>> March 11th, 2015, this is lecture 9 in Physiology. It's actually our first actual lecture devoted to the physiology of the nervous system. On Monday we reviewed some terminology, organization, anatomy, but now we are going to get down to the real operation of the system, which is fundamentally based upon electric principles. Bioelectricity, in other words electricity generated by living cells, namely neurons. Well, come to find out this electricity is no different than electricity anywhere. What makes it unique is that cells are generating and using this for purposes of communication, sensory, and motor function. So we're going to start with a fundamental rule of physics and chemistry. Something you already know, and that is unlike charges tend to exhibit an attractive force, they tend to come together, and like charges tend to repel. So with that as a premise, let's begin with some basic terminology, some basic principles that apply not just to bioelectric systems, but to electricity in general, and of course somewhere along the line, we are going to actually define electricity in the course of these terms. So the first of many terms, polarization, actually we've referred to that before. We've spoken of polar molecules, right? A polar molecule is when there was an unequal sharing of electrons. A polarized state is simply any condition where there's a physical separation of unlike charges. So here we see some sort of barrier. Maybe it's distance. Maybe there's an actual physical barrier of some sort. And we'll put positive charges on the right and negative charges on the left. And we know that these exhibit some sort of attractive force. At least that's the basic concept that we've already defined. But for whatever reason, they're separated, at least for the moment. And so this separation of unlike charges is a polarized state. And the degree of the polarized state, that is the extent of polarization is actually measured in units that you've heard of, that you know about at least, units called volts. So voltage is just a measure of the degree, the magnitude, the extent of polarization between any 2 points. So if we added more positive charges here on the right, if we added more negative charges on the left, what would we be doing to the voltage? Obviously, raising it. So voltage is not electricity. It's simply the measurement of the degree of polarization that exists between 2 points, also known as the potential difference. Now when this voltage is extreme, that is when there is a significant separation of unlike charges, the attractive force that we mentioned will tend to overwhelm whatever distance or barrier there might be. And charges will indeed move. And so here's a term which is actually electricity. Current is the movement, the physical movement of charges, whether they're ions or electrons. And based on this diagram, and based upon what we had moments ago, have charged moved? That is, have some of the positive charges moved left and some of the negative charges moved right? Yeah. So we have something called current flow. And it's a sensible word because current refers to, let's say, movement of water in a stream or in the ocean. So current implies movement, in this case movement of charge. Current is measured in units of its own. Those units may already be familiar to you as amps or amperes. So these are both terms that are based on actually people. That is, they're honorary terms. But yet the names and units are pretty familiar. So let's back up. When you have a separation of unlike charge, you have a what?

>> Polarization.

>> So let's take a practical or at least a familiar example. Here is the outdoors, up here a cloud that's looming. And as a result of atmospheric changes, it's possible for this cloud to develop a positive charge in reference to the earth, which might be negative. What do you call the physical separation of unlike charges?

>>Polarization.

>> Polarization. And what would we expect these charges to do if they are indeed opposites? Hmm. They would attract. But at least in this scenario, there's too much distance. And the voltage, or degree of polarization, is still not enough to allow for current flow. But you know from experience, you heard it told, that eventually the voltage difference is so great that there is actual current flow. And what's the name of that current flow? Well, we call it lightning. But it's literally electricity. That is current flow which tends to represent and be in this case the movement of charge. That said, what does current flow do to voltage? That is, does that improve or decrease the degree of polarization? Decreases it. And you know this from your own experience. We all devices which are powered by batteries, don't we? And maybe in your car, you're aware of that black box. It's got these markings on it, right? And certainly, if you leave your car, and you leave the lights on, let's say, sometimes, hmm, you come back, and your car won't start. So you complain. You say, oh, my car, my battery is what? You say it's dead. But it's actually not dead. It's just what? No longer polarized. And so there is a word. Depolarization is the reduction or the destruction of a polarized state. And depolarization then is the consequence of current flow. You all have seen batteries, right? Here's a 9-volt battery. If you look closely, there's a positive symbol and a negative symbol. If you do nothing with this battery, it will remain polarized for a long time. But

if you put a paperclip across these 2 terminals, what will flow and what will happen to that polarized state? Well, current will flow, and that battery will become quickly depolarized. So certainly if your car battery depolarizes, you call AAA, and you ask them to come out to do what?

>> Jump your car.

>> Ooh. No. You call them out to have it repolarized, right? So repolarization is the restoration of a polarized condition. And that can be done. Certainly it does happen in this atmospheric condition. It could happen to batteries. We always are charging our cell phones or charging our batteries. And sometimes, at least in systems, living systems, the polarized state is restored. That's called repolarization. And sometimes it's restored beyond the original. And there's a word for that. If we polarize beyond the original set point, the name for that is hyperpolarization. So these terms are so important, we're going to actually go over them again. Whenever charges are separated, as shown here, that's called a what?

>> Polarized.

>> Polarized state. And in what units do we measure the degree of that polarized state? Volts. And very often in cellular or biological context, we don't even deal in volts. We deal in fractions of volts, thousandths of volts. And so a millivolt, as you'd guess, is 1/1000 of a volt. But just because we have voltage, do we have electricity? Voltage, as you can see, is simply a measurement of the extent of polarization. But until and unless charges flow, there is no electricity. But when they do, when charges move across distance or some barrier, that's called current flow. And the result will always be what change to the voltage? The voltage will always go down, and that's called?

>> Depolarization.

>> Depolarization. Something then must occur and often does to reverse that. And what's the reversal of depolarization that's called?

>> Repolarization.

