>> Steve Langjahr: Tonight is February 13, the evil of Valentine's Day, so just putting that out there. This is lecture three for your favorite course, physiology. We've been dealing with chemistry, biochemistry, most recently cell membranes. Now we're going to transition into something quite a bit more, well physiologic, namely the notions of cell metabolism and the role of molecules known as enzymes. This will bear heavily on tomorrow's lab, but let's start. Everybody's heard the word metabolism and has a vague notion of what that might be, but to be exact metabolism is nothing more than all of the reactions that are happening in a cell. And obviously if there are no reactions occurring in a cell it has no metabolism. It's dead. So metabolism is essentially the definition of life. Metabolism, all the reactions, all the chemical reactions that are happening in a living cell. Now these reactions, these chemical reactions are really no different than reactions happening in a test tube, it's just that they're happening in a wad of cell. So there's nothing different from a metabolic reaction compared to a test tube reaction with some important caveats there. So before getting into metabolic reactions, let's spend some time talking about reactions in general, chemical reactions that you could do in a test tube in a chem lab. Very simply and very generically, a reaction means that two or more molecules have collided, they've reacted and; therefore, they're said to be reactants. And whatever you get when all is said and done, those things that result are called p word?

>> Products.

>> Steve Langjahr: Products. So in this simple description a and b represent reactants, and they indeed react and produce c and d, which are [inaudible] products. Many, but not all, reactions are reversible. That means a and b can form c and d, and c and d can react and form a and b. So this is a reversible chemical reaction. So in this scenario going to the right is said to be what?

[Inaudible]

Forward. Going to the left is the reverse. So this is a very simplistic statement, a generic description of a chemical reaction. So what are some issues here? If a reaction is reversible what determines whether it goes forward or reverse? It's not a matter of need or want. Reactions don't need anything, reactions don't want anything, they're just reactions. So why would a reaction go forward? Why and when would it reverse? It's basically – it's basically the result of a concept called the law of mass action. And it simply states this, that when you have an increase in the concentration of reactants, obviously they're going to encounter one another, they're going to collide, they're going to hit each other more frequently, and that's going to promote the forward reaction, that is a and b would be converted to c and d. And, of course, if there's increases in the concentration of products, then they would react. That is they would collide or hit each other, and that would turn the reaction around, that would promote the reverse. So what's this all about? What's it called? The law of mass action. To summarize, if we have a high concentration of a and b the reaction is going to go forward. If we have a high concentration c and d the reaction is going to go reverse. There's no need here, there's no want. It's just, well, the law of mass action. So with that answered, once we establish the direction, what determines how quickly it goes in that direction? Well, once again, concentration is going to be involved, because if we have a higher concentration of these molecules they're going to collide more frequently with each other and that will promote a faster speed, a faster r word?

[Inaudible]

Rate. So once again, if we have a high concentration of a and b and we make it even higher, then clearly the speed, the forward speed, would be faster. So higher the concentration of the reactants obviously promotes a higher rx, that means reaction rate, and vice versa. The other thing that has to happen in order for a reaction to occur at all is not just the presence of the reactants, not just a sufficient concentration of these reactants, but very often there has to be some input, some kick in the pants. So this little cartoon sort of explains that. Here's something that's going to be converted to b, but to get it to roll down that hill you got to push it up this little bump there. And that kick, that jumpstart, that incentive that will trigger reactants to indeed react is known as activation energy. So as an actual example, let's say we have a balloon, a kid's balloon, we put oxygen in there and we put propane in there, they're both gases, right? Oxygen and what?

>> Propane.

>> Steve Langjahr: Propane. Are these reactants? Are they known to react explosively actually? Will they? No, not unless we provide what? Activation energy. They'll just sit there until a spark or flame or something provides the minimum what? The minimum activation energy. Activation energy then is the minimum kinetic energy to get the ball rolling, to get the reaction going. Some reactions have a small amount of activation energy, meaning they go easy, some go hard. In short, some require more activation energy to get started, some require less, but that nevertheless is still necessary. In short, without activation energy nothing is going to happen. So activation energy is necessary to start a reaction. And if this reaction requires less activation energy than that one, which one is more likely to occur? The one that requires lower activation energy. So if a reaction requires little activation energy then it's going to tend to have a higher reaction rate, it's going to happen more frequently because it doesn't need, it doesn't require as much what, as much? Activation energy. So to say it again, here's a reaction that requires little activation energy. Here's a reaction that requires more. Which one is easier to start? That one, the one with lower activation energy required. Now remember, activation energy is kinetic energy, the energy of motion. And what's a way that you can enhance motion of molecules? Certainly you can apply increased temperature. So it's not surprising to see the temperature, can also determine reaction rates. And this is almost intuitive. If we have a lower temperature here, but over here we have a higher temperature, which is going to promote faster or more speedy reactions? The higher temperature. Because actually the temperature, the heat that we're talking about, causes molecules to move faster, to hit each other harder, so

it causes higher impact of the reactants and; therefore, imparts, that means bestows or essentially represents sufficient activation energy. In short, temperature often is the form of activation energy that triggers reactions. Therefore, in cool temperatures what typically would we expect for reaction rates? Cool slows things down, heat speeds things up. Indeed from your experience in chem lab, I mean, how do you promote a reaction there? Do you just stare at it or shout at it? No, you put it under some what?

>> Fire

>> Steve Langjahr: Some fire, that always helps, because that temperature causes higher impact collision, which actually imparts, that means provides, sufficient activation energy. Now all of these remarks so far apply to any reaction, whether in a test tube or whether in a cell, but cells are different in one way, certainly different from a test tube, because they're very intolerant of, very intolerant of too much?

>> Heat.

