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Functional Gastrointestinal Disorders

IFFGD

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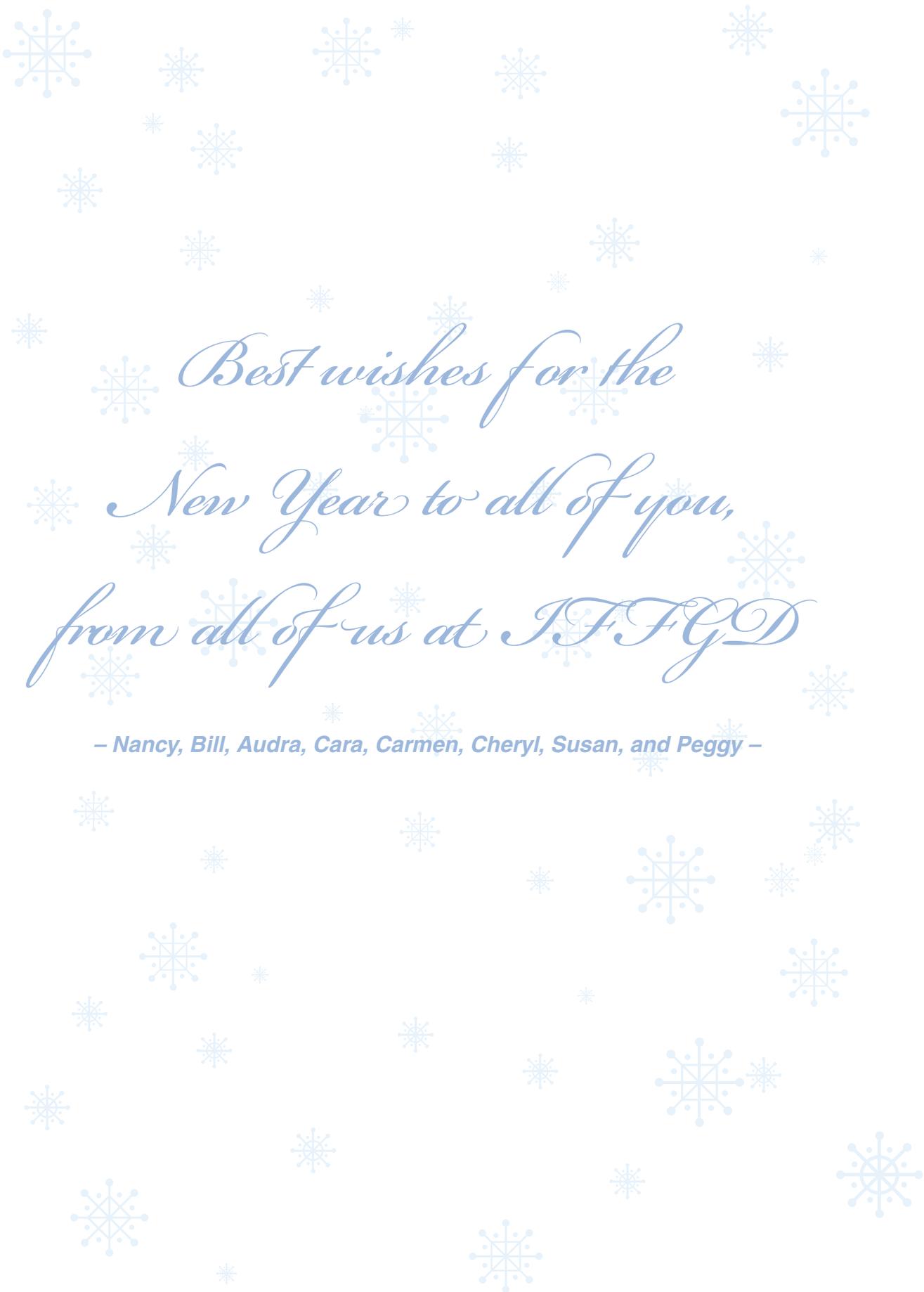
Digestive Health Matters

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A Little Knowledge can Make a Big Difference

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*Best wishes for the
New Year to all of you,
from all of us at J.F.F.G.D*

– Nancy, Bill, Audra, Cara, Carmen, Cheryl, Susan, and Peggy –

Dear Readers,

Many of you know of IFFGD through our various activities on behalf of the digestive disease community. Or you may be distantly aware of us through our publications and web sites. Our mission is to inform, assist and support people affected by gastrointestinal (GI) disorders. We achieve this through sustained efforts to advance education, advocacy, and research. But while these describe the things we do, they don't really tell you who we are.

IFFGD began in 1991. It was started out of the experiences of Nancy Norton. Several years earlier, she had sustained an injury to her pelvic floor that left her incontinent of stool. After two unsuccessful repair attempts it was clear the medical and surgical community could offer little beyond the words, "You will just have to learn to live with it." Sixteen years ago there was little, if any, help available about *how* to live with it.

"We must be the change we want to see in the world."

– Gandhi

The loss of bowel control is devastating and far reaching, touching on every aspect of daily living. Yet, this was the genesis for IFFGD. It set in motion a search for answers that led to others with shared concerns. We came together as the first few members and advisors who helped start the organization.

Many more have joined with us since then – many of you. We include patients, family members, and professionals in medicine, government, and industry. We all are united by a common goal to find solutions for the needs of individuals affected by functional GI and motility disorders.

There are many disorders that affect the GI tract, each with its own set of symptoms. These conditions – in the esophagus, stomach, intestines, and pelvic floor – affect children and adults, women and men. But what connects them all is lack of adequate treatment and a burden of illness that is often not recognized. In many people these disorders are mild, uncomfortable, and inconvenient. In others they are severe, painful, unpredictable, and deeply distressing; they can drain vitality from life. This needs to change.

Every publication, outreach, advocacy and support effort that comes from IFFGD is influenced by the personal experiences of people who live daily with these disorders. We share a common belief that something better can and must be offered. It is a goal that underlies all our efforts. Through IFFGD we offer a means to help realize that goal, to find answers that improve lives. Here we give voice to collective need, and here we take action.

Basic understanding of these disorders has progressed significantly since 1991. Now, however, traditional sources of funding for research – from government and industry – are being challenged and support is dwindling. Meanwhile too many unanswered questions about causes and treatment remain. Much more needs to be done. Who will do it? We each are a part of the answer.

Please stand up and be counted. Be a Member, make a donation, respond to our calls for action, or explore other ways to help through IFFGD. When we stand together, we are stronger. When we act, we are the instruments of change.

Thank you,
William F. Norton
Co-Founder and Editor



Symposium Summary Report

By: William F. Norton, Publications Editor, IFFGD; and Douglas A. Drossman, M.D., Co-Director, UNC Center for Functional GI & Motility Disorders, University of North Carolina, Chapel Hill, NC

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.

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.



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

How great are the distinctions between “functional” and “structural” disease? Perhaps not as great as we might think.

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.

SYMPOSIUM SUPPORT

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A number of factors lead to the experience of pain. These involve mostly areas of the brain.



Sex Differences in Abdominal Pain

By: Elie D. Al-Chaer, M.S., Ph.D., J.D., Director, Center for Pain Research, University of Arkansas for Medical Sciences, Little Rock, AK

AT A GLANCE

- Sex refers to a biological construct; for example, female or male.
- Gender is a socially constructed notion of what is feminine and what is masculine; for example, a person can be more feminine and less masculine, or vice versa.
- Pain is experienced differently by men and women; sex and gender both play roles.
- Women are generally more sensitive to pain than men.

Abdominal pain and functional bowel disorders

The abdomen is the area of the body between the chest and the hips.

Abdominal pain is a type of visceral

pain that affects internal organs such as the bowel. It can result from a number of causes ranging, for example, from something as simple as overeating, to a viral or a bacterial infection that may cause severe inflammation, or to something more serious. In the absence of a structural abnormality, abdominal pain may be an indication of a functional bowel disorder.

Functional gastrointestinal (GI) disorders are the most commonly presented GI illnesses seen by physicians in primary care or gastroenterology. In a functional bowel disorder, the primary problem is an alteration in the way the bowel works rather than an identifiable structural or biochemical cause. It generally cannot be diagnosed in a traditional way as an inflammatory, infectious, or structural abnormality that can be

seen by commonly used examination, x-ray, or laboratory test. In the GI tract, functional disorders are diagnosed based on symptoms. A detailed history, physical exam, and usually limited tests help in making a diagnosis. Some situations suggest the need for more extensive testing. The symptoms of these disorders can include discomfort ranging from inconvenience to deep personal distress and pain.

His and hers

Experimental and clinical studies highlight the existence of sex-related differences in the perception of and responsiveness to painful stimuli. Sex-related differences in pain processing and responsiveness in general have been documented in experimental studies using animal models. In these studies, female responses to painful stimuli, as well as



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Chronic Pain Management Tips

It is becoming increasingly clear that *chronic* pain may be more like a disease or pathology of the nervous system associated with abnormal responses in the brain and spinal cord. In this light, chronic pain is both a common and serious medical condition. It is medical because, at its root cause, chronic pain is always connected with the body and the brain.

