THE NEW YORKER

The Excrement Experiment

Treating disease with fecal transplants.

By Emily Eakin

Some disease sufferers have benefitted from fecal transplantation, in which a healthy person's stool is transferred to a sick person's colon.

Illustration by Oliver Munday

One morning last fall, Jon Ritter, an architectural historian living in Greenwich Village, woke to find an e-mail from a neighbor, who had an unusual request. "Hi Jon, This is Tom Gravel, from Apt. 4N," the e-mail began. "I wanted to check in and see if you may be open to helping me with a health condition." Gravel, a project manager for a land-conservation group, explained that he had Crohn's

disease, an autoimmune disorder that causes inflammation of the intestinal tract along with unpredictable, often incapacitating episodes of abdominal pain and bloody diarrhea. His doctor had prescribed a succession of increasingly powerful drugs, none of which had helped. But recently Gravel had experimented with a novel therapy that, though distasteful to contemplate, seemed to relieve his symptoms: fecal transplantation, in which stool from a healthy person is transferred to the colon of someone who is sick. He hoped to enlist Ritter as a stool donor.

"I realize this is really out there," Gravel wrote. "But I think you and your family are the nicest people in our building, and I thought I might start with lucky you."

Crohn's disease affects as many as seven hundred thousand Americans, but, like other autoimmune disorders, it remains poorly understood and is considered incurable. (Autoimmune disorders are thought to arise when the immune system attacks healthy tissue, mistaking it for a threat.) The standard treatments for Crohn's often don't work, or work only temporarily, and many have serious side effects. When the disease cannot be managed by drugs, surgery to remove part of the colon is often the only option. Gravel, who is thirty-nine, is slight and mild-mannered, with delicate features and floppy brown hair. He had endured nearly three years of debilitating symptoms, as well as a shifting regimen of enemas, suppositories, shots, supplements, and, for several months, intravenous infusions of Remicade, a potent immunosuppressant, at a cost of more than twelve thousand dollars each. "I would tell my wife in the morning, 'I'm getting out my arsenal,' " Gravel told me.

Even so, blood tests continued to show high levels of inflammation. His daily life was governed by calculations of proximity to the nearest rest room. "I'd get nervous if I had to go to the bank," he said. The checkout line at Whole Foods was an ordeal. By August, 2013, Gravel had stopped all his medications and was trying to manage his disease through a strict diet of broiled meat and fish and puréed vegetables. His mother showed him an article from the *Times* about a man who had been nearly bedridden by ulcerative colitis—a condition related to Crohn's—and who had largely recovered after a month or so of fecal transplants. Gravel found a how-to book on Amazon and bought the recommended equipment: a blender, a rectal syringe, saline solution, surgical gloves, Tupperware containers. His wife agreed to be his donor. Doctors and patient-advocacy Web sites stress that donors should be screened for transmissible diseases, but Gravel and his wife decided to skip this step. "She'd been healthy as long as I'd known her," he told me.

His doctor was unable to offer advice, saying that too little was known about fecal transplants. Nor could he legally provide the procedure. The Food and Drug Administration regards fecal transplantation as an experimental treatment, and doctors must apply to the agency for permission before offering it to Crohn's patients. Just as Gravel began to research the procedure, his wife received a diagnosis of breast cancer. They began daily transplants anyway, and soon he was feeling much better. But his wife was scheduled to have surgery, followed by chemotherapy. Gravel needed another donor, someone nearby. "I immediately thought of Jon," he said.

A strapping forty-eight-year-old partial to organic food, Ritter exuded good health. "At first I was kind of shocked," he told me. "Pretty quickly I realized I

didn't really have a problem with it. What he wanted was something I wasn't using—that was going to waste."

No one knows how many people have undergone fecal transplants—the official term is fecal microbiota transplantation, or FMT—but the number is thought to be at least ten thousand and climbing rapidly. New research suggests that the microbes in our guts—and, consequently, in our stool—may play a role in conditions ranging from autoimmune disorders to allergies and obesity, and reports of recoveries by patients who, with or without the help of doctors, have received these bacteria-rich infusions have spurred demand for the procedure. A year and a half ago, a few dozen physicians in the United States offered FMT. Today, hundreds do, and OpenBiome, a nonprofit stool bank founded last year by graduate students at M.I.T., ships more than fifty specimens each week to hospitals in thirty-six states. The Cleveland Clinic named fecal transplantation one of the top ten medical innovations for 2014, and biotech companies are competing to put stool-based therapies through clinical trials and onto the market. In medicine, at any rate, human excrement has become a precious commodity.

