8.3 Intestinal and Colonic Chemoreception and Motility

Learning Objectives

- List the three sections of the small intestine and six anatomic parts of the large intestine
- List those variables that comprise the enterogastric inhibitory reflex
- List three components of the intrinsic innervation of the intestine
- Describe the anatomic location of the myenteric plexus
- Describe the anatomic location of the submucosal plexus
- Define enteroendocrine cell
- Describe two pathways for the secretion of GLP-1 as an example of an EEC
- List four secretions of EECs and what stimulates their secretion, and the effect of those secretions
- Describe the origin of sympathetic and parasympathetic innervations of the intestine
- Distinguish between the motility patterns of segmentation, peristalsis, and migrating motor complex
- Describe what is meant by ascending contraction and descending relaxation during peristalsis
- Describe each of the following gut reflexes: receptive relaxation, enterogastric inhibitory reflex, gastrocolic reflex, gastroileal reflex, ileal brake, and rectoanal inhibitory reflex
- Describe the events that occur during defecation
- List the various causes of vomiting
- Describe what is meant by "chemical trigger zone"

THE SMALL INTESTINE CONSISTS OF *DUODENUM*, *JEJUNUM*, AND *ILEUM*

The small intestine extends from the pylorus at the end of the stomach to the beginning of the colon. It is about 6 m long, but its length varies with the degree of longitudinal smooth muscle contraction. The first segment of the small intestine, the **duodenum**, derives its name from anatomists who defined its length as being "12 finger breadths," about 25 cm. This shortest and widest part of the small intestine extends from the stomach to the **ligament of Treitz**. The ligament of Treitz is not really a ligament, but it is a suspensory muscle that attaches the duodenum to the posterior abdominal wall and causes the acute angle the small intestine makes at the end of the duodenum. Pancreatic and biliary secretions enter the intestine in the duodenum.

By definition, the **jejunum** consists of the upper two-fifths (40%) of the small intestine from the ligament of Treitz to the first part of the colon, the **cecum**. The distal three-fifths (60%) comprises the **ileum**. Although there are distinct histological differences between the upper jejunum and lower ileum, the tissues gradually make the transition so there is no clear demarcation between the two.

INTRINSIC NERVES, EXTRINSIC NERVES, PARACRINE AND ENDOCRINE HORMONES REGULATE INTESTINAL AND COLONIC MOTILITY

If your intestinal motility stops, you die. This function is so important that there are multiple levels of control. In Chapter 8.1, we described that a swallowing center in the medulla directs peristalsis in the esophagus as part of the swallowing program, mediated by the vagus nerve. If that nerve is cut, intrinsic nerves take over to produce propulsive action. If these are blocked, the smooth muscles of the esophagus can direct similar motor patterns. This redundancy of levels of control produces a robust system, one that is resistant to failure, because failure carries a high price. Smooth muscle contraction constitutes the final step in intestinal motility. These smooth muscle cells are regulated by specialized cells, called **interstitial cells of Cajal** (**ICC**), and also by intrinsic nerves within the intestinal wall. These are all modulated by extrinsic efferent nerves originating in the central nervous system, and both paracrine and endocrine secretions. The extrinsic nerves respond to sensory information that derives from afferent sensors in the intestine. Thus extrinsic nerves carry both sensory and motor information, with sensory afferents far outnumbering the motor efferents.

INTRINSIC INNERVATION OF THE INTESTINE CONSISTS OF THE *MYENTERIC PLEXUS*, *SUBMUCOSAL PLEXUS*, AND THE *INTERSTITIAL CELLS OF CAJAL*

THE INTERSTITIAL CELLS OF CAJAL GENERATE INTRINSIC INTESTINAL RHYTHM

The interstitial cells of Cajal (ICCs) were first described histologically by Ramon y Cajal nearly a century ago, but their function has only recently become

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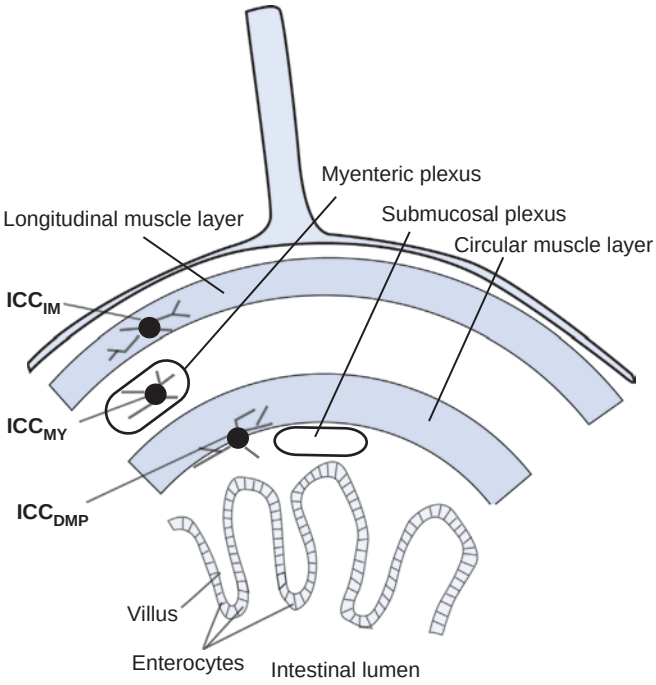

FIGURE 8.3.1 Schematic diagram of the location of interstitial cells of Cajal (ICCs) in a cross-section of small intestine. ICCs are stellate cells that may be found in the myenteric plexus (ICC$_{MY}$), in the muscle layers (ICC$_{IM}$), or in the inner surface of the circular muscle (ICC$_{DMP}$). These cells make connections to muscle cells and interneurons in the plexuses. The ICCs are shown in black.

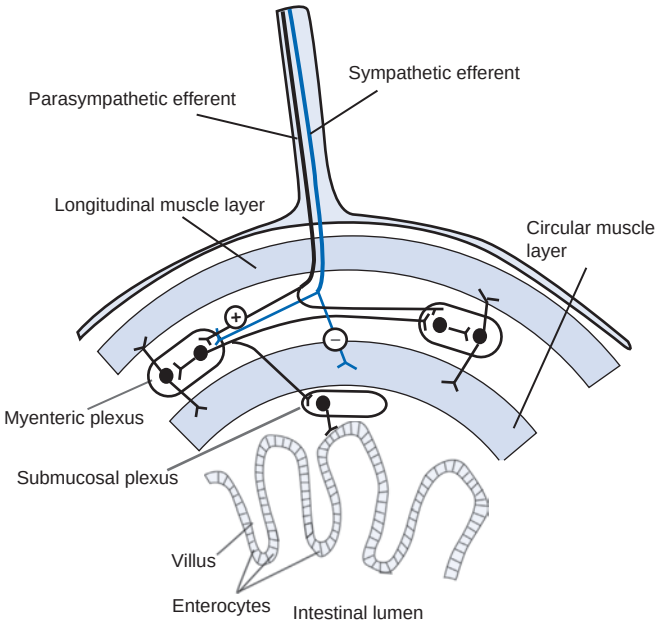

FIGURE 8.3.2 Schematic diagram of the myenteric plexus and submucosal plexus. These plexuses are collections of neurons and interstitial cells of Cajal located between the longitudinal and circular layers (myenteric plexus) or inside the circular layer (submucosal plexus). They receive innervation from the sympathetic and parasympathetic systems and project to muscle and secretory cells. They send connections up and down the intestine to connect with other ganglia.

known. These stellate cells are specialized smooth muscle cells that receive inputs from nerve cells within the myenteric and submucosal plexuses and also communicate electrically with smooth muscle cells in the longitudinal and circular muscle layers. There are several separate functional classes of ICC. A network of ICC$_{MY}$ cells lies within the myenteric plexus between the longitudinal and circular muscle layers. These cells set the rhythm and trigger slow waves. **The smooth muscle cells themselves do not originate slow waves**. A second network of ICCs, called intramuscular ICC or ICC$_{IM}$, is dispersed among the smooth muscle cells. In the small intestine, the ICCs are concentrated at the inner surface of the circular muscle layer to form ICC$_{DMP}$, denoting deep muscle plexus. Figure 8.3.1 highlights the ICCs.

THE MYENTERIC PLEXUS AND SUBMUCOSAL PLEXUS MAKE UP THE ENTERIC NERVOUS SYSTEM

As in most of the gastrointestinal tract, the small intestine contains an inner circular muscle layer that determines the caliber of the lumen and an outer longitudinal smooth muscle layer that sets the length. The myenteric plexus is a network of ganglia, connected by fiber tracts, that is sandwiched between these two layers. It receives sensory information from stretch receptors in the outer muscle layers and free sensory endings in the mucosa that respond to mechanical and chemical stimuli. The submucosal plexus is located between the circular smooth muscle and the muscularis mucosae. The function of the muscularis mucosa is poorly understood; it may help fold the epithelium into finger-like projections or villi (the singular form is villus). The enteric plexuses are highlighted in Figure 8.3.2.

INTRINSIC PRIMARY AFFERENT NEURONS REGULATE LOCAL RESPONSES

In response to local signals, enterochromaffin cells (EC cells) release 5-hydroxytryptamine (5-HT) and ATP to stimulate intrinsic primary afferent neurons (IPANs) in the submucosal plexus and myenteric plexus. These connect to interneurons that control secretion and motor activity of the mucosa and to interneurons within the myenteric plexus to control local contractile reflexes. The second component carries mechanosensory stimuli. Physiological information passes over the vagus nerve. Spinal afferents carry nociceptive (pain) information over the splanchnic nerves. The IPANs and sensory afferents are shown in Figure 8.3.3.

