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"Flora Power"—Fecal Bacteria Cure Chronic *C. difficile* Diarrhea

Persky and Brandt (1), in this issue of the *Journal*, amply demonstrated how normal human flora bacteria are capable of permanently eradicating *C. difficile* from the bowel. Lessons learned from this case may have far-reaching clinical implications. First, courage and an innovative spirit are required to carry out what was described by the authors as a "distasteful" procedure. The description reflects our cultural "fecophobia" and might have been viewed quite differently had the procedure been as routine as a blood transfusion—conceptually similar, but one that has largely lost its "hemophobia." Because the procedure is neither routine nor accepted, it is often dismissed even though it can be dramatically curative. The main lesson, then, is that patients with symptomatic, incurable *C. difficile* seeking out any form of help (2) are perhaps often maintained in a state of considerable suffering while a safe, rapid, and highly effective therapy is available to them virtually anywhere in the world. Yet the therapy is generally not discussed, published, or popularized. Clearly, with our patients' well-being in mind, this area requires further improvement through funded research and a scientific approach to its practice.

The second clear lesson is the dramatic and curative, effect of this treatment. In eight reports (3–10), the overall cure rate was 60 of 67 treated patients. Generally those patients who failed to be cured were treated late and died from overwhelming pseudomembranous colitis (PMC) (4). Clinical improvement usually occurred within 1–4 days and has been reported to be curative, without recurrence. In fact, there are few medical therapies that reverse severe illness so dramatically. This begs the question as to how such dramatic treatment works, and whether it could be used or modified to cure other bowel conditions that may be infection-driven. Tvede *et al*. demonstrated *in vitro* how some but not other bacteria can profoundly inhibit the growth of pathogenic strains (6). A similar although less powerful phenomenon has been described for lactobacillus GG (11). It would seem that inhibitory substances, perhaps bacteriocins elaborated by bacteria, possess powerful antimicrobial properties. Unlike available antibiotics, these substances seem to have the added power of eliminating bacterial spores. In addition, the accompanying incoming mix of bacteria implants missing flora components such as *Bacteroides* species, restoring fecal physiology (10, 12), and deficient composition (6, 13), which may have initially permitted implantation of the pathogen such as *C. difficile*. Hence, colonic infusion of enteric flora may serve both as an antimicrobial and replacement therapy.

The human fecal flora is a complex mix of organisms and is arguably the largest organ of the body, containing in a compact mass of living bacterial cells almost nine times more living cells than does the entire body (14). Given the bacteriacidal nature of fecal flora, as judged by the >95% cure of *C. difficile*, it is instructive to realize that *C. difficile* may be but one of many implanted infective agents mediating chronic GI disease. As *H. pylori* was found to be the infective cause of ulcer disease, so chronic clostridial (or other) infections may cause a portion of chronic GI disorders such as constipation, IBS, or IBD. Indeed, constipation responds to vancomycin (15, 16) and to fecal flora therapy (17, 18) as does IBS (5, 19). Ulcerative colitis (UC) has also been reported to go into prolonged remission after fecal flora infusion (20). We have confirmed this finding in our own prospective series of now seven patients with severe UC, five of whom remain in clinical remission without therapy 1–10 yr after treatment (19). In these conditions, no specific bacterial pathogens have yet been demonstrated. Similarly, when Eiseman *et al*. (3) treated his four PMC cases in 1957, *C. difficile* had not been discovered—yet the therapy was successful. This very finding teaches us that we can use bacteriotherapy to treat enteric infections without necessarily identifying the pathogen. Fecal bacteria home in on the pathogen, apparently because of their broad-spectrum activity. Hence, when the bacterial species is unknown, fecal bacteria can still dissect out the pathogen without the need to detect and diagnose the infection. Although scientifically it is satisfying to recognize the pathogen, strictly speaking this is not necessary. It is therefore feasible that progress in IBS/IBD treatment discovery could spring from a successful therapy rather than from pathogen identification.

For those contemplating the use of this treatment, practical issues that stem from the report by Persky *et al*. include a) the method of treatment, and b) selection of donor. It seems that the method of delivery of the fecal slurry into the bowel results in cure, whether given by an enema suspended in saline (3–5, 7–9, 19) or milk (10, 12), by a small bowel infusion via a nasoduodenal tube (5, 7), a gastrostomy (9), or a colonoscope (Persky *et al*.). However, there may be advantages delivering via a colonoscope to infuse as proximally as possible, and to detect any colonic pathology. Selection of the donor is of crucial importance to avoid infecting the recipient with a separate disease. The donor should be tested at least for HIV, hepatitis A, B, and C, cytomegalovirus, and Epstein-Barr virus, with stool negative for any detectable parasites or bacterial pathogens. In our experience, choosing the patient's partner offers a theoretical advantage that any transmissible disease would have been transmitted and emerged by now.

In the future, it is conceivable that "bacteriotherapy" using combined, selected bacterial strains resembling human fecal flora (6, 21, 22), perhaps in capsule form, may become a curative therapeutic agent for *C. difficile* infection

and perhaps for those GI disorders that we now call "idiopathic" but that may well have an infective etiology.

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