>> Steve Langjahr: Heat. A test tube can tolerate a lot heat, but a cell very intolerant heat, and thereby, of course, influencing the potential rate of reactions, in other words, limiting the speed of a reaction. So even though higher temperature normally would promote or speed up reaction rates, cells do not tolerate a lot of heat, as you probably would expect. And so what makes cellular reactions able to occur at relatively low temperatures are the presence of rather amazing mediators called catalyst. I think we've all heard that word, even if it's just in a generic conversational sense. They might say, oh, he's a catalyst, or she's a catalyst. What does that mean? Somebody who helps things out, a promoter basically. And that is the essence, that's the meaning of the word. A catalyst though is not a human being, but rather a molecule, which has the ability to lower the required activation energy and; therefore, allow a reaction to go faster than it otherwise would. It lowers the required activation energy; therefore, promoting a higher reaction rate. Back to this cartoon, what's this – what's this hump represent?

>> Activation energy.

>> Steve Langjahr: Activation energy. If the hump is smaller we can thank perhaps a catalyst, which somehow lowers the required activation energy; therefore, naturally speeds up the reaction which otherwise would be quite a bit slower. And that's important to stress, because before we go further, do catalysts make the impossible possible? Do they make reactions happen that otherwise would not occur? No, they simply allow them to go f word?

>> Faster.

>> Steve Langjahr: Faster. So catalysts aren't magic, they're not going to turn lead into gold, but they do – they do what? Lower required activation energy; therefore, they tend to speed up reactions. And this is golden for cells, because what is the usual form of activation energy? Heat. And what did we say about

cells and heat. Yeah, obviously cells have a limit to the amount of heat that they can handle, so catalysts allow metabolic reactions to happen at relatively low temperature, 98.6 as an example. So these are the determinants of reaction rates. To summarize, the speed depends upon the concentration, it depends upon the presence or absence of activation energy, which is often provided by changing heat, and certainly the speed can be enhanced by the presence of these things called catalysts. Now, when it comes to metabolic reactions, these are those, of course, that are happening in cells. And digressing from your lecture outline there, there is certainly a very fundamental kind of metabolic reaction that's been known since antiquity, and that is a process known as fermentation. Do sugar solutions fermate [phonetic], not fermate. Do sugar solutions ferment and produce alcohol?

>> Yes.

>> Steve Langjahr: Yes, they do. And that has always been a mystery, that is in antiquity it was a mystery, how does this sugar change into this intoxicating beverage? Well, it was indeed a complete mystery until it was discovered that it's a metabolic reaction made possible by these cells. What?

>> Yeast.

>> Steve Langjahr: Yeast cells. And actually it was Louis Pasteur who confirmed this. He confirmed that fermentation will not and cannot happen without the presence of living what? Living yeast cells. In fact, he proved that if you kill these yeast cells then fermentation would stop. So essentially among his discoveries, he demonstrated that this, which is sugar, plus this, which is oxygen, plus this, which is water, in the presence of yeast cells will actually ferment and produce products, namely CO2, what's that?

[Inaudible]

And ethanol, which of course is ethyl alcohol. Now, as simple as this equation appears, it's not that simple, it's not just one reaction. But to remind you, these on the left side would be r word, those are?

>> Reactants.

>> Steve Langjahr: Reactants. And these things here are p word?

>> Products.

>> Steve Langjahr: Products. The only thing we're telling you that was discovered by Pasteur is that what you have to have is not just sugar water, but you have to have living what? Yeast cells. So in that sense he essentially discovered that this is a metabolic reaction, one dependent on living cells living cells, living yeast cells. And, of course, he wasn't satisfied with that discovery. He thought, well, that's cool. There must be something in these yeast cells then that makes this happen, because he put sugar water in a test tube and waited around and nothing happened. He had to add what? The?

[Inaudible]

So he figured, he's pretty smart, those yeast cells must've added something which made this process occur. So he said, okay, well let's see, whatever this stuff is maybe we can break open these yeast cells and take whatever they have and then put it over here in a test tube, a test tube filled with what?

[Inaudible]

Sugar water, and maybe this extract from the what? The yeast cells would cause fermentation without the yeast cells. I mean, it's a logical thought. I mean, the yeast cells are needed. They must have something that we could move from here over to there, and so he tried that. He took the yeast cells and he put it on – put these yeast cells in a pan and he heated them up and sure enough they broke open and then he poured off what was left and he took that stuff over to a test tube, a test tube filled with?

>> Sugar water.

>> And nothing happened. He did it a 1000 times, nothing happened. So he was really stumped by this. He determined, it seemed logical, that whatever they had couldn't be moved. In other words, it wasn't something physical that you could actually transfer, it must be something magical or metaphysical. He gave up. Famous nonetheless for a process known as?

>> Pasteurization.

>> Steve Langjahr: Pasteurization, which is heating things like milk so it kills off microorganisms, a safe way of processing stuff, dairy products in particular. Okay, so famous guy, but he failed in this regard. And 50 years lapsed, 50 years came by before another guy who tried the same thing with a different approach, his name was Edward Buettner. And so he took yeast cells, but he didn't heat them up, he put them in a press and he applied pressure to these yeast cells until they popped. And then he put the soup from these ruptured cells, put them in a test tube, a test tube with sugar water and bingo, ethanol. So that was quite stunning, because he failed – excuse me, he succeeded where Pasteur failed. And he won the Nobel Prize for that because he went on to coin the word, the word is enzyme, which means in yeast. That word has much more meaning today, but he was the first to demonstrate that yeast cells had these c word, catalysts which made these reactions happen at much lower temperatures. So that's the sort of history behind the discovery of what today we know and take for granted as enzymes. In short, enzymes are metabolic or biological catalysts, and life as we know it simply could not exist without enzymes. And when we say the word enzymes it's definitely plural. There is no magic key. There is no magic enzyme. In your cells working now there are four or 5000 different kinds of enzymes, each one negotiating a very different reaction, a very different metabolic reaction. And so the sum total of your enzyme inventory is really going to; therefore, dictate your metabolism. In other words, what I just said, what a cell can do is obviously dependent on the?

>> Enzymes.

>> Steve Langjahr: Enzymes that it has. And, incidentally, there are genetic defects where people are missing certain?

