GIS 4

PHYSIOLOGY

Done by: Obada Froukh & Nabil Sweis

Scientific Correction: Obada & Nabil

Gramatical Correction: Obada & Nabil

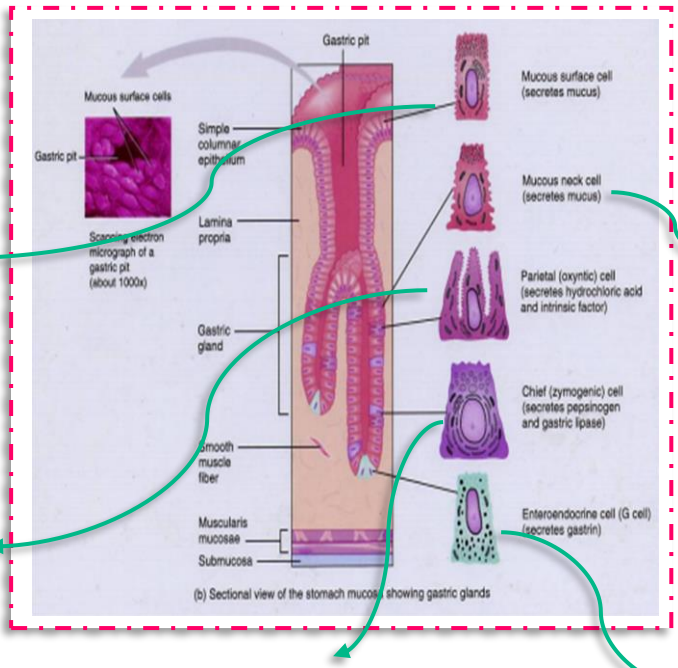
Doctor: Mohammad Khatatbeh

Please note that *underlined and italicized* statements are present in the handout but were not mentioned by the professor.

✓ In the previous lecture, we started talking about **"gastric secretions"** and the different cells participating in the secretory process in the stomach. We will briefly go over these again.

✓ In the stomach, secretion is carried out by cells in "gastric pits" or "gastric glands" (also known as "oxyntic glands"). Different parts of the gastric pit or gland are lined by different cells with different secretions. These are demonstrated briefly below:

Mucous Surface Cells:
-Located near the surface
-Secrete mucus.



Mucous Neck Cells:
-At the level of the gland.
-Secrete mucus

Oxyntic Cells (or Parietal Cells):
-Secrete:
- HCl
- Intrinsic factor (for vitamin B12 absorption)

Chief Cells (or "Zymogenic Cells" or "Peptic Cells"):
-Release the enzyme "pepsinogen" (the inactive form) which is later converted into pepsin (the active form) for protein digestion.

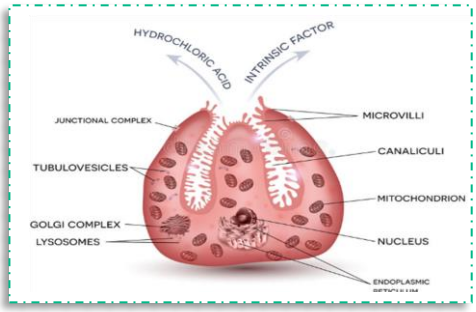
G cells:
-Secrete a hormone called "Gastrin".

✓ The professor also mentioned another type of cells: **D cells**, which secrete somatostatin.

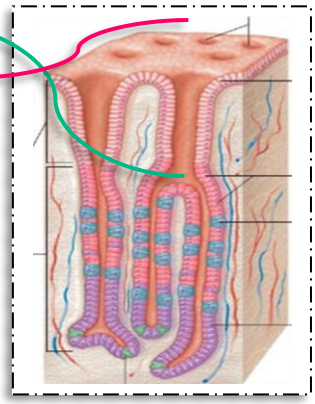
✓ We will now analyze each of the different secretions that take place in the stomach:

❖ Mechanism of HCl Secretion

✓ Oxyntic cells are responsible for HCl secretion. Notice that there are invaginations in the apical membrane of these cells towards the nucleus, forming "canaliculi" (singular: canaliculus).



