Physiology of *Gastrointestinal System (GIS)*

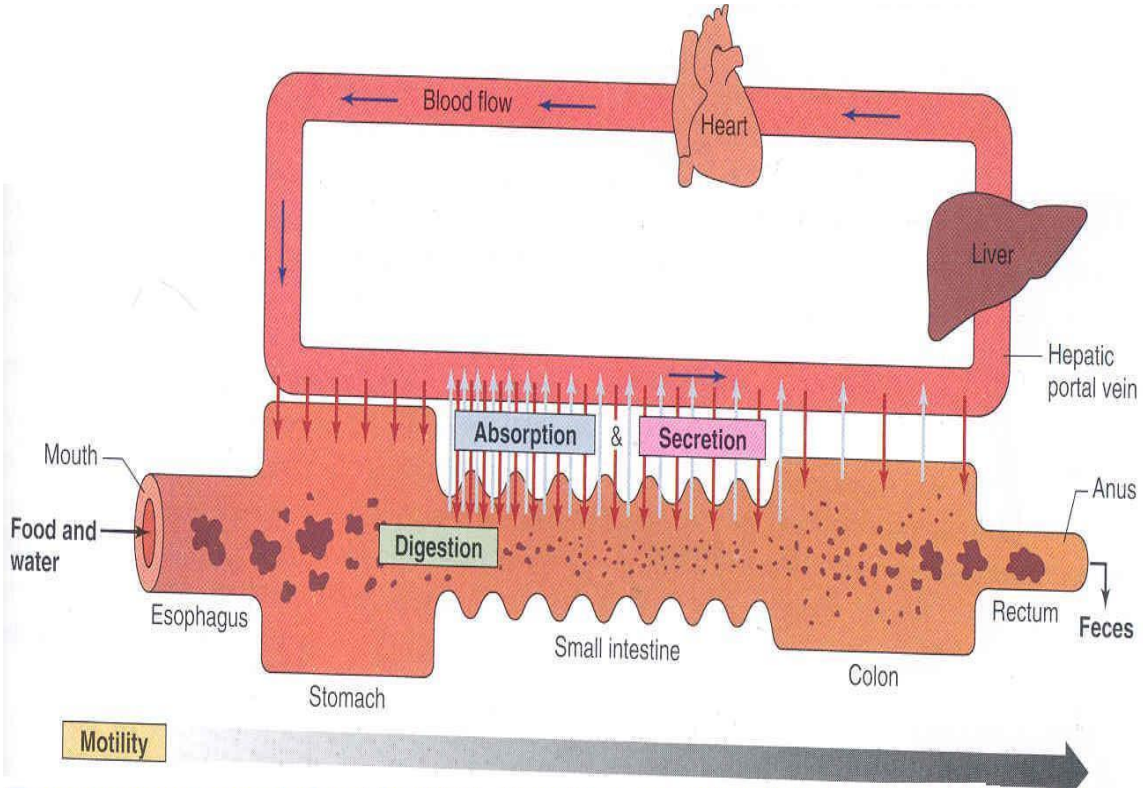
Organization & General Principles of GIT Physiology (L1)

The gastrointestinal system consists of the gastrointestinal tract (GIT) and associated organs that produce secretions

Functions of GIS

The major physiological functions of GIS are to digest foodstuffs and absorb nutrients molecules into blood stream. GIS carries out these functions by motility, secretion, digestion and absorption.

Motility: refers to the movements that mix and circulate the GI contents and propel them along the length of the tract in the forward (orthograde) direction (except in vomiting).



Four processes carried out by GIT, digestion, secretion, absorption and motility

Secretion: refers to the process by which the associated glandular organs release water and substances into GIT.

Digestion: is defined as the process by which food and large molecules are chemically degraded to produce smaller molecules that can be absorbed.

Absorption: refers to the process by which nutrient molecules are absorbed by cells that line the GIT and enter blood stream.

Control of all these functions is by nervous and hormonal systems.

Control of GIS functions

I- The neural control: includes

* Autonomic control (the extrinsic nervous system)
* The enteric nervous system.

1- The autonomic control: via sympathetic and parasympathetic controls.

A- **Sympathetic control** mainly via postganglionic adrenergic fibers whose cell bodies are located in prevertebral and paravertebral ganglia.

Functions:

1- Inhibits the motor activity.

2- Contracts the sphincters.

3- Causes vasoconstriction of splanchnic blood vessels.

4- Secretion is not necessary inhibited, may be moderately increased.

B- **Parasympathetic control**

Via preganglionic cholinergic fibers of vagus and pelvic nerves. They terminate on the ganglionic cells of the intramural (submucosal and myenteric) plexuses.

Functions:

a- Increases motility.

b- Relaxation of sphincters.

c- Causes vasodilatation of blood vessels.

d- Stimulates of secretion.

