To flush or not to flush ... that is a question

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Abstract The human gut microflora has drawn a lot of attention as a potent therapeutic tool for many decades. More recently, efforts have been developed to devise efficient ways of complementing or replacing deficient intestinal microflora associated with intestinal diseases that are resistant to conventional medical treatments. Aside from the medical and industrial applications that emerged from the use of gut microbiota, the complex constitution of this ecosystem raises fascinating questions regarding host-cell communication and host response mechanisms to the ever changing environment. This brief comment also points to questions raised by some unexpected applications that have recently emerged from this field.

Keywords Cell communication · Microbiota · Prebiotics · Probiotics · Fecal transplants · Microflora · Fecal metals · Sludge recycling · Symbiotic relationships

The human intestinal microflora, also known as « microbiota »¹ comprises a population of about 10^{14} various microorganisms that include bacteria, archaeobacteria, fungi, viruses, yeasts and parasites whose distribution in the gastro-intestinal track depends on physicochemical conditions. For example, it was

established that bacterial colonisation is affected by the environmental acidity in the stomach and presence of bile in the small intestine, whereas, the colon environment is more favorable to the establishment of a microbiological niche that is estimated as $\sim 10^{12}$ microorganisms (Ley et al. 2006; Guarner and Malagelada 2003; Gallo et al. 2016).

With an estimated mass of 1 kg, the microbiota that is roughly ten times larger than the number of human cells, is involved in wide symbiotic relationships with its host (Ley et al. 2006, 2008; Mondot et al. 2013). For example, the normal functions of the microbiota include metabolism of xenobiotic drugs, as well as fermentation of polysaccharides and oligosaccharides that cannot be digested by the human body (Cummings et al. 1996).

These reciprocal interactions which are at the center of species evolution (Ley et al. 2008) and adaptability to the changing environment (Sun and Chang 2014) are exemplified by the influence of the microflora on the intestinal epithelial cell proliferation and differentiation (Gordon et al. 1997) and by its role in the development of the gut intestinal immune system (Purchiaroni et al. 2013).

Modifications of the microbiota have been linked to several human intestinal dysfunctions resulting in a wide variety of diseases (Li et al. 2016; Gallo et al. 2016).

Hence, an altered composition of the microbiota has been associated with metabolic syndromes such as obesity, type 2 diabetes, cardiovascular diseases, and liver diseases (Zhao 2013; Li et al. 2016).

It is believed that the gut microbiota can have an impact on host metabolism by either extracting energy from nutrients, or altering the expression of genes involved in energy metabolism (Li et al. 2016).

The dysfunctioning of microbiota has also been associated with immunological diseases such as inflammatory bowel disease, irritable bowel syndrome and type 1 diabetes.

¹ Whiteside et al. (2015) have defined the microbiota as taxonomically defined microorganisms within a specific environment, the metagenome as the genes and genomes of the microbiota, including plasmids, highlighting the genetic potential of the population and the microbiome as the genes and genomes of the microbiota, as well as the products of the microbiota and the host environment.

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An association between gut microbiota and brain development, behavior, autism and multiple sclerosis has also been reviewed (Li et al. 2016; Schéle et al. 2016)

Over the past decades, intestinal inflammatory disorders that are associated with microflora modifications have been at the center of considerable attention that crystalized a wide array of attempts to use controlled microbiota modifications in order to counterbalance the increased occurrence of these diseases, that are believed to signal the accumulation of environmental and societal factors impacting human health.

The increased frequency of intestinal diseases associated with aging (Li et al. 2016) points to nutritional behaviors as critical factors. Indeed, a study of gut microbiome variations with age and geography emphasized « the importance of a history of numerous common environmental exposures in shaping gut microbial ecology » (Yatsunenko et al. 2012).

Ectopic modulation of gut microbiota

Several strategies were developed to act upon the intestinal microbiota with the hope that they could lead to a significant improvement in human health conditions related to microflora destruction or deficiency.

A striking example is provided by *Clostridium difficile* infection (CDI) which is the primary cause of healthcare-associated disease with a mortality ranging from 5 to 40%. Typical antibiotic treatments involve the use of metronidazole, vancomycin, or fidaxomicin.² As classical antibiotic treatments did not prove capable of avoiding the very high rate of up to 35% relapse, alternative methods using prebiotics,³ probiotics⁴ and faecal microbiota transplantation (FMT) have emerged.

² Metronidazole treats infections caused by bacteria or parasites, by inhibiting nucleic acid synthesis by disrupting DNA and causing strand breakage.

Vancomycin acts by inhibiting cell wall synthesis in gram-positive bacteria.

Fidaxomicin inhibits RNA polymerase. It was reported to be superior to vancomycin in achieving a sustained clinical response for CDI in patients infected with non-BI/NAP1/027 strains (Zhanel et al. 2015).

³ Prebiotics are defined as « non digestible food ingredients that benefit the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon » (Gibson and Roberfroid (1995). They include diateray carbohydrates, fibers such as non-starch polysaccharides, and oligosaccharides that can escape host enzymatic digestion and provide a substrate for gut bacteria that specify carbohydrate enzymes.

⁴ Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the consumer » (Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria. Report of the Joint Food and Agriculture Organization (FAO) of the United Nations/World Health Organization (WHO) Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria. Cordoba: FAO/WHO, 2001). They include microorganisms that survive gastric acid and bile. Aside from *E. Coli*, *Lactobacillus*, *Streptococcus*, *Lactococcus*, *Bifidobacterium* and *Enterococcus* species, the most commonly used is the yeast *Saccharomyces boulardii*

FMT is the process by which a suspension of fecal matter from a healthy donor is transferred into the intestinal tract of a patient suffering of a disease resulting from an altered microflora.

