

**ADDIS ABABA UNIVERSITY
FACULTY OF MEDICINE
PHYSIOLOGY DEPARTMENT**

GASTROINTESTINAL PHYSIOLOGY

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General Chapter outline

- Introduction
- Physiologic anatomy of GIT
- Layers of GIT and their physiology:
 - mucosa, submucosa, muscularis externa and serosa
- Smooth muscles of GIT
 - Characteristics of smooth muscles
 - Types of smooth muscles
- Control of GIT function
 - Neural control / innervations of GIT
 - Extrinsic : autonomic nervous system
 - Intrinsic: Enteric nervous system = "little brain of gut"
 - Hormonal control
- GI reflexes and their physiological implications
- GIT blood flow and importance of hepatic circulation

- **Four major digestive functions of GIT:**
 - **Motility of different parts of GIT and its regulation**
 - Motility of the esophagus and its sphincters - vagal control
 - **Clinical correlates: Achalasia and Heart burn**
 - The storage, mixing and emptying functions of the stomach
 - Gastric and duodenal factors affecting gastric emptying
 - gastric slow waves and contractions
 - Hunger pangs: Hunger contractions
 - The peristaltic and segmenting function of the small intestine and its inter-digestive motility
 - Mixing and propulsive movement of the colon
 - The storage function of colon
 - Defecation and defecation reflex

- **Secretions of GIT and its regulation**
 - Salivary secretion, its composition and regulation
 - **Clinical correlate:** **Xerostomia**
 - Gastric secretions, regulation
 - Endocrine and paracrine secretions of stomach: gastrin, somatostatin
 - Physiology of acid secretion
 - **Clinical correlates:**
 - **GERD- Heart burn**
 - **peptic ulcer disease (PUD), treatment options**
 - **Gastric outlet obstruction**
 - Pancreatic and biliary secretions and their regulations
 - Endocrine and exocrine secretion of pancreas
 - Function of bile, Enterhepatic circulation of bile
 - **Clinical correlates: Pancreatic disorders, Gall stones**
 - Intestinal secretion and its regulation
 - Secretion from Brunner's gland
 - Secretions from Crypts of Lieberkühn
- ❖ **Vomiting: means by which upper GIT gets rid of its contents**

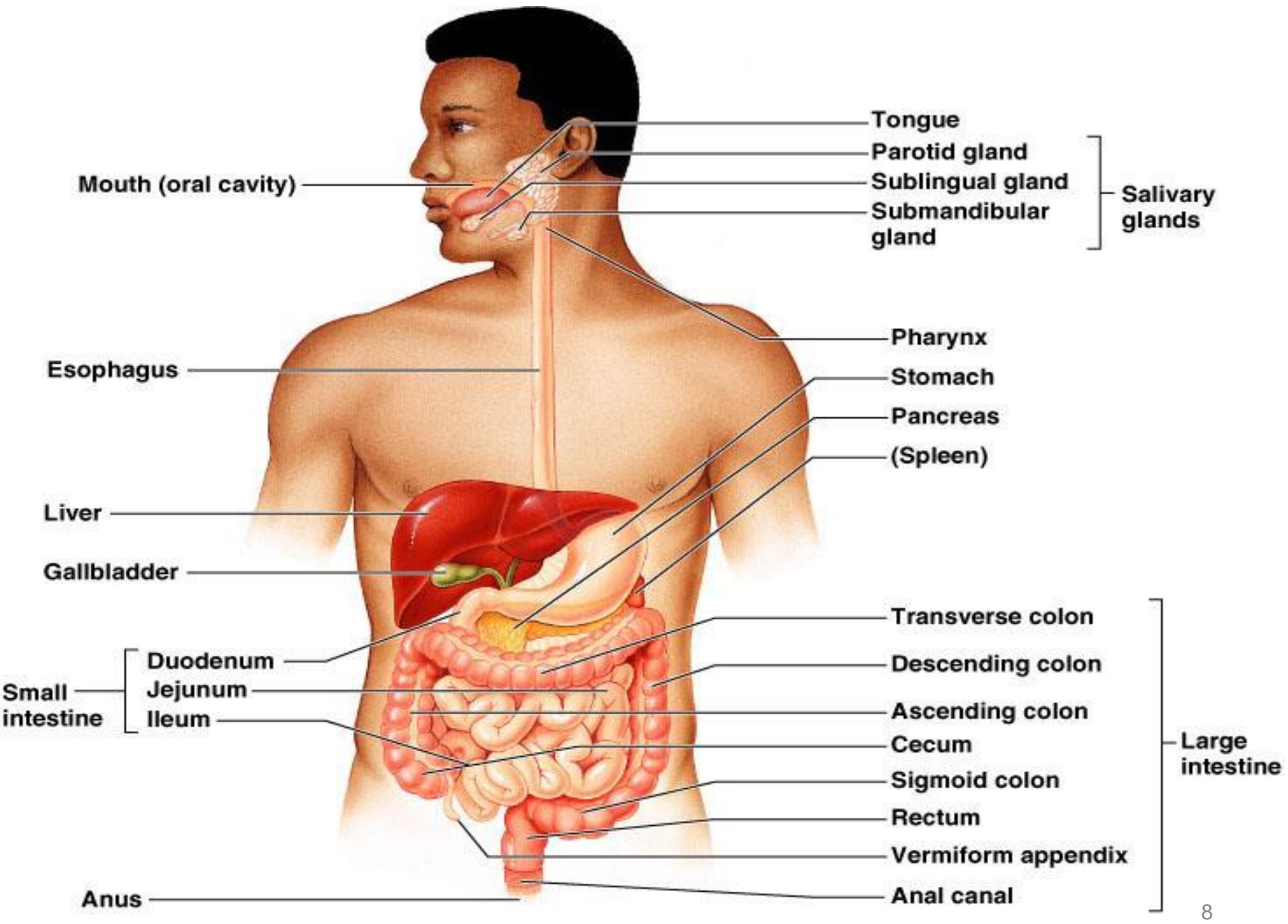
- **Digestive functions of GIT**
 - digestion of proteins, carbohydrates and fats in the In mouth, stomach, small intestine
 - **Clinical correlates: lactose intolerance**
- **Absorptive functions of GIT and its disorder**
 - Absorption in the stomach
 - Absorption in the small intestine
 - Mechanism of carbohydrate absorption
 - Mechanism of protein absorption
 - Mechanism of fat absorption
 - Absorption in the large intestine
 - Bacterial action in the colon
 - **Clinical correlates:**
 - **Disorders of absorption: sprue and steatorrhoea**
 - **Constipation**
 - **Colonic Diverticulosis and diverticulitis**
 - **Diarrhea**

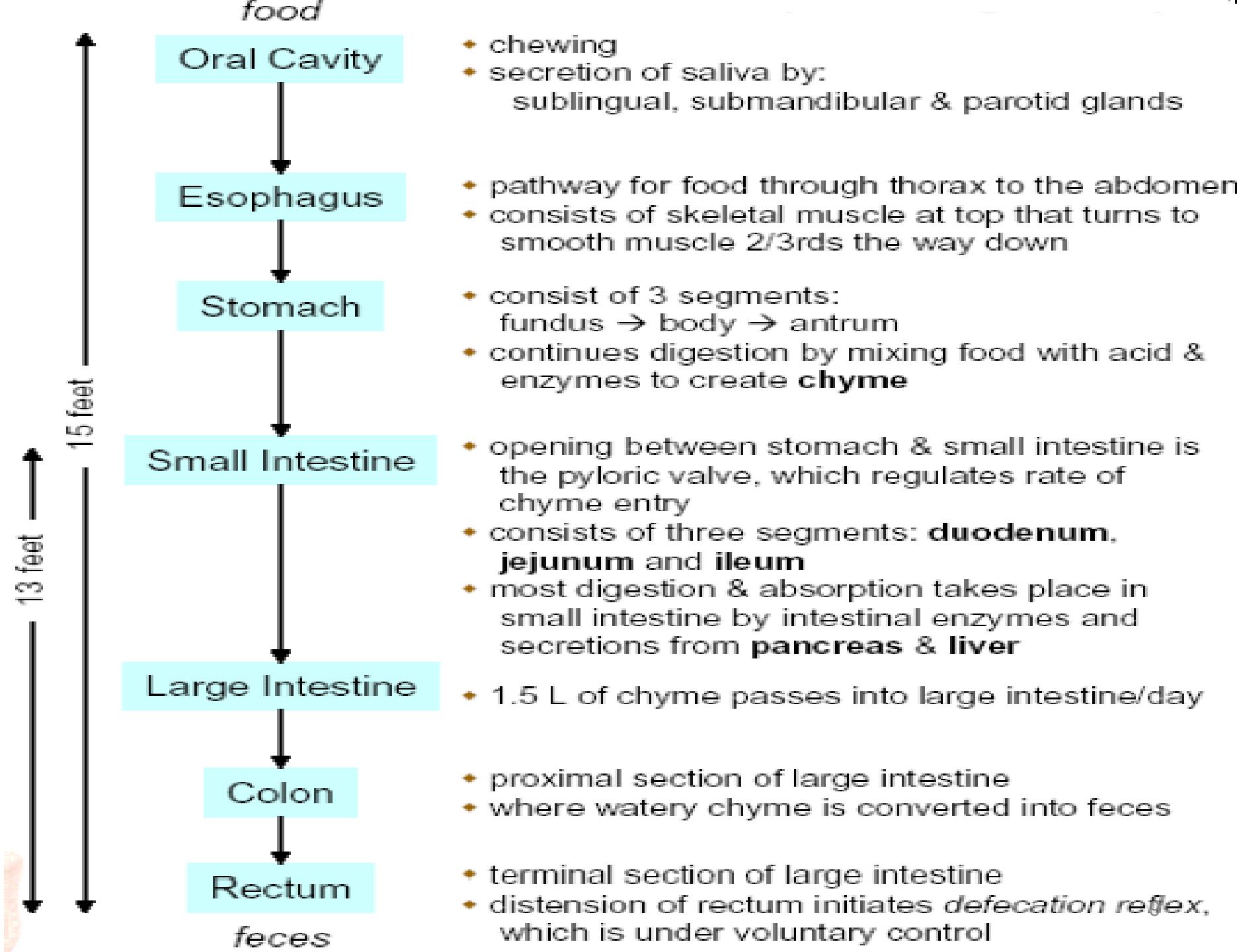
Introduction to GI Physiology

- The Goal of GIT: provide the body with a continual supply of soluble nutrients, water, and electrolytes.
- To achieve this goals it requires:
 1. Motility : peristalsis, mixing.....
 2. Secretion of digestive juices
 3. digestion of the food
 4. Absorption of Digestive end products, water, & various electrolytes
 5. Circulation of blood through the GI organs to carry away the absorbed substances
 6. Control of all these functions by nervous, and hormonal means

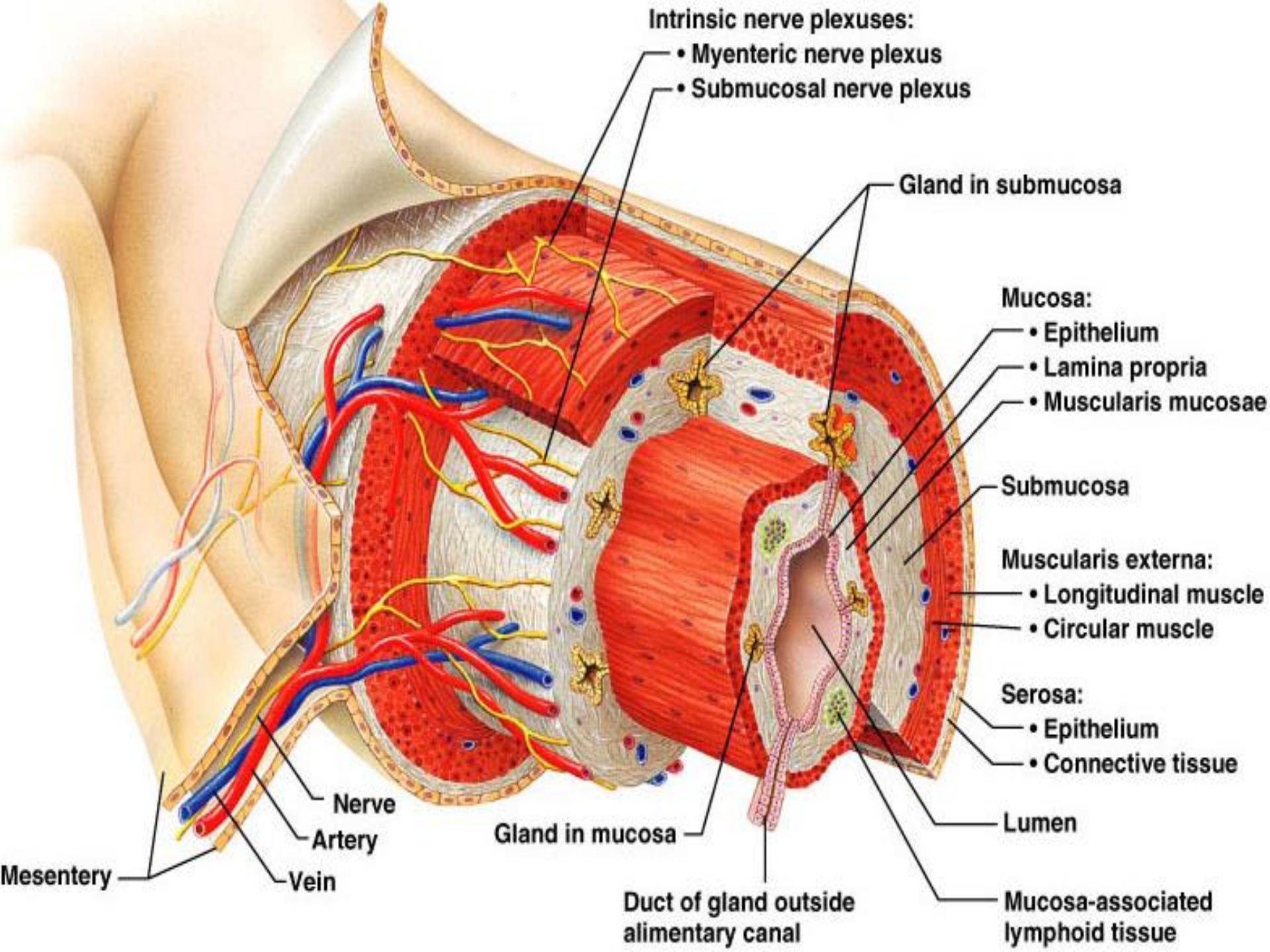
Physiologic anatomy of GIT

- The alimentary canal or GIT digests food and absorbs the digestive end products
- Major GIT organs (alimentary canal):
 - mouth, pharynx, esophagus, stomach, small intestine, and large intestine
- Accessory digestive organs:
 - teeth, tongue, salivary glands, gallbladder, liver, and pancreas
 - Digestion does not take place within these organs,
 - but each contributes something to the digestive process





- From esophagus to the anal canal the walls of the GIT have the same four tunics
 - From the lumen outward they are:
 - ✓ The mucosa- consists of:
 - epithelium,
 - lamina propria, and
 - muscularis mucosa
 - ✓ The sub mucosa,
 - ✓ The muscularis externa- consists of:
 - circular muscle layer -inner
 - longitudinal muscle layer - outer
 - ✓ The serosa or fibrosa
- Each tunic has a specific digestive function



I. Mucosa

- Innermost layer (faces lumen) or in contact with GIT content
- Moist epithelial layer lines the lumen of the alimentary canal
- Its major functions are:
 - Secretion of mucus, enzymes and hormones
 - Absorption of the end products of digestion
- Consists of three sub-layers: a lining epithelium, lamina propria, and muscularis mucosa

Mucosa: Epithelial Lining

- In contact with the GIT content
- **stratified squamous epithelial cells** in mouth, surface of tongue, pharynx and esophagus,
- **Columnar epithelial cells** in stomach and intestine
- Consists mucus-secreting goblet cells
 - Protect digestive organs from self digesting
 - Ease the passage of food along the tract.
- Contains stomach glands and small intestinal glands :
 - Enzyme-secreting cells
 - Hormone-secreting cells
- Is a single layer of absorptive barrier that nutrients must traverse to enter the body
- Specialized to villi in small intestine

Mucosa: Lamina Propria

Lamina Propria

- Loose connective tissue
- Nourishes the epithelium and absorbs nutrients
 - Because blood vessels do not normally penetrate an epithelium, all nutrients must pass out of the capillaries in the underlying lamina propria.
- Contains lymph nodes important in defense against bacteria
 - Mucosa associated lymphoid tissues
- Most epithelial tissues receive a rich supply of sensory nerve endings from nerve plexuses in the lamina propria

Mucosa: Muscularis mucosae - thin layer of smooth muscle

- Absent in mouth and pharynx but present from esophagus onwards
- separates mucosa from submucosa
- Has two thin layers of smooth muscle:
 - the inner layer is circular
 - the outer layer runs longitudinally
- contraction alters absorptive surface area by movement of villi
 - Its contractions change the shape of the mucosa, producing ridges and valleys that alter the absorptive or secretory area.

II. Submucosa - dense connective tissue

- contains:
 - blood vessels, lymphatic vessels, and lymph nodes
 - Glands (esophagus(esophageal gland proper) and duodenum(bruner's gland))
 - Other glands are in mucosa
 - submucosal nerve plexus (Meissner's plexus) at its juncture with the circular muscle layer

III. Muscularis externa - responsible for segmentation and peristaltic movement of food content through GIT

- smooth muscle cell layer that produce local movements of GIT
 - **inner circular layer** - contractions narrow the diameter of lumen
 - thicker and has more gap junction than the longitudinal
 - more powerful in exerting contractile forces on the contents of GIT
 - **outer longitudinal layer**
 - contractions shorten a particular segment of GIT
 - **Oblique layer** - the 3rd layer in the inner part of stomach only
 - Absent in intestines and esophagus
- Contractions of these layers move food through the tract, crush and mix the food with the GI secretions
- Contains myenteric nerve plexus (Auerbach's plexus)
 - Located between circular and longitudinal muscles

IV. Serosa/serous or fibrous layer

- the outer most protective layer of GIT wall
- **fibrous layer** formed by connective tissue in the pharynx and esophagus
- **Serous layer** formed by connective tissue and mesoepithelial cells in the stomach and intestine
 - Is a continuation of the **peritoneal membrane** (membrane lining the abdominal cavity)

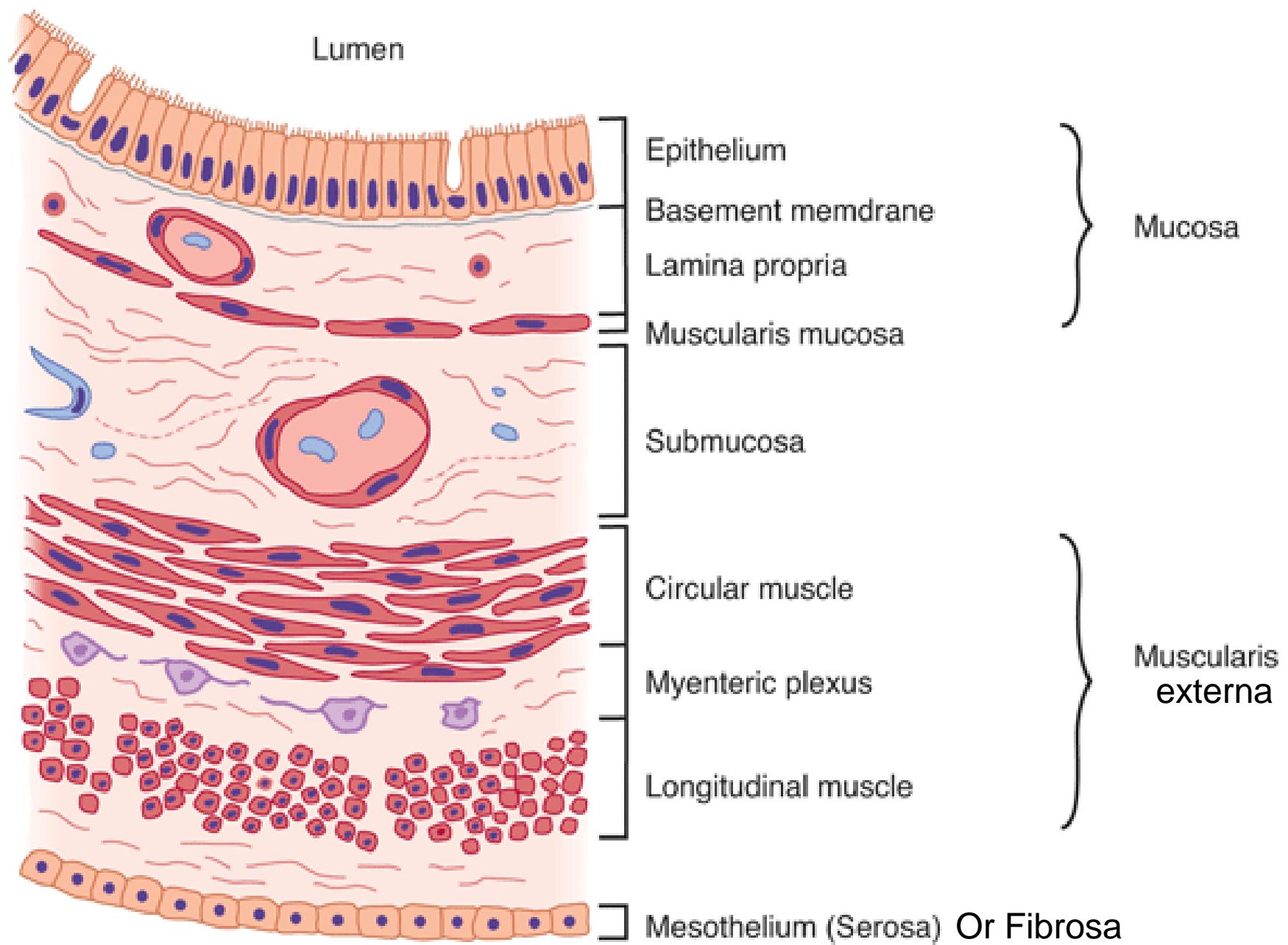
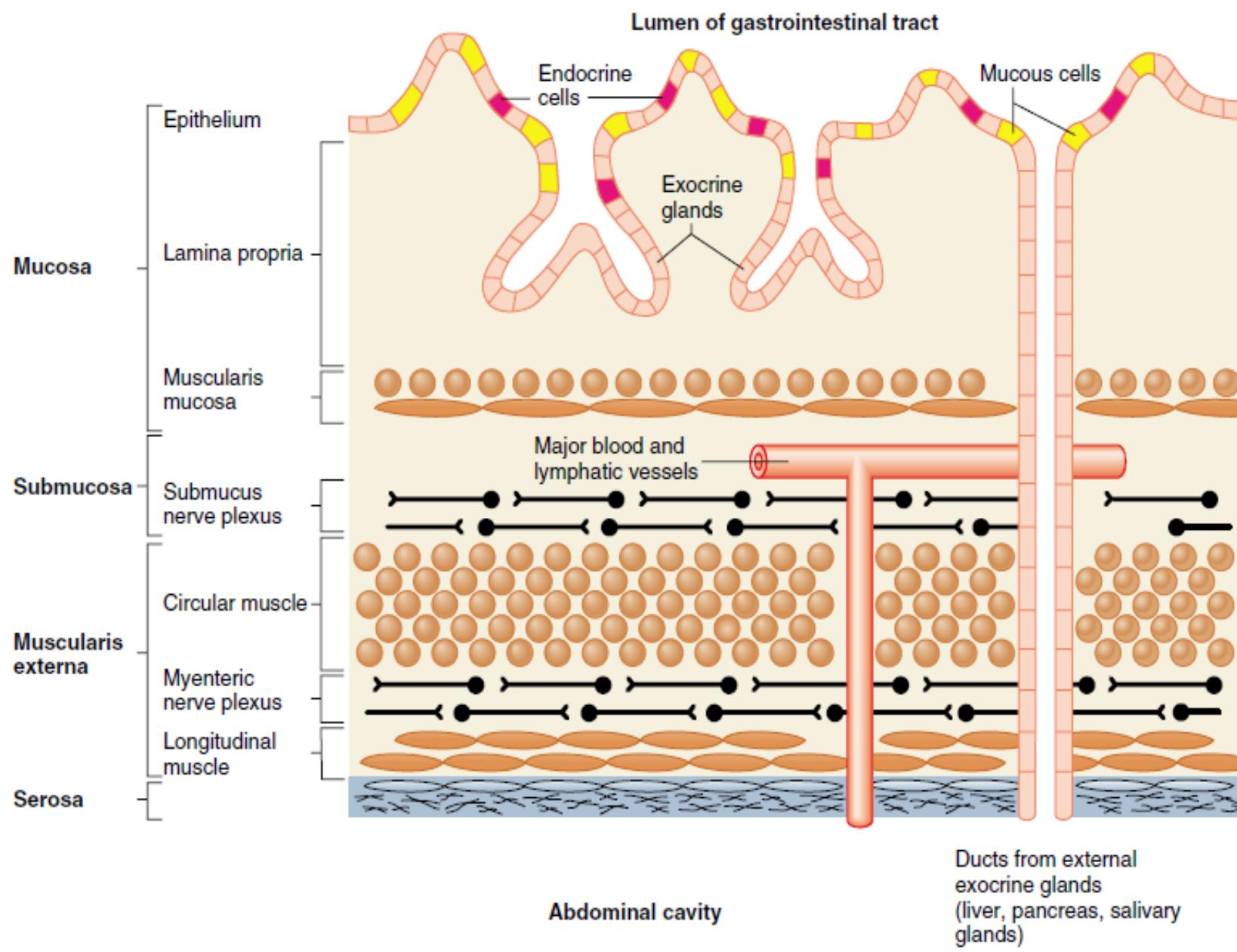


Fig. Organization of the wall of the GIT into functional layers



FIGURE

Structure of the gastrointestinal wall in longitudinal section. Not shown are the smaller blood vessels and lymphatics, neural connections between the two nerve plexuses, and neural terminations on muscles, glands and epithelium.

SMOOTH MUSCLES OF GIT

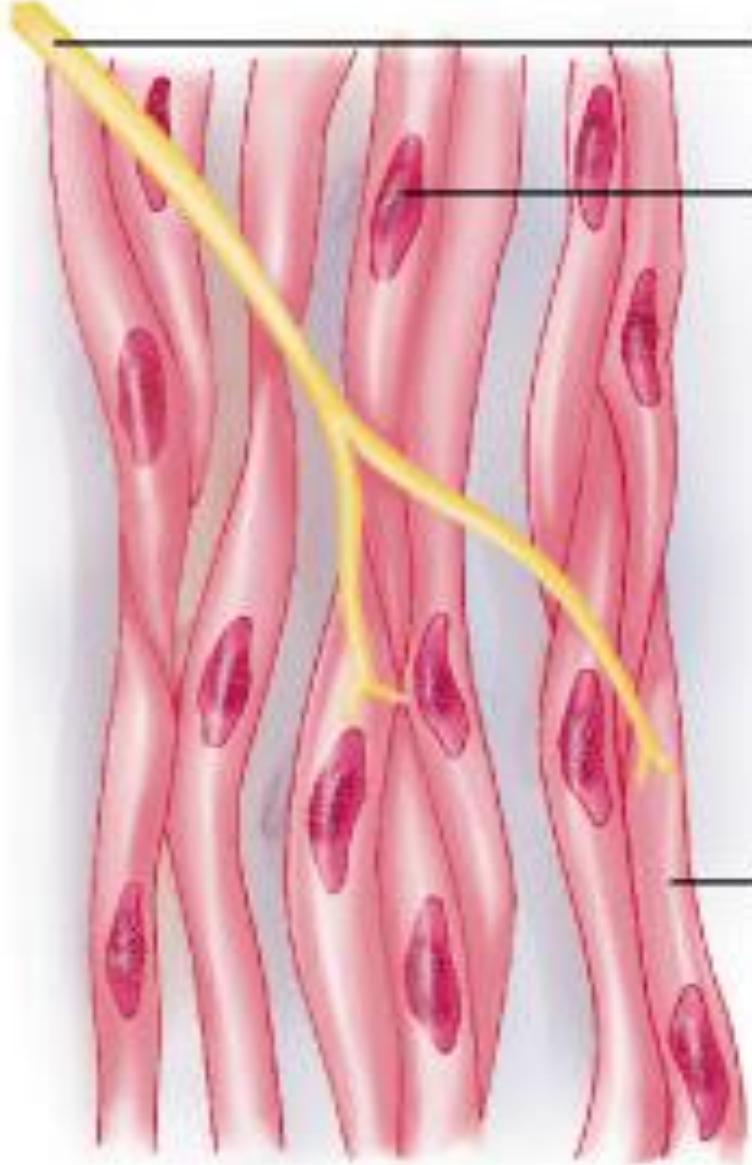
Two types smooth muscle (classifications):

➤ **Single unit or Unitary type**

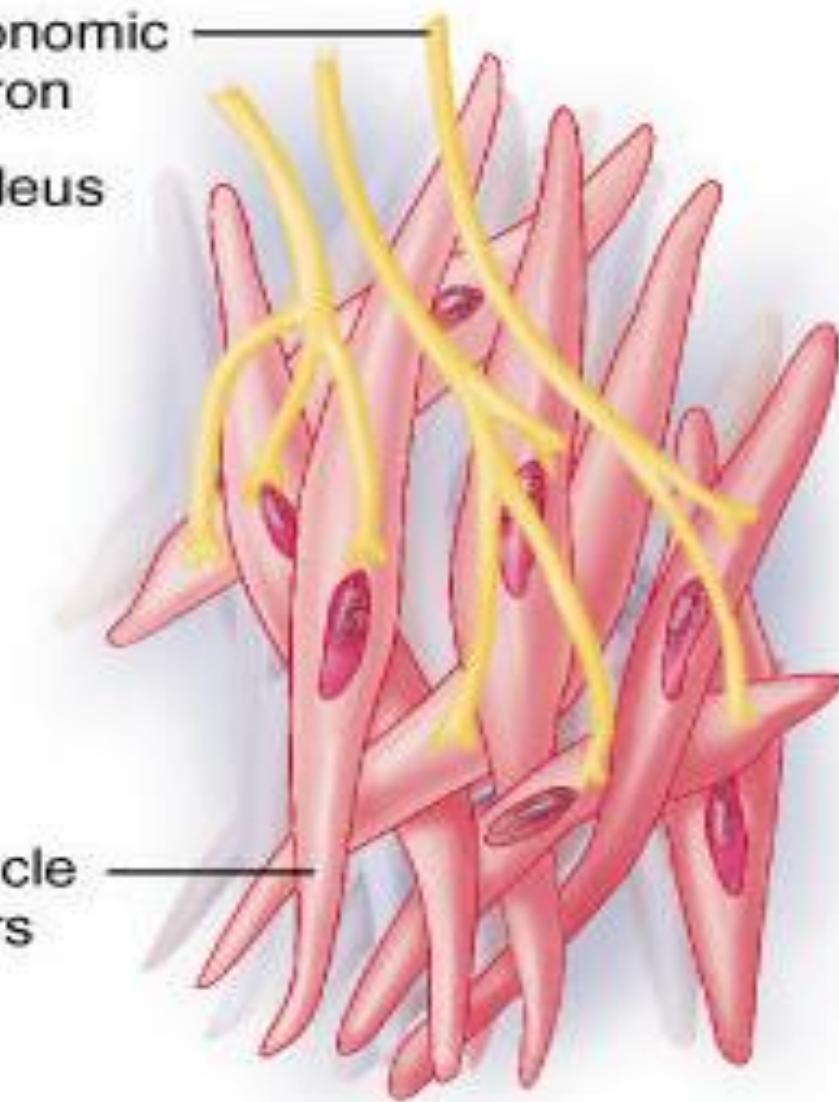
- Contract spontaneously in the absence of neural or hormonal influence but in response to stretch
- Cells are electrically coupled via gap junctions
- predominant type of muscles in GIT
- mostly in stomach and intestines

➤ **Multiunit type**

- Do not contract in response to stretch or without neural input
- Few if any gap junctions
- mostly in esophagus & gall bladder



(a) Visceral (single-unit)
smooth muscle tissue



(b) Multiunit smooth
muscle tissue

Characteristics of smooth muscle in the gut

- GI smooth muscles function as a syncytium
- Each bundle of smooth muscle fibers is partly separated from the next by **gap juction**,
 - ↓
- When an action potential is elicited anywhere within the muscle mass,
 - ↓
- it generally travels in all directions in the muscle.
 - The distance and direction of spread of AP are controlled by the ENS
 - A failure of nervous control can lead to disordered motility
 - Eg. spasm and associated cramping abdominal pain

Types of the smooth muscle contraction:

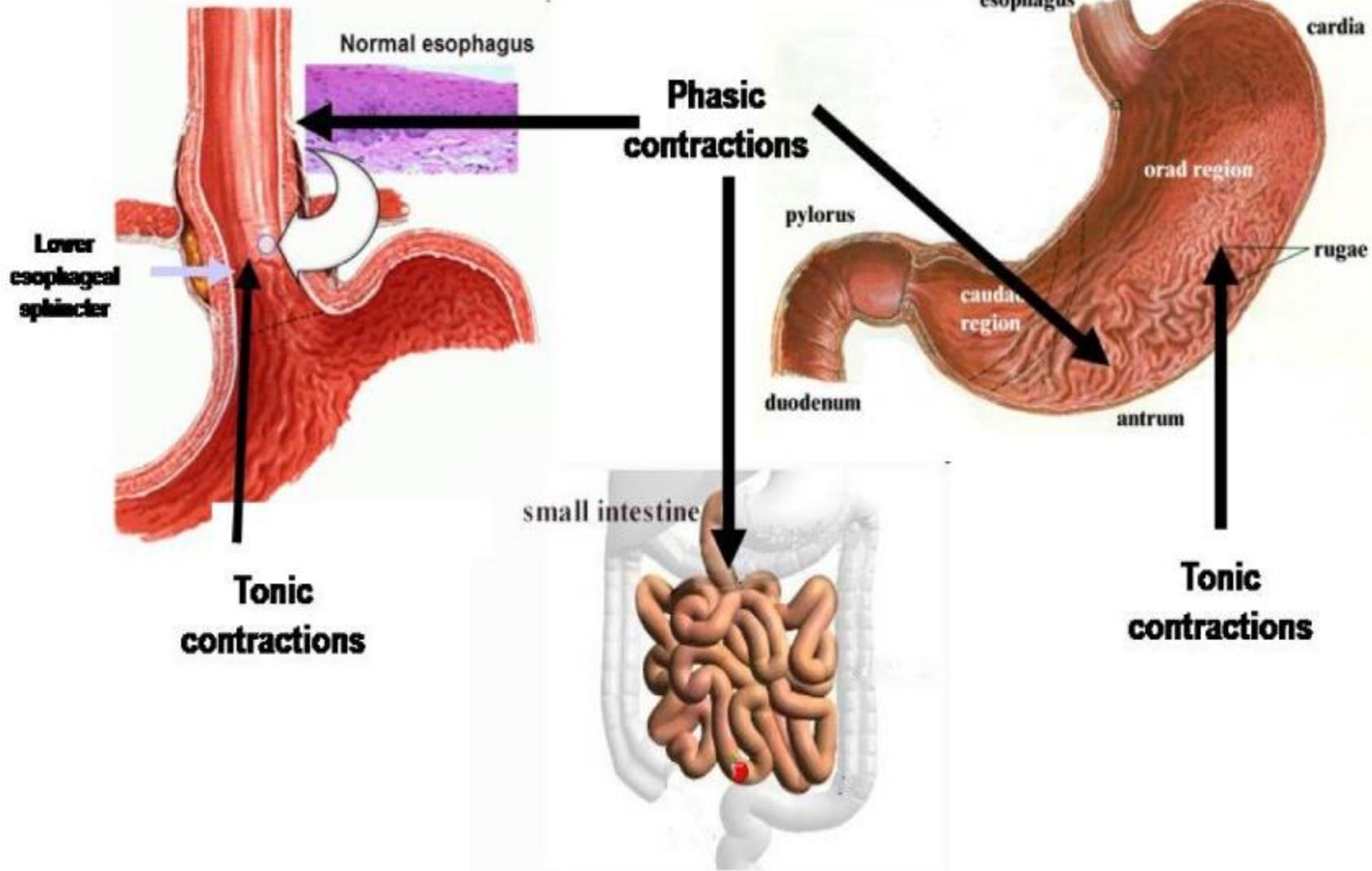
- **Phasic contractions**

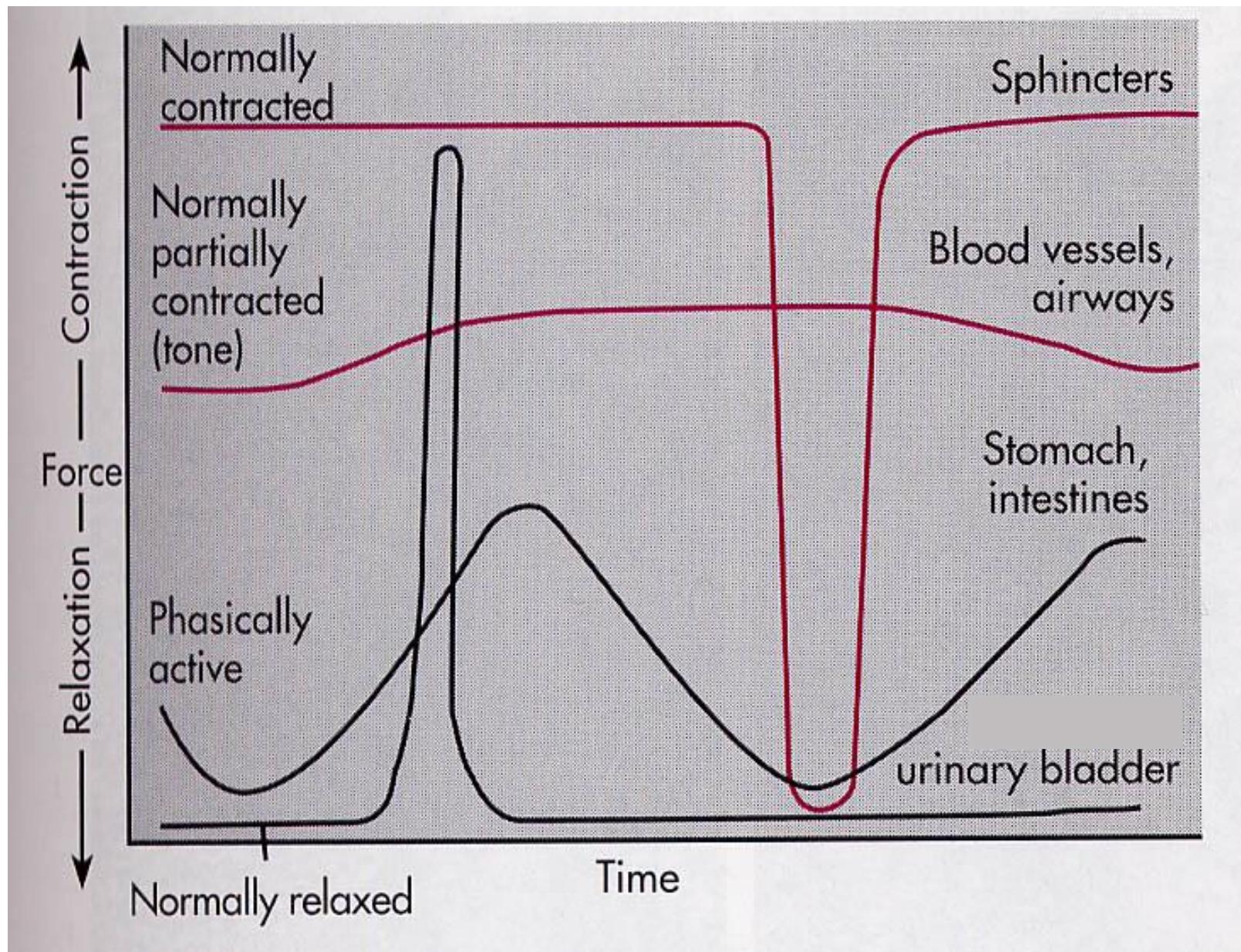
- periodic contractions followed by relaxation evoked by action potentials
- Frequency/number of APs grade the degree and duration of contraction.
- Triggering APs increases strength of contraction
- Dominant in esophagus, gastric antrum, and intestines

- **Tonic contractions**

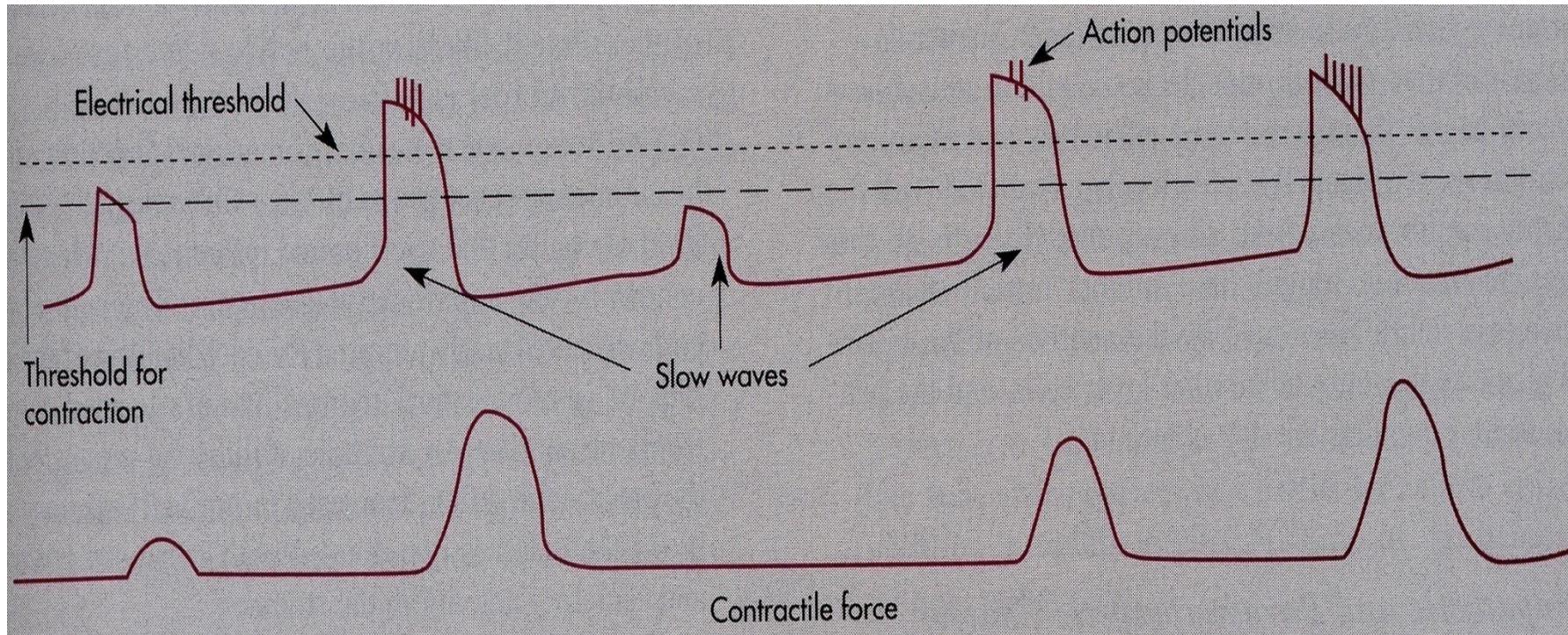
- maintained contraction without relaxation for prolonged periods of time
- in LES, orad region of stomach, ileocecal and internal anal sphincter
- not associated with slow waves

Phasic and Tonic contractions





GI smooth muscle electrophysiology and contraction



Resting membrane potential: -40 to -60 mV.

membrane potential oscillations

Slow waves

- ✓ Pacemaker activity
- ✓ Ionic events during slow waves: Na^+ , and Ca^+ currents
- ✓ Modulation by enteric neurons

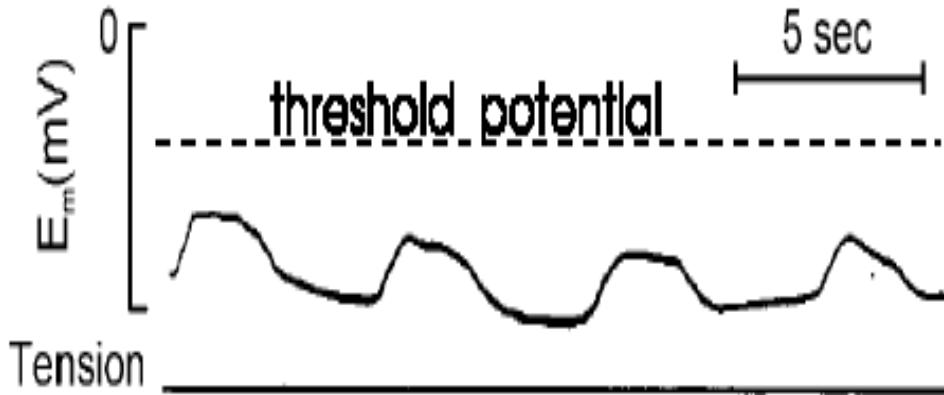
Action potentials = spike potential

- ✓ when slow-waves reach electrical threshold \Rightarrow burst of APs
- ✓ rising phase is carried by Na^+ and Ca^{2+} ions) through calcium-sodium channels, and voltage-gated Ca channels
- ✓ Falling phase(repolarization)is due to K^+ efflux

Slow Waves and Smooth muscle Contraction

- Slow, undulating change in RMP
- Slow Waves are regular changes in smooth muscle V_M .
- **Produced by Interstitial cells of Cajal (pacemaker) =ICC**
- Responsible for triggering AP in GI.
- They do not cause SM contraction unless they reach a threshold and cause action potentials.
 - Exception : may be in stomach?
- They propagate along the GI tract.

