Irritable bowel syndrome: how useful is the term and the 'diagnosis'?

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Ther Adv Gastroenterol
(2012) 5(6) 381–386
DOI: 10.1177/1756283X12442223

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Must a name mean something?

The novelist Lewis Carroll (1832–1898) addressed the importance of precision in terms in two novels. In *Through the Looking Glass*, chapter 6, note the dialog between Alice and Humpty Dumpty:

> "My name is Alice, but – "
>
> "It's a stupid name enough!", Humpty Dumpty interrupted impatiently. "What does it mean?"
>
> "Must a name mean something?", Alice asked doubtfully.
>
> "Of course it must," Humpty Dumpty said with a snort laugh. "My name means the shape I am – and a good handsome shape it is, too. With a name like yours, you might be any shape, almost."

In *Alice in Wonderland*, chapter 7, 'A mad tea party', the dialog with the March Hare and the Hatter proceeds as follows:

> "Do you mean that you think you can find out the answer to it?" said the March Hare.
>
> "Exactly so," said Alice.
>
> "Then you should say what you mean," the March Hare went on.
>
> "I do," Alice hastily replied. "At least – at least I mean what I say – that's the same thing, you know."
>
> "Not the same thing a bit!" said the Hatter. "You might just as well say that 'I see what I eat' is the same thing as 'I eat what I see'!

The term 'irritable colon syndrome' (subsequently changed to irritable bowel) is attributed to Walter C. Alvarez. Alvarez completed his medical education at Stanford University in 1910 and worked in the lab of Walter Cannon from 1913 to 1915. From an original paper by Alvarez in 1915, it is also clear that he considered both 'irritating lesions also raise the local tone' and a change in patterns of contractions that impact transit, 'factors such as differences in rhythm and irritability — play in altering the gradient of forces through the tract' [Alvarez, 1915: 389]. After joining the staff of the Mayo Clinic in Rochester, MN in 1926, Alvarez continued to study the gradient of 'irritability' of small intestinal muscle, reflecting the frequency and amplitude of contractions [Alvarez and Hosoi, 1929]. Alvarez attributed the concept of irritability to altered contractions or motor activity. However, as a practicing gastroenterologist at the Mayo Clinic, he was clearly aware of 'mucous colitis or the syndrome of the sore bowel or the spastic colon'. In a paper read at the Ontario Medical Association in Toronto in 1947, he stated:

> One of the commonest types of nervous indigestion is associated with a bowel that is sore much of the time. I say 'bowel' because the trouble is not limited to the colon. As is well known, in these cases the patient will from time to time pass considerable amounts of mucus in the stools. Such attacks are brought on commonly by nervous tension, an oncoming cold, or perhaps by constipation or the eating of some food to which the person is allergically sensitive. The great thing in handling these persons is not to reinforce their fear that there is something seriously wrong with the colon [Alvarez, 1947: 426].

Almost a century after the introduction of the concept of bowel irritability, there are reasons to analyze the utility of the term 'irritable bowel syndrome' (IBS). Is the bowel really 'irritable'? Does 'irritable' imply hypersensitivity? Or does 'irritability' denote that sensitivity is normal, and the response (e.g. motor) abnormal?

The demonstration that rectal hypersensitivity occurs in 95% of patients with IBS was based on the combination of results of lower sensation thresholds and greater viscerosomatic referral of pain during 'rectal' distension [Mertz *et al.* 1995], which led to the claim that rectal hypersensitivity was a biological marker for IBS. Other groups have been unable to replicate this high prevalence of rectal hypersensitivity in IBS, as reviewed elsewhere with prevalence of increased sensitivity ranging from 20% to 95%, and on average around50% [Camilleri, 2009].

A second interpretation of 'irritability' may reflect normal sensitivity (as demonstrated in many patients) with an abnormal response (e.g. motor). For example, we have demonstrated that colonic transit is accelerated in around 45% of patients with diarrhea-predominant IBS (IBS-D) and retarded in around 20% of constipation-predominant IBS (IBS-C) [Camilleri *et al.* 2008].

