To Fast or Not Too Fast:
Fasting: Intermittent vs. Mimicking

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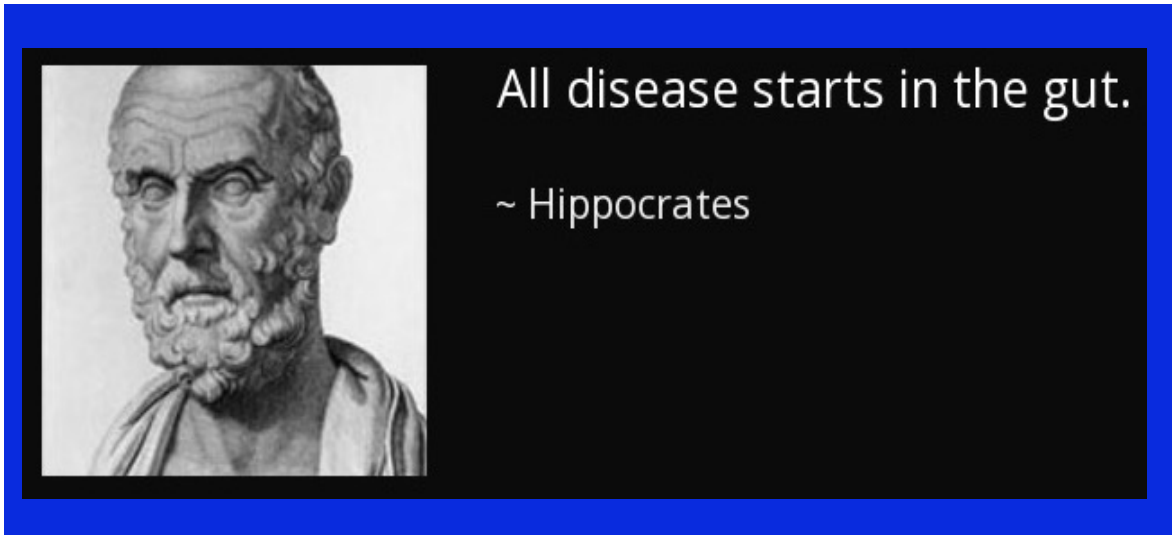
"Beware of false knowledge; it is more dangerous than ignorance" ~ George Bernard Shaw

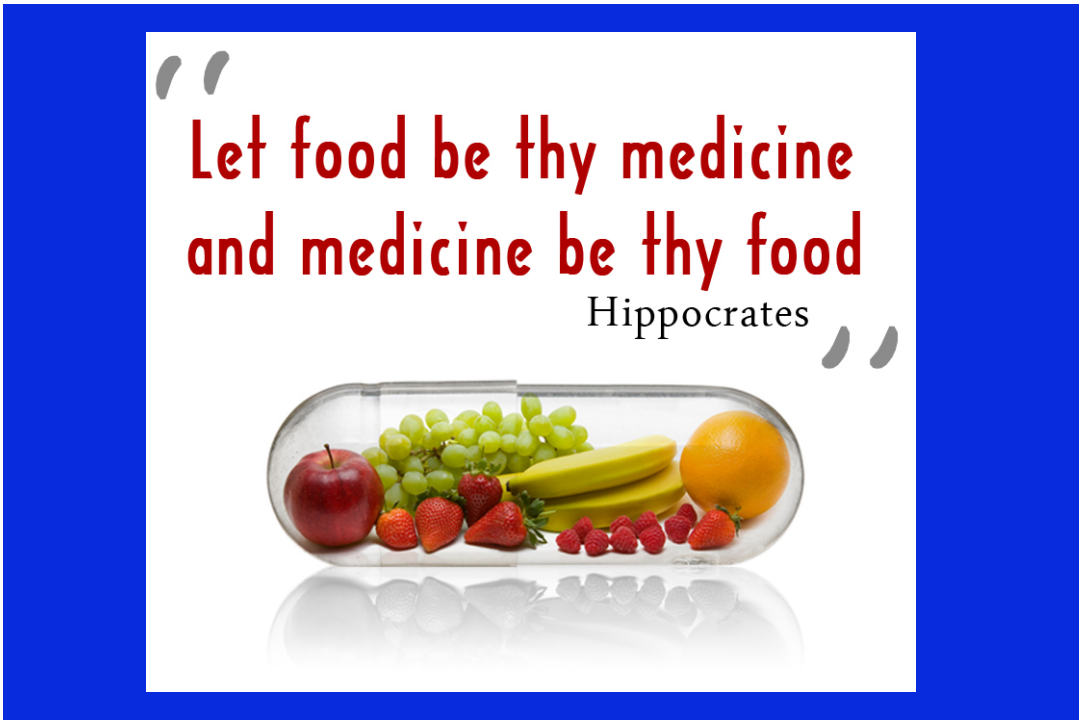
"There are two ways to live your life: One is as though nothing is a miracle. The other is as
though everything is a miracle." ~ Albert Einstein

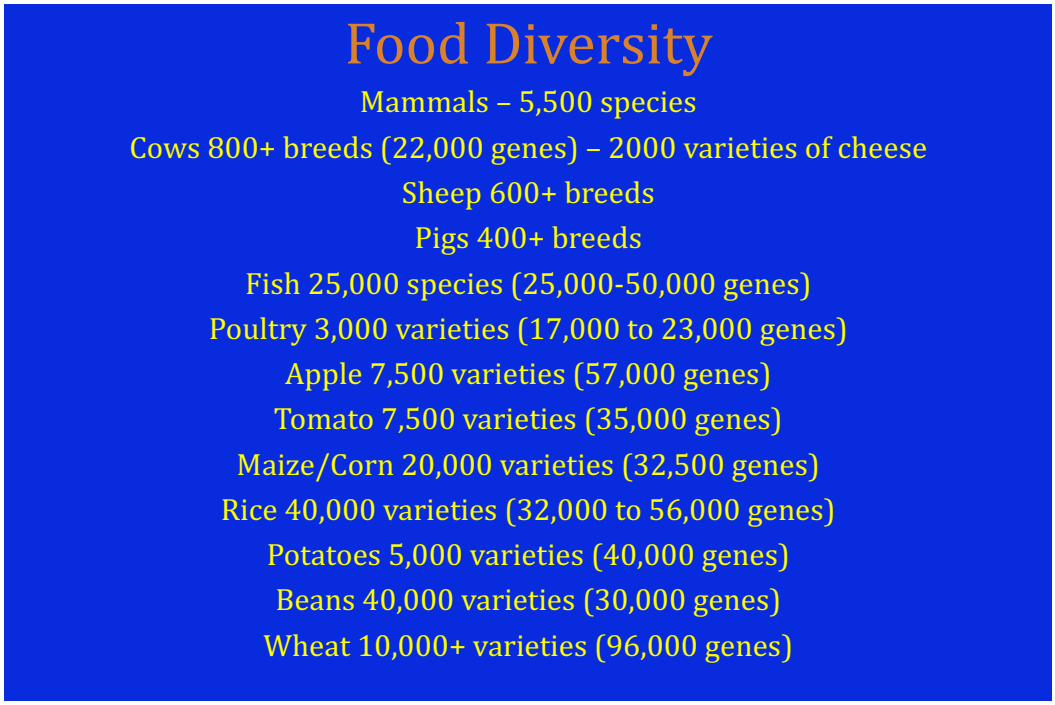
Humans are complex superorganisms that include other non-human species in the gut microbiome. Genes are shared between organisms and influenced by environmental epigenetics.
New understanding of the complex relationship between diet, microbiome, genomics, and human health and well-being opens new avenues to advance health and vitality through optimal nutrition acquired by embracing good eating habits.

Human health, well-being, and life itself is dependent on good nutrition. The role of the diet, and the interactions between the disciplines of food science, genomics, gut microbiome, psychology, biochemistry, physiology, and others have made extraordinary contributions and advances to our understanding. Technological innovations such as advanced gene sequencing have demonstrated how all life forms on planet Earth are interrelated by the universal language of DNA and RNA, sharing over twenty percent of their genes with others. The recognition that horizontal gene transfer is ubiquitous and allows for the introduction of genes outside of the direct inheritance mode of vertical gene transfer has revolutionized the field of genetics. The CRISPR tools for horizontal gene transfer found in microbes are opening new horizons in human medicine for gene therapy.



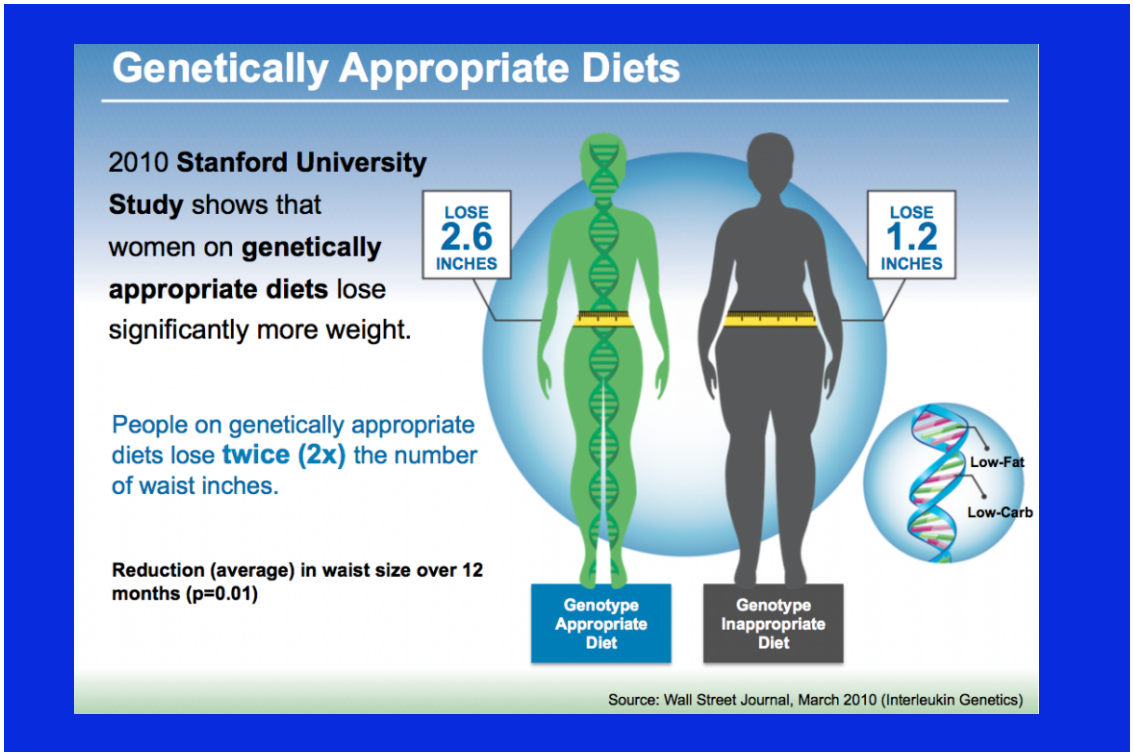
The wide diversity of food sources has its own intrinsically striking genetic diversity, with millions of genes directing the creation of unique metabolic products and chemicals that can affect human health and well-being. The vast majority of these molecules have yet to be identified and analyzed. Even common beverages consumed habitually like tea and coffee have hundreds of phytochemicals and compounds that are incompletely identified, much less understood. On occasion food components and molecules become the focus of intense interest and debate. With publicity the marketing of commercial products and fad diets often result. Lectins, lycopene, lutein, lignans, flavones, catechins, phytoestrogen, resveratrol, carotenoids, beta-glucan, omega-3-fatty acids, and dozens of other components and major subgroups such as probiotics and prebiotics have been popularized.





While an organism may create a chemical for its benefit that serves as a hormone, antimicrobial, attractant, or pesticide this same molecule may have beneficial or detrimental effects on humans. This response may be dependent on dose, time of day or season, frequency, means of exposure, modification by food preparation such as cooking, combination with other foods or products, further metabolism by enzymes or microbes, and dozens of other variables that make its inclusion or exclusion from the diet appropriate. With so many variables leading to an exponential number of combinations it is very challenging for scientific evidence to provide clarity about the benefits and risks of dietary manipulation. The ability of an individual to recognize how their unique body and physiology responds to dietary changes offers a simple and practical way to assess if a change in diet has benefits.

This program will share the current understanding of how these widely divergent disciplines converge to contribute to guidelines for good eating and a healthy diet. With each person a unique individual, it should come as no surprise that individual responses and needs will differ and may well change over time, but the concepts underlying appropriate food and diet selection remain consistent. Further advances in knowledge are to be anticipated, and it is not unusual for long-held beliefs to be challenged or disproved. It is human nature to establish habits, patterns, and beliefs, and when well entrenched as dietary habits often are, they are all the more difficult to modify and change. The psychology of eating and food allows for greater understanding of eating behavior and habits. The emphasis of this program will be on highlighting the science underlying the major roles that genomics, food diversity, food chemistry, food preparation, human physiology, and the gut microbiome contribute to human health. Examples of how these fields have greatly enhanced understanding, with valuable practical clinical pearls to enhance both professional and personal health, will be highlighted.



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

Science and technology of genomics and epigenetics (the factors that influence gene expression) have advanced our understanding of the human organism in evolutionary biology and the life sciences. Genes and epigenetic influence are an active form of communication between humans and all other life forms on the planet, including the microbes that live on and within us (microbiome), the living foods in our diet, and our exposure to the life forms and metabolites in our environment. Humans are not the unique and independent organism we once thought we were, and in fact, to a significant degree we are not even human. 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. Even more surprising is that at least 8% of the human genome has been discovered to be of viral origin.

This program will give you the tools to understand the revolutionary advances that have taken place in the world of genomics, nutrition, metabolism, digestion, food science, and the microbiome. You will have a new understanding of the interactions of the incredibly diverse microscopic world with diet, exercise, and newly identified hormones,

neurotransmitters, gasotransmitters, metabolites, and cytokines. You will gain a deeper appreciation of the profound impact of food, diet, exercise, hygiene, environment, medicines, and more on our microbiome (and vice versa), all contributing to human physical, mental, and emotional health and wellness.

