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REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Gastroparesis

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Gastroparesis is characterized by symptoms suggestive of, and objective evidence of, delayed gastric emptying in the absence of mechanical obstruction. This review addresses the normal emptying of solids and liquids from the stomach and details the myogenic and neuromuscular control mechanisms, including the specialized function of the pyloric sphincter, that result in normal emptying, based predominantly on animal research. A clear understanding of fundamental mechanisms is necessary to comprehend derangements leading to gastroparesis, and additional research on human gastric muscles is needed. The section on pathophysiology of gastroparesis considers neuromuscular diseases that affect nonsphincteric gastric muscle, disorders of the extrinsic neural control, and pyloric dysfunction that lead to gastroparesis. The potential cellular basis for gastroparesis is attributed to the effects of oxidative stress and inflammation, with increased proinflammatory and decreased resident macrophages, as observed in full-thickness biopsies from patients with gastroparesis. Predominant diagnostic tests involving measurements of gastric emptying, the use of a functional luminal imaging probe, and high-resolution antral duodenal manometry in characterizing the abnormal motor functions at the gastroduodenal junction are discussed. Management is based on supporting nutrition; dietary interventions, including the physical reduction in particle size of solid foods; pharmacological agents, including prokinetics and anti-emetics; and interventions such as gastric electrical stimulation and pyloromyotomy. These are discussed briefly, and comment is added on the potential for individualized treatments in the future, based on optimal gastric emptying measurement and objective documentation of the underlying pathophysiology causing the gastroparesis.

Keywords: Gastroparesis; Gastric Accommodation; Gastric Emptying.

Ingestion of food results in gastric accommodation, followed by development of antral contractions. After food is triturated to a small particle size, pyloric relaxation and antropyloroduodenal coordination lead to the emptying of food from the stomach. Foods of different physical nature and consistency follow distinct emptying patterns[1]: exponential for liquids with low calorie content under the pressure gradient provided by fundic tone with relaxation of the pylorus; and linear for nutrient liquids and homogenized solids. Posture influences the emptying of non-nutrient liquids, which is faster in the upright position.[2] Raised intragastric pressure increases emptying of liquids, but not solids.[3]

Solids are retained initially in the proximal stomach and are moved subsequently to the antrum to undergo trituration. This initial period without emptying is termed the *lag phase*. Antral phasic pressure activity is essential and significantly correlates with the rate of emptying of solid food from the stomach, as shown in healthy stomach[4] and by prolongation of gastric emptying in the presence of antral hypomotility.[5] Antral hypomotility is typically characterized by an average of <1 distal antral contraction per minute in the first postprandial hour.[6]

The timing and mechanistic steps responsible for pyloric regulation of gastric emptying are still incompletely understood.[7] From early cineradiographic studies in laboratory animals,[8] it was known that peristaltic contractions progress from corpus to pylorus, resulting in a brief period of emptying of liquid and small particles. As the peristaltic wave reaches the terminal antrum, pyloric constriction occurs, restricting emptying during the period of highest pressure in the terminal antrum. Contents are forcefully retropulsed back into the body of the stomach, setting up the shearing forces that cause trituration of solids. Thus, the antropyloroduodenal junction provides a sieving function whereby food particles must be reduced in size to ≤ 2 mm before emptying occurs.[9] Particles retrieved from duodenums of healthy dogs were <2 mm, whereas dogs with Billroth I gastrectomy with loss of the pylorus had larger solid food particles emptied,[10] and this may lead to malabsorption due to inefficient digestion after this form of gastric surgery.[11]

Failure of antral contractions or of pyloric relaxation may impede gastric emptying and constitute the predominant pathophysiological disturbances in gastroparesis,

Abbreviations used in this paper: **ENS, enteric nervous system; GES, gastric electrical stimulation; G-POEM, gastric peroral endoscopic myotomy; ICC, interstitial cells of Cajal; IM, intramuscular; MY, myenteric; NO, nitric oxide; NOS, nitric oxide synthase; SMC, smooth muscle cell; WMC, wireless motility capsule.**

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which are identified by classical clinical symptoms that include nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain, and documentation of delayed gastric emptying in the absence of mechanical obstruction.[12] A recent study has drawn attention to the observation that, 1 year after initial classification, patients with functional dyspepsia and gastroparesis assessed in tertiary referral centers are not distinguishable based on clinical and pathologic features or based on assessment of gastric emptying of a low-fat, relatively low-calorie, easily digestible meal.[13] This emphasizes the importance of accurate diagnosis based on optimal measurements of gastric emptying by scintigraphy or breath test (Supplementary Table 1) and the use of robust normative data, such as gastric retention >75% at 2 hours and >25% at 4 hours, based on normative data reported in 319 healthy volunteers.[14] Such strict cut-off criteria are extremely important, given the mean inter- and intraindividual coefficients of variation for gastric emptying $T_{1/2}$ of 24.5% and 23.8%, respectively, in healthy individuals, and the intraindividual coefficient of variation of 20% in a study of 60 patients (21 with diabetes) presenting with upper gastrointestinal symptoms when evaluated twice 15 days apart, on average.[15] In a more recent study[16] of 9 patients with proven gastroparesis (2 with type 1 diabetes and 7 idiopathic) measured twice at 3-day intervals, the range of mean gastric emptying $T_{1/2}$ was 20–240 minutes and the intraindividual coefficient of variation was 11.1%.

Myogenic Mechanisms

Smooth muscle cells (SMCs) provide the forces required for trituration of food and gastric emptying. SMCs are spindle-shaped, 40–100 μm long, 2–8 μm in diameter, and tightly packed with little connective tissue between cells. SMCs are organized into 3 layers (ie, circular, longitudinal, and oblique) in the stomach. As with other muscle cells, gastric contractions depend on coupling of electrical events to contractions through an increase in cytoplasmic calcium ions (Ca^{2+}). SMCs are electrically coupled by gap junctions, which facilitate synchronicity of contractions by conduction of electrical impulses between the cells.

From a functional perspective, the stomach is composed of the following 3 major regions: the proximal stomach (fundus), which generates tone that can be actively regulated to accommodate ingestion of food; the distal stomach (corpus and antrum), which processes food before emptying; and the pyloric sphincter, which regulates the rate of gastric emptying.[17] SMCs in these regions have both similar and different intrinsic properties that facilitate specialized functions. Common to all gastric SMCs is expression of voltage-dependent Ca^{2+} channels (dihydropyridine-sensitive, L-type channels) that comprise the main Ca^{2+} entry mechanism regulating excitation–contraction coupling. However, proximal, distal, and pyloric SMCs have different complements of potassium (K^+) channels that regulate resting membrane potentials and the state of basal excitability of the SMCs. Fundus cells are intrinsically more depolarized than antral cells. Fundus SMCs sit at potentials (approximately –50 mV) that facilitate continuous leak of Ca^{2+} into cells through voltage-dependent conductances. This facilitates the development and maintenance of tone. Antral and pyloric SMCs, in contrast, have more negative resting membrane potentials at which Ca^{2+} entry is minimal, facilitating relaxation between excitable events. The resting potentials of gastric SMCs are set at negative levels by highest permeability to K^+ ions.

The intrinsic features of SMCs, however, cannot generate the important motor patterns of the stomach. SMCs are electrically coupled to 2 types of interstitial cells. Interstitial cells of Cajal (ICC) and fibroblast-like cells (PDGFRα^+ cells) are coupled to SMCs by gap junctions,[18,19] forming an electrical syncytium known as the SIP (abbreviation for SMCs, ICC and PDGFRα^+ cells) syncytium.[20] The syncytial nature of gastric muscles means that electrical responses that develop in interstitial cells can conduct to SMCs and regulate the excitability and motor activity of SMCs. There are 2 basic classes of ICC: intramuscular ICC (ICC-IM), which are closely aligned with varicose projections of enteric motor neurons[21] (Figure 1*A*–*C*[22]); and ICC in the myenteric region (ICC-MY), which form a complex cellular network in the region between the circular and longitudinal muscle layers[23] (Figure 1*D*–*G*[22,24]). ICC-MY generate pacemaker activity.[25] More details about the functions of ICC-IM and PDGFRα^+ cells in the SIP syncytium (Figure 2*A*[26] and *E*[27]) are discussed in the section on Neuromuscular Control Mechanisms.

