Gut Instincts: Genes, Microbes, Brain, & Diet
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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

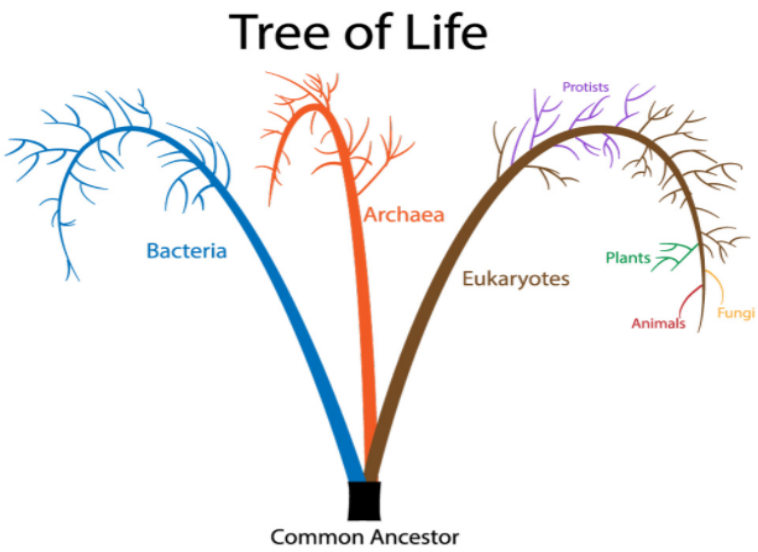
merely thinking out of the two-dimensional box, thinking out of the three-dimensional cube opens horizons.

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.

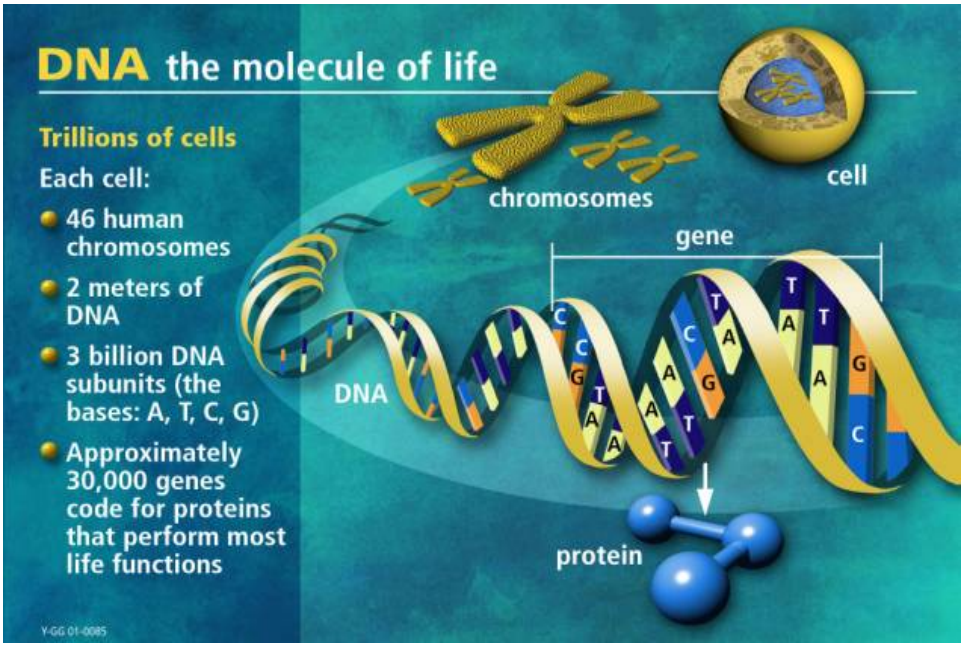
Human hair is 100 microns thick. The lining of the gut is only one cell layer thick, about 25 microns wide and 50 microns deep. At half the width of a human hair, this cellophane-like layer separates your vital body from the external environment. It allows the entry of nutrients, fluids, electrolytes, 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. Its speed is breathtaking, and 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

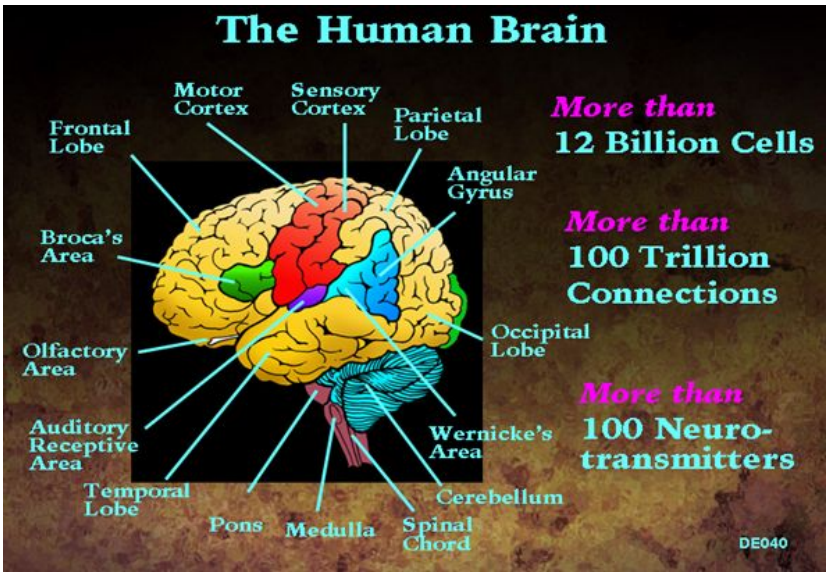
forms. The ‘junk DNA’ includes epigenetic information that influences the expression of genes. One way to think of the junk DNA is to consider it the grammar and punctuation to make sense of the genetic code. Take the series of letters that spell out GODISNOWHERE. Depending on where you place pauses, 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.

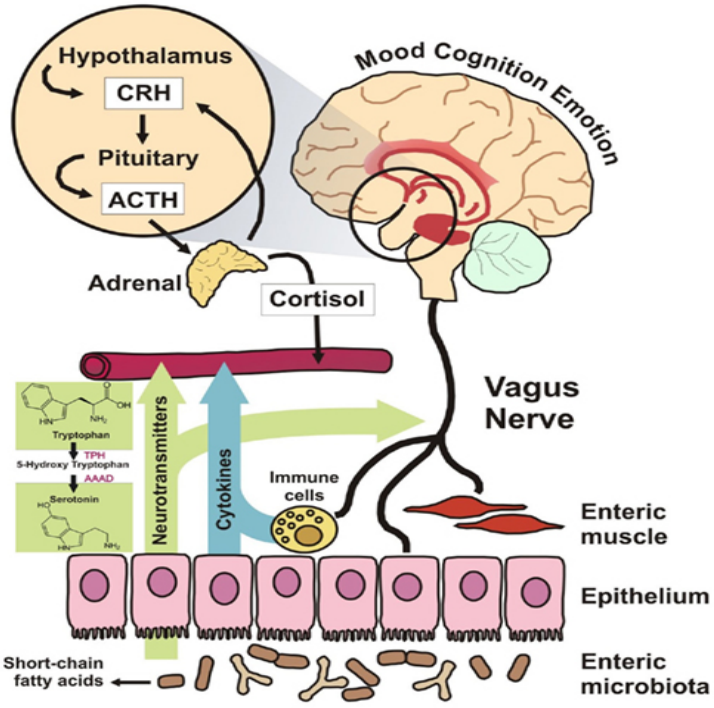
The enteric nervous system is remarkable in many levels. Over forty distinct neurotransmitters have been identified in its internal communications, and more are likely to be discovered. The major neurotransmitters of the body, which have a significant influence on cerebral cortex brain function, are 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.

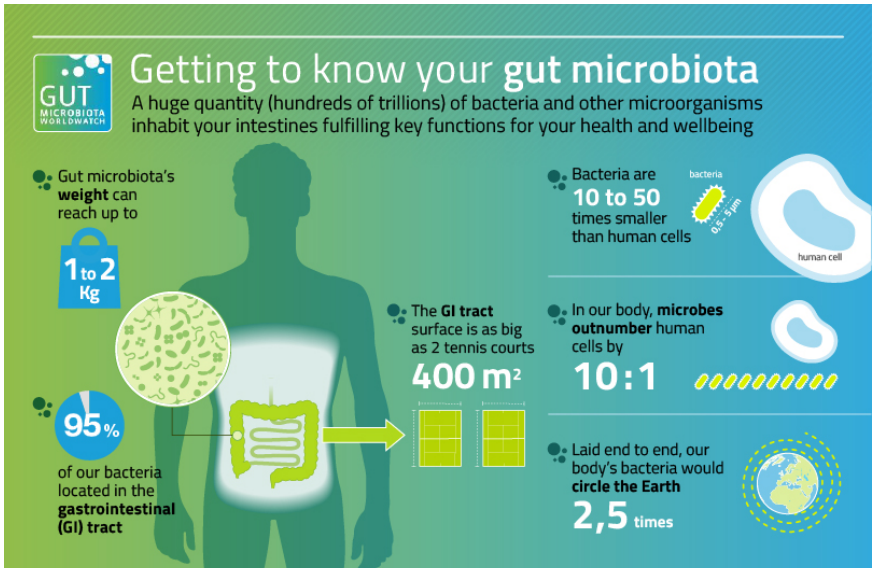
The digestive tract can be thought of as the opposite of an assembly line, as the food is broken down into its essential parts for ease of absorption and metabolism. The description of the anatomy and physiology of the alimentary tract is covered in another program 'Digest of Digestion'. As efficient 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.

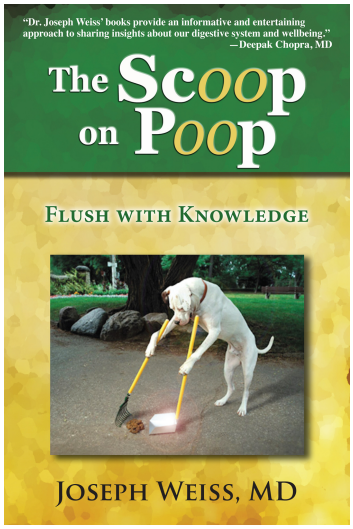
When the variables number in the thousands to millions and each variable may have options that run into the millions as well, the possible combinations are virtually infinite. Even the most powerful supercomputers available today cannot keep up with possible data combinations and consequences. The discipline 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.

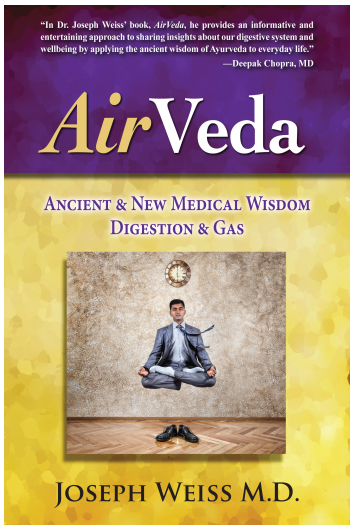
Human nature is difficult to change, and a similar disaster can be predicted with similar certainty. The biological activity of metabolites of species frequently crosses over with unrelated species. At a minimum, one-third of the genes and their directed proteins will be bioactive in humans. There are 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.

For those interested in learning more about the gut microbiome and digestive issues I have authored a number of books that may be of interest. *The Scoop on Poop: Flush with Knowledge* and *AirVeda, Ancient & New Medical Wisdom, Digestion & Gas* also covers additional digestive topics. They are available at www.smartaskbooks.com, Amazon, Barnes & Noble, and others.





Food for Thought: Digest of Digestion & Nutrition
Rancho La Puerta

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The purpose of the digestive tract is to support life by providing the nutrition and energy we need for all of our body functions. The average human has over 37 billion cells, with 25 million new cells created every second. Each existing cell requires energy to fulfill its metabolic function. All human cells, except for red blood cells, has mitochondria that serve as the equivalent of an energy power plant. It is believed that eons ago mitochondria were free living unicellular organisms, such as archaea or bacteria. In a process known as endosymbiosis, they became incorporated into human cells, where they serve a vital function. Perhaps as a residue of their previous independent lives, mitochondria carry their own DNA, inherited in a matrilineal pattern. The more metabolically active the cell, the more mitochondria it has. The liver cells, as well as nerve cells are some of the most active in the body, with each cell containing over 2,000 mitochondria in the cytoplasm. On average, a human cell has over one million chemical reactions occurring every second. The energy and nutrition needs of the human organism are enormous, and the digestive tract must provide for all of this and more, as it also supplies the gut microbiome with its needs.

