Postbiotic Metabolites: The New Frontier in Microbiome Science

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The human microbiome is now known to be relevant to virtually every branch of science, medicine, and human health; and microbiome science is evolving rapidly. The purpose of this article is to summarize the history of the human microbiome and to introduce readers to postbiotic metabolites, which is the new frontier in microbiome science.

Louis Pasteur (1822-1895) was the first microbiome scientist. Pasteur made breakthrough discoveries regarding vaccination, microbial fermentation, and pasteurization. Pasteur's medical discoveries enabled him to create cures for many of the world's major killer diseases during his time including rabies, anthrax, tuberculosis, cholera, and smallpox. Consequently, Pasteur became known, respected, and loved throughout the world; and he was the first scientist to become an internationally known "global rock star."

Pasteur's accomplishments are absolutely mind-boggling. A modern-day equivalent would be if one scientist today single-handedly created cures for cancer, heart disease, diabetes, and Alzheimer's disease. However, Pasteur's accomplishments also ushered in the widespread belief that germs are the cause of diseases, which initiated the germ theory of disease.[1] This resulted in a century of bacteria-phobia and gave rise to the era of antibiotic drugs. However, during the past several decades, the over-prescribing of antibiotics has resulted in microbiome destruction, weakened immune systems, and the rise of deadly antibiotic-resistant "superbug" infectious diseases.

Elie Metchnikoff (1845-1916) was a Russian-born scientist who developed an interest in the study of beneficial microbes. In 1888, Metchnikoff traveled to Paris to meet Pasteur and ask Pasteur's advice regarding some difficulties he was experiencing with his research. Pasteur was impressed with Metchnikoff and invited him to stay, setting him up with his personal laboratory. In 1904, Metchnikoff was promoted to deputy director of the Pasteur Institute where he remained for the rest of his highly productive career. In 1908, Metchnikoff won the Nobel Prize for medicine for his discovery of phagocytosis and its importance to the immune system.[2]

At the Pasteur Institute in the early 1900s, Metchnikoff became increasingly interested in human health and longevity. He learned that Bulgaria had a disproportionately high number of healthy elderly citizens. He conducted a study and compiled statistics from 36 countries, which led him to discover that Bulgaria had more people who lived to be 100 years of age than any of the other 36 countries he surveyed.

Metchnikoff believed that the aging process resulted from the activity of "bad" bacteria that produce toxic substances in the intestinal tract. According to Metchnikoff, these toxic compounds were responsible for what he referred to as "intestinal auto-intoxication," which caused the physical deterioration and breakdown associated with aging.

And then, Metchnikoff had a tremendous intuitive insight that made him the "Founding Father of Probiotics." Metchnikoff believed that the long healthy lifespans of Bulgarians was related to their daily consumption of fermented milk products like yogurt and kefir. He knew the bacteria responsible for the fermentation of milk produced lactic acid, which created an acidic environment in the GI tract. He theorized that the lactic acid created a slightly acidic environment, which, suppressed the growth of toxin-producing bacteria. The net result was a reduction of "intestinal auto-intoxication," which resulted in better health and longer life.

In 1907, just two years after making his landmark proposal that the ingestion of *Lactobacillus bulgaricus* was responsible for the health and longevity of Bulgarians, Metchnikoff published his findings in his book titled, *The Prolongation of Life: Optimistic Studies*.[3] Consequently, Metchnikoff is also credited as the founding father of the life extension movement.

The Modern Era of Microbiome Science

The human microbiome refers to the organisms (bacteria, fungi, and viruses) that reside in and on our body. When I

use the term microbiome in this article, I am limiting its scope to the bacteria that reside in the gastrointestinal tract.

The Human Genome Project, which cost an estimated $3 billion, was a 13-year (1990-2003) project that resulted in the first successful sequencing of the human genome. Scientists hoped that sequencing the human genome would lead to cures for many of today's chronic degenerative diseases. That goal was a complete failure; sequencing the human genome never led to successful treatments for any diseases.

