Stomach

The epithelial layer lining the stomach invaginates تدخل into the mucosa, forming many tubular glands. Glands in the thin-walled upper portions of the **body** of the stomach (**Figure 1**) secrete mucus, hydrochloric acid, and the enzyme precursor pepsinogen. The uppermost part of the body of the stomach is called the **fundus** and is functionally part of the body. The lower portion of the stomach, the **antrum,** has a much thicker layer of smooth muscle and is responsible for mixing and grinding the stomach contents. The glands in this region secrete little acid but contain the endocrine cells that secrete the hormone gastrin.

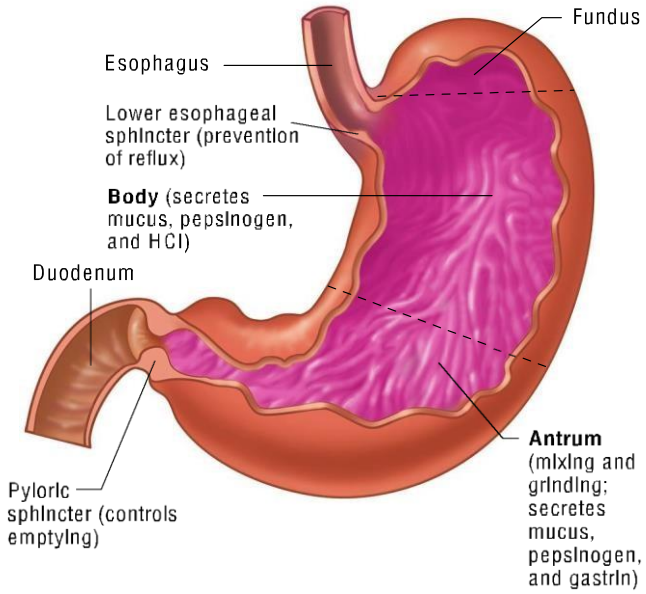

Figure 1: *The two regions of the stomach: body and antrum.*

The cells at the opening of the glands secrete mucus. Lining the walls of the glands are **parietal cells** (also known as oxyntic cells), which secrete acid and intrinsic factor, and **chief cells,** which secrete pepsinogen. The unique invaginations of the luminal membrane of parietal cells shown in Figure 2 are called **canaliculi** (singular, **canaliculus**); these increase the surface area of the parietal cells thereby maximizing secretion into the lumen of the stomach.

Each of the three major exocrine secretions of the stomach (mucus, acid, and pepsinogen) is secreted by a different cell type. The gastric glands in the antrum also contain enteroendocrine cells, which secrete gastrin. In addition, **enterochromaffin-like** (**ECL**) **cells,** which release the paracrine agent histamine, and endocrine cells called D cells, which secrete the peptide **somatostatin,** are scattered throughout the tubular glands or in surrounding tissue; both of these substances play roles in regulating acid secretion by the stomach.

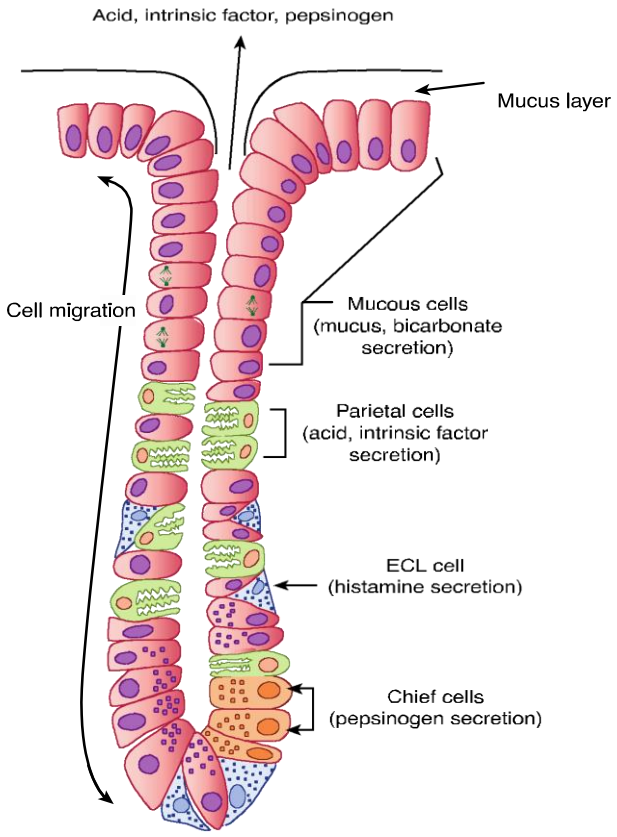

Figure 2: *A gastric gland in the stomach.*

HCL Production and Secretion

The stomach secretes about 2 L of hydrochloric acid per day. The concentration of H^+ in the lumen of the stomach may reach >150 mM, which is 1 to 3 million times greater than the concentration in the blood.

This requires an efficient production mechanism to generate large numbers of hydrogen ions. The origin of the hydrogen ions is CO_2 in the parietal cell. The enzyme carbonic anhydrase catalyzes the reaction between

CO_2 with water to produce carbonic acid, which dissociates to H^+ and HCO_3^-. Primary H^+/K^+-ATPases in the luminal membrane of the parietal cells pump these hydrogen ions into the lumen of the stomach (**Figure 3**).

This primary active transporter also pumps K^+ into the cell, which then leaks back into the lumen through K^+ channels. As H^+ is secreted into the lumen, HCO_3 is secreted on the opposite side of the cell into the blood in exchange for Cl^-. In this way, production and secretion of H^- are coupled.

Increased acid secretion, stimulated by factors described later, results from the transfer of H^+/K^+-ATPase proteins from the membranes of intracellular vesicles to the plasma membrane by fusion of these vesicles with the membrane, thereby increasing the number of pump proteins in the plasma membrane.

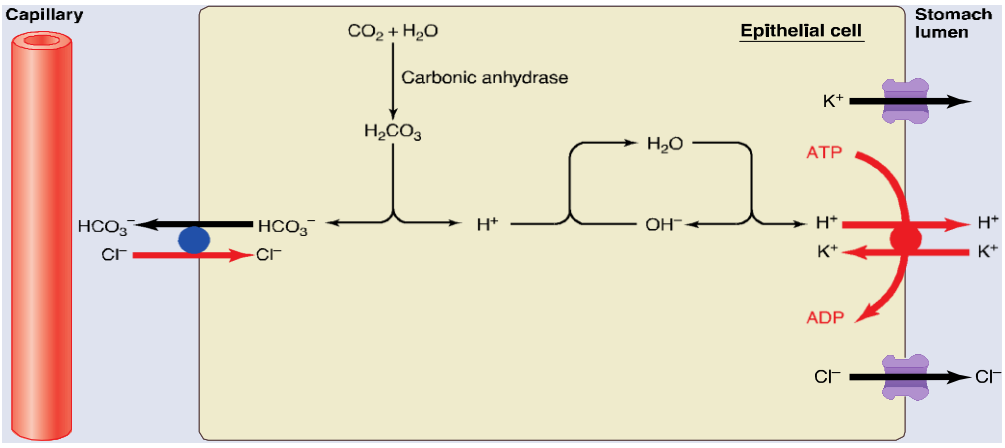

Figure 3: *Secretion of hydrochloric acid by parietal cells.*

The H^+ secreted into the lumen by primary active transport is derived from the breakdown of water molecules, leaving hydroxyl ion (OH^-) behind. This OH^- is neutralized by combination with other H^+ generated by the reaction between carbon dioxide and water, a reaction catalyzed by the enzyme carbonic anhydrase, which is present in high concentrations in parietal cells. The HCO_3^- formed by this reaction is transported out of the parietal cell on the blood side in exchange for Cl^-.

