Report on the 5th International Symposium for Functional Gastrointestinal Disorders

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International Foundation for Gastrointestinal Disorders (www.iffgd.org)

Reading time:50 minutes

In April 2003 the International Foundation for Gastrointestinal Disorders (IFFGD) held its 5th International Symposium on Functional Gastrointestinal Disorders in Milwaukee, Wisconsin. Once again, the meeting attracted an international audience of investigators, clinicians, industry leaders, and regulators to hear presentations on a wide range of topics from various disciplines that relate to the functional gastrointestinal and motility disorders in adults and children. These topics included:

Outcomes of Pediatric Functional GI Disorders
Epidemiology/Genetic/Behavioral Factors
Basic Principles – Brain-Gut
Brain Imaging
Emerging Techniques to Evaluate and Treat Functional GI and Motility Disorders
Clinical Applications of Diagnosis and Treatment

Clearly much progress is being made in our understanding of the processes that underlie the functional GI and motility disorders and in treatment development. But we still have a long way to go. New technologies are beginning to help shape our understanding of mechanisms within the body, down to the cellular level, that interact within complex systems and lead to wellness or illness. Nonetheless, as science broadens and deepens our fundamental understandings, new questions arise; how do we use these new findings, apply them to the diagnosis and treatment of disease, and improve the quality of life of those affected. As this fundamental knowledge base expands, the need grows for continued and increased levels of research so that what science finds can be sorted out and translated into useful and safe therapies for patients.

A significant feature of this Symposium was the presentation of IFFGD's first research awards. Our goal is for this to be the first step in our contribution to the future development of new and innovative research. Awards were given in seven categories to basic and clinical investigators. We were honored that Dr. Allen Spiegel, Director of the National Institute of Diabetes and Digestive and Kidney Diseases, a division of the National Institutes of Health (NIH) was the keynote speaker at the awards presentations.

As an organization IFFGD has the goal to fund seed grants for developing areas of research and making it possible for investigators to eventually obtain major NIH supported research grants. We invite your participation.

Nancy J. Norton
President and Founder, IFFGD

Our understanding of the functional GI disorders is changing, including the mechanisms that contribute to symptom generation, methods of assessing and diagnosing the disorders, and approaches to treatment. As indicated by data presented across multiple disciplines at this symposium – basic, mechanistic, physiological, clinical, and epidemiological – the clinical expression of the functional GI disorders includes a composite of several physiological components. In effect, there is no one factor that appears to be involved in the development of the disorders (etiology), nor is there one specific treatment. Rather, health care professionals need to identify which of several factors are operative to explain the symptom presentation, and apply this information in a rational and cost effective manner that is specific to the individual's condition and personal needs.

Recent efforts have been directed toward identifying underlying subsets of the disorders (e.g., motor/motility dysfunction, visceral hypersensitivity, post-infectious IBS or dyspepsia, brain-gut dysregulation of pain) that might permit better targets for dietary, pharmacological, and behavioral treatments.

It is hard to believe how much has evolved since the first IFFGD Symposium in 1995. Our scope of knowledge of the functional GI disorders continues to grow, which makes this

column so much more challenging. This publication attempts to cover the highlights of the many topics and themes addressed in the general sessions.

Friday April 4

Outcomes of Pediatric Functional GI Disorders

Moderator: Paul Hyman M.D.; Panel: Paul Hyman M.D., Suzanne Nelson M.D., David Fleisher M.D., Heather Chial M.D., John Campo M.D., Vera Loening-Baucke M.D.

Do infants who spit-up (reflux or regurgitate) become adults with GERD? Are there factors that will perpetuate pediatric functional GI disorders into adult life? Can patient outcomes be influenced with medical, psychological, or combination treatment? Does child development have anything to do with symptom expression?

Routine activities of daily living may be curtailed in children with functional gastrointestinal disorders and in their families. The disabilities caused by functional disorders may equal or surpass those accruing from organic disease. How can a clinician improve the coping style of a child and family or caregiver to ease suffering?

Pediatric functional GI disorders or symptoms are common and bothersome, yet many clinicians overlook the application of practical and simple solutions to these disorders. The presentations in this session summarize what we have learned so far, and provide a base of knowledge for us to build upon.

Paul Hyman, University of Kansas Medical Center, began by addressing the importance of understanding the pediatric disorders from the standpoint of the **Biopsychosocial Model**. Much like in adults, proper diagnosis and management requires an integration of the biological, psychosocial (i.e., methods of coping), and social (e.g., family) components of illness and disease. The traditional biomedical model assumes that symptoms result from disease that is defined by structural anatomic or biochemical abnormality. The biomedical clinician's responsibility is limited mainly to finding the abnormality and curing the disease. But without an easily discovered abnormality to explain symptoms, as in the functional gastrointestinal disorders, the biomedical model fails. In contrast to the biomedical focus on disease, the biopsychosocial model is concerned with illness, the subjective sense of suffering or reduced capacity to function. In the past decade, even as medical technology has advanced rapidly, there has been an appreciation of the value of the multidisciplinary biopsychosocial team approach for managing both functional disorders and chronic disease.

Suzanne Nelson, Northwestern University discussed **Infant Regurgitation**. This occurs during brief periods (transient) of relaxation of the lower esophageal sphincter (LES). The LES is a band of muscles at the junction of the stomach and esophagus, which normally acts, in conjunction with the diaphragm, as a barrier to prevent reflux of stomach contents into the esophagus. Transient relaxation of the LES is a normal physiological phenomenon, and usually does not require undue concern or specific treatments more than repositioning the infant to keep the head elevated. However, children with gastroesophageal reflux disease (GERD) seem to have more frequent episodes of reflux or regurgitation (reflux of stomach contents into the mouth). Although regurgitation is common in the first year of life, emerging evidence indicates that it may develop into other problems in some infants. Those beyond the age of 6 months who regurgitate may be at risk for developing feeding problems as well as symptoms such as vomiting, nausea, abdominal pain, heartburn, or acid regurgitation.

David Fleisher from the University of Missouri School of Medicine discussed **Cyclic Vomiting Syndrome.** Symptoms are recurrent episodes of nausea and vomiting lasting hours to days with symptom free intervals between episodes. These disorders have clinical features similar to migraine and they may be related to each other. Recent studies link this condition to alterations in CRF functioning (CRF, or corticotropin releasing factor is a neuropeptide, or messenger cell released from nerve endings involved with activation of the body's natural stress response). If so, this may open the way to novel new treatments that act on these hormones or their receptors.

Heather Chial from Mayo Clinic Rochester discussed **Rumination Syndrome**. This disorder is characterized by effortless regurgitation of recently ingested food into the mouth followed by re-chewing and re-swallowing or expulsion. This is a learned maladaptive behavioral pattern that is usually treated through raising awareness of the rumination behavior and using diaphragmatic breathing exercises.

Recurrent Abdominal Pain (RAP) is defined as at least 3 episodes of abdominal pain over a 3 month period accompanied by impaired function. John Campo, University of Pittsburgh School of Medicine discussed its high prevalence, impact on the health care system, and association with other conditions. Recurrent abdominal pain is common, affecting between 7% to 25% of school-aged children and adolescents. The prevalence of RAP and irritable bowel syndrome (IBS) increases with age into adolescence. The condition accounts for a substantial number of pediatric office visits each year and an increased risk of unnecessary medical investigations and procedures. Studies suggest that young adults with a childhood history of RAP are particularly vulnerable to preoccupations with physical health and to anxiety and depressive symptoms and disorders.

Children presenting with RAP in primary care are significantly more likely to be functionally impaired and temperamentally anxious than pain-free controls, with four of five affected children suffering from an anxiety disorder, and RAP developing after the onset of an anxiety disorder significantly more often than would be expected by chance; two of five children with RAP in primary care suffer from a depressive disorder.

