

Symposium Summary Report

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About the Symposium

The 7th International Symposium on Functional Gastrointestinal Disorders was held in Milwaukee on April 12–15, 2007. The meeting was sponsored by the University of Wisconsin School of Medicine and the International Foundation for Functional Gastrointestinal Disorders (IFFGD), in cooperation with the Functional Brain Gut Group (FBG).

The Symposium drew an international audience of over 300 people representing multiple health care disciplines, from basic science to clinical care, as well as representatives from the U.S. National Institutes of Health (NIH), and from the pharmaceutical and medical device industry. The faculty of 98 speakers presented their work in general sessions, specialty symposia that included pediatrics, and workshops.

This report highlights just some of the information presented at the Symposium. Nevertheless the information herein identifies several of the newer and more important research emerging in the field. Clearly many pieces of the puzzle are emerging, which will benefit patients with functional gastrointestinal (GI) and motility disorders. We invite readers to go online and view video recordings from key Symposium presenters. Find out more about new developments regarding research, diagnosis, and treatment of these disorders by going to IFFGD's web page at: www.iffgd.org/site/learning-center/video-corner.

Introductory Comments

Welcoming remarks and thanks to the Symposium contributors and participants were presented by Nancy Norton, President and Founder of IFFGD; Frank Hamilton, MD, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH); and G. Richard Locke III, MD, President of the FBG.

Dr. Hamilton noted that in 1992 the NIH realized it was time to bring some focus and attention to the functional gastrointestinal (GI) disorders, which had historically not been recognized as important areas of medical care. Over the past 15 years this has been changing and Dr. Hamilton expressed appreciation for the efforts of Nancy Norton of IFFGD, and Douglas Drossman, MD and William Whitehead, PhD of the University of North Carolina, noting the tremendous difference they have made in how patients are being treated in the U.S. today as a result of their hard work, unselfishness in making this happen, and steadfastness in working with the NIH and the NIH process.

Dr. Hamilton commented on the appointment of Griffin P. Rodgers, MD as Director of NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). He noted that Dr. Rodgers brings a very caring aspect to this position, which we will likely see in his leadership as he interacts with our digestive health community.

Dr. Hamilton closed by saying that this is the worst and also the best of times at NIH; we are being challenged at every front because of the shrinking NIH budget. In response to the need recognized by Congress, the NIH budget went through a phase of doubling from 1998 to about 2004. However, since that time, the budget has flattened or shrunk. The result is that NIH is being challenged in funding the best possible science research and is looking for ways to respond as they struggle to provide support.

Dr. Locke, President of FBG, commented on the many changes over the past 15–20 years noting the great progress in the field. The FBG is a professional organization with interest in brain-gut interactions and the care of patients with functional GI disorders. It was founded by Dr. Drossman and a small group of investigators. The FBG has worked closely with the IFFGD over these years. Dr. Locke noted that this symposium brings people together because of their interest in this field, and what's exciting is the fact that so many people are interested in this field. It is only through that interest that we will continue to make progress and hopefully provide better opportunities to help the lives of people with functional GI disorders; that is what this symposium is all about.

Overview: Newer Developments in Functional GI and Motility

We have accomplished a great deal in the last 10 to 20 years. There has been expansion of physiologic and translational investigations – looking at the underlying factors that are leading to symptoms as well as how best to use this knowledge in treating patients. These investigations started with motility, then gut (visceral) sensation, brain-gut interactions, and more recently biomarkers as well as work on basic mediators of stress and bacterial flora.

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We are still facing great challenges. The first is in the way illness and disease is understood. While it is getting better, the functional GI disorders are still not considered legitimate by many. We see this, for example, with conditions such as irritable bowel syndrome (IBS), which is viewed by many as a complaint rather than as a disorder, and therefore as a minimal condition that requires minimal therapies. Thus, there is reluctance by regulatory agencies to accept any degree of risk involved in IBS therapies.

