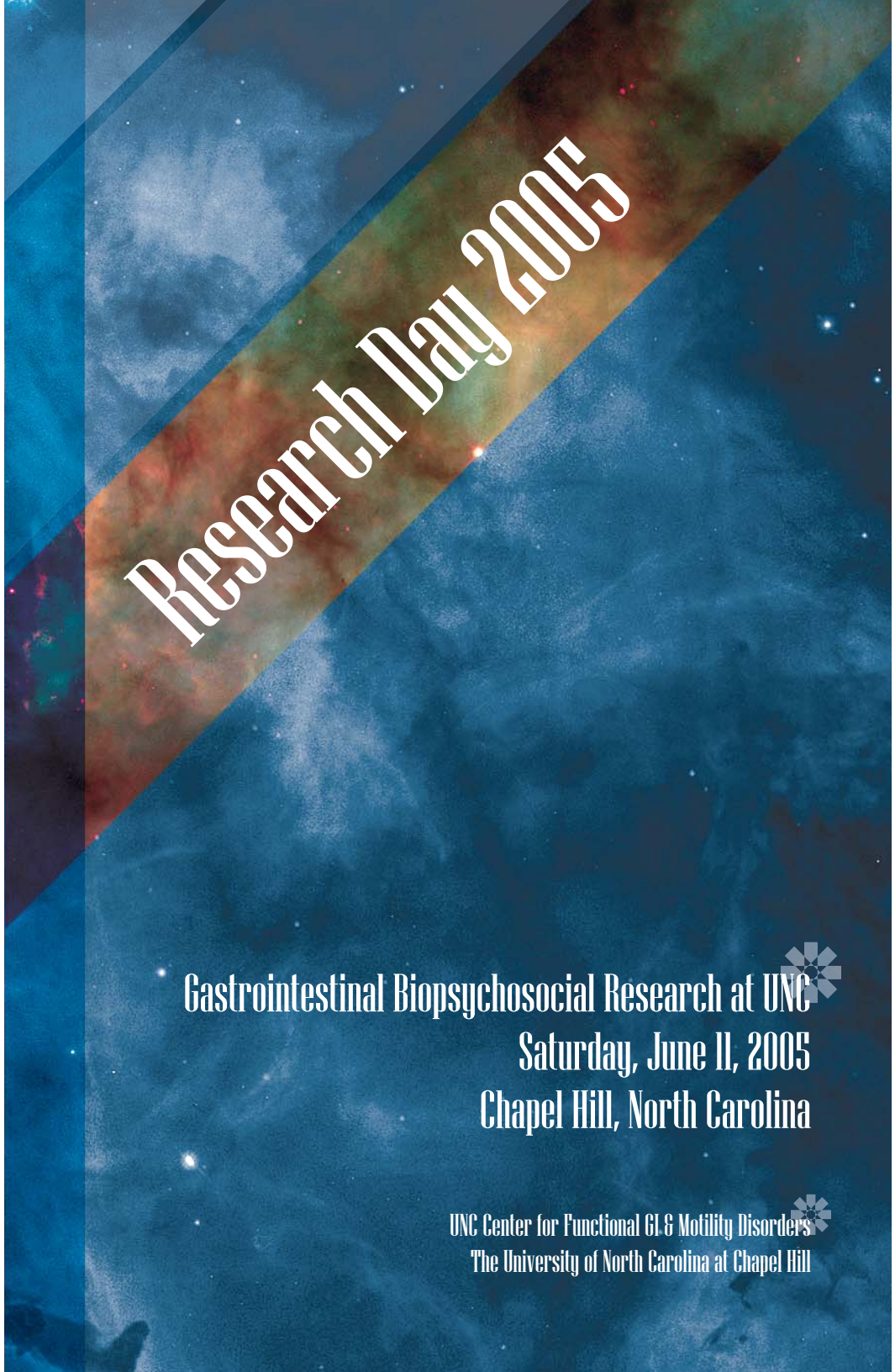
Research Day 2005
Gastrointestinal Biopsychosocial Research at UNC
Saturday, June 11, 2005
Chapel Hill, North Carolina
UNC Center for Functional GI & Motility Disorders
The University of North Carolina at Chapel Hill

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In October 2004, the UNC Center for Functional GI & Motility Disorders was awarded a grant from the National Institutes of Health (NIH) to foster interdisciplinary research on interactions between the mind and body in health and disease, with a specific focus on the causes and treatment of functional gastrointestinal (GI) disorders. We refer to this grant as the Mind-Body Infrastructure Grant (R24 DK67674).

As part of this NIH grant, the Center hosted Research Day 2005 on June 11, 2005, on the campus of the University of North Carolina at Chapel Hill. The program began at 8:00am and ended at 4:30pm. Seven research areas were discussed. The format was a presentation on the state-of-the-art in a particular area by a senior scientist followed by reviews of one or two related studies at UNC. Each presentation was followed by question and answer opportunities. This booklet provides a summary of all presentations.

This non-CME symposium was held in conjunction with the Center for Gastrointestinal Biology & Disease (UNC Division of Gastroenterology & Hepatology). There were over 60 registrants from Duke University, Wake Forest University, and North Carolina State University as well as UNC. We also had participants from out-of-state, Norway and Japan.

It is our plan to make Research Day an annual event for the duration of our NIH grant. We appreciate the educational grants from Novartis Pharmaceuticals, AstraZeneca Pharmaceuticals, and Solvay Pharmaceuticals that provided additional support essential for this symposium.

William E. Whitehead, PhD
Co-Director

Douglas A. Drossman, MD
Co-Director

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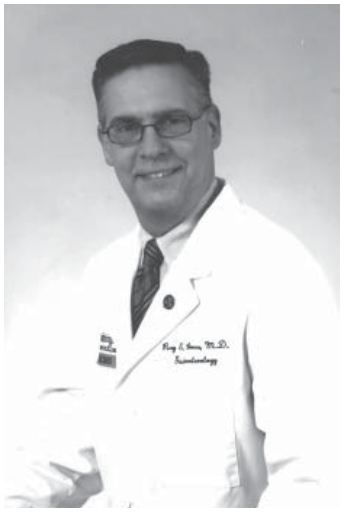
State-of-the-Art: Ray E. Clouse, MD
Professor of Medicine & Psychiatry,
Washington University School of Medicine, St. Louis, MO
Antidepressants and medical disorders — Various observations with reference to FGIDs


Ray Clouse

IBS has been linked to such comorbid conditions as anxiety disorders, affective disorders, and somatization disorder. Dr. Clouse posited at the onset of his presentation that FGID-related depressions and anxiety disorders may be different from those seen in other medical samples.

To develop this thought, he reviewed findings from other medical conditions. For example, studies of the prevalence of depression in persons with and without diabetes have found that depression doubles the risk of Type II diabetes and depression is associated with diabetes complications. In a 10-year prospective study of diabetic women conducted by Dr. Clouse, significant differences in the development of CHD (congestive heart disease) were found between study subjects who are depressed and those who are not depressed. Depression is linked to hyperglycemia in diabetes, and hyperglycemia improves with depression treatment (treatment of depression improves insulin sensitivity). In a study that compared rates of lifetime psychiatric diagnoses in NASH versus controls, there was a significantly higher frequency of general anxiety disorder and major depression in patients with NASH compared to matched controls (65% versus 33%). In addition, a psychiatric diagnosis was associated with a higher liver histology score, suggesting that a pre-existing psychiatric diagnosis may predispose to NASH and its histological severity in biologically susceptible hosts.

Dr. Clouse suggested that different groupings of co-morbidity may be associated with different types of depression. Medical depression, for example, is associated with NASH, hypertension, diabetes, CHD, and hyperlipidemia. Functional depression, on the other hand, is associated with fibromyalgia, chronic pelvic pain, headache, interstitial cystitis, and FGID. He also proposed that psychiatric disorders associated with FGIDs may have different clinical expressions than these disorders in patients with structural GI diagnoses, and they seem to be closely associated with somatization. For example, a 2001 study showed that lifetime anxiety and depression

R. Clouse, continued

are significantly more often found in those who have IBS with somatization than study subjects with ulcerative colitis or IBS without somatization. A 2004 study showed similar results comparing IBS study subjects with and without somatization disorder – across the board significantly higher rates of major depression, social phobia, panic disorder, PTSD, and any disorder excluding somatization. This suggests we need to recognize the psychiatric syndromes in patients with FGIDs in ways that are different from those traditionally taught for psychiatric patients. Possibly they represent a component of the underlying neurophysiology responsible for FGIDs – a neurophysiology that is "antidepressant responsive" for lack of a better term. Thus, treatment with antidepressants would be indicated for FGID clinical presentations that include general distress and functional impairment, even if the patient does not fulfill DSM criteria for a conventional psychiatric diagnosis.

