EDITORIAL

IRRITABLE BOWEL SYNDROME: RECENT PROGRESS IN PATHOPHYSIOLOGY, DIAGNOSIS AND MANAGEMENT?

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Irritable bowel syndrome (IBS) is one of the most common of all medical disorders, whether surveyed in the community, in a primary care practice or at a specialist gastroenterology referral centre.[1,2] Its prevalence has long been appreciated in the West; what is new is a recent accumulation of evidence to indicate that IBS is also highly prevalent in the East and even in developing nations like Pakistan.[3,4] These same studies have also revealed some interesting differences in demographics and mode of presentation between East and West. Thus, female predominance, a hallmark of IBS in Europe and North America, is not as striking in the East and may not even exist in certain countries, where male IBS subjects may be in the majority. Furthermore, symptom patterns may vary, with lower abdominal pain and a preoccupation with bowel habit being the foremost pattern in the West, whereas upper abdominal symptoms are common in the East where sufferers also seem less exercised about bowel dysfunction. The latter reminds us of the importance of overlap with another functional disorder, functional or non-ulcer dyspepsia (FD). Some, indeed, would refer to evidence such as this to emphasise the degree of overlap between these conditions and would question whether FD, a disorder which has proven difficult to define clinically, is really a distinct entity but rather a part of the spectrum of IBS, a much more accepted clinical entity.[5]

While research continues, in a variety of areas, on the pathophysiology of IBS, work on a possible inflammatory component to IBS is currently attracting the greatest attention. Three principal strands of evidence have been explored: the role of enteric infection in initiating IBS (post-infectious IBS, or PI-IBS), the possibility that alterations, be they quantitative or qualitative, in the enteric flora might be relevant to the genesis of symptoms in IBS and, finally, the suggestion that low-grade inflammation and immune activation may be a fundamental abnormality in IBS. With regard to the former, there is now an overwhelming body of epidemiological and clinical data to support the concept of PI-IBS, an entity that clinicians have recognised for decades.[6] Though the risk of developing PI-IBS following an episode of bacterial gastroenteritis is low, afflicted patients may endure prolonged and significant IBS-type symptoms and may exhibit an associated persistent inflammatory response in the rectal mucosa. Over the years a number of studies have suggested that the colonic (or, more correctly, the faecal flora) flora may demonstrate quantitative changes in IBS; studies on the faecal flora in IBS have, however, provided variable results, one of the few consistent findings being an apparent suppression of the population of *bifidobacteraia*. Given the limitations of faecal sampling as a reflection of the colonic flora and of current culture techniques, per se, more study is required on this issue. Very recent studies, using molecular techniques, have, not only begun to reveal the true diversity of the intestinal microbiota, but have begun to establish, on a firmer footing, differences between IBS and control subjects.[7] Even more controversial has been the suggestion that a significant proportion of the IBS population harbour bacterial overgrowth in their small intestines and that they can expect a significant symptomatic response to course of antibiotics.[8] Critics of this hypothesis have drawn attention to the poor specificity of the test (the lactulose breath hydrogen test) used to diagnose bacterial overgrowth in these studies, to the non-specificity of gastrointestinal symptoms, in general, and to the far from spectacular response to antibiotic therapy.[9,10] Furthermore, others have failed to reproduce this finding. This is an important issue, as the prospect of long-term, or even repeated, courses of antibiotics to subjects with a disorder as chronic and relapsing as IBS, is a cause for some considerable concern. The inflammatory concept, in contrast, continues to gather momentum. It began with the demonstration, in biopsy material from the rectum, colon and ileum, of evidence of increased numbers of a variety of cells (lymphocytes, mast cells) known to participate in an inflammatory response and to produce cytokines and other biologically active substances that could modulate enteric nerve and muscle function.[11] Since then, others have gone on to demonstrate elevated levels of pro-inflammatory cytokines in the peripheral blood of IBS patients and have even suggested that some IBS patients may be genetically predisposed to develop a low-grade, but sustained, inflammatory response to certain stimuli, including those that may originate in the lumen itself.[12-14] In this way, a luminal stimulus could initiate a local inflammatory response in the colon or small intestine and, through the local or systemic release of cytokines, generate the motor ("spasm"), sensory (visceral hypersensitivity and hyperalgesia) and mucosal responses that typify IBS. It is also feasible, based on evidence from animal models as well as from man, to reconcile these "inflammatory" findings with more central {aberrant cerebral activation and disturbances in the hypothalamic-pituitary-adrenal (HPA) axis} and even systemic disturbances (fatigue, fibromyalgia) associated with IBS. Whether these linkages between inflammation and other physiological perturbations represent mere associations or, indeed, even epiphenomena, or are truly causal remains to be determined. For now, these findings have raised the possibility that a targeted anti-inflammatory approach may ameliorate symptoms or even cure IBS is tantalizing one; evidence with a probiotic (*Bifdobacterium infantis infantis* 35624) with potent anti-inflammatory properties suggests that journeys down this therapeutic avenue may prove productive.[12]

For now, the management of IBS continues to pose significant challenges for the patient and the clinician, alike. The importance of the physician-patient interaction cannot be over-emphasised: it is critical that the physician recognise the patient's symptoms, their impact on their daily lives and any associated psychosocial dimensions. With regard to the evaluation of the patient presenting with IBS-type symptoms we have recently witnessed a sea-change in attitude. The concept of IBS as a diagnosis of exclusion (or even of exhaustion), arrived at only when a range of biochemical, radiological and endoscopic tests had eliminated other 'pathologies', has now been cast aside: in the right context and in the absence of symptoms or signs suggestive of other diseases, a positive diagnosis is, not only possible, but recommended.[15,16] This approach eliminates the need for the application of expensive, invasive and, almost certainly worthless, investigations, to all IBS patients. Given the heterogeneity of symptoms and modes of presentation in IBS it should come as no surprise that management strategies can seldom be generalised but require considerable nuance and even individualization. What may assist a patient with frequent bowel movements or even diarrhoea may significantly impair the patient with constipation in association with IBS. The concept of tailored therapy based on predominant stool frequency came to the fore with the development of IBS-targeted therapies that either accelerated (tegaserod) or inhibited (alosetron and cilansetron) gut transit. All of these agents were designed to modulate serotonergic (5-hydroxytryptamine, 5-HT) activity in the enteric nervous system. The universal adoption of these agents has been limited by regulatory issues (none of these agents has been approved for use in the European Union) and, in the case of the 5-HT_3 antagonists, by the spectre of ischemic colitis. Tegaserod, in turn, was withdrawn because of rare cardiac effects. The regulatory travails of all of these compounds, on both sides of the Atlantic, have revealed the challenges that face those that attempt to introduce, test and bring to market, new therapies in IBS.[17] It is, after all, a heterogeneous disorder of uncertain cause for which we have no validated biomarker and which is associated with a placebo response that averages 40% in clinical trials. Furthermore, IBS is regarded, by regulatory bodies, as a very benign disorder; as such adverse events of any magnitude or severity will not be tolerated. Most recently, Food and Drug Administration in the US has imposed a moratorium on new IBS studies pending definition, validation and acceptance of an appropriate primary outcome endpoint. These misgivings notwithstanding, research continues on a variety of chemical entities that may impact on IBS, be they located on sensory neurons, on gut smooth muscle, the central nervous system, in the intestinal lumen or inflammatory cells.

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