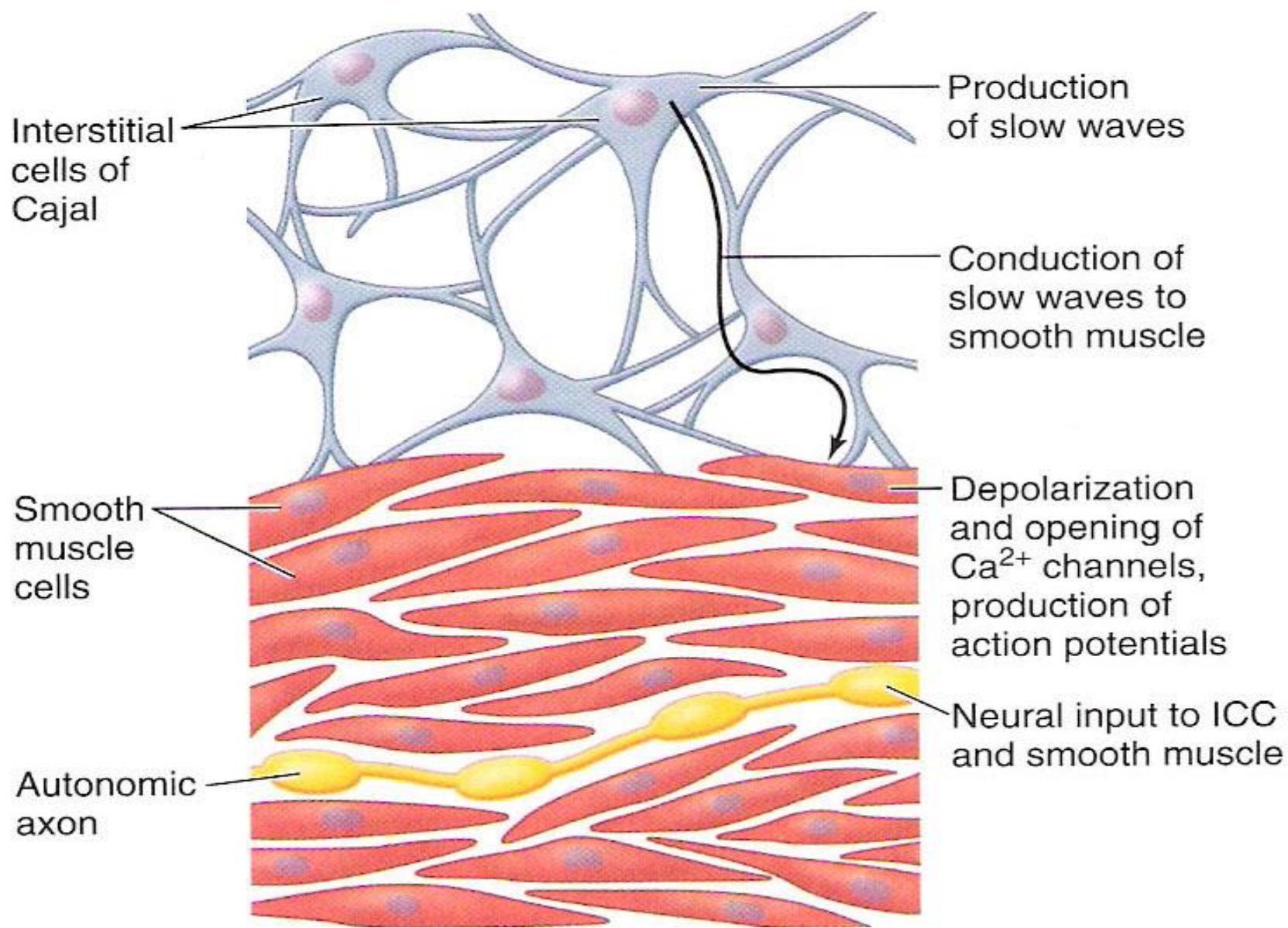
Slow waves without action potentials and contraction



Slow waves with associated action potentials and contraction



Structures



Functions

- Slow waves occur at different frequencies :

- stomach (3 waves/min)
- small intestine (duodenum, 12-18/min)
- ileum & colon (6-10/min)

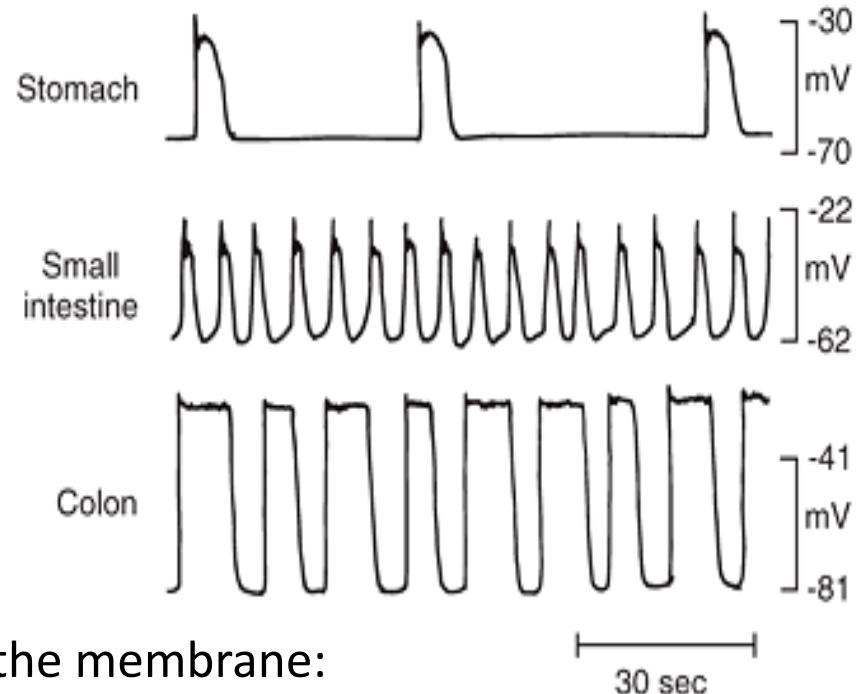
- May or may not be accompanied by AP

- Factors that **depolarize** (↑ excitability) the membrane:

- **Stretching of the muscles**
- **Ach**
- **Parasympathetic stimulation**
- **Hormonal stimulation**

- Factors that **hyperpolarize** (↓ excitability) the membrane:

- Norepinephrine/epinephrine on the fiber membrane
- Sympathetic stimulation



control of GIT function : neural and hormonal

1. Neural Control of GI Function

- Controls contraction, secretion, absorption and blood flow inside the walls of GIT
- GIT has two types of nerve supply:
 - ✓ Enteric or intrinsic nervous system and
 - ✓ Extrinsic or ANS
- **A. Enteric Nervous System** -little 'brain' in the gut
 - semi-autonomous nervous system in the wall of the GIT
 - lies entirely in the wall of the gut, in the esophagus to the anus.
 - major network of ganglia and interconnecting neurons (about 10^8 neurons!)
 - Important in controlling GI motility & secretion
 - Is composed mainly of two plexuses:
 - myenteric plexus (Auerbach's plexus)
 - submucosal plexus (Meissner's plexus)

1. Myenteric /Auerbach's plexus

- Outer plexus
- lies between the longitudinal and circular muscle layers
- controls gastrointestinal motilities
 - ↑ Myenteric/Auerbach's plexus activity ⇒ ↑motility

2. Submucosal/Meissner's plexus

- Inner plexus, which lies in the submucosa
- Function: regulation of GI secretions and local blood flow
 - Submucosal/Meissner's plexus ⇒ ↑secretion and BF
- stimulation by the parasympathetic and sympathetic systems can greatly enhance or inhibit the GI functions

Types of Neurotransmitters Secreted by Enteric Neurons

- Different NTs are released by the nerve endings of enteric neurons.
 - Are mixture of excitatory and inhibitory agents
 - common:
 - *Ach* - most often excites gastrointestinal activity
 - *NE*- almost always inhibits gastrointestinal activity
 - Others are:
 - *ATP, serotonin, CCK, substance P, Bombesin*
 - *dopamine, VIP, somatostatin,*
 - *leu-enkephalin, and met-enkephalin,.*

B. Autonomic Control of the GIT

i. Parasympathetic Innervation

- Stimulation of parasympathetic
 - ↓
- general increase in activity of the ENS
 - ↓
- enhances activity of most GI functions
 - ↑secretion, motility & BF

ii. Sympathetic Innervation

- Stimulation of sympathetic
 - ↓
- inhibits activity of the ENS and local blood flow
 - ↓
- Inhibits GIT activity
 - ↓secretion, motility & BF

Afferent Sensory Nerve Fibers from the Gut

- Many afferent sensory nerve fibers arise from the gut
 - Transmit sensory impulses
 - Sensory nerves can be stimulated by
 1. Irritation of the gut mucosa,
 2. Excessive distention of the gut, or
 3. Presence of specific chemical substances in the gut.
 - Signals transmitted through the fibers can then cause *excitation or, inhibition* of GIT movements or secretion.

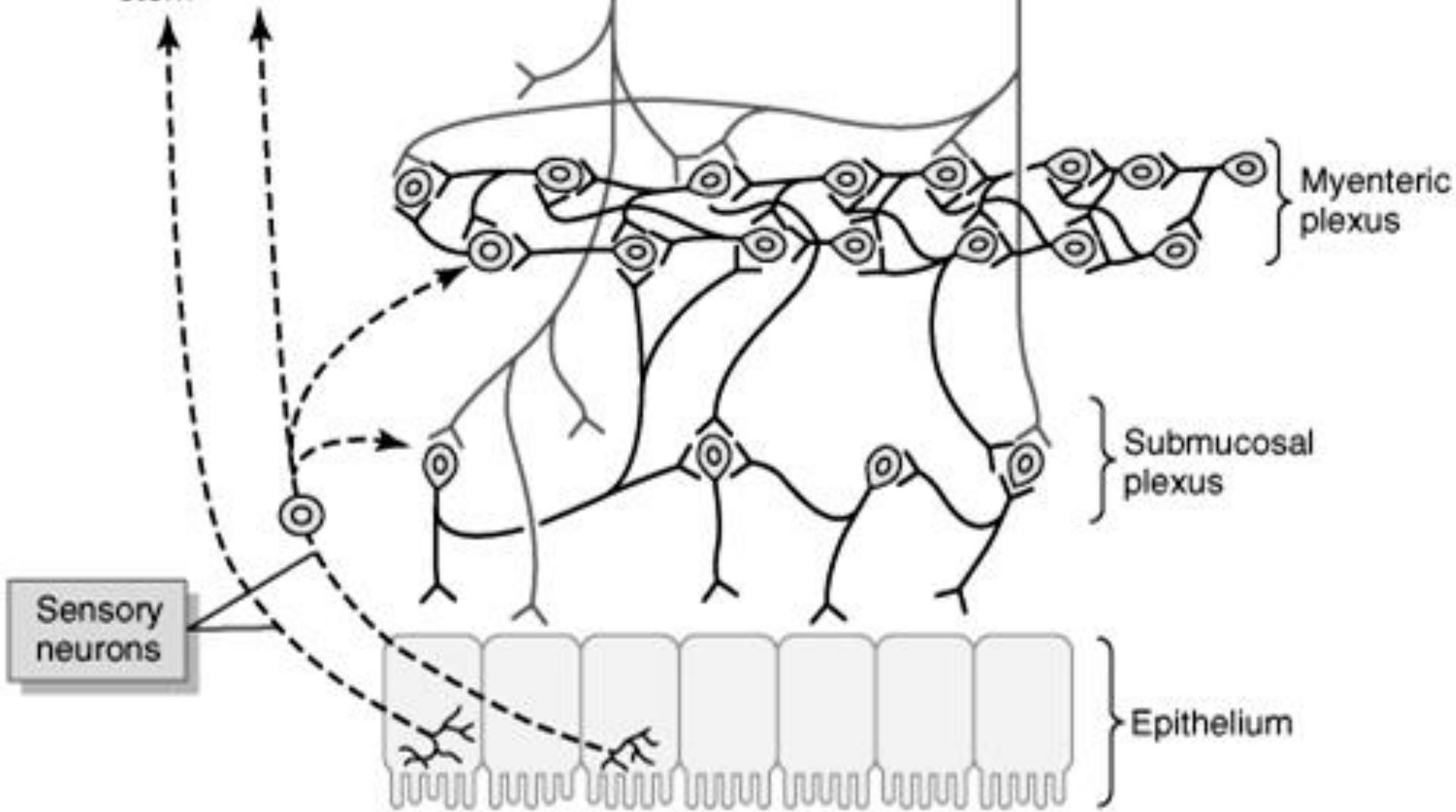
To prevertebral ganglia, spinal cord, and brain stem

Sympathetic

(mainly postganglionic)

Parasympathetic

(preganglionic)



Sensory neurons

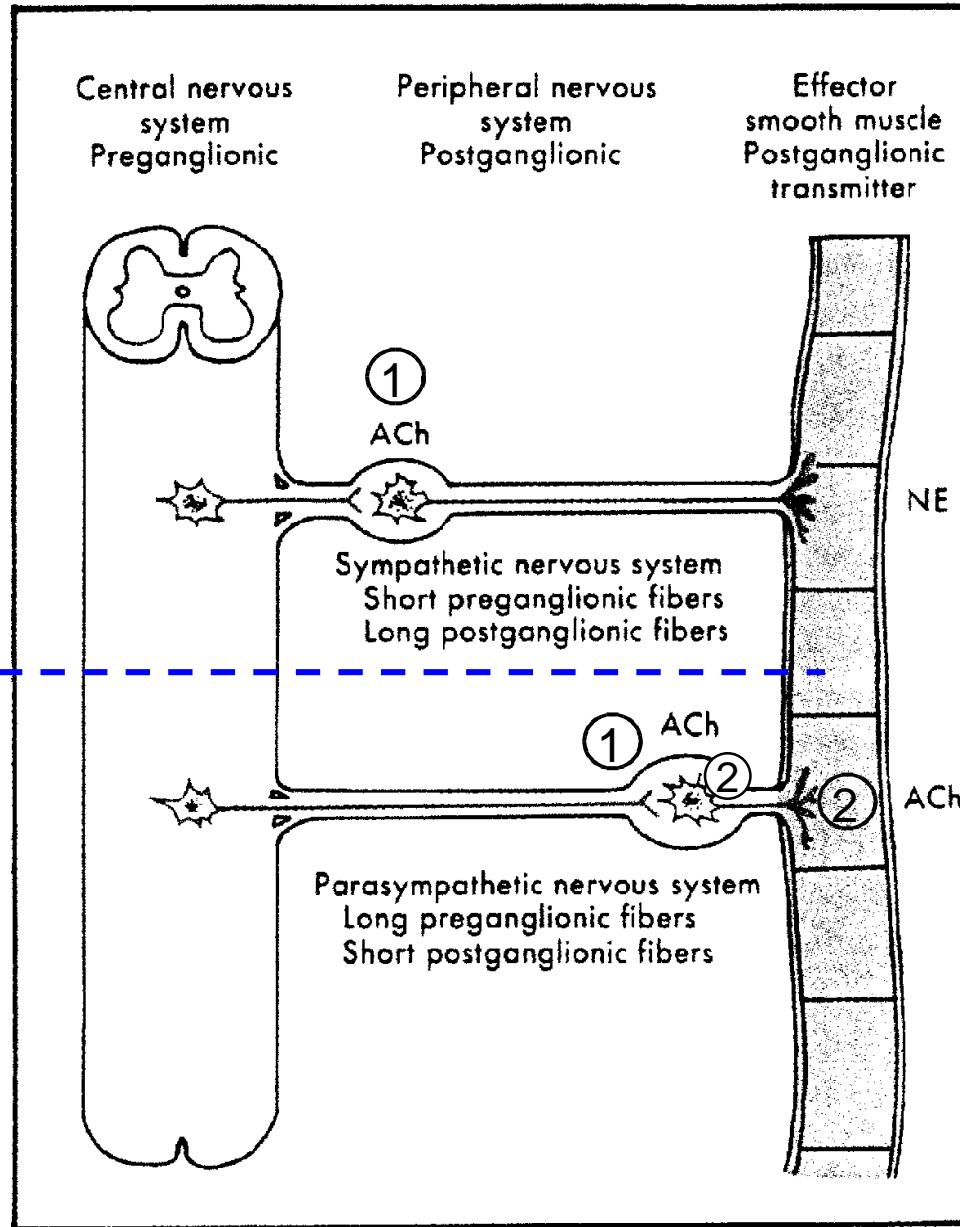
Myenteric plexus

Submucosal plexus

Epithelium

Neurotransmitters of the ANS

sympathetic
parasympathetic



Response of GI organs to ANS

	Parasympathetic Response	Sympathetic Response
Salivary secretion	Profuse watery secretion	Thick viscid secretion (α_1 receptors), Amylase secretion (β -receptors)
GI Motility	Increases	Decreases
Sphincter tone	Relaxation	Contraction
GI secretion	Stimulation	Inhibition
Gall bladder & ducts	Contraction	Relaxation
Liver	-----	Glycogenolysis
Pancreas: Acini : Islets	<p>↑ secretion of pancreatic juice</p> <p>↑ insulin & glucagon secretion</p>	<p>↓ Secretion pancreatic juice</p> <p>↓ insulin & glucagon Secretion (α_2 receptors)</p> <p>↑insulin & glucagon Secretion (β)</p>

Gastrointestinal Reflexes

- The anatomical arrangements of the ENS and its connections with the ANS support **three types of GIT reflexes**
- essential to gastrointestinal control
- The 3 types of reflexes are:
 - i. Reflexes integrated entirely within the gut wall ENS
 - ii. Reflexes from gut to prevertebral sympathetic ganglia & then back to GIT
 - iii. Reflexes from gut to spinal cord or brain stem & then back to GIT

i. **Reflexes integrated entirely within the gut wall Enteric nervous system.**

-Reflexes that control:

- much of the GI secretion
- Peristalsis
- Mixing contractions

-Local inhibitory Reflexes

ii. **Reflexes from gut to prevertebral sympathetic ganglia & then back to GIT**

- Transmit signals long distances from one to the other areas of GIT
 - signals from the stomach to cause evacuation of the colon
 - **Gastro colic Reflexes**
 - signals from the colon and small intestine to inhibit stomach motility and stomach secretion
 - **Enterogastric Reflexes**
 - reflexes from the colon to inhibit emptying of ileal contents into the colon
 - **Colonoileal Reflexes**

iii. Reflexes from gut to spinal cord or brain stem & then back to GIT

- Include:
 - Reflexes from stomach & duodenum to brainstem and back to stomach by way of vagus nerve
 - control Gastric motor & secretary activity
 - Defecation reflexes
 - travel from colon & rectum to spinal cord & back again to produce the powerful colonic and rectal contractions
 - defecation



2. Hormonal Control of GI function

important hormones are:

- Gastrin,
- Cholecystokinin,
- Secretin,
- Gastric inhibitory peptide,
- Motilin

Gastrin

- secreted from G cells of the antrum of the stomach
- Stimulus for gastrin secretion:
 - Distention of the stomach
 - Protein products
 - Gastric releasing peptide released by the nerves of the gastric mucosa during vagal stimulation.
- Action:-
 - Stimulation of Gastric acid secretion
 - stimulation of growth of the gastric mucosa

CCK(Cholecystokinin)

- Secreted from I cells in duodenum & Jejunum
- Stimulus:-fat, fatty acids, monoglycerides, proteins in the small intestine
- Action:-
 - gallbladder contraction, increased enzyme rich pancreatic secretion
 - moderate inhibition of stomach contractility

Secretin : secreted from S cells of duodenum + jejunum

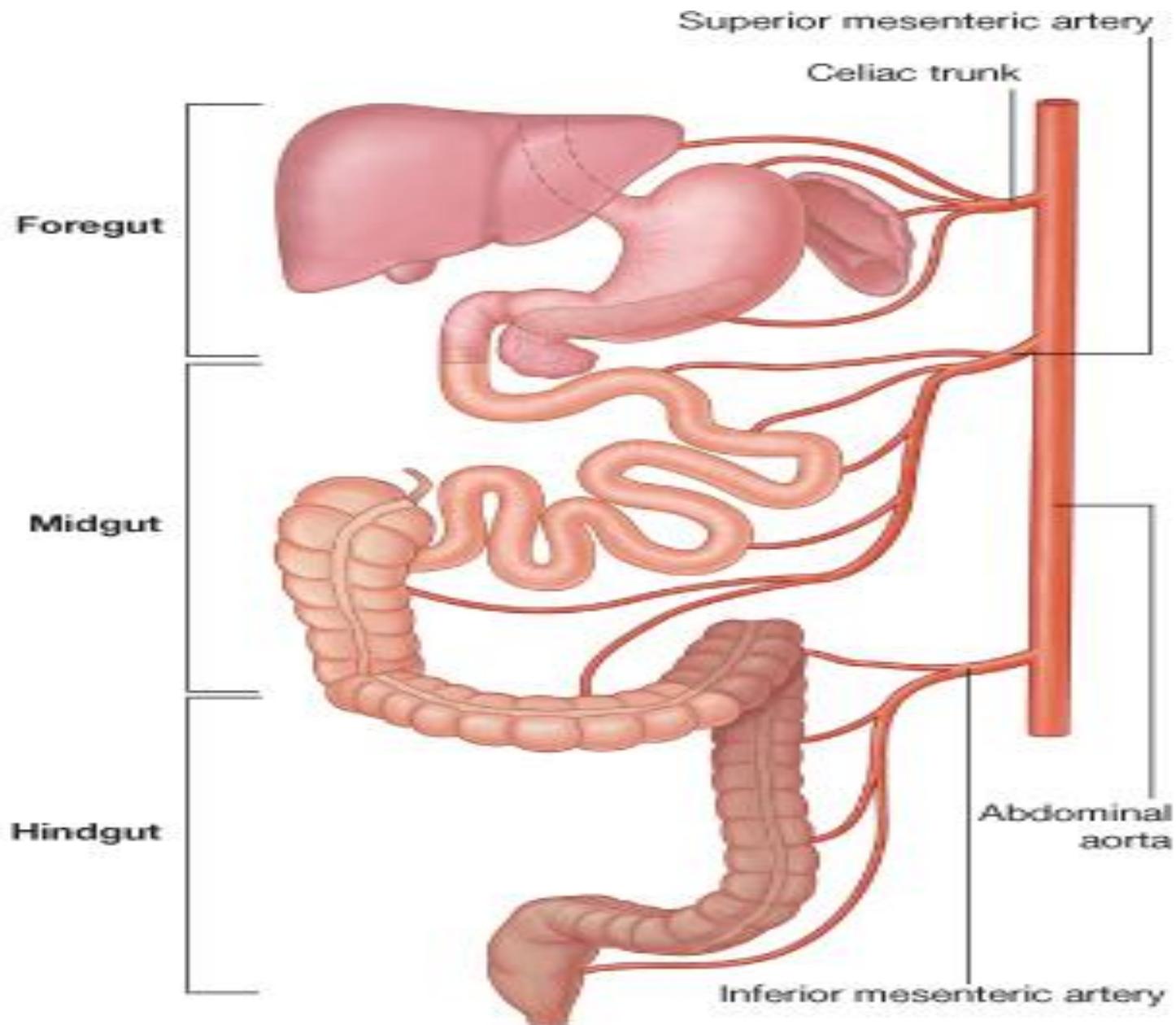
- Stimulus: acidic chyme
- Action: increased alkaline pancreatic juice secretion

Hormones	Secretary Cells & sites	Stimulus	Action
Gastrin	G-cells (Antrum of stomach)	-stomach distention -Protein -GRP	-stimulates : ✓ HCl secretion ✓ growth of gastric mucosa
CCK	I cells (in duodenum, jejunum)	Fat, fatty acids, monoglycerides, protein	✓ Gallbladder contraction ✓ Increased enzyme rich pancreatic secretion ✓ moderate inhibition of gastric motility
Secretin	S cells (duodenum, jejunum)	Acidic Gastric juice	✓ ↑ alkaline pancreatic juice ✓ Poor effect in motility
GIP	Mucosa of upper Small intestine	Fatty acids, amino acids	✓ ↓ stomach motor act
Motilin	Upper duodenum	During Fasting	✓ ↑ GI motility ✓ interdigestive myoelectric complexes(every 90 minutes) in fasted person.

Gastrointestinal Blood Flow

- The blood vessels of the GIT are part of a more extensive system called the **splanchnic circulation**.
- Includes:
 - the blood flow through the gut itself
 - blood flows through the spleen, pancreas, and liver.
- **The arterial blood supply to the gut is by:**
 - **celiac artery** to the stomach, liver, pancreas, spleen... = **foregut**
 - **superior mesenteric artery** mostly to small intestine, part of large intestine
 - **inferior mesenteric artery** to large intestines = **hindgut**

Blood supply to GIT

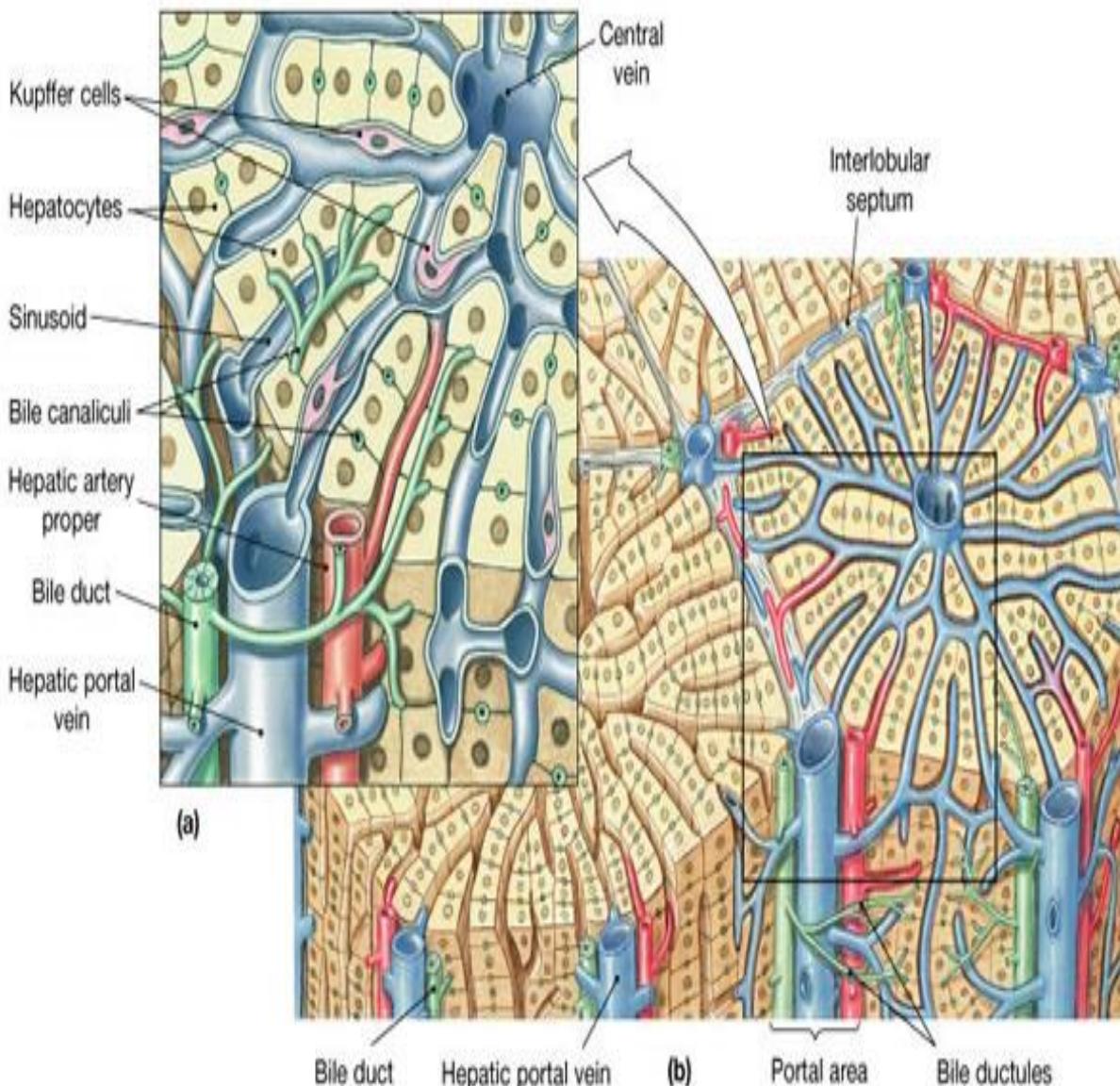


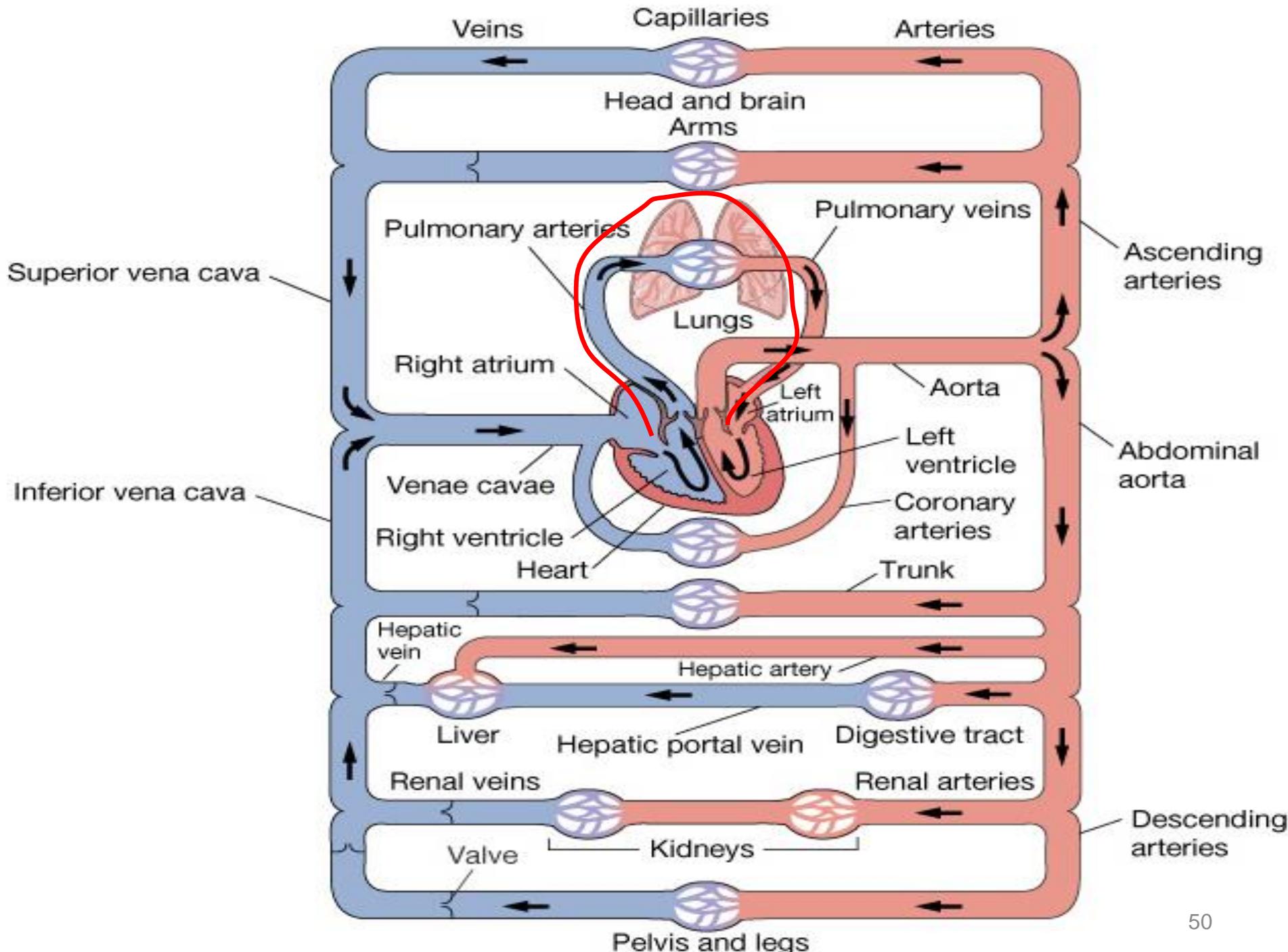
Hepatic circulation

- the blood that courses thro into the liver by way of the
- In the liver, passes through*
- by way of **hepatic veins** into

Functions of Hepatic circulation:

- Allows the liver sinusoids that might enter the bld
- Prevent transport of p
 - By Kupffer cells t
- ❖ Hence, liver serves as
- Collects nutrient-rich ve
- Delivers this blood to th





Four major digestive Functions of the GIT

A. Motility: Movement of food through the GI tract

- Peristalsis:
 - Rhythmic wave-like contractions that move food through GIT
- Segmentation
 - Rhythmic wave-like contractions that mix the food with GI secretions
- Involved in :
 - Mastication: Chewing the food and mixing it with saliva
 - Deglutition: Swallowing the food

B. Secretion and its regulation

C. Digestion

D. Absorption

A. GIT motility and its regulation

- *Functional Types of Movements in the GIT:*

1. Propulsive movements

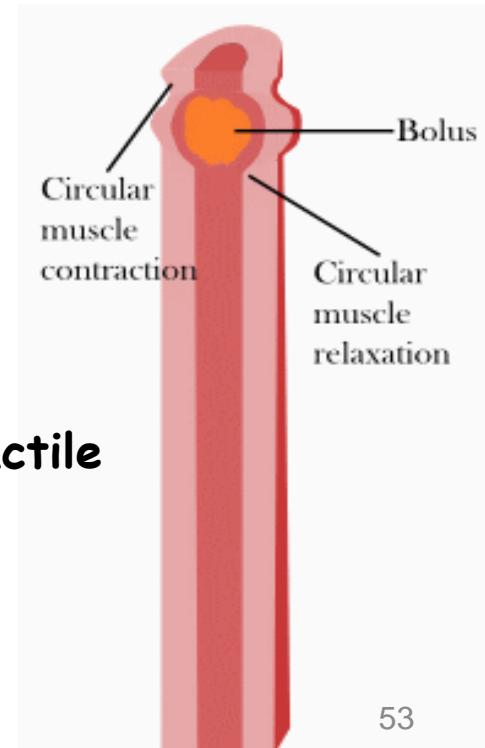
✓ peristalsis

2. Mixing movements

✓ segmentation

1. Propulsive Movements

- Peristalsis is an inherent property of GIT smooth muscles
- causes food to move forward along the tract at an appropriate rate to accommodate digestion & absorption
- The usual stimulus for intestinal peristalsis is **distention of the gut**
 - Distention of the gut due to accumulation of food
 - ↓
 - stretching of the gut wall
 - ↓
 - stimulation of the enteric nervous system
 - ↓
 - contraction of the gut wall 2 to 3 cm behind contractile ring and relaxation in front of the bolus.



2. Mixing Movements – mix the food with the GI content

- Differ in different parts of the alimentary tract
 - In some areas, the peristaltic contractions themselves cause most of the mixing.
 - At other areas local intermittent constrictive contractions occur every few cms in the gut wall.

Propulsion and Mixing of Food in the GIT

✓ **Ingestion of Food** - taking in food into mouth

- The amount of food ingested is determined by *hunger*.
- The type of food that a person preferentially *seeks* is determined by *appetite*.
- two areas in the hypothalamus are important for controlling appetite:
 - The "**satiety center**" is located in the ventromedial nucleus (VMN)
 - stimulation of this center elicits sensations of satiety
 - lesion of the center causes continuous eating
 - The "**hunger (feeding) center**" is in the lateral hypothalamic area (LHA)
 - stimulation of the LHA elicits a desire to eat
 - lesion causes a complete and long-lasting loss of hunger
- A Long-Term Factor That Suppresses Appetite
 - a hormone secreted by adipocytes



✓ Mastication (Chewing)

- ↑surface area of food particles for digestive enzymes
 - the rate of digestion is absolutely dependent on the total surface area exposed to the digestive secretions.
- prevents excoriation of the GIT and increases the ease with which food is emptied
- After adequate mastication and mixing with salivary juice the food content is swallowed through the esophagus

Esophagus and its motility

Esophagus is a tubular conduit (about 20 cm long) for food transport from mouth to stomach.

Structural and regulatory aspects:

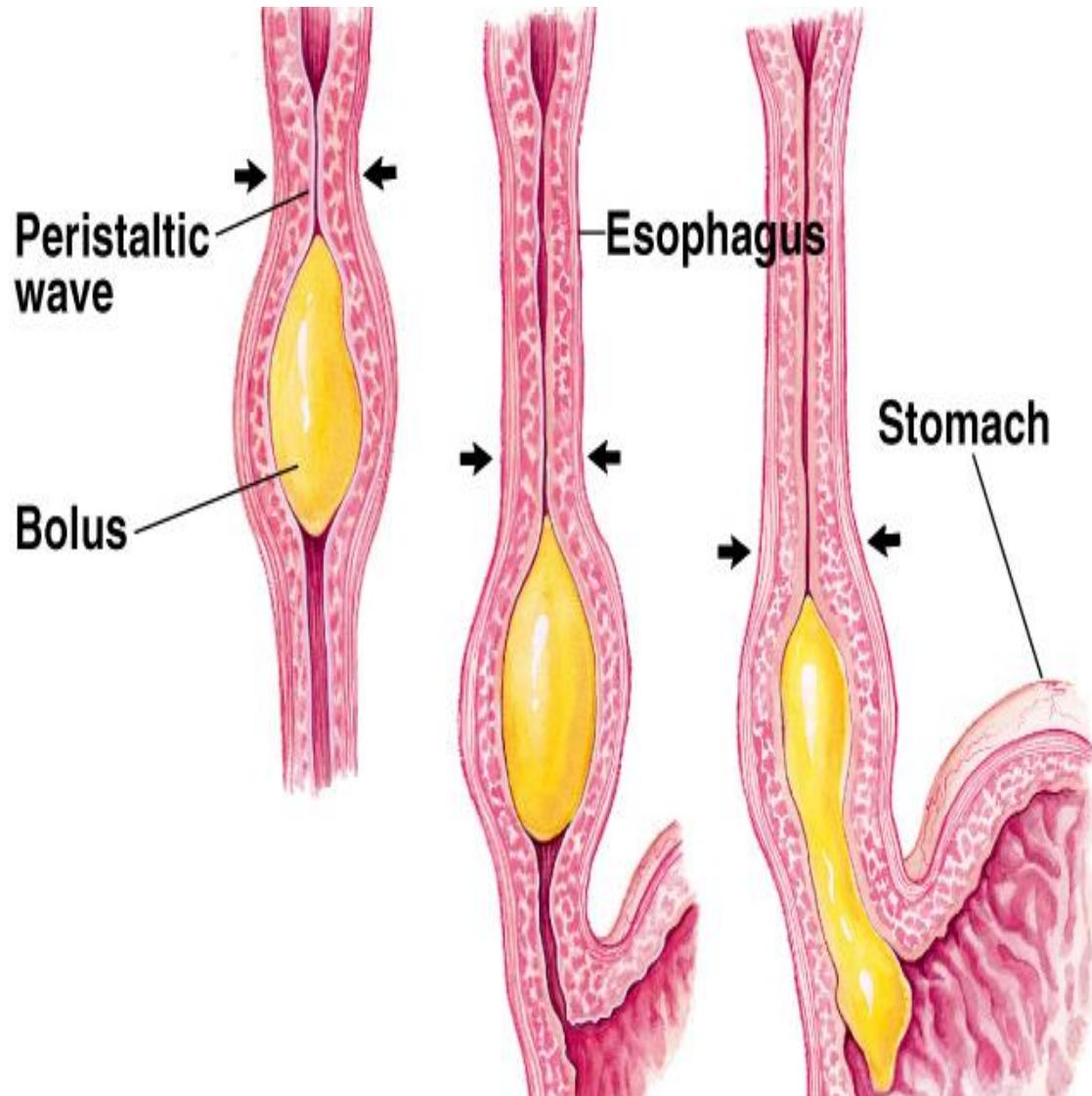
- **Upper third of the esophagus:** circular and longitudinal muscle layers are skeletal;
 - ✓ innervation via somatic nerves
- **Middle third:** coexistence of skeletal and smooth muscles
 - ✓ Primary innervation from vagus nerve
 - ✓ nerve input from neurons of myenteric plexus
- **Lower third:** smooth muscle,
 - ✓ enteric nerve system
 - ✓ vagal input to enteric nerve system

- **Peristalsis:**

- Produced by a series of localized reflexes in response to distention of wall by bolus.

- Wave-like muscular contractions:

- Circular smooth muscle contract behind, relaxes in front of the bolus.
 - Followed by longitudinal contraction (shortening) of smooth muscle.
 - Rate of 2-4 cm/sec.
 - After food passes into stomach, LES constricts.



• Swallowing (Deglutition)

- ✓ is a reflex response
- ✓ triggered by afferent impulses in **trigeminal, glossopharyngeal, and vagus nerves**



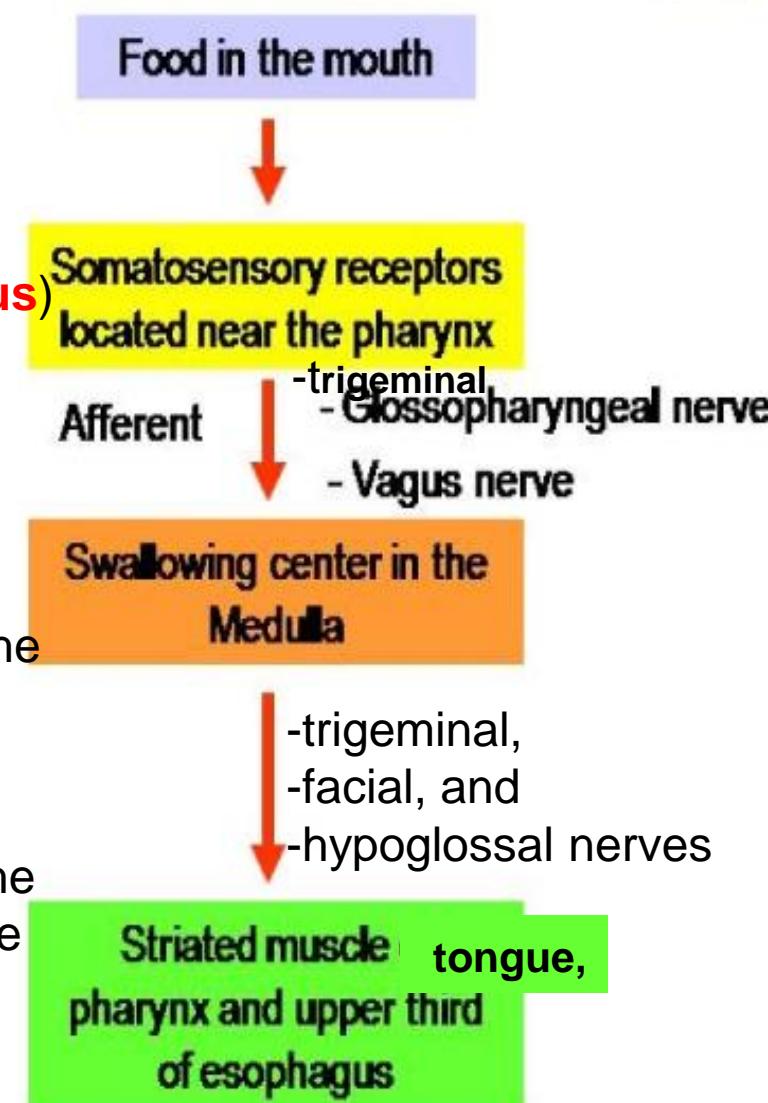
- ✓ These impulses are integrated in MEDULLA (**nucleus of tractus solitarius & nucleus ambiguus**)

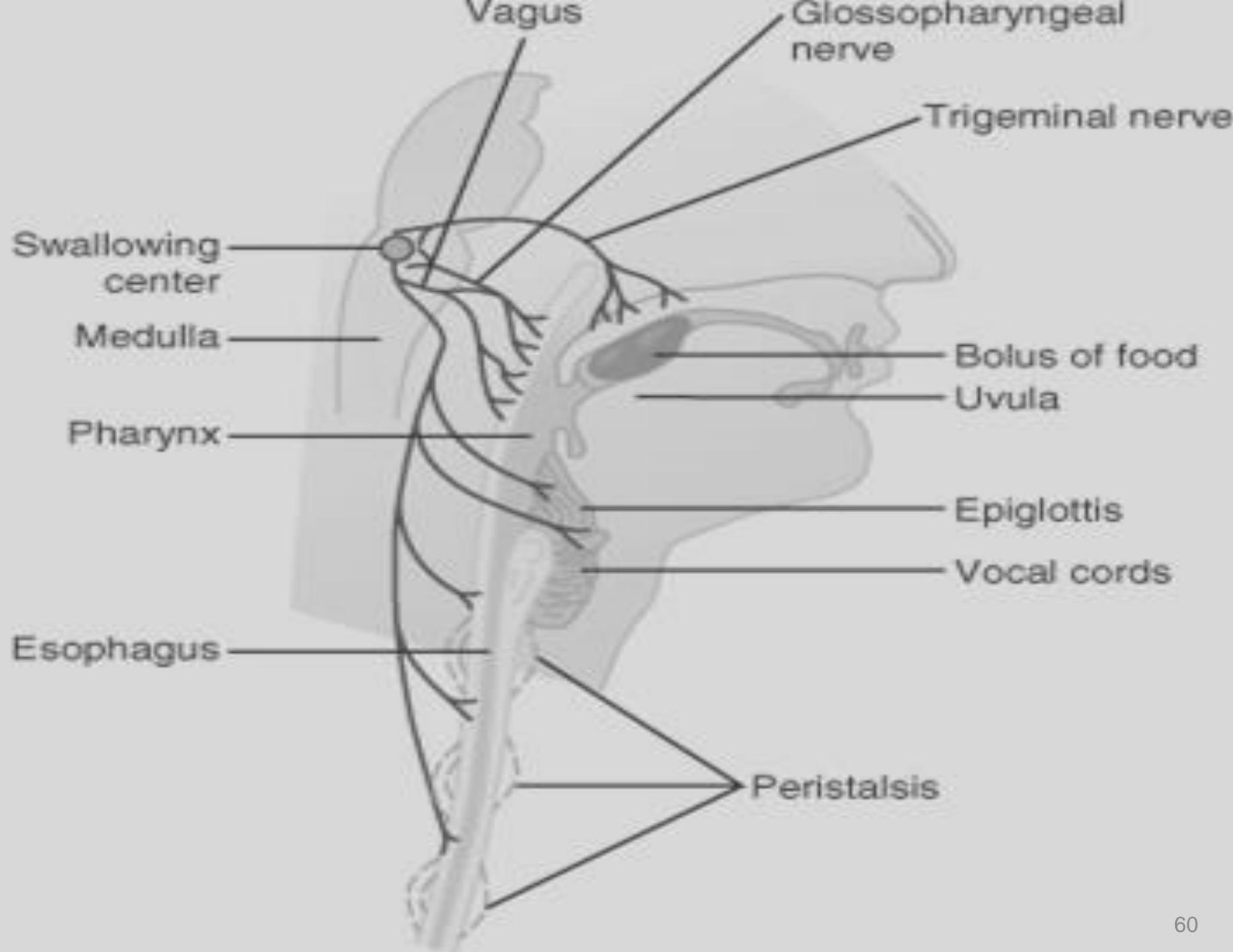


The efferent fibers pass to the pharyngeal musculature, tongue and upper esophagus via the **trigeminal, facial, and hypoglossal nerves**.

- ✓ it is initiated by the voluntary action of collecting the oral contents on the tongue and propelling them backward into the pharynx.

- ✓ This causes a wave of involuntary contraction in the pharyngeal muscles that pushes the material into the esophagus





Swallowing (Deglutition)

- swallowing can be divided into 3 stages:

1. **voluntary stage** - initiates the swallowing process;

- When the food is ready for swallowing,
 - ↓
- it is “voluntarily” rolled posteriorly into the pharynx by pressure of the tongue upward and backward against the palate

2. **pharyngeal stage** - involuntary

- constitutes passage of food through the pharynx into the esophagus
- the bolus enters the pharynx → stimulates epithelial swallowing receptors → impulses pass(via CN-5, 9 & 10) to the brain stem to initiate a series of automatic pharyngeal muscle contractions

3. **Esophageal stage** - involuntary phase

- transports food from the esophagus to the stomach.