Four chemical messengers regulate the insertion of H^+/K^+- ATPases into the plasma membrane and therefore acid secretion: **gastrin** (a gastric hormone), **acetylcholine** (ACh, a neurotransmitter), **histamine**, and **somatostatin** (two paracrine agents). Parietal cell membranes contain receptors for all four of these molecules (**Figure 4**). Somatostatin inhibits acid secretion, whereas the other three stimulate secretion. These chemical messengers not only act directly on the parietal cells but also influence each other's secretion. For example, histamine markedly potentiates the response to the other two stimuli, gastrin and ACh.

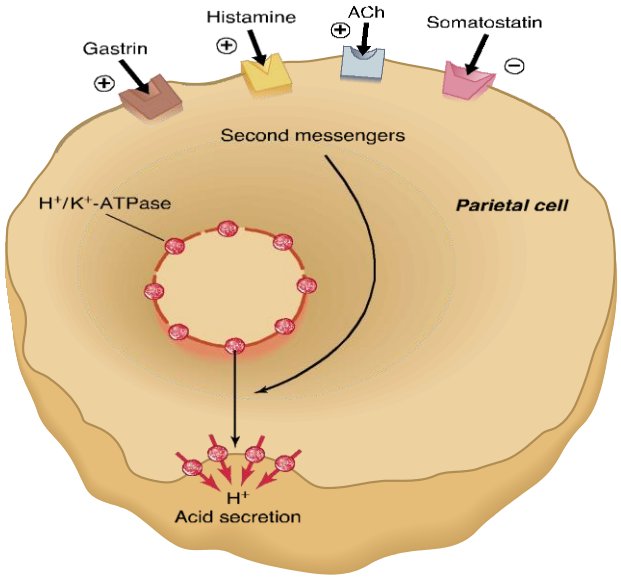

Figure 4: *The four-neurohumoral inputs to parietal cells that regulate acid secretion by generating second messengers. These second messengers control the transfer of the H^+/K^+-ATPase pumps in cytoplasmic vesicle membranes to the plasma membrane. Not shown are the effects of peptides and amino acids on acid secretion.*

During a meal, the rate of acid secretion increases markedly as stimuli arising from the cephalic, gastric, and intestinal phases alter the release of the four chemical messengers described in the previous paragraph. During the cephalic phase, increased activity of efferent parasympathetic neural input to the stomach's enteric nervous system results in the release of ACh from the plexus neurons, gastrin from the gastrin- releasing cells, and histamine from ECL cells (**Figure 5**).

Once food has reached the stomach, the gastric phase stimuli—distension from the volume of ingested material and the presence of peptides and amino acids released by the digestion of luminal proteins—produce a further increase in acid secretion. These stimuli use some of the same neural pathways used during the cephalic phase. Neurons in the mucosa of the

stomach respond to these luminal stimuli and send action potentials to the cells of the enteric nervous system, which in turn can relay signals to the gastrin-releasing cells, histamine-releasing cells, and parietal cells. In addition, peptides and amino acids can act directly on the gastrin-releasing endocrine cells to promote gastrin secretion.

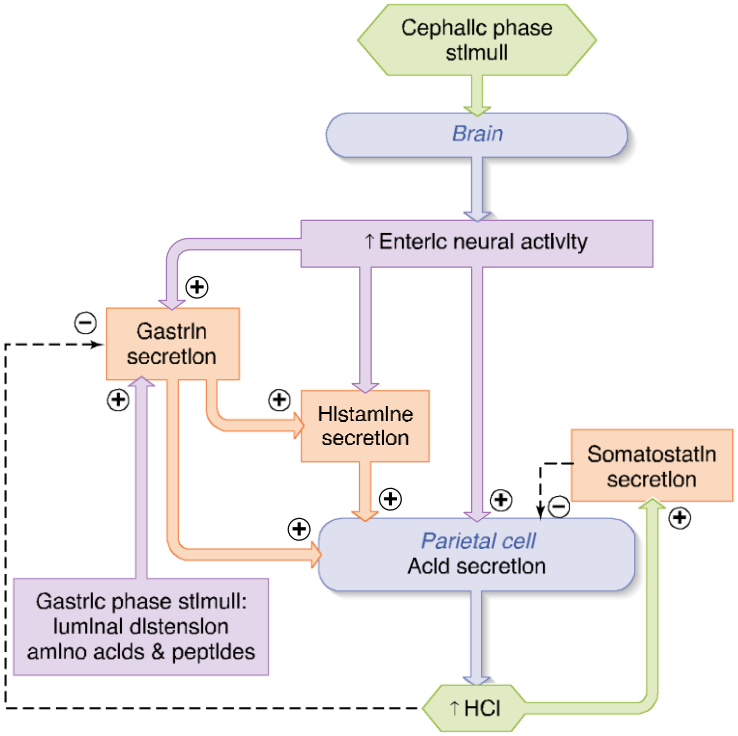

Figure 5: *Cephalic and gastric phases controlling acid secretion by the stomach.*

The concentration of acid in the gastric lumen is itself an important determinant of the rate of acid secretion because H^+ (acid) directly inhibits gastrin secretion. It also stimulates the release of somatostatin from endocrine cells in the gastric wall.

Somatostatin then acts on the parietal cells to inhibit acid secretion; it also inhibits the release of gastrin and histamine.

Increasing the protein content of a meal increases acid secretion. This occurs for two reasons. First, protein ingestion increases the concentration of peptides in the lumen of the stomach. These peptides, as we have seen, stimulate acid secretion through their actions on gastrin. The second reason is more complicated and reflects the effects of proteins on luminal acidity.

During the cephalic phase, before food enters the stomach, the H^+ concentration in the lumen increases because there are few buffers present to bind any secreted H^+. Thereafter, the rate of acid secretion soon decreases because high acidity reflexively inhibits acid secretion (see Figure 5).

The protein in food is an excellent buffer, however, so as it enters the stomach, the H^+ concentration decreases as H^+ binds to proteins and begins to denature them. This decrease in acidity removes the inhibition of acid secretion. The more protein in a meal, the greater buffering of acid and the more acid secreted.

High acidity in the duodenum triggers reflexes that inhibit gastric acid secretion. This inhibition is beneficial because the digestive activity of enzymes and bile salts in the small intestine is strongly inhibited by acidic solutions. This reflex limits gastric acid production when theH^+ concentration in the duodenum increases due to the entry of chyme from the stomach.

Acid, distension, hypertonic solutions, solutions containing amino acids, and fatty acids in the small intestine reflexively inhibits gastric acid secretion. The extent to which acid secretion is inhibited during the intestinal phase varies, depending upon the amounts of these substances in the intestine; the net result is the same, however—balancing the secretory activity of the stomach with the digestive and absorptive capacities of the small intestine.

The inhibition of gastric acid secretion during the intestinal phase is mediated by short and long neural reflexes and by hormones that inhibit acid secretion by influencing the four signals that directly control acid secretion: ACh, gastrin, histamine, and somatostatin. The hormones released by the intestinal tract that reflexively inhibit gastric activity are collectively called **enterogastrones** and include secretin and CCK.

