



Report on the 4th International Symposium on Functional Gastrointestinal Disorders

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There is a growing understanding of the multi-faceted nature of functional gastrointestinal disorders. Symptoms, behaviors, and treatment outcomes for individuals with these disorders relate to disturbances in gastrointestinal motility and sensation that is effected by interactions that take place via the brain-gut axis. To understand and study these conditions, physicians and researchers must become familiar with evolving knowledge that integrates basic science, physiology, clinical medicine, psychology, and psychiatry. Indicated below are some of the highlights of the presentations at the 4th International Symposium for Functional Gastrointestinal Disorders, which we believe truly reflect the developing areas of research in irritable bowel syndrome (IBS) and the functional gastrointestinal (GI) disorders.

Opening Remarks

The meeting opened with an introduction by Nancy Norton, President of IFFGD who welcomed the group and discussed the numerous educational activities of IFFGD and its role in encouraging federal support for research. Frank Hamilton M.D., Chief, Digestive Diseases Programs Branch of NIDDK of the U.S. National Institutes of Health (NIH) commented on the history of NIH support for functional GI disorders beginning with a September 1992 NIH workshop on IBS. In 2000, \$15 million in research support was provided for functional GI disorders. Victor Raczowski M.D., Deputy Director, Office of Drug Evaluation of the U.S. Food and Drug Administration (FDA) identified several members of the FDA gastrointestinal research team attending the symposium and addressed controversies related to drug approval. W. Grant Thompson M.D., Chair of the Functional Brain-Gut Research Group talked about the Group's association with IFFGD from its beginnings in 1992, and endorsed the ongoing association for future meetings with IFFGD.

Epidemiology and Behavioral Factors

Moderator: Douglas Drossman M.D.;

Panel: Richard Locke III M.D.,

Margaret Heitkemper Ph.D., Rona Levy Ph.D.

The general (plenary) sessions began by addressing new information about the predisposing features of the functional GI disorders: their epidemiology (i.e., risk factors, distribution,

and occurrence within populations), the role of gender, heritability (i.e., the degree to which variation among individuals can be attributed to genetic factors), and early learning.

Richard Locke from Mayo Clinic Rochester, Minnesota began by discussing the markedly high prevalence of the functional GI disorders, in some cases many times higher than other well-known disorders. For example, the incidence of irritable bowel syndrome is 20 times greater than that for inflammatory bowel disease. Risk factors may include life trauma, post-infectious state, genetic/familial factors, and possibly even certain pain relievers.

Gender plays a role in the functional GI disorders. Margaret Heitkemper from the University of Washington, Seattle, discussed gender differences relating to interpretation of symptoms (leading to increased health care seeking in females), intestinal sensitivity, and stool consistency and frequency. Gender effects seem to appear after puberty. It is important to consider that gender-related treatments need to be developed and tested.

Rona Levy, University of Washington, talked about childhood influences and heritability. Recent research has shown that children of IBS parents consume greater health care costs and have more clinical visits than children of parents without IBS. The genetic contribution (as evidenced by Dr. Levy's research on twins) is statistically significant. However, it is not sufficient to fully explain the development of IBS. Early learning factors are quite important.

BASIC SCIENCE PRESENTATIONS

Basic science is the fundamental approach to understanding how systems work. Basic research takes place in the laboratory and often involves the study of molecules and cells. From this body of knowledge is drawn the means to investigate practical applications and to formulate clinical practices. One of the unique features of this symposium is that it brings together basic scientists, at the more esoteric beginnings of accumulated medical or scientific knowledge, with the clinical practitioners who apply advances in medicine for the benefit of each unique individual patient.

Basic Principles: Brain-Gut

Moderators: Emeran Mayer M.D. and

Jackie Wood Ph.D.;

Panel: Michael Gershon M.D., Brent Vogt Ph.D.,

Stuart Derbyshire Ph.D., Santosh Coutinho Ph.D.

