THE ENTERIC NERVOUS SYSTEM
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The enteric nervous system is a collection of neurons in the gastrointestinal tract that constitutes the “brain of the gut” and can function independently of the central nervous system. This system controls the motility, exocrine and endocrine secretions, and microcirculation of the gastrointestinal tract; it is also involved in regulating immune and inflammatory processes. In the past decade, major advances in the understanding of the enteric nervous system have led to a greater appreciation of its importance in clinical medicine. In this review we highlight some of these advances.

Development of the Enteric Nervous System

The enteric nervous system is primarily derived from cells of the vagal segment of the neural crest that migrate to the cranial portion of the gut and subsequently move caudally to populate the entire gastrointestinal tract. The ganglia of the hindgut receive an additional contribution from the sacral segment of the neural crest. Several receptors with tyrosine kinase activity are important in the migration and development of neuroblasts in the gut. One of these receptors, Ret, is involved in the development of enteric ganglia derived from vagal-neural-crest cells. Targeted disruption of the RET gene in mice results in the lack of enteric ganglia and in renal agenesis. Mutations in the RET gene are associated with megalacol in humans. Kit, another receptor with tyrosine kinase activity, is involved in the development of the interstitial cells of Cajal. These are nonneural cells that serve as pacemakers and are responsible for the spontaneous, rhythmic, electrical excitatory activity of gastrointestinal smooth muscle that is referred to as slow waves. These cells are also important in modulating communication between nerve and muscle. Mice with mutations in the KIT gene lack interstitial cells and have changes in skin pigment and abnormal intestinal motility.

Endothelin-3 and endothelin-B receptors also have a role in the migration and development of the enteric nervous system, as well as in the development of melanocytes from the neural crest. Both targeted disruption of the endothelin-3 gene in mice and naturally occurring mutations of this gene (in lethal spotting mice) cause aganglionic megalacol and coat-color spotting. A similar phenotype results from targeted disruption of the gene for the endothelin-B receptor in mice and natural mutations of the receptor gene in piebald lethal mice. Mutations in this gene have been reported in patients with Hirschsprung’s disease.

Structure of the Enteric Nervous System

The enteric nervous system was originally thought to be part of the autonomic component of the peripheral nervous system, and the neurons in the gut wall were thought to be postganglionic parasympathetic neurons. The idea that the gut has a “brain of its own” arose in the early 1990s, however, when it was found that intestinal peristaltic contractions were coordinated reflexes involving the intramural nerves and that the majority of enteric neurons did not contact the parasympathetic axons of the central nervous system directly. Subsequent examination of the functional and chemical diversity of enteric neurons revealed that the enteric nervous system closely resembles the central nervous system. It contains some 100 million neurons, approximately the number found in the spinal cord. The enteric nervous system may perhaps best be regarded as a displaced part of the central nervous system that retains communication with it through sympathetic and parasympathetic afferent and efferent neurons. The part of the central nervous system that is connected with the enteric neurons is now known as the central autonomic neural network. Together with these connections, the enteric nervous system provides neural control of all functions of the gastrointestinal tract (Fig. 1).

In the enteric nervous system, the nerve-cell bodies are grouped into small ganglia that are connected by bundles of nerve processes forming two major plexuses, called the myenteric (or Auerbach’s) plexus and the submucous (or Meissner’s) plexus. The myenteric plexus lies between the longitudinal and circular layers of muscle and extends the entire length of the gut. It primarily provides motor innervation to the two muscle layers and secretomotor innervation to the mucosa, but there are numerous projections from the myenteric plexus to the submucosal ganglia and to enteric ganglia of the gallbladder and 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 innervates motor end plates with the inhibitory neurotransmitter nitric oxide. This innervation is unique to the esophagus.

The submucous plexus, located in the submucosa be-
between the circular muscle layer and the muscularis mucosa, is best developed in the small intestine, where it plays an important part in secretory control. Besides innervating the glandular epithelium, neurons in the submucous plexus innervate the muscularis mucosa, intestinal endocrine cells, and submucosal blood vessels. A ganglionated plexus similar to the submucous plexus is found in the gallbladder, cystic duct, and common bile duct, as well as in the pancreas.21

The ganglia consist of tightly packed nerve-cell bodies, terminal bundles composed of nerve fibers, and glial cells and their processes. Glial cells are an integral component of the enteric nervous system, and they outnumber enteric neurons.22 Enteric glial cells resemble the astrocytes of the central nervous system, and their laminar extensions cover most of the surface of enteric neuronal-cell bodies. Enteric glial cells produce interleukins and express MHC class II antigens in response to stimulation by cytokines.21 This suggests a role for the enteric glia in modulating inflammatory responses in the intestine.