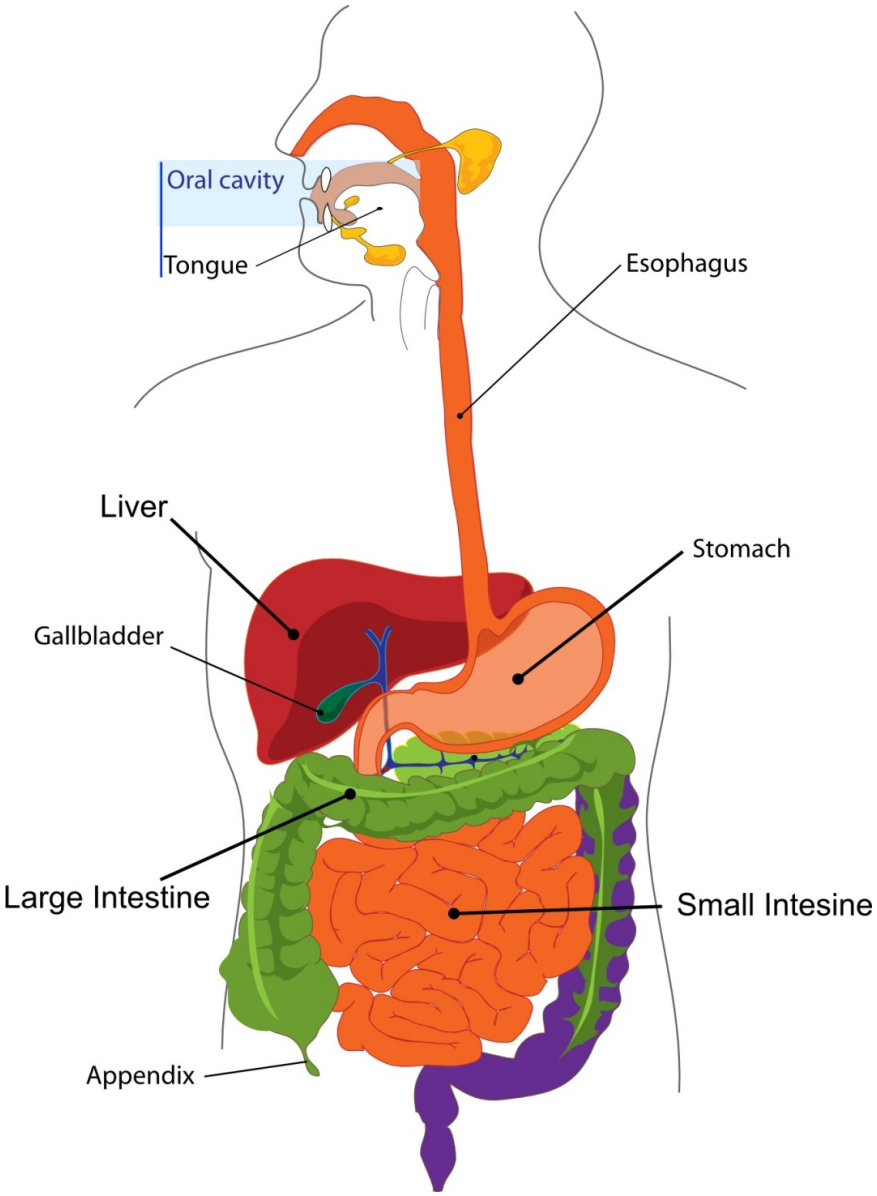
Perhaps the analogy is not the best one, but think of the digestive tract as the reverse of the assembly line, a disassembly line. A factory has a goal to be efficient and profitable, and may not win too many awards for architectural beauty. So too with the digestive tract, the process has
been refined over eons of evolution, yet still have its primitive origins and end products.
We begin our factory tour with a view much like you would get sitting in your car going through an automated car wash. Before you even go to the car wash, your brain has to make the conscious decision that this activity is what it wants to do. In the same manner, the mind begins the digestive process with the decision to satisfy its hunger call, or because an appetizing opportunity presents itself. When thinking about food and eating, the brain may activate the secretion of saliva and prime the digestive processes of the stomach and internal organs.

Much like the water hoses and spray that greet your vehicle as you enter the beginning of the car wash tunnel, the entrance of food to the mouth receives a similar welcome. Jets of saliva are secreted from the ducts of the salivary glands located strategically around the oral cavity of the mouth. Saliva that is in the resting mouth is viscous and coats and protects the teeth and the inner surface of the mouth. The

secreted saliva with eating or drinking is of a thinner waterier consistency. It has digestive enzymes including amylase to digest carbohydrates and lipase to digest fats.

If your carwash is as sophisticated as your digestive tract, it will have a crew to make sure your side mirrors are tucked in. It will also provide a prewash scrub of your tires to remove residue that would otherwise be difficult for the machinery to reach. The teeth, jaws, and tongue work together in a remarkable and powerful dance with very few of the missteps which would be the dance equivalent of stepping on toes, the biting of the tongue.

The food has to be processed into smaller more manageable portions than that what is found on your plate. Your dining utensils of fork, knife, and spoon are just the preliminary, as the teeth do the real work in preparing food for the process of digestion. The teeth are subdivided into distinct categories that have unique functions. The incisors cut the food as you bite into an apple and the canines tear the food apart as you dig into your pastrami sandwich. The molars crush and grind the salad and crunchy vegetables that you have as a side dish. The grinding and crushing break the plant cell walls apart that would otherwise protect its internal nutritious content from our digestive enzymes. They also increase the surface area of the food increasing their exposure to digestive acid and enzymes.



The chewing process assures that the saliva and its active enzymes are well mixed with the increased surface area of the food. They begin the process of breaking down the carbohydrates and lipids into their essential components to ready them for further digestion and absorption. The saliva also moistens the food and lubricates it for the coordinated swallowing motion of the tongue, teeth, palate, and pharynx. These muscles and organs work together to roll it into an easy to swallow food bolus. The muscles of the swallowing process include those that protect the larynx and airway. The epiglottis closes off the passageway to the trachea, bronchi, and lungs, to prevent aspiration into the airways as the food and saliva swallow takes place.

The coordinated action is developed with age, which is why small children should avoid foods, such as nuts, grapes, larger oval or rounded candies. These foods, if inappropriately swallowed into the airway, can lead to fatal choking episodes. Tragically a number of children die because the oval or rounded shape can completely block the airway. An irregular shaped object, which can be life threatening, rarely completely obstructs the airway and usually allows some air to pass. The complicated swallowing neuromuscular coordination can also be affected by neurological disorders, stroke, surgery or other conditions, which may lead to the risk of aspiration. Once swallowed, the food bolus is propelled down the esophagus by coordinated snakelike muscular action, known as peristalsis. It is not recommended, but the swallowing mechanism is so efficient that you can swallow against gravity while standing on your head.

The muscular valve at the junction of the esophagus and stomach is called the lower esophageal sphincter. The lower esophageal sphincter is designed to allow food and fluid to enter the stomach, with the door closed behind them once they leave the esophagus. If the valve opens at the wrong time, gastric acid, digestive enzymes, and food can flow back into the esophagus. The reflux of stomach contents into the esophagus can lead to symptoms of heartburn or mucosal damage. If the refluxed material goes all the way into the airway hoarseness, sore throat, aspiration, choking, or pneumonia can develop. If it occurs frequently gastroesophageal reflux disease (GERD) can predispose to a change in the normal flat squamous epithelium cell tissue lining the esophagus. The growth of columnar epithelium, more of an intestinal type tissue, in place of the squamous epithelium gives rise to a condition called a Barrett esophagus. This type of cell lining is at a higher risk for abnormal atypical cell changes and a higher risk of cancer development. Individuals with Barrett esophagus are frequently treated for GERD and monitored carefully with surveillance endoscopy and biopsy for pre-malignant changes.

The stomach is a churning caldron of muscular mixing contractions, concentrated acid secretion, and potent digestive enzymes. The vagus nerve and gut hormones play a crucial role in the intricate balance of enzymes, acid, nutrients, and motility. When the conditions are right, the pyloric sphincter of the stomach opens to allow the acid, enzyme, and food mixture to exit. This digestive material is now called chyme as it enters the first portion of the small intestine, known as the duodenum. In Greek, this means the width equivalent to twelve fingers, which is what its small size would measure using your digits. For its small size, the duodenum plays an amazing and complex part.

The highly acid chyme would quickly damage the lining of the duodenum if it did not respond quickly with the pouring on, much like a fire extinguisher, of sodium bicarbonate. The sodium bicarbonate is produced in the duodenum as well as by the pancreas. The sodium bicarbonate produced in the pancreas is released through the pancreatic duct, which empties into the duodenum through the Ampulla of Vater. The fire extinguisher analogy shares another aspect of the story. Perhaps you made a fire extinguisher in a science class, or home experiment, by adding baking soda that contains sodium bicarbonate and vinegar that contains acetic acid. This neutralization of acid is the same type of reaction that takes place in the duodenum, when the hydrochloric acid of the stomach meets the sodium bicarbonate released to neutralize it. When the two react they produce water, sodium chloride (salt), and large quantities of carbon dioxide. The carbon dioxide is released as large volumes of gas that appears as bubbles arising

from the reaction. The carbon dioxide is used as a fire extinguisher in the science experiment since it is heavier than air and cuts off the oxygen supply that the flame requires.

In the human duodenum, the carbon dioxide generated as a side product of acid neutralization only serves to bloat and distend the gut with gas. The body is pretty remarkable in getting rid of the bloat relatively quickly, in that it absorbs the carbon dioxide into the bloodstream where it travels to the lungs and is exhaled. The bile ducts from the liver join the duct from the pancreas bringing digestive enzymes and bicarbonate that enter the duodenum through the Ampulla of Vater. Within the ampulla lies the muscular sphincter of Oddi. The name sounds like a character from the story of *The Wizard of Oz*, and that would be an appropriate analogy. The coordinated release of hormones, enzymes, motility and vagal input is nothing short of wizardry.

Subconsciously, your body can sense what nutrients you have ingested. The body responds by releasing the correct recipe of enzymes, potent acid in the stomach, and bicarbonate in the duodenum, adjusting the pH as necessary. It adds just the right amount of bile to the mix, controls the timing and volume of stomach emptying, and controls the speed of transit and intensity of mixing contractions through the length of the intestinal tract. The majority of the sensing and control feedback takes place in a small confined space the width of twelve fingers, the duodenum.

Enzyme deficiencies can lead to inadequate digestion of foods, which can result in excess material for the gut microbes to ferment with excess gas production. Enzymes are large molecules that are highly selective catalysts that greatly accelerate metabolic reactions. These range from the digestion of food to the synthesis of proteins and DNA. They are often described as being analogous to a lock and key. Most enzymes are proteins that have specific three-dimensional structure that acts like a key, with the substrate acting as a lock.

The molecules at the beginning of the process are called substrates, and are converted into different molecules called products. Most enzyme reaction rates are millions of times faster than reactions without the presence of the enzyme catalyst, and the enzymes are not consumed by the reactions and can be reused. Enzyme activity can be affected by other molecules such as inhibitors that decrease enzyme activity and activators that increase activity. Many pharmaceutical products, active ingredients from plants, and poisons are enzyme inhibitors or activators.

There are a wide variety of enzyme deficiencies and food intolerances that can be major contributors to gaseous distension and flatulence. Taking a Sherlock Holmes approach and trying an elimination diet is certainly reasonable. Enzyme supplements are commercially available and are another approach for an empiric trial if the suspect foods are not well defined. Medications can also interfere with enzyme activity and give rise to flatulence. Enzymes include proteases that digest proteins such as pepsin, pepsinogen, trypsin, trypsinogen, chymotrypsin, and chymotrypsinogen. Other enzymes include amylase, lipase, invertase, sucrose, maltase, lactase, and about one thousand six-hundred others!

It is important to take the appropriate enzyme with the appropriate food. The right enzyme for the wrong food, or the wrong enzyme for the right food, will not make a bit of difference in helping your digestion. The most common enzyme deficiency is lactase resulting in lactose intolerance. With over one thousand six-hundred known enzymes it is best to do your own Sherlock Holmes detective work with elimination diets or challenges to identify the foods you are best to avoid, or others will be avoiding you because of the intestinal gas that results.

All plants harbor the ability to generate digestive enzymes to break down the starch content of their own seeds and fruit. That is how the fertilized seed gets its nutrition for growth. In fact, we can take advantage of this property to ease our digestion of plants by letting them germinate before ingesting them. For some

plants like sprouts and beans that is a very doable suggestion. For other fruits and plants by the time they germinate the starches have lost all culinary appeal to us. What may be surprising is the variety and diversity of enzymes the plants generate across various species. They number in the thousands and the vast majority have yet to be identified and analyzed. The development of plant genomics has accelerated our understanding of the vast diversity of enzymes we are exposed to. A number of plants also generate proteases to digest the plant storage proteins that a number of varieties have a rich storehouse of. For example, wheat has many endopeptidases. The plant world also uses proteolytic enzymes in defense against insect pests, to avoid being consumed by animals that do not assist them in their propagation.