ICC-MY express unique ionic conductances that generate and actively propagate electrical slow waves (Figure 1*H*[28]), the electrophysiological events that generate the phasic contractions of gastric peristalsis. A dominant pacemaker region exists in the proximal corpus at or near the greater curvature. ICC-MY in this location are the most excitable and generate slow waves at the highest frequency. Slow waves are initiated by small depolarizations due to spontaneous Ca^{2+} release in ICC-MY and activation of Ca^{2+}-activated Cl^- channels (encoded by *ANO1 or anoctamin 1* gene).[29] Transient activation of ANO1 channels and depolarization causes activation of low-threshold, voltage-dependent Ca^{2+} channels (dihydropyridine-insensitive, T-type Ca^{2+} channels), resulting in rapid depolarization, an event not unlike a Ca^{2+} action potential that can propagate regeneratively through the network of ICC-MY. This event is known as the upstroke of the slow wave. Ca^{2+} entry during the upstroke sets off additional Ca^{2+} release events through a process known as Ca^{2+}-induced Ca^{2+} release, maintaining the activation of ANO1 channels and creating the second component of the slow wave, the plateau phase. During the plateau phase, the elevated permeability of Cl^- ions (via sustained activation of ANO1 channels) is dominant relative to the permeability of other ions. This causes membrane potential to linger near the equilibrium potential for Cl^- ions, generating the depolarized conditions during the plateau potential. Termination of Ca^{2+} release causes deactivation of ANO1 channels (which are Ca^{2+}-dependent), switching back from dominant Cl^- permeability to dominant K^+ permeability, and this causes repolarization to the resting (ie, inter-slow wave) potential.

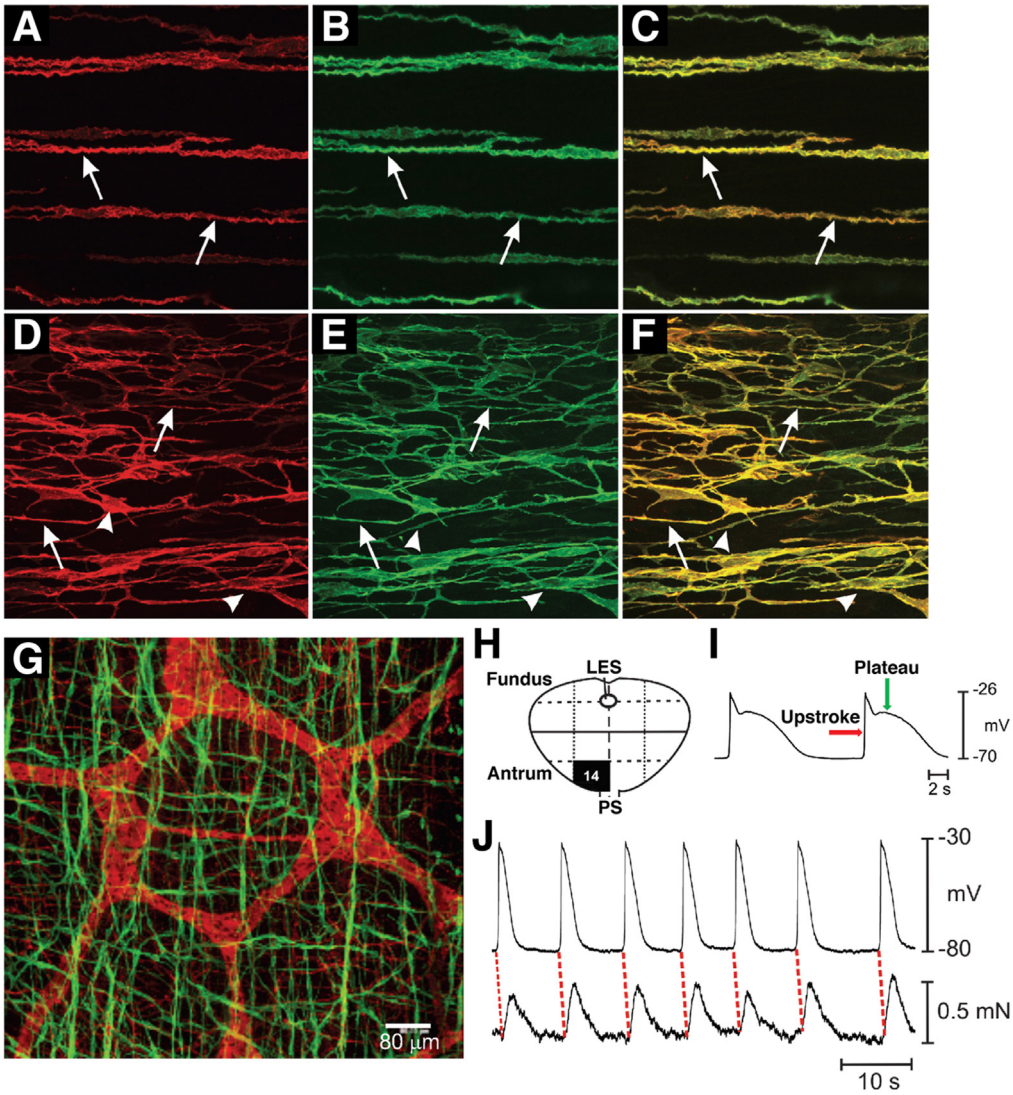

Figure 1. (*A*) c-Kit and (*B*) Ano1 immunolabeling and (*C*) merged files of ICC-IM from monkey gastric fundus. (*D–F*) ICC-MY shown by same immunolabels. (*D*) c-Kit, (*E*) Ano1, and (*F*) merged from monkey antrum. (*G*) Network of ICC-MY (c-Kit labeling) shown with myenteric plexus (PGP 9.5 labeling) of guinea pig stomach. (*H*) *Gastric map* used by surgeons to show where gastric muscles originate. LES, lower esophageal sphincter; PS, pyloric sphincter. (*I–J*) Slow waves recorded from human gastric antrum (area 14). *Red arrow* denotes upstroke phase of slow wave and the *green arrow* denotes the plateau phase. (*J*) Simultaneous recording of slow waves (*above*) and phasic contractions (*below*). These recordings are made from an impaled SMC within a small sheet of antral muscle. In the intact stomach, both the slow waves and the contractions they induce propagate from corpus to the pyloric sphincter, constituting gastric peristalsis. (*A–F*): From Blair et al,[22] reproduced with permission. (*G*) From Komuro,[24] reproduced with permission. (*H*) Redrawn from Rhee et al.[28]

Slow waves conduct to SMCs, causing depolarization, activation of L-type Ca^{2+} channels, and excitation–contraction coupling. SMCs do not express the ion channels required for active propagation of slow waves, and thus an intact network of ICC-MY is necessary for normal gastric motility.[30]

Neuromuscular Control Mechanisms

Most of what is described in the next sections is based on animal research. The enteric nervous system (ENS), which consists of about 100 million neurons throughout the entire gut,[31] regulates tonic contraction in the proximal stomach and the amplitude and frequency of phasic contractions in the distal stomach. The ENS is organized in distinct ganglionated plexi, including the submucous plexus, which is mainly involved in absorption and secretion, and the myenteric plexus, which regulates motility.[31] Innervation of the gastric muscularis results from both excitatory and inhibitory enteric motor neurons[32] (Figure 3[33]). Excitatory neurons release acetylcholine and tachykinins. Inhibitory neurons release nitric oxide (NO), vasoactive intestinal polypeptide, pituitary adenylate cyclase-activated peptide, and purines. Retrograde neural tracing has shown that cell bodies of muscle motor neurons are in myenteric ganglia, with excitatory neurons projecting proximally and inhibitory neurons projecting distally.[34]