Children with RAP deserve careful assessment for coexisting (comorbid) anxiety and depressive disorders, which should be taken into account in clinical management and in the design of future studies of intervention. Long term (longitudinal), family, and psychobiological studies will be necessary to illuminate the nature of the observed comorbidity.

Dr. Campo's collaborators at the University of Pittsburgh include Drs. Carlo Di Lorenzo, Jeff Bridge, Boris Birmaher, Satish Iyengar, and David Brent, as well as Ms. Sarah Altman and Mary Ehmann.

Vera Loening-Baucke of the University of Iowa discussed **Functional Fecal Retention**, the infrequent passage of large stools and occasional fecal soiling; and **Functional Non-retentive Fecal Soiling**, frequent defecation in an inappropriate social context without physiological evidence for constipation or structural abnormalities.

Functional fecal retention is the cause of fecal soiling in 80–90% of children, while non-retentive fecal soiling occurs in 10–20% of children who suffer with fecal soiling. Functional fecal retention is the most common cause of fecal soiling in children; it is caused by constipation. It happens when a fecal mass accumulates in the rectum, after repeated attempts to avoid defecation, because of fears associated with defecation.

The clinical features and outcomes are similar in both conditions except for the clinical finding of large fecal masses and large bowel movements in fecal retention. One year after treatment started, 50% of children in both groups will have successful control of constipation and/or fecal soiling, and 40% will have completely recovered.

While it has been proposed that fecal soiling in children with non-retentive fecal soiling is a manifestation of emotional disturbances, Dr. Loening-Baucke and others have observed that coexisting behavior problems actually improve with treatment of the fecal soiling in both fecal retention and non retentive soiling conditions, which indicates behavioral problems are secondary.

After the pediatric lectures, the audience had the opportunity to participate in a number of workshops, which covered topics such as treating pain, effective communication with adolescents and families, treating eating difficulties, and advances in bowel management techniques.

Saturday April 5

Interrelated feedback circuits can influence brain processes and bowel functions.

Introductory Comments

Nancy Norton, Kevin Olden M.D., Stephen James M.D.

The next three days were devoted primarily to the adult functional GI and motility disorders. The general sessions began with introductions by Nancy Norton, President of IFFGD who welcomed the group and discussed the numerous activities of IFFGD and its role in encouraging federal support for research. Following this, Kevin Olden M.D., President of Functional Brain-Gut Research Group (FBG), also welcomed the group and mentioned the longstanding partnership of the two organizations and the rapid growth of professional membership in FBG over the last few years.

Stephen James M.D., Deputy Director of the Digestive Disease Division of the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) division of the National Institutes of Health (NIH) discussed the ways in which NIH helps support research in the functional GI and motility disorders. This includes the clinical trials program and new initiatives with Requests for Applications (RFAs – requesting grant applications for a research area), support for new Centers, and small grants. Notably, Nancy Norton of IFFGD is a member of the NIDDK Advisory Council, which meets three times per year to advise the NIDDK about its research portfolio.

Epidemiology/Genetic/Behavioral Factors

Moderator: Douglas Drossman M.D.; Panel: G. Richard Locke III M.D., Lin Chang M.D., Rona Levy Ph.D., Shin Fukudo M.D.

Investigators continue searching for ways to identify risk factors for functional GI disorders. Recent studies of the disorders suggest a genetic contribution. A variety of genetic factors may possibly effect the development or severity of symptoms. However, the genetic component does not fully explain occurrence of the disorders found in families and environmental factors must also be considered.

The sessions began with an overview of the **Epidemiology of Functional GI Disorders** by G. Richard Locke, Mayo Medical School Rochester. These disorders, including irritable bowel syndrome (IBS), dyspepsia, constipation, chronic abdominal pain, diarrhea, fecal incontinence, functional heartburn, and noncardiac chest pain are ever-present and frequently

experienced in the community. Their prevalence varies depending on the population under investigation and the criteria (e.g., Manning, Rome I, Rome II) used. People often meet criteria for more than one disorder and symptoms can change over time.

Functional GI disorders are associated with significant time lost from work. While a minority of sufferers seek care, in the aggregate this still results in considerable healthcare utilization. Future goals are to identify risk factors that can be modified and lead to cost effective treatment options.

Lin Chang, University of California Los Angeles School of Medicine discussed **Gender and Sociocultural Influences on Functional GI Disorders**. Sex and gender-related differences may play a role in the physiologic and symptomatic responses in functional GI disorders. Dr. Chang reviewed emerging data to help explain why women report more symptoms – of IBS, constipation, nausea, bloating; symptoms outside the intestinal tract (extraintestinal); and psychological symptoms – than men.

Studies examining sex and gender-related differences in chronic pain conditions such as IBS are only recently emerging. Multiple factors may contribute to these differences and may influence clinical responses and outcomes in patients with functional GI disorders. These factors include biologic, behavioral, psychological, and sociocultural differences between men and women.

Sex and gender differences have been reported in sensory perception, autonomic responses, and stress response reactivity, and even different levels of central nervous system (CNS) activation of pathways that modulate pain. Women with IBS appear to have greater visceral (GI) sensitivity while men with IBS show greater autonomic (sympathetic) responses. There appears to be sex and gender-related differences in CNS networks, which play a role in pain regulation, autonomic, and neuroendocrine responses

Rona Levy, University of Washington discussed **Early Learning and Heritability**. Every individual inherits from their parents certain traits imbedded in the genetic code. Genetic traits interact with environmental influences to help shape individuality. *Heritability* describes the extent to which a trait is influenced by our genetic makeup. With data mostly from her research group, Dr. Levy reported the emerging conclusion that both early learning and genetics play a role in the clinical expression of functional GI disorders in childhood. Specifically, Dr. Levy made the following points on the relationship between parent behavior and children's response to illness:

1. There is a relationship between parents' and children's disability and illness behavior from functional gastrointestinal disorders.
2. There is evidence for a relationship between a parent's response to their child's illness and a child's disability from that illness.

Preliminary work also suggests that there may be family interventions that help reduce the impact of functional GI disorders on children.

Shin Fukudo, Tohoku University School of Medicine, Japan discussed **Possible Genetic Markers in Functional GI Disorders and Treatment Response**, an emerging area of research. For some time it has been believed that brain-gut interactions – autonomous activity in the GI tract and central nervous activity that influences bowel function in response to stressors – play a major role in the origin and development (pathogenesis) of irritable bowel syndrome (IBS). Studies suggest that IBS patients have hyper-reactive bowels and unusually stress-sensitive brains.

Studies by Dr. Fukudo's group include recent use of models to study serotonin (5-HT) reuptake transporter (SERT) genes, cross-cultural studies of 5-HT agents, and the effects of variations in the regions of the DNA strand that are the beginning of a gene (gene promoter regions) on one's responses to stress. Sensitization of the nerves (neurons) in the brain and the gut (intestines) may be due to a genetic effect as well as an acquired effect (resulting from a stimulus). More investigation on exploring genetic markers and therapeutic responses is warranted.

Basic Principles – Brain-Gut

Moderators: Emeran Mayer M.D., Robin Spiller M.D.; Panel: Robin Spiller M.D., Jackie Wood Ph.D., George Chrousos M.D., Yvette Taché Ph.D., Lisa Goehler Ph.D., G.F. Gebhart Ph.D., Emeran Mayer M.D.

The *brain-gut axis* refers to the continuous back and forth interactions of information and feedback that take place between the gastrointestinal tract, and the brain and spinal cord (which together comprise the central nervous system). These interrelated feedback circuits can influence brain processes and bowel functions – affecting pain perception, thoughts and one's appraisal of symptoms, gut sensitivity, secretions, inflammatory responses, and motility. The brain-gut circuits can be activated by an external or internal factor or stimulus that makes a demand on the system, such as a stressful event, an injury, an emotional thought or feeling, or even the ingestion of food. Symptoms of functional GI disorders may result from a maladaptive response to stimuli at some point within the complex interactions that take place along the brain-gut axis.

