# Overview of Gastrointestinal Function & Regulation

CHAPTER 25

## Second 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<br>overview of gastrointestinal function and regulation | • gastrointestinal secretion<br>• gastrointestinal regulation<br>• hormones and paracrine<br>• enteric nervous system |

- **Polypeptides** (**GI hormones**) secreted from **nerve** endings and **mucosal glands** during a meal act in **paracrine** fashion (local) and can **diffuse** into the **blood** to affect other tissues.
- They regulate GI **secretions** and **motility**

- **Type**: polypeptide
- **Source**: G cells in the antrum
- **Action**:
- **Stimulate** acid secreting **parietal** cells: stimulate **acid**, HCl secretion
- **Stimulate** pepsinogen secreting **chief** cells: stimulate **pepsin** secretion
- **Stimulate** gastric and intestinal **mucosal growth**: trophic action
- **Regulation**:

**Stimuli**:

1. **Stomach contents** (presence of protein digested **amino acids** phenylalanine and tryptophan)
2. **Gastric wall distention-** direct action on G cells
3. **Increased rate** of **vagus nerve** discharge via GRP
4. **Blood borne** factors (**calcium**, **epinephrine**)

**Effect of HCl on G cells**

1. **Direct inhibitory** effect
2. **Indirect** inhibitory effect through stimulation of **somatostatin** release from antral D cells

**Inhibitors**:

1. **Gastric** acid (HCl)
2. **Somatostatin**
3. **Blood borne factors (Secretin, GIP, VIP, Glucagon and Calcitonin)**

# HORMONES/PARACRINES

Biologically active polypeptides that are secreted by nerve cells and gland cells in the mucosa act in a paracrine fashion, but they also enter the circulation. Measurement of their concentrations in blood after a meal has shed light on the roles these **gastrointestinal hormones** play in the regulation of gastrointestinal secretion and motility.

# GASTRIN

Gastrin is produced by cells called G cells in the antral portion of the gastric mucosa .

principal physiologic actions are stimulation of gastric acid and pepsin secretion and stimulation of the growth of the mucosa of the stomach and small and large intestines (**trophic action**). Gastrin secretion is affected by the contents of the stomach, the rate of discharge of the vagus nerves, and bloodborne factors .
Gastrin secretion is also increased by the presence of the products of protein digestion in the stomach, particularly amino acids, which act directly on the G cells.

Acid in the antrum inhibits gastrin secretion, partly by a direct action on G cells and partly by release of somatostatin, a relatively potent inhibitor of gastrin secretion. The effect of acid is the basis of a negative feedback loop regulating gastrin secretion. Increased secretion of the hormone increases acid secretion, but the acid then feeds back to inhibit further gastrin secretion. In conditions such as pernicious anemia in which the acid-secreting cells of the stomach are damaged, gastrin secretion is chronically elevated.

- **Type**: polypeptide
- **Source**:
- Upper small intestine glands (**I cells**)
- Nerves cells of many parts of the body including **distal ileum**, **colon** and **cerebral cortex** (regulates food intake and related to anxiety and analgesia)
- **Actions in the GIT**:

1. **Stimulates pancreatic enzyme** secretion (**important action**)
2. **Stimulates gallbladder** wall **contraction** (from which it gets its name)
3. **Relaxes** the **sphincter** of **Oddi** (allow bile and pancreatic juice flow into the duodenum)
4. **Augments** the action of **secretin** in producing **alkaline** pancreatic juice
5. **Inhibits gastric emptying**
6. Exerts **trophic** effect on **pancreas**
7. **Increase** the **synthesis** of **enterokinase**
8. May **enhance** small **intestine** and **colon motility**

- **Regulation**:

**Stimuli**:

1. **Products of protein and fat digestion in the duodenum** (peptides, **amino acids** and fatty acids)
2. **Intestinal wall distention**

# CHOLECYSTOKININ

CCK is secreted by endocrine cells known as I cells in the mucosa of the upper small intestine. It has a plethora of actions in the gastrointestinal system, but the most important appear to be the stimulation of pancreatic enzyme secretion; the contraction of the gallbladder (the action for which it was named); and relaxation of the sphincter of Oddi, which allows both bile and pancreatic juice to flow into the intestinal lumen.