Table: *Control of HCl Secretion During a Meal*

Stimuli	Pathways	Result
Cephalic phase Sight Smell Taste Chewing	Parasympathetic nerves to enteric nervous system	HCl secretion
Gastric contents (gastric phase) Distension Peptides H^1 concentration	Long and short neural reflexes and direct stimulation of gastrin secretion	HCl secretion
Intestinal contents (intestinal phase) Distension H^1 concentration Osmolarity Nutrient concentrations	Long and short neural reflexes; secretin, CCK, and other duodenal hormones	HCl secretion

Pepsin Secretion

Pepsin is secreted by chief cells in the form of an inactive precursor called pepsinogen (**Figure 6**). Exposure to low pH in the lumen of the stomach activates a very rapid, autocatalytic process in which pepsin is produced from pepsinogen.

Pepsin is active only in the presence of a high H^+ concentration (low pH). It is irreversibly inactivated when it enters the small intestine, where the HCO_3^- secreted into the small intestine neutralizes the H^+. The primary pathway for stimulating pepsinogen secretion is input to the chief cells from the enteric nervous system. During the cephalic, gastric, and intestinal phases, most of the factors that stimulate or inhibit acid secretion exert the same effect on pepsinogen secretion. Thus, pepsinogen secretion parallels acid secretion.

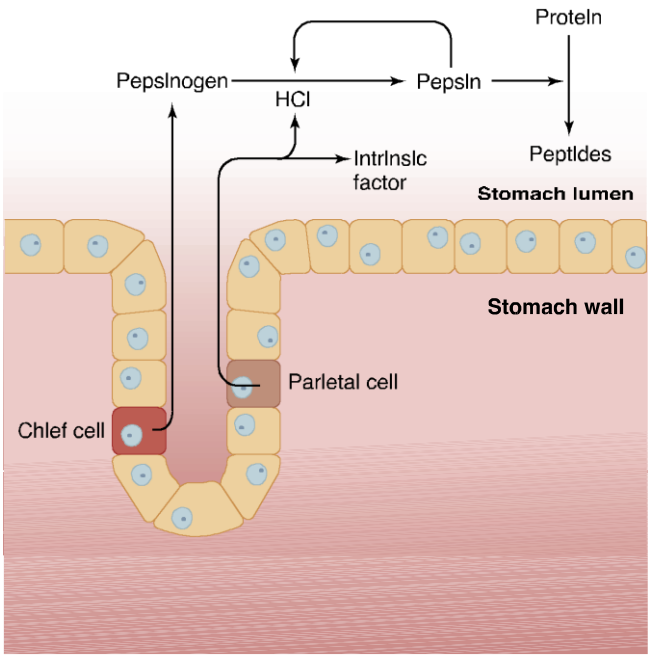

Figure 6: *Conversion of pepsinogen to pepsin in the lumen of the stomach. An increase in HCl acidifies the stomach contents. High acidity (low pH) maximizes pepsin cleavage from pepsinogen. The pepsin thus formed also catalyzes its own production by acting on additional molecules of pepsinogen. The parietal cells also secrete intrinsic factor, which is needed to absorb vitamin B_{12} in the small intestine.*

Pepsin is not essential for protein digestion because in its absence, as occurs in some pathological conditions, protein can be completely digested by enzymes in the small intestine. However, pepsin accelerates protein digestion and normally accounts for about 20% of total protein digestion. It is also important in the digestion of collagen contained in the connective- tissue matrix of meat. This is useful because it helps shred meat into smaller, more easily processed pieces with greater surface area for digestion.

Gastric Motility

An empty stomach has a volume of only about 50 mL, and the diameter of its lumen is only slightly larger than that of the small intestine. When a meal is swallowed, however, the smooth muscles in the fundus and body relax before the arrival of food, allowing the stomach's volume to increase to as much as 1.5 L with little increase in pressure. This **receptive relaxation** is mediated by the parasympathetic nerves to the stomach's enteric nerve plexuses, with coordination provided by afferent input from the stomach via the vagus nerve and by the swallowing center in the brain. Nitric oxide and serotonin released by enteric neurons mediate this relaxation.

As in the esophagus, the stomach produces peristaltic waves in response to the arriving food. Each wave begins in the body of the stomach and produces only a ripple as it proceeds toward the antrum; this contraction is too weak to produce much mixing of the luminal contents with acid and pepsin. As the wave approaches the larger mass of wall muscle surrounding the antrum, however, it produces a more powerful con- traction, which both mixes the luminal contents and closes the pyloric sphincter, a ring of smooth muscle and connective tissue between the antrum and the duodenum (Figure 7). The pyloric sphincter muscles contract upon arrival of a peristaltic wave. As a consequence of the sphincter closing, only a small amount of chyme is expelled into the duodenum with each wave.

Most of the antral contents are forced backward toward the body of the stomach. This backward motion of chyme, called retropulsion, generates strong shear forces that helps to disperse the food particles and improve mixing of the chyme. Recall that the lower esophageal sphincter prevents this retrograde movement of stomach contents from entering the esophagus.

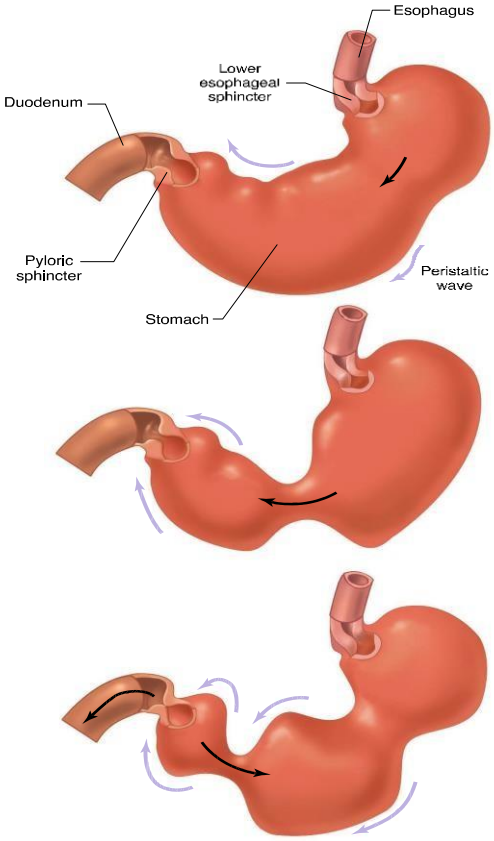

Figure 7: *Peristaltic waves passing over the stomach force a small amount of luminal material into the duodenum*

What is responsible for producing gastric peristaltic waves? Their rhythm (three per minute) is generated by pacemaker cells in the longitudinal smooth muscle layer. These smooth muscle cells undergo spontaneous depolarization– repolarization cycles (slow waves) known as the **basic electrical rhythm** of the stomach. These slow waves are conducted through gap junctions along the stomach's longitudinal muscle layer and also induce similar slow waves in the overlying circular muscle layer. In the absence of neural or hormonal input, however, these depolarizations are too small to cause significant contractions. Excitatory neurotransmitters and hormones act upon the smooth muscle to further depolarize the membrane, thereby bringing it closer to threshold. Action potentials may be generated at the peak of the slow-wave cycle if threshold is reached (**Figure 8**), causing larger contractions. The number of spikes fired with each wave determines the strength of the muscle contraction. Therefore, whereas the frequency of contraction is determined by the intrinsic basic electrical rhythm and remains essentially constant, the force of contraction—and, consequently, the amount of gastric emptying per contraction—is determined reflexively by neural and hormonal input to the antral smooth muscle.

