I. STRUCTURE AND INNERVATION OF THE GASTROINTESTINAL TRACT

A. Structure of the gastrointestinal (GI) tract (Figure 6-1)

1. Epithelial cells
   ■ are specialized in different parts of the GI tract for secretion or absorption.

2. Muscularis mucosa
   ■ Contraction causes a change in the surface area for secretion or absorption.

3. Circular muscle
   ■ Contraction causes a decrease in diameter of the lumen of the GI tract.

4. Longitudinal muscle
   ■ Contraction causes shortening of a segment of the GI tract.

5. Submucosal plexus (Meissner’s plexus) and myenteric plexus
   ■ comprise the enteric nervous system of the GI tract.
   ■ integrate and coordinate the motility, secretory, and endocrine functions of the GI tract.

B. Innervation of the GI tract

■ The autonomic nervous system (ANS) of the GI tract comprises both extrinsic and intrinsic nervous systems.

1. Extrinsic innervation (parasympathetic and sympathetic nervous systems)
   ■ Efferent fibers carry information from the brain stem and spinal cord to the GI tract.
   ■ Afferent fibers carry sensory information from chemoreceptors and mechanoreceptors in the GI tract to the brain stem and spinal cord.

a. Parasympathetic nervous system
   ■ is usually excitatory on the functions of the GI tract.
   ■ is carried via the vagus and pelvic nerves.
   ■ Preganglionic parasympathetic fibers synapse in the myenteric and submucosal plexuses.
   ■ Cell bodies in the ganglia of the plexuses then send information to the smooth muscle, secretory cells, and endocrine cells of the GI tract.
The vagus nerve innervates the esophagus, stomach, pancreas, and upper large intestine.

- Reflexes in which both afferent and efferent pathways are contained in the vagus nerve are called vagovagal reflexes.

The pelvic nerve innervates the lower large intestine, rectum, and anus.

b. Sympathetic nervous system

- is usually inhibitory on the functions of the GI tract.
- Fibers originate in the spinal cord between T-8 and L-2.
- Preganglionic sympathetic cholinergic fibers synapse in the prevertebral ganglia.
- Postganglionic sympathetic adrenergic fibers leave the prevertebral ganglia and synapse in the myenteric and submucosal plexuses. Direct postganglionic adrenergic innervation of blood vessels and some smooth muscle cells also occurs.
- Cell bodies in the ganglia of the plexuses then send information to the smooth muscle, secretory cells, and endocrine cells of the GI tract.

2. Intrinsic innervation (enteric nervous system)

- coordinates and relays information from the parasympathetic and sympathetic nervous systems to the GI tract.
- uses local reflexes to relay information within the GI tract.
- controls most functions of the GI tract, especially motility and secretion, even in the absence of extrinsic innervation.

a. Myenteric plexus (Auerbach’s plexus)

- primarily controls the motility of the GI smooth muscle.

b. Submucosal plexus (Meissner’s plexus)

- primarily controls secretion and blood flow.
- receives sensory information from chemoreceptors and mechanoreceptors in the GI tract.

II. REGULATORY SUBSTANCES IN THE GASTROINTESTINAL TRACT (FIGURE 6-2)

A. GI hormones (Table 6-1)

- are released from endocrine cells in the GI mucosa into the portal circulation, enter the general circulation, and have physiologic actions on target cells.
Four substances meet the requirements to be considered "official" GI hormones; others are considered "candidate" hormones. The four official GI hormones are gastrin, cholecystokinin (CCK), secretin, and glucose-dependent insulinotropic peptide (GIP).

1. Gastrin
- contains 17 amino acids ("little gastrin").
- Little gastrin is the form secreted in response to a meal.
- All of the biologic activity of gastrin resides in the four C-terminal amino acids.
- "Big gastrin" contains 34 amino acids, although it is not a dimer of little gastrin.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Homology (Family)</th>
<th>Site of Secretion</th>
<th>Stimulus for Secretion</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>Gastrin–CCK</td>
<td>G cells of stomach</td>
<td>Small peptides and amino acids, distention of stomach, vagus (via GRP), inhibited by H⁺ in stomach, inhibited by somatostatin</td>
<td>↑ Gastric H⁺ secretion, stimulates growth of gastric mucosa</td>
</tr>
<tr>
<td>CCK</td>
<td>Gastrin–CCK</td>
<td>I cells of duodenum and jejunum</td>
<td>Small peptides and amino acids, fatty acids</td>
<td>Stimulates contraction of gallbladder and relaxation of sphincter of Oddi, ↑ pancreatic enzyme and HCO₃⁻ secretion, ↑ growth of exocrine pancreas/gallbladder, inhibits gastric emptying</td>
</tr>
<tr>
<td>Secretin</td>
<td>Secretin–glucagon</td>
<td>S cells of duodenum</td>
<td>H⁺ in duodenum, fatty acids in duodenum</td>
<td>↑ Pancreatic HCO₃⁻ secretion, ↑ biliary HCO₃⁻ secretion, ↓ Gastric H⁺ secretion</td>
</tr>
<tr>
<td>GIP</td>
<td>Secretin–glucagon</td>
<td>Duodenum and jejunum</td>
<td>Fatty acids, amino acids, and oral glucose</td>
<td>↑ Insulin secretion, ↓ Gastric H⁺ secretion</td>
</tr>
</tbody>
</table>

CCK = cholecystokinin; GIP = glucose-dependent insulinotropic peptide; GRP = gastrin-releasing peptide.
a. Actions of gastrin
   (1) Increases $H^+$ secretion by the gastric parietal cells.
   (2) Stimulates growth of gastric mucosa by stimulating the synthesis of RNA and new protein. Patients with gastrin-secreting tumors have hypertrophy and hyperplasia of the gastric mucosa.

b. Stimuli for secretion of gastrin
   ■ Gastrin is secreted from the $G$ cells of the gastric antrum in response to a meal.
   ■ Gastrin is secreted in response to the following:
     (1) Small peptides and amino acids in the lumen of the stomach
         ■ The most potent stimuli for gastrin secretion are phenylalanine and tryptophan.
     (2) Distention of the stomach
     (3) Vagal stimulation, mediated by gastrin-releasing peptide (GRP)
         ■ Atropine does not block vagally mediated gastrin secretion because the mediator of the vagal effect is GRP, not acetylcholine (ACh).

c. Inhibition of gastrin secretion
   ■ $H^+$ in the lumen of the stomach inhibits gastrin release. This negative feedback control ensures that gastrin secretion is inhibited if the stomach contents are sufficiently acidified.
   ■ Somatostatin inhibits gastrin release.

d. Zollinger–Ellison syndrome (gastrinoma)
   ■ occurs when gastrin is secreted by non-$\beta$-cell tumors of the pancreas.