Introduction

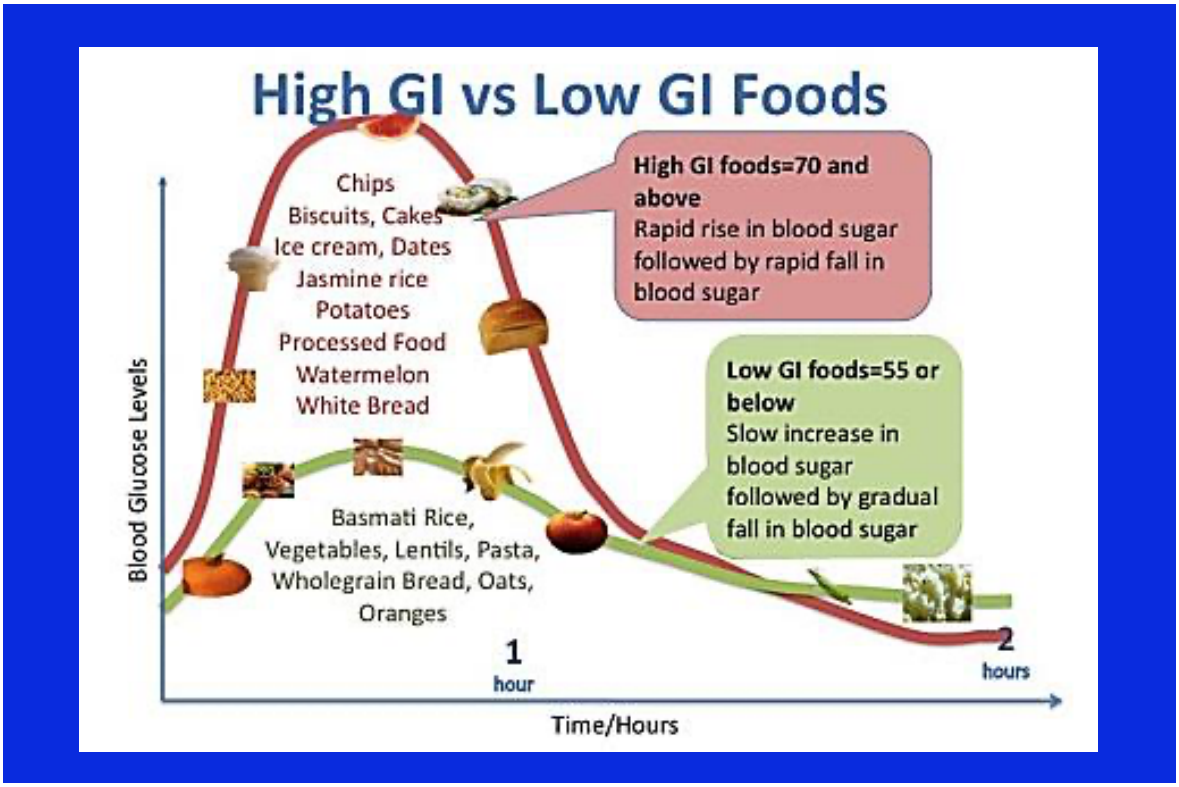
Beliefs may, or may not, be true.
Beliefs that are true are defined as knowledge.
Advances overturning beliefs occur with regularity.
Different perspectives allow multiple viewpoints, each of which may be supported.
It takes effort to release old beliefs and embrace new information and understanding.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

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

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

The higher the glycemic index the more rapidly sugars are absorbed, with blood glucose spikes contributing to insulin peaks and a greater likelihood of diabetes. The microbes of the gastrointestinal tract, the gut microbiome, play a critical role in determining the extent to which calories are extracted from the food ingested. The glycemic index, which used to be associated with specific food types, is now believed to be more closely related to the nature of the gut microbiome. It appears that the microbiome can determine whether a diet

leads to weight increase or decrease, as well as the glucose response which may contribute to diabetes. A number of companies are now offering gut microbiome analysis, with dietary recommendations tailored to the microbiome.

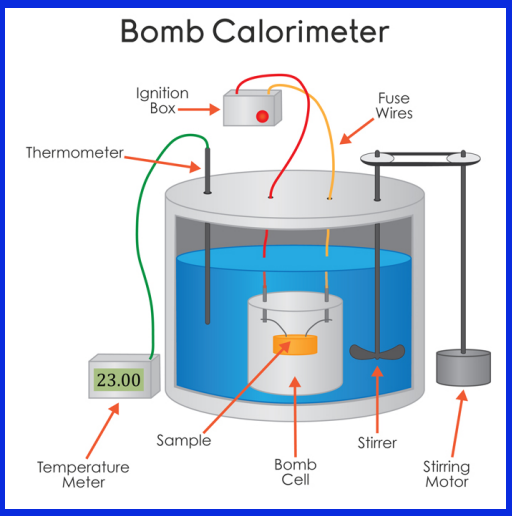


A calorie is a measurement of the energy contained within a food, and a calorie from one food has the same energy value as a calorie from a different food. What is important to remember is that the calorie count of the food is not as important as is the net calories that are absorbed by the body, minus the calories utilized to process and absorb the food. If you ate 100 calories of glucose, a simple sugar known as a monosaccharide, you would not need to expend any energy to digest it, and only a small amount of energy to swallow and absorb it. If it only took 5 calories to process 100 calories of glucose, the net calorie absorption would be 95 calories. Celery has a very low-calorie content, and you expend more energy than the food contains to chew, swallow, digest, and absorb it. If you ate 100 calories of celery, you may burn up 120 calories to process it. You can actually lose energy (and weight) because of its net negative calorie effect.

Protein takes the most energy to digest, with 20-30% of the total calories in protein consumed in its chewing, swallowing, peristalsis, digestion, and absorption. Carbohydrate processing usually utilizes 5-10% of its total calories, and fats only 0-3% of its calories. If simple glucose were packaged in difficult to open containers, theoretically you could lose weight by burning up more calories trying to get to the glucose than the food itself contains. In general, the calories in fat are more likely to be net calories, than the calories from carbohydrates, and the calories from carbohydrates are more likely to be net calories than the calories from proteins.

What is a Calorie???

- A calorie is a unit of measure that indicates the amount of energy we obtain from a particular food.
  - The scientific definition of a calorie is the amount of energy, or **heat**, it takes to raise the temperature of 1 gram of water 1 degree Celsius.



Calorie Density

Protein: 4 calories per gram

Carbohydrate: 4 calories per gram

Alcohol: 7 calories per gram

Fat: 9 calories per gram

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. 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. The villous blunting will also lead to the loss of digestive enzymes that reside on the villi. 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. The condition of Celiac Disease also known as Celiac Sprue or Gluten Sensitive Enteropathy, is an autoimmune response to the gliadin portion of the cereal protein gluten. Gluten is found in wheat, rye, barley, and sometimes oats, and is the protein that hives dough its consistency and texture. For those with Celiac Disease the gluten is toxic to the cells lining the mall intestine and leads to atrophy of the villi with malabsorption and other significant consequences. A gluten free diet is required as the basis of therapy.

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 appears that its major function is to

serve as a reservoir of intestinal bacteria, representing the healthy gut microbiome, from which the gut flora can be replenished after a bout of intestinal dysentery.

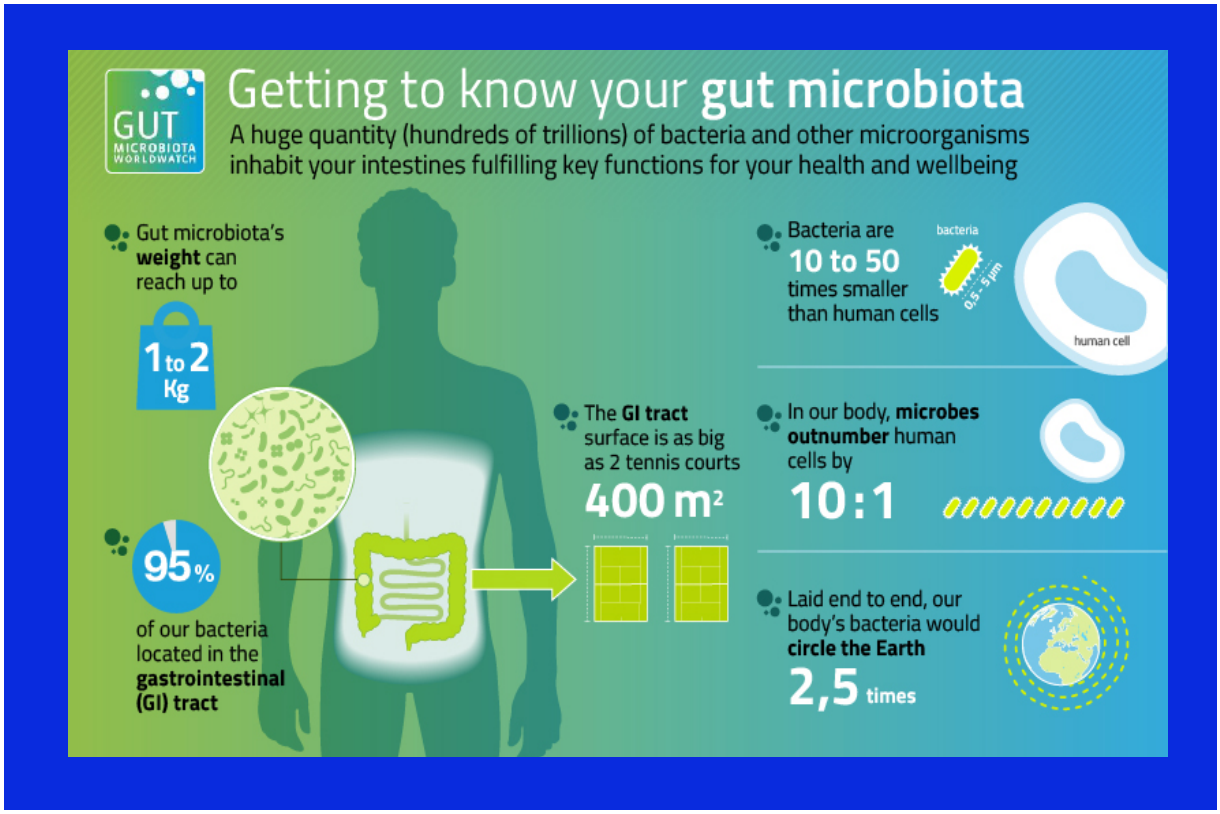
Human hair is just 100 microns thick, but the lining of the digestive tract is even thinner. It is only one cell layer thick, about 25 microns wide and 50 microns deep. At half the width of a human hair, this cellophane-like layer separates your vital body from the external environment. It allows the 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 commonly 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. 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 and are a requirement for our health and well-being.

As efficient as the digestive tract is, a large portion of the energy stored in food is not processed and metabolized by the human system. Undigested food travels through the intestinal tract and is often fermented and metabolized by the gut microbiome. These microbes have the ability to digest and metabolize the food content we cannot, and release absorbable nutrients for our benefit as well as waste products for elimination. Some these metabolites, such as Vitamin K, cannot be produced by humans yet are critical for our survival. It is not an understatement to say that the gut microbiome is as much a benefit to us, as we are to it by providing it with a home and nourishment. The populations and varieties of organisms in the gut microbiome are staggering. The advances in the field of genomics now allows for the identification of organisms that were previously hidden from view or undiscovered. 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 individual. It is also clear that the gut microbiome can be disrupted by illness, change in diet, and in particular following the ingestion of antibiotics.

The role of diet and its interplay with the microbiome extends beyond the food itself. The source of the food, such as when it comes directly from the soil may contribute large populations of microbes from the soil microbiome. Microbes transported by insects such as flies, ants, by pets such as dogs and cats, and even from other humans who share dishes and utensils are commonplace. The food preparation surfaces in kitchens, restaurants, refrigerators, tables, even menus harbor untold microbial populations. There are microbes that travel with the wind from remote locations that can land invisibly on uncovered dishes. Foods which are fermented are purposefully inoculated with microbes, and these are major contributors to the gut microbial population. The cooking process itself leads to chemical and enzymatic reactions that alter the food in ways which may influence the gut microbiome. Besides altering the microbiome cooking and food processing has a dramatic impact on the nutritional value of food, and the metabolites generated may also have significant impacts on human health and well-being.

Besides the important role in digestion and fermentation of food content, the microbiome plays a critical role in human cellular metabolism and function. 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. The gut microbiome has been found to have a dramatic influence on the enterochromaffin cells of the intestinal lining. These cells generate hormones that control appetite and satiety, produce neurotransmitters that affect mood, and cytokines that influence immune function.



The influence of the diet on the microbiome is profound, as 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, etc. are described as a pica, and may be influenced by the microbiome. It is somewhat similar to cravings during pregnancy, where a strong stimulus creates a dietary diversion for pickles. One curious aside is that traditional pickles, sauerkraut, and the Korean fermented cabbage kimchi are very rich in healthful probiotics.