Thus, the term 'irritable' is equivocal and does not inform the physician of the cause or mechanism of the disorder of function. Moreover, the same symptoms may be the result of 'irritation' rather than 'irritability' [Camilleri and Prather, 1992]. This is discussed below, as conditions that 'irritate' the colon may mimic IBS with diarrhea or constipation.

Has the term and diagnosis 'irritable bowel syndrome' outlasted its utility in gastroenterology practice?

There are several reasons why one might posit that the term IBS has outlasted its utility and is no longer effective as a diagnosis in the clinical practice of gastroenterologists.

(1) The term is used as a waste basket for a variety of disparate symptoms, from pain to excess straining or other bowel dysfunction or indigestion, that are at best misunderstood or potentially misdiagnosed by the physician.

(2) The term connotes a functional disorder which has psychosomatic implications rather than a disorder of gastrointestinal function that may be amenable to specific and effective treatment.

(3) There is evidence of significant overlap of 'subgroups' [Locke *et al.* 2005] or transitions between different subgroups as demonstrated in epidemiological 'transition' studies [Halder *et al.* 2007]. Examples of overlap are IBS-C and evacuation disorder, and examples of transitions are IBS-C and functional constipation, or IBS-C and functional dyspepsia, or epigastric pain syndrome and functional abdominal pain.

(4) Symptoms have been used to make a 'positive diagnosis' of a complex for which it is claimed that there is no biomarker or diagnostic test [Longstreth *et al.* 2006]. Yet, there is increasing evidence that biomarkers identify underlying mechanisms that differentiate subgroups. These include measurement of transit (around 45% of patients with IBS-D have accelerated colon transit; 20% of patients with IBS-C have delayed colonic transit) that identifies motor disorders [Camilleri *et al.* 2008] and flagellin antibodies [Schoepfer *et al.* 2008], and fecal bacterial populations (e.g. an increase in *Firmicutes*-associated taxa and a depletion of *Bacteroidetes*-related taxa [Jeffery *et al.* 2011]) or mucosa-associated microbiota (with increases in *Bacteroides* and *Clostridia* and a reduction in *Bifidobacteria* in patients with IBS-D [Parkes *et al.* 2012]) that may identify subgroups of patients with these disorders of gastrointestinal function.

(5) Even more explicit 'subgroups' have diverse etiologies and mechanisms, and the use of the diagnosis of 'IBS' is a lost opportunity to provide a precise diagnosis. There is increasing evidence that the symptoms of disturbed bowel function, pain, and bloating individually or in combination represent diverse etiological mechanisms that are not sought as the profession has embraced 'positive diagnosis' based on symptoms in the absence of objective and validated diagnostic markers. This also results in an opportunity cost as patients receive nonspecific treatments instead of more specific therapy tailored to the individual patient.

(6) Medications for 'IBS' are not targeting underlying mechanisms or at least pathophysiology, but are selected mainly according to bowel pattern. However, even with one type of bowel dysfunction, 'one size does not fit all'. For example, should all patients with 'IBS-C' based on symptom criteria receive colonic prokinetics or secretagogues?

(7) The adoption of the term by the regulatory agencies has led to the required standard that a drug has to improve both abdominal pain and bowel dysfunction to be potentially approvable for the 'IBS' indication. There have been several unintended consequences:
   (a) Patients whose bowel dysfunction is improved report reduced abdominal pain and bloating; however, this may provide only partial relief of the pain component.
   (b) There has been a duplication of 'indications' sought for drugs directed at the same pathophysiology. Several treatments directed at functional gastrointestinal disorders are as effective for functional constipation (or chronic idiopathic constipation) as they are for IBS-C, for example, tegaserod, linaclotide, lubiprostone [Camilleri, 2012]. The different subclassifications, therefore, serve only to confuse physicians and regulatory agencies, and to increase the societal costs of drug development and approval.
   (c) There has been no significant advance in the development of visceral analgesics for abdominal pain syndromes.