>> Repolarization, sometimes perhaps going so far as to hyperpolarize. These then are all terms we're going to use and depend on in the weeks ahead. So let's turn not car batteries or lightning in the atmosphere. But let's get down to the axon level because it is, after all, nerve cells that generate, as we'll see, voltages and allow for current flow. So we have to actually step down into the microscopic domain, showing here nondescript axon membrane, the membrane of the nerve cell axon. So this is the inside of the cell to the right, and this is the outside of the cell, except for now, the notion that the inside of the axon is packed with these ions. What are these ions, K positive?

>> Potassium.

>> Potassium ions, in fact, typically at a concentration of about 150 meq. Meq stands for milliequivalents. On the outside normally, a relatively low concentration of potassium ions, only what? Only 5 milliequivalents. So given that situation, do we have a concentration gradient?

>> Yes.

>> And which way would these potassium ions tend to diffuse if given the opportunity? They would move from the inside to the outside. So far, so good? They would move down their own concentration gradient. And indeed, they will. But also inside the cell are a great number of protein molecules, organic, large molecules, which have overall a negative charge. And these are large enough that they cannot follow. That is, they will not diffuse out of the cell. They remain inside the axon. So think about it. What is leaving? Well, potassium ions. What charge do they have?

>> Positive.

>> Positive. That moves positive charges to the outside and leaves the inside progressively now negative, negative by virtue of the highly concentrated organic ions. Eventually, this negativity will attract and hold these positive charges,

that is the potassium. In other words, as potassium leaves as a result of diffusional concentration forces, the inside's going to become negative. And eventually, that negativity will build up and hold and prevent the further diffusion of potassium. That negative charge that will attract and hold the potassium is called the electrostatic force. At some point, the electrostatic force will balance or equal the diffusional force, and then the potassium won't diffuse any further. The name of that situation, the name of that occurrence when the diffusional force is counteracted by the electrostatic force is called electrochemical equilibrium, not to be confused with chemical equilibrium because there still is a very large concentration gradient. Electrochemical equilibrium is simply when the diffusional tendency is matched or otherwise counteracted by this electrostatic force. And so by definition, electrochemical equilibrium is a static state where the ion is no longer diffusing. And that's because the diffusional tendency is counteracted by the electrostatic attraction of these organic ions inside. At that point in time, is there a difference, a separation of charge? Has the outside become net positive? And has the inside become net negative. And the answer is yes. And so, even though there's no net movement at this time, there very definitely is an equilibrium potential. That is a voltage which is produced as a result of these actions and this particular state. So the equilibrium potential is simply the voltage which is created or which is in existence when any ion reaches this electrochemical equilibrium. And for potassium, if we measure this with instrumentation, we would find that the inside is indeed net negative to the outside. And remember the units that we measure -- the units that we measure this potential in are volts. What's mv?

>> Millivolts.

>> Millivolts. So the so-called potassium equilibrium potential is the voltage which exists across an axon when that ion is in electrochemical equilibrium. And it happens to be rated at a negative 90 millivolts. We need just to accept that for the moment and move on. We'll come back. Let's add the second element to our story, which is another ion working more or less in cross purpose to the potassium because, unlike potassium, what's on the outside in high concentration is sodium, sodium ions. Notice the concentration of 150 milliequivalents. The inside, lower in concentration, but 15 milliequivalents, nevertheless, is this a concentration gradient?

>> Um-hmm.

>> And given a chance, what would sodium ions do?

>> They would move.

>> They would move from a high concentration to a low concentration. What charge would that deliver or carry to the interior?

>> Positive.

>> And what charge would that leave on the exterior? Negative. So that's indeed what happens. The movement of sodium down its concentration gradient will create a positive charge on the inside and a relative negative charge on the outside. Now don't confuse that. We're not saying the outside is all negative. It's just net negative because of the loss of these positive charges. And neither is the interior all positive. It's just net positive if we examine this effect by itself. But based on what we just said, as we discussed potassium, as the sodium ions move in, the outside becomes progressively more what?

>> Negative.

>> And will that eventually attract, hold, and prevent the further influx of sodium? Yes. What do you call that force that develops in opposition to the diffusional force which will eventually balance that force and prevent any further diffusion of sodium? It's called the electrostatic force. And when these 2 forces are equal, no further diffusion of the ion will occur. And the name of that state is electrochemical equilibrium. If we put instrumentation across this membrane, would we notice a difference a charge? And what would be the name? What would be the magnitude of that charge? The name of that voltage is the sodium equilibrium potential. And because by convention we reference this voltage to the interior, unlike potassium, its sign is positive. Positive what? Sixty. Now certainly that's mysterious perhaps. And before we go further, we need to review and clarify these very different voltages. So let's go back. We started with the notion that the

interior of the axon had a high concentration of?

>> Potassium.

>> Potassium. Therefore, it had a tendency to diffuse where? As it did, the inside becomes progressively what?

>> Negative.

>> And that creates a force which holds and prevents the further diffusion of potassium. That force is called the electrostatic force. When that is equal to the diffusional force, that ion will not diffuse anymore. The name of that condition is?

>> Electrochemical equilibrium.

>> And is there a measurable voltage across the axon at that time? Yes. What's it called? Equilibrium potential. Why is it measured at a 90? Well, it's just by convention that we examine the interior, and the interior is net negative in this case. And the number minus 90 mv, what's mv?

>> Millivolts.

>> Millivolts. Meanwhile, counteracting, that is working in an opposite fashion, sodium ions are at a high concentration outside. Their tendency is to move where?

>> Inside.

>> In. If they did, that would deliver what charge there?

>> Positive.

>> And create a gradual increase in negativity on the outside. Quickly, this negativity would counter the diffusional tendency. That would establish there something called electrochemical equilibrium. And at that point, the sodium would not be moving. And so it's called the sodium equilibrium potential rated at what?

>> Sixty.