2. CCK
   ■ contains 33 amino acids.
   ■ is homologous to gastrin.
   ■ The five C-terminal amino acids are the same in CCK and gastrin.
   ■ The biologic activity of CCK resides in the C-terminal heptapeptide. Thus, the heptapeptide contains the sequence that is homologous to gastrin and has gastrin activity as well as CCK activity.

a. Actions of CCK
   (1) Stimulates contraction of the gallbladder and simultaneously causes relaxation of the sphincter of Oddi for secretion of bile.
   (2) Stimulates pancreatic enzyme secretion.
   (3) Potentiates secretin-induced stimulation of pancreatic $\text{HCO}_3^-$ secretion.
   (4) Stimulates growth of the exocrine pancreas.
   (5) Inhibits gastric emptying. Thus, meals containing fat stimulate the secretion of CCK, which slows gastric emptying to allow more time for intestinal digestion and absorption.

b. Stimuli for the release of CCK
   ■ CCK is released from the $I$ cells of the duodenal and jejunal mucosa by:
     (1) Small peptides and amino acids
     (2) Fatty acids and monoglycerides
         ■ Triglycerides do not stimulate the release of CCK because they cannot cross intestinal cell membranes.

3. Secretin
   ■ contains 27 amino acids.
   ■ is homologous to glucagon; 14 of the 27 amino acids in secretin are the same as those in glucagon.
All of the amino acids are required for biologic activity.

A. Actions of secretin

- Stimulates pancreatic $\text{HCO}_3^-$ secretion and increases growth of the exocrine pancreas. Pancreatic $\text{HCO}_3^-$ neutralizes $\text{H}^+$ in the intestinal lumen.
- Stimulates $\text{HCO}_3^-$ and $\text{H}_2\text{O}$ secretion by the liver, and increases bile production.
- Inhibits $\text{H}^+$ secretion by gastric parietal cells.

B. Stimuli for the release of secretin

- Secretin is released by the S cells of the duodenum in response to:
  1. $\text{H}^+$ in the lumen of the duodenum.
  2. Fatty acids in the lumen of the duodenum.

4. GIP

- contains 42 amino acids.
- is homologous to secretin and glucagon.

A. Actions of GIP

- Stimulates insulin release. In the presence of an oral glucose load, GIP causes the release of insulin from the pancreas. Thus, oral glucose is more effective than intravenous glucose in causing insulin release and, therefore, glucose utilization.
- Inhibits $\text{H}^+$ secretion by gastric parietal cells.

B. Stimuli for the release of GIP

- GIP is secreted by the duodenum and jejunum.
- GIP is the only GI hormone that is released in response to fat, protein, and carbohydrate. GIP secretion is stimulated by fatty acids, amino acids, and orally administered glucose.

B. Paracrines

- are released from endocrine cells in the GI mucosa.
- diffuse over short distances to act on target cells located in the GI tract.
- The GI paracrines are somatostatin and histamine.

1. Somatostatin

- is secreted by cells throughout the GI tract in response to $\text{H}^+$ in the lumen. Its secretion is inhibited by vagal stimulation.
- inhibits the release of all GI hormones.
- inhibits gastric $\text{H}^+$ secretion.

2. Histamine

- is secreted by mast cells of the gastric mucosa.
- increases gastric $\text{H}^+$ secretion directly and by potentiating the effects of gastrin and vagal stimulation.

C. Neurocrines

- are synthesized in neurons of the GI tract, moved by axonal transport down the axon, and released by action potentials in the nerves.
- Neurocrines then diffuse across the synaptic cleft to a target cell.
- The GI neurocrines are vasoactive intestinal peptide (VIP), GRP (bombesin), and enkephalins.

1. VIP

- contains 28 amino acids and is homologous to secretin.
- is released from neurons in the mucosa and smooth muscle of the GI tract.
- produces relaxation of GI smooth muscle, including the lower esophageal sphincter.
stimulates pancreatic $\text{HCO}_3^-$ secretion and inhibits gastric $\text{H}^+$ secretion. In these actions, it resembles secretin.

- is secreted by pancreatic islet cell tumors and is presumed to mediate pancreatic cholera.

2. GRP (bombesin)
- is released from vagus nerves that innervate the G cells.
- stimulates gastrin release from G cells.

3. Enkephalins (met-enkephalin and leu-enkephalin)
- are secreted from nerves in the mucosa and smooth muscle of the GI tract.
- stimulate contraction of GI smooth muscle, particularly the lower esophageal, pyloric, and ileocecal sphincters.
- inhibit intestinal secretion of fluid and electrolytes. This action forms the basis for the usefulness of opiates in the treatment of diarrhea.

III. GASTROINTESTINAL MOTILITY

- Contractile tissue of the GI tract is almost exclusively unitary smooth muscle, with the exception of the pharynx, upper one-third of the esophagus, and external anal sphincter, all of which are striated muscle.
- Depolarization of circular muscle leads to contraction of a ring of smooth muscle and a decrease in diameter of that segment of the GI tract.
- Depolarization of longitudinal muscle leads to contraction in the longitudinal direction and a decrease in length of that segment of the GI tract.
- Phasic contractions occur in the esophagus, gastric antrum, and small intestine, which contract and relax periodically.
- Tonic contractions occur in the lower esophageal sphincter, orad stomach, and ileocecal and internal anal sphincters.

A. Slow waves (Figure 6-3)
- are oscillating membrane potentials inherent to the smooth muscle cells of some parts of the GI tract.
- occur spontaneously.
- originate in the interstitial cells of Cajal, which serve as the pacemaker for GI smooth muscle.
- are not action potentials, although they determine the pattern of action potentials and, therefore, the pattern of contraction.

1. Mechanism of slow wave production
- is the cyclic opening of $\text{Ca}^{2+}$ channels (depolarization) followed by opening of $\text{K}^+$ channels (repolarization).

![Image](image_url)
Depolarization during each slow wave brings the membrane potential of smooth muscle cells closer to threshold and, therefore, increases the probability that action potentials will occur. Action potentials, produced on top of the background of slow waves, then initiate phasic contractions of the smooth muscle cells (see Chapter 1 VII B).

2. Frequency of slow waves

- varies along the GI tract, but is constant and characteristic for each part of the GI tract.
- is not influenced by neural or hormonal input. In contrast, the frequency of the action potentials that occur on top of the slow waves is modified by neural and hormonal influences.
- sets the maximum frequency of contractions for each part of the GI tract.
- is lowest in the stomach (3 slow waves/min) and highest in the duodenum (12 slow waves/min).

B. Chewing, swallowing, and esophageal peristalsis

1. Chewing

- lubricates food by mixing it with saliva.
- decreases the size of food particles to facilitate swallowing and to begin the digestive process.

2. Swallowing

- The swallowing reflex is coordinated in the medulla. Fibers in the vagus and glossopharyngeal nerves carry information between the GI tract and the medulla.
- The following sequence of events is involved in swallowing:
  a. The nasopharynx closes and, at the same time, breathing is inhibited.
  b. The laryngeal muscles contract to close the glottis and elevate the larynx.
  c. Peristalsis begins in the pharynx to propel the food bolus toward the esophagus. Simultaneously, the upper esophageal sphincter relaxes to permit the food bolus to enter the esophagus.

