Faecal Matter Transplantation

Can poop ever be good for you? Would we sometimes need it to become healthy again?

Image by Mart Production via Pexels.com

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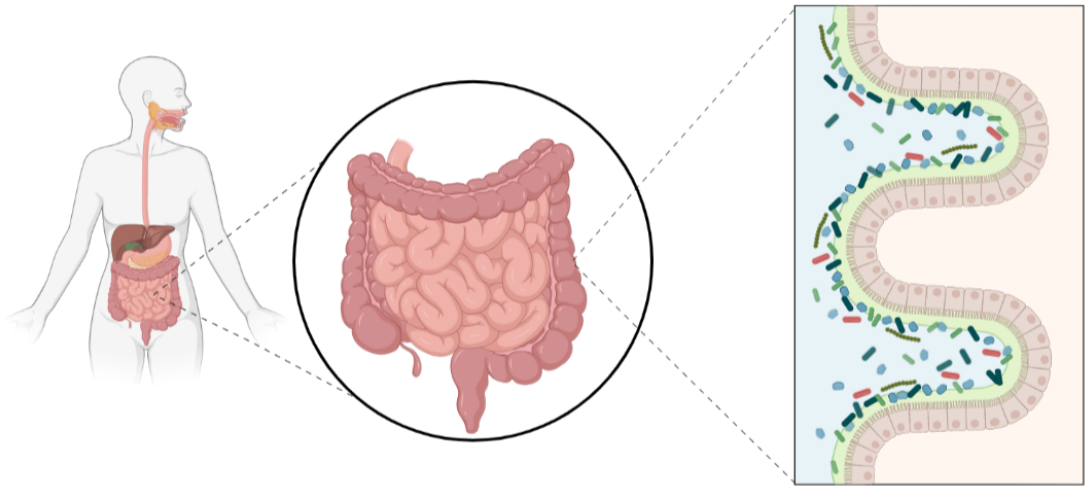
Faecal Matter Transplantation

Storyline

Human health and the contribution of gut microbes

Immediately after birth, humans are exposed to wide variety of different microorganisms that begin to colonize several areas of the human body, including the skin, mouth, and the gastro-intestinal (GI) tract (or our "gut"). These microorganisms are very much needed, since they have important roles in some of the functions of the human body, such as digestion, making vitamins, and fighting invading microbes, and they are necessary for general health as well. A collection of microorganisms (including such organisms as bacteria, fungi, and viruses) and their genetic material located in a specific area is called the microbiome[1]. During recent years, more and more research efforts have been aimed towards understanding the role of the gut microbiome (also known as the intestinal microbiome) in human health. Indeed, imbalance in gut microbiome composition has been linked to the development of a variety of gastrointestinal diseases, such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD)[2]. This imbalance, also called "dysbiosis", has been associated with the development of diseases outside of the intestine, such as disorders impacting heart and blood vessels, the processes controlling how the body is using and creating energy (metabolism), and even how people think, feel, and behave[3,4].



The gut microbiome contains all the microorganisms that inhabit the stomach, small intestines, and large intestine. The large intestine contains most of the microorganisms residing in the gut. Created with BioRender.com

Research over recent decades has proposed restoring the gut microbiome with the usual resident bacteria to prevent and treat diseases that arise from imbalance in gut microbiome composition. Among many possible solutions that have been suggested to alter the gut

[1] National Institute of Environmental Sciences. "Microbiome." *National Institute of Environmental Health Sciences*, 5 Apr. 2022, www.niehs.nih.gov/health/topics/science/microbiome/index.cfm. Accessed 10 Nov. 2022.

[2] Vijay, Amrita, and Ana M. Valdes. "Role of the gut microbiome in chronic diseases: a narrative review." *European Journal of Clinical Nutrition*, vol. 76, no. 4, 2021, pp. 489-501.

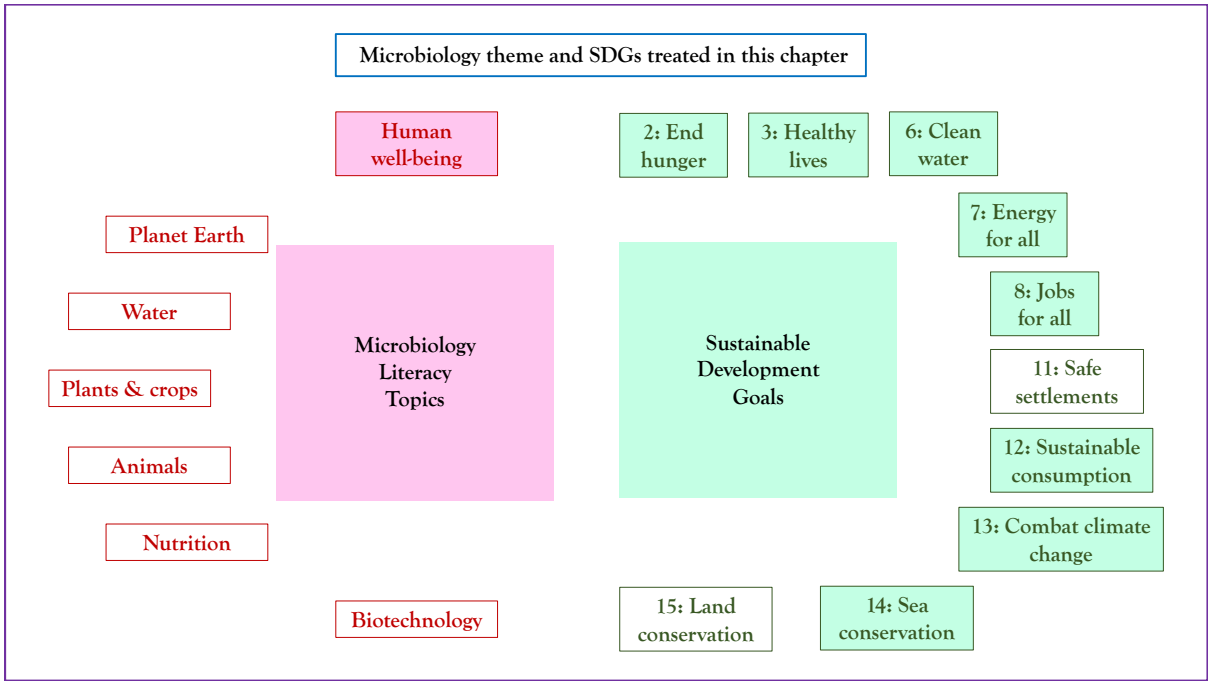
[3] Vijay & Valdes, 2021, pp. 489-501

[4] Gebrayel, Prisca, et al. "Microbiota medicine: towards clinical revolution." *Journal of Translational Medicine*, vol. 20, no. 1, 2022.

microbiome, faecal matter transplantation (FMT) has emerged as the most interesting and promising one. FMT is a procedure in which the patient's gut microbiome is intentionally modified by receiving a faecal sample from another person, who is healthy, to rebalance the composition for a therapeutic benefit[5].

