Dyspepsia is an umbrella term used to encompass a number of symptoms thought to originate from the upper gastrointestinal tract. These symptoms are relatively nonspecific; not surprisingly, therefore, a myriad of conditions may present with any one or a combination of these symptoms. Therein lies the clinician’s first challenge: detecting the minority who may have a potentially life-threatening disorder, such as gastric cancer, from a population whose symptoms are, for the most part, considered functional in origin. The second challenge lies in the definition and management of those individuals with functional dyspepsia (FD); the major focus of this review. The Rome process has addressed the issue of FD definition and a look back at the evolution of Rome criteria for this disorder illustrates the complexities that have so frustrated us. There has been no shortage of hypotheses to explain symptom pathogenesis in FD; initially focused on gastric sensorimotor dysfunction, these have now strayed well into the duodenum and have come to entertain such factors as immune responses and the microbiome. FD has proven to be an equally challenging area for therapeutics; while the staple approaches of acid suppression and eradication of Helicobacter pylori have some limited efficacy in select populations, strategies to ameliorate symptoms in the majority of sufferers based on presumed pathophysiology have largely faile. Lacking a validated biomarker(s) FD continues to be an elusive target and is likely to remain so until we can better define the various phenotypes that it must surely contain.

**Keywords:** Dyspepsia; Functional Dyspepsia; GERD; IBS; Helicobacter pylori; Proton Pump Inhibitor; Prokinetic; Gastroparesis.

Dyspepsia (literally bad digestion), or as it is more commonly referred to in general parlance, indigestion, has been around for millennia. References to indigestion/dyspepsia can be traced back to the writings of Hippocrates and Galen, if not earlier, and have featured in the works of great writers ever since. In Cymbeline, Shakespeare informs us that “if you are sick at sea or stomach-qualm’d at land, a dram of this will drive away distemper,” and in Coriolanus we learn that “no; but it is the bosom which first feels the load of repletion and indigestion” (perhaps a reference to impaired fundic compliance). James Joyce, a giant of 20th century literature and an individual (based on his own somewhat peripatetic engagement with the discipline) fascinated by medicine brings us right up to date in Ulysses: “Tom Rochford spilt powder from a twisted paper into the water set before him. —That cursed dyspepsia, he said before drinking. —Breadsoda is very good, Davy”.

The early medical literature was similarly preoccupied by the topic and various bodily dysfunction or humors identified as culprits. By the mid-19th century roles for gastric acid, motility, and maldigestion were discussed; overlap with heartburn mentioned; and a role for the duodenum proposed.

Dyspepsia is clearly a symptom that the general public experiences and one that impacts on their well-being; the dilemma lies in understanding and quantifying what patients are trying to tell clinicians. What do they mean when they complain of indigestion and what do clinicians seek to convey when using the term dyspepsia? How can this apparently common problem be translated into a terminology that can be objectively measured?

More than 25 years ago Crean et al in Glasgow, Scotland attempted to grapple with this task and as a result of their labors produced what is still one of the most comprehensive descriptions of dyspepsia in an urban environment. They defined dyspepsia as an “episodic recurrent or persistent abdominal pain or discomfort, or any other symptoms referable to the upper alimentary tract, excluding bleeding or jaundice, of duration 4 weeks or longer” and acknowledged that multiple symptoms could be included: “abdominal pain/discomfort, heartburn or other manifestations of gastroesophageal reflux, anorexia, nausea and vomiting, flatulence or air eructation (belching, burping or aerophagy), early satiety or undue repletion after meals, abdominal distension or ‘bloating’ and symptoms attributed by the patient to ‘wind’” thereby opening the
Pandora’s box that has bedeviled ever since. What symptoms should be included? Does one allow overlap with gastroesophageal reflux disease (GERD) and/or irritable bowel syndrome (IBS)? Crean’s study also provides a clear picture of the disease spectrum encompassed within this definition of dyspepsia in an era when Helicobacter pylori was in its infancy and such concepts as nonerosive reflux disease had yet to emerge. Of the 1433 outpatients that they studied, 26% had a duodenal ulcer, 9% had GERD, 4% gallstones, and 3% gastric cancer; in 37% dyspeptic symptoms were considered as being functional in origin and assigned a diagnosis of functional dyspepsia (FD) in 22% and IBS in 15%. Although rates of duodenal ulcer disease have fallen dramatically and those of GERD have risen in the United States and Western Europe since then,6–9 it must be remembered that duodenal and gastric ulcers remain common causes of dyspepsia elsewhere.10–14 These geographic variations in the relative prevalence rates of organic and FD are undoubtedly related in large part to varying rates of H pylori infection15 and also underscore a fundamental issue in the development of any diagnostic or therapeutic strategy in dyspepsia: the prevalence of organic disease. If the latter is high, diagnostic modalities, such as endoscopy, provide a high yield and therapeutic interventions, such as acid suppression and eradication of H pylori, have their greatest impact. National, regional, and ethnic variations in prevalence of gastric and esophageal cancer and complicated GERD also influence diagnostic approaches, given that even in gastric cancer alarm symptoms and signs are of modest predictive value.16 Indeed, the ability to predict the presence of most organic causes of dyspepsia (with the possible exception of GERD) based on presenting symptoms leaves a lot to be desired.5