Clouse showed two paradigms for antidepressant action in FGIDs. In these models, GI symptoms and "other factors" (referring to abnormalities in CNS neurotransmitters associated with major affective disorders) are two variables affecting global distress (leading to functional impairment, social limitations, work absenteeism). In the first paradigm, both variables have direct effects on global distress; antidepressants are used to treat/mitigate the "other factors" in order to lessen global distress. In the alternative paradigm proposed by Clouse, the GI symptoms have only a secondary impact on global distress, while the "other factors" have direct pathways to both global distress and possibly also to the GI symptoms; both pathways could be possible intervention opportunities for antidepressant treatment.

Tricyclic antidepressants produce global benefits for FGIDs and show greater benefit than SSRIs for functional symptoms/syndromes. However, some patients may have residual symptoms leading to continuing disability and relapse. In these cases, combined treatment with TCAs and SSRIs may be helpful. Antidepressants are also used in chronic non-cancer pain management. There is consistent, good-quality patient-oriented evidence to support the use of TCAs for treatment of chronic neuropathic and non-neuropathic pain syndromes. But, there is inconsistent or limited-quality patient-oriented evidence that TCAs are more effective than SSRIs in the treatment of neuropathic pain syndromes: an estimated 2.6 patients must be treated with TCAs and 6.7 patients with SSRIs to have 1 patient with >50% pain relief.

Dr. Clouse concluded: (1) the rationale for antidepressants in FGIDs extends well beyond a depression-treatment effect; (2) psychiatric co-morbidities in FGIDs seem to be providing clues to an underlying pathogenesis and drug mechanisms, and (3) some consideration should be given to syndromic management – encompassing co-morbidities in treatment response and addressing residual symptoms.

UNC: Douglas A. Drossman, MD
Professor of Medicine & Psychiatry, UNC School of Medicine, Chapel Hill, NC
Research on desipramine – NIH multi-center treatment trial


Douglas Drossman

Dr. Drossman summarized four studies based on data from an NIH-supported multi-center treatment trial (R01 DK49334). The primary aim of the first study published in 2003 was to compare cognitive behavioral therapy (CBT) versus education (EDU) and Desipramine (DES) versus placebo (PLA). The secondary aim was to determine if clinically meaningful subgroups are more or less responsive to treatment, using the following four categories: moderate and severe FBD, non-abused and abused participants, non-depressed and depressed participants, and predominant diarrhea and constipation symptoms. The recruitment period was 1996 to 2001 through advertisement or physician referral. During the screening visit, eligibility was determined (Rome II criteria, FBDSI), 14-day diary cards were provided (McGill Pain Questionnaire, stool frequency and consistency/Bristol, Global Well-Being) for pre- and post-treatment assessments, and a questionnaire for FBD diagnosis and severity. The study population of 431 was 78% IBS, 11% painful constipation, 7% FAPS, and 4% unspecified; 29% had moderate and 71% had severe FBD; and 58% had an abuse history. During the first week of the study visit, participants had a 3-hour psychological assessment and a 1-hour physiological assessment. They were then randomized to four different intervention arms: the psychological arm was either CBT (Toner modification of the Beck method) or EDU (reading and discussion of chapters from W.G. Thompson's Gut Reactions), and the medication arm (masked allocation) was either DES (increased by week from 50 to 15) mg by week 3, dose adjusted based on side effects, DES blood level taken at week 6) or placebo. During weeks 1 through 12, participants had various treatment sessions of 20 to 60 minutes each. At Week 12, the psychological and physiological assessments were repeated. Mail follow-up was done at weeks 24, 36, 48 and 60.

Using a Treatment Satisfaction Scale, participants were asked to rate the following on a scale of 1 to 5 (strongly agree to strongly disagree): I am satisfied with the results of my treatment; I am engaging in activities that I would not have done prior to treatment; I am better able to cope with my bowel symptoms due to treatment; treatment has helped me to cope better in other areas of my life; my bowel symptoms

D. Drossman, continued

have improved as a result of treatment; I would recommend this treatment to other people with FBD; my level of confidence has increased due to treatment; and I found the treatment to be more helpful than expected. Analysis of the data found that for women with moderate to severe FBD: (1) CBT is more effective than EDU, (2) DES is not significantly better than PLA in ITT, but is in per protocol (subjects who stay on drug), (3) DES arm dropouts relate mainly to side effects, (4) CBT and DES are equivalent in their effect, and (5) the main effect relates to treatment satisfaction. Ancillary analyses found that CBT is effective regardless of symptom severity or abuse status but is not effective for depression (BDI-II>16), and DES is more effective for subjects with moderately severe illness, abuse history, and diarrhea-predominant stool form but is not effective for subjects with depression.

The second study on factors predicting symptom reports of "side effects" when using tricyclic antidepressants (TCAs) was published as an abstract in 2005. The moderate to severe adverse effects identified for this study were: dry mouth, disturbed sleep, dizziness, constipation, hot flashes, tired, nervous, nausea, head ache, low appetite, and fast heart. Side effects reported after taking TCAs may be true side effects or may relate to a general tendency to report symptoms which, in turn, may result from psychological processes, e.g., somatization. The aims of the study were to assess which symptoms become worse (suggesting a drug effect) or not (suggesting somatization) between baseline and 2 weeks treatment with Desipramine, and to identify the predictors of reporting symptoms as side effects. For this study, 87 patients (57 DES, 30 PLA) in the drug arm of the above-cited treatment trial were studied. DES was prescribed at 50mg qhs for week 1 and 100mg qhs for week 2 if side effects were less than moderate in intensity. Subjects completed a 15-item symptom questionnaire at baseline before randomization and after 2 weeks on drug. Analysis of the data showed that certain symptoms were worse at week 2 compared to week 0, suggesting a drug effect (dizziness, feeling light-headed, dry mouth/thirsty, flushing), while other symptoms did not get worse at week 2, suggesting a non-drug related factor (nausea, trouble sleeping, blurred vision, tired). The conclusion was that physicians need to be aware of which symptoms are typically associated with drug side effects (e.g., dry mouth) versus a symptom reporting tendency (e.g., tired) when initiating or modifying treatment with TCAs.

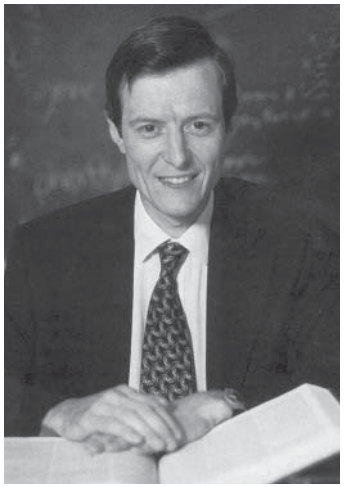
The third study published in 2005 pertained to DES dosage, plasma level and outcome. It is known that in high (i.e., psychiatric) dosages of DES, plasma levels correlate with clinical response. It was not known whether a similar response occurs with low-dose DES (levels used to treat FBD). The aim of this study was to determine if DES plasma levels or DES dosage predicts clinical response. Using data from the multicenter treatment trial, analyses showed only a modest correlation between DES dose and plasma level at week 6 and a lack of relationship between clinical response and DES dose or DES plasma levels. It was concluded that DES plasma levels do not determine efficacy with lower dosages, but they can be used to assess treatment adherence or toxicity.

D. Drossman, continued

The final study presented by Dr. Drossman (published as an abstract) pertains to placebo responders in the multi-center treatment trial. As background, Dr. Drossman noted how the definition and interpretation of placebo had changed from "an epithet given to any medicine adapted more to please than to benefit the patient" (Hooper's Medical Dictionary, 1811) to "…a dummy treatment administered to a control group in a controlled clinical trial in order that the specific and non-specific effects of the treatment can be distinguished" (Dorland's Medical Dictionary, 2001). Susceptibility to a placebo response does not relate to a specific medical or psychiatric diagnosis but instead to intrinsic features that are influenced by personal beliefs, expectancies and conditioning experiences. It is important both for research and clinical care to understand the determinants of a placebo pill response. The aim of the study was to determine the pre- and post-treatment factors that predicted a pill placebo response among women in the FBD treatment trial: placebo pill, demographic factors, clinical features and psychosocial factors. This analysis was confined to the 66 study subjects randomized into the placebo (PLA) arm of the study. Subjects were assessed pre-treatment and at completion of 12-weeks of CBT with regard to: visceral sensitivity, demographic factors, pain scores (diary cards), severity (FBDSI), stool habit (diary cards), psychosocial measures, process measures (Credibility Scale, Working Alliance Inventory/WAI), and response measure (Satisfaction with Treatment). The analysis found that among women with FBD, clinical response to a placebo pill was greatest when the study participant has: (1) confidence that the pill is being effective (regardless of pill placebo or active drug), (2) confidence in and a positive working alliance with the clinical trials coordinator, and (3) improvement in daily function. Furthermore, among women with FBD, clinical response in an FBD treatment trial is associated with: active treatment, Caucasian ethnicity, credibility (confidence that the treatment will be effective regardless of placebo or active drug), confidence in and a positive working alliance with the clinical trials coordinator, and improvement in QOL and daily functioning. Finally, clinical response to CBT for women with FBD is associated with: a sense of personal control, confidence in the CBT method and the effectiveness of the therapist, reduction in worry about illness, and improved functioning. Pre-existing and post-treatment cognitions are also associated with effective CBT.

