Gut Instincts: Genes, Microbes, Brain, & Diet
Rancho La Puerta

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***"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***

"The greatest enemy of knowledge is not ignorance, it is the illusion of knowledge." ~ Stephen Hawking

"Be careful about reading health books: you may die of a misprint." ~ Mark Twain

Take Home Points:

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.

Humans are egocentric, and overestimate our knowledge of new discoveries, especially in science and medicine. Some examples are covered in my program Medical WisDumb, but for this discussion one singular example is sufficient to make the point. At the turn of the twentieth century, the discovery of radioactive elements by Nobel Laureates Pierre and Marie Curie opened an entirely new field of science and medicine. These novel elements had remarkable properties, including the near-magical ability to make fluorescent compounds glow in a darkened room. The discovery of x-rays and radiographs opened new horizons in diagnosis, and the nightglow of radium quickly became famous for its application on the dials of watches and clocks. These radioactive compounds were thought to be beneficial to health and vitality and were popular for a variety of ailments, enhanced sexual energy, and everything else from furniture polish to insecticides. Radium has 2.7 million times the radioactivity of natural uranium.

The various promoted benefits of radium were never proven, and its safety taken for granted. Nuclear physicists at the Lawrence Livermore cyclotron at the University of California Berkeley raised concerns about the danger of radioactivity. A flaw in the experiment gave the correct answer for the wrong reasons. The marketplace and industry embarked on commercialization for profit, and eventually suppressed known and growing safety concerns leading to deaths of untold numbers of victims. The litigation and publicity of the scandal eventually resulted in an occupational health and safety board to protect workers.

It wasn't until decades later that the devastating consequences of overexposure to radiation became apparent. Marie Curie herself died of aplastic anemia and bone marrow failure and hundreds of young women employed to paint watch and clock dials succumbed to devastating radiation-induced cancers. The unsuspected radiation was so intense that their remains are encased in lead lined tombs to prevent ration exposure to those visiting the cemetery. The laboratory notebooks of Pierre & Marie Curie are also still too radioactive to be handled.

The situation of radiation exposure could have been much worse if it were not for a fortuitous experimental error that rose radiation concerns years before the cancers became rampant. John Lawrence was or firming pioneering work on radiation therapy for cancer in laboratory mice that showed significant promise. He wanted to see what radiation would do to a normal mouse, so he placed a healthy specimen in a chamber and exposed it to the beam of the giant cyclotron his brother developed at the University of California, in Berkeley.

The mouse was exposed to the lowest intensity of radiation and for the briefest time, and yet the mouse was dead as a doornail. Warnings and safety measures were introduced everywhere because of the now recognized power and danger of radiation. Years later he repeated the demonstration for observers from the Manhattan Project nuclear weapons program. A healthy mouse was placed in the chamber and when the switch to the cyclotron was turned on a power failure canceled the demonstration and the observers left. When John Lawrence went to retrieve the mouse, he was shocked to find the mouse had died, even though there was no radiation from the cyclotron. He was astounded to find that the mouse, as well as the first mouse, died from asphyxiation. The holding chamber was so small that the mice suffocated because there was so little air. Fortunately, the warnings about radiation were valid, even though the radiation experiment was completely flawed and misinterpreted.

The many thousands who had accepted assurances from the consumer marketplace of safety and benefits reaped the terrible consequences of misinformation. Discovery over years of subsequent litigation showed that the dangers of radium were apparent earlier, but warning signs and knowledge of the risk was suppressed by intense pressure from industry and commerce. The industry knowingly miss-blamed the deadly epidemic on syphilis. Radium paints click dials were sold until the 1960's.

The analogy to the gut-brain-microbiome-food-axis is that we are exploring a new body of knowledge, that is the equivalent of discovering life on a new continent or planet. This information will lead to significant advances and insight into the causes and treatment of disease as well as health maintenance and enhanced vitality. The life biology of humans and its relationship to the newly discovered axis is so complex that the consequences of changes are unknown. Undoubtedly there will be new therapeutic breakthroughs and specific microbes, metabolites, hormones, neurotransmitters, etc. will be found to have benefits in specific conditions. The full consequence of these changes will not be known for many years or even decades later. Industry and commerce have a profit motive that does not wait for evidence of effectiveness or safety. Tens of thousands of nutritional, herbal, dietary supplements, prebiotic, and probiotic products are already being aggressively marketed and promoted with promises and hype unsupported by scientific evidence or proof of safety. I will return to this subject again later in this paper.

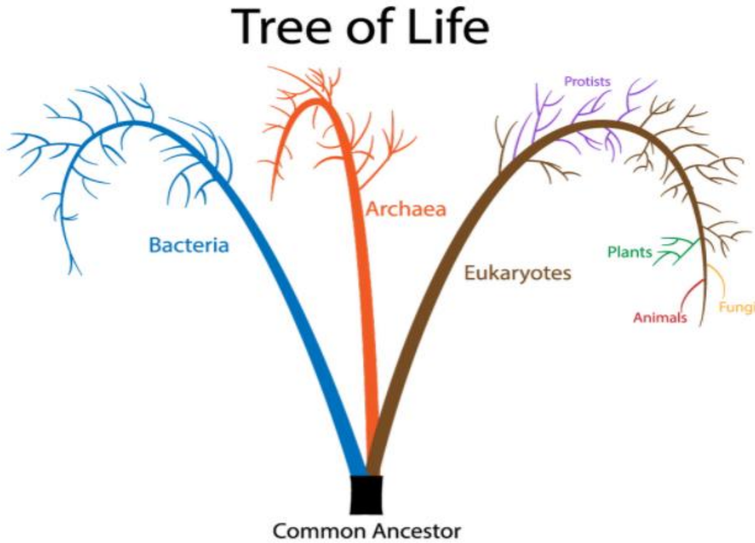
Medicine and science often take a reductionist approach, to break an issue to study down to its simplest components to understand its mechanisms and structure. While the approach has some value, nearly all the processes in the life sciences are influenced by multiple variables. A systems biology approach incorporates these variables, which the reductionist approach neglects to its detriment. Rather than merely thinking out of the two-dimensional box, thinking out of the three-dimensional cube opens horizons.

