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Fundamentals of Neurogastroenterology: Physiological Aspects and Clinical Implications

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The digestive tract plays a key role in maintaining homeostasis and the general well-being of the human body via complex physiological functions. These gastrointestinal functions include motility; mixing of ingesta with pancreatic, biliary, and enteric secretions; absorption of digested nutrients; and disposal of undigested residues. Such processes usually occur without conscious perception. However, approximately 30%–40% of the general population report digestive symptoms, often triggered by meal intake. Most of these people will be labeled as having a disorder of gut–brain interaction (DGBI). The pathophysiology of DGBI is complex and not only involves bidirectional dysregulation of gut–brain interaction (via the gut–brain axis), but also microbial dysbiosis within the gut, altered mucosal immune function, increased epithelial barrier permeability, visceral hypersensitivity, and abnormal gastrointestinal motility. In this article, normal physiology and pathophysiology of gastrointestinal function and processes underlying symptom generation are reviewed. This article provides a thorough appraisal of symptom profiles, pathogenesis, and functional tests of the wide array of DGBI.

Keywords: Disorders of Gut–Brain Interaction; Epithelial Barrier; Gastrointestinal Physiology and Pathophysiology; Immune Function.

The goal of this article was to appraise general and region-specific aspects of gastrointestinal (GI) physiology and pathophysiology along with clinical insights.

Physiology: Main Components

Perception

Peripheral nerves and afferent signaling. The GI tract is densely innervated to provide information on its luminal contents, potential threats, and all processes occurring as part of normal digestion and absorption. This information is collected by intrinsic and extrinsic afferent nerves and is of crucial importance to generate the appropriate physiological responses to guarantee homeostasis. Sensory neurons of the enteric nervous system (ENS) will activate local responses.

There is a vast array of receptors expressed on vagal afferents, and they can detect gut hormones,[1] neurotransmitters,[2] stretch,[3] tension and intestinal molecules, such as bacterial metabolites.[4] Specialized structures on enteroendocrine cells known as neuropods have been found to transduce sensory signals from the intestinal milieu to the brain through forming synapse-like connections to afferent nerves, including the vagus nerve.[5] The afferents of the vagus nerve have their cell bodies in the nodose ganglion and mainly connect to the nucleus of the solitary tract (NTS) and subsequently to the dorsal motor nucleus of the vagus. These afferent nerves detect physiological stimuli and are involved in the triggering of a variety of vagovagal reflexes, such as transient lower esophageal sphincter relaxations and meal-induced fundic accommodation. Conversely, the spinal afferents have their cell bodies in the dorsal root ganglia and synapse in the spinal cord and send information to the brainstem.[6]

Vagal fibers ascending from the GI tract synapse bilaterally on the NTS, and intestinal afferents synapse in the subnucleus commisuralis and medialis in the intermediate to caudal part of the NTS. From these areas, signaling

Abbreviations used in this paper: **CCK, cholecystokinin; CRH, corticotropin-releasing hormone; DGBI, disorders of gut–brain interaction; ENS, enteric nervous system; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; GI, gastrointestinal; HAPC, high-amplitude propagated contraction; IBS, irritable bowel syndrome; IBS-C, constipation-predominant irritable bowel syndrome; IBS-D, diarrhea-predominant irritable bowel syndrome; ICC, interstitial cells of Cajal; IL, interleukin; LES, lower esophageal sphincter; MMC, migrating motor complex; NTS, nucleus of the solitary tract; $t^1/_2$, half-life.**

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continues to other brainstem nuclei and forebrain structures. Multisynaptic pathways ascending from the NTS also communicate with the entire brain.

Elucidating the afferent and central mechanisms mediating the specific sensation of visceral pain is relevant in the context of disorders of gut–brain interaction (DGBI), especially irritable bowel syndrome (IBS) and functional dyspepsia (FD). The concept of visceral hyperalgesia to rectal or gastric distention has driven much mechanistic work in basic, preclinical, and clinical research, with implications for other chronic conditions such as inflammatory gastrointestinal disorders and eating disorders, which can all be conceptualized as disorders of gut–brain signaling, although they are not considered DGBI.[7,8]

The sensation of pain appears to be mediated by different afferents, depending on the part of the GI tract the noxious stimulus is applied to. Whereas pain from the rectum primarily involves pelvic pathways, more proximally it is mediated by thoracolumbar spinal afferents. Interestingly, as discussed in more detail below, inflammation can change both the response of specific classes of sensory neurons and the involvement of specific ascending pathways, which is relevant in the context of post-inflammatory hypersensitivity and postinfection IBS.[7,8] Apart from inflammation-induced hypersensitivity, the mechanisms and relevance specifically of altered peripheral afferent signaling in visceral hyperalgesia in DGBIs, such as IBS, remain unclear. For the sensations of hunger, satiety, fullness, and nausea, which play a prominent role in gastroduodenal DGBI, vagal afferent pathways play a primary role.

Given the complexity and variety of GI symptoms typically experienced by patients, it is likely that multiple or multimodal ascending and descending pathways are involved. Over the past decades, it is also becoming clear that the gut microbiota, the trillions of microorganisms within the gut, together with their genes, can also be a key player in moderating signals from the gut to the brain, in what is now known as the microbiome–gut–brain axis, with a direct relevance to DGBI (Figure 1).[9,10]

Brain processing. It is within the brain that the multiple facets that define the conscious experience of pain or other sensations are shaped, involving sensory-discriminative as well as affective-motivational aspects, behavioral-motor responses, and cognitive components. From the spinal cord, nociceptive ascending signals from the gut reach the brain via the anterolateral and dorsal column. The spinothalamic tract is the most important anterolateral pathway with projections to the ventral and medial nuclei of the thalamus. Connections from the ventral nuclei to the primary and secondary somatosensory cortex primarily mediate the sensory-discriminatory aspects of noxious stimulation, including information regarding intensity, duration, and location. Via connections between the medial thalamus and the limbic system, including the anterior cingulate cortex, as well as the midbrain, including the periaqueductal gray, affective-motivational aspects of pain are probably shaped. Descending cortico-limbic pain modulation via inhibitory pathways involving the brainstem modulate afferent visceral signaling. Disturbed endogenous pain modulation probably plays a role in visceral hyperalgesia and abnormal brain responsiveness to visceral pain stimuli in DGBI. These processes are only beginning to be understood in the visceral pain field in humans and involve not only functional but also structural brain alterations reflecting inter-individual differences in visceral sensitivity, the presence of chronic pain/patient status, affective disturbances, emotional context, genetic factors, trauma, personality, and sex.[7,11–13] With respect to altered neural processing of visceral stimuli in patients with DGBI, an increasing number of brain imaging studies using functional magnetic resonance imaging, positron emission tomography, or other emerging imaging technologies[12] have unequivocally described alterations in regional brain activation in patients with DGBI (mostly IBS and FD) during visceral stimulation compared with control groups. Although it has long been assumed that specific brain functions, such as pain processing, emotion, and cognition are attributable to the isolated operations of single brain regions, these processes are now viewed as resulting from the dynamic interactions of distributed brain areas operating in several large-scale networks.[12]

Ongoing efforts are focused on correlating these changes in brain imaging outcomes with clinical symptoms and other biomarkers. To date, effect sizes are generally small and causality has not been demonstrated for any of these parameters in longitudinal studies.[12]

Motility

The GI motor activity is aimed at propelling and mixing luminal contents as well as increasing the intestinal absorptive capacity. Moreover, the human digestive motility accommodates the transient storage of ingesta in some regions of the gut, thus preventing the retrograde movement of contents and facilitating the expulsion of residues. In the context of DGBI, GI dysmotility can develop through several mechanisms involving the gut–brain axis. First, various inflammatory, immune, infiltrative, or degenerative processes may directly affect the muscle and/or other elements of the ENS. Dysmotility may also be triggered indirectly in response to excess stimulation by visceral afferent (sensory) fibers that influence local GI motor function via modulation of motor neurons in prevertebral ganglia. In addition, activation of visceral afferent fibers induces autonomic changes integrated in the brainstem, including changes in heart rate and alterations in colonic tone (eg, vagally mediated gastrocolonic motor response) that may be increased in DGBI. Finally, psychosocial stressors can induce profound alterations in GI motility.