[Inaudible]

Therefore certain changes in metabolism suffer, sometimes to a lethal degree. So it's very hard to overestimate the importance of enzymes. In short, without enzymes life as we know it is not possible. But let's go on. What enzymes do, remember they are catalysts, they don't make the impossible possible, they just what?

>> Speed up.

>> Steve Langjahr: Speed up. And the amazing thing is that enzymes do this without being what? Without being altered. So enzymes don't get consumed. They don't get depleted. It's not like gas that suddenly disappears from a gas tank. Enzymes are not fuel. Enzymes are catalysts which speed up reactions but aren't consumed or altered themselves. And to go further, they don't cause reactions that otherwise wouldn't occur, they just make reactions go faster and they allow them to occur at lower levels of activation energy. We're going to see, and we've already implied, that your cells contain 1000's of different enzymes, each one orchestrating a particular reaction. And that leads us to our next statement about enzymes, they're very specific. This enzyme only works with this reaction, and the reactants that are fostered, or promoted, by an enzyme are called substrates. A substrate is a reactant, which is any organic molecule which becomes bound to, meaning acted on by an enzyme, producing ultimately a product, but an intermediated – an intermediate form called an ES complex. These are just terms, but let's now take those and put them into a statement, a generic expression of a typical metabolic reaction which is promoted by an enzyme. Enzyme, abbreviated what?

>> E.

>> Steve Langjahr: E, reacts on a specific reactant called a substrate. And these two physically attach. Notice I didn't use the word bond, because there's no sharing of electrons or transfer of electrons. It's a temporary affiliation, and that's called an ES complex, which then quickly dissociates into the products. But here's the good news, what else is kicked out is the what?

>> The enzyme.

>> Steve Langjahr: And is that enzyme altered or damaged or injured in any way? No; therefore, obviously ready to what? Ready to do it again. Enzymes are recycled. The enzymes you're using now, the same ones you're going to wake up with tomorrow, doing their thing then, just as they're doing their thing right now. That then is the generic scheme of things. On the previous page we said enzymes are always protein. Question first?

[Inaudible]

Once the enzyme has catalyzed the reaction what we form are, p word?

>> Products.

>> Steve Langjahr: But the enzyme is free, right. And; therefore, available to do it again. So that means the enzyme supply never really suffers, except, and this is an important exception, remember enzymes, as we skipped over here, enzymes are not just ordinary, miscellaneous molecules. They are always what? Here's the p word.

>> Protein.

>> Steve Langjahr: Protein. In fact, that's a fact we revealed previously. Remember when we discussed proteins? We said some proteins are antibodies, some proteins are muscle proteins, but we said some are, e word?

>> Enzymes.

>> Steve Langjahr: Enzymes. In fact, here's a blanket statement, all enzymes are?

>> Proteins.

>> Steve Langjahr: But not all proteins are?

>> Enzymes.

>> Steve Langjahr: Enzymes. We know that proteins are complex molecules. We know they are three dimensional, actually shaped up on the basis of the hydrogen bonds that are formed there. You might recall, I brought in this things, which I found somewhere, I don't remember, and I said, well, that's a cool little toy because it can be can be – it can be twisted into different shapes, huh. And so remember, proteins are made of subunits called amino?

>> Acids.

>> Steve Langjahr: Acids. And if these amino acids are that way then we get that. If we rearrange the amino acids then it might look like that. So every protein has a unique three-dimensional shape, which turns out to be incredibly important, indeed essential in determining the specificity of enzymes. But back to your questions. When enzymes are involved are they consumed? Are they altered? Are they mangled or otherwise changed in any way?

>> No.

>> Steve Langjahr: No, so they are completely recycled, except that remember, all proteins break down over time. So I said the enzymes you're going to wake up with tomorrow are the same ones today. But are they going to be the same ones 10 years from now?

>> No.

>> Steve Langjahr: No, nothing lasts that long, in the molecular world anyway. So they're going to be replaced, that is re-synthesized. But overall, in general, they are recycled. So to restate where we've been, enzymes catalyze reactions. They react with, s word?

[Inaudible]

Forming a temporary thing called a?

>> Enzyme.

>> Steve Langjahr: Enzyme substrate complex, which then is transformed into, p word?

>> Products.

>> Steve Langjahr: But the good news is the enzyme is reusable, essentially available for recycling. Now this is easy enough to stay – easy enough to describe, easy enough to illustrate, but there's some interesting, unanswered questions here. Remember, we said enzymes don't make the impossible possible, they just make these products appear quicker. They are not magic, they are just, the c word?

>> Catalysts.

>> Steve Langjahr: Catalysts. And then we've implied that there's some degree of specificity, that this enzyme will only work if they're given substrates. So there's two questions now we have to answer. What determines specificity? Why does this enzyme work with that reactant, but not with that reactant? And then, once we establish that it works with that one but not that one, why does it make it go any faster than it otherwise would? So two questions. The first one is the easiest one to answer. The question is, how and why is that enzyme able to recognize and work with that substrate, but not work with that substrate? It's actually based on chemical geometry, that is geometric specificity. In a sentence this means one enzyme, a given enzyme, will react only with what?

>> One specific –

>> Steve Langjahr: One specific substrate. Now, why is that? Do they have eyes or something? Is it all looks or something? Well, not exactly. Here's an animation which may convey this. Here's our enzyme. What kind of molecule is it?

[Inaudible]

Protein. Does it have a particular shape?

>> Yes.

>> Steve Langjahr: Yes. Is that shape critical? Yes, because it turns out that in every case enzymes have a specific location, a specific spot which is key. And that choice of words is not accidental. Think of a key. What makes that key special is not the thing you grab, but the thing you stick it into the lock, right? Is the shape of that key really all important?

>> Yes.

>> Steve Langjahr: If you screw up those ridges and valleys will it work?

>> No.

