

## **Section 6**

### **LECTURE**

### **Motility of the Alimentary Tract**

## Alimentary Tract Motor Function

### Overview

The motor activity of the alimentary tract helps to prepare the food for digestion and facilitate absorption as the residues are carried caudally for final expulsion. The alimentary tract consists of functionally distinct segments such as the esophagus, the stomach, and the small and large intestines, each of which possesses distinctive motor activity. Despite major differences in function and motor control, the different segments have a similar overall structural organization. The wall of the alimentary tube consists of an outer layer of longitudinal muscle and an inner layer of circular muscle. Internal to these muscle layers is the submucosa, which is delimited by the muscularis mucosa. The mucosa lines the lumen and is separated from the muscularis mucosa by the lamina propria.

The motor activity of each part of the gut is designed to provide propulsion appropriate for the particular physical character and viscosity of food at its level of the alimentary canal. The distinctive motor activities of the different segments of the gut also permit performance of certain specialized functions. For example, the esophagus transports small chunks of swallowed food, whereas the stomach temporarily stores, digests and grinds solid food into small particles and delivers them to the small bowel. The small bowel functions to allow digestion and absorption. The large bowel acts to retain food residues for several hours or days. Its motor activity allows absorption of water, so that watery food residues are converted to a semisolid or solid consistency. The large bowel also "turns over" residues, of which a small portion is expelled daily during defecation.

Various sphincters separate different segments of the alimentary tract. The sphincters act as one-way valves, normally allowing only forward flow. In addition to directing flow, some sphincters regulate the flow of volume and physical character of contents from one segment to another. Gastrointestinal motility is controlled by *myogenic, neural, and hormonal factors*. The distinctive motor activities of different segments of the gut and the sphincters are due to the heterogeneity and specializations of these controlling factors.

### MOVEMENT OF FOOD THROUGH VARIOUS GUT SEGMENTS

#### Oral Cavity and Pharynx

After food enters the mouth, it is chewed and formed into a bolus and is transported to the esophagus through the pharynx. The oral phase of swallowing is completely under voluntary control. As the bolus enters the oropharynx, an involuntary swallowing reflex is initiated by activation of sensory receptors on the posterior part of the oral cavity. The bolus enters the oropharynx, the nasal and laryngeal passages are occluded, and a wave of peristalsis sweeps the bolus ahead of it. The upper esophageal sphincter opens in anticipation of the arriving bolus. The pharynx and the upper esophageal sphincter are composed of striated muscles. They are innervated by lower motor neurons that accompany vagal and other cranial nerves. A pattern generator for the complex swallowing activity is in the so-called swallowing center in the brain stem. The activity of the swallowing center is modulated by cortical neurons. Neuromuscular disorders that involve these nerves or muscles cause pharyngeal

paralysis. Pharyngeal paralysis produces the characteristic symptoms of dysphagia, nasal regurgitation, and tracheobronchial aspiration.

### Esophagus

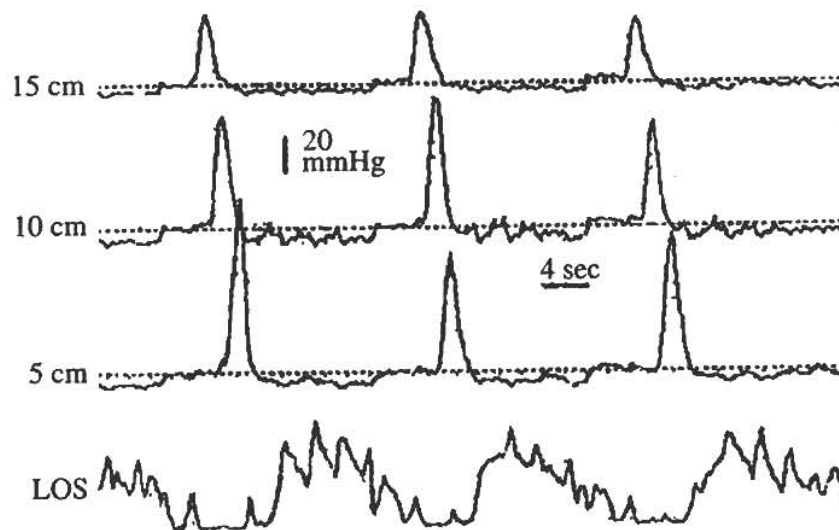
The peristaltic wave that starts in the pharynx continues through the esophagus at a speed of 3 to 4 cm per second, carrying the food bolus ahead of it. The normal transit time of a bolus of food through the esophagus is 5 to 6 seconds. The lower esophageal sphincter opens well before the arrival of the peristaltic wave so that food can pass into the stomach. When the bolus enters the stomach, the lower esophageal sphincter resumes the resting, contracted state.

Peristaltic contractions that occur in response to a swallow are called *primary peristalsis* and are always initiated in the pharynx. *Secondary peristalsis* occurs in response to esophageal distention and is not initiated by pharyngeal activity. The role of secondary peristalsis is to help clear the esophagus of food residue and reflux into it from the stomach.

The cervical esophagus is composed of striated muscle that is directly innervated by lower motor neurons. Primary as well as secondary peristalsis in the cervical esophagus are due to sequential activation in the brain stem of lower motor neurons that supply the progressively caudally placed musculature of the cervical esophagus.

The thoracic esophagus is composed of smooth muscle that is innervated by myenteric neurons, which are in turn innervated by vagal parasympathetic preganglionic fibers. In the thoracic esophagus, primary peristalsis involves a vagally mediated central mechanism as well as a peripheral mechanism that involves myenteric neurons. Secondary peristalsis, however, is due entirely to local myenteric reflexes. The inhibitory neurotransmitters VIP and NO are involved in lower esophageal sphincter relaxation and the latency gradient of peristalsis.

