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Inflammatory Bowel Disease, Irritable Bowel Syndrome, or What?: A Challenge to the Functional–Organic Dichotomy

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Abstract: Many patients with inflammatory bowel disease (IBD) in clinical remission continue to have symptoms of pain and diarrhea despite minimal or no ongoing inflammation. These patients may be considered to have an overlap of IBD and irritable bowel syndrome (IBD-IBS). In this month's Journal, a proposal is made that continued symptoms in patients with elevated calprotectin, a marker of inflammation, is related to IBD. We propose an alternate biopsychosocial model whereby mutual effects of peripheral and central factors influence symptom generation in both IBD and IBS. Understanding this model has important implications for treatment of patients with IBD-IBS.

Am J Gastroenterol 2010; 105:1796–1798; doi:10.1038/ajg.2010.162

As clinicians we seek to understand the patient's illness experience in the face of their disease. However, the patient's *illness*, that is their perception of ill health, may vary considerably in relation to their *disease*, the externally verifiable evidence of a pathological state. We note that in inflammatory bowel disease (IBD), the pathological, radiological, or laboratory markers of the disease may be associated with very different illness expressions. Some patients with active and ulcerating IBD may have few symptoms and may not even present for treatment until a complication such as bleeding, obstruction, or abscess arises. In contrast, it is not uncommon for us to see patients with IBD who report marked pain and diarrhea, but with endoscopic or radiological mild or microscopic disease, the latter being of a phenotype that is shared particularly with post-infectious irritable bowel syndrome (PI-IBS). We now call this entity IBD-IBS (1). In fact, as diagnostic tests become more sensitive, and newer, more potent anti-inflammatory medications reduce the disease burden, we are seeing increasing numbers of this cohort of patients. One may get confused as to how to categorize them. Is it IBD, IBS, or what?

The relationship between illness or symptom experience and its association with inflammation in patients with IBD in clinical remission is highlighted by the well-done study by Keohane *et al.* (2) in this month's journal. These patients were in remission as determined by reports of no activity via physician global assessment, Crohn's Disease (CD) Activity Index ≤150 for CD and Ulcerative Colitis (UC) Disease Activity Index ≤3 for UC, no treatment with steroids or biological agents for the previous 6 months, and serum C-reactive protein <10 (non-inflammatory range). The presence of IBS-like symptoms as defined by Rome II criteria was found in 60% of the patients with CD and 39% with UC, which is similar to the previously reported data of IBS symptoms in IBD patients in remission (3). The authors then investigated whether there is an association between these IBS-like symptoms and fecal calprotectin levels, a marker for polymorphonuclear cell inflammation. Notably, fecal calprotectin was significantly elevated in those with IBS symptoms as compared with those without ($P<0.01$), and this remained significant when smokers were excluded. Also noted was that UC patients with IBS-like symptoms had lower quality of life and higher anxiety and depression scores, thus potentially linking a role for psychosocial factors with these symptoms. The authors conclude that the sub-clinical inflammation found in IBD explains these IBS symptoms but does not equate to a diagnosis of IBS; they emphasize caution in diagnosing IBS when microscopic inflammation is present in IBD patients in remission.

Although the results are clear, we have concern about the interpretation proposed and the constructs underlying it. The authors conclude: "Bottom line, IBD is IBD unless proven otherwise!" This statement implies a dualistic, "either" IBD (i.e., structural) "or" IBS (i.e., functional) perspective, which has its limitations. Why not both?

We think it is of greater value to reframe this new knowledge into a more integrated biopsychosocial construct (4), because it has important scientific and clinical implications. In fact, the authors have helped bring us to this point by demonstrating

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Received 11 February 2010; accepted 16 March 2010

that even a mild gut inflammation (in the absence of structural disease) may enable the pain and diarrhea as seen with IBD in remission. Such data challenge reductionistic concepts that relate the degree of disease activity with the degree of pain and illness experienced. In fact they demonstrate "functionality" with IBD in remission, as there are painful symptoms with minimal disease burden. Conversely, IBS, a functional disorder, is "organified", as it can be associated with microscopic inflammation. Thus, their findings actually blur the boundaries of the functional–organic dichotomy and help to re-direct us toward a more effective explanatory model.

How can we better understand these observations? From the authors' previous work in IBS, we know that microscopic gut mucosal inflammation, associated cytokine activity, and possibly disrupted hypothalamic–pituitary–adrenal (HPA) axis function may contribute mechanistically to symptom generation (5,6), although the profile of cytokine activity may differ between IBS and IBD (7). Other studies show that cytokine activation and release of mediators from mast cells upregulate visceral neuronal signaling, thus producing visceral hypersensitivity (8,9).

