2. Gastrointestinal Physiology
Gastric structure

The stomach is a J-shaped sac-like chamber lying between the esophagus and small intestine. It is arbitrarily divided into four sections based on anatomical, histological, and functional distinctions: 1. the fundus, 2. the body, 3. the antrum, 4. the pyloric sphincter.

- Physiologically, it is more appropriately divided into (1) the “orad” portion, comprising about the first two thirds of the body, and (2) the “caudad” portion, comprising the remainder of the body plus the antrum.
- The stomach has three layers of smooth muscle-the usual longitudinal and circular layers, and a third oblique layer.

The smooth muscle layers in the fundus and body are relatively thin, but the lower part of the stomach, the antrum, has much heavier musculature.
Motor function of the stomach:
Gastric motility are:
The motor functions of the stomach are three folds:
A. Storage functions of the stomach (Gastric filling involves receptive relaxation):
- As food enters the stomach, it forms concentric circles of the food in the orad portion of the stomach, the newest food lying closest to the esophageal opening and the oldest food lying nearest the outer wall of the stomach.
- When empty, the stomach has a volume of about 50 ml; when food enters the stomach, a “vago-vagal reflex” from the stomach relaxes the stomach (receptive relaxation) up to the volume of 1.0 to 1.5 litters.

Receptor: stretch receptors (mechanoreceptors) in wall of stomach
Afferent: vagus
Center: vagal center
Efferent: vagus (neurotransmitter: Nitric oxide) ➤ enteric neurons
Effector organ: muscle relaxation
The stomach can accommodate such a 20-fold change in volume with little change in tension in its walls and little rise in intra-gastric pressure, through the following mechanism. The interior of the stomach is thrown into deep folds. During a meal, the folds get smaller and nearly flatten out as the stomach relaxes slightly with each mouthful.
• https://www.youtube.com/watch?v=hpS5kMn_B0I
• https://www.youtube.com/watch?v=WB19GKaZTog
B. Mixing and propulsion of food in the stomach (Basic electric rhythm of the stomach wall):

Peristaltic activity, manifested as “slow waves” of contraction of the stomach, occurs at the basal electrical rate (BER) of the stomach (which supposes a maximum of 3 waves/minute). These “slow waves” originate in the ‘pacemaker-cells’ (interstitial cells of Cajal) in the middle portion of the greater curvature (the proximal corpus), and travel distally towards the pylorus once every 15 to 20 seconds.

Propagating at a slightly faster velocity along the greater curve than along the lesser curve, the contraction waves reach the pylorus simultaneously. The waves are stronger and faster (traveling 3-4 cm/sec) in the antrum.

In the proximal stomach (fundus), contraction waves propagate more slowly (< 1 cm/sec) and are quite weak called mixing waves. This allows some mixing of ingested food and gastric secretions, but more importantly, serves to facilitate food storage.
In the early stages of the antral contraction cycle, the pylorus is open, thus allowing a few ml of gastric chyme to be propelled into the duodenum. This is soon followed by a forceful pyloric closure (as the wave reaches the pyloric sphincter), forcing intra-gastric contents back into the antrum and corpus. This retro-pulsion is referred to as the ‘pyloric pump’, and serves to effectively mix food and gastric secretions, and to grind gastric contents into chyme. This process is essential to the digestion and breakdown of food in the stomach.

Some evidence suggests that it is controlled by opiates, acetylcholine, and nitric oxide (NO). Liquids pass through the pylorus in spurts. Solids have to be reduced to between 1-2mm in size before they can be successfully delivered to the duodenum. As a consequence, relatively large, indigestible solids remain in the stomach unless they are eliminated by vomiting.
Intense Antral Peristaltic Contractions During Stomach Emptying—"Pyloric Pump."

Most of the time, the rhythmical stomach contractions are weak and function mainly to cause mixing of food and gastric secretions. However, for about 20% of the time while food is in the stomach, the contractions become intense, beginning in mid-stomach and spreading through the caudal stomach; these contractions are strong peristaltic, very tight ring-like constrictions that can cause stomach emptying. As the stomach becomes progressively more and more empty, these constrictions begin farther and farther up the body of the stomach, gradually pinching off the food in the body of the stomach and adding this food to the chyme in the antrum. These intense peristaltic contractions often create 50 to 70 centimeters of water pressure, which is about six times as powerful as the usual mixing type of peristaltic waves.

When pyloric tone is normal, each strong peristaltic wave forces up to several milliliters of chyme into the duodenum. Thus, the peristaltic waves, in addition to causing mixing in the stomach, also provide a pumping action called the "pyloric pump."
C. Stomach emptying:

Stomach emptying is promoted by intense peristaltic contractions in the stomach antrum. At the same time, emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus.

**Role of the Pylorus in Controlling Stomach Emptying.**

The distal opening of the stomach is the pylorus. Here the thickness of the circular wall muscle becomes 50 to 100 percent greater than in the earlier portions of the stomach antrum, and it remains slightly tonically contracted almost all the time. Therefore, the pyloric circular muscle is called the pyloric sphincter.

Despite normal tonic contraction of the pyloric sphincter, the pylorus usually is open enough for water and other fluids to empty from the stomach into the duodenum with ease. Conversely, the constriction usually prevents passage of food particles until they have become mixed in the chyme to almost fluid consistency.

The degree of constriction of the pylorus is increased or decreased under the influence of ① nervous and ② hormonal signals from both the stomach and the duodenum, as discussed shortly.
Chyme.
After food in the stomach has become thoroughly mixed with the stomach secretions, the resulting mixture that passes down the gut is called chyme. The degree of fluidity of the chyme leaving the stomach depends on the relative amounts of
① food,
② water, and
③ stomach secretions and on the
④ degree of digestion that has occurred.
The appearance of chyme is that of a murky semifluid or paste معجون.

Hunger Contractions.
Besides the peristaltic contractions that occur when food is present in the stomach, another type of intense contractions, called hunger contractions, and often occurs when the stomach has been empty for several hours or more.
These contractions are rhythmical peristaltic contractions in the body of the stomach. When the successive contractions become extremely strong, they often fuse to cause a continuing tetanic contraction that sometimes lasts for 2 to 3 minutes.
Hunger contractions are most intense in young, healthy people who have high degrees of gastrointestinal tonus; Hunger contractions are also greatly increased by the person’s having lower than normal levels of blood sugar. When hunger contractions occur in the stomach, the person sometimes experiences mild pain in the pit of the stomach, called hunger pangs. Hunger pangs usually do not begin until 12 to 24 hours after the last ingestion of food; in people who are in a state of starvation, they reach their greatest intensity in 3 to 4 days and gradually weaken in succeeding days.

C. Stomach emptying:
Stomach emptying is promoted by intense peristaltic contractions in the stomach antrum. At the same time, emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus.
Regulation of stomach emptying:

1. Gastric factors that promote emptying:
   Increase food volume in the stomach promotes increase emptying from the stomach.

A. The amount of chyme in the stomach.
   The stomach empties at a rate proportional to the volume of chyme in it at any given time.

Stomach distension triggers increased gastric motility through

① a direct effect of stretch on the smooth muscle as well as
② through involvement of the intrinsic plexuses,
③ the vagus nerve, and
④ the stomach hormone gastrin.

B. The degree of fluidity of the chyme in the stomach, increase fluidity influences gastric emptying
2. Duodenal factors that inhibit stomach emptying:
The factors that continually monitors in the duodenum are:

i) The degree of distension of the duodenum:
   According to Laplace law: \( T = P \cdot R \): tension \( T \) on wall of an organ is direct function of its radius \( R \). Therefore, tension in stomach wall acts as the adequate stimulus for peristalsis

ii) The presence of any degree of irritation of the duodenal mucosa.

iii) The degree of acidity of the duodenal chyme.
   Un-neutralized acid in the duodenum inhibits further emptying of acidic gastric contents until complete neutralization can be accomplished.

The enterogastric inhibitory reflexes are especially sensitive to the presence of irritants and acids in the duodenal chyme, and they often become strongly activated within as little as 30 seconds. For instance, whenever the pH of the chyme in the duodenum falls below about 3.5 to 4, the reflexes frequently block further release of acidic stomach contents into the duodenum until the duodenal chyme can be neutralized by pancreatic and other secretions.
iv) The degree of osmolality of the chyme.
The rate of gastric emptying is fastest when the stomach contents are isotonic. If the stomach contents are hypertonic or hypotonic, gastric emptying is slowed.
The hypo-osmolar chyme in duodenum causes distention of osmo-receptor, which causes mild inhibition of gastric emptying.
The hyperosmolar chyme in duodenum causes shrinkage of osmo-receptor, which causes marked inhibition of gastric emptying. These effects are neural.

Because water is freely diffusible across the duodenal wall, it enters the duodenal lumen from the plasma as the duodenal osmolarity rises. Large volumes of water entering the intestine from the plasma lead to intestinal distension, and, more importantly, circulatory disturbances ensue because of the reduction in plasma volume. To prevent these effects, gastric emptying is reflexly inhibited when the osmolarity of the duodenal contents starts to rise.

v) The presence of certain breakdown products in the chyme, especially breakdown products of proteins and fat.
Food rich in carbohydrate leaves the stomach in a few hours.
Protein-rich food leaves more slowly, and emptying is slowest after a meal containing fat.
Fat is the most potent stimulus for inhibition of gastric motility. The rate of emptying of a high-fat meal is six hours, a protein and carbohydrate meal is three hours.
https://www.youtube.com/watch?v=FZ7r2OVu1ss
The possible mechanism of duodenal factors that inhibits stomach emptying

A. Inhibitory effect of entro-gastric nervous reflexes from the duodenum (entro-gastric reflex):

When food enters the duodenum, multiple nervous reflexes initiated from the duodenal wall and pass back to the stomach to slow or even stop stomach emptying as the volume of chyme in the duodenum becomes too much.

These reflexes are mediated by three routes:

1. directly from the duodenum to the stomach through the enteric nervous system in the gut wall,
2. through extrinsic nerves that go to the pre-vertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach, and
3. probably to a slight extent through the vagus nerves all the way to the brain stem, where they inhibit the normal excitatory signals transmitted to the stomach through the vagi.