However, one great benefit that emerged from the Human Genome Project was the development of incredible technology that allows scientists to sequence genomes rapidly and at a vastly reduced price. For example, in January 2017, Illuminia, which is the world's leading producer of next-generation sequencing technology, announced that their new NovaSeq™ could sequence a genome in one day for only $100.[4] From 13 years and $3 billion to one day for $100. How's that for rapid scientific advancement!

The incredible power and speed of the new gene sequencing technology were partly responsible for the government's funding of the Human Microbiome Project (2007-2012).[5] Subsequently, the Human Microbiome Project resulted in the publication of over 350 studies, which are viewed as the "birth" of the modern era of microbiome science. In May 2016, the Obama administration committed to continue supporting microbiome scientific research by funding the National Microbiome Initiative. This program is sponsored with $121 million in funding from federal agencies and an additional $400 million from non-government institutions.[6]

The Genome Complexity Conundrum

When scientists successfully sequenced the human genome, they discovered that humans have about 23,000 genes, which is substantially fewer than they expected. This finding initially caused scientists to shake their heads in disbelief and created a situation that became referred to as the "genome complexity conundrum."[7]

The challenge was due to the following facts. Whereas humans have about 23,000 genes, the common rice plant (*Oryza sativa*) has about 45,000 genes. This led scientists to scratch their heads and say or think, "If we humans are as complex and evolved as we think we are, how can it be that we only have half as many genes as the common rice plant?"

The answer to the genome complexity conundrum began to emerge when scientists discovered that the intestinal tract of most humans is home to an estimated 100 trillion bacteria. A human harbors from 500-1,000 different species of bacteria and these bacteria contain over 3.3 million non-repeating genes. This means that over 99% of the DNA in your body is the DNA of your bacteria. This explains why humans can "get by" with only 23,000 genes. Bacteria utilize the information contained in their vast amount of DNA to produce compounds that are responsible for directing and regulating a great deal of the functioning of the human body. This explains why it is so critically important for people to learn how to create and maintain a healthy microbiome. Your bacteria are involved, either directly or indirectly, in the regulation and control of much of what happens in your body.

This realization has also resulted in a new understanding of what it means to be human as scientists began to realize that we are not just the product of our human genes. Instead, we are a bacteria-controlled superorganism. We are not just "us"...we are "us" plus "them."

Postbiotic Metabolites: The New Frontier in Microbiome Science

As scientists started to realize how incredibly important our probiotic bacteria are in the regulation of health, they began looking for mechanisms. How and why are probiotic bacteria capable of regulating so much of our human biological functioning?

Probiotic bacteria are amazingly complex little chemical manufacturing plants. Their metabolic processes enable them to digest and ferment the fibers in foods, which results in the production of a wide range of health-regulating compounds that known as "postbiotic metabolites."

In the new frontier of microbiome science, much more emphasis is being focused on identifying the compounds that various strains of bacteria produce, learning to understand the health-regulating effects of these compounds, and discovering which strains of bacteria are more efficient at producing these health-regulating compounds.

A PubMed search reveals that "postbiotics"[8,9] and "postbiotic metabolites"[10] are terms that are used with increasing frequency in the title of scientific studies. In *The Mind-Gut Connection*, respected author and microbiome scientist Emeran Mayer, MD, states that our bacteria utilize the information in their millions of genes to transform the food people eat into "hundreds of thousands of metabolites."

A pronounced shift is taking place in microbiome science. Until recently, a large portion of scientific research was devoted to isolating, identifying, and naming different species of bacteria. In the new frontier of microbiome science, much more emphasis is being focused on identifying the compounds that various strains of bacteria produce, learning to understand the health-regulating effects of these compounds, and discovering which strains of bacteria are more efficient at producing these health-regulating compounds.

