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# Subject Review

## Disorders of Gastrointestinal Motility in Neurologic Diseases

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**Neurologic diseases can affect the bowel at several levels of innervation—by altering the electrical activity that controls smooth muscle, the enteric nervous system, or the extrinsic neural pathways to the gut. This review concentrates on disorders of motility that occur in conjunction with diseases of the extrinsic neural supply (from the level of the brain to the postganglionic fibers) and those generalized disorders that affect gut smooth muscle. Modern technology, such as gastrointestinal scintigraphy and manometric techniques that measure esophageal, gastroduodenal, and anorectal motility (intraluminal pressures), has provided better methods to study the pathophysiologic aspects of gut motility in diseases of the nervous system. Distinguishing the neuropathies of the extrinsic nervous system from those of the intrinsic (enteric) nervous system is not always possible because the available techniques evaluate only the end-organ—that is, the motor function of the gut. Degenerative or infiltrative (myopathic) disorders of gut smooth muscle, however, can be distinguished from such neuropathies, and careful and systematic evaluation of autonomic function can often identify the level of disordered function in the neural-gut axis.**

The intimate relationship between neurologic function and gastrointestinal motility has been known for decades. Langley and associates<sup>1,2</sup> noted that intractable diarrhea developed in animals subjected to ganglionectomy. The inhibitory role of the sympathetic extrinsic supply to gut smooth muscle and its excitatory effects on gut sphincters are well known; nevertheless, clinicians rarely associate gastrointestinal dysfunction with disturbances in sympathetic control. In contrast, the effects of surgical or traumatic neural lesions are fully appreciated in

clinical practice, as in postvagotomy gastric stasis or diarrhea and acute transient ileus after transection of the spinal cord.

This review addresses the disorders that affect the extrinsic neural supply to the gut and generalized muscle disorders that involve the motor function of the gut. The emphasis is on gastric, small bowel, and colonic motility, inasmuch as discussions of deranged oropharyngeal, esophageal, or anorectal motility in neurologic disorders are readily available in standard texts<sup>3</sup> or recent reviews.<sup>4</sup>

A practical classification of these disorders is proposed, based on the anatomic level of the neural or muscular disease. Examples of such disorders are provided for each anatomic level, with additional detail for the more common conditions such as diabetic neuropathy. The discussion is focused on general neuromuscular

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disorders rather than disturbances of the myenteric plexus alone because the latter were extensively reviewed in the recent literature.<sup>5</sup> For each neurologic disease discussed, the salient clinical features, pathophysiologic characteristics, and histologic evidence of gut involvement are described. In several areas, the literature is limited to case reports or observations of few cases, a reflection of the rarity or the relatively unexplored nature of some neurologic disorders that may affect the gut. In contrast, the more commonly observed effects of surgical vagotomy and pudendal nerve injury are not discussed. A practical approach for the identification of extrinsic neurologic disease in patients with symptoms suggestive of gastrointestinal motor dysfunction is included at the end of this review. A discussion of treatment is beyond the scope of this article.

Whereas the morphologic features of the myenteric plexus and smooth muscle in patients with intestinal pseudo-obstruction have been studied extensively,<sup>5</sup> histologic and physiologic evaluations rarely have assessed the extrinsic neural control in such patients. Extrinsic denervation may be associated with a disturbance of the myenteric plexus, such as in experimental isoniazid-induced damage of the myenteric plexus<sup>6</sup> and in many conditions discussed in this review.

Before the clinical syndromes are considered, it is necessary to point out that diverse methods and terms are used to measure and describe "motility." Moreover, pressure activity, myoelectric activity, and transit data do not necessarily correspond to one another. There is also a plethora of overlapping terms, and purely descriptive terms, such as "bursts" of phasic pressure activity or "interdigestive motor complex-like activity," are used. An attempt has been made to use uniform terminology throughout this article. "Bursts" are defined as a series or a cluster of phasic contractions that last more than 2 minutes, usually unassociated with propagation and sometimes associated with tonic changes in baseline pressure. "Interdigestive motor complex-like activity" refers to a postprandially propagated activity front with the

same propagation velocity and maximal frequency of contractions as in phase III of the interdigestive motor complex.

## **INTERACTIONS BETWEEN EXTRINSIC NERVOUS SYSTEM AND GUT**

Brain and gut interactions have been explored experimentally in animals, and recently in humans, by using vestibular and central autonomic stimuli.<sup>7,8</sup> Perhaps these neural-gut interactions are best demonstrated by the disturbances of motor function of the gut in neurologic disease. In recent years, better methods have been developed to study gastrointestinal motility (by manometry and transducers that record intraluminal pressures) and transit (by radio-scintigraphy) in health and disease, including those conditions that affect its neuromuscular function. Other investigators have studied the morphologic features of the myenteric plexus neurons in gastrointestinal motor dysfunction and have drawn attention to derangements of the enteric plexuses in disease.<sup>5</sup> In general, no etiologic distinction can be made when myenteric plexus neurons have a similar histologic appearance.

A practical classification of neuromuscular disorders that affect gut motility is proposed in this article; it is based on the proven or likely anatomic level of the lesion (Table 1). The cited examples of disease processes at various levels affecting the motor function of the gut suggest that an anatomic approach should provide a useful framework for the clinical evaluation of patients with disorders of gut motility in whom neurologic disease is suspected. Assessment of the function of the autonomic nervous system and the histopathologic changes in the gut and its neural connections may provide clues to the cause and mechanisms of gastrointestinal symptoms and may lead to novel therapeutic strategies in the future. Although some of the available literature concerns only small numbers of patients or single cases, a thorough examination of these reports provides a framework that supports our strategy to classify and evaluate such conditions clinically on an anatomic basis from the level of the brain to the postganglionic fi-

Table 1.—**Neuromuscular Disorders Affecting Gastrointestinal Motility**

<i>Enteric nervous system</i>	
Idiopathic, degenerative, or inflammatory disorders of the myenteric plexus	
Some disorders of the enteric nervous system may be associated with diseases that affect extrinsic neural control	
<i>Extrinsic nervous system</i>	
Peripheral nerves	
Acute (for example, Guillain-Barré syndrome)	
Chronic (for example, diabetes mellitus, amyloidosis)	
Autonomic nervous system degenerations (for example, idiopathic orthostatic hypotension, pandysautonomia)	
Spinal cord (for example, injury, multiple sclerosis)	
Brain stem (for example, tumor)	
Higher centers (for example, epilepsy)	
<i>Smooth muscle</i>	
Infiltration of muscle by generalized disease (for example, amyloidosis, scleroderma)	
Generalized muscle disease affecting the gut (for example, dermatomyositis, dystrophia myotonica, other muscular dystrophies)	

bers (extrinsic), myenteric plexus, or smooth muscle.

## **NORMAL GASTROINTESTINAL MOTOR FUNCTION**

Esophageal motility is characterized by an organized propagation of phasic contractions through the esophagus with each swallow. In the upper and lower sphincters, relaxation occurs with swallowing, and subsequent contraction occurs with arrival at the sphincter of the pressure wave that is propagated through the pharynx or esophagus. Such contractions result in peristalsis of solid and liquid boluses and, to some extent, the prevention of reflux through the sphincters.

Normal motor function of the foregut and midgut is characterized by the occurrence of cyclic motor activity during fasting and the development of triturating, mixing, and propulsive activity postprandially. The fasting phase is characterized by the interdigestive motor complex (Fig. 1), which commences in the gastroduodenal region and propagates for a variable distance down the small bowel.<sup>10</sup> This cyclic

activity consists of three phases: phase I, quiescence; phase II, intermittent phasic pressure activity (contractile activity that is unassociated with alterations in muscle tone); and phase III, an "activity front" during which regular repetitive contractions occur at the maximal frequency typical of each region. The interdigestive motor complex propagates a variable distance down the gut and has been likened to a "housekeeper," sweeping residual products of digestion and fasting debris toward the colon. There is also evidence that similar, albeit less regular, cyclic motor activity occurs in the colon. Postprandially, gastric and small bowel contractions of variable amplitude occur irregularly (Fig. 1) although fairly consistently, depending on the size and the nutrient content of the meal. These contractions result in the trituration of solid food in the stomach and the steady propulsion of solids and liquids through the stomach and small bowel.