All these parallel reflexes have two effects on stomach emptying:

First, they strongly inhibit the “pyloric pump” propulsive contractions, and

Second, they increase the tone of the pyloric sphincter.

B. Hormonal feedback from the duodenum inhibits gastric emptying:

The most possible GIT hormones that inhibit stomach emptying are

1. CCK (can inhibit gastric emptying when excess quantities of chyme, especially acidic or fatty chyme, enter the duodenum from the stomach.),
2. GIP, and
3. secretin.

These hormones could act as they are stimulated by different type of food; this why fat is slowest to be emptied.
Emotions can influence gastric motility:
- Sadness and fear tend to decrease motility.
- Anger and aggression tend to increase motility.
- Intense pain from any part of the body tends to inhibit motility.

This response is brought about by increased sympathetic activity.

Gastric secretion

1. Gastric cell types and their secretions

Anatomic consideration:

The gastric mucosa contains many deep glands:

In the pyloric and cardiac region of the stomach: the glands secrete mucus.

The body region including fundus of the stomach: the glands contains the following cells:

I. Parietal (oxyntic) cells: secret hydrochloric acid and intrinsic factor.
II. Chief (peptic) cells: secret pepsinogen.
III. Neck mucous cells: secret mucous.
IV. Entrochromaffin (EC) cell: Histamine.
V. G cell: Gastrin.
VI. D cell: somatostatin.

The mucus is also secreted along with $\text{HCO}_3^-$ by mucus cells on the surface of epithelium between glands.

Oxyntic gland: in the body region; contains Chief cell, D cell and Parietal cell.

Pyloric gland: in the pyloric region; contains Entrochromaffin cell, D cell, and G cell.
The stomach absorbs alcohol and aspirin but no food: No food or water is absorbed into the blood through the stomach mucosa. Two noteworthy non-nutrient substances are absorbed:

1. **Alcohol** is somewhat lipid soluble, so it can diffuse through the lipid membranes of the epithelial cells that line the stomach and can enter the blood through the sub-mucosal capillaries.

2. **Acetylsalicylic (aspirin)**. In the highly acidic environment of the stomach lumen, weak acids are lipid soluble, so they can be absorbed quickly by crossing the plasma membranes of the epithelial cells that line the stomach.

Most other drugs are not absorbed until they reach the small intestine, so they do not begin to take effect as quickly.

**B. Mucus** cells secrete thin, watery mucus. Mucus serves as a protective barrier against several forms of potential injury to the gastric mucosa:

i. By virtue of its **lubricating** properties, mucus protects the gastric mucosa against mechanical injury.

ii. It helps protect the stomach wall from **self-digestion**, because **pepsin is inhibited** when it comes in contact with the mucus layer coating the stomach lining. (However, mucus does not affect pepsin activity in the lumen, where digestion of dietary protein proceeds without interference.

iii. Being alkaline, mucus helps protect against acid injury by neutralizing HCl in the vicinity of the gastric lining, but it does not interfere with the function of HCl in the lumen.
Gastric secretions:
The cells of the gastric glands secrete about 2500mL.
Gastric secretion includes hydrochloric acid, pepsin, and intrinsic factor.

A. Intrinsic Factor secretion:
The substance intrinsic factor is a 49-KDa glycoprotein.
The substance intrinsic factor is secreted by the pari
tal cells along with the secretion of hydrochloric acid. When the acid-producing pari
tal cells of the stomach are destroyed, which frequently occurs in persons with chronic gastritis, not only does achlorhydria (lack of stomach acid secretion) develop, but pernicious anemia also often develops.

B. Secretion and Activation of Pepsinogen.
Several slightly different types of pepsinogen are secreted by the peptic and mucous cells of the gastric glands. Even so, all the pepsinogens perform the same functions.
Pepsinogen released during food digestion. When pepsinogen is first secreted, it has no digestive activity. However, as soon as it comes in contact with hydrochloric acid, it is activated to form active pepsin. In this process, the pepsinogen molecule, having a molecular weight of about 42,500, is split to form a pepsin molecule, having a molecular weight of about 35,000.

Pepsin functions as an active proteolytic enzyme in a highly acid medium (optimum pH 1.8 to 3.5), but above a pH of about 5 it has almost no proteolytic activity and becomes completely inactivated in a short time.

Pepsinogen acts as a signal for the release of other digestive enzymes such as gastrin and cholecystokinin.

Hydrochloric acid is as necessary as pepsin for protein digestion in the stomach.
Mucosal barrier (mucus layer above gastric mucus membrane):
Gastric mucosa (and duodenum) is auto-protected against the
damaging effect (auto-digestion) of gastric juice by the mucosal
barrier.

The mucosal barrier is produced by

1. mucus (secreted by neck cells of gastric gland and surface
   mucosal cells) and

The hydrochloric acid crosses this barrier in finger-like channels,
leaving the gel layer intact.

Some of the resistance of the mucosa of the GIT to auto-digestion
is also provided by “trefoil peptides” in the mucus, which are also
acid resistance.

2. secreted $\text{HCO}_3^-$ (secreted by surface mucosal cells).

The bicarbonate is trapped in the mucus gel, so that a pH gradient
is established that ranges from pH 1.0 to 2.0 at luminal side to pH
6.0 to 7.0 at the surface of epithelial cells.

Prostaglandins stimulate mucus and bicarbonate secretion.
The gastric mucosal barrier protects the stomach lining from gastric secretion: How can the stomach contain strong acid contents and proteolytic enzymes without destroying itself? 

First, the luminal membranes of the gastric mucosal cells are almost impermeable to $\text{H}^+$, so acid cannot penetrate into the cells and damage them. 

Second, the lateral edges of these cells are joined together near their luminal borders by tight junctions, so acid cannot diffuse between the cells from the lumen into the underlying submucosa. 

Third, mucus provides a protective coating. 

The properties of the gastric mucosa that enable the stomach to contain acid without injuring itself constitute the gastric mucosal barrier. 

These protective mechanisms are further enhanced by the fact that the entire stomach lining is replaced every three days. Because of rapid mucosal turnover, cells are usually replaced before they are exposed to the wear and tear of harsh gastric conditions long enough to suffer damage. 

When the barrier occasionally is broken and the gastric wall is injured by its acidic and enzymatic contents. This occurs, an erosion, or peptic ulcer, of the stomach wall results.
A few stem cells rapidly divide and serve as the parent cells of all new cells of the gastric mucosa. The daughter cells that result from cell division either migrate out of the pit to become surface epithelial cells or migrate down deeper to the gastric glands, where they differentiate into chief or parietal cells. Through this activity, the entire stomach mucosa is replaced about every three days.

• The gastric mucosa is covered by surface epithelial cells, which secrete thick, viscous, alkaline mucus that forms a visible layer several millimeters thick over the surface of the mucosa.
A. Hydrochloric acid (HCl)

It performs several functions that aid digestion:

1. Activates the enzyme precursor pepsinogen to an active enzyme, pepsin, and provides an acid medium that is optimal for pepsin activity.

2. Aids in the breakdown of connective tissue and muscle fibers, reducing large food particles into smaller particles.

3. Denatures protein; that is, it uncoils proteins from their highly folded final form, thus exposing more of the peptide bonds for enzymatic attack.

4. Along with salivary lysozyme, kills most of the microorganisms ingested with food, although some do escape and continue to grow and multiply in the large intestine.

2. Mechanism of gastric H+ secretion

When stimulated, the parietal cells secrete an acid solution that contains about approximately 0.17 N HC, 160 mmol/L of hydrochloric acid (comparing to other cell which is 0.00004meq/L), which is nearly isotonic with the body fluids. The pH of this acid is about 0.8, demonstrating its extreme acidity. At this pH, the hydrogen ion concentration is about 3 million times that of the arterial blood. Yet the pH of the cytoplasm of the parietal cell is 7.0 to 7.2
To concentrate the hydrogen ions in this tremendous amount requires more than 1500 calories of energy per liter gastric juice.

Parietal cells secrete hydrochloric acid (HCl) into the lumen of the stomach and, concurrently, absorb HCO$_3^-$ into the bloodstream as follows:

a. In the parietal cells, CO$_2$ and H$_2$O are converted to H$^+$ and HCO$_3^-$, catalyzed by carbonic anhydrase.

b. H$^+$ is secreted into the lumen of the stomach by the H$^+$-K$^+$ pump (H$^+$, K$^+$-ATPase). Cl$^-$ is secreted along with H$^+$; thus, the secretion product of the parietal cells is HCl.

- The drug omeprazole inhibits the H$^+$,K$^+$-ATPase and blocks H$^+$ secretion.

- The HCO$_3^-$ produced in the cells is absorbed into the bloodstream in exchange for Cl$^-$ (Cl$^-$-HCO$_3^-$ exchange). HCO$_3^-$ is added to the venous blood, the pH of the blood increases ("alkaline tide"). (Eventually, this HCO$_3^-$ will be secreted in pancreatic secretions to neutralize H$^+$ in the small intestine.)

- If vomiting occurs, gastric H$^+$ never arrives in the small intestine, there is no stimulus for pancreatic HCO$_3^-$ secretion, and the arterial blood becomes alkaline (metabolic alkalosis).
The agents that stimulate and inhibits H+ secretion by parietal cell:

A. Inhibition:
   1. Prostaglandin
   2. Somatostatine

Somatostatin: is a 14-amino-acid peptide that is released in the gastrointestinal tract D cells (located in the antrum), and enteric nerves and pancreas from paracrine cells, as well as from the hypothalamus.

Somatostatin is a key regulatory peptide that has many physiologic effects:

a. Somatostatine inhibits the secretion of numerous hormones and transmitters, including GI hormones: gastrin, cholecystokinin, secretin, vasoactive intestinal peptide (VIP), and 5-HT
   b. Somatostatine reduces intestinal fluid secretion and pancreatic secretion.
   c. Somatostatine slows gastrointestinal motility and inhibits gallbladder contraction.
   d. Somatostatine induces direct contraction of vascular smooth muscle, leading to a reduction of portal and splanchnic blood flow.
   e. Somatostatine inhibits secretion of some anterior pituitary hormones.

