Human Physiology
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Lecture – 50
Secretory functions of Liver and Gallbladder

What were the two hormones we were talking about? Which are being released from the stomach, cells in the stomach? Gastrin and? Good, good, good. What is the receptor via which gastrin acts? CCK. Good, good. And CCK stands for what? All cholecystokinin and then what are the two hormones which we come across when we talk about duodenum? Secretin and? CCK. CCK. Secretin and what? CCK.

What is the chemistry of all these hormones basically? They are all peptide hormones. They are all peptide hormones. Good, good, good. And the secretin and CCK together they bring about the release of pancreatic juice from the exocrine pancreas cells and the bile from the liver, gallbladder actually and of course the bicarbonates etc, etc.

We will move on. I will show this to you at the end also but let us now move on with our lecture. So what we are doing right now is we are trying to familiarize ourselves with this very interesting organ called, what do you call it as? What do you call it as? Liver. Liver, what do you call it as? We have heard of it 100, liver. Now what we are going to do in another 5 minutes is try to understand the anatomy of liver.

It is very basic. Excuse me, I will do it now. So in the previous lecture we said that - it is made up of what? Lobules, what do you call them as? Lobules, they are cylindrical, not exactly with 6 faces and then it tapers and one lobule, another lobule, another lobule, another lobule, thousands of them they make the entire liver. And then the author gives us here this anatomy of a single lobule and then we have seen that the liver has blood supply from two sources. What were they respectively? One is hepatic portal and one is hepatic artery.

Hepatic artery is mainly for oxygen and hepatic portal is to bring all the, lot of food material other than fats from the intestine to the liver. And we have seen that at every angle or at every corner of the lobule we see 3 tubes. And what were the 3 tubes? The two of them are blood vessels. One of them is a branch of the, this is a branch, it is blue, it is hepatic portal. And then there is another branch of hepatic artery and the third green one is for what? Is for bile.

Now what I am going to tell you is very interesting. Follow the story. So I said that each lobule, each lobule we will consider as a cycle wheel. And through the center of the cycle wheel, now it is actually not like a wheel, if you take a transverse section - it is a wheel. But if you see in 3D each spoke of the wheel is like a wall.

So one wall, second wall, third wall, fourth wall and all the walls are projecting towards the center of the wheel like the spokes of a cycle, bicycle wheel. Are you with me? And at the center you have a very major vein, at the center is the vein. That is called as central vein, that is also called as hepatic vein and that will carry the blood away from the liver to the vena cava and to the heart. So how is the blood going from the liver back to the heart? That is vena cava. Are you okay so far? Alright.

Now we have, okay now I am going to talk about the wall, talk about the wall, vertical wall. So in the lobule vertical wall, vertical wall. Now each wall is made up of bricks. Each brick is a cell. So far each brick is a cell.

Now there is a wall around me, all around me. So one cell, second cell, third cell, fourth cell walls, you make a huge wall. Wall everywhere. On this face on my right, on my right there is a tube in which I pour the blood my left - there is a capillary. Okay so far? Okay, where is the, on this side there is a corner of the lobule, the central vein is somewhere there.

So here in my corner, here my, there are two tubes, two tubes. One of them is bringing the hepatic artery, branch of hepatic artery that is oxygenated blood and next to that is a hepatic portal and both of them are pouring blood into the capillaries and tiny, tiny capillaries and those capillaries are flowing this way, flowing this way. Where are they going? They are going in the center – somewhere here of the lobule. From there they will get into the central vein, hepatic vein and that hepatic vein will get into heart. So in this, so whether this is a red one is the branch of hepatic artery or the blue one is a part of hepatic portal vein, the blood is flowing this way, this way, this way and then this way and then this way and then back to the heart.

Hundreds of lobules, hundreds of them. Is it very clear? Okay so, let us see if you are somewhere, where are you? You are in an RBC. Where is that RBC? In the blood vessel, where? In the intestine. Okay, so you run along. Where do you run along? You run along, you enter, you find yourself in hepatic portal system.

Then you run along, run along, finally you will find one here. And then you get into the liver, okay and then you travel, okay on right and left there are walls, there are cells, hepatic cells. You go through a capillary, go to the central vein, okay. You suddenly find that you are joined by another, you are joined by another capillary. So you find that capillary is bringing the arterial blood from the hepatic artery.