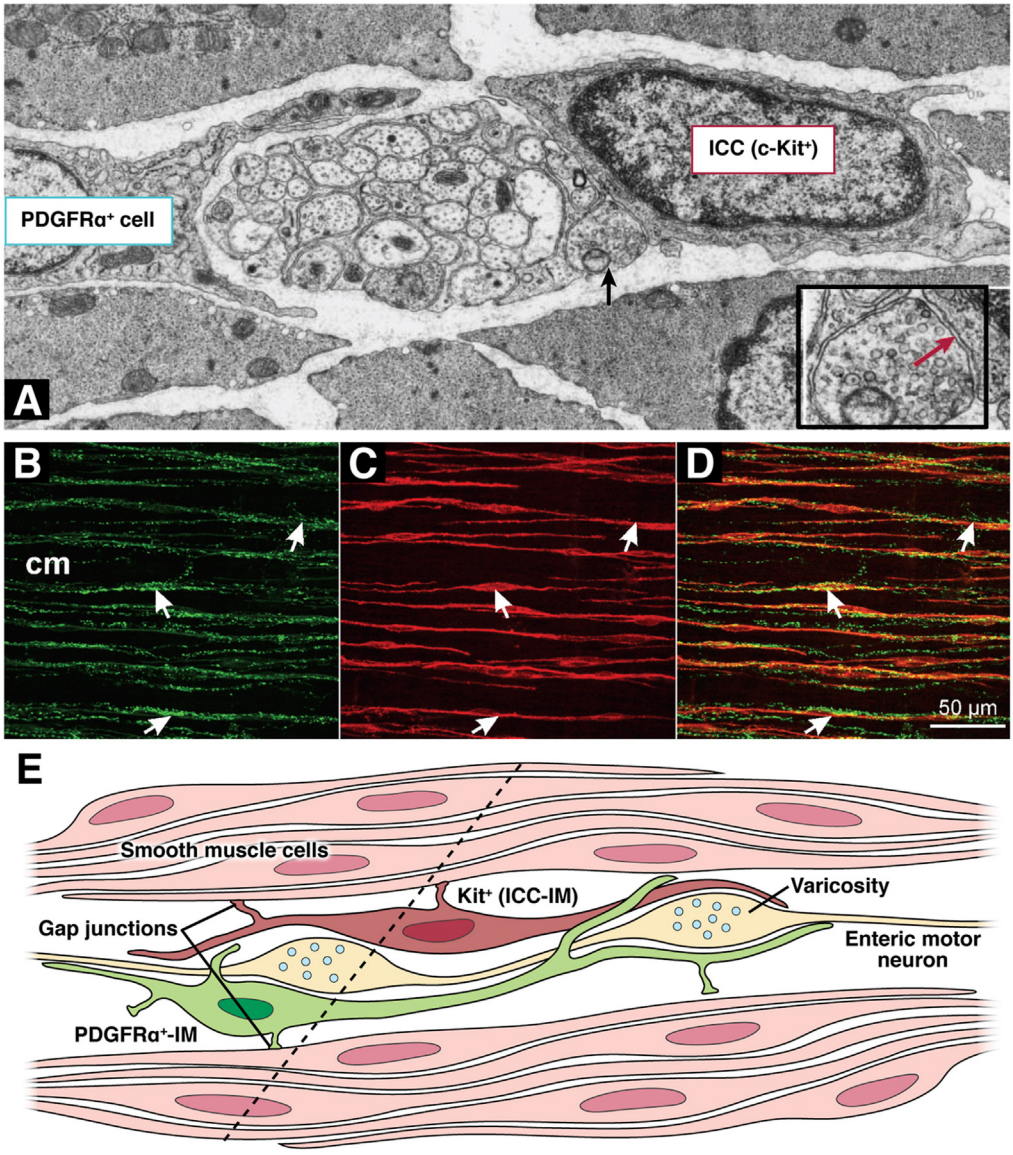

Figure 2. (*A*) *Electron micrograph* (×19,000) showing elements of the SIP (abbreviation for SMCs, ICC and PDGFRα^+) syncytium in the stomach of guinea pig. Both PDGFRα^+ cells and ICC (c-Kit$^+$ cell) make close contacts with bundles of enteric neurons. In some places, very close contact between varicosities and ICC occur (<20 nm; see area denoted by *red arrow* in the *inset* [×44,000]), which is a magnification of the varicosity noted by the *black arrow* in (*A*). Both PDGFRα^+ cells and ICC form gap junctions with SMCs (not shown in this image), forming an electrical syncytium. ICC transduce cholinergic and nitrergic inputs and PDGFRα^+ cells transduce purinergic inputs from enteric motor neurons. (*B–D*) Enteric motor neurons (PGP 9.5; *green* [*B*]) and c-Kit (*red* [*C*]) labeling in monkey stomach. (*D*) *Merged images* demonstrating the close relationship between the projections of motor neurons and ICC. (*E*) *Schematic* of SIP syncytium with ICC in *red* and PDGFRα^+ cells in *green*, also showing formation of gap junctions with SMCs. (*A*): From Mitsui and Komuro,[26] reproduced with permission. (*B–D*): From Sung et al,[36] reproduced with permission. (*E*): From Figure 2 in Sanders et al,[27] reproduced with permission.

Motor neurons innervate the SMCs through ICC and PDGFRα^+ cells[22,28,35] (Figure 2*B–D*[36]). ICC-IM mediate responses to cholinergic excitatory[37] and nitrergic inhibitory[21] neurotransmission. PDGFRα^+ cells mediate responses to purinergic inhibitory neurons in gastrointestinal muscles.[38] ICC-IM form synaptic-like connections with varicosities of enteric motor neurons that are thought to be sites of neurotransmission (Figure 2*A*). In the case of cholinergic neurotransmission, the tiny junctional volumes between ICC-IM and nerve varicosities facilitate rapid metabolism of acetylcholine, thereby limiting its diffusion through the interstitium. NO may have dominant effects in ICC-IM, which would also be due to the close proximity of ICC-IM to sites of synthesis and release. PDGFRα^+ cells, which are also closely associated with enteric motor neurons (Figure 2*A*), mediate purinergic response by dominant expression of key receptors and ion channels. Cholinergic nerve stimulation causes a dramatic increase in Ca^{2+} release in ICC-IM in colonic muscles[39]; however, this has not yet been documented in gastric ICC-IM. In contrast, NO inhibits

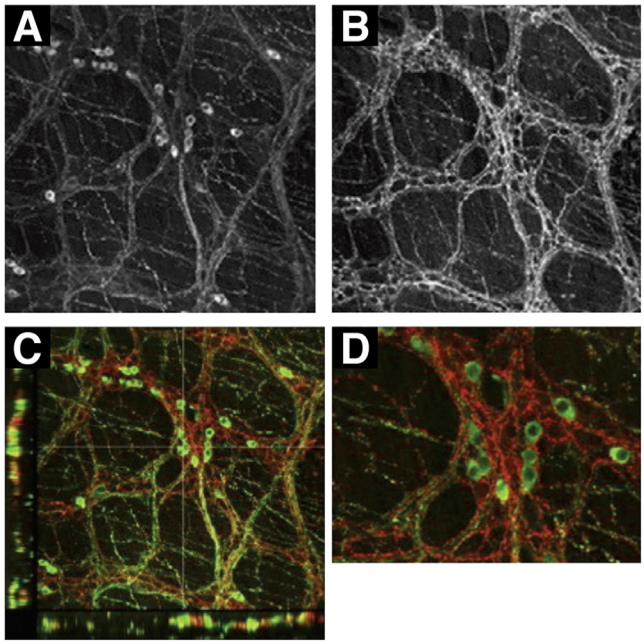

Figure 3. Myenteric plexus showing neurons labeled with neuronal NOS 1 (nNOS1) (*A*) and vesicular acetylcholine transporter (VChaT) (*B*). Some of the $nNOS^+$ neurons are inhibitory muscle motor neurons, and some of the VChaT neurons are excitatory muscle motor neurons. The *images* in (*A*) and (*B*) showing nNOS1 and VChaT neurons, respectively, are merged in (*C*). (*D*) A magnified view of a single ganglion from (*C*). From Cipriani et al,[33] reproduced with permission.

Ca^{2+} release in ICC-IM. As noted above, release of Ca^{2+} is coupled to activation of ANO1 channels, such that enhancing Ca^{2+} release would elicit a general depolarizing trend in the SIP syncytium and increase SMC excitability. Inhibiting Ca^{2+} release in ICC-IM would reduce ANO1 activation and reduce excitability.

Excitatory nerve stimulation in the stomach has both inotropic and chronotropic consequences. The inotropic effect is to enhance the amplitude and duration of slow waves, resulting in stronger peristaltic contractions. The chronotropic effects increase the frequency of slow waves. It does not appear that the chronotropic effects are due to direct cholinergic innervation of ICC-MY, the pacemaker cells. Instead, the depolarizations, caused by cholinergic stimulation of ICC-IM, are capable of enhancing pacemaker frequency.[40] Chronotropic effects of excitatory nerve stimulation are lacking in mutant animals lacking ICC-IM,[41] confirming the importance of ICC-IM in transducing neural inputs to regulate slow wave frequency.