Paralysis of Swallowing Mechanism

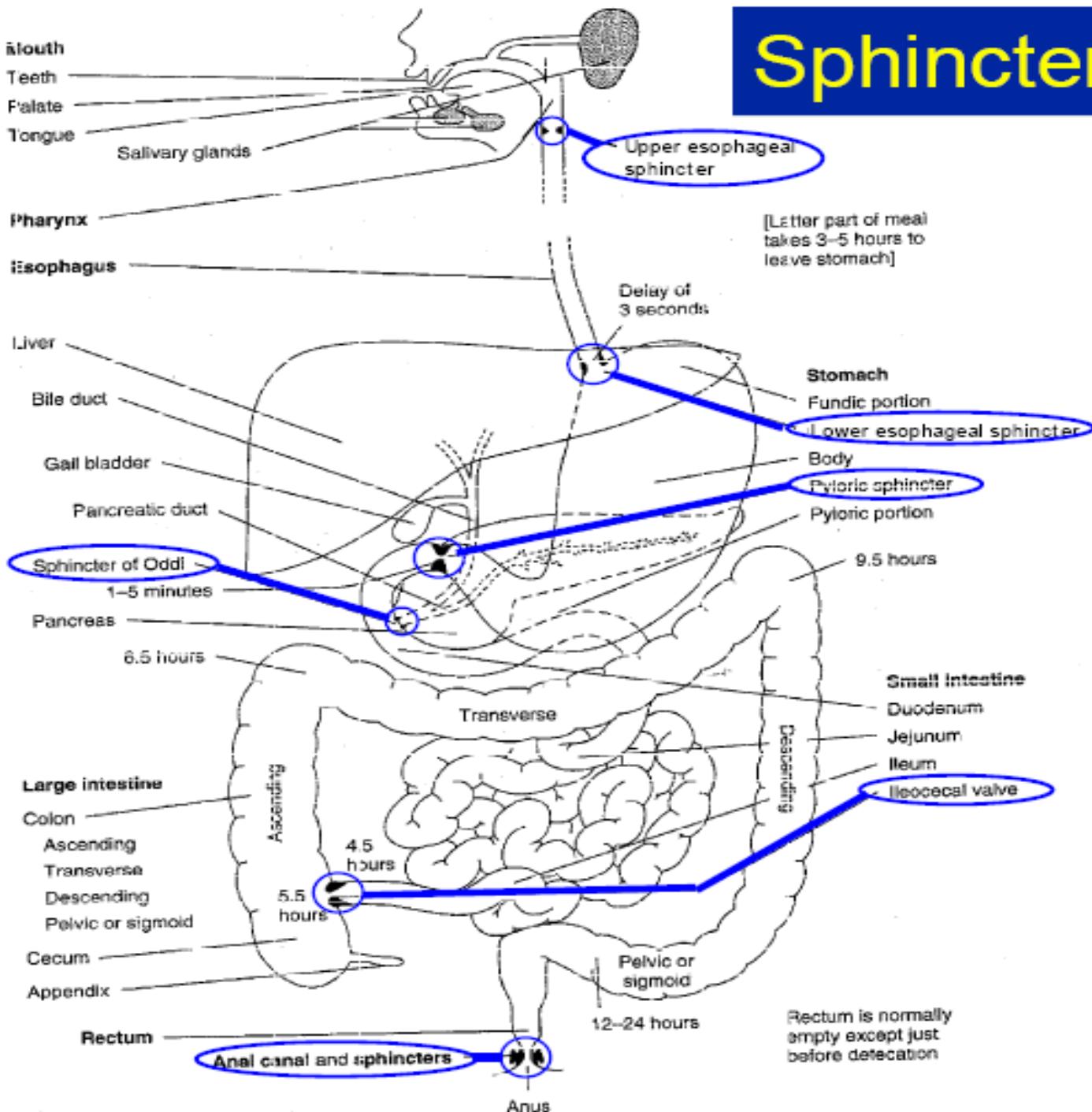
- **Dysphagia** is defined as difficulty in swallowing
 - ✓ Damage to the 5th, 9th, or 10th cranial nerves can cause paralysis of significant portions of the swallowing mechanism.
 - ✓ *Poliomyelitis* or *encephalitis* can prevent normal swallowing by damaging swallowing center in the brain stem
 - ✓ Paralysis of swallowing muscles by:
 - *Muscle dystrophy* or *myasthenia gravis* or *botulism*
 - ↓
 - ↓
 - ↓
 - Swallowing mechanism is partially or totally paralyzed
 - Complete abrogation of the swallowing act → swallowing cannot occur

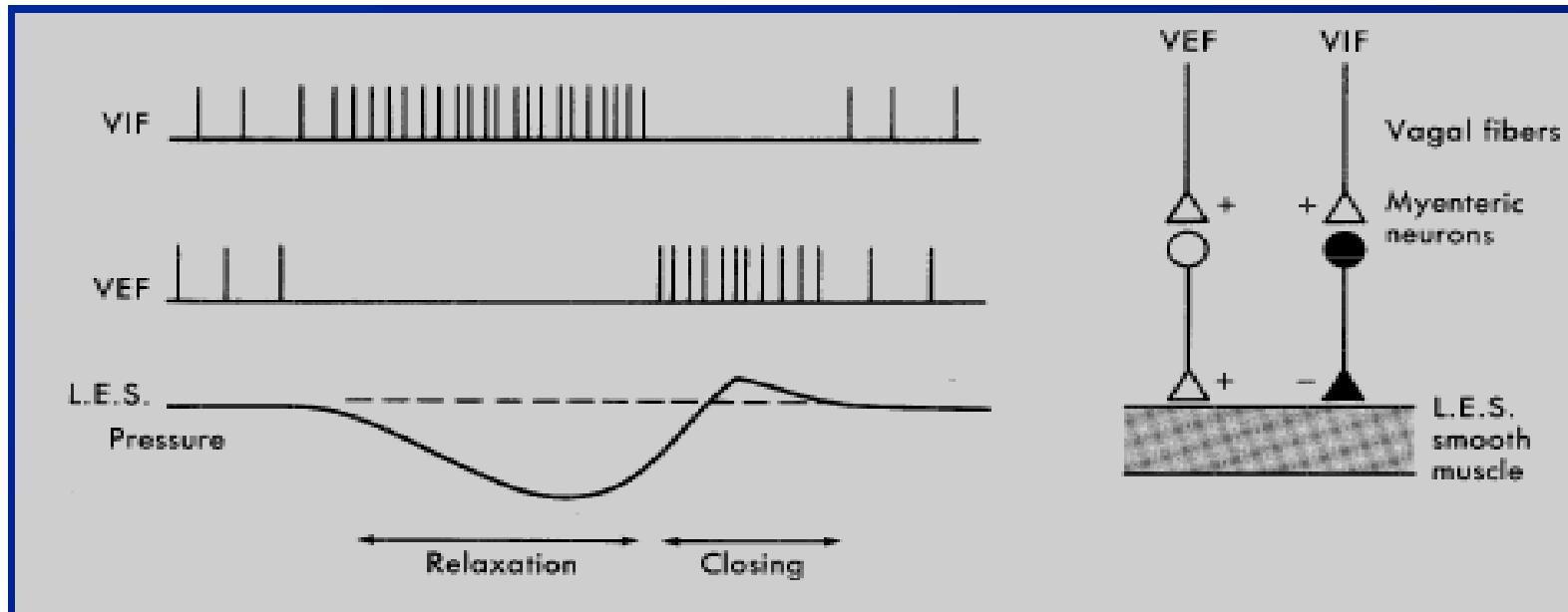
- sphincters prevent back flow of GI content

7 sphincters along the GIT:

1. Esophageal sphincter/*pharyngoesophageal sphincter*
2. Gastroesophageal sphincter,
3. Pyloric sphincter ,
4. Sphincter of Oddi,
 - ✓ regulate the flow of pancreatic secretion and bile to duodenum
5. Ileocecal sphincter,
 - ✓ b/n ileum and cecum & prevent back flow from cecum to ileum
6. External anal sphincter
7. Internal anal sphincter

Sphincters





Esophageal sphincters

- **Upper esophageal sphincter (UES):** prevents entry of air
- **Lower esophageal sphincter (LES):** LES = zone of elevated resting pressure (~ 30 mm Hg)
 - ✓ prevents reflux of corrosive acidic stomach content.
 - ✓ LES tone is regulated by extrinsic and intrinsic nerves, hormones and neuromodulators.
 - ✓ **Contraction:** vagal cholinergic nerves and sympathetic nerves (α -adrenergic).
 - ✓ **Relaxation:** inhibitory vagal nerve input to circular muscle of LES (neurotransmitters (VIP and NO) and reduced activity of vagal excitatory cholinergic fibers

Function of the lower esophageal sphincter

Or Gastro esophageal Sphincter.

- The stomach secretions are highly acidic and contain many proteolytic enzymes.
- The esophageal mucosa, except in the lower one eighth of the esophagus, is not capable of resisting the digestive action of gastric secretions.
- The tonic constriction of the LES helps to prevent significant reflux of stomach contents into the esophagus except under very abnormal conditions

Pyrosis (heartburn/esophagitis)—common esophageal discomfort

- Result of regurgitation or reflux of gastric content into lower esophagus \Leftrightarrow Acid reflux can cause esophagitis
- Mainly due to incompetence of the LES



- allows return of stomach contents into esophagus

This is called *Gastroesophageal reflux disease(GERD)*

Clinical manifestation consist of
dysphagia, heart burn, regurgitation of sour brash, hematemesis or melena

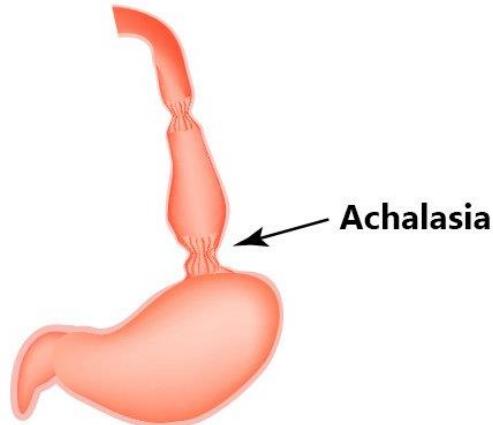
Consequences include

- ✓ **Bleeding**
- ✓ **Stricture**
- ✓ Tendency to develop **Barrett esophagus** - a complication of longstanding GERD Chara by replacement of the distal esophageal mucosa by metaplastic columnar epithelium as a response to prolonged injury (\uparrow risk of adenocarcinoma by 30-40 fold)

fig. esophagitis: inflammation of the lower part of esophagus



Achalasia



- ✓ Occurs when LES fails to relax during swallowing
 - ↓
- ✓ Food swallowed into esophagus fails to pass from esophagus into stomach.
- ✓ Due to damage in the neural network of the myenteric plexus in the lower two thirds of the esophagus
 - ↓
- ✓ myenteric plexus has lost its ability to transmit a signal to cause "receptive relaxation" of GES as food approaches the sphincter
 - ↓
- ✓ Musculature of the lower esophagus remains spastically contracted
This is called achalasia

✓ When achalasia becomes severe



esophagus becomes tremendously enlarged (can hold 1L of food)



infected during the long periods of esophageal stasis



→ The infection may cause ulceration of esophageal mucosa, sometimes leading to severe substernal pain, esophageal rupture and death

- The classic clinical symptom of achalasia is **progressive dysphagia**
 - Regurgitation and aspiration may occur ⇒ *aspirational pneumonia*
 - In about 5%, possibility of developing **SCC**
- Treatment:
 - Stretching the LES
 - antispasmodic drugs

Esophageal varices

- are extremely dilated sub-mucosal veins in the lower third of the esophagus due to portal hypertension
- The increased pressure in the esophageal plexus produces dilated tortuous vessels called varices

Varices develop in 90% of cirrhotic patients and are most often associated with alcoholic cirrhosis

Variceal rupture produces massive hemorrhage

Clinically varices produce no symptoms until they rupture

1 Lower oesophagus

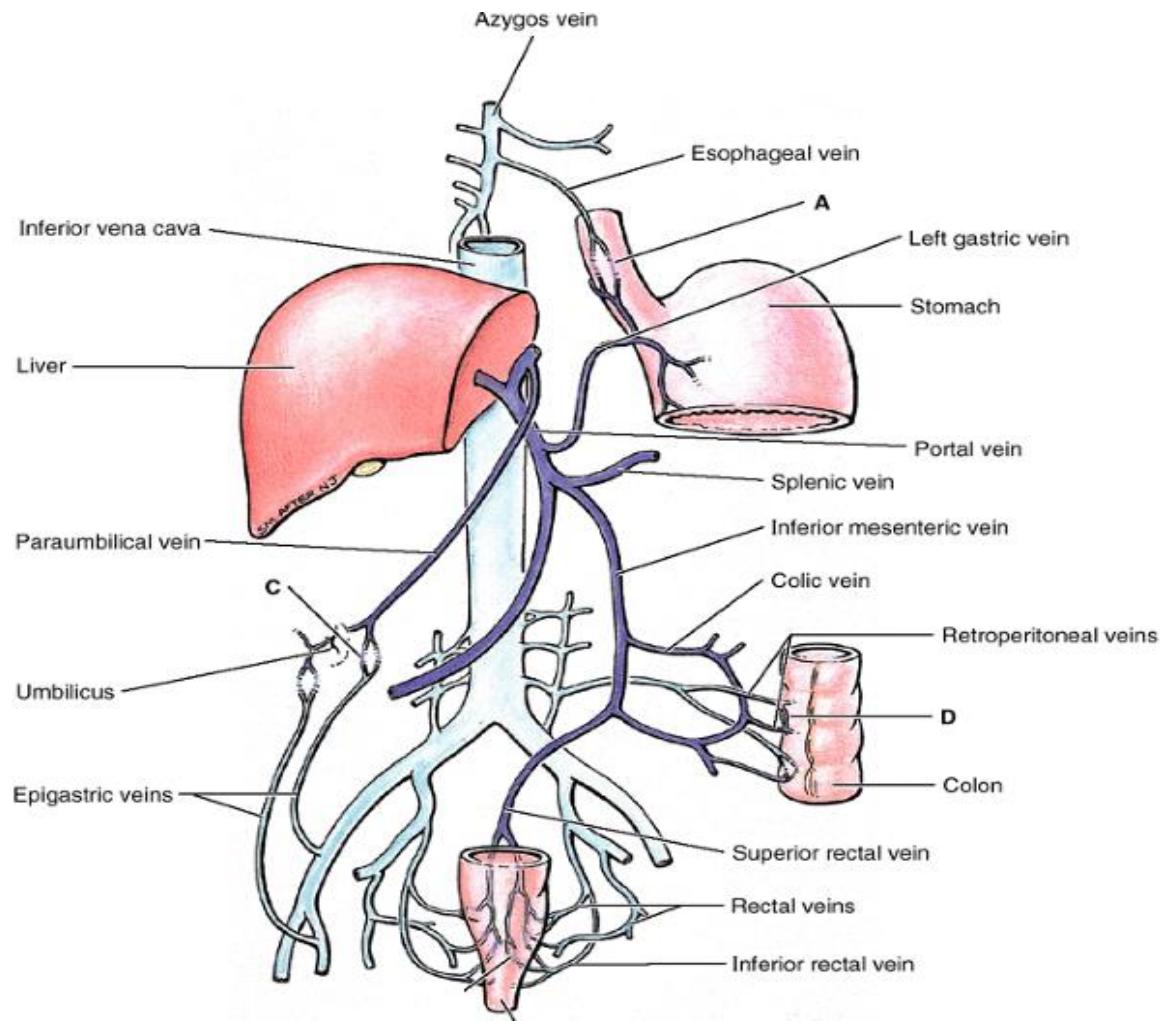
Portal: Oesophageal branches of left gastric veins
Systemic: Azygos veins

2 Upper anal canal

Portal: Superior rectal vein
Systemic: Middle/inferior rectal veins

3 Umbilical

Portal: Veins of ligamentum teres
Systemic: Superior/inferior epigastric veins



GASTRO-ESOPHAGEAL VARICES

- Are dilated veins in distal esophagus or proximal stomach due to elevated portal venous system pressure
- The second most common cause of UGIB
- About one-third of patients with histologically confirmed cirrhosis have varices.
- ~ 5–15% of cirrhotics per year develop varices,
- It is estimated that the majority of patients with cirrhosis will develop varices over their lifetimes.
 - ***90% of cirrhotic*** develop esophageal varices ultimately
- Roughly one-third of patients with varices will develop bleeding.
- ***MR is about 25% & repeated bleeding is 70%***

- Several factors predict the risk of bleeding,
 - **the severity of cirrhosis (Child's class, MELD score);**
 - the height of wedged-hepatic vein pressure;
 - **the size of the varix;**
 - the location of the varix ((IGV1 > GOV2 > GOV1)
 - certain endoscopic stigmata,: **red wale signs**, white-nipple spots...
 - **Patients with tense ascites are also at increased risk for bleeding**
- If untreated, recurrent VH occurs in 60% of patients,
 - usually within 1-2 years of index hemorrhage.
- Factors associated with poor outcomes in VH are the presence of :
 - Degree of decomponsation , bacterial infections and an HVPG >20 mm Hg

- **Sarin's classification GOV**
 - GOV1: EV extending below cardia into lesser curvature (75% of GV).
 - GOV2: extending into the fundus.
 - Isolated GV type 1(IGV1): located in the fundus (IGV1).
 - Isolated GV type 2 (IGV2):located elsewhere in stomach,
 - Extremely infrequent in patients with cirrhosis.
- GOV2 and IGV1 are aka “cardiofundal varices.”

Motor Functions of the Stomach

1. **Storage** of large quantities of food until the food is processed in the stomach and intestine
 - ✓ The stomach can progressively distend to accommodate 0.8 -1.5 L
2. **Mixing** of this food with gastric secretions until it forms a *chyme*
3. **Slow emptying** of the chyme into the small intestine at a suitable rate

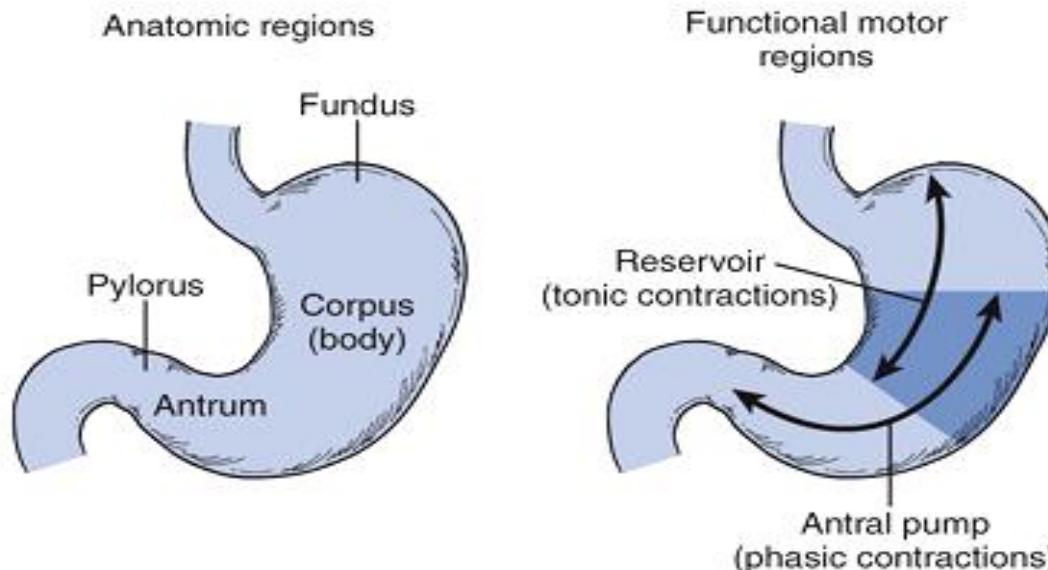
Gastric motility controls these function of stomach

Anatomically stomach is divided into 3 major parts:

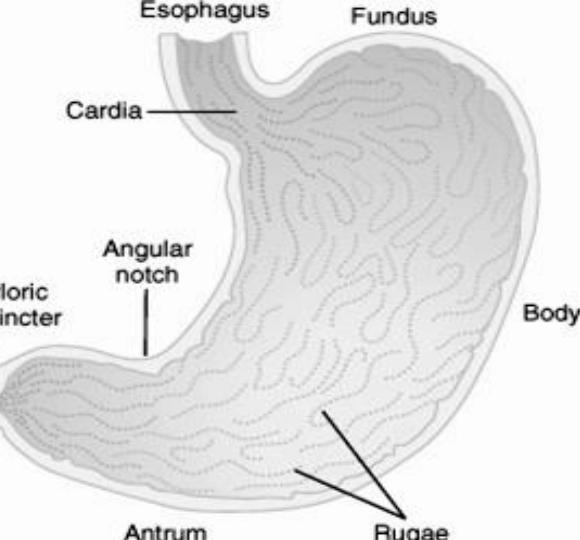
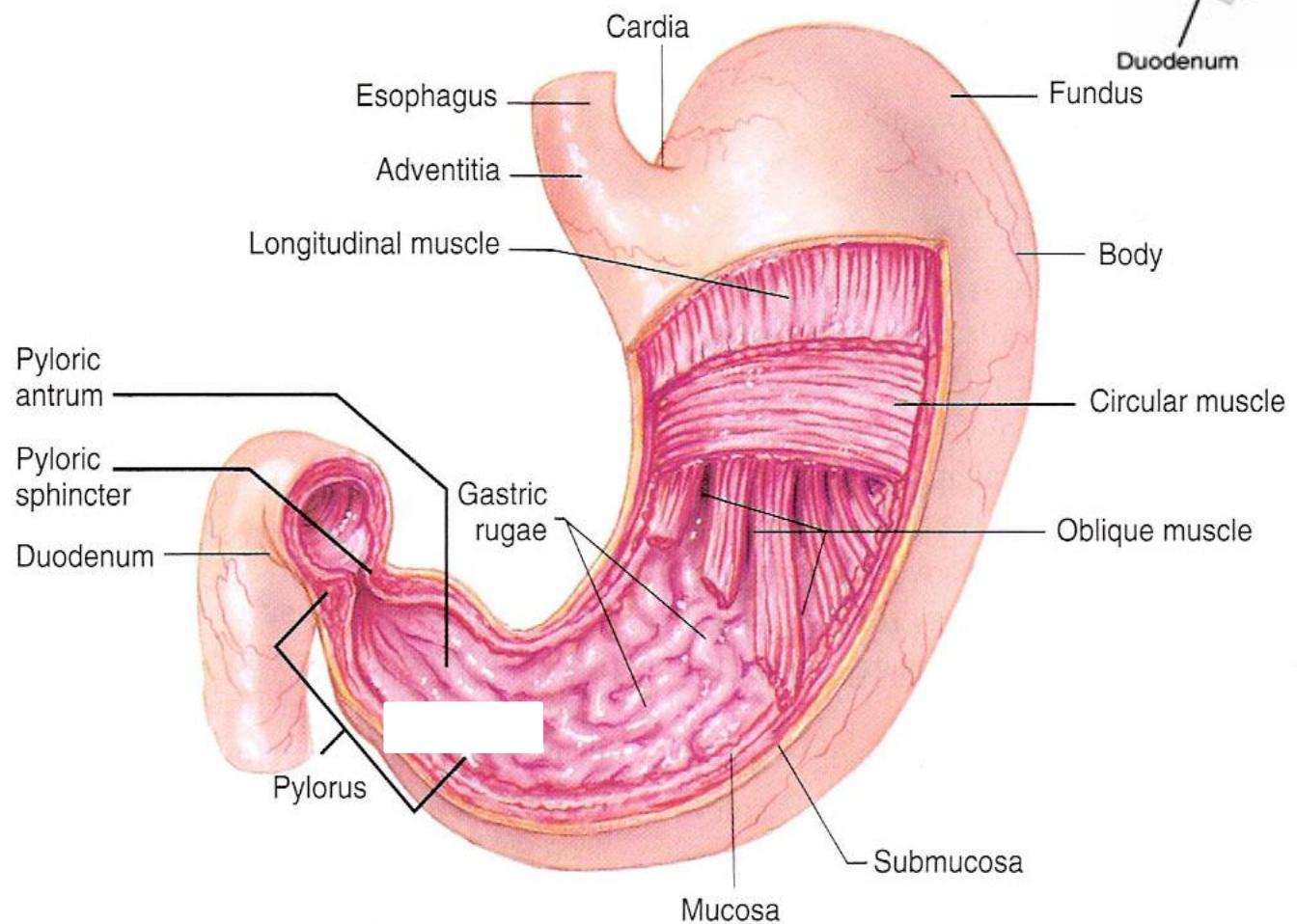
1. Fundus
2. Body
3. Antrum

Physiologically,

- 1. the "orad" portion (fundus + the first two thirds of the body)
 - The gastric reservoir is specialized for receiving and storing a meal
- 2. the "caudad" portion (the remainder of the body plus the antrum)
 - function in the mixing and emptying of the gastric contents



Anatomy of stomach



- **Two types of Gastric Motility**
 - Mixing movement:
 - Antrum contracts against closed pylorus
 - Moving Food =Peristaltic movement :
 - Antrum Contracts against open pylorus

Mixing mechanism in the stomach

- Presence of food in the stomach
 - ↓
- Distention of the stomach wall
 - ↓
- initiates a weak peristaltic constrictor waves, called *mixing waves*,
 - It is in the orad portion and progressively moves down.
 - They become more intense moving down to the antrum,
- The food in the stomach mixed with gastric secretions is called *chyme*

Hunger contractions

- Is rhythmical peristaltic contractions in the body of stomach
- occurs when the stomach is empty for several hrs
- When the successive contractions become extremely strong,
 - fuse to cause a continuing tetanic contraction, lasts 2-3 min
 - the person can experience mild pain in the pit of the stomach, called **hunger pangs**
 - usually begin 12 to 24 hrs after the last ingestion of food;
 - In starvation, reach greatest intensity in 3 to 4 days and gradually weaken in succeeding days.

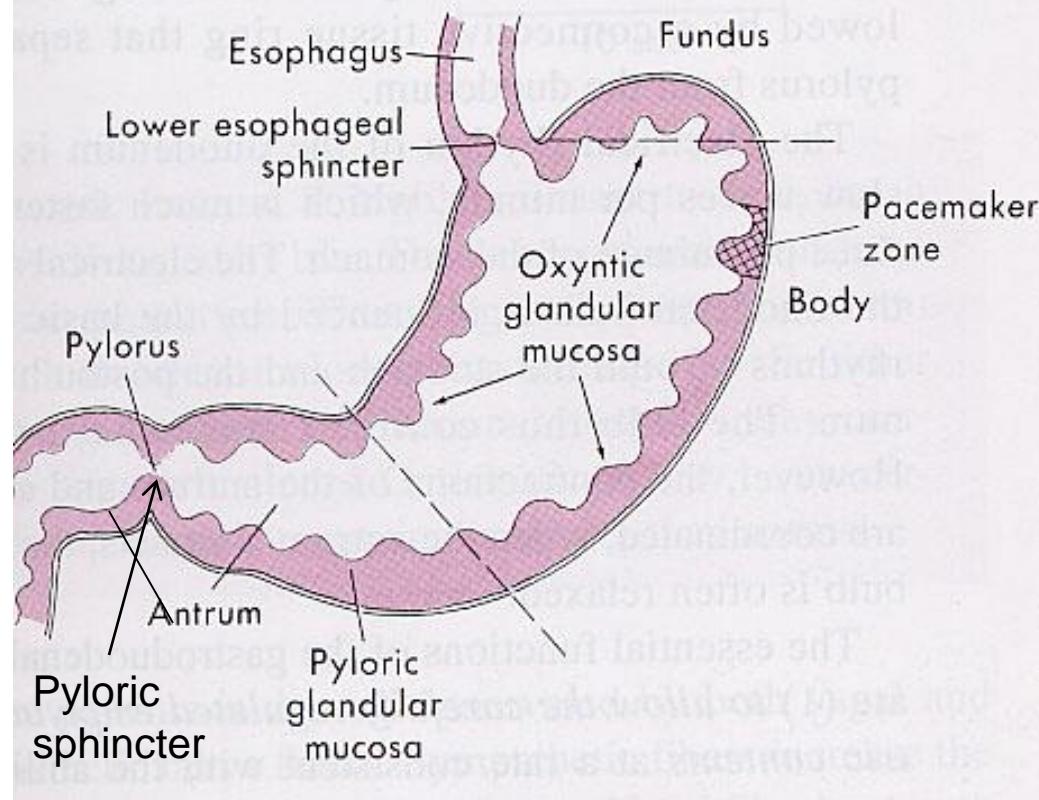
Stomach Emptying - flow of the chyme to the duodenum

- The distal opening of stomach is called **pylorus**
 - allows water and other fluids emptying with ease
 - prevents passage of food particles until mixed in the chyme to almost fluid consistency
 - Its degree of constriction ↑ or ↓ under the influence of nervous & humoral reflexes
- Most of the time, the rhythmical stomach contractions are weak
 - function mainly to cause mixing of food with gastric secretions
- For about 20% of the time while food is in the stomach, the contractions become intense
 - function mainly to cause strong peristaltic constrictions
 - cause stomach emptying



Pyloric sphincter

- regulates emptying of the chyme
 - prevents regurgitation of duodenal content
- ✓ Pyloric relaxation: by inhibitory vagal fibers (mediated by VIP & NO).



- ✓ Pyloric constriction: by excitatory cholinergic vagal fibers, sympathetic fibers and hormones: CCK, gastric inhibitory peptide and secretin
- ✓ The proximal stomach acts as an electrical pacemaker
 - Proximal stomach fullness determines distal stomach motor function

Regulation of Stomach Emptying

Gastric Factors That Promote Emptying:

1. Gastric Food Volume

- Increased food volume in the stomach → ↑ gastric emptying
 - Stretching of the stomach wall
 - elicit local myenteric reflexes → heighten activity of the pyloric pump

2. Fluidity: increased fluidity allows more rapid emptying

3. Hormones: Gastrin

- stimulates motor functions in the body of the stomach and enhance peristaltic contractions
- Secretion of gastrin stimulated by:
 - stretching of stomach
 - the presence of certain types of foods in stomach (esp. meat products)

Duodenal Factors inhibiting stomach emptying:

-The presence of any of the following in the duodenum inhibits stomach emptying:

- Enterogastric inhibitory reflex
- distention of the duodenum
- irritation of the duodenal mucosa
- acidity of the duodenal chyme
- osmolality of the chyme
 - either hypotonic or hypertonic fluids (especially hypertonic)
- breakdown products of proteins and fats

Hormonal factor: Cholecystokinin → ↓ emptying

- Stimulated mainly by fats in the duodenum
- Fat digestion takes longer time

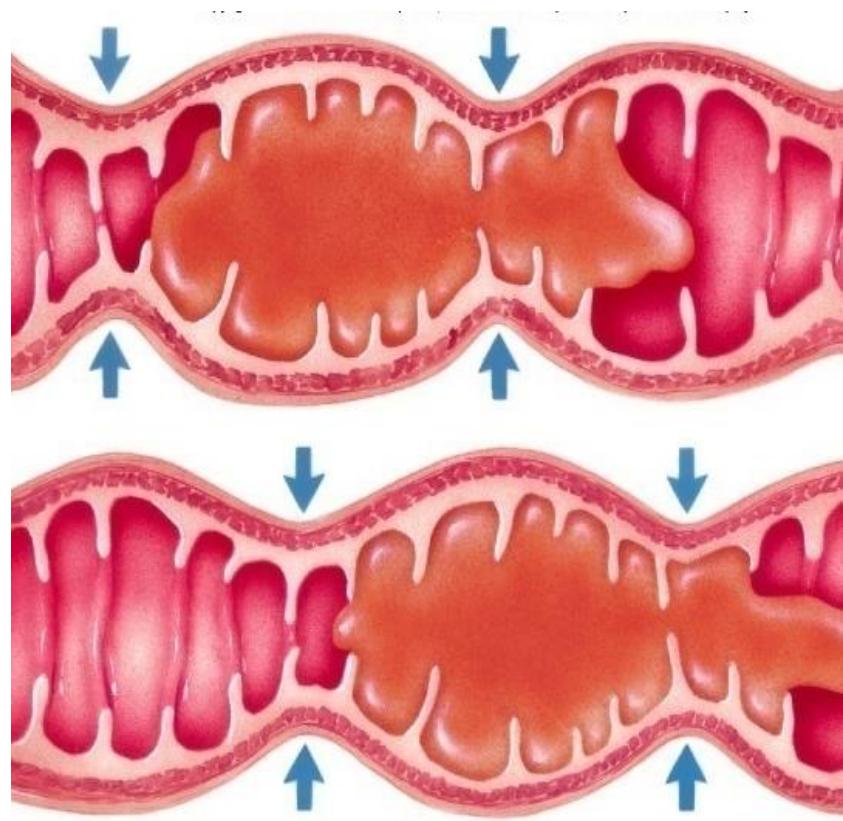
Movements of the Small Intestine

Types of motility of the small intestine:

- **Digestive motility pattern:**
 - ✓ **segmentation** = mixing contractions
 - ✓ **peristalsis** = moving or propulsive contractions
 - ❖ but mostly a mixture of the two
- **Interdigestive motility pattern:** migrating myoelectric complex (MMC)
 - ✓ occurs during fasting individuals
 - ✓ bursts (lasting 5-10 minutes) of intense electrical and contractile activity that propagate from stomach (origin) to the terminal ileum.
 - is initiated by motilin, at a rate of about 5 cm/min
 - ✓ serves to clear non-digestible residue from the small intestine (the intestinal "housekeeper").
 - ✓ Repeats every 75-90 minutes.

A. Mixing Contractions (Segmentation Contractions)

- Cause "segmentation" of the small intestine
- Chyme distends a portion of the small intestine
 - stretching of the intestinal wall
 - localized contractions spaced at intervals
- As one set of segmentation contractions relaxes, a new set often begins,
- but the contractions this time occur mainly at new points between the previous contractions.



B. Propulsive Movements in Small Intestine

- Peristalsis move toward the anus at a velocity of 0.5- 2cm/sec
- Controlled by Nervous and Hormonal Signals:
 1. **Nervous signal-** is greatly increased after a meal
 - ✓ Entry of chyme into the duodenum causing stretch of the duodenal wall
⇒ stimulates myenteric plexus ⇒ ↑ Peristalsis
 - ✓ Gastro enteric reflex (distention of the stomach stimulates the myenteric plexus of small intestine)
↓↓
 - Peristalsis in the small intestine
 2. **Hormones:**
 - ✓ *Gastrin, CCK, insulin, motilin, and serotonin*
↓
 - all of which enhance intestinal motility

Function of the Ileocecal Valve and sphincter

- **Gastroileal reflex**

- immediately after a meal, nervous signals from the stomach intensifies peristalsis in the ileum



- Increased emptying of ileal contents into cecum

- **Fluidity of ileal content**



- Increases emptying

- But the valve and sphincter prevent backflow of fecal contents from colon into the small intestine

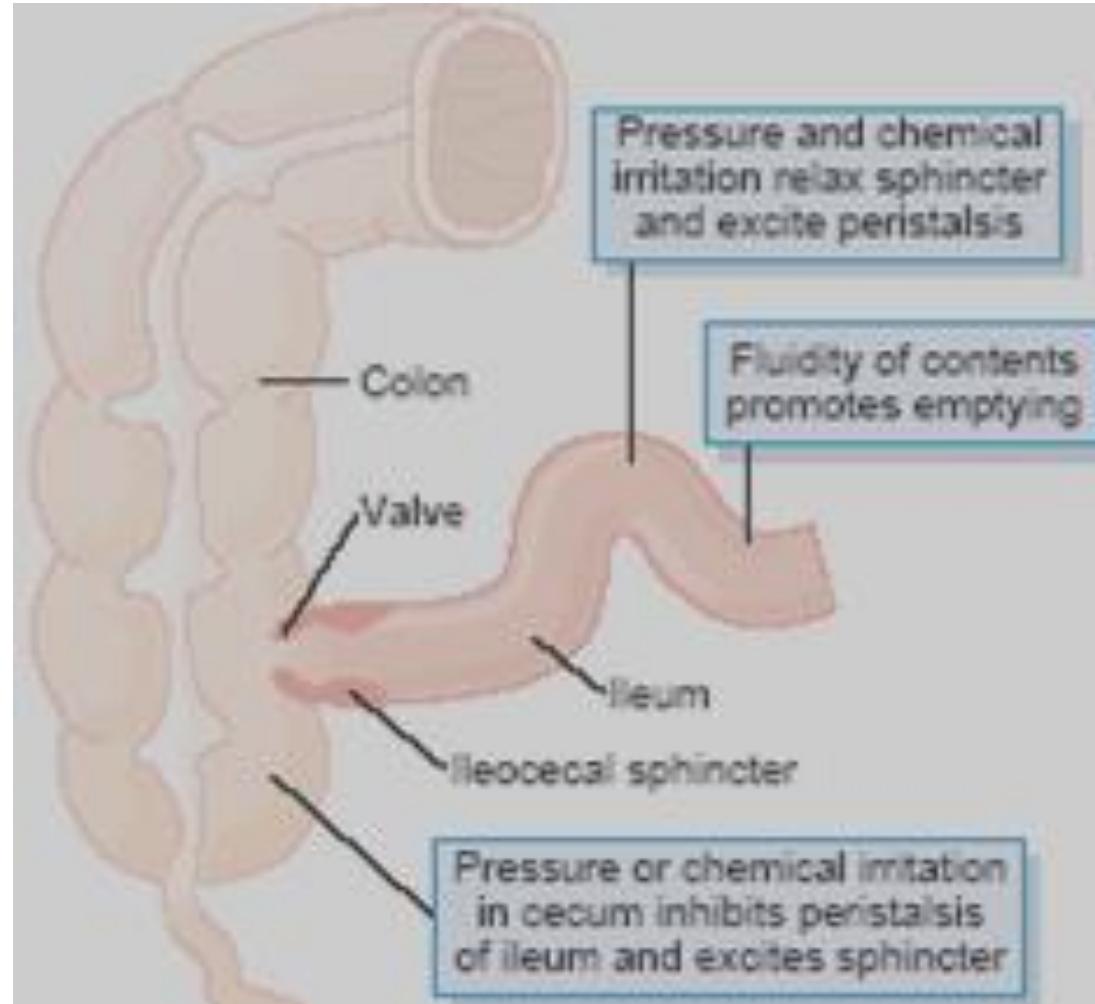


Fig. Regulation of emptying at the ileocecal valve

Movements of the Colon

- ✓ movements of the colon are normally very sluggish
 - ↓
- Important for the principal functions of the colon:
 1. absorption of water and electrolytes from the chyme to form solid feces
 - In the proximal portion of the colon
 2. storage of fecal matter until it can be expelled
 - In the distal portion of the colon

A. Mixing Movements- "Haustrations"

- large circular muscle constrictions occur in the large intestine
- At the same time the longitudinal muscle of the colon contracts
 - ↓ ↓
 - cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called **haustrations**
 - ↓
 - exposes the content to the surface of intestine to absorb water & electrolytes
- Provide minor forward propulsion of colonic contents

B. Mass movements- propulsive movement

Mass movement from cecum to sigmoid colon:

- is a modified type of peristalsis
- *propels the feces from colon towards the anus*
- occur only **one to three times each day!**
- In some people about 15 minutes after eating breakfast

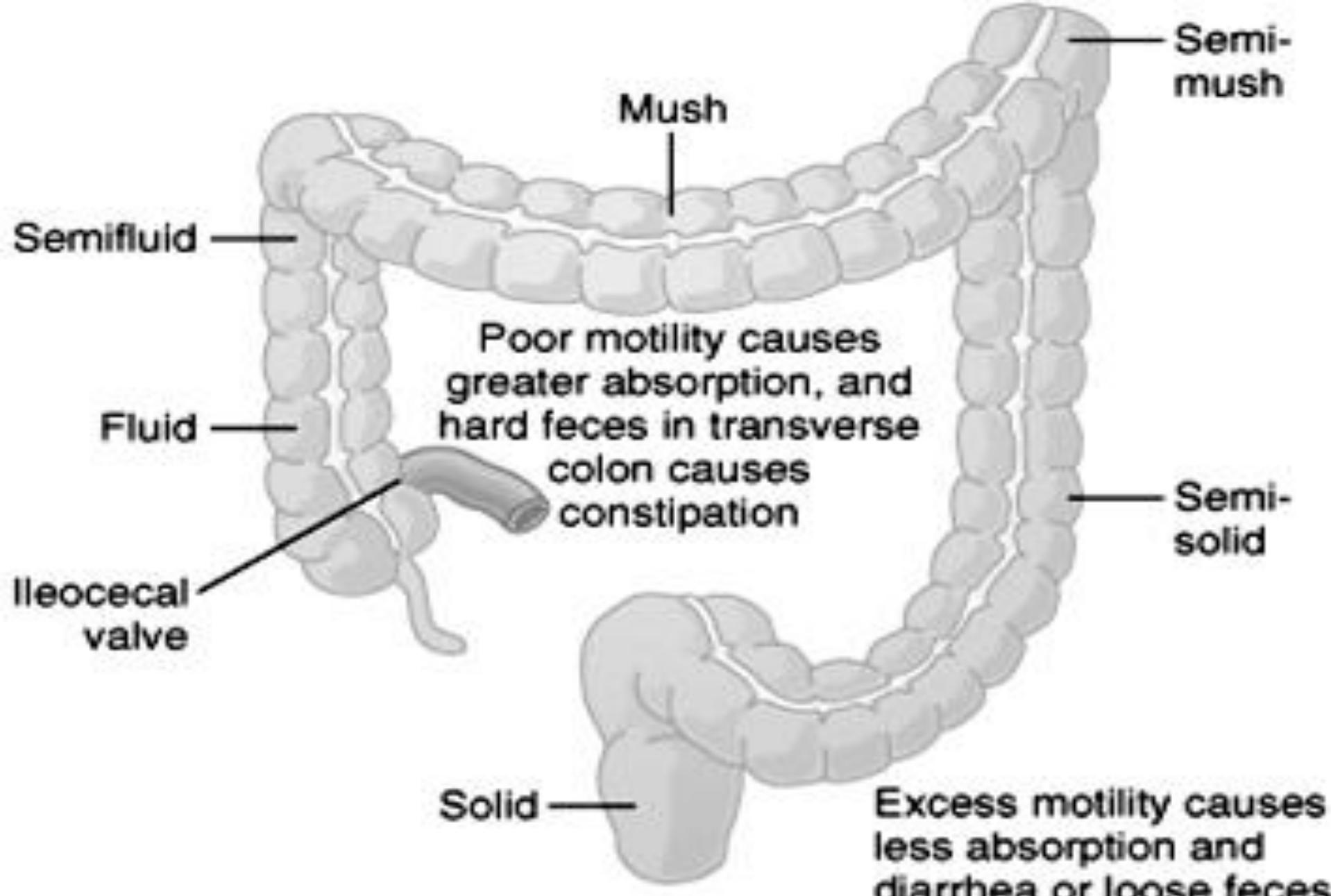


Fig. Absorption and storage function of large intestine

Defecation

- reflex expulsion of the contents of the rectum
- When a mass movement forces feces into the rectum, the desire for defecation occurs immediately,
- Continual dribble of fecal matter through the anus is prevented by tonic constriction of:
 1. *internal anal sphincter*,
 2. *external anal sphincter*

1. internal anal sphincter,

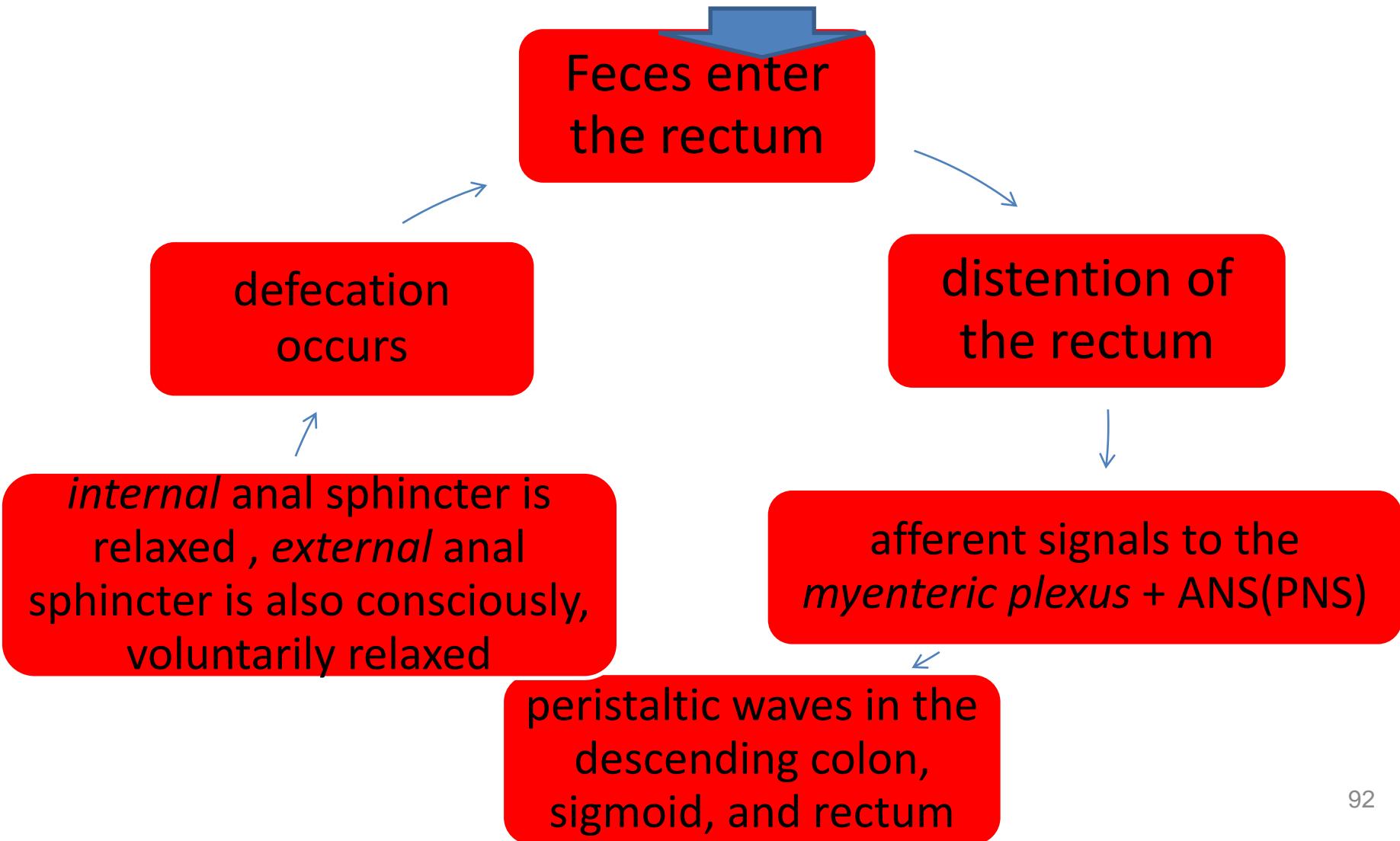
- ✓ a circular smooth muscle that lies immediately inside the anus,

2. external anal sphincter,

- ✓ composed of skeletal muscle that surrounds the internal sphincter
- ✓ Controlled by pudendal nerve (part of somatic nervous system)
 - Under voluntary control
- ✓ Normally is kept continuously constricted unless conscious signals inhibit the constriction.
- Defecation is initiated by defecation reflex

Defecation Reflexes

Intrinsic reflex – controlled by myenteric plexus, normally weak



parasympathetic defecation reflex (Extrinsic reflex)

- ✓ Greatly intensifies the peristaltic waves as well as relaxes the internal anal sphincter

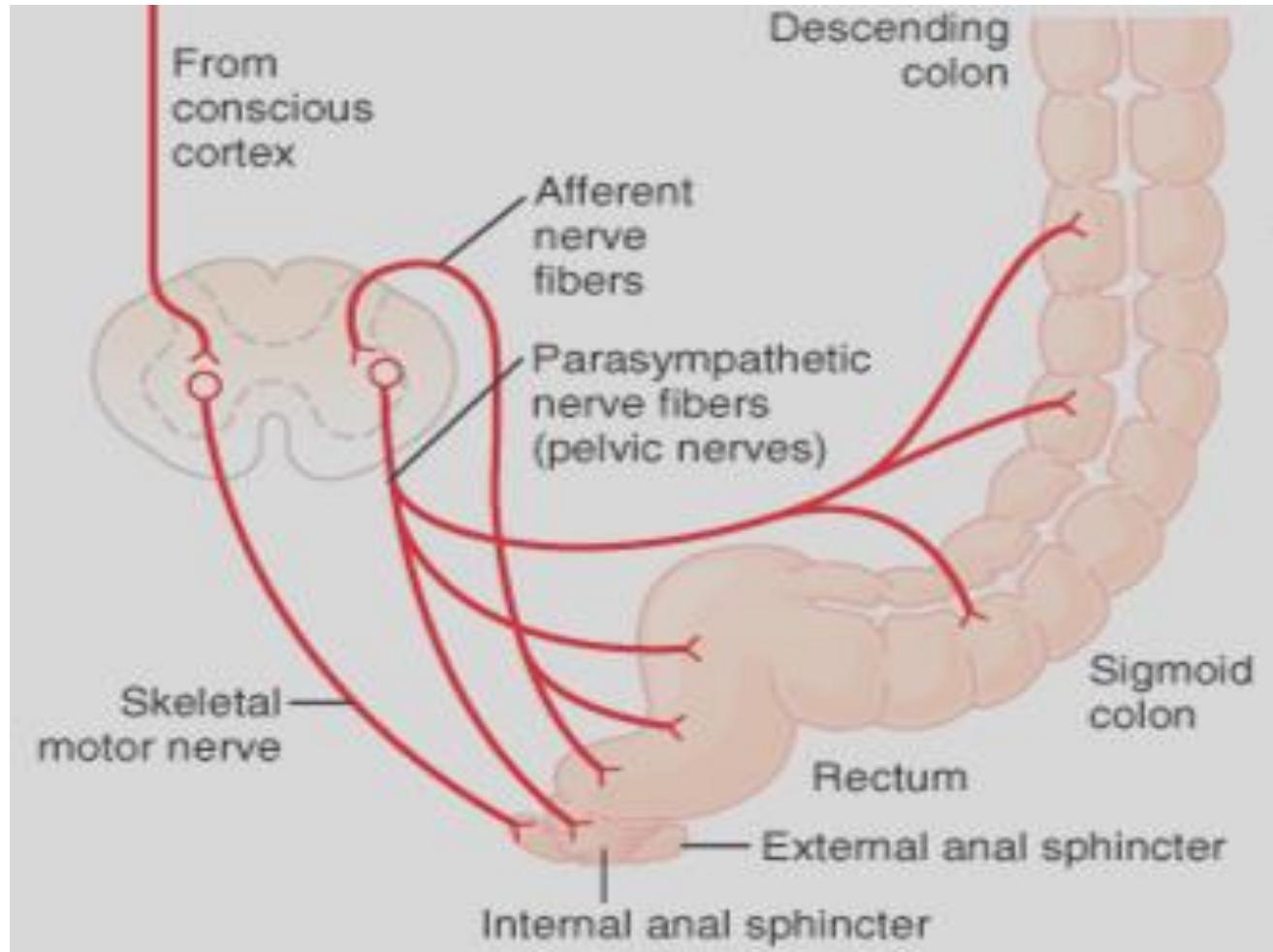
Mechanism of defecation

- Distension of rectum due to accumulation of feces
 - ↓
- Nerve endings in the rectum are stimulated
 - ↓
- Signals into the spinal cord and then reflexly back to:
 - the descending colon, Sigmoid, rectum
 - by way of *pelvic nerves* (parasympathetic nerve)
 - ↓

Defecation contraction of such parts of the GIT \Rightarrow defecation

other effects, such as taking a deep breath, closure of the glottis, and contraction of the abdominal wall muscles

Fig. parasympathetic defecation reflex



NB: Loss of continence can result from dysfunction of the anal sphincters, abnormal rectal compliance, decreased rectal sensation, altered stool consistency, or a combination of any of these abnormalities.