It is critical to clearly differentiate between uninvestigated dyspepsia and FD in any consideration of the management of these symptoms and to further consider the impact of prior therapy on endoscopic findings. Although the uninvestigated sufferer may harbor, given the nonspecificity of his or her symptoms, any one of a host of conditions, all organic causes have, by definition been excluded in the individual with FD. Unsatisfactory as it is, FD is a diagnosis of exclusion with the extent of the search for an organic cause being guided and tempered by the sufferer’s presentation, locale, prior history, and all other relevant personal and environmental factors. The shibboleths that clinicians cling to are not as sturdy as they seem; stress, so traditionally linked to functional disorders, is a precipitant of dyspepsia in general.5,17,18 Furthermore, language and cultural factors may inhibit a real understanding of the nature of the very symptoms that the sufferer seeks to convey and unconscious physician bias may unwittingly steer the diagnosis in a certain direction. Indeed, prospective surveys have confirmed what many suspected: FD is a label less commonly used in the United States, where patients with FD-type symptoms are designated as GERD, perhaps reflecting a greater level of comfort and optimism in treating the latter rather than the former.20 It is also evident that dyspepsia is among the most common symptom presentations in the rest of the world as evidenced, for example, by data from Latin America.21

**Functional Dyspepsia: Toward a Uniform Definition, a Visit to Rome**

Although Rome criteria for IBS have remained reasonably similar over the more than 30 years of the process, those for FD have undergone very significant changes.22 This reflects the aforementioned and continuing struggle with the very definition of FD. According to Crean et al5: “Although operational guidelines have been proposed for the diagnosis . . . functional dyspepsia, they fall short of explicit definition so that there are no critical rules or rigorous paradigms against which symptomatic diagnosis can be tested”; to put it simply, there is no gold standard for the definition of FD. The manner in which the definition of FD has evolved within the Rome process, from one that included any symptom referable to the upper gastrointestinal tract to a more specific symptom cluster in the latest iterations Rome III and IV, is testament to the confusion and controversy that surrounds this entity.

Rome III represented a major departure from prior definitions in 2 important respects.23 First, it subdivided FD into 2 distinct syndromes: post-prandial distress syndrome (PDS), characterized by meal-induced dyspeptic symptoms and defined as bothersome post-prandial fullness and early satiety for 3 or more days per week; and epigastric pain syndrome (EPS), where symptoms occurred in between meals. EPS was defined as epigastric pain and/or burning for 1 or more days per week. This subdivision was based on factor analysis performed on symptom data derived from more than 2000 adults from the general population in Belgium that identified meal-associated symptoms and predominant pain as separate and distinct, a finding that was subsequently confirmed by other epidemiologic studies.24,25 It also represented a significant departure from prior subclassifications that divided FD into “reflux-like,” “ulcer-like,” “dysmotility-like,” or unspecified dyspepsia.26 The relative contributions of PDS and EPS to FD have varied in different studies. In a Canadian study of 850 adults 41% had the PDS subtype and 41% were classified as an overlap of EPS and PDS27; in contrast, a study on 490 subjects with FD in Taiwan reported that 72% had PDS subtype and 34% had an overlap of EPS and PDS.28 The higher prevalence of PDS in Taiwan was thought to be secondary to a higher prevalence of H pylori infection, and particularly of the CagA-positive strain.28