SOME ENTEROENDOCRINE CELLS ARE CHEMORECEPTORS THAT RESPOND TO A VARIETY OF STIMULI

Fifteen distinct types of enteroendocrine cells (EECs) lie amid the absorptive cells of the intestinal epithelium. These are either "open," meaning that they have

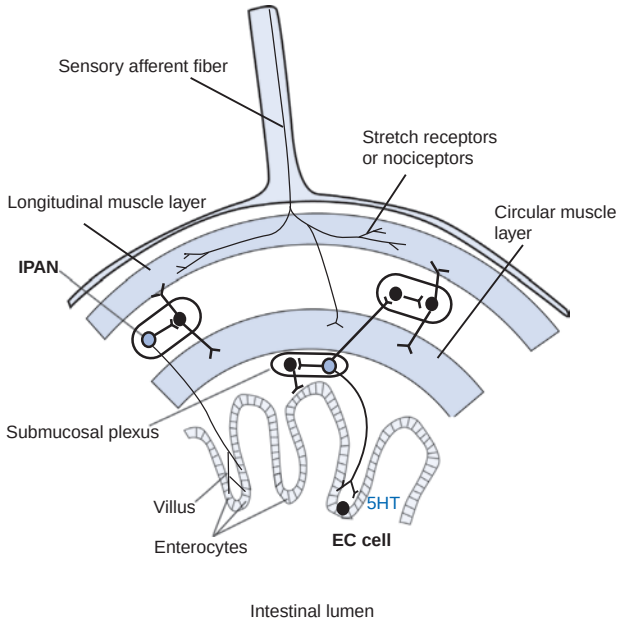

FIGURE 8.3.3 Intrinsic primary afferent neurons and sensory afferents. Enterochromaffin cells in the villus lining release 5-hydroxytryptamine or ATP onto terminals of intrinsic primary afferent neurons (light blue color) whose cell bodies lie in the submucosal and myenteric plexes. These control local contractile or secretory responses. Other sensory components sense either stretch or pain and are carried to the CNS over splanchnic nerves.

microvilli that extend into the lumen or "closed" because they do not have direct contact with luminal contents (see Figure 8.3.4). The EECs collectively sense a wide variety of materials in the intestinal lumen by various mechanisms including G-protein-coupled receptors (GPCR family) on the surface membrane of the EEC or through solute carriers (SLC family). The mechanisms for several luminal materials are identical to those found in the taste receptors of the tongue. Although these receptors do not contribute to the subjective perception of taste, in some sense the intestine "tastes" these chemicals to determine the nature of the materials being absorbed into the blood so as to regulate the gastrointestinal tract and adjust metabolism. The EEC and enterochromaffin cells release materials that act on afferent nerves or circulate in the blood to produce either local (paracrine) or systemic (endocrine) effects.

L-type enteroendocrine cells are heterogeneous. The mechanism of signal transduction for an L-type cell in the jejunum and ileum is shown in Figure 8.3.5. These cells release glucagon-like polypeptide-1 (GLP-1) in response to glucose in the lumen. There are two separate pathways by which these cells sense glucose as described in the figure legend. A summary of the enteroendocrine cells is given in Table 8.3.1.

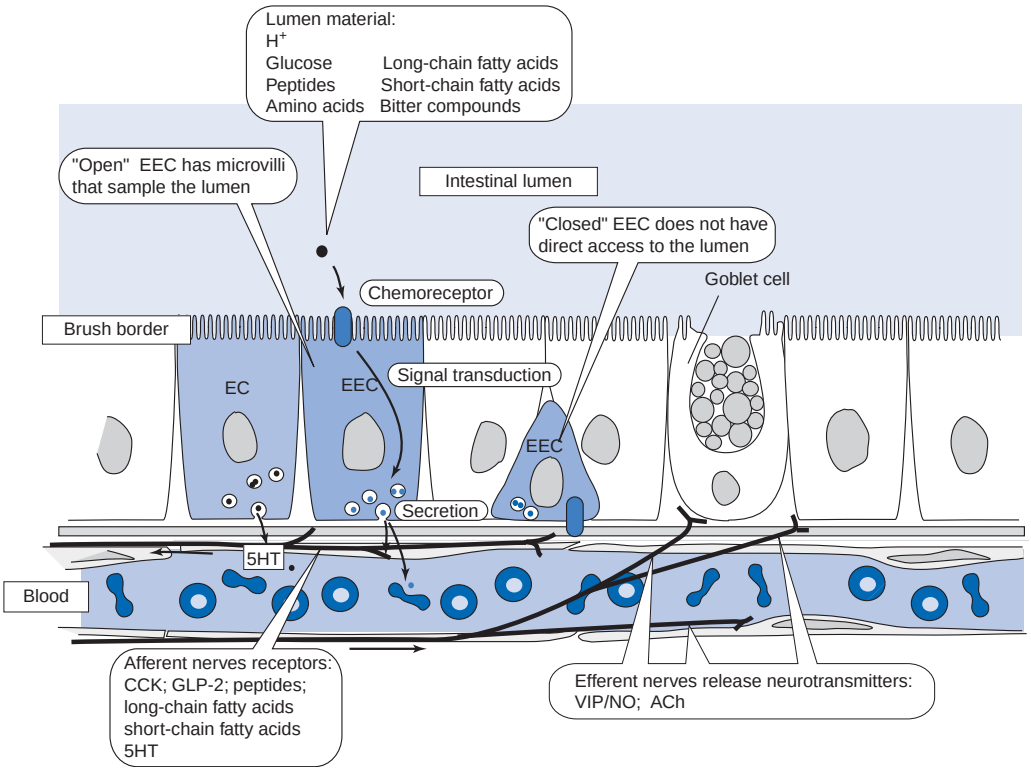

FIGURE 8.3.4 Chemoreception by enteroendocrine cells (EEC). EEC may be "open" if they have direct access to intestinal lumen contents, or "closed" if they do not. EEC cells come in many varieties. They sense materials in the lumen or blood and generally release polypeptide hormones in response to these materials. The materials that are actively sensed include H^+ (indirectly), glucose, peptides, amino acids, long-chain fatty acids, short-chain fatty acids, and bitter compounds. The chemoreceptors are coupled to signaling pathways that link chemoreception to secretion of polypeptide hormones. The released hormones include secretin, CCK, GLP-1 and GLP-2, PYY, SST. EECs are also in the stomach and release gastrin, SST, and ghrelin. These released polypeptides excite afferent nerves or travel in the circulation as hormones to have autocrine, paracrine, or endocrine effects. Efferent nerves can regulate secretion or blood flow. Enterochromaffin cells (EC) release 5-hydroxytryptamine (5-HT) that acts on nerves and circulates in the blood.

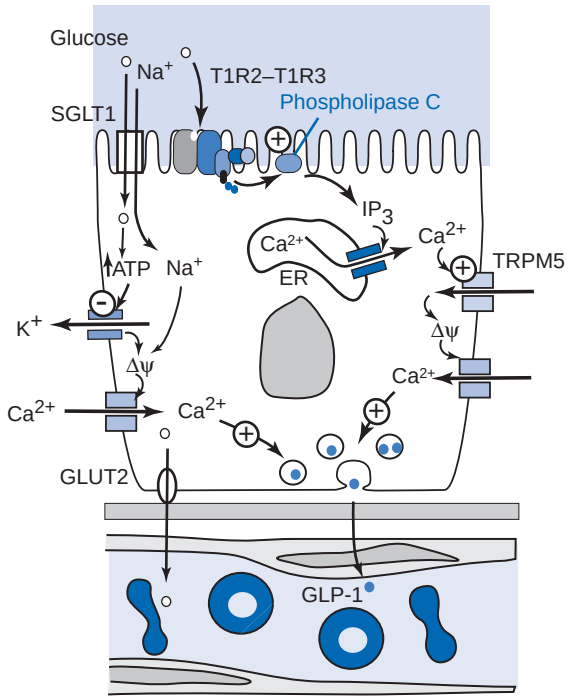

FIGURE 8.3.5 Mechanism of glucose sensing in enteroendocrine L cells to release GLP-1. There are two basic pathways proposed to explain glucose sensing, developed from localization of transport elements to these cells through knock-out models, immunological localization of proteins, and pharmacological effects on GLP-1 secretion. One pathway is identical to the taste receptors on the tongue, using T1R2–T1R3 that is coupled to the G protein, α gustducin, a G_q mechanism, to increase cytosolic [Ca^{2+}] to increase secretion of GLP-1. The second uses glucose entry into the cell coupled to Na^+ entry over the Na–glucose cotransporter, SGLT1. Na^+ entry depolarizes the cell, leading to increased [Ca^{2+}] and also increases cytosolic [ATP] that shuts down an ATP-sensitive K^+ channel that also leads to depolarization and increased influx of Ca^{2+}. The L cells in the ileum may differ from those in the colon. For example, glibencamide, a drug that inhibits the K_{ATP} channel, did not affect GLP-1 secretion from ileum explants, but did so from colonic explants.

