**Human Physiology**
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**Lecture – 48**
**Secretory functions of alimentary tract and Pancreas - Part : 2**

Now we will focus on yet another very interesting function of the parietal cell. What was the second important function of parietal cell? Intrinsic factor. Author has given this diagram of the parietal cell and shows - this is hydrochloric acid and it gives rise to what? Intrinsic factor is a large molecule, it is a glycoprotein and before I go, this I am not going to teach you because I am inviting you to read this article, beautiful article only two pages, wonderful.

Go to the website and read, what is the title of the article? Why doesn't what? Digestive acids corrode the stomach line. Very interesting question, okay, I am not going to teach you in the class but I will put a question. Very clear, that is my only method, okay, to lead you into reading that article. So you have to read this article.

Now this intrinsic factor is another very interesting story in the digestion. So where do we go? We go to the synthesis of RBCs which is happening where? In the bone marrow, where is it happening? In the sternum and the long bones of your body, the bone marrow RBC, RBC, RBC, particularly when the DNA gives rise to protein and synthesis, you need two vitamins. If the two vitamins are not there, your bone marrow cannot make healthy RBCs, very clear. Now what are the two vitamins? One of them is a folic acid which is called as what? also called as what? And the B12 which is also called as what? Why is cobalamin called as that? Because at the centre you can see the cobalt there. And interestingly you will find that this cobalt is also held in position by nitrogen, nitrogen as in the case of Hemoglobin.

So this vitamin B12 is very important, we get in the egg, we get it in the milk, we get it in the fish, meat, everywhere it is very common. Both are essential for synthesis of DNA, particularly for the formation of what? Thymidine, triphosphate, whatever. When you eat these vitamins as a part of regular food, the chances are that they will be destroyed. At that pH they will be destroyed. So the nature has to come up with a solution.

Are you with me? And here is the solution. What is the solution? Intrinsic factor is the solution. So what it does is when you eat the, what does this represent? It represents say vitamin B12, this, this in the stomach. So you have taken it as around the stomach. It would normally be destroyed.

It does not get destroyed because the parietal cell releases intrinsic factor and the intrinsic factor combines that molecule, combines with vitamin B12 and as long as the two molecules are bound to one another it is protected. It cannot be acted upon by the digestive enzymes. So what goes beyond in the duodenum is the combination of intrinsic factor plus vitamin B12 and then goes into the duodenum and then it goes beyond duodenum into the early part of the intestine and there, there the wall of the intestine, pinocytotically, take in the whole thing. It is a large molecule.

It cannot just diffuse. So the nature has come up with pinocytotic mechanism. Pinocytotically, take in the entire combination of intrinsic factor and vitamin B12. Take it to the liver, process it, separate them and use. Store vitamin B12 and use it as and when necessary. Did you get the message now? So what have we done really? What have we done? We are trying to understand the profound importance of intrinsic factor and its role in the absorption of the vitamin B12.

What happens when you do not have or when you do not take vitamin B12? Then you suffer from a condition which is called as, which is called as A. Read for me here. Megaloblastic anemia. Anemia because of course you do not have enough hemoglobin.

But when you take a blood sample of a patient who has inadequate amount of B12 and therefore not able to synthesize enough hemoglobin or the molecule is defective, you know the pathologist can easily make it out because the RBCs which are so big - they become so big. So can you see the two normal, on the left is the control and on the right is what? An RBC of a patient. What patient? Megaloblastic anemia. And also even the WBCs. They are large but they are very inefficient.

And therefore the person suffers from and this disease - it is also an autoimmune disease. What do I mean by that? The person has antibodies against his or her own intrinsic factor and then the person suffers from autoimmune disease. So what would be the treatment for this kind of scenario? You can take a tablet of vitamin B12 but you can inject it. Hello? This solution is very simple. Just take a shot.

It directly goes. So the treatment relatively is very simple these days. You can just take a shot of vitamin B12 and then you are quite good about it. Okay, okay. I will take you next step ahead and we are looking at, okay, now we are done with parietal cells.

Any issues with the parietal cells? Anybody? Hello? Are you okay? So now let us talk about the enzymes being secreted in the stomach and of course the number one candidate here is the pepsinogen which is the source for the enzyme. Where do they come from? They come from chief cells. Where do they come from? Chief cells. Where are the chief cells? Chief cells are deep, deep into the gastric pit.

