

Digestive Diseases Interagency Coordinating Committee Functional Gastrointestinal Disorders

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Welcome and Introductions

Dr. Stephen P James, Acting Director, Division of Digestive Diseases and Nutrition, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), opened the meeting with a description of the meeting's purpose and an invitation to attendees to introduce themselves. Congressionally mandated, the Digestive Diseases Interagency Coordinating Committee (DDICC) provides a venue for the exchange of state-of-the-art research activities and opportunities among experts from NIH, government agencies, industry, and academia.

Dr. Frank Hamilton, Chief, Digestive Diseases Program Branch, NIH, thanked speakers for their participation and extended a special welcome to Dr. Allen Spiegel, Director, NIDDK, whose support for functional bowel disease (FBD) research has been invaluable. Probably the most prevalent GI disorders seen by GI practitioners, functional gastrointestinal (FGI) disorders involve physiological, emotional, and psychological factors, making them a complex, multifactorial challenge for both patients and clinicians.

In a brief historical perspective, Dr. Hamilton described the movement of FBD research from the first NIH workshop on Irritable Bowel Syndrome (IBS) research held in 1992 to the current meeting, a journey which has included milestones such as the development of a Small Grants Program with emphasis on IBS disorders, national meetings during which researchers were encouraged to pursue RO1 grants, and an RFA for integrative studies in motility released in 1999. Dr. Hamilton acknowledged the instrumental contributions of the Advisory Council and the Office of Women's Health partnership in promoting the advancement of FBD research, and commended the NIH commitment to encouraging a multidisciplinary approach in both basic and clinical research.

Overview of the Epidemiology and Economic Burden of Functional Bowel Disorders

Dr. George F. Longstreth, Kaiser Permanente Medical Center, San Diego, CA

Dr. Longstreth described FGI disorders as those that are not definable by specific structure or biochemical abnormalities. Although there are associated pathophysiological abnormalities of various types, FGI disorders are primarily identified through characteristic symptoms using the Rome criteria. Dr. Longstreth summarized results of a U.S. Householder Survey (1993), which determined that 69% of those surveyed had at

least one of the 20 FGI disorders described in the questionnaire, and that those patients had four times as many physician visits for non-GI problems as for their GI problems. An Australian study found that multiple disorders were very common. In fact, 4% of respondents had more than five disorders, a finding which has significant cost implications. IBS prevalence ranges from 3 to 20%, depending on which diagnostic symptom-based criteria are used. Approximately twice as many women suffer from IBS as men. IBS is sometimes divided into categories based on symptom type (diarrhea, constipation, or alternating predominant symptom); data seem to indicate that these types occur in approximately similar proportions. Dyspepsia prevalence ranges from 7 to 41%, in part due to the definition used and whether it is distinguished from gastroesophageal reflux disease (GERD). The overlap and transition between these two major functional GI disorders are so common that even a modest cost increase in caring for these patients can have a major overall effect on total healthcare costs.

Two to 5% of primary care visits are for IBS; 2 to 5% for dyspepsia, compared to 10 to 50% of visits to gastroenterologists for those disorders. In general, specialists' patients tend to be those with more severe symptoms, who are experiencing more prominent psychological factors, and are subjects of more testing, resulting in a higher diagnostic accuracy. Dr. Longstreth pointed out that these patients often have non-GI specific conditions, such as polymyalgia or Chronic Fatigue Syndrome, and experience more non-gastrointestinal, psychiatric, and gynecological symptoms.

All direct costs (physician charges, drugs, tests, hospital costs) are increased in patients with IBS. Indirect costs (work absenteeism, income loss, transportation, rehabilitation, early retirement) are also increased. Citing data from several studies, Dr. Longstreth stated that the burden of gastrointestinal disorders in 2002 was \$1.4 billion in the United States alone, and that visit costs and drug costs alone exceed the costs for ulcerative colitis and food borne illness. Dr. Talley's study conducted at the Mayo Clinic in 1995, indicated approximately a 50% increase in annual cost for IBS patients over non-IBS control patients, a finding supported by subsequent studies performed by different researchers. Dr. Longstreth noted that, in one study, two-thirds of the cost difference between IBS and controls was unrelated to lower intestinal symptoms. Another study revealed that there was a progressive increase in costs as abdominal pain or discomfort severity increased.

Dr. Longstreth described a survey he recently conducted which examined the occurrence of surgery in patients who had received a physician's diagnosis of IBS. In those patients, cholecystectomies were performed in three times as many IBS-diagnosed patients versus the control patients, and appendectomy and hysterectomy occurred twice as often, a finding that emphasizes the potential for unnecessary surgery, perhaps through symptom misattribution or misdiagnosis in IBS patients.

