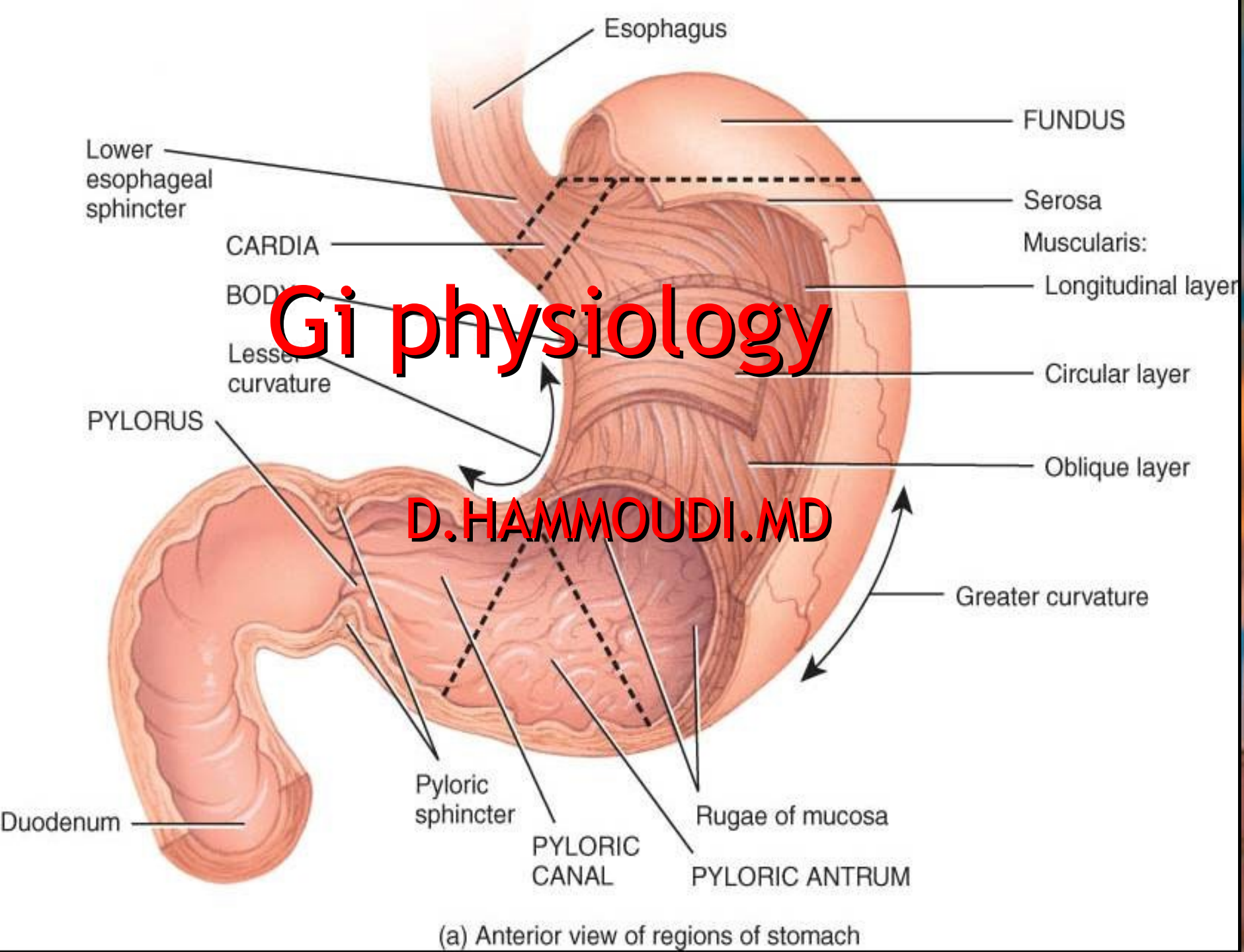
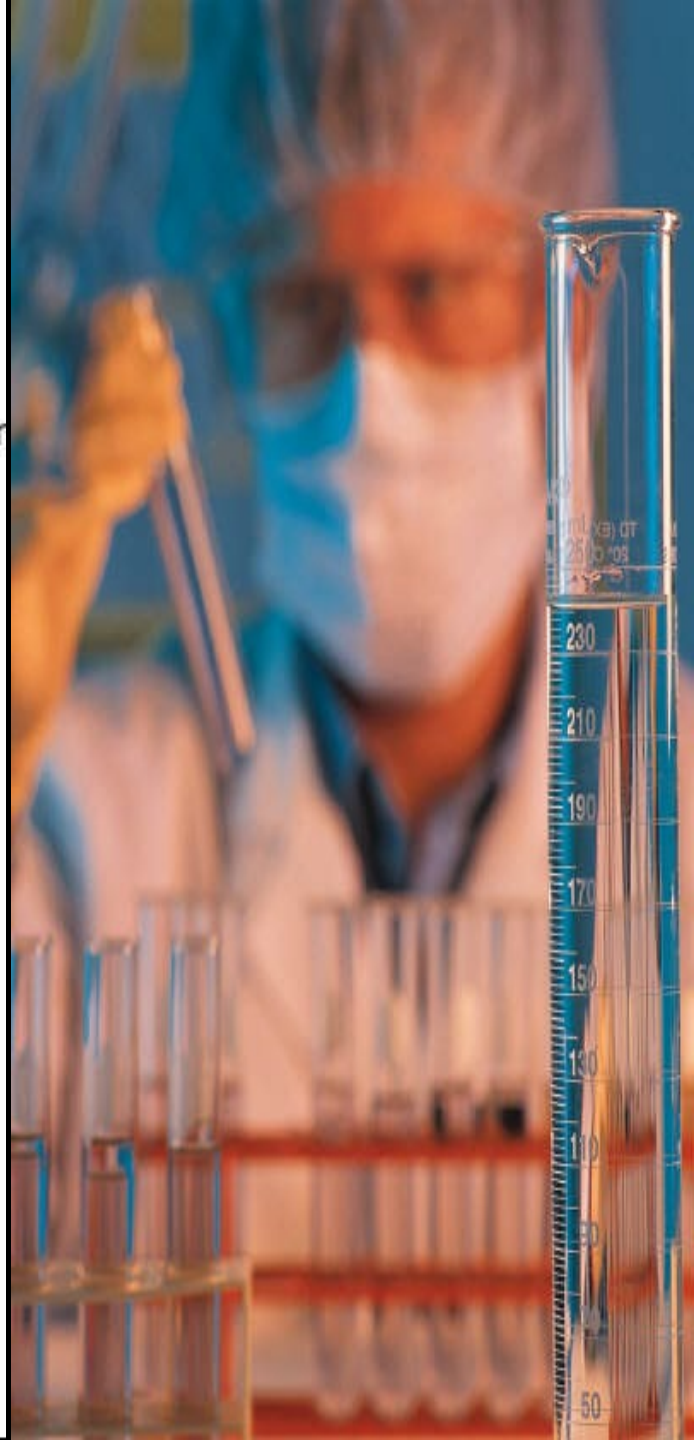
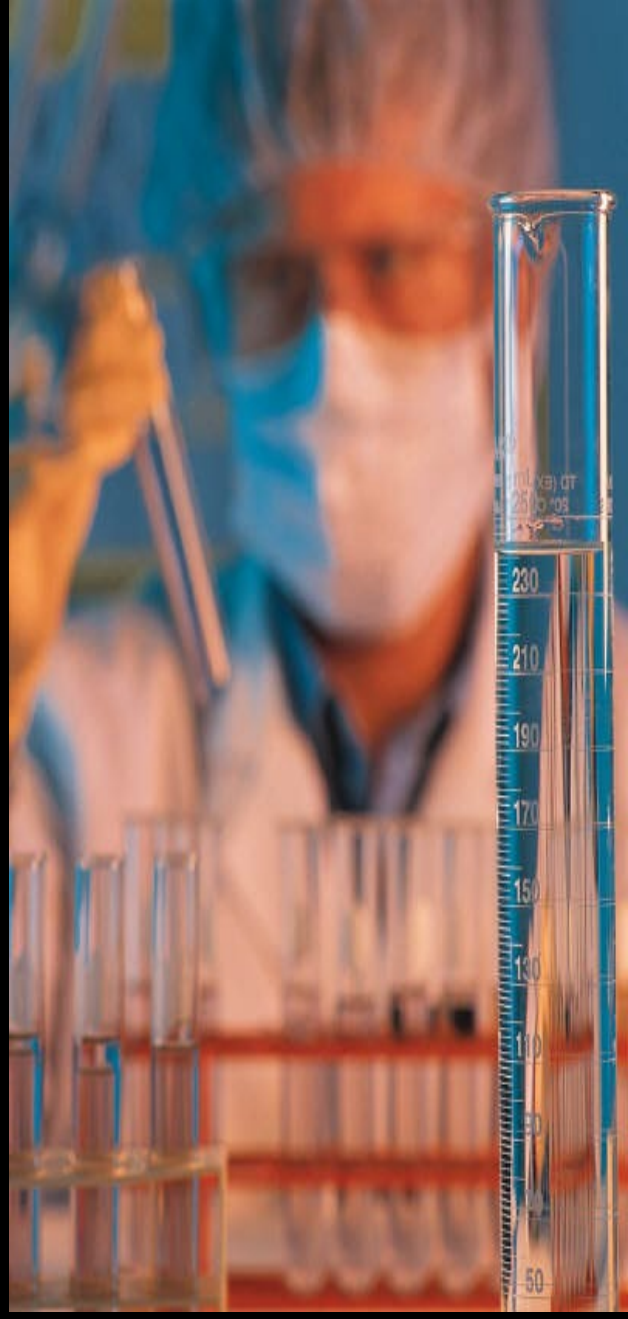


Gi physiology

D.HAMMOUDI.MD



- **The gastrointestinal tract consists of the**
  - oral cavity,
  - pharynx,
  - esophagus,
  - stomach,
  - small intestine, and large intestine.
- **The accessory organs are**
  - the teeth,
  - tongue,
  - glandular organs such as
    - salivary glands,
    - liver, gallbladder,
    - pancreas.



- **The digestive system functions to provide**
  - mechanical processing,
  - digestion,
  - absorption of food,
  - secretion of water,
  - acids, enzymes,
  - buffer, salt,
  - excretion of waste products.

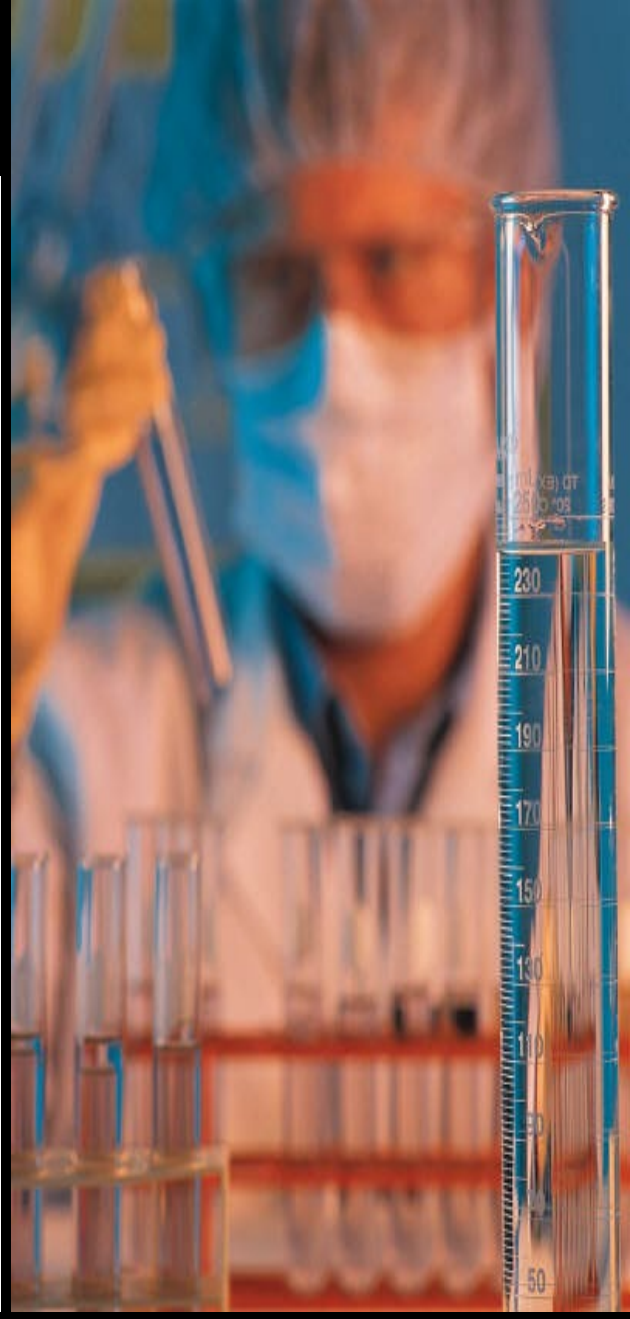
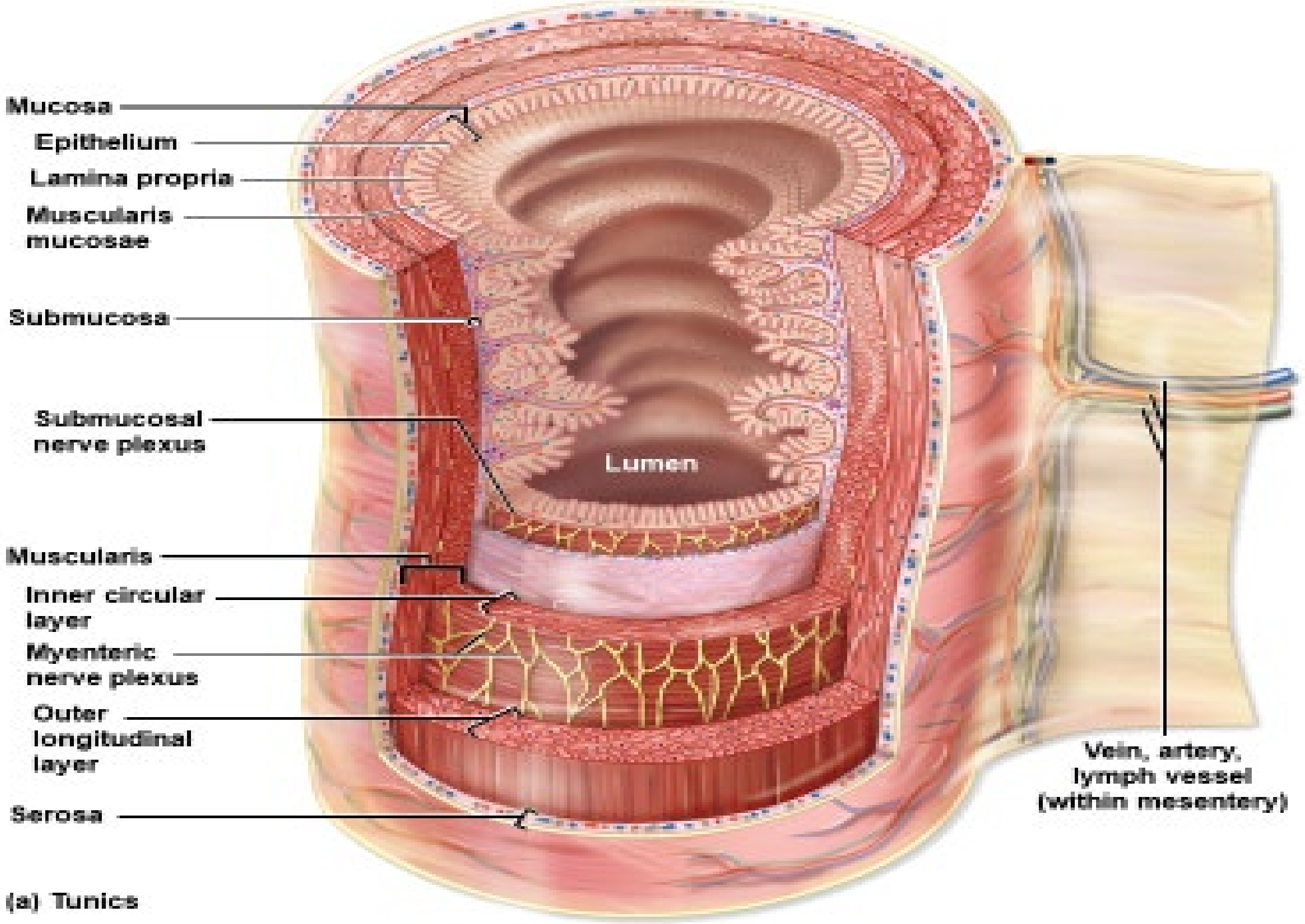


Fig. 26.2a



(a) Tunics

ENTERIC NERVOUS SYSTEM

SMOOTH MUSCLE: All smooth muscle is innervated by the autonomic nervous system.

- **General Properties:**
  - **Caveolae:** Micro-pits allow for increased surface area on smooth muscle.
  - No Striations: Thin and thick filaments run through in a random order. Smooth muscle has relatively more thin filaments than thick.
  - **Plasticity:** Smooth muscle is able to stretch to a greater length and compress to a shorter length than skeletal.
  - **Calcium** supply comes more from outside the cell rather than inside (in the SR), as compared to skeletal.
  - Slow, Sustained contraction as compared to skeletal muscle.

- **MULTI-UNIT SMOOTH MUSCLE**: Has high innervation density. This is the type of smooth muscle found in *Ciliary Muscle* and *Ductus Deferens*.

- **UNITARY SMOOTH MUSCLE:** The type of smooth muscle found in gut.
  - Sparse innervation compared to multi-unit muscle
  - **Functional Syncytium**: **Gap junctions allow intercellular communication**.
  - Shows spontaneous (basal) electrical activity even in the absence of innervation.
    - High basal resting potential (-57 mV -vs- -80 mV) as compared to skeletal muscle. Smooth muscle is more permeable to Na^+ which accounts for spontaneous electrical activity.

- **SMOOTH MUSCLE CHANNELS:**
  - **Electromechanical Channels:** Channels that transduce electrical activity, in one form or another, to mechanical activity of actin and myosin.
    - **Slow-Leaking Ca+2-Channels**
    - **Ligand-Gated Channels**
    - **Voltage-Gated Na^+-Channels**
  - **Pharmaco-mechanical Channels:** Channels that employ a second messenger, causing contractility *without a change in the cell's electrical potential*.

•**SMOOTH MUSCLE CONTRACTION:**

- **Ca^{+2} enters cell** ------> **Calmodulin** then activates **Myosin Light-Chain Kinase (MLCK)** ------> MLCK then phosphorylates myosin, turning it on and enabling it to interact with actin ------> contraction occurs.
- **Regulatory step is binding of Ca^{+2} with Calmodulin.**

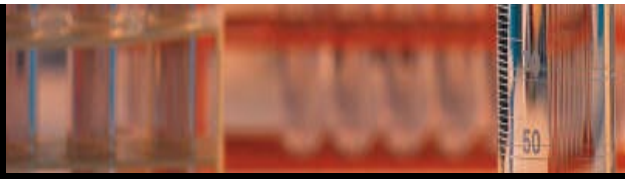
SLOW-WAVES: The basal electrical tone of smooth muscle. *No contraction occurs with slow-waves*.

•Also called the **Basal Electrical Rhythm (BER)**

•Magnitude of change is 5 - 15 mV, caused by *entrance of Na^{+}* into cell. No Ca^{+2} is associated with these waves so no contraction occurs with them.

•**Basal Rhythm in Different Regions: Remember these waves are only electrical -- *not mechanical*.**

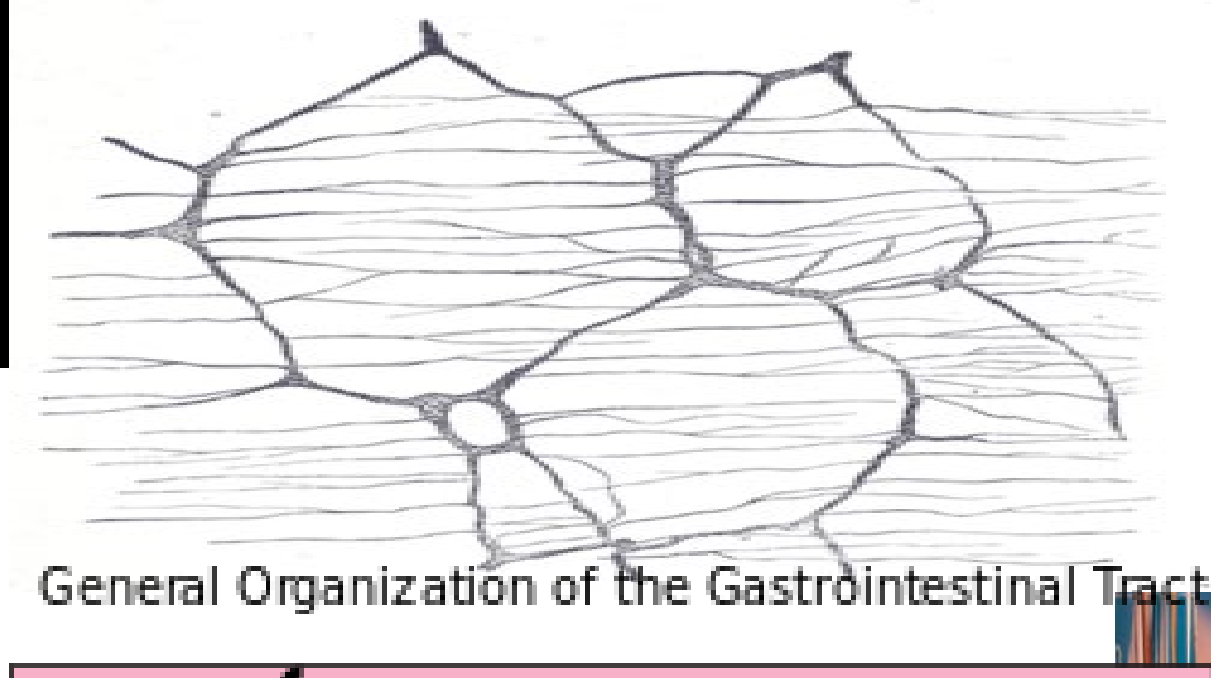
- **STOMACH: 3 waves per minute**
- **DUODENUM: 12 waves per minute. In the duodenum, 30-40% of slow-waves are associated with Ca^{+2} as Ca^{+2} is added to the cells.**



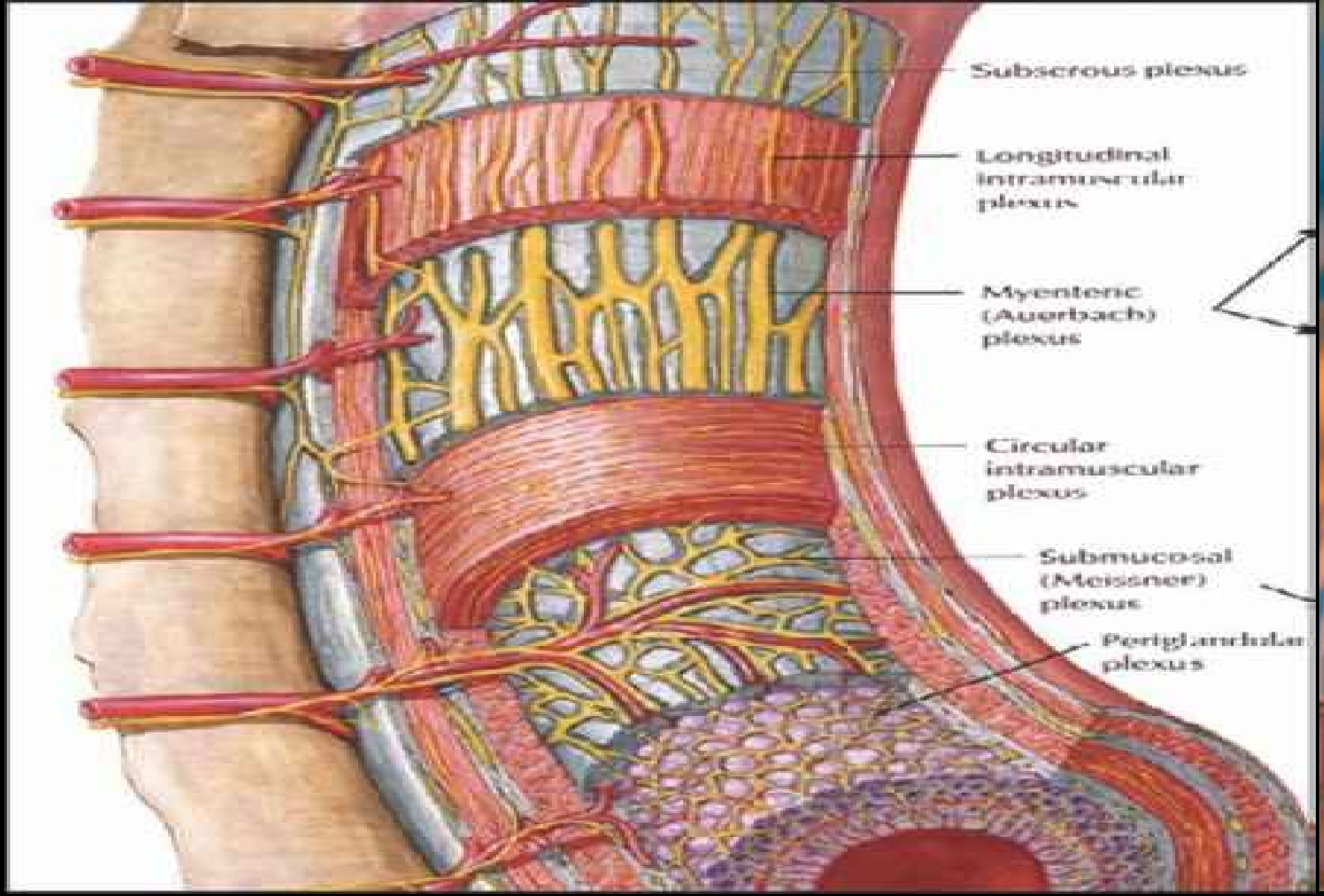
ENTERIC NERVOUS SYSTEM:

- **GI Plexuses:**
  - **MYENTERIC PLEXUS:**
  - **SUBMUCOSAL PLEXUS:**

- **EXTRINSIC REGULATORY INPUT:**
  - ***Chemoreceptors* and *mechanoreceptors***
  - **VAGO-VAGAL (long) REFLEX:**
  - **INTESTINO-INTESTINAL (short) REFLEX:**
  - **SYMPATHETICS are inhibitory to the GI-Tract.**



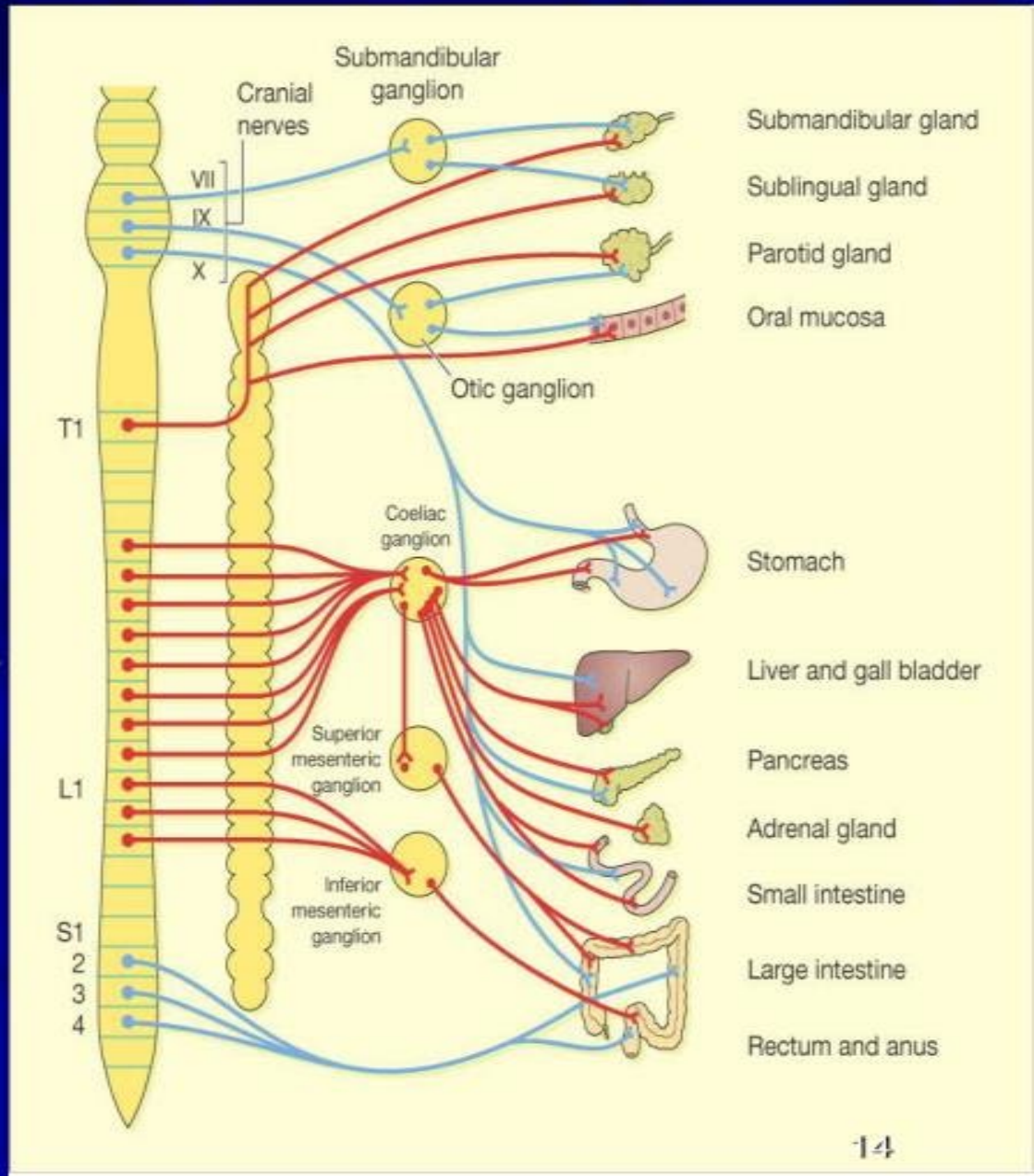
General Organization of the Gastrointestinal Tract


Subserous plexus
Longitudinal intramuscular plexus
Myenteric (Auerbach) plexus
Circular intramuscular plexus
Submucosal (Meissner) plexus
Perigl...rlular plexus

Extrinsic GIT Innervations

Sympathetic:

- Arises from thoracic and upper lumber spinal cord (T5-L2).
- Pre-ganglionic fibers synapse outside GI tract in pre-vertebral ganglia
- Post-ganglionic adrenergic fibers innervate the cells of the myenteric and submucosal plexus
- Elements from the two plexuses innervate the smooth muscle, secretory and endocrine cells.
- The postganglionic neurotransmitter is mainly Epinephrine (adrenaline).
- Increase of sympathetic nerve activity → inhibitory effects, e.g. ↓secretion, ↓ motility and ↓ blood flow.



ENTERIC NERVOUS SYSTEM: The GI nervous system is *independent of the CNS*. Activity can go on without any CNS input.

- **GI Plexuses:**
  - **MYENTERIC PLEXUS:** Outermost plexus located between the two layers of musculature -- between the ***muscularis circularis* and *muscularis longitudinalis***.
  - **SUBMUCOSAL PLEXUS:** Located in the submucosa, just outside the *Muscularis Mucosae*.

- **EXTRINSIC REGULATORY INPUT:**
  - ***Chemoreceptors* and *mechanoreceptors*** from the GI-Lumen are an important source of input. They are the origin of **short reflexes** (not involving the CNS) that go through the two GI plexes in the enteric NS.
  - **VAGO-VAGAL (long) REFLEX:** Generally stimulatory (increase motility, secretomotor, vasodilatory).
    - The Vagus carries both afferents (70%!) and efferents. Luminal receptors send afferent signal back to the CNS via the Vagus.
  - **INTESTINO-INTESTINAL (short) REFLEX:** Generally inhibitory, involving only the Enteric NS, and completely independent of the Autonomic NS.
  - **SYMPATHETICS are inhibitory to the GI-Tract**. *They work primarily by **presynaptic** inhibition,* thus inhibiting release of ACh. In this way we get smooth muscle relaxation.
    - Norepinephrine binds to **alpha1-Adrenoreceptors** on parasympathetic nerve terminals and thereby inhibit the release of ACh.

•NEUROTRANSMITTERS:

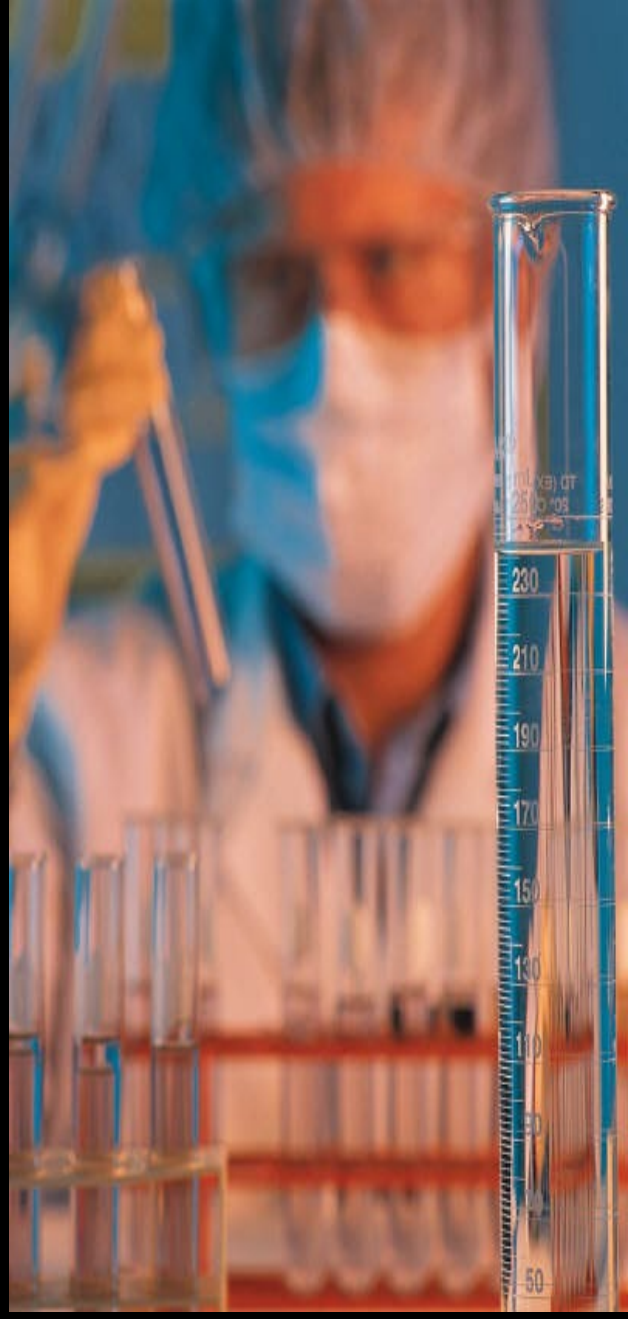
- **Acetylcholine** increases GI-Motility when it acts on smooth muscle.
- **Norepinephrine** decreases GI-Motility when it acts on smooth muscle.
- **Enkephalin (Opioid)** decreases GI-motility *by inhibiting the release of ACh*.
- **VASOACTIVE INTESTINAL PEPTIDE (VIP):** Acts directly on smooth muscle to cause smooth muscle relaxation.
  - **It is localized with ACh in the Vagus Nerve.**
  - **VIP is in local neurons, and is released when Vagal Fibers excite these inhibitory neurons to cause relaxation: Vagus (Excitatory synapse) ------> Turn on VIP neurons (Inhibitory synapse) ------> Relaxation.**
- **COLOCALIZATION:** ***Enkephalins, VIP, NO, Serotonin,*** and a whole bunch of other transmitters are *localized* along with ACh and NorE in the autonomic nervous system.
  - Depending on the nerve, whenever the ACh and NorE are released, so will the other substances be released.

MYOGENIC CONTRACTILITY:

The gut has some contractility **without any nervous input whatsoever.**

- Luminal contents will cause basal contractility without any nervous influence at all.

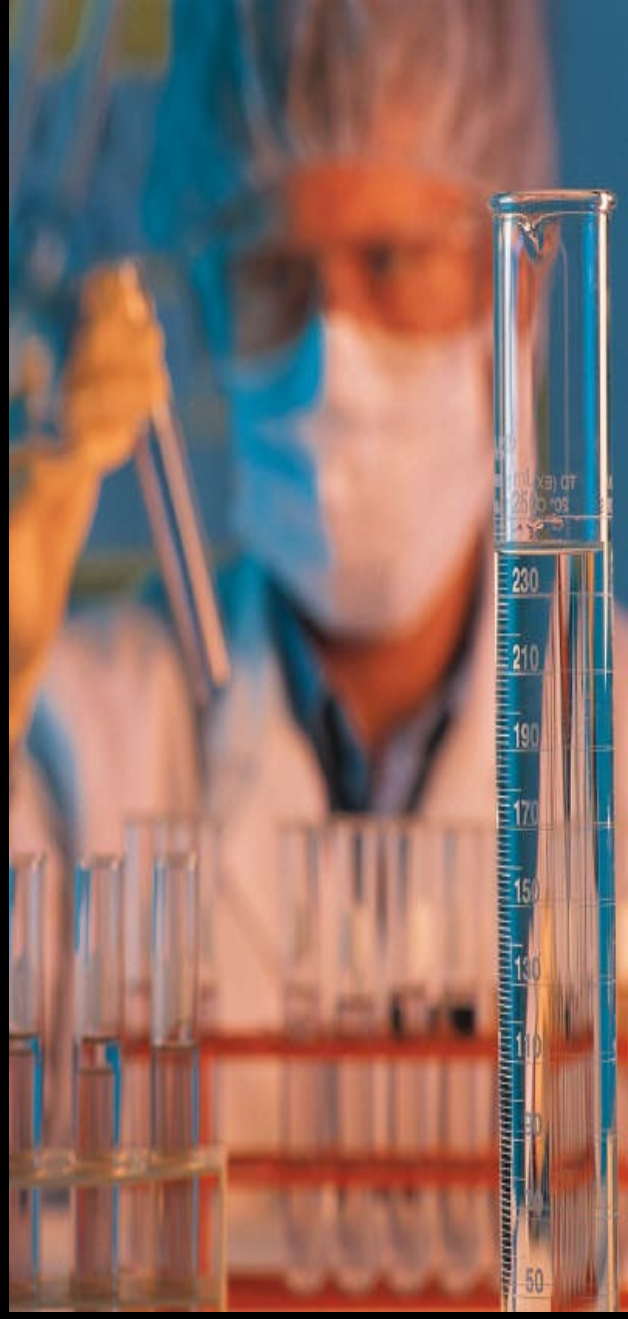
- Thus there is a constant **inhibitory tone** of **VIP** and **NO** on the gut, to prevent / slow down this contractility.



The Oral Cavity Functions

Provide

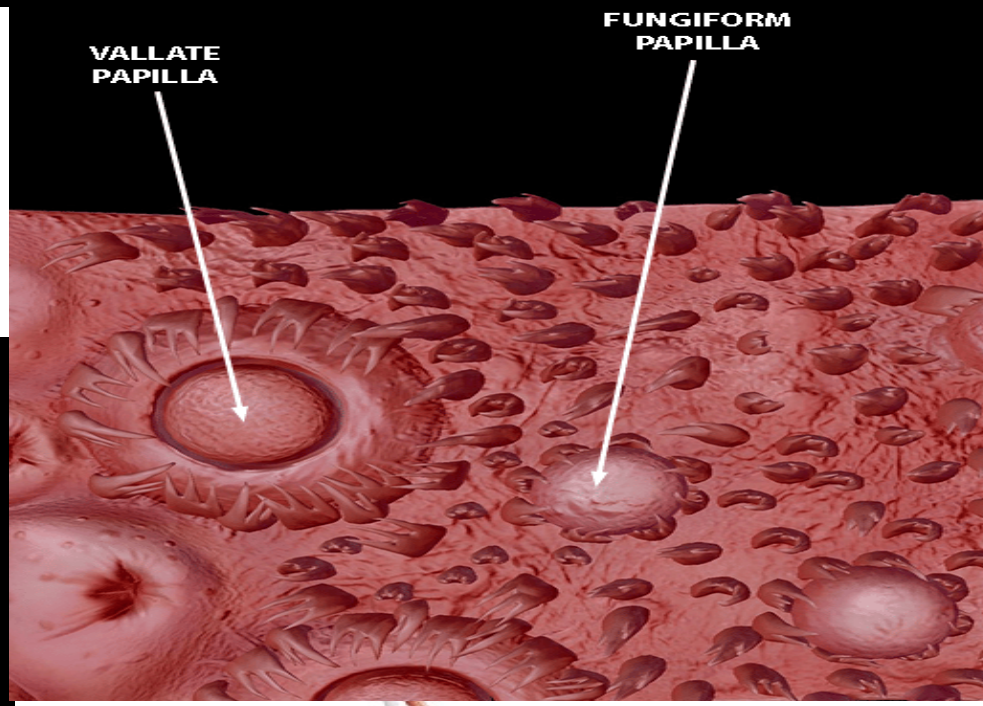
- sensory analysis of food material before swallowing
- mechanical processing via the action of the teeth, tongue, and palatal surfaces
- lubrication by mixing food material with mucus and salivary gland secretion
- limited digestion of carbohydrates and lipids

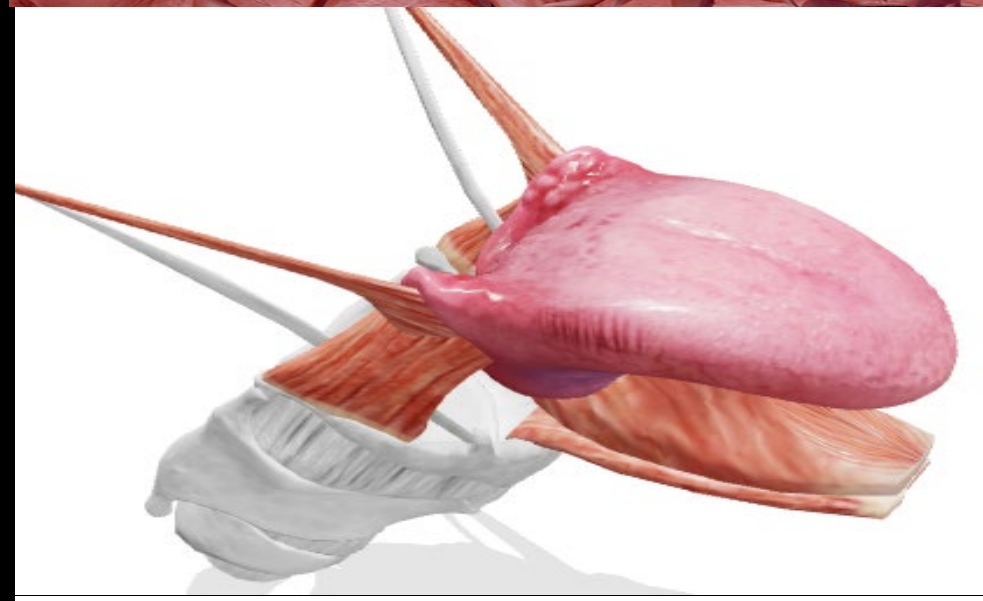


- nonkeratinized squamous epithelial cells (seen in cheeks, lips, and inferior surface of the tongue), these cells are not known to absorb **molecules except for the mucosa inferior to the tongue.**

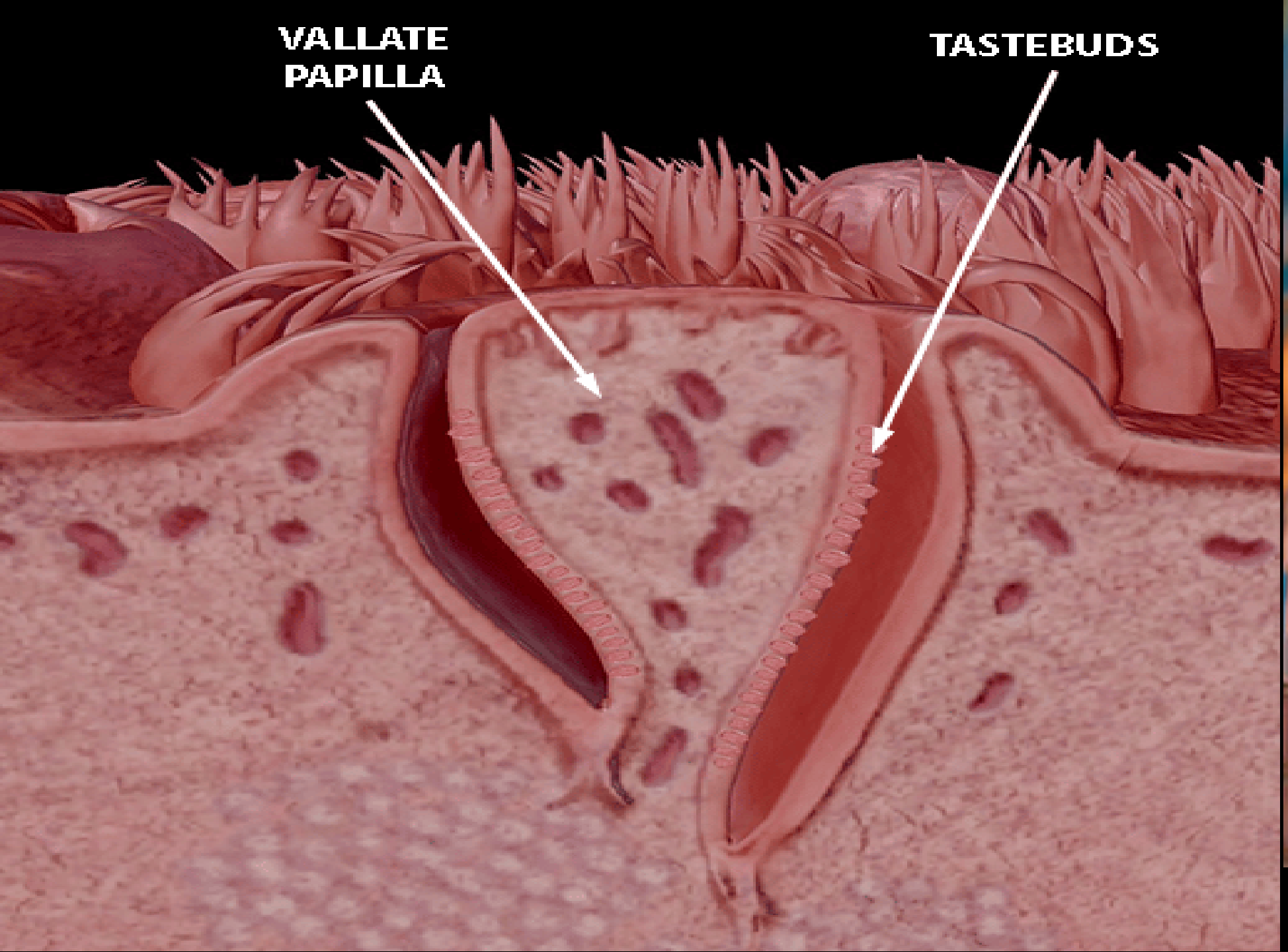
Functions of the tongue include ;

- mechanical processing by compression, abrasion, and distortion;
- manipulation to assist in chewing and prepare material for swallowing;
- sensory analysis by touch, temperature, and taste receptors; and secretion of mucins and lingual lipase.
- The lingual lipase has a broad pH and breaks down lipids (mainly triglyceride).
- The pH of 3.5 to 6 allows lingual lipase to work even in the acid environment of the stomach

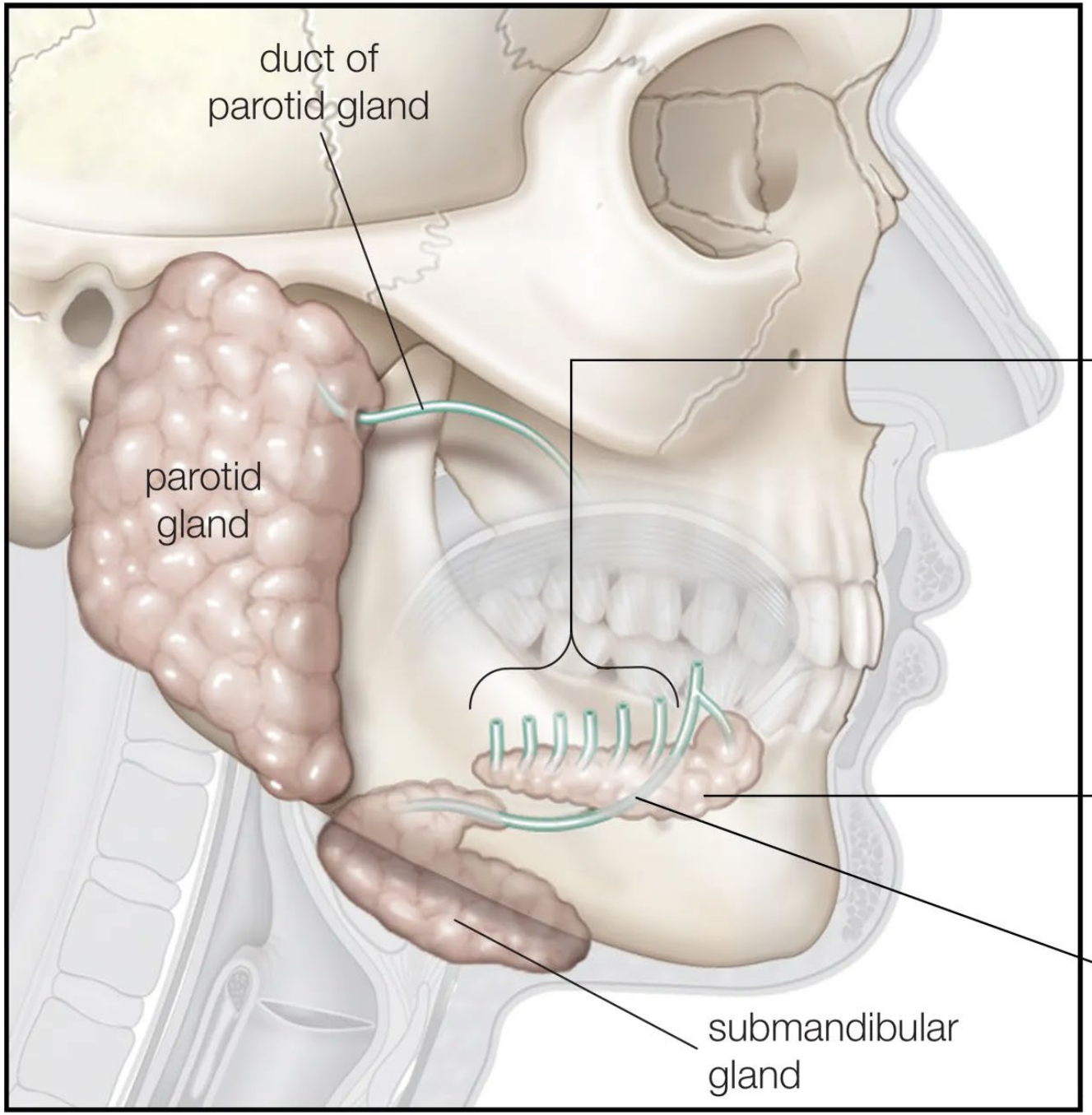


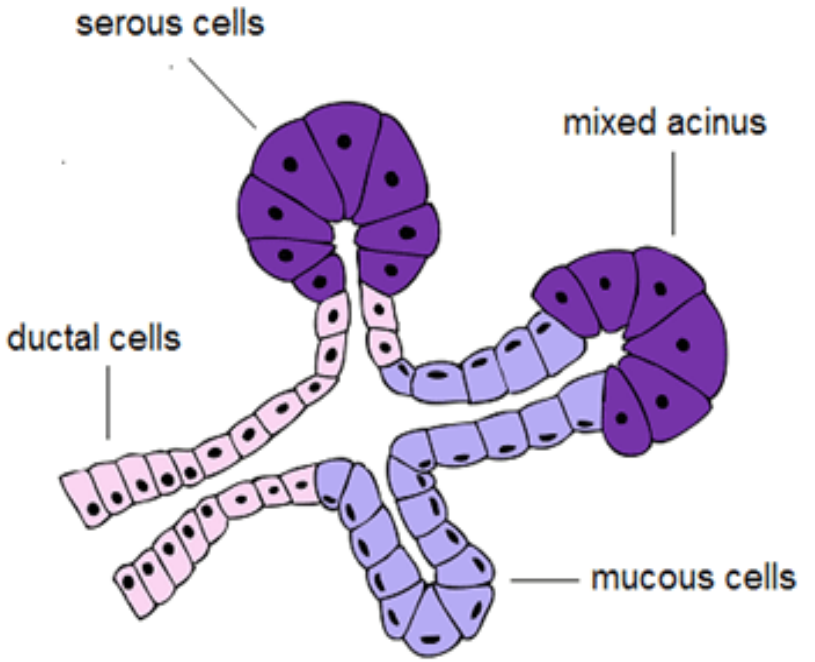


The four intrinsic tongue muscles work together to give the tongue great flexibility.


VALLATE
PAPILLA
TASTEBUDS

SALIVARY GLANDS





Within the oral cavity, there are three pairs of salivary glands.

- **Parotid salivary glands** produce serous secretions containing a large amount of salivary amylase, which breaks down carbohydrate complexes.
- **Sublingual salivary glands** produce a mucous secretion that serves as both a buffer and lubricant.
- **Submandibular salivary glands**, secreting a mixture of buffers, glycoproteins called mucins, and salivary amylase.

- 99.4% of the saliva produced is water
- the remaining 0.6% consists of electrolytes, buffers, glycoproteins (mucins), antibodies, enzymes, and waste products.
- These function to lubricate the mouth to prevent friction between the mucosa of the oral cavity and the food material;
- moisten the food material for easy swallowing process; and initiation of lipid and carbohydrate complex digestion.

