>> March 23rd, 2015, lecture twelve in Physiology. Let's back up just a bit. We finished our discussion last time with this idea of ways to restrict, to control, to filter, to block, excessive transmission of signals, both sensory and motor, and we said that this is quite important because a lot of information is bogus; it's what? It's spontaneous, meaning accidental. So we want to filter all but the meaningful information. It turns out there's two ways to do that; we described them both. One was called postsynaptic inhibition; this works by a kind of competition between inhibitory and exhibitory synapses with the inhibitory synapses generating something called an IPSP, an acronym for inhibitory postsynaptic potentials. We mentioned that this ability is perhaps lacking in individuals that are autistic; those folks tend to be very skittish, very disturbed by a lot of environmental noise or distractions; they tend to retreat into areas where it's quite and familiar. And so they do something which is called stiming [phonetic] They rock back and forth, they shake their hands. Maybe you're aware of that behavior. If you're curious at all, you can check out this video online, thedoctorstv.com and learn a little bit more about stiming, but it probably involves exercising or bringing to bear these postsynaptic mechanisms of inhibition. Then we talked about presynaptic, which is anatomically different. In this case the fiber actually inhibits an excitatory fiber, and therefore reduces the release of an excitatory transmitter, therefore reducing the amplitude of the EPSP, and therefore blocks the passage of sensory information. We mentioned this in the context of habituation; for instance, you can tune things out, can't you? If there's a reckless [phonetic] in the hallway or there's a buzzing in the lights, you can tune that out, and you do so voluntarily in an effort to focus your attention on meaningful things. So the advantage of this is to enable you to focus, to concentrate, to screen out things selectively, so that you can concentrate on what's happening that you deem to be meaningful. So that's where we've been, and today I'll finally look at the nervous system with a topic that we couldn't avoid not discussing because it's such an everyday and important issue, pain physiology. We think negatively of pain, but is it a good thing or a bad thing? Well, when it's excessive it can be tormenting and very troubling, but let's start with the definition. Pain is basically admittedly an unpleasant sensation, but it's also very protective, and it occurs whenever there's been tissue damaging or nearly tissue damaging forces. You might think how wonderful it would be if I didn't experience pain. Are there people born without the ability to experience pain and do they have a wonderful life or a short life? Very short because they tend to reinjure themselves over and over again and often get into serious trouble because they simply have no negative feedback, no concept of what damage they're doing to their body. So let's appreciate pain as unpleasant, but let's also acknowledge that it protects us from self destruction. So let's start with the mechanisms, which bring about the acknowledgment of pain. Are there receptors for pain in the same way that there are receptors for temperature, receptors for light, receptors for sound? And the answer is yes. It turns out there are at least two different kinds of pain receptors located throughout your body and especially in the skin, and these are collectively called nociceptors. The word nocir is Latin; it means to injure. So a nociceptor is a receptor that responds to injury. There are two kinds of nociceptors that we'll distinguish; the first of which is called the mechanothermal nociceptor; this is one that responds to extreme mechanical or extreme temperature application, intense mechanical stimuli or temperature extremes. Let's be clear, these don't respond to temperature per se, they don't respond to touch per se; they respond to extreme or intense mechanical stimuli or in extremes of temperature. What would be an example? Well, a pinch. Is a pinch something more than just touch? And so that produces an excitation of the mechanothermal nociceptors. Also you might have noticed if you take an ice cube and you put it on your skin, after you register the fact that it's cold, yes? But if you leave it motionless, then after a while that cold starts to become very painful because it's now stimulating the mechanothermal nociceptors. So these receptors react to extreme mechanical stimuli or extremes of temperature. The other kind of nociceptors is called a chemosensitivie nociceptor, and these are those that respond to chemicals released from tissues that are actually injured, maybe even destroyed. You see, when major trauma injures or kills a cell or group of cells, those cells release a family of compounds called, among others, bradykinin, histamines, and prostaglandins. These diffuse from the injury and affect, that is excite, nearby chemosensitive nociceptors. Let's be clear, these receptors do not produce these compounds; these compounds are released from injured cells and have an excitatory effect on nearby chemosensitivive noiceptors. And incidentally, a very familiar analgesic; there's a new word. An analgesic is a medicine or a procedure that reduces pain, not to be confused with that other A word, anesthetic. An analgesic is something that exclusively reduces pain, and certainly one of the oldest and the most frequently used analgesic is aspirin, yes? Actually, aspirin doesn't work in your brain; it blocks the release of prostaglandins from injured cells, and therefore minimizes its excitatory effect on chemosensitivie nociceptors; therefore diminishes pain by that mechanism. Some examples of trauma which would release these compounds and therefore stimulate the chemosensitive nociceptors are major infections that have gone unchecked, or maybe a metastasis, cancer, terminal cancer especially. So these are the two basic kinds of nociceptors; one responding to rather low level injury, one reacting to a higher level of injury, pain reception. And incidentally, as far as we know, all of us, all human beings, have the same number, the same kind, the same density of these nociceptors. I