The Microbiology and Societal Context

The microbiology: gut microbiome and diversity; dysbiosis and gut microbiome restoration. *And, peripherally for completeness of the storyline*: antibiotic resistance; clinical trials. *Sustainability issues*: health; food and energy; economy and employment; environmental pollution.



Faecal Matter Transplantation (FMT): the Microbiology

1. ***An ancient remedy– historical overview of FMT as a therapeutic option***. All humans share a common ancestry of microbes[6]. As humans have evolved from primates to modern day humans, the microbiome across various body sites has evolved as well to match the needs of today's humans. This common ancestry of microbes residing in the human gut across different populations is making it possible to transfer faecal matter between individuals. Despite the idea that FMT is a new innovative therapy to treat patients with gastrointestinal problems, the method itself dates to the 4th century in China, where human faecal matter was used to treat several health conditions, including food poisoning and severe diarrhoea[7].

FMT was first described in Europe by Acquapendente in Italy, who applied FMT in veterinary medicine. The first reported FMT in the USA was done in 1958 in Denver Colorado

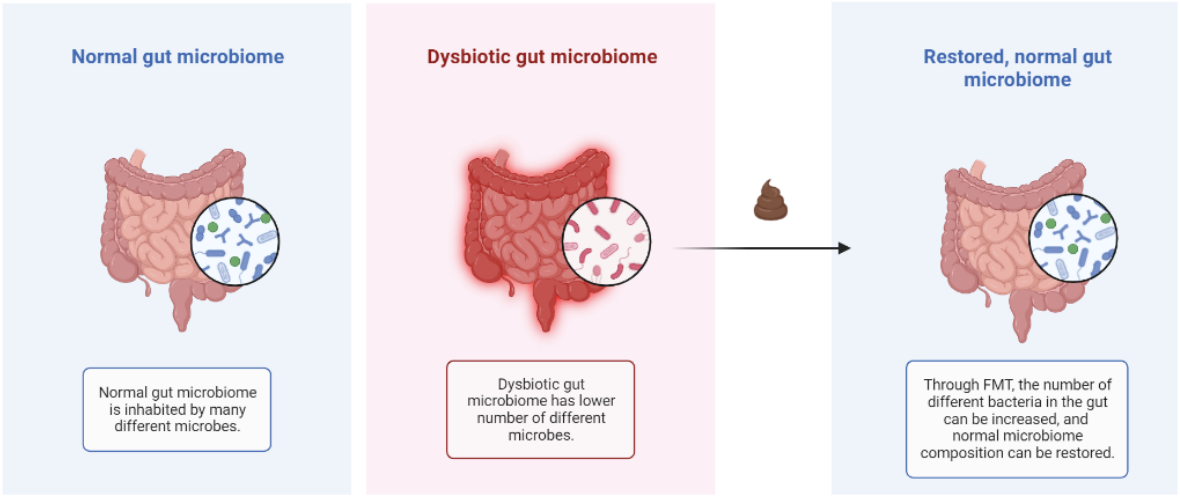
5 Merrick, Blair, et al. "Regulation, risk and safety of Faecal Microbiota Transplant." *Infection Prevention in Practice*, vol. 2, no. 3, 2020, p. 100069.

6 Moeller, Andrew H., et al. "Cospeciation of gut microbiota with hominids." *Science*, vol. 353, no. 6297, 2016, pp. 380-382.

7 Zhang, Faming, et al. "Should We Standardize the 1,700-Year-Old Fecal Microbiota Transplantation?" *American Journal of Gastroenterology*, vol. 107, no. 11, 2012, p. 1755.

by Ben Eiseman and his team to treat patients with inflammation in the large intestine[8]. However, it took more than 50 years after that before the first randomised controlled trial of FMT was carried out. The trial was crucial to determine the success of FMT in clinical use, since in a randomized controlled trial, participants of the study are divided into two groups randomly: one group that is receiving the specified treatment and one group that is working as a control group, i.e a group that does not receive the treatment [9]. This type of trial is considered the "gold standard" among clinical trials, since it minimizes the effect of the individual characteristics that may influence the results and therefore provides the best evidence, not only in individuals, but across a group of people, whether the treatment is working or not[10].

The FMT was used for a clinical condition called C. *diff* colitis. In this condition, harmful bacteria (called *Clostridioides difficile*) grow to large numbers in the contents of the intestine, and they produce poisons that injure the intestinal wall. One of the problems is that the normal bacteria that usually keep the C. *diff* in check are themselves affected, and their numbers are much reduced. That's why replacing them with normal bacteria (from another person) in the form of FMT might be beneficial. In fact, the FMT performed so much better than the control group (who received a standard course of antibiotics) that the randomized clinical trial had to be halted—it would have been unethical to continue with the study, since the test group gained such serious benefits from the FMT treatment.



Restoration of the normal gut microbiome composition. The normal microbiome in the gut is characterized by a high number of different microbial species. During dysbiosis, the number of different bacteria in the gut decreases, which can make people more prone to different diseases and inflammation in the gut. Through FMT, the number of different bacteria in the gut can be increased, which normalizes the gut microbiome composition. When this occurs on a long-term basis, the patient can become free of their symptoms. Created with BioRender.com.