We use a variety of methods to try to help patients manage chronic pain. You can learn to better manage and even decrease the severity and impact of pain in your life. The optimum pain management approach is based on making best use of the growing scientific knowledge of how pain is communicated and modulated (altered or modified) in the body and brain.

In order to enable our body to have the best information when it is needed, signals coming in are highly modulated. This means pain signals from specific areas can be amplified, suppressed, or altered in quality in the spinal cord or brain. In chronic pain we have strong evidence that our pain modulation system is not working well. Instead of suppression, the system may be over sensitized so that even normal sensations trigger pain transmission and suffering. As a result of the pain, patients may also have increased levels of anxiety and depression, decreased quality of life, fear of further pain and disability, sleep loss, and withdrawal from social and pleasurable activities. Both ancient and modern medicine has evolved a variety of ways to help cope with chronic pain and

maybe even return the system to more normal functioning.

If you have chronic pain it is important to develop a pain management plan that works for you. Some recommended elements include:

1. Understand your pain problem. Try to separate hurt from harm. The pain you experience is real, but the cause may be a heightened sensitivity of the nervous system and not increasing damage to some part of your body (even though it feels that way).
2. Maintain a cooperative but not dependent relationship with your doctors. Doctors have a difficult time

responses to pain relieving substances, depend on the stage of the reproductive cycle. Pain sensitivity was highest when the levels of circulating estrogen, a sex hormone, are at their highest just before and during ovulation, which corresponds to midway through a woman's monthly cycle.

In clinical studies, women are reportedly more likely to experience recurrent pain, have more sensitivity to pain (lower pain thresholds), and feel pain with higher intensity and less tolerance than men. Females are overrepresented in a variety of chronic pain disorders, including migraine headache, craniofacial pain, chronic low back pain, fibromyalgia, and irritable bowel syndrome (IBS). Likewise, research studies have demonstrated greater frequencies of pain-related symptoms among females than males in the general population. In this respect, a striking sex-related difference is evident in the prevalence of functional bowel disorders such as IBS, their treatment, and the perception of associated

abdominal pain. Furthermore, the menstrual cycle influences gut sensitivity in female IBS patients, who often show evidence of worsening of symptoms during menses.

IBS prevalence – The female to male IBS prevalence ratios for the general population vary from 1:1 to over 2:1 across a variety of studies. Females typically are seen in larger numbers than males in medical clinics and highly specialized (tertiary) care centers. In children before puberty, functional GI disorders, such as recurrent abdominal pain and certain forms of chronic functional constipation or diarrhea, occur about equally in boys and girls. This suggests that gender-related (psychosocial) or sex-related (hormonal) changes during development may lead

to the different rates of IBS apparent in adults.

IBS treatment – Sex-related differences have also emerged in the search for new IBS-specific medications. For example, alosetron (Lotronex, a 5-HT₃ antagonist) showed efficacy only in female subjects, which led the manufacturer to seek approval for the drug only as a treatment for women with IBS. Today, alosetron is approved for the treatment of IBS in women where diarrhea is the predominant bowel symptom and for whom conventional therapy for IBS has failed. It is evidence of the need for a closer look at the role of sex and gender in designing new medication for some pain conditions, at least in the case of IBS.



- treating chronic pain and may feel frustrated as well. Be honest and assertive with your doctors, but also let them know you understand they cannot perform miracles and that chronic pain management is a team effort.
3. Use medications wisely, as directed by your physician.
 4. Don't be afraid to acknowledge your emotional response to pain, be it fear, anger, or depression. Seek out psychological help if needed. Remember that the best chronic pain treatment should include both mental and physical elements.
 5. Use active and positive strategies in response to your pain as much as possible. Avoid passive strategies, which

- lead to increasing helplessness and dependence.
6. Seek support when needed but stay in control. Family, friends, and health care professionals are all important resources for you, but often they are not sure how best to help. Let all the important people in your life know that you appreciate their support and that you will ask them directly when you need their help or just someone to talk to.
 7. Remember that new knowledge and treatments are coming so stay in touch. Pain is a rapidly expanding area of research. New technologies in functional brain imaging and molecular biology are generating, for the first time, detailed portraits of our brains in action and the biochemistry of pain transmission.

- There is no doubt that improved pain treatments will not be far behind.
8. If your pain problem continues to be unmanageable, you can contact a pain specialty clinic. Be aware that many practitioners (medical and chiropractic) may call their own practice a "pain clinic." However, a **true pain management clinic** provides comprehensive care by including multiple medical specialties such as anesthesiology, neurology, psychology, and rehabilitation. Many of the best pain programs are located in university medical centers. Your primary care doctor should be able to refer you to a good one.
- From IFFGD Fact Sheet No. 140, "Understanding and Managing Chronic Pain." By: Bruce D. Naliboff, PhD.

Menstrual cycle-related variation in

IBS symptoms – Women with IBS report higher levels of IBS symptoms around their menstrual cycles, including altered motility and increased sensitivity within their gut to normal GI events. Although evidence indicates that sex hormones may influence IBS experiences, it is not clear whether worsening of GI pain is in part confused with menstrual pain or if it is entirely caused by changes in GI sensitivity. Both the lower GI tract and the female reproductive system are supplied with nerves that carry signals to the central nervous system and connect onto the same segments of the spinal cord. This leads to an overlap in the pattern of pain perceived from these organs. On the other hand, evidence suggests that the female hormones estrogen and progesterone modify GI function and slow gastric emptying of solids.



Mechanisms underlying sex-related differences in abdominal pain

Various systems could influence pain responses in a sex-related manner. These include, but are not limited to, sex hormones, internally produced (endogenous) substances that modify pain, and psychosocial factors.

Sex hormones and pain – Studies in animal models have emphasized the importance of sex hormone influence on pain responses. Sex hormones, such as the female hormones estrogen and progesterone, or the male sex hormone testosterone, can influence pain pathways in many ways by altering the processing of pain information in the peripheral (body) and central (brain and spinal cord) nervous systems. These complex actions affect the way the brain processes the body's pain sensations. Nerves to bodily organs, such as the bowel, appear to be affected by the reproductive cycle. For example, estrogen can affect how pain information is transmitted by these nerves and progesterone can influence nerve activity and how nerves respond to medications which reduce pain (local

Sex hormones can influence pain pathways in many ways by altering the processing of pain information in the peripheral (body) and central (brain and spinal cord) nervous systems.

anesthetics). These effects are similar to those seen during pregnancy when estrogen and progesterone levels are very high.

Receptors are structures on cells that receive a stimulus or message and, in turn, induce a functional response in the body. In animal studies, estrogen receptors can be found in the spinal cord and in nerves within the body, including areas that process pain information from the colon and other organs in the pelvis. This information suggests that certain nerves are able to make estrogen receptors that bind estrogen and result in specific functional changes in the body. Therefore, estrogen could be involved in the increased pain sensitivity seen in females with chronic pain conditions compared to males.

A number of brain imaging studies, which visualize brain activity, have shown that uncomfortable pressure applied in the rectum using a balloon device can cause changes in the activity of specific areas of the human brain commonly associated with pain perception or sensation. (These regions include areas in the cortex and brainstem including the anterior cingulate, insula, prefrontal cortex, thalamus, and cerebellum.) In one study, despite the fact that men and women rated a pain stimulus similarly, increased activity of certain brain regions were much stronger for men.

Internal (endogenous) pain modulators – A number of experimental scientific studies have reported sex-related differences as well as hormonal effects on several internally-produced substances or pathways which modify pain within our bodies.

In studies using animal models, females and males exhibit different responses to experimental stress. Females show more pain sensitivity in response to stress compared to males. These differences appear to be effected by sex hormones such as circulating estrogen and progesterone. Additionally, pain reduction in response to pregnancy is a hormonally-influenced process unique to females.

Substance P is a protein with effects on the nervous system (a neuropeptide). Substance P is involved in the transmission of pain impulses from receptors in the body to the central nervous system. An association, in animal models, between levels of circulating estrogen and substance P concentrations has been reported in females. Observations support a role for sex hormones in the regulation of genes, which program for different pain receptors in various parts of the body, especially the bowel. Estrogen was also found to change the role of Substance P receptors in increased bowel pain in response to stress.

NMDA is a selective agonist (stimulator) for a specific type of receptor that stimulates the cells in the nervous system. Activation of this receptor complex contributes to exciting nerve signals at sites throughout the brain and the spinal cord, and is changed by a number of internal and external substances. NMDA receptors play a key role in a wide range of physiological and disease related processes including chronic pain processing. A number of animal studies have demonstrated sex-related differences when it comes to the function of the NMDA receptors. Findings suggest that females, when exposed to the male hormone testosterone, can demonstrate the activation of NMDA-

specific pain pathways seen normally in males, indicating that these pathways are affected by sex hormones.

Psychosocial factors and gender – Several factors are linked with pain sensitivity and may differ between sexes, but the extent to which this occurs remains unknown. Symptoms such as depression and anxiety are more prevalent among women than men and are associated with increased pain and other physical symptoms. Psychosocial factors, such as coping and emotional distress, which can alter pain sensitivity, contribute to sex-related differences in the experience of pain. Individuals' expectations and anxiety can alter experimental pain responses and this may occur differently in men and women. Sex roles are also associated with the quality of the pain response. A high degree of masculinity is associated with less pain sensitivity (higher pain thresholds) for men but not for women. The degree of masculinity also seems to be associated with the way the brain responds when the body is exposed to pain. Nevertheless, even after controlling for masculinity factors, the differences in pain responses between men and women remains significant.

