[Background Conversations]

>> March 23, 2016. We're going to continue tonight with our look at skeletal muscle, briefly recapping it. We said skeletal muscle was very quick in its contraction. We said that it produces a voltage in the same way that neurons do. But, perhaps, the most interesting discussion we've had is that skeletal muscle is not uniform in its biochemistry. We had two very distinct kinds of skeletal muscle. The so-called "fast twitch" versus the so-called "slow twitch." The slow twitch were also called red, because they have a high concentration of a pigment, an oxygen binding protein, called myoglobin. And as a result, these cells are really geared up, and designed for high efficiency oxidative phosphorylation. Accordingly, they're difficult to fatigue. The fast twitch fibers have very little myoglobin, and really don't have the machinery then for oxidative phosphorylation, so they get most of their energy from glycolysis, which has the advantage of generating ATP quickly, although inefficiently. And for that reason these cells tend to fatigue quite a bit sooner. But don't get the idea that red are good, and white are bad. They're equally good, just for different things. For long-term contraction, the slow oxidative fibers have an advantage. For quick bursts of contraction, like jumping out of the way of a bus, that would be the fast twitch, or white fibers. Leading this category, we should mention, and maybe you're aware, that skeletal muscles are amitotic. They cannot divide. So if you lose 1,000 muscle cells, you're going to get them back tomorrow? No. They are not capable of dividing. And the same, incidentally, is true also for cardiac muscle. With that said, you might say, "Well, I don't quite get that, because what about bodybuilders? They start out looking puny, and now they're all buff." Are they getting more cells, or are their cells simply getting bigger? It's the latter, because, certainly, exercise will increase the size of the cell, specifically the concentration of actin and myosin. So will these cells be bigger? Yes. Will they be stronger? Yes. Will the person be healthier? Well, we could argue that. But, anyway, it's always a function of synthesizing. That is, adding or subtracting actin and myosin. In short, use it or lose it. And we'll have more to say about exercise, and its effect on skeletal muscle later. So after all, skeletal muscle's the dominant muscle. But let's at least pay some respect to the other two types, if only briefly. And, so, for no good reason, let's move on to cardiac muscle. We're going to spend most of our time naturally focusing on cardiac muscle when we get to the circulatory system. So we're just going to review, and hit some of the highlights here. Obviously, the function of cardiac muscle is to bring about movement of blood. That is, it provides a pumping mechanism for blood circulation. And we're not going to dwell too much now on the structure of the heart itself. So let's jump down to the muscle cells. They are, as you know from Anatomy, mononucleated. They're highly branched. They're connected, or you could say bonded, even welded, you could say, with these connections called "intercalated discs." So I know you've recognized, or come to recognize, cardiac muscle through a microscope naturally. Do they have myofibrils? Yes. And they actually may pierce or extend between cells making two cells more or less acting as one. Are there myofilaments? Are

there actin molecules? Are there myosin molecules? The answer's yes. And they're arranged, and they operate pretty much as do skeletal muscles. What are some of the unique or noteworthy characteristics of cardiac muscle? First, they also maintain arresting potentials similar to neurons. And, so, in this respect, they're very much like skeletal muscle. They have, however, involuntary spontaneous contraction. They contract all or none. And their autorhythmic. What's that mean? Self-rhythmic. So if we took your heart out of your chest, would it stop? Well, eventually. But would it continue for some time outside your chest? Yeah, because, essentially, it stimulates itself. It doesn't rely on the brain or motor nerves for its activity. And, so, even though it sets its own pace, it is subject to outside influences. Can the heart be accelerated in terms of its rate? Can it be slowed down? Yes. Number five, largely what? Slow twitch fibers. Isn't that, well, sort of logical? What are one of the notable characteristics of slow twitch fibers? Not just that they're slow, but they're very efficient. And if your heart was fast twitch, it would have fatigued a long time ago. So we're expecting, and thankful for, the fact that it's mainly slow twitch oxidative fibers, which permits maximum efficiency. Even though the heart rate is set by internal mechanisms, internal cells, known as pacemakers, its rate can change, and does change from outside influences. Namely the autonomic nervous system. And as you know, that's an antagonistic system. That is, a system of antagonistic divisions where sympathetic is counteracted by parasympathetic. Hence, these symbols, positive and what?

[Inaudible Speakers]

So the sympathetic and parasympathetic serve to regulate. That is, change the contractile rate of the heart, according to circumstances. And not only the autonomic nervous system, but, certainly, chemical control, which is best exemplified with hormones. The most notable of which is what? What hormone has a legendary, excitatory effect on heart rate? Adrenaline or epinephrine. So, certainly, the heart rate can change, and does so in response to autonomic nerves, and/or circulating hormones. Finally, as we've already mentioned, the heart also is amitotic. So when you suffer a heart attack, have you lost, have you destroyed a certain number of cardiac cells? Yes. Might you recover? Yes. But is your heart the same as it was before the attack? No. Will it get better? No. It may actually get worse. And that's because cells do not divide sadly. Cardiac muscles are amitotic. Turning over to smooth muscle. Smooth muscle is so called because there are no visible banding or striations seen under the microscope. The functions made possible here are largely wavy contraction along hollow, or otherwise circular, organs, such as the GI tract, the vagina, the bladder, and so on. It also brings about vascular contractility. What does that mean? What are the two types of blood vessels you know? Arteries versus?