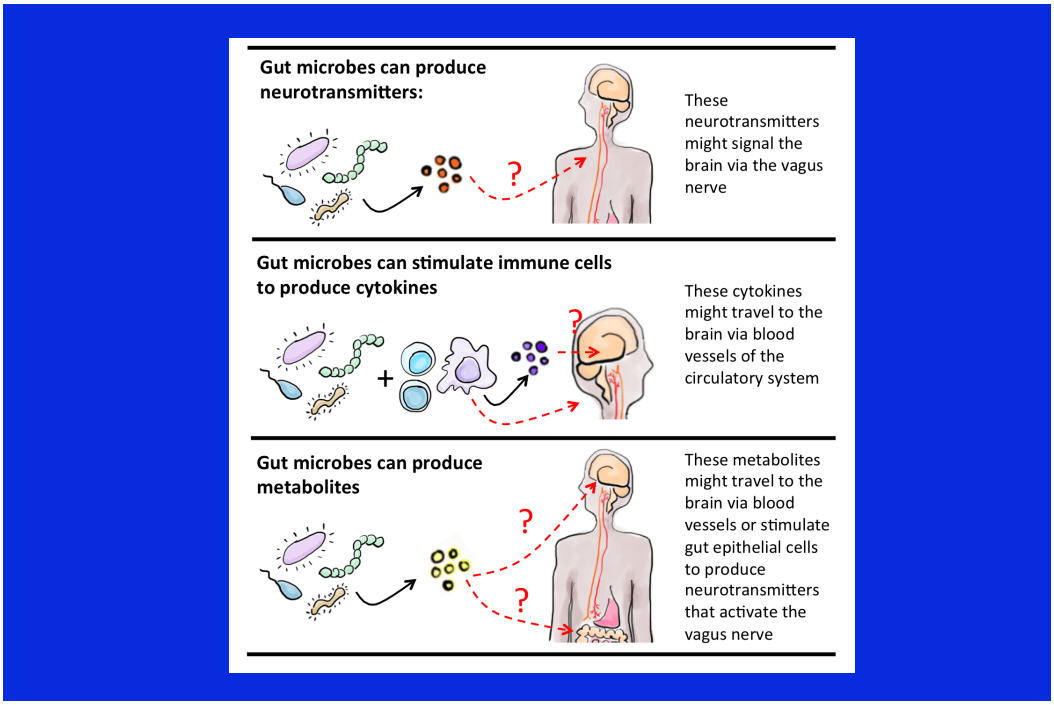
Toxoplasma gondii is a parasitic protist that has a life cycle that is meant to be between cats and mice. The parasite changes mouse brain behavior, markedly increasing its chances of being eaten by a cat, which allows the parasite to complete its life cycle. Hundreds of millions of humans interfere in this life cycle by becoming accidently infected from the infectious form of *Toxoplasma gondii* found in cat droppings, which are ubiquitous. The infection can be fatal to the human embryo, so caution is required to stay away from cats, litter boxes, gardens with cat droppings, etc. when pregnant. There is an increased 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, and it may have served a purpose to increase the chances of a human being eaten by a sabretooth tiger to complete the parasitic life cycle in prehistoric times!

Studies have repeatedly demonstrated that the gut microbiome influences calorie absorption of food, weight balance, and fat deposition. When the microbes of fat and skinny mice were exchanged, their weights changed to correspond to the microbiome even though the diet and exercise were unchanged. The findings of the critical role of the microbiome in weight management give credence to those who have claimed they could not lose weight regardless of what dietary or exercise changes they embraced. Whether the microbiome influences weight via absorption of calories, influence of hormones, metabolites, neurotransmitters, or other mechanisms are as yet unknown. New therapies to help with weight management are to be anticipated as further research identifies the optimal gut microbiome, which may be manipulated by administration of probiotics and prebiotics.

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 have metabolized them releasing byproducts that have nutritive and caloric value for further human digestion and absorption. 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 cellulase to break it down into absorbable sugars. Horses, cows, and sheep have this enzyme, as well as a ruminant digestive tract that contains microbes that can process that form of diet nutrition into simple absorbable sugars. When we eat prebiotic fiber the microbes' ferment and digest it into simpler sugars that we can absorb

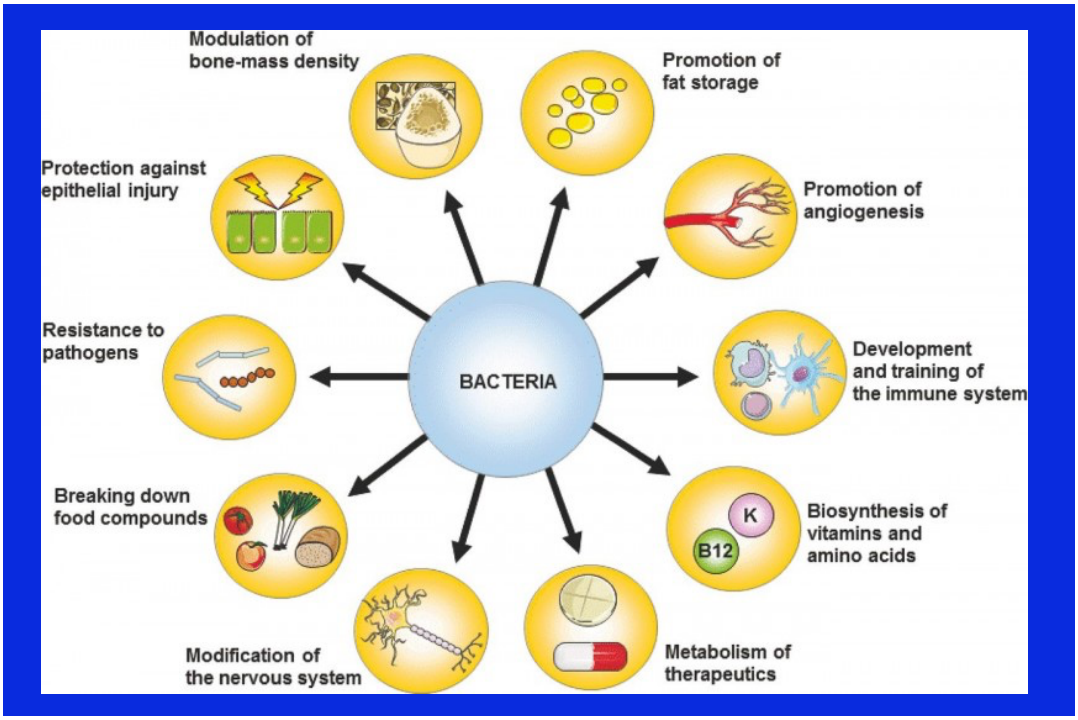
as calories. So even though on paper we cannot digest the prebiotic fiber, allowing it to be labeled as zero calories, the microbes may not have read the label and provide us with additional calories we may not have counted on.

The fields of genomics and the microbiome are expanding very rapidly. We are just beginning to identify and understand which organisms may be associated with various conditions of good or ill health. The concept of systems biology describes complex organisms with a multitude of variables. There are so many variables it is unlikely that additional diseases will be found to have been 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 microbiome it will likely be a variety of microbes interacting with each other in the proper combinations and proportions to have a recipe or formula for optimal health, or when out of balance for illness and disease. The use of genomics and systems biology will hopefully allow the implementation of personalized medicine where diet, microbiome, and medicine can be individualized for optimal outcome.



We are still discovering thousands of previously unidentified microbial species in the gut microbiome. 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, etc. As much as one would like to know what the optimal probiotic to take as a supplement is, science has not yet provided an answer, and that day remains in the distant future. When science does not offer a clear answer, health concerns and products meet in the marketplace with confusion, misinformation, and business opportunities to promote a new industry. The probiotic industry has arrived, for better or for worse.

There is a long history of experience with some of the probiotics that are most popular today. The long track record documented scientific research identifying benefits, apparent lack of adverse reactions, and millions of consumers self-reporting benefits who continue to use these products is sufficient evidence for an individual to consider a therapeutic trial to see if there is a beneficial response. Each individual human is unique, and 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 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, etc. 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 being evaluated per day. The number of candidates is believed to be virtually unlimited. 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, Metchnikoff 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.

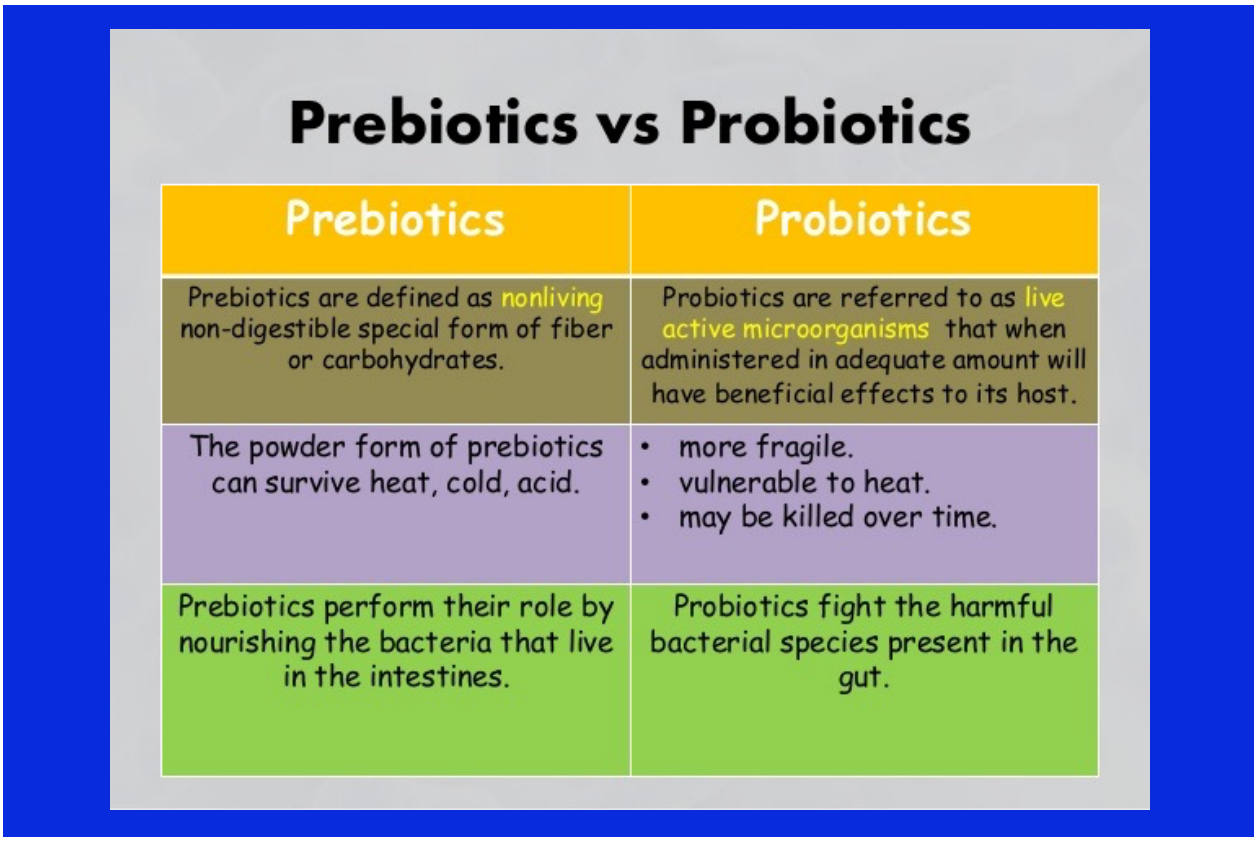
He traveled to Bulgaria to study the large population of centenarians, individuals who lived for a century and beyond. He noted that a common component of their diet was called sour milk, what we describe today as yogurt, and he suspected that this might hold an important clue. The microbe responsible 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 Dr. 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 not only by mouth, but by colonics as well, 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 as a prebiotic for intestinal health, and with his brother founded the Kellogg Cereal Company, which grew into one of the world's most successful enterprises.

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 precision medicine. Unfortunately, at present there is no way other than an individual identifying what works best for themselves by the traditional trial and error approach. The marketplace for probiotics is expanding rapidly with hundreds of products coming to market. Many companies are identifying and patenting subspecies and strains to deter competition and to market their products as unique. There is the minimal regulatory oversight, and the marketing often overpromises and under-delivers. In general, the mantra in medicine is 'above all do no harm'.



Many advocate that mood, depression, anxiety, autism, Parkinson, Alzheimer, mental illness and many other conditions are related to the gut microbiome and may be treated by changing the microbiome by colonics and probiotics. There is now a rapidly growing interest in this approach, with therapies ranging from antibiotics, prebiotics, probiotics, and fecal transplants. The understanding of the healthy and unhealthy microbiome is still at the earliest stages, 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 of 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 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 difficult 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 in North Africa 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 food that may be uncovered at a restaurant before serving, at the picnic table spread, or on your plate.

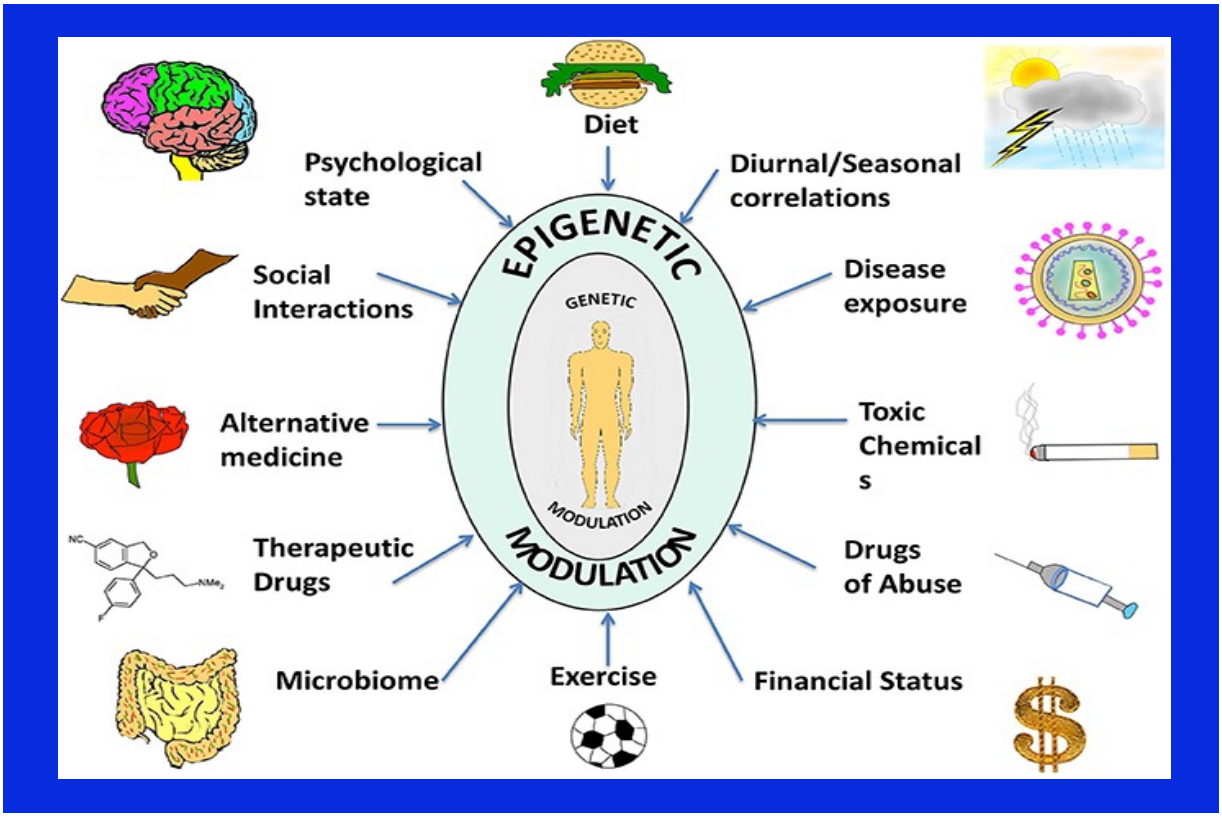
Another near universal source of coprophagia is found in countries like the United States which use toilet paper as the predominant means of anal hygiene rather than a bidet or high tech washlet toilet. The thin porous toilet paper wiped with a bare hand is very effective at transmitting fecal bacteria to the fingers, and then straight to the mouth with finger foods. Hand washing, particularly as practiced in most non-surgical settings is inadequate. For those who have their toothbrush sitting on the bathroom sink counter, it is being sprayed with fecal bacteria with every toilet flush, dramatically so if you don't lower the lid before flushing. Even the avoidance of paper towels and the use of hot air blowers to dry hands in a bathroom may lead to greater spread of fecal microbes because the hot air is contaminated by aerosolized microbes from the flushing toilets.