A calorie is simply a measure of the amount of energy within a food or substance. It is measured in a device called a bomb calorimeter, which incinerates the food in a chamber surrounded by a water bath, and measures the increase in water temperature. The number of calories in food is the optimal amount of energy within the food if completely incinerated, and obviously the digestive tract is rarely as efficient as a furnace. A large percentage, if not the majority, of the calories are not extracted from the food and are eliminated with the digestive waste. The glycemic index is an indication of the rapidity with which the food is digested to allow the release and absorption of simple sugars. The higher the glycemic index the more rapidly sugars are absorbed, with blood glucose spikes contributing to insulin peaks and a greater likelihood of diabetes.

The microbes of the gastrointestinal tract, the gut microbiome, play a critical role in determining the extent to which calories are extracted from the food ingested. The glycemic index, which used to be associated with specific food types, is now believed to be more closely related to the nature of the gut microbiome. It appears that the microbiome can determine whether a diet leads to weight increase or decrease, as well as the glucose response which may contribute to diabetes. A number of companies are now offering gut microbiome analysis, with dietary recommendations tailored to the microbiome.

The breakdown products of the digestive process are absorbed by a sea of finger-like projections called the villi. It looks like a field of waving wheat stalks; each upstanding villus is ready to use its enzymes and absorptive capacity to absorb nutrients. If you looked under the microscope, you would find that each villus has thousands of even smaller villi on its surface, given the appropriate name of microvilli.

All of these folds of absorptive tissue, if flattened out, would provide the equivalent absorptive capacity of a championship tennis court. A quote from Mark Twain also illustrates the concept of surface area: “If Switzerland were ironed flat it would be a very large country”. The long intestinal tunnel of eagerly awaiting absorptive villi is about twenty feet long, and it is an amazingly efficient system of digestion and absorption. If injured, the ability of the small bowel to digest and absorb nutrients is compromised. A condition that temporarily damages the small intestine, such as a viral or bacterial gastroenteritis often called stomach flu, can cause a blunting or shortening of the villi. The villous blunting will also lead to the loss of digestive enzymes that reside on the villi.

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

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

The 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.

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 billion 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 billion 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 22,000 genes. The number of unique species of microbes in the human microbiome is thought to number more than one million, with each having between 15,000 to 30,000 of their own unique genes. 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. A single human gene can make over 200 different proteins depending on the epigenetic influence.

Even more staggering than the hundreds of billions of genes, are the exponentially larger number of epigenetic factors, the majority of which arise from the 99% of DNA that do not code for genes. It is the height of irony that what scientists disparagingly labeled as 'junk DNA', is of critical importance to all life forms. The noncoding junk DNA generates 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.

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. Aside from direct toxicity concerns, glyphosate is known to have adverse consequences in the gut microbiome leading to the release of zonulin, which is associated with the disruption of the gastrointestinal cellular lining. Zonulin interferes with the cellular tight junctions, the proteins that allow the single cell thick gut lining from the mouth to the anus to efficiently act as a contiguous barrier to unwanted pathogens and metabolites. 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’.

The gut microbiome is heavily influenced by environmental factors, particularly the diet. Exposure to antibiotics, pharmaceuticals, toxins, probiotics, and virtually anything taken by mouth exposes the microbiome to its influence. Many people consume organic foods with the intent to protect their body and health. Unfortunately, even organic foods can be contaminated if the farmers use manure, an ‘organic

fertilizer', that is often contaminated with antibiotics, hormones, pesticides, and herbicides from commercial cattle and pig farms.

The gut microbiome is much more important than most people realize. The microbes of the body far outnumber the number of human cells. In fact, if you just go by the number of cells and not their mass, they outnumber human cells by ten to one. In other words, you as a living system are only ten percent human and ninety percent microbes! The vast majority of the microbes living within and on us are commensals. The term commensal is used to describe a symbiotic relationship from which both parties benefit. They are able to process foods that would otherwise be indigestible, and convert them to absorbable nutrients and metabolites. It is not an understatement to say that they are a requirement for our health and well-being.

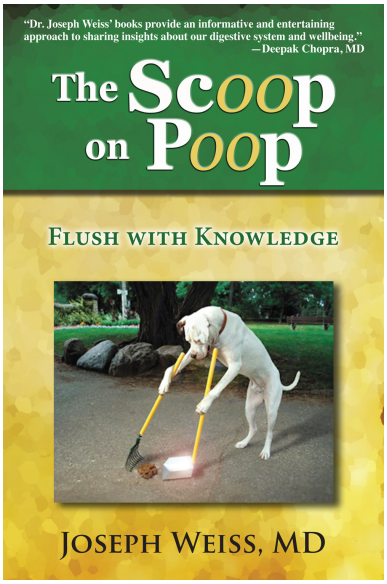
The colon, unlike the small intestine, is less involved in the digestion of foods and nutrients. It is primarily involved in the absorption of water and sodium, as well as some fat-soluble vitamins such as vitamin K. The colon removes the excess moisture from the watery chime solidifying the stool as it transits the gut. The ability to conserve water is necessary, and without this ability the risk of dehydration would be substantially increased. The fecal material of the stool is stored in the rectum, and sigmoid colon, awaiting the right opportunity to be eliminated through defecation. A process or illness that impairs the colon's absorption of water will lead to more fluid in the stool and diarrhea. The loss of water and electrolytes as a consequence of diarrhea, unfortunately, remains a life-threatening condition in many parts of the world, especially for infants and children.

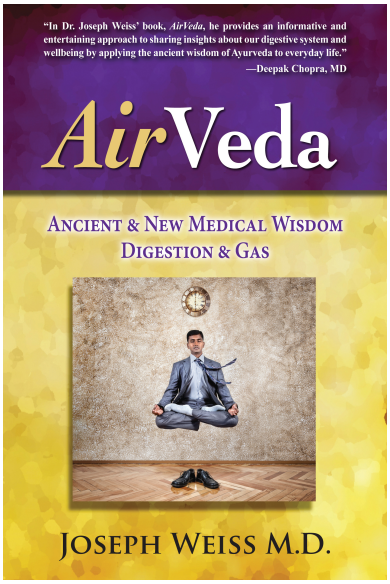
If the elimination of the feces is delayed, the moisture continues to be absorbed, and the stools can become harder resulting in constipation. Constipation itself can be self-perpetuating as it aggravates the situation because the stools become harder and more difficult to pass the longer they remain in the colon. The more common treatments for constipation attempt to increase the moisture content of the stool. The feces excreted can provide information about bowel health. For most people going about their daily activities, the passage of the feces itself is the end of the story of digestion. The human digestive system, like that of other animals, does not remove all of the contained nutrients from food. For other organisms, including the common housefly, the feces are thus an available source of nutrition. For them, the elimination of feces is just the beginning of their story of digestion and can play an important role in the transmission of disease back to humans.

By the way, there is something else besides feces which comes out of the 'tail pipe' of our digestive tract. Intestinal gas, also known as a fart (this is the proper English term, commonly found in the English literature and even used by royalty!), is also one of the waste products of digestion. Swallowed air also contributes to intestinal gas, and if makes you feel any better, the intestinal gas was for the most part created by your gut microbes, not you! Intestinal gas is ubiquitous. All living creatures generate gas from the cellular respiration of metabolism, and humans are no exception.

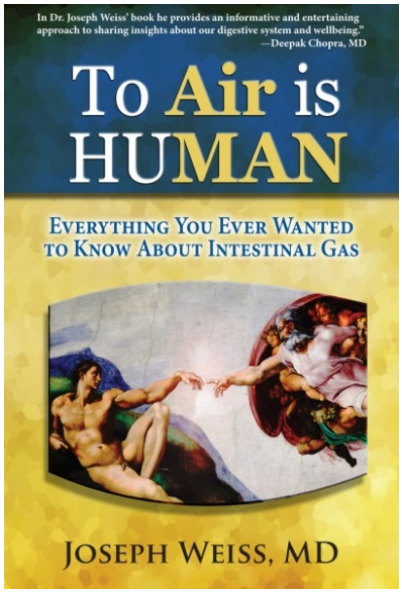
The bacteria in the colonic flora produce microscopic nanofarts and microfarts, which collect into larger bubbles of gas in the bowel. They are intermixed with the atmospheric air swallowed throughout the day and particularly at meals. As entertaining as they may be to adolescent males, there is growing evidence that they may be of social and scientific value as well. There have been discussions of reducing the methane production of cattle herds to reduce global warming. An alternative would be to capture the methane and use it for energy production. A graphic example of the energy potential is to imagine each cow with a permanently lit 100-watt light bulb under its tail, bringing a new meaning to the term 'tail light'. In medical diagnostics, the analysis of intestinal gas has demonstrated the ability to identify a variety of medical conditions, but it is unlikely to gain much popularity.

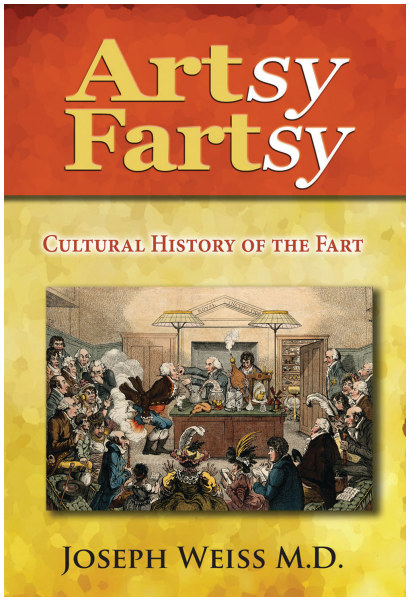
For those interested in learning more about the gut microbiome and digestive issues I have authored a number of books that may be of interest. *The Scoop on Poop: Flush with Knowledge* and *AirVeda, Ancient & New Medical Wisdom, Digestion & Gas* also covers additional digestive topics. They are available at www.smartaskbooks.com, Amazon, Barnes & Noble, and others.

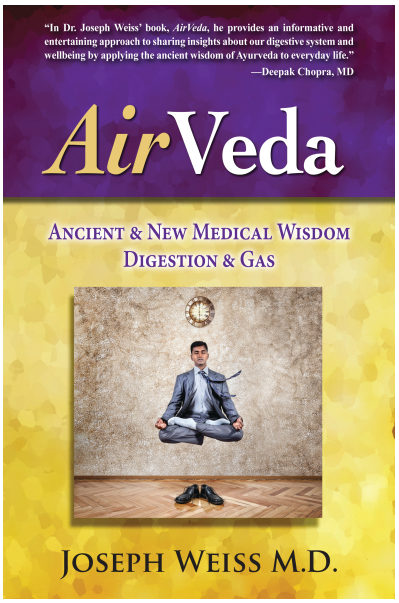




The nature of the intestinal gas may provide clues to digestive health and disease, and are the interesting and entertaining topic of three books I have written *To Air is Human: Everything You Ever Wanted to Know About Intestinal Gas*, and *Artsy Fartsy, Cultural History of the Fart*. The more comprehensive volume *AirVeda, Ancient & New Medical Wisdom, Digestion & Gas* also covers additional digestive topics. All are available at www.smartaskbooks.com, Amazon, Barnes & Noble, and others.

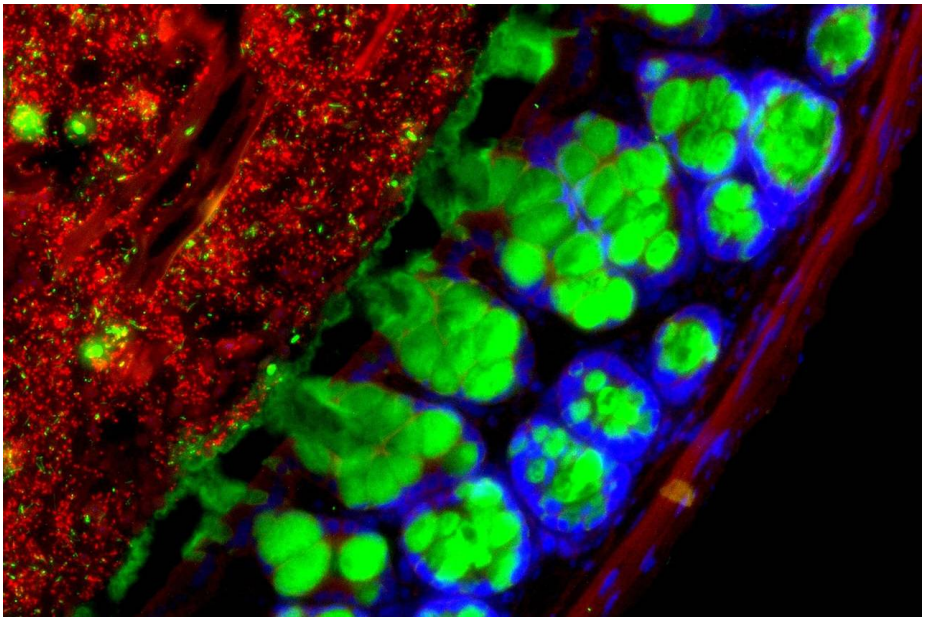






How Disrupting Your Gut's Rhythm Affects Your Health
The Wall Street Journal February 27, 2018

New research sheds light on how eating and sleeping habits can contribute to disease by disrupting the bacteria in the digestive tract



A healthy community of microbes in the gut maintains regular daily cycles of activities. PHOTO: WEIZMANN INSTITUTE

By Larry M. Greenberg

New research is helping to unravel the mystery of how disruptions to the bacteria in our gut, caused by an unhealthy diet or irregular sleep, can lead to a number of diseases.
Such research could someday result in new treatments for obesity, diabetes and other metabolic conditions by restoring the health of the gut-microbe community, known as the microbiota. Researchers are exploring how to do this through individualized diets and mealtimes or other interventions.

