>> Steve Langjahr: It's November 21st, 2016. This is Lecture 26. We finished with the urinary system and tomorrow's lab is devoted to urinalysis. Today's topic takes us a bit away from that system. It's entitled Functional States of Metabolism, in other words, nutritional aspects of metabolism which talks about essentially the fate, the dietary fate of nutrients which we consume in the food that we eat. That said, every 24-hour day is essentially divisible into two very distinct phases or periods. The first phase is called the absorptive state, and this is the time where nutrients are actually being absorbed from digestion and they're entering the circulatory system by way of the gastrointestinal tract. The absorptive state obviously occurs after meals, after breakfast, after lunch, after dinner. And if you never stop eating, then you're in the absorptive state all the time. But most of us take a break from eating and therefore we enter a postabsorptive state which means what it says, these are the minutes or hours after a major meal, four hours after breakfast, four hours after lunch, about four hours after dinner. And obviously, all throughout the night unless you get up in the middle of the night and raid the refrigerator. So basically, these are fasting periods. And the activities during the postabsorptive state, very different, the old– the overall strategy, the overall functions are quite distinct. And we'll now move into a description of each of these states with respect to the objective, with respect to the chemical effects that are taking place. So first, the absorptive pathways, what's going on during the absorptive hours? Obviously, the activities here are concerned with meeting the immediate energy needs and then storing excess calories in one way or another. And that really is not terribly different from your own household income. What do you do when you get a paycheck? Well, you pay the bills. And the extra money, you're supposed to put where? You're supposed to put into savings. So, whether you do that or not is really an individual choice, but the point is the absorptive period is like that. We pay the immediate bills, that is we use the resources to meet energy demands, and then we store the excess calories in one way or another. So with that said, what are the individual nutrients that are being absorbed at this time? You know, they are basically derivatives of carbohydrates, proteins and fats. So, let's take up first what are the fates of dietary carbohydrates? We consume carbohydrates as pasta and starch and breads and raw sugars. But regardless of the cuisine or the form of these carbohydrates, they all are converted pretty quickly into glucose. So, the question really becomes what happens to glucose during these hours known as the absorptive periods? First of all, do most cells have a craving, a demand for glucose all the time? Yes. And what do cells use glucose for? Well, they use it for the Krebs cycle, glycolysis and obviously for the production of ATP. And the byproducts of water and CO2 are naturally associated with the breakdown of glucose, fine. So, much of the glucose goes to the immediate production of ATP. Is there often extra glucose, and what then does the extra glucose change into? The liver, you're absolutely right. The liver takes glucose and hooks it together into very complex polysaccharides especially mainly glycogen, and the liver can store a sizable amount. And also, muscles can produce and store glycogen too, especially the so-called fast-twitch fibers which we've dealt with. But even though that's all true, the ability to store glycogen

is limited. The liver has a limited capacity to produce and store glycogen. So, what then happens to glucose beyond that which can be converted to glycogen? Well, here's the interesting thing, a glucose molecule can be converted into a glucose molecule. And glucose molecule can also be converted into what? And what do you know you can make if you have three fatty acids and one glycerol? A triglyceride, a TG, a fat. And those then can be stored in the liver where they're first made. But even the liver has a limited capacity to store fat. So, what happens to this fat that might be produced in the liver? It ends up in the blood. And what cells will take it out and store indefinitely? Obviously, adipose. So in summary, what happens to glucose during the absorptive period? Some is used to make ATP. The rest is used to make glycogen. The rest is used to make fat. So, this is hardly a shocker because can you get fat by eating a lot of carbohydrates? Of course, common knowledge. So, this is simply the chemistry behind that familiar observation. Item B, what happens to fat during the absorptive period? Remember, fat comes to us in many forms, certainly in the form of mayonnaise as an example. But when all is said and done, most fats are TG, what's that? Triglycerides, triglycerols. And these can be converted into fatty acids and glycerol. And these of course can enter the citric acid cycle to make, as you know, ATP. But why does it say here this is rarely resorted to immediately? Why during this time our fat is not likely to be used for energy, we have plenty of what? Glucose. So, fats are rarely used for energy during this time. What time? The absorptive period. Because usually, that demand is being met by the use of glucose. So even though this is possible, it rarely happens during this time. And so, what happens to most of the fat that is part of our breakfast, lunch or dinner? Most of it is stored as fat. So fat is not changed, but rather simply put away into adipose cells. What's the third predominant organic ingredient in the food that we eat? Obviously, protein. And protein is not absorbed as such, you know, it has to be broken down. And what are the building blocks of protein that are absorbed? Amino acids. So the question now becomes what happens to amino acids during the absorptive periods of the day? Do most cells have a need for at least some amino acids? Yes. Because most cells are engaged in what process which uses and depends on amino acids? Protein synthesis. But usually, that demand for amino acids is pretty easily met. And therefore, the question becomes what does the body do with excess amino acids? Is there a way for the body to store amino acids as such? The answer is yes, but not so much. In other words, liver and muscle tissue has the ability to store some amino acids in what we call an amino acid pool, meaning a basic reservoir which can be tapped during periods of protein synthesis. But here's the fact, most of our diets contain way more amino acids than we can use for what? And way more that can be stored. So then, the question is what happens to those amino acids beyond the level which we can use to make protein or even store away in the liver or muscles? Basically, the body deaminates these amino acids. Now, this is a typical formula for an average or typical amino acid. Notice it has in amine group, NH2, a carboxyl group COOH, and the rest of the amino acid may vary, as you know. There are, remember, how many different kinds of amino acids? Twenty. And so, they

all vary, but they all have this basic chemistry. So then, what does it mean to deaminate? To deaminate means to take that off. And what apparently is added in its place is O, which is what?