B. Secretory Functions of the GIT

- Secretary glands subserve three primary functions:
 - ☞ Production of *digestive enzymes* +
 - ☞ Production of *mucus*
 - ☞ Production of *electrolytes*
- the quantity secreted in each segment is almost exactly the amount needed for proper digestion

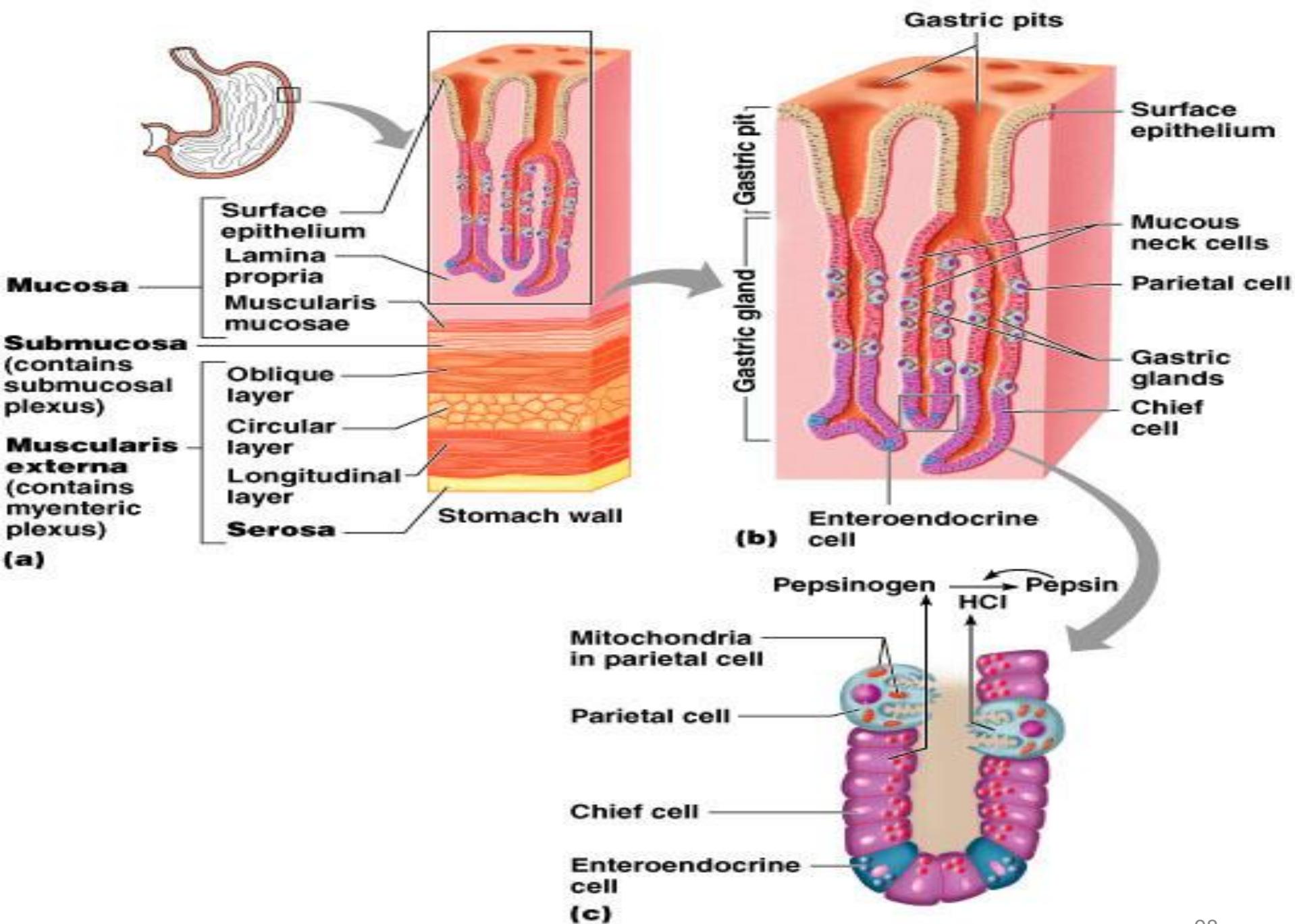
Daily Secretion of gastrointestinal Juices(about 6-7L)

	Daily Volume (ml)	pH
Saliva	1000	6.0-7.0
Gastric secretion	1500	1.0-3.5
Pancreatic secretion	1000	8.0-8.3
Bile	1000	7.8
Small intestine secretion	1800	7.5-8.0
Brunner's gland secretion	200	8.0-8.9
Large intestinal secretion	200	7.5-8.0
Total	6700	

General Principles of GIT Secretion

Anatomical types of glands:

- **mucous cells or goblet cells**
 - on the surface of the epithelium in most parts of the GIT
 - release mucus in response to local irritation of the epithelium
- **pits** - invaginations of the epithelium into the submucosa.
 - Eg. *crypts of Lieberkühn in the small intestine* \Rightarrow **Intestinal Juices**
- **Tubular glands**
 - eg. HCl and pepsinogen-secreting gland of the stomach
- **Complex glands** -Found associated with the alimentary tract
 - Eg. The *salivary glands, pancreas, and liver*



Basic Mechanisms of Stimulation of the GIT Glands

- Contact of Food with the Epithelium



- ✓ Enteric Nervous Stimulation
- ✓ Hormone production

.

- Autonomic Stimulation of Secretion
 - A. Parasympathetic simulation
 - B. Sympathetic stimulation

- **Mucus secretion**

- Mucus is a thick secretion
- composition: water, electrolytes, and a mixture of several proteins

Importance of Mucus in the GIT

- Excellent lubricant and a protectant for the GIT wall
- Has adherent qualities - adhere tightly to the food and to spread as a thin film over the surfaces.
- Has sufficient body - it coats the wall of the gut and prevents actual contact of most food particles with the mucosa.
- Has a low resistance for slippage - the particles can slide along the epithelium with great ease.
- Strongly resistant to digestion by the GI enzymes
- Buffering function

Secretion of Saliva

- The principal glands of salivation are:
 - **A pair of parotid** - the largest, Just below and in front of the ears
 - produce approximately 25% of saliva
 - **A pair of Submandibular (submaxillary)**- at the posterior corners of mandible
 - Produce approximately 70% of saliva
 - **A pair of sublingual** - below the floor of the mouth(below the tongue)
 - produce approximately 5% of saliva entering the oral cavity
- Daily secretion normally ranges between 800 and 1500 ml

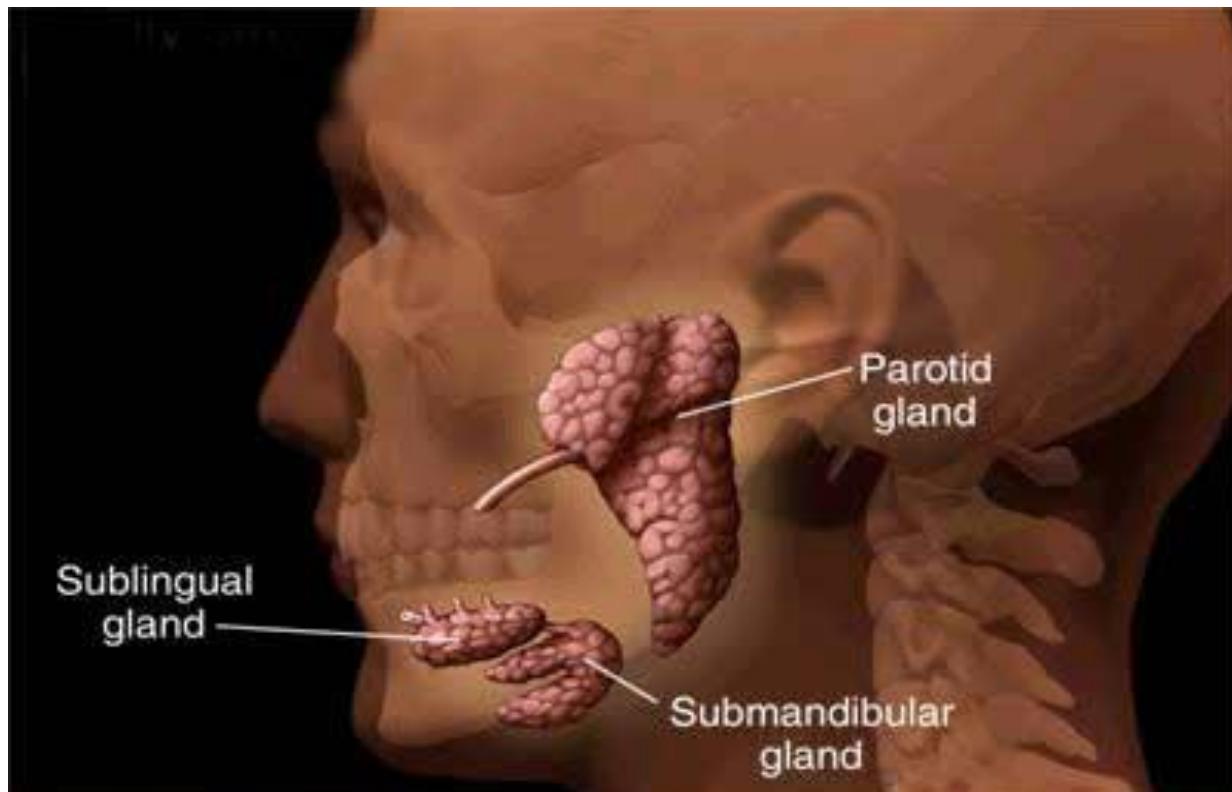
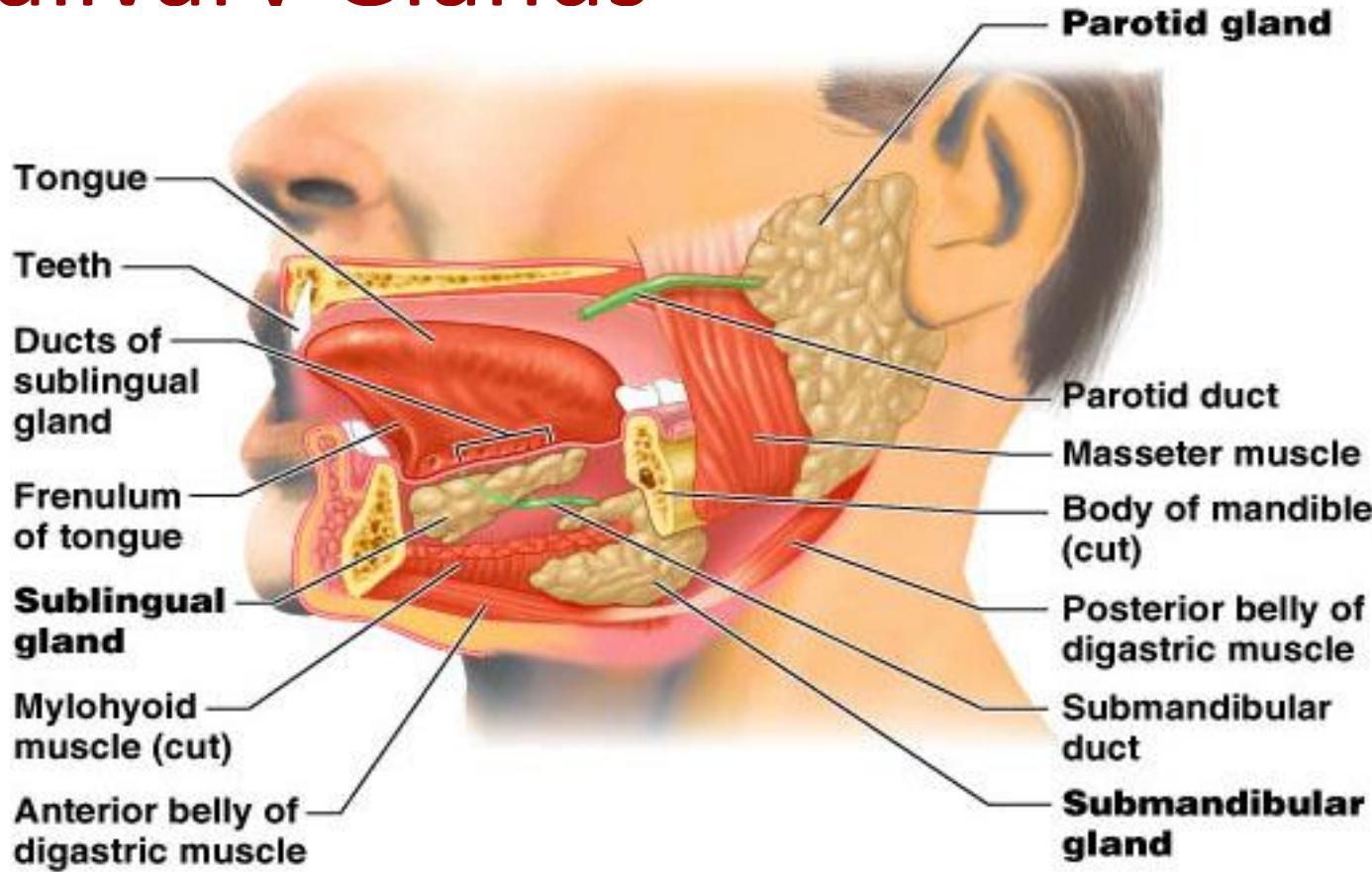


Fig. Salivary Glands

Salivary Glands



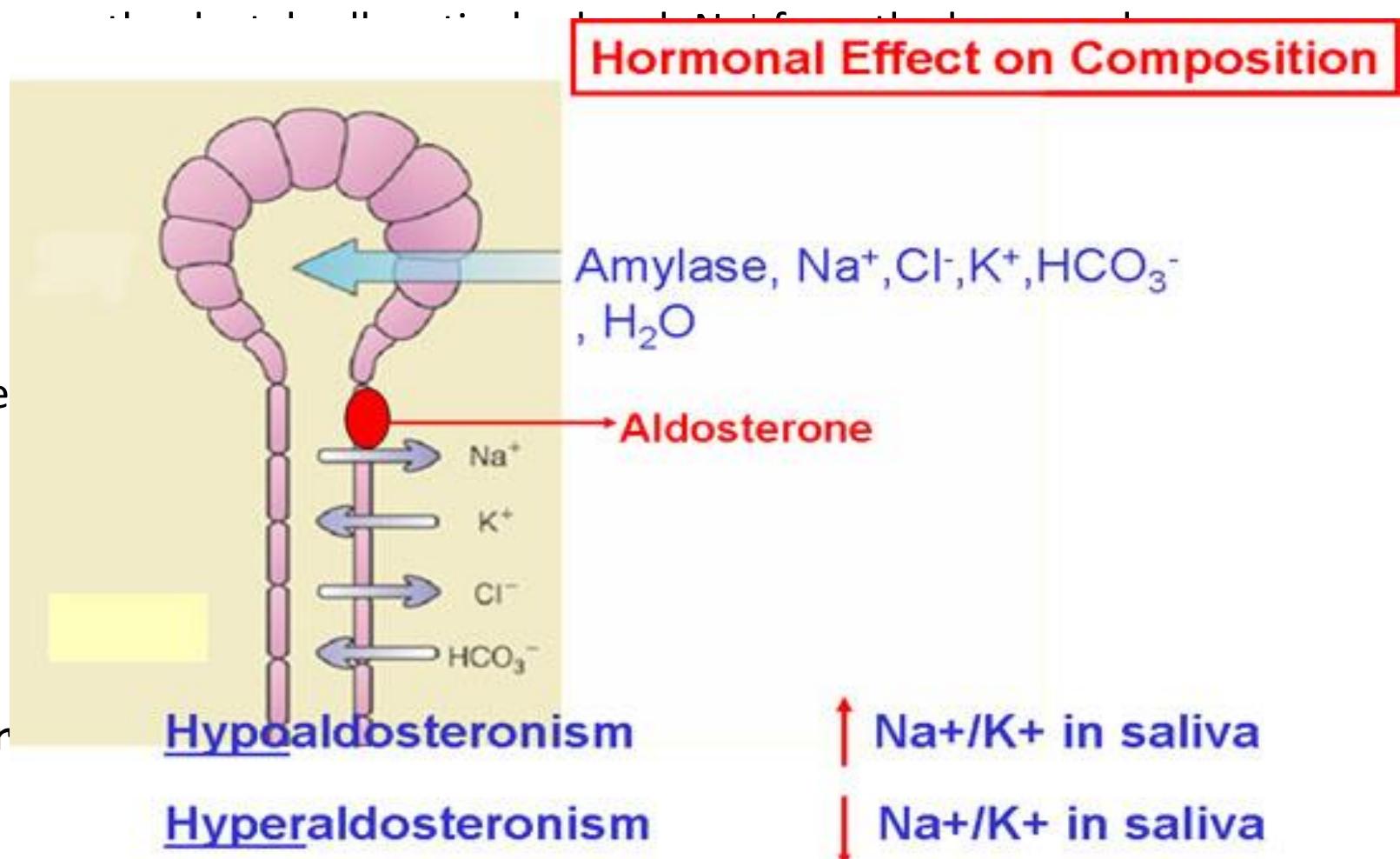
Sialolithiasis – Stones within the salivary glands or the salivary gland ducts.

Pathogenesis: relative stagnation of salivary flow and salivary calcium concentration

Risk factors: DHN, Diuretics, Anticholinergics, trauma, Hx of nephrolithiasis, periodontal disease

Symptoms — pain and swelling in the involved gland; aggravated by eating

- the primary secretion produced by the acinar cells resembles that of plasma
- modification of the primary secretion in the striated and excretory ducts
 - there is less Na^+ and Cl^- , more K^+ , and HCO_3^- in saliva than in plasma;
Because:



Saliva contains two major types of protein secretions:

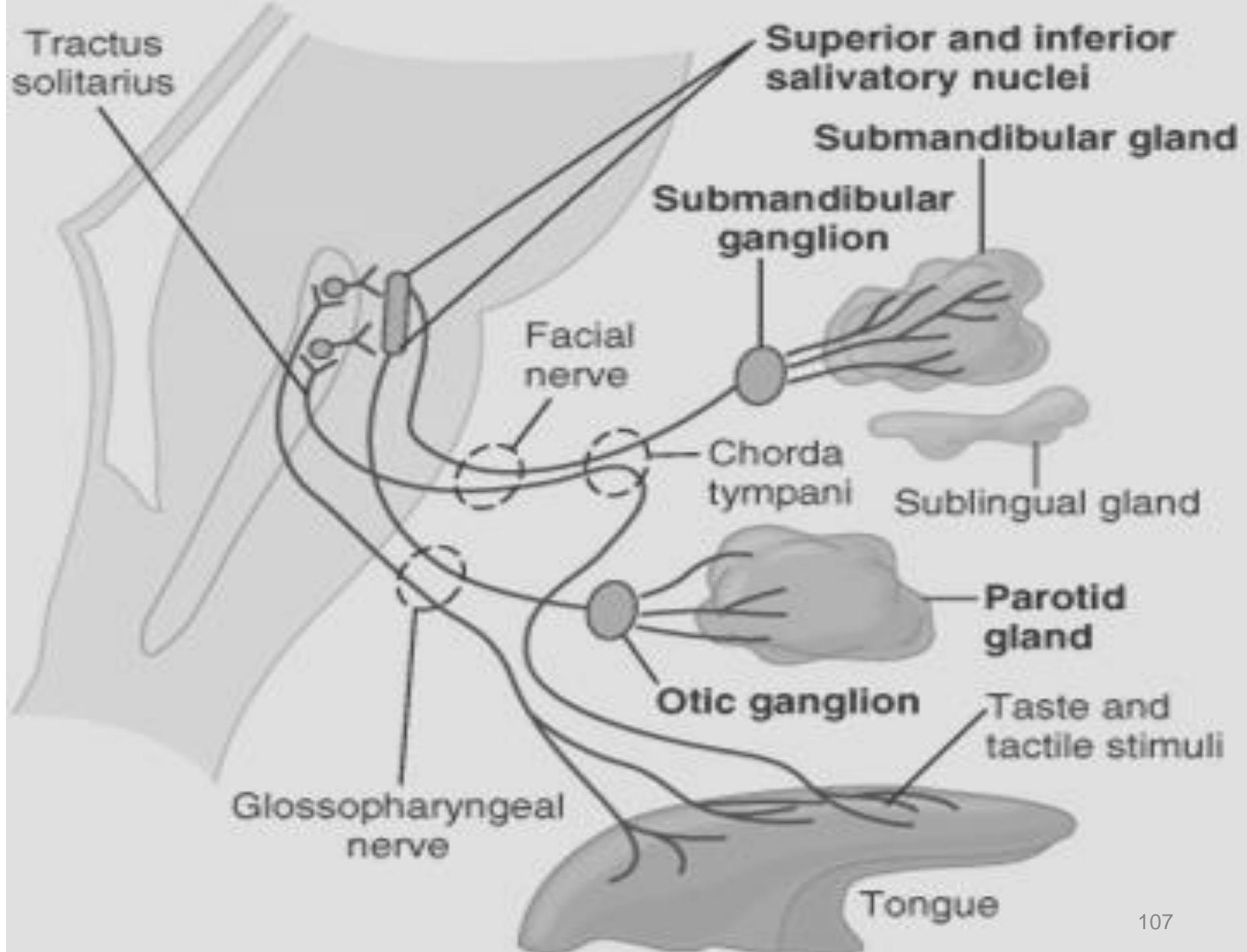
- 1. **serous secretion** - contains **ptyalin** (an α -amylase),
 - *Ptyalin* is an enzyme for digesting starches
- 2. **mucus secretion** - contains **mucin**
 - for lubricating and for surface protective purposes.
- 99.4% water, & the remaining 0.6% includes:
 - electrolytes (Na^+ , Cl^- , and HCO_3^- ...),
 - buffers,
 - glycoproteins, antibodies, enzymes, and waste products.
- Saliva has a pH between 6.0 and 7.0,
 - a favorable range for the digestive action of ptyalin.

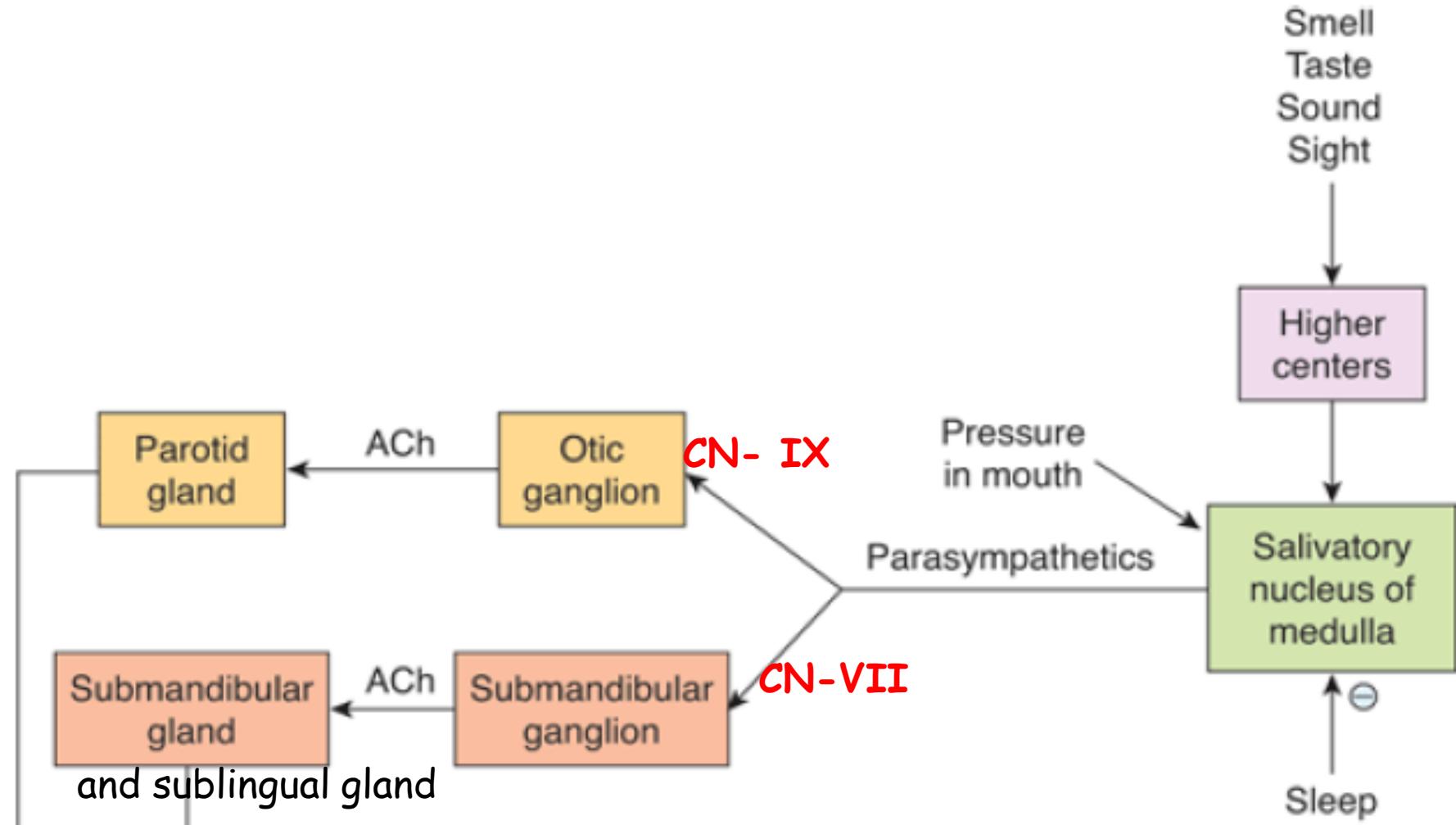
Function of Saliva for Oral Hygiene

- Saliva has important role for maintaining healthy oral tissues
 - Because it has bacteriolytic enzymes and antibodies
 - ↓
 - Destroy bacteria and viruses
 - the flow of saliva itself helps wash away pathogens and food particles
- Xerostomia- dryness of the mouth (low production of saliva), a major feature of sjogren syndrome
 - ↓
 - It leads to infection of mouth⇒ bad oral smell/halitosis
 - Patients complain of difficulty in swallowing dry food, inability to speak continuously

Nervous Regulation of Salivary Secretion

- **salivatory nuclei located in the medulla**
 - excited by both taste, and tactile stimuli.
- Salivation can also be stimulated or inhibited by nervous signals arriving in the salivatory nuclei from higher centers of the CNS.
 - Parasympathetic \Rightarrow Profuse watery secretion
 - Sympathetic \Rightarrow Thick viscid secretion (α_1 receptors), Amylase secretion (β -receptors)





Increased salivary secretion
via effects on

- Acinar secretion
- Vasodilatation

Esophageal Secretion

- ✓ Entirely mucous in character
 - provide lubrication for swallowing
- ✓ No digestive enzyme secretion

Gastric Secretion

i. Mucus-secreting cells - line the entire surface of the stomach

- secrete large quantities of a very viscid mucus that coats the stomach mucosa



- Provide a shell of **protection** for the stomach wall
- contribute to **lubrication** of food transport
- it is alkaline \Rightarrow **neutralization** of the acid

ii. Oxytic glands (gastric glands) - in the fundus & body

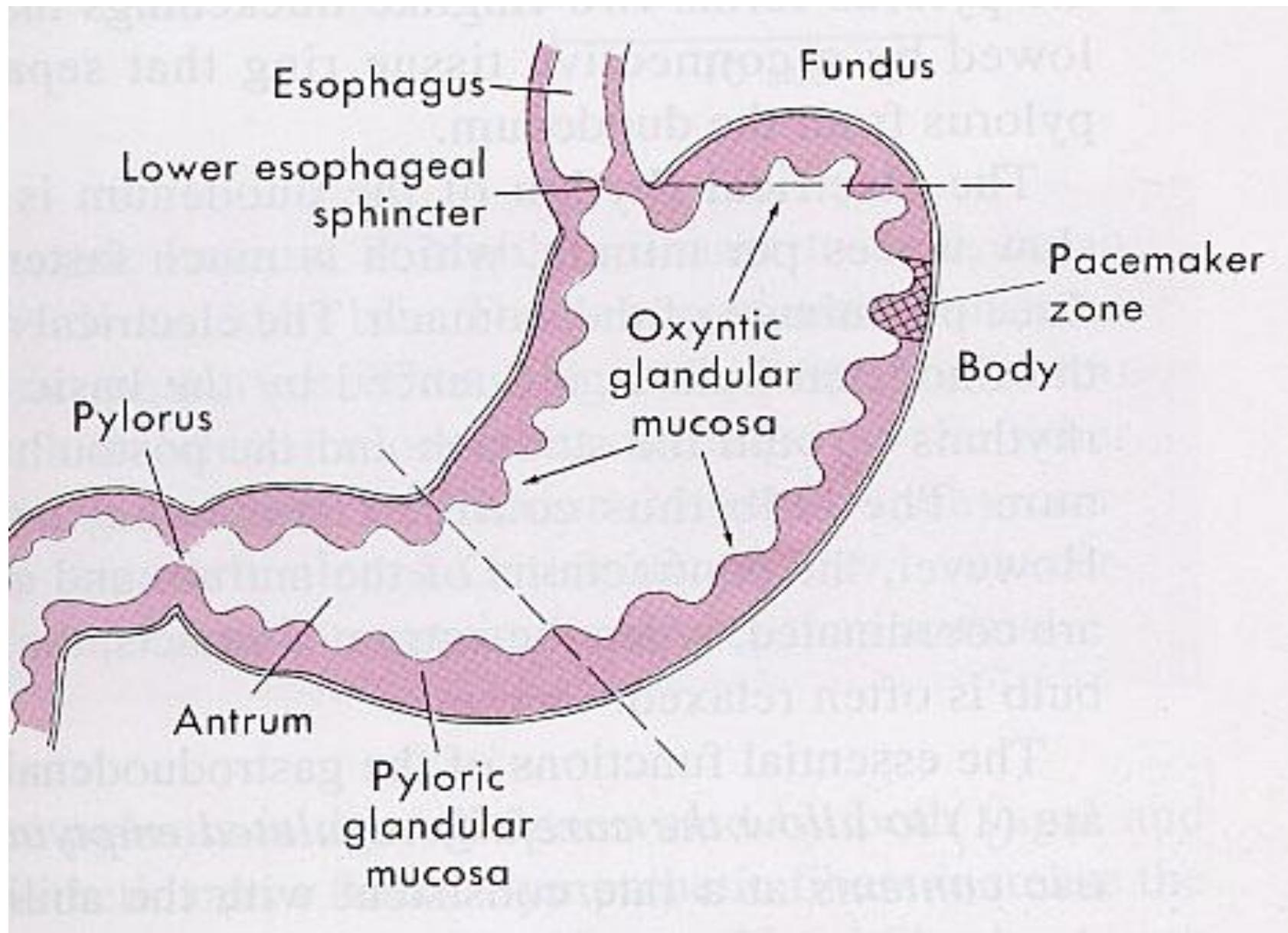
- ✓ secrete **pepsinogen, HCl, intrinsic factor, histamine, and mucus.**

iii. Pyloric glands - in the antrum of stomach

- ✓ Secrete:

- **mainly mucus** for protection of the pyloric mucosa from the stomach acid,
- **gastrin from G cells,**
- **Somatostatin from D cells**

Gastric Secretary glandular mucosa



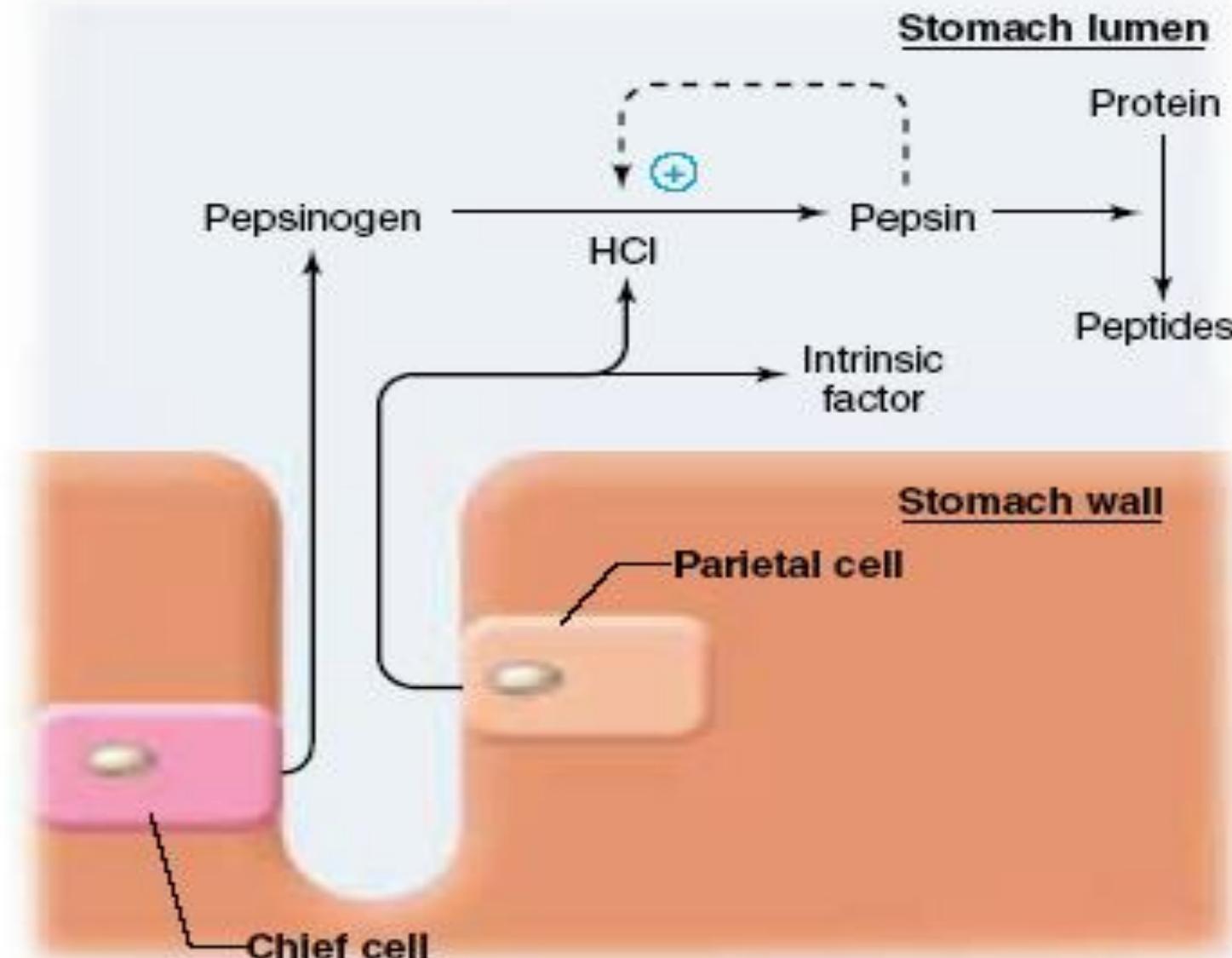
Secretions from the Oxytic (Gastric) Glands

- The glands are located on the inside surfaces of the body and fundus of the stomach,
- constitute the proximal 80% of the stomach
- Contain different secretary cells:
 - 1. **Mucous neck cells** - mainly secrete mucus

- **2. Chief or peptic cells** – produce **pepsinogen**
 - When pepsinogen is first secreted, it has no digestive activity
 - Pepsinogen is activated to pepsin by:
 - HCl in the stomach
 - Pepsin itself via a positive feedback mechanism
 - Pepsin is active proteolytic enzyme in a highly acid medium (**optimum pH 1.8 to 3.5**)

Regulation of Pepsinogen Secretion

- i. stimulation of the **peptic cells** by Ach released from the **vagus nerves** or from the **gastric enteric nervous plexus**, and
- ii. stimulation of **peptic cell secretion** in response to acid in the **stomach**.



Conversion of pepsinogen to pepsin in the lumen of the stomach.

- **3. Parietal or oxyntic cells** - secrete HCl and intrinsic factor
 - HCl provides acidic medium for stomach
 - Important for digestive enzymes:
 - pepsin (activated from pepsinogen) (pH = 1.8-3.5)
 - lingual lipase (pH optimum = 4).
 - pH at the canculus of parietal cells is as low as 0.8
 - HCl softens the food
 - gastric acidity has antibacterial activity

Function of intrinsic factor (IF)

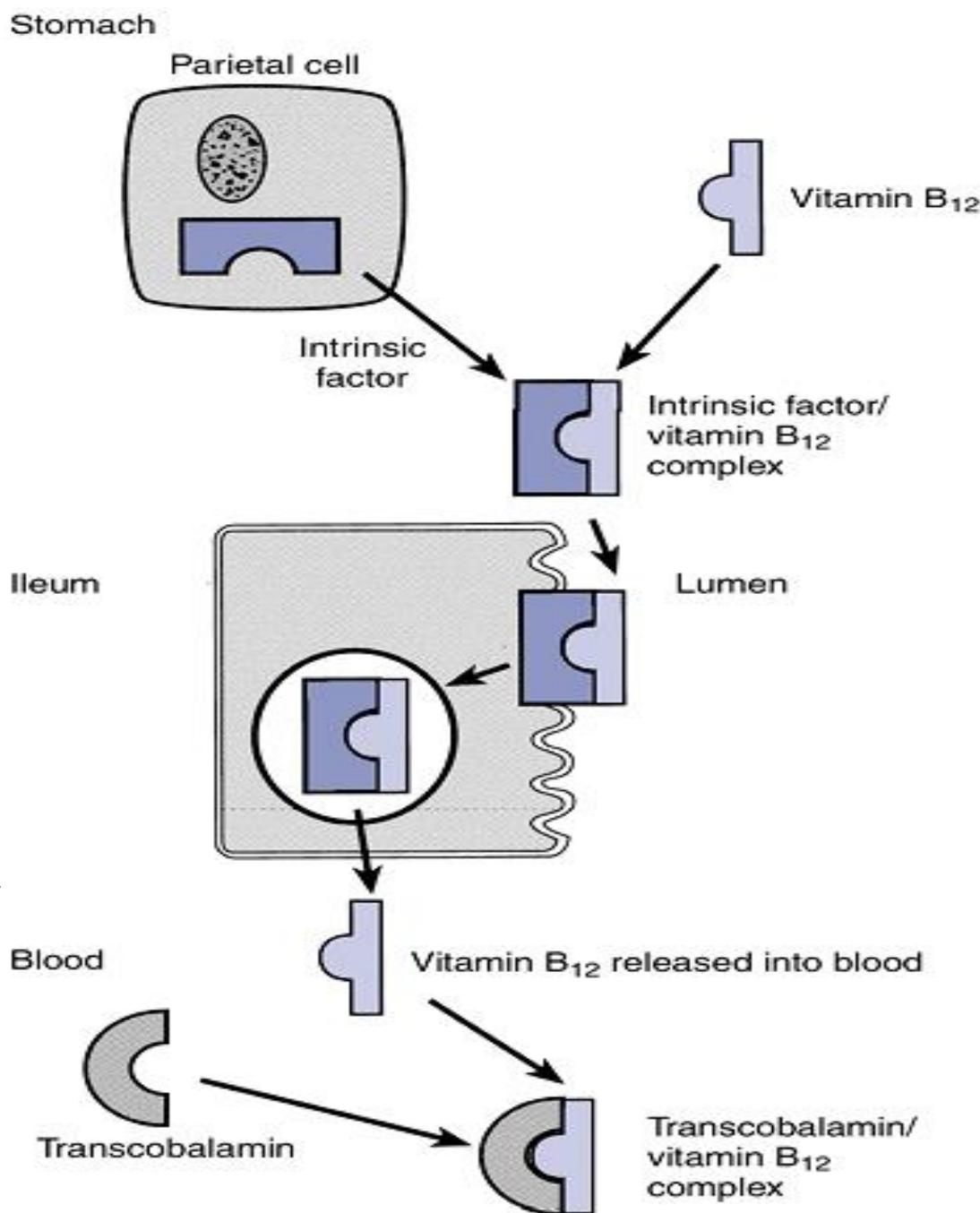
- Produced from parietal cells
- IF is essential for absorption of vitamin B12 in the ileum
 - IF binds Vit B_{12} and protects from gastric and intestinal digestion
 - Vit B12 is important for maturation of RBCs
- Destruction of parietal cells eg. Due to gastritis, gastroectomy....
 - ↓
 - **Pernicious anemia** due to failure of RBC maturation (due to lack of Vit B12)
 - **Achlorhydria** (lack of acid secretion)
 - diagnosed when the pH of gastric secretions fails to decrease below 6.5 after maximal stimulation
 - **Hypochlorhydria:** diminished acid secretion

Fig. Vitamin B₁₂ (cobalamin) absorption depends on a gastric intrinsic factor

VitB12 is cobalt-containing vitamin

Vitamin B₁₂ is transported in the portal blood bound to the protein transcobalamin.