Although up to eight morphologic forms of neurons have been identified in the enteric nervous system, there are two main types.1 Type I neurons have many club-shaped processes and a single long, slender process, whereas type II neurons are multipolar and have many long, smooth processes.

**Chemical Nature of Neurons**

The chemical mediators of the enteric nervous system were initially thought to be limited to neurotransmitters such as acetylcholine and serotonin. Subsequent research added purines to the list, such as ATP, amino acids such as γ-aminobutyric acid, and peptides such as vasoactive intestinal polypeptide. More recently, nitric oxide has emerged as a neurotransmitter in the enteric nervous system, as it has in the central nervous system. Overall, more than 20 candidate neurotransmitters have now been identified in enteric neurons (Table 1), and most neurons contain several of them.2 Distinctive patterns of colocalization of mediators appear to identify sets of neurons that perform different functions.2,3 Neurontamin functions have been clearly defined for only a few of these substances, however, including acetylcholine, substance P, vasoactive intestinal polypeptide, and nitric oxide. A wide variety of neurons that perform different functions may use the same neurotransmitter.

The neurons that make up the enteric nervous system can be classified as intrinsic afferent neurons, interneurons, and motor neurons. The intrinsic afferent neurons that form the sensory limb of all intrinsic mot-

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**Figure 1. Innervation of the Gastrointestinal Tract.**

The neural plexuses in the gut represent an independently functioning network known as the enteric nervous system, which is connected to the central autonomic nervous system by parasympathetic and sympathetic nerves. The enteric nervous system may influence the effector systems in the gut directly or may do so indirectly through its action on intermediate cells, which include endocrine cells, the interstitial cells of Cajal, and cells of the immune system, such as mast cells. The cell bodies of the primary vagal and primary splanchnic afferent neurons are located in the nodose ganglia and the dorsal-root ganglia, respectively, each carries distinct information from the gut to the central nervous system. The symbol Δ represents afferent-nerve endings, and the arrows show the direction of neural transmission.

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**Table 1. Putative Neurotransmitters Found in the Enteric Nervous System.**

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<td>Serotonin (5-hydroxytryptamine)</td>
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<td>Purines</td>
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<td>Peptide YY</td>
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<td>Pituitary adenyl cyclase–activating peptide</td>
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<td>Somatostatin</td>
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<td>Substance P</td>
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<td>Thyrotropin-releasing hormone</td>
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<td>Vasoactive intestinal contractor (an endothelin)</td>
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<td>Vasoactive intestinal polypeptide</td>
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tor and secretomotor reflexes are type II neurons and are located in both the myenteric and submucous plexuses. They project circumferentially to interneurons in the surrounding myenteric and submucous plexuses. Electrophysiologically, the sensory neurons are characterized by prominent after-hyperpolarization and are therefore called AH neurons. After-hyperpolarization inhibits further excitation. AH neurons lack a prominent fast excitatory synaptic input, but they do receive slow synaptic input, which regulates their excitability. They are all cholinergic and may or may not contain substance P.

Interneurons are interposed between the primary afferent neurons and the motor or secretomotor neurons. Interneurons involved in motor reflexes are directed orally or anally and are designated as ascending or descending, respectively. Interneurons form multisynaptic pathways the length of the gut that control the distances along the intestine for which peristaltic waves are propagated. Several subgroups of interneurons have been defined on the basis of their neurotransmitter content, but their various physiologic roles are unknown.

The motor neurons have type I morphologic characteristics, and those in circular muscle are either excitatory or inhibitory. The excitatory motor neurons project locally or orally to the circular muscle, and their main neurotransmitters are acetylcholine and substance P. The inhibitory motor neurons in the circular muscle project caudally and contain vasoactive intestinal polypeptide and nitric oxide. The enteric nervous system may also contain command neurons that generate motor patterns for the wide variety of intestinal activities.

