>> It's March 29th. This is Physiology, in the usual place at the usual time. This is Lecture 15. It's our last installment in this unit, this neuromuscular physiology. We've been dealing with muscle mechanics. That means kinesiology, the study of motion, and indeed we described two types of contraction last time. You might recall isometric and isotonic and in fact we measured some isotonic contractions just yesterday. So now we're going to look at additional factors that influence ordinary activities, things that you do throughout your daily life, things responsible for movement, stability, success in athletics, or what have you. So II - Factors That Influence Whole Muscle Tension. Let's say I want to lift a bowling ball. Can I do it? Well, I have to have enough what? Enough T word. Enough tension. And total tension is really just a simple expression that means the number of fibers multiplied by the tension produced per fiber. It's a simple equation. It's much like a tug-of-war team. What determines the strength of a tug-of-war team? Obviously, the number of people on that team and the tension that each one applies to that rope. So this formula is pretty basic. TT is a function of the number of fibers that are actually contracting and the tension that each fiber is producing. There may be an additional bonus. ET, what's that? Elastic tension, which may or may not be present. And then that's a function of whether the muscle is pre-stretched. We spoke of that briefly at the end of our last lecture. So whether that's there or not, it's pretty insignificant. The big factors are number of fibers contracting and the tension per fiber. So let's look at each of those. What determines the number of fibers that are actually contracting? Well, basically, you do. You decide, you calculate, you determine the number of active motor units that you determine to be necessary for what you're trying to do. Sometimes that works; sometimes it's a bit embarrassing. Maybe you've had something like this happen to you. You see an opaque container on the table there. You say, "Oh, ooh." Ever happened to you? You thought it was full, but what? It's empty. And so you applied a certain number of motor units only to be embarrassed because you launched this thing way too high. So whether you think about it or not, you do think about it. You calculate. If that's a bowling ball, I expect it to be heavy so I'm going to what? I'm going to activate a certain number of motor units. If it's heavier than I thought, then I'm going to bring in more motor units until I lift it, if possible. So this is something you determine through experience, through practice, through trial and error. And basically then, you recruit, that means you add more motor units, as necessary. If you want to lift that bowling ball, that's one thing. If you want to throw it across the room, that's another. So naturally, one or the other might require more motor units. As a side note, usually when we recruit motor units, we recruit those slow oxidative units first. Remember, the slow units are the so-called red fibers. What's their claim to fame? What's their advantage? Why are they red? Myoglobin, oxygen, oxidative phosphorylation. These are the ones that are typically involved for everyday activities, that is activities that require some degree of endurance. Now, the number of fibers per unit is also a factor in determining total tension, but that's really something that you can't control. That's kind of hardwired. And we'll have more to say about that later. That is

the number of fibers per motor unit varies and it's actually a function we'll see of early childhood exposure to activities. But here is a strange photo. Where'd that pop up? This is an airplane, not a jet, but one with motors, right, and it has propellers on it. So these could be analogous to motor units. And does – does this motor unit have a lot of propellers? Okay. So the number of fibers per motor unit can dictate, that is determine in part, the tension. In this analogy, the more propellers might provide more power. What else? What determines the tension per fiber? Are all fibers created equally? Is one muscle cell the same as any other? No. Certainly the biggest factor here which is under your control is the amount of actin and myosin. How do you get more? Exercise. How do you get less? Don't. And so that's just it. And so you can change this, not overnight, but you can bring about increased fiber strength by adding or subtracting motor – I should say actin and myosin. The other factor – the other factors include the duration of the activity. Is a fiber going to produce more tension early in its activity or late in its activity? You know from the work we did yesterday, the longer you squeeze that transducer, it got harder and harder, the contractions got weaker and weaker. So certainly, the state of fatigue. Fresh muscles produce more tension than shall we say muscles that have been active for a period of time. Also, we know from yesterday that if we simulate a muscle more frequently, we get more tension out of it. This is called summation and it leads to a greater overall contraction, a greater overall shortening. And finally, although this is kind of subtle and probably not significant, is the so-called cross bridge overlap story. That can be changed. That can suffer if the muscle is stretched too far. Remember, if you stretch a muscle too far, the cross bridges come, well, essentially disconnected or dislocated from the actin and that lessens the tension per fiber. No. 4, though, not a usual big deal. So in this category, the most important determinant of tension per fiber is obviously the presence or absence of actin and myosin. So this is the formula for total tension. Lifting an object. Whatever you want to do. And if you want to lift a heavier object, you have to recruit more motor units or you have to go away and exercise and develop more actin and myosin. It's important to have strength, but you know, we don't have to be, you know, Olympic bodybuilders or anything. So although this is important for everyday activities, carrying a backpack, carrying some books, and what have you, it's not really determining your finesse when it comes to muscle contraction. This is kind of a brute force formula for total tension. What matters to most of this most of the time is not whether we can lift that or whether we can lift this, but rather how well we can control our attention, that is muscle tension, how coordinated we can be when it comes to things which matter. And so controlling tension is really not a function of strength, but rather how well we can control our motor units and the tension that they develop. And this, this control of tension, is determined by the number and the size of motor units that you have in a particular muscle, whether it's the biceps, quadriceps, and so forth. So let's explain that. That is less diagram. You don't have this, but you don't need it. Here's a cartoon of a muscle. Let's say it's the biceps. And these are motor units. You know a motor unit is a group of muscle cells that are innervated by a single motor nerve.

