Research Day 2007

Gastrointestinal Biopsychosocial Research at UNC

September 28 & 29, 2007

UNC Center for Functional GI & Motility Disorders

The University of North Carolina at Chapel Hill

Gastrointestinal Biopsychosocial Research at UNC
September 28 & 29, 2007

In October 2004, the UNC Center for Functional GI & Motility Disorders was awarded a grant (R24 DK067674) 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 disorders. As part of this NIH grant, the Center hosted the third of what has now become an annual Research Day on September 28-29, 2007, on the campus of the University of North Carolina at Chapel Hill.

The program for this non-CME symposium was focused on six areas of research: (1) Brain-Gut Axis, (2) Gut Physiology, (3) Pelvic Floor, (4) Pediatric Functional GI Disorders, (5) Complementary and Alternative Medicine Treatments, and (6) Psychosocial Assessment. The format included presentations on the state-of-the-art in each of these areas by visiting senior scientists, followed by overviews of on-going studies involving UNC faculty and investigators. This booklet provides a summary of all presentations.

Research Day 2007 was held this year in association with the UCLA Center for Neurovisceral Sciences and Women's Health (CNS) and the UNC Center for Gastrointestinal Biology & Disease (CGIBD), UNC Division of Gastroenterology & Hepatology. We greatly appreciate the educational grants from Sucampo Pharmaceuticals, Takeda Pharmaceuticals, Microbia Pharmaceuticals, Novartis Pharmaceuticals, The Procter & Gamble Company, and AstraZeneca Pharmaceuticals that provided additional support for this event.

William E. Whitehead, PhD
Co-Director

Douglas A. Drossman, MD
Co-Director

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Brain-Gut Axis

Visceral Pain in Humans - Deconstructing the Brain's Response by Neuroimaging

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Emeran Mayer

Visceral pain and discomfort is a subjective, conscious experience, which results from an interpretation of the visceral afferent input influenced by emotional, motivational and cognitive factors in a particular context. Altered perception of visceral stimuli as observed in several functional pain disorders, including IBS, could thus result from alterations in the activity in visceral (and other homeostatic) afferent signal processing areas alone (reflecting increased visceral afferent input to the brain from the gut), in pain modulation circuits alone, in emotion/arousal regulation circuits, or from variable combinations of these overlapping circuitries. Due to the lack of rigorous study designs to isolate specific networks involved in various aspects of visceral stimulus processing and modulation, the precise mechanism(s) underlying enhanced perception ("visceral hypersensitivity") remains controversial.

Brain networks concerned with visceral afferent stimulus processing. Brain regions thought to belong to a central pain processing circuitry ("homeostatic afferent processing network") have previously been described in somatic pain studies and are well supported by neuroanatomical data. The principal regions of this afferent processing circuit are the thalamus, insula (interoceptive cortex), and the dorsal aspects of the anterior cingulate cortex (dACC). In general, few attempts have been made to selectively study visceral afferent information processing while minimizing the cognitive and emotional modulation of such input. While IBS patients have shown increased responses of the dACC to an aversive visceral stimulus in several reports, insula activation has not been different from healthy control subject.

Brain networks concerned with endogenous phasic pain modulation. Our ability to mentally represent perceptual events and anticipate the consequences of environmental stimuli is a fundamental aspect of consciousness and offers unique adaptive advantages. Anticipation of pain (or other potentially aversive events) is a complex state which may influence the immediate unpleasantness of pain and of non-noxious stimuli. Anticipation of a potentially aversive stimulus is likely to involve several interacting factors, such as cognitive appraisal of the stimulus and its context, memory retrieval, conditioning, arousal, and orienting or diverging attention from the source and site of the expected noxious input. The importance of these factors may vary according to the specific instructions given to the subject and past experience and, therefore, published study results are sometimes conflicting. One important factor resulting in fundamentally different brain responses to an anticipated pain stimulus is related to the question of if the stimulus is learned, predictable and inevitable, or if the stimulus is unpredictable and unlearned (not previously experienced).

E. Mayer, continued

Endogenous pain inhibition during predictable, inescapable expectation. One general mechanism when confronted with unavoidable aversive stimuli appears to be the inhibition of limbic and paralimbic arousal circuits by cortical regions. A series of imaging studies have implicated the lateral orbitofrontal (ventrolateral) PFC (vlPFC) as playing a role in inhibiting distal neural activity in limbic and paralimbic regions that are produced by or interact with pain processing ("corticolimbic pain inhibition"). Our own studies have demonstrated that, in contrast to healthy control subjects which clearly demonstrate such cortico limbic inhibition during expectation of a predictable visceral pain stimulus, IBS patients fail to show this mechanism both during expectation of visceral pain and during delivery of the stimulus.

Endogenous pain amplification during unpredictable expectation. In contrast to expectation of predictable pain, brain mechanisms (attention, arousal) may be engaged to enhance afferent sensitivity, thereby facilitating perception. Attention-related modulation of nociceptive neural activity has been observed throughout the afferent processing network. When confronted with novel aversive stimuli not previously experienced, a coping strategy of selective attention or vigilance towards the expected stimulus is typically engaged. Similar interactions of attentional and arousal mechanisms have previously been proposed. In summary, different cognitive strategies are able to increase and decrease the subjective experience of pain, and these effects on the subjective experience of pain are mediated by activation of different corticolimbic pontine networks.

Brain networks concerned with emotional and stress responsiveness. Converging evidence from preclinical, epidemiological, physiological and brain imaging experiments supports the concept of enhanced responsiveness of brain circuits concerned with emotional and stress reactivity in IBS patients. The output generated by these circuits in response to actual or expected perturbation of homeostasis results in adaptive patterned responses of the brain-gut axis, which have been reported in animal experimental as well as human studies. These include hypervigilence, increased autonomic responses, and stress-induced pain modulation. Consistent with the concept of enhanced stress and emotional reactivity, many of these effects seem to be magnified in IBS patients.

In summary, neuroimaging studies in healthy control subjects and patients with IBS are beginning to identify alterations in the activity and connectivity of brain circuits dedicated to specific aspects of human pain processing. To understand the contribution of altered brain responses to the pathophysiology of functional GI disorders, a characterization of these circuits will be essential.

Brain-Gut Axis

Brain Imaging: Effects of IBS and Abuse History

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Co-Director, UNC Center for Functional GI and Motility Disorders

Douglas Drossman

The biopsychosocial conceptual model for functional gastrointestinal disorders (FGIDs) posits that early life factors (genetics, environment) influence both physiology (gastrointestinal motility, sensation, inflammation, altered bacterial flora) and psychosocial factors (abuse/life stress, psychologic state, coping, social support). Physiology and psychosocial factors interact with each other through the brain-gut axis (central nervous system, enteric nervous system) and both influence and are influenced by FGID symptoms and behavior (pain reports, doctor visits, daily function, quality of life).

Outcome data from previous studies at UNC of abuse and gastrointestinal illness have shown that (1) abuse has adverse effects on GI health outcomes, (2) patients with IBS/FGID compared to those with structural disorders have poorer health outcomes, and (3) the effects on outcome of abuse and FGID appear synergistic. In a previous UNC study (n=196) of sexual abuse and health status, statistically significant predictors of health outcome were education, abuse severity, Ways of Coping (revised) Scale, positive problem solving Coping Strategies Questionnaire, and the Catastrophizing Coping Strategies Questionnaire/ability to decrease symptoms, together accounting for 41 percent of the variance in overall poor health. Age, race, GI diagnosis (functional vs. organic), neuroticism, other Ways of Coping scales, and Ability to Control Symptoms were not statistically significant. These data indicate that the strongest predictors of health outcome were abuse severity, maladaptive coping strategies, and perceived inability to decrease symptoms.

The evolution of brain imaging studies of visceral sensation has progressed from descriptive (broad anatomical regions, patient-control comparisons) to more detailed descriptive studies (more precise regions of the brain, subject subgroups) to hypothesis-driven studies of functional networks, subregions of the brain, and mechanistic evidence. Imaging has shown that increased dACC in the cingulate cortex among patients with IBS is consistent with greater affective pain experience. This was reflected in a case history, previously reported, where a patient with severe IBS showed increased activity in this region but after clinical improvement, activation of this area reverted to normal.

It was decided to carry this information further by studying a group of patients to answer the question: "Is the increased pain reporting in IBS patients with abuse history associated with enhanced activation of noxious brain areas?" This study, "Effect of Abuse History on Pain Reports and Brain Responses to Aversive Visceral Stimulation: An fMRI Study" is currently in press in Gastroenterology. The hypotheses for the study were: (1) patients having IBS+Abuse will show increased activation of MCC relative to that previously shown in IBS; (2) patients having IBS+Abuse will show reduced activation of the sACC/medial PFC region, similar to that previously shown in PTSD; and (3) increased activation of the MCC will be positively correlated with subjective pain ratings.

D. Drossman, continued

The patient population for this study was right-handed females, 18-65 years of age, recruited through advertising and clinic visits at UNC. All IBS subjects met Rome II criteria and had active symptoms. Abuse history was determined by interview using standard methods from our previous NIH grant on abuse. There were 10 patients with IBS and 10 patients without IBS, and five in each group had moderate to severe sexual/physical abuse history. This yielded four groups of five for the study: IBS+Abuse, IBS/No Abuse, No IBS+Abuse and No IBS/No Abuse.

Rectal distension was the method used to simulate gut pain. There were three sets of repeated 39-second rectal distensions separated by 39- second rest periods: four non-painful (15 mm Hg), four painful (50 mm Hg), and five alternating (15, 50, 15, 50, 15 mm Hg) distension trials. After each distension, subjects rated their pain (0 = none, 1 = weak, 2 = mild, 3 = moderate, 4 = strong, 5 = intense). We then compared non-painful (15 mm Hg) to summed painful (50 mm Hg) distensions from these trials.

A 1.5 Tesla MR scanner (Siemens, Germany) with a gradient strength of 25 mT/m was used. T2*-weighted echo planar imaging sequence was used to acquire images: repetition time 3 sec, echo time 54 msec, slice thickness 5 mm, field of view 192x192 mm2 with a matrix size of 64x64; and 16 slices. Statistical parametric mapping (SPM2) was used to preprocess images and identify significant effects. Images were processed prior to analysis through realignment, normalizing and smoothing procedures. All images were then reoriented to approximate a match to the origin and orientation of the MNI EPI template image. Graphic representations of the realignment were assessed to identify excessive movement within any block. One subject with excessive truncation was excluded from further analyses (IBS/no abuse). Realigned images from the remaining 19 subjects were moved into a standardized brain image space (MNI), using linear and non-linear transformations. Normalized images were spatially smoothed with a 5mm full width half maximum (FWHM) kernel filter.

For the data analysis, pain self reports (0=no pain, up to 5=intense pain) for three distension blocks (non-painful, painful and alternating) were compared using paired t-tests. The average of patients' pain ratings for four painful distensions and two painful alternating distensions (i.e., all 50mm Hg distensions) were used. Comparison of pain to rectal distension across groups was done using t-tests. Linear contrasts of brain responses for each inflation level were applied to the parameter estimates for each condition, with the resulting t-scores at each voxel constituting the SPM for that condition. Contrast images were generated for 15mm and 50mm Hg inflations. Second level analysis employed 2-sample t-tests to compare BOLD responses between experimental groups, and correlation analyses to assess covariation of responses with reported pain. Peak voxel t-values were interrogated in three a priori ROIs within the dorsal cingulate of each hemisphere: MCC and PCC and the portion of the most anterior cingulate above the genu of the corpus collosum (sACC). Peak t-scores with $p<0.05$ within the ROI constituted significant effects.

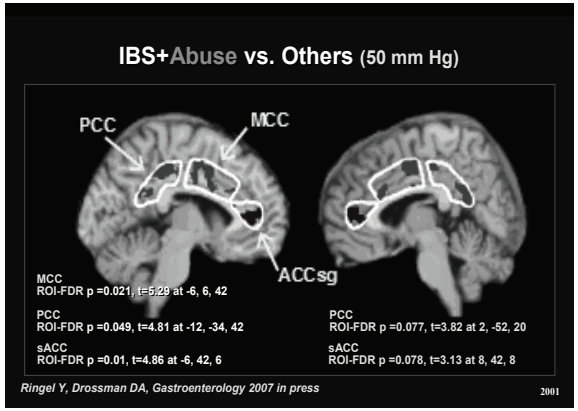
We found that abused subjects were less educated than non-abused; Abuse+IBS subjects were less educated than the remaining three groups; and the abuse group trended toward more depression (SCL-90) than non-abused. As expected, all patients reported more pain with 50 mm Hg (painful) than 15 mm Hg (non painful) distensions (3.6+0.38 vs. 1.8+0.62; $p<0.0002$). In addition, patients with IBS+Abuse compared to all other groups reported significantly greater pain during painful distensions (4.5 vs. 3.4; $p=0.004$), and there was a trend for more pain with non-painful distension (2.2 vs. 1.7; $p=.094$) as well.