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. *Translational science* converts basic science discoveries into the practical applications that benefit people.

One of the more exciting areas of recent research relates to the basic and translational aspects of the effects of stress on inflammation, *cytokine* and immune modulation, and pain. (Cytokines are a type of protein released by cells of the immune system, which act through specific cell receptors to regulate immune responses.) This series of presentations address three important research areas in the field of functional GI disorders, which have recently attracted considerable attention: the role of immune activation in the gut and the interactions of the gut immune and nervous systems; the role of the central nervous system in the regulation (modulation) of pain perception (nociception); and the emerging field of animal models with relevance for functional GI disorder research. This section demonstrates the rapid progress seen in the last few years in better understanding of basic mechanisms, in particular the neuroimmune interactions underlying symptom generation in patients with "functional" GI disorders.

There are immune responses to infections. To defend itself from a foreign substance or invader, such as a bacterium or virus, the body mounts an immune response controlled by the brain. There needs to be a balance between infection and the body's immune response; the immune system needs to turn on and turn off at the right times to destroy the invader but not to the degree that it may harm healthy tissue.

Robin Spiller, University Hospital, Nottingham, England began the session by noting the difficulty in separating disorders of structure ("organic") from disorders of function. He noted, *"The difference is based on how high the power of your microscope is."* This was elaborated upon in his presentation on **Post-infectious Functional GI Disorders**. It has been observed that IBS-like symptoms, that persist for 6 months to a year or longer, may appear after a bout with an acute infection in the gastrointestinal tract (e.g., food-poisoning). This is termed, "post-infectious IBS." A study by Gwee et al showed that the presence of unusual or amplified life stress at the time of onset of infection increased the chances of developing IBS symptoms. Inflammation persisted in patients with IBS-like symptoms but did not in patients whose symptoms resolved. This suggests that the brain's management of certain stressful stimuli (i.e., psychologic distress) affects the brain-gut system's ability to inhibit inflammation.

It has frequently been observed that some individuals with more severe symptoms of IBS have coexisting psychologic distress. Stress has been thought to influence health-care seeking behavior, either by increasing motility, visceral hypersensitivity or inflammation, or by enhancing one's perception of gut symptoms, all of which lead to a greater need to seek care for them. The concept of *post-infectious IBS* suggests that in some circumstances stress (the biological process by which the body adapts in response to a stimuli) may influence symptoms.

An initial response to an infection in the gastrointestinal tract can involve the neurotransmitter, serotonin, which acts as a messenger (mediator) to cells involved with the immune response. Immune cells – mostly in the blood, but also in the lymphatic system – enter the infected area and remove the invader. Additionally, the body adaptively removes the infection (e.g., via vomiting or diarrhea – normal beneficial responses that help the body expel an infecting organism). Persistence of the underlying inflammatory response may lead to post-infectious disorders of function. A variety of neuroimmune responses can lead to intestinal over-

We often talk about how the brain can affect immune function . . . but the reverse is also true, immune activation can influence brain function.

responsiveness (sensitization) and other clinical effects.

These responses include direct toxicity to nerves that influence intestinal contractions, alteration in gut immune activation, abnormalities of serotonin metabolism, and persisting low-grade inflammation. IBS developing after infective gastroenteritis is associated with subtle increases in enteroendocrine and chronic inflammatory cells in the gut mucosa. The net effect may be to increase serotonin availability in the gut and enhance secretion and propulsive motility patterns. Serotonin antagonists may be beneficial in such patients.

Notably, the concept of "post-infectious IBS" has grown to include studies of their application in post-infectious gastroparesis and dyspepsia.

Major inflammatory responses have not been observed in most IBS patients. However, in some studies subtle changes associated with inflammation have been noticed, such as increased presence of mast cells (a type of immune system cell present in blood and tissue). Jackie Wood, Ohio State University College of Medicine discussed the **Effects of Inflammation on the Gut Enteric Nervous System**, specifically noting the importance of mast cell *degranulation* (the release from within the cell of granules, or small sacs, containing chemicals that can digest microorganisms and fight infection).

In tissue mast cells accumulate around nerve endings of nerves that contain the neurotransmitter serotonin. The release of substances that can induce activity in excitable tissue (i.e., histamine, Interleukin-1 (IL-1), and bradykinin) by mast cells can affect receptor and neurotransmitter function in the enteric nervous system – the part of the autonomic

nervous system that controls function of the gastrointestinal tract. In other words, when mast cells in the intestinal lining empty their contents in response to an infection, they activate nearby nerve endings. In a subgroup of patients, this can have significance in terms of resulting clinical consequences of diarrhea and abdominal discomfort.

Yvette Taché, University of California Los Angeles discussed **Stress and Inflammation**. The experience of stress is an adaptive behavior common to all living organisms. The activation of corticotropin releasing factor (CRF) signaling pathway, is the major mediating mechanism involved with the body's stress response system in which gastric emptying is inhibited (with possible loss of appetite) while colonic motor activity is stimulated (producing a loose stool or a sensation of bowel urgency). There is growing evidence that activation of these CRF pathways impacts on inflammation, autonomic nervous system function, immunity, and clinical behavior or illness, all of which may be linked to the pathophysiology of the functional gastrointestinal disorders.

While we often talk about how the brain – influenced for example by arousal and/or psychosocial factors – can affect immune function, the reverse is also true. Immune activation, following infection for example, can influence brain function. Lisa Goehler, University of Virginia discussed **Cytokines and Vagal Afferents: Immune Signaling to the Brain**. *Cytokines* are substances that are produced by white blood cells to regulate certain functions during inflammatory and immune responses. The *vagus* is a nerve made of both sensory and motor fibers that innervates nearly every internal organ. The gastrointestinal (GI) tract, along with the lungs and liver, is an area of tissue that most commonly comes in contact with microorganisms (pathogens), such as bacteria or viruses, capable of activating an immune response. Cytokine mediators activate neurons that convey messages from tissue to the brain (afferent neurons) through the vagus nerve. The GI tract is richly supplied with *vagal afferents* that can signal immune activation in the tissue.

This process may underlie the mechanism that causes individuals to feel sick. The concept of "sickness symptoms" is not always recognized. The cytokine inflammatory and immune mediators distributed throughout the body (peripheral), which appear to interact through vagal pathways, have systemic effects that manifest as symptoms in the body. (*Mediators* are substances released from cells to regulate immune responses.) Such symptoms include fever, increased sensitivity to pain, loss of appetite, and decreased desire for social interaction. The process may provide the basis for a role of the vagus as an interface between the site of the immune response and the brain that results in symptoms of altered mood, including anxiety or depression, that are sometimes associated with gastrointestinal disease.

Gerry Gebhart, The University of Iowa discussed the **CNS Modulation of Visceral Nociceptive Responses**. The central nervous system (CNS) is composed of the brain and spinal cord. The brain interprets and influences our perceptions of the pain sensation signals transmitted from the gut (visceral nociceptive responses) to the spinal cord and then to higher centers. Several structures in the brain (periaqueductal gray, dorsolateral pons, and rostroventral medulla) can facilitate or inhibit signals sent to the CNS and influence the perceived discomfort, or even whether the signals are experienced as pain. Inflammation of the bowel can produce increased sensitivity to pain or enhanced intensity of pain sensation (hyperalgesia) via increased activity of certain cells (for example, those that contain nNOS) in these higher brain modulatory centers.