To offer 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. At restaurants bathrooms are cleaned regularly, but menus are not. The fecal coliform bacteria count of menus is much higher than toilet seats, so wash your hands after looking at the menu, otherwise you have a very good chance of ingesting fecal microbes with the next bite of bread. The good news is that the body has a remarkable immune defense system, and the healthy gut microbiome contributes to the defense against invading pathogens.

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 human’s most discriminating sense. It can pick out and identify an odorant present in a concentration of less than one part in two billion. The other senses including, taste, vision, hearing, and touch are carried by different cranial or spinal nerves.

Each of the hundreds of millions to billions of unique species has thousand to tens of thousands of genes. Each generates a unique protein that has a biological activity designed

to be of purposeful benefit for the source organism. Because of the high number of genes held in common across all life forms there is a substantial likelihood of biological activity in other organisms as well, but the results may be quite different. What may be beneficial to one organism may be harmful to another. The number of biologically active proteins 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 produced and 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 in nature yet to be discovered, or using chemical design synthesized. While the odds of finding a novel beneficial treatment is low, the numbers screened are so high that success is virtually assured. High throughput screening is now able to analyze hundreds of thousands of chemicals each day, and new targets are identified as research in the life sciences continues to expand.



Although not as astronomical as the numbers of chemicals, the number of species of microbes that are potential probiotics numbers in the millions. Even within a species there are tremendous variations in the biological activity of various subspecies and strains, so the potential number of probiotics is even a magnitude greater. The search for novel organisms and bioactive chemicals is extremely active and productive, as the potential value of a product identified and patented is significant. One of the more interesting recent success stories is an expedition to the isolated Easter Islands of 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 named Rapamycin in honor of the island.

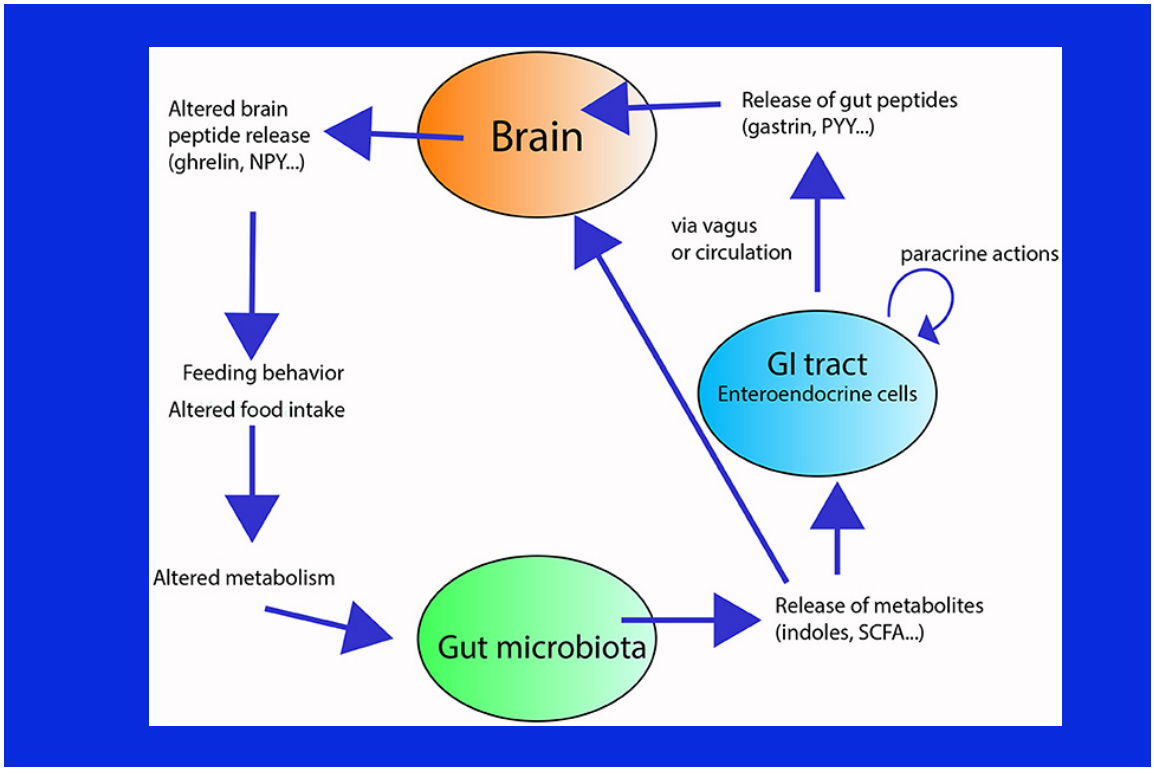
It was found to suppress the immune response to transplanted organs and was developed as an antirejection pharmaceutical with FDA approval. Further study of the roundworm *Caenorhabditis elegans* discovered a unique gene that the pharmaceutical had as a specific target. The gene was named m-TOR, which 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 associated with biological aging. In the roundworm, the inhibition of the M-TOR gene with the drug rapamycin 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 the roundworm and humans, 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. The diet also contains 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 US 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 the common fertilizer used in organic food production.

The number of chemicals found in other life forms and the environment that is toxic to humans also 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. With over 37 trillion human cells and over 100 trillion cells in the human microbiome, and with the average cell performing between thousands to millions of reactions per second, the metabolic activity that is continuously ongoing to maintain life is mind-boggling.

The brain contains over one hundred billion neurons with over 100 trillion 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. It is clear that the visual, auditory, gustatory, olfactory, and tactile sensations of food and drink provide a powerful influence on diet, appetite, satiety, weight, health, and illness. The psychology of eating, as well as these sensory influences, can play a very important role in nutrition, diet, and health.



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 a number of 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, the most sensitive human sense. Other animals have much greater olfactory sensitivity as the olfactory epithelium surface area is 1.5 share inches (10cm2) in humans, 3 square inches (20cm2) in cats, and 30 square inches (200cm2) in dogs. The bear has a sense of smell 2,000 times more sensitive than in the human. The effect of the chemical messenger, such as an olfactant, 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.

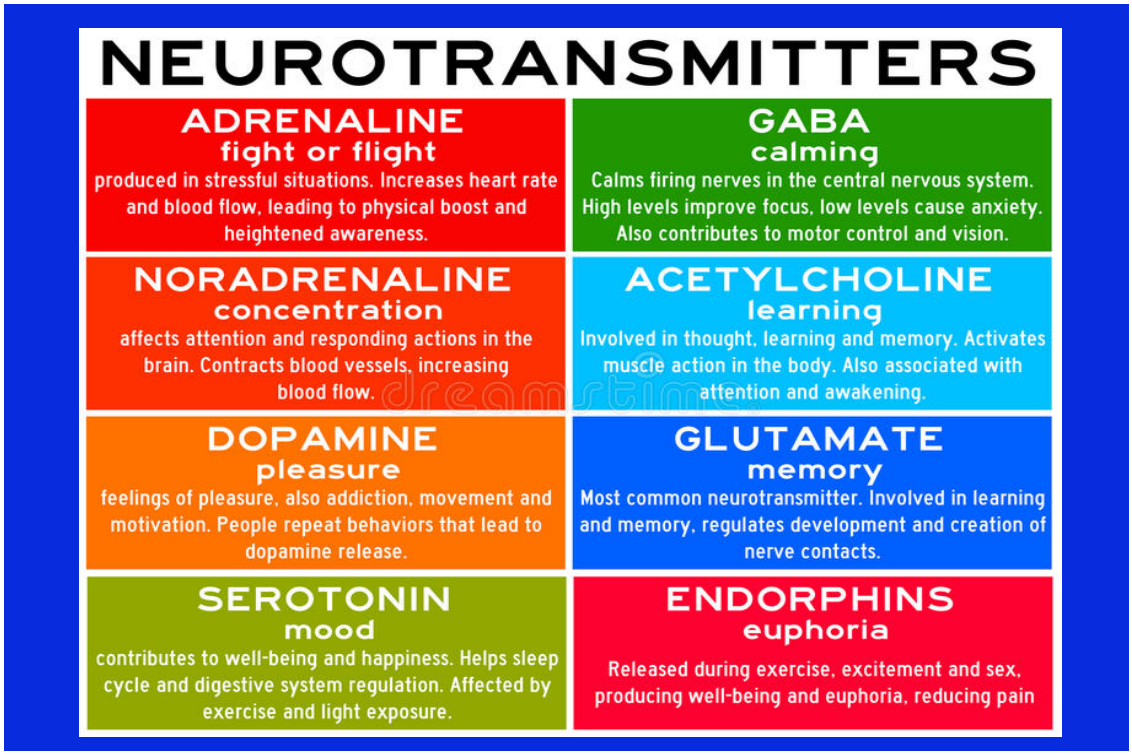
The optic nerve, cranial nerve II provides visual input from the eyes. Although the sharp area of focus is relatively limited, the peripheral vision ability to detect motion is an important defense mechanism to protect survival. Many animals and insects have a keener sense of vision as well as an expanded 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.

The vagus nerve has one the most varied and extensive networks of any cranial nerve and plays a major role in the autonomic and parasympathetic nervous systems. A 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 of the nerve fiber itself is an electrical impulse. Electrical stimulation of the vagus nerve is an effective FDA approved modality in the management of depression that is resistant to standard therapy. Vagus nerve stimulation also 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 continuously exposed to external stimuli, microbes, parasites,

pathogens (bacteria, protozoa, fungi, viruses, Archaea), 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 gastrointestinal 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.



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 channels 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 is yeast at 26%, bacteria 30%, roundworm *Caenorhabditis elegans* 40%, banana 50%, fruit fly at 65%, cow at 80%, cat at 90%, and mouse at 92%. When the number of genes is counted the 20,000 plus human genes are outnumbered by the million plus microbial genes of our multitude of guests of different species.

When the variables that effect human health and well-being number in millions, 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 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 a devastating condition like sickle cell anemia.

The interaction of the gut microbiome in human health and disease, and the influence of diet, are just beginning to be explored. The biological activity of metabolites of species frequently crosses over with unrelated species. At a minimum, one-third of the genes and their directed proteins will be bioactive in humans. There are millions if not billions of potential microbes that can become established in the gut microbiome. The consequences of these bioactive products may be beneficial, neutral, or harmful. The use of probiotics to manipulate the human gut microbiome has become a fad with marketing far exceeding the scientific credibility. While there is great potential, there is also a high likelihood of adverse consequences as we enter this exciting new era of understanding. We would be wise to recognize that probiotics can influence the gut microbiome populations in a fashion similar to antibiotics, and that they should be treated with the same degree of caution and respect.

When it comes to healthy eating, the most basic concept is to provide the essential nutrition by recognizing that humans are not able to produce all of the components, and that these must be supplemented by dietary intake. The other is to recognize the base materials such as the amino acids that are the building blocks that are required to produce additional essential products such as neurotransmitters, hormones, cytokines, etc. The protein consumed in the diet is the major source of these essential nutrients. The fats and carbohydrates also contribute in this regard, but their primary purpose is to serve as an energy source to drive the metabolic reactions required for life. As expected in complex systems, even minute quantities of trace elements and minerals can have critical functions and are required for health and well-being. The proper balance of all of these components is the challenge, as both deficiencies and excess can have adverse consequences to human

health and well-being. A number of examples will be provided demonstrating the complex interrelationship between diet, nutrition, food science, food chemistry, gut microbiome, and human health and well-being.