EXTRINSIC INNERVATION OF THE GUT ARISES FROM PARASYMPATHETIC AND SYMPATHETIC NERVES

POSTGANGLIONIC SYMPATHETIC NERVES ORIGINATE FROM THE CELIAC GANGLION, SUPERIOR MESENTERIC GANGLION, AND INFERIOR MESENTERIC GANGLION

Efferent preganglionic sympathetic neurons project from the spinal cord to the prevertebral ganglia, where they form nicotinic cholinergic synapses. The long postganglionic sympathetic fibers project to the myenteric plexus, where they release norepinephrine primarily onto α_2 receptors that inhibit excitatory cholinergic neurotransmission. Some sympathetic fibers directly innervate the sphincters, causing contraction, consistent with the inhibitory role of the sympathetic nervous system on GI function. Other sympathetic fibers make connections directly on smooth muscle cells to inhibit them. These smooth muscle cells contain β_2 receptors that increase cAMP in the muscle cells that relaxes the smooth muscle (see Chapter 3.8). The extrinsic innervation is highlighted in Figure 8.3.6.

THE VAGUS SUPPLIES PARASYMPATHETIC INNERVATION TO THE GUT

Parasympathetic preganglionic cholinergic fibers excite excitatory postganglionic neurons, which use a variety of neurotransmitters including **substance P, neurokinin A**, and **acetylcholine** as a neurotransmitter. The parasympathetic preganglionic fibers also excite inhibitory postganglionic neurons which use **vasoactive intestinal polypeptide (VIP)** and **nitric oxide (NO)** as neurotransmitters, among others.

AFFERENT FIBERS TRAVEL OVER SPLANCHNIC NERVES AND THE VAGUS

The vagus nerve contains both afferent and efferent fibers, with the afferent fibers outnumbering the efferents by a factor of 10. Vagus afferents travel to the nucleus solitarius in the brain stem and from there to the dorsal motor nucleus of the vagus and the nucleus ambiguus. These carry physiological information. In addition, sensory information outnumbers efferents 3:1 in the splanchnic nerves. Afferent information passes by way of the splanchnic nerves to the dorsal horn of the spinal cord. The afferent neurons have cell bodies in the dorsal root ganglia. Second-order neurons in the cord project to the brain stem and cerebral cortex. Most nociceptive information travels over the splanchnic nerves.

THE ENTERIC NERVOUS SYSTEM CAN FUNCTION AUTONOMOUSLY

The enteric nervous system contains some 10^8 neurons, whereas the vagus nerve has only about 2000 efferent fibers. There are as many neurons in the enteric nervous system as there are in the spinal cord. Although intestinal motility is modulated by central nervous system efferents, it contains all the elements necessary for reflex activity including sensory neurons, interneurons, and motor neurons and can regulate GI function autonomously using local sensory information.

SLOW WAVE ACTIVITY FORMS THE BASIS OF INTESTINAL SMOOTH MUSCLE CONTRACTION

Intestinal smooth muscle cells have resting membrane potentials between −40 and −80 mV. These membrane potentials rhythmically oscillate, a phenomenon called slow waves. The slow waves consist of a rapid depolarization followed by a partial repolarization and then a prolonged plateau phase of depolarization, ending with complete repolarization (see Figure 8.2.2). In the stomach the frequency of the slow waves is set by the pacemaker cells at about 3–5 min^{-1}. In the duodenum, the **basic electrical rhythm** is about 10–12 min^{-1}. The frequency decreases from 10–12 min^{-1} in the duodenum to 7–8 min^{-1} in the distal ileum. The basic electrical rhythm is set by the ICCs.

TABLE 8.3.1 Enteroendocrine Cells (EEC) in the Gastrointestinal Tract

EEC	Location	Secretion	Stimulus	Receptors	Main Function
G-cell	Antrum	Gastrin	GRP + peptides + amino acids + SST−	CaSR, GPRC6A, SSTR	Increases acid secretion by parietal cells
P-D1-cell	Fundus	Ghrelin obestatin	Sugars bitter	T1R3 T2R	Hunger control and release of GH
D-cell	Stomach antrum (open) stomach body(closed)	SST SST	H +, gastrin, CCK		Inhibits gastrin secretion Inhibits acid secretion
S-cell	Duodenum	Secretin	SRP		Stimulates pancreatic secretion Delays gastric emptying
I-cell	Duodenum	CCK	Fat products + peptides + amino acids	GPR120; FFAR1 GPR92 CaSR; T1R1-T1R3	Stimulate vagus nerves to increase pancreatic zymogen secretion and gallbladder contraction
K-cell	Duodenum−jejunum	GIP	Sugars LCFA amino acids	SGLT1 GPR120; FFAR1	
L-cell	Proximal s.i.	GLP-1	Sugars LCFA AA bitter	T1R2-T1R3; SGLT1 GPR120; FFAR1 GPRC6A T2R	Delays gastric emptying; increases insulin secretion
	distal s.i., colon	PYY, GLP-1	SCFA	FFAR2; FFAR3	Inhibits gastric and intestinal motility Inhibits gastric and pancreatic secretion
M-cell	Small intestine	Motilin			Initiates phase III of MMC
N-cell	Ileum	Neurotensin	Fatty acids		Inhibits gastric secretion and delays emptying; stimulates pancreatic and intestinal secretion

GRP = gastrin releasing peptide; SST = somatostatin; CaSR = extracellular Ca^{2+}-sensing receptor; GPR = G-protein-coupled receptor, many of which have trivial names (e.g., FFAR1 = GPR40); T1R1, T1R3, T2R = taste receptors; T1R1−T1R3 combination detects "sweet"; various T2Rs detect "bitter"; CCK = cholecystokinin; SRP = secretin releasing peptide; GIP = glucose-dependent insulinotropic polypeptide; LCFA = long-chain fatty acid; SGLT1 = sodium, glucose cotransporter type 1; FFAR1 = free fatty acid receptor type 1; AA=amino acids; PYY = protein YY; SCFA = short-chain fatty acid.

INTESTINAL MOTILITY HAS SEVERAL DIFFERENT PATTERNS: SEGMENTATIONS, PERISTALSIS, MIGRATING MOTOR COMPLEX OR MIGRATING MYOELECTRIC COMPLEX, AND REVERSE PERISTALSIS

SEGMENTATION CONTRACTIONS MIX INTESTINAL CONTENTS

Coordinated constriction or relaxation of the outer longitudinal muscle and inner circular muscle gives rise to stereotypical patterns of motility. Segmentation contractions involve local regions of the intestine in which the circular muscle contracts in one region and relaxes in adjacent regions. This moves materials in both directions, orad and caudad. Thus segmental contractions mix intestinal contents with digestive juices. This is the main pattern of motility after a meal (see Figure 8.3.7).

PERISTALSIS PROPELS THE CHYME

Peristalsis consists of a wave of circular muscle contraction that propagates caudally. Both circular and longitudinal muscle layers participate: caudad to the peristaltic wave the circular muscle relaxes and the longitudinal muscle contracts. Contraction of the longitudinal layer shortens the distance the chyme must move and helps increase the caliber of the intestine. At the wave front the circular layer contracts and the longitudinal muscle relaxes. Peristaltic waves generally do not propagate along the entire intestine but instead propel the chyme only a few tens of centimeters.

The peristaltic reflex is a neurally mediated reflex in the small intestine and colon that causes caudad propulsion of chyme. Mechanical or chemical stimulation of the mucosa causes EC cells to release 5-HT (serotonin) onto local receptors of IPANs. These neurons project to the myenteric plexus and submucosal plexus where they activate myenteric ganglion cells to send impulses up