>> Positive 60. But still, where'd these numbers come from? Why is this 90? Why is this 60? The magnitude of these numbers is a function of the concentration difference, the concentration gradient. Notice that potassium has 150 on the inside and 5 on the outside. It's a pretty steep gradient, whereas sodium, 150 out, 15 in. Is that a greater or lesser concentration gradient?

>> Lesser.

>> Lesser. And so the magnitude of this number is a function of the gradient. An easy idea if you think about it, what if the concentration of sodium on the outside were 150 milliequivalents, and the inside was also 150 milliequivalents? Would there be a concentration gradient?

>> No.

>> Would there be any movement of ions? Would there be any difference in charge? Would there be any voltage? The number would be what?

>> Zero.

>> So the size of that number is a reflection of the concentration gradient. And which of these ions has apparently a

greater gradient? So here's yet another question. What if this sodium concentration were 150 on the outside and 5 milliequivalents on the inside? What would that number be?

>> Ninety.

>> It'd be a positive 90. So the charge, that is the sign, positive or negative, is a reflection of how the interior is changed. The magnitude of the number is a function of the concentration gradient. Now there are other ions that are important players. But these are the 2 that are the stars. So we'll just draw a line under it at this point and simplify it to say that these are the 2 operating equilibrium potentials. That is, potassium is developing a negative 90 millivolts, and sodium has a tendency to create a positive 60 millivolts. What would you do in math? That is, what would be the expected sum of these 2 numbers if they were equal contributors? Hmm. If you add a positive 60 to a negative 30? Hmm.

>> Negative.

>> Negative what?

>> Thirty.

>> Negative 30. That's if each of these voltages contributed equally. But here's an interesting fact. The overall potential, the so-called net resting potential is, well, different than we just predicted because we haven't really told you all the details. Yes, these voltages are in fact as shown. But here's a bit of information that we've left out. When the axon is not stimulated, that is when it's at rest, the membrane, the axon membrane is 50 to what?

>> Seventy-five.

>> Seventy-five times more what? Permeable to potassium than sodium, so with that said, do these voltages contribute equally to the overall voltage? Remember, we said these voltages would develop if the ions were allowed to move. And we didn't offer any suggestion that they couldn't. But now we're saying when the axon is at rest, which of these ions is given some favoritism? Which of these ions has a greater permeability to the axon? So which of these voltages is going to have a greater influence on the number that we've yet to reveal? Which of these is going to have a greater influence on the overall voltage? Is it going to be 50/50, half and half? Nope. It's going to be much more weighted to this number. Why does the potassium equilibrium potential exercise a greater influence on the net resting potential? Because of that fact. In fact, before we reveal the number, if these voltages contributed equally, if the axon membrane were equally permeable to both ions, what would the net potential be?

>> Negative 30.

>> As we predicted, a negative 30. But it's a negative 70. And someone will ask you why it isn't a negative 30. And you say, well, these voltages don't contribute equally, and the reason is simply that the axon membrane is much more permeable to potassium at rest than it is to sodium. So this is the operating so-called net resting potential. Resting, of course, is a strange name. It makes it sound like the axon is asleep or something. And it certainly wouldn't be my choice, but it's nevertheless the name that is given to the voltage when the axon is not stimulating, when it's in standby mode, when it's waiting for something to happen. So I suppose you could compare that to a battery. What is the resting potential of this battery? Hmm, 9 volts. So the resting potential of an axon when it's doing nothing but waiting for something to happen is a negative 70 millivolts. Now so what? Before we can take that to the next level, we have to ask ourselves what could cause that resting potential to change? What could make it more negative? What could make it more positive? Certainly, if any of these equilibrium potentials changed, that would do it. And what would change these equilibrium potentials? What determined these numbers after all was the what? Concentration gradient, so if we change the concentration gradient, would that change these numbers? Yes. And would that change the resting potential? Yes. So that's one way that this resting potential could be changed or moved away from a negative 70. The other way to change it would be to do, as implied here, and that is change the membrane's permeability to 1 or both of these ions. If we increased or decreased permeability, that too would alter the resting potential. So that's summarized in this section. What are the factors, the 2 things really, that can change, move the resting potential off of this negative 70 millivolts? The 2 ways to do it are changing the ion concentration differences or changing membrane permeability favoritism. All

right. So what? Think about it. If we wanted to change this voltage, we could do so by changing the gradient, um-hmm. Or we could change the permeability that the membrane has to a given ion. Which of those do you think could be changed quicker in terms of time? Which would be easier to do, change the concentration gradient or change the permeability to these ions?

>> Concentration gradient?

>> You might say, well, how am I supposed to know? Well, we have to ask the question how do these ions move? They move through channels, ion channels. And that goes back to Unit 1, channels which we said were gated. Remember that term? That means they could be what?

>> Open or closed.

>> So with that reminder, I'll ask it again. If we could change this voltage by changing concentration gradients, and if we could do it by changing permeability, which would be easier to do? Which would be, in fact, very quick to change is the?

>> Permeability.

>> Permeability, because these ion channels can be instantly opened and closed. So even though the cell has 2 ways to upset or change the resting potential, altering the permeability is quicker, almost immediate, and brings about a rapid change in this voltage, which leads us to this critical and fundamental concept in neuroscience. And that is something called an action potential. Remember, the word potential just means voltage. What was the last time we used that word? Just on the previous page, we had potential. But it was the resting potential. Now we're talking about something called an action potential. Action implies some action, some change, some event, some exciting occurrence. And action potential is what most elementary school textbooks call a message. Ever read that? A message goes up to the brain, and then a message goes out to the muscle. We'll never use that term here. Messages don't go up. Messages don't go down. What goes up, what goes down are what?

>> Action.

