Human Physiology
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Lecture – 31
Excretory system: Nephron - Part 3

Look of thin descending thin ascending thin and thick where in the last part ok. Now in that part we have seen, if we take a section through that part, you see something like this and if you blow up one cell, it looks something like this. And there we find that in the tubular side we have a very interesting system of proteins what do we call it as? NKCC. NKCC what is it NKCC. Now NKCC draws the sodium NKCC chloride chloride from the lumen into the inside cell and all that is happening because on the basal side can you see that pump is there. I am doing it on the pump there hello and the and the what is the function of the pump? To make sure that the intracellular sodium is always low therefore, there is a gradient. Therefore, electrochemical gradient therefore, the sodium will go in and it will go out from here. So, sodium will go in sodium will get out. It will get into the interstitial fluid then into the capillary then it is returned to the circulation. But please remember, we are where are we, we are somewhere in the in the thick ascending part.

Thick ascending ok ok. Now please remember, you see as we go from one part to another part ok the profile keeps on changing. So, whenever you go to the new profile you have to remember where we are ok. So, if I will now directly take you from the thick ascending limb to I will take you to early distal tubule now this is the next part.

So, you again look at that part in the earlier slide we were here. So, those NKCCs were somewhere here now I am no more there I have move ahead and where have I gone? Early distal tubule. Are you with me so far? Please focus because the things keep on happening very rapidly ok. And then you will you will confuse between a part here and a cell which is not there ok. So, just be with me. Now this is also a part where these are the cells are thick there are plenty of pumps and a lot of reabsorption is there a lot of reabsorption is happening there Here we have again we are again, we look at the type of cell here this is different from that in what visit different look at this diagram whenever we look at the diagram we ask first question which is the apical side which is the basal side? Tell me what is what? As usual - first try to identify the ATP, ATP is the pump there? Yes. Ok the pump is always on what side? Basal side. Ok so can you see the pump on the basal side on the apical side you see a new protein system ok is that protein

system NKCC? No.

It is not it is not NKCC. It is just called as actually it is called as NCC but it is ok it is called as sodium chloride symport system what do you call it as? Sodium chloride system. So, if you go to the thick segment, you are having NKCC you move a little ahead in the tubule and what system do you have? Sodium chloride symport system ok. Now this system is also this system is called as electro neutral why electro neutral? Charge is constant. One positive so it is as far charge is constant it is electro neutral and then this is this system is also interesting from the point of view of clinicians. Because this is a target for yet another type of diuretics. The moment I use the word diuretics what does it mean? It is a it is a drug which is given to the high blood pressure patients. It is supposed to act on the kidney and bring about the increase in the formation of urine. Diuretic what does it mean increase in the formation of urine those which were acting those which were acting on this part were called as what diuretics? Very good what do you call it as? Loop diuretics.

Loop diuretics ok do you remember the name of the drug? Very good ok and then here we have another category of diuretics which inhibit this type of pump and we call them as what? Thiazide diuretics. Thiazide diuretics ok. And they are also and these two diuretics are very commonly used by the prescribed by the now I have moved ahead from the early distal tubule. Why are we using the word distal to contrast it with the proximal where is the proximal? Immediately after the Bowman's capsule that is proximal ok then we have gone down the loop of Henle, and then come up now we are in the distal ok. In the distal, where are we? We are in the late distal so now we are done with macula densa, hello. We are done we have gone ahead and we are in this part we call a late distal and collecting tubule and we take a transverse section and again we find cells the cells are large the inner wall is thrown into folds and there are plenty of pumps ok and in this we find that there are two types of cells. They are very interesting two types of cells ok. They are called as number one they are called as some of them are called as principal cells and some of them are called as intercalated cells. What do you call them as principal cells and what intercalated cells? Where you will get them where you get in the late distal and collecting tubule and there you will get them. There the two kinds of cells ok and what do they do let us see what is the functional role of each ok. We are again in that part author is using a code ok what code is he using? He is using red and green colour ok what is red and what is green. The red ones are what - principal and green ones are what ok if you diagrammatic there is even structural even in electron photo micrograph you can see the differences between the two. Can you see the difference between the two ok. Which one has more villi intercalated on the apical side we will have more villi ok. And now we will another two slides two three slides will focus on the principal cell we will talk about. Just focus on principal cells they are very