Peristaltic contractions in the smooth muscle consist of a wave of hyperpolarization followed by depolarization. The peristaltic behavior is due to a progressive increase in the duration of hyperpolarizations aborally along the esophagus. In disease states the esophageal contractions may lose their peristaltic behavior coincident with the loss of aborally increasing hyperpolarizations. Such contractions are called *nonperistaltic* or *tertiary* contractions. The specific neurotransmitters that participate in peristalsis are not fully known, but it appears that multiple inhibitory and excitatory transmitters – including acetylcholine, substance P, and NO—are involved. Weak or absent esophageal contractions (as occur in esophageal scleroderma) cause dysphagia, whereas strong but nonperistaltic contractions (as occur in diffuse esophageal spasm) cause dysphagia and chest pain. Defective relaxation of the lower esophageal sphincter (as in achalasia) also causes dysphagia, whereas inappropriate relaxation or basal hypotension of the sphincter causes gastroesophageal reflux and esophagitis.



**Figure 1.** Normal esophageal motility.

### Stomach

As swallowed food fills the stomach, the proximal stomach relaxes to accommodate the contents without causing an increase in luminal pressure. The distal stomach also becomes quiet, and any ongoing motor activity is inhibited. These responses are mediated by the vagus nerve along with intramural inhibitory neurons. Impaired gastric accommodation leads to symptoms of early satiety and enhanced gastric emptying of liquids.

A short time after a meal, peristaltic waves in the body and antrum of the stomach resume and then become stronger, carrying small bits of gastric contents into the terminal antrum. The terminal antrum contracts as a whole against a closed pylorus. This activity helps to grind coarse food into finer particles and mix it with gastric secretions. In the early phase of this activity the pylorus is partially open; allowing passage into the duodenum of small quantities of liquids and solid particles less than 2 mm in diameter. However, such passage of food into the small bowel occurs only if small intestinal contractions at that precise time are inhibited. This requires coordination of antral and duodenal contractions. As the antrum continues to contract, larger particles of food are repulsed into the main cavity of the stomach. The antrum then relaxes until the next peristaltic wave brings in another portion of food. Thus the antrum and the pylorus act in a coordinated fashion to limit as well as to achieve the emptying of gastric contents. This mechanism is of primary importance in the grinding of digestible solid food and its eventual emptying from the stomach. Vagal inhibitory and excitatory pathways are involved in mediating these responses.

The rate of gastric emptying of liquids and small particulate solids (less than 2 mm) is dependent on the volume of gastric contents. The larger the volume is, the faster the initial emptying rate. Gastric emptying is also regulated by the physicochemical properties of the chyme that enters the duodenum. The duodenal mucosa possesses sensory receptors that activate neurohumoral reflexes that influence gastric emptying. If the chyme coming out of the pylorus is drained so that it does not come in contact

with the duodenum, gastric emptying increases markedly. Emptying is inhibited by increasing osmolarity, pH below 3.5, and products of fat digestion. Products of carbohydrate and protein digestion have only a small inhibitory effect. During the digestive period, only liquids and small particles of ground digestible solids leave the stomach, whereas large pieces of indigestible food are retained. One or two hours after a meal, all liquids and digestible solids leave the stomach. At this time, trains of contractions appear that occur at a rate of three to five per minute (which is the rate of gastric slow waves) and move across the stomach. Vagal nerves play an important role in these migratory contractions. Normally the stomach is emptied of all food materials in 2 to 4 hours.

Delayed gastric emptying occurs in a variety of disorders involving myogenic, neural, or hormonal control systems. Myopathic diseases of the gastric smooth muscle (e.g., scleroderma or visceral myopathy) and abnormalities of gastric slow waves such as tachygastric (fast rate of gastric slow waves) or gastric arrhythmia (disorganized gastric slow waves) lead to gastric stasis and symptoms of postprandial fullness, nausea, and vomiting. Similarly, bilateral vagotomy or a vagal neuropathy such as diabetic neuropathy also leads to gastric stasis. Stasis of indigestible solids in the stomach can lead to formation of gastric bezoars. In diabetic gastroparesis the intradigestive migrating activity front is particularly abnormal, leading to delayed emptying of indigestible solids as an early manifestation of the disease. Disruption of neuronal nitric oxide synthase gene leads to gastric stasis and dilation. Gastric prokinetic agents such as metoclopramide, domperidone, or cisapride improve delayed gastric emptying by increasing the amplitude of antral contractions, improving antroduodenal coordination, and initiating "migrating activity fronts." Macrolide antibiotics such as erythromycin act on motilin receptors to initiate migrating motor complexes and to improve gastroduodenal coordination to enhance gastric emptying.

### **Small Intestine**

Liquids and finely ground food particles enter the small bowel with antral contractions. The pattern of small bowel motor activity observed when food is present in the small intestine is called the *fed pattern* and is characterized by segmental contractions. The segmental contractions are monophasic contraction waves that occur at different sites along the small bowel in a random fashion. Segmental contractions do not propagate in either an aboral or oral direction. These contractions are responsible for the mixing of food with digestive enzymes in intestinal, pancreatic, and biliary secretions. Additional stirring and mixing of the intestinal secretions and food are provided by the muscular activity movement of the villi. Mixing and stirring of intestinal contents are necessary not only for digestion but also for absorption of food. If segmental contractions are inhibited, as in certain disease states such as scleroderma or hallow visceral myopathy, intestinal digestion and absorption are impaired. In the absence of stirring, water layers develop between the intestinal mucosa and the food that is present in the lumen. The unstirred water layers impose a barrier between molecules of digested food and the intestinal mucosa.

Interspersed among the abundant segmental contractions during the fed pattern are also contractions that propagate aborally for distances of several centimeters. These contractions help gradually to move the food as it is being digested and absorbed. Impaired transit of food throughout the small intestine has been shown to



cause reflex inhibition of gastric emptying and may therefore contribute to early satiety, bloating, and anorexia.