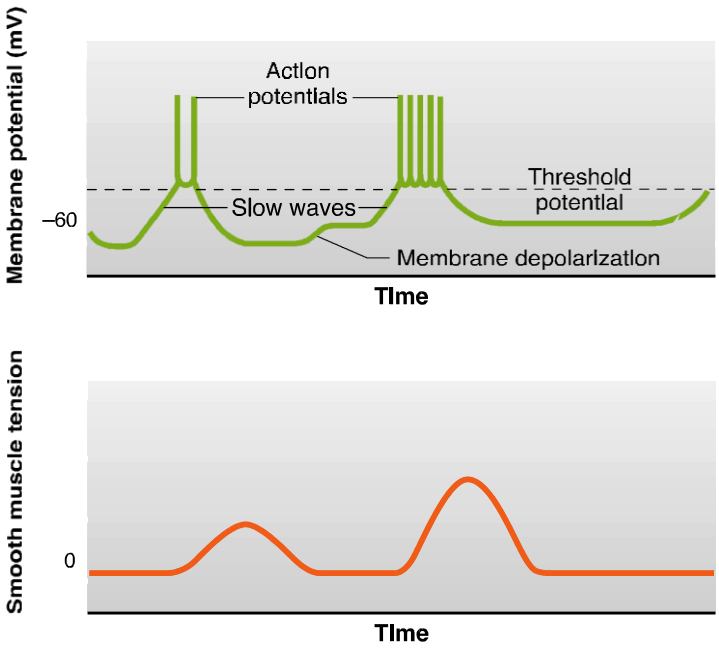

Figure 8: *Slow-wave oscillations in the membrane potential of gastric smooth muscle fibers trigger bursts of action potentials when threshold potential is reached at the wave peak. Membrane depolarization brings the slow wave closer to threshold, increasing the action potential frequency and thus the force of smooth muscle contraction.*

The initiation of these reflexes depends upon the contents of both the stomach and small intestine. All the factors previously discussed that regulate acid secretion can also alter gastric motility. For example, gastrin in sufficiently high concentrations increases the force of antral smooth muscle contractions. Distension of the stomach also increases the force of antral contractions through long and short reflexes triggered by mechanoreceptors in the stomach wall. Therefore, after a large meal, the force of initial stomach contractions is greater, which results in a greater emptying per contraction.

In contrast, gastric emptying is inhibited by distension of the duodenum or the presence of fat, high acidity (low pH), or hypertonic solutions in

the lumen of the duodenum (**Figure 9**). These are the same factors that inhibit acid and pepsin secretion in the stomach. Fat is the most potent of these chemical stimuli. This prevents overfilling of the duodenum. The rate of gastric emptying has significant clinical implications particularly when considering what food type is eaten with oral medications. A meal rich in fat content tends to slow oral drug absorption due to a delay of the drug entering the small intestine through the pyloric sphincter.

Autonomic nerve fibers to the stomach can be activated by the CNS independently of the reflexes originating in the stomach and duodenum and can influence gastric motility. An increase in parasympathetic activity increases gastric motility, whereas an increase in sympathetic activity decreases motility. Via these pathways, pain and emotions can alter motility; however, different people show different gastrointestinal responses to apparently similar emotional states. As we have seen, a hypertonic solution in the duodenum is one of the stimuli inhibiting gastric emptying. This reflex prevents the fluid in the duodenum from becoming too hypertonic. It does so by slowing the rate of entry of chyme and thereby the delivery of large molecules that can rapidly be broken down into many small molecules by enzymes in the small intestine.

Once the contents of the stomach have emptied over a period of several hours, the peristaltic waves cease and the empty stomach is mostly quiescent.

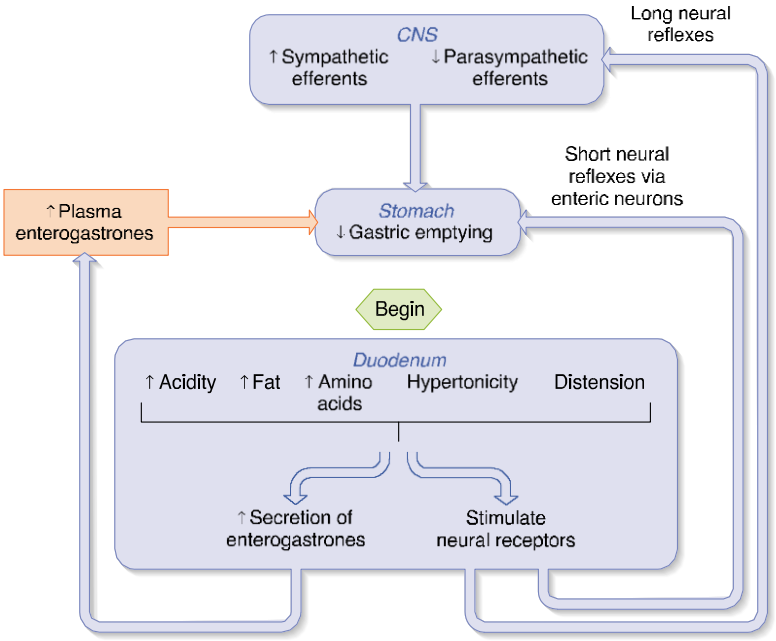

Figure 9: *Intestinal phase pathways inhibiting gastric emptying.*

Pancreatic Secretions

The exocrine portion of the pancreas secretes HCO_3^- and a number of digestive enzymes into ducts that converge into the pancreatic duct, which joins the common bile duct from the liver just before it enters the duodenum. The enzymes are secreted by gland cells at the pancreatic end of the duct system, whereas HCO_3^- is secreted by the epithelial cells lining the ducts (**Figure 1**).

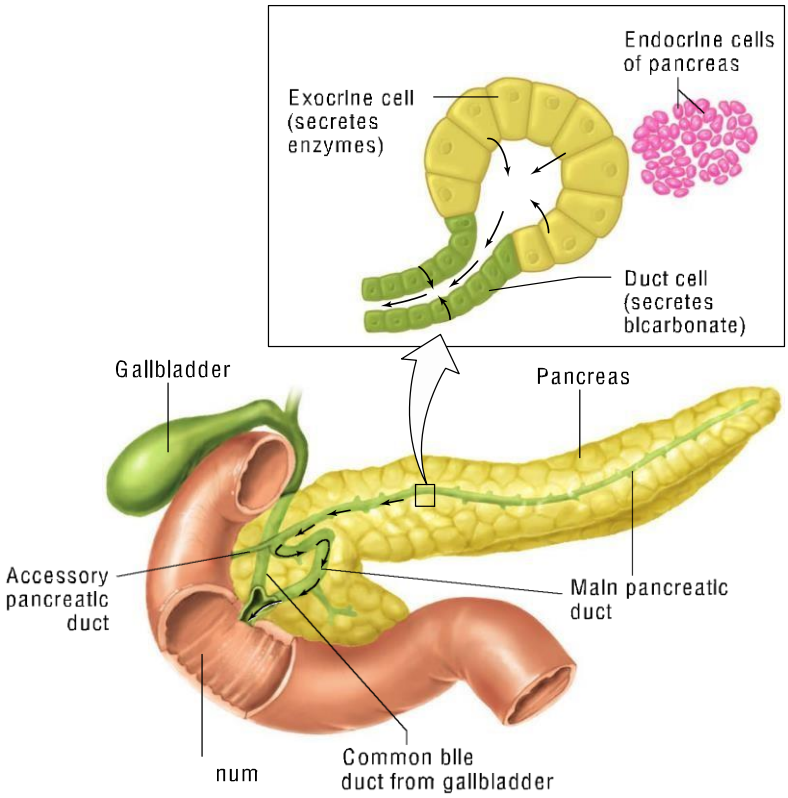

Figure 1: *Structure of the pancreas. The exocrine portion secretes enzymes and HCO_3^- into the pancreatic ducdocrine portion secretes insulin, glucagon, and other hormones into the blood.*