[cartoon id="a18709"]

Science writers love to cite the freakish fact that for every one of our cells we are hosts to ten microbial ones, and nowhere are there as many as in our digestive tracts, which house about a hundred trillion bacteria, fungi, viruses, and other tiny creatures. (As one gastroenterologist put it to me, with only mild exaggeration, "We're ten per cent human and ninety per cent poo.") Collectively, this invisible population is known as the gut microbiome, and lately it has become an object of intense scientific interest. "You can hardly mention a disease today where something hasn't been looked at regarding the microbiota," Lawrence Brandt, a gastroenterologist at Montefiore Medical Center, in the Bronx, who was among the first physicians in this country to perform fecal transplants, told me.

For years, efforts to study the microbiome were stymied by the number of species involved and the difficulty of culturing finicky strains in the lab. But the advent of genetic-sequencing technology has made it possible to identify microbes by their DNA, spawning a frenzy of research, whose highlights, routinely catalogued in the popular press, can have an air of science fiction. (A recent headline in the *Times*: "*how bacteria may control our behavior.*") Much of the research is still preliminary, and a lot of it depends on stool, which by dry weight is roughly forty per cent microbes and remains our best proxy for the brimming universe within.

FMT, the chief medical application of microbiome research to date, is also at a rudimentary stage. The procedure has been proven to work only in the case of a single disease: a bacterial infection known as *Clostridium difficile*. The infection, which causes symptoms similar to Crohn's, afflicts more than five hundred thousand people each year, killing fifteen thousand of them, almost all hospital patients who received antibiotics. Like a weed killer that slays not just the invading vine but, inadvertently, the entire garden, broad-spectrum antibiotics, which are prescribed prophylactically to patients undergoing surgery, can destroy gut flora, making it easier for *C. difficile* to take hold. Moreover, the standard treatment for the disease—vancomycin, itself an antibiotic—is often ineffective against drug-resistant, "hypervirulent" new strains.

Scattered case reports in the medical literature described *C. difficile* patients, some on their deathbeds, who received fecal transplants and recovered, often within hours. Then, in January, 2013, *The New England Journal of Medicine* published the results of the first randomized controlled trial involving FMT, comparing the therapy to treatment with vancomycin for patients with recurrent disease. The trial was ended early when doctors realized that it would be unethical to continue: fewer than a third of the patients given vancomycin recovered, compared with ninety-four per cent of those who underwent fecal transplants—the vast majority after a single treatment. A glowing editorial accompanying the article declared that the trial's significance "goes far beyond the treatment of recurrent or severe *C. difficile*" and predicted a spate of research into the benefits of fecal transplants for other diseases.

"Nothing in health care works ninety per cent of the time," Mark B. Smith, a microbiologist at M.I.T. who is a co-founder of OpenBiome, the stool bank, told me. Zain Kassam, a gastroenterologist who is OpenBiome's chief medical officer, put it this way: "It's the closest thing to a miracle I've seen in medicine."

Smith and his colleagues are stool's most enterprising pitchmen, displaying a zeal for the collection and distribution of human waste that, as much as any other single force, has helped to catapult FMT to the front lines of medical treatment. The inspiration for OpenBiome was a friend of Smith's, an otherwise healthy man in his twenties who, in 2011, acquired *C. difficile* following gallbladder surgery. "He ended up on seven rounds of vancomycin over a year and half," Smith told me. "He was very sick." The man found a doctor who was open to the idea of performing a fecal transplant and waited six months while the doctor researched the procedure. Finally, unable to wait any longer, he gave himself a transplant using his roommate's stool. "It worked for him," Smith, who was then completing his Ph.D., said. "But the whole thing seemed very bizarre to me: why is it so hard to get a treatment that is very effective?"

