Seymour Katz, M.D., Series Editor

Irritable Bowel Syndrome and Inflammatory Bowel Disease: Is There an Overlap?

Eamonn M. M. Quigley

Fergus Shanahan

Irritable Bowel Syndrome (IBS) is a common and sometimes disabling syndrome which has been reported to affect up to 10–15% of adults in North America (1) and Western Europe (2,3); inflammatory bowel disease (IBD), though less common, affecting approximately 0.5% of the Canadian population (4), is not rare. It should come as no surprise, therefore, that these entities should, on occasion, coincide or coexist, albeit by happenstance. Recent descriptions of immune activation and even subtle mucosal inflammation in IBS have raised the possibility of a more fundamental relationship between IBS and IBD. This review will address two issues: firstly, at a pathophsyiological level, the relationships between IBS and IBD and, secondly, in a clinical context, the interpretation of IBS-type symptoms among IBD patients in apparent remission.

Eamonn M. M. Quigley, MD FRCP FACP FACG FRCPI and Fergus Shanahan, MD FRCPI FRCP FACP FCCP FACG, Alimentary Pharmabiotic Centre, Department of Medicine, University College Cork, Cork, Ireland.

IS IBS PART OF THE SPECTRUM OF IBD?

In past decades, when IBS sufferers were commonly employed as "controls" in IBD studies, IBS was regarded as a mere nuisance to be occasionally tolerated by the hoi polloi of that rarefied community, the IBD confraternity. The very suggestion that IBD, a disorder populated by innumerable T-cell subsets and complexities of mucosal immunology and human genetics comprehensible only to that elite cadre of practitioners and clinical researchers possessed of the intellectual prowess to enter this field, had anything in common with IBS, a messy, vague and marginal entity, would be treated with the scorn it deserved and dismissed with derision. How things have changed? As yet another T cell subset failed to deliver, the litany of cytokines and chemokines possibly linked to IBD stretched even further into a darkening horizon and yet another gene mutation disappointed, the gaze of the IBD-ologist began to wander and, reluctantly, and secretly (as no self-respecting IBD aficionado could admit in public that he or she was dabbling in the dark arts of IBS) began to rest on IBS. Meanwhile, though handicapped by an inferior intellect and an ignorance

of the immunological lexicon, those lowly beings that labored in the dry barren fields that heretofore had been IBS research had stumbled (it was surely beyond their powers to actually develop new concepts) on some findings that brightened their landscape. Several of these observations have raised the heretical proposition that IBS and IBD may have some commonalities.

In IBD there is abundant evidence, firstly, from animal models, secondly, from such natural experiments, in man, as diversion of the luminal stream and, finally, from extensive immunological research, to indicate a central role for the gut flora in the initiation and perpetuation of the inflammatory process. Though still an emerging field, evidence to support a role for luminal factors in IBS can be garnered from two main sources; the role of prior infection in the initiation of IBS and the influence of alterations in the gut flora on IBS.

Clinicians who have dealt with IBS for several years will have seen patients, formerly in perfect health, who, following exposure to gastroenteritis, have gone on to develop frank IBS; the concept of post-infectious IBS (PI-IBS) has now been described in considerable detail in several large series (5,6). A variety of clinical and demographic factors have been shown to increase the risk for the development of IBS following bacterial gastroenteritis: female gender, past history of anxiety or depression, more severe clinical course of gastroenteritis and a persistent inflammatory response in the colonic mucosa. Most recently some genetic factors that seem to predispose to PI-IBS have been identified (7); interestingly, the genes implicated code for interleukins and epithelial barrier factors considered relevant to the pathogenesis of IBS, in general (8). The ability of infectious agents, such as *Clostridium difficile* (9), to trigger relapses of existing IBD have been recognized for decades; what is new is the possibility that the onset of IBD, like IBS, may be triggered by an enteric infection (10). While the above studies have examined the consequences of an acute enteric infection on the intestine, others have suggested that more chronic alterations in the enteric flora may also influence the development of IBS (11); a concept that is, as yet, supported by rather less evidence.