In addition to its secretion by I cells, CCK is found in nerves in the distal ileum and colon. It is also found in neurons in the brain, especially the cerebral cortex, and in nerves in many parts of the body . In the brain, it may be involved in the regulation of food intake, and it appears to be related to the production of anxiety and analgesia.

In addition to its primary actions, CCK augments the action of secretin in producing secretion of an alkaline pancreatic juice. It also inhibits gastric emptying, exerts a trophic effect on the pancreas, increases the synthesis of enterokinase, and may enhance the motility of the small intestine and colon.

The secretion of CCK is increased by contact of the intestinal mucosa with the products of digestion, particularly peptides and amino acids, and also by the presence in the duodenum of fatty acids .

Because the bile and pancreatic juice that enter the duodenum in response to CCK enhance the digestion of protein and fat, and the products of this digestion stimulate further CCK secretion, a sort of positive feedback operates in the control of CCK secretion.

- **Type**: polypeptide
- **Source**: Upper small intestine glands (**S cells**)
- **Actions in the GIT**:

1. **Stimulates bicarbonate** by ductal pancreatic and biliary cells (**important action**)
2. **Augments** the action of **CCK** in the secretion of pancreatic **zymogens**
3. **May contracts the pyloric sphincter**
4. **Decrease gastric acid** secretion

- **Regulation**:

**Stimuli**:

1. **Products of protein and fat digestion in the duodenum** (peptides, **amino acids** and fatty acids)
2. **Bile** bathing the upper intestinal mucosa
3. Neutral duodenal pH

# SECRETIN

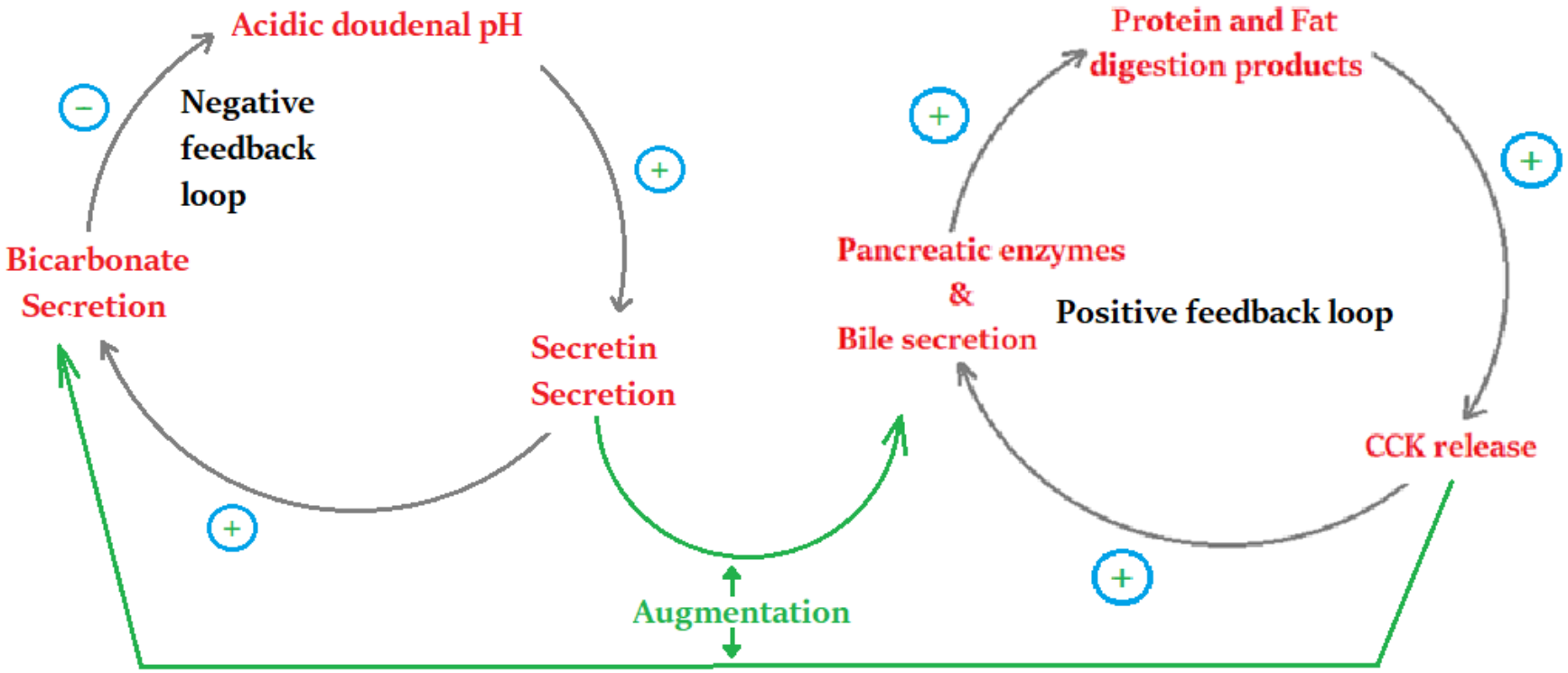
Secretin is secreted by S cells that are located deep in the glands of the mucosa of the upper portion of the small intestine.

