Functional Bowel Disorders

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In a series of publications in *Gastroenterology,* about seventy years ago, Thomas Almy published evidence of alterations in colonic function in healthy individuals in the setting of experimental stress and subsequently in patients with "spastic constipation" and "functional diarrhea."[1] Terms such as irritable colon, spastic colitis, mucous colitis and irritable bowel were used until the name irritable bowel syndrome (IBS) was determined as there was evidence that this condition affected the small as well as the large intestine.[2] "Syndrome" referred to the association of several clinically recognizable symptoms and signs that occur together to define a clinical entity.[3] Over the past three-quarters of a century, articles published in *Gastroenterology* have played a seminal role in the evolution of the diagnosis of functional bowel disorders (FBDs) and our understanding of the pathophysiology and treatment of these disorders, in particular IBS. Because of space limitations we can cite only a few examples of the numerous important contributions to the field published in *Gastroenterology*.

Symptoms and Diagnosis

In the first *Gastroenterology* article describing "The Irritable Bowel Syndrome", Drossman and colleagues characterized this condition as "altered bowel function with or without chronic abdominal pain and can be broadly divided into three clinical patterns, spastic colon, painless (nervous) diarrhea, and alternating diarrhea and constipation."[2] Due to the lack of a consistent structural, physiologic or biochemical abnormality to explain the symptoms, IBS and other GI symptom based disorders were referred to as functional gastrointestinal (GI) disorders. The first effort by experts to create symptom-based diagnostic criteria for IBS was the Manning criteria in 1978, which characterized a group of symptoms that would later be called IBS with diarrhea.[3] Several subsequent factor analyses demonstrated distinct symptom clusters, which supported the validity of symptom-based Rome criteria for multiple functional GI disorders. For example, the IBS bowel symptom cluster was composed of relief of pain with defecation, looser stools with pain onset, and more frequent stools with pain, while the ulcer-like dyspepsia symptom cluster was defined by pain unrelated to eating, pain relieved by eating and pain relieved by antacids.[4,5]

The Rome diagnostic criteria have been increasingly well accepted for use in clinical research studies. *Gastroenterology* published the Rome III and more recent Rome IV diagnostic criteria.[6] Rome IV introduced symptom criteria based on national normative data, diagnostic algorithms and the use of the Multidimensional Clinical Profile (MDCP) to further sub-classify patients in order to help guide for the most effective management in clinical practice.

The MDCP is particularly valuable as functional GI disorders are heterogeneous and clinical presentations can vary. For example, in some patients, functional GI symptoms develop after an infectious gastroenteritis. Post-infection IBS and post-infection functional dyspepsia have been particularly well described.[7] Chronic stress, anxiety and depression are risk factors for developing post-infection functional gastrointestinal disorder (FGID). Psychosocial and behavioral investigations have long recognized the association of functional GI symptoms and life stressors and psychological symptoms such as anxiety and depression. Two key papers demonstrated that IBS patients have a higher prevalence of psychological symptoms than normal subjects but IBS non-patients do not, suggesting that psychologic factors are associated with healthcare seeking and not the disorder per se.[8,9] Comorbidity with other chronic symptom-based disorders such as fibromyalgia has also been well recognized and suggest that these disorders have shared pathophysiology with FBDs.[10] Despite the importance of characterizing and establishing symptom based criteria for FBDs, they are not precise enough to identify meaningful pathophysiological subgroups or lead to more targeted treatment.

*Authors share co-first authorship.

Abbreviations used in this paper: **FBDs, functional bowel disorders; FGIDs, functional gastrointestinal disorders; GI, gastrointestinal; HPA, hypothalamic-pituitary-adrenal; IBS, irritable bowel syndrome.**

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Pathophysiology

Our understanding of the pathophysiology of FBDs has evolved significantly over the years (Figure 1[3]). While perhaps overly simplistic, we will discuss the evolution of our understanding of the pathophysiology of functional bowel disorders as occurring in three phases: Phase 1- FBDs and IBS are motility disorders, 2. Phase 2- The role of visceral hypersensitivity in FBD and IBS, and Phase 3- FBD and IBS represent dysfunction in the bidirectional brain-gut axis, intestinal barrier dysfunction and interactions with the microbiome and dietary factors.