You have what you call as the chief cells and here somewhere if you take a transverse section here, you have a lumen there of the gastric that canal like which goes and - you take a section and can you see here that is the canal through which the fluids will flow. And on the periphery the author has shown a parietal cell and a chief cell. They are there and little ahead you will also get mucous cells. So here we have, so what author has done is he has taken one chief cell from here and blow it up from there. We are looking at a single chief cell and in the chief cell we have those huge, huge vesicles and they are of course containing enzymes, digestive enzymes but all these digestive enzymes are at the moment inactive. They have to be activated little later.

And these vesicles are called as zymogen granules. What do you call them as? Zymogen granules. Here they are called as zymogen granules. Even in the pancreas, the pancreas will secrete different set of enzymes. We will still call them as zymogen granules.

So these are the zymogen granules and when the cell is excited it will release the zymogen granules and then from this zymogen the enzymes will come up. And it is actually not enzyme, it is a precursor of an enzyme. So what comes out is the molecule called as pepsinogen. What is the molecule? Pepsinogen. It is the molecule called.

Under the influence of acid, now it comes in contact with acid. Once it comes in contact with acid, pepsinogen starts getting converted, some of it gets converted to pepsin. Step number 1. What is did I say pepsinogen under the influence of acid gets converted into pepsin. The bigger molecule is about 42000 molecular weight.

It becomes smaller. Pepsin itself is about 35000 something molecular weight. So you have that pepsin. Now pepsin that is generated it starts and now you get the beauty. The pepsin that has been generated starts acting on the other pepsinogen molecules and convert them into pepsin.

Beauty of the nature. Are you getting it? To begin with you give a little acid and you start the process. So you have pepsin. That pepsin will act on other pepsinogen and give more pepsin, more pepsin, more pepsin. And then the pepsin will act on the and of course the pepsin needs strong very low pH, strong acidity because that is the pH where the pepsin acts.

So pepsin is an enzyme. Pepsin is what is one of the three principle protein degrading enzyme. Pepsin is of course in the stomach and in the duodenum we will have chymotrypsin and trypsin. I will talk about it a little later. Regulation of pepsinogen – depends on stimulation of the chielf cells by acetylcholine released by the vagus.

Again same. You remember at the very beginning we made a statement that different secretions appear along the length of the alimentary canal. Most of the secretions are stimulated by the parasympathetic nervous system which is by way of acetylcholine. Are you getting it? Everywhere. So, the parietal cell were also stimulated, the gastrin cell also stimulated, this chief cell is also stimulated by the same mechanism.

Yes. The conversion of pepsinogen to pepsin is it also assisted by an enzyme or was it completely dependent on acid? The answer to that question is acid can convert but at very low efficiency. So when pepsin comes and act and some of it has effect, but when even little pepsin is there, pepsin is efficiency 100-200, I do not know many fold, may be 1000 fold I do not exactly know. Okay. Now so fill in the blank. Tell me the name of hormone that is being secreted by the stomach.

Gastrin. Gastrin. It should come as an instant response. What is the answer? Gastrin. Gastrin. Okay. There is another shock, there is another hormone.

Okay. And the another hormone is called as ghrelin. G-H-R-E-L-I-N. It is again a peptide hormone, 28 amino acids. Ghrelin comes from where? Ghrelin secreting cells. Where are the ghrelin secreting cells? They are in the stomach.

So can you see the first image and the image on the left hand? Can you see those gastric pits little carefully? But can you see those black dots there? How did I get those black dots there and what do they represent? They are what? They are ghrelin secreting cells. How do I label them by using antibodies against ghrelin? So there is a stomach of rat. On the sections I put antibodies against ghrelin and I get that color so I can identify the ghrelin secreting cells. Are you okay so far? Now this ghrelin is amazing. It is a Hunger hormone.

It is a hunger hormone. Nice to remember. So every time you have not had food for some time and as a result of that the stomach is almost empty and as a result mechanically the stomach becomes small, okay, small, ghrelin cells are activated. What is activated? Ghrelin cells are activated. What do they do? They secrete ghrelin. Okay, it is a peptide hormone, 28 amino acids.

Where does the hormone go? Into the blood. It travels through the blood - it goes to the brain and it tells the brain. Tells the brain what? That I am hungry. Okay. So, so how does, there are different mechanisms, there are different ways but this is one of the very important way of telling the brain, okay, and then in the brain generates the feeling of hunger.

Okay. So then you trigger the behavior for search for the food and consume the food. Okay. So for initiating that behavior one of the earliest cues is ghrelin. Okay. And so I think that message is very clear here.

Can you see the empty stomach versus the full stomach? The when the stomach is empty can you see the ghrelin is being released. And then you have had your food, lunch and then the wall of the stomach are stretched. Okay. It is a mechanical signal. We can ask another question. Do ghrelin secreting cells have mechanoreceptors?

