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GUEST EDITORIAL
Functional bowel disease: a challenging frontier in gastroenterology

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ABSTRACT: Conquests and challenges in Gastroenterology

The last 30 years have seen incredible advances in the science and practice of gastroenterology and hepatology. In the 1970s, the fiberoptic endoscopic revolution facilitated the visualization of the mucosa of a large segment of the gastrointestinal tract and afforded the opportunity for specialized studies using histological and biochemical analyses. The impact of fiberoptic endoscopy on surveillance or screening for cancer of the colon will be more apparent in the next millennium. Novel pharmacological approaches have had a dramatic impact on gastroenterology. Initially, histamine H2 receptor antagonists and subsequently the discovery of the proton pump in the parietal cell and its inhibition by a number of agents as well as the discovery of the role of Helicobacter pylori in peptic ulceration changed the management of peptic ulcer. Gone are the long operation lists in which a variety of operations were performed to reduce acid secretion and facilitate gastric emptying; thankfully, the iatrogenic complications of those generally unphysiological procedures are also less frequently encountered! The recent explosion of information on inflammatory cytokines and the potential of blocking the inflammatory cascade that results in inflammatory bowel disease brings hope to significant improvement in the treatment of patients with Crohn's disease and fistulation e.g. with anti-TNF alpha antibodies. In hepatology, the advent of transplantation and novel immunosuppressive regimens have brought life to patients who would otherwise have suffered severe complications such as variceal bleeding, hepatic encephalopathy or death. Laparoscopic surgery, including cholecystectomy, fundoplication, Heller's myotomy and partial colectomy, has revolutionized management of several conditions. Though organic diseases of the gastrointestinal tract and liver draw most of our attention because of the severity of these conditions, it is important to note that the combined prevalence of peptic ulceration, inflammatory bowel disease and hepatic cirrhosis is insignificant when compared with that of the functional bowel diseases [1-3]. At the turn of the century, one of the greatest challenges, in terms of direct and indirect costs to society, is presented by these highly prevalent illnesses which affect up to 30% of all people in the community at any one time. It has been estimated that about 40% of patients seen by gastroenterologists and 10-15% of patients seen by primary care physicians in Western societies have one or other form of functional gastrointestinal disorder. Research in the last decade leads many to believe that we are on the threshold of significant advances in our understanding and treatment of these conditions.

The objectives of this short article are: to review the control of gut sensorimotor functions relevant to the functional disorders; to define functional bowel diseases, their economic burden and impact; to review the pathophysiology of these conditions; and to discuss novel pharmacological approaches to control the motor and sensory dysfunctions.

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Control of the sensory/motor functions of the gastrointestinal tract

Although the neuroanatomical pathways involved in gastrointestinal motor and sensory function have been known for decades, a brief summary of recent advances is presented to facilitate an understanding of the derangements in the functional diseases. The motor function of the gut is controlled by the extrinsic sympathetic and parasympathetic fibers, and by the intrinsic nervous system. The latter is a vast enteric brain with approximately the same number of neurons as are found in the mammalian spinal cord. The sympathetic nervous system is motor to sphincters and relaxatory to nonsphincteric muscle. In contrast, the parasympathetic nervous system is motor to nonsphincteric muscle. In the enteric nervous system, there are stereotyped hard-wired circuits that serve to facilitate certain responses, such as the interdigestive migrating motor complex during fasting and the response of the gut to feeding. The "law of the intestine" is the peristaltic reflex and, in recent years, the neurotransmitters and mediators primarily involved in this reflex have been the object of intense study. The excitatory components of the reflex that result in gut contraction are acetylcholine and tachykinins (substance P and K); descending inhibition in the aborad region is mediated predominantly by VIP and nitric oxide. The sensory arm of the peristaltic reflex involves a number of transmitters including calcitonin gene related peptide