✓ These canaliculi communicate with the lumen of the glands, which ultimately communicates with the lumen of the stomach.



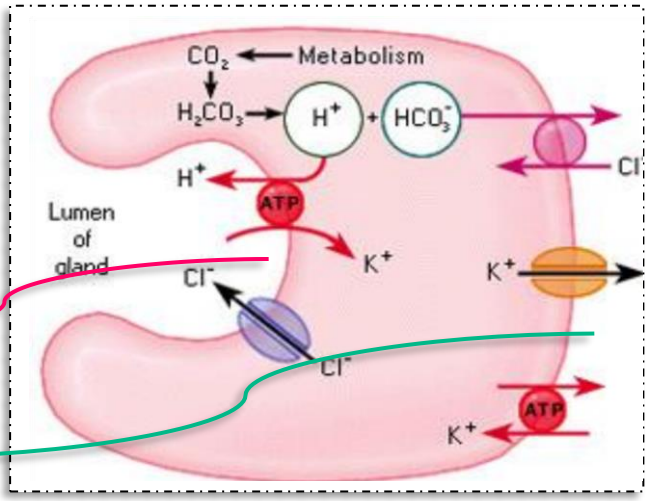
- Mechanism of HCL secretion:

✓ To secrete HCL, we need to secrete chloride (Cl-) and protons (H+).

Steps

1. Active transport of Chloride:

Chloride is actively transported into the cell (at the basolateral membrane), and then finally transported into the canaliculi, increasing Cl- concentration. This creates a negative transcellular potential (potential across the whole cell). The potential in the canaliculi becomes negative in comparison to the interstitial fluid at the basal/ basolateral side.



2. This negative potential attracts positively charged ions from the interstitial fluid into the canaliculi (across the cell) *through passive diffusion*.

One of the positive ions found in high concentrations in the interstitial fluid is: Na+. Therefore, this negative potential usually attracts sodium. Note that until now, we have not released protons.

3. Now in order to secrete protons, we need to produce them first, but how?

Carbon dioxide (CO_2) reacts with water (H_2O) to form carbonic acid (H_2CO_3), which dissociates into bicarbonate (HCO_3^-) and a proton (H+) (the previous reactions are catalyzed by carbonic anhydrase). There are pumps which subsequently take the protons and secrete them into the canaliculi. Overall, we have managed to secrete both Cl- and H+. ($H_2O + CO_2 \rightarrow H_2CO_3 <-> HCO_3- + H+$)

4. *Water is transported into the canaliculus by osmosis*.

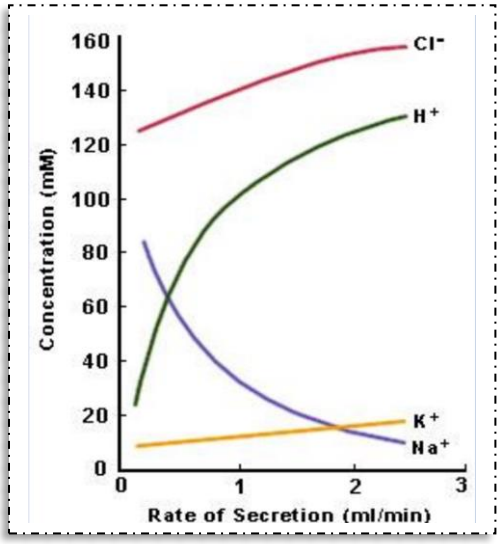
Note: Step 3 (formation and secretion of H+) is a STIMULATED PROCESS

Clarification: At rest or at low levels of stimulation (in between meals for instance), both proton production and secretion are greatly reduced, while steps 1 & 2 (transport of Cl- and Na+) still take place. Therefore, in the period between meals, the secretion (gastric juice) is mostly composed of Na+ and Cl-, or in other words, sodium chloride (NaCl) is being secreted instead of HCl.

(Notice that Cl- is constantly being secreted, even in the absence of stimulation)

✓ On the other hand, upon stimulation, production of protons increases as well as their subsequent secretion. In this case, we are mainly secreting HCl and less NaCl.