Prostaglandins and Somatostatine inhibit gastric H+ secretion by activating a Gi protein, inhibiting adenylyl cyclase and decreasing cAMP levels.
B. Stimulation:
1. Acetylcholine:
Acetylcholine, the receptor on the parietal cells is muscarinic (M3) receptor
2. Gastrine:
Gastrine, the receptor on the parietal cells is Chole-cysto-kinin-B (CCK-B) receptor; both the second messenger is IP3 and increased intracellular [Ca+].
3. Histamine:
Histamine the receptor on the parietal cells is H2 receptors. The H2 receptor is coupled to adenyl cyclase via a Gs protein. The second messenger for histamine is cAMP.
3. Mechanisms control gastric H+ secretion

a. Vagal stimulation

Increases H+ secretion by:

A. In the direct path, the vagus nerve innervates parietal cells (M3 receptor; ACh as a neurotransmitter) and stimulates HCl secretion directly.

B. In the indirect path,

1. The vagus nerve innervates G cells which stimulates gastrin secretion, which then stimulates H+ secretion by an endocrine action. M3 is receptor and Gastrin Releasing Peptide (GRP) is neurotransmitter and not acetylcholine.

2. The vagus nerve innervates entero-chromaffin-like (ECL) cells. M1 is receptor and Gastrin Releasing Peptide (GRP) is neurotransmitter and not acetylcholine which stimulates Histamine secretion, which then stimulates HCl secretion by an endocrine action on parietal cell

-Atropine, a cholinergic muscarinic antagonist, inhibits H+ secretion by blocking the direct pathway, which uses ACh as a neurotransmitter. However, atropine does not block HCl secretion completely because it does not inhibit the indirect pathway, which uses GRP as a neurotransmitter.

-Vagotomy eliminates both direct and indirect pathways.
b. Gastrin
First step: Release of gastrin.
Gastrin release from G cell in pyloric gland in the antrum
Gastrin secretion increased by either:
A. Directly on the G cells by stomach stimulation:
   - is released in response to eating a meal (small peptides, distention of the stomach)
B. Indirectly on the G cells by vagal stimulation (as discussed above)
Second step: Transfer of gastrin form the G cells in the antrum to body of stomach by blood to stimulate H+ secretion by:
A. Directly by acting on parietal cell: CCK-B (Chole-cysto-kinin type B) is receptor where gastrin bind
B. Indirectly by acting on ECL cell: CCK-B is receptor where gastrin bind; which stimulates Histamine secretion, and then stimulates HCl secretion by an endocrine action on parietal cell
c. Histamine

- is released from entero-chromaffin-like (ECL) cells are usually located close to parietal cells in the gastric mucosa and diffuses to the nearby (paracrine) to stimulated parietal cells H2 receptors thereby stimulating gastric acid secretion.

- These cells are stimulated by:
  1. Gastrin (by CCK-B receptor)
  2. Vagus (M1 receptor).

- H2 receptor-blocking drugs, such as cimetidine, inhibit H+ secretion by blocking the stimulatory effect of histamine.
d. Potentiating effects of ACh, histamine, and gastrin on H+ secretion

- The secretory response to Ach and histamine given together is greater than the combined effect of the same quantity of Ach and histamine given one at a time. This phenomenon, namely \((A+B) > (A) + (B)\) is known as potentiation.
- Potentiation occurs when the response to simultaneous administration of two stimulants is greater than the sum of responses to either agent given produce maximal effects. As a result, low concentration of stimulus given together can produce maximal effects.
- Potentiation is likely to be due to receptor-receptor interaction, i.e. occupation of one receptor alter the affinity or efficacy of another receptor.
- Potentiation of gastric H+ secretion can be explained, in part, because each agent has a different mechanism of action on the parietal cell.
  1. Histamine potentiates the actions of ACh and gastrin in stimulating H+ secretion.
  2. ACh potentiates the actions of histamine and gastrin in stimulating H+ secretion.
4. Inhibition of gastric H+ secretion

a. Low pH (< 3.0) in the stomach
   ① Negative feedback mechanisms inhibit the secretion of H+ by the parietal cells.
   ② inhibits gastrin secretion and thereby inhibits H+ secretion.

This occurs when:
   i. When the pH of the stomach contents is < 3.0 (After a meal is ingested)
   ii. When the stomach emptied, further H+ secretion decreases the pH of the stomach contents.

b. Somatostatin

Somatostatin is released from D cell.
   ① D cell in the antrum is stimulated by
      A. Indirectly by vagus in the antrum (muscarinic (M2) receptor)
      B. Directly by H+ is sensed by the D cells in the antrum

Somatostatin transfer from D cell to parital cell by blood
   ② D cell in the fundus is stimulated by vagus (muscarinic (M3) receptor); and neurotransmitter is calcitonin gene releasing peptide (CGRP).

Somatostatin transfer from D cell to parital cell or Eccell in paracrin fashion; in this pathway, somatostatin antagonizes the stimulatory action of histamine on H+ secretion

This provides negative feedback regulation for stomach acid secretion.
c. prostaglandin
This is why **NSAID** causes increase gastric secretion.

Other influences:
①Hypoglycemia act via the brain and vagal effects to stimulates acid and pepsin secretion.
②Alcohol and caffeine, both of which act directly on the mucosa to stimulates gastric secretions.

**Gastric secretion during the inter-digestive period.**
The stomach secretes a few milliliters of gastric juice each hour during the “inter-digestive period,” when little or no digestion is occurring anywhere in the gut. The secretion that does occur is usually almost entirely of the non-oxyntic type, composed mainly of mucus but little **pepsin** and almost no **acid**.
Peptic ulcer disease (PUD)

Peptic ulcers are most commonly caused by one of three etiologies:

1. Helicobacter Pylori (HP) infection,
2. Use of non-steroid anti-inflammatory Drugs (NSAIDs)
3. Stress-related mucosal damage (SRMD).

Stress-related mucosal damage occurs most frequently in critically ill patients (such as prolonged mechanical ventilation (i.e. > 48 h) and coagulopathy).

Stress-related mucosal damage is thought to be caused by factors such as compromised mesenteric perfusion rather than HP or NSAIDs.

Stress-related mucosal damage onset is usually acute, and in a small proportion of patients may progress to deep ulceration and hemorrhage.
<table>
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<th>Characteristics of Common Causes of Peptic Ulcer Disease</th>
<th>H. pylori</th>
<th>NSAID</th>
<th>SRMD</th>
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<tr>
<td>Onset</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Acute</td>
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<tr>
<td>Primary location of damage</td>
<td>Duodenum</td>
<td>Stomach</td>
<td>Stomach</td>
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<tr>
<td>Presence of symptoms</td>
<td>Frequent</td>
<td>Rare</td>
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<td>Primary mechanism for ulceration</td>
<td>Infection resulting in inflammatory state</td>
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<td>Deep</td>
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<td>Dependence on acid for mucosal damage</td>
<td>Greater</td>
<td>Lesser</td>
<td>Lesser</td>
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<tr>
<td>Characterization of GI bleeding</td>
<td>Minor</td>
<td>Major</td>
<td>Major</td>
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<tr>
<td>Responsive to acid-suppressive therapy</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

GI, gastrointestinal; H. pylori, Helicobacter pylori; NSAID, non-steroidal anti-inflammatory drug; SRMD, stress-related mucosal damage.
Less common causes of peptic ulceration include
1. Zollinger-Ellison syndrome (ZES),
   ZES is caused by a gastrin-producing tumor called a gastrinoma found in pancreas and results in gastric acid hyper-secretion.
2. cancer chemotherapy/radiation, and
3. illicit-drug use causing vascular insufficiency.

Gastric acid output occurs in two stages:
1. Basal acid output (BAO), which reflects the baseline output of acid during the fasting state.
   Basal acid secretion follows a circadian cycle in which it is highest at night and lowest in the morning.
   Basal acid secretion is modulated by the effects of acetylcholine and histamine acting on the parietal cell.
2. Maximal acid output (MAO), which occurs in response to meals.
   Food can cause maximal gastric acid secretion in two ways.
   A. In the cephalic phase of acid secretion, the vagus nerve stimulates acid secretion in response to the sight, smell, or taste of food.
   B. In both the gastric and intestinal phases of acid secretion, the physical distention caused by food in the gastric fundus and small intestine induces gastrin secretion resulting in acid production.

The proteolytic activity of pepsin appears to influence ulcer formation.
Helicobacter pylori (HP)

Helicobacter pylorus normally resides in the human stomach. Helicobacter pylorus is transmitted via the fecal-oral route or through ingestion of fecal-contaminated water or food.

Helicobacter pylorus Infection is more common in developing countries because of crowded conditions and the presence of contaminated food and water.

Helicobacter pylorus colonization does not necessarily reflect an active infection since the organism can attach itself to the gastric epithelium without invading cells.