>> Oxygen.

>> Steve Langjahr: Oxygen. So when we deaminate an amino acid, we produce what you can see here a typical what? Keto acid, because of this double bonded oxygen at that location. Now, you may not have heard the word keto acid, but you've certainly heard of the word pyruvic acid which is as it turns out this particular keto acid. And pyruvic acid is familiar because as you recall, it's the gateway into the citric acid cycle. And so, can we get energy from this kind of keto acid or others like it? Yes. In other words, this pathway is quite feasible because the keto acids can be processed through the citric acid cycle. Thus, making lots of what? ATP. But again, is this is likely to happen at this time? Is this method of making ATP the easiest and most likely during the absorptive period? No. Why not? What do we have plenty of which is much easier to use at this time?

>> Glucose.

>> Steve Langjahr: Glucose. So even though this is possible, it's not likely to occur simply because there's plenty of glucose, and this is more difficult and therefore, this is not likely to happen at this time, not likely to happen during the absorptive period. So, what then happens to these keto acids if they're not going to be metabolized and used through the citric acid cycle? Interestingly, the keto acids like pyruvic acid can be formed into what?

>> Fatty acids.

>> Steve Langjahr: Fatty acids. And then, you only need a what? You only need a glycerol that's hanging around. And once you have three fatty acids and a glycerol, you have everything you need to make a triglyceride which will end up being stored, as you know, as fat in adipose cells. So, this is rather shocking to a lot of people because there's this notion that if you eat a lot protein, you're going to build what? You're going to build muscle, that's nonsense. If you eat a lot of protein, the excess amino acids will be what? Deaminated, converted to keto acids, converted to fatty acids ending up as fat. So bottom line, do you have to eat fat to get fat? No. Can you get fat from glucose? Yeah. Can you get fat from fat? Yes. Can you get fat from eating too much protein? Yes. So, it's kind of sad, but yet it's quite logical because what is the way in which the body stores most of its calories? Fat. And so, this is certainly the way it's evolved, the way it's designed. Now, returning to our story, we said that taking the amine group off in amino acid was called?

>> Deamination.

>> Steve Langjahr: And so, we plugged in oxygen in the place of that NH2, but what happens to that NH2? The amine group picks up a hydrogen easily

enough and becomes NH3 which is a pretty nasty molecule, what's the name of NH3?

>> Ammonia.

>> Steve Langjahr: Now, ammonia is the stuff you use to clean windows or floors with, it's pretty toxic, and the body simply could not tolerate a buildup of ammonia. So, what's its solution to this? What happens to the ammonia which develops as a result of deaminating amino acids? Well, you take two ammonias and combine them with CO2, there's plenty of that, you can create this molecule which is called urea. Urea is much less toxic than ammonia and ends up, you know, being lost in the urine. So, this is a method of detoxifying ammonia producing instead urea which is more easily handled, more easily excreted from the body. So, this is a complicated element here. But to back up, we don't absorb protein, we absorb amino acids. Are those amino acids used immediately to make protein at least in some cells? Yes. What if we have amino acids far in excess of our demand for protein synthesis? What happens to the rest? Some will be stored as amino acids, but the far majority will be what, deaminated, converted into keto acids, converted into fatty acids, therefore ultimately stored as fat. So, those are the realities of the absorptive period. To back up, carbohydrates used immediately for energy or converted into glycogen, and then the excess converted into fat. Fat typically is stored as fat and even amino acids can be stored as fat once they're what, deaminated, changed into keto acids, changed into fatty acids. So as we leave this period of time, the so-called absorptive period, what is the goal or strategy to repeat? The goal has been to what? Meet immediate energy needs. And then, do what with the excess?

>> Store.

>> Steve Langjahr: Store. And what were the two ways in which storage could be achieved, the G word?

>> Glycogen.

>> Steve Langjahr: Glycogen, or the F word, fat. So, fat and glycogen are the two forms of potential energy now which will be consulted and used in the postabsorptive state. I mean after all, what is the definition of the postabsorptive state? What is not happening in the postabsorptive state is you're no longer absorbing anything, right, because you're fasting voluntarily or involuntarily. And so, the real problem here, the goal you could say is to maintain blood sugar at all cost. And there reason for that is simple, the brain is rather fussy, it insists on and prefers what substrate?

>> Glucose.

>> Steve Langjahr: Glucose. So the strategy, the metabolic goal of the postabsorptive state is to maintain blood sugar, which is not easy to do because you're no longer receiving anything. After all, this is the what? This is the postabsorptive state. So with that goal in mind, how can that goal be met? What are

the resources for maintaining blood sugar during these lengthy periods of time? What's the easiest resource to get glucose in the postabsorptive state?

>> Glycogen.

>> Steve Langjahr: Glycogen. Why is that easy? What is glycogen? It's just a bunch of what?

>> Glucose.