People who lack the intrinsic factor fail to absorb vitamin B₁₂ and develop pernicious anemia



• 4. Enterochromaffin like cells (ECL cells)

- Secrete histamine, has paracrine effect on parietal cells
- Ach, gastrin \Rightarrow act on ECL cells \Rightarrow \uparrow histamine \Rightarrow \uparrow HCl secretion by parietal cells

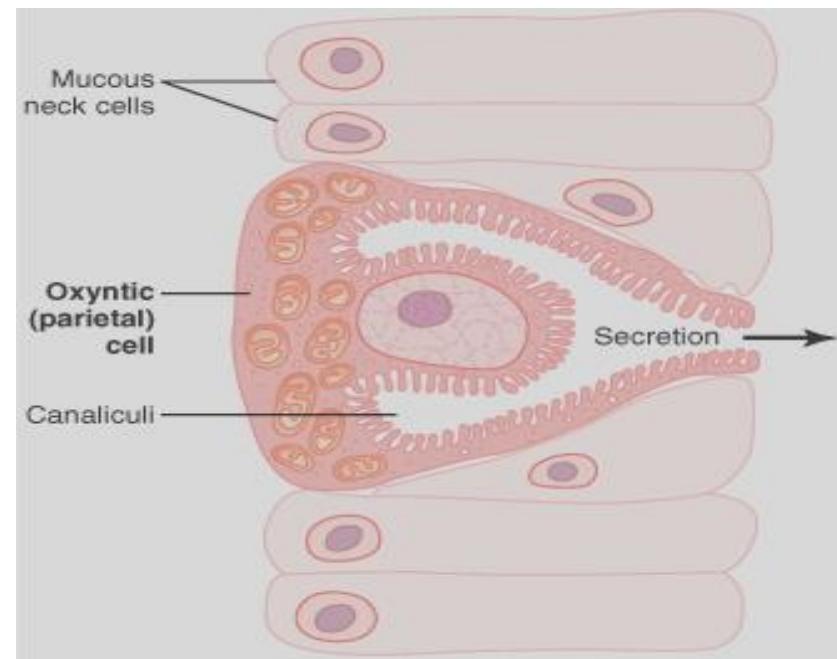
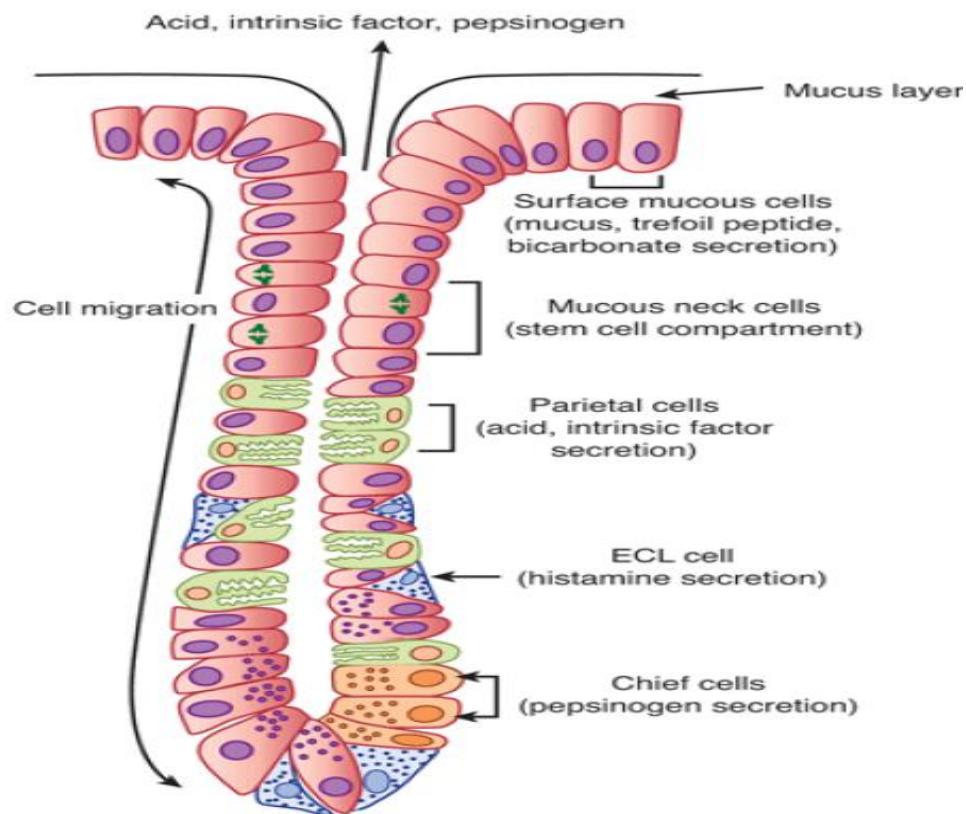


Fig. Acid Secreting cells; parietal cells

Fig. Structure of a gastric gland from the fundus and body of the stomach.

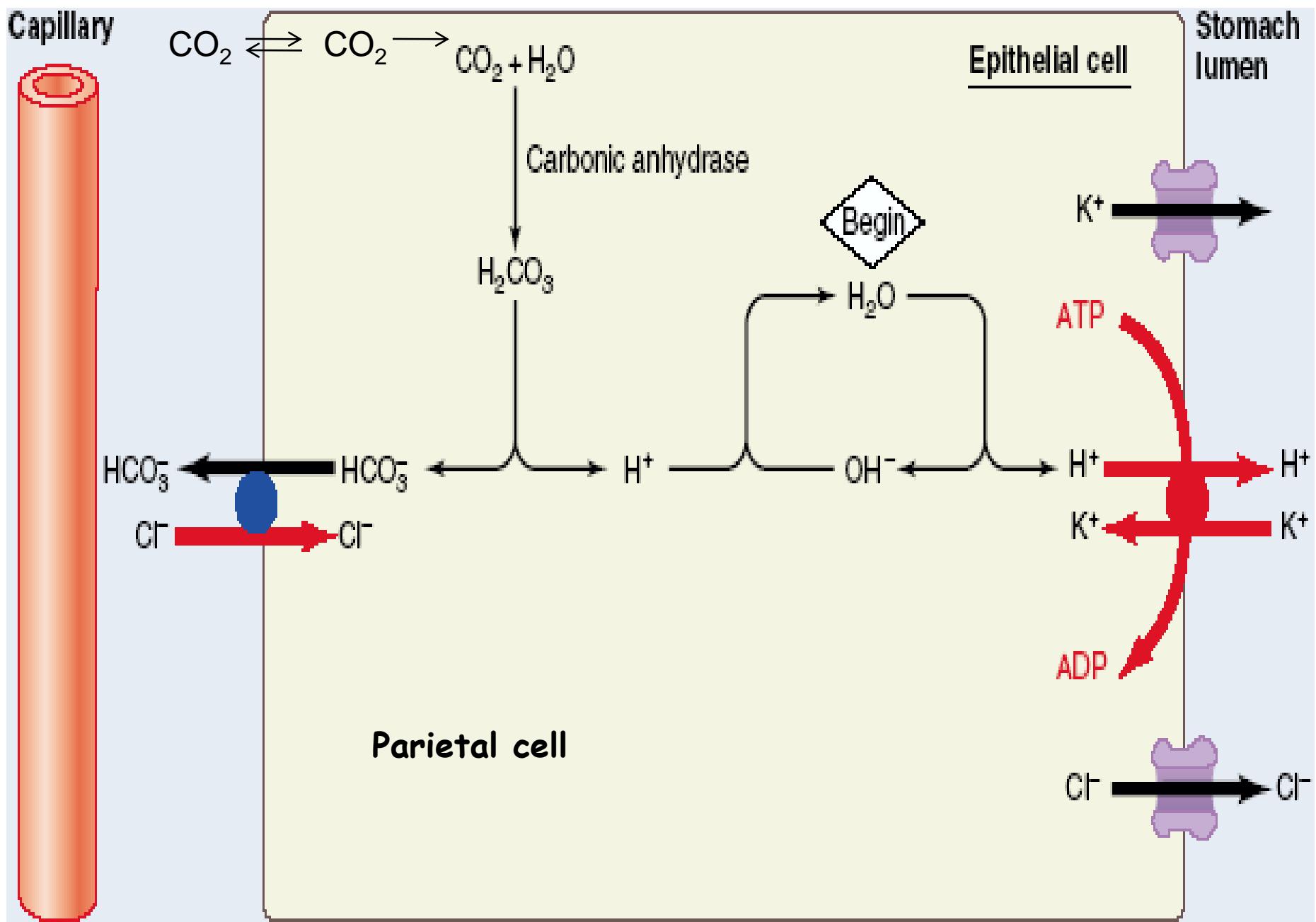
HCl Secretion

- Parietal cells secrete HCl which converts *inactive* pepsinogen to pepsin

Mechanism of acid secretion:

1. Within the parietal cell, CO_2 which diffused from ECF combines with H_2O to form $\text{H}_2\text{CO}_3 \Rightarrow \text{H}^+$ and HCO_3^-
2. At basolateral membrane, HCO_3^- released into blood in exchange with Cl^- via a Cl^- - HCO_3^- exchanger
 - Eventually HCO_3^- secreted back into GI tract by pancreas
3. At apical membrane, H^+ secreted into lumen of stomach via H^+ - K^+ ATPase or H^+ - K^+ pump
4. Cl^- follows H^+ into the lumen by diffusing through Cl^- channels in the apical membrane

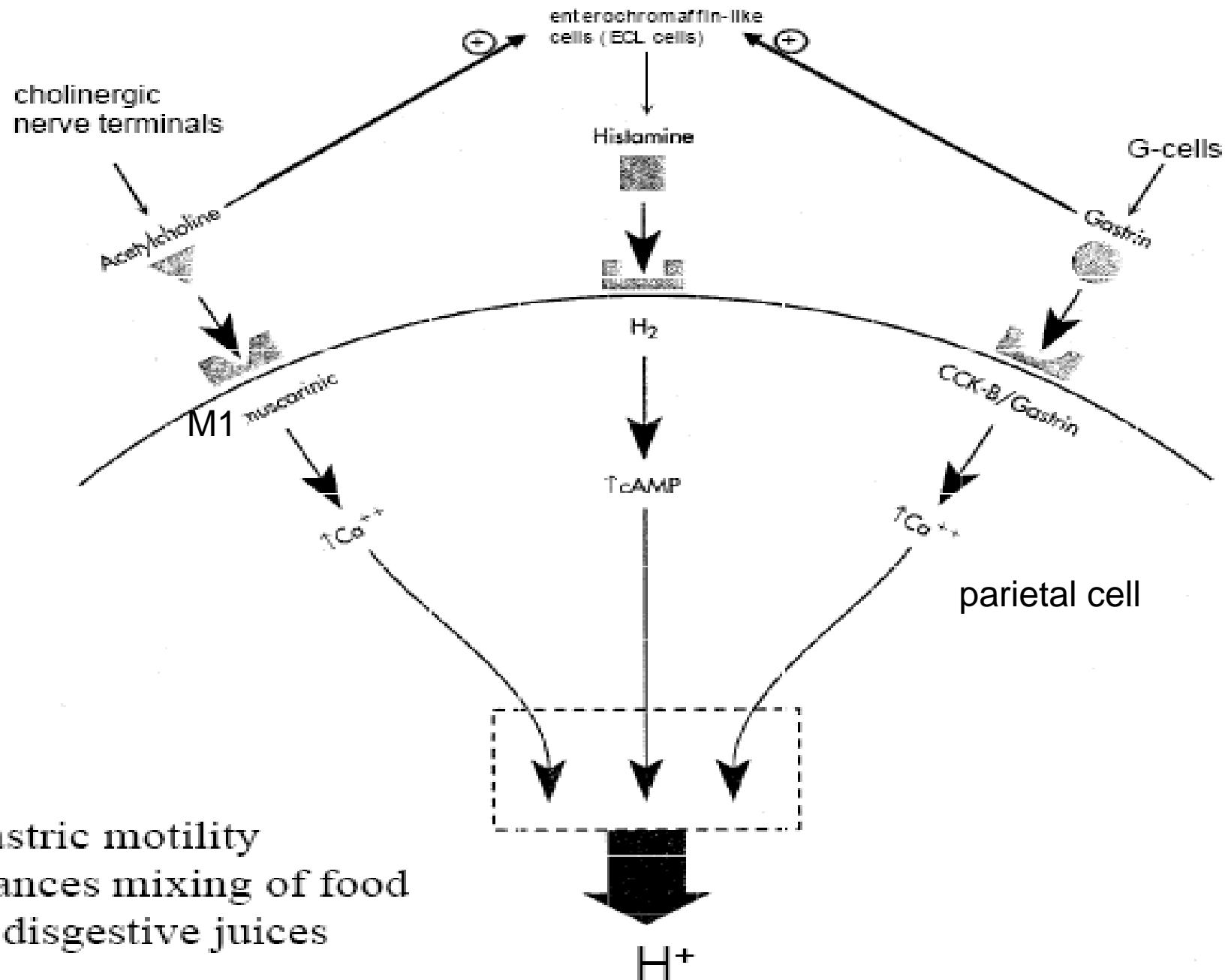
Mechanism of Acid secretion

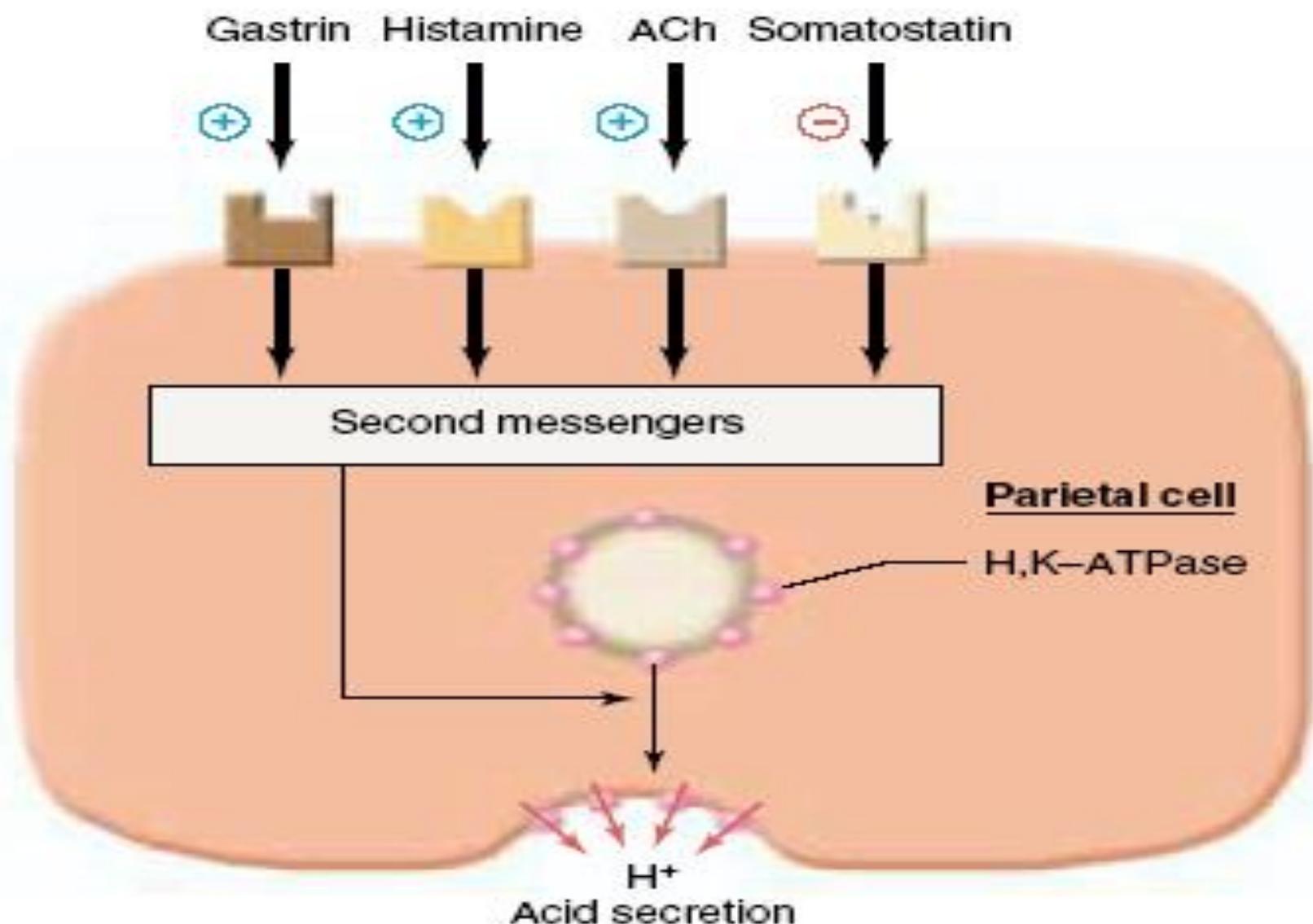


Regulation of HCl Secretion

- ❖ **Stimulation of Gastric Acid Secretion By:**
 - Vagal activation (Ach), Gastrin, histamine, Proteins in the food
- **ACh**
 - Released from vagus nerve
 - Binds to receptors on parietal cells $\Rightarrow \uparrow H^+$ secretion by parietal cells
 - **Atropine** blocks muscarinic receptors on parietal cells
 - **Pirenzepine** (selective M₁ antagonist)
- **Gastrin**
 - Released into circulation by **G cells** of stomach antrum
 - Binds to receptors on parietal cells \Rightarrow Stimulates H⁺ secretion
- **Histamine**
 - Released from mast cell -like cells in gastric mucosa called ECL cells
 - Binds to H₂ **receptors** on parietal cells
 - Produces H⁺ secretion by parietal cells
 - **Cimetidine , Ranitidine** \Rightarrow blocks H₂ receptors

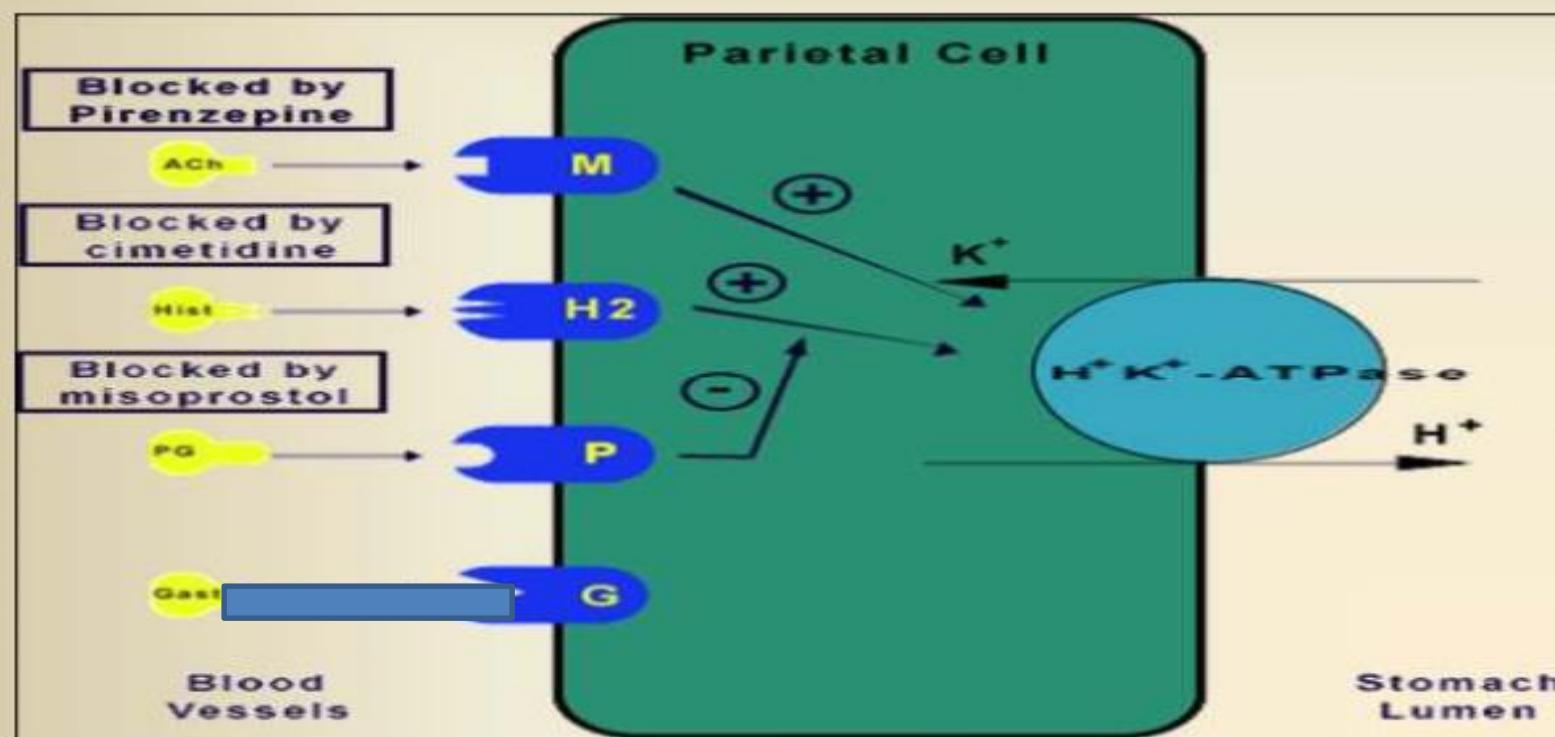
Regulation of acid secretion





The four inputs to parietal cells that regulate acid secretion by controlling the transfer of the H,K-ATPase pumps in cytoplasmic vesicle membranes to the plasma membrane.

Regulation of Gastric Acid Secretion



. Misoprostol

Analogue of prostaglandine E₂

Increased gastric **mucus production**

Enhanced duodenal **bicarbonate secretion**

Increased **mucosal blood flow**, which aids buffering of H⁺ that diffuses back across the mucosa

Direct effect on gastric acid secretion, reduce endogenous **histamine secretion**

Limit the damage caused by agents such as acid and alcohol to superficial mucosal cell

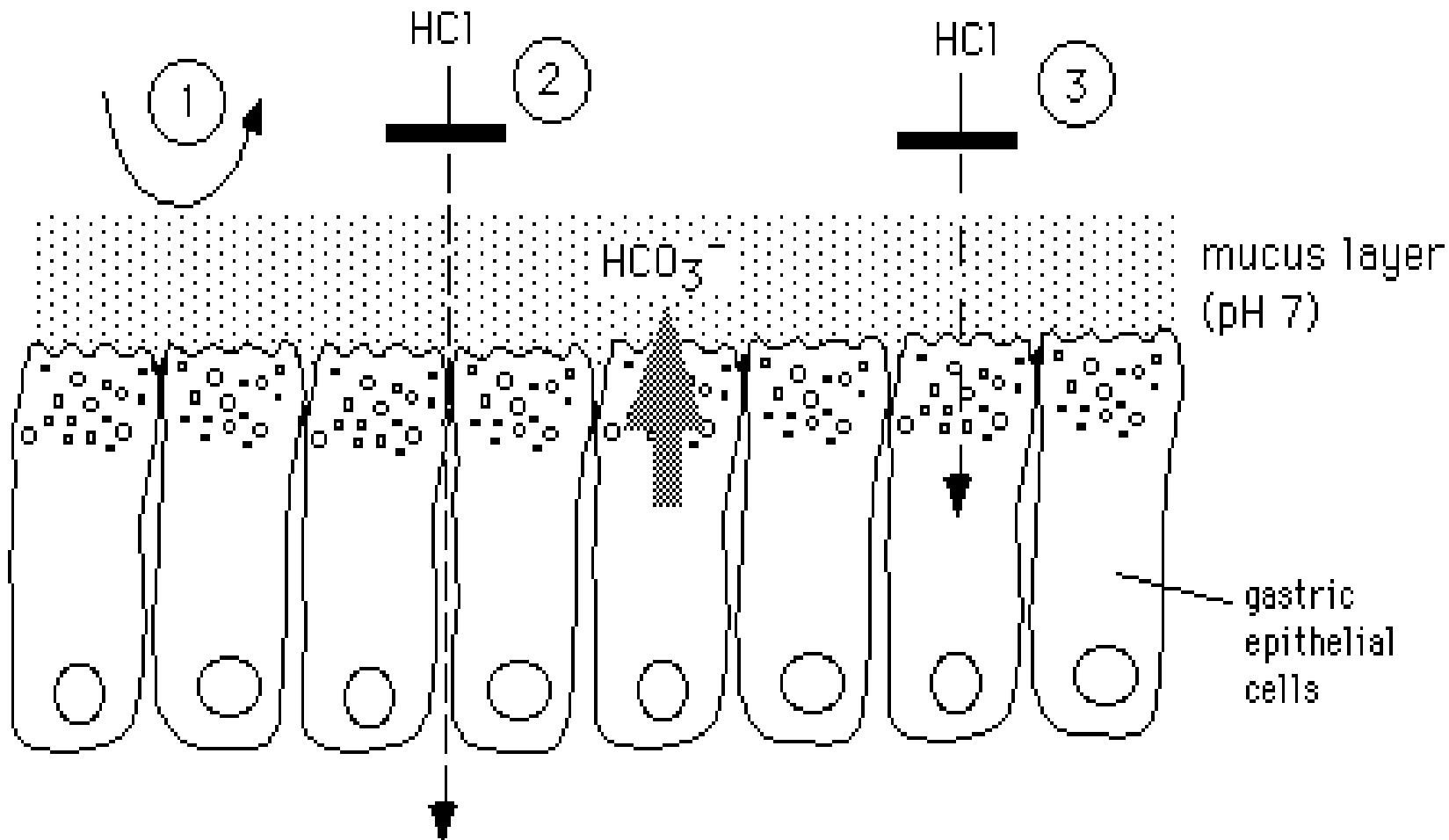
Used to reduce NSAID induced gastric damage

Stomach mucosal barrier

- The stomach is exposed to the harshest conditions in the digestive tract
- To keep from digesting itself, the stomach has a mucosal barrier with:
 1. A thick coat of bicarbonate-rich mucus on stomach wall (pH7)
 - protects gastric mucosa from gastric juice (pH 2)
 2. Epithelial cells are joined by tight junctions
 - prevent penetration of HCl between cells
 3. Gastric glands have cells impermeable to HCl
 4. high mucosal BF to rapidly remove H⁺ that crosses the mucus barrier

Gastric Mucosal Barrier

Luminal contents: pH 2 (gastric juice)



Protection against self-digestion by HCl

Phases of Gastric Juice Secretion

- Neural and hormonal mechanisms regulate the release of gastric juice
- Stimulatory and inhibitory events occur in 3 phases:
 - **Cephalic (reflex) phase**: prior to food entry to stomach
 - **Gastric phase**: once food enters the stomach
 - **Intestinal phase**: as partially digested food enters the duodenum

A. Cephalic Phase

- ✓ occurs before food enters the stomach, especially while it is being eaten.
- ✓ Stimulation results from :
 - the sight, or thought
 - smell, or taste of food \Rightarrow Stimulation of taste or smell receptors
- ✓ Mediated by vergus nerve
- ✓ the greater the appetite, the more intense is the stimulation
- ✓ accounts for about 20% of the gastric secretion associated with eating a meal.
- Inhibitory events include:
 - Loss of appetite or depression
 - Decrease in stimulation of the parasympathetic division

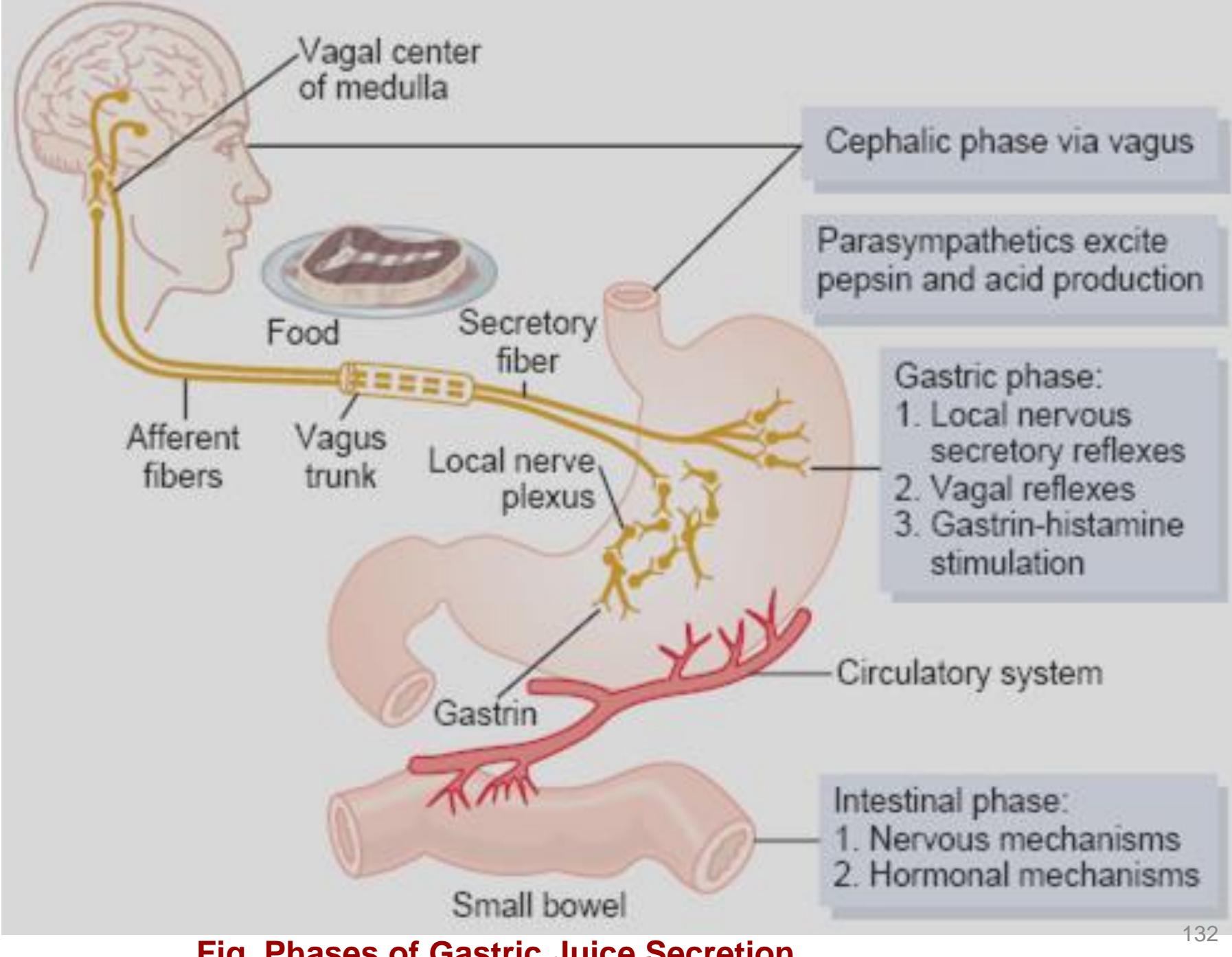
B. Gastric Phase

- Occurs when the food entered to the stomach
 - Under nervous & hormonal control
- 1. long vagovagal reflexes from stomach to the brain and back to the stomach - nervous mechanism
- 2. local enteric reflexes - nervous mechanism
- 3. the gastrin - hormonal mechanism
- Accounts for about 70% of the total gastric secretion.

- Excitatory events of the **gastric Phase** include:
 - Stomach distension
 - Activation of stretch receptors (neural activation)
 - Activation of chemoreceptors by peptides, caffeine, and rising pH
 - Release of gastrin to the blood
- Inhibitory events include:
 - A pH lower than 2
 - Emotional upset that overrides the parasympathetic division

C. Intestinal Phase

- Excitatory phase :
 - partially digested food enters the duodenum
 - ↓
 - small amount of **gastrin released by duodenal mucosa**
 - ↓
 - Causes small amount of stomach secretion (10%)
- Inhibitory phase :
 - distension of duodenum,
 - presence of fatty product
 - hypertonic chyme, and/or irritants in the duodenum
 - ↓↓↓↓
 - Inhibition of local reflexes and vagal nuclei
 - Closes the pyloric sphincter
 - Releases enterogastrones that inhibit gastric secretion



Gastritis - Inflammation of the Gastric Mucosa

- Usually superficial and therefore not very harmful,
- When sever, it can penetrate deeply into gastric mucosa
 - Causes almost complete atrophy of the gastric mucosa
- Clinical feature:
 - may be asymptomatic or
 - may cause variable epigastric pain with N-V or may cause haemorrhage
 - may present as overt hematemesis, melena, and potentially fatal blood loss

- In many people who have chronic gastritis, the mucosa gradually becomes atrophic until little or no gastric gland digestive secretion remains



- Loss of the stomach secretions in gastric atrophy
 - leads to *achlorhydria* and, to *pernicious anemia*.

Causes of gastritis:

- chronic bacterial infection(H. pylori) of the gastric mucosa.
- Is also associated with:-
 - Heavy use of NSAIDs
 - Excessive alcohol consumption
 - Heavy smoking
 - Severe stress (e.g. trauma, burn, surgery)
 - Ischemia and shock

Mechanisms include:

- Increased acid secretion with back diffusion
- Decreased production of bicarbonate buffer
- Reduced blood flow
- Disruption of the adherent mucus layer
- Direct damage to the epithelium

Peptic ulcer disease(PUD):>5mm

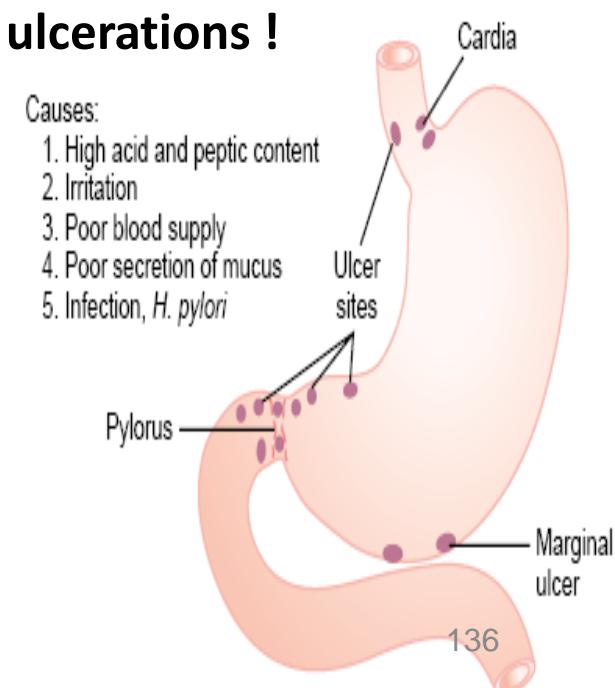
- chronic most often solitary lesions that occur in any portion of the GIT exposed to the aggressive action of acid-peptic juices
 - is an excoriated area of stomach or intestinal mucosa

Pathogenesis of PUD

- **Imbalance between the *gastroduodenal mucosal defence mechanisms* and the *damaging forces***
 - ✓ Occurs when the rate of gastric secretion > degree of protection
 - ✓ Gastric acid and pepsin are requisite for all peptic ulcerations !

❖ Occurs in the ff sites with decreasing order of frequency:

- ✓ 1. **Duodenum first portion (DU)**
- ✓ 2. **Stomach usually antrum**
- ✓ 3. Gastroesophageal junction
- ✓ 4. Within the margins of gastrojejunostomy
- ✓ 5. Duedenum, stomach, or jejunum of patients with Zollinger-Ellison syndrome



NORMAL

Aggressive Forces:

Gastric acidity
Peptic activity

IMPAIRED DEFENSE

Aggravating Causes:

H. pylori infection
NSAID, aspirin
Cigarettes, alcohol
Impaired regulation of acid-pepsin secretion

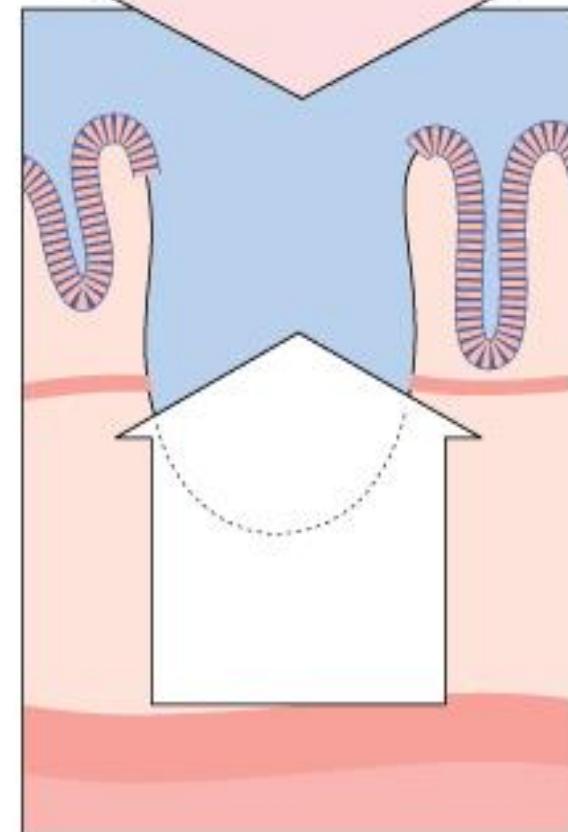
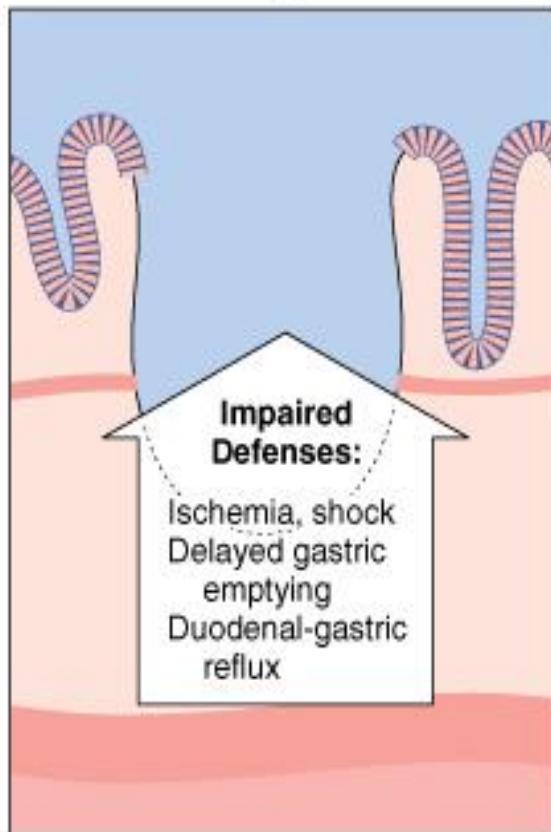
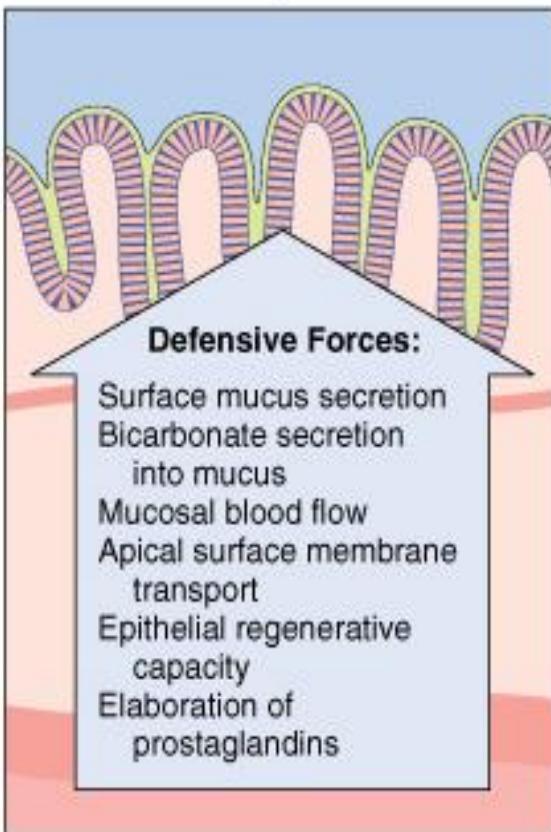
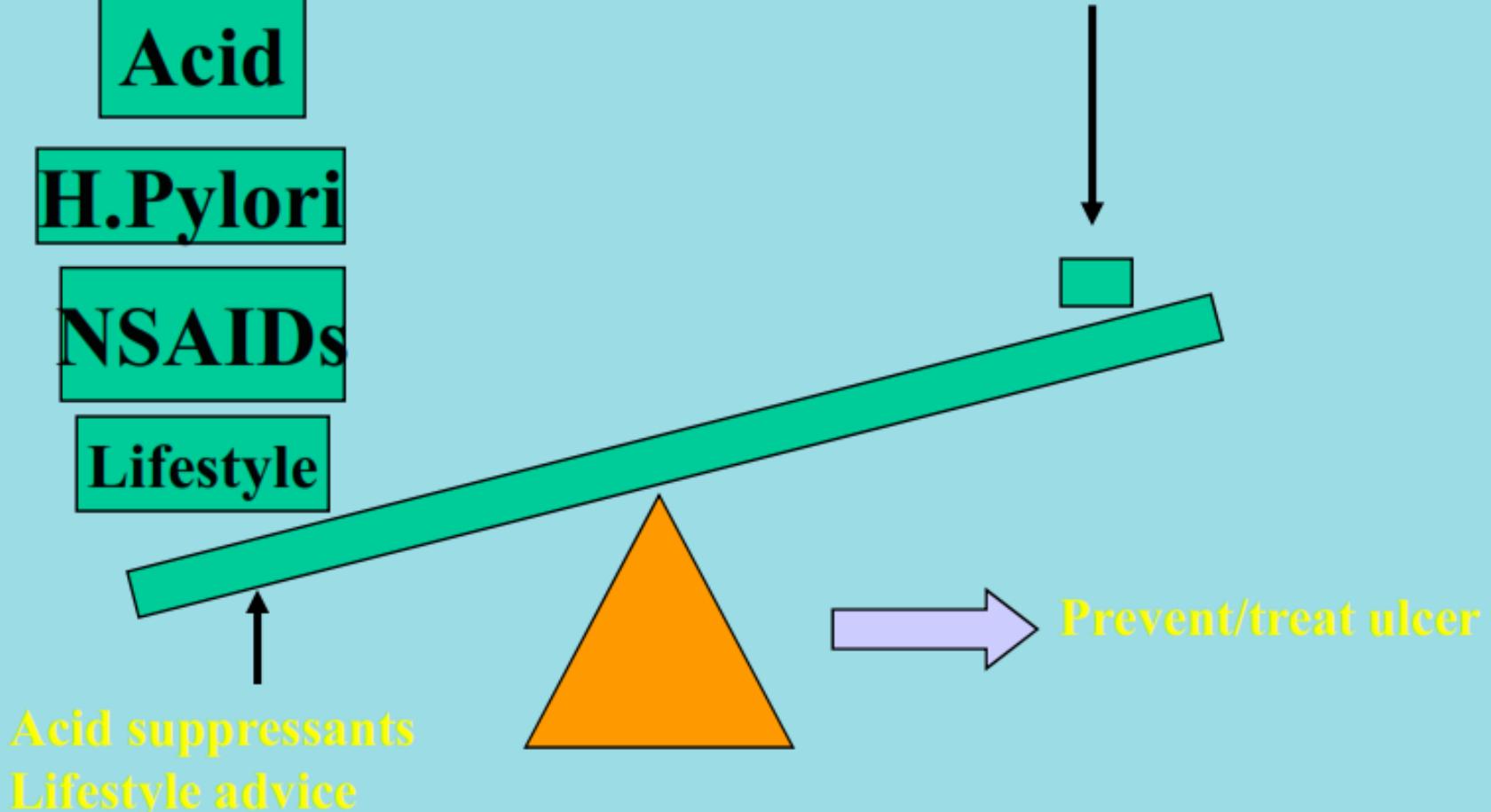


Fig. An imbalance between the gastroduodenal mucosal defenses and the damaging forces that overcome such defenses

Aggressive factors

- Acid**
- H.Pylori**
- NSAIDs**
- Lifestyle**

Mucosal defense

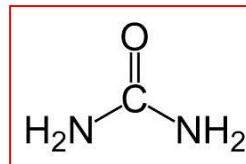


Acid suppressants
Lifestyle advice

NB: Acid plus pepsin is much more ulcerogenic than acid alone

Helicobacter pylori Infection

- Many PUD patients have chronic infection of the terminal portions of gastric mucosa and initial portions of duodenal mucosa
 - ***H. pylori* is commonly ascribed in 90% of DUs, and up to 80% of GUs**
- The bacterium is capable of penetrating the mucosal barrier by:
 - its physical capability to burrow through the barrier
 - Releasing bacterial digestive enzymes that liquefy the barrier.
 - Metabolize urea to NH₃ and CO₂ by an enzyme called **urease**
- The acidic stomach secretions can then penetrate into the mucosa
- literally digest the gastrointestinal wall \Rightarrow peptic ulceration



✓ One of the dx is “urea breath” test: radio-labeled urea is ingested

(radioactive C-14 or non-radioactive C-13)

- If *H. pylori* positive, urease will split urea to CO₂ (radio-labeled, exhaled) and NH₃
- finally the radioactivity is detected in the breath(detect c-14/C-13 in the exhaled air)

Other factors that predispose to ulcers include:

- **1. smoking**
 - because of increased vagal stimulation of the stomach secretory glands
- **2. alcohol**
 - because it tends to break down the mucosal barrier
- **3. aspirin and other non-steroidal anti-inflammatory drugs**
 - Strong tendency for breaking down the mucosal barrier

Clinical Features of PUD

- ✓ **Epigastric burning or aching pain**
- ✓ Few present with complications such as anemia, frank hemorrhage or perforation
- ✓ **Pain tends to be worse at night and occurs usually 1-3 hrs after meal (DU)**

Main complications are:

- ❖ **Bleeding**
- ❖ **Perforation**
- ❖ **Obstruction from edema or scarring**

	Gastric ulcer	Duodenal ulcer
Age	Between the age groups 50-60.	Between age groups of 20-50.
Male:Female Ratio	Almost equal.	2:1.
Pain	Epigastic area	It Felt above the umbilicus and right to the midline.
Radiation of Pain	No radiation.	May radiate to back.
Nature of Pain	Periodical.	Periodical.
Weight Loss	Present due to reduced intake.	No weight loss as patient feels better with eating and hence goes on eating.
Hemorrhages	Hamatemesis (blood vomiting) may be present	Black or bloody stools (malena) may be present
Gastric symptoms	Sensation of feeling fullness, indigestion, heartburn, gas trouble or belching.	Bloated feeling of intestinal gas.
Malignancy	Chances are Common.	Chances are Rare.
Aggravating factors	Immediately after food	1-2 hours after food, when the stomach gets empty, middle of the night or sleep.
Ameliorating factors	Vomiting or alkali foods.	After taking food.

Causes:

1. High acid and peptic content
2. Irritation
3. Poor blood supply
4. Poor secretion of mucus
5. Infection, *H. pylori*

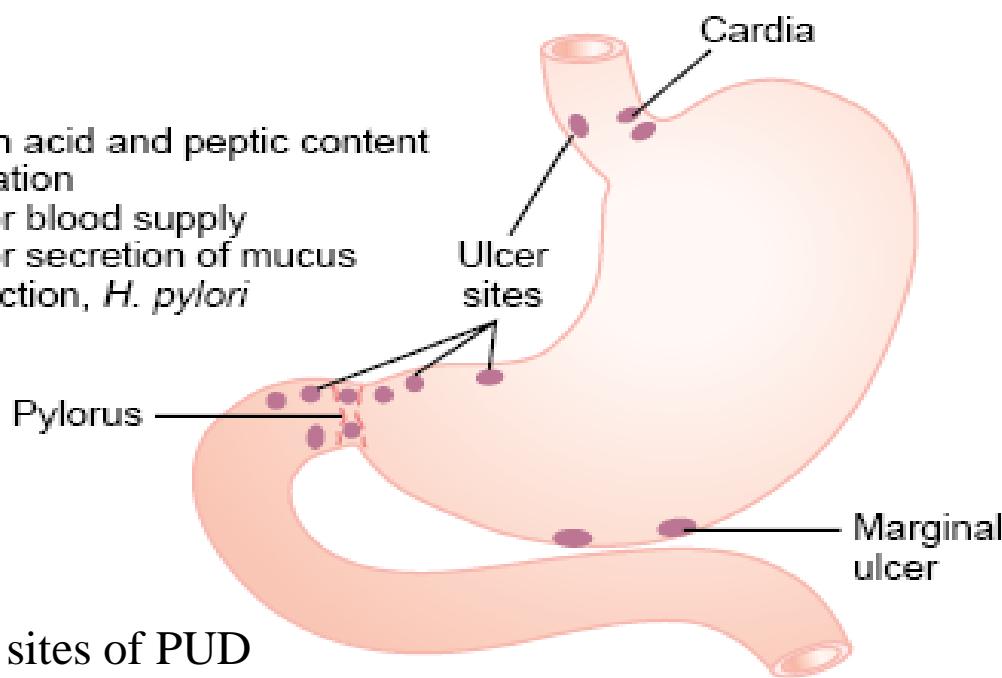


Fig. Causes and major sites of PUD

Zollinger-Ellison syndrome :first described by Robert Zollinger and Edwin Ellison

- ✓ Severe peptic ulcer secondary to gastric acid hypersecretion
- ✓ **due to unregulated gastrin release from an endocrine tumor (gastrinoma)**
- ✓ Tumor commonly occurs in the head of the pancreas (non- β) or duodenum
- ✓ Gastrin stimulates acid secretion through:
 - gastrin receptors on parietal cells and
 - inducing histamine release from ECL cells.

