Excerpt from *More to Consider in the Battle Against Ulcerative Colitis*
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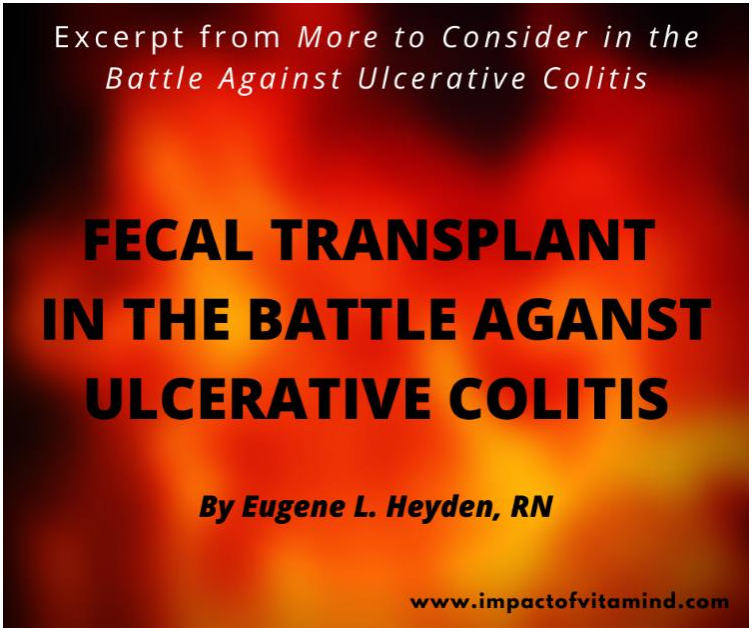

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Chapter 23

Fecal Microbial Transplantation (FMT)

Fecal microbiota transplantation is a therapeutic method via administration of fecal bacteria from a healthy individual into the intestinal tract of a recipient in order to directly change the recipient's gut microbiota composition and confer a health benefit. **~Qin et al., 2017**

The results were spectacular. Patients entered clinical remission immediately, remission was maintained in one case until the writing of this article and for two other cases for 10 to 12 months. **~Laszlo et al., 2016**

Of all the therapies discussed in this book, fecal microbial transplant (FMT) is perhaps the one I am most passionate about. Why? In the medical literature there is case after case of remission in ulcerative colitis using this form of therapy. And if it can happen to them, there's a good chance it can happen to you.

The concept is simple: Stool from one individual, a healthy individual, is transferred to the gut of another individual, a sick individual, an individual like you, to confer a health benefit. No one is chuckling or cracking a joke while performing this procedure. This is serious business! He or she knows they are playing with power. I know they are playing with power. And soon, so will you.

And with that, let's take a few minutes and go back in time.

FMT: Brief historical perspective

The history of fecal microbiota transplantation (FMT) dates back even to ancient China. Recently, scientific studies have been looking into FMT as a promising treatment of various diseases, while in the process teaching us about the interaction between the human host and its resident microbial communities. **~de Groot et al., 2017**

In China, sometime during the 4th century AD, the recorded history of FMT began (de Groot et al., 2017). Why someone thought transferring poop from one individual to another individual would be a good idea, is still a mystery. But a thought is a powerful thing, and a medical therapy was born. And if you believe your doctor knows what he or she is doing, you'll drink just about anything, particularly if your life is on the line. According to the historical record, the Chinese called this early form of FMT "yellow soup." It must have tasted like crap.

Taste buds be damned, the practice caught on and began its march through the pages of history.

> *By the 16th century, the Chinese had developed a variety of feces-derived products for gastrointestinal complaints as well as systemic symptoms such as fever and pain.* (de Groot et al., 2017)

I could go on and on about the "colorful" history of FMT, there are so many interesting things to discuss, but I need to move things along. However, I will add this: Be glad you don't live in a region where camel poop is in generous supply, or it could be offered to you in your hour of need. Astonishingly, and as recently as World War II, German soldiers ate camel poop to prevent infectious gastroenteritis (de Groot et al., 2017). They learned it from the locals. It must have tasted like . . . well, you know.

Fast forward to today. Thanks to the weight of scientific evidence, including an abundance of successful case reports, there is clear justification of the use of FMT in a variety of medical conditions, including ulcerative colitis—conditions where an abnormal intestinal microflora plays a supporting and decisive role. And due to its effectiveness, FMT is currently an FDA-approved treatment for one form of inflammatory bowel disease, pseudomembranous colitis. I should tell you more.

Pseudomembranous colitis is an extremely serious medical condition caused by the bacterium *Clostridium difficile* (*C-diff*). Worldwide, it costs *"over $4.8 billion per year in healthcare costs."* (Winston and Theriot, 2016) It used to kill a lot of people, and still does—to the tune of 29,000 individuals per year in the USA alone (CDC, 2017). But it doesn't have to. FMT can stop it, dead in its tracts, and with a high probability of success.

> *Fecal microbiota transplantation (FMT) is a highly effective therapy of recurrent Clostridium difficile infection (CDI) with consistent disease resolution rates of 85%–90% after 1 treatment and up to 100% after a second treatment, using either fresh or cryopreserved stool from healthy, well-characterized donors.* (Ott et al., 2017)

Antibiotic use in medicine gives rise to the growth of *C-diff*, as antibiotics kill off a lot of beneficial bacteria that ordinarily hold in check the overgrowth of this pathogen (Baktash et al., 2018; Wilson et al., 2019). *C-diff* is a major problem occurring in the general patient population and has apparently become more prevalent in those who suffer from ulcerative colitis (Kariv et al., 2010). And if suffering from ulcerative colitis alone wasn't bad enough, add *C-diff* to the mix to see what happens. This infection can *". . . worsen UC and increase the risk for colectomy or even death . . .."* (Seicean et al., 2014)

"Oh! Let's not get carried away, now," seems to be the attitude of the FDA. Unacceptable to me and disappointing to many others, in 2013 the FDA declared FMT a drug and restricted its use only for the treatment of *C-diff* (Aroniadis and Brandt, 2014). And with that, the FDA put the brakes on the use of FMT as a treatment for ulcerative colitis. They said, in effect, "You can't have it." Have they not heard of your plight? Have you no right to try? Is not your microbiome disturbed way beyond belief?

The microbiome is clearly disturbed in ulcerative colitis. One clear example: *". . . FMT from UC donors to normal recipient rats triggered UC symptoms, UC-prone microbial shift, and host metabolic adaption."* (Yan et al., 2018) As to be expected, once the rats realized what was going on, they demanded FMT from a healthy human (or a healthy rat) to reverse a disease process that was hideous, unacceptable, and destroying their lives. But they were out of luck. Characteristically, the FDA said, in effect, "You can't have it."

And so, we have arrived at a point in history of FMT where you may need it, you may want it, you may be at the end of your rope with nowhere else to turn, but in you hour of need it is placed beyond your reach.

I get it, the thought of FMT may not be appealing to you (I'll work on that), but it is appealing to the vast majority of ulcerative colitis patients who would jump at the chance to take advantage of this therapy (Kahn et al., 2013). To underscore,

Our patients showed that they were willing to receive this new method despite its unappealing nature, for its [sic] better to have FMT than to be tortured by the disease. (Wei et al., 2015)

And the reasons for choosing FMT, the reasons for its success, just keep piling up.

What it can do for you

The aim of FMT is to reintroduce a stable community of GI microbes from a healthy donor to replace the disrupted populations in a diseased individual. **~Guinane and Cotter, 2013**

FMT for Ulcerative colitis has been described in several publications which showed complete resolution of all symptoms even cessation of medications without relapse. ***Recent studies*** *have confirmed these findings; a meta-analysis of FMT for patients with IBD found that* ***63% of patients with UC entered remission, 76% were able to stop taking medications for IBD, and 76% experienced a reduction in gastrointestinal symptoms.*** **~Wei et al., 2015, emphasis added**

Dealing with inflammation using drug therapy is something quite different than dealing with a disturbed microbiome with FMT. Indeed, FMT challenges the status quo. I'm ok with that. Drug therapy and little else *should* be challenged. Why not throw at ulcerative colitis all the weapons we have at our disposal, particularly the ones most promising? And speaking of promising, FMT has "promising" written all over it. It has "success" written all over it, too.