When gut microbiota are healthy, they maintain regular daily cycles of activities such as congregating in different parts of the intestine and producing metabolites, molecules that help the body function properly. A disruption of the gut's circadian rhythms is communicated through the bloodstream and upsets many of the body's other circadian clocks, especially in the liver, one of the main metabolic organs, according to a study by Israel's Weizmann Institute of Science published in the journal Cell in December. The gut's circadian rhythms and those in other organs "dance together in a very profound way and go up and down in coordination with each other," says Eran Elinav, a physician and immunologist at the Weizmann Institute and one of the study's lead investigators. "By controlling the gut microbiota, you can modify many physiological capabilities" throughout the body, he says.

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In earlier studies, researchers at the University of Chicago Medical Center and other academic centers have found that gut microbiota in mice are significantly disrupted by high-fat foods, such as those included in typical Western diets. The time of day when people eat also can throw microbiota off-kilter.

The American Heart Association warned in a scientific statement in January that irregular eating habits, such as skipping breakfast and eating late at night, may disrupt the gut's circadian rhythms and increase the risk for diabetes, heart disease and other conditions.

Studies also have found that microbiota rhythms are compromised in people who do shift work and those with sleep apnea. Such people are at increased risk for developing metabolic conditions. "We now believe the microbiome may be one of the missing links to explain why these individuals may be more susceptible to conditions," says Eran Segal, a computational biologist at Weizmann and the study's other lead investigator.

The Weizmann researchers found that many of the genes in the liver lost their normal circadian rhythms or took on completely new rhythms in response to disruptions in the gut. The liver's ability to break down acetaminophen, a common pain reliever and fever reducer, also was compromised as a result of the organ's disrupted rhythms, says Dr. Segal.

The Weizmann research went beyond previous studies in the field in identifying interactive pathways in the body on a molecular and genetic level, says Eugene Chang, a professor of medicine at the University of Chicago. The study is "a tour de force in showing how complex this interaction is," says Dr. Chang, senior author of a 2015 study in the journal Cell Host & Microbe that also showed how gut-microbe rhythms coordinate with those of other organs.

There is no single solution for returning microbiota to a healthy state. Dr. Chang believes resetting a person's metabolism by implanting select microbes or microbe-produced metabolites could become an effective way to help prevent or treat some metabolic conditions.

Being able to predict how different foods affect people's blood-sugar level, based on the composition of their microbiota, also could potentially help maintain metabolic health. The Personalized Nutrition Project, another study led by Drs. Elinav and Segal, studied 1,000 people and about 50,000 meals and snacks for a week. People's metabolisms varied widely, it found. After eating ice cream, for example, blood-sugar levels would soar for some participants while hardly budging for others, Dr. Segal says.

Some of the participants were tested to see if adjusting the content and timing of food consumption could regulate metabolism. The study, published in Cell in 2015, succeeded in normalizing blood-sugar levels in some patients with prediabetes, Dr. Segal says. Further research will explore whether customized diets and mealtimes can also restore overall gut health, he says.

The technology to analyze gut microbiota, and algorithmic programs to predict the impact of food on blood sugar, have been licensed to a startup called DayTwo Inc., to which Drs. Elinav and Segal act as consultants.

Dietary Advice Based on the Bacteria in Your Gut
The Wall Street Journal February 26, 2018

Companies say the microbiome varies from person to person—and so should the most effective diet. Evidence is growing that the 100 trillion organisms in the human gut play a role in individuals' differing responses to food.

By Charles Wallace

For almost a decade, researchers have been sequencing the bacteria that live in the human gut. Now, some startups are claiming they can use that technology to help people diet more effectively—and in at least one case, scientists say the approach is showing some promise. The companies are aiming to address a problem identified in recent years: Standard nutritional advice doesn't work for everyone. Research shows that people fed identical foods can have vastly different blood-glucose responses, which may explain why one person can eat doughnuts daily without gaining weight and another can't.

While some of this variability is due to genetics, there is growing evidence that the 100 trillion organisms that live in the human gut—known as the microbiome—also play a role. Composed of more than 8,000 different types of bacteria, viruses and fungi living together in a complex ecosystem, the gut microbiome varies from person to person and is affected by a variety of factors, such as sleep, exercise, antibiotics use and, most important, diet.

The glucose response:
Thanks to advances in genetic sequencing, researchers increasingly believe that these bacteria affect the body's ability to harvest energy from food, a measure known as the postprandial glucose response, or PPGR. If untreated, high blood glucose is a risk factor for a host of metabolic conditions, including obesity and diabetes. DayTwo Inc., an Israeli startup, and Viome Inc., a company backed by Seattle entrepreneur Naveen Jain, say they can help people normalize their blood sugar by analyzing the mix of bacteria that influence their glucose response. Customers send in a stool sample, from which their microbiome is sequenced, along with other information, including a brief medical history, daily activity levels and blood-test results. The companies send back individually tailored diets via an app designed to keep each person's blood-sugar levels balanced.

Until now, most diets have been based on the glycemic index, a half-century-old list that ranks foods based on how they affect blood sugar. While this index is widely used by doctors to provide dietary advice, it is based on an average response and has been found wanting because many people aren't average. DayTwo, which charges $329 for its kit, bases its dietary recommendations on research at the Weizmann Institute of Science in Rehovot, Israel. In 2015 the institute produced a double-blind, peer-reviewed study that showed that individual glucose responses to the same exact meals varied dramatically. Using a test group of 800 people, the study showed that some people produce less glucose after eating a bowl of ice cream than they do after eating a portion of sushi, a food most people would consider to be more healthful. "We did a dietary intervention that showed that for different people, even people who were prediabetic, we could significantly lower their PPGR," says Eran Segal, one of the Israeli researchers and a consultant to DayTwo.

Doctors' views:
Until very recently, many doctors were hesitant to base any nutritional advice on the microbiome, saying researchers still didn't know what each type of micro-organism does exactly, how they interact with other bacteria, and whether they cause disease or are only a biomarker of disease.

But Jack Gilbert, faculty director of the University of Chicago's Microbiome Center, says he now believes

it's possible to give some dietary advice based on microbiome analysis, even though the microbiome's role isn't fully understood. "This is less about trying to identify the particular mechanisms of the microbes and more about identifying the potential correlated association between the microbial communities and how they positively associate with blood-glucose levels and response to different types of food," he says. Dr. Gilbert, who isn't connected to DayTwo, says he has put his own father, who is prediabetic, on the program.

The American Academy of Nutrition and Dietetics, which as recently as last year expressed reservations about microbiome-based diets, also has "evolved" its position, says Sonya Angelone, a San Francisco nutritionist and a spokeswoman for the academy. "I think this is the future of really good health care," says Ms. Angelone, though she suggests pairing such data with advice from a dietitian. Rob Knight, a professor of pediatrics at the University of California, San Diego, and faculty director of the university's Center for Microbiome Innovation, says the Weizmann research underlying DayTwo is "very solid and rigorous, which puts them ahead of the curve." But, he adds, "I think it is still very challenging to extend results like that beyond the population you have studied directly."

Perhaps because of these concerns, DayTwo, which bases its dietary advice on an algorithm licensed from the Weizmann Institute that connects microbiome composition with predicted glucose responses, has joined with Mayo Clinic to duplicate the Israeli study on 329 people in the U.S. The goal is to ensure that the diet advice works as well for Americans, whose genetics and diet are different from many Israelis. Nicholas Chia, assistant director of the Center for the Individualized Medicine Microbiome Program at Mayo Clinic, says the results of the follow-up study were close to the Weizmann's Institute's findings. "That's a pretty good sign that we've replicated the Israeli study and that it continues to work," he says.

A competing approach:
Viome, meanwhile, uses gene-sequencing technology to analyze not only bacteria but also viruses and fungi in the gut. The Bellevue, Wash., firm, which charges $399 for its analysis, compares users' microbiomes with 800 individuals the company has preselected as healthy specimens. It gives broad advice on foods to eat or avoid to improve glucose response, enhance sleep and focus, and reduce anxiety.

Though Mr. Jain says Viome's sequencing technology, licensed from the Los Alamos National Laboratory in New Mexico, is superior to other technologies, Viome's dietary advice isn't yet based on peer-reviewed research. Mr. Jain says Viome is conducting a microbiome study on 2,000 people that should be completed later this year. Drs. Gilbert and Knight and Ms. Angelone declined to discuss Viome, saying they hadn't seen its studies. A spokesman for Viome says hundreds of testimonials are evidence that Viome's service is working.

Other companies, including uBiome Inc., the American Gut project and Biohm also offer sequencing of the microbiome, but they focus on how an individual's gut bacteria differ from the average, not on helping people understand which foods elevate their blood glucose. Some sell probiotics that they say improve the mix of bacteria, though many experts caution that the rapid growth in marketing and use of probiotics may have outpaced scientific research for many of their proposed uses and benefits. "Although some probiotics have shown promise in research studies, strong scientific evidence to support specific uses of probiotics for most health conditions is lacking," the National Institutes of Health says.

As for microbiome-based diets, questions remain. Can these eating plans change a person's gut bacteria for the better, and if so, do people need to measure how much it has changed? "The right diet might change over time as the bacteria change," says Dr. Knight at UC San Diego. Viome includes a follow-up analysis as part of its annual fee; DayTwo has decided to wait for further studies to determine whether the changes in the microbiome are so significant that the microbiome needs to be assessed once more.

Do Probiotics Really Work?
Scientific American July 1, 2017

Although certain bacteria help treat some gut disorders, they have no known benefits for healthy people

By Ferrius Jabr

Friendly Microbes: Bacteria such as these lactobacilli, which are often added to yogurt and probiotic supplements, help to maintain a healthy environment in the intestine.

Walk into any grocery store, and you will likely find more than a few “probiotic” products brimming with so-called beneficial bacteria that are supposed to treat everything from constipation to obesity to depression. In addition to foods traditionally prepared with live bacterial cultures (such as yogurt and other fermented dairy products), consumers can now purchase probiotic capsules and pills, fruit juices, cereals, sausages, cookies, candy, granola bars and pet food. Indeed, the popularity of probiotics has grown so much in recent years that manufacturers have even added the microorganisms to cosmetics and mattresses.

A closer look at the science underlying microbe-based treatments, however, shows that most of the health claims for probiotics are pure hype. The majority of studies to date have failed to reveal any benefits in individuals who are already healthy. The bacteria seem to help only those people suffering from a few specific intestinal disorders. “There is no evidence to suggest that people with normal gastrointestinal tracts can benefit from taking probiotics,” says Matthew Ciorba, a gastroenterologist at Washington University in St. Louis. “If you're not in any distress, I would not recommend them.” Emma Allen-Vercoe, a microbiologist at the University of Guelph in Ontario, agrees. For the most part, she says, “the claims that are made are enormously inflated.”

The Numbers Game
This story has played out before, most notably with vitamin supplements, which decades of research have revealed to be completely unnecessary for most adults and, in some cases, dangerous, correlating with higher rates of lung, breast and prostate cancers. But that has not stopped marketers from pushing another nutritional craze. According to a National Institutes of Health survey, the number of adults in the U.S. taking probiotics or their cousins, prebiotics (typically nondigestible fibers that favor the development of gut bacteria), more than quadrupled between 2007 and 2012, from 865,000 people to nearly four million. San Francisco–based business consulting firm Grand View Research estimates that

the global probiotics market exceeded $35 billion in 2015 and predicts that it will reach $66 billion by 2024.