Duo

de

The pancreatic duct cells secrete HCO_3^- (produced from CO_2 and water) into the duct lumen via an apical membrane Cl^-/HCO^- exchanger, while H^+ produced is exchanged for extracellular Na^+ on the basolateral side of the cell (**Figure 2**). The H^+ enters the pancreatic capillaries to eventually meet up in portal vein blood with the HCO_3^- produced by the stomach during the generation of luminal H. As with most transport

systems, the energy for secretion of HCO_3^- is ultimately provided by Na^+/K^+-ATPase pumps on the basolateral membrane. Cl^- normally does not accumulate within the cell because these ions are recycled into the lumen through the **cystic fibrosis transmembrane conductance regulator** (**CFTR**).

Via a paracellular route, Na^+ and water move into the ducts due to the electrochemical gradient established by chloride movement through theCFTR.

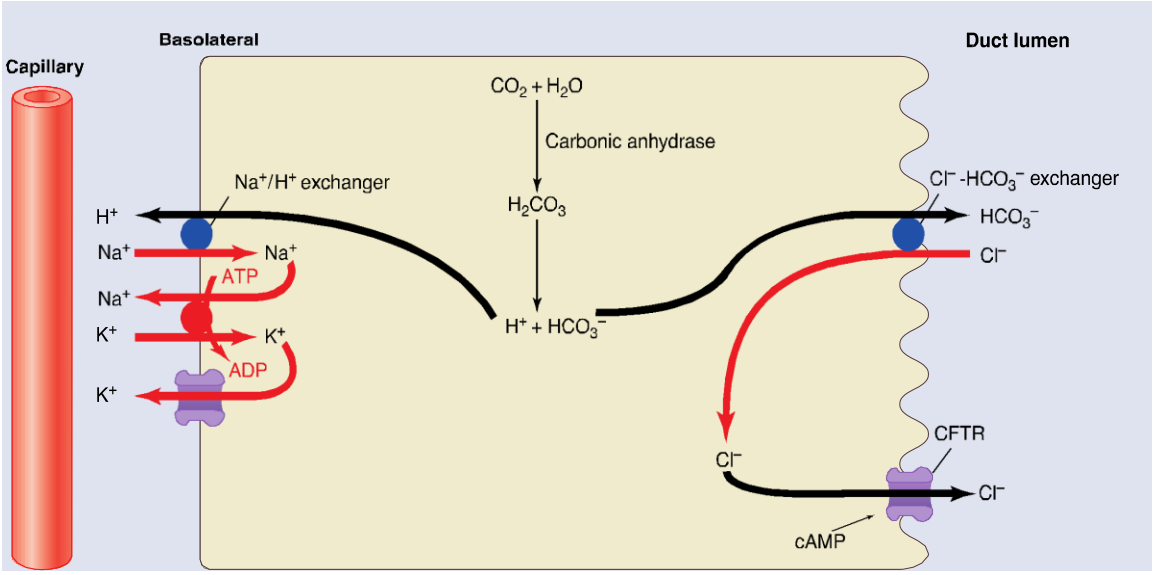

Figure 2: *Ion-transport pathways in pancreatic duct cells.*

The enzymes the pancreas secretes digest fat, polysaccharides, proteins, and nucleic acids to fatty acids, sugars, amino acids, and nucleotides, respectively. A partial list of these enzymes and their activities appears in **Table 1.** The proteolytic enzymes are secreted in inactive forms

(zymogens), as described for pepsinogen in the stomach, and then activated in the duodenum by other enzymes. Like pepsinogen, the secretion of zymogens protects pancreatic cells from autodigestion.

A key step in this activation is mediated by **enterokinase,** which is embedded in the luminal plasma membranes of the intestinal epithelial cells. Enterokinase is a proteolytic enzyme that splits off a peptide from pancreatic **trypsinogen,** forming the active enzyme trypsin. Trypsin is also a proteolytic enzyme; once activated, it activates the other pancreatic zymogens by splitting off peptide fragments (**Figure 3**). This activating function is in addition to the role of trypsin in digesting ingested protein. The nonproteolytic enzymes secreted by the pancreas (e.g., amylase and lipase) are released in fully active form.

Table 1: *Pancreatic enzymes.*

Enzyme	Substrate	Action
Trypsin, chymotrypsin, elastase	Proteins	Break peptide bonds in proteins to form peptide fragments
Carboxypeptidase	Proteins	Splits off terminal amino acid from carboxyl end of protein
Lipase	Fats	Splits off two fatty acids from triglycerides, forming free fatty acids and monoglycerides
Amylase	Polysaccharides	Splits polysaccharides into glucose and maltose
Ribonuclease, deoxyribonuclease	Nucleic acids	Split nucleic acids into free mononucleotides

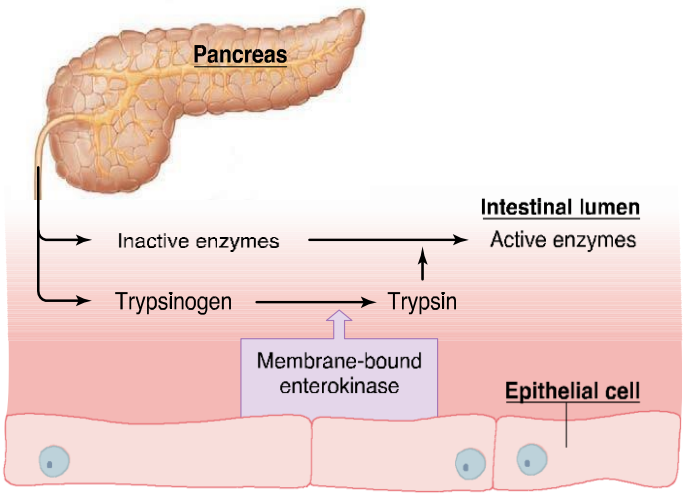

Figure 3: *Activation of pancreatic enzyme precursors in the small intestine.*

Pancreatic secretion increases during a meal, mainly as a result of stimulation by the hormones secretin and CCK. Secretin is the primary stimulant for HCO_3^- secretion, whereas CCK mainly stimulates enzyme secretion.

Because the function of pancreatic HCO_3^- is to neutralize acid entering the duodenum from the stomach, it is appropriate that the major stimulus for secretin release is increased acidity in the duodenum (**Figure 4**). In analogous fashion, CCK stimulates the secretion of digestive enzymes, including those for fat and protein digestion, so it is appropriate that the stimuli for its release are fatty acids and amino acids in the duodenum (**Figure 5**). Luminal acid and fatty acids also act on afferent nerve endings in the intestinal wall, initiating reflexes that act on the pancreas to increase both enzyme and HCO_3^- secretion. In these ways, the organic nutrients in

the small intestine initiate neural and endocrine reflexes that control the secretions involved in their own digestion.

