JOHN ESSIGMANN: Let's Look at Storyboard 17, Panel A. So far in 5.07, we've looked in detail at carbohydrate catabolism, we've seen that the complete catabolism of a molecule of glucose by way of glycolysis, pyruvate, dehydrogenase, and the TCA cycle results in the generation of about 36 to 38 molecules of ATP.

At this point, we're going to turn to catabolism of another metabolic fuel, lipids. As we'll see lipids, because they contain more energy per gram, because they're more highly reduced than carbohydrates, will produce much more ATP pundit weight than carbohydrates. For example, if we were to metabolize hexanoic acid, the six carbon hydrocarbon, the same number of carbons as glucose, we'd get over 50 ATPs rather than about 35 ATPs per molecule, which we would have got from glucose.

Now let's look at Panel B. Lipids have many roles in biological systems. The first that will be relevant to this lecture is that there are primary energy reserve. In fact about 80% of our stored energy is in the form of lipid. Second, as JoAnne taught us, lipids are key components of biological membranes, and thus, they contribute in a major way to the compartmentalisation that's critical for normal biological functions.

And the third role is that some lipids are signaling molecules. The one I've pictured here is Estradiol. While Estradiol may not look like a typical lipid it actually is. Indeed, it's made by a lipid biosynthetic pathway that starts with Acetyl Coenzyme A. And we'll see later that Acetyl CoA also serves as the precursor for the canonical lipid fatty acid.

Fatty acids are the classic lipid. They're hydrocarbon chains that are fully saturated or contain a small number of double bonds and sometimes branches. Sometimes the fatty acid moiety is esterified to the backbone of glycerol. If you have three fatty acids on a glycerol backbone, one to each of the hydroxyl groups, that's called a triacylglyceride. That's our primary storage form of energy.

With phospholipids, one of the hydroxyl groups of the glycerol backbone is esterified to either

phosphate or some kind of decorated phosphate where the decoration could be a sugar or some other moiety. As was seen in JoAnne's lecture's, phospholipids are the key building blocks of biological membrane.

Now take a look at Panel D. The rest of this lecture will deal with the details of how fatty acids are broken down to carbon dioxide with the intermediate production of reducing equivalents in the form of NADH and FADH-2 and ultimately energy equivalence in the form of ATP. Cells can acquire lipids directly from the blood where typically they're transported by albumin. They can come directly from our diet or from other organs or from breakdown of triacylglycerides within our cells.

We're going to be looking at four steps in fatty acid catabolism. The first step involves the appearance of the fatty acid in the cytoplasm of the cell. The fatty acid can come in either from breakdown of a triacylglyceride stored in the cytoplasm, or the fatty acid could appear from transport across the membrane from the blood. In the cytoplasm, the fatty acid, which is technically a carboxylic acid, will be thioesterified to form a fatty Acyl Coenzyme A.

The second step of fatty acid catabolism involves the transport of the fatty Acyl Coenzyme A ester into the mitochondrion, which is the site of fatty acid oxidation. The third step in fatty acid catabolism involves the actual oxidation process itself. The series of reactions is called beta oxidation. Beta oxidation results in the conversion of the carboxylic acid starting material to Acetyl Coenzyme A.

There can be several fates to the Acetyl CoA produced by beta oxidation. But the one we're going to be looking at is its entry into the TCA cycle, where the Acetyl CoA is metabolized to carbon dioxide with the generation of reducing equivalents. Those reduced electron carriers have the potential to be converted into energy currency in the form of ATP.

The fourth topic or stage in fatty acid catabolism that we'll deal with concerns specialized endings of the catabolic pathway. The first problem that we'll look at concerns the fact that some fatty acids have an odd number of carbons in them, whereas the classical fatty acid beta oxidation system was primarily designed to process fatty acids with even numbers of carbon units.

The second problem that we'll look at as an ending of fatty acid oxidation concerns the fact that some of the fatty acids in our diet have a double bond that is either in the wrong stereo chemistry or is in the wrong place to enable easy metabolism. Nature has worked out ways to

reposition the double bond to facilitate the entry of the molecule into classical beta oxidation schemes.

Let's look now at Panel E. The first step in fatty acid catabolism involves thioesterification of the carboxylate residue of the fatty acid. We're going to see in a couple of minutes that placing a Coenzyme A moiety on the carboxylate is going to enable chemistry at the beta carbon. Without the Coenzyme A group, chemistry at the beta carbon would be impossible.