Helicobacter pylorus Cellular invasion is necessary for an active infection. Helicobacter pylorus Cellular active infection is usually asymptomatic and leads to chronic active gastritis.
Pathophysiology: Helicobacter pylori are a (a) gram-negative (b) micro-aerophilic (c) rod shape (d) S-shaped bacterium (e) multiple flagella initially invade the gastric antrum but migrates to the more proximal sections of the stomach over time

75% of gastric ulcers and 90% of duodenal ulcers are attributed to Helicobacter pylori infection as well as two distinct forms of gastric cancer: mucosa-associated lymphoid tissue (MALT) lymphoma and adenocarcinoma
Four steps are critical for Helicobacter pylori colonization and pathogenesis:

1. Survival under acidic stomach conditions;
   a. Intra-bacterial urease activity

   HP is able to survive in the acidic conditions of the stomach because of its ability to induce a transient hypochlorhydria (ammonia and HCl will cause NH₄Cl and decrease HCl).

   b. Extracellular urease

   an enzyme that hydrolyzes urea into carbon dioxide and ammonia; ammonium hydroxide will be produced quickly when ammonia combines with water. Therefore, Helicobacter pylori can safely pass through the gastric juice when ammonia hydroxide neutralizes the acidic micro-environment close to the bacteria.
(2) Movement toward epithelium cells through flagella-mediated motility;
The motility provided by the flagella allows it to penetrate the mucous gel barrier, thus permitting a direct interaction with epithelial cells (the site where acute infection occurs).
Flagella can be considered as an early stage colonization/virulence factor

(3) Attaching to host receptors by adhesins;
When H. pylori colonizes on the mucosal layer lining the gastric epithelium, the interaction of bacterial adhesins with cellular receptors protects the bacteria from displacement from the stomach by forces such as those generated by peristalsis and gastric emptying, and then bacteria get metabolic substrates and nutrients to improve growth through releasing toxins to damage the host cells.
Although blood-antigen binding protein A (BabA) and sialic acid-binding adhesin (SabA) are the well-characterized adhesins studied so far, not all H. pylori strains express these adhesins; so adhesins is a family of protein

(4) causing tissue damage by toxin release.
Two major virulence factors:

a. Cytotoxin-associated gene A (Cag-A)

Several studies indicated that the **CagA-positive strains** are directly associated with **acute gastritis, gastric ulcer, and gastric cancer development**

The **cytotoxin associated gene-pathogenicity island (cag-PAI)**, a common gene sequence believed responsible for pathogenesis that contains over 40 genes. This pathogenicity island is usually absent from H. pylori strains isolated from humans who are carriers of H. pylori, but remain asymptomatic.

cagPAI carries at least **6 genes with homology to (Type IV secretion systems (T4SS) are macromolecular assemblies used by bacteria to transport material across their membranes)**, and thus **translocate the bacterial protein CagA** into the host gastric cell cytoplasm upon contact with epithelium cells. Once Cag-A injected into the cell it will be phosphorylated
Once Cag-A injected into the cell it will be phosphorylated. The phosphorylated CagA affects the ① adhesion (intracellular junction), ② spreading, and ③ migration of the cell. The phosphorylated CagA can affect the host cell in several aspects:

- ① Disruption tight junction,
- ② denude microvilli,
- ③ pedestal formation,
- ④ mucus depletion,
- ⑤ the change of the cytoskeleton (actin polymerization),
- ⑥ increase cell motility,
- ⑦ Nitric oxide and Cyclooxygenase (COX-2) induction,
- ⑧ affecting the proliferation and inflammation of cells (neutrophil infiltration),
- ⑨ apoptosis,
- ⑩ stimulating the gastric epithelium cells to secrete IL-8 (Interleukin-8) a chemotactic and inflammatory cytokine.

NF-κB (Nuclear Factor Kappa-light-chain-enhancer of activated B cells) is a protein complex that controls

i. transcription of DNA,

ii. cytokine production and

iii. cell survival.
b. Vacuolating cytotoxin A (Vac A)
Bacterial-surface adhesion components facilitate binding of HP to epithelial cells.

The Helicobacter pylori vacuolating cytotoxin (vac A: cytotoxin-associated gene A) binds target cells and is slowly internalized in the cytoplasm, where its biologic activity is expressed.

a. facilitates the binding of HP to the cell membrane ➤ b. enabling the HP organism better access to nutrients.

The effects of Vacuolating cytotoxin A are:

a. Vac A effect on endosomal maturation leading to vacuolation of epithelial cells
b. Induces host cell death through to localize to mitochondria where its effects may be responsible for triggering the apoptotic cascade
c. Causes leakage of ions and small molecules
d. bind to a protein on the cell membrane and induce inflammation
e. obstruct T-cell activation and proliferation
The complex interplay between bacterial virulence factors + enhanced inflammatory response ▼ results in a chronic HP infection ▼

elevates acid production and reduces various protective factors.

Infection causes
①gastric inflammation of the mucosa (superficial chronic gastritis) and
②polymorphonuclear infiltration (active chronic gastritis).
the effect of infection varies from individual to individual
①the majority becoming asymptomatic carriers,
②others develop peptic ulcers.
③individuals can develop chronic atrophic gastritis, a risk factor for the development of adenocarcinoma and gastric lymphoma.
A number of host and pathogenic factors contribute to the ability of HP to cause gastro-duodenal mucosal injury including:

1. Direct mucosal damage.
2. Alterations to host inflammatory responses.

H. pylori–induced pan-gastritis ➤ Hypochlorhydria

First step: inflammation of antrum ➤ Increase gastrin + decrease somatostatin ➤ increase gastrin go to body of stomach

Second step: inflammation of body ➤ gastrin cannot stimulate EC cell to secret histamine or partial cell to secret HCl ➤ decrease HCl

H. pylori–induced antral-predominant inflammation ➤ hyper-gastrinemia

First step: inflammation of antrum ➤ Increase gastrin + decrease somatostatin ➤ increase gastrin go to body of stomach

Second step: No inflammation of body ➤ gastrin can stimulate EC cell to secret histamine or partial cell to secret HCl ➤ increase HCl
Non-steroidal Anti-Inflammatory Drugs

NSAIDs are one of the most widely used classes of medications in the United States, particularly in the elderly. Chronic NSAID ingestion leads to symptoms of nausea and dyspepsia in nearly 50% of patients.

Peptic ulceration occurs in up to 30% of patients who use NSAIDs chronically, with gastrointestinal bleeding or perforation occurring in 1.5% of patients who develop an ulcer.

NSAID-related peptic ulcers usually occur in the stomach; duodenal ulcers are much less common. Risk factors for NSAID-induced peptic ulcers and complications are presented in Table 15–2.

<table>
<thead>
<tr>
<th>TABLE 15–2. Established Risk Factors for Ulcers and Gastrointestinal Complications Related to NSAID Use</th>
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<tbody>
<tr>
<td>Age over 60</td>
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<tr>
<td>Concomitant anticoagulant use</td>
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<tr>
<td>Preexisting coagulopathy (elevated INR or thrombocytopenia)</td>
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<tr>
<td>Concomitant corticosteroid therapy</td>
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<tr>
<td>Previous peptic ulcer disease or upper gastrointestinal bleeding</td>
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<tr>
<td>Cardiovascular disease and other comorbid conditions</td>
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<tr>
<td>Multiple NSAID use (e.g., low-dose aspirin in conjunction with another NSAID)</td>
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<tr>
<td>Duration of NSAID use (greater than 1 month)</td>
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<tr>
<td>High-dose NSAID use</td>
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<tr>
<td>NSAID-related dyspepsia</td>
</tr>
</tbody>
</table>

Several important principles should be considered when estimating the risk for developing PUD in a patient taking an NSAID

1. Risk factors are generally additive

2. Some risk factors (e.g., corticosteroid therapy) are not by themselves a risk factor for ulceration but increase PUD risk substantially when combined with NSAID therapy.

3. Many of the risk factors postulated to increase PUD risk in a patient taking an NSAID (e.g., rheumatoid arthritis, tobacco smoking, and alcohol consumption) remain unproven and thus should not generally be considered independent risk factors for NSAID-induced ulceration. Whether H pylori infection is a risk factor for NSAID-induced ulcer remains controversial. However, H pylori and NSAID act independently to increase ulcer-related bleeding and appear to have additive effect.
Pathophysiology

Non-selective NSAIDs [those that inhibit both cyclooxygenase-1 and -2 (COX-1 and COX-2)] cause gastric mucosal damage by two primary mechanisms:

1. Direct or topical irritation of gastric epithelium.
   Direct irritation of the mucosal lining by NSAIDs occurs because NSAIDs are weak acids. Topical irritation is therefore most pronounced with more acidic NSAIDs such as aspirin. While the direct irritant effects of NSAIDs play a contributory role in the development of NSAID-induced gastritis, this mechanism generally plays a minor role in the evolution of NSAID-induced PUD.

2. Systemic inhibition of endogenous mucosal prostaglandin synthesis.
   The systemic effects of NSAIDs are the primary cause of PUD. Cyclooxygenase (COX) is the rate-limiting enzyme in the prostaglandin synthesis pathway. Inhibition of prostaglandin production is the primary therapeutic effect of NSAIDs. COX is responsible for the conversion of arachidonic acid to prostaglandins (PGs) such as PGG2 and PGH2. There are two forms of the COX enzyme, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2).
   A. COX-1 is routinely found in body tissues that produce prostaglandins for normal physiologic maintenance.
   B. COX-2 is an inducible enzyme that is expressed during states in which cytokines and inflammatory mediators are elevated (e.g., fever and pain).
Administration of NSAIDs parenterally (e.g., Ketorolac) or rectally (e.g., indomethacin:) is associated with an incidence of PUD that is similar to that with oral NSAIDs. Topical NSAID (e.g. Diclofenac: voltarin) would be unlikely to cause PUD given the very low serum concentrations that are achieved with this route of administration compared to that observed with oral therapy.

Prostaglandins, through their effects on

a. Stimulation of both mucus and phospholipid production.

b. Promotion of bicarbonate secretion.

c. Increased mucosal cell turnover are important factors in gastric healing and protection.

Inhibition of prostaglandin production by NSAIDs compromises these important protective mechanisms.

Finally, the platelet effects of Prostaglandins may decrease bleeding complications associated with peptic ulcer
Other Causative Factors
1. Cigarette smoking is associated with a
   A. higher prevalence of ulcers
   B. impair healing of ulcers that develop.
   The exact mechanism(s) for the detrimental effects of smoking on the gastric mucosa are unclear but may involve
   (a) increased pepsin secretion,
   (b) duodeno-gastric reflux of bile salts,
   (c) elevated levels of free radicals, and
   (d) reduced bicarbonate and prostaglandin production.
   It is unknown whether nicotine or one of the many other ingredients found in cigarettes is responsible for these deleterious effects.
2. Psychosocial factors such as life stress, baseline personality patterns, and depression may influence PUD prevalence, a clear causal relationship has not been demonstrated.
3. Dietary factors such as coffee, tea, cola, beer, and a highly spiced diet may cause dyspepsia, but they have not been shown to independently increase PUD risk.
   Although caffeine increases gastric acid secretion and alcohol ingestion causes acute gastritis, there is inconclusive evidence to confirm that either of these substances are independent risk factors for peptic ulcers.
CLINICAL PRESENTATION AND DIAGNOSIS

Peptic Ulcer Symptoms

Obtaining a medical history, especially for 1 peptic ulcer disease, 2 H pylori infection, 3 ingestion of NSAIDs, or 4 smoking, is essential in making the correct diagnosis.

