IBS is a complex and chronic health problem that is often hard to treat successfully with the methods currently available in standard medical care. A substantial proportion of individuals with IBS who seek healthcare continue to have chronic and troublesome symptoms in spite of the best efforts of their doctors. Those patients require something more -- adjunctive therapy -- in order to achieve better health outcomes. Cognitive Behavioral Therapy (CBT) is one of the best approaches that have been identified for that purpose to date, and it has been investigated more than any other adjunctive therapy for IBS. CBT is a psychological treatment that helps people to change how they think (the “cognitive” part) and act (the “behavioral” part) in a way that improves their life functioning, physical symptoms and emotional well-being. It is a highly focused form of treatment where patients are aided by a therapist for a limited number of hours (typically 8-20) to examine how their own current patterns of thoughts and behavior contribute to their health problem and guided to work on systematically unlearning those patterns and adopting more health-supporting ways of thinking and acting. CBT has been put to the test for IBS treatment in dozens of published studies, including many randomized controlled trials, most of which have shown it to be highly effective for improving symptoms and quality of life for patients with chronic IBS.

Jeffrey Lackner, PsyD, Associate Professor of Medicine and Anesthesiology at the SUNY University of Buffalo School of Medicine, has emerged over the past decade as one of the foremost leaders in investigating and further developing this important treatment option for IBS. He has worked very many years to make CBT more efficient and streamlined and thereby better suited for widespread use. This work is based on his conviction that since most of the actual therapeutic activity of CBT happens not in the sessions with the therapist...
Over the past decade, the UNC Center for Functional GI and Motility Disorders has enjoyed significant grant support from a number of private foundations and corporations. These grants have ranged from sponsorships of specific events (symposia or CME courses) to unrestricted grants in support of fellowships and the Center’s education and training effort. Support for the Digest Newsletter is provided by Takeda Pharmaceuticals North America, Inc.

DIGEST is a quarterly publication of the UNC Center for Functional GI & Motility Disorders, a center of excellence within the Division of Gastroenterology and Hepatology, School of Medicine, University of North Carolina at Chapel Hill.

The Center’s director is William E. Whitehead, PhD, Professor of Medicine and Gynecology.

For more information about the Center, please visit our website at WWW.MED.UNC.EDU/IBS
Opinions expressed by authors are their own and not necessarily those of the UNC Center for Functional GI and Motility Disorders. We do not guarantee or endorse any specific product or any claim made by an author and disclaim all liability relating thereto. Occasionally, specific products are cited in articles or acknowledgements. However, no endorsement is intended or implied. Our intention is to focus on overall treatment or management issues or strategies.
Nurse-led Community–based Conservative Treatment of Fecal Incontinence: Effectiveness Trial

Steve Heymen, PhD

Fecal incontinence (FI) affects 9% of U.S. adults and occurs weekly or more often in 2.7%. Prevalence increases with age reaching 15% by 70 years. FI has a devastating impact on quality of life and substantially increases caregiver burden when patients have comorbid conditions requiring caregiver assistance.

We are conducting an effectiveness trial whose overall goal is to determine whether a conservative intervention which has been shown to be effective in tertiary care centers will sustain its efficacy when disseminated to a home bound population by home health care nurses and by nurses at Continuing Care Retirement Communities (CCRCs) and Assisted Living facilities (ALFs).

Subjects will receive one of two conservative treatments for fecal incontinence, both of which have been shown to be superior to standard care, but differ by the level of nurse contact and subject effort required. Patients are randomly assigned to one of the two treatment groups. The outcomes we are assessing are changes in the severity of fecal incontinence, impact on the subject's quality of life, and burden on family caregivers; these outcomes will be assessed by a research assistant using standard questionnaires. To minimize drift when the treatment is disseminated to a large group of providers, patient education and other basic components of treatment are included in a treatment booklet; however, nurse supervision to individualize treatment remains important.

The study will be carried out in 4 counties in central North Carolina which are served by the University of North Carolina Home Health Care agency (partner in this study). We have added several local CCRCs and ALFs to diversify the patient population and improve generalizability of the treatment intervention to a broader patient population, as well as increase opportunities for subject recruitment. After excluding patients with severe cognitive impairment and those with stomas, we estimate 190 patients with FI who are over age 18 will receive treatment. Participants will be recruited by the nursing staff at the Home Health Care agencies, CCRCs, and ALFs who will also provide the treatment. Patients may also be referred by their physician. Training for the nurses regarding how to implement the treatment and how to recruit participants will be provided by members of our team: Steve Heymen, PhD and Mary Palmer, RN, PhD.

Dr. Heymen is an Associate Professor in the School of Medicine and is a Senior Fellow of the Biofeedback Certification International Alliance. He has provided biofeedback and cognitive behavior therapy to adults for more than 25 years. In 1999 he was recruited to UNC at Chapel Hill to manage a 5-year NIH Biofeedback trial and has been the Director of the Biofeedback Services in the Department of Gastroenterology at UNC Hospital for 14 years. At UNC he has conducted research in the area of functional GI disorders and created a clinical Biofeedback program in the GI department.

Dr. Heymen is also in private practice where he provides Biofeedback and Cognitive Behavior Therapy for patients with anxiety and chronic pain disorders, as well as functional GI disorders. (www.steveheymen.com)

If you would like more information about participating in this study, please contact Steve Heymen, PhD at 919-966-2515.
but in between clinic visits, more of what produces improvement can be put directly in the hands of patients through well-designed structured materials designed for their independent use, thereby making the treatment less expensive and less dependent on expert therapists. From 2004 to 2007, Dr. Lackner and his colleagues conducted a clinical trial that tested this concept -- how well a “limited-contact” version of CBT that they had developed for IBS worked, that required less than half the typical number of therapist sessions. They compared outcomes for two groups of patients: One group received their novel limited-contact therapy, which consisted of only four therapist visits combined with self-administered home treatment with special structured learning materials and exercises designed by Dr. Lackner and his team. The other group was a comparison group of patients treated by a therapist in a more typical course of 10 CBT visits. The study found that 62% of the patients in the minimal-contact CBT group reported their IBS symptoms to be much or very much improved, compared to 58% in the ten-session CBT group [1]. In other words, this new variant of the treatment where patients themselves do the bulk of the therapeutic work on their own, worked just as well as the traditional approach.