Furthermore, stress and other psychosocial factors can increase pain and disease activity for all medical conditions including IBD (10). In a prospective study of women undergoing surgery for gynecological conditions, pre-operative anticipation of post-surgical difficulties, perceived severity of illness, and poor coping increased the pain scores up to 1 year after surgery (11). These observations have also been found in IBS (12,13). In a study of patients with UC, long-term perceived stress nearly tripled the risk of disease activation, as determined by intensified treatment and/or increased endoscopic rectal inflammation after controlling for other known risk factors (14).

Stress may increase the symptom experience by peripheral or central mechanisms. Peripherally, it may alter the bacterial flora to disrupt the mucosal barrier, leading to transmigration of bacterial products, thereby increasing inflammation and cytokine release, and ultimately increasing visceral hypersensitivity (15,16). Centrally, magnetic resonance brain imaging studies show that life stressors, such as a history of abuse, can affect anterior cingulate activation, leading to central disinhibition. This is evidenced by increased pain in response to rectal distension. Therefore, the central failure to downregulate incoming visceral signals (17) coupled with enhanced peripheral signaling dually enhances pain perception via the brain–gut axis (18,19).

A unifying biopsychosocial model that helps consolidate the mutual influences of peripheral and central factors in symptom generation for IBS and IBD in clinical remission is shown in **Figure 1** (1). In this model, life stress can influence (via the HPA axis and altered bacterial flora) the gut by altering immune function and increasing mucosal inflammation. In addition, psychological distress and poor coping can act via central nervous system pathways to produce central disinhibition of incoming visceral signals, thus amplifying the pain experience and exacerbating other gastrointestinal symptoms (1).

With this new understanding, we can move away from dualistic "either–or" models toward seeing IBD on a continuum of

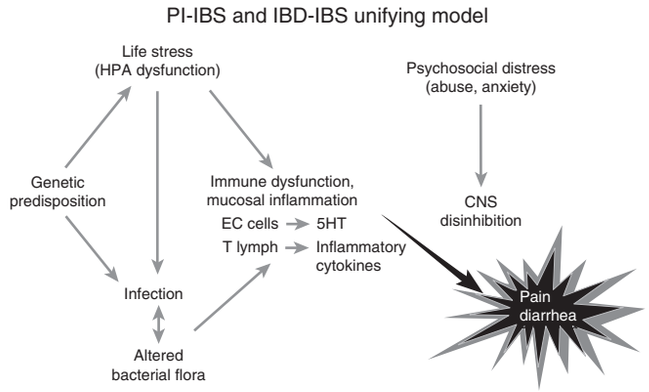

Figure 1. Unifying model for post-infectious IBD (PI-IBS) and IBD-IBS. There may be a chronic genetic predisposition that contributes both to susceptibility to responses to life stress via alteration of hypothalamic–pituitary–adrenal (HPA) function or infection, presumably through altered microbiota. These factors can produce immune dysfunction and inflammation via serotonergic and/or mucosal cytokine activation, ultimately resulting in symptoms of pain and diarrhea consistent with these conditions. The pain is influenced by the psychosocial environment of life stress or abuse, psychological distress, poor coping, or impaired psychological adaptation to illness. CNS, central nervous system; EC, enterochromaffin; 5HT, serotonin. Reproduced with permission from Grover *et al.* (1).

brain–gut interaction. Here, active disease may be associated with minimal symptoms given the proper adaptive psychosocial milieu. Reciprocally, even minimal disease may still have severe symptoms in the face of psychological distress. With this more integrated model, we can avoid potentially harmful and expensive consequences to managing symptoms in patients with IBD and mild inflammation. For example, we could minimize the efforts to focus solely on using immunosuppression, corticosteroids, or biological anti-tumor necrosis factor-α agents to reduce pain when treating patients with little or no inflammation. By understanding that even minor degrees of inflammation can facilitate sensory signaling in the gut, or that psychological distress may impair central downregulation of incoming signals, we can focus on augmenting treatment using antidepressants and psychological treatments (such as cognitive behavioral treatment) to reduce the visceral and central hypersensitivity.

Several implications arise from these important findings. Future work should include a larger study that can help determine the relationship of psychological distress and mediating psychosocial factors with mucosal inflammation in IBD. This was found to some degree in patients with UC in this study. As the authors have shown for IBS, this may be mediated through HPA axis dysregulation and would be amenable to further study. We might also want to study how best to treat patients with IBD in clinical remission and "IBS-like" symptoms. There may be a synergistic benefit to augmenting anti-inflammatory or immunosuppressive therapy used to maintain disease remission with centrally targeted treatments or probiotics (20). In the end, it is likely that these combined approaches will ultimately improve the patient's illness and disease, and potentially reduce health-care costs along the way.

CONFLICT OF INTEREST

Guarantor of the article: Douglas A. Drossman, MD.

Specific author contributions: Millie D. Long helped develop the outline for the editorial and drafted the editorial paper. Douglas A. Drossman proposed the editorial, developed the outline for the editorial, and revised the paper.

Financial support: None.

Potential competing interests: None.

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