(CGRP) and serotonin (5HT). Some of the major advances in pharmacotherapy are based on modulation of these transmitters. Sensation of the gut is mediated through a 3-order neuron chain, but the initial transducer of sensation at the level of the gastrointestinal tract is the enteroendocrine cell, which is both a mechanical and a chemical transducer[4-6]. Visceral signals result in reflexes that modulate motor and secretory functions and may not always project to the conscious brain because they synapse with efferent pathways in the prevertebral ganglia and in the spinal cord. Perception ultimately requires stimulation of the three neurons in the chain to bring the sensation up to conscious level. Pain is projected through spinal afferents that course along but are not sympathetic fibers, entering the cord in the dorsal horn. The dorsal horn neuron is a center for modulation of sensation. There is a balance between ascending information and descending modulation from the brainstem that determines the level of central projection of incoming signals from the dorsal horn neuron [6]. The dorsal horn is also a center for modulation of sensation since somatic afferents project to its neurons and result in viscerosomatic referral as well as modulation of sensation. The cerebral hemispheres determine the level of sensation and autonomic responsiveness following gut stimuli. There are centers of vigilance in the prefrontal cortex, and the limbic system and brainstem reflexes change the levels of satiety and modulate autonomic responses in pulse and blood pressure to gut stimulation.

Functional bowel disorders: definition and impact

A functional gastrointestinal disorder consists of symptoms that are attributable to the mid or lower gastrointestinal tract and that are not attributable to anatomical or biochemical disorders[1-3]. The symptoms include abdominal pain, early satiety, nausea, bloating, distention, and various symptoms of disordered defecation. The three commonest functional bowel disorders are irritable bowel syndrome, constipation and functional dyspepsia.

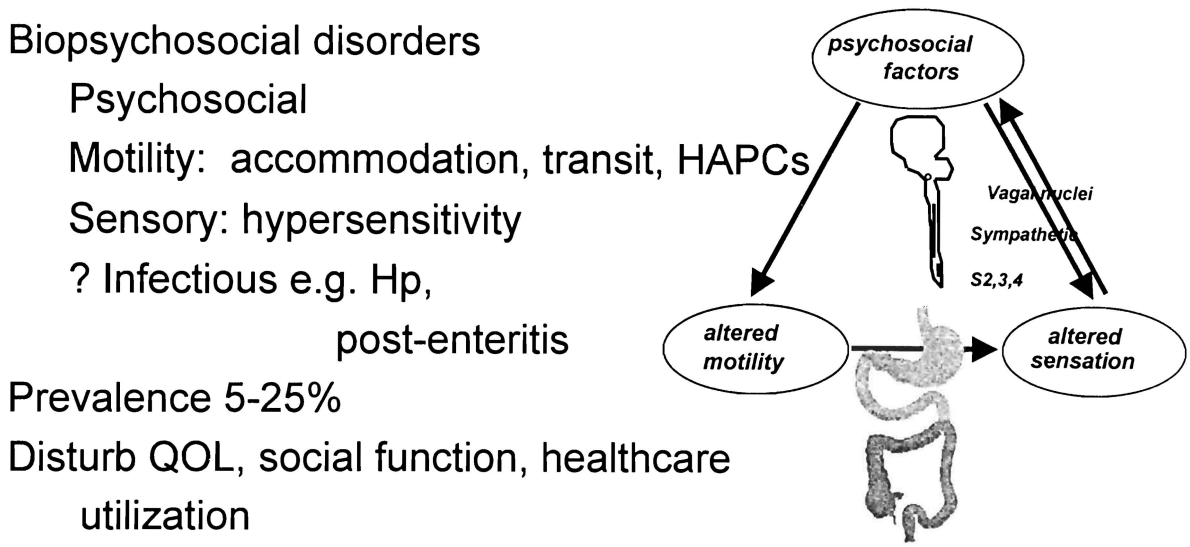
Irritable bowel syndrome is the most common functional bowel disorder and it is characterized by chronic or recurrent symptoms of lower abdominal pain related to bowel movements, change in bowel habit (diarrhoea, constipation, or alternating), a sense of incomplete rectal evacuation, passage of mucus with stool, and abdominal bloating and distention[2,3,7]. Its prevalence in most countries is approximately 10%.