Since then, more and more research projects have emerged to investigate the potential of FMT to treat a variety of different intestinal and extraintestinal diseases, such as inflammatory bowel disease (IBS)[11], atopic dermatitis (chronic inflammatory skin disease)[12], and type 2

[8] Bhidé, Amar, and Srikant Datar. "Fecal Microbiota Transplants (FMT): Case Histories of Significant Medical Advances." *Harvard Business School Working Paper*, June 2021, pp. 21-132

[9] Zabor, Emily C et al. "Randomized Controlled Trials." *Chest* vol. 158,1S (2020): S79-S87. doi:10.1016/j.chest.2020.03.013

[10] Zabor, Emily C et al., 2020, pp. S79-S87

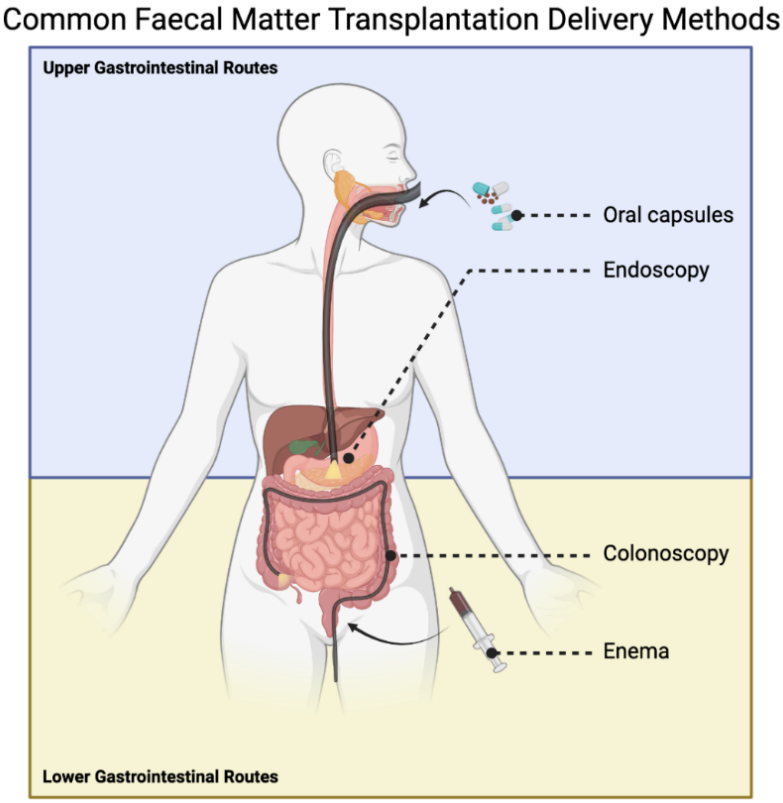
[11] El-Salhy, Magdy, et al. "Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study." *Gut*, vol. 69, no. 5, 2019, pp. 859-867.

[12] Kim, Jong-Hwa, et al. "Gut microbiota restoration through fecal microbiota transplantation: a new atopic dermatitis therapy." *Experimental & Molecular Medicine*, vol. 53, no. 5, 20 May 2021, pp. 907-916.

diabetes[13]. Interestingly, the exact mechanism of how FMT might be able to cure these diseases is still not fully understood. It has been proposed that FMT is able to restore the normal microbial community structure in the gut by increasing the number of different bacteria in the gut microbiome for the long-term and thus restore the proper gut microbiome function[14]. However, for these other conditions, there is little if any evidence as of yet, that FMT has any beneficial role.

2. ***FMT: A medical procedure.*** FMT delivery can be broadly classified into upper and lower gastrointestinal routes, through the mouth or the bottom, respectively. Common upper gastrointestinal routes include using oral capsules that are swallowed, or a thin tube that is guided from the mouth down to the stomach (called an endoscope). Common lower gastrointestinal methods include using a thin tube that is guided to the rectum directly, which is the end of the colon, (i.e an enema) or through the entire colon (i.e a colonoscopy).

Upper gastrointestinal delivery methods are typically faster, more cost-effective, and better tolerated compared to lower gastrointestinal methods, but usually use a smaller stool specimen which can lead to transplants failing[15]. There are also other concerns regarding the microbiota in stool samples dying when they reach the stomach and overall, there are less risky events associated with lower gastrointestinal delivery routes[16]. However, there is more and more research being done to create more effective 'poop pills'.



[13] Wang, Hui, et al. "Promising Treatment for Type 2 Diabetes: Fecal Microbiota Transplantation Reverses Insulin Resistance and Impaired Islets." *Frontiers in Cellular and Infection Microbiology*, vol. 9, Jan. 2020.

[14] Khoruts, Alexander, et al. "Changes in the Composition of the Human Fecal Microbiome After Bacteriotherapy for Recurrent Clostridium difficile-associated Diarrhea." *Journal of Clinical Gastroenterology*, vol. 44, no. 5, 2010, pp. 354-360.

[15] Bang, Byoung W., et al. "Fecal Microbiota Transplantation for Refractory and Recurrent*Clostridium difficile*Infection: A Case Series of Nine Patients." *The Korean Journal of Gastroenterology*, vol. 69, no. 4, 2017, p. 226.

[16] Ramai, Daryl, et al. "Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness." *Annals of Gastroenterology*, Feb. 2018

Colonoscopies are considered more successful for FMT because they allow for direct delivery of healthy gut bacteria into the colon[17], where they can take up residence and start to establish a healthy balance of bacteria. Until 1990, enemas were the method of choice for faecal transplant. They are less invasive, easier to perform and relatively less expensive compared to colonoscopies, however there are greater concerns regarding stool retention as well as its limited delivery to the entire colon[18].

Patients receive a transplant from a collection of carefully screened donors or from a family member. A suitable donor for faecal transplantation is a healthy adult who has not had any antibiotic exposure in the past six months, does not have a weakened immune system or live with chronic gastrointestinal disorders, such as inflammatory bowel disease[19]. A donor's blood and stool are tested to check for any potentially transmittable diseases and other tests are performed to evaluate the quality of the microbiota contained in the stool sample[20].

Previous surveys suggest that patients preferred to use unrelated donors, hinting that conversations discussing FMT with related donors may be unpleasant or difficult to have[21]. Another option is using an autologous donor, which means giving back a person their own feces. Typically, the stool would be obtained and stored when the person is healthy, but then it would be given back when their health was in question—after receiving antibiotics, or when receiving chemotherapy for cancer are two examples. Using your own stool sample that was collected from a time when your disease was in remission[22] can be a treatment for when the disease acts up again. This procedure effectively re-establishes the healthy bacterial populations while avoiding the risk of introducing new bacteria that the body has not encountered before, which makes it more well-tolerated[23].