During the last decade the concept of unique bi-directional interactions between the gut and the brain as an important factor in coordinated gut function in health has become widely accepted. More recent speculations have considered the possible role of these brain-gut interactions in brain function and the regulation of emotions. A dysregulation of brain-gut interactions is thought to play an underlying role in the functional GI disorders and may account for accompanying disorders related to emotional states (e.g., anxiety). This session focused on basic physiological principles (i.e., the characteristics of vital processes or functions).

Michael Gershon from Columbia University, New York began this session discussing the enteric nervous system (ENS). Also called “the little brain,” the ENS is a complex and independent division of the autonomic nervous system (ANS). It contains nerves and *neurotransmitters* (chemical messengers between nerve cells) that are also present in the brain. Certain cells within this system act upon sensory input to the central nervous system and amplify signals that can be associated with increased release of the neurotransmitter 5HT (serotonin, which affects intestinal motility) in response to pressure or injury within gut tissue. This action, and the recent work looking at the role of the serotonin *transporter* in mediating *reuptake* function may play a role in explaining why people develop IBS. (*Neurotransmitters* interact with nerve cell receptors to communicate from one nerve cell to another. They must be removed by a *transporter* in a process called *reuptake* before the cell receptor can reactivate.)

Stuart Derbyshire from the University of Pittsburgh gave an overview of nerve function going from the gut to the central nervous system (visceral afferent function) and an introduction to brain imaging. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) can help us study brain-gut connections, and differentiate brain activity in response to cognitive function, stimuli from the internal organs in contrast to other parts of the body, and input from specific areas in the gut. The receptive areas of the brain in this interaction can be influenced by localized stimuli and by emotion, memory, and cognitive function.

Brent Vogt from Wake Forest University, North Carolina discussed the important role of an area of the brain called the anterior cingulate cortex and its subdivisions in influencing the subjective experience of pain by translating emotion and cognitive awareness into pain regulatory actions. For example, one area of the cingulate cortex is rich in internally produced

opiates and may be an area of inhibition of pain through pathways descending to the spinal cord.

One of the foundations of basic science is the development of animal models to correspond to the study of disease processes in humans. Santosh Coutinho from UCLA discussed possible animal models for IBS. Mechanical or chemical inflammation in the rat colon, as well as maternal separation of rat pups, can lead later to excessive sensitivity to pain within the gut (hyperalgesia). Both factors may play a role in the origin and development of IBS in humans.

Inflammation

Moderator: Robin Spiller M.D.;

Panel: Jackie Wood Ph.D., Mary Perdue M.D.,

Robin Spiller M.D.

The last few years have led to a greater understanding of the role of inflammation in influencing intestinal hypersensitivity in the functional GI disorders. For example, a well-defined subgroup (up to 25% of IBS patients) appear to develop their IBS after an infectious illness. Jackie Wood from Ohio State University, discussed how inflammation alters the neurophysiology of the enteric nervous system (ENS) by activating nerves within the ENS. There are a variety of ENS neurons that can direct responses within the body leading to altered motility, sensation and secretion, and ultimately, symptoms of diarrhea, constipation, and pain.

Mary Perdue from McMaster University, Ontario discussed the importance of the epithelial intestinal barrier to maintain immune tolerance to potentially harmful matter, such as bacteria, ingested when we eat or drink. (Everything that enters the human body must pass through an epithelial layer. Various types of epithelial tissues line not only the body cavities, blood vessels, and most organs, but also our outer surface—our skin. Within the intestines, epithelial tissue forms an intestinal barrier involved with absorption, secretion, sensation, contractility, and protection.) Studies in animal models show that psychological stress can disrupt this barrier, leading to the penetration of bacteria into the gut, inflammation, an immune system response (inflammatory cytokines), and ultimately (as previously discussed) sensitization of neural signals from the gut to the brain that can heighten the perception of pain.

Robin Spiller from the University of Nottingham, UK brought this basic information to the human model of post-infectious IBS. The predictors of post-infectious IBS include increased life events and psychological distress, female sex, and longer duration of diarrhea episode. In response to bacterial infection, there is an increase in certain gut (enterochromaffin) secretory cells (5HT producing) and inflammatory cells (cytokine producing) leading to prolongation of pain and diarrheal symptoms, and this may be aggravated by the presence of psychological stressors.