Balance and Diversity: Critical Factors for Microbiome Health

Diversity refers to how many different strains of bacteria are present in the intestinal tract. Numerous human clinical trials report that a more diverse microbiome equates to better health.[11,12] Scientists estimate that a healthy human microbiome contains approximately 1,000 different species of bacteria.[13] On the other hand, low bacterial diversity in the intestinal tract can contribute to various diseases such

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as obesity[14] and inflammatory bowel disease.[15]

The Fiber Gap: America's #1 Nutritional Deficiency

Fiber is the required food for your probiotic bacteria. A recent article titled "The Fiber Gap and the Disappearing Gut Microbiome: Implications for Human Nutrition" discusses how low fiber diets are affecting people's microbiome and ultimately, their health. The authors of this study report that an alarming **90% of children and adults in America DO NOT consume the recommended amount of daily dietary fiber**.[16] Scientific studies provide convincing evidence that the microbiome is the very foundation of health.[17,18] It is becoming alarmingly clear that the Standard American Diet, known as the SAD diet, is more than just SAD, it is killing people.[19]

It's not enough to only take probiotics, you must learn to feed your probiotic bacteria well. Non-digestible carbohydrates and fibers are the "food" that your probiotic bacteria require. Different species of probiotic bacteria thrive on different kinds of fibers that are present in different kinds of plant-based foods. Eating a more diverse fiber-rich diet is the way to develop and maintain a more diverse microbiome. If your probiotic bacteria are not supplied with a diverse, fiber-rich diet, they will not thrive and survive.

The quantity of fiber in the daily diet is not the only fiber issue. A diversity of fiber-rich foods is required to promote the growth of a diverse microbiome. How many different kinds of colored, fiber-rich fruits and vegetables are you feeding your probiotic bacteria today?

Many people now take probiotics, which is confirmed by the dramatic increase in sales within this category. In 2005, sales of probiotics in the United States was $764 million.[20] In 2014, probiotic sales reached $1.41 billion, and from 2014 to 2017, sales nearly doubled to $2.14 billion.[21] However, since the vast majority of Americans are not consuming high-fiber diets, it can be assumed that many people are not getting much benefit from the probiotics they are taking.

For an easy way to increase the diversity of fiber-rich foods in your daily diet, I suggest you watch my 8-minute YouTube video which teaches people how to save an enormous amount of time making salads that contain a wide variety of fiber-rich vegetables. Just Google: Ross Salad Buzz.

Balance is also a critical factor in healthy microbiome. Unfortunately many people who purchase probiotics have the mistaken understanding that more is better. It is now common to see products claiming to be superior because they contain 50 billion bacteria or even 100 billion bacteria per dose. The fact is, massive doses of just one or several strains of probiotic bacteria does not promote microbiome balance; they actually work against balance, and this is why. Probiotics that deliver very high doses of just one or several strains of bacteria can cause the immune system to trigger an alarm reaction. The authors of one study made the following statement in their conclusion, "Probiotics can be ineffective or even detrimental if not used at the optimal dosage for the appropriate purposes."[22]

Balance and greater diversity are imperative because these factors result in the production of a broader range of postbiotic metabolites. Some of their benefits include reduced inflammation, regulating the acid/base balance in the GI tract, directly fighting pathogens, regulating digestion, absorption of nutrients, detoxification, regulating the immune system, gut-brain communication, and much much more. Remember, in *The Mind-Gut Connection*, Dr. Meyer stated that your bacteria would produce "hundreds of thousands of metabolites." This is why postbiotic metabolites are now becoming the new frontier in microbiome research.

A Microbiome Analogy

The "goal" in an automobile manufacturing plant is the production of vehicles such as cars, trucks, SUVs and vans. The workforce in an automobile manufacturing plant consists of hundreds of employees with a wide variety of skills and talents. However, the skills and abilities of this workforce are largely ineffective unless they have the thousands of parts that are required to produce different kinds of vehicles.

Similarly, in your microbiome, you have between 500 to 1,000 species totaling an estimated 100 trillion bacteria that function as the workforce. However, your probiotic "workers" must have available a wide variety of fiber-rich foods (the parts) in order to create the desired end products, which are the postbiotic metabolites. Probiotic bacteria are primarily a "workforce," and their "job" is to build/create postbiotic metabolites.