interesting because they are the target for a very very I will say very two more times very important hormone which is called as aldosterone. What did I say - say that again aldosterone. Aldosterone is a hormone in terms of chemistry - a steroid hormone and it is secreted by the adrenal cortex. By what? adrenal cortex. What are the hormones we are already introduced to which are secreted by the adrenal medulla ok and then adrenal cortex aldosterone there are several of them but let us just talk of aldosterone. So aldosterone is a hormone that is secreted by the adrenal cortex and it has many targets and one of its target is the principal cell. Are ok so far? We know we know the hormone which is we know the source it will of course get into the blood ok. And it will look for its receptor wherever it is and it will find its receptor in the principal cell and it will change the physiology of the principal cell. In what way will it change the physiology of the principal cell is an interesting question. And we will try to answer it. This is again a typical cell I just want you to forget everything just look at the the the the pump again hello so this is the basal side the blood is somewhere here the capillary is here. Done ok. So there is a pump here ok and here on the apical side there is yet another kind of system yet another kind of protein whose function is again to take in sodium sodium is so important that the nature has provided different different types of protein systems in different different segments of the nephrons whose function is to facilitate the influx of what? Sodium in this particular case the the the the the the protein system that is provided on the apical side on the apical side where the urine is actually flowing is called as ENAC, epithelial sodium chloride channel. E stands for what epithelial say that again ENAC. What do you call it as ENAC what do you call it as ENAC is a system of proteins ok. So this cell has again I am not I will not talk to you I will ignore this for the for the time being. I am just focusing on this which is always there and on the apical side this system of proteins now this system of proteins look something like this it there are there are six domains which go up and down and call as epithelial sodium epithelial sodium channel ok ok. Now let us try to link up the two points aldosterone ok secreted by the adenal cortex. It has plenty of receptors in the principal cells and when aldosterone combines with its receptor in the principal cell that complex that receptor plus aldosterone. Now aldosterone has activated that protein system that receptor that receptor is normally sitting in the cytoplasm of this cell once it is activated once it combines with its ligand the ligand is aldosterone. Once it combines with that then that complex which is which is called which is which is which then moves from the cytoplasm into the cell. I am sorry from the cytoplasm into the nucleus. In the nucleus, it combines with this and brings about the generation of several transcription factors. Are you with me? Those transcription factors eventually, greatly stimulate this. And this now what do you mean by greatly stimulate this and this I simply mean is before aldosterone came I will take arbitrary numbers before aldosterone came there were 1000 ATP molecule not ATP molecules that ATP a system are you with me. That system which is which is running the pump. How many were there initially thousand ok Under the

influence of aldosterone - now there are 5000. Got the message loud and clear. What aldosterone is doing to the cell it is to increase the capability of the cell to generate the pump ok. Is increased number 1 and number 2 the same thing also applies to applies to what ENAC so whatever on whatever the number of molecules which are there in the plasma membrane on the apical side ok ENAC molecules which we have seen the which we have seen there there those E NAC molecules the number of those molecules so the entire protein machinery in the cell ok which will finally give rise to ENAC molecules which are which go and then sit in the in the in the in the apical membrane and the ATP system which they are all they are all up regulated under the influence of what? Under the under the influence of aldosterone. Therefore I hope you appreciate as to why does aldosterone enter the cell? Any suggestions? Clues - it is a steroid had it been epinephrine nor epinephrine and peptide hormones ok. They would have hard time entering therefore the cell will provide the receptor right on the surface but this is a very nice slide tells us a lot what it tells us is there is a so MR MR. MR what is this MR? It is called as mineralocorticoid receptor mineralocorticoid receptor. Aldosterone is also called as mineralocorticoid receptor. Why mineral - because it is facilitating sodium therefore mineralo corticoid because it is coming from adrenal cortex - receptor because it is a receptor. So what does MR stand for what does MR stand for mineralocorticoid receptor ok. Where is it? where is it? In the cytoplasm of the principal cell ok. And what does the blue dot there are ok. There are 2 blue dots can you see those blue dot 2 blue dots yes or no? what does each blue dot represent? Aldosterone, aldosterone. So actually what happens is there is a receptor here there is a receptor here aldosterone will come what has happened is - dimerization happened once it is dimer the dimer will enter from the cytoplasm into the nucleus and then it will it will activate number of genes and one of the thing that it does is already in the cytoplasm there are vesicles and sitting on those vesicles are ENaC proteins are those ENaC proteins are really functional - no why? Because they are in the cytoplasm but under the influence of those new transcription factors, which have come, those vesicles are now trafficked and they are taken as far as the plasma membrane. They are inserted on the plasma membrane on apical side or basal side apical side. Very good. They were in the apical side now suddenly ENaC is available and ENaC can function. It can take in the take in the take in the sodium ions and and this is the this is the pump on the basal side etc. I think I hope you appreciate the appreciate the mechanism okay. A basic link is missing. Yeah. Go ahead. you your question first why do you want to go into that okay okay okay okay okay okay. Spironolactone is a drug okay and that drug inhibits the action of aldosterone. What is the action of aldosterone? To pick up sodium okay now picking up lot of sodium is not a very good idea for a heart patient. Therefore for heart patient we have different tools one is a furosemide, one is thiazide okay and one one aim is to inhibit the pump. How do you inhibit the pump by using a drug called as what okay You exchanging for what tell me tell me what is there bicarbonate and so anion exchanger is that simple anion exchanger.