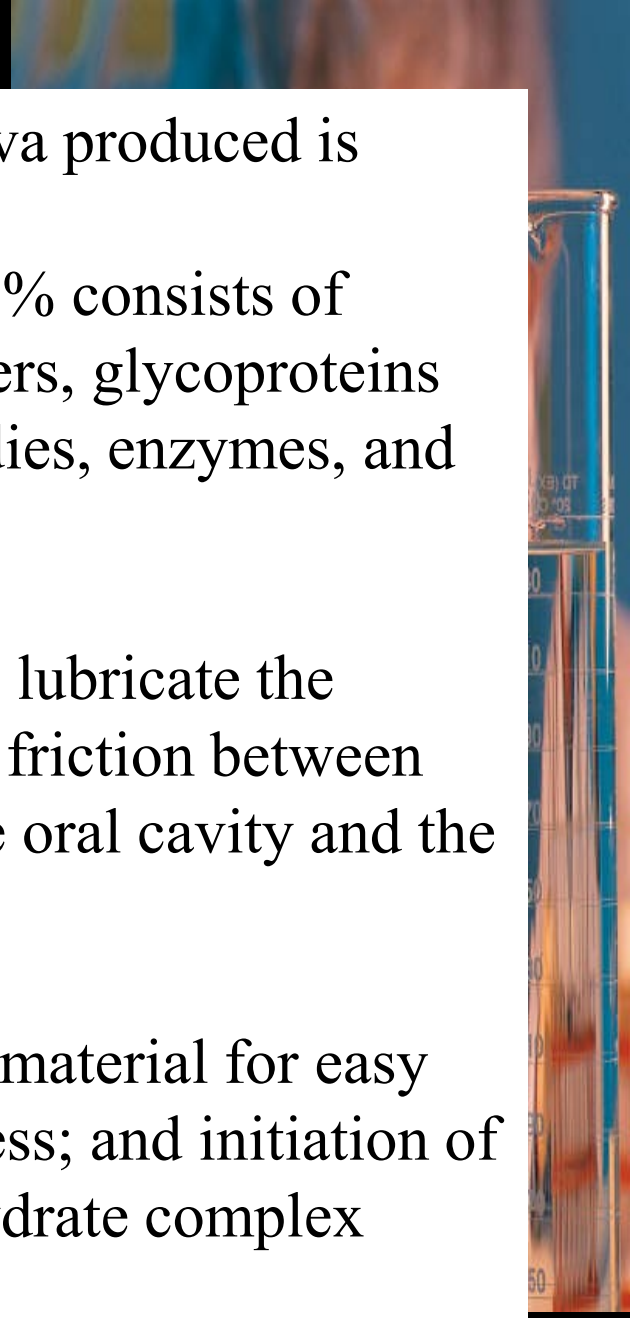


Table 26.1 Salivary Glands and Secretions

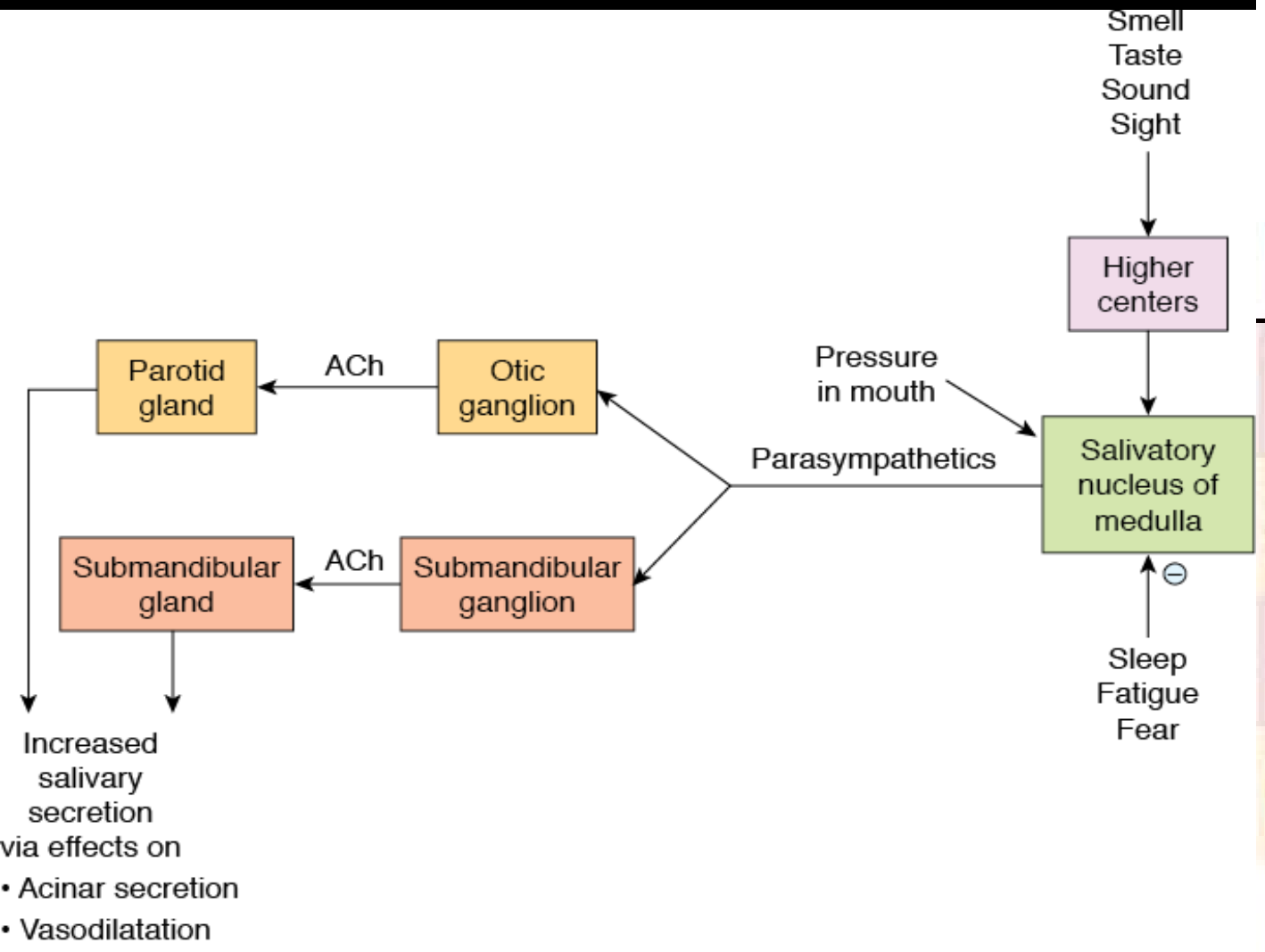
SALIVARY GLANDS

Gland	Structure and Location	Types of Secretion	Percentage of Saliva Produced
Parotid	Largest salivary gland; located anterior and inferior to ears; parotid duct opens into vestibule near second molar	Only serous secretions	25–30%
Submandibular	Located inferior to the floor of the oral cavity; duct opens lateral to lingual frenulum	Both serous and mucus secretions	60–70%
Sublingual	Smallest salivary gland; located inferior to tongue; ducts open into floor of oral cavity	Both serous and mucus secretions	3–5%

SALIVA CHARACTERISTICS

Production Rate	Solute Components	pH Range and Composition
1–1.5 liters per day	Salivary amylase, lingual lipase (from intrinsic salivary glands), mucin, ions (Na^+, K^+, Cl^-, HCO_3^-), lysozyme (antibacterial enzyme), immunoglobulin A (from plasma cells)	Slightly acidic (pH 6.4–6.8): 99.5% water, 0.5% solutes

Salivary gland secretion is a nerve-mediated reflex and the volume of saliva secreted is dependent on the intensity and type of taste and on chemosensory, masticatory or tactile stimulation.



Source: Barrett KE, Barman SM, Boitano S, Brooks HL: *Ganong's Review of Medical Physiology:* www.accessmedicine.com

Gland	Acinar Type	Viscosity	Percentage of Whole Unstimulated Daily Saliva
Parotid	Serous	Watery	25
Submandibular	Mixed	Semiviscous	71
Sublingual	Mucous	Viscous	3-4
Minors	Mucous	Viscous	Trace

From Mandel ID. Sialochemistry in diseases and clinical situations affecting salivary glands. *Crit Rev Clin Lab Sci.* 1980;12:321.

A

Ion channels/transporters related with 1° saliva secretion

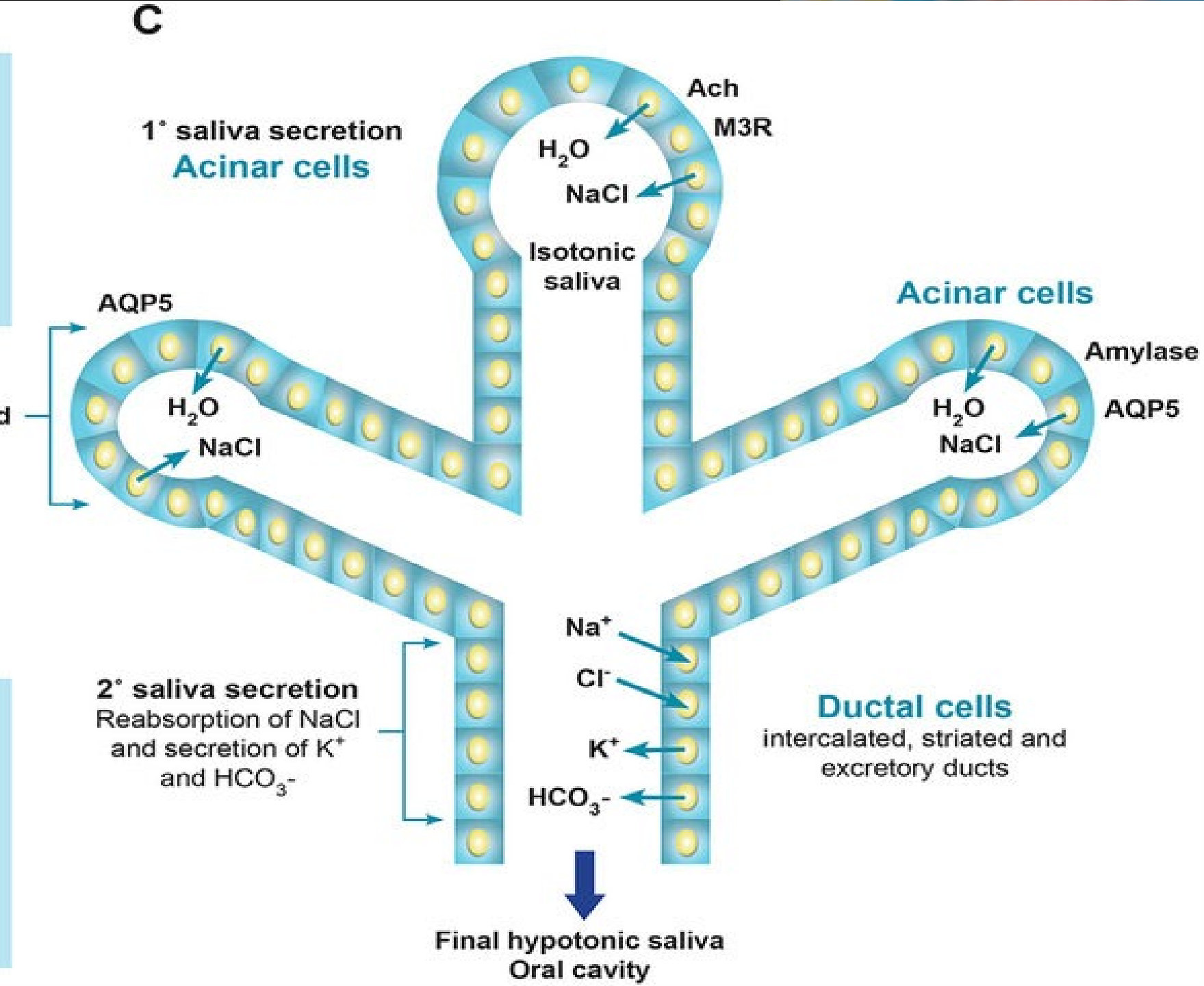
Na^+/K^+/ATPase
$Na^+/K+/2Cl^-$ cotransporter (NKCC)
Ca^{2+} activated K^+ channel
Ca^{2+} activated Cl^- channel
NHE1

B

Ion channels/transporters involved in ductal function

eNaC
NHE1
Cl^- channels
Cl^-/HCO_3^- exchanger
Apical K^+/H^+ exchangers,
K^+/HCO_3^- cotransporters

C



- The pharynx serves as a passageway of food material to the esophagus although it also has a respiratory function for air movement into the lung.
- During swallowing, **closure of the nasopharynx and larynx** occurs to **maintain the proper direction of food.**
- This process is **achieved by cranial nerves IX and X**.
- From the pharynx, food material goes to the esophagus.

- The esophagus's primary function is to empty food materials into the stomach via waves of contraction of its longitudinal and circular muscle known as peristalsis.
- The upper one-third of the esophagus is predominantly skeletal muscle.
- The middle one-third is a mixture of both the skeletal muscle and smooth muscle.
- The lower one-third is mainly smooth muscle.
- However, during the act of deglutition, the buccal phase is the only voluntary phase where one can still control the swallowing process.
- The skeletal muscles found in the pharynx and upper esophagus are all under **the control of the swallow reflex;** hence the pharyngeal and esophageal phases of swallowing are under **involuntary control help of afferent and efferent fibers of glossopharyngeal and vagus nerves**.
- The smooth muscles of the esophagus are arranged in a circular and longitudinal fashion and aid in peristaltic movement during swallowing.

Enzymes of the GI

1. Amylase

Function: Breaks down starches (polysaccharides) into sugars (maltose and dextrins).

Location:

•**Salivary amylase (ptyalin):** Produced in the salivary glands and acts in the mouth.

•**Pancreatic amylase:** Produced in the pancreas and acts in the small intestine.

2. Pepsin

Function: Breaks down proteins into smaller peptides.

Location:

•Produced in the stomach by **chief cells** as an inactive precursor (pepsinogen) which is activated by the acidic environment in the stomach.

3. Lipase

Function: Breaks down dietary fats into fatty acids and glycerol.

Location:

•**Salivary lipase:** Produced in the salivary glands and acts in the mouth.

•**Gastric lipase:** Produced in the stomach by chief cells and acts in the stomach.

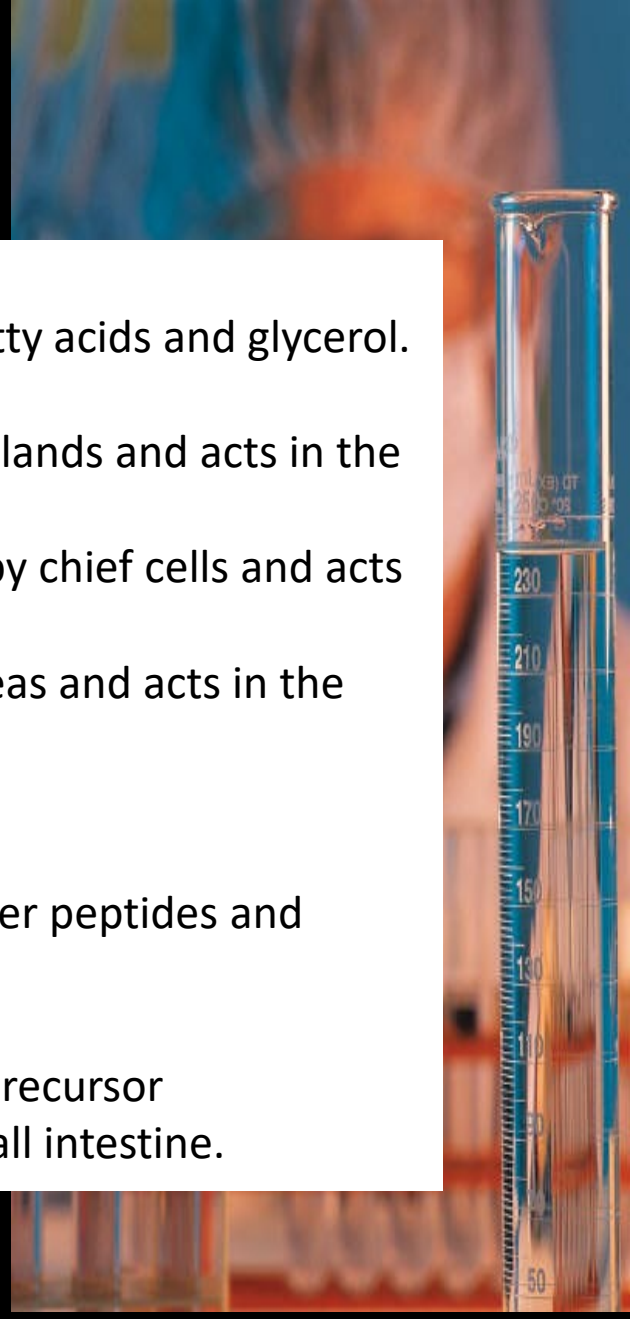
•**Pancreatic lipase:** Produced in the pancreas and acts in the small intestine.

4. Trypsin

Function: Breaks down proteins into smaller peptides and amino acids.

Location:

•Produced in the pancreas as an inactive precursor (trypsinogen) which is activated in the small intestine.



5. Chymotrypsin

Function: Breaks down proteins into smaller peptides and amino acids.

Location:

•Produced in the pancreas as an inactive precursor (chymotrypsinogen) which is activated in the small intestine.

6. Carboxypeptidase

Function: Cleaves the terminal amino acid from the carboxyl end of peptides.

Location:

•Produced in the pancreas and acts in the small intestine.

7. Elastase

Function: Breaks down elastin and other proteins.

Location:

•Produced in the pancreas and acts in the small intestine.

8. Nuclease

Function: Breaks down nucleic acids (DNA and RNA) into nucleotides.

Location:

•Produced in the pancreas and acts in the small intestine.

9. Maltase

Function: Breaks down maltose into two glucose molecules.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.

10. Sucrase

Function: Breaks down sucrose into glucose and fructose.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.

11. Lactase

Function: Breaks down lactose into glucose and galactose.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.

12. Dipeptidase

Function: Breaks down dipeptides into individual amino acids.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.

13. Enteropeptidase (Enterokinase)

Function: Activates trypsinogen into trypsin.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.

14. Phospholipase

Function: Breaks down phospholipids into fatty acids and other lipophilic substances.

Location:

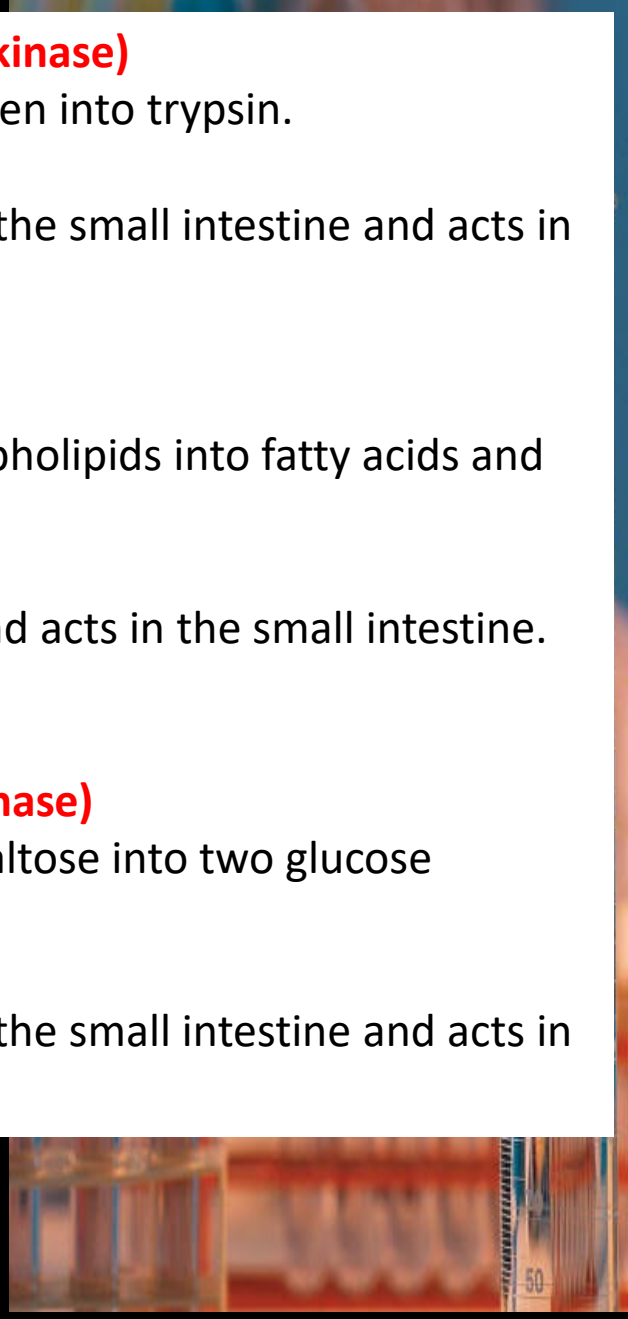
•Produced in the pancreas and acts in the small intestine.

15. Isomaltase (alpha-dextrinase)

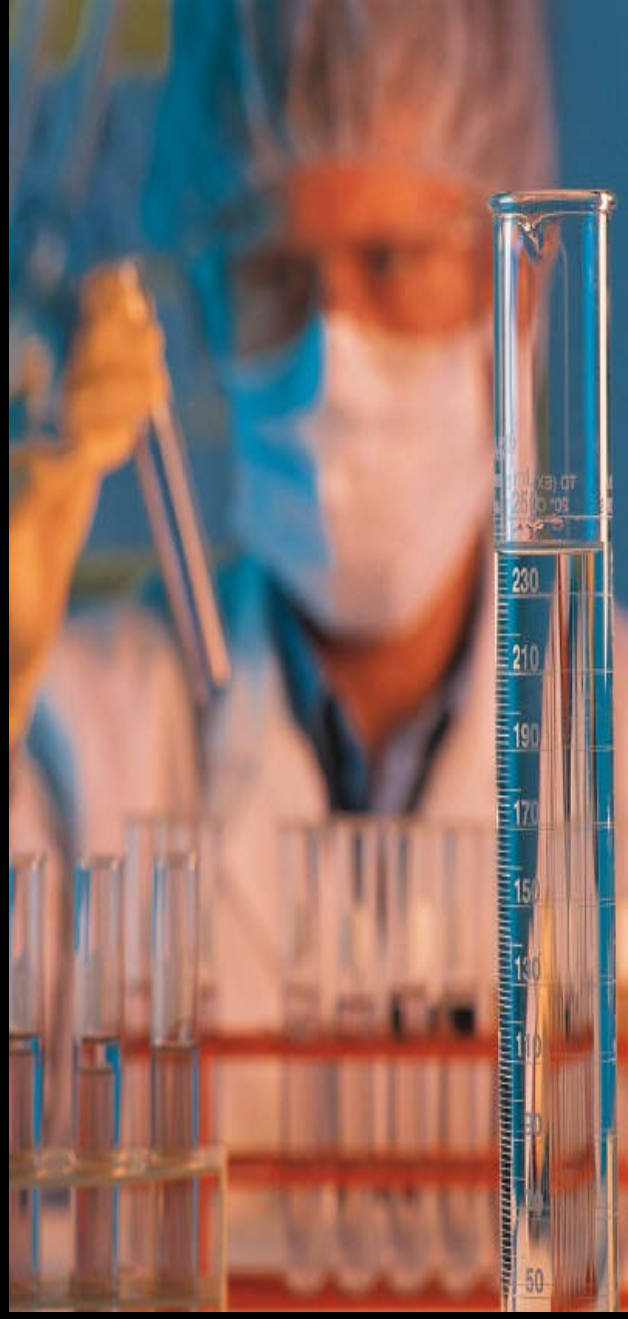
Function: Breaks down isomaltose into two glucose molecules.

Location:

•Produced by the cells lining the small intestine and acts in the small intestine.



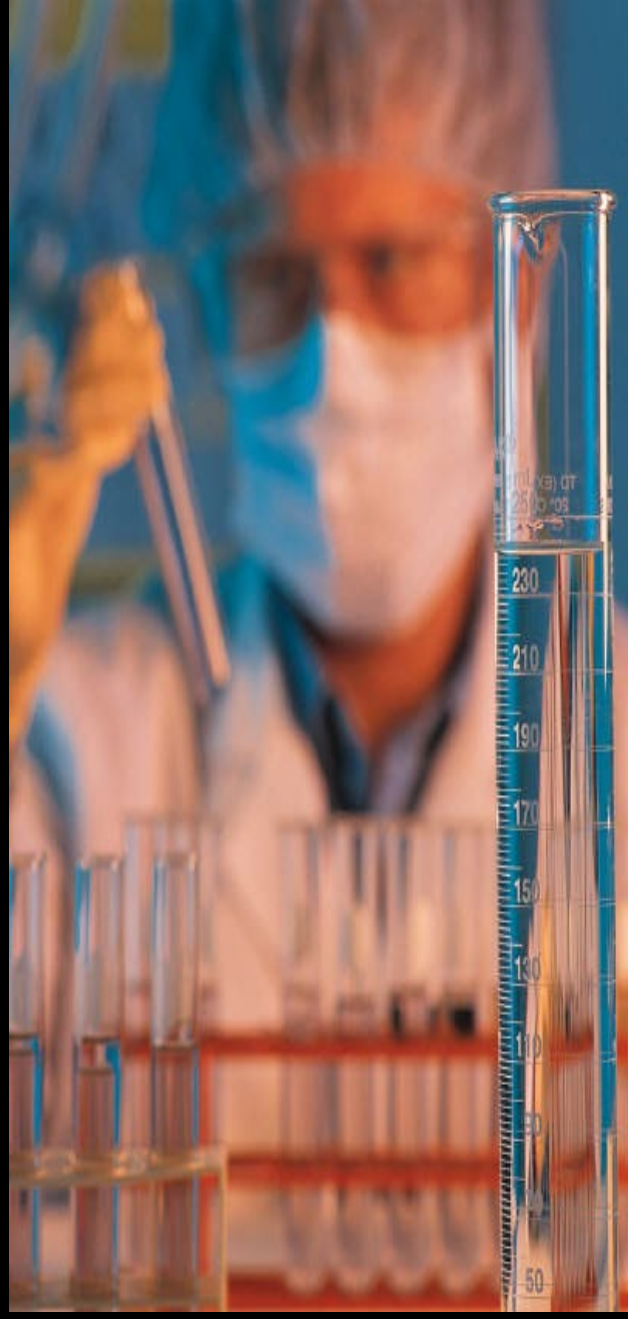
GI Function and production



Function of the GI system

4 basic digestive processes

- MOTILITY
- SECRETION
- DIGESTION
- ABSORPTION



overview of the digestion process:

1. Mouth

•**Mechanical Digestion:** Chewing breaks food into smaller pieces, increasing the surface area for enzymes to act upon.

•**Chemical Digestion:** Salivary glands secrete saliva, which contains the enzyme amylase. Amylase begins the breakdown of carbohydrates into simpler sugars.

2. Esophagus

•**Peristalsis:** Muscular contractions called peristalsis move the chewed food (now called a bolus) down the esophagus to the stomach.

3. Stomach

•**Mechanical Digestion:** The stomach churns food, mixing it with gastric juices to form a semi-liquid mixture called chyme.

•**Chemical Digestion:** Gastric glands secrete hydrochloric acid (HCl) and pepsinogen. HCl activates pepsinogen into pepsin, an enzyme that breaks down proteins into peptides.

4. Small Intestine

The small intestine is the primary site of digestion and absorption and is divided into three parts: the duodenum, jejunum, and ileum.

Duodenum

•**Bile:** Produced by the liver and stored in the gallbladder, bile is released into the duodenum. **Bile emulsifies fats, breaking them into smaller droplets.**

•**Pancreatic Enzymes:** The pancreas releases enzymes into the duodenum:

- **Amylase:** Continues carbohydrate digestion.
- **Trypsin and Chymotrypsin:** Continue protein digestion.
- **Lipase:** Breaks down fats into fatty acids and glycerol.
- **Nuclease:** Breaks down nucleic acids into nucleotides.

Jejunum and Ileum

•**Brush Border Enzymes:** The lining of the small intestine contains enzymes such as maltase, sucrase, and lactase that further digest carbohydrates. Peptidases break down peptides into amino acids.

•**Absorption:** **The majority of nutrient absorption occurs in the jejunum and ileum**.

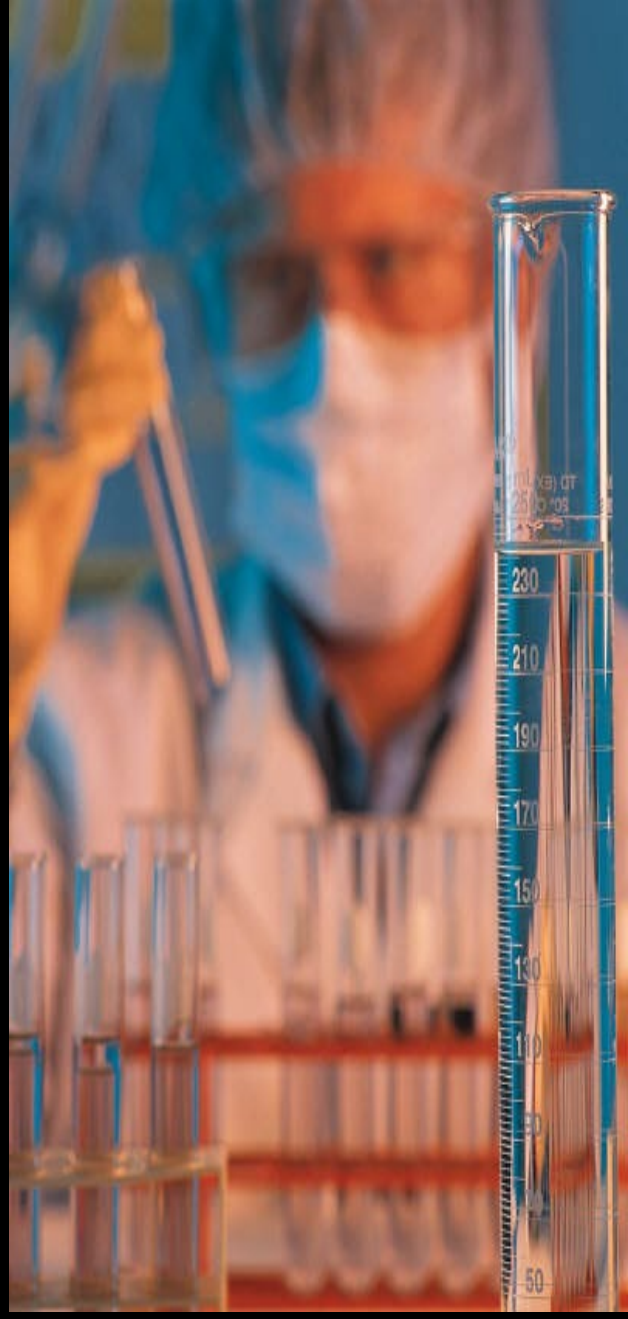
- The intestinal walls are lined with villi and microvilli, which increase the surface area for absorption.
- Nutrients pass through the cells lining the intestines and enter the bloodstream or lymphatic system.

5. Large Intestine (Colon)

- **Water Absorption:** The large intestine absorbs water and electrolytes from the remaining indigestible food matter.
- **Bacterial Fermentation:** Gut bacteria ferment some of the indigestible carbohydrates, producing short-chain fatty acids and gases.
- **Formation of Feces:** The remaining waste material is compacted into feces, which are stored in the rectum until eliminated through the anus.

6. Accessory Organs

- **Liver:** Produces bile, processes nutrients absorbed from the small intestine, and detoxifies harmful substances.
- **Gallbladder:** Stores and concentrates bile, releasing it into the small intestine when needed.
- **Pancreas:** Produces digestive enzymes and bicarbonate to neutralize stomach acid in the small intestine.



Summary of Digestive Enzymes and Their Actions

1.Salivary Amylase (Mouth): Breaks down starch into maltose.

2.Pepsin (Stomach): Breaks down proteins into peptides.

3.Pancreatic Amylase (Small Intestine): Continues breaking down starch into maltose.

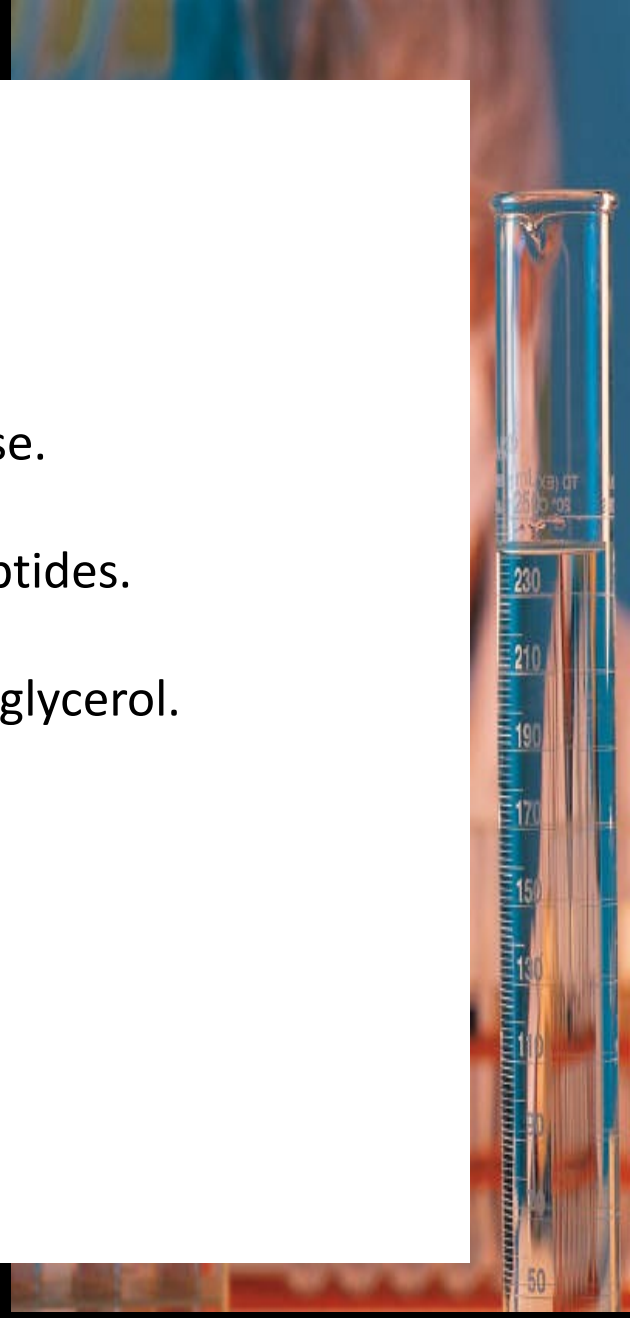
4.Trypsin and Chymotrypsin (Small Intestine): Break down proteins into smaller peptides.

5.Pancreatic Lipase (Small Intestine): Breaks down triglycerides into fatty acids and glycerol.

6.Nucleases (Small Intestine): Break down nucleic acids into nucleotides.

7.Brush Border Enzymes (Small Intestine):

1. **Maltase:** Converts maltose into glucose.
2. **Sucrase:** Converts sucrose into glucose and fructose.
3. **Lactase:** Converts lactose into glucose and galactose.
4. **Peptidases:** Break down peptides into amino acids.



Absorption Mechanisms

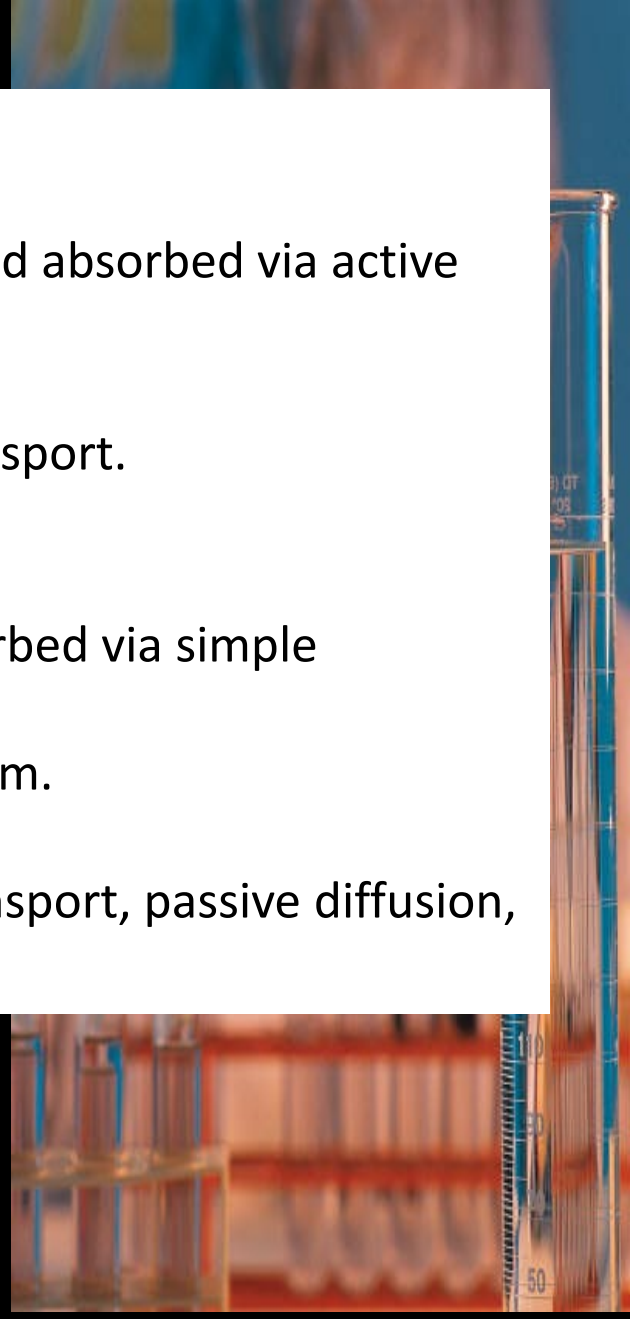
•**Carbohydrates:** Broken down into monosaccharides (glucose, fructose, galactose) and absorbed via active transport or facilitated diffusion.

•**Proteins:** Broken down into amino acids and small peptides, absorbed via active transport.

•**Fats:**

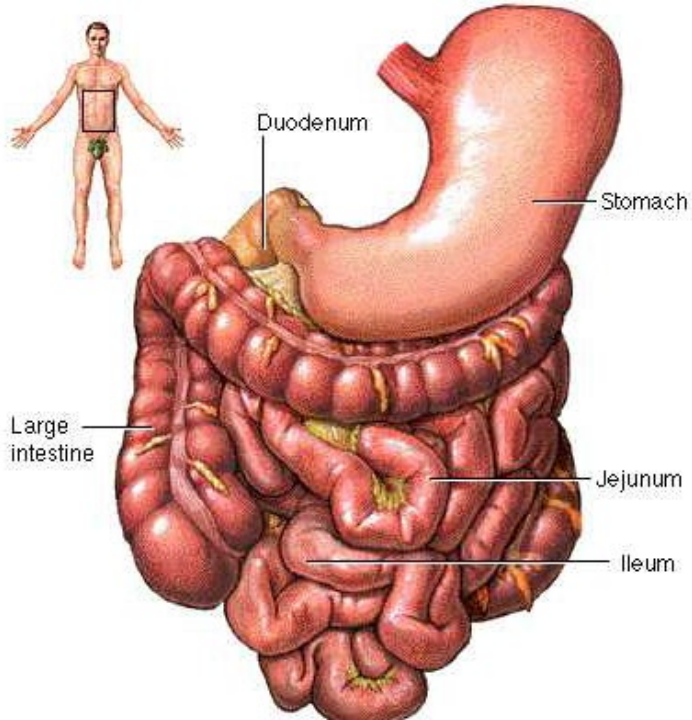
- Emulsified by bile salts, broken down into fatty acids and monoglycerides, absorbed via simple diffusion, and reassembled into triglycerides within enterocytes.
- Triglycerides are then packaged into chylomicrons and enter the lymphatic system.

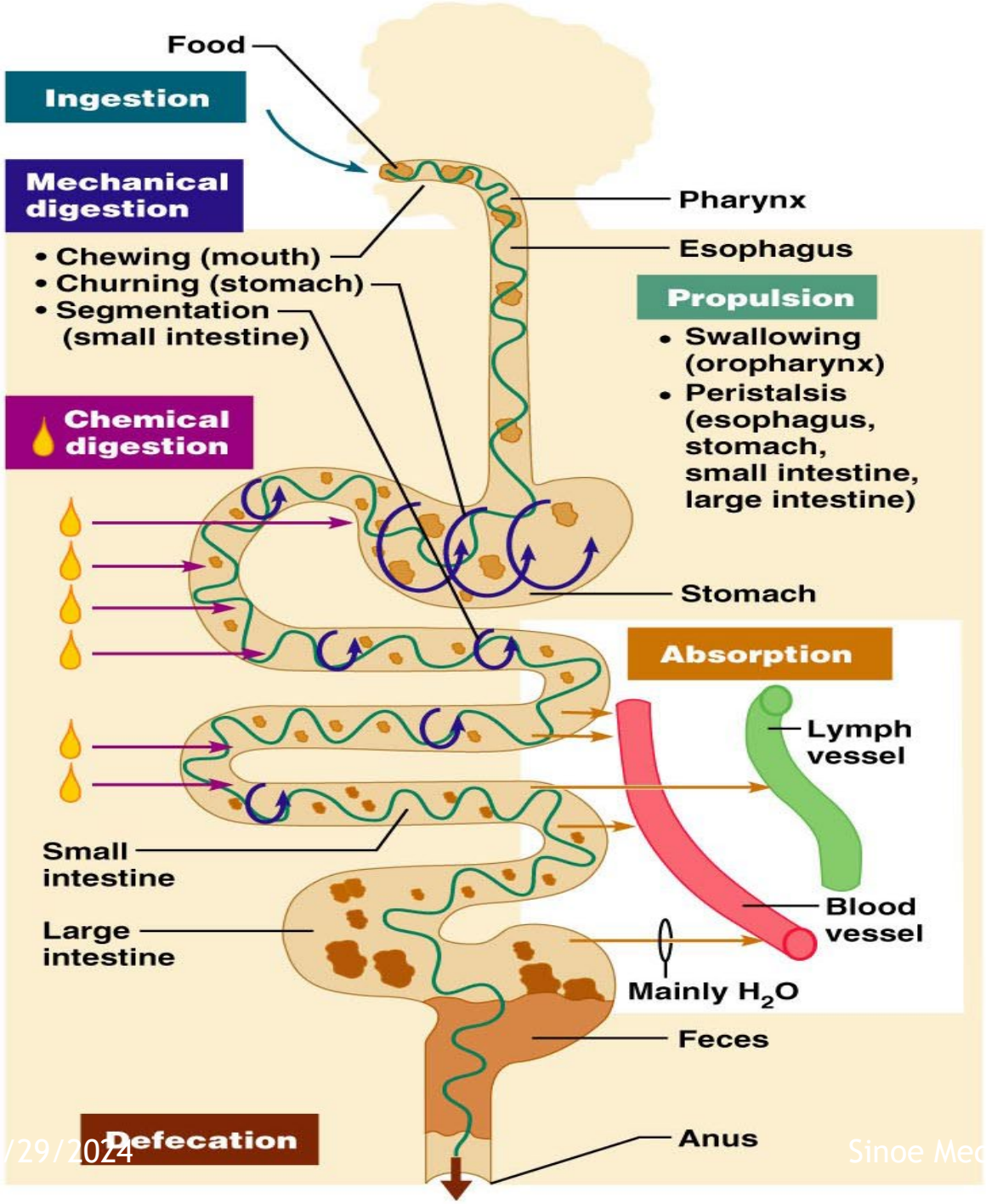
•**Vitamins and Minerals:** Absorbed through various mechanisms, including active transport, passive diffusion, and facilitated diffusion.



Digestive Process

- The GI tract is a “disassembly” line
  - Nutrients become more available to the body in each step
- **There are six essential activities:**
  - **Ingestion,**
  - **propulsion,**
  - **mechanical digestion**
  - **Chemical digestion,**
  - **absorption,**
  - **defecation**

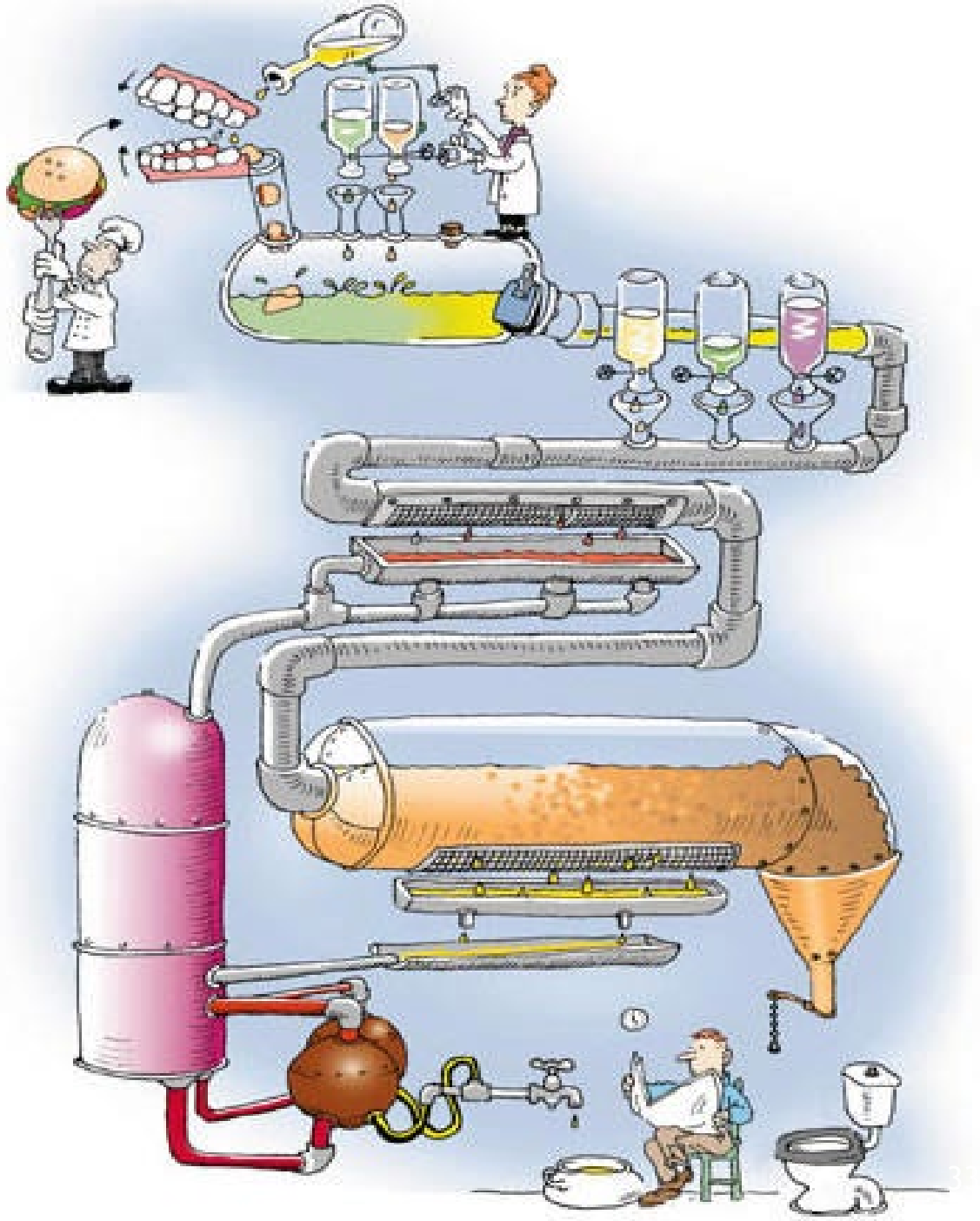




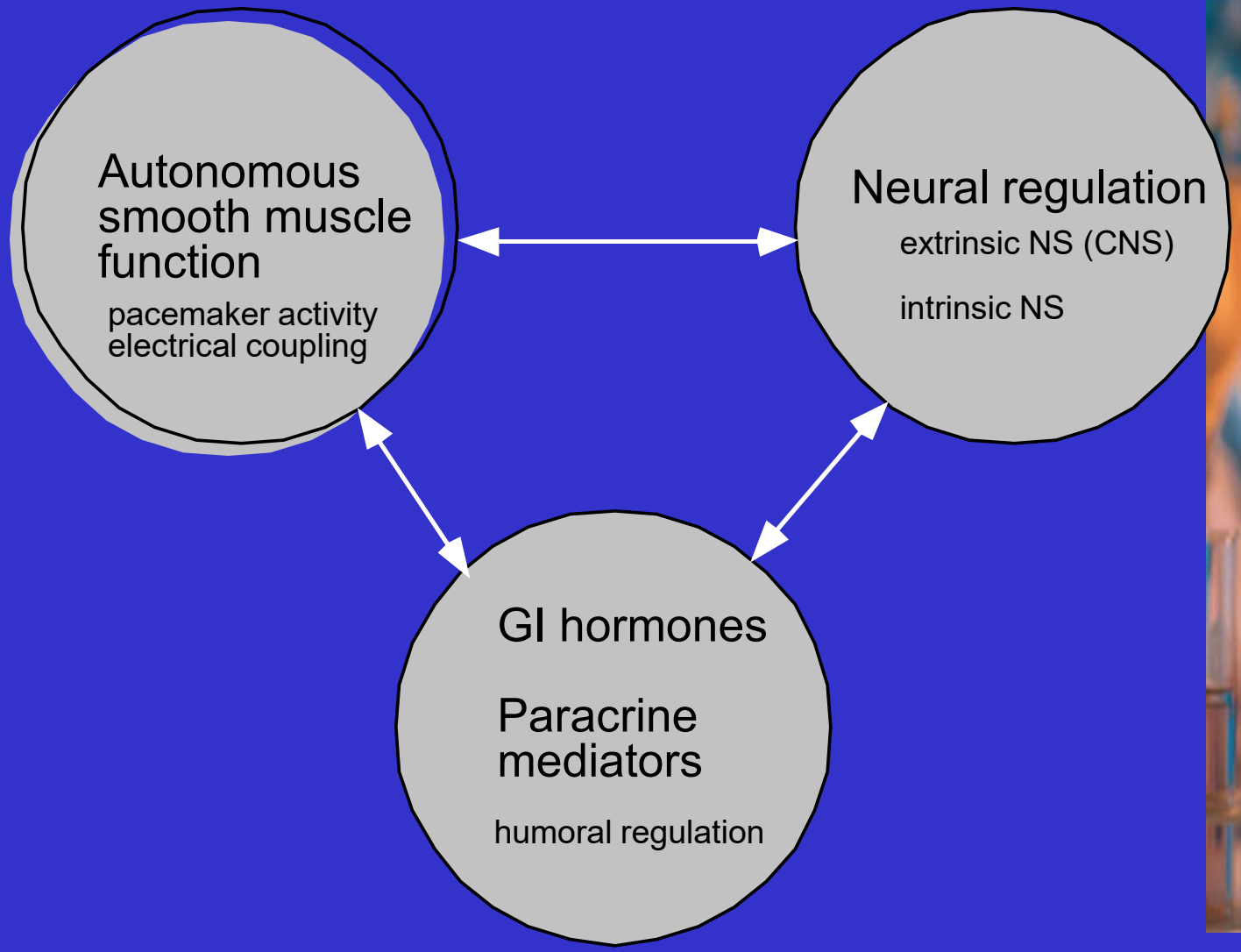
- Processing of food
- Types
  - **Mechanical (physical) need to have good teeth**
    - Chew
    - Tear
    - Grind
    - Mash
    - Mix
  - **Chemical**
    - Catabolic reactions
    - Enzymatic hydrolysis
      - Carbohydrate
      - Protein
      - Lipid

Digestion, what is it?