✓ Let's apply what we just discussed to graphs:



- In the adjacent graph, notice that at low rates of stimulation (i.e. low rates of secretion), the concentration of protons is low. Meanwhile, the concentration of Na+ is higher. (Secreting NaCl)
- Once stimulation takes place, more protons are produced, and we start secreting HCl. But notice that Na+ concentration decreases, why did this decrease take place?
- Recall that the driving force for Na+ across the cell and ultimately into the canaliculi was the negative transcellular potential. However, with the increased secretion of H+ due to stimulation, the newly secreted positive protons reduce this negative potential, thus weakening the attractive force that was responsible for Na+ transport to the canaliculi, so we notice a decrease in Na+ concentration upon stimulation.

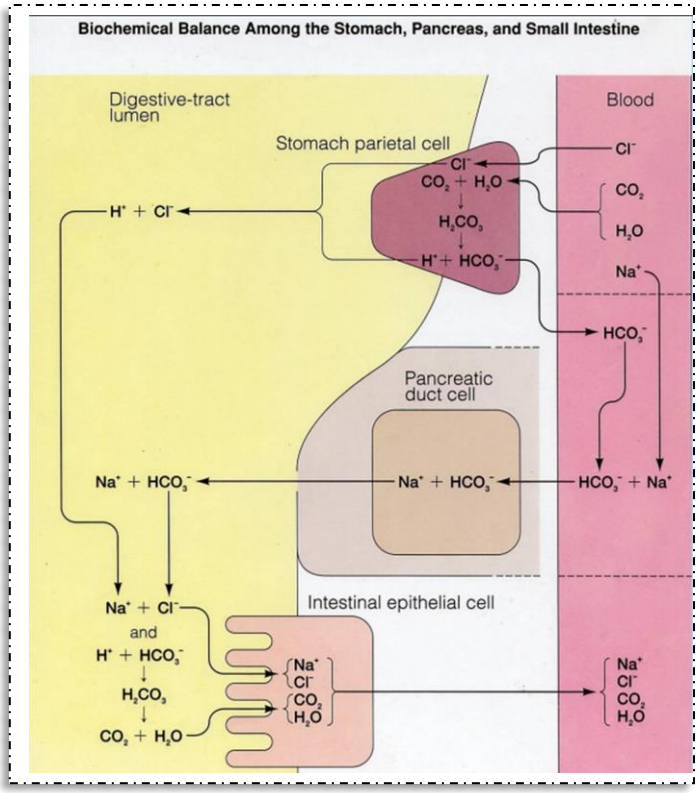
Notes

✓ The composition of the gastric juice varies according to the degree of stimulation. (No stimulation: NaCl … With stimulation: HCl). This actually serves to **protect us**, as it ensures that HCl concentration is not high in between meals (when it is not needed), as HCl can be harmful to the stomach. Once you start eating, HCl production is stimulated where it then assists in digestion of ingested food.

✓ What happens to the bicarbonate that is produced alongside the protons? HCO_3- is secreted into the interstitial fluid (absorbed back into the interstitial fluid).

✓ Side Note: Notice in the adjacent image that other cells (e.g. pancreatic duct cells) secrete bicarbonate into the lumen, unlike parietal cells which secrete bicarbonate into the interstitial fluid.

✓ Protons can be pumped into canaliculi by either proton pumps (H+ pumps only) or sometimes by H+/K+ pumps (exchange K+ for H+).



✓ There are drugs that target proton pumps, called: Proton Pump Inhibitors. They reduce the secretion of H+, and consequently reduce HCl secretion. These drugs can be used to treat ulcers that were caused by an increase in HCl secretion.

Functions of HCl

1. Conversion of pepsinogen into pepsin: HCl converts the enzyme into its active form, in addition to providing a low-pH environment which ensures optimal activity of this enzyme.
2. Helps in decomposition of food (e.g. decomposing and dissolving the connective tissue present in the meat we eat)
3. Defense: the gastrointestinal tract is a portal of entry for many pathogens. Many of the microorganisms ingested with food cannot survive the low pH provided by the secreted HCl.

❖ Secretion of Pepsinogen

✓ Pepsinogen is secreted MAINLY by peptic (chief) cells, with some literature stating small amounts of pepsinogen being secreted by mucous cells. The professor emphasized multiple times that secretion of pepsinogen is mainly by peptic cells, and we will be asked about the **MAIN** source of secretion, which is as mentioned: peptic cells.

