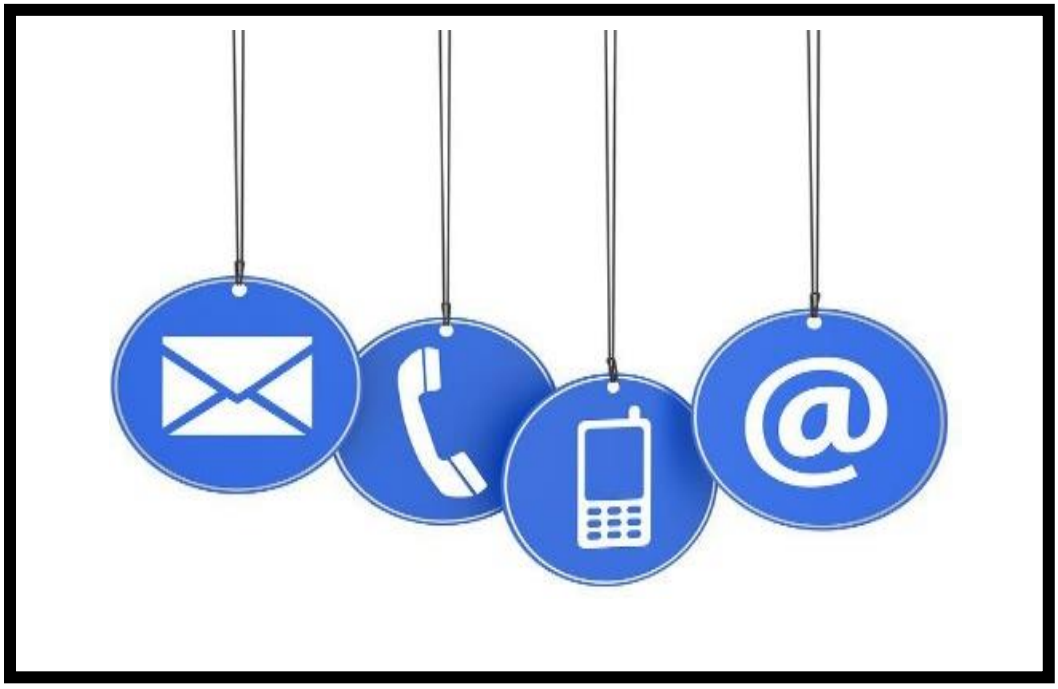
An Approach To Analyzing And Treating Chronic Digestive Disorders

Dean C. Kramer, M.D.



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The information presented in the monograph is not a substitute for diagnosis or treatment by qualified healthcare professionals. Those individuals considering

making changes to their existing treatment plan, are advised to discuss those changes first with their medical care providers.

Table of Contents

Caroline's Case History

My assessment of Caroline was the inspiration for writing this monograph. I am indebted to her for allowing me to relate her story and dedicate this monograph to Caroline and the many other patients with symptoms like Caroline.

Caroline's story is not an anomaly. Her history is shared by many--male and female, young and old.

Caroline is a 45-year-old legal secretary. She has a long history of multisystem complaints including nausea, chronic fatigue, abdominal fullness after meals, abdominal bloating, belching, abdominal distention, flatulence, migraine headaches, muscle aches, anxiety, depression, insomnia, irregular bowel habits, attention deficit and weight loss.

She had been evaluated by her primary care physician, two gastroenterologists, several functional and integrative medicine specialists, a psychiatrist, and a nutritionist. Her evaluations had included multiple blood tests, stool examinations, gallbladder x-rays, stomach emptying tests, CT scans of the abdomen, and esophagus/stomach and colon endoscopies. All her studies were reported to be within the normal range.

Caroline gave a significant history of dental pathology. By the time Caroline was an adolescent, many of her teeth had some degree of dental decay that required dental fillings many of which have been replaced with caps/crowns on her teeth. In the

last several years, she has been under the care of a periodontist (gum specialist) and has been having "deep cleaning" and "root planing and scaling" to control inflammation and infection. Three teeth have required root canal procedures.

Caroline was referred to a clinic that specializes in digestive diseases and after multiple normal studies was told she would be best be treated by a psychiatrist.

After her evaluation by a psychiatrist, she began taking antianxiety and antidepressant medications as prescribed but discontinued their use, indicating that they made her feel worse.

Caroline had tried lactose free diets, low-fat diets, low FODMAP diets, low histamine diets, sugar free diets, gluten- free diets, nightshade free diets, bone broth diets, keto diets, Paleo diets and intermittent fasting. She had been treated with several rounds of antibiotics to cover the possibility of bacterial overgrowth in her small intestines, small intestinal bacterial overgrowth (SIBO).

When first evaluated, Caroline was taking 27 different preparations--four prescription medications, seven minerals and vitamins, a probiotic and fifteen other unregulated supplements.

Caroline's story is not unique. Every medical care provider has evaluated many patients like Caroline in their practices. Most of

these patients have been diagnosed by their providers with "irritable bowel syndrome," "functional gastrointestinal disorder," or a "nervous stomach."

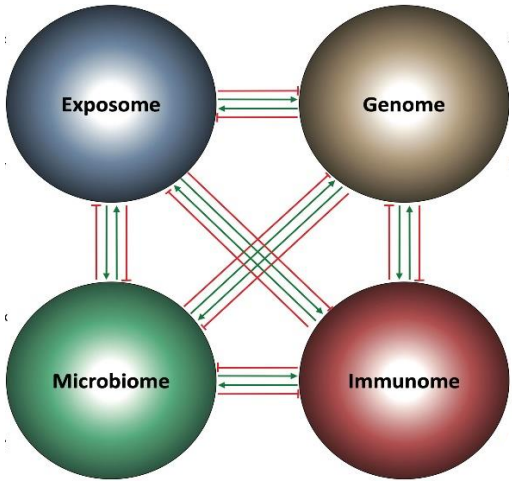
Most often, Caroline had been told that her symptoms were due to the stresses in her life. Many, like Caroline, have left the offices of their medical providers still having digestive issues, confused, belittled, frustrated and despondent.

PREFACE

The state of your health is the result of a compilation of multiple interacting factors that have occurred over your lifetime.

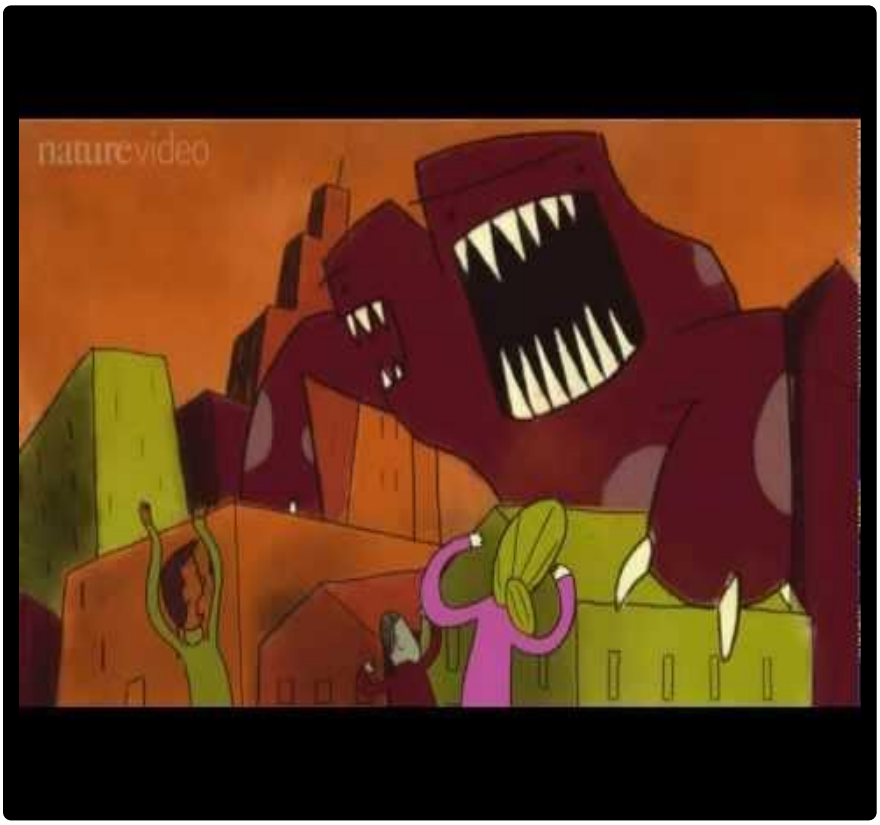
Some of those factors include the following: the genes you inherited from your parents, your lifetime of exposures, the microorganisms that coexist in your body, and the state of your immune system.

FACTORS THAT DETERMINE YOUR HEALTH



THE HUMAN GENOME

Defining the human genome



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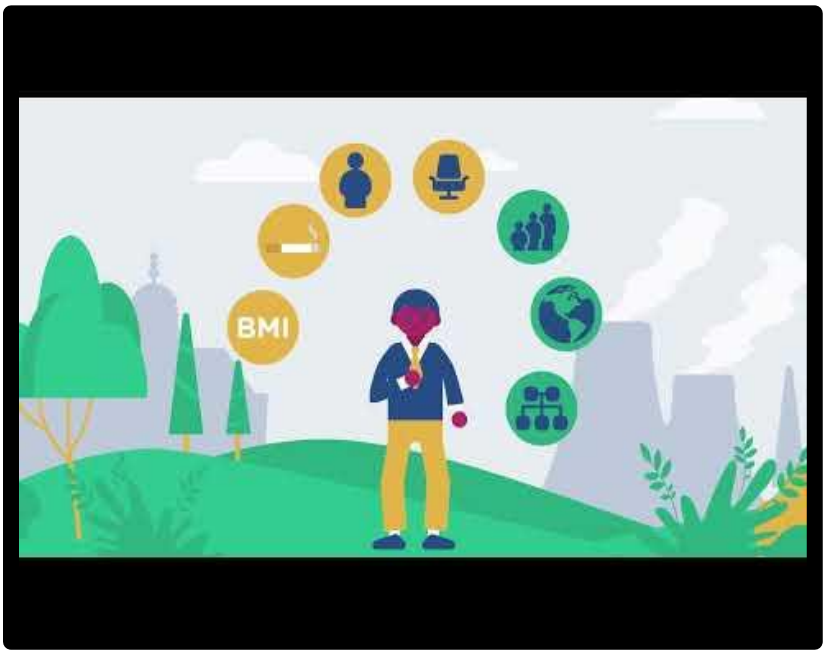
The human genome is the complete set of DNA and its genes which contain all of the instructions required for the body to make proteins.

The Human Exposome

Defining the human exposome



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The exposome is the totality of every exposure a human experiences from the moment on conception to death. This includes every nutrient ingested, every beverage consumed, every breath inhaled, every drug taken, every surgery performed, along with every environmental exposure including ambient temperature, air pollution, altitude, radiation and more. (See Table II at the end of the monograph). Because of the enormous variations in human exposures, each individual is unique.

Human Microbiome

Defining the human microbiome

The human microbiome is made up of all the microbes that live in and on the human body and their genes. Microbes live in communities within virtually every part of the body (so called ecosystems) with particularly large concentrations in the mouth, small bowel, large bowel and urogenital tract.

Those that live in the oral cavity may be highly destructive of gums and teeth while those that live in the large intestine carry out functions that are critical to human survival. A more detailed discussion later in the monograph will illustrate these points when the intestinal composition is defined in zones. (See the section: Dividing The Intestinal Tract Into Three Zones).

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Human Immunity

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All the genes and proteins that constitute the immune system are collectively known as the *immunome*. The immunome is a vastly complex and highly regulated structure that protects the human from infection and preserves health.

In the coming pages, you will have the opportunity to explore all these factors--and more--and how they may have influenced your health. Recommendations will be made about how some of these factors might be modified in hopes of maintaining or regaining your sense of well-being.

Introduction

For decades, medical care providers have concentrated on infectious communicable diseases caused by pathogenic organisms, e.g., tuberculosis, cholera, leprosy, plague, typhoid

fever, malaria, syphilis, etc. With the discovery of antibiotics many of these illnesses have been controlled or nearly eliminated.

In the last 40 years, non-communicable illnesses like cancer, diabetes, cardiovascular disease, Alzheimer's dementia, Parkinson's disease, and kidney disease have accounted for 70% of deaths worldwide.[1]

This monograph will focus primarily on non-communicable digestive illnesses. The monograph will introduce a different way of thinking about the body. It will elaborate on the theory that non-communicable digestive illnesses result, in large part, from the positive and/or negative interactions of digestive tract microorganisms with the cells of the human body.

It will embrace the concept that humans must encourage the growth of those microbes that are beneficial to them while discouraging the growth of those that may cause them harm.

After exploring these interactions between the body and the microbe populations, therapeutic interventions will be discussed.

[1] G.A. Roth, Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017, *Lancet.* 392 (10159) (2018) 1736-1788.)

Treating Caroline Required Consideration Of A Different Paradigm

Caroline's diagnostic evaluation by prior care providers had been exhaustive looking for dysfunction of her intestinal tract, its cells and its organs. The digestive tract, however, has more than just cells and organs. It contains trillions of microorganisms that interact with those cells, many of which are not only beneficial but essential for human existence.

A large portion of the body's beneficial microbes exist in the last portion of the small intestine and throughout the large intestine, (colon). They have many and varied functions, one of which is protect against other microbes trying to occupy their territory or niche within the gut.

As noted, humans rely on their microbes for protection of the lining surface and also take advantage of metabolites produced by resident microbes, like short chain fatty acids—acetate, butyrate, and propionate. Over the span of thousands of years, humans have evolved to be able to utilize these chemicals for numerous critical functions.

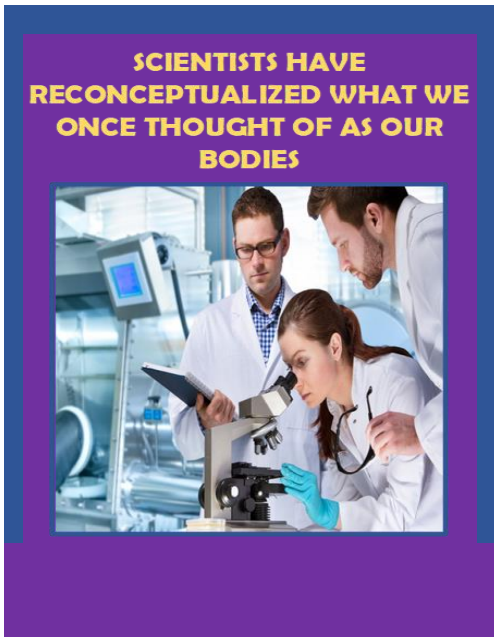
Not only do microbes provide protection, but they influence absorption, immune system activation, hormone stimulation, food substance digestion, mucus formation, antibody production, fluid secretions, motility regulation, fat and protein

modulation, bile transformation, brain-gut neural communication, and cancer protection among other things. (See the section: How Humans Rely on Their Microbes).

Scientific discoveries over the last 20 years using DNA testing, have identified thousands of new species, subspecies and strains of life forms (bacteria, viruses, protozoa, fungi, and archaea) that have never previously been known to exist in the digestive tract. The diverse and essential functions noted above of many of these microorganisms have just started to be appreciated.

The paradigm being proposed takes a holistic view of the digestive tract, *both* its organs and its microorganisms, parallel universes, living in the same space and sharing—or competing for—the same resources. The paradigm offers an approach to diagnosis and treatment of intestinal illnesses that goes beyond consideration of body cells and body organs alone.

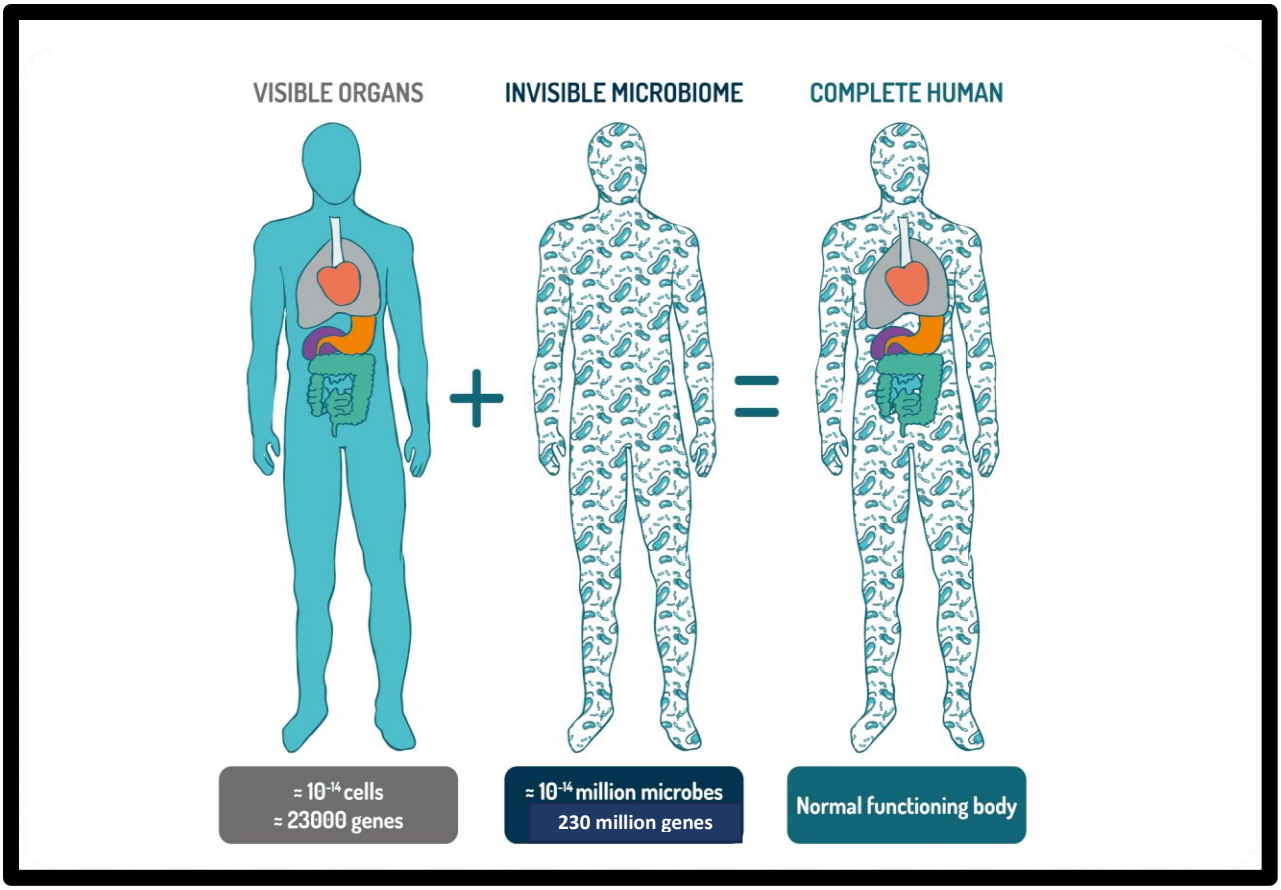
Alessio Fasano, M.D., chief of Pediatric Gastroenterology and Nutrition at Massachusetts General Hospital for Children has made the statement, "Studying one—namely the human cells and their genes—without analyzing the other--namely the microorganisms and their genes, will not provide the answers to why we develop diseases . . ." [1]



Digestive well-being requires that both the body cells and the intestinal microbe community beneficially interact in a symbiotic state with each other. To survive, each must receive nutrients as a source of energy. Feeding both will be covered in this monograph. Ways that the two systems might go awry and cause adverse reactions will be discussed. Methods of lessening gut-microbe conflicts will be suggested.

The importance of recognizing and modifying gut-microbe interactions ushers in a different approach to medical treatments. Hopefully, this monograph will serve as a useful guide.

