JOHN ESSIGMANN: Welcome to the metabolism portion of Biological Chemistry 5.07. My name is John Essigman and I teach this course with JoAnne Stubbe. I'm primarily a chalkboard teacher, as you'll notice from my notes. In order to make things as simple as possible, I use a lot of abbreviations, and my abbreviations list will be appended elsewhere.

Let's start by looking at a metabolic chart, figure 16-1 from the textbook. Obviously it looks very complex. Part of the challenge of both teaching and learning biochemistry is finding a way to look at this pig's breakfast of biochemical reactions and find its underlying structure.

For the purpose of this course, the underlying structure we're going to look for is the biochemical pathways that let us function. For example, a pathway could involve making ATP or it could be putting an amino group onto an alpha-keto acid in order to make an amino acid. Although few people think of biochemistry as simple, formatting the pig's breakfast into pathways that have functional meaning helps us simplify them and make them easier to remember.

The second simplifying point is that all biochemical pathways are reversible. The gray vertical bar in the middle of this figure is the biochemical pathway of glycolysis going from glucose to pyruvate. There are 10 steps. Some of these steps have a negative delta G. That is, they are favorable in the direction drawn, and some of them have a positive delta G. That is, those steps are favorable in the opposite direction.

But overall, when you sum them up, all of the free energies of the glycolitic pathway, you get a negative number, which means that the pathway of glycolysis is overall thermodynamically irreversible, and progresses from glucose to pyryvate.

It turns out that there's another pathway called gluconeogenesis. That pathway involves taking non carbohydrate precursors, such as pyruvate-- that's just one example molecule-- and converting that precursor to glucose. In other words, gluconeogenesis, in effect, is the reverse of glycolysis.

As I said, the pathway going from glucose down to pyruvate is exergonic. So what about the pathway from pyruvate up to glucose? In order to make the pathway go from pyruvate to glucose, what nature did was invent several biochemical steps that are highly exergonic. That is, what we'll see is they're going to require ATP or some other form of energy input in order to make the entire pathway of gluconeogeneisis exergonic, as is required of all pathways.

So we can indeed convert pyruvate to glucose, but it will require energy input to make the pathway of gluconeogenesis have a net negative delta G. That is, be favorable.

The third thing that actually makes biochemistry tractable is the fact that nature uses only a very limited repertoire of chemical reactions. JoAnne showed us that despite the complexity of this overall metabolic chart, there are only about nine or 10 discrete chemical reactions that nature uses. So, at any given step, for example, in glycolysis, you really only have about nine or 10 options, and of that nine or 10, only about one or two, perhaps three, would be chemically reasonable.

If you know your organic chemistry and these nine or 10 reaction types, you should be able to navigate the biochemical chart with comparative ease.

The fourth point I wanted to make is perhaps one of the most important. It's that all biochemical pathways are regulated. Chaos would result, for example, if you made glucose and at the same time took that molecule of glucose and degraded it. That's an example of what we call a futile cycle. Sometimes futile cycles can be beneficial to a cell. For example, that could be a way of generating heat, but most of the time we want to avoid them.

Because we usually want to avoid futile cycles, nature uses pathway regulation to avoid them. To provide directionality to pathways, what nature does is work thermodynamically irreversible steps into the front and back end of the pathway. Sometimes nature puts in an irreversible step in the middle of a pathway if that pathway has a branch point. That happens with glycolysis, as we'll see.

Sometimes regulation is effected by putting covalent functionalities, such as a phosphate, onto an amino acid on a protein. That modification could increase or decrease the biochemical activity of that protein. Often a phosphorylated protein is highly active, turning on a pathway, and it is dephosphorylated when the pathway needs to be turned off.

A second way to regulate a step in the pathway is by allosteric regulation of the enzymes of

the pathway. In that case, a small molecule will interact with the enzyme in order to increase or decrease its activity. JoAnne taught us about allostery when she taught us how hemoglobin is regulated.

To reiterate, nature uses these regulatable C enzymes at key places and overall metabolic pathways to enable us to be able to achieve the function of the pathway without wasting energy or resources.

The last introductory point I want to make is that all biochemical pathways tend to be compartmentalized, at least in mammalian cells, although it's increasingly becoming obvious that even in bacteria there is some form of compartmentalization. That is, clustering of enzymes for a particular pathway in a particular area of the cell. For example, in a mammalian cell, the mitochondrian is the site of fatty acid beta-oxidation, or break down.

The tricarboxylic acid cycle and enzymes of the pyruvate dehydrogenase complex are also mitochondrial. The cytoplasm is the site where we do fatty acid biosynthesis, most of gluconeogenesis, glycolysis, and the pentose phosphate pathway. Compartmentalisation helps keep the metabolic chart tidy and organized.