And so let's call this Muscle B. It has many but relatively what? Relatively small motor units. Let's compare that to Muscle A. How's that different? It has fewer but what? Larger motor units. For discussion, for the sake of this argument, let's say the number of cells in Muscle B and the number of cells in Muscle A is the same, and let's say that those cells have the same actin and the same myosin. You with me? This muscle has the total number of cells that we find here and they have the same actin and myosin content. So before we go further, which one's stronger? They're both the same strength, right. So when it comes to total tension, if they have the same number of cells and if those cells are endowed with the same amount of actin and myosin, they're going to have the same strength. But that's not the issue. The issue here is not strength but control of tension. Which of these two can exert finer gradations of tension? Obviously, Muscle B, I think, because you can recruit this one, then you can add that one, then you can add that one, then you can add that one. Whereas in Muscle A, you have what? Fewer larger motor units and that makes it, well, less capable of modulating, less capable of adjusting, tension. So this relationship, that is the number and size of motor units, is key when it comes to controlling muscle tension. And of course, the question that comes – well, how does this get done? Are we all wired the same in this regard? And the answer is "no". The number of cells per motor unit, that is their size, is established in youth as a result of activities that you engage in at that time. And most of us, let's say, having an average childhood exposure, are going to develop – are going to develop fine delicate control. That means muscles having what? Many motor units with fewer cells per unit. Where in the body would you expect? Where in the body do you know that that is present? Fingers. Where in the body do you not have such control? Back. And again, that's an okay situation because you don't use your back for fine delicate movements. So to summarize, what develops in most of us is many motor units with fewer cells in what? In the fingers, in the hand, and even in the tongue. Elsewhere, this kind of control is not important and typically not necessary, so along the back and along the legs. Again, this is not something that's the same in all of us. It's dependent on and determined by – determined by what? Childhood activities. A good example of this is cursive writing. Some of you don't know what I'm talking about, but there used to be writing called penmanship which was cursive and it was taught in schools. Controversial today, a lot of schools have just abandoned it as being unimportant. My mother in school, she would tell me stories that she would spend the entire afternoons with pencil and paper just practicing p's and f's and q's. And because of that early childhood experience, her penmanship was just amazing. Later in life, towards the end of her life, she'd send me letters. That was, you know, when people actually did that, you know. And I'd get the letters and she'd say I'm – she'd write this, you know, story of what's been happening and she'd say, "sorry, my – my handwriting is getting so bad." And I'd usually write her back and I'd say, "mom, you should see what I have to read." Now, no offense, but that's because cursive is just not emphasized or taught at all in a lot of schools. Here's an example of nice penmanship, wouldn't you say? That was my mother's. And here's a student from last semester. Not bad, but

certainly not really in competition with my mom. And then here's the worst I've ever had to read. Not readable, yeah. So the person said, "that's readable to me." I don't know. Didn't work. Now, you might say, "well, my writing is not that great, but I can get better with practice." No, you can't. Why not? When was this control over these muscles? When was the wiring? When was the establishment of these motor units available to you? Not now. In childhood. So you kind of missed the boat if you didn't really have that kind of training. Hence the justification for training in something like this. What about – what about somebody who was born without any arms or hands? What do you think what would they have to resort to for actions? Clearly their feet. I'm going to show you a video of just such a person and her name is – her name is Jessica Cox, and there are others like her, like her in the sense that they've had to resort to amazing abilities here. She's combing her hair not with her hand but with her foot. She's putting on mascara not with her hands but her food. And she's writing probably pretty well not with her hand but with her foot. You say, "well, I could do that with practice." No, couldn't. We could give you years and plenty of monies and you wouldn't be able to do it. Why? Because your feet are not wired this way and they won't be and can't be. Why are hers wired that way? Well, she was forced to do that from early childhood experience. And to add to her. I think. Astounding achievements is the fact that Jessica actually has learned to fly an airplane. No way, you say. Well, let's get this going. Jessica Cox.

>> Just three years ago, she had never been in an airplane because of the fear of flying. Now, 25-year-old Jessica Cox is a licensed pilot, which is pretty incredible considering she was born with no arms. [Inaudible] her story of triumph and courage.

>> This pilot is flying with no hands. Literally. Jessica Cox is the nation's first and only licensed pilot who has no arms.

>> When I tell people that I'm a pilot, they're like, "what?"

>> Jessica was born without arms, but she can do almost everything with just her feet, from putting in her contacts to texting her friends on her cellphone, even playing the piano.

[Piano]

Jessica has a black belt in taekwondo. She makes a living as a motivational speaker, but always had a fear of flying. So Jessica decided to face her fears head-on and got a pilot's license. She talked with [inaudible].

>> How is it possible to fly a plane without hands?

>> You know, I just – it's even hard for me to believe when I'm talking about it. You just do it.

>> Jessica invited us up for a spin high above the Arizona desert. Her lucky flying shirt reads "look ma, no hands". She showed us how she controls her plane.

>> And I would have my right foot right here on the [inaudible] and my left foot here on the throttle and I'm using my big toe to push on – to push the talk switch.