Colonic motility is characterized by fasting cyclic activity, intermittent irregular contractions, and mass movements. This last characteristic is associated with giant migrating contractions that result in bolus movements through the normal ileum and expulsion during defecation. For defecation, an integrated relaxation of the anal sphincter and the puborectal muscle is necessary.

Symptoms of gastrointestinal motor dysfunction are thought to originate from the regional abnormalities in contractile activity. Gastric emptying may be delayed as a result of impaired trituration of solid food (antral hypomotility) or impaired aboral flow of chyme (intestinal dysmotility) from the stomach;<sup>11,12</sup> constipation may be attributable to impaired colonic contractile activity, and incontinence results from dysfunction of the anal sphincter.

## **CONTROL OF GASTROINTESTINAL MOTILITY**

In order to understand the basis for disturbances in motor function of the gut due to extrinsic neuropathies, the factors that control gastrointestinal motility will be considered briefly. Gastrointestinal motility and normal transit are

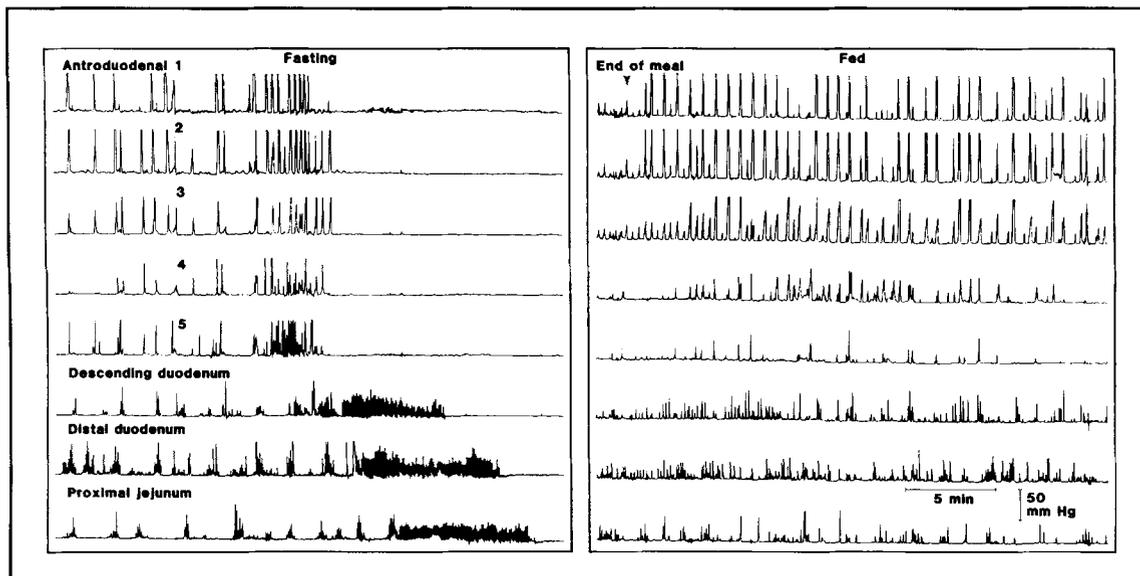


Fig. 1. Normal fasting and postprandial motility in healthy human volunteer. Note cyclic interdigestive migrating motor complex (*left panel*) and sustained, high-amplitude but irregular pressure activity after meal (*right panel*). Antroduodenal ports are separated by 1 cm; small bowel ports are each 10 cm apart. (From Malagelada and associates.<sup>9</sup>)

the end results of an intricately balanced series of control mechanisms: the electrical and contractile properties of the smooth muscle cell and control by the intrinsic nervous system, extrinsic neural pathways (sympathetic and parasympathetic), and gastrointestinal neuropeptides (which may act as neurotransmitters as well as having hormonal or paracrine functions).

The electrical properties of the smooth muscle of the gut<sup>10</sup> are the result of transmembrane fluxes of ions, which, as in other excitable tissues, alter the membrane potential. Spontaneous fluctuations in membrane potential lead to an inward calcium flux by altering calcium channels, and they serve to trigger muscle contraction.

Some regions of the gut (such as the outer lamella of jejunal circular muscle<sup>10</sup> and the internal anal sphincter<sup>13</sup>) generate transmembrane potential differences (slow waves) that are unassociated with a rapid action potential (or "spike"). Nevertheless, contractile activity may be seen. Other regions demonstrate both a slow wave and an action potential (for example, gastric and inner lamella of jejunal circular muscle<sup>10</sup>), and the contractile response occurs only when spikes

are generated (Fig. 2). The significance of these differences in myoelectric activity is unclear. Infiltrative or degenerative processes that affect the smooth muscle of the gut (see subsequent material) prevent the occurrence of normal contractions and result in disorders of gastrointestinal motility.

The intrinsic or enteric nervous system<sup>14</sup> contains about  $10^8$  neurons, approximately the number present in the spinal cord. This integrative system differs in form and is separate from the sympathetic and parasympathetic portions of the autonomic nervous system. This system has sensory receptors (for example, mechanoreceptors and chemoreceptors), interneurons that process this sensory input and that control effector units, and motor neurons that serve as the primary effector cells involved in motor activity of the gut. An integrative synaptic circuitry serves to control the coordinated behavior of the entire gastrointestinal tract. The synaptic pathways in the gut have been compared to a series of preprogrammed circuits that are capable of self-adjustment on the basis of sensory input; moreover, they can be altered by extrinsic control from the central nervous system.

As in other regions of the nervous system, neurochemical transmission at the cell bodies of enteric neurons involves excitatory and inhibitory, fast and slow postsynaptic potentials. Each type of postsynaptic potential has a specific neurotransmitter (or neurotransmitters) and ionic mechanism. For example, slow excitatory postsynaptic potentials (mediated by serotonin, substance P, and possibly other neurotransmitters) result in receptor-mediated decreases in the resting membrane conductance for potassium ions. They seem to be responsible for activation of a network of effector (for example, motor) neurons, such as the simultaneous development of a "slow wave" in smooth muscle cells. This "electromyogram of the gut" encompasses the entire circumference of a segment of the gastrointestinal tract. Slow excitatory postsynaptic potentials probably also facilitate the neuromodulation of conduction by other neural synaptic input and by paracrine and endocrine factors.<sup>14</sup>

The integration between the enteric and the autonomic extrinsic nervous system occurs partly through the excitatory vagal pathway. This pathway is composed of preganglionic cholinergic fibers that synapse with myenteric cholinergic neurons, which in turn excite smooth muscle. A second integrative mechanism is provided by the sympathetic supply, which inactivates neural circuits that generate motor activity while allowing continuous activity of intrinsic inhibitory innervation of the musculature. Extrinsic vagal fibers also synapse with nonadrenergic inhibitory intramural neurons in the gut. This presynaptic inhibition is mediated by several transmitters, including norepinephrine (at  $\alpha_2$ -adrenergic receptors), serotonin, opioid peptides, acetylcholine (at presynaptic muscarinic receptors), and histamine (at presynaptic  $H_3$  receptors). Loss of this inhibitory influence would be expected to result in excessive or uncoordinated phasic pressure activity in the gut. Indeed, as will be apparent throughout this review, patients with intrinsic or extrinsic neurologic disorders have such uncoordinated pressure activity.