With that in the way of an introduction, let's turn to my lecture notes, which I present in the format of storyboards. In the first storyboard, panel A, I give the definition of metabolism as the linked set of biochemical reactions by which we obtain and use free energy. That is, delta G, for life. We use that free energy for a lot of things, but the use is really divide into three areas.

The first is to do mechanical work, the second is to generate concentration gradients, and the third is for biosynthesis. In a few minutes, I'm going to be giving you an example of all three.

Panel B. Biochemists divide metabolism into two subcategories. Catabolism and anabolism. Briefly, catabolism consists of the energy yielding pathways, and anabolism is basically biosynthesis. We use the free energy that we generate through catabolism in order to assemble complex molecules by way of anabolism.

Let's look at panel C. We're going to start 5.07 with a discussion of catabolism. That is the energy yielding pathways. By way of definitions, a reduced molecule is one that is abundantly supplied with electrons. Examples are carbohydrates, fats, and proteins. These are typically our foods.

The process of catabolism involves finding a way to liberate the electrons from those reduced

substances and transfer those electrons to mobile electron carriers, such as NAD-plus to form NADH, or NADP-plus to form NADPH.

The process by which electrons are removed from a molecule is called oxidation, and the oxidation products are, for example, carbon dioxide that we breathe out, or in some organisms, lactate, or other simple molecules that are excreted. Simple, that is, compared to the complex reduced molecules that we consume as food.

NADH and FADH2, molecules that JoAnne taught us, are what I'll refer to as mobile electron carriers. They can usually move around inside the cell, although sometimes they're embedded within enzymes. That is usually the case with FADH2.

We consume an enormously large number of reduced substances due to the complexities of our diets, and catabolism involves taking the electrons out of this enormously vast array of substrates and transferring those electrons to a small number of reduced electron carriers. For example, NAD or flavins.

In the process of respiration, which we'll come to later, the electrons are further transferred from the reduced electron carriers all the way to molecular oxygen. The reduction of molecular oxygen is a highly exothermic reaction. We're going to be able to use the energy that's generated by oxygen reduction in order to make ATP, and to do some other important biochemical activities.

Now I'm going to introduce a physiological scenario and use it in order to introduce the pathway of glycolysis. In class at this point, I usually ask a student to stand up and sit down. As you can imagine, being called on in class creates more than a little bit of anxiety in the student.

Let's look at panel D. The signal to stand up and sit down is processed by the brain, and an electrical signal then goes by the nerves to the muscles enabling the student to stand up. The anxiety of being called on by the teacher in class results in a nervous excitation of the adrenal gland, specifically in the adrenal medulla, which releases epinephrine.

Epinephrine is also known as adrenaline. It goes to the muscles as well as other organs of the body, as we'll see later in 5.07. And the epinephrine will interact at cell membranes by way of transmembrane receptors in order to turn on pathways of catabolism, in order to generate the ATP that's needed to help the student deal with this stressful situation. This is sometimes called the fight or flight response.

At this point in the class, if I really wanted to make my point and have it transferred to every student, I'd announce a pop quiz. The announcement of a pop quiz would cause kind of this cold feeling throughout your gut. That's actually the feeling of adrenaline preparing your body to deal with the stress situation, in that case, of the quiz.

Let's look at panel E. As the scenario progresses, let me introduce a few biochemical players. Glycogen phosphorylase, glucose, glucose six phosphate, and glucose one phosphate.

In panel F we see a muscle cell. The epinephrine in the blood is only going to reach a concentration of about 10 to the minus 10 molar. That's a very, very low concentration. The epinephrine is going to interact at the beta and alpha adrenergic receptors in the muscle cell membrane.

This interaction results in the activation of a kinase, that is a molecule that transfers a phosphate group. And that kinase, which is called SPK, for synthase phosphorylase kinase, phosphorylate serine 14 on glycogen phosphorylase. Phosphorylation activates glycogen phosphorylase, which will then begin to degrade glycogen-- the polymeric storage form of glucose in us, that is, mammals-- to produce initially glucose one phosphate.

Glucose one phosphate will then go through a number of transformations and eventually be converted into other forms of glucose and then other molecules that will generate energy. In a nutshell, this stand up, sit down scenario results in the generation of energy in a matter of seconds which is one of the things that we use metabolism for.

Another thing I said earlier was that you use metabolic energy to generate concentration gradients. And it turns out that generation of concentration gradients is absolutely critical for muscle activity. The sarcoplasmic reticulum in our muscle cells must accumulate calcium and release it at precisely defined moments in order to enable the muscle to be able to work. That concentration grading of calcium has to be created, and it's created with the energy that we get from metabolism.

Again, we'll see how calcium gradients help boot up energy generation in the last lecture, which deals with pathway regulation.