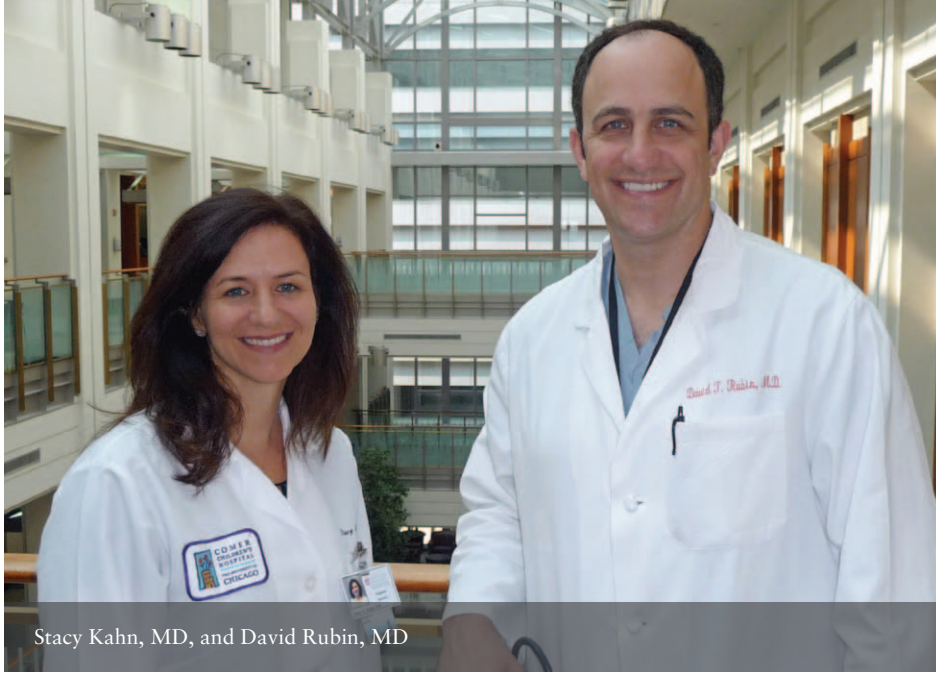


# A NEW HOPE

## A PROMISING THERAPY HELPS COMBAT DISEASE



Stacy Kahn, MD, and David Rubin, MD

**W**hen it comes to disease, we're accustomed to viewing bacteria as the enemy. But a promising therapy, under investigation by Assistant Professor of Pediatrics Stacy Kahn, MD, and Associate Professor of Medicine David Rubin, MD, appears to be standing this conventional wisdom on its head.

Ulcerative colitis is a form of inflammatory bowel disease (IBD) affecting the colon. It can inflict agonizing pain and discomfort on sufferers and raise their risk for cancer. The condition afflicts 700,000 Americans, and for one in four sufferers, the only relief is through radical surgery: removal of the entire large intestine.

Against this backdrop, a novel therapy administered to six ulcerative colitis patients by Australian doctor Thomas Borody achieved near-miraculous results: spontaneous, sustained remission in each one. The apparent magic bullet? Fecal matter, donated by healthy volunteers and implanted into the intestines of the patients.

### GOOD BACTERIA KEY TO IMPROVEMENT

The approach is an extension of the idea of probiotics, or “good” bacteria. The effectiveness of probiotics against ulcerative colitis remains unproven, but the thinking is that, appropriately prepared and screened, fecal matter offers a massive, concentrated infusion of healthy bacteria capable of quelling the rogue bacteria that have taken hold in the gut of people with ulcerative colitis.

The approach has been dubbed fecal bacteriotherapy, stool transplant, or most recently, fecal microbiota transplantation (FMT). In fact, it is nothing new; its use stretches back to 1958, largely as a last-gasp treatment for the potentially deadly hospital-borne infection *Clostridium difficile*. Last year, a before-and-after study at the University of Minnesota demonstrated FMT's success in restoring the disturbed microbial balance associated with *C. difficile*.

But despite such dramatic results, FMT has been administered only intermittently—the 2003 report of cases remains its only documented usage against ulcerative colitis—amid uncertainty about patient reception and lack of uniform, agreed-upon procedures.

### BROAD ROLLOUT OF THERAPY UNDERWAY

That may be about to change, however. Kahn and Rubin's studies could pave the way for broad rollout of the therapy, including ultimately, a bank of FMT

samples that could be tapped to help patients in the same way blood banks are used for transfusions.

Patients themselves would raise few objections, judging from the findings from the first phase of their research. Results from focus groups conducted with 15 adults with colitis and seven parents of children with the condition undergoing treatment at the Medical Center were published earlier this year in the journal *Inflammatory Bowel Diseases*.

“We found a surprising number of people who were eager for this treatment; in fact, they asked why we weren't doing it already,” says Kahn. “We're receiving one to two phone calls and emails a week requesting information on it.”

Patients quickly got past what they called the “yuck factor,” Kahn adds. “They perceived the treatment as more natural than chemicals, and understood conceptually that harnessing bacteria from someone with a healthy intestine has therapeutic potential in counteracting abnormal bacteria.”