>> Action potentials. So we need to understand and define exactly what these are. They're also known and frequently described as impulses, a word which has some connotation. An impulse is something that happens quick, right? People say I did that on an impulse. I was impulsive. So what does it boil down here? An AP, an action potential, is a brief, very brief depolarization followed immediately by a quick restoration of the voltage, something we've already said is called repolarization. So it's what? Depolarization followed by repolarization. Now what does that look like in a graphic, even mathematical context? Clearly, on the vertical axis, we're going to be illustrating the voltages. And notice that we need go no higher than a positive 60 millivolts. And we need go no lower than a negative 90 because these are the sodium and potassium equilibrium potentials. And what's important about this negative 70? That is, as described, the status of an axon when it's not stimulated, something called a what?

>> Resting potential.

>> All right. So what' going to change that resting potential, as we've implied, is some change in the permeability. And so as you can see here, this resting potential has been brought from a negative 70 and is now moving toward the positive 60. What would cause the interior of the cell to suddenly become less negative and actually run toward this voltage? Clearly, it would be the result of an influx of a positive ion, and namely, sodium ions. So the red side, the red slope here is in fact depolarization. And we need to stop. Why is this depolarization? We're going toward what? Why is this depolarization? We're going toward?

>> Zero.

>> Zero. And what's causing that is an influx of sodium. And what's causing that is obviously an increased permeability to sodium, for reasons that we'll describe at some point. So in short, the sodium channels have open. And what's flowing

in?

>> Sodium.

>> Sodium. What's that doing to the interior of the cell? It's turning it away from a negative 70 and bringing it -- bringing it toward the positive side of this measurement. Right here, though, notice it seems to have stopped abruptly. And that's because these sodium gates, these sodium channels opened so briefly. And at this point, they close just as quickly as they opened. And not only did the sodium channels close at this point, but the potassium channels opened hugely at this point. So think about it. Why has this voltage gone this way? It's due to the influx of sodium. And at this point, the sodium gates close, and the potassium gates open. So which way will potassium move? Potassium's high in the inside. So it's going to move to the?

>> Outside.

>> Outside. What will that do to this voltage which was been screaming toward this positive 60 value? Well, it's going to be turning right back around. And so the blue line is in fact repolarization of this resting potential, caused by not the influx. The what?

>> E.

>> Efflux. Efflux means the loss or exit of potassium ions. And an interesting thing is noted. This voltage repolarizes very rapidly and in fact seems to go for a moment beyond the resting potential. So this little dip here is a moment of polarization beyond the set point, beyond the resting potential. So this would be labeled and called what?

>> Hyperpolarization.

>> Hyperpolarization. Now this event cannot be felt. It can, however, be measured with instrument. And indeed, we'll do that in lab on Tuesday. But taken together, these 2 changes are what we've already said is called an action potential. Does it fit the description? Does it match the definition? Is it a brief what? Depolarization followed by a quick repolarization? How brief? Well, this is time, but it's not weeks and it's not minutes, not even seconds. It's what?

>> Milliseconds.

>> Milliseconds. In fact, that time from the moment this began to change to the moment that it's returned to resting potential, that's about a millisecond, 1/1000 of a second. So these voltages are called what? Action potentials. They are caused, apparently, by the influx of?

>> Sodium.

>> And the efflux of?

>> Potassium.

>> Potassium. And these are the fundamental signals which the nervous system uses, whether it's a motor nerve, a sensory nerve, association nerve, and so forth. We'll clarify that idea in a moment, but suffice it to say if you've seen 1 action potential, if you understand 1 action potential, you understand them all. They're all the same. Now think about that, though. This event, this action potential has been caused by the influx of what?

>> Sodium.

>> Through the sodium gates, and then finished off by the loss of potassium through the potassium channels. So every time one of these happens, what leaks in and what leaks out of an axon? What leaks in is a little bit of?

>> Sodium.

>> What leaks out is a little bit of?

>> Potassium.

>> So what do you imagine that would do to these concentration gradients, which we said were so important and fundamental for the creation of a resting potential? If every time one of these happens, the cell gains a little what?

>> Sodium.

>> And loses a little bit of?

>> Potassium.

>> What's going to happen to those gradients which were so critical, so fundamental for this to happen at all? In time, those gradients will level out. And if there is no gradient, there is no equilibrium potential. And if there is no equilibrium potential, there is no resting potential. And if there's no resting potential, there could be no action potential. And if there's no action potential, there couldn't be sensory function, i.e., anesthesia. There couldn't be motor function, i.e., paralysis, in other words, game over. So just as with a battery, if you run a paperclip across these terminals, what will happen to this polarized state? D-word, it will be what?

>> Depolarized.

>> And will it be good for anything?

>> No.

>> Nope. So where am I going with this inquiry? Every time we have an action potential, the cell gains a little what?

>> Sodium.

>> And loses a little bit of?

>> Potassium.

>> And if we do that over and over and over and over and over and over again, what's going to happen to these gradients? What's going to happen to this voltage? What's going to happen to the ability to even generate an action potential? So just as with any battery, whether it's in your car or your cell phone, in order for it to be ready to work, it has to be constantly?

>> Recharged.

>> Repolarized, constantly recharged. And so, there must be and is a way to maintain the resting potential of an axon. Otherwise, it would simply cease to function. And how then are these ions replaced, that is moved, moved back to create or maintain the concentration gradients? We've already said this. That is, we've alluded to the fact that ions can be pumped against a gradient. And built into the axon membrane, as diagrammed here, is a fundamental recharging system, which is called the sodium what?

>> Potassium.

>> Potassium exchange pump. Now an exchange pump is a pump that exchanges one thing for another, in this case obviously exchanging sodium for potassium. And it's a method of actively transporting and therefore returning these ions to their previous location so as to maintain the gradients, so as to maintain the resting potential, so as to allow for an action potential. Notice that this pump pumps what? Pumps 3 sodiums which way?

