>> Today is November 15th, 2017. Lecture 25, obviously following Lecture 24 which was an introduction to basic renal processes. All of those are involved in making urine, the process called urination. There are three aspects to the activities of the nephron, the first and foremost glomerular filtration, followed by some degree of tubular reabsorption, followed by some degree of tubular secretion. So we went through and defined those three interrelated processes. Then we went into electrolytes specifically a focus on sodium and potassium and to a lesser degree chloride and bicarbonate. And so we left you last time with the famous renin angiotensin mechanism which is right there on page 120. So that leads us to our next and final two concerns for the kidney and those are regulation of water and pH, both of them rather huge important responsibilities for the kidney. We'll start with water regulation. We'll end today with pH homeostasis. So first, we heard the term water balance but what does that mean? When something is in balance, it means the input matches the output or something of that nature. So, water balance is critical to avoid a very lurking possibility of dehydration. You see, that's the problem for the human body, we are not aquatic. We live on land. So water is sometimes very scarce. So the challenge for the human body is to conserve water but at the same time find a way to eliminate solutes which are often in high concentration. So let's first build the case, let's show how challenging water balance really is by looking at the water that we receive versus the water that we lose everyday unavoidably. This is not worth memorizing but it's worth appreciating. As we look on the gain side, we might drink maybe a liter, maybe a liter and a half of fluid, that's fine and then we have food, the food that we eat even though not necessarily liquid does contain some water and on average that might add another liter. And then remember, are you making water? Is metabolism producing water as a byproduct of the Kreb cycle? Sure. That's not a lot, maybe only 300 milliliters but it's worth putting up there. So these are the typical daily sources of water that is produced by or available to the human body. That's the plus side. What's the negative side of this teeter-totter? Well, we're going to lose water like it or not through breathing because we can't stop breathing. And when you exhale, is water a part of what we are exhaling? Yes. And you might not appreciate it but it's pretty sizable, almost a liter, 0.9 liters is lost every day just by breathing. And then we sweat. You know, you might say, well, I use an antiperspirant. But all of us sweat like it or not, some of us more than others and it doesn't amount to a lot but it's worth mentioning, probably less than 100 mLs, so it's down here as 0.1 liters. And are the feces water soaked? That is do feces contain water? The answer is yes and that would add maybe another 0.1 liters to water loss. So far, that total is 1.1 liters. And if this were all there was, we'd be in positive water balance. Why would that be positive? Because we have more coming in than being lost but what's obviously not included yet in this list is urine. And so if you do the math, you can see there's little room for excess urine. If we want to maintain water balance then, we have to find a way to excrete, to eliminate a rather small volume that is less than about 1.4 liters of urine everyday. And that urine has to be very hypertonic. Remember, we said the challenge for the human body is to conserve water but still get rid of solutes

which are almost always in surplus. So there's the challenge, maintaining water balance requires that we minimize or keep water loss to about 1.5 or 1.4 liters and at the same time that we find a way of eliminating large concentrations of solutes. So how does the nephron do that? What are the anatomical and physiological mechanisms that help to provide for water balance? The first and foremost and continuously operating mechanism is called the countercurrent multiplier mechanism, which at first seems to mean almost nothing. But it's a reference to the anatomy of the kidney specifically the anatomy of the nephron. As you recall from our work the other day, the nephron is the functional unit of the kidney. It consists of tubular and vascular components. The tubular components begin at a kind of bowl which is called Bowman's capsule that tapers into a twisted tube at the outset, the proximal convoluted tubule then dipping into a hairpin loop that's simply called the loop or loop of Henle and then that flares out into another twisted tube known as the distal convoluted tubule which eventually feeds into a rather large collecting duct which is called the collecting duct. So, the flow through the nephron is essentially countercurrent. The word countercurrent means that current is going or flow is going in opposite directions. So to make this very clear, the flow is down then it's up and then it's down again, hence the name what, hence the name countercurrent mechanism. But what's this multiplier mean? To multiply means that this design is no accident. It's designed as we'll see to create a very highly concentrated area of solutes deep within the kidney which help to attract water through osmosis and therefore achieve what we're trying to achieve and that is minimizing water loss, to keep water loss or excretion to less than a liter and a half. So does this diagram has some significance, because basically it reminds us of the meaning of these words, countercurrent multiplier mechanism. Here's the definition, essentially this mechanism exploits and uses the opposing flow of the loop of Henle to create a very highly concentrated area of solutes deep within the renal medulla. This shading is not an accident. This is a gradient fill and where is it darker? Right down here. And what does darkness mean? What are we trying to convey? The degree of darkness is an expression of salt concentration. So this is the area which becomes as we'll see very salty and therefore provides a mechanism for pulling water for extracting water in the final segments of the nephron therefore creating urine which is high in what? High in solutes but very low in volume achieving what needs to be achieved and that is conserving water but at the same time eliminating solutes. This is the anatomical essence then of the countercurrent multiplier mechanism. But what are the details? Let's go to a description of the activities that are happening and occurring in these three segments and let's give them a name. This segment is part of the loop. We're going to call that what? Descending loop. And this part which goes the opposite way is called the ascending loop, and of course, the collecting duct reverses that flow once again. So, descending loop, ascending loop and the collecting ducts. Each of these segments has very specific and unique activities which contribute to and are part of the countercurrent multiplier mechanism. So first, what's going on in the descending loop? Obviously, the filtrate is moving down here but the cells in the descending loop have no active transport mechanism which