[1]**Alessio Fasano, Gut Feeling, The Microbiome and Our Health, First U.S. edition. (Cambridge, MA: The MIT Press, 2021) p.20.**



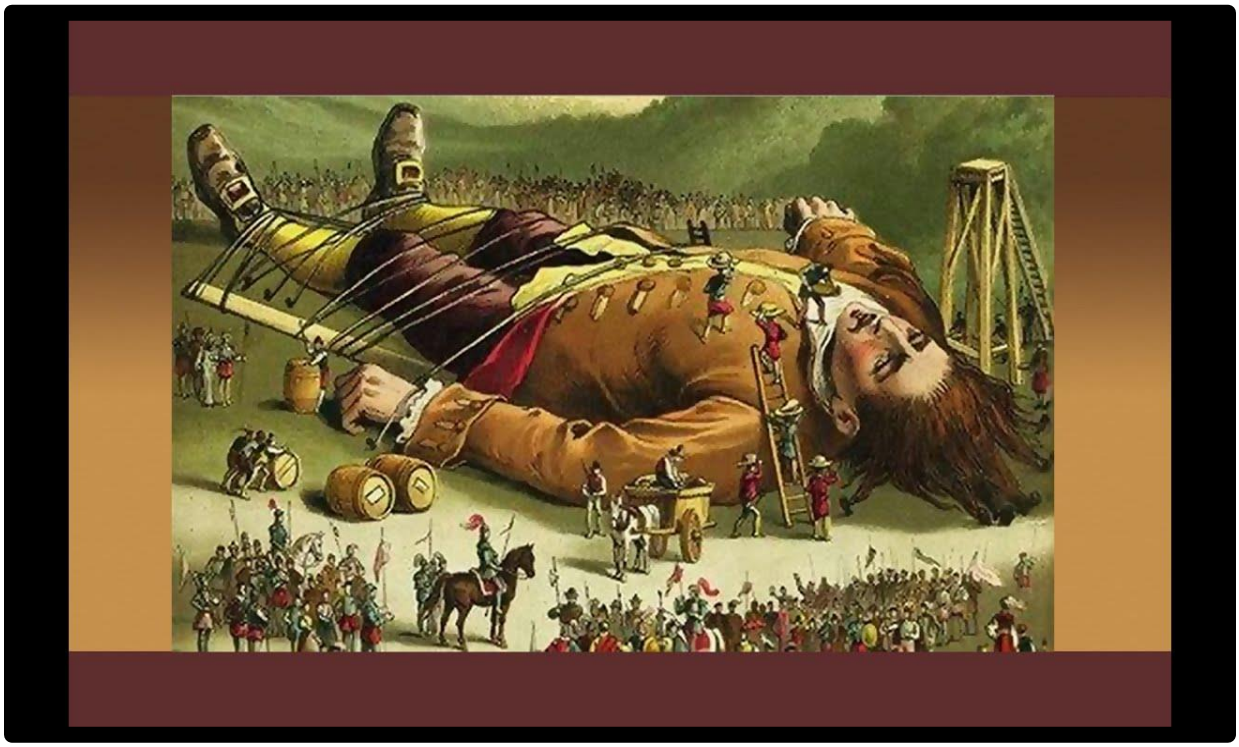
Comparing The Human Body To The Mythological Chimera

The body is much like the Greek mythological creature, the Chimera, which was composed of three different living animals, a lion, a goat, and a serpent, each with different DNA compositions living as one entity. The human body is thus chimeric with bacteria, viruses, protozoa, fungi, and archaea all coexisting together within the body.

The Mythological Chimera

Justin Sonnenburg, PhD, microbiologist at Stanford University, suggests that we regard the human body as just "an elaborate vessel optimized to accommodate our microorganisms."
If one accepts the paradigm shift suggested by Drs. Sonnenberg and Fasano, then all chronic diseases—both diagnosis and treatment--need to take into consideration the individual's microbe populations.

Perhaps Humans Are Like Gulliver In The Land Of The Lilliputians



In Jonathan Swift's satirical novel, Gulliver's Travels[1], written in 1726, the main character, Gulliver, after a journey that ends in disaster, awakens in a strange land, occupied by trillions of tiny inhabitants, the land of Lilliput. Individually, the Lilliputians were only a tiny fraction the size of Gulliver.

Gulliver's fate remained in the hands of his captors. He was bound and held captive as their prisoner. He realized that he was reliant upon them for his food, shelter, protection, and his right to remain alive.

Gulliver temporarily comes to terms with his Lilliputian captors during which time they provided him with nutrition and shelter. Gulliver, however, breaks the rules of the land of Lilliput and is sentenced to death but escapes. The remainder of the book is about Gulliver's travels.

Are we like Gulliver— suddenly dropped into a strange place at birth, a place occupied by trillions of tiny invisible forms of life, made up of bacteria, viruses, fungi, protozoa, and archaea?

Every surface in the universe into which each of us arrive, even the air, is filled with microorganisms.

These tiny lifeforms have predated humans by billions of years, existing long before human forms ever appeared. Over those billions of years, microorganisms have thrived by perfecting survival strategies.

Their gene composition, i.e., the "owners' manuals" defining how they make proteins, may be as much as 10,000 times more plentiful than genes in the human genome. In numbers, the microbiome exceeds the total population of cells of the human body by trillions—38 trillion microbial cells versus 30 trillion human cells. Without the cooperation and contributions of microbes, humans could not survive.

[1] MLA. Swift, Johnathan, 1667-1745, Gulliver's Travels. New York: Harper, 1950.

The following You Tube® recaps an overview of the microbial world. Click on one of the two yellow stars on page 1.

At the end of the video, tap on any black space to close the video and return to the monograph.

As described in the YouTube® video, some of the important ways that humans gain benefit from their microbes include the following: (See the section: How Humans Rely On Their Microbes)

- **They protect against other microorganisms that are constantly trying to invade and challenge the status quo.**

- **They process nutrients that humans select to pass through their bodies and harvest these nutrients to form energy**

primarily for their own survival but, incidentally, useful for the survival of human body cells.

- **They produce vitamins and amino acids that they share with human cells needed for human growth and development.**

- **They activate and deactivate drugs and other chemicals that humans swallow perhaps defending themselves against the toxic effects of these substances on their existence.**

- **They generate signals that regulate the human immune system, moderate human hormone production, and control the orderly cycles of birth, death, and renewal of human cells.**

Ed Yong, a Pulitzer Prize winning science journalist, in his book, I Contain Multitudes: The Microbes Within Us and a Grander View of Life[1], allows us to see how ubiquitous and vital microbes are. He summarizes their essential role stating:

> ***". . . they sculpt our organs, defend us from disease, break down our food, educate our immune systems, guide our behavior, bombard our genes with their genes, and grant us incredible abilities."***

Faced with such an overwhelming and dominant force as our microbes, the choice of mutual coexistence (i.e., mutualistic symbiosis) offers the greatest opportunities for humans to thrive.

If we adopt the paradigm that we are "Gullivers" in a universe of varied, prolific, and powerful microorganisms, then we are faced with the choice and challenge of either coexisting peacefully for mutual benefit, as Gulliver did during his early stay with the Lilliputians, or become adversaries bent on domination and destruction of each other.

Over the last century medical care providers have taken an adversarial approach to the body's microbe populations adhering to the principle that the only good microbe was a dead microbe.

If we adopt the paradigm, however, that we are "Gullivers" coexisting with our microbes, upon whom we rely, this will mean that all future scientific medical inquiries will have to be conducted with this question in mind: How does the medical or surgical intervention not only affect the body, but how does it affect the cohabiting microorganisms? Without answering that question, the study of every diet, drug, medical and surgical intervention might otherwise be incomplete and the results even misleading.

A much more nuanced view of humans and their relationship to microorganisms, like those described above, was ushered in about 20 years ago.

It is now accepted that many microbes in the body are critical partners helping to maintain a state of well-being in the human host.

How have such tiny microorganisms gained so much leverage over us? One answer is that animals made a bargain with microbes to fight off even worse microbial pathogens lurking in the environment. Although humans have a immune system capable of defending against pathogens, it's difficult for humans to keep up since microorganisms have the capability of multiplying every 20 minutes. With each multiplication microbes are capable of mutating into a more dangerous form. It became obvious that humans were incapable of accommodating to this frantic rate of reproduction, and, therefore, "recruited" their own population of microbes to work on their side.

Humans were able to offer the "recruits" a regular buffet of nutrients in a warm, dark, moist environment conducive for survival of the microorganisms. In exchange, microbes were able to defend against other disease producing microbes that might threaten the human host.

It has not been a perfect relationship, but it has worked reasonably well for nearly a half a billion years.

Much of this monograph reflects the change in thinking which recognizes the destructive capability of some microorganisms, particularly some of those that enter the body through the mouth, nose, facial sinuses, and lungs, but also appreciates the positive functions of microbes and their metabolic by-products in other parts of the digestive tract that keep us alive.

[1] Yong, Ed. I Contain Multitudes: The Microbes Within Us And A

Grander View of Life. First US edition, Bodley Head, 2016.

THERE ARE NO *GOOD* OR *BAD* MICROBES
MICROBES HAVE NO MORALS

Abstracted from Ed Yong's book,
I Contain Multitudes: The Microbes Within Us and a Grander View of Life.

Ed Yong writes ". . . in the 1870's experiments by a German physician Robert Koch and French scientist Louis Pasteur confirmed that microscopic organisms caused many diseases. Microbes, which had been largely neglected for a couple of centuries, were quickly cast as avatars of death. They were germs, pathogens, bringers of pestilence. Within two decades it was discovered that bacteria were associated with leprosy, gonorrhea, typhoid, tuberculosis, cholera, diphtheria, tetanus, and plague. Microbes became synonymous with squalor and sickness. They became foes for us to annihilate and repel."

“Today, we know this view is wrong” continues Yong. “Some bacteria cause disease but are in the minority. Most are harmless, and many are even beneficial. We now know that the trillions of microbes that share our bodies – the so- called microbiome – are an essential part of our lives. Far from making us sick, they can protect us from disease; digest our food, train our immune system, and influence our behavior.”

Yong goes on to say, “These discoveries have shifted the narrative. Many people now see microbes as allies to be protected. Slowly, the view that ‘all bacteria must be killed’ is giving ground to ‘bacteria are our friends and want to help us.

“The problem is that the latter view is just as wrong as the former. We cannot simply assume that a particular microbe is ‘good’ just because it lives inside us. There is no such thing as a ‘good microbe’ or a ‘bad microbe.’ These broad-brush terms belong in children’s stories. They are ill-suited for describing the messy, fractious, contextual relationships of the natural world.”

“In reality, bacteria exist along a continuum of lifestyles. If they do us harm, we describe them as parasites or pathogens. If they exist neutrally, we call them commensals. If they benefit us, we bill them as mutualists.”

“But these are hardly fixed categories. Some microbes can slide from one end of this parasite-mutualist spectrum to the other, depending on the strain and on the host they find themselves in.”

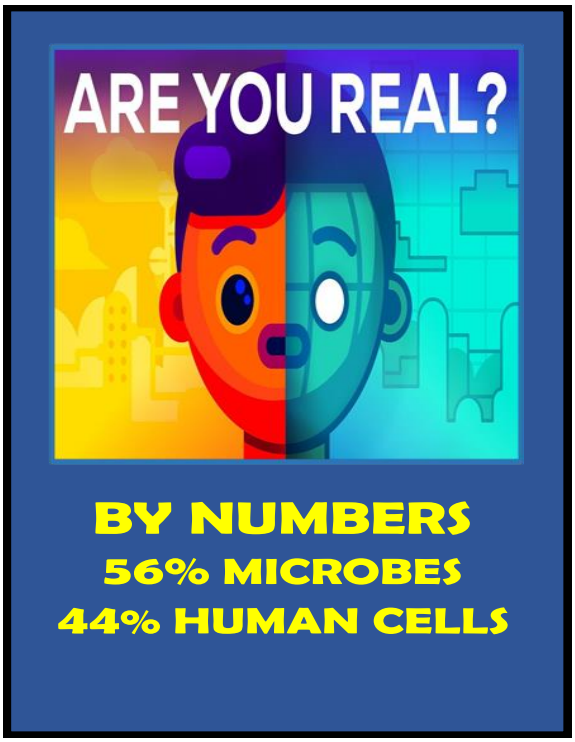
“Other microbes can be pathogenic and mutualist at the exact same time. The stomach bacterium Helicobacter pylori is well known as a cause of ulcers and stomach cancer. But it also protects against esophageal cancer – and it is the same strains that account for both these pros and cons. H. pylori is neither a good nor a bad microbe; it’s both.”

“The value of microorganisms within the body is situational--based on microbes’ density, diversity, location, and functional capabilities.”

Ed Yong concludes by saying, “All of this means that labels like mutualist, commensal, pathogen, or parasite don’t work as definitive badges of identity. These terms are more like states of being, like hungry, awake, or alive, or behaviors like cooperating or fighting. . .” They describe how two partners relate to one another but only at a given time and place.

Staggering And Fantastical Numbers

IT’S HUMBLING TO KNOW THAT LESS THAN HALF THE HUMAN BODY IS HUMAN



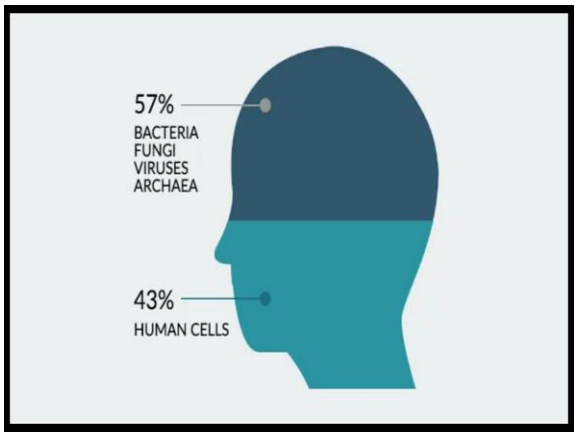
"Because we humans are big and clever enough to produce and utilize antibiotics and disinfectants, it is easy to convince ourselves that we have banished bacteria to the fringes of existence. Don't you believe it. Bacteria may not build cities or have interesting social lives, but they will be here when the Sun explodes. This is their planet, and we are on it only because they allow us to be."—Bill Bryson

Adult Humans Have 30 Trillion Cells With 22,000 genes

A consortium of researchers organized by the National Institute of Health mapped out the microbe population of large numbers

of healthy adult humans. Two hundred members from eighty universities and science institutions formed the Human Microbiome Project (HMP).

The researchers calculated that more than 10,000 different microbe species exist in adult humans. They established that the total number of microbial cells far outnumber those of the human host—39 trillion microbe cells versus 30 trillion human cells.



A New You . . .

About 330 billion of your cells are replaced every 24 hours, equivalent to about 1% of all your cells. In the course of 80 to 100 days, 30 trillion cells will have been replenished—the equivalent of a new you.[1]

[1] **Sender, R. The distribution of cellular turnover in the human body, *Nature Medicine*, Vol. 27; January 2021.**

Researchers Claim That the Cohabiting Microbes In The Human Body Contain 230 million Genes—Maybe More

Just like human cells, every microorganism contains genes. Dr. Brandon Tierney and colleagues at Harvard Medical School studied the microbiomes in 3,655 adults and estimated that the microbe population had over 10,000 times more genes (230 million) compared to the 23,000 genes in the human genome[1].

Their findings suggest that the mouth and the gut microbiomes have a staggering amount of microbial genetic diversity, and that at least half of the genes identified were unique to an individual.

Their research concluded that the adult human gut microbiota may contain as many as 150,000 different microbe strains, and that even minute variations in the composition of the microbiome may impact human health and disease. They further pointed out that even microbes of the same strains can carry different genes.

We can conclude. . . we are outnumbered, outpowered and outlived by our microbes. They have existed 10,000 times longer than we have as humans, and in that time, have perfected their survival skills. They conduct activities in the human body that humans cannot perform for themselves and without which we could not survive.

[1] **Tierney, BT, The landscape of genetic content in the gut and human microbiome, *Cell Host & Microbe*, Vol 26:2 (283-295)**

In The Beginning . . .
How Infants Get Their First Microbes

The newborn gets its initial collection of microorganisms at the time of birth as it passes through the birth canal (unless born by Cesarean section). The newborn acquires a veneer of maternal secretions containing five kingdoms of life— bacteria, viruses, fungi, protozoa, and archaea--the microbiota. The

microbiota combined with their genes are collectively known as the *microbiome.*

Large numbers of microbes enter the oral cavity and nasal passages of the baby during the birthing process and are swallowed, taking up residence in the digestive tract. These microbes are ideally suited for metabolism of breast milk.

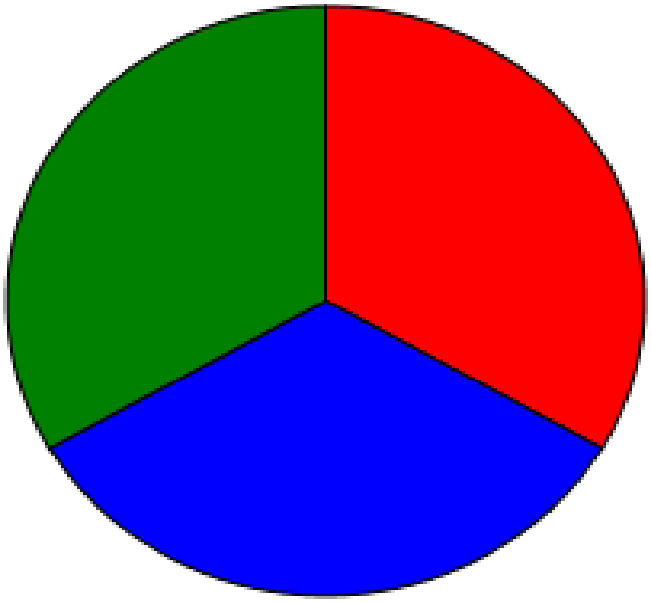
During the next few years of life, the infant's microbe population is remodeled primarily based on the infant's genes, diet, exposures to antibiotics, and environment and increases dramatically after weaning.[1] (*A comprehensive list of factors that influence the composition of the microbe population can be found in List I at the end of the monograph.)*

Every adult's microbiome is unique like their fingerprint. Even identical twins raised in the same household have different microbiomes.[2]

[1] Yatsunenko, T. et al., Human gut microbiome viewed across age and geography, *Nature* 486 222-227 (2012).

[2] Goodridh, J.K. et al., Human genetics shape the gut microbiome. *Cell* 159, 789-799 (2014).

Dividing The Digestive Tract Into Three Zones



Dividing the digestive tract into three functional zones may illustrate the importance of controlling the density, diversity and location of microorganisms in the digestive tract.

Zone One: The first functional zone of the digestive tract is made up of the oral cavity, esophagus, and stomach.

ZONE I

<u>Physical changes</u>: Zone I serves primarily as the body's food processor physically changing the size and the consistency of nutrients in preparation for absorption.

<u>Chemical changes:</u> Chemical alteration of nutrients in the oral cavity occurs~~,~~ but in modest amounts, with salivary amylase altering the chemical composition of sugars and oral lipase beginning the chemical alteration of fats. Chemical digestion of proteins, however, does not occur until nutrients reach the stomach where protein digesting enzymes are present.

<u>Microbial changes:</u> The first zone contains billions of microorganisms that are continually entering the oral cavity.

***Culling microorganisms*: Microorganisms entering the oral cavity are there to establish a new living space where they can thrive and replicate. Exposure to items containing sucrose (table sugar) results in rapid proliferation of *Streptococcus mutans*, a bacteria that is genetically programmed for sugar**

metabolism and, in so doing, produces chemicals that can destroy dental surfaces causing decay.

Saliva, produced by glands in the mouth, contains antibacterial chemicals that reduce overgrowth of microbes. Additionally, vigorous oral hygiene measures including brushing, flossing, using fluoride toothpaste, interdental brushes, and water irrigations along with visits to dental professionals to remove microbe deposits (plaque and tartar) help prevent decay and inflammation in the oral cavity.

Invasion of tissue by pathogenic microorganisms causes inflamed gums (gingivitis), dental decay (cavities), and deep gum disease (periodontitis). In every human, there is a continuous battle in the oral cavity between pathogenic organisms and the body's defense mechanisms.

Every 24 hours, humans swallow as many as 100 *billion* microorganisms. This number is based on studies done in those subjects with a "perfect" mouth—no gingivitis, no dental cavities, no caps/crown, no history of root canal procedures, no history of receding gums, no oral cavity ulcerations, tumors or mucosal disruption, and no deep gum disease, periodontitis.[1] (See the section: Staggering Numbers.)

> **[1] Schmidt, T., Extensive transmission of microbes along the gastrointestinal tract, *eLife.* Feb. 12, 2019; 8: e42694**

Humans defend against this tsunami of organisms coming into the stomach by producing gastric acid and protein dissolving enzymes. If there is sufficient gastric acid and proteolytic

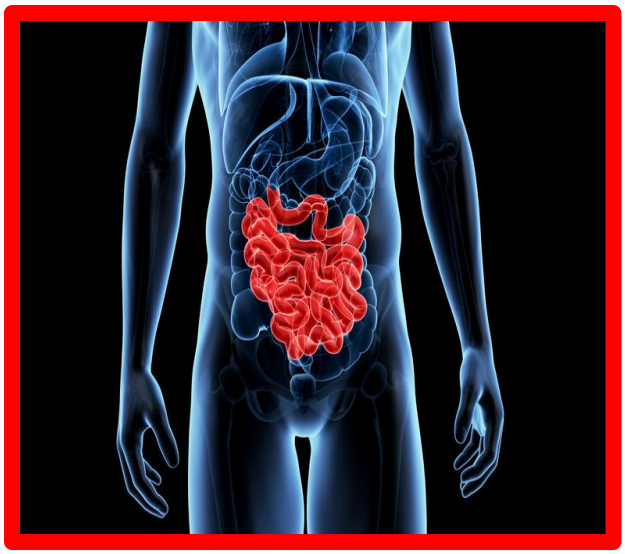
enzymes present in the stomach, 99% of swallowed organisms are destroyed. (See the section: Lessons Learned From The Turkey Vulture)

When the concentration of acid in the stomach is reduced, the risk of passing large numbers of microorganisms into the small intestine increases. (See the section: SIBO). Low gastric acid concentrations can exist in any of the following conditions:

- **The use of acid reducing medications and other medications that interfere with acid production**
- **Autoimmune diseases of the gastric lining, e.g., pernicious anemia**
- **Infection of the gastric lining with the bacteria H. pylori**
- **Weight reduction or other types of stomach surgeries that decrease the surface area of acid producing cells**
- **Retrograde flow of bile from the small bowel back into the stomach**

Zone II: The second zone in the adult human includes the 22 feet of small intestine and accessory digestive organs--liver, gallbladder, and pancreas. This zone can be considered the breadbasket of the gut, designed for quickly harvesting energy from sugars, fats, and proteins. It is the major source of digestion and absorption in the human body of nutrients, minerals, vitamins, and water.