Dr. Longstreth identified dyspepsia is a complicated issue, one which is affected by cost and availability of endoscopy, prevalence of *H. pylori*, the cutoff age for endoscopy, whether or not GERD is excluded, and the cost and risk of chronic PPI use. The cost of dyspepsia may be a function of the treatment and management program employed;

however, Dr. Longstreth described study findings which revealed that patients with dyspepsia had more than 50% medical visits than control patients, and over a doubling of their costs, amounting to \$1.1 million charges in 1 year for 288 adult patients.

Dr. Longstreth identified several areas for future research in the area of GI disorders. He suggested a need for more prevalence data on non-white, Hispanics, and other populations, and lifetime prevalence data on all populations. Annual incidence, natural history, particularly the subtypes and comorbidities which have major cost implications, and surgical history of IBD patients, are areas that warrant further attention. The field of functional dyspepsia is lacking information on the cost and epidemiology of the disease. Lastly, Dr. Longstreth emphasized that finding answers to practice research questions including health plan management, physicians' attitudes, and practice styles, will aid in the management of treatment and healthcare costs for FBD patients.

During discussion following Dr. Longstreth's presentation, it was pointed out that several studies are currently investigating the use and validation of the Rome criteria and prevalence/healthcare cost disparity. Further investigation needs to be conducted in multiple ethnic and cultural groups.

In response to a question regarding the possible correlation between IBS and other risk factors such as obesity and sedentary lifestyle, the comment was made that there is an association at both ends of the spectrum with eating disorders, but no connection has as yet been identified with sedentary lifestyle.

It was suggested that further analytic work be done, possibly a natural history study using specific diagnostic criteria observed over time, to distinguish between necessary and unnecessary surgeries. Discussion followed on the topic of unnecessary surgeries, including appendectomies, gallbladder removal, hysterectomies, and cholecystectomies that were later determined to be due to symptoms related to FGI disorders.

Brain-Gut Interaction Altered CNS Processing of Visceral Pain

Dr. Emeran A. Mayer, Director, CNS/WH Center for Neurovisceral Sciences & Women's Health, CURE: Digestive Diseases Research Center, Division of Digestive Diseases, UCLA, Los Angeles, CA.

Dr. Mayer, Director of the Center on Sex and Gender, explained that, in response to the challenge of applying functional brain imaging to complex disorders such as functional GI, the Center has developed a networked infrastructure of experts in the areas of women's health and brain-gut interactions.

In a brief overview, Dr. Mayer stated that temporal and spatial resolution began with the use of positron emission tomography (PET), which has been somewhat superseded by functional MRI. This technology aims to cover a wide range of temporal behavioral measures (from hours or days to real-time imaging of events as they occur) and spatial

imaging of the entire brain (from receptor distributions to synaptic function), a goal that is rapidly becoming a reality.

Enhanced perception of visceral and somatic events is a generally agreed upon hallmark of a whole range of functional disorders, making brain imaging studies critical in the gastroenterology field. Until recently, visceral sensitivity in human studies has been limited to subjective perception. However, functional brain imaging techniques are able to dissect the neural substrate of the multiple components involved. Dr. Mayer stated that a number of published studies in non-IBS, normal subjects have shown that some of the more consistently activated areas are the insular cortex and the anterinsular cortex, and that there are emerging differences between control subjects and IBS patients.

It is becoming increasingly apparent to investigators that areas being activated are more than what have been termed “pain circuits,” but brain regions that have to do with emotional responses to a particular stimulus and the context of the stimulus. Most recently, researchers are identifying deactivating parts in healthy brains in response to visceral stimulus.

Dr. Mayer described the advantage of using brain imaging in humans. Investigators combined brain imaging with subjective data and, using covariate analysis, found that the intensity rating of a stimulus correlates significantly with the insular cortex. This finding is becoming a consensus in pain literature in general: That the intensity and effective quality of a stimulus is encoded in different parts of the brain in parallel, but that these regions can be altered separately. Using this information, researchers can use brain regions for intensity coding, allowing for monitoring the effect of therapy. For example, an animal longitudinal study using brain scans determined emotional responses depending on the context and emotional state of the subject, results that even included extreme indications of expectation and anticipation. Dr. Mayer stressed that this information is important in that there are parts of the emotional motor system that have connections and that can monitor pain perception.