3. Esophageal motility

- The esophagus propels the swallowed food into the stomach.
- Sphincters at either end of the esophagus prevent air from entering the upper esophagus and gastric acid from entering the lower esophagus.
- Because the esophagus is located in the thorax, intraesophageal pressure equals thoracic pressure, which is lower than atmospheric pressure. In fact, a balloon catheter placed in the esophagus can be used to measure intrathoracic pressure.
- The following sequence of events occurs as food moves into and down the esophagus:
  a. As part of the swallowing reflex, the upper esophageal sphincter relaxes to permit swallowed food to enter the esophagus.
  b. The upper esophageal sphincter then contracts so that food will not reflux into the pharynx.
  c. A primary peristaltic contraction creates an area of high pressure behind the food bolus. The peristaltic contraction moves down the esophagus and propels the food bolus along. Gravity accelerates the movement.
  d. A secondary peristaltic contraction clears the esophagus of any remaining food.
  e. As the food bolus approaches the lower end of the esophagus, the lower esophageal sphincter relaxes. This relaxation is vagally mediated, and the neurotransmitter is VIP.
  f. The Oral region of the stomach relaxes ("receptive relaxation") to allow the food bolus to enter the stomach.

4. Clinical correlations of esophageal motility

a. Gastroesophageal reflux (heartburn) may occur if the tone of the lower esophageal sphincter is decreased and gastric contents reflex into the esophagus.
b. **Achalasia** may occur if the lower esophageal sphincter does not relax during swallowing and food accumulates in the esophagus.

C. **Gastric motility**

- The stomach has three layers of smooth muscle—the usual longitudinal and circular layers, and a third oblique layer.
- The stomach has three anatomic divisions—the **fundus**, **body**, and **antrum**.
- The **orad region** of the stomach includes the fundus and the proximal body. This region contains oxyntic glands and is responsible for receiving the ingested meal.
- The **caudad region** of the stomach includes the antrum and the distal body. This region is responsible for the contractions that mix food and propel it into the duodenum.

1. **“Receptive relaxation”**
   - is a **vagovagal reflex** that is initiated by distention of the stomach and is abolished by vagotomy.
   - The **orad region of the stomach** relaxes to accommodate the ingested meal.
   - **CCK** participates in “receptive relaxation” by increasing the distensibility of the orad stomach.

2. **Mixing and digestion**
   - The caudad region of the stomach contracts to mix the food with gastric secretions and begins the process of digestion. The size of food particles is reduced.
   - **Slow waves** in the caudad stomach occur at a frequency of 3–5 waves/min. They depolarize the smooth muscle cells.
   - If threshold is reached during the slow waves, action potentials are fired, followed by contraction. Thus, the frequency of slow waves sets the maximal frequency of contraction.
   - A **wave of contraction** closes the distal antrum. Thus, as the caudad stomach contracts, food is propelled back into the stomach to be mixed (retropulsion).
   - Gastric contractions are **increased by vagal stimulation and decreased by sympathetic stimulation**.
   - Even during fasting, contractions (the “**migrating myoelectric complex**”) occur at 90-minute intervals and clear the stomach of residual food. **Motilin** is the mediator of these contractions.

3. **Gastric emptying**
   - The caudad region of the stomach contracts to propel food into the duodenum.
   - 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.
   - **Fat inhibits gastric emptying** (i.e., increases gastric emptying time) by stimulating the release of **CCK**.
   - **H⁺ in the duodenum inhibits gastric emptying** via direct neural reflexes. H⁺ receptors in the duodenum relay information to the gastric smooth muscle via interneurons in the GI plexuses.

D. **Small intestinal motility**

- The small intestine functions in the **digestion and absorption of nutrients**. The small intestine mixes nutrients with digestive enzymes, exposes the digested nutrients to the absorptive mucosa, and then propels any nonabsorbed material to the large intestine.
- As in the stomach, **slow waves** set the basic electrical rhythm, which occurs at a frequency of 12 waves/min. Action potentials occur on top of the slow waves and lead to contractions.
- **Parasympathetic stimulation** increases intestinal smooth muscle contraction; **sympathetic stimulation** decreases it.
1. Segmentation contractions
- mix the intestinal contents.
- A section of small intestine contracts, sending the intestinal contents (chyme) in both oral and caudal 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.

2. Peristaltic contractions
- are highly coordinated and 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.

3. Gastroileal reflex
- is mediated by the extrinsic ANS and possibly by gastrin.
- The presence of food in the stomach triggers increased peristalsis in the ileum and relaxation of the ileocecal sphincter. As a result, the intestinal contents are delivered to the large intestine.

E. Large intestinal motility
- Fecal material moves from the cecum to the colon (i.e., through the ascending, transverse, descending, and sigmoid colons), to the rectum, and then to the anal canal.
- Hastra, or saclike segments, appear after contractions of the large intestine.

1. Cecum and proximal colon
- When the proximal colon is distended with fecal material, the ileocecal sphincter contracts to prevent reflux into the ileum.
  a. Segmentation contractions in the proximal colon mix the contents and are responsible for the appearance of hastra.
  b. Mass movements occur 1 to 3 times/day and cause the colonic contents to move distally for long distances (e.g., from the transverse colon to the sigmoid colon).

2. Distal colon
- Because most colonic water absorption occurs in the proximal colon, fecal material in the distal colon becomes semisolid and moves slowly. Mass movements propel it into the rectum.

3. Rectum, anal canal, and defecation
- The sequence of events for defecation is as follows:
  a. As the rectum fills with fecal material, it contracts and the internal anal sphincter relaxes (rectosphincteric reflex).
  b. Once the rectum is filled to about 25% of its capacity, there is an urge to defecate. However, defecation is prevented because the external anal sphincter is tonically contracted.
  c. When it is convenient to defecate, the external anal sphincter is relaxed voluntarily. The smooth muscle of the rectum contracts, forcing the feces out of the body.
    - Intra-abdominal pressure is increased by expiring against a closed glottis (Valsalva maneuver).

4. Gastrocolic reflex
- The presence of food in the stomach increases the motility of the colon and increases the frequency of mass movements.
  a. The gastrocolic reflex has a rapid parasympathetic component that is initiated when the stomach is stretched by food.
  b. A slower, hormonal component is mediated by CCK and gastrin.
5. Disorders of large intestinal motility
   a. Emotional factors strongly influence large intestinal motility via the extrinsic ANS. **Irritable bowel syndrome** may occur during periods of stress and may result in **constipation** (increased segmentation contractions) or **diarrhea** (decreased segmentation contractions).
   b. **Megacolon (Hirschsprung’s disease)**, the absence of the colonic enteric nervous system, results in constriction of the involved segment, marked dilatation and accumulation of intestinal contents proximal to the constriction, and severe constipation.