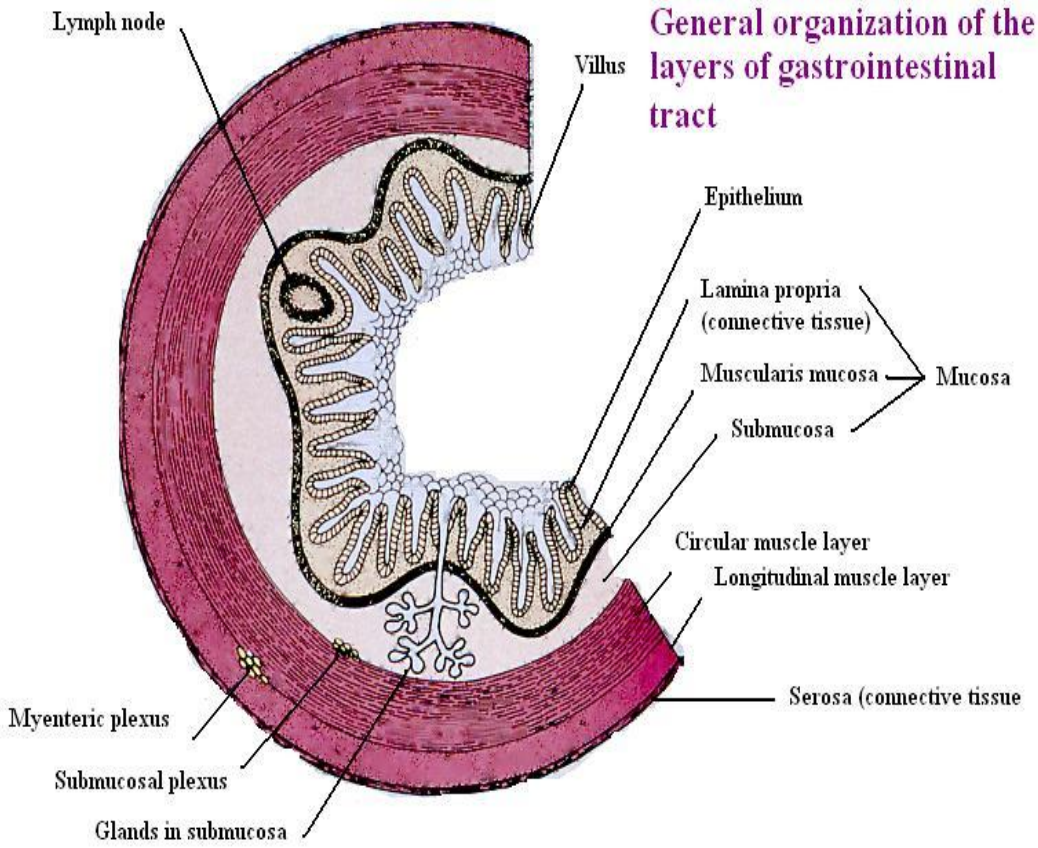
2- The ENS

* The neurons and fibers in the wall of GIT.
* They include the myenteric and submucosal plexuses.
* They are network of nerve fibers and ganglion cell bodies.
* They are about 100 million neurons (as in spinal cord).

* Interneurons in the plexuses connect afferent sensory fibers with efferent neurons to smooth muscles and secretory cells, and therefore form reflex arcs that are located wholly within the GIT wall.

* They can coordinate activity in absence of extrinsic innervation of GIT.

* They constitute the gut mini-brain that communicates with CNS.



Functions of Myenteric plexus

When it is stimulated, its effects are:-

1- Increase tonic contraction.

2- Increase intensity of rhythmic contraction.

3- Increase rate of rhythm of contraction.

4- Increase velocity of conduction of excitation waves along gut wall causing more rapid movement of the peristaltic waves.

N:B The myenteric plexus must not be considered entirely excitatory

Because some of the neurons are inhibitory, their fiber endings secrete an inhibitory transmitter possibly vasoactive intestinal peptide (VIP). The resulting inhibitory signals are especially useful for inhibition of some sphincter muscles such as lower esophageal sphincter.

Functions of submucosal

They respond to stretch and chemical composition of intestinal contents and concerned with control of:-

1- Local secretion.

2- Local absorption.

3- Local blood flow.

4- Local contraction of muscularis mucosa.

II- The hormonal control (the gut as an endocrine organ)

* Endocrine cells are located the pancreas, in the mucosa and submucosa of the stomach and intestine.

* They produce hormones that act on the secretory cells located in the wall of GIT, in the pancreas or in the liver to alter the rate or composition of their secretion.

* Other hormones act on smooth muscle cells or on sphincters.

* All the GI hormones are peptide such as gastrin, secretin and cholecystokinine.

Types of neurotransmitters secreted by ENS

* Acetylcholine excites G.I. activity.

* Norepinephrin & epinephrine inhibits G.I. activity.

* Vasoactive intestinal polypeptide VIP.

* Serotonin.

* Substance P.

* Cholecystokinine CCK.

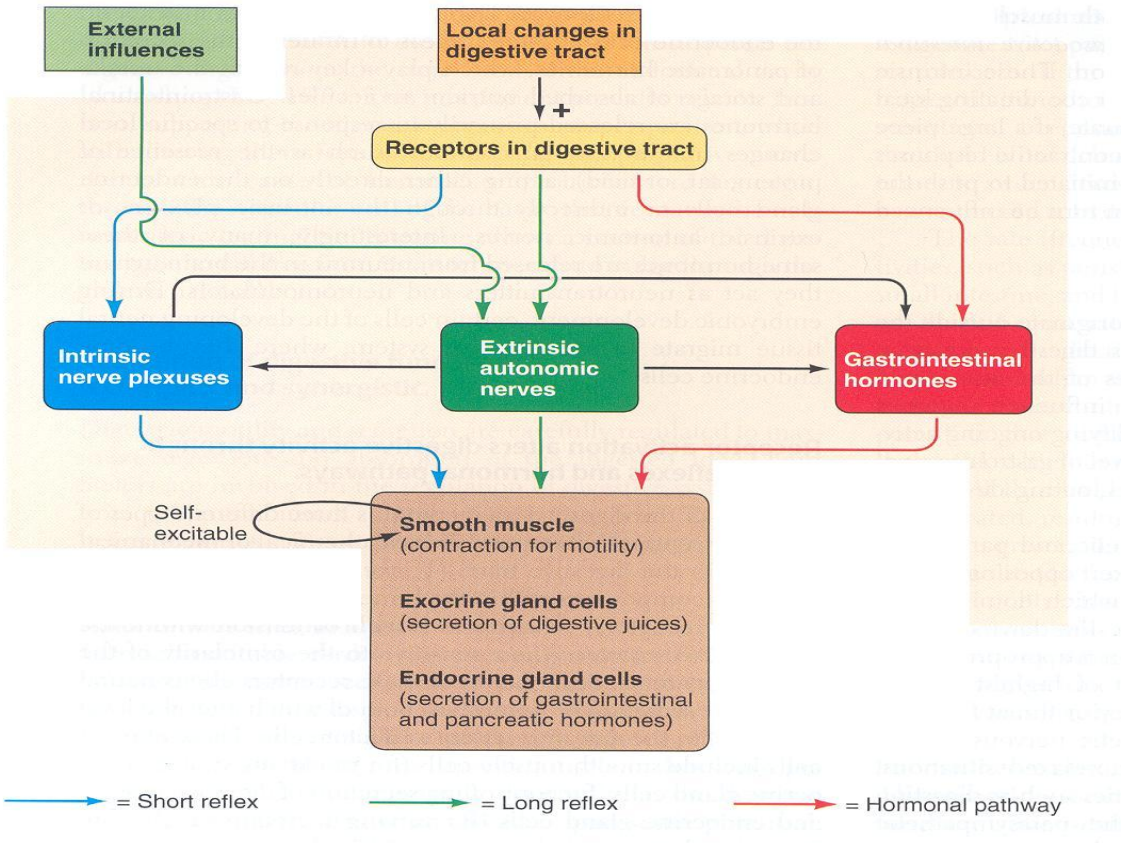
Gastrointestinal reflexes

3 Types of reflexes are essential for G. I control:-

1- reflexes that are integrated entirely within ENS e.g. reflexes that control G.I secretion, peristalsis and mixing contraction.