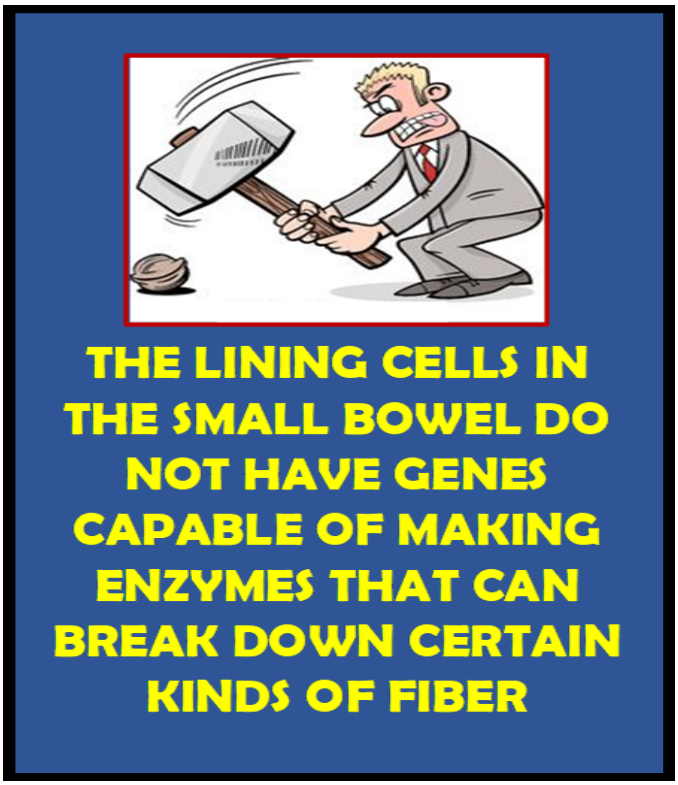
ZONE II



***Physical changes*:** **By the time nutrients reach the second zone from the stomach they have been converted into a semiliquid mass called chyme. The conversion to a liquid consistency increases its surface area to facilitate further digestion and absorption.**

Chemical changes: **Processing of nutrients by enzymes, takes place in the second zone in preparation for passage of the nutrients into the body.**

Since transit through the small intestine occurs over an average of five hours, processing must be done quickly. Zone II has only a modest repertoire of genes that are programmed to accomplish the digestive processes of breaking down sugars, fats, and proteins.



Undigested nutrients such as dietary fiber, proceed into the final 5 to 6 feet of the digestive tract, the large intestine, which, along with the last few feet of the small bowel, make up Zone III.

Microbial changes: **Although 99% of the swallowed 100 billion microorganisms may have been destroyed in the acid pool of the stomach, that still leaves a billion acid resistant microbes that survive and can pass into Zone II. An example of a surviving microbe is *Porphyromonas gingivalis,* which is one of the principal bacteria found in deep gum disease (periodontitis). *P. gingivalis* can evade the proteolytic enzymes and acid in the stomach and is able to resist the body's immune system thus facilitating its survival. *P. gingivalis* has been found to exist in feces and colon tissue samples from patients with colon cancer.[1]**

[1] **Kerdreux, M., Porphymonas gingivalis in colorectal cancer and its association to patient prognosis, *J. Cancer*, 2023; 14(9): 1479-1485.**

Some microbes exist as spores and are resistant to acid and enzymes in the stomach. They may, likewise, pass into the small intestine, i.e., Zone II.

Bile delivered from the liver and gallbladder and pancreatic secretions released from the pancreas gland have antimicrobial effects and mitigate overgrowth of microorganisms that may have survived passage through Zone I. Defects, however, in production of bile by the liver, alterations of bile by medications (including cholesterol lowering drugs), surgical alteration of bile flow following surgical removal of the gallbladder, or changing how bile reaches nutrients after certain weight reduction surgeries all may result in reducing the capability of bile to act as an antimicrobial agent.

Likewise, defects in pancreas production of enzymes due to pancreatic pathology may diminish pancreatic enzymes limiting their effectiveness as antimicrobial agents. In both instances, microbes may replicate in Zone II in large amounts resulting in a condition known as small intestinal bacterial overgrowth (S.I.B.O.).

S.I.B.O.

DEFINITION: The definition of SIBO presently lacks precision and consistency. The term is generally used when symptoms, clinical signs and laboratory tests are attributed to a change in the population of bacteria or the composition of the population of the small intestine.

The term arose from studies searching for an explanation for malabsorption. The findings from these studies demonstrated that bacteria populating the small intestine were able to metabolize amino acids, deconjugate bile acids, consume B12, synthesize folic acid, and cause injury to the small intestinal lining, and that clinical improvement or reduction in symptoms could be achieved with antibiotics.

DIAGNOSIS: Initial studies to diagnose SIBO were carried out by passing tubes into the small intestine of patients and culturing the fluids. The widespread application of this form of diagnosis

was limited, however, because of the invasive nature of the procedure, problems with contamination, and challenges presented by relying on bacterial cultures.

In recent years, the diagnosis of SIBO has been advanced with the use of breath tests.[1] Breath tests using various types of sugars have been designed to measure exhaled hydrogen, methane and hydrogen sulfide as surrogate markers for bacterial overgrowth. Issues, however, to this type of testing have included variability in study protocols, interference from confounding factors, contribution of gases produced in the oral cavity particularly in subjects with periodontal disease and lack of agreement on diagnostic criteria.

[1] Achufusi, T., Small intestinal bacterial overgrowth: comprehensive review of diagnosis, prevention and treatment methods*. Cureus* 12(6): e8860. DOI 10.7759/Cureus.8860.

A recent innovation using a capsule-based technology provides real-time measurements of the number of microorganisms that exist in the small intestine and their metabolites[2]. Until newer technologies advance the science, care providers may have to rely on treatment trials with antibiotics and judge the patient's response.

[2] Waimin JF, Smart capsule for non-invasive sampling and studying of the gastrointestinal microbiome. *RSC Adv.,* Apr 2023;10(28).

SYMPTOMS: **Symptoms linked to SIBO have included the following:**

- **Loss of appetite**
- **Abdominal pain**
- **Nausea**
- **Bloating**
- **Abdominal distention**
- **Diarrhea**
- **Unintended weight loss**
- **Vitamin and mineral deficiencies**

DISEASES AND DISORDERS ASSOCIATED WITH SIBO: **There are five general categories of diseases and disorders that have been associated with the presence of bacterial overgrowth. These five associated areas include the following:**

- **SIBO ASSOCIATED WITH ABNORMAL SMALL INTESTINAL MOTILITY**
  - **Hypothyroidism**
  - **Diabetes**
  - **Scleroderma**
  - **Amyloidosis**
  - **Acromegaly**
  - **Gastroparesis**
  - **Use of opiate drugs**
  - **Use of other motility suppressing drugs**
- **SIBO ASSOCIATED WITH ALTERED ANATOMY**
  - **Small intestinal diverticulosis**
  - **Surgical alterations—e.g., gastrectomy, bariatric surgery, colectomy**
  - **Intestinal strictures—e.g., Crohn's disease, radiation, surgery**
  - **Intestinal adhesions**

- Blind loops
- Fistula between the stomach and colon
- Fistula between the small bowel and colon
- Surgical or other impairments of the valve between colon and small bowel

- **SIBO ASSOCIATED WITH LOW CONCENTRATIONS OF STOMACH ACID**
  - Long term use of acid suppression
  - Helicobacter infection of the stomach
  - Atrophic gastritis
  - Duodeno-gastric reflux of bile
  - Pernicious anemia

- **SIBO ASSOCIATED WITH IMMUNE DEFICIENCY**
  - Inherited immune deficiency.
  - Acquired immune deficiency, e.g., AIDS, severe malnutrition.

- **SIBO ASSOCIATED WITH MULTIPLE FACTORS**
  - Chronic pancreatitis
  - Celiac disease
  - Tropical sprue
  - Crohn's disease
  - Abdominal radiation
  - Liver disease
  - Late stage kidney disease
  - Elderly

- **TREATMENT OF SIBO**

With the limitations of current diagnostic techniques, clinicians often initiate an empiric trial of antibiotics as a diagnostic tool in those suspected of having the condition.

The strategy, however, in itself, can be problematic since it places those patients who receive an empiric trial of antibiotics at increased risk of developing Clostridium difficile colitis and the development of antibiotic resistant organisms.

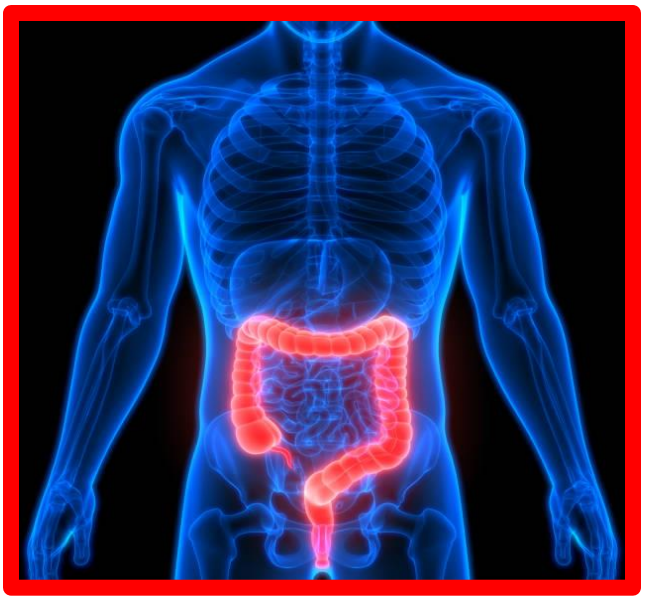
Several broad-spectrum antibiotics have been used for treatment including tetracyclines, fluoroquinolones, co-trimoxazole, and rifaximin. Rifaximin has emerged as the preferred antibiotic agent for SIBO management since it has a reduced toxicity profile and may be capable of preserving colon microorganisms while increasing the relative abundance of Lactobacillus and Bifidobacterium in the gut.[1]

A major drawback to using Rifaximin, however, has been the enormous cost to the patient.

> **[1] Maccaferri, S., Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. *J Antimicrob Chemother*. 2010, 65:2556-2565.**

Zone III: The last portions of the small intestine and the colon make up the third functional zone of the intestinal tract. These organs are more than a conduit for waste products but act as important multifunctional organs.

ZONE III



Motility slows in Zone III. In normal adults, it may take 20-40 hours for undigested residue to traverse the colon alone. During that time, complex interactions occur between colon microorganisms, absorptive lining cells and the body's immune system. (See the section: The Importance of The Large Intestine.)

BACTERIAL CONCENTRATIONS IN THE DIFFERENT ZONES OF THE HUMAN BODY[1]

Due to different conditions that exist in the different zones of the body, as noted above, the concentrations of bacteria vary widely. For example, the concentration per cc. of bacteria in dental plaque is nearly identical to the concentration of bacteria in the colon. (See the section: The Oral Cavity: A Potential Source of Chronic Inflammation).

LOCATION	NUMBER OF BACTERIA	VOLUME OF THE ORGAN
Colon (Large intestine)	100 billion/cc	400 cc
Dental plaque	100 billion/cc	Less than 10 cc
Ileum (lower small intestine)	100 million/cc	400 cc
Saliva	100 million/cc	Less than 100 cc
Stomach	10 thousand/cc	900cc
Duodenum (upper small intestine)	10 thousand/cc	400 cc

[1] Sender, R., Revised Estimates for the Number of Human and Bacteria Cells in the Body, *PLOS Biology*, 14(8): e1002533. doi: 10.1371/journal.pbio

Lessons Learned From The Turkey Vulture

The stomach of the turkey vulture illustrates some of the many attributes of having gastric acid. Acid produced by the vulture's stomach serves not only as a digestant but also as protection from infection.

The stomach acid concentration of the turkey vulture is stronger than battery acid and 100 times stronger than acid in

the human stomach. Turkey vultures have the lowest gastric acid pH of any animal in the animal kingdom.[1]

The gastric acid in the stomach of the turkey vulture aids in the digestion of dead flesh and bones of carcasses. The acid also protects the vulture from getting infected by pathogenic organisms that are present in rotting flesh including bacteria that cause anthrax and botulism. These bacteria do not affect the vulture but cause disease in other animals in the animal kingdom.[2]

Human gastric acid, likewise, serves both digestive and protective functions. Acid activates protein dissolving enzymes (pepsin) in the stomach that aids in digestion. It also destroys billions of microorganisms that are swallowed daily coming from the oral cavity, nasal passages, sinuses and lungs thereby minimizing their passage into the remainder of the digestive tract.

The acid pH in the stomach also reduces the toxicity of bile that refluxes from the duodenum into the stomach, so called, duodeno-gastric reflux (DGR). DGR is quite common following removal of the gallbladder and after various types of stomach surgery. It has also been shown that small amounts of duodeno-gastric reflux occur normally after feeding and during fasting[2,3] .

The benefits of gastric acid are, therefore, diminished when acid reducing medications are taken like Prilosec®, Nexium®, Protonix®, Prevacid®, Dexilant® and Zegerid®.

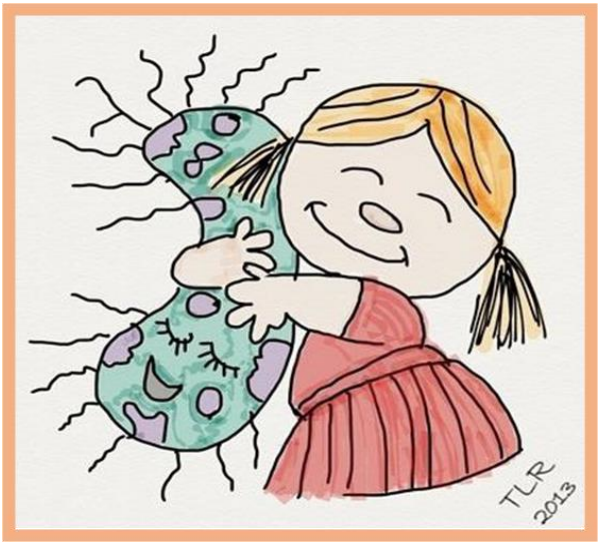
<u>Bottom line:</u> Medications that reduce acid production in the stomach may remove one of the body's major barriers to digestive illnesses, and thus should be used judiciously.

[1] National Wildlife Educational report.

[2] Miller-Lissner et.al, Novel approach to quantify duodenogastric reflux in healthy volunteers and in patients with type I gastric ulcers, *Gut*, 1983, 24, 515-517.

[3] Fein, M, et.al., Fiberoptic Technique for 14-Hour Bile Reflux Monitoring*, Dig. Dis. Sci*. 1996, 41, 216-225

How Humans Rely on Their Microbes



The body relies on many of its microbes to assist with essential functions. These functions include metabolism, immunity, protection, and communication with the brain.

EXAMPLES OF FUNCTIONS THAT MICROBES DO FOR THE BODY

(*PRIMARILY IN ZONE III)*

- **Help digest nutrients.[1]**
- **Generate metabolites used by the body as energy for intestinal cells.[1]**
- **Control blood sugar levels by stimulating insulin production.[2]**
- **Produce vitamins like vitamin B12 and vitamin K.[3]**
- **Regulate and control the storage of fat.[4]**
- **Regulate the secretion and composition of bile.[5]**
- **Modulate the sensation and sensitivity of the gut lining.[6]**
- **Regulate hormones responsible for hunger and satiety.[7]**
- **Regulate hormones responsible for bone growth.[8]**
- **Reinforce the gut lining defenses against toxins.[9]**
- **Reinforce the gut lining defenses against harmful microbes.[9]**
- **Reinforce the gut lining defenses against harmful food antigens (additives, preservatives, etc.).[9] (See List 2)**
- **Educate the immune system to respond appropriately to threats.[10]**
- **Regulate motility of the intestinal tract.[11, 12]**

- **Regulate transport across the endothelial surface lining of the intestines, i.e., permeability.[13]**
- **Influence the transport between the intestinal lining cells and the vascular system.[14]**
- **Stimulate production of hormones that control mood and behavior.[15]**
- **Help prevent the development of intestinal malignancies.[16]**
- **Regulate the metabolism of micronutrients including carotenoids, vitamin A, vitamin D, vitamin C, folic acid, iron and zinc.[17]**

[1] Brown, Rosa, *Effects of Gut Microbes on Nutrient Absorption,* Nutr Clin Pract 2012 April; 27(2): 201-214.

[2] Khan, Muhammad, *Microbial Modulation of Insulin Sensitivity*, Cell Metab., 20, Nov 4, 2014.

[3] Pham, Van, *Vitamins, The Gut Microbiome and Gastrointestinal Health in Humans,* Nutrition Research, (95), Nov 2021, 35-53.

[4] Backhed, Fredrik, *The Gut Microbiota as an Environmental Fact That Regulates Fat Storage,* PNAS 101 (44) 15718-15723.

[5] Guzior, Douglas, *Review: Microbial Transformations of Human Bile Acids,* Microbiome 9, Article:140 (2021).

[6] van Thiel, Isabelle, *Microbiota-Neuroimmune Cross Talk in Stress-Induced Visceral Hypersensitivity of the Bowel*, Am. J. Physiology, May 28, 2019.