Anatomic and functional considerations. In each region of the GI tract, the muscle layers of the gut wall and their innervation are adapted and organized to ensure motor patterns specific of that particular region. The entire GI tract interacts with the central nervous system, and communication between various parts of the gut is facilitated by the longitudinal transmission of myogenic and

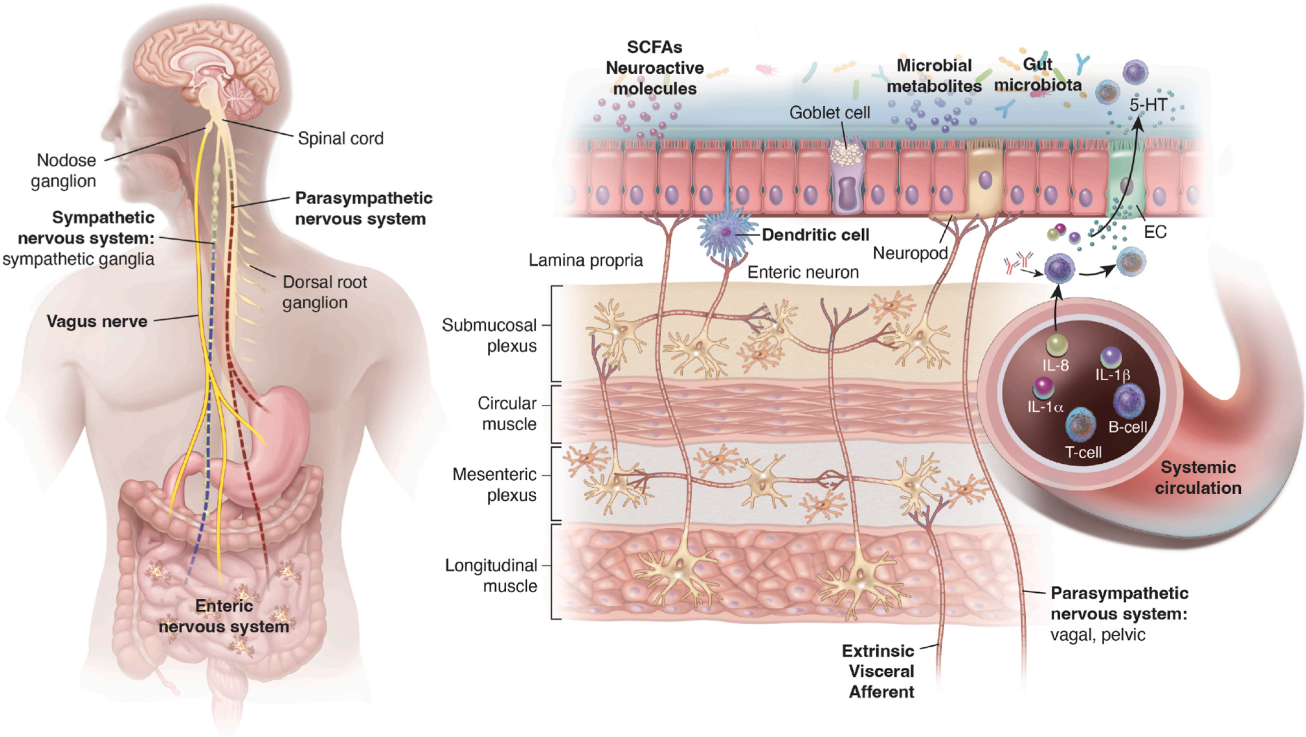

Figure 1. The microbiome–gut–brain axis. The gut microbiota, that is, the myriads of different types of microorganisms within the gut, can affect signal generation from the gut to the brain, hence playing a major role in physiological and pathophysiological conditions such as DGBI. EC, enterochromaffin cells; 5-HT, 5-hydroxytryptamine; SCFA, short-chain fatty acids.

neurogenic signals through the intrinsic neurons, as well as by reflex arcs through autonomic neurons. The aspects of gut motility that appear most relevant to the DGBI are contractile activity and tone, compliance and related phenomena, and transit.

Contractile activity and tone. Cyclic variations in the transmembrane potential of the smooth muscle cells occur in the stomach, small bowel, and colon. When recorded with extracellular electrodes, this electrical activity is usually referred to as slow-wave activity, electrical control activity, pacesetter potential, or basal electrical rhythm. In the presence of an excitatory neurotransmitter, such as acetylcholine, the transmembrane potential depolarizes further and, when the excitation threshold is exceeded, electrical spikes occur and superimpose on the plateau phase of the slow-wave activity. Phasic (short-duration) contractions originate from these electrical spikes, and thus the frequency of the phasic contractions in the stomach and small intestine are dictated by the slow-wave frequency. Because the slow-wave frequency varies along the length of the GI tract, the maximum contractile frequency varies similarly. The maximum contractile frequency in the stomach is approximately 3 per minute, while in the small intestine the frequency declines gradually from approximately 12 per minute in the duodenum to 7 per minute in the terminal ileum. A mixture of slow-wave frequencies is found in the colon and ranges from 1 to 12 per minute, while the correlation between electrical and contractile activities is much less clear. Whether the gut phasic contractions accomplish mainly mixing or propulsion depends on their temporal (eg, frequency and duration) and spatial (eg, spread of propagation) characteristics. In the small intestine, a phasic contraction is usually defined as a contraction in which the duration does not exceed the span of a slow-wave cycle. However, some longer lasting motor events are also considered phasic, for example, "prolonged propagated" or "giant migrating" contractions.

A more prolonged state of contraction, referred to as "tone," is not regulated by slow waves and may be clearly recognized in the proximal stomach (accommodation response to a meal) and the colon (response to feeding), as well as in some sphincteric regions. Tone is regulated by actin–myosin interaction mediated by cellular mechanisms that are modulated by neurogenic and mechanical stimuli. Phasic contractions, such as those regulating lumen caliber, may be superimposed on tonic activity.[14,15] Tone also modifies wall tension in response to gut filling and is therefore 1 determinant of perception of distention.[16]

Compliance and related phenomena. Compliance refers to the capability of a region of the gut to adapt to intraluminal distention. It is expressed as the ratio of the change in volume to the change in pressure and is obtained from the pressure-volume curve. Several factors contribute to compliance, including the capacity (diameter) of the organ, the elastic properties of the gut wall (ie, thickness, fibrotic component, and muscular activity), and the elasticity of surrounding organs (that can be influenced by fibrosis, ascites, and abdominal masses).[17]

A distending intraluminal volume produces a stretch and tension (force) on the gut wall, which determines the intraluminal pressure increment. In any given situation, wall tension, intraluminal pressure, and volume are interrelated by Laplace's law: $T = P \times R / 2$ for a sphere; and $T = P \times R$ for a cylinder (as a proxy for the gut), where T is wall tension; P is transmural pressure (intraluminal minus intra-abdominal pressure); and R is radius. However, this equation is influenced by the compliance of the organ. For instance, if the gut contracts (ie, tone increases), the same intraluminal volume will produce greater wall tension and higher intraluminal pressure than if the gut was not contracted. It has been shown that perception of gut distention is determined in part by wall tension, rather than by intraluminal volume or pressure. Hence, assessment of wall tension may be important in the interpretation of results of tests assessing perception of visceral stimuli,[16,18,19] but further data are required in each of the various regions of the gut.