Let me try to clarify this. This is the red vessel, it is bringing what kind of blood? And here is the blue vessel, what kind of blood? The capillaries both of them as they go towards the central vein, they mix with one another. The blood mixes. So the blood coming from two sources, okay those capillaries coalesce with one another, okay and then the mixed blood will pour into the central vein and then back to the heart. Is that very clear now so far? Now so this is a wall.

On the left are the capillaries. In the capillaries I am either getting a branch of the hepatic portal vein or I may be getting a branch from the hepatic artery or I may be getting the mixed blood, fine, I am fine with that. On the right I am a hepatic cell, I secrete bile and that bile goes into the bile duct. Now listen to this. That bile, the bile flows in the opposite direction.

In what direction does it flow? Opposites means those cells, now let us see here, let us see here, okay. So okay I will draw your attention now. When you see these cells, the green is indicating the, this green, all these green is indicating the flow of the bile and these cells, I think I can show this to you better in my next slide maybe. Hope I can do a better job here. I think I can do a better job here.

Okay okay good, good, good. Now can you see a wall like this, like this, like this, like this that goes to almost to the center. So where am I? I am at one of the corners, okay. And there is a wall which actually is a plate of cells, plate of cells, they go all the way towards the central vein but they do not open there, they close here. So they form a V, are you with me? And on the inner side of the V, they secrete bile which flows in this direction, it gets into the bile duct, okay and then it goes to the gallbladder, okay and then the common bile duct and then it opens to the duodenum.

Beautiful anatomy, beautiful anatomy. Look at the cell, on one side the blood flows in one direction and another side the bile flows in the other direction. Is it very clearly absorbed? Now this anatomy, okay, anatomy is amazing, the whole functioning of the liver, okay is based on this amazing anatomy of this organ. Now what happens is, yeah that is the most efficient way for the cells to keep on getting the material on one hand and then process it and then store whatever you can, whatever enzyme process, at the same time you cope on synthesis in bile, okay. So it makes sense and for every cell you have the access to a bile duct and that tiny bile duct which comes from a cell goes joins the bigger bile duct, that bigger bile duct will flow into the bile duct which is at the corner of the lobule.

So you try any other way and find that this is the most efficient architecture of the liver, okay. Now the blood that comes from the hepatic portlet system is, the blood that is coming to the hepatic portlet system, that blood has already been through the capillaries in the intestine, so the blood is under very low pressure - the pressure is actually found to be 8 or 9 mm Hg. The blood that comes from the arteries is slightly under higher pressure, okay. These very low pressure but the point is the liver is equipped with thousands and thousands of capillaries and those capillaries are relatively large, when their capillaries are large you call them as sinusoids. So there is hardly any resistance, so the blood can easily flow into the liver into the central vein and from the central vein into the vena cava. Now I just want you to be introduced to one very interesting cell and a name - whose name, I want you to know that name. In the, so what do we have? We have the, a wall of liver cell, wall is a bad word but I will still use it, another wall of liver cell, are you with me? And in the middle you have what? A capillary.

In the capillary you have a very special type of cell. They are called as a Kupffer cells - , K-

U-P-F-F-E-R cells - he was a German scientist, he discovered those, Kupffer cells, say that again, again. Kupffer cells are phagocytotic cells and obviously you know the material is coming from the intestine, along with what? Digested food, along with the digested food, what all viruses and bacteria and all that can come, are you with me? Their microbes are also very smart, okay. So the Kupffer cells is within our body, it is one of the lines of defense, okay, are you getting my argument? So if anything foreign that enters which should not have entered - apart from food, it will be consumed or it will be dealt with by the Kupffer cells, so remember the name Kupfer cells and appreciate their importance, Kupfer cells, okay. Now this is - now look at the two - healthy liver, okay and look at that liver, I put an extreme case there, that is called as a liver of a person who is suffering from liver cirrhosis. Now liver cirrhosis can happen under two conditions, one is regular consumption of alcohol for a very long time, okay, it results into what you call as liver cirrhosis or some infection, some hepatitis or some jaundice or some it can both of them can cause. Now when you get liver cirrhosis - actually happens because the infected liver - the regenerating liver gives rise to lot of fibrous tissue, remember we talked about elephantiasis. Why does the leg of a patient suffering from what? Okay, yeah, yeah, yeah, say that again, perfect because of that, so that similar fibrosis happens here and that beautiful anatomy of you liver is messed up, are you with me? And then the efficiency of liver goes down to 10%, everything may be, all the cells may be there, they may still be manufacturing bile but the anatomy and the efficiency, as you see every day within a period of 24 hours our liver secreted almost 300 to 400 ml of bile which is a lot, what did I say? Our liver secretes how much of bile? 300 to 400 ml of bile which is lot, that efficiency goes down. That you call as the cirrhotic liver and okay good, good, good, let us move on.