[7] **Aldock, J.** ***Is Eating Behavior Manipulated by Gut Microbiota? Evolutionary Pressures and Potential Mechanisms,*** **Bioassays, 36(10), 940- 949.**

[8] **Jau-Yi Li,** ***Parathyroid Hormone-Dependent Bone Formation requires Butyrate Production by Intestinal Microbiota*****, JCI, 1767-81, January 2020.**

[9] **Claus, S.** ***The Gut Microbiota: A Major Player in the Toxicity of Environmental Pollutants?*** **NPJ Biofilms and Microbiomes, 2017 June 22; 3: 17001.**

[10] **Katsnelson, A.** ***How Microbes Train our Immune System,*** **Nature (2021).**

[11] **Waclawikova, Barbora,** ***Gut microbiota—Motility Inter-regulation: Insights In Vivo, Ex Vivo and In Silico Studies,*** **Gut Microbes. 2022; 14(1): 1997296.**

[12] **TianRong Ma*****, Effect of the gut microbiota and their metabolites on postoperative intestinal motility and its undelying mechanisms,*** **Journal of Translational Medicine, (2023) 21:349**

[13] **Ghosh, S.,** ***Review: Regulation of Intestinal Barrier Function by Microbial Metabolites,*** **Cellular and Molecular Gastroenterology and Hepatology, 2021.**

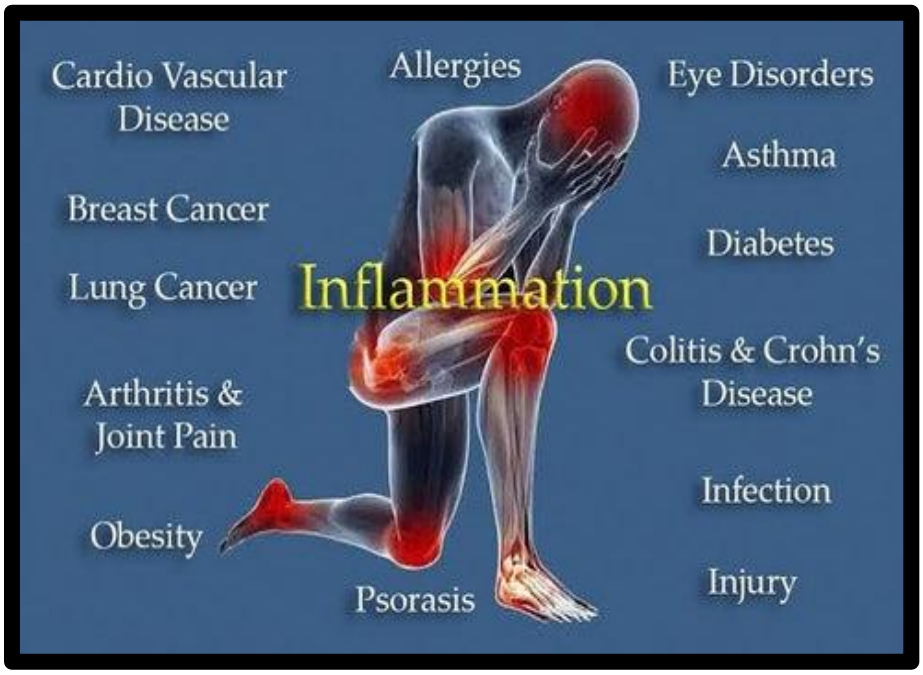
[14] **Tommaso, N.,** ***The Gut-Vascular Barrier as a New Protagonist in Intestinal and Extraintestinal Siseases*****, Int. J. Mol. Sci, 2023 Jan: 24(2).**

[15] **Appleton, J.,** ***Commentary: The Gut-Brain Axis: Influence of Microbiota on Mood and Mental Health,*** **Integrative Medicine, vol 17 (4), Aug. 2018.**

[16] **Yujie Zhao, *The Relationship Between Plant-Based Diet and Risk of Digestive System Cancers: An Analysis Based on 3,059,009 Subjects,* Frontiers in Public Health, June, 2022.**

[17] **Dingbo, L, *The microbiome as a major function of the gastrointestinal tract and its implication in micronutrient metabolism and chronic disease*, Nutrition Research, vol. 112, 2023, 30-45.**

INFLAMMATION-- THE BEDROCK OF CHRONIC ILLNESSES

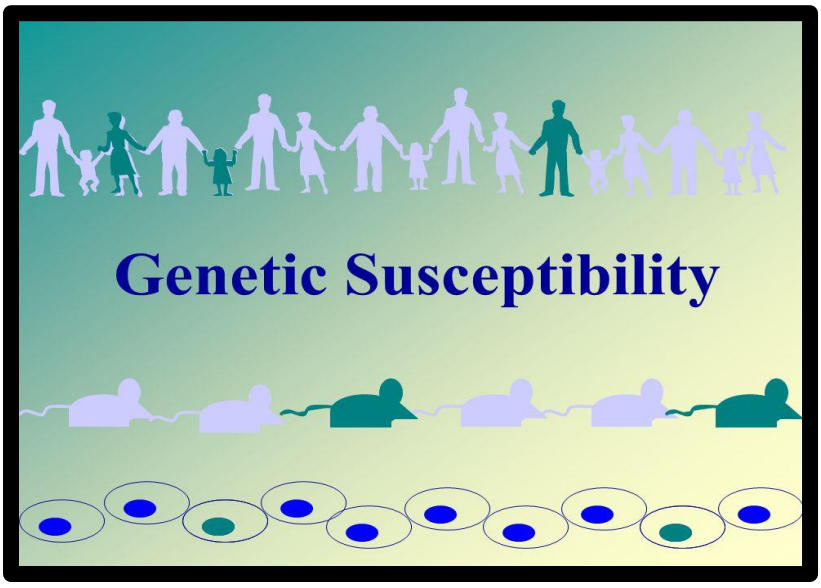


Dr. Alessio Fasano takes the position that inflammation is the underlying physiologic process causing most chronic illnesses. He describes five factors that are responsible for chronic inflammation. These five factors parallel those described previously as those which determine human health.

- **Genetics**—the inherited susceptibility to have an illness
- **Exposures**— the totality of every exposure including chemical, mechanical, environmental, and societal that have occurred since the moment of conception
- **Tissue permeability**—the regulation of entry of foreign substances into the body
- **Immunity**—the ability of the body to responses to threats
- **Microbiome**—the density, diversity, location and functionality of microorganisms that live in and on the body

Analyzing these factors is a helpful way for establishing a logical approach to the diagnosis and treatment of chronic digestive illnesses.

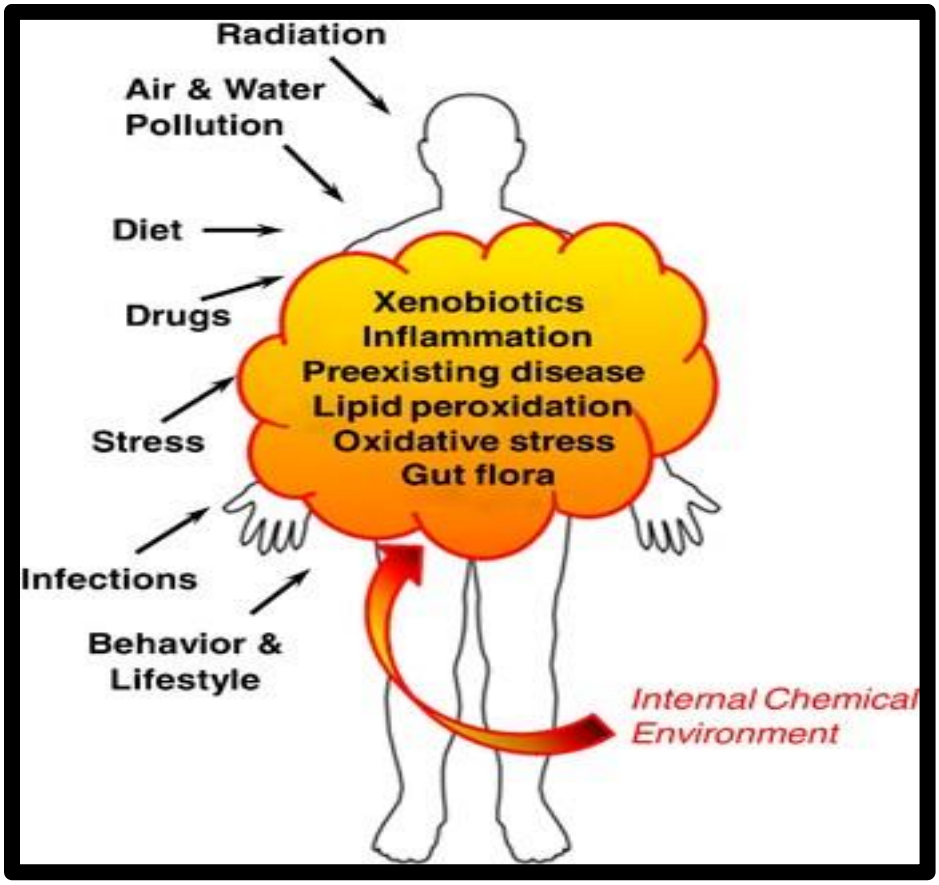
INFLAMMATION – GENETIC SUSCEPTIBILITY



Screening to identify genetic defects is available but only for a few conditions compared to all the potential illnesses that can befall a human, e.g., celiac disease, phenylketonuria, pernicious anemia, hereditary polyposis syndrome, iron storage disease, hemophilia, among others.

Modification of genes (splicing, editing and substitution of genes) to correct inflammation is presently not an option. Genetic susceptibility, however, is one of the essential elements of inflammation.

Inflammation–Exposures Exogenous and Endogenous



Exposures begin at the moment of conception. They can take two forms, external, i.e., exogenous, namely those received from outside the body and internal, i.e., endogenous, those that are present and expected inside the body. The number of exposures over a lifetime both *in utero* and after birth are innumerable.

Four major categories of external exposures in humans include the following:

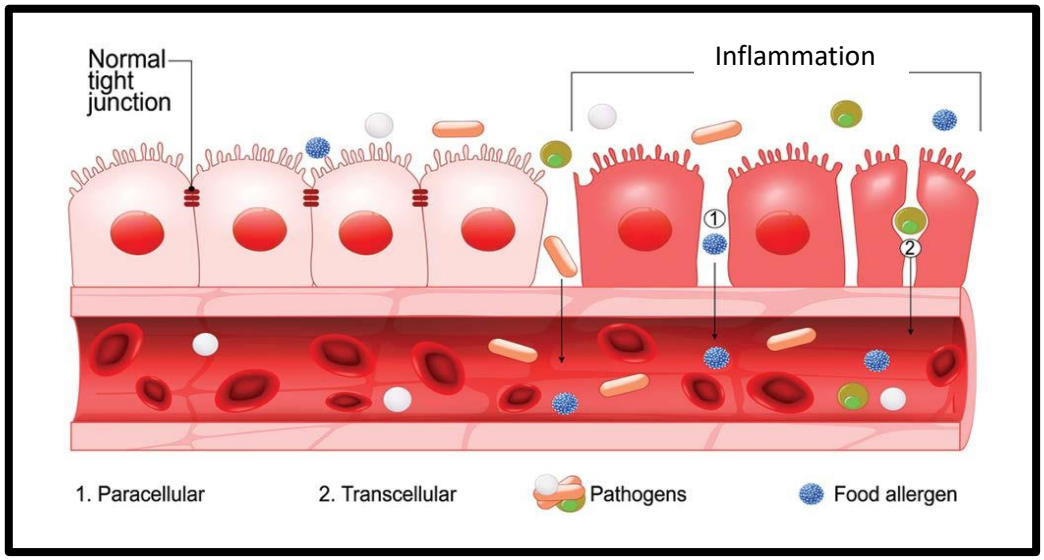
- **Nutrients (foods and beverages)**
- **Medications (both regulated pharmaceuticals and unregulated supplements, i.e., nutraceuticals) including alcohol, tobacco, and recreational drugs**
- **Environmental exposures including air, water, sunlight, radiation, gravity, temperature, gases, toxins, food additives and environmental pollutants**
- **Microorganisms**

Major internal exposures include the following:

- **Bile**
- **Enzymes**
- **Gases**
- **Hormones**
- **Mucus**
- **Pancreas secretion**
- **Saliva**
- **Stomach acid**

A more complete list of factors that influence the composition of the human microbiome can be found at the end of the monograph. (See Table I).

Inflammation–Abnormal Epithelial Permeability



The intestinal barrier is designed to prevent the entry into the body of microorganisms, toxins, food antigens and other harmful foreign elements while regulating the absorption of nutrients, electrolytes and water.

Disruption of the intestinal barrier has frequently been referred to as "leaky gut syndrome." "Leaky gut", however, is not a real medical diagnosis although some conditions exhibit changes of increased intestinal permeability. It is more appropriately known as "abnormal intestinal barrier function".

Some of the condition that have been associated with an abnormal intestinal barrier function including the following:

- **Bacterial and viral infections[1]**
- **Obesity[2]**
- **Fatty liver disease[3]**

- **Inflammatory bowel disease[4]**
- **Alcohol induced liver disease[5]**
- **Cirrhosis of the liver[6]**
- **Pancreatitis[7]**
- **Diabetes[8]**
- **Depression[9]**
- **Neurodegenerative disorders[10], and**
- **Cardiovascular disease[11]**

[1] Hussein, I, Role of gut microbiota in Covid-19: an insight into pathogenesis and therapeutic potential*, Front. Immunol.* 14 October 2021, volume 12.

[2] Nagpal, R. Obesity-linked gut microbiota dysbiosis associated with derangements and gut permeability and intestinal cell homeostasis independent of diet, *J. Diabetes. Res*. 2018, Sep 3.

[3] Kessoku, T., The role of leaky gut in nonalcoholic fatty liver disease: a novel therapeutic target, *Int J. Mol Sci.,* 2021 Aug; 22(15): 8161.

[4] Shunying, Y, Leaky gut in I.B.D: Intestinal barrier—gut microbiota interaction*, J. Microbiol Biotechnol*., 2022 July 28; 32 (7): 825-834.

[5] Zhanxiang, Z. Targeting the gut barrier for the treatment of alcoholic liver disease*, Liver Res*. 2017 Dec; 1 (4): 197-207.

[6] Fukui, H. Gut-liver axis in liver cirrhosis: how to manage leaky gut and endotoxemia*, World J Hepatol*. Mar 27, 2015; 7 (3): 425-442.

[7] Pagliari, D. Gut microbiota-immune system cross talk and pancreatic disorders*, Mediators Inflamm*. Feb 1, 2018.

[8] Sadagopan, *A,* Understanding the role of the gut microbiota men in diabetes and therapeutics targeting "leaky gut": A Systematic Review, *Cureus* 15 (7): July 8, 2023.

[9] Liu, L Gut microbiota and its metabolites in depression: from pathogenesis to treatment *eBio Medicine,* March 22, 2023, (https://doi.org/10.1016/j.ebiom. 2023.104527j.)

[10] Seguella, L, Leaky gut, dysbiosis, and enteric glia activation: the trilogy behind the intestinal origin of Parkinson's disease*, Neural Reg Res*. 2020 Jun; 15 (6): 1037-1038.

[11] Lewis, C., Intestinal barrier dysfunction as a therapeutic target for cardiovascular disease. *Am J Physio Heart Circ Physiol* 319: September 28, 2020

A *causal* relationship, between intestinal barrier dysfunction and all of the above referenced conditions still remains a matter of investigation and scientific debate. The question remains, "is the leaky dysfunction caused by the disease or is the disease caused by the leaky dysfunction?"

Inflammation – Immunity

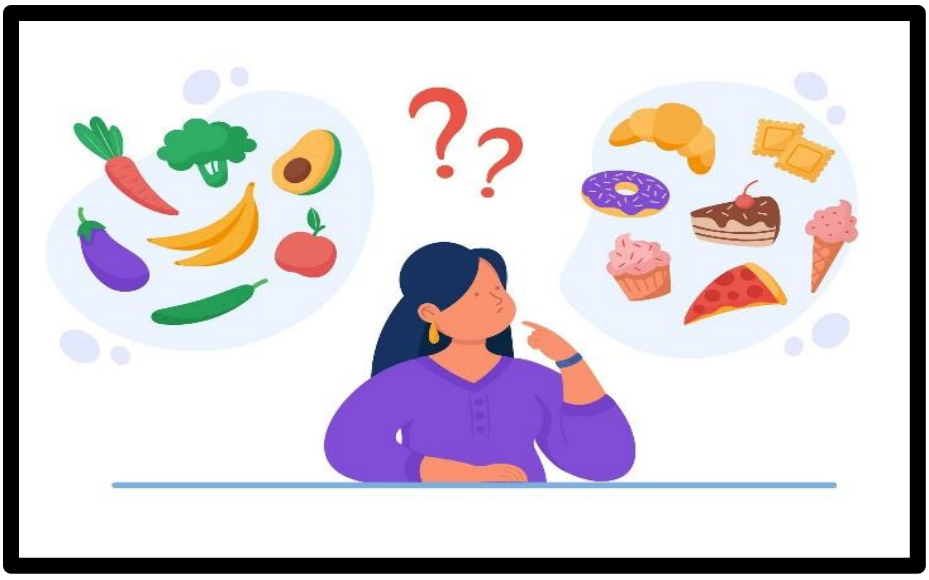
Immunity is the ability of the body to recognize and resist substances that are perceived to be harmful. A whole army of specialized cells within the body can recognize harmful bacteria, viruses, and fungi and can launch a defensive attack to prevent invasion of threatening substances.

Increased permeability can be compounded by the presence of an unruly, hyper-belligerent immune system that fails to initiate an appropriate response to the threats and/or lacks the discipline to withdraw from the fight when the threats have been neutralized. The chemical and antibody response initiated by the immune system in defense of the body may proceed unfettered causing local tissue damage as well as disease to distant organs.

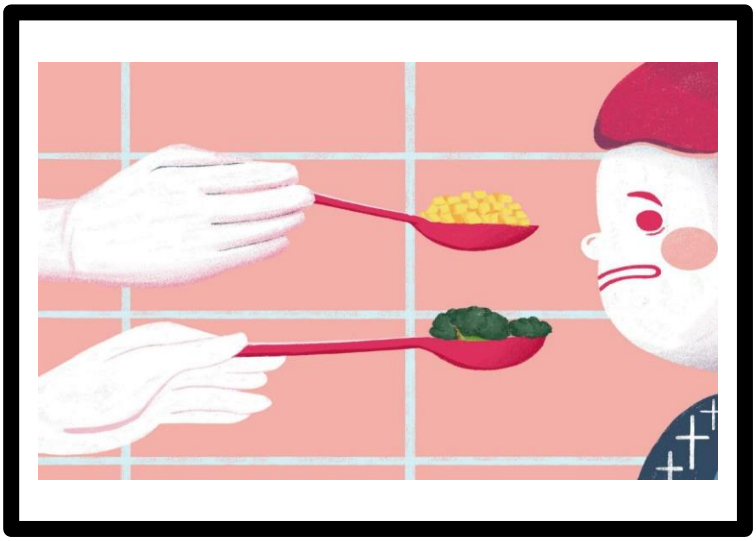
What To Eat Depends On Who You Are Feeding

"With every day we live and every meal we eat we influence the great microbial organ inside us--for better or for worse."

Giulia Enders



When you eat, you eat for two. You eat to provide the cells in your body with nutrients for growth and repair; but you also eat to sustain the beneficial microorganisms in your body.



Every time you eat or drink you are either feeding disease or fighting it."

Heather Morgan

To keep your intestinal microbiome healthy, many authorities recommend eating a plant-dominant diet containing fruits, vegetables, nuts, seeds, beans, lentils, legumes, whole grains, and resistant starches. Examples of recommended food items included in a plant-dominant diet can be found at the end of the monograph in List I.

Modest amounts of fish and poultry may be included in a plant-dominant diet as sources of animal protein. "Red meat,"[2] however, should generally be avoided. Studies confirm that intestinal microbes metabolize L-carnitine contained in red meats and produce TMAO (trimethylamine-N-oxide) which accelerates atherosclerosis ("hardening of the arteries").[3,4] Microbes, particularly in the large intestine, metabolize items in the plant-based diet through the chemical process of fermentation. It's been shown that some microorganisms prefer fermenting one type of nutrient compared to another. Not knowing which microbes prefer which nutrient or which microbes are present at any specific moment in the digestive tract, it is best to ingest a wide variety of fermentable carbohydrates, i.e., dietary fiber, resistant starches, human milk oligosaccharides, and polyols. Nutrition authorities suggest eating 30 or more different fiber containing products every week.

The following are categories of fermentable nutrients. They are also referred to as *prebiotics*:

- **Dietary fiber (i.e., microbe accessible and fermentable carbohydrates)**
- **Human milk oligosaccharides**

- **Resistant starches**
- **Polyols**

MICROBIAL ACCESSIBLE AND FERMENTABLE NUTRIENTS

DIETARY FIBER

Dietary fibers are diversified substances having varied biological effects. They are food substances that escape digestion in the small intestine and reach the large intestine (colon) intact where they are partially or completely metabolized by resident microorganisms. Dietary fiber is frequently referred to by the acronym MACs (Microbial Accessible and fermentable Carbohydrates).

Researchers emphasize that "MAC's" should not be viewed as a static characteristic of specific dietary components and instead represent the potential metabolic activity associated with carbohydrates that exist in a particular microbiome".[1]

Dietary fibers are commonly divided by subtype based upon solubility, viscosity, and fermentation properties with health benefits highly correlated with these attributes.

Depending on the solubility of the fiber in water, it can be classified as either soluble or insoluble. Soluble fibers have water holding capacity with high gel forming properties and are readily fermented by gut microorganisms. Common sources of soluble fibers include whole grains (e.g., oats and

barley), legumes, flesh of fruit and vegetables, and seeds (e.g. flaxseeds and chai seeds).

On the other hand, insoluble fibers lack water holding capacity and are less fermentable by microorganisms. Insoluble fibers are typically found in whole-wheat bread, pasta fruits and vegetable skins, nuts, and seeds[2]. Dietary fiber is the preferred substrate for metabolism by intestinal microbes.[1]

Many studies on fiber have focused on the benefits of consuming an isolated, single fiber or fiber extract. This is not, however, how humans generally consume dietary fiber. Plant-based foods such as fruits, vegetables, nuts, seeds, legumes, beans, and whole grains are not just one single source or extract of fiber but may contain a matrix of multiple different fiber types.

A Major Unknown: Although it's recommended that individuals try to ingest a plant predominant diet, it is still not understood just how much of food items that humans ingest interacts with their gut. The question remains: when you eat a given diet, what parts of the diet are feeding your microbes rather than feeding you? How much of that spinach leaf, for instance, makes it through the stomach and small intestine and reaches the large intestine? What is the actual fraction of the diet that the microbiome is seeing?

Of note, there are 2000 varieties of apples worldwide, one hundred of which are grown in the United States.[2] There are

10,000 varieties of grapes and hundreds of varieties of sweet potatoes that exist. Varieties in the same class of food may vary widely in their calorie content, acidity, polyphenols, and fiber composition.

With so many unknowns, individuals are encouraged to consume a wide variety of fiber containing foods hoping that they are providing the beneficial microbe population with the substances required for them to survive.

The Institute of Medicine, which provides science-based advice on matters of medicine and health, gives the following daily fiber recommendations for adults. These are generalities, at best, and do not distinguish how much of the fiber should be soluble and how much should be insoluble.