Second, Rome III excluded from FD those who had prominent heartburn or satisfied criteria for IBS.23 This was to have major implications given the frequency of
overlap among FD, IBS, and GERD and the much greater response to acid suppression among those with “reflux-like” dyspepsia; their removal not only flew in the face of clinical experience but impacted greatly on clinical trial outcomes. In terms of overall performance, and despite these fundamental changes, Rome III criteria identified patients with FD with a sensitivity of 60.7% and specificity of 68.7%; results that were not significantly different from previous criteria.27

The latest iteration of the Rome process, Rome IV, published in 2016, represents a significant departure from prior versions with a much broader approach to the definition and potential pathophysiology of functional gastrointestinal disorders,20 and now recognizes the possible contribution of such phenomena as low-grade inflammation, changes in the gut microbiota, and altered brain processing to symptom pathogenesis.30,31 The clinical definitions have also seen major changes.22 In relation to FD, the absolutist approach of Rome III has been dropped and Rome IV, instead, emphasizes that FD should no longer be considered as a single disease entity but rather as a spectrum where there is significant overlap with GERD and IBS.23 Indeed, it was also recognized that patients in this overlap experienced a higher intensity and frequency of symptoms with greater impact on daily life.33–37 In Rome IV, the syndrome of functional nausea and vomiting is now identified as a distinct entity and differentiated from FD;35; the implications of this change to diagnostic evaluation and management of nonorganic dyspepsia are yet to be realized. The subclassification of FD into PDS and EPS is preserved on the basis of some separation28,38 and while acknowledging some degree of overlap, especially, in referral populations.12 The definition of PDS is slightly altered to include epigastric pain or burning that worsens with meals along with post-prandial fullness and satiety. This alteration was based on a study that patients should be classified primarily on the post-prandial exacerbation of symptoms rather than on their presence per se.42

Other changes introduced in Rome IV sought to precisely define minimum thresholds for frequency and severity of symptoms primarily. Symptoms should be severe enough to be bothersome (ie, distract from usual activities) and should occur more frequently than the normal population; at least 3 days per week for PDS and 1 day per week for EPS.44 Only time will tell if these new Rome IV criteria are more effective in providing a coherent and clinically relevant definition of FD.

**Epidemiology of Functional Dyspepsia: Where East and West Do Not Meet**

The prevalence of FD has ranged between 10% and 30% among various studies, with a pooled global community prevalence of 21%.14,15 Here again the issue of definition raises its ugly head: prevalence ranged from 7.6% when FD was defined based on ROME III criteria to 29% when a broad definition of upper abdominal or epigastric pain or discomfort was used.15 Prevalence was higher in women, and among smokers, nonsteroidal anti-inflammatory drug users, and *H pylori*–positive individuals.14,15

Geography is an important variable; although dyspepsia is a global problem, there are significant differences in prevalence, definition, epidemiology, and clinical patterns between East and West, which can affect the approach to the management of FD. FD is consistently more common in Western than Eastern populations,14 “ulcer-like” and “reflux-like” subgroups were more prominent in Western populations,45 and dysmotility-like-dyspepsia dominated in the East.14 In Western populations, FD was associated with lower socioeconomic class; in Eastern studies, it was more frequent among those of higher socioeconomic status.14,15 In Western populations, *H pylori* eradication has resulted in a 10% therapeutic gain over placebo;46 this rate jumps to 15%–20% in studies of the same strategy conducted in the East.47,48 Several factors, including background prevalence of *H pylori*, diet, and lifestyle characteristics, may contribute to these differences.

The economic impact of FD is significant but also differs between East and West. The total direct and indirect costs attributable to FD in the United States were estimated at $18.4 billion or $80,000 per 1000 US population.49 Two population-based studies in Malaysia estimated the annual cost for uninvestigated dyspepsia to be $14,816.00 and $59,282.20 per 1000 population in a rural and urban setting, respectively, or an estimated $1.02 billion for the entire Malaysian population.50,51

**Pathophysiology of Functional Dyspepsia: All Bets Are On**

Although the presence of FD does not reduce life expectancy it may impact significantly on an individual sufferer’s quality of life.52,53 Thus efforts continue to understand the pathophysiology of this common affliction.