[Inaudible Speakers]

And are there smooth muscle in the walls of these? And does that affect their size, and, therefore, blood pressure, and, perhaps, blood flow? So vascular contractility plays a role in circulation, in blood pressure, and in blood flow.

Essentially, the cells here are unique, because they're not cylinders. They're tapered at both ends. So we say they're spindle-shaped, mononucleated, and definitely not striated, as the name implies. They are, however, tightly fitted. Tightly fitted. And, actually, you could say fused through what are called "gap junctions," so that each cell, essentially, affects the ones next to it, or attached to it. And this brings about the very familiar behavior of smooth muscle. It tends to contract in a wavic fashion, from point a to point b. And this wave of contraction is carried through the so-called "gap junctions," which, basically, bond or fuse these cells together. We do show in this illustration a nerve supply. But this is not to stimulate, but, rather, to regulate. As we're about to say, smooth muscle is also autorhythmic. That is, it sets its own pace. But we're getting ahead of ourselves. Why are these cells smooth? Why don't they have striations? They do have myofibrils. But they're not as regular. They're not as organized. What's the opposite of organized? Disorganized. And that is, the myofibrils are very scattered. That is, oriented in different directions. And that tends to muddle or hide or mask the striations which are so striking and typical in skeletal, and even cardiac muscle. So they do have myofibrils. And they do have myofilaments. But those myofilaments, again, are kind of diagonally arranged, rather than parallel to the long axis of these individual cells. So when a smooth muscle cell contracts, it contracts not only on the long axis, but it can also contract on the short axis, and sort of contract all around, rather than just end to end, so to speak. What are some interesting characteristics? Well, maintains a resting potential similar to neurons. That's not new or, by any means, unique. These are the slowest muscles. That is, they contract very slow. Sometimes taking as long as two or three seconds. And you shouldn't think of that as negative, or somehow inferior, because the kinds of things that they do are, obviously, slow, sustained efforts. Think of moving feces through the GI tract. That's an example of slow, sustained contraction. These cells are also self-stimulating, self-starters, self-excitatory. In a word, they are autorhythmic. They set their own pace. And it's unrelenting, 24/7. So if you take a stethoscope, and put it on your belly, will you hear sounds in there? You'll hear gurgling, and all sorts of things. And that's because of the 24/7 contraction of smooth muscle. Essentially, initiated by the muscle itself, not triggered by the brain. But, certainly, under the influence of the same factors that the cardiac muscle succumbs to. That is, its contractile rate, and its force is modified by autonomic nerves. Sympathetic versus parasympathetic. Also influenced by what?

[Inaudible Speaker]

Hormones. But the list goes on. Smooth muscle is very environmentally sensitive. That means it's regulated in part by prevailing pH, and by changing gas levels. That is, extracellular concentrations of oxygen and CO2. So smooth muscle is much more influenced by its environment than the other two types. And here, a sort of schematic look at some smooth muscle cells, showing what we've already said, that their activity is controlled by the ANS. What's ANS?

[Inaudible Speaker]

And we show two colors here just for reference. We show sympathetic in red, and parasympathetic in green. And that might seem a bit flip-flopped, because we normally think of sympathetic as that fight-or-flight component. But, actually, when it comes to the digestive system, sympathetic slows down digestive activity. And it's parasympathetic which ramps it up. So that's why I chose green for parasympathetic, and red for sympathetic. But, still, at any given moment, the activity of this muscle is a function of the balance, the tug of war between sympathetic and parasympathetic. Interestingly, and quite unique, number five, smooth muscle is pretty tolerant of stretch, which cannot be said for the other two types. What are the other two types?

>> Skeletal.

>> Skeletal and cardiac. Both of these are injured, or potentially damaged by stretch. But smooth muscle is very forgiving in that regard, In fact, some areas of smooth muscle are, actually, stimulated by stretch. And the easiest, and most familiar, example of that is the uterus. Does the uterus stretch during nine months of pregnancy? Maybe not that much. But does that stretch diminish or, actually, stimulate its contraction? Ultimately, it stimulates it, and brings about the delivery of a newborn. So the same could be said for the bladder when it gets too full. So smooth muscle behaves quite differently to stretch, and is tolerant to it. In fact, smooth muscle is never fully relaxed. It usually has some basic tension all the time. That is, it can contract more, or contract less. But it's almost always exerting some degree of tension. And that's called "tone," t, o, n, e. So, for instance, a blood vessel can contract more, or it can contract less. And that can change the size of these vessels, which, obviously, affects blood flow and blood pressure. And, lastly, quite unique, remember, the other two types of muscle we said were amitotic. Smooth muscle is capable of mitosis, something called "hyperplasia." And that is also best exemplified in the uterus. If all the uterus did in nine months was to stretch, it would be paper thin at the end of those nine months. But not only does it stretch, but it also builds more muscle cells, making it not just a larger organ, but a more powerful organ, which is, naturally, important in the delivery of a child. So these then are some comparisons of these muscle types. And just to review again, skeletal muscle is absolutely dependent on motor nerves. And those motor nerves trigger, that is, they're wired to, and stimulate a collection of nerve cells, thus forming a unit. What do we call a bunch of muscle cells which are innervated by the same motor nerve? Motor unit. So skeletal muscles are organized into units that act together. And those are called "motor units." Not so for cardiac muscle or smooth muscle. Cardiac muscle was unique, because it had these intercalated discs, highly branched, and, certainly, important in movement of blood. Smooth muscle, most important in tubular activities. That is, moving material through circular hollow organs. Most notably the digestive tract. So with that survey, and, really, that's just an overview of these three types now, we're going to spend the rest of our night here zeroing in, as we need to, on