Only one form of secretin has been isolated, and any fragments of the molecule that have been tested to date are inactive. Its half-life is about 5 min, but little is known about its metabolism.

Secretin increases the secretion of bicarbonate by the duct cells of the pancreas and biliary tract. It thus causes the secretion of a watery, alkaline pancreatic juice.

It also augments the action of CCK in producing pancreatic secretion of digestive enzymes. It decreases gastric acid secretion and may cause contraction of the pyloric sphincter.

The secretion of secretin is increased by the products of protein digestion and by acid bathing the mucosa of the upper small intestine. The release of secretin by acid is another example of feedback control: Secretin causes alkaline pancreatic juice to flood into the duodenum, neutralizing the acid from the stomach and thus inhibiting further secretion of the hormone.


Acidic doudenal pH
Negative feedback loop
Bicarbonate Secretion
Secretin Secretion
Protein and Fat digestion products
Pancreatic enzymes & Bile secretion
Positive feedback loop
CCK release
Augmentation

- **Type**: polypeptide
- **Source**: Duodenal and jejunal mucosa (**K cells**)
- **Actions in the GIT**:

1. **Inhibits** gastric **secretion (in larger doses)**
2. **Inhibits** gastric **motility (in larger doses)**
3. **Stimulates insulin secretion**

- **Regulation**:

**Stimuli**:

1. **Glucose** in the duodenum
2. **Fats** in the duodenum

**Notes:**

- **Gastrin, CCK, Secretin** and **glucagon** all stimulate insulin secretion
- **GIP** is the **only** one that **stimulate** insulin secretion when **administered** at blood level **comparable** to that produced by **oral glucose** so it is called glucose-dependent insulinotropic peptide, (i.e.; **its blood level parallel the glucose would be absorbed which would require sufficient insulin to deal with**)

## GIP

GIP is produced by K cells in the mucosa of the duodenum and jejunum. Its secretion is stimulated by glucose and fat in the duodenum, and because in large doses it inhibits gastric secretion and motility, it was named gastric inhibitory peptide.

In the meantime, it was found that GIP stimulates insulin secretion. Gastrin, CCK, secretin, and glucagon also have this effect, but GIP is the only one of these that stimulates insulin secretion when administered at blood levels comparable to those produced by oral glucose. For this reason, it is often called **glucose-dependent insulinotropic peptide**.

- **Type**: polypeptide 22 a.a.
- **Source**: **Enterochromaffin** cells and **Mo** cells in **stomach**, **small intestine** and **colon**
- **Target**: **GPCR** on **enteric neurons** in **stomach**, **duodenum** and **colon**
- **Actions in the GIT**: **Contraction** of smooth **muscles** in the **stomach** and **intestine** in the period **between meals**

## MOTILIN

Motilin is a polypeptide containing 22 amino acid residues that is secreted by enterochromaffin cells and Mo cells in the stomach, small intestine, and colon. It acts on G-protein–coupled receptors on enteric neurons in the duodenum and colon and produces contraction of smooth muscle in the stomach and intestines in the period between meals .