mention that because some of you might be thinking, oh, you know, I've heard of people that have high pain threshold. Have you heard of that expression? It's not because they have different receptors; it's just that they react differently to the sensation that ultimately registers in their brain and we'll have more to say about that. But let's accept the notion that all of us have these two kinds of nociceptors and therefore are equally sensitive to low level injury and high level injury. Now, how are these action potentials generated in effect by the activity of these nociceptors propagated? Remember, propagation occurs over dedicated unmixed, uncompromised sensory units; so what I'm saying is the information from these receptors travels over a different pathway than the action potentials generated by these. And so, mechanothermal nociceptors connect to and carry their signals along A-fibers. What did we say about A-fibers? Remember we classify neurons by the degree of myelination [phonetic] Remember there was A, B, and C? So the A-fibers where more or less myelinated? And as such did they propagate action potentials quicker or slower? So these are pretty fast tracks, and therefore they tend to have a faster conduction velocity, incidentally, you know, certainly in the order approaching a hundred meters per second. And so, the information from these nociceptors arrives in the brain rather quickly and has been described as first pain, which is just a description. I like to call it attention getting pain because it gets your attention. And how would first pain be described in most people? You would describe it as short lived; it doesn't linger. It's very sharp, maybe pricking, maybe stabbing, maybe stinging, and very definitely well localized; you can tell exactly where it comes from. So for instance, a pain prink would stimulate mechanothermal nociceptor and your impression would be a very sharp, short, stinging well localized kid of pain. What purpose does it serve? Yeah, it's first pain, but what did I describe it at just a moment ago? Attention getter, and what do you do? It gets your attention and you investigate right away, usually removing yourself form whatever offending stimulus it is so that further injury is avoided. So does it get your attention? Do you take corrective measures? Yeah. And so this is a very useful kind of pain because it avoids inflicting further damage. The second kind of pain is generated by and carried from chemosensitive nociceptors, and these use a different kind of axon, not A-fibers, but C-fibers, and what did we say about their degree of myelination? And so are they faster or slower? I don't mean poky; I mean, it's not going to be weeks before you get this information, but compared to A-fibers, these are pretty sluggish, maybe ten to twenty meters per second, and that's because they're thin and poorly myelinated, and have as a result a slow conduction velocity. Still, they're action potentials, and they arrive in the brain, but they are interpreted very different, and instead of being called first pain, this is described as second pain, and it has a very different quality. It's not short, it's not sharp, it's not stinging, it's what? Long, lasting, very often described as burning because it's not very localized; it's spread over a wide area, and tends not to be localized just in the skin; it can be coming from deep inside from internal organs and tissues. Second pain is what I like to call incapacitating pain. What does that mean? Incapacitating. You can't function; it's not just attention getting, you are completely incapacitated, unable to do anything. Have you had that sort of pain? I hope not, but perhaps you are aware of it and know the difference then between this and that. Do you have a question, Lucas?

[Inaudible Question]

>> Well, a fever is long lasting, and it might be unpleasant because your body is hot and you're very uncomfortable, but I really don't know whether that is painful per se. Now, you want to distinguish because in a fever you might have an infection, which is then of course generating this, but if fever is just high body temperature, that in itself doesn't produce pain, unless it's a result of an infection, in which case, of course, it would be second pain. So, let's take an example that you could relate to. Let's say you have a dental cavity, right? At first it gets your attention, at first you're a victim of what? First pain, but then let's say you don't have medical insurance or you're just, you know, unable to go to a dentist, then that infection, then that cavity becomes a full blown infection, and now you have what? Throbbing, intense, long lasting pain, and that's not attention getting; that's-what's the other description? When you can't do anything anymore? Incapacitating, and then you basically have to get some sort of relief, even if it is yanking out the tooth with a pair of pliers yourself. So you see the difference. Amy?

[Inaudible Question]

>> Old pains? Well, chronic pain is the result of chronic re injury as in arthritis and other things that don't go away. They don't go away because they don't heal, and they don't heal because you are constantly re injuring yourself. I'm sorry?

[Inaudible]

Well, there are certain things that are very unpleasant, but life goes on. In other words, when I say incapacitating, I mean you just don't want to do anything else and it certainly commands your attention; it makes it very hard for you to do anything, right? It makes you very much struggle to focus, to carry on normal life. Can you carry on normal life with first pain? Yes because, here's the keyword, it's short lived. This tends to be more chronic, and therefore, more disturbing and whether you're incapacitated or not, really depends upon you, the individual, you know, and what you need to do to get through the day, but we're just painting broad strokes here, and trying to distinguish these two. Can they coexist? Can first pain and second pain exist at the same time? Sure, but again, this tends to be the result of low level injury, this tends to be the result of major trauma to tissues as a result of, well, infection or other direct injury. Now, these signals that we said reach the brain and that are interpreted in the manner that we just described are, luckily, subject to modulation. To modulate means to tweak up or tweak down, and can these signals be suppressed or even amplified on their way up the spinal cord? And the answer is apparently yes. Certainly about thirty years ago, an interesting set of compounds were discovered in the human body which are now known as endogenous opioids. An opioid is a compound that resembles opium, which is an extract from the opium poppy. Opium, as you may know, has been used for millennia as a euphoriant [phonetic] that makes people high, and opium can also be distilled into morphine and then into heroin, OK? And stepping out of that context for a minute, what is, as far as you know, the most powerful analgesic still used today to relieve untraceable pain, especially as a result of, let's say, terminal cancer and so forth? What is the best analgesic available to anyone? Morphine, and morphine is the classic example of a compound that works through this endogenous opioid mechanism. But here's the definition. An opioid or endogenous opioids are opium or opium-like transmitter substances, which include two you may know by name, endorphins and enkephalins, that apparently have the ability to work presynaptically [phonetic] and inhibit the transmission of what? Now, what did we say C-fiber pain was connected with, the first sharp pain or the chronic incapacitating second pain? So this