Constipation is defined in many ways and perceived very differently among patients[8]! It is clear that a frequency definition of constipation is insufficient, although a bowel movement frequency of less than 1 every 3 days is generally regarded as being outside the normal range. However, most patients perceive that they are constipated when they have to strain excessively or have a difficulty passing stool from the rectum or completing the evacuation of stool. With such a variety of definitions, the prevalence of constipation in the community is difficult to ascertain with estimates ranging from 3 to 20%[9]. There is increasing evidence that a considerable proportion (perhaps as high as 50% in tertiary centers) of patients with constipation has a disorder of the process of rectal evacuation[10]. Normal defecation[5] requires coordination of colonic contractions, volitional rise in intraabdominal pressure, and relaxation of the pelvic floor and anal sphincters (Fig. 1).

Functional dyspepsia is also a common problem (prevalence estimated at 20%), and it is characterized by chronic or recurrent symptoms of upper abdominal pain or "discomfort" which is a summary term for such symptoms as early satiety, nausea, bloating, and vomiting[2,11]. In both irritable bowel syndrome and functional dyspepsia, no structural or biochemical abnormalities are identified. Around 30% of patients with irritable bowel syndrome have symptoms consistent with functional dyspepsia, either concurrently or at other times[12,13].

There is also overlap in the clinical symptomatology of patients with constipation-predominant irritable bowel syndrome and those who have constipation that results from an evacuation disorder. In patients with suspected irritable bowel syndrome, careful evaluation of the evacuation process and the dynamics of defecation is essential in order to exclude a disorder of rectal evacuation, to provide the best treatment and to avoid greater direct and indirect costs resulting from mismanagement.

Fig 1 - Functional gastrointestinal disorders: biopsychosocial disorders of high prevalence and impact.



One of the most important societal perspectives resulting from functional bowel disorders is the degree of absenteeism that is recorded among patients with these conditions[13]. For example, it has been estimated that patients with irritable bowel syndrome record work or school absences of up to 13 days per year compared to a normal control population of 5 days per year[13]. This level of absenteeism is equivalent to that of the common cold and flu and presents a significant burden to the nation's economy. Indeed, it is estimated that 0.1%[14] to 0.5%[15] of health care expenditures in industrialized countries are attributable to irritable bowel syndrome, and that 66-75% of all the economic burden from functional gastrointestinal disorders results from indirect costs secondary to loss of days at work or school[15].

Functional bowel disorders constitute a significant economic burden in the form of direct costs. It has been estimated that annual charges for healthcare delivery for irritable bowel syndrome is around 8 billion dollars in the U.S[16]. More recently the annual costs in 8 major industrialized countries in the world were estimated at about 41 billion dollars, including 25 billion dollars in the U.S. and over 4 billion dollars each in Japan and Germany[15].