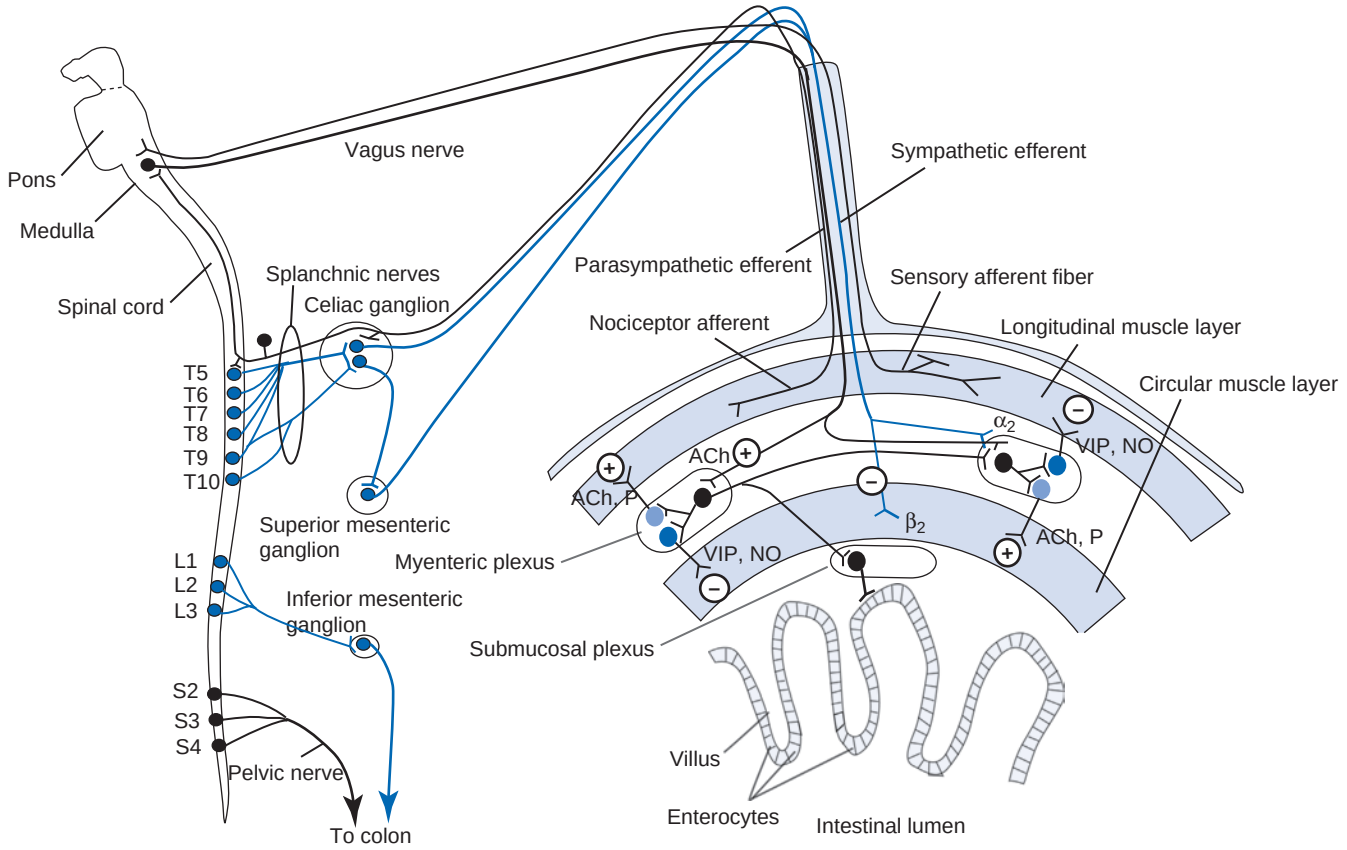

FIGURE 8.3.6 Extrinsic and intrinsic innervations of the intestine. A cross-section of the small intestine is shown. The vagus nerve carries parasympathetic innervation of the upper small intestine. Parasympathetic input to the colon originates in the sacral segments of the spinal cord (S2–S4) and travels over the pelvic nerve. Sympathetic efferents originate in T5–T10 and travel to the small intestine over the splanchnic nerves to the celiac and superior mesenteric ganglia. Sympathetic efferents to the colon originate in L1–L3 to the inferior mesenteric ganglia. The sympathetic postganglionic efferents mainly inhibit release of acetylcholine at parasympathetic preganglionic cholinergic fibers, mediated by α_2 receptors on the parasympathetic preganglionic terminals. Parasympathetic preganglionic fibers mainly release acetylcholine onto nicotinic cholinergic receptors in the myenteric plexus. One type of postganglionic cell (about 45–50% of myenteric neurons) uses substance P, acetylcholine, and neurokinin A as transmitter and these excite smooth muscle activity. A second kind, about 20–30% of myenteric neurons, uses VIP and NO as neurotransmitters, and these inhibit smooth muscle activity. The myenteric neurons mainly synapse on other myenteric neurons, interstitial cells of Cajal, and on circular smooth muscle. A smaller fraction connects to longitudinal muscle, which receives mainly excitatory input, and to the submucosal ganglia. Afferent sensory information flows over the vagus, pelvic, and splanchnic nerves. This includes stretch and chemosensory information that passes through the prevertebral ganglia where a second level of integration occurs. Pain stimuli are carried mainly over the splanchnic nerves.

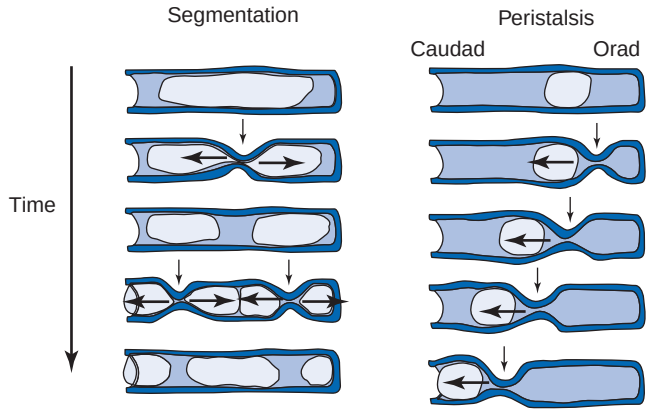

FIGURE 8.3.7 Segmentation and peristaltic motility in the small intestine. Segmentation (left) occurs when an area of circular muscle contracts. Material is propelled in both directions, orad and caudad. Segmental contractions do not propagate along the intestine and occur randomly along the intestine. The bidirectional movement of luminal contents mixes the chyme with digestive juices. Peristaltic contractions (right) consist of a propagating wave of contraction that generally moves from the orad to the caudad direction, sweeping luminal contents before it. It consists of a wave of contraction of the circular muscle, with longitudinal muscle contracting out of phase.

and down the intestinal tract through adjacent myenteric ganglia. Impulses traveling orad activate the **ascending contraction**. The neurotransmitters here are **acetylcholine**, **substance P**, and **neurokinin A**. The impulses traveling caudad activate a **descending relaxation** using **VIP**, **NO**, and **PACAP (pituitary adenylyl cyclase activating polypeptide)**. Figure 8.3.8 illustrates the enteric nervous system control of peristalsis.

THE MIGRATING MOTOR COMPLEX OCCURS IN THE FASTING STATE

The migrating motor complex (MMC), also called the migrating myoelectric complex, describes the pattern of motility during the interdigestive period. As discussed in Chapter 8.2, this stereotypical pattern consists of three phases over a period of 85–115 minutes. It is the "intestinal housekeeper" that propels undigested matter and everything else into the colon. Phase I of the MMC is a quiescent period lasting 40–60% of the cycle length. Phase II, lasting another 20–30% of the cycle length, consists of

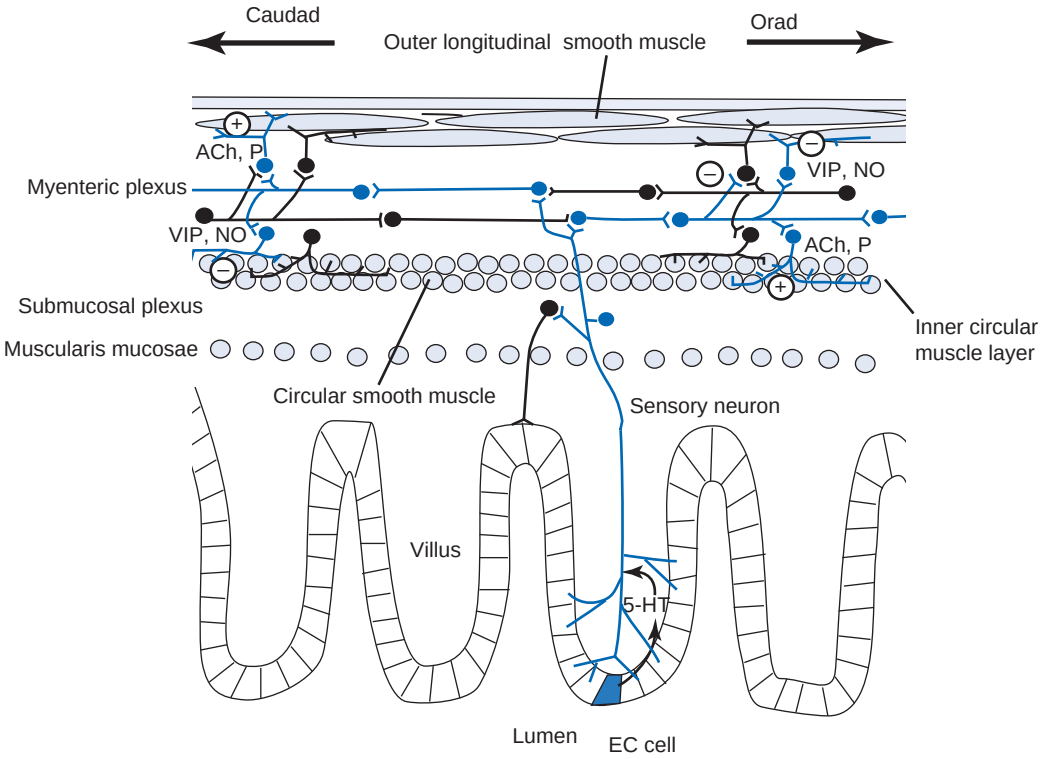

FIGURE 8.3.8 Nerve activity during peristalsis. A longitudinal section of the intestinal wall is shown. The activated cells are shown in blue, quiescent cells in black. Peristalsis generally begins with sensory afferent stimulation resulting in the release of 5-HT from EC cells in the mucosa lining. These sensory neurons make synapses on interneurons within the myenteric ganglia. The interneurons send impulses in the orad direction that activate excitatory myenteric motor neurons for the circular muscle and inhibit excitatory motor neurons for the longitudinal layer. The excitatory motor neurons release acetylcholine, substance P, and neurokinin A. The inhibitory neurons release VIP, NO, and others. These form the ascending contraction of the peristaltic reflex. At the same time, the sensory neurons activate interneurons that send signals in the caudad direction. These activate inhibitory myenteric motor neurons for the circular layer and excitatory myenteric neurons for the longitudinal layer. The result is a descending relaxation that precedes the contractile wave. In the figure, the blue axons are activated while the black lines are quiescent. Thus the longitudinal muscle in the orad direction relaxes while the circular muscle contracts; conversely, the longitudinal muscle in the caudad direction contracts and the circular muscle relaxes.

increasingly strong but irregular contractions. Phase III lasts 5–10 minutes but consists of strong contractions that propagate caudally and that completely occlude the lumen.