skeletal muscle, with much greater depth, much greater detail to how skeletal muscle operates. To understand how it contracts, we have to understand more about its microanatomy. So let's revisit and amplify things we've already said. Here's a skeletal muscle cell. We see it's striated. We know it's multinucleated. And we've just said that every skeletal muscle cell is absolutely dependent on, and will only respond, as a result of motor nerve stimulation. So this shows the classic neuromuscular junction, which we'll be dealing with tonight. But turning away from that just for now, let's remember that the inside of a skeletal muscle cell is stuffed, literally, crammed with hundreds, maybe thousands, of these sub-units called "myofibrils." If you've seen one myofibril, you've seen them all. So let's pull one out, as we've done up here, and examine it, not under a light microscope, but an electron microscope, which will reveal the actual molecules that make up these myofibrils. And those molecules are organized into repetitive, redundant units called "sarcomeres." And, so, again, if you've seen one sarcomere, you've seen them all. And if you understand one, you understand them all. So let's review and expand on what we know about sarcomeres. Maybe in anatomy, and even here, I've used this model. We paid a lot of money for it. And this is a plastic rendition of how many sarcomeres? Well,–

>> One.

>> One. A sarcomere is defined as a repetitive unit that's marked at its ends by this so-called "plate," which is more commonly called a "Z-line." It's not really a line at all. As you can see, it is a protenacious plate, upon which, or through which, actin molecules are anchored. So it's much like a paper plate that you might stab some pencils through. The paper plate being the Z-line, and the pencils being the actin molecules in that analogy. You know from Anatomy that there are how many actin surrounding every myosin? Six. And that creates a very definite void. That is, a space for the myosin to slide through, and among these actin molecules. And this, of course, is a two-dimensional drawing, so it can't show that. But over here, we have a cross-section, which shows that every myosin is surrounded by a hexagonal pattern of actin molecules. What we're zeroing in on now is not the actin and myosin, but notice that the myosin, and only the myosin, has visible projections, which are classically called the "myosin heads." So here, if I release or remove the actin, we can see the myosin more or less revealed, and looking a bit like a brush, maybe a mascara brush, or something. And those bristles, if you want, are called "myosin heads," or simply "myosin cross-bridges." They are the workhorses of this mechanism, because they are the ones that are going to grab, pull, and, therefore, move the actin over the myosin. So let's move on with our story. The myofilaments are proteins. And the thinner ones, you know, are called "actin." And they are anchored to, and pass through, these plates so-called "Z-lines" or "Z-discs." The thicker filaments are called "myosin." And they, and only they, have projections at either end. Projections called "cross-bridges" or simply "contractile heads." And these cross-bridges are arranged in a helical pattern, a spiral fashion, which makes them, incidentally, even more like a mascara brush, because sometimes mascara brushes have that kind of design. The cross-

bridges do the work. And they grab on to what are called "actin binding sites." The actin binding sites are just that. Sites for binding with actin. And the binding sites also serve to bind this energy molecule, which we've, certainly, been introduced to. And that's ATP. So the interesting thing is the myosin molecule is a protein, no doubt about it, a structural protein. But it also serves as an enzyme, because it serves as an ATPase, meaning it splits ATP into what? ADP, and inorganic phosphate. Therefore, serves to release the energy, which is going to power, or make possible, contraction in ways that we'll mention later today. It turns out that not all myosin is the same in this regard. Some myosin is fast acting. That is, serves as a fast ATPase. Presumably releasing energy quicker. And in other cells, in other types of muscle, it's more slow acting. And we correlate here with the red and white, which is not unexpected. I mean what's one of the notable descriptions of the white fibers. What's the alternative name for a white fiber? Fast twitch. And in part they're fast, because they have a faster acting enzyme called "ATPase." In a similar way, the red fibers, we called those "slow twitch," and they are a bit slower in their contraction, because they have a slower acting enzyme, a slower acting myosin ATPase. We're piecing this together. So if you're a little bewildered, hang on, because, again, pieces, ultimately, come together. And right now we're just laying out the pieces of this puzzle. Add to this puzzle, and add to this illustration now, additional proteins, which are not shown or labeled here, because it would just become too complex. But we're going to call them, and use these two important names, they are "regulator proteins," specifically two, which we'll get into later tonight. Those two are called "troponin" and "tropomyosin." Regulator proteins implies that they somehow regulate or dictate or control the contraction of the muscle. And we'll be very explicit on that role before we leave tonight. But in simple terms, they tend to inhibit cross-bridge binding. That is, they prevent these cross-bridges from gripping on to the actin. And with that said, obviously, if they inhibit this binding, they would prevent contraction, or at least bring on relaxation. So these are very important to break contact, and allow a muscle to relax in ways that we'll see. Also not shown here, so you'll have to sort of visualize, are a series of internal tubes or channels, which are, actually, specialized forms of endoplasmic reticulum. In this location they're called "SR." SR an acronym for sarcoplasmic reticulum. For simplicity, we'll just describe them as intracellular sleeves. In other words, membrane-like sleeves that surround, surround what? Each and every myofibril. In that sense, you can imagine them like a shirt sleeve or a sweater sleeve. Is this a sleeve? And its surrounding my arm. So my arm becomes the myofibril. And my sweater sleeve, the sarcoplasmic reticulum. What's important is not so much the anatomy, but the function. These sleeves store and collect important activators of contraction, namely calcium. Calcium what?