After the digestion and absorption of food are completed, the pattern of small bowel motor activity is replaced by patterns of cyclic motor activity called *interdigestive migrating motor complexes*. Each migrating motor complex consists of periods of inactivity alternating with segmental or propulsive contractions. The period of inactivity, which lasts around 20 to 60 minutes, is called *phase I*. Phase I activity is followed by irregular segmental contractions that last for a variable period and are called *phase II* activity. Phase II is followed by regular contractions of the activity front, which is designated *phase III*.

The activity front that is the hallmark of the migrating motor complex consists of an 8- to 10-minute cluster of regularly occurring contractions. The rate of contraction varies in different parts of the small bowel and is determined by the intrinsic frequency of the slow wave in that segment of the intestine. The contraction rate in the activity front is around 12 per minute in the human duodenum. This rate decreases distally along the intestine, so that in the ileum the rate of contraction is 3 to 5 per minute. The activity front migrates toward the terminal ileum at a rate of 4 to 6 cm per minute and gradually decreases to 1 to 2 cm per minute as it approaches the terminal ileum. The activity front reaches the terminal ileum in 1 ½ hours, triggering a new activity front to begin in the duodenum. Activity fronts are inhibited by ingesting a meal and are thought to be initiated by the hormone motilin. The migrating motor complexes are responsible for the slow propagation of food residues through the small bowel and have been called the *interdigestive housekeepers* of the small intestine. Somatostatin can initiate migrating motor complexes; however, its overall effects on small bowel motility are not well understood. Somatostatin delays intestinal transit in normal subjects, but in patients with intestinal pseudo-obstruction a stable analogue of somatostatin has been shown to enhance small bowel transit.

Another type of propulsive contraction in the small bowel is the *giant peristaltic contraction*, which normally occurs periodically and only in the distal small intestine and the colon. These contractions are called *giant* because their amplitude is 1.5 to 2.0 times larger and their duration 4 to 6 times longer than the usual intestinal contraction. The electrical correlate of giant contractions is not known. Giant peristaltic contractions involve simultaneous contractions of a large (20 to 30 cm) segment of small intestine, and they propagate uninterrupted and aborally at a speed of 1 cm per second. Thus a giant peristaltic contraction can sweep food residues through the whole length of the intestine in a few minutes.

In certain disease states, giant peristaltic contractions can originate in the proximal small bowel and proceed aborally uninterrupted. These peristaltic contractions in the small intestine can be induced by intraluminal administration of agents such as vinegar or short-chain fatty acids. They can also be induced by administration of antibiotics such as erythromycin. Irradiation therapy and parasitic infections have been reported to cause an increase in the frequency as well as being a more proximal origin of these contractions in the small bowel. Most of the manipulations that induce giant peristaltic contractions also cause diarrhea, and therefore it is reasonable to assume that these contractions may be involved in the pathogenesis of diarrhea. One of the interesting features of giant peristaltic contractions is their potential for producing painful abdominal cramps. These cramps are presumably related to vigorous, long-duration contraction involving large segments of the intestine. The occurrence of giant peristaltic

contractions in the ileum is often associated with the perception of abdominal pain and cramps in patients with irritable bowel syndrome. The neurohormonal mechanisms responsible for giant peristaltic contractions are not known.

### **Gallbladder and Sphincter of Oddi**

Bile flows continuously from the liver into the biliary tract. Between meals the sphincter of Oddi largely remains closed, and bile is directed to the gallbladder. The gallbladder concentrates and stores bile. A small amount of bile is emptied into the duodenum as the gallbladder contracts and as the sphincter of Oddi relaxes during the interdigestive motor activity in the small bowel. After a meal, particularly a fatty meal, the gallbladder contracts vigorously, the sphincter of Oddi relaxes, and the bile is emptied into the duodenum. This action is mediated by cholecystikinin, which is released by fat in the duodenum. Weakness of gallbladder contraction leads to enlargement of the gallbladder and stasis, which may predispose toward formation of gallstones. Impaired relaxation of the sphincter of Oddi may be responsible for biliary dyskinesia associated with pain and liver function abnormalities.

The purpose of the motor activity of the colon is to mix, store temporarily, and propel food residues of semisolid to solid consistency very slowly. The main role of the ascending colon is to receive and store mostly liquid contents discharged through the ileocecal valve. The role of the left side of the colon is to store food residues for periodic expulsion into the rectum. Colonic motor activity is quite complex and promotes stasis and retropulsion in addition to infrequent but vigorous aboral propulsion of fecal material. Colonic motor activity consists of segmental contractions of either short (less than 10 seconds) or long (around 1 minute) duration. The short-duration contractions occur as a result of spike bursts in association with colonic slow waves. Because colonic slow waves occur irregularly at a frequency of 3 to 12 minutes, these contractions have a similar rate of repetition. The long-duration contractions occur without respect to slow waves and are associated with either long-duration spike bursts or oscillating potentials. The short- and long-duration contractions may occur singly, but more often they occur in trains. These trains of mostly nonpropulsive but sometimes retropulsive activity constitute a large portion of the motor activity of the colon. Segmental contractions in the left side of the colon are also associated with haustral contractions. The haustra are formed by thin, annular contractions that produce transitory septa, breaking up the lumen into saccules. Segmental contractions in the left colon provide resistance to distal movements of the contents; these contractions are increased in patients with constipation and are decreased in patients with diarrhea.