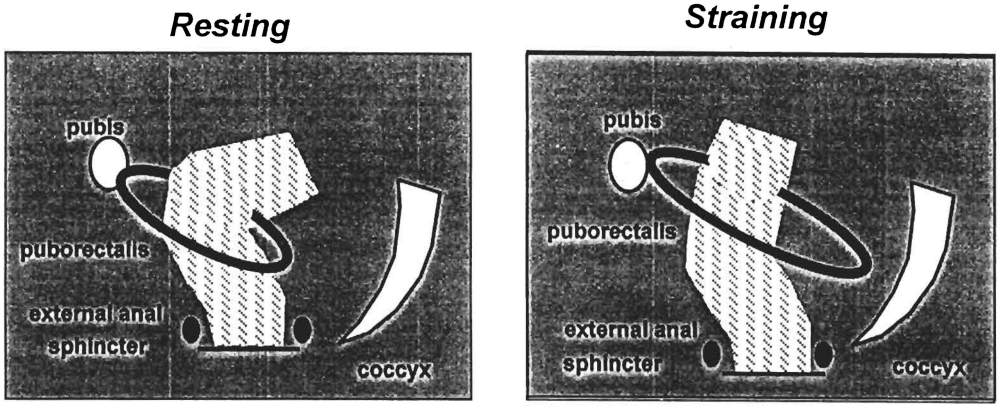
Irritable bowel syndrome

Irritable bowel syndrome is a biopsychosocial disorder in which psychosocial, motility, and sensation disturbances (Fig. 1) result in abdominal pain and disorders of defecation, that is constipation, diarrhea, or alternating bowel habits[17,18]. In community studies, the prevalence is around 10% and incidence 1-2% per year. The economic burden and impact in terms of healthcare utilization have been discussed above. A fourth possible etiologic factor that has recently received much attention is infection[19,20]. Thus, 25-33% of patients with diarrhea-predominant irritable bowel syndrome give a positive history of a previous "enteritis" episode[19,21]. However, the persistence of symptoms seems to be more closely related to the occurrence of stressful life events and hypochondriasis than to changes in physiologic function such as transit, sensation, or rectal compliance[20]. Hence, it appears that, in the post-enteritis irritable bowel syndrome model, the "mind factor" supercedes the influence of the abnormal physiology (e.g., transit, sensory thresholds) resulting from the infectious episode.

Motor dysfunctions are clearly demonstrable in patients with irritable bowel syndrome and may contribute to some of the symptoms[22]. The prominent colonic response to feeding results in the familiar symptoms of urgency, abdominal pain, and need to have a bowel movement in the early postprandial period. Abnormal transit profiles such as accelerated small bowel and colonic transit in diarrhea-predominant irritable bowel syndrome[23] constitute one of the major rationales for the use of medications that help restore normal transit profiles. Patients with urgency and diarrhea develop high amplitude, rapidly propagated colonic contractions (HAPCs), especially postprandially[24].

With greater appreciation of the role of the pelvic floor and anal sphincter muscles in the process of evacuation (Fig. 2) and of disturbances of the dynamics of defecation[10], it is clear that pelvic floor disorders may produce a syndrome virtually identical to the so-called constipation-predominant irritable bowel syndrome. Thus, a history of excessive straining, sense of incomplete evacuation, or need to digitate the rectum or vagina to facilitate emptying of the rectum are all features associated with pelvic floor or anal sphincter dysfunction[8,10,25]. In patients with constipation, it is essential to perform a careful rectal examination including assessments of the anal sphincter tone at rest, the ability of the puborectalis to relax during straining[10], and the descent of the perineum during straining[25]. Simple screening tests are available to confirm the diagnosis. This differentiation between evacuation

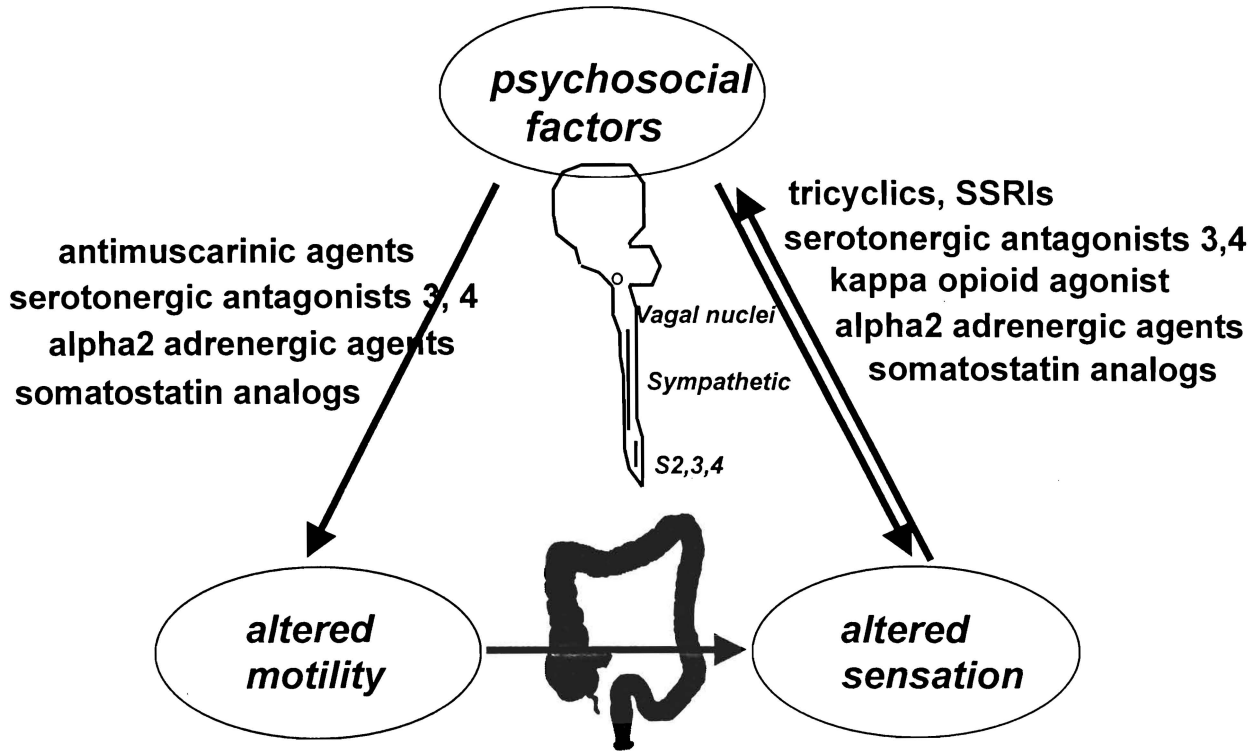
Fig 2 - Pelvic floor and anal sphincter functions involved in continence and defecation.
Adapted from ref. #8 - Camilleri M, Thompson WG, Fleshman JW, Pemberton JH. Clinical management of intractable constipation. Ann Intern Med 1994;121:520-8.