These encouraging results enabled Dr. Lackner to obtain funding as principal investigator for the largest ever research project on CBT for IBS, which he received an 8.9 million dollar grant to conduct from the National Institutes of Health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) [2]. This ambitious seven-year multi-site project, which will be completed in 2015, tests minimal-contact CBT against regular 10-session CBT in more than 400 people with IBS. If Lackner and his co-investigators are able to demonstrate again that minimal-contact treatment is as good at improving bowel symptoms and well-being of IBS patient as regular CBT, the positive impact for patients of this work could be vast. It will help counteract negative views of the cost of such adjunctive therapy in a climate of ever-rising healthcare costs where frugal use of healthcare dollars is a high priority, and where adjunctive therapies therefore can be seen as a luxury rather than essential services for medical problems. Additionally, with the Affordable Care Act legislation now in place, there will soon be a large new population of patients entering the health care system and requiring services that few suitably trained mental healthcare providers are available to offer. This evidence-based approach of largely self-administered therapy with very limited in-person contact will likely make it easier to routinely couple such treatment with pharmaceutical treatment to boost outcomes, and could also make it possible to provide such adjunctive treatment in underserved areas where there is little therapist availability.

Dr. Lackner’s work in this area is on the cutting edge of what is becoming a major new direction in CBT and some other psychological treatments -- the development and testing of partly or entirely self-administered treatment. What makes the work of Dr. Lackner and his co-investigators stand out is that their minimal-contact treatment is carefully structured to deliver the same “active ingredients” that work so well with in-person work with therapists, and secondly that it is thoroughly tested against more conventional CBT in multiple rigorous clinical trials.

Apart from currently leading this large multi-center study as Principal Investigator, Dr. Lackner also finds time to pursue other research interests, which include identifying psychological and social aspects that contribute to IBS, and research in conjunction with UCLA on what happens in the brain as a result of cognitive behavioral therapy. He is furthermore the Director of the Behavioral Medicine Clinic at the University of Buffalo School of Medicine, which provides treatment for individuals with a range of chronic health problems, and he personally provides clinical treatment there with CBT two days a week.

In his early college years, Dr. Lackner aimed for a law career, and he worked as a clerk for a Supreme Court justice. Over time, he became more interested in psychology and pursued that interest to obtain his Masters in Psychology at the College of William and
Mary and a Diploma in Social Psychology from the London School of Economics, followed by a Doctorate in Clinical Psychology at Rutgers University. His interest in clinical research began at Rutgers, where he had an opportunity of focus on the clinical science of psychology, clinical trials and outcome research on psychological treatments. As he studied the ins and outs of clinical trials, Dr. Lackner gained a deep appreciation for research methodology and formal testing of specific treatments as a more reliable and efficient way to develop effective treatment protocols. In a short time, he noticed differences in patient outcomes between unguided clinical practice and formal clinical trials in behavioral interventions. The clinical trials, he noted, where therapists followed carefully constructed treatment protocols, tended to have more consistent positive outcomes. He therefore determined to base his own clinical practice approach firmly on research evidence. He investigated different psychological treatment protocols tested in research, and requested treatment manuals from different investigators to develop a resource library to use in his clinical practice. In doing this, he happened to correspond with Edward Blanchard, PhD, a pioneer and prominent researcher of psychological treatment for IBS, who had developed a structured CBT treatment approach for IBS. Blanchard asked Dr. Lackner to participate as an investigator in a multi-site research study testing the effect of CBT in IBS patients. That project was the catalyst to launch Dr. Lackner's work in IBS and other functional gastrointestinal disorders, and these problems have been his main focus ever since, even though he continues to have an active interest in other chronic medical disorders as well.

Dr. Lackner is a prolific writer. He has authored about 50 published scientific papers, in addition to numerous research abstracts and book chapters in edited books. He is also the author of the 2007 self-help book “Controlling IBS the Non-Drug Way”, which received the ABCT Meritorious Book Award in 2011. He is an active speaker and educator, regularly teaching on CBT, behavioral medicine and gastrointestinal disorders for students, residents, fellows and faculty at his University, as well engaging in hands-on training of psychological treatment. He also presents his research regularly to professional and patient audiences at meetings nationwide. Our Center is honored to have Dr. Lackner as a participant in our educational efforts to provide the best information on functional GI disorders. In June 2012 he presented on CBT for IBS at our Patient Symposium in Chapel Hill. A video recording of his presentation can be viewed online at http://www.fgidpatientupdate.com/presentations/video6.html. He will again be visiting our Center and teaching in our symposium for health professionals “How to Treat IBS Effectively” on November 2nd, where he will be speaking on CBT as well.

References:


Dr. Lackner speaking at UNC Center for Functional GI and Motility Disorders Patient Day in June 2012 on the use of Cognitive Behavioral Therapy (CBT) in IBS.
The UNC Center for Functional GI and Motility Disorders will be presenting research findings on November 1, 2013 at the Rizzo Center, located at 150 DuBose House Lane in the MeadowMonte campus of Chapel Hill.

Research Day is free and open to students, employees, faculty, and the general public to attend. Investigators will be presenting on their research from the past 12 months and will be speaking about topics ranging from accidental bowel leakage, Internet facilitated Medical Research and Patient Care, and Diagnosis and Management of functional gastrointestinal disorders (FGIDs). There will also be panel discussions after each section to speak with the investigators about topics related to their research.