FMT is, of course, the transfer of healthy microbiome from donor to recipient, but it is so much more. The following is a review of the benefits FMT has to offer:

- FMT stabilizes/balances immune responses (Shen et al., 2018)

- FMT restores numbers of anti-inflammatory bacteria (Shen et al., 2018)

- FMT transfers secondary bile acids to the recipient, correcting a secondary bile acid deficiency and suppressing the growth of unfavorable bacteria (Nie et al., 2015; Baktash et al., 2018)

- FMT transfers antimicrobial peptides from donor to recipient (Baktash et al., 2018)

- FMT induces synthesis of immunoglobins IgA, IgG, IgM—antibodies that recognize and neutralize a variety of pathogens (Shen et al., 2018)

- FMT transfers a stable microbiome, an ecosystem of organisms in balance with each other (Guinane and Cotter, 2013)

- FMT transfers bacteriophages—viruses that attack and kill pathogenic bacteria and suppress their numbers (Bojanova and Bordenstein, 2016; Zuo et al., 2018; Baktash et al., 2018)

- FMT reduces intestinal permeability (Shen et al., 2018)

- FMT increases the production of butyrate (a fatty acid important to the health of the colonocyte and a modulator of immune responses) (Shen et al., 2018)

- FMT increases the acidity of the colonic environment, favoring the growth of beneficial bacteria and inhibiting the growth of pathogenic bacteria (Shen et al., 2018)

- FMT may help resolve extra-intestinal manifestations of IBD (e.g., skin lesions, remote infections) (Cui et al., 2015)

There is no single therapy in existence that offers more than one or a few of the above-mentioned benefits, those ascribed to FMT. With FMT

you get it all! No wonder it can induce remission in ulcerative colitis, rapidly and with long-lasting effect. And not a single taste bud need be involved.

A procedure, not a meal

> *FMT for refractory UC has been described in 3 publications, comprising 9 patients, all of whom had severe, active, long-standing UC . . .. FMT was administered as retention enemas and resulted in the complete resolution of all symptoms with cessation of UC medications within 6 weeks without relapse. Remission was maintained for up to 13 years, and follow-up colonoscopy in 8 of the 9 patients showed no evidence of UC . . . or only mild chronic inflammation . . ..* **~Aroniadis and Brandt, 2014**

Fortunately, advances in medical technology allows us to go beyond "yellow soup" and a camel poop energy bar in our quest to transfer gut bacteria from one individual to another. (Camels are individuals, too.) Today, we have colonoscopes, we have electric blenders, we have filters, we have capsules, we have donor screening strategies and technologies, we have successful case reports—we have it all!

FMT is, itself, a rather straight-forward and *"elegantly simple"* procedure (Borody et al., 2014). But before the procedure is performed (in straight-forward, elegant fashion), the FMT donor is carefully screened. I won't go into great detail on donor screening here, but obviously a suitable donor needs to be healthy and living a healthy lifestyle, is someone without recent antibiotic use, and should be an individual without a current or recent medical condition that could potentially transfer a pathogen to a recipient. Blood tests are used to rule out transmissible disease. Finally, a stool sample from the potential donor is screened for gastrointestinal pathogens and parasites before the potential donor receives the seal of approval. All this is exceptionally laid out in DeFilipp et al., 2019.

Although a family member may be the ideal donor, a suitable FMT donor may be a professional. In the crazy world you live in, some people

sell their poop to supplement their income, and some people sell that poop to earn a living. Today, stool can be purchased from a stool bank. As to be expected, the donors used are carefully screened and their stool is thoroughly examined to make sure it is disease-free and the best that money can buy.

So, it's a go! The stool has been collected (or purchased), and it's time to perform the procedure. But first, the stool is blinded with saline, filtered, then placed in large syringes to be instilled via a colonoscope or via an enema tube. If the stool is from a stool bank, ordinarily frozen, it must first be thawed; otherwise, the procedure is essentially the same as described above.

As an alternative to the above, FMT can be taken in pill form, with the donor and the donated stool meeting all safety requirements. If there is a happy face on the pill bottle, you know it can be trusted. Unfortunately, the "pill" is awfully big, and many pills need to be taken to constitute a single dose. FMT in pill form is a highly effective approach for *C-diff* (Ramai et al., 2019). And it looks like this approach will work for the ulcerative colitis patient, as well.

In 2017, seven patients suffering from ulcerative colitis were given something else to complain about (Cold et al., 2019). Can you imagine swallowing 25 poop-filled capsules (rather large) each day, taken on an empty stomach, and for a period of *50 days?!!* Just the regimen alone is enough to make one sick. But apparently it doesn't. *"All participants completed the treatment and no serious adverse events were reported throughout the study period."* (Cold et al., 2019) In the study, at two weeks, three of the seven participants were in clinical remission. By week eight, two more participants achieved clinical remission. And at six months, four participants remained in clinical remission. That's pretty impressive. But it better be impressive! The FMT pills cost about $65 each, and a fifty-day supply (1,250 poop-filled pills) will set you back $81,250.

Whether taken in pill form, whether delivered by a tube placed through the nose and into the stomach (NG tube), or administered in liquid form via an enema tube or colonoscope, there is no doubt that FMT

can be an effective and relatively safe therapy in the battle against ulcerative colitis. There are stories I could tell.

Stories of success

> *In January 1989, Bennet and Brinkman published a case of FMT in non-CDI [C-diff infection] UC, documenting reversal of Bennet's own colitis after large-volume retention enemas of healthy donor flora 6 months prior. Before FMT, he reported continuously active, severe UC of 7 years' duration. At 3 months post-FMT, however, the patient was asymptomatic in the absence of UC therapy for the first time in 11 years, with no active inflammation.* (Borody and Campbell, 2012)

Historically, the modern use of FMT as a therapy for ulcerative colitis began in 1988 (Bennett and Brinkman, 1989; Fang et al., 2018). Credited as the first ulcerative colitis patient to receive FMT, was a gastroenterologist who personally knew this disease all too well (Borody et al., 2014). Frankly, he hated it! This is his story:

Case report: Dr. Justin D. Bennet

For a period of eleven years prior to his fecal transplant, Dr. Bennet experienced *"continuously active, severe"* ulcerative colitis for seven of the eleven years he was battling this disease. *"The condition was refactory to standard management including steroids and sulphasalazine and every time daily prednisone dosage was reduced below 30 mg severe symptoms . . . recurred."* (Bennet and Brinkman, 1989) Motivated by the belief that gut bacteria were in some way behind a disease that was so unrelenting, he set up an experiment designed to replace his diseased microflora with an infusion of disease-free donor stool. The experiment was performed, and the rest is history. *"At 3 months post-FMT, . . . the patient was asymptomatic in the absence of UC therapy for the first time in 11 years, with no active inflammation."* (Borody and Campbell, 2012)

Case report: Johnathan

Dr. Bennet may not be the first ulcerative colitis patient to receive a fecal transplant, after all. It may be Johnathan. Both individuals received their FMTs in 1988, and both case reports were published in 1989 (Bennet and Brinkman, 1989; Borody et al., 2014) But regardless of who was first, they each have an impressive story to tell. Get used to the word impressive.

Johnathan was 45 years old at the time of his fecal transplant. His ulcerative colitis had only been of 18-month duration but was extensive and totally unacceptable. Current therapy (olsalazine) was inadequate. *"The patient underwent an exchange of bowel flora, and his condition improved sufficiently to cease all treatment within days."* (Borody et al., 1989) At three months post-FMT, his colonoscopy showed a normal looking colon and mucosal biopsies also looked normal (Borody et al., 1989). Twenty-three years later, Johnathan remained *"asymptomatic and in histologic remission."* (Borody et al., 2012). And all this was the result of ***only one FMT!***

Case Report: Shelly

Shelly's ulcerative colitis started at age 11. At the time of her FMT, she was *"A 21-year-old patient with a 10-year history of severe UC, uncontrolled with anti-inflammatory agents, steroids, antibiotics, and finally anti–tumor necrosis factor therapy . . .."* (Borody et al., 2012) Time to act! And there was no fooling around.