>> Ions.

>> Ions. And, incidentally, calcium is CA+2. So the sarcoplasmic reticula store and collect and release calcium ions. Very important for instigating, and also interrupting, contraction. Again, our story is yet to come. But the pieces

will fit at some point. So that's just what it needed to be. A description of the molecular inventory of skeletal muscle. And we're going to, naturally, talk about contraction as we finish later. But before we can get into the muscle, and talk about contraction, we have to sort of get out of the muscle again. And recall that the muscle won't contract, and can't contract, unless it's first stimulated, because it's highly dependent on a motor nerve for its activity. And, so, now we're going to look at the activity of this synapse, which we know connects, or makes possible, interaction between a motor nerve and the muscle itself. It's not called a "synapse." It's called a what?

[Inaudible Speaker]

A neuromuscular junction. But looking at this diagram, you can't help but, obviously, equate it to a synapse. And it really is a synapse. It's a nerve-to-muscle-cell synapse. And there'll be a lot of similarities, not just in its appearance, but in its action as well. So if you understand synapses, this will tend to be very similar. But a few exceptions or quirky things. Before we get into the blow-by-blow description, let's outline what's on the screen. We have a motor nerve, which forms a nerve terminal. Not unlike those found elsewhere. And it, basically, pushes its way into, but never touches, the motor, I should say the muscle cell membrane. So, as with the synapse, there's no physical contact. And there remains a gap, which in this location is called the "neuromuscular cleft," or simply the "synaptic cleft." The membrane seen here, which sort of folds over or somewhat around the motor neuron, is, of course, the muscle cell membrane. The sarcolemma. And notice we've put some symbols here. We have positive charge on the outside, and negative charge on the outside, to remind us of a fact we've already mentioned. And that is skeletal muscles produce, and maintain, a voltage very similar to neurons. So would there be a measurable voltage between the outside and the inside of this muscle cell? Yeah. And what number might be expected?

>> Negative 70.

>> Negative 70. So it generates, and utilizes, a resting potential pretty much as a neuron does. Just below the motor nerve, there's what's called the "motor end plate," which has receptors, obviously, sensitive to the chemistry of the neurotransmitter. So in that regard, these things are similar to synapses in general. So let's jump into it. Let's give you the blow-by-blow, step-by-step explanation for neuromuscular transmission. The first thing, we have the arrival of a series of a high frequency of what? Motor?

>> Nerve.

>> Nerve, APs. What are APs?

[Inaudible Speaker]

And these come in rapid succession. And their frequency will lead to the influx of CA. What's that? Through calcium channels, presynaptic calcium channels. So the arrival of these motor nerve APs will open calcium gates, and calcium

ions will flow in, down a concentration gradient. What determines the influx of calcium is not the amplitude of the action potentials, but, again, what? The frequency of the action potentials. And the influx of calcium, just as with any synapse, will dictate the number of synaptic vesicles that are actually released. In other words, there is a proportionate release, a proportionate rupturing of synaptic vesicles in accordance with the action potential frequency Now unique to this structure is the fact that all neuromuscular junctions, all of them, use the same neurotransmitter. And its name is simply "acetylcholine," abbreviated capital a, capital c, lowercase h. Acetylcholine is the universal neuromuscular transmitter. And its function, you would expect, is to attach to, and have a depolarizing action on the muscle cell membrane. And that's exactly what, in fact, happens. So Item C. ACh diffuses and attaches, literally, binds to ACh receptor sites on the postsynaptic side, or on the skeletal muscle membrane, you could say. And you'd expect that this would open certain ion channels. In an excitatory synapse, as you know, sodium channels are open. And often in an inhibitory synapse, potassium channels are open. But here's a curious thing. What happens here is that this transmitter, actually, opens not only sodium, but it also opens potassium. And at first read, that sounds odd, because if you open sodium gates, they're going to go in. And if you open potassium gates, they're going to go out. And, so, positive in, positive out. You wouldn't think there would be any change, any disturbance in the resting potential. But, here's the but, more sodium goes in than potassium goes out. And with that said, what happens to this voltage, which previously was negative 70? Now we have more positive ions coming in. So clearly and obviously, this will not hyperpolarize, but d-word, depolarize, which is what you'd expect and hope for if we're going to stimulate this muscle membrane, or bring it to threshold. So, in fact, backing up, release of acetylcholine, attachment to ACh receptor sites, opening of ion channels. But which ion is favored, or otherwise allowed greater access?