The roles of biogenic amines and peptides in the control of gastrointestinal motility are clear-

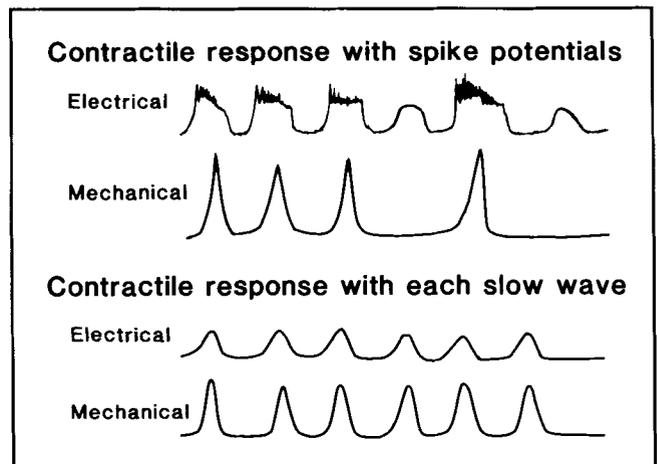


Fig. 2. Relationship between electrical control activity and contractile response of gastrointestinal smooth muscle. In some tissues (for example, antrum or inner circular muscle of jejunum), contractions occur only in conjunction with the development of spike potentials (*upper tracings*); in other tissues (for example, internal anal sphincter), each slow wave is associated with a mechanical response (*lower tracings*).

ly demonstrated by their involvement in the intrinsic and extrinsic neural control.

The extrinsic innervation of the gut<sup>15</sup> consists of the parasympathetic vagal and sacral nerves (S-2, 3, and 4) by means of the pelvic nerves and the sympathetic outflow from the intermediolateral column of the spinal cord, between the levels of the fifth thoracic and third lumbar segments (Fig. 3). The sympathetic nerves synapse in the celiac, superior mesenteric, and inferior mesenteric ganglia, and the territories of neural supply in the gut generally correspond to the vascular supply of the respective arterial trunks. Extrinsic nerves are intimately involved in the control of the striated muscle portions of the esophagus and the external anal sphincter. Although the smooth muscle portion of the gut can function fairly normally without the extrinsic nerves, the latter are known to modulate the intrinsic neural circuits and to integrate activity in widely separated regions of the gastrointestinal tract. Furthermore, extrinsic nerves exert more important control in certain regions (for example, the stomach and distal portion of the colon) than in others (such as the small bowel).

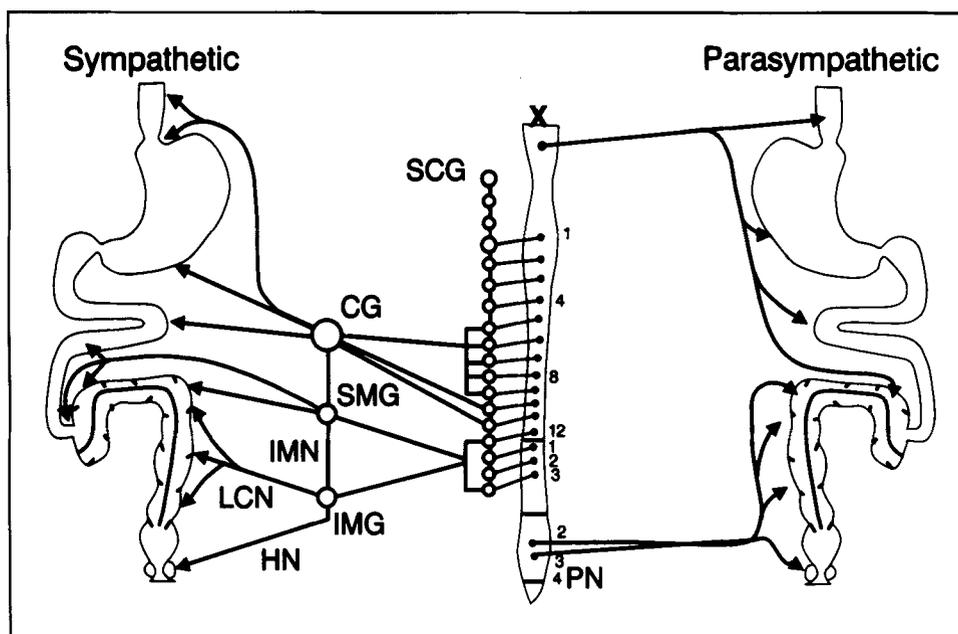


Fig. 3. Extrinsic innervation of the gut. CG = celiac ganglion; HN = hypogastric nerves; IMG = inferior mesenteric ganglion; IMN = inferior mesenteric nerve; LCN = lumbar colonic nerves; PN = pelvic nerves; SCG = superior cervical ganglion; SMG = superior mesenteric ganglion; X = vagal nuclei.

### EXTRINSIC NEUROLOGIC DISORDERS CAUSING GUT DYSMOTILITY

Although disturbed gut motility may result from alterations in the contractility or electrical control activity of the gut muscle cell, enteric nervous system, or extrinsic nerve supply, the intimate interrelationships among these three levels of control often make it difficult to determine the predominant disturbance along the pathway. In many instances, however, it is possible to distinguish the following (Table 1): disorders that affect the gut muscle ("myopathic disorders"); those of the myenteric plexus, usually in the form of an idiopathic, chronic intestinal pseudo-obstruction;<sup>15</sup> and diseases of the extrinsic pathways that supply the gut. Nevertheless, some diseases affect both intrinsic and extrinsic neural control. Because this review concentrates mainly on diseases of extrinsic control, those illnesses that affect both extrinsic and intrinsic neural function are considered in this section on extrinsic neurologic disorders.

**Acute Peripheral Neuropathy.**—Autonomic dysfunction associated with certain acute viral

infections may result in nausea, vomiting, abdominal cramps, constipation, or a clinical picture of pseudo-obstruction, as shown by review of several individual case reports. Thus, in the Guillain-Barré syndrome, visceral involvement may include gastric dilatation<sup>16</sup> or adynamic ileus.<sup>17</sup> Persistent gastrointestinal motor disturbances may also occur in association with infections with herpes zoster,<sup>18</sup> Epstein-Barr virus,<sup>19</sup> or botulism B.<sup>20</sup> Whether these infections result in an intrinsic or extrinsic neuropathy that affects the gut is uncertain; however, some investigators have shown that intestinal pseudo-obstruction may result from cytomegalovirus infection of the myenteric plexus.<sup>21</sup> No formal motility studies have substantiated the gastrointestinal motor dysfunction in these situations, and perhaps different viruses affect different levels of gut neural control but result in the same clinical picture.

**Chronic Peripheral Neuropathy.**—Chronic peripheral neuropathy, predominantly due to diabetes mellitus or amyloidosis, is the most commonly encountered extrinsic neurologic dis-

order that results in gastrointestinal motor dysfunction.

**Diabetes Mellitus.**—Diabetic autonomic neuropathy of the gut has been studied extensively during the past decade.<sup>22</sup> Gastrointestinal symptoms are exceedingly common in patients with diabetes; in one study, 76% of 136 unselected outpatients with diabetes reported having nausea and constipation.<sup>23</sup> Gastric emptying of digestible or nondigestible solids in patients with diabetes mellitus and gastrointestinal symptoms ("gastroparesis") is abnormal; however, little is known about the pathogenesis or treatment of this relatively common disorder. Studies in humans have demonstrated the paucity of antral contractions in the distal portion of the stomach during phase III of the interdigestive motor complex and during the postprandial period.<sup>24</sup> Other potentially important pathophysiologic changes (Fig. 4) in gastroparesis are decreased postprandial duodenojejunal phasic pressure activity, nonpropagated uncoordinated bursts of contractions in the proximal portion of the small bowel,<sup>25</sup> and pylorospasm.<sup>26</sup>

Constipation is a frequent, although often unreported, symptom in patients with diabetes,<sup>23</sup> but little is known about its pathogenesis. In contrast, diarrhea or fecal soiling (or both) may result from several mechanisms: dysfunction of the anorectal sphincter or abnormal rectal sensation that leads to incontinence;<sup>27,28</sup> osmotic diarrhea from bacterial overgrowth due to small bowel stasis or rapid transit from uncoordinated small bowel motor activity;<sup>25</sup> or associated gluten-sensitive enteropathy<sup>29</sup> or pancreatic exocrine insufficiency.<sup>30</sup> For treatment that is rational and effective, the underlying mechanism must be identified.