As Dr. Hamilton of the NIDDK pointed out, there is a cutback in funding at NIH. To the credit of NIH, they have created a National Commission on Digestive Diseases (Nancy Norton of IFFGD is a commissioner) with some key advocates and investigators trying to develop a strategic plan for the next 10 years of NIH digestive disease research. In addition to that IFFGD, as well as the Rome Foundation, is looking to identify other areas of funding eventually to provide alternate means of support for investigators in the field.

Defining functional GI and motility – People often ask, what is a functional GI disorder and what is a motility disorder. They are clearly interrelated. Motility disorders look primarily at altered motility, or movement within the gut; the functional GI disorders address the person and the symptoms. The differences between these relate, in part, to the fact that with functional GI disorders there can be other physiological factors that explain the symptoms in addition to motility. Many factors contribute to functional GI symptoms. The 5 major areas of investigation of the influences on functional GI disorders now include:

- Inflammation
- Motility
- Altered bacterial flora
- Visceral hypersensitivity (increased sensitivity of the gut)
- Brain-gut dysfunction

The biopsychosocial model is a conceptual way to integrate multiple factors based on the mutual interaction of various physiological systems. Rather than looking at linear causality (a single cause explaining a disorder), we look at how these many factors interact at a single point in time and over time at different points throughout a person's life. In effect, the biopsychosocial model is the research and clinical model to explain the complex determinants of the symptoms that patients experience, and what the doctors see in their patients. Within a given individual these factors can explain the remarkable variability of symptom experience between individuals with the same disorder, their level of severity, and response to treatment.

Research Areas

Genetics – In terms of the research areas, there is a lot of interest on genetic influences. These include:

- Genetic variations that effect motility, and the body's response to inflammation
- Changes in central nervous system pathways that effect the way a person perceives and responds to pain
- Linkage to psychological or emotional responses

For example, there are mutations of genes that result in making more or less of a given protein, which may lead to susceptibility to an infection or to stress or to one's bowel sensitivity. When triggers like inflammation or stress are added to a genetic predisposition, these individuals are more vulnerable to the development or flare up of the functional GI disorder, while others under the same exposure are not.

However, genetics is not going to be the sole answer, since they describe the predisposition to developing a condition rather than the leading to the condition itself. The functional GI disorders are heterogeneous; in other words, many factors contribute to the very specific symptoms of each functional disorder. In the future, we will probably identify subsets of patients where there are genetic

influences to explain why one is more prone to get one set of symptoms over another.

Pathophysiology – What are the physical and biochemical changes that lead to gut dysfunction? Research in the last few years has looked at changes in the way nerves transmit signals in the brain and the gut, and the role of hormonal responses, all of which can effect motility, secretion, and inflammation.

Serotonin – Serotonin (5HT) is a neurotransmitter, a chemical that acts on other targets within the body. Ninety-five percent of serotonin in the body is in the GI tract. It is contained in cells in the lining of the gut (enterochromaffin cells). When activated through a variety of stimuli it can cause increased motility or nerve sensitivity within the enteric nervous system – the autonomic nervous system within the walls of the digestive tract. Thus it affects gut function as well as influences the brain's experience of these symptoms as more or less painful. Serotonin may also have a role in our understanding some of the subtypes of IBS. For example, studies show that patients with IBS with diarrhea tend to produce more serotonin in their blood after a meal while those with constipation have less serotonin in their blood, compared to controls.

Additionally, after serotonin signals nerves in the gut, it has to be removed. This involves a process where a protein, called the serotonin reuptake transporter (SERT), removes the serotonin from the nerve cell space. In effect, we have a huge sponge in our gut for removing serotonin once it's released. We're finding that SERT activity may be different in the intestines of individuals with inflammation or who have IBS, where the sponge effect for serotonin is being lost. When serotonin sits around too long after release it can over-stimulate reflexes and it might also desensitize receptors so they stop responding. These shifts in serotonin signaling could underlie some of the changes in gut function.