Transit. Although flow reflects the local movements of intraluminal content, transit refers to the time taken for food or other material to traverse a specified region of the GI tract. In clinical terms, transit is one of the most important aspects of motility, as it represents the net interaction of a number of the other parameters discussed above and is a relevant and convenient index of organ function. Most measurements of transit are based on detecting intraluminal movements of an extrinsic marker labeling the luminal content. Transit depends on many factors, such as the physical (eg, solid, liquid, and gas) and chemical (eg, pH, osmolality, and nutrient composition) nature of both gut contents and the administered marker. Transit measurement is also influenced by the state of gut motility at the time of marker administration (eg, fasted vs fed motility) and any preparation of the gut (eg, cleansing of the colon). Summaries of transit measurements commonly used for solids and liquids include the half-life ($t^1/_2$) for emptying (eg, of the stomach or colon) and the amount (percentage) emptied from an organ at a given time after marker administration. In the esophagus, the transit time of the head of a swallowed bolus along the esophageal body is approximately 2–5 seconds. In the stomach, the $t^1/_2$ for the type of light meal commonly used in clinical testing is usually <90 minutes. In the small intestine, the head of such a meal usually reaches the cecum within 120 minutes. In the colon, the normal $t^1/_2$ for emptying is approximately 48 hours, but there is wide variability. The $t^1/_2$ for organ emptying and other parameters have been found to be abnormal in some DGBI.

The relationship between transit and phasic activity or tone is incompletely understood, but results of studies examining the movement of radiolabeled colonic contents in healthy subjects showed that only 28% are associated with propagating sequences, with the remainder associated with either nonpropagating activity (32%) or no pressure events (40%).[20] Moreover, patients with chronic constipation who have normal transit can exhibit reduced fasting and/or postprandial colonic tone.[15]

Factors Influencing Gastrointestinal Physiology

Immune Activation and Inflammation

Interest in the potential role of immune cell infiltration in DGBI increased significantly following the observation that the number of mononuclear cells and T lymphocytes remain elevated in rectal biopsies of patients who developed post-infection IBS.[21] Subsequent studies have, however, reported conflicting data on elevated numbers of lymphocytes in biopsies collected from patients with DGBI. However, to what extent these findings indicate a role for increased numbers of T cells in the generation of symptoms remains unclear.

Since the milestone article by Barbara et al[22] indicating increased mast cell counts localized in close proximity to nerve fibers in IBS, several studies have confirmed this finding in all IBS subtypes, mainly in the left hemicolon.[23] This finding is, however, not undisputed, as indicated by studies showing no increase or even a decrease in mast cell numbers.[24] In FD, evidence indicating a role for mast cells is rather limited and is directed more toward eosinophils.[25] In the initial reports, duodenal eosinophilia was suggested to represent a feature of postprandial distress syndrome,[26] but a recent meta-analysis showed similar counts in the different FD subgroups.[25] Taken together, the literature on increased counts of lymphocytes, mast cells, and eosinophils in DGBI is rather controversial, likely due to differences in patient selection, geographic differences, or variability in quantification methodology. Alternatively, not the number of immune cells, rather their activation status and mediator release play a more important role in symptom generation (Figure 2).

One approach to assess the activation status is to measure cytokine expression in biopsies or levels of circulating cytokines. A few larger studies in IBS[27,28] could identify an "immune-active" phenotype in one-fifth to one-third of the patients with IBS, as indicated by higher expression levels of interleukin (IL)1β and prostaglandin synthase 2.[28]

Most convincing evidence for immune activation in DGBIs is provided by studies evaluating bioactive mediators released by biopsies. Indeed, increased levels of pro-nociceptive mediators activating sensory neurons have been repeatedly reported in supernatant of biopsies collected from patients with IBS. Compared with control samples, IBS supernatant contains more histamine and tryptase and activates murine visceral afferents or human submucosal neurons, a phenomenon blocked by histamine antagonists and serine protease inhibitors.[29] Intestinal epithelial cells of patients with IBS release increased levels of the active protease trypsin-3, able to signal to enteric neurons and induce visceral hypersensitivity.[30] Notably, increased levels of the transient receptor potential cation channel subfamily V member 4 agonist, 5,6-epoxyeicosatrienoic acid, a metabolite of polyunsaturated fatty acids, have also been reported in IBS biopsies.[31] The evidence indicating altered synthesis and release of pro-nociceptive mediators in FD is rather limited, although increased spontaneous release of histamine and serotonin by gastric biopsies has been reported in patients with post-infection FD.[32]

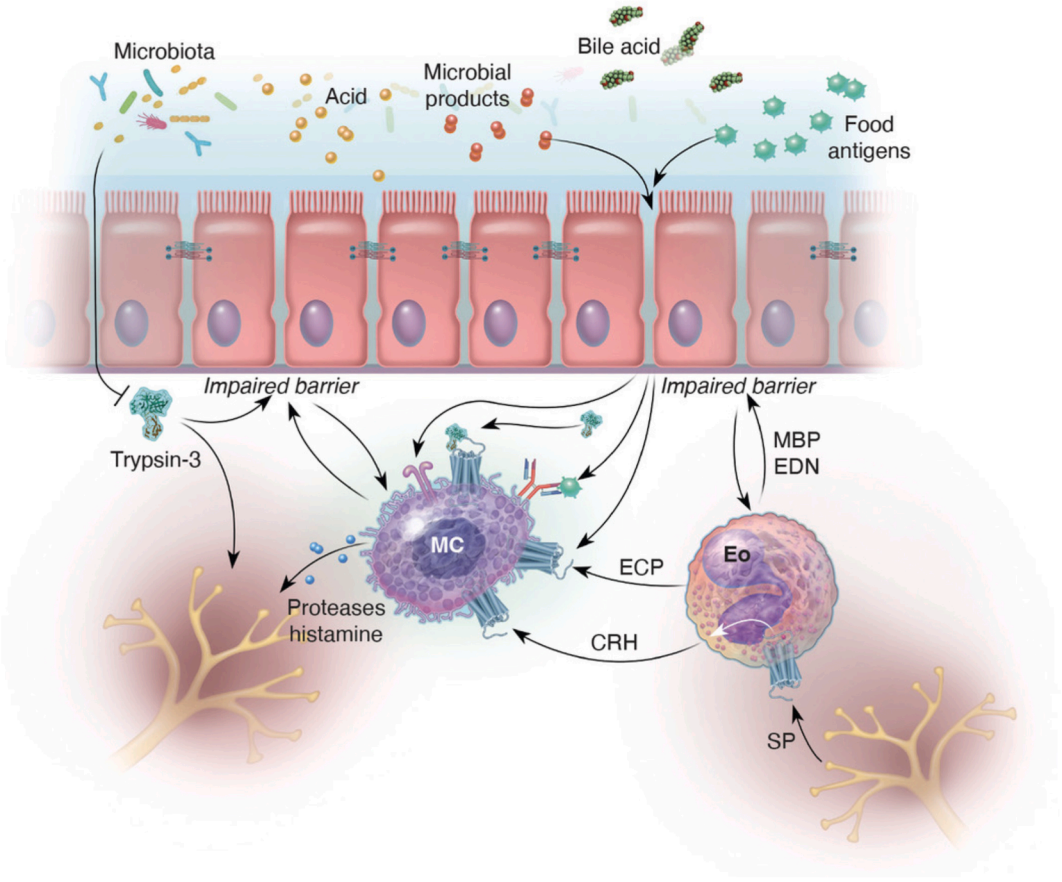

Figure 2. Increased presence and/or activation of mast cells (MC) and eosinophils (Eo) has been repeatedly reported in disorders of gut–brain interaction. Impaired barrier function allows luminal substances, including microbiota- and food-related antigens, to gain access to the subepithelial compartment and trigger activation of MC and Eo by a variety of mechanisms. MC and Eo-derived mediators can activate mucosal afferent neurons. Psychological stress impairs intestinal barrier function through a pathway involving locally secreted corticotropin-releasing hormone (CRH) and MC activation. ECP, eosinophil-derived cationic protein; EDN, eosinophilic-derived neurotoxin; MBP, major basic protein; SP, substance P.