90 Essential Nutrients Your Body Does NOT Make

60 Essential Minerals

Aluminum	Arsenic	Barium
Beryllium	Boron	Bromine
Calcium	Carbon	Chloride
Cobalt	Copper	Cerium
Cesium	Chromium	Dysprosium
Erbium	Europium	Gadolinium
Gallium	Germanium	Gold
Hafnium	Holmium	Hydrogen
Iodine	Iron	Lanthanum
Lithium	Lutetium	Molybdenum
Manganese	Magnesium	Neodymium
Nickel	Niobium	Nitrogen
Potassium	Selenium	Sodium
Sulfur	Rhenium	Rubidium
Samarium	Scandium	Silica
Silver	Strontium	Tantalum
Terbium	Thulium	Tin
Titanium	Vanadium	Ytterbium
Yttrium	Zinc	Zirconium
Oxygen	Praseodymium	Phosphorus

16 Essential Vitamins

Vitamin A	Vitamin B1
Vitamin B2	Vitamin B3
Vitamin B5	Vitamin B6
Vitamin B12	Vitamin C
Vitamin D	Vitamin E
Vitamin K	Biotin
Choline	Flavonoids
Bioflavonoids	Inositol
Folic Acid	

12 Essential Amino Acids

Valine	Lysine
Threonine	Leucine
Isoleucine	Tryptophan
Phenylalanine	Methionine
Histidine	Arginine
Taurine	Tyrosine

3 Essential Fatty Acids

Omega 3 (EPA, DHA, ALA)
Omega 6
Omega 9

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

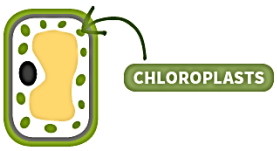
Foods to Support Select Neurotransmitters

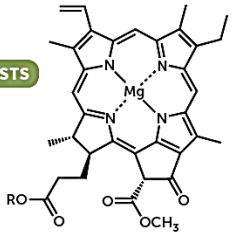
GLUTAMATE	Meat, such as turkey breast, pumpkin seeds, soybeans, eggs, sesame seeds, some cheeses
GABA	Created in the gut by *Bifidobacterium* and *Lactobacillus*, and in foods such as germinated chia seeds, fermented foods like kimchi, sourdough bread, cheese, and yogurt; fermented soybeans
SEROTONIN	Bananas , walnuts, pineapples
TRYPTOPHAN (to support serotonin)	Turkey, eggs, soybeans, pumpkin seeds, white beans, sesame seeds, mung beans, split peas, kidney beans, some nuts, some grains
TYROSINE (to support dopamine)	Turkey, eggs, soybeans
CHOLINE (to support acetylcholine)	Meat, eggs, grain-based products, turkey, soybean, chickpeas, lentils

THE CHEMISTRY OF BROCCOLI

COOKING COLOUR CHANGES

Like other green vegetables, broccoli's colour comes from chlorophyll. Chlorophyll is found within the chloroplasts of plant cells. What causes this colour to intensify during cooking?



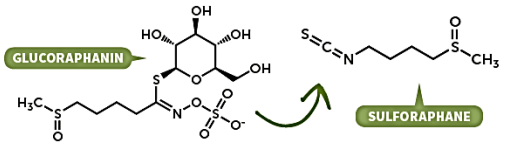


CHLOROPHYLL A

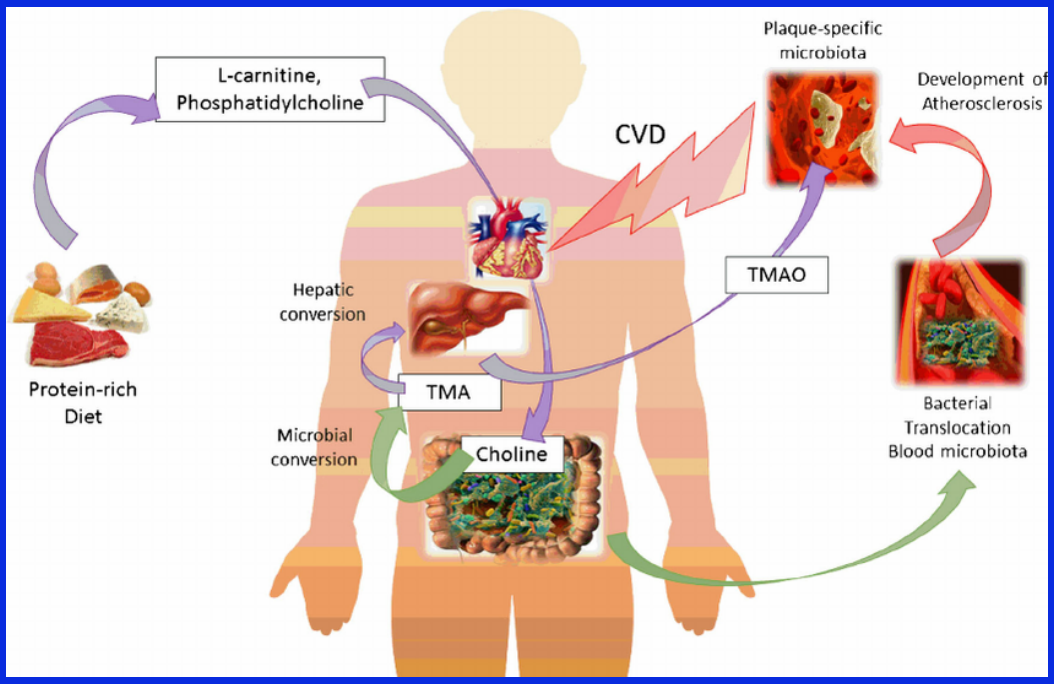
$R = C_{20}H_{39}$

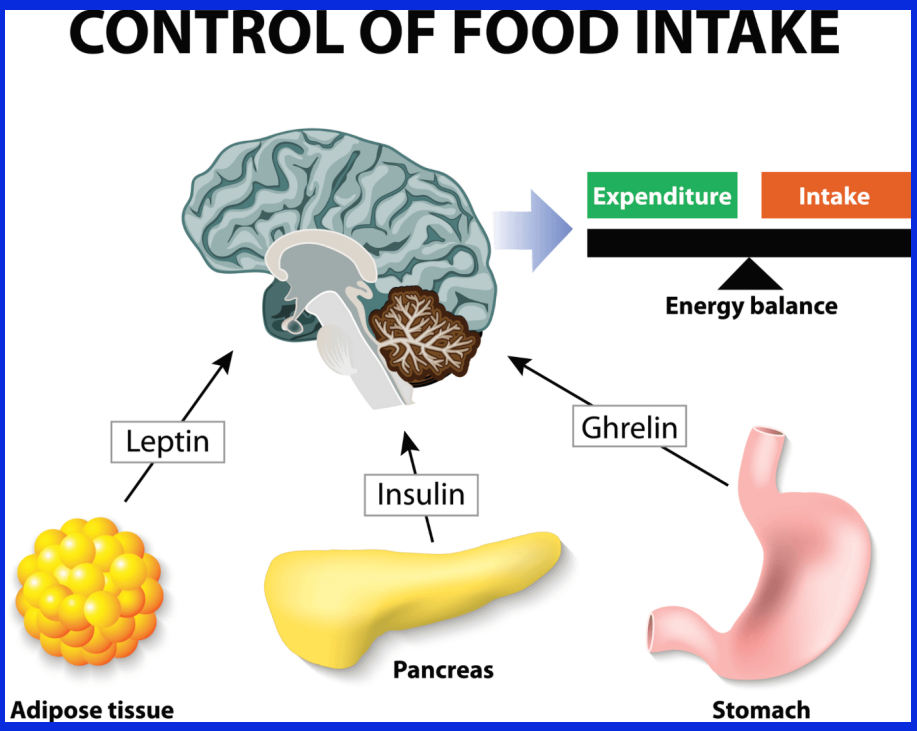
Pockets of air in the space between plant cells cause the green of chlorophyll to be slightly clouded. During cooking these gas pockets expand and escape. This makes the green colour intensify. The effect doesn't last long, however. Cooking also causes plant cells to burst, releasing organic acids. Hydrogen ions from these acids react with chlorophyll to form pheophytins, making the greens less vibrant.

SULFORAPHANE AND CANCER



Chopping broccoli releases the enzyme myrosinase from cells. This acts on the glucosinolate compound glucoraphanin; one of the products is sulforaphane. Sulforaphane has been investigated due to its ability to kill cancerous cells. As myrosinase is heat-sensitive, cooking method affects the amount of sulforaphane present. Other sulfur compounds give broccoli its odour when cooked.


L-carnitine,
Phosphatidylcholine
Plaque-specific
microbiota
Development of
Atherosclerosis
CVD
TMAO
Hepatic
conversion
TMA
Microbial
conversion
Choline
Protein-rich
Diet
Bacterial
Translocation
Blood microbiota


CONTROL OF FOOD INTAKE
Expenditure
Intake
Energy balance
Leptin
Insulin
Ghrelin
Pancreas
Adipose tissue
Stomach

Portion Distortion

What you're served

1/2 lb. cheeseburger, French fries, 3/4 cup ketchup, tomato slice and lettuce.
1,345 calories
53 grams fat

What's one serving

1/4 lb. cheeseburger, half the French fries, 2 tablespoons ketchup, tomato slice and lettuce.
685 calories
33 grams fat

Portion *Distortion*

20 YEARS AGO	TODAY	DIFFERENCE
333 Calories	590 Calories	257 MORE CALORIES

Lifting weights for **1 HOUR AND 30 MINUTES** burns approximately 257 calories* **Based on 130-pound person*

20 YEARS AGO	TODAY	DIFFERENCE
500 Calories	850 Calories	350 MORE CALORIES

Playing golf (while walking and carrying your clubs) for **1 HOUR** burns approximately 350 calories* **Based on 160-pound person*

20 YEARS AGO	TODAY	DIFFERENCE
1 cup spaghetti with sauce and 3 small meatballs 500 Calories	2 cups spaghetti with sauce and 3 large meatballs 1,025 Calories	525 MORE CALORIES

Housecleaning for **2 HOURS AND 35 MINUTES** burns approximately 525 calories* **Based on 130-pound person*

20 YEARS AGO	TODAY	DIFFERENCE
Coffee, 8 oz (with whole milk and sugar) 45 Calories	Mocha Coffee, 16 oz (with steamed whole milk and mocha syrup) 350 Calories	305 MORE CALORIES

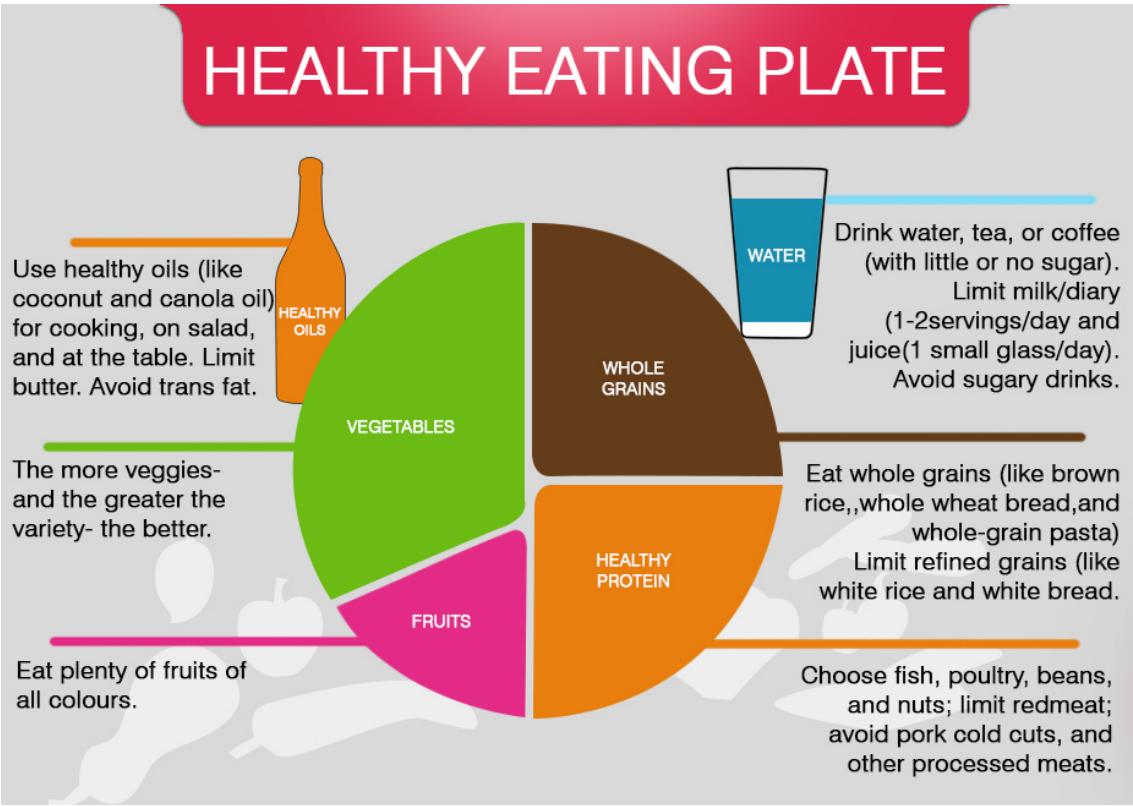
Walking **1 HOUR AND 20 MINUTES** burns approximately 305 calories* **Based on 130-pound person*