Age 50 or younger:	**Men 38 grams**	**Women 25 grams.**
Age 51 or older:	**Men 30 grams**	**Women 21 grams**

[1] Sonnenberg, E.D.; *Starving our microbial self: The deleterious consequences of a diet deficient in microbiota-accessible carbohydrates.* Cell Metab. 2014, 20, 779-786.

2 Morgan, J, (2002). *The New Book of Apples—The Definitive Guide to Over 2000 Varieties.* Ebury Press, London: United Kingdom.

Substances containing dietary fiber are found in fruits, vegetables, nuts, seeds, whole grains, legumes, beans, and certain forms of starch. (See List 1).

If intestinal microbes fail to receive fiber as a source of energy, they may consume dead and/or dying host intestinal cells that are sloughed from the lining or may digest the mucus layer of the intestinal lining which is rich in sugar and proteins.

It is also conceivable that they can survive by metabolizing other microbes and/or their components that have been killed in transit through gastric acid and bile and pancreatic juices, i.e. postbiotics (See the section: Postbiotics).

As previously noted, digestion of the intestinal lining results in increased permeability, i.e., leaky gut. Increased permeability allows penetration of food antigens, harmful microbes, and toxins.

Why The Low Fodmap Diet May Not Promote Digestive Health

As previously pointed out, it is well accepted that the body shares its existence with a vast number of microorganisms that carry out essential functions necessary for human survival. (See the section: How Human Rely On Their Microbes).

Like all living substances, our microorganisms require a source of energy to exist. Their preferential source of energy comes from dietary fiber ingested by the human host.

Dietary fiber is the non-digestible portion of a plant derived food that cannot be completely broken down by human digestive enzymes and, therefore, passes relatively unchanged through the stomach and small bowel into the colon.

The low FODMAP diet eliminates dietary fibers from the diet. Without dietary fiber, microbes enter a state of starvation.

In the absence of fiber, microbes turn to an alternative source of energy by digesting and metabolizing the mucus layer that coats the lining of the intestinal tract. (See the section: Dietary Fiber).

One of the functions of the mucus layer is to form a a semipermeable protective barrier separating the contents of the digestive tract from the rest of the body.

When microorganisms digest the mucus layer in search of energy, the barrier function of the mucus is compromised and harmful microbes, food antigens, and toxins are able to penetrate the intestinal wall.

It would, therefore, seem unwise to follow a strict low FODMAP diet for long periods that eliminates the great majority of fiber from the diet. Doing so, risks starving beneficial microorganisms and may thereby threaten the health of the human host.

Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs) are complex sugars found in human breast milk which pass undigested through the small intestine into the colon. Breast milk has over 200 structurally diverse HMOs. Unlike the nutritional components contained in breast milk, HMOs are not metabolized in the infant to serve as a source of energy but guide the growth of bacteria that are present in the infant's gut helping to train the infant's immune system.

Recent studies[1,2] suggest that specific HMOs that are commercially manufactured can have a beneficial effect on the gut barrier function in the adult intestinal tract. Researchers are moving toward preparing synthetic HMOs to give to sick adult patients capitalizing on the same biochemistry that gives infants their healthy microbiomes.

[1] **Suligoj, T, Effects of Human Milk Oligosaccharides on the Adult Gut Microbiota and Barrier Function, *Nutrients* 2020, 12, 2808.**

[2] **Button, J, Precision modulation of a dysbiotic adult microbiome with a human milk-derived symbiotic reshapes gut microbial composition and metabolites*, Cell Host & Microbe*, 2023, doi https://doi.org/10.1016/j.chrom.2023.08.004**

Resistant Starch

Starch is a carbohydrate made up of multiple branches of sugar-- glucose molecules. Plants make starch during photosynthesis and store the starch to supply them with energy. Foods that humans eat that are rich in starch are a good source of energy for humans.

When foods containing starch are eaten, the body breaks down the multiple chains of glucose molecules into smaller glucose units which can then be used to provide energy for the body. Some starchy foods, however, resist enzymatic digestion in the

small intestine and reach the large intestine (colon) either unchanged or slightly changed. These are referred to as "resistant starch" and are now classified as dietary fiber.

Once resistant starches enter the large intestine, they are fermented by gut microorganisms to produce bioactive metabolites (i.e., short chain fatty acids). Since resistant starches bypass the small intestine, they do not contribute to blood glucose levels. As noted previously, these metabolites are beneficial to the human host.

Categories of resistant starch:

Different types of resistant starches have been identified and classified into four types—Type I, II, III and IV.

Type I. RS type I is found in partially milled seeds and grains. This type of resistant starch is stored within the thick, fibrous, cell walls of the seeds or grains and, therefore, cannot be easily digested unless it is milled or ground. Main characteristic: physically inaccessible.

Type II. RS type II is found in starchy foods like unripe, green bananas or raw potatoes. RS type II starches are not digestible because they have a chemical configuration this is hard for small bowel digestive enzymes to break down. Main characteristic: contains resistant starch granules.

Type III. RS type III resistant starch is found in foods that have been cooked and cooled such as potatoes and rice. The process of cooling converts a portion of the starches into

resistant starches. Main characteristic: forms by retrograde chemical transformation when cooked and cooled--defined as "retrogradation": a recrystallization process in which disaggregated amylose and amylopectin molecules in gelatinized starches reassociate to form an ordered structure[1].

Type IV. RS type IV resistant starch is a chemically modified starch molecule and usually found in breads and cakes. Main characteristic: chemically modified.

[1] **Yan, W., Gelatinization, retrogradation and gel properties of wheat starch—wheat bran arabinoxylan complexes, *Gels*. 2021 Dec; 7(4): 200.**

Medicinal benefits of resistant starch:

- **Resistant starch, primarily RS type II, can be used as a liquid meal replacement and as a source of fiber when nutrients are required without the bulk of conventional foods going through the gut.**
- **Resistant starches can serve as a texture modified food for those with swallowing difficulties.**
- **Resistant starches made from corn and tapioca can be used as part of a gluten free diet.**
- **Resistant starches have a laxative effect and can be used when fibrous bulk agents need to be avoided.[1]**

- **Resistant starch can be used to assist in mucosal healing of those with ulcerative colitis[2].**

[1] Maki, K. Beneficial effects of resistant starch on laxation in healthy adults, *Intl Jour of Food Sci and Nutrition*, vol 60, 2009—Issue sup4: 296-305

[2] Montroy, J., The effects of resistant starches on inflammatory bowel disease in preclinical and clinical settings: a systematic review and meta-analysis*. BMC Gastroenterol* 20, 372 (2020). https://doi.org/10.1186/s12876-020-01516-4

Potato starch

Potato starch, in particular, has gained increasing attention as a dietary supplement. Potato starch is extracted from crushed potatoes and then dried into a powder form. It should not be confused with potato flour.

Potato starch has a neutral flavor. Its capacity for thickening food substances makes it useful for food manufacturers of breads and cakes.

Studies in animal experiments show that potato starch increases concentrations of the short chain butyrate, enhances mucosal immune defenses and improves barrier function.[1]

Potential side effects to ingesting resistant starches

Like all carbohydrates that are fermented in the intestinal tract, there may be an increase in gas production of carbon dioxide, hydrogen sulfide and methane when resistant starches are

consumed. These gases may result in side effects including abdominal bloating, distention and flatulence. Introducing resistant starch, therefore, must be done slowly in gradual increments to avoid the aforementioned side effects.

In addition to potato starch, the following seven food items are high in resistant starch:

1. Muesli: A cereal containing oats, nuts, seeds and fruit. It contains the same ingredients as granola but granola contains more sugar and fat than muesli.

2. Greenish (under-ripe) bananas: Bananas with a slight green tinge to the skin have 80% more resistant starch than fully ripened bananas.

3. Potatoes: Cooked then cooled potatoes contain resistant starch. As the potatoes cool, they undergo a chemical transformation whereby the digestible amylopectin starches in the potato convert into the resistant starch called amylose. A popular food item high in resistant starch is cold potato salad.

4. Rice: Like potatoes, rice converts with cooling into resistant starch. Cooling should take place over 24 hours for both rice and potatoes.

5. Cashews: In the category of nuts, cashews are high in resistant starch. They can be used as an out-of-hand snack or mixed into oatmeal, yogurt, or salads.

6. Beans: A large variety of beans contain resistant starch including black beans, pinto beans and chickpeas. Like rice and potatoes, they gain resistant starch by allowing them to cool for several hours before eating them.

7. Barley: Barley is a whole grain that also contains resistant starch and makes a good addition to soups and salads.

As with all dietary supplements, the use of resistant starches should be discussed first with one's medical care provider.

[1] Trachsel, Julian, Dietary resistant potato starch alters intestinal microbial communities and their metabolites, and markers of immune regulation and barrier function in swine. *Frontiers in Immunology*, 10, 1381, 2019.

FERMENTABLE POLYOLS

Polyols are another unique form of sugar molecules. They occur naturally in foods but can also be found in food products in their synthetic form. Polyols can frequently be found in low sugar and sugar free products since they provide a sweetness similar to sugar without the calories. Polyols do not pose the risk of promoting tooth decay or elevating blood sugar levels. They appear in processed foods like sugar-free candies, gum, jams, marmalades, and beverages. They can also be found in sugar-free toothpaste, medications, and mouthwashes.

Common examples of polyols include the following:

- **Erythritol Maltitol Xylitol**
- **Mannitol Isomalt**

- **Sorbitol Lactilol**

Humans lack the enzymes required to digest polyols, therefore, a large portion of the substances proceed undigested into the colon where they are fermented.

Polyols, however, have gotten a *bad rap*. Because they are fermented in the colon, they produce gases which can result in abdominal bloating, distention, flatulence and pain. When consumed in large amounts they also have an osmotic effect and can draw water into the colon leading to an *osmotic diarrhea*. These are many of the same symptoms that occur with ingestion of all fermentable carbohydrates.

Polyols can contribute to a healthy colonic environment. Polyols and polyol containing foods are, therefore, able to hydrate colon contents and aid in producing bowel movements. They contribute to the production of short-chain fatty acids that are required for a healthy colon lining. Food scientists, nutritionists, physicians, and dentists are beginning to describe a sensible approach to the slow introduction of polyols in gradual amounts as beneficial to humans.

The following are some natural foods that contain polyols:

▪ Apples	Cherries	Peaches
▪ Apricots	Dates	Pears
▪ Avacado	Bell peppers	Figs
▪ Butternut squash	Green beans	Prunes
▪ Cauliflower	Mushrooms	Sweet potatoes
▪ Celery	Nectarines	Plums

Limit the ingestion of food items with high concentrations of salt and sugars. The Harvard Health Letter[1] also emphasizes the incorporation of "healthy fats" in the diet stating the following: "Saturated fat, trans fat, and cholesterol are considered the *bad guys*. *Good* fats are monounsaturated (found in olive oil, for example) and polyunsaturated fats found in such foods as "fatty fish" like mackerel, herring, sardines, salmon, anchovies and albacore tuna".

Food is not consumed in a vacuum, and a study led by the Harvard T. H. Chan School of Public Health showed that those who also adhered to lifestyles that incorporated adequate amounts of sleep, lots of physical activity, regular meal patterns, and socialization with friends and family had lower risks of cardiovascular disease mortality.[2]

Although wine was considered at one time to be "heart healthy" and permitted on some plant dominant diets, recent evidence suggests that there is <u>no amount of alcohol</u> that can be considered safe or "heart-healthy." (See the section: Things To Avoid: Alcohol).

In 2022, the World Heart Federation published a policy brief debunking the notion that alcohol was beneficial for heart health stating, "Contrary to popular opinion, alcohol is not good for the heart". The report points out that some studies that previously showed cardiovascular benefits from drinking were flawed. Recent research points out that many chronic conditions are linked to alcohol usage. Studies have now found

that alcohol consumption may accelerate genetic aging, shrink brain tissue, and increase the risk of cardiovascular disease.

Dr Carina Ferreira-Borges, acting Unit Lead for Noncommunicable Disease Management and Regional Advisor for Alcohol and Illicit Drugs in the World Health Organization Regional Office for Europe states the following:

> ***"We cannot talk about a so-called safe level of alcohol use. It doesn't matter how much you drink – the risk to the drinker's health starts from the first drop of any alcoholic beverage. The only thing that we can say for sure is that the more you drink, the more harmful it is – or, in other words, the less you drink, the safer it is."***

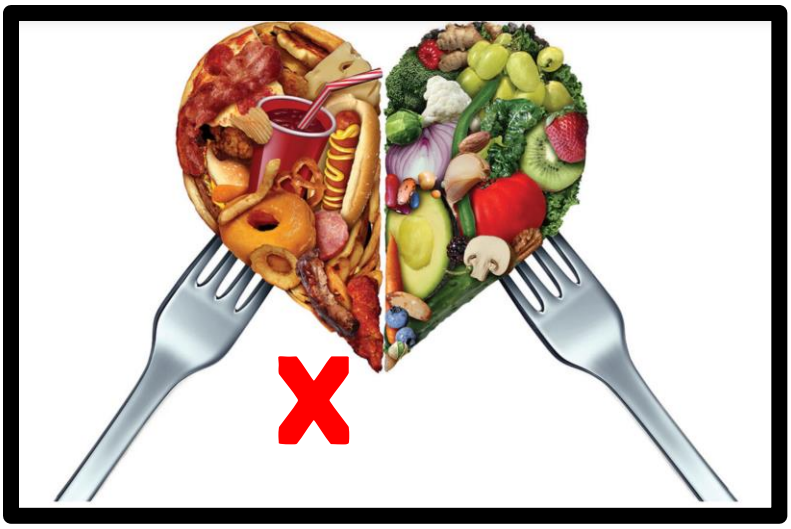
[1] Harvard Letter, Harvard University Press, 2023

[2] J. Maroto-Rodriguez et.al., Association of a Mediterranean Lifestyle with all-cause and cause-specific mortality: a prospective study from the UK Biobank, *http://doi.org/10.1016/j.mayocp.2-23.05.031, 2023.*

A Cautionary Note
Start Low--Go Slow

Don’t up your fiber intake too quickly. Doing so may precipitate side effects of abdominal bloating, distention, excess gas and abdominal pains. Foods that contain fiber should be introduced slowly allowing the gut to accommodate to the metabolic byproducts produced by microorganisms. By-products include the gases methane, carbon dioxide, and hydrogen sulfide. These gases may stretch the gut wall resulting in bloating and pain.

The gut wall may be hypersensitive to stretching when fiber is first introduced. In time, however, the gut may adapt to a new and more comfortable normal. The process of adaptation may take many months to reach a state of complete comfort, particularly in those whose diets contained only small amounts of plant dominant fibers initially.



Foods to Limit:

- **Added sugars: found in carbonated beverages, sport drinks, juice boxes, candies, ice cream, table sugar, syrup, and baked goods**
- **Refined grains: found in white bread, pasta, tortillas, chips, crackers**
- **Trans fats: found in margarine, fried foods, and other processed foods**
- **Refined oils: found in soybean oil, canola oil, cottonseed oil, grape seed oil**
- **Processed meats: found in processed sausages, hotdogs, deli meats, baloney, salami, beef jerky**

- **Highly processed foods: found in fast foods, convenience meals, microwave popcorn, granola bars**

- **Reduce wheat products in the diet like white bread, yeast rolls, and pie crusts. Gluten contained in wheat products is associated with increased gut permeability which may activate an immune response resulting in inflammation. Try to eat a "gluten *reduced*" diet. Unless diagnosed with celiac disease, complete absence of gluten from the diet is unnecessary.**

- **If seasonally available and affordable, eat organic foods.**

- **Although most non-prescription supplements are to be avoided, deficiencies in iron, magnesium, calcium, vitamin D, zinc and vitamin B12 are common enough to warrant supplementation. A single daily multivitamin (for example, Centrum®) can provide most of the recommended amounts of the above vitamins and minerals. Blood levels of the above vitamins and minerals should be checked periodically by your primary health care provider.**

The Consequences Of Neglecting the Intestinal Microbiome

Mary, Mary, quite contrary
How does your garden grow?

The last portion of the small intestine, the ileum, combined with the large intestine (colon) can be compared to a tropical rain forest. The rain forest is filled with large numbers of plants, flowers, bushes, vines, trees and other lush vegetation.

In like manner, the diverse community of trillions of microorganisms living in the small intestine and colon make up

a *microbial garden* composed of thousands of different species of microbes.

Like all living things, for the rain forest to thrive, the plants must be supplied with a source of energy, nutrients. Likewise, the *microbial garden* must receive nutrients to flourish.

As discussed before, nutrients for the *microbial garden* include dietary fiber, resistant starches, human milk oligosaccharides, polyols, and more. (See the section: What You Eat Depends On Who You Are Feeding).

Failure to provide the rain forest with nutrients for energy results in the withering and death of the plants.

Similarly, if humans fail to provide their *microbial gardens* with a source of energy, or if humans expose their *microbial gardens* frequently or for long periods to toxins, food additives, antibiotics, chemotherapy, radiation therapy, air pollutants, tobacco, alcohol, recreational drugs, industrial chemicals and environmental pollutants, their *microbial garden* may gradually wither and turn into a *microbial desert*.

The protective intestinal lining, which the microbe population helps generate, may diminish and no longer serve as a protective barrier thus allowing penetration of food antigens, toxins and microorganisms into the body.

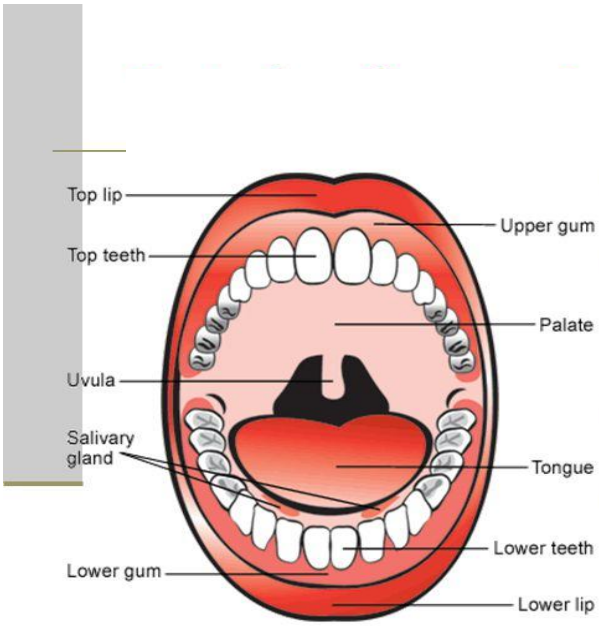
The immune system interprets incoming foreign substances as a threat and initiates defenses resulting in inflammation, and inflammation is the bedrock of chronic digestive illnesses. (See the section: Inflammation, The Bedrock of Chronic Illnesses).

Researchers continue to conduct studies to establish whether lack of nutrients to nourish the microbiome is the cause of

chronic illnesses or is merely associated with chronic illnesses. Although definitive evidence proving causation has yet to be achieved, compelling evidence is accumulating.

THE ORAL CAVITY A POTENTIAL SOURCE OF CHRONIC INFLAMMATION

(How Oral Health Is Central To Overall Health)



- The **Mouth** = food enters the digestive system here.
- The inside of the mouth is covered with a mucous membrane called the oral mucosa.
- The roof of the mouth is the hard palate.
- Uvula = prevents food from going up into the nasal cavity when you swallow.

THE ROLE OF INFLAMMATION: As previously stated, controlling inflammation is essential to reducing chronic digestive illnesses. (See the section: Inflammation, The Bedrock of Chronic Inflammation).

Because of the influx of large numbers of foreign substances, e.g., food antigens, microbes, drugs, toxins, and xenobiotics the oral cavity is always in a pro-inflammatory state.

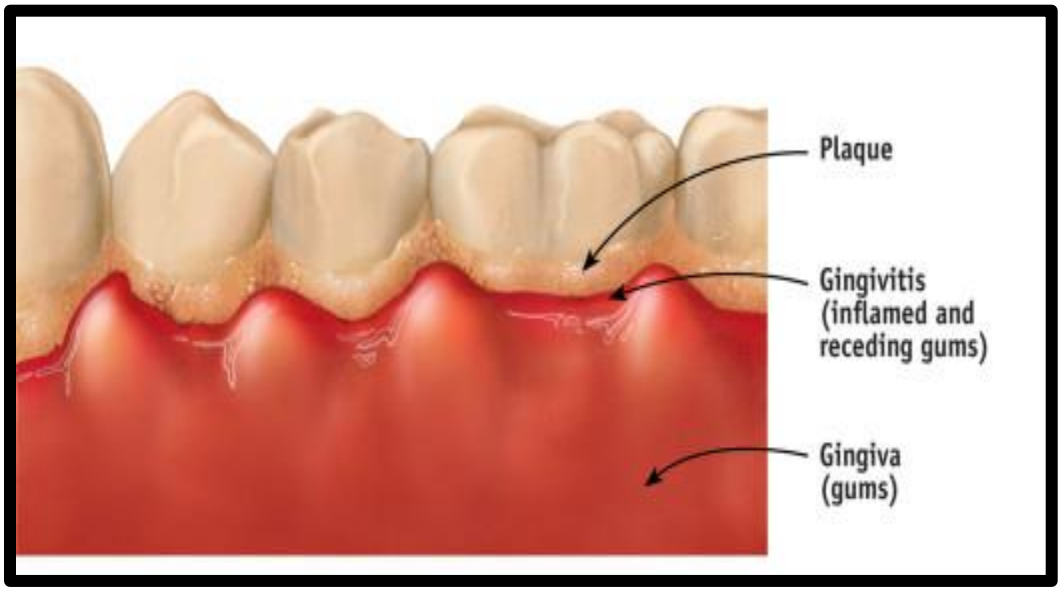
ASSOCIATIONS OF ORAL CAVITY INFLAMMATION WITH OTHER BODY ILLNESSES: Numerous chronic conditions in the body have been associated with oral cavity inflammation including the following: cardiovascular disease,[1,2] neurologic disease,[3] bone disease,[4-5] liver disease,[6-8] cancer,[9-12] kidney disease [13-14] lung disease,[15-16] Alzheimer's dementia, [17-19] Rheumatoid arthritis,[20] COVID outcomes,[21-22] macular degeneration[23] and outcomes of pregnancy[24].