Barrier Dysfunction

Since the first report in 2000, several groups reported increased small intestinal and colonic permeability in IBS using a variety of techniques.[33] The impaired barrier function was most consistently shown in postinfection IBS and diarrhea-predominant IBS (IBS-D),[33] and in constipation-predominant IBS (IBS-C), the majority of studies found no difference with healthy controls.[34,35] Permeability of the colonic mucosa, measured in Ussing chambers, was increased in IBS as a group.[36,37] In the majority of the studies, the permeability measures correlated to stool pattern or pain severity,[33] although this association was absent or even inverse in other reports.[34,38] Moreover, causal evidence linking increased permeability to symptoms and visceral hypersensitivity is still lacking. Interestingly, the observed barrier defect could be transferred by colonic infusion of fecal water of patients with IBS in mice or by incubating cell lines with biopsy supernatant, indicating a role for luminal mediators.[39–41] A smaller number of studies evaluated permeability in FD, demonstrating higher permeability in vitro[42,43] and in vivo.[44] In most studies there was no association between intestinal permeability and symptom severity.[45]

The expression of several tight junction–related proteins was altered in different regions of the GI tract in IBS and FD, although the reported abnormalities and the link to symptoms were not consistent between studies.[33,45] The etiology of the barrier defect in DGBI remains unclear, but luminal mediators, including proteases and (bile) acids,[30,41,46] psychological stress,[47] immune activation,[48] and decreased levels of glutamine[49] have all been implicated.

Psychological Factors and Stress

Acute or chronic stress disrupts the normal homeostasis of an organism, usually due to an actual or perceived threat.[50,51] The data on the effect of stress on GI physiology in humans is rather limited and most of our knowledge is based on animal data. Delayed gastric emptying, but a similar accommodation response, was observed after an acute stressor in healthy individuals.[37,52,53] However, in patients with FD, state anxiety and comorbid anxiety disorders were associated with impaired accommodation[54] and a history of physical abuse was associated with delayed gastric emptying.[55] Duodenojejunal contractions were

suppressed during acute psychological stress.[52,56] In contrast, colonic contractions were stimulated by an artificial stressor in patients with IBS but not in healthy individuals.[57] This enhanced colonic motility could be reproduced by exogenous corticotropin-releasing hormone (CRH) in male patients with IBS.[58] Exogenous CRH also stimulated esophageal contractility in healthy controls.[58]

Stress can impair intestinal barrier function through a mast-cell dependent mechanism.[59,60] The overexpression of CRH by intestinal eosinophils is correlated with background life stress and clinical severity in patients with IBS-D.[61] Visceral sensitivity is enhanced during states of psychological stress, which has been reported for esophageal acid perfusion,[62] colonic distention,[63–65] and anorectal electrostimulation.[66] Exogenous CRH has been also found to enhance esophageal sensitivity to distention in healthy individuals. In addition, a history of sexual and physical abuse was associated with lower discomfort threshold during gastric distention in patients with FD.[55]

Food and Meal Intake

Once food reaches the stomach, tension-sensitive mechanoreceptors become engaged and send gastric filling–related satiation signals to the brainstem through vagal afferents. The hormone leptin is thought to be involved in these processes.[67] Next, peristaltic contractions in the stomach advance the fragmented meal components into the duodenum, where mucosal enteroendocrine cells sense nutrient composition. This activates a negative feedback system, which enhances gastric accommodation and slows gastric emptying rate.[68] Duodenal enteroendocrine cells respond to nutrient exposure by releasing key peptides, such as glucagon-like peptide-1 or cholecystokinin (CCK), which subsequently activate vagal afferents or go into circulation. Glucagon-like peptide-1 infusion at physiological levels delays gastric emptying and results in increased satiety, making it an important anorexigenic hormone and therapeutic target in obesity.[69] CCK exerts negative feedback on gastric motility and slows down motility and influences satiety or satiation.[70]

Ghrelin and motilin are 2 key peptides involved in hunger signaling. Increases in circulating levels of endogenous ghrelin, following periods of food restriction, signal an increase in appetite and hunger and are correlated with a general increase in both “liking” and “wanting” of food.[71] The return of hunger seems driven by the release of motilin, which triggers a complex contractility pattern simultaneous with a hunger peak. The mechanisms controlling motilin release are poorly understood and require additional studies.[68]

From a clinical DGBI perspective, food intake is often associated with symptom occurrence.[72] For example, in patients with FD, gastric accommodation is impaired in a subset of patients and this is associated with early satiation and weight loss.[68] Moreover, dietary fermentable oligo-, di-, monosaccharides and polyols intake, the exclusion of which offers relief in a subset of patients with IBS, also influences the drop in intragastric pressure during food intake and its subsequent rise. This indicates that the size of gastric accommodation may respond to meal nutrient composition and be involved in triggering of meal-induced symptoms.[73]

Microbiome

Bidirectional communication along the microbiome–gut–brain axis is fundamental to the synergy between the GI microbiome and host (Figure 1).[8–10,74–76]

The gut microbiota–brain axis has increasingly received more attention in recent years for its apparent role in the pathophysiology of many DGBI disorders including IBS, characterized by visceral pain.[77–80] There is an increasing emphasis on the role of the microbiota in pain responses, particularly in visceral pain.[13,81,82] Studies in male germ-free mice (lacking a gut microbiota from birth) showed an increased visceral hypersensitivity to colorectal distention, which was reduced following microbial colonization of the GI tract.[83] Furthermore, it has also been reported that modulation of the gut microbiota in rodents by use of antibiotics in early life induces visceral pain.[84] Moreover, manipulation of the gut microbiota using probiotic bacterial species, including strains of *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*, as well as their soluble mediators, has been found to reduce the visceral pain response. Recently, studies have found that bacterial production of histamine may underpin visceral pain in animal models and a small subgroup of patients with IBS.[77]

Importantly, microbes in the GI tract communicate via metabolites similar to those recognized by host cells and that can interact with the intestinal epithelium.[76] Such neuromodulatory compounds include tryptophan precursors and metabolites 5-hydroxytryptamine, γ-aminobutyric acid, and catecholamines.[85–88]

Studies involving germ-free mice have found that the brain is affected by the absence of microbiota.[89] However, animals orally gavaged with specific strains of bacteria demonstrated alterations in behavior.[90] Even more promising, human studies involving similar bacterial strains confirmed the potential translatability of such findings.[90] In DGBI there is accumulating clinical evidence that there may be a microbiome-based signature in IBS.[78] Moreover, increasing numbers of meta-analyses showed that certain strains of probiotic bacteria may offer benefit in IBS.[91–93] A pilot study in patients with IBS also found that the probiotic *Bifidobacterium Iongum* NCC3001 reduces depression by reducing limbic reactivity in the brain.[94] However, the exact mechanism underpinning the relative contribution of the microbiome to DGBIs requires more attention. Finally, fecal microbiota transplantations are being studied clinically, although results so far are inconclusive.[95]

Genetics and Epigenetics

Gene-hunting efforts in IBS have been mostly limited to candidate gene surveys, with genome-wide association studies only recently reported in international large-scale population-based biobanks.[96] Compelling evidence for an IBS-predisposing role has been provided for the sucrase-isomaltase gene *SI*, coding for a brush border enzyme

breaking down carbohydrates like sucrose and starch.[97] By means of analogy with the congenital sucrase-isomaltase deficiency, a series of studies found that (1) adult congenital sucrase-isomaltase deficiency cases can be misdiagnosed as IBS-D[98]; (2) defective *SI* variants increase IBS risk[99–101]; and (3) *SI* carriers are less likely to benefit from a low fermentable oligo-, di-, monosaccharides and polyols diet.[102] This evidence highlights the role of food triggers in IBS, and provides rationale for personalizing (dietary) therapeutic approaches in *SI* genotyped patients.

Following early population-based pilot studies,[103,104] a few large-scale genome-wide association studies have been reported for IBS and its endophenotypes (gut motility studied as number of bowel movements via questionnaire data),[105–108] which led to the identification of genes previously associated with mood and anxiety disorders, and/or expressed in the central nervous system and ENS, and neuropeptide/neurotransmitter signaling pathways. This might explain the increased prevalence of mental health conditions in IBS and, possibly, the observed efficacy of psychotropic drugs and behavioral therapies in some patients.