>> Steve Langjahr: Just a bunch of glucoses. And so, all you've got to do is cut it up and you've got a lot of glucose. The name of that process that is the breakdown of glycogen is called glycogenolysis. What organ is the best source for glycogen at this time? Liver. And so, the liver will be involved in the early minutes of the postabsorptive state and indeed the liver can break down glycogen thus elevating what, elevating blood sugar. This is not a new fact. We spoke of that before. What do runners do the night before in order to ensure their endurance in a marathon event? They carb up. Therefore, they really stuff their liver with what? Therefore providing a source of blood sugar even as they run during a postabsorptive period. Do muscles produce glycogen? Yes, but they don't break it down to maintain blood sugar, they break down their glycogen to use for their metabolism. All they add to the blood is lactic acid. And you know that some of this ends up back in the liver and some of that can be manufactured again into glucose. But to put a fine point on this, where does most of the glucose come from in the early moments of a postabsorptive period? Liver. And is that limited or unlimited? Well, obviously, it's limited, but it's limited by the amount of glycogen that you have. And nobody can put a number on that, but we'll try. We'll say anywhere from 8 to 12 hours, and then this is what? Gone. So to back up, where does glucose come from in the early hours of a postabsorptive period? Liver. What's next? If we're beyond eight hours, if we haven't eaten for eight or nine or 10 hours, the glycogen in the liver is gone. So, what is the next apparent resource? What can we tap once the liver glycogen is gone? Do we have a fair amount of adipose on hand? Probably so. And the breakdown of adipose is called, there's the word, lipolysis. Adipose is found– you know where it's found, we don't need to go there. And adipose is made of triglyceride. So basically, it consists of a glycerol and three what, three fatty acids. Glycerol is itself already a carbohydrate. So as far as the liver is concerned, glycerol can easily be made into what? Glucose. And that adds to and supports blood sugar at this time. Remember, let's not forget, what's the goal of the postabsorptive state?

>> Maintain.

>> Steve Langjahr: Maintain what?

>> Blood sugar.

>> Steve Langjahr: Blood sugar, for what sake, for what purpose? The brain. The brain is very fussy when it comes to its source of energy. So, this provides some glucose. The thing is though fatty acids cannot, cannot be made into

glucose. They can be used by most cells because most fatty acids can be changed into acetyl, what, acetyl-CoA which you know is a substrate that immediately proceeds and enters the citric acid cycle. So, can you get energy from fatty acids? Yes. Not glucose, but at least you can generate acetyl-CoA which then can be processed through the Krebs cycle, and a lot of energy can come from that. Most cells have the ability to use fatty acids in this way. But here's the problem. When we're breaking down a fat molecule, we get how many glycerol?

>> One.

>> Steve Langjahr: And how many fatty acids?

>> Three.

>> Steve Langjahr: So, we have a ton of acetyl-CoA waiting in line so to speak to get into what pathway? Waiting in line to get into the Krebs cycle. Now, don't say that on the exam, but I think it's useful imagery. So if I'm a fatty acid and I'm waiting to get in line because what's the problem, the problem is there are a limited number of enzymes. So, this process can only go so fast. And that acetyl-CoA which cannot be processed or metabolized immediately is converted into what are called ketones. Again, this process occurs in the liver. Now, maybe you've heard the term ketones, maybe not. But ketones are organic molecules which essentially are one of the three, which I'll put up here, you don't need to memorize this, but I want to throw them up on the board. One ketone is called acetone, another ketone is called beta-hydroxybutyric acid, and the third ketone is called acetoacetic acid. Now, I said you don't need to memorize these, but why did I put them on the board? Three– These are the three ketones. Two of the three are obviously what? So if we have this developing accumulation of what?

>> Ketones.

>> Steve Langjahr: Ketones, what threat to pH would you imagine or foresee if these are not eliminated someway? Obviously, there's going to be a buildup of what? Acid. And in fact, some of you may know that that's referred to as ketoacidosis, obviously attributed to the breakdown of adipose also known as lipolysis. So lipolysis, even though an important contributor to blood sugar and helping to maintain survival during the postabsorptive state does run the risk, runs the risk of producing inadvertently what? And two of the three ketones are? Therefore, perhaps jeopardizing pH homeostasis, and therefore naturally dangerous in that regard. Now, the third possible source of energy during the postabsorptive state clearly could be or may be protein. And what's the word for breaking down protein? There it is, proteolysis, which really means the breakdown or metabolism of amino acids. Amino acids cannot enter the Krebs cycle as such until they've been– here's the word, until they've been what, deaminated and converted as we've said to keto acids, then they can and do enter the citric acid cycle where, of course, they can be used to make ATP. Don't forget, when we deaminate an amino acid, we also get ammonia and ammonia is converted thankfully into what, into urea. Some amino acids

incidentally can be changed into glucose, but most are not. Most are converted into keto acids. The process is deamination. So with all that said, can proteins provide an energy source in the postabsorptive state? Yes. Can fat? Yes. And so with what we've laid out on paper here, it makes it seem like what is the first resource in the early moments of a postabsorptive episode? Where do we get energy from in the first hours of a postabsorptive state? Breakdown of glycogen converted immediately into glucose. What comes 8 to 10 hours later? Lipolysis. And it makes it seem that protein or proteolysis occurs after lipid, but that's not true. It's not A, B, C. It's A, and then what, B, C. A, what, B, C. These occur simultaneously. And that should be a bit distressing because is it OK to break down fat for energy in the postabsorptive state? Yes, that's what fat is for. But, is it OK to break down protein for the sake of energy? Not OK. Why not? Where is this protein coming from? Do we have just protein laying around in a pile that's called protein use in case of emergency? No. That protein is what? Well, what are some functions of protein that you know are important and therefore not amenable to sacrifice? So, what are protein– are enzymes proteins? Are antibodies proteins? Do muscles contain protein? So when we talk about proteolysis, what is the source that's being broken down for the sake of these amino acids? What are we breaking down? We're breaking down enzymes. We're breaking down antibodies? We're breaking down muscle? Does this sound good? And so in terms of starvation, which is what we're talking about, what is the cause of death in starvation? It's typically the result of this process which is called proteolysis. Why do people die when they're starving? Well, you could say it's because they don't have energy, but really they have dismantled what? They've dismantled protein. And so it's tempting to say, oh, you're starving? Well, here, have a Big Mac. That's not going to help. Why not?