Gastric and duodenal ulcers usually cannot be differentiated based on history alone, although some findings may be suggestive.

Pain is the main symptom.

An ulcer is painful as the lining is no longer protected; acid comes into contact with it and causes pain.

1. The person feels a burning sensation recurrent middle of the upper part of the abdomen (epigastric pain)

Epigastric pain is the most common symptom of both gastric and duodenal ulcers.

2. Pain is characterized by a gnawing or burning sensation and occurs after meals—classically, shortly after meals with gastric ulcer and 2-3 hours afterward with duodenal ulcer.

3. Food or antacids relieve the pain of duodenal ulcers but provide minimal relief of gastric ulcer pain.

4. About 50-80% of patients with duodenal ulcers experience nightly pain, as opposed to only 30-40% of patients with gastric ulcers and 20-40% of patients with non-ulcer dyspepsia (NUD).

5. The pain worsens when 1 a person consumes food too greasy or stimulants such as tea, coffee or alcohol 2 Taking anti-inflammatory drugs or aspirin worsening the ulcer.

6. The severity of pain often fluctuates. The intensity of pain can vary widely (e.g., from dull to sharp).

Dyspepsia: indigestion
Nausea and vomiting

Nausea and vomiting are symptoms that can be due to a number of different causes. Various disorders of the gastrointestinal, cardiac, neurologic, and endocrine systems can lead to nausea and vomiting.

Postoperative nausea and vomiting (PONV) occurs in 30% of surgical patients overall, and in up to 70% of high-risk patients. This can be due to:

1. Severing or disturbing the vagus nerve leading to gastric motility abnormalities
2. The choice of anesthetic agents and
3. The duration of surgery.

The risk factors for PONV include:

1. Female gender,
2. History of motion sickness or PONV,
3. Non-smoking status,
4. Use of opioids in the postoperative period.

Pregnancy-associated nausea and vomiting is common, affecting 70% to 85% of pregnant women, especially early in pregnancy. Approximately 50% of pregnant women experience nausea and vomiting of pregnancy (NVP), 25% experience nausea alone, and 25% are not affected. In 0.5% to 2% of pregnancies, this can lead to hyperemesis gravidarum (may be due to raised levels of human chorionic gonadotrophin), a potentially life-threatening condition of prolonged nausea, vomiting, and consequently, malnutrition.

Some therapeutic drugs can cause nausea and vomiting including:

1. Cancer chemotherapy agents are rated according to their emetogenic potential, and antiemetic therapy is prescribed based on these ratings. Due to potentially severe nausea and vomiting, some patients are unable to complete their chemotherapy treatment regimen.
2. Radiation therapy can induce nausea and vomiting, especially when it is used to treat abdominal malignancies.
3. Oral contraceptives, hormone therapy, oral hypoglycemic agents, anticonvulsants, and opiates are other common therapies that can cause nausea and vomiting.

4. Some medications, such as digoxin and theophylline, cause nausea and vomiting in a dose-related fashion. Nausea and vomiting may indicate higher-than-desired drug concentrations.

5. Ethanol and other toxins also cause nausea and vomiting.

**PATHOPHYSIOLOGY**

Nausea and vomiting consist of three stages: (1) nausea, (2) retching, and (3) vomiting.

Nausea is the subjective feeling of a need to vomit. It is often accompanied by autonomic symptoms such as pallor, tachycardia, diaphoresis, and salivation.

Retching, which follows nausea, consists of diaphragm, abdominal wall, and chest wall contractions and spasmodic breathing against a closed glottis. Retching can occur without vomiting, but this stage produces the pressure gradient needed for vomiting, although no gastric contents are expelled.

Vomiting, or emesis, is a reflexive, rapid, and forceful oral expulsion of upper gastrointestinal contents due to powerful and sustained contractions in the abdominal and thoracic musculature. Vomiting, like nausea, can be accompanied by autonomic symptoms.

Regurgitation, unlike vomiting, is a passive process without involvement of the abdominal wall and diaphragm wherein gastric or esophageal contents move into the mouth. In patients with gastro-esophageal reflux disease (GERD), one hallmark symptom is acid regurgitation.
Various areas in the brain and the gastrointestinal (GI) tract are stimulated when the body is exposed to noxious stimuli (e.g., toxins), gastrointestinal irritants (e.g., infectious agents), or chemotherapy. These areas include the chemoreceptor trigger zone (CTZ) in the area postrema of the fourth ventricle of the brain, the vestibular system, visceral afferents from the GI tract, and the cerebral cortex. These in turn stimulate regions of the reticular areas of the medulla within the brain stem. This area is the central vomiting center, the area of the brain stem that coordinates the impulses sent to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles that lead to vomiting.
A. Chemoreceptor trigger zone (CTZ):
The CTZ, located outside the blood–brain barrier (BBB), is exposed to cerebrospinal fluid and blood. Therefore it is easily stimulated by uremia, acidosis, and the circulation of toxins such as chemotherapeutic agents.

The CTZ has many serotonin type 3 (5-HT3), neurokinin-1 (NK1), and dopamine (D2) receptors.

B. Visceral vagal nerve fibers are rich in 5-HT3 receptors. They respond to gastrointestinal distention, mucosal irritation, and infection.

C. Motion sickness is caused by stimulation of the vestibular system. This area contains many histaminic (H1) and muscarinic cholinergic receptors.

D. The higher brain (i.e., cerebral cortex) is affected by sensory input such as sights, smells, or emotions that can lead to vomiting. This area is involved in anticipatory nausea and vomiting associated with chemotherapy.
Small intestinal motility

- The small intestine functions in the digestion and absorption of nutrients. The small intestine 1 mixes nutrients with digestive enzymes, 2 exposes the digested nutrients to the absorptive mucosa, 3 and then propels any non-absorbed material to the large intestine.

1. Segmentation contractions
- mix the intestinal contents.
- A section of small intestine contracts, sending the intestinal contents (chyme) in both orad and caudad directions. That section of small intestine then relaxes, and the contents move back into the segment.
- This back-and-forth movement produced by segmentation contractions causes mixing without any net forward movement of the chyme.

The maximum frequency of the segmentation contractions in the small intestine is determined by the frequency of electrical slow waves in the intestinal wall. Because this frequency normally is not greater than 12 per minute in the duodenum and proximal jejunum, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this maximum frequency occurs only under extreme conditions of stimulation. In the terminal ileum, the maximum frequency is usually 8-9 contractions per minute.

The segmentation contractions become exceedingly weak when 1 the excitatory activity of the enteric nervous system is blocked by 2 the drug atropine. Therefore, even though it is the slow waves in the smooth muscle itself that cause the segmentation contractions, these contractions are not effective without background excitation mainly from the myenteric nerve plexus.
2. Peristaltic contractions

The function of the peristaltic waves in the small intestine is

1. cause progression of chyme toward the ileocecal valve but also
2. to spread out the chyme along the intestinal mucosa.

Peristaltic waves are highly coordinated

1. peristaltic waves propel the chyme through the small intestine toward the large intestine.

Ideally, peristalsis occurs after digestion and absorption have taken place.

• Contraction behind the bolus and, simultaneously, relaxation in front of the bolus cause the chyme to be propelled caudally.
• The peristaltic reflex is coordinated by the enteric nervous system.

These waves can occur in any part of the small intestine and move toward the anus at a velocity of 0.5 to 2.0 cm/sec—faster in the proximal intestine and slower in the terminal intestine. They are normally weak and usually die out after traveling only 3 to 5 centimeters. The waves rarely travel farther than 10 centimeters, so forward movement of the chyme is very slow—so slow that net movement along the small intestine normally averages only 1 cm/min. This rate of travel means that 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.
Activity of the small intestine is greatly increased after a meal. This increased activity is caused partly by the beginning entry of chyme into the duodenum, causing stretch of the duodenal wall.

Gastro-enteric reflex is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine.

Several hormonal factors:
- Enhance intestinal motility by: gastrin, CCK, insulin, motilin, and serotonin.
- Inhibit small intestinal motility by: secretin and glucagon.

Unlike peristalsis, which predominates in the esophagus, segmentation contractions occur in the large intestine and small intestine, while predominating in the latter. While peristalsis involves one-way motion in the caudal direction, segmentation contractions move chime in both directions, which allows greater mixing with the secretions of the intestines.
Peristaltic rush:
Although peristalsis in the small intestine is normally weak, intense irritation of the intestinal mucosa, as occurs in some severe cases of infectious diarrhea, can cause both powerful and rapid peristalsis, called the peristaltic rush. This phenomenon is initiated

1. partly by nervous reflexes that involve the autonomic nervous system and brain stem and
2. partly by intrinsic enhancement of the myenteric plexus reflexes within the gut wall.

The powerful peristaltic contractions travel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme and excessive distention.

Weak anti-peristalsis is sometime seen in the colon, but most waves pass regularly in an oral-caudal direction (Gut law).

Movements caused by the muscularis mucosae and muscle fibers of the Villi.

1. The muscularis mucosae can cause short folds to appear in the intestinal mucosa; The mucosal folds increase the surface area exposed to the chyme, thereby increasing absorption.
2. In addition, individual fibers from this muscle extend into the intestinal villi and cause them to contract intermittently (shortening, elongating, and shortening again) “milk” the villi so that lymph flows freely from the central lacteals of the villi into the lymphatic system.