handles sodium or chloride. There's simply no active transport of either of these electrolytes. It's a fact. And nevertheless these cells in the descending loop are permeable to water. So what would water do? Well, that depends upon the concentration. And because the concentration is rather high in solutes outside the descending loop, water tends to leave in this area and therefore making this filtrate even more concentrated as water leaves. So as we characterize the filtrate moving down here, it's becoming more and more C word, more and more what? Concentrated, because it's losing more and more water simply through the osmotic reabsorption at this location. So, we say the urine is becoming hypertonic as it moves down this element of the nephron. OK, great. Next, the urine starts to move upward and the name of this segment is called the ascending loop and this is very different from the descending loop because the cells of the ascending loop do indeed have and operate active reabsorption of what? Sodium, potassium and chloride. So in this segment, solutes are leaving and obviously being deposited outside this area. So all of these dots represent the variety of solutes which are being added or removed from the nephron in this location. Interestingly, even though that we're absorbing these electrolytes, the cells on this side, the ascending loop are impermeable to water. So even though I don't like to use the word like water would like to leave but it can't leave, why not, what's preventing water from being reabsorbed on the ascending loop is simply that the ascending loop is anatomically impermeable to water. So with that said, what's happening to the urine, the filtrate at this location? It's losing solutes but it's not losing any water therefore the urine is becoming in this location very hypotonic. But keeping in sight what's important is that all of these solutes now are being deposited especially at the tip of the loop here and this effort which has been in fact promoted by especially the ascending loop is creating a very concentrated area of solute especially electrolytes. In fact, this area is the most concentrated solute compartment in the human body. In other words, this is the saltiest area of the kidney, certainly the saltiest area of the body. And you might say, OK, well fine, but what good is that? Remember, urine has to go through this area one more time as it passes the homestretch here which is the collecting duct. And does this concentration serve some purpose? Was there indeed some goal, if you wish, in my mind because that concentration is going to serve as a kind of water magnet. Would water be drawn into this area given the opportunity? And the answer is yes, and the last and final opportunity is through this segment which is called the collecting duct. So let's move down the collecting duct and see what happens or at least what might happen. The collecting duct continues to have and operate active reabsorption of solutes. So even more solutes are being deposited here which further raises or maintains this very high concentration. So that much is similar to the ascending loop. But the key difference to the collecting duct is that it is permeable to water and not just uniformly permeable but there's the word you should highlight, what is it? Variably. What does that mean when something is variably whatever? Could change. And indeed you'll see a little asterisk there because the permeability of the collecting ducts is not at all fixed. At times, it can be very permeable, at times it can be almost impermeable. And as we're about to see, that's a

hormone influence that we're about to give a name to. But simply put, if the collecting ducts are permeable, what's going to happen to water? Water is going to leave and by osmosis enter this area of high concentration. And if the collecting duct is impermeable to water, obviously it will not reabsorbed and therefore it will pass right through and add to the volume of the urine. So it is the collecting duct which is the final determinant of the property of the urine. In other words, it decides whether the urine is going to be concentrated or not and it's all a matter of adjusting this permeability of the so-called collecting ducts. Usually, this area is permeable therefore allowing water by osmosis to enter this area therefore minimizing what? Minimizing the loss of water and creating at the same time what we said was important and that is urine which is very salty or otherwise highly concentrated. So, before we go on, let's just summarize and revisit this. I put some numbers to work for us here and these numbers are not worth memorizing but just follow along mentally as we return to this description. What's going on, on the descending loop? What's actually leaving our solutes but water cannot leave so these numbers, one, two, three, four, five express the concentration, why is the concentration getting more as we go down? What's able to leave is water and so the solute concentration on the descending side is increasing from a low to a high number. So to repeat again, solutes do not leave, water does and as a result these numbers are increasing and we say then that the urine or filtrate is becoming, H word? Hypertonic. Now, as we go up the ascending side, water is not able to leave but solutes are and therefore the solute concentration actually gets less hence the numbers are five, four, three, two, one. Therefore as we go up the ascending loop, the urine is becoming, what? Hy, what hy? Potonic. And finally, we'll have one more opportunity to move through here where it will become, to some degree, hypertonic again as water is allowed variably to go into the area described as a three X concentration, a very high concentration of solutes. So, what is the name given to this mechanism which helps to minimize water loss and maximize the excretion of solutes? Countercurrent multiplier mechanism, which is an ongoing 24/7 mechanism which is not without regulation but the only regulation is here in the collecting ducts because those are not continuously, not always but what's the word here? Variably permeable to water. In other words, sometimes they are, sometimes they aren't. And the key factor which determines that is a hormone that you may or may not know but certainly as well-named, it's called antidiuretic hormone. Before going on, what does that seem to imply? What's a diuretic? A diuretic, is that something that makes you pee? Yes. So this is not a diuretic. It's an antidiuretic. So, based on just that, would this then to conserve water or help eliminate water? Conserve water. This hormone is, of course, abbreviated ADH. It also goes by name of vasopressin because it is a vasopressor. It does cause some peripheral vasoconstriction. But its main action is stated in the name itself. This hormone actually comes from your brain, that is from the hypothalamus. It's stored and secreted from the posterior pituitary. These are anatomical reminders of things you may already know. So, the question before we get going is, OK, what's it do? Actually what it does is pretty easy to decipher and specifically what it does it increases water permeability of the