>> They don't have the enzymes.

>> Steve Langjahr: They don't have the enzymes to break it down. In fact, they often can't often swallow it. Why not? Because they have no muscle to get it down there. And even it gets down there, there is no enzyme to deal with it. So people who are on the brink of death, and I'm talking about skeletons practically, are very fragile, very brittle because they have a massive amount of proteolysis and they often die from infection or respiratory failure. Why would they die of respiratory failure? Well, the diaphragm just won't work. Why not? I mean, that's a muscle. So, they have massive muscle weakness. They have immune problems because of the lack of antibodies. They have a whole host of enzymatic issues because enzymes naturally are also made of protein. So back up, what is the first and logical resource for energy in the early moments of a postabsorptive period? Glycogen. Then comes what? Adipose and protein. So with this, it's important to realize that our starvation diet is healthy. You say, well, I've got a wedding coming up, I'm just going to starve myself for the next two weeks. I'm going to lose massive amounts of weight. Well, good luck. You are going to lose some adipose, but you're also going to lose some valuable protein. So sensible dieting certainly includes caloric restriction, but also you

want to include something in your diet namely what, namely protein to replace that which is being broken down unavoidably by proteolysis. Certainly, an interesting question comes from this, how long can you live in a postabsorptive state? And certainly, the answer to that depends upon how much what, how much adipose you have. Are there people that are carrying around 600 pounds of adipose? You can go to the TV and find those people. They have a show. Don't they have a show? I don't watch it, actually. But I think it's– I went through it quickly because– please. But it was called My 600-lb Life, and how much fun that can be. But I'm only half joking, how long can you live in a postabsorptive state depends upon how much what, how much adipose you have. Nobody has really done any real definitive studies on this. Most of our knowledge comes from people who've been stranded. What do I mean stranded? Not able to have any access to what, food and only access to water. And there are cases of people living four and five months without what?

>> Food.

>> Steve Langjahr: Four and five months without any food, only H2O. And obviously, they're living on their what, their adipose and their protein. So, those are interesting facts, but they simply point to the notion that we started with that what is fat for? It's not for padding. Fat is for these eventualities here namely the postabsorptive states. Now, the processes that we've outlined here are designed to produce and make available, G word, what? Glucose. And remember, what organ is fussy or otherwise insist on glucose in the postabsorptive or any other period of time?

>> Brain.

>> Steve Langjahr: Brain. So, there is a process that is a concept called gluconeogenesis, which deserves a definition gluco, glucose, neo means new, N-E-W, and genesis means to create. So, gluconeogenesis is making what? Glucose, from something that wasn't glucose or wasn't carbohydrate to begin with. In other words, gluconeogenesis is postabsorptive glucose formation from what? Non-carbohydrate. Is glycogenolysis then gluconeogenesis? No, because glycogen is itself already a CHO. What's CHO?

>> Carbohydrate.

>> Steve Langjahr: So, what is gluconeogenesis? The two things on this page marked now with an asterisk, this glucose came from fat, this glucose came originally from protein. So, these are true examples of gluconeogenesis. Now, these then are the transformations and the metabolic goals and activities in the postabsorptive state, but there are some interesting and rather amazing adaptations that kick in with prolonged starvation, strategies for survival and here's one. One day postabsorptive, that means one day without food. One day without food, the maximum amount of glucose that can be made by gluconeogenesis amounts to only what, 180 grams of what, grams of glucose. Now remember, this is glucose from gluco, what gluco? Neogenesis. Why is glycogen not part of this story? This is one day. This is 24 hours later. So, all of the

glucose is coming from this or this. And despite how much fat you might have, there's a limit to how quickly it can be broken down. So believe it or not, the maximum production of glucose by gluconeogenesis during this 24-hour postabsorptive moment here is 180 grams per day. OK. So, what? Well, the fact is that a single glucose molecule can only produce four calories, that's C-A-L with a capital C. And so if you do the math, 180 times 4 actually produces the number what, 720 calories for what, for 24 hours. Now, that may or may not be disturbing to you, but here's the basic reality. BMR, which is a new acronym for you, BMR stands for Basal Metabolic Rate, not basic, what?

>> Basal.

>> Steve Langjahr: Which means the minimum amount of energy needed to keep you alive, that means laying on a couch doing nothing but breathing, so– and some people do do that actually. But laying on the couch doing nothing but breathing still requires what in any average person, still requires a minimum of what 1,000, maybe as much as 2,500 calories per day. So obviously, there's a mathematical shortfall here, right? In case it's not clear, how many glucose molecules, that is how many grams of glucose can be made in a 24-hour day after one day postabsorptive, only what, 180 times 4, what? So obviously, there is a problem. We can't make enough glucose to survive one day postabsorptive. So, here's what happens one day postabsorptive. Most tissues, except CNS, what's that?

>> Central nervous system.

>> Steve Langjahr: Most tissues will shift, that is they'll turn away from glucose and begin to use what is plentiful, and those of course are fatty acids from the breakdown of fats. And this shift, shift away from what, away from glucose and onto fatty acids is called by this nickname, it's called what? Glucose sparing. And what is the glucose being spared for? In other words, where do most of these glucose molecules end up being processed or used?

>> Brain.

