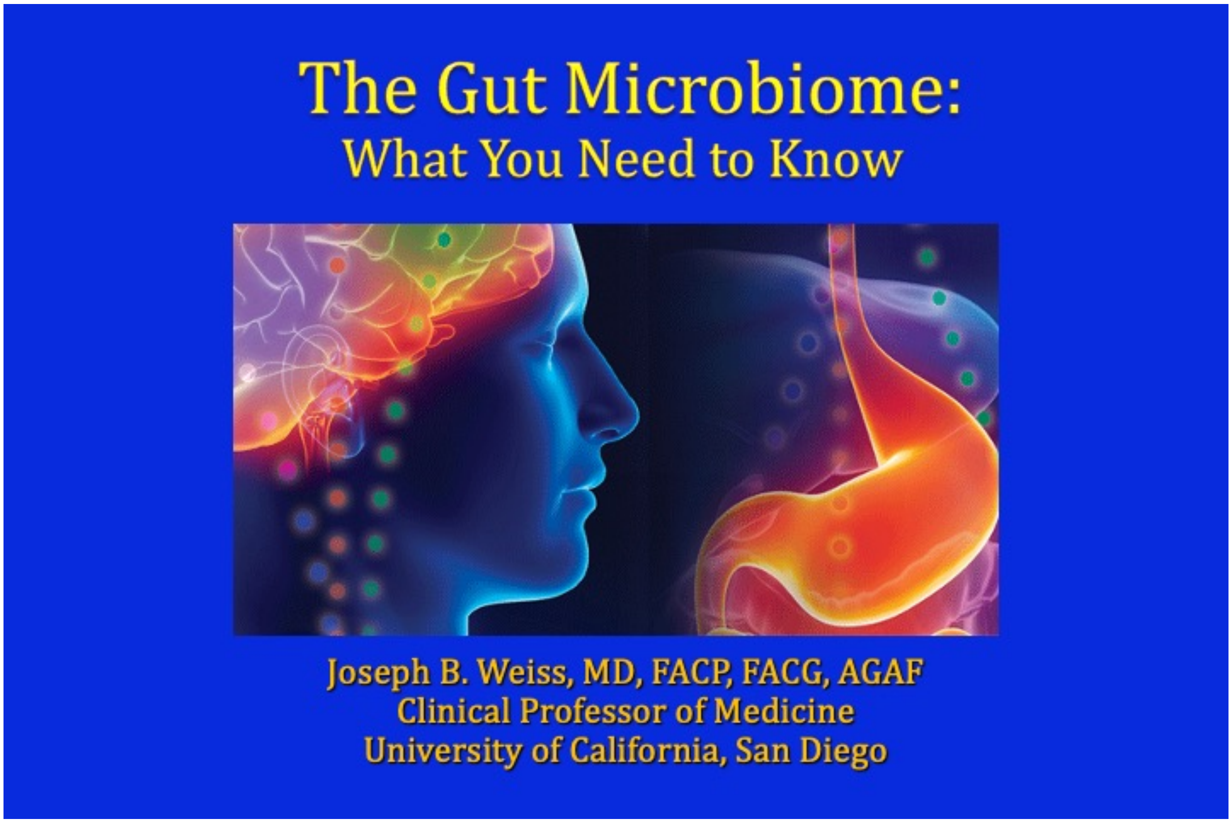


<u>Objectives</u>

Define the human microbiome and recognize that the gut microbiome in particular has a major role in a wide variety of health concerns.

Describe the healthy human gastrointestinal tract as hosting trillions of microorganisms, most of which are commensal and beneficial.

Summarize how diet influences the relationship between the gut microbiome and their human host.

Identify how specific microbes as well as the metabolites they produce may have a major role in health and disease.

Recognize that recent advances in genomic and metabolomics technology have revolutionized the understanding of the role of the microbiome in human health and disease.

Understand that the information concerning probiotics is preliminary, extremely limited, and has the potential to cause harm as well as benefit. Learn to differentiate the hype from the truth.

The human gut microbiome, the microbes that live in the human gastrointestinal tract, has become the most exciting research arena in the biomedical sciences. The gut microbiome weighs approximately five pounds, consists of over 100 trillion non-human cells, and is now considered a human organ system that is a requirement for life and health. It is under the continual influence of our diet and environment, and the bidirectional communication and interactions between the brain and the gut are more prolific and consequential than anyone had ever realized. It is not an understatement that the rapid advances in the field are revolutionizing many fields of medicine.

Science and technology of genomics and epigenetics have advanced our understanding of the human in evolutionary biology and the life sciences. Genes and epigenetic influence are an active form of communication between humans and all other life forms on the planet, including the microbes that live on and within us (microbiome), the living foods in our diet, and our exposure to the life forms and metabolites in our environment. Humans are not the unique and independent organism we thought we were, and in fact, to a significant degree we are not even human.

This program will give you the tools to understand the revolutionary advances that have taken place in the world of nutrition, metabolism, digestion, and the microbiome. You will have a new understanding of the interactions of the incredibly diverse microscopic world with diet, exercise, and newly identified hormones, neurotransmitters, gasotransmitters, and cytokines. You will gain a deeper appreciation of the profound impact of food, diet, exercise, hygiene, environment, medicines, and more on our microbiome (and vice versa), physical, mental, and emotional health and wellness.

Introduction
Beliefs may, or may not, be true.
Beliefs that are true are defined as knowledge.
Advances overturning beliefs occur with regularity.
Different perspectives allow multiple viewpoints, each of which may be supported.
It takes effort to release old beliefs and embrace new information and understanding.
With advances in research technology, breakthroughs with new knowledge appear.
To understand the big picture, the details must be understood as well.
The universe and life are complex, and have staggering diversity of size, form, and nature.

Basics and Vocabulary: Key to Understanding
Genetics, epigenetics, genomics apply to all life forms
Genes, amino acids, and metabolism are controlled by a universal language with the
five-letter alphabet of DNA and RNA
Life science, metabolism, and mutation are based on laws of chemistry & physics
Evolutionary tree of life shows all life forms are related, with at least 30% shared genes
Biodiversity on Earth includes 100,000,000+ unique species
Tremendous diversity even within one species, e.g. *Homo sapiens*
Vertical & horizontal gene transfer, cell free circulating DNA allows gene changes
Human genome is at least 9% non-human, including viral DNA
Evolution is being sped up dramatically by CRISPR, gene editing, and gene transfer

The Numbers:
Human species - one, *Homo sapiens*
Gasotransmitters - 10+
Diet, vitamins, minerals, & trace elements - 50+
Hormones - 75+
Neurotransmitters - 100+
Cytokines (chemokines, interferons, interleukins, lymphokines) - 120+

Human genes - ~20,000
Human diet animal & plant foods - species & varieties - 200,000+, genes – millions+
Non-human genes in human microbiome - millions+
Microbial species – 5,000,000+, Genes – billions+
Metabolites - billions+
Environmental epigenetic factors - billions+

Focus on the Details to See the Big Picture
Brain-gut-microbiome-diet axis has a multitude of variables interacting
Vagus cranial nerve X is a major conduit of communication, but just one of many
Microbiome and dietary genes, neurotransmitters, gasotransmitters, hormones, cytokines, metabolites, and nutrients communicate
Diet impacted by microbiome, e.g. glycemic index, enzyme activity, calorie extraction
Exercise and environment influence microbiome and facilitate communication
Human blood metabolites are at least 30% non-human, originating from gut microbiome
Systems biology, interrelationships, and influences are complex

Take Home Messages:
Brain-gut-microbiome-diet axis is complex, knowledge is early but accumulating rapidly
Exercise, diet, environment, individual genomics, and microbiome are key
Epigenetics allows manipulation of genome expression, all factors of axis may be modified
Prebiotics, probiotics, synbiotics make sense, but it is too early to make recommendations
Hippocrates' maxim: Above all, do no harm!

Where Do We Go from Here?
Identify millions of undiscovered species within gut microbiome
Associate interactions with disease and health, helpful, harmful, or neutral
Identify optimum microbiome components and populations tailored for each individual
Identify optimum prebiotic, probiotic, synbiotic for each individual
Develop therapeutic probiotics, e.g. neurotransmitter and hormone supporters, psychobiotics
Identify systems biology of microbiome, diet, brain, gut, and undiscovered interactions

The Future:
Prebiotic, probiotic, symbiotic, postbiotic, fecal transplant
Genomics, microbiome analysis
Precision, personalized, prescribed medicine including nutrients, probiotics
Knowledge advances will be rapid, dramatic, and disruptive to current practices
Current knowledge and beliefs may well be disproven

"Beware of false knowledge; it is more dangerous than ignorance" ~ George Bernard Shaw

"There are two ways to live your life: One is as though nothing is a miracle. The other is as though everything is a miracle." ~ Albert Einstein

Humans are complex superorganisms that include other non-human species.
The brain is in constant two-way communication with our environment and microbes
There are multiple communication pathways, and probably others yet to be discovered.
Genes are shared between organisms and influenced by environmental epigenetics
Diet, Microbiome, and Epigenetics open new horizons, as well as risks, to health and vitality.
Systems biology complexity makes the consequences of actions uncertain.

The overlap and homology of genes are so remarkable, that even when you would not expect it to, genes transplanted between species often have a biological effect. The gene that creates the protein enzyme luciferase that gives rise to the bioluminescent glow of a firefly has been transplanted into a cat, which now glows in the dark. The genes of an organism can be influenced by epigenetics and environmental factors. The genes also direct the manufacture of proteins, metabolites, neurotransmitters, hormones, enzymes, and a variety of products that modulate and influence distant cells and organisms. Because of the striking preservation of essential genes throughout evolution, the universal genetic language allows for bi-directional influence between widely divergent species. The insulin of the fruit fly brain serves the same purpose and function as insulin in the human brain.

The human pharmacopeia is derived from naturally occurring bioactive products of plants, animals, fungi, Archaea. Protista, and other life forms. There are thousands of psychoactive plants and other organisms. Toxins specific to nerves, respiration, coagulation, fluid balance, cellular oxidation, metabolism, and virtually every critical life function are found in nature. Even products commonly thought of as safe can harbor toxins that when accumulated become harmful. Toxic and fatal doses can range from the miniscule and microscopic to large amounts, depending on potency and site of action. If just a few milligrams of ricin can kill, and LSD can induce hallucinations, other products can have effects with similar minuscule dosing.

With evolution, the continuing diversity of genes and their expansion to multicellular organisms, led to a growing complexity of cellular specialization and organ systems. Each further step in development created a growing distance and greater diversity from the primordial source cell of all life. The changes in the genetic diversity allow science to identify relationships and look back at the evolutionary pathways of the different species. It also enables the ability to see how closely or distantly species are related to each other. Humans, chimpanzees, and bonobos are the closest relatives with 98.4% of their DNA sequence being identical. They are more closely related to each other than an African elephant is to an Indian elephant. Even amongst the single human species of Homo sapiens, the genetic diversity within the species is remarkable. Humans have 99.9% identical DNA, regardless of race, yet even that 0.1% difference of three billon base pairs is a very large number.

Most organisms retained many features of the primordial life form and remained unicellular. The unicellular organisms known as Archaea, Latin for ancient, are thought to be the oldest life form and closest to the primordial organism. Archaea were only first recognized as a distinct life form fifty years ago. They were originally thought to be bacteria, but advances in genomic analysis led to the discovery that they were an entirely new life form. One of the unique features of Archaea is that many of them are extremophiles, they can survive and thrive in environments they were thought to be incompatible with life. They flourish in volcanic vents, boiling water, acidic hot springs, deserts, and even inside of rocks miles underground. They survive the vacuum of outer space, radiation, and so many extremes that they are considered a prime example of life forms studied in the relatively new discipline of astrobiology. They have high commercial value, and many of the enzymes, proteins, and metabolites they generate have industrial applications, as they are functional in extreme conditions.

The genetic code derived from the first cell is based on the nucleic acids bound to the sugar bases ribose that forms the spine of the helical structure of DNA and RNA. The limited number of nucleic acids is paired with each other in a set pattern, each pair forming a unique character much like a letter of the alphabet. Every three letters correspond to a particular amino acid, so the blueprint to build a protein is encoded by the gene by virtue of the sequence of base pairs. Although there are only a few base pairs, the virtually unlimited length of the sequence of characters allows for an almost infinite variety of genetic codes. With evolution and increasing genetic diversity closely related organisms share more genes than those more distantly related. After millions of years of evolution, and an astronomical number of cell divisions and genetic replications with mutations, even the most distantly related life forms share about thirty percent of their genes. These structurally identical genes are functionally and metabolically interchangeable amongst widely divergent species. Many distantly related organisms share the same metabolic pathways and can have powerful interactions with each other despite being millions of years apart in evolutionary history. The language of the genetic code is universal and interconnects all life forms on the planet. The horizontal transfer of genes (nicknamed ‘jumping genes’) have been recognized for several decades. The advent of new technology, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), which was developed as a defense mechanism by bacteria to protect them from viruses, has brought gene transfer and correction of genetic mutations from the world of science fiction to present day reality.

One of the most investigated and analyzed organisms is the free living (non-parasitic) soil roundworm *Caenorhabditis elegans*. This small, and just barely visible to the naked eye, organism is common, inexpensive, and reproduces easily and readily in the laboratory. What makes them valuable as a research tool is that they have virtually the same number of genes as humans, about twenty-three thousand, and about thirty-five percent of these are identical to and interchangeable with their human counterpart. The organism is transparent, has less than one thousand cells, and each cell has been identified and mapped as to the source, location, and function. The nervous system and each nerve cell have been identified, and the connectome of nerve cell communication links has been completed. The research with this unique model has been so incredibly productive that it's initiator, Dr. Sydney Brenner, was awarded the Nobel Prize in Medicine or Physiology.

Humans contain over 37 trillion cells, with millions of chemical and metabolic reactions occurring every second in each individual cell. We produce 25 million new cells every second. We have to consume nutrients, energy, fluids, electrolytes, minerals, and metabolites through our digestive tracts to support all of the 37 trillion plus human cells, as well as the 100 trillion cells of the gut microbiome, and eliminate the waste produced by this enormous and extremely active population. With our size and biomass, it is easy to be deceived into thinking that we represent the majority, and the microbial world the minority, of the human superorganism. The fact is that the numbers that count the most are not the quantity of cells or mass, but the genes and epigenetic modifiers. The human species, Homo sapiens, has approximately 20,000 genes.

The number of unique species of microbes in the human microbiome is thought to number from over tens of thousands to more than one million, with each having on average between 15,000 to 30,000 of their own unique genes. Viruses have much lower gene counts, ranging from as few as only two genes, to over two thousand. Likewise, our human organism is exposed to the millions of other unique species inhabiting our planet. We are exposed through the air we breathe, the foods we eat, the fluids we drink, the odors we smell, and the objects we touch. Research has found that trillions of viruses and bacteria fall out of the air each day landing on each single square inch of soil or water. Besides the life forms themselves, we are also exposed to their metabolites, hormones, neurotransmitters, gasotransmitters, etc.

In human DNA, only 1.5% are genes that code for proteins. With over 3 billion base pairs, that still leaves 3 million unique base pair combinations to explain human diversity. Horizontal gene transfer means that not all transmission of genes is from one generation to the next, transmission of genes from one species to another can occur within a single lifetime. This also provides an explanation for the surprising discovery that over 8% of the human genome is not even human, it is of viral origin. A single human gene can make over 200 different proteins depending on the epigenetic influence. Even more staggering than the hundreds of billions of genes, are the exponentially larger number of epigenetic factors, the majority of which arise from the 99% of DNA that do not code for genes. It is the height of irony that what scientists disparagingly labeled as 'junk DNA', is of critical importance to all life forms.

The noncoding junk DNA generates micro-RNA which is distributed as exosomes throughout the nucleus, into the cytoplasm, into the blood, and then released into the environment via exhaled breath, sweat, bodily fluids, and waste. These active epigenetic factors can then influence the genes of others. Likewise, the microRNA exosomes of the gut microbiome are absorbed and enter into the human circulatory system. Over 35% of the metabolites and circulating microRNA exosomes in human blood are of bacterial origin, and an additional 15% are of fungal origin. They may have a profound epigenetic effect on human genome expression, and further analysis will undoubtedly find additional influencers from the rest of the microbiome such as Archaea, viruses, protists, prions, etc. The diverse life forms on Earth are much more closely interrelated than previously believed, and the very definition of human may need to be revisited. As we experience and influence our environment, the environment is also experiencing and influencing us.

We now know that genes can be transferred in ways other than the vertical transmission of inheritance. The horizontal transfer of genes from one species to another, commonly referred to as 'jumping genes', occurs with some regularity. Many people are familiar with the fact that about 2% of human DNA is not from Homo sapiens, but from a different species, the Neanderthals. Few people are aware of the more striking recent discovery that over 8% of the human genome is not even human at all, it is of viral origin. Undoubtedly as scientists shake the human genetic tree even more, further surprises will drop. Atmosphere scientists have proven that microbes are airborne and follow wind currents. On average over one million bacteria, and one billion viruses, are dropped from the wind and air over every square centimeter of planet Earth each day.