F. Vomiting
   - A wave of reverse peristalsis begins in the small intestine, moving the GI contents in the oral direction.
   - The gastric contents are eventually pushed into the esophagus. If the upper esophageal sphincter remains closed, **retching** occurs. If the pressure in the esophagus becomes high enough to open the upper esophageal sphincter, **vomiting** occurs.
   - The **vomiting center** in the medulla is stimulated by tickling the back of the throat, gastric distention, and vestibular stimulation (motion sickness).
   - The **chemoreceptor trigger zone** in the fourth ventricle is activated by emetics, radiation, and vestibular stimulation.

IV. GASTROINTESTINAL SECRETION (TABLE 6-2)

A. Salivary secretion
   1. Functions of saliva
      a. **Initial starch digestion** by α-amylase (ptyalin) and **initial triglyceride digestion** by lingual lipase

<table>
<thead>
<tr>
<th>GI Secretion</th>
<th>Major Characteristics</th>
<th>Stimulated By</th>
<th>Inhibited By</th>
</tr>
</thead>
</table>
| Saliva       | High HCO₃⁻          | Parasympathetic nervous system | Sleep  
               | High K⁺            | Sympathetic nervous system | Dehydration  
               | Hypotonic          |                           | Atropine  
               | α-Amylase          |                           |               
               | Lingual lipase     |                           |               |
| Gastric secretion | HCl              | Gastrin        | Stomach pH    |
|               |                    | Parasympathetic nervous system | ↓ Chyme in duodenum  |
|               |                    | Histamine      | (via secretin and GIP)  |
|               | Pepsinogen         | Parasympathetic nervous system | Somatostatin 
|               | Intrinsic factor   |                           | Atropine  
|               |                     |                           | Cimetidine  |
| Pancreatic secretion | High HCO₃⁻         | Secretin       |               |
|               | Isotonic           | CCK (potentiates secretin) | Omeprazole  
|               |                     | Parasympathetic nervous system |               |
|               | Pancreatic lipase,  | CCK             |               |
|               | amylase, proteases | Parasympathetic nervous system |               |
| Bile         | Bile salts         | CCK (causes contraction of gallbladder and relaxation of sphincter of Oddi) | Ileal resection  
|               | Bilirubin          | Parasympathetic nervous system |               
|               | Phospholipids      | (causes contraction of gallbladder) |               
|               | Cholesterol        |                           |               |

CCK = cholecystokinin; GIP = gastric inhibitory peptide.
200  Board Review Series: Physiology

b. **Lubrication** of ingested food by mucus
c. **Protection** of the mouth and esophagus by dilution and buffering of ingested foods

2. **Composition of saliva**
   a. Saliva is characterized by:
      1. High volume (relative to the small size of the salivary glands)
      2. High $K^+$ and $HCO_3^-$ concentrations
      3. Low $Na^+$ and $Cl^-$ concentrations
      4. Hypotonicity
      5. Presence of $\alpha$-amylase, lingual lipase, and kallikrein
   b. The composition of saliva varies with the salivary flow rate (Figure 6-4).
      1. At the lowest flow rates, saliva has the lowest osmolarity and lowest $Na^+$, $Cl^-$, and $HCO_3^-$ concentrations, but has the highest $K^+$ concentration.
      2. At the highest flow rates (up to 4 mL/min), the composition of saliva is closest to that of plasma.

3. **Formation of saliva** (Figure 6-5)
   - Saliva is formed by three major glands—the *parotid*, *submandibular*, and *sublingual* glands.
   - The *structure* of each gland is similar to a bunch of grapes. The *acinus* (the blind end of each duct) is lined with acinar cells and secretes an initial saliva. A *branching duct system* is lined with columnar epithelial cells, which modify the initial saliva.
   - When saliva production is stimulated, *myoepithelial cells*, which line the acinus and initial ducts, contract and eject saliva into the mouth.

   a. **The acinus**
      - Produces an initial saliva with a composition similar to plasma.
      - This initial saliva is *isotonic* and has the same $Na^+$, $K^+$, $Cl^-$, and $HCO_3^-$ concentrations as plasma.

   ![Figure 6-5](https://example.com/figure6-5.png)  Modification of saliva by ductal cells.
b. The ducts

- **modify the initial saliva** by the following processes:
  1. The ducts **reabsorb Na\(^+\) and Cl\(^-\);** therefore, the concentrations of these ions are lower than their plasma concentrations.
  2. The ducts **secrete K\(^+\) and HCO\(_3\)\(^-\);** therefore, the concentrations of these ions are higher than their plasma concentrations.
  3. **Aldosterone** acts on the ductal cells to increase the reabsorption of Na\(^+\) and the secretion of K\(^+\) (analogous to its actions on the renal distal tubule).
  4. **Saliva becomes hypotonic** in the ducts because the ducts are relatively impermeable to water. Because more solute than water is reabsorbed by the ducts, the saliva becomes dilute relative to plasma.
  5. **The effect of flow rate** on saliva composition is explained primarily by changes in the contact time available for reabsorption and secretion processes to occur in the ducts.
    - Thus, at **high flow rates**, saliva is most like the initial secretion from the acinus; it has the highest Na\(^+\) and Cl\(^-\) concentrations and the lowest K\(^+\) concentration.
    - At **low flow rates**, saliva is least like the initial secretion from the acinus; it has the lowest Na\(^+\) and Cl\(^-\) concentrations and the highest K\(^+\) concentration.
    - The only ion that does not “fit” this contact-time explanation is HCO\(_3\)\(^-\); HCO\(_3\)\(^-\) secretion is selectively stimulated when saliva secretion is stimulated.

4. Regulation of saliva production (Figure 6-6)

- Saliva production is controlled by the parasympathetic and sympathetic nervous systems (not by GI hormones).
- Saliva production is unique in that it is **increased by both parasympathetic and sympathetic activity.** Parasympathetic activity is more important, however.

![Figure 6-6 Regulation of salivary secretion. ACh = acetylcholine; cAMP = cyclic adenosine monophosphate; IP\(_3\) = inositol 1,4,5-triphosphate; NE = norepinephrine.](image-url)
a. Parasympathetic stimulation (cranial nerves VII and IX)

- Increases saliva production by increasing transport processes in the acinar and ductal cells and by causing vasodilation.
- Cholinergic receptors on acinar and ductal cells are muscarinic.
- The second messenger is inositol 1,4,5-triphosphate (IP₃) and increased intracellular [Ca²⁺].
- Anticholinergic drugs (e.g., atropine) inhibit the production of saliva and cause dry mouth.

b. Sympathetic stimulation

- Increases the production of saliva and the growth of salivary glands, although the effects are smaller than those of parasympathetic stimulation.
- Receptors on acinar and ductal cells are β-adrenergic.
- The second messenger is cyclic adenosine monophosphate (cAMP).

c. Saliva production

- Is increased (via activation of the parasympathetic nervous system) by food in the mouth, smells, conditioned reflexes, and nausea.
- Is decreased (via inhibition of the parasympathetic nervous system) by sleep, dehydration, fear, and anticholinergic drugs.

