Human Physiology
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Lecture – 47
Secretory functions of alimentary tract and Pancreas – Part 1

We are still trying to understand the physiology of stomach, okay, stomach, stomach, hello, physiology of stomach, okay. In the previous class, we focused on a very interesting aspect - that was parietal cell, you know parietal cell. Parietal cell, what is the, yeah, it is cell secretes hydrochloric acid and then we have - so we will carry on now. So let us look at this diagram, we saw it also last time.

You can see the oesophagus is coming that way, okay and then you have the fundus part and the lower part that is towards the duodenum will be the antrum part, okay. So far, good, good. And in the fundus part we have those, the author is showing us two cells, okay both are the parietal cells and both are, both of them are capable of secreting what and what? HCl and intrinsic factor, so thousands of cells - so the same cell can secrete the two substances we will talk about each. And then there are deep gastric pit, deep into the gastric pit we have chief cells, okay which are secreting the most important protein digesting enzyme - that is pepsin that is also in the stomach. And then the author draws our attention to very interesting group of cells which are in the antrum part. Now I am talking about it, okay and we call them as G cells, what do you call them as? G cells.

We call them as G cells because they secrete a peptide hormone - 28 amino acids, how many amino acids? 28. What is the name? Gastrin. Gastrin, G-A-S-T-R-I-N. Name indicates that it is coming from stomach, okay - and at the end indicates that it is a protein, okay, okay. So G cells secrete a peptide hormone which is called as what? Gastrin. Gastrin, okay and it gets very interesting, so stomach is an endocrine gland. We made this point in the previous class and let us see now what gastrin essentially does, amazing.

This is just to tell you it is a peptide, okay and has a certain sequence of amino acids. Now this is a very interesting diagram and I want you to focus and understand, you have to understand this, you cannot run away from this, beautiful diagram, beautiful diagram. We are looking at the stomach, very clear, very clear we are looking at the stomach. In the stomach as we have said or as we have observed in the previous one, if we focus on the fundus part and there are cells we have already seen that those cells are parietal cells and they are secreting acid intrinsic factor. We are looking at the same thing, so this is the cell here - the black dot represents the cell, what cell it is? What cell? Parietal cell, what cell? Be in the class, what cell? Parietal cell, very good. This is the parietal cell and for our convenience author has taken this square here and blows it up here. And here

is our parietal cell and the parietal cell is secreting HCl. Good. Now this parietal cell, on its basal side, author has clearly shown three different types of receptors, how many types you have to remember each? Three different types of receptors and stimulated by any one of these receptors the cell gets highly excited and they start pumping hydrochloric acid.

So tell me, so how many factors are there that will control the release of hydrochloric acid by the parietal cell? Three, okay and the three agents are number one, very simple one is acetylcholine, one is what? Acetylcholine. So where is this acetylcholine coming from? Very simple, this acetylcholine could be coming from the vagus - which means parasympathetic nervous system, okay, preganglionic, postganglionic. It could either directly go or it could go on the neurons of the, remember, entering nervous system, okay but then whatever it is, it is still acetylcholine and the cell is getting acetylcholine the molecule is acting via a receptor, what kind of receptor would you find? What kind of acetylcholine receptor will you find on the basal side of the parietal cell, basal side? M3, what type? So muscarinic 3 kind receptor is also 7, it is 7 transmembrane, okay - G protein coupled system and when excited it will excite the cell to generate hydrochloric acid secretion. The second stimulation is H2, what does H represent here? Histamine, histamine comes from a different type of cell which is sitting in the vicinity very close. Sitting right in the neighbourhood is another cell, what do we call it as? H cell is the source for what? Histamine say that loudly, we have seen the structure of histamine in the previous one, okay. Do we call histamine as a hormone? No, no, we do not call it as a hormone, okay, some people also call it as a local hormone, okay or an autocoid. Means what? Means what? Histamine will be released, not in the blood, in the vicinity and once it is in the vicinity it will travel around and it can travel generally, generally it can travel half mm or 1 mm. What happens after that - there are enough enzymes in the extra-cellular space which will chew it up. So histamine released will act in the neighbourhood, so within the circle, okay, within a sphere of about 1 mm on all the sites - all the parietal cells there, they would have receptors for histamine and they would be stimulated - what kind of histamine receptor? Histamine receptors also two kinds, H2 type, which again is 7 transmembrane G protein coupled system. What am I talking about? Histamine as a signalling molecule, coming from what kind of cells here? Enterochromaffin. Say that loudly, enterochromaffin cell - which is also sitting in the neighbourhood in the stomach, okay. Then there is third kind of receptor which is called as CCKB or CCK2 - whatever. Now CCK stands for cholecystokinin, say that again, again cholecystokinin, this funny name comes from the - this is interesting – cholecystokinin. Cholecystokinin itself is a peptide hormone, what is it? It is a peptide hormone, okay, now the moment you say it is a peptide hormone, you should ask yourself what is the source. It is abundant in the cells in the duodenum - are we talking of duodenum, we are not there yet, we are still in the stomach, okay, I am giving a broader picture. So if you just fill in the blanks, cholecystokinin comes from where? It comes from certain cells in the duodenum, what is it? It is a peptide hormone, what does it do? Basic function, its function is to get released in the duodenum, it is a hormone, get into

