Overview of Gastrointestinal Function & Regulation

CHAPTER 25

First Part

OBJECTIVES

After studying this chapter, you should be able to:

- Understand the functional significance of the gastrointestinal system, and in particular, its roles in nutrient assimilation, excretion, and immunity.
- Describe the structure of the gastrointestinal tract, the glands that drain into it, and its subdivision into functional segments.
- List the major gastrointestinal secretions, their components, and the stimuli that regulate their production.
- Describe water balance in the gastrointestinal tract and explain how the level of luminal fluidity is adjusted to allow for digestion and absorption.
- Identify the major hormones, other peptides, and key neurotransmitters of the gastrointestinal system.
- Describe the special features of the enteric nervous system and the splanchnic circulation.

Chapter 25 overview of gastrointestinal function and regulation	• gastrointestinal secretion • gastrointestinal regulation • hormones and paracrine • enteric nervous system

GI parts:

1. **Mouth**
2. **Esophagus**
3. **Stomach**
4. **Duodenum**
5. **Jejunum**
6. **Ileum**
7. **Cecum**
8. **Colon**
9. **Rectum**
10. **Anus**

GI Function: **absorption** of **nutrients** and **water**

Nutrients: **Carbohydrates**, **Proteins**, **lipids**, **Vitamins** and **minerals**

Processes: meal **mixing** with secretions (juices), **digestion** and **absorption**

Sources of secretions:

1. From **accessory glands** (salivary glands and liver)
2. From **GI glands** (stomach and intestine)

Control: control of **secretions** and control of **GI movements**

Properties of intestine: efficient **mixing**, complete **digestion** and high **absorptive** power (due to large surface area)

INTRODUCTION

The primary function of the gastrointestinal tract is to serve as a portal whereby nutrients and water can be absorbed into the body. In fulfilling this function, the meal is mixed with a variety of secretions that arise from both the gastrointestinal tract itself and organs that drain into it, such as the pancreas, gallbladder, and salivary glands.

STRUCTURAL CONSIDERATIONS

The parts of the gastrointestinal tract that are encountered by the meal or its residues include, in order, the mouth, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, and anus. Throughout the length of the intestine, glandular structures deliver secretions into the lumen, particularly in the stomach and mouth. Also important in the process of digestion are secretions from the pancreas and the biliary system of the liver. The intestine itself also has a very substantial surface area, which is important for its absorptive function.

Salivary glands and salivary secretion:

Glands: Parotid (the largest), **submandibular** (the medium) and **sublingual** (the smallest)

Saliva: secretion of salivary glands that drain into the mouth

Compositions: digestive enzymes, **mucin**, **IgA**, **lysozymes**, **electrolytes** and **water**

- ✓ **Digestive enzymes:** **α-amylase** to digest the **starch**
- ✓ **IgA and lysozymes**: **protect** the oral cavity **from bacteria**
- ✓ **Mucins**: **lubricate** the food **bolus**
- ✓ **Electrolytes**: low in Na^+ and Cl^- rich in K^+ and bicarbonates (saliva is **hypotonic** fluid)
- ✓ **pH**: **alkaline** (6.0-7.0), this pH is **essential** for **amylase** activity and to neutralize any gastric secretions that reflux into the esophagus

Function of Saliva:

1. Facilitates **swallowing**
2. Keeps the **mouth moist**
3. Serves as a **solvent** for molecules that stimulate teste buds
4. **Aids speech** by facilitating movements of lips and tongue
5. Keeps the **mouth** and **teeth clean**

Control of secretion:

1. **Parasympathic** nervous system (the most predominant): **increase volume** of **serous** (loose) saliva
2. **Sympathetic** nervous system: **change** saliva **composition** to **mucous** (**proteinaceous**) **BUT** **has little effect on volume**

Stimulus and inhibitors of salivation:

- **Stimuli**: **smell**, **taste**, **sight**, **pressure** in mouth and medications (**pilocarpine**)
- **Inhibitors**: **sleep**, **fatigue**, **fear** and medications (**atropine**)