Slow and rapid caudal shifts of colon contents occur during its propulsive motor activity. Slow shifts of colonic contents occur with migrating trains of short- or long-duration contractions, which migrate at rates of 4 to 6 cm per minute and 0.5 to 2 cm per minute, respectively. The mean duration of these trains of contractions is 10 minutes, and they recur every 30 minutes. These migratory contractions move caudally over half the length of the colon. The migratory trains of contractions are separated by a period of quiescence, which may be interrupted by nonmigratory trains of short- or long-duration contractions. Rapid shifts of large volumes of colonic contents from the proximal colon to the middle or distal colon occur secondary to motor activity called *mass movement* or *giant peristaltic contractions* of the colon. Mass movements can occur without defecation or during defecation depending on their propagation through either a part or the entire length of the colon. The giant migrating contraction is two to

three times larger in amplitude than are other colonic contractions, and its duration is around 1 minute. It propagates at a fast velocity of 0.2 to 3 cm per second. These contractions can occur singly or in trains of two or more contractions.

Mass movements are induced in the left colon as a reflex response to certain stimuli, such as eating (gastrocolic reflex) or rising in the morning (orthocolic reflex). During these movements, distal segments of the colon are relaxed to accommodate food residues that are pushed forward by the contractions. These reflexes are mediated by neurohumoral mechanisms and are affected by conditioning, but the precise role of neurohumoral control factors in the production of colonic motor activity is not fully understood. The gastrocolic reflex is heightened in some patients with the irritable bowel syndrome. Weak colonic contractions lead to colonic stasis, megacolon, and constipation. Diminished mass movements also lead to constipation, whereas frequent mass movements may lead to frequent defecation. Increased segmental contractions may lead to abdominal pain and constipation. Prolonged haustral contractions may mold feces into fecal pellets like rabbit stools, which sometimes occur in patients with the irritable bowel syndrome. Defective relaxation of distal colonic segments also leads to functional obstruction of the passage of fecal contents and megacolon.

### **Defecation**

The rectum is normally empty. Mass movement of the left side of the colon displaces feces into the rectum. When the rectum is distended with fecal matter, the defecation urge is experienced. It is associated with reflex relaxation of the internal anal sphincter and reflex contraction of the external anal sphincter. This urge may be suppressed, in which case both of the anal sphincters become contracted. Contraction of the rectum then propels the feces back into the colon, or the rectum simply accommodates the feces. However, if the subject decides to answer the call, the defecation reflex is activated. Intra-abdominal pressure is increased by contractions of the abdominal muscle and diaphragm. The external and internal anal sphincters remain relaxed, and feces are expelled.

In Hirschsprung's disease the internal anal sphincter and the aganglionic segment of the colon fail to relax, causing constipation and megacolon. Fecal incontinence occurs when liquid feces appear in the rectum, and the anal sphincters, particularly the external anal sphincter, are paralyzed. This may also occur when the threshold of rectal sensations becomes greater than the threshold of rectosphincteric inhibitory reflex, as may happen in patients with diabetic neuropathy.

## **CONTROL SYSTEMS OF MOTOR ACTIVITY**

### **Myogenic Factors**

Muscles are the ultimate mediators of motor function. Whereas striated muscles have no myogenic tone, the smooth muscle of the gut possesses an intrinsic ability to generate tone or cause phasic contractions. Smooth muscle cells are normally in an electrically polarized state (i.e., the inside of the cell is negative in relation to the outside). The potential difference across the smooth muscle plasma membrane is called the *resting membrane potential* and is due to asymmetric distribution of charged cations and anions across the cell membrane. Muscle contraction is usually associated with

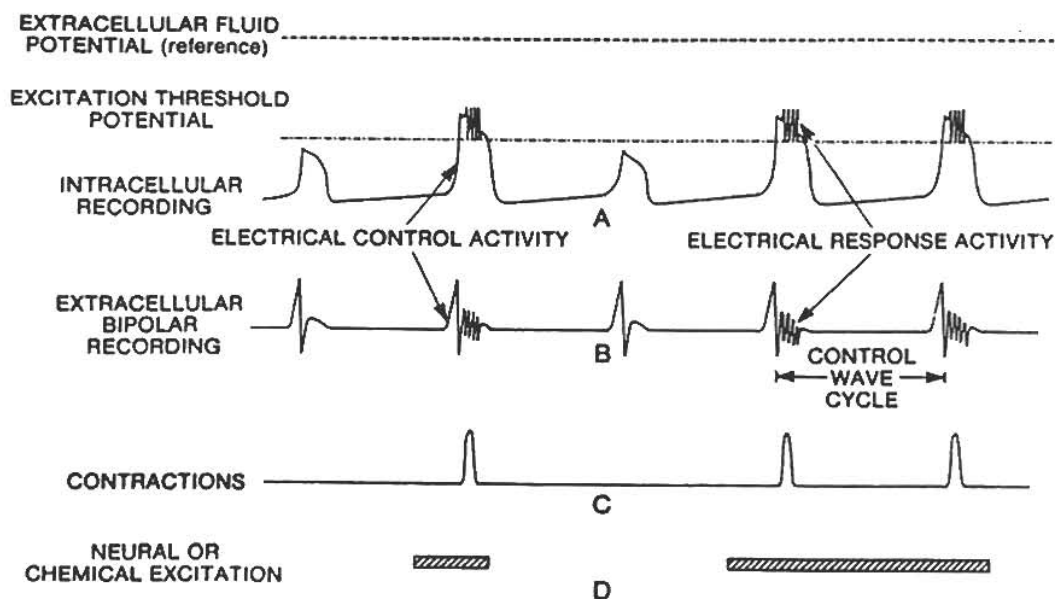


depolarization, and inhibition of contraction is associated with hyperpolarization of the smooth muscle membrane. There is, however, marked heterogeneity in the specific electrical and mechanical behavior of smooth muscle in different regions of the gut.

The excitability of smooth muscle is determined by the resting membrane potential. Smooth muscles that have a less negative membrane potential (*depolarized*) are more excitable than those with a more negative membrane potential (*hyperpolarized*). Smooth muscles in several regions of the gut exhibit oscillatory changes in the membrane potential. These oscillatory changes are called *slow waves*. Slow waves are not found in the esophagus but occur with remarkable consistency and regularity in the stomach and the small bowel. Slow waves occur irregularly and inconsistently in the colon.