2- Reflexes from gut to prevertebral ganglion & then back to GIT. e.g. signals from stomach to cause evacuation of colon.

3- Reflexes from gut to brain & spinal cord, then back to GIT. e.g. reflexes from stomach to brain stem to stomach to control gastric motor & secretory activity.



***Electrophysiology* of G.I smooth muscle**

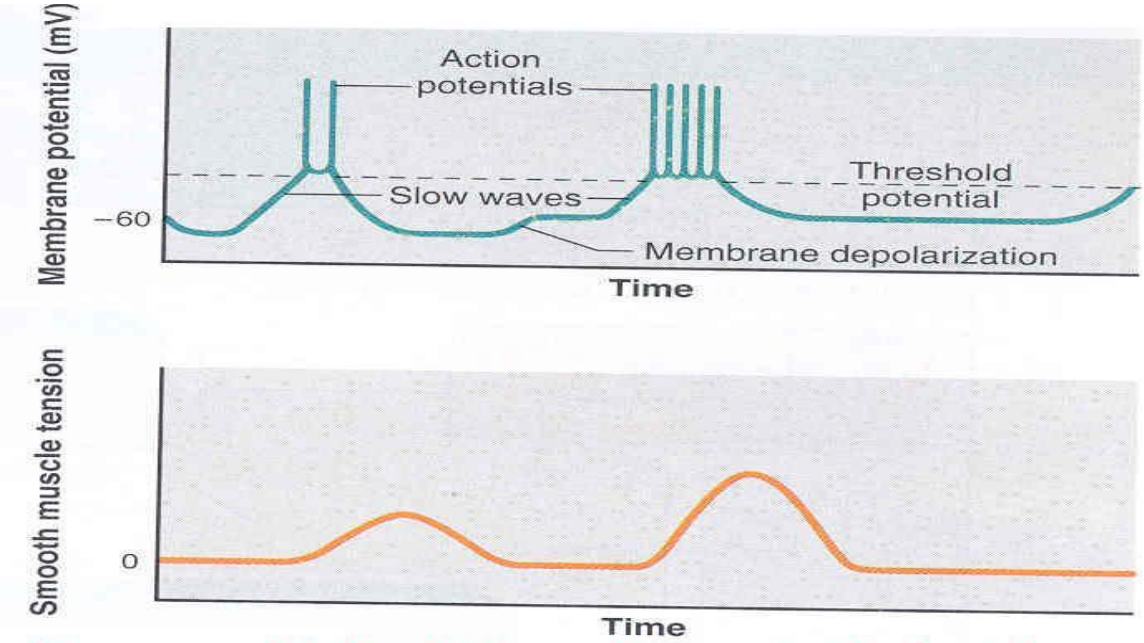
The smooth muscles of GIT undergoes continual activity that have 2 basic types of electrical waves:- 1) Slow waves 2) Spikes

1- The slow waves- basic electrical rhythm

* These are slow spontaneous change in RMP (cyclic waves of depolarization & repolarization).

* Their intensity varies between 5-15 mv.

* Their frequency ranges between 3/min. in stomach body to 12/min in duodenum and change to 8/min. in terminal ileum.



Slow waves oscillations in the membrane potentail of gastric smooth muscle fibers

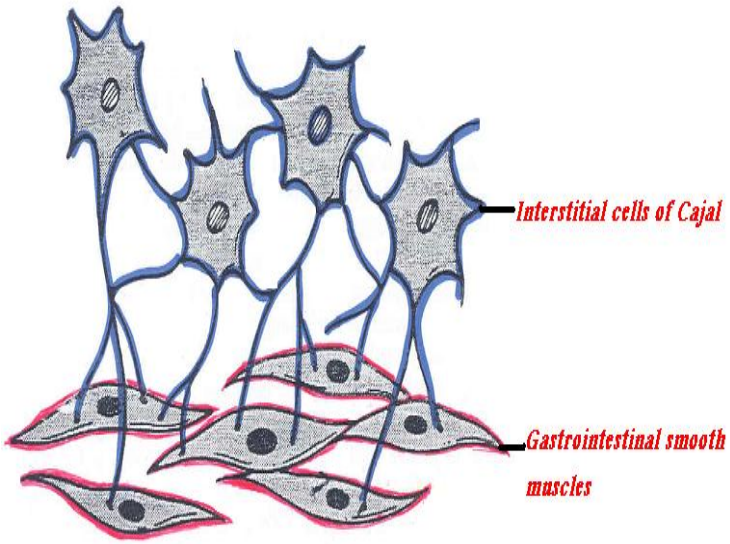
* They do not directly cause contraction.

* Spikes of action potential are superimposed on the depolarization phase of slow waves followed by contraction.

* They are generated by interstitial cells of Cajal located between the longitudinal & circular muscle layers.

* Parasympathetic ↑ their amplitude and frequency.

* Sympathetic ↓ their amplitude and frequency.



2) The spike potentials

* They are true action potentials that occur when RMP rises above -40 mv (RMP= -50-(-65) mv).

* AP of G.I muscles are more prolonged than those of skeletal muscles.

* The rising phase of AP is caused by Ca^{++} and Na^{+} inflow through channels that are slow to open. Ca^{++} that enters cells helps to initiate contraction.

(N.B: slow waves do not cause Ca^{++} entry).