collecting ducts therefore promotes water absorption, therefore minimizes what? Minimizes water loss. And before going on, what would be your expectation that is what would be the consequence of lack of this hormone? If you didn't have ADH, what would be the obvious and serious consequence of it? You wouldn't be able to promote what? Therefore you'd have huge water loss and would that be dehydrating, would it be lethal? In fact, yes. Incidentally, the name of that syndrome is right now. It's called diabetes insipidus which you could easily confuse with the other diabetes. You might know diabetes is more commonly as a result of lack of insulin and that diabetes is called diabetes mellitus. This is not diabetes mellitus. It's diabetes what? Insipidus. And this is due to the lack of what hormone? What hormone are we talking about? So this is low levels of ADH. What about the word? Diabetes as a word means to pass through and insipidus means tasteless. Compare that to that other diabetes. What's the other kind of diabetes, the more common diabetes? Diabetes mellitus. That means to pass through but mellitus means sugary, meaning sweet. So what's my point? The word diabetes simply means water loss. Both forms of diabetes lead to water loss, in other words watery urine. But in diabetes mellitus the urine is sugary, in diabetes insipidus the water is tasteless, the urine is tasteless. So I wanted to give you the background for those names because if you hear the word diabetes you normally associate it with diabetes mellitus but there is this which is totally different and the lack of this hormone. Apparently and obviously often result of what? Where is the source? What would be the cause, what would be the culprit in lack of this hormone? It would probably be the hypothalamus. All right, but let's go on. Basically what this hormone does, it acts right here in the collecting duct, it improves permeability therefore it promotes water reabsorption, but its other name, remember, is vasopressin. So, aside from that it also causes some peripheral vasoconstriction so it helps to support blood pressure, but this is a minor effect and its most important effect is water conservation. Which of course a statement but our concern is, OK fine, when is this hormone secreted and what is the mechanism, what are the mechanisms which might actually cause it to be secreted or not? Now on a teleologically base– basis, we would answer that easily. In other words, it would go something like this. Well, this hormone would be released when you need to what? When you need to promote watery absorption and when you don't, it wouldn't. OK. But is that an explanation or justification? That's just justification. So we know intuitively that this hormone would be, should be secreted in situations where water is scarce, but that's again not physiology, let's go, let's describe, let's explain when and why it is or isn't secreted. Basically, the hypothalamus reacts to, meaning it's sensitive to changes in plasma volume or– and/or changes in extracellular osmolarity. In other words, the hypothalamus is monitoring, monitoring plasma volume and monitoring extracellular osmolarity, and thereby decides or secretes or not this particular hormone. So naturally, there are two very different mechanisms, one which would relate to volume, the other which would relate to osmolarity. So, let's go into each. The first of the two mechanisms is called the volume mechanism and this is triggered by changes in plasma volume. And as you know, do we have receptors that are sensitive

to plasma volume or at least ramifications of plasma volume? You might have thought we left this in the last unit, but let's just follow a scenario and let's make it real or specific. Let's say you just drank a liter of water, OK. Would that water be absorbed and would that elevate your plasma volume? Yes. And what would that do to your blood pressure at least in the short-run? It would raise blood pressure. Do we have receptors that would react to the sudden increase in blood pressure? Yeah. What are they? Where are they? Remember, these are the familiar baroreceptors also called pressoreceptors. And do they react to low pressure or high pressure? Well, this is high pressure, right? So, they're going to react. And remember what do they do before we forget, do they have an effect on the cardiovascular center? Yeah. I know it's not up there but at least it's in your head. So, when these receptors are excited, the cardiovascular center is inhibited which reduces heart rate and therefore blood pressure and blah, blah, blah. But let's turn away from that and look at what it's doing in this case. These pressoreceptors not only inhibit the cardiovascular center but they also inhibit the hypothalamus which is the source of what hormone? ADH. So naturally that would lower ADH and its effect would be felt where? What is the target of ADH? Where exactly does it work? Yes the kidney, yes the nephron, but specifically right there. And what's it do? It basically allows this part of the nephron to become more permeable to? And therefore water will osmotically move out of the nephron, therefore conserving water, therefore minimizing water loss. In other words, there would be minimum or reduced water reabsorption and maximum water excretion. Did I say that wrong? Oh OK. Sometimes I'm speaking without thinking. I'm sure we all do that. So let's back up. We're going to inhibit the hypothalamus therefore what? Less ADH. Therefore this will not be permeable but remain what? Therefore water will continue through leading to water what? Less water reabsorption therefore more water excretion. Sorry about that. Let's do it one more time. Starting at the top. You just drank a lot of water, that's going to expand your plasma volume, that's going to raise your what? That will be detected by your friends, the carotid, pressoreceptors, that will inhibit the hypothalamus. The result will be less ADH, therefore less reabsorption, therefore more excretion which would obviously reduce plasma volume and help to normalize or return blood pressure. That much is logical and now we see tied to what receptors? Pressoreceptors. Does this mechanism operate in reserve? In other words, if there's low blood pressure, would this turn it around? Yes it would. But low blood pressure is not usually the result of low plasma volume although it could be in the case of hemorrhage. And so, what I'm trying to say is this mechanism works best when there's high plasma volume. It doesn't really react as well to low plasma volume because other mechanisms prevent that low plasma volume from ever really manifesting or effecting the release of the hypothalamus. But this definitely would work in conditions where the plasma volume is raised. And speaking of that, that's exactly one of the two things we're going to do in lab on Tuesday. We're going to create two groups. Group of four, group of four. And one group of students is going to drink almost a liter of water just as I described. And they're going to go to the restroom every 30 minutes.