For those not familiar with the Mobius Strip, it is a very simple demonstration of the vast difference an additional dimension can make. The Möbius strip is easily constructed by taking a piece of paper, as a convenient example one in wide by ten inches long. Draw a line down the center of the ten-inch length of both sides of the paper. Make one single twist in the length of the paper and tape the ends together. Now take a pair of scissors and cut along the full length of the centerline. How many pieces of paper will you have? Common sense would suggest the answer would be two strips of paper, each a half-inch wide and ten inches long. The actual results are illuminating and show what happens when you make a two-dimensional object a single dimension.

Another dimension that is more readily appreciated with an example is exponential growth, also known as logarithmic growth. The concept is universal in the life sciences where single cells commonly divide into two daughter cells with maturity and growth. These two cells then each undergo division, continuing through multiple generations. The rapidity of population growth is usually underestimated as most people forget the power of exponents and logarithmic scale. The example often used is to offer a person a choice; they can either accept one million dollars now or accept the alternative of accumulating one penny on day one, doubling the amount of each preceding day for a thirty-day month. With one penny on day one, two pennies on day two, four pennies on day three, eight pennies on day four, sixteen pennies on day five, thirty-two pennies on day six, sixty-four pennies on day seven, the total collections for the first week is a whopping one hundred and twenty-seven pennies.

People who don't instantly jump for the million dollars may start to do the math. They are only up to $1.27 after a full week, and up to a total of $163.83 at the end of the second week, nearly halfway through the month. The third week is better, but the total is still only $20,971.51 nearly three-quarters of the way through the month with only ten more days left. At this point, most believe they have made a big mistake, and will gladly accept the $1,000,000 now instead of continuing with the math. For the patient person who did not jump to conclusions, the reward of allowing the penny amount to double each day would mean that on day thirty alone they would receive $5,368,709, bringing the thirty-day total to $10,737,418.23. That penny made the choice nearly ten times as good an investment. If the contestant were really smart, they would have asked for a thirty-one-day month!

Humans on Earth use 6,500 different languages and 46 different alphabets. Imagine the world with one universal language and one alphabet with only four main characters or letters. Welcome to the world of genomics. Life remains a great mystery and the theory of evolution posits that the first life form on Earth was most likely a pre-cellular or unicellular organism like a Bacteria or Archaea. Over the millions of years of prehistory, these early life forms changed the environment and atmospheres the planet by releasing oxygen as a waste product of photosynthesis. They may have been warned by ancient sage microbes about the dangers of global oxidation destroying their anaerobic atmosphere, but the new generations of microbes would not listen and accelerated mass extinctions as the atmospheric oxygen levels increased. Evolution continued, favoring organisms that could survive and thrive in the new atmosphere and surface of a planet in transition. Each and every organism on the planet was an ever more distant relative of the first living organism, and the genetic inheritance of each succeeding generation evolved ever so slightly from the generation before. Via random mutations and epigenetics, changes persisted if they provided a survival or propagation benefit. If survival were not enhanced the genetic changes would not have future generations available to transmit them forward, and they would join the millions of other unsuccessful life experiments that ended in extinction.



All life forms are believed to the descendants of the very first living cell on the planet. The evolutionary theory of both life and the planet Earth itself has this single cell multiplying and growing exponentially over millions of years. With the evolution and the mutations of genes subsequent generations developed new properties and differentiated into different species. Today there are approximately nine million species of multicellular life forms on Earth, with fifteen thousand new species discovered each year. The Earth harbors about one and a quarter million species of animals and three hundred thousand species of plants. The number of cellular species is larger, with some estimates suggesting a billion species. The metabolic processes of these new organisms had consequences for the environment and planet.

One of the significant changes in the metabolic processes was the development of photosynthesis, which released oxygen into the atmosphere. Earlier in the planet's evolution the oxygen was bound to other elements, but with the release of increasing amounts of free oxygen the atmosphere changed dramatically. Oxygen is one of the more unstable and reactionary elements, and its growing presence led to mass extinctions if species that were unable to adapt. It also encouraged the evolutionary development and success of new species that could tolerate or take advantage of the unique properties of oxygen. Today the percentage of free oxygen in the atmosphere is a relatively high twenty-one percent. Even though humans and many other organisms now require oxygen for life, oxygen and oxidation are associated with cellular injury and aging. Excess oxygen is toxic to humans, and in neonatal care excess oxygen has led to blindness.

Bacteria and Archaea are the predominant biomass on Earth, exceeding all and plants and animals combined. Only a minority has been identified, and the vast majority cannot be grown or cultured in the laboratory. One gram of soil has an average of forty million bacteria; one milliliter of seawater has over 1 million bacteria. The complexity of life processes and organisms grew at an exponential pace. Multicellular organisms, various modes of reproduction, mobility, environmental specialization, cell and organism structure, multiple energy systems, and broad and wild diversity of life forms we have today all arose from the first living organism. The millions of now extinct species, all of whom are our distant relatives, had their moment in time, as part of this grand evolutionary experiment.