>> Steve Langjahr: Brain. And the other tissues shift away from that and start to use instead fatty acids. Why is this good? Well, it keeps the brain happy. And when the brain is happy, you're happy. What's this called? This is called– here's the word, glucose sparing. The brain cannot shift away, but other tissues that can use fatty acids do use fatty acids. And by that, I mean they use the acetyl-CoA and essentially depend on the citric acid cycle which is receiving acetyl-CoA from the breakdown of fats. And so as a result of glucose sparing, most of the glucose that's produced by gluconeogenesis is available to and used by the brain, nice. Then, what if you've gone five days without eating? This is an interesting and amazing adaptation that I've never exploited because I've never been without food for five days, luckily, but there are people that are forced into this scenario because of being stranded at sea or whatever, unavailable food supplies. And so, what happens in this dire situation is that the central nervous system begins to metabolize what?

>> Ketone.

>> Steve Langjahr: Ketones. Now, let's back up. Ketones were last mentioned as a byproduct of lipolysis. Ketones we've said include acetone, beta-hydroxybutyric acid, and acetoacetic acid. We suggested that these are basically not wonderful molecules, right? Because at least the latter two can contribute to acidosis, something that is often then called ketoacidosis. Why is this sudden change valuable? Why is it nice to see the brain using ketones? Where have these ketones been going up to now? Well basically, they've been going into the urine and the kidney is trying its best– [inaudible] teleology, using its best efforts to eliminate what? Ketones. But now in this situation, the brain has started to develop enzymes which will now actually metabolize, that means use ketones for energy, and why is that strategy valuable? What's the physiological significance of this five-day adaptation? If the brain is using ketones, then obviously it's reducing its need for and dependency on what?

>>Glucose.

>> Steve Langjahr: Glucose. Does that take some load off? Does that reduce the burden a bit? And then after all, if we're using ketones, we're less likely– that is we're going to minimize the demand on– or the breakdown of protein. And is that a worthwhile development? Are we happy to see that protein catabolism has been minimized? If you break down protein, what are you going to cut into, what are you sacrificing, what is diminishing? Your muscle mass, antibodies, enzymes and so forth. So, this really helps minimize the damage done to protein catabolism. And if you're using ketones for energy, then these things are not going to be building up in the blood, are they, because we're using them for energy. And therefore, we minimize the development of the tendency for what? Acidosis. And going back to Wednesday's lecture, what's so bad about acidosis? Can acidosis kill you? It does. It causes C-O-M-A, what's that? Coma, unconsciousness. People die from acidosis. And naturally, this alleviates– it doesn't eliminate, but alleviates that tendency. So as we finish this topic and move into our next one, the body is quite clever at using fats and proteins for energy source and especially five days, it actually starts to use ketones as an energy source which reduces the demand on glucose, it reduces the tendency to break down protein and therefore, reduces the buildup, the potential buildup of acids which could be life-threatening in itself. So OK, before moving on, we just described two states, two metabolic periods. When we have plenty of food, that's called the absorptive state. When food is not available or when we choose not to eat, that's called the postabsorptive state. The absorptive state is all about using what calories we need and then doing what? Storing the rest, storing it as glycogen and much more in the form of fat. Then the postabsorptive state is designed to what? Maintain blood sugar, and that means utilizing the things that have been stored during the absorptive state. So clearly, this is analogous to economics, right, economics. When you have plenty of money, what do you do with that money? You spend– OK, you spend some of it, then you put the rest into a savings. Why do you put it

into savings? Because you know you're going to run out of money sooner or later. And so, you have that to use during the periods of lack of money, right? So, that's a nifty and kind of easy analogy. Much more scientific would be to ascribe these designations. One of these periods is called an anabolic state. One of them is a catabolic state. Anabolic states are those where molecules are being built up. Catabolic are those where molecules are being what? So, which of these states compares or represents an anabolic state? OK, multiple choice. Is it absorptive or postabsorptive? Which are molecules being built up and put away? Absorptive. Which is a catabolic state? Postabsorptive. If you want an even simpler analogy, which is a savings plan, which is a spending plan? Savings plan is what?

>> Absorptive.

>> Steve Langjahr: Absorptive. Spending plan?

>> Postabsorptive.

>> Steve Langjahr: Postabsorptive. So, those are useful analogies to what we've just said. And although those are now clear, clear distinctions and clearly very different strategies and goals, the question that we haven't even addressed is how does the body know that it's in an absorptive state? How does it know that it's in a postabsorptive state? What are the signals which cause these transitions from absorptive strategy to postabsorptive strategy? What is the control over these metabolic states? And the answer is basically hormones. Hormones are the signals which respond to and have an effect on these transitions. So by definition, hormones that are directly involved in these transitions are the ones we'll focus on starting with one that everybody knows by name, insulin. So just in case you don't know about insulin, insulin is a small protein, that is it's a polypeptide secreted by the pancreas, specifically the beta cells of the pancreas, and is important, that is its main action is to escort, to stimulate glucose entry into cells, essentially taking glucose from the blood and putting it into cells. In other words, it facilitates the uptake of glucose from the blood into most cells except, except what? Neurons. Neurons don't require insulin, an important fact. But not only does insulin simulate glucose entry, it also helps to remove what from the blood? Amino acids. And although that might sound bad, remember, where is this glucose– where are these amino acids going? They're going into cells to be used for energy or protein synthesis. So, it's perfectly logical and necessary. Insulin also inhibits the breakdown of the G word, breakdown of what? So, it blocks the breakdown of glycogen most of which appears or occurs in what organ? What organ normally breaks down most of the glycogen? Liver. So, this inhibits glycogen breakdown in the liver, but it promotes glucose and amino entry– amino acid entry into most cells. That said, what effects– what benefits are likely, what happens in adipose? When adipose gets a lot of glucose with the assistance of insulin, it basically produces a lot of fatty acids. And from that, it can make more what? So, the effect that insulin has on fat or adipose is that it causes it to pull more glucose out of the blood and therefore allows it to make more lipids. In muscle, most of these glucose is not converted to fat, it's

