"In the early days of oral antibiotics we were plagued by frequent diarrhea in our patients due presumably to kill- ing off intestinal bacteria. I was Chief of Surgery at the VA and simplistically considered merely reintroducing normal organisms to counter such absence. Those were days when if one had an idea, we simply tried. It seemed to work and I wrote it up. It made a small splash...Best Wishes."
Ben Eiseman. Emeritus Professor of Surgery. (E-mail, September 20, 2011)

The first description in modern Western Medicine of fecal enemas is generally attributed to Dr. Ben Eiseman who in 1959 reported a series of four patients suffering from intestinal failure caused by pseudomembranous enterocolitis, miraculously cured by enemas consisting of blended stool from healthy donors. Today we know that pseudomembranous colitis is caused by *Clostridium difficile* or 'C. diff' bacteria. These bacteria infect the colon and produce toxins, which damage intestinal lining causing inflammation. 'Pseudomembranes' are literally explosions of pus coming from the walls of the colon. In most patients C. diff leads to severe diarrhea, but sometimes the inflammation is so severe that the intestine stops working. In these cases the standard treatment is surgical removal of the colon. Patients described by Dr. Eiseman in 1959 faced 75% chance of the death rate with surgery. Today the death rate for patients with similar presentation is 50% within 30 days of surgery! Not much better.

In 2013 *C. difficile* was listed by the Centers for Disease Control and Prevention as the top most urgent threat among different infections in the US, affecting ~ 500,000 people and causing ~ 30,000 deaths every year. Some of the most vulnerable populations are the elderly and patients with inflammatory bowel diseases, such as Crohn's and Ulcerative Colitis. The infection is most commonly triggered by antibiotics, which suppress the normal intestinal microbes and disrupt their protective functions. Until recently most C. diff infections were associated with being in the hospitals or nursing homes. However, today approximately half of C. diff infections are community acquired! This suggests that C. diff spores are finding their way into the general environment.

One common clinical challenge associated with C. diff is recurrent infections. This is because the standard treatment for this antibiotic-triggered disease is more antibiotics. However, antibiotics against C. diff cannot kill its spores. Instead, every round of antibiotic treatment kills more normal intestinal microbes and further weakens the defenses against C. diff. Therefore, many patients develop many cycles of C. diff recurrences. The solution is simple and highly effective – normal microbes have to be implanted back. This was the idea that Dr. Eiseman had back in the 1950s. However, only in the past decade this treatment has become widely available in treatment of C. diff and proven to be superior to antibiotics in a number of controlled, randomized clinical trials in different countries across the world.

How does one obtain these gut microbes? Well, most are shed in stool. In fact, the early forms of this microbial-based therapy used raw fecal material. It is easy to see how this kind of a procedure would have difficulty to be accepted as mainstream medicine. Fortunately, a great deal of progress was made over the recent years. In 2010 our group demonstrated that infusion of donor stool into a patient suffering with recurrent C. diff infection resulted in prompt and sustained engraftment of donor microbes into the patient. Following this demonstration we named the treatment 'Fecal Microbiota Transplantation' or FMT. The name stuck and became

known in the lay media as ‘Fecal Transplants’. It may be a good idea to revisit the name in a future discussion.

However, our most pressing next challenge was to standardize the treatment. To accomplish this we established the first in the world fecal donor program. Furthermore, we developed a protocol to separate the microbes away from the rest of the fecal material and freeze these microbes in a preservative that would allow banking the material for years. This protocol literally revolutionized the field. Other institutions and organizations adapted our methodology and today tens of thousands of sufferers of C. diff infections have been saved with this treatment option.

Yet, administration of liquid suspension of gut microbes requires an invasive procedure, most commonly a colonoscopy. Our next objective was to develop a shelf-stable preparation of gut microbes that could be administered orally. We worked systematically for several years to develop such a preparation. We finally had our first generation capsule product, which we started using in 2015. Thus far we treated over 100 patients with the oral preparation. The treatment is remarkably simple. There is no purgative as would be needed for a colonoscopy. The patients swallow several capsules on an empty stomach with water. That is it. The capsules have no taste. The contents are released in the intestine and the donor microbes normalize the intestinal microbial composition. The success rate is 90% cure in patients who failed all standard antibiotics! Consider that our average patient has gone through ~ 10 months of antibiotic treatments. Imagine their reaction when they learn that the cure all along was as simple as swallowing a couple capsules in one day!

Imagine also that none of our patients were charged a penny for their cure! The fact is that many may not have been able to afford the treatment if we were to charge the full cost of maintaining the donor program with all the rigorous testing and the laboratory work that goes into manufacture. Achieving Cures Together played a key role in making the treatment available to all these patients! Furthermore, we carefully studied how the microbes establish themselves following the treatment. We published the results and presented the work at major conferences so that more people can benefit from our work.

The encapsulated microbes are now heading into controlled clinical trials. One of these is a national multi-center trial by the Veterans Administration, which tapped our program to provide the capsules for them. This trial is anticipated to start in 2018 with our program. This would not be possible without Achieving Cures Together. THANK YOU!

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