* They usually do not propagate more than a few mm. in intestinal muscles. Instead slow waves are propagated & spike potentials occur at the peak of slow waves.

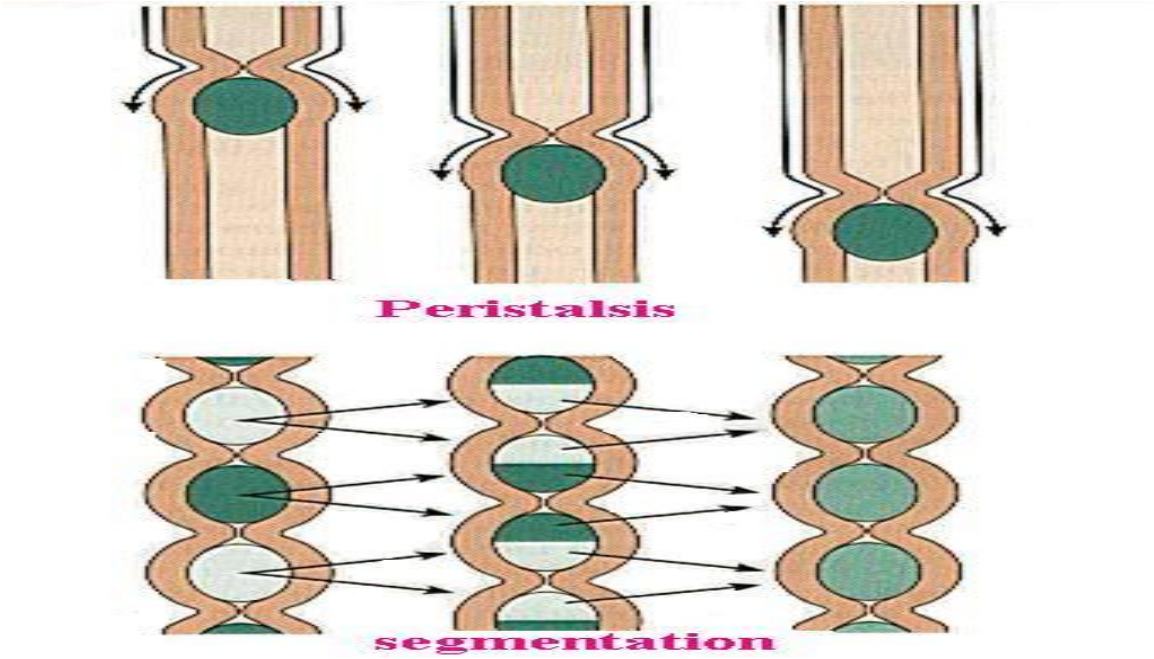
Functional types of movements in GIT.

Mixing movements- segmentation

Which keep intestinal contents mixed. They are cause by either peristaltic contraction or local contrictive contraction.

Propulsive movements- peristalsis

Which cause food to move forward along the tract. A contraction ring appears around gut, then moves forward.



Physiology of Esophageal Motility and Pathophysiology of Reflux (L2)

* The esophagus functions primarily to conduct food from the pharynx to the stomach. This process is controlled mainly by the swallowing centre.

* Transport is accomplished by peristalsis, with propulsive and receiving segments produced by neurally organized contractile behavior of the logitudinal and circular muscle layers.

* The esophageal musculature, both striated and smooth, is mainly innervated by branches of vagus nerve. Neurons of myenteric plexus directly innervate the smooth muscle cells of esophagus .

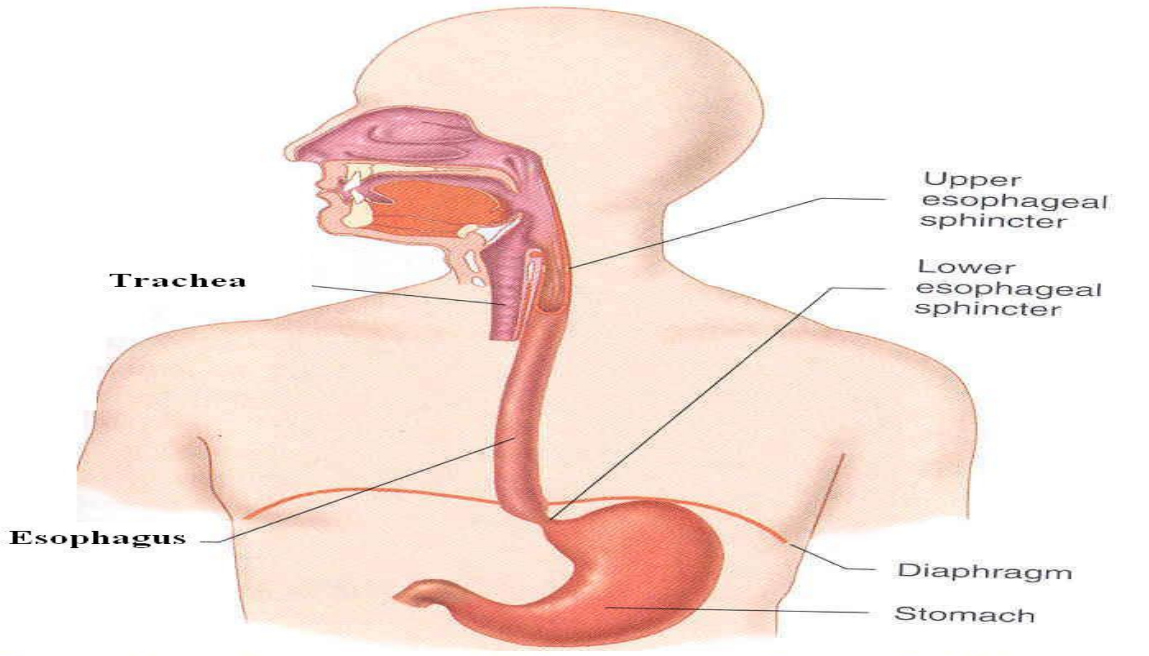
Physiologically:

The esophagus is divided into three functionally distinct regions:

A- The upper esophageal sphincter.

B- The esophageal body.

A- The lower esophageal sphincter.