The other area, which has revealed a convergence of factors that seem to be relevant to the pathogenesis of both IBS and IBD, is that of the host immune response. Clearly central to the development and course of IBD, mucosal and systemic immune responses are now generating considerable interest in IBS. With some consistency, elevated levels of the pro-inflammatory cytokines interleukin (IL)-6 and IL-8 have been demonstrated in the peripheral circulation in IBS (12–14). Others have examined various components of the mucosal immune response and have variably demonstrated activation of mast cell (15–19) and lymphocyte populations (20–23), as well as increased epithelial barrier permeability (24,25), altered expression of cytokine-related genes (26,27), upregulation of Toll-like receptors (TLR's) (28) and increased levels of β-defensin 2 (29). Involvement of TLR's and β-defensin 2 provides support for engagement of the microbiota with the host immune system in IBS.

One is tempted to ask, therefore, is IBS part of the spectrum of IBD? Not only is this suggestion premature given the preliminary and often unconfirmed nature of these observations, but the evidence that is available points to both quantitative as well as qualitative differences in the immune response between IBS and IBD. Thus, whereas in IBD the response is overt inflammation which can be visualized both macroscopically and microscopically, the changes in IBS are much more subtle and should be referred to as immune activation rather than inflammation. Furthermore, as evidenced by the description of normal fecal levels of calprotectin (29,30), neutrophils do not participate in the response in IBS, in contrast to IBD and the profile of cytokine gene expression in, and release from, the colonic mucosa differs quite dramatically between the two disorders (26). That these immunological differences are clinically relevant is evidenced by the observation that IBS does not transition to IBD. Other pathophysiological differences also speak to the separateness of these disorders: whereas IBS reflects the interactivity of the central nervous systems (as evidenced, for example, by the primacy of stress as a symptom precipitant and by the demonstration of abnormalities in CNS perception of visceral events) IBD is dominated by pathology peripherally in the gut and is far less influenced by central input. The bottom line: IBS may feature some interesting immunological

(continued on page 34)

(continued from page 32)

and microbiological aspects, whose primacy in its pathophysiology remains to be defined, but it is not IBD. Clinical observations support this conclusion. While the IBD patient may give a history of IBS-type symptoms extending over several years before the diagnosis of IBD is ultimately made (31), this represents a failure to diagnose IBD rather than the evolution of IBS into IBD. Indeed, the prevalence of IBD is no greater among those with a definitive diagnosis of IBS than among the general population (32). Furthermore, lymphocytic (or microscopic) colitis, a disorder that bears some clinical and pathophysiological similarities to IBS, has also been rarely observed to evolve into full-blown IBD (33).

WHAT IS THE SIGNIFICANCE OF IBS-TYPE SYMPTOMS IN THE IBD PATIENT?

It has long been recognized that some IBD patients can present with IBS-type symptoms during periods of apparent remission of their IBD. Indeed, a number of studies have associated the occurrence of these IBS-type symptoms with impaired quality of life among IBD patients in remission (34,35). One study evaluated patients with either UC or CD who had been in apparent remission of their IBD for at least one year; 23% of ulcerative colitis patients and 57% of the Crohn's patients reported IBS-type symptoms (35). Furthermore, while the psychological well being of the IBD patients, as a whole, was no different from that of a control population, those who reported IBS-type symptoms experienced more anxiety and depression and a reduced sense of well being. Another example of a potential interaction between IBS and IBD is the irritable pouch syndrome (IPS), described among patients who have undergone a total colectomy with the creation of an ileal pouch for ulcerative colitis and who present with symptoms suggestive of pouchitis but whose pouch looks normal (36).

Do these disparate findings represent a true association between IBD and IBS or, rather, the effects of sub-clinical IBD on a gut that has a limited symptomatic repertoire? The pathology and pathophysiology of intestinal motor changes in inflammatory bowel diseases, as well as the effects of inflammation on the enteric nervous system, certainly provide a pathophysiological basis for the development of IBS-type symptoms in IBD (37,38). In muscle, altered contractility, increased collagen deposition, enhanced expression of MHC class 2 and ICAM-1 and modified cytokine production have all been documented in relation to inflammation (39). Abnormalities described in the enteric nervous system include morphologic changes in neurons and glial cells, alterations in the release of a variety of neuro-peptides and neuro-transmitters, such as nitric oxide, vaso-active intestinal peptide (VIP) and PACAP, enhanced expression of nerve growth factor (NGF), activation of sensory afferents (perhaps via calcitonin gene-related peptide (CGRP) and, very interestingly, expression of MHC class 2 (HLA-DR) antigens on enteric glial cells and glial sheaths in the mucosa and submucosa. The latter observation indicates that chronic inflammation, such as occurs in IBD, may lead to significant changes in the phenotype of both smooth muscle and enteric neurons, to the extent that they can assume immunological functions, leading to a self-perpetuating cycle of interactions between inflammatory cells and the enteric neuro-muscular apparatus, per se. These changes have been noted in the context of inflammation limited to the mucosa and even at sites remote from the area of inflammation.