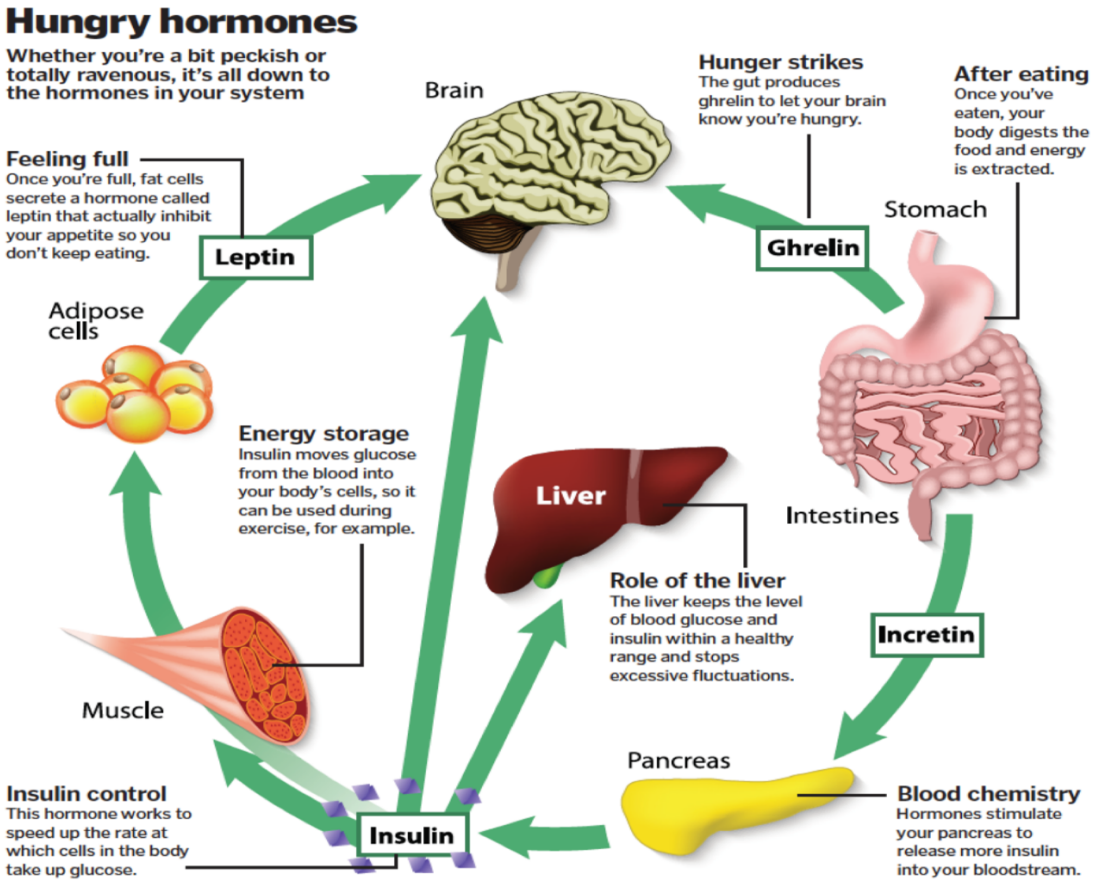
20 YEARS AGO	TODAY	DIFFERENCE
1.5 oz 210 Calories	4 oz 500 Calories	290 MORE CALORIES

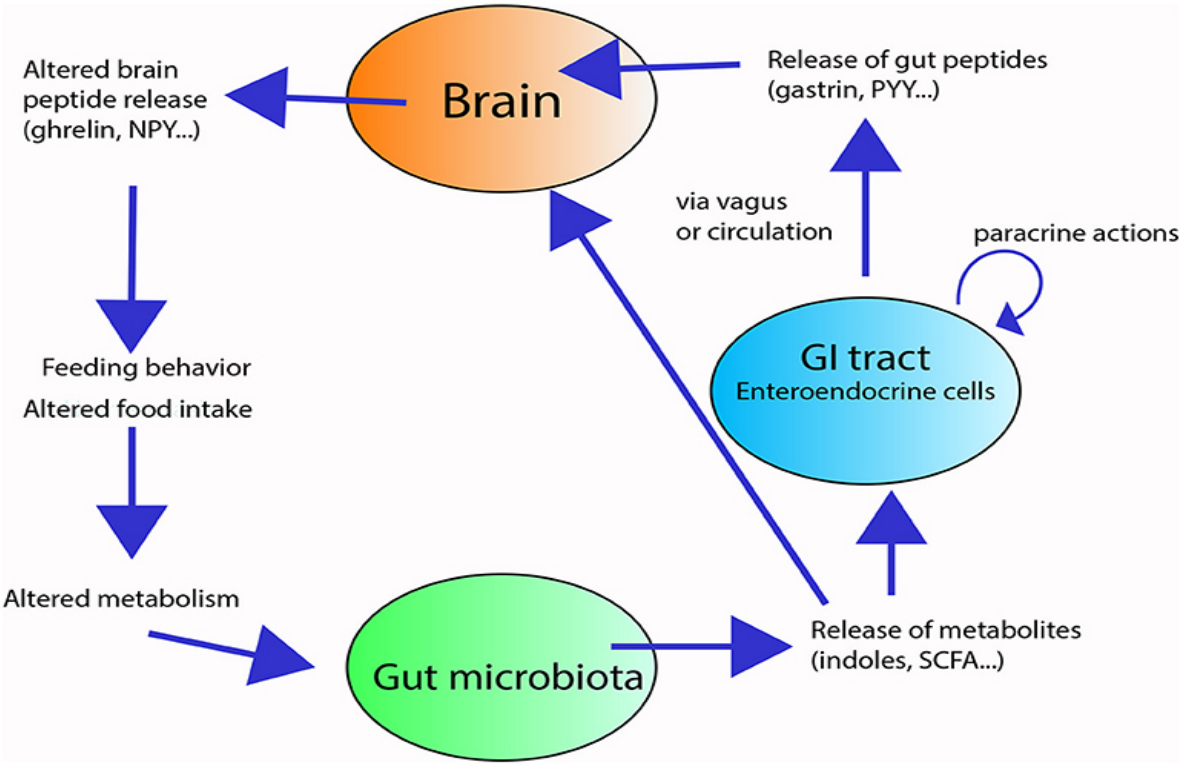
Vacuuming for **1 HOUR AND 30 MINUTES** burns approximately 290 calories* **Based on 130-pound person*

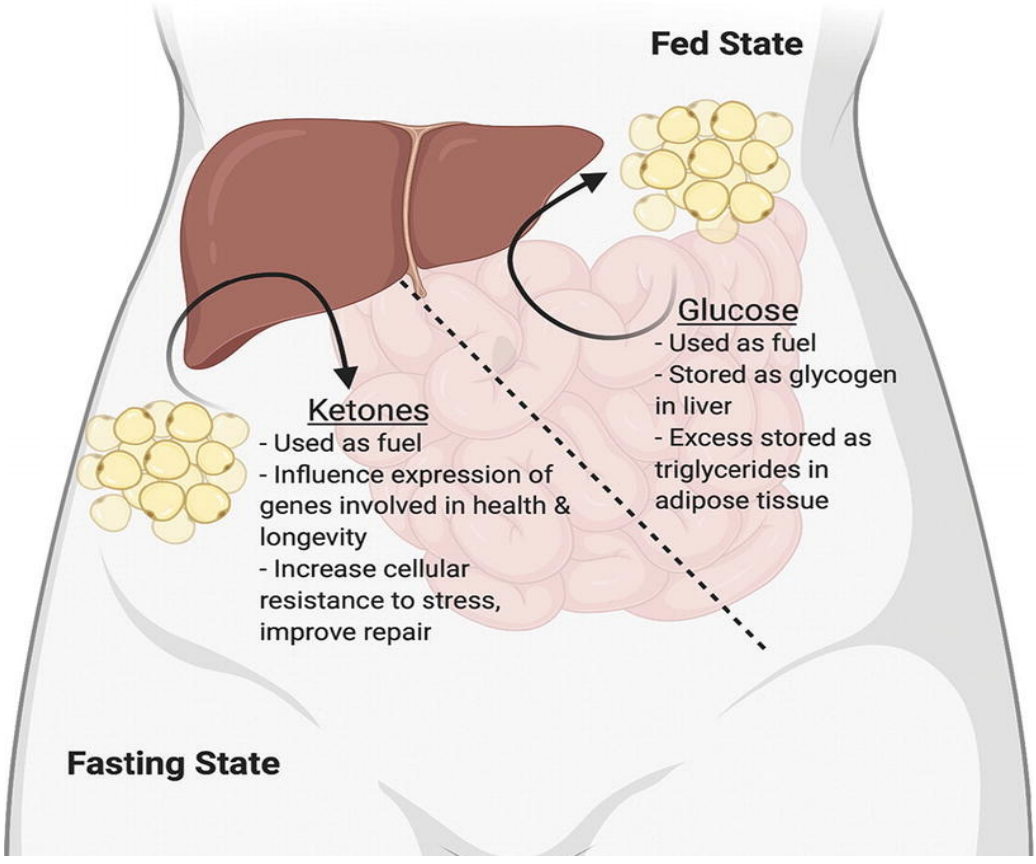
20 YEARS AGO	TODAY	DIFFERENCE
1.5 diameter 55 Calories	3.5 diameter 275 Calories	220 MORE CALORIES

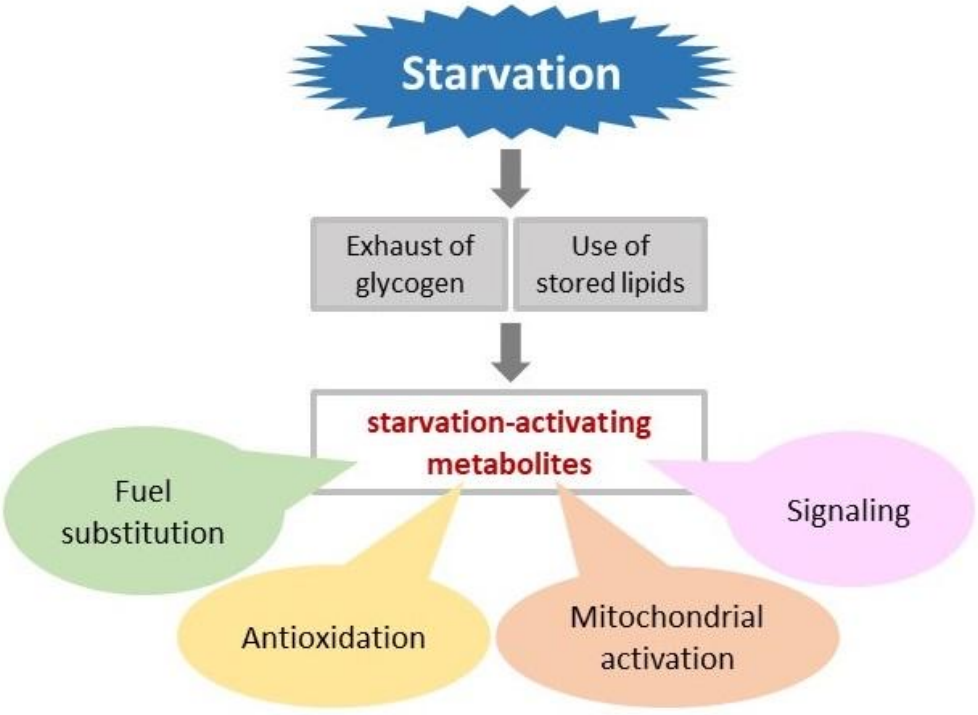
Washing a car for **1 HOUR AND 15 MINUTES** burns approximately 220 calories* **Based on 130-pound person*

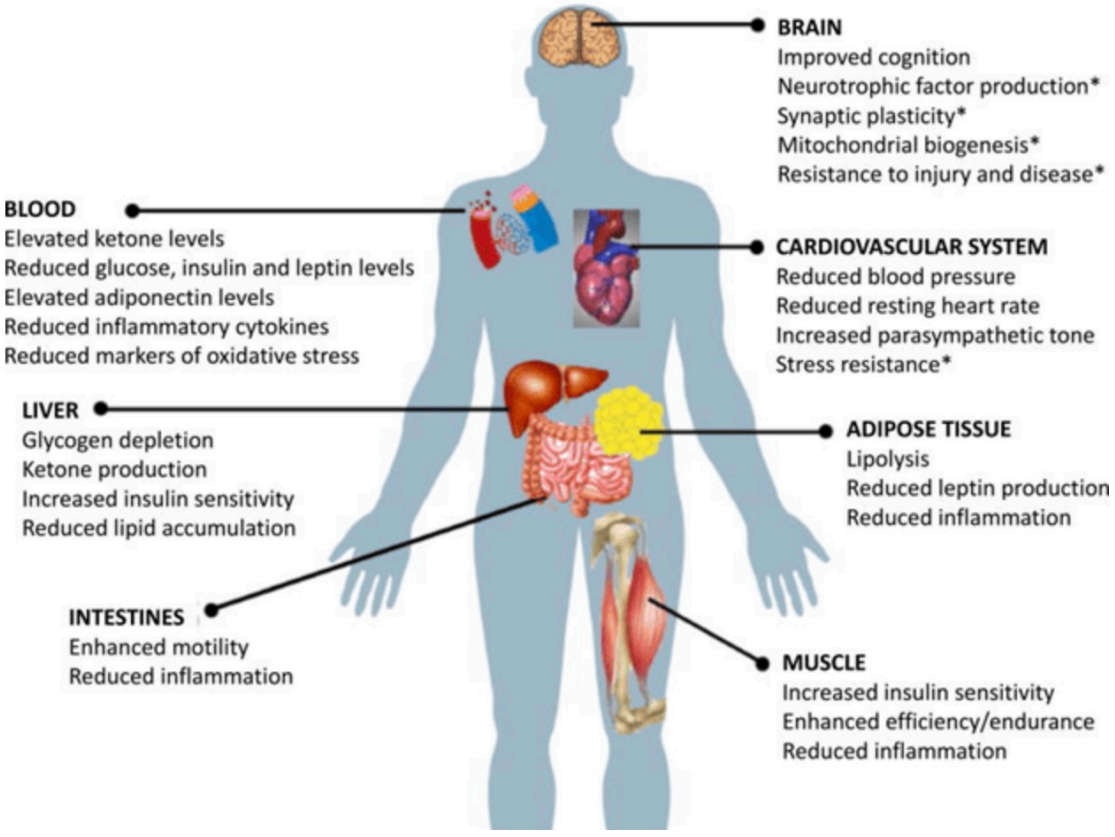

HEALTHY EATING PLATE
Use healthy oils (like coconut and canola oil) for cooking, on salad, and at the table. Limit butter. Avoid trans fat.
HEALTHY OILS
VEGETABLES
WHOLE GRAINS
WATER
Drink water, tea, or coffee (with little or no sugar). Limit milk/diary (1-2servings/day and juice(1 small glass/day). Avoid sugary drinks.
The more veggies- and the greater the variety- the better.
Eat whole grains (like brown rice,,whole wheat bread,and whole-grain pasta) Limit refined grains (like white rice and white bread.
HEALTHY PROTEIN
FRUITS
Eat plenty of fruits of all colours.
Choose fish, poultry, beans, and nuts; limit redmeat; avoid pork cold cuts, and other processed meats.