Now, what do you think? What do you know is going to happen to their urine output? And that's the mechanism right there. So these folks are going to go to the restroom not with a little cup, but they're going to take along a bucket, maybe not, but a lot of cups because this urine is going to come pouring out, it's in your own experience, right? I mean you've all had this happened so you know and expect that it will happen. Now you know the reason or the mechanism behind it. But, with that said, we mentioned there are two mechanisms, this is the so-called volume mechanism. The other mechanism that has an influence on ADH is called the osmolarity mechanism which doesn't respond to volume but rather to concentration. And this one is especially influenced by things that tend to dehydrate the body. So, let's just step in with that sort of initial scenario. I mean literally after all, what is dehydration? A lack of water. And if there is a lack of water, they may or may not be any change in plasma volume that could be supported or corrected by other means. But definitely if there's a lack of water, your extracellular solutes will become high. OK. But remember the pressoreceptors aren't going to react to that but there are other receptors that we have yet to speak of and this, well, they have the funny name, what? They're called osmoreceptors. I don't make this up. The osmoreceptors are located in the brain specifically in the hypothalamus. You can think of these osmoreceptors as basically cellular bags which are going to react to the surrounding solutes. And if the area outside these receptors is salty, then water inside would obviously leave and that would do what to do these receptors? It would shrink them. So, essentially high extracellular osmolarity will cause these osmoreceptors to lose water, something we'll call shrinkage. And because these are already in the hypothalamus, they have a direct and predicable effect on ADH and that would be the increase ADH release. Once again, the target of ADH is down here in the kidney. And what is this ADH going to do to the permeability of the collecting ducts? And what will water do as a result? It will be reabsorbed. So this will maximize water reabsorption and minimize water excretion therefore it will conserve water. And let's make a point to that. This hormone cannot make water. The best it can do is minimize water loss and it does that by exploiting this mechanism. What was the mechanism we began with? What was that fancy name for all of this that's happening here, countercurrent multiplier mechanism. So this hormone takes advantage of the countercurrent multiplier mechanism therefore maximizes what? Maximizes water reabsorption and therefore minimizes water loss. Indeed, that's the name of the hormone. What is the name of the hormone? Antidiuretic, which is essentially aimed at water conservation. You might wonder, are we going to demonstrate this in lab? How would we do it? Well, obviously we'd have to send you away and say don't drink for the next two days then come to lab. No, we can't do that. That'll be unethical, immoral, illegal, and somebody we get fired. So, we're not going to ask you to become dehydrated but we are going to ask for volunteers who don't mind eating a very salty snack. And so, I went up and down aisles of grocery stores trying to find the saltiest stuff that I thought would actually be, to some degree, safe and palatable. And not surprising in the end I found it was pretzels, which is a no-brainer. Because when you look at

pretzel, what is obviously there? Salt. So, duh, it's a very salty food. So we're going to ask some students, volunteers mind you, to consume a bag of pretzels but no what?

>> No water.

>> No water. Therefore, be clear, they're not actually literally dehydrated but they are going to develop what? High extracellular osmolarity. And will that trigger their osmoreceptors? Yes. And will that trigger the release of ADH? Yes. And will their urine output be much, much lower than normal or certainly the people who drink the water? Yeah. So that's easy to demonstrate and we will. Notice this little side remark here. ADH not only targets the descending– I should say the collecting ducts, but it also affects the brain which is kind of interesting because where did ADH come from? The brain. So it's affecting the hypothalamus which you know and have known is responsible for appetite and thirst. So high levels of ADH obviously cause what? Thirst. Which usually helps because you're thirsty, what do most people do? I'm thirsty, I'm going to go drink, right? And does that compensate or at least work in favor of replenishing water depletion? Absolutely. Now this fact has not been lost on salon owners, yeah. Because you go into bars, and believe or not, there are bowls of potato chips there and peanuts which believe it or not they're giving away for free. And you say, well, my goodness, how can they afford to give away for free these peanuts? Well, duh, they know that this will cost your osmoreceptors to shrink and they know, they're smart cookies, they know it will cause the release of ADH and they know that will cause you to be thirsty, and they know that you whip out your wallet and pay huge amounts of money for a water down margarita because you are just so damn what? Thirsty. So, do they make it up on the other end? Yeah, they're giving away pretzels but they're overcharging you for these diluted margaritas. OK. So, nevertheless, this is all physiology. So to repeat, in lab we're going to have two groups. One group is going to what? Drink a lot of water and they're going to demonstrate the inhibition of the hypothalamus which will actually lead to water loss, that is a high degree of water loss through the lack of this hormone. Meanwhile, the folks that drink the pretzels, not– we can't drink pretzels. I guess you could. But they're eating pretzels. They're not literally dehydrated but they will be of course very quickly thirsty and that will be because of a high extracellular osmolarity. So that's part of what we're going to be doing in Tuesday which obviously revolves around this hormone. But, before leaving this topic, there are other hormones that are involved that we've already mentioned by name. One from the adrenal cortex, was called aldosterone and one from the heart, that one is called ANP. So when we discuss and when you draft up your report for this work, it's not just going to be as simple as ADH. We have to integrate the other two hormones. And what are they again? ADH, aldosterone and ANP. And we'll be looking not just water output but also solute concentration of the urine. So, that's a preview of what we're going to do on Tuesday. So now, that was all about water balance. The second and final issue for us as we leave the kidney is its role in maintaining pH. And before we go there, we need to emphasize as we did already with the