Histopathologic studies of the vagus nerve in a patient with diabetes revealed a severe reduction in the density of unmyelinated axons and a small caliber of the surviving axons.<sup>31</sup> In patients with diabetic diarrhea, the sympathetic nervous system demonstrates giant sympathetic neurons, dendritic swelling of postganglionic neurons in prevertebral and paravertebral ganglia,<sup>32</sup> and reduced fiber density in the splanchnic nerves.<sup>33</sup> Although histologic studies of the

myenteric plexus in the gut of humans with diabetes demonstrated no abnormalities,<sup>34,35</sup> the streptozocin-treated rat had a reduction in sympathetic fibers in the myenteric plexus.<sup>36</sup> Studies in such rats also showed abnormal release of acetylcholine in response to administration of veratridine<sup>37</sup> and abnormal release of vasoactive intestinal polypeptide and calcitonin gene-related peptide in response to electrical field stimulation from myenteric plexus neurons.<sup>38</sup> The same authors also noted selective damage of neurons that contained calcitonin gene-related peptide in the myenteric plexus of rats with diabetes.<sup>39</sup> The abnormal voltage-tension curves of diabetic gastric smooth muscle studied *in vitro* (Szurszewski JH: Unpublished observation) suggest an abnormality in neural control. The earlier report of hyaline bodies of unknown origin in gut smooth muscle<sup>40</sup> has not been confirmed by other groups.

Peripheral cholinergic agonists such as metoclopramide,<sup>24</sup> bethanechol,<sup>24</sup> and cisapride,<sup>41</sup> as well as agents that affect the adrenergic nerve supply to the gut such as the  $\alpha_2$ -adrenergic agonist clonidine,<sup>42</sup> have been used to treat diabetic gut neuropathy. A complete understanding of the mechanism of these complications is lacking, however, inasmuch as all available therapeutic options have resulted in only transient relief.<sup>43,44</sup> Measures that reverse the metabolic derangement in diabetic nerves, such as aldose reductase inhibition,<sup>45,46</sup> provide another approach, one that may correct abnormal peripheral nerve conduction in short-term<sup>47</sup> and long-term studies<sup>48</sup> and increase the number of regenerating myelinated fibers.<sup>46,48</sup> This strategy is clearly important because glucose control alone does not substantially improve peripheral nerve function in patients with diabetes.<sup>49</sup>

**Amyloid Neuropathy.**—Amyloid neuropathy may lead to diarrhea and steatorrhea,<sup>50</sup> in contrast, some patients with amyloidosis have infiltration of gut smooth muscle and a low-amplitude pressure profile<sup>9</sup> that commonly leads to a myopathic pseudo-obstruction or constipation.<sup>51-54</sup> Patients with amyloid neuropathy demonstrate uncoordinated nonpropagated phasic pressure bursts in the small bowel<sup>55</sup> that

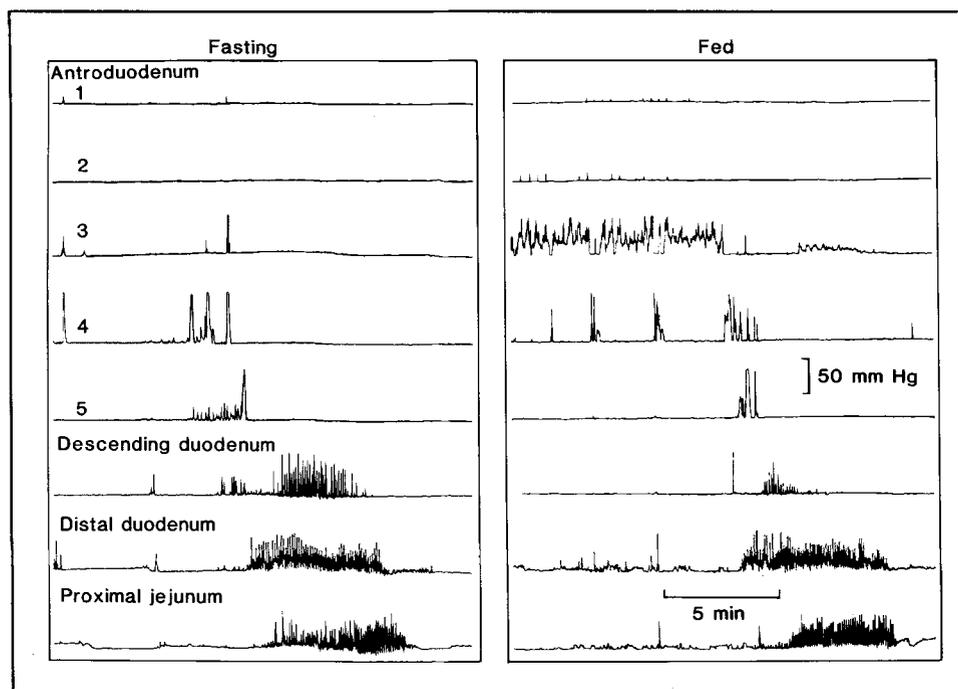


Fig. 4. Classic abnormalities in manometric profile of diabetic gut dysmotility. Position of manometric ports as in Figure 1. Note absence (leads 1 through 5) of antral component of fasting interdigestive motor complex and abnormal propagation of activity front (phase III) through proximal small bowel (retrograde propagation between leads 6 and 7). In postprandial period, frequency of antral contractions is reduced, phasic and tonic pressure activity is prominent at level of pylorus, and meal fails to inhibit interdigestive motor complex. (From Colemont LJ, Camilleri M: Chronic intestinal pseudo-obstruction: diagnosis and treatment. *Mayo Clin Proc* 64:60-70, 1989.)

are similar to the intestinal myoelectric disturbances in animals that have been subjected to ganglionectomy.<sup>56</sup> Familial amyloidosis may also affect the gut.<sup>51-59</sup> Severe reduction in number or degeneration of ganglion cells occurs without extensive deposition of amyloid in the enteric plexus in familial cases;<sup>59</sup> the mechanism of this degenerative process is unclear.

Manometric studies and monitoring of the acute effects of cholinomimetic agents<sup>54</sup> can distinguish between neuropathic (uncoordinated but normal-amplitude pressure activity) and myopathic (low-amplitude phasic pressure activity) types of amyloid gastroenteropathy.<sup>55</sup> Such approaches may also indicate which patients should respond to cholinomimetic agents.

**Chronic Autonomic Neuropathy With Neuronal Intranuclear Inclusions.**—A rare familial, autosomal recessive disorder known as

chronic autonomic neuropathy with neuronal intranuclear inclusions<sup>60</sup> can be associated with gut dysmotility. Some patients have autonomic dysfunction that affects the eyes, sweat glands, and heart. Other patients have impaired spinocerebellar function and, less commonly, extrapyramidal features. The 3- to 10- $\mu$ m-diameter protein intranuclear inclusions occur in the myenteric plexus and various other regions in the nervous system.<sup>5</sup> Thus, the same disease process may affect the neural control of gut motility at more than one level; identification of a lesion of the myenteric plexus does not exclude a concomitant disorder of the extrinsic pathways.