Significance of sex differences in abdominal pain

Abdominal pain is a symptom/marker of many GI disorders, particularly IBS. Progress has been made in understanding some of the nervous system pathways, and the nervous system functional and chemical mechanisms involved in abdominal pain. However, pain in general remains an individual experience. Understanding the subjective pain experience in individuals presents unique scientific challenges. Even though the basic bodily processes may be similar, people react to pain in very different ways due to many factors, including sex and gender. These represent but one set of variables within the many interacting systems in the mind and body that can alter pain responses. The magnitude of sex-related influences on pain in relation to other factors, such as age, race, and coping skills, has yet to be determined.

Further investigation of sex differences in abdominal pain could reveal three areas of practical importance: 1) it may enhance our understanding of the functional aspects of certain pain conditions; 2) it can have implications for developing pain treatments tailored to each individual's needs; and 3) it could lead to new gender-sensitive treatments for pain, especially in the area of hormonal manipulations.

Related Reading:

Al-Chaer ED and Willis WD. Neuroanatomy of visceral pain: pathways and processes. In: "Chronic and Abdominal and Visceral Pain" by Pasricha PJ, Willis WD and Gebhart GF (Eds). Chapter 4, pp. 33-44. Informa Healthcare, USA, New York, NY, 2007.

Camilleri M. Management of the patient with chronic abdominal pain and clinical pharmacology of non-opioid drugs. In: "Chronic and Abdominal and Visceral Pain" by Pasricha PJ, Willis WD and Gebhart GF (Eds). Chapter 18, pp. 271-285. Informa Healthcare, USA, New York, NY, 2007.

Chang L, Toner BB, Fukudo S, Guthrie E, Locke GR, Norton NJ and Sperber AD. Gender, age, society, culture, and the patient's perspective in the functional gastrointestinal disorders. *Gastroenterology* 130(5): 1435-1446, 2006.

Sex and gender represent but one set of variables within the many interacting systems in the mind and body that can alter pain responses.



Helping Children and Adolescents Cope with Abdominal Pain

From an IFFGD interview with Lynn Walker, Ph.D., Professor of Pediatrics, and Professor of Psychology, Vanderbilt University, Nashville, TN

Health professionals use the term “cope” to describe how we respond to difficult or unwanted situations. Children or adolescents who have bowel disorders need help to cope effectively with symptoms of recurrent abdominal pain and unpredictable bowel symptoms as they go about their daily lives. A physician or therapist who is knowledgeable about functional GI disorders can help provide the family and the child with positive skills to help respond effectively.

At the 7th International Symposium on Functional GI Disorders held in April 2007 by IFFGD, we talked to Lynn Walker, PhD about managing school related issues while living with recurrent abdominal pain. Here is a portion of Dr. Walker’s comments talking about:

- Going to school
- Using the bathrooms
- Interacting with teachers and classmates

You may view a video of Dr. Walker talking about these issues on our web page at www.aboutKidsGI.org by clicking on the Learning Center and going to the Video Corner link.

Who are your patients and how do you begin treatment?

My patients are primarily referred by pediatric gastroenterologists. They are children who have been seen by their primary care provider, often several times. Sometimes they have been to the emergency room because of abdominal pain. They go into our GI clinic and are evaluated for abdominal pain. Many of them have functional gastrointestinal disorders, like irritable bowel syndrome (IBS), or functional pain where a problem hasn’t been found that can be treated medically with a pill or surgically, and they are referred to me for assistance. They are children who are having trouble coping with the pain or with going to school or with peers.

I always start with a parent and with the patient, and sometimes a sibling, whoever is there in the consultation room, and I talk to the various family members about what they think is going on or what their concerns are. Then I have separate time with the child or adolescent and separate time with the parent. Based on the age of the child and what I find out is going on, my subsequent sessions might be exclusively with the family or exclusively with the child. Typically I’ll bring the family in again at least briefly and at each session I’ll have some contact.

What is the most significant change in treating recurrent abdominal pain you’ve seen in the past 5 years?

I think the thing that has been the biggest change is that we no longer think of the pain as “all in the head” or not “real.” There’s much more recognition that the pain is real and it involves an interaction between emotions and visceral (gut) sensations. We can tell families a little bit

more about how that happens, and that there is a biological basis; something is happening in the body that is creating this pain. It is associated with emotions and with stress and those are things we can do something about. Even if we don’t have a magic bullet pill that they can take there are other things that they can do.

What are those things?

Parents can help their children cope by helping them learn to distract themselves and engage in activities even though they are not feeling comfortable. They can continue going to school, for example, even if they have some discomfort. Abdominal pain by itself isn’t a reason to stay home. So, if a parent will help encourage a child be able to do that, it’s something that is helpful. We do relaxation training with the kids. We work on stress management.

One of the things that happens frequently in my practice is I see kids who have been out of school for quite a while because there has been concern about the symptom and a lot of medical tests; they may have had to go to the hospital and miss school and they are way behind. So even though school may have not been stressful when this whole thing started it is now stressful because they’ve got this huge pileup of work to do. One of the things we do is work with them – and this involves negotiating with the school as well – on how can we break that down into little steps of things that they need to do so it won’t be so overwhelming that they just can’t imagine ever being able to deal with it.

Another issue in school is that kids are concerned that they may not have time to get to the bathroom with some of these conditions. In some schools there is very



little time between classes so they can't have the time to do that without being late. We have to work with the schools on why it's okay for this child to be late. We have to also sometimes work out a system where the child can get up and go to the bathroom without asking and drawing attention to him or herself. It's embarrassing to raise your hand and announce what it is you have to do. There are concerns that kids have about the cleanliness and privacy in bathrooms. So we might, for example, work it out so that the child could use a bathroom at a time when other kids weren't as likely to be there.

There can also be more of a situation where the child is afraid to go to bathrooms outside of his own home. In that case we might have the child gradually, with the parent's help, begin to get comfortable using a bathroom at a friend's house or at the mall, for example, so that he gets desensitized to this fear of strange bathrooms.

I have a standard letter that I will write to the school saying that the child has a gastrointestinal disorder – I don't say what – but a gastrointestinal disorder that requires him or her to use the bathroom more frequently. I explain she may not have a lot of anticipation of when it's going to happen that she's going to need to use the bathroom. That note relieves the child so much, just knowing that she can use the bathroom when she needs to, that the need to use it decreases quite a bit. Anxiety influences our bowels and when we are anxious we need to go to the bathroom more so if we decrease the anxiety we can also decrease the need. That was not the reason that I started sending these letters, but that's a helpful side effect.

The kids who've missed school a lot have sometimes had the experience that people make comments like, "Oh you're just trying to get out of school or faking it," that sort of thing. So another obstacle for the child to getting back into school

is, what am I going to tell people, what if somebody asks me, "Why have you been out or what's wrong with you." They need to have rehearsed a response. They are afraid that they are going to have to say nothing is wrong and that's going to reinforce the notion that they were just faking it. So working on saying, "I had something wrong with my stomach and it's getting better but it still bothers me sometimes," and to cut it off at that and not feel they have to provide this long explanation of what's wrong helps. The other kids don't want to know all that much. They are curious and the child who has been out is feeling kind of vulnerable and defensive and like they owe an explanation. But they don't owe an explanation; something just to satisfy the other kids' curiosity is enough.

Irritable Bowel Syndrome (IBS) and a Healthy Holiday Season

By: Barbara Bradley Bolen, Ph.D., Farmingdale, New York

Everyday, ordinary life is challenging enough if you suffer from irritable bowel syndrome (IBS). Add the obligations, deadlines, family dynamics, food focus, and travel issues that are associated with the holiday season, and it can be easy to feel anxious and overwhelmed. This busy time can also be one of great joy, as you get to experience the security of tradition, the warmth of being with loved ones, and the time to reconnect with spiritual roots. In order to achieve a healthy balance, self care becomes essential.

Cognitive behavioral therapy (CBT) is a form of psychotherapy that has consistently been shown to be effective in reducing the symptoms of IBS. CBT works by teaching individuals different ways of thinking about things and different ways of handling situations so as to feel better. By applying some basic CBT principles, you can actively work to reduce your stress and free yourself up to enjoy the holidays.

Healthy Thinking

At the heart of CBT is the fact that what we think affects how we feel, both emotionally and physically. The human brain needs to modify data coming in so that we can make sense of things. Sometimes that modification backfires, leaving us with distortions that are not really based on reality. The following is a list of some common distortions, with examples that are more specific to IBS. Each example offers a healthy alternative. When you find yourself thinking in one of these unhealthy ways, see if you can replace your unhealthy thought with a more helpful alternative.

Fortune Telling – If we could truly predict the future, the lottery system would be out of business rather quickly! One of the major difficulties with this distortion is that our anxious minds rarely predict that things will go well. Another

difficulty is that this type of projecting into the future takes away the energy needed for planning how you would cope with the variety of possibilities that you might face.

Distortion – My family lives five hours away. I know that as soon as I get in that car, my IBS is going to act up and I will be miserable.