Indeed, there is a disincentive to develop much needed treatments for abdominal pain since, mechanistically, the only drug classes likely to significantly affect pain and bowel dysfunction (and therefore 'qualify' for approval as 'IBS' drugs) are 5-hydroxytryptamine 3 (5-HT_3) antagonists and mu-opiates. Tachykinin antagonists have been disappointing to date, the 5-HT_3 antagonists have already had a chequered regulatory history because of excessive constipation and, possibly, ischemic colitis; and the mu-opiates may induce dependence and should be avoided in chronic conditions because of their addictive potential [Camilleri, 2011a, 2012].

Irritable bowel syndrome: a diagnosis of exclusion . . . but the exclusions have changed

For the past 30 years, the diagnosis of IBS has been based on the positive diagnosis of compatible symptoms and exclusion of organic disease, specifically, colon cancer and Crohn's disease. After the seminal paper by Manning and colleagues [Manning *et al.* 1978] recommending the positive symptom-based diagnosis of IBS that coincided with the paper by Kruis and colleagues [Kruis *et al.* 1984], in which simple screening tests such as hemoglobin level and erythrocyte sedimentation rate were part of a screen for alarm features, consensus criteria were developed to codify the diagnosis based on symptoms.

Different estimates of 'missed' diagnoses were published with the inclusion of alarm features or red flags. Some claim that red flags may be useful for identifying patients who require additional diagnostic evaluation, but incorporating them into the Rome II criteria would not improve sensitivity and would result in too many missed IBS diagnoses [Whitehead *et al.* 2006]. However, specificity of Rome II criteria is modest (about 0.7), but can be improved to 0.9 by the addition of red flag signs and symptoms [Whitehead and Drossman, 2010]. Compared with the consultant's final diagnosis as the gold standard, a retrospective series of 98 patients who met the Rome criteria and lacked red flags showed that this combination had a sensitivity of 65%, a specificity of 100%, and a positive predictive value of 100%; moreover, none of these patients required revision of their diagnosis during a 2year follow up [Vanner *et al.* 1999]. In that paper, specificity was defined as identification of colorectal malignancy, inflammatory bowel disease, or pseudo-membranous colitis.

The diagnostic approach based on symptoms assumes that colon cancer, in particular, is excluded through colonoscopy or other colonic imaging, especially in patients presenting over the age of 50 years, or 45 years among African Americans. This enhanced the 'safety' of symptom-based diagnosis. Follow-up data from 2 years [Vanner *et al.* 1999] to a median 29 years suggest that 'IBS' is a safe diagnosis; in the latter series, 10 of the 112 patients had developed organic gastrointestinal diseases within a median of 15 years' follow up, but only two (one small bowel obstruction and one gastric ulcer) were within 3 years of the diagnosis of IBS [Owens *et al.* 1995]. Stool and serological markers are also effective in screening for inflammatory bowel disease and these include fecal calprotectin and lactoferrin (reviewed in [Camilleri, 2011b]).

Consensus criteria for the symptom complexes such as IBS have been extended to individual symptoms, such as functional bloating, functional diarrhea, and functional constipation. The provision of a 'label' gives the false sense

Table 1. Mimics of diarrhea-predominant irritable bowel syndrome [adapted from Camilleri (2009)].

Disorder/disease	Management
Food allergy/intolerance	Dietary exclusion
Sugar maldigestion	Sugar breath H_2 test; exclusion diet
Celiac disease	Prevalence ~1:80; TTG serology; GFD
Gluten intolerance, not celiac disease	HLA-DQ_2 positive, 5:1 respond to GFD
Microscopic colitis	Colon biopsy; bismuth, budesonide
Idiopathic bile acid malabsorption	^{75}Se methionine retention; serum 7-αHCO; fecal bile acids, bile acid binding therapeutic trial
Bacterial overgrowth	Unclear prevalence; find the underlying cause
Carcinoid syndrome	Urine 5-HIAA

7-αHCO, 7α-hydroxy-4-cholesten-3-one; 5-HIAA, 5-hydroxyindole acetic acid; GFD, gluten-free diet; TTG, tissue transglutaminase.

that the cause of the symptom and, presumably, its treatment are clearly understood. There is a growing appreciation that a significant number of conditions may mimic the symptoms associated with lower gastrointestinal dysfunction. Identification of these diverse diseases (such as celiac disease and bile acid malabsorption) is indicated, especially when there are specific treatments. Examples of conditions mimicking IBS-D are summarized in Table 1.