Treatment options for PUD: - can be treated by:

- 1. Use

(e.)

- 2. Adm

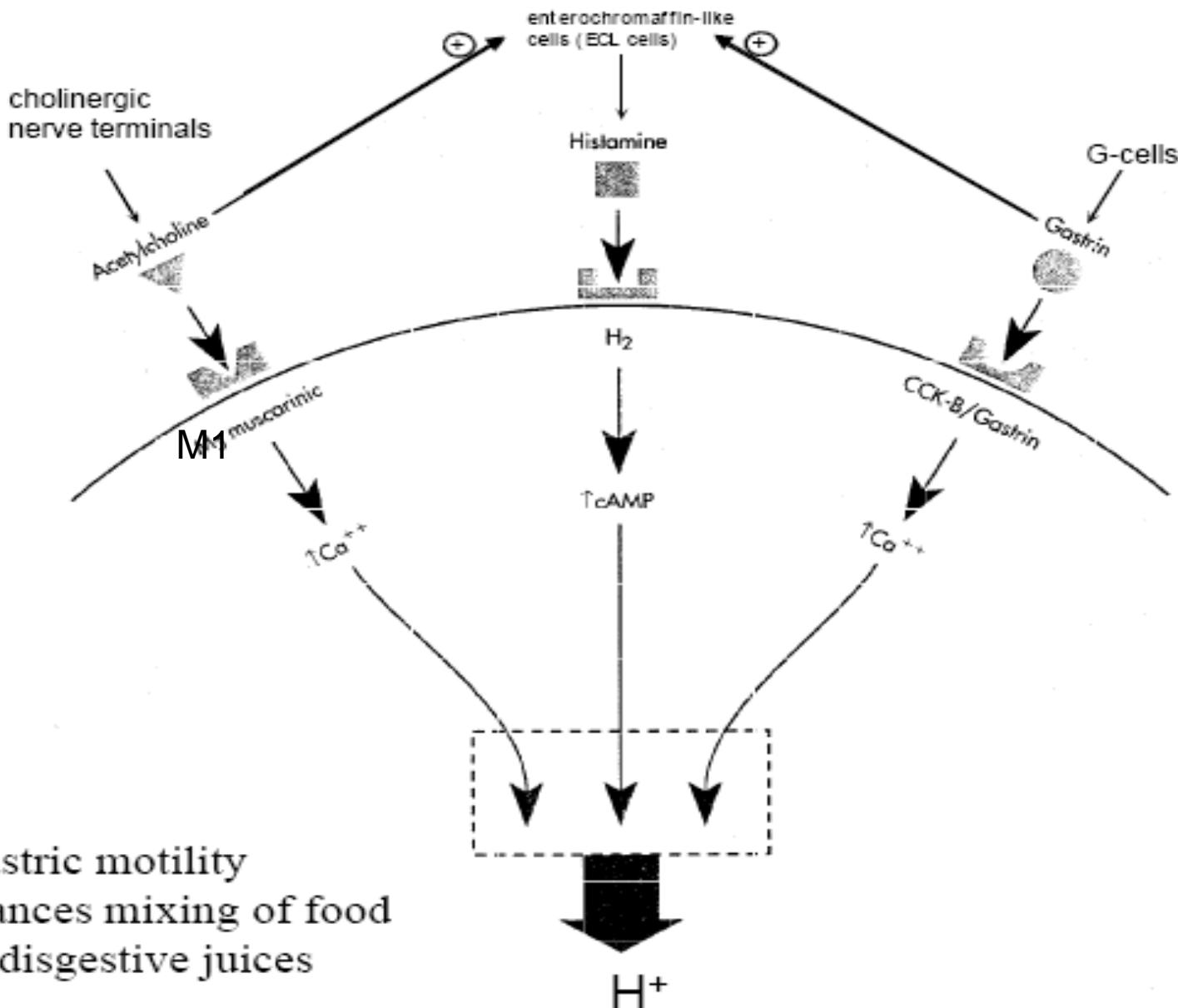
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- I
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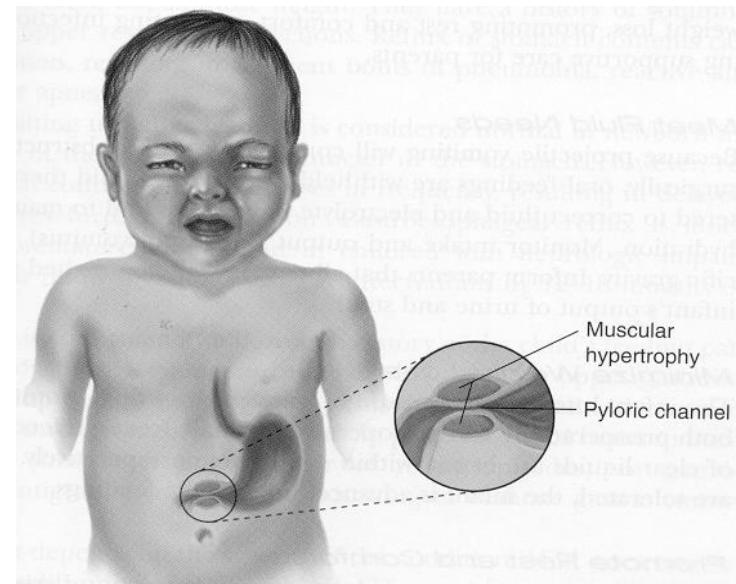
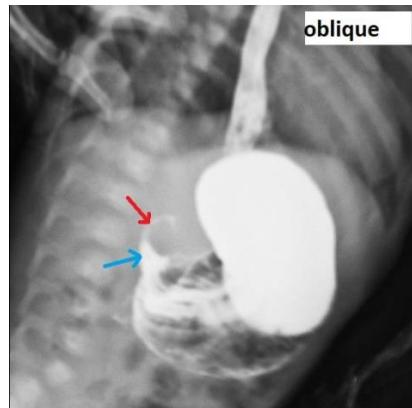
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- 3. Anti + gastric motility
enhances mixing of food
- Eg. A and digestive juices



Gastric outlet obstruction/pyloric stenosis

- Is ulcer-related complication of PUD
- Common Cause:
 - fibrotic constriction after peptic ulceration
 - mechanical obstruction secondary to scar formation in the peripyloric areas
 - **Hypertrophic pyloric stenosis (HPS)**- the most common cause of GOO in infants
 - **hypertrophy** and hyperplasia of the muscular layers of the **pylorus**.
- Vomiting becomes projectile
(ACIDIC VOMITUS)



Gastrointestinal obstruction: GO

The GIT can be obstructed at almost any point along its course

- ✓ Obstructions of upper GIT (pyloric, small intestine) cause vomiting

- ✓ Obstructions of large intestine cause constipation

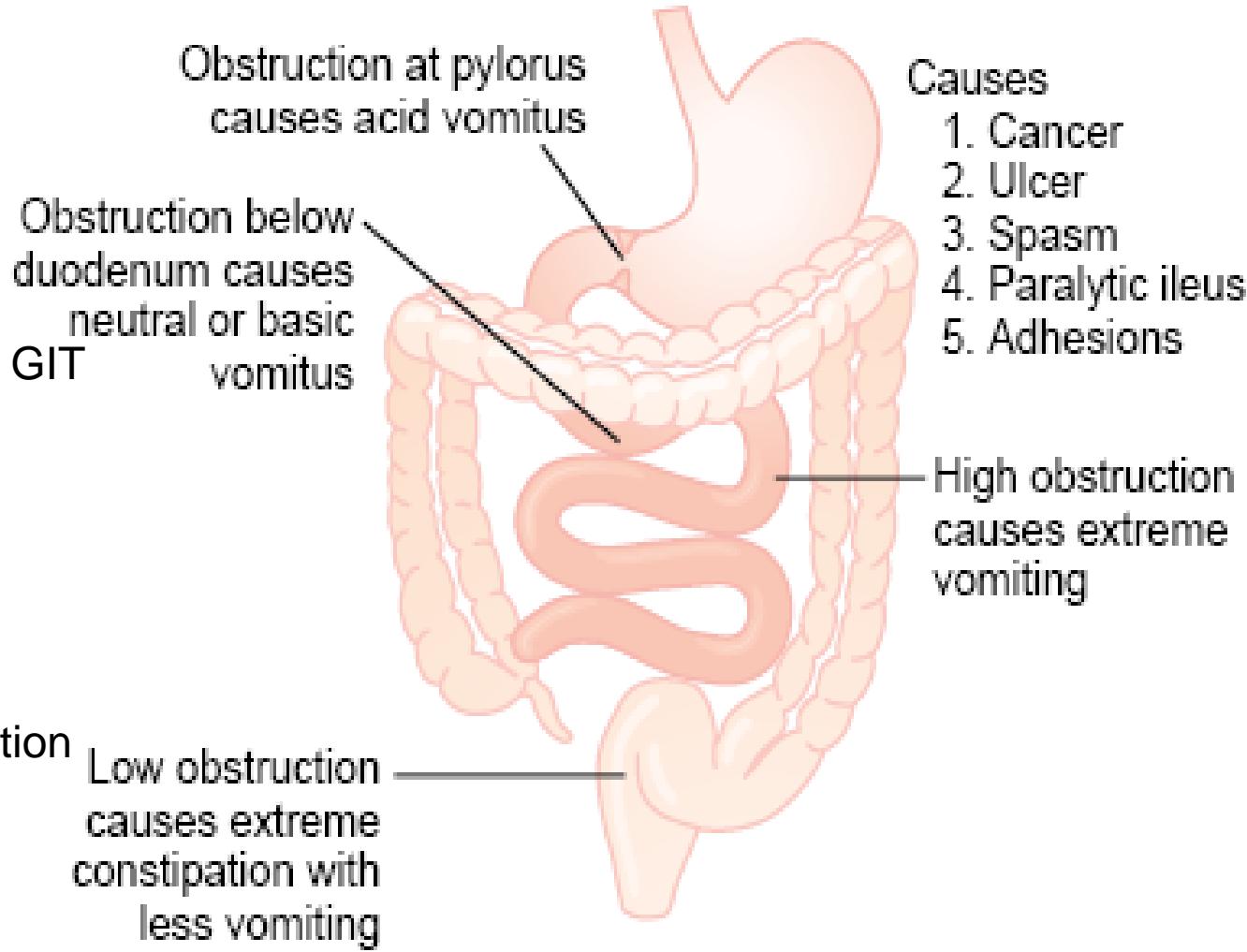


Fig. Obstruction in different parts of the gastrointestinal tract.

Pancreas

- Has endocrine and exocrine function
- **The endocrine function:** islets of langrhans with cells releasing;
 - **insulin** from beta cells
 - **Glucagon** from alpha cells
 - **Somatostatin** from Delta cells
 - **Pancreatic polypeptide** from PP cells

↓↓↓↓

❖ essential for regulation of metabolism
- **Exocrine function**
 - Secretes pancreatic juice: breaks down all categories of foodstuff
 - Acini (clusters of secretory cells) contain zymogen granules with digestive enzymes

Pancreatic exocrine secretion

- The pancreatic digestive enzymes are secreted by *pancreatic acini*
- large volumes of HCO_3^- secreted by the small ductules and larger ducts leading from the acini
 - ↓↓
- flows through a long *pancreatic duct*
 - ↓
- empties into the duodenum through the *papilla of Vater*, surrounded by the *sphincter of Oddi*
- The sphincter controls the emptying

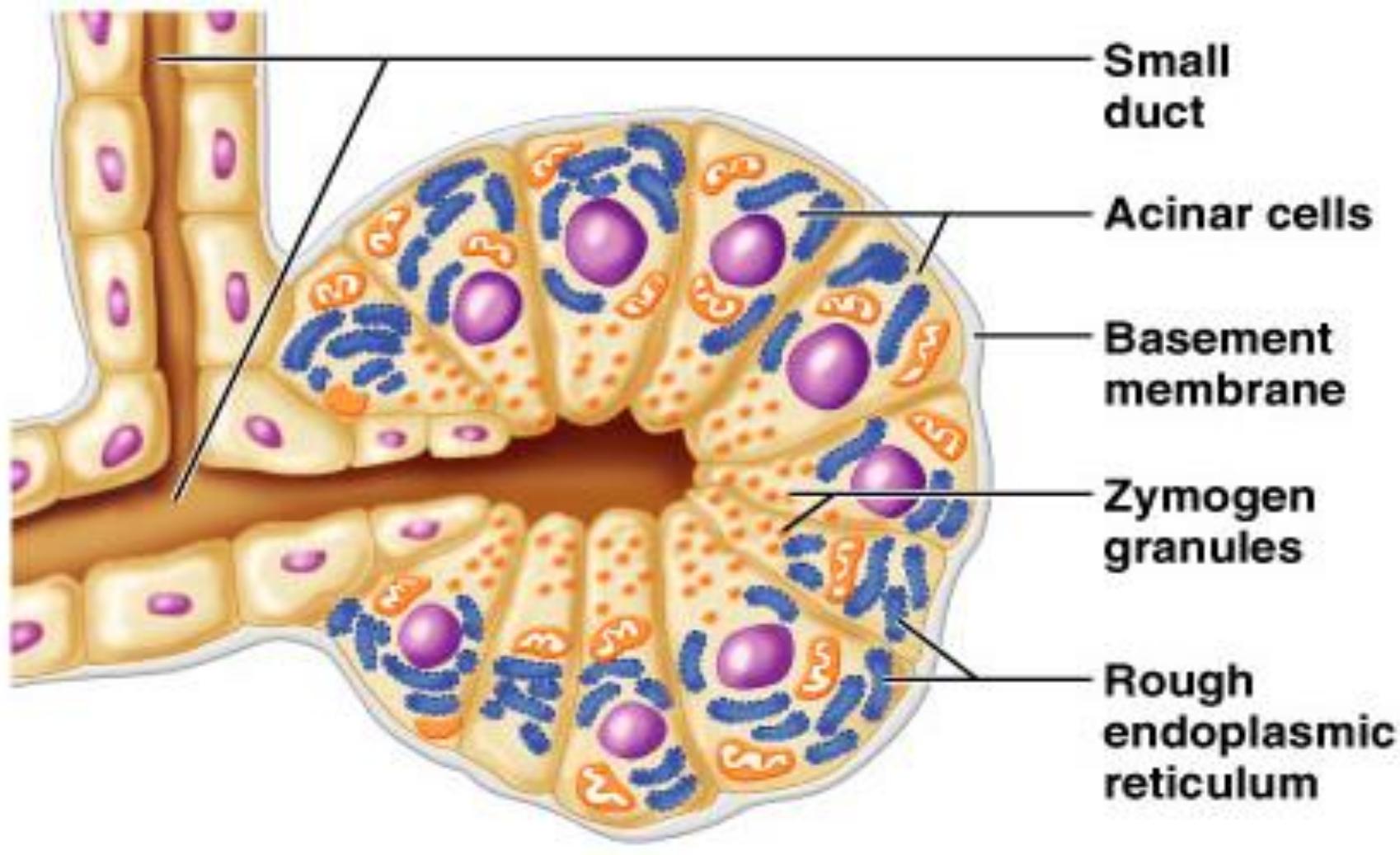


Fig. Acini of the Pancreas

Regulation of Pancreatic Secretion

Basic stimuli for pancreatic secretion:

1. Parasympathetic nervous stimulation

- ✓ causes release of pancreatic juice

2. Cholecystokinin

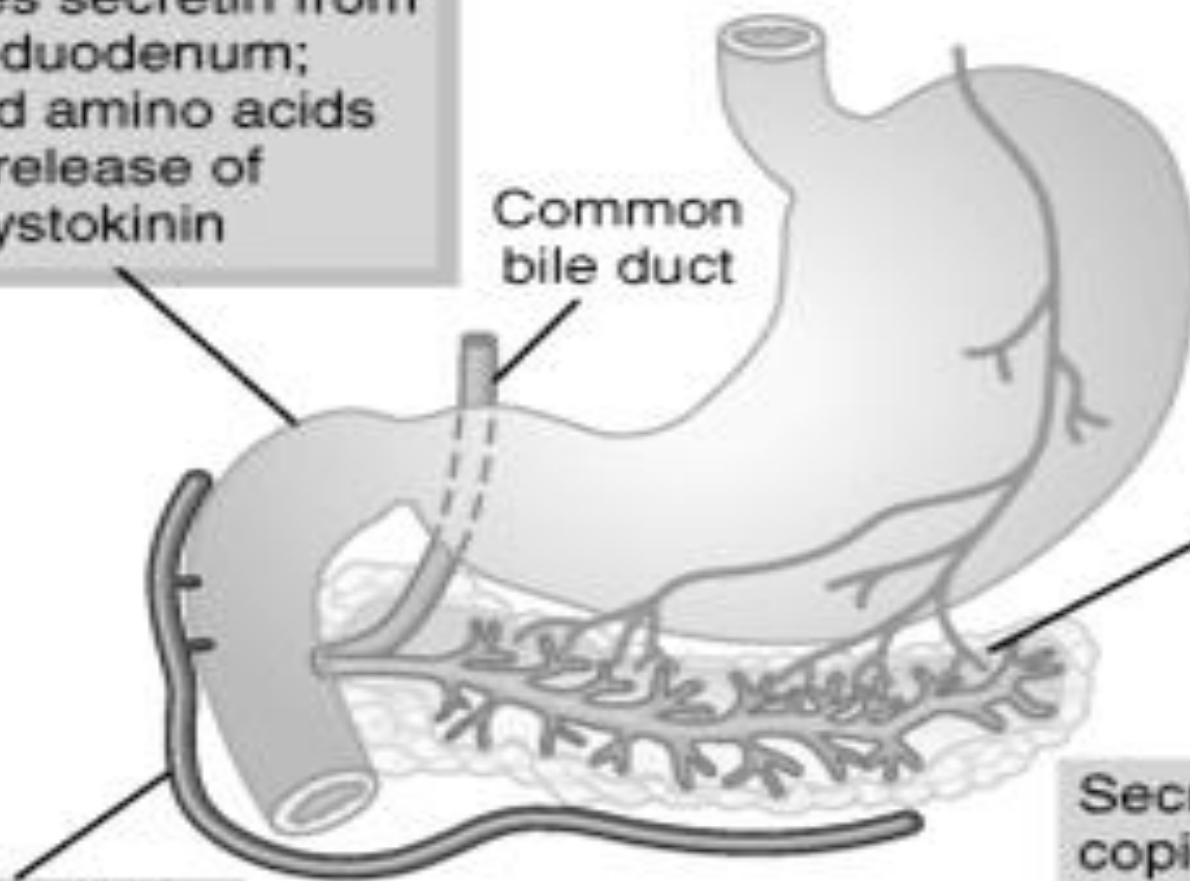
- ✓ secreted by the duodenal and upper jejunal mucosa
 - when food enters the small intestine
- ✓ causes release of pancreatic juice rich in enzymes

3. Secretin

- ✓ secreted by the duodenal and jejunal mucosa
 - when highly acidic food enters the small intestine
- ✓ causes release of pancreatic juice rich in bicarbonate but poor in enzymes

- **Acinar cells (enzymatic secretion)**
 - Have receptors for **CCK**, and muscarinic receptors for ACh
 - **CCK** is the most important stimulant from I cells
 - Secreted in presence of amino acids and fatty acids in intestinal lumen
 - **ACh** also stimulates enzyme secretion
- **Ductal cells (aqueous secretion of HCO_3^-)**
 - Have receptors for **secretin**, CCK, and ACh
 - **Secretin** (from S cells of duodenum) is major stimulant
 - Secreted in response to H^+ in intestine
 - **Effects of secretin are potentiated by both CCK and ACh**

Acid from stomach releases secretin from wall of duodenum; fats and amino acids cause release of cholecystokinin



Secretin and cholecystokinin absorbed into blood stream

Common bile duct

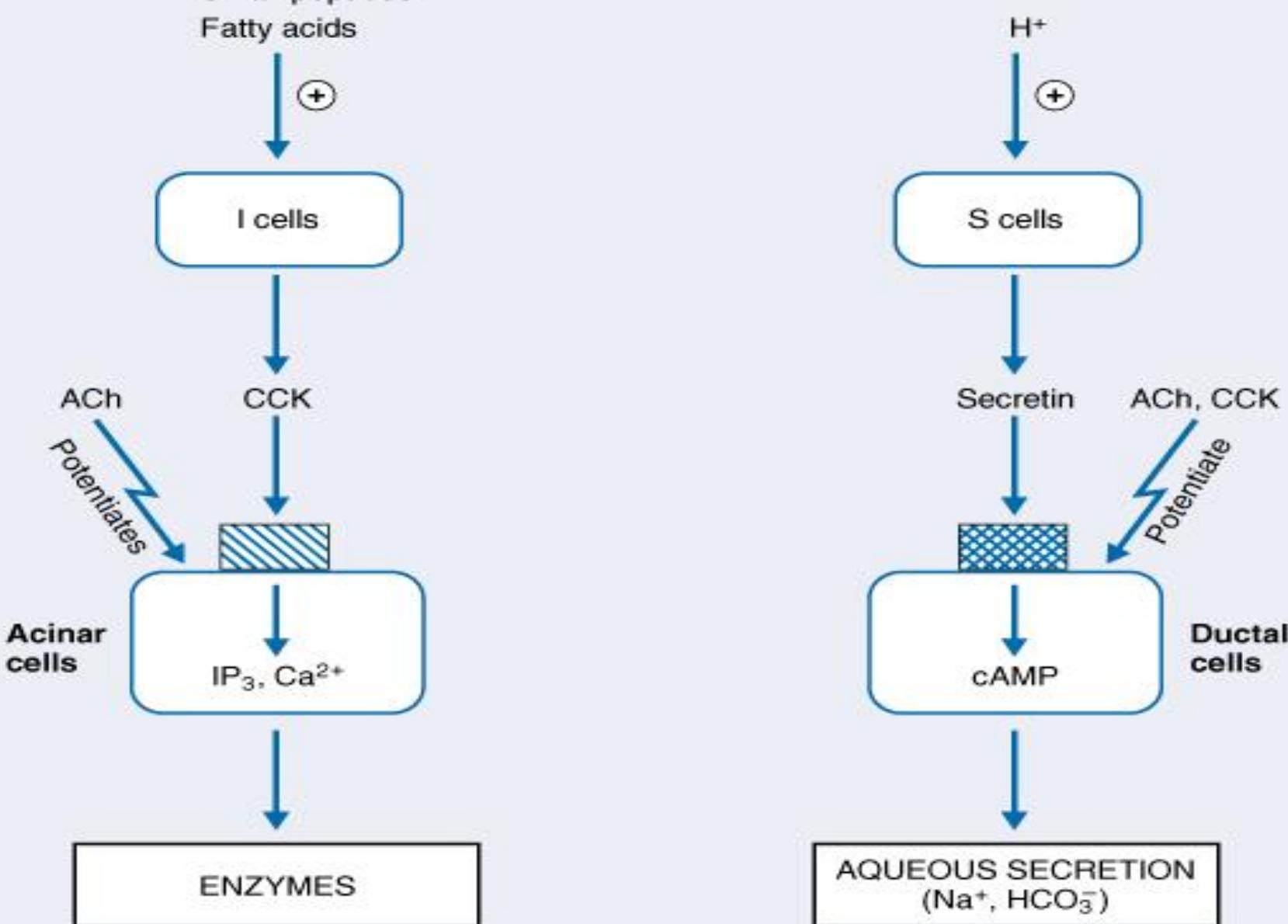
Vagal stimulation releases enzymes into acini

Secretin causes copious secretion of pancreatic fluid and bicarbonate; cholecystokinin causes secretion of enzymes

Fig. Regulation of pancreatic juice secretion

REGULATION OF PANCREATIC SECRETION

Phenylalanine, methionine, tryptophan
Small peptides
Fatty acids



Phases of Pancreatic Secretion

- *Cephalic phase, gastric phase, and intestinal phase*
- **1. Cephalic and Gastric Phases.**
 - The same nervous signals from the brain that cause secretion in the stomach
 - 20 % of the total secretion of pancreatic enzymes after a meal.
- **2. Intestinal Phase**
 - After chyme leaves the stomach and enters the small intestine
 - pancreatic secretion becomes copious
 - **mainly in response to the hormones secretin and CCK**



Functions of pancreatic secretions

i. Digestive function

- secretion of digestive enzymes
- neutralization of acidic chyme
 - ✓ provide optimum pH for pancreatic enzymes

ii. Protective function

- neutralization of acidic chyme \Rightarrow protection from acidic damage of intestinal mucosa

Pancreatic Digestive Enzymes

- Contains multiple enzymes for digesting all of the three major types of food:
 - proteins
 - carbohydrates, and
 - fats
- also contains large quantities of bicarbonate ions,
 - important in neutralizing the acidity of the chyme
 - Provide optimal environment for pancreatic enzymes

Enzymes of Pancreatic Juice

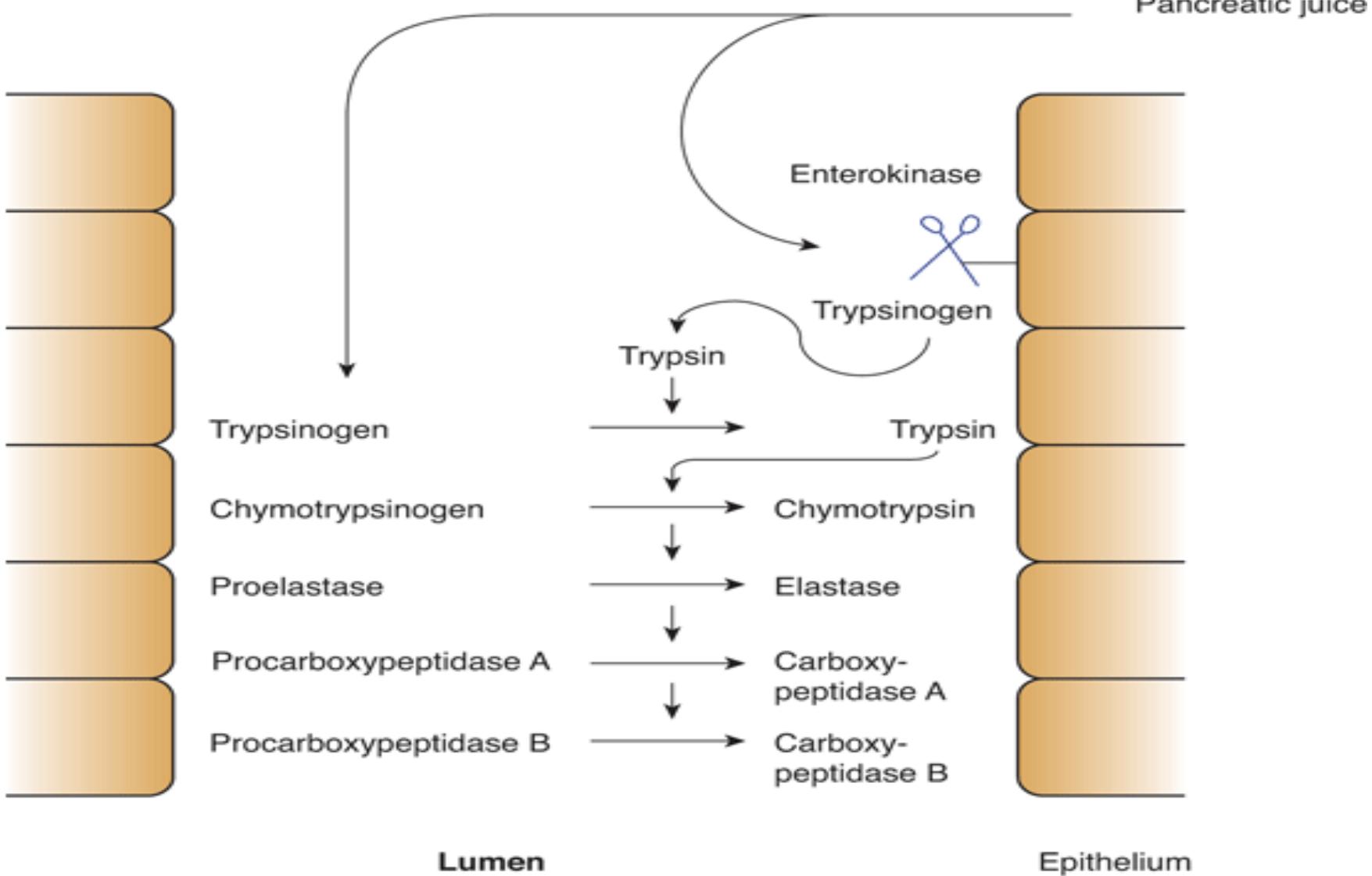
- ✓ Some enzymes are released in inactive form and activated in the duodenum
- Examples:
 - *trypsinogen*, *chymotrypsinogen*, and *procarboxypeptidase*

Activated only after they are secreted into the duodenum

- Trypsinogen Enterokinase, trypsin → Trypsine
- Chymotrypsinogen Trypsin → chymotrypsin
- Procarboxypeptidase Trypsin → carboxypeptidase

❖ Enterokinase deficiency occurs as a congenital abnormality and leads to protein malnutrition.

- ✓ Active enzymes secreted are:
 - Amylase, lipases, and nucleases
 - ❖ These enzymes require ions or bile for optimal activity



- ❖ The formation of active peptidases from their inactive precursors
- ❖ This occurs only when they have reached their site of action,
- ❖ it is secondary to the action of the brush border hydrolase, called **enterokinase**

- pancreatic enzyme for digesting carbohydrates is
 - ✓ *pancreatic amylase*
- Fat digesting enzymes are:
 - ✓ *pancreatic lipase* - hydrolyze neutral fat into fatty acids + monoglycerides
 - ✓ *cholesterol esterase* - causes hydrolysis of cholesterol esters
 - ✓ *phospholipase* - splits fatty acids from phospholipids
- Protein digesting enzymes:
 - ✓ *trypsin*
 - ✓ *chymotrypsin*
 - ✓ *carboxyproteases*

- Trypsine inhibitor is secreted along with the other secretions



- prevent self digestion of the pancreas

- No or weak trypsin inhibitor \Leftrightarrow pancreatic damage \Leftrightarrow pancreatitis

- **Pancreatitis** – inflammation of pancreas

- When pancreas is severely damaged or duct is blocked,



- pancreatic secretion may be pooled in the damaged areas of pancreas



- the effect of trypsin inhibitor is often overwhelmed,



- the pancreatic protease secretions rapidly become activated



- can literally digest the pancreas \Leftrightarrow a condition called **acute pancreatitis**

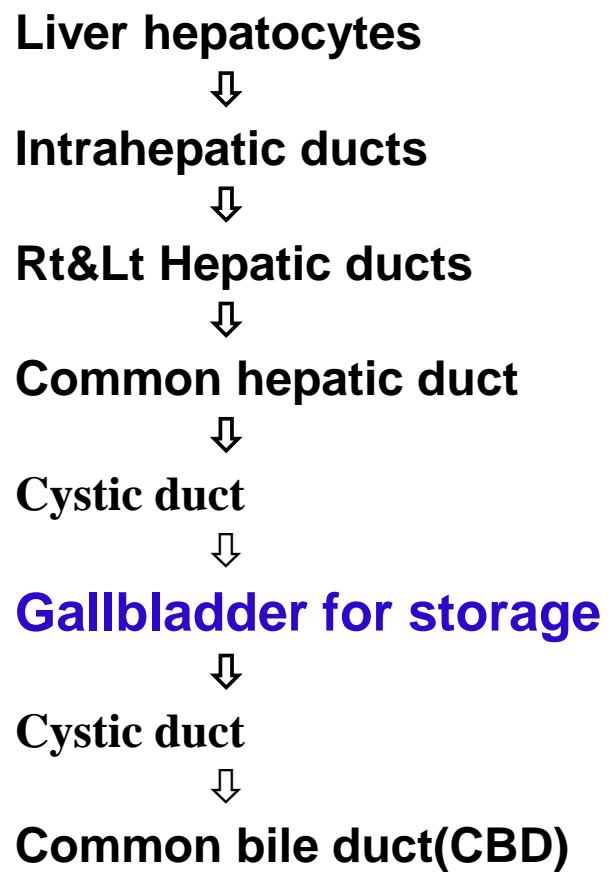
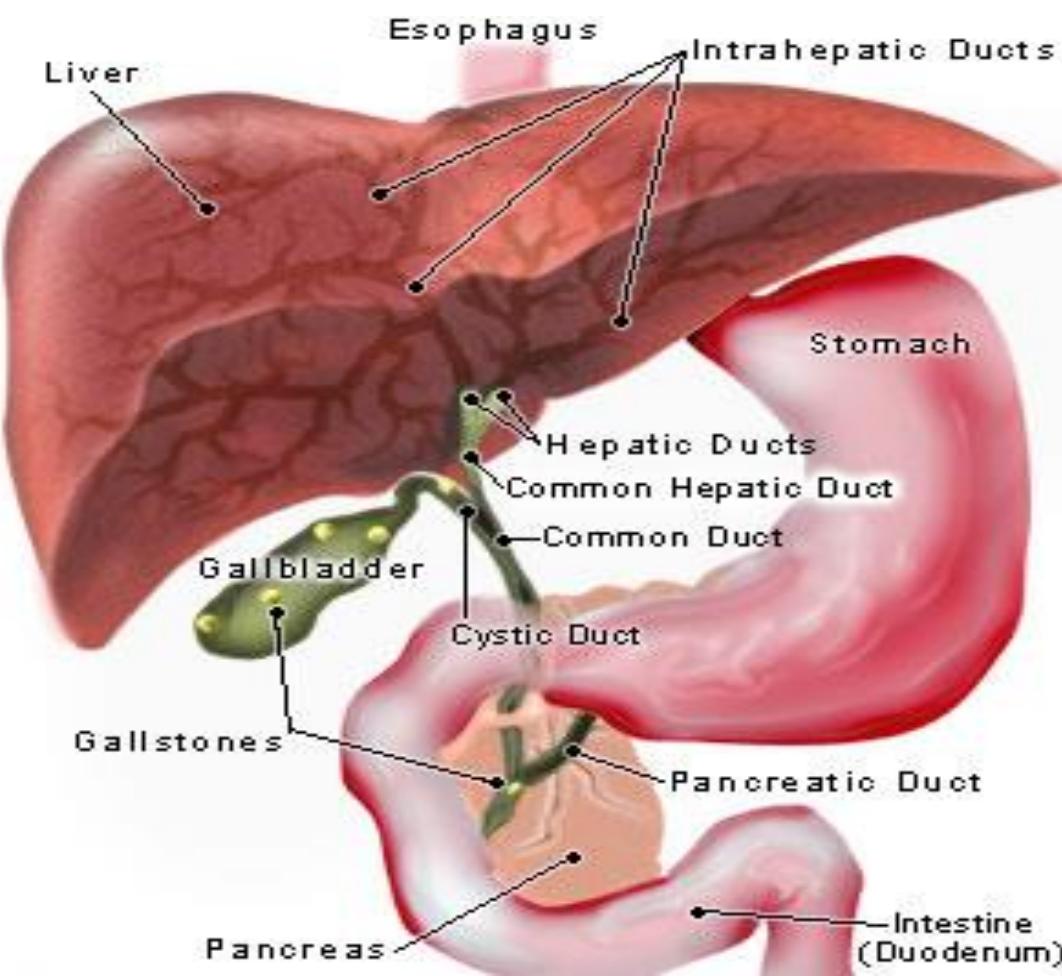
❖ **Risk: Gallstones and alcohol account for 80–90% of cases the acute pancreatitis**

Secretion of Bile by the Liver

- *Bile* is secreted by the liver hepatocytes + ductules (secrete electrolytes)
 ↓
- stored in the gallbladder until needed in duodenum.
 ↓
- Released from gallbladder into small intestine when GB contracts
- water, NaCl, & other small electrolytes absorbed through gallbladder mucosa
 ↓
- concentrating the remaining bile constituents: bile salts, cholesterol, lecithin, and bilirubin

<u>Composition of Bile</u>	<u>After concentration</u>	
Lecithin	0.04 g/dl	0.3 g/dl
HCO ₃ ⁻	28 mEq/L	10 mEq/L
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl

Bile synthesis and secretion



- ✓ Unconjugated bile salts are reabsorbed from the bile ducts (cholehepatic circulation)
- ✓ Conjugated bile salts enter the duodenum
 - reabsorbed from terminal ileum by Na⁺ symport carrier ISBT (**ileal sodium bile acid co-transporter**) after carrying out its function
 - **circulated back to the liver (enterohepatic circulation) after** used for fat digestion

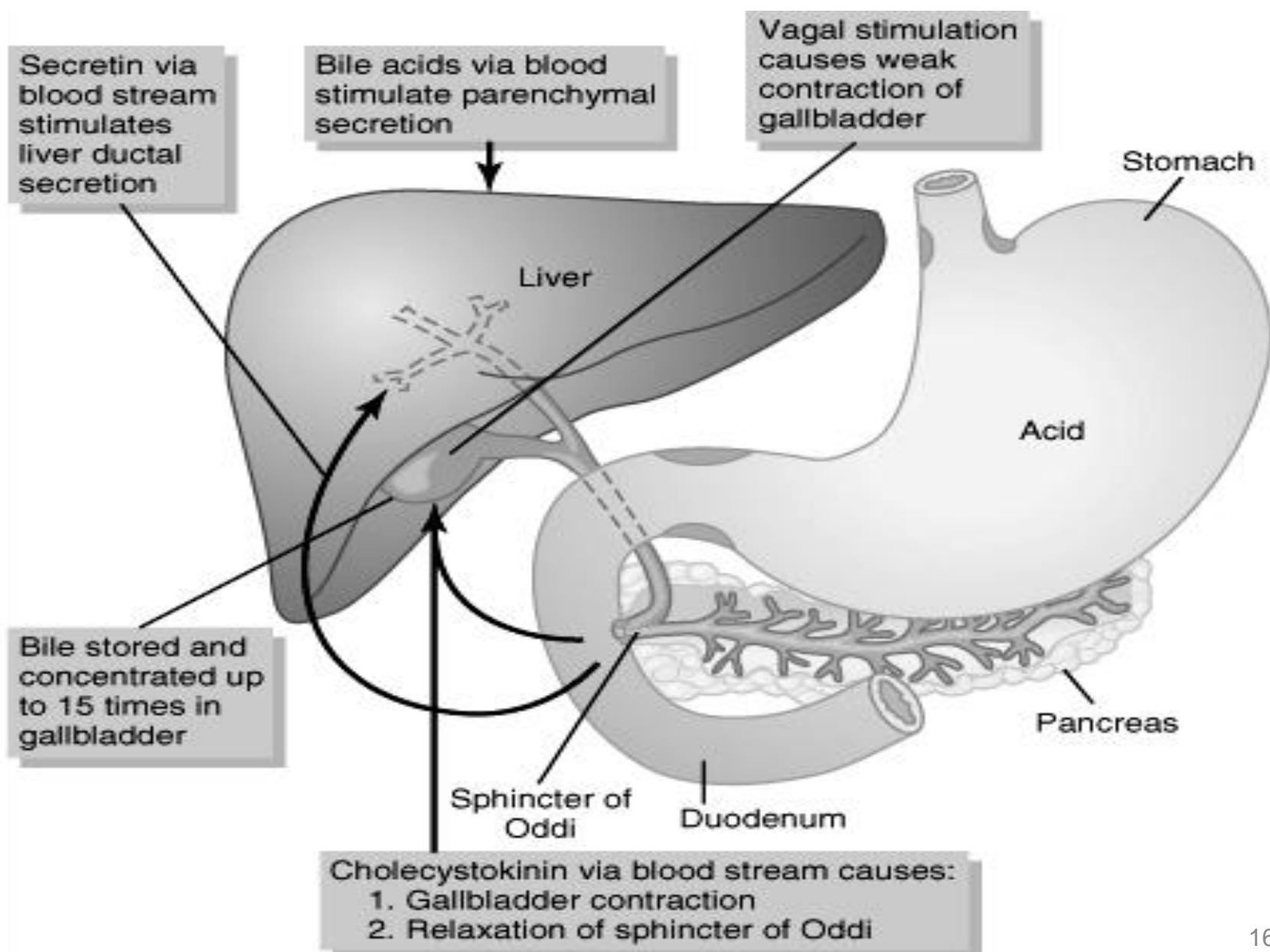
Functions of bile:- two important functions:

- bile plays an important facilitatory role in fat digestion & absorption
- bile serves as a means for excretion of waste products from blood:
 - Bilirubin - an end product of hemoglobin destruction
 - excesses of cholesterol

Function of Bile Salts in Fat Digestion & Absorption

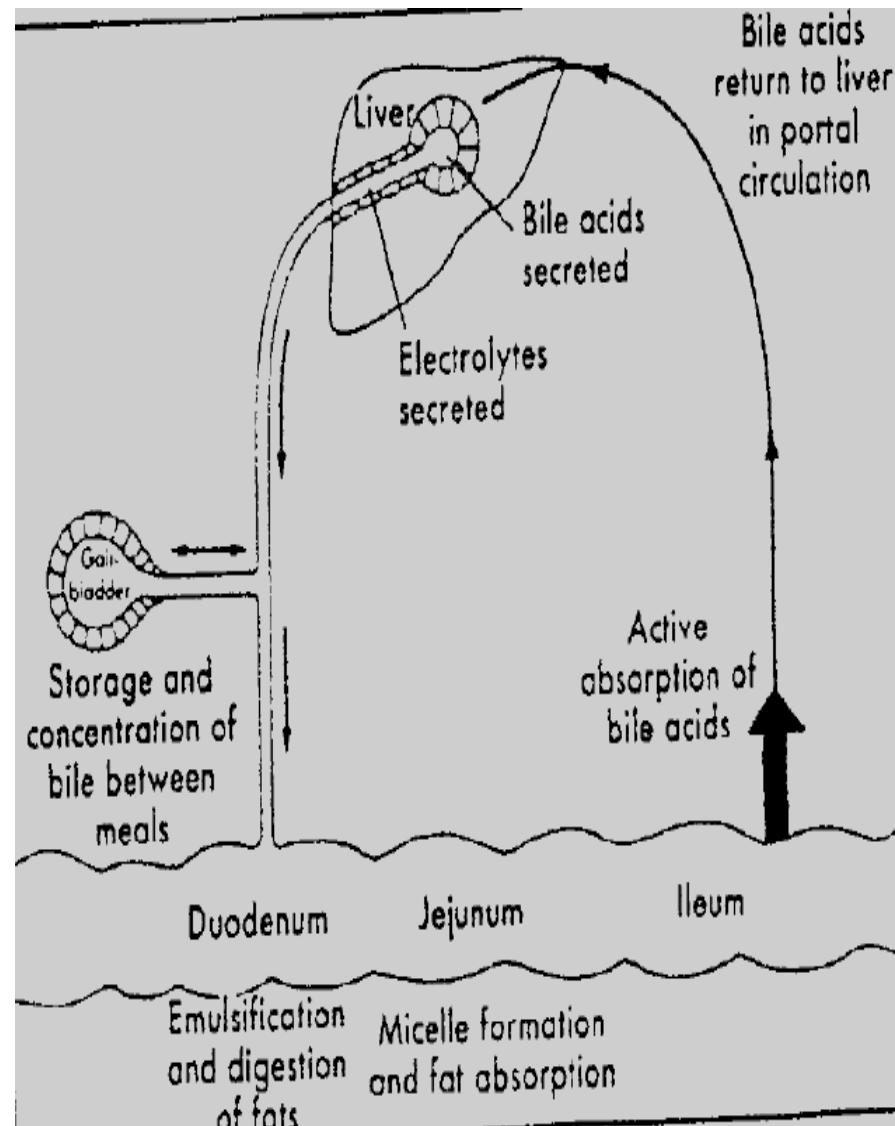
- Have a detergent action on the fat particles in the food.
 - Emulsifying or detergent function of bile salts \Rightarrow breaks the fat globules into minute droplets \Rightarrow \uparrow SA for lipase action
- helps in the absorption of digestive products of lipid
 - ❖ By forming micelles

Regulation of bile secretion

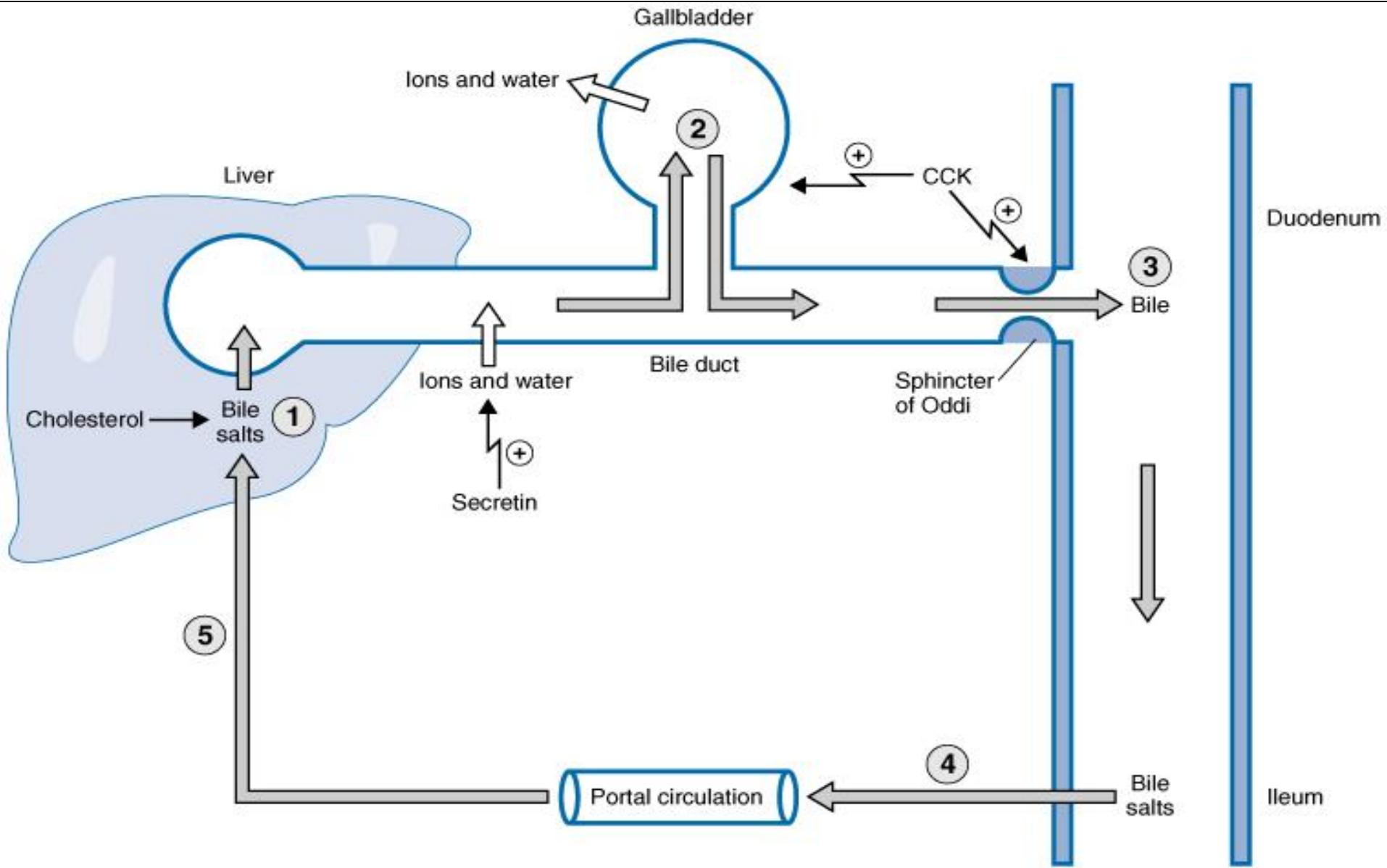


Enterohepatic circulation of bile salt (conjugated bile salt)

- ✓ is recirculation of the bile salts
 - ❖ Between intestine and liver
- ✓ About 94 % of bile salts are reabsorbed to blood mainly in ileum (few jejunum and colon)
 - ❖ primarily by an active, ISBT in ileum
 - ❖ Lesser extent by non-carrier-mediated transport in jejunum, ileum, and colon
- ↓
- ✓ then enter the portal blood and pass back to the liver
- ↓
- ✓ salts are absorbed almost entirely back into liver and then are resecreted into bile.