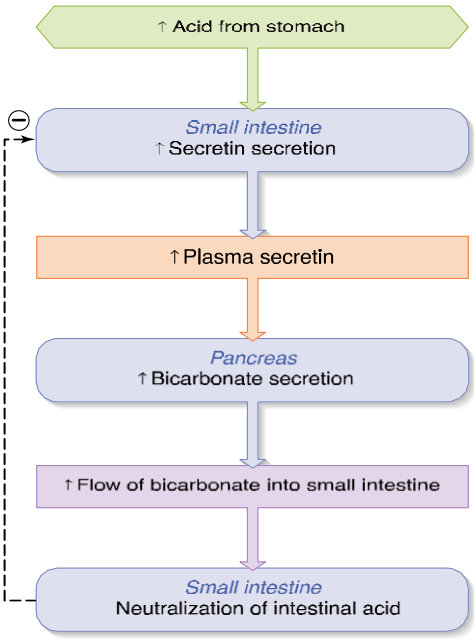

Figure 4: *Hormonal regulation of pancreatic HCO_3^- secretion.*

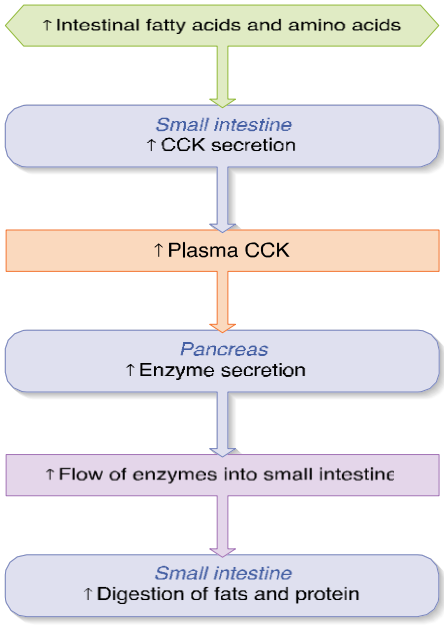

Figure 5: *Hormonal regulation of pancreatic enzyme secretion.*

Although most of the pancreatic exocrine secretions are controlled by stimuli arising from the intestinal phase of digestion, cephalic and gastric stimuli also play a role by way of the parasympathetic nerves to the pancreas. Thus, the taste of food or the distension of the stomach by food will lead to increased pancreatic secretion.

Bile Secretion

The functional unit of the liver is the **hepatic lobule** (**Figure 6**). Within the lobule, the **portal triad** is composed of branches of the bile duct, the portal

veins, and the hepatic artery (which brings oxygenated blood to the liver).

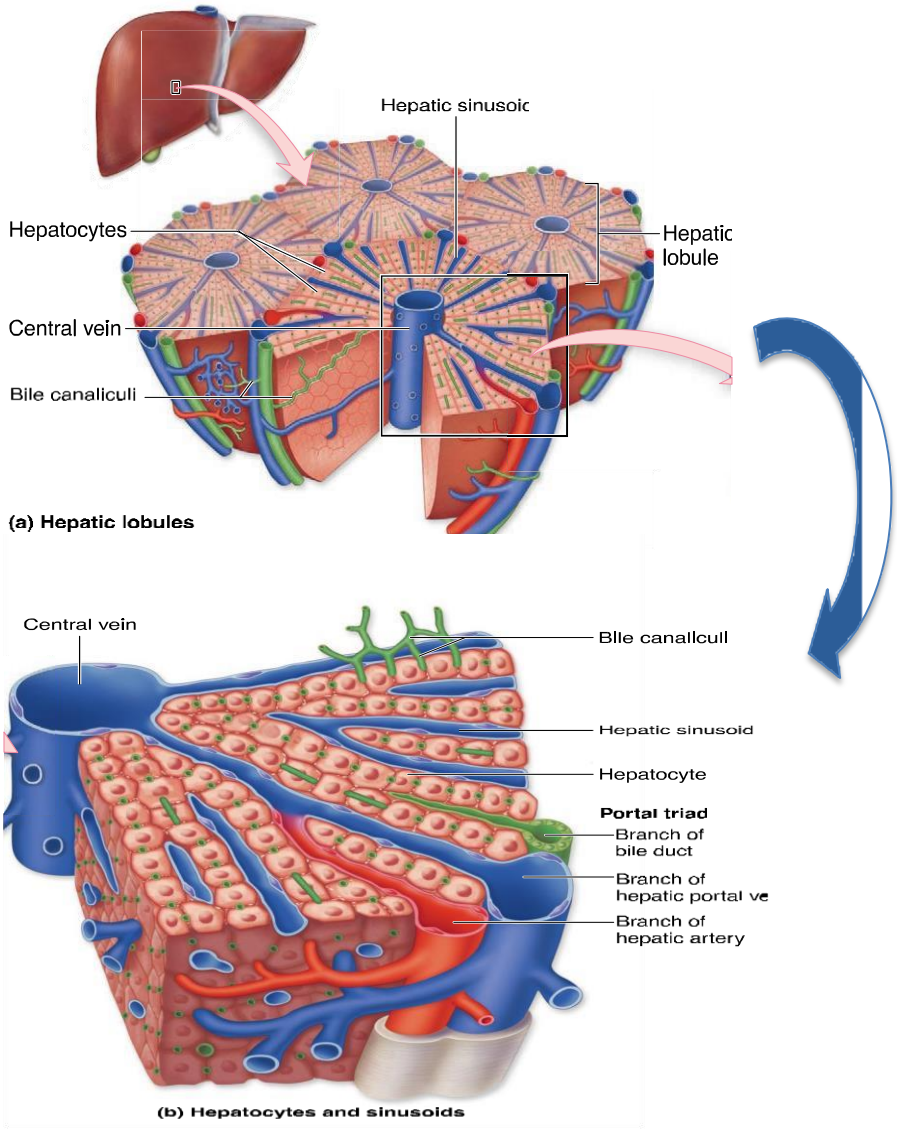

Figure 6: *Microscopic appearance of the liver. (a) Hepatic lobules are the functional units of the liver. (b) A small section of the liver showing the location of bile canaliculi and ducts with respect to blood and liver cells (hepatocytes).*

The hepatic portal veins communicate with the hepatic sinusoids and bring absorbed substances to the liver from the small

intestines. Hepatocytes take up and process nutrients and other factors from the hepatic sinusoids. Bile is formed by uptake by hepatocytes of bile salts and secretion into bile canaliculi. Finally, central veins, located at the center of each lobule, drain blood from the lobules into the systemic venous circulation.

Substances absorbed from the small intestine wind up in the hepatic sinusoid either to reach the vena cava via the central vein or are taken up by the **hepatocytes** (liver cells) in which they can be modified. Hepatocytes can rid the body of substances by secretion into the **bile canaliculi,** which converge to form the common hepatic bile duct.

Bile contains six major ingredients: (1) bile salts, (2) lecithin (a phospholipid), (3) HCO_3^- and other salts, (4) cholesterol, (5) bile pigments and small amounts of other metabolic end products, and (6) trace metals.

Bile salts and lecithin are synthesized in the liver and, as we have seen, help solubilize fat in the small intestine. HCO_3^- neutralizes acid in the duodenum, and the last three ingredients represent substances extracted from the blood by the liver and excreted via the bile.