In conclusion, when combining antidepressants and psychological treatments, clinical observations are that antidepressants improve (lessen) pain, vegetative signs and hopelessness, and increase motivation for psychological treatments. Psychological treatments, in turn, improve coping, cognitive function and effects of trauma, and increase adherence to medication. Brain imaging studies show that antidepressants may have "bottom up" effects, acting on the paralimbic (cingulate, insula), while psychological treatments may have "top down" effects on prefrontal cognitive areas improving "executive" function. Clinical trials show that combined treatments are better than monotherapy for headache, depression and other psychological disorders.

State-of-the-Art: Robin C. Spiller, MD
Professor of Gastroenterology, University Hospital, Queens Medical Centre, Nottingham, UK
Abnormalities of serotonin in IBS


Robin Spiller

Ninety-five percent of the serotonin found in the body is in the gut; of the remainder, about 2% is in the brain and 2% resides in platelets (blood). Within the gut, serotonin is found in enterochromaffin (EC) cells. EC cells play an important role in signal transduction – they release serotonin in response to mechanical stimulation by the contents of the gut, and this serotonin acts as a key neurotransmitter in the peristaltic reflex (motility). EC cells also respond in the upper gut to bacterial toxins and nutrients and in the distal gut to short chain fatty acids. EC cells appear to be inducible by inflammation -- they proliferate following enteric infection. These cells are distributed throughout the gastrointestinal tract but with the highest concentrations in the upper gut (stomach and duodenum) and in the distal end of the gut (sigmoid colon and rectum).

Post-infectious IBS (PI-IBS) refers to the persistence of abdominal pain and altered bowel habits long after the bacterial pathogens responsible for gastroenteritis have cleared. Recent studies suggest that 7-31% of patients who develop bacterial gastroenteritis will develop PI-IBS, which in turn may account for 25% of all IBS cases. The persistence of IBS symptoms is associated with persistent elevations in the numbers of T-lymphocytes and persisting increases in the number of EC cells. Dunlop has shown that the postprandial rise in serotonin (found in platelet-depleted blood) is greater in PI-IBS than in controls, although there is considerable between-subject variability. This appears to be due to greater turnover, since the number of EC cells is increased but the serotonin content of each EC cell is decreased relative to controls.

The Dunlop study also provides evidence for decreased serotonin turnover in IBS patients with constipation-predominant symptoms (IBS-C): the IBS-C group had normal numbers of EC cells in mucosal biopsies, but the concentration of serotonin per cell was greater than normal. IBS-C patients also showed reduced postprandial plasma levels of serotonin compared to controls and they had a reduced 5HIAA/5HT ratio,

R. Spiller, continued

indicating reduced turnover of mucosal serotonin. However, in PI-IBS, the 5HIAA/5HT ratio was paradoxically decreased even though release was increased. This suggests a defect of SERT in PI-IBS patients.

T-lymphocytes appear to play a key role in determining the numbers of EC cells in the gut: (1) In human studies, the number of T-lymphocytes is correlated with the number of EC cells. (2) In T-lymphocyte receptor knock out mice, there is less serotonin, and the increase in the number of EC cells that normally occurs following T spiralis (parasitic) infection does not occur. (3) Other T-lymphocyte mediated diseases (ulcerative colitis and celiac disease) exhibit abnormalities in serotonin similar to PI-IBS including EC cell hyperplasia and, in the case of celiac disease, elevated postprandial plasma levels of serotonin. There are other parallels between IBS, celiac disease and ulcerative colitis -- all three appear to have decreased levels of SERT, suggesting that inflammation decreases the availability of the serotonin reuptake transporter.

Evidence for the influence of serotonin on GI physiology – both sensation and motility – comes from studies of the serotonin 5HT3 antagonist, alosetron, and the 5HT4 partial agonist, tegaserod. Alosetron slows whole gut transit, decreases intestinal secretion, and attenuates the gastrocolic response to a meal, with associated reductions in the symptoms of diarrhea predominant IBS. Other 5HT3 antagonists reduce nausea and vomiting. Tegaserod accelerates gastric emptying, small bowel transit, and whole gut transit, with an associated reduction in the symptoms of constipation-predominant IBS.

UNC: William E. Whitehead, PhD
Professor of Medicine, UNC School of Medicine, Chapel Hill, NC
Is IBS one disease or many? Test of the heterogeneity hypothesis & implications for heritability studies


William Whitehead

Dr. Whitehead presented preliminary findings from an NIH grant on the psychophysiology of IBS. The overall goal of this grant is to understand causes for the comorbidity of IBS with other somatic and psychiatric disorders, with the following specific aims or research questions: (1) Are there unique associations between IBS and specific other disorders which might provide clues to shared pathophysiological mechanisms? (2) Is comorbidity explained by psychological mechanisms, i.e., is IBS a variant of a somatization disorder? (3) Is IBS a heterogeneous disorder in which one subtype has a primarily psychological etiology and is associated with comorbidity, while other subtypes are associated with distinct biological etiologies? Dr. Whitehead and his team refer to this as the "heterogeneity hypothesis." Studies addressing the first two aims have been completed and presented at meetings. This presentation focused on an on-going study that addresses the heterogeneity hypothesis.

In the first phase of the study, 150 IBS patients (medical diagnosis of IBS and meeting Rome II criteria) and 50 healthy controls (no chronic GI disorder) will be studied using a comprehensive battery of physiological and psychological tests. Cluster analysis will be used to identify subgroups – independent clusters of patients who are associated with one or more specific physiological or psychological etiologies. Since cluster analysis is a descriptive form of data analysis which can be influenced by the particular sample of patients investigated, the investigators plan to replicate the findings in a second panel of 150 IBS patients.

The effort has been to test as many as possible of the physiological and psychological measures that were identified in a systematic review of the literature as causes of IBS symptoms. Physiological measures include: pain sensitivity measured by both the ascending method of limits and signal detection; contractions of the colon measured both during fasting and in response to a standard meal; smooth muscle tone measured fasting and after the meal; small bowel bacterial overgrowth; lactose mal-

W. Whitehead, continued

absorption; blood chemistries suggestive of a systemic infection; screens for celiac disease (IgG & IgA, IgE); serotonin measured fasting and postprandially, VIP, Substance P; autonomic nervous system activity (heart rate variability, electrodermal activity); stress hormones (cortisol, epinephrine, norepinephrine, acetylcholine); and genetic polymorphisms in the serotonin reuptake transporter mechanism (SERT). Clinical history measures include: Rome criteria for IBS, chronic functional abdominal pain, and functional dyspepsia; predominant bowel habits; onset following gastroenteritis; the Comorbid Medical Conditions Questionnaire; the Recent Physical Symptoms Questionnaire (a measure of somatization trait); the IBS Symptom Severity Scale; IBS-specific quality of life; and demographics (age, gender, ethnicity). Psychological measures include: a general psychiatric symptom scale (BSI-18); a standard personality inventory (NEO-PI; the Prime MD to screen for psychiatric disorders; a portion of the SCID interview (Somatization Module G); a Pain Coping Inventory (catastrophizing scale); Trauma Symptom Checklist–40; Sexual and Physical Abuse Checklist; Family Inventory of Life Events (stress scale); and Perceived Stress Scale.

Preliminary findings were presented for 130 IBS patients and 24 healthy controls tested to date in the first phase of the study. Among the IBS patients, 32.8% were diarrhea-predominant IBS by self-report, 38.9% were constipation-predominant IBS, and 28.2% were IBS patients with alternating bowel habits.

- Motility (contractions) of the colon: The motility response to two different provocative stimuli was studied. In response to distention of the colon with a balloon at the threshold pressure required to produce a sense of urgency to defecate, IBS patients show a greater increase in contractions (motility index) than controls. In response to a standard meal, IBS patients and controls both show an increase in contractions (gastrocolic response), but the differences between patients and controls are not statistically significant.
- Smooth muscle tone: Muscle tone (measured by barostat volumes) was significantly greater in IBS patients at baseline, during distention to the urge threshold, and during recovery. However, there was no difference in muscle tone following the meal.
- Sensory thresholds: IBS patients had significantly lower thresholds for pain and urgency compared to controls. Fifty-two percent of IBS patients compared to 16% of controls had abnormal pain thresholds.
- Psychological distress: IBS patients had significantly higher scores on the BSI-18 scales for somatization, anxiety and overall psychological distress, but not for depression.
- Comorbid conditions and somatization: IBS patients reported significantly more comorbid somatic symptoms than controls, and they had more comorbid diagnoses. However, 40% of IBS patients had numbers of comorbid conditions that were within the normal range.

