Human Physiology
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Lecture – 30
Excretory system: Nephron - Part 2

So, what are we doing really? So, we are going to ask a basic question and we are tracking the filtrate. Hello filtrate okay as a result of what ultrafiltration where in the Bowman's capsule and we have got the filtrate okay and the filtrate is flowing along with the proximal convoluted tubule, proximal convoluted tubule we are still in cortex, cortex okay. And then it will go into the it will descend towards the medulla okay and then you will be in the loop of Henle descending limb okay and then you will take a U-turn and then it will be an ascending limb thin thin thin still thin and after little it will become thick and then you will have a distal convoluted tubule and just as you have the distal convoluted tubule you talk to your own Bowman's capsule by a very specialized group of cells called as very good what do you call it as loudly macula densa. What do you call it as macula densa okay. And then you continue as distal convoluted tubule you are still in the cortex okay and then you join the cortical collecting tubule which is in the cortex and then go into the medullary collecting tubule and then you are in the pelvis and that so what we are really doing is you see the each Bowman's capsule is nephron has an enormous enormous enormous duties to perform like what almost look at every molecule and find out whether I need you or I do not need you where do I need to take you back how is my homeostasis in the blood okay. If I if I keep you am I disturbing my the homeostasis how much and in how much percentage each molecule or ion has to be there okay so so kidney has to we have, we have that elaborate system of tubules in the epithelial cells of the tubules and those cells are continuously interacting with the filtrate as it passes okay. Then you have to decide whether how much of water is there okay you have taken one liter of water ingested one liter of water there is suddenly too much of water in your blood, the blood is getting diluted. Its osmolarity is falling so the kidney has to make sure that no no no no I need sodium potassium need to be conserved particularly sodium and chloride need to be conserved but the water needs to be excreted okay. So the kidney has to and what we are really doing is what are the mechanisms which the kidney the cells along the tubules what tubules which we have seen just now how does those cells interact with the filtrate and how do you how do you deal with it is the question that we are asking. Now I am here because to focus on a very interesting point we are looking at the capability of the so I am I do not have to explain this diagram to you the there are certain molecules which we do not want what it does not want in in particular the we take drugs okay we take drugs. The drugs we take them because there is a problem in our physiology so we resort to pharmacology and take a truck okay so

that our physiological process are ameliorated or in a sense homeostasis is restored and the function of breaking down those molecules is mainly performed by the liver. It is huge number of it has huge number of enzymes it can look at any molecule find out where I can cut it so that it becomes small so that I can send it to kidney and kidney can throw it out if I cannot do that then let the molecule go into the bile from the bile into the from into the gallbladder from the gallbladder into the duodenum and then finally to the outside so these are mainly the two options okay which by which the molecules can be thrown out of out of your system . Particularly it has been found that the some of the molecules like bile salts, oxalates, urates and catecholamines, epinephrine nor epinephrine okay even they they can be they are they are readily secreted by the tubule into the nephron secreted okay are those where those molecules ultra-filtered they may be they could be filtered okay they are small they could work but those which are not filtered could be actively secreted now this this property of the tubule to actively secret a certain range of molecule comes with a very interesting dimension. I tell you why it is really very interesting the point is even some of the molecules particularly I will draw your attention to the molecules like penicillin and salicylates. When I say salicylate I mean aspirin what do I mean aspirin and penicillin molecule those molecules if they happen to be in the kidney the tubule is so efficient so efficient it will readily throw away everything from the tubule into the ultrafiltrate and throw it out of your body. Are you with me what is the consequence of that can somebody can somebody help me to work it out. The consequence is that if you take a penicillin tablet now the chances are that in two hours everything is thrown out are you with me are you so the biological half-life of penicillin and aspirin is so short in the blood because you have the problem there so does it mean that you should take penicillin tablet every two hours okay that's a that's a problem with the pharmacy people have to answer okay and therefore we have a very elaborate branch of pharmacy which you call as bio pharmaceutics in which they find out as to how do we what is that what is the you can look at the molecule in what way you can change the molecule slightly so that it's biological activity remains but it's biological half-life increases so that the patient can do with a tablet having every eight hours. Are you with me so I have told you a a dimension of this process of secretion of a large number of substance okay very interesting. See you wouldn't believe till 1990 okay 88 90 okay it's not too far off pretty. how does water molecule go how does water molecule go from this side of plasma to that sort of problem of plasma membrane and the general feeling in the science was that the water molecule is so small that it can cross the plasma membrane in spite of having charged no charge whatever it is charged on water molecules but it can still cause why because the molecule is too too small and if there is enough osmotic pressure difference across the membrane the molecule can go. But that still did not explain that across some cells there was bulk flow of water bulk flow bulk flow. You understand what you mean a bulk flow and one classical example of the bulk flow is RBC water just flows as if there is no membrane how can water flow so easily