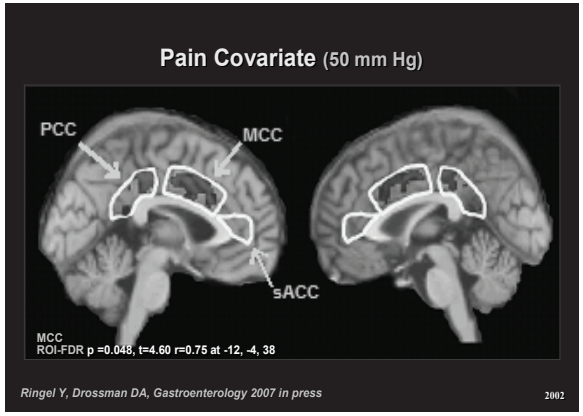
D. Drossman, continued

Furthermore, the pain ratings correlated with anxiety (anxiety $r=0.69$ $p<0.001$ for painful $r=0.48$ $p=0.03$ for nonpainful distensions) as well as depression ($r=0.70$ $p<0.001$ for painful and $r=0.42$, $p=0.07$ for non-painful distensions).

Results: (1) Patients with IBS+Abuse report more pain with rectal distension than remaining patient groups (IBS alone, abuse alone, or no IBS/no abuse). (2) Patients with IBS+Abuse when compared to other groups had (a) stronger activation of the dorsal cingulate gyrus (MCC/PCC - pain noxiousness) and (b) greater deactivation of the sACC (pain inhibition). (3) Pain reports to distension correlate with MCC/PCC activation and psychological distress. (4) Despite significant findings, the results are limited by small sample sizes.

Conclusion: The increased pain reports of IBS+Abuse may be mediated by dorsal ACC activation and sACC deactivation. This provides mechanistic evidence for understanding how abuse and other psychosocial factors influence increased pain reporting at a central level.





CNS Modulation of Somatic Pain in IBS: Diffuse Noxious Inhibitory Controls

Steve Heymen, PhD
Instructor of Medicine

Steve Heymen

Visceral hyperalgesia is observed in most patients with Irritable Bowel Syndrome (IBS). Recent investigations showing somatic hyperalgesia, not seen in earlier IBS studies, suggest the possibility of a dysfunction in central pain regulatory mechanisms. Dysregulation of the endogenous pain regulatory mechanism known as Diffuse Noxious Inhibitory Controls (DNIC) has been consistently demonstrated in two other chronic pain conditions, Fibromyalgia and Temporomandibular Disorder, which show high comorbidity with IBS. In DNIC, descending serotonergic and opioidergic pain inhibitory signals are initiated by one pain stimulus that then suppresses pain from a second heterotopic pain stimulus. Testing DNIC requires administering a phasic, noxious, test stimulus (TS), prior to and concurrent with administering a tonic noxious conditioning stimulus (CS). The reduction in pain perception of the TS during the CS is identified as the DNIC effect.

The hypothesis of the study was that IBS patients will demonstrate compromised DNIC compared to healthy controls (HC). Inclusion criteria for the study were pre-menopausal women 18 years of age and older, and IBS subjects had to meet Rome II criteria and currently suffer from painful symptoms of IBS. Exclusion criteria for the study: healthy subjects could not have a history of any chronic pain conditions; menopause, pregnancy or nursing; major clinical depression or anxiety disorder; hypertension, history of abnormal EKG or heart disease; diabetes, seizures, asthma, thyroid disorder, kidney disease; or be taking analgesics, narcotics, or anti-depressants. To control for their influences on pain perception: no visit was allowed during the follicular phase (days 4-8); no caffeine or nicotine was permitted 2 hours prior to testing; all study subjects were tested in the afternoon to control for fluctuations in cortisol; there were practice session to minimize apprehension; and blood pressure and heart rate were monitored throughout testing protocol. Symptom and psychological measures were: Irritable Bowel Syndrome Severity, Revised Physical Symptoms Questionnaire, State-Trait Anxiety Inventory, Beck Depression Inventory, Beck Anger Expression Inventory, Perceived Stress Scale, and catastrophizing subscale of the Coping Strategies Questionnaire.

Subjects were 48 pre-menopausal females (27 with IBS), mean age 29 years. The TS was produced by a phasic heat thermode [peak temperature of 500C, inter-stimulus interval of 3 seconds] applied to the left palm. The CS was submersion of the right hand in painful 120C water. Reductions in Average Pain Ratings (APR) from the TS during baseline to the APR during the TS + CS were compared between IBS patients and HC. In addition, subjects were retested (counter-balanced) using a non-painful CS (hand submersion in 320C water) to control for non-specific effects. Group differences in psychological and cardiovascular reactivity measures were also assessed to further control for known influences on DNIC.

S. Heymen, continued

The results of this study showed that IBS subjects demonstrated a smaller DNIC effect than HC ($p = 0.011$, Repeated Measures ANOVA). IBS subjects also reported significantly greater stress than HC on measures of state anxiety, depression, catastrophizing, and anger-out expression. After controlling for non-specific effects occurring during the non-painful CS (such as distraction and psychological measures), IBS subjects showed further decreases in DNIC ($p = 0.002$). There were no group differences in cardiovascular reactivity, age, body mass index, race, APR, or pain ratings for the 120C CS.

This study extended the findings from previous studies by controlling for (1) psychological factors, (2) hormonal factors, (3) cardiovascular reactivity factors, and (4) non-specific effects on pain perception. Group differences remained significant even after controlling for this array of factors known to influence DNIC scores. Limitations of this study were that only pre-menopausal women were included, and the removing of non-specific effects from DNIC effect was done statistically. Future research will focus on testing DNIC using a physiological outcome measure (fMRI; nociceptive flexion reflex/RIII); testing DNIC using visceral pain stimuli as well as somatic stimuli; and test for temporal summation as well as DNIC.

In conclusion, this study found (1) compromised DNIC in IBS, suggesting a deficit in endogenous analgesic mechanisms, and (2) disinhibition independent of many psychological mechanisms including distraction, suggesting that central pain dysregulation may play a role in IBS pain. This is the first study to adequately control for alternative explanations of pain reduction during counter-irritation. Only by controlling for non-specific effects can evidence of deficient DNIC be attributed to dysregulation in endogenous analgesic mechanisms.

Probiotics in Irritable Bowel Syndrome

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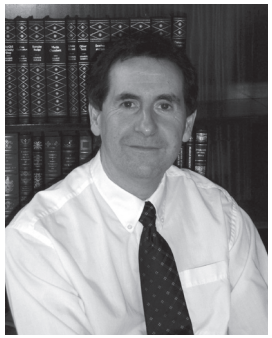

Peter J. Whorwell

The rationale for investigating probiotics in IBS comes from prior studies suggesting a link between IBS and previous gastroenteritis (post infectious IBS which as a prevalence of 4 to 31%), persistent inflammation, bacterial imbalance, small bowel bacterial overgrowth, and treatment with antibiotics. This research suggests that something of interest is going on around inflammation and bacteria. However, it should be remembered that at least 80% of gut bacteria cannot be cultured using current techniques.

Probiotics are preparations containing live organisms that exert a potential health benefit on the host. Properties of probiotic bacteria include: enhancement of the host's anti-inflammatory and immune response (Bifidobacteria achieve this more than Lactobacillae); stimulation of anti-inflammatory cytokines; restoration of the balance between pro- and anti-inflammatory cytokines; improvement of the epithelial cell barrier; epithelial adhesion; inhibition of bacterial translocation; inhibition of growth of pathogens (e.g., salmonella); inhibition of the adhesion of viruses (e.g., rotavirus); elaboration of active proteins and metabolites. In addition, probiotics have been shown to reduce hypermotility and visceral hypersensitivity in animal models. They also appear to have benefits outside the gut, as demonstrated by the reduction of inflammation in the liver and the attenuation of rheumatoid arthritis as well as having been shown to be active when administered subcutaneously. It is also noteworthy that different organisms have different properties and thus may not have the same therapeutic benefit.

Examples of probiotics include Lactobacillae, Bifidobacteria, E. Nissle; S. Salivarius; and S. Boulardii. For a probiotic to be useful in gastroenterology it is helpful if it is acid and enzyme resistant (so that it will survive passage through the stomach) and adherent to the gastrointestinal mucosa. These organisms have to be administered in high concentrations, because they do not normally colonize the gut.

Several controlled clinical trials of probiotic preparations in IBS have been conducted with variable results. Three of 9 studies had negative outcomes, but the remainder had a positive effect on pain, bloating, flatulence, or a combination of symptoms. The studies used different organisms and some used mixtures of probiotics. Mixtures may not necessarily be ideal as there is theoretically the possibility that some organisms might actually inhibit the beneficial effects of others.

In one treatment study comparing Bifidobacterium (B. infantis 35624), Lactobacillus salivarius and malted milk placebo (25 patients in each group), pain scores and composite scores were significantly lower for the Bifidobacterium group compared to the other groups. Before treatment, the IL10/IL12 ratio (interlukin 10 to interlukin 12) was indicative of a pro-inflammatory state, and after treatment the ratio

P. Whorwell, continued

was normalized. This study showed that Bifidobacterium infantis 35624 had promising effects in IBS, but metabolic delivery (malted milk cocktail) was cumbersome and capsules would be preferable.

In a more recent multi-center, placebo controlled, dose ranging capsule study of Bifidobacterium infantis 35624 in IBS conducted at 20 general practitioner sites in the U.K., subjects were randomized to three different doses of the probiotic or placebo (one capsule/day). Study subjects were females aged 18-65, with all bowel habit subtypes (Rome II criteria). They were not allowed to be taking antibiotics, dietary supplements, or probiotics. To avoid extremes of severity, they had to score 2-4 on a 0-5-point symptom scale and 3-6 on the Bristol Stool Form Scale. On a daily basis, subjects scored their symptoms from 0=none to 5=very severe for the following: abdominal pain (primary outcome), bloating/distension, incomplete evacuation, straining, urgency, gas, mucus, and overall symptom assessment. They also rated their satisfaction with bowel habit (0=very satisfied to 5=very dissatisfied) as well as completing the Bristol Stool Form Scale (1-7), and recording rescue medication intake (Loperamide/bisacodyl). Weekly outcomes assessed were overall adequate relief, adequate pain relief, whether they thought they were on an active treatment or placebo, and a composite score (pain/bloating/bowel satisfaction). Quality of life (IBS-QOL) and Hospital Anxiety Depression scores were assessed at baseline, end of treatment, and end of follow-up.

At the end of treatment (4 weeks), the Bifido 8 dose group had significantly greater global assessment of relief compared to Bifido 6 dose or placebo, and they were significantly more inclined to believe they were on active treatment rather than placebo. No significant change was found in Quality of Life or Hospital Anxiety Depression Score, and there were no significant differences between active and placebo in adverse events. The 10 dose of B. infantis was not effective, but this was shown to be due to the fact that at this concentration the organism coagulates due to an excess of exopolysaccharide which is intensely hygroscopic. Conclusions from this study were that (1) Bifidobacterium infantis 35624 is effective in capsule form at concentration of 108 cfu/capsule, (2) a wide range of symptoms improved, (3) the 10 concentration is unsuitable for capsule delivery, and (4) the slow onset of action suggests that longer study periods may be necessary in studies assessing the efficacy of probiotics.

Prebiotics and synbiotics are also of interest. Prebiotics are compounds that stimulate the growth and activity of beneficial bacteria by providing a preferred substrata. For example, oligosaccharides seem to be more useful in promoting bifidobacteria than lactobacillae. There are no data on prebiotics and IBS. Synbiotics are a mixture of prebiotic and probiotic bacteria, and although there have been some studies in IBS, the quality of these is highly questionable.

In conclusion, (1) probiotics differ and formulation is critical; (2) mixtures may not be ideal; (3) the next generation of probiotics which could be specifically engineered to suit specific purposes may be even more effective, and (4) probiotics have an exceptionally high patient acceptability.