>> Sodium.

>> And sodium rushing in will cause a local d-word, depolarization. Local meaning right here, just here, just under this motor nerve at a location called the "motor end plate." So what are we going to call this voltage? Well, it's called an "EPP." Another lovely acronym. EPP stands for? End plate potential. It's the voltage, which is being produced here, as a result of acetylcholine acting on these ACh sites. It is a local what?

>> Depolarization.

>> Depolarization. And that depolarization, incidentally, even though it's local, will not stay local. That is, it will trigger depolarization left, depolarization right. And, so, the function of the EPP is to produce or trigger propagated bidirectional muscle action potentials. What's that mean "bidirectional?" That way, and that way. That is, spreading in both directions toward opposite ends of this single muscle cell. And, remember, yesterday we did a lab called the "EMG." And what were we indeed measuring were muscle action potentials, which are,

of course, a prerequisite to contraction. The muscle will not contract without first depolarizing without these muscle action potentials. So that's good. Let's just back up again. Release of transmitter, attachment to ACh sites, opening of gates, depolarization. What's that voltage called? End plate potential. We say it's local, because it's produced here. But does it stay at this site? No. It, actually, triggers, that means causes, propagated bidirectional action potentials. So that's good. And we'll pick up the story from there. But we've got a very important consideration. We've depolarized the motor end plate. And that's well and good, because it caused these action potentials to then be propagated. But if we want to depolarize this again and again and again and again, we can't leave it depolarized. We have to do what before we can depolarize it again?

[Inaudible Speakers]

R-word, repolarize. So a very important follow up must occur after every EPP. That is, there has to be a mechanism to chemically destroy, or at least get rid of, this transmitter, because if acetylcholine lingers or dwells in this location, as long as acetylcholine attaches to these receptor sites, this membrane is going to remain in what state? Depolarized. And that may have succeeded in causing one muscle action potential. But no others. So depolarization has to be followed by the r-word what?

[Inaudible Speaker]

And the only way you're going to repolarize is get rid of that transmitter, or physically, chemically break it down. Luckily, lurking in this synaptic cleft is an enzyme. Not surprisingly called "acetylcholinesterase," or simply "cholinesterase," which does as the name implies. It breaks acetylcholine into acetyl and choline. In other words, it neutralizes its effects allowing the muscle to do what? Once we get rid of this transmitter, now its effects are removed. And, therefore, the membrane returns to its normal status in terms of permeability. And, so, the removal or the destruction of acetylcholine allows for what? Repolarization. And there's no way to overstate that importance, because if a muscle doesn't repolarize, then it can't then again depolarize. And, therefore, the muscle will cease to contract. And that's called "paralysis." In this context it's called "flaccid paralysis," f, l, a, c, c, i, d. In other words, the muscle will cease to contract. And is that serious? Deadly. How is that deadly? Does this affect the heart? Not at all. But what skeletal muscle cannot tolerate paralysis, and, therefore, sustain you is the? Diaphragm. So this would lead to rapid respiratory arrest, which raises the question then, what would cause such a failure to what? Failure to repolarize. Well, most notably, it would be anything that would inhibit this enzyme. What enzyme? Acetylcholinesterase. If you inhibit that enzyme, it won't be able to break down acetylcholine. Therefore, acetylcholine will remain in effect, and the membrane, the muscle membrane will maintain a constant d-word. Depolarization. Unable to r-word. And, therefore, paralysis. This is not just imaginary or a hypothetical, because there are agents that are called "nerve agents," they're actually neuromuscular blockers, which have been used for agricultural use, but has also been improved,

you could say, into nerve agents, which kill people. So terrorists have, certainly, caught on to this. And there have been instances of, you've heard of nerve gas, sarin, s, a, r, i, n, which has not been without its lethal impact in terrorist settings. So that's an important example of how repolarization is so important. And I say this sort of tongue-in-cheek. But you, actually, have these nerve agents around your house, because if you have a can of raid or any insecticide, those are, basically, chemicals which inhibit what? This enzyme. What is it? Acetylcholinesterase. You say, "OMG, why aren't I just dying every time I spray raid?" Well, it's a low concentration. So don't inhale this stuff. But it works on insects just as it does you. It paralyzes their muscles, and kills them on the spot, kills them dead! Just like the commercials want, you know. Double dead! All right. So I hate to be silly when something's so serious, but it is a good example of how important repolarization is. So here's a summary. And your book, of course, has an equally intimidating diagram. So your job is to be able to explain the animation, which is not even here. In other words, describe in words, as we just did, the step-by-step explanation for neuromuscular transmission. And, certainly, it's very similar to excitatory synapses, with a few notable exceptions. Speaking of animations, all of you know about YouTube. So I'm sure you're already there. But there are good animations and bad animations. If you find a good one on this, give me the link, because some of these are actually kind of entertaining. Some of them are dumbed down to the point of being useless. But let me know if you find a good animation of the neuromuscular junction. But here's our finale. We've been building up to this. What are the mechanisms that bring about skeletal muscle contraction? We understand the basic activity. We've talked about the sliding filament concept where actin is pulled over the myosin. That's a description of what happens. But it's not an explanation. It's just saying, "This is what we see." But how does it actually happen? And speaking of what we actually see, we have actually seen this. It's not just somebody's harebrained notion. These molecules can be, and have been, photographed. Not with light microscopes, like we have on this campus. But with electron microscopes, which can see down to the molecular level. So to recapitulate what we've already said, the basic activity occurs here in a unit called the s-word.