Information about registration can be located on our website, http://www.med.unc.edu/ibs/news/ibs-cme. In order to receive a lunch, you must register for the program. No CME credits will be awarded during the Research Day presentations.
This Continuing Medical Education event brings together the world’s leading experts in the field of medicine and psychology to speak about current medical and psychological practices for the management of Irritable Bowel Syndrome. Multiple topics will be discussed including: etiology of IBS, Pharmacologic treatment options, Probiotics, Antibiotics, and Diet, Effective psychological interventions, and the Rome Criteria in Clinical Practice. Participation for this event will be available in two formats; (1) in-person and (2) a live streaming video webinar. In-person participation is limited to 60 slots so space is limited. Webinar participants will be able to submit questions online and have them addressed during the discussion panels at the end of each session. Information on registration and credits awarded can be found at http://www.med.unc.edu/ibs/news/ibs-cme

The symposium will also benefit psychologists by describing cognitive behavior therapy, hypnosis, and complementary medicine techniques that have proven effectiveness in IBS. Psychologists will also learn how to collaborate with gastroenterologists in the management of these patients.

**Program Agenda**

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### Energy Metabolism in Pediatric Chronic Abdominal Pain

This study is looking at the way cells handle energy and how they play a role in children who have chronic stomachaches. We are studying both patients and healthy controls.

Parents of children between the ages of 4 - 18 with and without chronic stomachaches will be asked to complete a phone interview about their family’s health history. Participation involves one phone interview and no visits to UNC.

We are looking for mothers of children who either:
- Have been diagnosed, by a physician, with chronic abdominal pain (This includes functional abdominal pain, recurrent abdominal pain, or irritable bowel syndrome) OR
- Control subjects who have never been diagnosed with chronic abdominal pain.

**Principal Investigator:**
Dr. Miranda van Tilburg

**Contact Information:**
Dr. Miranda van Tilburg
919-843-0688
abdominalpainstudy@unc.edu

**More information:**
abdominalpainstudy.doodlekit.com

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### Parents of Children who suffer from frequent stomachaches needed for a Research Study

Would you like to learn new ways to manage your child’s stomachaches?

Researchers at UNC are conducting a research study evaluating different methods for parents to manage their child’s stomachaches.

You may be eligible if:
- Your child is between the ages of 7 - 12.
- Your child has frequent stomachaches.

**Participation**
- 3 - 30 minute training sessions
- Parents and children complete 5 surveys over the course of 1 year
- Parents receive $150 and children receive $25.

**Principal Investigator**
Dr. Miranda van Tilburg

**Contact Information**
Dr. Miranda van Tilburg
919-843-0688
tilburg@med.unc.edu
**Recruiting adult women with diarrhea predominant irritable bowel syndrome for a research study**

We are looking for adult women with a specific type of irritable bowel syndrome (IBS) to join a research study assessing a potential new medication for IBS.

The RESTORE 5 Study will last for up to 8 weeks and involve about 5 clinic visits.

You may be able to take part in the RESTORE 5 Study if you:
- Are a woman 18 - 65 years of age
- Have had symptoms of IBS (including abdominal pain/discomfort and diarrhea) for at least 6 months
- Have loose or watery stools > 25% of the time and hard or lumpy stools < 25% of the time.

To participate in this trial, you must NOT:
- Have been diagnosed with:
  - Crohn’s Disease
  - Ulcerative Colitis
  - Diabetes mellitus
  - Lactose Malabsorption
  - Malabsorption syndromes
  - Celiac Sprue
- Be pregnant or planning to become pregnant.

Qualified participants will receive study-related care including comprehensive physical exam and investigational study drug at no cost. Monetary compensation for study visits will be provided.

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**Men and Women Needed for Anal Fissure Research Study**

Has your physician diagnosed you with an anal fissure? The UNC Center for Functional GI and Motility Disorders is conducting a research study to evaluate an investigational drug (diltiazem).

Eligibility: To be eligible, you must be over the age of 18 and less than or equal to 75 years old, and diagnosed with an anal fissure. You must be able to complete a daily phone diary for the entire study about overall anal fissure related pain.

Participation includes:
- Documenting anal fissure pain daily
- Documenting bowel movements and symptoms
- Giving blood samples
- Completing a no-cost physical exam
- Completing 5 visits during the 5-week study
- Self - administering study medication three times a day

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**Principal Investigator**
Lisa Gangarosa, MD

**Research Coordinator**
Angela Kibi, RN, MPH
919-537-3841
angela_kibi@med.unc.edu

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**Contact Information**
Renuka Kelapure
919-843-7892
renuka_kelapure@med.unc.edu
The UNC Center for Functional GI and Motility Disorders is currently conducting a Phase III drug trial to investigate the long-term efficacy of Rifaximin for the treatment of IBS-D symptoms.

Rifaximin is a non-absorbed antibiotic currently approved by the FDA for the treatment of Traveler’s Diarrhea and Hepatic Encephalopathy. Previous studies have shown significant improvement of symptoms with Rifaximin treatment in subjects with IBS-D.

Eligibility requirements:
• At least 18 years of age
• Diagnosed with IBS-D or have experienced the symptoms (abdominal pain, bloating, and diarrhea) at least 3 days per month over the last 3 months.
• No history of inflammatory bowel disorders
• Colonoscopy with biopsy within the last 10 years or willing to have one for the study

Eligible participants will be asked to complete up to 9 visits during which vital measurements will be taken along with blood, urine, and stool samples. In addition, participants will be asked to keep a daily log of their symptoms over the course of the study.