To close the Brain-Gut sessions, Emeran Mayer, University of California Los Angeles discussed **Evolving Animal Models of Visceral Hypersensitivity**. In contrast to most other disorders of the digestive system, functional disorders of the gut continue to be defined by symptom criteria rather than by biological markers. Realistic animal models of functional gastrointestinal (GI) disorders in which to test hypotheses have not been available until recently. While it is unlikely that there will ever be an animal model to replicate all complexities of the human functional GI disorders, animal research is likely to help us understand some of the key underlying mechanisms responsible for symptom generation. This includes over-responsiveness of central stress circuits to visceral and psychological stimuli, resulting in altered autonomic responses (motility, secretion), increased pain sensitivity (visceral hypersensitivity) and possibly altered immune function of the gut. Future studies with genetically altered (i.e., transgenic) mice that become models for studying specific human diseases and their treatments may further increase our understanding of these mechanisms.

Very recent imaging studies have begun to explore the mechanisms of symptom generation and treatment response in GI disorders.

Brain Imaging

Moderator: Reza Shaker M.D.; Panel: Reza Shaker M.D., Bruce Naliboff Ph.D., David Thompson M.D.

Only recently, significant progress has been made in brain imaging technology, which allows noninvasive imaging of brain function. Using this technology helps to understand the relationships between specific areas of the brain and the functions they perform in response to stimuli. Common brain imaging procedures include computed tomography scan (CT

Scan), positron emission tomography (PET Scan), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), and angiography.

In just the past 5–6 years, functional brain imaging has taken its place in the study of the role of the central nervous system (CNS) in visceral pain and other gastrointestinal functions. This field of research is still young and developing. Information obtained is dependent upon the accuracy and sensitivity of various imaging techniques and the reliability of unbiased protocols. Adding difficulty to the field is the inherent influence of individual perception and its consequences on the human brain processing function.

Reza Shaker, Medical College of Wisconsin began the session with a presentation on the **Methodology of Brain Imaging Systems.** Computer assisted imaging techniques allow evaluation within the living body (in vivo) of blood flow and metabolism in the brain, and imaging of the nerve cells that receive and transmit sensory information (neuroreceptors). Among the various techniques discussed was the technology and application of positron emission tomography (PET), which measures changes in cerebral blood flow using radioactively labeled substances that have been injected into the body to provide an image of brain activity and function.

Also discussed was functional magnetic resonance imaging (fMRI), a newer method of scanning the brain's activity that needs no radioactive materials and produces images at a higher resolution than PET. It measures changes in blood flow to particular areas of the brain (hemodynamic changes – e.g., deoxygenation of blood) providing an indirect marker of neuronal activity. These measurable changes are the current basis for the imaging commonly used in brain-gut axis research.

Bruce Naliboff, University of California Los Angeles discussed brain imaging **Findings in the Lower GI Tract**. It has been only six years since the first published study using functional brain imaging to examine visceral sensation appeared in scientific literature. A small but growing number of studies have been published. Most of these studies have focused on describing what areas of the brain seem to activate in response to a colon stimulus such as balloon distension, and how these areas differ between individuals with and without symptoms. Very recent studies have begun to explore the mechanisms of symptom generation and treatment response in GI disorders.

Although the technology is not yet refined enough to give us completely consistent information, several patterns emerge with regard to the interpretation and memory (central representation), and regulation (i.e., modulation – the brain's ability to enhance or inhibit neural messages) of visceral signals. One area of the brain (the anterior cingulate cortex or ACC) is consistently activated along with discomfort and pain that arises in internal (visceral) organs, such as the GI tract.

Another area (the somatosensory cortex) is more relevant to somatic pain related to tissue damage or stimulation of the skin, muscles, or bones. Still another part of the brain (the insula) registers information on intensity of pain from both somatic and visceral sources. In addition, lower GI signals more than upper GI signals lead to greater activity in frontal areas of the brain associated with negative emotions, as well as in pathways from the brain to visceral organs such as the gut (autonomic regulation), and in areas that pertain to mood or emotional states (affective regulation).

Central activation – the rapid short-term biophysical and biochemical changes in neurons that make possible such activities as thought, perception, and voluntary movement – appears to increase as intensity of stimulus increases. However, repeated exposure can lead to adaptation, as the brain adjusts to the stimuli, with decreased central activation. In studies, IBS patients are differentiated from healthy controls by showing greater activation of an area of the brain essential for conscious pain (the anterior mid-cingulate component of the anterior cingulate cortex). It is in this region in the brain where the systems concerned with emotion or feeling, attention, and working memory interact. On the other hand, controls (and also patients with inflammatory bowel disease who have adapted to the visceral signals) show greater activation of the descending pain inhibitory pathways in areas of the brain involved in the suppression of pain (in the brain stem in the region of the periaqueductal gray).

In summary, brain imaging is a rapidly growing new technology for studying how pain is processed as well as how pain treatments may work. Although there are many similarities between the brain response to visceral and somatic pain some consistent differences have emerged with visceral stimulation showing greater affective responses. Patients with IBS show some differences in how their brains respond to a visceral event and these effects may relate directly to both the hypersensitivity and hypervigilance associated with this disorder.

David Thompson, University of Manchester, England discussed **Findings in the Upper GI Tract** using brain imaging procedures such as PET, fMRI, and magnetoencephalography (MEG), which is a non-invasive technique for examining the electrical activity of the central nervous system. The findings in the esophagus are similar, as described in the preceding paragraph with regard to central representation, as is found in the lower gut. Furthermore, like the lower GI system, greater stimulus intensity leads to greater activation of cognitive, sensory, and motor areas of the brain. Additional observations include abnormalities in the swallowing center among patients who

suffer the sensation of food sticking in the esophagus (dysphagia) after a stroke.

Emerging Techniques to Evaluate and Treat Functional Gastrointestinal and Motility Disorders

Moderator: Arnold Wald M.D.; Panel: Ravinder Mittal M.D., Richard McCallum M.D., Charlene Prather M.D., Arnold Wald M.D.

In this session new techniques were reviewed for evaluating and treating functional gastrointestinal and motility disorders from the esophagus to the anorectum. Ravinder Mittal, University of California San Diego began with a presentation on **Esophageal Symptom Assessment**. He discussed some of his research showing that chest pain and heartburn may relate to a variety of stimuli – not just acidity from the back flow of stomach contents (reflux). Other stimuli may include distension within the esophagus with reflux, abnormal movement (primary motor effects) including sustained contraction of the outer muscular layer (longitudinal muscle) of the esophagus, and exaggerated perception within the tissue lining the esophagus (mucosal hypersensitivity) to esophageal distension.

Richard McCallum, University of Kansas Medical Center discussed the use of **Electrogastrography and Gastric Stimulation**. Electrogastrography (EGG) is a method for detecting stomach problems that measures the electrical activity (the gastric slow wave) in muscle in the stomach. The EGG abnormalities that can be detected include: decreased postprandial power of the signal; an increased frequency in stomach electrical signals (tachygastria); and a decreased frequency in the gastric slow wave (bradygastria). All of these abnormalities may be associated with delays in gastric emptying. The clinical application for EGG is growing, as related to the assessment of patients with gastroparesis, a disorder where food moves out of the stomach more slowly than normal; assessment of functional dyspepsia; as well as preparatory information for gastric electrical stimulation. This is a treatment method that uses electrical stimulation to reduce the symptoms of gastroparesis, specifically double-blind and open labeled data show that gastric electrical stimulation can improve symptoms of nausea, vomiting, and quality of life, (but not gastric retention), in patients with gastroparesis (diabetic, idiopathic and post-gastric surgery/vagotomy).