Region-Specific Physiology

The Esophagus

Physiology. *Esophageal motility and function of the esophagogastric junction.* The main function of the esophagus is the propulsion of an ingested bolus from the oral cavity to the stomach through a peristaltic contraction. The contraction of the proximal striated muscle fibers follows the pharyngeal phase of deglutition and is directly controlled by sequential activation of somatic motor fibers, which originate in the nucleus ambiguus and nucleus retrofacialis, and reach the esophagus via the recurrent laryngeal branches of the vagus nerve.[109] In the distal part of the esophagus with predominantly smooth muscle fibers, the peristaltic contraction is orchestrated by the myenteric plexus combined with central input from the vagus.[110] This extrinsic innervation of the distal esophagus is supplied by neurons coming from the dorsal motor nucleus of the vagus, which synapse in the ganglia of the myenteric plexus instead of directly innervating the motor endplates, as in the proximal esophagus.[111]

In the myenteric plexus, there is a gradient along the length of the esophagus with a progressive increase of inhibitory motor neurons from proximal to distal. The time to contraction is determined by an intrinsic latency gradient, which is longer in the distal esophagus due to the predominantly inhibitory motor neurons of the myenteric plexus. The progressive increase in density of inhibitory neurons with an ensuing prolongation of the latency to contractions from proximal to distal contributes to esophageal peristalsis.[112]

Contraction of the longitudinal muscle layer results in shortening with concentration of circular muscle fibers orally to the bolus, maximizing contractile strength.[113]

The esophagogastric junction consists of the superimposed lower esophageal sphincter (LES) and crural diaphragm and prevents reflux of gastric contents into the esophagus by a tonic contraction, while at the same time allowing passage of a swallowed bolus by deglutitive inhibition. The tone of the LES is largely myogenic but modulated by neuronal input.[114] Upon swallowing or esophageal distention, release of nitric oxide by inhibitory neurons will result in an active relaxation of the esophagogastric junction.[115] Finally, the esophagogastric junction can also relax as a result of increased pressure in the stomach in a vagovagal reflex triggering a transient LES relaxation. This is a normal phenomenon in healthy individuals allowing gastric belching, but is also the main mechanism of gastroesophageal reflux disease (GERD) and is also involved in vomiting and rumination.[116]

Sensation. Vagal afferents innervating the smooth muscle layer and serosa are sensitive to pressure and stretch, whereas mucosal vagal afferents are triggered by various stimuli, including chemical (acid and bile), thermal, and mechanical stimuli from the lumen.[117] Vagal afferents are not involved in visceral pain transmission to the brain, but rather convey physiological stimuli. In contrast, spinal afferents, which have their cell bodies in the dorsal root ganglia and synapse in the dorsal column nuclei, are predominantly acting as nociceptors, transmitting (potentially) noxious stimuli to the brain.[117]

Main Symptoms and Pathophysiology

Symptoms. Dysphagia refers to the subjective sensation of difficult or slow bolus passage or the feeling that a food bolus gets stuck in the chest after swallowing. Dysphagia can result from organic lesions such as strictures and carcinoma, with dysphagia for solid substances preceding dysphagia for liquids, and with variable progression over time, depending on the underlying cause. In case of motility disorders, dysphagia for solids and liquids typically coexist from the onset even if solids typically cause more pronounced symptoms.

Heartburn is a burning-type sensation in the retrosternal area, which usually starts in the upper epigastrium or lower chest region and typically rises behind the breastbone toward the neck. Heartburn is the most typical symptom of GERD.[118] It is an intermittent symptom, which is often triggered by a meal, exercise, or when lying down. However, heartburn can also occur in the absence of pathologic reflux, as a result of esophageal or central hypersensitivity.

Chest pain from esophageal or central origin or noncardiac chest pain differentiates itself from heartburn because of the absence of a burning quality and usually manifests as pressure or a sharp pain. The most common cause of chest pain from esophageal origin is GERD, but it may also result from motility disorders, such as achalasia or esophageal hypercontractility.[119]

Belching indicates the retrograde movement of air through the esophagus followed by eructation. Excessive air in the stomach will trigger a transient LES relaxation followed by gastric belching as a physiological venting mechanism. However, the most common mechanism in

case of bothersome, repetitive belching is supragastric belching, when air is drawn or injected into the esophagus and released immediately without the air reaching the stomach.[120]

Regurgitation refers to the retrograde movement of gastric contents into the pharynx. Regurgitation is a typical symptom of GERD, but can also result from rumination, when gastric contents are pushed back in the esophagus by a sudden increase in intra-abdominal pressure through contraction of the abdominal wall. Rumination is often difficult to distinguish from GERD-related regurgitation or vomiting, but the effortless regurgitation of the recently ingested and pleasantly tasting food in the absence of retching or nausea is suggestive of rumination.[121]

Pathophysiology

Esophageal dysmotility. Significant abnormalities of esophageal motility detected by manometry will exclude the presence of a DGBI and lead to a diagnosis of a motility disorder, as defined by the Chicago classification, version 4.0,[122] which is beyond the scope of this overview. Nevertheless, esophageal muscle contractions may provoke symptoms, for example, sustained contractions of the longitudinal muscle layer, which are not detected with manometry, were closely associated with heartburn and esophageal pain sensation.[123]

Hypersensitivity. Similar to other DGBIs, visceral hypersensitivity is a well-described phenomenon in esophageal conditions including noncardiac chest pain,[124] globus,[125] and subtypes of GERD.[126] Hypersensitivity of the esophagus is a multimodal phenomenon, including mechanosensitivity to distention and chemosensitivity to luminal substances such as acid, and thermosensitivity.[127] Moreover, hypersensitivity can be both peripheral or central or a combination of both.

Dysfunction of the Upper Esophageal Sphincter

Upper esophageal sphincter (UES) abnormalities, including elevated resting pressure[128] and post-swallow residual pressure,[129] have been described in patients with globus sensation. However, it is a matter of debate whether this is causal to symptom generation or a consequence of tension or anxiety. One study supporting this disease mechanism found a globus sensation in one-third of healthy volunteers treated with intravenous citalopram, which was associated with higher post-swallow residual pressure.[130]

Stomach

Physiology. *Gastric emptying.* Gastric emptying depends on meal characteristics. Digestible solid emptying exhibits an initial lag phase, which depends on size and caloric load, followed by linear phases that empty >90% of the meal after 4 hours at 1–4 kcal/min.[131] Gastric emptying of indigestible solids >7 mm occurs later upon resuming fasting antral contractions.[132] Emptying of water is faster, exhibiting 50% emptying over <18 minutes. Nutritive liquids are emptied slower. Ghrelin and motilin regulate gastric motility, emptying, hunger, and satiety. CCK antagonists accelerate gastric emptying, reflecting inhibitory actions of CCK. Glucagon-like peptide-1 agonists slow emptying, while antagonists accelerate emptying.

Region-specific gastric motility. Motor patterns in the proximal stomach (ie, fundus and proximal corpus), distal stomach (ie, distal corpus and antrum), and pylorus have separate roles in regulating gastric emptying.

The main proximal gastric response to eating is accommodation, a decrease in tone and increase in volume that creates a storage reservoir. Accommodation begins with receptive relaxation upon oropharyngeal or gastric stimulation, followed by adaptive gastric relaxation, and peaking 15 minutes after eating, which is mediated by vasovagal reflexes.[133] Proximal tone then increases with gradual food transfer to the antrum. Accommodation is regulated by nitrergic and 5-hydroxytryptamine$_{1B/1D}$ pathways.