Even patients who received fecal transplants from doctors had to find a donor themselves and pay for screening tests. Moreover, there was little consensus about what pathogens to screen for or how to perform a transplant. Enemas, colonoscopes, nasogastric tubes, gelatine capsules—all had served as delivery methods. Some doctors were mixing random amounts of stool and saline solution in blenders. "It's not sterile, it's not completely safe," Smith told me. "I thought, Gosh, we should just start a stool bank." He persuaded a friend, who was about to enter business school at M.I.T., to join the project. "Eventually, we decided that the right model is the Red Cross, but for poop. It's a medical commodity, and we'll try to make it available in a safe and standardized way."

Last spring, OpenBiome moved from a lab at M.I.T., where it had been storing stool in a borrowed freezer, to an office suite in Medford, a Boston suburb. In September, it sent out its thousandth stool treatment. At eight-thirty one morning last month, the office was already busy. In one room, a technician was preparing for the day's stool donations by donning protective gear—a white coat, safety goggles, surgical gloves. A few feet away stood three industrial freezers, set to -80 degrees Celsius and stocked with small containers of stool, like so many bottles of chocolate milk. Smith, dressed in jeans and a blue-and-white plaid shirt, darted from room to room. "Who's coming this morning?" he asked a colleague bent over a laptop. "Donor 29?" He poked his head into another room, where, near a cooler packed with dry ice, a whiteboard listed the

destinations of a dozen shipments that had recently gone out. “We’ve added twenty-three hospitals this month!” he said approvingly. [cartoon id="a18636"] Twenty-seven years old, with cornflower-blue eyes and a closely trimmed beard, Smith tends to speak in exclamations, punctuated by a pealing laugh. When, at ten after nine, the doorbell rang, he bounded to the door. In the hallway stood a stocky man in a faded baseball T-shirt cradling a blue plastic bag: Donor 29, a.k.a. Winnie the Poo. (All OpenBiome donors are given code names. A current staff favorite: Vladimir Pootin.) Smith gingerly received his package, still warm. (OpenBiome requires that no more than an hour elapse between defecation and delivery.) Like all of the organization’s donors to date, Donor 29, a bioengineer who works elsewhere in the building, was recruited by Smith and his staff. “They were at the gym one morning, at seven-fifteen,” the donor explained. “They had a table outside, and they were just so enthusiastic.”

In fact, OpenBiome’s screening process is extremely strict: fewer than twenty per cent of recruits pass the blood and stool tests. Use of antibiotics in the previous six months is cause for rejection, as is travel to the developing world and the presence in a stool test of pathogens like *B. hominis*, a parasite that is found in up to ten per cent of healthy people. Approved donors are given blue Cool Whip-style containers and paid forty dollars a specimen. Size is important: an ample donation can provide up to ten treatments, and a monthly prize is awarded for “the most generous contribution.”

The technician, working under a sterile hood, weighed Donor 29’s container: a hundred and twenty-seven grams. (The record is five hundred and eight.) “Not his best work,” murmured Smith. Even so, the effort yielded five treatments. First, the technician transferred the stool to what looked like a large ziplock bag, divided down the middle by a fine mesh panel. Then she hung the bag inside a stainless-steel machine, about the size of a microwave, and flipped a switch. For two minutes, the bag was pummelled by metal paddles, leaving food particles on one side of the mesh and a homogenized slurry of microbes on the other. Using a long pipette, the technician distributed the slurry among five sterilized plastic bottles. Every so often, a faint odor wafted out from the hood, then dissipated. The doorbell rang again. It was Donor 28 (Dumpledore) with a delivery, and, close on his heels, Donor 26 (Albutt Einstein), who mumbled apologetically that he had nothing to offer but promised to return in the afternoon. Smith nodded sympathetically.

It’s a safe bet that few other miracle cures have had to overcome such repellent associations. The first known account of fecal transplantation dates to a fourth-century Chinese handbook by the physician Ge Hong, who prescribed “yellow soup”—a fecal suspension—as a remedy for severe diarrhea. (Ge Hong also discusses his cure for malarial fevers: a formula containing artemisinin, an herbal extract, which, rediscovered in the nineteen-seventies, is now part of the standard treatment for the disease.)