**INTERACTIONS BETWEEN THE CENTRAL AND THE ENTERIC NERVOUS SYSTEM**

Although the enteric nervous system can function independently of the central nervous system, the latter has an important role in coordinating the diverse functions of the enteric nervous system. The enteric nervous system is well connected to the central autonomic neural network in the central nervous system through both motor and sensory pathways of the sympathetic and the parasympathetic nervous systems (Fig. 1).

**Motor Input from the Central Nervous System**

The parasympathetic motor pathways consist of the vagus nerves that control the motor and secretomotor functions of the upper gastrointestinal tract and the sacral nerves that regulate the functions of the distal colon and rectum. The parasympathetic preganglionic neurons are all cholinergic and exert excitatory effects on enteric neurons through nicotinic and, in some regions, muscarinic receptors. These neurons provide rich connections to the myenteric neurons in the upper gastrointestinal tract and the distal colon and anorectum. In the small bowel, however, vagal preganglionic neurons innervate only small clusters of select myenteric neurons, which may serve as command neurons or pattern generators. These differences in the intensity of innervation by parasympathetic preganglionic fibers reflect the fact that the central nervous system exerts more direct control in the most proximal (i.e., the esophagus and stomach) and the most distal (i.e., the rectosigmoid) parts of the gastrointestinal tract and less direct control on the functions of the small intestine and proximal colon. Studies of the activation of parasympathetic effector pathways by chemical mediators in the central nervous system have elucidated important interactions between the central nervous system and the enteric nervous system that are involved in the gastrointestinal responses to stress, eating, and behavior.

The sympathetic fibers entering the gut are adrenergic, postganglionic fibers with cell bodies in the prevertebral ganglia. They have at least four distinct targets in the gut: secretomotor neurons containing vasoactive intestinal polypeptide, presynaptic cholinergic nerve endings, submucosal blood vessels, and gastrointestinal sphincters. Adrenergic nerve-cell bodies are not found in the enteric plexuses.

**Sensory Output to the Central Nervous System**

Neurons that carry sensory information to the central nervous system are termed primary afferent neurons. They are carried in the vagal and splanchnic nerves. Vagal primary afferent neurons have cell bodies in the nodose ganglia. It has been estimated that 80 percent of the fibers in the vagal trunk are afferent fibers. The primary vagal afferent neurons in the smooth-muscle layer are sensitive to mechanical distention of the gut; they have very low thresholds and convey information about physiologic motor activities in the gut. Certain vagal primary afferent neurons in the mucosa are sensitive to luminal concentrations of glucose, amino acids, or long-chain fatty acids, whereas others respond to a wide variety of chemical and mechanical stimuli.

Chemical transmitters released by mucosal endocrine cells are involved in transducing the actions of some stimuli on the vagal afferent neurons. For example, severe vomiting associated with certain forms of chemotherapy is due to the excessive release of serotonin (5-hydroxytryptamine) by damaged mucosal enterochromaffin cells. The high levels of 5-HT activate 5-HT3 receptors on the vagal primary afferent neurons, which are connected with brain-stem neurons, which in turn are involved in the vomiting reflex. The 5-HT3 receptor antagonist ondansetron, an antiemetic drug used to counteract chemotherapy-induced vomiting, suppresses the activation of vagal primary afferent neurons.

Splanchnic primary afferent neurons have their endings in the gut wall and their cell bodies in the dorsal-root ganglia. These afferent neurons are nociceptors and are involved in sensing pain in the gastrointestinal tract. They are usually multimodal and respond to high-intensity mechanical, thermal, and chemical stimuli that damage or threaten tissue. Many contain calcitonin gene–related peptide, and some also contain substance P. These neurotransmitters may be important in visceral nociception and in the activation of no-
Splanchnic primary afferent neurons not only transduce intestinal sensation but under certain circumstances also act directly on nearby gastrointestinal effector systems. They have long, bifurcated processes that allow them to execute the “axon reflex.” In this reflex, the activation of one limb of the bifurcated axon causes excitation to spread to the collateral limb, which then releases neurotransmitters such as calcitonin gene-related peptide and substance P to produce effects on the cells it innervates. The axon reflex is important in submucosal vasodilatation, duodenal secretion of bicarbonate, and mast-cell degranulation.

**Targets of Enteric Neurons**

The five primary targets of the enteric nerves of the gut are smooth-muscle cells responsible for gastrointestinal motility; mucosal secretory cells; gastrointestinal endocrine cells; the 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.