FD is undoubtedly a heterogeneous disorder and the various symptoms associated with the disorder may well be initiated or perpetuated by diverse pathophysiological mechanisms (Figure 1). For decades the focus, understandably, was on the stomach as the likely origin of symptoms; more recently, the possibility that these same symptoms could arise from the duodenum and elsewhere has gained currency.

**Delayed Gastric Emptying**

Traditionally, delayed gastric emptying was thought to be one of the main players in the pathophysiology of FD. Various studies reported a prevalence of delayed
gastric emptying ranging from 20% to 50% among dyspepsia sufferers. Overall, gastric emptying of solids was 1.5 times slower than control subjects and significantly delayed emptying noted in 40%. A source of major clinical and therapeutic confusion emanates from the overlap in symptomatology between the PDS subtype of dyspepsia and so-called idiopathic gastroparesis. Furthermore, the relationship between gastric emptying delay and most FD symptoms remains unclear, because similar symptoms have been recorded among patients with normal gastric emptying. The one exception seems to be post-prandial fullness; studies have shown with reasonable consistency an association between delayed gastric emptying and this symptom. To confuse matters further rapid emptying has been observed in a small proportion of patients with PDS-type FD and, in this subgroup, correlated with symptom severity.

Gastric Accommodation

Gastric accommodation is mediated by a vasovagal reflex initiated by food ingestion and generated via the activation of nitricergic nerves that relax the fundus and upper body of the stomach. An antrofundic reflex, relaxation of the fundus in response to antral distention, also contributes to accommodation. Tack et al identified impaired gastric accommodation in 40% of their FD patients; early satiety alone (reported by 90% of those with impaired accommodation) proved predictive of the presence of impaired accommodation. Others have failed to reproduce this relationship between proximal gastric function and symptom pattern.

Several approaches to the assessment of gastric accommodation (and, simultaneously, sensation) have been developed and evaluated in humans. Of these, the barostat is considered the gold standard. This involves the placement, under fluoroscopic guidance, of a polyethylene balloon connected to a barostat device in the fundus. Although the test has excellent reproducibility, it is not used in clinical practice because of the invasive nature of the procedure and interference with normal gastric physiology. Several less invasive methodologies that have been explored, such as drink challenge tests using either water or nutrient, offer an apparently simple, yet physiological alternative. In the water load test the patient drinks water until he or she becomes full; the volume at which maximum satiety is reached is regarded

Figure 1. Schematic representation of the various factors that may be involved in the pathophysiology of FD. Not included in the figure: diet and lifestyle factors (e.g., tobacco, alcohol, nonsteroidal anti-inflammatory drug use), and impact of psychosocial factors, such as stress, anxiety, and depression.
as a surrogate marker for gastric accommodation.65 FD patients ingest considerably lower volumes and experience greater severity of symptoms.65 A nutrient drink test produced similar findings in relation to volume tolerated and symptoms generated in FD; indeed, caloric density was not a determinant of the maximum tolerated volume.66,67 Correlations between results of drink challenge tests and barostat measurements in the assessment of gastric accommodation have not, unfortunately, been consistent.66,67 Others, using either conventional 2-dimensional or the more sophisticated 3-dimensional imaging technique, have used abdominal ultrasonography to provide noninvasive measurements of gastric accommodation.68 Ultrasonography has the additional advantage of permitting simultaneous measurements of other parameters of gastric motility including gastric emptying. There are limitations, however, which include operator expertise, and technical challenges posed by anatomic structures and gas interposition.69

Single-photon emission computed tomography involves imaging of the gastric wall by a single-photon emission computed tomography gamma camera following the intravenous administration of 99m Tc pertechnetate; this approach provides assessments of gastric volume and its response to a meal.70 Studies comparing correlation of single-photon emission computed tomography with barostat showed variable results; utility in clinical practice has also been limited by radiation exposure and the need to perform the test in the supine position.71 Although magnetic resonance imaging techniques provide accurate measurements of gastric volumes and gastric emptying rate without any radiation exposure their application has been limited to a few research centers because of access to scanning time, expense, prolonged imaging times, and the need to perform the study in the supine position.72

Gastric Hypersensitivity

Gastric barostat studies revealed that patients with FD had lower thresholds for first perception, discomfort, and pain during distention of the proximal stomach.73,74 Hypersensitivity to gastric distention has been documented in 34% of FD patients and associated with postprandial epigastric pain, belching, and weight loss.75 Hypersensitivity in the post-prandial period seems to be especially discriminating for FD.76 Some,76 but not others,77 have also noted that epigastric pain is prevalent among those with hypersensitivity. In further support of the importance of this phenomenon Vandenberghe et al78 demonstrated the upregulation of multimodal afferent pathways in FD.