The distal stomach exhibits propagating phasic contractions. Their frequency and directionality are

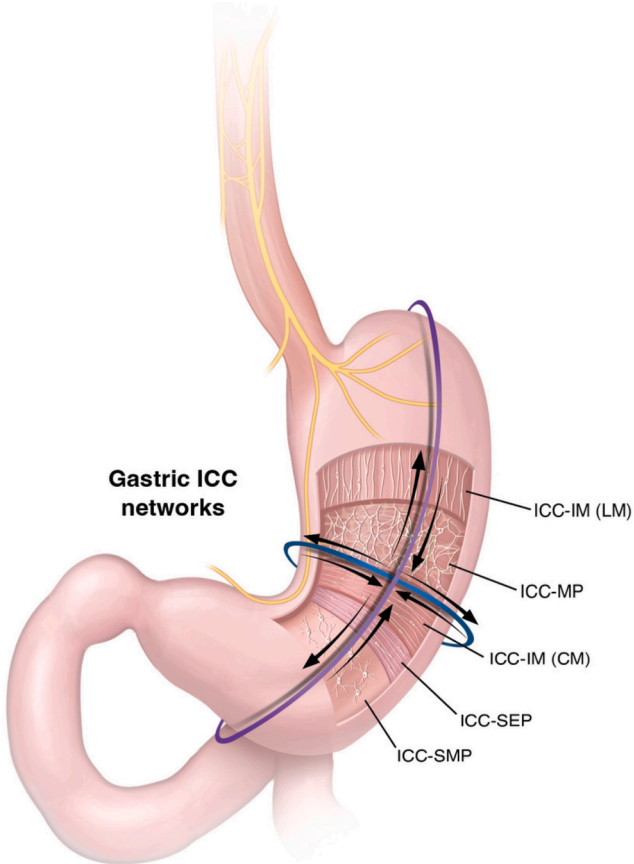

Figure 3. (*Left*) Locations of ICCs within the gastric wall (from outward to inward). (*Right*) Bidirectional coupling of slow-wave propagation through ICC networks, switching between rapid circumferential and slow longitudinal propagation. IM (CM), intramuscular (circular muscle); IM (LM), intramuscular (longitudinal muscle); MP, myenteric plexus; SEP, septal; SMP, submucosal plexus. From O'Grady et al,[134] adapted with permission.

coordinated by rhythmic electrical oscillations (slow waves) at a frequency of 3 cycles per minute and are initiated by gastric corpus pacemaker interstitial cells of Cajal (ICCs) (Figure 3).[134] Phasic contractions are elicited when action potentials exceed contractile thresholds. Fasting contractility is part of the migrating motor complex (MMC), which recurs every 84–122 minutes (see also Small Bowel section). A 5- to 10-minute period of regular intense contractions (phase III) clears the stomach of residual undigested residue. Meals suppress MMCs and elicit a 2- to 4-hour fed pattern of irregular contractions. Neurohormonal triggers of fed patterns are less well understood.

The pylorus generates both tonic and phasic contractility. The pylorus is mostly open during phase III and closed for much of the fed period. After eating, distally propagating contractions in the corpus promote pyloric closure causing food trapping followed by retropulsion into proximal regions for further trituration; with this antegrade-retrograde movement increasing with higher calorie-dense meals. Brief pyloric relaxations permit evacuation of small, ground particles into the duodenum. On ultrasound, a common antro–pyloro–duodenal channel is formed during transpyloric flow. The pylorus is regulated by enkephalins, substance P, nitric oxide, and vasoactive intestinal polypeptide.

Secretory processes on gastric motility. Secretion in the stomach (ie, gastric acid and pepsin), duodenum (ie, bicarbonate), and pancreas (ie, bicarbonate and digestive enzymes) influences gastric motility. Proton pump inhibitors delay emptying. Duodenal acidification inhibits gastric phase III. Fasting pancreatobiliary output cycles in phase with MMCs.[135]

Sensation. Afferent dysfunction contributes to gastroduodenal symptoms. Mechanoreceptor activation triggers accommodation, acid production, and gastric emptying via vagal afferent pathways. Vagal afferents activated by distention project to nerves in the NTS and area postrema with subsequent forebrain and midbrain activation to control food intake.[136]

Main symptoms and pathophysiology. *Symptoms of gastric dysfunction.* Nausea is the sensation of an impending need to vomit. Vomiting is the oral expulsion of stomach contents. Nausea is a defining symptom of chronic nausea vomiting syndrome and is nearly universally reported with gastroparesis. Vomiting is requisite for cyclic vomiting syndrome and cannabinoid hyperemesis syndrome and is common in chronic nausea vomiting syndrome and gastroparesis.

Early satiety and postprandial fullness refer to the sense of feeling full before meal completion and the sensation of being full for long period of time (many hours) after a normal meal, respectively. Early satiety and postprandial fullness are reported with the postprandial distress syndrome subtype of FD and gastroparesis. In gastroparesis, these symptoms are associated with reductions in body mass index.

Anorexia refers to loss of appetite, which occurs in FD, gastroparesis, and organic conditions.

Bloating and distention are 2 distinct clinical features. Bloating is the sensation of fullness, excessive gas, or feeling of being distended without obvious abdominal distention, whereas distention is the visible objective enlargement of abdominal girth. Bloating and distention frequently coexist but can occur independently. Bloating and distention are commonly reported in postprandial distress syndrome and gastroparesis.

Epigastric pain is the painful sensation located in the epigastrium and is often described as burning. It is the defining symptom in the epigastric pain syndrome (EPS) subtype of FD. Severe epigastric pain is predominant in 20% of patients with gastroparesis.

Pathophysiology. *Delayed gastric emptying.* Gastric emptying testing confers a diagnosis of gastroparesis in the setting of characteristic gastric symptoms. Only 25%–36% of patients with suspected gastroparesis exhibit delayed emptying.[137] The group without delayed emptying is given alternate diagnoses, including chronic nausea vomiting syndrome. One-third of patients with FD have emptying delays.

The importance of delayed gastric emptying for symptom generation is controversial. Most studies report poor gastroparesis symptom correlation with delayed emptying of low-fat meals. Conversely, delayed emptying of high-fat meals is associated with greater nausea, vomiting, fullness, and early satiety.[138] In FD, fullness weakly associates with emptying delays. Meta-analyses including only studies describing high-quality emptying methods observed stronger associations between emptying and nausea, vomiting, pain, early satiety, and fullness.[139] Emptying rates are labile, with changes in gastric emptying status (delayed vs normal) noted in 47% of patients on repeat testing at 48 weeks in 1 study.[140]

The impact of delayed emptying on longitudinal symptom outcomes is unclear. One study, reported better 48-week outcomes in patients with moderate or severe emptying delays and another noted greater 6-month symptom and quality of life improvements with non-delayed emptying.[141,142]

Impaired gastric accommodation. Accommodation can be blunted in FD and gastroparesis, with associated food redistribution to the antrum, limiting fundic storage. In FD, accommodation impairments relate to early satiety and epigastric pain.[133]

Increased gastric sensitivity. Enhanced perception of gastric distention is observed in FD and idiopathic gastroparesis.[143] Distention-evoked pregenual anterior cingulate cortex activation is blunted in FD, showing central nervous system participation.[144] Postprandial hypersensitivity correlates better with meal-related symptoms than fasting sensation. Gastric hypersensitivity may contribute to epigastric pain, nausea, bloating, belching, and weight loss.[143]

Accelerated gastric emptying. Accelerated gastric emptying was first described with dumping syndrome after vagotomy or gastric resection and can present with an early phase with associated vasomotor symptoms or a late phase mediated by reactive hypoglycemia. Rapid emptying

is also described with FD, diabetes, and cyclic vomiting syndrome. Symptoms may be indistinguishable in those with rapid, normal, or delayed gastric emptying. The importance of rapid gastric emptying to any symptom profile is unproved.

Inconsistent criteria have been used to define rapid emptying. In older dumping syndrome studies, accelerated gastric emptying was measured using radiolabeled water. Recently, solid emptying tests have been used. Different methods to measure rapid emptying identify different populations. In 1 study, 14.1% exhibited rapid emptying of a digestible scintigraphic meal, and 3.4% showed rapid emptying of an indigestible wireless motility capsule.[145]

Small Bowel

Physiology

Motility and secretion. The small bowel plays a crucial role in digestion and absorption, integrating motility with secretions, like water, electrolytes, bile, digestive enzymes, and brush border enzymes (eg, lipases, isomaltase, and sucrase) for carbohydrate assimilation.