So what does the bile do? It helps us to, okay, now do you all understand the meaning of the word, word emulsification of fats, what is emulsification of fats? So I take a beaker, in the beaker I take half the beaker of water, on the top I put some oil, okay and I find that the oil makes a layer at the top because its relative density is less, lighter than water. I stir, but again they separate into layers, now I want to somehow mix them, they cannot dissolve, out of question then what do I do? I put one spoon of detergent there, a soap, okay and then stir it, okay and as a result of that I find that the fat is now broken into tiny, tiny, tiny pieces, okay and then it can, now it can uniformly spread in water and now what I say is I have an emulsion of oil in water, what do I have? Emulsion of oil in water and the best example of emulsion in water is the milk, okay. So when I make curd out of that milk I am breaking the emulsion, are you with me? Hello, that is an emulsion, okay, blood is an emulsion, okay. See that particles of different densities are spread around, okay because of the, because of the detergent action. Now the one of the very important functions of bile is to, okay just, okay, okay, okay, this is just to, we are talking about the gallbladder, I will come back to that. Come back to detergent action in a while but let me, let me address this slide, we are talking of a gallbladder, the bile comes into the gallbladder, the gallbladder does a lot of processing, gallbladder absorbs a lot of water, okay, it is good that concentrates the bile - but if it over concentrates, okay, then the materials crystallize out and once they crystallize then they can give rise to stones. If the stone is there then it serves a nucleus for formation of, for making the stone bigger, okay but that is the thing we have to leave. Can you see there is a dotted

line and then can you see the red arrows, what do they represent? They represent the action of cholecystokinin on the smooth muscles of the gallbladder, okay, so it constricts and then it pumps, actually pumps the bile into the bile duct and then from the bile and this will happen under the signal that it gets from the CCK and the CCK will be released when fatty food, okay or amino acids they arrive from the stomach into the duodenum. Okay, the cells will release the CCK. So CCK is a key factor that will determine the timing at which you want the bile to arrive in the duodenum, good, good. This is just to show you the structure, it is a peptide, what peptide are we talking about? Okay, this is just to show you - this is the bile as it is being secreted by the liver, then the bile may directly go directly to the duodenum as it happens when you are actually having food. Or when you are not having food the bile secretion may go on and the bile may be stored in the gallbladder. While it is stored in the gallbladder, it undergoes a lot of processing for that I just draw your attention to the bile salts, bile salts. How much is there in the freshly secreted bile, how much is it? And then how much is it in the gallbladder? So you see lot of processing, lot of processing is happening, okay. Another function of the blood - hemoglobin is being broken down, hemoglobin being broken down at the level of spleen, okay and the broken molecules give rise to what you call as bilirubin. You got to get rid of bilirubin, you throw it off your body, it goes into the bile from bile into the undigested food and by way of feces it is thrown out. Let me move on, on, on, okay. Now I am going back to the earlier step, what was my earlier step? My earlier step was how does bile serve as an emulsifying agent? Why do you need that? Because you see if you eat a spoonful of butter, okay and if that spoonful of butter more or less like spoonful of butter till it goes to the intestine it will be very difficult for the enzymes to act on it.