THE *ILEOCECAL SPHINCTER* PREVENTS REFLUX OF COLONIC CONTENTS INTO THE ILEUM

The junction between the terminal ileum and the colon produces a region of high pressure that resists movement of material from the colon into the ileum. However, the slow electrical waves and MMC migrate through the ileocecal junction and evoke colonic contractions. Movement of materials from the ileum into the colon is characterized by bolus movements separated by periods of no flow. Distension of the colon produces reflex relaxation of the ileum and contraction of the ileocecal sphincter. This effect is not blocked by transection of either the vagus or pelvic nerves, but it is blocked by transection of the splanchnic nerves. This suggests that the extrinsic sympathetic nerves are involved in this reflex. Distension of the ileum promotes contraction of the ileum and propulsion of material into the cecum.

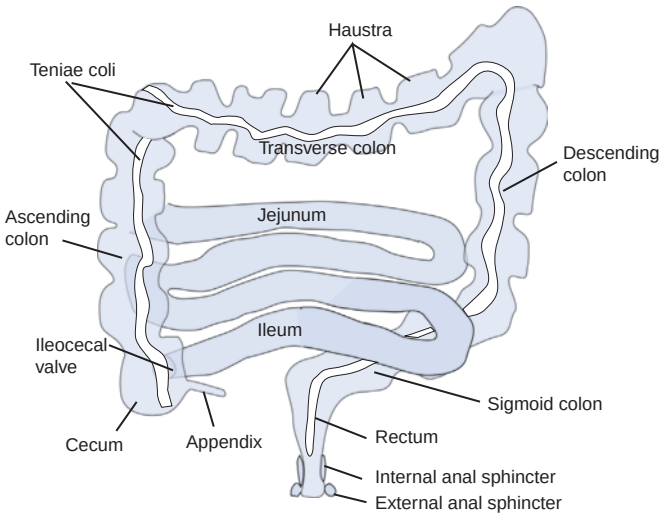

FIGURE 8.3.9 The gross anatomy of the large intestine.

THE LARGE INTESTINE OR COLON HAS SEVERAL ANATOMIC REGIONS

The colon begins at the ileocecal sphincter and consists of the **cecum**, the **ascending colon**, the **transverse colon**, and the **descending colon**. This leads to the **sigmoid colon** and the **rectum** (see Figure 8.3.9). As in the

rest of the gastrointestinal system, the colon contains an inner layer of circular muscle that is continuous from cecum to rectum. In the rectum, this layer thickens to form the **internal anal sphincter**. Contraction of the circular muscle divides the colon into segments called **haustra**, giving the appearance of a chain of small sacs. The haustra disappear during contractions of a segment and their locations shift. The outer longitudinal muscle layers are not continuous in the large intestine but instead form three bands called **teniae coli** that run the length of the large intestine. They fan out and become continuous at the rectum. The external anal sphincter consists of striated muscle that overlaps the internal anal sphincter. This muscle provides voluntary control over defecation.

COLONIC MOTILITY SHOWS SEVERAL DISTINCT PATTERNS

Short duration contractions mix colonic contents to aid in water extraction. Each day some 7–10 L of ingested or secreted fluid enters the GI tract, and about 0.6 L of this reaches the colon. The colon absorbs an additional 0.5 L and compacts the feces for excretion. These short duration contractions do not propagate. They last less than 15 seconds and have a frequency of 2–13 min^{-1}.

Long duration contractions last 40–60 seconds. These contractions propagate either orally or caudally. They both mix and propel colonic contents. Both long and short duration contractions may occur simultaneously, giving a mixed pattern of contraction.

Giant migrating contractions are high-amplitude contractions that propagate caudally over extended distances in the colon. They produce mass movement of fecal material caudally. At their onset, haustra disappear. After the contents are propelled caudally for some distance, the haustra reappear and short and long duration contractions occur again. These mass movements of feces precede the conscious need to defecate by propelling fecal matter into the sigmoid colon and rectum.

LOCAL AND EXTRINSIC NERVOUS INNERVATIONS CONTROL ILEAL AND COLONIC MOTILITY

COLONIC STRETCH RECEPTORS INITIATE A LOCAL CONTRACTION REFLEX

Colonic distension or sensing of fecal material mediated by short-chain fatty acids activates receptors that in turn activate circular muscle contraction through local reflexes mediated by the myenteric plexus. As mentioned above, distension of the ileum promotes contraction of the ileum and movement of material into the colon. Part of this response is the reflex relaxation of the colon to accept material from the ileum. These responses are probably mediated by the local myenteric plexus.

DISTENSION OF THE STOMACH EXCITES ILEAL AND COLONIC MOTILITY AND RELAXES THE ILEOCECAL SPHINCTER

Centrally mediated pathways account for longer reflexes. The proximal large intestine is supplied by sympathetic nerves arising from the superior mesenteric ganglion. Sympathetic nerves arising from the inferior mesenteric ganglion supply the descending and sigmoid colon and rectum. The large intestine receives parasympathetic nerves from the pelvic nerve arising from spinal segments S2–S4. Ingesting a meal increases ileal contraction and relaxes the ileocecal sphincter. This is the **gastroileal reflex**, which appears to be mediated by extrinsic nerves. Similarly, eating a meal increases colonic activity simultaneously throughout all of the colon. This is the **gastrocolic reflex**. The gastrocolic reflex can produce mass movement of feces in the colon and stimulate defecation. The sensory afferents involved in the reflex include stretch receptors in the stomach and chemoreceptors in the small intestine. Figure 8.3.8 summarizes the excitatory and inhibitory feedbacks of motility between different regions of the gastrointestinal tract.

DEFECATION INVOLVES VOLUNTARY AND INVOLUNTARY MUSCLES

The combined action of the internal anal sphincter and the external anal sphincter retains fecal matter in the rectum. The ability to do this is called **continence**, and the loss of this ability is called **incontinence**. As in the rest of the GI tract, nervous control of colonic and rectal motility is set by a balance between parasympathetic stimulation of peristalsis and inhibition of the sphincters and sympathetic inhibition of peristalsis and excitation of the sphincters. The parasympathetics originate in the sacral cord and sympathetics in the thoraco-lumbar cord. Involuntary parasympathetic nerves traveling over the **pelvic nerve** control the tone of the internal anal sphincter. The external anal sphincter consists of striated muscle that is controlled voluntarily by somatic motor neurons that exit the spinal cord at S2–S4 and travel over the pudendal nerve. The internal anal sphincter makes the largest contribution to continence; about 85% of the resting anal tone of 40–80 mmHg comes from the internal anal sphincter.

Epithelial nerve endings in the rectum and anus inform the CNS of the nature of rectal contents (solid, liquid, or gas). This information allows a conscious decision about how to evacuate the rectal contents. The anal passage of gas is technically called **flatulation** and the gas is referred to as the **flatus**.

Stretch receptors in the sigmoid colon and rectum send afferent signals to the spinal cord along the pelvic nerve. These afferents excite preganglionic parasympathetic neurons that send efferent connections to postganglionic parasympathetic neurons in the smooth muscle of the large intestine. This initiates contractions that

further move fecal material toward the rectum. At the same time, the afferent sensory information ascends the spinal cord to the cerebrum to create the conscious urge to defecate. Voluntary contraction of the abdominal muscles can help move fecal matter into the distal large intestine, thereby bringing on defecation. Distension of the rectum reflexly relaxes the internal anal sphincter and contracts the external anal sphincter. This switches control of defecation from involuntary retention by the internal anal sphincter to voluntary retention by the external anal sphincter. Voluntary contraction of the external anal sphincter can increase pressure within the anal sphincter to 150 mmHg. The inhibition of internal anal sphincter tone by rectal distension is called the **rectoanal inhibitory reflex**. It is mediated by intrinsic neural pathways in the wall of the rectum and anus, mediated by VIP and NO.

Distension of the rectum provides the initial sensory stimulation for defecation. Actual defecation involves parasympathetic relaxation of the internal anal sphincter, opening of the angle between the rectum and the anus, voluntary relaxation of the external anal sphincter, and increasing the pressure within the sigmoid colon and rectum to propel the feces out through the anus. The increase in pressure is caused by a peristaltic wave in the sigmoid colon and rectum and is assisted by increasing intra-abdominal pressure by voluntarily contracting the abdominal muscles and diaphragm. The nerves involved in defecation are shown in Figure 8.3.10. These pathways are essentially the same as those used for micturition, and there is cross-talk between the defecation and micturition pathways.

SUMMARY OF REGULATORY CONNECTIONS WITHIN THE GI TRACT

The inhibition of gastric emptying by stimuli in the small intestine is called the **enterogastric inhibitory reflex**. The sensory stimuli in the duodenum that inhibits gastric emptying include:

distension of the duodenum
irritation of the duodenum
acid pH in the duodenum
increased osmolarity of duodenal content
amino acids (particularly tryptophan) in the duodenum
fat digestion products (fatty acids, monoglycerides, and diglycerides) in the duodenum.