And under the influence of that mechanical stimulation do they stop secreting ghrelin? Because here stomach becomes large, what is the, what is the, what is happening to the hunger goes down, what is happening to the appetite? It goes down. So an amazing phenomenon. Is it crossing the blood-brain-barrier? Which one? That is a very interesting question.

It is a peptide hormone. It is relatively large hormone. Listen to this. It is a very fundamental question and I am giving you, I am giving you a complete answer. I will ask you a counter question. Does insulin, so you have food, as a result of that beta cell secrete lot of insulin, does that insulin go to the brain? I do not expect an answer. Okay. Because you do not know the answer, I will give it to you now.

Okay. These are very relevant questions he has asked me. Very relevant question. What is it? Does it cross the blood-brain-barrier? Look, every time somebody makes a statement that something is going to the brain and acting on it, you should first stand up and ask does it cross the blood-brain-barrier? Period. That is it. Unless you get an answer to that question, do not go ahead. Does it cross the blood-plane barrier? Very pertinent question, very correct answer.

Does it cross the blood-plane barrier? Okay. So have I hammered on you the importance of that question? Good. Now let us see the answer. Whereas the capillaries in the brain have a barrier, there is a twist in the tail. It is there in the 99% of the capillaries of the brain. What about the 1% capillaries in the brain? They are devoid of blood-brain barrier.

And one of the places where they are devoid, they are called as circumventricular organs. And one of the very interesting circumventricular organ is present in the median eminence. I am going to, this word I am going to pronounce 10 times.

Median eminence. I am not going to pronounce it 10 times now. But I will pronounce the word when I talk about the control of the pituitary gland. Just above the pituitary gland at the base of the hypothalamus, there is a neural structure called as? Median eminence. Median eminence. Median eminence has capillaries where there is what? No blood-plane barrier. And it is through this blood-plane barrier that these hormones like insulin, leptin and ghrelin get in from the blood and directly have access to the neurons. So the brain on one hand it has taken steps to protect itself by inserting a blood-brain barrier where it is necessary it says okay, okay I don't care, I don't need there.

But that is only in few places. And one very important place I told you just now, what is it? Median eminence. Median eminence. Have I answered your question, gentlemen? Okay, remember that is very good you asked. Median eminence.

You know how it happened? You should have not asked that question. Then I will stop this and talk only about that. You know how blood-plane barrier was discovered, the story goes to about 1934 when they injected a dye like methyl blue or methyl green - injected the rat - and they took out the brain and they took out all the organs. The muscle were stained, liver stained, pancreas stained, stained, stained, stained, stained, stained. But brain was white. Brain was white. So, my dye which I inject intravenously - it goes everywhere why doesn't it go to the brain? There must be something - blood-brain barrier was discovered.

But when you look at the brain carefully you find that median eminence is stained. Therefore they knew that blood-brain barrier is everywhere - but 99 percent. Places like median eminence and there are couple of more places, organum vasculosum lamina terminalis (OVLT).

You remember something? No, no, I think I should tell it to you. You remember we talked about the osmoreceptors? Osmoreceptors in strict sense - the cells of the OVLT are osmoreceptors, are what? Enough of neurobiology. So, here we are measuring the, you keep on drawing the blood, a human, ok and keep on monitoring over a period of entire day and you find that, the profile of ghrelin and what is this point - breakfast? Ok, so at this point, so he is hungry, hungry, has breakfast, goes down, are you with me? Hungry, hungry, hungry, has lunch, so there is a very clear correlation between what and what? Hunger, hunger, take in food, hunger, hunger, hunger, ghrelin, ok and you have food and the ghrelin level goes down. Ok, we will move on now and talking about what? Talking about pancreas. Ok, so here is the beautiful organ, these are like the salivary gland, there are acini, there is single layer of cells and there is a duct there. This is the entire organ and the contents are poured into the duct, duct, duct, hundreds of them, they all pool together, so this is a single acinus and these are the cells and this is a rich with endoplasmic reticulum which means that it is a protein synthesizing cell and then it also has and this histological section - you can see the acini and I put this section because these are all the acini and that you can clearly see what? Islet of Langerhans. So these are the cells which are pancreatic cells, they are the exocrine cells, exocrine cells, endocrine cells and exocrine cells are responsible for, so these are again you can see the, can you again see the zymogen granules there? Ok, what do they contain? They will contain the enzymes.

