The Era of Fecal Microbiota Transplantation

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The human microbiome, recently termed "the forgotten organ," refers to the ecological communities of commensal, symbiotic and pathogenic microorganisms that inhabit our bodies. The intestinal microbiome, the most dominant portion of the human microbiome, is crucial for carbohydrate digestion, energy storage, immune function, degradation of xenobiotics, hormone synthesis, and protection against pathogens [1,2]. When the balance between microbial communities is interrupted (dysbiosis), a vicious cycle begins in which one or more species overgrows and other species decrease in abundance. Microbial balance is important in preventing overgrowth of particular microorganisms, and dysbiosis has been linked to several disease states. These include obesity, metabolic syndrome, autoimmune disorders, necrotizing enterocolitis, chronic fatigue syndrome, skin diseases, inflammatory bowel disease and irritable bowel syndrome [3].

Clostridium difficile infection (CDI) appears to be the best clinical model of near-complete disruption of the intestinal microbiota, resulting in dysfunction of the gastrointestinal system. The pathophysiology of recurrent CDI is not totally clear. Broad-spectrum antibiotics suppress the distal bowel microbial communities that normally limit the growth of *C. difficile*. As *C. difficile* spores are generally resistant to antibiotics, they can germinate back into vegetative forms after antibiotic treatment has been completed. The expansion of *C. difficile* in the human gastrointestinal tract causes dysbiosis which results in severe colitis [4].

Recurrent CDI is typically treated with a tapered or pulsed treatment regimen of metronidazole or vancomycin, but the outcomes are poor [5]. An alternative to the standard antibiotic therapy is "transplanting" the intestinal microorganisms from a healthy donor to the gut of an ill person through enema, colonoscopy or nasodoudenal tube with the purpose of restoring the normal healthy intestinal microbiota. First documented in modern medicine in 1958 [6], fecal microbiota transplantation (FMT), also termed fecal bacteriotherapy, may be a useful treatment option for CDI through restoration of the healthy intestinal microbiota.

In this issue of *IMAJ*, Cohen and fellow-researchers [7] review the latest developments in the growing field of FMT to cure *C. difficile*-associated diarrhea. They also describe their recently established 'Bacteriotherapy Service' at the Tel Aviv Medical Center.

The concept that microbiota transfer can affect the well-being of the organism has been known for many years. It occurs as a natural process in utero and after birth when the mother transfers her microbiota to her offspring. There are many examples of such transfer in the animal world. Female hoopoe birds smear secretions containing symbiotic bacteria at a high density onto the eggshells to protect the embryos against infections [8]. The hatchling of iguanas and foal of horses eat the feces of the adults, a phenomenon known as coprophagy, ensuring that the gastrointestinal tract of the hatchling is colonized by the appropriate microorganisms [9]. In other animals, mothers simply feed feces to their offspring. For example, koalas inoculate their young directly with a special fecal pellet to colonize the infant intestine with bacteria that detoxify secondary toxic compounds of eucalyptus leaves [10]. In other mammalian species that are non-coprophagic, parental care alone is sufficient to ensure that offspring are colonized by the 'correct' microorganisms. In humans, increasing evidence suggests that the initial inoculum of the infant can be provided by its mother before birth and is supplemented by maternal bacteria transferred during delivery and breastfeeding [11].

These fascinating observations bring us back to the lab. The preferred model for the study of the interaction between the host and the microbiome is FMT to germ-free mice. This model enables investigation of how the microbiome influences certain phenotypes of the host. It has been shown that particular physiologic features can be transferred from one organism to another solely by FMT. For example, FMT from third-trimester pregnant women to germ-free mice induced weight gain and a greater inflammatory response compared to mice receiving feces from pregnant women in their first trimester [12]. Stool transplanted from twin pairs of donors discordant for obesity into germ-free mice led to increased total body fat mass and obesity-associated metabolic syndrome in the recipients from obese donors when compared with the mice that received stool from the lean twin [13]. Similarly, fecal transplantation from twin pairs discordant for kwashiorkor, a state of severe protein malnutrition, into germ-free mice led to weight loss in recipient mice that received microorganisms from the thin twin [14].

Although the first reports of FMT in humans came from ancient Chinese traditional medicine during the 4th century, the first randomized controlled trial investigating FMT was published only 2 years ago. This relatively small study consisted of only 43 patients with recurrent *C. difficile*-associated diarrhea. Patients in the control groups received antibiotics alone or antibiotics with bowel irrigation, while those in the test group received antibiotics with fluid derived from filtered feces delivered directly into the upper small intestine through nasal tubes. This small trial (designed to include 120 patients) was terminated ahead of schedule because the combined treatment was more than twice as effective in resolving symptoms when compared to antibiotic treatment alone or antibiotics combined with irrigation [15].

In May 2013, the U.S. Food and Drug Administration (FDA) announced that it would regulate human stool as a drug. This new classification required physicians to submit a time-consuming detailed Investigational New Drug (IND) application before performing FMT. After 2 months the FDA revised its new approach and decided not to enforce the IND requirement for recurrent *C. difficile* infections. Although this policy complicates research of FMT for other conditions, such as inflammatory bowel diseases (IBD) or obesity, clinical trials on FMT in IBD are in progress.

We believe the future holds some exciting clinical applications of FMT for extra-intestinal diseases including metabolic diseases, neuropsychiatric diseases and autoimmune disorders. An example is metabolic syndrome; a randomized controlled clinical trial [16] has shown that FMT from lean donors could increase insulin sensitivity in recipients with metabolic syndrome, probably by increasing butyrate-producing bacteria and increasing gut microbiota diversity. The effect of FMT on autoimmunity can be explained by the fact that the education of the immune system is a result of its interaction with the colonic microbiota, and changes in the microbiome may affect autoimmunity. An example of an autoimmune disease is the neuropsychiatric disorder multiple sclerosis (MS); three wheelchair-bound MS patients who were treated with FMT for constipation showed a dramatic amelioration in their neurological symptoms and regained the ability to walk unassisted [17]. Another example of an autoimmune disorder describes a patient with immune thrombocytopenic purpura who was treated with FMT for ulcerative colitis which led to prolonged normalization of platelet levels [17]. These applications, which rely on small study groups, should be studied further and must be better understood before more extensive clinical trials are initiated.

The future of FMT in routine clinical practice, whether transferring the entire spectrum of human intestinal bacteria or using cultured products with smaller numbers of bacteria, is promising for gastrointestinal diseases such as IBD and irritable bowel syndrome. FMT is progressing rapidly, with advances in both basic research and clinical application. Due to these encouraging results, ease of performance and high safety profile, FMT will increasingly be adopted by more centers and for additional clinical indications.

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"Never think that war, no matter how necessary, nor how justified, is not a crime. Ask the infantry and ask the dead"

Ernest Hemingway (1899-1961), American author and journalist. His economical and understated style strongly influenced 20th-century fiction, while his life of adventure and his public image influenced later generations. A Nobel laureate , his most famous books include *For Whom the Bell Tolls*, *The Sun Also Rises*, *The Old Man and the Sea*, and *A Farewell to Arms*