The most important digestive components of bile are the bile salts. During the digestion of a fatty meal, most of the bile salts entering the intestinal

tract via the bile are absorbed by the ileum (the last segment of the small intestine). The absorbed bile salts are returned via the portal vein to the liver, where they are once again secreted into the bile. This recycling pathway from the liver to the intestine and back to the liver is known as the **enterohepatic circulation** (**Figure 7**).

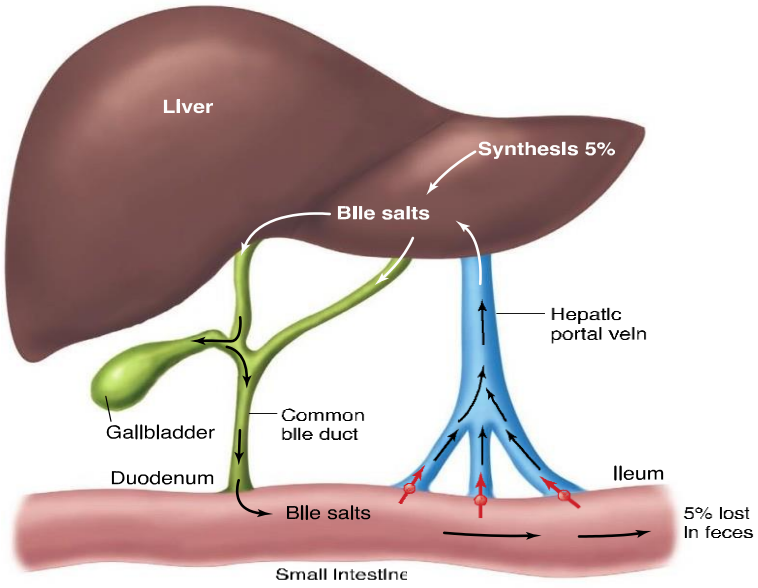

Figure 7: *Enterohepatic circulation of bile salts. Bile salts are secreted into bile and enter the duodenum through the common bile duct. Bile salts are reabsorbed from the intestinal lumen into hepatic portal blood. The liver (hepatocytes) reclaims bile salts from hepatic portal blood.*

In addition to synthesizing bile salts from cholesterol, the liver also secretes cholesterol extracted from the blood into the bile. Bile secretion, followed

by excretion of cholesterol in the feces, is one of the mechanisms for maintaining cholesterol homeostasis in the blood.

Dietary fiber also sequesters تعزل bile and thereby lowers plasma cholesterol.

This occurs because the sequestered bile salts escape the enterohepatic circulation. Therefore, the liver must either synthesize new cholesterol, or remove it from the blood, or both to produce more bile salts. Cholesterol is insoluble in water, and its solubility in bile is achieved by its incorporation into micelles (whereas in blood, cholesterol is incorporated into lipoproteins).

Bile pigments *are substances formed from the heme portion of hemoglobin when old or damaged erythrocytes are broken down in the spleen and liver. The predominant bile pigment is* ***bilirubin,*** *which is extracted from the blood by liver cells and actively secreted into the bile. Bilirubin is yellow and contributes to the color of bile. During their passage through the intestinal tract, some of the bile pigments are absorbed into the blood and are eventually excreted in the urine, giving urine its yellow color. After entering the intestinal tract, some bilirubin is modified by bacterial enzymes to form the brown pigments that give feces their characteristic color.*

The components of bile are secreted by two different cell types. The bile salts, cholesterol, lecithin, and bile pigments are secreted by hepatocytes, whereas most of the HCO_3^--rich solution is secreted by the epithelial cells lining the bile ducts.

Secretion of the HCO_3^--rich solution by the bile ducts, just like the secretion by the pancreas, is stimulated by secretin in response to the presence of acid in the duodenum.

Although bile secretion is greatest during and just after a meal, the liver is always secreting some bile. Surrounding the common bile duct at the point where it enters the duodenum is a ring of smooth muscle known as the **sphincter of Oddi.** When this sphincter is closed, the dilute bile secreted by the liver is shunted into the gallbladder. Here, the organic components of bile become concentrated as some NaCl and water are absorbed into the blood.

Shortly after the beginning of a fatty meal, the sphincter of Oddi relaxes and the gallbladder contracts, discharging concentrated bile into the duodenum. The signal for gallbladder contraction and sphincter relaxation is the intestinal hormone CCK—appropriately so, because, as we have seen, the presence of fat in the duodenum is a major stimulus for this hormone's release.

Small Intestine

Secretion

Approximately 1500 mL of fluid is secreted by the walls of the small intestine from the blood into the lumen each day. One of the causes of water movement (secretion) into the lumen is that the intestinal epithelium at the base of the villi secretes a number of mineral ions—notably, Na^+, Cl^-, and HCO_3^-—into the lumen, and water follows by osmosis. These secretions, along with mucus, lubricate the surface of the intestinal tract and help protect the epithelial cells from excessive damage by the digestive enzymes in the lumen. Some damage to these cells still occurs, however, and the intestinal epithelium has one of the highest cell-renewal rates of any tissue in the body.

As stated earlier, water movement into the lumen also occurs when the chyme entering the small intestine from the stomach is hypertonic because of a high concentration of solutes in the meal and because digestion breaks down large molecules into many more small molecules. This hypertonicity causes the osmotic movement of water from the isotonic plasma into the intestinal lumen.

Absorption

Normally, virtually all of the fluid secreted by the small intestine is absorbed back into the blood. In addition, a much larger volume of fluid, which includes salivary, gastric, hepatic, and pancreatic secretions, as well as ingested water, is simultaneously absorbed from the intestinal lumen into the blood. Thus, overall there is a large net absorption of water from the small intestine. Absorption is achieved by the transport of ions, primarily via Na^+ and nutrient co-transport from the intestinal lumen into the blood, with water following by osmosis.

Motility

In contrast to the peristaltic waves that sweep over the stomach, the most common motion in the small intestine during digestion of a meal is a stationary contraction and relaxation of intestinal segments, with little apparent net movement toward the large intestine (**Figure 8**). Each contracting segment is only a few centimeters long, and the contraction lasts a few seconds. The chyme in the lumen of a contracting segment is forced both up and down the intestine. This rhythmic contraction and relaxation of the intestine, known as **segmentation,** produces a continuous

division and subdivision of the intestinal contents, thoroughly mixing the chyme in the lumen and bringing it into contact with the intestinal wall.