Charlene Prather, St. Louis University School of Medicine discussed the variety of **Gastrointestinal Functional Testing** available including various tests of movement through the GI tract (transit). *Breath tests* measure levels of hydrogen gas exhaled after ingestion of a carbohydrate while measuring the time it takes for levels to change. *Scintigraphy* is an imaging method in which a mild dose of a radioactive substance is swallowed that shows how material moves through the GI tract. A *colonic marker study* is a simple test that measures the movement of substances that enter and leave the colon over time, generally after ingestion of a capsule containing a number of tiny rings that appear on two or three x-rays taken over the next several days.

Arnold Wald, University of Pittsburgh Medical Center ended this session by addressing **Anorectal Assessment and Treatment**. Assessment is used to suggest appropriate treatment and help predict chances of success. In recent years ultrasound (an imaging method in which high-frequency sound waves are used to outline a part of the body) of the anal canal and anal sphincter muscles (anal endosonography) has enhanced our understanding and evaluation of fecal incontinence. It is particularly helpful in detecting defects in sphincter muscles. Pelvic MRI is a more recent method of examination that can recognize diminished anorectal muscle tone (atrophy) and can provide more information about the structure and function of these muscles.

Treatment approaches to incontinence including biofeedback, surgery, and a new method of sacral stimulation were also discussed. While biofeedback has been reported to be effective in many patients, its use remains controversial because of flaws in existing studies. Surgery appears to benefit some but not all patients with fecal incontinence, depending on the underlying defect.

As assessment methods improve, more accurate evaluation should improve the selection and prognosis for surgical patients. Sacral nerve stimulation appears to be a promising new approach to treat fecal incontinence for those who do not respond to other therapies. It involves electrical stimulation of the sacral nerve, which is involved in continence function. Improved evaluation methods are still needed to identify which patients might benefit from this procedure.

Sunday, April 6

Clinical Application

Moderator: Kevin Olden M.D.; Panel: Douglas Drossman M.D.

In order to bring together the diverse number of research developments relating to the functional GI disorders into a conceptual framework that can be applied in clinical practice to the treatment of patients, Douglas Drossman, University of North Carolina, Chapel Hill discussed the **Integrated Approach to Functional GI Disorders**. Evolving concepts have moved our view of these disorders from solely disorders of motility to an integrated understanding that involves several components, including enhanced motility, over-responsiveness (visceral hypersensitivity) within the gut, inflammation, and alterations in brain-gut regulation.

Within this framework, psychosocial factors may interact with other mechanisms such as physiologic abnormalities in the bowel, central nervous system disturbances, and genetic factors, which then affect the experience of a functional GI illness and the treatment outcome. The emphasis is to understand that the changes or alterations in function (pathophysiology) of these disorders are multiple and overlapping. In time there will be the clearer separation of physiologically meaningful subgroups (e.g., post-inflammatory, motility, central nervous system modulation) that will be receptive to more specific treatments. The clinical expression of these disorders must be understood from a biopsychosocial framework rather than looking for one cause and specific treatment.

Evolving concepts have moved our view of functional GI disorders from solely disorders of motility to an integrated understanding that involves several components.

Functional Gastrointestinal Disorders
Moderator: W. Grant Thompson M.D.; Panel: Enrico Corazziari M.D., W. Grant Thompson M.D., Ray Clouse M.D., George Longstreth M.D., Arnold Wald M.D., Gregor Lindberg M.D., Nicholas Talley M.D.

This session was devoted to the history, application, and controversies related to the *Rome Criteria*, a symptom based method of diagnosing functional GI disorders. The introduction and use of these criteria in clinical trials has shifted the classification of these disorders from physiological abnormalities of motility to symptoms. Certainly this approach has its opponents and is not without limitations.

After a brief eulogy to Aldo Torsoli M.D. the founder of the Rome process, Enrico Corazziari, Università Degli Studi "La Sapienza," Roma, Italy and W. Grant Thompson, University of Ottawa, Canada and the first Chair of the Rome IBS committee gave a presentation on the **History and Concepts of Symptom-based Criteria**. The Rome Criteria, developed by consensus of an international group of specialists in the field of functional GI disorders, first offered a method to make a "positive" diagnosis of these disorders based on symptom expression, replacing the older "negative" diagnostic view that regarded the functional disorders as "diagnoses of exclusion"; that is, diagnosed only after testing excluded many organic disorders that could possibly cause the symptoms. (This older view even led some to question the validity of the disorders.)

Over the last decade, the symptom-based Rome Criteria have become the basis for diagnosing the functional GI disorders for clinical studies and treatment trials. However, within clinical practice, these criteria are not as well utilized, and studies suggest that the current Rome Criteria may be less sensitive (for IBS) than other criteria or general clinical judgment. This has led to the use of simple markers suggestive of organic disease (e.g., unexplained weight loss, blood in the stool, fever, an abnormal physical examination, an abnormal blood test, nocturnal symptoms that awaken the patient, or a family history of cancer or inflammatory bowel disease) that when absent, increase the accuracy of the Rome Criteria. There is now greater interest in identifying physiological or biological markers that may further enhance diagnostic accuracy.

Following this, the main subgroups of the **Rome II Classification System** were presented by the Rome II subcommittee chairs or co-chairs: *Functional Esophageal Disorders* by Ray Clouse (chair), Washington University School of Medicine, Missouri; *Functional Gastroduodenal Disorders* by Vincenzo Stanghellini (chair), University of Bologna, Italy; *Functional Biliary Disorders* by Enrico Corazziari (chair), Università Degli Studi "La Sapienza," Italy; *Functional Bowel Disorders* by George Longstreth (co-chair), University of California San Diego; and *Functional Anorectal Disorders* by Arnold Wald (co-chair), University of Pittsburgh Medical Center.

Perhaps the highlight of this session was a spirited debate initiated by Gregor Lindberg, Karolinska Institutet, Sweden who presented the **Case for a Physiological Based Classification System**. Dr. Lindberg presented the results of a consensus group that established a classification system for the functional GI disorders based on intestinal motor (motility) dysfunction as an alternative to the Rome symptom-based classification system. However, he noted that conditions like irritable bowel syndrome (IBS) and functional dyspepsia do not fit this physiological based system. (Some have misinterpreted this statement to mean that IBS and functional dyspepsia do not exist!) There are now newer diagnostic technologies that continue to help expand knowledge of gut motor function and thus have led to this new classification system.

Dr. Lindberg emphasized that the measurement studies (modalities) needed for a motility based diagnosis include *contrast radiology* in which a contrast material (i.e., Barium) is used to coat the rectum, colon, and lower part of the small intestine so they show up on an x-ray; *scintigraphy*, an imaging method in which a mild dose of a radioactive substance is swallowed to show how material moves through the GI tract; and *manometry*, a test that measures pressure or contractions in the intestinal tract.

These can be used to identify four classes of diagnoses: 1) well defined entities (e.g., slow transit constipation); 2) entities with variable dysfunction/symptom relationships (e.g., gastroparesis); 3) questionable entities (e.g., hypertensive [high] lower esophageal sphincter pressure); and 4) entities associated with behavioral disorders (e.g., rumination syndrome). Dr. Lindberg also pointed out the possibility that

some “functional” disorders may later be found to have neural structural abnormalities when full thickness intestinal tissue samples (biopsies) are undertaken. In order to advance knowledge in this field we need to improve our methods for studying the relation between functional and structural changes in patients with unexplained gastrointestinal symptoms.

Following this, Nicholas Talley, Mayo Clinic Rochester gave a **Rebuttal in Support of the Rome Criteria**. He favored the idea that there is a “disconnect” between symptoms and physiological abnormalities for many of the gastrointestinal conditions; that symptoms are generated by abnormal functioning rather than by observable anatomical change. Currently, the disorders underlying the vast majority of gut symptoms are not now understood. Dr. Talley contended that what is needed is a classification system such as the Rome Criteria for the patients who present symptoms, but where the causes and mechanisms of their symptoms are unknown.