In the United States, the first description of FMT appeared sixteen centuries later, in 1958, when Ben Eiseman, a surgeon at the V.A. Hospital in Denver, published four case reports in the journal *Surgery*. Stool was then widely assumed to be mainly a source of disease; there was little empirical support for the notion that bowel bacteria were important for health. Several of Eiseman’s patients had become deathly ill after the requisite preoperative course of antibiotics, however, and he concluded that the drugs were destroying normal

gut flora. He sent a resident to collect stool specimens from a nearby maternity ward, reasoning that pregnant women were likely to be young and healthy and to have avoided antibiotics. The stool, transferred to Eiseman's patients, saved their lives.

The year that Eiseman began performing fecal transplants, Stanley Falkow, who went on to renown as a microbiologist at Stanford, was working in a lab at a hospital in Newport, Rhode Island. A doctor on staff shared Eiseman's belief that antibiotics were hard on gut microbes and instructed patients to bring a stool specimen when they were admitted for surgery. Falkow's job was to prepare capsules of the patients' stool for them to swallow after they'd been discharged, on the hunch that these would help to prevent postoperative infections. "I was all for it," Falkow told me. "When we tried to culture the stool from patients who'd had antibiotics using conventional culture methods, you got no growth. Their stool doesn't even smell. Very few stools can make that statement."

A hospital administrator discovered what was going on and, as Falkow recalls it, confronted him, saying, "Is it true that you've been feeding the patients shit?" Falkow was fired on the spot. (He was reinstated when a doctor intervened on his behalf.) "It's a repulsive thought," Falkow says of fecal transplantation, "and people are still repulsed by it."

For years, virtually the only proponent of FMT was Thomas Borody, a gastroenterologist in Sydney, Australia, who, in 1988, after reading Eiseman's paper, decided to try a fecal transplant on a patient who had contracted an intestinal ailment in Fiji. The patient recovered, and Borody estimates that he has since performed the procedure five thousand times, including, with stool supplied by his father, on his mother, who suffered from crippling constipation. In addition to *C. difficile* patients, Borody says that he has successfully treated people with autoimmune disorders, including Crohn's and multiple sclerosis.

In the case of *C. difficile*, the impact of a fecal transplant is straightforward: normal gut bacteria overwhelm and suppress the pathogen. In patients suffering from other conditions, the effects of FMT are harder to predict or to explain, and until rigorous trials are undertaken reports of spectacular recoveries are merely anecdotes, without scientific value. It's known that Crohn's patients have a gut microbiome that is less diverse than average and is lacking in key species of bacteria. But many also carry genetic mutations not found in healthy people. How such mutations interact with the immune system and gut microbes to cause disease is not fully understood. [cartoon id="a18765"]

Some of the most promising research is still at the animal stage. In a 2006 study, researchers at Washington University, in St. Louis, transferred gut microbes from mice carrying a mutation that caused them to be obese to mice lacking the mutation. The mice that received the transplants subsequently became obese themselves, despite eating the same amount of food as a group of mice that received transplants from lean donors. (Presumably the microbes in the obese mice were able to extract more energy from food than were the microbes in their lean counterparts.) The study was the first to show that a disease trait could be transmitted from one animal to another through the microbiome.

"A lot of people my age who are moving into the field of microbiome research were really moved by that paper," Mark Smith, of OpenBiome, told me. "It's one thing to show that there are a lot of bacteria in humans, and these bacteria are associated in some cases with disease and health. But in this case the researchers

changed the composition of a microbial community, and that totally changed the health of this animal. And that could potentially happen in humans."

It's possible that no Americans have gut microbiomes that are truly healthy. Evidence is mounting that over the course of human history the diversity of our microbes has diminished, and, in a recent paper, Erica and Justin Sonnenburg, microbiologists at Stanford, argue that the price of microbial-species loss may be an increase in chronic illness. Unlike our genes, which have remained relatively stable, our microbiome has undergone radical changes in response to shifts in our diet, our antibiotic use, and our increasingly sterile living environments, raising the possibility that "incompatibilities between the two could rapidly arise." In particular, the Sonnenburgs stress the adverse effects of a standard Western diet, which is notoriously light on the plant fibre that serves as fuel for gut microbes. Less fuel means fewer types of microbes and fewer of the chemical by-products that microbes produce as they ferment our food. Research in mice suggests that those by-products help reduce inflammation and regulate the immune system. Noting that rates of so-called Western diseases—including heart disease and autoimmune disorders, all of which involve inflammation—are thought to be much lower in traditional societies, the Sonnenburgs write, "It is possible that the Western microbiota is actually dysbiotic and predisposes individuals to a variety of diseases."