Primary Investigator: Yehuda Ringel, MD
Contact Information
Daniel Temas
919-843-1003
daniel_temas@med.unc.edu

Expert Update on Treatments for Functional GI Disorders (FGID’s): A Symposium for Patients. Listen and watch videos from prominent experts in the field of functional GI disorders with the latest information on available treatments

HTTP://FGIDPATIENTUPDATE.COM/
How to Treat IBS Effectively: Expert Update for Health Professionals

A Continuing Medical Education (CME) Event
November 2, 2013

Participate in-Person at the Rizzo Center in Chapel Hill, NC or via Webinar

TOPICS ADDRESSED DURING THE SYMPOSIUM

- Pathophysiology of IBS
  
  Dr. Bill Whitehead

- Importance of the Doctor-Patient Relationship
  
  Dr. Doug Drossman

- Pharmacologic Treatment Options
  
  Drs. Bill Chey & Lin Chang

- Probiotics, Antibiotics, & Diet
  
  Drs. Magnus Simren & Sheila Crowe

- Effective Psychological Interventions
  
  Drs. Jeff Lackner, Laurie Keefer & Olafur Palsson

- The Rome Criteria in Clinical Practice
  
  Drs. Doug Drossman, Bill Whitehead & Lin Chang

Check-In Online and on-site begins at 7:30am. Breakfast is included on-site. Program will conclude at 5:45pm.

Registration Fees/Target Audience:

- Physicians (MD, DO): $100
- Psychologists: $75
- Mid-Level Providers (NP, PA, RN)
  
  Interns, Residents: $50

7.75 AMA PRA Category 1 Credit(s)™
7.75 Contact Hours (Category A) for NC Psychologists
0.78 CEU for Other Health Care Professionals

The Carolinas HealthCare System/Charlotte AHEC designates this Live Activity for a maximum of 7.75 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

For more information about registration and participation in-person and online, visit our website at

http://www.med.unc.edu/ibs/professional-training/ibs2013

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Carolinas HealthCare System/Charlotte AHEC and The University of North Carolina at Chapel Hill Center for Functional GI and Motility Disorders. The Carolinas HealthCare System/Charlotte AHEC is accredited by the ACCME to provide continuing medical education for physicians.
Irritable bowel syndrome (IBS) is characterized by altered bowel habits—constipation or diarrhea—along with abdominal pain, and bloating. The cause of these symptoms is unknown, lacking clear observable abnormalities. New research suggests that these symptoms could be the result of multiple interacting environmental, genetic, biological, and psychosocial factors that interact with the brain-gut axis: a network of nervous system communication between the brain and the digestive system. The bacteria in the intestines—both native and pathogenic—and abnormal immune function have been implicated as potential contributing factors to IBS symptoms. Studies have shown various ways in which these systems may be functioning abnormally in patients with IBS and how they may interact with each other and with the brain-gut axis to collectively serve as the underlying cause of IBS.

The large intestine is host to a variety of naturally occurring bacteria that play an integral role in the normal function in the GI tract including digestion, metabolism, and immune function. Alterations in the growth and/or composition of these bacteria can affect the health of the GI system and may play a role in the development of IBS symptoms. IBS symptoms that arise following infectious gastroenteritis, called post-infectious IBS (PI-IBS), and the association of IBS with small intestinal bacterial overgrowth (SIBO) highlight how changes in the intestinal bacteria are associated with IBS symptoms. These observations are strengthened by the efficacy of antibiotic and probiotic treatments for IBS symptoms. Emerging studies have also shown overall differences in the composition of the intestinal bacteria between IBS and healthy patients. Altered bacterial composition could contribute to bloating symptoms through excess carbohydrate fermentation or changes in the health and functioning of the intestinal lining. In the broader examination of the immune and nervous system aspects of IBS symptoms, it is unclear whether the abnormal composition of the intestinal bacteria is a cause or a consequence of IBS. It is also unclear whether abnormal reaction to the native bacteria or colonization of foreign bacteria contributes more significantly.

Immune function in the gut is comprised of the inner lining of the intestine, which controls what is absorbed into the system along with the immune cells that are found throughout the body. The role of the immune system in IBS, specifically the role of low-grade inflammation in the lining of the intestine is an area of study that has recently garnered attention. Some studies have shown increased concentrations of inflammatory markers as well as immune cells in IBS patients compared to healthy controls. Some evidence suggests that the immune system in patients with IBS reacts differently to foods and stimuli compared to healthy controls, which could contribute to their symptoms. Certain foods may interact with immune cells in the intestines of patients with IBS, incorrectly identifying the food as infectious agents, causing the immune system to respond with inflammation and changes in intestinal functioning. Evidence of this can be seen in the symptom improvement of IBS patients on diets that eliminate foods that activate certain antibodies. This evidence suggests that the immune response plays a significant role in the development of IBS symptoms and treatments that target these immune responses may significantly improve symptoms.

The interaction between intestinal bacteria and the immune system affects the health and functioning of the intestinal barrier. The lining of the intestine is responsible for combating infectious agents in the intestines. The native gut bacteria play an important role in the health and maintenance of this barrier by regulating the permeability of the barrier, which may allow for increased likelihood of colonization by pathogens. Furthermore, changes in bacterial functioning could impair the functioning of the barrier, allowing more foreign agents to pass the barrier, instigating an immune response. Inflammation in the intestinal lining has also been implicated as a possible cause for the increased permeability observed in IBS patients, which would increase the likelihood of infections in the intestines of IBS patients. This interaction between bacteria and the immune system could be a possible explanation for the development of IBS symptoms, especially following enteric infections such as infectious gastroenteritis.

Intestinal functioning is mediated by a complex network of nerves located in the gut—the enteric nervous system (ENS)—and the brain—the central
nervous system (CNS). The two-way relationship between the ENS and CNS appears to play a role in IBS symptoms. The ENS, which controls intestinal motor function and sensation in the intestines, responds to food, bacteria, metabolites, and toxins with changes in intestinal contractions and activation of the intestinal immune system. These changes can increase IBS patients’ sensitivity to intestinal functioning and alter intestinal transit. At the CNS level, stress—both physical and psychological—have been shown to affect patients’ perception of and may potentially worsen GI symptoms. This is evidenced by the improvement in GI symptoms and intestinal sensitivity following treatment with antidepressants or psychological interventions.