With time, we have evolved along widely divergent pathways, yet we have some key features that remain remarkably alike. The language and alphabet of genes have remained universal, even though evolution may have changed some spelling over the eons, the language remains universally understood across all life forms. Our closest relatives, the chimpanzee, and bonobo have a ninety-eight-point four percent similarity in DNA to humans. Our most distant and ancient relatives, unicellular bacteria and Archaea have a thirty percent overlap where we share identical genes. The same genes, written in the same language, can be exchanged between humans and microbes, and they function as if at home. Even when the spelling has changed, such as the structure of insulin in pigs and cows is ever so slightly different from humans, it works nearly as well and for many decades was the treatment of choice for persons with diabetes.

The overlap and homology of genes are so remarkable, that even when you would not expect it to, genes often work. The gene that creates the luminescent glow of a firefly has been transplanted into a cat, which now glows in the dark. By studying the genes of simpler organisms, in particular those with less genes, remarkable properties have been identified that offer new insights into longevity, regeneration, immunity, cellular repair, and a host of other potentially significant life enhancements. 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.

Because genes are coded in a universal language, their products can have biological effects even in rudely divergent species. 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, 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 if rich can kill, and LSD induce hallucinations, other products can have effects with similar minuscule dosing.

Unicellular organisms remain a single cell throughout their lifespan. When they do divide, they become two independent unicellular organisms. Most of the organisms on the planet Earth are unicellular. Unicellular life forms include the bacteria and Archaea, which compose the vast majority of the Earth population, both by numbers of organisms and by biomass that is the total weight and volume of living matter. With evolution, the continuing diversity of genes and their expansion to multicellular organisms, and 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.

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 the 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 which 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) has brought gene transfer and correction of genetic mutations from the world of science fiction to present day reality.

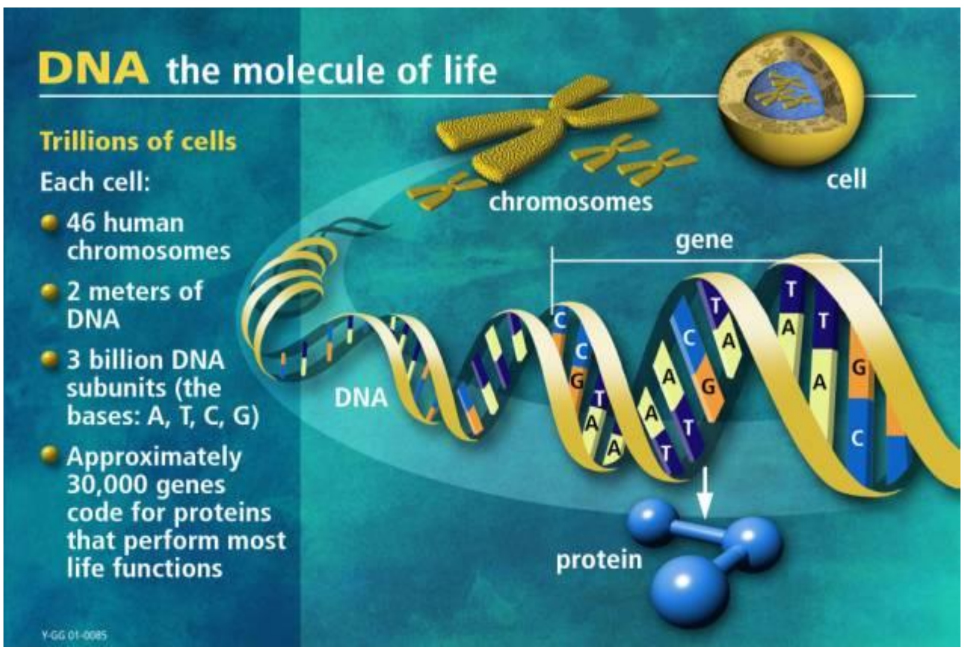
One of the most investigated and analyzed organisms is the free living (non-parasitic) soil roundworm *Caenorhabditis elegans*. This small but visible to the naked eye organism is common, inexpensive and reproduces easily and readily in the laboratory. What makes them valuable as a research tool is that 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 gas been identified and mapped as to the source, location, and function. The nervous system and each nerve cell gave been allocated, 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; Sydney Brenner was awarded the Nobel Prize in Medicine or Physiology.

Human hair is 100 microns thick. The lining of the gut 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 ant is a remarkable and intelligent insect, with complex social networks and interactions. The ant colony has a sophisticated society with specific division of labor, with groups of ants assigned to food production, including farming and herding, feeding and rearing the next generation, soldiers for defense and offense, reconnaissance, and a variety of other activities. The ant has over two million individual cells, including over 250,000 cells in its well-developed brain. As amazingly complex as the ant is, especially compared to the single cell life form of a bacteria, the average human is over 20 million times its size by volume. Although small it is very powerful, and can lift over one hundred times its own weight. It can run at speeds that would be the equivalent of a speeding automobile if compared to human size.

Even though much smaller than the whale, dinosaur, or elephant, humans are a staggeringly large and complex organism and life form. We contain over 37 trillion human 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 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 enormous size and biomass, it is easy to be deceived into thinking that we represent the majority, and the microbial world the minority. 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 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. Humans have 99.9% identical DNA, regardless of race. Humans and chimps 98.8% identical.



Human DNA, only 1.5% are genes that codes 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 explains how over 8% of the human genome is not human, it is of viral origin. A single human gene can make over 200 different proteins depending on the epigenetic influence.