The first step to determining whether our ancestors' guts were healthier than our own is to figure out what might have lived in them. Jeff Leach, an anthropologist who is collaborating with the Sonnenburgs, has spent much of the past year in Tanzania, conducting research among three hundred Hadza, one of Africa's last remaining hunter-gatherer tribes. "We need to go to places where people don't have ready access to antibiotics, where people still drink water from the same sources that zebra, giraffes, and elephants drink from, and who still live outside," Leach told me. "There are a number of people like that, but only the Hadza still live in a place that gave rise to our genus, *Homo*." Based on a preliminary analysis of the tribe's stool, he said, "it looks like the Hadza have one of the most diverse gut ecosystems in the world of any population that's been studied." (A previous study led by Stephanie Schnorr, of the Max Planck Institute for Evolutionary Anthropology, found that the Hadza harbored bacterial species that had never been seen before and lacked others that in Western guts have been associated with good health.)

Among the Hadza, Leach is known as Doctor Mavi—Swahili for "shit." His own also gets collected and analyzed, in an effort to measure the impact of a Hadza life style on a Western gut. In September, Leach gave himself a fecal transplant, with the aid of a turkey baster and a bemused Hadza man, who served as his donor. Afterward, Leach marvelled, "I probably had the most diverse ecosystem of any white person in the world."

When I spoke with him, he had been back in the United States for two days, "drinking tequila and eating hamburgers," and generating stool samples. These might show whether the microbes that he acquired from his Hadza donor could survive a Western diet or, as he predicted, would die off. If the microbes fail to take up residency in his gut, he said, "then I've effectively re-created the last ten thousand years of human history."

Leach has a daughter, now fourteen, who, as a toddler, was given a diagnosis of Type 1 diabetes, an autoimmune disease. His interest in gut microbes grew out of

a desire to understand her condition. “Hadza kids are born in the dirt, play in the dirt, and they’re literally chewing on animal bones,” he said. “They’re covered in microbes, and it’s been that way for millions of years. Maybe because we’ve un-wilded our children, that might play a role in some of the diseases we see in them.”

In September, I visited a scientist in San Diego who has thought as much about the relationship between gut microbes and autoimmune disease as anyone: Larry Smarr, a computer scientist at U.C.S.D. who directs the California Institute for Telecommunications and Information Technology. Smarr has Crohn’s. More than ten years ago, in an effort to lose weight and get fit, and before he had experienced any symptoms, he began to record his every bite, step, and sleep wave. When he discovered that he could order blood and stool tests online, he started tracking those results, too—eight times a year. *The Atlantic* dubbed him “The Measured Man.” The BBC aired footage of him holding a ziplock full of frozen stool.

[cartoon id="lcu-2007-11-26"]

Smarr’s enthusiasm for data predates his obsession with his health; in the early nineteen-eighties, he helped persuade the National Science Foundation to fund the first national network of supercomputers, a precursor to the Internet. But it was an inadvertent discovery in a stool analysis that led to his Crohn’s diagnosis and, eventually, to a new calling: as an evangelist for an impending medical revolution, “quantified health.” In the future, as Smarr sees it, doctors won’t have to rely on symptoms and guesswork, because they’ll have computer files detailing a patient’s genes and microbes. Stool is central to this vision, and Smarr is an expert on the stuff.

“As I came to realize, stool is the most information-rich material you have ever laid eyes on,” he told me. Smarr is sixty-six, tall and thin, with a comic’s range of facial expressions and talent for quips. We met in his fifth-floor office on campus, at a conference table overlooking a dusty eucalyptus grove. On his desk lay a small white sculpture with spiny protrusions, like a piece of bleached coral. It was a scale model of a six-inch region of Smarr’s colon that is chronically inflamed by Crohn’s. “It’s the Rodney Dangerfield of organs and substances,” he said when I admired it.