can be very relieving, very soothing in certain scenarios, and these compounds, these endogenous opioids are naturally manufactured by and found in the spinal cord and the brain. How they operate when they are put to use is summarized or theorized in this concept that we're about to discuss called the gate control theory of pain, and it is an analogy. I mean, what's a gate? What are the two conditions a gate can be in? Open door, closed; so this is an analogy, which involves and attempts to explain the action of enkephalins and endorphins. So here's the spinal cord cut in cross-section, and let's just paint the picture that we already discussed. This is a C-fiber, meaning poorly myelinated, and what is the nociceptor, the kind of nociceptor which it is connected to? Chemosensitive nociceptor, and this reacts to serious injury, producing action potentials which are carried into the spinal cord, cross the synapse, and are carried up to the brain. And just to repeat, when these signals reach the brain, how are these signals translated or felt? What does someone feel when these signals arrive in their brain? Yes, pain, but it's long, lasting, agonizing, debilitating, overwhelming, and certainly, perhaps in some people, incapacitating; in other words, serious pain. Meanwhile we have these, which are shown in red for no reason, but they're thicker and what does that have to do with anything? Thicker because they are more myelinated. These are associated with the different kind of nociceptor, not the chemosensitive, but the mechanothermal. So these react to lesser or greater injuries? Lesser, and when these signals get up to the brain, what does the person say or feel or report? Ouch, that was an attention getting, but it's quick and more or less not disturbing, so those are the two very, very distinct forms of pain that we described so far. Now, it's more complicated, of course, and so the gate control theory implies that in certain instances the pain over the C-fiber pathways can be mitigated, can be modulated; that means turned down, especially as a result of anything that terms or turns down or closes this hypothetical gate. And here's the way it supposedly works. Whenever there's a dominance of A-fiber activity; in other words, a higher frequency over a A-fibers, this can exert, as you can see; it can stimulate and enkephalins releasing interneuron within the spinal cord, which would operate, as you can see here, presynaptically on or upon the C-fiber pathway; therefore, blocking its transmission of action potentials; therefore, blocking what otherwise would be intense pain. So the closed gate occurs whenever there's a dominance of A-fiber activity, which exerts a presynaptic inhibitory effect through these enkephalin releasing interneurons [phonetic] And therefore, blocks the transmission, not of A-fibers, but blocks the transmission of C-fiber action potentials. And what would that mean? What would the person report? What would be their claim or pleasure in reporting? Oh, well, that feels a little better because you're taking away the very unpleasant kind of pain, the so called second pain. Examples of these are many, and include something that you'd do and know about intuitively or through experience. If you're hammering away at something and the hammer hits your hand, oh, wow, what do you do other than just shut out and complain? You might shake the hand, you might rub it. Does that help? It does, it does, and we all do it because it feels better and nod or not we are exercising what's called counter irritation, basically accentuating this for the sake of diminishing the C-fiber pain. Another example which is perhaps more bizarre but still well known and documented is acupuncture. Kind of a paradox, isn't it? because what are the instruments used in acupuncture? Needles, and needles inflict pain, but yet why are they used to diminish pain?

Because they, what's the concept here? Close the gate and therefore block the propagation of very disturbing action potentials across the C-fiber path. Acupuncture, of course, was invented in China, and now available in any major city and certainly found to be effective against chronic or high intensity pain. And some of you may know of these things. They're in the market; you can buy them now without a prescription. They're called TENS units. These are a little electronic units about the size of an iPad or iPod, I should say, t-e-n-s, transcutaneous [phonetic] electrical nerve stimulation. You put little electrons in your body, and basically they stimulate the skin, but the idea is to create a? dominance of A-fiber activity, therefore presynaptically blocking the transmission of C-fiber pain, therefore alleviating some pain. So the closed gate can be taken advantage of or exploited for the sake of minimizing that kind of disturbance. So I've shown out here with a little graphic. Now, you see there's a high level of action potentials over here and a relatively low level of action potentials here, so this can block presynaptically the transmission of these signals, and therefore reduce what otherwise would be an overwhelming sense of pain. But remember, if the gate can be closed, it certainly can be opened. And remember, let's not forget that C-fiber pain does serve some function. Yes, it's unfortunate; yes, it's unpleasant; but yes, it's also incapacitating, and when you're not incapacitated, you're not able to do what? You're not able to function, and you're therefore allowing your body to do what? Heal itself, so it gives you time for your body to remedy itself. So remember, let's not think of this pain as bad; it may be unpleasant, but it is a way to prevent you from further injury, and also at the same time allow your body to recover. So acupuncture is useful in closing the gate, but the gate would open whenever there's a dominance of C-fiber pain and that is certainly the case with a major injury. In other words, if we have a high frequency of action potentials over this pathway, some are going to get through even with some degree of presynaptic inhibition. So the open gate occurs whenever there's a dominance, an overwhelming number of C-fiber action potentials, and this overrides-you know what that means-overrides, overwhelms any A-fiber inhibition, and therefore leads to prolonged, high intensity pain, which is then incapacitating, therefore forcing you to cease and desist from whatever you're doing so that your body can recover and therefore heal itself. So an open gate then is sometimes the result of an injury that can be blocked; that is, it produces pain that can be blocked or filtered by that. Examples would be headaches, which sometime don't go away; muscle and joint pain, especially as a result of arthritis or chronic joint disease; and tumors, which tend not to get smaller, but they tend to get bigger. And so, terminal cancer is a sad case of pain which is overwhelmingly disturbing and cruel really. Why is it cruel? Well, it may incapacitate, but