✓ The optimal activity of this enzyme is at a pH of (1.8-3.5), and this low pH is maintained by the secretion of HCl.

Function of Pepsin

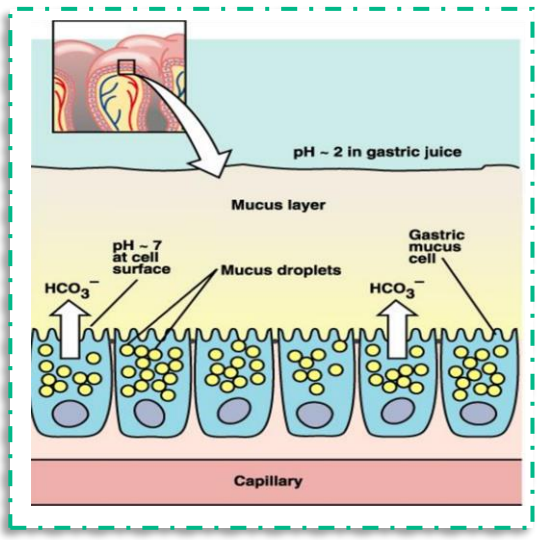
Pepsin (an active proteolytic enzyme) cleaves long peptides into smaller fragments. Note that we do not achieve final digestion at this level, we are merely starting the digestive process. Final digestion of protein takes place later at a more distal part in the GIT. So, again, we are cleaving large peptides into smaller ones here (not final digestion).

❖ Mucus Secreting Cells

✓ At the surface, we have mucous surface cells which secrete mucus. There are also other mucous cells at the neck of the gland. The released mucus forms a barrier between the lumen and the tissue.

✓ The pH of mucus is almost 7 (towards alkaline), while the pH in the lumen is very low.

✓ The mucus barrier protects the gastric mucosa by preventing the acids in the lumen from reaching the cells, or by even neutralizing the acid if it manages to enter.



✓ Some types of ulcers result from atrophy that takes place at the mucosa, resulting in lower release of mucus, which results in less protection of the mucosa.

Function of Mucus

- ❖ Lubrication functions
- ❖ Protection of the mucosa from chemical injury by preventing the activity of the proteolytic enzymes to act on the mucosa, and by neutralizing HCl by its alkaline character.

❖ Gastrin Secretion

✓ Gastrin is secreted by G cells. The process of gastrin release is stimulated by:

1. Gastric Distension: these are local changes that cause G cells to release gastrin.
2. Presence of proteins in chyme: High amounts of protein can act as a chemical stimulus for the secretion of gastrin.
3. Vagal Stimulation: parasympathetic fibers from the vagus nerve can act on endocrine cells and stimulate the release of gastrin.

Function of Gastrin

1. Increases HCl and pepsinogen secretion. (Hormonal control of gastric secretion).
2. Trophic effect on gastric mucosa to maintain growth of mucosal cells. (Trophic effect: maintain survival of cells. This is also useful if destruction occurs to the mucosal cells, as the trophic effect may assist in the repair process).

❖ Intrinsic Factor

✓ Intrinsic factor is secreted by parietal cells (oxyntic cells).
✓ It is essential for vitamin B12 absorption.

✓ Several medical conditions involving anemia are related to the stomach. What is the relationship between anemia and gastric problems?

- Patients suffering from gastric atrophy, for example, are vulnerable to developing anemia, due to decreased secretion of intrinsic factor, and consequently decreased absorption of vitamin B12 (which is needed for the production of mature blood cells). Our diet is generally rich in vitamin B12, but the issue here involves reduced absorption rather than availability of the vitamin in our diet.

Another disorder associated with vitamin B12 deficiency is pernicious anemia.

❖ Control of Gastric Secretion:

✓ We have many means of control over gastric secretion, these include neural, hormonal and paracrine control.