>> So you feel perfectly safe?

>> I do, yes.

>> Is there any issue of safety at all?

>> You know, there's not. After, you know, an hour, it's like driving with her in a car. After an hour or so, you don't even realize she has no arms.

>> Our cameras were mounted inside the small plane to see Jessica in action. Watch as she takes off. Jessica uses her left foot to control the throttle, then her right foot pulls up the wheel as she lifts off. It looks scary, but she does it like a pro. And watch after she makes a picture-perfect landing, she stretches her leg and opens the cockpit windows.

>> How was the flight?

>> That was fun.

>> Good for her. Doctors have never been able to come up with an explanation as to why Jessica was born without arms. Now take a –

>> But amazing, huh. So is there justification for learning the violin early in life? Think of somebody like an athlete. Let's take a golfer. Let's choose tiger woods. Did he start golfing at the age of 15 or 16? Nope. He picked it up at the age of 3. Did that contribute to his success? When you hit golf ball after golf ball after golf ball, then you get pretty good at it. Why? Especially in youth, because you establish this control over muscle tension. And so people who start something like that later in life have a decided disadvantage because they're working with motor units that just aren't really set up for that kind of activity. So let's move on. We said on many occasions, obviously, that muscle contraction depends upon ATP. So let's investigate the sources of that ATP. We know fundamentally it comes from mitochondria so that's really not anything new, but let's actually dissect or characterize muscle contraction at three levels. Let's investigate the sources that are necessary for a muscle that's resting, a muscle that's contracting, and one that's contracting for a long, long time. Three very different requirements. You might think a muscle that's resting doesn't need any ATP. I mean, after all, it's not contracting. But are there applications for ATP even in a muscle when it's not contracting? The answer is "yes". Does a muscle cell have to maintain a resting potential? Does that require maintaining the sodium and potassium exchange pumps? So even a resting muscle has a demand for ATP. Not much, but nevertheless some. And this can be provided by intracellular glucose, in other words glucose that's available on hand. And if that's in short supply, muscle cells can turn to FFA, free fatty acids. Fatty acids can be plugged into the citric acid cycle. So whether it's glucose or whether it's fatty acids, those can be processed aerobically through the citric acid cycle

and naturally we get CO2, water, and a lot of ATP, certainly enough to meet the demands of a muscle that's resting. But what about a muscle that begins to contract? Does it need more ATP right now to do that? So it really has to ramp up its production of ATP. And so what are the sources that kick in when a muscle actually begins to contract? It turns out that muscle has an interesting adaptation, that is a molecule not found in other tissues called creatine phosphate. And as you can tell, this must be a molecule that has, well, phosphate. Creatine phosphate is just that. It's a molecule with one phosphate group. And it has the ability to transfer that phosphate group immediately onto existing ADP, therefore making ATP very quickly. Because it's a one-step reaction. It doesn't require any oxygen, nothing fancy. The creatine phosphate is giving it's what? Phosphate to what? To make what? And this is really quick. So this will happen within the first seconds of a muscle which is now being stimulated and contracting. And knowing it's necessary then is ADP and there's plenty of that. Creatine phosphate, there's plenty of that. And this enzyme called creatine kinase. So let's not misunderstand. Is creatine phosphate taking the place of ATP? No. It's being used to make ATP. And so the next tantalizing question is, okay, how long can this last. How long can energy be made from existing creatine phosphate? The answer is five or six seconds. Five or six seconds. And you think, well, that's not very significant then, is it? But it is significant because in those first five seconds, we need energy quickly and this provides it, and it buys some time so that other mechanisms which are slower and more complicated can come online, namely, usually, the breakdown of glycogen. Do muscle cells have glycogen? Yes. What is glycogen? A bunch of glucose molecules. Can we cut that up and make glucose available? Yeah. And so muscle glycogen is quickly hydrolyzed into glucose and then is made available for either aerobic or anaerobic activity. Aerobic, of course, being more efficient, producing just CO2 and water and plenty of ATP. Anaerobic is less efficient, as you know, producing what byproduct or end product and much less ATP. But let's be clear, the muscle doesn't decide. It doesn't say, well, we're not going to work too hard, let's just go anaerobic. It always goes what? Always aerobic unless what's not there? So naturally, this is the typical way in which muscle glucose is used. And so I guess the question would be how long can a muscle continue to contract using glucose derived from its own glycogen. The answer to that is obviously a function of how much glycogen was there. And are all muscle cells equipped with the same amount of glycogen at any given time? No. Remember, we talked about red fibers and white fibers, and we actually said white fibers have more glycogen. However, of course, white fibers have no myoglobin. Therefore, they're forced pretty much to go anaerobic, so they don't use that glycogen as efficiently. But I guess I'm being around this question. What was the question? How long can a muscle continue using its own onboard glycogen? Let's say 15 minutes to maybe an hour. That would be tops. And that depends on the kind of muscle, that is the amount of glycogen that's there from the get-go. So can muscles contract for more than an hour? Sure they can, but they're not going to be running on muscle glycogen and they're certainly not going to be running on creatine phosphate. So what then keeps a muscle