How then does the clinician interpret IBS-type symptoms in the IBD patient who seems to be in remission; is he or she dealing with coincident IBS, a statistically plausible occurrence, or do these symptoms reflect on-going inflammation generating the various complaints that constitute IBS through the mechanisms outlined above? These are important questions, which have very significant implications for the further assessment and ultimate management of the patient. No one wants to embark on steroids, immunosuppressants and immunomodulators for what turns out to be IBS!

We recently addressed this issue in 106 consecutive IBD patients attending an IBD clinic and who appeared to be in clinical remission by standard criteria; 62 had Crohn's disease (CD) and 44 had ulcerative colitis (UC). Despite being considered to be in clinical remission by the predefined criteria, 37 (60%) of CD patients and 17 (39%) of UC patients fulfilled Rome II criteria

(continued on page 36)

(continued from page 34)

for IBS (30). CD patients with IBS symptoms were more likely to be smokers and to have a higher Crohn's disease activity index (CDAI) though all CDAI's were less than 150. Among the UC patients, those with IBS symptoms had significantly impaired quality of life scores. Most revealing, however, were results of assays for faecal calprotectin in both forms of IBD. Calprotectin is a calcium- and zinc-bound protein which accounts for 60% of the soluble proteins in the cytosol of neutrophil granulocytes and has been shown to be a very sensitive indicator of ongoing inflammation in IBD (40). In our study, calprotectin levels among both CD and UC patients with IBS symptoms were eight to twelve-fold higher than both control subjects and IBS patients and two to three-fold higher than those CD and UC patients who were symptom free. Given that calprotectin levels are within the normal range in IBS patients, in general (29,30), these findings provide clear-cut evidence that low-grade IBD can produce IBS-type symptoms but this is not IBS! Instead, the presence of these symptoms in the IBD patient must be assumed, until proven otherwise, to represent the effects of low-grade inflammation and to reflect the non-specificity of the gut's symptomatic repertoire. To further increase the clinical challenge, it has been demonstrated in experimental animal models and observed in man that persistent low-grade inflammation may give rise to motor and sensory changes at some remove from the site of inflammation (37–39). Given what we know of interactions between immune activation and motor and sensory nerve function in the gut it stands to reason that the IBS patient who actually develops IBD will be more likely to exhibit motor dysfunction and visceral hypersensitivity accompanied by their associated symptoms.

CONCLUSIONS

Despite recent explorations of contributions of low-grade inflammation and immune activation to irritable bowel syndrome, these changes are subtle and quantitatively and qualitatively different to those seen in IBD. While these observations provide insights into clinically relevant interactions between immune activation at a molecular level and gut dysfunction, the intensity of the immune response is orders of magnitude less than that seen in IBD; IBS is not a form of IBD. Though it stands to reason, given their prevalence in the West, that IBS and IBD are likely to occur in the same patient by mere coincidence, IBS-type symptoms need to be interpreted with great caution in the IBD patient, even when they appear in remission. Recent clinical evidence, as well as a considerable body of experimental data, suggests that such symptoms reflect low-grade inflammation and its effects on gut muscle and nerve, and should, therefore, be regarded as indicative of IBD activity until proven otherwise. ■