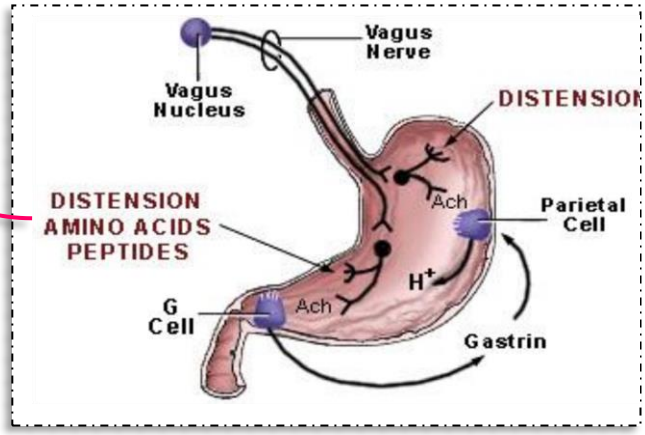
❖ Neural Control

✓ Neural control can be achieved through the effects of ENS and ANS.

Enteric Nervous System

There are neurons within the ENS that secrete Ach, which binds to muscarinic receptors on the membrane of secretory cells, causing direct stimulation of parietal and peptic cells.

What activates these neurons in the first place? Local changes (distension, chemicals, proteins in food) which are sensed by the ENS neurons. These stimuli increase the activity of the Ach neurons, increasing Ach release, leading to more stimulation and secretion.



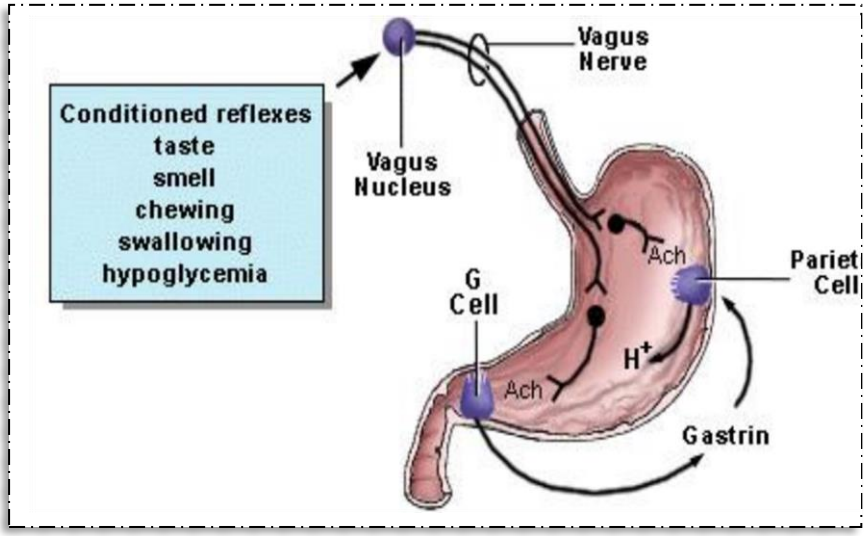
Parasympathetic Nervous System

✓ It can act directly on secretory cells by releasing Ach.

✓ It can also have many indirect effects on secretory structures, how? These indirect effects occur through acting on the ENS first, which in turn acts on secretory cells. Examples of these indirect effects:

A. Some of the autonomic neurons stimulate enteric excitatory neurons to release Ach, and that potentiates the activity of the secretory cells.

B. In addition, some neurons in the autonomic nervous system activate other enteric neurons which innervate another type of cells called "Enterochromaffin-like cells" which release histamine (involved in what is called Paracrine control).



✓ *ANS (parasympathetic):*
vagal activation during cephalic and gastric phases (via long arc reflex).

Remember: In Paracrine secretions, cells release ligands that act on nearby cells without the need for these ligands to enter the blood to reach their target cells (unlike endocrine secretions).
Example of paracrine control: enterochromaffin-like cells release histamine which acts on nearby cells (secretory cells).
Example of endocrine secretions: gastrin is released into the blood and once it reaches the stomach, it acts on secretory cells to affect their activity.

C. In addition, the autonomic nervous system can activate some enteric neurons to release GRP (gastrin releasing peptide) which activates G cells to release gastrin.

✓ So, the parasympathetic ANS can activate acid secretion directly, or indirectly by activating ENS first, which then activates: Paracrine control or Hormonal control.