**Chronic Sensory and Autonomic Neuropathy of Unknown Cause.**—A nonfamilial form of slowly progressive neuropathy affecting various autonomic functions has recently been reported.<sup>61</sup> A sensory neuropathy also devel-

oped in this patient after about 20 years. During life, abnormalities of the postganglionic sympathetic and parasympathetic systems were detected; at postmortem examination, degenerative changes were detected in the posterior roots, dorsal columns of the spinal cord, peripheral nerves, sympathetic trunk, vagal nerve, and myenteric plexus. In contrast, neurons in the intermediolateral columns of the spinal cord were preserved. Patients may have only a chronic autonomic disturbance present for many years as a gastrointestinal dysfunction before involvement of the sensory nerves becomes apparent or in the absence of peripheral nerve dysfunction.<sup>62</sup> In most patients, however, cardiovascular or sweating abnormalities precede involvement of the gut.<sup>55</sup>

Other investigators have reported familial cases of intestinal pseudo-obstruction with degeneration of the myenteric plexus and evidence of sensory or motor neuropathies (or both) affecting peripheral or cranial nerves.<sup>63,64</sup> The autonomic supply to other viscera was not assessed in these reports.

**Neurofibromatosis.**—Von Recklinghausen's disease affects the motor function of the gut predominantly because of a lesion of the myenteric plexus<sup>65-67</sup> rather than the usual neurofibromas along the nerves. It has been associated with megacolon, which may be congenital<sup>67</sup> or may occur in the early infantile period<sup>68</sup> or later in adult life.<sup>67,68</sup> More commonly, however, gastrointestinal tumors occur in these patients, and 10% of patients with von Recklinghausen's disease in a study at the Massachusetts General Hospital<sup>69</sup> had pathologically proven gastrointestinal neurofibromatosis. In approximately 7% of patients, neurofibromas or leiomyomas were identified, most commonly in the jejunum and stomach. Gastrointestinal symptoms should lead to a search for a mass lesion in the gut before these symptoms are attributed to myenteric plexiform neuropathy. Jejunal manometric studies performed in one patient with this condition could not distinguish an intrinsic from an extrinsic gut neuropathy;<sup>9</sup> no signs of a mass lesion or mechanical obstruction were evident on small bowel roentgenography or manometry.

The histopathologic changes observed are angiomatosis,<sup>65</sup> a plexiform pattern on the dendritic processes of the ganglion cells in the myenteric plexuses,<sup>65</sup> and neuronal intestinal dysplasia.<sup>66</sup> Whereas these reports confirm the derangement of the enteric nerves in neurofibromatosis, they provide no information on the extrinsic nerves that supply the gut. There is, however, some evidence that the latter may be affected. In a patient with an achalasia-like disorder of the esophagus due to neurofibromatosis,<sup>70</sup> the lower (smooth muscle) portion of the esophagus was hypertrophic and contained few ganglion cells in the myenteric plexus, whereas muscle atrophy of the proximal third of the esophagus was attributable to vagal perineural fibrosis, findings that suggested an extrinsic neuropathy.

**Paraneoplastic Neuropathy.**—Autonomic neuropathy and gastrointestinal symptoms have been reported in association with carcinoma of the lung<sup>9,71-73</sup> or pulmonary carcinoid.<sup>73</sup> In the largest series (seven patients), all suffered constipation, six had gastroparesis, four had esophageal dysmotility suggestive of spasm or achalasia, and two had other evidence of autonomic neuropathy that affected bladder and blood pressure control.<sup>73</sup> Recently, my colleagues and I examined two patients with paraneoplastic intestinal pseudo-obstruction, both of whom had signs of cardiovagal or sympathetic dysfunction.<sup>74</sup> In four patients described in the literature,<sup>9,74</sup> results of manometric studies of the upper gastrointestinal tract were abnormal; treatment of a pulmonary tumor in one patient resulted in cessation of nausea and vomiting and restoration of the motility in the upper gut to normal.<sup>9</sup>

Histologically, the myenteric plexus showed degeneration and a decline in neurons and axons, inflammatory cell infiltration with lymphocytes and plasma cells, and glial cell proliferation. The submucous plexus was unaffected, and the extrinsic nerves were not examined.<sup>73</sup>

**Drug-Induced Neuropathy.**—Ileus caused by the alkaloid vincristine<sup>75</sup> is an example of a drug-induced neuropathy that affects motor function of the gut. The neuropathy is presum-

ably due to the effects of this agent on the peripheral nervous system, including autonomic nerves; however, direct toxic effects on the myenteric plexus cannot be excluded. Among adrenergic agents that are used in clinical practice, the centrally acting  $\alpha_2$ -agonist clonidine may induce reversible constipation and intestinal pseudo-obstruction,<sup>76</sup> but it does not result in a chronic neuropathic process. Nevertheless, these medications may aggravate gastrointestinal symptoms in those patients (such as patients with diabetes who have hypertension) who may require their concomitant use.

**Autonomic System Degenerations. Pandysautonomia or Selective Dysautonomias.**—Pandysautonomias are characterized by preganglionic or postganglionic lesions in both sympathetic and parasympathetic nerves. Gastrointestinal involvement, which is manifested as vomiting, paralytic ileus, constipation, or a pseudo-obstruction syndrome, has been reported in acute,<sup>77-82</sup> subacute,<sup>83</sup> or congenital<sup>84</sup> pandysautonomia. Motor disturbances of the gut have been substantiated in the esophagus (abnormal pressure in the lower esophageal sphincter, simultaneous contractions with swallowing, and multiple high-amplitude nonperistaltic contractions<sup>85</sup>); the stomach (antral hypomotility in one patient); and the small bowel (bursts in the fasting and postprandial periods in two patients<sup>55</sup>). Four published reports<sup>78,81,83,86</sup> have described patients with selective cholinergic dysfunction and disorders of gastrointestinal motor activity.

Histologic studies of the gut have been limited in these conditions. In a patient with pandysautonomia who had apparent achalasia of the distal esophagus, a biopsy specimen of the cardia taken during a Heller procedure showed apparently normal ganglia of the myenteric plexus.<sup>81</sup> This study suggested that the lesion was extrinsic to the gut. Most other reports that included morphologic studies of peripheral nerves in these syndromes provided no description of the myenteric plexus or extrinsic nerves.

**Failure of Muscarinic Cholinergic Receptors.**—Bannister and Hoyes<sup>87</sup> described a patient with constipation, recurrent small bowel

pseudo-obstruction, delayed gastric emptying, and a dilated duodenal loop. The number of ganglion cells in a rectal biopsy specimen and the perikaryon and dendrites of neurons in the submucous and myenteric plexuses were normal. The unique feature of this case was the absence of any response or denervation hypersensitivity response to exogenously administered cholinergic agonists or anticholinesterase drugs. Because the morphologic features of the smooth muscle itself were also normal, the authors postulated a postjunctional defect of the muscarinic receptor, but no confirmatory *in vitro* studies were performed.

**Idiopathic Orthostatic Hypotension.**—Idiopathic orthostatic hypotension is sometimes associated with motor dysfunction of the gut, such as alteration in bowel movements and fecal incontinence.<sup>88</sup> Cardiovascular and sudomotor abnormalities usually precede gut involvement. My colleagues and I observed similar alterations in bowel movements, heartburn, abdominal pain, and weight loss in three patients with idiopathic orthostatic hypotension.<sup>55</sup> One of our patients also had postprandial antral hypomotility, whereas phasic pressure bursts in the small bowel were observed during fasting in two of these three patients. More recently, other investigators have reported altered esophageal motility and gastric emptying in patients with idiopathic orthostatic hypotension.<sup>89</sup> The precise level of the lesion along the neural axis and the appearance of the neurons of the myenteric plexus are unknown.