Continence requires:
- Contraction of puborectalis
- Maintenance of anorectal angle
- Normal rectal sensation
- Contraction of sphincter

Defecation requires:
- Relaxation of puborectalis
- Straightening of anorectal angle
- Relaxation of sphincter

Fig 3 - Classes of novel medications undergoing trial in functional gastrointestinal disorders.
Reproduced from Camilleri M, Choi M-G: Irritable bowel syndrome. Aliment Pharmacol Ther 1997;11:3-15.



disorder and IBS-constipation has important practical implications. For example, a prokinetic agent for constipation is unlikely to work in patients with evacuation disorders. Much direct and indirect cost attributable to irritable bowel syndrome might be saved if more attention is placed on the rectal examination during appraisal of these patients.

Another component of motor dysfunction that may contribute to heightened sensitivity of the colon is spasm. While this is well appreciated by radiologists during colon x-ray and by clinicians in practice (the colon "squelch" sign on deep palpation of the descending or sigmoid segment), it has been difficult to objectively demonstrate motor disturbances in the descending or sigmoid colon in patients with irritable bowel syndrome. Hence, pharmacological approaches to correct motor dysfunction have been empirically based [e.g., use of antimuscarinic or, more recently, antiserotonergic agents[17,18]].

Colonic and rectal hypersensitivity are very relevant in IBS patients with diarrhea and urgency[26-28]. Indeed, this has been proposed as a biological marker of the condition[28], although the lack of responsiveness of rectal hypersensitivity in clinical trials[29] and its poor correlation with symptom responses question whether it can be used as a biological marker[30]. Anxiety, psychosensory function and limbic system activation may contribute to the increased rectocolonic sensitivity[31-33]. In summary, the evidence for hypersensitivity in irritable bowel syndrome is considerable, but the proof of its clinical relevance will depend on the development of effective therapies and documentation of clinical benefit by restoring normal sensation[34].

Several novel approaches to treatment of irritable bowel syndrome are based on these improved insights on the motor and sensory functions of the colon and rectum (Fig. 3). Thus, novel 5-HT4 agonists which stimulate colonic transit and motor function [prucalopride[35], tegaserod[36]] are being developed for the constipation and pain predominant irritable bowel syndrome. The consistent relief of pain without side effects in irritable bowel syndrome has always presented a considerable challenge. In the past, anticholinergic agents have been used[37], but they tend to induce tachyphylaxis and systemic side effects. The appreciation of the role of 5-HT3 receptors in visceral afferents, as well as the demonstration that a 5-HT3 antagonist can reduce the colonic motor response to meal ingestion[38] have led to the large phase II and phase III clinical trials with a novel 5-HT3 antagonist, alosetron. Recent studies from phase II[39] and phase III[40] trials suggest that this medication provides adequate relief of pain and discomfort, while reducing frequency and urgency and improving consistency of stool in diarrhea-predominant IBS patients (Fig. 4).