Location of upper and lower esophageal sphincters

Esophageal peristalsis

* The peristaltic waves are initiated by vagal reflexes that are part of the overall swallowing mechanism.

* These reflexes are transmitted through vagal afferent fibers from esophagus to medulla and then back again to esophagus through vagal efferent fibers.

* Esophageal peristalsis may occur as primary peristalsis or secondary peristalsis

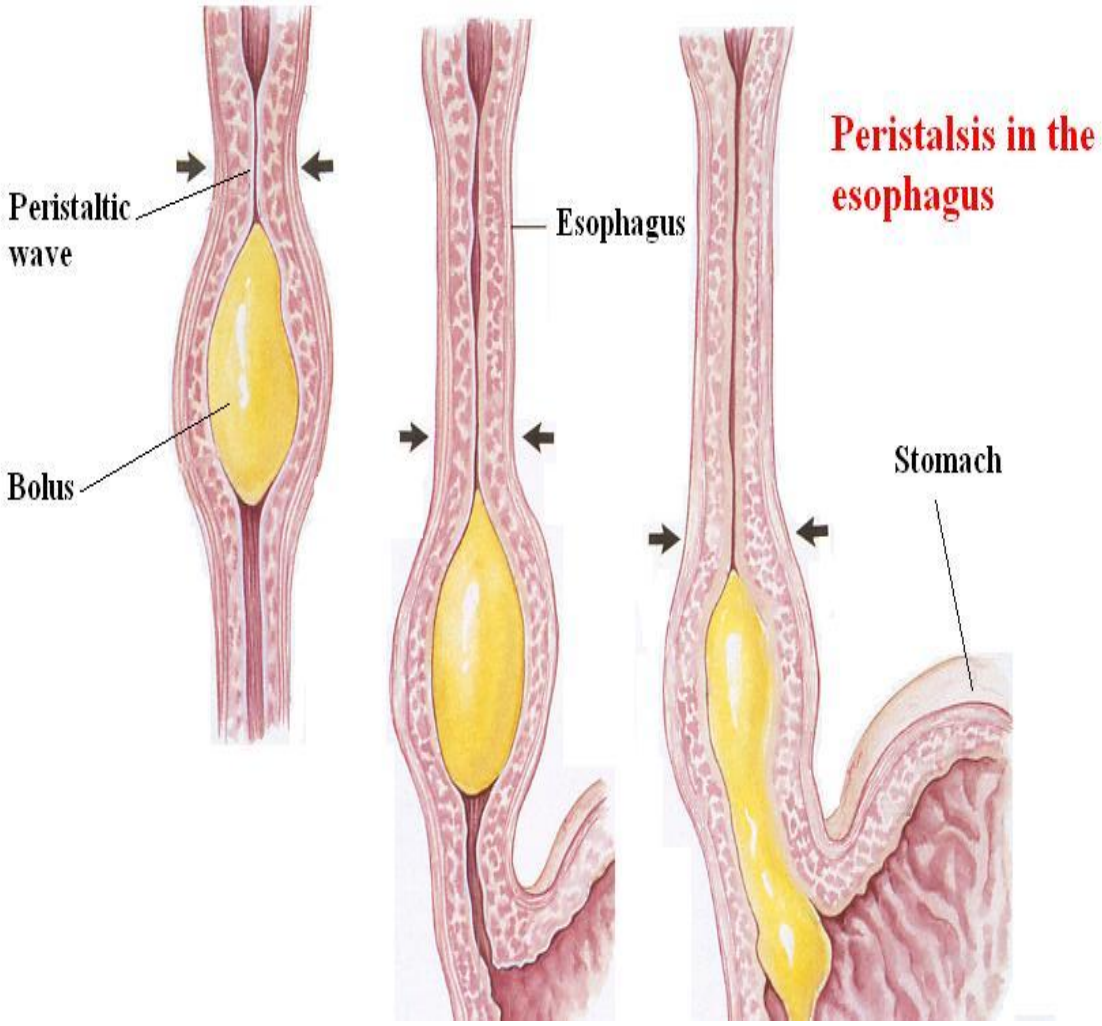
Esophageal peristalsis

1- Primary peristalsis:

* Is initiated by voluntary act of swallowing irrespective of the presence of food in the stomach.

* It is coordinated locally by myenteric plexus.

* It travels at 3-5 cm / sec. and traverse the entire esophagus in less than 10 sec.



Esophageal sphincters

1- The upper esophageal sphincter (UES)

* It prevents entry of air into esophagus.

* It relaxes during swallowing for about 1 second allowing the bolus to be forced through the relaxed UES.

1- The lower esophageal sphincter (LES)

* With initiation of esophageal peristalsis, The LES opens mediated by impulses in vagus nerve.

* In absence of esophageal peristalsis, the sphincter remains tightly closed to prevent reflux of gastric contents into esophagus.

Functions of LES

* Anatomically this sphincter is not different from the remainder of the esophagus. However, physiologically it normally remain tonically constricted, in contrast to the mid and upper portions of the esophagus which normally remain completely relaxed.

* However when a peristaltic wave of swallowing passes down the esophagus, it relaxes the LES (for 7-10 sec.) and allows easy propulsion of the swallowed food into the stomach.

* It is necessary to have a barrier at the gastroesophageal junction (why?).

* Pressure in the esophagus is the same as the intrathoracic pressure i.e. mostly

–ve (except for a short intra-abdominal segment). So that pressure in the stomach is always higher than the esophagus.