- Mechanical breakdown of food
-
- Chemical breakdown of food
-
- Absorption of nutrients

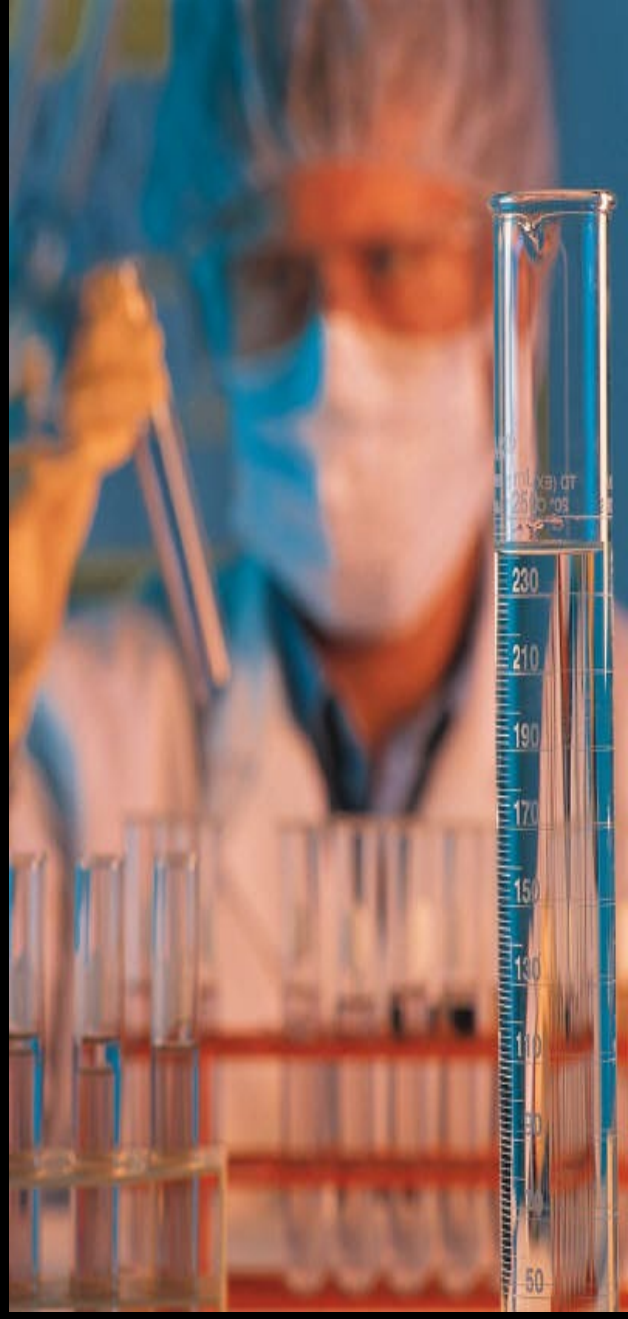


Regulation of GI function



5

- Enzymes Are divided into classes by targets (see details enzymes and function slides above):
  - carbohydrases:
    - break bonds between simple sugars
  - proteases:
    - break bonds between amino acids
  - lipases:
    - separate fatty acids from glycerides



Control of the digestive system

- Movement of materials along the digestive tract is controlled by
  - Neural mechanisms
    - Parasympathetic and local reflexes
  - Hormonal mechanisms
    - Enhance or inhibit smooth muscle contraction
  - Local mechanisms
    - Coordinate response to changes in pH or chemical stimuli

TYPES OF MOTILITY

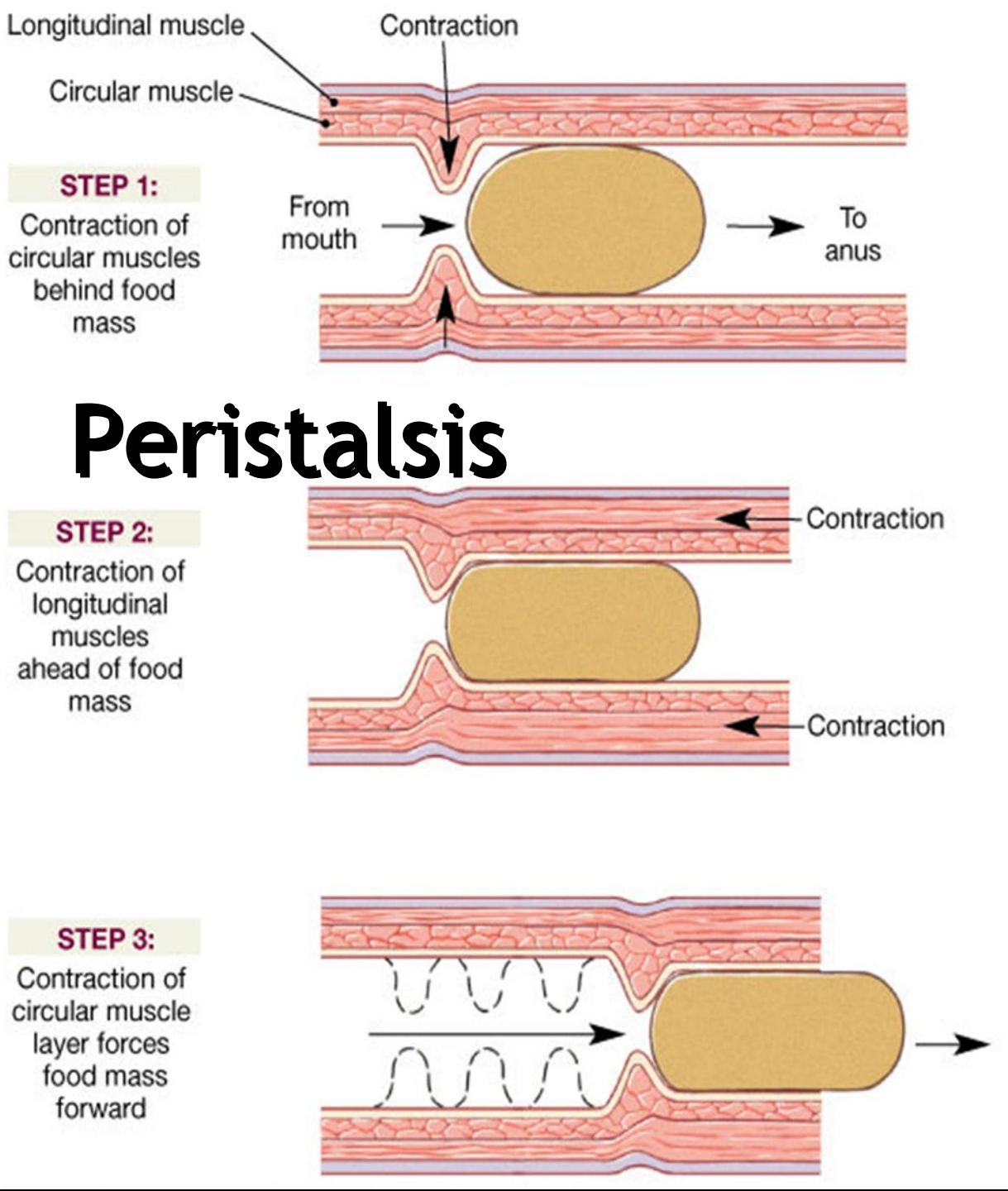
- **PERISTALSIS:** Propulsion of material in the **aboral** (away from mouth) direction.
  - Rate of peristalsis varies in region, but peristaltic generally gets slower as we move down the tract.
  - **Peristalsis occurs by *segmental hyperpolarization followed by depolarization of muscle***.
  - **Mechanism:** Bolus of food in a particular location stimulates mechanoreceptors and chemoreceptors in the GI lumen, ultimately resulting in peristalsis:
    - ***Relaxation*** of the muscle occurs distal to the bolus, so that the food can go forward. This is mediated by VIP / NO.
      - **Contraction of *Longitudinal Muscle* layer also occurs distal to bolus, because longitudinal contraction causes widening of the GI lumen.**
    - ***Contraction*** of the muscle occurs proximal to the bolus, in order to propel the bolus forward.
    - **There is a basal level of VIP inhibition in the muscle, and a bolus of food turns off this inhibition: distension of lumen by a bolus will cause *inhibition of release of VIP / NO* ------> contraction of proximal region.**

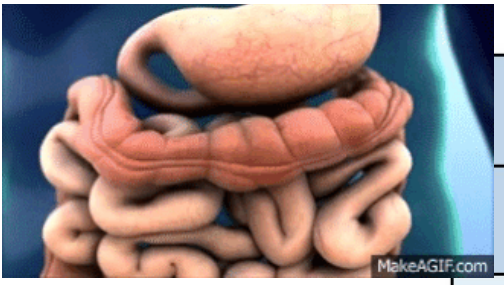
- **RHYTHMIC SEGMENTATION:** Mixing and churning of materials without propelling them forward in the tract.
  - Only involved the circular muscle -- not longitudinal
  - Common in small and large intestine

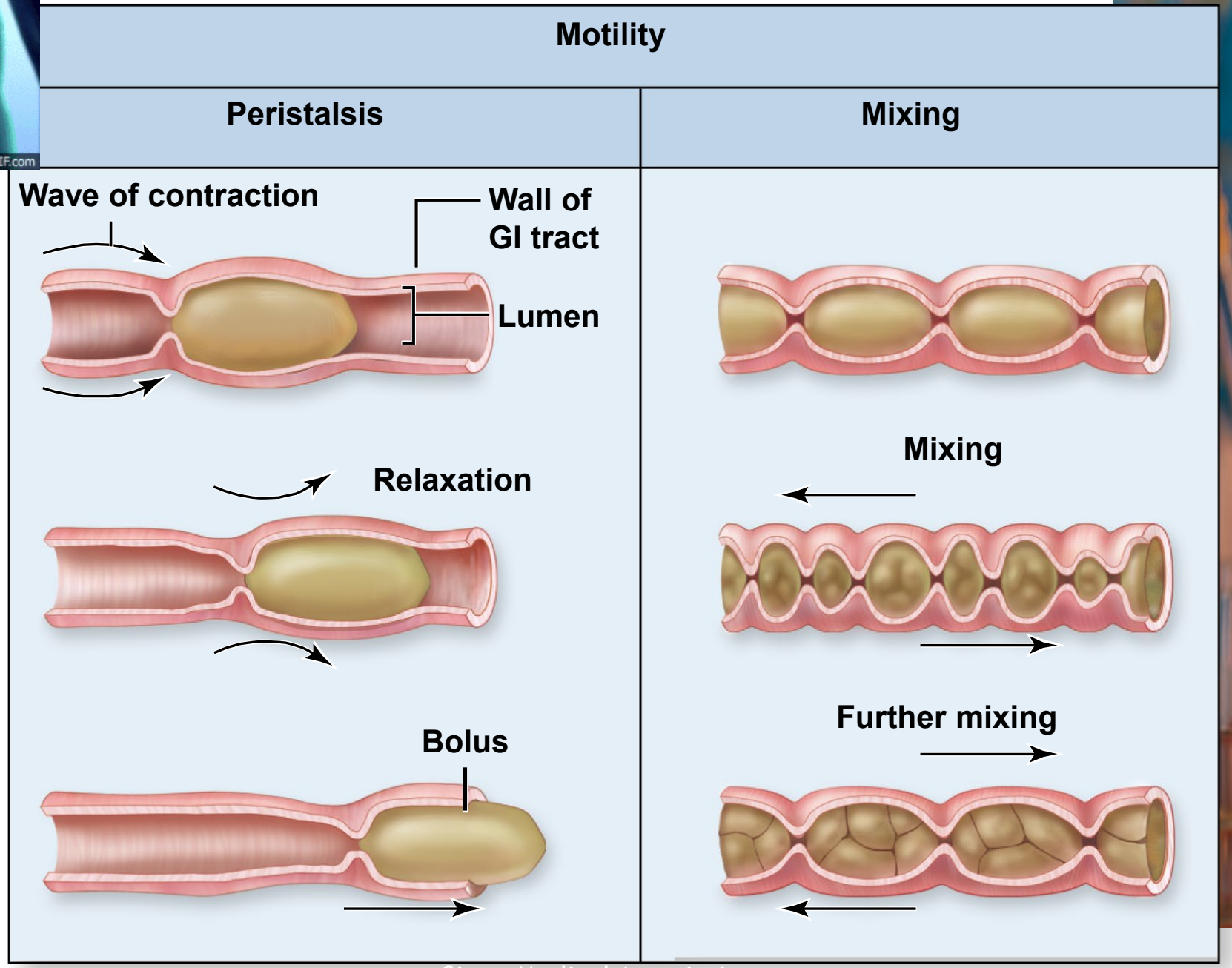
- **TONIC CONTRACTION:** Blocking of the passage of material, as in **sphincters**.
  - Tonic Contraction *is myogenic* -- it doesn't depend on innervation.

Movement of digestive materials

- Visceral smooth muscle shows rhythmic cycles of activity
  - Pacemaker cells
- Peristalsis
  - Waves that move a bolus
- Segmentation
  - Churn and fragment a bolus







(c) Muscularis: Motility

The Swallowing Process

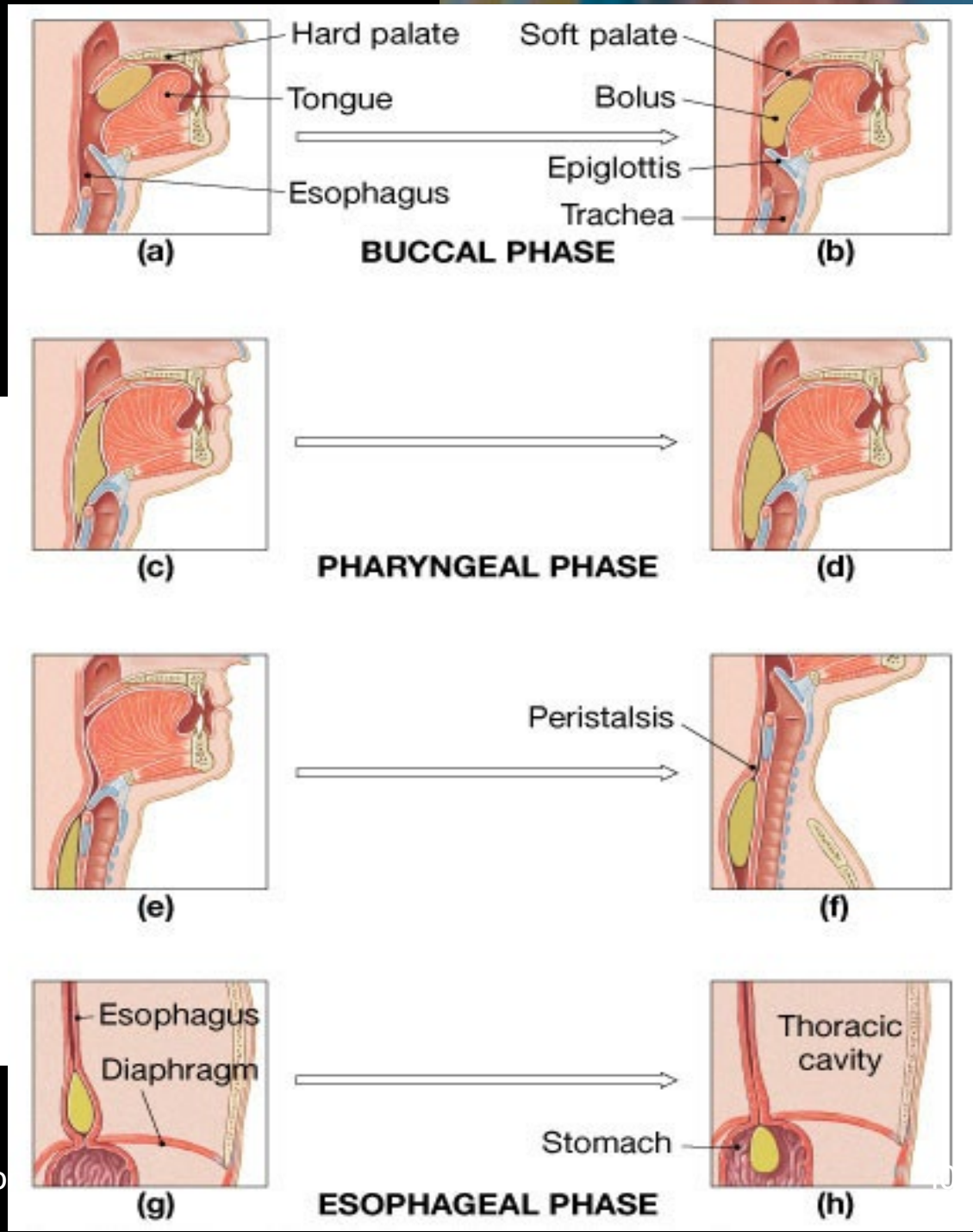
- Deglutition (swallowing)

- Involves the **coordinated activity of the tongue, soft palate, pharynx, esophagus and 22 separate muscle groups**

- **Buccal phase** - bolus is forced into the oropharynx

- **Pharyngeal-esophageal phase** - controlled by the medulla and lower pons - all routes except into the digestive tract are sealed off

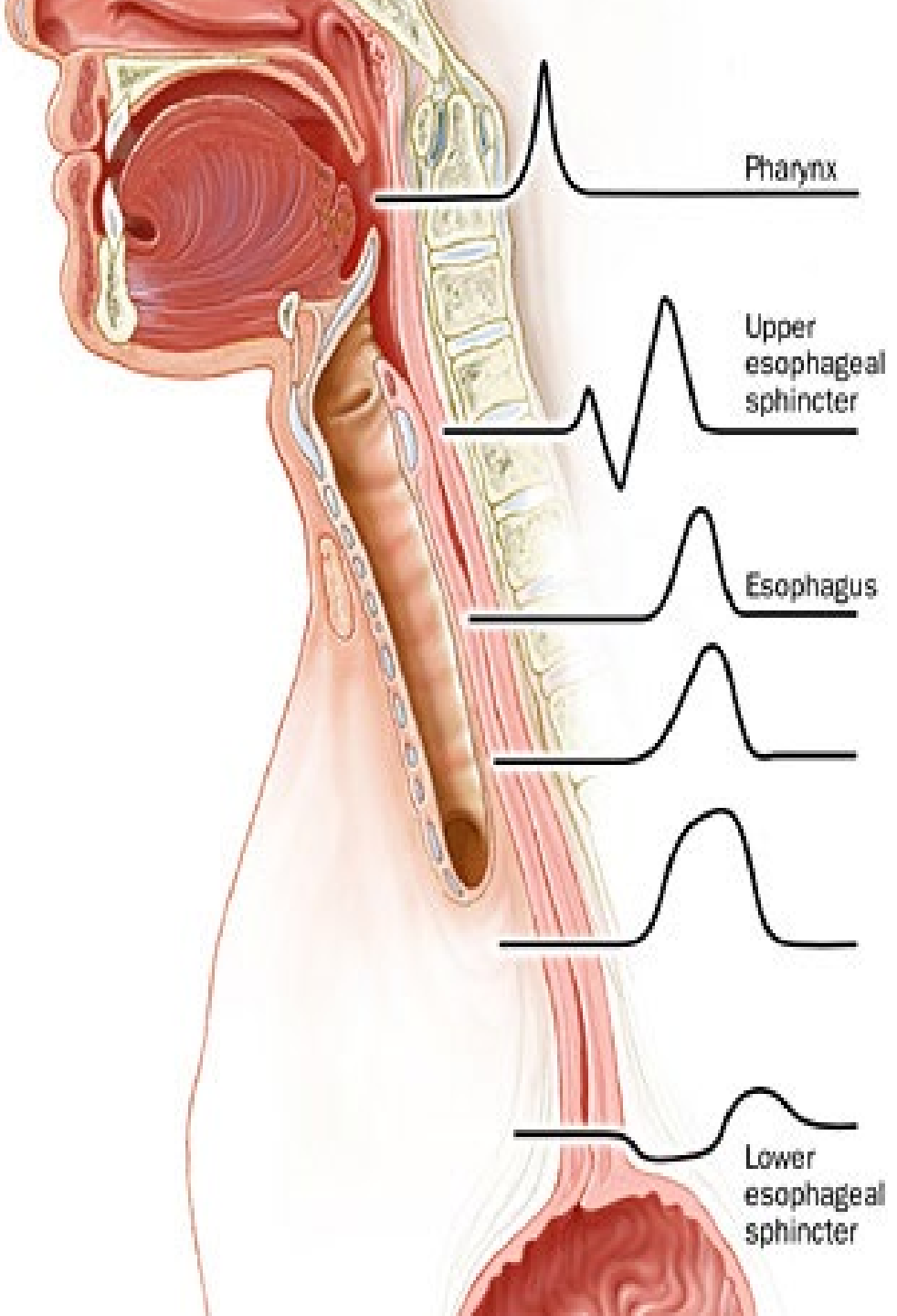
- **Peristalsis** moves food through the pharynx to the esophagus

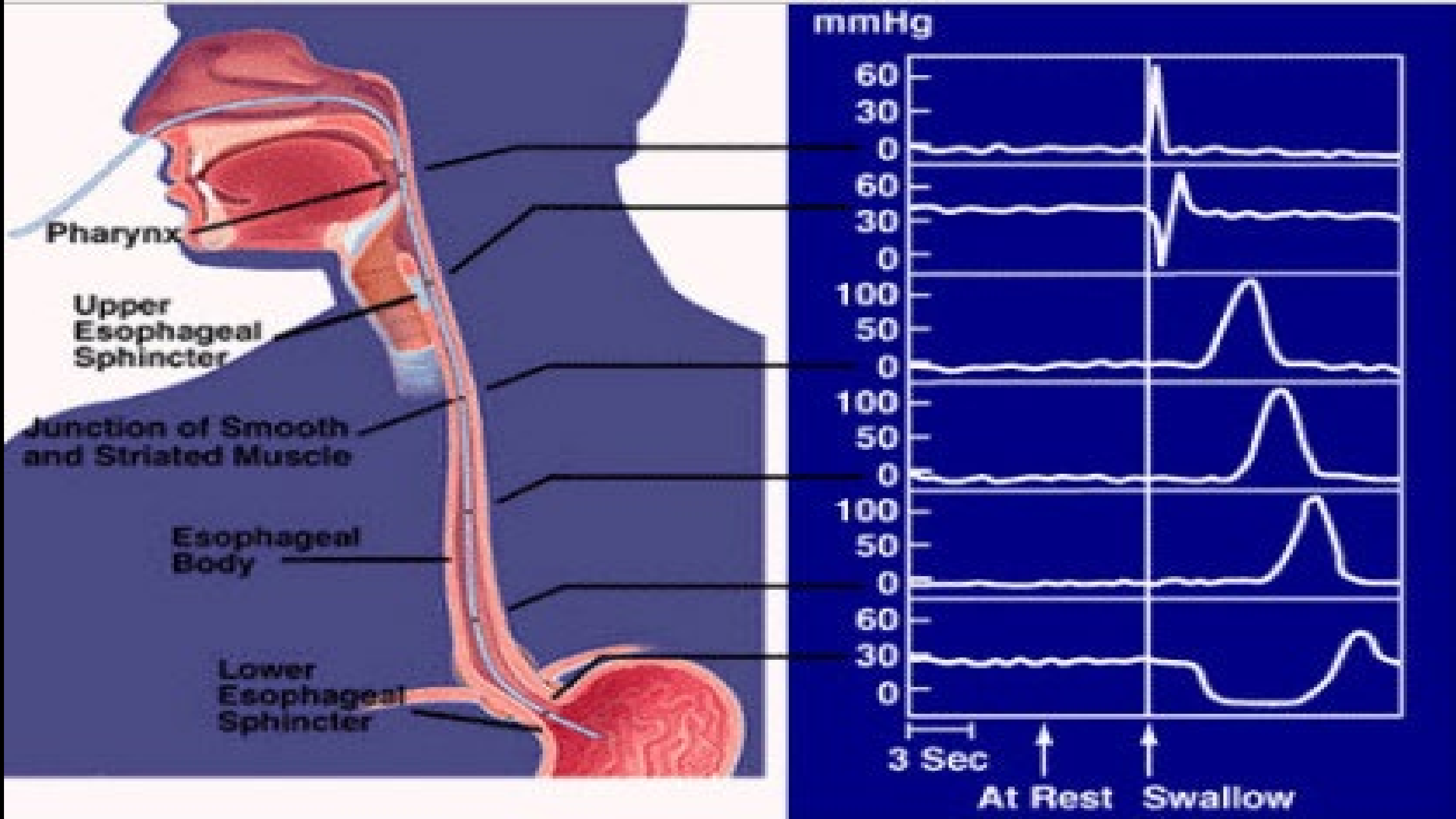


THE ESOPHAGUS:

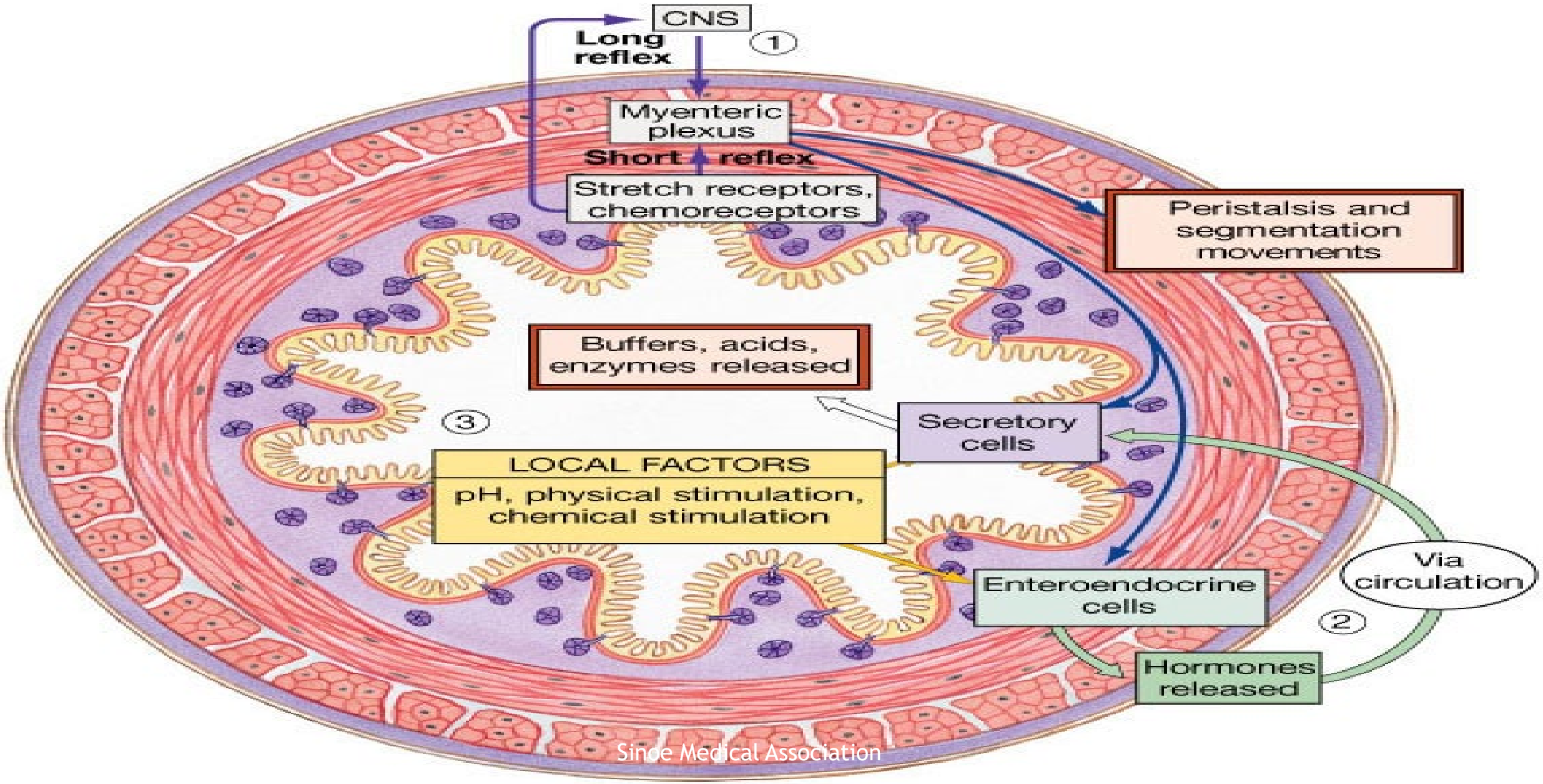
•Anatomy and Pressures:

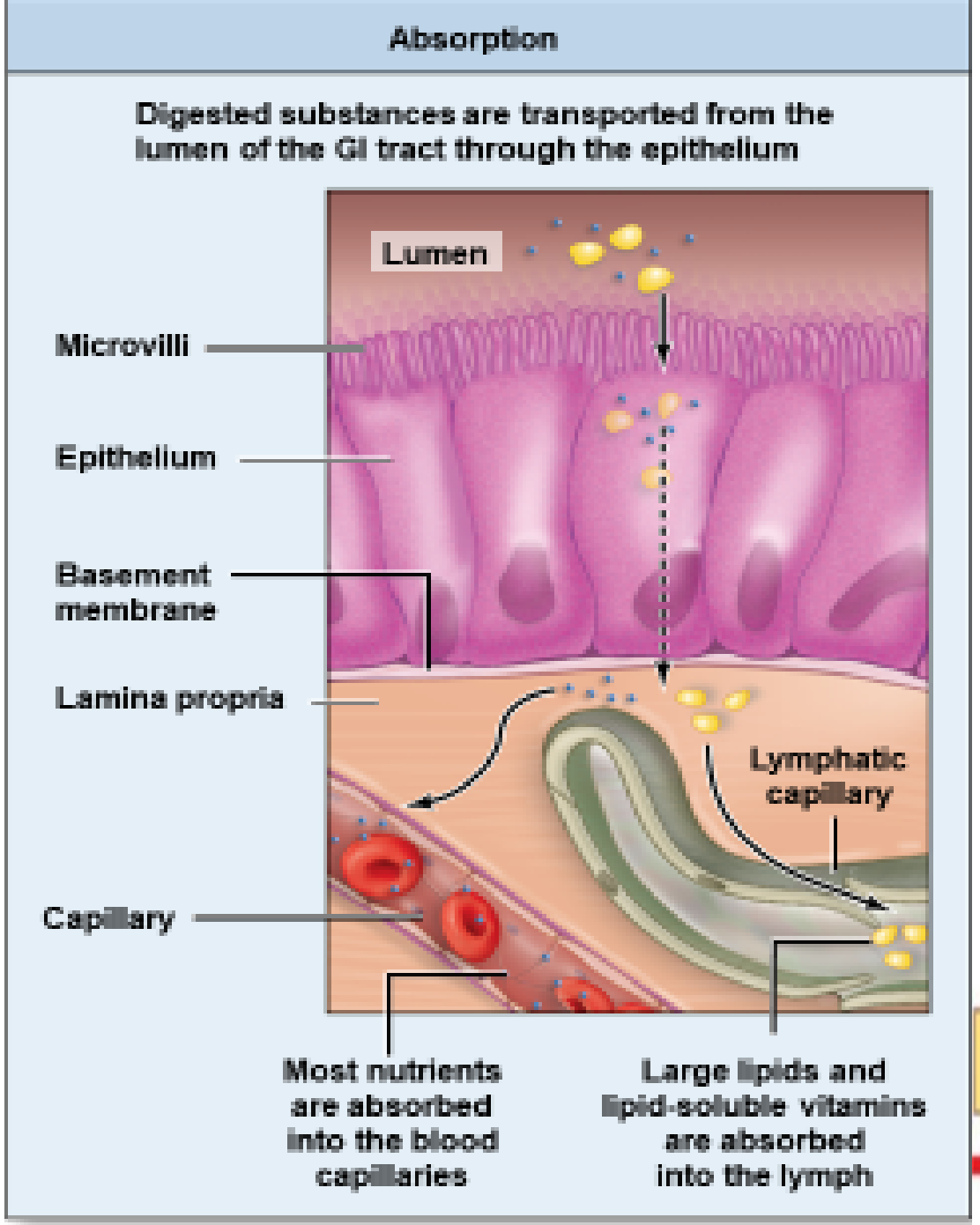
- **Upper Esophageal Sphincter (UES):** Skeletal muscle, essentially comprising the cricopharyngeus muscle.
  - Resting pressure **= *50-60 mm Hg* to prevent swallowing of air.**
  - Muscle tone is **neurogenic** and depends on CNS neural input from *swallowing center* to remain active.
- **Body:** Combination of skeletal and smooth muscle.
  - Resting pressure = *-5 mm Hg*
- **Lower Esophageal Sphincter:** Smooth muscle, normally closed in order to prevent gastric reflux.
  - Resting pressure = *30 mm Hg*
  - **LES contractility is myogenic.** The way we relax the LES is by putting tonal amounts of VIP / NO on the sphincter.
  - VIP inhibition of LES is Non-Adrenergic, Non-Cholinergic (NANC). We know this because Atropine does not prevent the inhibition:
    - Give atropine, and the LES will still relax because VIP is not stopped.
    - Give a **VIP-Antibody** and the LES will no longer relax because inhibition has been removed.



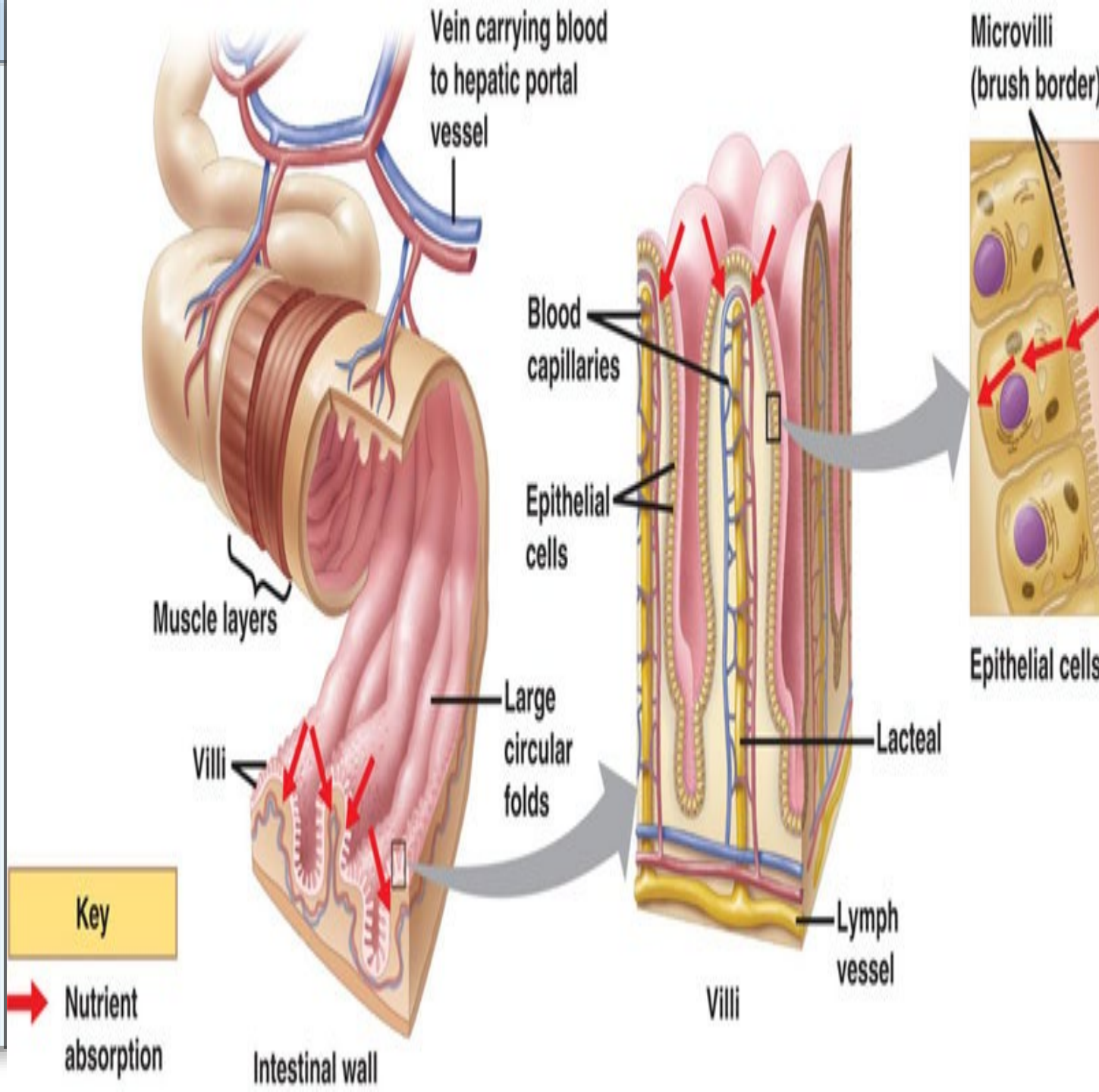

Pharynx
Upper Esophageal Sphincter
Junction of Smooth and Striated Muscle
Esophageal Body
Lower Esophageal Sphincter
mmHg
60
30
0
60
30
0
100
50
0
100
50
0
100
50
0
60
30
0
3 Sec
At Rest
Swallow

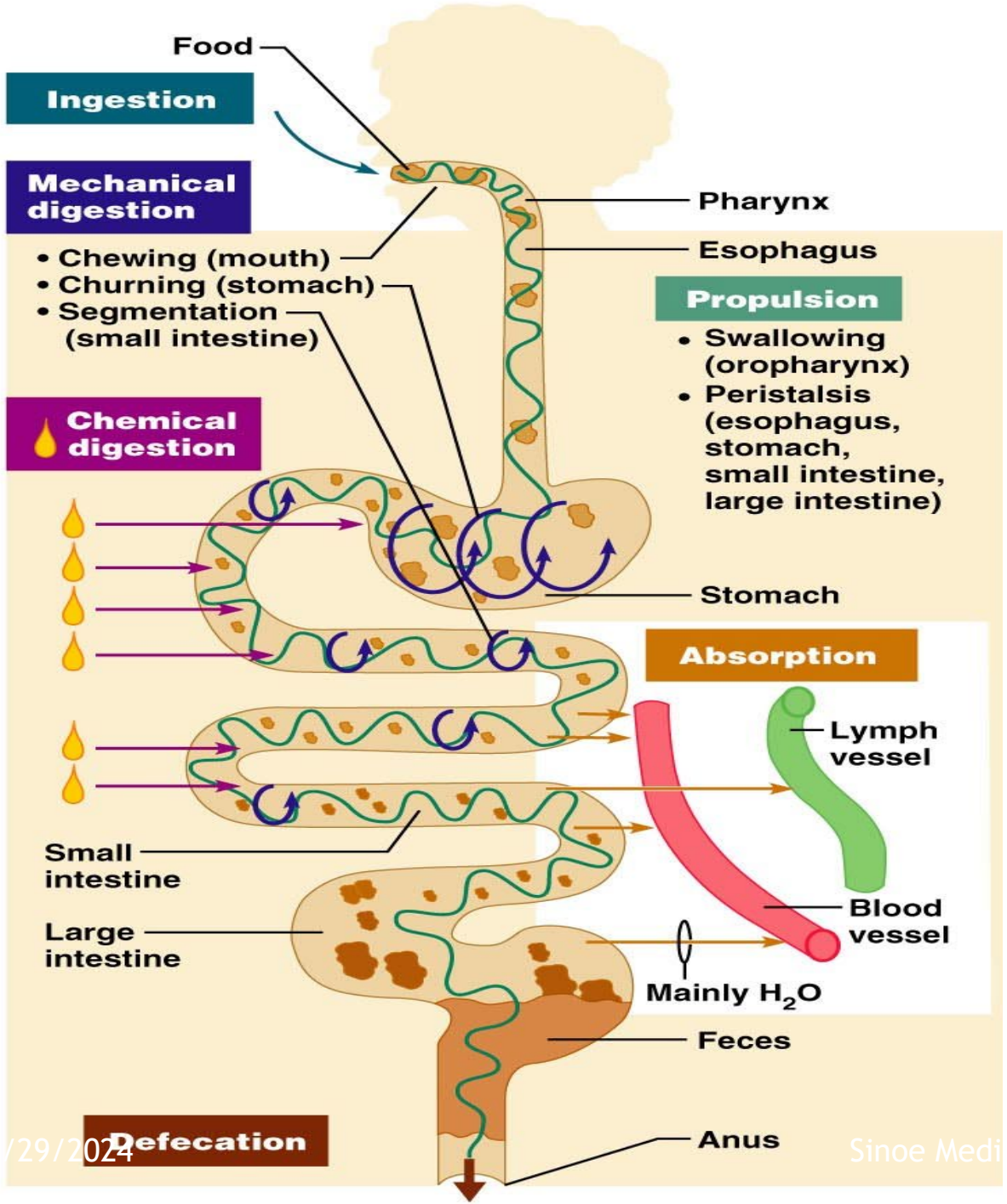
The Regulation of Digestive Activities

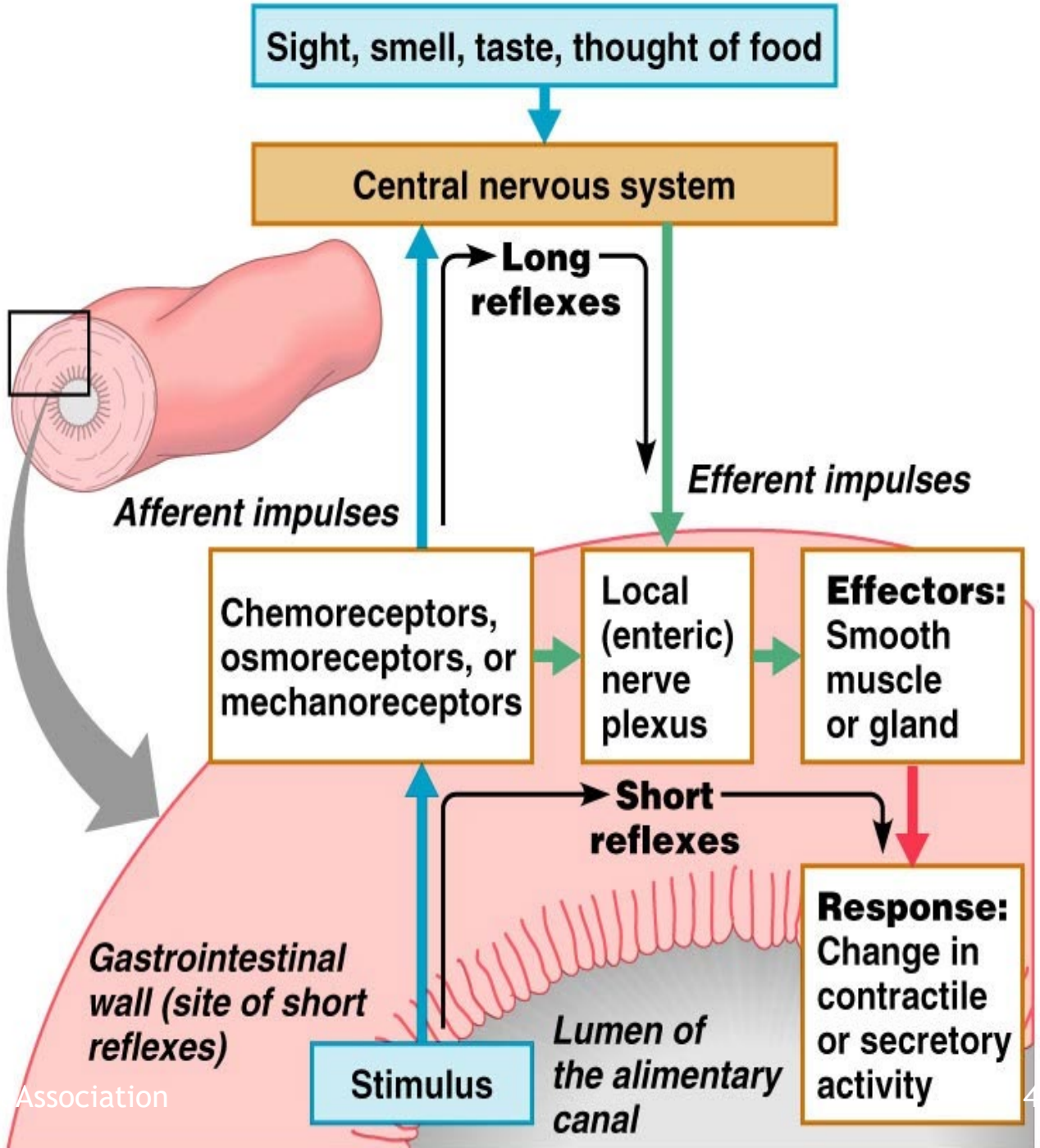


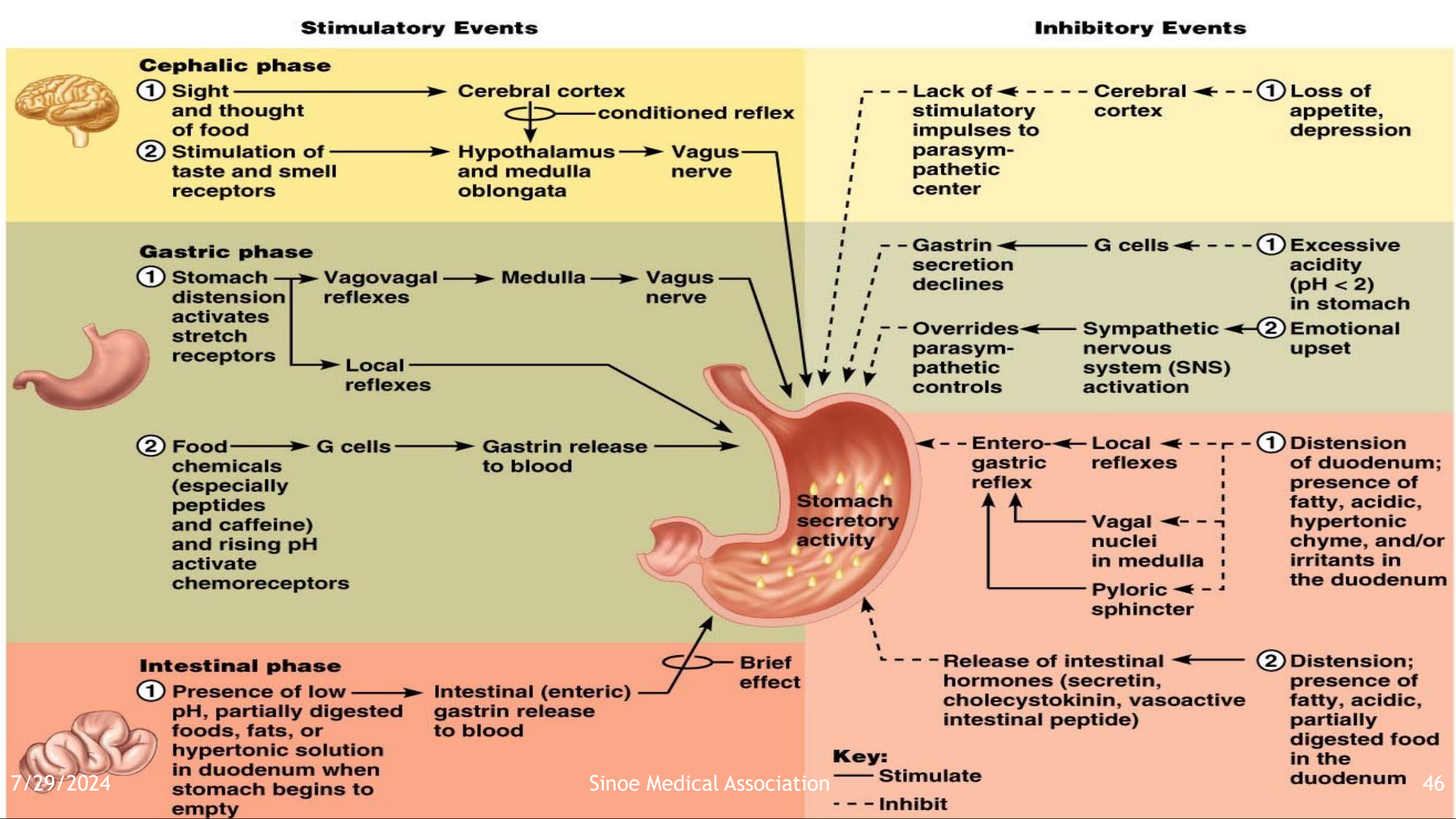


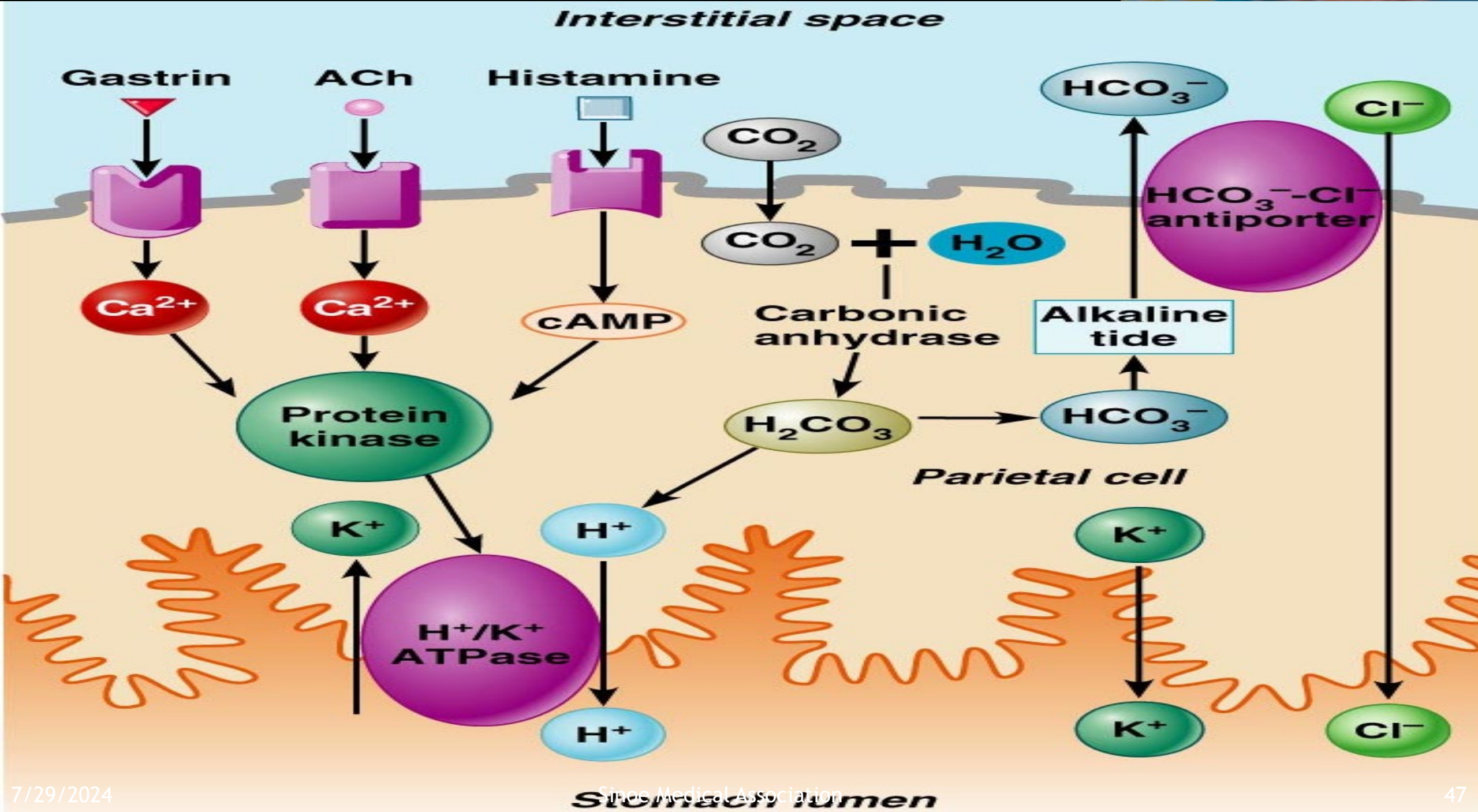
(b) Mucosa: Absorption

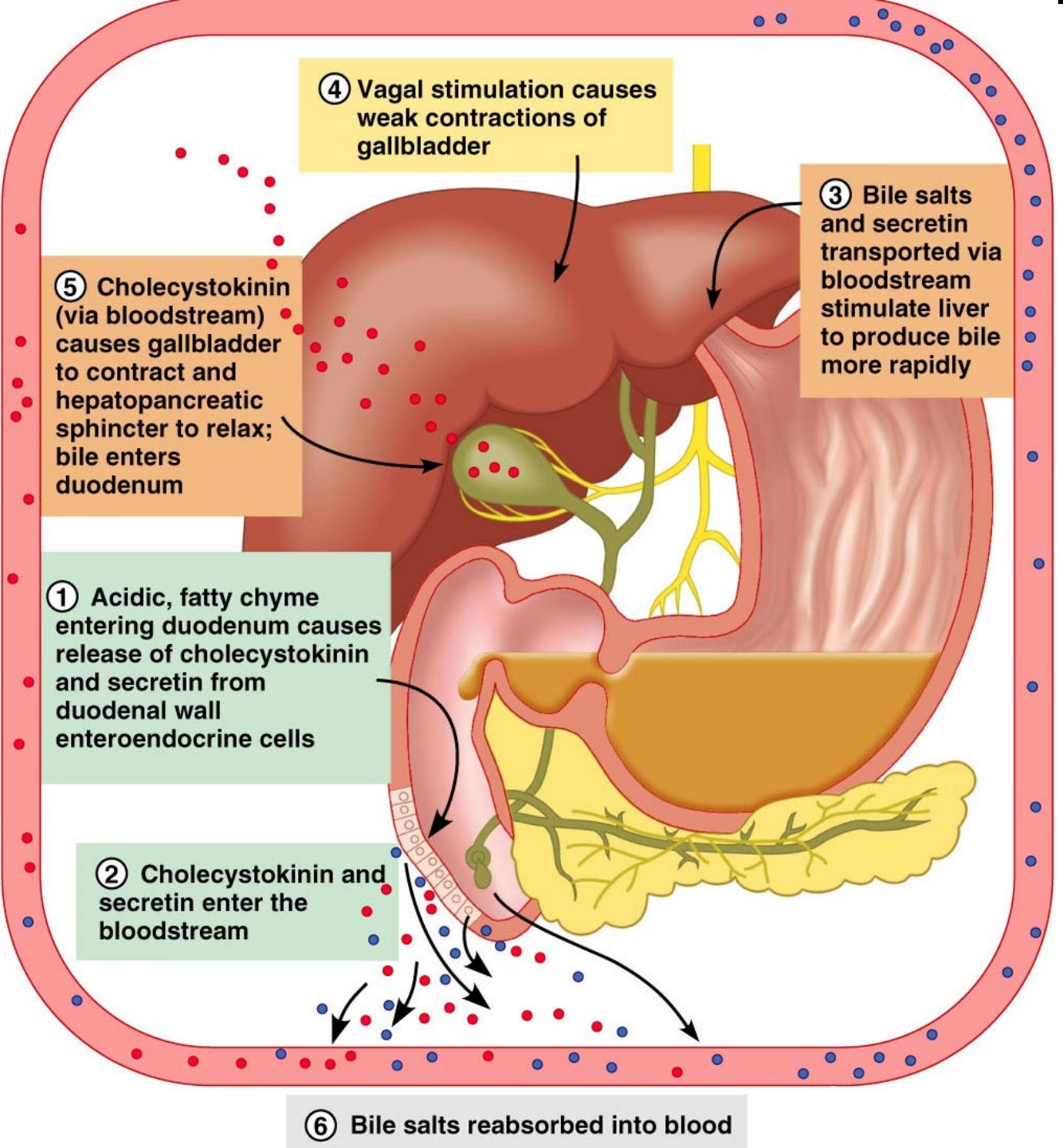



Food
Ingestion
Mechanical digestion
• Chewing (mouth)
• Churning (stomach)
• Segmentation (small intestine)
Chemical digestion
Pharynx
Esophagus
Propulsion
• Swallowing (oropharynx)
• Peristalsis (esophagus, stomach, small intestine, large intestine)
Stomach
Absorption
Lymph vessel
Blood vessel
Small intestine
Large intestine
Mainly H_2O
Feces
Defecation
Anus


Sight, smell, taste, thought of food
Central nervous system
Long reflexes
Afferent impulses
Efferent impulses
Chemoreceptors, osmoreceptors, or mechanoreceptors
Local (enteric) nerve plexus
Effectors: Smooth muscle or gland
Short reflexes
Response: Change in contractile or secretory activity
Gastrointestinal wall (site of short reflexes)
Lumen of the alimentary canal
Stimulus


Stimulatory Events
Inhibitory Events
Cephalic phase
1 Sight and thought of food
2 Stimulation of taste and smell receptors
Cerebral cortex
conditioned reflex
Hypothalamus and medulla oblongata
Vagus nerve
Lack of stimulatory impulses to parasym-pathetic center
Cerebral cortex
1 Loss of appetite, depression
Gastric phase
1 Stomach distension activates stretch receptors
Vagovagal reflexes
Medulla
Vagus nerve
Local reflexes
Gastrin secretion declines
G cells
1 Excessive acidity (pH < 2) in stomach
Overrides parasym-pathetic controls
Sympathetic nervous system (SNS) activation
2 Emotional upset
2 Food chemicals (especially peptides and caffeine) and rising pH activate chemoreceptors
G cells
Gastrin release to blood
Stomach secretory activity
Entero-gastric reflex
Local reflexes
1 Distension of duodenum; presence of fatty, acidic, hypertonic chyme, and/or irritants in the duodenum
Vagal nuclei in medulla
Pyloric sphincter
Intestinal phase
1 Presence of low pH, partially digested foods, fats, or hypertonic solution in duodenum when stomach begins to empty
Intestinal (enteric) gastrin release to blood
Brief effect
Release of intestinal hormones (secretin, cholecystokinin, vasoactive intestinal peptide)
2 Distension; presence of fatty, acidic, partially digested food in the duodenum
Key:
Stimulate
Inhibit