Now I want you to remember the anion exchanger term. I will tell you why this term will repeatedly hit us when we go back to studying the circulatory system and focus on the function of RBC. Same AE1 same this same protein system which is sitting here okay you will encounter this protein system again when we go to and another very interesting function. There function is the same there it is anion exchanger which means what it will it will do what it will it will take the bicarbonate here it will take the chloride ions there do as they keep on circulating and here is here is what here is what this is structure of how amazing these proteins are now we are going to this part. And now I am ready for the last part of the collecting duct yeah. Why is it there like sodium hydrogen? I did not understand could you please go to proximal convoluted tubule okay okay. At that stage I mean I have forgotten, can you refresh me? What the system was doing in proximal convoluted tubule? There was a sodium hydrogen I thought on the basal side, there was a bicarbonate sodium okay okay so similar system but that did use okay. There the gradient is not in favor of hydrogen ions means what if you do not apply any energy hydrogen ion just one go from here to there. Therefore why would cell use ATP at any given point because you want to do work okay. So if you at earlier stage, I do not know it might be there might be a problem with the pH but I do not know that. I cannot comment on that but here the hydrogen ion needs to go against the gradient there is maybe already there is too much hydrogen ions maybe there is already too much positive ion there for some reason it is just not possible for the hydrogen and to go on its own or go by some some antiport system you have to give energy therefore I think ATP is given. I do not know if I have really answered your question. But I will talk about it. Now comes a very interesting part. The medulla that part of the tubular in the middle of the kidney does it contain aquaporins. It does contain aquaporins. it does it does it does but whereas the aquaporins which were present in the proximal convoluted tubule earlier part aquaporins were present in the basal as well apical membrane, I decided not tell you earlier, but I am telling you now. Aquaporins were present in the proximal convoluted tubule in the apical as well as basal membrane. They are constitutionally there what do I mean by that? They are always there. They are always there. Are you with me so far okay. In the case of this part of the tubule okay, the aquaporin on one side is inserted it is not there. It is inserted only under the influence of a hormone and that hormone is nothing but antidiuretic hormone. Are you getting the story? It is beautiful. Aquaporin is there. They are there but here no here no they have to be inserted okay. They have to be inserted why why should they be inserted. Well let us try to find out now okay let us continue with that. It is a very good question. There are different types of aquaporins okay on one side they are constitutionally there on another side they are inserted. I will let me okay. You remember. We had that slide you know where we started we had the Bowman's capsule and from there we had the proximal convoluted tubule, we had divided into five sections and we had collected samples at each stage. And we had said we had said that glucose is absorbed all across so now what we are doing is we are

collecting the sample here here here here here here here here all along at different intervals and we are plotting their concentrations and comparing with what? Comparing with the filtrate at the level of Bowman's capsule and whatever sodium potassium whatever whatever whatever I will call it as one the moment it is filtered in the Bowman's capsule. And then I find that by the time I go from the and then I will take the samples, I find that part of the graph tells you that that the three things what are they glucose, proteins and amino acids. They are completely absorbed by the time the fluid is done with the proximal convoluted tubule. It is completely absorbed okay. What about bicarbonate well it comes comes comes this some some bicarbonate is still being excreted. If you see the potassium and sodium it is almost one it is almost one concentration is same why is concentration same we answered this question in that lecture very good very good okay then then then it goes up and it comes down can somebody explain as to why this is happening at the level of loop of Henle. The answer is water okay and then and then what is happening to the things like what is this molecule can you please read for me creatinine. It is coming from what phosphocretin okay. And are we interested in retaining this molecule? No we want to get rid of. So look at look at look at creatinine okay it goes up and up okay in case of kidney failure this will come down which means creatinine is being retained in the blood which is a reflection of kidney not doing its function properly. Now I am going to answer that question why aldosterone is being secreted I left you with that question. You remember okay the answer to that question lies in the hormone angiotensin II. Now angiotensin II - you already know okay angiotensin system because we have fall in blood pressure, okay. Renin hello renin renin then what is the next word I am going to pronounce renin-angiotensin system. What is the source for angiotensinogen liver - acted upon by renin gives rise to what – angiotensin I - it goes through which organ lungs which organ lungs acted upon by which enzyme – it is converted into what angiotensin I to II. Very interesting targets for angiotensin II is the adrenal cortical cells and response is profound - release of aldosterone okay. So we stimulating the release of aldosterone – do you get angiotensin II receptors on the cells of the cortex – yes you do. So aldosterone will come are you with me. So this author tells us that Angiotensin II does many functions okay. So that a lot of action of angiotensin are okay okay. We have already seen that angiotensin has direct action on the smooth muscles okay. That is also to improve the blood pressure increase the blood pressure okay. Another function is to retain sodium retain sodium if you retain sodium you retain water okay. If you retain water, you are again helping to maintain the blood pressure. Are you with me? Are you getting that those steps in the logic very simple. That is why if you have high blood pressure, the doctor advises you to do what reduce sodium intake, the doctor will tell you while you are taking food whatever salt comes it is okay but you do not take more. Are you with me? Okay, that is one thing is you do not, you do not it is you mean look even otherwise you take too much salt on sugar let us not comment okay, so here we are - please read for me here