W. Whitehead, continued

- Support for heterogeneity hypothesis: Although these data have not yet been subjected to cluster analysis, preliminary analyses support the heterogeneity hypothesis by showing:
  - Both the motility response to distention and the pain threshold distinguish IBS patients from healthy controls, but these measures are not correlated with each other. This suggests that abnormal motility and abnormal pain sensitivity identify different patients who meet the criteria for IBS.
  - Both the motility response and psychological symptoms distinguish IBS patients from healthy controls, but these measures are not correlated, suggesting that abnormal motility and abnormal levels of psychological distress identify different patients all of whom meet the symptom criteria for IBS.
  - Sensory thresholds are also poorly correlated with psychological distress, which would also be consistent with the heterogeneity hypothesis.

As next steps in this research, Dr. Whitehead outlined the following: (1) complete the initial cluster analysis in Summer 2005; (2) revise the test panel and begin the replication study (working with Dr. Ringel to collect stool specimens and test for stool pathogens specific for IBS & abnormal immune responses); and (3) expand genotyping studies.

The goal of the cluster study – to identify distinct subtypes of IBS associated with independent etiologies – has important implications for the treatment of functional bowel disorders. It offers the promise that treatments can be more clearly targeted to the patients most likely to benefit from them, and it may identify new targets for drug development. The outcome of this study may also significantly advance studies of the genetic contributions to IBS by identifying distinct phenotypes which may be associated with different genetic polymorphisms.

Future directions for this research include an expanded genotyping protocol. In the grant application, Dr. Whitehead had originally proposed testing only SERT polymorphisms, but recent studies suggest that polymorphisms in other genes – those controlling the expression of adrenergic receptors and COMT – may also be important to the etiology of IBS. These studies also suggest that the same genes believed to be associated with IBS are also involved in the etiology of other disorders such as fibromyalgia, chronic fatigue, and psychiatric disorders that commonly occur as comorbid disorders in patients with IBS. Expanded genotyping studies would entail recruiting additional UNC collaborators, securing additional funding to expand genotyping of existing data, and gaining access to DNA from new, large samples of IBS patients.

State-of-the-Art: Rona L. Levy, PhD
Professor, School of Social Work, University of Washington, Seattle, WA
Intergenerational transmission of the FGIDs: Nature or nurture?


Rona Levy

The basic question raised in Dr. Levy's presentation is whether the intergenerational transmission of functional GI disorders (FGIDs) is a result of nature or nurture -- or nature and nurture. A focus on the genetic hypothesis (nature) would emphasize research to confirm that FGIDs are disease entities, to develop new insights into pathophysiology, and to identify new targets for drug development. An interest in the environmental influence hypothesis (nurture) would include research on prevention through parent education, explaining the effectiveness of cognitive behavior therapy (CBT), and exploring the overlap of FGIDs with other somatic disorders.

Illness behavior is a key concept in the social learning hypothesis. It refers to the ways people perceive and react to somatic sensations that may be associated with a disease -- such as health care visits, reports of symptoms, and general disability. Dr. Levy reviewed a number of published and on-going studies demonstrating the relationship between a parent and child's disability and illness behavior. However, she noted that evidence of family aggregation and intergenerational transmission are consistent with either a genetic or an environmental (social learning) hypothesis, and do not resolve the nature-nurture question.

Dr. Levy then reviewed a study conducted by her group of twins with IBS, both monozygotic (MZ) and dizygotic (DZ). The study found that having an MZ twin with IBS increases one's risk of developing IBS by about 9 percent, supporting a genetic explanation. But, by examining mothers as well as twins, the study found the contribution of learning to having an FGID was even stronger than the genetic contribution. This raises the question of how the manner in which parents respond to a child's somatic complaints relates to the magnitude (severity) of these complaints. Prior studies have already shown that adults with IBS are likely to report that, when they were children, they received reinforcement from their parents when they were ill. In a prospective study, Levy et al. have found that higher levels of parental solicitousness in response to their child's illness behavior appear to be related to higher levels

R. Levy, continued

(severity) of the child's symptoms.
Dr. Levy has also conducted research on how psychological traits influence the decision to bring a child with abdominal pain to the pediatrician (consulting behavior). The study looked at the mother's psychological symptoms (somatization, anxiety, overall psychological distress), the child's psychological symptoms, and/or the severity of child's pain. She has found that the decision to take a child to the clinic for abdominal pain is related to psychological distress in the mother. An on-going study of Levy et al. is focused on assessing whether changes in the environmental factors associated with the intergenerational transmission of FGIDs – parental response and modeling -- result in a decrease in the encouragement of illness behavior by parents and a decrease in abdominal pain and other GI symptoms in children from baseline to post-treatment and follow-up.

From a review of the literature and her own research, Dr. Levy has concluded that, at any moment, an explanation for illness expression can shift between genetic vulnerability and environmental factors. She posited that heritability may make a large contribution to a small group of subtypes of FGIDs rather than a weak contribution to all subtypes of FGIDs. As a guide for further research opportunities and challenges, Dr. Levy outlined a model of illness behavior that begins with basic biology, progresses to the presence of a sensation and an individual's recognition of the sensation, to whether or not action is taken by the individual who notices the sensation, and culminates with whether the environment increases, decreases or has no effect on the behavior of the individual. From this model, she suggests several psychosocial research opportunities: (1) psychosocial problems in parent or child that contribute of anxiety or somatization, (2) ways to measure and modify parent and child cognition, and (3) ways to modify parent and child behavioral response and symptoms.

Dr. Levy's final thought was if we accept the fact that FGIDs are actually heterogeneous disorders – a collection of disorders with different etiologies -- then it would make sense to explore the extent to which biology and heritability make contributions to the behavior and cognitions of selected subtypes of IBS and other FGIDs.

UNC: Denesh Chitkara, MD
Assistant Professor of Pediatrics, UNC School of Medicine, Chapel Hill, NC
Functional dyspepsia in children: one disorder or many?


Denesh Chitkara

Dr. Chitkara presented a study to evaluate the physiological abnormalities contributing to symptoms in adolescents with functional dyspepsia (FD). Symptoms of dyspepsia are quite common -- 20% of adolescents in the community report nausea – and most children who undergo an evaluation for dyspepsia have no identified organic cause. He used validated non-invasive tests of gastric motor and sensory function to investigate the pathophysiology of symptoms in adolescents with FD. His study population included 15 adolescents who met Rome II criteria for FD within the preceding 12 months (persistent or recurrent pain or discomfort in the upper abdomen, no evidence that organic disease is likely to explain the symptoms, and no associated symptoms of IBS), and 15 healthy adolescents from the community. All adolescents underwent: Questionnaire of Pediatric Gastrointestinal Symptoms (QPGS), satiation nutrient drink test, and 13C S.platensis breath test (stable isotope test for solid GE). Adolescents with FD also underwent fasting and postprandial gastric volume measurement with SPECT. Fifteen healthy young adults (18 to 25 years) who underwent gastric volume by SPECT were used for comparison. His study showed that adolescents with FD had increased symptoms on a nutrient drink test, delayed solid gastric emptying, and reduced gastric volume post-meal as compared to healthy controls.

Dr. Chitkara then discussed additional potential environmental, mucosal and psychosocial factors that may contribute to FD symptoms in adolescents. From the literature, he observed that abdominal pain severity and frequency are higher in adolescents with depression than without, and frequent headaches are more common in adolescents with abdominal pain (58%) than without (25%). Areas for further research include examining the role of parental influence, comorbidity and mucosal inflammation along with gastric sensory motor abnormalities that may further explain symptoms of FD in children.

Brain Imaging

State-of-the-Art: Emeran A. Mayer, MD
Professor of Professor of Medicine, Physiology and Psychiatry, David Geffen School of Medicine at UCLA, Los Angeles, CA
Brain imaging in functional GI disorders


Emeran Mayer

Dr. Mayer began his presentation with an overview of the evolution of brain imaging studies pertaining to the perception of visceral stimuli ("visceral sensation"). The first studies were descriptive of broad anatomical regions and included patient-control comparisons. The next phase was improved descriptive studies of more precise regions of the brain and subject subgroups. The phase we are in now is hypothesis-driven, looking at functional networks, sub-regions and neurotransmitters, and using correlations with genetic information. Dr. Mayer presented information about: (1) group differences between IBS and control subjects, (2) cortico limbic interactions, (3) sex-related differences between male and female IBS patients, and (4) therapy effects which correlate with IBS symptoms.