> *Pre-FMT symptoms included severe diarrhea with marked urgency and presence of blood and mucus. The patient underwent colonoscopy where the first FMT was administered. After this, daily rectal infusions were performed for 7 days followed by 26 weekly rectal infusions. The patient experienced an immediate reduction in symptoms, passing 2 formed stools daily without blood, urgency, or mucus. Follow-up colonoscopy at 12 months revealed virtually nil*

inflammation or edema and she remains clinically well at 12 months on no medication. (Borody et al., 2012)

I'm happy for Shelly. Shelly is happy for Shelly. Her doctor is still smiling.

Case Report: Li Jie

Li Jie lives in China. He was 24 years old at the time of his FMT—presenting with a 7-year history of recurrent ulcerative colitis (Ni et al., 2016). His disease was extensive, involving the entire colon. As a constant reminder of the severity of his disease, Li Jie found himself passing 4-6 mucopurlent, bloody stools per day. I can certainly see why FMT was offered. Aside from the removal of his entire colon, there was nowhere else to go. Interestingly, in his case the route of passage was via a tube placed through the abdominal wall, with the tip of the tube residing in the cecum, the terminal portion of the small intestine which is positioned right above the beginning of the colon. How innovative! Makes sense.

The donor in this case was Li Jie's father, who was carefully screened and certified free of transmissible disease. With the tube in place and the stool produced and processed, it was time to turn things around. But was it too late?

In this case, in addition to the donor stool, 3 grams of mesalazine was also given (route not specified). Additionally, Li Jie was maintained on IV and tube feeding during his hospitalization, with tube feeding supplying his nutritional needs until 1 month post-FMT. After which, a normal diet was resumed. Clearly, Li Jie was very ill and FMT was offered as a last-resort, rescue therapy. Clearly, his physicians were putting FMT to the test. Likely, fingers were crossed.

Well, it worked. But it was not easy. After the initial FMT, it was repeated once a day for one month. This, of course, kept Dad very busy and eating with purpose. Once Li Jei was released from the hospital, the fecal transplants continued twice weekly for another three months. After

two months at home, his tube feedings ended and he resumed a normal diet. The fecal transplants ended a month later. Let the historical record show, Dad was all pooped out.

Within a week after his first FMT, Li Jie was symptom-free. At one-month post-FMT, his colonoscopy showed only small scattered ulcers in the rectum, with the rest of the colon looking relatively normal. The use of mesalazine 2 grams daily ended at that point in time. At three months post-FMT the colonoscopy showed no signs of disease in colon or rectum. Twelve months later, Li Jie remained symptom free. His life was back.

Comment: If only I had written this book 10 years earlier, if only it had been translated into Chinese, if only Li Jie had read my book and put into practice at least some of the life-style changes and alternative and complimentary therapies outlined therein, then perhaps he would have achieved remission much earlier and would not have reached the point of requiring such extreme measures to turn things around.

Case Report: Eddie

Eddie was 25 years old at the time of his fecal transplant (Borody et al., 2003). Six years dealing with ulcerative colitis was long enough. His life revolved around passing frequent bloody stools, revolved around diarrhea 6-7 times a day, revolved around abdominal pain, abdominal cramping, fevers, weight loss, nausea, and revolved around misery. The medications used to treat his ulcerative colitis became ineffective. A more potentially dangerous drug, azathioprine (Imuran), was offered to the patient but was refused. Also, at the time of his FMT, Eddie's liver enzymes were elevated indicating substantial liver injury, secondary to sclerosing cholangitis.

Prior to his FMT, *"Colonoscopy confirmed pancolitis with granular mucosa, contact bleeding, microulceration and histologically active chronic colitis."* (Borody et al., 2003)

The donor was his female partner, appropriately screened to rule out transmissible disease.

Before fecal transplant, Eddie took antibiotics for a number of days, as a measure employed to suppress the numbers of specific bacteria.

Rather than via a colonoscopy, the fecal transfer was through an enema tube. Five transplants were given on consecutive days. Eddie's current medications (salazopyrin, prednisone) were continued. At the end of the transplant series, salazopyrin was discontinued and a five-week prednisone taper was initiated. Eddie was on his way to a better life.

At one-week post-transplant, Eddie's symptoms markedly improved, along with reductions in stool frequency. By four months post-fecal transplant, he was asymptomatic without medical treatment and defecating 2-3 times/day without bleeding. Furthermore, his liver enzymes returned to normal. And to put icing on the cake,

> *On his most recent review* ***after 13 years follow-up without other therapy he had no clinical or colonoscopic evidence of UC and histopathology samples from several sites around the colon were normal.*** (Borody et al., 2003, emphasis added)

Case report: Arjun

Arjun was 6 years old at the time of his fecal transplant (Butta et al., 2018). He was facing a life of permanent damage, at the hands of a hideous disease. His ulcerative colitis was advanced; his meds and specialized diet were not up to the task. According the report, Arjun had ulcerative colitis for at least two years prior to his fecal transplant. Imagine, an ulcerative colitis victim at 4 years old! Boy, do I hate this disease.

He presented in clinic *"with history of loose, watery stools with mucus and blood for one year associated with periumbilical pain."* (Butta et al., 2018) His colonoscopy was *"suggestive of pancolitis."* Enough was enough, and his parents requested FMT to save their son from the clutches of this disease. It is safe to say, they are glad they did.

The donor choice was Arjun's father, who was screened and tested and met safety requirements. I don't think the long arm of the FDA reaches all the way to India, so I don't believe the message "You can't have it" got through.

Arjun did not receive antibiotics or bowel prep prior to this fecal transplant, as is often the case. The first transplant was delivered as a small-volume enema every 15 minutes for one hour. This treatment protocol was repeated daily for 5 days. Each small volume enema (60 ml each) was instilled slowly over a 5-minute period, and Arjun was turned 180 degrees, from left side to right side during each transplant session—an effort to disperse the enema to reach areas further up in the colon.

By the end of the 5 days of therapy, Arjun's Paediatric Ulcerative Colitis Disease Activity Index dropped from 35 to 15. Three years later, he was eating a normal diet and his ulcerative colitis meds were being tapered. *"The child is showing improvement in symptoms and has not had any relapse since then."* (Butta et al., 2018)

Although not out or the woods yet, Arjun was clearly improved and may continue to progress to a point where victory can be declared. That being said, I'm still a little worried about him. In the future, Arjun may need a repeat series of FMTs to turn things around and again head him in the right direction. I hope someone doesn't say . . . well, you know.

Case report: Kumar

Kumar was forty-four at the time he received a 2-week series of fecal transplants—presenting with a history of ulcerative colitis extending over a period of 11 years and undergoing a severe relapse (Seth et al., 2016). For the eleven-year period, Kumar reported *"frequent relapse despite daily sulfasalazine 4 g, azathioprine 125 mg, and rectal 5-aminosalicylic acid. Repeated use of corticosteroids led to cataract. At enrollment, he was passing eight stools a day with blood with a Mayo score of 9 (3+1+3+2)."* (Seth et al., 2016)

The donor of choice was Kumar's brother-in-law, who was carefully screened and declared to be one heck of a brother-in-law (and free of transmissible disease).