across the plasma membrane of an RBC was a question and the answer to that question was provided by whom by whom okay and what did he say he discovered a system of protein molecules which sits in the plasma membrane of many cells okay. Either it sits there or it can be trafficked it can be trafficked so that it's there if I want and if I don't want I can remove it how that happens I'll tell you a little later okay and those molecules we are called as called as called as what aquaporins. what do you call them as aquaporins. So aquaporins we haven't known them for a very long time okay Nobel Prize of Chemistry 2000 it's very recent I mean 2003 okay so what does he say he says that this is a protein system that sits in the plasma membrane and through if the protein molecule is there in that the water molecule can pass one two three four one at a time it's not opening a big channel thousands of molecules go hello you get the point. So look at that molecule okay look at the protein molecule through which the water molecules are going in what in what you call a single file what do you call them as in a single file what should be you why should water go from one side to another side at all what is there to drive the water I have to given the answer 10 times osmosis osmosis there is nothing else there is no water pump. There hello there is no water pump there okay it is osmosis okay you dilute more osmality less osmality the water will go that's it so now let's see about why this is very important is because so far to my knowledge a total of 13 aquaporin have been cloned today. If there are two more I don't know okay so how many how many I am aware of good enough for our work how many are there 13 we also don't care about 13 for we put all them into one category aquaporin is aquaporin okay now this is a look look I want you to be smart enough to have a photographic memory and memorize this figure okay. Now it's very easy I tell you why I don't want you to bother about 1 2 3 4 aquaporin you see I what you have given you see aquaporin one is what to say red so where is red dot where the wherever there is red dot what is author trying to convey that's where aquaporin I don't care you don't care okay okay. For us aquaporin is aquaporin. Ask very carefully are aquaporin is there in the Bowman's capsule? No. Are aquaporin there in the proximal convoluted tubule. Yes. Are the aquaporin there down into the loop of Henle, yes. now now now are aquaporin is there by the time the loop of Henle takes a u-turn and as it starts ascending yes or no no then you go into the thick part of the loop of Henle yes or no no and then you go into the proximal convoluted to be yes or no yes or no no and then you go into the into the into the collecting duct yes or no yes this has to remain with you okay this information okay has to remain with you without that you can't understand how it is possible for the kidney to make if you have taken one liter of water may dilute urine with osmolarity of 50 milliosmoles 50 milliosmoles or if you are dehydrating okay you haven't had water to drink then the same kidney is capable of making urine which is 1400 milliosmoles just look at the difference 28 times difference what look at the capability of kidney lowest as dilute as 50 milliosmoles as strong as what 1200 or 1400 milliosmoles okay you can't really understand why kidney how kidney does it if you forget this diagram have I have I emphasized enough as to you

have to remember where the aquaporins are and where the aquaporins are not there good now we are looking at you see if you remember so far we have focused on on what you know we have done everything what happens in the proximal convoluted to be in the previous lecture we know how glucose is absorbed we know about the glut hello we know about SGLT hello SGLT okay and then we also know that how the bicarbonates are exactly how creatinine is not absorbed we have we have we have the background of proximal convoluted tubule and now we go on look at this diagram the author has darkened this part which is what descending part of the loop of Henle which is the thin segment hello thin segment okay all right so that is what this is an image from Guyton and we are going to look at this. Number one this is the thin segment what do you mean by the individual cells are thin the individual cells are thin by that you mean. And the inner inner the the apical surface of the plasma membrane it is not thrown into many folds so overall the proteins that take part in active primary or secondary transport no no no they are not there really no they are not really okay. Mitochondria very few okay all right. But but proximal convoluted to be descending aquaporins yes or no yes aquaporins yes no yes. And therefore therefore you can immediately understand what water water can go out. Why will water go out water will go out only if outside osmolarity is more hello. Otherwise the water may not go okay. How that happens I'll tell you eventually but now you fully understand the meaning of that arrow now why for two reasons number of there are abundance of abundance of what aquaporins number one and outside outside the tubule there must be higher osmolarity that can draw okay that can draw the water draw the outward there about 20 of the filtered water is really absorbed in the loop in this part about 20% of the water is is absorbed okay. Now we go to the ascending limb okay. In the ascending limb is this is the part of the tubule where minimum action is happening minimum action. Not not not no why minimum action first of all it is thin limb so are there any mitochondria many mitochondria no okay is the inner tubule thrown into folds no are there lots of enzymes and pumps no. okay uh Are there aquaporins yes or no are there aquaporins no no. Is is water freely flowing out no this this difference between the descending and ascending limb has to be firmly ingrained in your mind okay so as we are going up now we are in the medulla as we are going up there is but as you go from the thin limb into the thick limb of what loop of the loop of Henle descending thin thin thin thin thin thin thin thin thin thin thin and that's the end of loop of Henle. Now I'm done from the ascending thin I'm going to where thick limb ascending. Thick ascending limb is of different cells, they are big and the cells are thrown into inner wall is thrown into what brush boulder. So, there are lot of lot of enzymes are there and abundantly equipped with all kinds of pumps and abundantly equipped with mitochondria lot of action is going to happen there. Now, what actions happens there is there are lot of systems symport and antiport or whatever, which are going to pump what out of the out of the lumen of the lumen in the thick segment of the ascending limb limb. You need for me there sodium, calcium, potassium, chloride, bicarbonate they are all