>> Out.

>> Out, and puts 2 potassium in. And this moves -- this moves these ions against their gradient and clearly then requires what? There it is, ATP, something you know and expect for anything called active transport. So what's this called? The sodium potassium exchange pump, dependent on carriers? Yes. Dependent on ATP? Yeah. So let's just pause and go through a what if scenario. What if the cell, what if the axon, what the nerve cell was short of ATP? Then it wouldn't be able to operate the?

[ Inaudible comment ]

Therefore sodium would leak in every time there's an action potential. And potassium would defuse out in the repolarizing phase of every action potential. And eventually the gradients that made this diffusion possible would disappear. And with it, what would happen to the resting potential? And if the resting potential is zero, what can't be made or what won't happen?

[ Inaudible Comment ]

And if that doesn't happen, there's no sensory function, no motor function, game over. So is this pump critical to maintain the resting potential to keep that neuron in a ready to go mode? Absolutely. And if it's not already clear, is ATP dependent? That is, is ATP the driving force behind all this? Yeah. Much of the neuron's energy consumption then is to maintain this resting potential by maintaining the potassium sodium pump. Now all we've done so far is describe voltage. We described that static state, that ready state. What was that ready state that a nerve is holding as it waits for something to happen?

>> Resting.

>> Resting potential. Then when something does happen it produces this event. This event is called an action potential. So now we want to go at least this far in the time that we have left. We want to go beyond defining an action potential. We want to explain what causes it. That is what triggers an action potential and what propagates it. Now there's a new word. To propagate means to reproduce it over and over again, generation and propagation. Action potential generation, you know we haven't said this, but it's time that we do. Here we have a model of an axon, and these areas where I wrapped some duct tape represents -- well, those represent Schwann cells, and the gaps or naked spaces between are the nodes. Remember we might have said this, I'm sure we did, that the nodes are the only locations for the sodium and potassium gates. So this action potential that we just described can only occur and does only occur at these nodes. But that doesn't really answer this question. If this node right here is minding its own business, that is if nothing's happening, it's maintaining a voltage called?

>> Resting potential.

>> Resting potential. So the question is what causes it to depolarize? What causes it to produce an action potential? What generates the creation of an AP at that location? Clearly, it's not going to happen spontaneously, hopefully not accidently. There has to be some provocations, some event that triggers it. And that event or provocation is called threshold stimulation. Threshold is a concept that I think makes some sense. That is, you use it from time to time. You might say I'm on the threshold of -- I don't know -- marriage or something, in other words, almost there. Threshold stimulation is defined as the minimum level of depolarization that's necessary to trigger this critical sodium ion permeability change and therefore bring about the creation of an action potential. So before describing that in any further detail, let's go back to this graphic relationship. Here's a potential of zero. Here's a negative 70, which is the prevailing what?

>> Resting potential.

>> The prevailing resting potential. And for reference, we'll put a positive 60 here and a negative 90 there. Remember, these are mv. What's that?

>> Millivolts.

>> Millivolts. So the axon for the moment is minding its own business, that is cruising along and maintaining this voltage called the resting potential. But what if this node is depolarized from some local influence, depolarized enough to reach this trigger point called threshold? To quantify that, we'll put a dotted line somewhat above the resting potential, and we'll mark and circle that as T, meaning the threshold level. Threshold, by definition, is the what?

>> Minimum.

>> Minimum depolarization to trigger the sodium permeability change, which would bring about an action potential. So if that's understood, let's say something occurs at a node and depolarizes it to this level, which is less than threshold. Isn't it? Will the axon respond or produce an action potential if we depolarize it only to this degree? No. It will simply what? Repolarize. What do we have to do? What level of depolarization do we have to apply to get it to respond? We have to bring it up to that level. What's that level called?

>> Threshold.

>> And if we do, what will happen then?

>> Action potential.

>> Yeah. Sodium ions will flow in, causing what? D-word.

>> Depolarization.

>> And at that point, the sodium channels will close, and potassium ions will exit. That's called what?

>> Repolarization.

>> Repolarization. And this whole event, depolarization alongside repolarization, that whole thing is now what?

>> Action potential.

>> An action potential. What caused it to occur was the local application of something called what? Threshold stimulation. And anything less than threshold would obviously deserve the name sub-threshold. Sub-threshold produces nothing because by definition we need to get at least threshold to receive or cause an action potential. This might be easy enough to accept or, say, memorize. But the nagging question is why should there be threshold? Why not have any depolarization trigger an action potential? Why have this minimum level of depolarization? Think about it. Would you want your nerves to go off with the slightest little provocation, or would you want there to be a meaningful, real event that triggers their voltage change? So, threshold stimulation allows the nerve to be insensitive to rather random and insignificant events and only to respond to real, significant voltage changes. And so, anything that's less than threshold, anything called sub-threshold, would not produce a response at all. With that, we now realize or can easily summarize that idea in this interesting catchphrase. It's what? An action potential is what? All or none. That means it either happens or what?

>> It doesn't.

>> Doesn't. There's no such thing as a tiny action potential. There's no such thing as a big action potential. They all have the same amplitude. That means the same voltage. And that typically is around a positive 30 or 40. And they all have the same duration, tending to be around 1 ms. What's ms?

>> Millisecond.

>> Millisecond. So this is somewhat surprising because we tend to think of sensory and motor actions as being great, that some are intense. Some are weak. But when it comes to action potentials, are some intense and some weak? Nope. They're all the same. Thus that comment I made a moment ago, you've see one action potential?

>> Seen them all.