It all went well. Three sessions of FMT, at 2-week intervals, was all it took. (It also took a colonocope and a blender.) And the results were pleasing:

> *Clinical response to FMT was noted within 2 weeks of first session of FMT. Complete remission with Mayo scores improving to 0 for stool frequency, blood in stool, and colonoscopy were noted at weeks 4, 8, and 12, respectively. Significant histological improvement, as determined with Geboes score, was noted at 16 weeks. Azathioprine and 5- ASA were tapered, and he remains in clinical and endoscopic remission 10 months after FMT and 5 months after withdrawal of all medication. Histopathology at 10 months follow up was normal.* (Seth et al., 2016)

Case report: Daniel

Daniel (whose story is also told in *Chapter 7*) presented in clinic with worsening ulcerative colitis. Previously, he was successfully treated with corticosteroids, 5 ASA, and Azathioprin for the better part of 12 years (Laszlo and Pascu, 2014). Then, due to a return of symptoms, biological therapy (Infliximab; Remecade) was started and quieted his symptoms and gave Daniel another year of remission. Unfortunately, ulcerative colitis symptoms returned. A decision was made to give FMT a try, and a first degree relative was screened and determined free from transmissible disease.

The fecal transplant procedure was described as "transcolonic," performed using a colonoscope. Post-FMT, the patient was given medications to slow GI mobility, and was instructed to stay in a supine (lying flat on back) position for a non-specified period of time. Obviously, the goal here was to allow the transplanted stool to remain in Daniel's colon as long as reasonably possible, allowing, within the colon, a

prolonged exposure time to the transplanted material (before it's time to go).

For Daniel, *"clinical and biological remission was achieved."* (Laszlo and Pascu, 2014). *"Immediately after FMT the biological therapy was stopped."* (Laszlo and Pascu, 2014). At follow-up, 5 months post-FMT, clinical and endoscopic remission was confirmed. Daniel continued on ASA 2g/day. Intriguingly, all this progress from 1 fecal transplant.

But is only one enough? How about 80 FMTs? Will 80 be enough?

Case report: Shawn

Let's let Dr. Borody and colleagues tell Shawn's story.

> *A 33-year-old male with ulcerative colitis presented with abdominal pain, bloody diarrhea, and mucus discharge. Failing standard antiinflammatory drugs with frequent relapses, fecal microbiota transplantation (FMT) was introduced. FMT was first administered via a transcolonoscopic route followed by daily enemas, reducing to twice weekly, weekly, and then fortnightly. After 80 FMT infusions, he was passing normal stool once per day and was off all drugs for 7 months. He was recolonoscoped, and the difference is shown."* (Borody et al., 2013)

If you would like to see Shawn's pre- and post-FMT photos, go online and find the following paper:

> Borody TJ, Paramsothy S, Agrawal G. **Fecal microbiota transplantation: indications, methods, evidence, and future directions**. Current gastroenterology reports. 2013 Aug 1;15(8):337.

Case Report: Ethan

Again, let's let Dr. Borody and colleagues tell the story. I go on forever. They know how to be brief and get right to the point. Here is Ethan's story:

A 38-year-old man with a 6-year history of ulcerative colitis, concurrent multiple sclerosis, sacroilitis and sclerosing cholangitis was treated with an initial transcolonoscopic FMT infusion, followed by over 100 FMT enemas during the next 12 months. After 4 weeks of daily FMT enemas, the patient's IBD symptoms had dramatically improved, liver biochemical tests had normalized and sacroilitis pain was absent. (Borody et al., 2014)

We've got pictures! If you would like to see Ethan's pre- and post-FMT photos, go online and find the following paper:

Borody TJ, Brandt LJ, Paramsothy S. **Therapeutic faecal microbiota transplantation: current status and future developments.** Current opinion in gastroenterology. 2014 Jan;30(1):97.

Case Report: Keiko

Keiko is a 11-year old Japanese girl with severe ulcerative colitis, refractory to both steroids and Infliximab (Remicade) (Shimizu et al., 2016). *"Before FMT, she had been hospitalized five times within 6 months because of disease flare and had missed most school days."* (Shimizu et al., 2016) Although she was enjoying a brief period of remission from clinical symptoms, her disease had reached a point where it was recommended that she have her colon removed. Who wants this? Keiko didn't. Mom didn't. Dad didn't. Mom knew what *this* was like! She, too, had a history of ulcerative colitis and her colon was removed because of colon cancer. This is a family who knew, firsthand, what life is like without a colon. Unsurprisingly, the patient and both parents requested a fecal transplant *"to save her colon"* (Shimizu et al., 2016).

Due to Mom's medical history, she was automatically disqualified from being the stool donor. However, Dad was healthy, and careful screening qualified him to be the donor.

The fecal transplants were described as follows:

> *The first FMT was performed via colonoscopy to distribute the suspension throughout the colon and observe the colonic mucosa. The patient had undergone bowel preparation with magnesium citrate the day before the first colonoscopic FMT. After the first colonoscopic FMT, FMT by retention enema were performed for the next 4 days. After this 5 day sequential course, 11 additional FMT by retention enema were performed every 2 to 4 weeks over 10 months. FMT by retention enema was performed as described by Kunde et al. with minor modifications. Fecal material was prepared in five–six 50 mL syringes. Each aliquot was infused over 5 min followed by positional change of the recipient in order to move the fecal content proximally. The recipient was asked if she was willing to proceed after each aliquot. She successfully received all fecal material prepared for FMT throughout the treatment course.* (Shimizu et al., 2016)

And the results were quite remarkable. And keep in mind, this was the experience of an 11-year old girl who was on the verge of undergoing a colectomy.

> *Shortly after the first 5 day course, UC recurred, and scheduled IFX [Infliximab] infusion improved her condition. As the FMT continued, the patient remained in clinical remission with a tapering dose of corticosteroid and scheduled IFX. At week 40, she was in clinical remission with only 1.5 mg corticosteroid.* (Shimizu et al., 2016)

Forty weeks post-FMT, Keiko remained in clinical remission. At the time, *". . . endoscopy showed relative improvement in the sigmoid colon and continuous inflammation in the transverse colon while pathology showed active inflammation with crypt abscesses and paucity of crypts."* (Shimizu et al., 2016)

I hope Keiko continues to improve. If things start heading in the wrong direction, it is my hope that there will be another series of FMTs in her future.

Time for one more case report? Of course you do.

Case Report: Olivia

Olivia was 28 at the time she underwent a series of 5 fecal transplants in her battle against ulcerative colitis (Borody et al., 2003). Imagine having one half of your entire life dominated by this dreadful disease. Fourteen years is enough—all the diarrhea, bleeding, cramping, nausea, vomiting, fever and fatigue Olivia had to endure. Her meds—prednisone, olsalazine, mercaptopurine—were no match for the disease.

After Olivia's series of fecal transplants, using stool donated by her brother-in-law, mercaptopurine was immediately stopped, and apparently a taper of her prednisone began. Olsalazine was continued for a further 6 weeks. Post-FMT, *"Immediate improvements included reduced bleeding, urgency, nausea, and vomiting, while abdominal cramping persisted for 1 week."* (Borody et al., 2003)

Unfortunately, *"The patient experienced 1 episode of bleeding 3 weeks post-HPI [post-FMT] and the total withdrawal of prednisone was delayed until week 6."* (Borody et al., 2003) Other than this little "speed bump" on the road to recovery, two months following fecal transplant Olivia was *"well, with no urgency or bleeding."*

I like this story. I like all these stories!

> *At 2 years follow-up, she had had no more UC relapses despite episodes of stress and continued to be clinically, colonoscopically, and histologically disease-free without treatment.* (Borody et al., 2003)

Note: With the exception of Dr. Justin D. Bennet, the names in this section are fictious.