By 2008, Smarr had lost twenty pounds and become a convert to the Zone diet, a regimen that emphasizes foods containing copious amounts of Omega-3 fatty acids, which are thought to fight inflammation. (Inflammation is a normal immune response to a toxin or irritation, but chronic inflammation is a risk factor for disease.) Smarr, eager to measure the fatty acids in his blood, found a Web site that offered such a test. The site also advertised stool analyses, and impulsively he added one to his order. “At that point, I had no idea that I was anything but healthy,” he recalled.

The stool test indicated that Smarr had twenty times the advisable level of lactoferrin, a marker of inflammation. Two years later, Smarr’s lactoferrin had climbed to a hundred and twenty-five times the advisable level. “If you ever got something like that back, you’d fall over in a faint,” he told me, his eyes wide. A search of the medical literature revealed that highly elevated lactoferrin was closely correlated with Crohn’s and ulcerative colitis. But Smarr’s gastroenterologist was skeptical: a colonoscopy had shown only a small area of inflammation. Besides, most patients are given the diagnosis as young adults,

and, apart from a passing infection of the colon, Smarr had been largely free of symptoms. He found a new doctor, William Sandborn, a leading Crohn's researcher who had just been recruited to U.C.S.D., and underwent a second colonoscopy. He received a diagnosis of late-onset Crohn's.

The diagnosis was a relief, confirming Smarr's data. Still, if Crohn's had caused the inflammation, what had caused the Crohn's? In 2008, he had sent a saliva sample to 23andme, the genetics testing company, and had a portion of his genome (the unique pattern of DNA in his body) sequenced. After his diagnosis, he typed "Crohn's disease" into 23andme's online database, which retrieved those snippets of his DNA associated with the illness. Smarr learned that he had DNA aberrations on a gene that several studies suggest may be a "master regulator" in Crohn's, and which, by exacerbating the immune system's inflammatory response, confers a greater than average risk for the disease.

The gene was a clue, but not everyone with a genetic predisposition gets the disease. New research pointed to the microbiome as a likely factor. So Smarr sent a stool specimen to the J. Craig Venter Institute, the genetics-research organization, where a colleague agreed to sequence his microbes—into two hundred million strings of DNA. In a typical Western gut, two phyla of bacteria are overwhelmingly dominant: Bacteroidetes and Firmicutes. Together, they comprise roughly ninety per cent of our microbes. Smarr's gut was nearly devoid of Bacteroidetes—a finding consistent with other Crohn's patients. Equally disconcerting, Smarr had abundant archaea, obscure microorganisms known for their ability to survive in harsh environments, such as the hot springs at Yellowstone National Park. "At my highest level of inflammation, I was twenty-per-cent archaea," Smarr said. "I've probably got the world's record."

Ten per cent of his bacteria were *E. coli*, a species that in healthy people is found in minute amounts, typically representing less than one per cent of the microbiome. A researcher at Smarr's lab consulted a database at the National Institutes of Health containing DNA sequences for all the *E. coli* strains that had been identified at the time—about eight hundred—and found a match for Smarr's strain. Known as "adherent-invasive *E. coli*," the strain is often found in the guts of Crohn's patients, where it digs through the mucus lining the colon and latches on to the healthy cells beneath. (Smarr: "Very sci-fi!")

Finally, he felt that he had solved much of the puzzle of his disease: "The immune system senses that there's a strain of *E. coli* that's pathogenic, so it fires up, and when the body fires up the immune system you have inflammation." Sandborn, Smarr's doctor, called this hypothesis "very plausible." But, he cautioned, it's not clear whether an abnormal microbiome causes the inflammation or whether it's the other way around.

Smarr doesn't know what led the invasive *E. coli* to bloom in his gut. "The issue is, what do you do about it?" he told me. "How do I get my Bacteroidetes back? Given that the immune system is reacting badly to something in the microbiome, it's sort of logical that if I could get the microbiome back to normal the immune system would calm down." Smarr had read about fecal transplants, and in 2011 he asked Sandborn about them. At the time, no doctor at U.C.S.D. offered the procedure. When Smarr developed uncomfortable Crohn's symptoms, Sandborn prescribed drugs, which didn't seem to help, and eventually Smarr stopped taking them. His symptoms abated—perhaps the drugs had done some good

after all—and he has been in remission for nearly a year. [cartoon id="sipress-2009-05-25"]

Sandborn now performs fecal transplants, and Smarr says that if his symptoms return he will consider having one. “If I knew I could get five or ten years of remission out of it, I’d do it.”

