Collins SM. Translating symptoms into mechanisms: functional GI disorders. Adv Physiol Educ 31: 329–331, 2007; doi:10.1152/advan.00058.2007.—Functional gastrointestinal disorders are the most common problem in gastroenterological practice. They are defined by chronic abdominal symptom complexes that occur in the absence of underlying structural abnormalities. The pathogenesis of these disorders is heterogeneous and involves behavioral, infective, and inflammatory components. Common symptoms are abdominal pain, diarrhea, constipation, and bloating. Mechanisms underlying these symptoms include alterations in gastrointestinal motility, visceral perception, altered epithelial function, and disturbances in fermentation activity by gut commensal bacteria.

In clinical gastroenterology, there are several categories of disorders, and these include inflammatory bowel disease, infectious gastrointestinal problems, acid peptic disease, ischemic disease, malignancy, and functional gastrointestinal (GI) disorders. Chronic functional GI disorders constitute the most common of all gastrointestinal conditions. They impose a substantial socioeconomic burden on our society (8, 12, 15). They are defined as chronic abdominal symptom complexes for which there are no discernible underlying structural abnormalities and are therefore considered disorders of function and reflect altered gastrointestinal physiology (23).

The symptoms of functional GI disorders are nonspecific and mimic those of organic disease such as peptic ulcer or inflammatory bowel disease. The challenge of diagnosing these disorders is based on the nonspecificity of the symptoms as well as the absence of any biomarkers for these conditions (26). Furthermore, these disorders are poorly conceptualized, and it is therefore difficult to develop disease-modifying therapies. As a result, treatment is symptom based, and the choice of therapy should be based on an understanding of the putative underlying mechanisms (25). In the absence of biomarkers, these conditions have been traditionally diagnosed by the exclusion of organic gastrointestinal disease, although recently efforts have been made to define symptomatic criteria (26). As a result of the limited efficacy of available treatments, and a strategy that often involves the exclusion of organic disease, the socioeconomic burden of these conditions is high.

The conceptualization of chronic functional GI disorders is problematic. Traditionally, these conditions have been considered to be “psychosomatic” (12). In this model, psychological comorbidity and attention-seeking behavior are prominent, and the GI tract is almost considered to be an innocent bystander. Another model invokes a peripheral trigger, such as GI infection, that triggers responses in the GI tract resulting in the persistence of altered physiology as a basis for symptom generation (6, 19). Until recently, these two models were considered to be mutually exclusive. However, research on the brain, gut, and brain-gut axis has generated information that could potentially unify these hypotheses. These include the observations that altered behavior can change GI physiology as well as susceptibility to inflammatory stimuli such as infection. Conversely, triggering abnormalities in the GI tract, by infection, inflammation, or other processes, can result in alterations in behavior (6, 19, 20).

The common symptoms of functional GI problems include abdominal pain or discomfort, indigestion, postprandial fullness, bloating, excessive gas, diarrhea, constipation, and a variety of behavioral symptoms.

A careful history is by far the best diagnostic tool in the evaluation of patients with these disorders, and this provides a rational basis for the selection of therapy (3, 19). For example, abdominal pain, the most common of all symptoms, can be classified into a cramping abdominal pain, often in the left lower quadrant of the abdomen, and related to alterations in bowel habit. Epigastric pain can also occur in relation to eating. Alternatively, patients can complain of a more persistent abdominal pain that is not cramping in nature. These two types of abdominal pain can be ascribed to specific alterations in GI physiology (3, 27). The cramping abdominal pain is likely related to abnormal motility and would involve alterations in smooth muscle, enteric nerves, or interstitial cell function (2, 24). In contrast, the noncramping abdominal pain or discomfort is likely related to the altered processing of sensory information from the gut. This would include alterations in peripheral sensitization of effenter nerves or alterations in the central processing of these impulses (1, 7).