Osmoreceptors are limited to the duodenum, whereas receptors for acid, glucose, or oleic acid are present within the first 1.5 m of the small intestine. Perfusion of the ileum with glucose or lipids delays gastric emptying. This last phenomenon is called the **ileogastric reflex** or the **ileal brake**.

Similarly, distension of the stomach causes contraction of the ileum and colon, referred to as the **gastroileal reflex** and **gastrocolic reflex**. Distension of the ileum causes relaxation of the ileocecal valve, whereas distension of the ascending colon constricts it. Distension of the rectum inhibits internal anal sphincter tone, the **rectoanal inhibitory reflex**. Figure 8.3.11 summarizes the excitatory and inhibitory feedbacks of motility between different regions of the gastrointestinal tract.

VOMITING REMOVES POTENTIALLY DANGEROUS MATERIAL FROM THE GUT

A variety of stimuli in the GI tract results in emesis or vomiting. These include specific irritants instilled in the stomach, and distension of the stomach or the intestine. Some stimuli, such as hypertonic saline and copper sulfate, excite mucosal sensory receptors, whereas emesis caused by distension begins with smooth muscle stretch receptors. These sensory afferents travel to a vomiting center, located in the medulla, over the vagus nerve. Stimulation of sensory receptors over the splanchnic nerves causes pain and not emesis. Emetic agents such as **syrup of ipecac** cause emesis through activation of stomach afferents.

Other stimuli also can cause emesis. These include mechanical stimulation of the back of the pharynx. This is the **gag reflex** that normally prevents us from swallowing large pieces of material.

The dorsal surface of the medulla at the caudal aspect of the fourth ventricle of the brain responds to a wide variety of circulating chemicals by initiating emesis. This region is called the **chemical trigger zone** or **CTZ**. Administration of a number of compounds directly to this area causes emesis and surgical removal of the area prevents the effect. The vomiting that accompanies certain cancer medications and radiation therapy may act through the CTZ. However, some radiation therapy and other cancer medications may also act through gastrointestinal receptors because vagotomy removes their effect. Infusion of epinephrine causes emesis and may explain emesis upon strenuous exertion.

Motion sickness and a variety of diseases of the inner ear cause emesis by activating the brain stem vestibular nuclei. Anticholinergic drugs, such as **dramamine**, bind to M1 receptors and prevent motion sickness by increasing the habituation to motion stimuli. Figure 8.3.12 shows the stimuli that can lead to vomiting.

Exceedingly unpleasant sensory stimulation, including noxious odors, taste, visual stimulation, or pain, can result in emesis through cerebral cortical afferents. The smell of vomit itself is a powerful stimulant for vomiting.

VOMITING IS A COMPLICATED PROGRAMMED EVENT

Vomiting, like swallowing, entails complicated reflexes that are controlled by a vomiting center in the medulla. This center coordinates the gastrointestinal muscles and

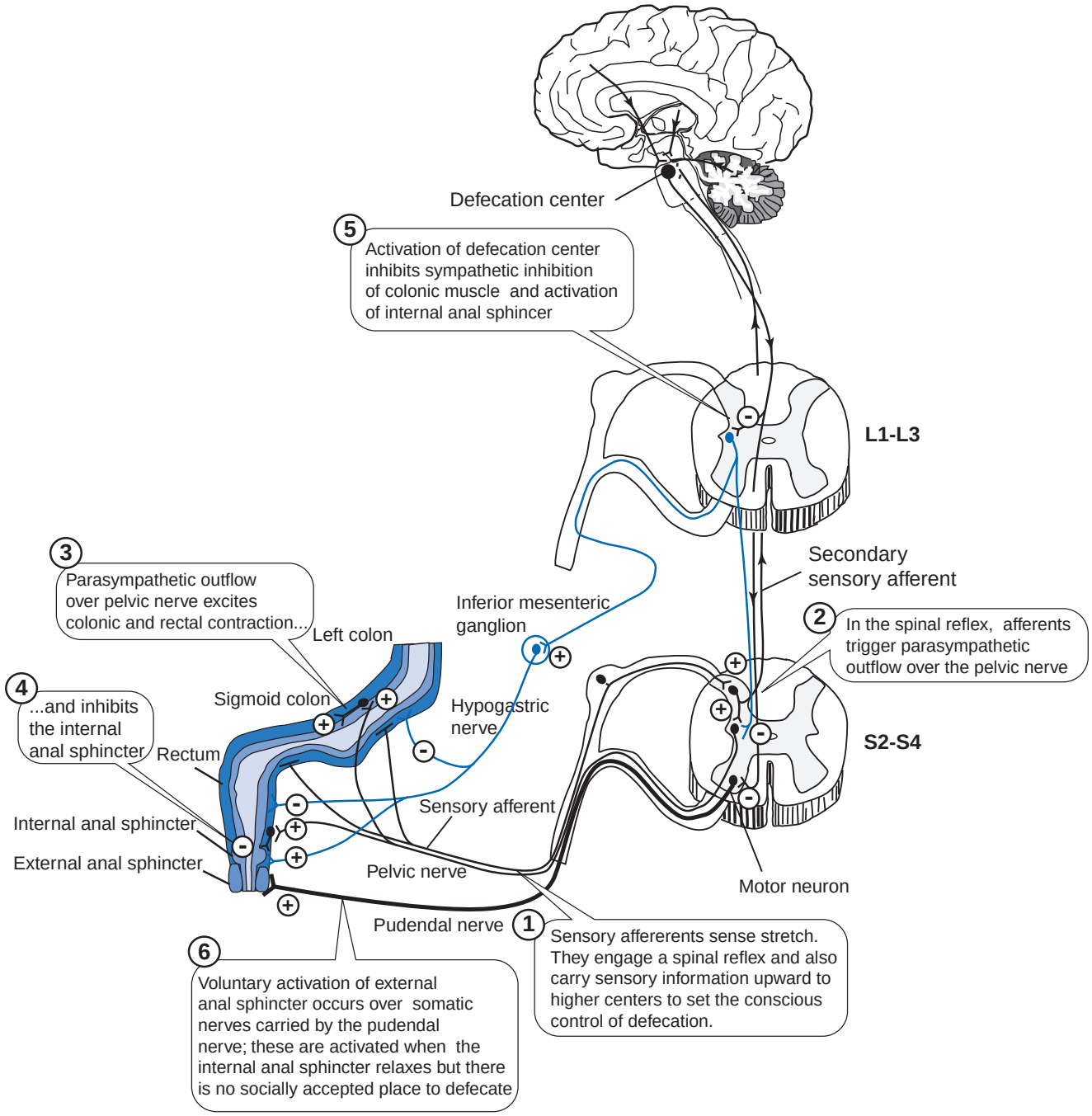

FIGURE 8.3.10 Nervous control of defecation. When material or fluid is presented to the distal colon and rectum, it stretches the tissues and activates stretch-activated sensors in the walls of the gut. These send afferent fibers to the sacral cord over the pelvic nerve, and this begins a reflex but also sends fibers up the cord to higher centers in the brain. This upward flow of sensory input informs the brain of the status of the colon and creates the urge to defecate. In the cord, parasympathetic outflow over the pelvic nerve causes contraction of the left colon, sigmoid colon and rectum, and relaxation of the internal anal sphincter. At the same time, outflow from the brain inhibits sympathetic inhibition of colonic and rectal motility and activation of internal anal sphincter contraction. These combined activities relax the internal anal sphincter and contract colonic and rectal muscles. These actions can be overridden by conscious contraction of the external anal sphincter, mediated by voluntary motor nerves exiting the cord in the sacrum, and traveling over spinal roots that form the pudendal nerve.

somatic motor systems to expel potentially noxious luminal contents from the gastrointestinal tract. It is often preceded by **nausea**, the subjective feeling of being about to vomit. Vomiting is generally also preceded by **reverse peristalsis**, which is controlled by extrinsic nerves and is entirely abolished by vagotomy. Intraluminal pressures generated by reverse peristalsis are nearly twice as great as those produced by normal