is there any real prospect for recovery from terminal cancer? So what is the humane way to deal with this kind of pain which no longer serves any purpose at all? Well, then we have to resort to very powerful analgesics, which include morphine. Controversial, though, as you may know, but usually in the hands of professionals, what are those agencies that deal with the terminally ill called? Hospice, and do they use morphine almost exclusively in the terminal states of cancer? And why is that controversial? Does it alleviate pain? Yes, but there's some that say, well, it's terribly addicting, but that's so ridiculous because these people are not going to be addicts; they are basically on their way to death, so this is a way to ease their suffering, and therefore allow them to succumb in peace. So here's yet another interesting fact, and we add this to our diagram. Remember the other day we said there are descending tracts that come down from the brain, showing here in blue. And notice that it's apparently synapsing [phonetic] with this enkephalin releasing interneuron, and therefore can excite that, blocking some degree of transmission across C-fiber pain. So this is suggesting that it might be possible for you to mentally exercise some control, some gate control through these descending pathways, and that leads us to this section called simply Descending Inhibition. Descending inhibition, as we mentioned last week, is a kind of inhibitory mechanism, which originates from your brain and can act on, that is have stimulating effect on enkephalin releasing fibers, and therefore exercise some degree of spinal gate closure. So to make that graphically easier to understand, here's the C-fiber, and here it's connecting to, synapsing, going up to the brain; so let's just remember, C-fibers carry what sort of signals, that is what would this action potentials be felt like when they reach the brain? Intense, overwhelming, very disturbing pain. OK, good. And here's a descending fiber, not going up the cord, but coming down, and apparently acting on and stimulating this enkephalin releasing interneuron, which presynaptically blocks the release of excitatory transmitter, therefore blocks or reduces somewhat the transmission across that synapse, which would be a good thing. Would you welcome the ability to exercise voluntarily some way of blocking or at least reducing the passage of these action potentials? Of course you would. And that then is called descending inhibition, which is exemplified and documented in a couple of very interesting examples; the first of which is called the placebo effect. The word placebo is Latin; it means to please, and here's the scenario. Doctor comes in, you're sitting there on the bench being examined, and you're complaining, oh, I have this massive ache or pain; it won't go away. And you say, well, I've tried this, and I've tried that, and nothing seems to work. So the doctor pulls out a prescription pad or maybe just a bottle of a sample and says, here, take this once or twice a day as needed and I think they'll work real well for you. And he gives it a fancy name and you say, OK, good, I'll try that. And it turns out that what he's just given you is a sugar pill, basically glucose, and you know

that that now is called a placebo. But here she was very coy about it that you believed it, and that you had reason to think it was going to help you. And did it help you? Yeah, what's that called when it happens? The placebo effect. Now, you think, oh, that's trickery, or that's magic or hocus pocus, but no, when you believe that something is going to relieve your pain, know it or not, you are stimulating this descending fibers and releasing, what? releasing enkephalins, which presynaptically block some of this pain. So it is an imaginary pain relief or is it a real physiological pain relief? It is, so time and time again, this has been shown to be in fact a physiological mechanism, which is interesting because answer this questions. Do you think acupuncture works better in China or in the US? Why does it work better in China? Are they better at it? Maybe, but those people, what? Those people-those people believe it, and so now they're getting what additional benefit here? Whereas you, skeptic as you are, OK, whereas me, skeptic that I am, walk in, I don't know about this acupuncture BS, but OK, I'll do it. And so is it going to work as well for me? No because I don't expect and therefore will not exercise a placebo effect. And this fascinates me because I just read this the other day. They're continuing to research the placebo effect and they did this study where a doctor came in and offered a medication to a patient that was in pain and said, well, here's two; this one is blah-blah-blah, this one is blah-blah-blah. This one is ten times more expensive, and so the patient says, I'll take that one, and guess what? It works way better, but it's still glucose. So if you pay more for something, do you expect better results? Do you get better results? Yes, so believe it or not the placebo effect is a very powerful thing. And so any medication which is being tested as a pain relieving medicine has to be compared to, has to be studied alongside what? a placebo because a placebo effect alone is responsible for a lot of pain relief. The second thing here is something called combat anesthesia, which is more or less a vague description obviously of combat injuries, and you can read about this; maybe you've already been aware, but sometimes soldiers in battle have had serious trauma, like their entire arm is just blown off, and yet when they're evacuated and ultimately saved at, let's say, a mass shooting or something, they'll sometimes say, you know, during that episode I really didn't feel any pain. And you think, well, how can that be? Your entire arm was blown up; that'd be hugely painful. But in that situation, pain is counterproductive. Why is pain counterproductive in a combat situation? If you're going to be overwhelmed, and what's that word? Incapacitated, you're basically going to be blown away a second time by something else, and so, is pain productive or counterproductive in that scenario? So descending inhibition would actually save your life because it would allow you to escape, otherwise do something crafty or lifesaving to yourself and that can be a very, very useful. Also, let's take it up into a more pleasant example. Is childbirth painful? I've heard that it is, and so often times women are asked to think or to be distracted, to think of other things, right? the Lamaze method you may be aware of, and that shades another example of descending inhibition, and you all do this. Let's say you've got a massive headache, but then somebody calls you on the phone and now it's somebody you want to talk to, you really engage. What happens to that pain during the conversation? And that's what? That's another case of descending inhibition, kind of a distraction which mitigates that pain