>> Seen them all. They are no different. No matter what kind of nerve, no matter what kind of event, they either develop fully, or they don't develop at all. And that seems hard maybe to accept. But we'll explain how that is the case and why that works in the manner that it does in a moment. But moving back to this threshold idea, what might determine the excitability of a nerve? Sometimes you hear that phrase I have a low threshold to pain. Ever heard -- hear that? Meaning that you're more likely to react to pain than somebody else. It turns out that this point here that we call threshold is pretty constant in nerves throughout the nervous system. So if the threshold doesn't change, what might influence the excitability of a nerve, meaning making it more or less excitable? Well, essentially, is the resting potential subject to change? And the answer is yes. So anything that would make the resting potential more negative, stay with me. Anything that would make the resting potential more negative would move that resting potential further from?

[ Inaudible Comment ]

And make it harder or easer to excite?

>> Harder.

>> Harder. On the contrary, anything that would bring that resting potential closer to threshold would make it easier to excite, and therefore, well, more excitable. So what are the factors that determine or influence neuron excitability? Well, first, hyperpolarization. What's the word mean? Hyperpolarization, to make it more what?

>> Negative.

>> Negative. And if we make the resting potential more negative, it's going to do what to the excitability of the axon? If we pull it in this direction, is it going to be more or less excitable? Less excitable. What things do that, as a matter of fact? What are causes of hyperpolarization across an axon? Well, one cause is anything that interferes with sodium influx. Anything that diminishes the sodium equilibrium potential will allow the potassium equilibrium potential to become even more dominant, moving, moving more negative, that is, further negative toward the negative 90. Anything that what? Interferes with?

>> Sodium.

>> Sodium influx. And let's not be abstract. There are things that do that in nature. Many of you have had the thrill of being in a dental chair and having your wisdom teeth extracted. And he or she, the dentist, might have given you compounds that they describe as Novocain or Lidocaine, right? And did that numb up your jaw? What do those compounds do? Well, the interfere with sodium influx, therefore causing the resting potential to become more negative or less negative?

>> More.

>> Therefore further from?

>> Equilibrium.

>> Therefore easier or harder to depolarize?

>> Easier.

>> And what do you call it when something is harder to excite? Well, that's decreased membrane excitability. Would

that be therapeutic? Would that be nice? Would that be a good thing if you're going to have your wisdom teeth yanked out? Yeah. And aside from Novocain, another thing that can interfere with sodium influx is, oddly enough, changes in Ca plus 2. What's that?

>> Calcium.

>> Anything that increases extracellular calcium tends to diminish sodium influx and therefore have this effect. So that's a fact that we'll leave for now. And as we've just said, some local anesthetics do indeed work by interfering with sodium influx. How could we make the membrane more excitable? Hmm. If we make the resting potential less negative, we move it closer to? And that's exactly what depolarization means, leading to an increase in membrane excitability. And what do you think? If interference with sodium influx caused -- caused what? Hyperpolarization, then something that enhanced sodium influx would obviously what? Obviously bring about increased membrane excitability. And if increased extracellular calcium does this, decreased extracellular calcium does that. Let's make this meaningful to some degree. Decreased what?

>> Extracellular calcium.

>> Extracellular calcium means calcium ions in the blood or interstitial fluid. So here's the scenario. What gender at what time tends to have declining levels of calcium in their blood and extracellular fluid?

>> Females.

>> Females during what?

>> Menopause.

>> Not menopausal. During pregnancy. Why do women at pregnancy tend to have declining extracellular levels of calcium? Where's this calcium going?

>> To the baby.

>> It's going to the baby's skeleton. Okay. So far, so good? What would decreased extracellular calcium do to sodium influx across axons? And therefore, what does that do to the resting potential as a result?

>> Raising it.

>> Bringing it closer to?

[ Inaudible Comment ]

Making axons more or less excitable?

>> More excitable.

>> And therefore triggering action potentials perhaps prematurely or even spontaneously? What does that do? Remember, action potentials are action potentials. Some go along sensory nerves and give rise to sensation. Some go along motor nerves and give rise to contraction. So is anybody ahead of me here? Okay. Let's back up. Pregnant women have low what?

>> Calcium.

>> Extracellular levels of calcium. This tends to enhance. That means promote. Promote what?

[ Inaudible Comment ]

That causes the resting potential to be not H, but D. What's that? Depolarized closer to?

[ Inaudible Comment ]

Making that axon more or less excitable?

>> More.

>> More or less prone to generate action potentials?

>> More.

>> And now we're going to have action potentials going along motor nerves that normally wouldn't. And where do motor action potentials go?

[ Inaudible Comment ]

>> To muscle. And what causes -- or what happens then is that muscles contract. What complaint do pregnant women often have? Well, they have many complaints, I'm sure. But I'm just trying to fish into your memory banks. Don't they sometimes complain of cramps?

>> Yeah.

>> Oh, cramps. Yeah. And what are cramps? They are spontaneous, involuntary skeletal muscle contractions caused by? What's the root cause? The root cause is?

[ Inaudible Comment ]

So how do you fix that? Well, don't get pregnant. Or? Or what? Raise this, right? So maybe we've been abstract. Maybe we've been beating around the bush here. But we've got to come home to this fundamental fact. The threshold level is pretty well fixed in axons. What changes, though, is resting potential. And if the resting potential is brought closer to threshold by any means, then that axon is going to be more?

>> Excitable.

>> Excitable. On the other hand, anything that pulls that resting potential away from threshold is going to make it harder to stimulate, make it not more excitable but less excitable and putting a very blunt set of words to play. When an axon is more -- when it's more excitable, it's going to generate more action potentials. And when it's less excitable, it's going to be producing less action potentials. What do you call producing less action potentials along a motor nerve? You know it. What do you call producing less action potentials along a motor nerve?

>> Paralysis?