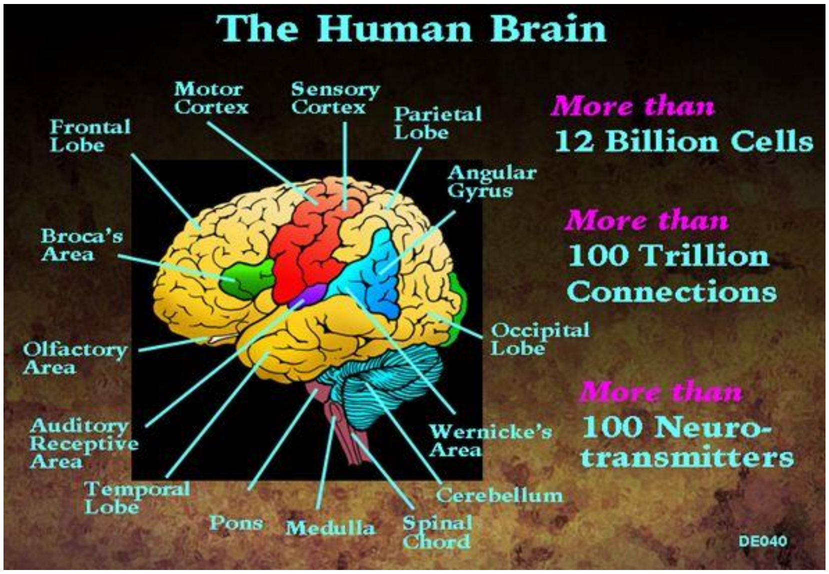
Even more staggering than the hundreds of billions of genes, are the exponentially larger number of epigenetic factors, the majority of which arise from the 99% of DNA that do not code for genes. It is the height of irony that what scientists disparagingly labeled as 'junk DNA', is of critical importance to all life forms. The 'junk DNA' includes epigenetic information that influences the expression of genes. One way to think of the junk DNA is to consider it the grammar and punctuation to make sense of the genetic code. Take the series of letters that spell out GODISNOWHERE. Depending on where you place pauses, spaces, and grammar the same message can read GOD IS NOWHERE, or an alternative and profoundly different message is received if it is read as GOD IS NOW HERE!

The noncoding junk DNA generates microRNA which is distributed as exosomes throughout the nucleus, into the cytoplasm, into the blood, and the 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 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.

As if this were not mind-boggling enough, 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 about 10% 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 foot of planet Earth each day.

A relatively small number of microbes are pathogens, 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 can 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 gave raises similar concerns.

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.



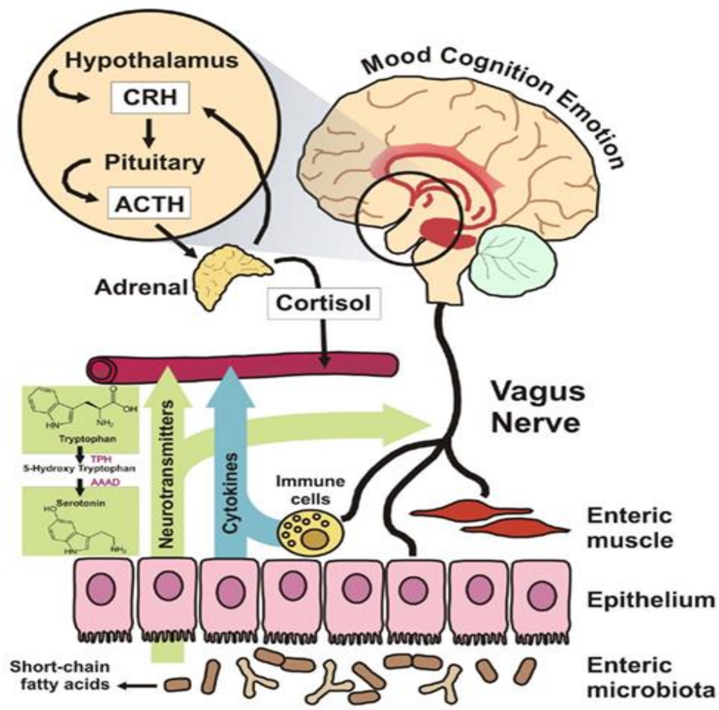
The human brain is often described as consisting of three distinct levels. The cerebral cortex or neocortex allows consciousness, thought, and cognitive function. Man, in his uniquely human egocentricity, believes this is the latest and greatest evolutionary advance in the brain. The emotional centers 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, and spinal cord and nerves. This organizational network is the enteric nervous system, also called the gut nervous system, and by many experts us 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 in 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 was that over eighty percent of the nerve fibers were 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 tremendous swelling of the gland in the neck region. Hypothyroidism causes profound brain effects with decreased cognition, a described 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 thorax, 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 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 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 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, mind 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 dramatically altered. In fact, even how we consider what it means to be human, and the nature of our 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 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 ate, 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 (separate blog Digest of Digestion & Nutrition). 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-five thousand genes, and the microbiome well in excess of a million, making us only one percent human genes. The gut microbiome is much more than just fermenting or metabolizing 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 miles at sea, to the recently discovered elephant communication at infrasound wavelengths, an extremely low frequency below the range of human hearing.

Now don't get too disappointed as I am not going to surprise you and tell you that the microbes speak to you in quiet internal voices, the microbial whisperers. Besides, you already know that humans and other species frequently communicate, as we do routinely with 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, hormones, and metabolites. This is a language the microbes, body, and brain instantly recognize and understand.