- **Type**: polypeptide
- **Source**: Gastric and intestinal mucosa (**D cells**)
- Forms: Somatostatin 14 and Somatostatin 28
- **Inhibitory actions in the GIT are directed on**:

1. Gastrin, VIP, GIP, secretin and motilin
2. Pancreatic exocrine secretion
3. Gastric acid secretion
4. Gastric acid motility
5. Gallbladder contraction
6. Absorption of glucose, amino acids and triglycerides

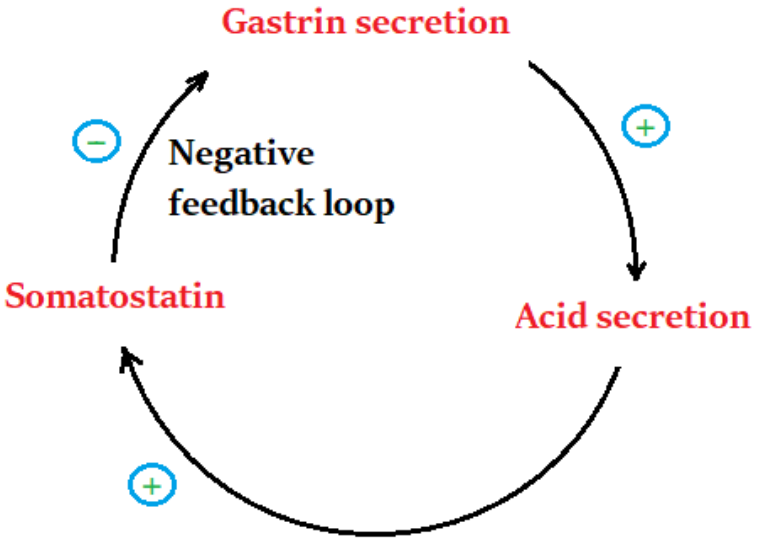
- **Regulation**:

**Stimuli**:

1. **Acid** in the lumen (in stomach and intestine)

# SOMATOSTATIN

**Somatostatin**, the growth hormone–inhibiting hormone originally isolated from the hypothalamus, is secreted as a paracrine by D cells in the pancreatic islets (see Chapter 24) and by similar D cells in the gastrointestinal mucosa. It exists in tissues in two forms, somatostatin 14 and somatostatin 28, and both are secreted. Somatostatin inhibits the secretion of gastrin, VIP, GIP, secretin, and motilin. Its secretion is stimulated by acid in the lumen, and it probably acts in a paracrine fashion to mediate the inhibition of gastrin secretion produced by acid. It also inhibits pancreatic exocrine secretion; gastric acid secretion and motility; gallbladder contraction; and the absorption of glucose, amino acids, and triglycerides.



### Ghrelin

- **Source**: Stomach
- **Role**:
  1. act on brain to control food intake
  2. stimulate GI motility
  3. Stimulate GH secretion by pituitary gland

### Substance P

- **Source:** Gastrointestinal endocrine cells and nerve cells (may found in the circulation)
- **Role**: Increase the motility of small intestine
- **Note**: Substance P is a co-transmitter of Ach in nerve endings in intestine. Thus it stimulate GI motility as do Ach

# OTHER GASTROINTESTINAL PEPTIDES

**Ghrelin** is secreted primarily by the stomach and appears to play an important role in the central control of food intake . It also stimulates growth hormone secretion by acting directly on receptors in the pituitary