Extrinsic innervation comes from both sympathetic and parasympathetic nerves.[30,42–44] Parasympathetic efferent neurons, with cell bodies in the dorsal motor nucleus in the brainstem, innervate myenteric neurons, with 70% or more of gastric neurons, including both excitatory and inhibitory motor neurons, receiving direct input from vagal efferent neurons.[45] Vago-vagal reflexes are responsible for many of the gastric responses to eating. For example, ingestion of food leads to relaxation of the proximal stomach, gastric accommodation, through a vago-vagal reflex that ultimately activates enteric inhibitory motor neurons to release NO.[46,47] Sympathetic innervation originates in the intermediolateral cell column of the thoracic spinal cord levels 5–10 and synapses with post-ganglionic neurons in the celiac and superior mesenteric ganglia. Sympathetic neurons regulating motility are focused on myenteric ganglia, but sympathetic fibers, labeled with tyrosine hydroxylase antibodies, also innervate the muscle layers directly. Sympathetic input inhibits gastric contraction, but this occurs primarily when vagal excitatory nerves are active, suggesting prejunctional targeting of sympathetic fibers to vagal inputs to excitatory motor neurons.

Specializations of the Pyloric Sphincter

The pyloric sphincter is a narrow zone of thickened muscularis and increased luminal pressure (radiologically estimated to be 1.2 cm in width) at the junction between the stomach and duodenum. Pyloric contractions and relaxations also depend on transduction of neural signals by ICC and conduction of responses to SMCs.[48]

Studies of pyloric muscles in vitro suggest that there are at least 2 independently controlled, functional areas of the pyloric musculature: the circular muscle close to the myenteric plexus, which is dominated by the propagation of gastric slow waves and results in sphincteric contractions at the termination of each gastric peristaltic event; and the deeper, thickened circular muscle regulated by motor neurons, as slow waves do not propagate into this region.[49] Independent control of the 2 regions may provide temporal and functional regulation of pyloric resistance.

At the gastroduodenal junction, there is separation of the electrical and mechanical functions of the stomach and pylorus from the duodenum, despite clear anatomical connections between the muscular tissues. ICC generate and propagate slow waves in both the stomach and small intestine,[30] and there is reduction in the density of ICC networks within a narrow zone between the pylorus and duodenum that appears not to support propagation of slow waves, thereby facilitating independent electrical and motor activities in the 2 organs.[48]

Enteric inhibitory neurotransmission, measured by inhibitory junction potentials in canine pyloric muscles, is mediated primarily by NO and by a purine neurotransmitter[50,51] acting through activation of small conductance Ca^{2+}-activated K^+ channels. Inhibition of inhibitory junction potentials unmasked excitatory junction potentials in the myenteric region and increased the excitability of SMCs and contractions in the submucosal region of the pylorus. Both the myenteric and submucosal layers of pyloric muscles are innervated by nitrergic neurons, as confirmed by NO synthase (NOS)-like immunoreactivity.[48,52]

As in the main areas of the stomach, post-junctional nitrergic responses depend on ICC.[48,53] Lesions in the nitrergic pathway that regulates pyloric motor activity, whether due to loss of NOS, loss of NOS neurons, or loss of ICC that contribute to neurotransduction of nitrergic signals, result in abnormal regulation of pyloric relaxation and, therefore, could impede gastric emptying. It should be noted

that loss of ICC appears to have clinical relevance because reduction or morphologic abnormalities in ICC have been noted in full-thickness biopsies from gastric muscles of patients with idiopathic and diabetic gastroparesis.[54,55] Recent studies have also shown reduced pyloric ICC in patients with gastroparesis.[56]

Enkephalinergic nerve fibers are also present in the tunica muscularis of dogs,[57] cats,[58] and humans,[59] suggesting regulation of neural responses by endogenous opiates, including inhibition of both cholinergic excitatory and nitrergic inhibitory junction potentials in canine pyloric muscles.[60] Endogenous opiate peptides (eg, met-enkephalin) participate in regulation of pyloric contraction (eg, in response to duodenal acidification)[61] and exogenous opioids interfere with normal neural regulation of the pylorus and cause stimulation of pyloric tone and phasic contractility.[62] The effects of opioids to increase pyloric tone are mediated by inhibition of nitrergic relaxation[56] or cholinergic stimulation.[63]

Functions of the pyloric sphincter regulating gastric emptying are not entirely understood. Instillation of acid into the duodenum, but not the antrum, increased the frequency and amplitude of phasic contractions in the pylorus, and this response was antagonized by tetrodotoxin (implying neural mediation) and intraluminal naloxone (opioid antagonist). Conversely, there was no effect noted with cholinergic, adrenergic, or serotonergic modulation of pyloric contraction in response to intraduodenal acid.[64]

Pathophysiology of Gastroparesis

Neuromuscular Diseases Affecting Nonsphincteric Gastric Muscles

Figure 4 summarizes the disorders of extrinsic and enteric neural control and muscle resulting in motility disorders.[44] Idiopathic and diabetic gastroparesis are typically associated with postprandial antral hypomotility with reduced frequency (mean, <1/min postprandially) and normal amplitude contractions[49]; infiltrative disorders, such as scleroderma, result in low-amplitude contractions antral (<40 mm Hg) and intestinal contractions (<2 mm Hg)[6,65]; the latter resulting in delayed gastric emptying and small bowel transit and absence of ileocolonic bolus transfers. In more than 1280 patients with upper gastrointestinal symptoms who underwent both gastric emptying and gastric accommodation studies, it was found that increased accommodation (postprandial to fasting ratio >3.85) was more prevalent in patients with delayed compared with accelerated gastric emptying.[66] Higher postprandial gastric volumes are also associated with delays in gastric emptying of solids measured simultaneously.[67]

Post-Surgical or Post-Bariatric Endoscopy Gastroparesis

Vagotomy performed for peptic ulcer disease is invariably associated with a drainage procedure, either pyloroplasty or gastrojejunostomy. Post-surgical gastroparesis[68] is associated with partial gastrectomy and is associated with either extrinsic denervation of the gastric remnant or abnormal motility in the anastomosed jejunal loop.[69,70] Proximal gastric vagotomy inhibits gastric tone and delays gastric emptying of liquids without altering antral contractility.[71]

Fundoplication may result in gastroparesis[72] due to vagal injury, and this is associated with impaired antral motility.[73] Transient vagal injury may result from endoscopic variceal sclerotherapy[74] or from radiofrequency ablation[75] of accessory conduction pathways in the heart and may be manifest by dysphagia, nausea, vomiting, and nonspecific esophageal motor disorders, accelerated gastric emptying of solids at 1 hour, or delayed gastric emptying of solids. The restoration of vagal function is associated with relief of symptoms or normalized objective tests.

Partial gastrectomy results in acceleration of gastric emptying of liquids and overall stasis if there is associated vagotomy, as was the norm in surgery performed for peptic ulceration, and was associated with either dumping syndrome (involving mainly liquids) or gastric stasis of solids.[76] Dogs with Billroth I gastrectomy with loss of the pylorus had larger solid food particles emptied, and this may contribute to malabsorption after this form of gastric surgery.[10]

Uncomplicated fundoplication[77] and sleeve gastrectomy[78] accelerate gastric emptying of solids, as the reservoir capacity of the stomach is reduced and repeated esophageal peristaltic contractions induce isobaric pressurization of the proximal stomach,[79] thus providing the drive to pressurize and empty the vertical compartment of the gastric sleeve.

Sleeve gastroplasty produces a funnel-shaped stomach with a constricted middle and distal stomach, resulting in delayed gastric emptying.[80] Inclusion of the distal antrum in the gastroplasty may impact the solid trituration and emptying of the solid phase of the meal from the stomach.

Pyloric Dysfunction

Pyloric dysfunction was first described in diabetic gastroparesis in 1986[7] as unusually prolonged, but intermittent contractions characterized by marked increases in baseline tone at the pylorus, or "pylorospasms." These findings were reported in 24 diabetic patients with symptoms of gastroparesis.[7] Concomitant pylorospasm, antral hypomotility, and evidence of extraintestinal autonomic neuropathy in 13 of 24 patients suggested the pylorospasm was secondary to diabetic neuropathy.[7] Because loss of ICC has also been reported in diabetic gastroparesis,[54] it is also possible that these effects could be due to a damaged ICC-MY network (antral hypomotiity) or loss of pyloric ICC-IM (pylorospasm). In recent years, the pylorus has become a potential target for endoscopic treatment, as described below. Pyloric dysfunction and gastric stasis may also result from effects of opioid use, which is becoming increasingly prevalent in patients with gastroparesis.