GASTROINTESTINAL SECRETIONS

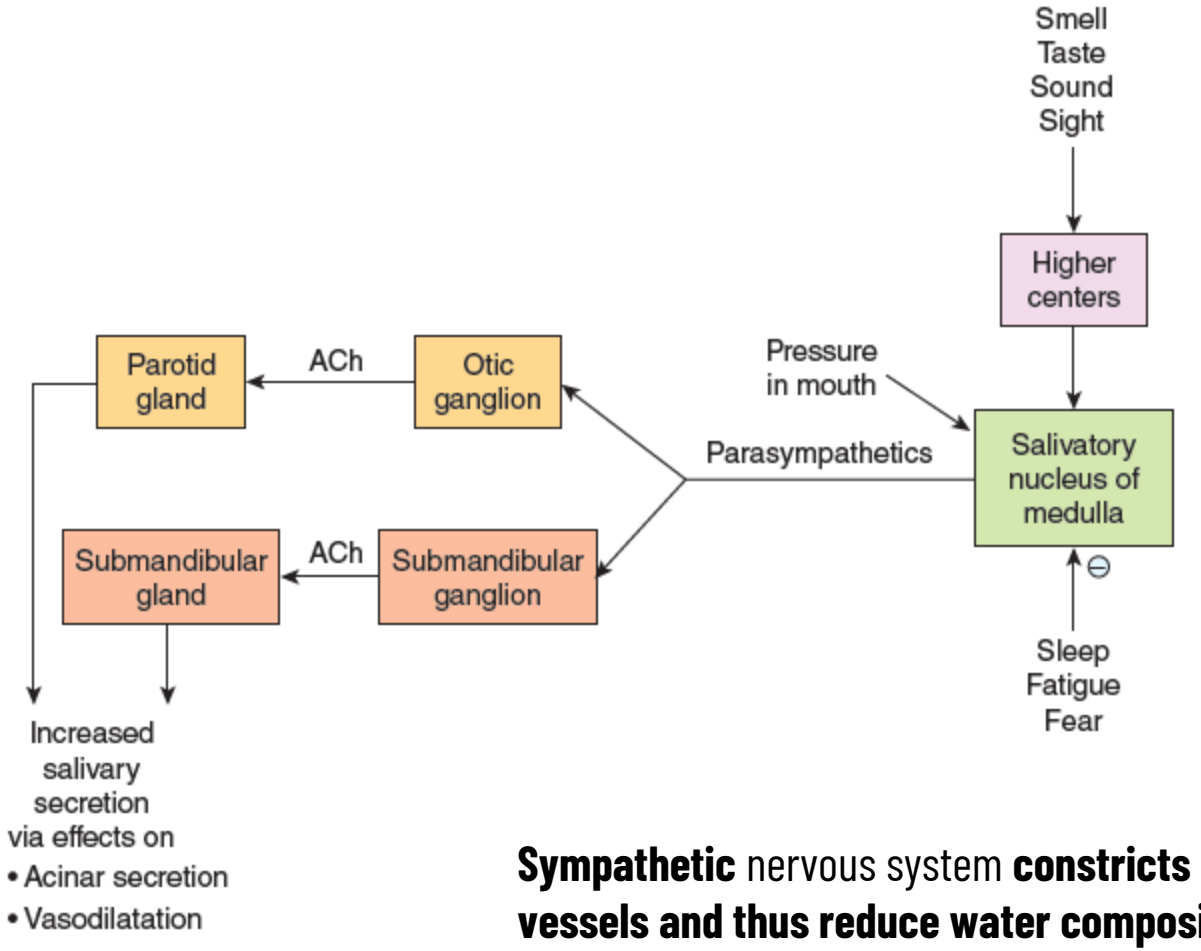
SALIVARY SECRETION

The first secretion encountered when food is ingested is saliva. Saliva is produced by three pairs of salivary glands (the **parotid, submandibular,** and **sublingual glands**) that drain into the oral cavity. It has a number of organic constituents that serve to initiate digestion (particularly of starch, mediated by amylase) and which also protect the oral cavity from bacteria (such as immunoglobulin A and lysozyme). Saliva also serves to lubricate the food bolus (aided by mucins). Secretions of the three glands differ in their relative proportion of proteinaceous and mucinous components, which results from the relative number of serous and mucous salivary acinar cells, respectively. Saliva is also hypotonic compared with plasma and alkaline; the latter feature is important to neutralize any gastric secretions that reflux into the esophagus.