Phase 1- FBD and IBS Are Motility Disorders

As previously mentioned, the earliest citations in Gastroenterology that we could identify were prescient articles by Almy and Tulin in 1947 and 1949 that focused attention on the role of stress as a trigger for colonic motor dysfunction in healthy individuals and patients with spastic constipation.[1] These classic studies set the stage for numerous contributions over the next two decades that focused on the hypothesis that IBS was primarily a problem of dysfunctional motility resulting in a "spastic" colon. Attempts to identify an underlying cause for the colonic dysmotility included reports of abnormal myoelectric activity in the colon of IBS patients but this observation was shown to be non-specific. During this phase articles appearing in *Gastroenterology* extended the dysmotility hypothesis into the proximal Gi tract but there was a growing appreciation that there were missing pieces to the puzzle that we now call IBS.

Phase 2- The Role of Visceral Hypersensitivity in FBD and IBS

Reports that implicated enhanced perception of abdominal pain, ie, visceral hypersensitivity/hyperalgesia as a feature FBD/IBS date to the early 1970s,[11] but were firmly established by articles published in *Gastroenterology* by Whitehead et al and confirmed by others in the 1990s.[12,13] These studies relied on the now well-established methodology of performing pain assessments and psychometric testing in controls and IBS patients in response to colorectal balloon distention. Patients with IBS will report pain at a level of balloon distention that is not painful in healthy controls. The concept of visceral hypersensitivity as a potentially universal feature in FBD has been extended to the proximal gut including the stomach and esophagus in elegant studies published in *Gastroenterology*.[14] As this phase was advancing it became clear to investigators that there were critical missing pieces to explain the pathophysiology of FBD and IBS.

Phase 3- FBD and IBS Represent Dysfunction in the Bidirectional Brain-Gut Axis, Intestinal Barrier Dysfunction and Interactions With the Microbiome and Dietary Factors

The observation that visceral hyperalgesia is a sine qua non for the diagnosis of FBD/IBS, along with altered bowel habits as discussed above has led to the vigorous pursuit of the underlying mechanisms. Because of the clinical observation that stress exacerbates the perception of abdominal pain in IBS patients, considerable attention has focused on the hypothesis that validated animal models and patients

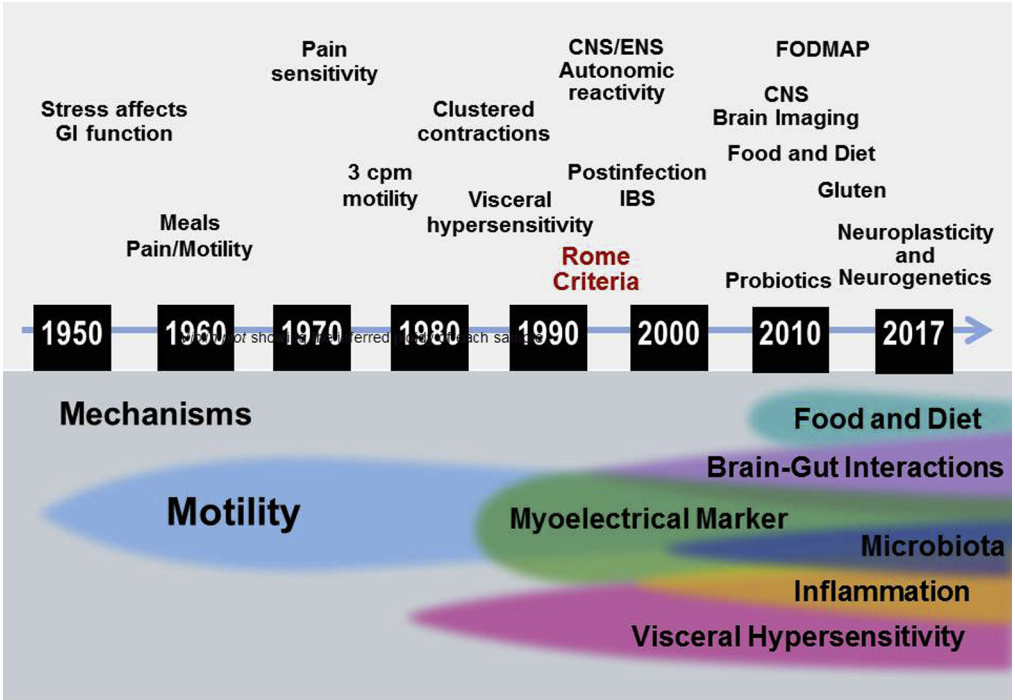

Figure 1. History of physiological research in IBS and FGIDs. This timeline shows some of the key research study areas at the top of the figure and the domains of research at the bottom. From 1950 until 1990, research was conducted primarily in the motility domain; however, after 1990, new research began to take place in the areas of visceral hypersensitivity, brain-gut interactions, inflammation, the microbiota, and food and diet. The development and use of the Rome classification system and criteria allowed for identification of patients with FBDs for research in these other domains. Modified with permission from Drossman et al.[3]