PREVALENCE OF UNTREATED ORAL CONDITIONS: In 2015 the number of people globally with untreated oral conditions was 3.5 billion. This represented 47% of the world population.[25] Of that, 538 million people had severe periodontal disease.

In the United States, the Communicable Disease Center (CDC) reported that gum disease (periodontitis) affected 42% of adults over the age of thirty and by age sixty-five, nearly 70% have mild to severe deep gum disease, periodontitis[26]. These numbers have likely increased with population growth and aging.

PLAQUE—A MAJOR CAUSE OF ORAL INFLAMMATION:
Once in the oral cavity, microorganisms form plaque. Plaque is a clear sticky coating containing millions of microbes that form on the teeth. It protects the microbe population in the plaque from being brushed, swallowed, washed or rinsed away.

Plaque allows microbes to share nutrients and genetic information with each other. The accumulation of plaque leads to dental issues like tooth decay and gum disease.

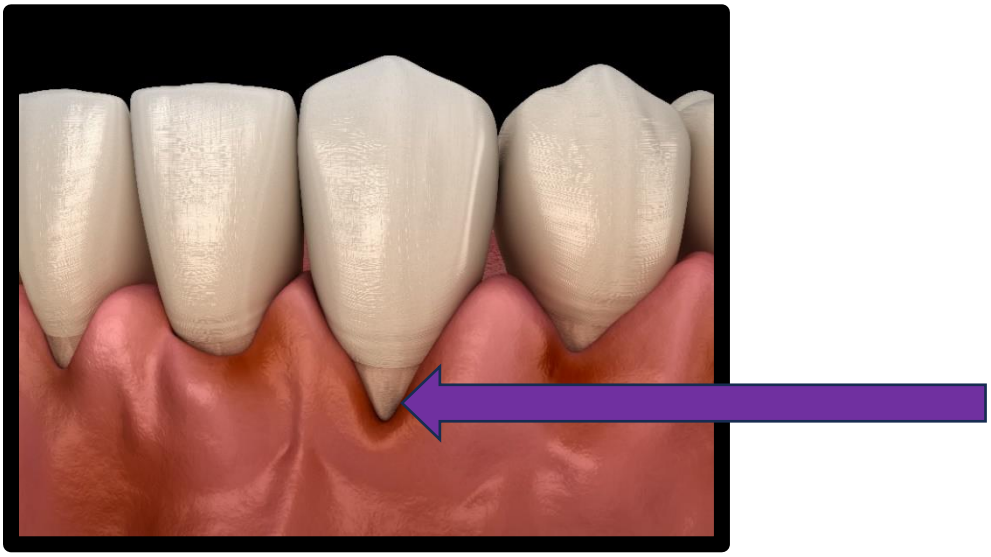


Plaque can form within hours after microbes enter the mouth if not removed by oral hygiene measures. Dental plaque left on the teeth and gums will calcify into a substance called tartar in a matter of days. Tartar cannot be easily removed with dental brushing or interdental aids but requires vigorous cleaning methods with ultrasonic power washing and sharp scraping tools used by dental professionals for removal.

Plaque can form between teeth, on the front and back of teeth, on chewing surfaces, along the gumline and below the gumline. It is the leading cause of gum inflammation.

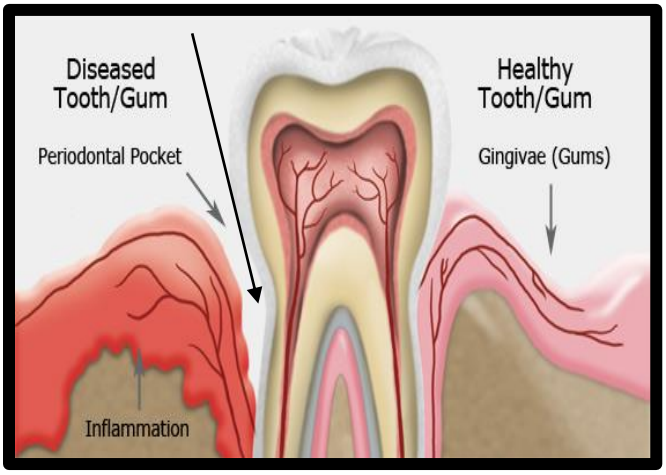
RECEDING GUMS AND PERIODONTAL POCKETS: In response to inflammation, gums pull away from the tooth exposing the root. This process is known as receding gums.

RECEDING GUMS



As gums pull away, they form periodontal pockets between the gum and the tooth. Periodontal pockets become *incubators* for the proliferation of millions— and frequently billions—of microorganisms.

PERIODONTAL POCKETS



Microbes within periodontal pockets can damage local tissues and destroy the attachments of the tooth to the jawbone resulting in loss of teeth. Failure to control the proliferation of

microbes in the gum surfaces leads to deeper levels of gum inflammation, i.e., periodontitis.

FACTORS INFLUENCING INFLAMMATION: Factors that influence the development of oral inflammation include poor dental hygiene, diabetes, use of tobacco products, exposure to high concentrations of refined sugars, immune system disorders, medications, genetics, hormonal changes, and malnutrition.

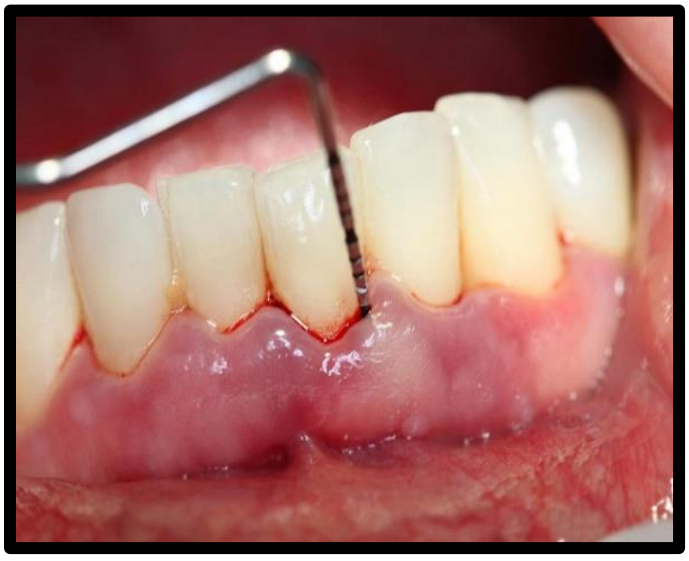
SYMPTOMS OF GINGIVITIS: Gingivitis is characterized by reddening of the gums at the margin between the teeth and gums, swelling of the gum tissue, and bleeding with brushing and/or flossing.

Gingivitis is treatable and reversible with rigorous oral hygiene measures. Untreated gingivitis, however, may progress to deeper levels of inflammation, periodontitis.

PERIODONTITIS DEFINED: **Periodontitis represents a group of pathologies that have in common the destruction of the tooth support system. In more advanced stages of periodontitis, pain as well as bleeding from gums with brushing and flossing may increase, and gums may lose their attachments to the teeth resulting in receding gums.**

Periodontitis is *always* preceded by gingivitis and, therefore, is preventable.

DIAGNOSING GUM DISEASE: **The dentist or dental hygienist can measure the depth of periodontal pockets around each tooth using a special dental ruler. The depth correlates with the severity of infection. The dentist or dental hygienist can also note whether the gum tissue below the gum line is inflamed enough to cause bleeding.**



DANGERS OF PERIODONTITIS: **One of the major pathogenic organisms that causes periodontitis is *Porphymonas gingivalis (PG).* PG is a virulent organism resistant to antibiotics. PG also resists destruction by stomach acid and can avoid being destroyed by the human immune system.**

Major virulence factors of PG are protein dissolving chemicals (proteinases) contained in vesicles that PGs expresses from their surface. These chemicals are known as "gingipains". Gingipains are involved in the ability of the organism to adhere to and colonize lining tissues, coagulate blood, breakdown red blood cells, and disrupt the protective immune response.[1]

Gingipains have been found in multiple organs throughout the body and support the hypothesis that pathology in the oral cavity can initiate other chronic illnesses.

[1] N. Li, Gingipains from Porphyromonas gingivalis—Complex domain structures confer diverse functions, *Eur J Microbiol Immunol (Bp).* 2011 Mar; 1(1): 41-58

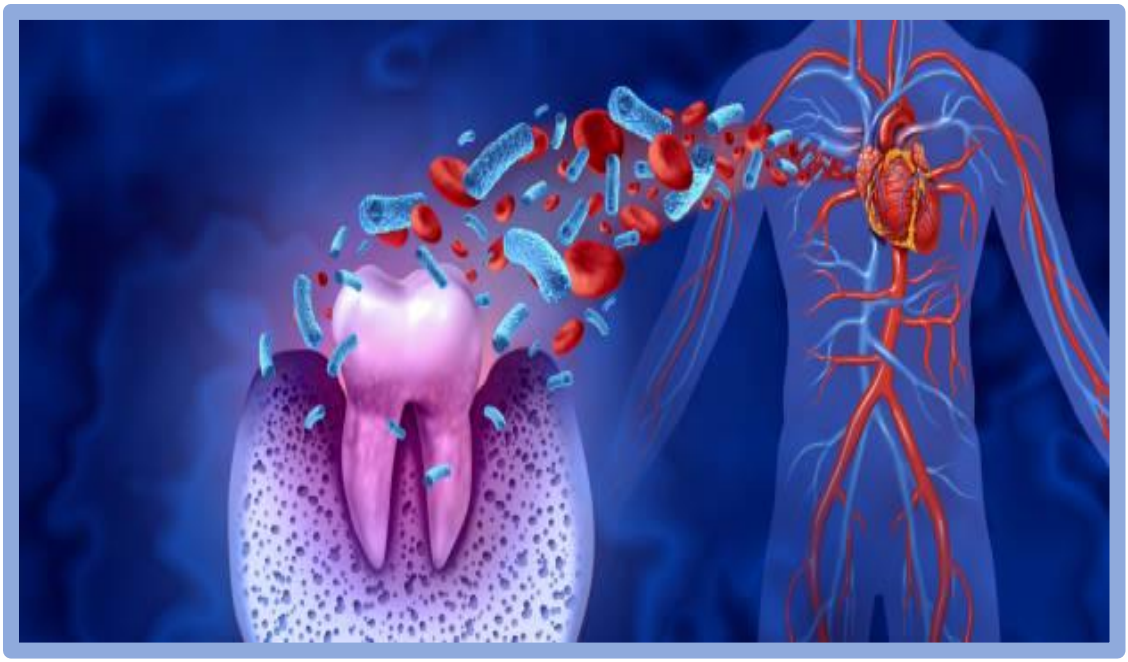
TREATMENT METHODS FOR GUM DISEASE: **The treatment of periodontal disease may be done by a dentist or a periodontist, i.e. a dentist who specializes in the diagnosis and treatment of gum diseases.**

The goal of treatment is to thoroughly clean the pockets around the teeth to prevent damage to the surrounding gum tissue and bone. The removal of plaque and tartar by dental professionals is usually prescribed for early stages of periodontitis. The more advanced stages may require deep scaling of teeth beneath the

gum line, gum surgery to reduce bacterial deposits beneath the gums and other specialized techniques to reduce the microbial load in the tissue.

Rigorous personal oral hygiene routines are critical for preventing the accumulation of microorganisms in the mouth. Regular brushing and flossing along with the use of interdental brushes can reduce the risk of developing teeth and gum disease.

HOW ORAL CAVITY MICROBES SPREAD TO THE REST OF THE BODY--TRANSMIGRATION



In addition to localized gum and teeth damage, transmigration of microbes from periodontal pockets can take place. This

movement of pathogenic organisms from the mouth to adjacent tissues can cause inflammation and infection.

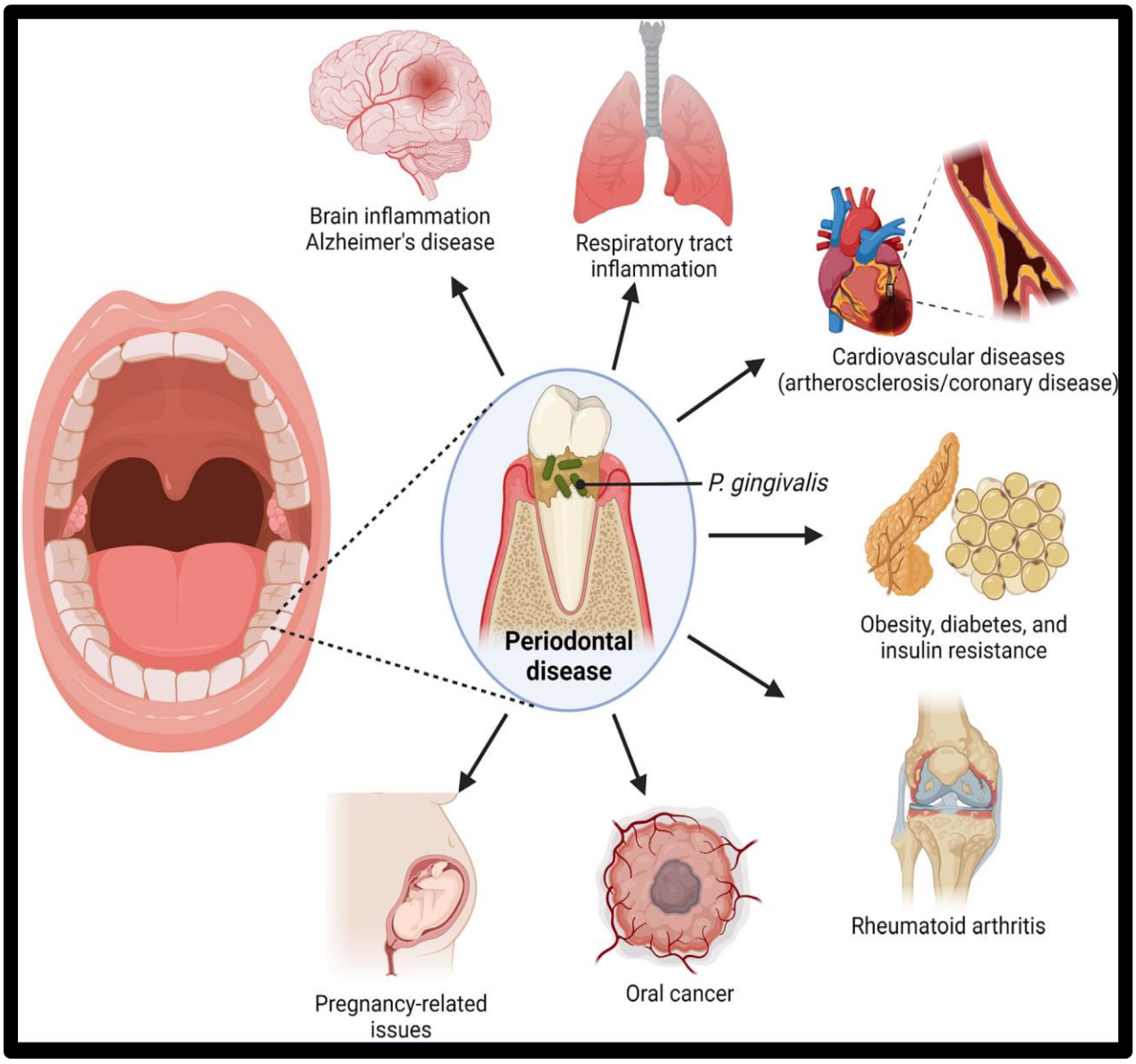
Adjacent tissues that may be affected by extensive exposure to pathogenic microorganism include Eustachian tubes that drain the middle ear, nasal cavity which drains facial sinuses, lacrimal ducts that drain tears from the eyes, salivary glands, and tonsillar tissue.

SIGNS AND SYMPTOMS OF ADJACENT SPREAD: Signs and symptoms of microbe transmigration to adjacent tissues may include recurrent sinus inflammation, nasal pathology, salivary gland dysfunction, headaches, earaches, facial pain, loss of hearing, chronic sore throat, and burning mouth and tongue.

SPREAD THROUGH BLOOD AND LYMPH TISSUE: In addition to nearby movement of microorganisms, oral cavity microorganisms can pass into the bloodstream and lymph tissues allowing the microbes to travel throughout the body and infect pacemakers, heart valves, joint implants, catheters, implanted drug delivery devices, and more.

SPREAD BY SWALLOWING MICROBES. Billions of microorganisms that are produced every 24 hours in periodontal pockets are also swallowed, potentially causing symptoms like chronic sore throat, chest pain, heartburn, difficulty swallowing, nausea, vomiting, stomach pains, overgrowth of microbes in the small intestine, malabsorption, vitamin deficiencies, diarrhea and/or constipation, abdominal

bloating, abdominal distention, eructation, flatulence, and weight loss.



The Associations Between Periodontal Disease And Systemic Disorders

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[26] Eke, PI, Prevalence of periodontitis in adults in the United States: 2009 and 2010, *J Dent Res,* 30 Aug 2012: 1-7

General Recommendations Mouth

- **Brush your teeth a minimum of twice daily, a.m. and p.m. Ideally, brush your teeth upon arising, after meals, and at bedtime.**

- **Brush your teeth using a rechargeable, electronic, oscillating toothbrush. Brush for a minimum of two minutes each time. The electronic, oscillating toothbrush can clean teeth far better than a hand held manual toothbrush. Two leading brands of electronic toothbrushes are Sonicare® and Oral B®.**

- **Brush your tongue or use a tongue scraper every time you brush your teeth.**

- **Change the tip of the electronic oscillating toothbrush at one to three month intervals.**

- **Do not share a toothbrush with another person.**

- **Do not store your toothbrush in the open near your toilet to avoid contamination of your toothbrush from aerosolized waste in the toilet water upon flushing.**

- **Floss your teeth with dental tape or use interdental brushes (G-U-M Dental Picks®), or both, after meals and especially before going to sleep. Leaving food particles on and between the teeth during hours of sleep is an invitation for dental decay, microbe proliferation, plaque formation and bacterial transmigration.**

- **Schedule visits to the dentist and dental hygienist at least once every six months. Those who have had multiple dental issues and restorations in the past, root canals, or gum disease, should see their dentist and dental hygienist more frequently at the intervals recommended by their dental professionals.**

- **Avoid allowing sugary foods and beverages to remain in prolonged contact with gums and teeth enamel. Do not eat nutrients or confections prepared as a "gummy" or take medications suspended in gum drops. Avoid sugar containing mints and gum.**

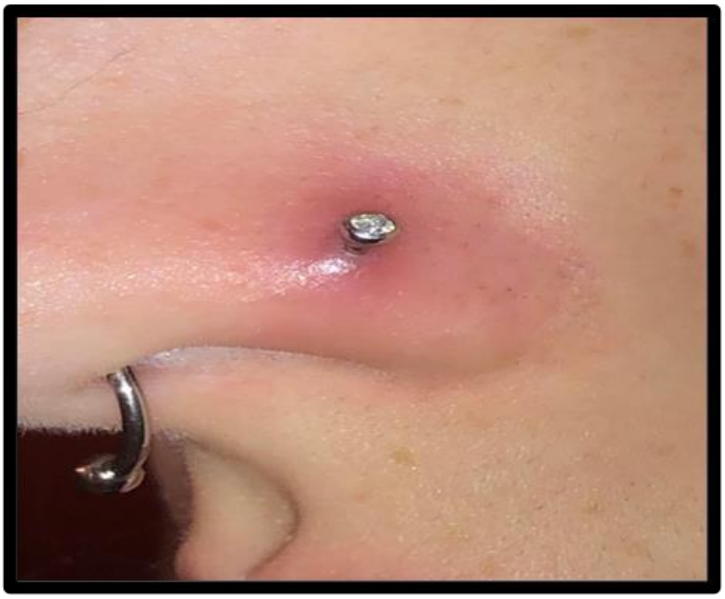
GENERAL RECOMMENDATIONS

Eyes and Nose

- **Only use steroid containing nasal inhalers, eye drops and oral inhalers when recommended by your healthcare provider.**

- **Minimize the use of nasal decongestants.**

- **Avoid piercings of the nose that can serve as an entry point for pathogens.**



- **Contact lens wearers should consider wearing daily replaceable contact lenses when possible.**

- **Apply moisturizing eyedrops without preservatives before going to sleep and upon awakening.**

- **Avoid the placement of cosmetic jewelry in the eyebrows.**

- **Minimize eye cosmetics such as mascara, artificial lashes, glitter, and eyeliners, which block the natural secretions of glands surrounding the eyelashes.**

Hydration

Every organ in the body requires water to function properly. It makes up 50 to 70% of the body weight of an adult human and is needed to survive. Water is required to get rid of waste products that accumulate in the body. It helps maintain normal body temperature. It lubricates joints and protects sensitive tissues.