The poll also pinpointed practical issues that must be resolved before FMT can be offered more widely.

“People had significant concerns about screening of donors and specimens,” says Kahn.

### MEDICAL CENTER PATIENTS PART OF CLINICAL TRIAL

It is issues like this that Kahn and Rubin are tackling in the next phase of their work, already underway: a clinical trial of FMT among a sample of Medical Center patients with ulcerative colitis that will seek to identify optimal ways to collect, test, store, and administer samples—with a view to establishing formal protocols other hospitals can emulate.

“There are lots of details,” explains Rubin. “Who's the right donor? How do you prepare samples so they can be transported without killing all the microbes? How often does someone need to be treated? Is it really safe to do this in an inflamed colon with impaired immune function? It is complicated.”

The effort epitomizes what Rubin and Kahn, both trained at the University's MacLean Center for Clinical Medical Ethics, call the “Chicago approach” to medical ethics.

“Rather than doing the innovation first and asking questions later, we're trained to ask questions beforehand about what makes this treatment appropriate, who should not do it, and other concerns,” says Rubin. To tease further apart these issues, Kahn and Rubin are now conducting follow-up patient surveys.

In fact, Kahn and Rubin's work represents the first attempt to wrestle with the social and ethical implications of a whole new therapeutic approach that researchers are interested in applying to multiple conditions. The agent would not necessarily be fecal matter in each case—it could be another probiotic, for instance—but the principle is the same: manipulating the microbes that live in our bodies.

This new front in combating disease is being opened up by research into the “human microbiome,” the collective term for the trillions of microbes that colonize our bodies. Instead of being incidental squatters, these microbes perform functions essential to our survival, such as harvesting energy from food or governing our

ability to fight infections. And when the delicate balance between them is upset by a few bad apples (pathogens, for instance), scientists are discovering a growing number of conditions to which this is linked, from asthma and obesity to diabetes and cancer.

The nascent field, in which the University of Chicago is a leading player, is being propelled by advances in genome sequencing capabilities that now enable scientists to piece together the genetic material within whole communities of microbes—a technique dubbed metagenomics.

As part of their studies, Kahn and Rubin are also hoping to delve into the precise mechanisms by which FMT works against ulcerative colitis.

“We don’t really understand if it is a disturbed immune state and genetic factors that predispose ulcerative colitis sufferers to disruption in their normal healthy bacterial population, or if it is the bacteria themselves that cause changes to the way the immune system adapts,” says Kahn.

“We hope to contribute some important information about the therapeutic potential and microbiological impact of this new therapy,” adds Rubin. “Most of the work to date has been descriptive studies of the microbiome; we’re hoping to take it from bench to bedside.”

For this part of their inquiry Kahn and Rubin will team up with Martin Boyer Professor of Medicine Eugene B. Chang, MD, harnessing Chang’s work with a specific type of mice, specially reared in germ-free conditions to offer a blank slate against which the effect of microbes may be evaluated.

“We’ve been performing FMT on mice for years and have seen dramatic results,” says Chang. “The mouse studies offered a proof of concept that made us think this might be feasible in humans.”

The project forms part of a broad-based research effort at the University to illuminate the role of the microbiome in health and disease. The University is the

site of the largest study within the National Institutes of Health’s \$157 million Human Microbiome Project. The study, in which the University is collaborating with the University of Michigan, the Marine Biological Laboratory, and Michigan State University, is evaluating the changes in gut bacteria before, during, and after the onset of pouchitis, an inflammatory condition affecting half of patients operated on for ulcerative colitis. The participants hope to get a glimpse into the role of microbes in the emergence of a disease. In addition, the University is home to MG-RAST (metagenomics analysis server), the principal data analysis platform for metagenomics researchers.

## THE UNIVERSITY IS THE SITE OF THE LARGEST STUDY WITHIN THE NATIONAL INSTITUTES OF HEALTH’S \$157 MILLION HUMAN MICROBIOME PROJECT.

Building on this work, University researchers are now branching into studying the impact of diet on the microbiome, says Chang. “We’re trying to see if certain supplements or vitamins can reshape the microbiome,” he explains. “If we can achieve this, we may be able to restore immune function in certain conditions and improve health outcomes.”

Such breadth of activity offers a rich environment in which to work, say Kahn and Rubin.

“There are lots of synergies here,” says Rubin. “Where else could two gastroenterologists who are experts in IBD and trained in ethics partner with Dr. Chang, a world leader in basic and translational research and IBD? Add the patient population to the mix, and we think of it as the perfect storm of opportunity for us to learn and advance the science.” ■

## WHY I GIVE

“The University of Chicago Medical School allowed me to realize my life’s dream of becoming a physician. From the moment I entered Billings Hospital, I knew I had made a wise choice. As students, we saw and cared for patients with a wide variety of illnesses—some common, some rare—and we graduated with extraordinary diagnostic skills and compassion which would carry us far and wide into the world of modern medicine.

Over the past 50-plus years, I have watched, with great pride, the tremendous growth of the facilities and the high standards for faculty and students, and feel fortunate to have been able to help with that growth.”

SUSAN COOK SHUMWAY, MD’60, RETIRED PEDIATRICIAN