B. Gastric secretion

1. Gastric cell types and their secretions (Table 6-3 and Figure 6-7)

- Parietal cells, located in the body, secrete HCl and intrinsic factor.
- Chief cells, located in the body, secrete pepsinogen.
- G cells, located in the antrum, secrete gastrin.

2. Mechanism of gastric H⁺ secretion (Figure 6-8)

- Parietal cells secrete HCl into the lumen of the stomach and, concurrently, absorb HCO₃⁻ into the bloodstream as follows:
  a. In the parietal cells, CO₂ and H₂O are converted to H⁺ and HCO₃⁻, 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 (a “proton pump inhibitor”) inhibits the H⁺,K⁺-ATPase and blocks H⁺ secretion.
  c. The HCO₃⁻ produced in the cells is absorbed into the bloodstream in exchange for Cl⁻ (Cl⁻−HCO₃⁻ exchange). As HCO₃⁻ is added to the venous blood, the pH of the

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Part of Stomach</th>
<th>Secretion Products</th>
<th>Stimulus for Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal cells</td>
<td>Body (fundus)</td>
<td>HCl</td>
<td>Gastrin, Vagal stimulation (ACH), Histamine</td>
</tr>
<tr>
<td>Chief cells</td>
<td>Body (fundus)</td>
<td>Pepsinogen (converted to pepsin at low pH)</td>
<td>Vagal stimulation (ACH)</td>
</tr>
<tr>
<td>G cells</td>
<td>Antrum</td>
<td>Gastrin</td>
<td>Vagal stimulation (via GRP), Small peptides, Inhibited by somatostatin, Inhibited by H⁺ in stomach (via stimulation of somatostatin release)</td>
</tr>
<tr>
<td>Mucous cells</td>
<td>Antrum</td>
<td>Mucus, Pepsinogen</td>
<td>Vagal stimulation (ACH)</td>
</tr>
</tbody>
</table>

ACh = acetylcholine; GRP = gastrin-releasing peptide.
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).

3. Stimulation of gastric H$^+$ secretion
   (Figure 6-9)
   a. Vagal stimulation

   - increases H$^+$ secretion by a direct pathway and an indirect pathway.
   - In the direct path, the vagus nerve innervates parietal cells and stimulates H$^+$ secretion directly. The neurotransmitter at these synapses is ACh, the receptor on the parietal cells is muscarinic (M$_3$), and the second messengers for CCK are IP$_3$ and increased intracellular [Ca$^{2+}$].
   - In the indirect path, the vagus nerve innervates G cells and stimulates gastrin secretion, which then stimulates H$^+$ secretion by an endocrine action. The neurotransmitter at these synapses is GRP (not ACh).
   - Atropine, a cholinergic muscarinic antagonist, inhibits H$^+$ secretion by blocking the direct pathway, which uses ACh as a neurotransmitter. However, atropine does not...
block H⁺ 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**

- is released in response to eating a meal (small peptides, distention of the stomach, vagal stimulation).
- stimulates H⁺ secretion by interacting with the cholecystokinin B (CCKB) receptor on the parietal cells.
- The second messenger for gastrin on the parietal cell is IP3/Ca²⁺.

c. **Histamine**

- is released from enterochromaffin-like (ECL) cells in the gastric mucosa and diffuses to the nearby parietal cells.
- stimulates H⁺ secretion by activating H₂ receptors on the parietal cell membrane.
- The H₂ receptor is coupled to adenylyl cyclase via a Gₛ protein.
- The second messenger for histamine is cAMP.
- 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**

- **Potentiation** occurs when the response to simultaneous administration of two stimulants is greater than the sum of responses to either agent given alone. As a result, low concentrations of stimulants given together can produce maximal effects.
- 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.
Thus, H₂ receptor blockers (e.g., cimetidine) are particularly effective in treating ulcers because they block both the direct action of histamine on parietal cells and the potentiating effects of histamine on ACh and gastrin.

(2) ACh potentiates the actions of histamine and gastrin in stimulating H⁺ secretion.

Thus, muscarinic receptor blockers, such as atropine, block both the direct action of ACh on parietal cells and the potentiating effects of ACh on histamine and gastrin.

4. Inhibition of gastric H⁺ secretion

- Negative feedback mechanisms inhibit the secretion of H⁺ by the parietal cells.

  a. Low pH (< 3.0) in the stomach

  - inhibits gastrin secretion and thereby inhibits H⁺ secretion.
  - After a meal is ingested, H⁺ secretion is stimulated by the mechanisms discussed previously (see IV B 2). After the meal is digested and the stomach emptied, further H⁺ secretion decreases the pH of the stomach contents. When the pH of the stomach contents is < 3.0, gastrin secretion is inhibited and, by negative feedback, inhibits further H⁺ secretion.

  b. Somatostatin (see Figure 6-9)

  - inhibits gastric H⁺ secretion by a direct pathway and an indirect pathway.
  - In the direct pathway, somatostatin binds to receptors on the parietal cell that are coupled to adenyl cyclase via a G i protein, thus inhibiting adenyl cyclase and decreasing cAMP levels. In this pathway, somatostatin antagonizes the stimulatory action of histamine on H⁺ secretion.
  - In the indirect pathway (not shown in Figure 6-9), somatostatin inhibits release of histamine and gastrin, thus decreasing H⁺ secretion indirectly.

  c. Prostaglandins (see Figure 6-9)

  - inhibit gastric H⁺ secretion by activating a G i protein, inhibiting adenyl cyclase and decreasing cAMP levels.

5. Peptic ulcer disease

- is an ulcerative lesion of the gastric or duodenal mucosa.
- can occur when there is loss of the protective mucous barrier (of mucus and HCO₃⁻) and/or excessive secretion of H⁺ and pepsin.
- Protective factors are mucus, HCO₃⁻, prostaglandins, mucosal blood flow, and growth factors.
- Damaging factors are H⁺, pepsin, Helicobacter pylori (H. pylori), nonsteroidal anti-inflammatory drugs (NSAIDs), stress, smoking, and alcohol.

  a. Gastric ulcers

  - The gastric mucosa is damaged.
  - Gastric H⁺ secretion is decreased because secreted H⁺ leaks back through the damaged gastric mucosa.
  - Gastrin levels are increased because decreased H⁺ secretion stimulates gastrin secretion.
  - A major cause of gastric ulcer is the gram-negative bacterium H. pylori.
  - H. pylori colonizes the gastric mucus and releases cytotoxins that damage the gastric mucosa.
  - H. pylori contains urease, which converts urea to NH₃, thus alkalining the local environment and permitting H. pylori to survive in the otherwise acidic gastric lumen.
  - The diagnostic test for H. pylori involves drinking a solution of ⁱ³C-urea, which is converted to ¹⁴CO₂ by urease and measured in the expired air.
b. Duodenal ulcers
- The duodenal mucosa is damaged.
- Gastric $H^+$ secretion is increased. Excess $H^+$ is delivered to the duodenum, damaging the duodenal mucosa.
- Gastrin secretion in response to a meal is increased (although baseline gastrin may be normal).
- H. pylori is also a major cause of duodenal ulcer. H. pylori inhibits somatostatin secretion (thus stimulating gastric $H^+$ secretion) and inhibits intestinal $HCO_3^-$ secretion (so there is insufficient $HCO_3^-$ to neutralize the $H^+$ load from the stomach).

c. Zollinger–Ellison syndrome
- Occurs when a gastrin-secreting tumor of the pancreas causes increased $H^+$ secretion.
- $H^+$ secretion continues unabated because the gastrin secreted by pancreatic tumor cells is not subject to negative feedback inhibition by $H^+$.