being pumped out.

So, as a result of that the osmolality is going out hello. All the all the all these ions they will add to the osmolality. So, there is huge amount of all those factors which will add to the osmolality are going out is the water following that action. No water is not following that action water remains there water remains there. So, in the thick segment the water remains there as a result of that osmolality of the fluid as it is ascending in the thick ascending limb falls and falls and falls and the whole thing becomes very dilute. Therefore, it is also called as diluting segment of the nephron what did I say? Diluting segment of why is diluting segment is diluting segment? You are absolutely correct because it pumps out the it pumps out all the ions.

So, let us see what pumps out. So, how does that happen? How does that happen? Here is the moment this image comes the first thing you should look at the moment that image comes first thing you should look at where is the lumen hello where is the interstitial side and where is the capillary. You are there. So, look at that image and this is the tubular lumen. So, the filtrate is going the now we are in the ascending limb where are we? So, I will say that the fluid is going this way are you getting my imaginary the fluid is going that way and the fluid will come in contact with hundreds of cells one of them is drawn here and on the and that on the apical side or with the filtrate there is a system. And what is that system? That system is I already told you have done this system once can you tell me the abbreviation of that system? N K system.

Very good what do you call it as? NKCC system. NKCC system does the NKCC system itself use ATP? No, no it does not use ATP it is a secondary secondary, secondary pump then what is the primary pump? Primary pump is here on the basal side you can see that that is on the and one thumb rule which I have given to you what was the thumb rule I given to given to you? No, no the pump is always on the basal side. The pump is on the basal side. So, check whether the rule I stated is applies here it does not apply here can you see the ATP there? So, so why is this pump work I am sorry why is this secondary transport working because this pump we keeps on working it throws the with every cycle of utilization of single ATP you are going to pump out 3 ions of sodium and take in how many ions of potassium? 2 ions and as a result of that we have the we have the concentration of sodium ion falls as a result of that sodium from outside is drawn in and it goes because it can the sodium ions just cannot go on their own. So, you have this system of proteins which we call as NKCC are you ok so far? Now this is a protein this is a big protein here I will show you the image there is a big protein huge protein it goes up and down several number of times it goes in the plasma membrane outside means on the apical surface where that protein is coming out that protein actually comes in contact with the filtrate comes in contact with filtrate and it will come in if it comes across with

a there is a binding site on the protein where sodium can combine another site where potassium can combine another site where where NLCC there must be 2 sites hello NKCC there must be 2 sites and it is only when all these seeds are occupied then the protein undergoes a configuration change and then and all the 4 ions all the all the 4 ions NKCC are with me they are taken from outside to inside who is the driving force sodium why sodium because there is a huge amount of sodium here very less sodium here.

So, the power comes from the sodium the difference in the concentration of sodium and the charge because of that the sodium the protein molecule undergoes a configurational change and all those things are delivered to the outside. So, what am I showing you now listen to this this is becoming more interesting. What am I drawing here. This is a protein here huge protein molecule here. This is just a symbol this is a huge protein molecule there are you ok. And there is a site where sodium can combine there is a site where potassium can combine there are 2 sites where chloride can combine. There is a drug which is popularly given which is very commonly given for the treatment of high blood pressure and they are called as loop diuretics. What do you call them as and there the somewhat the philosophy is that those drugs increase the amount of urine formation. So, you throw lot of more fluid from your body and when you throw more fluid from the body the blood there could be relief on the blood pressure. Are you with me hello hello this is one of the strategy not a great strategy, but we have to do with what we have such molecules are called as what loop diuretics. What do you call them as loop diuretics. So, when a patient of high blood pressure doctor prescribes in loop diuretics the some of the agents which are available in pharmacy are given there can you read the name of the first chemical first drug for me say that loudly. Furosemide.