>> Steve Langjahr: So the enzyme has a similar physical spot, which turns out to be important. Here are some substrates, there's three. Which of these substrates would seem to have any geometric fit, or ability to form an enzyme substrate complex? Not this, not this, but that. Do you see a kind of complementary suggestion there? That is, a kind of lock and key fit there? And indeed, these substrates will be rejected. That substrate will be recognized. And it's recognized only here, which then assumes the name active site, because it is the site where the attachment of the substrate will occur. So every enzyme has a position, a spot, that fits exactly, the geometric configuration, of not every, not many, but just what?

[Inaudible]

A specific substrate. So are these three molecules all potential substrates? Yes. Which one will work with this enzyme? Only that, because only that one has the capacity, the physical capacity, to fit at that location. And this animation will now show that. What do we call this temporary union?

[Inaudible]

An enzyme substrate complex. Be careful not to call that a bond, because there's no sharing or exchange of electrons. It's just a temporary union, an enzyme substrate complex. And, as a result of that, products are formed. But remember, the enzyme is unharmed, able to repeat, and participate in this reaction over and over again. This idea, this concept, is very analogous to, and often compared to, a lock and key. Isn't that kind of what we're talking about? And if you get that, what is the enzyme, the lock or the key?

[Inaudible]

I hear 50 50 there. It must be one. Which is it? Is the enzyme the lock or is the enzyme the key?

[Inaudible]

Think about it. What is changed in this reaction? Is the enzyme changed or is the substrate changed?

>> Substrate.

>> Steve Langjahr: Substrate. What is changed in this? Is the key changed? No. Isn't the key able to do that again and again again and again and again? So back to the question, the key represents the enzyme. The lock represents the substrate. In fact, the key is further obviously the enzyme because does this key fit all locks? No, it only fits that lock or that lock. And what determines that is this pattern on the key itself, which would be analogous to what?

[Inaudible]

Something we call the active site. And if the active site is changed, will that key work on that particular lock? No. So the analogy is pretty good in the sense that it matches what we're talking about. In summary, the key is what?

>> Enzyme.

>> Steve Langjahr: Enzyme. The lock is the?

>> Substrate.

>> Steve Langjahr: Substrate. And this whole concept is geometric specificity. Do all keys fit all locks?

>> No.

>> Steve Langjahr: Well, if they did we'd have no reason to have keys. So obviously specificity is what is the important idea here. Back to our notion, what makes this cell able to do things that that cell can't? Why is that cell able to do things that that cell can't? That must have what?

[Inaudible]

Enzymes, which are not present over here and; therefore, enzymes control not just the speed of reactions, but which ones happen or which ones don't. So this is the summary of our first question, it is the answer to the first question. What was the question? How does this enzyme recognize that substrate and reject all others? Geometric specificity. It all comes down to the shape, not the shape of the substrate, but the shape of the?

>> Enzyme.

>> Steve Langjahr: Enzyme. And what spot on the enzyme is all important?

>> The active site.

>> Steve Langjahr: The active site. Now you probably don't need this, but I made – again Home Depot came to the rescue. I made this little thing out of some gizmo you buy there, and so this represents an enzyme for us. What are enzymes made of?

[Inaudible]

So if we examine this we would find that this molecule is made up of a bunch of?

>> Amino acids.

>> Steve Langjahr: Amino acids. And it has a very nice, very specific shape, which in this case offers a location here, which would seem to represent, or perhaps qualify as a active site. Okay. So here's a substrate. I know, it's a mug full of pens. But that's not going to work. But here is a molecule which fits right in there, isn't that cool? So this must be the, s word?

>> Substrate.

>> Steve Langjahr: Which forms a enzyme substrate complex. And the result of this produces these guys, which are?

>> Products.

>> Steve Langjahr: Products, but does not harm, or disturb, or in any way change this. So the enzyme is able to recycle. What if this active site were to change? Yikes, obviously it would not provide this opportunity to form a what? Enzyme substrate complex. This whole concept, again, geometric specificity. Now it's important to stress that this relationship is purely physical. It sounds like a romance novel. But, hey, it's not romance. I see sometimes people resort to, they say, oh, I got it. They see each other, they know they're meant for each other, and they run into each other's arms. They don't see, they don't run. What caused this to happen? It was just dumb diffusion, right? Sometimes that's the way it is in real life, too, accident. But, okay, just don't romanticize this. Don't say, oh, it's a love affair, okay, they're meant for each other. No, no, just dumb luck that this happened. But obviously if we have a higher concentration of these things then that would happen. So all right, let's leave that. We've spent too much time on it. The second question was, okay fine, once this thing is formed, what do we call this union?

[Inaudible]

Why does that make the reaction happen faster? Isn't it possible for this substrate to form these products without the enzyme? Sure, it's possible. Why does it work better? Why does it happen faster in the presence of the enzyme? Can't this happen? Yeah, but it happens much faster with the enzyme. What's the explanation for that? How is this going to speed up things? What is the explanation for enzymes ability to do this, to make things occur quicker? We identified, in fact, we equated enzymes with the c word. Enzymes are?

>> Catalysts.

>> Steve Langjahr: Catalysts. And catalysts had this magic ability to lower what?

[Inaudible]

And; therefore, what might've taken more heat is now going to happen with less heat. And enzymes are just that way, they lower the required activation energy. And they also help to distort, to stress, to weaken the existing bonds. This substrate has bonds holding the atoms together. In the presence of the enzyme those bonds are now, w, weakened; d, distorted; s, stressed, and now they're more likely to what? React then otherwise. Now it takes not more but less activation energy. So the enzyme physically weakens or distorts the existing bonds in a substrate so that the available activation energy, the available heat in a cell, are now – is now sufficient to bring about a reaction. But with that said, let's not generate the wrong idea. Substrates don't always form smaller products. Can enzymes take and bring together and create new bonds and; therefore, a more complex product? That's possible. So it's not always a matter of weakening or distorting existing bonds, sometimes it's a matter of promoting new bonds by properly orienting two substrates. What's that mean, orienting them?