the blood, travel with the blood as far as the liver and as far as the gallbladder, okay, gallbladder contains lot of substances, no enzymes but one of the very important system is cholesterol, chole- and -cyst is a bladder - so cholecystokinin, okay. So what is cholecystokinin? It is a hormone, where will it go and act? It will go and act on the smooth muscles of the gallbladder which will have receptors for cholecystokinin and under that influence it will do what? The gallbladder will do what? Contract and it will expel what? Bile, okay. Where will the bile go? Bile will go into the duodenum and it will do its function, what function? I will tell you eventually, okay, have you observed this point? Now here the story gets a little bizarre, we got cholecystokinin, cholecystokinin, we got its receptor - earlier, earlier in the history of science, we got it, so we knew earlier 1960s, 70s we got cholecystokinin. We got its function, got the receptor, okay, we call it cholecystokinin receptor, okay, so far, are you okay so far? Now we find that gastrin which comes from the endocrine cells in the antrum part which we have seen in the previous slide, can act on the same receptor, can act on the same receptor, therefore instead of calling it as a gastrin receptor, what do we call it as? CCK receptor. We did not change the name, so whenever you look at this image you may be slightly confused as to, confused with what? Well, I will tell you, now keep the confusion in your brain, I will sort it out within 2 minutes. Just as we have seen this cell here, I will draw your attention to yet another cell with which I spoke to shortly and this cell is nothing but a gastrin cell, we have already seen gastrin is a peptide, okay, it is in the antrum part and it is a hormone. So it gets into the blood, so here you will understand the meaning of this gastrin cell is being released by this cell, okay, and where does the gastrin go - through the blood it goes to parietal cells. This is the parietal cell and on the parietal cell there is a receptor - that is also 7 transmembrane G-protein coupled receptor. Somewhere outside it can bind with gastrin - it can bind with what? gastrin, it can also bind with cholecystokinin, it can also bind with cholecystokinin, okay. That is why the name, that is why the name, but here it is combining with cholecystokinin. Life is never simple, two types of receptors, cholecystokinin A, cholecystokinin B, some people, some people, books also called as cholecystokinin 1, cholecystokinin 2, but cholecystokinin 2 is same as B, A is same as 1, simple, okay. Hello, done, great, okay.

So now what author has done for convenience is - you pull out a cell from here and blow it up here, good so far. And then author tells us that this is a G cell and what does it secrete? Gastrin and it comes into the blood and goes, goes, goes, goes and acts on it receptor, CCKB receptor, what receptor? CCKB. And whenever it gets information from CCKB receptor, so parietal cell, parietal cell is stimulated - with acetylcholine, okay, go ahead, stimulated with M3 acetylcholine receptor, yes, go ahead, I am sorry, I am sorry, see this is what and what, histamine, I am sorry, acetylcholine via M3, histamine via H2 and then via CCKB. These are all the three stimulants, okay. Now let us go to this original diagram and try to understand. You take in food, you are starving, okay, none of this is stimulated, you do not need to, you do not need to, you have food, once you have the food, the food has arrived and the arrived food here can directly stimulate. Let us see, it can directly stimulate the parietal cell, some of it can go down, it

can stimulate the gastrin cell, okay and then the gastrin cell will further, okay, okay.