Salivary secretion is almost entirely controlled by neural influences, with the parasympathetic branch of the autonomic nervous system playing the most prominent role (Figure). Sympathetic input slightly modifies the composition of saliva (particularly by increasing proteinaceous content), but has little influence on volume.

Saliva performs a number of important functions: it facilitates swallowing, keeps the mouth moist, serves as a solvent for the molecules that stimulate the taste buds, aids speech by facilitating movements of the lips and tongue, and keeps the mouth and teeth clean.

Parasympathic nervous system **dilates blood vessels and thus increases water composition of saliva**



Sympathetic nervous system **constricts blood vessels and thus reduce water composition of saliva**

Functions of stomach: (1) **store** food, (2) **mix** food with acid, pepsin and mucus, (3) gastric **emptying** of mixed food into duodenum at steady rate

Composition of gastric juice (Table):

1. **Organics:** mucus, pepsins, lipase, intrinsic factor
2. **Inorganics:** electrolytes (Na^+, K^+, Mg^+, **H^+**, **Cl^-**, PO_4^{2-}, SO_4^{2-})
3. **Water**

Gastric pH: ~ 3.0

Gastric secretion rate: **2.5 L/day**

Phases of gastric secretion:

1. **Cephalic phase**: when **food NOT in** the **stomach**
   The stomach readies itself to receive the meal before it is actually taken it
2. **Gastric Phase** (the **most significant**): when **food in** the **stomach**
   The food in stomach produce reflex secretions and gastric emptying
3. **Intestinal Phase**: when **food in** the **intestine**
   The food in the stomach produce reflex inhibition of gastric secretion and gastric emptying

Each Phase is **regulated** by **local** (neural and hormonal) and **distant** (neural) **triggers**

Exocrine gastric glands: in the **body** and **fundus**

1. **Parietal** (oxyntic) cells: secrete **HCl** and **intrinsic factor**
2. **Chief** (peptic, zymogen) cells: secrete **pepsin** and gastric **lipase**
3. **Mucus** secreting cells: on the surface of the glands
4. **Bicarbonate** secreting cells: on the surface of the glands

The mucus and bicarbonates protect the stomach from digesting itself

Endocrine gastric glands: in the **antrum**

- **G cells**: secrete **gastrin**

GASTRIC SECRETION

Food is stored in the stomach; mixed with acid, mucus, and pepsin; and released at a controlled, steady rate into the duodenum .