The electrical activity associated with a contraction is called an *action potential*. The most obvious electrical activities associated with muscle contraction are rapid transient depolarizations called *spike potential*. The most obvious electrical activities associated with muscle contraction are rapid transient depolarizations called *spike potentials*. The spike potentials occur in bursts to cause phasic contractions, and they may occur continuously to cause sustained tonic contractions. Spike potentials are initiated when the cell membrane depolarizes to a value that is above the threshold for spike generation. Depolarization with superimposed spike potentials in many gastrointestinal smooth muscles occurs as a myogenic rebound following the hyperpolarizing action of inhibitory neurotransmitter substances released from the nerves. In smooth muscle cells that exhibit slow waves, spike bursts are more likely to occur during the depolarization phases of the slow wave. Because each smooth muscle segment has its own characteristic slow wave frequency, the maximal rate of spike bursts is distinctive for each part of the gut. The slow waves are also called *pacesetter potentials* because they set the pace at which spike bursts will occur. They are also called *electrical control activities*, because they determine the occurrence of a spike burst. The pacemaker activity is provided by specialized cells called the *interstitial cells of Cajal*. Development of these cells depend upon a tyrosine kinase, cKit. Mutations in the cKIT gene are associated with intestinal motility disorders. The spike potentials in turn are called *electrical response activity*. An intense excitatory stimulus is associated with a large depolarization that may overwhelm the effect of a slow wave. With such stimuli, spike burst activity can occur regardless of the phase of the slow wave and can be prolonged to cover several slow wave cycles. The frequency and amplitude of the spikes and the duration of spike bursts determine the amplitude and duration of contractions. A weak spike burst may not be associated with contraction.

Smooth muscle contraction can also occur in association with electrical activities other than spikes. Slow waves themselves may cause a small degree of contraction during their depolarization phases. In the stomach, excitatory agents may cause an increase in the amplitude of slow wave depolarizations, which in turn are associated with contractions. These depolarizations in the stomach are therefore also called *action potentials*. In the esophagus, spike bursts occur without an underlying slow wave. In colonic smooth muscle a prolonged spike burst covering several slow waves induces long-duration contractions.



**Figure 2.** Slow waves, spikes and contractions.

Depolarization of gastrointestinal smooth muscle membrane results from influx of positively charged ( $\text{Na}^+$  and  $\text{Ca}^{2+}$ ) ions or efflux of negatively charged ( $\text{Cl}^-$ ) ions. Depolarization also results from the inhibition of  $\text{K}^+$  efflux. On the other hand, hyperpolarization results from either an increase in  $\text{K}^+$  or a decrease in  $\text{Cl}^-$  efflux. Depolarization in the membrane leads to opening of the voltage sensitive  $\text{Ca}^{2+}$  channels and  $\text{Ca}^{2+}$  influx. Hyperpolarization serves to inhibit the voltage-dependent  $\text{Ca}^{2+}$  channels and, thus, inhibit  $\text{Ca}^{2+}$  entry into the cells. The coupling between electrical depolarization and muscle contraction is called *electromechanical coupling* and is caused by depolarization-induced increase in intracellular  $\text{Ca}^{2+}$ .

Sometimes, smooth muscle contraction or relaxation can occur without any associated electrical events. Such mechanical phenomena are due to the direct action of endogenous neurotransmitters and hormones or exogenous pharmacologic agents on intracellular  $\text{Ca}^{2+}$  or other mediators of contraction. This phenomenon is called *pharmacomechanical coupling*. Because  $\text{Ca}^{2+}$  plays a critical role in the contraction of smooth muscles, calcium channel blockers serve as effective agents inhibiting contractions of gastrointestinal smooth muscle. Intracellular messengers such as cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and phosphoinositols are involved in the actions of hormones and neurotransmitters in the smooth muscle. These messengers act by modulating various ion channels and intracellular  $\text{Ca}^{2+}$  concentrations in the smooth muscles. In general, intracellular increases in both cAMP and cGMP lend to relaxation, and activation of the PI pathway leads to contraction of muscles. However, there is marked heterogeneity in the cellular mechanisms of contraction in the different gastrointestinal smooth muscle.

Of the several muscle layers in the alimentary canal, contraction of the circular muscle is largely responsible for luminal occlusion and movement of food through the gut. These contractions occur either as a single monophasic contraction or as a train of contractions and may be either propagated or nonpropagated. The propagated waves

may move forward (that is, aborally [*peristaltic contractions*]) or backward (that is, orally [*antiperistaltic contractions*]). The nonpropagated waves may occur as simultaneous contractions along a portion of the alimentary canal (*spastic contractions*) or as isolated contractions that occur randomly in time and space (*segmental contractions*).

Nonpropagated contractions help in digestion by facilitating mixing and absorption. Measurements that merely document the presence of intestinal contractions without indicating their propagational properties give no information about the movements of the intestinal contents. When contractions are spastic or segmental or when there are no contractions, there is little movement of intestinal contents. Only peristaltic contractions are associated with significant caudal movement of intestinal contents. In turn, antiperistaltic contractions cause retrograde movement.

The longitudinal muscle contractions also play an important role in the movement of luminal contents by sliding the intestine over the food in the lumen, just as one slides a pillowcase over a pillow. Contractions of the muscularis mucosa may be important both in the mixing of food and enzymes and in the expulsion of glandular secretions into the bowel lumen.

### Hormonal Control

Almost two dozen circulating hormones have been shown to modify gastrointestinal motility, although their physiologic importance is not fully known. For example, gastrin increases lower esophageal sphincter pressure and delays gastric emptying. Secretin, VIP, somatostatin, and opioids delay gastric emptying and may decrease small bowel transit time. Calcitonin gene-related peptide may be involved in both the sensory and motor neural pathways. Although opioids cause constipation, motilin increases gastric emptying and enhances transit through the small intestine. Motilin induces and coordinates interdigestive migrating motor complex (MMC) activity in the stomach and small bowel.