These segmenting تجزئة movements are initiated by electrical activity generated by pacemaker cells (the **interstitial cells of Cajal**) in the circular smooth muscle layer. As with the slow waves in the stomach, this intestinal basic electrical rhythm produces oscillations ذبذبة in the smooth muscle membrane potential. If threshold is reached, action potentials are triggered that increase muscle contraction. *The frequency of segmentation is set by the frequency of the intestinal basic electrical rhythm; unlike the stomach, however, which normally has a single rhythm (three per minute), the intestinal rhythm varies along the length of the intestine, each successive region having a slightly lower frequency than the one above. For example, segmentation in the duodenum occurs at a frequency of about 12 contractions/min, whereas in the last portion of the ileum the rate is only 9 contractions/min. Segmentation produces, therefore, a slow migration of the intestinal contents toward the large intestine because more chyme is forced downward, on average, than upward.*

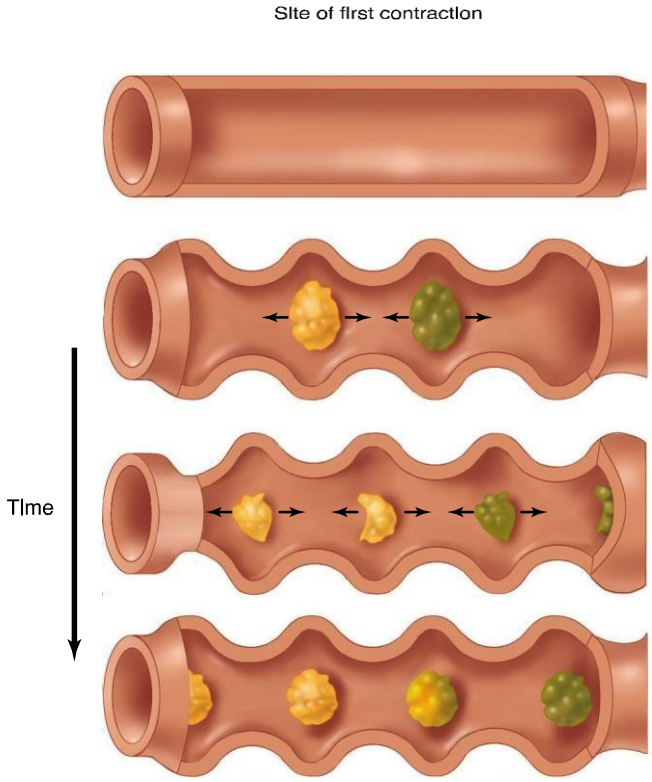

Figure 8: *Segmentation contractions in a portion of the small intestine in which segments of the intestines contract and relax in a rhythmic pattern but do not undergo peristalsis. This is the rhythm encountered during a meal. Dotted lines are reference points to show the site of the first contraction in time (starting at the top). As contractions occur at the next site, the chyme is divided and pushed back and forth, mixing the luminal contents.*

The intensity of segmentation can be altered by hormones, the enteric nervous system, and autonomic nerves; parasympathetic activity increases the force of contraction, and sympathetic stimulation decreases it. Thus, cephalic phase stimuli, as well as emotional states, can alter intestinal motility. As is true for the stomach, these inputs produce changes in the force of smooth muscle contraction but do not significantly change the frequencies of the basic electrical rhythms.

After most of a meal has been absorbed, the segmenting contractions cease and are replaced by a pattern of peristaltic activity known as the ***migrating myoelectrical complex*** *(**MMC**). Beginning in the lower portion of the stomach, repeated waves of peristaltic activity travel about 2 feet along the small intestine and then die out. The next MMC starts slightly farther down the small intestine so that peristaltic activity slowly migrates down the small intestine, taking about 2 h to reach the large intestine. By the time the MMC reaches the end of the ileum, new waves are beginning in the stomach, and the process repeats.*

The MMC moves any undigested material still remaining in the small intestine into the large intestine and also prevents bacteria from remaining in the small intestine long enough to grow and multiply excessively. In diseases characterized by an aberrant MMC, bacterial overgrowth in the small intestine can become a major problem. Upon the arrival of a meal in the stomach, the MMC rapidly ceases in the intestine and is replaced by segmentation.

An increase in the plasma concentration of the intestinal hormone **motilin** is thought to initiate the MMC. Feeding inhibits the release of motilin; motilin stimulates MMCs via both the enteric and autonomic nervous systems.

As much as 500 mL of air may be swallowed during a meal. Most of this air travels no farther than the esophagus, from which belching eventually expels it. Some of the air reaches the stomach, however, and is passed on to the intestines, where its percolation through the chyme as the intestinal contents mix produces gurgling sounds that can be quite loud.

Large Intestine

Anatomy and Function

The large intestine is a tube about 6.5 cm (2.5 inches) in diameter and about 1.5 m (5 feet) long. Although the large intestine has a greater diameter than the small intestine, its epithelial surface area is far smaller because the large intestine is shorter than the small intestine, its surface is not convoluted, and its mucosa lacks villi found in the small intestine. The first portion of the large intestine is the **cecum.** A sphincter between the ileum and the cecum is called the **ileocecal valve** (or **sphincter**) and is composed primarily of circular smooth muscle innervated by sympathetic nerves. The circular muscle contracts with distension of the colon and limits the movement of colonic contents backward into the ileum. This prevents bacteria from the large intestine from colonizing the final part of the small intestine. The **appendix** is a small, fingerlike projection that extends from the cecum and may participate in immune function but is

not essential (**Figure 9**). The **colon** consists of three relatively straight segments—the ascending, transverse, and descending portions. The terminal portion of the descending colon is S-shaped, forming the sigmoid colon, which empties into a relatively straight segment of the large intestine, the rectum, which ends at the anus.

The primary function of the large intestine is to store and concentrate fecal material before defecation. The secretions of the large intestine are scanty, lack digestive enzymes, and consist mostly of mucus and fluid containing HCO_3^- and K^+.

About 1500 mL of chyme enters the large intestine from the small intestine each day. This material is derived largely from the secretions of the lower small intestine because most of the ingested food is absorbed before reaching the large intestine. Fluid absorption by the large intestine normally accounts for only a small fraction of the fluid absorbed by the gastrointestinal tract each day.

The primary absorptive process in the large intestine is the active transport of Na^+ from lumen to extracellular fluid, with the accompanying osmotic absorption of water. If fecal material remains in the large intestine for a long time, almost all the water is absorbed, leaving behind hard fecal pellets. There is normally a net movement of K^+ from blood into the large

intestine lumen. Severe depletion of total-body potassium can result when large volumes of fluid are excreted in the feces. There is also a net movement of HCO_3^- into the lumen coupled to Cl^- absorption from the lumen, and loss of this HCO_3^- (a base) in patients with prolonged diarrhea can cause metabolic acidosis.

The large intestine also absorbs some of the products formed by the bacteria colonizing this region. It is now recognized that the colonic bacteria make a vital metabolic contribution to health. Undigested polysaccharides (fiber) are converted to short-chain fatty acids by bacteria in the large intestine and absorbed by passive diffusion as well as actively via specific short-chain fatty acid transporters. This route of absorption can represent a significant source of ingested calories and can be even more in obesity. The HCO_3^- secreted by the large intestine helps to neutralize the increased acidity resulting from the formation of these fatty acids. These bacteria also produce small amounts of vitamins, especially vitamin K, for absorption into the blood. Although this source of vitamins generally provides only a small part of the normal daily requirement, it may make a significant contribution when dietary vitamin intake is low. An individual who depends on absorption of nutrients and vitamins formed by bacteria in the large intestine

can have adverse health consequences if treated with antibiotics that inhibit other species of bacteria in addition to the disease-causing bacteria.

Motility

Contractions of the circular smooth muscle in the large intestine produce a segmentation motion with a rhythm considerably slower (one every 30 min) than that in the small intestine. Because of the slow propulsion of the large-intestine contents, material entering the large intestine from the small intestine remains for about 18 to 24 h. This provides time for bacteria to grow and multiply. Three to four times a day, generally following a meal, a wave of intense contraction known as a **mass movement** spreads rapidly over the transverse segment of the large intestine toward the rectum. The large intestine is innervated by parasympathetic and sympathetic nerves. Parasympathetic input increases segmental contractions, whereas sympathetic input decreases colonic contractions.