A relatively small number of microbes are pathogens, and they can be the cause of specific diseases or alternatively cause illness in those who have an immune deficiency or are otherwise compromised. Although antibiotics are designed to eradicate specific bacterial pathogens, it is commonplace for them to be distributed throughout the whole body, not just the location of the infection. When taken orally, the highest concentration is often delivered to the gut microbiome, and many microbes besides the targeted pathogen will be eradicated or suppressed. As the microbiome is disrupted, opportunistic microbes replace those adversely affected by the antibiotic. Even a single brief course of antibiotics can generate long term or permanent consequences and disruption of the microbiome. The use of antibiotics has become so pervasive that most children have had several courses, unless limited access to health care or familial religious beliefs were in place. Newer classes of drugs to address pathogens include agents designed to treat viruses, protist, parasites, and fungus give rise to similar concerns. Making the matter more complicated, many products used in our environment, including food additives, have antimicrobial properties and act as antibiotics.

While society and medical knowledge has reduced the indiscriminate use of these biological agents in human disease, the same cannot be said for the agriculture and food industry. The quantity of antibiotics used as a vehicle to increase gross food production is a high multiple of that used in human medicine. In addition, the use of hormones, pesticides, herbicides, and chemical toxins is rampant, with measurable levels found in the majority of the food supply, including produce, dairy, meat, poultry, fish, and grains. The popular herbicide glyphosate is structurally related to the amino acid glycine, and actually is classified as an antibiotic, antifungal, and antiparasitic, as it that targets unicellular life forms found in the soil and plant microbiome. It blocks the important shikimate enzyme pathway that produces ringed aromatic amino acids, including phenylalanine, tyrosine, and tryptophan. Tryptophan is the source of serotonin, phenylalanine and tyrosine are the source for dopamine, so they are critical for human brain and neurotransmitter functions.

The human brain is often described as consisting of three distinct levels. The cerebral cortex or neocortex allows consciousness, thought, and cognitive function. Man, in his uniquely human egocentricity, believes this is the latest and greatest evolutionary advance in the brain. The emotional centers, including the limbic system and hypothalamus, are considered the middle level of brain design features. The brain stem, somewhat derogatorily referred to as the reptilian brain, is the control center for basic physiological functioning including respiration and circulation. There is another level of coordinated neuronal activity in the body besides the central nervous system consisting of the brain, cranial nerves, spinal cord, and nerves. This organizational network is the enteric nervous system, also called the gut nervous system, and by many experts is known casually as the second brain. As it is the first nervous system developed in evolution, it should more rightly be considered the first brain. The distinctions are entirely arbitrary and irrelevant, as they are all intrinsically and intimately intertwined.

The enteric nervous system is remarkable on many levels. Over forty distinct neurotransmitters have been identified in its internal communications, and more are likely to be discovered. The major neurotransmitters of the body, which have a significant influence on cerebral cortex brain function, are derived from the gastrointestinal tract and enteric nervous system. Ninety-five percent of the serotonin, and fifty percent of the dopamine, in humans is located in the enteric nervous system. The prominent vagus nerve, also known as cranial nerve X, is a direct communication pathway between the gut and the brain and other vital organs. The name means wanderer in Latin, and true to its name, it has a meandering course through the chest, abdomen, and pelvis. One of the surprising findings from research of the vagus nerve and its function is that over eighty percent of the nerve fibers are arranged to deliver information and instructions to the brain, not the other way around.

The gastrointestinal tract and its associated enteric nervous system are also a very rich source of hormones, dozens of which have been identified. They have multiple and critical functions, this most well-known of which are insulin and glucagon, which control blood sugar homeostasis. The multitude of other hormones, new ones being continually discovered, play significant roles in metabolism, gut physiology, appetite, fat deposition, and weight control. New hormones are frequently identified and manipulating the enteroendocrine cells that are the source of gut hormones to assist with management of obesity is an area of primary research interest. The gastrointestinal tract also influences hormones from other endocrine organs that have profound effects on the brain.

A prime example are the thyroid hormones, with an underactive hypothyroid condition commonly found when the trace element iodine is lacking in the diet and not absorbed through the gastrointestinal tract. As the thyroid gland tries to ramp up production of the deficient hormone it often grows markedly enlarged, causing a goiter that can exhibit swelling of the gland in the neck region. Hypothyroidism causes profound brain effects with decreased cognition, described as 'brain fog', and inactivity. Before the condition of the underactive thyroid was recognized, and treatment with dietary iodine supplements or thyroid replacement hormone initiated, many tens of thousands of underactive thyroid patients were mistakenly committed to mental institutions. The effect of testosterone on aggression, steroid hormones inducing frank psychosis, the hormonal fluxes of premenstrual syndrome and menopause, the emotional bonding of the 'love hormone' oxytocin, and many other examples are often not recognized yet are powerfully experienced by millions during the course of an average life span.

The enteric nervous system, neurotransmitters, and gut hormones are intimately involved with the gut immune system, microbiome, and diet. The gut is the primary exposure border of the internal body to the external environment. The gastrointestinal tract is a long tunnel that travels through the chest, abdomen, and pelvis bringing access to the external environment deep within the physical confines of the body. The material inside the gastrointestinal tract is considered external to the body until the lining cells absorb it or it breaches the tight junctions between cells. The surface area of the gut is the largest in the body, and as this is the interface with the external environment, is the body's primary concentration of immune system activity and protection. The population of immune and inflammatory cells, and their products such as cytokines, complement, and immunoglobulins are at their highest concentration here.

Communication between the gut and the brain, including input from the microbiome and diet, can follow neural pathways such as the vagus nerve, also known as Cranial Nerve X. Also, there is absorption from the bowel through and between mucosal cells. There are over fifty human hormones, over one hundred neurotransmitters, 42,000 metabolites 28,000 food components, 3,600 environmental toxins, 20,000 human genes, 1,000,000+ microbial genes. The number of microbial species is unknown, some believe it will exceed one million, and their metabolites a multiple of that. The ability of a minute quantity of a small molecule to change and disrupt a much larger and multi-organ system complex of a higher animal can be dramatic and profound. In the action of psychotropics, such as LSD, hallucinogenics, and opiates, the inducement of activities that lead to suicide and death are not infrequent. A number of smaller organisms, such as protist and parasites are believed to induce behavior changes in the host that are specially designed to be an advantage to the parasite, even at the expense of the life of the host.

The genes that direct the production of metabolites that change host behavior may be found in a variety of life forms. It may be found in the organisms that reside in the microbiome of the host or organisms that live on or in the food the host might ingest. The genes may also be found in the life forms that comprise the food itself, as animals, plants, fungi, and other food sources arise from living matter have genes and the byproducts of gene-directed metabolism. The food also affects the microbiome and can influence its behavior via this mechanism. Likewise, the host genes and metabolites can also affect the microbiome. The blood-brain barrier is a mechanism to protect the brain from potentially harmful metabolites that enter the circulation. Astrocytes surround the blood vessels in the brain in the attempt to intercept and prevent these products from reaching the brain itself.

The microbiome is the world of microorganisms, too small to be seen with the naked eye; that exist in our environment, as well as on, in, and within our body tissue. The fact that we are surrounded by and immersed in a world of microbes has been known for a long time. What is new and surprising is the revelation that we are much more interdependent with the microbiome than science and medicine ever knew or believed. The human microbiome is constantly changing, responding to its environment and involved with every aspect of human physiology. The gut microbiome plays significant roles in neurological, immunological, gastrointestinal, and metabolic functions.

The microbiome is the community of microscopic organisms that reside on and within the human body. They are found in all surfaces with exposure to the external environment, as well as some internal and intracellular locations when they breach body defenses. The gut microbiome has the greatest numbers of microbes both by population as well as by diversity. It was initially thought that the gut microbiome might consist of a dozen or so of the several dozen species of microbes found in the gut. With the advent of genomic sequencing, identification of microbes that could not be identified by laboratory culture has rapidly expanded. The number of unique species of gut microbes has already reached into the thousands, and many experts believe the number may well exceed one million species. Each species is likely to have thousands of unique genes. The genes themselves may have biological activity, as well as having an epigenetic effect on human genes.

The human organism produces over 200,000 different proteins. It used to be thought that each protein required a specific gene to give it the instructions for its manufacture. Yet there are only 20,000 genes in the human organism DNA, and most of the DNA does not code for genes at all, thus leading to the categorization of non-gene DNA as 'junk DNA'. It has been discovered that the junk DNA generates micro-RNA which is released into circulation in the blood, which has an influence known as epigenetics on a gene when it is transported to a cell. One single gene can direct the production of over 200 different proteins, highlighting the powerful influence of epigenetics without any alteration in the sequence of nucleic acid bases comprising the gene. Even more astounding was the recent finding that over 40% of the microRNA, which induces the epigenetic changes in the human gene, are not of human origin, that is they do not arise from the human 'junk DNA'. They are generated from the diet and by the microbes of the microbiome, predominantly the gut microbiome. The diet and gut microbiome can thus have a profound impact in the health and well-being of the human organism.

Each gene codes for unique proteins, including neurotransmitters, hormones, and metabolites that may well have bioactivity. These products are frequently absorbed into the gut lining cells, or may enter via a gap in the intercellular tight junctions, often described as a leaky gut. From there they may enter the bloodstream unless blocked by the blood-brain barrier formed by the astrocytes that surround blood vessels in the central nervous system. Genomic sequencing of metabolites found circulating in normal humans without a 'leaky gut' demonstrates that thirty percent originate from the gut microbiome. These circulating metabolites may have a profound influence on the brain and body.

The microbiome also affects the digestion, metabolism, and absorption of nutrients, metabolites, neurotransmitters, hormones, genes, environmental agents, toxins, nutraceuticals, drugs, foods, pharmaceuticals, hallucinogens, stimulants, depressants, plant-derived bioactive chemicals, psychotropics, etcetera. The most remarkable finding is that the human body and its microbiome are in nearly constant communication with each other. It would not be an overstatement to describe these discoveries as revolutionary, and our understanding of health and disease is being dramatically altered. In fact, even how we consider what it means to be human, and the definition and nature of the human body is being revised and redefined. But before we explore our relationship with the microbiome in detail, let's get some more background information, and start by taking a closer look at where microbes are within the remarkable evolutionary diversity of life on our planet Earth.

The forms of life on the planet range from the simplest organisms of a single cell or less to multicellular organisms of increasing complexity and size. There are also a variety of major life forms that were previously classified as Kingdoms, ranging from the commonly known plants, animals, fungi, bacteria, viruses, and protozoans. Over the last few decades, scientific advances have also identified new life forms including the controversial prions that are the cause of exotic diseases such as mad-cow disease (Bovine Spongiform Encephalopathy) and kuru. Even more surprising has been the discovery of a new life form called Archaea (Latin for 'ancient one').

The reason this was such an unexpected discovery is that they are in fact commonplace and thrive in places where life was not even thought possible. One of the reasons they were not recognized, even though found in abundance, was that their external appearance is similar to bacteria. It was only with the advent of genomic sequencing that it was recognized that Archaea were not just a little bit different than bacteria, but so entirely different that it appears as if they came from an alien planet. As strange as that thought might sound, there is a field of science called astrobiology that theorizes that that is exactly what happened. Archaea live and thrive within fuming volcanic vents, boiling springs, even deep inside of rocks mined miles underground. They have been transported to outer space and survived and thrived when left exposed to the unearthly vacuum outside of the international space station. Because they survive and thrive in extreme environments, they have been designated as extremophiles (Latin -loving extremes).

What many people find surprising is that the intestinal tract, typically considered an internal organ, is an external organ just like the skin as far as the body is concerned. The reason for this 'inside out' logic is that the external environment continues all the way through the gut, from mouth to anus. The material within the digestive tract is considered outside of the body until it is absorbed through the intestinal lining. Because this is a potential source of infection and allergies, the body has a powerful and vigilant immune system that is extremely active in the gut. As you can imagine, a lot of microbes live in the mouth, between the teeth, under the gums, in the nasal passages, etcetera. A large number of microbes entered your mouth on the surface or within the food you eat, joining with the microbes that have already established this part of your body as their permanent home. These microbes are feasting on small particles of food and debris left over from the chewing process, even when you brush and floss well.

The microbes in the mouth and within the food are regularly swallowed and travel down the digestive tract on an incredible voyage that would make any theme park ride pale in comparison. For many of the bacteria, this is a nightmare journey at the ends of their lives, and for others it is the equivalent of being transported to heaven. The microbes making this trip contribute to the gut microbiome, which is the largest microbiome of the body, numbering over 100 trillion organisms. This astronomical number is greater than the number of stars in the universe and collectively weighs in at about three pounds. Measured by cell populations the average human is ten percent human cells and ninety percent microbial cells. If you look at a more important factor, gene activity, the human genome has about twenty thousand genes, and the microbiome well in excess of a million, making us only one percent human by gene count. The gut microbiome is much more than just fermenting or metabolizing the food products our intestinal tract cannot digest. Amazingly, the gut microbiome engages in an active two-way communication with the human brain, and through epigenetics with every aspect of the human experience.

Communication is one of the hallmarks of higher animals, and language has traditionally been thought to be a uniquely human trait. Science is exploring the communication of other animals and it appears that they also use the language of a limited vocabulary that is primarily used to warn of danger. More research is ongoing into the modes of communication of other animals, from the vocalization of whales that communicate over distances of many dozens of miles at sea, to the recently discovered elephant communication over distant miles by infrasound wavelengths, an extremely low frequency below the range of human hearing. Other species also frequently communicate, as we do routinely with our pets. This is especially apparent when cats command their human servants to feed them.

From dog whisperers and trainers to the recognizable dog facial expressions of joy and remorse, nonverbal communication is a regular occurrence. Even plants communicate with each other, often through the air by releasing volatile chemical messengers warning of pathogens and danger. In the case of the microbiome, the communication takes place in the common language of most living organisms, chemical neurotransmitters, gasotransmitters, hormones, and metabolites. This is a language the microbes, body, and brain instantly recognize and understand. The gut microbiome weighs in at about three pounds, roughly the same weight as the human brain, and interestingly enough, is part of what is now commonly known as the 'second brain' comprised of the gut-microbiome-brain-diet axis. This 'second brain' is adding a scientific understanding of what has often been described as gut feelings or gut instincts.

The purpose of the digestive tract is to support life by providing the nutrition and energy we need for all of our body functions. The average human has over 37 billion cells, with 25 million new cells created every second. Each existing cell requires energy to fulfill its metabolic function. All human cells, except for red blood cells, has mitochondria that serve as the equivalent of an energy power plant. It is believed that eons ago mitochondria were free living unicellular organisms, such as archaea or bacteria. In a process known as endosymbiosis, they became incorporated into human cells, where they serve a vital function. Perhaps as a residue of their previous independent lives, mitochondria carry their own DNA, inherited in a matrilineal pattern. The more metabolically active the cell, the more mitochondria it has. The liver cells, as well as nerve cells are some of the most active in the body, with each cell containing over 2,000 mitochondria in the cytoplasm. On average, a human cell has over one million chemical reactions occurring every second. The energy and nutrition need of the human organism are enormous, and the digestive tract must provide for all of this and more, as it also supplies the gut microbiome with its needs. Perhaps the analogy is not the best one but think of the digestive tract as the reverse of the assembly line, a disassembly line.

A calorie is simply a measure of the amount of energy within a food or substance. It is measured in a device called a bomb calorimeter, which incinerates the food in a chamber surrounded by a water bath and measures the increase in water temperature. The number of calories in food is the optimal amount of energy within the food if completely incinerated, and obviously the digestive tract is rarely as efficient as a furnace. A large percentage, if not the majority, of the calories are not extracted from the food and are eliminated with the digestive waste. The glycemic index is an indication of the rapidity with which the food is digested to allow the release and absorption of simple sugars. The higher the glycemic index the more rapidly sugars are absorbed, with blood glucose spikes contributing to insulin peaks and a greater likelihood of diabetes. The microbes of the gastrointestinal tract, the gut microbiome, play a critical role in determining the extent to which calories are extracted from the food ingested. The glycemic index, which used to be associated with specific food types, is now believed to be more closely related to the nature of the gut microbiome. It appears that the microbiome can determine whether a diet leads to weight increase or decrease, as well as the glucose response which may contribute to diabetes. A number of companies are now offering gut microbiome analysis, with dietary recommendations tailored to the microbiome.

A calorie is a measurement of the energy contained within a food, and a calorie is a calorie. What is important to remember is that the calorie count of the food is not as important as is the net calories that are absorbed by the body, minus the calories utilized to process and absorb the food. If you ate 100 calories of glucose, a simple sugar known as a monosaccharide, you would not need to expend any energy to digest it, and only a small amount of energy to swallow and absorb it. If it only took 5 calories to process 100 calories of glucose, the net calorie absorption would be 95 calories. Celery has a very low-calorie content, and you expend more energy than the food contains to chew, swallow, digest, and absorb it. If you ate 100 calories of celery, you may burn up 120 calories to process it. You can actually lose energy (and weight) because of its net negative calorie effect. Protein takes the most energy to digest, with 20-30% of the total calories in protein consumed in its chewing, swallowing, peristalsis, digestion, and absorption. Carbohydrate processing usually utilizes 5-10% of its total calories, and fats only 0-3% of its calories. If simple glucose were packaged in difficult to open containers, theoretically you could lose weight by burning up more calories trying to get to the glucose than the food itself contains. If you were to simplify the concept, in general the calories in fat are more likely to be net calories, than calories of carbohydrates, and even more than the calories of proteins.