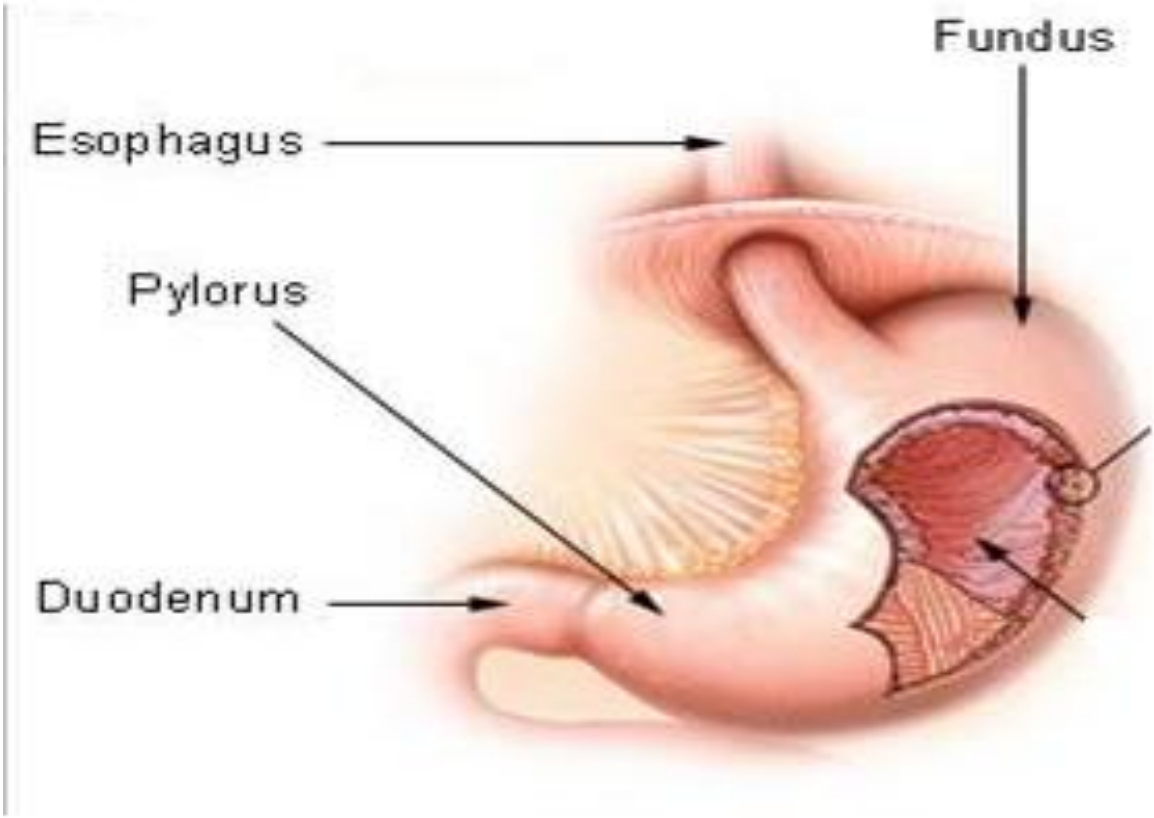
*. The principle function of the LES is to prevent reflux of stomach contents into the esophagus.

Competence and the antireflux functions of the LES is due to:-

1- Its resting pressure (15-30 mmHg).

2- A valve like mechanism of the distal end of the esophagus that lies immediately beneath the diaphragm and is exposed to +ve intra-abdominal pressure. This flutter-valve closure of the lower esophagus by the increased intraabdominal pressure prevents the high pressure in the stomach from forcing its contents into the esophagus.

3- The crura of the diaphragm wrap around the esophagus at the level LES, contraction of the diaphragm helps to increase the pressure in the LES with each inspiration.



Control of LES function

* Contraction of the circular musculature of the sphincter is regulated by nerves, (extrinsic & intrinsic), hormones and neuromodulators.

* Between swallows, tonic vagal cholinergic impulses maintain contraction to keep the sphincter closed.

* Stimulation of sympathetic nerves to the sphincter also causes the LES to contract.

* During swallowing, efferent impulses in the vagus are inhibitory causing the sphincter to relax. The transmitter probably being nitric oxide or vasoactive intestinal peptide (VIP).

* The hormone gastrin, released from the stomach by food, contracts LES.

* Secretin and cholecystokinine (CCK) released from the upper intestine relax the LES.

Achalasia

* It is a condition due to high resting pressure of the LES so; it fails to relax during swallowing. As a result, food transmission from the esophagus into the stomach is impeded or prevented.

* Physiological basis of this condition is either pathology of or absence of the myenteric plexus containing VIP & NO in the lower third of esophagus.

* The musculature of the lower esophagus instead remains contracted and the myenteric plexus has lost the ability to transmit a signal to cause relaxation of the LES.

When achalasia becomes sever, the esophagus may not empty the swallowed food into the stomach for many hours.

The esophagus becomes enlarged which may be infected and cause ulceration, sever substernal pain or even rupture and death.

The food often reflux into the pharynx and is then aspirated into the lungs.

Therapy of Achalasia

Therapy of achalasia involves:

* Mechanically dilating LES.

* Surgically weakening the LES.

* Administering drugs that inhibit the tone of the LES.

Incompetence of the LES

* Incompetence cause esophageal reflux and result in chronic exposure of esophageal mucosa to acid. The stomach contents are highly acidic and contain many proteolytic enzymes.

* The esophageal mucosa, except in the lower eighth of esophagus, is not capable of resisting for long the digestive actions of gastric secretions.

* It can lead to reflux esophagitis, heart burn, esophageal ulcer and dysplastic changes that may become cancerous.

Physiology of The Stomach and Regulation of Gastric Secretion

(L3 & 4)

Histologically the gastric mucosa is divided into 3 areas:-

1- The cardiac area (10 % of mucosa)

Most of cells secrete mucus.

2- The main gastric area (70-80 %)

Includes mucosa of fundus & body. Its glands secrete all constituents of gastric juice.

* Parietal (oxyntic) cells secrete HCl & intrinsic factor.
* Peptic (chief) cells secrete pepsinogen.
* Mucous neck cells secrete mucus & pepsinogen.
* Endocrine cells secrete peptides & amines as histamine.

Functions of stomach

1- Stomach stores food & regulates its passage to small intestine.

2- Stomach secretes juice that liquefies & partly digests food.

3- Stomach has protective function:

* HCl kills ingested bacteria.
* Mucus & HCO_3^- protect stomach.
* Vomiting is a protective reflex.

4- *Stomach* produces intrinsic factor necessary for vitamin B_{12} absorption.

5- Gatric HCl is necessary for iron & Ca^{++} absorption.

6- Gastric HCl catalyzes cleavage of inactive pepsinogen into active pepsin.