going after it's depleted all of its glycogen and all of its creatine phosphate? Prolonged contraction over hours is really dependent then on outside sources, outside sources of glycogen. And what organ aside from muscle contains most of your body's glycogen? Liver. And when called upon, the liver will cut up that glycogen, hydrolyze it, and put it into the blood not as glycogen but as glucose. And that will be then taken up by muscle cells and used for as long as, well, as long as it's there. Now, aside from liver glycogen, we also carry with us a lot of adipose. Adipose is, of course, a triglyceride, a lipid, and it can be broken down into glycerol and FFA. What's that? Free fatty acids. Those can enter the bloodstream and muscle doesn't really mind that. It really doesn't care. It – it will use glucose or it will use free fatty acids. Both of those can be processed through the Krebs cycle and keep the muscle happy, that is keep it supplied with ATP. These facts are well known to marathon athletes. A marathon athlete has to continue to perform for hours. Yes? Are they going to be using creatine phosphate? No. Are they going to be using their own internal glycogen? Only at the beginning. So if they're going to finish that race, they obviously have to have plenty of liver glycogen and a fair amount of adipose. Adipose is kind of a double-edged sword, though. That is this remark here makes it sound like a sumo wrestler would be a good marathon runner, but not because they have to carry that with them, and so that's going to demand more energy and more muscle activity. So for marathon activity, most of the substrate, most of the resource for ATP, is provided by liver glycogen. And you know probably what is the behavior, what is the strategy of these runners the night before an event. They carb up, eat a lot of pasta. And what are they trying to do? They're trying to build out their liver glycogen because typically you're not eating when you're running. I guess you can, but it's better to rely on liver glycogen. How long can you survive, that is how long can you continue to contract with liver glycogen? Nobody knows, but certainly hours and hours and hours. And of course, some of that energy also comes from breakdown of fat, which I suppose is part of the justification for exercise, right. Why do people get on a treadmill? They're not trying to win any events. They're trying to lose what? They're trying to lose weight. And that will happen, but they first have to deplete what? They have to deplete or at least get rid of some of the liver glycogen before they're going to start touching much of the adipose. So in summary, a resting muscle needs energy? Yeah. Does it have enough glucose on board to probably meet that demand? Yeah. And then it starts to contract, it's going to need what? Creatine phosphate. But is that a short or long resource for ATP? Short. Perhaps you're aware that many health food stores sell creatine and a lot of athletes swear by it, but it's a little bit exaggerated because no. 1 it doesn't make muscles bigger and no. 2 it provides ATP only for what? Only for a short period of time. Will this help a sprinter? Yes. Would it help a marathoner? No. So that's the science behind creatine phosphate. If you're going to contract muscles for a long period of time, forget about muscle glycogen. That's going to be gone within 15 minutes or so, and so then you have to rely on what other source of glycogen? Liver glycogen and/or adipose, which, you know, is available to some extent in all of us. But sooner or later in all of us, something

like fatigue happens. Although it's interesting because if you look back here, if we had a constant source of food coming in, we'd be able to maintain blood sugar indefinitely, yes. And that would mean that we'd be able to contract muscles indefinitely. And in fact, we can. I mean, think of a muscle like your diaphragm. Does that contract throughout your life? Does it ever fatigue? So interesting, and what limits endurance is often not the muscles but the brain. I love these facts. You know, you can go to Google and find out anything, so here's an interesting question. What's the world record for extreme walking? That means walking without stopping, no rest, no sleep, walking. What do you think? Well, that's pretty good. It's six days. 154 hours and five minutes non-stop walking. And it wasn't the muscles that gave out. It was what? Because you just can't go on without sleep, so I'm trying to make the case that muscles provided with glucose can go on indefinitely, but can supply not meet demand, and do muscles in most of us suffer from fatigue from time to time. So what is muscle fatigue? We discussed it. We just really investigated it yesterday. The definition is reduced muscle strength associated with prolonged activity usually. So okay, there are two types of muscle fatigue, you recall. One's called, well, the fancy name for it is central fatigue because it's an issue with the brain. We're going to call it psychological fatigue. And it's basically where there is a reduced development of motor what? AP's because of a sense of what? Pain or exhaustion. So to some extent this is voluntary. In other words, the activity gets very unpleasant and so you what? You say this is no fun anymore, I'm not going to do it, I'm done. And to me, that usually is where I stop, but – and remember, we shouldn't think of this as wimpy because is pain something we should acknowledge and, you know, consider? Sure, because if we ignore pain, then we're going to push beyond it and perhaps get into serious trouble, actual injury to our joints or bones or who knows what. So actually, psychological fatigue is good because it prevents us from injury which might require a long recovery or even be lethal in some cases. But of course, athletics is based upon going beyond what? Going beyond this psychological fatigue and pushing the envelope. And so the next level of fatigue is called physiological fatigue. It's perhaps easy to think that it's due to a lack of ATP, but we made this case yesterday. It's not due to an exhaustion of ATP nor is it due to a buildup of lactic acid, two popular theories which have been disproven. Even in a muscle that's physiologically fatigued, only about 30% – there's only been about a 30% decline in ATP. In other words, a muscle which is physiologically fatigued still has ATP. It might have a buildup of lactic acid, but that's more circumstantial. What would cause lactic acid to be present in any cell? Anaerobic. But is that the cause or is that just a marker of what's going on? It's an indication of anaerobic conditions, but we can't just say, oh, well, there's your cause. So what is the cause? Theories abound but not necessarily proven. One of them is it's a buildup of ADP, an inorganic phosphate which is generated in huge quantities when muscles contract, and this interferes with the power stroke, so it seems, and may reduce the release of calcium from the sarcoplasmic reticulum. Maybe also in some cases failure of the neuromuscular junction because after all the performance of that synapse depends upon this transmitter which