Thoughts on case reports and clinical trials

ClinicalTrials.gov currently lists more than 300 studies evaluating FMT for various indications, primarily gastrointestinal, but also for neurologic, behavioral, and metabolic conditions. **~DeFilipp et al., 2019**

The treatment effects on patients who have undergone FMT to treat UC appear very promising, especially for patients with multiple infusions administered via the lower gastrointestinal tract. **~Fang et al., 2018, emphasis added**

Additionally, FMT provided greater therapeutic benefit in patients whose onset of UC was associated with an alteration in the fecal microbiota from antibiotic use or concomitant colonic infection. Experience with FMT for UC is just beginning, and controlled trials are needed to establish its safety, administration regimen, and therapeutic role, if any. **~Aroniadis and Brandt, 2014**

Impressive care reports are one thing, clinical trials composed of groups of individuals (who are all basically treated the same), are quite another. But taken together, they teach us several valuable lessons. And with respect to FMT, we have learned the following:

First, not everybody responds to FMT. **Second**, one FMT session, or even a few, may not be enough. In fact, as the case reports previously discussed confirm, many, many sessions may be necessary. A relentless effort is often required to defeat a relentless disease. **Third**, the continuation of ulcerative colitis medications may be necessary—helpful in association with FMT to achieve and maintain remission. **Fourth**, complications from FMT are rare**. Fifth**, FMT is often used as a rescue therapy rather than used as a front-line treatment, offered earlier in the course of the disease and at a time when FMT, combined with medication, may be more effective. **Finally**, not everything FMT goes smoothly. There can be initial symptoms such as nausea and abdominal pain. The patient may also experience a flare in symptoms. Furthermore,

serious complications, although extremely rare, may occur and may result in death (more later).

Studies evaluating FMT in groups of individuals report many cases of success as well as many cases of failure—sounds like what happens with standard drug therapy! By way of example, if a study only shows, say a 38% success rate, that means 62% did not respond to therapy. However, 38% means welcome relief to one in three. Not too bad! But in ulcerative colitis, the FMT response rate appears to be much higher.

> *Recent studies have confirmed these findings; a meta-analysis of FMT for patients with IBD found that **63% of patients with UC entered remission, 76% were able to stop taking medications for IBD, and 76% experienced a reduction in gastrointestinal symptoms.*** (Wei et al., 2015, emphasis added)

Published a year later from the above report, an analysis of twenty-five studies, comprising of 234 ulcerative colitis patients, found that FMT induced **remission in 41% of study subjects and demonstrated a clinical response rate of 65%** (Shi et al., 2016). Not quite as good as the above report, but still impressive. Of note: *"Most adverse events were slight and self-resolving."* (Shi et al., 2016)

Most recently, a meta-analysis found only **26%** of adults and only **10%** of pediatric ulcerative colitis patients achieved clinical remission from FMT (Fang et al., 2019). I would say "Goodbye" to this meta-analysis and show it to the door. The study subjects involved were treated so differently in the various studies analyzed, that it can only muddy the waters. Some subjects were given fresh stool; some were given frozen then thawed stool. Some fecal transplants were given by colonoscopy; some by enema. Some subjects were given 2 fecal transplants; some were given 40. **Now, is this any way to judge the effectiveness of a therapy?** I think not. If it takes 40 FMTs for some subjects to achieve and sustain remission, why would two or three FMTs tell us anything of value regarding the percentage of effectiveness of this therapy? Should FMT be denied to the ulcerative colitis patient based on this kind of foolishness? I think not.

From case reports and research studies, it seems clear: FMT can be a very effective therapy to achieve remission, but likely it will take many transplant sessions to turn things around. There is a great case to be made for FMT to be offered to the patient in need, particularly so if nothing else is working.

What's up with that?

Fortunately, advances in medical technology allow us to go beyond "yellow soup" and a camel poop energy bar in our quest to transfer gut bacteria from one individual to another. (Camels are individuals, too.)
~The Author, 2020

With a therapy as truly bizarre as FMT, there is bound to be a few strange things about this therapy that show up unannounced, pop up from out of the blue, things no one would *ever* expect to see. I'll point out a few.

Surprisingly, at least with respect to *C-diff*, filtered donor stool, filtered to remove all bacteria, works just as well as normal, bacteria-replete FMT (Ott et al., 2017; Zuo et al., 2018). Incredible! So unexpected. When it comes to the effectiveness of FMT, it may not be the bacteria after all! Apparently, the other things that are found in stool, such as bile acids, bacteria-killing viruses, or factors that promote healing, are what make FMT an effective therapy. (see Bojananova and Bordenstein, 2016; Baktash et al., 2018).

Even more surprising, you, the ulcerative colitis patient, can actually donate your own stool, have it processed, return it to the very colon from whence it came, and remission can be achieved (Costello et al., 2019). Placebo response? Some cases, maybe. But in every case? Maybe not. **It should be pointed out that stool, once processed in typical FMT-fashion, is modified in a substantial way.** It is not the same coming back as it was coming out. The reason? When you blend stool you aerate it, and by doing so, the oxygen kills perhaps a majority of the good bacteria you were counting on to come to the aid of the FMT recipient. Therefore,

the bacteria that are not killed by oxygen, those capable of thriving in the presence of oxygen, are selected to dominate. An aerated stool is a modified stool—but, amazingly, it still works! However, it is suggested by some investigators that aerated stool may have reduced effectiveness in FMT (Rogers and Bruce, 2013; Costello et al., 2019).

The promise and success of FMT has given rise to a few variations of the theme. It has been suggested that an ulcerative colitis patient could donate stool when his or her disease is in remission, to be frozen, banked, then later returned as a FMT in the event that relapse occurs.

> *For those patients with mild IBD, it may be good that the fecal samples can be collected and stored in the remission stage and offered to the same patients when they come into the active stage of IBD.* (Wang et al., 2014)

Think of it! You are both the donor and recipient! No screening required! You come to your own rescue, and you do it with your own poop! This is a very novel concept when it comes to FMT. Might work! I can't wait to see this thing really put to the test.

Related to the above, is a study that demonstrated the feasibility of banking stool from a patient before antibiotic therapy, to be returned later, to the same patient, to restore microbiota diversity post-antibiotic use (Taur et al., 2018). It worked!

Another strange thing we have learned along the way is that obesity, long linked to a person's fecal microbiome, can be transferred to the FMT recipient (Alang and Kelly, 2015). *"We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor."* (Alang and Kelly, 2015) And that brings us up to this: The choice of a donor may make a *big* difference when it comes to success.

Apparently, although certified as healthy and free of transmissible disease, not all donors are created equal. Observations that some donors produce better results than do other donors, has given rise to the concept of a *"super donor"* (Wilson et al., 2019). Donor diet may be a factor. My belief is, a vegetarian or semi-vegetarian (and free of transmissible

disease) would be an excellent choice, a "super donor" if you will. These two dietary practices promote an exceptional healthy bowel microflora, as previously discussed.

A final, related strange thing to consider, and I've mentioned this before, but it bears repeating: A fecal transplant from an ulcerative colitis patent given to a healthy rat, transfers ulcerative to the rat. *". . . FMT from UC donors to normal recipient rats triggered UC symptoms, UC-prone microbial shift, and host metabolic adaption."* (Yan et al., 2018) My firm belief is, if you hate a rat so much that you would intentionally give it ulcerative colitis, you need to get a hold of yourself and seek professional help. You are really messed up.

Not without risk, not without danger

> *FMT is generally of safety and tolerance with few serious adverse events. As many patients need to receive more than one FMT therapy, more procedural complications will probably be reported due to the invasion of procedure. Despite rigorous donor selection and screening for infectious agents, known and unknown risks still remain a major problem for widely application of FMT in UC.* **~Shi et al., 2016**

> *Although no serious adverse events were reported, some patients experienced fever, chills, bloating, flatulence, vomiting, diarrhea, and abdominal tenderness. The adverse events were more likely with nasogastric route of administration for FMT. Flares of UC following FMT were also described.* **~Seth et al., 2016**

Medicine poses risks, but generally acceptable risks. But for a few, the ultimate price may be paid. (Oh, the stories I could tell.) This is true with drug therapy; this is true with FMT.

In the modern day, there are at least three individuals who have lost their life as a result of complications from FMT. As horrifying as this sounds, FMT is still regarded as generally safe. Keep in mind, there is always a risk to be assumed when on the receiving end of medical care.

Despite my little disagreement with the "You can't have it" FDA, I will cut the FDA (and other regulators) some slack. Clearly, they are committed to safety. They want every therapy to be safe, as safe as possible. Clearly, they have your best interests in mind.