So to make sure that your enzymes which are say lipases - which are secreted at the level of your duodenum have access to every tiny, tiny bit molecule of fat so the least you can break down fats into tiny, tiny, tiny, tiny bits, are you okay so far? And for that we need a detergent and detergent comes from what you call as bile salts, bile salts, what did I say just now? Understand bile salts, now let us see how the bile salts are formed, okay. Now first thing I want you to remember is this structure, this molecule called as cholesterol, very widely distributed. It is a part of the plasma membrane everywhere, cholesterol, cholesterol it is everywhere. What is cholesterol? It is a molecule, it is a steroid, what is it? Cholesterol, cholesterol it is a steroid, okay. It is made up of 4 rings, 6 membered, 6 membered, 6 membered, 5 membered, got it? Call them as what? A, B, C, D look at the arrangement A, B, C, D and there is a side chain and the entire molecule put together has 27 carbon atoms, how many? Remember this, okay? So a student of physiology, cholesterol has to be remembered, okay? When we talk, when we eventually talk about, which I will hopefully in another week or so when I talk about the steroidal hormones, okay, like the hormones of the adrenal cortex and the sex steroid hormones. All the stories begin with cholesterol, okay. So this cholesterol, okay, from this cholesterol this side chain, okay it is acted upon by an enzyme, side chain cleavage enzyme, whatever and then you get 2 compounds which one is called as cholic acid, the same similar but only some part is cut away from here, are you with me? And so what are you getting from cholesterol? We are capable of synthesizing cholic acid. I am sorry, we are not capable of synthesizing our own cholesterol but lot of it comes from our food. So both the sources are there, okay. So you have the, it is converted either

into cholic acid or this is chenodeoxycholic acid, are you okay so far? I am talking of 2 molecules, okay, what are the 2 molecules I am talking about? cholic acid and chenodeoxycholic acid, they are both derived from where? Cholesterol, okay and where is all this happening? This is all happening in the liver, the hepatocytes are doing it, okay.

Now what happens is these 2 are fats, cholesterol, they are lipophilic molecules, okay they can go anywhere to anywhere and they have no charge, are you okay so far? Now one interesting thing that happens is these 2 molecules combine with amino acids and what amino acids are generally chosen for this purpose? The 2 amino acids are largely glycine and to some extent, taurine, are you with me? And these amino acids, these 2 amino acids combine either with cholic acid or with this, what is it, chenodeoxycholic acid - whatever - then you get what you call as, what is it, taurocholic acid and what is it, whatever it is, you remember the name, I do not care, okay you got it? So that amino acid now, that amino acid has been hooked in here and that amino acid will be hooked here, the moment that happens, you call them as bile salt, what do you call them as? Again, what do you call it as? Bile salt. Now here is the beauty, the beauty is because of the amino acid, can you see NH here, hello, NH here, so nitrogen is introduced here and because there is a charge, so you have a molecule in which one end there is a charge, at another end there is no charge. That is the beauty of biology, hello, charge at one end and no charge at another end. So that no charge at another end can have free conversation with the fat molecule and the other one can have free conversation with the water molecule, are you getting the story now? So what am I talking about, I will just use a word common bile salt, what will I use the word? Bile salt, by that I mean what? This compound and this compound, you know how these compounds have come into being, they are all derived from cholesterol, done so far? Now yeah, it is amino acid, it is not among the 20 amino acids, no, no, no, it is not among, you are right, it is not among the 20 - like GABA, it is not, when we talk of amino acids, 20 are the basic blocks for protein, they are beyond that. Now here is a clear story, the author shows that the molecule being divided into two components. For our understanding, that yellow part is the earlier part derived from cholesterol and there is no charge on this and this is that glycine has been added here and this red one is what? So the red one is called as what? Because there is charge, it is what? And this is what? Now if you remember this story, we are again talking about, this water at the bottom, oil at the top, you have added detergent - as a result of that, you have finally what? An emulsion, what emulsion is there? Emulsion of oil into water. Emulsion of oil into water, very good. And that is because the detergents give certain charge on those oil droplets and then it can form the emulsion and as a result of that we are capable of having this organisation in which we have the lipid molecule, not lipid molecule, tiny droplets of lipid, not a single molecule, tiny droplets of lipids and they are being surrounded by the bile salts.