These mucosal and villous contractions are initiated mainly by local nervous reflexes in the submucosal nerve plexus that occur in response to chyme in the small intestine.
The ileocecal valve prevents backflow from colon to small intestine:
The ileocecal valve consist of:

a. the ileocecal valve
The ileocecal valve **protrudes** into the lumen of the cecum and therefore is forcefully closed when excess pressure builds up in the cecum and tries to push cecal contents backward against the valve lips. The valve usually can resist reverse pressure of at least 50 to 60 centimeters of water.

b. the ileocecal sphincter:
The wall of the ileum for several centimeters immediately upstream from the ileocecal valve has a thickened circular muscle called the ileocecal sphincter. This sphincter normally remains mildly constricted.

The main function of ileocecal valve
1. **Prevent backward food** of cecum to ileum
2. **Slows emptying of ileal** contents into the cecum: Resistance to emptying at the ileocecal valve prolongs the stay of chyme in the ileum and thereby facilitates absorption.

Normally, only **1500 to 2000 milliliters** of chyme empty into the cecum each day.
Control of ileocecal valve

1. Immediately after a meal, a gastro-ileal reflex (food in stomach causes relaxation of ileocecal valve) intensifies peristalsis in the ileum, and emptying of ileal contents into the cecum proceeds.

2. Ileal causes:
   a. **Fluidity of content** of ileum promotes emptying
   b. **Pressure and chemical irritation** relax sphincter and excite peristalsis

3. Cecal causes:
   a. When the cecum is distended delays emptying
   b. any irritant in the cecum delays emptying. For instance, when a person has an inflamed appendix, with both causes
      a. contraction of the ileocecal sphincter becomes intensified
      b. ileal peristalsis is inhibited,
   both of which greatly delay emptying of additional chyme into the cecum from the ileum.

The reflexes from the cecum to the ileocecal sphincter and ileum are mediated both by way of
1. the myenteric plexus in the gut wall
2. the extrinsic autonomic nerves, especially by way of the pre-vertebral sympathetic ganglia.
Pancreatic secretion

• contains a high concentration of HCO₃⁻, whose purpose is to neutralize the acidic chyme that reaches the duodenum.
• contains enzymes essential for the digestion of protein, carbohydrate, and fat.

1. Composition of pancreatic secretion
   a. Pancreatic juice is characterized by:
      (1) High volume
      About 1500 ml of pancreatic juice is secreted per day.
      (2) Pancreatic juice is alkaline.
      Pancreatic, bile and intestinal juice neutralize the gastric acid, raising the pH of the duodenal contents to 6.0 to 7.0. By the time the chyme reaches the jejunum, the reaction is nearly neutral.
      (3) Virtually the same Na⁺ and K⁺ concentrations as plasma
      (4) Much higher HCO₃⁻ concentration than plasma
      (5) Much lower Cl⁻ concentration than plasma
      (6) Isotonicity
      (7) Pancreatic lipase, amylase, and proteases
b. The composition of the aqueous component of pancreatic secretion varies with the flow rate

- At low flow rates, the pancreas secretes an isotonic fluid that is composed mainly of Na+ and Cl-.
- At high flow rates, the pancreas secretes an isotonic fluid that is composed mainly of Na+ and HCO3.
- Regardless of the flow rate, pancreatic secretions are isotonic.

2. Formation of pancreatic secretion
- Like the salivary glands, the exocrine pancreas resembles a bunch of grapes.
- The acinar cells of the exocrine pancreas make up most of its weight.
  a. Acinar cells
  - produce a small volume of initial pancreatic secretion, which are mainly Na+ and Cl-.
  b. Ductal cells
  - modify the initial pancreatic secretion by secreting HCO3- and absorbing Cl- via a CI-HCO3- exchange mechanism in the luminal membrane.
Secretion of Bicarbonate Ions

Although the enzymes of the pancreatic juice are secreted entirely by the acini of the pancreatic glands, the other two important components of pancreatic juice, bicarbonate ions and water, are secreted mainly by the epithelial cells of the ductules and ducts that lead from the acini.

When the pancreas is stimulated to secrete copious quantities of pancreatic juice, the bicarbonate ion concentration can rise to as high as 145 mEq/L, a value about five times that of bicarbonate ions in the plasma. This provides a large quantity of alkali in the pancreatic juice that serves to neutralize the hydrochloric acid emptied into the duodenum from the stomach.
The basic steps in the cellular mechanism for secreting sodium bicarbonate solution into the pancreatic ductules and ducts.

They are the following:

1. Carbon dioxide diffuses to the interior of the cell from the blood and, under the influence of carbonic anhydrase, combines with water to form carbonic acid (H$_2$CO$_3$). The carbonic acid dissociates into bicarbonate ions and hydrogen ions (HCO$_3^-$ and H$^+$). Additional bicarbonate ions enter the cell through the baso-lateral membrane by co-transport with sodium ions (Na$^+$). The bicarbonate ions are then exchanged for chloride ions (Cl$^-$) by secondary active transport through the luminal border of the cell into the lumen of the duct. The chloride that enters the cell is recycled back into the lumen by special chloride channels (Cystic fibrosis transmembrane conductance regulator (CFTR)).
2. The hydrogen ions formed by dissociation of carbonic acid inside the cell are exchanged for sodium ions through the baso-lateral membrane of the cell by secondary active transport. Sodium ions also enter the cell by co-transport with bicarbonate across the baso-lateral membrane. Sodium ions are then transported across the luminal border into the pancreatic duct lumen. The negative voltage of the lumen also pulls the positively charged sodium ions across the tight junctions between the cells.

3. The overall movement of sodium and bicarbonate ions from the blood into the duct lumen creates an osmotic pressure gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution. Because the pancreatic ducts are permeable to water, H2O moves into the lumen to make the pancreatic secretion isosmotic.
3. Stimulation of pancreatic secretion
a. Secretin

Secretin Stimulates Copious Secretion of Bicarbonate Ions, Which Neutralizes Acidic Stomach Chyme.
The second messenger for secretin is cAMP.

Secretin is a polypeptide, containing 27 amino acids (molecular weight about 3400), present in an inactive form, pro-secretin, in so-called S cells in the mucosa of the duodenum and jejunum.

When acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then absorbed into the blood. The one truly potent constituent of chyme that causes this secretin release is the hydrochloric acid from the stomach.

Secretin in turn causes the pancreas to secrete large quantities of fluid containing a high concentration of bicarbonate ion (up to 145 mEq/L) but a low concentration of chloride ion.
The secretin mechanism is especially important for two reasons:

First, secretin begins to be released from the mucosa of the small intestine when the pH of the duodenal contents falls below 4.5 to 5.0, and its release increases greatly as the pH falls to 3.0. This immediately causes copious secretion of pancreatic juice containing abundant amounts of sodium bicarbonate. The net result is then the following reaction in the duodenum:

\[
\text{HCl} + \text{NaHCO}_3 \rightarrow \text{NaCl} + \text{H}_2\text{CO}_3
\]

Then the carbonic acid immediately dissociates into carbon dioxide and water. The carbon dioxide is absorbed into the blood and expired through the lungs, thus leaving a neutral solution of sodium chloride in the duodenum.

In this way, the acid contents emptied into the duodenum from the stomach become neutralized, so further peptic digestive activity by the gastric juices in the duodenum is immediately blocked. Because the mucosa of the small intestine cannot withstand the digestive action of acid gastric juice, this is an essential protective mechanism to prevent development of duodenal ulcers.

Second: Bicarbonate ion secretion by the pancreas provides an appropriate pH for action of the pancreatic digestive enzymes, which function optimally in a slightly alkaline or neutral medium, at a pH of 7.0 to 8.0. Fortunately, the pH of the sodium bicarbonate secretion averages 8.0.
b. Cholecystokinin
Cholecystokinin Contribution to Control of Digestive Enzyme Secretion by the Pancreas.
The presence of food in the upper small intestine also causes a second hormone, CCK, a polypeptide containing 33 amino acids, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. This release of CCK results especially from the presence of proteases and peptones (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach. Cholecystokinin, like secretin, passes by way of the blood to the pancreas but instead of causing sodium bicarbonate secretion causes mainly secretion of still much more pancreatic digestive enzymes (amylase, lipases, and proteases) by the acinar cells. This effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70 to 80 percent of the total secretion of the pancreatic digestive enzymes after a meal.

The differences between the pancreatic stimulatory effects of secretin and CCK
(1) intense sodium bicarbonate secretion in response to acid in the duodenum, stimulated by secretin;
(2) a dual effect in response to soap (a fat);
(3) intense digestive enzyme secretion (when peptones enter the duodenum) stimulated by CCK.

CCK potentiates the effect of secretin on ductal cells to stimulate HCO$_3^-$ secretion.

The second messenger for CCK is IP$_3$ and increased intracellular [Ca$^{2+}$]. The potentiating effects of CCK on secretin are explained by the different mechanisms of action for the two GI hormones (i.e., cAMP for secretin and IP$_3$/Ca$^{2+}$ for CCK).
c. Acetylcholine (via vago-vagal reflexes)
-is released in response to 1 H+, 2 small peptides, 3 amino acids, and 4 fatty acids in the duodenal lumen.

Like CCK
1. It stimulates enzyme secretion by the acinar cells
2. It potentiates the effect of secretin on HCO3- secretion.

Multiplicative Effects of Different Stimuli.
When all the different stimuli of pancreatic secretion occur at once, the total secretion is far greater than the sum of the secretions caused by each one separately. Therefore, the various stimuli are said to “multiply,” or “potentiate,” one another. Thus, pancreatic secretion normally results from the combined effects of the multiple basic stimuli, not from one alone.
Bile secretion and gallbladder function

Composition of bile

Bile contains bile salts, which account for about one half of the total solutes also in the bile. Also secreted or excreted in large concentrations are bilirubin (bile pigments), cholesterol, lecithin, and the usual electrolytes of plasma.

Bile is about between 600 and 1000 ml/day.

1. Bile secretion:

Bile secretion occurs in two stages:

Stage one:

The initial portion is secreted by the principal functional cells of the liver, the hepatocytes through minute bile canaliculi and terminal bile ducts to the hepatic duct and common bile duct. From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder.