3. ***FMT: clinical applications and risks.***

a. FMT is considered a validated therapy for managing recurrent *Clostridioides difficile (C. diff)* infections (rCDI). *C. difficile* is a pathogenic bacterium, meaning it can cause disease or infection in its host. It can colonize not only humans but animals, like cows and pigs, and it affects their intestines, especially their colon (or large intestine) and can cause diarrhoea. In *C. difficile* infections, the more severe cases include symptoms that range from dehydration, tearing of the wall of the large intestine (colon perforation), intestinal paralysis, inflammation throughout the whole body and intestinal bacteria circulating in the blood (called sepsis) and ultimately the patient may die. Usually antibiotics, such as vancomycin, are prescribed but around 25% of patients have multiple recurring infection episodes (rCDI) and some physicians opt for an FMT therapy as a form of therapy. All FMTs that originate from a healthy donor appear to be comparably effective: there is no significant difference observed in outcomes for rCDI treatment between healthy donors who are relatives or unrelated, patient-selected, or

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17 Bang et al., 2017, p. 226

18 Kassam, Z., et al. "Fecal Transplant via Retention Enema for Refractory or Recurrent Clostridium difficile Infection." *Archives of Internal Medicine*, vol. 172, no. 2, 2012, p. 191.

19 "Fecal Transplant." *Johns Hopkins Medicine, Based in Baltimore, Maryland*, 4 Apr. 2022, www.hopkinsmedicine.org/health/treatment-tests-and-therapies/fecal-transplant. Accessed 19 Oct. 2022.

20 Nicco, Carole, et al. "From Donor to Patient: Collection, Preparation and Cryopreservation of Fecal Samples for Fecal Microbiota Transplantation." *Diseases*, vol. 8, no. 2, 2020, p. 9.

21 Bakken, J. S., et al. "Treating Clostridium difficile infection with fecal microbiota transplantation." *Clinical Gastroenterology and Hepatology*, vol. 9, no. 12, Dec. 2011, pp. 1044-1049.

22 Wang, Jiunn-Wei, et al. "Fecal microbiota transplantation: Review and update." *Journal of the Formosan Medical Association*, vol. 118, no. 1, Mar. 2019, pp. 523-531.

23 Taur, Ying, et al. "Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant." *Science Translational Medicine*, vol. 10, no. 460, Sept. 2018.

anonymous[24]. Overall, FMT is generally considered safe with most short-term risks attributable to the method of administration rather than the FMT itself and is also well-tolerated without excess side effects in patient groups who are at high risk for bad outcomes[25]. In December 2022, the FDA, the major regulatory agency in the USA, approved the first faecal microbiota product, Rebyota, for the prevention of recurrence of CDI in adults, which is administered rectally[26]. Thus, FMT is now an approved procedure!

i. *Amsterdam clinical trial.* In 2013, Josbert Keller and his team from the Haaglanden Medical Center in Amsterdam, conducted the first randomised controlled clinical trial of FMT to treat rCDI. One group of patients was randomly selected to receive FMT treatment, and the other did not and, as such, was used as a control group*. Although this historical trial had a small number of patients, the results showed a clear improvement in the group that received a faecal matter transplant. Overall, 94% of the patients who received FMT recovered from rCDI, while only 31% recovered with just the control treatment (with the antibiotic vancomycin)[27].

Microbial diversity is key to our health, since it helps us in many ways including aiding in digestion of food, synthesizing vitamins that we cannot, stimulating our immune system to stay alert to intruders, and it is itself a barrier of defence against invading pathogens. Microorganisms compete fiercely amongst themselves in our gut for space and food; our normal microbes (called our commensals) do not allow for outsiders to intrude and cause disease. This phenomenon is also known as colonization resistance. For this to be possible, diversity, or having many different species, is key. In this trial, it was observed that patients had very low microbial diversity prior to FMT and after it they recovered their diversity to the same level as their donor, while they improved their clinical state.

b. <u>FMT as therapy for other illnesses.</u> After the Amsterdam trial, more studies were done trying to assess the potential of FMT in treating other pathologies such as IBD, obesity, metabolic and autoimmune diseases[28]. Currently there are 517 clinical trials registered at ClinicalTrials.gov concerning FMT treatment for different diseases, such as bacterial and fungal infections, neurodevelopment diseases, and nutritional disorders all over the world[29].

There are some studies that reveal correlations between specific gut microbiota profiles (the abundance or presence/absence of species) and other health-related conditions. However, correlation does not equal causation. We still need to study if there is a direct link between a gut microbiota profile and a certain disease, like diabetes or obesity. Nonetheless, due to this uncertainty, some researchers and physicians are concerned about the possible increased risk for the recipient if given a particular FMT with a microbiota profile that potentially could lead to the development of a non-infectious condition[30].

i. *Infections caused by an antibiotic-resistant organism (ARO).* Some bacteria have genes ("blueprints" or "instructions") that instruct them how to produce proteins, and other molecules, that can fight the effect of antibiotics. Bacteria developed this as a defence mechanism

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24 Ramai, Daryl, et al. "Fecal microbiota transplantation: donor relation, fresh or frozen, delivery methods, cost-effectiveness." *Annals of Gastroenterology*, Feb. 2018.

25 Merrick et al., 2020, p. 100069

26 U.S Food and Drug Administration. "FDA Approves First Fecal Microbiota Product." *U.S. Food and Drug Administration*, 30 Nov. 2022, www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product. Accessed 7 Dec. 2022.

27 Van Nood, Els, et al. "Duodenal Infusion of Donor Feces for Recurrent*Clostridium difficile*." *New England Journal of Medicine*, vol. 368, no. 5, Jan. 2013, pp. 407-415.

28 John Hopkins Medicine, accessed 19 Oct. 2022

29 ClinicalTrials.gov. Accessed 11 Dec. 2022.

30 Merrick et al., 2020, p. 100069

*Control is very important in science. Having proper controls, is what helps us scientists to be more certain of the conclusions we take from our experiments. Without them we wouldn't be so sure if what we saw was real or just an artifact, something that happened by chance and not because of what we wanted to test.

even before antibiotics were used in modern medicine. An example of this is the first record of resistance to penicillin.

This antibiotic was first discovered in 1929 by Alexander Fleming, who observed that a substance produced by the fungus *Penicillium notatum* could kill bacteria he was growing in his lab. Years later, in 1940, it was mass-produced as 'penicillin' and used widely in hospitals to treat patients. However, soon after it was found that some *Escherichia coli* bacteria produced penicillinase, a protein that inactivates penicillin. It means the mechanism already existed even before we used penicillin as an antibiotic. Most likely, *E. coli* had evolved to produce penicillinase to defend itself from the fungus.

Interestingly, 2 years later, another bacterial species, *Staphylococcus aureus*, was found to be resistant to the action of the antibiotic in hospitalized patients. By the late 1960's more than 80% of *S. aureus* found in patients were penicillin resistant. This means that only a small number of patients could be treated with that antibiotic.