### Disorders of the Enteric Nervous System

Disorders of the enteric nervous system may result in motor, secretory, and inflammatory and immunologic dysfunction of the gut. The disorders associated with the degeneration or deficiency of enteric neurons are characterized by disturbances in gastrointestinal transit or functional obstruction. Intestinal secretory responses may also be suppressed, but the secretory deficiencies remain clinically unrecognized. On the other hand, disorders associated with pathologic excitation of motor and secretomotor enteric reflexes by toxins and inflammatory mediators are generally not associated with morphologic abnormalities of the enteric nervous system, but may appear clinically as secretory diarrhea. Activation of the axon reflex involving intramural splanchnic primary afferent neurons may be important in immunologically mediated and inflammatory bowel diseases.

#### Motility Disorders

The movement of the intestine was the first function assigned to the enteric nervous system. Several types of motor activity are involved in intestinal propulsion, including peristalsis (Table 2), a wavelike propagation of a reflex that consists of contraction proximal to and relaxation distal to a bolus of food. The aboral propagation of this reflex results from the successive activation of afferent neurons, triggered by distention as the bolus moves down the gut. Figure 2 shows the basic circuits involved in this reflex.

Deficient or defective enteric neurons cause obstruction of function and lack of intestinal propulsion. The clinical disorders of the enteric nervous system can be classified according to the specific segment of the gastrointestinal tract they affect, but most of these diseases are generalized and involve more than one segment (Table 3).

**Achalasia**

Achalasia is characterized by a tonically contracted lower esophageal sphincter that fails to relax, resulting in functional obstruction of the esophagus. The lower two thirds of the esophagus, composed of smooth muscle, is also involved, and there are no peristaltic contractions. Achalasia is due to the nonselective loss of all myenteric neurons or to a selective loss or dysfunction of inhibitory neurons containing vasoactive intestinal poly-
Peristalsis is the result of a series of local reflexes, each consisting of a contraction of intestinal muscle above an intraluminal stimulus and a relaxation of muscle below the stimulus (inset, upper-left-hand corner). The release of 5-HT by mucosal stimulation or mechanical distention of the gut lumen (main panel) triggers activity in the intrinsic afferent neurons (●). Above the site of the stimulus, ascending cholinergic interneurons (□) relay this signal to excitatory motor neurons (▼) containing acetylcholine (ACh) and substance P. As a result, the circular-muscle layer above the stimulus contracts. At the same time, below the stimulus site, descending cholinergic interneurons activate inhibitory motor neurons that contain nitric oxide (NO), vasoactive intestinal polypeptide (VIP), and ATP, causing relaxation. The resultant forces propel the bolus in an antegrade direction. As the bolus moves, it triggers similar local peristaltic reflexes at successive sites along the gut. The symbol ▲ represents afferent-nerve endings, ▼ efferent-nerve endings, the plus sign excitatory influence, and the minus sign inhibitory influence.

including paraneoplastic syndromes, Chagas’ disease, and Parkinson’s disease (Table 3). Herpesvirus, a neurotropic virus with a predilection to infect the squamous epithelium that lines the esophagus, has been reported with increased frequency in the myenteric plexus of patients with achalasia.

Gastric Stasis and Outlet Obstruction

Infantile hypertrophic pyloric stenosis is a congenital disorder characterized by functional gastric-outlet obstruction. Although the myenteric neurons appear normal, those innervating the circular-muscle layer of the pyloric sphincter lack nitric oxide synthase. In laboratory mice, disruption of the gene encoding the neuronal form of nitric oxide synthase results in functional gastric-outlet obstruction and gastric dilatation. Gastric stasis and dilatation can also occur after surgical vagotomy, with neuropathy associated with diabetes mellitus, with the use of anticholinergic drugs and opiates, and with sympathetic-nerve overactivity.