❖ Hormonal Control

Gastrin

✓ Hormonal control is achieved by gastrin.
✓ Gastrin is secreted by G cells into the blood and acts on parietal cells to increase HCl secretion.

✓ The membrane of oxyntic cells contains receptors for gastrin, called CCK-B receptors (both gastrin and CCK (cholecystokinin) can bind to these receptors). Binding of gastrin *increases intracellular Ca^{+2}* and activates oxyntic cells to secrete HCl.

✓ However, when CCK binds to these receptors, it causes minimal stimulation, whereas gastrin binding induces more profound stimulation.

✓ Although CCK's effect upon binding is stimulation (very small), its effect can be viewed as inhibition by preventing the stronger ligand (i.e. gastrin) from binding and strongly activating the receptor (they compete with each other). (EXTRA: This resembles the concept of partial agonists acting as antagonists when administered with full agonists, as we previously discussed in pharmacology).

✓ What happens if we have high amounts of CCK?

- Inhibition of the activity of secretory cells will occur, because we have both ligands (CCK & Gastrin) competing for the same receptor, and this high concentration of CCK is causing less of gastrin to bind.
  (The final result will be less stimulation → inhibition).

✓ On the other hand, if we have a high concentration of gastrin —> more stimulation of gastric secretion.

❖ Paracrine Control

Histamine

✓ Enterochromaffin-like cells release histamine *(in response to vagal stimulation and local inflammation)* which can bind to H2 receptors on parietal cells.

✓ Histamine diffuses into the extracellular space, binds to and activates H2 receptors on parietal cells, which increases cAMP, causing increased HCl secretion.

✓ What happens if we block these receptors (H2 receptors)?
Acid secretion will decrease, and this is indeed the action of drugs called H2 blockers (such as Cimetidine).

- These blockers are useful for treating some types of ulcers that are caused by increased secretion of HCl.
- As mentioned previously, we have other drugs called "proton pump inhibitors (PPIs)" which inhibit proton pumps ➡ less acid secretion.

✓ Duodenal ulcers are mostly caused by increased gastric acid secretion. Once you have increased HCl, this acid will enter the duodenum (which is not as well protected by mucus). The mucosa will be affected by the high release of acid, leading to the development of duodenal ulcers. These patients can be treated by drugs that decrease acid secretion (H2 blockers and PPIs).

✓ Note: Increased acid secretion during a meal is normal and occurs in healthy individuals, as this acid is "consumed" in dissolving ingested food. However, increased acid secretion leads to ulcers if it occurs in the period in between meals when there should normally be very minimal or no acid secretion at all (This occurs due to disturbances in the systems that control acid secretion). In the latter case, the secreted HCl is not consumed and this increases chances of HCl interacting with the tissue, causing damage and ulcers.

✓ Therefore, we notice that the pain experienced by patients with ulcers can be relieved by eating, so food can act as a buffer.

Somatostatin

In addition to histamine, somatostatin is also involved in paracrine control. In the stomach, D cells release somatostatin which binds to the SS receptor on parietal cells causing inhibition of secretion (decreased HCl secretion).

❖ Role of HCl in controlling secretion

✓ HCl itself can control secretion. Excess of acids (HCl) causes feedback inhibition of gastric secretions (decreases HCl secretion) in 2 ways:

1. Reduction in gastrin release
2. Initiation or activation of inhibitory reflexes.

(This maintains pH at a certain level and prevents it from falling below 3 or to very low values)