Helpful Substitution – While it is possible that I might have symptoms while in the car, I do not know that for sure. Worrying about it is only going to make it more likely that my system will act up. Let me focus on keeping my body as calm as possible and develop a plan for how I will handle the situation if I start to feel really uncomfortable or if I need quick access to a bathroom.

Perfectionism – Yes, we all want things to go well. Unfortunately, this desire can turn into a self-imposed pressure to do things perfectly, often at the expense of our well-being. Watch out for this one, our

perfectionism isn't all that obvious, but it is what can keep us up well past midnight tying little bows onto things!

Distortion – I am in so much pain all the time that I don't know how I am going to find the energy to cook the holiday meal. But I'm going to do it, because it is always at my house, everyone is counting on me, and I don't want to let everybody down.

Helpful substitution – I need to come to grips with the fact that I am not well right now and so I can't do all of the things that I usually do. It is okay for me to ask for help or ask somebody else to take over. I need to remember that my family cares

about me and that my health is more important than following a tradition that is harmful to my health.

Mind reading – This distortion involves worrying about what others will think. Sound familiar? Like fortune-telling, our worries rarely tell us that other people are having positive or caring thoughts about us. More likely, we have convinced ourselves that other people are watching us closely and finding fault with what we say, do, or look like. Remember most people are too busy worrying about what others are thinking of them, to be worrying about what we might be doing wrong. As for the people who truly are critical and judgmental, do you really want to let their unhappy minds determine how you feel?

Distortion – My spouse wants me to spend the holiday weekend at his parent's house. When they see how much time I need to spend in the bathroom, his family is going to think that I am weird.

By applying some basic principles, you can actively work to reduce stress and free yourself up to enjoy the holidays.

Helpful substitution – Even people without IBS know what it is like to need to spend time in a bathroom dealing with diarrhea or constipation. If someone were to actually notice that I am in the bathroom a long time, they will most likely have sympathy for my plight and will not be judging me.

Awfulizing – Often hidden behind a "What if..." thought, awfulizing is when we imagine something that has the potential to be uncomfortable or embarrassing and see it as an absolute catastrophe. When having a "What if..." thought, our brains are really thinking "That would be the worst thing that could happen!"

Distortion – What if I am at the company party and I was to pass some really nasty smelling gas?

Helpful substitution – Everyone passes gas. If an unpleasant smell arises, other people will ignore it or at worst, make a joke about it. Although this would be embarrassing, it is not the end of the world.

Active Self Care

Now that we have covered some ways that you can think differently as you make your way through the holiday season, we can move on to discussing some helpful behavioral strategies. Practicing these new skills will help you to keep your focus on your own well-being rather than just being caught up with all of the myriad tasks that this time of year seems to require. Again, watch out for hidden perfectionism. Like any new skill, it is going to take practice and some trial and error for the skill to feel comfortable and natural.

Plan ahead – The unpredictability of IBS can make it difficult to manage some of the demands of the holiday season. Having a well thought-out plan for handling whatever scenario arises can significantly reduce your stress level. Consider the following questions as you devise your own personal holiday survival plan.

- What will I need in order to feel most comfortable?
- Would I feel better if I told the host of the gathering about my IBS?
- How can I make sure that I have access to a bathroom?
- How would I handle it if I needed to leave early because I didn't feel well?

Practice relaxation exercises – If you do not practice any kind of relaxation exercises on a regular basis, you should. Of the many factors that contribute to the strength of IBS symptoms, anxiety is one that you can actually do something about.

The ability to relax your body, whether it be through progressive muscle relaxation, breathing exercises, yoga, or meditation, is an important tool to have in your bag of tricks for managing your IBS.

- Practice at least two times a day in a quiet setting,
- Like a boxer who keeps himself loose between punches, monitor your muscle tension throughout your day to make sure you stay as relaxed as possible.
- Use visualization. While in a relaxed state, imagine yourself attending and enjoying a holiday get-together and picture your body and intestines remaining calm and quiet.

Kind and gentle feeding – Even with the best planning and good relaxation skills, the holidays can be stressful. This stress could have the effect of making your digestive system more reactive than usual. You can work to counteract this by actively trying to not abuse your body with too much of the wrong kinds of food. Unfortunately, these are just the types of foods that always seem to be everywhere during the holidays! Treat your body with the kind of tender, loving care that you would bestow upon a small child and make the kind of food choices that you know your body needs.

- Eat small meals throughout your day: Often in a misguided attempt to prevent the onset of symptoms, IBS sufferers will avoid food before a big event. The problem with this strategy is that your body may overreact when food is finally introduced, particularly if introduced in a large quantity. Your system is more likely to work in a smooth manner if you provide it with small meals throughout the day and during the course of the holiday outing.
- Choose stomach-friendly food: Avoid alcohol and the fatty, nutritionally empty foods that are all too present during the holidays. As envious as you may be

when you see others indulging, remind yourself that your body is worth taking extra special care of. Those who are over-indulging are certainly not doing themselves any favors and even if they don't have IBS, odds are that they will be suffering from the effects of their splurging the next day.

Assertiveness and limit setting – The holidays can be a mixed blessing when it comes to dealing with other people. On the one hand, we get to spend time with people that we care about that perhaps we don't get to see over the rest of the year. On the other hand, we may find ourselves forced to spend time with people that we may not really like or whose behavior is upsetting to us. In order to keep your stress level to a minimum, it becomes important to connect with positive people and protect yourself from those whose negativity can become toxic.

- Tell the caring people in your life about your IBS: Like anyone who is suffering from a major health problem, you deserve the benefits that come from the care and concern of others. Given the high prevalence of IBS, you may be surprised to find out who else is walking in your shoes.
- Speak up about any special needs that you have: People cannot read your mind; they cannot know what will help you unless you tell them.
- Take steps to protect yourself from critical people: Family gatherings are often not quite as comforting as is portrayed in the movies. Dysfunctional family dynamics and unresolved sibling rivalry issues can result in criticism or conflict. This unpleasantness can increase your stress level and set off your system. When possible, practice good self care and remove yourself. If that is not possible, it is okay to actively



tune people out – thinking “blah, blah, blah” when someone else is talking can be surprisingly effective!

Summary

This year, make a promise to yourself to do things differently. Turn your IBS into a good reason to focus on your own needs as you proceed through this hectic time of year. Use the challenges of the season to practice self care skills, whether that means eating healthy foods or telling others what your special needs might be. Remind yourself that it is okay to be human, that you do not have to do it all and that it is okay to delegate or just take a pass on obligations. Keep things positive. If you make it to a gathering and have to leave because your symptoms are too uncomfortable, focus on the fact that at least you got there. Most importantly, don't lose sight of the true gift of the season, that of being around the people in your life that you really care about. Happy Holidays!

Barbara Bradley Bolen, PhD is a clinical psychologist in private practice in Farmingdale, New York. She is the author of “Breaking the Bonds of Irritable Bowel Syndrome: A psychological approach to regaining control of your life.” Along with Jeffrey Roberts, she compiled postings from the Internet-based IBS Self Help and Support Group into the self-help book, “IBS Chat: Real life stories and solutions.” She currently is the guide of the IBS Health Topics section on www.about.com.

Traveling this Holiday or New Year Season?

Managing irregular and often painful bowel symptoms involves much more than accommodating minor inconveniences. Travel can present special challenges. Here are some tips designed to help you create a sense of being more in control when traveling.

IFFGD's Travel Tips:

- Allow enough time in the morning to get to the airport on time without worry. When traveling to and from your destination, bring an extra bag with a change of clothes in the event that your luggage is lost.
- Carry a “survival kit” with you. Choose something you are comfortable with, such as a computer bag, briefcase, large purse, or back-pack. Throughout your trip, always have a change of clothes with you, and bring a small supply of tissue in case there's none available when you are out.
- Traveling by plane can be difficult for those who suffer from bowel symptoms. Ask to sit as close to the restroom as possible. Also, sit on an aisle for easy and fast access so you will not have to ask others to move.
- When planning your trip, consider driving if possible. You may feel a greater sense of control when you don't have to be on someone else's schedule or timetable.
- If you are making a long drive to get to and from your destination, know how much distance there is between rest areas or highway exits with available restrooms. Map your routes ahead of time and determine how to get from point A to point B as quickly and directly as possible.
- Avoid lodging where multiple rooms share a single restroom. To help ensure access to a restroom, if you know you will be arriving before check-in time, ask for early check in; if you need to check out later, don't hesitate to ask. Most hotels will accommodate your needs.
- Avoid foods and beverages that you know can aggravate your symptoms. Meals that are large or high in fat, fried foods, coffee, caffeine, or alcohol may provoke or worsen symptoms of abdominal cramps and diarrhea. This is not the time to experiment. Stick with foods with which you are comfortable.
- If you are traveling outside your home country, know how to ask where the restroom is in the local language, and always have change for pay toilets. Public restrooms are usually available and accessible in the United States, but may not be in other countries.
- Know what documentation may be necessary to refill prescriptions at your destination.



The Clinical Corner

Answers to your Questions
about Digestive Health

Do you have a question about digestive health? We want to help.

If you or a family member is struggling with chronic or recurring GI symptoms, you probably know how challenging it can be to find reliable treatment information. We want to help you find ways to manage symptoms and understand why they occur. We are always happy to hear from you, so please send us your question.