Interstitial space
Gastrin
ACh
Histamine
CO_2
HCO_3^-
Cl^-
HCO_3^--Cl^- antiporter
CO_2 + H_2O
Ca^{2+}
Ca^{2+}
cAMP
Carbonic anhydrase
Alkaline tide
Protein kinase
H_2CO_3
HCO_3^-
Parietal cell
K^+
H^+
K^+
H^+/K^+ ATPase
H^+
K^+
Cl^-
Stomach lumen


④ Vagal stimulation causes weak contractions of gallbladder
③ Bile salts and secretin transported via bloodstream stimulate liver to produce bile more rapidly
⑤ Cholecystokinin (via bloodstream) causes gallbladder to contract and hepatopancreatic sphincter to relax; bile enters duodenum
① Acidic, fatty chyme entering duodenum causes release of cholecystokinin and secretin from duodenal wall enteroendocrine cells
② Cholecystokinin and secretin enter the bloodstream
⑥ Bile salts reabsorbed into blood

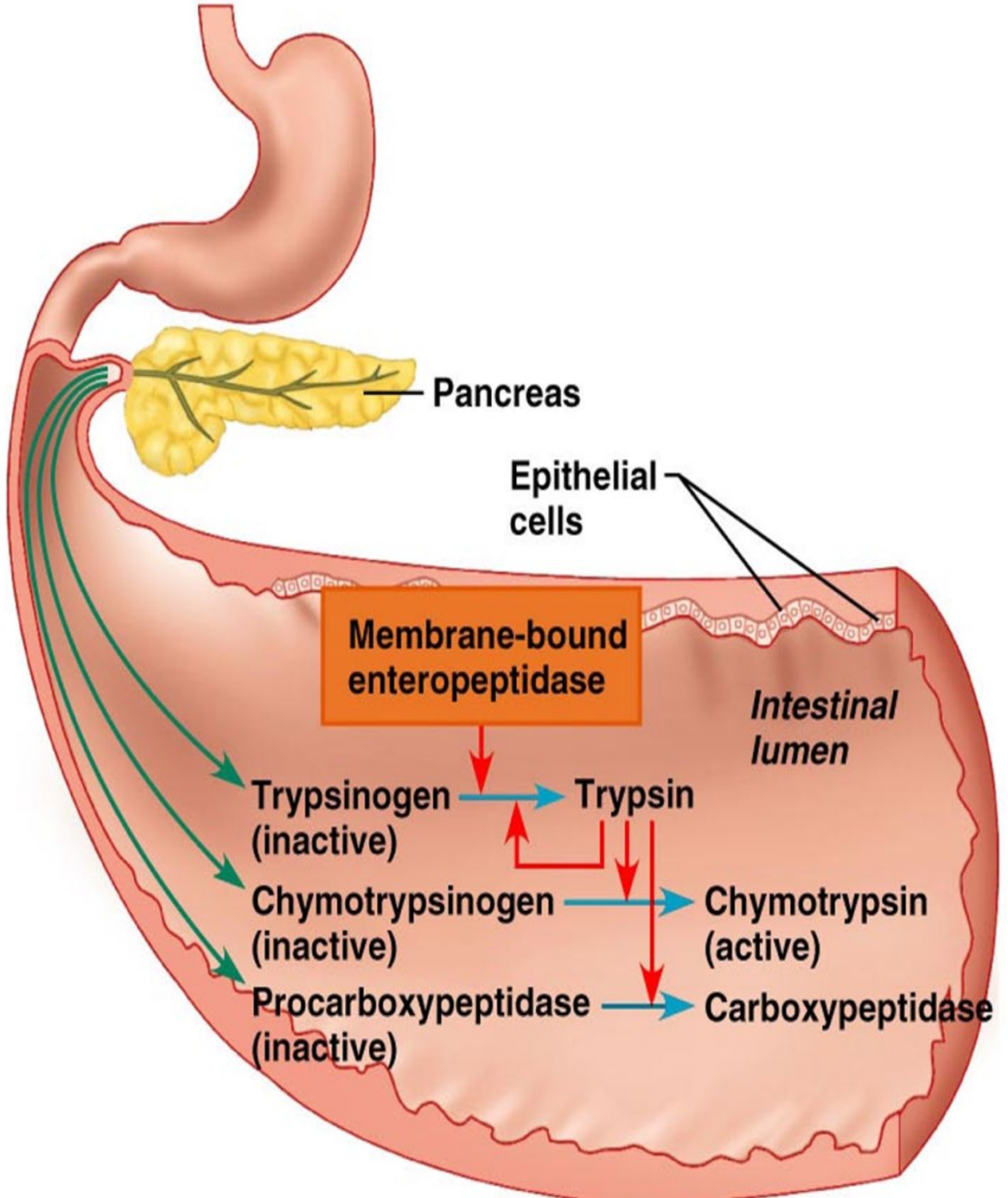
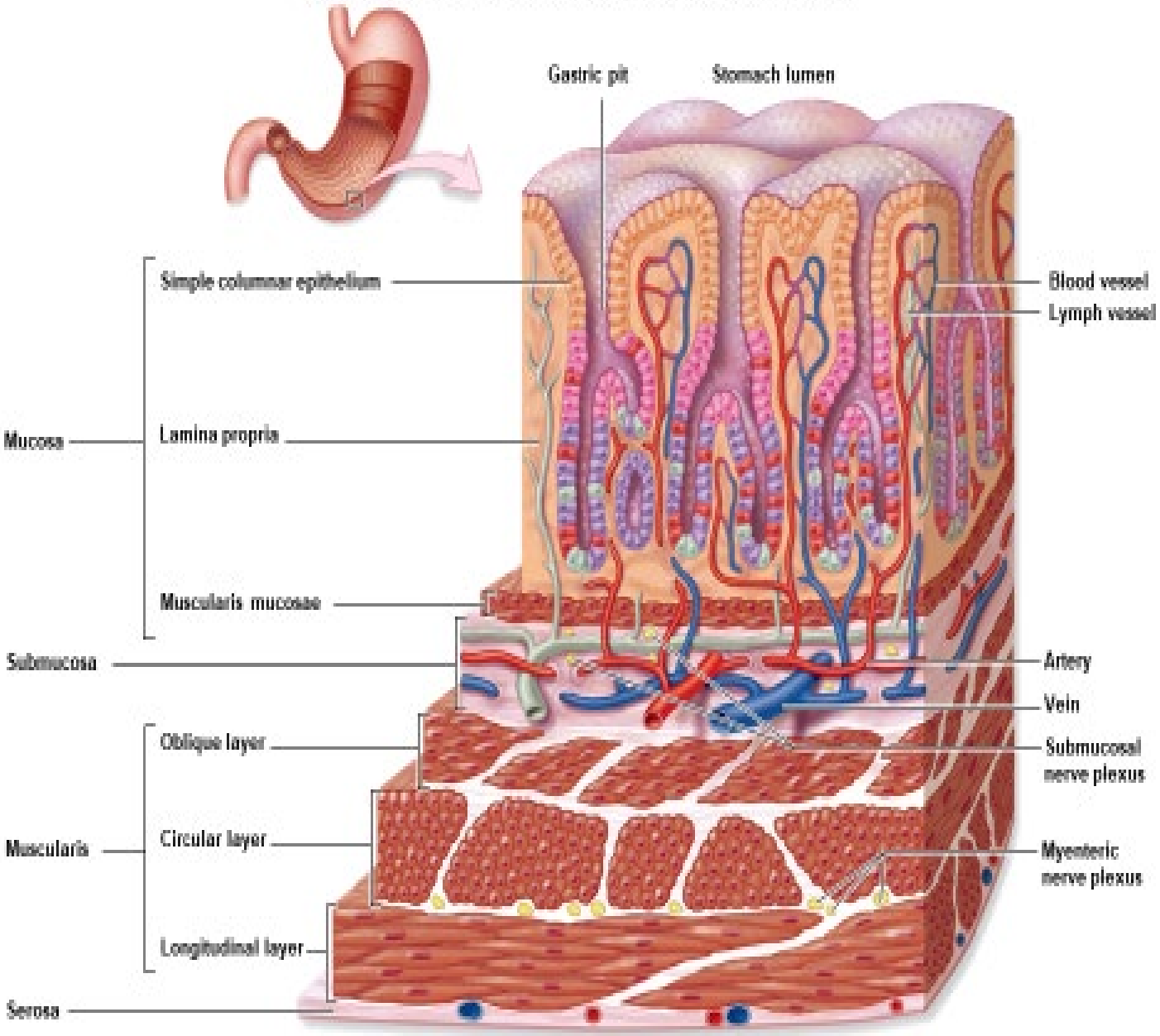
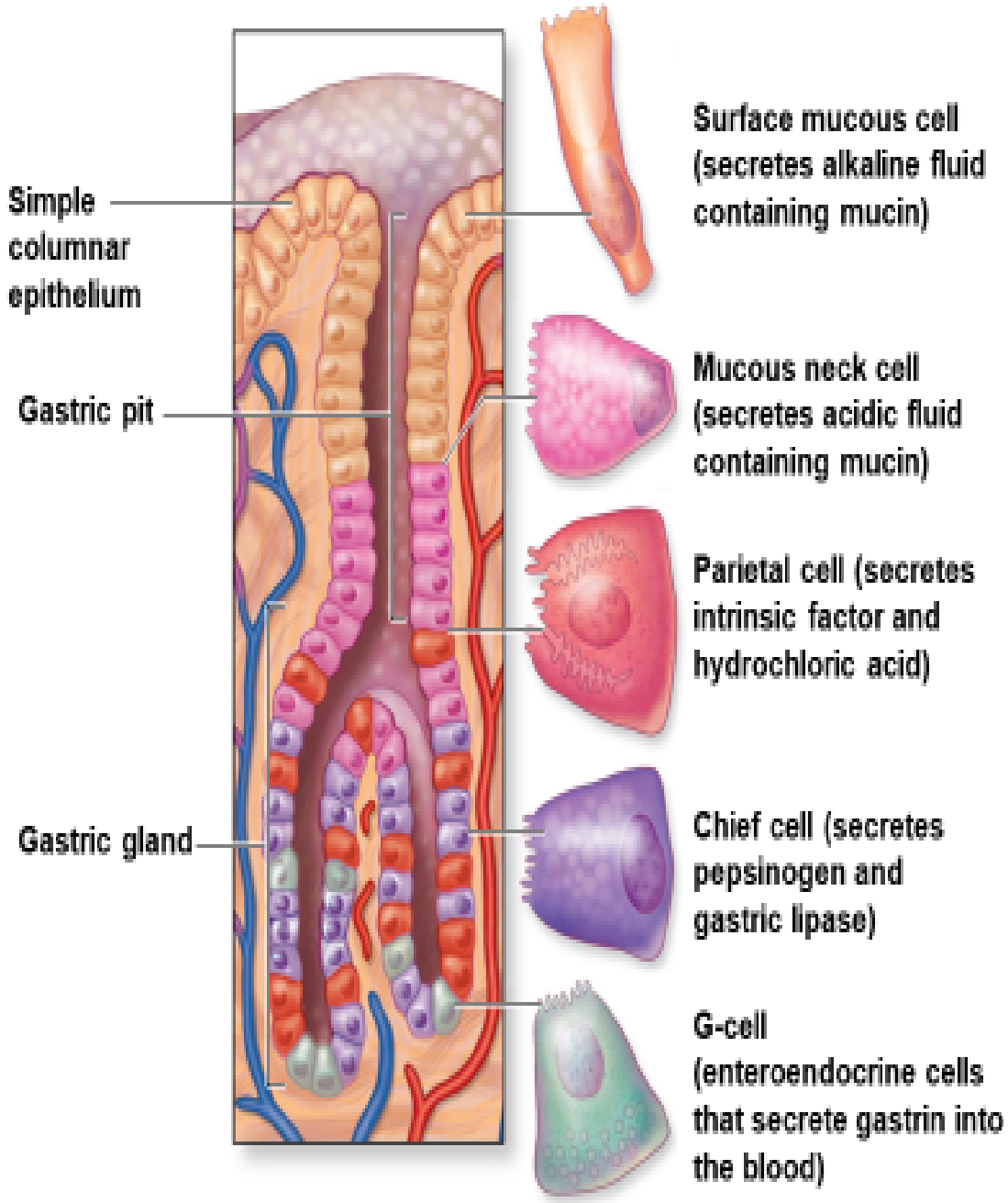

Pancreas
Epithelial cells
Membrane-bound enteropeptidase
Intestinal lumen
Trypsinogen (inactive)
Trypsin
Chymotrypsinogen (inactive)
Chymotrypsin (active)
Procarboxypeptidase (inactive)
Carboxypeptidase

Fig. 26.10a

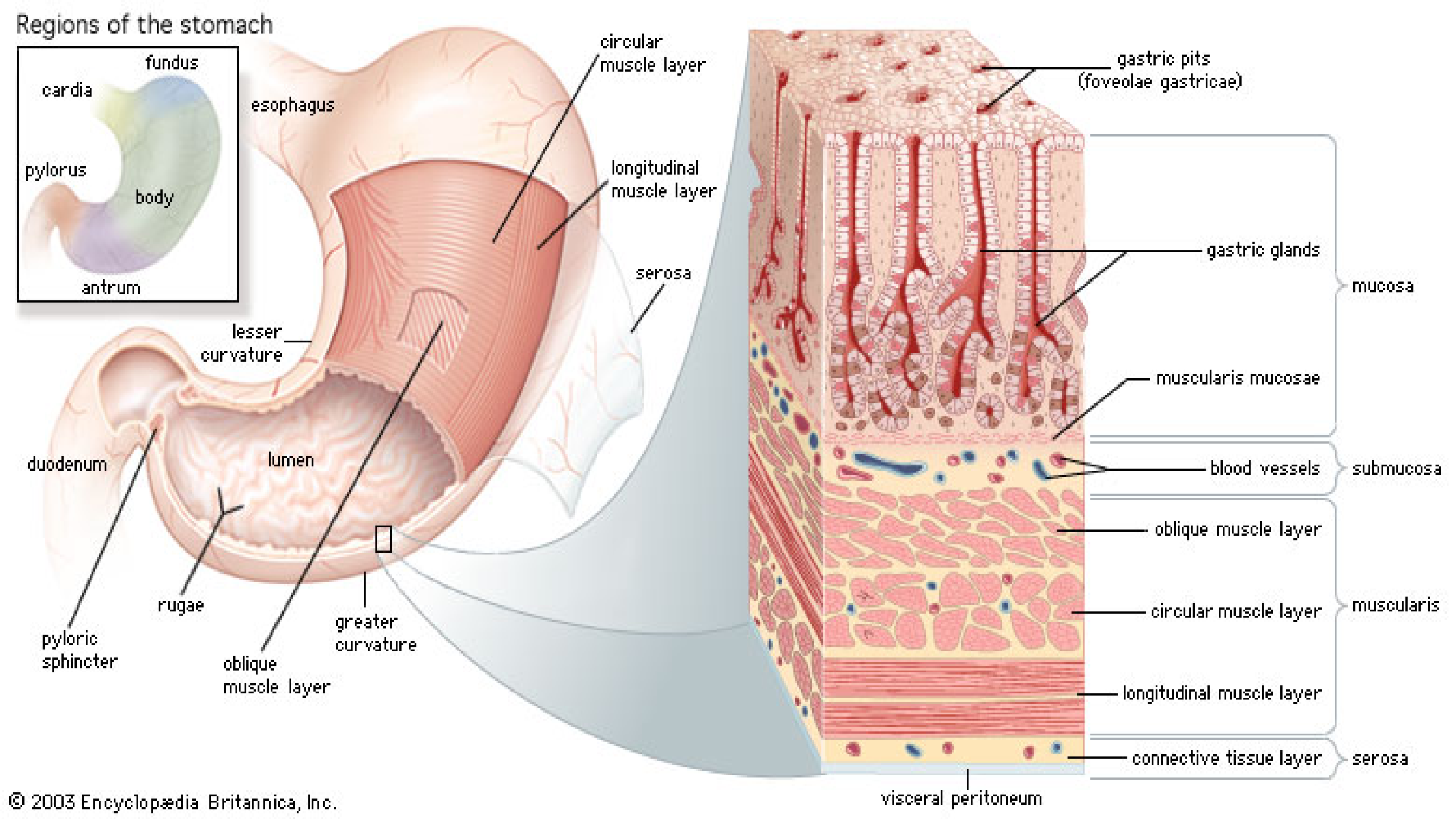


(a) Stomach wall, sectional view

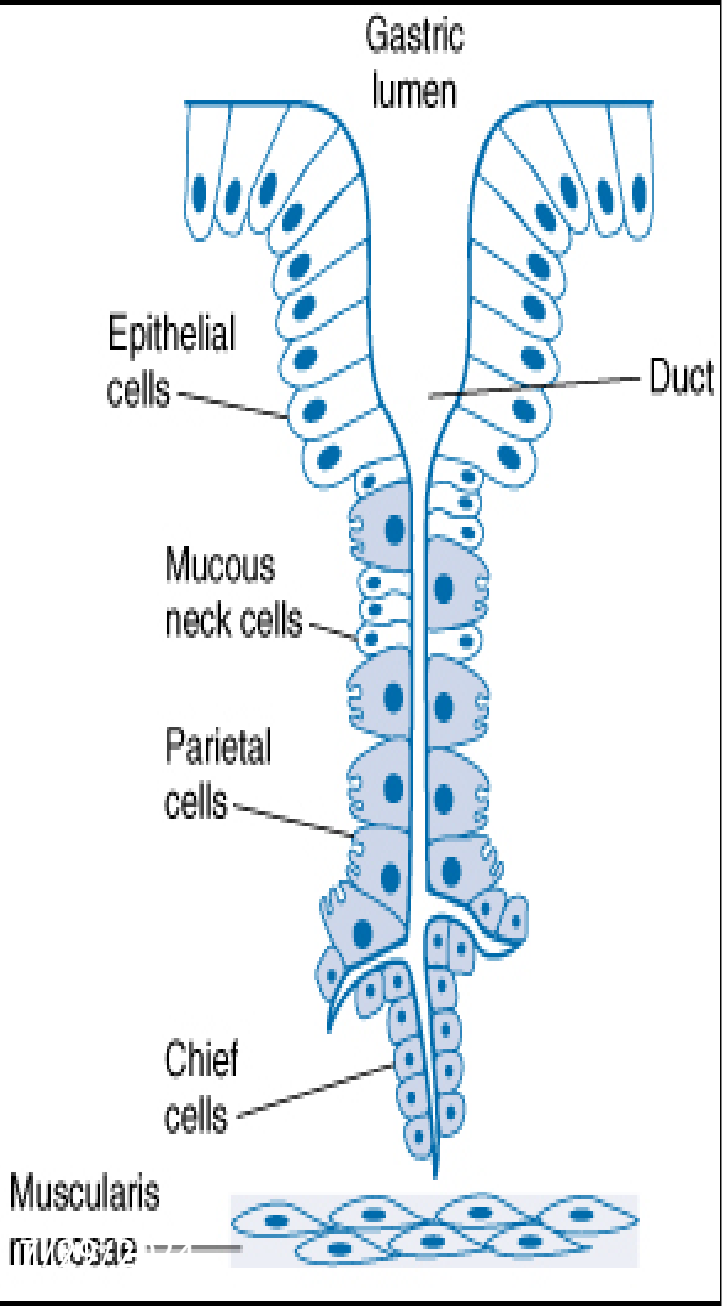
C

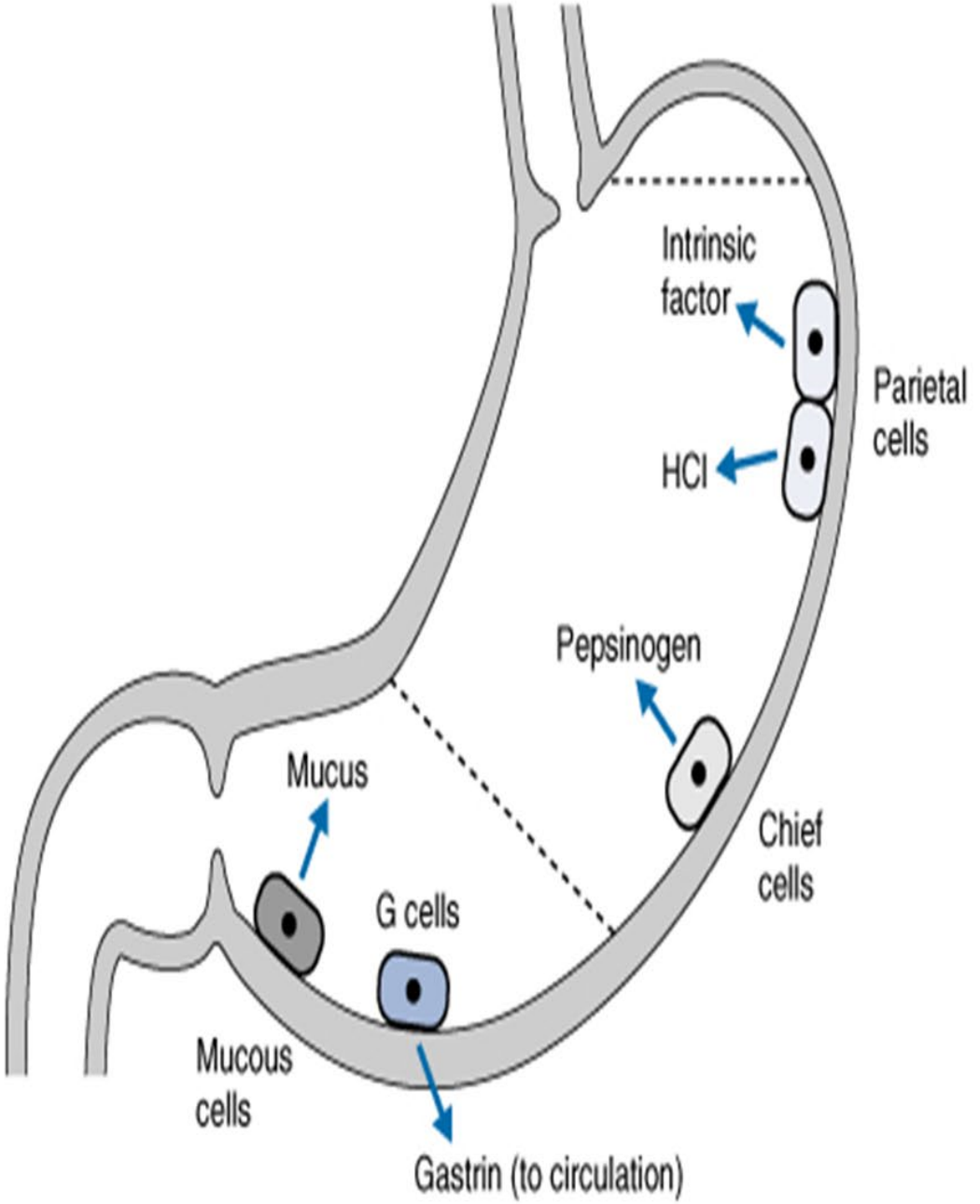


(c) Gastric pit and gland

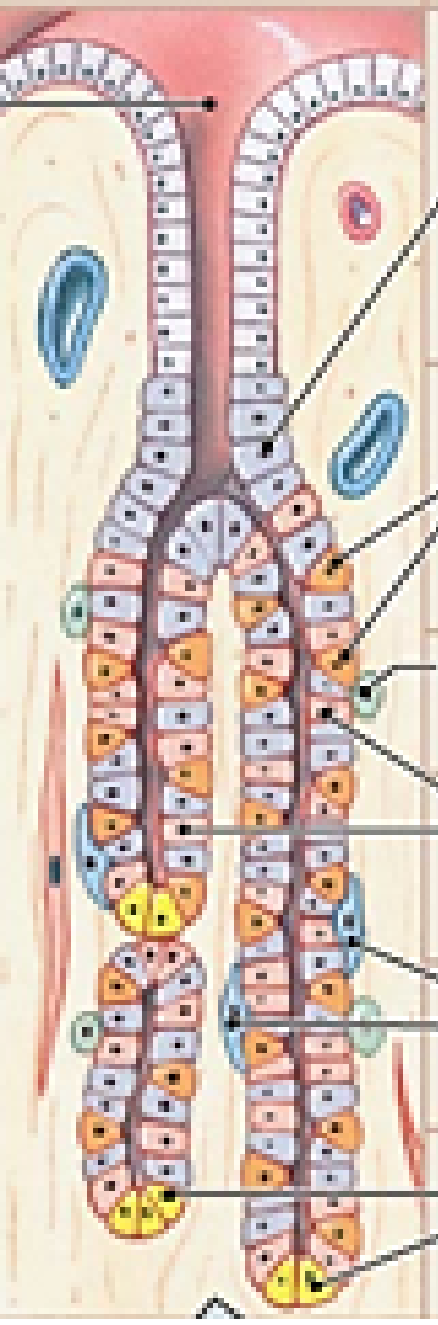


Gastric Glanc

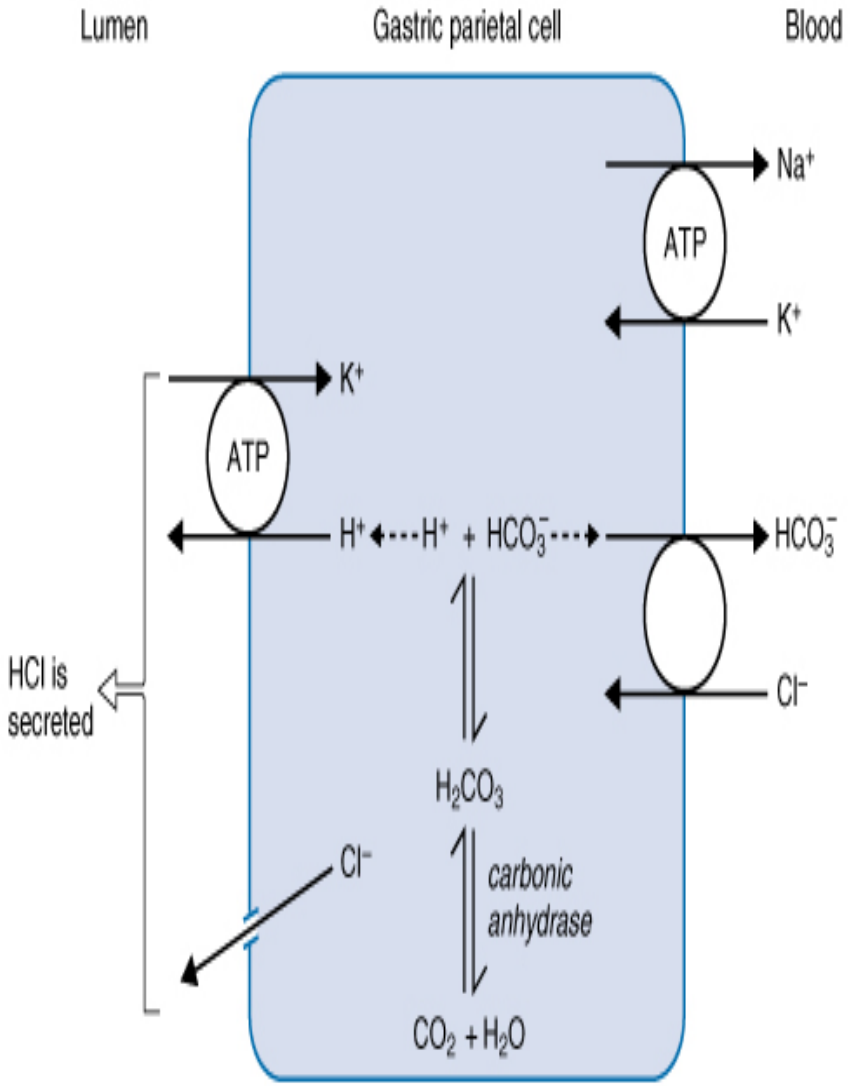


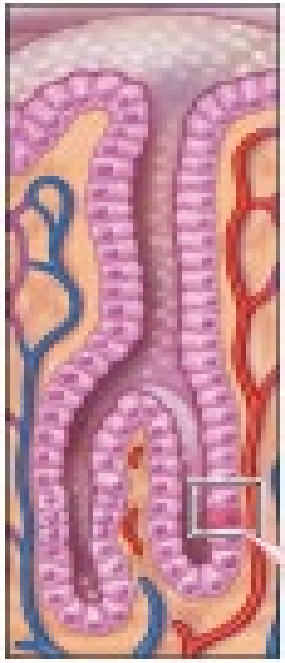


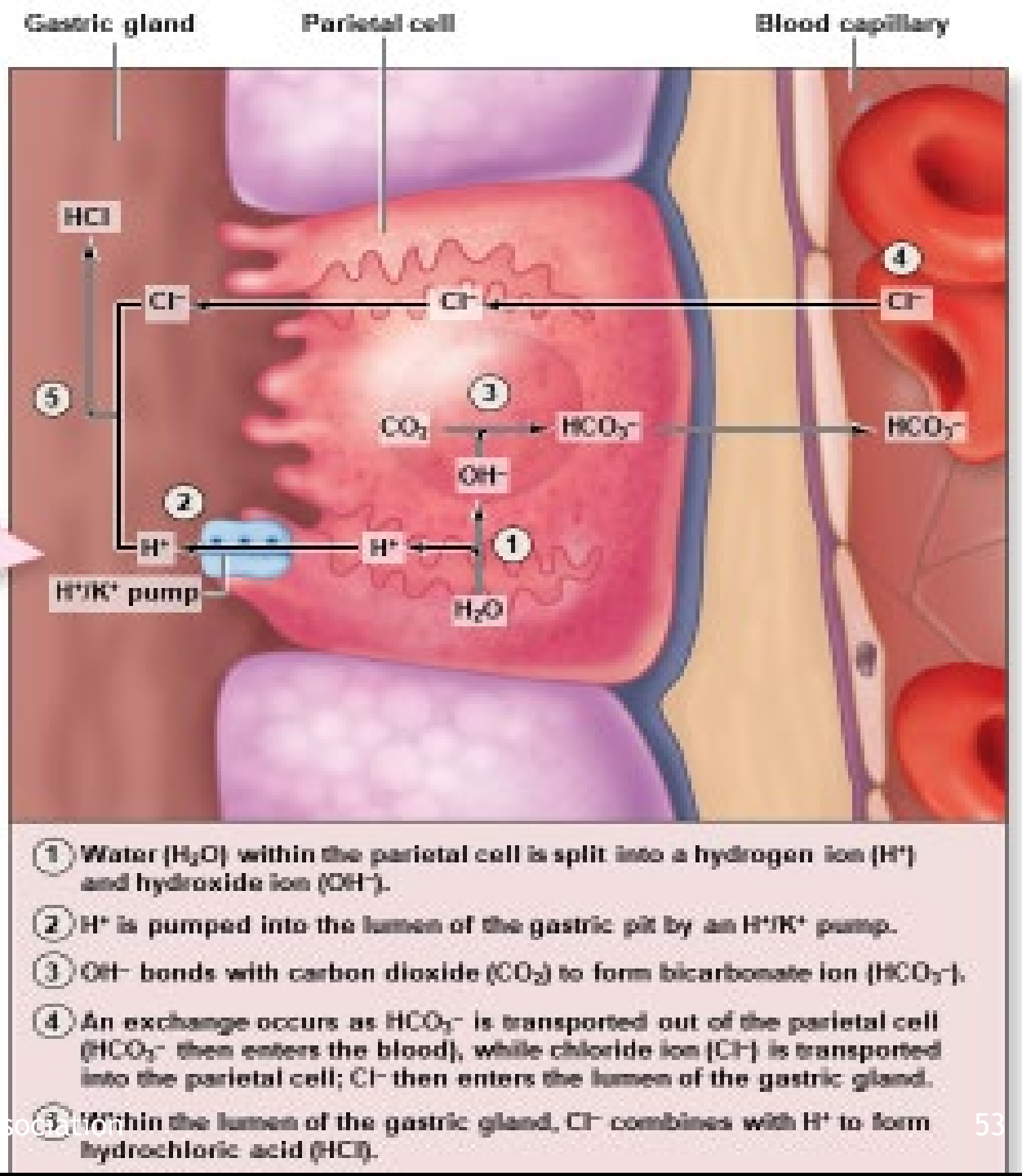
Cell Type	Location	Secretion
Parietal cells	Body	HCl Intrinsic factor
Chief cells	Body	Pepsinogen
G cells	Antrum	Gastrin
Mucous cells	Antrum	Mucus Pepsinogen

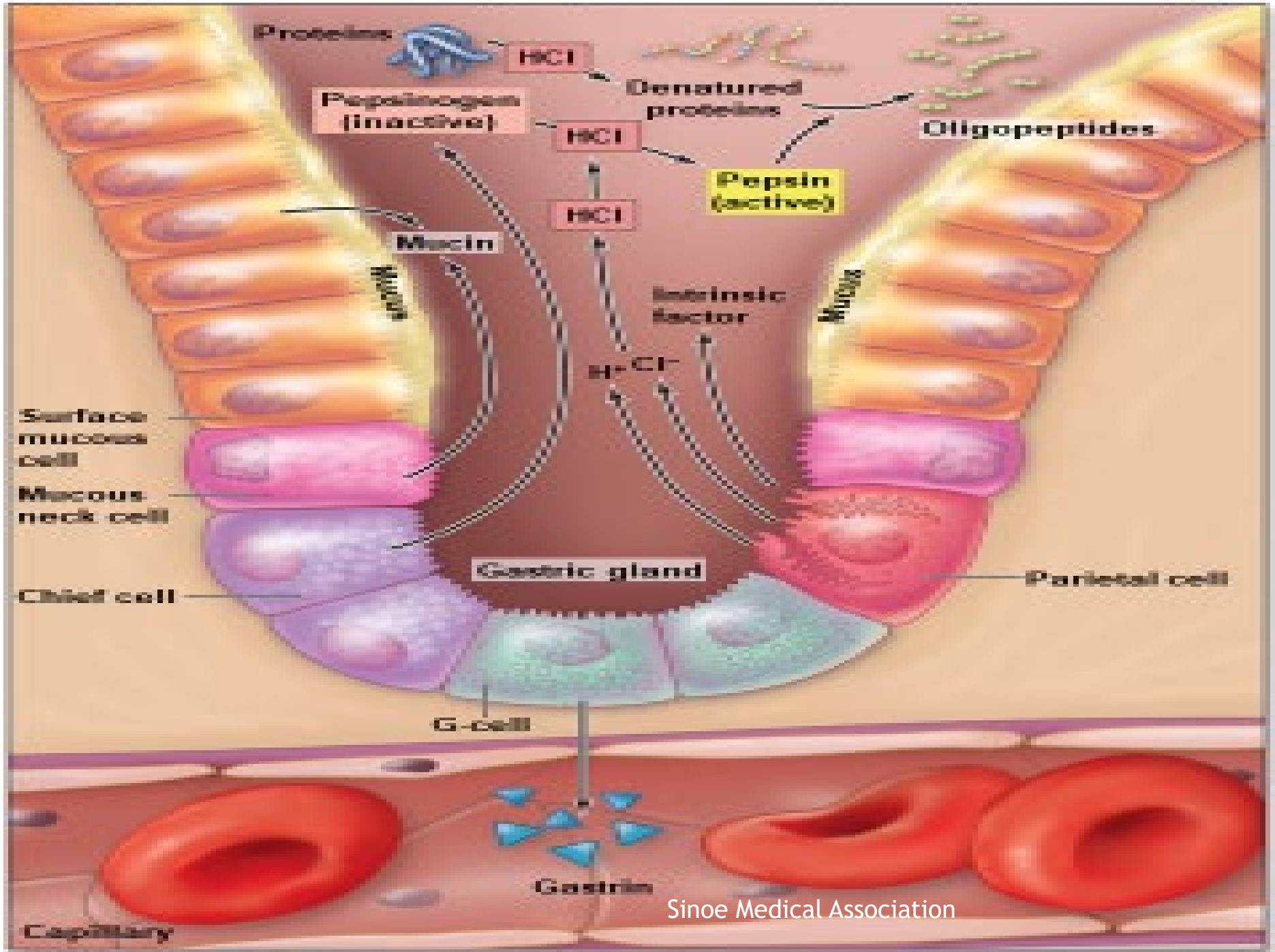
GASTRIC MUCOSA	CELL TYPES	SUBSTANCE SECRETED	STIMULUS FOR RELEASE	FUNCTION OF SECRETION
	Mucous neck cell	Mucus	Tonic secretion; with irritation of mucosa	Physical barrier between lumen and epithelium
		Bicarbonate	Secreted with mucus	Buffers gastric acid to prevent damage to epithelium
	Parietal cells	Gastric acid (HCl)	Acetylcholine, gastrin, histamine	Activates pepsin; kills bacteria
		Intrinsic factor		Complexes with vitamin B_{12} to permit absorption
	Enterochromaffin-like cell	Histamine	Acetylcholine, gastrin	Stimulates gastric acid secretion
	Chief cells	Pepsin(ogen)	Acetylcholine, acid secretion	Digests proteins
		Gastric lipase		Digests fats
	D cells	Somatostatin	Acid in the stomach	Inhibits gastric acid secretion
	G cells	Gastrin	Acetylcholine, peptides, and amino acids	Stimulates gastric acid secretion

HCl Secretion

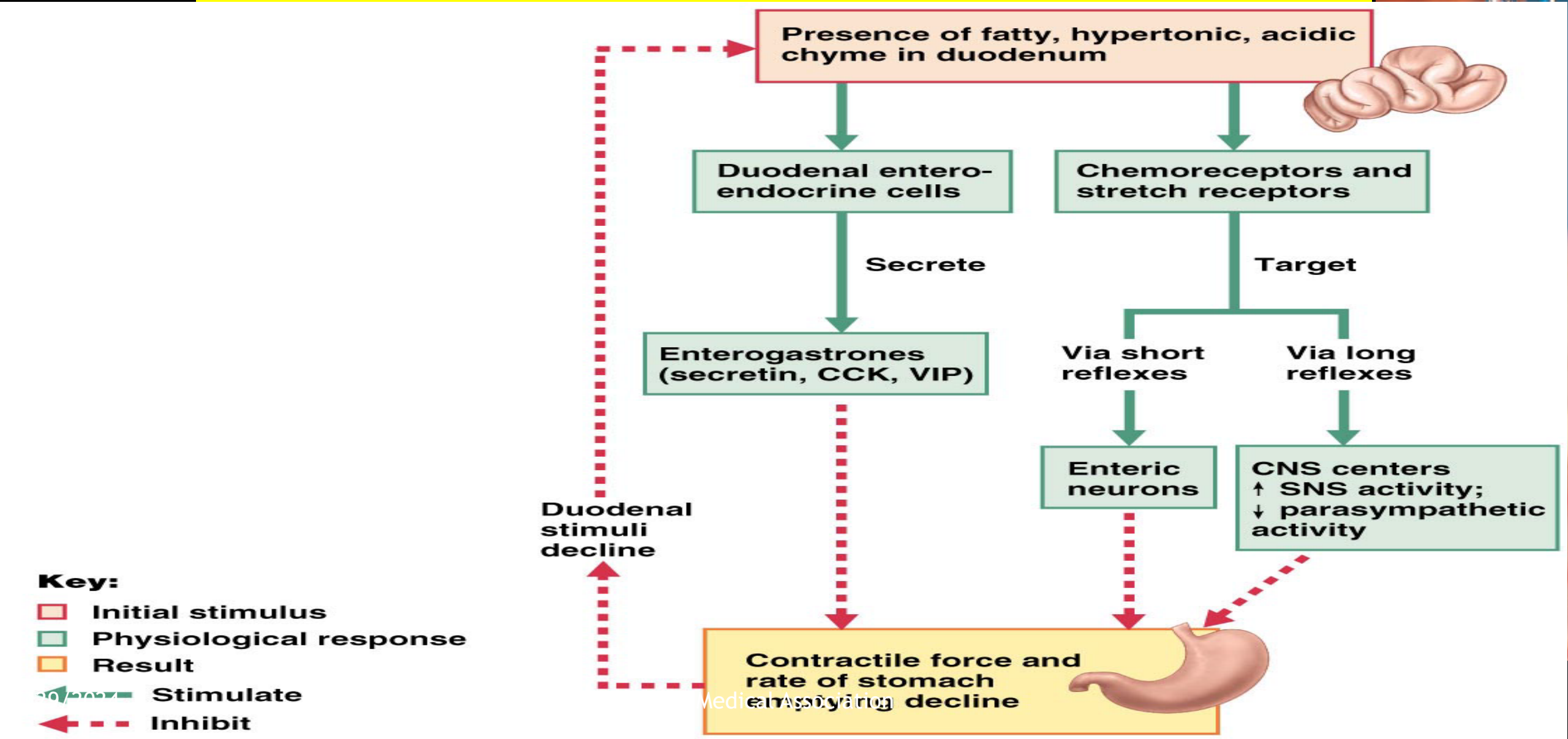


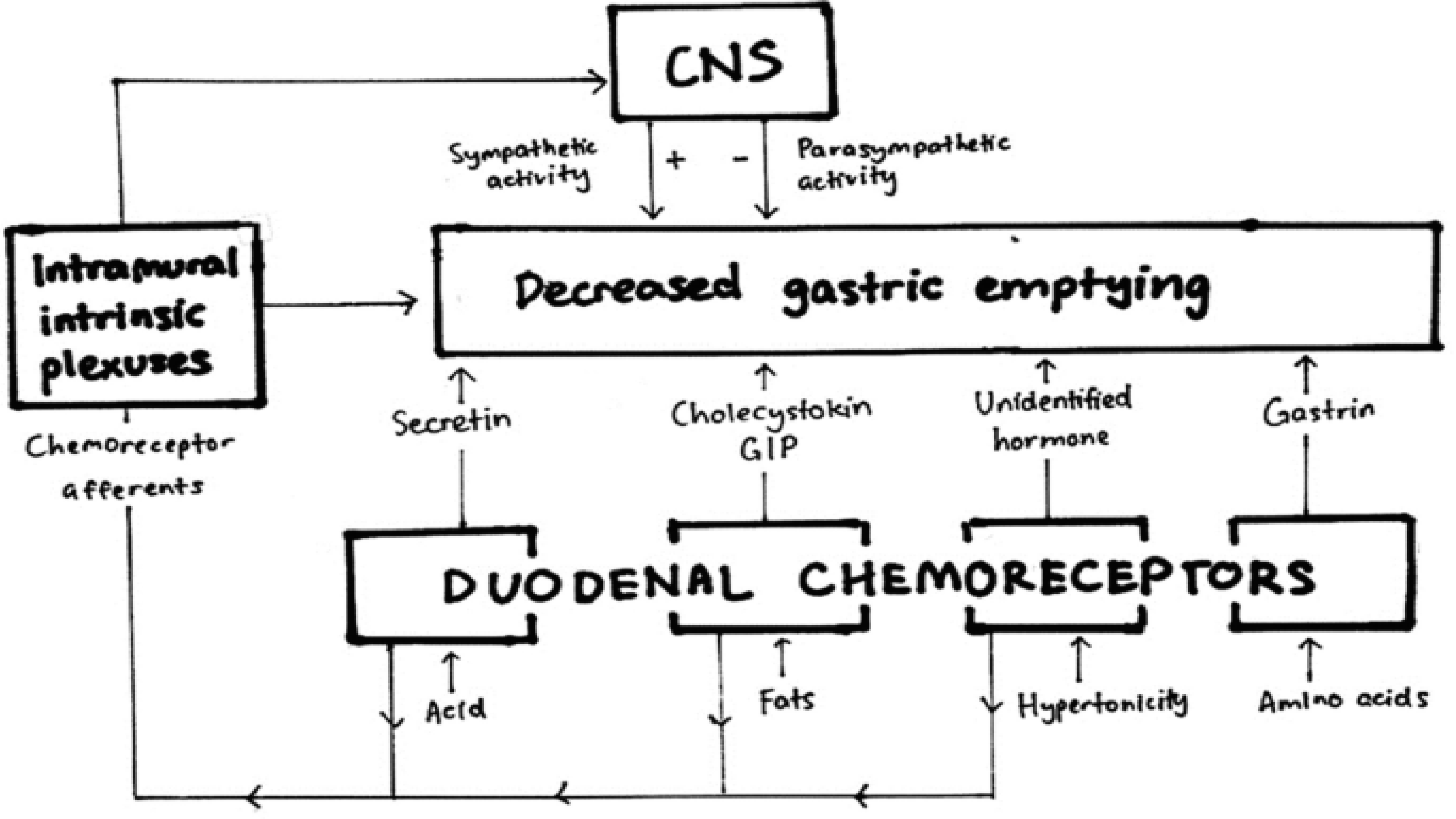






Regulation of Gastric Emptying




CNS
Sympathetic activity
+
-
Parasympathetic activity
Intramural intrinsic plexuses
Decreased gastric emptying
Chemoreceptor afferents
Secretin
Cholecystokin GIP
Unidentified hormone
Gastrin
DUODENAL CHEMORECEPTORS
Acid
Fats
Hypertonicity
Amino acids

- The stomach's function in breaking down food materials mechanically is due to its sophisticated muscular dimensions.

- The contraction and relaxation of these 3 muscular layers of the stomach assist in the mixing and churning activities essential in the formation of chyme.
- Then the chemical breakdown of food material in the stomach is propagated by the gastric glands produced majorly by the parietal cells, the chief cells, G-cells, the foveolar cells (surface mucous cells), and the mucous neck cells.

- The parietal cells secrete intrinsic factors and hydrochloric acid.

- **The intrinsic factor produced is essential in the absorption of vitamin B12. It binds to B12, allowing for proper absorption at the ileum of the small intestine.**
- **The hydrochloric acid produced by the parietal cell keeps the stomach pH between 1.5 to 2.0.**

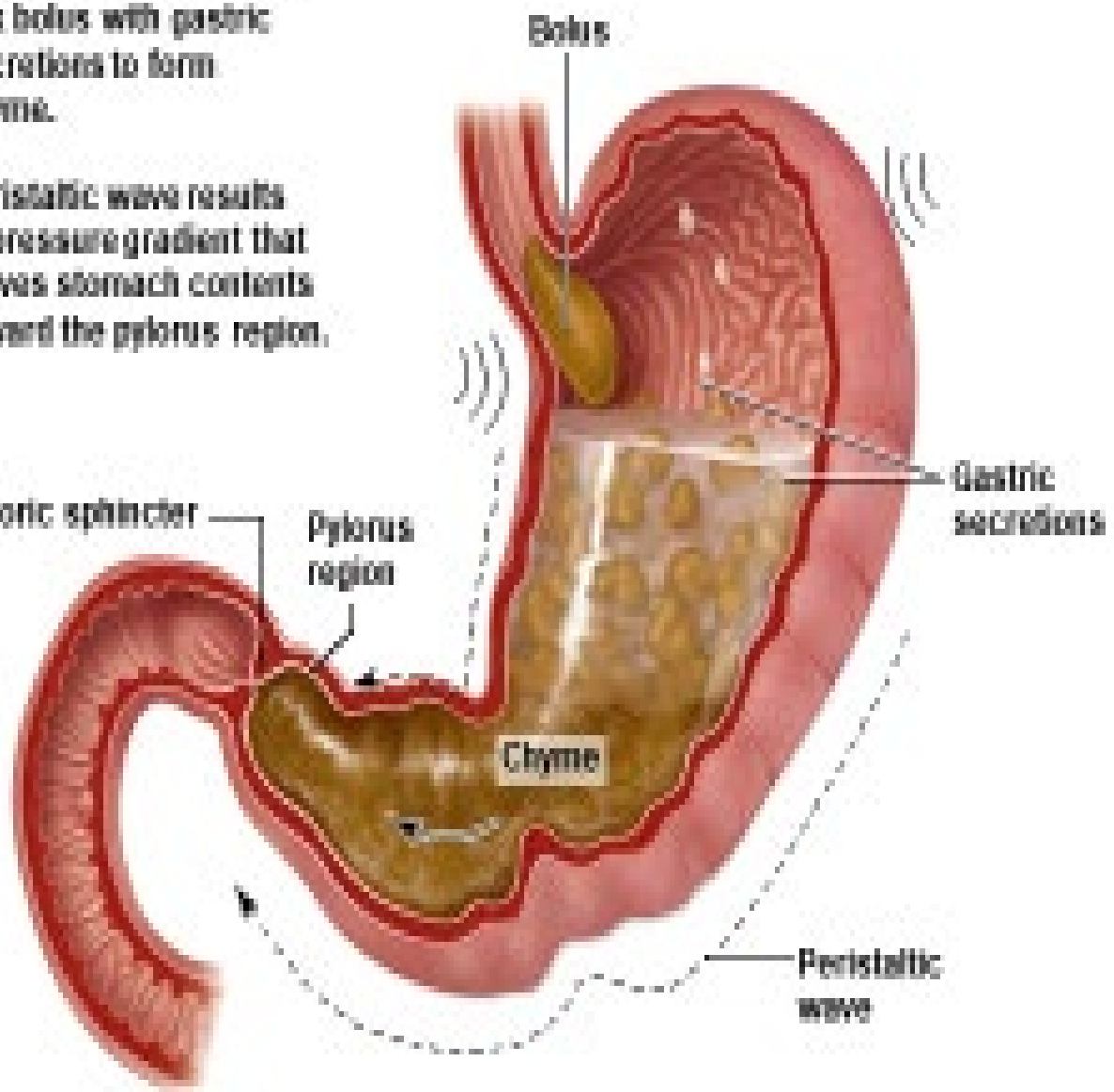
- **The acidity of the stomach brought on by hydrochloric acid destroys most of the microorganisms ingested with food, denatures protein and breaks down plant cell walls, and is essential for the activation and function of pepsin, a protein-digesting enzyme secreted by chief cells.**

- The chief cells produce a zymogen called pepsinogen, which gets activated at pH between 1.5 to 2 to become pepsin.
- The foveolar cells and mucous neck cells produce mucous, which protects the gastric epithelium from acidic corrosion.

- **The G cells are abundant within the pyloric section of the stomach.**
- They produce gastrin which stimulates secretions from the parietal and chief cells.
- Within the pyloric section of the stomach, **D cells produce somatostatin, which inhibits gastrin release**

1. Contractions of smooth muscle in stomach wall mix bolus with gastric secretions to form chyme.

2. Peristaltic wave results in pressure gradient that moves stomach contents toward the pylorus region.

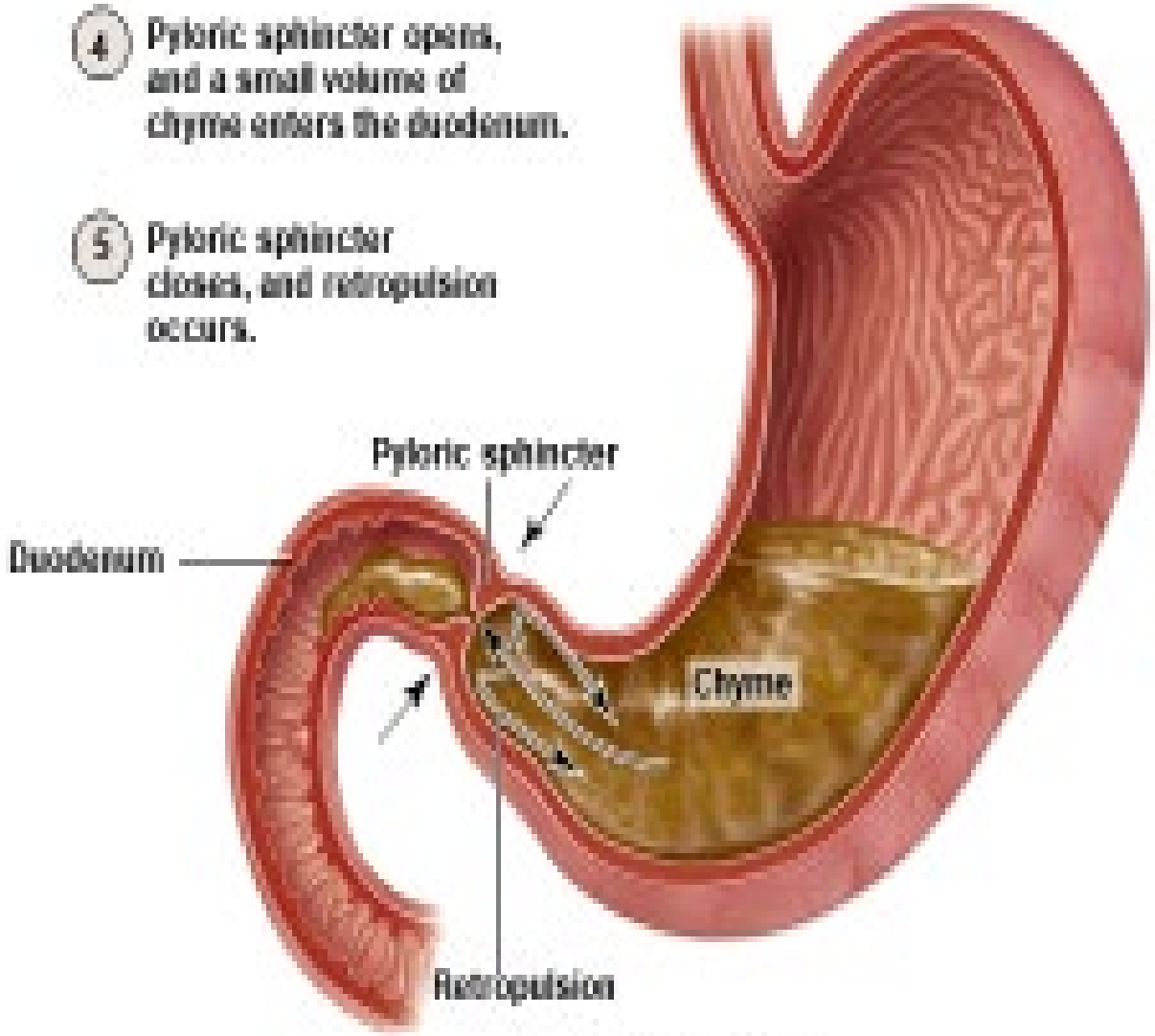


(a) Gastric mixing

3. Pressure gradient increases force in pylorus against pyloric sphincter.

4. Pyloric sphincter opens, and a small volume of chyme enters the duodenum.

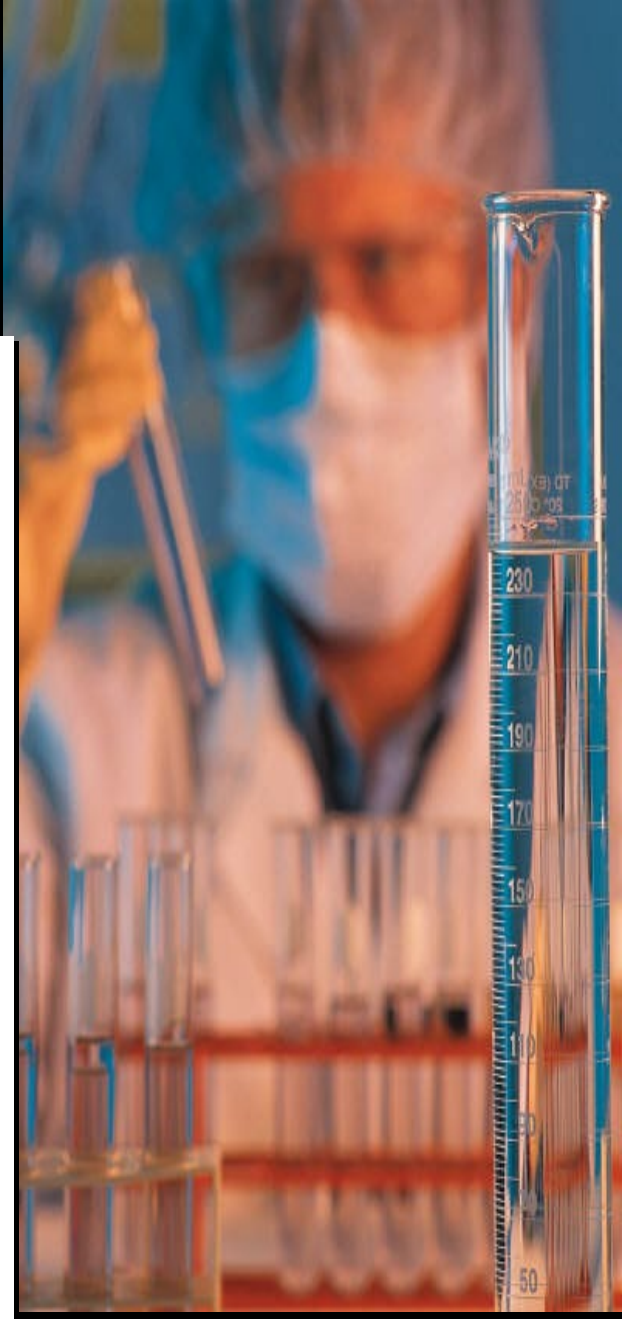
5. Pyloric sphincter closes, and retropulsion occurs.