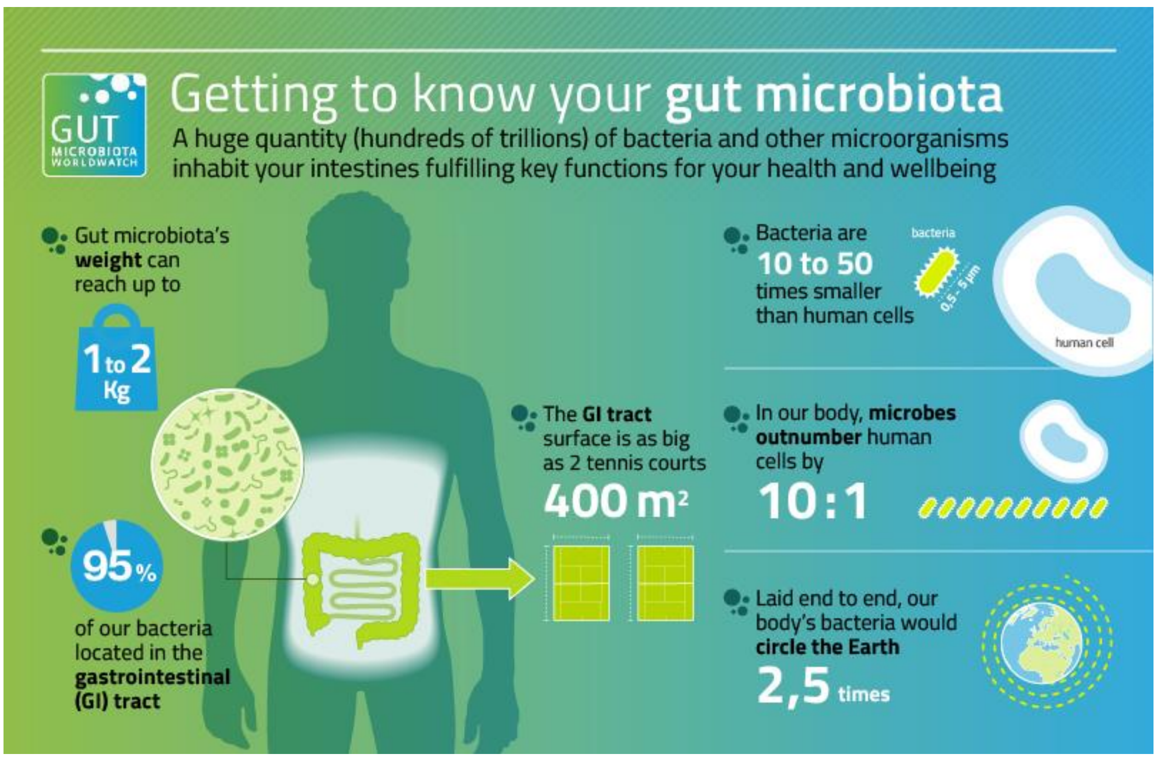
The gut microbiome weighs in at about three pounds, roughly the same weight as the human brain, and interestingly enough, is part of what is now commonly known as the 'second brain' comprised of the gut-microbiome-brain axis. This 'second brain' is adding a scientific understanding of what has often been described as gut feelings or gut instincts.

The digestive tract can be thought of as the opposite of an assembly line, as the food is broken down into its essential parts for ease of absorption and metabolism. The description of the anatomy and physiology of the alimentary tract is covered in another program 'Digest of Digestion'. 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 nerve cells and fibers within the digestive tract are known as the enteric nervous system. It is directly connected to the brain and spinal cord of the central nervous system. The vagus nerve, autonomic sympathetic, and parasympathetic nervous systems are all intimately interconnected. What many people find surprising is the degree of gut involvement with the two major neurotransmitters of the human body. It is impressive that fifty percent of the dopamine in the body is found in the brain and the other fifty percent in the gut. What is particularly striking is that only five percent of the serotonin in the body is found in the brain, and the other ninety-five percent is found in the gut. There are over thirty active neurotransmitters found throughout the enteric nervous system. With the further exploration of the remarkable enteric nervous system, perhaps we will need to reconsider what is considered the second brain and what is the first brain.

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.

Toxoplasmosis 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 saber tooth tiger to complete the parasites life cycle in prehistoric times.

Remarkable studies are showing 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 the correspond to the microbiome even though the diet and exercise were unchanged. The cartoon above may lead to the punch line being changed to blame the microbiome rather than the genes. 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 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 field of genomics and the microbiome is 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 (described in a future blog) where diet, microbiome, and possibly 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 big business 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 more than sufficient evidence for an individual to consider a trial to see the response. An important point to remember is that each 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 beginning but will take years to complete.

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 typically 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.

A 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. 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 a 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 U 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 22,000 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. In the mechanical physical world and example would be the space shuttle Challenger disaster where the most complex vehicle and lives of astronauts tragically lost because of the failure of the 'O' ring because of a drop of a few degrees of temperature at launch time. Compounding that tragedy was that spacecraft engineers warned that the temperature drop was potentially catastrophic. Some engineers were so convinced of the danger that they predicted that the tragedy would take place, exactly as it subsequently did.

Human nature is difficult to change, and a similar disaster can be predicted with similar certainty. 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 microbes that can become established in the gut microbiome. The consequences of these bioactive products may be beneficial, neutral, or harmful. If the harmful effect is significant or potentially life-threatening, with time and with the millions of potential consumers each with their risk profile, an adverse event is inevitable. Without any knowledge of the risk, consumers today are being offered tens of thousands of probiotic products with the numbers growing exponentially as the marketing and promotional hype accelerate.

It should not come as a surprise that the human gut microbiome is partially populated by the microbiome of the foods we eat, including the soil and plants. Glyphosate (Roundup) is water soluble and so heavily overutilized by industry (four and a half billion pounds per year) that 75% of windborne soil samples and rainfall are contaminated. Even organic farms that have never used the product now produce crops with measurable amounts unless protected from wind and rain. As damaging as glyphosate is to the microbiome, there is a perhaps even greater concern. It is directly toxic to the tight junctions that preserve the integrity and continuity of the digestive tract as its barrier function between the human body and the external environment. Any agent, such as glyphosate, alcohol, non-steroidal anti-inflammatory drugs (e.g. ibuprofen), laxatives, that impairs the tight junctions and damages this barrier function can lead to what is described as a 'leaky gut'.