Intestinal Microflora in Irritable Bowel Syndrome

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Yehuda Ringel

The intestine of an adult human contains approximately 1014 bacteria, which is 10 times the number of human cells. The human microbiome including all luminal bacteria contains 100 times the number of genes in the human genome. More than 500 different species and sub-species have been identified, however this is less than a third of the intestinal bacteria and many bacteria remain unculturable.

The question is what do we know about intestinal microflora and Irritable Bowel Syndrome (IBS)? There have been very few studies and results are not consistent. Most of the data come from relatively old studies using classic culture techniques and only a few studies were done using more advanced molecular biology techniques. These studies suggest there are quantitative and qualitative differences in intestinal microflora between IBS patients and healthy controls.

Why study intestinal bacteria in IBS? Epidemiological, physiological and clinical data already provide evidence for an important role of bacteria in IBS. With regard to epidemiological studies, considerable research has already been conducted on Post Infectious IBS (PI-IBS): (1) approximately 10 to 30% of patients who have acute bacterial infection develop chronic IBS symptoms; (2) acute infectious gastroenteritis is considered the strongest identified predictor for the development of IBS; and (3) acute infection may lead to persistent changes in GI function that may lead to chronic IBS symptoms. It is also evident that there is a high prevalence of Small Bowel Bacterial Overgrowth (SIBO) in patients with IBS, diagnosed with the hydrogen breath test. Evidence also suggests that antibiotic treatment can improve IBS symptoms in a large proportion of patients with SIBO.

In addition, bloating and gas are very common complaints in patients with IBS. A recent epidemiological study conducted on 337 patients with IBS showed that bloating and gas: (1) are reported by 82.5% of patients with IBS, (2) constitute the second most bothersome symptom, exceeded only by abdominal pain, (3) are the most commonly reported symptom in patients with constipation-predominant IBS (88.7%), (4) constitute the fourth (out of 14) most important reason to seek medical care, and (5) are associated with a decrease in quality of life (QOL) and an increase in healthcare utilization and use of medications.

Further evidence for the role of bacteria in the pathophysiology of IBS comes from physiological data in animal studies. Several studies have shown significant abnormal intestinal function in germ-free animals and profound effects of altered intestinal flora on intestinal myoelectric and motor activity.

Finally, evidence for bacterial effects on gastrointestinal function comes from clinical studies of probiotics and antibiotics. Prospective, placebo-controlled studies examining antibiotics in IBS suggest: (1) benefits are modest and may be largely due to effects on bloating, (2) the mechanism/s of these effects are not clear, and (3) data is limited (single center, low placebo response, varying outcomes/statistical analysis.

Gut Physiology

Y. Ringel, continued

Several studies are underway at UNC on intestinal bacteria in functional bowel disorders (FBD). These studies investigate the role of intestinal microflora on intestinal motor and sensory function and symptoms. Another study investigates the relationships between intestinal microflora, intestinal inflammatory/immune function and their effects on intestinal function and symptoms.

The investigational approach taken by our team is based on comparing groups of bacteria and calculating the ratio between beneficial and detrimental intestinal bacteria. We have developed an approach that provides a sensitive and comprehensive evaluation of the intestinal microflora considering the current limitations in this area of research. A pilot study investigated the association of intestinal microflora to mucosal inflammation and immune activation in patients with IBS. Aims of the study were to develop and refine protocols for investigating (1) sub-clinical intestinal inflammation and immune alterations in patients with IBS and (2) alterations in intestinal microflora relevant to intestinal mucosal inflammation. Ten patients who met the Rome III criteria for diarrhea predominant IBS and 10 healthy controls were included in the study. Fresh fecal and mucosal biopsy samples were acquired during un-prepped, un-sedated flexible sigmoidoscopy. Samples were put on ice and transferred immediately to the lab in anaerobic conditions, and all the analyses were done in anaerobic conditions. Intestinal bacteria were analyzed using a combination of three methods: classic culture analysis, quantitative PCR (q-PCR), and terminal restriction fragment length polymorphism (T-RFLP), which is a fingerprinting technique allowing identification of complex microbial communities and comparisons of bacterial communities in different diverse ecosystems. The results of this pilot study will be presented at DDW 2008.

Finally, we are conducting two clinical studies on the manipulation of intestinal flora in functional bowel disorders (probiotics trials); one study has been completed and another is ongoing. The completed study aimed to assess the clinical benefit of daily supplementation of probiotic bacteria (Lactobacillus acidophilus NCFM (L-NCFM) and Bifidobacterium lactis Bi-07 (BL-Bi07) in patients with non-constipation functional bowel disorders. This is a prospective, randomized, double blind, placebo controlled study that includes patients with FBD who met the Rome II criteria for non-constipation-IBS, functional diarrhea, or functional bloating. The primary outcome measure was global relief of GI symptoms, as assessed by Global Symptom Assessment (GSA). The secondary outcome measures were improvement of various FBD-related symptoms and Health Related Quality of Life. Overall, the study showed a significant improvement in symptoms of bloating and distention in patients in the active arm compared with placebo. The detailed results of this study were submitted for presentation in DDW 2008.

Going forward with our intestinal microbiology studies, our team aims to complete T-RFLP analysis, conduct microbiology analysis of mucosal samples, and investigate correlations with mucosal inflammatory cytokines. For intervention/probiotic studies, we are conducting a study of the clinical efficacy of a yogurt drink containing bifidobacterium lactis (BB12) in subjects with functional gastrointestinal symptoms. This study will also involve investigation of the mechanisms of effects by measuring physiological parameters and conducting microbiology analyses.

Small Intestinal Bacterial Overgrowth in IBS: Association with Colon Motility, Bowel Symptoms, and Psychological Distress

Madhusudan Grover, MD
PGY 2, Internal Medicine, Michigan State University

Madhusudan Grover

Estimates of the prevalence of small intestinal bacterial overgrowth (SIBO) in irritable bowel syndrome (IBS) range widely from 10% to 70%, largely due to inconsistency in the method of diagnosing SIBO. Some authors claim SIBO is the etiology for all or most of IBS patients, but this is controversial. Usual symptoms of SIBO are diarrhea, flatulence, abdominal pain, and bloating. However, more recently, constipation has been associated with methane production during hydrogen breath testing (HBT). The association of visceral hypersensitivity and psychological distress in IBS with SIBO has not been well studied.

The aims of a study conducted at UNC were: [1] to determine the prevalence of SIBO in IBS; [2] to compare SIBO-IBS and non-SIBO-IBS by (a) clinical parameters -- IBS subtype, IBS symptom severity (IBS-SS), IBS quality of life (IBS-QOL), (b) physiological variables -- pain and urge thresholds, phasic contractions during fasting and in response to distension and eating a meal, and (c) psychological variables -- Brief Symptom Inventory (BSI 18), Recent Physical Symptom Questionnaire (RPSQ), and Catastrophizing Scale; and [3] to compare H2 & CH4 producers by (a) IBS subtype, IBS-SS and IBS- QOL, (b) pain and urge thresholds and phasic contractions, and (c) self-reported bowel patterns. Subjects for the study were recruited through advertisement and physician referrals. They had to fulfill Rome II criteria and have no history of IBD, heart disease, diabetes mellitus, or major GI surgery. Controls recruited for the study had to have no history of significant GI problems with exclusion criteria of: (1) stool frequency (<3/week or >3/day), (2) use of laxatives or anti-diarrheal medications >2/year, (3) alcohol or substance abuse, or (4) psychiatric diagnosis. Validated questionnaires used in the study were: IBS-QOL; IBS-SS (overall pain intensity, frequency, abdominal distension, dissatisfaction with bowel habits, interference with usual activity); BSI 18 (global severity index, anxiety, depression, and Somatization scales); and subjective bowel patterns ("In last three months, how often did you have… fewer than 3 bowel movements in a week, more than 3 bowel movements in a day, hard or lumpy stools, loose, mushy or watery stools). Equipment used in the study were: barostat (testing sensory thresholds, smooth muscle tone); motility catheter (to inflate or deflate the bag, monitor pressures inside and outside the bag), pneumohydraulic pump (hydraulic capillary infusion system), and physiological recorder (records phasic and tonic motility changes above and below the balloon). Physiological variables recorded were: (1) thresholds for pain and urgency to defecate measured by the ascending method of limits, and (2) motility index (sum of the area under the curve for all individual phasic contractions divided by artifact-free recording time). The HBT protocol entailed administering 50gm of sucrose in 250ml water, and breath sampling at baseline and every 15 minutes. The criteria were: baseline H2 $\geq$ 20 ppm; first 60 minutes- Increase of H2 and/or CH4 $\geq$ 12 ppm from baseline in the first 60 minutes; and first peak ($\geq$12 ppm) after 60 minutes with a second peak $\geq$ 20 ppm from baseline that was separate from the first peak. Subjects with positive HBT were subdivided into hydrogen and methane producers based on the predominant gas.

M. Grover, continued

The study included 158 IBS patients and 34 healthy controls (HC). Data analyses included student-t test to compare the groups, Chi-square test with continuity correction for categorical variables, and Spearman correlations. Results showed that:

1) 52/158 (32.9%) of IBS had abnormal breath tests compared with 6/34 (17.9%) of controls (χ2=0.079)
2) Patients with SIBO (SIBO+) and Non-SIBO (SIBO-) did not differ in the prevalence of IBS subtypes, IBS-SS, IBS-QOL, or psychological distress
3) SIBO- patients showed a trend towards lower pain thresholds compared to SIBO+ patients (25.9% vs. 30.1%, p=0.055)
4) Compared to controls, both SIBO+ and SIBO- had greater post-distension increase in MI (625.6 and 642.9 vs. 313.3, p<0.05), but the MI was not different between these two groups.
5) Predominant methane producers (PMP) had higher urge thresholds (28.4 vs. 18.3, p<0.05) and higher baseline MI (461 vs. 301.45, p<0.05) than SIBO- IBS patients, and they were more likely to report hard or lumpy stools at least 25% of the time when compared to predominant hydrogen producers (PHP) (90% vs. 52%, p<0.05) and SIBO- IBS (90% vs. 53%, p< 0.05).
6) The IBS-SS scale did not significantly correlate with peak hydrogen in the PHP group (rho=-0.06) or peak methane production in the PMP group (rho=-0.11)

We conclude that SIBO is unlikely to contribute significantly to the pathogenesis of IBS, and that visceral hypersensitivity and SIBO are probably independent mechanisms for the development of IBS. It is also unlikely that psychological distress could mediate the association between SIBO and bowel symptoms. Methane production seems to be associated with a constipation bowel pattern. Limitations of the study are: (1) sucrose breath test (glucose is a better substrate), (2) invasive test protocol (which may have biased recruitment), (3) average age 35.8 years (younger than the average age of IBS), and (4) failure to assess small intestinal motility, which may correlate better than colon motility with SIBO.

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IBS Genetics Program

William E. Whitehead, PhD
Professor of Medicine & Adjunct Professor of OBGYN
Co-Director, UNC Center for Functional GI & Motility Disorders

William Whitehead

Dr. Whitehead presented ongoing and planned studies at UNC in the genetics of IBS. Reasons for investigating the genetic contributions to IBS include (1) the potential for gaining new insights into the pathophysiology of IBS, (2) identification of new targets for drug development, and (3) pharmacogenomics -- the potential to individualize treatment based on knowledge of individual differences in drug metabolism. Genetics is a natural extension of the IBS heterogeneity research already underway at UNC. The last 5 years of an IBS grant from NIH have been devoted to identifying four IBS subtypes, each with a distinct etiology that may require different treatments. These subtypes/phenotypes may allow for more consistent genetic associations. Genetic markers may, in turn, improve the precision of IBS subtyping.

Another reason for pursuing IBS genetics is the success of Drs. Maixner and Diatchenko at UNC in genotyping other chronic pain conditions and the opportunity to collaborate with them. Based on a systematic review of the literature, Bill Maixner and Luda Diatchenko developed a Pain Panel of 300 genes including 3500 single nucleotide polymorphisms (SNPs) that cover the major pathophysiological pathways thought to be important in chronic pain: pain sensitivity and analgesia, inflammation, and psychological distress/somatization. They looked for markers common to many chronic pain disorders (e.g., temporomandibular joint distress/TMJ, fibromyalgia, headache), and this approach led to the discovery of four new genetic markers related to pain amplification and somatization -- traits that are important in IBS as well as other chronic pain conditions. Previous studies have shown that IBS aggregates in families and that there is stronger concordance in monozygotic as compared to dyzygotic twins, supporting heritability.