The main mimics of IBS-C are evacuation disorders and slow transit constipation, which can only be definitively identified by formal testing, although clinical examination by experts may be quite helpful [Tantiphlachiva *et al*. 2010].

It follows, therefore, that in 2012, diagnostic specificity in patients with suspected IBS needs to be defined more precisely than with exclusion of cancer and inflammatory bowel disease. Such specificity requires understanding of the broad differential diagnosis and the ability to identify disorders of gastrointestinal function.

Application of tests to specify disorders of gastrointestinal function

While much research has centered around the 'validation' of different versions or 'generations' of symptom-based criteria, there have been conceptual breakthroughs and a subtle paradigm shift during the past 30 years which have the potential to significantly impact the management of the disorders of gastrointestinal function. These practical tests that are widely applied in clinical practice include measurements of anorectal function and rectal evacuation, and measurements of gastrointestinal and colonic transit [Nullens *et al*. 2011; Rao *et al*. 2011; Sadik *et al*. 2008] which have well defined coefficients of variation (around 10–15%) and validated performance characteristics [Deiteren *et al*. 2010].

The availability of such tests, which together cost about a third as much as a single colonoscopy or abdominal computed tomography scan, has led to more precise and specific diagnosis of the disorders of motor function or evacuation, rather than all being lumped as IBS. Thus, after excluding patients with chronic nonorganic abdominal pain, it is possible to diagnose conditions such as rectal evacuation disorder (pelvic floor dyssynergia; its spastic variant, anismus; or its flaccid variant, descending perineum syndrome [Bharucha and Fletcher, 2007; Rao, 2010], slow transit constipation, normal transit constipation, rapid transit diarrhea, and normal transit diarrhea. Greater specificity through 'physiological diagnoses' enhances outcomes for the primary symptoms and secondary abdominal symptoms. For example, randomized, controlled studies of biofeedback retraining for rectal evacuation disorders have demonstrated relief of defecatory symptoms [Enck *et al*. 2009] and abdominal symptoms such as pain and bloating [Chiarioni *et al*. 2005]. Second, diverse pharmacological agents have demonstrated significant improvement in colonic transit measurements with scintigraphy. The same agents have also been effective in large phase IIB and III randomized, controlled clinical trials using patient response outcomes as the primary endpoints [Camilleri, 2010].

In summary, disorders of function require physiological measurements for their identification. However, as with symptoms, a disorder of function does not constitute an etiological diagnosis; it merely brings us one step closer to identifying the cause. In the future, we have to integrate into practice those tests that identify the etiology such as celiac disease, bile acid malabsorption, or carcinoid tumor [Wilson, 2009] if we are going to best serve the needs of the patient.

Conclusion

Acceptance of the term 'IBS' and the waste basket approach to lumping unexplained gastrointestinal symptoms as IBS dissuade the clinician from establishing a pathophysiological or etiological diagnosis, thus preventing the use of more specific therapy based on objective findings. Disorders of function require physiological measurements for their identification which can lead to evidence-based treatment. Such treatment should translate, ultimately, into lower costs by avoiding repeat testing, which may be risky because of radiation exposure or instrumental perforation. In addition, this approach would match the more expensive treatments to the patients with demonstrated pathophysiology that increases the likelihood of positive results. Thus, among patients with constipation, differentiation of evacuation disorder from slow transit and normal transit constipation would allow appropriate patient selection for biofeedback retraining of the pelvic floor disorder, treatment with the newer prokinetics and secretagogues in patients with slow transit constipation, or treatment with simple and inexpensive laxatives.

Almost a century after its introduction, it is time to avoid use of the term 'IBS' and replace it with more meaningful pathophysiology-based diagnoses that reflect the dysfunction causing the patient's ailments and which can be treated with greater selectivity.

Acknowledgements

The author thanks Mrs Cindy Stanislav for excellent secretarial assistance.

Funding

This study was supported in part by the NIH (grant numbers 1RC1-DK086182 and R01-DK092179 to Dr M. Camilleri).

Conflict of interest statement

The author has no conflicts of interest.

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