is acetylcholine. Could we be stimulating the muscle so rapidly that there's insufficient restoration of ach? Sure, it's possible. Also a theory is that there's a buildup of extracellular potassium. Now, you can memorize that, but why would there be such a thing? Every time a muscle depolarizes, the cell gains what? Sodium. And loses what? And if the pump can't keep up with that, you're going to have a buildup of extracellular potassium. That will lead to persistent, persistent maintained what? Maintained depolarization, which very definitely would interfere with muscle contraction and bring about fatigue. So these are some of the theories that explain physiological fatigue. For most of us, this is a nonissue because we rarely get there, but at least in theory, muscles can be brought to the point of complete exhaustion mainly because of a buildup of ADP and these other factors. Muscle fatigue. Aside from fatigue, can muscles fail for other reasons not related to fatigue? The answer's "yes". So I thought it would be fun to outline some of the other neuromuscular scenarios which lead to dysfunction, in other words weakness, because that's fundamentally what we're talking about here. Muscle fatigue is really just a kind of weakness. Can muscles become weak for other reasons, pathological or otherwise? The answer is "yes". What if we had something in a bottle which could occupy ACH receptor sites? What would that mean? Something which would occupy ACH receptor sites. Those sites are supposed to only accept what? Ach. But what if we had an imposter? What if we had a molecule which could act like acetylcholine but not do what acetylcholine does? There are a number of things in medicine and in nature which are exactly that. One of the first to be discovered is curare, which was actually discovered off the bark of a tree in the amazon rain forest. But this occupies ACH receptor sites, therefore causes paralysis due to what? What does ACH normally cause or bring about? D word. Depolarization. If you're blocking those sites, what's not going to happen? Depolarization. And so this is going to be the cause of paralysis in those cases. Actually, a friend of mine was traveling in the amazon and he brought this back. This is actually a blow dart which is used by the natives there. It's tipped with curare. You've seen this on videos or movies, you know, Indiana Jones and stuff like that. So you know, you just launch this out there and some mammal gets killed right on the spot. I'm saving this one for a special occasion. Alright. Yeah, curare. You say, well, that's interesting, but it doesn't have any practical application. The answer is, no, it does. Curare, or things like curare, are used all the time in hospitals, in surgery. Why? To kill people? No. To relax muscle. Is it easier to cut on muscle when it's relaxed? Yeah. So curare and those things like it are used as muscle relaxants in surgical settings. Dangerous though because what skeletal muscle do you not want to relax? Diaphragm. So you're not going to mess around with curare in, you know, a home operating room. You just might kill somebody. Next, inhibition of acetylcholine esterase, which is an enzyme. We spoke of this previously. What's the function of that enzyme? That function is to break down acetylcholine and allow the muscle membrane not to depolarize but to repolarize. So if we inhibit that enzyme, the muscle will be able to depolarize, but it won't be able to repolarize. And if it can't repolarize, then guess what. It can't depolarize. In other words, this is paraly-

sis. You might think there's no application for this. Certainly many nerve gases which are weapons will exploit this and that's not a therapeutic function, but there are medicines, such as neostigmine, which can be used carefully for some patients. Patients who have myasthenia gravis have a reduction in the number of ACH receptor sites. Now how can inhibiting this enzyme be helpful? Do they still have some acetylcholine? Yes. If we delay the breakdown of acetylcholine, would it have a chance to linger, accumulate, and therefore trigger these ACH receptor sites? Yes. So neostigmine is a drug of choice to treat something like myasthenia gravis. Would it be good for you or I? No. If you take this, you'd be bad. Why? Because it would prevent the r word, repolarization. So naturally a therapeutic but also a dangerous drug at the same time. What if we inhibit the release, the very exocytosis, of acetylcholine? Pretty obviously, if you don't release acetylcholine, it's not going to find or act on these ACH receptors, therefore the muscle will not contract because it won't be able to d word, depolarize. The most famous member of this group is Botulinum toxin, trade name Botox, which is wildly popular and in fact a whole cover of time magazine was devoted to this because its uses seem to be increasing and increasing and increasing. You know it as what? Those – what's the most famous, if sort of frivolous, function of it? It's to treat wrinkles, right, and the truth is it doesn't treat wrinkles at all. All it does is relax facial muscles so that there's no real buckling of the skin and it gives your skin a kind of smoother texture. But wrinkles, the function of ultraviolet exposure and changes in the chemistry of the dermis. So whatever. People are wildly happy with Botox. But what's it do? It causes paralysis of skeletal muscle because of a failure to depolarize muscle membranes. Back in our not so distant history, there was, well, during the bush administration, weapons of mass destruction. Remember that phrase? And we sent troops into Iraq because who – Hussein, Saddam Hussein had weapons of mass destruction and it was allegedly that he had huge quantities of Botulinum toxin. He wasn't using it for cosmetic surgery. But could this be leashed – unleashed in the form of a weapon? Yeah. Wouldn't take much to kill the entire world population. So this is serious stuff. But it can be used on a more useful level to not just cosmetically release muscle contraction in the face, it can also be used to treat migraine headaches, to treat spasticity of the eyes, something called torta callous, because obviously it relaxes muscle. But what muscle do you not want to relax ever? The diaphragm. What about depletion of ATP? Could that cause neuromuscular dysfunction? Well, we've already argued that that never happens during life, but it does happen after death and it produces a kind of paralysis called rigor mortis, and this has, well, this is stiffness due to the inability of muscle cells to remove what ion? Calcium. Because how is calcium removed? How is calcium returned back to the sarcoplasmic reticulum? It's through active transport which depends upon ATP. So rigor mortis has no clinical significance because you're dead, but it can be useful in determining the time of death, that is it can be used in forensic investigation, crime scene investigations. Rigor mortis due to the absolute depletion of ATP. And finally, as a category, what about so-called electrolyte imbalances? That's a catchphrase which everybody uses. Oh, it must've been an electrolyte imbalance. What does that mean?