Considerable clinical and experimental evidence is consistent with the concept that IBS symptoms in a large number of IBS patients result from variable combinations of autonomic dysregulation and altered visceral perception. According to this concept, IBS symptoms of abdominal pain and discomfort are likely to be related in part to the presence of visceral hypersensitivity, while altered bowel habits suggest underlying autonomic dysregulation. As current defined, IBS symptoms are non-specific with regard to underlying pathophysiology and may result from a variety of central and/or peripheral causes. For example, mucosal immune activation can be brought on by allergies, celiac disease, microscopic colitis, IBD, GERD, bacterial overgrowth, or mastocytosis. While many of these peripheral events may produce visceral afferent stimulation or sensitization, central factors (spinal and/or supraspinal) are likely to play a crucial role in determining symptomatic responses in predisposed individuals. This "central pain amplification" (or lack of pain inhibition) may determine which patients develop typical IBS symptoms. Factors that can engage these central mechanisms include symptom-related anxiety and psychological distress.

E. Mayer, continued

It has been suggested that lamina I spinothalamic pathways (together with vagal afferents) represent "homeostatic" afferents that process afferent information about the body's homeostatic state. They are located in the superficial dorsal horn of the spinal cord. Signals transmitted in these pathways ("interoceptive stimuli") usually do not reach conscious awareness, but mediate homeostatic responses of the organism to such perturbations as pH changes, tissue irritation and luminal gut events. Reflexes are organized at multiple levels of the brain gut axis, all the way to the cortical level (dorsal anterior cingulate and insular cortices). By modulating perception of interoceptive events and the autonomic responses to such perturbations, these cortical regions are plausible brain regions involved in IBS symptom modulation.

The IBS symptom complex reflects an alteration in autonomic (e.g., altered bowel habit) and perceptual (e.g., increased pain and discomfort) homeostatic responses, and the cortex modulates these responses. The brainstem antinociceptive network (involving the PAG, dorsal pons and rostral ventromedial medulla) allows a fast response and powerful analgesia in direct response to noxious stimulus. Using functional brain imaging, it has been demonstrated that healthy controls successfully activate the endogenous pain inhibition system in response to noxious stimuli (including the periaqueductal grey area, PAG). In contrast, IBS patients appear to differ in this response from healthy control subjects as well as from patients with longstanding colonic inflammation (ulcerative colitis patients) by showing less activation of these brainstem regions. IBS patients show greater activation of limbic and paralimbic regions during visceral stimulation as compared to these two control groups.

Dr. Mayer then reviewed imaging studies testing simple models of cortico limbic interactions through the use of connectivity analysis. He presented a model tested in healthy controls and quiescent UC patients showing functional connectivity between the right lateral prefrontal cortex, the medial prefrontal cortex and the dorsal pons, including the PAG. He suggested that such networks could mediate the stimulatory effect of belief systems (generated in the lateral prefrontal cortex) on endogenous pain inhibition systems. Since this connectivity pattern was not seen in IBS patients, one may speculate that inadequate corticolimbic interactions may play a role in the greater perceptual and autonomic response of certain IBS patients to visceral stimuli. He reviewed other data showing a growing body of evidence supporting altered corticolimbic interactions as an important component in the pathophysiology of affective disorders.

The third group of studies reviewed by Dr. Mayer was focused on identifying sex-related differences in IBS patients with regard to symptoms and visceral perception. The prevalence of IBS is estimated at a ratio of 3:1 or 3:2 for women relative to men. In addition, women are more at risk for post-infectious IBS, and women have a greater degree of visceral hypersensitivity. IBS co-morbid conditions -- fibromyalgia, interstitial cystitis, anxiety -- are also more common in women. Brain imaging work at

E. Mayer, continued

UCLA has shown that females show greater activation of limbic structures (areas of the anterior cingulate cortex and amygdala) while male patients show greater activation of the dorsal pons (including the PAG) which may be associated with greater descending inhibitory responses to pain. These preliminary findings suggest there may be sex-based differences in the response pattern of IBS patients to incoming afferent signals from the pelvic viscera.

The final group of studies reviewed by Dr. Mayer is focused on identifying therapy effects which correlate with IBS symptoms. Studies looking at cognitive-behavioral treatment (CBT) for IBS patients show a reduction in limbic and paralimbic brain activity in post-treatment patients. Similarly, IBS patients receiving a tricyclic antidepressant (TCA) have a reduction in stress-induced ACC activity when compared to placebo. There is strong evidence that effective IBS drugs, such as the 5-HT3 receptor antagonist Alosetron, have central effects on limbic structures, in particular the amygdala. These drug-induced central changes were found to be correlated with subjective symptom improvement. Consistent with other reports in the placebo literature, IBS patients responding to placebo showed activation of a corticolimbic pontine network, involving the right lateral prefrontal cortex, and dorsal anterior cingulate sub-regions. The activation of this network was associated with subjective IBS symptom improvement.

Dr. Mayer concluded his remarks with the following summary:

- functional brain imaging techniques are the only objective way to dissect brain processes involved in altered brain-gut interactions in IBS patients
- rapidly evolving technologies and analysis techniques have changed "Blobology" into a hypothesis-driven discipline based on functional neuroanatomy
- the future will be dominated by neural network analysis, PET ligand studies and imaging genomics approaches.

UNC: Yehuda Ringel, MD
Assistant Professor of Medicine, UNC School of Medicine, Chapel Hill, NC
Past and proposed brain imaging work in IBS


Yehuda Ringel

Functional brain imaging research at UNC is characterized by a comprehensive integrative approach, investigating multiple dimensions of visceral sensation/pain experience, including the role of psychosocial factors (e.g., history of abuse, stress) in IBS. The first UNC study, published in 2003, was a PET study of 12 subjects. For the subsequent fMRI-based studies, preliminary results have been published in six abstracts.

Dr. Ringel presented three studies. The first study was titled Anterior Cingulate Cortex Activation in Response to Painful Rectal Distention in IBS and Sexual/Physical Abuse. The aim of this study was to determine regional brain activity in response to painful rectal distention in subjects with one of four conditions: IBS/no abuse, abuse/no IBS, IBS/abuse, and no IBS/no abuse controls. The fMRI images were obtained on a 1.5T MR scanner. Images were acquired continuously during repeated rectal distentions. The 40 seconds of imaging between balloon distentions served as the baseline. Statistical parametric mapping (SPM) analysis was performed to identify activation differences between baseline and distentions. With regard to the effect of abuse history, the results from the fMRI study were in agreement with what was found in the PET study. Results: (1) compared to non-IBS subjects, IBS patients show higher activation in the posterior cingulate in response to distention but less activation at the perigenual anterior cingulated cortex (pACC); (2) compared to non-abuse subjects, abuse subjects show higher activation in the posterior and mid cingulate and lack of activation at the pACC; and (3) the IBS/abuse patients also show higher activation in posterior and mid cingulate and failure to activate pACC when compared to all other subjects. The conclusion from this study is that abuse history, independent of IBS, leads to decreased activation of pACC in response to painful rectal distention. This may explain the greater response to pain among patients with an abuse history. The lack of pACC activation, attributed to IBS diagnosis in previous studies, may be associated with abuse history and not to IBS diagnosis.

Y. Ringel, continued

The second study was titled Association of Anterior Cingulate Cortex (ACC) Activation with Psychosocial Distress and Pain Reports. The aim of this study was to determine the relationship among psychological factors, pain experience, and brain activation during rectal balloon distention. The hypothesis was that greater psychological distress will be associated with greater pain reports, and both will be associated with changes in brain activation evoked by rectal distention. ROI analysis was used to measure the activation for each condition/distention at each specific region of the brain. The association between brain activation at a specific region, the subject's reports of pain, and psychological variables were assessed by Pearson correlation. The analysis showed that psychological factors are associated with increased pain experience and pACC activation. This study provides novel evidence for an association between psychological factors, pain experience, and regional brain activation. This may suggest a mechanism by which psychological factors modulate pain experience and behavior, and explain the experience of more severe pain and illness during psychological distress.

The final study was titled Absolute Regional Cerebral Blood Flow - MRI Study in Patients with IBS. Currently available imaging techniques enable relative measurements of differences or changes in brain activation between different conditions (e.g., baseline vs response to stimulus), but absolute activity is not measured. Therefore, reported data of low or lack of activation at a specific region of the brain might be inaccurate, since it may be affected by a "ceiling effect." The aims of this study are to measure baseline cerebral blood flow in specific areas of interest, and to measure the effect of balloon insertion only (without distention) on baseline cerebral blood flow (anticipatory effect) at specific areas of interest (anticipatory effect). Ten female subjects were studied by IV injection of non-diffusible paramagnetic MRI tracer. Analyses of regional CBF were done using specific software that was developed at the UNC Brain Imaging Research Center. Various regions in the gray and white matter were selected as references assuming that they are not involved in the brain response to pain or the anticipation of pain, i.e., background activity. This study provides novel information about regional cerebral blood flow at baseline in specific brain regions of interest. The study results suggest that: (1) the reported low or lack of activation of the pACC in response to pain in patients with IBS is a true measure and not a result of a "ceiling effect", and (2) the insertion of a balloon does not cause a significant change in the baseline CBF (i.e., there is no significant anticipatory effect).