The stomach grinds food into particles <3 mm for passage into the duodenum. During fasting, the MMC—a cyclic, neutrally mediated motility pattern—clears residual contents from the stomach and small bowel into the colon.[146] MMC has 3 phases over 60–90 minutes, propagates in 30- to 50-cm segments, and produces lumen-occluding contractions. Waves travel at approximately 120 cm/min, although the complex moves more slowly (1–12 cm/min) in the proximal jejunum (Figure 4).

The MMC is generated by the ENS but modified by the vagus nerve and gut hormones. Motilin from M-cells triggers premature MMCs in the stomach, associated with plasma motilin peaks. Ghrelin from P/D1 cells also induces phase III-like activity that starts in the stomach.[147] In contrast, somatostatin from D-cells can induce MMCs in the small intestine without gastric involvement, likely via ENS or pancreatic polypeptide inhibition.[148]

Transition from fasting to fed motility requires vagal integrity. CCK, released by I-cells in response to fats, protein hydrolysates, and amino acids, promotes pancreatic and bile secretion, delays gastric emptying, and enhances satiety. Feeding disrupts the MMC, promoting irregular contractions that mix chyme to optimize absorption. Coordinated GI motility also prevents small intestinal bacterial overgrowth.[149]

Main symptoms and pathophysiology. *Symptoms resulting from small bowel dysfunction.* Abdominal pain has multifactorial origin. In the small bowel, distention is a key cause, mediated by stretch receptors that signal through polymodal splanchnic and vagal nerves. Injury may lead to hyperalgesia through nociceptor sensitization and activation of "silent nociceptors."

Bloating, distention, and bowel habit changes can result from food intolerances, dysbiosis, visceral hypersensitivity, delayed transit, or abnormal viscero-somatic reflexes.[150] Distention is associated with slower orocecal transit and harder stools in patients with IBS-C.[151] Duodenal lipids impair jejunal gas clearance more in patients with IBS than in healthy controls.[152] Patients with enteric dysmotility retain more gas than patients with IBS, despite similar symptoms, suggesting abnormal reflexes.[153]

Diarrhea due to maldigestion or malabsorption in the small bowel can be further enhanced by bacterial fermentation in the colon.

Pathophysiology. *Small intestinal bacterial overgrowth.* Small intestinal bacterial overgrowth often arises from chronic dysmotility or ileocecal valve removal, which normally prevents colonic microbiota migration. Small

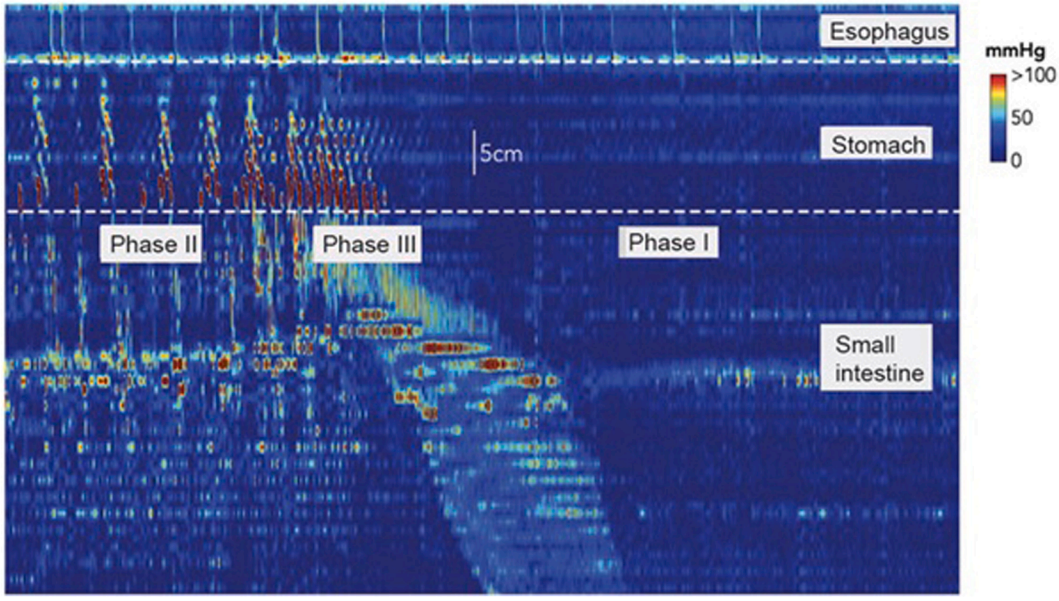

Figure 4. High-resolution manometry recording with sensors located in esophagus, stomach, duodenum, and jejunum. The recording from the small bowel shows the 3 phases of the MMC. Note the increase gastric activity coincides with the commencement of phase III of the MMC (original unpublished recording provided by Phil Dinning).

intestinal bacterial overgrowth is defined as $\geq 10^5$ colony-forming units of bacteria per milliliter in proximal jejunal fluid.[154] However, most microbes are unculturable, and culture-independent techniques are underused.

Altered small bowel transit. The clinical utility of small bowel transit measurement is unclear. Delayed transit may indicate dysmotility.[155] However, studies are limited, and colonic dysfunction will influence small bowel transit.[156] Fasting transit is governed by MMC phase III activity, while fed transit depends on food type.[157] Transit assessment methods vary by center and include barium contrast (ie, small bowel follow-through),[158] radio-opaque markers,[159] scintigraphy,[160] lactulose,[161] inulin,[162] or lactose-^{13}C-ureide breath tests,[163] and recently the wireless motility capsule.[164]

Large Bowel and Anorectum

Physiology

Motility and sensation. The colon's motor functions include propulsion, storage, and waste elimination. Manometry has identified key motor patterns involved in the processes. High-amplitude propagated contractions (HAPCs) are the primary propulsive force (Figure 5). These are inhibited at night and increase in number after waking and meals and preceding defecation.[165] Other motor events propel contents short distances for mixing and storage. The distal colon exhibits a cyclic motor pattern, consisting of pressure waves (2–8 cycles/min) traveling short distances (typically <10 cm). Originating at the rectosigmoid junction, this pattern increases during sleep and post meal, potentially acting as a rectosigmoid brake to control rectal filling.[166]

Accommodation and storage allow for fluid and nutrient absorption via bacterial metabolism. Colonic tone and phasic activity mediate this process, influenced by caloric intake and meal composition. Fat and carbohydrate stimulate, while proteins inhibit, motor activity.[167]

Anorectum: motility and sensation. The anorectum controls defecation and continence through coordinated motor events in the colon, rectum, and anal canal.[168] Content entering the rectum triggers rectal afferents and a sensation of rectal fullness. The rectoanal inhibitory reflex is induced and this leads to internal anal sphincter relaxation and external sphincter contractions. Relaxation of the puborectalis muscle and external anal sphincter straightens the rectoanal angle, and the rectosigmoid, diaphragm, and abdominal muscles contract, generating propulsive force. The smooth muscle of the internal anal sphincter, under autonomic control, maintains most resting anal tone, and the striated muscle of the external anal sphincter and pelvic floor muscles are innervated by sacral roots and the