The breakdown products of the digestive process are absorbed by a sea of finger-like projections called the villi. It looks like a field of waving wheat stalks; each upstanding villus is ready to use its enzymes and absorptive capacity to absorb nutrients. If you looked under the microscope, you would find that each villus has thousands of even smaller villi on its surface, given the appropriate name of microvilli. All of these folds of absorptive tissue, if flattened out, would provide the equivalent absorptive capacity of a championship tennis court. A quote from Mark Twain also illustrates the concept of surface area: “If Switzerland were ironed flat it would be a very large country”. The long intestinal tunnel of eagerly awaiting absorptive villi is about twenty feet long, and it is an amazingly efficient system of digestion and absorption. If injured, the ability of the small bowel to digest and absorb nutrients is compromised. A condition that temporarily damages the small intestine, such as a viral or bacterial gastroenteritis often called stomach flu, can cause a blunting or shortening of the villi. The villous blunting will also lead to the loss of digestive enzymes that reside on the villi.

Without the ability to digest and absorb nutrients, the unabsorbed material can cause what is known as an osmotic diarrhea. People are often advised to avoid dairy products for a week or so after stomach flu to allow the villi and enzymes to recover. If you eat or drink lactose without waiting until the recovery is complete, you may end up with symptoms of temporary lactose intolerance such as gas and diarrhea. When the liquid chyme leaves the jejunum and ileum of the small intestine, it goes through the ileocecal valve to enter the colon. In the cecum of the colon lies the infamous appendix, which for thousands of years mystified science as to its purpose. It looks like its function has finally, and only very recently, been identified. It stores a reservoir of intestinal bacteria, representing the healthy gut microbiome, from which the gut flora can be replenished after a bout of intestinal dysentery.

Human hair is just 100 microns thick, but the lining of the digestive tract is even thinner. It is only one cell layer thick, about 25 microns wide and 50 microns deep. At half the width of a human hair, this cellophane-like layer separates your vital body from the external environment. It allows the entry of nutrients, fluids, electrolytes, beneficial metabolites, neurotransmitters, hormones, and chemicals, while excluding toxins, parasites, pathogens, and harmful products. The gut lining is the interface with the external environment and supports over 90% of the entire human adaptive and humoral immune defense system that is continuously on guard. Each gut lining cell has a tight junction with the adjacent gut lining cells to provide a complete, contiguous, and continuous active defensive barrier. If the tight junctions are weakened, it becomes a potential breach of this critical defensive system and the condition is known as a 'leaky gut'.

The gut microbiome is heavily influenced by environmental factors, particularly the diet. Exposure to antibiotics, pharmaceuticals, toxins, probiotics, and virtually anything taken by mouth exposes the microbiome to its influence. Many people consume organic foods with the intent to protect their body and health. Unfortunately, even organic foods can be contaminated if the farmers use manure, an ‘organic fertilizer’, that is often contaminated with antibiotics, hormones, pesticides, and herbicides from commercial cattle and pig farms. The gut microbiome is much more important than most people realize. The microbes of the body far outnumber the number of human cells. In fact, if you just go by the number of cells and not their mass, they outnumber human cells by ten to one. In other words, you as a living system are only ten percent human and ninety percent microbes! The vast majority of the microbes living within and on us are commensals. The term commensal is used to describe a symbiotic relationship from which both parties benefit. They are able to process foods that would otherwise be indigestible and convert them to absorbable nutrients and metabolites. It is not an understatement to say that they are a requirement for our health and well-being.

As efficient as the digestive tract is, a large portion of the energy stored in food is not processed and metabolized by the human system. Undigested food travels through the intestinal tract and is often fermented and metabolized by our allies in the gut microbiome. These microbes have the ability to digest and metabolize the food content we cannot, and release absorbable nutrients for our benefit as well as waste products for elimination. Some these metabolites, such as Vitamin K, cannot be produced by humans yet are critical for our survival. It is not an understatement to say that the gut microbiome is as much a benefit to us, as we are to it by providing it with a home and nourishment. The populations and varieties of organisms in the gut microbiome is staggering. The advances in the field of genomics now allows for the identification of organisms that were previously hidden from view or just unknown. Before this technology, the number of species of microbes in the human intestine was thought to total a few dozen. To date over five thousand different species have been identified, and some scientists expect the number may reach a million or more before the counting is complete. The populations and diversity vary by location within the gut, as well as age, diet, and a multitude of other factors. Much like a fingerprint, it appears that the gut microbiome may be unique for each. It is also clear that the gut microbiome can be disrupted by illness, change in diet, and in particular following the ingestion of antibiotics.

Besides the important role in digestion and fermentation of food content, the microbiome plays a critical role in metabolism. The microbes generate metabolites that can serve as neurotransmitters, hormones, and other products that have bioactive properties. When the microbes in the intestinal tract create them, the absorptive process brings them from the external environment of being inside the lumen of the tube of the digestive tract, into the cells and circulation of the body. When a blood specimen is analyzed using genomic sequencing scientists were surprised to find that twenty percent of the metabolites in the circulation were of microbial origin. The interplay within the gut, microbiome, and brain is striking, but one of the most surprising findings is the direction of communication. Although we like to think our brains are in charge, the vast majority of communication was not from the brain to the gut, but in the other direction!

The influence of the diet on the microbiome is profound and is perfectly logical. Much like us, the microbes rely on the human diet for all of their nutritional needs. A good portion of the food we ingest is not digestible by humans, such as the fiber often found in plant-based foods. Although they are not digestible by us, they are digestible by microbes and are critical for their health and survival. As we are just as dependent on a healthy gut microbiome, the nutrients needed by the microbes, known as prebiotics, are critical for our welfare as well. One of the more interesting findings of microbiome research was that the microbes might be influencing our dietary behavior, much like sending our brains a shopping list of what they would like on the menu. Some peculiar dietary habits such as a craving to eat non-edible products such as dirt, starch, paper, etcetera are described as a pica, and may be influenced by the microbiome. It is somewhat similar to cravings during pregnancy, where a strong stimulus creates a dietary diversion for pickles. One curious aside is that traditional pickles, sauerkraut, and the Korean fermented cabbage kimchi are very rich in healthful probiotics.

Toxoplasma gondii is a parasitic protist that has a life cycle designed to be between cats and mice. The parasite changes mouse brain behavior, markedly increasing its chances of being eaten by a cat, which allows the parasite to complete its life cycle. Hundreds of millions of humans are accidently infected because cat droppings are ubiquitous. The infection can be fatal to the human embryo, so caution is required to stay away from cats, litter boxes, gardens, etc. when pregnant. There is a striking association between those who have been exposed to the toxoplasma organism and schizophrenia. Perhaps it is an analogous effect to the brain changes induced in the mouse, to apply dark humor to a serious problem, it was designed to increase the chances of a human being eaten by a sabretooth tiger to complete the parasites life cycle in prehistoric times.

Studies have repeatedly demonstrated that the gut microbiome influences calorie absorption of food, weight balance, and fat deposition. When the microbes of fat and skinny mice were exchanged, there weights changed to correspond to the microbiome even though the diet and exercise were unchanged. The findings of the critical role of the microbiome in weight management give credence to those who have claimed they could not lose weight regardless of what dietary or exercise changes they embraced. Whether the microbiome influences weight via absorption of calories, influence of hormones, metabolites, neurotransmitters, or other mechanisms as yet unknown new therapies will undoubtedly be devised to help with weight management.

Prebiotics are not typically considered nutritive for humans but are so for the microbes. Even though they may carry labels saying they are calorie free, that may no longer be true once the microbes are finished with them. For example, if you were to eat hay or grass the cellulose of the plant would not be digestible because humans do not have the necessary enzyme called cellulase to break it down into absorbable sugars. Horses, cows, and sheep have this enzyme as well as a ruminant digestive tract that contains microbes that can process that form of diet into simple absorbable sugars. When we eat prebiotic fiber (do pass on the hay) the microbes ferment and digest it into simpler sugars that we can absorb as calories. So even though on paper we cannot digest it, allowing it to be labeled as zero calories, the microbes may not have read the label and provide us with calories we may not have counted on.

The fields of genomics and the microbiome are expanding very rapidly. We are just beginning to identify and understand which organisms may be associated with various conditions of good or ill health. The concept of systems biology describes complex organisms with a multitude of variables, such as humans. There are so many variables it is unlikely for the remaining unexplained diseases to be caused by a single microbe pathogen, like the historical discoveries of the etiologic agents of salmonella, shigella, and cholera. It is much more likely to be a combination of various factors such as genetics, environment, diet, activity, hormones and a host of other factors. When it comes to the input from the microbiome it will most likely be from a variety of microbes interacting with each other in the proper proportions to have a recipe or formula for optimal health, or when out of balance for illness and disease. The use of genomics and systems biology will hopefully allow the implementation of personalized medicine where diet, microbiome, and medicine can be individualized for optimal outcome.

We are still discovering tens of thousands of previously unidentified microbial species in the gut microbiome. The balances of species mix and populations for optimal health and disease avoidance are not known. We also realize that the proper balance will be different for each individual based on his or her genomics, epigenetics, immunity, previous illnesses, activity, medications, etcetera. As much as one would like to know what the optimal probiotic to take as a supplement is, the science has not yet provided an answer. When science does not give a definite answer, health concerns and products meet in the marketplace with confusion, misinformation, and business opportunities to promote a new industry. The probiotic industry has arrived, for better or for worse, but mostly for the better.

There is a long history of experience with some the probiotics that are most popular today. The long track record, documented scientific research identifying benefits, apparent lack of adverse reactions, and millions of consumers self-reporting benefits who continue to use these products is sufficient evidence for an individual to consider a trial to see the response. An important point to remember is that each individual human is unique. There are tremendous variations in our genetic makeup, environmental exposures, existing microbiomes, medical history, and dozens of other variables that may confound our response to individual probiotics. While there may be some general categories of probiotics that have benefits, the identification of the ideal microbiome for each is still some time off in the future. The research into the identification of the organisms of the microbiome is still in its infancy. Their association with health and disease, as individual organisms and in combinations with others, will become apparent from the research studies that are just at the earliest stages, but will take years to complete and analyze.

The plant and animal worlds have long been a source of products that influence human health and behavior. The virtually unlimited genetic diversity has been a rich source of identifying products for human use for health, recreation, disease treatment, religious rituals, poisons, etcetera. The number of chemical agents is so vast that pharmaceutical research companies have developed protein libraries with millions of candidates targeting specific biological activity. What used to take days of painstaking analysis to evaluate one compound has accelerated to hundreds of thousands of candidates per day. The number of candidates is believed to be virtually infinite. The selection of the right probiotic, or mix of probiotics, for a general population is as challenging as being asked to select a perfume or cologne that is suitable for a large community of individuals. The answer is that most of the population will do well with certain base fragrances such as jasmine or musk, but the concentration of the essence, and the unique final aroma is dependent on the other ingredients and the chemistry of the individual. With that general disclaimer, there are some probiotics that contain microbes thought to be beneficial to human health.

The pioneer in the effort to identify the optimal organism of the gut microbiome was Ukrainian scientist Élie Metchnikoff) (1845 - 1916) who received the Nobel Prize in Medicine or Physiology in 1908 for his earlier pioneering work in immunology. He discovered that immune cells were able to surround and devour microbes, described as phagocytosis, as a protective mechanism against pathogens. In this age of discovery of microbes and their role in infections and disease, his discovery of phagocytosis was as striking as if science fiction became a reality. Indeed, many leading scientists of the day, including Louis Pasteur, the namesake of pasteurization, took years to be convinced that he was right. Appointed to a prestigious position at the Pasteur Institute in Paris, and with his international stature already assured, he began to study a previously unexplored area of medicine, aging and longevity. He is credited by some sources with coining the term gerontology to describe this field of research. His interest in longevity is somewhat curious in that he tried to shorten his life, not lengthen it, by attempting suicide on two occasions in his life. Fortunately for science and posterity, his many talents did not include success in these endeavors.

He traveled to Bulgaria to study the large population of centenarians, individuals who lived for a century and beyond. He noted that a common component of their diet was called sour milk, what we describe today as yogurt, and he suspected that this might hold an important clue. The microbe responsible for fermenting the milk into yogurt was identified as *Lactobacillus delbrueckii bulgaricus*, which generated lactic acid. Mechnikov developed his famous theory that toxic bacteria in the gut cause aging, and that lactic acid produced by microbes could prolong life as evidenced in the Bulgarian centenarians. He drank sour milk every day and wrote a landmark paper The Prolongation of Life: Optimistic Studies, in which he promoted the potential life-lengthening properties of lactic acid bacteria. His work inspired Japanese microbiologist Minoru Shirota (1899 - 1982) to develop a stronger strain of lactic acid bacteria, named *Lactobacillus casei shirota.* He believed the lactic acid production could destroy the harmful bacteria living in the intestines and improve health and longevity. Shirota developed Yakult, kefir, and other fermented milk products as the first probiotics brought to market in 1935, which developed a worldwide interest and popularity.

Another pioneer of prebiotic and probiotics was John Harvey Kellogg (1852 - 1943). A graduate of New York University Medical School, he was the medical director of a Seventh Day Adventist medical facility in Battle Creek, Michigan with a particular focus on nutrition, exercise, and intestinal health. Kellogg was an advocate of vegetarianism and following the research of Élie Metchnikoff advocated yogurt for its beneficial probiotic benefits. The Battle Creek Sanitarium became an internationally renowned center for health and wellness. Part of the regimen at the sanitarium was colonic cleansing, with several high-volume enemas a day to empty the intestine. Kellogg's unique application of yogurt by mouth as well as by enema was meant to assure that the gut microbiome was saturated with beneficial organisms. He recognized the value of probiotics, as well as the need for prebiotics to provide sustenance to the microbes. His best-known invention was a process for flaking cereal, inventing corn flakes with his brother William Keith Kellogg. Kellogg promoted whole grains and fiber for intestinal health, and with his brother founded the Kellogg Cereal Company, which grew into one of the world's most successful enterprises. (For those interested in biography the life and times of the Kellogg brothers is an incredible and colorful story with surprising twists and cameo appearances of many noted figures).

The most popular probiotics today belong to two large groups *Lactobacillus* and *Bifidobacterium.* There are thousands of species and subspecies of these and other probiotics, and the ones with optimal benefit are dependent on the many variables of each. The uniqueness of the individual is the basic premise of the valuable concept of personalized medicine (discussed in detail in a separate blog). Unfortunately, at present there is no way other than an individual identifying what works best for themselves by the trial and error approach. The marketplace for probiotics is expanding rapidly with hundreds of products coming to market. Many companies are identifying and patenting subspecies and strains to deter competition and to market their products as unique. There is the minimal regulatory oversight, and the marketing often overpromises and under-delivers. In general, the mantra in medicine is 'above all do no harm'. I would suggest trying the probiotics with the longest track record of safety, *Lactobacillus*, and *Bifidobacterium*. First one at lower doses, increase as tolerated. If the response is not satisfactory, try the other. Combining both is reasonable, if one alone did not provide sufficient benefit. Branching out to other probiotics is reasonable, but obviously back off if the results are not satisfactory. The good news is that the gut microbiome can be changed rapidly with probiotics and can also be changed again if the results are less than described. In the coming years, there will be clear identification of specific diets and probiotics which will bring us 'back to the future', fulfilling the ancient adage of Hippocrates, the father of modern medicine: "Let food be thy medicine!"

The theory that mental illness is related to the gut microbiome, and may be treated by changing the microbiome by colonics and probiotics, has been known for many decades. There is now a rapidly growing interest in this approach, with therapies ranging from antibiotics, prebiotics, probiotics, and fecal transplants. It is still much too early in the understanding of the healthy and unhealthy microbiome, but the approach holds considerable promise, with numerous anecdotal reports of benefits in everything from depression and schizophrenia to autism and inflammatory bowel disease. Just as there is a risk with antibiotic use, there is also a risk with probiotics and fecal transplants. Most of the general risks of antibiotics are known, but how they can influence the microbiome is still an ongoing investigation.

Although there are research reports showing the conclusive proof of benefit and safety with probiotics and fecal transplants in certain conditions (such as pseudomembranous colitis caused by the pathogen *Clostridia difficile*), the risks and benefits in other conditions remain unknown. One of the significant challenges is that there are likely tens of thousands to a million or more species of microbes in the gut flora that are unidentified and unstudied. Each species may generate unique metabolites or have genetic and epigenetic effects that are yet unknown, with unknown consequences.

The gut microbiome is seeded upon entering the world at birth. While there are suggestions of some prenatal activity, the vast majority are seeded with the vaginal microbiome of the birth mother. The microbiome is markedly different if the birth is through Cesarean delivery. The health advantages of the vaginal microbiome are so high that many infants born by Cesarean delivery are purposefully exposed to the birth mother's vaginal flora by direct application. The initial microbiome of the infant has lifelong effects in the setting of the immune system and its response to future microbes and allergens. Another disadvantage to the microbiome of the infant born by Caesarean section is that they are routinely exposed to antibiotics administered to the mother at the time if delivery. Antibiotics disrupt the normal microbiome and may allow pathogens to become established. The administration of antibiotics at any time is disruptive to the microbiome, and its route of administration, dose, duration, and anti-microbial activity will impact the outcome. When antibiotics are administered supplements with probiotics are often suggested, primarily to prevent the dreaded condition of antibiotic-associated colitis, also known as pseudomembranous colitis. This is a potentially life-threatening infection of the colon caused by the pathogen *Clostridia difficile*. It is a pathogen that is hard to eradicate, and the most effective treatment is a fecal transplant from a healthy donor. The transplant is usually by enema, but capsules containing healthy fecal flora is an alternate route. In ancient China and other cultures, the ingestion of healthy feces has a long history of use as a medical therapy. During World War II, the invading German forces often came down with dysentery, and they found the local Bedouin tradition of eating fresh camel feces to be the most effective therapy.