In diabetic gastroparesis, excessive postprandial pyloric tonic and phasic pressure activity may accompany antral

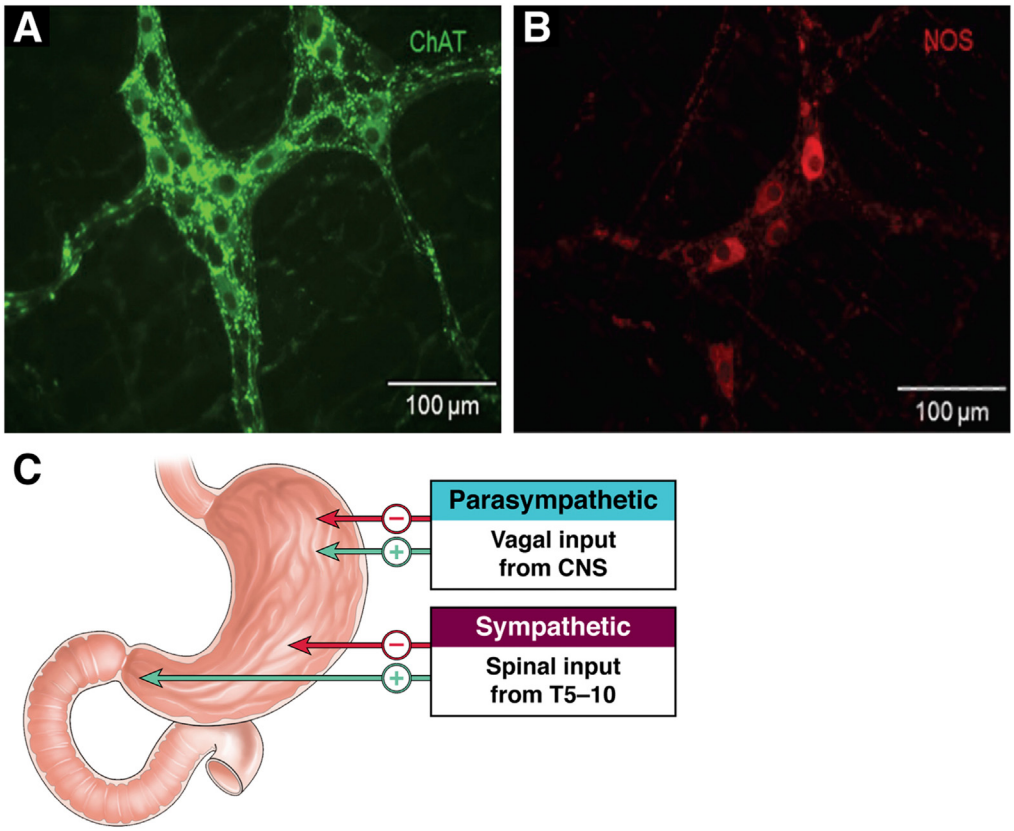

Figure 4. (*A*) Intrinsic excitatory cholinergic neuron. ChAT, choline acetyl transferase. (*B*) Intrinsic inhibitory nitrergic neuron (NOS). (*C*) Extrinsic neural control of gastrointestinal motor function. Parasympathetic supply is generally excitatory (indicated by *plus sign* [+]) to nonsphincteric muscle or excitatory to inhibitory intrinsic nerves (indicated by *minus sign* [–], eg, nitrergic neurons). Sympathetic nerves are generally inhibitory to nonsphincteric muscle and stimulatory to sphincteric muscle, such as the pylorus. CNS, central nervous system.

hypomotility,[7] and both may be due to damage of ICC-MY (antral hypomotility) and ICC-IM (pylorospasm). Researchers at Temple University[81] performed pyloric studies using the EndoFLIP device (composed of 17 impedance electrodes spaced 4 or 8 mm apart and 1 solid-state pressure transducer to determine intraballoon pressure) in 39 patients with idiopathic and 15 patients with diabetic gastroparesis. They measured the pressure, diameter, cross-sectional area, and distensibility index (cross-sectional area in cm^2 divided by the simultaneous intraballoon pressure in mm Hg), and documented the wide range in diameter (5.6–22.1 mm) and distensibility (1–55 mm^2/mm Hg) of the pylorus. Symptoms of early satiety and postprandial fullness were inversely correlated with pyloric sphincter diameter and cross-sectional area.[81] Several studies have shown that pyloric distensibility was decreased in gastroparesis and correlated with gastric emptying as well as gastroparesis symptoms.[82]

Potential Cellular Basis for Gastroparesis: Oxidative Stress and Inflammation

Experimental models of gastroparesis show a reduction in, or remodeling of, ICC-IM, leading to secondary effects in SMCs because of the lack of trophic factors (eg, stem cell factor).[83] A few case reports document the reduced numbers of ICC-IM in patients with gastroparesis.[84] This loss of ICC appears to result from imbalance between processes that injure ICC networks and those that generate and maintain ICC. For example, relative insulinopenia and insulin growth factor-1 deficiency in diabetes leads to reduced production of stem cell factor by SMCs, an important ICC survival factor.[85] Moreover, diabetes is associated with high oxidative stress, which may result from down-regulation of macrophage heme oxygenase-1.[86,87] Loss of $CD206^+$, anti-inflammatory M2 (resident) macrophages, and increased expression of genes associated with pro-inflammatory M1 macrophages in full-thickness gastric biopsies from patients with gastroparesis have also been reported. Depletion of M2 macrophages, which express heme oxygenase-1, leads to oxidative damage to the pacemaker cells.

Light microscopic studies of full-thickness gastric biopsies from patients with idiopathic and diabetic gastroparesis showed no significant differences in nerves or SMC cell markers, except for reduction in expression of neuronal NOS in diabetic compared with idiopathic gastroparesis.[54] At the ultrastructural level, diabetic gastroparesis was associated with a thickened basal lamina around SMCs, and altered neuronal cell bodies and nerve endings and fibrosis around nerves were noted as more severe in idiopathic than diabetic gastroparesis.[55]

From proteomics and deep sequencing of gene transcripts[88–90] of full-thickness gastric body biopsies, it was shown that granulocyte adhesion and diapedesis, as well as a macrophage-based immune dysregulation pathway, are the most significantly affected pathways altered in both diabetic and idiopathic gastroparesis. M1 (pro-inflammatory) macrophages were increased in idiopathic

gastroparesis samples compared with their controls. In addition, diabetic gastroparesis was associated with proteins involved in the complement and prostaglandin synthesis pathway. However, the same study revealed no enrichment of genes associated with M1 (marrow-derived) or M2 (resident) macrophages in the biopsies relative to diabetic control samples. Finally, diabetic gastroparesis biopsies had reduced expression of inflammatory markers. The significance of these findings is unclear because diabetic gastroparesis has been associated with M2 macrophage deficiency, which would be expected to result in increased inflammation.

Overall, further research on both human biopsies and animal models of diabetes is needed to understand the molecular and cellular bases for gastroparesis. The challenges include potential of sampling error impacting morphologic or expression studies; the need to clarify the role of inflammatory mechanisms; the impact of vagal denervation (eg, associated with diabetes mellitus) on inflammation, given the anti-inflammatory ENS–macrophage nicotinic acetylcholine receptor cholinergic pathway[91]; and the need for treatments to effectively inhibit oxidative stress on the gut neuromuscular apparatus. A recent controlled drug trial of hemin failed to achieve the pharmacokinetic goals to test its efficacy,[92] so tests of other therapies are needed.

Symptoms in Relation to Gastric Motor Dysfunctions

The relationship between impairment of gastric emptying of a mixed radiolabeled meal or gastric accommodation (by single-photon emission computed tomography) and upper gastrointestinal symptoms was examined in almost 1300 patients at Mayo Clinic.[66] Nausea, vomiting, weight loss, and abdominal discomfort were more prevalent in those with delayed gastric emptying compared with those with accelerated or normal gastric emptying; bloating was associated with accelerated gastric emptying. In 108 of those tertiary referral patients with diabetes and upper gastrointestinal symptoms consistent with gastroparesis,[93] the most common presenting symptoms were nausea (80.6%), vomiting (53.7%), and abdominal pain (52.8%). The most frequent symptom associated with abnormal gastric accommodation was belching.

In the National Institutes of Health Gastroparesis Consortium multicenter database,[94,95] severely delayed gastric emptying of a 2% fat, 255-kcal meal was associated with worse vomiting, more severe anorexia, and overall gastroparesis symptoms, as well as stomach fullness, postprandial fullness, and early satiety.[96]

However, gastroparesis symptoms showed little association with profiles of emptying of a wireless motility capsule (WMC).[97] This discrepancy may reflect the different results[98] obtained with an easily triturated egg-substitute meal compared with a relatively large WMC that is usually emptied from the stomach with the return of phase 3 of the interdigestive migrating motor complex.[99] Hinder and Kelly[17] demonstrated previously that emptying of 7-mm diameter radiopaque spheres from canine stomach did not occur for at least 4 hours after ingestion of liver cubes and water.