[Inaudible]

Bringing them into proper alignment. So here's substrates, could they form this product on their own?

>> Yes.

>> Steve Langjahr: They could, but that's not very likely, much more likely in the presence of a enzyme, because the enzyme helps to?

>> Promote.

>> Steve Langjahr: Promote new bonds by properly positioning, properly orienting the substrates. So enzymes are not magic, but they are indispensable. What's that mean? Can we have metabolism without enzymes? No. You might say, well, just heat them up. But heat does what to cells?

[Inaudible]

Destroys them. And so clearly enzymes save the day by allowing reactions to happen at much lower temperatures. Tomorrow's lab, then, is all about things that can influence, that means help or hinder enzyme action. And we're going to go through this very quick because it is, after all, what we're doing tomorrow in lab. So we're going to revisit these few pages in lab. I just want to give you a kind of preview, a kind of quick introduction to various factors which indeed do influence enzyme action. And here's a blanket statement right off the bat, is the shape of an enzyme important for its ability to work?

>> Yes.

>> Steve Langjahr: So clearly, right off the bat, anything that can change the shape of an enzyme, or the electrical charge of an enzyme, certainly has the ability, the prospect of altering its activity, either for the good or in the negative way. So here's a list of factors. Here's a list of influences that can sharply affect enzyme behavior, enzyme action. First, modifiers. A modifier is an environmental factor, which includes, right off the bat, heat. Heat is not a property of enzymes. Do enzymes have heat?

>> No.

>> Steve Langjahr: If you put your cheek up to them are they warm?

>> No.

>> Steve Langjahr: No, that's stupid. But heat is not a proper – not a property of enzyme, it's a property of the environment, right. Does heat affect an enzyme? Absolutely. Positive, negative? Actually both, because a certain amount of heat is necessary, after all. Remember, any and all reactions require this jumpstart, this, what's it called?

>> Activation.

>> Steve Langjahr: And activation energy usually is provided by heat. So is heat a good thing? Yes. But if we apply too much heat, that not only destroys the cell but it can and does change the shape of complex organic molecules. Are enzymes complex organic molecules?

>> Yes.

>> Steve Langjahr: And when this happens we say the protein has been, here's the word, denatured. Now I don't make – I didn't make that up. In fact, I don't even understand why it's called that. But the synonym for denatured is distort, meaning to physically change the shape. We all know that from experience. If you get your hair too close to a flame, you know that your hair is protein, yes? Does the hair change? Yeah. Some people – some women actually have appliances which deliberately wrap their hair around this thing and so they can be denatured, that is curled up into fun little, you know, curls, okay. I don't bother with that personally. I'm just joking. And certainly when you drop an egg into a skillet, is that albumen protein and does it change shape? Yeah. So my point is, heat is very disfiguring to protein, and usually irreversibly. So here's our molecule. This is a what?

>> Enzyme.

>> Steve Langjahr: And, yes, it's made of a protein. Now we're going to put it under a Bunsen burner. Now it looks like that. Is it still the same protein?

>> Yes.

>> Steve Langjahr: Trick question. It is still the same protein, but is it the same shape?

>> No.

>> Steve Langjahr: No. Is it going to work like an enzyme?

>> No.

>> Steve Langjahr: I take a key out of my pocket, demonstrate that it works on this lock, then I put it in a flame and cause it to go, is it going to work?

>> No.

>> Steve Langjahr: No. So denaturation, usually permanent, disfiguring and; therefore, problematic because it invariably changes what about the enzyme?

>> Shape.

>> Steve Langjahr: Shape, especially and mainly the active site. And if Louis Pasteur was listening, that's your problem, Louis, because he was going to extract these goodies from the yeast cells and he made the fatal mistake of doing what?

[Inaudible]

He heated them. And he didn't know that he was denaturing the, later to be called, enzymes. Now neither did Buettner. Buettner was trying something different. And he succeeded where Pasteur failed, because he didn't use heat, he used pressure to break open the cells; therefore, not harming, not denaturing the enzymes. So in short as we leave this, is heat a good thing to metabolic reactions? Yeah, a little bit good, but a little bit bad. Too much heat, definitely negative. Another environmental, another modifier that can influence enzyme behavior, again, not a property of the enzyme, a property of the solution in which the enzyme lives or is basically a solute, is the pH. In chemistry you measure pH's of solutions. That one's acidic, that one's alkaline. You learned about this concept. It turns out that alkalinity or acidity, in other words the pH, is really influential in changing the charge, the electric charge, of molecules, not the least of which would be enzymes. So if this area, what's this area called?

>> Activation site.

>> Steve Langjahr: If it's normally positive but we put it in this solution which is, let's say, acidic, and now that positive becomes negative, is that going to influence the ability of the substrate to attach there?

>> Yes.

>> Steve Langjahr: Yeah, it might be – it might be repelled instead of being nicely fitted there. So every enzyme has a condition of pH where it works best. But please be careful, I didn't say enzymes have pH, are they influenced by pH? Yes. Do you have weather? I know it sounds stupid. You don't have weather, but are you influenced by weather?

>> Yes.

>> Steve Langjahr: That's the idea, pH is not a property of the enzyme, pH is a property of the solution in which these enzymes live. And, if I were to tell you that most enzymes in cells, or if I say it this way, if cells maintain a pH of around seven, you would guess that most enzymes prefer or otherwise work best in a pH of seven. Not all, but certainly that's a fair assumption. Moving through this quickly. We're going to revisit tomorrow. The second thing that can influence enzymes are the presence or absence of what are called cofactors. A cofactor, meaning a factor, a thing, which might assist or be necessary for an enzyme to work. In this model I made, this of course is the area called the what?

[Inaudible]

And this little yellow spot is a cofactor. In other words, it's a metallic ion which is necessary apparently to what? To complete the structure of an enzyme's active site. Let's say this yellow spot is Fe. What's Fe?

>> Iron.

>> Steve Langjahr: Iron, and now it's not there. Is the active site the same?