The thought of purposefully ingesting feces, formally known as coprophagia, is unattractive to most people in the majority of human society and culture. What many will find surprising is that coprophagia is nearly universal on a microscopic level. The feces of insects such as dust mites are almost ubiquitous in the air we breathe in homes and offices. Most of the fruits and vegetables are contaminated, with residual fecal microbes remaining even after washing. Although organic foods are believed by many to have superior nutritional value, they are more often fertilized with manure and have higher levels of fecal bacteria. Many consumers are not aware that organic farms may use manure from livestock yards where the animal droppings contain traces of the antibiotics, hormones, and pesticides from the animals and their feed. Many foods such as meat, poultry, eggs, and seafood harbor fecal microbes. For those who enjoy their shrimp dipped into the cocktail sauce, be sure that the shrimp has been deveined. It is very common for consumers to eat the shrimp with the dark speckled vein intact, most unaware that the vein is the shrimp's intestinal tract and the dark specks within are shrimp feces. Another common cause of coprophagia is the housefly who stands on animal manure with bare sticky feet and then walks all over your food at the restaurant before serving, at the picnic table spread, or on your plate.

Another near universal source of coprophagia is found in countries like the United States which use toilet paper as the predominant means of anal hygiene rather than a bidet or high tech washlet toilet. The thin porous toilet paper wiped with a bare hand is very effective at transmitting fecal bacteria to the fingers, and then straight to the mouth with finger foods. Hand washing, particularly as practiced in most non-surgical settings is inadequate. For those who have their toothbrush sitting on the bathroom sink counter, it is being sprayed with fecal bacteria with every toilet flush, dramatically so if you don't lower the lid before flushing. Even the avoidance of paper towels and the use of hot air blowers to dry hands in a bathroom may lead to greater spread of fecal microbes because the hot air is contaminated by aerosolized microbes from the flushing toilets. To give you an example of transmission via the fecal-oral route look at the outbreaks of norovirus gastroenteritis on cruise ships, or the fact that virtually everyone in a household will get pinworms if even just one child comes down with the initial infestation.

The brain also receives influential stimuli from other sensory input. The olfactory nerve, the cranial nerve I, is the only nerve in the body when the actual neural receptors are exposed to the external environment. The odorant chemical is volatile and free floating in the air inhaled into the nasal passages, where it binds to the olfactory nerve receptors. The odorant can have neurological and biological activity such as pheromones, hallucinogens, toxins, stimulants, etc. As the olfactory nerve goes directly to the brain, an odorant bypasses the blood brain barrier. Briefly revisiting the gut brain connection and the microbiome, smelling the characteristic odor of feces is the physical binding of volatile chemical odorants that traveled from the feces to bind to the receptors of the olfactory nerve. If you can smell the feces, it has literally reached and touched your brain. Because of the direct connection to the brain, olfaction is considered the humans most discriminating sense. It can pick out and identify an odorant present in a concentration of less than one part in two billion. The other senses including, taste, vision, hearing, and touch are carried by different cranial or spinal nerves.

Each of the hundreds of millions to billions of unique species has thousand to tens of thousands of genes. Each generates a unique protein that has a biological activity of the source organism, and a high likelihood of activity in others. The number of biologically active protein in nature is virtually infinite. Many have been identified and developed over the course of human history for medicinal, cultural, religious, or recreational use. Nearly all of the herbal remedies have had the active ingredient identified and then marketed as a pharmaceutical therapeutic. There are many millions more that have yet to be screened, identified, purified, and developed for commercial applications. The pharmaceutical and chemical industries have developed vast data banks with millions of proteins to screen, and a virtually limitless supply yet to be discovered. The odds of finding a novel treatment is low, but the numbers screened are so high that success is virtually assured. High throughput screening is now able to analyze hundreds of thousands if chemicals each day.

Although not as astronomical as the numbers of chemicals, the number of species of microbes that are potential probiotics is in the hundreds of millions. Even within a species there are tremendous variations in the biological activity of various subspecies and strains, so the potential number of probiotics even a magnitude greater. The search for novel organisms and bioactive chemicals is extremely active and productive. The potential value of a product identified, and patented makes diamond mining pale in comparison to the rewards of success. One of the more interesting success stories is an expedition to the isolated Easter Islands if the Pacific Ocean, one thousand miles west of the coast of Chile in South America. Tunneling beneath the iconic moa statues on the island of Rapa Nui a rare microbial species was identified and one of its unique bioactive compounds was found to have immunity properties and was thus named Rapamycin.

It was found to suppress the immune response to transplanted organs and was developed as an antirejection pharmaceutical with FDA approval. Further study of the roundworm *Caenorhabditis elegans* discovered a unique gene that the pharmaceutical had as a specific target. The gene was named m-TOR, which stood for the mechanistic target of Rapamycin. What was surprising was that this gene has been associated with Alzheimer's disease as well as autism and other neurological disorders. What was even more remarkable was that the gene is dramatically involved with biological aging. In the roundworm, the inhibition of the M-TOR gene with the drug resulted in an astonishing decrease in the rate of aging, with a tenfold increase in lifespan. If the drug had the same effect in humans those who live to age one hundred could live to age one thousand. *Caenorhabditis elgans* and humans share approximately one-third of their genes, even though they are widely separated in the evolutionary pathway. The m-TOR gene is identical in both and studies in Alzheimer’s, autism, and aging are underway.

The diet contains vast quantities and varieties of a whole host of factors that can affect the brain directly by absorption into the blood stream, or by influencing the microbiome and its metabolic activity.

Nutrients, bioactive food components such as caffeine, alcohol, nicotine, opioids, enzymes, chemicals, toxins, genes, proteins, hormones, biological agents, neurotransmitters, etc. are just one side of the effect of diet intake. On the other are billions of new microbes ingested with food and drink. The diet rapidly changes the microbiome, and its influence can be profound. The common animal protein sources have a multitude of components that have bioactivity in humans. Even vegetarians can be exposed to these animal products when manure is used as fertilizer, as is particularly common in organic farming. Animal manure is known to contain hormones, antibiotics, pesticides, and heavy metals such as Cadmium, Zinc, Arsenic, Lead, and Chromium. Food animals receive 80% of the antibiotics sold in the USA and may have contributed to the 23,000 US deaths per year from antibiotic-resistant infections. Animal manure is also the source of parasites and pathogens such as E. Coli, salmonella, and others. Manure is used as fertilizer, as is common in organic food products.

The number of chemicals found in other life forms and the environment that is toxic to humans numbers in the tens of thousands. Toxicity is a function of dose, but for some products such as the toxin ricin, as little as five milligrams can be fatal to a human who is ten million times larger. Toxicity results from interference with cell metabolism. The word metabolism comes from the Greek word metabolē meaning ‘ to change’. Metabolism is the series of life-sustaining chemical transactions that occur within living organisms. The majority of reactions have a specific enzyme that serve as a catalyst allowing the reaction to take place more efficiently and with less energy expenditure. The metabolic systems of particular organisms determine which substances will be nutritious and supportive of life, and which will be toxic leading to injury or death. For example, hydrogen sulfide is a source of energy for some organisms, and cause of death for others.

Many of the metabolic pathways are shared by widely divergent species because they appeared early in the evolution of life and were retained because of their extraordinary efficiency. For example, the foundation of cellular energy, the Krebs citric acid cycle, is identical in single cell bacteria as well as multicellular elephants. The ubiquity and interchangeability of the metabolism and structure of proteins, carbohydrates, lipids, and nucleic acids are other common denominators of virtually all-living organisms. The most recent scientific estimate is that there are over 37 trillion human cells and over 100 trillion cells in the human microbiome. The average cell performs between thousands to millions of reactions per second. The metabolic activity that is continuously ongoing to maintain life is mind-boggling. At the same time, it is vulnerable to innumerable potential interruptions that can permanently end the incredible machinery of life. Using the human as one singular example, one milligram of ricin toxin can end the life of an individual that is twenty million times larger.

The brain contains over one hundred billion neurons with over 100 trillion of synaptic connections. The average neuron fires between five and fifty times per second. The internal communication amongst the central nervous system neurons is phenomenal. The external communication to the brain including the key senses of smell, vision, hearing, taste, and touch with the Cranial Nerves providing significant sensory input is no less impressive. With language skills, supplementary forms of visual and auditory communication are possible, especially between individuals. The degree of communication between the brain, the body, and its environment is just beginning to be recognized. The gut-brain-microbiome-food axis is the current descriptive term, but it falls short, as it does not include the sensory input of the other cranial nerves.

The enteric nervous system consists of some 500 million neurons, 0.5% of the neurons in the brain, but five times as many as the one hundred million neurons in the spinal cord. The enteric nervous system is embedded in the lining of the gastrointestinal system, beginning in the esophagus and extending down to the anus. The communication between the central and enteric nervous system is extensive and follows some alternate pathways. The clearest and most direct pathway is via the cranial nerves, which arise from the brain and brain stem. The olfactory nerve, the cranial nerve I, provides sensory input via the sense of smell. It is the only nerve in the body in which its receptors are exposed to the external environment. Odorants are volatile chemicals, which bind to the receptor and the signal is transmitted directly to the brain. It is our most sensitive sense, yet other animals have much greater olfactory sensitivity. The bear sense of smell is 2,000 times more sensitive than human. The effect of the chemical messenger can be dramatic and virtuously instantaneous. Pheromones, hormones, toxins, and other bioactive products can induce a response even if the brain considers it odorless and unidentifiable.

The optic nerve, cranial nerve II provides visual input from the eyes. Although the sharp area of focus is relatively limited, the peripheral vision ability to detect motion us an important defense mechanism to protect survival. Many animals and insects have a keener sense of vision as well as an expanded spectrum of wavelengths they can visualize, such as ultraviolet and infrared. The auditory, acoustic, or vestibulocochlear nerve, cranial nerve VIII provides sensory information of sound, position, and balance. The facial nerve, cranial nerve VII, carries the gustatory sense of taste from the anterior two-thirds of the tongue, and the gesso pharyngeal nerve, cranial nerve IX, carries taste sensations from the posterior third of the tongue.

The vagus (Latin- wanderer) nerve, also known as Cranial Nerve X, has a long meandering path throughout the body traveling from the brain to the throat, lungs, heart, stomach, intestines, pancreas, uterus, and a host of internal sites in the chest abdomen and pelvis. It has one the most varied and extensive network of a cranial nerve and plays a major role in the autonomic and parasympathetic nervous systems. A very surprising finding was that the two-way communication was not evenly distributed, over 80% of the nerve fibers and messages were going from the gut to the brain. As with all nerve fibers, neurotransmitters are utilized to communicate between neurons while the message is traveling along the length if the nerve fiber itself is an electrical impulse. One of the more remarkable findings has been that electrical stimulation of the vagus nerve is an effective FDA approved modality in the management of depression that is resistant to standard therapy. Another surprising fact about the vagus nerve is its role in the immune response. Vagus nerve stimulation inhibits inflammation by suppressing pro-inflammatory cytokine production. The vagus nerve activates the efferent arm of the Inflammatory Reflex, the neural circuit that stimulates the spleen to inhibit the production of tumor necrosis factor (TNF) and other pro-inflammatory cytokines by macrophages.

Another communication pathway is the immune and inflammatory response process itself, including cytokines, chemoreceptors, complement cascade, lymphocytes, plasma cell, interferon, immunoglobulins, and other mechanisms. The gastrointestinal system plays a central role in immune system homeostasis. It is the main route of contact with the external environment and is overloaded every day with external stimuli, microbes, parasites, pathogens (bacteria, protozoa, fungi, viruses) toxic substances, as well as food, fluids, minerals, micronutrients, etc. The immune system charged with protecting this sprawling border with the external environment is the Gut associated lymphoid tissue (GALT), the prominent part of mucosal associated lymphoid tissue (MALT). It represents almost 70% of the entire immune system. About 80% of plasma cells, which are the main immunoglobulin A (IgA)-bearing cells, reside in GALT.

The digestive tract is approximately 9 meters or 30 feet long. The extensive neural network of some 500 million neurons has thousands of miles of circuitry traversing the entire length of the tract. The immune system has to protect the interface of gut mucosa with the external environment, the entire surface area of the human gut is about 300 square meters, or about the size of a tennis court. 3,200 square feet. By comparison, the skin in contact with the external environment is less than 2 square meters, approximately 20 square feet. Lungs contain approximately 2,400 kilometers (1,500 mi) of airways and up to 500 million alveoli. The surface area of lungs in contact with the external environment in the average adult is up to 100 square meters, 1,100 square feet.

The olfactory epithelium surface area is 1.5 share inches (10cm2) in humans. 3 square inches (20cm2) in cats, 30 square inches (200cm2) in dogs. The olfactory cranial nerve is the only nerve tissue in the body that is directly exposed to the external environment. It is the sense of the greatest sensitivity and acuity since stimulation comes directly from the environment when an odorant binds to the neural receptor it has direct access to the central nervous system and completely bypasses the blood-brain barrier. Pheromones, nasal sprays of hormones or other bioactive agents can have a rapid and profound central nervous system effect. Drug usage such as the snorting of cocaine is one example of this pathway. This also explains why the freshwater protozoan Naegleria can directly infect the brain via the olfactory nerve, and rapidly progress to fatal encephalitis

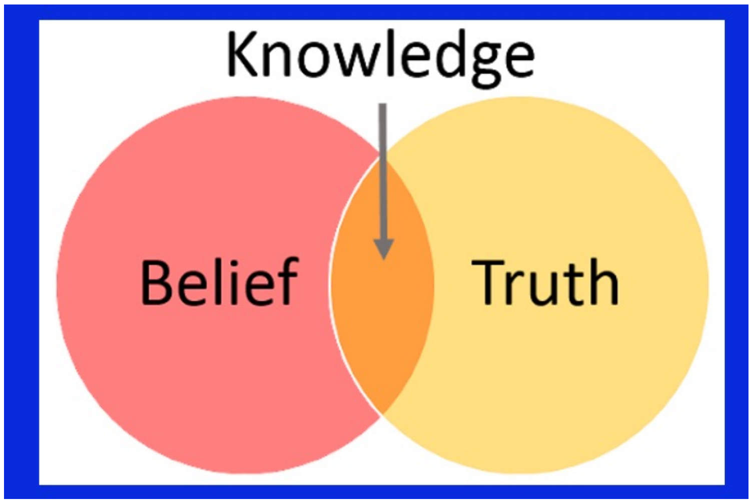
There are dozens of neurotransmitters; amongst the most prominent are serotonin, dopamine, norepinephrine, acetylcholine, GABA, and glutamate. Over 95% of serotonin is manufactured in the gut, where the microbiota controls the host tryptophan metabolism along the kynurenine pathway. The enzymes of this pathway are immune and stress-responsive. The gut microbiome can manufacture neurotransmitters from precursors such as tryptophan, tyrosine, choline, etc. found in the diet. These can be absorbed directly by gut mucosal cells, or in between the cell junctions in the case of a 'leaky gut'. These absorbed neurotransmitters can influence mood, cognition, stress, immune response, and a variety of cascading responses. In addition to the production of neurotransmitters, other metabolites, hormones, bioactive products from microbial metabolism can be absorbed and influence the central nervous system and other organs.

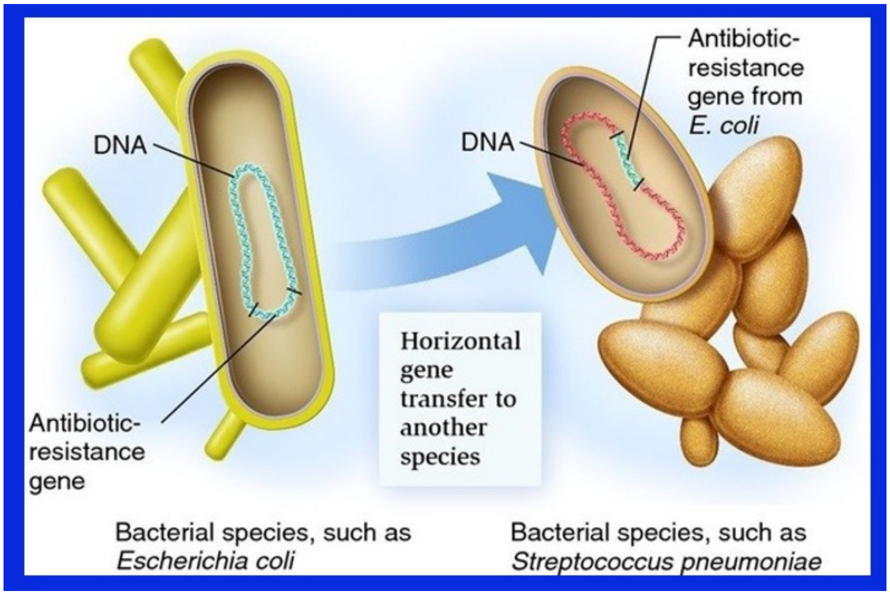
Another communication network is via the genes, from which proteins including hormones, neurotransmitters, bioactive peptides, and other metabolites are derived. Since all life forms evolved from a single source, there is overlap in the genomics, with greater homology suggesting a closer relationship. The percentage of the human genome found in the Chimpanzee, our closest relative, is a remarkable 98.5%. Perhaps more surprising us the mouse at 92%, cat at 90%, cow at 80%, fruit fly at 65%, banana at 50%, Roundworm *Caenorhabditis elegans* 40%, bacteria 30%, and yeast 26%. When the numbers of cells in the human body are counted only 10% are human, the rest are microbial. When the number of genes is counted the 20,000 plus human genes are outnumbered by the million plus microbial genes of our multitude of guests of different species. Adding to the 100 trillion microbes, we have myriad immune modulators, neurotransmitters, hormones, and metabolites of the millions of genes all potentially active within us. Then of course we have our diet, environmental hazards, 35,000 prescription drugs, over one hundred thousand over the counter drugs, 100,000 plus nutraceutical, prebiotics, probiotics, etc. By the way, of the hundreds of thousands of products on the market the FDA has evaluated safety and efficacy of fewer than 1,500, the rest have been grandfathered.