We already have a tragic example of the regulatory failure of the health care industry, consumer advocacy, and government oversight. There are three hundred thousand oral over the counter health products, thirty-five thousand prescription products, and hundreds of thousands of nutraceuticals, herbs, probiotics, nutrients, supplements, etc. The adverse reactions from interactions between these products, as well as the innate risk of each product itself, leads to tens of thousands of accidental fatalities each year in the United States. In US hospitals, each year 440,000 deaths from accidental medical errors, often drug related, tragically occur. The vast majority of prescription drugs, and virtually all of the hundreds of thousands of OTC products in the marketplace today have never been tested for safety or efficacy. The institution of a national database if these products could identify patterns of interaction and safety concerns that would lead to tens of thousands of lives saved, and injuries and disabilities prevented, each year. Although this has repeatedly been suggested over the past fifteen years, the industry has resisted because it will impact short-term sales of their products. Apparently, a sale today killing a customer is better for business than a potential sale from one more living consumer years in the future. It looks like we have a lot more evolution ahead of us before we leave this primitive mindset behind.

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Joseph B. Weiss, M.D. is Clinical Professor of Medicine in the Division of Gastroenterology, Department of Medicine, at the University of California, San Diego. Accepted to university at age fifteen he attended the University of Michigan, University of Detroit, and Wayne State University. Reflecting his broad interests, he majored in Medieval English Literature, Astrophysics, and Invertebrate Zoology. Following his graduation from the Wayne State University School of Medicine in Detroit, Michigan, he completed his internship and residency in Internal Medicine at the University of California, Irvine Medical Center in Orange, California. Under the auspices of the World Health Organization and others, he has pursued interests in Tropical and International Medicine and Public Health with extended stays in Africa, the Middle East, and Latin America. Subsequently completing a clinical and research fellowship in Gastroenterology at the University of California, San Diego, he has remained active on the clinical faculty of the School of Medicine. Dr. Weiss is a Fellow of the American College of Physicians, a Fellow of the American Gastroenterological Association, and a Senior Fellow of the American College of Gastroenterology. Double board certified in Internal Medicine and Gastroenterology, Dr. Weiss has over thirty years of clinical, administrative, and research experience. He has also served on the Board of Directors of the Scripps Clinic Medical Group, Clinical Board of Governors of the Scripps Clinic and Research Foundation, and Chancellor's Associates of the University of California, San Diego

He is the author of more than a dozen books on health (www.smartaskbooks.com) and has had numerous papers published in prestigious national and international medical journals, as well as in the lay press. Dr. Weiss is also an accomplished humorist and professional speaker having given over three thousand presentations nationally and internationally. He has presented at international conferences and conventions, universities, medical schools, hospitals and medical centers, Fortune 500 companies, YPO/WPO, Bohemian Grove, Esalen Institute, Renaissance Weekend, Aspen Brain Forum, IDEA World Convention, international destination spas & resorts (Golden Door, Canyon Ranch, Rancho La Puerta), etc.

The programs offered are continuously updated with cutting edge information. Well-spoken, enlightening, and entertaining the programs are also visually engaging. Frequently requested programs include To 'Air' is Human (intestinal gas), The Quest for Immortality (longevity & vitality), The Scoop on Poop (gut microbiome & scatology), Digest on Digestion (digestive health & nutrition), Medical WisDumb (marketing hype to health advances), Laughter (& Chocolate) is the Best Medicine (humor in health & wellness), Food for Thought (brain-gut-microbiome axis) and others. For further information, contact Dr. Weiss at speakingofhealth@gmail.com or weisscme@ucsd.edu.

These colorful, informative, and entertaining volumes are available at www.smartaskbooks.com, Amazon.com, BarnesandNoble.com, and major booksellers.

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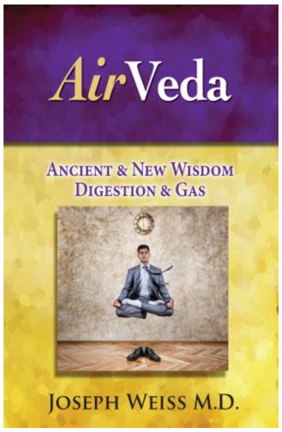