Resistance to antibiotics occurs naturally and is promoted the more we overuse (and misuse) antibiotics. So far, many researchers and pharmaceutical companies have directed their efforts towards the development of new drugs and are constantly trying to halt the spread of the bacteria and their genes that promote resistance. This in turn can be particularly difficult since some bacteria share their resistance genes broadly with other species [31]. We now have a threat to our health: Antibiotic Resistant Organisms (ARO) which are organisms that have genes that confer resistance to antibiotics.

Our gut is recognized as a reservoir for AROs. Although they may be there, they might not cause disease at all. In this aspect, our microbiota plays a key role in keeping these bacteria "in check" and preventing their expansion. Regardless, when a patient is ill and it is an ARO that is the causative agent of an infection, it becomes extremely difficult to treat them, since the organism is resistant to the antibiotics that doctors would ordinarily use. In some cases, there are few therapeutic options available, with last-of-the-line antibiotics as the last resort. Antibiotics such as these tend to be more difficult for patients to process and have worse side effects affecting their liver or kidneys[32].

As explained above, a diverse microbiota can keep pathogens from colonizing and causing disease to the host. Hence, FMT can be a potential therapy to deal with ARO, since it might restore microbiota diversity levels, which in turn will help to expel ARO from the patient's gut.

ii. *Alleviating Inflammatory Bowel Disease (IBD) symptoms*. IBD is a group of related diseases in which the patient suffers from chronic inflammation of the gastrointestinal tract. In other words, affected people have prolonged pain and swelling in their intestines. It is unclear what triggers IBD and, as such, effective targeted therapy is hard to implement. As gut inflammation is a characteristic of IBD, the best therapeutical option would be one that does not exacerbate this symptom. Moreover, some IBD-related studies point to bacterial infection as a possible cause for the disease, that will trigger an inflammatory response. Antibiotics are used to relieve the patient from the pathogen. Consequently, the patient will be in a dysbiotic state, being more susceptible to other pathogens. This is a never-ending cycle, in which the patient does not recover its microbiota as it will be taking antibiotics to treat the infection. FMT was suggested as a possible therapy as it helps restore microbiota members.

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31 Lobanovska, Mariya, and Giulia Pilla. "Penicillin's Discovery and Antibiotic Resistance: Lessons for the Future?." *The Yale journal of biology and medicine* vol. 90,1 135-145. 29 Mar. 2017

32 Björnsson, Einar S. "Drug-induced liver injury due to antibiotics." *Scandinavian journal of gastroenterology* vol. 52,6-7 (2017): 617-623. doi:10.1080/00365521.2017.1291719

The figure bellow illustrates several ways to perform the procedure. Nowadays, the donor's microbiota is not thoroughly tested, so it is unknown if the donor's faeces will cause inflammation in the recipient. As an alternative the microbiota should undergo further testing to ensure that it will not cause any harm (more inflammation or carriage of potentially harmful bacteria) to the patient. Another option would be to use the patient's own faeces, when the disease is inactive, and the inflammation levels are low; this would minimize risks after FMT procedure [34]. However, some studies report low efficacy of FMT in IBD patients, while others show some return to the healthy state[33]. Once again, these results emphasize the lack of proper control groups in many studies, making it difficult to understand whether a therapy is effective[34].

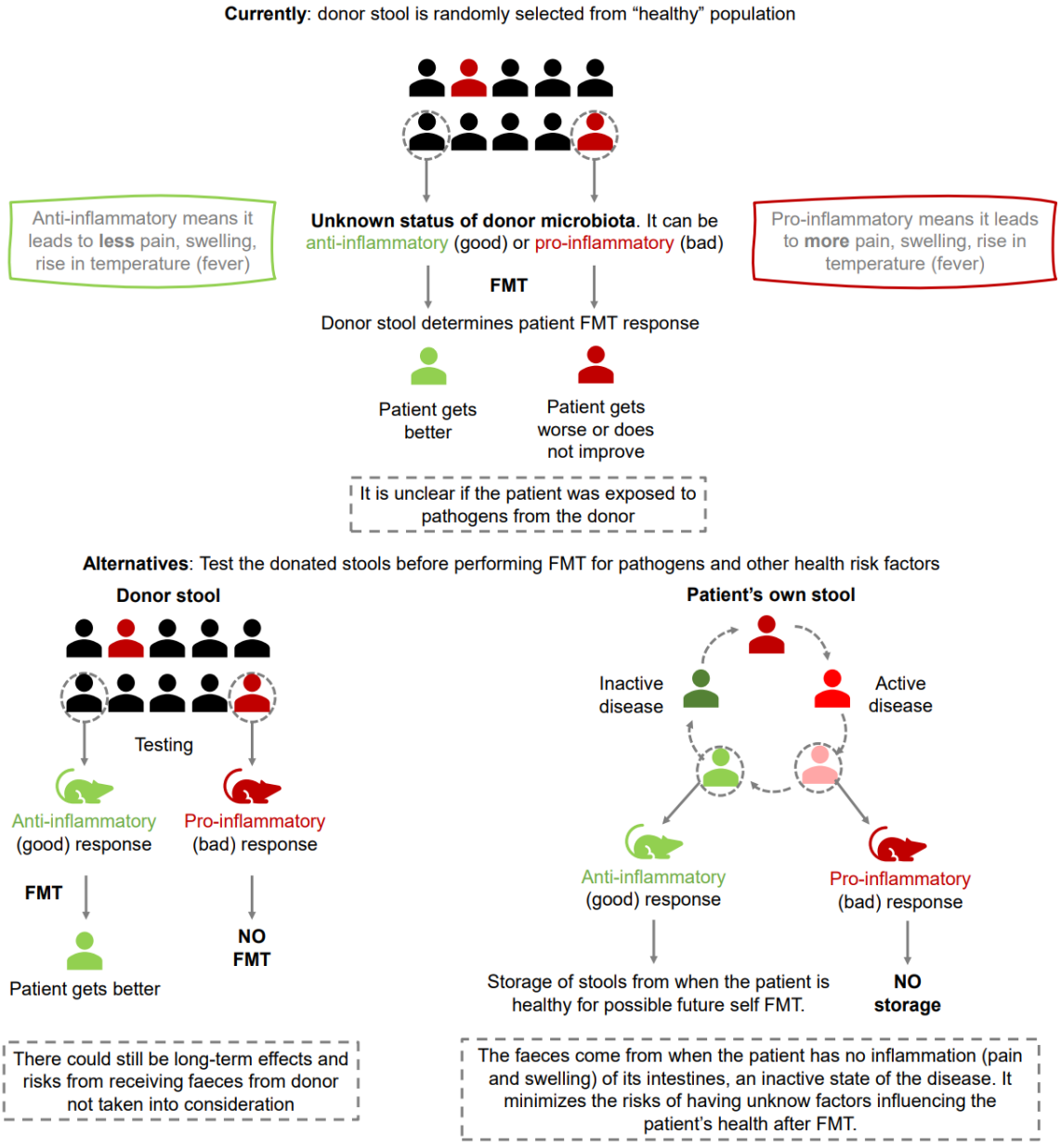
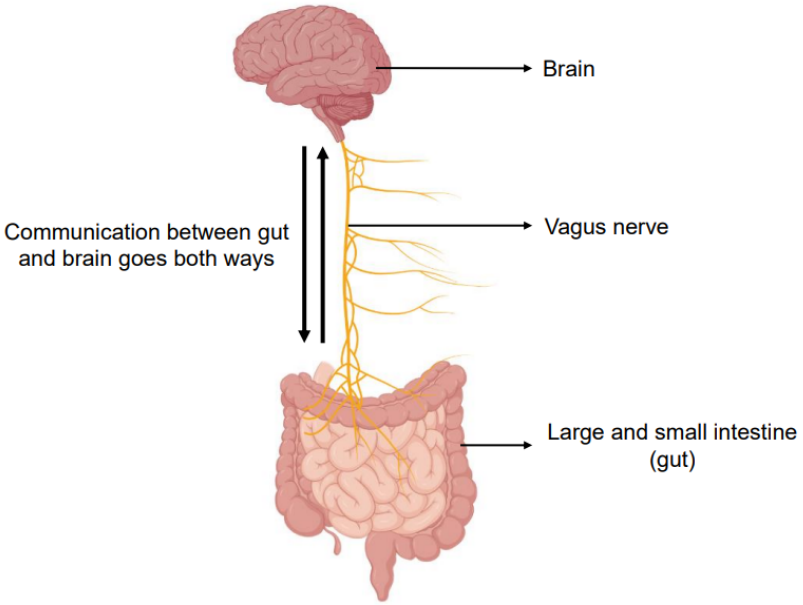