case of water, we need to emphasize the importance of pH homeostasis. Is maintaining body pH important? Can we die from mismanagement of that very fragile factor? The answer is yes. But, let's first define what pH even is. It's lowercase p, uppercase H. Some people say it's the power of hydrogen or potential hydrogen, whatever you like. But basically, here are some fundamental and familiar definitions. An acid, as you learned in chemistry, is any compound which liberates or releases or creates or adds to hydrogen ion concentrations. And the base is the opposite, a base which soaks these hydrogen ions up, removes them from solution so we can define a base as a hydrogen ion acceptor. It's also equally permissible to refer to a base as something with a large number of what? Hydroxyl groups. And this might not seem to mesh well or mean the same thing as a hydrogen ion acceptor. But trust me, any molecule which has a high number of hydroxyl groups will be a hydrogen ion acceptor. So these definitions are equivalent and clearly should be familiar. This is not in your syllabus so you just have to look and listen because it is important in terms of terminology. We've just described what an acid is and an acid is anything that liberates hydrogen ions. Would we– Could we describe a strong acid versus a weak acid? You've heard the term. A strong acid would be something that liberates a lot of hydrogen ions and a weak acid would be one that doesn't ionize as freely. So here in this example, we have two acids, both familiar by name, what's HCl. And you know, you probably know this is a strong acid. And that's represented or illustrated by these arrows. Notice the arrows are reversible, but the arrow going from left to right is much longer than the arrow going from right to left. That means this molecule, what is this molecule? It's actually called hydrogen chloride. This molecule tends to ionize almost completely and that means it forms a lot of hydrogen ions. Therefore, what we've already said and what you already know, hydrochloric acid is not a weak acid. It's what? Very strong acid because it ionizes so completely and therefore is a very powerful hydrogen ion liberated. Now the chloride here is not without significance. We're actually defining here and reminding you of an idea called the conjugate base. Whenever an acid ionizes, of course it will release hydrogen ions, but it will also produce something else which is called the conjugate base. In this case, it's chloride. By definition, a conjugate base is a substance that may or at least can accept hydrogen ions, i.e. protons, and therefore reform the acid. But even though chloride is a conjugate base, we want to stress that it's not a very strong conjugate base because already indicated here which direction prevails, not right to left but left to right. So chloride is a conjugate base but it's a weak conjugate base. In other words, it doesn't have much attraction for, much ability really to soak up hydrogen ions. So it's a base but a very weak base. However, compare that to this. What's this molecule we're now using as the second example, H2CO3? That's carbonic acid. And notice the tables are turned here. The arrows are still reversible but would you say from this information that carbonic acid is a strong acid or a weak acid? It's a weak acid. It doesn't ionize very well or completely. It does. And so by virtue of that, it does add to or elevate hydrogen ion concentrations. And it also produces a conjugate base, one that you know by name, HCO3 negative, which is pronounced or otherwise

spoken of as? Bicarbonate. Unlike chloride, bicarbonate is a strong conjugate base. That means it has a high affinity for, a high capacity to actually remove hydrogen ions and that's indicated by this arrow which is longer, that is longer from right to left than the one above it from left to right. So this was just background. It was an overview section here. Acids can be strong or? If they're strong, they ionize fully and they produce a weak conjugate base. If an acid is a weak acid, then ionizes poorly and produces a very strong conjugate base. Here are two examples of each– one example of each. Now, speaking of acids, what are the acids that are produced routinely and unavoidably as a result of living? Here's a short list, lactic acid, carbonic acid and lesser known phosphoric acid. You might wonder right off the bat, why hydrochloric acid is not on this list. Is hydrochloric acid produced in the body? Yes, but only one location. And that's not even in the body. What? The hydrochloric acid that's going into the stomach is not going into the blood. It's going into the stomach. So, we left hydrochloric acid off of this list because its production is of little effect on pH in the bloodstream. These are the prevailing acids that are produced and do in fact regulate hydrogen ion concentration. Based on these arrows, what blanket statement can you say about all of them? Are these acids strong acids or weak acids? Weak acids and we're happy about that. Remember, carbonic acid is a weak acid producing the strong conjugate base bicarbonate. Lactic acid is produced occasionally as you know with anaerobic activity and it produces the conjugate base called lactate, lesser known to you phosphoric acid which produces hydrogen phosphate here, another relatively strong conjugate bases. But the reason for reminding you of this is simply this. Is the body generating acids all the time unavoidably therefore jeopardizing or at least changing the body's pH? Absolutely. And with that said, what exactly are the numbers that we use to calibrate pH? You learned this in chemistry. But specifically the very meaning of the word pH refers to the concentration of hydrogen ions. From chemistry, it's actually the logarithm of the reciprocal of the hydrogen ion concentration which is mathematical mumbo jumbo. What is it? pH is the logarithm of the reciprocal of the hydrogen ion concentration. Forget all of that, the important thing is that this scale is a logarithmic scale. And you know it goes from zero to what? Fourteen. And the reason I'm pausing and stressing that is that this is a logarithmic scale. That means the difference between a pH of 2 and a pH of 3 is not just one. The difference between a pH of 2 and 3 is 10 times. And so I'm trying to stress the point that small numerical changes actually mean big upsets to hydrogen ions. And this, you already know, the pH numerical scheme is such that pH decreases as acidity increases. So if we say that is acidic, that means it has a low what? And if we say it's not acidic then it's probably a higher pH. You know that already. OK. So with all that said and with what you know about the importance of maintaining bodily pH, it's not surprising to find that the normal range of pH that the body can tolerate is pretty narrow. It doesn't fluctuate widely. In fact, the range of survivability is right here, pretty tight, what– between what, 7.35 and 7.45. Now, don't get me wrong. There are areas of the body where the pH might be above or below that but this is the prevailing normal healthy range of most bodily fluids. And