The United States National Academy of Sciences, Engineering and Medicine recommends a daily intake of 3 to 4 liters of fluids for men (90-120 ounces) and 2 to 3 liters for women (60-90 ounces).[1] These recommendations include, not just water, but other foods and beverages that contain water.

The amount of water to drink, however, may vary based on several factors including the following:

- **Age and gender**

- **Exercise: Activities that cause substantial amounts of sweating require increased water intake to cover the losses.**

- **Environment: Hot and humid environmental conditions increase fluid requirements as does altitude.**

- **State of health: Losses from fever, vomiting, diarrhea, require fluid replacement. Increased fluid intake is therapeutic for those with urinary tract infections and kidney stones.**

- **Breast feeding: Breast feeding requires increased fluid intake to remain hydrated.**

There are multiple ways to maintain hydration. Non-alcoholic beverages like tea, coffee, sports drinks, soft drinks, and lemonade have a water content of 95-100%. Soups like mushroom soup, cream soups, and chicken noodle soup have a water content between 80 and 95%. Dairy products have varying degrees of water content, for example, whole milk (90%), yogurt (85%), ice cream (65%), and cheese (60%).[2]

[1] Dietary reference intakes for electrolyte and water. U.S. National Academy of Sciences, Engineering, and Medicine, *https//: www.national academics.org/hour-work/dietary-reference-intakes-for electrolytes-and water.* Accessed October 2, 2020.

[2] **Water content in common foods and beverages. Available from: https://www.europeanhydrationinstitute.org/nutrtion and beverages/**

CONTROLLING INFLAMMATION

As previously mentioned, achieving and sustaining well-being depends on the human geneome, the exposome, the microbiome and the immunome and minimizing those things that cause chronic inflammation in the body. The following recommendations may help achieve that goal:

AVOID ULTRAPROCESSED FOODS.
(SEE LIST II: BADDATIVES)

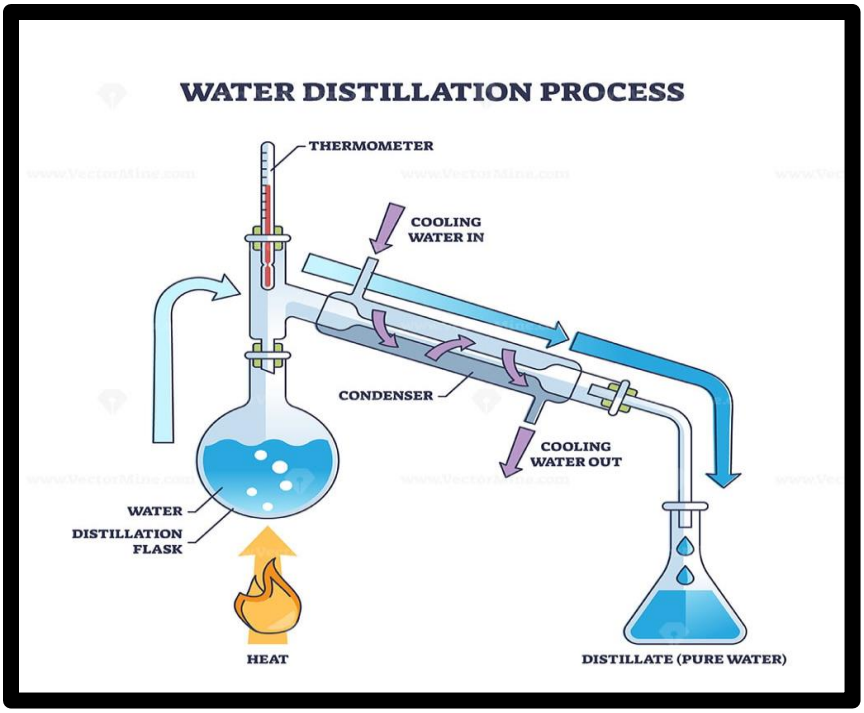
AVOID TOXINS AND CONTAMINANTS IN WATER

DRINK DISTILLED WATER

Drinking water comes in many different formulations including tap water, filtered water, "purified water," alkaline water, spring water, artesian well water, carbonated water (Seltzer) and distilled water. Distilled water should be your water of choice.

Distilled water is prepared by boiling water and condensing the steam. Any chemical element that has a boiling point of more than 212^{o} (F) does not rise in the steam. Over 90% of all elements that are known to exist have boiling points over 212^{O} (F) and remain in the water distillation boiling chamber. The other 10% that rise in steam are almost all gases which are vented out before the steam is condensed to form distilled water.

Distilled water has virtually no remaining chemicals in it. That makes it the purest form of commercially available water.



The purity of water is based on four things:

- **Amount of sediment**
- **Presence of microorganisms**
- **Presence of dissolved gases (volatile organic compounds)**
- **The number of chemical ions present in the water including lead, mercury, arsenic, chromium, etc.**

There is a commonly expressed thought that distilled water is harmful and leaches chemicals from the body. There is no scientific evidence that has shown this notion to be true.

MINIMIZE OR ELIMINATE THE USE OF ALCOHOL

Alcohol use is a leading cause of disease and death worldwide. The perspective that alcohol-related diseases are solely caused by tissue damage done by alcohol metabolites has evolved to include the multiple adverse effects of alcohol on gut microbe populations.[1,2]

Scientists have demonstrated that alcohol can cause an increase in pathogenic bacteria and an increase in intestinal permeability commonly referred to as "leaky gut". As shown before, increased permeability of the gut lining facilitates translocation of microorganisms, toxins, and food antigens into the body. The flow of these substances from the gut through a permeable gut lining into the vascular system and to the liver has been proposed as a major factor in the cause of liver diseases.[3]

Damage to the liver may include fat accumulation in the liver (alcohol induced fatty liver disease), liver cell inflammation (alcohol-related hepatitis), tissue scarring (fibrosis), advanced scarring (cirrhosis) and liver cancer (hepatocellular carcinoma).

Alcohol has also been proven to have a significant adverse effect on multiple organ systems including the liver[4], and brain[5], in addition to the intestinal microbiome[6]. Now evidence shows that alcohol not only lacks beneficial effects on heart health but can be harmful[7].

For many years, stakeholders have heavily promoted the use of alcohol as beneficial for heart disease. Studies, however, show that position has been reversed. According to the World Health Federation " . . . research in the last decade has led to a major reversal in the perception of alcohol in relation to health in general and cardiovascular disease in particular. Contrary to popular opinion, alcohol is not good for the heart."[8]

All recent evidence points to the conclusion that alcohol ingestion should be totally avoided when possible. There are no defined safe limits of alcohol.

[1] Day, A. Gut microbiome dysbiosis in alcoholism: consequences for health and recovery, *Front. Cell. Infect. Microbio.*, Vol. 12, March 3, 2022.

[2] Engen, P.A., The gastrointestinal microbiome: Alcohol effects on the composition of intestinal microbiota, *Alcohol Res*. 2-15;37(2):223-36.

[3] Nicoletti, A. Intestinal permeability in the pathogenesis of liver disease: From non-alcoholic fatty liver disease to liver transplantation, *World J Gastroenterol*. 2019 Sep 7; 25(33): 4814-4834.

[4] **V Subramaniyan, S et al. Alcohol-associated liver disease: A review on its pathophysiology, diagnosis and drug therapy. *Toxicology Reports*, vol 8: 2021, 376-395.**

[5] **A. Topiwala, No safe level of alcohol consumption for brain health: observational cohort study of 25,378 UK Biobank participants*, medRxiv 2021-- Toxicology Reports*, 2021**

[6] **BA White, The impact of alcohol in inflammatory bowel diseases, Inflammatory Bowel Diseases, 2022**

[7] **K. J. Biddinger et al. JAMA Netw Open. 2022;5(3):e223849.doi:10.1001/jamanetworkopen.2022.384**

[8] **World Heath Federation Policy Brief—The Impact of Alcohol Consumption on Cardiovascular Health: Myths and Measures.**

AVOID ALL FORMS OF TOBACCO INCLUDING E-CIGARETTES (VAPING)

The Centers for Disease Control and Prevention (CDC) publications[1] have stated the following:

"E-cigarettes produce an aerosol by heating a liquid that contains nicotine—the addictive drug found in regular cigarettes, cigars, pipe smoke and other tobacco products. The cigarettes come in multiple shapes and sizes. Most contain a battery, a heating element, and a reservoir to hold the liquid."

Flavorings and other chemicals that help aerosolize the liquid can be found in e-cigarette liquid. E-cigarettes carry many different names including "e-cigs," "e-hookahs," "mods," "vape pens," "vapes," and "electronic nicotine delivery systems (ENDS).

Users inhale the aerosol into their lungs as do bystanders. The use of e-cigarettes is frequent referred to as "vaping."

Studies show that "vaping" can adversely alter the microbe population in the mouth and lungs[2]. The inhaled aerosol can also contain harmful substances including, but not limited to:

- **Nicotine**
- **Flavorings such as diacetyl which has been linked to serious lung disease**
- **Volatile organic compounds**
- **Cancer-causing chemicals, and**
- **Heavy metals including nickel, tin and lead**

[1] **US Department of Health a Human Services. *E-cigarette use among youth and young adults: a report of the Surgeon General,* Atlanta GA, CDC, 2016**

[2] **Scott, C., Electronic cigarette use promotes a unique periodontal microbiome. *Clinical Microbiology*, Feb 22, 2022, DOI: https://doi.org/10.1128/mbio.00075-22**

AVOID RECREATIONAL DRUGS.

Avoid recreational drugs unless otherwise directed by a medical care professional. Recreational drugs can be defined as a drug taken for their mind-altering effects. These drugs have been shown to alter the intestinal microbiome. Examples include cocaine[1], heroin[2], ecstasy[3], methamphetamines[4], and LSD[5]. Serious potential short term and long-term side effects have been described for all of them.

[1] **Cuesto, S., Gut colonization by Probacteria alters host metabolism and modulates cocaine neurobehavioral**

responses, *Cell Host & Microbe*, 30:11, Nov 9, 2022, 1615-1629.

[2] Yang, J., The association of altered gut microbiota and intestinal mucosal barrier integrity in mice with heroin dependence, *Front. Nutr,* (8) Nov 4, 2021.

[3] Baslam, A., Modulation of gut microbiota in Ecstasy/MDMA-induce behavioral and biochemical impairment in rats and potential of post treatment with Anscyclus pyrethrum L. aqueous extract to mitigate adverse effects, *Int J Mol Sci.* 2023 May; 24 (10): 9086

[4] Yuansen L., Related effects of methamphetamine on the intestinal barrier via cytokines, and potential mechanisms by which methamphetamine may occur on the brain-gut axis, *Front. Med*, 2022; 9: 783121, May 10, 2022.

[5] Inserra, A., Effects of repeated lysergic acid diethylamide on the mouse brain endocannabinoidome and gut microbiome. *Br J Pharmacol*. 2023 Mar; 180 (6): 721-739.

AVOID AIR POLLUTION BY ADDING A PORTABLE AIR FILTRATION UNIT TO SLEEPING AREAS

Air pollution has long been recognized as a risk factor for multiple diseases including asthma[1], cardiovascular disease[2], obesity[3], diabetes[3], and cancer.[4] Recent studies have also linked air pollution with pathologies of the gastrointestinal tract.[5]

The gastrointestinal tract is exposed to air pollution through both direct and indirect routes. Inhaled particles are quickly cleared from the lungs and passed to the intestines.[6]

Particulate matter that is inhaled becomes trapped within the mucus layer coating the lower airways and then is transported back to the throat and consequently swallowed.[7]

Particulate matter may also gain access to the gastrointestinal tract by direct dietary ingestion of food and water that is contaminated with air pollutants.[8] Studies have shown that within a typical Western diet an individual may consume up to 100 billion particulate particles per day.[9, 10]

Air pollutants have been shown to disrupt the protective intestinal lining barrier. A recent study examined the relationship between air pollution and a baby's developing gut microbiome.[11]

Researchers found that air pollution in the first six months of life is associated with a gut microbe composition linked to allergies and inflammatory illnesses. Comparable results have been found in adolescents and young adults.

The gastrointestinal tract may, therefore, be an important organ system where air pollutants cause inflammation and alter microbe density and diversity (dysbiosis).

One way to reduce exposure to air pollution is to install a portable air filtration unit that contains a HEPA filter and an activated carbon filter in sleeping and recreational areas within the household.

EXAMPLE (IQ Air®)

[1] **Villeneuve P. J, Outdoor air pollution and emergency department visits for asthma among children and adults: a case-crossover study in northern Alberta, Canada, *Environ. Health 6* (2007) 40.**

[2] **Brook, R.D., Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association, *Circulation* 121 (21) (2010) 2331-2378.**

[3] **Eze, I.C., Association between ambient air pollution and diabetes mellitus in Europe and North America: systemic review and meta-analysis, *Environ. Health Perspect*. 123 (5) (2015) 381-389.**

[4] **Hamra, G.B., Outdoor particulate matter exposure and lung cancer: a systemic review and meta-analysis*. Environ. Health Perspect.* 122 (9) (2014) 906-911.**

[5] **Jeng, F, Impact of air pollution on intestinal redox lipidome and microbiome, *Free Radical Biology and Medicine*, 151 (2020) 99-110.**

[6] **Moeller, W. Mucociliary and long-term particulate clearance in the airways of healthy non-smoker subjects, *J. Appl. Physio.* 97 (6) (2004) 2200-2206.**

[7] **M. Semmler-Behnke, Efficient elimination of inhaled nanoparticles from the alveolar region: evidence for intestitial uptake and subsequent reentrainment onto airways epithelium. *Environ. Health Perspect.* 115 (5) 2007) 728-733.**

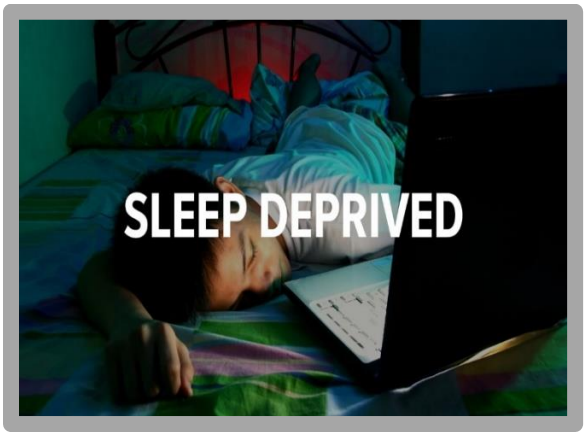
[8] **Beamish, L. A., Air pollution: An environmental factor contributing to intestinal disease, *J. Crohn's Colitis* 5 (4) (2011) 279-286.**

[9] **Lomer, M.C., Fine and ultrafine particles of the diet: influence on the mucosal response and association with Crohn's disease*, Proc. Nutr. Soc*. 61 (1) (2002) 123-130.**

[10] **Lomer, M.C., Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease, *Br. J. Nutr*. 92 (6) (2004) 947-955.**

[11] **Bailey, M.J., et. al., Postnatal exposure to ambient air pollutants is associated with the composition of the infant gut microbiota at 6-months of age, Gut Microbes, 14:1, 2022**

AVOID CONDITIONS THAT CAUSE SLEEP DEPRIVATION



Sleep is an essential physiologic activity that takes up approximately one third of human life and is crucial to the proper functioning of the body. Sleep disturbances are becoming increasingly prevalent and have been associated with a multitude of illnesses.[1] Numerous studies have established a strong association between sleep fragmentation, sleep deprivation, and obstructive sleep apnea, with cardiovascular disease, obesity, diabetes, cancer, and neurologic dysfunction.

Accumulating evidence suggests that a deficiency of beneficial gut microbes is associated with these sleep deprivation induced human diseases.[2]

[1] Ali, T. Sleep disturbances in inflammatory bowel disease. *Inflamm. Bowel Dis*. 2014, 20, 1986-1995

[2] Sun, J. Sleep deprivation and gut microbiota dysbiosis: current understandings and implications, *Int J Mol Sci.,* 2023 Jun; 24 (11): 9603

AVOID DRUGS, BOTH PHARMACEUTICAL AND SUPPLEMENTS, THAT ADVERSELY AFFECT THE DENSITY, DIVERSITY, AND FUNCTIONALITY OF BENEFICIAL MICROBES IN THE BODY

The Dangers Of Hyperpolypharmacy[1]

The body is under a constant state of siege. Not only is it challenged by the day-to-day contaminants, pollutants, and toxins in the air, food and water, but also by the enormous numbers of pills, tablets, capsules, powders and potions prescribed by medical care providers and self-administered by individuals as supplements.

Many supplements are made in foreign countries where conditions of cleanliness are unknown. Most unregulated preparations have never been the subject of published scientific studies and/or scrutinized by experts in the field of microbiology and pharmacology.

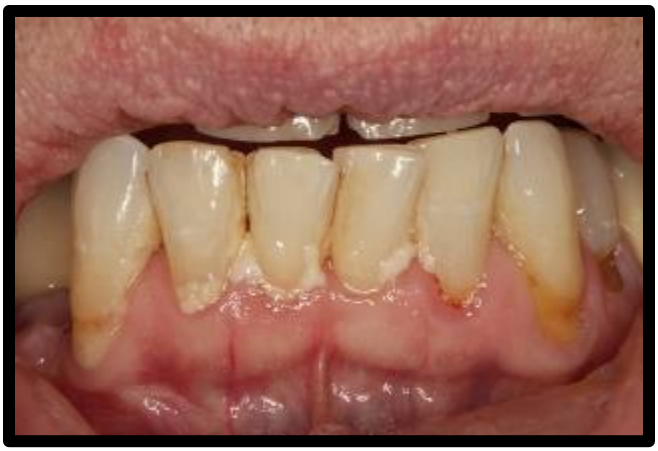
The body can react to this siege of chemicals with stomach pains, altered bowel function, nausea, gaseous distention, muscle and joint discomfort, mental status changes, migraine headaches, skin rashes, cardiac rhythm disturbances, liver and kidney dysfunction, asthma, and more.

Combining multiple, unregulated, over the counter supplements, known as hyperpolypharmacy, may result in serious unintended consequences including the development of toxic levels of the supplement or interference of the supplement with the metabolism of some other regulated prescription medication being taken. Less is better.

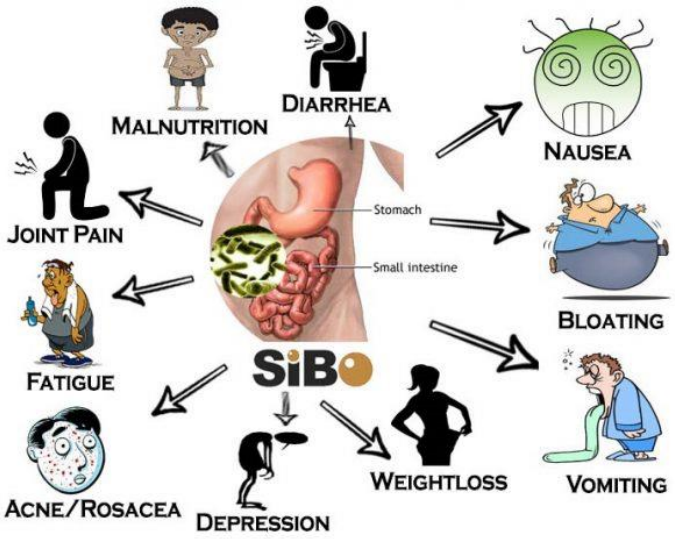
[1]Hyperpolypharmacy: Commonly defined as the use of over 10 medications.

AVOID HARMFUL DOSES OF EXTERNAL ENVIRONMENTAL RADIATION (I.E., SUN EXPOSURE).