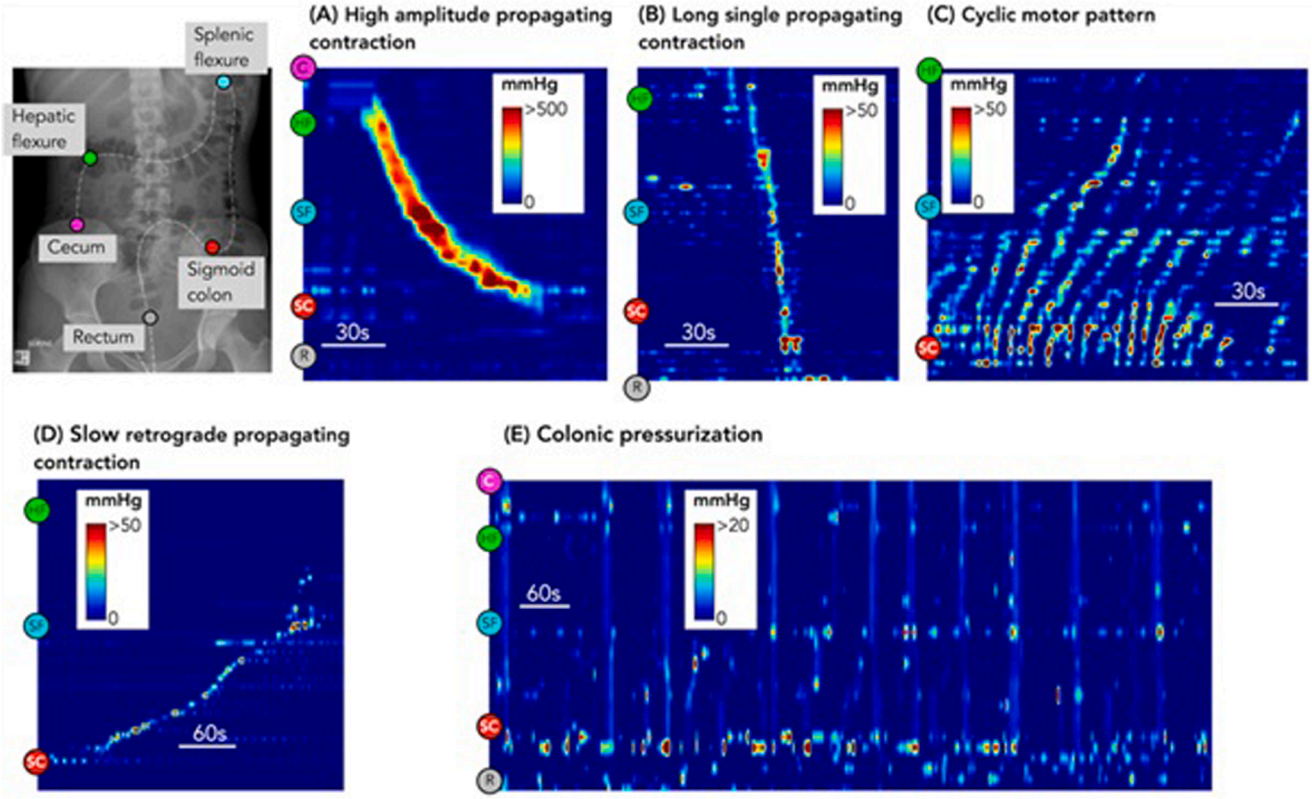

Figure 5. X-ray images show the placement of a high-resolution manometry catheter in an adult human colon. The *colored circles* represent the location of a sensor in the cecum (C), hepatic flexure, splenic flexure, sigmoid colon, and rectum. These *colored circles* are also displayed on the manometry traces (*A–E*) to indicate the colonic region from which the recordings were made. The manometry traces are displayed as spatiotemporal color plots, and panels *A–E* display a different commonly recorded propagating motor pattern (original unpublished recordings provided by Phil Dinning).

pudendal nerve. The anorectum integrates somatic and autonomic functions, making it vulnerable to neuromuscular disorders.

Main symptoms and pathophysiology. *Abnormal transit.* Constipation can result from slow transit, a rectal evacuation disorder, or even normal transit.[169] Opiate use delays colonic transit[170] and diabetic constipation does not.[171] Patients with IBS-C showed delayed transit correlating with abdominal distention.[151] Rapid transit occurs in cases of watery diarrhea[172] and neuroendocrine tumors,[173] and in ulcerative colitis transit can be delayed in the right colon, prolonging whole gut transit.[174]

Abnormal motility. Defining abnormal motility is challenging, as no motor pattern uniquely identifies dysfunction. In slow transit constipation, HAPCs can be absent or diminished, coupled with a blunted meal response.[175] Opioid-induced constipation shows reduced "long fast movements" (the transit equivalent of the HAPC) correlating with delayed transit.[170] Conversely, patients with IBS-D exhibit increased HAPCs compared with healthy individuals.[176]

Increased and decreased sensitivity. Colonic sensitivity changes are linked to dysfunction. Patients with IBS experience discomfort and/or pain at lower distention volumes/pressures,[177] a phenomenom known as hyperalgesia, and magnetic resonance imaging studies found patients with IBS report more symptoms, despite similar gas production as healthy individuals.[178] Postprandial pain may stem from colonic contractions, often mistaken for gastric pain, termed "secondary hyperalgesia." In constipation, left colon or rectosigmod obstruction can trigger epigastric pain. Colonic contractions also contribute to diverticulosis pain.[179] Glycerol-induced strong contractions cause pain in patients with IBS-C,[180] and HAPCs can or cannot be associated with pain. Pain can also occur in the absence of HAPCs or in response to a normally nonpainful stimulus, termed "allodynia."[176]

Anorectal abnormalities. Visceral hypersensitivity to distention is found in 20%–90% of patients with IBS.[181] Conversely, 25%–60% of constipated individuals have rectal hyposensitivity,[182] with up to 50% of constipated patients experiencing abnormal urge perception.[183] Hyposensitivity is less common in IBS-C than chronic constipation.[184] Painless rectal distention can slow gastric emptying and inhibit small bowel motility,[185] consequently nausea and vomiting may be present in patients with slow colonic transit and rectal evacuation disorders.[185] Rectal evacuation issues are also linked to rumination syndrome.[186] Hyposensitivity correlates with infrequent defecation, prolonged toileting, and enema use in chronic constipation.[182]

Clinical and Research Tools to Evaluate Gastrointestinal Function

Various tests can be performed to assess function throughout the GI tract in both clinical practice and research settings (Supplementary Table 1).[187–199] Transit and contractility are the most commonly assessed parameters in the various segments of the GI tract. Transit can be measured using scintigraphy, wireless capsules, and radiopaque markers; contractile activity can be examined by manometry, capsule measures of pressure, or dynamic imaging techniques. Many of the clinical tools in Supplementary Table 1 showed benefits in detecting specific gut sensorimotor disorders and affecting treatment decisions with good prediction of outcomes, such as tests measuring LES and anal function. Measurement of regional gut transit and most research tools have not yet reached proven clinical usefulness (eg, treatment decision making or responses to therapies). Future investigations will aim at validating existing physiologic measurements as biomarkers to phenotype DGBI and guide effective treatment strategies. New technologies will be crucial to define the role of central and peripheral nervous systems on gut sensation and investigate key GI functions, including longitudinal muscle contractions and gut wall elasticity and distensibility. A further challenge will be to develop novel sensorimotor assessment tools at the interplay with a number of gut-physiology modifiers, for example, gut microbiota (and dysbiosis), immune system (with inherent activation), and stress responses, to provide thorough understanding of symptom generation in the wide array of DGBI.

Concluding Remarks and Recommendations for Future Research

- Define new features of gut motility beyond the classic phasic and tonic contractions, including longitudinal muscle contractions, elasticity, and distensibility.
- Improve differentiation of health from disease using standardized stimuli when basal conditions are not discriminatory.
- Perform tests aimed at investigating patients with DGBI during symptomatic phases.
- Investigate various factors (eg, luminal components, dysbiosis, stress and immune activation and their interplay with intestinal epithelial barrier).
- Concerning gut microbiota and dysbiosis, large-scale, longitudinal studies together with interventional studies will be important in resolving mechanisms in which microbes may influence the gut–brain axis.
- Further characterization of peripheral and central mechanisms of normal and abnormal sensory function.
- Apply physiological measurements as biomarkers to phenotype DGBI and address effective therapeutic options.
- Development and validation of disorder-specific biomarkers using the integration of multi-omic databases, requiring next-generation platforms and dedicated bioinformatics.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2026.02.004.

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