Changes to the ENS have been observed in relation to the altered immune function seen in IBS patients. It is known that intestinal inflammation can cause changes in the anatomy of the ENS and can increase production of proteins involved with intestinal motility and sensation. Additionally, some immune markers have been shown to interact with ENS directly and can affect its functioning through changes in hormone secretion. This suggests that the immune response may play a role in the altered intestinal transit, increased sensitivity to intestinal activity, and abdominal pain seen in IBS patients.

Intestinal bacteria have been shown to interact with the brain-gut axis in a number of ways. Enteric bacteria can affect the ENS by changing contractility and sensation in the intestines in IBS patients and by instigating the release of immune cells. Furthermore, altered functioning of the intestinal bacteria could be responsible for changes in bile acid absorption, which can stimulate motility and secretion. The intestinal bacteria interacts with the CNS through immune, hormonal, and neural mechanisms and alterations in the bacteria may lead to long term increases in anxiety, which in turn can worsen the symptoms of IBS. Various stressors on the CNS have been shown to alter the composition of the intestinal bacteria and overall functioning of the brain-gut axis, including immune response and intestinal sensation. The interaction between the intestinal bacteria and the brain-gut axis appears to be a two-way interaction, with each factor potentially exacerbating disease outcomes in the others, to contribute to the overall disease condition observed in IBS patients.

Underlying genetic factors appear to play a role in the abnormal functioning across all of these systems, which highlights a potential predisposition for the development of IBS. Genetic factors have been implicated in the altered immune response in IBS patients, notably the immune response associated with food hypersensitivity and the development of post-infectious IBS. Bacterial functioning also plays a role in genetics and been shown to affect gene expression in the ENS in a way that promotes faster transit.

IBS has generally been characterized as a set of symptoms lacking a definable cause, but recent studies point to observable changes in body systems, which could indicate possible underlying mechanisms for the symptoms. The mounting evidence for the role of genetic predispositions combined with interactions between interconnected systems—the intestinal bacteria, the immune system, and the central and enteric nervous systems—involved with IBS symptoms suggests that treatments and/or combinations of treatments that target these systems may be effective in managing the symptoms of IBS.

Article information derived from:
"The Intestinal Microbiota and Immune Function in the Pathogenesis of Irritable Bowel Syndrome.
Authors: Yehuda Ringel[1] and Nitsan Maharshak[2]
1. Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC
2. Department of Gastroenterology and Liver Diseases, Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
Published in the American Journal of Gastroenterology and Liver Physiology July 25, 2013

http://med.unc.edu/ibs
On August 19 and 20 of this year (2013) I attended a symposium on fecal incontinence (FI) on the National Institutes of Health (NIH) Campus in Bethesda. This event was titled “Developing a Research Agenda for Fecal Incontinence” and was sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, which is one part of NIH. The symposium brought together many of the key experts in the U.S. involved in fecal incontinence research, with the goal of taking stock of where research on this problem currently stands and how scientists should focus their investigations into FI in the future. One of the co-directors of this meeting was our Center’s director, Dr. William Whitehead. Between the presenters and the audience members, there were about a hundred people at this gathering. The program was an information-packed day-and-a-half long series of talks and panel discussions. Most of it was devoted to an incredibly thorough status update of the knowledge and clinical research findings in this area, but toward the end, future research priorities were addressed. It is impossible for me to describe (or remember!) all that was presented and discussed in this symposium. However, I will describe my personal impressions here of this event and summarize key information, conclusions and recommendations from the various presentations that might be of interest to individuals who suffer from FI, or for those who are interested in knowing what the present state of scientific knowledge is about this problem.

Dr. Alayne Markland, a geriatrician from the University of Alabama at Birmingham, gave an overview of the epidemiology and prevalence on FI. She described how several different definitions of FI have been used by researchers (for example, specifying different minimum frequency or amount of bowel contents lost to to qualify as FI, including or excluding passing gas, etc.), and consequently, the estimates of how prevalent FI is have varied widely. However, the bigger and better studies that have been published in recent years have tended to use loss of liquid or solid stool at least once a month as the definition of FI. This has settled the best estimates of the general prevalence of the problem into a range between about 7 to 15 percent of the adult population, with the highest prevalence seen in elderly individuals. Dr. Markland reported that various factors have been identified that put individuals at higher risk for FI. Beside aging, these include physical injury to the rectal area (in women especially damage to the sphincter muscles from giving birth, whereas in men it is commonly the effect of radiation or surgical damage from prostate cancer treatment), various diseases and physical problems like diabetes and obesity and reduced physical mobility, and diarrhea. Identifying these risk factors can help health professionals know which patients to screen for FI.

Dr. Catherine Matthews from our UNC OB-GYN department provided a review of the costs associated with FI. She reported that 3 studies (2 U.S. studies and one in the Netherlands) have all put the added costs of FI in a range of about 3-4000 dollars per year. She also cited a study by Mellgren and colleagues which looked at the lifetime costs of FI in women whose incontinence was caused by obstetric injury, and found these to be $31,071 (in 2012 dollars) over the women’s lifetime on average. Such cost estimates provide a context for evaluating the cost-effectiveness of treatments for FI. Even though costs and savings are obviously not the only considerations about whether treatments for FI are worthwhile – the degree of life improvement achieved for patients is also key, for example -- it is still important to know whether the interventions make sense in financial terms. Surgeries are the most expensive type of treatment for FI. They are only done on a tiny fraction of FI sufferers: I was surprised to learn from Dr. Matthew’s talk that only about 3,500 patients per year get surgery for FI – a number that has stayed pretty stable for many years. This infrequent use of surgery is undoubtedly in no small part due the fact that the costs of such operations are huge. The surgery and hospital costs average about $100,000 per patient, which is certainly not a cost-effective option as a general treatment for FI. New and less expensive surgical options are emerging, though, such as sacral nerve stimulation (which I will describe below) that is estimated to cost $29,000 over 5 years. Compared to surgical options in general, conservative treatment (such as pelvic floor exercises, biofeedback and fiber adjustments) are far less expensive options that can also help many patients, costing an average of $4,250 per patients. Dr. Matthews concluded that much
more research work is needed on cost-effectiveness of different treatment options for FI.