Stage two:

In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100%. The second secretion is stimulated especially by secretin, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach). Therefore, secretin cause bile-independent fraction of biliary secretion (fluid and electrolytes) and thus is called hydro-choleretic agent.
2. Storing and concentrating bile in the gallbladder.

Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum. The maximum volume that the gallbladder can hold is only 30 to 60 milliliters. Nevertheless, as much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin.

Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorption of chloride ions, water, and most other diffusible constituents.

Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.
3. Contraction of the gallbladder
• Chola-gogue agents: Gall bladder evacuates lead to increase release of bile from gall bladder

The mechanism of gallbladder emptying is *rhythmical contractions of the wall of the gallbladder*, but effective emptying also requires simultaneous *relaxation of the sphincter of Oddi*, which guards the exit of the common bile duct into the duodenum.

a. CCK
• *causes contraction of the gallbladder* and relaxation of the sphincter of Oddi

b. Ach (and vagus stimulation)
• *causes contraction of the gallbladder*

During the inter-digestive period, the gallbladder is relaxed, the sphincter of Oddi is closed, and the gallbladder fills with bile.

4. Functions of gallbladder:
1. The gallbladder serves as a *reservoir* for bile while it's not being used for digestion.
2. Water absorption: The gallbladder's absorbent lining concentrates the stored bile; and *water concentration decreased from 97% in liver bile to 89% in gallbladder.*
3. Acidification of bile secretion
Bile salts
The bile salts have two important actions in the intestinal tract: **First**, they have a detergent action on the fat particles in the food. This decreases the surface tension of the particles and allows agitation in the intestinal tract to break the fat globules into minute sizes. This is called the **emulsifying or detergent function of bile salts**.

The bile salts are **amphipathic** molecules because they have both hydrophilic and hydrophobic portions. In aqueous solution (is any solution in which water \( \text{H}_2\text{O} \) is the solvent), bile salts orient themselves around droplets of lipid and keep the lipid droplets dispersed (emulsification) – aid in the intestinal digestion and absorption of lipids by emulsifying and solubilizing them in **micelles**.

Micelles
- The bile salts tends to form cylindrical disks called (micelles; with the hydrophilic surface facing out and the hydrophobic surface facing in)
- Bile salts are positioned on the outside of the micelle, with their hydrophilic portions dissolved in the aqueous solution of the intestinal lumen and their hydrophobic portions dissolved in the micelle interior.
- Free fatty acids and mono-glycerides are present in the inside of the micelle, essentially "solubilized" for subsequent absorption.
Second, and even more important than the emulsifying function, bile salts help in the absorption of (1) fatty acids, (2) monoglycerides, (3) cholesterol, and (4) other lipids from the intestinal tract. They do this by forming small physical complexes with these lipids; the complexes are called *micelles*, and they are semisoluble in the chime because of the electrical charges of the bile salts. The intestinal lipids are “ferried” in this form to the intestinal mucosa, where they are then absorbed into the blood. Without the presence of bile salts in the intestinal tract, up to 40 percent of the ingested fats are lost into the feces and the person often develops a metabolic deficit because of this nutrient loss.

2. Formation of bile

- Choleretic agents: An agent that stimulates the liver to increase output of bile salt from liver.

Bile salt and acid are the only choleretic agent (there is no hormonal or neural control).
Bile is formed by the following process:

a. **Primary bile acids** (cholic acid and chenodeoxycholic acid) are synthesized from cholesterol by hepatocytes.
   - In the intestine, bacteria convert a portion of each of the primary bile acids to **secondary bile acids** (deoxycholic acid and lithocholic acid); where dehydroxylation (i.e. removal of OH group) causes these changes.
   - Synthesis of new bile acids occurs, as needed, to replace bile acids that are excreted in the feces.

b. The primary bile acids are conjugated with two **Non-essential amino acids** (glycine or taurine) to form their respective conjugated bile acid, which are named for the parent bile acid (tauro-cholic acid (is cholic acid conjugated with taurine) glycocholic acid, Glycochenodeoxycholic acid and Taurochenodeoxycholic acid. By means of conjugation the primary bile acid which initially are barley water soluble become anion and are thus rendered hydrophilic.

The acid group on the glycine is converted to a salt by adding sodium. Example (sodium-glyco-cholate) so its name now bile salt

The primary Bile salt represent 75% and secondary bile salt represent 25% of total bile salt

**Not**

Some books considered the conjugation with amino acid will change the bile acid to bile salt other consider this conjugation will only converted to conjugated bile acid and will be converted to bile slat only after the amino acid react with Na or K
Recirculation of bile acids to the liver

90% to 95% of bile salts are absorbed from the small intestine. The absorbed bile salts are transported back to the liver in the portal vein and re-excreted in the bile (entero-hepatic circulation).

Bile salt in the intestinal lumen are absorbed via

1. Bile salt are absorbed throughout the entire small intestine by passive diffusion, but only small fraction of total amount of bile salt is absorbed in this manner.

2. Bile salt are absorbed in the terminal ileum by an active carrier-mediated (the most important and efficient way of absorption); Na-bile salt co-transport system in which usually less than 5% of bile salt escape in the colon.

3. Bacteria in the terminal and colon de-conjugate the bile salt to form bile acid which are more lipophilic than bile salt and thus can be absorbed passively.

The same bacteria are responsible for transformation the primary bile salt ► secondary bile salt ► secondary bile acid (de-ox-y-cholic acid and litho-cholic acid) by removal of

① OH (hydroxylation),

② Na,

③ Amino acid (taurine or glycine)

Deoxy-cholic is absorbed, while litho-cholic acid is relatively insoluble and mostly exerted in stool, but only 1% is excreted. Those lost in the stool are replaced by synthesis in the liver; where cholesterol is changed to primary bile acid.
The normal rate of bile pool of bile synthesis is 0.2 to 0.4 g/d; the liver can increases its production of bile salts 6- to 10-fold. The average these salts make the entire circuit some 17 times before being carried out in the feces.

• The total bile salt pool of approximately 2.5 g recycles repeatedly via the entero-hepatic circulation. It has been calculated that the entire pool recycles twice per meal and six to eight times per day.

• Because bile acids are not re-circulated until they reach the terminal ileum, bile acids are present for maximal absorption of lipids throughout the upper small intestine.

• After ileal resection, bile acids are not re-circulated to the liver, but are excreted in feces. The bile acid pool is thereby depleted and fat absorption is impaired, resulting in steatorrhea.
Colon motility
Anatomic consideration:
The diameter of the colon is greater than that of the small intestine. Its length is about 100 cm in living adult and about 150 cm in autopsy. The fibers of its external muscular layer are collected into three longitudinal bands, the "taeniae coli". Because these bands are shorter than the rest of the colon, the wall of the colon forms out-pouching "haustra" between the teniae. There are no villi on the mucosa. The colonic glands are short inward projections of the mucosa that secrete mucus. The principal functions of the colon are
(1) absorption of water and electrolytes from the chyme to form solid feces and
(2) storage of fecal matter until it can be expelled. The proximal half of the colon is concerned principally with absorption, and the distal half with storage.
Colonic movement:
The movement of the colon includes:
A. Segmentation movements (mixing movement or Haustration):
In the same manner that segmentation movements occur in the small intestine, large circular constrictions occur in the large intestine. At each of these constrictions, about 2.5 centimeters of the circular muscle contract, sometimes constricting the lumen of the colon almost to occlusion. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the teniae coli, contracts. These combined contractions of the circular and longitudinal strips of muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called haustrations.
Each haustration usually reaches peak intensity in about 30 seconds and then disappears during the next 60 seconds. At times they also move slowly toward the anus during contraction, especially in the cecum and ascending colon, and thereby provide a minor amount of forward propulsion of the colonic contents. After another few minutes, new haustral contractions occur in other areas nearby. Therefore, the fecal material in the large intestine is slowly dug into and rolled over in much the same manner that one spades the earth. In this way, all the fecal material is gradually exposed to the mucosal surface of the large intestine, and fluid and dissolved substances are progressively absorbed until only 80 to 200 milliliters of feces are expelled each day.
B. Propulsive Movements—“Mass Movements.”

Much of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions. From the cecum to the sigmoid, mass movements can, for many minutes at a time, take over the propulsive role. These movements usually occur only one to three times each day, in many people especially for about 15 minutes during the first hour after eating breakfast.

A mass movement is a modified type of peristalsis characterized by the following sequence of events:

- A constrictive ring occurs in response to a distended or irritated point in the colon, usually in the transverse colon.

Then, rapidly, the 20 or more centimeters of colon distal to the constrictive ring lose their haustrations and instead contract as a unit, propelling the fecal material in this segment en masse further down the colon.

The contraction develops progressively more force for about 30 seconds, and relaxation occurs during the next 2 to 3 minutes.

Another mass movement then occurs, this time perhaps farther along the colon.

A series of mass movements usually persists for 10 to 30 minutes. They then cease but return perhaps a half day later.

When they have forced a mass of feces into the rectum, the desire for defecation is felt.

The movements of the colon are coordinated by the BER of the colon. The frequency of this wave, unlike the wave in the small intestine, increase along the colon, from about 2/min at ileo-cecal valve to 6/min at the sigmoid.
Initiation of Mass Movements by Gastrocolic and Duodenocolic Reflexes.

1. The appearance of mass movements after meals is facilitated by gastro-colic and duodeno-colic reflexes. These reflexes result from distention of the stomach and duodenum. They occur. the reflexes almost certainly are transmitted by way of the autonomic nervous system.

2. Irritation in the colon can also initiate intense mass movements. For instance, a person who has an ulcerated condition of the colon mucosa (ulcerative colitis) frequently has mass movements that persist almost all the time.

Transit time in the small intestine and colon:

- The first part of a test meal reaches the cecum in about 4 hours, and all of the indigestible portions have entered the colon in 8 or 9 hours.
- Requiring as many as 8 to 15 hours to move the chyme from the ileocecal valve through the colon, while the chyme becomes fecal in quality—a semisolid instead of a semifluid slush.
- On average, the first remnants of the meal reach the hepatic flexure in 6 hours, the splenic flexure in 9 hours, and the pelvic colon in 12 hours.
- From the pelvic colon to the anus, transport is much slower.
Absorption in the colon:
- Na\(^+\) is actively transported out of the colon, and water follows along the osmotic gradient.
- Normally, there is net secretion of K\(^+\) and HCO\(_3\) into the colon.
- The absorptive capacity of the colon makes rectal instillation a practical route for drug administration, especially in children.