Hungry hormones
Whether you're a bit peckish or totally ravenous, it's all down to the hormones in your system
Brain
Hunger strikes
The gut produces ghrelin to let your brain know you're hungry.
After eating
Once you've eaten, your body digests the food and energy is extracted.
Feeling full
Once you're full, fat cells secrete a hormone called leptin that actually inhibit your appetite so you don't keep eating.
Leptin
Ghrelin
Stomach
Adipose cells
Energy storage
Insulin moves glucose from the blood into your body's cells, so it can be used during exercise, for example.
Liver
Intestines
Role of the liver
The liver keeps the level of blood glucose and insulin within a healthy range and stops excessive fluctuations.
Incretin
Muscle
Pancreas
Insulin control
This hormone works to speed up the rate at which cells in the body take up glucose.
Insulin
Blood chemistry
Hormones stimulate your pancreas to release more insulin into your bloodstream.


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


Fed State
Glucose
- Used as fuel
- Stored as glycogen in liver
- Excess stored as triglycerides in adipose tissue
Ketones
- Used as fuel
- Influence expression of genes involved in health & longevity
- Increase cellular resistance to stress, improve repair
Fasting State


Starvation
Exhaust of glycogen
Use of stored lipids
starvation-activating metabolites
Fuel substitution
Signaling
Antioxidation
Mitochondrial activation


BRAIN
Improved cognition
Neurotrophic factor production*
Synaptic plasticity*
Mitochondrial biogenesis*
Resistance to injury and disease*
BLOOD
Elevated ketone levels
Reduced glucose, insulin and leptin levels
Elevated adiponectin levels
Reduced inflammatory cytokines
Reduced markers of oxidative stress
CARDIOVASCULAR SYSTEM
Reduced blood pressure
Reduced resting heart rate
Increased parasympathetic tone
Stress resistance*
LIVER
Glycogen depletion
Ketone production
Increased insulin sensitivity
Reduced lipid accumulation
ADIPOSE TISSUE
Lipolysis
Reduced leptin production
Reduced inflammation
INTESTINES
Enhanced motility
Reduced inflammation
MUSCLE
Increased insulin sensitivity
Enhanced efficiency/endurance
Reduced inflammation

The Science of Intermittent Fasting

1 **Growth Hormone Increases** which not only preserves muscle mass but can actually help cause growth in muscle, bone density, and cartilage.

2 **Norepinephrine** increases which has been shown to have an effect on the mind as well as the body. High Norepinephrine levels have been shown to increase mental alertness, and boost the metabolism of fat.

3 **Leptin Sensitivity** increases which means you feel less hungry.

4 **Brain-Derived Neurotrophic Factor** increases which helps to stimulate neural growth in the brain.

5 **Insulin Sensitivity** increases. Short term this can benefit you by directing carbs to your muscles for muscle gains, rather than being converted to fat. Conversely being insulin insensitive long term can lead to Type 2 diabetes, Alzheimer's and heart disease.

6 **Autophagy increases** which reduces oxidative damage and inflammation in the body, there by healing the body.

Fasting Protocols

Intermittent Fasting

Time-restricted Feeding (TRF)	Alternate Day Fasting (ADF)	Modified ADF (mADF)	5:2 Protocol	Short-term Fasting	Prolonged Fasting	Caloric Restriction
Restricting caloric intake to 6-8-hour eating window each day, allowing at least 16 hours fasting	Fasting (no caloric intake) every other day and consume habitual diet on non-fasting days	Limited caloric intake (~25% total kcal) on fasting days and habitual intake on feeding days	Limited caloric intake (~25% total kcal) 2 consecutive or nonconsecutive days/ week, unrestricted intake on other 5 days	No caloric intake (foods or drinks) for 72 hours or less	No caloric intake (food or drinks) for periods longer than 72 hours	Eating pattern that involves a continuous reduction in caloric intake without malnutrition

Summary of Benefits

Time-restricted Feeding (TRF)	Alternate Day Fasting (ADF)	Modified ADF (mADF)	5:2 Protocol	Short-term Fasting	Prolonged Fasting	Caloric Restriction
▪ Can be integrated with other protocols, including ketogenic diets ▪ Improves insulin sensitivity and fasting glucose levels ▪ Intermittent ketosis ▪ Reduced fat mass ▪ Preserved or maintained lean mass ▪ Reduced body weight ▪ Spontaneous reduction in energy intake ▪ Improved blood pressure	▪ Variable schedule suits restricted intake on certain days of the week ▪ Intermittent ketosis ▪ Improves insulin sensitivity and fasting glucose levels ▪ Improved lipid profile ▪ Reduced fat mass ▪ Reduced body weight ▪ Improved clinical scores in multiple sclerosis rodent models ▪ Prevention of cognitive deficits in mouse model of Alzheimer's Disease	▪ Intermittent ketosis ▪ Reduction in fasting insulin ▪ Improved lipid profile ▪ Reduced fat mass ▪ Reduced body weight	▪ Variable schedule suits restricted intake on certain days of the week ▪ Higher ketone levels on fasting days ▪ Reduced body weight ▪ Reduction in HbA1c in type 2 diabetes patients ▪ Improved insulin sensitivity ▪ Reduced postprandial insulin ▪ Improved blood pressure and lipid profile	▪ Higher ketone levels ▪ Improved insulin sensitivity and fasting glucose levels ▪ Acute changes in body weight and both lean and fat mass ▪ Reduced inflammation	▪ Higher ketone levels ▪ Improved insulin sensitivity and fasting glucose levels ▪ Reduced body weight ▪ Reduced fat mass ▪ Reduced inflammation ▪ Improved blood pressure and lipid profile ▪ Activation of autophagy and other longevity/healthspan benefits	▪ Most scientific evidence for improved healthspan and longevity ▪ Consistent eating plan ▪ Improved blood pressure and lipid profile ▪ Prevention of cognitive deficits in mouse and non-human primate models of age-related neurodegenerative diseases ▪ Increased synaptic plasticity and neurogenesis

Types Of Intermittent Fasting

The 5:2 fasting

The 5:2 fasting method allows you to eat normally for five days and then restrict your calorie intake to **500-600 calories** on the other two days.

16:8

You should hold off from any food for **16 hours** and eat during the remaining 8 hours of the day. When following this method of fasting, you have to consume lots of high-protein foods and eat carbohydrates on rotation.

12-hour fast

Good option for beginners. A **12-hour fast** means that you eat within the first 12 hours of the day and abstain from food for the next 12 hours.

Fasting on alternate days

As the title suggests, this plan allows you to fast **every second day.**

OMAD

You should fast from breakfast to breakfast, from lunch to lunch, or from dinner to dinner – **whichever you prefer.** You can have one meal during that time to tide you over and use it to take medications that must be taken with food.

Random meal skipping

You can **skip meals randomly** once or twice a week. It basically helps you to reduce your calorie intake. If you had a really heavy lunch, you might want to let your body rest and skip dinner, or at least, have a light one.

The Warrior Diet

It allows you to eat **small portions of certain food types** at dinner. During that dinner period, you should also work out. At the end of the day, you would have a feeding window.

What is Autophagy?

Autophagy is a well-regulated, orderly process to break down and recycle various cellular components. A type of self-renewal method focusing on removing older structures so that the new ones can take their place..

Autophagy Prevents Cancer

Autophagy plays an important role in preventing the onset and early growth of cancer cells. It is has been known to suppress several processes leading to cancer, such as DNA damage, chronic inflammation, and genome instability.

Autophagy Enhances Muscle Performance

As you exercise, you are put stress on your cells. As this happens, energy use increases and the cell components get worn out at a faster rate. Autophagy makes sure to balance energy use within a cell.

Autophagy Prevents Neurodegenerative Diseases

Stimulating autophagy can help protect your brain by properly removing misfolded proteins inside neurons that cause cell death in your brain and loss of mental capacity.

Autophagy Regulates Inflammation

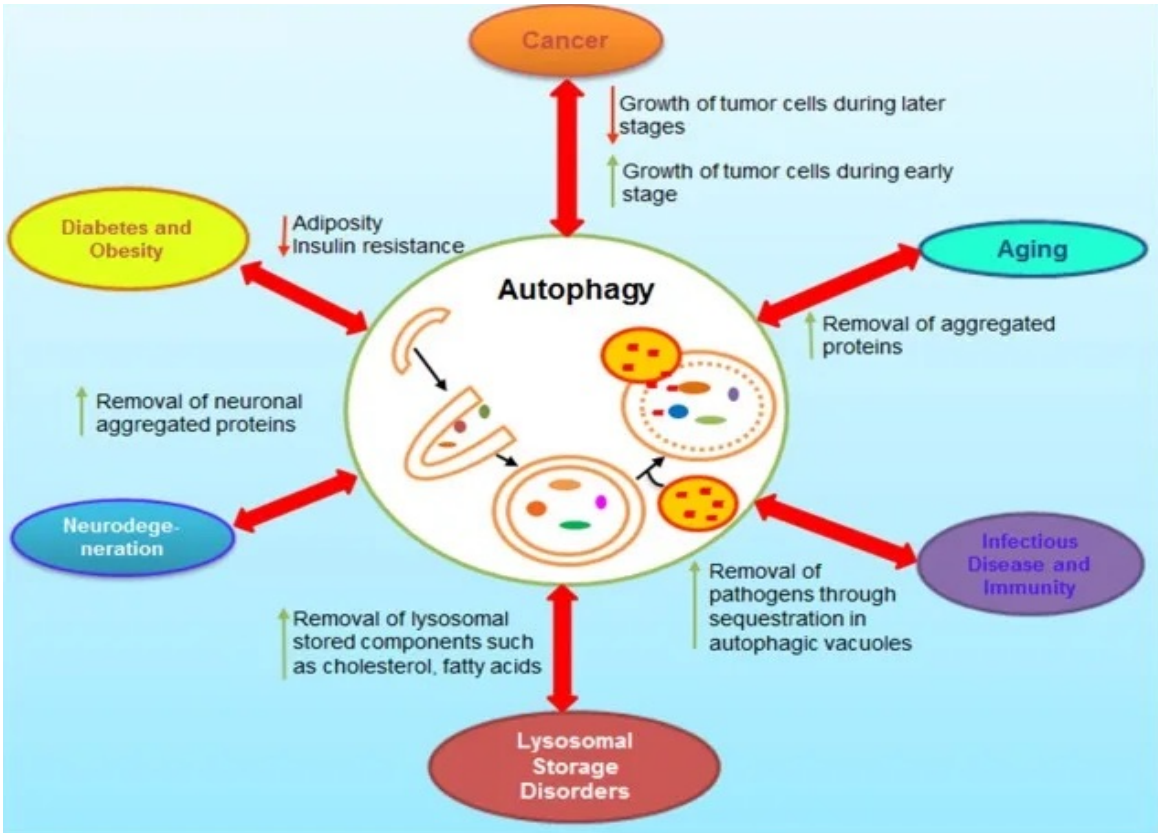
Autophagy can help decrease inflammation within your body. It also gets rid of any pro-immune response molecules from the body to lower down the level of inflammation.

Autophagy Reduces the Effects of Aging

Autophagy along with intermittent fasting boosts the production of Human Growth Hormone (HGH). HGH is largely associated with an increased healthy muscle growth but also provides powerful anti-aging benefits.

Enhances Cellular Energy

The mitochondria undergo an autophagy process called "mitophagy" that favors the development of new and stronger mitochondria that can produce more cellular energy.



4 DIFFERENT TYPES OF FASTING

Water fasting.

Consuming only water or other zero calorie beverages.

Calorie restriction.

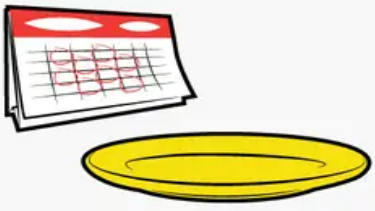
Participants reduce daily caloric intake significantly, often by 10-45%.

Fasting mimicking diet.

For five days a month participants drastically limit their caloric intake.

Intermittent fasting.

Refrain from food regularly, usually one or two days a week.



Types of Intermittent Fasting

Modified Fasting

5:2 - Eat normally <u>five</u> days a week; cut back to 20-25% of usual daily calories for the <u>two</u> remaining fasting days
~500 calories for women;
~600 calories for men

Alternative Day Fasting

Alternate ***fasting days*** with ***eating days***. <u>Fasting days</u> - no consumption of energy-containing foods or beverages. <u>Eating days</u> - no restriction on food or drink.

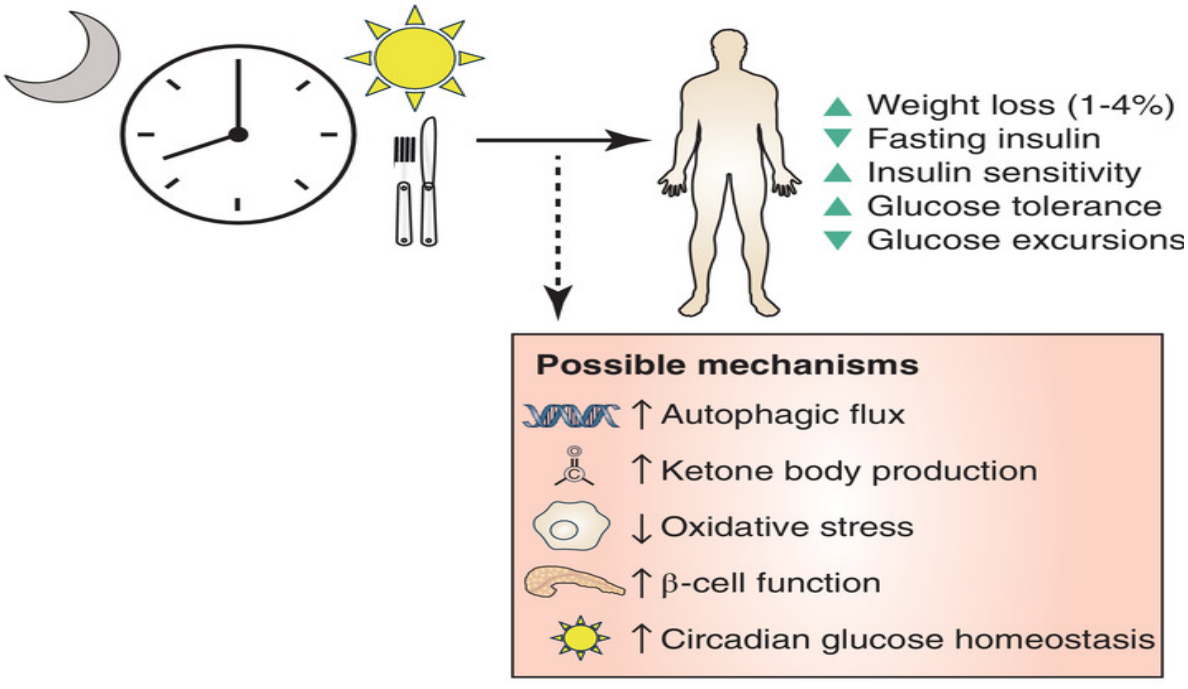
Time Restricted Feeding

Eat only during ***specific windows of time***. For example, eat during an 8 hour window and fast for the remaining 16 hours.
Known as the 16:8 Diet.