[Inaudible Speakers]

, Sarcomere, which is made of the thin myofilaments called? Actin, which interdigitate with the thicker ones called? Myosin. Myosin have these so-called "contractile heads," AKA cross-bridges, which we said before grab on to the actin, pull it over the myosin, and, therefore, lead to a telescoping, a shortening of the sarcomere. And this has been documented, because these are actual photographs of muscle in different states. Clearly, above here you see the Z-line separated by considerable distance. And notice apparent light or empty space here, which is obliterated as this process goes to completion. Demonstrating, as we can with this model, that there is no actual contraction of the molecules. Does actin itself contract or shorten? No. Does the myosin contract? No. There's no contraction to speak of. What's going on here is not contraction,

but sliding of these filaments, so that this represents a sarcomere in what state? Relaxed. This is it in a contracted state. And if we were to shine some light through here, you don't see a lot of light passing, but when the muscle's relaxed, you can see and photograph these voids, which allow for the sliding of the actin and myosin. This also is photographic proof, this is the diagrammatic representation of what we're about to describe. But then again, it's one thing to describe it, it's another thing to explain it. And that's our challenge, because the mechanism makes sense. And we can build models that actually show what's going on. But what are the chemical molecular factors that bring this about? To untangle that, and explain it, we're going to tease out just the basic players here. So this big structure here is a single myosin filament. And above it, we've shown a single actin filament, even though we know that there's not one actin for every myosin, but actually what? Six. We didn't put the other five in here, because then it would be too crowded and too complicated. So we're showing one actin next to one myosin. Notice the myosin molecule, which is a protein to reiterate, is actually built up of sub-molecules. And the best analogy that I can convey is taking a bunch of golf clubs, got that idea, about your golf clubs, and gathering their shafts together, and then having the heads poking out around that cluster. That's, basically, what a myosin is all about. It has tails, the myosin tails, which form the basic body of this protein. And then the heads of these golf clubs, if you will, project out. And those are known simply as "myosin heads," later to be called "cross-bridges." And, remember, this pattern of myosin heads is spiral. That is, it's in a spiral pattern, only at the ends of the myosin molecule, somewhat crudely shown there. So that builds up our story of myosin. And now we have to turn to actin, which we've only described up to now as being a thin protein. But now we're adding the other two proteins that we introduced earlier, namely what? Troponin and? Tropomyosin. These are wrapped over the actin also in a spiral fashion, and in ways that we're about to detail, they regulate when and how long the contraction actually persists. So we're about to really go down this step-by-step. But let's just make the statement clear from the outset. That what's going to go on here, is the myosin is going to be pulling actin by a repetitive action known as simply flexion and release, of the myosin heads, also known as cross-bridges. And this isn't really a hard concept. And, certainly, a lot of everyday examples are useful and similar. If there were a rope hanging from the ceiling, a big beefy rope, and you were asked to climb that rope without using your legs, obviously, what you'd do is grab on with one hand, and then what? F-word. Flex that arm. And then you'd reach out and extend with the other arm, before you what? Before you let go here. And, so, you would do a hand-over-hand effort. And before you know it, you'd be, hopefully, at the ceiling. So that's the kind of thing that's going on here. A series of repetitive flexion and release cycles, which, eventually, propels the myosin right up against the Z-line. And, incidentally, it will always go right to the Z-line. There's no halfway contraction. Remember, earlier we said skeletal muscles contract all or none. And that applies right down here to the molecular level. So all right. Here we go. Step-by-step. Actually, we have to, of course, back up just a tad. And, so, we'll begin where we left off. The

spread of muscle action potentials, which have been generated from that motor end plate. Remember that? So, certainly, as we've already said, the muscle cannot and will not contract unless there is, first, a depolarization spreading from the motor end plate. In other words, muscle action potentials. So what do these voltages in turn do? What does a have to do with b? This spread, the propagation of these muscle action potentials, actually triggers the release of CA. What's that? Calcium ions from their storage site within the muscle. What were those sleeves that surround every myofibril that's served to store this calcium? Sarcoplasmic reticulum. From now on we'll just call it SR to save some energy there. So we're going to release calcium ions from the SR. And let's keep in mind the sarcoplasmic reticulum is not outside the muscle, but inside the muscle surrounding, and intimately close to, every single myofibril. And this is critical, because if calcium is, in fact, the trigger which ignites this process, it's great that the calcium is nearby. What do I mean nearby? It's right there in the vicinity. So here's maybe a simplified view of what we already have. What's missing is the sarcoplasmic reticulum. Imagine it as a membrane here, or, for that matter, all around. And to repeat, what does the SR contain, and, in this sense, release?