Illustration of current FMT procedure, adapted from Basson *et al.*, 2020

[33] Basson, Abigail R., et al. "Autologous fecal microbiota transplantation for the treatment of inflammatory bowel disease." *Translational Research*, vol. 226, Dec. 2020, pp. 1-11.
[34] Basson et al., 2020, pp. 1-11

iii. *Neurological diseases or syndromes*. In recent years, scientists realised that microbiota also have an impact in other organ systems (groups of organs that work together to perform one or more functions) outside the gastrointestinal tract. It was discovered that our gut and brain have a bidirectional route by which they communicate, in what is known as the "gut-brain axis" where molecules from the gut to the brain, and vice-versa, travel through the vagus nerve (the longest nerve that goes from our brain to our intestines).



Gut-brain axis illustration.

Our microbiota stimulates our brain to produce certain hormones (signalling molecule, a chemical messenger, that helps in the inter-organ communication, regulating our physiology and behaviour) like serotonin (also known as "the happiness hormone") for example. Serotonin has been at the centre of the "gut-brain axis" as the main communication molecule. Bacteria supply key ingredients for its production to the cells of our nervous system present in our gut. Serotonin will then travel up the vagus nerve and reach the brain where more of it is produced. The brain, on the other hand, can control several functions of the gut, like how much mucous is produced that will act as a barrier that microbes cannot cross, keep our immune cells (our "protectors") alert to distinguish friend from foe, produce products (like bile salts from the liver) that will kill some pathogens as soon as they enter our gastrointestinal tract. All these functions keep the microbiota in check[35]. Due to this interaction, studies have tried to link microbiota disorders to neurological diseases that impact brain functions. In some reported cases of neurological diseases there is a link between different levels of serotonin, which were then correlated with dysbiosis. In these, some of the therapeutic approaches were related to the manipulation of the gut microbiota through FMT, in an attempt to restore the diversity and levels of serotonin [36,37].

[35] Beyi, Ashenafi F., et al. "Impacts of Gut Microbiota on the Immune System and Fecal Microbiota Transplantation as a Re-Emerging Therapy for Autoimmune Diseases." *Antibiotics*, vol. 11, no. 8, Aug. 2022, p. 1093.

[36] Biazzo, Manuele, et al. "Clostridioides difficile and neurological disorders: New perspectives." *Frontiers in Neuroscience*, vol. 16, Sept. 2022.

[37] Layunta, Elena, et al. "Crosstalk Between Intestinal Serotonergic System and Pattern Recognition Receptors on the Microbiota–Gut–Brain Axis." *Frontiers in Endocrinology*, vol. 12, 2021.

4. Future perspectives. FMT has shown promising results in the restoration of the gut microbiome composition and the potential applications of the procedure seem endless. However, there are some important issues that hinder the clinical application of FTM. Notably, the procedure is still lacking standardized methods for different parts of the process, such as the consistency of the stool, route of administration, and donor/recipient screening, all of which are critical to ensure patient safety[38].

In the U.S, Food and Drug Administration (FDA) is closely monitoring the patients who have received a FMT, and they have had to reinforce additional screening of the donors after patients who received a FMT experienced a life-threatening infection after the transplantation, and one of the patients even died [39,40]. The global pandemic caused by the SARS-CoV2 virus (COVID-19 pandemic) also encouraged the FDA to create protocols for FMT specifically to prevent the disease transmission[41]. Even though these efforts were put in motion after devastating events, these steps are critical for ensuring patient safety and creating standardized protocols for FMT.

Furthermore, to study the impact of individual variation in the microbiome composition on the success of FMT[42], and how FMT is realizing its therapeutic effect, is difficult due to a high number of factors that can impact the human-gut microbiome relationship. The connection between the gut microbiome and drug metabolism, diet, and underlying diseases can change as the microbiome composition between individuals change, and it can have a crucial impact on the outcome of FMT. More research needs to be done to understand the underlying dynamics in the gut microbiome before FMT can become a wide-spread clinical application. These efforts could also then facilitate the implementation of personalized FMT procedures.