(b) Gastric emptying

Regulation of HCl Secretion

- **ACh**
  - Released from vagus nerve
  - Binds to receptors on parietal cells
  - Produces H^+ secretion by parietal cells
  - **Atropine** blocks muscarinic receptors on parietal cells
- **Histamine**
  - Released from mastlike cells in gastric mucosa
  - Binds to **H_2 receptors** on parietal cells
  - Produces H^+ secretion by parietal cells
  - **Cimetidine** blocks H_2 receptors
- **Gastrin**
  - Released into circulation by **G cells** of stomach antrum
  - Binds to receptors on parietal cells
  - Stimulates H^+ secretion



Inhibition of Gastric Secretion

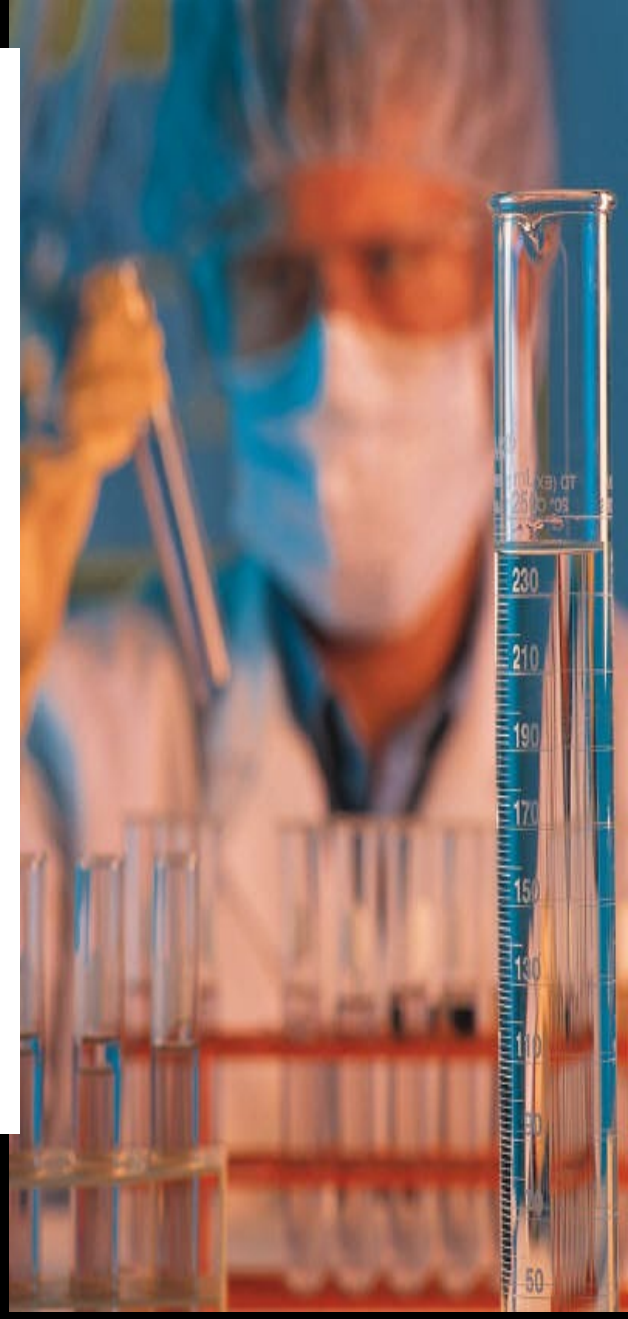
- Important for protection of duodenum

- **Gastric pH < 3 ---> gastric D cells release somatostatin which inhibits gastrin release**

- **Acid in duodenum ---> secretin & CCK---> inhibits gastric secretion and motility**

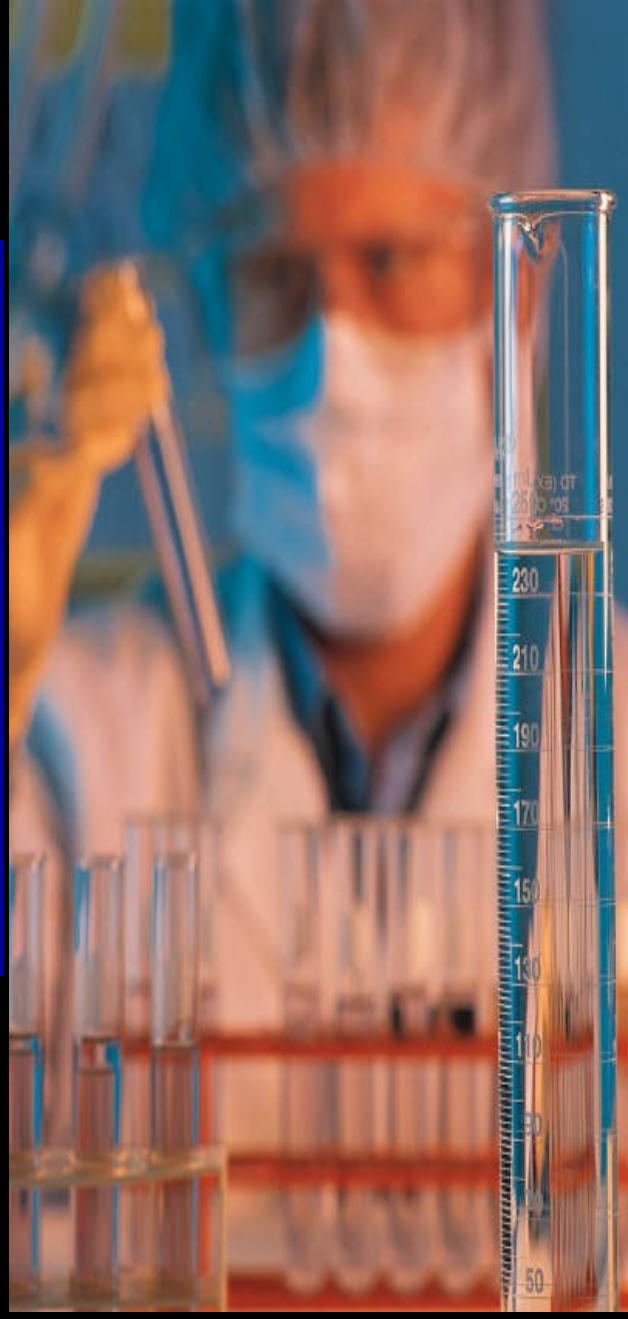
- **Acid, fats, hyper-osmotic solutions in the duodenum ---> release of enterogastrones ---> inhibit gastric motility and secretion**
-
- **Gastric Inhibitory Peptide (GIP) from duodenum ---> inhibits parietal cell function**

- **Inhibitors of Gastric Secretion**
  - **GIP**
  - **CCK**
  - **Secretin**



Parietal Cell

- Stimulated by histamine, gastrin, acetylcholine
- Inhibited by somatosatin, prostaglandins

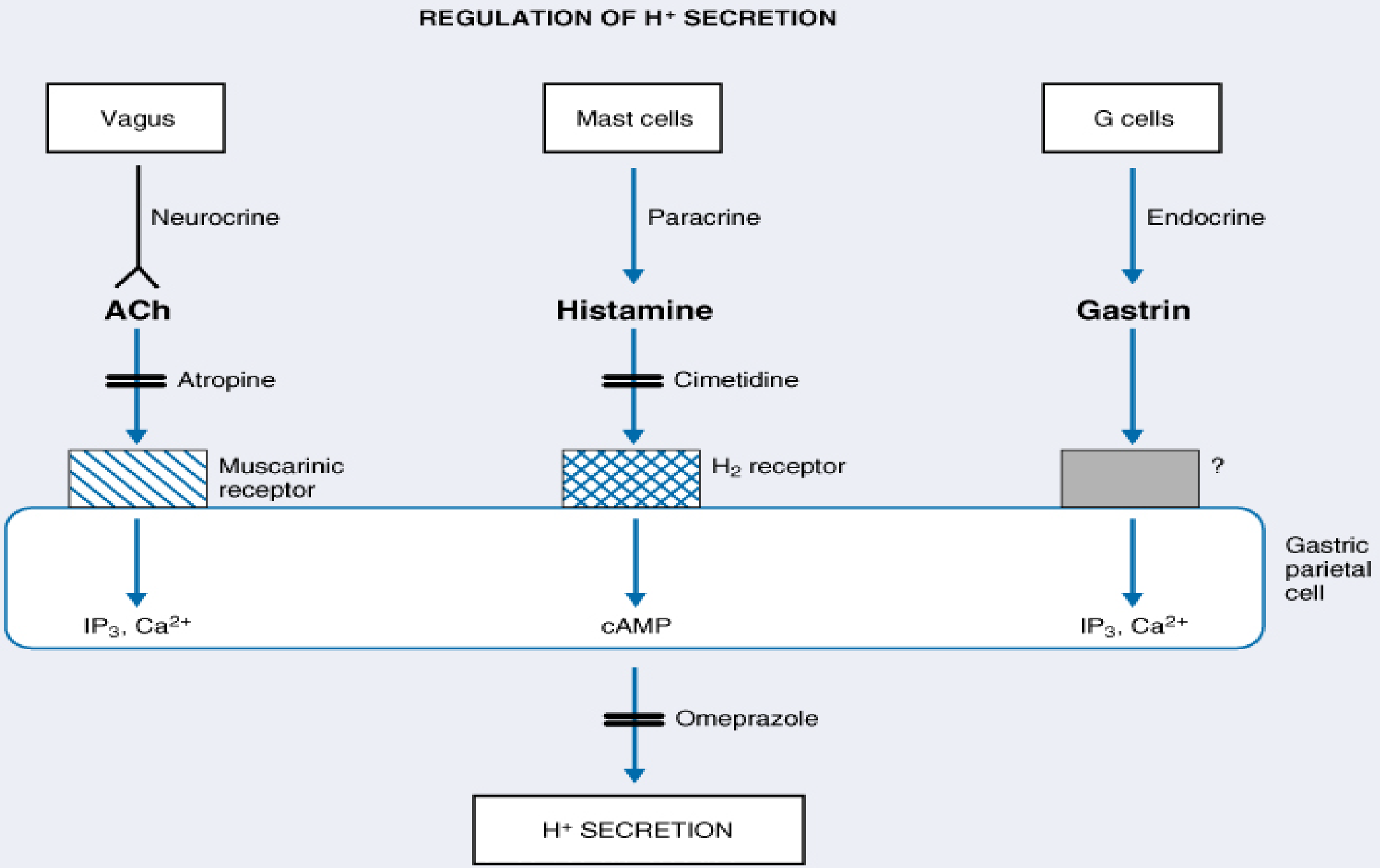


- **GASTRIN** stimulates exocrine glands in stomach to release gastric juice

- Acids (chyme) from stomach, fatty acids in duodenum stimulate release of ***SECRETIN***
  - Stimulates secretion of alkali (bicarbonate ions) from pancreas
    - Neutralises acidity from intestinal contents
    - When pH reaches neutrality, secretion of secretin is inhibited
  - Inhibits gastric gland secretion

- Acidic chyme from stomach, fat, amino acids in **duodenum** stimulate release of **CHOLECYSTOKININ-PANCREOZYMIN CCK-PZ**
  - Activates smooth muscle contraction/emptying of gall bladder (to release bile)
  - Triggers secretion of enzymes from pancreas
  - Stimulates Medulla oblongata which give a satiety signal
  - Once molecules stimulating CCK are digested → CCK inhibited again

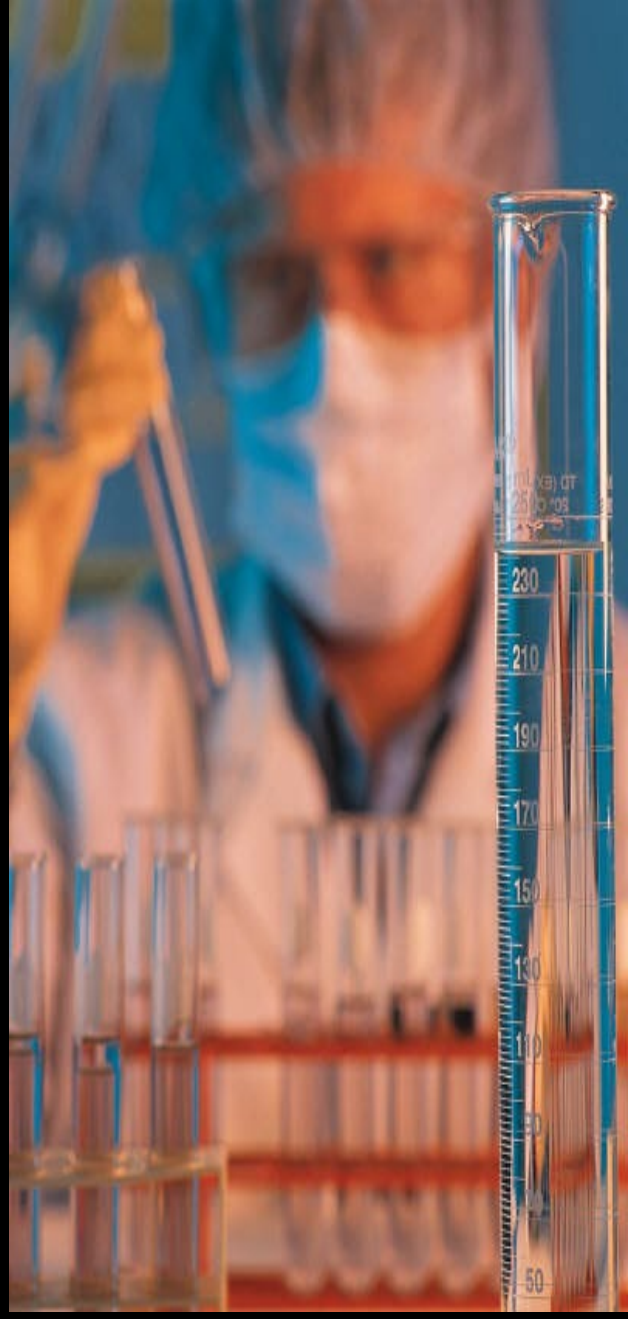
- **SOMATOSTATIN**
  - Acts on stomach, duodenum, pancreas
  - Inhibits release of gastrin, secretin, and CCK-PZ


REGULATION OF H+ SECRETION
Vagus
Mast cells
G cells
Neurocrine
Paracrine
Endocrine
ACh
Histamine
Gastrin
Atropine
Cimetidine
Muscarinic receptor
H2 receptor
?
IP3, Ca2+
cAMP
IP3, Ca2+
Gastric parietal cell
Omeprazole
H+ SECRETION

1. **Hormones that affect the stomach:** the first 4 (Gastrin, CKK, Secretin, GIP)

2. **The inhibitory hormone:** Somatostatin

3. **Hormones that affect intestinal motility:** (NO, VIP, and Motilin)



1. **Stomach distension** increases motility of the stomach (via **Gastrin**) and intestine (via **VIP**). When the stomach's full, you want the food to move along to the next part of the GIT.

2. **Acidity**: when the stomach is too acidic, you'll want to bring the pH back to normal by decreasing acid secretion. This is done by decreasing **Gastrin** (which normally increases acid secretion), and increasing secretin and **Somatostatin** (which decrease acid secretion).

3. **Glucose**: when there's glucose in your GIT, you'll want to get ready for it by having insulin available. This is done via **GIP**. Note that GIP secretion is also stimulated by amino acids and fatty acids.

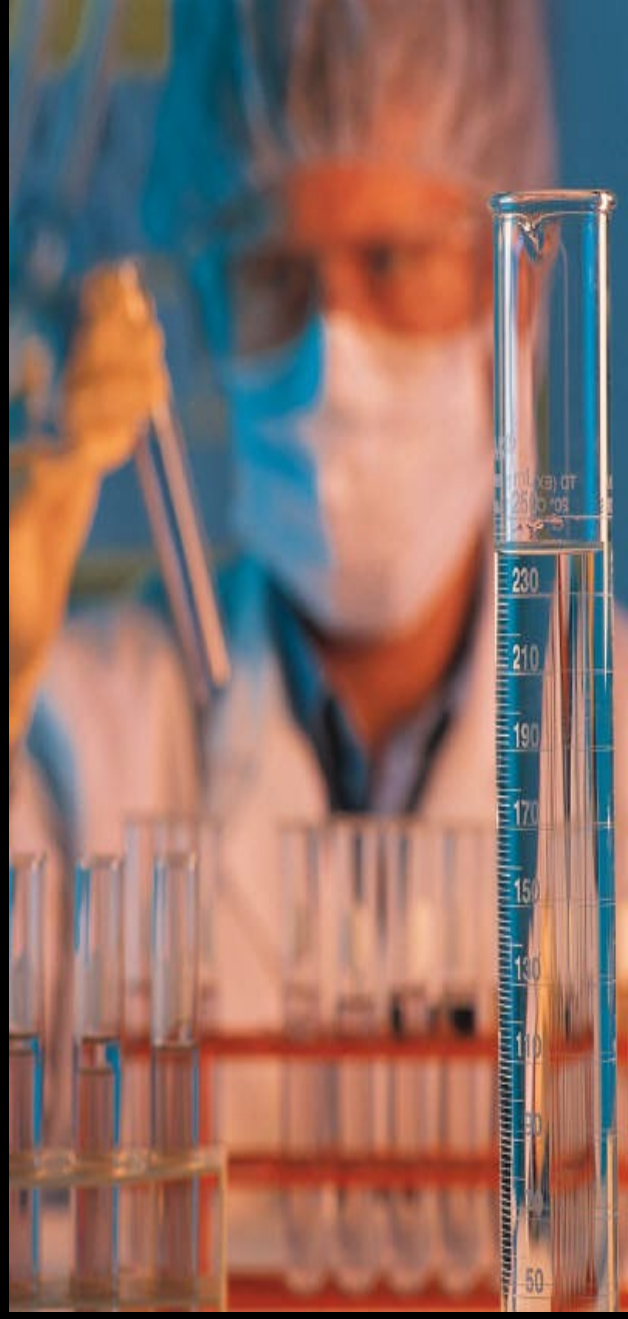
4. **Fatty acids** and **amino acids** each increase the secretion of 3 hormones.

a. **Both amino acids and fatty acids increase the secretion of CCK and GIP.**
b. Amino acids also **increase secretion of Gastrin** [think: proteins are digested by **pepsin**, which is derived from activation of pepsinogen by acid].
c. **Fatty acids** also increase secretion of **Secretin** [think fatty acids are digested by **pancreatic lipases** which require an alkaline pH to function]

5. **Vagal stimulation** increases **Gastrin** and **VIP**.
It also decreases Somatostatin.

G Hormones location and action

know only those with a star



1. Gastrin*

Location: G cells in the stomach antrum and duodenum

Actions:

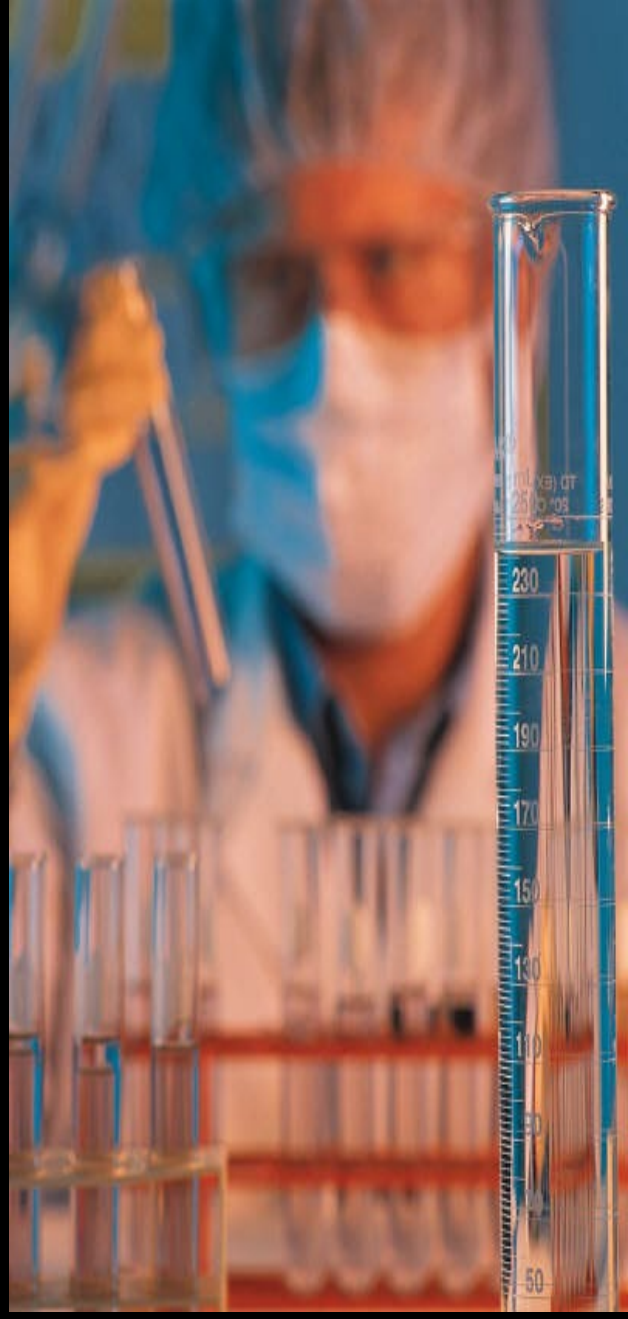
- •Stimulates secretion of gastric acid (HCl) by parietal cells in the stomach.
- •Promotes growth of the gastric mucosa.
- •Increases gastric motility.

2. Cholecystokinin (CCK)*

Location: I cells in the duodenum and jejunum

Actions:

- •Stimulates the gallbladder to contract and release stored bile into the intestine.
- •Stimulates the pancreas to secrete digestive enzymes.
- •Slows gastric emptying.
- •Promotes satiety (feeling of fullness).



3. Secretin*

Location: S cells in the duodenum

Actions:

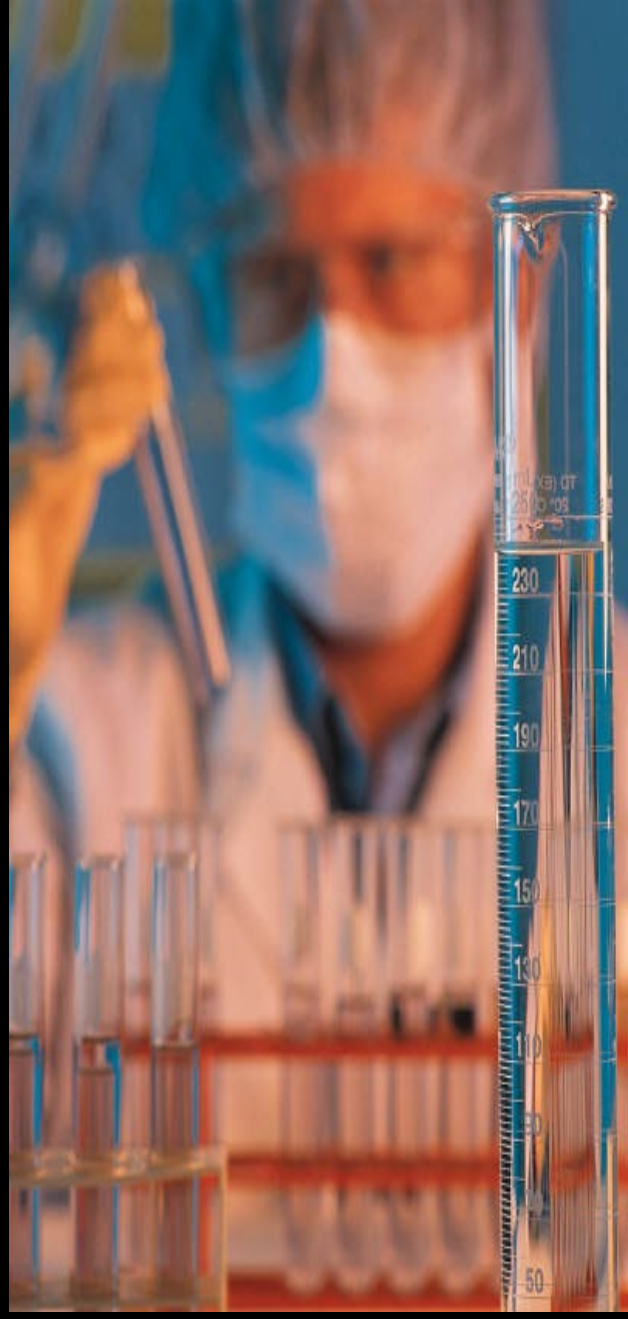
- Stimulates the pancreas to release bicarbonate-rich fluid, which neutralizes stomach acid in the duodenum.
- Inhibits gastric acid secretion.
- Enhances the action of CCK.

4. Gastric Inhibitory Peptide (GIP) / Glucose-dependent Insulinotropic Peptide*

Location: K cells in the duodenum and jejunum

Actions:

- Stimulates insulin secretion in response to oral glucose intake.
- Inhibits gastric acid secretion.
- Slows gastric emptying.



5. Motilin*

Location: M cells in the small intestine, mainly in the duodenum and jejunum

Actions:

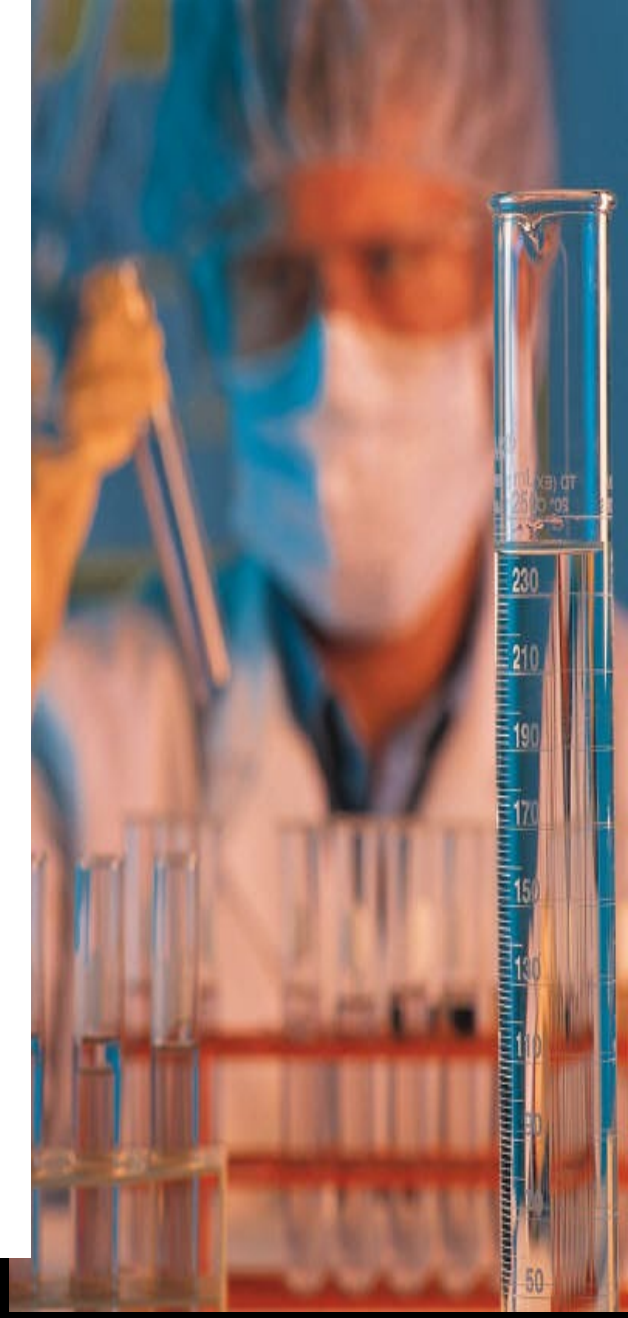
- Stimulates migrating motor complex (MMC), which is responsible for periodic gut motility between meals.
- Increases gastric and small bowel motility.

6. Somatostatin*

Location: D cells in the stomach, duodenum, and pancreas

Actions:

- Inhibits the release of several other GI hormones, including gastrin, CCK, secretin, and GIP.
- Inhibits gastric acid and pepsinogen secretion.
- Reduces gastric motility and bile flow.
- Decreases pancreatic secretion.



7. Ghrelin*

Location: P/D1 cells in the stomach and epsilon cells of the pancreas

Actions:

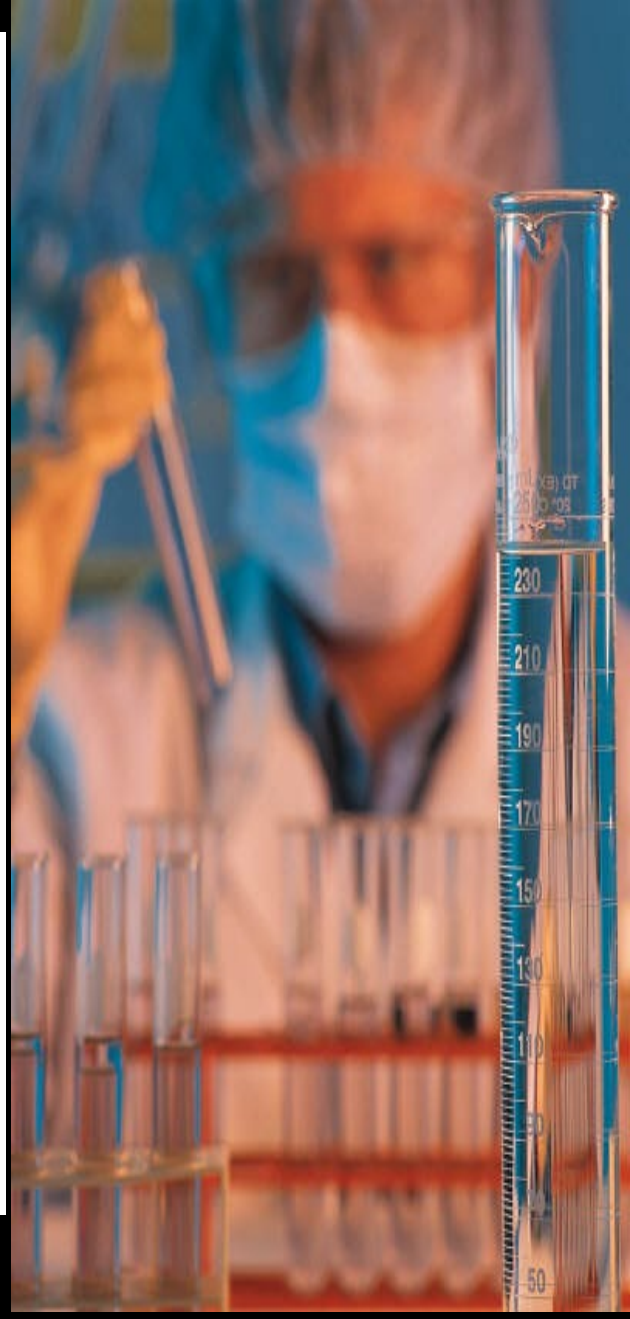
- Stimulates appetite and increases food intake (the "hunger hormone").
- Promotes gastric motility.
- Stimulates growth hormone release from the pituitary gland.

8. Peptide YY (PYY)*

Location: L cells in the ileum and colon

Actions:

- Inhibits gastric motility and slows gastric emptying.
- Reduces appetite by acting on the brain.
- Inhibits pancreatic secretion.



9. Vasoactive Intestinal Peptide (VIP)*

Location: Nerve fibers throughout the GI tract

Actions:

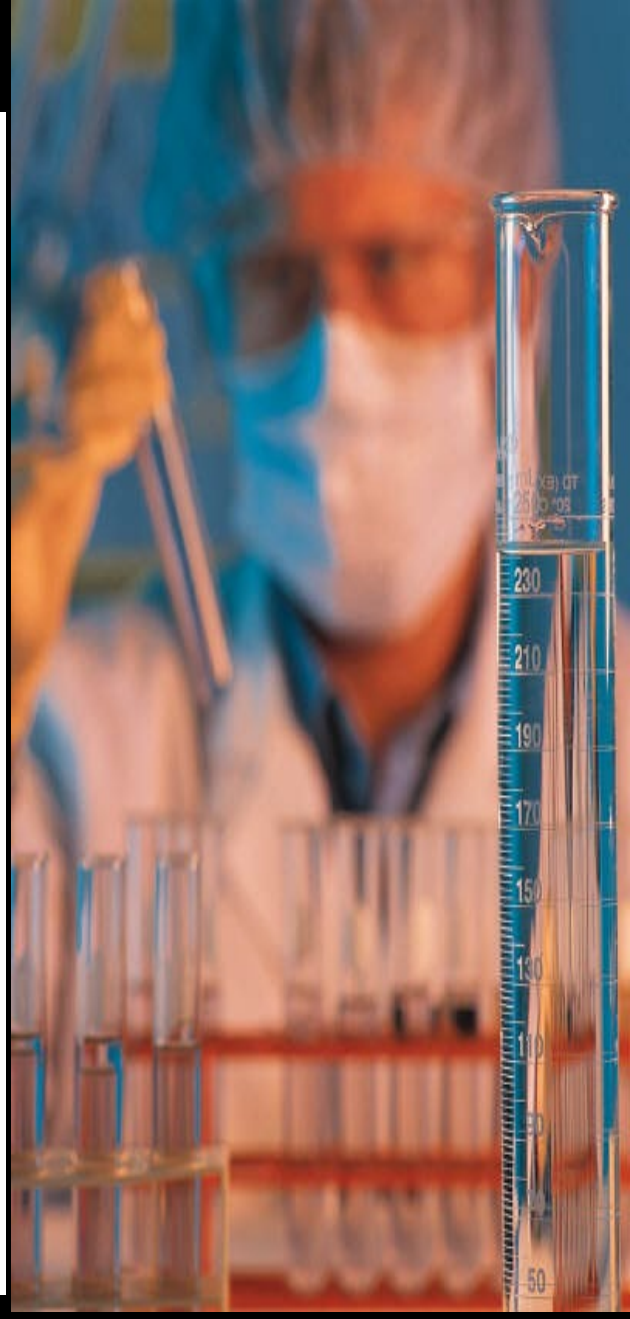
- Relaxes smooth muscle in the GI tract, causing vasodilation.
- Stimulates the secretion of water and electrolytes in the intestines.
- Inhibits gastric acid secretion.
- Increases bile flow.

10. Neurotensin

Location: N cells in the small intestine

Actions:

- Relaxes smooth muscle in the lower esophageal sphincter, stomach, and small intestine.
- Inhibits gastric acid secretion.
- Modulates pancreatic enzyme secretion.

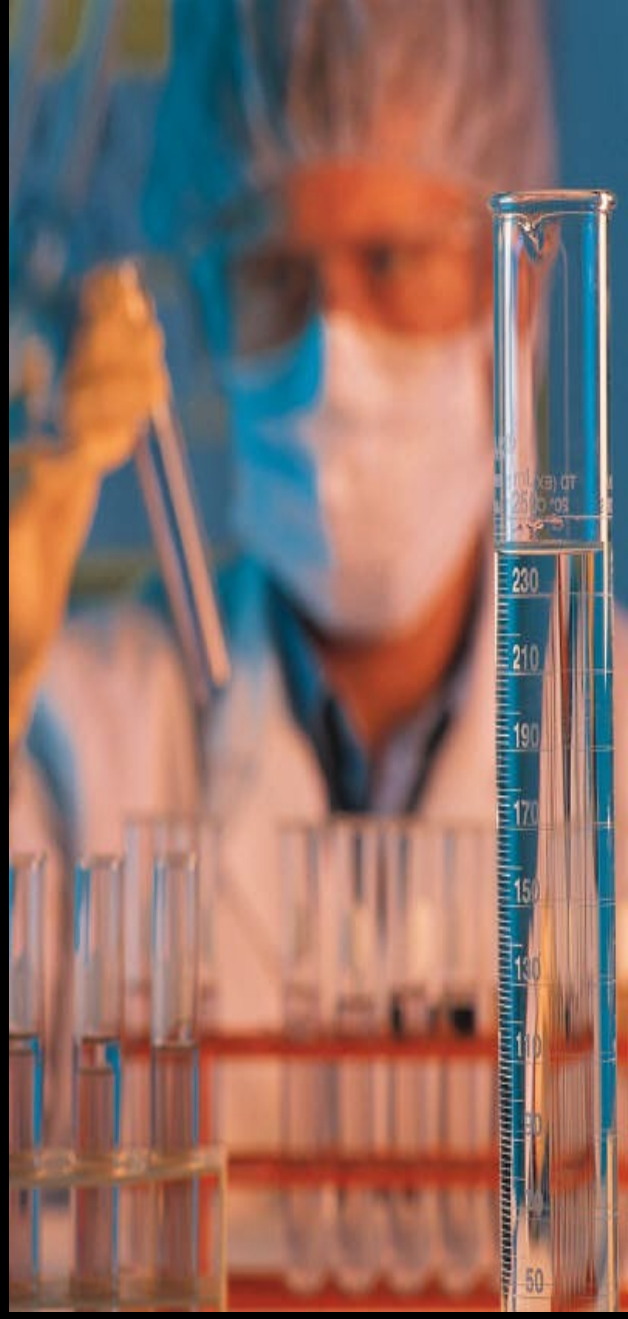


11. Enteroglucagon*

Location: L cells in the distal ileum and colon

Actions:

- Slows gastric emptying and intestinal motility.
- Stimulates insulin secretion.
- Increases hepatic glycogenolysis and gluconeogenesis.



12. Incretins (GLP-1 and GIP)

Location: L cells in the small intestine (GLP-1) and K cells in the duodenum and jejunum (GIP)

Actions:

•Glucagon-like peptide-1 (GLP-1):

- Enhances insulin secretion in response to oral glucose intake.
- Inhibits glucagon release.
- Slows gastric emptying.
- Promotes satiety and reduces food intake.

•Glucose-dependent insulinotropic peptide (GIP):

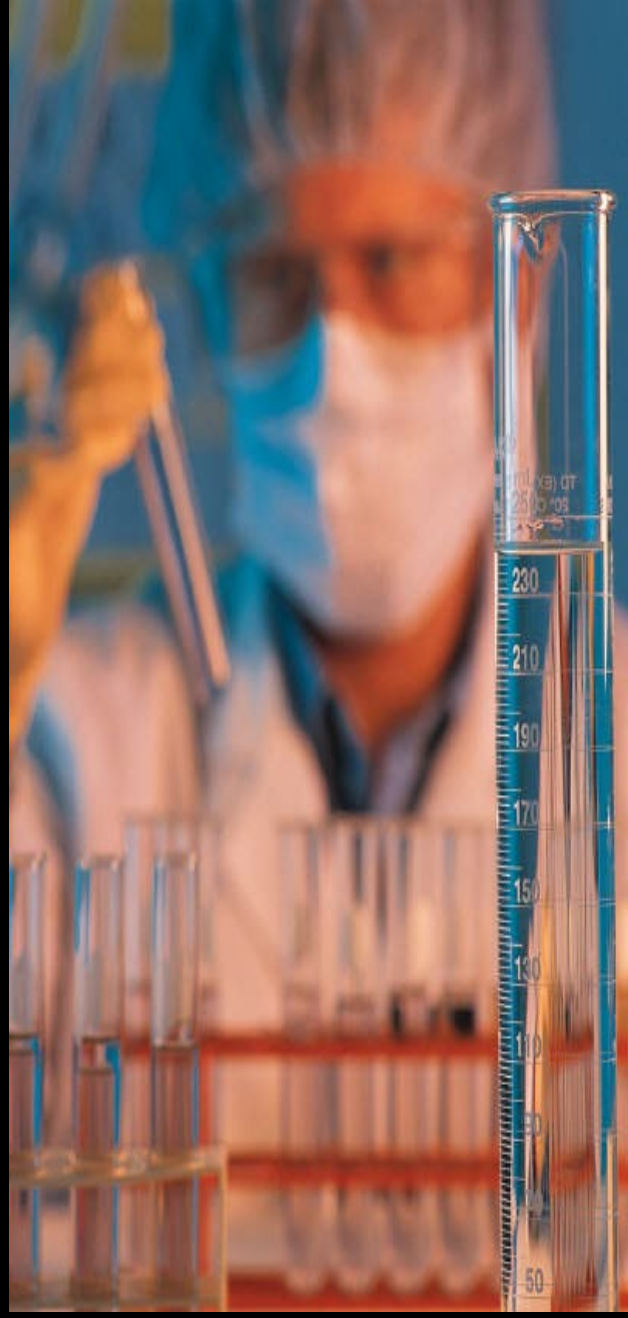
- Stimulates insulin secretion in response to oral glucose.
- Inhibits gastric acid secretion.
- Modulates fat metabolism by promoting lipogenesis in adipose tissue.

13. Oxyntomodulin

Location: L cells in the small intestine

Actions:

- •Inhibits gastric acid secretion.
- •Reduces appetite and food intake.
- •Increases energy expenditure.



14. Pancreatic Polypeptide (PP)*

Location: PP cells (F cells) in the pancreas

Actions:

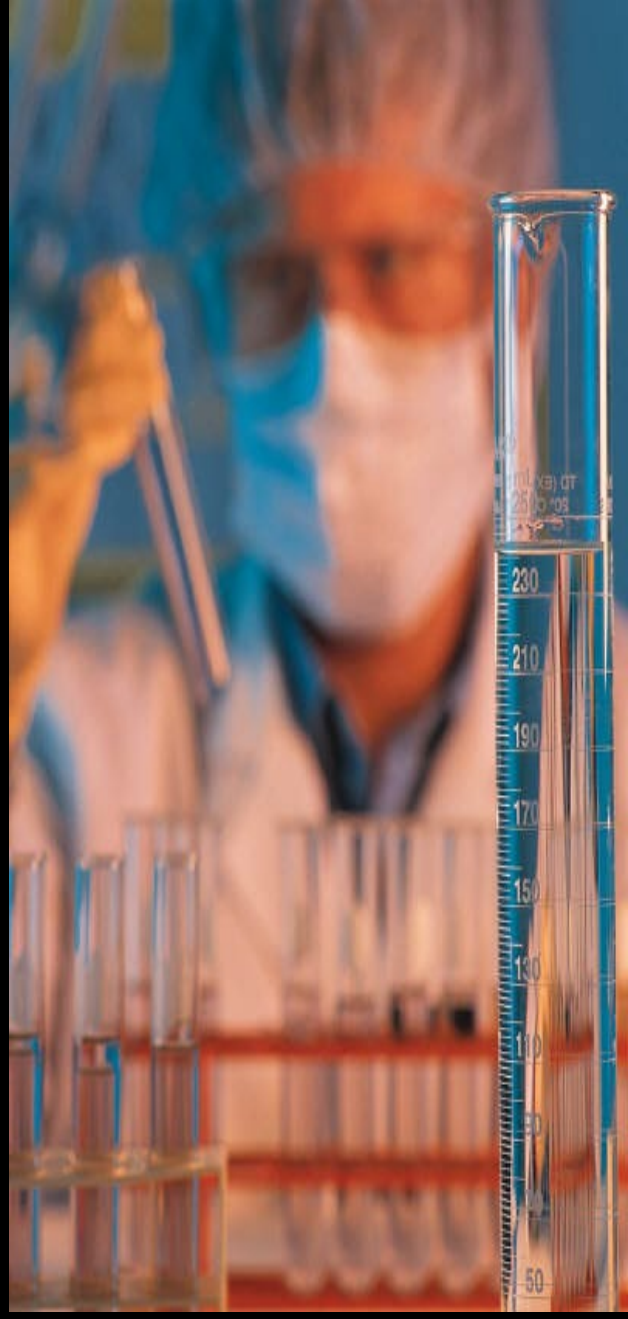
- Inhibits pancreatic exocrine secretion.
- Regulates hepatic glycogen levels.
- Affects gastrointestinal motility.

15. Neurotensin

Location: N cells in the small intestine, particularly the ileum

Actions:

- Relaxes smooth muscle in the gastrointestinal tract.
- Inhibits gastric acid secretion.
- Stimulates the release of pancreatic enzymes.



16. Substance P*

Location: Enteric neurons and enterochromaffin cells

Actions:

•Mediates pain perception.

•Stimulates smooth muscle contraction in the GI tract.

•Increases blood flow to the GI tract by vasodilation.

17. Serotonin (5-HT)*

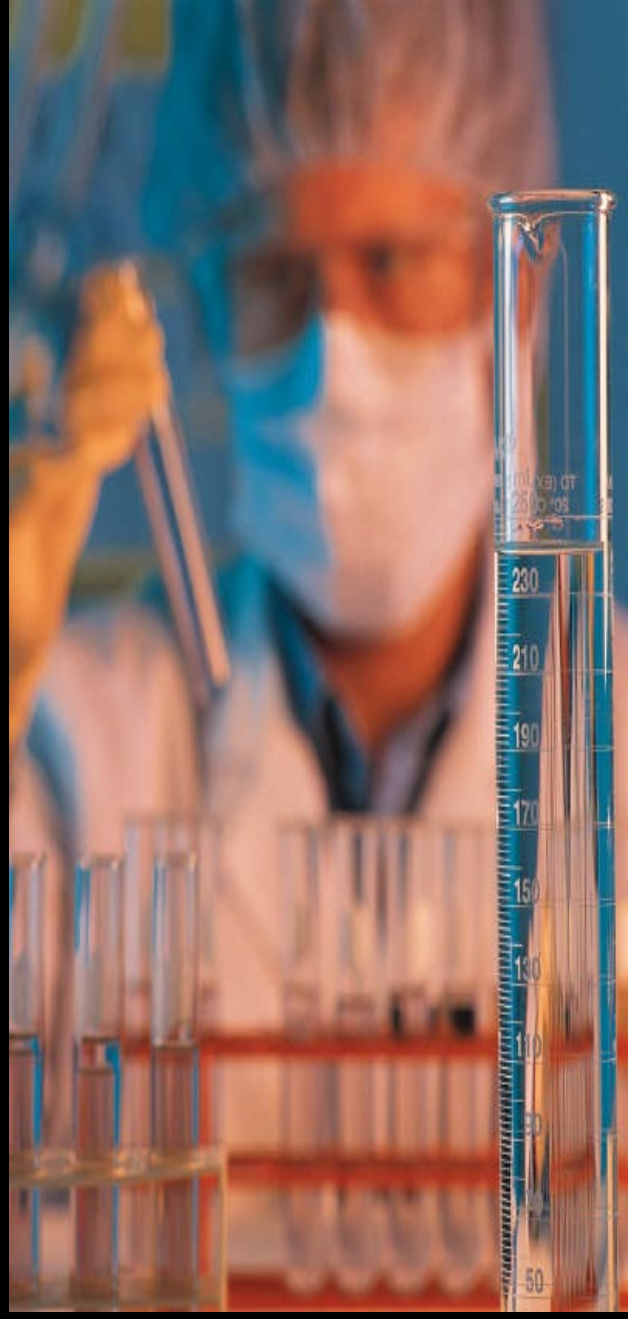
Location: Enterochromaffin cells in the GI tract

Actions:

•Regulates intestinal movements by modulating smooth muscle contractions.

•Affects sensation and pain perception in the gut.

•Influences secretion of digestive enzymes and fluids.



18. Histamine*

Location: Enterochromaffin-like (ECL) cells in the stomach

Actions:

- Stimulates gastric acid secretion by acting on H2 receptors on parietal cells.
- Modulates immune responses in the GI tract.

19. Bombesin*

Location: Nerve endings and enteroendocrine cells

Actions:

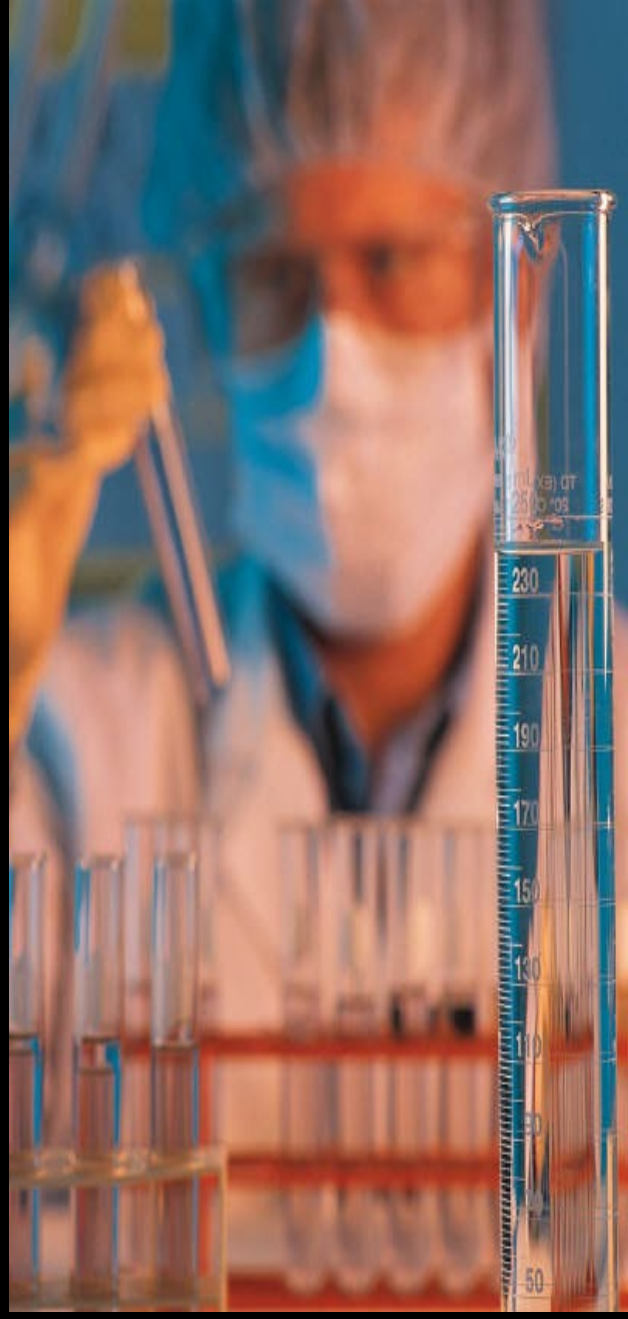
- Stimulates the release of gastrin and pancreatic enzymes.
- Modulates smooth muscle contraction and gastrointestinal motility.

20. Prostaglandins*

Location: Produced by cells throughout the GI tract

Actions:

- Protect the gastric mucosa by stimulating the secretion of mucus and bicarbonate.
- Regulate blood flow to the stomach and intestines.
- Modulate inflammation and pain in the GI tract.



21. Leptin*

Location: Adipocytes (fat cells) and gastric mucosa

Actions:

- Regulates energy balance by inhibiting hunger.
- Modulates the secretion of various GI hormones.
- Influences gastrointestinal motility.

22. Enterostatin

Location: Pancreatic acinar cells

Actions:

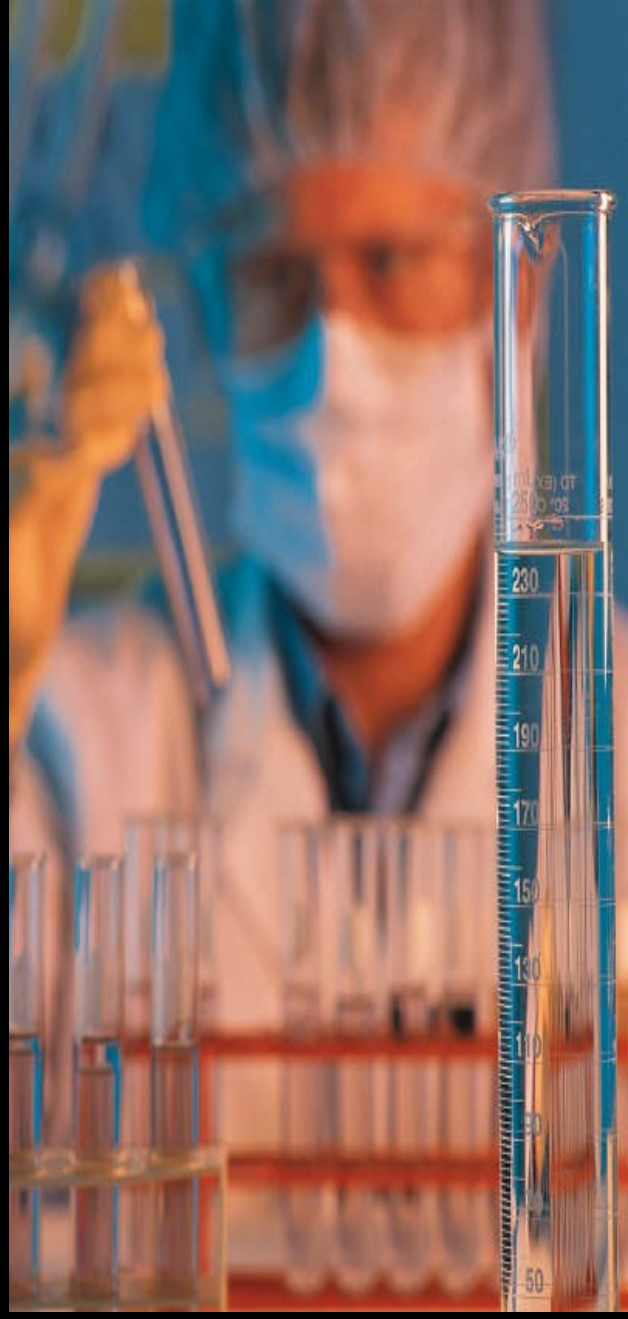
- Inhibits fat intake by reducing appetite.
- Modulates fat digestion by affecting pancreatic lipase activity.