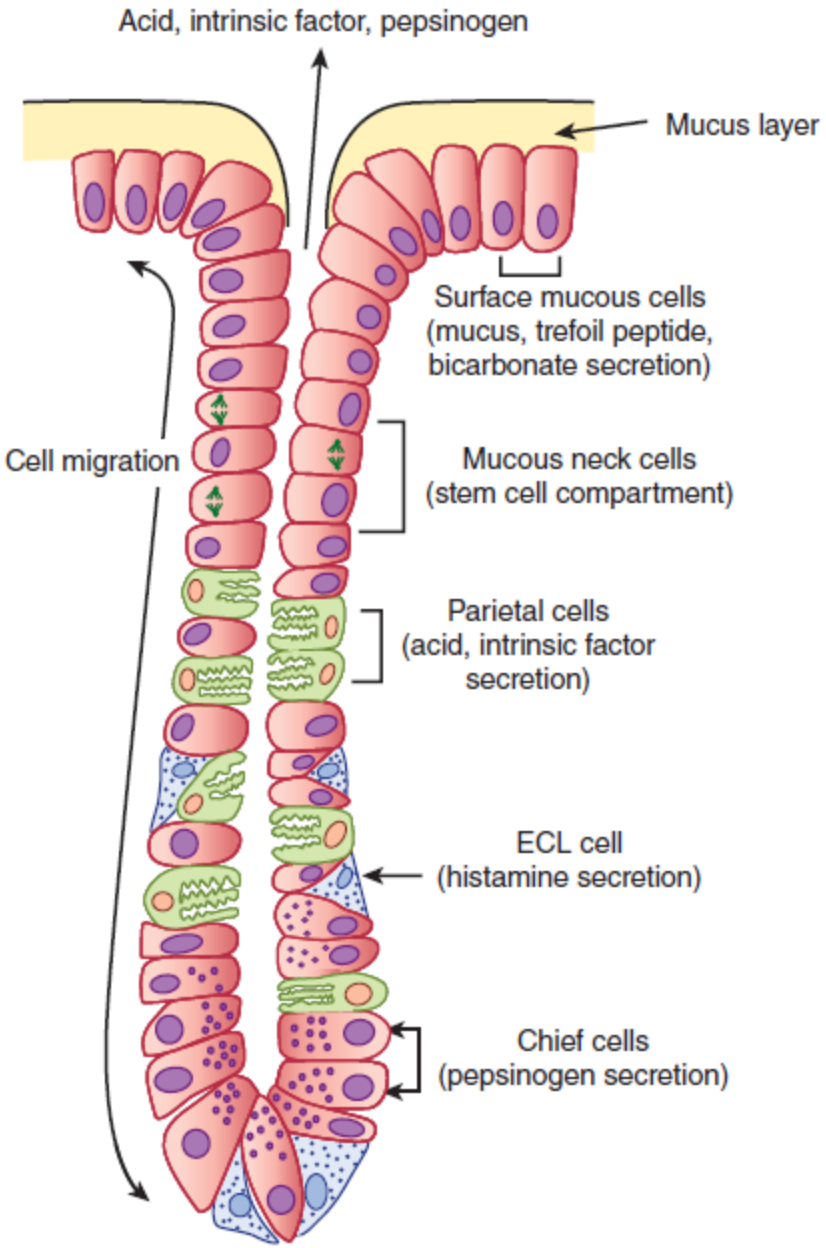
ORIGIN & REGULATION OF GASTRIC SECRETION

The stomach also adds a significant volume of digestive juices to the meal. Like salivary secretion, the stomach readies itself to receive the meal before it is actually taken in, during the so-called cephalic phase that can be influenced by food preferences. Subsequently, there is a gastric phase of secretion that is quantitatively the most significant, and finally an intestinal phase once the meal has left the stomach. Each phase is closely regulated by both local and distant triggers.

The gastric secretions (Table) arise from glands in the wall of the stomach that drain into its lumen, and also from the surface cells that secrete primarily mucus and bicarbonate to protect the stomach from digesting itself,

Gastric secretion adds about 2.5 L/day to the intestinal contents.

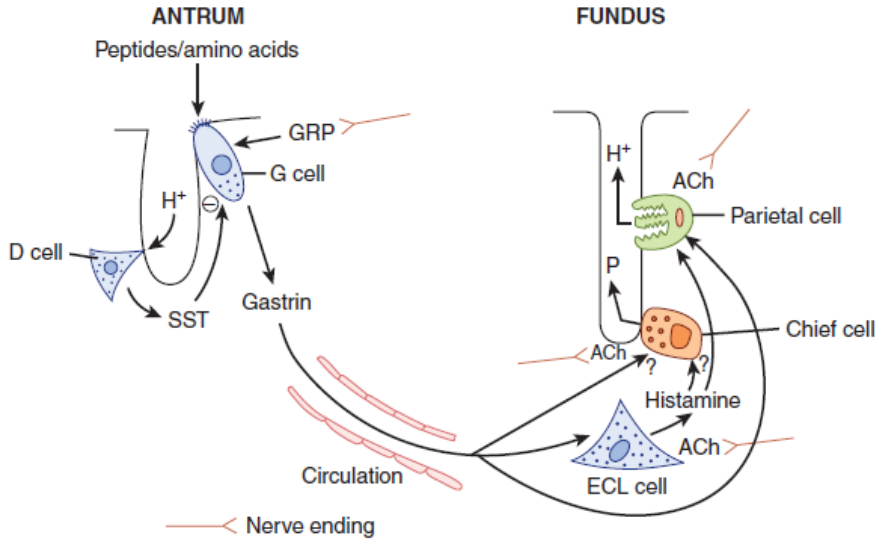
The most characteristic secretions derive from the glands in the fundus or body of the stomach. These contain the distinctive parietal cells, which secrete hydrochloric acid and intrinsic factor; and chief cells, which produce pepsinogens and gastric lipase (Figure).