>> Paralysis. What do you call producing less action potentials along a sensory nerve? A-word? Anesthesia. What do you call producing more action potentials along a motor nerve? Contraction or cramping. What do you call producing more action potentials along a sensory nerve? Whoa. That's called -- can be called hallucinations. That is something called paresthesia. It's where you feel something that's really not there, a false sensation. So I hope that this makes some sense. That is, it's important for the resting potential to be stable so that the nerve responds appropriately in terms of the action potentials that are produced. Now we've got to finish this topic because we said we would. All we've done is explain the generation, the creation of an action potentials. In other words, where and how has that occurred? First of all, where does an action potential start or otherwise begin?

>> In the node.

>> Right there in the node. What triggers -- what triggers it is T. What's T?

>> Threshold.

>> And if we don't have T, then nothing, right? Once we get an action potential, we know it's always what? Always what?

>> All or none.

>> All or none. Will a node respond the same way all the time, or is it subject to influences? And what are those influences? Anything that hyperpolarizes, causes the membrane to be what?

>> Less.

>> Less excitable. Anything that depolarizes it makes it?

>> More.

>> More excitable. But none of this answers the question we're about to tackle. And that is, okay, here's an action potential. But how does it get here? How does it get here? How does it get here? How does it move? It doesn't move like a ball bearing rolling down a hill. So the first thing we have to establish is that 1 action potential does not travel like sound traveling through air because actually that's a good analogy. Sound traveling through air, does it go on infinitely? Or does it fade out with distance? So action potentials are not like sound because if they were, they would fade out with what?

>> Distance.

>> And clearly, that could not be tolerated. That is, we want the action potential to faithfully get to the brain, faithfully get to the muscle. It turns out then that 1 action potential does not travel uninterrupted. It's made possible by an interesting, if not amazing, process called saltatory propagation. First of all, the word propagation is not totally unfamiliar to you. If you're going to propagate something, that means you're going to reproduce it. So when it comes to the propagation of action potentials, they are literally reproduced brand-new at each and every one of these spots. What are these spots?

>> Nodes.

>> All right. And in fact, we're going to see that they skip. That is, there is no action potential produced, nor can it be produced in the spaces between nodes because what is this material that I've made here with duct tape? That's actually M-word?

[ Inaudible Comment ]

>> And there are no ion channels there. So action potentials can only occur at nodes. And so literally, action potentials occur here, then here, then here, then here, then here, skipping over considerable distance, skipping over the myelinated regions. So this idea is called saltatory propagation, which means the repeated regeneration of action potentials. And that means that every action potential is brand-new and identical to the one that just occurred. Action potentials are recreated, propagated, at each node. So let's look at this in an animated or diagrammatic sense. Here are the Schwann cells, let's say, which create this tight, phospholipid insulation. The naked spots are called what?

>> Nodes.

>> Nodes. Nodes are [inaudible]. And here in long section, we see that only here we have channels for? Hmm. Sodium. And channels for?

>> Potassium.

>> Potassium. Also here, we have the built-in sodium-potassium exchange pump. So how does saltatory propagation occur? And when we leave in a moment, we'll fill in these 2 important conclusions with regard to its advantages, meaning why it's important. First of all, let's start in a timeline or in a chronological sense. This node is maintaining a resting potential. So what's the voltage at this node if it's un-stimulated?

>> Negative 70.

>> Negative 70. And something arrives here, something we're going to call what? Local threshold depolarization. Threshold, meaning enough to trigger what? What changes are triggered by the achievement of threshold depolarization? What gates open? Sodium, followed by what gates? Potassium. So this event, local stimulation, I love that. Local stimulation causes the sodium gates to what?

>> Open.

>> All right. And what do sodium ions do in response to those open gates? They go in. And what does that do to the voltage which has previously been a negative 70 at the interior? What does the influx of this positive charge do to that resting potential? Well, of course, D-word?

>> Depolarize.

>> Depolarizes it. Does this -- does this location remain depolarized? No, because no sooner do these gates open that they close. And what gates open at the same time that the sodium gates are closing? Potassium. That allows potassium to do what? Well, it will move out. Why will it move out? It moves out because it's moving down its own concentration gradient. And the loss or efflux of potassium will reverse this voltage change. In other depolarization will be followed by?

>> Repolarization.

>> Repolarization. And what do you call the combination of these 2 events which have occurred back-to-back? What do you call depolarization followed by immediate repolarization? What's that whole thing called?

>> Action potential.

>> An action potential. And where has it happened? It's happened right here and only here at this node. Does this node have any knowledge about what's going on here? No. Minding its own business, so this is, as we've said, a local action potential. We generated it, but our question still remains how does it move? Well, remember, the first part of this action potential was dictated by the influx of sodium. And what charge is sodium?

>> Positive.

>> And what's the status? What's the voltage status of this node downstream here? This node minding its own business, maintaining a voltage we assume is a negative what?

>> Seventy.

>> So what do we know about positive charges anytime, anyplace? They're going to move toward any area what?

>> Negative.

>> So will these charges move in that direction? Yeah, they will. And what do you call the movement of charges anywhere, anytime? C-word, current flow. So these charges will indeed move there almost immediately. And, ooh,

that's cool. I want to see that again. Those charges will what?

>> Move.

>> Move. Why are they moving that way? Well, positive charges moving toward negative, what's it called? There it is. Current flow of positive charges away from the active area to this area of inactivity. Current flow toward the next node, and these charges will do what then to the resting potential of this node, which is previously held at a negative 70? If these positive charges arrive, they're obviously going to do what to that resting potential? D-word?

>> Depolarize?