[Inaudible Speakers]

And what prompts it to do that are muscle action potentials. Okay. Where do we go from here? Imagine now this laser light being calcium. Calcium has left, or come out of, the nearby? And now calcium ions are flooded, or, otherwise, prevalent in this area. What does calcium do? Calcium binds to troponin, this molecule right here, troponin, and causes the repositioning of the molecule affiliated with it called "tropomyosin." Repositioning means it causes this, what is it, the tropomyosin to turn. And, remember, that's wrapped around in a spiral fashion. So if we turn that spiral, it will uncover what previously was covered by this protein. So the repositioning of the tropomyosin will uncover something, uncover what? Cross-bridge binding sites on the actin. Sites that have previously been blocked, previously covered by this molecule. But now they're exposed. Now they're what? Uncovered. So now this binding site, which was previously covered, is now exposed, allowing what to attach? What to grab on? It couldn't before. Item D. This allows ATP to bind to the myosin heads. ATP, of course, readily available. And the molecule myosin will then split that ATP releasing energy. And the cross-bridges will extend, and attach to the actin. What does that mean extend? Let's be anatomical. This is what? Extension. This is what? Flexion. So maybe I can use my arm to represent what's going on here at the myosin head. The binding sites are uncovered. ATP binds to the myosin head. Then it what? Extends and latches on to what? Latches on to the actin binding site. Okay? This is called the "cocked" position, meaning it's cocked and ready to go. What do we expect or hope would happen? This molecule has reached out and grabbed on. And, so, now what has to happen, it has to bend. The f-word. It has to flex. So e will lead to f. Cross-bridge will flex. This is the real effort. This is the so-called "power stroke," which, of course, is ATP driven. And the flexing of this head will at the

same time kick off or release ADP and P. Where did these come from? They came from the splitting of ATP. So just to slow down, or animate this again. Backing up a bit. Calcium binds to troponin. Tropomyosin rotates or turns exposing the actin binding sites. ATP then attaches to the myosin head. The myosin head reaches out. That is, extends and grabs on to the what? Actin binding sites. Then it quickly and immediately flexes, kicking off at that moment also ADP and P. But let's not lose sight of what's happened here. What is the net result of that motion? What's happened to the juxtaposition of these two molecules? One's going to go this way, and one's going to go that way. Not unlike what happens in a rowboat. When oars go into the water, and someone pulls on those oars, water goes that way, boat goes that way. So, clearly, the myosin is going to be propelled in this direction. The actin is going to be pulled in this direction. And, clearly, that's going to bring together, ultimately, the Z-lines in a manner that we mentioned. But it's not that simple. No single action by any single myosin head would have the faintest chance of moving this sarcomere very far. And, so, it takes a collective, cooperative effort. Just as you reaching the ceiling on the rope. Could you get there with just one effort? No. It has to be what? Hand-over-hand. So needless to say, when some of these heads are flexing, others are extending. And there's a cooperative effort, a very synchronized effort to advance the myosin in the opposite direction from the actin. So, basically, f goes back to d. So it's def, def, def, def, until what? Until that myosin is finally right up against what, and can go no further? Right up against the Z-line. And that takes a fraction of a second. But, nevertheless, is not the result of any single effort. So now we've got the muscle contracted in an all-or-none fashion. Do we want to keep it contracted, or do we want to maybe relax it? Well, the answer is could be either one. But sooner or later, the muscle would and should relax. So to speculate what would be necessary to stop or disallow this process, which has occurred up to this point? What was the trigger which started it all? So if we remove that calcium, would things, essentially, stop and spontaneously revert? Yes. So sooner or later, there's going to be active transport of calcium back into the sarcoplasmic reticulum. In fact, I want to stress, this removal of calcium is automatic and instantaneous. Yeah. So then you would say if it's immediate and automatic, the muscle couldn't stay contracted. Good question. It wouldn't and couldn't stay contracted. But what about this? If the calcium is returned, but then it's released again, can you see a kind of revolving door there? So as long as the muscle's being restimulated, the calcium will be released. It will be returned. But then it what? Released again. And, so, is it possible for calcium to linger for a considerable time, even though it's spontaneously returned? Yes. But, ultimately, when stimulation stops, what will prevail will be the unavoidable active transport of calcium. And let's stress, it's not passive, it's what? And that implies the use of what?

>> ATP.

>> Against a concentration gradient. So this is critical to allow for the reversal of these steps, and, therefore, the relaxation of a muscle. And we want to stress that this removal of calcium is not dependent on repolarization. That