Answers are provided by digestive health professionals familiar with these disorders. In this issue you'll find answers to these questions:

- How long can a person not have a bowel movement before needing medical attention?
- Can a person have “constipated diarrhea”?

If you have a question, please contact us by mail at: IFFGD, PO Box 170864, Milwaukee, WI 53217.
Or email to: clinicalcorner@iffgd.org

QUESTION – How long can a person go without having a bowel movement before seeking medical attention? Could this ever become urgent and warrant a trip to the emergency room?

ANSWER – Constipation is a symptom, not a disease. The exact definition of constipation is problematic. Patients and doctors often define constipation differently. Doctors relate primarily to the frequency of bowel movements in a given time period (usually per week). Patients usually relate to the effort required (straining), to the consistency of the stool (hard), and to

the feeling that they cannot entirely empty themselves.

Most people have their own “personal” bowel habit. They may have a few bowel movements a day or a bowel movement every few days. Doctors usually define constipation as less than three bowel movements per week and may define severe constipation as waiting more than a week for a bowel movement. However, some people have less than a bowel movement a week and are not bothered by this at all, while others may find this physically uncomfortable or emotionally distressing.

Just as there is no “magic” number of bowel movements that an individual should have, there is also no magic number that defines when constipation is a medical problem requiring immediate evaluation or intervention.

An important question that should be addressed when deciding whether constipation should be evaluated or even justifies a trip to the emergency room is whether it is acute (of recent onset) or chronic (of long duration). Cases of acute constipation are more worrisome and might indicate a significant underlying medical condition such as bowel obstruction.



If constipation is associated with “alarm symptoms” such as severe, worsening abdominal pain, extreme abdominal swelling, fever, nausea and vomiting, or if new-onset constipation occurs in an older person who is usually regular an immediate medical consultation should be obtained.

Most cases of constipation are chronic, having lasted for years, and are not associated with “alarm symptoms.” It is usually related to a functional bowel disorder, such as irritable bowel syndrome (IBS). However, there are other possible causes of chronic constipation including medication use, hormonal problems, pelvic floor disorders, neurological disorders like Parkinson’s disease, and other conditions. Thus, if any of these possibilities appears relevant, a non-urgent medical evaluation would be logical.

– *Ami D. Sperber, MD and Roy Dekel, MD*

QUESTION – Has anyone else experienced “constipated diarrhea”? I have been dealing with IBS for about 10 years. My symptoms are constant and occur daily and include bloating, gas, and constipation. Strangely enough, more times than not I experience what I refer to as “constipated diarrhea.” I found it disturbing that the doctors I visited wanted to know if I was either constipated or if I experienced diarrhea. My IBS (as I’m sure is most of yours) cannot be so easily classified as one or the other. *[Taken from “Courageous Stories,” a feature on IFFGD’s web sites; this question and story appeared on www.aboutIBS.org.]*

ANSWER – Pain and discomfort related to altered bowel habit are the hallmarks of IBS. But what is “altered bowel habit”? The commonly used terms diarrhea and constipation mean different things to different people . . . and to physicians as well. Yet bowel symptoms affect treatment choices, so it is important that you and your doctor speak the same language.

How do we “translate” bowel symptoms in a meaningful way? Does diarrhea mean frequent stools, or loose stools? Most people endorse a loose stool as diarrhea more than the frequency of bowel movements. What about constipation? Doctors consider constipation a hard pellet-like stool, because that reflects that the stool has remained in the colon for a long time. But to many individuals, constipation means infrequent stools, difficulty or straining at stools, the sensation of wanting to go but cannot or of not having finished a bowel movement. So while it may seem strange to have “constipated diarrhea,” if one has difficulty having a bowel movement or feels he or she hasn’t finished but has a loose stool it all makes sense.

The Rome III committees have designated 4 subtypes of IBS based on criteria that describe diarrhea, constipation, mixed (both diarrhea and constipation), and alternating (shifting pattern of diarrhea and constipation). The diarrhea subtype of IBS has been designated to be loose/watery stools more than 25% of the time and hard pellet-like stools less than 25% of the time. Conversely, the constipation subtype of IBS is the hard pellet-like stools more than 25% of the time and loose watery stools less than 25% of the time. In “mixed IBS” individuals have both loose watery stools more than 25% of the time AND hard pellet like stools more than 25% of the time. When this pattern shifts between diarrhea and constipation it is called “alternating IBS.”

– *Douglas A. Drossman, MD*

Contributors:

Ami D. Sperber, MD, Associate Professor of Medicine, Department of Gastroenterology, Soroka Medical Center; Faculty of the Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Roy Dekel, MD, The Gastroenterology Institute, The Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Douglas A. Drossman, MD, Co-Director, UNC Center for Functional GI & Motility Disorders; Professor of Medicine and Psychiatry, University of North Carolina, Chapel Hill, NC

Digestive Health Research: A Sampling of Recently Published Studies

Why is Medical Research Important?

Although great progress has been made over the past decades, much remains to be understood about the functional and motility GI disorders. To those affected by chronic symptoms it often may seem like what we do not know outweighs what we do know. While our understanding is improving, important questions remain:

- What causes these disorders?
- Why do certain people get them?
- How do we best treat the conditions?
- How do we prevent and cure them?

Medical research is needed to explore these questions. Through research, answers will be found, and the burden of illness endured by those affected will be relieved.

The good news is researchers are starting to understand some of the biological mechanisms responsible for the symptoms people feel. Clinicians are examining various treatments to determine which are most effective. With this increased understanding, new treatment approaches and medications are being developed. Some are now available to help certain groups of patients. We do not have all the answers yet, but we are getting closer.

In this column, we report just a few research studies that provide clues to better understanding GI disorders. Each new study adds another small piece to the puzzle, making the big picture clearer.

If you are interested in learning more about medical research, please visit our web site at www.giResearch.org. On this web site we also maintain a listing of various clinical studies or clinical trials (they mean the same thing) in which you can participate, including over the Internet. Go to our site at www.giResearch.org and click on GI Research; then go to Clinical Trials and Studies.

The Narcotic Bowel Syndrome

Narcotics are drugs, usually opiates such as morphine or oxycodone, which can relieve pain. In the U.S. narcotics are commonly prescribed for treating patients with pain, usually injuries, sudden painful conditions, or cancer. However, persons with chronic functional GI disorders should *not* be treated with narcotics, though this may at times be done. We are learning that under some circumstances, the use of narcotics can actually cause pain. Over time, narcotics can make nerves more sensitive, and make pain worse; they also can slow the bowel, and lead to symptoms of constipation, bloating, or nausea. This relates to the well known effects of narcotics on the bowel, opiate bowel dysfunction.

In a review article by a group from the University of North Carolina, a subset of opiate bowel dysfunction called narcotic bowel syndrome (NBS) is described. This under-recognized syndrome may be becoming more prevalent because of increasing use of narcotics for chronic painful disorders as well as lack of awareness that increased sensation to pain may be caused by long-term narcotic use. The syndrome is characterized by chronic or periodic abdominal pain that gets worse when the effect of the narcotic drug wears down. In addition to pain, which is the primary feature, other symptoms may include nausea, bloating, periodic vomiting, abdominal distension, and constipation.

The UNC group has developed the following diagnostic criteria for narcotic bowel syndrome:

Chronic or frequently recurring abdominal pain that is treated with acute high-dose or chronic narcotics and all of the following:

- The pain worsens or incompletely resolves with continued or escalating dosages of narcotics;
- There is marked worsening of pain when the narcotic dose wanes and improvement when narcotics are re-instituted (soar and crash);
- There is a progression of the frequency, duration, and intensity of pain episodes;
- The nature and intensity of the pain is not explained by a current or previous GI diagnosis.

The key to diagnosis is the recognition that long-term or increasing dosages of narcotics lead to continued or worsening symptoms rather than benefit.

The UNC group has also developed a treatment approach. The narcotic is withdrawn and substituted with effective alternative medications to help manage the pain and the bowel symptoms until the narcotics are removed from the system. This requires the doctor and patient working closely together. The doctor must take time to explain the condition, the reasons for withdrawing the narcotics, and the alternative treatment plan. The treatment process may take several weeks or months to implement satisfactorily, with the doctor staying in touch with the patient during this period.

Source: Grunkemeier DMS, Cassara JE, Dalton CB, Drossman DA. The narcotic bowel syndrome: clinical features, pathophysiology, and management. *Clin Gastroenterol Hepatol* 2007;5:1126-1139.



Books of Interest

Here is a list of books, authored by knowledgeable healthcare professionals, which provide trustworthy information about a variety of topics relating to gastrointestinal disorders and digestive health. These books are published by outside publishers – not by IFFGD.

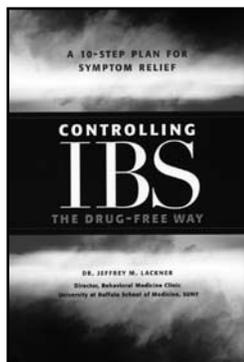
Title: Controlling IBS the Drug-Free Way: A 10-Step Plan for Symptom Relief

Author: Jeffrey M. Lackner, Psy.D.