Dysbiosis

Dysbiosis is generally considered to be an imbalance between the good and bad bacteria in the intestinal tract. However, dysbiosis is more than just bad bacteria. In dysbiosis, the gastrointestinal environment or the microbiome ecosystem has become upset and damaged. In addition to bacterial imbalance, the acid/base balance is usually far too alkaline, the cells that line the GI tract are highly inflamed, the protective mucous layer can be compromised, the gut barrier is damaged and allows intestinal permeability, and cell-to-cell communication and gut-brain communication is dysfunctional. Ideally, the best way to fix gut dysbiosis problems is to address the whole microbiome ecosystem.

The Microbiome Ecosystem's Two Pieces

Postbiotic metabolites are the compounds that control and regulate the microbiome ecosystem. There are two pieces to this puzzle. Probiotic bacteria AND fiber-rich foods are needed to produce postbiotic metabolites. And, a wide diversity of probiotic bacteria AND a wide diversity of fiber-rich foods are necessary in order to have a wide

diversity of postbiotic metabolites produced.

Reestablishing the Microbiome Ecosystem

Most people take probiotics to address dysbiosis-related intestinal problems. However, for probiotics to be effective, those bacteria need access to high-fiber foods in the GI tract. Then, the bacteria have to begin the process of breaking down the foods so they can access the fibers and start the process of converting fibers into postbiotic metabolites. This process takes time.

Confounding the process is the fact that the ingested probiotic bacteria are likely entering into a very hostile environment that is highly inflamed, 10 to 100 times too alkaline, and overrun with "hostile" pathological bacteria. As an analogy, consider the problem of sending Eskimos to fight in the Sahara Desert, or desert nomads to fight in freezing Alaska. They will have great difficulty being effective.

The Benefits of Fermented Food

Fermentation is a process in which bacteria break down sugars, carbohydrates and fibers in foods and convert them into alcohol and organic acids. Fermentation has been used by humans for thousands of years as a method to preserve foods. Over time, people realized that fermented foods also conveyed health benefits.

Until recently, people thought the health benefits from fermented foods such as sauerkraut, kimchi, miso,and tempeh were due to the ingestion of probiotic bacteria contained in the fermented foods. However, it is becoming clear that the food preservation properties AND the health benefits from fermented foods are primarily due to the postbiotic metabolites produced by the bacteria during the fermentation process.[23]

Several metabolites produced during fermentation are classified as short-chain fatty acids (SCFAs) such as acetic, propionic, and butyric acid. These small molecular weight acidic compounds are postbiotic metabolites that play a critical role in food preservation because they create a slightly acidic pH which inhibits the growth of pathogens.

Recent human clinical trials have revealed strong associations between consumption of fermented foods and improved health for conditions such as obesity,[24] type 2 diabetes,[25] hyperlipidemia,[26] hypertension,[27] osteoporosis,[28] and depression.[29] These studies emphasize that an individual's probiotic bacteria and the postbiotic metabolites they create have important effects far beyond just gut health.

Most people take probiotics to address dysbiosis-related intestinal problems. However, for probiotics to be effective, those bacteria need access to high-fiber foods in the GI tract.

Directly Ingesting Postbiotic Metabolites = FAST ACTION

As mentioned previously, it takes time for ingested probiotic bacteria to locate fibers, break them down and produce postbiotic metabolites. A faster and more effective way to address dysbiosis-related problems is to ingest postbiotic metabolites.

When ingested orally, postbiotic metabolites immediately begin asserting their health-promoting activities such as readjusting the acid/base level, reducing inflammation, accelerating the growth of healthy new cells in the lining of the GI tract, "fighting" and killing pathological bacteria, and re-establishing healthy gut-brain communication. This circumvents the time-consuming process of probiotic bacteria needing to locate fibers and begin producing postbiotic metabolites.