Prolonged Fasting

Consume ***water only*** for 2 or more consecutive days. 1-2 times per month instead of once per week.

Time restricted eating (TRE)



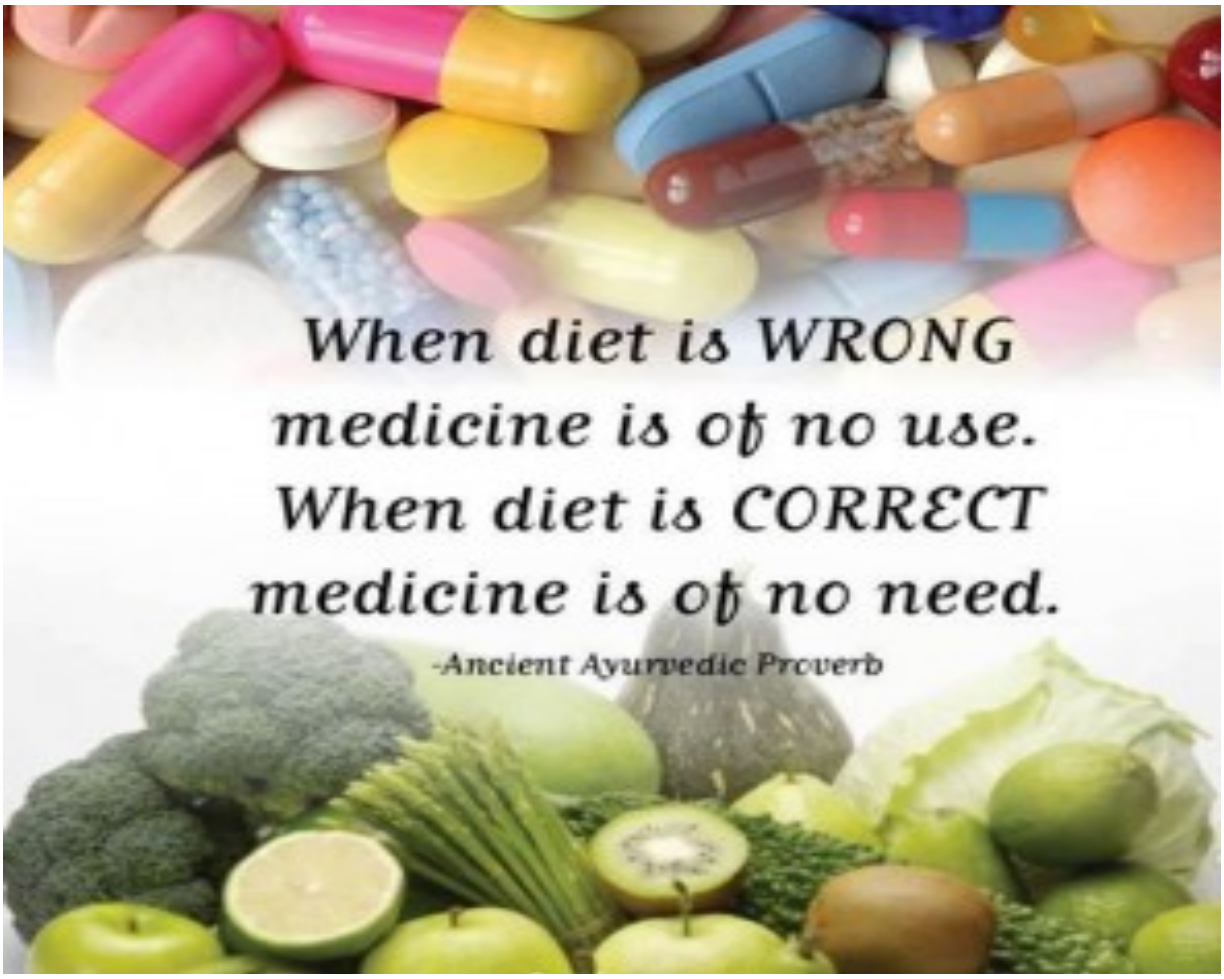
Hormones balancing benefits of intermittent fasting

Increases

- Leptin and insulin sensitivity
  Helps in preventing and treating Diabetes, cardiovascular problems and even cancers
- Ghrelin sensitivity increases
  Helpful in reducing hunger
- Increases fat burning

Decreases

- Triglycerides
  Risks of heart diseases
- Inflammation and free radicals
- Weight gain and metabolic diseases



Bite Size Clinical Pearls: Part 1

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

Bite Size Clinical Pearls: Part 2

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

Joseph B. Weiss, MD, FACP, FACG, AGAF

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

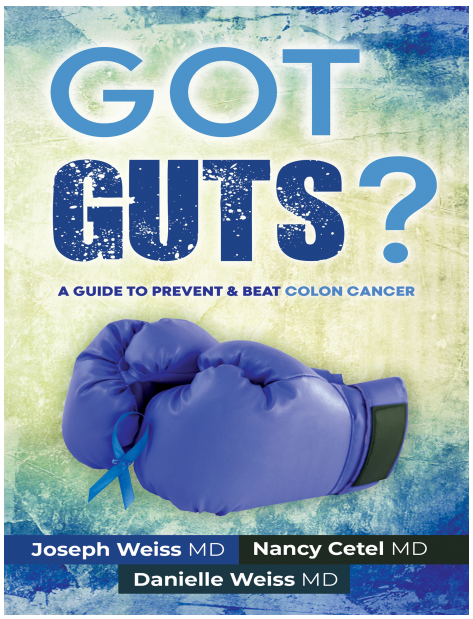
He is the author of more than a dozen books on health (www.smartaskbooks.com) and has had numerous papers published in prestigious national and international medical journals, as well as in the lay press. Dr. Weiss is also an accomplished humorist and professional speaker having given over three thousand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

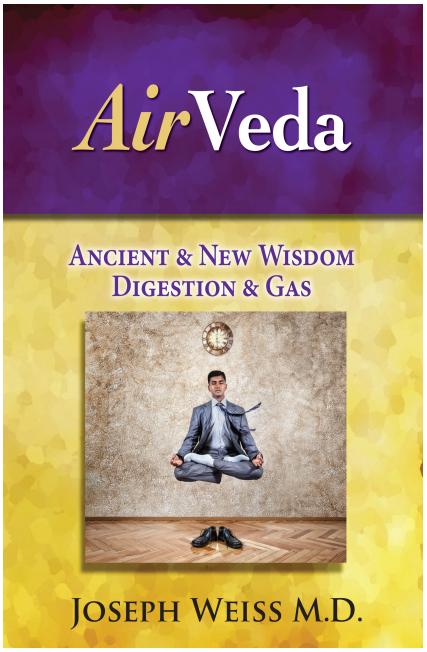
"Joseph Weiss, M.D. has a gift for books that are uniquely informative and entertaining. **Jack Canfield** Coauthor of the Chicken Soup for the Soul® series

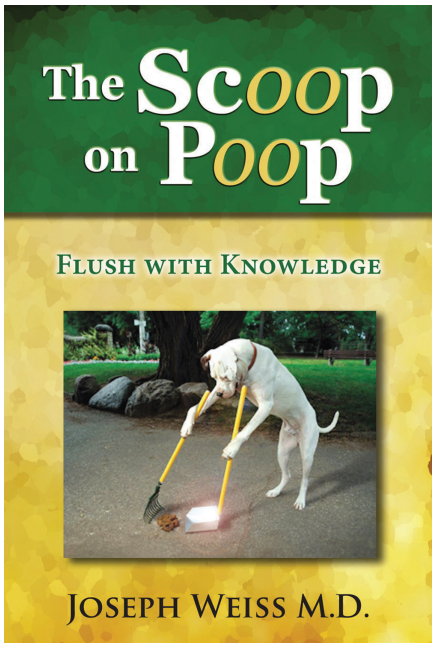


Got Guts! A Guide to Prevent & Beat Colon Cancer (ISBN:978-1-943760-97-8 Color Pages: 146 Words: 60,935 Images: 15) offers a clear understanding of the importance and value of prevention and screening in colorectal cancer. Written for the general public, it is a practical common-sense guide. Colon cancer is one of the most common and deadly cancers. It is both preventable and curable when found early, but devastating when discovered too late. It begins silently without any signs or symptoms, and rarely gives any warning until too late. In spite of painless, accurate and inexpensive screening tests, too many people mistakenly believe they are safe and fail to protect themselves.

From young movie stars and professional athletes, to world political and religious leaders anyone can get colon cancer. Nearly 50,000 needlessly die in the United States each year from this preventable and curable disease. When it is detected early nearly all of these lives could have been saved. Recently the greatest increase in colon cancer is seen in adults 18 to 49 years of age. In this book you will learn how: your diet, weight, family history, gender, and other significant factors contribute to your potential risk. You will begin to understand the essentials in personalizing your best approach to prevent colon cancer. The multiple options range from one minute painless and inexpensive tests, to the more involved invasive colonoscopy tests that require sedation or anesthesia. Understanding the options available , and selecting wisely based on your personal risk factors, is clearly explained in this potentially lifesaving book.

Written by expert physicians who offer an unbiased and logical approach, *Got Guts!* assists in identifying your best path. This guide may well be the most important book you will read to protect your health now and in the future. All three authors have experienced the hardships that follow a loved one diagnosed with colorectal cancer too late. They are dedicated and compassionate physicians with extensive clinical, academic, and research experience. Don't miss an opportunity to make life-saving decisions for yourself and your loved ones!

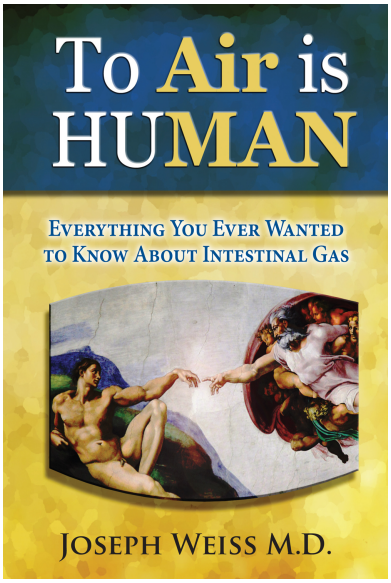


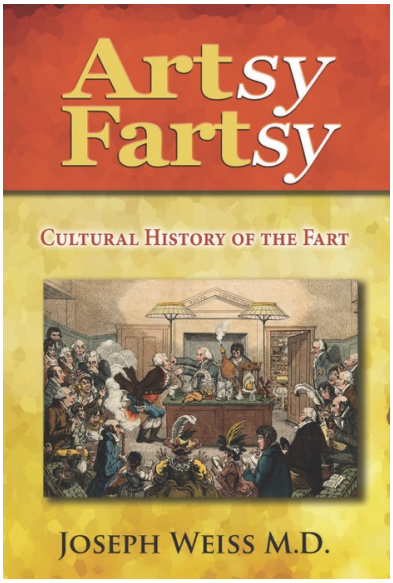


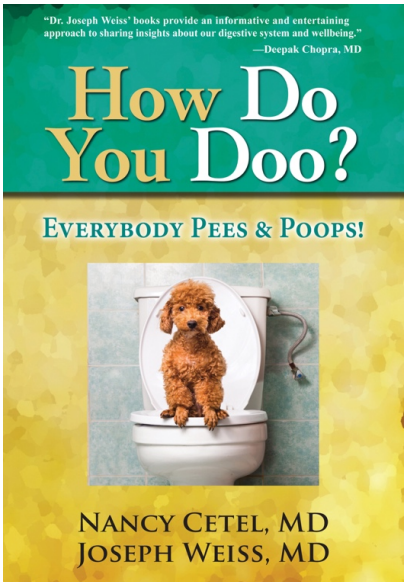
AirVeda: Ancient & New Wisdom, Digestion & Gas (ISBN: 978-1-943760-10-7 Color Pages: 467 Words: 150,062 Images: 399) covers the remarkable advances in the understanding of digestive health and wellness from Ayurveda to genomics and the gut-brain-microbiome-diet axis. The knowledge gained opens new avenues to optimal health and wellness.

The Scoop on Poop! Flush with Knowledge (ISBN: 978-1-943760-00-8 Color Pages: 426 Words: 111,763 Images: 378) 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. It has been provocatively and cheekily retitled as ***You Don't Know Sh*t! Until You Read This Book*** (ISBN: 978-1-943760-04-6 Color Pages: 426 Words: 111,768 Images: 378). 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







To 'Air' is Human, Everything You Ever Wanted to Know About Intestinal Gas (ISBN: 978-1-943760-02-2 Color Pages: 321 Words: 92,567 Images: 297) 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. https://www.amazon.com/Air-Human-Everything-Wanted-Intestinal/dp/1943760020

Artsy Fartsy, Cultural History of the Fart (ISBN: 978-1-943760-03-9 Color Pages: 322 Words: 79,364 Images: 266) 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.

How Do You Doo? Everybody Pees & Poops! (ISBN: 978-1-943760-06-0 Color Pages: 88 Words: 17,844 Images: 61) 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.