>> No.

>> Steve Langjahr: No. Will the enzyme work? No, because it doesn't have the necessary cofactor. Do all enzymes require cofactors? No. Do they all use the same cofactor? No. Is the cofactor itself a catalyst? No, but it completes what? The –

[Inaudible]

Structure of the enzyme's active site. So these are often referred to as essential trace elements, essential trace elements, meaning your diet must have these things otherwise certain enzymes will be lacking? Certain enzymes will be lacking certain cofactors and; therefore, they would fail or otherwise not work well. But to repeat, do all enzymes require cofactors? No. Do they all use the same cofactor? No. Next, things called coenzymes, which is a bit of a misnomer because coenzymes are not enzymes any more than a copilot is a pilot. I mean, they are but they're not the pilot, if you what I mean. So coenzymes are not enzymes. In fact, they're not even what? They're not protein. So in a way you might say, well, that's a stupid name. If they're not enzymes why call them coenzymes? Well, they assist an enzyme, just as a copilot assists the pilot. What they do is transfer, that means bring to or take from the substrate certain components and; therefore, they are essential. And, as it turns out, coenzymes are made available from things in your diet, things you know to be important, these magic things called what? Vita –

>> Mins.

>> Steve Langjahr: Mins. Now digressing a bit, vitamins come in two basic kinds, those that are water-soluble and those that are fat-soluble. The water-soluble vitamins include, among others, vitamin C, and pretty much all the B vitamins. So what? These water-soluble vitamins are necessary to make certain what?

[Inaudible]

Which are necessary to fulfill the functionality of certain what?

[Inaudible]

All right, so this isn't any more complex than that. It's simple. If your diet lacks certain, v word?

>> Vitamins.

>> Steve Langjahr: Vitamins, then your cells are not to be able to make certain, c word?

>> Chemicals.

>> Steve Langjahr: Therefore, certain enzymes won't work as well; therefore, certain reactions will not work as well. So are vitamins part of this story in terms of health and maintenance of metabolism? Yeah. Are all vitamins coenzymes? No, but many are; therefore, your diet must contain these vitamins, otherwise

your cells would lack certain coenzymes; therefore, certain enzymes wouldn't work, not because the enzyme is not there, but because there's missing what?

>> Coenzymes.

>> Steve Langjahr: Coenzymes. The importance of this will reveal itself later, but for now, clearly, your diet must contain certain vitamins, because by definition they can't be made. They have to be acquired from the stuff you eat. Can you be vitamin deficient then?

>> Yes.

>> Steve Langjahr: And would this impact coenzymes and, therefore, metabolism in specific or general ways? Yes. Next, inhibitors. Inhibitors are, well, it sounds like a negative thing, and they come in two forms, competitive and non-competitive. A competitive inhibitor is, one, a molecule which resembles what?

>> A substrate.

>> Steve Langjahr: It's not the substrate, but what, r word?

[Inaudible]

So it's similar in shape. So what? Well, if it's similar in shape it can occupy, that means fit on the what?

[Inaudible]

And; therefore, block the attachment of the real substrate. Make sense? So if you need an animation I got one. That's a what?

[Inaudible]

Says so. All right, and this thing here is the?

>> Substrate.

>> Steve Langjahr: Substrate. How do we know? It says so, but okay. How do you know? Complementary fit. What's this area here?

>> Active site.

>> Steve Langjahr: Active site. Okay, all is good, or at least it's looking good. Oh no, but now there's this thing, it's black. What does that have to do with anything? Nothing, but it's a what? It's a competitive what?

>> Inhibitor.

>> Steve Langjahr: Inhibitor. How do you know it's a competitive inhibitor?

>> It says so.

>> Steve Langjahr: It says so, I know. But it's shaped like the what?

>> Substrate?

>> Steve Langjahr: Is it the substrate?

>> No.

>> Steve Langjahr: No. Is it close?

>> Yes.

>> Steve Langjahr: Therefore, what can it do?

>> It can block it.

>> Steve Langjahr: It can block that. That is, it can fit there. And now is the enzyme distorted? No. But is it able to work? No, because what's blocking is the?

>> Competitive.

>> Steve Langjahr: Competitive inhibitor, competitive enzyme inhibitors. Would this – would this reduce the formation of product?

>> Yeah.

>> Steve Langjahr: Would it stop the formation of product?

>> No.

>> Steve Langjahr: Tricky, it wouldn't necessarily stop it because, again, what determines whether the enzyme reacts with this or reacts with that?

[Inaudible]

Well, they both can fit the active site, so what determines whether this forms or whether the ES complex forms? Chance. In other words, concentration. If you have a way greater concentration of this and not so much of that, then it won't even be felt. But if you have tons of this and not so much of that, big impact. So concentration, important. When these kinds of inhibitors get involved it's usually irreversible. That is, this is permanently gummed up, so to speak, and therefore this would definitely, in time, have an impact. It sounds like competitive inhibitors would be bad, but often times, certainly in medicine, pharmaceutical companies design a molecule like this. Why would a chemist in a pharmaceutical company making big money make a competitive inhibitor? What value would that be? Well, obviously it would be designed to fit not every enzyme, but what?

>> Specific.

>> Steve Langjahr: Therefore, block not every reaction, but just –

[Inaudible]

One. Might that be therapeutic in some sense?

>> Yes.

>> Steve Langjahr: So designer molecules, which are actually competitive enzyme inhibitors, and they can be useful as medicine. Noncompetitive inhibitors, what do you think? Competitive inhibitors resemble, s word?

>> Substrate.

>> Steve Langjahr: Substrate; therefore, they fit the active?

>> Site.

>> Steve Langjahr: Site. So apparently noncompetitive would be what? If competitive resemble the substrate, the noncompetitive probably don't, because if they did they'd be competitive. So these have no chemical similarity to the substrate. Okay, fine, how do they work? Here's our enzyme again. And this spot here we already identified and gave a name to. That's the active site. This spot over here may exist on some proteins, some enzymes, it's called the allosteric site, or the alternative site. And here's the what? The substrate. Is that going to fit there? Uh-huh, looks good so far. And the inhibitor – oh here it comes again, it's black. How do we know this is not a competitive inhibitor?