Duodenal Hypersensitivity to Acid

That the duodenum might play a role in the genesis of FD symptoms was first suggested by a study that showed that 59% of patients with FD developed nausea during a brief period of duodenal acid perfusion; the same stimulus failed to induce any symptoms in healthy control subjects.79 Subsequently, FD patients were shown to demonstrate an impaired duodenal motor response to acid perfusion, resulting in reduced clearance of exogenous administrated acid from the duodenal bulb.80 This explains the increased prevalence of spontaneous duodenal acid exposure during the daytime and after meals in FD subjects with the most severe symptoms occurring among those patients with abnormally high levels of spontaneous duodenal acid exposure.81 Others noted a correlation between an inability to finish a meal and lower duodenal pH values.82 It is unclear whether duodenal acid exposure provokes symptoms directly via duodenal receptors and sensory nerves or indirectly through feedback changes in proximal gastric function.82–85

Duodenal Sensitivity to Lids

Dyspeptic symptoms are commonly induced by the consumption of fatty foods.86 In FD, in contrast to control subjects, intraduodenal infusion of lipids sensitized the stomach to distention and provoked symptoms of fullness, discomfort, and nausea.87 The involvement of cholecystokinin in this response is suggested by the ability of the CCK receptor antagonist desloroxiglumide to prevent lipid- and distention-induced dyspeptic symptoms.88

Postinfectious Functional Dyspepsia

In a manner analogous to postinfectious IBS (PI-IBS) several studies have identified the de novo development of FD following an enteric infection.89 In 1 survey, 17% of patients with FD thought that their symptoms were PI in origin.90 These individuals had more prevalent early satiety, nausea, and weight loss; symptoms were attributed to impaired accommodation resulting from dysfunction of gastric nitrergic neurons.90 In a prospective 1-year follow-up study following food-borne Salmonella enteritis the relative risk for the development of FD was 5.2 for exposed individuals with the occurrence of abdominal pain and vomiting during an acute attack being identified as positive predictive.91 Indeed, in this study, the likelihood of developing PI-FD was greater than that of PI-IBS. Giardia lamblia infection has been shown to provoke visceral hypersensitivity and delay gastric emptying.92

Inflammation and Immune Activation

In a manner analogous to IBS, several studies have explored the role of inflammatory pathways in FD. In comparison with those with FD in general, subjects with PI-FD were more likely to exhibit focal aggregates of
T cells and CD8⁺ cells in the duodenum with gastric emptying being slower among those patients with focal aggregates. The number of CD4⁺ cells per crypt was reduced, whereas the number of macrophages surrounding crypts was increased in PI-FD.⁹³ In a related study histologic duodenitis, characterized by inflammatory cells and macrophages, was found to be more prevalent in PI-FD in comparison with healthy volunteers; furthermore, the symptom of epigastric burning correlated with the degree of duodenitis.⁹⁴

Inflammation may not confined be to PI-FD. Although the number of mast cells was increased in all FD sufferers, the number of enterochromaffin cells was increased in all PI-FD.⁹⁵ Systemic immune activation has also been observed, as evidenced by increased levels of peripheral blood mononuclear cells, tumor necrosis factor-α, interleukin-1β and -10, and gut-homing T cells. Each correlated with various FD symptoms.⁹⁶

**Duodenal Eosinophilia**

In a study of 51 FD subjects and 48 healthy control subjects, Talley et al⁹⁷ found that the odds ratio for the presence of FD in subjects with high duodenal bulb eosinophil counts was 11.7. Of note, gastric eosinophilia was not evident and the symptom of early satiety was associated with duodenal eosinophilia after adjusting for age, sex, and H pylori status.⁹⁷ The same group has now confirmed this association in children.⁹⁸ Duodenal eosinophilia has also been observed in PI-FD⁹⁴ and, in some studies, associated with mast cell infiltration.⁹⁹ The presence of duodenal eosinophilia has also been associated with allergy and the PDS subtype of FD,¹⁰⁰ suggesting that a hypersensitivity to luminal contents may be involved.¹⁰⁰ In a subsequent study it was noted that duodenal eosinophilia was evident in the second part of duodenum in subjects experiencing early satiety and post-prandial fullness, whereas abdominal pain was associated with eosinophilia in both the bulb and second part of duodenum.¹⁰¹