23. Tachykinins (Substance P, Neurokinin A, Neurokinin B)

Location: Enteric neurons and enteroendocrine cells

Actions:

- Modulate smooth muscle contraction in the gut.
- Influence secretion of digestive juices.
- Mediate pain and inflammatory responses in the GI tract.



24. Urocortin

Location: Enteric neurons and various tissues

Actions:

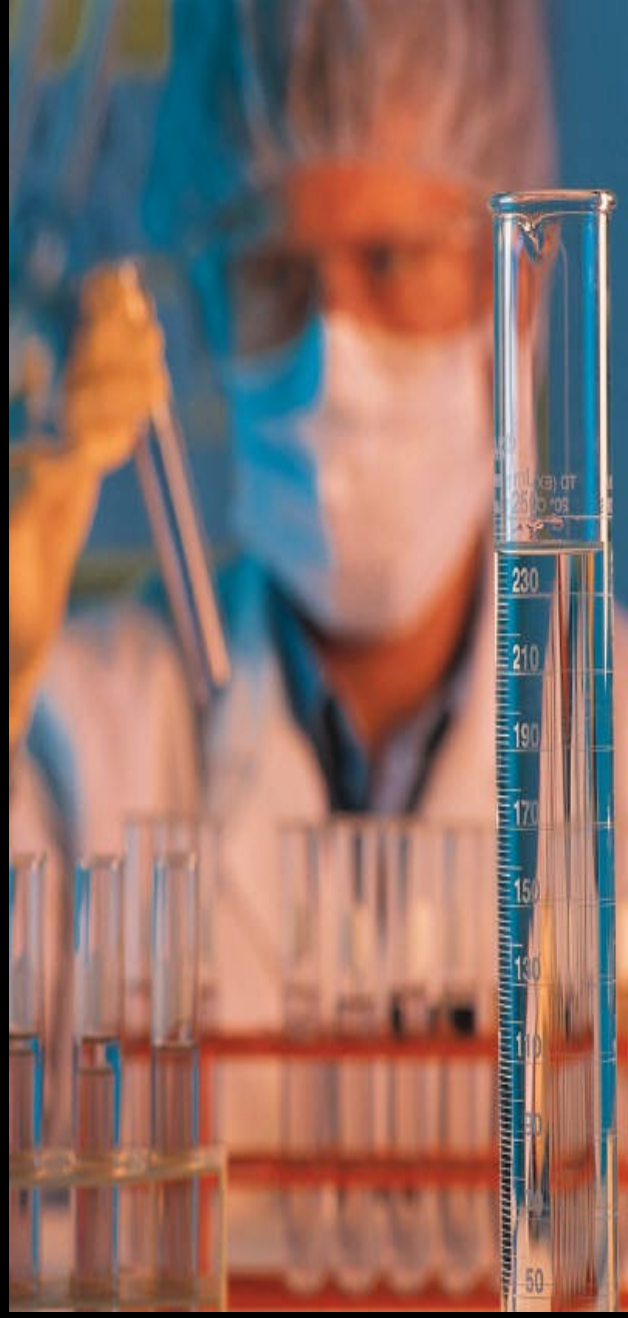
- •Regulates gastrointestinal motility.
- •Modulates stress-related responses in the GI tract.
- •Influences fluid and electrolyte balance.

25. Somatostatin*

Location: D cells in the stomach, duodenum, and pancreas

Actions:

- •Inhibits the release of several other GI hormones, including gastrin, CCK, secretin, and GIP.
- •Inhibits gastric acid and pepsinogen secretion.
- •Reduces gastric motility and bile flow.
- •Decreases pancreatic secretion.



Important actions of GI hormones

Action	Gastrin	CCK	Secretin	GIP
Acid secretion	S		I	I
Pancreatic HCO_3^- secretion		S	S	
Pancreatic enzyme secretion		S		
Bile HCO_3^-			S	
Gallbladder contraction			S	
Gastric emptying			I	
Mucosal growth		S		
Pancreatic growth		S	S	
S = stimulates; I = inhibits				

Additional GI hormones

Hormones are produced by enteroendocrine cells in the GI tract in stomach, small and large intestine

Motilin	increases intestinal motility
Serotonin	increases intestinal motility
Substance P	neurotransmitter for intestinal smooth muscle
Vasoactive intestinal peptide (VIP)	stimulates secretion of water and ions
Neurotensin	decreases intestinal motility increases blood flow to ileum

Additional GI hormones (cont.)

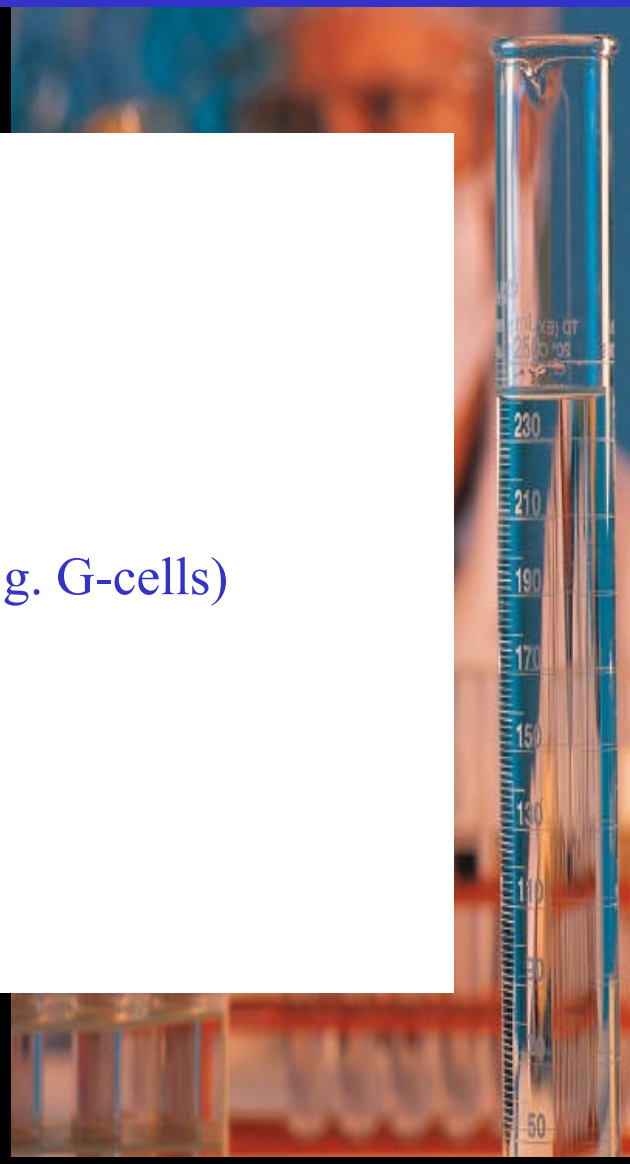
- **Glucagon**
- **Entero-glucagon** → stimulate hepatic glycogenolysis

- **Glicentin**
- (glucagon-like substance) → stimulates hepatic glycogenolysis

- **Somatostatin** → local inhibition of other endocrine cells (e.g. G-cells)

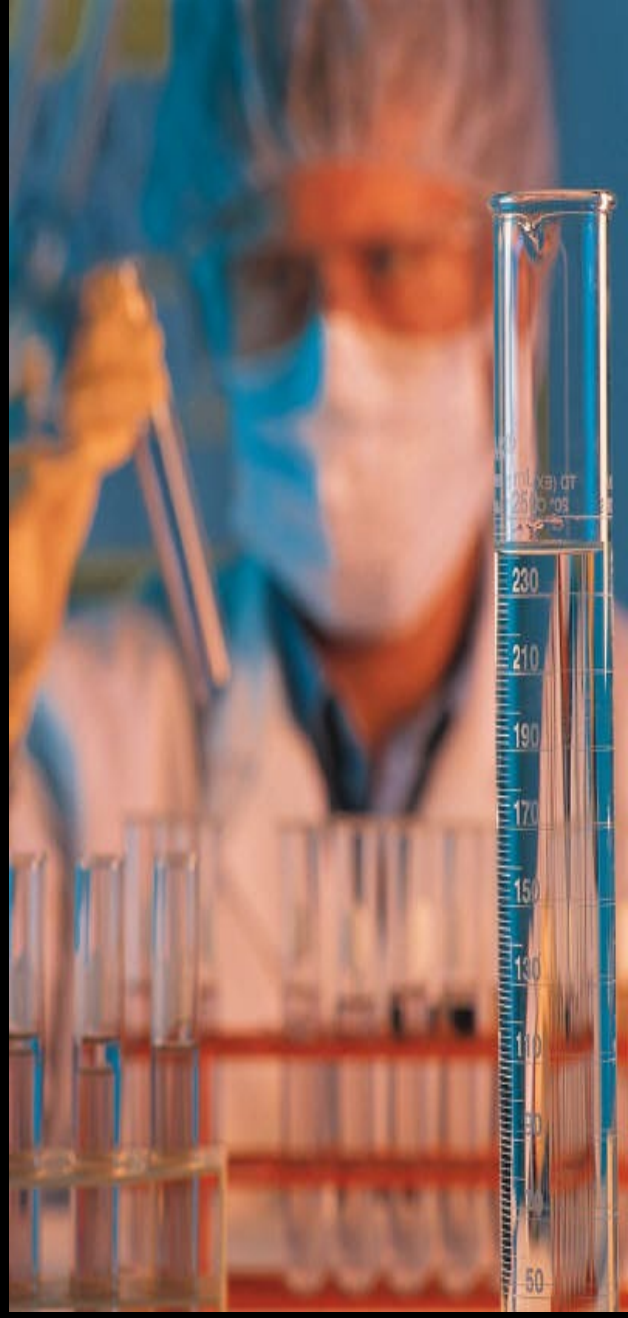
- **Urogastrone** → inhibits secretion of HCl; increases epithelial growth
- **(Epidermal Growth Factor)**

- **Histamine** → increases secretion of HCl

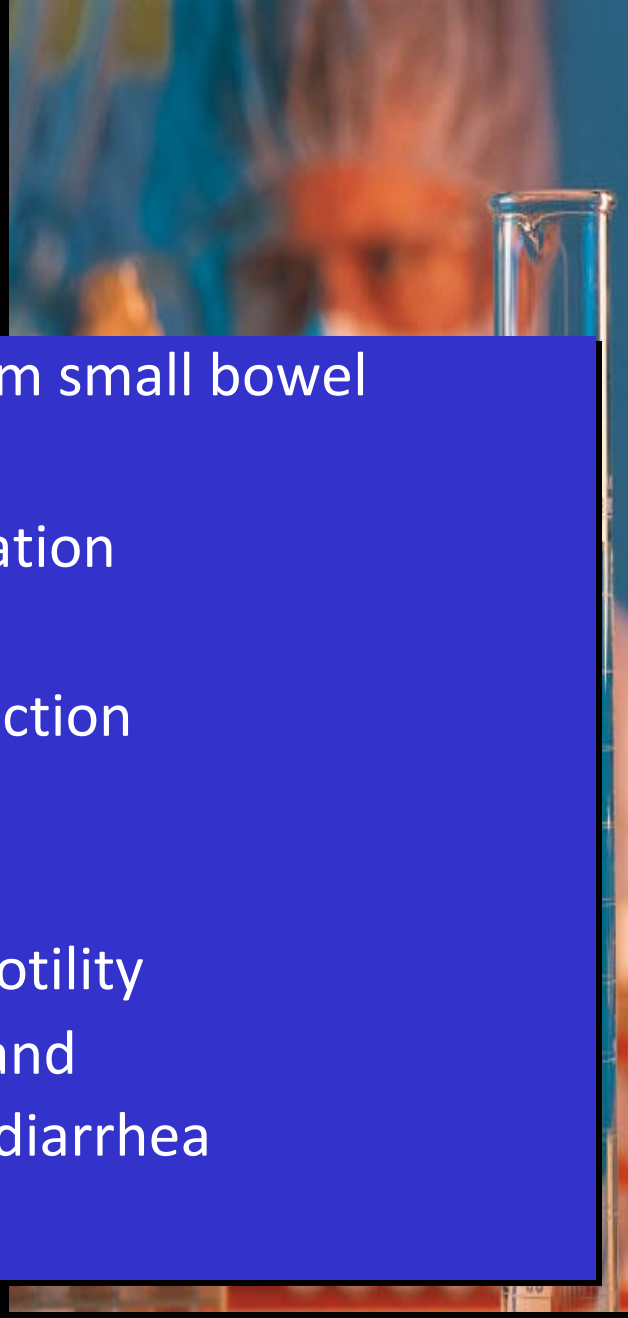


Intrinsic Factor

- Secreted by parietal cells
- Binds cobalamin(B_{12}) to facilitate absorption
- 2 cobalamin binding proteins – IF/R
- Initially binds to cobalamin R in acidic stomach then is cleaved in duodenum and binds to IF
- Attaches to ileal mucosa
- B_{12} malabsorption may result from IF deficiency, achlorhydria or hypochlorhydria, bacterial overgrowth, pancreatic insufficiency, ileal receptor defect, ileal disease, ileal resection



Vasoactive intestinal peptide (VIP)



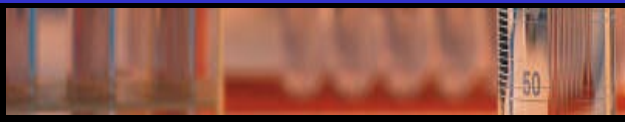
- Found in ENS (enteric nervous system) neurons (both myenteric and submucosal plexus), brain, autonomic nerves
- **Released in response to esophageal and gastric distention, vagal stimulation, fatty acid and ethanol in duodenum**
- **Amino acid and glucose don't affect VIP release**
- Half life 2 min in circulation

- ↑ secretion of E'lyte and water from small bowel
- Intestinal circular smooth ms relaxation
- Longitudinal smooth muscle contraction
- ↑ pancreatic secretion
- Inhibit gastric acid secretion and motility
- Potentiate axn of Ach in salivary gland
- VIPoma : presented with profused diarrhea

Motilin

- **Secreted by enterochromaffin cell and M cell in duodenum, jejunum**
- Acts on G-protein coupled receptor on enteric neurons in stomach, duodenum → GI tract smooth muscle contraction
- Its circulating level increased at interval of 90-100 mins in the interdigestive state

- Major regulator of MMCs (Migrating Motor Complex) that move through the stomach and small intestine every 90 mins in fasted person
- Motilin secretion is inhibited after ingestion
- Vagal nerve may play some role in motilin secretion
- Erythromycin bind to motilin receptor ⟶ ↑ GI motility in constipated person



Somatostatin

- **Growth hormone inhibitory hormone (GH-IH)**
- First found in hypothalamus
- Secreted by D cell in stomach, duodenum, pancreatic islet
- Secreted in larger amount into gastric lumen > circulation
- Released in response to acid in stomach

- Presented in 2 forms

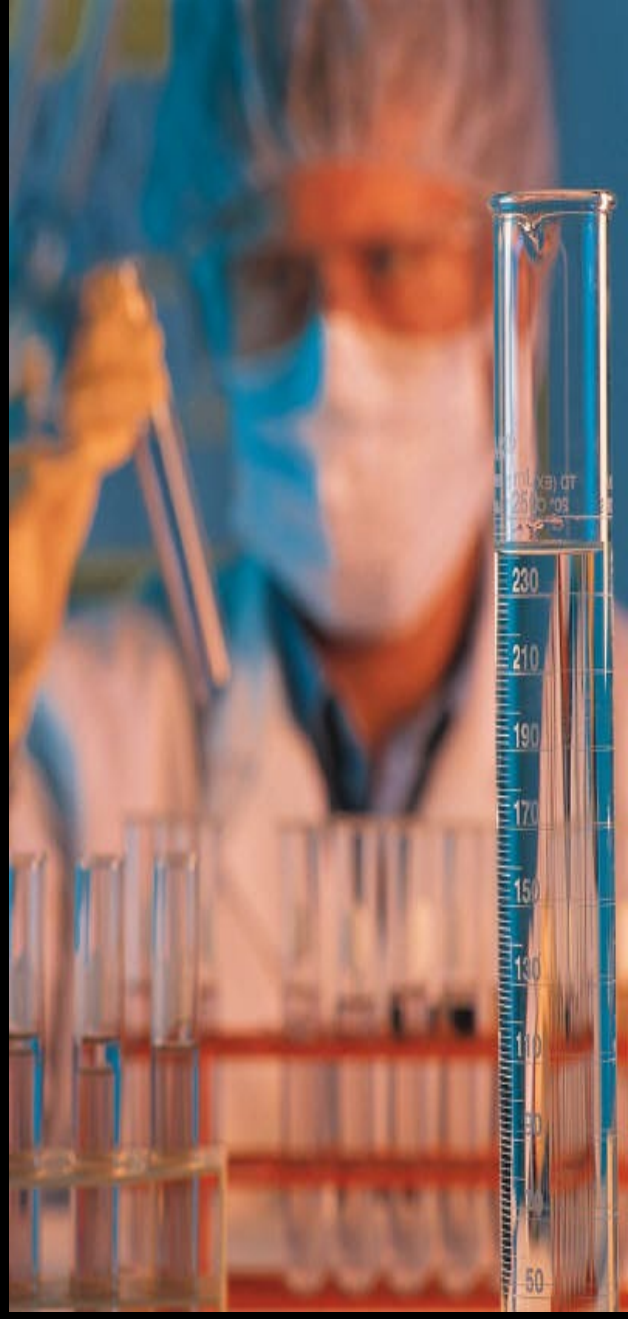
1. **Somatostatin 14 :** prominent in hypothalamus

2. **Somatostatin 28 :** prominent in GI tract

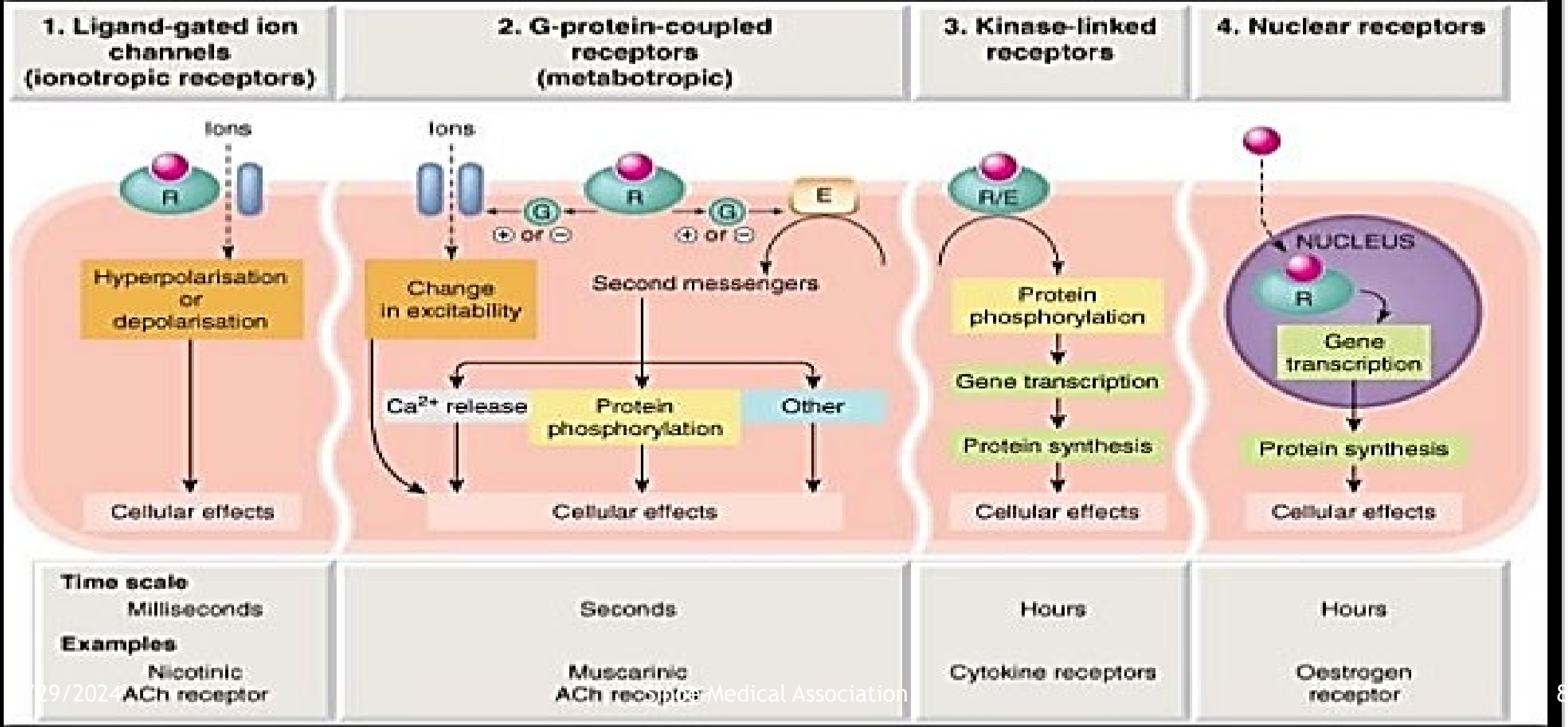
- Acts through G-protein couple receptor (inhibit adenylate cyclase)

Action of somatostatin

- **Inhibit secretion of gastrin, VIP, GIP, secretin, motilin, GH, insulin, glucagon**
- **↑ fluid absorption and ↓ secretion from intestine**
- **↓ endocrine and exocrine pancreatic secretion**
- **↓ bile flow and gall bladder contraction**
- **↓ gastric acid secretion and motility**
- **↓ absorption of glucose, amino acid, triglyceride**



Types of receptors



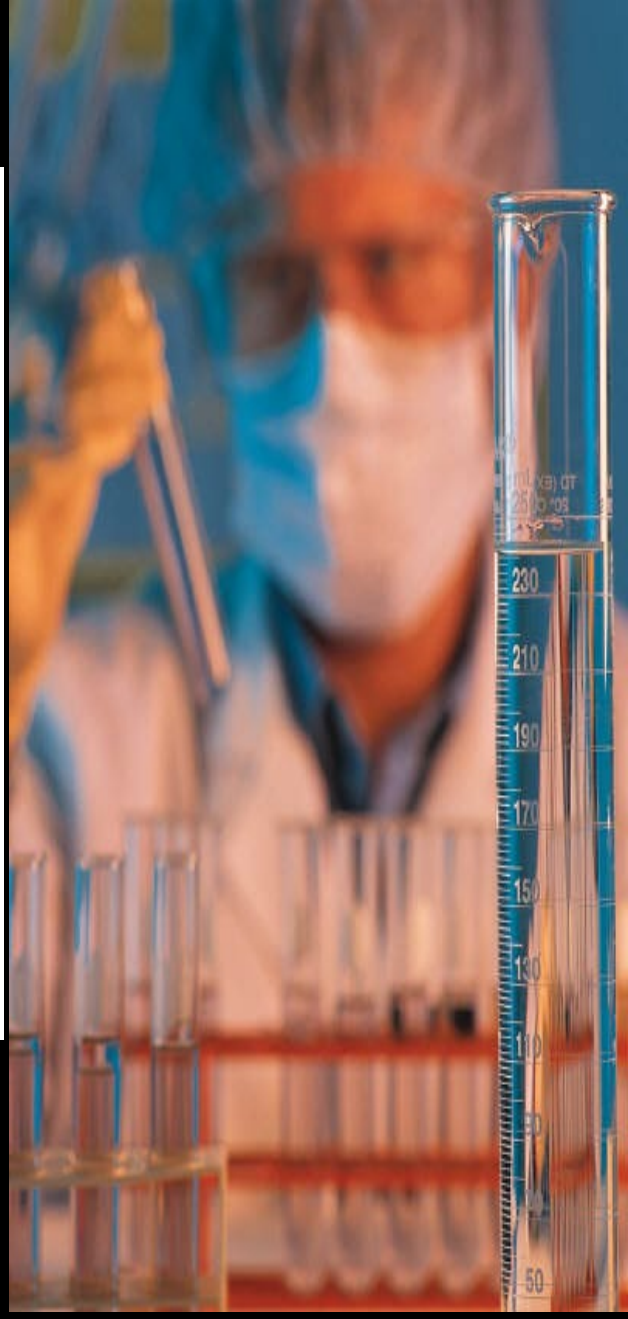
PREGNANCY:

•Pregnant women **tend to gain weight because they have increased levels of CCK** (**higher fat and protein absorption**) and **lower levels of Somatostatin.**

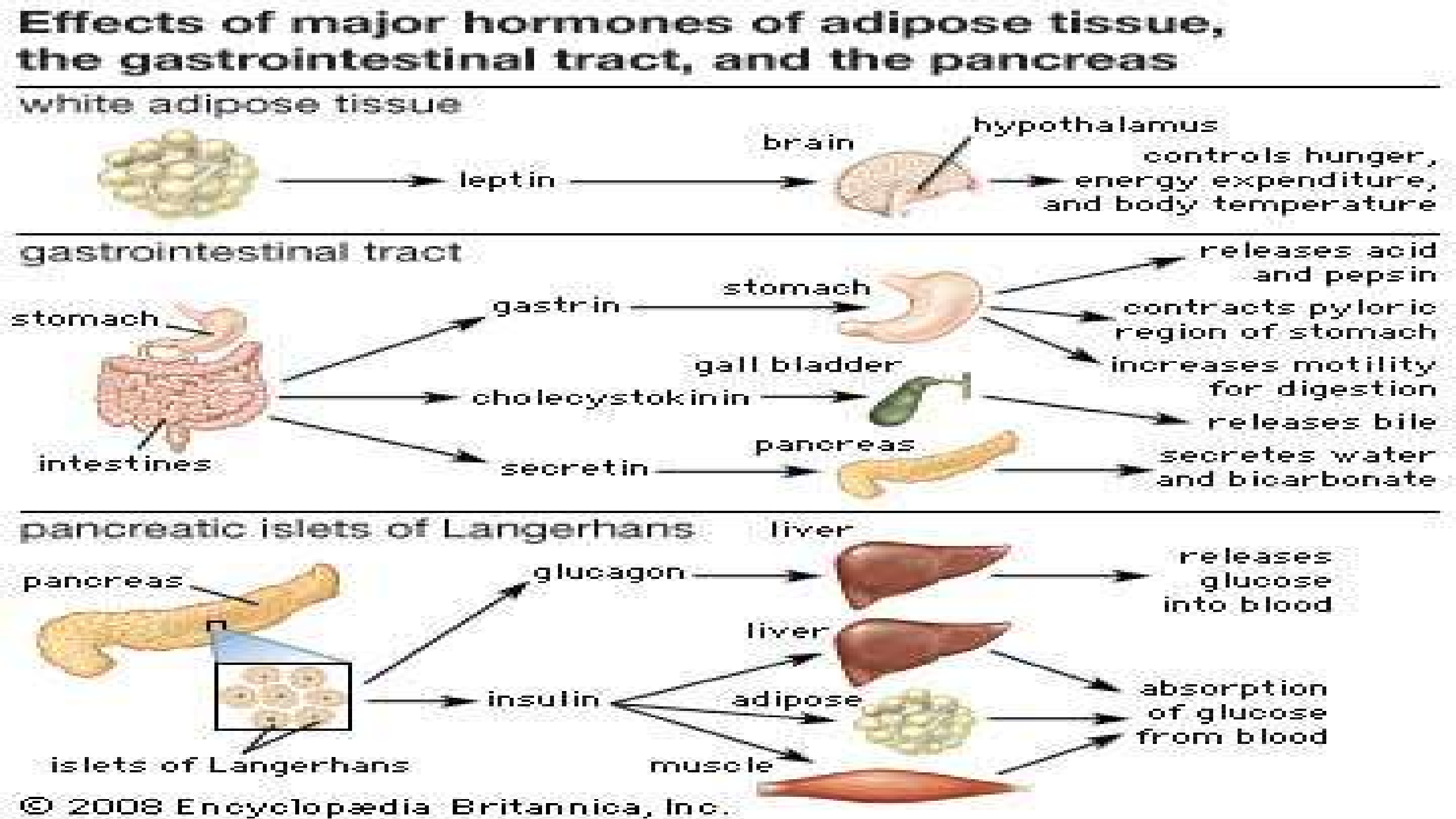
- **Higher CCK is especially marked during first trimester.**

•**INFANTS** have **very high levels of Gastrin to accompany their very high calorie-per-body-weight intake.**

•Gastrin interacts with hypothalamus to somehow promote anabolic growth in infants.



Effects of major hormones of adipose tissue, the gastrointestinal tract, and the pancreas



Pancreatic physiology

Functional Anatomy of Pancreas

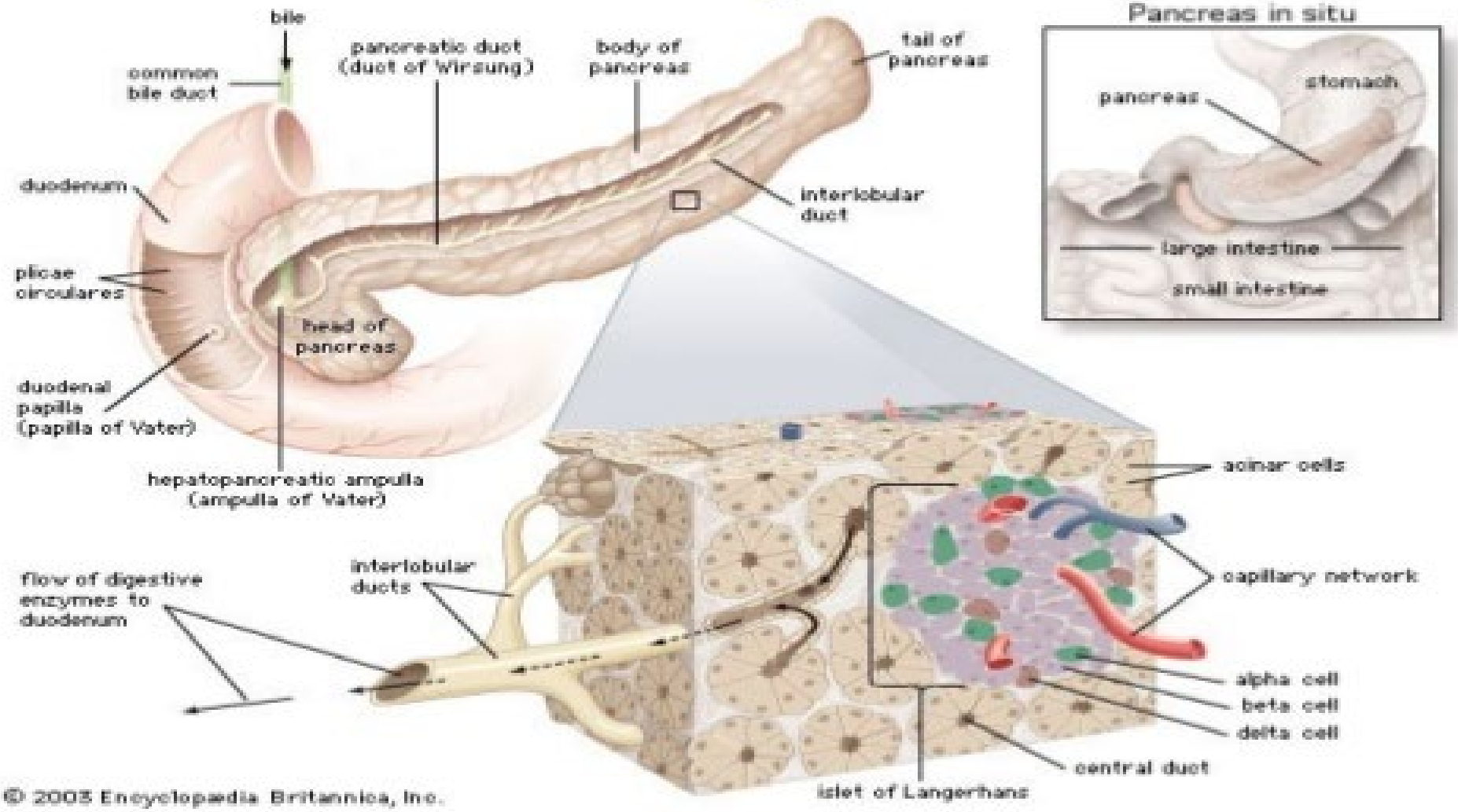
-an exocrine and endocrine gland.

→ 1 to 2 % endocrine cells

→ 80% exocrine,

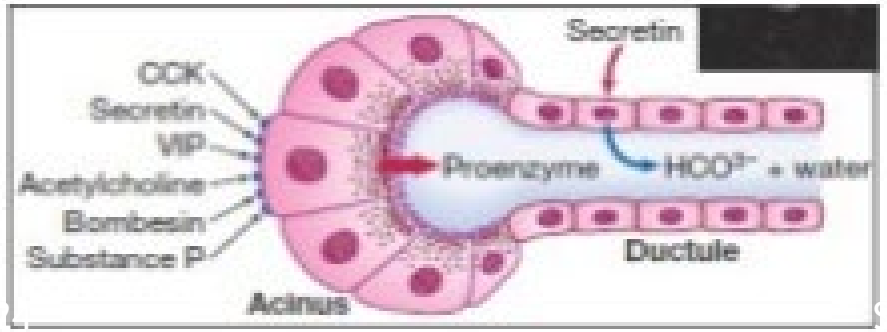
→ 18 to 19% ducts & blood vessels

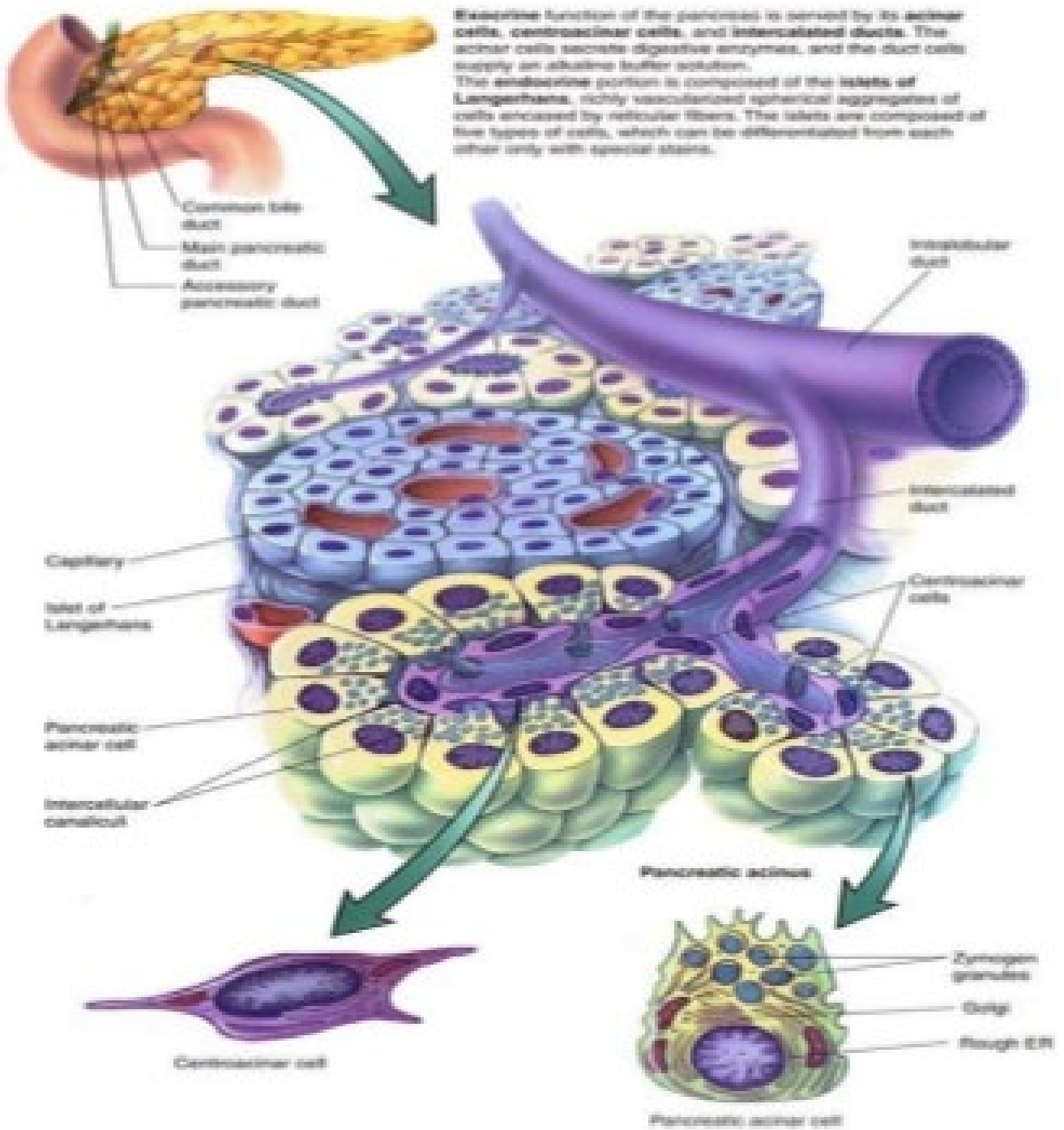
-insulin secretion begins at 10th week of gestation.



EXOCRINE PANCREAS

- ~1-2 L of secretion/day into the lumen of the duodenum
- The centroacinar and ductal cells secrete the aqueous HCO3--containing component of the pancreatic secretion.
- Acinar : proenzymes





Pancreatic Secretion

- Exocrine pancreas secretes ~1 L/day into duodenum
  - Fluid consists of HCO_3^- and enzymes
    - **HCO_3^-** neutralizes H^+ delivered to duodenum from stomach
    - **Enzymatic portion** digests carbohydrates, proteins, and lipids into absorbable molecules

- **Structure of Pancreatic Exocrine Glands**
  - Comprises ~90% of pancreas
    - **Rest of pancreatic tissue is endocrine pancreas and blood vessels**

  - **Acinar Cells**
    - **Line blind end of branching duct system**
    - **Secrete enzymatic portion**

  - **Ductal Cells**
    - **Line the ducts**
    - **Secrete aqueous HCO_3^- component**

Types of Pancreatic Secretions

1.Enzymatic Secretion

1. **Source:** Acinar cells.
2. **Regulation:** **Primarily regulated by CCK**, which binds to CCK receptors on acinar cells, stimulating the secretion of digestive enzymes (proteases, lipases, amylases, and nucleases).
3. **Neural Control:** **The vagus nerve (via ACh) also stimulates enzyme secretion through muscarinic receptors on acinar cells.**

2.Aqueous Secretion (Bicarbonate)

1. **Source:** Ductal cells.
2. **Regulation:** Secretin is the primary regulator, stimulating ductal cells to secrete bicarbonate-rich fluid. This fluid helps to neutralize the acidic chyme entering the duodenum from the stomach, providing an optimal pH for enzyme activity.
3. **Neural Control:** **The vagus nerve (via ACh**) also contributes to stimulating bicarbonate secretion, although its role is less significant compared to secretin.

Feedback Mechanisms

1.Negative Feedback:

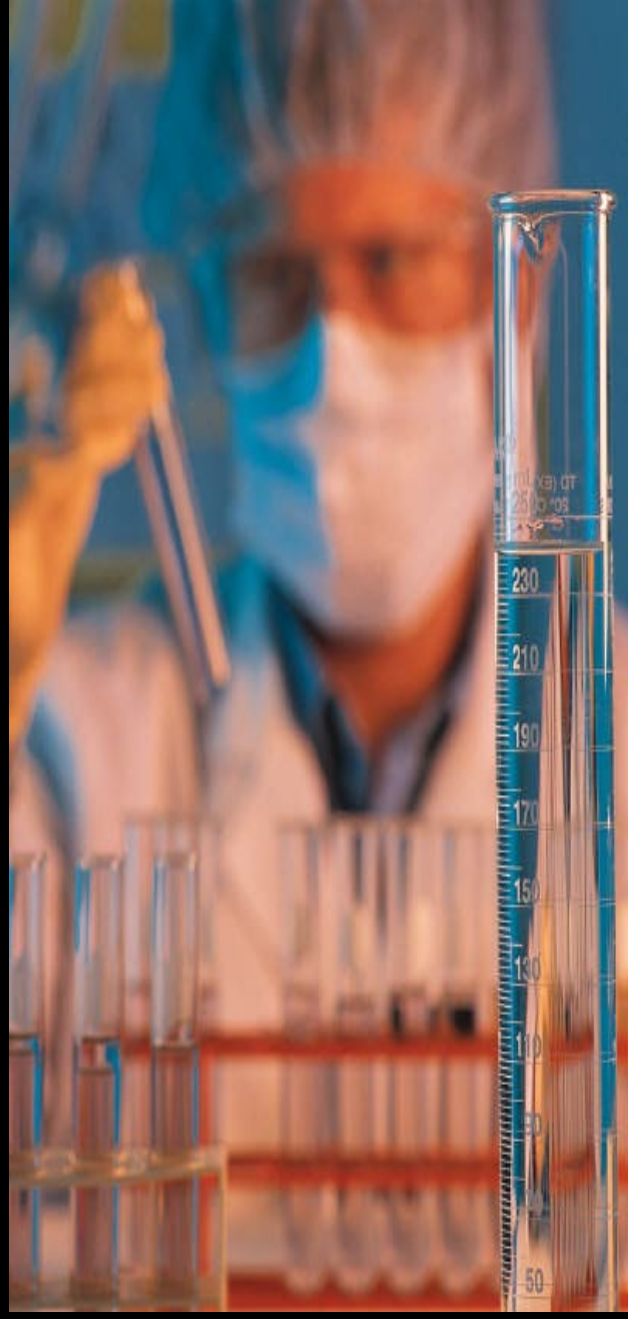
1. Once the chyme is neutralized and digestion is underway, the stimuli for secretin and CCK release diminish, reducing pancreatic secretion.

2. The presence of fats and proteins in the duodenum stimulates the release of somatostatin, which inhibits the release of CCK and secretin, thereby decreasing pancreatic secretion.

Paracrine Regulation

- **Enteroendocrine cells in the duodenum:** Release hormones like CCK and secretin in response to the presence of chyme, directly affecting nearby pancreatic cells.

- **Somatostatin:** Released by D cells in the stomach and duodenum, inhibits the release of several gastrointestinal hormones, including CCK and secretin, thus reducing pancreatic secretions.



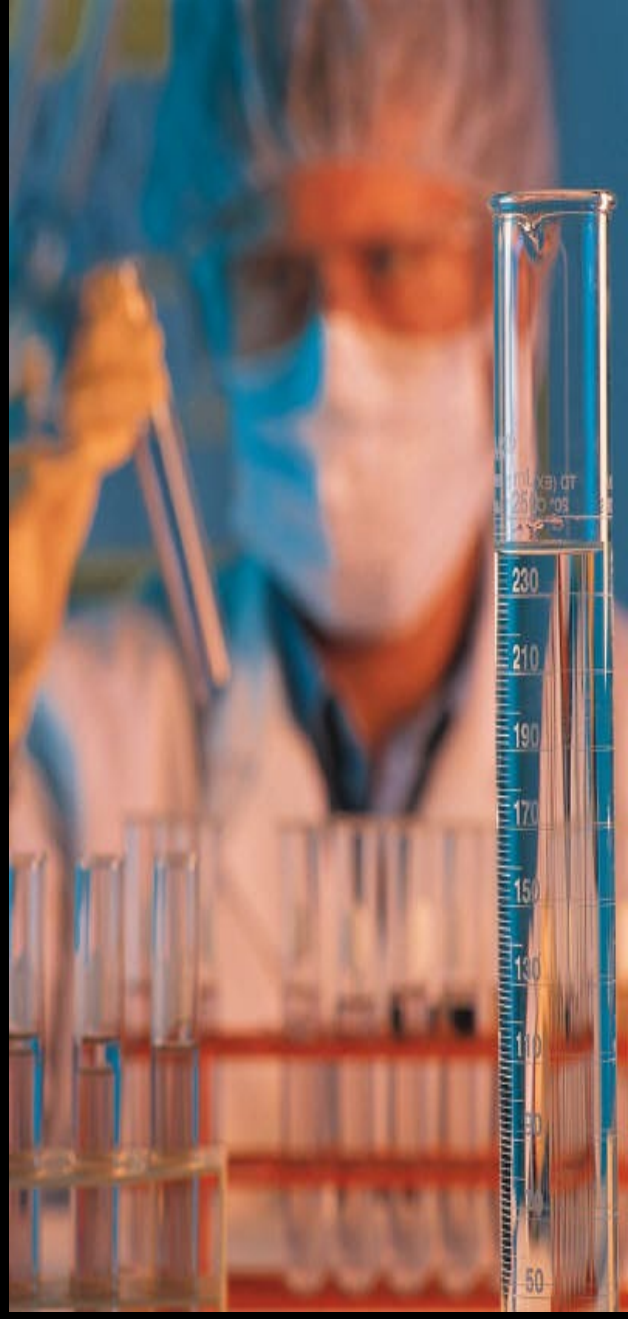
Summary

•**Neural Regulation:** Vagus nerve via acetylcholine stimulates both enzymatic and aqueous secretions.

•**Hormonal Regulation:**

- **Secretin:** Stimulates bicarbonate secretion from ductal cells.
- **CCK:** Stimulates enzyme secretion from acinar cells and potentiates the effect of secretin.
- **Gastrin:** Has a minor role in enzyme secretion.
- **Somatostatin:** Inhibits pancreatic secretion by suppressing CCK and secretin release.

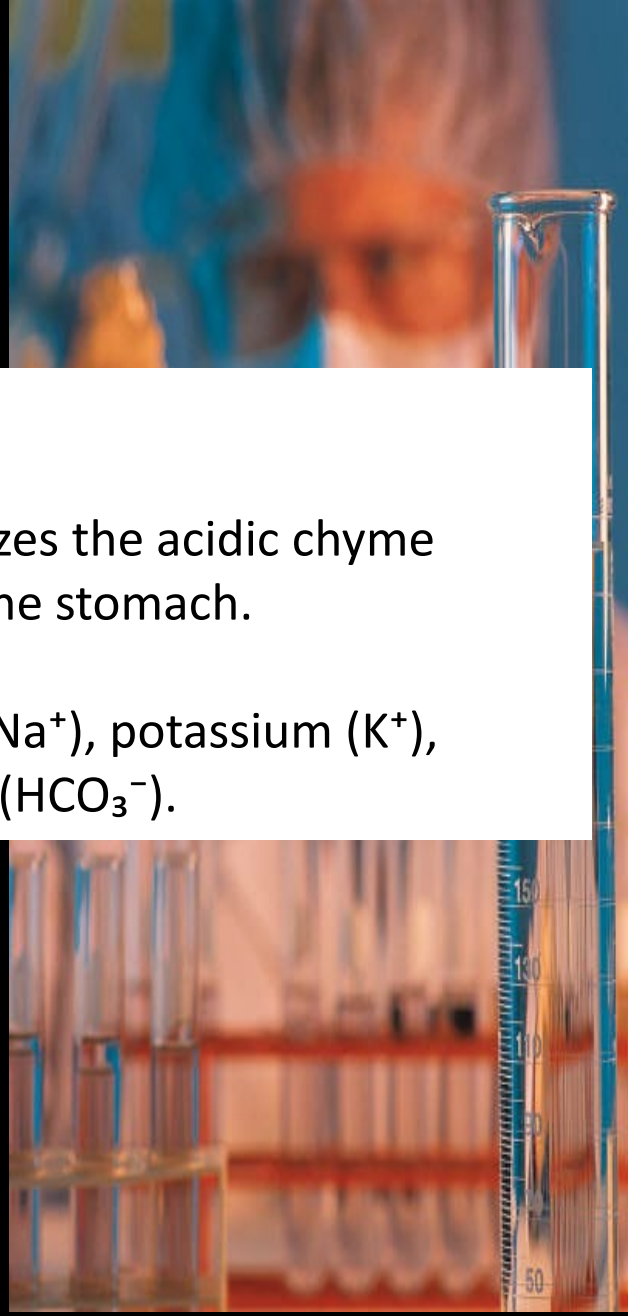
•**Feedback Mechanisms:** Ensure that pancreatic secretion is closely matched to the digestive needs and prevents over-secretion.



Components of Pancreatic Secretions

1.Enzymatic Component

1. **Proteases:** Break down proteins into peptides and amino acids.
    1. **Trypsinogen:** Activated to trypsin in the small intestine, which then activates other proteases.
    2. **Chymotrypsinogen:** Activated to chymotrypsin.
    3. **Procarboxypeptidase:** Activated to carboxypeptidase.
2. **Lipases:** Break down fats into fatty acids and glycerol.
    1. **Pancreatic lipase:** The primary enzyme for fat digestion.
3. **Amylase:** Breaks down carbohydrates into simple sugars.
    1. **Pancreatic amylase:** Continues the digestion of starches initiated by salivary amylase.
4. **Nucleases:** Break down nucleic acids into nucleotides.
    - **Ribonuclease** and **Deoxyribonuclease:** Digest RNA and DNA, respectively.



Aqueous Component

•**Bicarbonate (HCO_3^-):** Neutralizes the acidic chyme entering the duodenum from the stomach.

•**Electrolytes:** Include sodium (Na^+), potassium (K^+), chloride (Cl^-), and bicarbonate (HCO_3^-).

PANCREATIC SECRETIONS

- pancreatic secretions are crucial for digestion and consist of both enzymatic and aqueous (bicarbonate) components.
- These secretions aid in the breakdown of food and the neutralization of stomach acid in the small intestine.

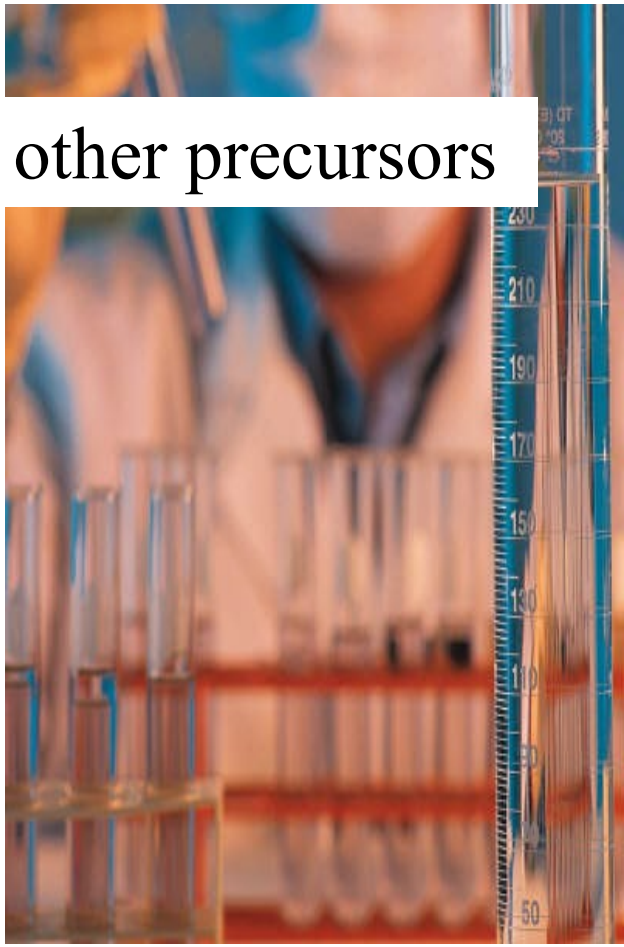
1. PROTEASES (70%)

Endopeptidases (trypsin, chymotrypsin, elastases)

Exopeptidases (carboxypeptidases)

trypsinogen → trypsin → activates all other precursors

enterokinase
(duct walls)



2. NUCLEASES (DNAase, RNAase)

3. PANCREATIC AMYLASE (hydrolyse starch and gl;ycogen)

4. **PANCREATIC** LIPASE (triglycerides → **fatty acids and glycerol)**

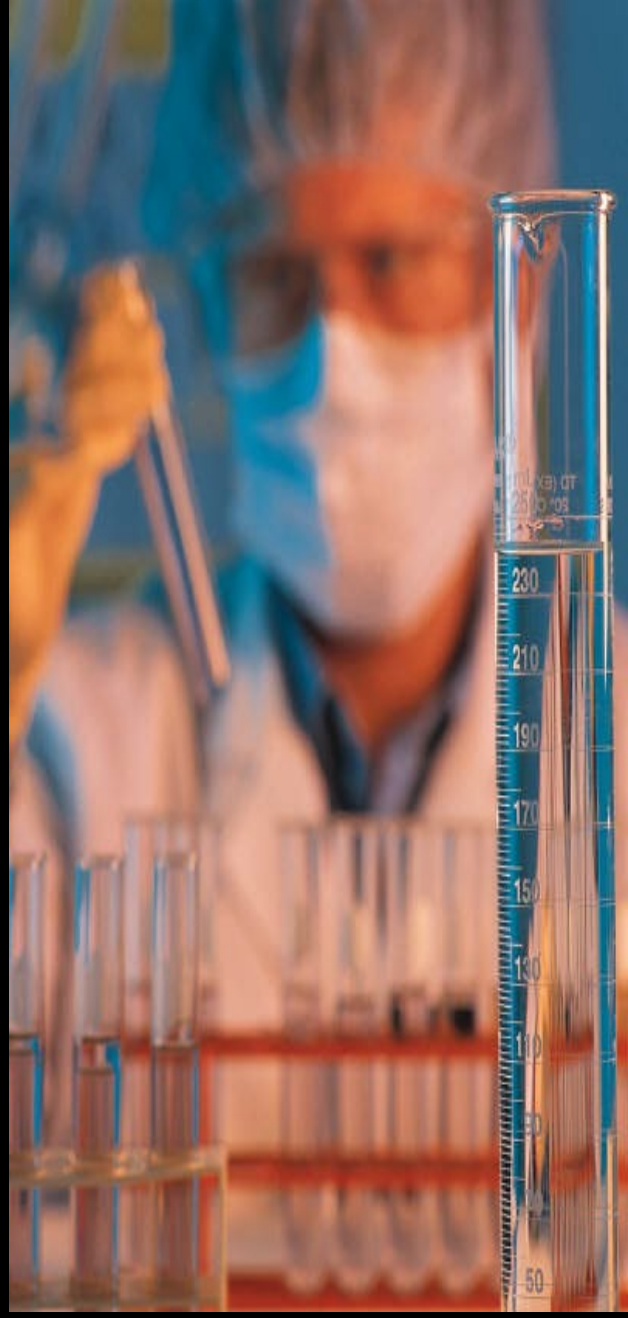
Regulation of Pancreatic Secretion

- Acinar cells (enzymatic secretion)
  - Receptors for CCK and muscarinic receptors for ACh
  - **CCK** is most important stimulant
    - I cells secrete CCK in presence of amino acids and fatty acids in intestinal lumen
  - **ACh** also stimulates enzyme secretion

- Ductal cells (aqueous secretion of HCO_3^-)
  - Receptors for CCK, ACh, and secretin
  - **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

Digestive Enzymes and Their Actions

- **Trypsin:** Activates other proteases and breaks down proteins into smaller peptides.
- **Chymotrypsin:** Breaks down proteins into peptides.
- **Carboxypeptidase:** Cleaves amino acids from the carboxyl end of peptides.
- **Pancreatic Amylase:** Converts starches into maltose and dextrins.
- **Pancreatic Lipase:** Breaks down triglycerides into fatty acids and monoglycerides.
- **Ribonuclease and Deoxyribonuclease:** Digest RNA and DNA into nucleotides.