The popular frenzy surrounding probiotics is fueled in large part by surging scientific and public interest in the human microbiome: the overlapping ecosystems of bacteria and other microorganisms found throughout the body. The human gastrointestinal system contains about 39 trillion bacteria, according to the latest estimate, most of which reside in the large intestine. In the past 15 years researchers have established that many of these commensal microbes are essential for health. Collectively, they crowd out harmful microbial invaders, break down fibrous foods into more digestible components and produce vitamins such as K and B12.

The idea that consuming probiotics can boost the ability of already well-functioning native bacteria to promote general health is dubious for a couple of reasons. Manufacturers of probiotics often select specific bacterial strains for their products because they know how to grow them in large numbers, not because they are adapted to the human gut or known to improve health. The particular strains of *Bifidobacterium* or *Lactobacillus* that are typically found in many yogurts and pills may not be the same kind that can survive the highly acidic environment of the human stomach and from there colonize the gut.

Even if some of the bacteria in a probiotic managed to survive and propagate in the intestine, there would likely be far too few of them to dramatically alter the overall composition of one's internal ecosystem. Whereas the human gut contains tens of trillions of bacteria, there are only between 100 million and a few hundred billion bacteria in a typical serving of yogurt or a microbe-filled pill. Last year a team of scientists at the University of Copenhagen published a review of seven randomized, placebo-controlled trials (the most scientifically rigorous types of studies researchers know how to conduct) investigating whether probiotic supplements—including biscuits, milk-based drinks and capsules—change the diversity of bacteria in fecal samples. Only one study—of 34 healthy volunteers—found a statistically significant change, and there was no indication that it provided a clinical benefit. “A probiotic is still just a drop in a bucket,” says Shira Doron, an infectious disease expert at Tufts Medical Center. “The gut always has orders of magnitude more microbes.”

Real Benefits

Despite a growing sense that probiotics do not offer anything of substance to individuals who are already healthy, researchers have documented some benefits for people with certain conditions. In the past five years, for example, several combined analyses of dozens of studies have concluded that probiotics may help prevent some common side effects of treatment with antibiotics. Whenever physicians prescribe these medications, they know they stand a good chance of annihilating entire communities of beneficial bacteria in the intestine, along with whatever problem-causing microbes they are trying to dispel. Normally the body just needs to grab a few bacteria from the environment to reestablish a healthy microbiome. But sometimes the emptied niches get filled up with harmful bacteria that secrete toxins, causing inflammation in the intestine and triggering diarrhea. Adding yogurt or other probiotics—especially the kinds that contain *Lactobacillus*—during and after a course of antibiotics seems to decrease the chances of subsequently developing these opportunistic infections.

A 2014 review by Cochrane—an independent network of experts who serve as rigorous arbiters of medical research—found that probiotics may be particularly useful in a hospital's neonatal intensive care unit. The addition of beneficial bacteria to a nutritional regimen seems to significantly reduce the likelihood of developing necrotizing enterocolitis, which is a devastating, poorly understood and often fatal gut disease that primarily afflicts preterm infants—especially the smallest and most premature among them. Researchers think that many cases of the disease begin with an opportunistic bacterial infection in the not yet fully developed intestine of an infant. As the illness progresses, gut tissue becomes

increasingly inflamed and often starts to die, which can, in turn, rupture the intestine and flood the abdominal cavity with pathogenic microbes that proliferate to dangerous levels. Researchers estimate that 12 percent of preterm infants weighing less than 3.3 pounds will develop necrotizing enterocolitis and that 30 percent of them will not survive. Standard treatment involves a combination of antibiotics, feeding via intravenous tubes, and surgery to remove diseased and dead tissue. Probiotics probably prevent the disorder by boosting the numbers of beneficial bacteria, which may deter the harmful ones.

Probiotics also seem to ameliorate irritable bowel syndrome, a chronic disease characterized by abdominal pain, bloating, and frequent diarrhea or constipation (or a mix of the two). A 2014 review of more than 30 studies, published in the *American Journal of Gastroenterology* by an international team of researchers, determined that in some cases, probiotics help to relieve the symptoms of irritable bowel syndrome for reasons that are not entirely clear, although it may be that they impede the growth of harmful microbes. The researchers concluded, however, that they did not have enough data to recommend any particular strains of bacteria. Microbiologists often caution that a promising study on a single strain of a particular species of bacteria should not be taken as proof that all probiotics work equally well. “Bacterial strains are so genetically different from one another, and everybody has a different gut microbiota,” Allen-Vercoe says. “There will probably never be a one-size-fits-all probiotic.”

But what if investigators could design probiotics to treat specific individuals? Many researchers think personalized probiotics are the most promising path forward for patients with compromised gut microbiomes. Last year Jens Walter of the University of Alberta and his colleagues published a study that gives a glimpse of this potential future. The researchers decided to see what it would take to get the bacteria in a probiotic to successfully colonize the intestines of 23 volunteers. They chose a particular strain of *Bifidobacterium longum* that earlier studies had indicated could survive in the human intestine. In the study, the volunteers consumed either a drink containing 10 billion live *B. longum* bacteria or a placebo in the form of a glucose-based food additive (maltodextrin) each day for two weeks. Periodic fecal samples revealed higher than typical levels of *B. longum* in participants who did not consume the placebo.

In seven people, however, these bacterial levels persisted for more than five months after the treatment ended. “We never expected they would survive more than a few weeks,” Walter says. A follow-up analysis determined that these seven people had begun the experiment with lower levels of *B. longum* in the first place. In other words, their gut ecosystems had a vacancy that the probiotic filled. That is exactly the kind of insight that clinicians need to create and recommend more effective probiotics. If a doctor knows that an individual with severe diarrhea has an undersized population of a particular beneficial microbe, for example, then prescribing the missing strain should increase the chance of a successful treatment.

“The key is taking an ecological perspective,” Walter says. “We need to think about which microbes have the right adaptations to survive in a particular gut ecosystem.” Put another way, treatments for microbe-related disorders are most successful when they work in tandem with the human body's many microscopic citizens, not just against them.

Quest for Immortality & Vitality
Rancho La Puerta

Joseph Weiss, MD, FACP, FACG, AGAF
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"I don't want to achieve immortality through my work. I want to achieve it through not dying." ~ Woody Allen

The timeline from the first flight to supersonic transport and the first rocket to a manned mission to the moon have been breathtakingly brief. The first theory that a chemical means of transmission of genetic information, to the identification of DNA, took a few years. The progress since then leading to new fields of genomics, epigenetics, gene sequencing, gene correction, and transfer has been nothing short of revolutionary. The life span of various rodents is remarkably varied, and even more varied are the lifespans of different animals. Some life forms have been identified that have lifespans measured in the thousands of years, others appear to be immortal. The Nobel Prize in Medicine was given to Dr. Sydney Brenner for his work on the genetics of the roundworm, which has parallels to the genomics of man. Modifying one single gene led to a near ten-fold increase in its lifespan, the human equivalent of reaching an age one thousand years. The single cell at fertilization, through replication and cell division, becomes over 37 trillion specialized cells in the adult. Each cell carries a duplicate of the DNA of its parent cells unless a mutation occurs. The power of exponential or logarithmic growth is often vastly underestimated. Human life expectancy has increased, predominantly through reductions in infant mortality.

Free radicals, oxidation, and inflammation and are the biological equivalent of rust and aging. Genes are not destiny; epigenetic influences from the environment modify genes as well as turning them on and off. Telomeres, the ends of the chromosomes that act as the equivalent of shoelace caplets, prevent the unraveling of DNA and cell death. The enzyme telomerase prevents the shortening of telomeres and enhances cell longevity. Cancer cells use telomerase to maintain cancer cell viability and propagation, making some cancer cell lines virtually immortal. Genetic mutations that trigger accelerated aging, such as progeria, are providing important insight into the mechanisms of aging that offers potential therapy to control the aging process. One of the control genes of aging found in the roundworm is also present in mouse and man. A metabolite of a microbe found in the soil of Easter Island influences this gene and leads to extended lifespan in the roundworm, and evidence of age reversal in mice. This compound is FDA approved for treating post organ transplant patients to prevent rejection, and human trials to assess its effect on aging are ongoing. Laboratory advances in roundworms and mice are providing important insights, but applications in humans require extensive study, even if the sane genes are shared between species. 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.

On occasion, the result of a new scientific advance meets or exceeds the initial hype. Stem cells are one example where the advances have rapidly moved from the laboratory to clinical applications. Stem cell

therapy has moved from the laboratory to clinical applications relatively rapidly. The first stem cell transplant took place over fifty years ago with bone marrow transplants. The condition amenable to new approaches with stem cells is expanding rapidly. Organ regeneration and replacement, as well as cloning for organ retrieval, are no longer science fiction but on the horizon. Limb and organ regeneration from stem cells and gene transfers to correct mutations or provide new properties are within technological reach. The image of the glowing cat is an actual demonstration that the gene of the firefly can be transplanted into a completely different species, and function as it was designed to physiologically. The other images are fictional and humorous representations of what is theoretically possible if carried to the extreme. Advances in technology have made prosthetics that have similar or superior properties to the human original possible. Further advances will accelerate advances over the natural features, and even today the Olympics disallow blade runners who have a speeds advantage over normal limbs. Many of the diseases that result in death today, such as myocardial infarction and heart failure, are theoretically curable with a mechanical prosthetic heart or one regenerated from stem cells.

Nanotechnology is rapidly advancing, and an entirely new field of technology and medicine will offer remarkable diagnostic and therapeutic advances. Hormones were the original focus of aging and vitality research and continued to have an important role to play. Testosterone and growth hormone supplements are not without risks, and the science of longevity and age management is rapidly advancing beyond hormone therapy. Lifestyle, diet, stress, inflammation, and a variety of factors have been identified by studying centenarians, those who have lived a century or more, in 'blue zone' communities around the world where they are found in sizeable number. Caloric restriction extends lifespan in mice and other organisms. Some humans are adapting this approach, with the results unknown as yet. Laboratory research has identified compounds that mimic the effect of caloric restriction, so it is possible that in the future you can literally have your cake and eat it too! Diet plays an important role in inflammation and its management. Many people believe inflammation should be referred to as inflamed-aging because of its profound effect on the aging process. Red wine and resveratrol have received a lot of publicity for anti-aging effects, but to date the results of resveratrol compounds have been disappointing. One of the lessons learned from the concept of systems biology is that individual components may require other factors to achieve results. So even though resveratrol by itself may not have proven benefits, perhaps when taken with other key components in the elixir of red wine, it is beneficial. The Mediterranean diet, as well as the red wine industry, suggests this is the correct path to take, in moderation of course.

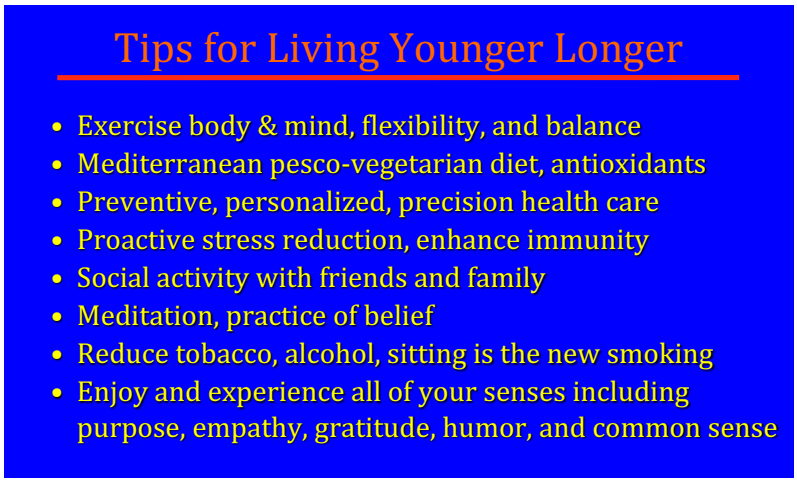
Without a doubt, exercise appears to have the greatest anti-aging effects known to date. Perhaps one day the benefit will be available in pill form, but even then you should take the pill for a long walk each day before swallowing it! The diet we consume undoubtedly is another key to our health and longevity. It may have a direct influence by its components, or indirect via changes in epigenetics and the microbiome. Even when the diet appeared to play a direct role, such as fat content and cardiovascular risk, the truth was much more complicated. For example, phosphatidylcholine is a vital phospholipid substance found in every cell of the human body. As it was first identified in eggs it was given the name lecithin derived from the Greek word lekithos (λεκιθος, egg yolk). The Western diet is rich in lecithin, which the gut microbes use to create trimethylamine, which is then absorbed by the gut and converted by the liver to TMAO. Choline, betaine, and trimethylamine N-oxide (TMAO) are metabolites of lecithin and are associated with cardiovascular risk in humans. TMAO has been associated with accelerated atherosclerosis, enhanced playlet hyper-reactivity, and thrombosis risk. Vegetarian, vegan, and Mediterranean diets (dairy, eggs, legumes, vegetables, seafood) are associated with lower TMAO levels. Gut microbial suppression with antibiotics reduces plasma levels of TMAO. Who would have imagined that the food was influenced by the microbiome, and then metabolized by the liver, and then could affect the cardiovascular system?