Acid, intrinsic factor, pepsinogen
Mucus layer
Surface mucous cells
(mucus, trefoil peptide,
bicarbonate secretion)
Cell migration
Mucous neck cells
(stem cell compartment)
Parietal cells
(acid, intrinsic factor
secretion)
ECL cell
(histamine secretion)
Chief cells
(pepsinogen secretion)

Functions of gastric juice components:
Acid: sterilize the meal and begins dietary **macromolecules hydrolysis**
Intrinsic factor: important for **vitamin B12** absorption from ileum
Pepsin: initiates **protein** digestion (**digest** matrix **collagen**)
Lipase: begins dietary **fats** digestion

Chemical stimuli for gastric secretion:

1. **Gastrin** hormone: released from G cells in the antrum in response to gastrin-releasing peptide (bombesin); a specific neurotransmitter released from enteric nerve ending
2. **Histamine**: released from enterochromaffin-like cells (ECL) in gastric glands
3. **Ach**: released from enteric nerve endings in the fundus



The acid secreted by parietal cells serves to sterilize the meal and also to begin the hydrolysis of dietary macromolecules. Intrinsic factor is important for the later absorption of vitamin B_{12}, or cobalamin. Pepsinogen is the precursor of pepsin, which initiates protein digestion. Lipase similarly begins the digestion of dietary fats.

There are three primary stimuli of gastric secretion, each with a specific role to play in matching the rate of secretion to functional requirements (Figure).

1. Gastrin is a hormone that is released by G cells in the antrum of the stomach both in response to a specific neurotransmitter released from enteric nerve endings, known as gastrin-releasing peptide (GRP) or bombesin, and also in response to the presence of oligopeptides in the gastric lumen.

2. Histamine is also a trigger of parietal cell secretion, via binding to H_2-receptors.

3. Finally, parietal and chief cells can also be stimulated by acetylcholine, released from enteric nerve endings in the fundus.

Note:
- Stimulatory effects of gastrin on gastric glands are:
  1. Stimulate **ECL** cells
  2. Stimulate **Chief** cells
  3. Stimulate **Parietal** cells
- Parietal cells have 3 receptor types on their surfaces for:
  (1) Gastrin: PLC-IP3 system
  (2) Histamine (H_2)**: AC-cAMP system**
  (3) Ach (M_1)**: : PLC-IP3 system**

Triggers of gastric secretion during gastric phase:

1. **Meal constituents (meat)**: **specifically** trigger **gastrin** secretion
2. **GI wall distention**: **initiates vago-vagal** as well as **local reflexes** that further amplify secretions during gastric phase
3. **Buffering action** of the meal: **enhance** acid secretion

Termination of gastric secreting:

1. **Increased gastric acidity** **stimulate somatostatin** that inhibits G cells and ECL cells function and hence inhibits acid secretion by parietal ells
2. **When food in the stomach:** the **meal buffers** that gastric **acidity** and enhances acid secretion thus remove (shut off) the inhibitory action of somatostatin
3. **When food in the intestine (out of stomach): No buffering** action of meal is presents thus **somatostatin terminates** acid secretion (gastrin and histamine effects)