Publisher: STC Healthy Living (2007)

Pages: 256 (paperback)

ISBN: 978-158479-575-9



For more than 10 years, Dr. Jeffrey M. Lackner has been helping patients gain control of their symptoms. His NIH supported research shows that these skills can help, whether

their IBS involves diarrhea, constipation, or both.

In this book, Dr. Lackner offers IBS sufferers the same tools that have helped many patients control their bowel problems. Research shows that the techniques featured in this book can improve IBS patients' conditions and help them reclaim lives lost to this common gastrointestinal problem. The book offers a step-by-step approach that anyone with IBS can easily follow to reduce symptoms without drugs or professional help. User-friendly worksheets, interactive exercises, self-assessment checklists, and diaries for tracking symptoms and trigger foods are included to help readers master each skill. Also included are up-to-date overviews of medications and dietary strategies that readers can use to maximize symptom control.

Jeffrey Lackner is director of the Behavioral Medicine Clinic and Assistant Professor in the Department of Medicine at the State University of New York at Buffalo School of Medicine. Available through booksellers.

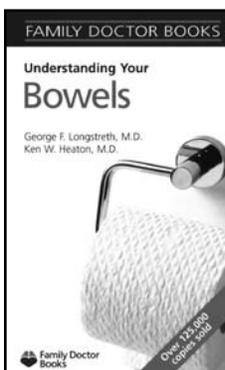
Title: Understanding Your Bowels

Authors: George F. Longstreth, M.D. and Ken W. Heaton, M.D.

Publisher: Family Doctor Publications (2006)

Pages: 140 (paperback)

ISBN-10: 142850012X



Here is a concise, easy to read book designed to help any reader understand how their bowels work, what can go wrong, and what can be done to fix the problems. Topics range from chronic symptoms such as constipation,

diarrhea, or bloating, to disorders such as IBS or diverticulosis. An explanation of the physician visit and tests will help patients get the most out of their doctor visits. Originally published in Great Britain, the book has recently been re-published for U.S. readers.

Dr. Heaton and Dr. Longstreth are prolific writers and dedicated clinicians with many years of experience in the field of digestive health and illness. Dr. Longstreth is Chief of Gastroenterology with the Kaiser Permanente Medical Care Plan and is Clinical Professor of Medicine at the University of California San Diego School of Medicine. Dr. Heaton was until recently Reader in Medicine at the University of Bristol, U.K. and Honorary Consultant Physician to the United Bristol Hospitals Trust. Together they have written this user-friendly volume. The book contains colorful and understandable illustrations, a list of useful resources, and a helpful glossary of terms. Recommended for anyone seeking to understand a bowel disorder and how to find help. Available through booksellers.

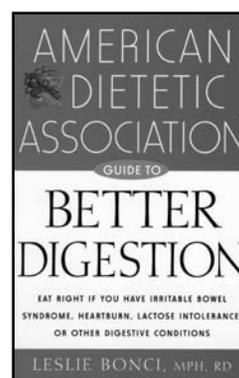
Title: American Dietetic Association Guide to Better Digestion

Author: Leslie Bonci, R.D., M.P.H.

Publisher: Wiley (2003)

Pages: 256 pages (paperback)

ISBN: 0471442232



Leslie Bonci is the director of sports medicine nutrition for the Department of Orthopedic Surgery and the Center for Sports Medicine at the University of Pittsburgh Medical Center

and is an adjunct assistant professor of nutrition at the University of Pittsburgh School of Health and Rehabilitation Sciences. Backed by the American Dietetic Association, this user-friendly guide shows you how to analyze your eating habits so you can map out a dietary plan to manage and reduce the uncomfortable symptoms of digestive disorders.

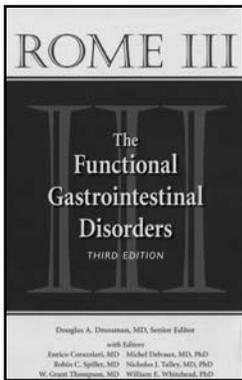
You'll find practical recommendations for implementing changes in your lifestyle and advice on steering clear of common dietary mistakes. Your meals will be pleasurable and nourishing experiences – not painful ones – when you discover how to make the best and most comfortable food choices so you can embark on the road to digestive health. Available through booksellers.

Title: Rome III: The Functional Gastrointestinal Disorders

Senior Editor: Douglas A. Drossman, MD

Pages: 1,048 pages (hardback)

ISBN: 096568376 (hardback); 0965683753 (paperback)



Five years in the making, Rome III is designed for “one stop” learning for health professionals. It serves as a valuable resource to general and specialist physicians, mental health professionals, and basic and clinical investigators involved

in the study and care of patients with functional GI disorders. Rome III provides the most up-to-date information on the epidemiology, pathophysiology, diagnosis, and treatment of irritable bowel syndrome and over 20 more functional GI disorders commonly seen in clinical practice. Available online at www.romecriteria.org/.

Report – Digestive Disease Awareness Day

Saturday, September 29, 2007 was **Digestive Disease Awareness Day in Pennsylvania**. This was an initiative started by the Pennsylvania Society of Gastroenterology and officially proclaimed by the Governor of Pennsylvania, Edward Rendell. The purpose of this was to increase the awareness of Digestive Diseases in Pennsylvania. The goals of this initiative were threefold:

1. Improve recognition of Gastroenterology and GI disorders to the public;
2. Educate the public about a common GI disorder – irritable bowel syndrome – as well as GI disorders in general;
3. Discuss the advantage of patients to see a gastroenterologist for treatment of GI conditions and for colon cancer screening.

The day chosen was the start date of the Pennsylvania Society of Gastroenterology Annual Scientific Meeting. In the morning, there were scientific sessions for physicians at the annual meeting. In the afternoon, a symposium on irritable bowel syndrome for patients was held.

Advertisements were placed in the *Philadelphia Inquirer*, the city newspaper, and the Metro, the transportation newspaper. Patients registered on line.

What happened was beyond expectation. There was a tremendous outpouring of people – 150 patients attended the patient symposium.

The program consisted of:

- Introduction
- What is IBS? How common is it?
- Evaluation of patients with possible IBS
- How do you treat it?
- Questions from the Audience

The presentations were short, 10 minutes each, leaving approximately 45 minutes for questions and answers. Many, many questions from patients were addressed by the physicians. The patients thought this was very worthwhile. Brochures were distributed on IBS developed by the International Foundation for Functional Gastrointestinal Disorders (IFFGD). Thanks to IFFGD!

– *Henry P. Parkman, MD*
President of the American Neurogastroenterology and Motility Society (ANMS)



Announcements

NIH State-of-the-Science Conference: Prevention of Fecal and Urinary Incontinence in Adults December 10-12, 2007

The NIH Consensus Development Program was established in 1977 as a mechanism to judge controversial topics in medicine and public health in an unbiased, impartial manner. NIH has conducted 118 consensus development conferences, and 28 state-of-the-science (formerly “technology assessment”) conferences, addressing a wide range of issues. For more information about the program, past conferences and statements, or upcoming conferences, please visit www.consensus.nih.gov.

Fecal and urinary incontinence – the inability to control bowel movements or urination, respectively – are conditions with ramifications that extend well beyond their physical manifestations. Many people find themselves withdrawing from their social lives and attempting to hide the problem from their families, friends, and even their doctors. The embarrassing nature of these conditions poses a significant barrier to seeking professional treatment, resulting in a large number of unreported, untreated individuals. Therefore, it is difficult to determine the accurate prevalence of these conditions, as well as any associated medical history trends. Incontinence is more likely to affect the aging population, although it is not considered a normal consequence of aging. As baby boomers approach their 60s, the incidence and public health burden of incontinence are likely to increase.

Fecal incontinence is a serious and embarrassing problem that affects up to 5 percent of the general population and up to 39 percent of nursing home residents. It affects people of all ages, but is more common in women and the elderly. Bowel function is controlled by three factors: rectal sensation, rectal storage capacity, and anal sphincter pressure. If any of these are compromised, fecal incontinence can occur. This condition can have many causes, including constipation, diarrhea, complicated childbirth, muscular or nerve damage, reduced storage capacity due to scarring or irritation, or pelvic dysfunction.

Although urinary incontinence can affect people at all stages of life, it has been estimated that urinary incontinence affects 38 percent of women and 17 percent of men 60 years of age and older. Urinary incontinence can occur if muscles in the wall of the bladder suddenly contract, or if muscles surrounding the urethra suddenly relax. Women who have undergone childbirth are the most commonly associated at-risk population for urinary incontinence. Pregnancy and delivery can weaken pelvic muscles, and reduced levels of the hormone estrogen following menopause can cause reduced muscle tone around the urethra, increasing the chance of leakage. Additionally, neurologic injury, birth defects, strokes, multiple sclerosis, and physical problems associated with aging have been reported to contribute.