In addition, more randomised clinical trials are needed in the future to further assess the efficacy of the FMT treatment for different diseases, and to understand the relationship of the microbiome with a disease of interest. A lot of research is being done to find cures for specific conditions, and FMT provides an opportunity to assess the possible underlying causes, but without proof of the causal link between the disease phenotype and gut microbiome, FMT is not an efficient treatment option.

It is also important to not underestimate the importance of communication between professionals and the public to increase awareness of the safety and risks of FMT: how it works, where stool samples come from and who is suitable for FMT. Due to the current hype of FMT and its effectiveness in treating rCDI, some entities have started to sell unregulated FMT capsules to consumers directly, marketing them with unsubstantiated claims to cure diseases, such as autism[43]. To avoid such practices, and to improve current FMT applications, it is important to increase efforts to educate the public about the FMT procedure and the uncertainties that are associated with it. After all, the method is here to stay, and hopefully it will become a standardised and more widely used procedure for the treatment of a variety of diseases in the future.

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38 Shao, Tihong, et al. "The Evolving Landscape of Fecal Microbial Transplantation." *Clinical Reviews in Allergy & Immunology*, 2023.

39 Food and Drug Administration (FDA). "Safety Communication on Use of FMT and MDROs." *U.S. Food and Drug Administration*, 4 Dec. 2020, www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/important-safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse. Accessed 12 Feb. 2023.

40 Shao, Tihong, et al., 2023

41 Food and Drug Administration (FDA). "Information Pertaining to Additional Safety Protections Regarding Use of Fecal Microbiota for Transplantation - Screening Donors for COVID-19 and Exposure to SARS-CoV-2 and Testing for SARS-CoV-2." *U.S. Food and Drug Administration*, 9 Apr. 2020, www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/information-pertaining-additional-safety-protections-regarding-use-fecal-microbiota-transplantation-1. Accessed 12 Feb. 2023.

42 Shao, Tihong, et al., 2023

43 "Naturopath Accused of Using Nephews' Stool to Make Fecal Transplants in Basement Apartment | CBC News." *CBC*, 9 Jan. 2020, www.cbc.ca/news/canada/british-columbia/bc-naturopath-fecal-transplants-college-naturopathic-physicians-response-1.6216051. Accessed 11 Nov. 2022.

Relevance for the Sustainable Development Goals and Grand Challenges

The microbial dimension of FMT procedures relates to several SDGs (*microbial aspects in italics*), including:

- **Goal 2. End hunger, achieve food security, and improved nutrition and promote sustainable agriculture** (*end hunger and malnutrition, increase agricultural productivity*). The potential of FMTs is not only limited to humans, but could also be carried out in animals in the future. FMTs could play a critical role in preserving diverse animal populations, including livestock animals, and thereby contribute to enhancing food security efforts.
- **Goal 3. Ensure healthy lives and promote well-being for all at all ages** (*improve health, reduce preventable disease and premature deaths*). The potential health advantages resulting from FMT are vast and could substantially improve the quality of life across various life stages. Re-establishing diversity in the gut microbiome could also have a positive impact on mental well-being via the gut-brain axis. However, further investigation is necessary to establish FMT as a safe standard medical procedure for patients undergoing the transplant.
- **Goal 8. Promote sustained, inclusive, and sustainable economic growth, full and productive employment, and decent work for all** (*promote economic growth, productivity, and innovation, enterprise, and employment creation*). FMT has the potential to stimulate economic growth, as there are commercial interests associated with the procedure. 'Poop pills' have emerged as an appealing business opportunity, providing a non-invasive means for individuals to receive FMT. Furthermore, if FMT proves effective in treating a wide range of medical conditions, commercializing the procedure could make a substantial contribution to the global market and generate employment opportunities worldwide.
- **Goal 10. Reduce inequality within and among countries** (*promote the social, economic, and political inclusion of all irrespective of age, sex, disability, race, ethnicity, origin, religion or economic or other status, ensure equal opportunity and reduce inequalities of outcome, including by eliminating discriminatory laws, policies, and practices and promoting appropriate legislation, policies, and action in this regard*). FMT research is conducted primarily in high-income countries where it is available to select patient groups. Once safety concerns associated with FMT are addressed and secure protocols for administering the transplant are established, it is important that the procedure becomes accessible to individuals residing in low-income countries to prevent the creation of further inequalities between nations.
- **Goal 14. Conserve and sustainability use the oceans, seas, and marine resources for sustainable development** (*reduce pollution of marine systems by toxic chemicals/agricultural nutrients/wastes such as plastics, develop mitigation measures for acidification, enhance sustainable use of oceans and their resources*). FMTs present a challenge due to the emergence and persistence of antibiotic-resistant organisms (AROs), which can enter marine ecosystems via inappropriate antibiotic usage, such as over-prescription and inadequate recycling practices. AROs can harm the microbiomes of fish and other marine animals, thereby compromising their health and the overall health of the marine environment. Educating individuals on the proper use of antibiotics is crucial to prevent their entry into oceans, seas, and other bodies of water. Additionally, FMT could serve as a potential solution to reduce antibiotic use, as it could be offered as a primary treatment option for conditions that are presently treated with antibiotics.
- **Goal 15. Protect, restore, and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation, and halt biodiversity loss** (*take urgent and significant action to reduce the degradation of natural habitats, halt the loss of biodiversity, protect, and prevent the extinction of threatened species, integrate ecosystem and biodiversity values into national and local planning, development processes, poverty reduction strategies and*

accounts). By conducting thorough donor screening, FMT can help preserve biodiversity on land and in water ecosystems. Many diseases pose a threat not only to humans, but also to animals, and a robust microbiome could serve as a first line of defense against such pathogens. FMT has the potential to increase microbiome diversity in captured animals before their release into the wild, thereby promoting healthy microbiome composition in various animal groups and mitigating the spread of disease.

Potential Implications for Decisions

1. ***Individual***
    a. Would you be willing to get an FMT? Why or why not? Under which circumstances might it be beneficial?
    b. Do you think it is a good idea to bank your stool for possible later use in FMT? This creates some costs (for long term storage in cold): would you be willing to pay, or should the society (the healthcare system) pay instead?
2. ***Community policies***
    a. Education about FMT
    b. Promotion of FMT in community hospitals
3. ***National policies***
    a. Research support for exploration of the potential of FMT and other types of microbiome transplants
    b. Safety, authorization, regulations, and oversight of FMT products and practices

Pupil participation

1. ***Class discussion of the issues associated with FMT***

2. ***Pupil stakeholder awareness***
    a. FMT is relevant for a number of SDGs. Which of these are most important to you personally/as a class?
    b. There are many things that need to be considered before an FMT is performed. What do you think would be the most important things to consider if you were:
        i. A doctor carrying out a FMT procedure
        ii. A patient receiving the FMT
    c. Can you think of anything that can be done to reduce the negative outcomes of FMT?
    d. What would be the potential issues with using an autologous (self) stool sample?