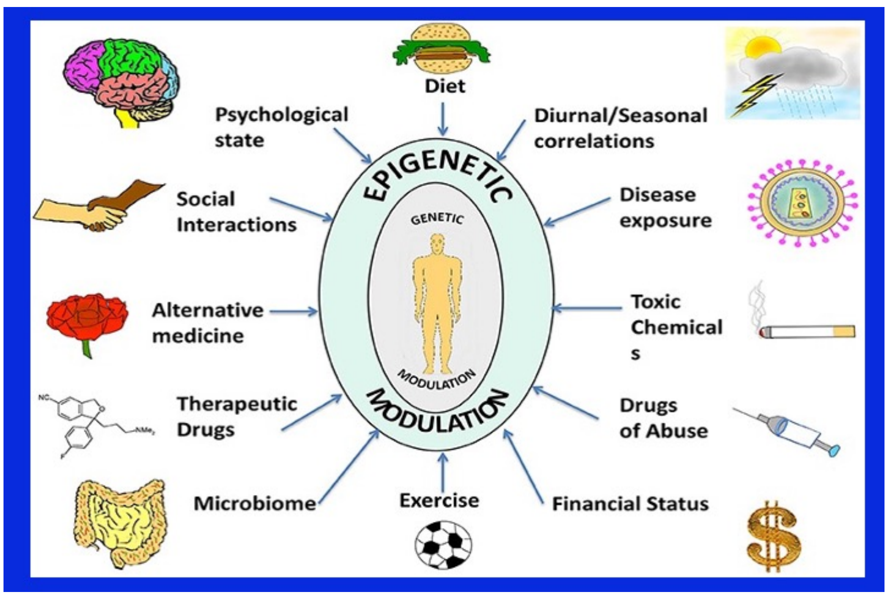
When the variables number in the thousands to millions and each variable may have options that run into the millions as well, the possible combinations are virtually infinite. Even the most powerful supercomputers available today cannot keep up with possible data combinations and consequences. The discipline of systems biology attempts to grapple with this astounding complexity. As with any complex system, the devil is in the details and the weakest link can be the source of disaster. In the biological world, one example is the single character mutation out of the three billion base pairs of DNA that leads to the misfolding of the hemoglobin molecule that is the cause of sickle cell anemia.

The interaction of the gut microbiome in human health and disease, and the influence of diet, are just beginning to be explored. The biological activity of metabolites of species frequently crosses over with unrelated species. At a minimum, one-third of the genes and their directed proteins will be bioactive in humans. There are millions if not billions of potential microbial species that can become established in the gut microbiome. The majority will be commensals or symbionts, but singular pathogens will also be identified and result in new therapeutic approaches. The consequences of microbial metabolites that are bioactive products may be beneficial, neutral, or harmful. The number of diverse conditions known to be affected by the gut microbiome continues to expand. Conditions such as inflammatory bowel disease and irritable bowel syndrome would be expected to have gut microbiome influences. Autism, Parkinson, Alzheimer, asthma, multiple sclerosis, diabetes, cardiovascular disease, arthritis, cancer, and others have identified how widespread the influence of the gut microbiome is on human health and disease. The use of antibiotics, prebiotics, probiotics, synbiotics, postbiotics, and fecal transplants are being reevaluated as new research findings are revealed.

Unfortunately, the use of probiotics to manipulate the human gut microbiome has become a fad with marketing far exceeding the scientific credibility. While there is great potential, there is also a very high likelihood of adverse consequences as we enter this exciting new era of understanding. I would suggest that we recognize that probiotics can influence the gut microbiome populations in a fashion similar to antibiotics, and that they should be treated with the same degree of caution and respect.







DIET

Greek *diaita* 'a way of life.'

Alkaline
Ayurveda (Vata, Kapha, Pitta)
Atkins
Blood Type
Clean Eating
Dairy Free
Elimination
Esselstyn
Flexitarian
Food Combining
Fruitarian
Grain Free
Gluten Free
High Protein
Ketogenic
Lacto-vegetarian

Low Carbohydrate
Low Fat
Low FODMAP
Macrobiotic
McDougall
Mediterranean
Nutritarian
Ovo-vegetarian
Paleo
Pollotarian
Pesco-vegetarian
Raw Food
South Beach
Vegan
Vegetarian
Volumetrics

Food Diversity

Mammals – 5,500 species
Cows 800+ breeds (22,000 genes) – 2000 varieties of cheese
Sheep 600+ breeds
Pigs 400+ breeds
Fish 25,000 species (25,000-50,000 genes)
Poultry 3,000 varieties (17,000 to 23,000 genes)
Apple 7,500 varieties (57,000 genes)
Tomato 7,500 varieties (35,000 genes)
Maize/Corn 20,000 varieties (32,500 genes)
Rice 40,000 varieties (32,000 to 56,000 genes)
Potatoes 5,000 varieties (40,000 genes)
Beans 40,000 varieties (30,000 genes)
Wheat 10,000+ varieties (96,000 genes)

Essential	Conditionally Non-Essential	Non-Essential
Histidine	Arginine	Alanine
Isoleucine	Asparagine	Asparatate
Leucine	Glutamine	Cysteine
Methionine	Glycine	Glutamate
Phenylalanine	Proline	
Threonine	Serine	
Tryptophan	Tyrosine	
Valine		
Lysine		

NEUROTRANSMITTERS

ADRENALINE
fight or flight
produced in stressful situations. Increases heart rate and blood flow, leading to physical boost and heightened awareness.

GABA
calming
Calms firing nerves in the central nervous system. High levels improve focus, low levels cause anxiety. Also contributes to motor control and vision.

NORADRENALINE
concentration
affects attention and responding actions in the brain. Contracts blood vessels, increasing blood flow.

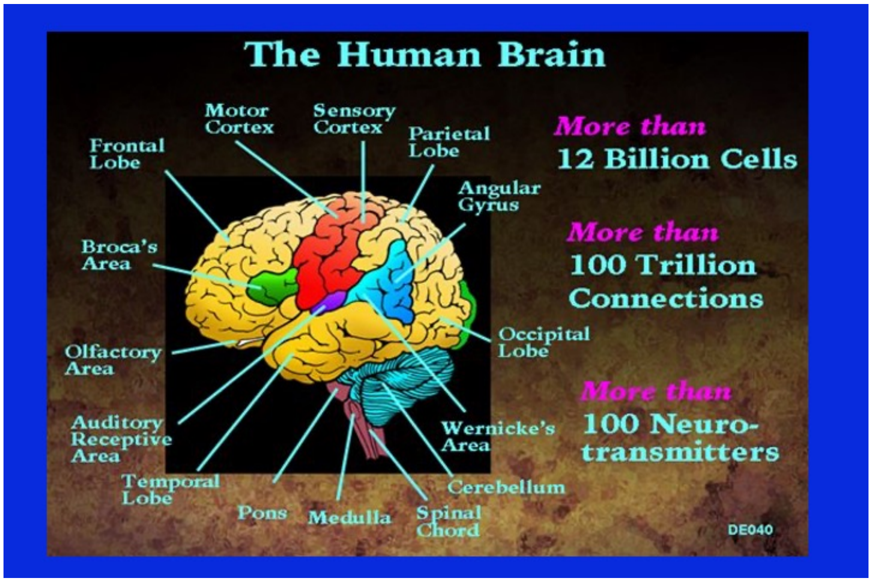
ACETYLCHOLINE
learning
Involved in thought, learning and memory. Activates muscle action in the body. Also associated with attention and awakening.

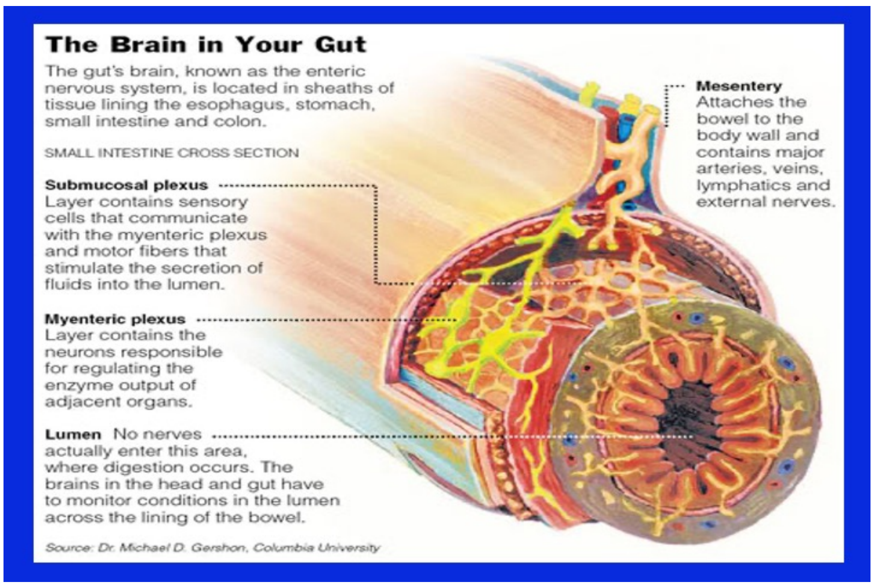
DOPAMINE
pleasure
feelings of pleasure, also addiction, movement and motivation. People repeat behaviors that lead to dopamine release.

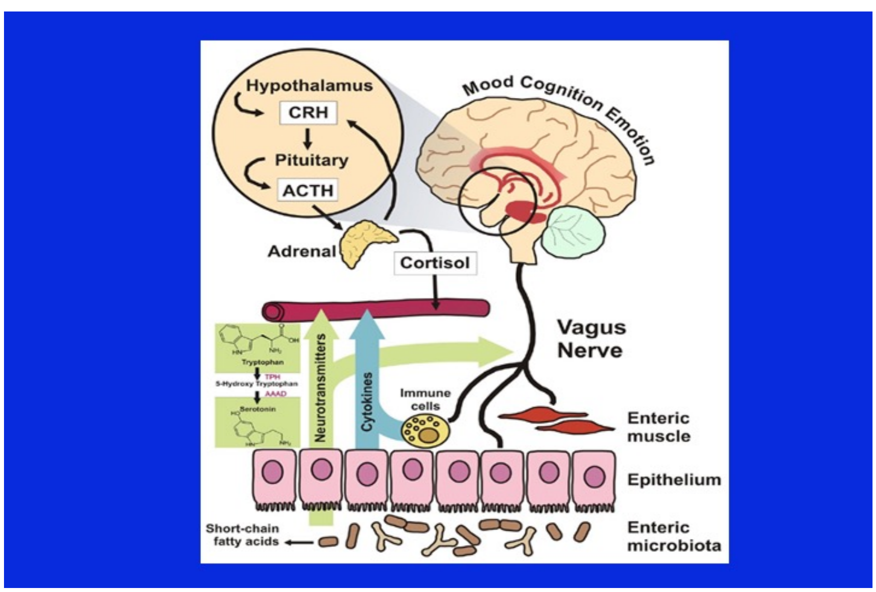
GLUTAMATE
memory
Most common neurotransmitter. Involved in learning and memory, regulates development and creation of nerve contacts.

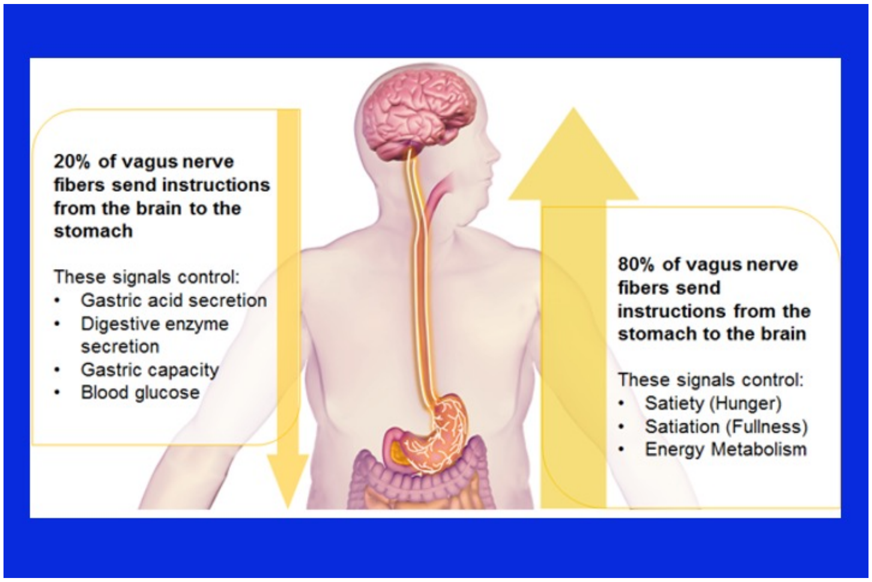
SEROTONIN
mood
contributes to well-being and happiness. Helps sleep cycle and digestive system regulation. Affected by exercise and light exposure.

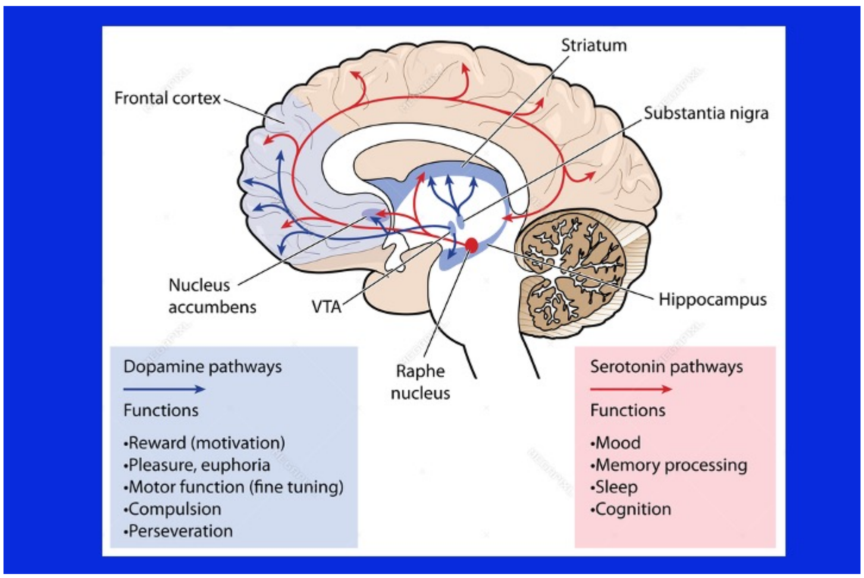
ENDORPHINS
euphoria
Released during exercise, excitement and sex, producing well-being and euphoria, reducing pain

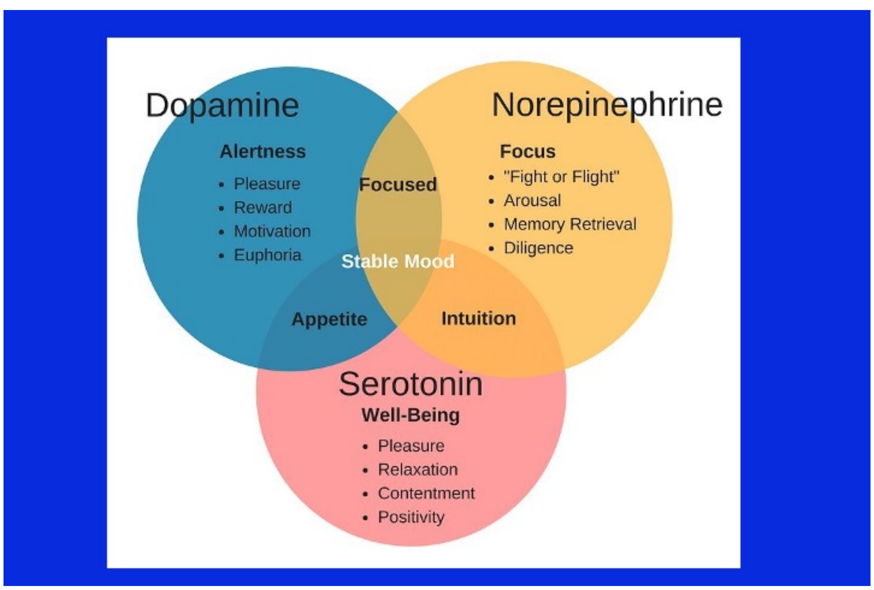

The Human Brain
Motor Cortex
Sensory Cortex
Parietal Lobe
Frontal Lobe
Angular Gyrus
Broca's Area
Olfactory Area
Auditory Receptive Area
Temporal Lobe
Pons
Medulla
Spinal Chord
Cerebellum
Wernicke's Area
Occipital Lobe
More than
12 Billion Cells
More than
100 Trillion Connections
More than
100 Neuro-transmitters
DE040