References

1. Hungin AP, Chang L, Locke GR, Dennis EH, Barghout V. Irritable bowel syndrome in the United States: prevalence, symptom patterns and impact. *Aliment Pharmacol Ther*. 2005;21:1365-75.
2. Hungin APS, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther*. 2003;17:643-50.
3. Quigley EMM, Bergmann J-F, Bytzer P, Fried M, Hunt R, Hungin APS, Kellow J, Koch G, Laine L, Schoenfeld P, Spiegel BMR, Tack J, Tytgat G. An evidence-based approach to the management of irritable bowel syndrome in Europe. *Eur J Gastroenterol Hepatol* 19(suppl 1):S1-S37, 2007.
4. Bernstein CN, Wajda A, Svenson LW, MacKenzie A, Koehoorn M, Jackson M, Fedorak R, Israel D, Blanchard JF. The epidemiology of inflammatory bowel disease in Canada: a population-based study. *Am J Gastroenterol*. 2006;101:1559-68.
5. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: The incidence and prognosis of post-infectious irritable bowel syndrome. *Aliment Pharmacol Ther*. 2007;26:535-44.
6. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2009;136:1979-88.
7. Villani AC, Lemire M, Thabane M, Belisle A, Geneau G, Garg AX, Clark WF, Moayyedi P, Collins SM, Franchimont D, Marshall JK. Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. *Gastroenterology*. 2010;138:1502-13.
8. Craig OF, Quigley EMM. Bacteria, Genetics and Irritable Bowel Syndrome (IBS). *Expert Rev Gastroenterol* 2010; (in press).
9. Clayton EM, Rea MC, Shanahan F, Quigley EM, Kiely B, Hill C, Ross RP. The vexed relationship between Clostridium difficile and inflammatory bowel disease: an assessment of carriage in an outpatient setting among patients in remission. *Am J Gastroenterol* 2009;104:1162-9.
10. Gradel KO, Nielsen HL, Schønheyder HC, Ejlertsen T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology*. 2009;137:495-501.
11. Quigley EMM. Do patients with functional gastrointestinal disorders have an altered flora? *Ther Adv Gastroenterol* 2009; 2(suppl 1):S23-S30.
12. Dinan TG, Quigley EMM, Ahmed SMM, Scully P, O'Brien S, O'Mahony L, O'Mahony S, Shanahan F, Keeling PWN. Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker? *Gastroenterology* 2006;130:304-311.
13. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology* 2007;132:913-20.