Studies have also been conducted which demonstrate that cognitive factors are able to shut off emotional areas, a self-regulatory mechanism especially applicable to IBS patients. In healthy individuals, a deactivation of the emotion areas occurs at times. Dr. Mayer stated that such a mechanism to control the process may be lacking in IBS patients.

Dr. Mayer presented data from a study showing that healthy control subjects demonstrated a greater number of activated pain suppression areas compared to IBS patients, indicating that healthy patients are better able to engage a system in the brain that actually suppresses pain perception. The main difference between controls and IBS patients seems to be in the emotional modulatory circuits.

This technique can be used to evaluate the mechanism of a drug, such as Alosetron, in that effects seen during a visceral stimulation were compared to those observed during anticipatory anxiety in expectation of an aversive stimulus. Results indicated no effect

during visceral stimulation of patients on day of testing; however, at baseline and during anticipation, the drug decreased anticipatory anxiety.

Differences between male and female prevalence rates may ultimately be explained through an understanding of anticipatory rates indicated by brain imaging techniques. Female subjects given medications which act on emotional circuits were more effective, since brain imaging shows an increase in activation of the amygdale, emotional modulatory region.

Dr. Mayer suggested that inhibitory effects on limbic structures may be the reason placebo subjects respond to symptom improvement or deactivation through inhibition of the anteriorcingular cortex. These findings extend beyond placebo effect, and may be implicated in the success or failure of cognitive behavioral therapy and physician-patient interactions.

PET as a brain imaging technique has moved from animal models to human studies, allowing investigators to test hypotheses about altered receptor ligand systems in the brain, since decreased radioactivity in certain brain areas indicates the locations of both receptors and antagonists.

Dr. Mayer described another method for moving from animal models to humans. Using high strength magnet scanners, investigators are able to image directly, correlating a mean image for each subject with the individual's subjective experience.

Given the complexity of functional GI disorders, the ultimate challenge in the field of brain imaging is to combine many of these techniques in a single session. Future research endeavors will require a sophisticated infrastructure and multidisciplinary interaction.

During discussion, one participant mentioned that current attempts to harness cross-cutting techniques and approaches to science across multiple institutions will be dependent on the development of advanced brain imaging techniques, novel probes, and a strong infrastructure, in order to ultimately apply the information to actual clinical research protocols. Dr. Mayer suggested that the linking of multiple institutions and sharing of instrumentation mechanisms will further the dissemination of ideas and information.

In response to a question regarding differences in IBS subject responses to treatment mechanisms, Dr. Mayer stated that brain imaging may provide information regarding brain activation that will be very useful for matching therapies to patients.

Is There a Role of Bacteria in Functional Bowel Disorders?

Dr. Henry Lin, Kaiser Permanente Medical Center, San Diego, CA

Dr. Lin opened with a statement that, although the medical community has historically attempted to subclassify IBS patients into different groups, those efforts have been resisted by the patients themselves, who claim to have multiple symptoms. Since 80 to 90% of IBS patients report abdominal distention or gas, Dr. Lin suggested that perhaps a more effective means of understanding the postprandial bloating of IBS would be to examine similarities among patients' complaints.

Current ideas regarding IBS (such as psychosocial factors, abnormal motility and transit, enhanced stress response, visceral hypersensitivity, and physical stressor to the gut) do not explain postprandial bloating. Dr. Lin noted that the increased gas in the small intestine is accompanied by abnormal bacterial fermentation. Since two factors are involved in gas generation—substrate and bacteria—it may be that bacterial overgrowth is the underlying cause of postprandial bloating. Dr. Lin described a database study in which 76% of the referred patients who met Rome I criteria for IBS experienced abnormal lactulose breath tests, indicating bacterial overgrowth. Following antibiotic treatment, second breath test results were normal. In fact, nearly 50% of the patients with documented eradication no longer met Rome criteria for IBS. A later study concluded that 75% of IBS patients claimed symptom improvement following normalized lactulose breath tests.

In a recent double-blind, placebo-controlled, randomized trial, bacterial overgrowth explained the overlap of accelerated transit profiles of diarrhea patients and delayed transit profiles of constipated patients, in that methane gas was found only in the breath tests of those patients who complained of constipation. In fact, a larger study was conducted in which methane was proven to be an exclusive predictor of constipation.

Efforts to identify the cause of bacterial overgrowth in IBS patients have shown that a lower frequency and decreased duration of Phase III of interdigestive motility (MMC) is found in IBS subjects with abnormal lactulose breath tests. Since bacterial overgrowth leads to the adverse consequence of bacterial translocation (the passage of endogenous bacteria across the mucosal layer) and immune activation, avoiding bacterial overgrowth would decrease the incidence of IBS. Ninety percent of IBS patients have evidence of immune activation, and immune activation is actually greater in IBS patients without a history of an acute onset of gastroenteritis, indicating widespread immune activation in IBS exists across the entire GI tract, irrespective of outcome measure studied.