These findings suggest ways in which infection-induced inflammation might interact with chronic stress to produce long lasting bowel dysfunction. They also suggest possible treatments that need study.

Brain Imaging

Moderator: David Thompson M.D.;

Panel: Qasim Aziz Ph.D., Howard Mertz M.D.

Pain is a subjective experience that is interpreted differently from person to person. This makes precise understanding of individual pain symptoms difficult. Objective measures of gastrointestinal signal processing in the brain, that could differentiate between people with functional GI disorders and those without the disorders, would help to measure symptoms such as intestinal pain. New imaging techniques offer the prospect of measurements independent of symptom reporting and the use of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in humans with GI disorders has become an active area of investigation. These tests identify areas of the brain that respond to stimulus by detecting an increase in blood flow.

Qasim Aziz from the University of Manchester, UK reviewed the concept of central sensitization. This can occur when an event, such as acid reflux injury to the esophagus or an infection in the gut results in sensitization of nerves in the spinal cord. This central sensitization can sometimes persist long after the original injury or inflammation has healed. When this happens, a sensation that was previously non-painful may now be perceived as painful. Additionally, Dr. Aziz discussed how emotional states can influence symptom severity in some individuals with painful functional disorders, such as IBS. Individuals with functional GI disorders with this type of response would likely benefit from appropriate psychological therapies.

Howard Mertz from Vanderbilt University, Tennessee discussed the effects of rectal distension on brain activation as measured with fMRI. Compared to controls, IBS patients had increased activity in areas of the brain (anterior cingulate and prefrontal cortex) associated with emotional arousal, pain memory and interpretation, and physiological response. Disruption of this circuitry may be a factor leading to increased pain in IBS.

Altered Bowel Function

Moderator: John Kellow M.D.;

Panel: Charlene Prather M.D., Juan Malagelada M.D., John Kellow M.D., Arnold Wald M.D.

Charlene Prather from St. Louis University reviewed the role of motility abnormalities in explaining symptoms of diarrhea and constipation among patients with functional bowel disorders. Clustered contractions, which are brief bursts of intestinal activity that occur in people both with and without IBS, may be

associated with abdominal pain and discomfort. High Amplitude Propagated Contractions are propulsive contractions that often are followed by an urge to defecate. These contractions appear to occur less frequently and of shorter duration in people with constipation. Efforts are being made to move toward non-invasive assessment of bowel motility and more standardized testing methods.

Juan Malagelada from Autonomous University of Barcelona, Spain discussed the possible role of physiological handling of intestinal gas in IBS. Those who usually do not experience bloating have greater efficiency in expelling gas compared with those with IBS or functional bloating who have altered gut motility that results in greater retention of gas. This effect, coupled with heightened sensitivity (which can be aggravated by large fatty meals) within the gut may doubly contribute to symptoms of pain and bloating. Treatments may be directed toward increasing the speed of movement through the gut (transit rate) of accumulated gas with medication or increasing flexibility (compliance) of the bowel wall, possibly with medication, to better accommodate the distension.

John Kellow from University of Sydney, Australia discussed how diarrhea is associated with more rapid transit related to altered motor activity, an exaggerated contractile response to food, CCK (Cholecystokinin, a hormone that stimulates intestinal motility) and other physiological stressors, increased sensitivity of the intestines (compared to patients with constipation), and possibly altered colonic and rectal muscle tone. Dietary restriction of poorly absorbed carbohydrates (e.g., fructose or sorbitol) may reduce diarrheal symptoms.

Arnold Wald from the University of Pittsburgh discussed the subgroups of constipation. About half of individuals reporting constipation to their physician have normal transit, or movement through the colon. People with uncomplicated constipation may benefit from dietary fiber and bulk laxatives such as psyllium or methylcellulose. Wheat bran is one of the most effective fiber laxatives, however not everyone responds well or tolerates fiber. Other laxatives may be useful when prescribed by a physician and used appropriately.