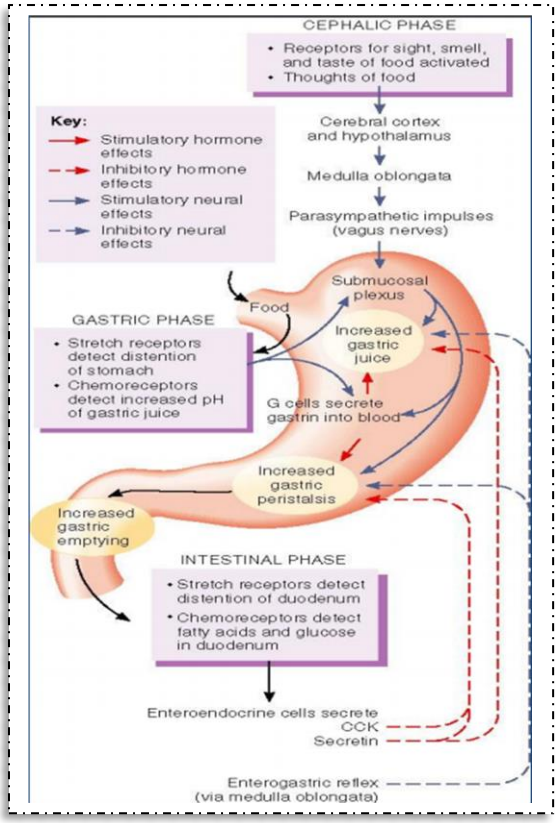
✓ HCl can act indirectly by initiating enteric reflexes that cause an increase in pepsinogen secretion by peptic cells. (Regulation of pepsinogen secretion).

❖ Summary of Control

Cephalic Phase

(Cephalic: Head). So in this phase, we have stimuli from the head when we taste, smell, swallow or think of delicious food. This increases gastric activity

Which system is involved here? The parasympathetic nervous system (ANS) (More specifically: parasympathetic fibers of the vagus nerve) activate gastric secretion in this phase and stimulate G and parietal cells (before food reaches the stomach).



Gastric Phase

This phase occurs once food has been ingested, causing distension of the stomach, in addition to other local changes (chemicals and proteins in the food) which cause maximal stimulation of gastric secretions. These changes activate local and long reflexes.

Which nervous system is involved here?

The Enteric nervous system (ENS). Also, you are potentiating the ANS as well as the hormonal system, so there is complex control over gastric activity during the gastric phase. (Caffeine and alcohol also stimulate gastric secretions even if no food is present in the stomach).

Intestinal Phase

Once the contents of the stomach have been emptied into the duodenum, this will cause local changes in the duodenum. These changes have an inhibitory effect on gastric activity (decrease gastric secretion). This is achieved by activating the Enterogastric reflex (inhibitory reflexes from the small intestine to inhibit the activity of the ANS over the stomach including secretion**).**

- ✓ Also, during the intestinal phase, there is high release of hormones such as cholecystokinin, secretin and GIP (Gastric inhibitory peptide), *enterogastrone* all of which decrease gastric activity.
- ✓ **Note:** Some literature states that in the very beginning of the intestinal phase, some excitatory effects take place. However, the bulk of the intestinal phase has an inhibitory effect on the stomach.
- ✓ Now, what causes this initial excitatory effect?

Well, the upper part of the duodenum is actually equipped with G cells, so, once the contents have been emptied into the duodenum, the duodenal G cells are stimulated,

causing release of gastrin, leading to more gastric secretion (excitation). Now, when the contents move to lower parts of the duodenum, these G cells are no longer stimulated, but instead, CCK-releasing cells and other cells are activated, causing more release of CCK and GIP causing inhibition.

✓ We previously discussed ulcers that result from increased acid secretion. In addition, ulcers may also be related to reduced mucus production as in atrophic gastritis, and that means less protection → more susceptibility to developing ulcers.

✓ What is the relationship between stress and ulcers?

- More stress → higher susceptibility to developing ulcers

Explanation: More stress means more activation of the sympathetic nervous system, leading to vasoconstriction and less blood flow ➡ less healing.

The mucosa is constantly subject to damage by acid, but the healing process often manages to repair the minor damage that occurs to tissue. However, when blood flow is reduced, the damaged tissue fails to heal properly, and the individual becomes more vulnerable to developing ulcers.

Notes from the handout

-Regarding HCl secretion: At rest, the potential difference across the cell is about (-70mV), and drops to about (-30mV) during stimulation.

-Concentration of H+ in the canaliculus is about 3 million times that in blood which results in a decreased pH during gastric secretions. This process needs ATP for H+ pump activity.

-Pyloric glands: contain mucus cells and G cells that secrete gastrin. The mucus secreting cells are similar to mucus neck cells of the gastric glands

Good Luck