### Neural Control

The skeletal muscles at either end of the gastrointestinal tract connect directly with the central nervous system (CNS) through the lower motor neurons. The nervous system exerts total mastery over these muscles. When the nerves are destroyed, these muscles become paralyzed. The lower motor neurons cause muscle contractions by releasing acetylcholine at the motor end plate. Acetylcholine acts on the striated muscles via nicotinic acetylcholine receptors.

The neural control system for smooth muscle consists of extrinsic nerves composed of motor sympathetic and parasympathetic nerves, and intrinsic or "intramural" enteric nerves, which include the myenteric and submucous plexuses. The intrinsic nerves of the gut constitute the *enteric nervous system*, which can integrate and execute gastrointestinal function independent of the central nervous system. The neurons in the enteric nervous system exhibit morphologic, chemical, and functional characteristics that are similar to those of the central nervous system. The enteric nervous system represents the "local brain" of the gut, whereas the sympathetic and parasympathetic pathways provide connections between the central and enteric nervous systems. There are major differences in the anatomic details, chemical nature of transmitters, and organization of neural functions in the different regions of the gut.

Sympathetic nerves exert their effect by releasing norepinephrine and other catecholamines. The sympathetic nerves in general exert an inhibitory effect on the

motor activity of the gut except in sphincters, which contract in response to sympathetic stimulation. Sympathetic overactivity may produce *adynamic ileus*, which is sometimes erroneously called *paralytic ileus*, a misnomer because there is no true muscular paralysis involved. On the other end of the spectrum, pharmacologic or surgical sympathectomy may cause diarrhea resulting from the increased propulsive activity in the gut.

Parasympathetic nerves exert a more discrete effect on the motor activity of the gut than do sympathetic nerves. Parasympathetic nerves have both excitatory and inhibitory effects on gastrointestinal smooth muscle. The vagus nerves mediate esophageal peristalsis and control gastric emptying. Vagal denervation impairs esophageal peristalsis and delays gastric emptying. Because the influence of parasympathetic nerves on the small bowel and colon is relatively small, nearly normal function continues in their absence. Sacral parasympathetic nerves exert an important influence on anorectal activity, and their lesions cause disorders of defecation. Neuronal pattern generators in central nervous system provide programmed patterned activation of vagus splanchnic nerves to produce complex motor activities such as swallowing and defecation and other reflexes that express the motility changes in stress behavioral alterations.

There are separate sets of excitatory and inhibitory enteric motor nerves. The muscle inhibition and excitation work in concert to produce a wide spectrum of motor activity that is seen in different parts of the gut, including the peristaltic reflex. The intramural neurons coordinate and organize activities such as peristalsis, sphincter relaxation, and more complex motor activities. Contractions can occur in smooth muscles in the absence of neural control; however, they are purposeless. Because extrinsic nerves exert their effects via the enteric neurons, lesions of enteric neurons may mimic some of the effects of extrinsic denervation in addition to- producing some effects that are characteristic of lesions of the enteric nerves alone. Chagas' disease, which is due to the involvement of myenteric neurons by *Trypanosoma cruzi*, causes widespread derangement in gastrointestinal motility. This disease results in the loss of peristalsis in the esophagus as well as impaired relaxation of the lower esophageal sphincter, together producing the clinical picture of achalasia gastric stasis, small intestinal pseudo-obstruction syndrome, and megacolon resembling that of Hirschsprung's disease. Many nerve growth factors and receptors with tyrosine kinase activity participate in development and caudal migration of the enteric nerves in the gut. Mutations in the genes for endothelin-3 or its receptor or RET protooncogene are associated with Hirschsprung's disease.

### **Role of The Enteric Nervous System**

The enteric nervous system (ENS) is a name given to a collection of neurons within the gastrointestinal tract. The ENS constitutes the "brain of the gut" which functions in parallel with the central nervous system (CNS). The enteric nervous system controls gastrointestinal motility, exocrine and endocrine secretions, and microcirculation; it is also involved in the regulation of immune and inflammatory processes in the gut.

Examination of the functional and chemical diversity of enteric neurons have revealed that the ENS closely resembles the CNS. It contains on the order of 100 million neurons, approximating the number found in the spinal cord. The ENS functions at a level similar to the spinal cord and perhaps can best be regarded as a displaced



part of the CNS that retains communication with the CNS via sympathetic and parasympathetic afferents and efferents (Figure). The part of the CNS which is connected with these afferents and efferents is now known as the central autonomic neural network (CANN). Together with these connections, the ENS provides neural control of all functions of the gastrointestinal tract.

### **General Organization**

In the normal ENS, the nerve cell bodies are grouped in small ganglia, which are connected by bundles of nerve processes, forming two major plexuses called the myenteric or Auerbach's plexus and the submucosal or Meissner's plexus. The myenteric plexus lies between the longitudinal and circular muscle layers and extends throughout the length of the gut. This plexus provides motor innervation to the two muscle layers and secretomotor innervation to the mucosa. Recent studies have demonstrated numerous projections from the myenteric plexus to the submucosal ganglia and to enteric ganglia of the gallbladder and the pancreas. There are also a substantial number of projections from the myenteric neurons to the sympathetic ganglia. The myenteric plexus is also present in the striated muscle portion of the esophagus, where it has recently been shown to innervate motor end plates using the inhibitory neurotransmitter, nitric oxide. Such innervation to the motor end plates is unique to the esophagus and is not seen in motor end plates of other striated muscles. The submucosal plexus, located in the submucosa between the circular muscle layer and the muscularis mucosa, is most well developed in the small intestine. Neurons in the submucosal plexus innervate glandular epithelium, endocrine cells and submucosal blood vessels. A ganglionated plexus, similar to the submucosal plexus, is found in the gallbladder, cystic duct and common bile duct as well as in the pancreas.