Another pharmacological approach that has been proposed is to use kappa opioid (peripheral) agonists in order to reduce the pain sensation arising in the gut without having any central effects[41]. In the next 5 to 10 years we should see further validation of these concepts for the purpose of treating irritable bowel syndrome. At the experimental level, it is also known that alpha-2 adrenergic agents modulate motor and sensory functions of the bowel (Fig. 5), particularly the sensation of pain arising during mechanical distention of the colon[42]. Thus, studies at Mayo Clinic showed that the alpha-2 agonist, clonidine, reduces pain sensation but has no effect on gas sensation during distention experiments.

Fig 4 - Comparison of effects of a novel 5HT3 antagonist, alosetron, and placebo on abdominal pain (upper panel, 1 mg b.i.d. alosetron vs. placebo) and frequency of defecation (4 doses of alosetron vs. placebo) in female patients with diarrhea-predominant IBS. Note that a significantly larger percentage of patients report adequate relief of pain compared to placebo.
Adapted from ref. #39 - Camilleri M, Mayer EA, Drossman DA, Heath A, Dukes GE, McSorley D, Kong S, Mangel AW, Northcutt AR. Improvement in pain and bowel function in female irritable bowel patients with alosetron, a 5HT3-receptor antagonist. Aliment Pharmacol Ther (in press)

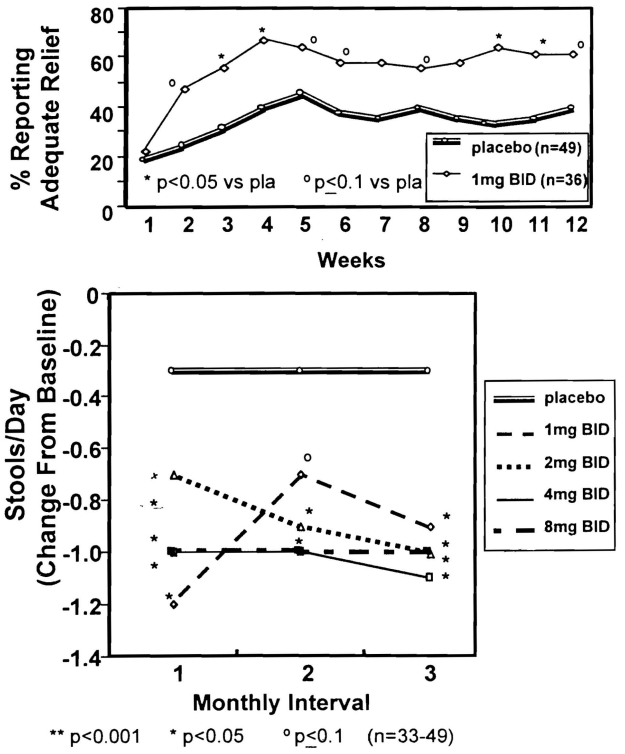
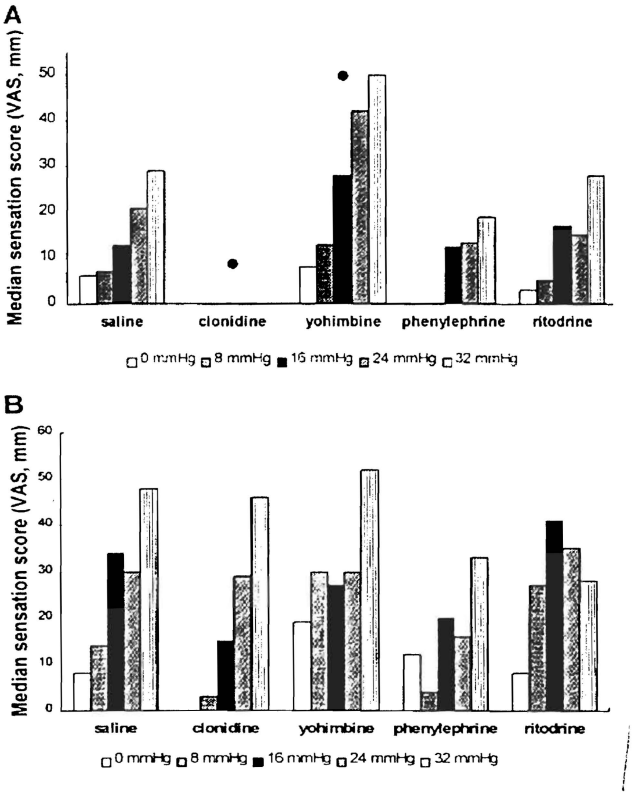