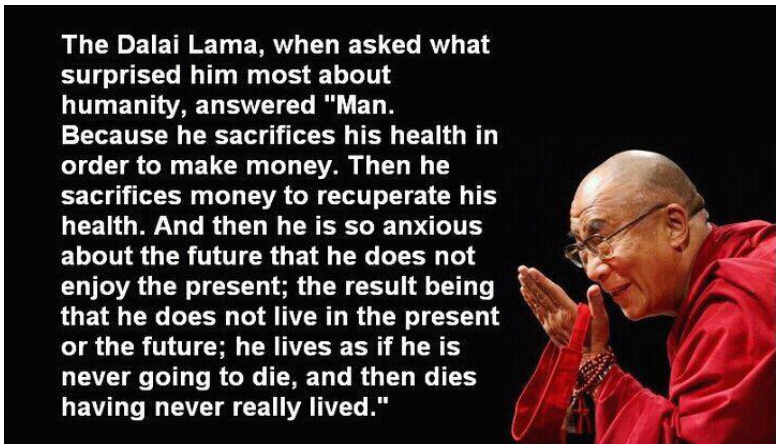
The human microbiome and its genes have a profound influence on human health. We are constantly exposed to new organisms, and the microbiome is always adapting. The use of probiotics, antibiotics, prebiotics, dietary supplements, nutraceuticals, prescription and over the counter drugs can affect the

microbiome in so many ways that the consequences cannot be predicted with certainty. What can be predicted is that they will be heavily marketed and promoted because there is a huge profit to be made, and safety and efficacy are secondary afterthoughts. Sometimes the wisdom of sages past cannot be improved upon, this is one of them. Some cancers, such as breast and colon, can be identified early when highly curable. Surveillance for those at higher risk is suggested. Further advances in genomics may identify populations at risk, and blood tests may replace the screening tests we use today. Colon cancer screening is suggested for those over fifty years of age, and for younger individuals who have a history or family history of colon cancer, colon polyps, inflammatory bowel disease, and specific genetic markers.

Colonoscopy has been the 'gold standard', but new options include capsule colonoscopy, a high-tech image transmitter that is swallowed and sends images for review. The latest FDA-approved test was a fecal (stool) DNA test for markers of colon cancer and polyps. Technology and approaches are changing, but getting screened may well be a lifesaver, as these cancers often do not exhibit signs or symptoms until they are no longer curable. Freezing the whole body, or just the head, for hopeful revitalization has a market and a rationale, but a whole host of obstacles make the technological feasibility of returning in the future uncertain. Personalized medicine, utilizing genomics and other technology, is the future of medicine. The 'one size fits all' approach to population-based medicine has been a disaster that the public is, for the most part, unaware of.

The cover of Time magazine prophesizing 2045 as the year man becomes immortal is based on the concept of singularity, downloading your consciousness and brain onto a computer cyborg equivalent. This will probably become an option, to have a virtual life and existence, with equally complex moral and social choices. The possibility of becoming an electronic mind reminds me of a cartoon image of a janitor unplugging a complex life support technology to plug in his floor polisher.





Patient Advocacy - A Step in the Right Direction
San Francisco Chronicle February 22, 2017

By Deepak Chopra MD, Lizabeth Weiss, BA, Nancy S. Cetel, MD, Danielle Weiss, MD, Joseph B. Weiss, MD

When the average American goes to the doctor, shows up at the ER, or enters the hospital, the risks and complexities of our healthcare system strike home vividly. Besides the expense of care and the intricate tests and procedures a patient faces, there is a widely under-reported risk of medical mistakes and "adverse events," as they care called, which can range from minor to disastrous.

The new idea whose time has come is the patient advocate, someone who represents the patient's best interest in any medical situation. An advocate might be a well-meaning relative who helps an older patient understand what's going on, stepping in to do attendant tasks like picking up prescriptions and organizing medical bills. But more and more we see the need for an advocate who is professionally trained to buffer the mounting risks in a healthcare system where less and less time is spent between doctor and patient, raising the possibility of a wide range of bad outcomes.

What the patient is all too aware of is the doctor visit that goes by in the blink of an eye. A 2007 analysis of optimal primary-care visits found that they last *in toto* 16 minutes on average. From 1 to 5 minutes is spent per topic discussed. Although a visit to a primary-care physician or specialist has increased to 20 minutes, a shift in a doctor's workload in recent years, some of it mandated by law, finds more time being allocated to computer and desk work, such as entering data in the Electronic Health Record (EHR).

The actual face-to-face time with a doctor or other health care provider actually comes down to 7 minutes on average. Therefore, a patient advocate clearly has a huge gap to fill. The advocate can begin by simply observing the visit or procedure to make sure that simple mistakes and errors in communication don't occur. Many of these are unavoidable byproducts of nurses changing shifts, hospital doctors on rotation, etc.

But in an aging population, the advocate's efforts become even more critical. An advocate can take time to take a detailed patient history, something often lacking in our rushed system. They can translate information into the patient's first language as needed, calm nerves in the stressful and unfamiliar surroundings of a hospital or clinic, and thereby bring to the fore the questions and answers that need to be transmitted. In the stress of a medical event, it's very common for patients, particularly the elderly, to be so flustered and anxious that they forget to ask important questions or give important information.

Not everything is potentially positive if patient advocates become a standard part of health care. If they have their own agenda because their employer is a hospital or insurance company, the patient's best interests may not be uppermost. One anticipates antagonism between the advocate and the doctor, who isn't used to third-party input and values his autonomy. And if the advocate isn't calm, professional, and common-sensical, adding another anxious person in the examining room would be a detriment.

Still, we feel that the benefits far outweigh the potential downside. The key is for advocates to be accepted as a positive extension of the existing system, not an opposition party. A concerted effort to standardize a curriculum and certification for advocates is now being developed. It needs all the support it can get. The creation of an educated, licensed workforce of professional advocates can and should be an integral part of improving the safety and efficacy of our national health care. With your eyes now opened, you'll see how great the need is the next time you need to see the doctor.

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All of Us - Doctor and Patients - Need to Face Up to Healthcare Hazards
San Francisco Chronicle, February 15, 2017

By Deepak Chopra MD, Nancy S. Cetel, MD, Danielle Weiss, MD, Joseph B. Weiss, MD

Medical mistakes are a touchy subject in the medical community. Both sides of the healthcare system fear them - patients because of their general anxiety about going to the doctor, physicians because of the looming threat of malpractice. The situation needs to be faced squarely, with candor and above all, with reliable statistics. These have varied widely over the years. While the numbers of fatalities reported annually in US hospitals has had estimates from 44,000 to 440,000, even the lower estimate is a public health catastrophe.

We say this against the background of the vulnerable position even the best cared for patient faces. Entering the hospital represents a loss of freedom, exposure to anxiety-producing procedures, a sterile environment, and being handled, physically and emotionally, by strangers. Adding medical mistakes to the list must become unacceptable.

At present, however, preventable mistakes continue to persist and are often graver. Several publications over the past two dozen years, including our own, have highlighted the alarming frequency and consequences of adverse events during medical treatment. Among the most credibly researched and analyzed findings are the following:

- The US Department of Health & Human Services, Office of the Inspector General, reported that a review of in-patient records from 2008 confirmed 180,000 fatalities occurred in the Medicare population alone, because of medical errors.
- A 2013 evidence-based estimate, using a weighted average of 4 databases, suggested that the current range of annual deaths in US hospitals from adverse events was between 210,000 to over 400,000.
- Most recently, in 2015, journal authors from Johns Hopkins estimates the number as over 250,000 deaths per year, making hospital errors the third leading cause of US hospital deaths after heart disease and cancer.

Regarding the last citation, Dr. Martin Makary, Professor of Surgery and Health Policy at the Johns Hopkins School of Medicine, comments that medical care gone wrong is commonly due to “a communications breakdown, poorly coordinated care, or a misdiagnosis,” but these are rarely mentioned when a doctor fills out “primary cause of death” on a death report.

As a result, Makary notes, “these are issues that have lived in locker rooms, doctors’ lounges, and nurses’ stations…in the form of stories and not epidemiological errors.” A recent review of 4,000 medical journal articles showed that even the most accurate medical record review protocol identified adverse events in 2.9% to 18.0% of records, with preventable errors identified in 1% to 8.6% of records. Although alarming in its own right, this number is a significant underestimation of the true frequency of errors. In a telling report that interviewed nearly 1,000 patients in Massachusetts 6 to 12 months after discharge, patients recalled three times the number of adverse events reported in the medical record.

The many reasons why errors would be underreported is all too readily apparent. Avoidance of identification, liability, blame, guilt, financial penalty, malpractice action, job security, disciplinary action, hearings, reviews, etc. are just some of the powerful motivations to avoid reporting an error. Surveys of physicians confirm the obvious, that under-reporting is widespread. Yet without accurate statistics the full extent of the endemic problem, as well as the ability to monitor efforts to reduce errors, cannot be

accurately assessed. Human error is inevitable, but every effort must be made to minimize the risk and consequences.

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One Solution to America's Health Care Crisis
San Francisco Chronicle, January 11, 2016

By Deepak Chopra, MD, Rudolph E. Tanzi, PhD, Joseph B. Weiss, MD, Nancy Cetel Weiss, MD, and Danielle E. Weiss, MD

Complications in medical care occur at a staggering rate, resulting in over 440,000 accidental deaths from medical errors (the vast majority not considered malpractice, such as side effects from drugs) in U.S. hospitals each year. Self-governance by health systems and providers has not made significant inroads to reduce this catastrophic failure in patient safety. The inefficient and expensive medical malpractice lawsuit industry has neither reduced nor prevented the ever-growing numbers of medical injuries and death, nor provided compensation or justice to the vast majority of those injured.

The main beneficiaries of malpractice lawsuits are the attorneys, whose contingency fees can lead to multimillion-dollar windfalls, and insurance companies collecting high malpractice premiums. They profit at the expense of others and contribute to the continually escalating costs of medical care. The vast majority of medical injury and death does not result in a malpractice claim, and of those filed most fail at trial. In spite of this high failure rate, malpractice actions have worsened the situation by further encouraging excessive, expensive, and higher risk care under the rationale of defensive medicine.

Both our health and medical malpractice systems are severely dysfunctional and in critical need of corrective action. There is a better approach that can reduce medical errors and injury, enhance patient safety, and provide timely and fair compensation to those injured. A no-fault medico-legal compensation program should replace the present malpractice system with dedicated judges and expert panels to award compensation based on injury and need. Health care service providers should fund the program by the mandatory assessment of a fee that replaces malpractice insurance, based on a formula that incorporates practice type, volume, revenue, and quality assurance outcomes records.

Health care licenses should be issued based on results of the quality review, including input from reports of the error compensation program. Licenses of negligent and error-prone providers should be suspended or revoked on a national basis, with mandatory re-education and reassessment before being allowed to resume patient care. The billions of dollars consumed by the industry of medical malpractice lawsuits and insurance should be redirected to serve those injured, and to programs and services enhancing patient safety and welfare.

Most importantly we need to proactively and aggressively address medical errors at the source, and correct the existing health care and malpractice system that contributes to the ongoing catastrophic status quo. The dysfunction is multifactorial and includes poor communication, incomplete data and records, and a system designed for population-based treatments that ignore the unique characteristics of each patient. The system needs to be redesigned to place patient safety and health outcomes as the singular priority, and to embrace the coming paradigm shift of personalized precision medicine.

The present health care system is also deficient in that it allows health care providers to be lax in incorporating new information into their practice of medicine. Recertification, educational programs, and examinations should be available, with participation actively encouraged by being inclusive in the health professional licensing fee. The individual health professional can select self-education or participation in formal course programming, but time-limited licensure to practice in any health care discipline should require ongoing demonstration of competence. The licensing examinations and demonstration of clinical competence should be under national standards, and removed from agencies such as specialty boards that may have a conflict of interest such as limiting practitioners under the guise of quality, but in actuality engaging in the restraint of trade.

While the above suggestions can make a meaningful reduction in medical errors, as well as provide reasonable and reliable compensation to those insured, a more holistic solution is dawning. We as a society need to recognize that a once in a lifetime historic paradigm shift in medicine is taking place, with more efficient and safer therapy on the horizon. As the knowledge base expands exponentially, our old population-based medicine with one-size fits all approach has been exposed as a weak approximation of optimal care. The number of adverse events, fatalities, and disabilities that have resulted from the focus on the treatment of the 'average' patient highlights how primitive the approach has proven to be. Even the present medical malpractice system has supported this dysfunction by the acceptance of a 'standard of care defense' that excuses harm because it is commonplace.