Most previously published research on the genetics of IBS dealt with the gene regulating the reuptake of serotonin by axons following its release into the synaptic cleft. Inhibiting reuptake of serotonin increases the amount of serotonin available and thereby enhances and prolongs the effects of serotonin release. The gene regulating this process is SCL6A4, but in early studies it was referred to by its function as the Serotonin Transporter (SERT) gene. Previous studies of the association of this gene with IBS are summarized below:

- Camilleri showed that SCL6A4 polymorphisms predict treatment response to alosetron.
- Pata reported that the short/short (s/s) polymorphism is associated with constipation-predominant IBS (IBS-C).
- Yeo and colleagues described an association between the s/s polymorphism and diarrhea-predominant IBS (IBS-D).
- Two studies – one by Kim et al and another by Heitkemper – reported no association between SCL6A4 and IBS.
- Our laboratory reported a weak association between the long/long (l/l) polymorphism and IBS-C.

W. Whitehead, continued

Other genes linked to IBS by previous investigators include:

- ADRA2C and ADRA2A (alpha-2 adrenoreceptor genes) were found to be associated with IBS-C by Kim et al.
- Polymorphisms in the IL-10 gene were found to be associated with IBS by Gonskorale & Whorwell but not by Van der Veek.
- Van der Veek found an association between the TNFalpha gene and IBS.

At UNC, we analyzed pilot data collected on 223 young adult females recruited as healthy subjects in a study of incident cases of TMJ. From this sample, IBS was "diagnosed" using questions in a psychological questionnaire (PILL somatization questionnaire). IBS diagnosis required abdominal pain at least monthly, plus constipation or diarrhea at least monthly. Based on a review of the literature, 10 genes of interest were assessed. Data were analyzed using a recursive partitioning approach implemented in the Helix Tree software. Results are summarized below.

- ADRA1A – strong associations ($p<.005$) were found for all IBS phenotypes with SNPs rs11781115 and rs17334323. The biological significance is unknown.
- ADRA2A – All IBS phenotypes associated with rs1800763 ($p<.05$). A previous report by Kim of an association with rs1800544 was not replicated.
- ADRA2C – All IBS subtypes showed a significant association with rs10009405, rs7696139, and rs12507954, consistent with the findings of Kim.
- ADRB2 – IBS-C but not IBS-D showed possible associations ($p<.05$) with rs35283004 and rs1042713. Diatchenko and Maixner previously showed that these two SNPs form a haplotype that is associated with somatization and is predictive of the development of temporomandibular joint disorder.
- ADRB3 – All IBS phenotypes showed possible associations ($p<.05$) with rs4994.
- COMT – IBS-C was associated with the SNP A-287G, which is in the promoter region of the membrane bound isoform.
- GCH1 – Possible association of IBS-C with Rs74292600.
- IL-10 -- No association
- TNFa – All IBS phenotypes showed possible associations ($p<.05$) with SNPs rs1800683 and rs1800629, replicating Veek.
- OPRM1 – No association with IBS phenotypes were found.

Two studies are proposed for further research into the genetics of IBS. The first study is the competitive renewal of the on-going IBS grant. The first aim is to identify genetic markers that discriminate IBS patients from controls and genes that separate subtypes of IBS from each other. Using accumulated DNA from 300 IBS and 200 health controls, the UNC team plans to genotype the DNA using the Pain Panel of 300 genes and 3500 SNPs developed by co-investigators Diatchenko and Maixner, and to replicate findings in additional samples of 300 IBS and 300 controls. The second aim is to determine whether genetic markers predict response to treatment with Lubiprostone.

A second grant application proposes a genome-wide survey in 1000 IBS patients and 2000 healthy controls taken from the Swedish Twin Registry. This will be a genome-wide survey, proposed in response to RFA-HG-07-012. Co-investigators for this second study are Bruce Weir, a biostatistician specializing in genome-wide statistical analysis, and Nancy Pedersen, director of the Swedish Twin Registry.

Randomized Controlled Trial Shows Biofeedback to be Superior to Pelvic Floor Exercises for Patients with Fecal Incontinence

Steve Heymen, PhD, BCIAC
Instructor of Medicine

Steve Heymen

This study aimed to compare biofeedback to a credible, alternative treatment for patients with fecal incontinence (FI) in a randomized, controlled trial (RCT). The study design included a run-in period for all study subjects and then randomization to 6 weeks of either biofeedback or pelvic floor exercises (PFE). The run-in intervention was medication, education and behavioral strategies to cope with a strong urge. Results from the run-in: 168 subjects enrolled, 24 withdrew during run-in (14 %), 35 responded to run-in (21 %), 89 % continued to have adequate relief at 3-month follow-up, and 108 (the Intent to Treat population [ITT]) received pelvic floor muscle retraining (45 biofeedback; 63 PFE). Subjects for the treatment groups were: 77% female; 90% Caucasian, and 8% African American; median age was 59.6 years (23 - 85); symptom duration was 7.3 years; and FI was severe with 3.6 health-care visits for FI in the previous 6 months. All subjects in both treatment groups received (1) PFE retraining during six 1-hour training sessions (bi-weekly), (2) instructions for daily home practice; (3) education and medications to normalize stool consistency continued from run-in; and (4) behavioral strategies (e.g., "Walk, don't run").

The goals of biofeedback training for FI are (1) to increase the strength of pelvic floor muscles through exercise, (2) to improve the patient's ability to sense rectal distention (the cue to contract pelvic floor muscles), (3) to coordinate pelvic floor contractions with the sensation of rectal distention, and (4) to teach the patient to avoid contracting abdominal wall muscles when squeezing pelvic floor muscles (a commonly seen but inappropriate response). In the biofeedback arm of the study, electronically augmented feedback was used to train the subject, but all biofeedback subjects also received PFE. In the PFE group, pelvic floor exercises were taught verbally. Analyses showed no significant differences between the two treatment groups at baseline for demographic, physiological, anatomical, psychological, or symptoms variables. With regard to credibility of treatment, there were no group differences in expectation of benefits, measured at the beginning of the second training session.

The primary outcome measure (at 3 months follow-up) was: "Compared to before your enrollment in this study, have you had adequate relief of your fecal incontinence symptoms?" For the primary analysis, (1) the proportion of subjects reporting adequate relief of FI symptoms at 3 months follow-up was 76% of the biofeedback group and 41% of the PFE group ($p<.001$), and (2) the per protocol primary outcome was 85% for biofeedback and 49% for the PFE group. With regard to secondary outcomes comparing biofeedback and PFE, (1) there were no significant group differences in intra-rectal perception, (2) the biofeedback group was significantly higher in squeeze strength for 3 months ($p < 0.05$), and (3) the biofeedback group was significantly less likely to inappropriately contract abdominal

S. Heymen, continued

wall muscles during squeeze at 3 months ($p < 0.01$). At 3-months follow-up, (1) the biofeedback group was significantly lower than the PFE group on the Fecal Incontinence Severity Inventory, and (2) the biofeedback group had a greater reduction in FI episodes (55% vs. 35% reduction, $p < 0.09$).

In summary: (1) biofeedback was superior to an equally credible alternative treatment for FI; (2) there was no difference in the expectation of benefit between groups; (3) both groups received identical treatment, except for the addition of biofeedback, (4) biofeedback patients demonstrated significantly stronger squeeze strength, less abdominal muscle interference, and somewhat better intra-rectal perception than controls; (5) biofeedback patients reported greater decreases in Fecal Incontinence Severity; and 6) group differences were not due to placebo, or the effects of education and medical management which were controlled for in the run-in intervention. This RCT provides definitive support for the efficacy of biofeedback for fecal incontinence.

Education and Medical Management of Fecal Incontinence

Yolanda V. Scarlett, MD
Assistant Professor of Medicine

Yolanda Scarlett

This presentation is an overview of the diagnosis and management of individuals with fecal incontinence (FI). FI is uncontrolled evacuation of rectal contents in an individual older than 4 years of age without developmental delays. Complaints of FI range from recognized involuntary passage of flatus to unrecognized passage of stool. FI affects both sexes and has great personal impact, social disability and economic burden. The true prevalence of FI is not known, but is reported to range from 0.8 to 18 % of the population.

In normal physiology, the anus and rectum represent the distal gut. The anal canal, internal anal sphincter (IAS), external anal sphincter (EAS), puborectalis muscle, and rectum function to allow evacuation. The IAS is smooth muscle under autonomic nervous system control and provides approximately 70% of the resting anal canal tone. The EAS is striated muscle that blends into the puborectalis and levator ani muscles. It provides for voluntary contraction and relaxation of the anal canal. The puborectalis wraps around the posterior aspect of the anorectal junction and attaches to the symphysis pubis muscle anteriorly to create a sling; it contracts to produce an approximate 80 degree acute angle. The rectum is a compliance organ that responds to rectal distention. Defecation is initiated when stool leaves the sigmoid colon and enters the rectum. Rectal distention causes relaxation of the IAS and the anal contents are exposed to the anal mucosa. Discrimination then occurs, allowing perception of the fecal consistency. EAS contraction maintains continence to allow for rectal accommodation. After feces fill the rectum to a certain degree, stretch receptors or mechanoreceptors in the rectal wall send the signal for an urge to defecate. Defecation is delayed until there is a conscious decision to evacuate the bowel.

The etiologies of fecal incontinence are broad and any condition affecting the anatomical or functional components of the pelvic floor can cause FI. Common causes of anatomic anal sphincter disruption include: obstetrical injury, anorectal surgery, anorectal trauma, inflammatory processes, and malignancy. Pelvic floor muscle and anal sphincter denervation can result from pudendal neuropathy, autonomic neuropathy, radiation induced neuropathy, obstetrical injury, spinal cord injury, and congenital abnormalities such as spina bifida. Neurological conditions associated with FI include dementia, stroke, multiple sclerosis, brain tumor, spinal cord tumor, tertiary syphilis, and cauda equina syndrome. Any condition contributing to loose stools or diarrhea is a risk factor for FI. Irritable bowel syndrome, ulcerative colitis, Crohn's disease, infectious diarrhea, laxative abuse, radiation enterocolitis, short bowel syndrome, and celiac disease can also trigger FI. Any condition limiting the rectal compliance or capacity predisposes to FI. Such conditions include collagen vascular diseases such as scleroderma, amyloidosis, rectal malignancy, proctitis, ischemia, and irritable bowel syndrome.

Taking a detailed history is the most important factor when evaluating an individual with FI. The number of bowel movements in a 7-day period should be documented along with the number of incontinent stools. The volume of stool loss should be noted as well as the awareness or lack of awareness of rectal

Y. Scarlett, continued

leakage. Anorectal manometry testing provides useful information about rectal sensation and anal sphincter strength and function. Testing is performed by placing pressure recording catheters across the anal sphincters. Nerve function can be evaluated by electromyography (EMG) with skin pads or an anal plug. Pudendal nerve latency testing involves stimulating the pudendal nerves with an electrode to cause contraction of the external anal sphincter. Anal sphincter integrity can be assessed by ultrasound. Sphincter disruption identified by ultrasound correlates well with decreased anal canal resting pressures and diminished squeeze pressures on manometry, respectively. Magnetic resonance imaging (MRI) can also be used to evaluate the sphincter anatomy. If FI due to overflow is suspected, colonic transit time determination can provide useful information. The most cost effective method of calculating the colonic transit time is by ingestion of radiopaque markers in conjunction with having one or more abdominal x-rays several days post ingestion. The number of retained markers is used to calculate the transit time. Colonic transit time can also be determined by radionuclide gamma scintigraphy. This test is not readily available, but correlates well with determination of colon transit time when compared to radiopaque markers. Defecography is useful for identifying rectal prolapse that may cause FI. A soft barium paste is introduced into the rectum then the patient is asked to evacuate during fluoroscopic examination.

Successful medical management of FI requires accurate identification of the underlying etiology. Therapy is specifically directed to the underlying cause of FI. A major goal of medical management is to modify the stool consistency and frequency because the risk of FI decreases with more regular evacuation of formed stool. For diarrhea associated with FI, the mainstay of management is to treat the underlying cause of the diarrhea. Anti-diarrheal medications can be helpful in normalizing the stool consistency, with resultant decrease or elimination of incontinent episodes. Anti-diarrheal agents used to manage diarrhea associated with FI are loperamide, diphenoxylate with atropine and alosetron. Constipation should be avoided, as fecal impaction can be associated with overflow incontinence. Establishing an oral laxative regimen in combination with bowel retraining and/or digital stimulation can be helpful. Enemas and rectal suppositories may be incorporated into the evacuation regimen to decrease the risk or impaction with overflow. Successful management of fecal incontinence often involves a multidisciplinary approach including medical and behavioral therapy.