Ok and what are the enzymes they contain? They contain, ok, let me give a correction.We call them as proenzymes, makes sense ok because they are inactive. Ok, you know what? There is a disease in which that duct you know that we saw in the previous one, that duct gets clogged and then this enzyme, I am sorry, this inactive enzyme is not able to flow and then if we obstruct it then for some reason we still don't know, the enzyme gets activated and if the enzyme gets activated the enzymes eat up the pancreas, very dangerous situation. Are you with me? The enzymes, so and it is called as acute pancreatitis, acute pancreatitis, are you getting the meaning? Ok and it is absolutely fatal, it is very difficult if the pancreatic enzymes are activated, ok, when they are still, they are still in the pancreas. Well you can imagine they are extremely powerful, powerful enzymes. So this is the electron photomicrograph, you can see this zymogen glands, that is a diagrammatic and they are huge containing, they are containing the enzymes like chymotrypsin and trypsin. The trypsinogen means what? Proenzyme, trypsinogen, you can also call the chymotrypsinogen and what? Carboxypolypeptidase, whatever, these are all, the proenzymes will be released when the pancreas are, when the pancreas is stimulated, how it is stimulated I will tell you very shortly.

So lot of proteins are already digested, ok, and they are broken into smaller molecules, ok, they are further acted upon by the chymotrypsin and trypsin, ok. So you have dipeptides and tripeptides - means what? Tiny tiny fragments, see proteins are huge molecules, ok, they are broken down, broken down, our ultimate aim is to bring it to single amino acid, ok. So that it can be absorbed, ok. So can somebody read for me what is written in the blue font, read loudly. Trypsin and chymotrypsin split whole and partially digested proteins into peptides of various sizes but do not cause the release of individual amino acids. However, carboxypolypeptidase does split some peptides into individual amino acids. Please remember, this is over simplification, there could be, there could be different trypsins with little difference in amino acid here and there, ok. The release of each could depend on the type of food you are eating, ok. We are generally lumping them into one but the life is not so simple, ok. Now this is interesting, just follow the story. we are looking at the wall of the duodenum and the intestine, innermost wall, the mucosa, ok. Sitting on the mucosa there is an interesting enzyme, can you please read for me the name of that enzyme? Enterokinase, what do you call it as? Enterokinase.

Say that again. Enterokinase. So, just sitting there on the top, just, just look at the top, the enterokinase is sitting there. Now what does enterokinase do - means what? Trypsinogen, ok, trypsinogen can be converted into trypsin, how that happens? Let us see. The trypsinogen is coming, where is this coming from? It is coming from pancreatic cells, where into the lumen of the duodenum, ok, so far, this trypsinogen is acted, is being acted upon by what? Enterokinase. Enterokinase, what is the net product? Trypsin. Once trypsin is there, it acts on further trypsinogen to give rise to trypsin, something like, something like pepsin, you know, the pepsinogen was converted first initially by the effect of the acid into pepsin, a very similar phenomenon is happening here also.

So, trypsinogen - to initiate the first push – it is given by enterokinase. So, once the enterokinase acts upon trypsinogen, you get trypsin. Once the trypsin is available, the guy takes over the entire job and then trypsin converts chymotrypsinogen into chymotrypsin active enzyme and trypsinogen into trypsin, ok -and now these enzymes are available there. But this enterokinase has a very interesting role to perform. Did you observe the point, everybody? Great. So, we will talk about - this is what I was talking about pancreatitis.

Here is actually an example of that. I said the pancreatic, ok, ok, ok, let us see. So here is a common duct. This is a part of the duodenum, here is a common duct. What is the duct bringing? It is bringing bile and pancreatic juice.

So, when the duct releases its content into the duodenum – note that bile has a habit of forming stones, ok. You may be surprised to know that even several of us might have stones in our gallbladder. Normally they do not bother, ok, so we do not worry about it. They could be there, they could be there. Supposing they start getting bigger and then they flow along and that is where they go and sit, at the mouth of the tube.

Papilla of Vater - it is called as, but do not bother about the name. That is where they sit. And if they sit there, then the pancreatic juice cannot go into the stomach. So pancreatic juice accumulates. You have taken food, the food has gone from the stomach into the duodenum, the signal has gone to the pancreas that you keep on pumping, secreting lot of pancreatic juice, but pancreatic juice cannot find its way into duodenum, it gets stuck there.

Once it is stuck there, we do not know why all the enzymes could get activated. How we still do not know? And as a result of that you could have this entire organ being eaten up and the condition is called as what? Pancreatitis. Very dangerous situation.  I think I will stop now.  Thank you.