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Swapping Germs

A potentially beneficial but unusual treatment for serious intestinal ailments may fall victim to regulatory difficulties

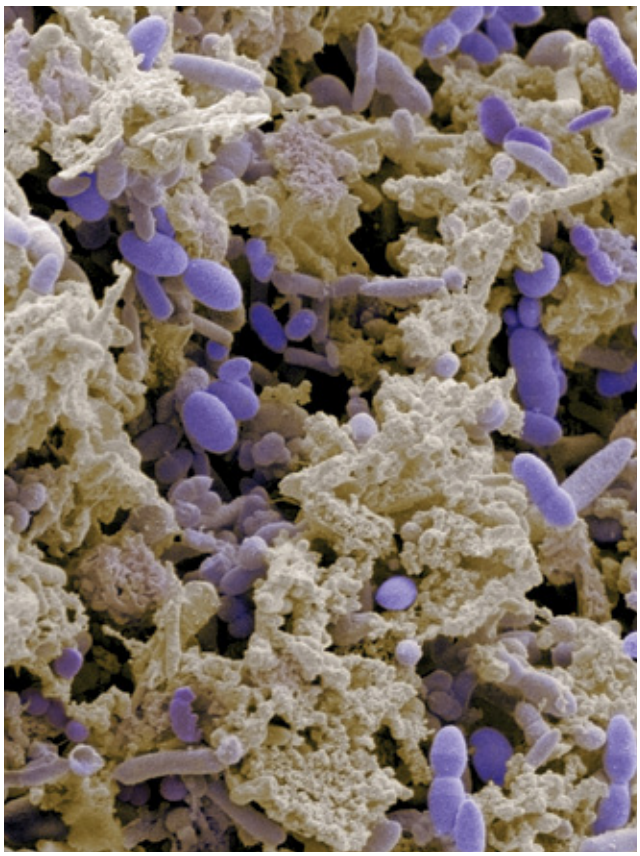
Marion Browning of North Providence, R.I., was at her wit's end. The 79-year-old retired nurse had suffered from chronic diarrhea for almost a year. It began after doctors prescribed antibiotics to treat her diverticulitis, a painful infection of small pouches in the wall of the colon. The regimen also killed friendly bacteria that lived in Browning's intestines, allowing a toxin-producing organism known as *Clostridium difficile* to take over and begin eating away at the entire lining of her gut.

For months Browning was in and out of her doctor's office, getting big-gun antibiotics to suppress the *C. difficile* infection. Each time a course of treatment ended she would feel better for a while. But her strain of *C. difficile* was stubborn: a few of the destructive bacteria always survived. Within a few days they would begin multiplying, and the racking diarrhea would recur. After four rounds of antibiotics, her gastroenterologist told her that he had done all he could think of. He recommended that she see Colleen Kelly, a clinical faculty member at Brown University's medical school, who was trying something new.

Kelly proposed a treatment that sounded both logical and strangely unmedical. Normally, she told Browning, the friendly bacteria that reside in the human intestine maintain a seesawing balance that keeps pathogenic bacteria in check. That equilibrium can be temporarily disrupted—as with standard antibiotic treatment—but it nearly always returns to stability. Browning's own bacterial community had lost that ability, probably for good. Still, there was a way to restore normality, Kelly said. She could replace Browning's bacteria completely, by inserting into her colon a diluted sample of stool from someone whose intestinal health was good. If the good bacteria in the donated stool took hold and recolonized her intestine, the *C. difficile* would be crowded out, and she would be cured.

Browning had never heard of such a procedure—variously called fecal transplant, fecal bacteriotherapy or fecal flora reconstitution—but she was ready to try anything. Kelly asked her to recruit a healthy donor. Browning chose her 49-year-old son. In the fall of 2009 Browning performed the bowel-cleansing routine that precedes a colonoscopy, while her son took an overnight laxative. Kelly diluted the donation, then used colonoscopy instruments to squirt the solution high up in Browning's large intestine. The diarrhea resolved in two days and has never recurred.

"I can't understand why more doctors aren't doing this," says Browning, now 80. Yet a complex combination of federal regulations and research rules—along with just plain squeamishness—could keep the procedure from helping potentially thousands of people who might benefit.



Straight poop: **Bacteria shed from the intestine (*some of which are colored purple here*) make up much of human feces.**

TONY BRAIN Photo Researchers, Inc.

A GROWING THREAT

Browning is not alone in being a success story. In medical journals, about a dozen clinicians in the U.S., Europe and Australia have described performing fecal transplants on about 300 *C. difficile* patients so far. More than 90 percent of those patients recovered completely, an unheard-of proportion. "There is no drug, for anything, that gets to 95 percent," Kelly says. Plus, "it is cheap and it is safe," says Lawrence Brandt, a professor of medicine and surgery at the Albert Einstein College of Medicine, who has been performing the procedure since 1999.