with– this is a benchmark. What would you call anything that is one way or the other? Well, any pH which is much below 7 is appropriately called, there's the word? Acidosis. Acidosis is just that, anything that lowers the pH less than 7 in most cases. And the reason this is important or life-threatening is that it causes depression, that means it shuts down the CNS. What's that? Central nervous system, leading to unconsciousness, unconsciousness which is coma and death. So this is pretty significant. The flip side, the opposite of acidosis is alkalosis. And in terms of clinical numbers, that's usually starting at about 7.8. Its effect is also mainly on the nervous system, but it doesn't cause depression, it causes neuromuscular hyperexcitability which in terms of neuronal effect is going to cause action potentials along motor pathways leading to the T word, what's that? And tetany could be lethal. So how could tetany, through these means, be lethal? Diaphragm. So we've made the case. Acidosis can kill you. Alkalosis can kill you. But which of these you think is the most common threat, the most lurking or insidious threat? Does the body tend to drift into acidosis or mostly alkalosis? Acidosis, for reasons that are obvious because normal metabolism produces a whole host of acidic products. So by far, acidosis is a more common risk and therefore something that is more commonly seen. And with that said, what do you imagine the urine would be? I mean, here is this thing, are we making acids unavoidably through routine metabolism? And would that otherwise cause what? So what would you expect the urine to be in order to counteract that? Well, not surprisingly, the pH of urine is usually acidic. I don't mean it's going to burn holes in carpet or anything but it's pretty nasty and again this is normal. And I want to stress, can the pH of the urine be outside these ranges? Yes, but this is the normal sort of day-to-day typical pH of the urine. And the reason is easy to justify because if we know our body tends to lean toward acidosis, it would be expected that the kidneys would somehow be involved in preventing or counteracting that acidosis. So, OK, we set the stage with a lot of information about what pH is and the fact that our bodies tend to drift mainly, usually toward acidosis. But how's the kidney involved? We know at least we've already said that it tends to generate usually an acidic urine, but that's a statement, that's not an explanation. And in fact, even that statement is not true. Is the urine always acidic? No. But at least we know that it very often is. Before we get to the kidney, before we discuss the kidney's role, we need to really discuss pH homeostasis in general. Now incidentally, this word is not hemostasis. It's what? Homeostasis. You learned that in biology. Homeostasis just means the body's ability to maintain the status quo, to keep things normal. And so, it's a simple idea, what are the mechanisms which prevent or guard against upsets in pH. Is the kidney involved? Yes, the kidney is involved. But it's not necessarily and luckily not the only organ or system that we have to defend against upsets in pH. And so we're going to list three, A, B, C. And C will be the kidney. But before we get to C, we're going to go through A and B. And the first of the three mechanisms is not really an organ system at all, but something familiar also from chemistry, the definition and the ability of something called a buffer. Now, to a lot of people, the word buffer would mean some sort of barrier or some sort of pillow or cushion or something. And in fact,

that is not too far off the mark. But here is the clinical, chemical definition for a buffer. A buffer is anything, any compound that can what? Combine with or what? Or release hydrogen ions. Now, if you've got a highlighter, you want to emphasize that and that, because too often when the discussion is about a buffer, the notion is that buffers soak up stuff but they don't soak up, they don't just soak up, they combine with or what? Or release. I can't emphasize that enough. It is fair enough though to compare this action, at least as an analogy to a sponge, a kitchen sponge. What's a kitchen sponge famous for? It can soak up water. OK, great. But what else can it do? It can release water too. So let's remember, this is a very important two-way path here. Buffers don't just combine with, they also can and do release hydrogen ions. And that is central to their significance because this ability allows buffers to stabilize, that means keep in check hydrogen ion concentration therefore slowing, not stopping but at least slowing the shifting in pH and that's pretty important. So here is the generic summary of what we've said. Without giving specifics, here's a buffer, B-U-F-F-E-R. And what have we said that it can do? Well, it might, C word? And when it does, it forms something called H buffer. OK, great. But it can also not just combine, it can what? And that means it might do the opposite. Notice these arrows are equal and opposite, which of course raises the question what determines the direction in which this reversible reaction might go. Well, it's simple. It goes back to that concept very early in this course called the law of mass action, remember that? So, when would this reaction go from left to right? Wherever you have a lot of? And where would it go from right to left? Wherever you don't have a lot of that, right? So let's avoid the word need here. A buffer doesn't say, oh, I need to soak that up. No, it simply will when there's a high concentration of hydrogen ions and it will release them when there's a low concentration. It's nothing fancy. It's nothing magical. It's nothing, you know, ephemeral or spooky about it. It's just that concept. What was it? The law of mass action. So what are some examples of buffers? This is just the word. But what are some important buffers that are in fact doing this as we speak? There are a number of them. And one that you didn't expect or probably wouldn't expect is our friend Hgb. What's that? Now, you say, whoa, hemoglobin, that's inside a red blood cell. Sure. And, whoa, that's supposed to carry oxygen. Yes, it does, it also carries carbon dioxide, but here yet another function of hemoglobin. Once it loses an oxygen, it will or at least can soak up what? Can soak up hydrogen ions and that makes it a bu-bu-bu-bu-bu-bu-buffer, right? In fact, hemoglobin is the most common intracellular buffer which is not just a tidbit of information, because just getting off track a bit, what do you call a shortage of hemoglobin? I mean, what's the common name, the A word? So if somebody is anemic, they would have low levels presumably of hemoglobin. Would they therefore suffer in their buffer department so to speak? Yes. And therefore what? They would have less capacity to what? Combine with or release. And with that said, they would have a greater tendency for which of these two consequences? They would have a greater tendency for acidosis. The next and most important extracellular buffer is one that we have mentioned more than once, HCO3. Of course, that's stated as bicarbonate, it