Never forget homeostasis, okay. You have stimulated parietal cells and the parietal cells are - they have become active and generate H+ ions, H+ ions, H+ ions, H+ ions and as a result of the pH falls, falls - you need to stop somewhere. Are you with me, you got to stop somewhere. So you need to decide that okay, okay. I want so much acid but not more than that. How do you achieve that, for that the author shows that once the pH is so much - the parietal cells which are releasing hydrochloric acid, once the pH goes lesser than 3, then they start inhibiting the gastrin cells, are you with me. So whatever is the protein content in your diet, listen to this, whereas the protein content in your diet will stimulate the gastrin cells to release gastrin which will go up into the fundal part and stimulate the parietal cells to release hydrochloric acid, more, more, more, more and then stop, stop, stop, stop, that stop comes. Stop comes from the acid itself, so in this area, so you can ask a question. I do not know the answer to that question. Do the gastrin cells okay, have sensors for pH, okay. And once the pH goes to a particular limit do the gastrin cells get inhibited, so that it no more is sent. The signal to the parietal cell, got the point, I am not saying, I am telling you that it is, I am just, I am just asking you to think about it, good, good, good, good. Now let us see, so what are the 3 stimulants again, acetylcholine, histamine and CCK okay good, good, good. Now there is a fourth character okay and the fourth character is called as somatostatin. What do you call it as? Somatostatin, say that again, somatostatin, say that again, somatostatin. Now somatostatin is an excellent example, excellent example of the same peptide doing absolutely different things in different areas, hello. One signalling molecule, what is it, somatostatin, what is it, somatostatin okay. But let us see what it does. First of all the cells which secret somatostatin okay. I will take the story from a different point of view. Let us go to pancreas. In the pancreas we have islets of Langerhans. In the islets of Langerhans there are beta cells, they are source for what, you have done it, Nixon has dealt with it. Then there are alpha cells, okay, okay. Then there are delta cells, what are they, there are delta cells. Delta cells are also called as D cells and they are source for a hormone, somatostatin. What do you call it as? Somatostatin. So somehow that terminology which we started at the level of pancreas - where we have alpha, beta and delta, delta - is same as D. That terminology we have taken here and these somatostatin secreting cells therefore we call as what, got the answer. Why D cells? Because they secrete somatostatin. We also get an interesting lesson here that somatostatin is a peptide, it is coming from the islets of Langerhans, it has one particular set of function, here somatostatin has, here somatostatin has, has what, okay, - here is a D cell here, in which part? Fundus or antrum? Fundus, in fundus, you are getting D cells. This D cell when stimulated, okay, stimulated, how is it being stimulated, again via the vagus, okay. Can you see the vagus nerve there, preganglionic, postganglionic, the postganglionic nerves will secrete again acetylcholine, yeah, okay, it is secreted along with yet another peptide, okay, which is called as calcitonin gene related peptide called CGRP. Biology can be fun, so what am I doing, I am bombarding with lot of peptides, okay. So I am telling you one more peptide, you got it, I mean you came here, okay, so what is the new

peptide I am talking about now, calcitonin gene related peptide, everybody, again, that peptide is being co-secreted by that neuron along with acetylcholine that CGRP. It talks to the D cells, okay, and then D cells release somatostatin which - look at the red colour of the arrow - which means what – inhibitory. If it is an inhibited cell - then this axis is stopped and the stimulation of the pancreatic, I made a mistake of the parietal cell is retarded, okay. So when you want the parietal cell to secrete, secrete, secrete, you have so many avenues when you want to stop it, okay, then via the D cells, okay. You have an inhibitory path by which you can control. Okay, I can see, the pH goes less than 3, okay, it stimulates the D cells, okay, the D cells secrete somatostatin, somatostatin, okay, it is called as SIH, somatotrophin inhibitory factor. one word, but it is same, it is what, somatostatin and somatostatin receptor also there on the G cells. But look at the red arrow, so somatostatin is doing two functions, two functions, here it is inhibiting the G cells and here it is inhibiting the H+ cells, okay. And both ways, it is ultimately inhibiting the secretion of the parietal cells and inhibiting the release of hydrochloric acid. Are we okay so far? I would urge you to go home and spend, just keep on looking at this diagram, just keep on looking and do it today, today when this talk is still fresh in your mind, spend half an hour. If you ask me what is the beauty of physiology, it is here, amazing. You see the review from which I got this – the author says this is the highly simplified version, okay, I said okay, I am happy with it, I do not want anymore, so this is what, okay, alright, let us move on.