Health Status and Abuse/Trauma History in Chronic Pelvic Pain

Jane Leserman, PhD
Professor of Psychiatry and Medicine

Jane Leserman

Chronic pelvic pain consists of non-cyclic pain in the pelvic region (e.g., pelvis, anterior abdominal wall, lower back) of at least six month duration and severe enough to cause disability and medical care. It includes diverse symptoms such as painful intercourse, painful menstruation, pain in the vulvar region, and diffuse abdominal pain. Often, the cause of this pain is unknown and the response to treatment is poor. It is estimated that 15% of women of reproductive age have chronic pelvic pain. About 35% of women with IBS have chronic pelvic pain, and 35% of those with chronic pelvic pain have IBS.

Population-based epidemiological studies have shown that women who have sexual or physical abuse histories have greater odds for reporting symptoms of chronic pelvic pain. In a study of 713 women with chronic pelvic pain, we found that those with more traumatic life events, including abuse history, had worse physical functioning, more pain, more non-pelvic medical symptoms, and more lifetime pelvic surgeries. Given the heterogeneity of those with chronic pelvic pain, we defined diagnostic subtypes of this disorder. We found that patients with diffuse abdominal pain had worse health, more pain, more medical symptoms, more pelvic surgeries, and more traumatic life events than those with more focused disorders, such as vulvovaginal pain (e.g., vulvar vestibulitis syndrome) or cyclic pain. Endometriosis was unrelated to health status, despite being the primary reason for hysterectomies in these patients.

Although we are only beginning to understand the neurobiology and physiology of how trauma may affect the development and course of pain syndromes such as chronic pelvic pain, some suggested mechanisms include the association of abuse and trauma with (1) symptom amplification due to hypervigilence to bodily sensations; (2) central nervous system (CNS) dysregulation resulting in visceral hypersensitivity to pelvic sensation; (3) increased autonomic activation and dysregulation of the HPA axis associated with post-traumatic stress syndrome (PTSD), thereby aggravating pelvic pain symptoms (4) exaggerated motor reactivity in response to stress or vaginal penetration; and (5) communication of psychological distress through physical symptoms. More research is needed to aid us in understanding the mechanisms underlying the health effects of trauma and abuse.

Pediatric Functional GI Disorders

Cognitive Behavior Therapy for Functional Abdominal Pain and Inflammatory Bowel Disease in Children

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Rona Levy

Past observational research described by Dr. Levy suggests that (1) children of irritable bowel syndrome (IBS) patients make more healthcare visits overall, (2) children of IBS patients make more healthcare visits for gastrointestinal (GI) symptoms, and (3) children of IBS parents report more severe GI symptoms when interviewed separately from their mothers. One question is whether these findings are related to social learning or genetics. In one study which provides support for a stronger contribution by social learning, Levy and colleagues found the chance of one dyzygotic twin having IBS was 6.7% if the other twin had IBS, and the chance of a mother of dyzygotic twins having IBS if a twin has IBS is 17.1%, a statistically significant difference.

The question then is how does a child learn illness behavior, with illness behavior defined as the ways people perceive and react to somatic sensations that may be associated with disease (i.e., missing school. symptom complaints, doctor visits, etc.). More specifically, Levy and colleagues asked if the way parents respond to children's somatic complaints predicts children's illness behavior. A series of observational studies came out of this work. Some key findings from her group were:

- A strong relationship exists between the level of maternal reinforcement and seriousness of child stomachaches, as well as between maternal reinforcement, parents' IBS status and the child's illness behavior – specifically the child's school absences and clinic visits for GI reasons.
- Investigating what predicts consultation behavior (visits to the doctor), their research has shown a statistically significant association between the number of physician consultations and the psychological symptoms of mothers, as measured by various SCL-90R Subscales (somatization, anxiety, depression, overall psychological distress).
- In a validation study of the protectiveness measure developed by Walker, their research has also shown that mothers' scores on the Adult Response to Child Symptoms (ARCS) Protect Scale were significantly correlated with their subsequent diary reports of protective responses to their children's abdominal pain.
- Predictors of maternal protectiveness in response to their children's abdominal pain symptoms include: male child gender, maternal non-Caucasian race, maternal lower educational status, no father in the home, perceived severity, and an interaction between child gender and perceived severity.

The next step in their research program was to conduct experimental research which attempted to alter maladaptive illness behavior. Dr. Walker and colleagues have demonstrated that symptom talk can be

R. Levy, continued

affected by teaching parents to distract the child from symptoms versus paying attention to symptoms in a laboratory setting. They found that, for both children with pain and well children, child symptoms talk was significantly lower under distraction conditions compared to attention conditions.

We have been conducting a randomized controlled trial to see if it was possible to alter children's illness behavior by teaching parents and children to respond differently outside the laboratory. Their study included children referred for functional abdominal pain, and the interventions were either (1) a combination of social learning and cognitive behavior therapy (working with children and parents) or (2) education and support (diet education attention placebo). The data from this study are currently being analyzed, but Levy reported that the findings are very encouraging.

Our next planned study will explore whether it is possible to alter the illness behavior of children with inflammatory bowel disease (IBD) by teaching parents and children to respond differently. Pilot data reported from this work supports proceeding with this study.

In conclusion, our observational research has shown: (1) children of IBS patients make more health care visits and independently report greater symptoms, and (2) these results appear to have a strong learning component, especially related to parental response to illness behavior. In experimental research, (1) preliminary analysis is promising that an intervention aimed at children and parents can be effective in altering both children's response to symptoms as well as parental response to children for functional abdominal pain., and (2) studies to apply the same approach to IBD are planned.

Home Based Guided Imagery to Treat Functional Abdominal Pain in Children

Miranda A.L. Van Tilburg, PhD
Assistant Professor of Medicine

Miranda Van Tilburg

As defined by the *American Academy of Pediatrics & American Society for Pediatric Gastroenterology, Hepatology and Nutrition*, Functional Abdominal Pain (FAP) is abdominal pain without demonstrable evidence of a pathologic condition, such as an anatomic, metabolic, infectious, inflammatory, or neoplastic disorder. FAP may present with symptoms typical for functional dyspepsia, irritable bowel syndrome, abdominal migraine, or functional abdominal pain syndrome. Standard medical care can be effective, but many patients continue to have debilitating symptoms.

Hypnosis and guided imagery have been shown to be effective in treating FAP. In guided imagery, the therapist uses verbal guidance to help the patient experience specific detailed vivid imagery that has beneficial effects on their behavior, cognitions, emotions, or physiology. However, gut-directed guided imagery is not available for most patients because there are few therapists that offer such treatment for gastrointestinal (GI) disorders, insurance coverage is limited, and guided imagery requires multiple clinical visits, resulting in days missed from school (child) and work (parents).

Guided imagery can be self-taught. At UNC, we developed a 2-month self-directed guided imagery therapy for FAP in children delivered through the use of video/audio materials that are used at home, eliminating the need for a trained therapist or multiple clinic visits. We compared home-based guided imagery to standard medical care in 30 children aged 7-15 with a physician diagnosis of FAP. Children were randomly assigned to either 2 months of guided imagery or 2 months of standard medical care; the standard medical care group was crossed over to guided imagery after 2 months.

The treatment program was easy to use and well-liked. Adherence was 98.5%. Children generally did not need help from their parents and none of the study subjects contacted the research staff. Guided imagery resulted in significant changes in abdominal pain frequency, duration, intensity and quality of life, while standard medical care did not. School absences were significantly reduced after both types of treatment. The majority of parents (85%) reported their children were somewhat to markedly better after guided imagery; only one child did not report any change at all, and none of the children became worse. After treatment, 35% of children in the guided imagery group were pain free compared to 7% in the standard medical care group.

Our study showed that a self-taught guided imagery program that children can use at home without much guidance from parents and clinicians is effective in reducing abdominal pain complaints in children with FAP. Delivering guided imagery in the convenience of one's home without dependence on a therapist can make this type of treatment available to more children. It will enable guided imagery to be prescribed by pediatricians who do not have access to this type of treatment in their community.

Recollection of Childhood Abdominal Pain in Adults with Functional Gastrointestinal Disorders

Denesh K. Chitkara, MD
Assistant Professor of Pediatrics

Denesh Chitkara

Recurrent functional abdominal pain (FAP) in children in children is common, and approximately 8% of otherwise health children will experience this condition. FAP in children usually has no underlying organic cause and is considered to be a functional gastrointestinal disorder (FGID). Similar features between FAP in children and irritable bowel syndrome (IBS) in adults exist, such as abdominal pain with disturbed bowel function, and this suggests that FAP may be an initial manifestation in the natural history of IBS. However, previous studies have not examined this in a population-based setting to determine if this observation is applicable to community-based adults with IBS.

We utilized a validated self-report questionnaire of gastrointestinal (GI) symptoms that was mailed to a random population-based sample in Olmsted County, MN. Logistic regression models adjusting for age, gender, body mass index (BMI), somatization, and other factors were used to estimate the odds ratios (OR) for having a functional GI disorder in individuals recalling bouts of stomach or belly pain (AP) as a child (before age 15).

For this study 2,298 (55%) from a total of 4,194 eligible adult subjects returned a completed questionnaire. Of the respondents, 213 (9%) recalled experiencing AP as a child. Adults who recalled experiencing AP as a child had greater odds for reporting symptoms of a FGID (OR 1.9; 95% C.I. 1.4-2.7). Recalling AP as a child was significantly associated with IBS (OR 2.5; 95% C.I. 1.7-3.6) but not with gastro-esophageal reflux, dyspepsia, constipation or diarrhea, adjusting for age, sex, body mass index, somatic symptoms, marital status, and education. Therefore, it appears that recollecting abdominal pain as a child is specifically associated with IBS in adults. This suggests that a proportion of adults with IBS may have the onset of symptoms of abdominal pain during childhood. In the future, we intend to examine if adults with IBS with childhood symptoms differ from adults with an onset of IBS during adulthood with regard to their levels of health care utilization and level of disability from work.

Complementary and Alternative Medicine Treatment

Mindfulness Meditation Treatment for IBS

Susan Gaylord, PhD
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Susan Gaylord

Mindfulness meditation is one of the oldest and most widely practiced mind-body therapies. Recently, there has been increased appreciation for meditation as a therapeutic tool in clinical care, due in part to the renewed emphasis on the mind's role in health and disease. Mindfulness-based stress reduction programs have been introduced into many medical centers. The evidence base for mindfulness interventions is increasing: controlled clinical trials have demonstrated an increased sense of well being; decreased stress, anxiety and depression; and improvements in other psychosocial indicators. Mindfulness combines concentrative and awareness techniques. It utilizes both external and internal focal points as well as non-judgmental awareness of sensory, cognitive, and emotional experience.

As a functional bowel disorder, Irritable Bowel Syndrome (IBS) has been shown to respond well to biopsychosocial interventions. Although cognitive behavioral therapy (CBT) and hypnosis have been tested for their usefulness in IBS, little research and no well-controlled clinical trials have examined the usefulness of mindfulness for IBS. Mindfulness, a self-regulatory technique taught in a group setting, has been shown to reduce symptoms in other complex functional disorders with significant psychosocial components, e.g., fibromyalgia and depression. Mindfulness meditation's emphasis on shifting the focus of attention away from thoughts about the past and the future by focusing in a nonjudgmental, non-discursive manner on ongoing, current experiences may be uniquely suited to treat symptoms associated with IBS. These symptoms include increased sensitivity to pain from intestinal distention, anxiety about the significance of these sensations, and selective attention to gastrointestinal sensations.

The primary goal of the study underway at UNC is to test the feasibility of conducting a Mindfulness Program (intervention) and a Support Group (control) in preparation for a large clinical trial. The study involves collecting data on IBS outcomes, psychological and health-related quality of life outcomes, and process outcomes. Funding for this study has been secured through a seed grant from the UNC Center for Functional GI & Motility Disorders and an R21 grant from the National Institutes of Health (NIH). Specific aims of the study are as follows: (1) to determine the feasibility of developing a clinical trial comparing effectiveness of a Mindfulness Program (treatment group) with an IBS Support Group (control group) in reducing the severity of symptoms in women with IBS; (2) to identify relevant secondary outcomes in the Mindfulness Program and IBS Support Groups, including psychological symptoms (e.g. anxiety, depression and anger) and coping strategies (e.g. catastrophizing) as well as health-related quality of life and work productivity; (3) to evaluate two currently available process measures of mindfulness for their use in future prospective randomized controlled trials of a Mindfulness

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Program with IBS patients; and (4) to identify, and find solutions for, potential problems in conducting a future large clinical trial to assess the efficacy of a Mindfulness Program for improvement in IBS.