General Principles of Treatment

Moderator: Nicholas Talley M.D.; Panel: Nicholas Talley M.D., Douglas Drossman M.D., Christine Dalton PA-C, Charlene Prather M.D.

This session was a prelude to the more specific treatments to be presented on the following day. The functional gastrointestinal disorders are common, and place an immense burden on health care services. For example, IBS affects approximately 15% of the U.S. population. Seventy percent of IBS patients have mild severity symptoms and are seen in primary care practice settings, 25% of patients have moderate severity symptoms and are treated in gastroenterology practices, and the remaining 5% of patients with severe symptoms seek treatment in specialized clinics of different disciplines. Yet there is no well-documented information on whether the health care methods and services at these levels of severity are the proper ones.

Issues of care that warrant exploration include how best to investigate and manage the treatment of individuals with these disorders in the most effective and cost-efficient way. The objective of this session was to provide a view of incorporating and utilizing new and different healthcare services with established services in the management of this large population of patients.

Nicholas Talley, Mayo Clinic Rochester spoke on the **Burden of Illness and Health Care Costs**, which emphasized the very high monetary cost and impact of these disorders to society. It is estimated that in the U.S. alone the functional GI disorders place a $20 billion annual cost on the health care system, including indirect costs of work absenteeism.

Douglas Drossman, University of North Carolina, Chapel Hill discussed **The Therapeutic Value of the Medical Interview**, and emphasized that data from primary care studies now show that active listening, facilitating the individual patient’s expression of thoughts and feelings, and working together on a mutually agreed on plan of care is associated with greater patient satisfaction, adherence to treatment, and symptom reduction. It also leads to improvement in health outcomes and reduced health care utilization. Dr. Drossman also provided guidelines for physicians on how to more effectively implement a physician-patient interaction, which include:

1. Listen Actively
2. Be Aware of Questioning Style and Non-Verbal Messages. “It’s not what you say, but how you say it that makes the difference”
3. Elicit, Identify, and Communicate the Agenda(s). (Both the patient’s and the physician’s) and Work Toward a Mutually Specified Set of Goals
4. Acknowledge the Pain and Provide Empathy
5. Validate the Patient’s Feelings
6. Don't Overreact
7. Educate (i.e., elicit the patient’s understanding; address misunderstandings; provide information that is consistent with the patient's frame of reference or knowledge base; and check the patient’s understanding of what was discussed)
8. Reassure (Identify the patient’s worries and concerns; acknowledge or validate the concerns; respond to specific concerns; and avoid “false” reassurances [e.g., *“Don’t worry, everything’s fine”*] particularly before the medical evaluation is complete, since this may be viewed as a doctor’s lack of commitment)
9. Negotiate
10. Help the Patient Take Responsibility (e.g., rather than asking a patient: *“How is your pain?”* one might ask: “*How are you managing with your symptoms?”* The former question tends to leave the responsibility for dealing with pain with the physician, while the latter acknowledges the patient’s role)
11. Establish Boundaries (This would include setting time limits and guidelines for narcotic use, etc.)

Christine Dalton PA-C, University of North Carolina Chapel Hill discussed the **Role of the Physician Assistants** and other medical care extenders. These are relatively new professions in health care. Physician assistants and nurse practitioners are fully trained professionals who may work dependently or independently with their supervising physicians. They are trained to provide diagnostic and therapeutic services, while taking on other tasks such as providing health education and follow-up phone counseling. The use of physician extenders has been shown to ease physician workload and increase

Drugs, which act on sensory pathways that modify pain perception or that affect gastric emptying and colonic transit . . . are currently undergoing active investigation.

patient satisfaction. Employing mid-level practitioners can result in an expanded practice, greater practice efficiency, greater access to care for patients and high patient acceptance. Physician extenders can increase productivity in a practice while being very cost effective. Although most physician extenders currently practice in the United States, other countries are interested in developing similar programs.

Charlene Prather, St. Louis University School of Medicine followed up with an elaboration on the **Models of Health Care Delivery**. Family nurse practitioners and physician assistants can assume many different types of functions and be utilized as part of a multi-disciplinary healthcare team approach. These *physician extenders* are clinicians who can assist and augment the work of the supervising physician according to interests and needs.

Monday, April 7

Pharmacological Treatment

Moderator: Lionel Bueno Ph.D.; Panel: Michel Delvaux M.D., Ph.D., Lionel Bueno PhD, Nicholas Talley M.D., Kevin Olden M.D.

Recent improvements in our knowledge of the abnormalities of digestive function have led to new and more selective treatment of symptoms and improved management of pain. Data gathered in laboratory and clinical studies suggest that alterations in perception, affecting pain or discomfort in the digestive tract, originate not just in the nerve pathways to the gut, but also in the central nerve pathways that process information sent from the gut to the brain. Based on this approach, new treatments have been created or are being developed that target several neurotransmitters having a role in these processes.

The pharmacological treatment session began with a presentation by Michel Delvaux, University of Toulouse, France on **Antispasmodics.** These are drugs that inhibit smooth muscle contraction in the gastrointestinal tract. By reducing spasms they have the potential to reduce abdominal pain. Dr. Delvaux emphasized that there is empirical evidence from basic and physiological studies for the clinical usefulness of these medications. However, many past treatment trials have had methodological limitations. Some recent *meta-analyses* (a method of summarizing previous research by reviewing and combining results from multiple studies) have supported the value of these agents in treating irritable bowel syndrome, although many of the agents studied are not available in the U.S.

Lionel Bueno, Institut National de la Recherché Agronomique, France presented information on the receptor effects of the **Peripheral Serotonergic Agents**. Serotonin (5-hydroxytryptamine, or 5-HT) is a chemical *neurotransmitter* (a chemical in the nervous system that helps transmit messages). It is found in three main areas of the body: the intestinal wall, blood vessels, and the central nervous system. Specific serotonin receptors appear to be important in gastrointestinal motility and sensation. *Receptors* are structures on the surface of cells or inside cells that selectively receive and bind a specific substance, such as a hormone or a neurotransmitter. A receptor *antagonist* inhibits or blocks this action and a receptor *agonist* stimulates this action. The new generation of serotonergic drugs being evaluated to treat IBS either block or stimulate the action of serotonin at specific receptor sites that affect the GI tract.

Serotonin (5-HT) interacts with an array of receptors. Many types of serotonin receptors have been identified in humans, each having a different role. These receptor sites are numbered. (For example, serotonin receptor site 1 is labeled 5-HT1, site 2 is 5-HT2, etc.) There are four known major serotonin receptor sites that can be affected in the gut – 5-HT1, 5-HT2, 5-HT3, and 5-HT4 – and each may have up to 7 sub receptors. Increased understanding of the location and actions of these receptors has opened the door to newer treatments of which alosetron (a 5-HT3 antagonist) and tegaserod (a partial 5-HT4 agonist) are currently on the market.

Other 5-HT3 antagonist and 5-HT4 agonist compounds are being investigated, as well as one compound with mixed properties. In addition, some medications being used for other conditions (e.g., sumatriptan for migraine and buspirone for anxiety) act at 5-HT1 receptors and can possibly reduce fullness/discomfort after eating (post-prandial).

Nicholas Talley, Mayo Clinic Rochester discussed **Other Peripherally Acting Agents** that work on different receptors. In addition to acting on nerves that control voluntary skeletal muscles, peripheral agents act on the nerves that facilitate automatic, or involuntary activities of the smooth muscles that line the blood vessels, stomach, digestive tract, and other internal organs. These include drugs that act on sensory pathways to modify pain perception or that affect gastric emptying and colonic transit. Most of these agents are not available or are currently undergoing active investigation. (Examples include opioid kappa receptor agonists, such as fedotozine and asimadoline; alpha2 receptor agonists such as clonidine and lidamidine; cholecystokinin antagonists such as dexloxiglumide and loxiglumide; and tachykinin receptor antagonists that act on neurokinin A and neurokinin B receptors.)