Dr. Lin outlined several studies in which bacterial overgrowth seems to explain the role of serotonin and visceral hypersensitivity in IBS, as well, in that serotonin levels decreased following antibiotic treatment and exposure to LPS resulted in increased expression of visceral hypersensitivity in IBS patients. Additionally, bacterial overgrowth may explain the altered brain-gut interaction, since inflammation of the small bowel activates multiple brain changes, including altered firing of hypothalamic neurons,

changes in neurotransmitters in the brain, alteration of psycho-social measures, and alteration of hypothalamic-pituitary-adrenal function.

Dr. Lin stated that bacterial overgrowth may very well be the unifying explanation of IBS because it accounts for postprandial bloating, which is the overwhelmingly predominant symptom of IBS patients. It explains the repeatedly confirmed physical findings of distention, increased small bowel gas, and abnormal fermentation, and the prevalence of abnormal breath tests in IBS patients. Eradication of bacterial overgrowth accounts for 75% improvement when the breath test is completely normalized. Bacterial overgrowth is the basis for differences in GI transit profiles, abnormal motility, immune activation, the role of serotonin, and the presence of visceral hypersensitivity. Altered brain-gut interactions and changes in psychosocial factors can also be explained by bacterial overgrowth.

Dr. Lin concluded by stating that bacterial overgrowth is an exciting possibility because it provides a framework target for productive research investigation that could lead to new diagnostic tests for IBS, useful and effective treatments for doctors, and hope for patients.

During discussion, Dr. Lin was asked whether or not bacterial overgrowth is a universal IBS phenomenon, to which he replied that the double-blind study showed it to be exhibited by 84% of IBS patients.

The issue of technical challenges for culturing bacteria outside of the gut was raised. Researchers currently rely on indirect tests which have been assigned low sensitivity and specificity, such as the lactulose breath test.

In response to a question regarding direct correlation between bacterial overgrowth and other non-GI symptoms, Dr. Lin responded that a double-blind, randomized, placebo-controlled trial tested the idea that fibromyalgia was an overlapping symptom that has been artificially separated from IBS, when in fact it is hypersensitivity in the patient. The study found that 100% of those subjects had abnormal lactulose breath tests. After eradication was achieved with normalization of the breath test, the number of tender points that were detected blindly by the study's rheumatology collaborator dropped below the threshold for fibromyalgia.

Long-term follow-up for IBS patients indicate that the long-term effect of antibiotics might not be maintained. A chronic relapsing condition, bacterial overgrowth certainly indicates a need for much more effective therapy. Remission is prolonged when Phase III motor events are induced. However, first Dr. Lin recommended that a better understanding of the interaction between bacteria and host, and the determinance or persistence of the state, is required.

Concern was expressed that the classification using Rome criteria might include patients in studies who do not have IBS, but who do have a variety of other low-grade inflammatory conditions that would not necessarily be considered functional, such as microscopic colitis. However, although classification might ultimately prove to be

problematic, investigators should nonetheless pursue the identification of subsets, since IBS is irrefutably a complex phenomenon.

Pelvic Floor Dysfunction as a Factor in Functional Bowel Disorders

Dr. Anne M. Weber, National Institute of Child Health and Human Development (NICHD), NIH, Bethesda, MD

Dr. Weber explained that NICHD has been involved in the area of pelvic floor disorders for the past 4 or 5 years, as a topic related to women's reproductive health and childbearing issues. Pelvic floor disorders in general involve a combination of conditions: pelvic organ prolapse, disorders of storage/emptying of the urinary tract, and GI disorders of rectal storage and evacuation.

Dr. Weber commented that it has been consistently under-recognized, especially in the fields of urology and gynecology, that many women have a bowel disorder coexisting with a urinary disorder or prolapse affecting the genital tract, and that there is a great deal of overlap in the pathophysiology of pelvic floor disorders. A better understanding of the differing levels of damage and capacity for recovery following childbirth would greatly aid in providing opportunities for intervention at the primary level of prevention of pelvic floor disorders, as well as the secondary level.

Most complex disorders have both inherited and acquired components. Dr. Weber identified several inherited risk factors for pelvic floor disorders, including differences in collagen and pelvic floor anatomy. Acquired risk factors are those such as childbirth, physical activity, obesity, menopause, and aging. Some researchers have raised the issue that identifying women at higher risk for sustaining the type of damage that would result in long-term disorders may allow those individuals the option of elected Caesarian deliveries.