Metabolomics and Metagenomics

Metabolomics and metagenomics are two scientific disciplines that are barely twenty years old. These relatively new fields of science are developing very fast, in large part, due to the fundamental importance of the microbiome.

Metabolomics is the branch of science that identifies small molecule metabolites in biological systems, such as the postbiotic metabolites produced by bacteria in the gastrointestinal tract. Rapid advances in metabolomics have resulted in the discovery of thousands of bacteria-produced small-molecule metabolites, or postbiotics.[30]

Microbes run our world. The new science of metagenomics is unlocking the secrets of our microbial planet. Metagenomics, defined as the *genomic analysis of microorganisms*, is discovering the genes in bacteria that are responsible for the production of postbiotic metabolites.[31]

A couple of terms that are synonymous with postbiotic metabolites are microbial metabolites and bacterial metabolites. In a review article titled "Bioactive Microbial Metabolites," the author states that as of 2002, over 22,000 bioactive secondary metabolites are published in the scientific literature.[32] And, in *The Gut-Mind Connection*, Dr. Mayer noted that we will ultimately learn that bacteria probably produce hundreds of thousands of metabolites.

Postbiotic Metabolites

Some of the better known postbiotic metabolites include the following:

a. B-vitamin synthesis (biotin, cobalamin, folates, nicotinic acid, pantothenic acid, pyridoxine, riboflavin, and thiamine)[33]
b. Vitamin K[34]
c. Short-chain fatty acids (SCFAs): acetic, propionic and butyric acid.[35]
d. Glutathione: synthesized by *Lactobacillus fermentum* ME3.[36]
e. Antimicrobial peptides (AMPs)[37]
f. Phenyllactic acid[38]
g. D-amino acids[39]
h. Hydrogen peroxide[40]
i. Volatile organic compounds (VOCs)[41]
j. Phytoestrogens: Equol, enterolactone, enterodiol.[42]
k. Urolithin A and urolithin B[43]
l. Fulvic acids[44]

It is beyond the scope of this article to attempt to name and list the health-regulating effects of thousands of microbial metabolites/postbiotic metabolites that been identified to date.

Dr. Ohhira's Probiotics®: Directly Delivering Postbiotic Metabolites

Dr. Ohhira's Probiotics is a fermented food product that is produced utilizing a multi-year fermentation production process under cleanroom conditions. The initial process takes place in large 80-gallon fermentation vats. Dozens of different kinds of organically grown foods (vegetables, fruits, seaweeds and mushrooms) are shredded and added to the fermentation vats along with 12 strains of probiotic bacteria. Then the bacteria are allowed to ferment/digest the high-fiber prebiotic foods they have been supplied with for a period of three to five years, which results in the production of a wide range of postbiotic metabolites.

There are two versions of Dr. Ohhira's Probiotics. The Original Formula undergoes three years of fermentation. The final product is a thick, dark-colored paste-like substance that is encapsulated and is sold at the retail level in fine health food and vitamin stores throughout the United States.

The Professional Formula originates by transferring paste from the 80-gallon vats after the initial three-year fermentation cycle into different containers for an additional two years of anaerobic fermentation. Over 99% of your microbiome consists of anaerobic bacteria that reside in your large intestines and colon. Thus, the additional two years of anaerobic fermentation results in the production of larger amounts of the postbiotic metabolites from the anaerobic bacteria. The Professional Formula is primarily marketed to healthcare professionals.

Dr. Ohhira's fermentation production system simulates nature. Humans ingest food into our digestive tract where bacteria convert the food into a wide range of health-regulating postbiotic metabolites. Dr. Ohhira created an external system that allows probiotic bacteria to function like they do in the GI tract, which results in the production of postbiotic metabolites.

Recent research conducted by an independent laboratory in Japan reported that Dr. Ohhira's Probiotics contain over 400 different postbiotic metabolites.[45] This explains why Dr. Ohhira's Probiotics has achieved a reputation for rapidly improving dysbiosis-related intestinal symptoms. When taken, the postbiotic metabolites immediately begin to initiate healthy changes in the intestinal microbiome ecosystem.