Mast cells – Mast cells are a type of immune cell. When activated, certain chemicals contained in packets in the cell are released (degranulated), thus exposing the bowel lining to these secreted substances that influence other cells. The mast cell and the effects of degranulation is an area of great interest in understanding IBS since it is involved with many regulatory functions of the intestines. We have known for many years that there are increased mast cells in certain areas of the bowel in patients with IBS. Increased mast cell activity is a feature of patients with IBS and we are beginning to better understand how this activity may have effects on the gut. For example it may stimulate nerves to become more sensitive and can increase permeability of the intestinal barriers, thus leading to invasion by bacteria and production of toxic substances. The increased sensitivity of the nerves within the gut (visceral hyperalgesia) can lead to pain or discomfort, even in response to normal events such as eating a meal. Permeability is essential, allowing the passage of fluids and nutrients from the intestines into the body. But too much permeability can be harmful, allowing unwanted substances, like bacteria and its components, to pass into the wall of the gut and lead to inflammation.

Cytokines are one type of molecule involved with regulating our immune response (an inflammatory mediator) associated with mast cell activity in addition to other types of cells like lymphocytes. Interestingly, there are good and bad types of cytokines. The bad types are associated with greater inflammation and sensitization, and the good types of cytokines reduce that. We are seeing that there are differences here in people with IBS compared to controls. Some IBS patients are seen to have more of the bad cytokines that increase inflammation.

Bacteria – Another area being looked at is the bacterial flora – the ecology of the gut. There are bad bacteria, which can be associated with infection (inflammation), and there are good bacteria (probiotics) which can help prevent infection. These

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good bacteria may have other beneficial effects, not only on inflammation. For example, *lactobacillus* was recently reported to activate certain receptors which suggest that it may have effects on pain. *Bifidobacterium*, in a study of IBS treatment that compared it to *lactobacillus* and to placebo, was associated with improvement in symptoms related to normalization of the inflammatory response, similar to healthy volunteers. That favorable response did not happen in the groups treated with *lactobacillus* or placebo.

Stress – We are finding that stress has an effect on the gut flora, permeability, and secretions. The normal gut flora provides a barrier within the intestines to inflammatory types of bacteria. Stress can cause changes in this epithelial barrier, which can allow greater access by the flora to the intestine and in turn lead to increased inflammation. Stress can also significantly modify the immune response to the gut flora. So these are factors that could be affecting the sensitization in IBS and the condition itself.

Brain-gut – The brain plays a role as well. The brain and the gut are connected. Thinking and feeling can have affects, influencing release of proteins that interact with the nervous system (neuropeptides), which can affect motility, secretion, blood flow, and inflammation. Stress may influence inflammatory pathways causing a dysregulation that can lead to emotional conditions and more stress – a vicious cycle. It is not a question as to whether this cycle begins in the gut or in the brain. The problem is that both systems are effected concurrently thus producing a disturbance of the regulation between the brain and gut; a “vicious cycle” with no beginning or end. Understanding this will open the door to more specific treatments.

We can see examples of brain-gut interactions by looking at post-infectious IBS (PI-IBS) or dyspepsia. A study done after a *salmonella* infection outbreak showed that 10–15% of patients continued with their symptoms of either dyspepsia or IBS after the initial infection subsided. Some recent studies show that this is associated with greater levels of immune cell activity. In IBS, the subgroup of patients with diarrhea as the predominant bowel symptom is the group where more of this inflammatory response is seen; there is also increased psychological distress occurring at the time of the initial infection, which may be enabling the post-infectious response. In the gut we see infection followed by an inflammatory response, altered motility, and increased sensitivity. But these factors alone are not enough – the brain has a role in regulating these factors. If there is psychological distress around the time of the initial infection, it can result in the expression of the post-infectious symptoms. Thus, the brain and the gut are interacting so with this disorder the brain can influence the inflammation in the bowel while the bowel inflammation can produce psychosocial – emotional and social – distress. Similarly the pain experienced may occur more when there is psychological distress. Both factors are predictive of post-infectious IBS.