6. Drugs that block gastric $H^+$ secretion (see Figure 6-9)
a. Atropine
- Blocks $H^+$ secretion by inhibiting cholinergic muscarinic receptors on parietal cells, thereby inhibiting ACh stimulation of $H^+$ secretion.

b. Cimetidine
- Blocks $H_2$ receptors and thereby inhibits histamine stimulation of $H^+$ secretion.
- Is particularly effective in reducing $H^+$ secretion because it not only blocks the histamine stimulation of $H^+$ secretion, but also blocks histamine's potentiation of ACh effects.

c. Omeprazole
- Is a proton pump inhibitor.
- Directly inhibits $H^+,K^+\text{-ATPase}$ and $H^+$ secretion.

C. Pancreatic secretion
- Contains a high concentration of $HCO_3^-$, 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:
   - High volume
   - Virtually the same Na$^+$ and K$^+$ concentrations as plasma
   - Much higher $HCO_3^-$ concentration than plasma
   - Much lower Cl$^-$ concentration than plasma
   - Isotonicity
   - Pancreatic lipase, amylase, and proteases
b. The composition of the aqueous component of pancreatic secretion varies with the flow rate (Figure 6-11).
   - 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 $HCO_3^-$. 
   - Regardless of the flow rate, pancreatic secretions are isotonic.

2. Formation of pancreatic secretion (Figure 6-11)
- 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 is mainly Na\(^+\) and Cl\(^-\).

b. Ductal cells
- modify the initial pancreatic secretion by secreting HCO\(_3^-\) and absorbing Cl\(^-\) via a Cl\(^-\)-HCO\(_3^-\) exchange mechanism in the luminal membrane.
- Because the pancreatic ducts are permeable to water, H\(_2\)O moves into the lumen to make the pancreatic secretion isosmotic.

3. Stimulation of pancreatic secretion
a. Secretin
- is secreted by the S cells of the duodenum in response to H\(^+\) in the duodenal lumen.
- acts on the pancreatic ductal cells to increase HCO\(_3^-\) secretion.
- Thus, when H\(^+\) is delivered from the stomach to the duodenum, secretin is released. As a result, HCO\(_3^-\) is secreted from the pancreas into the duodenal lumen to neutralize the H\(^+\).
- The second messenger for secretin is cAMP.

b. CCK
- is secreted by the I cells of the duodenum in response to small peptides, amino acids, and fatty acids in the duodenal lumen.
- acts on the pancreatic acinar cells to increase enzyme secretion (amylase, lipases, proteases).
- potentiates the effect of secretin on ductal cells to stimulate HCO\(_3^-\) secretion.
- The second messengers for CCK are 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).

**FIGURE 6-10** Composition of pancreatic secretion as a function of pancreatic flow rate.

- Acinar cells
  - produce a small volume of initial pancreatic secretion, which is mainly Na\(^+\) and Cl\(^-\).

- Ductal cells
  - modify the initial pancreatic secretion by secreting HCO\(_3^-\) and absorbing Cl\(^-\) via a Cl\(^-\)-HCO\(_3^-\) exchange mechanism in the luminal membrane.
  - Because the pancreatic ducts are permeable to water, H\(_2\)O moves into the lumen to make the pancreatic secretion isosmotic.

**FIGURE 6-11** Modification of pancreatic secretion by ductal cells. CA = carbonic anhydrase.
c. **ACh (via vagovagal reflexes)**
   - is released in response to $H^+$, small peptides, amino acids, and fatty acids in the duodenal lumen.
   - stimulates enzyme secretion by the acinar cells and, like CCK, potentiates the effect of secretin on $HCO_3^-$ secretion.

4. **Cystic fibrosis**
   - is a disorder of pancreatic secretion.
   - results from a defect in $Cl^-$ channels that is caused by a mutation in the **cystic fibrosis transmembrane conductance regulator (CFTR) gene**.
   - is associated with a deficiency of pancreatic enzymes resulting in malabsorption and steatorrhea.

**D. Bile secretion and gallbladder function (Figure 6-12)**

1. **Composition and function of bile**
   - Bile contains bile salts, phospholipids, cholesterol, and bile pigments (bilirubin).
   - **Bile salts**
     - are amphipathic molecules because they have both hydrophilic and hydrophobic portions. In aqueous solution, 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**
     - Above a critical micellar concentration, bile salts form micelles.
     - 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 monoglycerides are present in the inside of the micelle, essentially "solubilized" for subsequent absorption.

2. **Formation of bile**
   - Bile is produced continuously by hepatocytes.
   - Bile drains into the hepatic ducts and is stored in the gallbladder for subsequent release.

*FIGURE 6-12* Recirculation of bile acids from the ileum to the liver. CCK = cholecystokinin.
Choleretic agents increase the formation of bile.

Bile is formed by the following process:

- **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).
  - Synthesis of new bile acids occurs, as needed, to replace bile acids that are excreted in the feces.

- The bile acids are conjugated with glycine or taurine to form their respective **bile salts**, which are named for the parent bile acid (e.g., taurocholic acid is cholic acid conjugated with taurine).

- Electrolytes and H₂O are added to the bile.

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

- Bile is **concentrated** in the gallbladder as a result of isosmotic absorption of solutes and H₂O.

3. **Contraction of the gallbladder**
   - **CCK**
     - is released in response to small peptides and fatty acids in the duodenum.
     - tells the gallbladder that bile is needed to emulsify and absorb lipids in the duodenum.
     - causes contraction of the gallbladder and relaxation of the sphincter of Oddi.
   - **ACh**
     - causes contraction of the gallbladder.

4. **Recirculation of bile acids to the liver**
   - The terminal ileum contains a Na⁺–bile acid cotransporter, which is a secondary active transporter that recirculates bile acids to the liver.
   - Because bile acids are not recirculated 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 recirculated to the liver, but are excreted in feces. The bile acid pool is thereby depleted and fat absorption is impaired, resulting in steatorrhea.