Direct and indirect damage to pelvic muscles, nerves, and connective tissues sustained during childbirth influence the overall risk of prolapse, urinary incontinence, and fecal incontinence. Dr. Weber also stated that there is a high risk of damage directly to the internal and external anal sphincters at the time of delivery (up to 8 to 12% of women have direct anal sphincter damage at the time of delivery). One of the strongest risk factors for predicting whether or not a woman is going to sustain direct sphincter damage during delivery is whether or not a midline episiotomy is performed.

Dr. Weber suggested that the problem is at least partially preventable, in that if the use of episiotomies was decreased, the number of women with pelvic floor disorders and complications would be correspondingly lowered. This is a critical point, since the effectiveness of surgery to repair the anal sphincter either primarily at the time of delivery or remote from delivery for women who do develop symptoms later in life is poor. For that reason, future research endeavors ought to include the development of more effective methods for the repair of anal sphincter damage, especially at the time of occurrence.

In addition to childbirth, Dr. Weber remarked that another area of overlap is excessive straining. Women who experience excessive straining may damage the pudendal nerve over time, and straining is believed to be a risk factor for pelvic organ prolapse. If nerve damage occurs due to excessive straining, concomitant muscle dysfunction and connective tissue damage may also take place, even in women who have Caesarian deliveries, and especially as women age.

Possible risk factors beyond childbirth include menopause and estrogen loss, aging with other effects on neuromuscular function and deterioration over time, and factors outside the pelvis such as cognitive decline and mobility limitations.

Dr. Weber stated that a further research priority in terms of influencing care for women ought to be the examination of the possible benefits of adjuvant therapy (such as pelvic muscle rehabilitation) following childbirth where some level of damage has been sustained to prevent the development of clinical conditions.

Treatment of Functional Bowel Disorders: Cognitive Behavioral Therapy as Well as Biofeedback in the Management of Functional Bowel Disorders
Dr. William E. Whitehead, University of North Carolina Chapel Hill Center for Functional GI & Motility Disorders, Chapel Hill, NC

Dr. Whitehead began with a summary of sources of bias in clinical trials, including investigator bias, subject expectancy or placebo effects, ascertainment bias, and nonspecific effects. In drug trials, there are standard methods for countering biases, such as random assignment of subjects, parallel group design, placebo controls, and double-blinding. However, Dr. Whitehead pointed out that behavioral research presents unique challenges to these approaches. It is difficult, if not impossible, to blind the therapist involved in the trial. Probably the most important factor in the design of effective clinical trials, but also most difficult, is to identify a control condition that is both inactive and that generates a similar expectation of benefit. Nonspecific, relationship variables are also more important in the behavioral research setting than for drug trials.

Dr. Whitehead shared what he described as an emerging consensus of standards for carrying out trials of behavioral intervention for functional bowel disorders. Parallel group design and random assignment are standards that are appropriate to drug trials and behavioral research trials alike. Although it is impossible to double-blind subjects, if not the investigators, subjects can nevertheless be blinded to what is expected or intended to be the most active component, as can the individual performing the outcome evaluation. Control conditions that are weak active treatments (biofeedback/verbal guidance, patient-led support groups, education) seem to be among the most successful alternatives, whereas waiting list control groups and standard medical management techniques are probably the worst possible controls for expectancy. Questionnaires can measure subject expectancy and process variables. It is recommended that similar frequency and duration

of contact with therapists be provided, and that in multi-center trials, multiple therapists be used.

Dr. Whitehead stated that interpersonal psychotherapy involves the discussion of current interpersonal problems and feelings, and usually an analysis of the doctor-patient relationship to identify inappropriate ways that the patient copes with interpersonal relations. This goal of analysis is to teach the patient more effective means for coping, resulting in a reduction in stress.

This approach to treatment has been illustrated by several pivotal studies which showed superiority to standard medical care and a reduction of symptom severity, gains which persisted or increased during follow-up. Although relatively expensive to administer, at least initially, psychotherapy appears to reduce overall healthcare costs. This type of treatment generally requires 6 to 12 individual therapy sessions with a highly trained and experienced therapist. However, following proof-of-concept, Dr. Whitehead suggested that behavioral or psychological technicians could be trained to deliver the sessions more inexpensively.

Cognitive behavioral therapy (CBT) is based on the concept that automatic, irrational, self-defeating thoughts cause psychological distress, which can cause or exacerbate the symptoms of functional bowel disorders. Therapy involves identifying these thoughts for the patient and substituting more positive thoughts and coping mechanisms. Often, CBT is combined with relaxation and coping skills training, but is increasingly offered alone.