The regulation of pancreatic secretion is a highly coordinated process involving neural, hormonal, and paracrine signals to ensure that digestive enzymes and bicarbonate are released in appropriate amounts at the right times.

Phases of Pancreatic Secretion

1.Cephalic Phase

1. **Stimuli:** The sight, smell, taste, and thought of food.
2. **Mechanism:**
    1. These stimuli activate the vagus nerve (part of the parasympathetic nervous system), which stimulates the pancreas to secrete a small amount of digestive enzymes and bicarbonate.
    2. Acetylcholine (ACh), released by vagal nerve endings, acts on acinar cells to promote the secretion of digestive enzymes.

2.Gastric Phase

1. **Stimuli:** The presence of food in the stomach.
2. **Mechanism:**
    1. Gastric distension activates stretch receptors and triggers a vagovagal reflex that further stimulates the pancreas.
    2. Gastrin, a hormone released from G cells in the stomach, slightly enhances enzyme secretion from the pancreas.

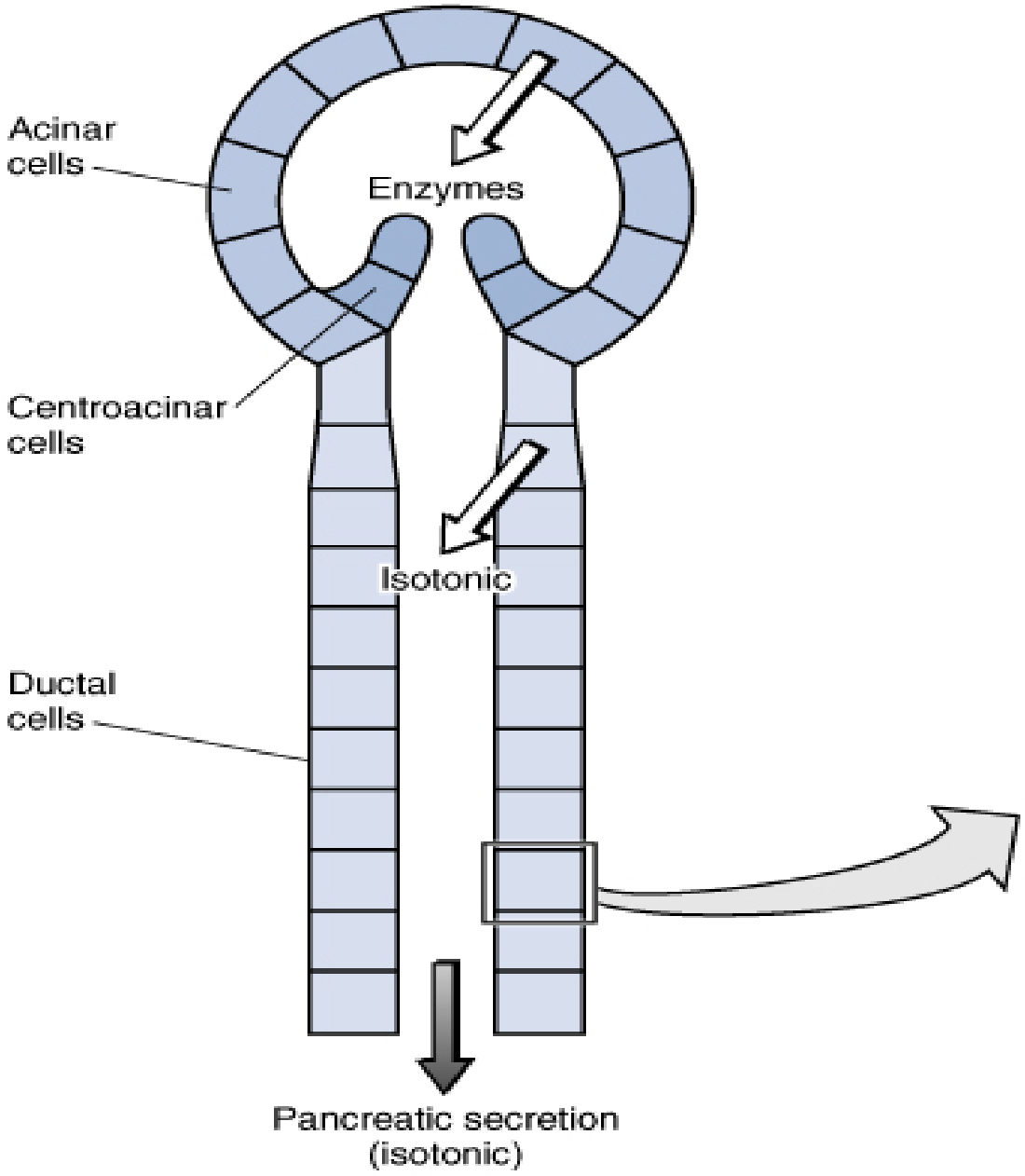
Intestinal Phase

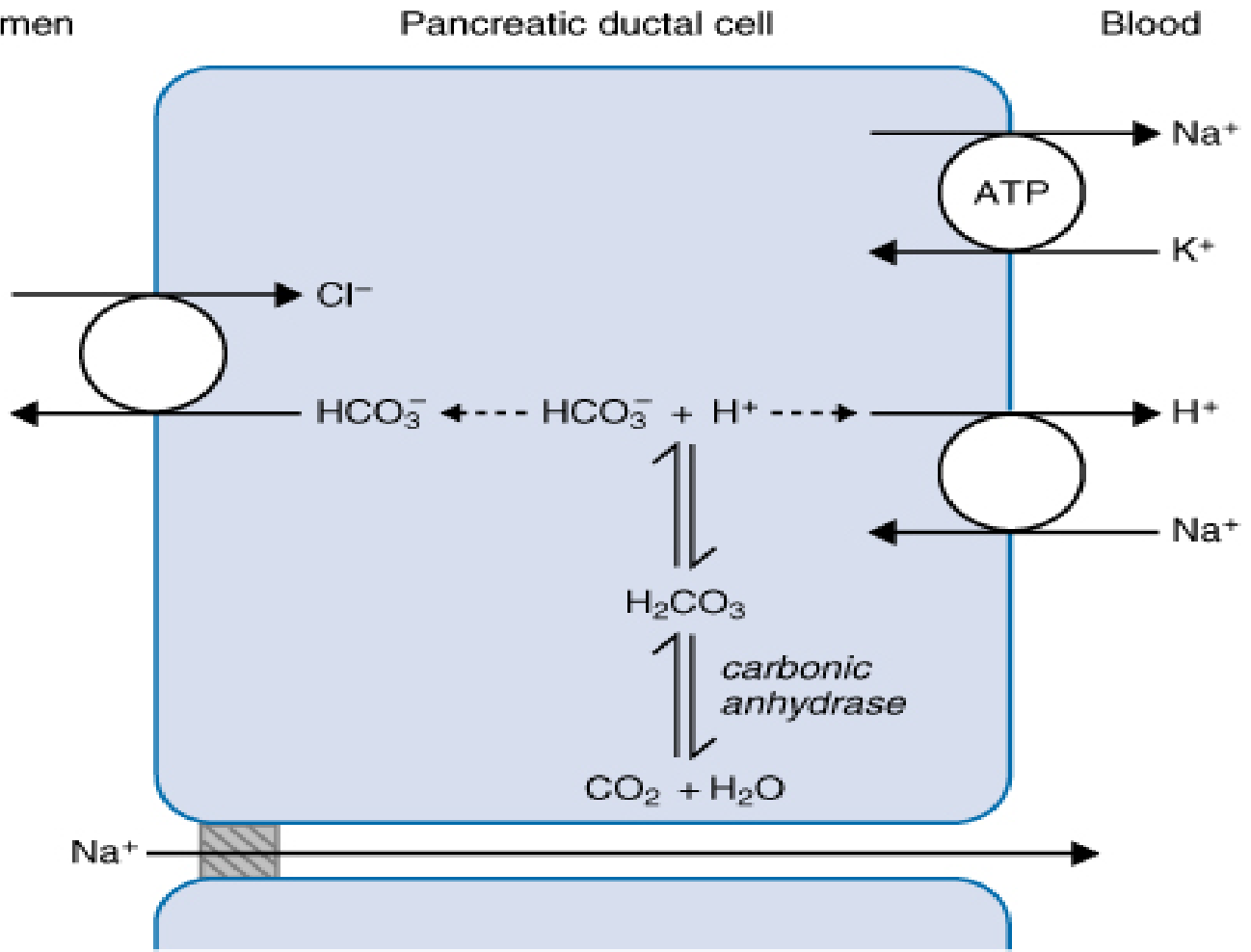
•**Stimuli:** Chyme entering the small intestine (particularly the duodenum).

•**Mechanism:**

- This phase is the most important for pancreatic secretion and involves several key hormones:
    - **Secretin:** Released by S cells in the duodenum in response to acidic chyme. Secretin stimulates the duct cells of the pancreas to secrete bicarbonate-rich fluid, which neutralizes the acid in the duodenum.
    - **Cholecystokinin (CCK):** Released by I cells in the duodenum in response to fats and partially digested proteins. CCK stimulates acinar cells to release enzyme-rich pancreatic juice. It also enhances the effects of secretin.
    - **Gastric Inhibitory Peptide (GIP) and Vasoactive Intestinal Peptide (VIP):** These hormones have a minor role in stimulating pancreatic secretion.

PANCREATIC SECRETION

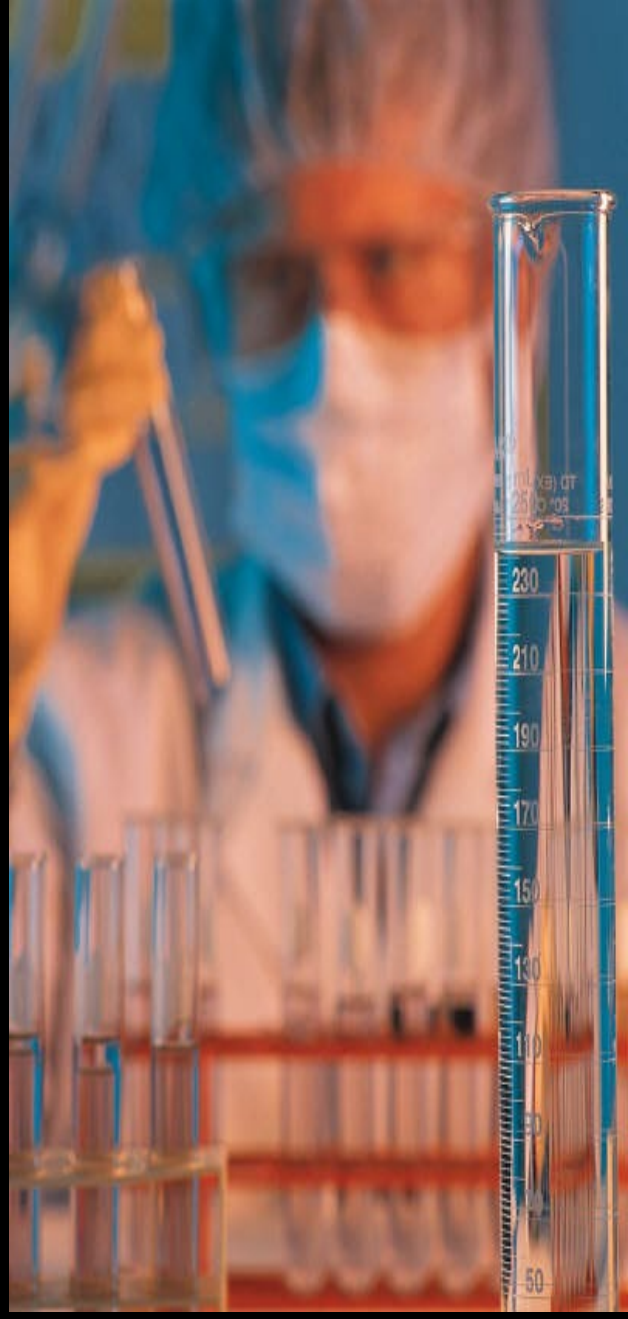


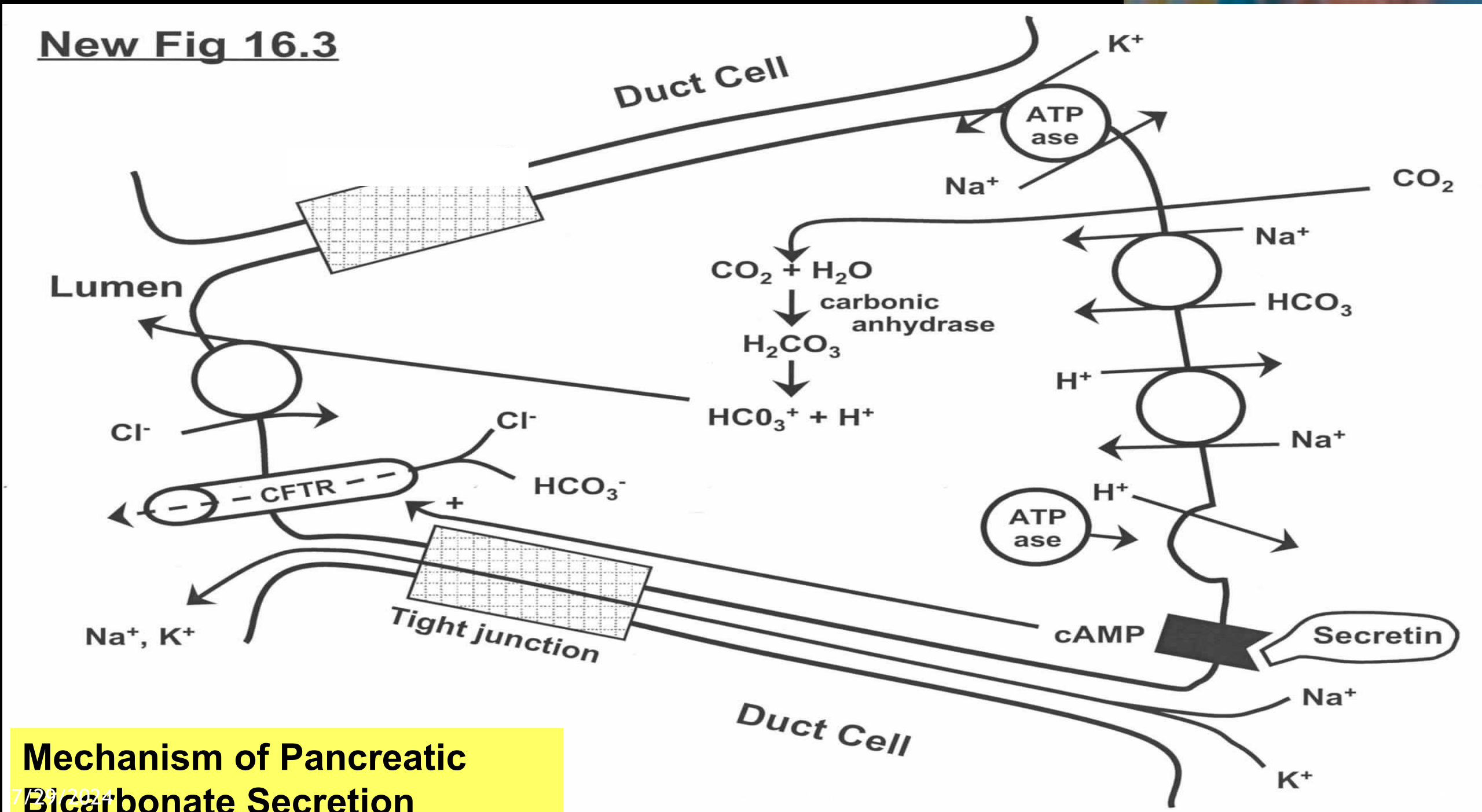


$HCO3^-$ Secretion

- **Apical membrane of ductal cells contains a Cl^--HCO_3^- exchanger**
- **Basolateral membrane contains Na^+-K^+ ATPase and a Na^+-H^+ exchanger**

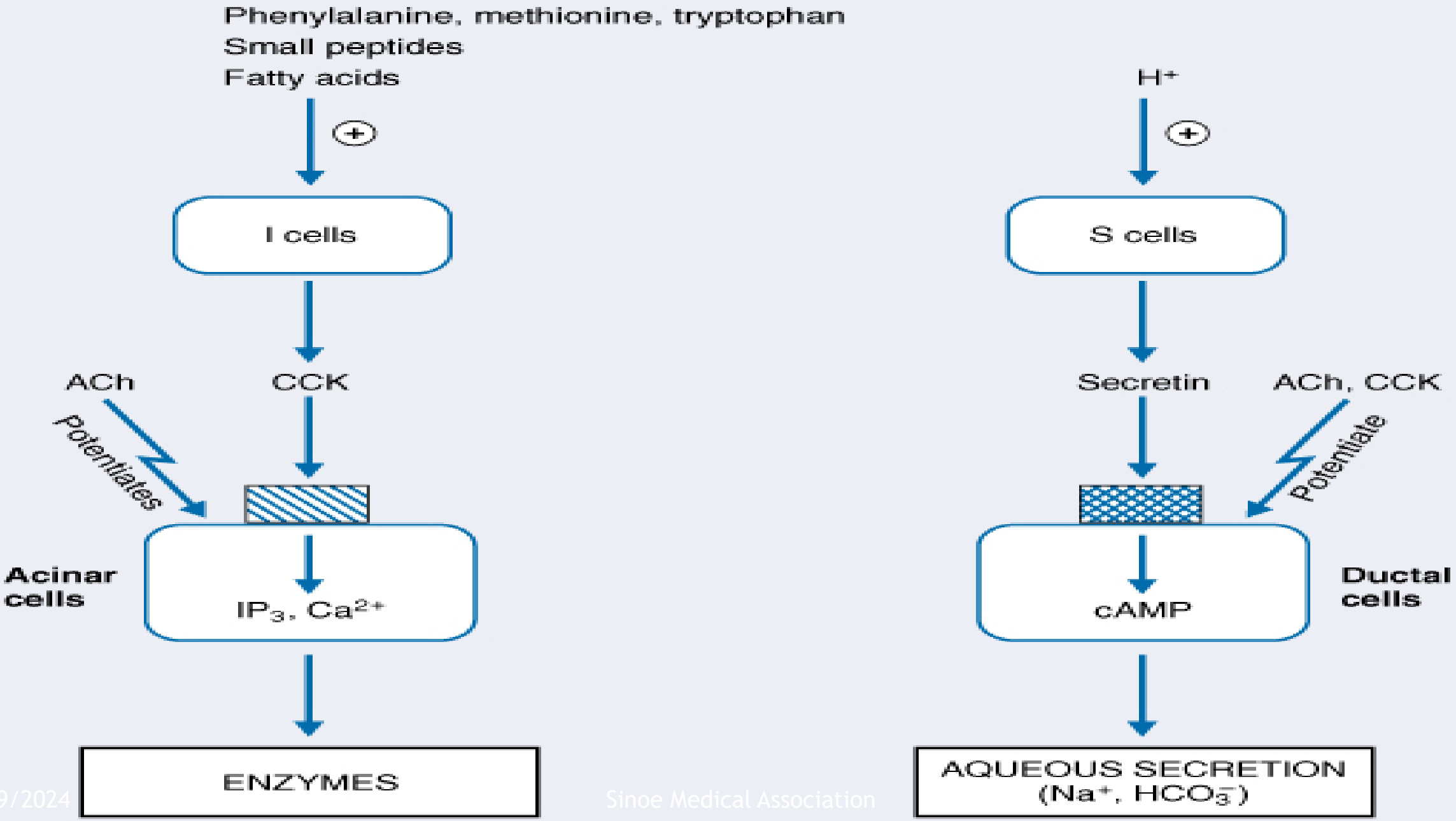
1. **CO_2 and H_2O combine in cells to form H+ and HCO_3^-**
2. **HCO_3^- is secreted into pancreatic juice by Cl^--HCO_3^- exchanger**
3. **H^+ is transported into blood by Na^+-H^+ exchanger**
    - **Absorption of H^+ causes acidification of pancreatic venous blood**

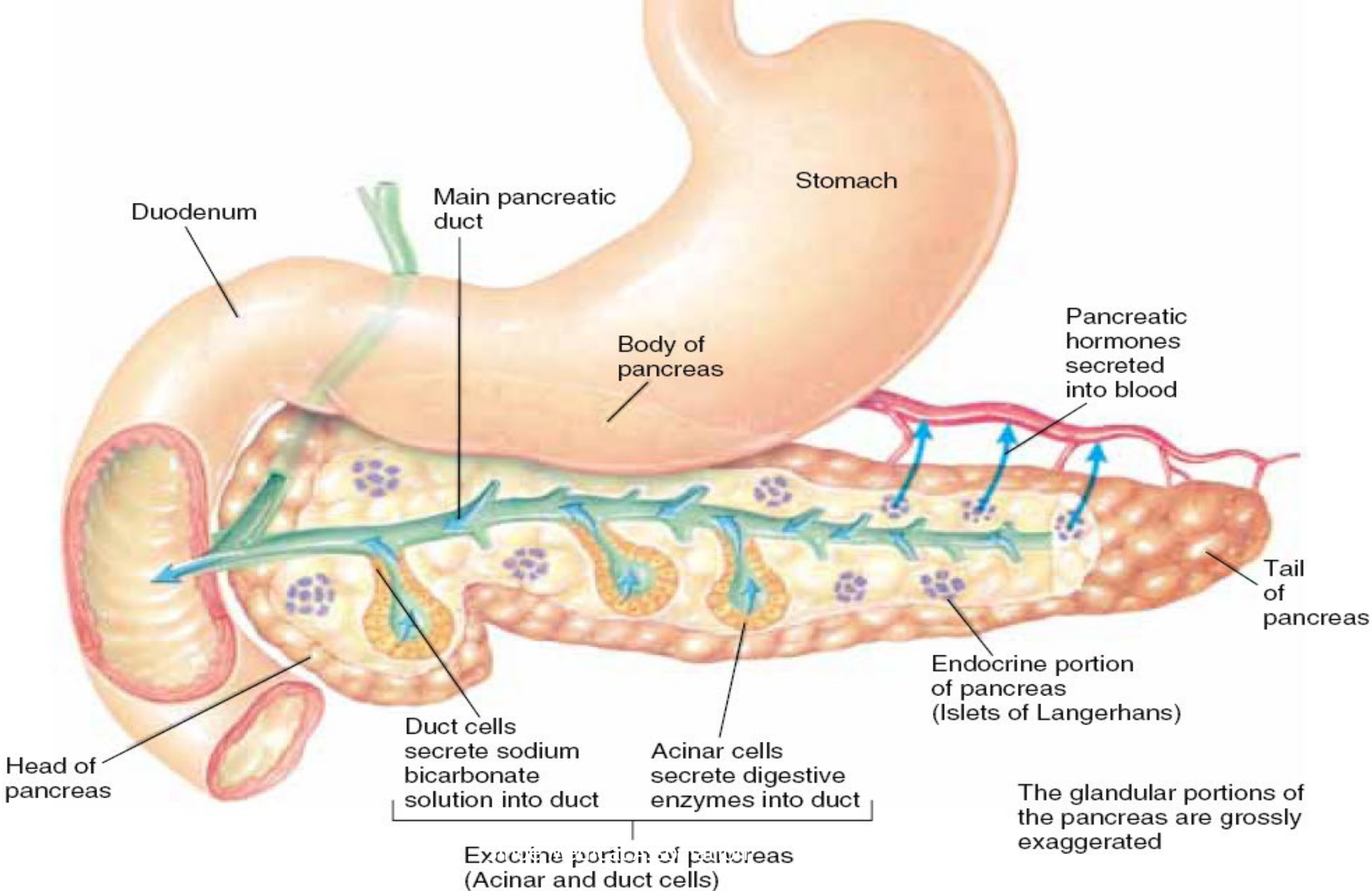




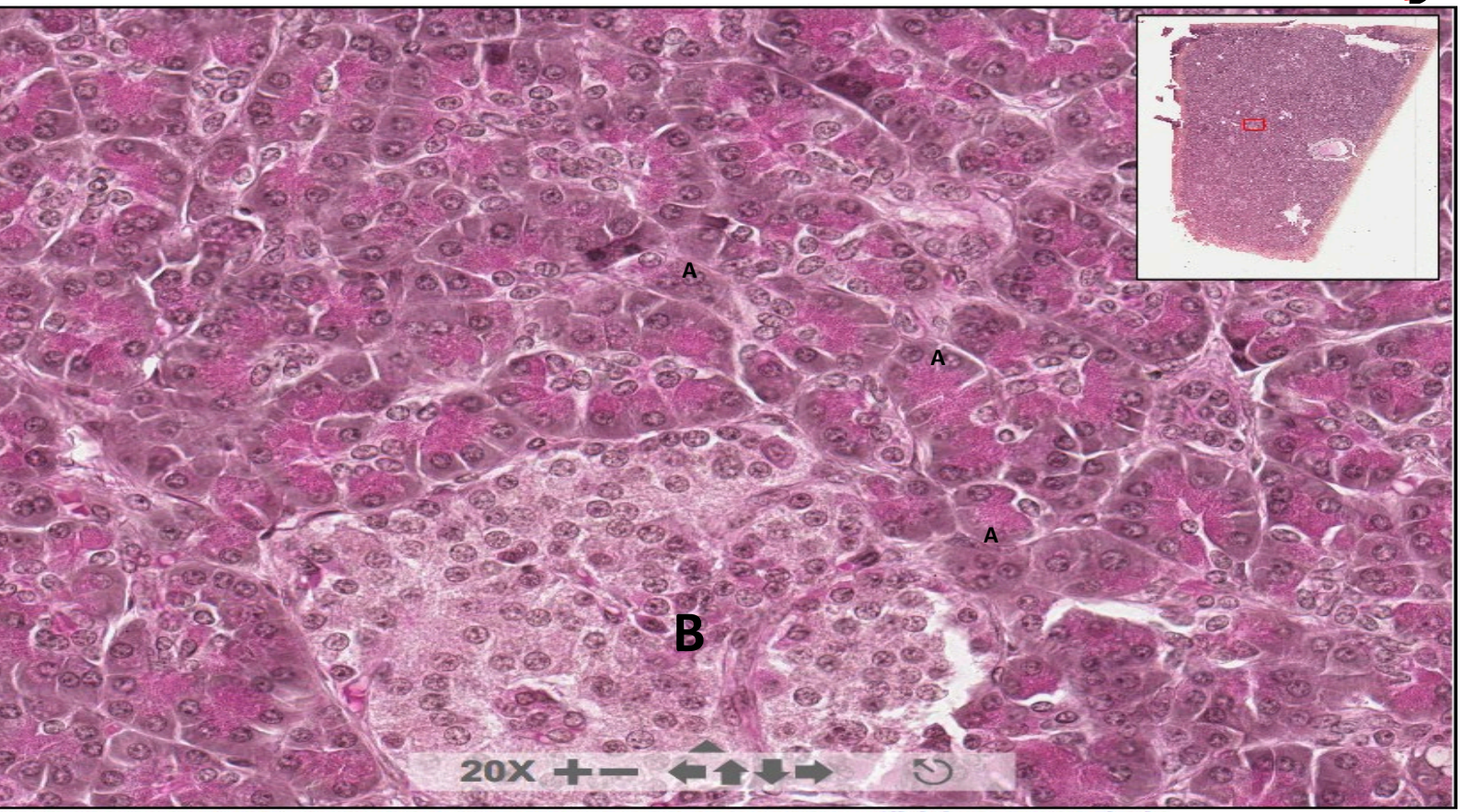
Mechanism of Pancreatic Bicarbonate Secretion

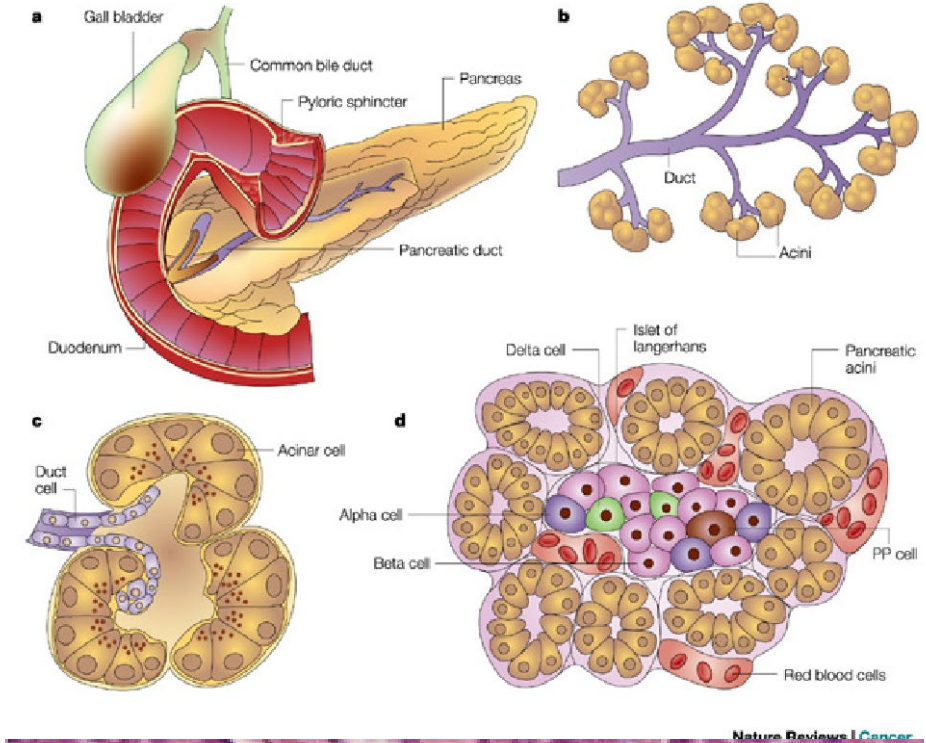
REGULATION OF PANCREATIC SECRETION

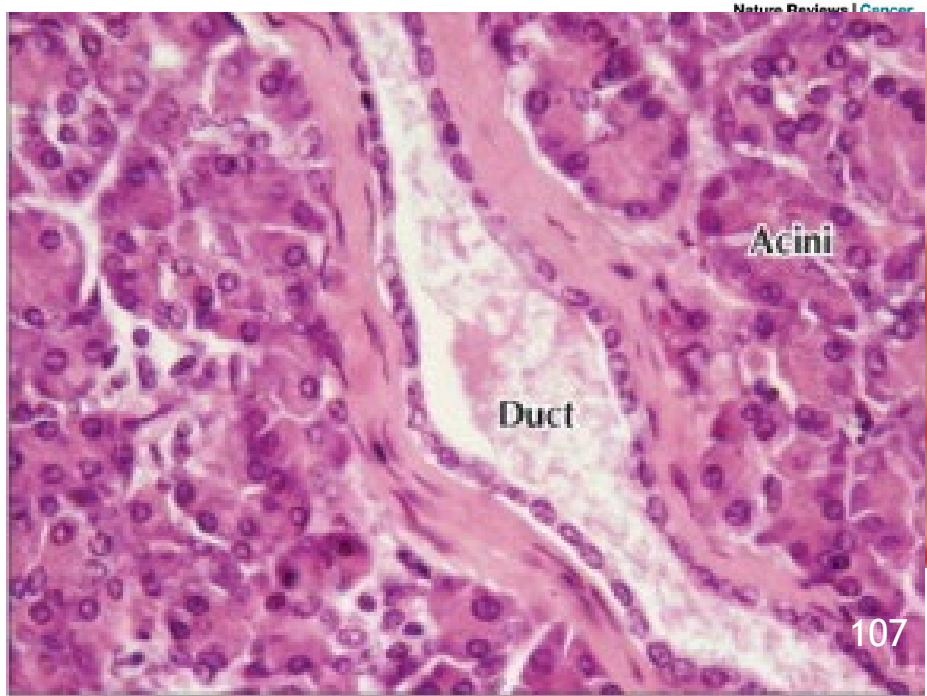



Stomach
Duodenum
Main pancreatic duct
Body of pancreas
Pancreatic hormones secreted into blood
Tail of pancreas
Endocrine portion of pancreas (Islets of Langerhans)
Head of pancreas
Duct cells secrete sodium bicarbonate solution into duct
Acinar cells secrete digestive enzymes into duct
Exocrine portion of pancreas (Acinar and duct cells)
The glandular portions of the pancreas are grossly exaggerated

Pancreatic Microanatomy





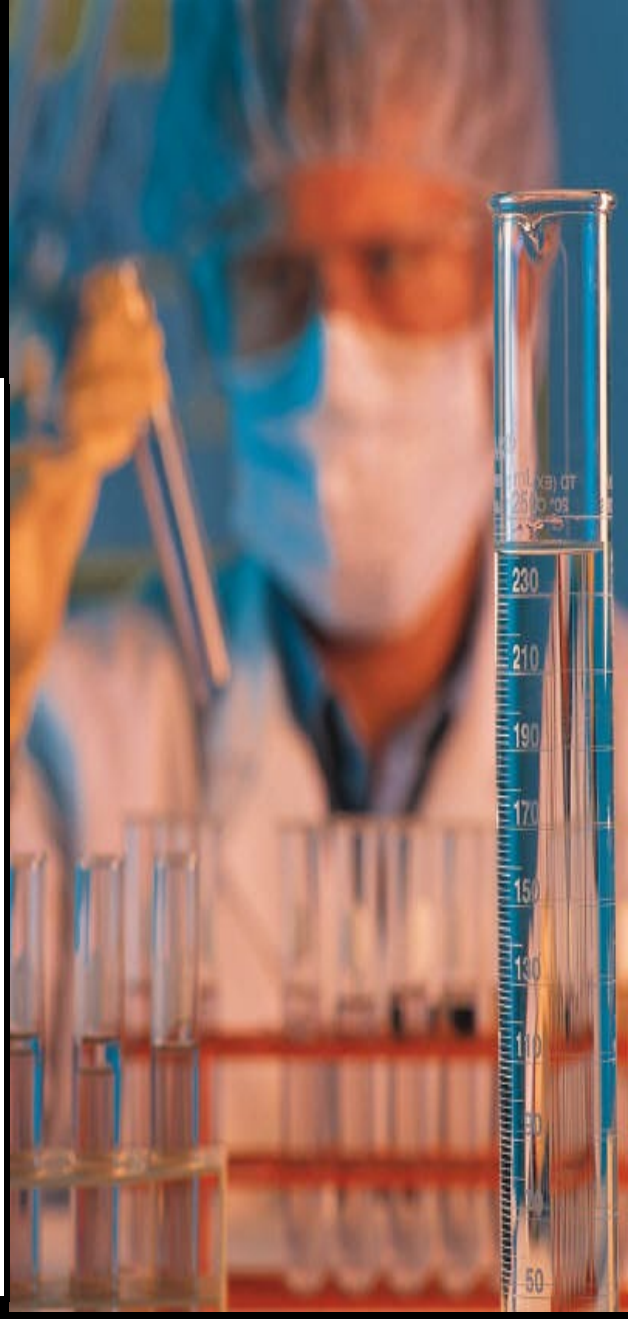


A. Exocrine pancreas-- ascinar cells filled with secretory granules, cuboidal duct cells secrete bicarbonate-rich fluid

B. Endocrine pancreas– Islet of Langerhans

Nature Reviews Cancer **2**, 897-909 (December 2002) used with permission

- The endocrine cells are the islets of Langerhans:
  - There are five types of cells in the islets of Langerhans:
  - **beta cells secrete insulin**;
  - **alpha cells** secrete glucagon;
  - **PP cells** secrete pancreatic polypeptide;
  - **delta cells** secrete somatostatin;
  - **epsilon cells** secrete ghrelin.



- **Exocrine function** - Secretes pancreatic juice which breaks down all categories of foodstuff Water solution of enzymes and electrolytes (primarily HCO3-)
  - Neutralizes acid chyme
  - Provides optimal environment for pancreatic enzymes

- **Enzymes are released in inactive form and activated in the duodenum**
  - Examples include
    - Trypsinogen is activated to trypsin
    - Procarboxypeptidase is activated to carboxypeptidase

- **Active enzymes secreted**
  - Amylase, lipases, and nucleases
  - These enzymes require ions or bile for optimal activity

- **The pancreas also has an endocrine function - release of insulin and glucagon**
- Regulation of Pancreatic Secretion Secretin and CCK are released when fatty or acidic chyme enters the duodenum
- CCK and secretin enter the bloodstream
- Upon reaching the pancreas:
  - CCK induces the secretion of enzyme-rich pancreatic juice
  - Secretin causes secretion of bicarbonate-rich pancreatic juice

Pancreatic Secretions:

- Hydrelatic (SET IN MOTION OR EFFECT OF STIMULATION)
  - HCO_3^- rich aqueous fluid
  - neutralizes stomach HCl
  - dilutes the chyme

- **Ecbolic** = CREATE A CONTRACTION
  - enzyme rich secretion
  - Proteases - endopeptidases
  - **Trypsinogen ---> trypsin**
  - **Chymotrypsinogen --> chymotrypsin**
-
  - Proelastase --> elastase
  - Proteases - exopeptidases
  - Procarboxypeptidase --> carboxypeptidase
  - Proaminopeptidase --> aminopeptidase
-
  - **amylase**
  - **Lipases**
  - **Ribonuclease**
  - **Deoxyribonuclease**

Protease Activation

- Pancreatic secretion contains trypsinogen and trypsin inhibitor
- Enterokinase in intestine activates trypsin
- Trypsin inhibitor is diluted by chyme

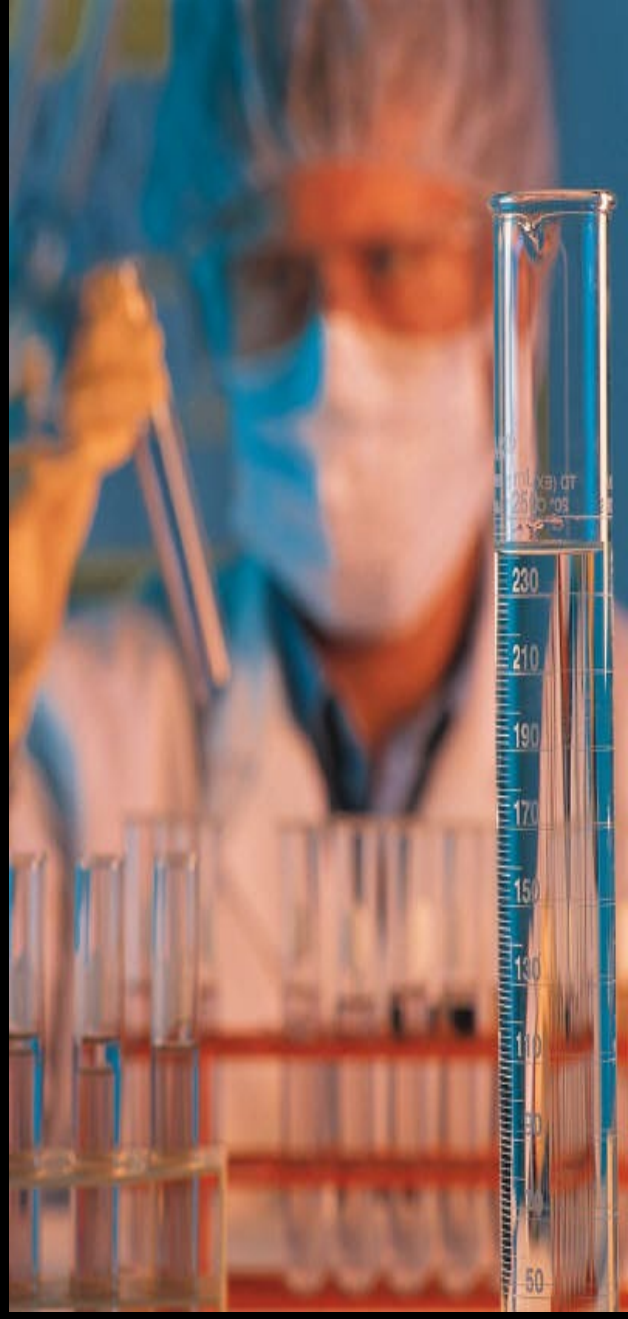
Hormonal Regulation of Pancreatic Secretion

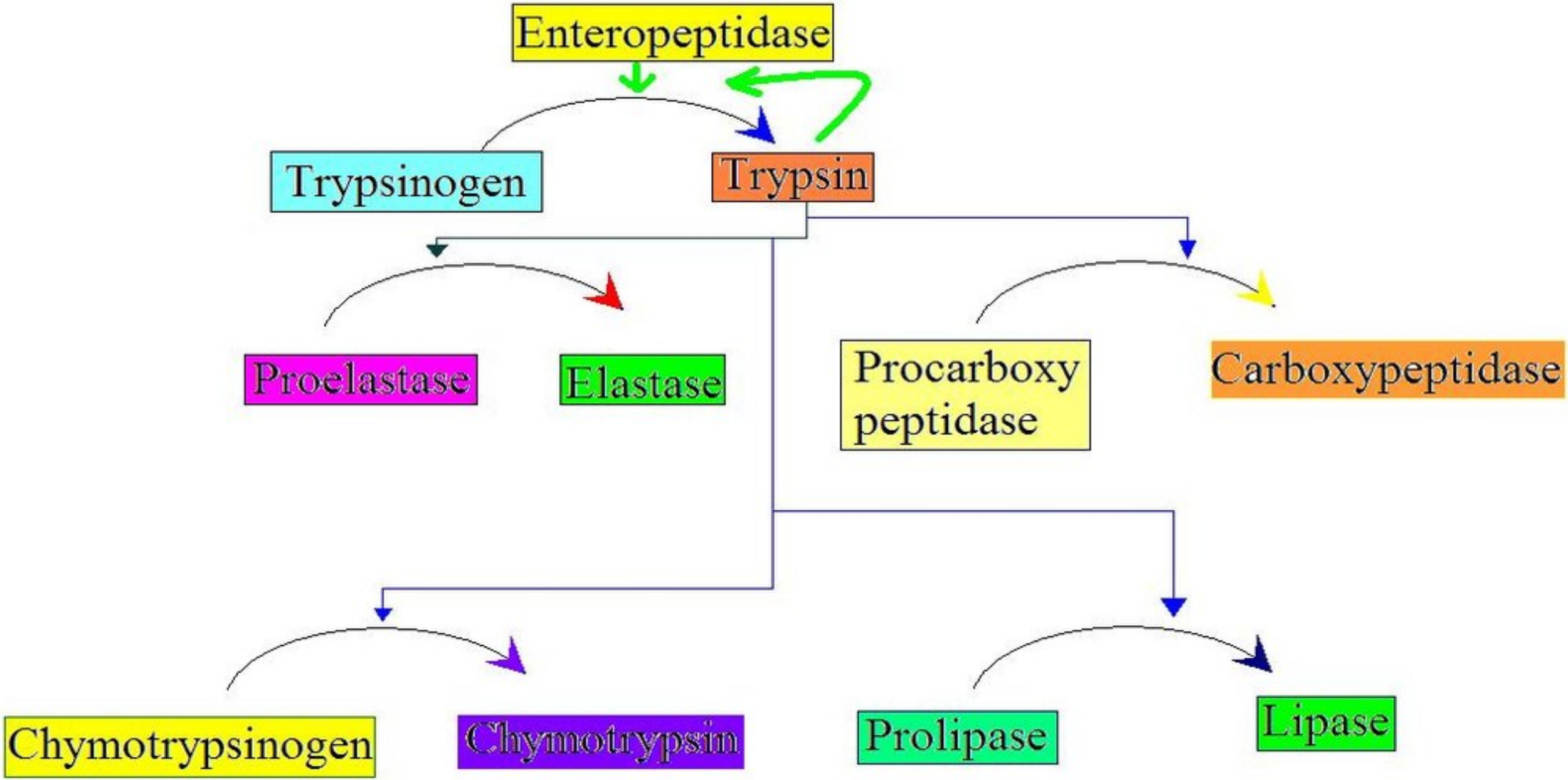
- Secretin peptide hormone pancreatic secretion rich in $HCO3^-$
- Cholecystokinin (CCK) peptide hormone (33 amino acids) pancreatic secretion rich in enzyme

Enzymes secreted:

- **Proteases**
  - *Chymotrypsinogen* and *Trypsinogen*
  - Digest proteins and peptides to single amino acids
- Pancreatic **lipase**
  - Digests triglycerides, monoglyceride and free fatty acids
- **Amylase**
  - Starch and maltose (disaccharides)

Other enzymes include *ribonuclease, gelatinase, elastase* etc.



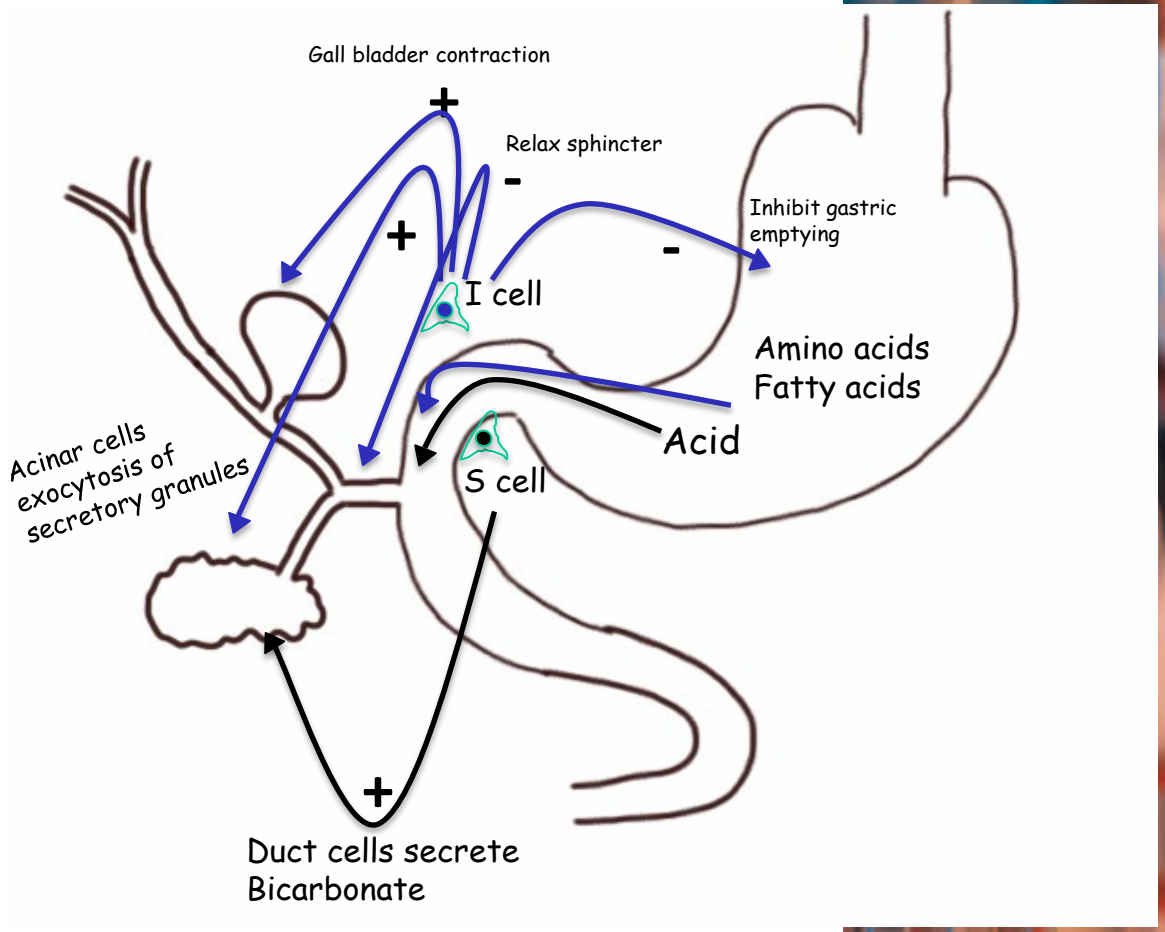

Enteropeptidase
Trypsinogen
Trypsin
Proelastase
Elastase
Procarboxy peptidase
Carboxypeptidase
Chymotrypsinogen
Chymotrypsin
Prolipase
Lipase

Acinus and Duct physiology

Organ system-based Regulation

- S cells Secretin- **'pH sensor'**
  - pH <4.5➔ activation
- I cells CCK- **'food sensor'**
  - Fatty and amino acids
  - Endocrine mechanism AND

  Vago-vagal reflex (CCK activates afferent vagus)
- CCK influences the following
  - GB contract
  - Sphincer of Oddi relax
  - Stomach ↓emptying
  - Ascini release enzymes
- Synergy between CCK and Secretin



REGULATION OF SECRETION

1. SECRETIN

food in stomach → release of stomach acid into duodenum → release of secretin into blood by duodenal cells → secretion of bicarbonate by duct cells → alkaline pH (ideal for pancreatic enzymes)

2. PANCREOZYMIN (cholecystokinen)

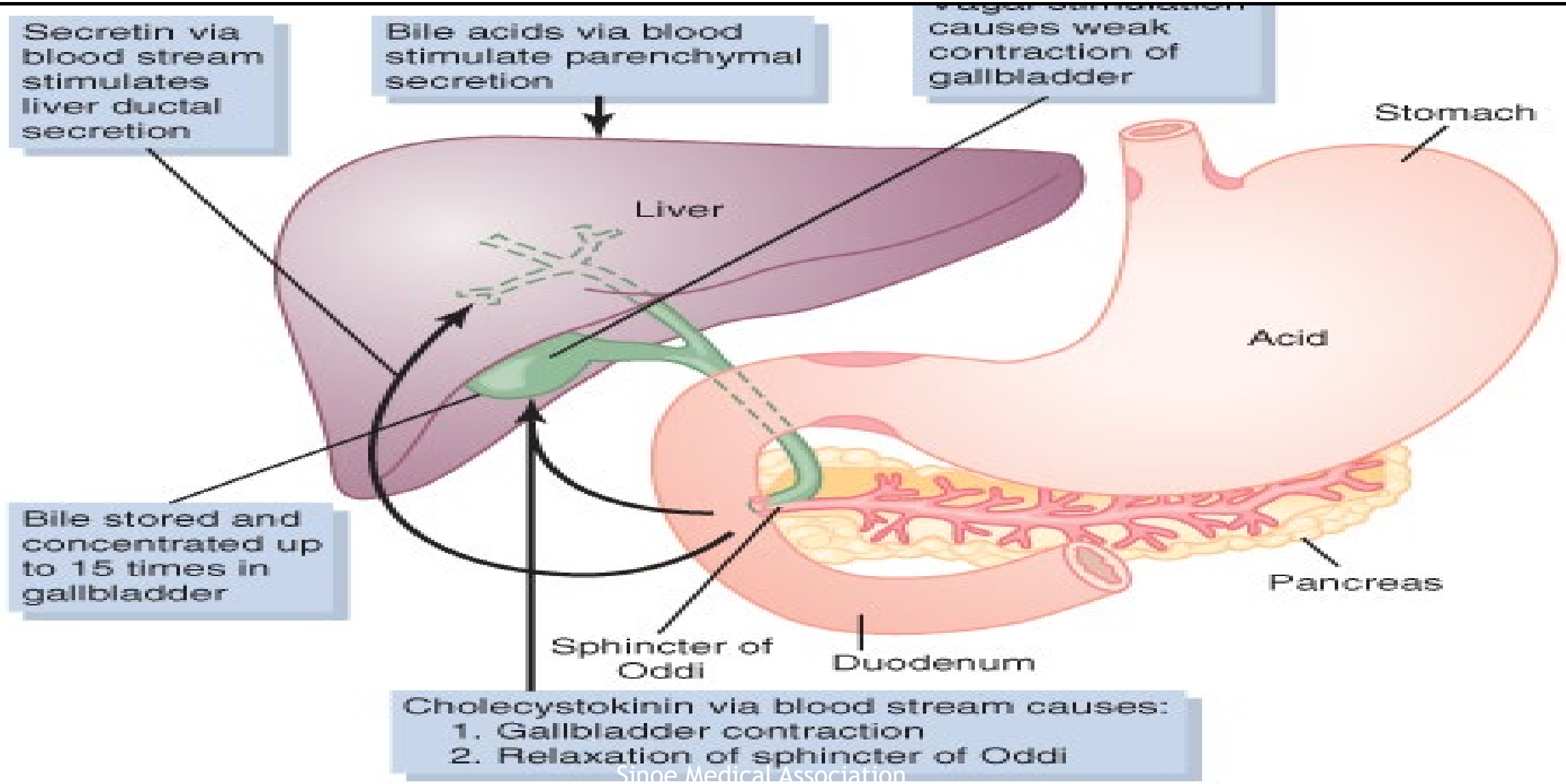
amino acids and fats in intestine → release of pancreozymin by intestinal mucosa into blood → relase of pancreatic enzymes into the intestine

