Exploring the Microbiome:

The Good, The Bad, and The Hungry

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Abstract

This paper offers an overview of the human microbiome, what it is made up of, where it is found, who it affects, and the possible consequences of an unbalanced internal flora. The discoveries that led to current microbiome research will be discussed. The largest such exploration to date, the Human Microbiome Project, supplied us with the more information about our microbes than all studies before it. Much of the research presented in this paper was made possible by the Human Microbiome Project. The microbiome's influence on the immune system and disease states, such as Crohn's Disease and ulcerative colitis, will be introduced. Good and bad bacteria, as well as prebiotics, probiotics, and fermented foods will also be included. The conclusion will include personal views, that will never be the same due to this project.

The invention of the first compound microscope in the late 16th century would forever change the world. We would no longer be bound by our own vision or of that through a single magnifying lens. Imagine how strange it must have seemed to, for the first time ever, be able to see things that were so tiny they were invisible to the naked eye! Not long after, during the mid-1600s, the first microbes were described. Antonievan Leeuwenhoek discovered bacteria in 1676. By the 1800s the connection between microbes and disease had been made. Cultures, staining, and microscopy have been used since the 1800s to study many microbes. The word "microbiome" was coined in the 1950s; from the words micro, meaning very small, and biome, a community. It was not until the 1990s that a new technology would be created that would allow scientists to study microbes that were not able to be cultured. DNA sequencing would change microbiology indefinitely.

We are not alone. The body is home to trillions of microbes, forming the microbiota, existing in symbiosis with their host every day. A microbe is a microscopic organism; a living thing so tiny that we must use a microscope to see them. Microbes include bacteria, protists, archaea, fungi, viruses, and microscopic animals. Together the trillions of microbes found on and inside of each living person make up a community called the microbiota. Rogers (2011) stated "the sheer microbial abundance suggests that the human body is in fact a 'superorganism,' a collection of human and microbial cells and genes and thus a blend of human and microbial traits." The human genome includes the complete set of genes or genetic material in each cell or person as a whole. The microbiome includes the genetic material of all the microorganisms in a specific environment, such as the human body. The microbiome may be made up of as many as 1000 more genes than are present in the human genome. Despite the large quantity of microbes in the body, they are so tiny that they make up only 1 to 3 percent of the human body mass.

A symbiotic relationship is one between two or more organisms that live closely; categorized as commensalism, no organism harmed or helped; mutualism, benefiting both organisms; or parasitism, benefiting one organism while causing harm to the other. Symbiosis requires a delicate balance. Many years of cohabitation have fostered these relationships. The Genetic Science Learning Center (2014) stated "bacteria were the first living things on the planet, and all of the Earth's other creatures have been living and evolving with them for hundreds of millions of years." Bacteria make up the largest percent of the microbiome; and even outnumber the somatic cells.

Although there are a few microbes that can be very harmful, most are harmless, and some are even essential. Microbes assist the breakdown of food for essential nutrient absorption, as well as produce vitamins that human genes are unable to produce on their own. They are also very important to the immune system. Microbes help to recognize invaders, fight off pathogenic microbes, and manufacture anti-inflammatory compounds. They help to prevent harmful bacteria from colonizing the gut as well.

Plant and animal development would not be what it is today without microbes. The Wolbachia bacteria, for instance, infects arthropods and roundworms, sometimes causing sexual incompatibility. This results in the infected animals only being able to reproduce with other infected animals; the uninfected animals only being able to reproduce with other uninfected animals. The Genetic Science Learning Center (2014) explains that the "Wolbachia infection may create the 'reproductive isolation' necessary for one species to diverge into two."

"Personal space", three feet specifically, has been spoken about for years. Now there is science to back up asking for 36 inches. There is such a thing as a microbial cloud Hanae Armitage reported in a 2015 issue of Science. These clouds of "airborne bacteria may be

entirely unique to each person, like a microbial fingerprint," (Armitage, 2015) she explained. It is estimated that the cloud surrounds each person 90-centimeters in each direction, or 35.4 inches. Armitage (2015) stated "researchers speculate that when microbes mix, humans may take bacterial souvenirs from one another, a potential contributor to how we develop our individual microbiomes."