The Evidence Base, Further Reading, and Teaching Aids

Merrick, B., Allen, L., Masirah M Zain, N., Forbes, B., Shawcross, D. L., & Goldenberg, S. D. (2020). Regulation, risk and safety of faecal microbiota transplant. *Infection Prevention in Practice*, *2*(3), 100069. https://doi.org/10.1016/j.infpip.2020.100069

Wang, J., Kuo, C., Kuo, F., Wang, Y., Hsu, W., Yu, F., Hu, H., Hsu, P., Wang, J., & Wu, D. (2019). Fecal microbiota transplantation: Review and update. *Journal of the Formosan Medical Association*, *118*, S23-S31. https://doi.org/10.1016/j.jfma.2018.08.011

U.S Food and Drug Administration. (2022, November 30). *FDA approves first fecal microbiota product*. U.S. Food and Drug Administration. https://www.fda.gov/news-events/press-announcements/fda-approves-first-fecal-microbiota-product

Shao, T., Hsu, R., Hacein-Bey, C., Zhang, W., Gao, L., Kurth, M. J., Zhao, H., Shuai, Z., & Leung, P. S. (2023). The evolving landscape of fecal microbial transplantation. *Clinical Reviews in Allergy & Immunology*. https://doi.org/10.1007/s12016-023-08958-0

Glossary

Clone: Genetically identical progeny produced by the natural or artificial asexual reproduction of a single organism, cell, or gene[44]
Colonisation: Occupation of a habitat or territory by biological community or an ecological niche by a single population of species[45]
Colonoscopy: Medical procedure during which the inner lining of the colon and rectum are viewed[46]
Commensal bacteria: Bacteria that supply the host with essential nutrients and defend the host against invading organisms[47]
Disorder: A disturbance of the normal functioning of the mind or body either due to genetic factors, disease or trauma[48].
Dysbiosis: Imbalance in the host associated microbial community[49]
Enema: Introduction of fluid into the rectum[50]
Gene: Genes are segments of DNA that contain the information for making a specific protein in the body[51]. Genes are passed from parent to their biological children.
Gut: Also known as the gastrointestinal (G.I.) tract. The tube-like organs that food and liquids travel through when they are swallowed, digested, absorbed, and leave the body as faeces. These organs form a continuous tube including the mouth, pharynx (throat), oesophagus, stomach, small intestine, large intestine, rectum, and anus.[52]
Inflammation: Redness, swelling, pain, and/or a feeling of heat in an area of the body[53].
Hormones: Substances that are made by glands in the body. These substances circulate in the blood system and can control the actions of different cells and organs[54].
Microbiome: A community of microorganisms (such as bacteria, fungi, and viruses) that live in each environment, including the human body or part of the body, such as the G.I. tract[55]
Organ system: Group of organs that work together to perform a specific function[56].

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44 Adapted from "Clone." *TheFreeDictionary.com*, 2003, medical-dictionary.thefreedictionary.com/clone.

45 Onofri, S. (2011). Colonization (Biological). In: , *et al.* Encyclopedia of Astrobiology. Springer, Berlin, Heidelberg

46 "Colonoscopy." *TheFreeDictionary.com*, medical-dictionary.thefreedictionary.com/colonoscopy. Accessed 10 Nov. 2022.

47 Martín, R., Miquel, S., Ulmer, J. *et al.* Role of commensal and probiotic bacteria in human health: a focus on inflammatory bowel disease. *Microb Cell Fact* 12, 71 (2013). https://doi.org/10.1186/1475-2859-12-71

48 National Cancer Institute. "NCI Dictionary of Cancer Terms." *National Cancer Institute*, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/disorder. Accessed 15 Dec. 2022.

49 Tiffany, Connor R., and Andreas J. Bäumler. "Dysbiosis: from fiction to function." *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 317, no. 5, 2019, pp. G602-G608.

50 "Enema." *TheFreeDictionary.com*, medical-dictionary.thefreedictionary.com/colonoscopy. Accessed 10 Nov. 2022.

51 National Cancer Institute. "NCI Dictionary of Cancer Terms." *National Cancer Institute*, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/gene. Accessed 15 Dec. 2022.

52 National Cancer Institute. "NCI Dictionary of Cancer Terms." *National Cancer Institute*, www.cancer.gov/publications/dictionaries/cancer-terms/def/gastrointestinal-tract. Accessed 10 Dec. 2022.

53 National Cancer Institute. "NCI Search Results." *National Cancer Institute*, www.cancer.gov/search/results?swKeyword=inflammation. Accessed 10 Dec. 2022.

54 National Cancer Institute. "NCI Search Results." *National Cancer Institute*, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hormone. Accessed 15 Dec. 2022.

55 National Cancer Institute. "NCI Search Results." *National Cancer Institute*, www.cancer.gov/search/results?swKeyword=microbiome. Accessed 10 Dec. 2022.

56 LibreTexts Biology. "10.4: Human Organs and Organ Systems." *Biology LibreTexts*, 13 Dec. 2021, bio.libretexts.org/Bookshelves/Human_Biology/Book%3A_Human_Biology_(Wakim_and_Grewal)/10%3A_Introduction_to_the_Human_Body/10.4%3A_Human_Organs_and_Organ_Systems. Accessed 15 Dec. 2022.

Proteins: Proteins are complex molecules that play many critical roles in the body. They do most of the work in cells and are required for the structure, function, and regulation of the body's tissues and organs[57].
Rectum: The last several inches of the large intestine closest to the anus[58]

[57] National Library of Medicine. "MedLinePlus: What are proteins and what do they do." *National Library of Medicine*, https://medlineplus.gov/genetics/understanding/howgeneswork/protein/#:~:text=Proteins%20are%20large%2C%20complex%20molecules,the%20body's%20tissues%20and%20organs. Accessed 10 Dec. 2022.

[58] National Cancer Institute. "NCI Dictionary of Cancer Terms." *National Cancer Institute*, www.cancer.gov/publications/dictionaries/cancer-terms/def/rectum. Accessed 10 Dec. 2022.