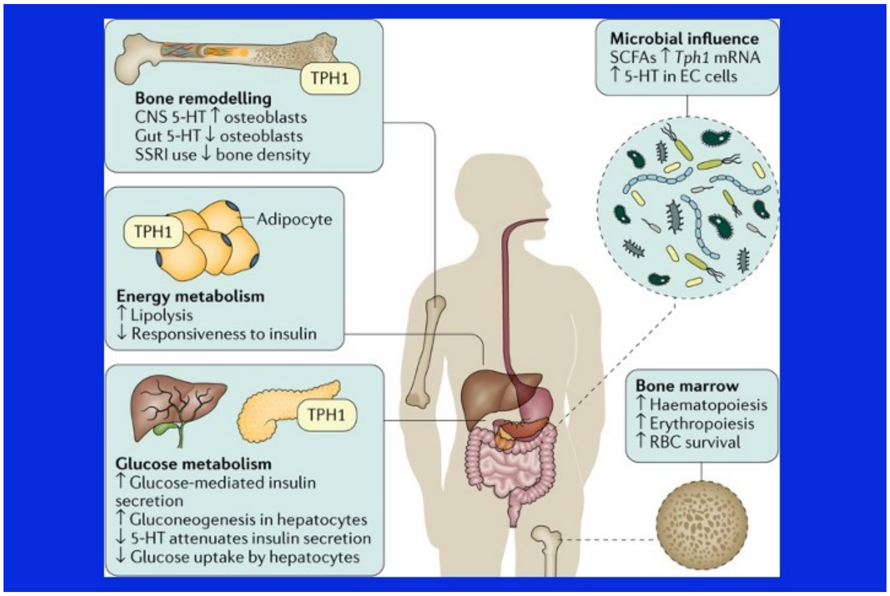

The Brain in Your Gut
The gut's brain, known as the enteric nervous system, is located in sheaths of tissue lining the esophagus, stomach, small intestine and colon.
SMALL INTESTINE CROSS SECTION
Submucosal plexus
Layer contains sensory cells that communicate with the myenteric plexus and motor fibers that stimulate the secretion of fluids into the lumen.
Myenteric plexus
Layer contains the neurons responsible for regulating the enzyme output of adjacent organs.
Lumen No nerves actually enter this area, where digestion occurs. The brains in the head and gut have to monitor conditions in the lumen across the lining of the bowel.
Mesentery
Attaches the bowel to the body wall and contains major arteries, veins, lymphatics and external nerves.
Source: Dr. Michael D. Gershon, Columbia University

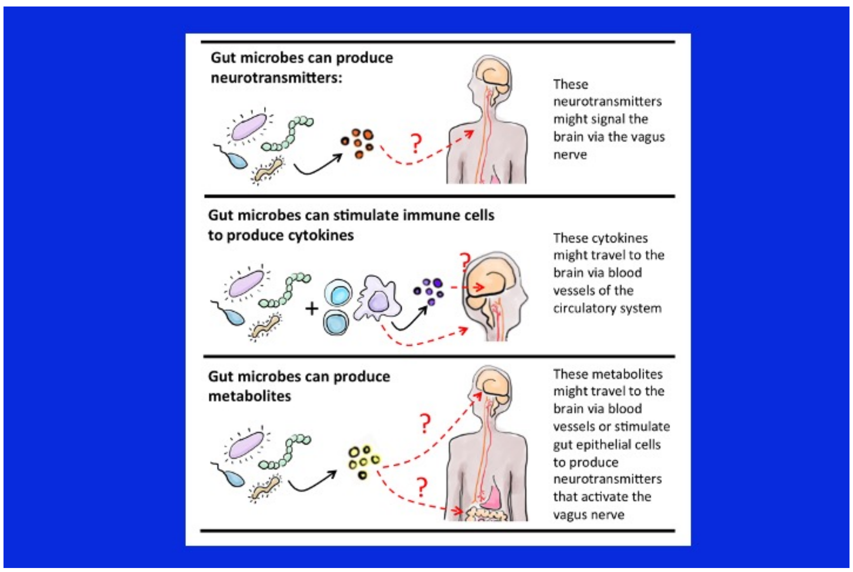

Hypothalamus
CRH
Pituitary
ACTH
Adrenal
Cortisol
Mood Cognition Emotion
Vagus Nerve
Tryptophan
TPH
5-Hydroxy Tryptophan
AAAD
Serotonin
Neurotransmitters
Cytokines
Immune cells
Enteric muscle
Epithelium
Enteric microbiota
Short-chain fatty acids

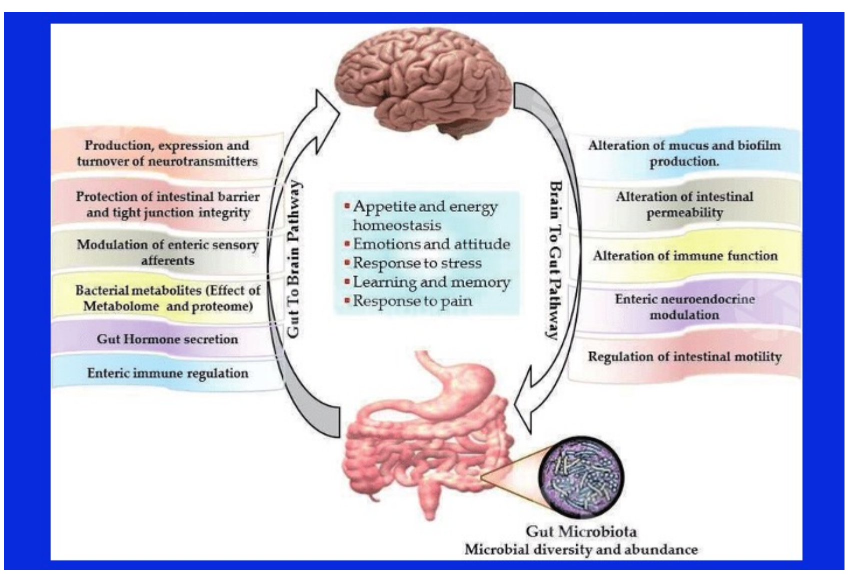

20% of vagus nerve fibers send instructions from the brain to the stomach
These signals control:
• Gastric acid secretion
• Digestive enzyme secretion
• Gastric capacity
• Blood glucose
80% of vagus nerve fibers send instructions from the stomach to the brain
These signals control:
• Satiety (Hunger)
• Satiation (Fullness)
• Energy Metabolism

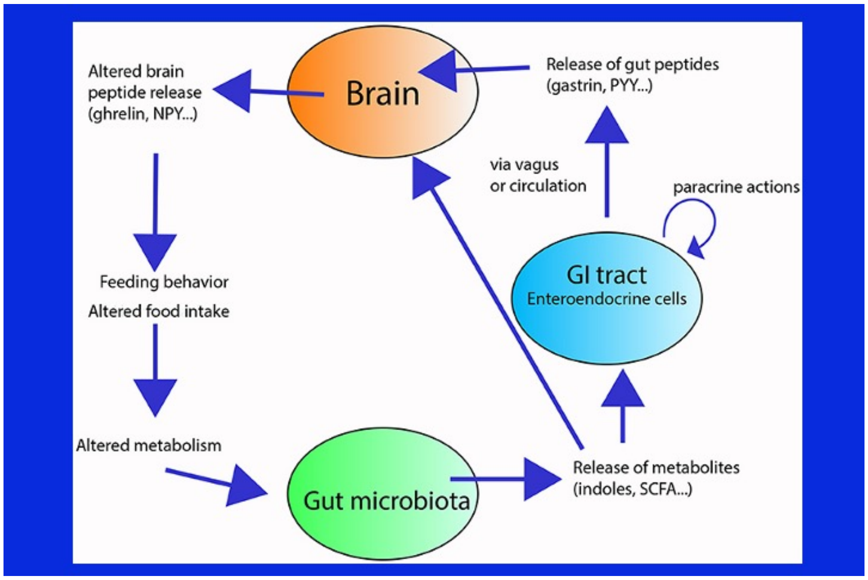

Striatum
Frontal cortex
Substantia nigra
Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
Dopamine pathways
Functions
•Reward (motivation)
•Pleasure, euphoria
•Motor function (fine tuning)
•Compulsion
•Perseveration
Serotonin pathways
Functions
•Mood
•Memory processing
•Sleep
•Cognition

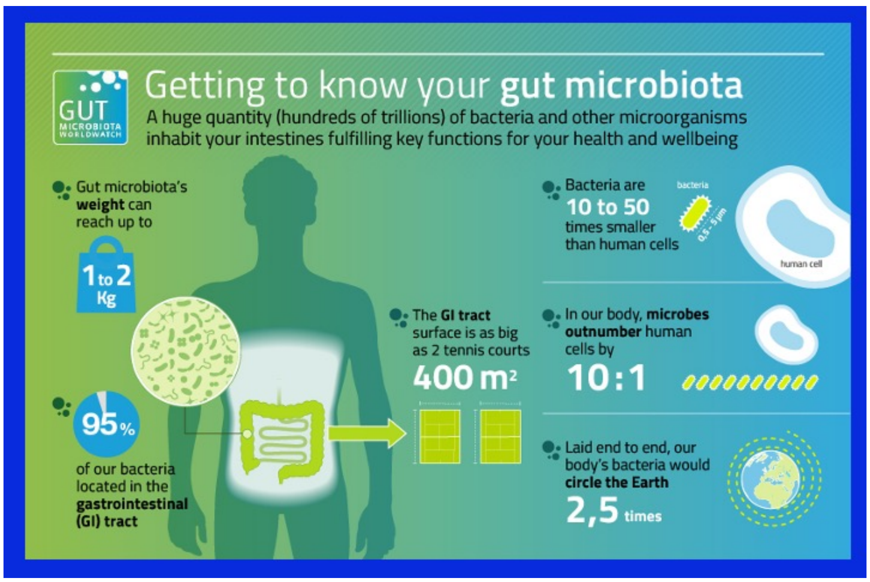

Dopamine
Alertness
• Pleasure
• Reward
• Motivation
• Euphoria
Norepinephrine
Focus
• "Fight or Flight"
• Arousal
• Memory Retrieval
• Diligence
Focused
Stable Mood
Appetite
Intuition
Serotonin
Well-Being
• Pleasure
• Relaxation
• Contentment
• Positivity

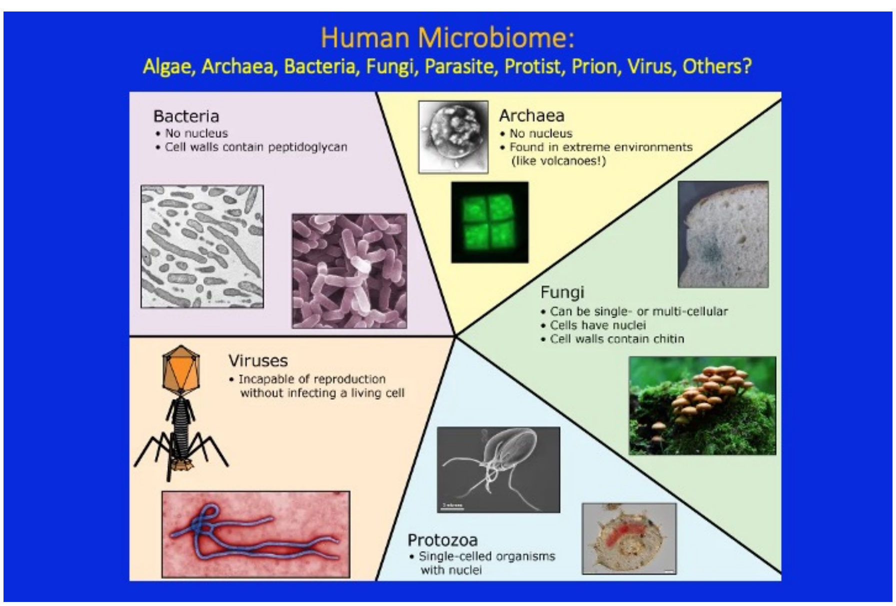

Bone remodelling
CNS 5-HT ↑ osteoblasts
Gut 5-HT ↓ osteoblasts
SSRI use ↓ bone density
TPH1
Microbial influence
SCFAs ↑ Tph1 mRNA
↑ 5-HT in EC cells
Adipocyte
TPH1
Energy metabolism
↑ Lipolysis
↓ Responsiveness to insulin
TPH1
Glucose metabolism
↑ Glucose-mediated insulin secretion
↑ Gluconeogenesis in hepatocytes
↓ 5-HT attenuates insulin secretion
↓ Glucose uptake by hepatocytes
Bone marrow
↑ Haematopoiesis
↑ Erythropoiesis
↑ RBC survival

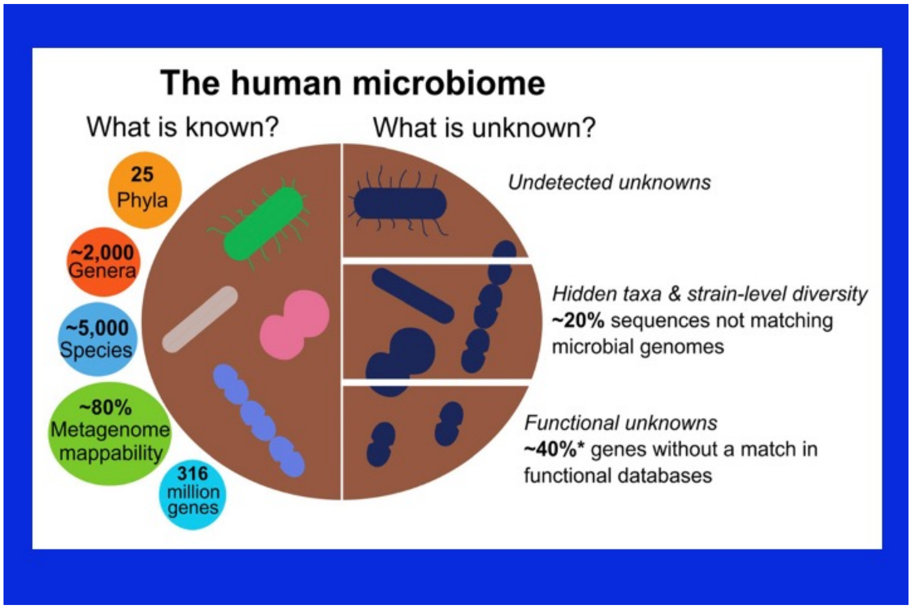

Gut microbes can produce neurotransmitters:
These neurotransmitters might signal the brain via the vagus nerve
Gut microbes can stimulate immune cells to produce cytokines
These cytokines might travel to the brain via blood vessels of the circulatory system
Gut microbes can produce metabolites
These metabolites might travel to the brain via blood vessels or stimulate gut epithelial cells to produce neurotransmitters that activate the vagus nerve

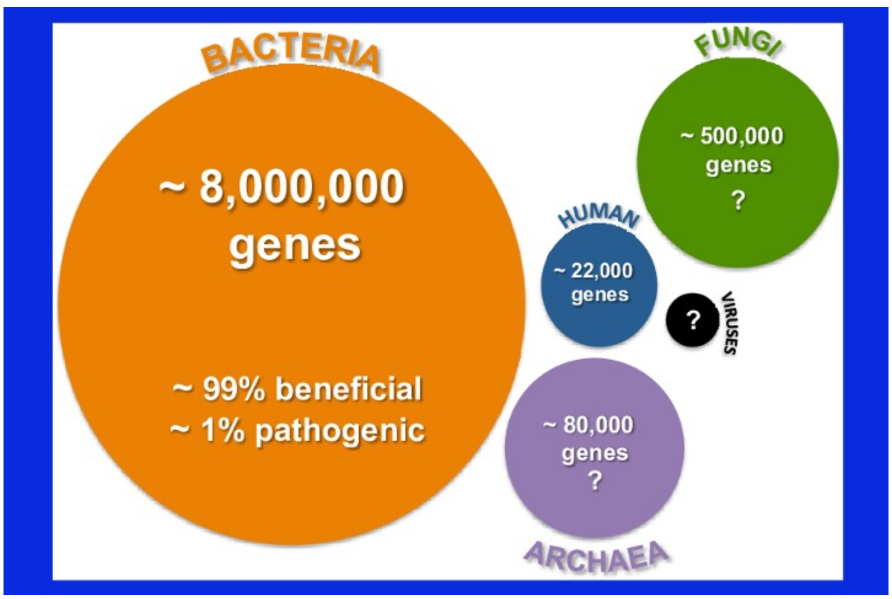

Production, expression and turnover of neurotransmitters
Protection of intestinal barrier and tight junction integrity
Modulation of enteric sensory afferents
Bacterial metabolites (Effect of Metabolome and proteome)
Gut Hormone secretion
Enteric immune regulation
Gut To Brain Pathway
Appetite and energy homeostasis
Emotions and attitude
Response to stress
Learning and memory
Response to pain
Brain To Gut Pathway
Alteration of mucus and biofilm production.
Alteration of intestinal permeability
Alteration of immune function
Enteric neuroendocrine modulation
Regulation of intestinal motility
Gut Microbiota
Microbial diversity and abundance

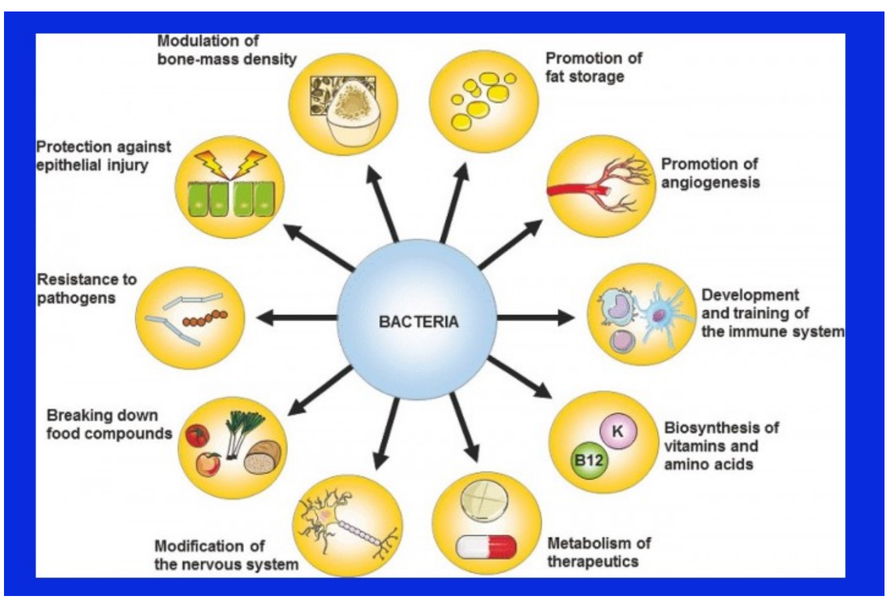

Brain
Altered brain peptide release (ghrelin, NPY...)
Release of gut peptides (gastrin, PYY...)
via vagus or circulation
paracrine actions
GI tract
Enteroendocrine cells
Feeding behavior
Altered food intake
Altered metabolism
Gut microbiota
Release of metabolites (indoles, SCFA...)