Parietal cells

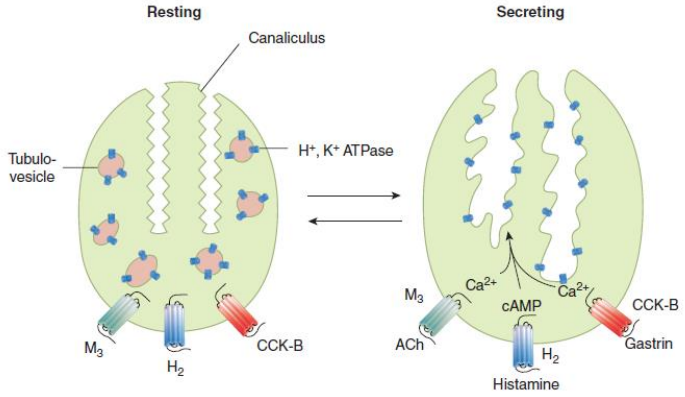
- Contains high number of mitochondria (i.e.; **high ATP requirement**)
- Contains **apical H^+, K^+-ATPase** (proton) pump
- **Pumping H+ into the lumen against conc. gradient (> million-fold)** is accompanied by the **release of equivalent amount of bicarbonate into the blood** (that will use latter to neutralize gastric acidity once stomach function is complete)

Once the meal is swallowed, on the other hand, meal constituents trigger substantial release of gastrin and the physical presence of the meal also distends the stomach and activates stretch receptors, which provoke a "vago-vagal" as well as local reflexes that further amplify secretion during the gastric phase. The presence of the meal also buffers gastric acidity that would otherwise serve as a feedback inhibitory signal to shut off secretion secondary to the release of somatostatin, which inhibits both G and ECL cells as well as secretion by parietal cells themselves

This probably represents a key mechanism whereby gastric secretion is terminated after the meal moves from the stomach into the small intestine.

Gastric parietal cells are packed with mitochondria that supply energy to drive the apical H^+,K^+-ATPase, or proton pump, that moves H^+ ions out of the parietal cell against a concentration gradient of more than a million-fold.

The secretion of protons is also accompanied by the release of equivalent numbers of bicarbonate ions into the bloodstream, which are later used to neutralize gastric acidity once its function is complete .



CLINICAL BOX 25–1

Peptic Ulcer Disease

Gastric and duodenal ulceration in humans is related primarily to a breakdown of the barrier that normally prevents irritation and autodigestion of the mucosa by the gastric secretions. Infection with the bacterium *Helicobacter pylori* disrupts this barrier, as do aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the production of prostaglandins and consequently decrease mucus and HCO_3^- secretion. The NSAIDs are widely used to combat pain and treat arthritis. An additional cause of ulceration is prolonged excess secretion of acid. An example of this is the ulcers that occur in the **Zollinger–Ellison syndrome**. This syndrome is seen in patients with gastrinomas. These tumors can occur in the stomach and duodenum, but most of them are found in the pancreas. The gastrin causes prolonged hypersecretion of acid, and severe ulcers are produced.

THERAPEUTIC HIGHLIGHTS

Gastric and duodenal ulcers can be given a chance to heal by inhibition of acid secretion with drugs such as omeprazole and related drugs that inhibit H^+–K^+ ATPase ("proton pump inhibitors"). If present, *H. pylori* can be eradicated with antibiotics, and NSAID-induced ulcers can be treated by stopping the NSAID or, when this is not advisable, by treatment with the prostaglandin agonist misoprostol. Gastrinomas can sometimes be removed surgically.

Pancreatic juice components:

1. Enzymes:

- Found in **zymogen granules** and secreted by **exocytosis** into pancreatic ducts.
- Most of them secreted as **inactive forms** and **only activated** when they reach the **intestinal lumen** (i.e.; by acidic chyme)
- They are **activated** following **proteolytic cleavage** by **trypsin** (see in chapter 26)
- They digest large peptides, fats and polysaccharides

2. Trypsin inhibitor protein

Trypsin is a **danger proteolytic enzyme** released from the pancreas as inactive trypsinogen, therefore; the pancreas normally secrete also **trypsin inhibitor** protein to abolish any possible activation of trypsinogen in pancreatic juice