The vast majority of the extraordinary health care expenditures today are on the treatment and management of existing and chronic disease. The critical importance of public health and preventive medicine, with an emphasis on healthy lifestyle choices and disease avoidance, has been severely underfunded. The multiple descriptors of healing arts as complementary, integrative, and alternative are not mutually exclusive. They are now scientifically evaluated, with proper and efficient therapy consolidated under the umbrella of medicine. Acupuncture, meditation, exercise, diet, nutrition, rest, laughter, yoga, are being rediscovered by science and included in the armamentarium of contemporary modern medicine.

The new era of a safer and more efficient form of the healing arts and sciences is due to the dramatic advances in the life sciences, the result of a remarkable confluence of technology, knowledge, and insight. The ability to sequence genes and completion of the Human Genome Project has opened an ever-expanding horizon into the understanding and treatment of disease. The recognition of the profound role of epigenetic factors, the environmental influences that alter gene behavior and function, further amplifies these breakthroughs. The extraordinary importance of the microbiome, the trillions of organisms that reside within and on our bodies, in human health and disease is at the forefront of scientific exploration. Stem cells, regenerative medicine, biotechnology with organ replacement, gene transfers to replace defective genes, personalized precision medicine with prescriptions tailored to the individual, and a cornucopia of advances are opening vistas to a safer and more effective approach to maintaining health, prevention, and curing disease.

Personalized precision medicine will integrate the latest breakthroughs in technology and the life sciences with the rediscovered and newly appreciated wisdom of other healing arts and science. A recently published book *Super Genes: Unlock the Astonishing Power of Your DNA for Optimum Health and Wellbeing (*Harmony Books 2015) by Drs. Deepak Chopra and Rudolph Tanzi, provides a clear look at the groundbreaking advances in the life sciences. The book provides a holistic approach that integrates the rapidly advancing states of knowledge in a broad range of disciplines that are interdependent for optimal health, into a readable and proactive guide for the general public.

While the advances and enhanced safety will become integrated into the standard of medical care over the coming years, the patient and health care provider must remain vigilant partners in avoiding and reducing medical errors. The health of the public and the individual is dependent on a knowledgeable population of health care consumers, as well as health care professionals. Those without sufficient experience to make informed decisions about their care in today's complicated heath care system should have access to the guidance and advice of medical advocates.

The empathy and compassion of a caring health care provider have been negatively impacted by ever-increasing stress leading to epidemic rates of 'burnout'. The loss of health care providers to this disabling malady aggravates the already critical shortage of health care providers. The degree to which stress and fatigue contribute to the extremely high error rate in health care requires further investigation into the

implementation of effective strategies for its management. The prevention of the loss of empathy and burnout would not only provide benefits in health care but in other relevant fields and aspects of society such as education, justice, business, etc.

As Dr. Francis Peabody so eloquently stated over one hundred years ago “the secret in the care of the patient is in caring for the patient.” All of society needs to care, health care providers, lawyers, insurance companies, health systems, and pharmaceutical companies included. Patient care and safety must become a non-negotiable priority. Human health and welfare are too important to allow any self-serving interests to detract from this moral and societal obligation.

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A Hidden Solution to America's Health-Care Crisis
Huffington Post June 25, 2016

By Deepak Chopra, MD, FACP, Dan Blumenthal, MD, MPH, FACP, David Brenner, MD, FACP, Nancy S. Cetel, MD, Linda L. Hill, MD, MPH, FACP, Bess Marcus, PhD, Paul J. Mills, PhD, Sheila Patel, MD, Larry Smarr, PhD, and Joseph B. Weiss, MD FACP

American health care is caught in a vise, which has created a dire situation. The squeeze comes from the positive gains in life expectancy on one side and unsustainable medical costs on the other. Meanwhile, headlines are being grabbed by crises as serious as the outbreak of Ebola, vaccine-preventable diseases such as measles, and an obesity epidemic. Hence, our call for a dose of preventive medicine.

Our health care costs are almost 150% as much per capita as the next most expensive health care system, Norway. And what do we get for this lavish outpouring of an estimated three trillion dollars a year? In rankings by the Commonwealth Fund of 11 western countries, the US ranked last in quality and health outcomes. And over the past fifteen years, preventable hospital deaths in the US due to medical errors in treatment quadrupled from an estimated 110,000 to 440,000.

At present, the most effective way to reduce health care costs is by reducing the rate of illness. We have a mechanism in place to do this — preventive medicine. Prevention and health education don't drain the national treasury but provide a strong return on the dollar. For every person who understands how to avoid heart disease, hypertension, and obesity, learns about effective contraception, or who gets health education on the dangers of tobacco and alcohol, the medical system benefits economically, not to mention the gains by humanity.

In 1900, the top three leading causes of death were influenza, tuberculosis and gastrointestinal infections. Thanks to preventive medicine and public health programs, including sanitation and vaccines, the rates of these diseases have plummeted over the last 100 years. Now, however, chronic diseases such as heart disease, cancer and non-infectious lung disease are the leading causes of death in the United States. One-half of adult Americans have at least one chronic disease, and the majority of these are preventable or lessened by the adoption of healthy lifestyles: physical activity, good nutrition and healthy weight, and the avoidance of tobacco. The adoption of these lifestyle factors alone is associated with a 93 percent reduced risk of diabetes, 81 percent reduced risk of heart attack, 50 percent reduced risk of stroke and 36 percent reduced risk of cancer. The acquisition of a positive lifestyle isn't as simple as 'Just Say No', as we have learned the hard way, but requires a concerted prevention and public health approach, incorporated into individual health care, community interventions, and the built environment.

Yet the funding for preventive medicine and public health is minuscule compared to the overall health care budget. Preventive Medicine has been a specialty for over 60 years (American Board of Preventive Medicine), but comprises only 0.8% of the physician workforce. There is an inadequate focus on prevention in medical school curriculum. Physician training in preventive medicine as a specialty is currently in a fiscal crisis due to the lack of training dollars. Medical Centers are reluctant to divert their graduate medical education Medicare training dollars from acute care to prevention, and the federal government's Health Resources Service Administration funds only a fraction of preventive medicine training programs. Despite the gains in access to health care achieved with the Affordable Care Act, including an emphasis on quality of care and improved outcomes, prevention training funds have not followed.

We all need to accept and build a future where prevention becomes a dominant force. Waiting to get sick before going to the doctor makes no economic sense. We need a proactive and prepared health care system to work with health-literate, motivated individuals to attain the widespread adoption of evidence-

based preventive measures. Nutrition, physical activity and stress reduction should be the backbone of a truly integrative, prevention-focused health care system. Without it, health care costs will continue to climb, while, paradoxically, the health of the nation suffers. We need to focus our efforts on the implementation of the vast amount of prevention science already well described. To do this, health care dollars will need to be directed to prevention and public health training programs. Senator Tom Udall and Representative Gene Green are leading this effort in the U.S. Congress. The rewards are potentially enormous.

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Bring Prevention Back from the Brink
San Francisco Chronicle March 5, 2018

By Deepak Chopra, MD, Robert Carr, MD, MPH, Linda Hill, MD, MPH, Nancy Cetel, MD, Joseph Weiss, MD

A crucial fact about American medicine goes largely ignored, even by doctors. Dollar for dollar, more people will gain years of healthy lifespan from prevention than from drugs or surgery. We don't tend to think that prevention costs money. Once you learn that cigarettes cause lung cancer, you can decide not to smoke. The choice is free if you were a non-smoker to begin with. If you get up off the couch and start a brisk walking program to help prevent heart disease, that choice also doesn't cost a penny.

What isn't free, however, is getting information out there. Poor and less educated Americans are known to have a higher prevalence of major lifestyle disorders like heart disease, obesity, hypertension, and type 2 diabetes. The reverse is also true: better lifestyle choices are made by the affluent and well educated.

You can't prevent what you don't know about. That makes it essential that we keep funding the most dollar-wise education for physicians so that young residents can go on to spearhead prevention programs. America cannot continue to rely on a reactionary stance of simply treating health issues. It must refocus its efforts and investments in prevention. The surgery to treat a lung cancer patient is highly unlikely to succeed and will be very expensive. Informing a middle-school classroom about the risks of smoking potentially saves lives at a fraction of the cost.

It's alarming, in the face of these facts, that the President's proposed budget for the fiscal years 2018 and 2019 calls for eliminating funds to Preventive Medicine residencies. Residencies (training programs after medical school) provide the knowledge base, skills, and experience to be experts at preventive medicine and public health. Compared to overall healthcare dollars, these programs cost pennies. It's unreasonable, inefficient, and against the public interest to cut these residencies.

Prevention is neither glamorous nor lucrative, but its importance is greater than ever. While the 20th century saw the average lifespan increase by 30 years (thanks to vaccinations, controlling infectious diseases, declines in heart disease, motor-vehicle safety, and reductions in smoking), life expectancy has now declined in this country for two consecutive years. Medical costs continue to rise, and serious new threats arise like the opioid epidemic, the Zika virus, and the decreased effectiveness of standard antibiotics.

Health care spending is out of control, which worries everyone. There is no medical argument against prevention as the best way to dramatically reduce the nation's medical bill. Who will avoid the ill effects of obesity? The person who doesn't gain weight to begin with. How do you increase the number of these people? Good habits go viral in a society, and so do bad habits. Teach the good habit of sensible eating on a wide basis, and you can start a lifestyle movement that will be set for coming generations.

America faces a serious problem over income inequality. The richest are getting richer while average income barely increases or stagnates for decades. When a Rolls-Royce passes you on the road, it's easy to see who's prosperous. Information inequality, however, is invisible, and far more crucial. The world's most expensive car won't add years of healthspan, which is a better measure than simple lifespan. Living longer when you're sick or disabled is not as valuable as a longer healthy life.

The average life expectancy in the U.S. is now 79.3 years, but there is no reliable statistic on how many of those years are healthy. What is known, however, is that the onset of major disorders of old age is either the same as in the recent past or getting worse. As more people live longer, they need to get sick at a later age, and that's not happening.

Yet the concept of healthspan is just now catching on in the general public, a prime example of why information is critical.

The future of preventive medicine in this country will be threatened if lawmakers don't take action. You must contact your members of Congress today and ask them to join two champions of prevention in Congress, Representative Gene Green and Senator Tom Udall—they are leading the fight for funding residencies in preventive medicine.
American healthcare costs are nearly three times developed countries, but our life expectancy is shorter than 30 other nations. We all need to build a future where a culture of prevention becomes a dominant force. The Center for Disease Control (CDC) acknowledges this; the science is there; the economic benefits are clear. What's needed now is to get Congress to do the right thing.
Deepak Chopra MD, FACP, founder of The Chopra Foundation and co-founder of The Chopra Center for Wellbeing, is a world-renowned pioneer in integrative medicine and personal transformation, and is Board Certified in Internal Medicine, Endocrinology and Metabolism. He is a Fellow of the American College of Physicians and a member of the American Association of Clinical Endocrinologists. Chopra is the author of more than 80 books translated into over 43 languages, including numerous New York Times bestsellers. His latest books are *The Healing Self* co-authored with Rudy Tanzi, Ph.D. and Quantum Healing (Revised and Updated): Exploring the Frontiers of Mind/Body Medicine.
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Dr. Robert Carr is President of the American College of Preventive Medicine, retired Corporate Medical Director with GSK, and runs a family foundation focused on population health. Dr. Carr is also Associate Professor at Georgetown University's newly established Executive Master's program in Health Systems Administration. Dr. Carr received his Doctor of Medicine from the University of Miami School of Medicine and his Masters of Public Health and Preventive Medicine Residency from The John Hopkins Bloomberg School of Hygiene & Public Health. Dr. Carr chairs the Occupational Residency Advisory Committee at the University of Pennsylvania, is on the Health Advisory Board at Johns Hopkins Bloomberg School of Public Health and the Dean's Advisory Board at the Drexel School of Public Health.

Dr. Linda Hill is a Professor in the Department of Family Medicine and Public Health at UCSD. She is the Director of the UC San Diego Training, Research and Education for Driving Safety (treds.ucsd.edu), Director of the Center for Human and Urban Mobility, Director of the UCSD-SDU General Preventive Medicine Residency, and senior staff physician at SD Family Care. She is immediate past-president of the California Academy of Preventive Medicine. She is engaged in prevention research and teaching with current/past support from the NIH, the California Office of Traffic Safety, Robert Wood Johnson, American Cancer Society, and Health Services Resource Administration, and the AAA Foundation for Traffic Safety, including research in injury prevention, driving safety, obesity, decision making, compliance, physician training, physical activity, and refugee health. Dr. Hill is a graduate of the University of Ottawa School of Medicine, with post-graduate training at McGill, UC San Diego and San Diego State University.