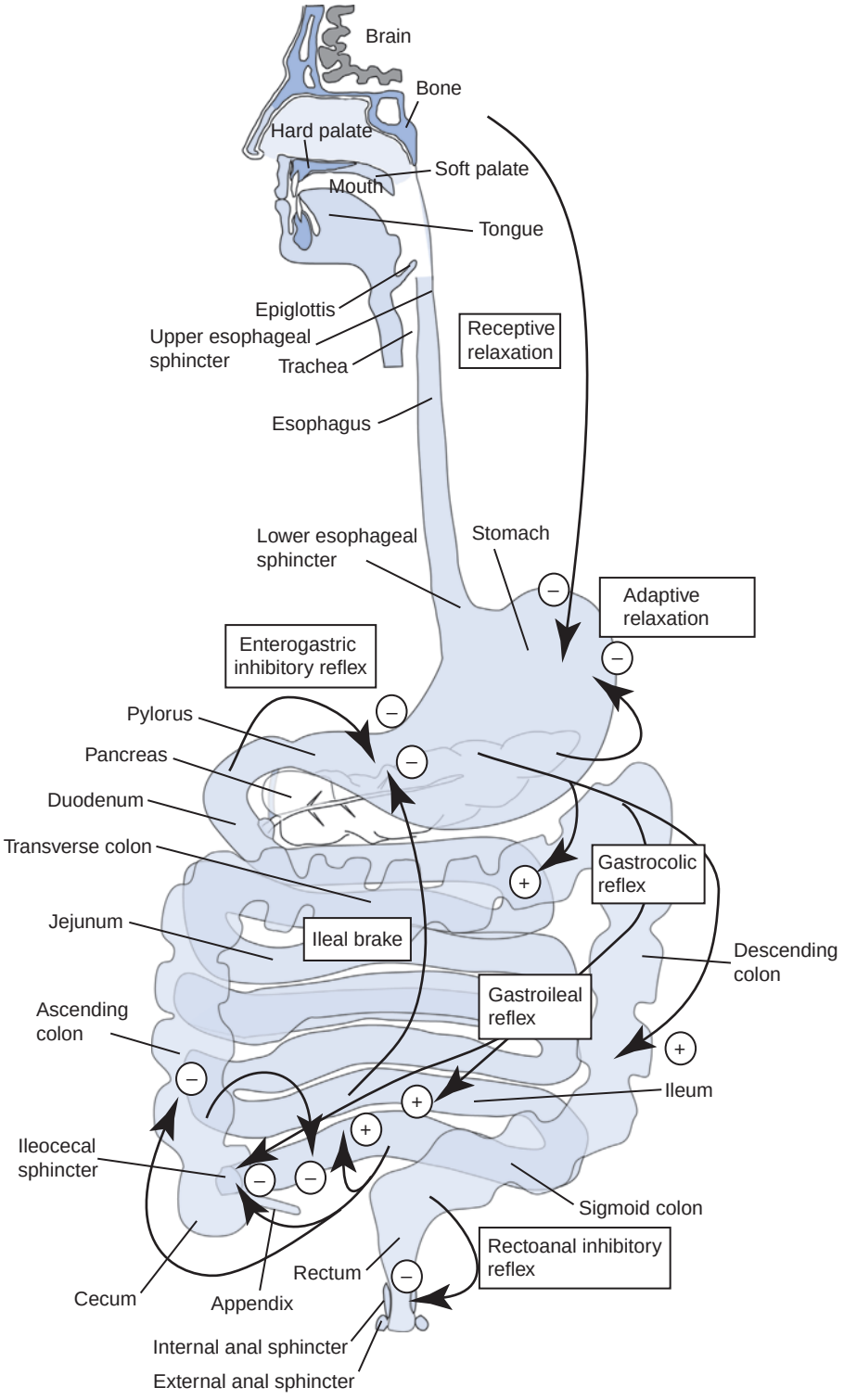

FIGURE 8.3.11 Regulation of gastrointestinal motility by remote parts of the gastrointestinal tract. Each arrow represents the effect of stretch or other stimulation on motility in another part of the GI tract. Receptive relaxation refers to the relaxation of stomach muscle caused by the swallowing center in the medulla. Distension of the stomach causes a further relaxation of the orad stomach as part of adaptive relaxation. Emptying of the stomach is inhibited by a variety of reflexes arising from the duodenum and proximal jejunum. This includes acid pH in the lumen, distension of the duodenum, hyperosmolarity of duodenal contents, irritation of the duodenum, amino acids, and lipolytic products within the duodenum and proximal jejunum. This comprises the enterogastric inhibitory reflex. Nutrients in the ileum also inhibit gastric emptying; this is the ileal brake. However, normally these nutrients are absorbed by the time the material reaches the ileum, so that the ileal brake is an abnormal pattern. Food in the stomach and in the duodenum excites motility throughout the large intestine in the gastrocolic reflex. This is mediated by stretch and by chemosensors in the duodenum. This same information promotes ileal contractions and relaxes the ileocecal valve in the gastroileal reflex. Stretch of the ileum promotes its own contraction, relaxes the ileocecal valve, and relaxes the cecum and ascending colon. Distension of the ascending colon, on the other hand, relaxes the ileum. Distension of the rectum relaxes the internal anal sphincter in the rectoanal inhibitory reflex.

phasic intestinal contractions. They last several times longer and are propagated over longer distances at greater speeds. Reverse peristalsis brings intestinal contents into the stomach from which it can be expelled during vomiting. Contraction of the abdominal muscles produces a large positive intra-abdominal pressure that forces gastric contents past the lower esophageal sphincter and into the esophagus. Reverse peristalsis also occurs in the esophagus, and the propulsion of the vomitus through the mouth is aided by moving the hyoid bone and larynx upward and forward. Ventilation is suppressed during vomiting, and the glottis is closed. Parasympathetic stimulation increases saliva secretion to help protect the teeth when exposed to the acid vomit.

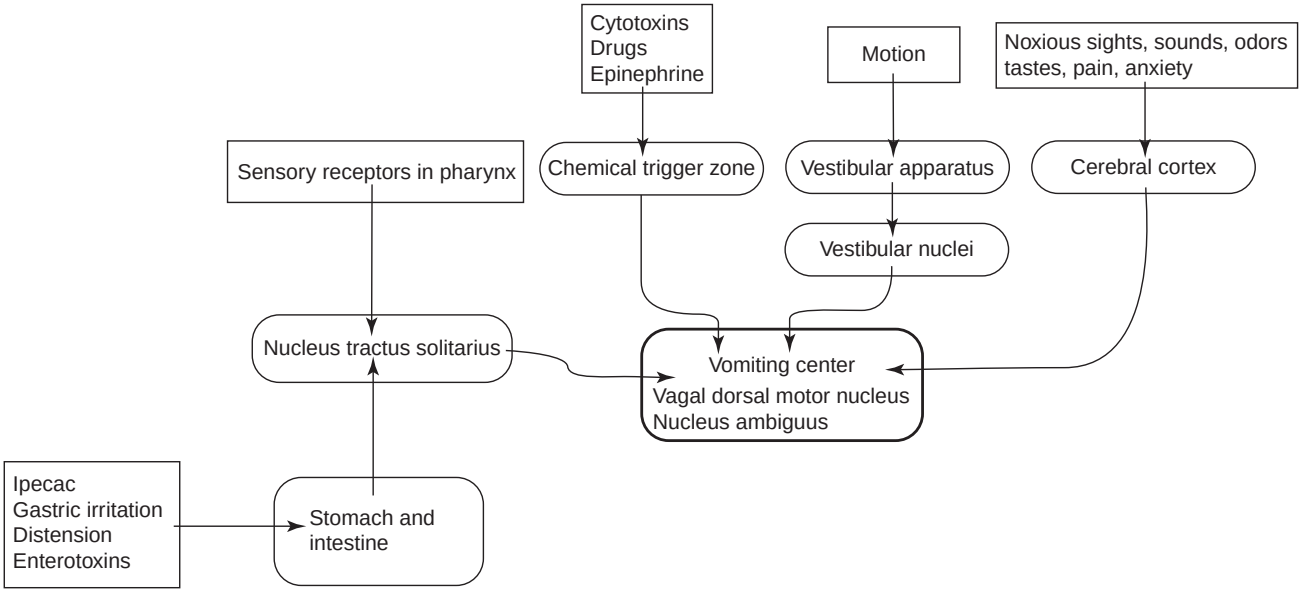

FIGURE 8.3.12 Block diagram of sensory stimulation that causes emesis. Emesis can arise from five different sensory afferents: (1) sensory stimulation of the pharynx; (2) distension or irritation of the intestine or stomach; (3) motion stimulation of the vestibular apparatus; (4) chemical stimulation of the CTZ; and (5) sensory processing through the cerebral cortex.

Clinical Application: Opioid-Induced Constipation

Physicians prescribe opioids as an analgesic to treat persons with a variety of pain conditions ranging from chronic pain resulting degenerative diseases of the back, knees, and hips, other musculoskeletal pain, neuropathic pain, and cancer pain, to acute pain resulting from sprains, strains, fractures, dental work, and surgery. Opioids act centrally on μ-receptors, κ-receptors, δ-receptors, and the opioid-receptor like ORL-1 to alleviate pain. However, they also act on μ-receptors, κ-receptors, δ-receptors in the GI tract, resulting in opioid-induced bowel dysfunction, OIBD, commonly producing opioid-induced constipation, OIC. Approximately 5% of the adult population in the United States is treated with opioids for chronic pain and many develop OIBD as a complication. The effects on the gut appear to be mediated mainly through the μ-receptor.

In the human gut, μ-receptors mainly are found in the myenteric and submucosal plexuses, as shown in Figure 8.3.13. In normal physiology, these receptors bind endogenous ligands such as enkephalins, endorphins, and dynorphins. Analgesic drugs also bind to these receptors and inhibit neurotransmitter release through a G_i mechanism. The result is reduced coordination of motility.