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**V. DIGESTION AND ABSORPTION (TABLE 6-4)**

- Carbohydrates, proteins, and lipids are digested and absorbed in the small intestine.
- The surface area for absorption in the small intestine is greatly increased by the presence of the brush border.

**A. Carbohydrates**

1. **Digestion of carbohydrates**
   - Only monosaccharides are absorbed. Carbohydrates must be digested to glucose, galactose, and fructose for absorption to proceed.
     - **α-Amylases** (salivary and pancreatic) hydrolyze 1,4-glycosidic bonds in starch, yielding maltose, maltotriose, and α-limit dextrins.
     - **Maltase, α-dextrinase, and sucrase** in the intestinal brush border then hydrolyze the oligosaccharides to glucose.
     - **Lactase, trehalase, and sucrase** degrade their respective disaccharides to monosaccharides.
210  Board Review Series: Physiology

Lactase degrades lactose to glucose and galactose.
Trehalase degrades trehalose to glucose.
Sucrase degrades sucrose to glucose and fructose.

2. Absorption of carbohydrates (Figure 6-13)
   a. Glucose and galactose

   - are transported from the intestinal lumen into the cells by a Na⁺-dependent cotransport (SGLT 1) in the luminal membrane. The sugar is transported “uphill” and Na⁺ is transported “downhill.”
   - are then transported from cell to blood by facilitated diffusion (GLUT 2).
   - The Na⁺–K⁺ pump in the basolateral membrane keeps the intracellular [Na⁺] low, thus maintaining the Na⁺ gradient across the luminal membrane.
   - Poisoning the Na⁺–K⁺ pump inhibits glucose and galactose absorption by dissipating the Na⁺ gradient.

   b. Fructose

   - is transported exclusively by facilitated diffusion; therefore, it cannot be absorbed against a concentration gradient.

   FIGURE 6-13  Mechanism of absorption of monosaccharides by intestinal epithelial cells. Glucose and galactose are absorbed by Na⁺-dependent cotransport (secondary active), and fructose (not shown) is absorbed by facilitated diffusion.
3. Clinical disorders of carbohydrate absorption

- **Lactose intolerance** results from the absence of brush border lactase and, thus, the inability to hydrolyze lactose to glucose and galactose for absorption. Nonabsorbed lactose and H₂O remain in the lumen of the GI tract and cause **osmotic diarrhea**.

B. Proteins

1. Digestion of proteins
   a. **Endopeptidases**
      - degrade proteins by hydrolyzing interior peptide bonds.
   b. **Exopeptidases**
      - hydrolyze one amino acid at a time from the C terminus of proteins and peptides.
   c. **Pepsin**
      - is not essential for protein digestion.
      - is secreted as pepsinogen by the chief cells of the stomach.
      - Pepsinogen is activated to pepsin by gastric H⁺.
      - The **optimum pH for pepsin is between 1 and 3**.
      - When the pH is >5, pepsin is denatured. Thus, in the intestine, as HCO₃⁻ is secreted in pancreatic fluids, duodenal pH increases and pepsin is inactivated.
   d. **Pancreatic proteases**
      - include trypsin, chymotrypsin, elastase, carboxypeptidase A, and carboxypeptidase B.
      - are secreted in inactive forms that are activated in the small intestine as follows:
        1. Trypsinogen is activated to **trypsin** by a brush border enzyme, enterokinase.
        2. Trypsin then converts chymotrypsinogen, proelastase, and procarboxypeptidase A and B to their active forms. (Even trypsinogen is converted to more trypsin by trypsin!)
        3. After their digestive work is complete, the pancreatic proteases degrade each other and are absorbed along with dietary proteins.

2. Absorption of proteins (Figure 6-14)

- Digestive products of protein can be **absorbed as amino acids, dipeptides, and tripeptides** (in contrast to carbohydrates, which can only be absorbed as monosaccharides).

   a. **Free amino acids**
      - **Na⁺-dependent amino acid cotransport** occurs in the luminal membrane. It is analogous to the cotransporter for glucose and galactose.
      - The amino acids are then transported from cell to blood by facilitated diffusion.
      - There are **four separate carriers** for neutral, acidic, basic, and imino amino acids, respectively.

   ![Mechanism of absorption of amino acids, dipeptides, and tripeptides by intestinal epithelial cells.](image-url)
b. Dipeptides and tripeptides
- are absorbed faster than free amino acids.
- \( \text{H}^+ \)-dependent cotransport of dipeptides and tripeptides also occurs in the luminal membrane.
- After the dipeptides and tripeptides are transported into the intestinal cells, cytoplasmic peptidases hydrolyze them to amino acids.
- The amino acids are then transported from cell to blood by facilitated diffusion.

C. Lipids
1. Digestion of lipids
a. Stomach
(1) In the stomach, mixing breaks lipids into droplets to increase the surface area for digestion by pancreatic enzymes.
(2) Lingual lipases digest some of the ingested triglycerides to monoglycerides and fatty acids. However, most of the ingested lipids are digested in the intestine by pancreatic lipases.
(3) 
   CCK slows gastric emptying. Thus, delivery of lipids from the stomach to the duodenum is slowed to allow adequate time for digestion and absorption in the intestine.

b. Small intestine
(1) Bile acids emulsify lipids in the small intestine, increasing the surface area for digestion.
(2) Pancreatic lipases hydrolyze lipids to fatty acids, monoglycerides, cholesterol, and lysolecithin. The enzymes are pancreatic lipase, cholesterol ester hydrolase, and phospholipase A_2.
(3) The hydrophobic products of lipid digestion are solubilized in **micelles** by bile acids.

2. Absorption of lipids
a. Micelles bring the products of lipid digestion into contact with the absorptive surface of the intestinal cells. Then, fatty acids, monoglycerides, and cholesterol diffuse across the luminal membrane into the cells. Glycerol is hydrophilic and is not contained in the micelles.

b. In the intestinal cells, the products of lipid digestion are re-esterified to triglycerides, cholesterol ester, and phospholipids and, with apoproteins, form **chylomicrons**.

   - Lack of apoprotein B results in the inability to transport chylomicrons out of the intestinal cells and causes abetalipoproteinemia.

   - Chylomicrons are transported out of the intestinal cells by **exocytosis**. Because chylomicrons are too large to enter the capillaries, they are transferred to **lymph vessels** and are added to the bloodstream via the thoracic duct.

3. Malabsorption of lipids—steatorrhea
- can be caused by any of the following:
  a. Pancreatic disease (e.g., pancreatitis, cystic fibrosis), in which the pancreas cannot synthesize adequate amounts of the enzymes (e.g., pancreatic lipase) needed for lipid digestion.
  b. Hypersecretion of gastrin, in which gastric \( \text{H}^+ \) secretion is increased and the duodenal pH is decreased. Low duodenal pH inactivates pancreatic lipase.
  c. Ileal resection, which leads to a depletion of the bile acid pool because the bile acids do not recirculate to the liver.
  d. Bacterial overgrowth, which may lead to deconjugation of bile acids and their “early” absorption in the upper small intestine. In this case, bile acids are not present throughout the small intestine to aid in lipid absorption.
  e. Decreased number of intestinal cells for lipid absorption (tropical sprue).
  f. Failure to synthesize apoprotein B, which leads to the inability to form chylomicrons.
D. Absorption and secretion of electrolytes and H₂O

Electrolytes and H₂O may cross intestinal epithelial cells by either cellular or paracellular (between cells) routes.