Kevin Olden, Mayo Clinic Scottsdale discussed the **Psychopharmacological Agents**. Results of studies of antidepressants for the treatment of irritable bowel syndrome have reported significant improvement in reducing abdominal pain as well as other IBS symptoms, such as diarrhea, constipation, bloating, nausea, or urgency. Dr. Olden emphasized that it is not entirely clear why antidepressants

work for the treatment of IBS symptoms; they may be influencing motility, have peripheral effects on pain, or modify nerve functions that influence pain perception in the brain (central neuromodulation). Some meta-analyses, while having flaws in design and involving small sample sizes, tend to show clinical efficacy.

Data supporting use of the new class of selective serotonin reuptake inhibitors (SSRIs) are not available, though they may have some pain relieving (analgesic) effects. One of the main issues with use of antidepressants is that they do produce side effects that can affect the patient's decision of whether or not to continue using the drug.

Psychological Treatment

Moderator: Douglas Drossman M.D.; Panel: Brenda Toner Ph.D., James Moorey M.Sc., Peter Whorwell M.D., Bruce Naliboff Ph.D.

Psychological treatments have become more popular in recent years in the face of newer empirically based studies of better design that show their effectiveness. There are currently several types of psychological treatments available for patients with functional GI disorders. Cognitive behavioral treatment strategies embrace a variety of methods, rather than one standard model. Hypnotherapy for treatment of functional GI disorders has been looked at for many years, and specifically focuses on bowel relaxation techniques. A growing number of studies from around the world have looked at this treatment method in attempts to understand the mechanisms for the effect of hypnosis, as well as for ways to make it more widely available. It is currently recognized that no one behavioral intervention works best. Some researchers have proposed combining treatment methods to improve clinical outcomes for patients.

Brenda Toner, University of Toronto, Canada highlighted the theoretical basis for **Cognitive-behavioral Treatment of IBS**, a method of therapy that facilitates self-help in a person by focusing on how their thoughts (cognition) and behaviors affect their well-being. There are many approaches to this treatment methodology. The common themes that unify these approaches for the treatment of IBS center on an exploration of how certain thoughts and behaviors influence symptoms and associated distress. Examples of themes addressed include establishing associations among thoughts, feelings, behavior relating to GI symptoms, pain management, bowel performance anxiety, anger, assertion, shame, confidence (self-efficacy), and concern with the opinion of others (social approval). Another theme is the control paradox – needing to give up control to gain control (concerns about losing control may lead to arousal, and hypervigilance with regard to bowel symptoms – hence, by focusing on "staying in control" the brain activates its pain enhancing processes rather than pain reducing processes).

The results of smaller clinical trials show benefit for overall (global) symptoms of IBS, however they all suffer from design issues and do not address gender variables. Dr. Toner alluded to the fact that a large multi-center study of several hundred patients will be presented at the 2003 Digestive Disease Week meeting.

James Moorey, Manchester Royal Infirmary, England discussed the rationale and method for **Interpersonal or Dynamic Psychotherapy**, a method developed in England for which there now is empiric evidence of treatment benefits for IBS and dyspepsia. The treatment involves a long first visit and several follow-up visits to establish a relationship between patient and therapist and then to work on developing a shared understanding of emotional factors and relationship issues that may exacerbate symptoms. This method was tested in a recent study that showed improvement in GI symptoms (though not better than other groups) but with reduction in health care costs at one year.

Peter Whorwell, University of Manchester, England discussed his group's work using **Hypnotherapy for Functional Gastrointestinal Disorders**. Nearly 20 years ago, Dr. Whorwell's group undertook the first controlled trial of hypnotherapy to treat IBS. At the time, it was thought IBS seemed amenable to hypnosis treatment because of the absence of structural damage while various possible underlying mechanisms of the disorder might be susceptible to influence by the mind.

Therapy helps both the psychological and physical aspects of the problem. Recent studies have shown improvement in symptoms, psychological scores, motility, and quality

of life. There is even some preliminary data to show possible effects on anterior cingulate cortex activation, an area of the brain concerned with emotion that influences sensory perception and pain. Nevertheless, up to 25% of patients fail to respond to hypnosis therapy and even those who do improve should not necessarily ignore conventional approaches to treatment as well, such as lifestyle factors or medication as needed. Although the treatment is often effective, helping up to 75% of patients, it is time consuming and can be costly, particularly for patients with more severe symptoms. Nonetheless, the beneficial effects are long lasting, and most patients require less medication following treatment.

Bruce Naliboff, University of California Los Angeles discussed **Multi-component Psychological Treatment of IBS** packages, which are based on the biopsychosocial model where there are multiple interacting cognitive, physiological, and behavioral factors that are targets for treatment. This is also the most common form of treatment for these disorders.

Several reviews have shown similar findings but differing interpretations of the results. Psychological treatments appear to be helpful but it is not clear if these effects are due to specific changes targeted by the treatment or more general positive change due to attention or expectation of benefit. Some of the limitations of existing studies relate to the methodology (e.g., whether there is an active control condition). Future studies will need to involve large-scale studies as well as smaller more mechanistic studies to understand the basis for the observed clinical effects.

Summary

It was a pleasure to again be part of the 5th International Symposium on Functional Gastrointestinal Disorders. Since the first IFFGD Symposium held 8 years ago, the breadth and depth of our understanding of the functional GI disorders has grown tremendously. We are moving closer to discerning pathophysiological subgroups of the disorders that will be amenable to more specific treatments, but there likely will not be any simple cure.

While basic investigation continues to define the underlying mechanisms that help characterize these disorders, clinical studies must also be supported in order to address *now* the needs of patients. In the end, all will benefit from collaborations among basic and clinical investigators, healthcare professionals, and patients.

not know about functional disorders. Much has changed in 12 years with better approaches to diagnosis and treatment, and growing interest in the field. While there has been success, there is still a long way to go. These awards are just another small part of what is hoped will be an ongoing effort by IFFGD to fund research on a continual basis.

It is the intent of IFFGD to expand its own ability to fund more substantial grants in the future with the hope that investigators will be able to move on to NIH funded grants and that NIDDK will continue to expand its portfolio of functional GI and motility disorder support.

Allen Spiegel M.D., Director of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) then spoke. After a generous acknowledgment of the contributions that Nancy Norton of IFFGD makes through service on NIH panels and the NIDDK Advisory Council, he addressed **Research Priorities at the National Institutes of Health** (NIH). Dr. Spiegel noted that while there is clearly significant and rapidly advancing science that is tremendously important to the understanding of functional GI disorders, there is also a long way to go in bridging the gap between a pathophysiologic based classification of this group of

IFFGD Research Initiative – Helping Drive Medical Research with New Funding

On April 6, 2003 the International Foundation for Functional Gastrointestinal Disorders (IFFGD) presented its first research awards to seven investigators in the field of gastroenterology. Presentation of the awards was made at a ceremony held during the 5th International Symposium on Functional GI Disorders in Milwaukee, Wisconsin.

Nancy Norton, President of IFFGD began the awards ceremony with introductory remarks, welcoming and thanking all in attendance for their efforts on behalf of those affected by digestive disorders, and congratulating the investigators who would receive the 2003 IFFGD Research Awards.

IFFGD has spent 12 years moving toward this research initiative, while working to raise awareness around functional gastrointestinal and motility disorders, and to legitimize disorders that have been dismissed by some for years. These efforts have been directed toward patients, families, the general public, professionals, employers, regulators, industry, and members of congress.