Bile Secretion and Recycling [enterohepatic circulation]

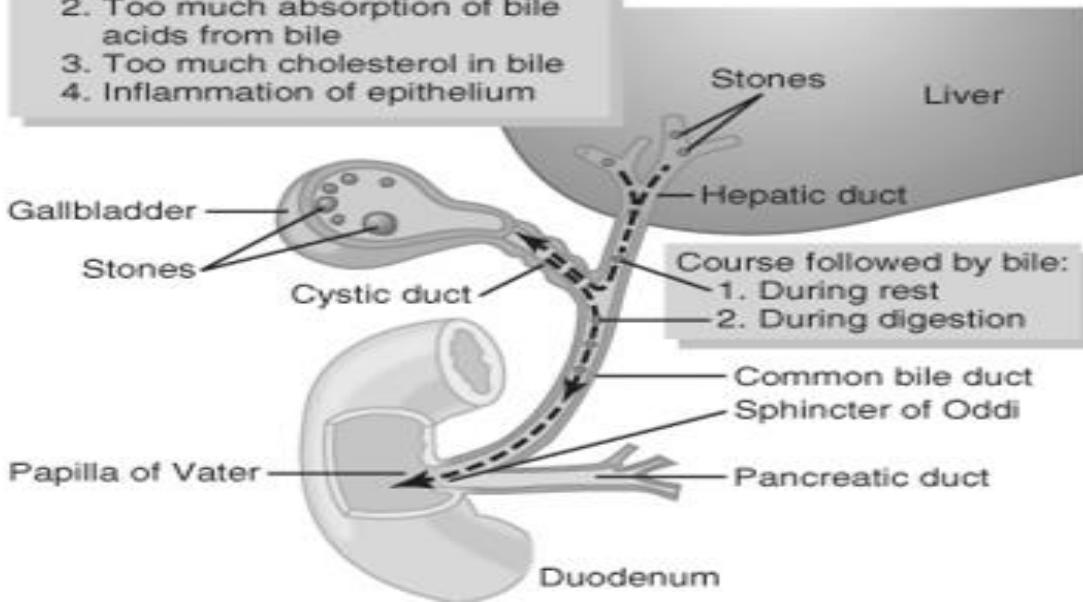


Formation of gallstones (cholelithiasis)

- When the bile becomes excessively concentrated in the gallbladder due to:
 - too much absorption of water and bile acid from the bile
 - Too much cholesterol in the bile \Rightarrow cholesterol precipitation \Rightarrow **cholesterol gallstones**
 - Bile salts and lecithin in the bile help solubilize cholesterol
 - But \uparrow [cholesterol] in bile to the point that it cannot be solubilized, it starts to crystallize, forming gallstones
 - Inflammation of the epithelium altering its absorptive character

Causes of gallstones:

1. Too much absorption of water from bile
2. Too much absorption of bile acids from bile
3. Too much cholesterol in bile
4. Inflammation of epithelium



- **Cholecystitis:** inflammation of the GB
- **Choledocholithiasis:** stone in the CBD
- **Cholangitis:** inflammation of CBD and CHD

- **If a gallstone is small**, it may pass thru the CBD into intestine with no complications
- **If a gallstone is large**
 - A larger stone may become lodged in the opening of the gallbladder,
 ↓
 - **causing painful contractile spasms of the smooth muscle.**
 - when a gallstone lodges in the common bile duct (choledocholithiasis)
 - prevents bile from entering the intestine
 - The absence of bile in the intestine decreases the rate of fat digestion and absorption,
 ↓
 - approximately half of ingested fat is not digested and passes on to large intestine and eventually appears in the feces⇒ **steatorrhea**
- **Cholecystectomy:**
 - surgical removal of gall bladder for treatment of sever gall stone
 - generally must avoid foods that are particularly high in fat content.

Secretions of the Small Intestine

i. Mucus by Brunner's Glands in the Duodenum

- The mucus contains excess of bicarbonate ions
 - protect the duodenal wall from acidic chyme from the stomach
- large amount of alkaline mucus is secreted in response to:
 1. Tactile or irritating stimuli on the duodenal mucosa
 2. Vagal stimulation
 - ✓ causes increased secretion concurrently with stomach secretion
 3. Gastrointestinal hormones: specially secretin \Rightarrow \uparrow secretion
- ❖ Brunner's gland secretion inhibited by sympathetic stimulation
 - one of the factors that causes duodenum to be the site of PUD in about 50% of ulcer patients

ii. Secretion of Intestinal Digestive Juices

- By crypts of Lieberkühn
 - small pits over the entire surface of small intestine
 - Secret digestive enzymes, mucus, electrolytes

Digestive Enzymes in the Small Intestinal Secretion

1. **peptidases**: for splitting small peptides into amino acids:
 - ✓ aminopeptidase & dipeptidase
2. **Four amylolytic enzymes**: split disaccharides into monosaccharides
 - ✓ maltase, isomaltase, sucrase, and lactase
3. **Small amounts of Enteric lipase**:
 - split neutral fats into fatty acids + monoglycerides

- **Functions of succus entericus (intestinal juice)**
 1. Digestive function
 - ✓ by the effect of digestive enzymes
 2. Protective function
 - ✓ the alkaline mucus protects the intestinal wall from acidic chime
 3. Activator function
 - ✓ the enterokinase activates trypsinogen

Secretions of the Large Intestine

- **Mucus Secretion**- from large intestinal crypts of Lieberkühn
 - The mucosa of the large intestine, like the small intestine, has many crypts of Lieberkühn
 - Unlike small intestine, large intestinal crypts of Lieberkühn have:
 - No villi
 - No enzyme secretion,
 - secrete only mucus with bicarbonate
 - Functions of the alkaline mucus secretion:
 - protects the large intestinal wall against excoriation
 - Provide adherent medium for holding fecal matter together
 - Alkalinity of the secretion ($\text{pH}=8$) protects the mucosa from acids formed in the feces

Vomiting or Emesis

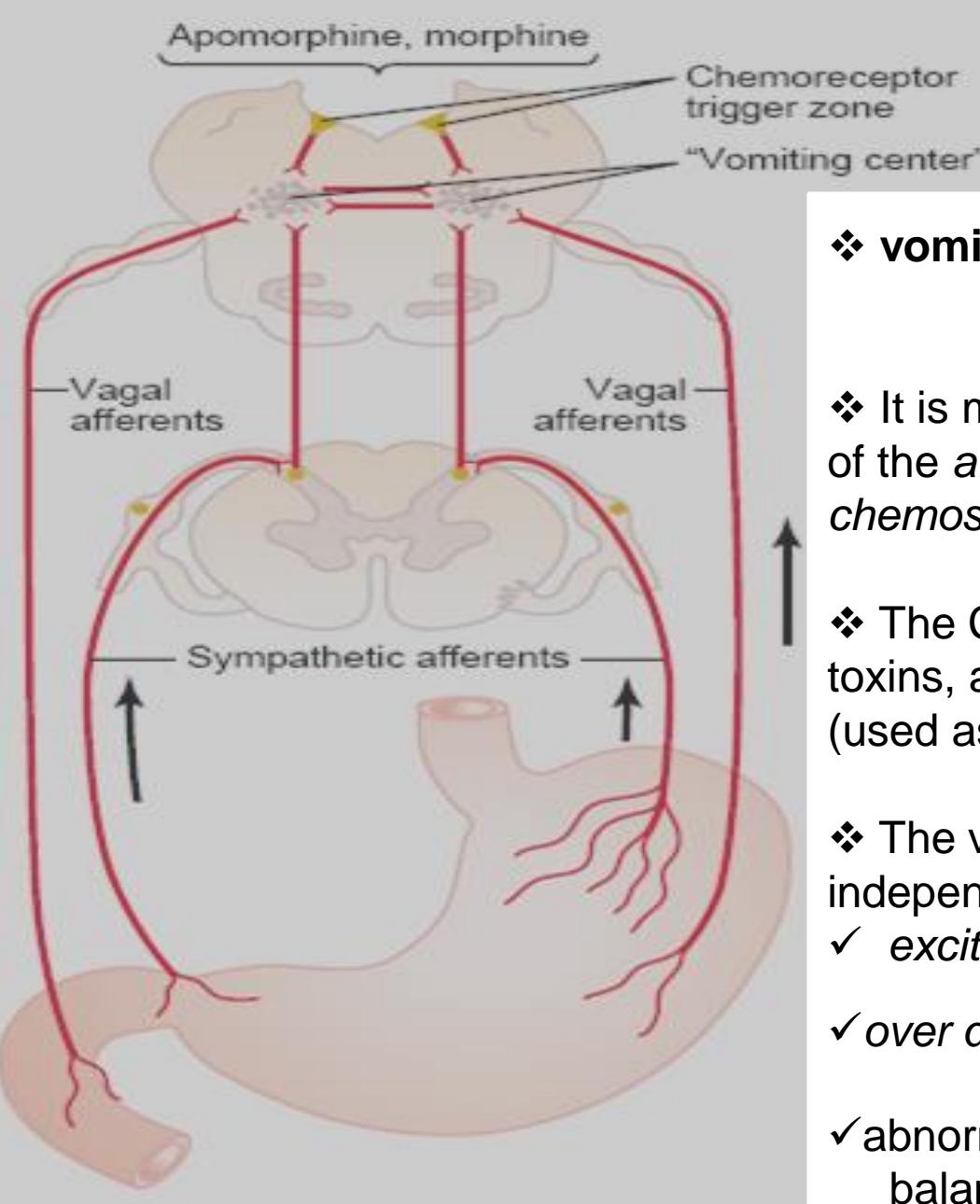
- is the means by which upper GIT forcefully rids itself of its contents
- Occurs when almost any part of upper tract becomes:
 - **excessively irritated,**
 - **overdistended, or**
 - **overexcited**
- Excessive distention or irritation of the **duodenum** provides especially strong stimulus for vomiting.



- Sensory signals that initiate vomiting originate mainly from:
 - pharynx, esophagus, stomach, & upper portions of small intestine

↓
- the nerve impulses are transmitted by both vagal and sympathetic afferent nerve fibers to vomiting center in brain stem

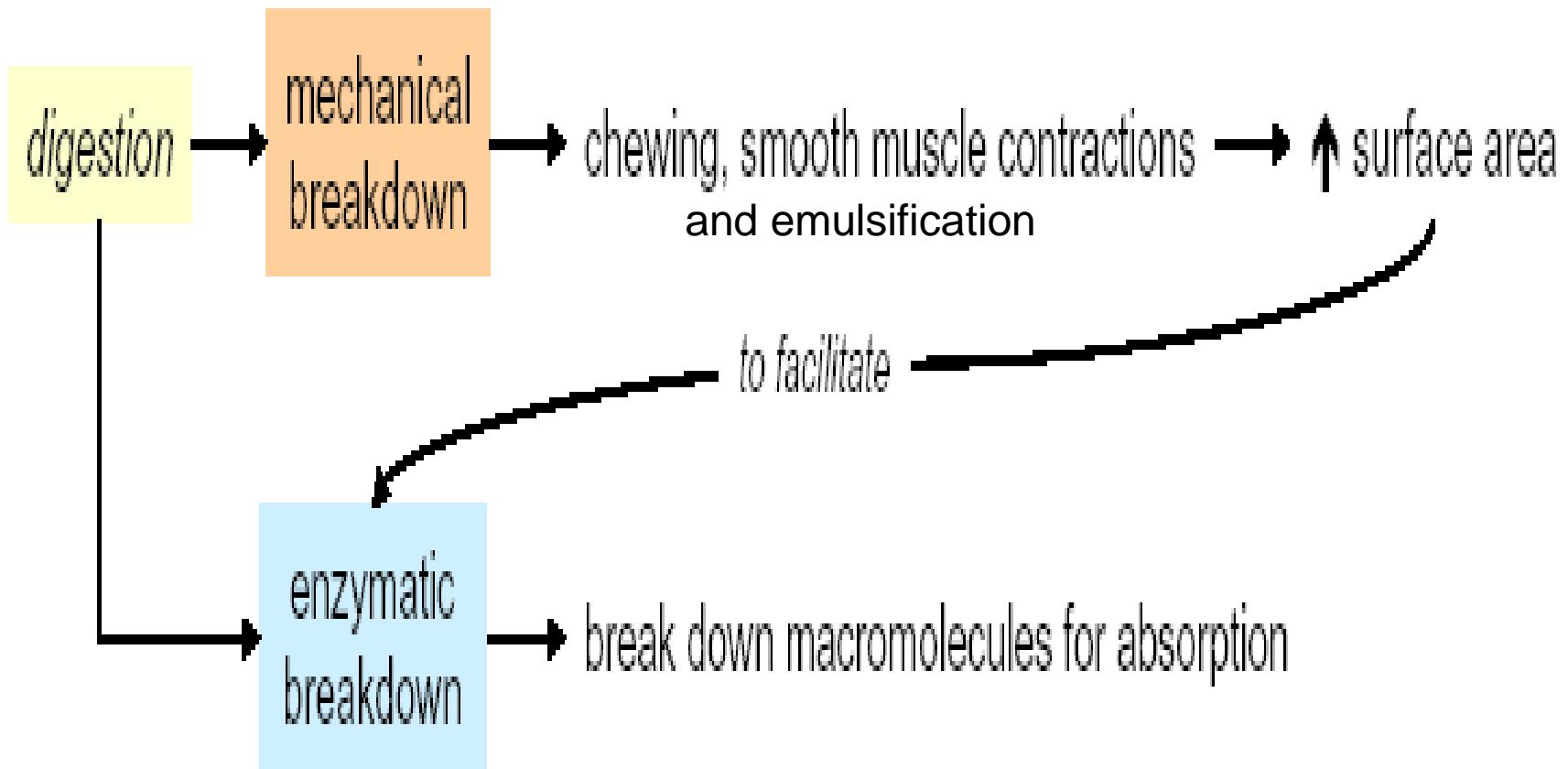
↓
- *motor impulses* that cause actual vomiting are transmitted from vomiting center by way of:
 - 5th, 7th, 9th, 10th, and 12th cranial nerves to upper GIT
 - spinal nerves to diaphragm and abdominal muscles



- ❖ vomiting center is located in the medulla oblongata
- ❖ It is mainly controlled by chemosensors of the *area postrema*, called the *chemosensory trigger zone (CTZ)*.
- ❖ The CTZ is activated by nicotine, other toxins, and DA agonists like apomorphine (used as an emetic).
- ❖ The vomiting center can also be activated independent of CTZ; due to :
 - ✓ *excitation* and inflammation of upper GIT
 - ✓ *over distension of stomach or intestines*,
 - ✓ abnormal stimulation of the organ of balance (*kinesia, motion sickness*),

Fig. Neural connections of the “vomiting center”

C. Digestion in the GI Tract



Digestion of Carbohydrates in the Mouth and Stomach

- When food is chewed, it is mixed with saliva
- saliva contains the digestive enzyme *ptyalin* (an α -amylase)
 - hydrolyzes starch into *maltose*
 - Accounts for only **5% of all starches digestion**
- Starch digestion may continue in the fundus and body of the stomach
 - before the food is mixed with the stomach secretions
- Then activity of the salivary amylase is blocked by acid of the gastric secretions
 - **amylase become inactive as the pH of the medium falls below 4.0**

Digestion of Carbohydrates in the Small Intestine

1. Digestion by Pancreatic Amylase

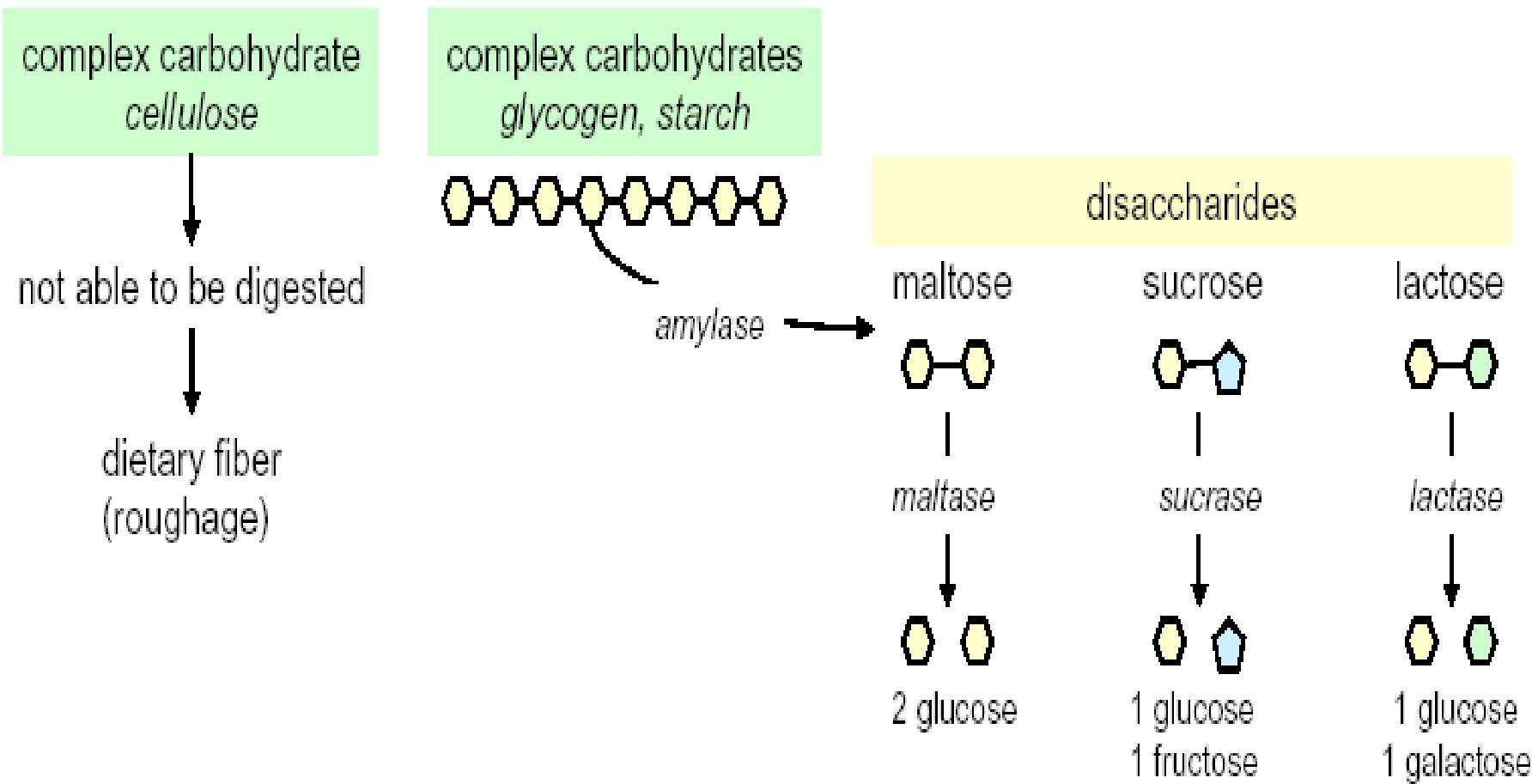
- Pancreatic amylase is almost identical in its function with the α -amylase of saliva **but is several times powerful.**
- Convert starch in to maltose

2. Digestion by Intestinal Epithelial Enzymes

- Lining of the villi of the small intestine contain four enzymes;
 - *lactase, sucrase, maltase, and α -dextrinase*
- ↓
- capable of splitting the disaccharides lactose, sucrose, and maltose, plus other small glucose polymers,
- ↓
- into their constituent monosaccharides

* Carbohydrate digestion

Almost half of calories from carbohydrates (sucrose & complex carbohydrates)



- In the ordinary diet, which contains far more starches than all other carbohydrates combined,
 - glucose represents about 80% of the final products of carbohydrate digestion
 - galactose and fructose about 20 %

Lactose intolerance – incomplete digestion of the lactose (eg. in milk)

- due to low levels of the intestinal brush border disaccharidase enzyme **lactase**.
 - primary lactase deficiency, a congenital absence of lactase- most common
 - Acquired
- Lactose is the primary carbohydrate in milk and other dairy foods.
 - **Lactase** is necessary to digest lactose in the small intestine
- If lactase is deficient \Rightarrow undigested lactose enters the large intestine,
 - ↓
- fermented by colonic bacteria, producing short chain organic acids and gases (hydrogen, methane, carbon dioxide).
- drinking a milk is followed shortly by bloating, gas, abdominal pain, and diarrhea

Digestion of Proteins

- The dietary proteins are chemically long chains of amino acids
 - ✓ bound together by peptide linkages

1. Digestion of Proteins in the Stomach

- *Pepsin* - peptic enzyme of the stomach
- most active at a **pH of 1.8 to 3.5** and is inactive at a pH above 5.0.
- Pepsin only initiates the process of protein digestion,
 - ✓ **converts the protein to proteoses, peptones, and a few polypeptides**
- provide only 10 to 20% of the total protein digestion

2. . Protein Digestion in the small intestine

2.1. Digestion of Proteins by Pancreatic Secretions

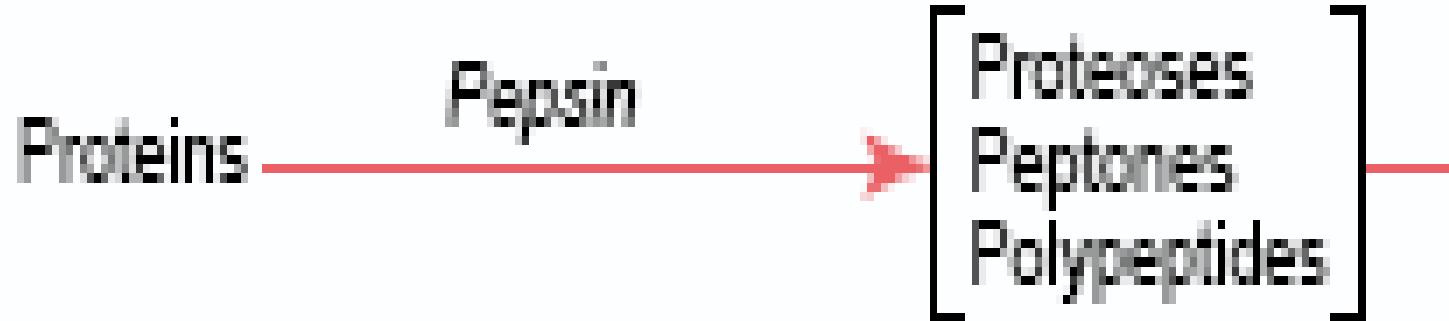
- Most protein digestion occurs in the upper small intestine
 - **in the duodenum and jejunum**
 - under the influence from pancreatic secretion.
- Immediately on entering the small intestine from the stomach,
 - the partial breakdown products of protein are digested by proteolytic pancreatic enzymes:
 - Trypsin
 - Chymotrypsin
 - Carboxypolypeptidase A and B
 - Elastase



- Both trypsin and chymotrypsin split protein molecules into smaller polypeptides: **ENDOPEPTIDASES**
- carboxy polypeptidases then cleave individual amino acids from the carboxyl ends of the polypeptides: **EXOPEPTIDASES**
- *Proelastase* is converted into *elastase*,
 - Elastase then digests elastin fibers that partially hold meats together

2.2. Protein Digestion by intestinal peptidases

- The last digestive stage of the proteins in the GIT lumen
- Occurs in the enterocytes that line the villi of the small intestine,
 - mainly in the duodenum and jejunum.
- Two types of peptidase enzymes:
 - *aminopolypeptidase* and several *dipeptidases*
↓
▪ split larger polypeptides into tripeptides and dipeptides and amino acids
- More than 99% of the final protein digestive products that are absorbed are amino acids, with only rare absorption of peptides.



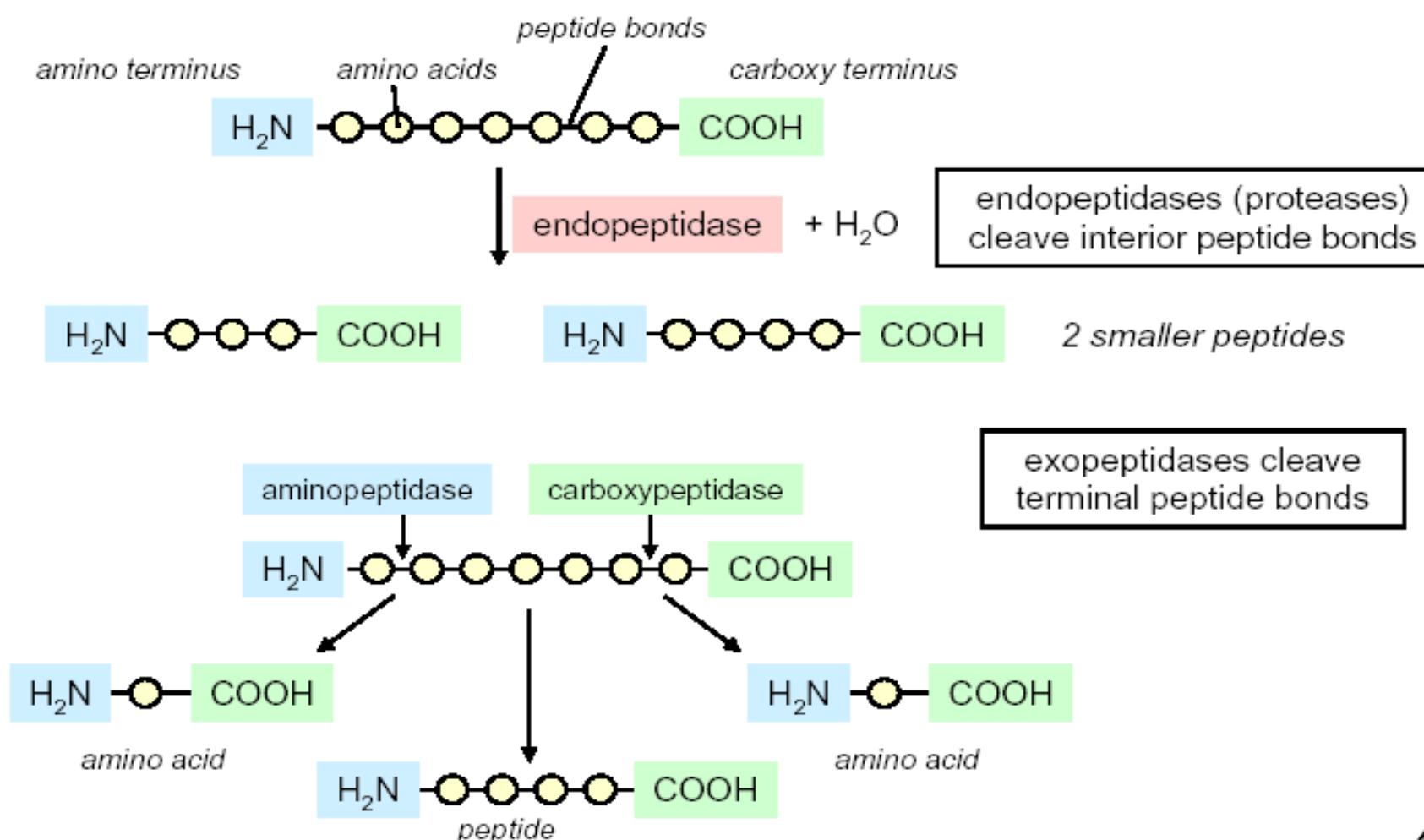
Trypsin, chymotrypsin, carboxyproteopeptidase,
proelastase



Digestion of proteins

* Protein digestion

- Most are ingested as *proteins* (>100 amino acids) or *polypeptides* (10 – 99 amino acids)
- Different protein sources vary greatly in their ability to be digested
 - Most digestible → Egg protein (85-90% can be absorbed)
 - Least digestible → Plant proteins (as low as 15% absorbed)
- 30-60% of the protein in the intestinal lumen comes from dead cells and proteins secretions (enzymes, mucus)



- **Endopeptidase**: hydrolyzes internal peptide bonds:
 - trypsin (P)
 - chymotrypsin (P)
 - elastase (P)
 - pepsin (G)

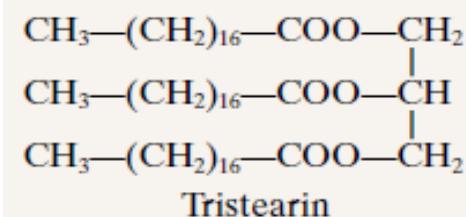
- **Exopeptidase**: hydrolyzes external peptide bonds:
 - carboxypeptidase A (P)
 - carboxypeptidase B (P)
 - aminopeptidase (P, BB, C)

P = pancreas, BB = brush border, C = cytoplasm of epithelial cells

Digestion of Fats

Fats of the Diet

- The most abundant fats of the diet are the neutral fats,
 - also known as *triglycerides*, each of which is composed of:
 - one glycerol nucleus and
 - three fatty acid side chains



1. Digestion of Fats in the stomach

- small amount of triglycerides is digested *in the stomach*
 - by *lingual lipase*
 - secreted by lingual glands in the mouth and swallowed with the saliva
 - Works in acidic medium (pH optimum = 4)
 - By *gastric lipase secreted by cells in the fundus*
 - The churning and mixing in distal stomach break lipids into small droplets

2. Digestion of Fats in the small intestine

2.1. Digestion by Pancreatic Lipase

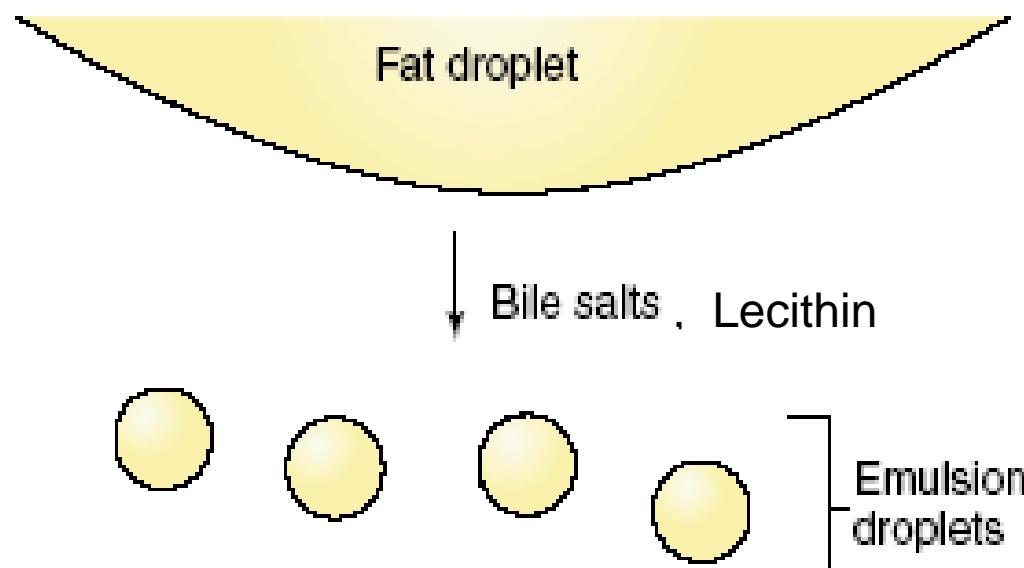
- **pancreatic lipase**- hydrolyzes neutral fat into 2fatty acids + monoglyceride
 - By far the most important enzyme for digestion of the triglycerides
 - present in enormous quantities in pancreatic juice,
 - digest within 1 minute all triglycerides that it can reach
- **cholesterol esterase**- causes hydrolysis of cholesterol esters
- **phospholipase A2**- splits fatty acids from phospholipids
 - digesting phospholipids and forming lysophospholipids and fatty acids.

2.2. Digestion by Enteric Lipase

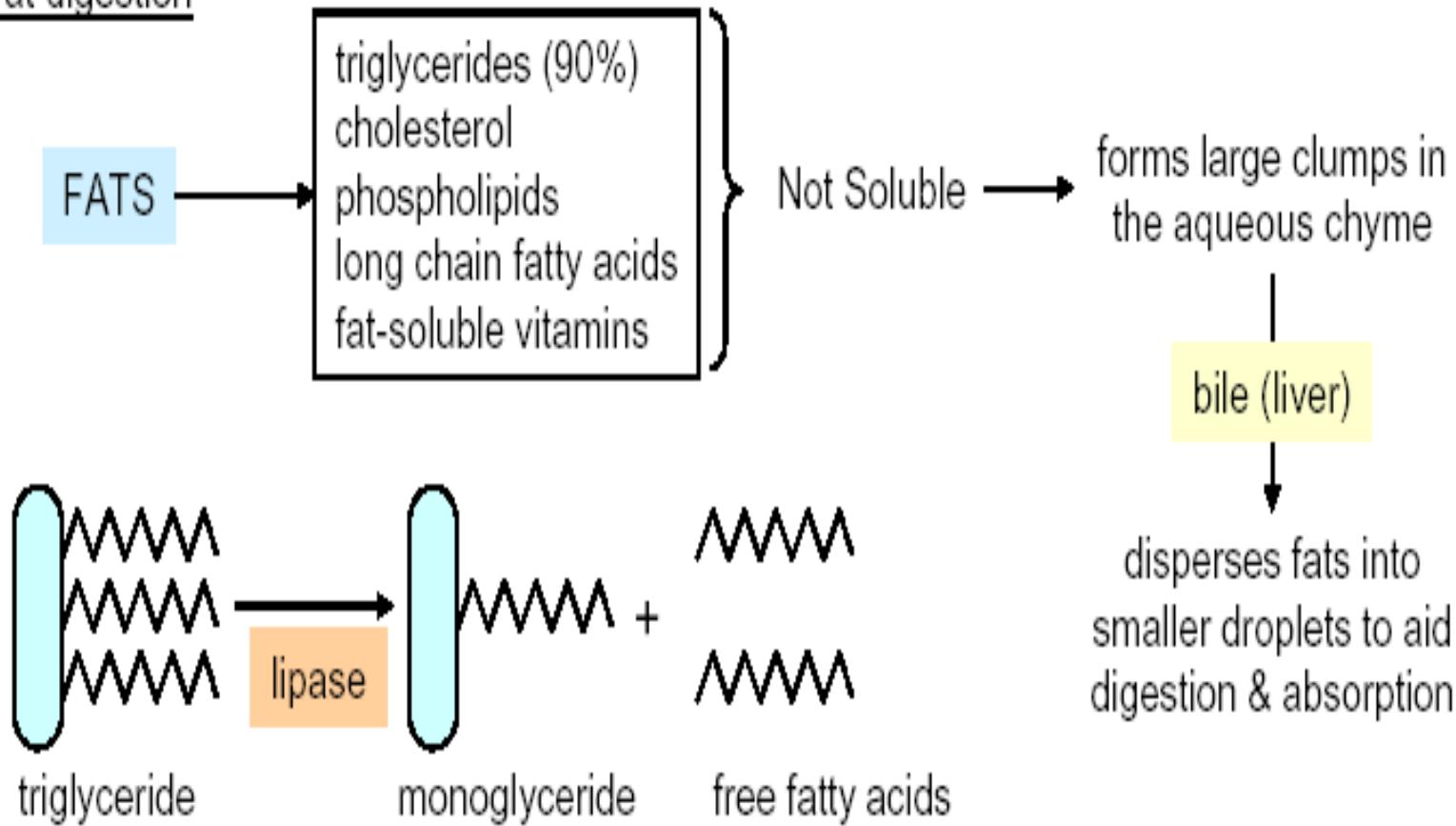
- the enterocytes of the small intestine also contain lipase,
 - known as *enteric lipase* – digests the TG

Emulsification of Fat by Bile Acids and Lecithin

- The first step → physically to break the fat globules into very small sizes
↓
- Increase the surface area for lipase action
- This process is called *emulsification of the fat*
↓
- the water-soluble digestive enzymes act on the emulsion droplet surfaces.



* Fat digestion



cholesterol, long chain fatty acids, vitamins → absorbable
phospholipids → broken down by phospholipase

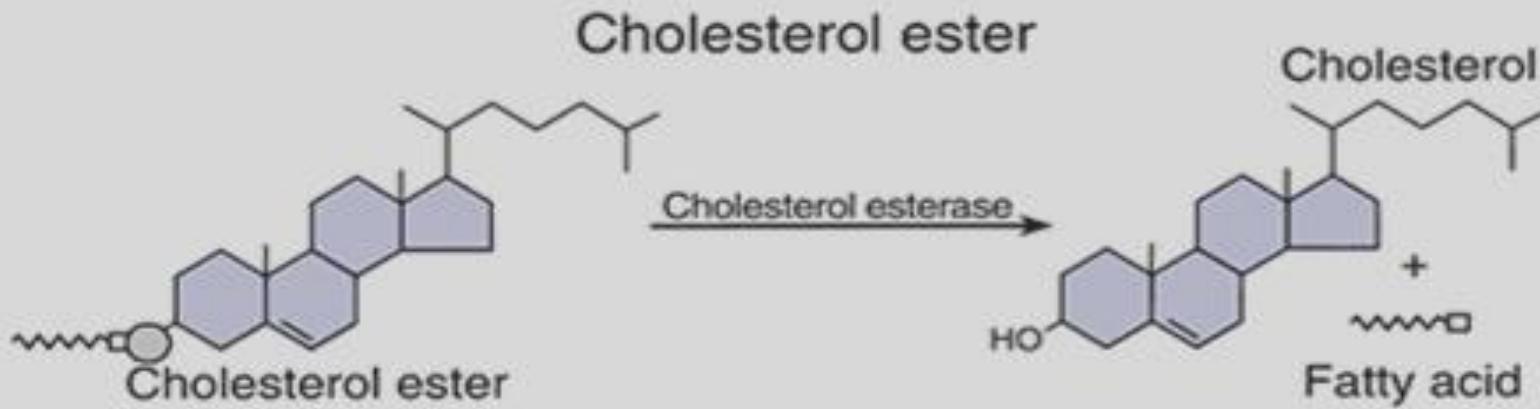
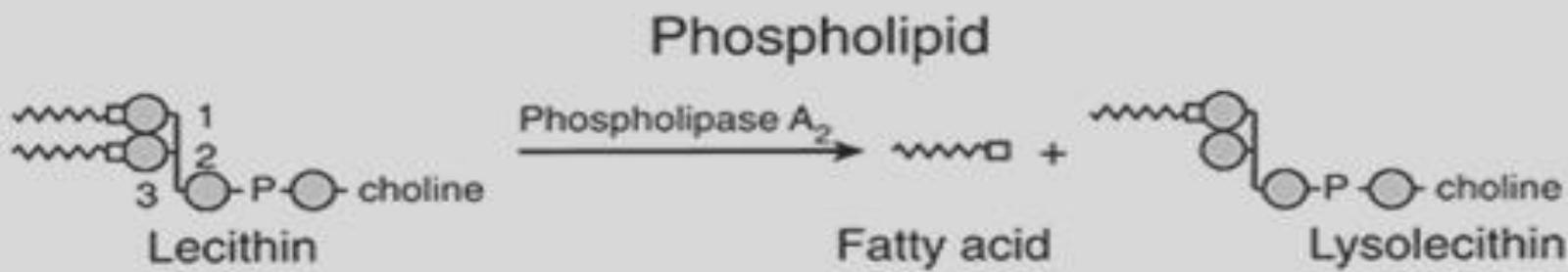
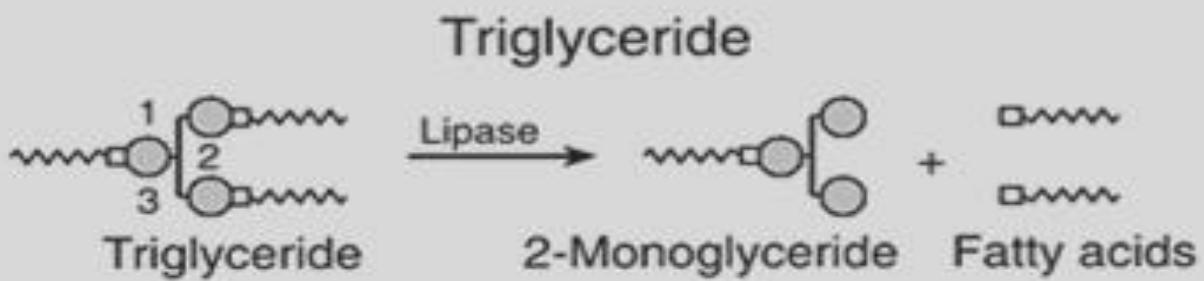


Fig. Different pancreatic lipases carry out lipid hydrolysis in the intestine
Solid circles represent oxygen atoms.

D. Absorptive function of GIT

Absorption in stomach

- The stomach is a poor absorptive area of the GIT because:
 - it lacks the typical villi type of absorptive membrane
 - the junctions between the epithelial cells are tight junctions
- Only a few highly lipid-soluble substances can be absorbed in small quantities
 - such as alcohol and some drugs like aspirin

Absorption in small intestine

- Absorptive surface of intestinal mucosa has many folds called *valvulae conniventes* (or *folds of Kerckring*)
- on the epithelial surface (from the folds) millions of *villi project to the lumen*
- each villus *contains as many as 1000 microvilli*
 - The villi are longest in the duodenum and shortest in the distal ileum
- The combination of :
 - the folds of Kerckring,
 - the villi, and
 - microvilli



↑total absorptive area of the mucosa by 1000-fold!

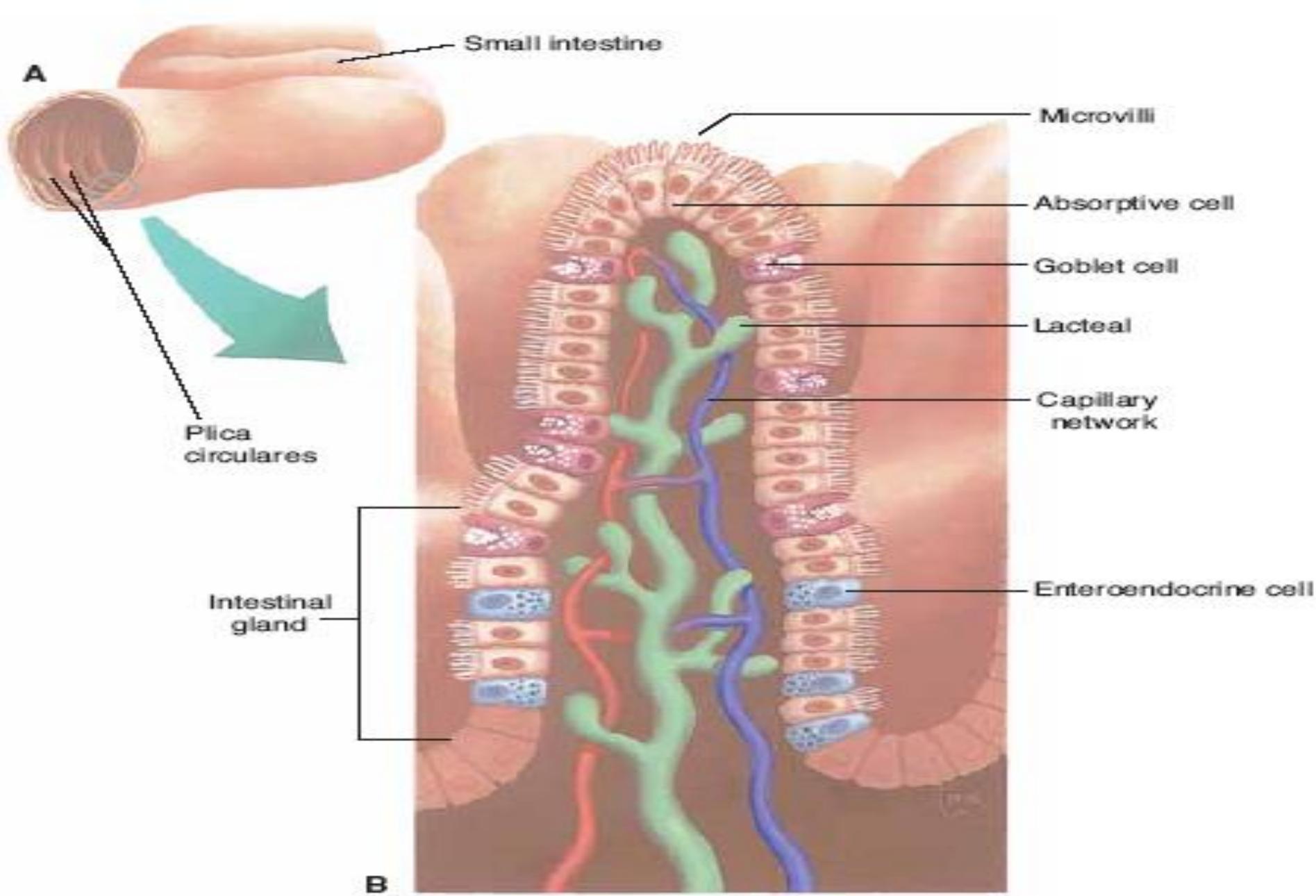


Fig. Microscopic view of a villus depicting the internal structures

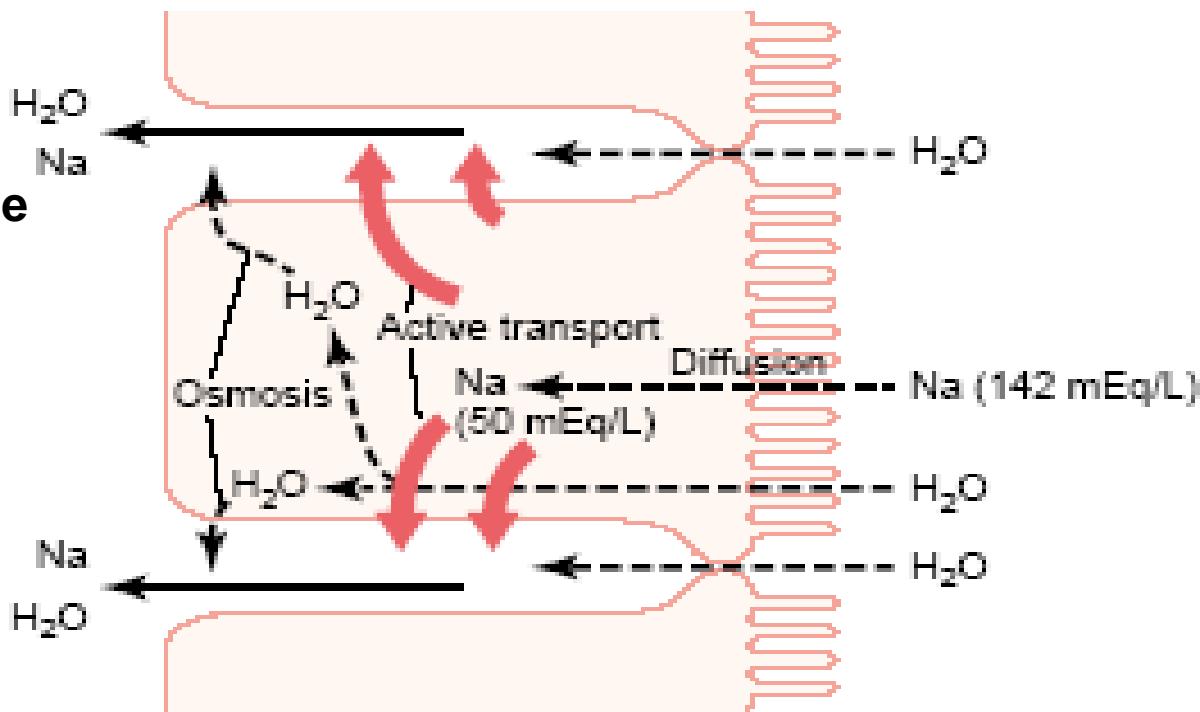
Absorption of Water: Isosmotic Absorption

- Water is transported via intestinal membrane entirely by osmosis
- diluted chyme \Rightarrow osmosis through intestinal mucosa into the blood
- hyperosmotic chyme \Rightarrow osmosis from plasma into the chyme
 - make the chyme isosmotic with the plasma



Absorption of Na⁺ through the intestinal epithelium:
passive + active

osmotic absorption of water:
water “follows” Na⁺ through epithelial membrane



✓ Average water intake (in beverages and foodstuffs) is roughly **1.5 L/day**.