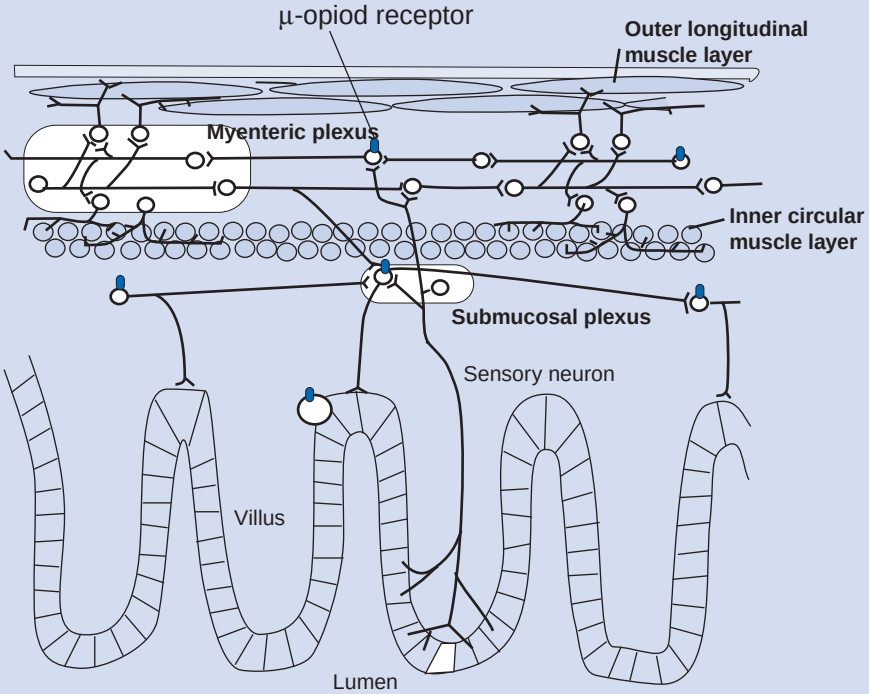

FIGURE 8.3.13 Opioid receptors in the enteric nervous system. *From Brock, C. et al., Opioid-induced bowel dysfunction.* Drugs *72:1847—1865 (2012).*

Clinical Applications: Diverticular Disease of the Colon

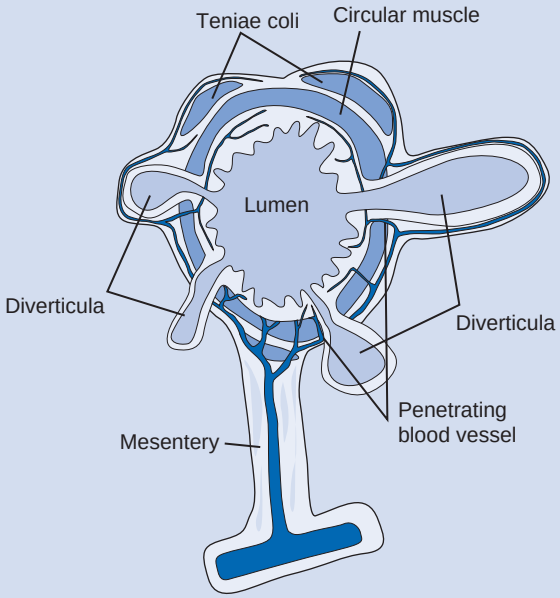

FIGURE 8.3.14 Cross-section of the colon showing diverticula that form as pouches of mucosa and submucosa that bulge outward through the muscle layers of the colon. *Redrawn from C.M. Friel and J.B. Matthews, Diverticular disease of the colon,* Clin. Perspect. Gastroenterol. ***3****:187–197, 2000.*

Diverticulosis refers to the presence of small saccules in the colon that form when the wall of the intestine bulges out through weaknesses in the muscle layers. There are two types of diverticula: true diverticula have all of the normal components of the gut wall, whereas false diverticula contain only mucosa and submucosa. True diverticula are uncommon and probably congenital. False diverticula are acquired as a consequence of chronically increased luminal pressure. A diagram of diverticula is shown in Figure 8.3.14.

The prevalence of diverticulosis in undeveloped countries in Asia and Africa is less than 10%, whereas in developed countries it increases with age from about 10% in persons over 40 years old to 80% in persons over 85 years of age. Dennis Burkitt first championed the idea that many diseases of the colon, including diverticulosis, ulcerative colitis, and colon cancer, were related to the lack of dietary fiber in the purified and enriched diets of developed countries. Dietary fiber expands the colon, increasing its radius, r. According to the Law of Laplace for a cylinder, $P = T/r$, where P is the pressure, T is the wall tension, and r is the radius. When r decreases, P increases for the same wall tension. Thus the reduced caliber of the colon when ingesting a fiber-poor diet causes an increase in the pressure. Whether this hypothesis adequately explains the pathophysiology of diverticular disease is unknown. The decreased stool size might initiate other changes, such as thickening of the muscle bands, that exaggerate the colonic pressure response to food and other agents that increase colonic pressure.

Inflammation of the pouches causes diverticulitis. Although many people have asymptomatic diverticulosis, the condition can lead to serious complications including abscess formation, perforation leading to peritonitis (an infectious inflammation of the **peritoneum**, the membrane lining the abdominal cavity), stricture of the colon, and bleeding.

SUMMARY

The small intestine begins at the end of the pyloric sphincter and continues to the ileocecal sphincter. The duodenum makes up the first short segment, followed by the jejunum, and then the ileum. The large intestine begins at the ileocecal sphincter and consists of the cecum, followed by the ascending, transverse, descending, and sigmoid colon. The colon leads to the rectum and the anus.

Intestinal function is regulated by extrinsic nerves arising from the parasympathetic and sympathetic nervous systems and an intrinsic enteric nervous system consisting of the myenteric plexus, the submucosal plexuses, and the ICCs. The ICCs come in several varieties. These cells set the basic electrical rhythm of the gut. The myenteric plexus lies between the outer longitudinal muscle layer and the inner circular muscle layer. The submucosal plexuses lie between the muscularis mucosa and the inner circular muscle layer.

Sensory information comes to the enteric nervous system and CNS through mechanosensitive enterochromaffin cells (EC) and chemosensitive and mechanosensitive enteroendocrine cells (EEC). Multiple types of EEC use sensory mechanisms similar to those of the taste buds to monitor types and amounts of nutrients in the ingested food. Enteroendocrine cells detect a variety of materials including glucose, amino acids, peptides, long-chain fatty acids, short-chain fatty acids, and stretch. They release a large number of endocrine peptides including secretin, gastrin, cholecystokinin, somatostatin, protein YY, glucagon-like polypeptide-1 (GLP-1), ghrelin, and motilin.

The parasympathetic system promotes motility and secretion. Parasympathetic efferents arrive over the vagus nerve and release acetylcholine on nicotinic receptors on postganglionic parasympathetic neurons. These excite motility by releasing substance *P*, neurokinin, or acetylcholine. The parasympathetic nervous system also may stimulate inhibitory postganglionic neurons that use VIP or NO as neurotransmitters. Parasympathetic innervation of the colon originates in spinal segments S2–S4 and travels over the pelvic nerve. Sympathetic nerves arrive from the prevertebral ganglia: the celiac and superior mesenteric ganglia are supplied from sympathetics from T1 to T10 and supply the proximal gut; the distal

gut is supplied by the inferior mesenteric ganglion from L1 to L3. Afferent sensory information travels over the vagus nerve and pain information travels over the splanchnic nerve. Sensory information begins with EC cells that release serotonin or ATP onto IPANs whose cell bodies lie within the enteric plexuses. The intestine has as many neurons as the spinal cord and can function autonomously without extrinsic innervation.

Gastrointestinal motility has three basic patterns: segmentation contractions that mix the contents, peristalsis that moves the contents a short distance, and the MMC that propels the contents forward during the fasting state. Segmentations and peristalsis result from local stimulation of the mechanosensors in the intestinal epithelium. These project to the myenteric plexus where they cause an ascending contraction and a descending relaxation. The ascending contraction occurs above a bolus of food. It involves contraction of the inner circular layer and relaxation of the outer longitudinal layer. The descending relaxation involves relaxation of the inner circular layer and contraction of the outer longitudinal layer. Peristalsis occurs when the areas of ascending contraction and descending relaxation move along the GI tract.

Colonic motility also shows three patterns. Short duration contractions mix the contents and produce the haustra, segments of the colon divided by regions of circular muscle contraction. Longer duration contractions propel material either orally or caudally. Giant migrating contractions propel material into the sigmoid colon or rectum.

Regions of the gut influence other regions through long reflexes. Distension and other stimuli in the duodenum inhibit gastric emptying in the enterogastric inhibitory reflex. Distension of the stomach promotes motility in the ileum and relaxation of the ileocecal sphincter in the gastroileal reflex. Distension of the stomach promotes colonic motility in the gastrocolic reflex. Distension of the ileum promotes its contraction, whereas distension of the colon inhibits ileal contraction. Distension of the rectum inhibits the internal anal sphincter in the rectoanal inhibitory reflex and contracts the external anal sphincter, switching control of defecation from the involuntary internal anal sphincter to the voluntary external anal sphincter.

REVIEW QUESTIONS

1. Where is the myenteric plexus? The submucosal plexus?
2. What are interstitial cells of Cajal? Why are they important?
3. What are intrinsic primary afferent neurons? To what to they respond? What cells do they activate?
4. Where do sympathetic nerves to the intestine originate? What do they do? What neurotransmitter do they use?
5. Where do parasympathetic nerves to the intestine originate? What do they do? What neurotransmitters do the preganglionic and postganglionic fibers use?
6. What are enterochromaffin cells?
7. What are enteroendocrine cells? What do they sense? What do they secrete?
8. What is peristalsis? What is meant by "ascending contraction" and "descending relaxation"?
9. What are receptive relaxation, gastric accommodation, enterogastric inhibitor reflex, ileal brake, and gastrocolic reflex?
10. Where is the vomiting center? Why is it necessary for vomiting to be a programmed event? What is the chemical trigger zone?