is, it will happen whether or not the muscle repolarizes, which is important, because even if the neuromuscular junction doesn't depolarize, the calcium will still come back, and, therefore, the muscle will be in a relaxed state. And when the calcium's removed, what happens? If we remove the calcium, what happens to the positioning of the tropomyosin, which was temporarily altered? With the calcium gone, the troponin and the tropomyosin will once again turn back, and recover what? Recover these active binding sites. And that forces what? When these binding sites are covered, can the cross-bridges grip anymore? No. So they're, essentially, oars outside the water. That is, they're unable to grab. And the muscle, as a result, will relax. And this is a very important distinction, or point of fact, because sometimes students will say, "I get this." Muscles contract because the myosin is what? Flexing and extending, and all of that. And then when it gets to the end, it reverses that. No. How's it work? It does this. But then what? Let go. Just as if you would get to the ceiling, and then what? What's the fastest way to get down? Let go. And, so, relaxation is not a reversal of contraction. It's not backpedaling. It's simply letting go. And you say, "Well, how does that accomplish anything?" Well, the muscle during contraction has been compressed. Right? When you compress something that's resilient, when you release that effort, it will what? It will automatically resume. So this couldn't be more important, because a very often misconception here is that muscles contract, and then they expand. Muscles never expand. They just what? Contract. And then they return to their resting length. That's not to say that relaxation is effortless, because think about it. What did it take to initiate relaxation? Active transport. And, so, if there is no active transport, then there'd be no return of what? And, therefore, calcium would linger. And this is exemplified in a familiar, although clinically unimportant, condition called "rigor mortis." What's rigor mortis? Rigor means "stiffness." Mortis means "death." So rigor mortis is stiffness after death. That's why it has no clinical significance, because you're dead, so it hardly matters. But it does have forensic significance. We'll get to that in a minute. But what exactly is rigor mortis? You've watched CSI. Anyway, what is rigor mortis? The entire body, that is skeletal muscles, after death will contract within about four hours, and stay contracted for another eight hours. So what does that do to the body, which is at first very limp upon death? It becomes stiff. And you can prop it up against the wall, or put it between two sawhorses, or something. And, hence, the name what? Rigor mortis. Now what's the cause of that? Certainly, the person's brain is not engaged. It's not motor nerve activity. It's not neuromuscular junctions.

[Inaudible Speaker]

You got it. After death is there a diminishing supply of ATP? Yes. But is there at least some for some time? Enough ATP to do what? Contract. But not enough ATP to what? And, therefore, the muscle contracts, but does not relax. Now it does relax after about eight hours. But that's not really relaxation. It's decomposition. That is, the muscles are just falling apart as cells die. So it's an interesting testimony to the importance of returning calcium back to the

sarcoplasmic reticulum. And, incidentally, these principles, these ideas, which were , of course, mentioned in the context of skeletal muscle. Does cardiac muscle contract pretty much the same way? Yeah. So is calcium dependent, or involved in cardiac contraction, too? Yeah. And here's an interesting thing. What if I had a drug which could improve the entry of calcium into cardiac muscle cells, improve the entry of calcium? Now is calcium necessary for cardiac muscle contraction in the same way as skeletal? So I now have a drug that will make it easier or quicker for calcium to get in. Sound good? Would the muscle contract maybe quicker, maybe harder, maybe lasts a little longer? Yeah. So that drug is not just an imaginary drug, it's widely used, and has been known for a long time. Digitalis aka digoxin. Who takes that drug? People with normal hearts? No. People that have weak hearts. Would this help their heart contract harder, better, more efficiently? Yes. Then why don't we have this drug available at vending machines at Walmart? Well, it might be good for a person with a failing heart, but why would it not be good for you or I, or why would it be lethal, in fact, for anybody if taken in excess? Now you have all this calcium coming in. Oh, good. But now what? A great burden on getting it out. And, so, now the heart's contracting all right. But not able to what? What do you call it when the heart contracts, but doesn't relax? Death. You call it cardiac arrest. Right? Because even though the heart's contracted, what matters here is not just contract, but we've got to relax. So my point is is digoxin therapeutic for people with failing hearts? Yes. Is it dangerous even to those people? Should it be, therefore, closely regulated, and dosages carefully controlled? Yes. One final thing. What about a drug that could act on smooth muscle, and block the entry of calcium there? Is smooth muscle contracting pretty much the same way? Yes. Is calcium important in the same way there? Yes. So now we have a drug that blocks calcium entry into smooth muscle. And those drugs are called "calcium channel blockers." All right. Now what would that do? If you block the entry of calcium into smooth muscle then, clearly, it wouldn't do what very well? It wouldn't contract. And, therefore, it would r-word.

>> Relax.

>> Relax. And you think, "Well, why would you want smooth muscle to relax?" Well, it would slow down peristalsis, which might not be welcome. But these drugs are used especially in cardiovascular medicine, because earlier we mentioned that arteries and veins have walls made of what? Smooth? And we mentioned that smooth muscle is never fully contracted, never fully relaxed. So if we cause it to relax, this vessel is now going to be what? Bigger. And is a bigger vessel better? Well, it is if you have high blood pressure, because high blood pressure is often due to narrowed vessels. So relaxing these vessels will do what to blood pressure? So if you know somebody that's on calcium channel blockers, it's because they have what?

>> High blood pressure.

>> High blood pressure. So those three examples–rigor mortis, digoxin and

calcium channel blockers–all focus on the importance of calcium. Because as we step back and look at this, what actually triggered the contraction was the arrival of what? And what triggered the relaxation is the removal of calcium. So it is calcium which is really in control here, even though it's action is more specifically on this regulator protein called "troponin." At the bottom of your page there, on the newer syllabuses, I have a link which is a YouTube link. I'm not sure it's current. But go ahead and try it, because it's the best video or animation of this mechanism that I've come up with. And it's very important for you to take these words, and understand them in a physical sequential manner. And the video I think does a pretty good job of that. If you find something better, that'd be great, too. So I bid you a good night, and a good afternoon, and safe drive home.

[Background Conversations]