Furosemide what do you call it as now that furosemide combines with the protein molecule at the site where chloride is supposed to bind hello hello. So, this is the molecule on this molecule there are 2 sites where Cl and Cl are supposed to combine on those sites those sites are now being occupied by what there is a competition between the molecules chloride and furosemide are you with me, but the binding of furosemide in that competition furosemide wins. So, does the chloride have an opportunity to bind with the space no and if and and and the beauty or whatever of the pump is even if one of them is not there the pump would not work the pump would not work. So, you have literally inhibited the pump. So, because you have inhibited the pump the chloride does not go then the potassium does not go and the sodium also does not go when the sodium does not go the sodium remains remains in the tubule when sodium remains in the tubule, proportionately water remains in the tubule and when the person passes the urine more water goes away therefore, we use the word diuretic. It is a diuretic what do you call it as diuretic and this particular class of this particular class of drugs which have their mode of action by specifically inhibiting inhibiting the protein. What is that protein

- NKCC - within the nephron where is this protein located where is this protein located? In the thick segment of the loop of Henle layer thick segment on the loop of Henle. Is it on the apical side or on the basal side very good good good. Alright in the which one furosemide it works wherever this pump is there it will work yeah it works there also.

So, we are looking at the we are looking at the same molecule we have the again again look at look for the ATP look for the basal side look at the apical side. I given this because I want you to read this description it tells you how the okay. We are looking at the NKCC molecule just can you tell me how many times the protein you can you can you have to appreciate the protein molecule how many times it is going up and down 12 times okay. And it allows what okay one of this one of this and two of this two will move on now. So what have we done just now we have tried to understand how the how the fluid in the thick segment of the ascending limb of the loop Henle is being is being treated by or being handled by okay. Now if you go early so now we are so this was the thick segment now I am going to the now we are in the cortex and I will call this as what will I call it as early we are in the cortex cortex of the kidney. What do you call it as early distal tubule. Now early distal tubule is interesting because that is where the macula densa will begin that is where macula densa is we are familiar but we are not talking about macula densa now okay. Then forms a part of juxtraglomerular apparatus that we have already done. Is avidly reabsorbed most of the ions including sodium potassium and chloride. But can you read there is virtually impermeable why there are no you are right there are no aquaporins. Therefore this is still a part of diluting segment. Why is the diluting part of the segment so important I have told you the answer 10 minutes back I just want to answer back from you Because yes because if you have ingested a lot of water, 1 liter of water over a period of 10 minutes we can do that okay if you but within a matter of another 15 to 30 minutes no okay let us see what is the osmolarity of human blood - 300 milliosmoles a little wrong but good enough for government work. It is about 285 to 290 but 300 is okay good 300 milliosmoles so that is osmolarity of the blood, that is the osmolarity of the plasma that is the plasma in the extra cellular fluid that is the osmolarity of the intracellular fluid 300, 300. Good everywhere easy to remember good. Now you have to ingested 1 liter of water okay as a result of that from 300 within a matter of it is water has gone to the stomach absorbed and then within about 15 minutes you will find that blood osmolarity has fallen from 300 to 290 okay or maybe 285 or maybe 280 okay. Now we have osmosensors how osmosensors work. We will see in the next lecture osmosensors okay. There are neurons in the brain which will which will monitor the homeostasis and tell the brain that it is a little it is a little too much of water okay. And then and then so the kidney will say okay you need to form dilute urine and you have to throw out. Had it not been for the diluting segment it would not be possible for the kidney to form a dilute urine. Are you with me and why do you want to form a dilute urine because if you do not form a dilute urine

along with the urine will throw a lot of sodium you do not want to do that okay. Okay you see you have taken water how much of sodium was there in that water? Very little osmolarity of the water that you drink maybe 10 milliosmoles it is so dilute if you have taken one liter of that water okay. You are diluting the whole system so your kidneys is an amazing organ. It seems that you get rid of water but it also makes sure that you do not lose salts. For doing that you have the diluting segment where it is water water water water relatively less salt and if you keep it like that you throw it out. So what really is throwing out of the body is what extremely dilute urine okay but the but but the beauty is, we have only two kidneys and the same organs have to function on one hand if you have taken too much of water on another hand if we haven't taken water okay then how does your kidney deal with the other extreme okay that is something we will see in the next class.