Dr. Barucha from the Mayo Clinic detailed the causes of FI, which can be divided into changes in sensation (often due to nerve injury or disease), changes in muscle functioning (due to muscle weakness or muscle injury or tear), or stool consistency (typically diarrhea, but sometimes constipation), or a combination of these causes. He explained that failure to clearly identify and classify the causes of individual cases of FI likely hampers overall rate of treatment success for this problem, as different classes of FI likely respond to different treatment. He emphasized that better diagnostic methods are needed to identify the specific muscle and nerve damage that often causes this problem, and that a clear classification system for different types of FI is desirable to improve treatment. He then proposed a classification system that he and his colleagues have been developing that classifies FI by combining (a) type of FI (that is, the way it expresses itself – whether it is associated with sudden urge to defecate, or without any warning sensation, or a combination of both), (b) the cause, and (c) the severity. Finally, he stressed that formal research needs to be done to test whether offering targeted treatment based on such classification can improve outcomes.

Dr. Rebecca Rogers from the University of New Mexico gave a review of outcome measures of fecal incontinences. As several other speakers noted throughout this symposium, the lack of a commonly used definition of FI has been a major shortcoming in this field of research. This is also reflected in the fact that FI has been measured in different ways by different researchers. Dr. Rogers pointed out that there are over forty different questionnaires or rating scales to measure FI, but most of them have not been validated (meaning that they have not been tested sufficiently to know if they really measure the phenomenon of FI well or reliably), and in fact only a few have been used extensively in research. The most commonly used questionnaires used in research so far, according to Dr. Rogers, are the Wexner scale, the Fecal Incontinence Severity Scale, and the St. Marks Score. Quality of life impact questionnaires have also been developed specifically for FI and used in conjunction with these FI severity questionnaires to evaluate the effects of the problem on patient’s lives.

A couple of presentations focused on FI in particular populations. Dr. Emily Lukacz, a urogynecologist from the University of California in San Diego summarized the research on FI in women that results from childbirth. Childbirth is one of the clearest risk factors for FI; as many as 1 in every 4 women experience some FI after bearing a child. Damage to the anal sphincters during pregnancy or birth is commonly the cause, but the factors that lead to this damage are somewhat unclear. For example, it is not certain that vaginal birth poses any more risk of FI than a cesarean birth. However, episiotomy (a surgical cut in the back of the vagina to prevent tearing of the vagina during during the birth, which used to be fairly routinely done in the U.S. as a part of delivery but is now much less common) and use of forceps to deliver the child both clearly increase risk of FI. The use of episiotomy and forceps delivery have decreased in the past decade, and there appears to have been a corresponding drop in delivery-related FI.

Dr. Patricia Goode, a geriatrician from the University of Alabama in Birmingham, presented on FI in aging individuals. The elderly have higher prevalence of FI than younger age groups, but the risk for elderly person of developing this problem varies greatly according to health and functional status. FI prevalence is 15 percent in the elderly populations living in the community, 18-33 percent among those who are in an acute care hospital, 38 percent in elderly people receiving home healthcare, and 50-70 percent in nursing homes. A whole range of risk factors contribute to FI being so much more common in the elderly. Physical aging in and of itself poses increased risk of unwanted loss of bowel contents because anal sphincter muscles weaken (just like muscles everywhere in the body), and the wall of the bowel also becomes less elastic so the rectum is less able to expand to hold fecal material. The constipation that plagues many older individuals furthermore increases risk for
FI, as do impaired mobility and cognitive impairment -- factors that make people unable to respond properly to warnings of need to defecate. On top of this, various medical problems become more common in the elderly that affect either the anal muscles themselves or impair anal muscle control or sensation, such as problems related to diabetes, stroke, cancer, or Parkinson's disease. Finally, medical treatments such as pelvic radiation or anorectal or pelvic surgeries can also cause fecal incontinence as a side effect.

Dr. Gena Dunivan from the University of New Mexico summarized research on barriers that keep patients and doctors from addressing FI. She reported that studies show that only 8-34% of individuals with FI seek care from doctors for the problem even though it can affect their lives profoundly. This is due among other things to embarrassment about talking about the problem (a common social taboo), the belief that FI is merely a normal a part of aging rather than a health problem, and lack of motivation to seek care due to a belief that effective treatments are not available or that the doctors will not be helpful in treating the problem. Dr. Dunivan added that research indicates that patients are more likely to seek care if they feel that symptoms related to their FI may be dangerous, such as pain; if their FI is solid stool; if they have a primary care doctor; and if they are aware of effective treatments. Doctors rarely ask their patients about FI or diagnose it: Amazingly, a couple of studies that compared self-reported FI of patients visiting healthcare clinics to medical diagnoses in HMO and outpatient GI settings found that only 2-3 percent of all patients who admitted to having FI had a diagnosis of FI documented in their medical record. Dr. Dunivan stated that the prevalent failure by doctors to screen for FI may be due to poor awareness of how common and burdensome it is. She suggested that providers might also feel uncomfortable with management of FI and may in fact, like patients, sometimes be unaware of effective treatment options. A series of three presentations by GI surgeons reviewed surgical treatments and medical devices used for FI treatment. The presenters were Dr. Ann Lowry from St. Paul, MN, Dr. Deborah Nagle from Beth Israel Deaconess Medical Center in Boston and Dr. Madhulika Varma from the University of California in San Francisco. These surgeon explained how older surgical methods for addressing FI typically put in an artificial sphincter or created a new sphincter using a thigh muscle (so-called graciloplasty) but that these methods had high rate of complications -- in some cases as high as 80%. However, surgery to repair anal muscle tears resulting from childbirth has been fairly successful, with an average of 66% having good outcome at least short-term. Newer surgical methods for FI more commonly favor a less invasive and aggressive approach, such as increasing the bulk of the sphincter or implanting a nerve stimulation devices or a sling of mesh fabric that provides support to help keep the sphincter closed. Two of these methods involve devices have been approved for use in the U.S. by the FDA: These are sacral nerve stimulation, which involves implanting an electronic device into the patient's body, under the skin, which sends electric pulses that stimulate nerves that help maintain continence. It has shown good or acceptable outcomes in 42% of patients, with 18-63% gaining full continence long-term Surprisingly, even though the FDA has approved the use of this method in the U.S. it is still poorly understood how or why it helps improve FI. The other FDA-approved treatment is Solesta™, a gel that can be injected with a needle directly into the anal sphincter to create a ring of gel beads that bulk up the sphincter to help it stay closed better. Research indicates that Solesta reduces fecal incontinence episodes by 44% (from an average of 15 to 8.6 per two weeks) and this reduction in FI frequency lasts beyond one year. Solesta has the clear advantages of being a simple, relatively inexpensive and benign method of treatment, which can be administered in an outpatient visit to a doctor's office. However, the degree of improvement it provides is likely to be insufficient for a lot of patients with FI, and I suspect that it will end up being more useful as an addition to whatever other treatments the patients receive for their incontinence.