angiotensin II stimulates aldosterone secretion which in turn increases sodium. Now this function of angiotensin II is slightly - I will not use the complex or complicated, bit I will use word interesting, okay. It is interesting okay. So we have seen this figure hundred times - that figure and there is an afferent artery, there is a different artery on the smooth muscles these ones these ones these smooth muscles have receptors for angiotensin II and in response - smooth muscle they have receptor for what? Angiotensin II and under that what are they doing constriction, okay. As a result of constriction okay the blood supply now where will the blood from the efferent arterial go in the peritubular network so the blood per blood supply in the peritubular network goes down. The blood pressure goes down so in the peritubular network. If earlier pressure was 18 mm Hg it may fall to 12 mm Hg. Are you with me? Less blood pressure means it facilitates the reabsorption of material hello are you getting the argument, okay. And this is how angiotensin II facilitates the reabsorption of material including sodium. Angiotensin directly also has action on the, okay. Look at that image on the top. There is a there is a shift in the gear where are we now proximal convoluted why am I showing you this because angiotensin II, which I am referring for the first time now in the earlier slide - here angiotensin II, it also has receptors in the proximal convoluted tubule. Therefore I put that slide there okay so angiotensin II has receptors there. And also here okay. So I take one more cell from the proximal convoluted tubule and blow it up here and here I can find that which is the tubular lumen the lumen is here the filtrate is going this way, are you, okay. There and of course this is the ATP so this is the basolateral side. Now something very funny is happening in this slide. I want you to I want to find out how smart you are in detecting that something funny on both sides. Wait angiotensin II and you tend to and also receptor and what is your argument and just attention to the lumen and in blood capillary - yes you are right absolutely right I think you are right but I want you to improve okay okay good. Improve yes is in the blood okay. First of all no no first of all why can it not go itself fluid it is there in the blood from the capillary it can come out okay okay one reminder for you what is the size of angiotensin II, it is a small molecule. It is a small molecule it can readily come out of the capillary and a having angiotensin II in the interstitial fluid is a matter of routine. I mean if insulin can go if insulin with 51 amino acids they can all go - no problem there the real problem is on the other side. How are you getting are there do you mean to say that angiotensin II is there in the urine pre-urine. Answer is to the answer to that question is yes. It is such a small molecule that it is also filtered angiotensin is filtered it is filtered, okay. So, here is a totally absolute new concept in which we are talking about a hormone which is coming not through blood, but through, sounds funny, it is coming through what - filtrate which is eventually going to be urine okay. So in the proximal convoluted tubule and therefore on both these sides you have angiotensin II receptor, angiotensin II receptors of different types what kind of receptor is also talking about okay and angiotensin II can combine angiotensin II can combine and what it does it stimulates? This protein system this

protein system and this protein system okay. All right so we are talking of angiotensin receptor. It is again a protein system transmembrane receptor okay. You can see in this system can you appreciate the cortex and the medulla can you identify cortex and medulla in the kidney, okay. In the in the medullary region, can you see the intense reaction there okay that reaction indicates the occurrence of angiotensin receptor, okay. You are you have you have label there and auto binding of angiotensin receptors in the kidney of dog okay. So this is just a summary slide. It tells us about the total amount of sodium that is being absorbed 67% is absorbed proximal convoluted tubule not much action is happening here, 25% is absorbed here, 5% here. So this tells us as to how the sodium ions are being absorbed and I will stop now and I will move on to my to my next lecture which I hope to this is so far we have raised a several number of questions and most important question was how does the water move? Osmolarity how does the water move? Osmolarity but that is not an answer how does the osmolarity how is the how are the changes in osmolarity accomplished? How are the changes accomplished? I mean you see yeah I say osmolarity that is fine but how do you but for that you have to make more osmolarity somewhere and less how do you make more osmolarity.