In the original description of gastroparesis diabeticorum, Kassander[100] identified that diabetic triopathy (ie, retinopathy, nephropathy, and neuropathy) was highly prevalent. In more recent cohorts,[93] diabetic triopathy was uncommon at the time of presentation with upper gastrointestinal symptoms: 10% of patients with type 1 diabetes and 3% with type 2 diabetes had triopathy with gastroparesis. Indeed, 39% of patients with diabetes and gastroparesis did not have any complications of diabetes.[101] Examples of diseases causing GI motility disorders are shown in Figure 5.

Diagnostic Tests

Typically, diagnostic testing is guided primarily by symptom pattern and severity. Delayed gastric emptying can be documented by scintigraphy and stable isotope breath test; however, presence of retained food in the stomach at endoscopy is of limited predictive value[102] unless the patient has a known underlying disease predisposing to gastric retention. Barium studies and scintigraphy using labeled liquid or semi-solid meals are typically normal and of limited diagnostic value, even in the presence of moderately severe symptoms. The tests that are available to measure gastric emptying noninvasively are summarized in Supplementary Table 1.[103]

Scintigraphic assessment of solid emptying over 4 hours is a more sensitive test, with a well-defined normal range, and with the proportion retained at 2 and 4 hours having a sensitivity of 90% and a specificity of 70% to identify delayed emptying.[104] It is not accurate to extrapolate the emptying pattern from scans taken for a shorter duration (typically 90 or 120 minutes).

Another useful test for measuring solid-phase gastric emptying uses a standardized biscuit enriched with a ^{13}C-enriched substrate. When metabolized, the proteins, carbohydrates, and lipids of the *Spirulina platensis* or the medium-chain triglyceride, octanoate, result in a rise in respiratory $^{13}CO_2$ that is measured by isotope ratio mass spectrometry, allowing for estimation of gastric emptying $T_{1/2}$.[105–107]

The WMC, which senses pressure, temperature, and pH, has been approved by the US Food and Drug Administration for the evaluation of gastric emptying and colonic transit time in people with suspected slow transit constipation.[108] Gastric emptying time is identified by a rise in pH from gastric baseline to >4.0 in the duodenum.[108] The estimated gastric emptying time with the WMC is not as accurate as scintigraphy with a digestible solid meal. The WMC identified lower numbers of contractions and motility indices in gastroparesis.[109] Use of the capsule is contraindicated in children and those with a known history of esophageal stricture or possible intestinal obstruction.

For people with severe upper gastrointestinal symptoms, antropyloroduodenal manometry assesses pressure profiles in the stomach and small bowel; neuropathic disorders are associated with distal antral contractile

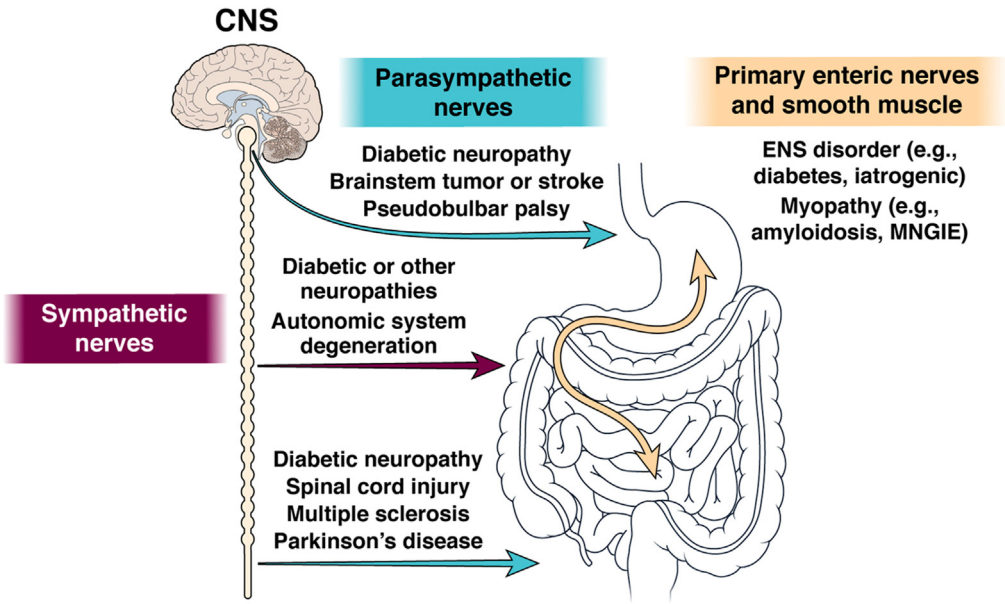

Figure 5. Examples of diseases causing gastrointestinal motility disorders. These disorders, including gastroparesis, may result from abnormalities in parasympathetic nerves as occurs in diabetic neuropathy or brainstem diseases affecting vagal and other autonomic nuclei; disorders affecting sympathetic nerves, including neuropathies and dysautonomias; and diseases affecting primarily the enteric nerves (ENS) or smooth muscle, including myopathies, such as amyloidosis and mitochondrial neurogastrointestinal encephalopathy (MNGIE). CNS, central nervous system. From Camilleri,[44] reproduced with permission.

frequency of less than an average of 1/min during the first postprandial hour, whereas myopathic disorders are associated with amplitude <40 mm Hg and small intestinal amplitude <10 mm Hg.[6,110] Manometry may also reveal excessive tonic and phasic pressure activity at the pylorus,[7] although the sensitivity of manometry for measurement of pyloric function is not established. Pyloric dysfunction is also documented with a functional luminal imaging probe performed during endoscopy (EndoFlip), which assesses diameter and distensibility of the pylorus.[104,108,109,111,112] It has been proposed that this measurement might facilitate selection of those for pyloric interventions for gastroparesis.

Management

Management of gastroparesis should include assessment and correction of the nutritional state, relief of symptoms, improvement of gastric emptying, reversal of iatrogenic gastroparesis (chiefly due to opioids), and, in patients with diabetes, glycemic control.

Nutrition

The first step in the management of gastroparesis is to educate the person to use a small-particle diet, aided with cooking of nondigestible fiber and homogenization of solids to a small particle size.[113] Although nutritional requirements and symptoms can be addressed to a variable extent in persons with mild and compensated gastroparesis, those with severe gastroparesis often require hospitalization for 1 or more of the following measures: intravenous hydration and correction of metabolic derangements (eg, ketoacidosis, uremia, hypoglycemia, or hyperglycaemia), nasoenteric decompression, or enteral nutrition to manage vomiting and nutritional requirements.[114]

For individuals with severe gastroparesis who do not respond to the measures outlined above, it may be necessary to bypass the stomach with a jejunal feeding tube.[115] This procedure should be preceded by a trial of nasojejunal feeding for a few days, with infusion rates of at least 60 mL of iso-osmolar nutrient per hour. It is preferable to place jejunal feeding tubes directly into the jejunum either by endoscopy or, if necessary, by laparoscopy, rather than via percutaneous endoscopic gastrostomy tubes. Such tubes allow restoration of normal nutritional status, but they are not without adverse effects, and it is important to allow for a few days of habituation, escalating the infusion rate stepwise and slowly from 10 mL/h to the goal of 60 mL/h.

Parenteral nutrition may become necessary in cases of malnutrition. Ideally, this is a temporary measure for patients presenting with severe weight loss and poor oral tolerance, with conversion to long-term enteral nutrition in order to avoid risks. such as central line infection and metabolic complications.

Bezoars may be mechanically disrupted during endoscopy, followed by gastric decompression to drain residual nondigestible particles.

Pharmacological Interventions

Stimulation of nonsphincteric muscle contractility. Erythromycin, at a dose of 3 mg/kg body weight intravenously every 8 hours, can accelerate gastric emptying.[116,117] When oral intake is resumed, treatment with oral erythromycin, 250 mg 3 times per day for 1–2 weeks, is worthwhile. The prokinetic effects of erythromycin are limited by tachyphylaxis.

In the United States, the only available medication is metoclopramide, a peripheral cholinergic and antidopaminergic agent. During acute administration, it initially enhances gastric emptying of liquids in diabetic gastroparesis, but its symptomatic efficacy (data summarized in Camilleri et al[12]) is probably related to its central antiemetic effects. However, its long-term use is restricted by a decline in efficacy and by central nervous system adverse effects, most commonly reversible involuntary movements and tardive dyskinesia (irreversible), in the range of 0.1% per 1000 patient-years.[118] Therefore, it is preferred to prescribe a dose of 10 mg 3 times per day, administered 30 minutes before meals and the US Food and Drug Administration guidance suggests a period of up to 3 months only. Intranasal formulation of metoclopramide[119] has been approved for treatment of adults with gastroparesis, although its efficacy was only proven in women in the controlled trial.