The study design includes a support group as a control intervention. A psycho-educational support group has been validated as an effective placebo-control condition in a randomized controlled trial of cognitive behavior therapy for the treatment of IBS. The support group in the UNC study matches the mindfulness group in terms of time/dose exposure and attention/group dynamics, thereby effectively controlling for these variables. Women only are eligible for the study, because of the higher prevalence of IBS among women as compared with men (2:1 ratio) and because all-female groups allow for an emotionally safe environment where sensitive and potentially embarrassing topics can be discussed.

Changes to the intervention and experimental design were implemented based on these findings from the seed grant:

1) Participants in the mindfulness group appeared to have difficulty generalizing mindfulness skills to address their IBS symptoms. Therefore, the mindfulness intervention was tailored to an IBS population by highlighting the relevance to bowel symptomatology.
2) Group cohesion appeared to be greater in the support group because, in the mindfulness intervention, comparatively little time was devoted to group process. To balance group cohesion between the groups, additional time was allowed for group discussion in the mindfulness group.
3) The instructor for the support group had inadvertently used some individual psychotherapy interventions within a group context, including cognitive restructuring, reframing, solution-focused, and narrative therapy techniques. The support group intervention protocol was modified to follow a strict, client-centered support group format with the instructor serving only as a facilitator.
4) We found that there were practical difficulties in having one instructor lead both interventions, both from the perspective of subject randomization (needing to be equally available for two different days and/or time slots) and due to the impracticality of having one instructor teach two different classes for which she/he may not be equally well trained or available. We have therefore decided to have different instructors for the two intervention arms, and will have multiple instructors so as not to introduce an "instructor effect" bias.

Both interventions (mindfulness and psycho-educational support group) consist of eight weekly 2-hour sessions, plus one 4 hour class held on a Saturday during the second half of the eight-week intervention. The mindfulness intervention is led by a certified health coach trained in mindfulness-based stress reduction. The format outlined in the Kabat-Zinn training manual is used as a guide for the Mindfulness Program participants, and includes the following elements: (1) "tasting the raisin" – an exercise that focuses on the immediacy of the experience of the senses and differentiates sensation from thoughts about sensation; (2) body scan; (3) sitting and walking meditation; (4) being in the present moment; (5) thought labeling; (6) mindful eating; and (7) informal practice in everyday life. The support group intervention is led by a licensed clinical social worker. It strictly follows a client-centered protocol, using only reflective listening and group facilitation techniques, and addresses the following topics: (1)

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experience of IBS symptoms; (2) the effect of stress on IBS; (3) concerns about medical IBS treatments; (4) IBS diagnosis and symptom change over time; (5) fears associated with IBS; (6) the influence of food and drink on symptoms; and (7) the need for others to understand the IBS experience.

The primary outcome measure is IBS symptom severity, using the IBS Symptom Severity Scale. Secondary outcomes include the following: 1) relief of symptoms (Adequate Relief); (2) symptom frequency (daily symptom diary); (3) IBS-related anxiety (Visceral Sensitivity Index); (4) economic impact (Work Productivity and Activity Impairment for IBS); (5) co-morbid symptoms (Recent Physical Symptoms Questionnaire); (6) general psychological distress (Brief Symptom Inventory); (7) anger and its expression (State-Trait Anger Expression Inventory); (8) quality of life specific to IBS (IBS-QOL); and (9) maladaptive coping methods (Coping Strategies Questionnaire). Effect modification measures are the expectancy of success of intervention (Borkovec and Nau Credibility Scales), a catalogue of distressing prior events (Family Inventory of Life Events), and demographics (age, race, education, marital status, income). Process measures are the Five Factor Mindfulness Questionnaire (FFMQ) and the Toronto Mindfulness Scale.

Subjects are being recruited from within a 50 mile radius through advertisements in local newspapers and fliers placed in both the UNC Health Care clinics and community medical practice offices. Subjects are also recruited from the UNC Gastroenterology Registry of IBS Patients. Eighty to 100 subjects is the initial enrollment target, with a final group size of at least 30 in each of the two groups. Based on UNC experience in IBS research, it is anticipated that the majority of subjects will be 20 to 50 years of age. The first cohort of subjects has completed the intervention and assessments up to the 3 month post-intervention follow-up. A preliminary analysis has been conducted on the process measures. Results suggest statistically significant pre-post differences on several factors of the FFMQ, but the sample is too small to be conclusive. The second cohort of subjects has recently been completed. Several drop-outs have occurred due to caregiving demands common to women in this age group and unexpected life events. Subject recruitment continues to be a challenge.

Ginger: A New Treatment for IBS?

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Miranda Van Tilburg

Irritable bowel syndrome (IBS) is a chronic condition for which no cure exists. The course is unpredictable and variable, and many patients continue to experience symptoms such as pain, diarrhea, constipation and bloating despite medical attention. Only approximately 50% of IBS patients are satisfied with treatments currently available to them from their primary care physician, thus many patients turn to alternative ways to treat their symptoms. Some of the alternative treatments may be legitimate and prescribed by physicians, such as the use of peppermint oil or hypnosis, but many others have no scientific evidence for their efficacy in IBS. Despite the lack of evidence, alternative supplements and treatments are a growing market. In a study of more than 400 health maintenance organization (HMO) patients who suffer from IBS, 35% reported using alternative medicine to treat their symptoms. Close to 15% of these patients used ginger root or ginger tea, making ginger one of the most common alternative treatments in IBS.

It is reasonable to assume that ginger can positively affect IBS symptoms. Ginger has been used for medicinal purposes since antiquity to treat indigestion, upset stomach, diarrhea and nausea. Even today, ginger is widely known and used to combat nausea and vomiting. Several well-designed studies have provided empirical evidence for ginger's antiemetic effect on pregnancy, motion sickness, and surgical procedures. Ginger may also be useful in the treatment of IBS, since there is evidence that ginger may affect the three most commonly proposed etiological pathways for IBS. First, ginger has been shown to affect gastroduodenal motility and this may explain its antiemetic effect. Second, ginger contains anti-inflammatory compounds; it inhibits prostaglandin synthesis through COX 1 and COX 2 enzyme activity similar to non-steroidal anti-inflammatory drugs. Third, ginger has been shown to reduce pain.

Given its common use, easy availability and known gastrointestinal effects, ginger is a potential new treatment for IBS that is inexpensive and safe to use. (Ginger is on the FDA's Generally Recognized as Safe list.) At UNC, we are planning to apply for NIH grant funding to test the effect of ginger on IBS symptoms in a double-blind placebo-controlled study. In order to do so, we are currently running two pilot studies. One is a study to show that subjects can be blinded from the taste and smell of ginger, and the other is a small single-blind randomized controlled study looking at the effects of ginger on the symptoms of IBS.

Gastrointestinal-Specific Anxiety: Development of the Visceral Sensitivity Index

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Bruce Naliboff

Gastrointestinal-specific anxiety (GSA) or visceral anxiety refers to cognitive, affective, and behavioral responses to fear of gastrointestinal (GI) symptoms and the context in which visceral sensations and symptoms occur. GSA is hypothesized to perpetuate IBS symptoms through alterations in autonomic and pain facilitation, as well as cognitive mechanisms. Therefore, GSA may be an important variable in outcome and mechanistic investigations in IBS. Visceral anxiety is characterized by fear, vigilance, worry, avoidance, and safety-seeking and has been hypothesized to be affected by: (1) genotype and early life events, (2) psychosocial distress, (3) trait anxiety, (4) psychological symptoms, and (5) visceral symptoms.

The Visceral Sensitivity Index (VSI) is the first instrument developed to assess GI-specific anxiety. It consists of 15 items scored from 'strongly agree' to 'strongly disagree'. Themes include worry, fear, vigilance, sensitivity, and avoidance related to visceral sensations and contexts. The VSI has demonstrated excellent reliability and validity in an initial sample of IBS patients. In the VSI validation study, an initial pool of 103 items was narrowed down to 86 items through review by experts. These items were pilot tested in a focus group, which further narrowed the proposed set down to 15 items. The item evaluation criteria were good face validity (2 or 3 raters agree on the construct); no ceiling or floor effects (item mean between 1 and 3); strong internal consistency (item correlates with total score > .50); good predictive validity (item correlates with severity > .25 ($p < .05$)); moderate relationship with Hospital Anxiety and Depression (HAD); and items written for general use (i.e., applicable to non-patients). Item response scoring is on a 6-point scale from strongly disagree to strongly agree.

A cross-validation study was conducted to further evaluate the psychometric properties of the VSI in non-IBS patient samples using a known-groups validity approach, and to compare the role of GSA and more general distress in symptom severity and health care seeking in non-clinic samples of IBS patients. The study subjects were two UCLA undergraduate student samples (N>500) participating in a non-IBS related survey, and a sample of subjects responding to an advertisement for IBS research participants (n=82). Measures included: ROME II IBS survey criteria; GI symptom severity; non-GI pain complaints; GI health care use (past year); measures of anxiety, depression, vitality, neuroticism, and anxiety sensitivity; and the VSI. Study subjects identified as IBS negative were individuals who did not endorse abdominal pain/discomfort. Those identified as IBS positive were individuals meeting Rome II diagnostic criteria, who were then further classified as IBS patients (reporting visits to either a physician or gastroenterologist for lower GI problems in the past year) and IBS non-patients (not endorsing health care utilization for lower GI-symptoms in the past year).

The specific research questions were: (1) Does the VSI maintain internal consistency when examined in non-IBS and non-patient samples? (2) Is GSA distinct from other distress measures in non-IBS

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patients? (3) Is the VSI more strongly related to presence of IBS than other affective measures? (4) Does the VSI successfully discriminate between IBS non-patients, and IBS patients? (5) Does GSA mediate the relationship between trait anxiety and symptom severity?

Results: (1) The VSI showed excellent reliability in "community" samples (Cronbach's alphas from .90 to .92, and a single factor solution indicating one primary dimension, accounting for 48% of variance). (2) The correlation between VSI and general anxiety is lower in non-patient samples compared to IBS patients, and the VSI is only correlated with GI symptom severity (Sample 2). (3) The VSI predicts the presence of IBS. (4) The VSI is the strongest discriminator of all three groups (IBS negative, IBS patients, IBS non-patients). (5) GSA mediates the relationship between state anxiety as well as trait anxiety and symptoms in IBS, as well as the relationship between general medical anxiety and IBS symptom severity.

Conclusions: (1) The VSI maintains good psychometric properties across IBS and non-IBS populations. (2) GSA as measured by the VSI appears to be a sensitive marker of affective processes in IBS and accounts for the relationship between measures of general affect and symptom presentation. (3) The VSI may be a very useful outcome measure in treatment trials, mechanistic studies, and population studies related to IBS.

Investigating the Role of Comorbidity in Irritable Bowel Syndrome

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Oli Palsson

Irritable bowel syndrome (IBS) comorbidity is the coexistence of one or more non-gastrointestinal (non-GI) medical diagnoses or non-GI symptoms with IBS. Numerous studies have reported that patients who have IBS have an excessive frequency of co-existing somatic, visceral and psychiatric disorders. Somatization is a related but somewhat different construct. It has been defined as "the tendency to report numerous physical symptoms in excess to that expected from physical findings" (Escobar et al., 1987). Several studies have reported that IBS patients report an excess number of non-GI physical symptoms. In other words, they have an elevated somatization tendency as a group.

IBS comorbidity and somatization tendency appear to be characteristic of IBS across cultures and nationalities. For example, Kanazawa and colleagues (Gastroenterology 2007;132 (4):A680-681) found that Japanese and US patients reported identical and elevated numbers of comorbid diagnoses (an average of 3.2 diagnoses) when completing the same questionnaire (the CMCQ). Patients tested in the two countries had similar frequencies for most of 16 diagnoses on this questionnaire, differing significantly on only 3 diagnoses: tension headaches (Japan vs. US: 12.2% vs. 45.7%), depression (19.3% vs. 44.8%), and interstitial cystitis (24.6% vs. 2.4%).