> *The regulators have a formidable task to develop policies that optimize access to important therapies, ensure their safety and efficacy, and allow innovation so that next-generation products can benefit future patients even more. It is clear that FMT opened a new frontier of medicine and demonstrated the healing powers within our own bodies. It is important that we are guided by up-to-date science on this journey. At the same time we need to be careful not to allow limited scientific knowledge turn into arrogance. We are still taking only the initial steps, even though they have already saved thousands of lives.* (Khoruts, 2017)

Back to the three deaths associated with FMT, I should tell you more. One death was from fecal aspiration (fecal material entering the lungs) which accidently occurred during the procedure (Aroniadis and Brandt, 2014). I can't begin to tell you how dreadful fecal aspiration is. Another reported death was due to fecal material entering the abdominal cavity due to a dislodged transabdominal gastric tube, the route used for the fecal transfer to treat the patient's *C-diff* (Solari et al., 2014). Under such circumstances an overwhelming infection results, which can lead to death. And tragically, in this case, death occurred. The third recorded death occurred quite recently and was related to an unanticipated transfer of an antibiotic-resistant *E. Coli* bacterium from donor to recipient using FMT in pill form, resulting in an overwhelming blood infection called sepsis (DeFilipp et al., 2019). Importantly, this unfortunate patient was concurrently being treated by chemotherapy drugs that <u>profoundly</u> suppress the immune system. Is this case report an appropriate example to be used to justify withholding FMT . . . from you?

Clearly, with respect to FMT, care should be taken. *Clearly!* Care to comprehensively screen the health of the potential donor. Care to

adequately screen the stool of the potential donor, and to the latest standards. Care to administer the stool with care—with tubes and devices carefully evaluated to ensure a safe procedure will occur. Care to exclude patients who are profoundly immunosuppressed. Such are the lessons of the three patients whose fecal transplants ended in disaster.

> *FMT is often perceived as "natural" remedy by many patients and physicians. However, considering the fact that the transfer of complex microbiota can modify the host phenotype with unknown long-term effects, it is preferable to exclude certain categories of patients in which the delivery of FMT may worsen their condition, or it may even be fatal. For example, patients with severe bowel disease cannot undergo colonoscopy, while those with severe immunosuppression and decompensated liver cirrhosis are excluded considering the potential risk of enteric microbe transmission from donor's stool.* (Sunkara et al., 2018)

Meeting safety requirements is *so* important. With respect to fecal transplants destined to be delivered through a nasogastric (NG) tube, it is necessary for the correctness of tube position to be *"verified with x-ray before transplant"* (Shi et al., 2016).

Of course, there is always a risk of bowel perforation anytime instrumentation is performed (Ramai et al., 2019). Furthermore, there are risks associated with anesthesia, required for procedures involving a a colonoscope, the instrument typically used in clinic to perform the fecal transplant (Ramai et al., 2019).

In Medicine, there are risks everywhere! But, by and large, these are acceptable risks both physician and patient are willing to take.

Maybe you can have it (after all)

People are going the do-it-yourself route to relieve everything from a child's autism to male pattern baldness to bad breath, according to Catherine

Duff, executive director of The Fecal Transplant Foundation, a nonprofit that is advocating for safer, more widespread access to the treatment. Based on telephone and Internet inquires to her site, she estimates that about 10,000 people do at-home fecal transplants in the U.S. each year. **~*Web*MD, 2015**

Experts Fear FDA Crackdown on FMT Could Backfire **~Blair, 2019**

There is precedent for physician-approved DIY fecal transplantation (Silverman et al., 2010). In the treatment of *C-diff*, multiple relapses can occur and require prompt treatment, which can be readily accomplished in the home setting—no waiting list, no appointment necessary. In the Silverman et al study, seven patients each received a DIY fecal transplant at home, with the donor stool obtained from a carefully screened relative. The results: No adverse effects occurred, and with 100% success, which persisted at 14-month follow-up. A conclusion was reached:

> *Fecal transplantation by low volume enema is an effective and safe option for patients with chronic relapsing CDI, refractory to other therapies. Making this approach available in health care settings has the potential to dramatically increase the number of patients who could benefit from this therapy.* (Silverman et al., 2010)

These are the instructions given to both donor and recipient:

- *Equipment needed: (1) bottle of normal saline (200 mL); (2) standard 2 quart enema bag kit available at a drug store (Life Brand Hot Water Bottle and Syringe kit; Shoppers Drug Mart, Toronto, ON, Canada); and (3) standard kitchen blender (1 L capacity) with markings for volume on side, available at any department store.*

- *Stop vancomycin/metronidazole 24–48 hours before procedure.*

- *Continue S boulardii during transplant and for 60 days afterwards.*

- *Add 50 mL of stool (volume occupied by solid stool) from donor obtained immediately prior to administration (less than 30 minutes) to 200 mL normal saline in the blender.*

- *Mix in the blender until liquefied to 'milkshake' consistency.*

- *Pour mixture (approximately 250 mL) into the enema bag.*

- *Administer enema to patient using instructions provided with enema bag kit. Patient should hold the infusate as long as possible and lie still as long as possible on his or her left side so that the urge to defecate is prevented. Ideally perform the procedure after the first bowel movement of the day (usually in the morning).*

- *If diarrhea recurs within 1 hour, the procedure may be immediately repeated.* (Silverman et al., 2010)

With respect to ulcerative colitis, home FMT is perhaps the only realistic approach, as many follow-up fecal transplant therapy sessions are likely necessary. Recall, some patients require forty, even eighty fecal transplants before victory can be declared. The cost of FMT in clinic, as well as the cost of handful after handful of FMT capsules for home use, are cost prohibitive. Apart from the initial costs of donor screening, which may be as high as $3,600 (Blair, 2019), home FMT is very inexpensive.

This takes us to the question of who the ideal donor would be. In view of the literature, someone who is relative, close friend, or committed neighbor would be the ideal donor, due to the possible need of continuous donor availability and the possibility that many stool donations will be required before victory can be declared. Obviously, such an individual should be living a healthy lifestyle (including diet?), will need to be carefully screened for transmissible disease, and should probably be someone who is not obese, as this can be transmitted.

The bottom line: If you can find a willing physician to approve and guide you in your efforts to treat your ulcerative colitis (or recurrent *C-diff*) with FMT, maybe you can have it after all. Of course, donor selection and screening to the latest standards is essential. FMT is certainly one of the therapies you should *not* undertake all on your own.

My fear—and I share this fear with others (see Kahn et al., 2013)—is that you will go out on your own, FMT yourself without physician approval or guidance, make a mistake with screening or technique, have a negative outcome, and give FMT a bad name. I don't want you to make a mistake. I want you to be safe.

There is a legitimate concern that the strict requirements of the FDA will lead to a backlash—people will be pushed in the direction of doing it themselves regardless of the warnings and restrictions imposed by the FDA, perhaps doing so without proper donor screening and without the direction and guidance of a physician (Blair, 2019). Although unwise, who can blame them? In FMT, there is a readily available, generally safe therapy that can rescue even severe cases of ulcerative colitis, yet someone in the background is saying "You can't have it."

But what if there was a way around this roadblock?

This just might work

> *Despite these hurdles, compassionate drug use does happen. The FDA receives over 1,000 individual use applications per year, and approves over 99% of those requests.* **~American Cancer Society, 2019**

So, you are convinced. FMT is the route you wish to take. There is a strategy for obtaining approval that just might work. Hasn't the FDA declared FMT to be a drug? Investigational drugs can be allowed on the basis of compassion, regardless of their investigational classification (American Cancer Society, 2019). Perhaps you can get a "Yes" by appealing to the FDA to approve FMT for you on compassionate grounds. If willing, your doctor can assist you in this effort.

Alternatively, perhaps you can enroll in a new clinical study, or be somehow tacked on to a clinical study in progress, with the FMT to be performed locally by your physician in clinic or even performed at home.