- **Tight junctions** attach the epithelial cells to one another at the luminal membrane.
- The permeability of the tight junctions varies with the type of epithelium. A "tight" (impermeable) epithelium is the colon. "Leaky" (permeable) epithelia are the small intestine and gallbladder.

1. Absorption of NaCl

   a. Na⁺ moves into the intestinal cells, across the luminal membrane, and down its electrochemical gradient by the following mechanisms:
      (1) Passive diffusion (through Na⁺ channels)
      (2) Na⁺–glucose or Na⁺–amino acid cotransport
      (3) Na⁺–Cl⁻ cotransport
      (4) Na⁺–H⁺ exchange

   - In the **small intestine**, Na⁺–glucose cotransport, Na⁺–amino acid cotransport, and Na⁺–H⁺ exchange mechanisms are most important. These cotransport and exchange mechanisms are similar to those in the renal proximal tubule.
   - In the **colon**, passive diffusion via Na⁺ channels is most important. The Na⁺ channels of the colon are similar to those in the renal distal tubule and are stimulated by aldosterone.

   b. Na⁺ is pumped out of the cell against its electrochemical gradient by the Na⁺–K⁺ pump in the basolateral membranes.

   c. Cl⁻ absorption accompanies Na⁺ absorption throughout the GI tract by the following mechanisms:
      (1) Passive diffusion by a paracellular route
      (2) Na⁺–Cl⁻ cotransport
      (3) Cl⁻–HCO₃⁻ exchange

2. Absorption and secretion of K⁺

   a. Dietary K⁺ is **absorbed in the small intestine** by passive diffusion via a paracellular route.

   b. K⁺ is actively **secreted in the colon** by a mechanism similar to that for K⁺ secretion in the renal distal tubule.

   - As in the distal tubule, K⁺ secretion in the colon is stimulated by aldosterone.
   - In diarrhea, K⁺ secretion by the colon is increased because of a flow rate-dependent mechanism similar to that in the renal distal tubule. Excessive loss of K⁺ in diarrheal fluid causes hypokalemia.

3. Absorption of H₂O

   - is secondary to solute absorption.
   - is isosmotic in the small intestine and gallbladder. The mechanism for coupling solute and water absorption in these epithelia is the same as that in the renal proximal tubule.
   - In the colon, H₂O permeability is much lower than in the small intestine, and feces may be hypertonic.

4. Secretion of electrolytes and H₂O by the intestine

   - The GI tract also secretes electrolytes from blood to lumen.
   - The secretory mechanisms are located in the **crypts**. The absorptive mechanisms are located in the villi.

   a. Cl⁻ is the primary ion secreted into the intestinal lumen. It is transported through Cl⁻ channels in the luminal membrane that are regulated by cAMP.

   b. Na⁺ is secreted into the lumen by passively following Cl⁻. H₂O follows NaCl to maintain isosmotic conditions.
c. *Vibrio cholerae* (cholera toxin) causes diarrhea by stimulating Cl⁻ secretion.
   - Cholera toxin catalyzes adenosine diphosphate (ADP) ribosylation of the α₃ subunit of the Gs protein coupled to adenylyl cyclase, permanently activating it.
   - Intracellular cAMP increases; as a result, Cl⁻ channels in the luminal membrane open.
   - Na⁺ and H₂O follow Cl⁻ into the lumen and lead to secretory diarrhea.
   - Some strains of *Escherichia coli* cause diarrhea by a similar mechanism.

### E. Absorption of other substances

1. **Vitamins**
   a. Fat-soluble vitamins (A, D, E, and K) are incorporated into micelles and absorbed along with other lipids.
   b. Most water-soluble vitamins are absorbed by Na⁺-dependent cotransport mechanisms.
   c. Vitamin B₁₂ is absorbed in the ileum and requires intrinsic factor.
      - The vitamin B₁₂–intrinsic factor complex binds to a receptor on the ileal cells and is absorbed.
      - Gastrectomy results in the loss of gastric parietal cells, which are the source of intrinsic factor. Injection of vitamin B₁₂ is required to prevent pernicious anemia.

2. **Calcium**
   - Absorption in the small intestine depends on the presence of adequate amounts of the active form of vitamin D, 1,25-dihydroxycholecalciferol, which is produced in the kidney. 1,25-dihydroxycholecalciferol induces the synthesis of an intestinal Ca²⁺-binding protein, calbindin D-28K.
   - Vitamin D deficiency or chronic renal failure results in inadequate intestinal Ca²⁺ absorption, causing rickets in children and osteomalacia in adults.

3. **Iron**
   - Is absorbed as heme iron (iron bound to hemoglobin or myoglobin) or as free Fe²⁺. In the intestinal cells, “heme iron” is degraded and free Fe²⁺ is released. The free Fe²⁺ binds to apoferritin and is transported into the blood.
   - Free Fe²⁺ circulates in the blood bound to transferrin, which transports it from the small intestine to its storage sites in the liver, and from the liver to the bone marrow for the synthesis of hemoglobin.
   - Iron deficiency is the most common cause of anemia.

### VI. LIVER PHYSIOLOGY

A. **Bile formation and secretion (see IV D)**

B. **Bilirubin production and excretion (Figure 6-15)**
   - Hemoglobin is degraded to bilirubin by the reticuloendothelial system.
   - Bilirubin is carried in the circulation bound to albumin.
   - In the liver, bilirubin is conjugated with glucuronic acid via the enzyme UDP glucuronyl transferase.
   - A portion of conjugated bilirubin is excreted in the urine and a portion is secreted into bile.
   - In the intestine, conjugated bilirubin is converted to urobilinogen, which is returned to the liver via the enterohepatic circulation, and urobilin and stercobilin, which are excreted in feces.

C. **Metabolic functions of the liver**

1. **Carbohydrate metabolism**
   - Performs gluconeogenesis, stores glucose as glycogen, and releases stored glucose into the circulation.
2. **Protein metabolism**
   - Synthesizes nonessential amino acids
   - Synthesizes plasma proteins

3. **Lipid metabolism**
   - Participates in fatty acid oxidation
   - Synthesizes lipoproteins, cholesterol, and phospholipids

**D. Detoxification**
- Potentially toxic substances are presented to the liver via the portal circulation.
- Liver modifies these substances in “first pass metabolism.”
- **Phase I reactions** are catalyzed by cytochrome P-450 enzymes, which are followed by **phase II reactions** that conjugate the substances.