As the study of the ever-changing human microbiome progressed, countless questions arose, giving life to the Human Microbiome Project (HMP) in 2008. Established by the National Institutes of Health (NIH), the HMP set out on a mission to generate resources that would allow for the in-depth characterization of the human microbiome and the investigation of the role it has on health and disease. The NIH Human Microbiome Project (2017) reported that "an ever-growing number of studies have demonstrated that changes in the composition of our microbiomes correlate with numerous disease states, raising the possibility that manipulation of these communities could be used to treat disease."

Microbiology is the study of microorganisms, traditionally via cultures, staining, and microscopy. These methods were not without limitations. Many species were unable to be studied because they ceased to grow once removed from their environment. Metagenomics is a new field of research based on the advances made in DNA sequencing, making it possible for comprehensive exploration of the human microbiome without microbe cultivation. Rather than studying lab-grown genomes, independently, metagenomics allows for the examination of groups of genomes as they would live in microbial communities in their natural habitats.

With these technological advancements, the Human Microbiome Project was able to collect and study ground-breaking information revealing the mysterious human microbiome more than ever before. By 2012, when the HMP contributors published multiple articles and

created a database of their findings, they had made several major accomplishments. They had isolated and sequenced over 2,200 reference strains from the human body. There had been over 11,000 samples derived from 5 major body sites (oral cavity, nasal passages, skin, GI tract, and urogenital tract), 15 specific body sites of men, 18 specific body sites of women, collected from 300 healthy adults aged 18 to 40. They made both the raw and the processed sequencing data for reference and metagenomic strains available via the legacy HMP1 Data Browser. In the June 14, 2012 issue of Nature, two critical papers were published by the iHMP Consortium, followed by a number of complementary papers in multiple PLoS journals. The HMP (2017) described these papers as having established "a foundation to catalyze and aid a myriad of studies ranging from basic to transitional to clinical." In one of the landmark papers published in Nature, The Human Microbiome Project Consortium, Hutlenhower, and Gevers (2012) concluded "the HMP's unique combination of organismal and functional data across body habitats, encompassing both 16S and metagenomic profiling, together with detailed characterization of each subject, has allowed us and subsequent studies to move beyond the observation of variability in the human microbiome to ask how and why these microbial communities vary so extensively."

It is now possible to explore which microbes are beneficial and which are harmful, in more depth than ever before. The HMP (2015) explained that "an ever-growing number of studies have demonstrated that changes in the composition of our microbiomes correlate with numerous disease states, raising the possibility that manipulation of these communities could be used to treat disease." One way to alter the human microbiome is with probiotics. These are microorganisms that may be administered orally, vaginally, even anally through fecal transplant. When properly dosed, probiotics may have health benefits for the host. Probiotics, just like the natural human microbiome, are beneficial to the immune system, digestive system, vitamin

production, and nutrient absorption. Probiotics are a newer field of study, yet there has been strong evidence associated with several specific health benefits. Sanders (2016) found probiotic supplementation beneficial with "reducing antibiotic associated diarrhea, improving mild to moderate IBS and other digestive symptoms, reducing crying time in colicky but otherwise healthy infants, reducing the incidence and duration of common upper respiratory tract infections and helping manage vaginal infections."

The majority of the immune system's role is maintaining homeostasis with the microbiome. Buford (2017) points out, this is evident "by the fact that 70% of the body's lymphocytes reside in the gut-associated lymphoid tissue." Lymphocytes are small white blood cells found in the lymphatic system, which help to remove waste and toxins from the body, and transport lymph, fluid containing the infection fighters. The microbiota and the immune system work along-side each other throughout a host's entire life. Human exposure to microbes is seen first, just after birth. The lungs and gastrointestinal tract are affected the most. Olszak, et al. (2012) stated "epidemiologic observations further suggest that the immune effects of early-life microbial exposure are durable and persist into later life because they can be associated with prevention of diseases such as inflammatory bowel disease and asthma."

Research is currently being carried out to further our knowledge on probiotics, as well as prebiotics. Salvin (2013) stated the updated definition of a prebiotic as being "a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits" (p. 1417). She includes them if they meet the following criteria: "resists gastric acidity, hydrolysis by mammalian enzymes, and absorption in the upper gastrointestinal tract; is fermented by the intestinal microflora" and "selectively stimulates the growth and/or activity of intestinal bacteria potentially associated with health and

well-being" (Salvin, 2013, 1417). According to Scott (2016) prebiotics may benefit those with or at risk for osteoporosis, diabetes, and colorectal cancer by increasing the absorption of calcium, enhancing the reaction of carbohydrates, possibly decreasing blood-glucose spikes, and contributing to superior colon microbiota, ultimately speeding up waste removal.