Why should we care about comorbidities and somatization? First, these phenomena are clearly major modulators of health care costs and needs of IBS patients. Research in an HMO in Seattle (Levy et al. Am J Gastroenterol 2001;96:3122-29; Levy et al. Am J Gastroenterol. 2000 Feb;95(2):451-6) has shown that annual healthcare utilization is double among IBS patients compared to other individuals, and 66% of the excess healthcare costs associated with IBS patients is unrelated to GI symptoms. In fact, only 9% of healthcare costs among IBS patients are due to their lower GI problems.

Spiegel and colleagues (Am J Gastroenterol. 2005 Oct;100(10):2262-73) have demonstrated in a large study (N=1,410) that among IBS patients receiving medical care from a gastroenterologist, the impact of somatization on the use of gastrointestinal health-care resources in patients with irritable bowel syndrome is linear and substantial in dollar value. For example, they found that patients with the highest somatization scores had mean annual GI healthcare costs that were $2,481 higher than those with average scores. We have found a similar potent linear relationship of somatization scores with overall healthcare costs of IBS patients in our recent MAPS study, but those data have not been published yet.

Another reason why there is a reason to be concerned about the role of comorbidity in IBS is that it has substantial adverse effects on the well-being of patients. Our own studies and those of other researchers, such as Ami Sperber and Lin Chang, have found that both somatization and the presence of co-morbid medical conditions is associated with more severe GI symptoms, greater impairment in QOL, and more missed work/school due to illness. We developed and validated IBS-specific questionnaires to measure

broadly and reliably the presence of IBS comorbidity and somatization (the CMCQ and RPSQ scales, respectively), which has facilitated our work in this area.

Since the impact of both of these phenomena on health status and healthcare among IBS patients often appears to be similar, one question is whether both constructs are needed? Is it necessary to measure somatization and comorbidity separately, or can one measure be used as a proxy for the other? Some clues to answering this question are emerging from our on-going Cluster Study, where we are looking at the correlation of these two variables with other psychological and physiological variables. Our results indicate that the correlations of somatization and comorbidity with physiological variables are somewhat different. In particular, it seems that comorbidity scores on our CMCQ scale correlate with lower visceral pain thresholds in balloon inflation tests, but the same is not seen for somatization scores (RPSQ scale). Furthermore, the inter-correlation between comorbidity and somatization scores is only moderate (r = 0.39), suggesting that perhaps these are better considered separate phenomena.

Another question about comorbidity in IBS is whether there are specific (i.e., unique) IBS comorbidities. Prior research has already identified several chronic medical disorders with reported excess overlap with IBS. In particular, fibromyalgia (16 studies), chronic fatigue (7 studies), chronic pelvic pain (5 studies), and temporomandibular disorder (2 studies) have been a focus of interest in this regard. All of these conditions show a very high overlap with IBS. Does this mean there is shared etiology? Or that these conditions are all the same syndrome, as some have proposed? There is a certain appeal and logic to that idea, because the most well-documented co-morbid disorders with excess overlap with IBS generally have characteristics similar to IBS: (1) predominantly female patients; (2) vague immune response irregularities; (3) onset commonly in early-to-mid adulthood; (4) increased pain sensitivity, (5) excess stress reactivity/high chronic stress levels; (6) trauma history unusually common; (7) pain as a central symptom; (8) high prevalence of psychiatric diagnosis/symptoms; and (9) autonomic hyper-reactivity.

However, there are a number of problems with drawing firm conclusions from most past studies reporting IBS co-morbidity. (1) Typically the research has been done using tertiary care patient samples. (2) Often, the patients are sampled because they are seeking treatment through clinics and research programs. This has a potential for self-selection bias -- the patients may be more refractory and have more severe and complex problems than the average IBS patient. (3) The samples studied have typically been small. (4) The diagnosis of co-morbid conditions is often based on symptom questionnaires or diagnosis self-report rather than physician diagnosis or tests. Bigger and better research, conducted on medical records data from a very large sample of normal run-of-the-mill IBS patients in an HMO, is now showing a strikingly different picture – one where there do not seem to be particularly strong associations of IBS with particular disorders, but rather a general elevation in comorbidity across most medical conditions.

A recently published large HMO study of IBS medical diagnoses conducted by our group (Whitehead et al. Am J Gastroenterol. 2007 Dec;102(12):2767-76) included 3,153 IBS patients (clinical diagnosis), 3,153 matched HMO controls and 571 IBD patients. All diagnoses recorded over a 4-year period were compared between the groups. The most striking findings were that most diagnoses of any kind had significantly higher incidence in IBS compared to control patients: 48 of 51 non-specific non-GI disorders, all 10 psychiatric diagnoses sampled, and 16 of 25 diagnoses with objective signs and tests. Somatic disorders with objective diagnostic signs or tests were also more common in IBS than in age

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and gender matched controls. What can be causing such wide and general elevation of incidence in rates of medical conditions co-present with IBS? Based on the research to date, there seem to be several possibilities, and it is quite possible that some or all of these are multiple synergistic contributors:

1. More frequent visits to doctors by IBS patients may results in a greater number of diagnoses as a side effect.
2. IBS patients may be hyper-vigilant or sensitive to minor bodily symptoms (due to somatization tendency), and therefore detect symptoms of mild cases of disorders more readily than other people and seek healthcare for them.
3. Social learning may cause chronic illness transmission across generations. We have recently found that IBS patients report significantly more instances of chronic medical conditions in their immediate childhood families (parents and siblings) than control subjects (Palsson et al. Gastroenterology 2007;132 (4):A520). The amount of chronic medical problems present in the childhood family environment was associated with greater somatization and worse health-related QOL in the adult patients.
4. Trauma history and elevated psychological distress are highly prevalent in IBS, and these characteristics are also associated with more medical symptoms and diagnoses outside of IBS, so it is possible that psychological factors play a causal role in IBS comorbidity.
5. Genetic factors may contribute to producing somatization that translates into more diagnoses and health problems over time. Recent evidence published by our colleagues at UNC-Chapel Hill (Diatchenko et al. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, Volume 141B, Issue 5 , 2006, Pages 449 – 462) points to the role of certain haplotypes of adrenergic receptor beta-2 (ADRB2), which plays a critical role in mediating physiological and psychological responses to environmental stressors, in elevated somatization tendencies, and our pilot data to be presented at the next Digestive Disease Week in San Diego in 2008 suggest that ADRB2 might be at play in IBS.

In summary:

- IBS comorbidity has a substantial impact on GI symptom severity, quality of life, disability, and health care utilization and costs.
- Data on IBS show higher incidence of the great majority of medical diagnoses of any kind, including disorders with objective tests or signs; the overall odds ratio is about 1.6.
- Low threshold to experience and report generic symptoms and consult physicians, as well as psychological distress and trauma history, genetic vulnerability and childhood learning history, may contribute to medical comorbidities in IBS.

Several major issues relating to understanding IBS comorbidity are currently unresolved and will likely determine future directions in this area of investigation:

- Can medical comorbidities be predicted, treated or prevented?
- Do the comorbid disorders increase or decrease together (if so, is it an inverse or direct relationship) or are they independent?
- Is comorbidity characteristic of a specific type of IBS patients rather than patients with this disorder in general?
- What are the causes, or the relative weight of a combination of causes, of somatization and high comorbidity in IBS? Is it genes, learning history, traumatic events, or other factors that play the greatest roles?

Association of Psychosocial Factors and Disease Markers with Health Status in Celiac Disease

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Spencer Dorn

Celiac disease, a chronic inflammatory disease of the small intestines caused by gluten sensitivity, affects approximately 1% of the U.S. population. In these individuals, health status (i.e., health related quality of life and health care utilization) is highly variable. This variability is typically assumed to relate directly to underlying disease activity (i.e., histopathologic severity) and clinical presentation (i.e., classical or silent disease). However, this relationship has not been proven for celiac disease, and evidence from other digestive diseases suggests that it might be weaker than anticipated. For example, in inflammatory bowel disease (IBD), histopathologic severity and health care utilization are only weakly associated. In irritable bowel syndrome (IBS), physiologic abnormalities are poorly related to symptoms and quality of life. Instead, in both IBD and IBS, health status is strongly predicted by psychosocial factors, such as depression and abuse. As such, these patients benefit from a biopsychosocial treatment approach. However, whether patients with celiac disease will benefit from a similar approach first requires that the key determinants of health status be identified.

Over a 2-year collaboration between UNC and the Celiac Disease Center at Columbia University, Dr. Drossman and I have led a pilot study that explores the association of biological components of disease activity, psychosocial factors, and health status in celiac disease. All adults who presented to the Columbia Celiac Disease Center with newly diagnosed, biopsy proven celiac disease were recruited. Excluded from the study were those who (1) were on a gluten free diet for > 6 weeks, (2) had a history of other structural GI disease, (3) had a history of bowel resection or gastrectomy, or (4) were asymptomatic and diagnosed on routine screening. Health status was assessed in terms of the following: pain, health related quality of life (Sickness Impact Profile, IBS-Quality of Life, Self-Report of Health), and health care utilization (number of physician visits). Independent variables included demographic factors (race, gender, age, level of education), disease based measures (symptomatology, histopathology/Marsh, tissue transglutaminase levels, body mass index, albumin, hemoglobin, cholesterol, and IBS), and psychosocial factors (sexual and physical abuse history, recent life stress, overall psychological symptoms, depression, and coping style).

To date, 70 of an anticipated 85 patients have completed the study and complete data are available for 24 patients (median age 39; 62% male). Preliminary analyses demonstrated the following: (1) Pain (median VAS = 16.8; sd=18.3) was not associated with demographic nor disease based measures, but was predicted by several psychosocial factors (somatization, depression, anxiety, and catastrophizing). (2) Health Related Quality of Life (median IBS-QOL=79.0; sd=24.8) was not associated with any demographic factors, but was associated with one disease based measure (classical disease presentation) and several psychosocial factors (somatization, depression, anxiety, and catastrophizing). (3) Patient self-report of health (on a scale from 1=poor to 5=excellent; median=3.5; sd=1.1) was associated

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only with psychosocial factors (coping style). (4) The number of physician visits over the prior 3 months (median=3; range=0-40) was not predicted by any demographic, disease based or psychosocial factors.

A complete analysis is currently in progress. Based on these results, future directions may include: (1) studies to test any hypotheses that are generated; (2) use of antidepressant or behavioral intervention for refractory patients with high psychosocial distress; and (3) investigation of the correlation of cytokines with disease activity and psychosocial distress.

Using Ecological Momentary Assessment (EMA) Research Methods in the Study of IBS

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Stephan Weinland

The Rome III diagnostic criteria for irritable bowel syndrome (IBS) require the patient or study subject to recall the following: Recurrent abdominal pain or discomfort at least three days/month in the last three months associated with two or more of the following: (1) improvement with defecation, (2) onset associated with a change in frequency of stool, or (3) onset associated with a change in form (appearance) of stool. Dr. Weinland pointed out that retrospective examination may be flawed.

Ecological Momentary Assessment (EMA) is the collection of repeated measurements of phenomena as they occur in naturalistic settings. "Ecological" refers a focus on the usual environment (home, work, school) where symptoms normally take place. "Momentary" refers to randomly spaced intervals throughout the day. "Assessment" means, when prompted, subjects record their immediate experience. The number of Medline references on topics related to EMA -- "Ecological Momentary Assessment," "Experience Sampling," "Ambulatory Assessment" – has increased significantly between 1980 and 2005.

Previous studies show that the onset of diarrheal stool was associated with significantly more pain than was the onset of constipated stool and that there is a trend for the onset of diarrheal stool (more than a constipated stool) to be associated with a decrease in wellbeing, Dr. Weinland explained why EMA should be applied to the study of IBS. First, he suggested that clinical and research assessment of IBS is flawed. Previous studies have shown that systematic bias makes detection of IBS triggers and response to triggers more difficult, and retrospective reports of bowel pattern do not correlate with prospective diary card assessment. Second, there is a need to validate the Rome III definition of IBS as "pain relieved by bowel movement". Finally, psychophysiological studies in the lab show motility changes to immediate stressors. It would be helpful to know if this occurs in the course of actual bowel symptoms.