converted to glycogen, which is used as a potential energy source in muscles and especially when they're active over a long period of time. Let's not forget that insulin also facilitates the movement not just the glucose, but also amino acids which would help muscles to do what? Muscles could make more what? Protein. And incidentally, just an unrelated comment, a lot of body builders use insulin even though they're not diabetics. And why would they mess with that? Well, insulin would help promote what? Amino acid entry, and that translates to what when it comes to muscle? Basically, you know, protein, actin, myosin and so forth. Now, the liver, what does it do, that is how does it respond to insulin. And when it gets glucose, it makes more glycogen, it'll also– eventually unable to store glycogen indefinitely, so it'll then convert some of that that is used– some of that glucose to make fatty acids which promotes fat synthesis at that location. So in summary, what does insulin do? It promotes glucose entry and amino acid entry which leads to lipid storage, glycogen storage, even protein synthesis. And so, there's lots of positive benefits for insulin, of course. What controls the secretion of insulin? Well, naturally, it shouldn't be secreted all the time. And when would you wanted to be secreted? Think teleologically, and that is when is blood sugar high and when would we like to move it out of the blood into tissues, obviously in the absorptive period. So whenever blood sugar is high or whenever amino acids are high, this tends to stimulate the beta cells of the pancreas and therefore promote insulin release. Likewise, what would happen to that if you have low blood sugar? Low blood sugar and/or low amino acids inhibits the beta cells, therefore insulin is not released at that time. So, let's summarize and give name and meaning to these effects. Insulin is a hormone. Is it a hyper or a hypoglycemic hormone? Let's make it clear. A hypoglycemic hormone would be one that tends to lower blood sugar. A hyperglycemic hormone would be one that tends to raise blood sugar. And so with what you know, how would you label insulin? It's a hypoglycemic hormone. It tends to lower blood sugar. And although that might seem dangerous, remember, it's taking glucose from the blood and putting it into what, putting it into cells. So, this is a very essential and obviously important function. And that goes to a common piece of information. What is the most common endocrine abnormality on the planet?

>> Diabetes.

>> Steve Langjahr: Diabetes. And what hormone is lacking in many of those cases? Insulin. So, what is the primary symptom that develops in untreated diabetes? High blood sugar because insulin is not available to lower that blood sugar, and this has ramifications and consequences that we'll get to later. But getting back to this word, what does insulin normally do? It lowers blood sugar and therefore is by definition a hypoglycemic hormone. And next, does this hormone tend to be active or important in the absorptive period or is it more valuable, is it secreted more in the postabsorptive period? Absorptive, because that's when blood sugar is high. And therefore, naturally, the release of insulin would help to lower blood sugar and also at the same time escort amino acids in. This naturally is something that's taken care for you that is you don't worry about insulin. These are mechanisms that respond to what? Blood sugar and

amino acid changes. But what if you're a diabetic? Then, you have to inject yourself with what? And that means the responsibility is on you. And what if you were to forget and give yourself insulin in a postabsorptive period of day? Well, by definition, your blood sugar is already probably what? And now, you just give an insulin. So now, you're going to what? And you can kill yourself. Can insulin in that context then be deadly? Can it even be used as a method of homicide? Yes. Can people use insulin to kill other people? Yes. How does it kill? Because it lowers what? Blood sugar. And what organ suffers? And you go into hypoglycemic coma and death. So, I'm not suggesting. I'm just giving you information. Luckily, you can't get insulin, you know, easily. Maybe you can, but it isn't available at Costco over the counter. All right. So, let's move on. The next hormone out of three that we're going to deal with is a related molecule, it's a hormone also produced by the pancreas, that's a peptide, a small protein, but not produced by the beta cells, it's produced by the alpha cells. Its actions are quite diametrically opposed to insulin. In other words, it doesn't promote glucose entry. It actually stimulates the breakdown of glycogen and fat. The breakdown of fat, you know, is called lipolysis. The breakdown of glycogen, you know, is called glycogenolysis. And this effect is mainly targeted at the sources of these two things. In other words, where is there a lot of glycogen and where is there a lot of fat, well, the liver and adipose. So in the liver, glucagon promotes glycogenolysis and therefore releases into the blood glucose. At adipose tissue, it promotes lipolysis which then provides some glucose. But remember, it also produces as byproducts what, ketones which we said were undesirable for their acidic components. Here's the important thing, this hormone, what is it, glucagon, does not affect glucose uptake into cells and you need to really understand that that is very often at least in some courses, they'll say insulin does this, glucagon fights insulin or works against insulin. Well, it doesn't really fight insulin, but it does do the opposite of insulin. To put it simply, glucose is transported by insulin, but not affected by glucagon per se. What controls a secretion? Some of this is predictable, that is logical, but here's the story. Low blood sugar tends to stimulate secretion. Why would that be logical? Why is that easy to remember? What does glucagon do? It promotes the breakdown of glycogen, and therefore provides glucose for the blood. So, not surprising to find that it would be involved or stimulated when there is low blood sugar. But here's a surprise, glucagon is also stimulated by what? High amino acids. Even though from what you've seen so far, it has no direct effect on amino acid uptake, but it's stimulated by high amino acids in the blood. We'll explain that in a moment, but the opposite side of this coin is pretty predictable. When there's high blood sugar, this inhibits the secretion of this hormone. So with what's on the screen so far, how would you classify glucagon? Does it tend to raise blood sugar or lower blood sugar? And so, it's called a hyperglycemic hormone. And when would it be most useful, most highly secreted, during an absorptive or a postabsorptive state? Postabsorptive, because it helps protect against the low blood sugar that otherwise might develop. So, it's definitely a postabsorptive hormone. So, most of this information is fairly logical and easy to understand if you give it a little chance that is if you ponder it for a while, but