14. Scully P, McKernan DP, Keohane J, Groeger D, Shanahan F, Dinan TG and Quigley EMM. Plasma cytokine profiles in females with irritable bowel syndrome and extra-intestinal co-morbidity. *Am J Gastroenterol* Apr 20. [Epub ahead of print].
15. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126 :693-702.
16. Barbara G, Wang B, Stanghellini V, de Giorgio R, Cremon C, Di Nardo G, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007;132:26-37.
17. Cenac N, Andrews CN, Holzhausen M, Chapman K, Cottrell G, Andrade-Gordon P, Steinhoff M, Barbara G, Beck P, Bunnett NW, Sharkey KA, Ferraz JG, Shaffer E, Vergnolle N. Role for protease activity in visceral pain in irritable bowel syndrome. *J Clin Invest*. 2007;117:636-47.
18. Guilarte M, Santos J, de Torres I, Alonso C, Vicario M, Ramos L, Martinez C, Casellas F, Saperas E, Malagelada JR. Diarrhoea-predominant IBS patients show mast cell activation and hyperplasia in the jejunum. *Gut*. 2007;56:203-9.
19. Buhner S, Li Q, Vignali S, Barbara G, De Giorgio R, Stanghellini V, Cremon C, Zeller F, Langer R, Daniel H, Michel K, Schemann M. Activation of human enteric neurons by supernatants of colonic biopsy specimens from patients with irritable bowel syndrome. *Gastroenterology*. 2009;137:1425-34.
20. Chadwick V, Chen W, Shu D et al. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; 122: 1778–83.
21. Holmen N, Isaksson S, Simren M, Sjovall H, Ohman L. CD4+CD25+ regulatory T cells in irritable bowel syndrome patients. *Neurogastroenterol Motil*. 2007;19:119-25.
22. Ohman L, Isaksson S, Lundgren A, Simren M, Sjovall H. A controlled study of colonic immune activity and beta7+ blood T lymphocytes in patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2005;3:980-6.
23. Cremon C, Gargano L, Morselli-Labate AM, Santini D, Cogliandro RF, De Giorgio R, Stanghellini V, Corinaldesi R, Barbara G. Mucosal immune activation in irritable bowel syndrome: gender-dependence and association with digestive symptoms. *Am J Gastroenterol*. 2009;104:392-400.
24. Quigley E. Gut permeability in irritable bowel syndrome: more leaks add to slightly inflamed bowel syndrome conspiracy theory. *Gastroenterology*. 2009;137:728-30.
25. Barbara G. Mucosal barrier defects in irritable bowel syndrome. Who left the door open? *Am J Gastroenterol* 2006;101: 1295-8.
26. MacSharry J, O'Mahony L, Fanning A, Bairead E, Sherlock G, Tiesman J, Fulmer A, Kiely B, Dinan TG, Shanahan F, Quigley EM. Mucosal cytokine imbalance in irritable bowel syndrome. *Scand J Gastroenterol*. 2008;43:1467-76.
27. Aerssens J, Camilleri M, Talloen W, Thielemans L, Göhlmann HW, Van Den Wyngaert I, Thielemans T, De Hoogt R, Andrews CN, Bharucha AE, Carlson PJ, Busciglio I, Burton DD, Smyrk T, Urrutia R, Coulie B. Alterations in mucosal immunity identified in the colon of patients with irritable bowel syndrome. *Clin Gastroenterol Hepatol*. 2008;6:194-205.
28. Brint EK, MacSharry J, Fanning A, Shanahan F, Quigley EMM. Differential Expression of Toll-Like Receptors (TLRs) in patients with Irritable Bowel Syndrome. *Am J Gastroenterol*. 2010 (in press).
29. Langhorst J, Junge A, Rueffer A, Wehkamp J, Foell D, Michalsen A, Musial F, Dobos GJ. Elevated human beta-defensin-2 levels indicate an activation of the innate immune system in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2009;104: 404-10.
30. Keohane J, O'Mahony C, O'Mahony L, O'Mahony S, Quigley EM, Shanahan F. Irritable Bowel Syndrome-Type Symptoms in Patients With Inflammatory Bowel Disease: A Real Association or Reflection of Occult Inflammation? *Am J Gastroenterol*. 2010 Apr 13. [Epub ahead of print]
31. Burgmann T, Clara I, Graff L, Walker J, Lix L, Rawsthorne P, McPhail C, Rogala L, Miller N, Bernstein CN. The Manitoba Inflammatory Bowel Disease Cohort Study: prolonged symptoms before diagnosis—how much is irritable bowel syndrome? *Clin Gastroenterol Hepatol*. 2006;4:614-20.
32. Brandt LJ, Bjorkman D, Fennerty MB, Locke GR, Olden K, Peterson W, Quigley E, Schoenfeld P, Schuster M, Talley N. Systematic review on the management of irritable bowel syndrome in North America. *Am J Gastroenterol* 2002;97(Suppl II):S7-S26.
33. Pardi DS, Ramanath VR, Loftus EV, Tremaine WJ, Sandborn WJ. Lymphocytic colitis: clinical features, treatment, and outcomes. *Am J Gastroenterol* 2002;97:2829-2833.
34. Isgar B, Harmann M, Kaye MD, Whorwell PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983;24:190-192.
35. Simren M, Axelsson J, Gillberg R, Abrahamsson H, Svedlund J, Bjornsson ES. Quality of life in inflammatory bowel disease in remission: the impact of IBS-like symptoms and associated psychological factors. *Am J Gastroenterol* 2002;97:389-396.
36. Shen B, Achkar J-P, Lashner BA, Ormsby AH, Brzezinski A, Soffer EE, Remzi FH, Bevins CL, Fazio VW. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol* 2002; 97:972-977.
37. Geboes K, Collins S. Structural abnormalities of the nervous system in Crohn's disease and ulcerative colitis. *Neurogastroenterol Mot*. 1998;10:189-202.
38. Shanahan F. Enteric neuropathology and inflammatory bowel disease. *Neurogastroenterol Mot*. 1998;10:185-187.
39. Collins SM. The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. *Gastroenterology* 1996;111:1683-1699.
40. Schoepfer AM, Beglinger C, Straumann A, Trummler M, Vavricka SR, Bruegger LE, Seibold F. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol*. 2010;105:162-9.