>> Depolarize. And probably depolarize to what level or degree? Hmm. So this event called current flow is essentially going to represent and create the necessary local threshold depolarization for the next node. And you get it from there, right? Well, once we depolarize this, what happens? Same thing, sodium gates open. Um-hmm. Depolarization, potassium gates open. Sodium gates closed, repolarization. Brand-new action potential, right? And so on and so on and so forth. So even though it's not visible, we can imagine it moving as it does from node to node. And what's the name of that hopscotch-like movement from node to node? Right there at the top, saltatory propagation. There's a fact to elucidate here that's mentioned. And that is this current flow that we animated here is decremental, a word for losing strength with amplitude, just like sound loses strength with distance. So this voltage, which set out at this node, will indeed spread to the next node. But it loses amplitude. It loses strength with distance. To what degree? What is the degree of that decremental loss? It's what, 50% decline in what for every? Every mm. What's mm? A millimeter. Turns out that along axons, these nodes are 1 millimeter apart. So that means this voltage that's set out from this location, by the time it gets to that location, which is just a millimeter away, that voltage, that voltage, will it be the same strength here? It'll be how much less?

>> Fifty percent.

>> But that's okay. Why is that okay? It's still going to represent and serve to be. And therefore, what will be created here is just a brand-new?

>> Action potential.

>> Action potential. So there is no loss in strength. Said another way, is the action potential that's produced here the same as the one here?

>> Yes.

>> Well, yes and no. It is the same amplitude, but it's not the same action potential. Does it have the same strength? Yes. And so, there is no loss in strength because of this propagation from node to node. We said we were going to leave you with 2 -- apparently 2 advantages that this has. That is 2 reasons that this is a good thing. And 1 of them is that it's just plain faster. Faster than what?

[ Inaudible Comment ]

Well, no, but it is faster than if it weren't saltatory. Imagine if these nodes were closer together, say 1/2 millimeter? Hmm. That means we'd have to produce twice as many action potentials to go the same distance. Do you get that? And would that be faster or slower?

>> Slower.

>> That'd be slower because we'd have to generate, then generate, then generate, then generate, then generate. But here we can go -- we can skip over great distances. So is faster important? Do we want information to go from your toe to your brain today sometime? Yeah. Or do you want to get that tomorrow and say, yeah, I'm finally getting there. I'd guess I'd better probably take a look. Yeah. Fast is always good. And the other thing, notice that there are these active

transport pumps, which are located, clearly, only at the nodes. And what do these pumps do? We've made a case that they take the sodium and put it back out and grab the potassium and bring it back in, in order to maintain what? Resting potential. Is that sodium-potassium pump important? Well, yes, we made that case. But what is the cost of operating that pump? I mean is there a cost?

>> ATP.

>> The cost is in ATP, right? So what's the other thing? If we had nodes which were closer together, we would be generating twice as many action potentials, which would slow things down. But also we would be acquiring more sodium and losing more potassium, therefore putting a greater burden on?

[ Inaudible Comment ]

And therefore using more ATP. So what's the second advantage of saltatory propagation? It's not only faster. It's cheaper, uses less ATP. And are both of those important? Do we care about being faster? Do we care about that? Sure. It's always faster and cheaper, right? You know, if you're going to go to New York, you don't call your agent and say, I want a -- I want the slowest plane possible, and I want to pay the most I possibly can. No. You want it what? You want everything faster and cheaper. So what does faster do for the nervous system? Does it deliver information to the brain sooner?

>> Um-hmm.

>> Does it deliver information to the muscles sooner? Is that important? Do you want those muscles to act now or sometime today? So anyway, faster and cheaper. Let's finish with this by reviewing. Oh, let's take it all away. This node is minding its own business, maintaining a voltage of?

>> Negative 70.

>> Negative 70. Along comes what? It's not lightning. That's what?

[ Inaudible Comment ]

And that does what to this resting potential? D-word?

>> Depolarize.

>> To what critical level? T-word?

>> Threshold.

>> Which causes what changes to the ion gates? Well, sodium gates open, causing what to go in?

>> More sodium.

>> That causes?

>> Depolarization.

>> As soon as that's done?

>> They close.

>> Sodium gates close. Potassium gates open. What ion moves?

>> Potassium.

>> Where does it move?

[ Inaudible Comment ]

Why does it move that way?

>> Concentration gradient.

>> Concentration gradient. What does that achieve? Well, that achieves repolarization. These 2 events in rapid succession produce this thing, which is called a?

>> Action potential.

>> Action potential. Has it gone anywhere yet?

>> No.

>> No. Will it? Well, because the positive charges that were let in as a result of the sodium influx are actually going to move. And they're going to move where? Why are they going to move there? Not because they want to move there or think they should or whatever. These positive charges always go toward any area of negativity. Is this area negative?

>> Um-hmm.

>> Will they go there? What do you call that? You call that current flow. What does that achieve? Why are we glad to see it? That current flow served to deliver essentially local threshold depolarization there, which caused everything to be repeated. And so certainly, as you can see, this is a kind of repetitive thing, often compared to dominoes. You know how you stack dominoes up? One domino what? Trips the next, which trips the next, which trips the next. And is that final falling of that final domino any different than the one at the beginning? No. So will this action potential somewhere out here be different than that one? No. Will it be the same action potential? No. But the important thing is that we're not going to lose any amplitude. Do we lose amplitude between nodes? Does the electric signal diminish from node to node?

>> Yes.

>> Yes. We don't care though because it's still enough to represent local threshold depolarization. Thus, we get a brand-new action potential, and the sum total of that is saltatory propagation. Why is it good?

>> Faster and cheaper.

>> Faster and cheaper. So a lot to absorb, but you've got some days to do that. So take heart with the sample exams, and we'll see you on Monday. I hope you have a great weekend.

>> I just wanted to ask about days.

>> Sure. Let me turn this off.