The remaining group of individuals reporting constipation have either colonic inertia (slow transit) associated with decreased colonic motility and decreased reactivity to meals and other bowel stimulants, or ineffective defecation (e.g., pelvic floor dyssynergia – failure to relax or inappropriate contraction of the muscles in the anal canal) which may respond to anorectal biofeedback treatment. It may be difficult for a physician to distinguish these subgroups based on the clinical presentation and tests may be required (e.g., colonic transit study, anorectal manometry).

CLINICAL APPLICATIONS

Introduction

Moderator: Nicholas Diamant M.D.;

Panel: Douglas Drossman M.D.

To provide a bridge between the previous basic topics and the clinical topics, Douglas Drossman from the University of North Carolina presented an overview of the functional GI disorders linking the newer physiologic observations on abnormal motility, heightened intestinal sensitivity (visceral hypersensitivity), inflammation, and psychosocial factors (e.g., life stress, abuse, coping) to clinical application using an integrated, biopsychosocial model. It is not helpful, and possibly harmful, to apply dualistic (separation of body from mind) and reductionistic (search for a single cause) concepts in the understanding and care of patients with these disorders. The functional GI disorders are disorders of brain-gut dysfunction. The central nervous system (CNS) can influence motility, sensation, secretion and inflammation, and gut disturbance that can in turn influence mental and emotional status. The clinician has the unique role to be able to elicit and integrate the dietary, lifestyle, gut physiology, and psychosocial features unique to each person, and to use this information through application of a multidisciplinary treatment approach. The importance of good interview skills and an effective physician-patient relationship was emphasized.

Functional GI Disorders

Moderator: W. Grant Thompson M.D.;

Panel: Ray Clouse M.D., Vincenzo Stanghellini M.D., Enrico Corazziari M.D., George Longstreth M.D., William Whitehead Ph.D.

This section presented a discussion of the functional GI disorders, broken down by organ group (esophageal, gastroduodenal, biliary, bowel, anorectal) consistent with the Rome II classification system.

Ray Clouse from Washington University School of Medicine, St. Louis discussed esophageal disorders, which are sub-categorized into five disorders. He pointed out that globus (sensation of a lump in the throat) and rumination syndrome are distinctly different from the remaining three disorders, functional chest pain, heartburn, and dysphagia (difficulty swallowing). What may be different from previous assumptions is that the latter three diagnoses overlap in development, and are not as easily distinguished physiologically.

Vincenzo Stanghellini from University of Bologna Medical School, Italy discussed the functional gastroduodenal disorders, which are most often seen in clinical settings as functional dyspepsia. This common disorder is characterized by upper abdominal pain or discomfort and may frequently co-exist with IBS. Functional dyspepsia is subclassified into ulcer-like pain (possibly responsive to proton pump inhibitors) and

dysmotility-like discomfort. Heartburn-like dyspepsia is no longer included as a sub-category.

Enrico Corazziari from Università La Sapienza, Rome discussed the functional biliary (gallbladder or sphincter of oddi) disorders and emphasized the importance of excluding other conditions (e.g. GERD, ulcer disease, functional bowel disorder), which may mimic the less common biliary disorders. He emphasized the value of using newer non-invasive tests to assess bile duct emptying, thereby reducing the risks related to invasive tests such as endoscopy and biliary manometry.

George Longstreth from Kaiser Permanente, San Diego discussed the functional bowel disorders, and in particular the evolution of the Rome II Criteria for IBS. Applying these criteria has simplified the diagnosis, though may be more restrictive than other clinical criteria

William Whitehead from the University of North Carolina discussed the functional anorectal disorders including fecal incontinence, pelvic floor dyssynergia, and functional anorectal pain (levator ani syndrome and proctalgia fugax). Unlike most functional GI disorders (though similar to the functional biliary disorders) diagnostic testing using physiological methods is important in confirming the diagnosis and directing treatment, which can include anorectal biofeedback.