there is a very important and unexpected idea in here, and that is this hormone is promoted by what? The buildup of amino acids. So, here's the value of that response. On this axis, BG, blood glucose. And as you know, I may know blood sugar is measured in milligrams per deciliter, and that'll come later. But let's say an average blood sugar is 80, I'm just going to put that in there for reference. So right here at zero time, you just had a meal, OK? And let's assume that it's– well, let's assume that it's not exactly a balanced meal. Let's assume that it's a Twinkie and a liter of Coke, OK? That sounds good. What's going to happen to your blood sugar after that? It goes like that, all right. And so, what hormone responds to high blood sugar, certainly not glucagon. What hormone will pour out of the pancreas when there's high blood sugar? Insulin. What will insulin do to this blood sugar? Well, it transports it into cells. So, what's this going to do? It's going to turn around and it's going to go screaming down like this. And right about here, you're dead because the blood sugar is now way too low, right? Now, obviously, people don't die from a liter of Coke and Twinkie. So, there must be something that rescues the situation. And when blood sugar gets this low or even earlier, what happens to the secretion of insulin that was at first so strong? Well, it stops. And now, blood sugar is definitely no longer high. Now, it's what? It's low. So, what hormone comes to your rescue? Glucagon, but it may or may not be able to pull this out because the problem is this insulin has a very long half-life, that means even though the blood sugar has been brought under control, that insulin is still out there continuing to do what? So, this is a very dangerous, potentially dangerous thing which can be mitigated with common and sensible dietary practices. In other words, instead of having that Twinkie and Coke, it might have been a good idea throwing some peanuts in there. Why? Because a normal meal should contain carbohydrates, fats, and hopefully what?

>> Protein.

>> Steve Langjahr: Protein, which would provide what, and provide amino acids. And so, instead of just insulin being released, there would also be a little bit of G word, glucagon. This would change this transformation, that is it would bring blood sugar down, but it would tend to do it in a more moderate, more natural way, and therefore prevent this embarrassing descent into what? What is this dangerous area down–

>> Death.

>> Steve Langjahr: Yeah, death. But it's also called– well, here's the word, hypoglycemia. And that word is very common. People say, I'm kind of having a hypoglycemic episode here. And why is that? Well, probably, you had that Twinkie and a liter of Coke there. So now, you're way down here. And so, the body is struggling to get out of that situation. So with all that said, why is it nice that glucagon responds to amino acids, high amino acids? It brings glucagon out at an earlier stage, therefore helps to prevent this descent into what? Hypoglycemia. All right. Now, the third hormone that you thought we had left in the desk and hopefully never talked about again is epinephrine, but

here it is, back on the scoreboard. You know about epinephrine is produced by, secreted by the adrenal medulla. It's an amine which means it's a nitrogenous compound, not a protein. Its actions are familiar to you. You know it acts on adrenergic receptors, you know you have alpha-1, beta-1, beta-2, all of that, forget all that. Don't forget it, but it's not relevant now. What it does in this context is that epinephrine promotes these two processes, glycogenolysis and lipolysis. What's it mean glycogenolysis?

>> Breakdown of glycogen.

>> Steve Langjahr: And what is lipolysis? Breakdown of fat. So with that said, what are the targets of epinephrine in this context? Never mind the heart, never mind blood vessels. What are the targets of epinephrine? Where do we have all the glycogen? Liver. Where do we have all the fat? Adipose. So at least in this new context, epinephrine targets the liver and adipose tissue. In the liver, when we promote glycogenolysis, we get glucose, and that much supports blood sugar. And then when it comes to fat, the breakdown of fat of course produces fatty acids which then can be converted into, well, such things as ketones, but it does promote at least some gluconeogenesis, but those are the effects that it has there. Epinephrine also affects muscle where it promotes there what, the same thing, glycogenolysis. And this doesn't raise blood sugar because most of the glycogen that muscle has is– has been put there and intended for what? Why did our muscle go to all this trouble to make glycogen? It wasn't thinking about the brain, the muscle is storing this glycogen for what? Its own use. So this sugar, this glucose is not going to be added to the blood, but it does help support muscle metabolism especially with exercise. And finally, in adipose, epinephrine promotes lipolysis which produces fatty acids and glycerol. And as a final remark, epinephrine also improves, improves what?

>> Glucagon.

>> Steve Langjahr: Glucagon secretion. So at this point without going any further, and if you really studied what's on the screen, you would be sort of bewildered because it seems that these hormones are very much alike. Do they both tend to support or improve blood sugar? Yeah. They do it by slightly different means, but there's a lot of overlap, a lot of shared functionality here in these two hormones. And so as we will go on, we find that certain patterns of secretion are not unexpected. Let's just ask it this way, when would you want epinephrine to be released in this context? Never mind fight of flight or any of that. But based upon what it does to blood sugar, when would you hope it responds? Do you need it in a high blood sugar situation or a low blood sugar situation?

>> Low.

>> Steve Langjahr: Low. So not surprisingly, it responds to blood sugar. Specifically, and strangely, it's not the adrenal gland, but rather the hypothalamus which controls the adrenal gland. Because in the hypothalamus, there are receptors there called glucoreceptors. And these respond, as you would ex-

pect, to blood sugar. So when there's high blood sugar, these receptors do not respond. Therefore, there's a decrease in sympathetic action. And remember, the adrenal gland is controlled by sympathetic nerves. So when you decrease sympathetic action, that's going to inhibit secretion and therefore the release of epinephrine. Conversely, when there's low blood sugar, now that's going to stimulate this glucoreceptors which increases sympathetic action and therefore stimulate secretion of this hormone. What hormone we're talking about?