Dr. Whitehead summarized data from a study comparing CBT alone to self-help support groups, which showed that credibility between the two treatment arms was found to be equal and that process measures showed appropriate changes in cognition and attitudes which were not reflected in the control group. At the end of treatment, patients in the CBT group exhibited a two-fold increase in percentage of individuals who had a change in their primary symptom index, which was significantly superior to the patients in the self-help support group, a difference maintained over a 3-month follow-up.

In a study conducted at UNC comparing CBT to an educational placebo, patients receiving CBT showed significant improvement over the placebo group in two separate outcome measures, both a composite score integrating symptoms with measures of subjective satisfaction and a responder analysis in which patients rated satisfaction with treatment.

Dr. Whitehead commented that one trial currently in press did not find significantly greater improvement in the CBT group compared to a control group, and that long-term follow-up data is not as yet available for CBT trials.

Hypnotherapy for IBS involves techniques which narrow patients' focus of attention and heightens their suggestibility. Done partly through techniques such as arm levitation and relaxation, patients are taught to use imagery to relax the GI tract. Patients are

encouraged to practice autohypnosis daily, and suggestions for improved health and well-being are also provided in conjunction with hypnotherapy.

Dr. Whitehead presented dramatic results from two studies which compared hypnosis and pill placebo/counseling treatment for IBS patients, and hypnosis, placebo/counseling and standard care for functional dyspepsia patients. In both trials, hypnosis was the superior treatment method, providing a significant, sustained benefit through long-term follow-up and an apparent reduction in direct healthcare costs.

Two approaches using biofeedback therapy in functional bowel disorders are: 1) the use of nonspecific types of biofeedback, such as hand-warming, to teach relaxation; and 2) direct biofeedback, in which patients are taught to suppress contractions of the colon by measuring pressures in the rectum and colon and providing feedback. While initial investigators observed some promising results using nonspecific biofeedback, subsequent trials suggest the active component was actually CBT, and direct biofeedback has been found to be less effective than simple stress management in improving symptoms. Neither method is currently being pursued in clinical trials for the treatment of functional bowel disorders.

Dr. Whitehead recommended that the evidence for efficacy could be strengthened by attention to trial design issues and methodological considerations.

Given the success of CBT trials, both in terms of symptom reduction and healthcare costs, Dr. Whitehead identified the following unmet needs and research priorities:

- combined treatment of antidepressants with psychological intervention such as CBT;
- accessibility to treatment through primary care physicians, through group treatment, brief (1-3 session) treatment, and CD or internet delivery of care;
- further assessment of the benefits of healthcare cost reduction, including the evaluation of health economic outcome measures;
- comparison of different psychological interventions to match patient characteristics and process measures/mechanisms most effectively to treatment options; and
- attention to pediatric functional GI disorders, especially treatment of recurrent abdominal pain and IBS and the prevention of intergenerational transmission.

Research Opportunities for Complementary and Alternative Approaches to Functional Bowel Disorders

Dr. Margaret Chesney, Deputy Director, National Center for Complementary and Alternative Medicine (NCAM), NIH, Bethesda, MD

Dr. Chesney described complementary and alternative medicine (CAM) as a collection of medical and healthcare practices and procedures outside the realm of conventional medicine, which have not as yet been validated using scientific methods.

Complementary therapies are those approaches used in addition to conventional therapy, such as the use of cognitive behavioral therapy with antidepressants in the treatment of functional bowel disease. Alternative therapies are those used in place of conventional practices.

Interest in the area of complementary and alternative therapies has been spurred by factors such as the absence of effective conventional treatments or the adverse effects of conventional regimens, the lack of practitioner time and patient dissatisfaction with technical approaches, and the fragmentation of care by specialists. Additionally, media reports of dramatic success stories, the public perception that CAM approaches are natural treatments that focus on spiritual and emotional wellbeing and promote patient empowerment, together with the fact that CAM practitioners spend more time talking and listening to their patients, has encouraged widespread attention to CAM therapies.

Recent areas of interest in this field have included the biological based systems of diets and herbals, manipulative or body-based interventions (massage, chiropractic, acupuncture), mind-body or psychosocial interventions (yoga, prayer, meditation), and cognitive behavioral therapy or hypnosis. Dr. Chesney pointed out that evidence certainly exists which shows the effectiveness of stress management and cognitive behavioral therapies for heart disease, indicating that some treatments should be more accurately considered as integrative medicine. CAM also is examining alternative medical systems such as naturopathy and homeopathy.