Acute Intestinal ileus and Chronic Intestinal Pseudo-obstruction

Acute intestinal ileus is characterized by the lack of motor activity in the intestine. Intestinal activity can be inhibited by the selective suppression of excitatory motor reflexes through sympathetic nerves or by sustained intrinsic inhibitory neural overactivity. Increased production of nitric oxide due to activation of the non-neuronal, inducible nitric oxide synthase may also result in acute intestinal ileus. However, intestinal ileus cannot be produced by the generalized suppression of neural activity in the gut. For example, the experimental application of tetrodotoxin, a puffer-fish toxin that blocks all neural transmission, removes tonic, neurogenic inhibition and unmasks spontaneous, myogenic excitation in the gut, producing increased contractile activity rather than ileus. The increased contractile activity is uncoordinated and therefore nonpropulsive, leading to functional bowel obstruction. In this manner, the degeneration and chronic dysfunction of enteric neurons can lead to chronic intestinal pseudo-obstruction. Acute ileus and chronic intestinal pseudo-obstruction

peptide and nitric oxide in the myenteric plexus of the esophagus. The relative preservation of cholinergic innervation to the lower esophageal sphincter may be 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 treating patients with achalasia. The cause of primary achalasia in most patients in the United States is not known. Several diseases that cause enteric neural dysfunction may result in secondary forms of achalasia,
Hereditary cerebellar ataxia
Autosomal recessive disorder associated with cerebellar ataxia and degeneration of esophageal myenteric-ganglion cells.
Childhood disorder characterized by ataxia and diffuse esophageal spasm in patients and family members. Some patients have mental retardation.

Congenital esophageal stenosis
Congenital disorder involving a narrowed esophageal lumen, often associated with tracheobronchial remnants or multiple webs. Lack of enteric innervation with nitric oxide reported in some patients.

Functional gastric-outlet obstruction

Intestinal pseudo-obstruction
Autosomal recessive disorder characterized by dilatation of jejunum and ileum and degeneration and loss of neurons.

Megacolon
Congenital disorder characterized by colonic dilatation proximal to an aganglionic, contracted distal colon and rectum. Caused by gestational failure of neural crest cells to migrate to distal colon. An autosomal dominant form has been reported with mutations of the RET gene, and an autosomal recessive form with mutation of the endothelin-B–receptor gene.

Waardenburg’s syndrome
Hirschsprung’s disease characterized by a white forelock, white eyebrows and lashes, and a light-brown iris with a mosaic pattern. Phenotype resembles that of piebald lethal mouse with mutation of the endothelin-B–receptor gene.

Santos’ syndrome
Hirschsprung’s disease with renal agenesis, polydactyly, hypertelorism, and deafness. Phenotype resembles that of RET knockout mouse.

Multiple endocrine neoplasia type 2A (MEN-2A)
Features similar to those of Hirschsprung’s disease. Medullary thyroid cancer, parathyroid hyperplasia, and phaeochromocytoma are characteristic. Mutation of RET gene reported.

Generalized, with hyperganglionosis
Achalasia and pseudo-obstruction reported with ganglioneuromatosis of myenteric and submucosal plexuses. Medullary thyroid cancer, phaeochromocytoma, and mucosal neuromas are characteristic. Mutation of RET gene reported.

Neurofibromatosis (von Recklinghausen’s disease)
Achalasia and megacolon reported, with neuronal dysplasia of the myenteric plexus. Central nervous system tumors, neurofibromas, pigmented iris hamartomas, café au lait spots, and mental retardation are characteristic.

Myotonic dystrophy
Autosomal dominant disorder characterized by dilatation of jejenum and ileum and degeneration and loss of neurons.

Neuronal intranuclear-inclusion disease
Esophageal dysmotility, delayed gastric emptying, achalasia, and pseudo-obstruction reported, with intranuclear neuronal calcifications.

Polymicrogyria, ophthalmoplegia, leukoencephalopathy, and intestinal pseudo-obstruction (POLIP) syndrome
Gastric and duodenal dilatation, with endoneural fibrosis and vacuolation of enteric neurons. Sensorimotor polyneuropathy is thought to account for the lack of relaxation of the diseased segment.

Hirschsprung’s disease is a congenital disorder characterized by the absence of enteric neurons in the distal colon and rectum. The aganglionic gut loses its tonic neural inhibition and thus remains contracted, obstructing the passage of food residue. The absence of inhibitory neurons containing nitric oxide and vasoactive intestinal polypeptide is thought to account for the lack of relaxation of the diseased segment.

Hirschsprung’s disease is a heterogeneous genetic disorder that leads to problems with the migration and development of undeveloped ganglion cells in the myenteric plexus and a reduced number of argyrophilic neurons.