It can mean anything because electrolytes run the gamut. Is sodium an electrolyte? Is potassium an electrolyte? Is calcium an electrolyte? Is chloride an electrolyte? Sure. So what are we talking about here? Well, at least the most common offender in this category is calcium. We mentioned this early in this unit because situations which lower extracellular calcium – be sure to underline that – not intracellular. Let's make a distinction. What's the calcium inside the sarcoplasmic reticulum? Is that intra or extracellular? Intra. So we're not talking about that. We're talking about extracellular calcium, which turns out to influence sodium permeability. And in fact low extracellular calcium causes more or improved sodium permeability. So think about that. Here's something which improves sodium permeability, therefore more sodium's going to go which way? In. And what's that going to do? Well, remember, sodium influx is what depolarizes muscles and nerves and so this is going to cause spontaneous and unwelcome depolarization. And when that happens along motor nerves, what's the net effect? When motor nerves are spontaneously depolarizing because of a low extracellular calcium level, that's going to cause cramping and maybe something called unwelcome tetany. And if you recall, we mentioned this in the context of pregnancy. Why is pregnancy connected to this story? Pregnant females tend to have low extracellular calcium. Why is that? Well, because their fetus is basically grabbing it all out of maternal circulation. So how do you treat this in a pregnant woman? Might she suffer from cramping or unpleasant muscle tone? Yeah. How can you treat it? It's pretty easy. You just give them some calcium in the form of a supplement. So ABCD, these are somewhat common or at least possible cases that can interfere with neuromuscular performance. Next category, next topic, something called oxygen debt, which may be a foreign phrase to you or you may have heard it. But what does it mean? Here's the definition. Oxygen debt is the oxygen needed not during exercise but what? After exercise to completely restore, that is to bring about complete metabolic or physiological recovery. Okay, so that's a understandable definition, but what's this really all about and what's the significance of this. Let's put it into a scenario. Here you are sitting at your desk and you're consuming a certain amount of oxygen. Okay, fine. And then we say get up, run around the building, and so that running around the building is some activity which starts here, ends there. Now, what if we superimpose oxygen consumption? We're not talking about breathing rate. We're talking about actual oxygen consumption. At rest, you're consuming this much. Okay, fine. During the exercise, would you expect oxygen consumption to go up? Sure. But the surprising thing is that oxygen consumption remains high even after what's done, even after exercise has stopped. And you know this from personal experience. If we ask you to run around the building, you'd do that and then you'd be sitting down here, and for a long time you'd be – you'd be noticeably exerting, that is you would be moving more air and indeed consuming more oxygen. So this amount of oxygen that we use above and beyond normal after exercise is apparently oxygen that is essentially being used to achieve this, that is to restore the muscle to its previous condition, to bring about complete metabolic recovery. And, okay, what are the actual reasons for or value of this oxygen which is so excessively