Constipation is also a common component of functional GI disorders. There are multiple definitions of constipation, but these are often unhelpful in the management of patients. A basic understanding of colonic physiology is required to evaluate the mechanistic basis of constipation. The function of the colon is to delay the transit of fecal material arriving at the ileocecal valve. Approximately 3.5 liters of fluid equivalent arrive at the cecum on a daily basis, yet a normal stool equivalent is ~200–300 ml of solid stool. Thus, the colon is required to absorb almost 90% of the fluid from ileal content. The contractile apparatus of the colon is often nonperistaltic and allows time for the reabsorption of water to occur in the proximal colon. As the solidifying luminal content moves toward the rectum, colonic motility becomes more peristaltic, and the stool solidifies and is pushed toward the rectum. Upon reaching the rectum, distension occurs, and this relaxes the internal anal sphincter. The process up to now is subconscious but once the internal sphincter is relaxed, the anal canal, which has somatic innovation, senses the presence of material and
signals the brain. At this time, the individual is aware of a need to defecate. Thus, a mechanistic approach to constipation would consist of either poor intake of fluid or fiber, slow colonic transit due to an enhancement of nonperistaltic activity, or to altered sensation, accommodation, and outlet dysfunction in the anorectal area. With this knowledge, it is easy to clinically classify constipation based on the patient’s symptoms (16). Those who present with infrequent bowel movements probably have disorders of colonic motility, whereas those who present daily with an urge to defecate but have difficulty with the expulsion of stool likely have problems of outlet function.

Abdominal bloating and fullness are very common but poorly understood clinical problems. Early postprandial fullness probably reflects alternations in gastric physiology, including impaired accommodation as well as possible disorders of gastric antral motility. Bloating in the lower abdomen is more difficult to understand. A number of hypotheses have been generated regarding altered perception of gaseous distension, abnormal movement of gas through the intestine, or increased fermentation of dietary components by commensal bacteria (13, 22).

The commensal bacteria of the GI tract constitute the new horizon for scientific research (11, 15). The average human body consists of $10^{13}$ cells, but the gut contains in excess of $10^{14}$ microorganisms. Bacteria make up most of the microbes in the colon and constitute 60% of fecal mass. The gut microbiota consists of more than 500 different bacterial species. Fungi are also part of this GI ecosystem. The majority of bacteria are strict anaerobes and cannot be cultured using traditional laboratory methods. The present approach is to analyze these using DNA- or RNA-based approaches (10). Gut flora play a role in providing nutrition to the host and regulating fat handling and storage. They also instruct the mucosal immune system and specifically the innate system and maintain what is commonly known as physiological inflammation within the GI tract (11, 15). The metabolites of commensal bacteria also regulate epithelial growth and function. Studies from several decades have indicated that the human genome is incapable of maintaining normal GI physiology and that commensal bacteria play a substantial role in regulating what is considered to be normal gut physiology. Experimentally, perturbation of commensal bacteria either in germ-free mice or mice treated with antibiotics or probiotics result in disturbances of GI physiology and can mimic changes found in patients with irritable bowel syndrome (28). There include, for example, altered motility as well as altered pain perception.

Diarrhea is also a prominent symptom of functional GI conditions. In these conditions, diarrhea is usually associated with eating and disappears on fasting. Typically, the diarrhea is low volume, and stool consistency is variable (8, 24). These findings would therefore indicate that a secretory component plays a minor role in the generation of diarrhea in functional disorders. Diarrhea is more likely due to alterations in GI motility and rapid transit (8, 24). In some patients, disturbances of rectal sensory physiology produce a “pseudodiarrhea” where the patient feels the need to evacuate but passes small amounts of stool. In functional GI conditions, there is no weight loss, and the malabsorption is not considered to be a component of the underlying pathophysiology (9). However, some studies have indicated abnormalities in the epithelium of patients with functional bowel disorders with changes in carbohydrate absorption documented in a small proportion of patients with diarrhea-predominant irritable bowel syndrome (9). In addition, bile acid reabsorption is also abnormal in some patients with diarrhea. Recently, attention has been drawn to the role of intestinal permeability in irritable bowel syndrome. Increases in permeability have been documented using lactulose or mannitol probes and are abnormal in patients with a postinfective type of irritable bowel syndrome (17).

Transient and acute bacterial infection of the GI tract are now recognized as strong risk factors for the development of irritable bowel syndrome (5). This is referred to as postinfective irritable bowel syndrome and is characterized by the persistence of GI symptoms for up to 7 yr or more following an acute episode of gastroenteritis. This occurs in ~7–32% of patients following an acute enteric infection. Low-grade inflammation is thought to play a role in this model, and animal studies have indicated that low-grade inflammation in the mucosal compartment results in alterations in GI physiology, including altered epithelial, muscle, intestinal, and enteric neural function (5).

Thus, symptoms of functional GI disorders reflect a broad spectrum of disturbance of GI physiology as well as mucosal immunology. A careful history by clinicians should provide insights into underlying mechanisms and direct appropriate therapy.

REFERENCES

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