7- *Stomach* has endocrine function. It produces gastrin, somatostatin, VIP.

Gastric juice

Volume about 2-3 L/day

Main constituents are HCl, digestive enzymes, mucus, intrinsic factor.

Gastric HCl

Secreted by parietal cells. These are pyramidal in shape. They have to concentrate H^+ more than 10^6 times to secrete it into gastric juice. This is provided by presence of numerous mitochondria & enzymes.

Mechanism of HCl formation

1- Cl^- is actively transported from cytoplasm into luminal canaliculi. This creates –ve potential which causes passive diffusion of K^+ from cytoplasm into canaliculi. Thus K^+ & Cl^- enters canaliculi.

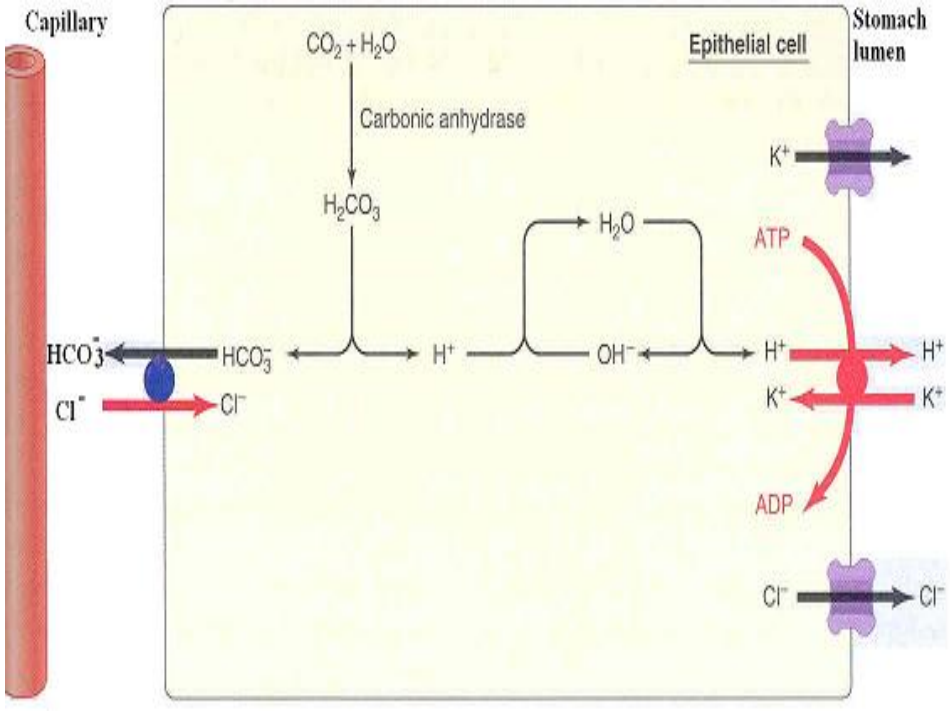
2- Intracellular H_2O dissociates into H^+ & OH.

3- H^+ is actively transported across canalicular membrane against concentration gradient by H^+-K^+ ATPase which exchange H^+ with K^+. It can be inhibited by omeprazole.

4- Water passes through the cell into caniliculi by osmosis.

5- CO^2 & H_2O form H_2CO_3 which dissociate into H^+ and HCO_3^- . H^+ combine with OH^- released in step (2) to form water.

6- HCO_3^- diffuses from the cell to plasma and CL^- enters via a carrier mechanism that facilitates exchange between 2 ions.



Gastric digestive enzymes

Pepsin enzyme

Several types of pepsinogen secreted from chief cells. They are activated by HCl into pepsin and once activated, they can activate more pepsinogen. The optimum pH is 1.5-3.5. Pepsin breaks down proteins into peptones & polypeptides. Pepsinogen secretion is stimulated by Ach, acid, gastrin, secretin & CCK.

Lipase enzyme

Secreted from fundic mucosa. It hydrolyses TG into MG & FA. Its activity is less than pancreatic lipase.

Gastric mucus

It is glycoprotein. Its secretion is stimulated by mechanical & chemical irritation of mucosa.

It is about 0.2 mm thick and separate surface epithelial cells from acidic contents thus it allows neutral pH at epithelial cells despite luminal pH about 2.

Functions:-

1- It protects the mucosa against mechanical injury by lubricating of chyme.

2- It protects the mucosa against chemical injury by acting together with HCO_3^- as a barrier to HCl & pepsin. It also neutralizes HCl and arrest action of pepsin.

Aspirin & nonsteroidal anti-inflammatory agents inhibit secretion of both mucus & HCO_3-. Prolonged use of these drugs may produce gastritis or ulcer.

Intrinsic factor

It is glycoprotein secreted by parietal cells. It is the only essential function of stomach as it is essential for vitamin B_{12} absorption. Atrophy of gastric mucosa leads to pernicious anemia.

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Control of gastric secretion

1- Cephalic phase, elicited before food reaches stomach and responsible for 1/10 of gastric secretion.

2- Gastric phase, elicited by presence of food in stomach, accounts for 2/3 of total gastric secretion in response to eating a meal.

3- Intestinal phase, elicited by mechanisms that originate in duodenum & jejunum.

I- The cephalic phase

It occurs by conditioned & non conditioned reflexes

In non conditioned reflex, presence of food in mouth stimulates receptors. Afferent impulses travel to vagal nucleus in medulla. Efferent impulses reach stomach in vagus nerve to stimulate secretion.

The conditioned reflex follows psychic stimulation by seeing, smelling, hearing or thinking of appetizing food. Afferent impulses travel to vagal nucleus which sends impulses to gastric glands through vagi. Vagal impulses descending to stomach stimulates gastric glands to secrete gastric juice by 2 mechanisms:

1- Directly through the release of Ach.

2- Indirectly by release of gastrin hormone.

II- The gastric phase

It is mediated by nervous & hormonal mechanisms. It is elicited by presence of food in stomach. The stimuli are distension of stomach and presence of amino acids & peptides.

A- Nervous mechanism

* Distension of either body or antrum of stomach stimulates mechanoreceptors in gastric wall. Gastric secretion occurs by long vagovagal reflex and also by short intramural cholinergic reflexes.