consumed even after the exercise? What are the post exercise oxygen uses? Well, all of this ate – all of this oxygen that's being used is basically being used to synthesize ATP, which is necessary for this metabolic recovery. So let's list the actual applications of this oxygen for metabolic recovery. When you've exercised, did you deplete creatine phosphate pretty quick? Does it take ATP to restore that creatine phosphate? Yes. Does it take oxygen to make that ATP? Yes. So some of the oxygen that's part of this O2 debt is being used to restore, rebuild, the creatine phosphate. Not a lot, but some. Certainly during exercise, has myoglobin been depleted? What is myoglobin? Protein that stores what? Now, myoglobin is still there, but remember, myoglobin stores what? Oxygen. During exercise would that oxygen be gone or otherwise used? Yes. So to reload the myoglobin so to speak and also to restore oxygen levels on the hemoglobin, that's going to use up or account for some of this oxygen that's being used in the O2 debt. Let's remember, myoglobin is physically found where? Inside a muscle. Where's hemoglobin? Inside a red blood cell. Do both of these give up oxygen in the course of a muscle effort? Do both of them need to be recharged or otherwise restored with oxygen? Does some of that post exercise oxygen go for this purpose? Yes. So re-oxygenating these molecules is part of the O2 debt. But the biggest burden, the biggest explanation for this excessive oxygen consumption is to oxidase – to oxidize a lot of byproducts that have probably been produced during the activity, not the least of which are pyruvic acids and lactic acid. Pyruvic acid also known as pyruvate. Lactic acid also known as lactate. And this is achieved in the liver and it requires oxygen to do so. So let's just paint this scenario. Can exercise produce lactic acid? Yes. We know that's not responsible for fatigue, but nevertheless that lactic acid will leak into the blood and find its way to the liver. Is the presence of lactic acid going to put a burden on or at least require some oxygen to oxidize that acid? Yes. So as you know, if you think back to unit 1, can we take lactic acid and push it back to pyruvic acid? And can we then take it into the citric acid cycle? Yes. But what does it take to do that? Oxygen. So the availability of oxygen and the consumption of a lot of oxygen in the post exercise mode is used to just do that, that means convert lactic back to pyruvate. And then we can push it down through the citric acid cycle and generate what? What do we get when all is said and done? We get CO2, water, and what? ATP. So this is interesting because it puts a new light on lactic acid. A lot of people think lactic acid is evil, but is lactic acid a source of energy in the post exercise situation? Yes. But it requires what? You can't use lactic acid for fuel until and unless what's available? And that is available and will be consumed in larger quantities than in a post exercise mode. Also interestingly, some of that lactic acid, is much as 50%, can actually be used to make glucose. That seems odd, but after all, where did lactic acid normally come from? It came from a breakdown of glucose. Can we push those reactions in the other direction? Yes. But to do so requires a lot of what? ATP. And that's going to require a lot of oxygen, so this also explains why there's a greater consumption of oxygen in the post exercise mode. And why bother making glucose? Well, remember, during exercise have we depleted some of the glycogen. Do we need to restore that? And how do you

restore glycogen? Well, you have to make available glucose. So the interesting connection here is that lactic acid can be used to make glucose which then can be used to restore glycogen, but all of this depends upon a greater consumption of oxygen, hence the O2 debt. Some of the lactic acid is lost in the kidneys and therefore, you know, that's just that. But the final thing that has to be achieved before we can say the muscle is fully restored is that we have to build back up whatever liver glycogen or muscle glycogen has been depleted. And remember, glycogen's made of what? Glucose. And how can we make glucose? Well, we can make it turns out from lactate, but is that going to require oxygen? Yes. So all of these require a greater consumption of oxygen than normal and in fact that's the definition of the O2 debt. The O2 debt is not the amount of oxygen you use during exercise. It's the amount of oxygen that you use when? After exercise. To do these things. And speaking of these things, ABCD, which of these can be completed sooner or easier and which takes way more time? Well, A and B are pretty quick. Those can be done in a matter of minutes. C and D take much more time, especially D. And with that said, it may explain why, for instance, that a marathon runner doesn't run a second marathon right after the first one, right. Do they just say, well, I'm done, I'm going to do another one tomorrow in Boston? No, because they haven't yet fully repaid the what? Their O2 debt, and that means the status of their liver glycogen and muscle glycogen is not back up where it needs to be. But let's be clear about this and let's focus on not just what it is but what's the significance of it. Does all activity produce an oxygen debt? No. Let's take two activities just to compare. Here's a 15-minute wrestling match, and I don't mean, you know, the stuff you see on TV where people are just acting but a real Olympic style Olympic wrestling match, as opposed to an hour of jogging, okay. Hour of jogging, 15 minutes of wrestling. Which would produce, you think, the greater oxygen debt? Actually, the wrestling. You think, whoa, an hour, 15 minutes, but that hour of jogging is probably aerobic, right, and therefore less likely to produce a lot of lactic acid. On the other hand, that wrestling is very fast and furious, probably largely anaerobic, probably using a lot of white fibers. So which of those two would produce the most lactic acid? The wrestling. Which would therefore have a greater O2 debt? Wrestling. But true or false, if you produce no lactic acid, you have no oxygen debt? Well, that's false because even if you produce no lactic acid, you still have to restore what? The creatine phosphate. You still have to recharge the myoglobin and the hemoglobin and you still got to restore liver or muscle glycogen to some extent. But is it fair to say the more lactic acid you produce, the higher the O2 debt? Yes. But still we're avoiding the central question because if we go back to the definition, O2 debt, the oxygen needed after exercise to bring about complete physiological recovery, okay, that's the definition, but what's the significance of that. I mean, why is this good? Or is it good? I guess we can sort of get at it as we focus just on this word here. Debt. Do – does everybody in this room have financial debt? Yes. Why do we do that? Is it a good thing? It must be good or we wouldn't do it. But what is the advantage of acquiring debt? You can get it now and what? Pay later. Isn't that the American way? Get now, pay later, maybe never. I'm just