>> Epinephrine.

>> Steve Langjahr: Epinephrine. Now, this has connections to real world scenarios. Remember this Twinkie and a liter of Coke thing? Now, blood sugar went down into what? The hypoglycemic world and the glucagon get released, yes. But that would also stimulate the glucoreceptors and cause the release of this hormone, what is it? Epinephrine. Does epinephrine have other effects that you know of and that you sometimes feel in these hypoglycemic moments? Ever notice how your heart is kind of raising like that and you kind of feel a little jittery and maybe a little sweating? That's due to what hormone? Epinephrine. A side effect, it's really working in your way– in your benefit. How is epinephrine helping you at this time? Well, it's promoting blood sugar. And so with that said, how would classify this hormone? Does it tend to raise blood sugar or lower it? Raise it. So, the word is hyperglycemic. And is it typically released in an absorptive or a postabsorptive state?

>> Postabsorptive.

>> Steve Langjahr: Postabsorptive. Now, there are other hormones, but we're drawing the line here. And so, how many have we mentioned that have anything to do with these absorptive and postabsorptive states? Three. And you might think, well, you know, that's weird, why not four, why not 20? Or at the very least, I know I was struck by this when I first was informed about it. I said, OK, well, wait a minute, you've got one hormone that, what, lowers blood sugar, but you had two that do what? And it just didn't seem fair to me that that should be that way. But actually, if you stop and think, it's not only fair, it's perfectly appropriate, because what's more dangerous, high blood sugar or low blood sugar?

>> Low.

>> Steve Langjahr: Low blood sugar. So, having two hormones which help to what?

>> Raise.

>> Steve Langjahr: Raise blood sugar is very important. In fact, what is the most common scenario, are we constantly worried about high blood sugar or low blood sugar? Because low blood sugar is associated with starving and of course other scenario. So when you think of it in that way, it makes perfect sense. And so yes, there are two hormones that are hyperglycemic, only one which tends to lower blood sugar, and that's insulin. So now as we leave you,

we'll summarize and try to ball this all up into a simple expression, that is let's analyze the hormones that are important and secreted or not in the absorptive state versus the postabsorptive state. So before we go into that, what is the definition? What's happening in the absorptive state? What is the trend with respect to blood sugar at this time? Why is it going up? Because you're eating stuff, right? You're eating sugar, you're eating carbohydrate. So, blood sugar is on the rise, that much is fairly obvious. And what hormone of those that we mentioned would respond to that high blood sugar and be helpful at this time? Insulin. But remember, at this time, we not only have blood sugar on the rise, but what else is rising we hope?

>> Amino acids.

>> We hope amino acids are rising, but only if you've eaten some protein. So, that's just sort of a hoped for scenario. Yes, you're going to have high blood sugar and increasing levels of amino acids. So, what about these hormones that we've named, certainly which one would be very high in terms of its levels at this time?

>> Insulin.

>> Steve Langjahr: Insulin, responding directly to both the high blood sugar and also to the high amino acids. But what about glucagon? We mentioned that it doesn't respond to high blood sugar, but it does respond to what? And so, glucagon is going to be secreted a little bit. So, notice that arrow. It's a little area, not a big arrow. And so, it doesn't get secreted a lot. And whatever glucagon is secreting, it is not due to the high blood sugar, but rather the high or increasing levels of amino acids. The one hormone that's not secreted at all during this time naturally is epinephrine. And you can say, of course, that's because it's not needed, but that's whenever you use the word need, you're talking what? So, the reason epinephrine is not secreted is just that blood sugar is high and it doesn't respond to high blood sugar, it responds to low blood sugar. So now, let's flip the coin. If we flip the coin, it's now the postabsorptive period. And what is the trend, what's going on with respect to blood sugar if you're not eating? Why is it going down? In case that's not obvious, why is blood sugar going down in the postabsorptive state? Well, you're using it and you're not getting anything replaced. So, it's obviously on its way down. And of course, amino acids are also following at this time because it's the postabsorptive state and there's no incoming source of amino acids. And so with that said, what hormones would be secreted in response or correlated with this change? Insulin? No way. Why no insulin? Because insulin doesn't respond to low blood sugar, it responds to high blood sugar and high amino acids. And so once again, this is important for diabetics to know because if a diabetic injects him or herself with insulin during the postabsorptive state, what's going to happen, their blood sugar is going to go what? From low to lower. In other words, into this dangerous scenario here of hypoglycemia. Well, hormones are expected to be high and logically should be high at this time, epinephrine responding directly to the low blood sugar and the sympathetic

activity that results from that, and glucagon as well. And so, this helps to support blood sugar. And remember, why is blood sugar so important? What organ is pretty fussy that way?

>> Brain.

>> When blood sugar is too low, brain checks out, you check out, game over. So as a final remark, what's more dangerous or risky, low blood sugar or high blood sugar? Low blood sugar, which is not to say high blood sugar doesn't have problems. But of the two, low blood sugar is way more problematic and potentially lethal. All right. So, those of you that came in late and plan to come to the lab, we have some urine cups for you. These are spill-proof and we'd like you to come with some urine, preferably your own. Don't try to sneak your dog's urine in here. And we have little brown bags so that you won't be upset in transporting it and people won't point fingers at you and stuff. See you tomorrow in lab. It should be fun.