All prebiotics are fiber, yet not all fibers are prebiotic. The microbes of the large intestine require fiber to thrive. Courage (2016) stated "as fiber intake declines, so, too, does the range of bacteria that can survive in the gut." She goes on to present that many researchers, including Erica Sonnenburg (microbiologist) of Stanford University, have been lead to "suspect that the well-documented low diversity of gut microbes among people in developed countries – some 30% less diverse than in modern hunter-gatherers-is, in part, a product of drastically reduced fiber intake." Long ago, the fiber intake was estimated to be around 100 grams per day. Currently it is recommended that women consume a minimum of 25 grams of fiber per day, men 35 grams per day. In reality people currently consume about 15 grams of fiber per day, if that. At this time, it is recommended that people ingest fructooligosaccharides (FOS) or galactooligosaccharides (GOS) as the most effective types of probiotics; 5 to 8 grams per day for best practice.

Recently, it has been found that not only the natural microbiome, and supplemented probiotics could influence disease state, but that prebiotics, too, could make a difference. Scott (2016) stated "new research is investigating how prebiotics might be used in the management of gut diseases like inflammatory bowel disease (ulcerative colitis and Crohn's disease) and irritable bowel syndrome, and even obesity." It is not unlikely she added that "in future, specific prebiotics could be designed to boost numbers of specific bacteria known to be less abundant in certain diseases" (Scott, 2016).

There are several conditions categorized as inflammatory bowel diseases (IBD). Cenit, Matzaraki, Tigchelaar, and Zhernakova (2014) explain that the colon and the small intestine house many of these inflammatory conditions, including the most common two: Crohn's Disease (CD) and ulcerative colitis (UC). While ulcerative colitis is generally limited to the colon (as the name hints), Crohn's Disease can inflame any part of the gastrointestinal tract. Cenit, et al. (2014) described that "typically, IBD patients show an overall decreased diversity of gut bacteria and, specifically, a reduction in the members of the dominant Firmicutes and Bacteroidetes compared to healthy people." Patients with ileal and colonic Crohn's Disease have been noted to have different microbial profiles; higher levels of Lachnospiraceae seen in ileal CD patients, but not those suffering with colonic CD.

Patients with different types of IBD have also been shown to share many microbial similarities. Cenit, et al. (2012) stated "a greater relative abundance of proteobacteria, which include common enteric pathogens such as the family of Enterobacteriaceae and a reduction in beneficial microbes, such as those producing butyrate, with Faecalibacterium prausnitzii being the main producer, have been observed in IBD patients." These findings and many more were made possible by the Human Microbiome Project and DNA sequencing. Cenit, et al. (2012) also noted that in both UC and CD, fungal diversity had expanded, but more research would be necessary to uncover the relation.

Peptic ulcers, including those of the stomach and the upper portion of the small intestine, are either caused by long-term use of painkillers, or an infection of the bacteria Helicobacter pylori (H. pylori). Some studies have been done in an effort to show that while H. pylori has a harmful effect in the gastrointestinal tract, it may be beneficial in the esophagus. At the completion of a multiple work review, Polyzos, et al. (2017) stated that some of the studies and

all of the meta-analyses reviewed "reported an inverse association between H. pylori infection and EAC, interpreted as a protective effect by some authors, our personal relative consideration and those of the others do not agree." In order to test the theory, H. pylori would have to be injected into people at risk for esophageal cancer. Would the reward outweigh the risk? Polyzos, et al. (2017) concluded that it would not, due to ethical constraints.

In the 1940s, antibiotics were discovered. They could be used to kill bad bacteria in the body, but were not selective; they would kill the good bacteria also. Alexander Fleming warned the public of such during his Nobel Prize acceptance speech in 1945. "There is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant," Fleming forewarned (Tete, 2013). Antibiotics have their benefits, both for the sick person, and for their community, so that the contagious agent does not circulate. They are harmful for two reasons. The first, that people would build up a resistance. The second, as Blaser (2016) explained, is "the cost that an antibiotic exerts on an individual's own health via the collateral damage of the drug on bacteria that normally live on or in healthy humans: our microbiota."