I am leading a study titled The application of EMA to IBS, which proposes to evaluate time-specific relationships between variables of pain, stress, and bloating in the onset of IBS-related diarrhea and constipation symptoms using EMA. This study is being sponsored by Takeda Pharmaceuticals. The primary objectives of the study are: (1) to determine pain and bloating scores – (a) average pain and bloating scores prior to defecation onset and (b) their reduction after defecation compared to prior to defecation in patients with IBS in general and IBS subtypes (IBS-C, D, M) as well as in relation to constipated and diarrheal stools; (2) to determine the association of acute stress with increased pain and bloating scores or with defecation onset in IBS and it's subtypes as well as for constipated and diarrheal stools; and (3) to understand the correlation between EMA and standard diary card measures as a means to validate their use

S. Weinland, continued

For this study, 20 study subjects will be recruited for each of the following categories: diarrhea-predominant IBS, constipation-predominant IBS, mixed diarrhea-constipation IBS, and non-symptomatic controls. Over a 14-day period, data will be collected on variables at three semi-random times over the course of the day. "Morning" data include (1) Sleep Diary Data (Bed Time, Wake Time, Quality of Sleep, Awakenings During the Night), (2) Current Abdominal Pain (VAS), (3) Current Global Perceived Stress (VAS), (4) Current Global Perception of Wellbeing (VAS), and (5) Current Bloating Symptom Rating. "Midday" and "End of Day" variables are Pain, Stress, Wellbeing, Bloating. Study participants will also be asked to provide pre-defecation ratings (Pain, Stress, Wellbeing, Bloating, Urgency) and post-defecation ratings (Pain, Stress, Wellbeing, Bloating; Straining; Bristol Stool Form Scale). Data collection will be accomplished through pocket PC devices loaned to study subjects, using Pendragon Forms to collect data that is stored on a memory stick and then imported directly into Microsoft Access.

Future implications of the study include: (1) clarification of Rome III classification of IBS symptoms and subtypes; (2) relationship between variables of pain, stress, bloating and time-variable defecation events; (3) relationship between daily diary cards and EMA collected data; (4) development of further real time data collection techniques (internet, cell phone) for use in research; and (5) potential for predictive modeling of symptom experience to allow for greater symptom control.

Atypical Antipsychotic Quetiapine in the Treatment of Severe Refractory Functional Gastrointestinal Disorders

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Up to 20 percent of all functional gastrointestinal disorder (FGID) patients and up to 70% of patients seen in referral centers are considered to have symptoms that are severe and refractory. These patients generally experience greater pain and have higher rates of psychiatric disorders (40-50%- anxiety or depression), post-traumatic stress disorder (PTSD), sleep disturbances (50-70%), and somatization (overlap with somatic pain disorders). This subgroup of FGID patients demonstrates higher health care utilization and treatment dissatisfaction. In addition to a therapeutic patient-physician alliance, the treatment includes centrally acting agents -- tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) -- to modulate pain processing and peripherally acting agents for bowel symptoms. Augmentation therapy involving the combination of two antidepressants or an antidepressant with an anxiolytic may maximize efficacy and minimize side effects.

The atypical antipsychotic quetiapine is an anxiolytic with inhibitory effects on 5HT2, 5HT3 receptors. It is being used in the treatment of social anxiety and PTSD (reduces re-experiencing, hyperarousal, nightmares). It also provides a sleep benefit (anti-H1, anti-adrenergic action) and increases total sleep time, efficiency and subjective quality. It is also a potential analgesic (anti-dopaminergic action) and has been used to treat fibromyalgia, migraines, chronic low back and cancer pain. The rationale for augmenting treatment with quetiapine in FGID patients was: (1) treatment failure of a single drug or combination of traditional antidepressants; (2) minimize side effects of traditional agents by targeting different receptor sites at smaller doses; (3) reduce associated anxiety and/or sleep disturbances; and (4) potential augmentation of analgesia.

In our retrospective review of open labeled treatment with quetiapine at UNC, a total of 23 patients treated with quetiapine from January 2006 to June 2007 were identified and 21 were included in the study. Structured data extraction from electronic medical records regarding the visit at quetiapine initiation and most recent follow-up visit and a telephone interview were conducted for these 21 patients. Patient characteristics were: mean age 40.8 years, 90.5% female, 85.7% white, and mean duration of FGID 89.9 months. The most common FGID diagnoses were severe IBS (28.6%) and Functional Abdominal Pain Syndrome (52.4%). The remaining 19% included functional chest pain, functional nausea and vomiting, and functional constipation. Sleep disturbances were experienced by 90.5% of the patients and mood disturbances by 66.7%. Several patients were concurrently undergoing treatment with a psychiatrist (19%) or a psychologist (52.4%). Reasons for quetiapine initiation were refractory abdominal pain (37.8%), anxiety (33%), sleeping problems (18%), or depression (9.5%). At the time of the interview, eleven patients (52.4%) were continuing to take quetiapine and ten patients (47.6%) had stopped. Outcome measures for response of patients who stayed on quetiapine included global relief of

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symptoms, treatment efficacy questionnaire (TEQ), and change in gastrointestinal and psychological symptoms. Patients who had stopped taking quetiapine were queried about the duration of use, reasons for stopping, and how they rated their GI-related health when they were taking quetiapine.

Of the 11 patients who were still taking quetiapine, six (54%) reported adequate relief of symptoms. Nine were satisfied with the results of their treatment, engaged in more activities, were coping better, and reported improved symptoms. Four found the treatment to be more helpful than expected. Compared to pre-treatment, nine of the 11 patients reported overall improvement (81.8%) and no patient reported worsening symptoms. Nine of the 11 reported improvement in abdominal pain, 10 reported improved sleep and mood, and seven reported improvement in bowel habits. The mean dose was 50 mg and mean duration of treatment at the time of interview was 145 days. All 11 patients were also receiving antidepressants: seven duloxetine, two desipramine, and two amitriptyline.

Ten of the 21 patients (47.6%) had stopped quetiapine at the time of the interview. Although the mean duration on quetiapine use was 90 days, three had stopped within 3 days of starting due to somnolence, lack of perceived GI benefit and dizziness. With regard to the clinical response, three reported feeling somewhat or significantly better, five reported no change, and two reported feeling somewhat worse when on treatment. Six patients (60%) had weight gain, but only one patient discontinued for that reason.

Atypical antipsychotics have gained wide acceptance for treatment of bipolar disorder and schizophrenia because of their efficacy and low toxicity. They can also be beneficial for patients with FGIDs because of their analgesic, sedative and anxiolytic effects. Thus, these medications can augment treatment of patients with refractory FGIDs, particularly those having incomplete response to antidepressants, sleep disturbances or associated anxiety.

In conclusion, in this study over one-half of patients with severe, refractory FGIDs who stayed on quetiapine to augment the effects of an antidepressant benefited. A more effective patient-physician relationship, closer follow-up, and careful dose readjustments could reduce non-adherence. Considering the severity and refractoriness of the symptoms, this response rate is notable and warrants additional studies, preferably in a controlled clinical trial.

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Research at UNC Center for Functional GI & Motility Disorders

The Center has developed a broad portfolio of research on the mechanisms of functional GI and motility disorders, as well as their psychosocial correlates, health outcomes, and treatment. The Center's Co-Directors have a long history of research support from the National Institutes of Health (NIH), pharmaceutical companies, and other sources. Other Center investigators have established their own independent research programs and funding. The research activities of faculty and investigators associated with the Center are supported through a variety of grants and contracts – 57% from the National Institutes of Health (NIH), 24% from pharmaceutical companies, and 19% from foundations and other sources. In 2007, funding support for Center research activities was increased by an additional $3.4 million in grants and contracts.

The Center's research programs are multidisciplinary, involving collaborations between gastroenterologists, psychologists, neuroradiologists, psychiatrists, physician assistants, and nurses. Within UNC at Chapel Hill, collaborators came from the departments of Medicine, Psychology, Psychiatry, Surgery and Gynecology, as well as the schools of Dentistry and Public Health. Research at the Center has included studies on the pathophysiology and treatment of such prevalent functional GI disorders as IBS, functional dyspepsia, functional abdominal pain, fecal incontinence, and constipation. These disorders greatly impair quality of life and result in aggregate annual health care costs in the United States exceeding $25 billion.

Mind-Body Infrastructure Grant

In 2004, the Center was awarded a grant (R24 DK067674) from 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 GI and motility disorders. The five-year, $4.45 million grant establishes a *Gastrointestinal Biopsychosocial Research Program* within the Center. The Center's Co-Directors--Drs. Whitehead and Drossman--are Co-PIs for this grant. An Infrastructure Grant Advisory Board of leaders from within the UNC School of Medicine and School of Public Health as well as a Scientific Advisory Board of leading national and international experts in functional GI and motility provide advice to the Center on ways to make the best possible use of the infrastructure grant.

This multi-year "infrastructure grant" is being used to build on the Center's longstanding record of NIH-funded research in mind-body interactions and to carry out longer-term collaborations with other disciplines in health and medicine at UNC and with other institutions throughout the US and other countries. Examples of mind-body research at the Center include studies on the role of stress, abuse history and other psychosocial factors in IBS and their outcomes; brain imaging to assess the association between psychological factors and central pain regulation; hereditary and learned-behavior aspects of IBS and recurrent abdominal pain (RAP); the effects of reproductive hormones on IBS; and the tendency of IBS to co-exist with other disorders. Center researchers have also studied the effectiveness of treatment strategies that combine cognitive behavior therapy (CBT), hypnosis, antidepressants, and/or patient education with medications for IBS; biofeedback combined with medical management for fecal incontinence and constipation; and complimentary and alternative medicine techniques such as Mindfulness Meditation.

Research Resources

Research Administration Core: The purposes of the Research Administration Core are to provide (1) a central resource for recruiting research subjects, (2) assistance with the recruitment of Hispanic and other minority research subjects, and (3) a team of research coordinators. The Research Administration Core also assembles and maintains records and forms that are made available to investigators who are dealing with regulatory issues that affect the conduct of research (i.e., IRB and GCRC forms, website where grant applications can be obtained, etc.).

Research Network Core: In addition to collaborations with investigators in a variety of disciplines at UNC, the Center has an ever-expanding Research Network of collaborating institutions outside UNC for large-scale, multi-center studies. These strategic alliances have been developed to take advantage of the specialized skills and expertise of investigators at other sites and to increase the pool of research subjects participating in Center studies. The Research Network has benefited from the development of new technologies for web-based data acquisition/sharing and research subject recruitment, as well as a growing library of FGID-related scannable and Internet-based questionnaires in different languages. The purposes of the Research Network Core are to (1) provide administrative support from the UNC Center for funded research collaborations; (2) provide data management for multi-center studies; and (3) provide Center investigators with research-ready sites with proven abilities, both nationally and internationally, to facilitate the funding of large-scale, multi-center studies.

Biometry Core: The primary purposes of the Biometry Core are to provide (1) consultation and advice on experimental design and statistical analysis; (2) data entry and data management for selected projects; and (3) data analysis for selected projects. Other capabilities of this core are: (4) developing questionnaire booklets for research studies; (5) developing data management and quality assurance procedures and manuals; (6) developing data management programs; (7) coding, entering and cleaning data; (8) developing random generation schemes for clinical trials; (9) overseeing the production of reports for data and safety monitoring boards and for regulatory agencies; and (10) assisting investigators in analyzing the data and developing research reports for publication.

Data Acquisition & Technology Applications Core (DATA): The DATA Core provides researchers with sophisticated data acquisition and data-sharing methodologies, data management, and archiving of research data to facilitate the conduct of large studies (especially multi-site studies) by our UNC research team and our national and international Research Network collaborators. Capabilities of this core include (1) creating and scanning of machine-readable questionnaires, (2) internet surveys, (3) programs and websites for managing multi-site studies, (4) secure server for multi-site studies, (5) PDA-based symptom surveys, and (6) automated telephone data entry.

Education & Dissemination Core: The goals of the Education & Dissemination Core are to (1) meet the educational needs of patients and the general public, (2) educate health care providers in the diagnosis and treatment of functional GI and motility disorders, (3) disseminate research findings to professional and lay audiences, and (4) to utilize the Internet for the recruitment of research study subjects and for the conduct of internet-based surveys and other research projects.

Seed Grant Core: The NIH infrastructure grant provides funding for a Seed Grant Program (SGP) to support up to three pilot projects each fiscal year (each for $37,500 in direct costs), with application deadlines in December, April and August. The goals of the SGP are to encourage and develop new investigators by providing (1) funds to collect the pilot data essential to successful NIH applications, and (2) mentoring in grant writing as well as the conduct of a research project.

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