### **Neuronal Diversity**

Although up to eight different morphological forms of neurons have been identified in the ENS, a structure-function relationship is best delineated in the two main types originally described by Dogiel (Dogiel, 1899), as Type I and Type II neurons. Type I cells have many short, club-shaped processes and a single long, slender process. Type II neurons are multipolar and have many long, smooth processes.

The chemical mediators of the ENS were initially thought to be limited to amines such as acetylcholine and serotonin. Subsequent research added purines such as ATP, amino acids such as gamma amino butyric acid (GABA), and a wide-variety of peptides such as vasoactive intestinal peptide (VIP), to the list of enteric neurotransmitters. More recently, gases such as nitric oxide have also emerged as neurotransmitters in the ENS as they have in the CNS. Overall, over 20 neurotransmitter candidates have now been localized in enteric neurons (Table 1).

**TABLE 1: Putative Neurotransmitters of the Enteric Nervous System**

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**Amines**

Acetylcholine (Ach)\*  
Norepinephrine (NE)\*  
5-Hydroxytryptamine (5-HT)\*

**Amino Acids**

Gamma-amino-butyric acid (GABA)

**Purines**

Adenosine triphosphate (ATP)

**Gases**

Nitric oxide (NO)\*  
Carbon monoxide (CO)

**Peptides**

Calcitonin gene related peptide (cGRP)  
Cholecystokinin (CCK)  
Galanin (GAL)  
Gastrin-releasing peptide (GRP)\*  
Neuromedin U  
Neuropeptide Y (NPY)  
Neurotensin (NT)  
Opioids  
    Dynorphin (DYN)  
    Enkephalins (ENK)  
    Endorphins (END)  
Peptide YY (PYY)  
Pituitary adenylyl cyclase activating peptide (PACAP)  
Somatostatin (SOM)  
Substance P (SP)\*  
Thyrotropin releasing hormone (TRH)  
Vasoactive intestinal contractor (VIC, an endothelin)  
Vasoactive intestinal polypeptide (VIP)

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\* Denotes established neurotransmitter

## Targets of Enteric Nerves

The five primary targets of the enteric nerves of the gut are: smooth muscle cells that are responsible for gastrointestinal motility; mucosal secretory cells; gastrointestinal endocrine cells that in turn influence motility and secretion by releasing a variety of gastrointestinal hormones; gastrointestinal microvasculature that maintains mucosal blood flow during intestinal secretion; and the immunomodulatory and inflammatory cells of the gut that are involved in mucosal immunologic, allergic, and inflammatory responses. Table 2 summarizes the role of enteric neurons in some of these activities.

**TABLE 2:** The role of the enteric nervous system in selected physiological activities of the gastrointestinal tract

| Activity  | Role of ENS  |
|---|--|
| <b>MOTILITY</b>   |  |
| Tonic Inhibition  | Suppression of spontaneous myogenic contractions by NO/VIP neurons.  |
| Segmental Contractions                                      | Mixing of luminal contents of small intestine. Involves transient suppression of inhibitory neurons in a localized area of the gut.  |
| Forward Propagating Contractions<br>Migrating motor complex | Cyclical (every 1-2 hrs) train of contractions with frequency set by electrical slow waves generated by interstitial cells. Serves as intestinal "housekeeper" between meals. Initiated by motilin, somatostatin, prokinetic agents, opioids and enteric pattern generators. |
| Primary esophageal peristalsis                              | Centrally-mediated contraction sequence of the esophagus coordinated by inhibitory (NO) and excitatory (Ach) nerves of myenteric plexus which is activated by swallowing.  |
| Local reflex peristalsis                                    | Motor sequence consisting of contraction above and relaxation below a distending luminal stimulus. Peristalsis is achieved through continued aboral movement of the distending stimulus. Activated by 5-HT containing intrinsic primary afferent neurons.                    |
| Giant peristaltic contraction                               | High amplitude and long duration contractions representing heightened peristaltic reflex. Electrical correlate is the migrating action potential complex (MAPC). Sequence is induced by cholera toxin and is seen in patients with irritable bowel syndrome.                 |
| Backwards Propagating Contraction                           | Involved in retrograde propulsion as occurs with vomiting. Neural circuitry is not understood.   |
| Sphincteric Function  | Sphincters possess intrinsic tone which is myogenic in origin. Relaxation occurs via NO and VIP neurons; contraction via cholinergic neurons.  |

**SECRETION**

|                        |  |
|------------------------|--|
| Gastric Acid Secretion | Stimulation of acid secretion via vagal activation of parietal, histamine and gastrin cells. Inhibition of acid by vagal activation of somatostatin cells. |
| Pancreatic Secretion   | Pancreatic enzyme secretion induced by CCK activation of primary vagal afferents and vago-vagal reflex.  |
| Intestinal Secretion   | Secretory reflexes activated by peristalsis, MMC and giant peristaltic contractions.   |

**MICROCIRCULATION**

Sympathetic efferents produce vasoconstriction (ATP mediated); intrinsic submucosal secretomotor neurons (VIP/Ach) and the axon reflex (cGRP/SP) produce vasodilation.