physiologically for some time. So, descending inhibition works to one degree or another, especially if you expect good results as with the placebo or other strategies. Now, finally, quantification. How is pain quantified? Never mind the type of pain. How do we rank it? Have you ever been in a hospital and they say, rank your pain? They may hold up a sign with a happy face and sad face, you know, one through ten. Do you know what I mean? So we rank it one through ten, one through five, whatever. But how is the brain quantifying pain? How does the brain quantify anything? Well, it does it by the number of active pain fibers that are actually being stimulated and also the F word, what's that? Frequency. So remember, this goes to what we said before. Let's say these are pain fibers. One of them [tapping] then what? [tapping] Then what? [tapping] Then what? [tapping] You get the point, right? More and more are added into the game. So quantification is a function of two things, the frequency and the number of fibers that are involved; clearly the more damaged, the more injury, the more fibers would be disturbed, and as a result also there would be greater frequency of incoming action potentials. So pain can really get out of hand, especially if the damages widespread and affect in as many pain fibers. Item five here, localization and perception. Perception is what we actually feel or report or describe; localization, of course, where in the body is it coming from. Essentially, there is at first a very objective feeling and sensation. What's the opposite of objective? You say, you're being very objective. The opposite of being objective is being very subjective, OK? So objective is a very analytical, a very analytical processing of the information, and this is done first by the thalamus and then fine tuned by the primary sensory cortex, which tells you exactly where that pain is coming from. And this is especially precise when it comes to the areas of the body that are mapped out more completely on the somatosensory cortex. What parts of your body are represented more on the somatosensory cortex, your back or your hand? So can you feel? Can you pinpoint literally where a pain or a splinter or an injury might be in your hand, but less so in your back? So, yeah, the primary sensory cortex is better at localizing pain in your hand than it is, for instance, in your back, simply because there is more area in the primary sensory cortex devoted to the hand than there is elsewhere. In other words, there's a greater distribution, a greater density of mechanothermal nociceptors in the hand, which enables a very precise

localization of first pain. And so, if you step on a thorn, do you know that it is your foot? Do you know exactly where in your foot is? Could you even-if someone drew a picture of the bottom of your foot, could you put an X where you're actually feeling it? Yeah, and that's because of this greater distribution, higher density of the mechanothermal nociceptors in the skin than the other type. What's the other type of receptor, the other type of nociceptor? Hmm, the other type was a chemosensitive nociceptor. Now, in the end, in the end, pain is not objective, but it is more subjective, and that comes back to this earlier remark. We said that very often people would say, she has a very low pain tolerance or threshold or words like that. Have you heard that expression? Whereas he or she or somebody else has a higher pain tolerance; and remember, it's not because the receptors are different; it's because this is different. The interpretation and the reaction is what we often express to others, and it's not objective; it's very subjective, and full of emotion and full of extraneous influences. Are there people, are there cultures that tend to, shall we say, feel some degree of reluctance to express pain? Are there people that are stoic? What does stoic mean? Don't express pain. Are there other people that are very freely expressive of their pain? Alright, so I don't want to name names or otherwise, you know, malign whole cultures there, but some cultures are taught that pain is a sign of weakness and you're not supposed to what? Show any signs of pain; whereas other, other families, other cultural backgrounds are a little more permissive about that. So that's what I mean by this subjective feeling and the emotional elements. And essentially then this is an interaction between the parietal area and the frontal area. Remember, this is more objective; this is more subjective, even circumstantial in some cases. So I described this story, which is purely fiction, but I think you can get the gist of it. Let's say two toddlers the same age are playing at a playground and they both are running up the stairs or whatever, and they both trip or stow their toe at the same time, and inflict a similar injury, OK? at the same moment. But one of those toddlers has their parents sitting over there on the bench, and the other toddler, his parent is, well, not there for whatever reason. So, which individual, which child do you think would manifest more pain? The one with the parent there. Why? Is that because they're feeling more pain? I don't know, we don't know, we can't be inside their head, but why would they be more likely to cry and carry on and carry on, whereas the other toddler might just get up and start playing again? Injury is the same. It's not the objective; it's the subjective, it's the context of the whole thing. And so, certainly, in a hospital setting, would you as nurses sometimes find patients that are a little, shall we say, on the whiner side, if you know what I mean? And so you might be thinking, oh, quit your whining; I've been through this. But, no, you can't say that. You have to just treat them very professionally. So the bottom line is, if they say they're pain is a ten, it's a ten because it's not up to you to decide that. And so, what distinguishes one reaction to another, and what we call pain tolerance is just a matter of how we feel about it. And in fact, morphine is not so much an analgesic; morphine works at this level, that is it blocks the interpretation and the reaction to pain. So someone who has been treated with morphine would say, yes, I still have pain, but doesn't bother me anymore. And that's OK because if you have pain, but it what? doesn't bother you, then we're good, right? Because the only thing bad about pain is that it bothers you; and if it's not bothering you, then OK, it's just another sensation. So pain tolerance is how we interpret and react to pain and has little to do with the physiology more of this subjective interpretation, especially by the frontal association cortex. So that's as far as we need to go and we'll go with respect to pain. Turning the pain-turning the page literally and segueing into the second half of this unit now, Muscles, which are the motors that drive the skeleton and make movement and breathing, and so forth possible. So naturally we're going to spend