Pelvic Floor Disorders

State-of-the-Art: Anne M. Weber, MD, MS
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Associate Professor of OBGYN & Reproductive Sciences,
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Pelvic floor disorders: Unmet needs and next steps


Anne Weber

Pelvic floor disorders (PFD) include pelvic organ prolapse, urinary incontinence and other disorders of bladder filling and emptying, and anal/fecal incontinence and other GI disorders of rectal storage and evacuation. It has been estimated that 20% of women with prolapse or urinary incontinence also have a functional bowel disorder.

In terms of costs, the public health burden of urinary incontinence is estimated to be $16 billion, of which less than 2% is for treatment. For prolapse it is $1 billion per year in direct medical costs of surgery, plus an unknown amount for non-surgical treatment, indirect medical costs, and non-medical costs. There are no cost figures for fecal incontinence. The public health burden of PFDs will increase with an aging US population – from 2000 to 2030, the number of Americans over age 65 will more than double, with 39 million women by 2030. The prevalence of PFDs is very high:

» lifetime risk of 1 in 11 for surgery for prolapse or urinary incontinence
» 200,000 surgeries for prolapse per year
» 85,000 surgeries for urinary incontinence/year.

PFDs may have a common pathophysiology -- dysfunction affecting the neuromuscular and connective tissue supports of the pelvic organs. Some of the inherited risk factors for PFDs are differences in collagen (such as Ehlers-Danlos syndrome and possibly joint hypermobility as examples of connective tissue deficiency) and differences in pelvic anatomy (e.g., pelvic muscle mass, bony architecture of the pelvis). Acquired risk factors for PFDs may include life events such as childbirth, physical activity, obesity, menopause, and aging.

With regard to childbirth, risk factors include: (1) direct and indirect damage to pelvic muscles, nerves and connective tissue, (2) direct damage to the internal and external anal sphincters, and (3) midline episiotomy (greatly increased risk of direct sphincter damage). Prevention is essential to reducing anal sphincter damage at childbirth. Women with recognized anal sphincter damage at childbirth have a higher risk of PFD symptoms. However, some women with apparently intact sphincters also develop PFD symptoms, even women who delivered by cesarean. An important question is whether there is more than one mechanism of dysfunction. There are also risk factors beyond childbirth – changes associated with menopause (possibly related to estrogen loss), aging with loss of neuromuscular function, and factors outside the pelvis such as cognitive decline and mobility limitations.

A. Weber, continued

The Pelvic Floor Disorders Program includes several NICHD initiatives: workshop on terminology, various RFAs (Basic Science, Epidemiology, Clinical Trials Network), and collaboration with NIDDK on the Urinary Incontinence Treatment Network. The "Nun Study" led by Dr. Buchsbaum has shown the same prevalence of urinary incontinence in nulliparous women (nuns) as in the parous sisters of these nuns. The average age in this study was 61 years. By current definitions, almost all women have some degree of prolapse. Pelvic symptoms are very common, especially incontinence, but not necessarily related to parity.

The PFD Network was started in July 2001 with a data coordinating center at the University of Michigan (Principal Investigator, Dr. Morton Brown) and seven clinical sites: UNC (Dr. Anthony Visco), Johns Hopkins (Dr. Geoff Cundiff), University of Iowa (Dr. Ingrid Nygaard), Loyola (Dr. Linda Brubaker); Baylor (Dr. Paul Fine), University of Pittsburgh (Dr. Halina Zyczynski), and University of Alabama Birmingham (Dr. Holly Richter).

Future needs include a continuation and expansion of the Pelvic Floor Disorders Network, and stimulation of collaboration between basic and clinical scientists across disciplines to study pathophysiology and prevention of pelvic floor disorders in women.

UNC: Steve Heymen, MS
Instructor in Medicine, UNC School of Medicine, Chapel Hill, NC
Biofeedback for constipation and fecal incontinence


Steve Heymen

Constipation occurs in 4% of US adults. Pelvic floor dyssynergia (PFD) is estimated to account for 25-50% of this group. There are differences in normal pelvic floor physiology in patients with slow transit constipation and the abnormal pelvic floor physiology in patients with outlet dysfunction constipation. When treating constipation with biofeedback, the goal is to train subjects to coordinate pelvic floor muscle relaxation with adequate downward abdominal pressure to allow for defecation. Through "trial and error", patients receiving biofeedback treatment learn to improve their ability to push without paradoxically contracting pelvic floor muscles.

In a review of the literature of mostly uncontrolled studies, the success rate of biofeedback for constipation is approximately 74%. To improve on these studies, the goals of an on-going PFD study at UNC are to: (1) compare biofeedback to placebo or diazepam treatment strategies (all subjects received PFM retraining and stool softeners), (2) identify predictors of a successful treatment outcome, (3) demonstrate improvements in quality of life (QOL) in successfully treated subjects, and (4) develop a treatment manual.

Prior to randomization to treatment groups, all patients received education and conservative medical management consisting of (1) recommendations to use stool softeners and high fiber diet to improve stool consistency; (2) education regarding the role of diet, exercise, and toileting schedule; and (3) advice on appropriate posture, behavior, and attitude while attempting defecation. Patients who did not obtain satisfactory relief of constipation from these conservative measures were randomized to three treatment groups: pelvic floor biofeedback training, 5 mg diazepam one hour before the evening meal, or a placebo tablet one hour before the evening meal. Patients in all three groups met one-on-one with a therapist every two weeks for six one-hour training visits, and all received education concerning pelvic floor physiology (video) and pelvic floor muscle training. The biofeedback group received, in addition, visual feedback on the success of their efforts to relax the pelvic floor during defecation.

S. Heymen, continued

The first hypothesis (Hypothesis 1.a) was: EMG biofeedback will be more effective than a skeletal muscle relaxant or placebo for the treatment of constipation when measured by the proportion of patients reporting "adequate relief" of constipation. The primary outcome measure (at 3-month follow-up) was: "Compared to before your enrollment in this study, have you had adequate relief of your constipation symptoms?" We found the percentage reporting adequate relief was 70% for biofeedback, 38% for placebo, and 23% for diazepam.
Additional hypotheses are:

» Hypothesis 2: One or more variables measured during the screening or run-in phases of the study will predict the response to treatment. However, none of the physiological, psychological, demographic, or symptom variables was a significant predictor of adequate relief.
» Hypothesis 3: Improvements in QOL will be associated with successful treatment outcome. The study found that improved QOL was correlated with successful treatment and increased unassisted bowel movements (UBMs).

Our analyses have shown that: (1) biofeedback is superior to alternative treatment for PFD constipation, (2) biofeedback patients report greater increases in UBMs than patients in alternative treatment, and (3) there were significant reductions in straining for all treatment groups. There were no significant predictors of treatment success. The treatment manual has been written and is being edited, and 6-month and 12-month follow-up visits are ongoing.

UNC: Anthony Visco, MD
Assistant Professor, Div. of Urogynecology & Reconstructive Pelvic Surgery, Dept. of OB/GYN, UNC School of Medicine, Chapel Hill, NC
Pelvic floor disorders


Anthony Visco

Incontinence research is generally in three areas -- prevalence and incidence, modifiable risk factors, and prevention. A primary aim of the Pelvic Floor Disorders Network "CAPS" study ("Childbirth and Pelvic Symptoms") was to compare the prevalence and incidence of postpartum urinary and fecal incontinence in three cohorts of women: (1) vaginal delivery with no anal tear, (2) 3rd or 4th degree tear, and (3) non-labored cesarean control. Other aims were to evaluate the quality of life (QOL) associated with symptoms and identify risk factors for postpartum urinary incontinence (UI) and fecal incontinence (FI). Data analysis for the CAPS study is ongoing.

Another study assessed whether occiput posterior (OP) fetal head position conferred an incrementally increased risk of anal sphincter injury during forceps-assisted vaginal deliveries. Factors considered include nulliparity, birth weight and episiotomy, in addition to fetal head position. Data were based on forceps-assisted vaginal deliveries at UNC between January 1996 and October 2003. Exclusion criteria were multiple gestations, non-vortex presentations, failed forceps, and stillbirths.

3rd or 4th degree lacerations were found at the following rates: 35% of all forceps deliveries, 51.5% of OP deliveries, and 32.9% of occiput anterior (OA) deliveries. There was a statistically significant difference between OP and OA groups. To assess the odds ratio for 3rd or 4th degree lacerations for unadjusted OR and adjusted relative OR, the considerations were: OP position, BMI, length of 2nd stage, episiotomy, birth weight, use of rotational forceps, and head circumference. It was found that OP increased the risk of 3rd and 4th degree lacerations – 52% absolute risk and adjusted OR 2.7. The conclusions were:

» OP position confers an increased risk of 3rd and 4th degree lacerations in forceps deliveries
» Forceps delivery is a significant modifiable risk factor for anal sphincter injury
» Given the potential long-term sequelae of anal sphincter injury, serious consideration should be given prior to performing a forceps delivery with an OP position.