Fig 5 - Effects of adrenergic agents on human colonic sensation during mechanical distentions (4-32mmHg). Note clonidine markedly reduces pain but not gas sensation, suggesting a specific antinociceptive action.
Reproduced from ref. #42- Bharucha AE, Camilleri M, Zinsmeister AR, Hanson RB. Adrenergic modulation of human colonic motor and sensory function. Am J Physiol 1997;273:G997-1006.



Constipation

Constipation is a very common clinical problem, and a questionnaire study in Olmsted County, Minnesota demonstrated that up to 20% of patients report constipation[9]. Approximately 40% of such patients have historical evidence of needing to strain excessively to pass bowel movements. These features might suggest that they also have a component of an evacuation disorder, although the questionnaire-based data do not allow a sufficient distinction between an evacuation problem and slow transit constipation. In a tertiary center study, 50% of 70 patients with severe, unresponsive constipation referred to a single gastroenterologist over a 3-year period had impaired evacuation, and the remainder of patients had either normal or slow transit constipation[10].

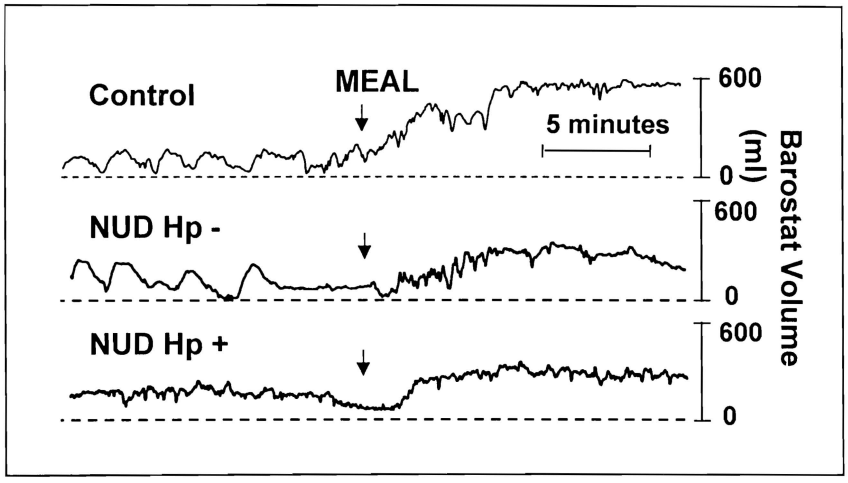
Physiological characterization of constipated patients is important for several reasons. First, it has been shown that, among patients with slow transit constipation, drug-induced constipation, or evacuation disorders, supplementation of up to 30 grams of fiber per day did not result in any improvement in constipation[43]. Second, it is important to identify evacuation disorders because a biofeedback treatment program with muscle relaxation of anal sphincters and puborectalis results in a 70% or greater cure rate for the constipation [44]. Surgical and other aggressive strategies that have been used in the past for evacuation disorders have been shown to be either unnecessary or damaging to patients, resulting in incontinence. Finally, characterization of pelvic floor function and transit profiles by radiopaque markers or scintigraphy[45,46] facilitates a more physiological approach to relieving constipation. Thus, patients with slow transit constipation tend to benefit from fiber, osmotic laxatives, and stimulant laxatives (e.g., bisacodyl), whereas patients with evacuation disorders do not need medication other than fiber supplementation after the pelvic floor is rehabilitated.