General Principles of Treatment

Moderator: Anthony Lembo M.D.;

Panel: George Longstreth M.D., Douglas Drossman M.D.

There is a high cost, both social and economic, associated with the functional GI disorders. Health care utilization, which directly effect medical costs, is higher within this population than among the general population. Indirect costs include loss of productivity and loss of potential as patients miss work and school. Although slowly changing, a pervasive lack of understanding of functional GI disorders exposes individuals to the risk of unnecessary medications, invasive tests, and even surgeries. Not only is it necessary for physicians to understand the underlying pathophysiology of the disorders, but it is also necessary to understand the individual patient and the perspective they bring to their disorder. The physician-patient relationship is a key component to effective care and treatment. This "patient-centered" or "relationship-centered" approach requires a reshaping of a traditional one-sided physician directed procedure and this may be difficult given the time constraints of managed care. However, the cost savings associated with more effective treatment, greater patient satisfaction and adherence to treatment, and improved outcome outweighs the initial additional time spent establishing the patient-centered relationship.

George Longstreth discussed costs and economics of the functional GI disorders. The high health costs and unnecessary

procedures (including hysterectomy and abdominal surgery) may be avoided through physician education about diagnostic criteria. In addition physicians who address psychosocial factors may further reduce health care costs. The previous deficiencies caused by use of obsolete terminology of the International Classification of Diseases (ICD) coding methods are being modified by the Rome committees to reflect current classification terms for IBS and constipation. (Diagnostic coding is important for research and reimbursement purposes.)

Douglas Drossman from UNC emphasized the value of good communication skills. Building an effective physician-patient relationship depends on active listening, providing empathy, validating the patient's feelings, educating and reassuring through interactive dialog, and mutually arriving at treatments. This is associated with improved patient satisfaction, adherence to treatment, and improved clinical outcome.

Pharmacologic Treatment

Moderator: Ray Clouse M.D.;

Panel: Michel Delvaux M.D., Lionel Bueno Ph.D., Kevin Olden M.D.

Although treatment with medications is commonly offered to people with functional GI disorders, proven effectiveness is often lacking. Generally, a medication is prescribed or suggested to treat a predominant symptom (e.g. a laxative for constipation). While this may remain appropriate for transient or limited symptoms, the functional GI disorders often present multiple symptoms. Increased understanding of the processes involved in symptom generation is leading to fresh investigation of newer medications.

Michel Delvaux from University Hospital Rangueil, Toulouse, France discussed "traditional" pharmacological approaches in IBS. He noted that there are considerable differences between medication uses in North America (primarily antispasmodics [anticholinergics], antidiarrheals, and antidepressants) with Europe (wider variety of classes of smooth muscle relaxants and fewer antidepressants). Interestingly, an analysis of combined results from independent studies (meta-analysis) of drugs in IBS showed benefit with antispasmodics that are not available in the U.S.

Lionel Bueno from Institut National de la Recherche Agronomique, Toulouse, France discussed some of the newer GI pharmacological agents that are just coming out, or are under investigation. These include agents to treat multiple symptoms including diarrhea or constipation, and chronic pain. Examples include the 5HT₃ agents (e.g., Alosetron, a 5HT₃ antagonist recently withdrawn from the market; Cilansetron, another 5HT₃ antagonist; and Tegaserod, a 5HT₄ partial agonist soon to be reviewed by the FDA) and other agents (e.g., NK receptor antagonists, the gabapentinoids, and nerve-growth factors). Our growing understanding of the

neurotransmitters and receptors in these disorders has paved the way for all new classes of medications soon to be released.

Kevin Olden from Mayo Clinic Scottsdale, Arizona noted that antidepressants are off-label indications for the functional GI disorders. This is based on the rich nerve supply of the gut (which provides a therapeutic target for these drugs), the fact that antidepressants have an established track record with other chronic painful disorders, and in some instances the association of these conditions with coexisting psychological issues. There are now 3 meta-analyses that attest to the benefit of antidepressants in selected patients. While no particular drug stands out, the tricyclic antidepressants as a generic class, are better supported in the literature for their analgesic benefit, even in low doses.