Among the desperately ill, FMT’s reputation as a wonder cure has outstripped the science supporting its use. The lure of a potential remedy that is widely available, inexpensive, and considered relatively low-risk has yielded an improvisational approach to treatment and a growing D.I.Y. transplant population. When Jon Ritter agreed to serve as a donor for Tom Gravel, the Greenwich Village Crohn’s patient, Gravel paid the charges for the blood and stool screening that Ritter’s insurance didn’t cover. But these tests can cost hundreds of dollars, and many patients are circumventing the medical system altogether. On YouTube, FMT how-to videos have received thousands of views, and on Facebook there are private forums where people trade advice about the procedure. “There are a lot of people who are doing this at home,” Lawrence Brandt, of the Montefiore Medical Center, says. “Some of them are doing it under the instructions of their physicians. Some of them are doing it by reading the Internet.” One of his patients, ill with *C. difficile* and unable to find a donor, asked whether she could use her dog’s feces. (The answer was no.) Another placed an ad in her local paper; more than forty-five people responded. Instances of FMT going terribly wrong are hard to find, although there have been anecdotal reports of people developing bacterial and viral infections following the procedure.

Like Mark Smith, of OpenBiome, the F.D.A. watched the surging demand for fecal transplants with concern. In the early nineteen-eighties, at least twenty thousand people became infected with H.I.V. after receiving blood transfusions contaminated with the virus, because doctors didn’t know to screen for it. Could a similar, as yet unknown threat be lurking in a donor’s stool? In May, 2013, agency officials convened a public workshop on FMT in Bethesda, where they explained that the F.D.A. considers stool to be a drug. This wasn’t particularly surprising. The agency defines a drug as any material that is intended for “use in the diagnosis, cure, mitigation, treatment, or prevention of disease.” An exception has been written into law for body parts, including skin, bone, and cartilage, which are classified as tissue. But the statute excludes most human secretions from this category.

Substances labelled drugs are subject to a rigorous approval process. Pharmaceutical companies typically spend many years and millions of dollars researching and testing a drug before submitting it to the agency for approval. Until the F.D.A. approved a fecal-transplant therapy, the procedure would be considered experimental. In order to offer it to patients, doctors would need to file an investigational new-drug application, or I.N.D., and obtain the agency’s permission. “That hit the whole field like a ton of bricks,” Smith, who attended the workshop, told me. “There was this increasing momentum around fecal transplants, and all of a sudden the whole field hit the brakes.”

I.N.D.s are intended to capture every aspect of a prospective therapy in exacting detail. At the Bethesda workshop, one gastroenterologist said that it had taken her hundreds of hours to complete the paperwork. Many others lacked the resources and staff to devote to such a task. “What do we do with the fifteen

thousand patients who are really desperate for something that works?" a doctor from the Mayo Clinic asked F.D.A. officials. "If your mother shows up with severe or recurrent *C. difficile*, are you going to not offer something that you know how to do safely, effectively, and say, 'I can't do it because the regulatory agencies in the United States have decided that this requires a special licensure'?"

At the time of the workshop, OpenBiome had not yet started its operation; the F.D.A.'s ruling implied that the organization's plan to send stool across state lines to hospitals and clinics would be illegal. "They were planning to ship this stuff around the country," Peter Safir, a lawyer at Covington & Burling, in Washington, D.C., who is an expert on F.D.A. regulation and has advised OpenBiome, told me. "There's really no way around the idea that once the F.D.A. says it's a drug you either have to have approval, which no one's going to get in the near term, or you set up some kind of system where there's an I.N.D."