So far, though, fecal transplants remain a niche therapy, practiced only by gastroenterologists who work for broad-minded institutions and who have overcome the ick factor. To become widely accepted, recommended by professional societies and reimbursed by insurers, the transplants will need to be rigorously studied in a randomized clinical trial, in which people taking a treatment are assessed alongside people who are not. Kelly and

several others have drafted a trial design to submit to the National Institutes of Health for grant funding. Yet an unexpected obstacle stands in their way: before the NIH approves any trial, the substance being studied must be granted "investigational" status by the Food and Drug Administration. The main categories under which the FDA considers things to be investigated are drugs, devices, and biological products such as vaccines and tissues. Feces simply do not fit into any of those categories.

The physicians performing the transplants decry the regulatory bottleneck because new treatments for *C. difficile* infection are critically needed. *C. diff,* to use the common medical shorthand, has risen in the past 30 years from a recognized but tolerated consequence of antibiotic treatment to a serious health threat. Since 2000, when a virulent new strain emerged, cases have become much more common, occurring not only in the elderly but in children, pregnant women and people with no obvious health risks. One study estimated that the number of hospitalized adults with *C. diff* more than doubled from about 134,000 patients in 2000 to 291,000 patients in 2005. A second study showed that the overall death rate from *C. diff* had jumped fourfold, from 5.7 deaths per million in the general population in 1999 to 23.7 deaths per million in 2004.

C. diff has also become harder to cure. Thanks to increasing antibiotic resistance, standard treatment now relies on two drugs: metronidazole (Flagyl) and vancomycin. Both medications are so-called broad-spectrum antibiotics, meaning that they work against a wide variety of bacteria. Thus, when they are given to kill *C. diff* infection, they kill most of the gut's friendly bacteria as well. The living space that those bacteria once occupied then becomes available for any *C. diff* organisms that survive the drugs' attack. As a result, roughly 20 percent of patients who have had one episode of *C. diff* infection will have a recurrence; 40 percent of those with one recurrence will have another; and 60 percent of those who experience a second bout are likely to suffer several more. Some victims with no other options must have their colon removed. (A new drug, fidaxomicin, which was approved for *C. diff* infection by the FDA in late May, may lead to fewer relapses because it is a narrow-spectrum antibiotic.)

A SIMPLE PROCEDURE

The details of how the transplantation of microbes eliminates *C. diff* infection have not been well studied, but Alex Khoruts, a gastroenterologist and immunologist at the University of Minnesota who has performed two dozen fecal transplants over the past two years, has demonstrated that the transplanted bacteria do take over the gut, replacing the absent friendly bacteria and outcompeting *C. diff*. In 2010 he analyzed the genetic makeup of the gut flora of a 61-year-old woman so disabled by recurrent *C. diff* that she was wearing diapers and was confined to a wheelchair. His results showed that before the procedure, in which the woman received a fecal sample from her husband, she harbored none of the bacteria whose presence would signal a healthy intestinal environment. After the transplant—and her complete recovery—the bacterial contents of her gut were not only normal but were identical to that of her husband.

Most clinicians who perform fecal transplants ask their patients to find their own donors and prefer that they be a child, sibling, parent or spouse. "For me, it's aesthetic," says Christina Surawicz, a professor of medicine at the University of Washington, who has done transplants on two dozen patients and published an account of the first 19. "There's something very intimate about putting someone else's stool in your colon, and you are already intimate with a spouse."

To ensure safety, the physicians performing the procedure require that donors have no digestive diseases and put them through the same level of screening that blood donation would require. That process imposes a cost in time and logistics because standard rules for medical confidentiality require a donor to be interviewed separately from the potential recipient. It also carries inherent financial penalties. The donor's lab work most likely will not be covered by insurance; the transplant procedure may or may not be covered by the patient's insurance.

Proponents have come up with work-arounds for those possible barriers. Khoruts no longer uses related donors—which requires finding a different individual for every case—but instead has recruited a cadre of "universal donors" from among local health care workers. (He has seen no change in how often the transplants "take.") Last year Michael Silverman of the University of Toronto boldly proposed a yet more streamlined solution: having patients perform the transplants at home with a drugstore enema kit. A drawback, he cautioned in *Clinical Gastroenterology and Hepatology,* is that too much of the stool solution might leak out for the transplant to take. Nevertheless, seven patients with recurrent *C. diff* have safely performed the home version, he wrote, with a 100 percent recovery rate.

NEXT STEPS

Even without large-scale rigorous investigations of fecal transplants, the medical community appears to be coming around to the practice. The *Journal of Clinical Gastroenterology* editorialized in September 2010 that "it is clear from all of these reports that fecal bacteriotherapy using donor stool has arrived as a successful therapy." Albert Einstein's Brandt recently suggested in the same journal that fecal transplants should be the first treatment tried for serious *C. diff* infection rather than a last resort. Increasing research interest in the influence of gut flora on the rest of the body—and on conditions as varied as obesity, anxiety and depression—will likely bring pressure for transplants to be adopted more widely.

Currently three clinical trials of fecal transplants have begun in Canada. In the U.S., however, the research logjam persists. An FDA spokesperson said in an interview that there is no way to determine how the agency might rule on an investigational application until the application is brought. That tosses the initiative back to Kelly and her collaborators, who include Khoruts and Brandt. They hope to file with the FDA before much longer, but Kelly admits to being apprehensive over the possible outcome.

"We hope they will not ask things that we cannot answer," she says. Medical centers need to be able to study the procedure, Kelly argues, "because people are trying it on their own." SA

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