The enzyme involved is called Fatty Acyl Coenzyme A synthetase, sometimes called ligase. And it additionally goes by the more common name Thiokinase. This enzyme uses ATP to adenalate the carboxalate residue. And then it allows Coenzyme A to replace the AMP residue with the resulting product being a fatty Acyl Coenzyme A. This reaction happens in the cytoplasm of the cell. Beta oxidation however, is going to occur in the mitochondrial matrix. So we have to find a way to get this fatty Acetyl Coenzyme A into the mitochondrial matrix.

Let's go now to Storyboard 18, Panel A. Panel A shows the cytoplasm, the mitochondrial outer membrane, the intermembrane space, the inner membrane, and the mitochondrial matrix. As I just said, the matrix is going to be the site at which beta oxidation occurs. The intermembrane space contains a small alcohol called Carnitine. And the mitochondrial outer membrane contains an enzyme called Carnitine Acyl Transferase I or CAT-I.

CAT-I removes the Acyl group from the Fatty Acyl Coenzyme A in the cytoplasm and transfers it to the alcoholic residue in the center of the carnitine molecule forming an ester of the fatty acid with carnitine. This ester is delivered to CAT-II, which is embedded in the inner membrane on the matrix side.

CAT-II will then transfer the Acyl functionality to a Coenzyme A, restoring the fatty Acyl Coenzyme A molecule. Thus, CAT-I and CAT-II working in a concerted way, result in the effective transfer of a fatty Acyl Coenzyme A from the cytoplasm into the mitochondrial matrix, the site of beta oxidation, which will be our next step.

Let's now look at Panel B. This panel shows an inset with the mitochondrial inner membrane, the electron transfer complex, and ETFP, the electron transferring flavor protein, which is going to be the entry point of electrons from the initial step of oxidation of the Fatty Acyl CoA into the electron transport chain. We also see in this panel, the fatty acid polmitate the C-16 Straight Chain Carboxylic Acid. The hydrogen beta to the Coenzyme A ester is relatively acidic, therefore this hydrogen will be taken off to form an alkene. And the hydride will be

transferred from the beta carbon, the third carbon from the right.

Those electrons are transferred to a flavin in the electron transferring flavor protein, ETFP. Eventually, those electrons are transferred to Coenzyme Q to form the reduced form of Coenzyme Q. Those electrons then travel along through the electron transport chain. The Organic product of this reaction is a trans enoyl Coenzyme A.

Now let's take a look at Panel C. In the next step, water is added to the 3 Carbon of the enoyl Coenzyme A. Resulting product is a 3 Hydroxy Fatty Acyl Coenzyme A. We've seen oxidation of alcohols that looks something like this many times. For example, malate being oxidized by malate dehydrogenase to oxaloacetate.

And as we have seen before, the hydroxyl group is converted to a keto functionality. Hydride transfer goes to NAD+ to form NADH. The enzyme that does this conversion is 3 Hydroxy Fatty Acyl Coenzyme A Dehydrogenase. At this point, we have generated one FADH-2 and one NADH in the overall process of the beta oxidation scheme.

The 3 Keto Acyl Coenzyme A is now set up to release a first molecule of Acetyl Coenzyme A. The enzyme beta ketothiolase has a cystine on it. The thiol of the cystine will attack the carbon that has the keto group and release Acetyl Coenzyme A. The residue is a thioester in which the residual 14 carbons of the polmitate that we started with are now connected to beta-ketothiolase.

Lastly, beta-ketothiolase will transfer this residual 14 carbons to a Coenzyme A molecule, forming the Fatty Acyl Coenzyme A that will be 14 carbons long, that is, it's two carbons shorter than the 16 carbons of polmitate that we started with. Overall, this process is called beta oxidation.

The system is now set up to allow the 14 carbon molecule to go to 12 to 10 and so on, until the entire 16 carbon hydrocarbon has been reduced through seven rounds of beta oxidation to eight molecules of Acetyl Coenzyme A. If these eight molecules of Acetyl CoA are further oxidized by the TCA cycle, you'll get 96 ATP molecules.

And of course, along the way, in each round of beta oxidation, you will also produce seven FADH-2s. The seven FADH-2s will be converted into 14 ATPs. You will also get seven NADHs, and they will be converted into 21 ATPs. So the full conversion of the 16 carbon hydrocarbon polmitate will result in a total of 131 ATPs.

In order to put together a full balance sheet, however, keep in mind that we needed to use several ATPs early in the process in order to prime the system. That is Fatty Acyl Coenzyme A synthetase used 2 high energy phosphate bonds in order to prime the fatty acid for production of the Coenzyme A intermediate that's necessary for beta oxidation.