So each one - outside there is a bile salt and it is organised like this because this is the hydrophobic side which comes in contact with the lipid part and this is what part? I am sorry hydrophilic is on this side, hydrophobic is on the side of the lipid and then it forms a cover. Although it is oil, it can move freely, it is very small, what will you call once this happens in the what you call it as? Emulsified. It is emulsified fat. And each such fat droplet is called

as a micelle, M-I-C-E-L-L-E, it is tiny, I want somebody to read the line in the blue font please can somebody help me out? Very tiny, very tiny, you cannot even see it with an eye. Now, now, now duodenum is also secreting lipases, so there is a micelle there, can you see that? This one and these are the bile salts and here is a lipase, lipase entering into the micelle, so the lipase will be released, it will act on this fat, what is this fat? Triglyceride and then this triglyceride will be broken down into what? Broken down into monoglyceride and fatty acids, I forgot fatty acids, monoglycerides, cholesterol - it will now be broken down and then you will get the this that can be absorbed across. Actually, it is the agitation at the level of this, as a result of, we know peristalsis, okay, at the level of intestine. The aim of the peristalsis is not only to move the bolus of food along but also to bring about the agitation.

And how it does is, this I put a tube, okay and then I press it, release it, press it, release it, press it, release it alternately. Not that I am moving the food forward, no, I will do it after 5 minutes, are you getting my argument. Hello, press it, so the food goes here, press it, so it may go back actually, okay. What I am really doing is facilitating the free movement of the enzyme we saw earlier - one or all the enzymes, okay. Particularly, so that they have got one is break down of the big chunk of lipid into tiny, tiny micelles which are so small. How small we have seen in the previous one, okay and then in the process bile salts are there. So the bile salts will form - we are actually digesting and it takes about 6 hours, 7 hours, 8 hours. It is a slow process, okay and during that time the fats are being digested. So here we have a part of the intestine, these are the large circles are what, fat droplets in what form are they, triglycerides are there from the bile duct, okay, you are having what you call as the bile salts, the bile salts combine, the lipase is introduced there and then you get the micelles which will play an important role, okay. Listen to this, liver has spent lot of its energy in synthesis of bile salts, okay. The nature is economical, okay, so what trick the nature is playing here is once a bile salt is released in the duodenum, by way of bile, and then it has played its function in the intestine, what function, emulsify the fats, okay. Then the nature has said can I recover some of those bile salts, get the problem. If I can recover those bile salts I do not have to go through the trouble of making the bile salts once again. Are you getting the argument. Therefore the nature has come up with an very interesting phenomenon which is written at the top. Please read for me, enterohepatic circulation of bile salts, so let us see what is the story. So this is the part of the intestine, the fats have come, the bile salts have come via the bile duct and here somewhere in the intestine. What all we have seen in the earlier slides has happened and the micelles have been formed and they are ready to be absorbed. After that function is done, there in the wall of the intestine, in the latter part of the intestine we have a pump, what pump it is, secondary active sodium symport system. Okay, so in those cells there will be ATPase somewhere on the basal side, on the apical side there will be a symport system. That symport system now specifically picks up the bile salts, okay, it puts them in the hepatic portal system and the hepatic portal system will carry the bile salts back to the liver and those bile salts will be reused. Are you with me, what is it called as entero-hepatic circulation. Look, I am going to tell you something very funny, I have been teaching this very clearly to the best of my ability for last, I do not know how many. I will not tell you how many years, then in the examination I ask a question, describe in brief the significance of the enterohepatic system and half of you will write about hepatic portal

system.

Hello, are you awake? It is so irritating for me, no, no, not that you are awake is irritating for me, no, I am good with that, okay, what is my problem? I say I shout hoarse my word trying to explain to you the difference between what and what, hepatic portal system and the enterohepatic circulation, they are two different things. They are two different things but when I ask a question this, this, this, generally hepatic portal system is fine but enterohepatic means people will write, half of you even now I challenge you, half of you I will tell you, I will ask a question, maybe I do, I do not, the you will, half of you will still write about hepatic portal system. Have I given you enough dressing down so that you do not make the mistake. Look, all your seniors have done it, all your seniors, okay, good, good, so I think I will now, I will not teach you the rest of the things where I talk about the absorption of glucose, very simple, we have done kidney - so you can do this here, absorption of fat, how the micelles and the fats are absorbed and how the amino acids are absorbed and with that I will come to the conclusion of our topic on digestive system and without, without wasting even 5 seconds I will move on to the next topic. Thank you.