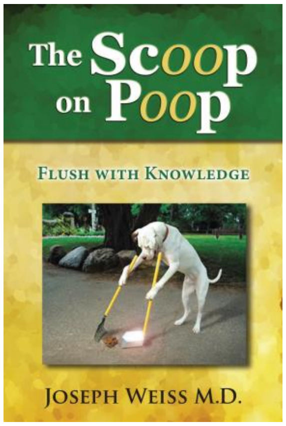

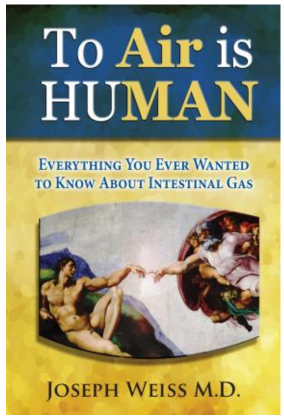

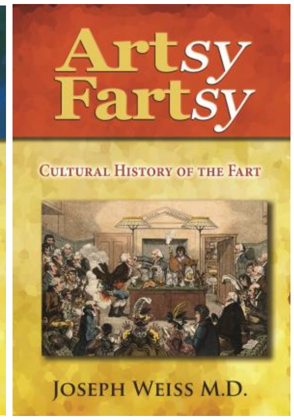

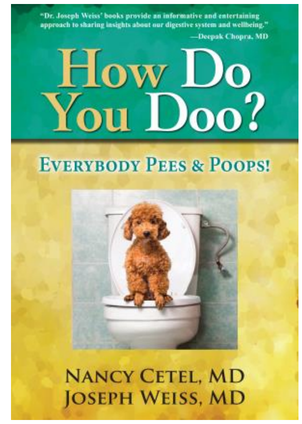

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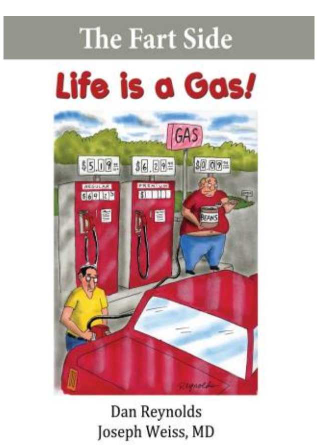

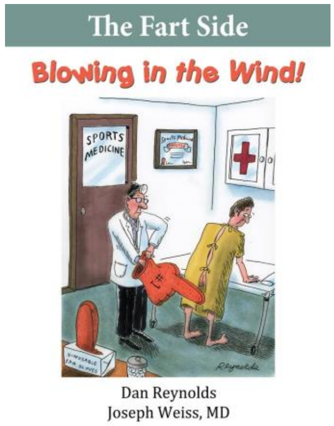

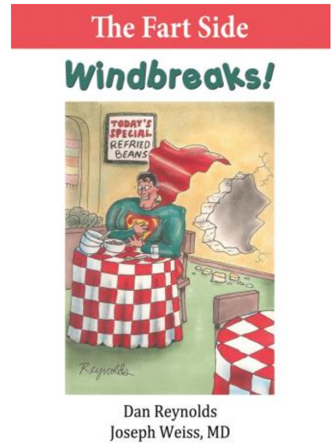

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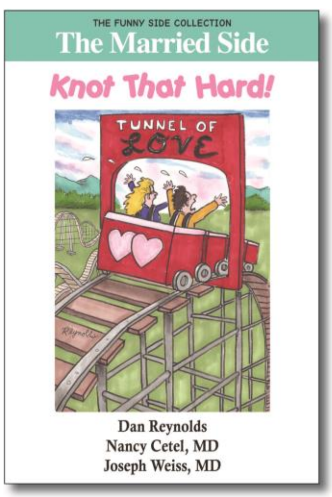