3. GASTRIN

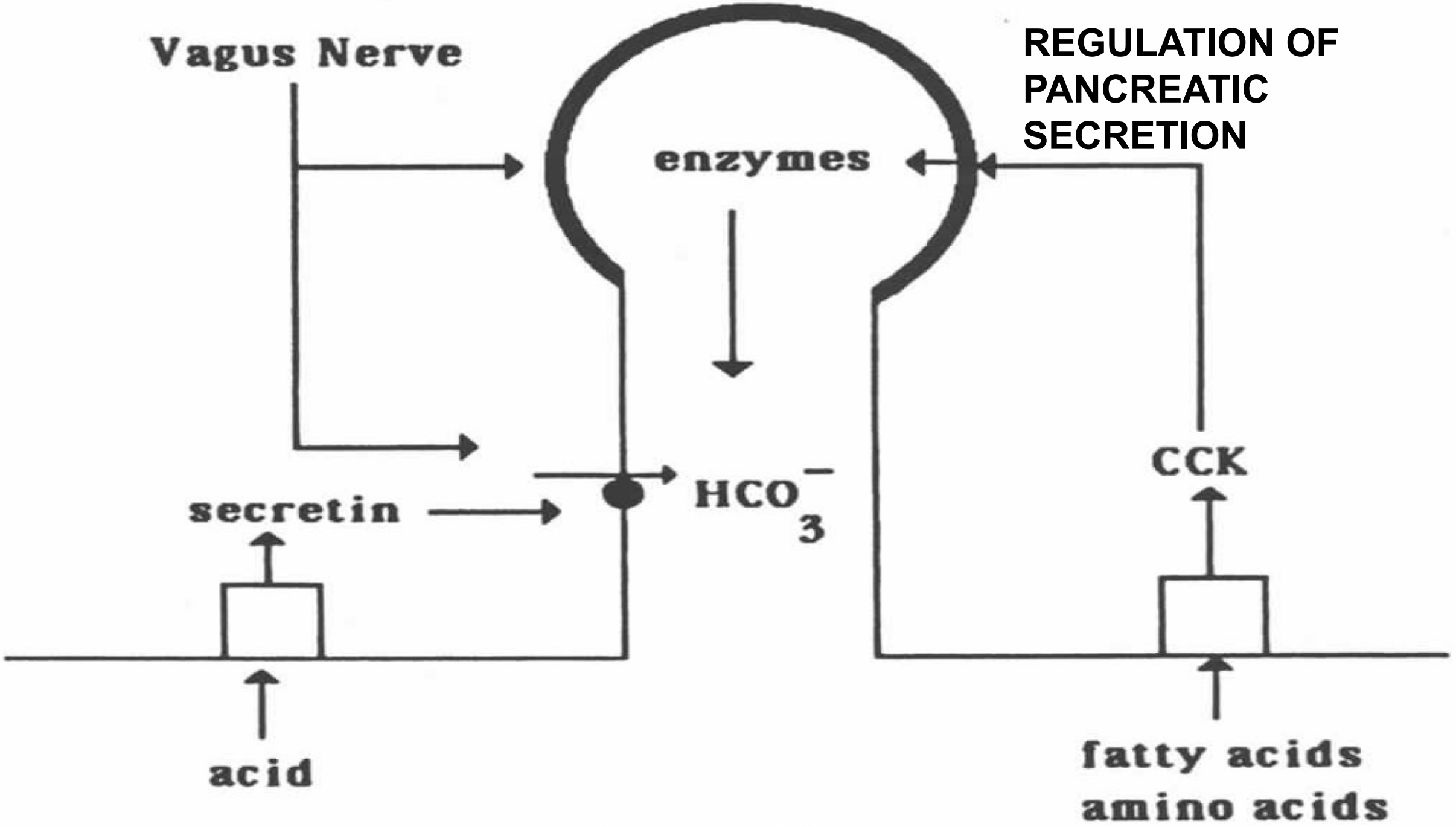
food in stomach → gastrin secretion by stomach mucosa → release of pancreatic enzymes into the intestine

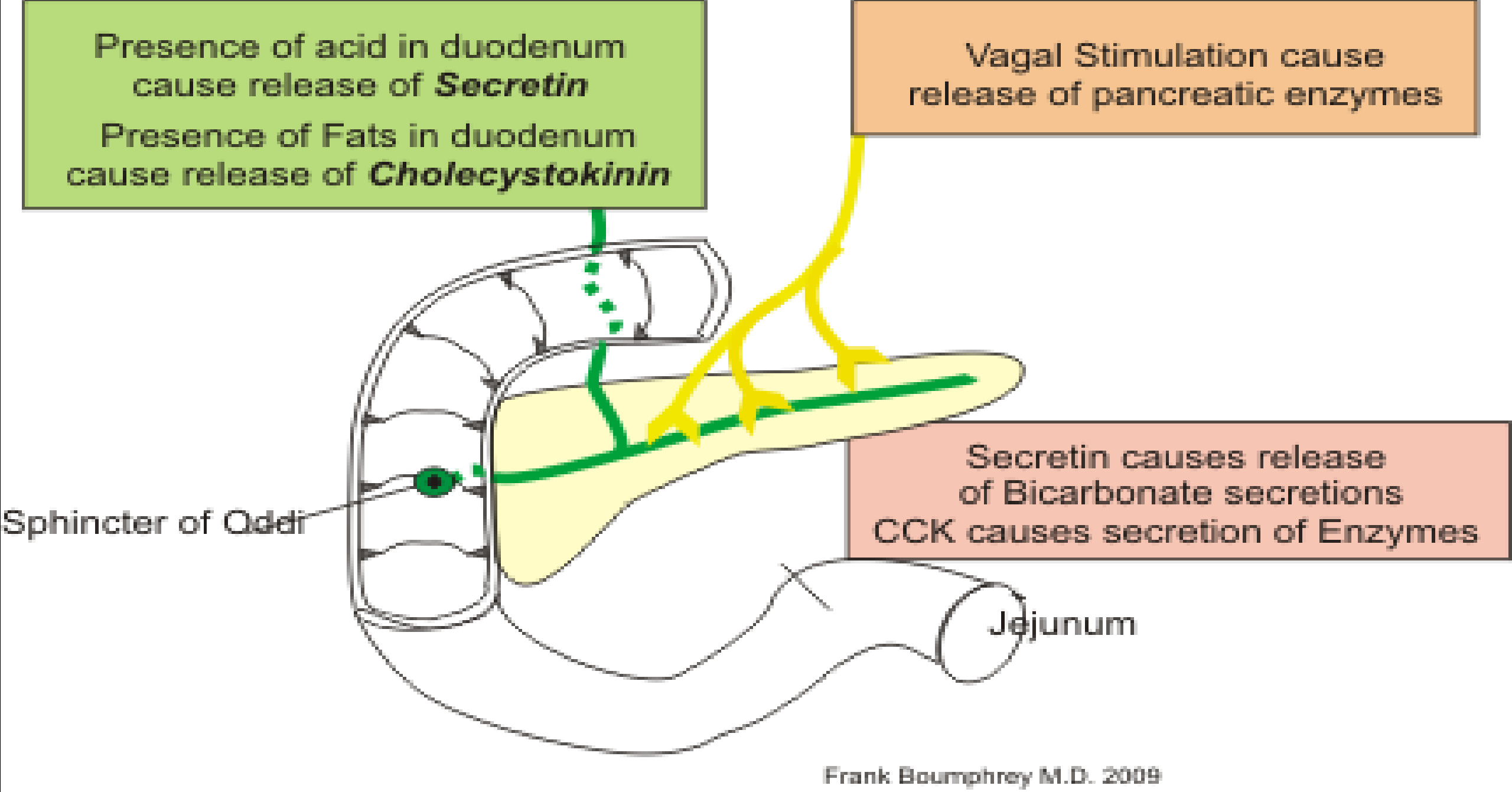
4. AUTONOMIC INNERVATION (vagus nerve)

Effect of secretin and CCK in bile secretion



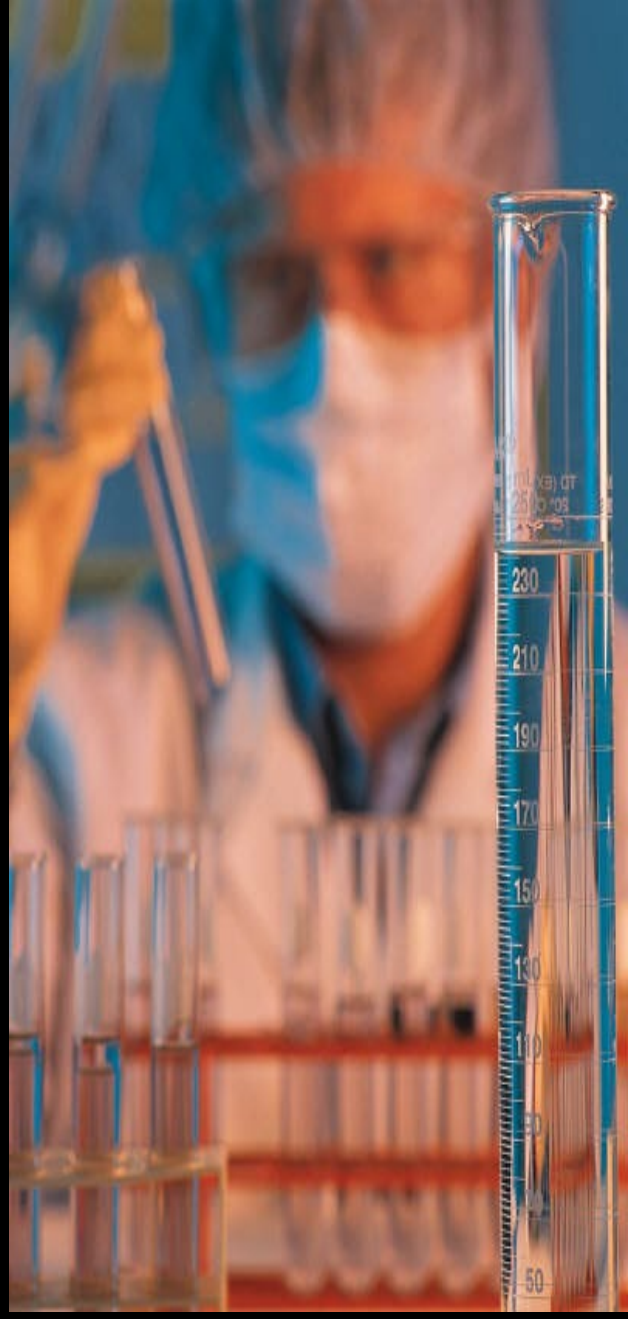
REGULATION OF PANCREATIC SECRETION





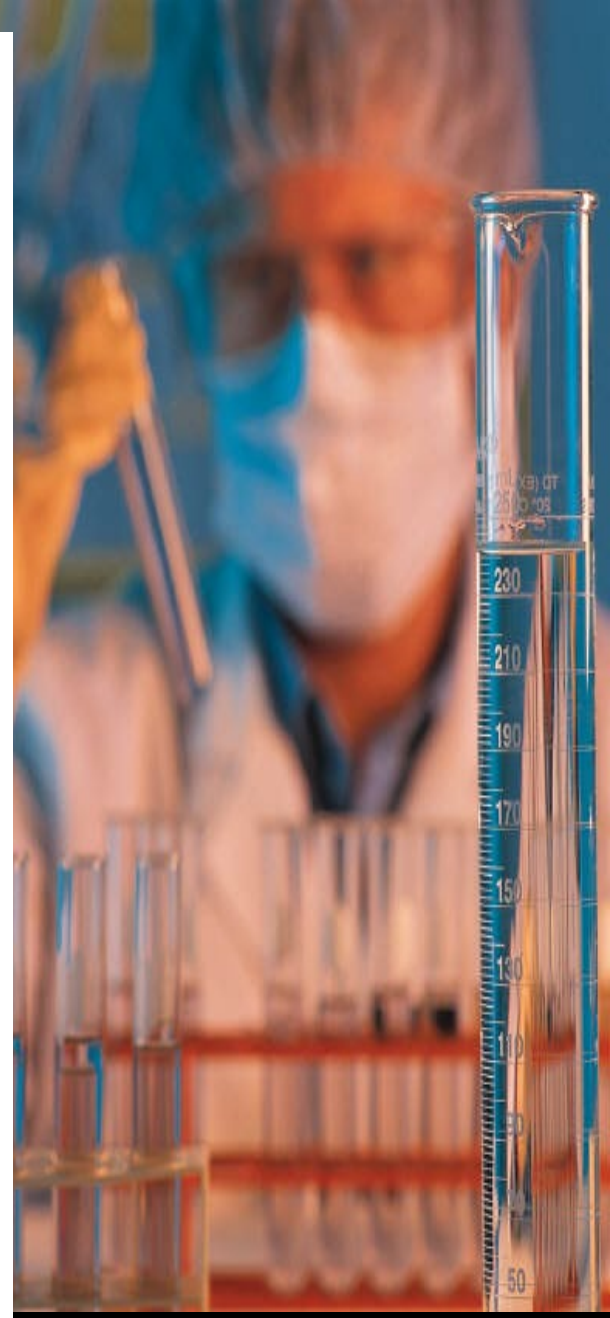
Control of Pancreatic Secretions

To resume hormones



The intestine has both endocrine and exocrine glands that produce hormones, enzymes, and alkaline mucinous material. The hormones released by the small intestine include:

- Gastrin produced by G-cells in the upper small intestine (but mostly found in the stomach)
- Cholecystokinin (CCK) produced by I-cells in the upper small intestine;
- secretin produced by the S-cells in the upper small intestine in response to decreased upper intestine pH;
- Gastric inhibitory peptide (GIP) produced by K-cells in the upper small intestine in response to fat, amino acids, and glucose
- Pro-glucagon produced by the L-cells in the distal ileum and colon in response to glucose and fat
- Somatostatin produced by D-cells in the small intestine, including the stomach and pancreas
- Vasoactive intestinal polypeptide (VIP) produced by parasympathetic ganglia in the small intestine in response to distention
- Motilin produced by M-cells in the upper small intestine



Hormone/peptide	neurocrine	endocrine	paracrine
VIP	+		
Substance P	+		
Neuropeptide	+		
Somotostatin	+	+	+
Cholecystokinin	+	+	
Gastrin		+	
Secretin		+	
GIP		+	
Motilin		+	+
Neurotensin	?	+	+
Guanylin		+	+

TABLE 8–1. Neurotransmitters and Neuromodulators in the Enteric Nervous System

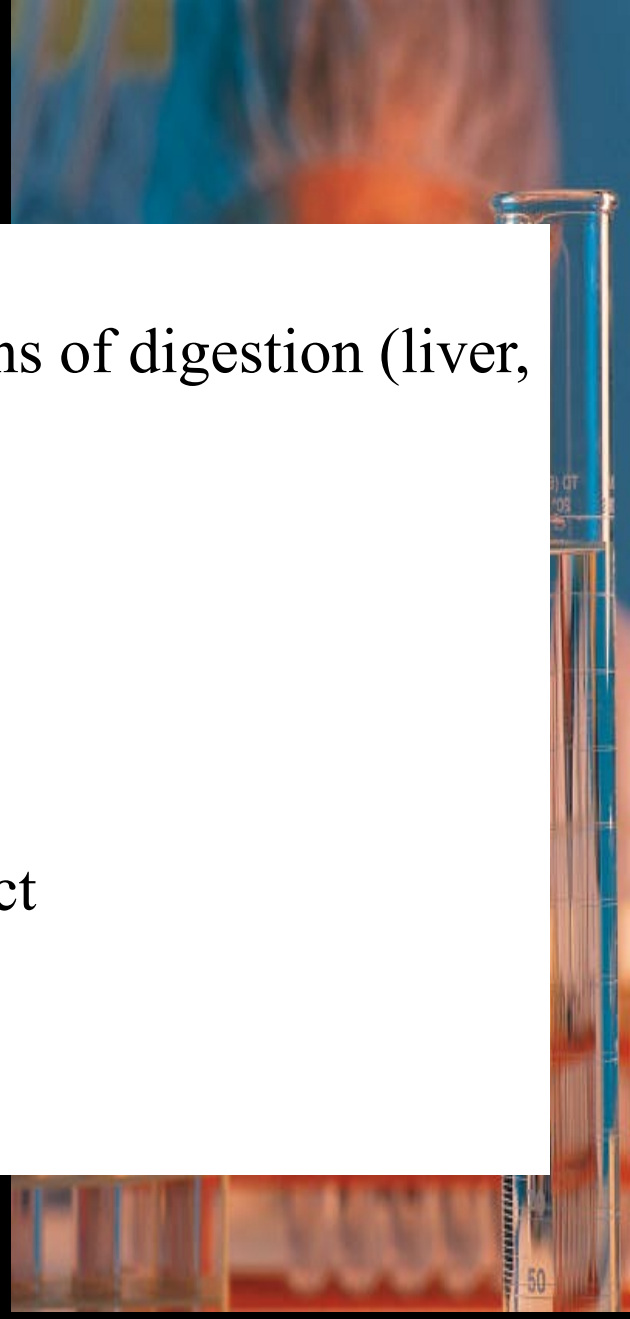
Substance	Source	Actions
Acetylcholine (ACh)	Cholinergic neurons	Contraction of smooth muscle in wall Relaxation of sphincters ↑ Salivary secretion ↑ Gastric secretion ↑ Pancreatic secretion
Norepinephrine (NE)	Adrenergic neurons	Relaxation of smooth muscle in wall Contraction of sphincters ↑ Salivary secretion
Vasoactive intestinal peptide (VIP)	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↑ Intestinal secretion ↑ Pancreatic secretion
Gastrin-releasing peptide (GRP) or bombesin	Neurons of gastric mucosa	↑ Gastrin secretion
Enkephalins (opiates)	Neurons of mucosa and smooth muscle	Contraction of smooth muscle ↓ Intestinal secretion
Neuropeptide Y	Neurons of mucosa and smooth muscle	Relaxation of smooth muscle ↓ Intestinal secretion
Substance P	Cosecreted with ACh	Contraction of smooth muscle ↑ Salivary secretion

TABLE 8–2. Summary of Gastrointestinal Hormones

Hormone	Hormone Family	Site of Secretion	Stimuli for Secretion	Actions
Gastrin	Gastrin-CCK	G cells of the stomach	Small peptides and amino acids Distention of the stomach Vagal stimulation (GRP)	↑ Gastric H^+ secretion Stimulates growth of gastric mucosa
Cholecystokinin (CCK)	Gastrin-CCK	I cells of the duodenum and jejunum	Small peptides and amino acids Fatty acids	↑ Pancreatic enzyme secretion ↑ Pancreatic HCO_3^- secretion Stimulates contraction of the gallbladder and relaxation of the sphincter of Oddi Stimulates growth of the exocrine pancreas and gallbladder Inhibits gastric emptying
Secretin	Secretin-glucagon	S cells of the duodenum	H^+ in the duodenum Fatty acids in the duodenum	↑ Pancreatic HCO_3^- secretion ↑ Biliary HCO_3^- secretion ↓ Gastric H^+ secretion Inhibits trophic effect of gastrin on gastric mucosa
Gastric inhibitory peptide (GIP)	Secretin-glucagon	Duodenum and jejunum	Fatty acids Amino acids Oral glucose	↑ Insulin secretion from pancreatic β cells ↓ Gastric H^+ secretion

The Ultimate Study Guide for Gastrointestinal Hormones

	Source	Action						Regulation						Notes
		Stomach		Intestine	Pancreas									
		Motility	Acid	Motility	Enzymes	HCO_3^-	Other	Stomach distension	Acidity	Glucose	Fatty acids	Amino acids	Vagal stimulation	
Gastrin	**G cells:** stomach antrum	++	++				++ Growth of gastric mucosa	++	--			++	++	• ++ in **Zollinger Ellison syndrome**. • **Phenylalanine and tryptophan** are potent stimulators
CCK (Cholecystokinin)	**I cells**: duodenum, jejunum	--			++		Contraction of gallbladder				++	++		• In **cholelithiasis**, pain worsens after fatty food ingestion due to ++ CCK
Secretin	**S cells:** duodenum		--			++	-- bile secretion		++		++			++ HCO_3^- neutralizes gastric acid in duodenum and thus allows pancreatic enzymes to function.
GIP (Glucose dependent insulinotropic polypeptide)	**K cells:** duodenum, jejunum		--				++ insulin			++	++	++		• An oral glucose load is used more rapidly than the equivalent given by IV.
Somatostatin	**D cells**: pancreatic islets, GI mucosa		--		--	--	-- pepsinogen -- insulin and glucagon		++				--	• Antigrowth hormone effects (digestion and absorption of substances needed for growth). • Used to treat VIPoma and carcinoid tumors.
Nitric oxide		--		--			Relaxes LES							• Loss of NO secretion is implicated in ++ LES tone of achalasia.
VIP (Vasoactive intestinal polypeptide	**Parasympathetic ganglia** in sphincters, gallbladder, small intestine			++			++ intestinal fluid secretion	++					++	• **VIPoma**: islet cell pancreatic tumor that secretes VIP. Copious diarrhea.
Motilin	Small intestine			++			Increases MMCs	Increases during fasting						



In general, the gastrointestinal (GI) tract includes what structures?
The entire gut tube from mouth to the anus, as well as the accessory organs of digestion (liver, gallbladder, and pancreas)

What is the primary function of the GI (alimentary) tract?
Nutrient absorption

Gut motility refers to what?
The movement of food (in various stages of digestion) through the GI tract

What is the innermost surface of the gut tube?
The mucosa

What is the main muscle type in the GI canal?
Visceral smooth muscle (VSM)
Where in the GI tract do we have skeletal muscle?
In the oropharynx and esophagus (absent by the distal third of the esophagus) where we have voluntary control over swallowing and chewing, and the external anal sphincter which we gain control of during infancy
What is unique about the muscle in the GI tract?
The smooth muscle cells are interconnected by gap junctions and function together as a single unit, much like cardiac muscle. Thus, an action potential generated in one muscle cell can easily spread to adjacent cells, allowing the cells to peristalse
Describe the roles of the following anatomical regions of the GI tract:
Oropharynx : Chewing breaks food into smaller pieces which provides more surface area for digestion, also houses some glands which begin secreting hydrolyzing enzymes
Esophagus: Propels food from oropharynx to stomach
Stomach : Grinds and mixes food with stomach acids to provide a suitable slurry to enter the small intestine
Small intestine : The workhorse of nutrient absorption; entry into small intestine is coordinated with the secretion of the various exocrine enzymes from the liver and the pancreas
Large intestine: Water and electrolyte reabsorption along with storage of fecal waste

How long does transit through the following GI segments take?

Esophagus

Seconds

Stomach

2 to 5 hours, conventionally we talk about the stomach being 50% empty after 3 hours.

Small intestine

Also 2 to 5 hours

Large intestine

Approximately 30 to 50 hours

What is the collective term for the immune defense of the gut?

Gut-associated lymphoid tissues (GALT); this term encompasses a number of different lymphatic tissues throughout the gut tube

List some of the major component lymphatic tissues in the GI tract.

Tonsils, Peyer patches, lymphoid aggregate in the appendix

Name the two main nervous systems of the gut.

1. Enteric or intrinsic system
2. Autonomic or extrinsic system

What are the components of the extrinsic system? (Not including the control of the oropharynx)

Parasympathetic nervous system (PNS) and sympathetic nervous system (SNS)

Name the main function of the SNS in the GI tract.

Excitation

Which nerves carry PNS fibers and what structures/organs do they innervate?

Vagus: esophagus, stomach, pancreas, small intestine, and first portion of the large intestine

Pelvic splanchnic nerves: second portion of large intestine, rectum, and anus

Name the main function of the SNS with respect to the GI tract.

Inhibitory

Which GI nerves carry SNS fibers?

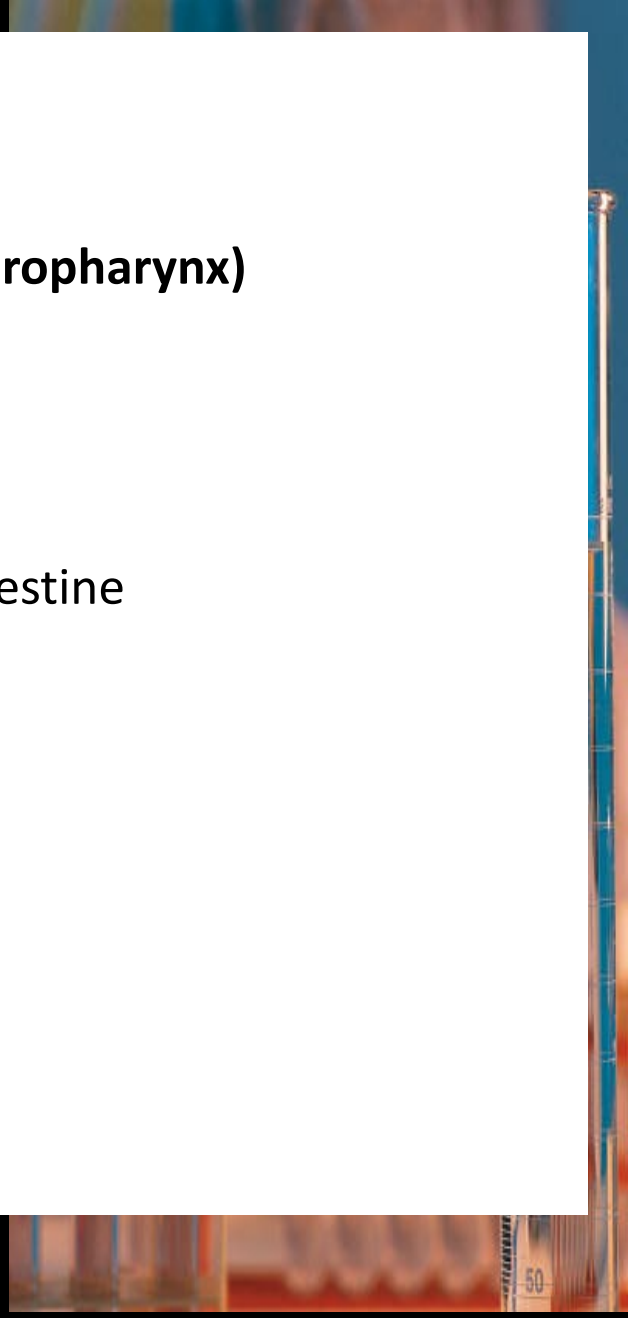
Spinal nerves

Is the action of SNS exclusively inhibitory?

No

Where are the exceptions?

Lower esophageal sphincter, pyloric, and internal anal sphincter



Why does sympathectomy not affect alimentary motility?

Reuptake of norepinephrine (NE) by sympathetic nerve endings is so rapid that only a great rise in NE concentration during a sympathetic discharge can have a significant effect on normal GI motility

Overexcitation of the extrinsic nervous system can produce what common syndrome?

- Irritable bowel syndrome (IBS)

What afferent information is carried by the extrinsic system?

- All conscious sensations from the gut: fullness, pain, nausea, etc.

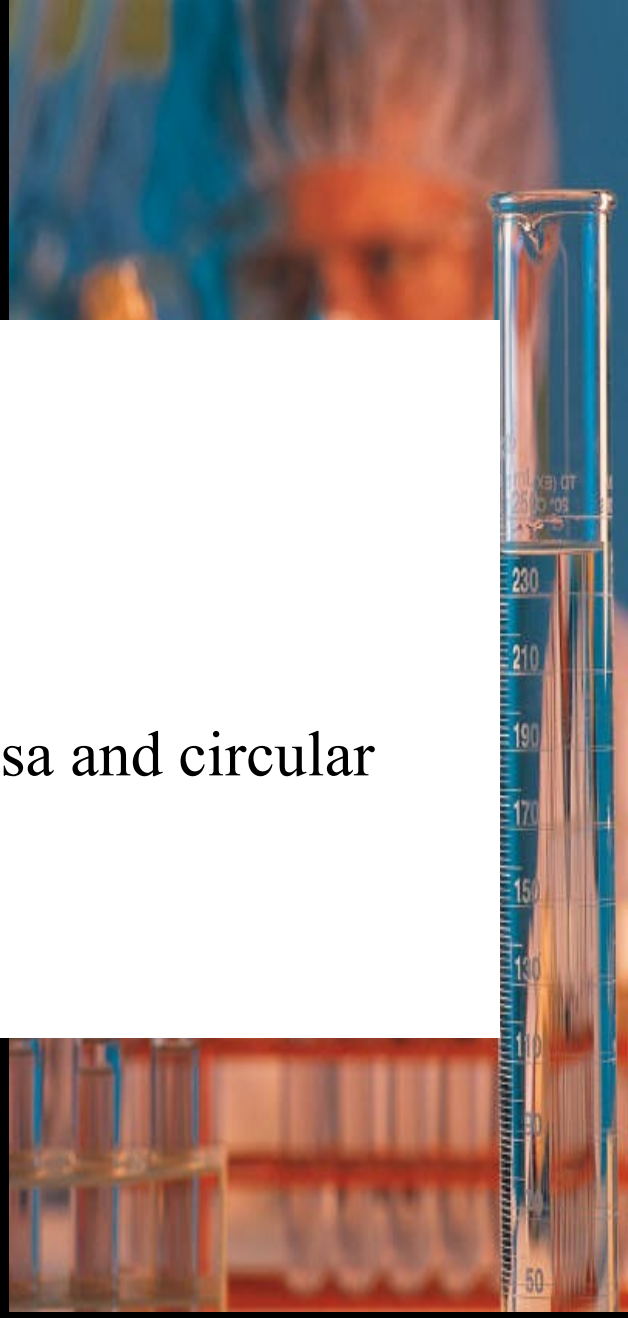
What are the two anatomical components of the intrinsic system?

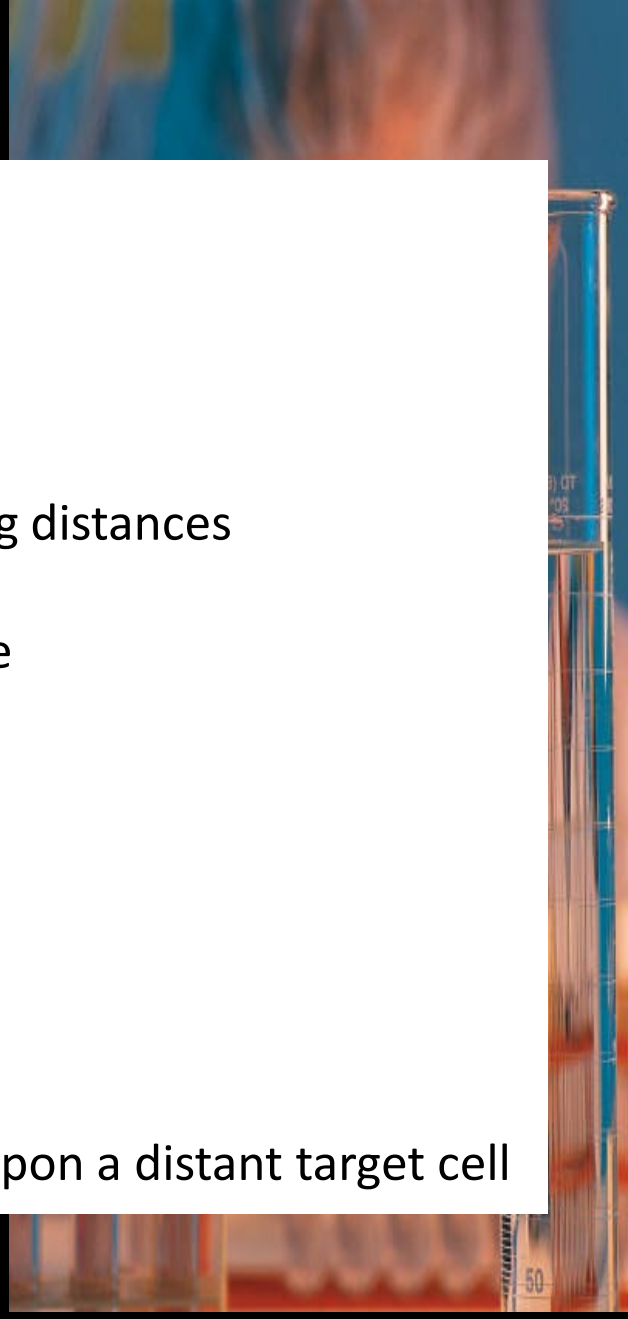
- Myenteric or Auerbach plexus
- Submucosal or Meissner plexus

What are the functions of the intrinsic system?

- Acts as mediator of information between the extrinsic nervous system and the alimentary
- tract
- Commands most functions of the GI tube especially motility and secretion
- Can execute neural function of the gut without extrinsic innervations

Where is the myenteric plexus located?
It lies between the longitudinal and circular muscle layers
What is the main function of the myenteric plexus?
Controls and coordinates motility
Where is the submucosal plexus located?
It lies in the submucosa (hence the name), between the muscularis mucosa and circular muscle layer
What is the main function of the submucosal plexus?
Controls secretion and absorption as well as local blood flow





What is the main stimuli for hormone release?
Food lying adjacent to GI mucosa
What is the main function of GI hormones?
Regulate the digestive process by influencing secretion, motility, and blood flow
What are hormones?
Chemical signals that fall into many categories, which help relay signals across varying distances
Define neurocrine.
Process in which one nerve fiber releases messenger that acts across a short distance
upon a target cell (nerve fiber, muscle cell, or gland cell)
Define paracrine.
Released messenger acts upon adjacent cells
Define endocrine.
Stimulus acting upon a receptor causes the cell to release a messenger into the
bloodstream that then acts on a distant target cell
Define neuroendocrine.
Action potential causes release of messenger that enters the bloodstream and acts upon a distant target cell

Name the main gastric hormones.

- Gastrin
- Cholecystokinin (CCK)
- Secretin
- Gastric inhibitory peptide (GIP)

Name the cells that secrete gastrin.

G cells in the antral mucosa of stomach

Of the above types of hormonal systems, which is used by gastrin to exert its effect?

Endocrine (and to a lesser degree neuroendocrine)

Which form of gastrin is most abundant and potent?

Little gastrin

Which form has the longest half-life?

Big gastrin (42 minutes)

Which amino acids confer physiological activity?

Last four amino acids at the carboxy terminal (i.e., little gastrin: AA 14 to 17)

What are the major stimuli for gastrin's secretion?

1. Amino acids; notably L-amino acids like phenylalanine, tryptophan, cysteine, tyrosine
2. Vagal stimulation
3. Stomach distention

What are the functions of gastrin?

1. Primary: *Increases hydrochloric acid (HCl) secretion (via parietal cells)*
2. Stimulates growth of gastric mucosa
3. Increases gastric motility
4. Increases LES contraction (preventing reflux)
5. Decreases ileocecal sphincter contraction (dubbed the gastrocolic reflex; this allows defecation)
6. Increases pepsinogen secretion

What are some other stimuli for gastrin's secretion?

- Epinephrine
- Calcium
- Acetylcholine (ACh)

What are the inhibitors of gastrin secretion.

- pH < 2 (feedback inhibition) Somatostatin
- Secretin
- Calcitonin
- GIP
- Glucagon
- Vasoactive inhibitory peptide (VIP)

Which other GI hormone is chemically "related" to gastrin?

- CCK, which shares five amino acids on the carboxy terminal, the extra amino acid of CCK offers receptor specificity, but cross activation is possible

While the two enzymes share five amino acids, how do they differ in their shared function?

Potency

What cells secrete CCK?

I cells of the duodenum and jejunum

Which hormonal system is used by CCK to exert its effects?

- Endocrine

What are the major stimuli for CCK's secretion?

Protein and fat digestion products in the small intestine

What product of fat digestion does not stimulate CCK secretion?

- Triglycerides

Why don't triglycerides stimulate the release of CCK?

- They cannot cross the intestinal membranes

Which form is most abundant and potent?

- CCK 8 (octapeptide)

On which amino acid sequence is the physiological activity located?

- On the octapeptide on the carboxy terminal

What are the functions of CCK?

- Increase gallbladder and pancreatic contraction
- Decrease contraction of the sphincter of Oddi, allowing pancreatic secretion
- Slow gastric emptying
- Increase pepsinogen secretion
- Decrease LES contraction
- Stimulate growth of the exocrine pancreas
- Work synergistically with secretin to increase bicarbonate secretion in the small intestine

What syndrome occurs when non-β-cell tumors of the pancreas secrete gastrin (e.g., gastrinoma)?
Zollinger-Ellison syndrome
Name the cells that secrete secretin.
S cells of the duodenum
What is the *primary* stimulus for secretin secretion?
H+ in the duodenum
What is another stimuli for secretin release?
Protein and fat digestion products in the small intestine
What system of cellular communication is used by secretin to exert its actions?
Endocrine and paracrine
What are the functions of secretin?
1. Stimulates bicarbonate secretion from pancreatic and biliary duct cells
2. Decreases HCl secretion
3. Enhances activity of CCK on pancreatic secretion and gallbladder contraction
4. Decreases gastric and intestinal motility
5. Increases pepsinogen

Which hormones are part of the secretin-glucagon family?
- Secretin
- Glucagon
- Vasoactive intestinal peptide (VIP), sometimes called vasoactive *inhibitory* peptide
- Gastric inhibitory peptide (GIP)

What cells secrete GIP?
K cells of the jejunum and duodenum
What are the major stimuli for GIP's release?
Products of carbohydrate and fat breakdown in the small intestine
What system is primarily used by GIP to exert its actions?
Endocrine
What are the functions of GIP?
Stimulates insulin release and inhibits H+ secretion
What are the GI paracrine hormones?
Somatostatin, serotonin, and histamine
Name the cells that secrete somatostatin.
Multiple cells in the GI tract
What is the stimulus for somatostatin release?
Presence of H+ in the lumen

What inhibits the secretion of somatostatin?
Vagal stimulation
What is the function of somatostatin?
Think: "stasis"
1. Inhibits release of all GI hormones
2. Inhibits gastric H+ secretion
3. Inhibits gallbladder and pancreatic contraction
Name the cells that secrete histamine.
Enterochromaffin-like (ECL) cells within the gastric mucosa
What is the function of histamine in the GI tract?
Increases gastric H+ secretion (both directly and by potentiation of the effects of gastrin and vagal stimulation)
Why does that relationship make sense? (think about mast cell activation → increased acid secretion)
Histamine functions, in general as an immune cytokine, in the gut it has a similar function- acidification of the gastric lumen makes the environment far more hostile to arriving pathogens

What cells secrete serotonin?
Enterochromaffin (EC) cells in the gut wall
What is their primary stimulus for secretion?
Distension of the gut lumen
What does serotonin do in the gut?
It is primarily excitatory and leads to increased gut motility
What are the GI neurocrine hormones?
VIP
Gastrin-releasing peptide (GRP) (bombesin)
Enkephalins
What other GI hormone is VIP homologous to?
Secretin
Name the cells that normally secrete VIP.
Neuronal cells in the mucosa and smooth muscle of the GI tract
What tumor type can also secrete VIP?
Pancreatic islet cell tumors

What are the functions of VIP?
Relaxes GI smooth muscle (including LES)
Stimulates pancreas to secrete HCO_3^-
Inhibits gastric H^+ secretion
Name the cells that secrete GRP.
Vagal nerves that innervate G cells
What is the function of GRP?
Stimulates gastrin release
What are the types of enkephalins?
Met-enkephalin and Leu-enkephalin
Name the cells that secrete enkephalins.
Neurons in the mucosa and smooth muscle of the GI tract
What are the functions of enkephalins?
1. Contract GI smooth muscle (especially lower esophageal, pyloric, and ileocecal sphincters)
2. Inhibit secretion of fluid and electrolytes by the intestines
What hormone is secreted into the bloodstream to increase appetite?
Ghrelin
What is ghrelin's stimulus for secretion?
Hypoglycemia
What cells secrete ghrelin?
X cells in the body of the stomach

Name the types of electrical waves found in the alimentary tract.
Slow waves and spike potentials
What are slow waves?
Fluctuating changes in the resting membrane potential
What are slow waves *not?*
Action potentials
Where are slow waves generated?
Cells of Cajal (pacemaker of the alimentary tract)
Why are slow waves important?
Determine the rhythmicity of the GI tract's contractions by controlling the pattern of spike potentials
Where in the tract are the waves the slowest?
Stomach at 3 waves/min
Where in the tract are the waves the fastest?
Duodenum at 12 waves/min
What are spike potentials?
Action potentials of the alimentary tract
How are spike potentials generated?
They occur when the resting gut pacemaker membranes depolarize
Name three factors that cause increased depolarization of gut pacemaker cells.
1. Muscle stretch
2. ACh
3. PNS

Which channels are involved in the generation of the action potential?
Ca2+-Na+ channels, just like anywhere else in the body
How does a spike potential cause contraction?
Like other muscle cells, Ca2+ enters the smooth muscle cell interior

Define motility.
Mechanical activity of the GI tract that is divided into mixing (segmentation) and propelling (peristalsis)
Describe segmentation.
Contraction around the bolus sends intestinal contents (chyme) backward and forward.
The area then relaxes and the material moves back into the segment, mixing the contents.
Describe peristalsis.
Contraction behind the bolus is coupled with relaxation in front of it, which propels the bolus distally
What factors promote inhibition of peristalsis?
Ileogastric reflex and CCK
Name the functions of small intestinal motility.
- Allows for mixing of food bolus with digestive enzymes
- Exposes food molecules to absorptive mucosa
- Propels nonabsorbed material to the colon

Which aspect of motility is most important in the small intestine?
Segmentation: allows for increased surface area for digestion and absorption of chyme
What is the frequency of slow waves in the following segments of the small intestine?
Duodenum
12 waves/min
Proximal jejunum
12 waves/min
Terminal ileum
8 to 9 waves/min
What other factor is important for segmental contraction?
Excitation by the myenteric plexus
What is the average velocity of peristalsis waves in the small intestine?
0.5 to 2.0 cm/s
What factors stimulate increased peristalsis activity?
- Gastroileal reflex (neural regulation)
- Gastrin
- CCK
- Serotonin
- Insulin

What factors inhibit peristalsis activity?
Secretin and glucagon

Name the two types of motility found in the colon.

1. Haustral segmental movement
2. Mass movement

What are haustra?

Invaginations of the circular and longitudinal muscles of the large intestine which provide some compartmentalization

What are mass movements?

Modified peristalsis that is characterized by uniform contraction and movement of colonic contents down the descending colon

How often do mass movements occur per day?

1 to 3 times/day

Name some factors that stimulate mass movement.

- Gastrocolic reflex
- Duodenocolic reflex
- Irritation of the colon
- PNS stimulation
- Over distention of a colonic segment

Where is the vomiting center located?

Medulla

What stimuli does the vomiting center respond to?

- Gag
- Gastric distention
- Vestibular stimulation

Where are the chemoreceptors that can induce vomiting?

Fourth ventricle

What stimuli do the chemoreceptors respond to?

- Emetic substances
- Vestibular stimulation
- Radiation

What is vomiting?

Reverse peristalsis that propels GI contents in the stomach towards the oropharynx and out through the upper esophageal sphincter

What occurs if the peristalsis is not strong enough to overcome the pressure in the upper esophageal sphincter (UES)?

Retching

Where does the reverse peristalsis begin?

Small intestine

Course reduction in food particle size is accomplished by what process?
Mastication
During this process what fluid is introduced to the food bolus?
Saliva
What are the principal glands of salivation?
1. Submandibular (70%)
2. Parotid (25%)
3. Sublingual (5%)
Name the functions of saliva.
1. Dissolves and alkalinizes ingested food particles
2. Protects the oral cavity
3. Moistens the mouth (lubrication)
4. Begins hydrolysis of complex starches
Name and describe the two types of salivary secretions.
1. Serous secretions: contain enzymes for starch digestion
2. Mucous secretions: contain mucin for lubrication and protection

What is the enzyme found in salivary secretions responsible for carbohydrate digestion?
Salivary amylase
In what ways does saliva help protect the oropharynx?
1. Salivary piece: IgA—binding protein which activates secreted IgA
2. Lactoferrin secretion: chelates iron to make it unavailable for bacteria
3. Lysozyme: attacks bacterial cell walls
4. Acquired pellicle: a thin layer of glycoproteins that adheres to teeth to help protect them
Name the type of secretions for the principal glands:
Parotid
Serous
Submandibular
Serous and mucous
Sublingual
Serous and mucous

Describe the glandular process of saliva secretion:

Initial saliva from gland (isotonic to plasma)

↓

Ducts secrete K^+ and HCO_3^-

Na^+ reabsorption occurs in the salivary ducts in proportion to the time spent there, usually leading to hypotonic saliva

In periods of fasting, when salivary flow is low, how does the composition of saliva change?

The saliva remains in the duct longer and more sodium and chloride are reabsorbed without water, so it becomes hypotonic.

What regulates saliva production?
PNS and SNS
What effect does the PNS have on saliva production?
Increases it
What effect does the SNS have on saliva production?
Increases it as well
What stimuli increase saliva production?
- Presence of food in the mouth
- Smells
- Conditioned reflexes (e.g., Pavlov dog)
- Nausea

What stimuli decrease saliva production?
- Dehydration
- Fear
- Anticholinergic medications
- Sleep

Describe swallowing.
A highly coordinated, complicated series of muscular contractions that propels a bolus of food toward the stomach
Where is the swallow center located?
Medulla and lower pons

Which nerves contain the motor impulses from the swallow center?
Cranial nerves (CN) V, IX, X, XII, and the superior CN
Name the stage of the swallow reflex that is described by the following:
Involves voluntary action that squeezes food into the pharynx and against the palate
Voluntary stage (oral)

Involves closure of the trachea, opening of the esophagus, and generation of a peristaltic wave (primary peristalsis) that forces the food bolus into the esophagus
Pharyngeal stage

Involves continuation of primary peristalsis, the relaxation of the upper esophagus,
and the entrance of the food bolus into the esophagus
Esophageal stage
How long does it take the primary wave to reach the LES?
5 to 10 seconds (travels at 3-5 cm/s)

When is a secondary peristalsis generated?
When the primary peristalsis wave is insufficient to clear the esophagus of the food bolus
What is receptive relaxation?
A vagovagal reflex that relaxes the LES prior to the peristaltic wave
Why is receptive relaxation important?
Allows for easy propulsion of food bolus into the stomach
What types of secretions are found in the esophagus?
Mucoid
Name its main function.
Provides lubrication for swallowing
What is the mechanism by which gastric contents are able to reflux into the esophagus (e.g., gastroesophageal reflux disease or GERD)?
Decreased LES tone
What can result if the LES tone is increased and it does not relax with swallowing?
Achalasia

What are the physiologic divisions of the stomach and what are their boundaries?
Orad portion: extends from the fundus to the proximal body
Caudad portion: extends from the distal body to the antrum
What are the three major functions of the stomach?
Store food
Make chyme
Empty food at a rate suitable for proper digestion and absorption by the small intestine
What is the maximum amount of food that can be stored by the stomach?
1.5 L
What is chyme?
Semifluid paste that results from the food bolus mixing with gastric secretions
What promotes gastric emptying?
Stretch and gastrin
What inhibits gastric emptying?
Increased osmolarity
Products of fat digestion
pH <3.5

The stomach has five main exocrine secretions. What are they?

- Water
- Acid
- Enzymes (gastrin and pepsin lipase)
- Intrinsic factor
- Mucus (barrier to protect the mucosa)

Name the cell types with the following description:

Found in the fundus and secretes HCl and intrinsic factor

Parietal cells

Found in the fundus and secretes pepsinogen

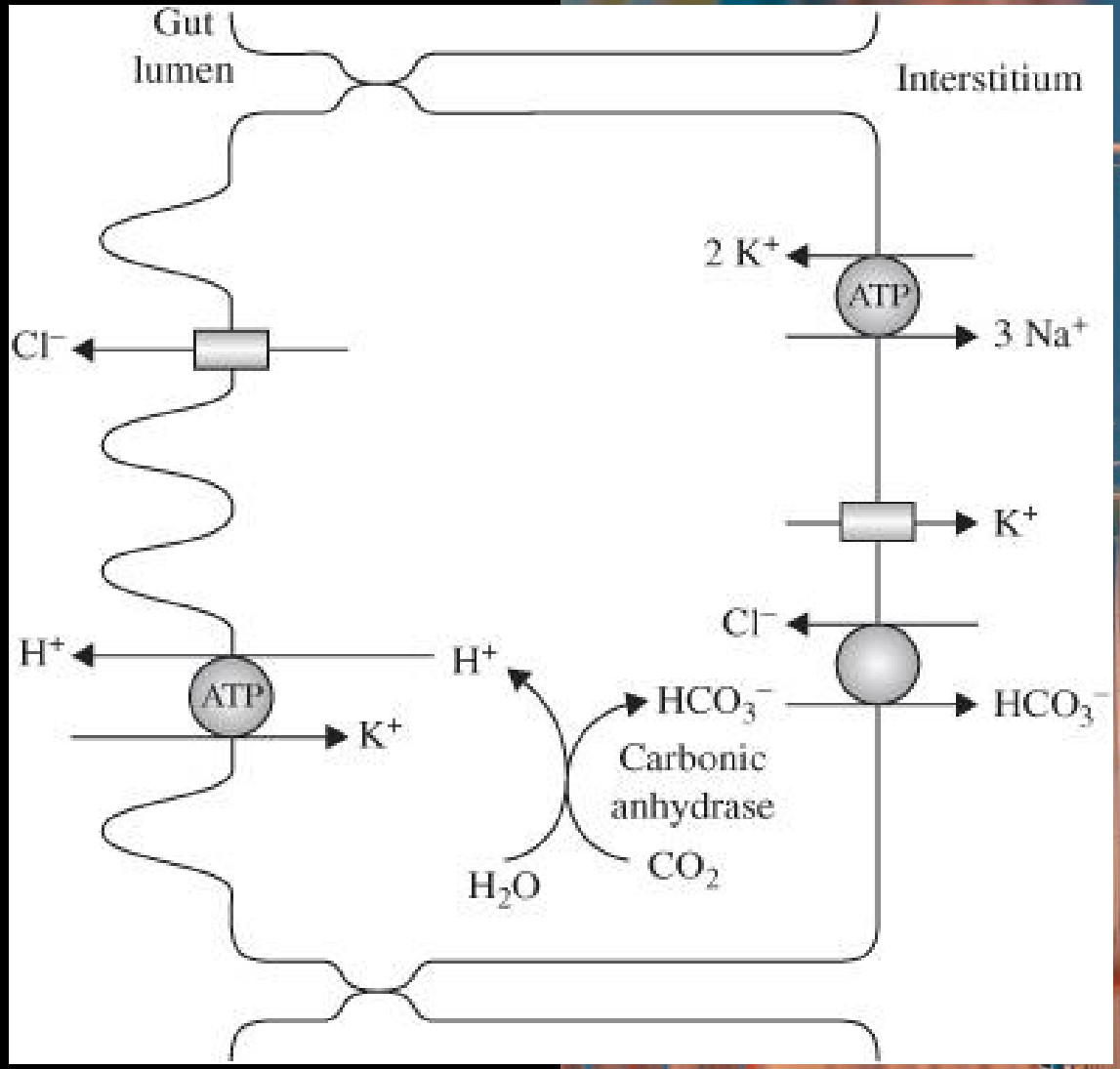
Chief cells/peptic cells

Found in antrum and secretes gastrin

G cells

Found in the antrum and secretes mucus and pepsinogen

Mucous cells

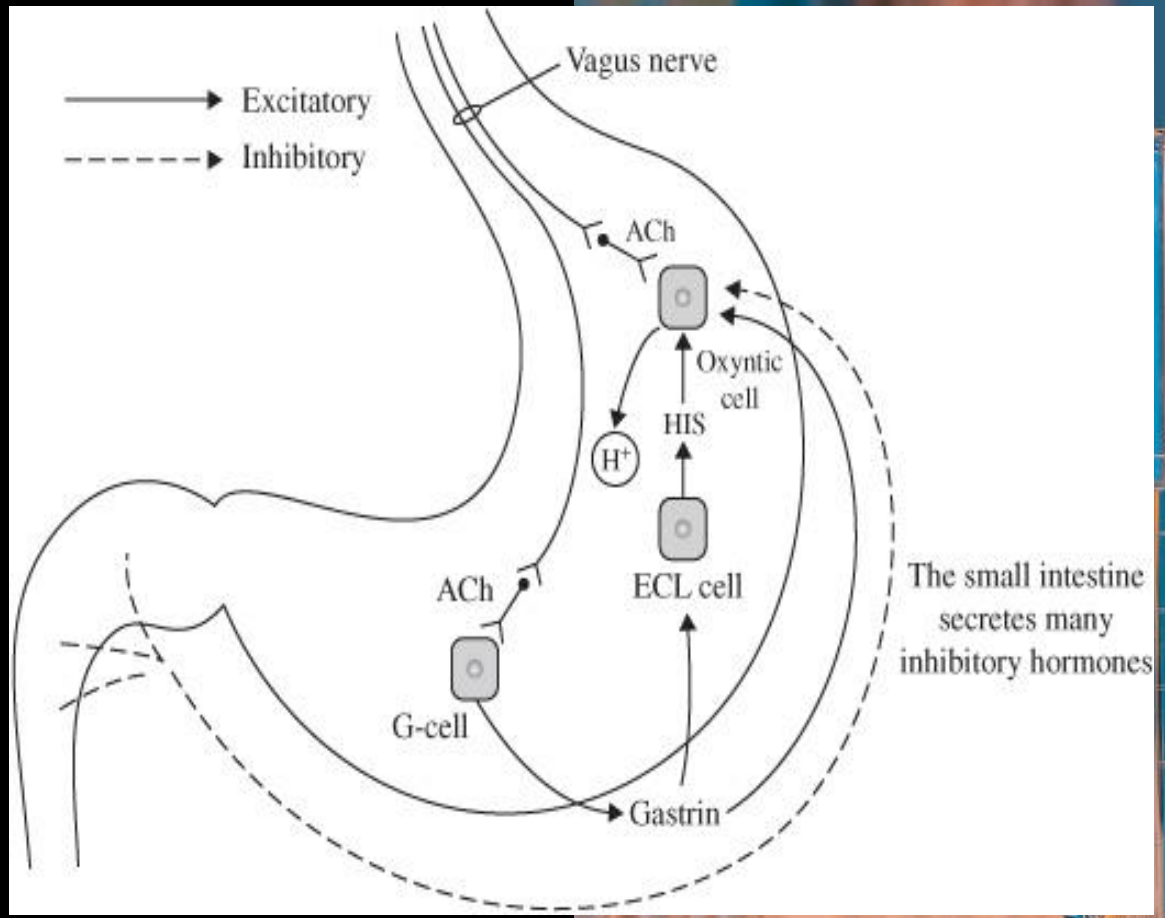


Name the three factors that work synergistically to promote HCl secretion.

1. Histamine
2. Gastrin
3. Acetylcholine

Name the three different receptors that those factors bind to on parietal cells to stimulate acid secretion.

1. H2 receptor
2. Gastrin receptor
3. Muscarinic (acetylcholine) receptor



What induces ACh stimulation of H+ secretion?
Vagus nerve, which directly innervates parietal cells (ACh is the neurotransmitter)

What induces gastrin stimulation of H+ secretion?
- Small peptides present in the lumen
- Distension of the stomach
- Vagal stimulation (e.g., response to eating)

Name the compounds that can inhibit the following elements of HCl secretion:
- **ACh**
- Cholinergic muscarinic antagonists

Histamine
H2 receptor-blocking agents

Gastrin
None known at this time