Table 3. Motility Disorders of the Enteric Nervous System.
mment of neural-crest cells into the enteric nervous system of the distal gut. Some patients with an autosomal dominant form of the disease have mutations in the \(\text{RET}\) gene,\(^{16,47}\) and many patients with an autosomal recessive form of the disease have a mutation of the gene for the endothelin-B receptor.\(^{16}\) Patients with Santos’ syndrome,\(^{50}\) which includes Hirschsprung’s disease but also renal agenesis and other anomalies, similarly, patients with Waardenburg’s syndrome\(^{49}\) have not only Hirschsprung’s disease accompanied by extraintestinal manifestations that include pigmentary disorders. Patients with piebaldism, a disorder of hypopigmentation,\(^{66}\) and patients with multiple endocrine neoplasia type 2B (MEN-2B) and are due to ganglioneuromas of the gastrointestinal tract that cause achalasia and pseudo-obstruction\(^{17}\); some patients with MEN-2B have mutations in the \(\text{RET}\) gene.\(^{18}\) That muta-

**Generalized Disorders of Motility**

More than one segment of the gastrointestinal tract is involved in patients with generalized motility disorders of the enteric nervous system. These disorders can be divided into two groups on the basis of hyperganglionosis or hypoganglionosis of the enteric nervous system. Hyperganglionosis is also referred to as neuronal dysplasia or ganglioneuromatosis. Gastrointestinal symptoms are common in patients with multiple endocrine neoplasia type 2B (MEN-2B) and are due to ganglioneuromas of the gastrointestinal tract that cause achalasia and pseudo-obstruction\(^{17}\); some patients with MEN-2B have mutations in the \(\text{RET}\) gene.\(^{18}\) That muta-

**Figure 3. Secretomotor Actions of Cholera Toxin.**

According to a view held earlier (inset), cholera toxin binds to brush-border receptors in the intestinal crypts and activates adenyl cyclase. The resulting increase in the intracellular concentration of cyclic AMP leads to the secretion of chloride from enterocytes, with a net secretion of fluid. In the current understanding (main panel), cholera-toxin–induced diarrhea results from the actions of the toxin at three distinct sites, indicated by numbered circles. Besides its direct action on enterocytes (site 1), cholera toxin acts through enteric neurons to stimulate enterochromaffin cells (ECC, site 2) and cause the release of 5-HT, which stimulates intrinsic afferent neurons (C) that activate three distinct groups of interneurons (denoted by \(\square\) in myenteric ganglia. The first group (A) activates secretomotor neurons (> containing vasoactive intestinal polypeptide (VIP), causing submucosal vasodilation and secretion by crypt cells. The second group (B) activates motor neurons, causing giant peristaltic contractions that are electrically identified as migrating action-potential complexes. The third group (C) activates a series of interneurons that transmit the secretory effects of cholera toxin to distal sites. Finally, cholera toxin can stimulate secretomotor neurons directly (site 3). Neurons containing somatostatin (SOM) and postganglionic sympathetic neurons containing norepinephrine (NE) may act on secretomotor neurons containing vasoactive intestinal polypeptide to inhibit secretion. The symbol \(\wedge\) represents afferent-nerve endings, and \(\wedge\) efferent-nerve endings.

tations in the same gene may cause hyperganglionosis on the one hand and hypoganglionosis (Hirschsprung’s disease) on the other hand may be explained by the degree of loss of the \(\text{RET}\) gene product that results from different mutations.\(^{67}\)

Most of the generalized disorders associated with hypoganglionosis are caused by acquired diseases that lead to the destruction or degeneration of enteric neurons, as in Chagas’ disease and the paraneoplastic syndromes. Congenital generalized syndromes in which the enteric ganglia are deficient can also occur, as for example the syndrome of short small bowel, malrotation, and pyloric hypertrophy.\(^{68}\) Moreover, gastrointestinal motility disorders could result from developmental abnormalities of other elements of the enteric nervous system, such as the interstitial cells. Defects in the interstitial cells due to mutations in the \(\text{KIT}\) gene in patients with piebaldism, a disorder of hypopigmentation, could explain the functional gut abnormalities reported in some patients.