A. Visco, continued

With regard to prevention, there is on-going enrollment in the Cesarean after Sphincter Tear (CAST) Study. This study will assess the role of cesarean delivery in patients after a sphincter tear during a prior vaginal delivery. The population includes primiparous women with singleton gestations, with previous 3rd or 4th degree laceration. Baseline urinary, bowel and QOL questionnaires are being collected, and participants are randomized at 36-37 weeks gestation to either elective cesarean section or trial of vaginal delivery. The primary outcome measure is the rate of anal incontinence at 12 months. The secondary outcomes are:

» Imaging -- endoanal ultrasound and pelvic MRI
» Rate of pelvic organ prolapse
» Rate of immediate and short-term complications
» Urinary, bowel and sexual function and QOL
» Hospital costs/utilization.

Patient (mother and infant) safety concerns are: feasibility, informed consent, risks of placenta previa/accreta with future pregnancies, and minimizing operative risks/complications (antibiotics, double-layer uterine closure). The investigators proposed this well-designed randomized controlled trial to: (1) evaluate how route of delivery influences rates of fecal incontinence and other pelvic floor disorders, (2) adequately counsel patients, and (3) give both patients and physicians the data to make informed decisions. The goal is a healthy mother and baby. This study is ongoing.

State-of-the-Art: Peter J. Whorwell, MD
Senior Lecturer/Professor in Gastroenterology,
Univ. Hospital of South Manchester, Manchester, UK
Hypnotherapy for functional GI disorders


Peter Whorwell

Hypnotherapy is among the alternative medicine treatments for functional GI disorders (FGIDs) that also include yoga, transcendental meditation, healing, aromatherapy, relaxation, and reflexology. Hypnotic inductions can vary from dramatic to simple techniques and from light to deep concentration (trance), depending on the therapist and patient.

Studies on the use of hypnosis for IBS date back to an article published in Lancet in 1984 which showed that the hypnosis treatment group scored better than a control group (receiving supportive psychotherapy and placebo pills) in mean scores of weekly pain, distention, bowel habits, and general well-being. A later study in 1996 showed post-hypnosis improvement in a variety of symptom scores: overall, abdominal pain, bloating, bowel dissatisfaction, incomplete evacuation, and urgency. Extra-colonic symptoms have also been shown to improve following hypnosis treatment (nausea, backache, dyspareunia, urinary symptoms, and lethargy), as well as quality of life (QoL) scores for psychic and physical wellbeing, mood, locus of control, and work. IBS patients effectively treated through hypnosis have been shown to take less time off from work, are more effective at work, and have fewer GP consultations for IBS and other conditions.

Dr. Whorwell's program of hypnosis treatment for FGIDs at the University Hospital of South Manchester (U.K.) includes six therapists. Using their first 250 patients as subjects, a study by Dr. Whorwell and colleagues in 2002 confirmed improvement in IBS symptom severity scores (overall, pain severity, pain frequency, bloating, bowel habit dissatisfaction, life interference), extra-colonic features and QoL, as well as anxiety and depression.

Studies are also showing the long-term benefits of hypnotherapy -- both total and individual symptoms scores remain improved for as long as five years post-treatment. Beneficiaries are no longer taking medications for their GI symptoms or they are taking medications less often, and they are consulting general practitioners less often about their GI or other symptoms. Similarly promising results from hypnotherapy are being reported for functional dyspepsia (FD), as well. In 2002, Whorwell's team published a controlled study that showed changes in FD symptoms were highest for hypnotherapy as compared to conventional treatment and supportive treatment, as much as 50-60 weeks post-treatment.

P. Whorwell, continued

The mechanism of action in hypnosis treatment appears to be both psychological (non-specific cognitive change) and physiological (visceral sensitivity, central processing). In a study of cognitive changes, post-hypnosis results showed statistically significant improvements in bowel performance anxiety, pain, control, self-efficacy, anger/frustration, shame, disease conviction, and social approval. Improvements correlated with reductions in IBS symptom score, extra colonic symptom score, and anxiety and depression scores.

A 1990 study by Whorwell's team published in Gut tested visceral sensitivity before, during and after hypnotherapy for diarrhea-predominant IBS patients. Sensory thresholds for gas, stool, urgency, and discomfort were tested using fixed volume distentions. Visceral sensitivity was reduced both during and after hypnotherapy. A more recent study by the same team, using fixed pressure distention (barostat), found that visceral thresholds of hypersensitive patients normalized after a course of hypnotherapy. Interestingly, the thresholds of patients who were less than normally sensitive to pain in their gut tended to normalize as well (although this finding was not statistically significant). Furthermore, improvement in rectal hypersensitivity was correlated with IBS symptom improvement.

Simren and colleagues have recently measured colonic sensory and motor responses to duodenal lipid infusion. This is a model for measuring gastrocolonic response to food. They demonstrated that hypnotherapy resulted in reduced reactivity to lipids. This may be important, because IBS symptoms are often worse after food.

The ACC is an important pain processing area in the brain. Painful rectal stimulus activates the ACC in IBS more than in controls. It has been demonstrated in brain imaging work that hypnotic suggestion reduces suffering from but not the perception of a painfully hot stimulus.

In sum, hypnotherapy appears to provide sustained relief of symptoms, modifies motility, modifies visceral sensitivity, improves quality of life, causes patients to have less time off work and get back to work sooner, leads to fewer GP consultations, and reduces medication needs. It can be very effective and help with all symptoms. It is time-consuming and costly to provide, and there needs to be a back-up strategy for patients who fail to benefit from hypnotherapy.

UNC: Olafur S. Palsson, PsyD
Associate Professor of Medicine, UNC School of Medicine, Chapel Hill, NC
Hypnosis treatment for IBS – the North Carolina model


Olafur Palsson

The North Carolina model for hypnosis treatment of IBS was designed in 1994-1995 at UNC-Chapel Hill. The protocol is used verbatim regardless of people's differing rate of response or cognitive style, and is a combination of permissive but directive and formal/experimental style of hypnosis delivery. Elements of the standardized protocol include:

- Imagination-driven physical relaxation
- Deepening in classic ways with counting, combining imagery with sensory experiences of going deeper
- Vivid therapeutic scene (metaphor) imagined in multiple senses that suggests protection from disturbance and discomfort, feeling comfortable inside
- Tying each visualizing scene to GI-related changes
- Post-hypnotic suggestions to neutralize catastrophizing and neuroticism, change attention focus and attention threshold, neutralize triggers, gradually diminish symptoms, increase comfort and improve health, and changes happening automatically without active effort by the patient.

The course of treatment is seven biweekly sessions (about ½ hour of hypnosis) over approximately 12 weeks, or one session every other week. The patient receives a home practice tape after the second treatment session and strong emphasis is placed on regular home practice. Dr. Palsson discussed three hypnosis-related studies he and his colleagues at UNC have published. The aims of the first study were to:

- evaluate the feasibility of delivering effective hypnosis treatment by using completely standardized word-for-word scripts, which is highly advantageous to facilitate generalization of the treatment across settings and therapists
- assess the impact on IBS symptoms, psychological well-being and somatization
- evaluate the effects on gut pain thresholds and muscle tone to elucidate the mechanism of the therapeutic effect
- examine whether suggestions to reduce pain sensitivity add to the effectiveness of the treatment.

Eighteen adults participated in this study. All had 1+ years of IBS and had been medically evaluated. All except one had unsuccessfully tried multiple treatment methods

O. Palsson continued

recommended or prescribed by their physicians, such as fiber and medications. Half the subjects were randomized to treatment with all pain-specific suggestions omitted, to examine whether this would affect benefit and pain changes. In a second study, the aims were: (1) to replicate the treatment effects of the standardized protocol observed in the first study on IBS symptoms, somatization and psychological well-being, and (2) to assess the effect of hypnosis treatment on autonomic nervous system functioning. Twenty-four patients were enrolled using the same inclusion criteria as in Study I and all had symptoms that had proven refractory to medical management. Patients were randomized to two groups: Group A received hypnosis treatment immediately following 2-week baseline and a laboratory test session, while Group B was a waiting-control group.

Significant improvement was found after treatment in both studies for all measured GI symptoms – abdominal pain, bloating and bowel consistency. More than 80% of the patients responded to hypnosis treatment in both studies. They also improved in scores for somatization, number of psychiatric symptoms, anxiety, and depression. Improvement was well maintained at 4 and 10-month follow-up.