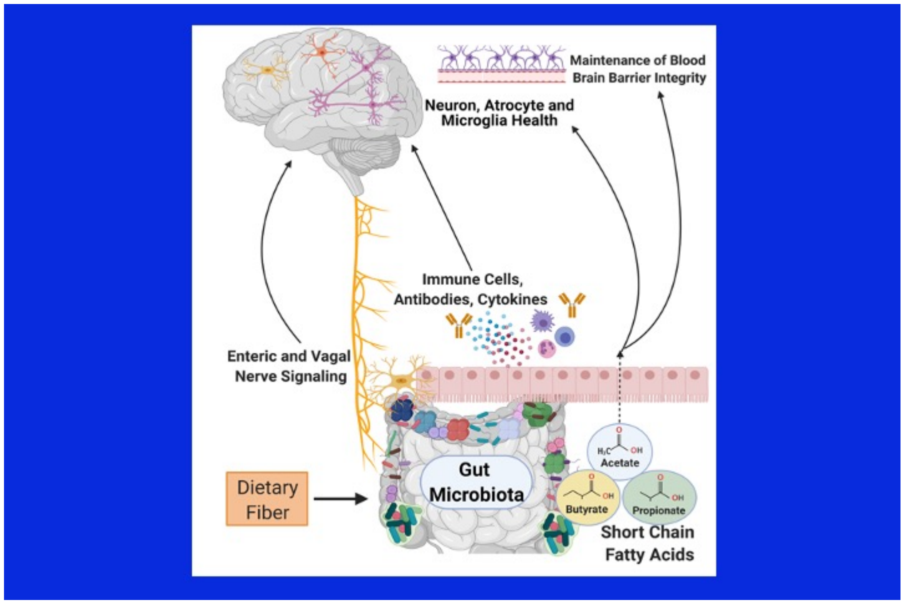

Getting to know your gut microbiota
A huge quantity (hundreds of trillions) of bacteria and other microorganisms inhabit your intestines fulfilling key functions for your health and wellbeing
GUT MICROBIOTA WORLDWATCH
Gut microbiota's weight can reach up to
1 to 2 Kg
95%
of our bacteria located in the gastrointestinal (GI) tract
The GI tract surface is as big as 2 tennis courts
400 m²
Bacteria are 10 to 50 times smaller than human cells
bacteria
human cell
In our body, microbes outnumber human cells by
10:1
Laid end to end, our body's bacteria would circle the Earth
2,5 times

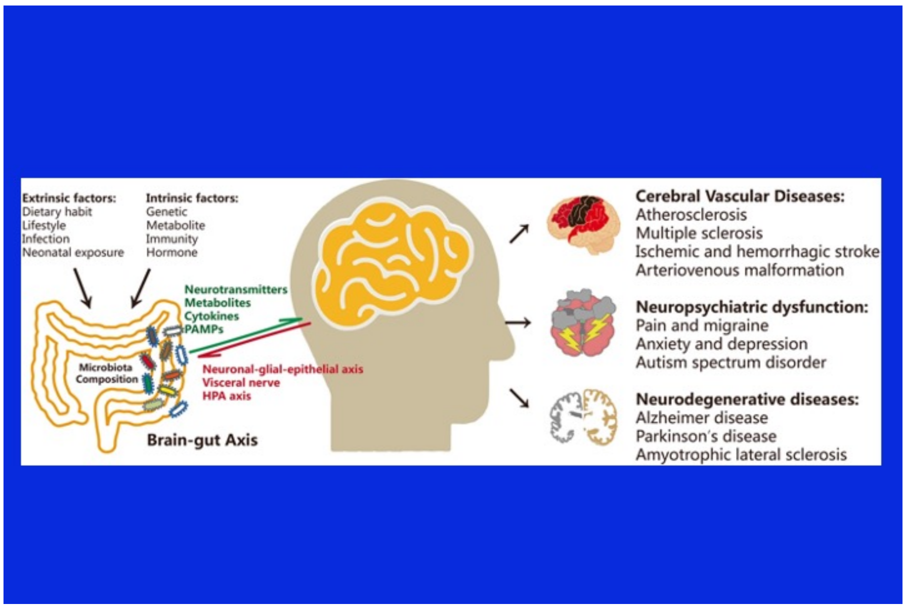

Human Microbiome:
Algae, Archaea, Bacteria, Fungi, Parasite, Protist, Prion, Virus, Others?
Bacteria
• No nucleus
• Cell walls contain peptidoglycan
Archaea
• No nucleus
• Found in extreme environments (like volcanoes!)
Fungi
• Can be single- or multi-cellular
• Cells have nuclei
• Cell walls contain chitin
Viruses
• Incapable of reproduction without infecting a living cell
Protozoa
• Single-celled organisms with nuclei

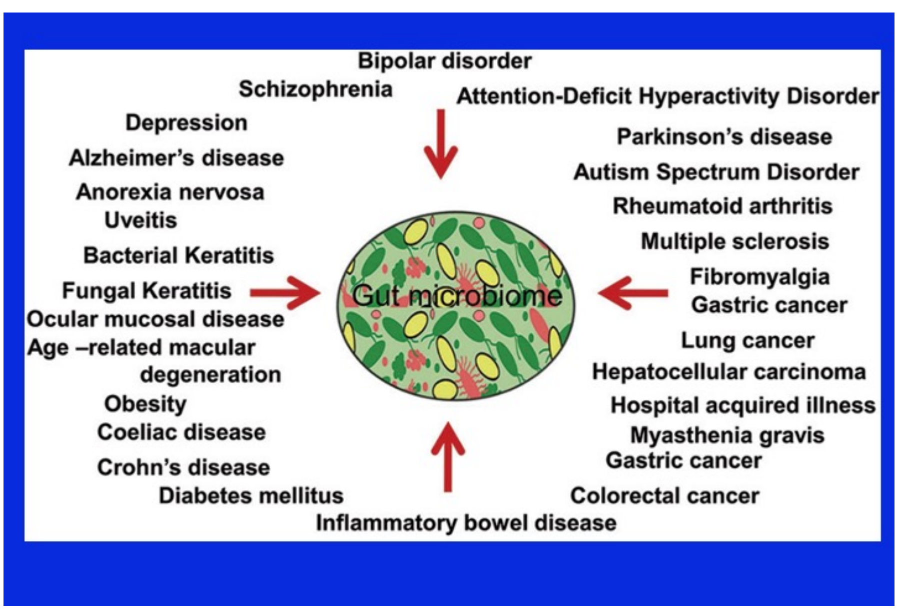

The human microbiome
What is known?
What is unknown?
25 Phyla
~2,000 Genera
~5,000 Species
~80% Metagenome mappability
316 million genes
Undetected unknowns
Hidden taxa & strain-level diversity
~20% sequences not matching microbial genomes
Functional unknowns
~40%* genes without a match in functional databases

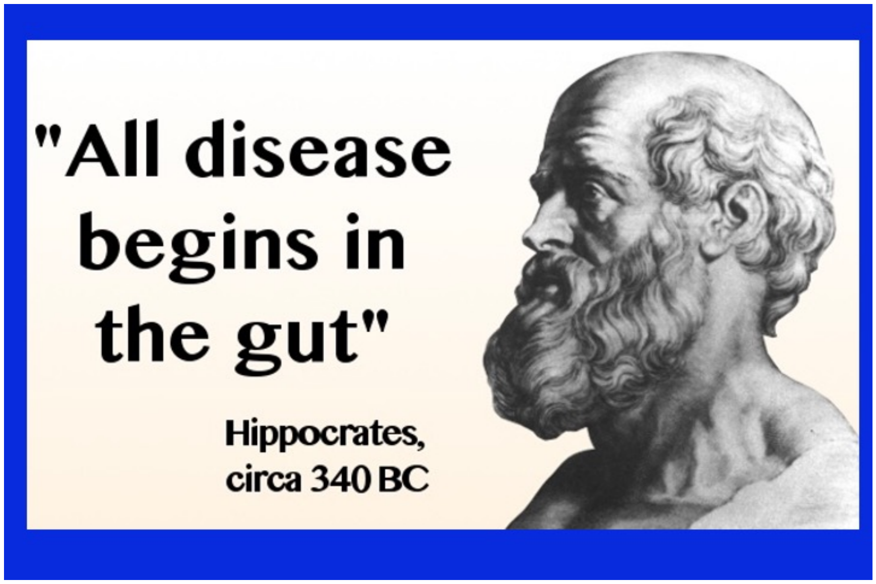

BACTERIA
~ 8,000,000 genes
~ 99% beneficial
~ 1% pathogenic
FUNGI
~ 500,000 genes
?
HUMAN
~ 22,000 genes
?
VIRUSES
~ 80,000 genes
?
ARCHAEA

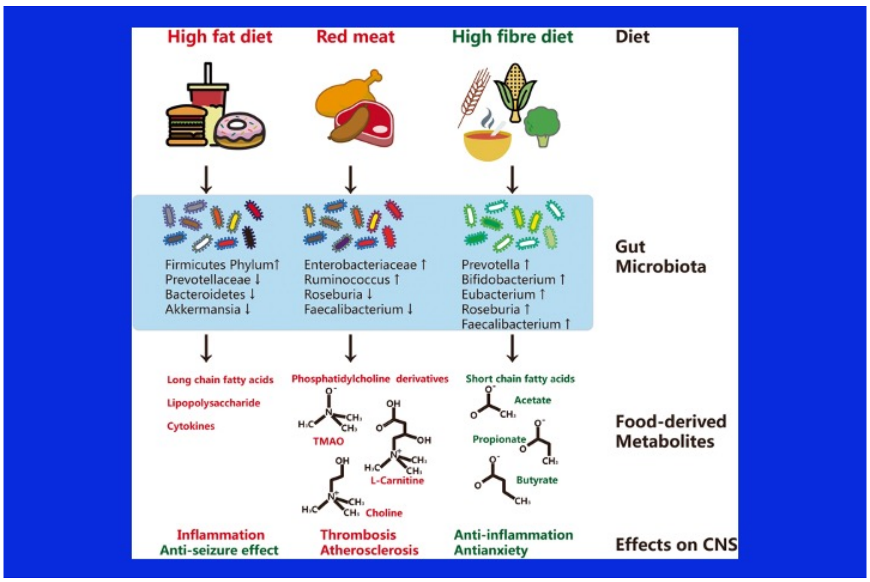

BACTERIA
Modulation of bone-mass density
Promotion of fat storage
Protection against epithelial injury
Promotion of angiogenesis
Resistance to pathogens
Development and training of the immune system
Breaking down food compounds
Biosynthesis of vitamins and amino acids
K
B12
Modification of the nervous system
Metabolism of therapeutics

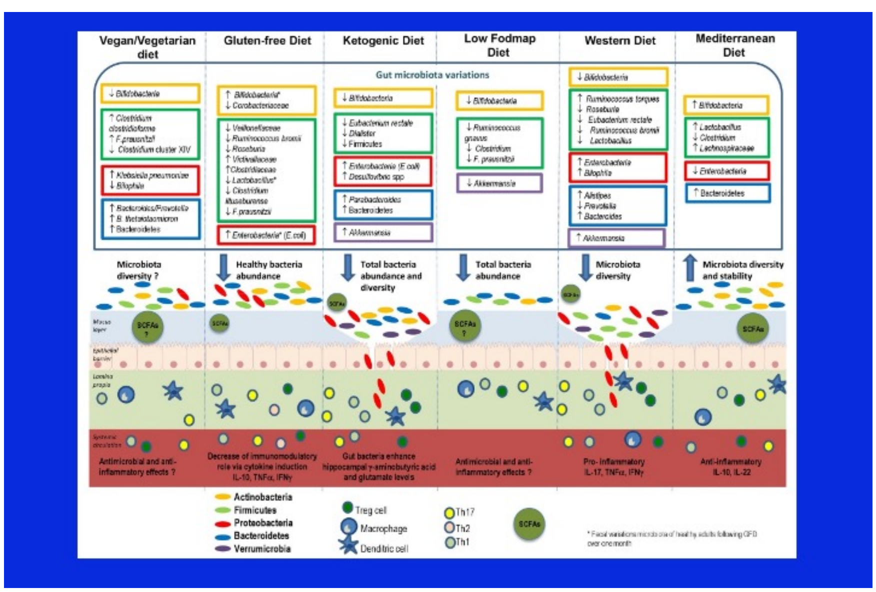

Maintenance of Blood Brain Barrier Integrity
Neuron, Atrocyte and Microglia Health
Immune Cells, Antibodies, Cytokines
Enteric and Vagal Nerve Signaling
Dietary Fiber
Gut Microbiota
Acetate
Butyrate
Propionate
Short Chain Fatty Acids

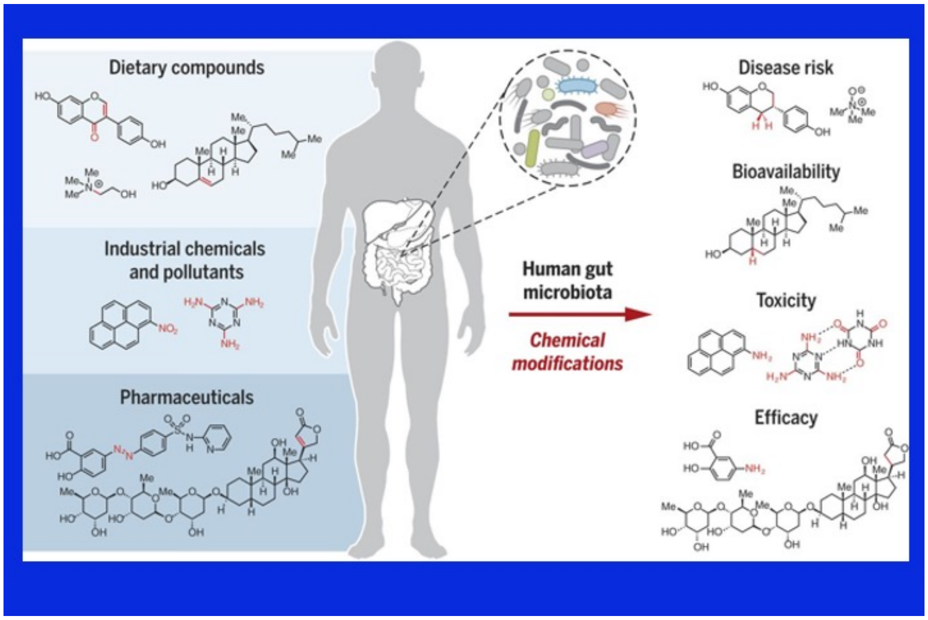

Extrinsic factors:
Dietary habit
Lifestyle
Infection
Neonatal exposure
Intrinsic factors:
Genetic
Metabolite
Immunity
Hormone
Neurotransmitters
Metabolites
Cytokines
PAMPs
Microbiota Composition
Neuronal-glial-epithelial axis
Visceral nerve
HPA axis
Brain-gut Axis
Cerebral Vascular Diseases:
Atherosclerosis
Multiple sclerosis
Ischemic and hemorrhagic stroke
Arteriovenous malformation
Neuropsychiatric dysfunction:
Pain and migraine
Anxiety and depression
Autism spectrum disorder
Neurodegenerative diseases:
Alzheimer disease
Parkinson's disease
Amyotrophic lateral sclerosis