Citing a recent study in which 29% of adults reported they use complementary and alternative strategies, Dr. Chesney stated that the popularity of CAM is increasing, even among patients who do not have alternative treatments available to them or who are willing to pay out-of-pocket expenses for CAM because those treatments are not covered by insurance. Women and people with higher education levels are more likely to use CAM remedies than people with less education.

However, despite the number of individuals using CAM and the rising interest in CAM treatment options, little efficacy evidence exists. Therefore, NCAM's mission is to conduct rigorous, randomized clinical trials on CAM practices, to educate and to train CAM researchers, and to inform consumers and healthcare practitioners about the efficacy and safety of CAM approaches.

Dr. Chesney outlined areas of research currently funded by NCAM, including illness (addiction, cancer, arthritis, cardiovascular disease, neurological disorders, craniofacial

health), populations (women, pediatrics, minorities and the aging), and modalities (botanicals, chiropractics). A number of large phase III clinical trials are also funded by NCAM.

CAM approaches to functional bowel disorders include herbal therapies, dietary supplements, dietary modifications, acupuncture, and psychological therapies such as mind-body and behavioral approaches. Of these approaches, evidence suggests that the best is Traditional Chinese Medicine, an herbal therapy. However, Dr. Chesney pointed out that research in herbal therapies is challenging because of several factors. Safety of herbal medicines is assumed, not proven. There is a lack of product standardization and herbal medicines are often contaminated with drugs, and especially with heavy metals. Allergic reactions are common, and herbal medicines are sometimes inherently toxic and adversely interact with other drugs. Nevertheless, patients are increasingly replacing proven therapies with complementary and alternative medicines.

Randomized controlled trials have demonstrated some efficacy of Traditional Chinese Medicine and psychological therapies for reducing gastroenterology- and patient-rated symptoms. Dr. Chesney suggested the success of those studies argues for further research attention in the CAM areas. Challenges in doing so include the fact that, unlike most areas in medicine, there is a broad spectrum of CAM strategies already widely used by the public, despite the lack of proven efficacy and safety of the treatments. Also of concern are inconsistent product standards which are complicated and compounded by market disincentives for research in this area.

Nevertheless, Dr. Chesney stressed NCAM's commitment to the conduct of rigorous research. In addition, NCAM communicates and provides outreach to the public through the use of mechanisms such as websites, clearinghouses, newsletters, public education, town meetings, exhibits and lectures.

Research Advances over the Last Decade

Dr. Douglas A. Drossman, Co-Director, University of North Carolina Chapel Hill Center for Functional GI & Motility Disorders, Chapel Hill, NC

As a participant in the 1992 NIH workshop on IBS, Dr. Drossman brought an historical perspective his presentation by describing the movement from that meeting's emphasis on basic physiology, motility, and the introduction of visceral hypersensitivity to the current trend toward acknowledgement of the disorder's complexity and the identification of a connection between its physiologic substrates. Dr. Drossman emphasized the need to identify correct definition criteria, since undoubtedly those criteria will change over time, affecting physiologic subsets and their response to mechanisms and treatment.

Dr. Drossman presented data from research activities in the areas of genetics, epidemiology, and healthcare burden. It is important to note that children of people with IBS are more likely to have higher costs and more physician visits for a variety of reasons than their non-affected counterparts. Additionally, IBS frequency, when combined with

functional diarrhea, is as high as GERD; in terms of healthcare burden, total costs for IBS exceed those for the treatment of IBD.

The movement from a focus on motility to consideration of IBS as a complex disorder involving multiple factors has been evidenced by the change in the Rome II definition from a functional bowel disorder to a group of functional bowel disorders, to include subgroups such as motor dysfunction, visceral hypersensitivity, post-infection immune dysfunction, and central pain dysfunction. At a more basic level, Dr. Drossman stated that researchers have been investigating the “circuitry” between the brain and the gut, including histamine 5HT, substance piece synaptic transmission, pericrine activity, and mucosal and anochrominal cell activity in the myenteric area.

Dr. Drossman described animal models examining afferent firing in pelvic nerves following inflammation which have advanced understanding of the concepts of sensitization and visceral hypersensitivity. Although research has demonstrated some role of serotonin (5HT) in terms of putative mediation of gut function (motility, sensation, and perception), Dr. Drossman stated that one challenge for investigators is to look beyond serotonin to other neurotransmitters.

