The Pathophysiology of Irritable Bowel Syndrome – An Update*

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The irritable bowel syndrome is a complex, multifactorial disorder of gastrointestinal function that is manifested clinically as chronic lower abdominal pain and irregular bowel habits. Due to its complexity, it would be unreasonable to expect to identify a single abnormality as the basis for its pathogenesis. Indeed, the biomedical model in which the identification of a biological abnormality leads to the resolution of a medical problem is irrelevant for complex disorders such as IBS and its attempted application can only lead to frustration and dissatisfaction for patients and physicians alike.

The number of research projects and scientific publications on the pathophysiology of IBS has grown exponentially over the last decades, attesting to the importance of the subject and the progress that is being made. Table 1 presents a detailed, but not necessarily exhaustive, list of areas of active research. Obviously many of these aspects of IBS pathophysiology are intertwined and their listing as separate items is artificial. Since an abbreviated review such as this cannot possibly encompass all these issues, its scope will be limited to an update of visceral hypersensitivity, the brain-gut axis dysregulation, post-infectious IBS and evidence of related inflammation.

The multitude of proposed factors and mechanisms for IBS has led to the search for a unifying or integrating conceptual model. These attempts have grown more complex as our knowledge base increases. The somewhat simplistic view that the two components of IBS, pain and irregular bowels, are associated specifically with hyperalgesia and disrupted motility, respectively, has been replaced by a more complex, sophisticated approach to the problem that incorporates the previously and newly recognized factors associated with the pathogenesis of IBS.

Hyperalgesia/hypersensitivity

IBS patients have abnormal responses to non-painful and painful stimuli [1]. Many studies of rectal and sigmoid distension have shown that 60–95% of IBS patients have lowered thresholds for aversive sensations, feel an increased intensity of sensation, or are hypervigilant to painful stimuli [2]. Over the past decade rectal distension has been combined with simultaneous scanning of brain activity, significantly furthering our knowledge and understanding of hypersensitivity and the brain-gut axis [3–5]. However, the results of these studies may also be affected by research methodology. Hypersensitivity appears to be more salient in patients with diarrhea-predominant IBS and in females, and may be affected by patients' emotional states [6].

The search for the source of these abnormal responses in IBS patients has led to increasing focus on the brain-gut axis. The disorder can stem from dysregulation at one or more potential stations along the bi-directional communication pathways between the viscera and the higher cortical centers, through the enteric and central nervous systems. These include the end organ or viscera (receptors, transmitters), the spinal cord (ganglia, dorsal horn, spinal tracts), the brainstem and mid-brain (reticular activating system, thalamus), or higher centers (anterior cingulate gyrus, insula, prefrontal cortex). Research efforts are being invested to study each of these and other potential sites of brain-gut dysregulation. For example, spinal hyperexcitability may result

Table 1. Areas of current research interest in IBS (the order of appearance does not necessarily reflect relative importance)

- Brain-gut dysregulation, central processing of afferent stimuli
- Visceral hypersensitivity, spinal hyperalgesia
- Post-infectious IBS and chronic intestinal inflammation
- Gender
- Genetics
- Chronic stress and autonomic nervous system function
- Celiac sprue
- Bacterial overgrowth
- Psychosocial pathology
- Motility
- Sexual and physical abuse
- Gas retention and bloating
- Motility
- Extra-intestinal disorders of function and their association with IBS

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IBS = irritable bowel syndrome

from a sensitizing event and lead to the development of pain memory with the facilitation of pain transmission along spinal pathways. Studies of brain activity during visceral stimulation have shown that central processing of afferent stimuli may be affected in IBS patients. Pain has been classified into sensory-discriminative and affective-motivational components that represent different ways in which individuals process and experience pain stimuli. Indeed, pain is probably multi-dimensional rather than bi-dimensional [7]. The limbic and frontal systems that are involved in the emotive interpretation of afferent stimuli may process these signals differently in IBS patients than in healthy controls. Centers involved in the inhibitory control of afferent pain signals may be less active in IBS patients than in healthy controls, facilitating the stimulation of higher cortical centers by pain signals [8].

Post-infectious IBS and inflammation

The entity of post-infectious IBS and the uncovering of evidence of intestinal inflammation in IBS have generated a great deal of interest and excitement over recent years. Many physicians have treated patients with normal bowel habits in whom a bout of acute dysentery or gastroenteritis led to the development of chronic abdominal symptoms. These cases come to light more frequently with the higher level of awareness that now exists, although reports of this phenomenon were published as early as 1950 [9] and 1962 [10]. Present epidemiologic data suggest that an acute intestinal infection preceded the development of IBS in 6–17% of cases [11] and that over 30% of severe bacterial gastroenteritis can result in IBS [12,13]. Higher rates are associated with psychosocial pathology, female gender, severity of the acute disease, and specific bacterial toxins. The recovery rate has been reported to be 50% over 6 years [14] and is affected adversely by chronic stress, depression and anxiety.