[Inaudible]

Because it doesn't resemble the?

>> Substrate.

>> Steve Langjahr: So can this black thing fit on the active site? No. So it's not a competitive enzyme inhibitor. But can it attach here?

[Inaudible]

That site is called the allosteric site, also called the regulator site. And so, okay, fine, now that guy is going to attach there because it can. And now, what happened to the enzyme? It looks pretty much the same, but in case you missed it we'll go back there. There it is without the inhibitor. There it is with the inhibitor. What's this up here?

>> Active site.

>> Steve Langjahr: Is the active site different?

>> Yes.

>> Steve Langjahr: Will the substrate be able to attach?

>> No.

>> Steve Langjahr: No. So would this slow down, maybe even block, the formation of product? Yeah. So, oh, you see the substrate can't fit. Watch that again, it's so cute. Oh, it can't get in. But the good news is this is what? This is not irreversible, it's?

>> Reversible.

>> Steve Langjahr: Reversible. So if this black thing goes away, well, guess what? The enzyme rebounds. That is, it recovers and returns, that is, regains the shape of its active site. So this kind of inhibitor is actually very useful because it helps to temporarily slow down a reaction, but in the absence of the inhibitor the reaction resumes again. So it's a way of blocking but then restoring the rate. That is, without the inhibitor the substrate is free to attach and the reaction proceeds. This is exemplified in something called feedback inhibition, which we'll talk about tomorrow in greater detail. But these were those that were called, r word?

[Inaudible]

There's also those that don't, that don't break away and; therefore, they permanently, d word?

>> Denature.

>> Steve Langjahr: Permanently denature the enzyme, and that means permanently. And these are nasty, meaning universally bad. And examples are, notorious, heavy metals. I'm not referring to bands or anything here. But what are some heavy metals that you know, or something you want to stay away from in?

>> Mercury.

>> Steve Langjahr: All right, mercury, lead, and so forth. Because these are indiscriminate, that is they change irreversibly, permanently denature, enzymes indiscriminately, not just that enzyme, not just that enzyme, but what?

>> All.

>> Steve Langjahr: All enzymes. And; therefore, universally b a d for metabolism. And we'll have more examples, but we already gave you, what are some heavy metals that would seem to be intuitively bad for you? Lead and mercury, because they're indiscriminate in their ability to, not destroy, what's the word?

>> Denature.

>> Steve Langjahr: Denature enzymes. And incidentally, while I'm thinking about it, never say kill an enzyme, please. Why is that not a good choice of words? You can't kill something that's not alive. So when you boil water you don't say, oh, I killed the water. No, so we don't – we don't kill enzymes. It's just d word, what?

>> Denature.

>> Steve Langjahr: All right, thank you. All right, we're going to revisit all this tomorrow. Let's finish off for tonight. This final blurb here is an introduction to where we go now that we've defined metabolism. Metabolism is the sum total of all reactions that are happening in a cell, yes? Do these reactions require

enzymes? Yes. Wouldn't they occur without enzymes? Yeah, but way too, s word?

>> Slow.

>> Steve Langjahr: Slow and requiring way too much, h word? Heat, and so without enzymes cells are literally dead. You can use that. You can take that to the bank. But, okay, we know that apart from enzymes that cells require an input of energy, just as your household requires an influx of money, right. There has to be some driving force, because in effect life is expensive. So what do we mean by energy, and what is the role of this molecule you've known about, ATP? If we go back to some basic questions, and if we ask you where does a cell get its energy, just that simple question, where does a cell get its energy? Where does a human cell get its energy? It's not from the sun. Can we live in the dark?

>> No.

>> Steve Langjahr: We do. So the sun is not involved in our energy source. You say, well, it must be our food, right? And it is. So the food that we eat obviously provide energy for our survival. And when we speak of food we mean organic molecules, whether it's – whether it's Chinese food, or Spanish food, it's all basically a very delicious combination of organic molecules. And is water involved? Is that a necessity? Sure. Is oxygen involved? Yeah, okay. So this is very abstract, but very simplistic. Apparently we need a constant source of delicious organic molecules, equally nice water and the lovely gas, oxygen. And somehow we get energy out of that, whatever that actually means. But you know from physics, or basic science, and here's a fact, you know – you know this, energy is never actually ever created or what?

>> Destroyed.

>> Steve Langjahr: Energy is never created. So don't say energy is made. Energy is never made, it's never created, never destroyed, just converted from one form to another. Okay, fundamental law of thermodynamics. So where exactly does this energy come from if it's not made? It basically is extracted from bonds, usually covalent bonds then complex molecules such as this C6H12O6. What's that?

>> Glucose.

>> Steve Langjahr: So glucose is certainly a common, available, tasty organic molecule, which in the presence of water and oxygen will participate in metabolic reactions producing these products, what products? CO2 and what? And also some energy. Energy is not made but, r word? Released. Released from the breakdown of glucose. You can do this in the chem lab. Take a test tube, put sugar in it, put some water, stick it under a Bunsen burner. The oxygen comes from the room air. Will sugar literally burn?

>> Yes.

>> Steve Langjahr: And will heat be given off? Yes. And so that heat is the energy, which previously was locked up in the covalent bonds of the glucose. Now, that's in a test tube. Can a cell tolerate that kind of shenanigans? Can we heat up cells and get them to burn glucose? We hear that a lot, burn your glucose. Well, it's not really that, but we are dismantling the molecule. So as a matter of chemistry, energy is released, not created, what?