some time reviewing muscle tissue. The first and most abundant kind of muscle that we'll cover at least to some degree today is skeletal muscle. Skeletal muscle makes, we hope, most of your body weight, and its function is to move the skeleton, hence the name skeletal muscle. Even though if I remain motionless, am I using still skeletal muscle? Skeletal muscle to maintain posture, skeletal muscle to breathe; so skeletal muscle is important in moving the skeleton, and also stabilizing it against gravity and the collapse of the skeleton. The structure of skeletal muscle you've learned a lot about in Anatomy, you gave names to all these skeletal muscles, you might even remember some of the funnier ones. I don't know what's a funny muscle, the Sartorius, the sternocleidomastoid, on and on. So we're not going to go there; we're going to reduce skeletal muscles to the cellular level because that's where our interest lies, how do they work. And, as you know, skeletal muscles are multinucleated and they're enervated by, that means supplied with, a branch of a motor nerve, and dependent on that motor nerve, needless to say. And these motor nerves and their cells that they enervate create a very important unit called a motor unit. A motor unit, by definition, is a motor nerve and all of the cells that it-what's the I word? that enervates. So this is a very simplistic diagram, but we've got, how many motor units shown on the screen? Well, there's the red one and the blue one. The red one has three cells apparently; the blue one has more. In reality though, a motor unit is never that small, but at a minimum would have ten cells, maybe a couple of thousand. So a motor unit is a motor nerve and all of the cells or muscle cells that it enervates; and these would contract all or none, as we'll mention in a moment. So if we stimulate this red motor nerve, how many cells would contract? All three. If we stimulate that one, how many cells would contract? All of those. So a motor unit is just that; it is a group of cells, muscle cells that would contract together

when the associated motor nerve is stimulated. And maybe it's not obvious, there are some motor units that have fewer; some have more muscle cells. Inside a single muscle cell, you'd recall from anatomy, there are literally dozens, sometimes hundreds, even thousands of what are called myofibrils; and these are packed into the interior of a cell. So this is a cell now and we've taken a one, one what? one myofibril. Examined under a microscope, we see a repetitive pattern of light and dark, light and dark, which is really responsible in the end for one of the characteristics of skeletal muscle. What's the other name for skeletal muscle? We don't see it up there, but you recall they're called striations, the result of this pattern, which is seen on the sub cellular level. And if we blow up a myofibril, we get down to the molecular level, which you recall is made of proteins, it interdigitate [phonetic] Interdigitate means these proteins slide pass one another like fingers on opposite hands, and the two proteins by name are actin and myosin. Actin are the thinner ones seen here in blue; and myosin are the thicker ones, which are dark or sort of red color on the screen now. And the actin are anchored to and passed through these fuzzy lines here, which were once called z-lines, now not known more appropriately as z-discs, which stabilize these proteins. So, if this is all coming back to you, and I wish it were, I hoped that it is, there are two steps of a sarcomere [phonetic] shown here. A sarcomere is defined as the unit between one z-line and another z-line. And so, if you haven't already done so, is this the sarcomere in a contractive or a relaxed state? And this is the contractive state. So you recall what's going on here. The filaments are sliding one another, telescoping in a bit, and the big difference is the dimension, the length between z-lines is now shorter, and this is compounded or multiplied thousands of times down the length of a given myofibril. So the z-lines or z-discs anchor the actin and allow essentially these extensions; they used to call them myosin to grab on to the actin and pull through what's called a sliding filament motion. If this is brand new to you, don't worry. We're going to spend a lot of time on this because this is a brief review or description, but how it works each step in this action extremely important, and clearly, do you think this is going to use some ATP to get this job done? Does muscle contraction consume a lot of energy? Of course. So we'll differ that for later, but remember, overall what's going on is that the myosin contained these so called cross bridges, which grip on to the actin, and therefore pull the actin over the myosin, something that's been called the sliding filament concept; and so it's almost as if the myosin is walking along with the actin. You can see lots of wonderful animations on YouTube. Just Google sliding filament theory and you'll get overwhelmed with some of the options, the video options there. So it's well documented what's going on here, and we'll spend a lot more time with that later. So for now, before we do that, let's step back and just describe some of the familiar and maybe not so familiar characteristics of skeletal muscle because this bears heavily on what we're going to do tomorrow in lab. First of all, skeletal muscle produces and maintains a voltage similar to neurons. And what's that name for a voltage which exists across a cell membrane anywhere? The resting potential, and what is the normal voltage difference across a neuron? What's the number? Negative seventy. So now we're saying that muscle cells do the same thing and by the same means. So if you understand the sodium equilibrium potential and the potassium equilibrium potential, all of those ideas now carry over here to the muscle. Muscles have and maintain a resting potential just like neurons. Of course what muscles do and nerves don't is they contract, and skeletal muscles contract real quick; that is as quick as point zero, zero one seconds. What is point zero, zero one seconds? That's one millisecond, isn't it? You might say, well, I've never seen any of my muscles contract that fast. But if you think of the wink of your eyelid, did your eyelid come down and go back up real quick? You don't notice any darkness there, right? So, anyway, there are muscles, certainly they contract very quick; some are a little poky, maybe a tenth of a second, but overall, skeletal muscles contract faster than the other two. What are the other two types of muscle? Cardiac and smooth; we'll get to those later, but certainly skeletal muscle is very quick and also under your voluntary control. Do you decide what skeletal muscles contract and when they contract? I hope so. And when they do contract, they contract all or none, and that's just what it says, but that concept applies not to a muscle bundle like the biceps. Does the biceps have to