**IMMUNOLOGIC AND INFLAMMATORY RESPONSES**

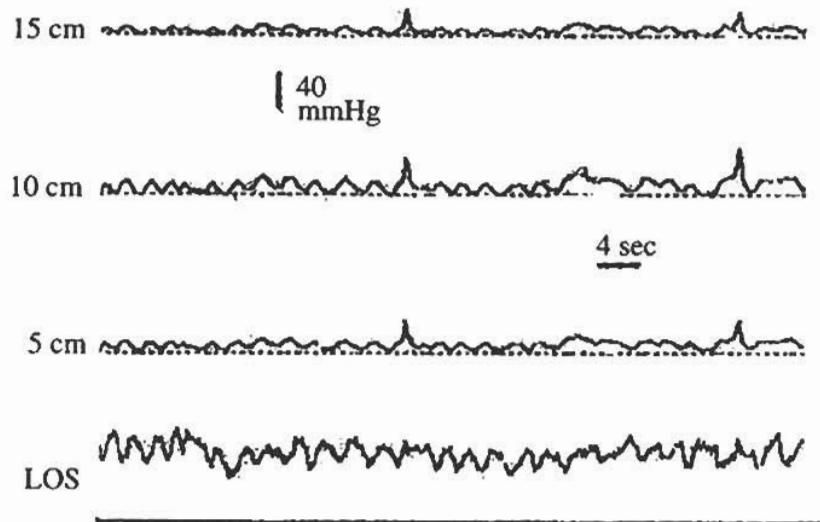
CGRP and SP containing primary splanchnic afferents innervate mucosal mast cells which degranulate, releasing inflammatory mediators

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**Motility Disorders of the ENS***Achalasia*

Achalasia is characterized by a tonically contracted lower esophageal sphincter that fails to relax, resulting in functional esophageal obstruction. The body of the esophagus is also involved and lacks peristaltic contractions. Achalasia is due to either non-selective loss of all myenteric neurons or a selective loss or dysfunction of VIP/NO-containing neurons in the myenteric plexus of the esophagus. In some patients with achalasia, selective loss of the inhibitory neurons and relative preservation of cholinergic innervation to the lower esophageal sphincter is responsible for the high sphincter pressures characteristic of the disorder. Local injection of botulinum toxin blocks this unopposed cholinergic activity and may be useful in the treatment of select patients with achalasia. The etiology of primary achalasia in most patients in the United States is not known. Several diseases that produce enteric neural dysfunction may cause secondary forms of achalasia, including paraneoplastic syndromes, Chagas disease, and Parkinson's disease. Recently, herpes virus, a neurotropic virus with predilection to infect squamous epithelium such as that lining the esophagus, has been reported with increased frequency in patients with achalasia.





**Figure 3.** Esophageal motility in achalasia.

#### *Functional Gastric Outlet Obstruction*

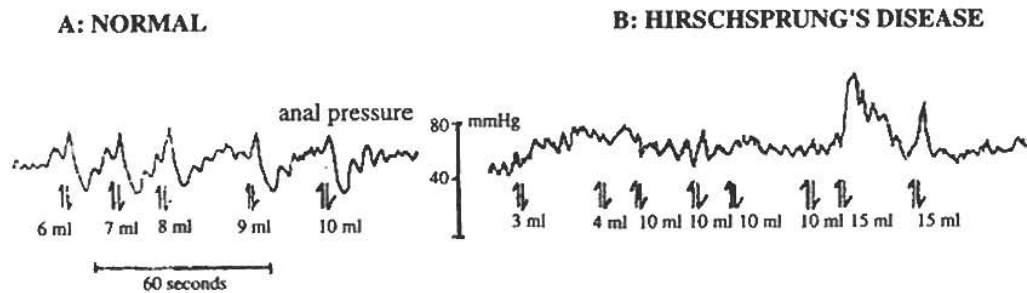
Infantile hypertrophic pyloric stenosis is a congenital disorder characterized by functional gastric outlet obstruction. Although the myenteric neurons appear normal on routine morphologic studies, histochemical and immunochemical studies show lack of nitric oxide synthase in the neurons innervating the circular muscle layer of the pyloric sphincter. Experimental disruption of the gene encoding the neuronal form of nitric oxide synthase results in animals lacking this enzyme in their enteric neurons. These mutant mice have functional gastric outlet obstruction and gastric dilatation. Gastric stasis and dilatation can also occur after surgical vagotomy, neuropathy associated with diabetes mellitus, with the use of anticholinergic agents and opiates, and with sympathetic nerve over activity.

#### *Acute Intestinal Ileus and Chronic Intestinal Pseudo-obstruction*

Acute intestinal ileus is characterized by absent motor activity in the intestine. Intestinal activity can be inhibited by the selective suppression of excitatory motor reflexes via sympathetic nerves and by sustained intrinsic inhibitory neural over activity. Increased production of nitric oxide due to activation of the non-neuronal inducible nitric oxide synthase may also result in acute intestinal ileus. It is noteworthy that intestinal ileus cannot be produced by suppressing neural activity in the gut. The puffer fish toxin tetrodotoxin blocks all neural function and causes increased contractile activity in the gut rather than ileus. This is due to the release of tonic neurogenic inhibition with unmasking of myogenic contractions. The increased contractile activity is uncoordinated and therefore non-propulsive, leading to functional bowel obstruction. Degeneration and chronic dysfunction of enteric neurons can lead to chronic intestinal pseudo-obstruction. Acute ileus or chronic intestinal pseudo-obstruction is usually part of generalized involvement of the gut.

### Megacolon

Hirschsprung's disease is a congenital disorder characterized by the absence of enteric neurons from the distal colon. The aganglionic gut loses its tonic neural inhibition and thus remains contracted, obstructing the passage of food residue. The absence of NO and VIP-containing inhibitory neurons is thought to be responsible for the non-relaxing diseased segment. Hirschsprung's disease is a heterogeneous genetic disorder that leads to problems with neural crest migration and development into the enteric nervous system of the distal gut. Frame shift and missense mutations in the RET gene are seen in some patients with an autosomal dominant form of Hirschsprung's disease. Furthermore, many patients with an autosomal recessive form of the disease have a missense mutation of the endothelin B receptor gene. Patients afflicted with the Waardenber-Shah syndrome and Santos' syndrome also present with Hirschsprung's disease accompanied by extra intestinal manifestations including pigmentary disorders and renal agenesis. These extra intestinal features could be due to the involved tissues originating from common neural crest of RET expressing cells.



**Figure 4.** Anal rectal motility.

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