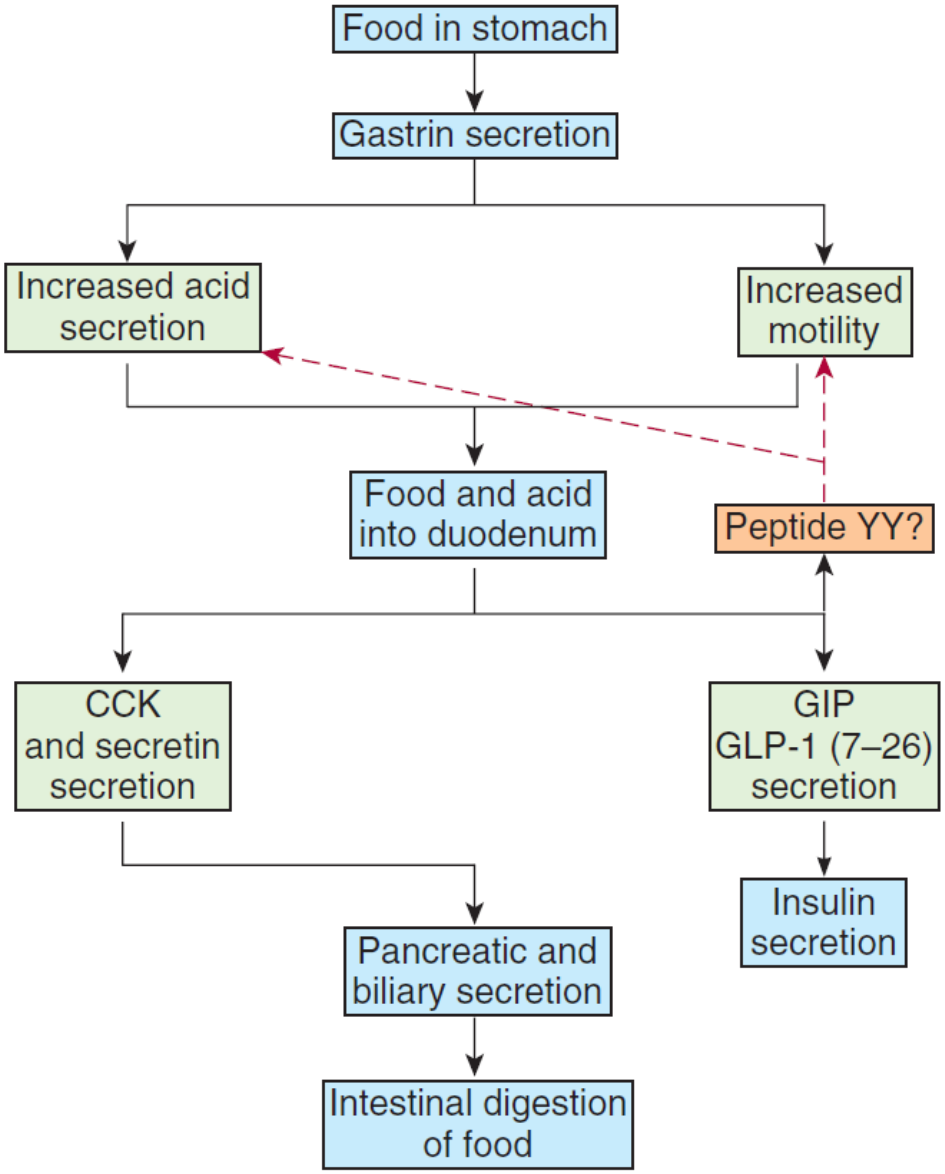
**Substance P** is found in endocrine and nerve cells in the gastrointestinal tract and may enter the circulation. It increases the motility of the small intestine.

- **Composition**: 100 million neurons (sensory, interneurons and motor)
- **Divisions**:
  1. **Myenteric plexus (Auerbach plexus):**
     - **Location**: between the outer longitudinal and the middle circular muscle layers
     - **Innervates**: longitudinal and circular muscles
     - **Function**: control GI movements
  1. **Submucosal plexus (Meissner plexus):**
     - **Location**: between the middle circular muscle layer and the mucosa (near exocrine and endocrine glands)
     - **Innervates**: glandular epithelium, endocrine cells and submucosal blood vessels
     - **Function**: control GI secretions
- **Neurotransmitters**
  1. **Acetylcholine** (ester)
  2. **Epinephrine** and **serotonin** (amines)
  3. **GABA** (amino acid)
  4. **ATP** (purine)
  5. **NO** and **CO** (gases)
  6. **Peptides** and polypeptides

  Some of the peptides act in **paracrine** fashion and others enter blood and becoming **hormones**
- **Connections**
  1. Between the two divisions **themselves**
  2. With **CNS** by means of parasympathetic and sympathetic nerves

# THE ENTERIC NERVOUS SYSTEM

Two major networks of nerve fibers are intrinsic to the gastrointestinal tract: the **myenteric plexus** (Auerbach plexus), between the outer longitudinal and middle circular muscle layers, and the **submucous plexus** (Meissner plexus), between the middle circular layer and the mucosa . Collectively, these neurons constitute the **enteric nervous system**. The system contains about 100 million sensory neurons, interneurons, and motor neurons in humans—as many as are found in the whole spinal cord—and the system is probably best viewed as a displaced part of the central nervous system (CNS) that is concerned with the regulation of gastrointestinal function. It is sometimes referred to as the "little brain" for this reason. It is connected to the CNS by parasympathetic and sympathetic fibers but can function autonomously without these connections . The myenteric plexus innervates the longitudinal and circular smooth muscle layers and is concerned primarily with motor control, whereas the submucous plexus innervates the glandular epithelium, intestinal endocrine cells, and submucosal blood vessels and is primarily involved in the control of intestinal secretion. The neurotransmitters in the system include acetylcholine, the amines norepinephrine and serotonin, the amino acid γ-aminobutyrate (GABA), the purine adenosine triphosphate (ATP), the gases NO and CO, and many different peptides and polypeptides. Some of these peptides also act in a paracrine fashion, and some enter the bloodstream, becoming hormones.