IFFGD's education efforts have helped raise awareness about the unmet needs of patients and of what we do and do

disorders and the current pragmatic reality of a symptom based approach. The goal of NIDDK is to support the research that helps bridge the gap for disorders such as IBS and for the other disorders still not precisely understood from a pathophysiologic, prevention, or treatment point of view.

The NIH budget has doubled in the 5 years from 1999 to 2003, from $13.5 to $27 billion. In some perspectives that is a vast amount of money per year. Yet looked at as a denominator in terms of certain other expenditures, particularly the burden of disease of many illnesses, not the least the functional GI disorders, it's not necessarily so vast a figure. With this boost in support, NIDDK has been able to support a whole series of new kinds of mechanisms, and digestive disease centers throughout the country.

With this new increased budget and a new director, Dr. Elias Zerhouni, NIH now has a very broad expansive vision for action for the 21st Century. Specifically this is a process undertaken with public input, with expert and scientific input, and with input from staff and institute directors, looking at

three overarching themes: One is new pathways to discovery and new technologies. Understanding how complex systems work will involve the interaction of multiple and diverse disciplines. A second theme has to do with the kinds of research that will be supported. One approach is multi-disciplinary teams and this is particularly pertinent to the group of functional GI disorders. Specialists from disciplines as diverse as physics, math, imaging, bioengineering, and behavioral science will need to work together in ways that provide the synergism that is lacking now. Public-private partnerships also will be an important component of this theme. The third theme is a very ambitious one and one that almost everyone involved with this Symposium will play an important role in, and that is re-engineering the clinical research enterprise to make it more efficient and effective in translating the basic science discoveries into areas that have a meaningful impact on patients and disease.

There are many issues that must be dealt with, including the issue of translation from the bench to the bedside and beyond, from clinical research into practice, the issue of training, and the issue of clinical research as a discipline, which is in and of itself a science and needs to be validated as such. There is the idea of a national network for clinical research where individuals at multiple levels can be enrolled in the research enterprise.

Ultimately, the goal of the National Institutes of Health is science in the interest of health. Without outstanding science, we really can't achieve optimal health. Yet it's clear that science alone will not bring optimal health. Physician-patient interaction and the effective transfer of information are important as well. The goal in terms of supporting research is to understand these disorders with some precision and be able to facilitate diagnosis, intervention, and prevention at an early stage, and where that's not possible to provide rational and effective therapy.

Douglas Drossman MD, Chair of the awards Selection Committee described **The IFFGD Directive for Research Funding**. Dr. Drossman expressed personal satisfaction in being a part of this research program by IFFGD with the view that this initiative further solidifies the importance of IFFGD to the GI community and to the advancement of science.

From its inception IFFGD, led by its founder Nancy Norton, has been a tireless and outspoken advocate in support of research for patients with digestive disorders. These efforts have included raising awareness about patient issues, organizing and supporting meetings such as this Symposium, and being heard in Washington DC by those who provide funding for research. The organization has also successfully brought together the medical community to talk about current science issues.

IFFGD has established a track record for innovation and continues in its commitment to providing education and raising awareness. By directly acknowledging and funding investigators the foundation embarks on a new path that is hoped will help shape scientific advancement, further legitimize the growing research in functional GI and motility disorders, and by that process improve the quality of life of many patients so afflicted.

Looking to the future, the goal is to encourage not only existing young and established investigators but to also address the larger spectrum of clinical and basic scientists involved in many different disciplines. This will allow work in a more comprehensive fashion to advance understanding of functional GI and motility disorders in adults and children.

Dr. Drossman pointed out that these awards are only the first step in IFFGD's long-term vision. It is hoped that these awards, now given in recognition of the contributions of notable investigators will also be a prelude to the development of a more formal peer reviewed research process. That is something that the award committee has been discussing with the organizers. This new IFFGD effort will seek to raise money necessary to support new, novel, and innovative research and provide seed grants that will ultimately lead to NIH supported research. It will provide the basis for which IFFGD can establish peer-reviewed research. It is also expected that the foundation effort will help to legitimize to other funding agencies the need to provide more research dollars in order to advance our common goals.

IFFGD is pleased to be able to present research awards to these individuals who are striving to broaden the medical community's understanding of functional gastrointestinal disorders while laying the foundation for more and better treatment options for patients. We congratulate the 2003 award recipients for their outstanding achievements:

Senior Investigator, Clinical Science - $7,500
William E. Whitehead, Ph.D., University of North Carolina at Chapel Hill.

Senior Investigator, Basic Science - $7,500
Jyoti N. Sengupta, Ph.D., Medical College of Wisconsin.

Pediatric Investigator, Clinical Science - $7,500
Caroline Elder Danda, Ph.D., University of Kansas.

Pediatric Investigator, Basic Science - $7,500
Terry Buchmiller-Crair, M.D., Cornell University.

International (Developing Nation) Investigator Clinical or Basic Science - $5,000
Dan L. Dumitrascu, M.D., Ph.D., University of Medicine

and Pharmacy in Romania.

Junior Investigator, Clinical Science - $5,000
Adil E. Bharucha, M.D., Mayo Clinic.

Junior Investigator, Basic Science - $5,000
Klaus Bielefeldt, M.D., Ph.D., University of Iowa.

These IFFGD research awards were given to active investigators who have a record of research interest in basic mechanisms or clinical aspects of functional gastrointestinal and motility disorders. The awards are intended to encourage the participation of clinicians and scientists in multidisciplinary efforts aimed at advancing the understanding of gastrointestinal disorders in adults and in children.

About IFFGD

The International Foundation for Gastrointestinal Disorders (IFFGD) is a 501(c)(3) nonprofit education and research organization. We work to promote awareness, scientific advancement, and improved care for people affected by chronic digestive conditions. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. Founded in 1991, we rely on donors to carry out our mission. Visit our website at: www.iffgd.org.

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About the Publication

The 5th International Symposium on Functional Gastrointestinal Disorders was held in Milwaukee, WI from April 4, 2003 to April 7, 2003. Noted international experts in the field of functional gastrointestinal (GI) disorders presented new and developing knowledge for the benefit of investigators, health care providers, and ultimately patients. The biennial meeting is sponsored by the International Foundation for Functional Gastrointestinal Disorders (IFFGD) and the Office of Continuing Medical Education of the University of Wisconsin Medical School, in cooperation with the Functional Brain-Gut Research Group (FBG).

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 new and evolving knowledge that integrates basic science, physiology, clinical medicine, and psychology.

This Symposium was developed to enhance the knowledge and skills of physicians, psychologists, nurses, and allied health professionals in their care of patients with functional GI disorders. For the first time we included a one-half day symposium dedicated exclusively to pediatric functional GI disorders, and notably there was a large proportion of pediatric gastroenterologists that attended this meeting. The sessions provided participants with opportunities to learn about advances in the pathophysiology of the functional gastrointestinal disorders; learn about newer technologies involved with diagnostic assessment of the functional GI disorders; develop clinical skills in the diagnosis and care of patients with functional GI disorders; develop strategies and skills relating to patient-centered care in order to improve patient satisfaction, adherence, and clinical outcome; and share information and experiences with other conference participants.

In addition to the general (plenary) sessions described in this article, there were numerous small group sessions that included luncheon presentations with the presenters, and workshops on design of treatment trials, patient interview techniques, case study sessions, psychological testing and treatment, brain imaging, basic aspects of the brain-gut axis, and alternative-integrative medicine. There was remarkable energy among the participants, as well as a high degree and quality of scientific and social interactions that made the meeting memorable. We extend our thanks to the IFFGD staff, the Wisconsin CME office, and the symposium planning committee for a remarkable symposium.

Symposium Support

We gratefully acknowledge the unrestricted educational grants from the supporters of the Symposium:

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