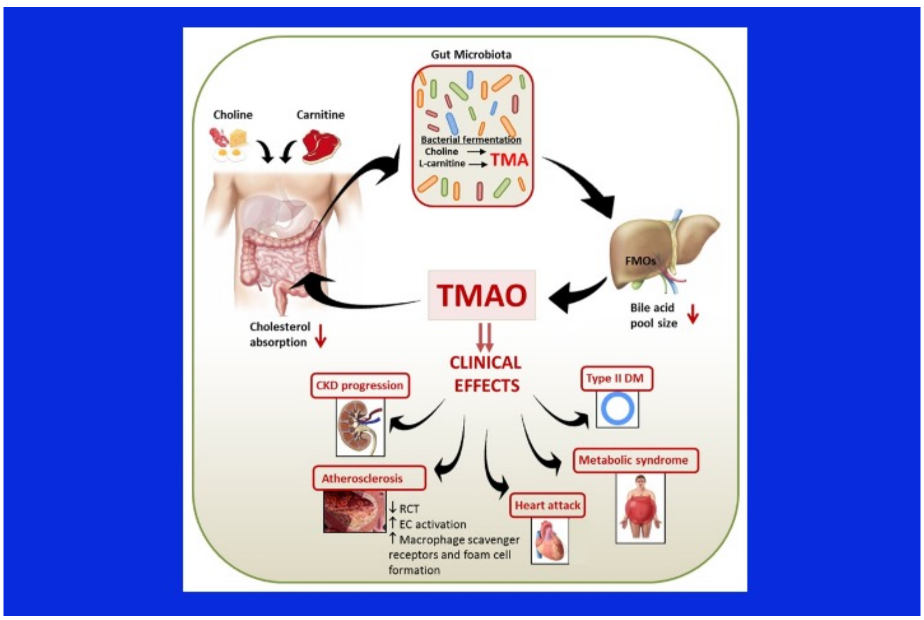

Bipolar disorder
Schizophrenia
Attention-Deficit Hyperactivity Disorder
Depression
Alzheimer's disease
Anorexia nervosa
Uveitis
Bacterial Keratitis
Fungal Keratitis
Ocular mucosal disease
Age –related macular degeneration
Obesity
Coeliac disease
Crohn's disease
Diabetes mellitus
Inflammatory bowel disease
Parkinson's disease
Autism Spectrum Disorder
Rheumatoid arthritis
Multiple sclerosis
Fibromyalgia
Gastric cancer
Lung cancer
Hepatocellular carcinoma
Hospital acquired illness
Myasthenia gravis
Gastric cancer
Colorectal cancer
Gut microbiome

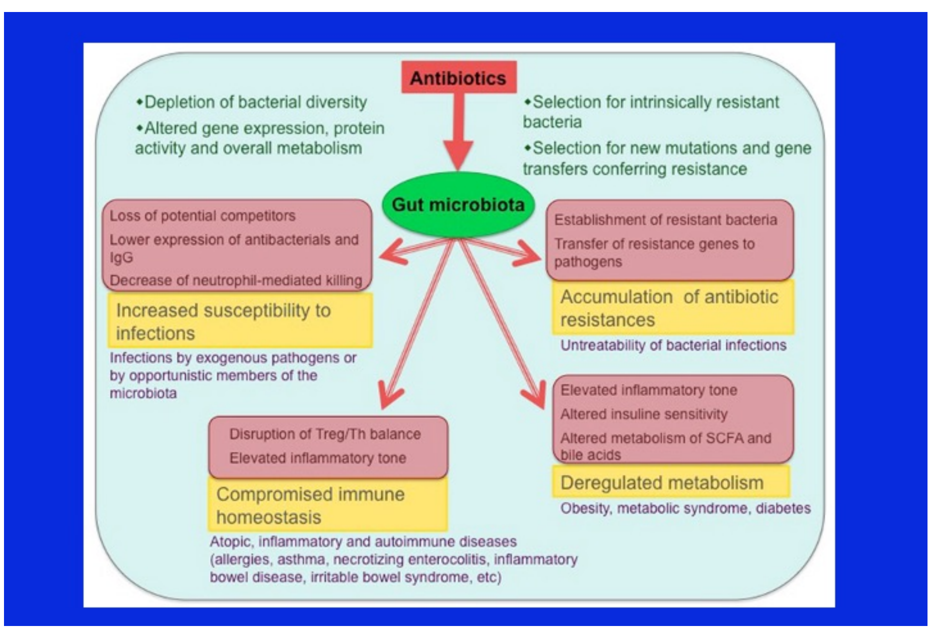

"All disease begins in the gut"
Hippocrates, circa 340 BC


High fat diet
Red meat
High fibre diet
Diet
Firmicutes Phylum↑
Prevotellaceae↓
Bacteroidetes↓
Akkermansia↓
Enterobacteriaceae↑
Ruminococcus↑
Roseburia↓
Faecalibacterium↓
Prevotella↑
Bifidobacterium↑
Eubacterium↑
Roseburia↑
Faecalibacterium↑
Gut Microbiota
Long chain fatty acids
Lipopolysaccharide
Cytokines
Phosphatidylcholine derivatives
TMAO
L-Carnitine
Choline
Short chain fatty acids
Acetate
Propionate
Butyrate
Food-derived Metabolites
Inflammation
Anti-seizure effect
Thrombosis
Atherosclerosis
Anti-inflammation
Antianxiety
Effects on CNS

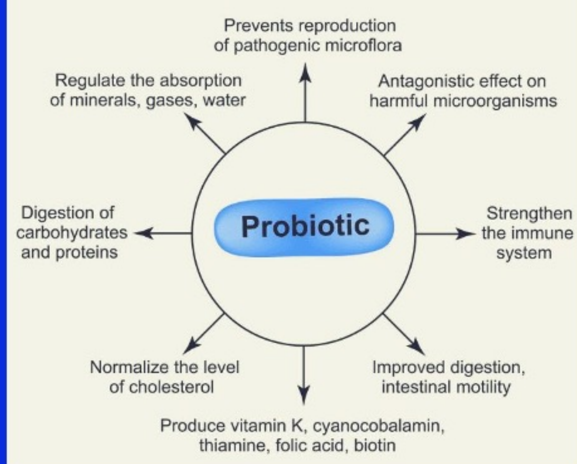

Vegan/Vegetarian diet
Gluten-free Diet
Ketogenic Diet
Low Fodmap Diet
Western Diet
Mediterranean Diet
Gut microbiota variations
Microbiota diversity ?
Healthy bacteria abundance
Total bacteria abundance and diversity
Total bacteria abundance
Microbiota diversity
Microbiota diversity and stability
SCFAs
Antimicrobial and anti-inflammatory effects ?
Decrease of immunomodulatory role via cytokine induction IL-10, TNFα, IFNγ
Gut bacteria enhance hippocampal γ-aminobutyric acid and glutamate levels
Antimicrobial and anti-inflammatory effects ?
Pro-inflammatory IL-17, TNFα, IFNγ
Anti-inflammatory IL-10, IL-22
Actinobacteria
Firmicutes
Proteobacteria
Bacteroidetes
Verrumicrobia
Treg cell
Macrophage
Dendritic cell
Th17
Th2
Th1
SCFAs


Dietary compounds
Industrial chemicals and pollutants
Pharmaceuticals
Human gut microbiota
Chemical modifications
Disease risk
Bioavailability
Toxicity
Efficacy


Gut Microbiota
Choline
Carnitine
Bacterial fermentation
Choline → TMA
L-carnitine → TMA
FMOs
TMAO
Bile acid pool size
Cholesterol absorption
CLINICAL EFFECTS
CKD progression
Type II DM
Atherosclerosis
Metabolic syndrome
Heart attack
↓ RCT
↑ EC activation
↑ Macrophage scavenger receptors and foam cell formation


Antibiotics
•Depletion of bacterial diversity
•Altered gene expression, protein activity and overall metabolism
•Selection for intrinsically resistant bacteria
•Selection for new mutations and gene transfers conferring resistance
Gut microbiota
Loss of potential competitors
Lower expression of antibacterials and IgG
Decrease of neutrophil-mediated killing
Increased susceptibility to infections
Infections by exogenous pathogens or by opportunistic members of the microbiota
Establishment of resistant bacteria
Transfer of resistance genes to pathogens
Accumulation of antibiotic resistances
Untreatability of bacterial infections
Elevated inflammatory tone
Altered insuline sensitivity
Altered metabolism of SCFA and bile acids
Deregulated metabolism
Obesity, metabolic syndrome, diabetes
Disruption of Treg/Th balance
Elevated inflammatory tone
Compromised immune homeostasis
Atopic, inflammatory and autoimmune diseases (allergies, asthma, necrotizing enterocolitis, inflammatory bowel disease, irritable bowel syndrome, etc)

FUNCTIONS OF PROBIOTICS



Prebiotics vs Probiotics

Prebiotics	Probiotics
Prebiotics are defined as nonliving non-digestible special form of fiber or carbohydrates.	Probiotics are referred to as live active microorganisms that when administered in adequate amount will have beneficial effects to its host.
The powder form of prebiotics can survive heat, cold, acid.	• more fragile. • vulnerable to heat. • may be killed over time.
Prebiotics perform their role by nourishing the bacteria that live in the intestines.	Probiotics fight the harmful bacterial species present in the gut.

HOW MUCH FIBER DO WE NEED?

The Institute of Medicine has established a recommended daily amount (RDA) for fiber intake:

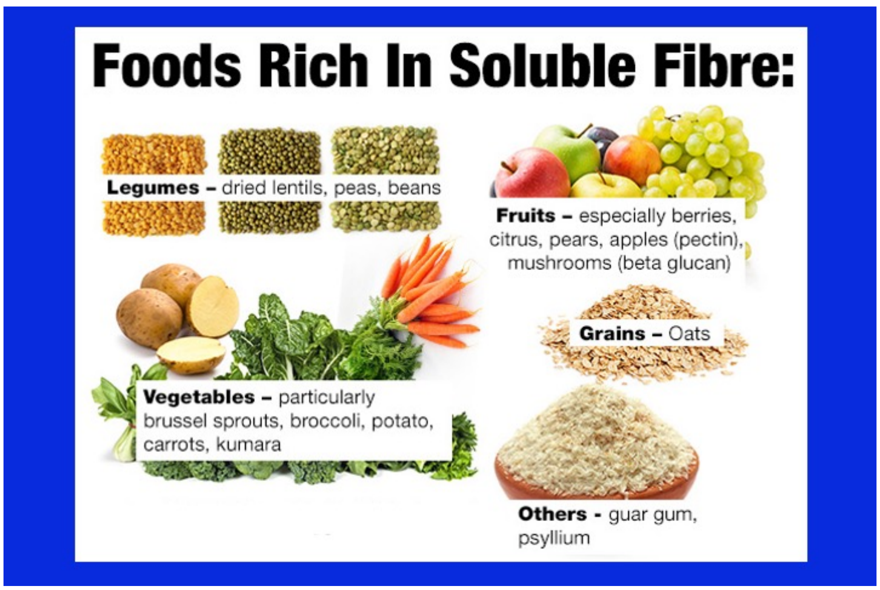
MEN

Men ages 50 and younger should consume 38 grams of fiber per day.
Men ages 51 and older should consume 30 grams of fiber per day.

WOMEN

Women ages 50 and younger should consume 25 grams per day.
Women ages 51 and older should consume 21 grams per day.


Foods Rich In Insoluble Fibre:
Grains – mixed grain or wholemeal bread, whole wheat pasta, brown rice, corn
Outer Skins - vegetables & fruits
Legumes - kidney beans, chickpeas
Nuts & Seeds


Foods Rich In Soluble Fibre:
Legumes – dried lentils, peas, beans
Fruits – especially berries, citrus, pears, apples (pectin), mushrooms (beta glucan)
Grains – Oats
Vegetables – particularly brussel sprouts, broccoli, potato, carrots, kumara
Others - guar gum, psyllium


Broccoli, Cruciferous Vegetables
Packed with Glucosinolates
Fight Inflammation and Cancer
Bananas
Fight Inflammation
Stabilize Gut Bacteria
Beans
Release Short-Chain Fatty Acids
Boost Vitamin Absorption, Satiety
Jerusalem Artichokes
Rich in Inulin Fiber
Strong Prebiotic
Boost Healthy Gut Bacteria with Plant-Based Foods
Enhance Immune Function
Prevent Colon Cancer
Fight Inflammation
Boost Metabolism
Blueberries
Enhance Immune System
Destroy Harmful Bacteria
Polenta
High in Fiber
Fermentable Component
Kimchee, Sauerkraut
Improves Health of Intestinal Walls
Boosts Immune Function
Tempeh
Crowds Out Unhealthy Bacteria
Boosts Nutrient Absorption

Bite Size Clinical Pearls: Part 1

Preload with water, soup
Select low calorie density foods
Select high nutrient density foods
Start each meal with salad including bright colors
Eat whole fruits, not juices
Chew foods well
Enjoy meal without rush
Record weight daily
Time window for eating, intermittent fasting
No food after 7PM

Bite Size Clinical Pearls: Part 2

Avoid processed foods
Avoid artificial sweeteners
Reduce salt, oil, sugar (S.O.S.)
Prebiotic fiber to support gut microbiome
Fermented foods with live microbes beneficial
Avoid antibiotic over use
Mindful eating without distractions
Adequate high quality sleep
Avoid char-broiled foods
Great food if a real plant, not from a factory plant

The secret to living well and longer is:

"Eat half, walk double, laugh triple,
and love without measure."

Tibetan Proverb

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CME QUIZ

1) How does the number of bacteria of the human gut microbiome compare to the human cell population of the average person?
   A) There numbers are about equal.
   B) There are twice as many human cells as bacterial cells.
   C) There are five times as many human cells as bacterial cells.
   D) There are three to ten times as many bacterial cells as human cells. *

2) The use of antibiotics and probiotics can alter the human gut microbiome.
   A) Probiotics are always beneficial.
   B) Antibiotics are always harmful.
   C) They can be either harmful or beneficial. *
   D) There effect is minor and inconsequential.

3) The gut microbiome generates nutrients and metabolites that are necessary for human health.
   A) Only in infancy.
   B) Throughout life. *
   C) Only if the diet is inadequate.
   D) Only if probiotics are added.

4) The human gut microbiome consists of the following.
   A) Bacteria only.
   B) Bacteria, viruses, and fungi only.
   C) All forms of microbial life including parasites. *
   D) Beneficial organisms only.

5) The effect of dietary changes on the human gut microbiome is best described as?
   A) A limited and slow process.
   B) A profound and rapid process. *
   C) Diet does not affect the gut microbiome.
   D) Only related to gluten intake.

6) The Gut-Brain-Microbiome-Diet axis of communication demonstrates the following.
   A) That the brain is its most important and controlling feature.
   B) That the brain may be influenced by the other components of the axis. *
   C) That each component is independent of the others.
   D) That the microbiome is relatively unimportant.

7) The skin microbiome is
   A) Not influenced by antibacterial soap and deodorants.
   B) Influenced by physical contact in team sports. *
   C) Is the same on all areas of a person's body.
   D) Is not an important factor in health or disease.

8) Which of the following is considered the least contaminated in terms of concentrations of bacteria?
   A) Toilet seat. *
   B) Kitchen sink sponge.
   C) Refrigerator handle.
   D) Restaurant menu.

9) Which of the following statements about the Gut-Brain-Microbiome-Axis is false?
   A) The brain is the dominant influence in the axis. *
   B) The vagus nerve is one of several axis pathways of communication.
   C) The gut microbiome produces metabolites and neurotransmitters.
   D) The axis may play an important role in mood and neurological disorders.

10) The human genome is believed to contain approximately 20,000 genes. At a minimum, how many genes is the human gut microbiome believed to contain?
   A) 10,000
   B) 25,000
   C) 100,000
   D) 1,000,000 *

11) Which of the following health concerns has not yet been found to have an association with the human microbiome?
   A) Obesity
   B) Immunity
   C) Cancer
   D) Accident *

12) Which organ system has over ninety percent of the entire human body's concentration of the major neurotransmitter serotonin?
   A) Endocrine System
   B) Central Nervous System
   C) Gastrointestinal System *
   D) Musculoskeletal System

13) The 'hygiene hypothesis' suggests that Western society's obsession with cleanliness and germ avoidance has resulted in a major increase of what type of health disorder?
   A) Mental
   B) Cardiovascular
   C) Allergy & Immunology *
   D) Obesity

14) If a client tells you that they have tried every possible diet and exercise routine without success, and they believe it is their gut microbiome that is to blame, your response should be.
   A) They need to see a mental health professional.
   B) They should stop reading tabloids with their double scoop of Häagen-Dazs.
   C) They may well be right. *
   D) Uncontrolled laughter.

15) In general, foods that contain prebiotics are best categorized as
   A) Dairy products
   B) Meats
   C) Fats and oils
   D) Fiber *