Because incontinence is likely widely under-diagnosed and under-reported, it has been difficult to identify both at-risk and affected populations. Also, because the biological mechanisms that cause both fecal and urinary incontinence are not well understood, it has been difficult to develop robust prevention and management strategies. Toward that end, the National Institute of Diabetes and Digestive and

Kidney Diseases (NIDDK) and the Office of Medical Applications of Research (OMAR) of the National Institutes of Health (NIH) will convene a State-of-the-Science Conference from December 10 to 12, 2007, to assess the available scientific evidence relevant to the following questions:

- What are the prevalence, incidence, and natural history of fecal and urinary incontinence in the community and long-term care settings?
- What is the burden of illness and impact of fecal and urinary incontinence on the individual and society?
- What are the risk factors for fecal and urinary incontinence?
- What can be done to prevent fecal and urinary incontinence?
- What are the strategies to improve the identification of persons at risk and patients who have fecal and urinary incontinence?
- What are the research priorities in reducing the burden of illness in these conditions?

Nancy J. Norton, IFFGD President will present on the topic of: Impact of Fecal and Urinary Incontinence on Health Consumers – Barriers on Diagnosis and Treatment – A Patient Perspective.

Webcast and Speakers' Abstracts

The proceedings will be webcast live and for one week following the conference. Go to the NIH Videocast Web site (<http://videocast.nih.gov>) to view using RealPlayer software, which can be downloaded free of charge from the NIH Videocast Web site. Once the conference opens, abstracts of the speakers' presentations will be available at <http://consensus.nih.gov>.

Vulvodynia Awareness Campaign

The Office of Research on Women's Health (ORWH) serves as a focal point for women's health research at the U.S. National Institutes of Health (NIH). It was established in 1990 within the Office of the Director. Among its many activities, ORWH works in partnership with the NIH institutes and centers to ensure that women's health research is part of the scientific framework at NIH and throughout the scientific community. The ORWH promotes, stimulates, and supports efforts to improve the health of women through biomedical and behavioral research on the roles of sex (biological characteristics of being female or male) and gender (social influences based on sex) in health and disease and supports research on women's health issues. Nancy Norton, President of IFFGD, serves on the Advisory Committee on Research on Women's Health, which meets periodically to advise and make recommendations to the Director of the Office on women's health issues.

On October 24, 2007 the ORWH announced a new women's health awareness campaign about vulvodynia, a chronic unexplained pain or discomfort of the vulva. To address this serious women's health issue, the Office of Research on Women's Health at NIH, in partnership with the National Institute of Child Health and Human Development, the National Institute of Neurological Disorders and Stroke, the NIH Pain Consortium, and other partners, has established the Vulvodynia Awareness Campaign.

Vulvodynia, also referred to as "the pain down there" or also as "feminine pain," is chronic discomfort or pain of the vulva, which is the area around the outside of the vagina. While a number of causes have been proposed, researchers still don't know why vulvodynia happens to some women. An estimated 14 million American women may have vulvodynia at one point in their lives. However, many health care providers are not aware of the condition, so they aren't always able to diagnose it. As a result, many women may go for a long period of time without a diagnosis. This campaign is designed to raise awareness of the condition that is frequently not discussed, but can greatly affect the lives and personal relationships of women of all races, ethnic groups and ages.

The website of the Office of Research on Women's Health, the National Institutes of Health, U.S. Department of Health and Human Services (<http://orwh.od.nih.gov/health/vulvodynia.html>) has additional information on electronic and print resources regarding vulvodynia.

Autonomic Dysfunction in Adults with Cyclic Vomiting Syndrome (CVS)

Subjects are currently being recruited for participation in study at the Medical College of Wisconsin to start around December 2007. The aim of the study is to prospectively evaluate the presence of autonomic dysfunction in patients with CVS. Studies will take place in Milwaukee, Wisconsin.

Criteria for participation

Adults who meet the following three criteria and had episodes at least 6 months before they were diagnosed:

1. Episodes that are similar in when they start and how long they last
2. Three or more discrete episodes in the prior year
3. Absence of nausea and vomiting between episodes

In addition, all subjects will have had the necessary work up to exclude other organic diseases resulting in cyclic vomiting.

Exclusion criteria

Exclusion criteria include the presence of other diseases that affect autonomic testing (e.g., any chronic pain disorder, or endocrinological, cardiovascular or other neurological diseases).

If you are interested, please contact:
Thangam Venkatesan, MD
Medical College of Wisconsin
Division of Gastroenterology
Phone: 1-414-456-6836
Email: kcieszk@mcw.edu



When IFFGD began, in 1991, there was little communication between patients living with functional gastrointestinal (GI) and motility disorders and the companies with the means to develop treatment products and services. Subsequently, IFFGD has worked hard to make the needs of our members known – not only to the clinicians who see patients, but also to the researchers and providers of diagnostic and treatment methods and tools.

In 1998, in an effort to strengthen our voice, we formed the IFFGD Industry Council. The Council provides a forum to help ensure that the voice of our membership is heard. The purpose of the Industry Council is to help fulfill the mission of IFFGD: to inform, assist, and support people affected by gastrointestinal disorders, or bowel incontinence.

We invite participation from companies with a demonstrated interest in these disorders. While we are grateful to our Industry Council members for their support, we do not endorse any specific product or company. IFFGD retains unrestricted control over the planning, content, objectives, methods, and execution of all initiatives and projects.

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Industry Sponsored Clinical Trials

Industry Sponsored Clinical Trials

A clinical trial is a research study to answer specific questions about new products, therapies, or new ways of using known treatments. Through these research studies, investigators find new and better ways to treat, control, prevent, diagnose, or detect conditions, or to improve the quality of life for those with an illness. Trials can take place in a variety of locations, such as hospitals, universities, doctors' offices, or community clinics.

Although efforts are made to control risks to clinical trial participants, some risk may be unavoidable because of the uncertainty inherent in clinical research involving new medical products. It's important, therefore, that decisions to participate in a clinical trial are made only after obtaining a full understanding of the entire process and the risks that may be involved.

Choosing to participate in a clinical trial is an important personal decision. It is often helpful to talk to a physician, family members, or friends about deciding to join a trial. General information about clinical trials can be found at this IFFGD web page, www.giResearch.org/AboutClinicalStudies.html or at this National Institutes of Health web site, www.clinicaltrials.gov, among others.

After identifying some trial options, the next step is to contact the study research staff and ask questions about specific trials. Here is a list of studies, sponsored by members of the IFFGD Industry Council, which are currently seeking participants.

Gastric Stimulation for Vomiting, Nausea and Related Symptoms Associated with Gastroparesis Using Enterra Gastric Stimulation System

Purpose of Trial: A research study to determine if an implanted device (Enterra Therapy) to stimulate the stomach will improve symptoms (such as nausea and vomiting) associated with gastroparesis (a disorder in which the stomach takes too long to empty its contents).

Sponsored by: Medtronic, Inc. Find more details on-line at: www.giresearch.org/IndustryStudies.html.

Locations and Contact Information

- Indianapolis, IN, St. Vincent Hospital – Contact: Kativa Leal, RN, (317) 338-6743
- Louisville, KY, University of Louisville – Contact: Jennifer Koopman, (502) 852-3365
- San Francisco, CA, California Pacific Medical Center – Contact: Lesley Scott, MS, (415) 600-1593
- Santa Ana, CA, Lovelace Scientific Resources – Contact: Selene Alvarez, CRC, (714) 444-4048
- Washington, DC, George Washington University – Contact: Elizabeth Drenon, (202) 741-3168



Report from IFFGD Research Award Winner

Role of the Central Immune System in Functional Disorders

By: Sylvie Bradesi, Ph.D., Center for Neurovisceral Sciences and Women Health & CURE: Digestive Diseases Research Center, David Geffen School of Medicine at UCLA, Los Angeles and VA Greater Los Angeles Health Care System, Los Angeles, California

Dr. Bradesi is the recipient of the 2007 IFFGD Research Award for Junior Investigator – Basic Science. Her research has looked at neuroimmune interactions in the spinal cord at the molecular level and the role of this response in chronic pain.

At a Glance

- **Functional pain disorders are common; they affect many areas of the body.**
- **Chronic stress activates certain immune cells (glia) in the spinal cord.**
- **Immune changes in the spinal cord, even when there is no infection or injury, may play a role in increasing pain sensitivity in the colon.**

Functional pain disorders are clinical syndromes – groups of signs or symptoms – in which patients experience persistent or recurrent bodily pain or discomfort that cannot be explained by current injury or visible abnormalities. Functional pain disorders are common and have been clustered into various distinct syndromes defined by medical subspecialties depending on their predominant symptoms. Examples include irritable bowel syndrome (IBS), fibromyalgia, chronic pelvic pain, interstitial cystitis, chronic fatigue syndrome, and migraine.

Health professionals in clinical practice frequently observe that patients diagnosed for one specific functional syndrome often report symptoms of other syndromes and are much more likely to have or develop another functional syndrome during their lifetime. For example, bloating, feeling of abdominal distension, abdominal pain, headache, and fatigue are reported in most of the different functional pain syndromes; patients suffering from IBS are more likely to suffer from fibromyalgia, chronic fatigue syndrome, or chronic pain.

To date, the management of functional pain syndromes has failed to provide adequate relief to many patients. The lack of effective therapeutics available illustrates the limited understanding of the biological mechanisms underlying the expressions of symptoms in these conditions.