3. Minerals: rich in **bicarbonates**

4. Water:

5. pH: alkaline (*in addition to neutral or alkaline bile and intestinal secretion)* this pH **neutralize** the **acid** gastric **contents** entering duodenum and **raising duodenal pH to 6.0-7.0**

Secretion rate: 1500mL/day

Hormonal Control during intestinal phase:

1. **CCK** hormone: primarily stimulate enzyme secretion
2. **Secretin**: primarily stimulate bicarbonate secretion

Neural Control during intestinal phase:

- **Ach** : primarily stimulate aqueous secretion

Neural control during cephalic phase:

- **Ach**: released from vagus nerve causes pancreatic secretion **even** during cephalic phase

PANCREATIC SECRETION

The pancreatic juice contains enzymes that are of major importance in digestion . Its secretion is controlled in part by a reflex mechanism and in part by the gastrointestinal hormones secretin and cholecystokinin (CCK).

Granules containing the digestive enzymes (**zymogen granules**) are formed in the cell and discharged by exocytosis from the apexes of the cells into the lumens of the pancreatic ducts .

About 1500 mL of pancreatic juice is secreted per day. Bile and intestinal juices are also neutral or alkaline, and these three secretions neutralize the gastric acid, raising the pH of the duodenal contents to 6.0–7.0.

The pancreatic juice also contains a range of digestive enzymes, but most of these are released in inactive forms and only activated when they reach the intestinal lumen

The enzymes are activated following proteolytic cleavage by trypsin, itself a pancreatic protease that is released as an inactive precursor (trypsinogen). The potential danger of the release into the pancreas of a small amount of trypsin is apparent; the resulting chain reaction would produce active enzymes that could digest the pancreas. It is therefore not surprising that the pancreas also normally secretes a trypsin inhibitor.

Secretion of pancreatic juice is primarily under hormonal control.

Bile components:

1. Bile acids:

- Synthesized by liver from cholesterol and secreted into the bile.
- They are important in digestion and absorption of fats

2. Cholesterol: as **native form**

3. Pigments: bilirubin and **biliverdin**

Bile acids and **bile pigments** are responsible for the **golden yellow color** of bile

4. Minerals: rich in **bicarbonates**

5. Water: low contents (bile is **concentrated juice**)

6. pH: alkaline (*in addition to neutral or alkaline pancreatic and intestinal secretion)* this pH **neutralize** the **acid** gastric **contents** entering duodenum and **raising duodenal pH to 6.0-7.0**

Secretion rate: 500mL/day

Function:

1. **Bile acids** facilitate the digestion and absorption of fats by emulsifying fat droplets

Hormonal control during intestinal phase:

- **CCK**: contracts gallbladder wall and relax the sphincter of Oddi cause bile ejection into the duodenum

BILIARY SECRETION

An additional secretion important for gastrointestinal function, bile, arises from the liver. The bile acids contained therein are important in the digestion and absorption of fats.

Bile is also the only route by which the body can dispose of cholesterol—either in its native form, or following conversion to bile acids.

Bile

Bile is made up of the bile acids, bile pigments, and other substances dissolved in an alkaline electrolyte solution that resembles pancreatic juice. About 500 mL is secreted per day. Some of the components of the bile are reabsorbed in the intestine and then excreted again by the liver (**enterohepatic circulation**).

The glucuronides of the **bile pigments**, bilirubin and biliverdin, are responsible for the golden yellow color of bile.

When considering bile as a digestive secretion, it is the bile acids that represent the most important components. They are synthesized from cholesterol and secreted into the bile

General functions of GIT that require regulation:

1. **Secretion**
2. **Digestion**
3. **Absorption**
4. **Motility**

Modalities of regulation (integrate in complementary fashion)

1. **Endocrine regulation:** (hormones release by triggers associated with the meal) to affect local and distant areas from their site of release
2. **Paracrine regulation:** short-lived mediators alter the cell function in the local area where they are released
3. **Neural regulation:**
   A. **Extrinsic innervation**: include connections with **CNS**
   B. **Enteric nervous system**: include **sensory** and **secretomotor** neurons of the GIT

GASTROINTESTINAL REGULATION

The various functions of the gastrointestinal tract, including secretion, digestion, and absorption , and motility , must be regulated in an integrated way to ensure efficient assimilation of nutrients after a meal. There are three main modalities for gastrointestinal regulation that operate in a complementary fashion to ensure that function is appropriate.