**Helicobacter pylori Infection**

It has long been assumed that H pylori–related gastritis could cause dyspeptic symptoms via a variety of disturbances in acid secretion, motility, and neuroendocrine signaling¹⁰²–¹⁰⁴; although multiple pathways could be involved, their relative roles in the genesis of dyspeptic symptoms in FD related to H pylori remain to be defined. In relation to motility, infection with H pylori has been linked to increased expression of glucagon-like-peptide-1 and accelerated gastrointestinal transit in 1 animal model¹⁰⁵; in patients with FD, however, the presence of H pylori infection did not seem to affect gastric emptying rate.¹⁰⁶ Although H pylori infection does not seem to influence gastric accommodation,¹⁰⁷ studies in FD¹⁰⁷ and IBS¹⁰⁸ suggest that it may trigger visceral, including gastric, hypersensitivity; a highly plausible hypothesis given the known effects of inflammation on visceral sensation.¹⁰⁹

**Psychosocial Factors**

It has been recognized for decades that FD is commonly linked with psychological comorbidities, such as anxiety and depression.¹¹⁰ Comorbid anxiety and depression are thought to not only contribute to the basic pathogenesis of symptoms in some FD sufferers, but also to drive health care–seeking behavior.¹¹⁰ Functional brain imaging studies have examined gut-brain interactions, the processing of these signals and their interactions with various parts of the brain and their circuitry in FD and generated plausible explanations for the roles of emotion, stress responses, and psychological processes and psychiatric comorbidity in FD.¹¹⁰,¹¹¹ Indeed, Van Oudenhove et al¹¹⁰ have proposed an integrated model of FD as a disorder of gut-brain signaling, analogous to IBS.⁹⁶ Interestingly, somatization seems to be equally common in subjects with either FD or organic dyspepsia.¹¹²

**Other Associations**

FD, along with other functional gastrointestinal disorders, has been linked to the joint hypermobility syndrome (Ehlers-Danlos type III); the basis for this association is unknown.¹¹³

**Management of Functional Dyspepsia: the Challenges Persist**

The first step in the management of a patient with FD is to reassure him or her of the nonfatal nature of the disease.¹¹⁴ In so doing one must not belittle the seriousness of the sufferer’s complaints but rather devote time to understanding the true nature of their symptoms and their impact on daily life.

**Diet**

Visceral adiposity has been associated with an increased risk of FD.¹¹⁵ Consumption of canned food and use of alcohol weekly have been associated with the induction of FD symptoms.¹¹⁶ Diets high in fat and salt have also been associated.¹¹⁷ Because of the overlap between IBS and FD, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols may well be relevant to symptom development in FD.¹¹⁷ Other
studies have shown that dyspeptic symptoms are triggered by carbonated drinks and hot spices.  

**Antidepressants**

Based on the aforementioned prevalence of comorbid psychological distress among patients with FD, and on their effects on gastrointestinal physiology, there has been considerable enthusiasm for the use of antidepressants in this disorder. However, evidence for therapeutic benefit for antidepressant therapy in FD has been mixed. A meta-analysis comparing the efficacy and safety of selective serotonin reuptake inhibitors and tricyclic antidepressants found that tricyclic antidepressants, but not selective serotonin reuptake inhibitors, were effective in alleviating symptoms in FD. A recently updated meta-analysis came to similar conclusions; here benefit was limited to antipsychotics and tricyclic antidepressants and to those who had a coexistent mood disorder. In a comparative study, amitriptyline, 50 mg daily, was more effective than escitalopram, 10 mg, or placebo daily over 10 weeks. Those with ulcer-like epigastric pain and normal gastric emptying were most likely to respond to amitriptyline. In keeping with this finding, nortriptyline, in another study, failed to improve symptoms in idiopathic gastroparesis.  