In the 4th century China, Ge Hong, a traditional Chinese medicine doctor, described the use of fecal suspensions to treat diarrhea and poisoning. The concept was also possibly used in 17th century Italy (see letter to the editor by Zhang et al. 2012). In the late 90s' it has been used in occidental medicine to treat patients with pseudomembranous colitis (Eiseman et al. 1958) Since then, it has been successfully applied as a method with much better success than antibiotics for treating CDIs.

FMT can be performed either with a nasogastric or nasoduodenal tube, or a colonoscope, via enema, or by capsule ingestion.

In addition to its use against *Clostridium difficile* infections, FMT appears as an interesting approach for obesity treatment, providing that rigorous donor screening is performed in order to avoid spread of transmissible diseases and to avoid transmission of an unwanted phenotype, as exemplified by a case study which reported the transmission of an obese phenotype to a lean patient following FMT for CDI treatment (Marotz and Zarrinpar 2016)

Although concerns have been raised regarding the adverse effects of fecal microbiota transplants and the need for standardization before industrialisation (Baxter and Colville 2016; Lagier 2014), FMT has found its way to the market, as shown by the number of internet advertisements claiming the benefits of using « poop pills » to fight obesity.⁵

Whether the use of stools will create a new opportunity for anyone in good health to make money is not absolutely certain but new findings point to fecal matter as an unexpected source of revenue....

Recycling golden stools

For many years, industrial research has worked on human domestic sewage treatment. The nutrient-rich materials that are extracted and processed from the treated sewage sludges

⁵ A few examples of web sites for fecal pills marketing include :

<http://www.thehealthyhomeeconomist.com/as-antibiotic-failure-grows-poop-pills-filling-the-void/>; <http://www.dailymail.co.uk/news/article-2442891/Poop-pills-feces-healthy-people-guts-patients-infections.html>; <https://www.washingtonpost.com/news/innovations/wp/2016/01/14/eating-poop-pills-could-make-you-thin-seriously/>; www.openbiome.org/fmtcapsules; http://www.nytimes.com/2015/11/10/health/fecal-transplants-made-somewhat-more-palatable.html?_r=0; <http://www.mirror.co.uk/news/technology-science/science/frozen-poo-pills-made-donated-4435372>; <http://www.foxnews.com/health/2013/10/03/pills-made-from-poop-could-cure-serious-gut-infections.html>; <http://www.nydailynews.com/lifestyle/health/poop-pills-tested-obesity-treatment-article-1.2493003>; <http://www.themarysue.com/poop-pills-pills-made-from-poop-could-fight-serious-infection/>; <http://www.sciencealert.com/human-trials-will-test-freeze-dried-poop-pills-as-a-weight-loss-treatment>; <http://healthland.time.com/2013/10/04/the-latest-thing-in-pills-ones-made-from-poop/>

can be recycled and used as fertilizers to improve the quality of soils, and plant growth.

Because the crops and other living organisms that are grown on fertilized soils are likely to be transformed into food for humans, governmental regulations apply to each of the physical and chemical steps of the recycling activity to remove the solids from wastewater in order to produce biosolids which can be used safely.

Today, in the USA, biosolids⁶ are used as fertilizers in all states, on about one percent of all agricultural land. The use of biosolids also has to comply with specific rules.

The federal register 40CFR Part 503⁷ establishes the standard for the use or disposal of sewage sludge.

Biosolids that belong to class A contain no detectable levels of pathogens and meet strict numerical limits for metal content, as it is well established that metal ingestion can be harmful to human.

New methods for metals and energy recovery from sewer sludges have been reviewed recently (Mulchandani and Westerhoff 2016). These technologies are aimed to better recover metals while inactivating pathogens and eliminating or destroying organic pollutants.

The results of a recent study reported by Westerhoff et al. (2015) indicated that metals contained in biosolids from a community of 1 million people are valued up to \$13 M per year.

Among these are 13 valuable elements that include silver (Ag), Copper (Cu), Gold (Au), Phosphorus (P), Iron (Fe), Manganese (Mn), Zinc (Zn), Palladium (Pd), Lawrencium (Ir), Aluminium (Al), Cadmium (Cd), Titanium (Ti), Gallium (Ga), and Chromium (Cr).

According to Mulchandani and Westerhoff (2016), extracting these metals from sewage sludges could lead to an economic value of \$280 per ton of sludge of which phosphorus reaches \$24 per ton.

One can easily envision the potential monetary return for a society that would make the effort to extract these metals if the cost of wastewater treatment is worth the process.

For a nation like France, provisional calculation indicates that about 800 millions euros per year could be drawn from such recovery processes.⁸

What if the recycling of human stools, applied to health improvement via the use of fecal pills, becomes a profitable activity? So profitable that it becomes another internet-based « very big business ».

Would it signal the dawn of a new era where selling human « waste » would be permitted?

And what if concentration of municipal effluent at the arrival of the water at the treatment plant (Verstraete et al. 2009) has become so efficient that the chemical recycling of the stools to produce fertilizers is combined with its biological treatment?

Would that affect the way we deal with our « solid biological waste »?

These are certainly questions that the next generation will have to address.

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⁶ Frequent questions about biosolids : <https://www.epa.gov/biosolids/frequent-questions-about-biosolids>

⁷ Legal information institute CFR Title 40, chapter 1, Subchapter O, Part 503. <https://www.law.cornell.edu/cfr/text/40/part-503>

⁸ A. Alberti « Il y a de l'or dans vos WC » *Energie et matières premières* 5 septembre 2016

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