**Shy-Drager Syndrome.**—The Shy-Drager syndrome is discussed subsequently in the section on extrapyramidal disease.

**Conditions of the Spinal Cord. Spinal Cord Injury.**—During the acute phase after spinal cord injury, ileus is a frequent finding, but it is rarely prolonged.<sup>90</sup> Fealey and associates<sup>91</sup> studied patients in whom gut function had been recovered subsequent to the initial ileus after spinal cord injury. They identified only minor abnormalities in the interdigestive antral motility; postcibal pressure activity in the distal part of the stomach and the proximal aspect of the small bowel was normal. Thus, impaired gastric

emptying is unusual in such patients,<sup>90,92</sup> and the improvement in gastric emptying in response to metoclopramide<sup>92</sup> suggests neuronal rather than muscle dysfunction as the cause of transit delays.

The single report that gallstone disease is more prevalent in patients with spinal cord injury than in control subjects<sup>93</sup> necessitates confirmation. This complication may be the consequence of either abnormal motility of the gallbladder or decreased enterohepatic cycling of bile acids as a result of slow small bowel transit.<sup>93</sup>

In contrast to the rarity of motor disorders of the upper gut after spinal cord injury, disturbances in colonic and anorectal function are common, probably as a result of interruption of supraspinal control of the sacral parasympathetic outflow. Thus, reports have described a decrease in colonic compliance<sup>94,95</sup> and an absence of postprandial colonic motor and myoelectric activity<sup>94,96</sup> in several patients with thoracic spinal cord injury. The entire large bowel transit may be affected in patients with paraplegia,<sup>97</sup> possibly because of slow transit throughout the colon or obstruction of the distal aspect of the colon due to an abnormal parasympathetic supply. Dysfunction of the anorectal sphincter is common and distressing.<sup>98</sup> Recent work with neuroprosthetic stimulation of the sacral anterior roots may pave the way for normalizing the pelvic colon and anorectal sphincter mechanism in these patients.<sup>98</sup>

In summary, spinal cord injury has more devastating effects on the distal part of the bowel than on the foregut or midgut, which may be spared because of the preservation of vagal nerve function. The effect of spinal cord injury on the morphologic features or *in vitro* function of myenteric plexus neurons in the gut has not been reported.

**Multiple Sclerosis.**—Severe constipation is a frequent accompaniment of urinary bladder dysfunction in patients with advanced multiple sclerosis. Excessive increases in intracolonic pressure occur in response to a volume stimulus in patients with multiple sclerosis in comparison with responses in healthy control subjects;<sup>99</sup>

this response is similar to detrusor hyperreflexia, a common cystometric disturbance in such patients. Some patients fail to have increased postprandial colonic motor and myoelectric activity, in contrast to the responses seen in healthy control subjects.<sup>99</sup> In one study, colonic transit of radiopaque markers was prolonged in 14 of 16 patients with multiple sclerosis and urinary bladder involvement.<sup>100</sup> In that series, 10 patients also had evidence of fecal incontinence, and 5 had spontaneous rectal contractions. The studies performed to date have not been sufficiently detailed to assess the relative contributions of the sympathetic and parasympathetic nervous systems. Nonetheless, pelvic colon dysfunction is more likely due to impaired function of the supraspinal centers or descending pathways that control the sacral parasympathetic outflow. Further studies need to address the mechanism of impaired gut transit in multiple sclerosis, which, as with spinal cord injury, results in motility disturbances more frequently in the lower than in the upper gut.

**Diseases of the Brain. Extrapyramidal Disease.**—Patients with parkinsonism are known to have delayed gastric emptying that is aggravated by treatment with levodopa.<sup>101</sup> In the original description of the Shy-Drager syndrome,<sup>102</sup> constipation and fecal incontinence were included among the classic features of the disorder. One patient with the Shy-Drager syndrome had substantial reduction in fasting and postprandial antral and small bowel pressure activity.<sup>55</sup> Abnormalities in esophageal motility were also evidenced by cineradiography and by frequent simultaneous low-amplitude peristaltic waves during esophageal manometry in two patients with the Shy-Drager syndrome and cholinergic dysfunction.<sup>103</sup> Megacolon and dilatation of the small bowel have been recognized in patients with parkinsonism;<sup>104,105</sup> rarely, colonic dilatation may lead to sigmoid volvulus.<sup>106,107</sup> Constipation is common in patients with parkinsonism, and determining the relative contributions of gut hypomotility, generalized hypokinesia, and the effects of various anticholinergic and dopamine agonist medications to the cause of this symptom is difficult.

The bioavailability of medications can be considerably altered by these effects on gut transit.

Apart from the degenerative changes in central structures, recent reports have suggested that degenerative changes and Lewy inclusion bodies are present in myenteric plexus ganglion cells in the esophagus<sup>108</sup> and the colon.<sup>108,109</sup>

Esophageal malfunction has been reported in a patient with Wilson's disease who had dysphagia.<sup>110</sup> Parkinsonian features and choreoathetosis may occur in neuronal intranuclear inclusion disease.<sup>60</sup>

**Epilepsy.**—Visceral autonomic epilepsy may occur in conjunction with nausea and vomiting, which may not be associated with obvious alteration of consciousness.<sup>111-114</sup> Recently, Peppercorn<sup>115</sup> described 10 female adults with abdominal pain, nausea, bloating or diarrhea, neurologic symptoms, sleep electroencephalographic abnormalities, and prompt and nearly complete resolution with anticonvulsants. Assessment of gastrointestinal motor function concomitantly with electroencephalography in such patients with evidence of visceral epilepsy has not been performed to date; hence, the relationship between the abnormal brain discharges and their effect on gut motility remains unknown.

**Brain-Stem Lesions.**—The association of brain-stem lesions and symptoms of upper or lower gut dysfunction has been established for many years. Recent reports have described the motility of the gut in patients with such lesions. For example, my colleagues and I<sup>116</sup> reported the abnormal velocity of propagation of an interdigestive migrating motor complex and abnormal postprandial motility in the upper gut in a patient with a medullary astrocytoma. Whether this motor dysfunction of the gut is due to mechanical stimulation of the vomiting center in the area postrema,<sup>117</sup> a disturbance of neural connections,<sup>118</sup> or chemical activation of the emetic chemoreceptor trigger zone by an endogenous substance<sup>119</sup> is uncertain.

Brain-stem strokes have also been associated with small bowel or colonic pseudo-obstruction,<sup>55,120</sup> colonic inertia, and esophageal incoordination.<sup>121</sup> Moreover, some patients have an

inability to perceive rectal distention and lack the rectoanal inhibitory reflex.<sup>121</sup>

## GENERALIZED MUSCLE DISORDERS CAUSING GUT DYSMOTILITY

As in the material on disease of neural control, muscle disorders that selectively affect the gut without systemic involvement will not be discussed herein.

**Amyloidosis.**—As previously emphasized, amyloidosis may result in gut dysmotility by infiltration of the muscle layers; the presence of such a myopathy can be confirmed by manometric studies.<sup>9</sup>

**Systemic Sclerosis.**—Systemic sclerosis is frequently associated with symptoms of gastrointestinal motor dysfunction. Whereas esophageal involvement is most commonly identified in clinical practice, some evidence has shown that anorectal involvement is just as common.<sup>122</sup> Cohen and co-workers<sup>123-125</sup> suggested a two-stage process in the natural history of the motility disorder of the gut: (1) a neuropathic process initially and (2) a myopathic disturbance subsequently (Fig. 5) as a result of infiltration of the muscle layers with fibrous tissue. The original observations that suggested an early neuropathic process in the esophagus and anorectal region have recently been confirmed in the small intestine. Thus, uncoordinated fasting and postprandial phasic pressure bursts associated with tonic elevation of baseline pressure in the small intestine<sup>126</sup> in a minority of patients with scleroderma who have gastrointestinal features suggest an initial neuropathic disturbance. Other investigators have substantiated the lack of cyclic interdigestive motility in patients with systemic sclerosis.<sup>127,128</sup> The histopathologic findings in gut muscle in this disorder have been well characterized and may be distinguishable from those of familial hollow visceral myopathy.<sup>129</sup> More recent studies have suggested, however, that it may not always be possible to distinguish the histologic appearances from those of sporadic hollow visceral myopathy.<sup>130</sup> Further studies on the myenteric plexus are awaited.