Psychologic and Psychophysiological Treatment

Moderator: Francis Creed M.D.;

Panel: Brenda Toner Ph.D., Elspeth Guthrie M.D., Charles Burnett Ph.D., Lesley Houghton Ph.D., Philip Miner Jr. M.D.

Psychological treatments are sometimes part of an integrated approach to treating functional GI disorders. There are a variety of psychological and psychophysiological treatments available for the functional GI disorders, each with varying benefit depending on the skill of the therapist and motivation of the patient. Several methods were discussed in this section, and it was emphasized that the selection of treatment also depends on the particular needs of the individual patient.

Brenda Toner from the University of Toronto, Ontario began by discussing cognitive-behavioral treatment, which focuses on a collaborative interaction where the patient is informed about the techniques of the treatment, and efforts are made to demystify the therapeutic process and establish an egalitarian, participatory therapeutic relationship. This is an active form of treatment that requires high patient motivation. Group or individual treatment, tailored to personal needs can be provided. Cognitive behavioral therapy can be viewed as complementary to other medical treatments and combining the therapy with antidepressants was recommended in patients with more chronic or recurrent symptoms.

Elspeth Guthrie from the University of Manchester, UK discussed the use of psychodynamic-interpersonal treatment among patients with moderate to severe symptoms. Here a longer initial session focuses on addressing difficult feelings as they emerge in interpersonal relationships, and this information is used in later sessions to help the patient gain insight into these feelings. Ultimately, this can effect a positive change in feelings and relationship and improvement in GI symptoms.

Charles Burnett from the University of North Carolina, Chapel Hill discussed behavioral and stress management techniques. Biofeedback targets neuromuscular conditions, autonomic arousal, and vascular conditions, and can be used in situations like rumination and functional vomiting. Progressive muscle relaxation and breathing techniques are often used with other treatments, and are ways to reduce anxiety and arousal. Mindfulness stress reduction encourages and supports positive cognitive and behavioral lifestyle, and requires high motivation. Dr. Burnett also emphasized the importance of communicating with the patient on how these methods can break a vicious cycle of: symptoms → arousal/anxiety → hypervigilance to symptoms → increased symptoms → repetition of the cycle.

Lesley Houghton from University Hospital of South Manchester, UK discussed the work done primarily in the UK on hypnosis for IBS. Several studies have shown benefit, as evidenced by improvement in symptoms, motility, and rectal hypersensitivity, and reduced need for pharmacological treatment. The technique works best with “classical” IBS (i.e., chronic intermittent abdominal discomfort or pain, and associated bowel dysfunction) and is less effective with patients having more refractory or severe IBS/chronic pain or in males with predominant diarrhea.

Philip Miner Jr. from Oklahoma Foundation for Digestive Research discussed the use of biofeedback specifically for disorders of defecation (fecal incontinence and constipation), which are not readily amenable to medical or surgical treatments. Biofeedback is safe, easily applied, and when administered by a knowledgeable practitioner can lead to reduced symptoms via actual changes in physiological functioning, and ultimately improved clinical outcome.

The Symposium was designed to cover the recent major advances in the study and care of patients with functional GI disorders. In addition to the basic and clinical research presentations, a great deal of effort was placed on helping participants understand and care for the patient with functional GI disorders. Accordingly, workshops focused on patient care issues. In addition to the plenary sessions, Meet the Speaker Luncheons, and numerous workshops were held on topics such as design of treatment trials, interview techniques, patient education, alternative medicine-integrative medicine, and pediatric functional GI disorders, among others.

What also will be remembered is the remarkable energy among the participants over the course of the meeting, and the degree and quality of the scientific and social interactions that occurred in the plenary sessions, during breaks, and in the hallways and lounges, as well as during the wonderful social functions where ideas flowed among the participants long into each night. Nancy Norton, the staff of IFFGD, and the

symposium planning committee deserve our thanks for a remarkable Symposium. And for this field of functional gastrointestinal disorders, we believe the best is yet to come.

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