joking. But that helps us get at the significance because if we couldn't borrow or otherwise acquire an O2 debt, would that limit our ability to do things? If we had to pay for this as we go, it would clearly restrict the intensity, maybe even the duration of our activities. So what is the advantage? What is the significance of the oxygen debt? It's the same as if we were talking about financial debt. It allows you to do what? Something right what? Now. And then pay it back what? Later. And what is that something? That's intense activity. Can that activity be sometimes lifesaving? If you're running from a lion our, I don't know, somebody in L.A.? You get the idea. So an oxygen debt is a good survival mechanism because it allows us to engage in high-intensity effort and worry about the consequences, that is pay back that and paid back through restoration of these things at a later date. Oxygen debt. Now finally, in the moments we have left, and we'll fit this in easily, activity related changes in muscle. Certainly something we've observed and known about but yet there are some mis-concepts about what actually is going on. Muscle, skeletal muscle, can change in two obvious ways. It can get stronger or it can get weaker. And when it gets weaker, that's called atrophy. And not just weaker in terms of tension, but obviously also smaller in size. What do you suppose happens to the leg muscles of a paraplegic person who's been in a wheelchair for 10 years or more? What happens to those muscles? They definitely what? They atrophy. Is that because of bad nutrition? Is that because of bad hygiene or bad anything? No. It's because these muscles are unable to do what? Contract. And if they're unable to contract, these muscles essentially dismantle their contractile proteins, that is they get rid of myofilaments. And therefore is the muscle weaker? Yes. And is it therefore going to be smaller? Yes, of course. So this is sometimes voluntary, sometimes involuntary. Are kids in the United States typically these days suffering from some disuse atrophy? Why is that? I don't want to get into a controversial thing, but they're sitting on a couch somewhere exercising their thumbs, you know, playing PlayStation or something. So not everybody, but you know what I mean. So it can be voluntary or involuntary. It can be due to hospitalization. It can be due to paraplegia. It can be due to simply not wanting to exercise. What's the opposite? The opposite of atrophy is hypertrophy. And do the muscles get stronger, maybe even bigger? Yes. Hypertrophy as a concept means an increased capacity to do work, increased capacity to do work, which is only going to happen in response to placing demands on the muscle, demands beyond the normal activity. So if I just go to work and go home, go to work and come home, are my muscles going to hypertrophy? No. Are they going to atrophy? I hope not, but they're certainly not going to hypertrophy, right. You've got to ask more of them. You've got to pushy them into things, into activities that they're normally not involved in. So there are two kinds of activities that can generate different changes, both of which are more or less associated with hypertrophy. And one of those is weight training or aerobic ex – excuse me, I'm skipping around. The two basic types of activities which can transform muscle are aerobic exercise versus weight training. Aerobic exercise is just what we're talking about, jogging, running, and so forth. This causes an increased production and concentration of mitochondria and Krebs cycle en-

zymes. And therefore do these muscles have more efficiency, more capacity to generate ATP? Yes. And they also will have as a result of this aerobic daily activity increased creatine phosphate and increased myoglobin. Are these muscles now more efficient? Are they better for the long run? You bet. Are they larger? Not appreciably because what makes a muscle bigger is not aerobic exercise but rather weight training. They will have increased vascularity, they will have increased myoglobin, they will have increased creatine phosphate, they will have increased mitochondria, but these changes basically bring about improved metabolic efficiency. How do we get muscles big? We have to lift big weights, and that's called weight training. Because that puts more L word. More load and therefore requires more T word. Tension. And muscles respond to that by building, synthesizing, more actin and more myosin. And so this is the function or I should say the outcome of weight training, building more myofibrils. And let's be clear. Does exercise of any kind increase the number of muscle cells? Does it change the number of motor units? No. So exercise does not affect muscle control of tension. It only increases total tension, at least in the case of building actin and myosin through weight training. And there will be along with this an increase in glycolytic enzymes that is associated with glycolysis. So simply put, if someone were to engage in weight training and weight training alone, would they be good for a marathon? No. And if someone was engaging in jogging, would they be good for lifting motorcycles? No. So naturally, a balance of these two make some sense. A certain degree of weight training builds muscle strength, muscle size, and aerobic exercise builds capacity, endurance, and overall efficiency. So any so-called trainer is going to insist that you do a little bit of what? Weight training and a little bit of aerobic exercise. It's the healthy and obvious proper balance. But finally, never mind hypertrophy or even atrophy, what is muscle soreness? Not to be confused with muscle pain. We've all experienced pain. Many of you yesterday when you squeezed that thing and you said this is getting painful. Muscle soreness is something that develops the day afterwards and is not due to a buildup of lactic acid because that lactic acid is quickly oxidized, as we said, in the first 24 hours usually. So when a muscle is sore, it's because of actual physical damage to the soft tissue, which may not even be the muscle. It could be the tendons. It could be the ligaments. It could be the fascia. And that's usually the result of, well, overdoing it. Is everybody guilty of that from time to time, overdoing it? The classic scenario is, you know, you got a subscription to 24 Hour Fitness or a membership, somebody gave it to you. They gave you a water bottle and a towel, too. And you say, well, I better go. So you go there and you see all these people and you say, well, I guess I better get on the bandwagon here. And you get on the treadmill and might you overdo it? And what happens the next day? And that's the end of your trips to the gym, right. You won't go there anymore. I know I'm just being flippant here, but muscle soreness, can that be avoided? Yes. And so this adage of "no pain, no gain" is that really true? Can you gain without pain? You can, but most of us are inpatient, so most of us suffer what? Pain and then maybe some gain if we can get past this period of anxiety and regret and muscle soreness there. So that's it. That wraps up this unit. I hope

you have a great holiday. I guess it's a – it is a holiday. We'll see you next week if not maybe Wednesday.