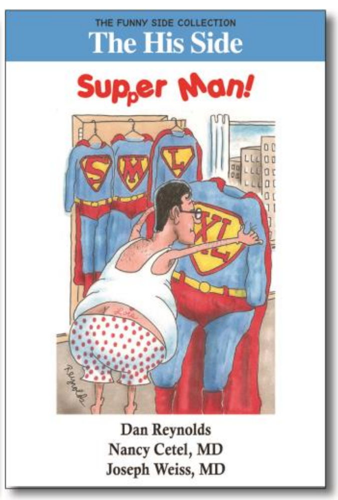

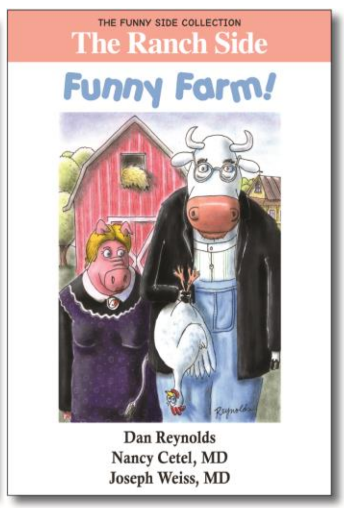

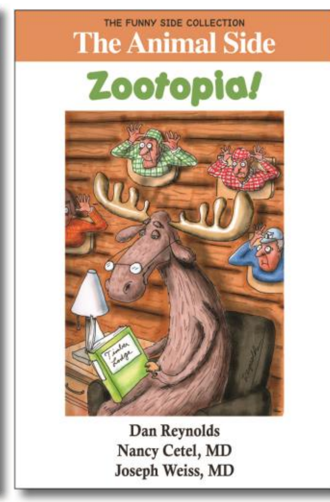

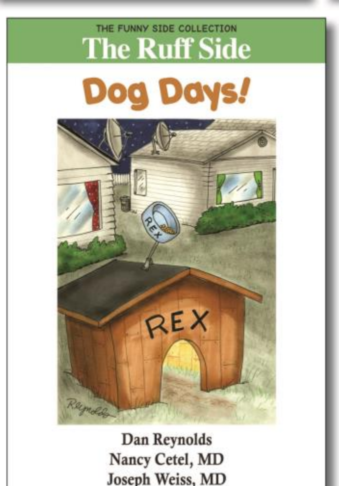

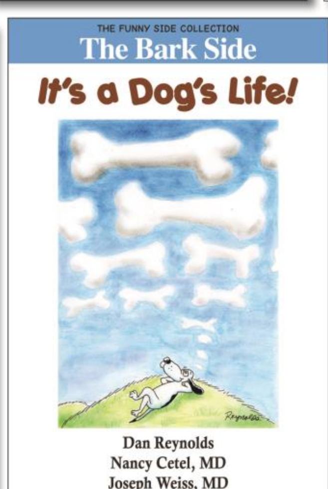

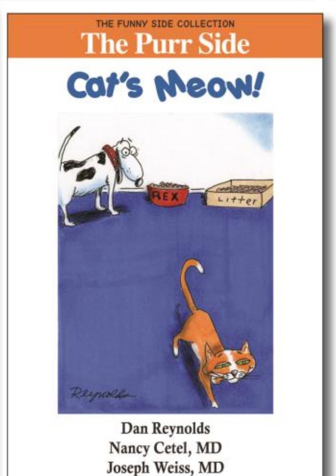

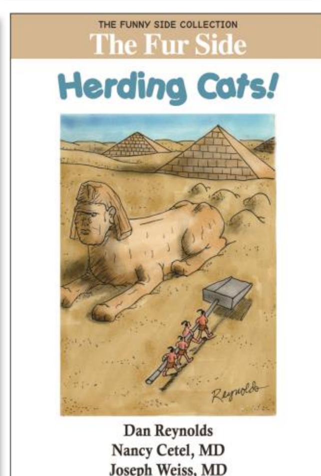

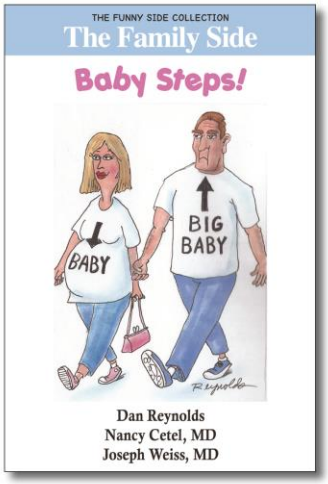

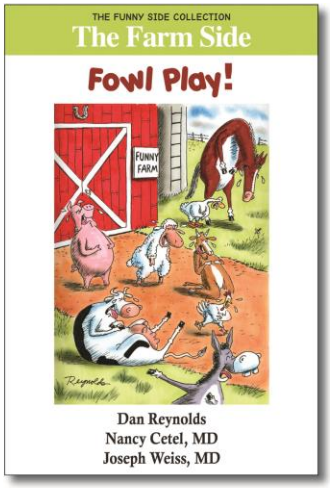

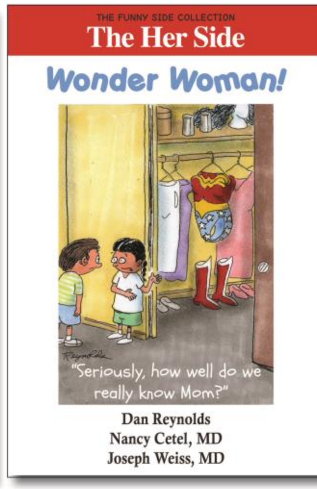

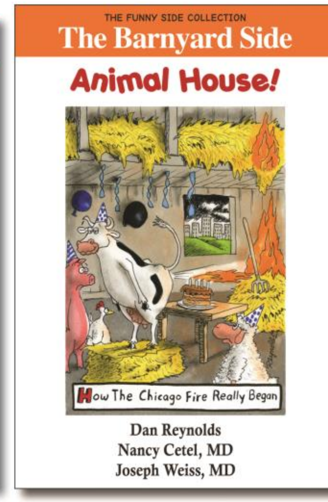

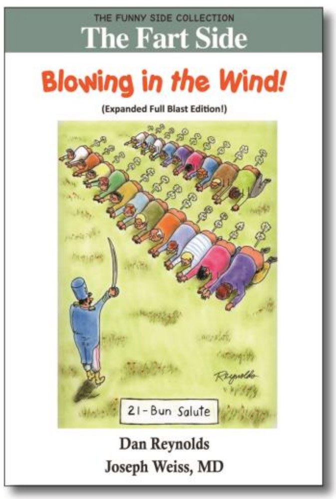

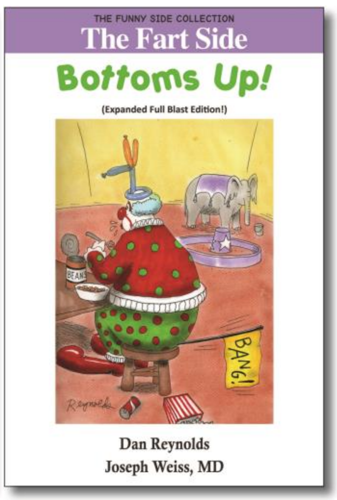

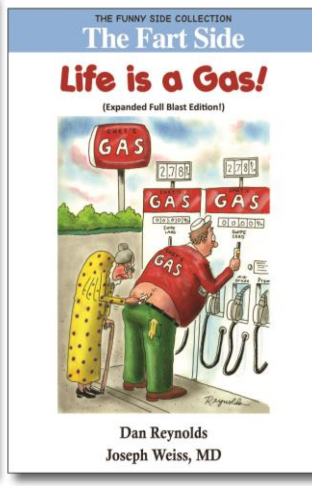

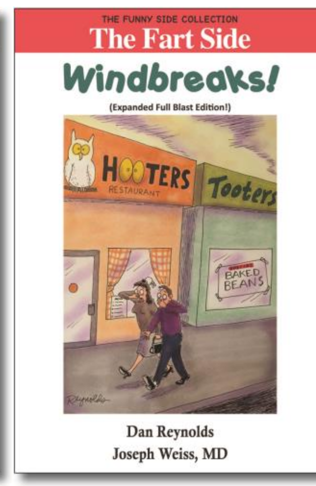

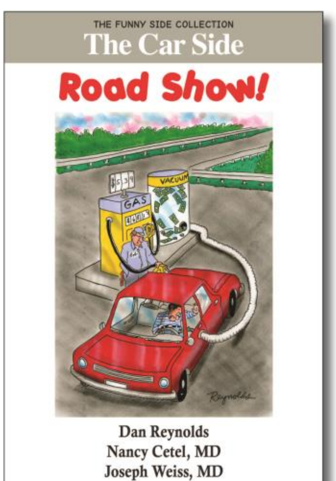

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