normally hangs out with sodium, but it can and will– it can and will C word? Combine with hydrogen and when it does so, of course, it forms this compound, H2CO3 which is carbonic acid. Now, it will do that if there's an abundance of hydrogen ions. But remember, buffers don't just combine. They may also what? And when would that happen? That would happen wherever there is a low concentration. So as you see, a buffer does what we said, it stabilizes. It changes and stabilizes the hydrogen ion concentration so that there is not radical shifts. The other and final buffer here of lesser concentration, lesser importance, the phosphate buffer which also can do the same thing. Now, before we leave this category, a couple of obvious and blanket statements. If your inventory of buffers is low, if your supply of buffers is somehow less than it should be, that would obviously jeopardize your ability to do this therefore making it possible that there would large shifts in pH. And what would be the most common, most likely way things would go? Acidosis. With that said, we'll also state that chemical buffers are– here's the catch phrase, chemical buffers are the first line of defense against what? First line of defense against what otherwise would most certainly become acidosis. And remember, buffers are really not part of any system or any organ. So this is purely a chemical on-the-spot mechanism, but it is the first mechanism which protects against, meaning stabilizes any upsets in hydrogen ion concentration, buffers. The second of three mechanisms, respiration, which you thought we were done with. But this is nothing new so it should be comforting. How's the respiratory system involve in, let's say, the story of pH homeostasis? Remember long time ago, we said that metabolism produces this gas and this basically water. And what do these things do, that is how do they react? Where do they react? They react inside the red blood cell. They produce carbonic acid. And does that ionize into these two things? Yes. And how does the respiratory system factor into this? What happens to minute volume when acidity increases for this or any reason? When acidity increases, the respiratory system is stimulated. Remember that, the inspiratory center, and minute volume goes up? What does that do as a result? When you are breathing more, what are you throwing out or getting rid off? And which otherwise would add up to or produce more carbonic acid? So is the respiratory system very important in eliminating or protecting you from acidosis? Now, don't get me wrong. We don't expire acids. We don't exhale acids. What do we exhale? CO2 and water. But if we don't exhale those, what would happen to those? They would add to and raise the level of carbonic acid and therefore further aggravate the hydrogen ion concentration. So with that said, what is an obvious clinical expectation for respiratory impairment? Yes, there will be hypoxia, no doubt about it. But in terms of pH, how would respiratory disease impact pH homeostasis? You're going to have acidosis, plain and simple. And what are we going to call that? Well, let's call it respiratory acidosis. Now, I know that's too simple but what is respiratory acidosis? That's acidosis due to a failure of what? What's failing here? What's not working is the respiratory system. And so acidosis is acidosis. And what after all is the lethal element of acidosis? Why do we even care about acidosis? Previous page, acidosis causes depression of the central nervous system and death. So could acidosis be the

fault of the lungs? And if so, what would it be called? Respiratory acidosis. So backing up, what's the first line of protective defense against changes in pH? What's the second one? All right. So, first buffers then the respiratory or respiratory system. The third is, of course, the kidney. Now, how exactly is the kidney involved? We've already mentioned that it produces an acidic urine, at least normally. But it does that very specifically through its capacity to secrete what? To secrete or not hydrogen ions or to secrete or not bicarbonate. And therefore, adjusting these two things really manages nicely the pH of the extracellular fluid. And mainly, it works right through here, that is in these two final segments of the nephron, the distal tubules. Now, it's interesting that there is no active what, R word? So that means it's always the S word, right? What's the S word? That means there's no way to reabsorb hydrogen ions but there is a way to, S word. And it's not only secretion but we can adjust the secretion. Can we increase it? Can we make the secretion more or less? So it all hinges on the degree of hydrogen ion secretion. And this goes to this horrible-looking diagram on the next page, which is where we'll finish off in the time we have left. So, that next page you have to flip back and forth to and it's the one that causes you to turn the page around. But before we launch into it, we have to describe what is being shown here. So here labeled are these boxes which are basically epithelial cells along the distal tubules, in other words, the cells right in here. And over here on– over here is the tubular– what's that word? Tubular filtrate. And on this side is the blood. So before getting too technical, anything that remains here is going to end up in the toilet. Anything that gets over here is going to be reclaimed or returned to the what? So, this is going to be lost or E word? Excreted, and this is going to be maintained or C word? Conserved. So that's important to understand what we're about to describe. Anything that remains in the filtrate will be part of the final urine. Anything that ends up in the blood will be conserved and returned to the body. So the filtrate, as it reaches this part of the nephron of course has a whole host of compounds but we're focusing on the fact that it probably will have at this location fair amount of NaHCO3. What's that? Sodium bicarbonate. What's going to happen? The sodium will be actively reabsorbed and that means at the expense of what molecule? What molecule drives active transport? OK. And this sodium ion will not just linger here in the distal tubule cell but it will be further brought into the blood, actually through this potassium-sodium exchange pump which you know a lot about. OK, so what? This reabsorption of sodium in this location is also an exchange pump. What does that mean, an exchange pump? We're moving things against their gradient but were exchanged, exchanged, exchanged. That means one thing is exchanged for another. So sodium is being reabsorbed but hydrogen is being, S word. What's this? So be sure you label this reabsorption and that is secretion. It's a one-to-one ratio there. OK, fine. And just speaking sort of generically, do we expect and want hydrogen ions to be secreted? I mean, if we don't, what's going to happen? If we don't get rid of these hydrogen ions, they're going to add to and certainly elevate the pH, right– not elevate actually, lower the pH. So getting rid of hydrogen ions is sort of an implicit expectation here. But incidentally, you can secrete hydrogen ions