Dr. Satish Rao from the Medical College of Georgia reviewed the current state of knowledge regarding drug and behavioral treatments for FI. He reported that anti-diarrheal medications like loperamide and lomotil are commonly used to treat FI, and these as well as fiber have been shown in controlled trials to be effective. Research trials using simple treatments such as pelvic floor exercises and adjustment in fiber intake can benefit about half of FI patients in some studies, as does anorectal biofeedback (a method where sensors are used to measure the moment-to-moment changes in anal muscle activity and show patients this activity on a computer screen so that they can learn to control the muscle activity). Some biofeedback trials, such as a large study done by our UNC research team, have shown even higher success rate -- 77% in the case of our team's trial.

One of the most exciting future advancements in FI treatment was described in a presentation by Dr. Khalil Bitar from the Wake Forest Wake Forest Institute for Regenerative Medicine in Winston Salem, North Carolina. Dr. Bitar and his colleagues have been able to use muscle and nerve cells and grow a living anal sphincter in the laboratory which they can then graft in place and use to replace a damaged anal sphincter. They have successfully implanted such lab-grown sphincters in animals (mice, rats and rabbits).
and demonstrated that the muscles and nerve cells of these sphincters do their job and make the sphincters function. Human tests of this medical engineering solution to fecal incontinence are likely to be conducted within the next few years, according to Dr. Bitar. Based on the success so far, it seems likely that in near future, doctors will be able to order a custom-made (and custom-size) replacement anus grown in a laboratory for individuals with FI due to severely damaged sphincters.

A very thought-provoking complement to all the research based presentations at the symposium was a deeply personal life story about the devastating effects of FI related by Louise Mott from Canada. She is a former nurse and midwife who sustained extensive damage to her pelvic floor muscles giving birth to her first child. She described how the uncontrollable and unpredictable stool incontinence that followed her birth injury crippled her life. She felt compelled due to shame to keep the problem a secret for a long time even from her husband and other people closest to her, and it plunged her in to deep depression, isolated her and made her unable to engage in her normal activities outside the home or in her intimate relationship with her husband. Her first efforts to consult a doctor about the problem was discouraging and gained her no help, making her feel even worse about the FI problem. After several years of leading life as a reclusive, she was finally able to get good medical care that led to some improvement, and she was gradually able to use her professional background to become an advocate for women going through similar situations and gain self-esteem and emotional recovery. It was obvious to me from looking around the room as she spoke, that Ms. Mott's account struck a cord with the researchers and reminded them vividly of the huge importance of the research effort that they had come together to talk about for the wellbeing of countless thousands of real people who suffer every day due to FI.

Toward the end of the symposium, our Center Director Dr. Whitehead presented recommendations for design of FI treatment studies and future priorities of this research area. He stated that the four research topics that are most likely to advance the treatment of fecal incontinence in coming years are: (1) to identify the reasons why FI sufferers do not consult doctors and why doctors do not ask their patients about FI, and how to overcome these barriers; (2) to compare different treatments directly against each other in side-by-side tests in terms of effectiveness, cost, and safety; (3) to develop and study novel FI treatment approaches; and (4) to improve the measurement of FI severity and make such measures uniform across researchers. These priorities were right on target with the thinking and unresolved issues that had been presented in the various topic summaries by other presenters throughout the symposium, and were also supported by the results Dr. Whitehead presented from an opinion survey of 40 different published FI researchers that he had conducted via e-mail just before the symposium.

It was heartening to see NIH making such an important effort to help move FI research forward by bringing together all of these leading researchers, and also to see so many key experts heed the call and put their heads together about the current state of this research domain and future directions for two days. Although it was clear from the meeting, as acknowledge by multiple researchers, that FI is barely out of infancy as a clinical research topic, the symposium illustrated that there are multiple growth buds about to bloom in this research domain, which promise much progress in the coming years. New and better treatment options are emerging, and comparative effectiveness studies of different treatment are now a high priority and will enhance understanding of what works best overall to help FI sufferers of various types. The uniform recognition of an urgent need for common standards for diagnosis (of FI overall as well as subtypes of it with different causes) and measurement of FI will almost certainly lead to better research studies and help clinical treatment as well. And finally, the rapidly emerging picture of what the specific barriers are that keep patients and health providers from addressing FI effectively will hopefully lead to practical solutions that enable many more FI sufferers to get the treatment they need. There are already rumors after the symposium that NIH may provide some new funding opportunities attached to requests for specific studies to broaden these important avenues of progress in FI research.
Predicting the future is risky. Therefore this is of necessity a personal view that is based on two principles: The first is that new instruments or methodologies for collecting data often lead to an explosion of new knowledge. An historical example is the invention of the microscope and the telescope. The methodological innovations that I think are most likely to impact IBS research are (1) high through-put bioassays, (2) bioinformatics advances that make it possible to track specimens and manage large databases, and (3) the maturation of the internet making instantaneous world-wide communication at virtually no cost a reality. These innovations have made it possible to collect large banks of biological specimens through research networks and to carry out analyses of the whole human genetic code (GWAS), and studies to identify all the proteins in samples of blood, urine, or feces instead of testing only for what the scientist predicts will be present. They have also made it possible to do global, cross-cultural surveys. The second principle I have drawn on to predict future trends is that scientists build on past successes by continuing to explore concepts and questions that have already paid off. The five specific research topics I believe are likely to produce new insights into pathophysiology and new approaches to treatment of IBS are listed below. I will illustrate each topic with sample data.