**Eradication of Helicobacter pylori**

Eradication of *H pylori* has been shown to lead to a small (10%) but significant improvement in symptoms with FD. In a meta-analysis, improvements in dyspepsia symptoms were greater in the treatment group (odds ratio, 1.38) 1 year later with symptomatic improvement rates at 3 months being predictive of improvement at 1 year. Males and those with a higher body mass index were more likely to respond. There was no symptomatic advantage for sequential therapy over standard triple therapy; eradication rates were also similar. Whether the addition of bismuth subsalicylate to standard triple therapy would provide additional benefits in FD has yet to be established. These results notwithstanding, the critical question is how the “test-and-treat” approach, a long-time staple in the management of dyspepsia, stacks up against other management strategies. When compared with “test-and-treat,” prompt endoscopy has been associated with a small, but significantly greater, benefit in terms of symptom outcomes, although at a greater expense. When test-and-treat was compared with empiric proton pump inhibitor, there were no significant differences in symptoms or costs at 12 months. Not surprisingly benefits from eradication increased in parallel with the prevalence of *H pylori*; where it is greater than 10% to 20%, test-and-treat is more cost-effective than empiric proton pump inhibitor therapy.

**Prokinetic Agents**

The most widely used prokinetics in the United States, metoclopramide and domperidone (although not approved in the United States, it is commonly sourced from Mexico and Canada), have never been shown convincingly to be effective of FD. A meta-analysis of the selective 5-HT4 receptor agonist, mosapride, failed to identify any benefit. Cinitapride, a 5-HT4 agonist and D2 antagonist, was compared with domperidone in PDS; although rates of overall symptom relief were similar at 85.8% versus 81.8%, respectively, cinitapride produced greater decreases in the severity of post-prandial fullness, early satiation, and bloating.  

Itopride is a novel prokinetic agent that inhibits acetylcholinesterase and is a dopamine D2 receptor antagonist. In a meta-analysis involving 2620 patients, itopride resulted in superior rates of global assessment of dyspepsia symptoms. Behind this meta-analysis lies a more complex and instructive story. Considerable enthusiasm for itopride in FD was generated by a phase II study that demonstrated significant symptomatic benefit. Unfortunately, 2 phase III randomized controlled trials, 1 international and 1 North American, failed to confirm these findings. This stark difference in outcomes was thought to have resulted from a subtle difference in study populations; the phase II study was liberal in its inclusion of subjects with heartburn, whereas the phase III studies were much more restrictive and a reanalysis of the phase II study found that most of the benefits attributable to the drug were found among those with significant heartburn. These observations serve as a timely reminder of how the precise nature of a given study population can influence response to therapy.  

Acotiamide, a muscarinic antagonist and acetylcholinesterase inhibitor, was shown to improve FD symptoms in several phase II trials and proceeded to a large, multicenter phase III study in Japan among patients with PDS-predominant FD. The elimination rates of 3 meal-related symptoms (post-prandial distress, upper abdominal bloating, and early satiation) were higher in the acotiamide group (15.3%) than in placebo (9.0%). In a subsequent 48-week open-label extension symptom relief rates for these symptoms remained stable at 13% from 8 weeks onward. Studies are currently underway in Europe and the United States to assess efficacy and safety in other ethnicities.  

**Enhancing Gastric Accommodation**

Buspirone, an antidepressant that is a serotonin 5-HT1A receptor partial agonist and, thus, may facilitate relaxation of the gastric fundus and body, significantly reduced overall symptom severity and that of post-prandial fullness, early satiety, and upper abdominal bloating, without an appreciable increase in adverse events, in FD.
Nonpharmacologic Therapies

In both the short (10 weeks) and longer (6 months) psychotherapy was shown to provide additive benefit to conventional medical therapy. Psychodynamic therapy has also proven to increase the symptomatic response *H pylori* eradication. Although these approaches seem promising, their cost effectiveness remains to be evaluated. Acupuncture, according to 1 meta-analysis of 20 trials of performed in Asia, is superior to placebo or standard interventions. These studies, however, had a high risk of bias; other studies have shown that gastrointestinal-specific acupuncture is superior to nonspecific acupuncture in the treatment of FD.