Since post-infectious IBS has inflammation in the intestine, it challenges the concept of functional vs. structural, since there are features here of both. This raises the question, how great are the distinctions between “functional” and “structural” disease? Perhaps not as great as we might think. To illustrate this, in addition to patients with post-infectious IBS, there is a subset of patients with inflammatory bowel disease called IBD/IBS. These are patients who have ulcerative colitis, for

example, get treated, go into remission and have minimal or no inflammation in the rectum and the colon, but they still have severe pain and diarrhea. In these cases the entities of post-infectious IBS and IBD/IBS have some things in common. They're pain predominant, usually with diarrhea; infection initially brings it on around a time of high emotional distress; there is minimal gross or microscopic inflammation found; and there seems to be activation of the immune system both in the gut and in the brain.

Thus with functional GI disorders, PI-IBS, and even IBD/IBS we see a feature of there being more pain in the presence of minimal disease, save for some microscopic inflammation. The evidence for this seems to be that it is the combination of central nervous system distress along with the inflammation that might lead to the pain syndrome and post-infectious IBS or IBD/IBS. It may essentially be that this all starts with having a genetic predisposition, which can increase susceptibility to getting the disorder. Furthermore, combined with factors that lead to immune system dysfunction, and with inflammation in the gut, exposure at a time when there are high levels of psychologic distress may be enough to lead to the development of the post-infectious IBS or IBD/IBS.

Central regulation of visceral sensitivity: pain perception – A number of factors lead to the experience of pain. These involve mostly areas of the brain. When a pain signal is generated in the intestines, there is an ability of the brain to regulate this signal. We are learning that there are areas of the brain that stimulate or potentially cause more pain, which seem to be more associated with hypervigilance and attention. Alternatively, there are areas of the brain that turn down the pain signal. This can be viewed on brain imaging. We are moving toward an understanding that

patients with greater pain severity have a dysregulation not so much at the level of the gut, but at the level of the brain.

Biomarkers

How can a functional GI disorder be diagnosed when the patient reports symptoms but there is no abnormality, or biomarker, that can be seen on a standard test or examination? Symptom based diagnostic criteria, like the Rome criteria, help define these conditions. Twenty or 30 years ago that was not the case when there was no standard way to identify similar groups of patients, thus making these conditions seem not legitimate. Now, we are able to identify the disorders based on well defined clusters of symptoms unique to each functional GI disorder. Once we have the diagnosis, we can look deeper into seeing what determines those symptoms, whether motility, visceral sensitivity, inflammation, brain-gut interactions, or a combination.

Presently, biomarkers can help to exclude conditions other than functional GI disorders that have different treatments, like a parasitic infection or inflammatory bowel disease. These conditions are diagnosed based upon a physical finding. In the future we may come up with biomarkers that not only exclude other conditions, but help to define sub-groups within a particular functional GI disorder; shared features that underlie the symptoms. Using a biomarker to define sub-groups of patients would help to target treatment more effectively. For example, an individual having a set of symptoms where the focus needs to be on visceral hypersensitivity would receive a different treatment from one where the focus needs to be altered bacterial flora.

Future directions

From mechanisms at the gut level and the micro flora, to the spinal cord and brain our understanding of the functional

disorders has grown tremendously over the past 5 years. On one end new techniques allow us to probe the living human brain to understand its structure, activity, and receptor systems. On the other end we are just beginning to view the universe of our gut micro flora its influence on bowel mucosal integrity and the cross-talk taking place between it and the brain. Growing understanding of how many systems within the body interact has implications for various disorders such as pain, irritable bowel syndrome, fibromyalgia, interstitial cystitis, gastroparesis, and others. Like a puzzle, many pieces are beginning to emerge.

While the tremendous progress in our understanding of the functional GI disorders over the last 5 years is providing exciting possibilities, it remains important to keep building upon it so that these research advances are translated into meaningful therapies for patients. Ironically, this momentum is threatened by dwindling financial support from traditional resources such as the National Institutes of Health (NIH) for young and established researchers. Regulatory agencies such as the FDA in the U.S. and those in Europe seem also to be struggling with understanding the needs and the appropriate risk/benefit ratio to apply to drug treatment for patients with functional GI disorders. These are issues that IFFGD is confronting and where every stakeholder – patient, clinician, and investigator alike – has an opportunity to step forward, to join with us and help make a difference.

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