Experimental medications in development for gastroparesis are felcisetrag (5-HT_4 agonist),[120] tradipitant (NK1 antagonist),[121] relamorelin (ghrelin agonist),[122] and trazpiroben (dopamine D_2/D_3 receptor antagonist).[123]

Supplementary Table 2 lists current[117,120–136] and investigational[137] prokinetic drugs for gastric motility disorders, as summarized recently.[138]

Two pharmacological approaches pursued to reverse pyloric dysfunction. First is reversal of the reduced neuronal NOS expression and decreased guanosine 3′,5′-cyclic monophosphate content with the phosphodiesterase-5 inhibitor, sildenafil. Sildenafil had no significant effect on gastric emptying in gastroparesis associated with uremia.[136] Second, given that naloxone corrected gastric stasis in patients with gastric hypomotility,[139] 2 studies[140,141] tested peripherally active μ-opioid receptor antagonists, methylnaltrexone (subcutaneous 0.30 mg/kg) or naloxegol (25 mg), daily on opioid-induced delay in gastric emptying and noted they did not reverse the retardation of gastric emptying in healthy volunteers treated with codeine 30 mg 4 times per day.[141] However, alvimopan, administered at 1 log higher than the dose used for opioid-induced constipation, reversed the retardation of transit induced by the same dose of codeine.[142]

Anti-nausea medications are critical for relief of nausea and vomiting, however, their efficacy is based predominantly on mechanisms of action rather than formal randomized controlled trials. Ondansetron (4–8 mg 3 times per day as tablet or oral dissolving tablet) is a 5-HT_3 antagonist that reduces nausea without affecting gastric compliance or postprandial accommodation.[143] The 5-HT_3 antagonist, granisetron, is available as a sustained-release transdermal patch,[144] which was shown in an open-label study to reduce nausea and vomiting in gastroparesis. Prochlorperazine and promethazine reduce nausea through effects on dopamine (D2) and histamine (H1) receptors, respectively, and are available as oral or rectal formulations. Drowsiness, dry mouth, and constipation are common adverse effects. Promethazine may be habit-forming and is reserved as a "rescue" agent. In a placebo-controlled trial, the NK1 receptor antagonist, aprepitant (which acts on the vomiting center and is approved for chemotherapy-induced emesis), improved nausea.[134] Many patients with gastroparesis use $^{\Delta 9}$THC[145] for symptomatic relief; however, marijuana[146] and the nonselective cannabinoid receptor agonist, dronabinol,[147] retard gastric emptying.

Gastric electrical stimulation. A systematic review and meta-analysis[148] documented 5 studies that randomly allocated patients to periods with or without gastric electrical stimulation (GES) and showed no significant differences in the total symptom severity scores between these periods, in contrast to 16 open-label studies of GES, which showed a significant total symptom severity decrease. A 48-week observational study from the National Institutes of Health Gastroparesis Consortium[149] demonstrated a significant benefit for 1 symptom (ie, nausea) in 81 patients with GES compared with 238 patients without GES. In a randomized, double-blind, crossover trial[150] of 172 patients with refractory vomiting (133 with confirmed gastroparesis), GES improved vomiting score, but not gastric emptying or quality of life.

Relationship of Symptoms, Gastric Emptying, and Response to Prokinetic Agents

Efficacy of pharmacological agents in the treatment of gastroparesis has been documented in systematic reviews and meta-analyses in critically ill patients with feeding intolerance requiring enteral nutrition,[151] as well as in patients with gastroparesis.[152,153] However, questions have arisen regarding the association of gastric emptying delay and symptoms suggestive of gastroparesis.[154] Recent studies based on meta-regression of symptoms and gastric emptying measurements obtained with scintigraphy and stable isotope breath tests demonstrated that, when emptying was measured using a solid meal and there was assessment of emptying for >2 hours (ie, 3 or 4 hours) after ingestion of the test meal, there was a significant association between gastric emptying and symptoms.[155] In addition, when the same criteria to identify studies with optimal measurement of gastric emptying were used to select the studies for analysis, meta-regression demonstrated an association between acceleration of gastric emptying and reduction in symptoms[153]; specifically, a 20.4-minute reduction in gastric emptying $T_{1/2}$ was associated with a clinically relevant improvement in symptoms.

Interventions to Increase Pyloric Diameter or Distensibility and Impact on Symptoms and Gastric Emptying

The advent of procedures directed at the pylorus (botulinum toxin injection, surgical, or endoscopic pyloromyotomy) has renewed interest in the role of the region in the pathophysiology of gastroparesis.

Multiple open-label trials of intrapyloric botulinum toxin injections for gastroparesis suggested efficacy,[156–158] but the 2 randomized controlled trials[159,160] failed to show any improvement in symptoms. It is unclear whether participants had pyloric dysfunction at baseline, and it is unclear whether the neurotoxin had the expected effects on the pylorus, although 1 trial[159] confirmed improved gastric emptying compared with placebo. However, fasting pyloric compliance (based on measured pressure and pyloric diameter) was decreased in patients with gastroparesis and was associated with delayed gastric emptying, symptoms, and quality of life.[161] These data suggest that it may be useful to target pyloric compliance by pyloric dilation or botulinum toxin injection in patients with gastroparesis[161]; however, rigorous controlled trials are required that also include measurements of pyloric diameter and distensibility and impact on patient response outcomes in addition to motor functions.

Surgical pyloroplasty has been associated with short-term improvements in symptom severity scores 3 months post procedure and accelerated gastric emptying in several case series.[162–164] The standard Heineke-Mikulicz pyloroplasty involves transverse closure of a longitudinal incision across the pylorus, which involves both longitudinal and circular muscle layers. These studies set the stage for gastric peroral endoscopic myotomy (G-POEM),[165] which divides the pylorus from the mucosal surface and presumably cuts the circular muscle layer predominantly, while maintaining the longitudinal muscle to avoid perforation. Improved gastric emptying with G-POEM has also been documented.[166] Current evidence on the efficacy of G-POEM for gastroparesis is summarized in Table 1,[167–177] which shows results of exclusively uncontrolled trials. There is a critical need for a controlled study of the effect of G-POEM in patients with well-characterized gastroparesis, including baseline and post-treatment measurements of antropyloroduodenal motor function and the diameter, distensibility, and compliance of the pylorus itself, in order to ascertain whether there are predictors of responsiveness to the G-POEM procedure.

Several individual studies and published systematic reviews and meta-analyses based on 10 studies involving 292 patients[178] have documented early and medium-term efficacy of G-POEM in the treatment of gastroparesis and improvement of gastric emptying, as well as the superiority of this approach to GES for gastroparesis and equivalence of results to surgical pyloroplasty based on 332 patients with G-POEM (11 studies) and 375 patients who underwent surgical pyloroplasty (7 studies).[179]

It has been suggested that the change in diameter and distensibility index of the pylorus after G-POEM is associated with improved therapeutic outcome.[82,112,180] Two studies found that the average change in diameter of the pylorus may be about 2 mm[112] or 1.2 mm,[180] and this has led to the reiteration that, if antral hypomotility is a component of the pathophysiology in a patient undergoing G-POEM, then merely widening the pyloric diameter may not be sufficient therapy.[181] In fact, the average post–G-POEM changes in the diameter of the pylorus in those with clinical success and clinical failure were estimated to be 7.46 mm and 1.92 mm, respectively,[180] with the EndoFLIP device distended to 50 mL. Watts et al[112] also showed that after G-POEM, the number of phasic contractions of the pylorus remained unchanged compared with recordings before G-POEM, and this is consistent with the known antropyloric coordination because the circular muscle close to the myenteric plexus propagates gastric slow waves to the pyloric region, resulting in sphincter contraction.[49] It is unknown whether the phasic contractions at the pylorus actually provide resistance to flow of content out of the stomach; the option of extending the pyloromyotomy to the distal antrum in order to reduce pyloric phasic contractions might further aggravate gastric emptying by impacting antral trituration of solids. A recent study reported that gastroparesis symptoms were unrelated to the inner diameter or length of the pylorus or thickness of the pyloric wall, before or after G-POEM.[182] Further details on how to optimize functional benefit from the endoscopic pyloroplasty are therefore required. In addition, it is important to note that such surgical or endoscopic procedures may be complicated by development of dumping syndrome.