More than 44 herbal preparations have been studied and reported to be of benefit in the treatment of FD. Various studies have evaluated the efficacy of herbal extracts in the treatment of FD. In a recent meta-analysis of the herbal preparation STW5 (Iberogast; Steigerwald Arneimittelwerk GmbH, Darmstadt, Germany) it was found that, in comparison with placebo, patients receiving Iberogast enjoyed a significantly greater improvement in their symptoms after 4 weeks of treatment. Rikkunshito, a ghrelin enhancer, has been studied in several clinical trials, and has also been shown to be superior to placebo in FD and seems to be especially effective in addressing epigastric pain and post-prandial fullness. Although ginger has been shown to accelerate gastric emptying in patients with FD, there was no impact on gastrointestinal symptoms; however, small study population sizes complicate interpretation. Mentacarin, a peppermint/caraway oil combination, administered for 2 weeks, has been shown to improve quality of life and symptoms in both the EPS and PDS subgroups of FD.

Novel Approaches

In a small study that used positron emission tomography to target the cannabinoid-1 receptor, patients with FD were found to have higher cannabinoid-1 receptor availability in the cerebral regions involved in visceral nociception and the homeostatic regulation of food intake. Although these findings need to be replicated in larger samples, they suggest that the cannabinoid-1 receptor could serve as a novel target in FD.

Dyspepsia: a Clinical Guide

Dyspepsia presents a formidable challenge for the clinician. How to make sense of the multiplicity of proposed pathophysiologic mechanisms and profusion of (for the most part) marginally effective therapeutic options? Figure 2 provides a simplified approach to the patient presenting for the first time with dyspeptic symptoms. The evidence in support of the main management options has already been presented but can be summarized as follows. Their shortcomings notwithstanding, one should first seek to identify alarm features (red flags); their presence in the right context (age, ethnicity, prior disease) should prompt a search for organic disease, a strategy that usually begins with endoscopy. In the absence of alarm symptoms and in an individual or population where the presence of *H pylori* is likely, “test and treat” is a cost-effective approach; if *H pylori* prevalence is low and reflux-type symptoms are prominent, an empiric trial of a proton pump inhibitor should be considered. Failure should prompt endoscopy but do not expect to find a lot. Once these options have been exhausted what comes next? Right now the prokinetic cupboard is pretty bare in the United States; metoclopramide carries a black box warning and is
limited to short courses of treatment and none of the other prokinetics are currently available. Other off-label approaches should be considered, such as tricyclic antidepressants and buspirone. My own preference is to opt for the former if pain dominates and the latter if post-prandial fullness and/or early satiety are more problematic. Along the way, attention must be paid to comorbid psychopathology and overlap with other functional gastrointestinal disorders, such as IBS and constipation; relieving constipation may substantially improve upper gastrointestinal symptoms. For resistant and disabling symptoms, consider nonpharmacologic approaches, such as psychotherapy or acupuncture, if a skilled therapist is available.

Conclusions

In describing dyspepsia "as a disease space of undefined dimensions occupied by many conditions that share a more or less common core of symptoms, some of which may coexist," Crean et al. aptly summarized the challenge this symptom complex presents: protean manifestations, causes, and potential therapies. It is no wonder that "we find it difficult to define" and manage.

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Dedicated to the memory of Gerard Patrick Crean, MB PhD (1927–2005); scientist, gastroenterologist, teacher, and mentor.

Conflicts of interest
The authors disclose no conflicts.

1. Agents that appear to be effective in FD include
   a. Tricyclic antidepressants, particularly amitriptyline
   b. SSRI's
   c. Buspirone
   d. Domperidone

2. A 25 year old otherwise healthy American female presents with dyspeptic symptoms predominantly consisting of early satiety and post-pandrial discomfort. There are no alarm signs or symptoms. She denies heartburn or regurgitation. The best empiric therapy for this patient would be:
   a. buspirone
   b. diagnostic endoscopy
   c. PPI
   d. domperidone

**True or False**

3. Among herbal preparations, iberogast and peppermint oil have shown some benefit in therapy of FD

4. The majority of patients with functional dyspepsia have hypersensitivity to gastric distention

5. Metoclopramide provides symptomatic improvement to most patients with FD

6. Post-prandial fullness as a main complaint of FD correlates fairly well with delayed gastric emptying

7. Early satiety as the main symptom of FD points towards accelerated gastric emptying as the culprit