contract all or none? No, but we're talking not about the whole muscle but the motor units; so when a motor unit contracts, do all cells of that unit contract together, and do they contract all or none? Yes, so the overall force that we bring to bear is a function of how many motor units we employ. Am I employing a certain number of motor units to keep this cup up here, and am I using more now? Apparently. Isn't that more weight? So I'm now using even more what? more motor units. Could we keep doing this to the point where I couldn't hold it up anymore? I'd like to think I can manage anything you put in there, but certainly a bowling ball would be hard to hold. My point is our ability to move or stabilize something is a function of how many motor units we have and how strong each of those motor units are, but motor units contract in an all or none fashion. That is they contract fully, simultaneously, or not at all. Now, here's a brand new concept, one that you didn't hear in Anatomy because it's not related to Anatomy, but rather Physiology, and that is the simple truth that not all skeletal muscles are chemically, biochemically the same. They have some degree of biochemical specialization. That is they're different, not in their anatomy, but in their biochemistry. And there are three types, but we're going to simplify to two for you. First those that are called red fibers, as compared to those that we'll nickname white fibers. Red fibers, the

proper name for them, slow oxidative; slow meaning they contract relatively slowly, and oxidative implying that they get their energy from what source? Oxidative phosphorylation [phonetic] These cells have a rather slow and sustained, that means long term contraction; they have a high concentration of a pigment, a protein, called myoglobin. Now, myoglobin reminds you of another name with a similar sound to it, what's that? Hemoglobin. Hemoglobin is found where? Red blood cells. And what do you know about hemoglobin? What does it do? Hemoglobin carries oxygen. Myoglobin is not found in the red blood cell; it's found in these, these so called slow oxidative fibers. Myo, you might have guessed, means muscle. Myoglobin is like hemoglobin in that it stores, binds, concentrates, oxygen, and therefore makes these cells capable of using more oxygen, thus generating their ATP by what process you assumed? oxidative phosphorylation. And not surprisingly, these cells have many mitochondria, with many cytochromes, and somewhat paradoxically, these cells have very little glycogen, which you recall is a polysaccharided [phonetic] glucose. That might seem odd because wouldn't more be better? But the simple reason that these have less glycogen is that they're constantly contracting, therefore have little opportunity to stock pile glycogen; in other words, they're contracting all the time, so they don't have any surplus glucose to actually put into glycogen synthesis. These cells have a lot of capillaries; they receive a very rich blood supply; they tend to be part of small-size motor units; and they tend to be difficult to fatigue, which is pretty easy to speculate or imagine. Why do you suppose these are difficult to fatigue? Why do tire rather late? Why are they difficult to tire out? They have oxidative phosphorylation, they have lots of mitochondria. Do they have lots of oxygen or are they very efficient in their production of ATP? So that sentence makes sense in light of this information. Now, let's compare those so called red fibers, and incidentally, why are they called red? What color you think myoglobin is? Red, and it's red because of the iron that it contains. So if there's lots of myoglobin, that makes these very, very red. The other type, which is distinct are less red and so are called white. These are specialized; that is, called basically fast glycolytic fibers; instead of being slow and oxidative, they're fast and glyocolytic. Their claim to fame, their specialty is not slow sustained contractions, but what? Quick brief contractions, and these as you might have guessed have very little myoglobin, therefore stored what to a lesser degree? Therefore are they more or less likely to carry out oxidative phosphorylation? Less, and therefore because they have few mitochondria, they're going to have many glycolytic enzymes. So their metabolism is not so much aerobic but tends to be largely or frequently what? Anaerobic, and that is also necessitated by the fact that these guys have fewer, what? So not only do they have less myoglobin, but they're getting less blood supply because of the fewer capillaries which surround them. Now, that makes it seem like the white fibers are somehow inferior, and it's easy to oversimplify this and say, oh, I get it, red fibers are good; white fibers are not so good. But actually, each of these is good, but they're very different things. Which of these is better at initiating quick burst of contraction which can get you out of a situation that might be life threatening? Which of these is good for marathons, for long distance day to day activities? It's the reds. So don't think these are good and those are bad; they're equally good, just for different applications. The fast fibers also have an extensive sarcoplasmic reticulum, which means nothing to you right now, but later you'll make sense of that as we explain how that enables these to contract faster. And they have a very high storage, a very high concentration of glycogen. Remember, glycogen is that polysaccharide, which provides glucose, and the reason they have a lot of glycogen is that they are relaxed a lot of the time, therefore what do they do with their glucose but synthesize glycogen? Also, these so called quick fibers or fast fibers tend to be part of larger size motor units; that would make them more sense weighted too. And compared to the reds, they have a larger cross-sectional diameters. So these are attributes, basic distinctions, but what matters is, in short, these guys are more efficient because they produce ATP by oxidative means. These guys are better for quick contraction, but they're relatively inefficient because they rely not on oxidative, but more glycolytic sorts of pathways. And accordingly, they are easily or more easily tired out because their production of ATP is not nearly as efficient. Now, here's an interesting extension of these ideas, a practical application of these ideas, which when discovered were immediately put to use into sports circles. Would it be interesting to know the composition of red fibers versus white fibers in a perspective athlete? And would that perhaps influence a coaching decision? You should do this, you should do that, based upon knowledge of the ratio of red to white. And before answering that, let's take it out of human context because let's just think of, well, Thanksgiving. What's that bird on the table? That's a turkey, right? And what are the two types of meat that are known to exist in that turkey or chickens for that matter? You've got the white meat in and you've got the dark meat. The white meat is fast glycolytic fibers and the red meat is slow oxidative. Now, what's the white meat in a turkey, in the breast? And what are the pectoral muscles do for the turkey or anybody else? Do turkeys fly over great distances or migrate over thousands of miles? Do they use their wings for much anything other than amusement? So what kind of muscle is perfectly expected and appropriate there? Why are the breasts muscles white in a turkey? because they are specialized for what? Quick, brief, contractions. Does that find [inaudible] Yes. Where's the red meat in a turkey? What do the turkeys do all day? They're not flying; they're standing around socializing, right? So are the legs going to be red? Now, incidentally, what do you think of other pigeon? Totally