Future Treatment of Gastroparesis: Individualize Treatment Based on the Disorder of Function

Gastric emptying of solids needs to be measured for >2 hours (ie, 3 or 4 hours) to show correlation with symptoms and beneficial symptom responses in gastroparesis.[153,155] Patients should be selected for prokinetic agents based on delayed gastric emptying of solids. In a meta-regression[153] that included 9 studies with low risk of bias and optimal gastric emptying test methodology, there was a significant association between change in gastric emptying and upper gastrointestinal symptoms in response to prokinetic agents (specifically, cisapride, revexepride, domperidone, ghrelin, relamorelin, and the motilin receptor agonists, TZP-101 and TZP-102).

There is increased recognition of the overlap of functional dyspepsia and gastroparesis with common symptom profiles and variation in gastric emptying in the patients over time.[13] Additional studies are required to explore functions of ICC-IM and ICC-MY in functional dyspepsia. Because a link between loss of ICC and gastroparesis has been made, future investigation into how loss of these cells might be avoided or how the ICC phenotype might be restored should be pursued. Given that the origin of symptoms suggestive of gastroparesis may reflect other mechanisms, such as gastric hypersensitivity or alteration in gastric accommodation, other pathophysiologic mechanisms may also be targets for pharmacological therapy. Pharmacological agents have been used to target sensory mechanisms, such as mirtazapine,[183] an antagonist of the histamine receptor H1, the α2 adrenergic receptor, the serotonin receptors 5-HT_{2C} and 5-HT_3, and the NK1 antagonist, aprepitant,[134] which

Table 1. Published Studies on Gastric Peroral Endoscopic Myotomy

Patients, n	Gastroparesis type/no. of patients	Changes in GE	Changes in symptoms	Duration of follow-up	Adverse events	Reference
29	Diabetic, 7 Idiopathic, 15 Post-surgical, 5 Scleroderma, 2	70% normalized	79% at 3 mo; 69% at 6 mo GCSI improved from 3.5 to 0.9 at 3 mo	3 and 6 mo	17% (2/12) pneumoperitoneum requiring decompression	167
16	Diabetic, 9 Idiopathic, 5 Post-surgical, 1 Post-infectious, 1	75% normalized, 25% improved	81% improvement. GCSI improved from baseline of 3.4 to 1.46 12 mo later	12 mo	None	168
47	Diabetic, 12 Idiopathic, 27 Post-surgical, 8	4h retention improved: from 37.2% to 20.4%	GCSI improved from 4.6 to 3.3	3 mo (follow-up in 31/47 patients)	1 death (unrelated)	169
30	Diabetic, 11 Idiopathic, 7 Post-surgical, 12	47% normalized	No validated outcome measure available	6 mo	2/30 (6%): 1 prepyloric ulcer and 1 capnoperitoneum	170
13	Diabetic, 1 Idiopathic, 4 Post-surgical, 8	4/6 improved; % retention at 4 h improved from 49% to 33%	In 11: 4 considerably, 4 somewhat better, 1 no change, 2 worse	3 mo	3 accidental mucosotomy closed with clips; 1 pulmonary embolism	171
16	Diabetes, 3 Post-surgical, 13	Mean % retention (radiolabeled bread) at 2 h from 69.3% to 33.4%	Mean total symptom score from 24.25 to 6.37; 13/16 substantial improvement	3 mo	1 pyloric stenosis at day 45	172
20	Diabetic, 10 Nondiabetic, 10	% retention at 4 h improved from 57.5% to 15%; and 30% normalized	GCSI improved from 3.5 to 1.3; QOL improved	3 mo	3 mild hemorrhage, 3 gastric perforation, 1 moderate dyspepsia	173
40	Diabetic, 15 Nondiabetic, 25 (of which 18 were idiopathic)	% retention at 4 h reduced by 41.7%	Improved GCSI, nausea/vomiting, not bloating	Median 15 mo	1 tension capnoperitoneum, 1 exacerbation of COPD; 1 (Ehlers-Danlos syndrome) disrupted mucosotomy + ulcer	174

Table 1. Continued

Patients, n	Gastroparesis type/no. of patients	Changes in GE	Changes in symptoms	Duration of follow-up	Adverse events	Reference
22	Diabetic, 8, idiopathic, 14, all with GES and most with diverse other procedures	7/11 with post-G-POEM GE were normal	GCSI improved (reduction 1.63 points); improved all subscores	1 and 3 mo	1 laparoscopy for pain due to capnoperitoneum and adhesions	175
38	Post-surgical gastroparesis (76% for fundoplication or hiatal hernia repair)	% retention at 4 h improved from 46.4% to 17.9%; 50% normalized	GCSI improved (mean reduction 1.29 points); improved all subscores	1 mo	2 readmissions: 1 melena; 1 dehydration	176
80	Idiopathic (41.3%), postsurgical (35%) and diabetes (23.8%)	GE improvement in 64.2% and normalized in 47.2% (of 53 cases with test) at 3 mo	Decrease in total GCSI $>1+$ $>25\%$ decrease in at least 2 of the subscales in 66.6% at 12 mo	3 mo GES, 12 mo clinical	3 symptomatic capnoperitoneum, 1 mucosotomy; 1 thermal mucosal injury	177

NOTE. GCSI scores are mean values pre or post G-POEM.
COPD, chronic obstructive pulmonary disease; EDS, Ehlers-Danlos syndrome; GCSI, Gastroparesis Cardinal Symptom Index; GE, gastric emptying; QOL, quality of life.

in addition to effects on nausea, also increases gastric accommodation.[135]

Finally, it is anticipated that selection of patients for G-POEM should be based on objective measurements, such as diameter and distensibility index by EndoFLIP[103,180] or postprandial pyloric hypercontractile responses on antropyloroduodenal manometry. EndoFLIP can measure antropyloric propagated contractions or isolated pyloric contractions,[112,180] and the impact of such measurements on outcomes of G-POEM are awaited. Nevertheless, a recent study did not identify predictors of benefit with G-POEM based on EndoFLIP or antroduodenal manometry.[184]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.10.028.

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Conflicts of interest
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Supplementary Table 1. Noninvasive Measurements of Gastric Emptying

Feature	Gastric emptying by scintigraphy	Stable isotope breath test	Wireless pressure and pH capsule
Indication/function measured	Gastric emptying	Gastric emptying	Emptying and pressure amplitude
Device, assembly, or special requirements	External gamma camera and isotope-labeled meal	Breath collection vials and stable isotope-labeled meal	Intraluminal capsule with miniaturized strain gauge and pH measurement
Placement of device	—	—	Capsule swallowed
Performance/ versatility/ interpretation	Excellent, standardized meals, data acquisition and interpretation	Becoming standardized Performance related to mathematical analysis	Standard acquisition, delayed emptying fairly valid; pressures of unclear significance
Duration of study	Typically 4 h, could be added to small bowel and colon transit	3–4 h	6 h, could be added to small bowel and colon transit
Availability/potential use[a]	+	+++	+
Costs[a]	++	+	++

NOTE. From Shin and Camilleri,[103] adapted with permission.
[a]The plus signs signify the lowest (+) to the highest (+++) availability or potential use.

Supplementary Table 2. Current and Investigational Prokinetic Drugs for Gastric Motility Disorders

Drug name	Disease	Effect on gastric motor function	GP symptoms	Reference
5-HT_4 receptor agonist				
Tegaserod	GP	↑ GE	Not studied	137
Prucalopride	IG and DG	↑ GE	Improved	124
Velusetrag	IG and DG	↑ GE	Improved	125
Felcisetrag	IG and DG	↑ GE	Not studied	120, 126
$D_{2/3}$ receptor antagonist				
Trazpiroben (TAK-506)	IG and DG	↑ volume to fullness, No Δ in GE	Improved	123
Ghrelin receptor agonist				
Relamorelin	DG	↑ GE, ↑ antral contractions	Improved	122, 127–130
Motilin receptor agonist				
Erythromycin	IG and DG	↑ GE, ↑ fundic and antral contractions, ↓ pyloric contractions	Improved	117, 131, 132
Azithromycin	GP	↑ GE	Not studied	133
NK_1 receptor agonist				
Aprepitant	IG and DG	↑ GA, No Δ in GE	Improved	134, 135
Tradipitant	IG and DG	Not studied	Improved	121
Phosphodiesterase-5 inhibitor				
Sildenafil	GP with uremia	No Δ in GE	Not studied	136

NOTE. From Camilleri and Atieh,[138] reproduced with permission.
DG, diabetic gastroparesis; FD, functional dyspepsia; GA, gastric accommodation; GE, gastric emptying; GP, gastroparesis; IG, idiopathic gastroparesis.