Six weeks later, in July, 2013, the F.D.A. declared an exception for doctors treating recurrent *C. difficile:* they would be allowed to perform fecal transplants without an I.N.D. In revising its position, the agency said that it would be exercising "enforcement discretion"—a temporary measure. As an F.D.A. spokeswoman later explained in an e-mail, the directive did not reflect a change of policy; it was intended as an acknowledgment that "there are often few or no other treatment options for these patients." According to Safir, "What they mean is they're not doing anything. They're not going to go after a doctor and they're not going to go after OpenBiome." [cartoon id="vey-2011-10-03"]

That August, OpenBiome screened its first donor, and early that fall sent out its first stool treatment, to a clinic in California. In the past year, orders for OpenBiome's stool have increased at a rate of about eighteen per cent a month. Its success has unnerved biotech companies that are developing stool-based enemas and capsules—or, as they're known in the field, "crapsules"—for eventual sale on the commercial market. "OpenBiome is selling an unapproved drug without any kind of F.D.A. clearance, so in my opinion they're breaking the law," Lee Jones, the C.E.O. of Rebiotix, a company in Minnesota that is developing an enema for the treatment of *C. difficile*, told me. "They may parade as a nonprofit, but what they're doing is selling a product to be used on patients."

When, in a year or two, Rebiotix submits its enema to the F.D.A. for approval, it will have spent tens of millions of dollars on research and trials—costs that are typically factored into a drug's retail price. OpenBiome charges two hundred and fifty dollars for a treatment, which just covers its costs. "This is a highly unusual situation," Peter Safir, the lawyer, said. "There's no question that in the United States we want our drugs approved. We want the F.D.A. to say a product is safe, effective, and is manufactured according to good practices, and that costs a lot of money. But here you've got an almost identical competitor that is virtually giving it away, without F.D.A. approval." Once a company like Rebiotix obtains approval to sell its stool therapy, he went on, it could pressure the F.D.A. to shut down OpenBiome.

The agency may be moving in that direction. In March, it proposed a new guideline for fecal transplants: that the stool donor should be "known to either the patient or the treating licensed health care provider." It wasn't immediately obvious what the agency meant by "known," and the guideline, which was circulated for public comments, has not yet been formally adopted. Clearly, though, doctors relying on OpenBiome, whose donors are anonymous, would be

unable to meet such a requirement. ("The F.D.A. is now reviewing the comments received on this draft guidance document," an agency spokeswoman said in an e-mail.)

In an editorial in *Nature* earlier this year, Smith and two co-authors argued that stool should be reclassified as a tissue. Unlike drugs, tissues are not subject to clinical trials or to F.D.A. approval; when someone gets a bone graft, its efficacy isn't in doubt. As Safir put it, "A tissue doesn't require clinical trials, because you're just substituting it for what everyone knows it already does." Tissues are still obliged to meet strict safety standards, and Smith and his co-authors proposed that a screening system like the one currently in place for blood, which is in a category of its own, could be adapted for stool. Classifying stool as a drug "threatens to restrict FMT mainly to companies with the resources to fund large clinical trials," they wrote.

To amend the federal statute governing the regulation of body parts and substances would require an act of Congress, and Smith and his colleagues understand that this is unlikely to happen. "We've always had a view that OpenBiome might have to go away," James Burgess, the stool bank's executive director, told me. But he warned, "If the cost of FMT goes up by an order of magnitude, you'll see a big jump in the D.I.Y. approach."

Even if OpenBiome were to stop shipping stool to hospitals, it could presumably continue to operate as a resource for researchers. When I visited in October, there was a tray of shiny white capsules on Smith's desk—"poop pills that we've been working on," he explained. Doctors at Massachusetts General Hospital had just announced the results of a study showing that capsules were as effective as colonoscopes for treating *C. difficile*, and the field was abuzz with the news, since, as Smith pointed out, "everyone would rather swallow a pill." He had hit on a way to improve on the doctors' methods: lining capsules with cocoa butter, which is solid at room temperature, thus insuring that they won't disintegrate prematurely—on the shelf or in someone's mouth.

Such research requires patients. Not only are D.I.Y. fecal transplants likely to be less safe than procedures administered by doctors but each one also represents a case lost to science. Researchers are unlikely to study Tom Gravel, the Greenwich Village Crohn's patient, who recently cut back his fecal transplants to one every two weeks. "In a way, it is like I am a different person," he told me, recalling the symptoms and medications that once dominated his life. He believes that he has found an effective therapy, not a cure. "Provided Jon is still up for it, which he generously seems to be, I will continue the transplants indefinitely," he said. "Crohn's is a very persistent disease." ♦

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