**Diarrhea Due to Noninvasive Secretagogues**

A wide variety of luminal chemicals and noninvasive secretagogue toxins, including ethanol, bile salts (deoxycholic acid), heat-stable toxins of *Escherichia coli*, and cholera toxin, activate intestinal secretomotor reflexes by stimulating mucosal receptors that are exposed to luminal contents. In vitro, cholera toxin stimulates enterocytes by binding to brush-border receptors and activating adenyl cyclase, leading to elevated intracellular concentrations of cyclic AMP that cause chloride and water to be secreted from crypt cells. In the past, the secretory action of cholera toxin was thought to be solely due to its action on enterocytes (Fig. 3). In vivo, however, the secretion of fluid in response to the application of cholera toxin to the mucosal surface of the rat ileum
can be reduced by nerve blockers, such as lidocaine or tetrodotoxin, or by nicotinic-receptor blockade with hexamethonium.7 This response was also reduced by a combination of 5-HT$_3$- and 5-HT$_2$-receptor antagonists, but not by extrinsic denervation or treatment with capsaicin, which selectively destroys splanchnic primary afferent nerves containing substance P.$^{59-71}$ Therefore, the secretory response to cholera toxin appears to involve an intrinsic secretomotor reflex (Fig. 3). Moreover, interneurons or secretomotor neurons in the myenteric rather than the submucosal plexus appear to participate, because the response is reduced by the serosal application of benzyl ammonium chloride, which destroys the myenteric plexus.72 The secretory effects of cholera toxin applied in the jejunum are evident not only locally but also distally in the colon. The colonic effect does not seem to involve humoral mediators or extrinsic nerves, but rather to involve intrinsic neural reflexes, indicating widespread activation of the enteric nervous system.73 Therefore, the enteric nervous system has a major role in the secretory action of cholera toxin in vivo. Agents that cause intestinal hypersecretion may also induce motor abnormalities that contribute to diarrhea. Toxigenic E. coli, cholera toxin, and ricinolic acid elicit giant peristaltic contractions and associated migrating action-potential complexes in the intestinal musculature distal to the segment where the toxin is applied.$^{30,31}$

**Inflammatory and Immunologically Mediated Bowel Diseases**

*Clostridium difficile* toxin A is known to cause a necrotic-inflammatory response, with infiltration of neutrophils and increased fluid secretion in the gut. The inflammatory and secretory effects of this toxin, like those of cholera toxin, involve intrinsic neural pathways, but different pathways are involved (Fig. 4). Through these pathways, *C. difficile* toxin A leads to mast-cell degranulation and the secretion of multiple inflammatory mediators, including prostaglandins, histamine, and 5-HT. These mediators may stimulate secretomotor reflexes, including submucosal vasodilatation.75 The release of calcitonin gene–related peptide from primary afferent neurons innervating submucosal arterioles is also involved in the vasodilatation.76 The mast-cell degranulation and inflammatory effects involve the activation of nerves, because these effects of the toxin are suppressed by neural blockade.77 Furthermore, pretreatment with capsaicin, which selectively destroys substance P–containing primary afferent neurons as well as antagonists to substance P,78 also inhibits the secretory and inflammatory response to toxin A, suggesting that the action of the toxin is transduced by substance P–containing primary splanchnic afferent fibers. In addition to its secretory effects, *C. difficile* toxin A also produces a pattern of intestinal motility that is characterized by trains of contractions representing repeated bursts of action potentials.

Several lines of evidence support a possible role for the enteric nervous system in the pathogenesis of inflammatory bowel disease. Psychological stress may exacerbate inflammatory bowel disease, suggesting important interactions among the brain, enteric nervous system, and gastrointestinal tract. In both Crohn’s disease and ulcerative colitis, the immunoreactivity of substance P is increased and binding sites for the substance P receptor are expressed more widely.$^{79,80}$ Substance P probably has proinflammatory actions in the gut, and substance P–receptor antagonists decrease the infiltration of granulocytes in rats with colitis that is induced by trinitrobenzenesulfonic acid.$^{81}$ Finally, the topical and
The enteric nervous system is increasingly recognized as having a central role in the physiologic and pathophysiologic features of the gastrointestinal tract. Despite recent progress, little is known about the details of the neural circuitry and the neurotransmitters involved. Further advances in our understanding of the enteric nervous system will have important implications for the treatment of a wide variety of gut disorders. While illuminating the workings of the “little brain” of the gut, these advances may also help unravel the workings of the brain itself.

REFERENCES