First, **endocrine** regulation is mediated by the release of hormones by triggers associated with the meal. These hormones travel through the bloodstream to change the activity of a distant segment of the gastrointestinal tract, an organ draining into it (eg, the pancreas), or both.

Second, some similar mediators are not sufficiently stable to persist in the bloodstream, but instead alter the function of cells in the local area where they are released, in a **paracrine** fashion.

Finally, the intestinal system is endowed with extensive neural connections. These include connections to the central nervous system (**extrinsic innervation**), but also the activity of a largely autonomous **enteric nervous system** that comprises both sensory and secretomotor neurons.

MCQ: Salivary constituent that play a role in killing of bacteria is

A. Lysozyme
B. IgE
C. Mucin
D. α-amylase
E. Sodium

MCQ: The ability of saliva to neutralizes the gastric acidity that may reflex into the esophagus is related to

A. Absorption of Na^+ and Cl^- in salivary acini
B. Secretion of Na^+ and Cl^- in salivary ducts
C. Absorption of bicarbonate and K^+ in the salivary acini
D. Secretion of bicarbonate and K^+ in the salivary ducts
E. All of above are related

MCQ: Regarding saliva composition; which of the following statements accurately describes saliva tonicity?

A. Saliva is hypertonic to blood plasma.
B. Saliva is isotonic to blood plasma.
C. Saliva is hypotonic to blood plasma.
D. Saliva tonicity varies based on the composition of ingested food.
E. Saliva has a tonicity comparable to cerebrospinal fluid.

MCQ: Oxyntic glands are important glands in stomach; they secrete all of the followings EXCEPT

A. Hydrochloric acid
B. Pepsinogen
C. Gastrin
D. Mucus
E. Intrinsic factor

MCQ: All the following statements regarding pancreatic secretion are true EXCEPT

A. The intestinal phase is the predominant phase
B. The cephalic phase could be initiated by smelling
C. Vagal stimulation mediates the cephalic phase only
D. Ach and secretin are important mediators for aqueous secretion
E. Acinar and ductal cells are stimulated during the intestinal phase

MCQ: The characteristics of pancreatic secretion

A. In response to vagal stimulation is copious rich in bicarbonate but poor in enzymes
B. In response to acid in the duodenum is scanty but rich in enzymes
C. In response to secretin secretion is low in bicarbonate
D. Contains enzymes that digest neutral fat to glycerol and fatty acids
E. Contain enzymes that convert disaccharides to monosaccharides

MCQ: The composition of bile is

A. Contains enzymes requires for digestion of fats
B. Contains unconjugated bilirubin
C. Salts make cholesterol more water soluble
D. Pigments contains iron
E. Becomes more alkaline during storage in the gallbladder

MCQ: MCQ: Enterochromaffin-like (ECL) cells are important cells. ECL cells secrete

A. Ach
B. Gastrin
C. NEP
D. Histamine
E. GIP

MCQ: Regarding protein digestion, which of the followings has the ability to digest collagen?

A. Trypsin
B. Pepsin
C. Elastase
D. Chymotrypsin
E. Carboxypeptidase

MCQ: Which of the following has the lowest pH?

A. Gastric juice
B. Colonic luminal contents
C. Pancreatic juice
D. Saliva
E. Bile

MCQ: A 50-year-old man complaining of severe epigastric pain, frequent heartburn, and unexplained weight loss over a 6-month period. He have no relief from H2 receptor blockers. The upper endoscopy reveals erosions and ulcerations in the proximal duodenum and an increased output of gastric acid in the fasting state. The patient is most likely to have a tumor secreting which of the following hormones?

A. Secretin
B. Somatostatin
C. Motilin
D. Gastrin
E. Cholecystokinin