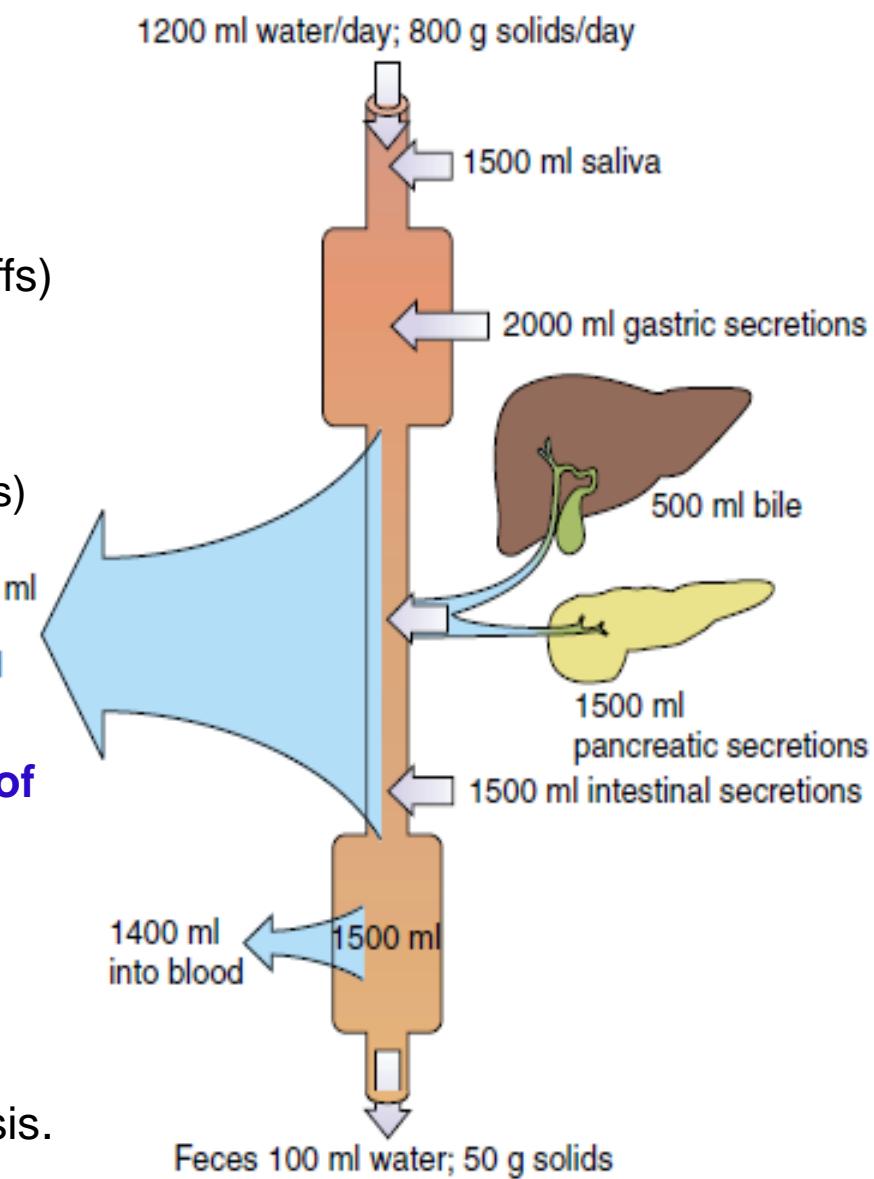
✓ **7L/d** of fluid secreted into GIT (saliva, bile, gastric, pancreatic & intestinal secretions)

✓ **only about 0.1 L/day eliminated in the feces.**

✓ The GIT must therefore absorb a net volume of at least **8.4L of water per day**.

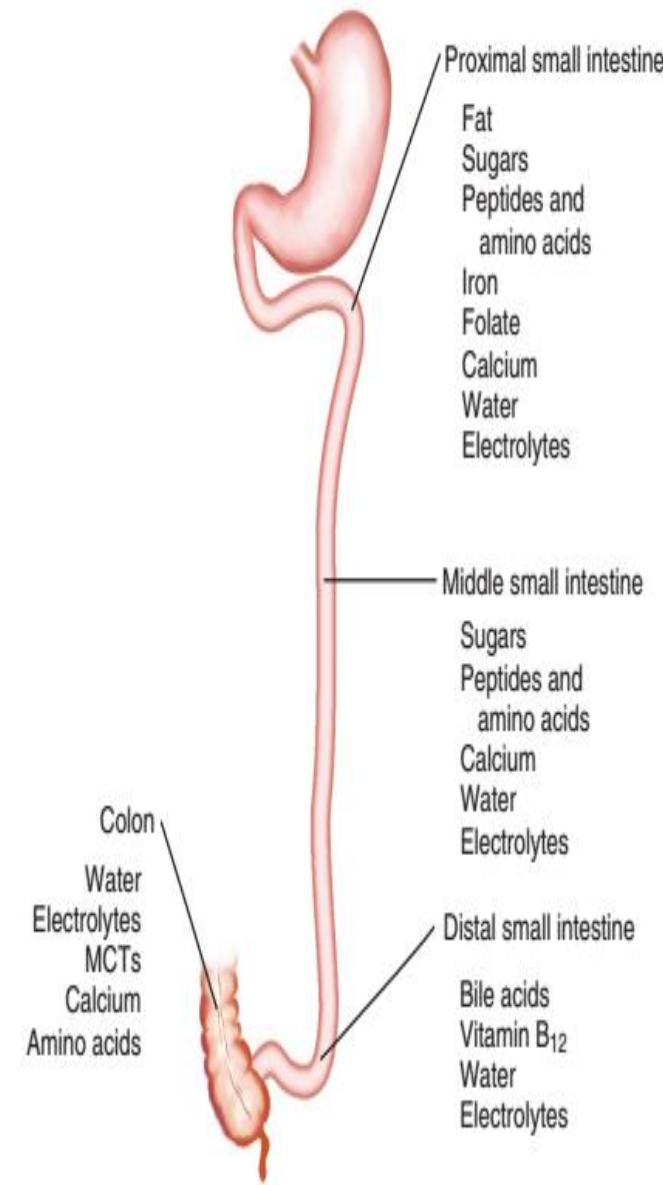
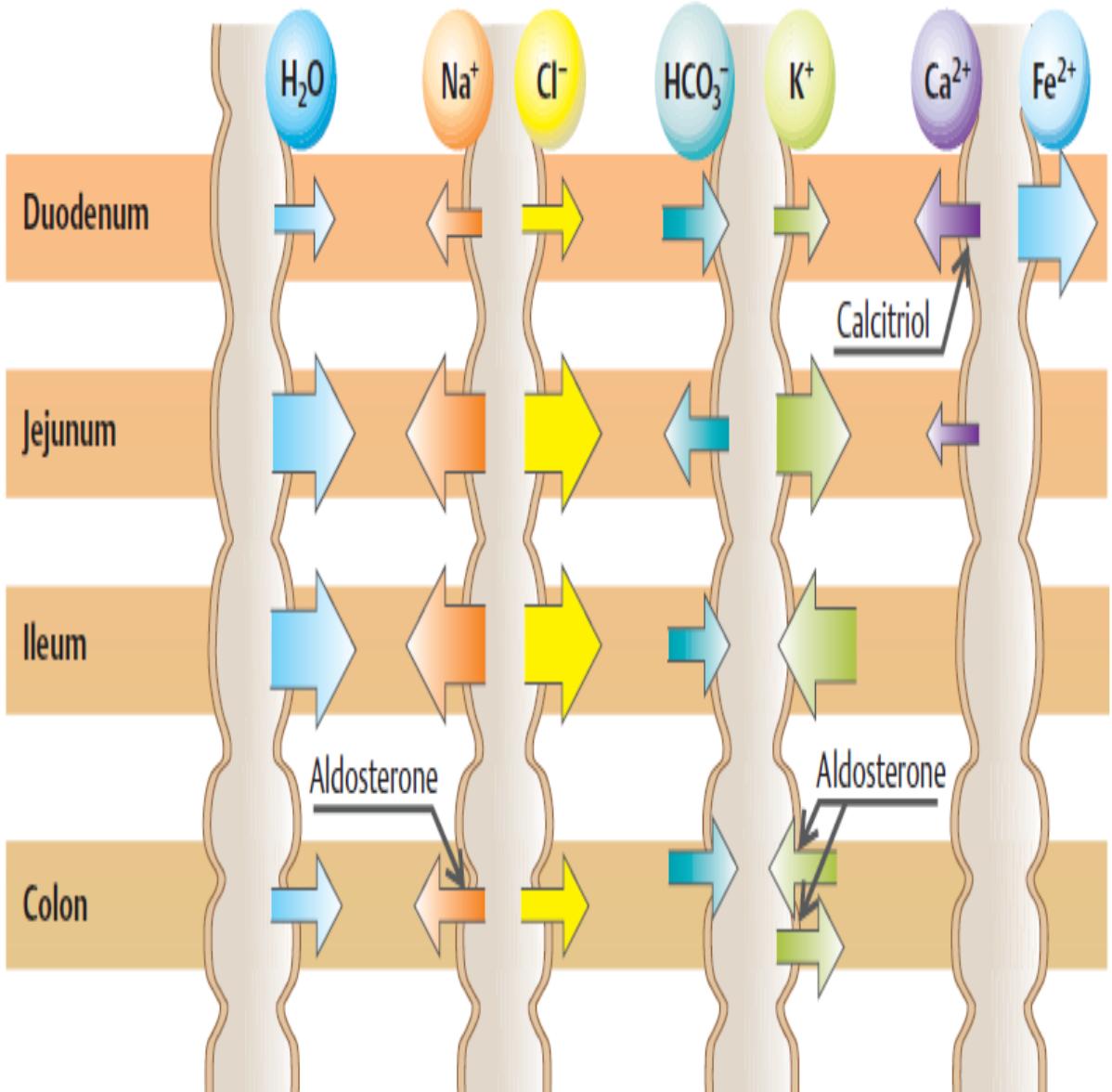
✓ GI absorption of water occurs mainly in **jejunum and ileum**, with smaller quantities in the colon.

✓ Water through the intestinal epithelium by osmosis.



✓ Fig. Average amount of fluid and solid ingested, secreted, absorbed, and excreted from GIT/day

A. Water and electrolyte absorption in the gut



Absorption of Carbohydrates

- Essentially all the carbohydrates in the food are absorbed in the form of monosaccharides;
- only small fractions are absorbed as disaccharides
- almost none as larger carbohydrate compounds
- the most abundant absorbed monosaccharides is *glucose*
 - account for about 80% of carbohydrate calories absorbed.
 - The remaining 20% of absorbed monosaccharides: *galactose* and *fructose*

Carbohydrate Absorption

end products of carbohydrate digestion are glucose, galactose & fructose

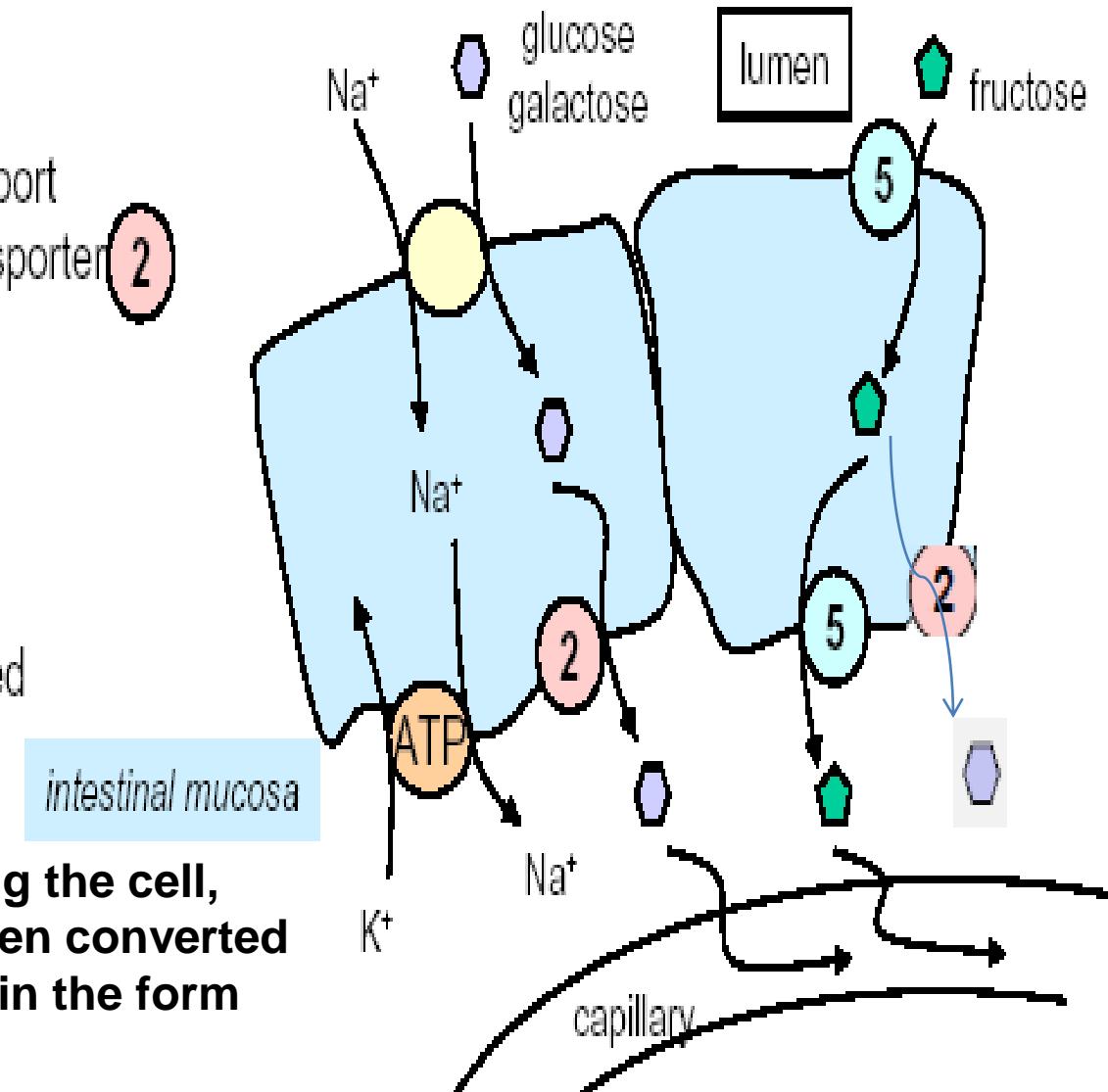
Glucose & galactose:

utilize apical Na^+ -glucose symport
and a basolateral GLUT2 transporter
(facilitated diffusion)

Fructose:

utilizes apical and basolateral
GLUT5 transporters (facilitated
diffusion)

**Much of fructose , on entering the cell,
becomes phosphorylated, then converted
to glucose \Rightarrow transported out in the form
of glucose**



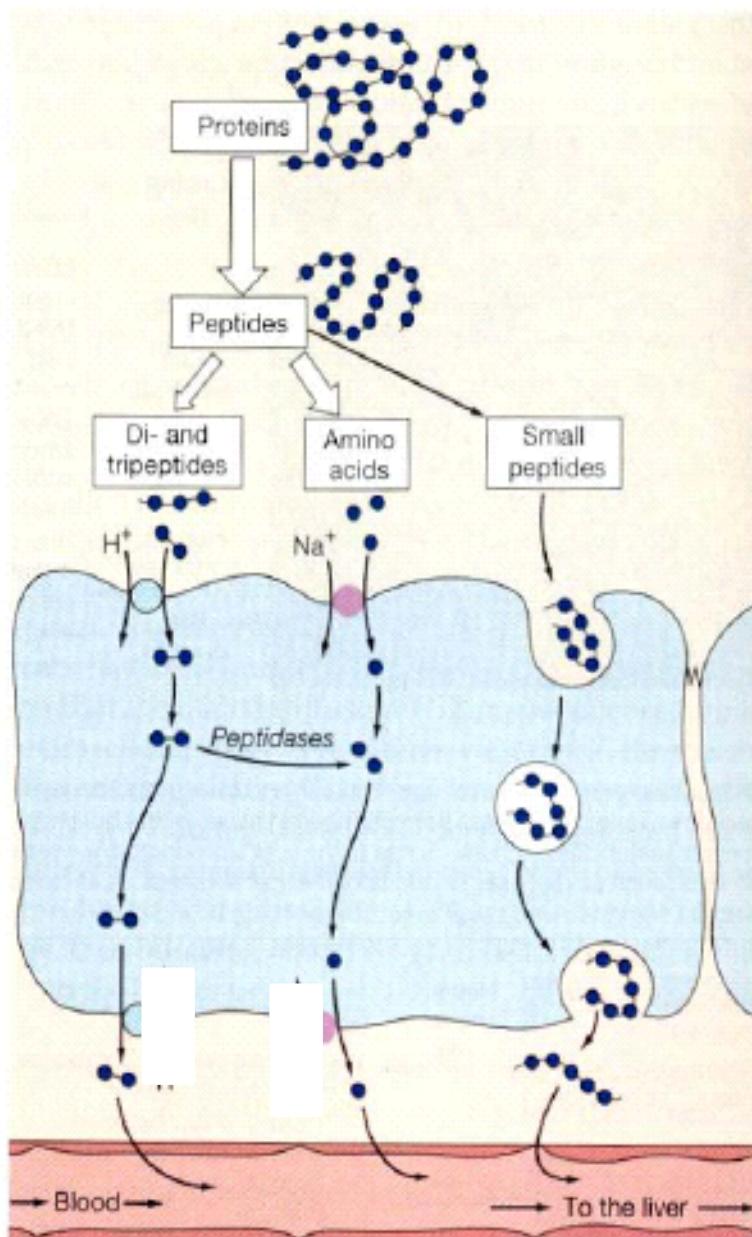
Absorption of Proteins

- proteins are absorbed through the luminal membranes of the intestinal epithelial cells in the form of:
 - **free amino acids**
 - dipeptides
 - tripeptides
- Mechanisms: By coupled transport (secondary active transport)
 - **Na⁺- Amino acid co-transport (Na⁺ - Amino acid symport) ,**
 - **some as H⁺- Amino acid symport**
 - **Dipeptides and tripeptides are coupled to H⁺ by peptide transporter 1 (PepT1)**
 - Na⁺ or H⁺ diffuses passively down the concentration gradient
- Larger peptides are absorbed by transcytosis



Protein Absorption

end products of protein digestion are free amino acids, dipeptides and tripeptides



- ❖ free amino acids carried on Na⁺-dependent (some on H⁺-dependent) cotransport proteins
- ❖ di- and tripeptides are transported using H⁺-dependent cotransport systems
 - most are broken down in the cell by intracellular peptidases → amino acids
- ❖ some larger peptides are moved by **transcytosis**

Absorption of Fats

- In the presence of abundant bile micelles



- about 97% of the fat is absorbed

- in the absence of the bile micelles



- only 40% to 50% can be absorbed

- Micelles help the digestive fat products to cross the unstirred layer and reach the surface of the mucosal cells

- A layer of poorly stirred fluid called the unstirred water layer coats the surface of the intestinal villi

- This layer reduces the absorption of lipid digestion products

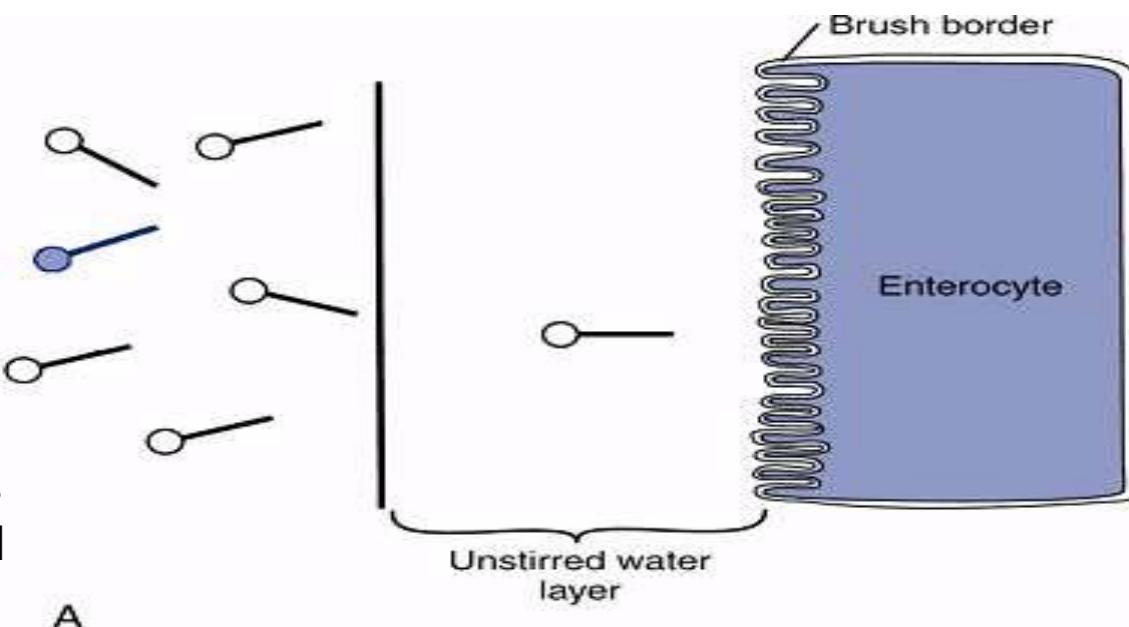
- because they are poorly soluble in water.

- Micellar solubilization by bile salts in lumen renders them water-soluble

- Enterocytes then absorb the lipid digestion products, mainly by passive diffusion

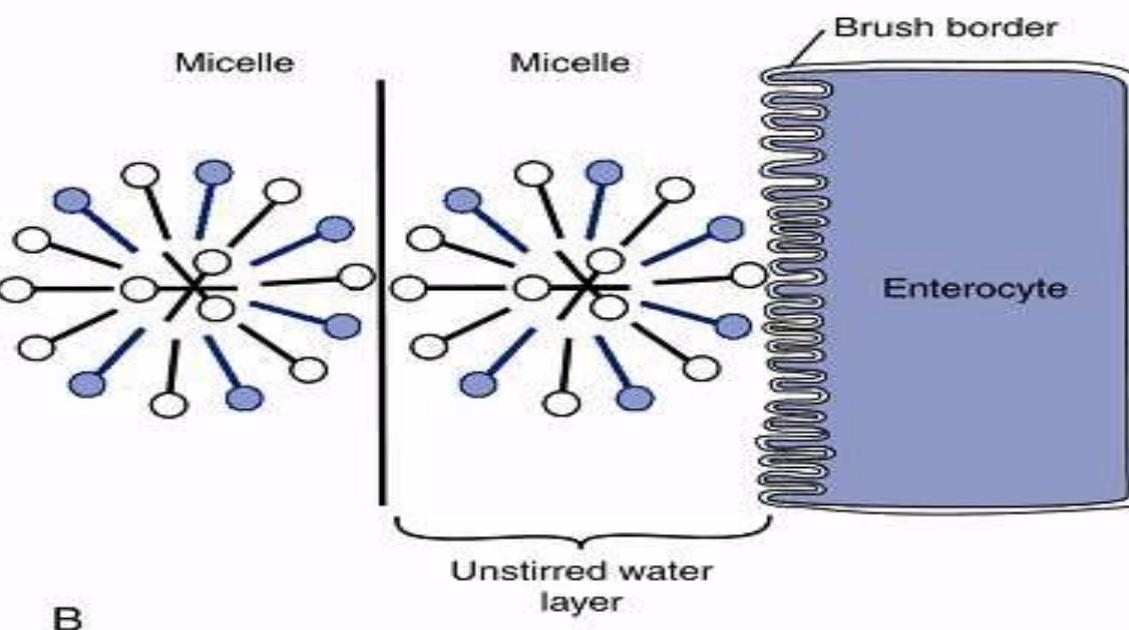
Fig. Bile salts emulsify lipids for absorption

- ✓ Micelles are formed from emulsified lipid,
- ✓ micellar solubilization enhances the delivery and absorption of lipid to the brush border membrane.



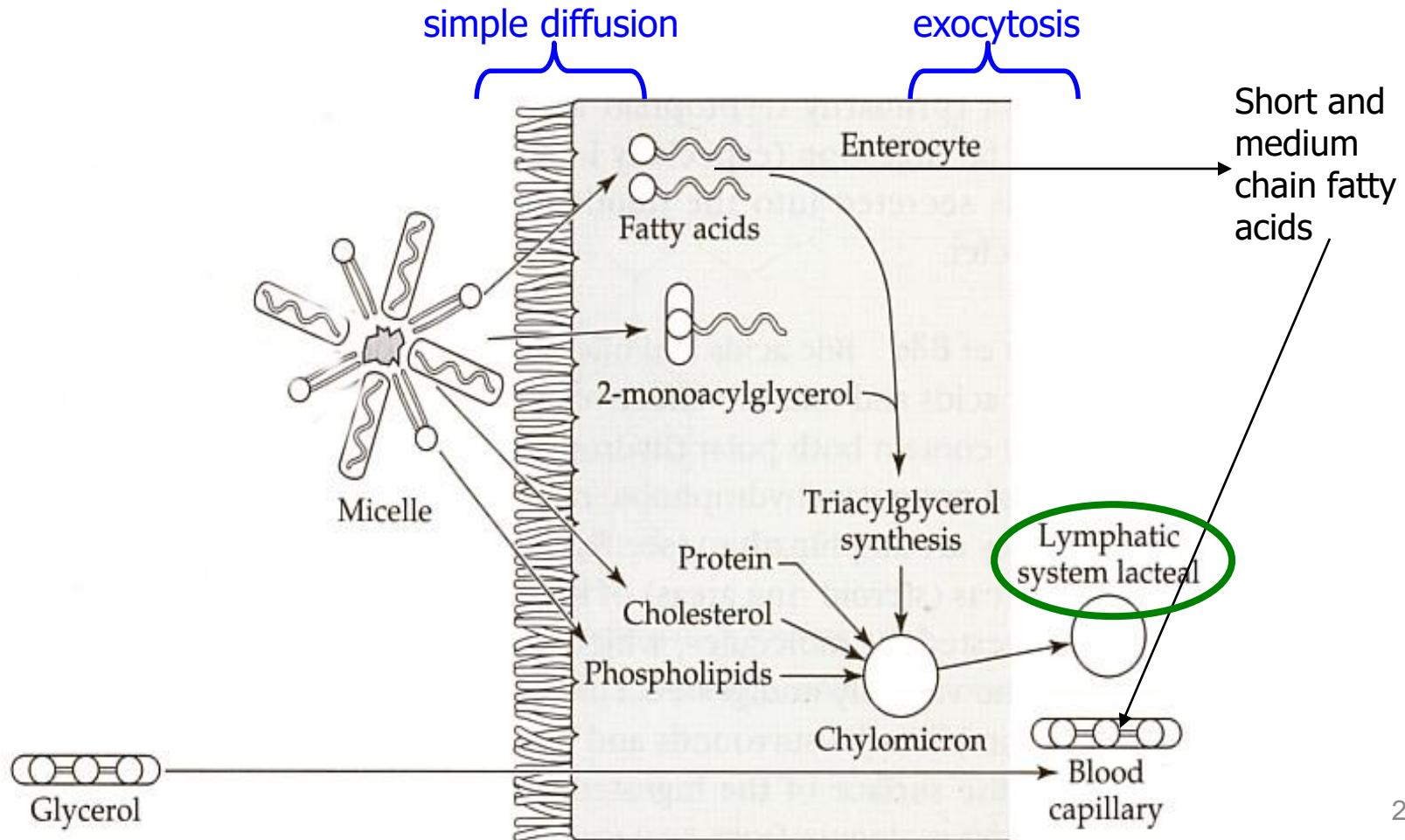
A. The absence of micelles when bile salt is absent.

B. The presence of micelles when bile salt is present



Most fat absorption takes place in the duodenum and jejunum

micelles carry end products of fat to the brush border from where they diffuse into enterocytes



Fat Absorption

digestion is carried out primarily by **pancreatic lipase**, which requires a **colipase** to penetrate the bile salt coating.

→ *end products are free fatty acids & mono- and diglycerides*

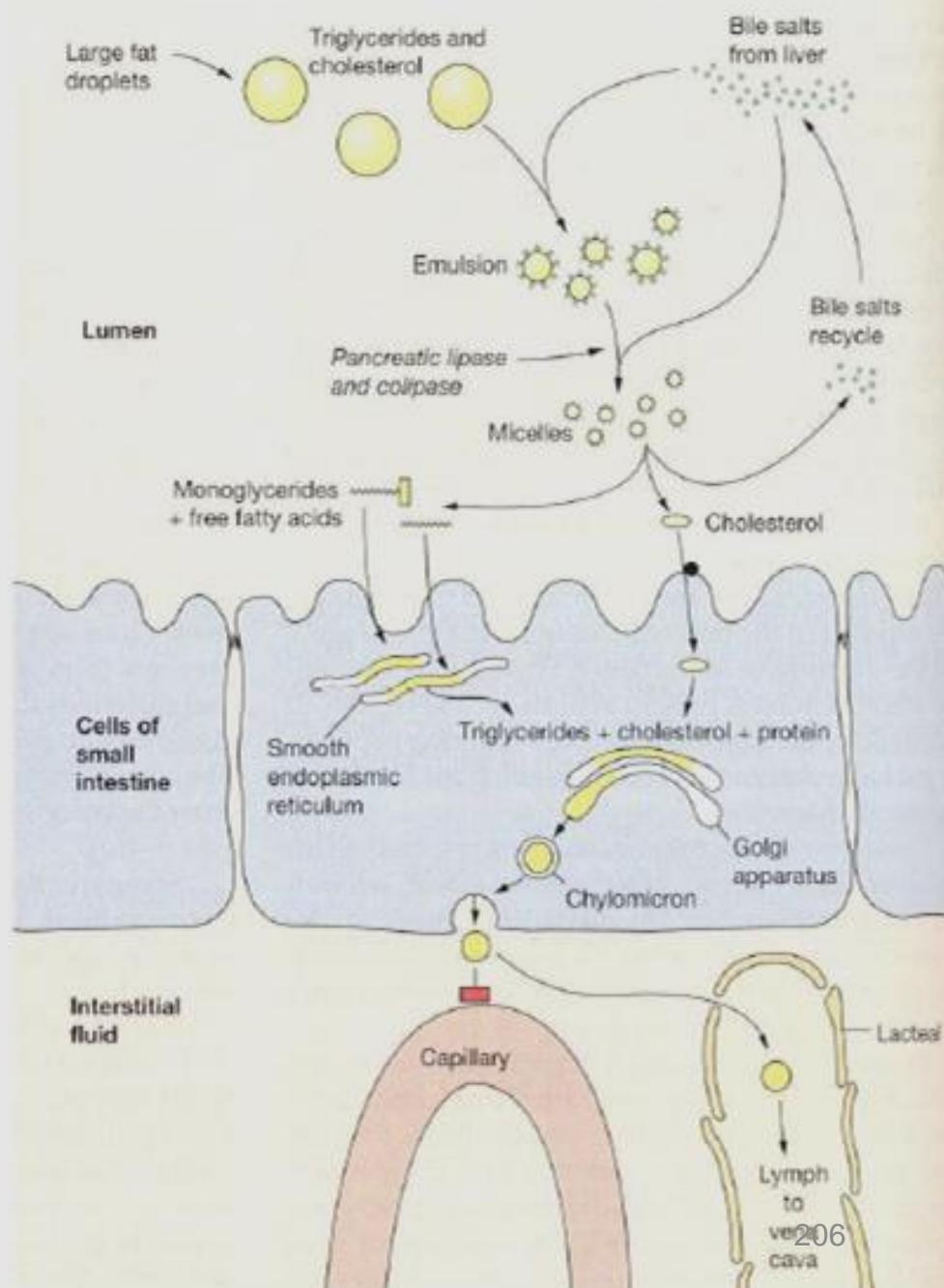
Most fats absorbed by simple diffusion into intestinal cells.

Are resynthesized into triglycerides in the smooth ER.

Triglycerides combine with protein & cholesterol to form a large particle called a **chylomicron**, which are packed into secretory vesicles and exit by **exocytosis**

Chylomicrons are picked up by lymphatic vessels and returned to the circulation

Shorter fatty acids (<10 carbons) may be directly be picked up by the capillaries



Sprue

- Is malabsorption of nutrients by small intestinal mucosa
 - Due to pathologies causing villus atrophy
- occurs even though the food is well digested
- Several diseases can cause intestinal malabsorption
 - they are often classified together under the general term "*sprue*"
- also can occur due to removal of large portions of small intestine
- fat absorption is more impaired than other digestive products
 - excess fats in the stools
 - the condition is called **steatorrhea**

- In very severe cases of sprue
 - also impaired absorption of proteins, carbohydrates, calcium, vitamin K, folic acid, and vitamin B12
- As a result, the person suffers:
 - **1. severe nutritional deficiency**, often developing wasting of the body
 - **2. osteomalacia** (demineralization of the bones): due to lack of calcium
 - **3. inadequate blood coagulation**: due to lack of vitamin K
 - **4. pernicious anemia**: due to lack of vitamin B12 and folic acid absorption

Absorption in the Large Intestine

- About 1.5L of chyme normally passes into the large intestine each day
 - Most of the water and electrolytes are absorbed in the colon
 - usually leaving less than 0.1L of fluid to be excreted in the feces
- Most of the absorption occurs in the proximal one half of the colon
 - Hence this portion is called **absorbing colon**
- The distal colon functions principally for feces storage until defecation time
 - hence this portion is called **storage colon**

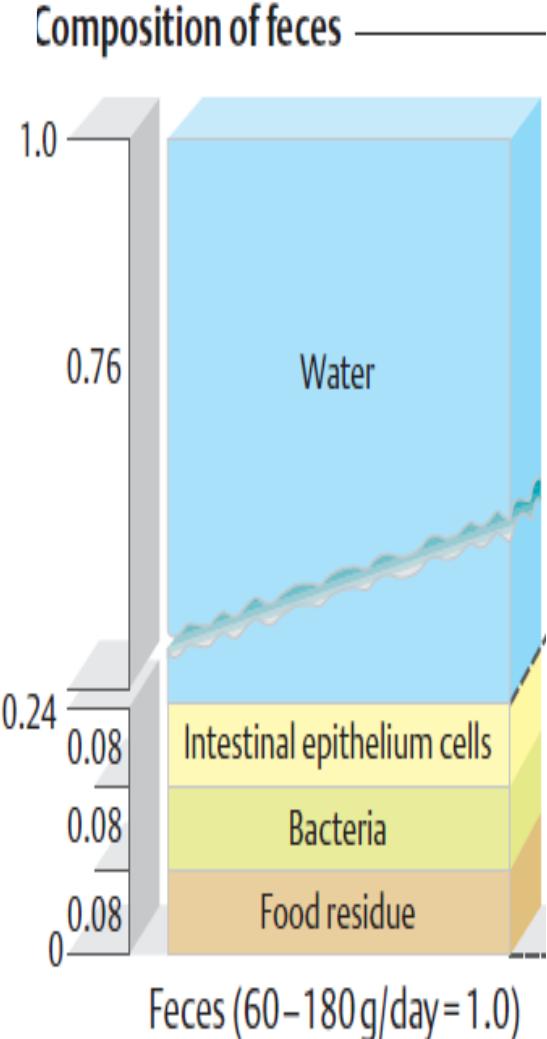
Bacterial Action in the Colon

- Numerous bacteria, especially colon bacilli, are present even normally in the absorbing colon
- They are capable of digesting small amounts of cellulose
 - **Can provide a few calories of extra nutrition for the body**
- Other substances formed as a result of bacterial activity are:
 - **vitamin K, vitamin B12, thiamine, riboflavin,**
 - **various gases that contribute to *flatus* in the colon: CO₂, H₂, & C₄H₄**
- The bacteria-formed vitamin K is especially important
 - Because vit K in the daily ingested foods is normally insufficient to maintain adequate blood coagulation

Composition of the Feces:

- About three-fourths *water* ??
- About one-fourth *solid matter*??
that is composed of about:
 - 30% dead bacteria
 - 10 to 20% fat
 - 10 to 20% inorganic matter
 - 2 to 3 % protein
 - 30% undigested roughage
 - from the food and dried constituents of digestive juices

} from intestinal epithelial cells



❖ The brown color of feces is caused by *derivatives of bilirubin such as stercobilin and urobilin*,

Constipation

- Characterized by infrequent, excessive straining, and hard stool defecation
- Due to slow movement of feces through large intestine
 - over-absorption of fluid
 - large quantities of dry, hard feces in the descending colon
- Any pathology of intestines that obstructs movement of intestinal contents:
 - tumors, adhesions that constrict intestines, or ulcers,
 - can cause constipation
- Functional cause of constipation is irregular bowel habits
 - Due to inhibition of the normal defecation reflexes (tonic colon)
 - ***Functional fecal retention- by far the commonest cause of constipation***

Diverticulosis and diverticulitis

- the colon develops small pouches that bulge outward through weak spots during forceful straining , this is called **Diverticulosis**
 - Due to low fiber diet which can make stools hard and difficult to pass
 - If the stool is too hard, muscles must strain to move it
- Increased pressure in the colon \Rightarrow weak spots bulge outward
- pouches can also be infected or inflamed—a condition called **diverticulitis**

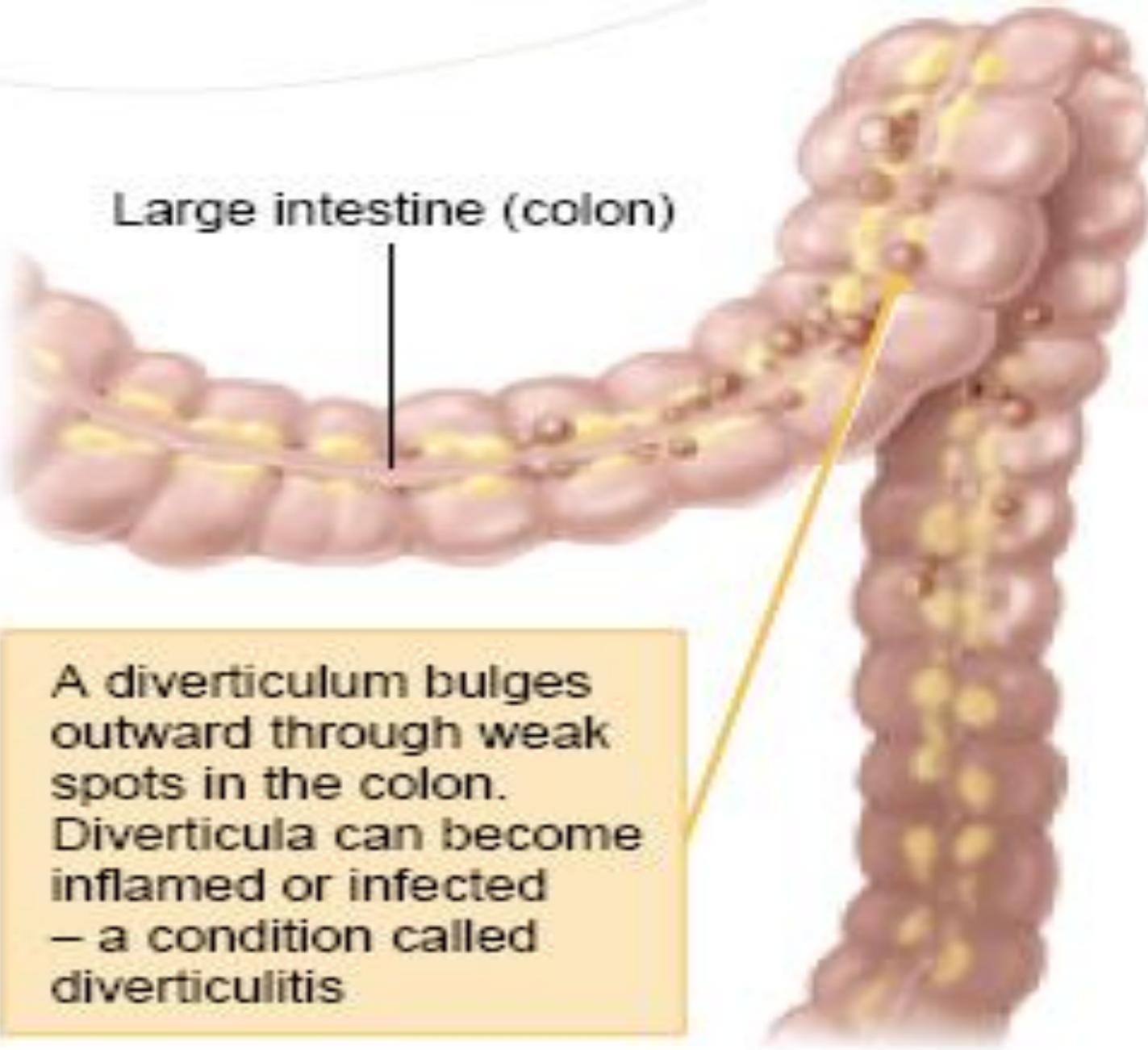
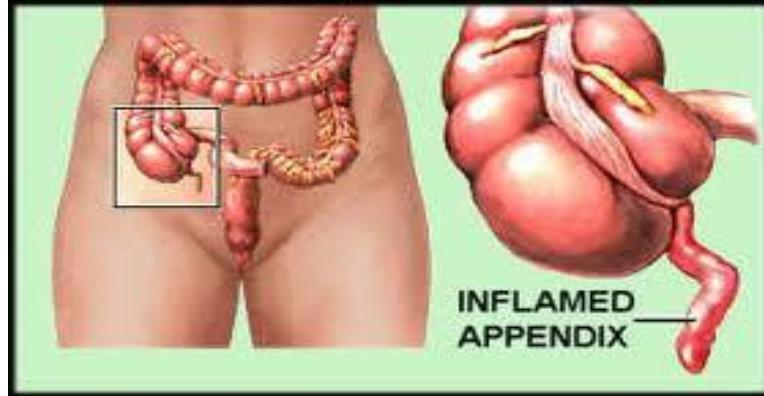


Fig. Diverticulosis and diverticulitis

Acute appendicitis



- is a medical emergency characterized by inflammation of the appendix
- usually (50-80%) associated with obstruction (fecalith, tumor, or ball of worms (*oxyuriasis vermicularis*)
- Obstruction can cause ischemic injury which favors bacterial proliferation with additional inflammatory exudate and edema
- Nevertheless a significant minority of inflamed appendices have no demonstrable luminal obstruction



Morphology

- initially serosa is transformed to dull granular red membrane
- later fibrinopurulent exudate covers the serosa
- **abscess formation leads to *acute suppurative appendicitis***
- further progress leads to ***acute gangrenous appendicitis***
- histologic criterion for the diagnosis of acute appendicitis is **neutrophilic infiltration of the muscularis**
- **clinical features include:**
 - **abdominal pain (first periumblical then moves to the RLQ)**
 - **Nausea-vomiting**
 - **Fever**
 - **Tenderness(RLQ)...**

Diarrhea

- Defin: passage of abnormally liquid or unformed stools at an increased frequency (>3 times/day).
 - **Acute diarrhea-** lasting: <2 weeks,
 - Affects >1 billion individuals Worldwide/yr
 - **> 90% of cases of acute diarrhea are caused by infectious agents**
 - **Fluid & electrolyte replacement are of central importance!**
 - **Persistent diarrhea:** if 2–4 weeks
 - **Chronic diarrhea-** lasting >4 weeks
 - **In contrast to acute, most of the causes of chronic diarrhea are noninfectious**
- It is one of the most common clinical signs of GIT disease,
- can also reflect primary disorders outside of the digestive system.
- disorders affecting either the small or large bowel can lead to diarrhea.
 - from decreased fluid absorption, increased fluid secretion, or both

Etiologic classification of Diarrhea

- In almost all cases; it is a manifestation of **1 of 4 Mechanisms:**
 - **Osmotic diarrhea-** typically results from one of the two situations:
 - *Ingestion of poorly absorbed substrates*
 - **Malabsorption**
 - Osmotic diarrhea stops when offending agent (e.g. sorbitol, milk) is stopped
 - **Secretory diarrhea-**
 - occurs when secretion of water into intestinal lumen exceeds absorption
 - The most common cause is a cholera toxin (from *Vibrio cholerae*)
 - Activates Na⁺ & Cl⁻ secretion
 - Cholera can cause massive watery diarrhea, dehydration, and death in healthy persons within 12 h of the onset of illness
 - **Infectious diarrhea**
 - Disruption of the epithelium of the intestine due to microbial pathogens
 - **Diarrhea associated with deranged motility Eg. thyrotoxicosis**
- ✓ More than one of these mechanisms may be involved in the pathogenesis of a given case.