all you want but they won't stay here unless they are buffered by something. And luckily, we have a buffer also present in the filtrate which is bicarbonate. So these hydrogen ions will combine with bicarbonate forming this familiar acid by– what is this called? It's carbonic acid which will then dissociate on its way along the nephron into CO2 and water, water will continue and be part of the filtrate hence this water was or at least created by these hydrogen ions being secreted. The important part is the CO2, the gas will enter– reenter the distal tubular cells. Is there water in here? Uh-huh. Is there an enzyme in here? Yup, that's called carbonic anhydrase. So the CO2 combining with water, which is everywhere anyway, will reform carbonic acid and therefore ionize as you know making available hydrogen ions, but most importantly providing for the return of this. What is this? HCO3, which by any other name is a buffer, the most important buffer. So as we summarize what has happened here, have we eliminated hydrogen ions? Yes, but not as hydrogen ions. We eliminated them in the form of water, they previously were hydrogen ions, and at the same time, we have conserved or returned to the blood bicarbonate. This is sort of the standard thing that's going on. So returning to the previous page, we'll call this normal secretion, in other words normal day-to-day expectation. In short, hydrogen ions are secreted in the manner that we said. They're secreted in exchange for what incidentally? These hydrogen ions are secreted in exchange for sodium and it's this ATP-dependent, OK. And those hydrogen ions are going to be buffered by bicarbonate and then they're going to be excreted as H2O, at the same time the sodium and the bicarbonate are going to be reabsorbed therefore the pH is stabilized, prevented from becoming acidic. This is a very important mechanism. Hence, if this didn't work, what wouldn't happen? Let's just look at it that way. If this didn't work, we wouldn't be able to secrete, H word? And therefore they would build up. And what's the name of that? Acidosis. So, OK. Now, let's go back to this diagram which at first basically depicted something we called normal settings here, normal bicarbonate. But are there times when acidosis is really extreme and has overwhelmed the respiratory system, overwhelmed the chemical buffers? What's going to take up the slack if the buffers are doing their thing and if the lungs are doing their thing? What's the only other organ that can really make the difference in the final analysis is the kidney. You might think, oh OK, that's easy, the kidney would just hype up or secrete more what? Secrete more hydrogen ions, and it can and will do that. But the problem is, just secreting these hydrogen ions doesn't really necessarily get the job done unless there's something in here that can, B word? Buffer them. And there's going to be a shortage of bicarbonate certainly in this scenario we're about to describe which would be extreme acidosis. Now, if there is a shortage of bicarbonate, other electrolytes are not going to be able to fit the bill. Is chloride a good conjugate base? We mentioned it earlier. Is chloride going to be able to hold on to these hydrogen ions and drag them out? No. And so, it's kind of a strange or certainly a desperate situation. There is no bicarbonate, that is there is no spare bicarbonate. Chloride is not going to be a decent buffer. So rather amazingly and only in the circumstance, the kidney itself will begin to deaminate some of its own amino acids. Whoa. Now, this goes back to a

previous definition, but to deaminate an amino acid is just that, taking off the amine group which is NH3. Now, why would this be important? NH3 is an amine group but it is a useful buffer because it can easily attract the hydrogen ion therefore becoming NH– hold on, NH3 plus a hydrogen will be NH4, and that then will combine with chloride forming this molecule which is ammonium chloride. Now, how's that helpful? Well, it's managed to hold and keep out here hydrogen ions. Otherwise, remember, if they're not buffered, what would happen to these hydrogen ions if we just secreted them but left them in here, would they scoop back? Would high concentration of hydrogen ions eventually move this way? Yeah. Which would return them where? So obviously, if we want to get any benefit from this, we've got to not just secrete the hydrogen ions, we got to keep them out there. And so there's a shortage of bicarbonate, what does the kidney do? It makes its own buffer, what buffer? Ammonia, NH3. And it does that through what process? What is it turning to? What is it resorting to? What is it doing here? It's deaminating amino acids which it never does until this dire situation. Now, you might say and you should say, why didn't you mention ammonia previously when you listed buffers? Didn't we list buffers? We listed oxyhemoglobin in blood. Why didn't we mention ammonia? Well, because ammonia is very toxic and it's just not useful as a buffer? How can we get away with it here? I mean, it's just as toxic here but why is it OK to make it here? Where is this going? Out of the body. So we don't care if it's toxic. And more importantly by producing it, we manage to get rid of more hydrogen ions and still not throw away what? We're still conserving, we're still returning back to the blood bicarbonate which is the most precious buffer. So the beauty of this mechanism, which incidentally happens in addition to this, I mean be clear, this first column here was routine, this happens when? When does this side of the story occur? When there's a shortage of bicarbonate? In other words, extreme acidosis. And so this happens not instead of this, this happens in addition to this. And what it basically involves is the ability of the kidney to de–what? It's amino acids producing ammonia which then can serve as a buffer which can drag out or help remove more hydrogen ions. Now, finally, well, let's finish this. This is what happens when there is severe acidosis, basically increasing the hydrogen ion secretion. And at this location for the first time actually making a buffer, what's the buffer that's being made here by what means? Ammonia which is being made by the deamination of amino acids. Remember, ammonia is toxic elsewhere in the body but why is it OK to make it here? It's going to be excreted anyway. And it's not just that it's going to be excreted, it's– we're making a buffer so that we can spare and reabsorb what buffers are important, namely the bicarbonate, all of the sodium and bicarbonate is retained and this helps, again, minimize this trend toward acidosis, in other words raises the pH. Now, the final scenario is rare but what about this? Are there occasions where the body actually has a shortage of hydrogen ions? And what would that be called incidentally? It wouldn't be acidosis, it would be alkalosis. What things can cause alkalosis? Well, it's pretty rare but certainly vomiting is one. Why is vomiting going to produce alkalosis? You're throwing out what on the pavement there? And so that hydrochloric acid is not going to be reabsorbed. So, vomiting

or diarrhea as it turns out very often lead to that. But nevertheless, regardless of how it occurs, what would be the logical reaction of the kidney? Would it be prudent for the kidney to continue to secrete hydrogen ions in the phase of alkalosis? No. So it simply does what? It simply stops secreting hydrogen ions. And that allows what? Well, it shuts down this exchange mechanism and allows the sodium and what? Sodium bicarbonate to go straight on through. That accomplishes two things. It can serve or saves hydrogen ions and at the same time eliminates bicarbonate, which in this particular scenario is relatively in surplus. So as we leave this diagram, which requires you not just to memorize but understand what's being said here, there's really a story. Actually, there are three stories here. What are the three stories that we've just gone through? Normal, acidosis and alkalosis. Each of these is design to protect against what would be upsets in pH. So as a final remark, what are the three mechanisms that regulate or having a– have an impact on pH homeostasis? Buffers, respiratory system, kidney. And if any of these are weak or inadequate, you're going to be probably suffering from some form of acidosis. Whoa. That's a lot. Have a good weekend. We'll see you on Monday.