Response to Drs. Famularo *et al.*

TO THE EDITOR: Persky and Brandt (1) may have generated hypotheses—one reason case reports are published—but did not set out to prove anything, as asserted by Famularo *et al.* Rather, they alerted us to a mechanism of action of fecal flora that now demands further study to answer the many questions this case report generated.

In their letter the authors raise the issue of "fecal heterogeneity" and then state that fecal enemas from different individuals cannot be standardized. No one will disagree with this view, but similarly, it has long been known that blood transfusion cannot be standardized, as different blood groups occur—yet, generally blood transfusions give the same result, and this seems to hold true for fecal enemas. Unlike the authors' unfounded claims, published reports suggest that feces from subjects A, B, and C are indeed likely to prove effective against *Clostridium difficile* (2). This is probably because feces possess antibiotic activity, a property that can be abolished by heat treatment (3).

Furthermore, rather than failing "in a substantial proportion of a statistically significant sample of patients" or showing a "marginal effectiveness" in *C. difficile* colitis, the published results are totally opposite. Famularo *et al.* attempt to support their statement by quoting Bowden *et al.* (4), Schwan *et al.* (5), Tvede and Rask-Madsen (6), and Gustafsson *et al.* (7). Here, the authors need to be taken to task, because upon rereading these papers it is clear that results of fecal bacteriotherapy quoted in these articles are anything but "marginal." Bowden *et al.* (4) state in their abstract that "the patients responded dramatically." In pseudomembranous colitis at the time of Bowden's series the death rate was around 74% (8). Meanwhile, 13 of 16 patients in Bowden's series were cured very rapidly, and the three who died may have been cured had the treatment not been delayed. In fact, two of these three did not have a pseudomembrane at death, and one had involvement of the small bowel where a fecal enema did not reach. Schwan and

colleagues' (5) patient recovered completely and was also cured of an accompanying irritable bowel syndrome. Gustafsson *et al.* (7) state that in 31 patients "clinically, most enema-treated patients recovered within days and had no relapses within 18 months." Tvede and Rask-Madsen (6) cured one of two patients, albeit using two low volume fecal enemas. The true situation is that far from having a "marginal" effectiveness, fecal bacteriotherapy is overwhelmingly successful.

Famularo *et al.* next suggest that bacterial composition of the fecal enema should have been reported. Unfortunately, reliable methods for obtaining such a composition are not generally available, and such a report would have contributed little to the case report. More to the point, the donor stools were found to be free of pathogens, and after all, the treated patient did remain well for ≥5 yr after the therapy. Though the potential for transmitting pathogenic organisms to the recipient does exist, if the donor is a spouse or a close relative with negative stool tests the risk has been minimized. Indeed, if a prospective donor has been a healthy person with negative stool tests and had this "natural probiotic" within his or her bowel for many years, this in itself suggests safety. Because fecal bacteriotherapy is not being promoted for widespread use but as a therapy of last resort, the fact remains that risk of transmission of infection is negligible, with no reported transmitted infections to date (2).

The article by Persky and Brandt (1) and the accompanying editorial (2) are in no way misleading. Neither of the articles suggests that fecal bacteriotherapy has been demonstrated to be better than probiotics for treatment of intestinal diseases. The converse, however, is also true. It is also an incontrovertible fact that fecal bacteriotherapy utilizes the "ultimate probiotic," which can never be copied by use of cultured bacteria that ultimately originate from human feces. Some probiotics, especially *Lactobacillus GG*, have been more effective in trials than placebos but have never been trialed against fecal bacteriotherapy in chronic relapsing *C. difficile* diarrhea or colitis. Until such a trial is carried out, the Persky and Brandt article and accompanying editorial stand.

There is growing interest and research in the use of single and mixed probiotics in intestinal diseases. These at best copy the fecal flora but have not been shown to implant long term. Ideally, we all would like to come up with probiotics for gut disorders, and our center has an interest in the development of this technology (9). It appears, therefore, that our research efforts are similar to those of Famularo *et al.* We would all dearly like to dissect out the metabolic, functional, and enzymatic properties of various bacteria and have a product that could reproduce the power of fecal infusions. However, as with blood transfusions and bone marrow transplants, we still have not dissected out their components to create artificial blood and artificial bone marrow, and such dreams with probiotics are yet a little way off.

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Received Feb. 19, 2001; accepted Apr. 5, 2001.