Food in stomach
Gastrin secretion
Increased acid secretion
Increased motility
Food and acid into duodenum
Peptide YY?
CCK and secretin secretion
GIP GLP-1 (7–26) secretion
Insulin secretion
Pancreatic and biliary secretion
Intestinal digestion of food

MCQ: Gastrin is one of the important gastrointestinal hormones. Which of the followings is not related to gastrin?

A. Produced by G cells in the antral portion of the gastric mucosa
B. It stimulates intestinal mucosal growth
C. It enhances acid and pepsin secretion by gastric glands
**D. Its secretion is increased when gastric pH is more acidic**
E. Its rate of secretion is parallel the amount of protein in the diet

MCQ: The rate of gastrin hormone secretion is enhanced by the followings EXCEPT

A. Gastric wall distention
B. Presence of phenylalanine and tryptophan among gastric contents
**C. Increased rate of acetylcholine release by vagus nerve**
D. Presence of epinephrine in blood
E. Hyperparathyroidism

MCQ: The rate of gastrin hormone secretion is inhibited by the followings EXCEPT

A. Secretin
B. Somatostatin
**C. Atropine**
D. Glucagon
E. Calcitonin

MCQ: CCK is secreted by endocrine cells in the upper small intestine. CCK actions are the followings EXCEPT

**A. Inhibits gastric acid secretion**
B. Increases enterokinase synthesis
C. Enhances bicarbonate secretion by pancreas
D. Relaxes the sphincter of Oddi
E. Stimulates pancreatic zymogens secretion

MCQ: Which of the followings is not an inhibitor of CCK release?

**A. Duodenum luminal acidity**
B. Inhibition of vagus nerve
C. Atropine
D. Somatostatin
E. None of the above

MCQ: Secretin is secreted from S cells of duodenal mucosa. The followings are actions of secretin EXCEPT

A. Stimulates bicarbonate secretion by pancreatic ductal cells
B. Augments the action of CCK on pancreatic zymogen secretion
C. Inhibits gastric acid secretion
**D. Inhibits gastric motility**
E. May contracts the pyloric sphincter

MCQ: Stimulation of submucosal plexus induces which of the followings?

A. GI motility
B. Gastric pH
C. Sphincter tone
**D. GI secretions**
E. Constipation

MCQ: One of the followings is not an action related to CCK but is mainly an action related to secretin when the chyme is in the duodenum.

A. Contraction of gall bladder
B. Relaxation of the sphincter of Oddi
**C. Bicarbonate secretion by pancreas**
D. Trypsin secretion by pancreas
E. None of the above

MCQ: The CCK hormone does not ____

A. Secreted by jejunal mucosa
**B. Contract the stomach**
C. Contract the gall bladder muscles
D. Synergize secretin-induced pancreatic bicarbonate secretion
E. Relax the sphincter of Oddi

MCQ: The hormone _____ is released during processing of food in small intestine and inhibits the gastric motility caused by gastrin

A. GIP
B. Motilin
**C. CCK**
D. Secretin
E. None of the above

MCQ: The secretin hormone ___

A. Secreted by the pylorus
B. Cause the release of pancreatic amylase
**C. Increase duodenal pH**
D. Augment the action of gastrin on the stomach
E. All of the above

MCQ: The duodenum reflexly inhibits stomach motility in the flowing conditions EXCEPT

A. Mucosal irritation
B. Presence of excess fats in the meal
C. Presence of excess protein in the meal
D. Duodenal wall stretching
**E. Alkaline pH of duodenum**

MCQ: Which is true about motilin?

A. Secreted from jejunum
**B. Secreted during fasting**
C. Secreted in response to fats
D. Secreted continuously through the day
E. Secretion is inhibited by food

MCQ: Which of the following paracrine hormones does not stimulate GI motility

A. Gastrin
B. Substance P
**C. GIP**
D. Ghrelin
E. Motilin