Functional dyspepsia

Functional dyspepsia is also a biopsychosocial disorder in which disturbances of psychosocial function, altered motility, and altered sensation (Fig. 1) interact to induce the condition[47]. Whereas, much time and effort has been spent in the last decade exploring the role of infectious organisms such as Helicobacter pylori in the

Fig 6 - Measurement of gastric accommodation response with an intragastric barostatically-controlled balloon. Note the greater increase in volume (suggesting greater gastric accommodation) in the healthy control compared to two patients with functional (nonulcer) dyspepsia.

Reproduced from ref. #57 - Thumshirn M, Camilleri M, Saslow SB, Williams DE, Burton DD, Hanson RB. Gastric accommodation in nonulcer dyspepsia and the roles of Helicobacter pylori infection and vagal function. Gut 1999;44:55-64.



context of nonulcer dyspepsia[48,49], it is now clear from eradication and outcome studies that the organism is probably an innocent bystander in the absence of ulceration. Depending upon how it is defined in different epidemiologic studies, the prevalence of functional dyspepsia ranges from 5% to 25%[12]. As with the irritable bowel syndrome, this disorder results in considerable disturbance of quality of life, social function, and healthcare utilization[15].

Among the mechanisms of nonulcer dyspepsia in adults, approximately 30% have impaired gastric emptying of solids[50-53], and these patients respond to prokinetic medications[53]. A second major motor abnormality is impaired postprandial gastric accommodation (Fig. 6), which is associated with early satiety and weight loss [54].

The other major pathophysiologic disturbance of functional dyspepsia is gastric hypersensitivity[55-57]. The elastic properties (compliance) of the stomach are unimpaired[55-57], yet patients experience pain or discomfort at lower thresholds. Thus, the visceral afferents are considered hypersensitive. Dyspeptic patients also have evidence of hyperalgesia, since the same stimulus produces higher pain scores than in healthy volunteers [57].

In several studies performed in recent years, a lack of gastric accommodation has been noted in association with hypersensitivity in the fasting or postprandial periods [54,57]. This lack of accommodation may suggest that a pharmacological relaxation of the stomach would improve the dyspeptic symptoms of such patients. Relatively simple tests[58-60] can assess the degree of accommodation and hypersensitivity. Such simple techniques include a water load or nutrient drink test in those with impaired accommodation or hypersensitivity. However, only 50% of dyspeptic patients are hypersensitive using these noninvasive methods [59,60].

Recent evidence suggests that pharmacological relaxation of the stomach alone would not necessarily reduce postprandial pain. In experiments in which an intragastric balloon is inflated at different pressures, cisapride results in increased accommodation of the stomach, but it also lowers (rather than raises) the threshold pressures for the induction of discomfort[61]. Similarly, work at Mayo Clinic in healthy subjects has demonstrated that the nitric oxide donor, nitroglycerin, results in marked, dose-related relaxation of the stomach but no change in pain sensation in response to balloon distention[62]. In fact, there was a worsening in the sensation of bloating in these subjects. By way of contrast, clonidine, an alpha-2 adrenergic agonist with central antinociceptive action, was associated with reduction in pain sensation during gastric distention; relaxation in gastric wall tension due to the clonidine accounted for about 40% of the variance in pain sensation[62]. These data suggest that novel approaches to therapy for functional dyspepsia will require a visceral antinociceptive effect rather than an exclusive relaxatory action.

Conclusion

Insights into the pathophysiology of motor and sensory functions of the functional gastrointestinal disorders, as well as collaboration between academia and industry to understand the conditions and develop novel therapies augur well for major advances in the functional gastrointestinal disorders. While the last quarter of the 20th century was characterized by tremendous advances in endoscopy, surgical approaches including laparoscopy and transplantation, and novel pharmacology for acid hypersecretion and inflammation, we appear to be on the threshold of very significant therapeutic advances in the context of the highly prevalent functional bowel disorders. The spiraling costs of healthcare and economic burden from indirect cost for these conditions require a concerted effort to respond to the challenges presented to our patients and to society.

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