Nancy S. Cetel, MD, is President and Founder of Speaking of Health and specialist in women's health and reproductive endocrinology.

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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

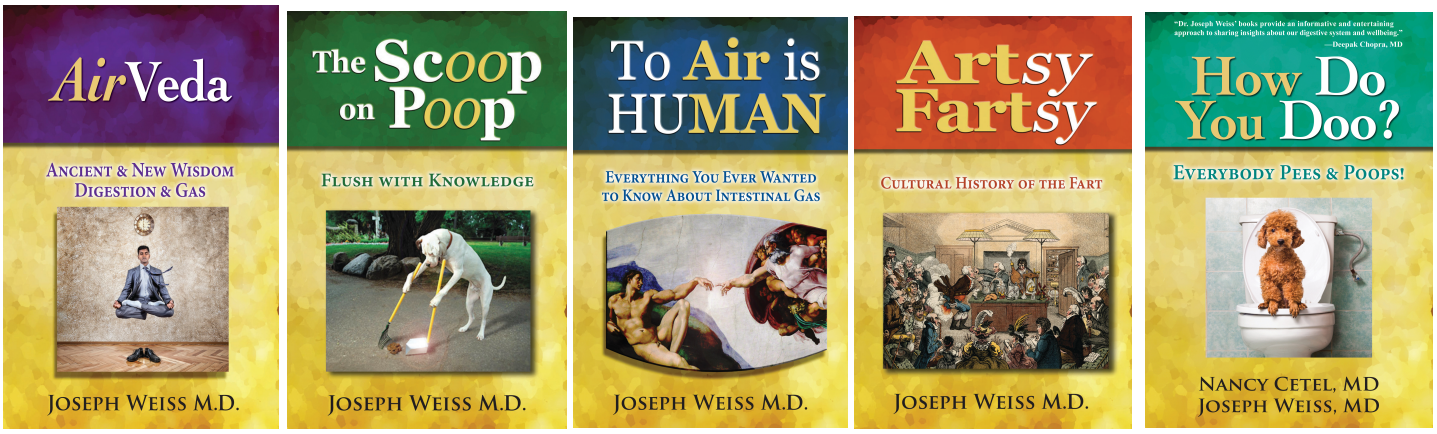
He is the author of more than a dozen books on health (www.smartaskbooks.com) and has had numerous papers published in prestigious national and international medical journals, as well as in the lay press. Dr. Weiss is also an accomplished humorist and professional speaker having given over three thousand 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.

"Dr. Joseph Weiss' books provide an informative and entertaining approach to sharing insights about our digestive system and wellbeing." ***Deepak Chopra, MD***

"Joseph Weiss, M.D. has a gift for books that are uniquely informative and entertaining. **Jack Canfield**
Coauthor of the Chicken Soup for the Soul® series



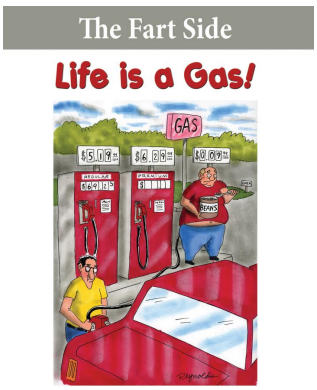
The Scoop on Poop! Flush with Knowledge is a uniquely informative tastefully entertaining, and well-illustrated volume that is full of it! The 'it' being a comprehensive and knowledgeable overview of all topics related to the remains of the digestive process. Whether you disdain it or appreciate it, it is part of the human (and animal) experience. The purpose of this volume is to share rarely discussed but very important knowledge about the important role of digestion and the gut microbiome in human health and wellness www.amazon.com/Scoop-Poop-Flush-Knowledge/dp/1943760004

AirVeda: Ancient & New Wisdom, Digestion & Gas covers the remarkable advances in the understanding of digestive health and wellness from Ayurveda to genomics and the gut-brain-microbiome-diet axis. The knowledge gained opens new avenues to optimal health and wellness. www.amazon.com/AirVeda-Ancient-New-Wisdom-Digestion/dp/1943760128

To 'Air' is Human, Everything You Ever Wanted to Know About Intestinal Gas covers everything you ever wanted to know about the burp, belch, bloat, fart and everything digestive but were either too afraid or too embarrassed to ask. This volume is overflowing with practical information, fascinating facts, surprising trivia, and tasteful humorous insight about this universal phenomenon. amazon.com/Air-Human-Everything-Wanted-Intestinal/dp/1943760020

Artsy Fartsy, Cultural History of the Fart is a fascinating and colorful review of the fart through human culture and history. A cough, sneeze, hiccup, stomach rumble, burp, belch, and other bodily sounds simply cannot compete with the notoriety of the fart. Whether encountered live and in person or through the medium of literature, television, film, art, or music it may leave a powerful and lingering memory. www.amazon.com/Artsy-Fartsy-Cultural-History-Fart/dp/1943760039

How Do You Doo? Everybody Pees & Poops! A delightfully informative, entertaining, and colorfully illustrated volume with valuable practical insights on toilet training. Tasteful color photographs and illustrations of animals answering the call of nature allows the child to understand that everybody does it! Additional informative relevant content to entertain the adult while the child is 'on the potty' is included. www.amazon.com/How-Do-You-Doo-Everybody/dp/1943760063



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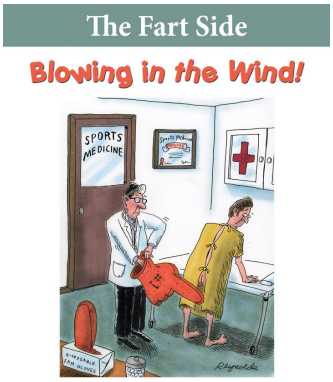

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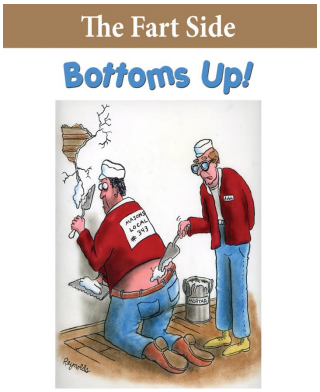

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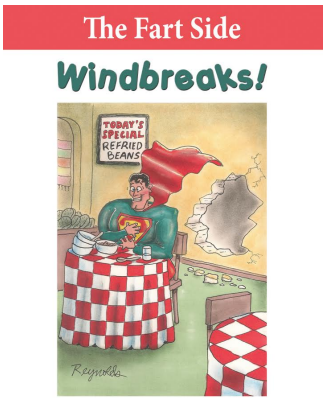

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The Fart Side series is an enjoyable and informative collection of tasteful hilarious cartoons, fascinating factoids, and obscure trivia that will entertain and enlighten. Combining the award-winning talents of both a master cartoonist, and a physician professor, the volumes are proof that **'Laughter is the best medicine!'** The compact Pocket Rocket Edition! is 5" x 7", 96 pages, with 62 images and full color cartoons. The Expanded and Full Blast Edition! is 6" x 9", 122 pages, with 70 images and full color cartoons.

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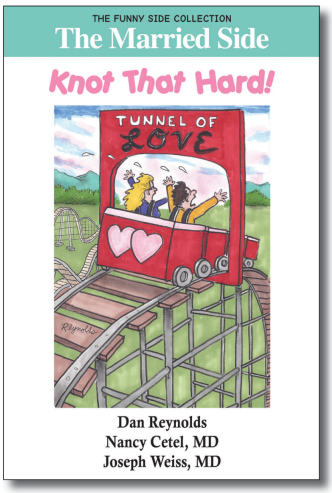

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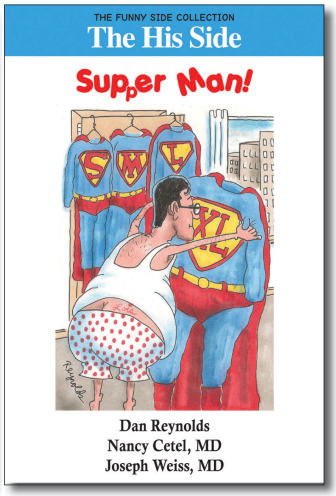

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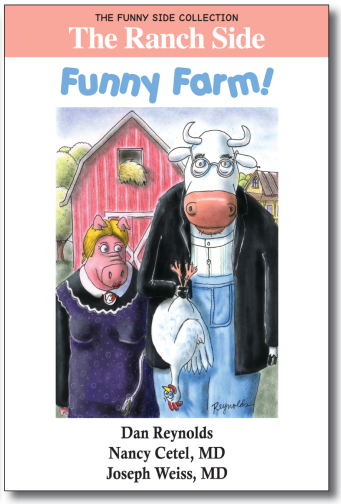

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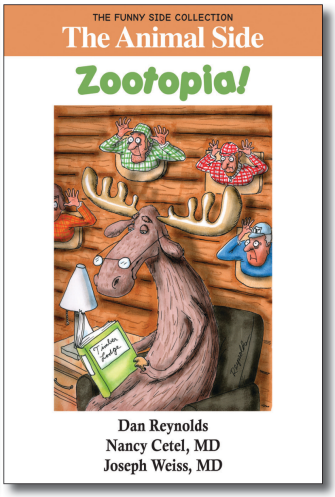

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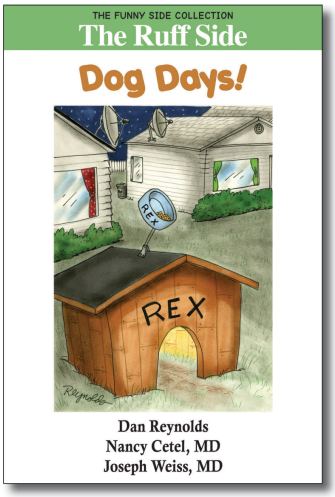

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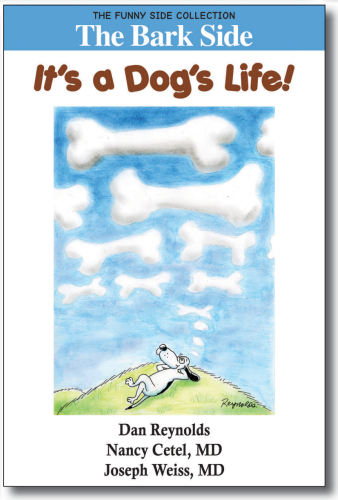

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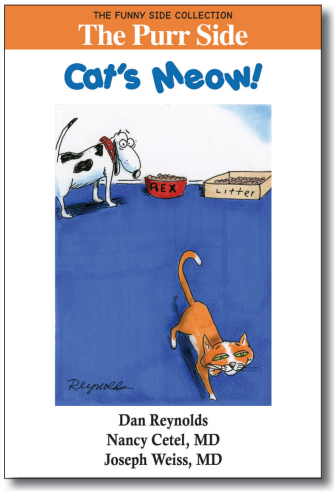

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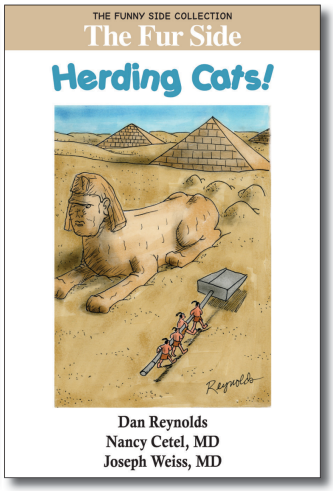

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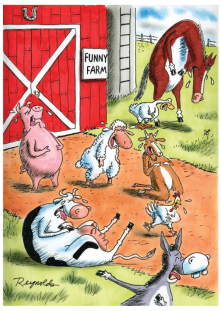

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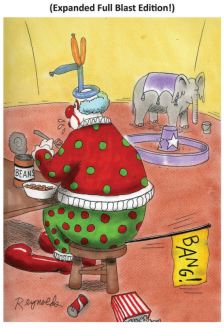

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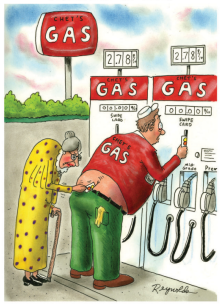
The Fart Side

Life is a Gas!

(Expanded Full Blast Edition!)



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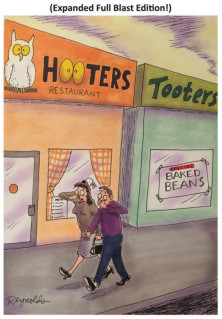
Windbreaks!

(Expanded Full Blast Edition!)



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