[Inaudible]

Released whenever chemical bonds are broken, and by that we mean the organic bonds in such a thing as glucose. And so that energy is represented and released as heat, which is fine and dandy if you're trying to warm a room, but not terribly great for cells. Because can cells really use or take advantage of heat? Are cells tolerant of heat? No. So this process, which works great for a test tube, doesn't work great for cells, because they do not tolerate a lot of – for two reasons. Heat will destroy the cell, it will also denature the enzyme. So there's got to be a workaround. Isn't there always a workaround? So here's the workaround. Cells cannot really use heat, at least a lot of heat, for their functions; therefore, the workaround is this. Certainly enzymes are going to be involved but, as you'd expect, we still have to rely on glucose. We're still going to use water. We're still going to involve and consume oxygen. That's just the way we're built. But metabolism has this clever workaround, we plug in a molecule an organic nucleotide called ADP, and we're going to also toss in PO4, what's that?

>> Phosphate.

>> Steve Langjahr: A phosphate group. Now what's happened beyond the arrows here? We still get as before, what? CO2, as before we still get water. Those are products. That's not going to change. But now we've got this new molecule that previously wasn't there, it's called a what?

>> TP.

>> Steve Langjahr: And clearly, in case you didn't know, ATP stands for adenosine triphosphate. So to identify the players here, this is glucose. This is water. This is oxygen. This is ADP, standing for adenosine diphosphate. PO4 is a k a, inorganic phosphate, also abbreviated sometimes PI, PI standing for inorganic phosphate. And the product, the real gem, the real payoff, the money, is ATP. So show me the money? Right there, ATP. Now this is the actual formula for ATP. Don't panic, I'll never ask you to draw the formula for ATP, but if that were to flash into your head, or on the screen, or in a book, you'd say, oh, that's ATP. How do you know? Well, let's break it up. This is ribose. This is an organic base called adenine. The two of those together form adenosine. And then if you look out here, here's the business end of the molecule, that's PO4, PO4, PO4. What's PO4?

>> Phosphate.

>> Steve Langjahr: Phosphate. How many you got?

>> Three.

>> Steve Langjahr: So what's the – what's the fun name for this molecule? ATP. Is there energy wrapped up in there? Sure, there's energy in every single one of these bonds. But the only bonds that are broken and made, made and broken, are these last two, usually just that one, these are called high-energy phosphate bonds. And the energy which is transferred there, the energy which is transferred to create that bond, is actually derived from the breaking of these bonds. So simply put, how were we able to make ATP? Well, we hooked together an ADP and a?

>> Phosphate.

>> Steve Langjahr: Phosphate. But that isn't going to happen spontaneously, we had to get energy, we had to transfer it from the?

>> Glucose.

>> Steve Langjahr: Glucose and there it is. So you've heard this cliché, it is a cliche science, that ATP is the universal energy currency, unlike the world where we have pesos and dollars and rubles and euros. What is the universal dollar bill for all life on this planet, all life on this planet? It is ATP, that is the fundamental energy currency. And like currency it can be spent. It can be used to make or otherwise drive things. But when you spend money you're going to obviously deplete that currency. So when ATP is used, what do we get back? What is the result? We get back ADP, inorganic phosphate, and we release small bits of energy which can be put to use. Now, this is the big picture, which we're going to obviously examine with great detail, but we've said that the energy to make ATP is derived from the breakdown of such molecules of glucose. So glucose is a reactant. The products are on the right. What are the products? CO2, water, and heat energy. There's always a bit of wasted heat. But the real useful thing, remember, cells don't really use – they don't have the ability to harness heat, but they do love and use what? ATP. Apparently, and this is – this is still being debated, the amount of ATP made from a single glucose is somewhere around 38. Now you would think by 2017 we'd have this nailed, but let's just take 38 as kind of generally agreed upon, somewhere in that vicinity. And if we're going to make 38 ATP's we have to have 38 ADP's, but remember, what's really providing the energy to make this molecule is the bonds that are being broken in what? Glucose. This reaction that's boxed up there is not a reaction. It's actually what? Nineteen steps that are behind the curtain right now, but we're going to get to those. As we leave this notion, as we leave for tonight, we can't impress upon you too much the importance of ATP. Without ATP, game over. Without money, game over. What exactly do cells use this ATP for? Here we go. First, the synthesis of big molecules. Are cells making protein? Yeah. Are they big molecules? Yeah. Does it take money to do that? Yes. So macromolecules mean such things as polysaccharides, and most importantly proteins. Because think about, it's as simple as this, if a cell doesn't have ATP it's not going to be able to make, p word?

>> Proteins.

>> Steve Langjahr: And if it can't make protein it's not going to make enzymes, it's not going to make antibodies, it's not going to make muscle protein, on, and on, and on. Obviously, game over. B, active transport. We already said the other day, drives molecules not down but? Up a concentration gradient. Does that require energy?

>> Yes.

>> Steve Langjahr: Does that require energy?

>> Yes.

>> Steve Langjahr: Does it require energy to move bowling balls uphill? Yeah. So think about this, no ATP, no active transport. No active transport, cell is not going to get amino acids. No amino acids, can't make protein. No protein, no enzyme. Game over. Next, muscle contraction. What are the – what's the connection? Does it take ATP to contract muscles? Obviously. I mean, isn't it true that without energy you're weak or tired? So, so what? If muscle contraction fails, game over. Why? Your heart is not beating, your muscles are not moving, you get it. Finally, d, so division. You've seen videos of cells dividing, and you must be blown away. Wow, that's really impressive. It is. Does it take energy to do that? Of course. Cell division represented in the process mitosis and meiosis. You might say, well, at least I don't have to worry about that because I'm done with this meiosis stuff, and I'm an adult so I'm not doing the mitosis thing either. No, no, no. Are you making new cells every day?

>> Yes.

>> Steve Langjahr: If not, check your calendar because you'll be dead shortly. So, do cells need ATP to divide? Of course. Do they need ATP to contract muscle? Absolutely. So is ATP indispensable? Is it essentially the energy source for all of these things that add up to living and normal health? Yes. So we'll get into that more. Tomorrow's lab, though, all about enzymes. Have a great night. Drive safe.