Feces:
- The stools contain (1) inorganic material, (2) undigested plant fibers, (3) bacteria, and (4) water.
- Their composition is relatively unaffected by variations in diet because a large fraction of the fecal mass is of non-dietary origin. This why appreciable amount of feces continue to be passed during prolonged starvation.

Intestinal bacteria:
- The chyme in the jejunum normally contains few if any bacteria. There are more micro-organisms in the ileum, but it is only the colon that regularly contains large numbers of bacteria.
- The bacteria in GIT can be divided into three types:
  1) Pathogenic: that causes diseases.
  2) Symbiotic: that benefits the host and vice versa.
  3) Commensal: bacteria get benefit from human and human not affected. Great masses of bacteria are passed in the stool, at birth, the colon is sterile, but the intestinal bacterial flora becomes established early in life.

Antibiotics improve growth rate in a variety of species, including humans; and small amount of antibiotics are frequently added to the diet of domestic animals.
The main functions of intestinal bacteria are:

1. Bacteria is responsible for maintaining normal metabolites including:
   a) **Vitamins**: It can utilize (Vitamin C, Vitamin B₁₂, and choline), and synthesize (Vitamin K, Vitamin B, and folic acid).
   b) **Short chain fatty acid**: it is produced by colonic bacteria.
   c) **Cholesterol**: intestinal bacteria appear to play a role in cholesterol metabolism.

2. It is responsible for maintaining general characteristics of stool including:
   a) **Stool color**: the brown color of the stool is due to pigments formed the bile pigments by the intestinal bacteria.
   b) **Stool gases**: Some bacteria produce some of the gases in the flatus.
   c) **Stool pH**: Organic acids formed from carbohydrates by bacteria are responsible for the slightly acid reaction of the stools (pH 5.0 to 7.0).
   d) **Stool odor**: amines formed by the intestinal bacteria (especially indole and skatole) contribute to the odor of feces, as do sulfides.

When normal animal with the usual intestinal bacterial flora are exposed to ionizing radiation, the body defenses that prevent intestinal bacteria from invading the body break down, and a major cause of death in radiation poisoning is overwhelming sepsis. **Germ-free animals are much more resistance to radiation than animals with the usual intestinal flora because they have no intestinal bacteria to cause sepsis.**

Commensal bacteria (bacteria get benefit from human and human not affected) have recently been genetically engineered to **produce the anti-inflammatory cytokine IL-10**, and then fed to experimental animals with promising results in terms of relieving inflammatory diseases of the intestines.
DEFECATION

Most of the time, the rectum is empty of feces, partly because

1. A weak functional sphincter exists about 20 centimeters from the anus at the juncture between the sigmoid colon and the rectum.

2. A sharp angulation is also present here that contributes additional resistance to filling of the rectum.

Continual dribble of fecal matter through the anus is prevented by tonic constriction of

- an internal anal sphincter, which is a several-centimeters-long thickening of the circular smooth muscle that lies immediately inside the anus, and
- an external anal sphincter, composed of striated voluntary muscle that both surrounds the internal sphincter and extends distal to it.

The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore is under voluntary, conscious, or at least subconscious control; subconsciously, the external sphincter is usually kept continuously constricted unless conscious signals inhibit the constriction.
Defecation Reflexes.
When a mass movement forces feces into the rectum, the desire for defecation occurs immediately, including reflex contraction of the rectum and relaxation of the anal sphincters.
Defecation is initiated by defecation reflexes:

1. The local enteric nervous system in the rectal wall.
   When feces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus; if the external anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs.

2. A parasympathetic defecation reflex
   Normally when the intrinsic myenteric defecation reflex is functioning by itself, it is relatively weak. To be effective in causing defecation, it usually must be fortified by another type of defecation reflex called a parasympathetic defecation reflex that involves the sacral segments of the spinal cord.
   When the nerve endings in the rectum are stimulated, signals are transmitted first into the spinal cord (S2, S3, and S4); and then reflexly back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the "pelvic nerves". The descending colon, sigmoid, rectum contracts and the internal anal sphincter relaxes (recto-sphincteric reflex).
These parasympathetic signals greatly intensify the peristaltic waves and relax the internal anal sphincter, thus converting the intrinsic myenteric defecation reflex from a weak effort into a powerful process of defecation that is sometimes effective in emptying the large bowel all the way from the splenic flexure of the colon to the anus.

Defecation signals entering the spinal cord initiate other effects (Valsalva maneuver or straining: taking a deep breath, closure of the glottis, and contraction of the abdominal wall muscles) to force the fecal contents of the colon downward, and at the same time they 1) cause the pelvic floor to relax downward and 2) pull outward on the anal ring to evaginate the feces.

When it becomes convenient for the person to defecate, the defecation reflexes can purposely be activated by taking a deep breath to move the diaphragm downward and then contracting the abdominal muscles to increase the pressure in the abdomen, thus forcing fecal contents into the rectum to cause new reflexes. Reflexes initiated in this way are almost never as effective as those that arise naturally, and thus people who too often inhibit their natural reflexes are likely to become severely constipated.

The urge to defecate first occurs when rectal pressure increase to about 18 mmHg. When pressure reaches 55mmHg, the external as well as the internal sphincter relaxes and the contents of the rectum are expelled. Many normal humans defecate only once every 2 to 3 days, even though others defecate once a day and some as often as three times a day.

In newborn babies and in some people with transected spinal cords, the defecation reflexes cause automatic emptying of the lower bowel at inconvenient times during the day because of lack of conscious control exercised through voluntary contraction or relaxation of the external anal sphincter.
Secretion of mucus in small intestine

An extensive array of compound mucous glands, called Brunner's glands, is located in the wall of the first few centimeters of the duodenum, mainly between the pylorus of the stomach and the papilla of Vater, where pancreatic secretion and bile empty into the duodenum. These glands secrete large amounts of alkaline mucus in response to

1. tactile or irritating stimuli on the duodenal mucosa;
2. vagal stimulation, which causes increased Brunner gland secretion concurrently with increase in stomach secretion; and
3. gastrointestinal hormones, especially secretin.

The function of the mucus secreted by Brunner’s glands is to

1. protect the duodenal wall from digestion by the highly acidic gastric juice emptying from the stomach.
2. the mucus contains a large excess of bicarbonate ions, which add to the bicarbonate ions from pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach.

Brunner’s glands are inhibited by sympathetic stimulation; therefore, such stimulation in very excitable persons is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the gastrointestinal tract to be the site of peptic ulcers in about 50 percent of persons with ulcers.
Over the entire surface of the small intestine there are small pits called (intestinal glands or crypts of Lieberkühn). These crypts lie between the intestinal villi. The intestinal surface of both the crypts and the villi are covered by an epithelium composed of two types of cells:

1. **Goblet cells**, which secrete mucus.
2. **Enteroctyes**:
   - The enteroctyes in the small intestine are formed from mitotically active un-differentiated cells in the crypts of Lieberkühn. They migrate up to the tip of the villi, where they **undergo apoptosis and are sloughed into** the intestinal lumen in large numbers. The average life of these cells is **to 5 days**. The number of cells shed per day has been calculated to be about **17 billion** in human, and the amount of protein secreted in this fashion is about **30gm/day**. Mucosal cells are also rapidly sloughed and replaced in the stomach.
   - The enterocytes in the crypts, secrete large quantity of water and electrolytes and over the surface of the villi, reabsorb the water and electrolytes along with the end product of digestion. The intestinal secretions are formed by enterocytes at rate of about **1800ml/day**. The secretions are almost **pure extra-cellular fluid** and **have slightly alkaline pH in range of 7.5 to 8.0**. The secretions also are rapidly reabsorbed by the villi. This circulation of fluid from the crypts to the villi supplies a **watery vehicle** for absorption of substances from chyme as it comes in contact with the villi.
When secretion of the small intestine are collected without cellular debis, they have almost no enzymes. However, the enterocytes of the mucosa, especially those cover the villi, do contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium. These enzymes are the following:

① Several peptidases for splitting small peptides into amino acids,
② Four enzymes for splitting disaccharides into monosaccharides,
③ Intestinal lipase.

Paneth cells (endocrine cells located in the depths of the crypts of Lieberkühn) secrete defensins (naturally occurring peptide antibody).

The migrating entero-cytes are exposed to a high concentration of the defensins, and this may protect them as they move to the tops of the villi.

Secretion of mucus in large intestine

Mucus secretion of large intestine.
The mucosa of the large intestine, like that of the small intestine, has many crypts of Lieberkühn; however, unlike the small intestine, it contains no villi.
The epithelial cells secrete almost no digestive enzymes. Instead, they contain mucous cells that secrete only mucus. This mucus contains moderate amounts of bicarbonate ions secreted by a few non–mucus-secreting epithelial cells.

The rate of secretion of mucus is regulated principally
① by direct, tactile stimulation of the epithelial cells lining the large intestine and
② by local nervous reflexes to the mucous cells in the crypts of Lieberkühn.
Stimulation of the pelvic nerves from the spinal cord, which carry parasympathetic innervation to the distal one half to two thirds of the large intestine, also can cause a marked increase in mucus secretion. This increase occurs along with an increase in peristaltic motility of the colon.

During extreme parasympathetic stimulation, often caused by emotional disturbances, so much mucus can occasionally be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30 minutes; this mucus often contains little or no fecal material.

Mucus in the large intestine
- protects the intestinal wall against excoriation
- provides an adherent medium for holding fecal matter together.
- protects the intestinal wall from the great amount of bacterial activity that takes place inside the feces
- mucus plus the alkalinity of the secretion (a pH of 8.0 caused by large amounts of sodium bicarbonate) provides a barrier to keep acids formed in the feces from attacking the intestinal wall