> *People who aren't in clinical trials might be able to get access to an unapproved drug from the company that makes it in 2 ways:*
>
> - *Through **expanded access programs (EAPs)***
> - *Through **"Right to Try"*** (American Cancer Society, 2019, emphasis added)

Of the two pathways mentioned above, your physician can help you decide the best path to take and can help you navigate through all the paperwork. Get used to the word "paperwork" and the phrase "Try, try again."

The following sources can help you understand it all—compassionate use qualifications, expanded access program inclusion parameters, and "Right to Try" qualifications:

Compassionate Drug Use. American Cancer Society; November 19, 2019 https://www.cancer.org/treatment/treatments-and-side-effects/clinical-trials/compassionate-drug-use.html

Compassionate use Navigator | Information for Patients. kidsvcancer.org; Accessed 01-30-2020 http://www.kidsvcancer.org/wp-content/uploads/2016/01/Navigator-One-Document.pdf

Expanded Access | Information for Patients. U.S. Food & Drug Administration; May 20, 2019 https://www.fda.gov/news-events/expanded-access/expanded-access-information-patients

FDA Fact Sheet | Right to Try. U.S. Food & Drug Administration; 01-14-2020 https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try

Emergency Use and Compassionate Use of Experimental Drugs and Devices. University of California San Francisco; Last update: 06-06-2019 https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=11&ved=2ahUKEwiV3efKrqznAhUWr54KHT3HBRMQFjAKegQIAhAB&url=https%3A%2F%2Firb.ucsf.edu%2Fprintpdf%2F736&usg=AOvVaw1Gyn6DF7gYQmeEzdcIwiGF

In your quest to obtain FMT therapy, when it comes to seeking compassionate care or "Right to Try," ***sell yourself!*** Be rentless in advocating on your behalf. It's your bowel. It's your life. Get your physician on board. Resubmit approval applications, as needed, should the answer come back "You can't have it." Call whomever you think may be of help. Call the Surgeon General. Call the Governor. Call your Representative. Call research centers involved in active FMT studies. Ask them if there is some way they can help. Let everyone know you mean business. Search out every lead. Keep in mind, many patients have declared victory over ulcerative colitis with FMT. And keep in mind, if it can happen to them, there is a good chance it can happen to you.

Loose ends

There are a few more things to discuss before we wrap things up.

First, one drawback to FMT is the cost of donor screening, but there is a nifty way to cut donor screening costs. Find an existing blood donor, or one who is willing to donate blood, to be your prospective stool donor. To qualify to be a blood donor, an individual will first be asked important health screening questions, and their blood will be screened for several transmissible diseases. And as far as transitioning from blood donor to an acceptable stool donor, other relevant laboratory tests can be conducted elsewhere to complete the process of certifying that a person is free from transmissible disease and good to go. As a blood donor, he or she can help other people by donating blood and help you out by pooping for your benefit.

Second, when it comes to FMT, there is reason to believe "the earlier the better." Why wait for ulcerative colitis to get way out of hand? Consider this:

> *FMT may be more efficacious in patients with a recent diagnosis of UC, and this is biologically plausible, as a perturbation in the microbiome might be more easily restored early in the course of the disease. The efficacy of this approach may also be donor dependent and this may explain why some case series have shown promise, and others have had disappointing results.* (Moayyedi et al., 2015, emphasis added)

Third, and for future reference, you should be aware that there is a push for a name change. Instead of Fecal Microbial Transplantation (FMT), in the future it many go by the name, Intestinal Microbiota Transplantation (IMT) (Blair, 2019). Whatever. Just keep in mind, regardless of the name, it is still the same old . . . well you know.

Finally, there is an alternative to FMT, at least with respect to *C diff.* You should probably have an interest in this, as *C-diff* can happen to you, the ulcerative colitis patient. And this alternative may be a substitute for FMT to treat ulcerative colitis and other diseases as well. We'll take up this discussion in the following gray box.

An alternative to FMT

> *These results support the idea that* ***intra-colonic bile acids play a key mechanistic role in the success of FMT****, and suggests that novel therapeutic alternatives for treatment of R-CDI [recurrent-C-Diff] may be developed by targeted manipulation of bile acid composition in the colon.* **~Weingarden et al., 2016A, emphasis added**

> *Although FMT may combat C. difficile [CDI] by multiple mechanisms, including competitive niche exclusion, elaboration of targeted bacteriocins, and upregulation of host immunity, more recent investigations have* ***built a compelling case for a central role of secondary bile acid metabolism in curing CDI.*** **~Weingarden et al., 2016B, emphasis added**

Indeed, the potential for orally administered bile acids as an alternative to FMT is supported by a recent study demonstrating that ***UDCA inhibits the germination of C. difficile spores*** *in vitro [in laboratory setting] and effectively induced and maintained remission from recurrent CDI in a human subject.* **~Hegyi et al., 2018, emphasis added**

Surprisingly, bile acids—specifically secondary bile acids—can come to the rescue of the person with *C-diff*, serving as an alternative to FMT. Likely, secondary bile acids can successfully treat *C-diff* in the ulcerative colitis patient, as well. With respect to *C-diff*, bile acid therapy has been put to the test.

We have successfully treated a patient with refractory, recurrent C. difficile pouchitis with ursodeoxycholic acid (UDCA) after demonstrating that this minor secondary bile acid was inhibitory to her C. difficile isolate. Unfortunately, UDCA is efficiently absorbed into the enterohepatic circulation and might not be applicable to the majority of patients with CDI [C. difficile infection] in the colon. However, certain modified bile analogues can be made resistant to intestinal uptake and achieve high intracolonic concentrations." (Khoruts and Sadowsky, 2016)

So, here is the scoop (FMT term): It has been discovered that patients who have recurrent *C-diff* have a high concentration of primary bile acids in their stool, *"whereas,* ***secondary bile acids are nearly non-existant."*** (Aroniadis and Brandt, 2014, emphasis added) Notably, the fecal bile acid profile of the FMT recipient transitions to resemble the fecal bile acid profile of the donor. Problem solved.

We had previously demonstrated that ***patients with RCDI [recurrent C-diff] completely lack secondary bile acids in their feces****, but have increased levels of taurocholic acid. Within days following FMT, however, the fecal levels of secondary bile acids increase and primary bile acids drop to levels found in the donors.* (Weingarden et al., 2016B)

So clearly, measures that increase secondary bile acids are justified in the battle against *C-diff.* "*The spore germination of C. difficile can be stimulated by some primary bile acids" whereas, C. diff "can be inhibited by secondary acids."* (Nie et al., 2015) And one of the secondary bile acids that inhibit *C-diff* growth is **UDCA** (Nie et al., 2015).

If you will recall from *Chapter 18, Bile acid advantage*, both ***"TUDCA and UDCA are essentially identical molecules."*** (Vang et al., 2015, emphasis added). The exception being, with TUDCA, there is a taurine molecule attached to the UDCA molecule. In the scheme of things, after TUDCA is ingested, a bacterium in the small intestine will remove the taurine and turn it immediately into UDCA. TUDCA is now UDCA. I don't want to get lost in the weeds here, but one should expect that TUDCA is at least as good as UDCA in the treatment of *C-diff*. And may be better as there seems to be a little problem with UDCA.

> *A major limitation of UDCA for this indication is its rapid uptake into the enterohepatic circulation in the small intestine, resulting in low achievable intracolonic concentrations.* (Weingarden et al., 2016B, emphasis added)

Aside from the above, UDCA still seems to be effective. But TUDCA may even work better because *"TUDCA requires active absorption in the terminal ileum whereas UDCA may be absorbed passively throughout the small intestine . . .."* (Rudolph et al., 2002) It is likely, due to increased hang-around time, TUDCA is more capable of being carried by fecal material into the colon than would be the more easily absorbed and removed UDCA.