Because postbiotic metabolites have such wide-ranging health-regulating effects, postbiotic metabolites are now being recognized as a new frontier for the pharmaceutical industry. Drug companies recognize that medications based on postbiotic metabolites will be more stable and have far fewer side effects because they are based on compounds that are naturally produced in the body.[46]

Postbiotic metabolites are now being recognized as a form of communication in the body. A recent article titled "Human Microbial Metabolites as a Source of New Drugs," in the journal *Drug Discovery Today*, reviews the rapidly emerging science about how postbiotic metabolites communicate with the immune system and various organs in the body to regulate many aspects of human health.[47] The mechanisms behind these health-regulating effects involve what scientists call "cross-talk" between the probiotic bacteria-produced metabolites and receptors on cells throughout the body.

Many gastrointestinal problems can be improved and/or resolved by increasing the quantity and the diversity of postbiotic metabolites in the microbiome. One method involves two actions:

a. Adopt a healthy plant-based, fiber-rich diet. The dietary fibers will "feed" your beneficial probiotic bacteria which will enable them to grow and proliferate
b. Eliminate the high fat, high sugar, processed foods that alter the microbiome ecosystem and promote the proliferation of pathological bacteria.

However, if your microbiome is unbalanced, it is important to realize that consuming high-fiber foods doesn't guarantee fast results because you have a deficiency of probiotic bacteria present. It takes time for your reduced population of beneficial bacteria to process dietary fiber and create postbiotic metabolites, which will begin to shift the microbiome ecosystem back to a healthy state.

A much faster method of resolving intestinal problems is to ingest post-biotic metabolites directly. As mentioned previously, each dose of Dr. Ohhira's Probiotics delivers over 400 postbiotic metabolites. Thus, Dr. Ohhora's Probiotics deliver a balanced microbiome formula that contains probiotics, prebiotics and most importantly, a multitude of postbiotic metabolites. This is why Dr. Ohhira's Probiotics work fast and effectively to improve many intestinal problems. This is the Dr. Ohhira's Difference!

I want to make an analogy between NASA's mission control center, which regulates our space flights and your microbiome. Many scientists and engineers work in NASA's mission control center. However, it is the hundreds of computers making millions of computations per second that control our space flights. The scientists and engineers are critically important, and the system wouldn't work or even exist without them. However, it is the computers that are the master regulators of space flights.

Similarly, your probiotic bacteria are critically important for the functioning of your microbiome ecosystem. However, it is the multitude of postbiotic metabolites that are the "mission control center" that send millions of biochemical signals, which influence every organ system. Postbiotic metabolites are the master health-regulating compounds in the body. This

is why postbiotic metabolites are the new frontier of microbiome science.

In closing, I want to emphasize that the most critical factor in creating and maintaining a healthy microbiome is a healthy plant-based, fiber-rich diet. If you don't feed your probiotic bacteria well, they won't thrive and survive. When people consume high sugar, high fat, processed foods, they promote the growth of pathological bacteria that can cause many health problems. Remember, when you eat, you are not just eating for yourself, you are feeding 100 trillion guests. This is why a healthy diet is the most significant factor for a healthy microbiome and a healthy life.

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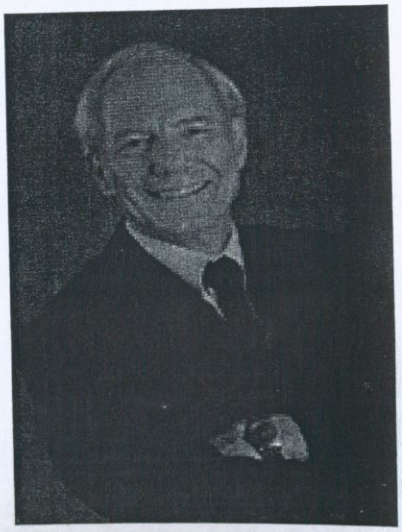

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