different bird, right? They're not standing around chatting all day. Well, some of the time they do; they're lazy, but the breast meat there is going to be what? Red, and the legs are going to be fast twitch. Bringing that back into humans, do humans have white meat and dark meat? The answer is no. Most muscles that we describe or name are going to be mixtures of red and white, but what about the ratio? Is it always fifty/fifty? And if it's not, would that influence a decision about, let's say, training or sports applications? So when this was first worked out, biopsies were done of quadriceps muscles in an effort to compare different people with different athletic abilities. So here's the average male, whatever that is, and in the average male, we're talking about the quadriceps; these are the ones that are involved in, you know, extending your legs, and kicking footballs and such. What is the ratio of fast twitch to slow twitch? It's pretty much, pretty much fifty/fifty in the average male. But let's say we were to biopsy, that means sample the ratio, and you do that with a needle biopsy. Just pull out some muscle and look at the ratio of fast twitch to slow twitch; it doesn't harm anything; may be painful, but it's worth it. So what about, well, let's think about high jumpers versus marathon runners or swimmers before weight lifters? So what do you think? A sprinter, somebody that's good at short distance, fast, acceleration, quick paced activity, like a hundred meters. What do you expect for these muscles in somebody that's competitive, let's say, Olympic quality? Would you expect fifty/fifty? You'd expect way more what? and fewer of those. On the other hand, what about a marathoner, somebody that is good at running twenty five miles, pretty much none stop? What do you think? He's going to have what? way more reds; that would be your expectation, and that is indeed what we find. So in marathoners, look at this, eighty two percent slow twitch, only eighteen percent fast twitch. And in swimmers that goes down, and what about sprinters and high jumpers? Both of these activities are short term, aren't they? So we have a flip side, much more fast twitch, quite a bit fewer of the slow twitch. So does this correlate with success in these activities? Of course, and so the question that comes from this, and I bet it's in your mind? It's OK. I understand that; it makes sense, but how did it get that way? Was it training or were your born that way? In other words, is it nature or nurture? And the answer is both. You've heard it said. Don't people throw this phrase around, oh, he's a born runner? Forest Gump comes to mind. Run, Forest, run. He was a what? Well, it's a fictitious-it's Tom Hanks, I don't know, but anyway. Are there people like that, that excel from very early age at sprint running, and the question is, were they born that way or did they just enjoy it and therefore pursued it? And the answer is both. So when you rise up from, let's say, amateur sports to Olympic sports-I had a friend who was very good at college on the [inaudible] I don't know what you call that. Rowing team, yeah, anyway, was great in college, top of his class, so he got singled out to go to the Olympics, you know the tryouts for the American team, and he was the crÃ¨me de la crÃ¨me; he was great, but when he got there, guess what? Now we have all the best, and he found that it wasn't a matter of diet, it wasn't a matter of will power, it wasn't a matter of no pain no gain; it's just that he didn't have the genetic makeup and he didn't make the team, not because he wasn't good, but because some of this is inborn. Can you modify this through training, through practice, through repetition, through coaching, maybe even through diet? The answer is yes, but in some dimension it's limited by a certain genetic factors. So are there for instance, Olympic teams that do well in a marathon year after year after year? And I'm not thinking US. Are there some African teams that do really well? And is what, that they have some secret formula over there? Do they have some voodoo or something? No. It's just probably that they have this genetic advantage. So this idea of biochemical specialization is not just scientifically interesting; it has application in sports, certainly for the sake of Olympic activities, let's say. And finally today, let's finish with this. Skeletal muscles are amitotic, which is a word meaning what? Cells don't divide, and that's hard to accept and many students protest; they say, I don't know what you're talking about. I've seen pictures of this crony ninety pound weakly pathetic guy, and then, you know, he goes to Power House Gym and all of a sudden he is buffed. You're telling me his muscles didn't increase in number? The answer is yes, they did not increase in number. So exercise doesn't increase the number of cells or the number of motor units, but it does increase what? vascularity [phonetic] mitochondria, and especially and mainly, the amount of active in myosin. So would exercise make you stronger? Would it make your muscles bigger? Yes, but believe it or not, my biceps has no more, no less muscle cells than, you know, somebody who can bench press, you know, a Volkswagen or something. So it's not a matter of cells; it's a matter of what? Actin and myosin, and with that we'll close with one more thing. Have you ever heard of muscle cancer? We don't hear that much. Why not? There is such a thing as muscle cancer, but why is it rare? What causes cancer is the M word. You forgot that already? It's m-u-t, you got the rest of it? Mutation, and mutation happens during what process? And DNA replication happens as a prerequisite to M word, mitosis. So if a cell is amitotic, is it going to replicate its DNA much? Is it susceptible then to mutation? So what was the statement? Skeletal muscle cells rarely suffer from cancer because they don't undergo mitosis; and incidentally the same is true for the heart. Ever heard of heart cancer? because cardiac muscle is also amitotic. So, anyway, we'll carry this forward in tomorrow's lab, and we'll move, of course, into other types of muscle on Wednesday.