Cross-cultural research. The revolution in communication that resulted from the internet and the tendency for young scientists to move around the world for training both provide a foundation for increasingly sophisticated cross-cultural studies. These studies provide an opportunity to distinguish what is universally true about IBS from what is a product of culture and environment. What I mean by environment includes differences in diet, pathogen exposure, and health-care practices. The Rome Foundation is making a major commitment to global research by (1) organizing an international network of investigators, (2) translating the Rome Diagnostic Questionnaire into 30 languages, and (3) organizing global studies of IBS epidemiology and diagnostic standards. An example of a cross-cultural study is the comparison of IBS diagnosis and management in Japan and the U.S. which is being carried out between Motoyori Kanazawa and Shin Fukudo at Tohoku University and investigators at the University of North Carolina. This study shows that males are more likely to seek treatment in Japan while it is females who seek care in the U.S.. Additionally, the study shows that IBS is treated more aggressively in Japan and that motility agents are a mainstay of treatment in Japan but are unknown in the U.S.

Symptom diaries. This is a method for very accurately studying day-to-day variation in symptoms, which has great potential for clinical management and drug testing. This has already produced important new insights: For example ¾ of IBS patients fluctuate between loose/watery stools (diarrhea) and hard/lumpy stools (constipation), and the symptoms of diarrhea, constipation, and pain occur in episodes of 2-4 days duration. Patterns of episodes that emerge from this work indicate that patients can follow simple rules to identify the beginning and termination of symptom episodes so they would know reliably when to start and stop taking medications on a prn basis. This method lends itself to prn dosing studies and to the assessment of environmental triggers for symptoms in individual patients.

Biomarker studies in large cohorts. The development of high through-put bioassays and bioinformatics techniques has made it possible to do types of studies that were not previously possible – whole genome genotyping and characterization of types and numbers of bacterial species in the gut, for example. However, these techniques come with special challenges: Genetic studies of the whole human genetic code require at least 2000 well-characterized subjects per group, and protein identification studies require about
500 subjects per group. Collecting these samples requires highly structured research networks, lots of money, and new ways of communicating between investigators. The most successful networks to date have been organized by the National Institutes of Health and directed by strong project leaders. One example of such a research network is the OPPERA Study led by Bill Maixner at the University of North Carolina. This is a study of the genetic and biological predictors of temporo-mandibular joint disorder (TMJD). The network consists of 4 institutions plus a commercial data manager and a central repository for biospecimens. It has formal rules governing study management decisions, paper priorities, and authorship. Even so, the project cost $19 million and took 7 years to publish the first papers. Another example is our study of the psychophysiology of IBS. This was a single site study but took 10 years to collect sufficient cases for key analyses.

Symbiotic relationship between microbes, food, and mucosal immunology. The idea that IBS might be due to infectious agents, similar to H. pylori in peptic ulcer disease, has been around for 15 years, supported by numerous studies documenting the development of chronic IBS-type bowel symptoms after gastroenteritis, but only recently has it become possible to identify specific strains of bacteria in the gut. At about the same time, new information was emerging on food sensitivity and on the role of intestinal permeability in the immune response to bacterial pathogens (the so called “leaky gut”). This confluence led to the hypothesis articulated by Magnus Simren that there is a symbiotic relationship between the human host and intestinal micro-organisms that involves alterations in intestinal permeability, the immune system, and food sensitivity.

CNS mechanisms responsible for comorbidity. The tendency for IBS patients to have multiple other health problems is well known but poorly understood. This is an important phenomenon because the number of comorbid conditions is the single best predictor of symptom severity, quality of life impact, treatment responsiveness, and health care costs. One hypothesis about comorbidity is that it reflects shared pathophysiological mechanisms, and by studying patterns of comorbidity it might be possible to learn more about these pathophysiological mechanisms. We investigated this concept in a study of 7000 HMO patients and learned that there are no diagnoses that are uniquely associated with IBS; rather the same disorders that occur most frequently in the general population are the ones most likely to occur in IBS. However, IBS patients are about 60% more likely to have these diagnoses in their medical record than is the average person. We also found that IBS patients are more likely to be diagnosed with infections and broken bones – diagnoses that have a clear biological marker for diagnosis – as well as disorders with softer diagnostic criteria such as fibromyalgia. We concluded that comorbidity in IBS is likely influenced by cognitive and psychological traits which are amenable to treatments such as cognitive behavior therapy. We believe further investigations into the CNS mechanisms responsible for comorbidity – perhaps involving fMRI studies, selective attention paradigms, and hypnosis – would be a fruitful area for future research.

In this brief overview, I have tried to show that there have been some exciting new developments in understanding how food and intestinal bacteria contribute to the development of IBS and the beginnings of a global science of IBS. There are also new technological developments -- computerized biological testing, new mathematical models for making unanticipated discoveries without being constrained by theory, and the potential of the internet to provide instantaneous and global communication at low cost – which are creating new opportunities for research. Based on these developments we can expect the pace of scientific discovery and the development of new treatments to accelerate in the next few years.
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