Immune activation in the central nervous system: a new concept linking the multiple symptoms of functional pain disorders

Recently, a new concept of activation of immune cells within the central nervous system (CNS), including the brain and the spinal cord, has been proposed as a major factor contributing to the generation and maintenance of chronic pain. Immune cells in the CNS are part of a group of cells called glia. Glial cells are not nerve cells. They include several types of cells, each with different functions. Glia were initially considered as a silent support (also called “glue”) for neurons (nerve cells). Recent evidence indicates that glia play an important active role in the proper functioning of neurons and in many chronic disease states, including Alzheimer’s disease, spinal cord injury, and chronic pain.

In general, the function of glia is to provide a stable internal environment around neurons and to take part in

the communication between neurons. Recently, it has been discovered that glia in the spinal cord play a major role in the transmission of pain signals in conditions of chronic pain associated with inflammation or injury. In these conditions, glia was found to be activated and to communicate with neurons via the releases of several chemical substances, triggering a chain of reaction leading to increased pain perception. Experimental studies have demonstrated that if glia activation is chemically blocked, then, the pain associated with inflammation or injury is decreased.

Recently, signs of immune activation have been described in certain patients suffering from functional pain disorders (in which they have no signs in the body of inflammation or injury). Furthermore, recent observations indicate immune activation in the CNS of patients suffering from mood disorders such as depression. Based on these reports, we have proposed that glia activation in the CNS may be an underlying mechanism for the expression of multiple symptoms of pain and depression in patients suffering from functional pain syndromes. We propose that immune activation in the CNS may be considered as a possible physiological basis for the overlap of the different symptoms in functional disorders, including functional bowel disorders. To date, the role of glia in

We propose that immune activation in the CNS may be considered as a possible physiological basis for the overlap of the different symptoms in functional disorders, including functional bowel disorders.

experiments of functional chronic pain has not been investigated.

Chronic stress and activation of the CNS immune system: implication in increased pain sensitivity (visceral hyperalgesia)

Observations of patients have demonstrated that chronic life stress can play a major role in the onset or worsening of symptoms in individuals suffering from functional disorders, and in particular IBS. In our laboratory, we study the mechanisms of the influence of stress on visceral pain in the colon, and we have developed an experimental model to represent repeated psychological stress. We have demonstrated, in an animal model, that exposure to stress daily for 10 consecutive days results in increased pain response to stimulation of the colon (visceral hyperalgesia), which lasts for about a month.

In view of the observations reported above, we have recently focused our research efforts to study whether or not chronic pain sensitivity in the colon in response to stress may be linked to activation of the immune system (glia) in the CNS. Our interest in the effect of stress on glia activation was supported by other recent published work showing experimental glia activation in the brain. However, there is no data available on the effect of stress on glia in the spinal cord. We were able to demonstrate that chronic stress leads to activation of spinal glia and that blocking glia activation during stress can prevent the development of colonic pain sensitivity. This is the first demonstration that chronic visceral pain may be related to immune changes occurring at the spinal cord level and that these changes can happen in response to chronic stress, without exposure to any inflammatory stimuli or tissue insult.

Summary

In summary, accumulating evidence indicates that immune activation within the CNS plays a crucial role in the increased pain perception observed in conditions of inflammation or injury in the body (peripheral). In addition, an increasing number of reports from experimental animal studies show that glia activation in the brain and spinal cord (the central nervous system) can occur in response to stress. Combined with increasing reports that chronic stress plays a key role in the worsening or intensity of symptoms in functional gastrointestinal disorders or functional pain disorders, these data provide a conceptual framework supporting a possible role of CNS glia activation in the development of multiple symptoms in syndromes of functional pain.

To date, the management of functional pain syndromes, in particular the pain component of these syndromes, relies on drugs primarily targeting neurons, which has failed to provide adequate relief to many patients. The current state of evidence illustrates the need for innovative research challenging this current drug development strategy.

We propose a new conceptual model in which modification of the interaction between neurons and immune cells in the central nervous system, responding to chronic stress, plays a predominant role in the pain sensitivity of pain signaling pathways. This provides a new basis for drug development for the treatment of chronic functional pain.

Capitol Hill Minute

IFFGD is involved in many efforts in the U.S. Capitol, Washington, DC, on behalf of our members – both patients and professionals. These efforts include advocating for support of research to help improve patient care and for availability of safe and effective treatments.

Among these activities, IFFGD is a member and participant in two nonprofit, non-partisan advocacy groups, The Coalition for a Stronger FDA and The FDA Alliance, whose purpose is a strengthened and improved Food and Drug Administration (FDA). The FDA is the U.S. government agency responsible for regulating food, drugs, dietary supplements, cosmetics, medical devices, biologics (e.g., vaccines), and blood products. Through the Coalition for a Stronger FDA (www.fdacoalition.org/) and the FDA Alliance (www.strengthenfda.org/) we help in the effort to increase the FDA's resources needed to protect the public. In this effort we join with many other nonprofit organizations, consumer advocates, public health organizations, companies, and a number of leading public health advocates including former Health and Human Services Secretaries Tommy G. Thompson, Donna E. Shalala, and Louis Sullivan, as well as 6 former FDA Commissioners.

On September 19, 2007, the U.S. House of Representatives voted 405–7 to adopt compromise FDA reform legislation that increases prescription drug user fees for fiscal years 2008–2012. The U.S. Senate passed the new FDA reform bill, H.R. 3580, by unanimous consent on the following day.

The higher user fees will help pay for new FDA drug safety initiatives created by the legislation. The new safety money totals \$25 million in fiscal year 2008 and increases by \$10 million per year through fiscal year 2012. In addition, FDA will receive user fees of \$396 million per year, plus adjustments for inflation and other factors, to pay for new drug review and post-market safety programs previously negotiated with industry.

What's New from IFFGD

Videos on IFFGD Web Sites

We have added a video section to all of our web sites. Here you can watch and listen to noted experts talk about a variety of digestive health topics, from diagnosis to treatment and daily management strategies to the promises and challenges of future research. Go to any of our web sites, for example, www.iffgd.org, click on the Learning Center and open the Video Corner.

IFFGD IBS Survey

In mid-July 2007 IFFGD began an online survey designed to help determine the unmet needs of people diagnosed with irritable bowel syndrome. To date, more than 2,000 people have participated in the survey. This is not a quick poll, but rather a comprehensive study. The survey methodology is intended to provide enduring and publishable data for wide dissemination through the medical literature and other media. The data will be analyzed and reported periodically over time. The first report will soon be available. If you have a diagnosis of IBS from a medical professional and have not taken part in the survey, we invite you to do so now. You will find the online survey link toward the bottom of our web pages at www.iffgd.org and www.aboutIBS.org.

IBS Focus Group

In October 2007 IFFGD, working with the Rome Foundation (www.romecriteria.org/about), conducted three focus groups to help better understand the personal impact of irritable bowel syndrome. A total of 16 persons with an IBS diagnosis participated. The groups met in Milwaukee and were moderated by Douglas A. Drossman, MD and Lin Chang, MD, both well known for their work in treating and studying IBS. The participants each described multiple symptoms that ranged from moderate to severe. Their candor and lively discussion will help in making sure that the patient perspective is accurately represented in clinical research. This will benefit not only those involved with studying and developing treatments for IBS, but also those patients who ultimately will benefit from treatments. For the participants, planning and traveling with this painful and unpredictable condition was challenging. On behalf of IFFGD and the IBS community that we are committed to supporting, our heartfelt thanks go out to each of those who took part in the focus groups.

Stand Up and Be Counted ... Give to IFFGD

"I always wondered why 'somebody' didn't do something. Then I realized I was that somebody."

— Lily Tomlin

Your donation to IFFGD does more than support digestive disease research. It tells the world that you believe better treatments and more solutions are needed. It demonstrates your commitment to the need. It shows you care.

Today, in light of decreasing government support of research, numbers count, and we need you to help us show political leaders and health care professionals that we are not a lone voice, that millions of patients want and need help. We need you to join the cause, to make our voice stronger.

Commit to the cause, no matter how much you can give. Every person, every dollar counts. By joining in our campaign you will be heard. Your name, your contribution will make a difference. Step forth. Be counted. Show the world that digestive health matters.

For information about the many ways you can give to IFFGD, visit our Web site at www.iffgd.org, or phone, toll-free, 1-888-964-2001. Thank you.



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Where is the cure?

There is hope in research
To learn more, visit IFFGD.org or call toll-free 1(888)964-2001

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Occasionally, specific products are cited in articles or acknowledgments. However, no endorsement is intended or implied. Our intention is to focus on overall treatment or management issues or strategies.

The articles in *Digestive Health Matters* are in no way intended to replace the knowledge or diagnosis of your doctor. We advise seeing a physician whenever a health problem arises requiring an expert's care.

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Our Unique Mission: The International Foundation for Functional Gastrointestinal Disorders (IFFGD) is a nonprofit education and research organization dedicated to informing, assisting, and supporting people affected by gastrointestinal disorders. IFFGD has been working since 1991 with patients, families, physicians, practitioners, investigators, employers, regulators, and others to broaden understanding about gastrointestinal disorders and support research.



International Foundation for
Functional Gastrointestinal Disorders
IFFGD

P.O. Box 170864

Milwaukee, WI 53217-8076

Toll-free: 888-964-2001

Business: 414-964-1799

Fax: 414-964-7176

E-mail: iffgd@iffgd.org

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