**Dermatomyositis.**—Motor disturbances of the gut have been a well-recognized, although

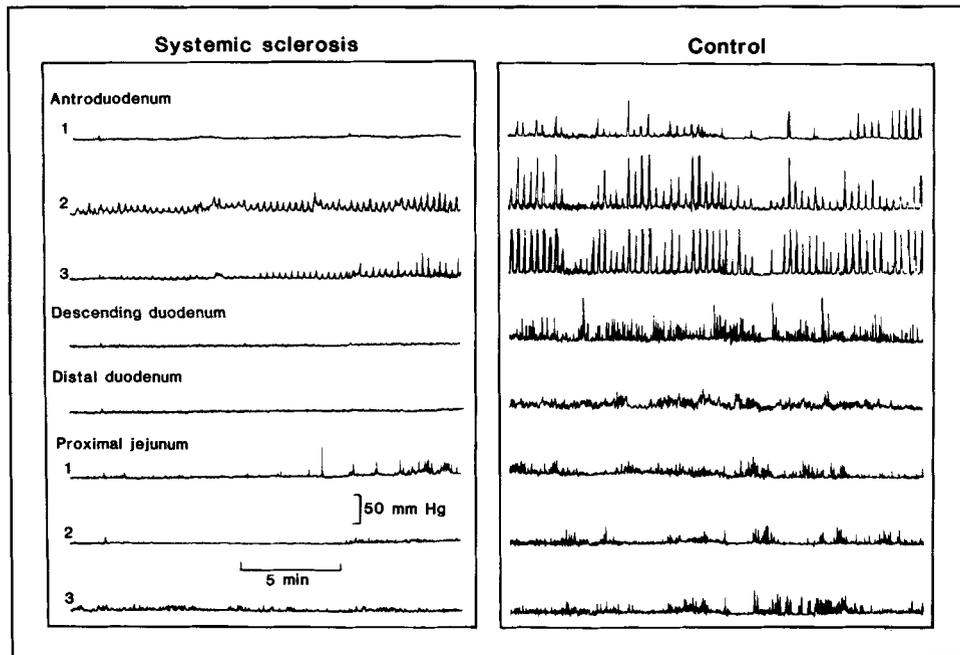


Fig. 5. Manometric profile of myopathic pseudo-obstruction due to systemic sclerosis: note low amplitude of phasic pressure activity (contractions) at antral, duodenal, and jejunal levels in comparison with amplitude of contractions in a healthy control subject. (From Greydanus and Camilleri.<sup>126</sup> By permission of the American Gastroenterological Association.)

rare, feature of dermatomyositis.<sup>131</sup> Esophageal symptoms occur more commonly than symptoms suggestive of gastric stasis,<sup>132</sup> and investigators have found evidence of delayed transit of solids in the esophagus and of both solids and liquids in the stomach.<sup>131</sup> The impairment of propulsive activity of the upper gut correlates with the weakness of skeletal muscle groups.<sup>133</sup> Morphologic abnormalities of gut smooth muscle are rarely seen,<sup>134</sup> and dysphagia most likely results predominantly from skeletal muscle involvement.

**Dystrophia Myotonica.**—Various studies have found abnormal muscle function at virtually all levels of the gastrointestinal tract in patients with dystrophia myotonica, from the pharynx to the anal sphincters.<sup>135-141</sup> The study by Lewis and Daniel<sup>139</sup> demonstrated increased duodenal contractions in association with variability of the maximal rate of contractions, and these authors postulated that these effects resulted from smooth muscle damage, which caused partial depolarization. In one patient, my col-

leagues and I noted increased tonic and phasic pressure activity in the proximal jejunum during fasting.<sup>9</sup> Enhancing cholinergic transmission with the anticholinesterase edrophonium did not result in antral stimulation,<sup>139</sup> hence, the mechanism for the beneficial effect of metoclopramide on emptying of solids from the stomach<sup>138</sup> is unclear.

The degenerative changes in small intestinal and colonic smooth muscle with fatty infiltration and collagen formation among smooth muscle cells are similar to those observed in dystrophic skeletal muscle.<sup>140</sup> In one study, degenerative changes were noted in the myenteric plexus, whereas gut smooth muscle was histologically normal.<sup>142</sup> Recent immunohistochemical studies disclosed a decrease of substance P and enkephalin-immunoreactive fibers in the muscularis externa.<sup>142</sup>

Congenital myotonic dystrophy may similarly affect gut smooth muscle function and result in gastroparesis,<sup>143</sup> subacute obstruction, megacolon, and constipation in children of patients

with dystrophia myotonica.<sup>144</sup> Gastrointestinal involvement has been recorded in other rare variants of muscular dystrophies, including oculogastrointestinal and Duchenne muscular dystrophy.<sup>145,146</sup>

**Mitochondrial Myopathy.**—A single case of chronic intestinal pseudo-obstruction due to mitochondrial myopathy was recently reported.<sup>147</sup> This patient also had ophthalmoplegia (restriction of ocular movements to a few degrees in all directions, slight ptosis, and myopia), hearing loss, generalized muscle atrophy, and, in the gut, absence of esophageal peristalsis, delayed gastric emptying, and dilatation of the duodenum and small intestine. No details on gastrointestinal smooth muscle were provided in the report of this unusual case.

#### IDENTIFICATION OF EXTRINSIC NEUROLOGIC DISEASE IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL SYMPTOMS

Clearly, patients with lesions at virtually any level of the nervous system may have symptoms of gastrointestinal motor dysfunction. Because functional gastrointestinal disorders are by far the most commonly seen conditions in gastroenterologic practice,<sup>148</sup> it is necessary to develop a strategy to identify those in whom such a neurologic disturbance may be present, and this strategy is only part of the diagnostic evaluation of disordered gastrointestinal function and its cause.<sup>149</sup> Patients should undergo further testing if they have clinical features suggestive of autonomic or peripheral nerve dysfunction, such as orthostatic dizziness, sweating abnormalities, repeated bladder infections, paroxysmal tachycardia, or paresthesia.

The first steps are elicitation of the history and performance of a physical examination (Table 2) to identify any evidence of a generalized neurologic disorder. The physician should thoroughly evaluate all systems and inquire about past history and family history. It is essential to record the use of any medications that may influence gut motility.

Gastrointestinal motility and transit measurements help the clinician to identify or to

Table 2.—Components in the Evaluation for Extrinsic Neurologic Disease in Patients With Gastrointestinal Motor Dysfunction

Component	Specific features
History	Postural dizziness, control of blood pressure Disturbances of vision Sweating Urinary disturbances or infections Sensory or motor deficits
Medications	Calcium channel blockers, anticholinergic agents, antiarrhythmic drugs, antipsychotic agents, antihypertensive agents
Past history	Diabetes mellitus, spinal cord injury
Family history	Amyloidosis, other neuropathy
Examination	Blood pressure and pulse (with patient supine and standing) Pupils (size, reaction to light) Cranial nerves Sensation Motor function
Studies	Gastrointestinal manometry ( $\pm$ ) RR interval (electrocardiographic) responses to Valsalva maneuver and pulse rate variation (oscillation) with deep breathing Pupillary responses to 0.1% epinephrine, 0.125% pilocarpine, 5% cocaine drops Thermoregulatory sweat test Quantitative sudomotor axon reflex test (to iontophoresed acetylcholine) Blood pressure and plasma norepinephrine (with patient supine and standing) Screen for peripheral neuropathy Magnetic resonance imaging of the brain

confirm a substantial disturbance in the motor function of the gut and to distinguish between neuropathic and myopathic disorders.<sup>9</sup> Thus, neuropathic conditions usually present a picture of uncoordinated but normal-amplitude phasic pressure peaks, whereas myopathic conditions show considerably reduced amplitude of contractions in the affected regions on manometry. Such studies, however, generally do not allow the distinction between intrinsic (myenteric plexus) and extrinsic neuropathies. Indirect tests of autonomic function (Table 2; Appen-

dix) are exceedingly useful for identifying the presence of other visceral denervation.<sup>150-153</sup> The close concordance of abdominal vagal dysfunction with cardiovagal neuropathy in patients with diabetes<sup>154</sup> suggests that these tests may provide a realistic evaluation of the overall function of autonomic supply to the viscera, including the gastrointestinal tract.