Epidemiologic and clinical data (psychological stress, women, younger ages, increased duration of diarrhea and increased duration of abdominal pain) has been used to predict individuals who will experience symptoms of enteric infection 3 to 4 months post-infection. These same individual have also demonstrated retention of increased levels of serotonin-producing cells during this same time period. A similar study showed that subjects with acute gastroenteritis who retained symptoms for 3 months were more likely to have experienced psychological distress at the time of the acute infection and more inflammation during the follow-up period. Dr. Drossman identified the link between brain-gut interaction as an area which warrants further investigation.

Dr. Drossman described several studies which offer further evidence of brain-gut interaction, and reiterated Dr. Mayer’s point that while people with IBD do not have central perception of the pain associated with the disorder, visceral sensitization from below is not identical to perception. It may be that the brain learns to adapt to and diminish the pain signal. Unfortunately, post-infectious IBS patients who have experienced greater psychological distress may be less adept at this adaptation, and may retain symptoms for a longer period of time.

The brain-gut interaction involves an inhibitory pathway with signals traveling in both directions. Dr. Drossman suggested that one of the features of the brain-gut aspect for IBS patients is not only the visceral hypersensitivity from the gut and the motility, but a failure to down-regulate incoming visceral afferent signals, resulting in the complications brought about when patients experience pain in a more anxious manner.

Dr. Drossman stated that, given the multifactorial presentation of IBD, the key for effective diagnosis criteria will be identifying simple methods for predictive disease

markers. Markers currently under investigation include fecal calprotectin and rectal pain thresholds.

Physician-patient interaction is an area for further investigation, since effective communication between patients and their healthcare providers has been shown to reduce office visits and to increase both patient and physician satisfaction with treatment effects, including the use of placebos. Communication is especially important in encouraging patients to continue medications which produce significant side effects, to reduce dropouts, and to increase motivation to participate in efficacy studies.

Even patients with marginal effects with regard to pain improvement have indicated high effects in terms of satisfaction with treatment. Understanding that IBS involves subsets of symptoms and dysfunctions dictates that treatment methods offer a corresponding choice of options ranging from antibiotics or 5HT agents, to cognitive behavioral therapy and antidepressants, and beyond. Providing patients improved function and quality of life has been part of the impetus for the NIH and the Rome committees to move toward subject global measures rather than symptoms measures.

Dr. Drossman recommended that future basic research include:

- biobehavioral influences on brain-gut function (stress effects on gut function, inflammatory effects on CNS function, and central processing of painful stimuli);
- mucosal immunology/histopathology (mechanisms for neurogenic inflammation, and stem cells and undifferentiated neurons in the enteric nervous system); and
- neuropeptide signaling other than 5HT (CRH, CCK, and ATP in terms of the brain, and afferent nerves and enteric nerves as well).

Clinical research efforts ought to consider:

- genetics and genetic epidemiology;
- brain-gut interactions (including physiology and coping/adaptation to chronic illness);
- pharmacological treatments targeted to physiological subgroups and defining outcomes/understanding placebos;
- combined treatment trials for proof of concept and application in primary care (access/delivery); and
- education of healthcare providers through clinical skill training and patients in self-management strategies.

Discussion and Summary

Functional GI disorders are generally acknowledged to be complex and multifactorial, presenting a number of challenges to researchers, physicians, and patients. It is important to consider that much of the morbidity associated with IBS is related to comorbid conditions, many of which are not strictly GI disorders. The point was stressed that IBS may be a heterogeneous group of disorders, with subsets that may respond to different approaches and treatment.

Participants identified a number of areas that warrant further research, including:

- correct definition criteria, including identification of simple methods for disease markers;
- prevalence data, especially of minority populations;
- natural history of the disorder, particularly with regard to subtypes and comorbidities;
- surgical history of IBD patients;
- abnormal bacterial fermentation in the small intestine;
- effective methods for the prevention and repair of anal sphincter damage;
- attention to pediatric functional GI disorders;
- combined treatment therapies; and
- brain-gut function/interactions, mucosal immunology/histopathology, and neuropeptide signaling.

Better measurement techniques will enable investigators to more closely target specific symptoms. It is especially important to distinguish between extra-intestinal manifestations, and to identify those components which are rapidly reversible, as well as secondary phenomena, which will result in improvement of primary symptoms and patients' quality of life.

The group indicated that, since most healthcare providers administering treatment to IBD patients are primary care physicians, a priority ought to be to train those doctors to better communicate with patients and to be able to offer effective treatments. Doing so may require multidisciplinary teams working with patients to increase accessibility and to ensure appropriate application of treatment methods, but will ultimately reduce healthcare costs. Therefore, translation research is especially important.