Okay so this is the summary of what we have done, we are looking at the acid secreting parietal cell, the author has made our life simple, gastrin, histamine, acetylcholine stimulate, stimulate, stimulate, somatostatin inhibit and here is a list of the factors which will stimulate, which will bring about the stimulation of the parietal cell and bring about the, okay. I spoke to you about this point in one of the previous lectures and what was that? In the earlier days in 90s, 90s, so 1990s to almost 2000, what was the tool available for the treatment of gastric acidity? Cimetidine, what was it? Cimetidine, it is there in bracket, okay and how did it work? It was a histamine H2 receptor blocker. So histamine would not come, okay. However, we had a wonderful magical drug almost, amazing drug, in last, which has come up in last 20 years or so. It is freely available in pharmacy, it is one of the most widely used drugs. That drug falls into what you call as PPI. What does PPI stand for? Proton, say that again, proton pump inhibitors, okay. Here in the earlier one - histamine and then going to the parietal cell. Here the proton, proton, we are just inhibiting the release of the, release of the H ions, am I with me? Are you with me? So how that happens is a, these drugs are among the most widely sold drugs across the world, okay.

So one of the most commonly used drug available in the market is called omeprazole, what do you call it as? Omeprazole, what is it called as? Omeprazole and let us see now how the omeprazole works. I have got a very nice slide from this paper in nature - this is review on drug discovery, a beautiful slide, just appreciate the slide, look at the beauty of the diagram. Author has drawn in front of us, a single parietal cell. So far, on the basal

side the author is drawing the three receptors - we are very familiar. This gastrin, okay and that is what? That is acetylcholine and what is that? That is histamine and they can be inhibited by the histamine blocker there, can you see that blocker there? And this can be inhibited by an acetylcholine blocker, okay and here all the three of them can stimulate and then on the apical side the author has shown a single pump, there are millions of them, okay. Once the pump is activated - you have the release of acid, acid, acid, acid, we have done this. Now you take a tablet of omeprazole, now omeprazole molecule has no charge on it, okay because there is no charge, it is good, it goes everywhere, everywhere in the body.

Out of that whatever molecules happen to go into the parietal cell just by diffusion - it can easily cross the plasma membrane because there is relatively small molecule without any charge - it goes everywhere. Once it goes into the parietal cell because of the presence of H+ ions within the cell, the molecule omeprazole gets protonated. I will draw your attention to the omeprazole molecule that we have seen in the previous slide. That is the molecule and somewhere on this position, can you see there is a tiny N there, hello, that tiny, can you see that, it is NH plus, means at that site, it is protonated. Then it goes into what the chemistry people can tell you better - it goes through three steps and this molecule is converted into more or less this molecule, this all is happening in the parietal cell. I am not going to tell you about the chemistry of those because I myself do not understand, but if you go into the literature, each and every step is been fully described, are you with me so far? Now once you get this molecule in this cell, this molecule can combine, one molecule can combine with one proton pump molecule, so sodium, so I am not sorry, not sodium, hydrogen-potassium ATPase which is your pump for H+ ions, one molecule combined with one molecule and the molecule is ineffective - you have killed the molecule. So how many molecules of H-KATPase you can kill, as many molecules of you have provided, how many molecules of proton, I am sorry, how many molecules of omeprazole modified like this you have provided, one molecule, one molecule, one molecule killed, did you get the story here? Hello, it is a very powerful and it is irreversible. The active form will covalently and irreversibly bind to the gastric proton pump deactivating the pump, so you would not have any more hydrochloric acid, yeah, sure. So yesterday you said that these cells are protected by a mucous layer they have a pH of 7, but then won't the molecule be deprotonated? The answer to that question lies in the, that is a very interesting question and people have toiled with it for a very long time, the answer to that question is here, see here you will get a very thick layer where the pH is 7, the layer here is relatively very thin and what we talked just now, all that drama is happening here deep inside, okay and the omeprazole is getting through the blood, okay, oh no, omeprazole you eat, gets absorbed, gets into the blood, goes everywhere, it does not, no, no, no, it does not happen, no, no, it is good you ask, it does not happen that way, it has to be absorbed, going to the way, it will pass through liver everywhere, whatever it and then whatever happens to reach into the parietal cell, it will show its action.