Evidence points to both UDCA and TUDCA as viable alternatives to FMT for the treatment of *C-diff*. These two secondary bile acids appear to compensate for the *"nearly non-existent"* secondary bile acids in the stool of the *C-diff* patient. Of note: *"When UDCA or TUDCA was administered, total fecal bile acid excretion increased markedly . . .."* (Invernizzi et al., 1999)

As we have learned in *Chapter 18*, IBD patients have reduced microbial diversity leading to an impaired bacterial conversion of primary to secondary bile acids (Heinken et al., 2017; Van den Bossche et al., 2017). Reduced microbial diversity (as found in ulcerative colitis) leads to ***"reduced production of secondary bile acids*** *and decreased levels of sulfated bile acids"* (Joyce and Gahan 2017, emphasis added). So, addressing this issue using UDCA or TUDCA, seems to be warranted. It may save an individual from *C-diff*, even in the context of ulcerative colitis, and prevent the need for a fecal transplant.

What about AS?

> *The presence of a wide variety of bacterial species in both RA [rheumatoid arthritis] and other forms of chronic arthritis was an unexpected and novel discovery and indicates that* ***arthritic joints are not sterile, as thought previously****.* **~Kempsell et al., 2000, emphasis added**

There is another disease that may benefit from FMT, the arthritic disease known as ankylosing spondylitis (AS). As if having one hideous disease wasn't enough, it is reported that 8–12 out or every 100 IBD patients also contract AS (Salem et al., 2019). Let's take a look.

AS is a disease in which genetics play a pivotal role in determining who contracts this disease and who does not, but not every time. Only 5% of those with the marker for this disease, HLA B27, will develop this form of arthritis (Tam et al., 2010). But with ulcerative colitis, there is a distinct disadvantage that makes contracting AS more likely; for this disease is one where bacterial translocation from the gut is a way of life . . . because dysbiosis is a way of life. And one problem with dysbiosis is this:

> ***Dysbiosis can be considered an important pathogenetic factor with advancement of growth of invasive bacteria. It can also facilitate bacterial translocation through the mucosal barrier to the mesenteric lymph nodes.*** (Comito and Romano, 2012, emphasis added)

Unfortunately, bacteria don't just arrive and stay in the lymph nodes of the gut. They somehow show up in the joints, unannounced, or they find themselves carried to the joints by immune cells that circulate from gut to joint.

> *Microbes or their components may enter the joints via blood vessels either as whole organisms that may circulate in the blood or within the cells or as a part of immune complexes. Peripheral blood mononuclear cells [monocytes and macrophages] that contain intracellular bacterial fragments are especially prone to bind to synovial high endothelial venules and transmigrate through the endothelial cell monolayer.* (Colmegna et al., 2004)

Is it any wonder that inflammation in the joints occurs under such circumstances? Inflammation is, of course, how we deal with threats. Bacteria in joints are certainly a threat, one that is bound to provoke an inflammatory response.

But there is an out:

> *A tight relationship between gut and joint inflammation has been revealed in prospective follow-up studies of patients with SpA [spondyloarthritis, e.g., AS]:* ***clinical remission of joint inflammation was associated with resolution of gut inflammation, whereas the presence of gut inflammation was associated with persistent joint inflammation.*** (Van Praet et al., 2012, emphasis added)

And there is a very good way to resolve gut inflammation and perhaps eliminate this driver of joint inflammation. We call it FMT.

> *Clarifying the pathogenesis of ankylosing spondylitis will undoubtedly have therapeutic implications. If innate immunity is primarily responsible for its pathogenesis, it makes sense that the inhibition of tumor necrosis factor alpha would be an effective therapeutic. But the inhibition of TNF alpha could also itself have an*

effect on bacterial flora and this effect could potentially be counter therapeutic. ***We have entered an era in which some have begun to explore the benefit of fecal transplantation to alter endogenous flora. The reduction of arthritogenic flora or the induction of non-arthritogenic flora are potential avenues of therapy which might be efficacious with fewer risks and even a safety profile that would justify their use for prophylaxis.*** *Perhaps, nearly forty years after HLA B27's impact on susceptibility to spondyloarthropathy was discovered,* ***we at last have the tools to elucidate the mechanism for this remarkable association.*** (Rosenbaum and Davey, 2011, emphasis added).

FMT may be a means to bring AS to an end, as well as bring to an end an associated ulcerative colitis, in those who are now being told "You can't have it."

For more on this, I have written a post called *Ankyosing Spondylitis: The Story Not Being Told.* You can access this post at www.impactofvitamind.com

And then we have the unexpected

Detailed fecal microbiome analysis has revealed that MS had [a] distinct microbial community profile compared to healthy controls. **~Chen et al., 2016**

Let me assure you, what I am about to share occurred quite unexpectedly, and at a time when little was known about the role gut bacteria play in multiple sclerosis (MS). This is quite a story.

In 2001, Borody et al. reported three wheelchair-bound patients with MS treated with FMT [fecal microbiota transplantation] for constipation. Bowel symptoms resolved following FMT; however, in all cases, there was also a progressive and dramatic improvement in neurological symptoms, with all three patients regaining the ability to walk unassisted. Two of the patients with prior indwelling urinary catheters experienced restoration of urinary function. In

one patient of the three, follow-up MRI 15 years after FMT showed a halting of disease progression and 'no evidence of active disease. (Borody et al., 2014, emphasis added)

And why would FMT come to the aid of the patient with MS?

A growing body of evidence in animal models of MS implicates the gut microbiota in the induction of central nervous system (CNS) autoimmunity. (Berer and Krishnamoorthy, 2012)

In brief: There is growing suspicion that gut bacteria play a pivotal role in initiating and perpetuating neuroinflammatory disease, MS included. That bacteria within the gut could influence a disease process occurring in the brain and spinal cord is, indeed, quite surprising. In the not too distant past, to even consider such a thing would have been crazy. But not now. We have learned so much! Suspicions are giving way to conclusions.

In a laboratory model of MS, known as experimental autoimmune encephalomyelitis (EAE), the administration of non-absorbing antibiotics *"beginning 1 week prior to sensitization, altered the composition of gut flora and, intriguingly, also ameliorated the development of EAE."* (Yokote et al., 2008) And astonishingly, **FMT, using the stool from a MS patient and transplanted into an undeserving mouse, will transfer the disease from human to mouse** (Berer et al., 2017).

Furthermore,

Certain populations of commensal [normally found] bacteria are capable of attenuating CNS inflammation. The gut microbiota has the capacity to affect the development of autoimmune central nervous system (CNS) disorders. (Kamada et al., 2013)

Combined, . . . data indicate that early dysregulation in MS involves an increase in pro-inflammatory and a decrease in anti-inflammatory gut microbiota milieu. (Tremlett at al., 2016, emphasis added)

FMT normalizes gut bacteria. That's what it does. In view of the experiences of the three wheelchair-bound MS patients mentioned above, and in view of emerging data, the time has come to allow MS patients to choose FMT—or at the very least allow FMT as a compassionate therapy, but perhaps also as an approved alternative to drug therapy, which so often fails to induce and/or sustain remission in MS.

I have a great little post on this on my website, entitled ***Multiple Sclerosis: The Next Frontier.*** You can access this at www.impactofvitamind.com

Let me conclude with this: If I had MS, hearing the words "You can't have it" would not be acceptable. No, not in the least.

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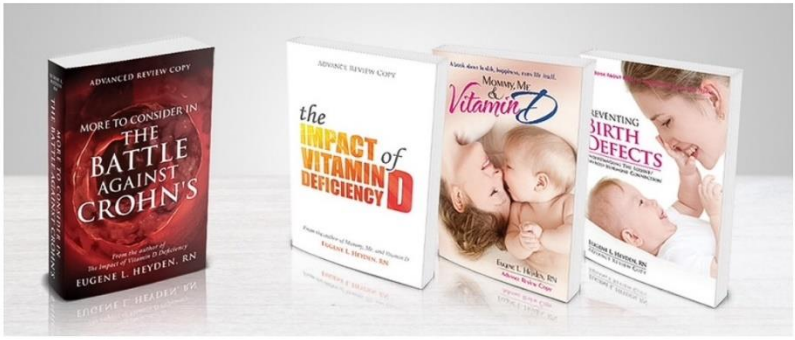

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