B- Hormal mechanism (Gastrin hormone)

Gastrin is secreted from G cells in antrum, enters the blood and stimulates gastric glands via release of gastrin releasing peptide.

Stimuli of gastrin release:

1- The presence of amino acids & peptides.

2- Gastric distension,

3- Alcohol & caffeine.

4- Vagal excitation.

5- Rising of pH of gastric juice.

Actions of gastrin.

1 - Stimulation of gastric acid secretion, secretion of pepsin and I.F.

2- Stimulation of intestinal secretion.

3- Stimulation of pancreatic secretion of enzyme & HCO_3^-.

4- Stimulation of biliary secretion of HCO_3^- & H_2O.

5- Stimulation of gastric motility.

6- Stimulation of intestinal motility & relaxes ileocaecal sphincter.

7- It contract LES.

8- It has trophic effect on gastric mucosa.

Control of HCl secretion at the level of parietal cells

* Gastrin reaches parietal cells via blood stream to stimulate HCl secretion (endocrine action).

* Ach is released near parietal cells by cholinergic nerve endings to stimulate HCl secretion (neurocrine action).

* Histamine is released from enterochromaffin cells in gastric mucosa and diffuses to parietal cells to act on H2 receptors to stimulate HCl secretion (paracrine action).

* Cimetidine & ranitidine are H_2 receptor blockers and potent inhibitor of G.A secretion and both are used for treatment of peptic ulcers.

Differences between gastrin & vagal

Gastrin mechanism is a less potent acute mechanism than vagal stimulation.

Gastrin mechanism continues for several hours in contrast to a much shorter period of time for vagal stimulation.

Gastrin mechanism is equally important as vagal mechanism, the 2 multiply each other.

III- The intestinal phase

The presence of chyme in duodenum causes neural & hormonal responses that first stimulates & later inhibits gastric acid secretion.

Gastric secretion is enhanced by:-

1- Distension of duodenum, it stimulates G.A. secretion by means of vagovagal reflex that stimulates parietal & G- cells.

2- Presence of protein digestive products as peptides & A.A. in duodenum. This stimulates G- cells in duodenum & proximal jejunum to release gastrin.

The inhibitory mechanisms that limit G.A secretion

1- The presence of food in small intestine initiates enterogastric reflex, transmitted through ENS & autonomic NS that inhibits G.A secretion.

2- Drop the pH in pyloric antrum to < 2.5 reduces G.A secretion via release of somatostatin from antral & duodenal D-cells.

3- The presence of acid, fat, protein digestive products, hypertonic solution in upper intestine inhibits G.A secretion. These effects are mediated mainly by hormonal mechanisns.

Enterogastrones

Are hormones released from intestine and affect G.A secretion as:-

1- Bulbogastrone

2- Gastric inhibitory peptide.

3- Secretin & CCK.

4- Pancreatic glucagone.

5- Other peptides as VIP, somatostatin, and certain types of prostaglandins.

The functional purpose of the inhibition of G.A secretion by intestinal factors is to slow the release of chyme from stomach when the small intestine is already filled.

Electrical activity of gastric smooth muscle

2 types of potentials can be recorded:-

1- Basal electrical rhythm

2- Action potential spikes

3- The migrating motor complex

It is bursts of depolarization accompanied by peristaltic contraction that occur in empty stomach during interdigestive period. MMC moves on a long whole length of small intestine to reach ileocaecal valve after 1.5-2 h. where it disappears. A new wave of MMC starts. The activity of MMC terminates as soon as food is ingested.

The function of MMC is to sweep remnants in stomach & small intestine into colon.

The motility function of stomach

Functionally stomach is divided into a proximal reservoir & distal antral pump.

The proximal stomach (fundus and upper 1/3 of body)

As food enters stomach, it relaxes to accommodate food (receptive relaxation).

Slow sustained tonic contraction in proximal stomach provides pressure gradient for pushing & emptying of chyme.

The distal stomach (lower 2/3 of body ,antrum & pylorus)

The main activity in distal stomach is peristaltic contractions.

Its function is grinding of solids, liquefaction of chyme, so chyme is propelled to duodenum.

Gastric emptying

It occurs through coordinate contraction of antrum, pylorus & duodenal bulb (gastroduodenal pump). As gastric contents are propelled into distal stomach, the antrum, pylorus & proximal duodenum are relaxed. Liquified chyme is pushed into duodenum by tonic contraction of proximal stomach.

The terminal antrum then contracts aiding food propulsion. This is followed by contraction of pylorus which closes off stomach & arrests emptying to allow grinding of solids. The proximal stomach then contracts moving the contents into distal duodenum & jejunum. The antrum, pylorus & duodenal bulb then relax & the sequence is repeated.

Control of gastric emptying

I- Gastric factors that promote emptying

A- Gastric food volume

The greater the volume of gastric contents, the faster the rate of emptying.

Liquids are emptied more rapidly than solids.

B- ***Effect of gastrin on gastric emptying***

II- Duodenal factors that inhibit emptying

A- Enterogastric reflex

When chyme arrives in duodenum, its chemical characteristics affect various duodenal receptors. Reflex nerve signals are transmitted from duodenum to stomach to inhibit its motility, thus reducing further release of acidic contents into duodenum until chyme is neutralized.

The type of factors that can elicit enterogastric reflex include:-

1- The presence of hypertonic chyme in duodenum.

2- The drop of pH of chyme in duodenum to < 3.5-4.

3- The presence of emulsified fat, peptides & A.A in duodenum.

4- The presence of any degree of irritation of duodenal mucosa.

5- Duodenal distension.

6- Emotion as fear prolongs gastric emptying.

B- Hormonal feedback mechanisms from duodenum that inhibit emptying

Mixture of hormones called enterogastrone are released from upper intestine by acids, fats & hypertonic chyme and slow gastric emptying. These hormone include:-

Secretin , CCK, GIP.

Gastrin slows gastric emptying due to:-

1- It stimulates duodenal motility & ↑ its resistance

2- It stimulates gastric acid secretion that stimulate release of secretin & CCK. Both ↓ gastric emptying.