Based on the positive results from these studies, Dr. Palsson has concluded that this brief fully-standardized treatment protocol benefits about 4 of every 5 patients with moderate and severe symptoms who are refractory to other treatments, and leads to lasting improvement in all the central symptoms of IBS. The standardized protocol tested in these studies is currently used by over 200 clinicians in the U.S. and at least 6 other countries.

Dr. Palsson's third study was an exploratory assessment of hypnosis home treatment for IBS. Nineteen IBS patients completed the 3-month hypnosis home treatment via audio CD recordings and were evaluated pre-and post- treatment and at 3 and 6-month follow-up. 57 patients were enrolled as controls; they were Rome II IBS patients from a different study, age and gender matched and identical to the hypnosis subjects in mean IBS severity. They completed the same outcome measures as the hypnosis subjects 6 months apart but received only standard medical care. In this study, 53% of the hypnosis subjects were found to be treatment responders (defined as reporting over 50% reduction in their IBS symptom severity score), whereas 26% of the control group receiving standard medical care were responders. Additionally, it was found that home-based hypnosis treatment seems to benefit non-anxious patients (75% of them) more than anxious patients (only 14%).

With regard to future directions for research on hypnosis treatment for IBS, Dr. Palsson suggested: (1) larger, controlled multi-center trial of the standardized protocol in therapist-delivered format, (2) parallel and combined tests with other IBS therapies, (3) randomized field trial of the home-hypnosis version of the protocol in normal clinical settings, and (4) creation and testing of a similar standardized and easily generalizable approach to treating IBS or RAP in children.

UNC: Miranda Van Tilburg, PhD
Assistant Professor of Medicine, UNC School of Medicine, Chapel Hill, NC
Treating pediatric IBS with guided imagery

Miranda Van Tilburg

Recurrent abdominal pain (RAP) is a prevalent condition, affecting 9-25% of school age children, of whom 2/3rds fulfill criteria for IBS. Standard medical care for RAP includes acknowledgment that the pain is real, reassurance that there is no organic cause for the pain, coping advice, dietary changes, and medications. This can be effective, but many patients need additional therapies.

Published studies of additional therapies have shown that cognitive behavior therapy (CBT) can be an effective treatment for RAP, and the combination of guided imagery and relaxation exercises can be particularly effective in relieving abdominal pain in children. Therefore, psychological treatment can be of great benefit to most patients. But, they can also be expensive, time-consuming, and require highly trained therapists. As a consequence, they are not available to most patients. One solution is to develop group therapies. They are cost-efficient and have been proven effective in other disorders, but their main drawback is that patients often lack flexibility in adhering to the schedule for group therapy sessions, causing low or diminishing attendance rates. Therefore, another alternative is to develop home-based therapies that are inexpensive and time efficient. Dr. Olafur Palsson at UNC has developed and is currently testing a 3-month self-hypnosis treatment course for adults with IBS using audio CDs. Pilot test data have already revealed promising effectiveness.

The question is whether self-hypnosis can be effective in children with RAP. The hypotheses for Dr. Van Tilburg's on-going pilot study are: (1) self-hypnosis reduces abdominal pain, and (2) live therapies and self-hypnosis are more effective than symptom monitoring and standard medical care. For her study, she is recruiting three groups of 10 children each, age 7-12 years, assigned as follows: 10 receive hypnosis treatment with a therapist, 10 engage in home-based self-hypnosis, and 10 receive standard medical care followed by home-based self-hypnosis. Therapy entails three bi-weekly sessions, one booster session, and daily exercises. The outcome variables to be studied are abdominal pain, psychological distress, functional disability, and quality of life.

Patient Education

UNC: Albena Halpert, MD
Clinical Instructor, Boston Medical Center, Boston University School of Medicine, Boston, MA
Ongoing research at UNC and BUMC in patient education

Albena Halpert

Dr. Halpert is conducting a nationwide survey – known as the Patient Education Questionnaire (PEQ) – that is seeking a total of 1,000 respondents. She presented preliminary findings based on an analysis of 200 responses from patients seen in the IBS clinics at Boston Medical Center and UNC Hospitals. The on-line version of the PEQ is generating 4-5 responses per day, for a current total of 400 responses, the data from which is currently being analyzed.

The aim of the PEQ is to identify the content and process by which effective patient education on IBS can be provided. The specific objectives are to ascertain: what patients know about IBS, what patients would like to know about IBS, patients' preferred media for getting information about IBS, and patient expectations from their health care education providers. Dr. Halpert provided an overview of preliminary findings:

- Survey respondents had misconceptions about IBS and the development of cancer, colitis or malnutrition.
- Survey respondents wanted to know more about: foods to avoid, coping strategies and medications to reduce IBS symptoms, the causes of IBS, and psychological factor in IBS.
- They prefer to get IBS information from their doctor, but they also utilize brochures and newsletters.
- The survey also asks what patients expect their medical provider do. She found that patients expect their physicians to listen to them, tell them more about IBS studies and medications, provide support/hope, and return their phone calls.

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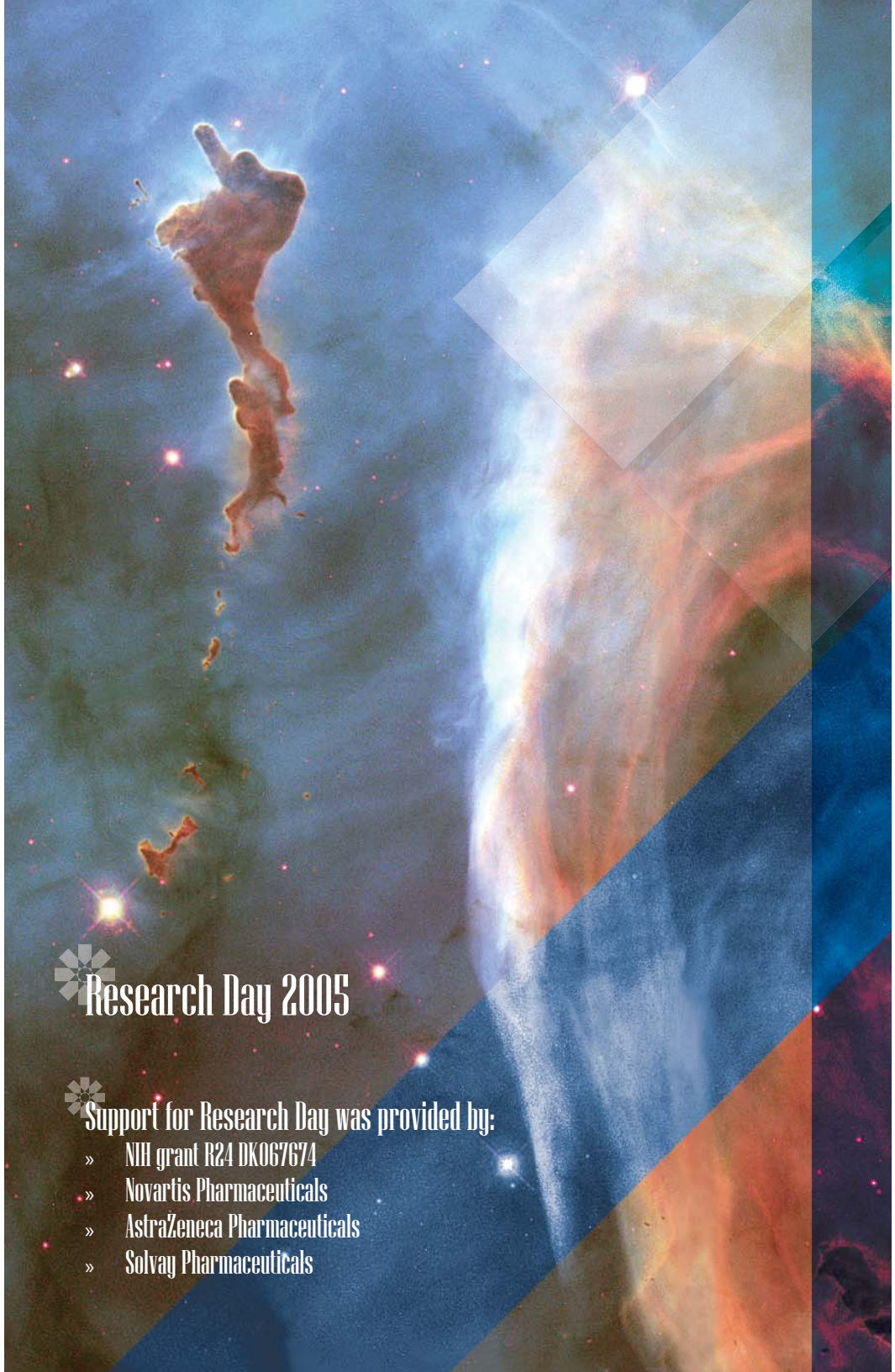

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