and acetyl-CoA substrates, rather than having to start from scratch when the gun is fired. Recovery will be enhanced due to the warm up, even if the performance itself is not. Moderate exercise during recovery (continuing to walk or even jog) will speed the recovery process, primarily by causing lactic acid to be reconverted to pyruvic acid and then to acetyl-CoA to be consumed for energy in the TCA cycle. Complete rest during recover will slow down the removal of lactic acid.