Recently, the beliefs that antibiotics could possibly put people at risk for obesity, asthma, and inflammatory bowel disease have been entering the research field. Bad bacteria, Nutritionfacts.org (2017) described, may "putrefy protein in our gut, produce toxins, mess up our bowel function, and cause infections." As if resistance, gastrointestinal issues, putrefied protein, and infection were not enough, excessive antibiotics may cause a person to develop Clostridium difficile (C. diff). This infection causes nausea, abdominal cramping, and severe diarrhea. Rogers (2011) related the effective treatment as being "through fecal, or stool, transplantation, in

which fecal material from a healthy person is transferred to a patient, thereby restoring populations of beneficial gut microbiota."

With all the possible side effects of antibiotics, it is sometimes hard to distinguish what is worse, no bacteria or bad bacteria. One example of a very harmful bacteria is Toxoplasma, a parasitic protist that infects rodents (mice and rats), and also people. To sexually reproduce, the protist must infect a cat. Once the parasite has infected a rodent, it will enter their brain, changing their behavior. The host rodent will become less fearful of cats, more active, and consequently more likely to be caught and eaten. Toxoplasma does not only negatively affect the brain of rodents. The infection has been correlated with mental condition, such as: obsessive-compulsive disorder, autism, and schizophrenia. The Genetic Science Learning Center (2014) stated that "the link between toxoplasma infection and schizophrenia is stronger than for any single gene identified to date."

Although we have learned an immense amount of information in the previous several decades, majority during the most recent, there is still so much left undiscovered. Buford (2017) explained that "a variety of biologic, medical, and lifestyle factors appear to contribute to gut dysbiosis in late-life, and interventions specifically designed to target these factors may be useful in restoring microbial balance and attenuating inflammation." There has been much research started that perhaps one day will show how the microbiome may relate to autism, Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Many disease states show age-related increases. Buford (2017) stated "it seems relevant to explore the possibility that age-related inflammation may stem at least partially from changes to the gut microbiome."

With so much room to explore, and so many things still to learn, the best thing people can do for their own gut health is to eat a healthy, varied, plant-based diet. Fermented foods,

prebiotics, and probiotics may all add to the existing microbiome. Scott (2016) explains "eating whole grains, fruits and vegetables, and other fibre-rich foods can also help boost numbers of our 'healthy' microbiota, and in turn contribute to gut health." Prebiotic and probiotic supplements are no replacement for a healthy and diverse diet though. Even the top-rated probiotic supplements come nowhere close to supplying all the different types of microbes naturally found in the human microbiome.

Prebiotics may be found naturally occurring in foods including: chicory, artichoke, garlic, onion, asparagus, leeks, soybeans, bananas, wheat, and oats. A large quantity of these foods would be required in order to reach the recommended 5 to 8 grams of prebiotic fiber per day. Fermented foods may help to add probiotics to the microbiome. Not all fermented foods contain live organisms though. Wine, beer, tempeh, and chocolate, all undergo different processes that eliminate the live organisms. In order to get the probiotic effect from fermented foods, raw and less processed types must be consumed; including: kefir, fresh yogurt, aged cheese, and fresh kimchi. Fermented foods are believed to benefit the health by aiding in the upkeep of a healthy microbiome, and also reducing the risk of some diseases. The organisms found in fermented foods may not be the same strains found in probiotic supplements, but they may still share many of the beneficial traits.

The microbiome is amazing. There has been so much research already completed and countless stones left unturned, regarding the human microbiota. Advances in DNA sequencing made it possible to begin exploring how the human microbiome effects disease states, such as Crohn's Disease, ulcerative colitis, obesity, asthma, and Alzheimer's disease. The science world has only just begun to delve into all the ways the microorganisms inside us may be affecting our

health, and how what we consume may be the reason they do what they do. The possibilities seem endless!

Writing this paper has answered some of my questions about probiotics, but has me asking so many more questions about the human microbiome. As a science major, I wanted to study nutrition. I had recently been considering a dual major of nutrition and biochemistry. Reading all of the articles and papers that I have come across the last few months has me questioning exactly what I want to do again. I had no idea how interesting the microbiome would be! I have numerous articles that I could not get to for this paper, saved on my browser for later review. This paper could easily be part one of a trilogy. There is no turning back now. We are not alone.

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