Once a defect of the sympathetic nervous system has been identified, the effect of intravenous administration of edrophonium on norepinephrine levels may provide a further assessment of the integrity of postganglionic sympathetic nerves.<sup>155,156</sup> Similarly, dysfunction of the vagus nerve identified by cardiac reflexes may be further assessed by means of the plasma pancreatic polypeptide response to either sham feeding or hypoglycemia.<sup>157</sup> This test, however, is rarely necessary in clinical practice because cardiac autonomic responses are easier and less expensive to determine and are sensitive indicators of autonomic dysfunction of abdominal viscera.<sup>154</sup>

Screening of a patient with visceral autonomic neuropathy must include tests that identify occult causes of a peripheral neuropathy, such as lung tumors or amyloidosis. In those patients with autonomic disturbance of viscera other than abdominal organs, imaging of the brain becomes essential, particularly when the supine plasma norepinephrine levels and their response to administration of edrophonium are normal, findings that suggest normal function of postganglionic fibers. In our experience, magnetic resonance imaging has been preferable,<sup>116</sup> particularly for demonstrating lesions in the brain stem.

## CONCLUSION

The recent surge of interest in gastrointestinal motility and the availability of techniques that provide a better evaluation of gastrointestinal motor function have necessitated broader collaborations between gastroenterologists and neurologists. The gastrointestinal tract is an important component of the area supplied by the autonomic nervous system and may be involved in systemic disorders that affect other muscle systems. In a few patients with functional gas-

trointestinal symptoms, identification of a specific neurologic disorder will be possible. This disorder may be at any level of the extrinsic neural control of the gut, from the brain to the postganglionic fibers, the enteric nervous system, or the smooth muscle itself. These considerations emphasize the importance of the interaction between the neural axis and the gut and should provide a framework for the investigation of operative mechanisms in patients with motor disorders of the gut.

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## APPENDIX

### SUMMARY OF COMMON AUTONOMIC FUNCTION TESTS

**Pupillary Function Tests.**—Responses to light and accommodation assess the parasympathetic supply (Appendix Table 1); dilatation in dim light assesses the sympathetic supply. Drops are instilled to search for signs of denervation hypersensitivity of the pupillary muscles: (1) dilute (0.125%) pilocarpine (an alkaloid that acts directly on end-organs affected by acetylcholine) induction of pupillary constriction implies parasympathetic denervation; (2) 0.1% epinephrine (direct stimulant of  $\alpha$ -adrenergic receptors) induction of pupillary dilatation indicates a postganglionic sympathetic lesion. Instillation of 4 to 5% cocaine drops blocks uptake of norepinephrine by the nerve ending and indirectly dilates the pupil. No such dilatation occurs if impulses do not reach the sympathetic nerve endings because of a preganglionic or a postganglionic lesion.

**Cardiovascular Tests. Orthostatic Hypotension.**—In response to an 80° tilt, a decline in systolic or diastolic pressure without a compensatory increase in pulse rate indicates sympathetic dysfunction.

**Heart Period Responses to Deep Breathing.**—Inflation and deflation of the lungs stimulate vagal afferents that reflexly change the pulse rate through vagal efferents. Thus, reductions in pulse rate occur with inspiration, and increases accompany expiration. This pulse rate variation (oscillation) is related to the age of the patient; if oscillations are impaired, they indicate vagal dysfunction.

**Valsalva Maneuver.**—Forced expiration against a closed glottis is achieved by maintaining pressure in a sphygmomanometer at 40 to 50 mm Hg for 15 to 20 seconds by blowing into the sphygmomanometer. This maneuver results in a complex series of changes in pulse rate and blood pressure involving both vagal and sympa-

Appendix Table 1.—**Interpretation of Results of Autonomic Function Tests**

Test of autonomic function	Normal value	Abnormal result implies dysfunction of:
<b>Pupillary tests</b>		
Response to light		
Latency	0.2-0.3 s	Parasympathetic
Constriction	2-4 mm	Parasympathetic
<b>Pharmacologic tests</b>		
0.125% pilocarpine	0-0.5-mm constriction	Parasympathetic
0.1% epinephrine	No change	Postganglionic, sympathetic
5% cocaine	>1.5-mm dilatation	Sympathetic
<b>Blood pressure reduction on tilt to 80°</b>		
Systolic	<25 mm Hg	Sympathetic
Diastolic	<15 mm Hg	Sympathetic
Valsalva ratio	>1.5	Sympathetic or parasympathetic
Pulse rate change with deep breathing	Age related, 6-18 beats/min	Parasympathetic
<b>Thermoregulatory sweat test</b>		
% surface area of anhidrosis	M: 0%; F: <3%	Sympathetic
<b>Quantitative sudomotor axon reflex test</b>		
Sweat output ( $\mu\text{l}/\text{cm}^2$ )		
Forearm		
	M: 0.76-5.51	
	F: 0.34-1.33	
Foot		
	M: 0.92-5.73	
	F: 0.25-1.95	
Latency (min)		
Forearm		
	M: 1-2.4	
	F: 0.9-1.9	
Foot		
	M: 1-2.7	
	F: 1-2.8	
<b>Plasma norepinephrine</b>		
Patient supine		
	70-750 pg/ml	Postganglionic, sympathetic
Patient standing		
	200-1,700 pg/ml	Sympathetic
Response to intravenous administration of edrophonium	>35% increase above baseline within 2-8 min	Postganglionic, sympathetic

thetic responses. In autonomic dysfunction, the phase IV responses of blood pressure overshoot and compensatory bradycardia are typically lost. A useful index is the Valsalva ratio, which compares the longest (usually in phase IV) and shortest (usually in phase II) RR intervals measured on the electrocardiogram during and after the Valsalva maneuver. A reduced index indicates autonomic dysfunction.

**Sweat Tests. Thermoregulatory Sweat Test.**—After being covered with alizarin red powder, the patient is exposed to an environ-

ment of 44 to 50°C and 40 to 50% relative humidity for up to 30 minutes. An increase in core body temperature of 1°C is required. The percentage surface area of anhidrosis is determined and indicates sympathetic (preganglionic or postganglionic) dysfunction.

**Quantitative Sudomotor Axon Reflex Test.**—A sweat capsule assesses the latency between stimulation and appearance of sweat and the output of sweat in the upper and lower limbs in response to iontophoresed 10% acetylcholine solution. This transmitter is charged and enters

the skin in response to the application of a weak electric current (2 mA for 10 minutes). The acetylcholine results in antidromic stimulation of the postganglionic sympathetic fiber, which, in turn, orthodromically stimulates a sweat gland. A delay or lack of output of sweat implies a postganglionic sympathetic lesion.

**Plasma Norepinephrine.**—A low plasma norepinephrine concentration *with the patient supine* suggests a postganglionic sympathetic lesion. Failure of the plasma norepinephrine

level to increase *when the patient stands* suggests either a preganglionic or a postganglionic disturbance.

*Intravenous administration of edrophonium* produces a transient amplification of endogenous cholinergic activity in the sympathetic ganglia by rapid inhibition of acetylcholinesterase. The result is a rapid release of norepinephrine into the plasma from the postganglionic sympathetic fibers. Thus, this test assesses the integrity of the postganglionic sympathetic fibers.