The development of IBS following acute intestinal infection is associated with chronic inflammation that cannot be diagnosed with the usual battery of tests and procedures that IBS patients undergo; i.e., blood and stool tests, endoscopic procedures, and conventional histology studies of biopsy specimens. The manifestations of this chronic inflammatory state may include increased mast cell counts in the ileocecal area, enteroendocrine hyperplasia, increased intraepithelial lymphocyte counts, increased levels of CD3+ and CD25+ T lymphocytes in the lamina propria, increased serotonin levels, increased small bowel permeability, altered intestinal neuromuscular activity and colonic transit time, and chronic changes in visceral sensitivity. The level of immunopathology and immune system activation in these patients is higher than in healthy controls, but lower than in patients with IBD.

Dunlop et al. [15] took colonic biopsies from 76 IBS patients and 40 controls. Conventional histology studies were normal in all. However, immunohistochemical tests were positive in the IBS patients, with those with post-infectious diarrhea-predominant IBS showing evidence of increased CD3+ cells, mast cells and enteroendocrine cells. Chadwick et al. [16] took serial biopsies from 77 IBS patients and 28 controls and performed conventional histopathology, morphometry and immunohistochemical tests. All IBS subgroups had evidence of increased immunopathology compared to controls, including increased intraepithelial cells and CD3+ cells in diarrhea-predominant IBS, increased mast cells in constipation-predominant IBS, and increased CD25+ cells in both. Although the levels of these inflammatory cells were higher in IBS patients than in controls, they were lower than those in patients with IBD.

It has been suggested that the presence of increased amounts of CD25+ cells is responsible for the controlled intestinal inflammatory response that has been termed inflammation "in check" [17]. These changes are most common in patients with persistent post-infectious diarrhea-predominant IBS.

Many issues remain to be addressed in relation to post-infectious IBS and persistent intestinal inflammation [18]: Is IBS caused directly by or does it result indirectly from the infectious agent or its toxins? Do viruses also cause post-infectious IBS? Is there a genetic predisposition? Does psychopathology play a role?

Are we closer to the elucidation of a unifying conceptual model of IBS? All recently proposed models include predisposing factors (genetic and environmentally acquired, including psychosocial variables), potential triggers or stressors (infection, abuse, prior surgery, adverse life events, etc.), the effect of these factors on the enteric and central nervous systems, and the development of brain-gut dysregulation with hypersensitivity and disturbed motility. It should be noted that the distinctions among many of these categories are artificial and the degree of overlap may be great, making the delineation of a conceptual model even more difficult. For example, personality, coping style, gender, and genetic makeup may be both predisposing and modulating factors.

In summary, IBS is a multifactorial "disorder of function" with "organic" pathophysiologic components. Knowledge regarding its pathophysiology is growing exponentially and new areas of research are continually opening up. The present update addresses only a small subset of these areas of interest. A major challenge is to develop a unifying conceptual model of IBS that includes recently acquired pathophysiologic data and psychosocial variables. New insights into the pathophysiology of IBS can be expected to underpin the development of new drugs and non-pharmacologic therapeutic strategies.

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If you can't stand the heat, get out of the kitchen

Harry S. Truman (1884-1972), U.S. politician who became President after the death of F.D. Roosevelt.

Capsule

Anthrax regulation

Bacillus anthracis is distinguished from its more benign relations among the bacilli by the possession of plasmids containing virulence genes. The virulence genes are transcribed in response to elevated environmental temperature and carbon dioxide levels – key host signals. The plasmid pXO1 carries the anthrax toxin gene and its regulating genes. Mignot et al. have discovered that the toxin gene regulator AtxA on the plasmid also regulates the expression of cell surface proteins of the semi-crystalline S-layer, via the PagR transcription factor. In the presence of carbon dioxide only one of the S-layer genes is expressed. Since the S-layer genes lie on the bacterial chromosome, AtxA appears to be a master regulator on the plasmid coordinating the expression of many genes throughout the genome, leading to successful infection. The need for *B. anthracis* to shift S-layer type *in vivo* may relate to structural constraints on toxin secretion. Therefore, plasmids alone do not a pathogen make.

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Capsule

Effective multidrug-resistant tuberculosis treatment

Individualized and community-based treatment can greatly help patients with multidrug-resistant tuberculosis (MDRTB) in one of the world's poorest regions. A recent report by Mitnick et al. claims that modifying DOTS (directly observed treatment, short-course) strategy can substantially increase the MDRTB cure rate. Contrary to expectations for resource-poor communities with standardized DOTS therapy – where cure rates are reportedly as low as 5% – modified therapy can produce an 83% cure rate. Mitnick and colleagues reported on the addition of second-line drugs and drug-susceptibility testing to the established Peruvian DOTS program treating 75 patients with MDRTB in northern Lima. Known as DOTS-Plus, this treatment strategy was completed by 66 patients, 55 of whom were cured as defined by at least 12 months of consecutive negative cultures during therapy. The high reported cure rate suggests that DOTS-Plus works as well as treatment delivered to MDRTB patients in hospital-based settings. Besides improved cure rates for MDRTB patients, the study argues for the cost-effectiveness of using DOTS-Plus in resource-poor countries. Based on outpatient treatment, the study suggests that DOTS-Plus can cut financial costs by better tailoring treatment and providing affordable second-line drugs to patients earlier in their disease. Cost is further cut by reducing transmission.

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