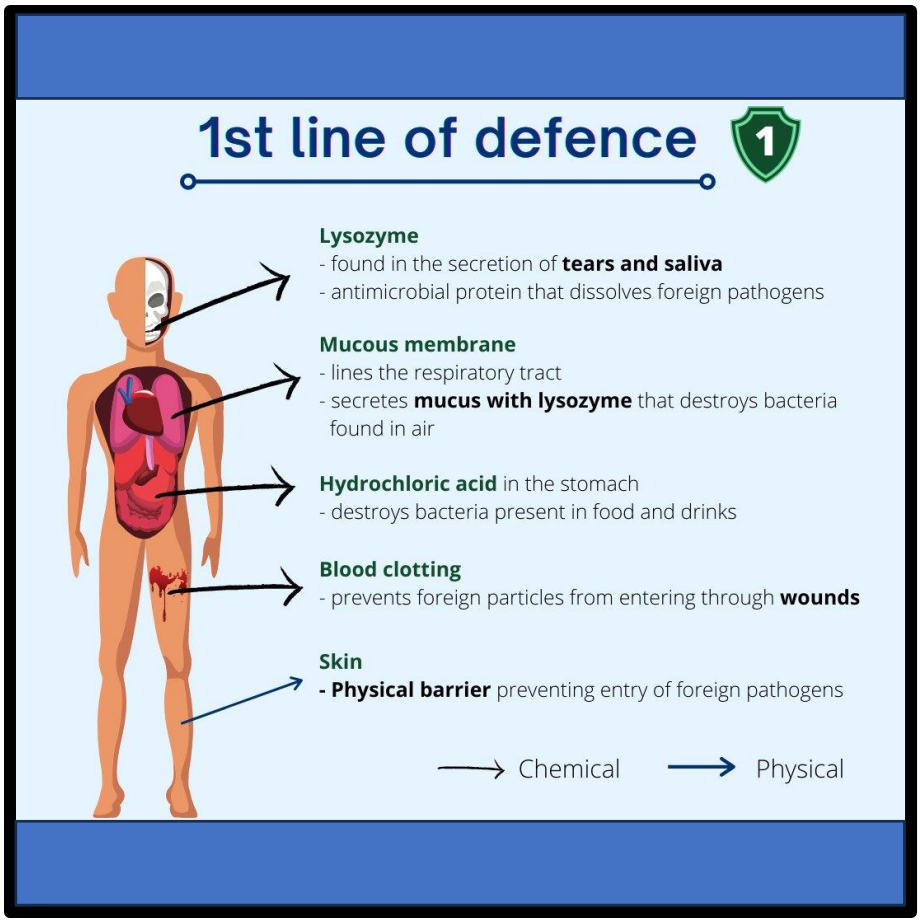
AVOID CONDITIONS THAT PROMOTE THE GROWTH OF HARMFUL MICROBES IN THE BODY LIKE PLAQUE AND TARTAR IN THE MOUTH (*SEE THE SECTION: ORAL CAVITY*)



AVOID CONDITIONS THAT PROMOTE THE OVERGROWTH OF MICROBES IN THE SMALL INTESTINE *(SEE THE SECTION: SIBO).*



AVOID THE ELIMINATION OR REDUCTION OF PROTECTIVE BODILY SECRETIONS (E.G., SALIVA, GASTRIC ACID, SWEAT, MUCUS, BILE, PANCREATIC DIGESTIVE ENZYMES) THAT DEFEND THE BODY FROM HARMFUL MICROBES, TOXINS AND CONTAMINANTS.



GET 20-30 MINUTES OF MODERATE PHYSICAL ACTIVITY AT LEAST 5 DAYS PER WEEK

Multiple studies have shown that physical activity has well-established health benefits.[1-4] These include reduced risk of cardiovascular disease, type II diabetes, and psychiatric conditions like depression.

Conversely, sedentary behavior which has been defined as sitting or non-sleep lying activity with low expenditure of energy is associated with an increased risk of type II diabetes and cardiovascular mortality.

Regular physical activity has been shown to affect the gut microbiome through various mechanisms including moderation of the intestinal immune system, reduction in intestinal transit time, alteration in blood flow through the intestinal tract, alterations in intestinal permeability, and interaction with bile metabolism.

A recent study using accelerometer-based physical activity suggests that benefits of physical activity may be mediated by the intestinal microbiome.

A majority of population-based studies have used self reporting of moderate and vigorous self exercise. Since the studies have been self reported, the information provided may have been subject to reporting bias.

The current study, however, used a sensor-based physical activity assessment with an accelerometer. Accelerometers are considered to provide more valid estimate of physical activity compared to self reporting data.

The study confirmed that sedentary behavior and physical activity are linked to the intestinal microbiota. In particular, sedentary behavior was associated with microorganisms having a lower capacity to metabolize dietary fiber.

The findings of the study suggest that physical activity is capable of modifying the gut microbe composition with positive benefits on human health.

Studies have shown that exercise may be beneficial to the health of the host.

[1] **Monda, V., Exercise Modifies the Gut Microbiota with Positive Health Effects, *Oxidative Medicine and Cellular Longevity*, vol 2017, Article ID 3831972 pages 1-9.**

[2] **Berman, S The microbiota: an exercise immunology perspective, *Exercise Immunology Review*, vol. 21, 70-79, 2015.**

[3] **Clark, S. F., Exercise and associated dietary extremes impact on gut microbial diversity*. Gut*, volume 63, number 12, pages 1913-1920, 2014**

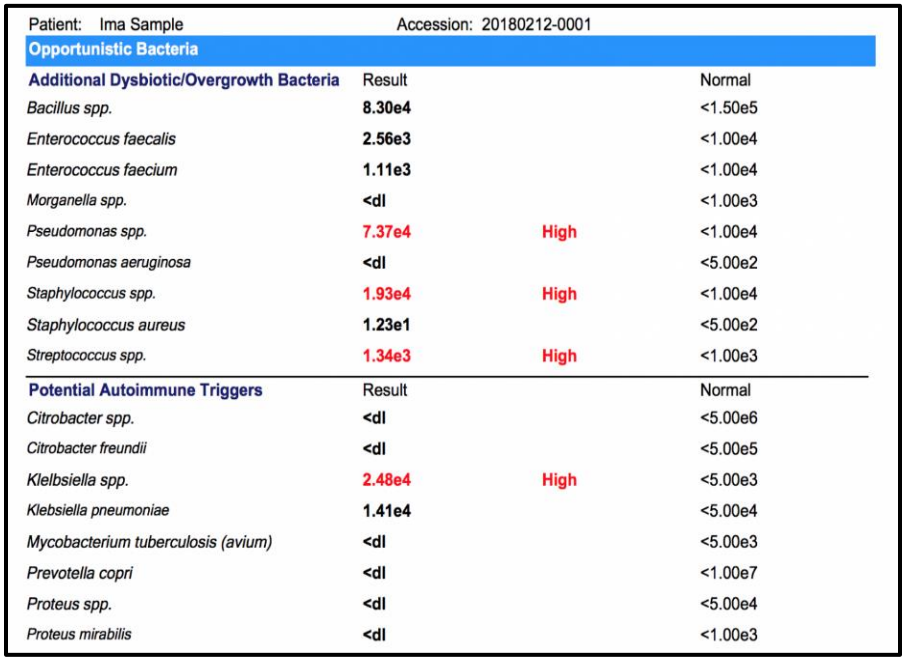
[4] **Peters, H. P. F. Potential benefits and hazards of physical activity and exercise only gastrointestinal tract, *Gut*, vol. 48 (3), 435-439, 2001**

The following health benefits have been associated with regular physical activity in adults:

- **Lower risk of all-cause mortality**
- **Lower risk of cardiovascular disease mortality**
- **Lower risk of cardiovascular disease (including heart disease and stroke)**
- **Lower risk of hypertension**
- **Lower risk of type II diabetes**
- **Lower risk of adverse blood lipid profiles**
- **Lower risk of cancer of the bladder, breast, colon, endometrium, esophagus, kidney, lung and stomach**
- **Improved cognition**
- **Reduce risk of dementia (including Alzheimer's disease)**
- **Improve quality of life**
- **Reduced anxiety**
- **Reduced risk of depression**
- **Improved sleep**
- **Slowed or reduced weight gain**
- **Weight loss, particularly combined with reduced calorie intake**

- **Prevention of weight regain following initial weight loss**
- **Improved bone health**
- **Improved physical function**
- **Lower risk of falls particularly for older adults**
- **Lower risk of fall-related injuries particularly for older adults.**

Is There Value To Doing A Stool Analysis Of Density And Diversity Of The Gut Microbiome?



Patient: Ima Sample Accession: 20180212-0001

Opportunistic Bacteria			
Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	**8.30e4**		<1.50e5
Enterococcus faecalis	**2.56e3**		<1.00e4
Enterococcus faecium	**1.11e3**		<1.00e4
Morganella spp.	**<dl**		<1.00e3
Pseudomonas spp.	**7.37e4**	**High**	<1.00e4
Pseudomonas aeruginosa	**<dl**		<5.00e2
Staphylococcus spp.	**1.93e4**	**High**	<1.00e4
Staphylococcus aureus	**1.23e1**		<5.00e2
Streptococcus spp.	**1.34e3**	**High**	<1.00e3
Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	**<dl**		<5.00e6
Citrobacter freundii	**<dl**		<5.00e5
Klelbsiella spp.	**2.48e4**	**High**	<5.00e3
Klebsiella pneumoniae	**1.41e4**		<5.00e4
Mycobacterium tuberculosis (avium)	**<dl**		<5.00e3
Prevotella copri	**<dl**		<1.00e7
Proteus spp.	**<dl**		<5.00e4
Proteus mirabilis	**<dl**		<1.00e3

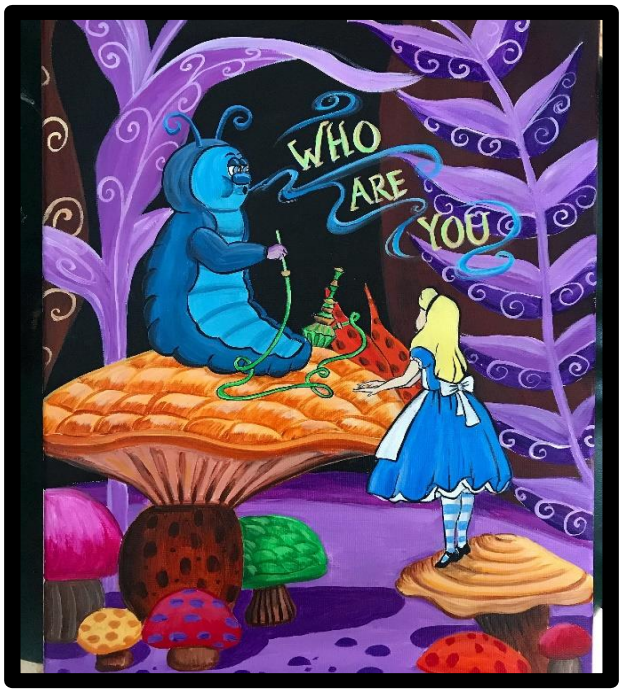
The ability to identify species and quantity of microorganisms in the human microbiome is an exciting breakthrough. As yet, however, medical care providers do not have the tools to interpret the data. There is no agreed upon definition of a "normal" microbiome.

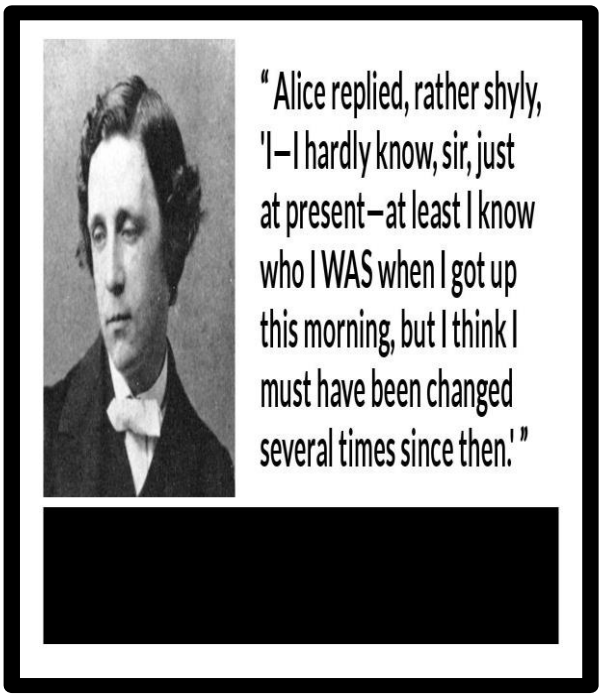
Though certain microbes may be present, providers still do not know if those microbes are functionally active and what factors activate or deactivate them.

Furthermore, medical care providers still do not fully understand how organisms interact with each other. Nor do they know whether microbes affect many prescription medications and supplements that the individuals may be taking.

Knowing which microbes are present in the gut is an important first step. Knowing what these microbes are doing, how they do it, and how and when to manipulate them is the next challenge in patient care.

The study of the gut microbiome is complicated further by knowing that the gut microbiome constantly fluctuates throughout the day and across seasons. It is never the same.





Lewis Carroll (Alice's Adventures in Wonderland)

New research has shown that gut microbes vary from morning to night and from season to season.[1,2] Profound fluctuations have been found between summer and winter.

According to one investigator, Dr. Carolina Machado, University of California, San Diego, "The seasonal variations that we see in conditions like allergies, or the flu occur in context of completely different microbiomes."

The researchers believe that diet and sleep are two big factors accounting for the daily fluctuations. They point out that, "the gut environment is radically different in terms of nutrients, water availability and pH when one is sleeping compared to when one eats."

These findings are important, not only to researchers who are studying the microbiome but also researchers whose results could be affected by variations in the microbiome such as medication studies where the microbiome may be involved in the metabolic transformation of the medication.

Finally. . . the time of day when a stool specimen is collected could profoundly influence research results in unexpected ways.

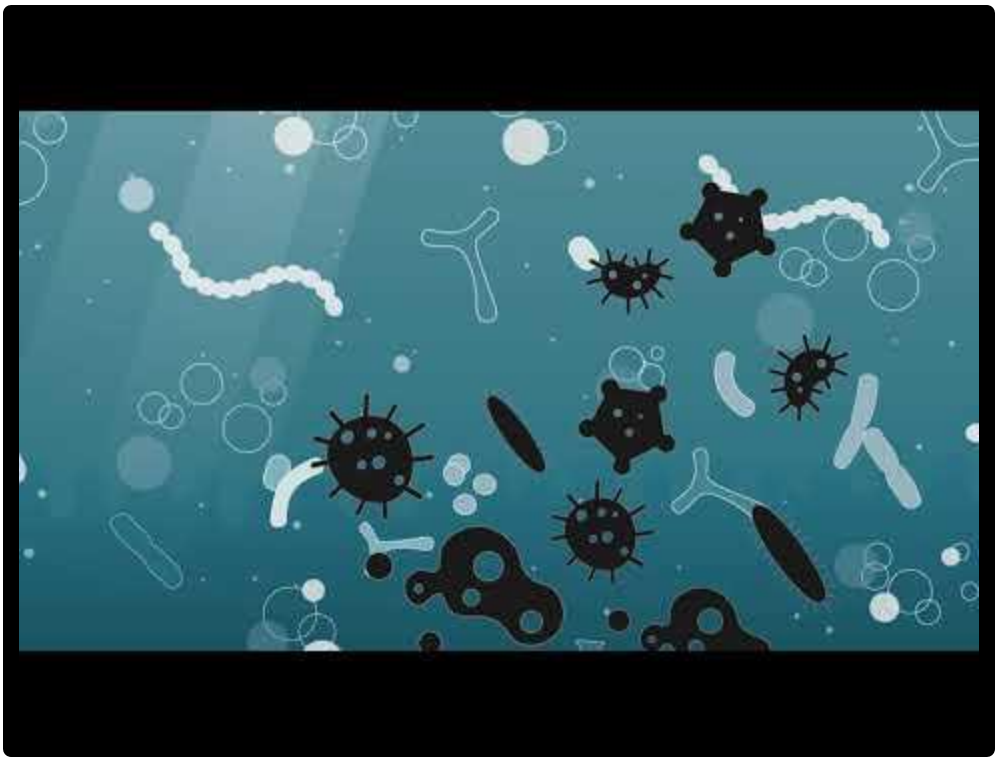
[1] Machado, D, The human gut microbiome displays diurnal and seasonal rhythmic patterns, *Digestive Disease Week, Abstract* 395, 2023.

[2] Wang, H., New insights into the diurnal rhythmicity of gut microbiota and its crosstalk with host circadian rhythm, Animals *2022*, *12*(13),1677; https://doi.org/10.3390/ani12131677

THE "BIOTICS" FAMILY
PROBIOTICS, PREBIOTICS AND POSTBIOTICS

PROBIOTICS

(ON A WINDOWS BASED COMPUTER, LEFT CLICK THE MIDDLE OF THE IMAGE BELOW. AT THE NEXT SCREEN, LEFT CLICK THE "SHARE" TAG IN THE UPPER RIGHT CORNER OF THE SCREEN. THEN LEFT CLICK THE HTTPS:// ADDRESS OF THE VIDEO TO START THE PRESENTATION.)



Probiotics have been defined by the World Health Organization as live microorganisms that when ingested in adequate amounts may confer health benefits.[1] Probiotics may be obtained from the diet by the ingestion of fermented food items (See Table 3) or manufactured as food supplements.

Probiotics that are manufactured as food supplements are not considered drugs in the United States and thus are not held to the same regulatory standards as pharmaceuticals.[2]

Since manufacturers of probiotic supplements are unregulated by the Food and Drug Administration, their products can be marketed without providing direct and consistent proof of effectiveness.[2]

The hype and hope for using probiotics may have gotten ahead of the science. It has been established, as pointed out before, that every human intestinal microbiome is unique containing trillions of microorganisms representing thousands of different species—bacteria, viruses, protozoa, fungi, and archaea. No single microbiome composition can be defined as "normal" since any number of microbe combinations exist in healthy humans.

Choosing a probiotic to influence a specific individual's intestinal microbiome becomes problematic since recommending a probiotic presupposes the knowledge of which microorganisms are missing or deficient as the cause of a human ailment—information that is largely unknown.

Although laboratories advertise their ability to identify microbial strains that might exist in a human fecal sample, they do not identify which microbes exist that have active gene expression at any specific time.

Improving microbe diversity may be but one possible mechanism that provides a benefit for probiotics. Another possible explanation for benefit is that probiotics largely may not survive the harsh environment of acid in the stomach or bile and pancreatic juices in the small bowel thereby in their inanimate state becoming postbiotics. As postbiotics they may be of benefit to the existing microbe population enhancing their growth, i.e. acting as prebiotics.

In 2020, the American Gastroenterolgy Association published their official recommendations regarding the use of probiotics in select conditions[3]. In most of the conditions they studied, the evidence for the use of probiotics was poor to support the use of probiotics.

Patients are, therefore, advised to consult a knowledgeable medical care provider to assist them if a probiotic is being considered and which strain or strains of microbes should be included if a probiotic is chosen.

[1] Food and Agriculture Organization and World Health Organization Expert Consultation. Evaluation of health and nutritional properties of powder milk and live lactic acid bacteria. Córdoba, Argentina: Food and Agriculture Organization of the United Nations and World Health Organization; 2001. [cited 2005 September 8]. Available from: ftp://ftp.fao.org/es/esn/food/probioreport_en.pdf.

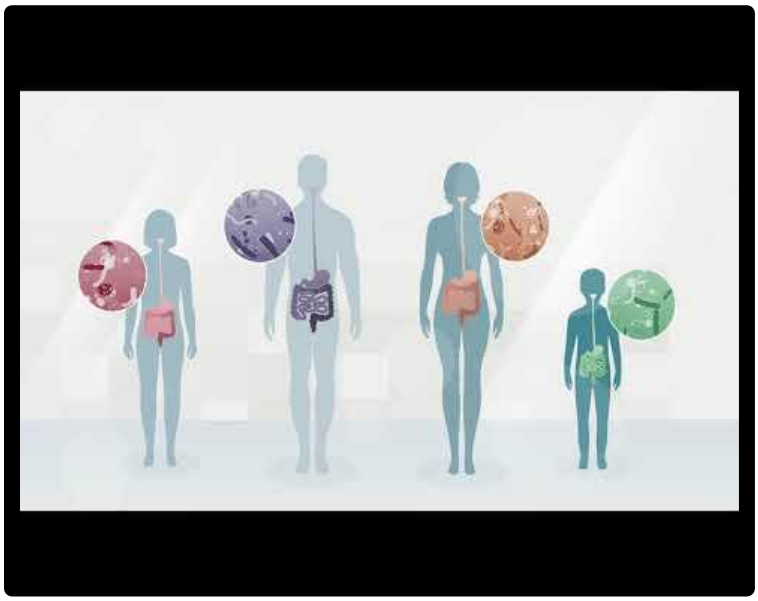
[2] deSimone, C. The unregulated probiotic market*, Clin. Gastroenterol. Hepatol*., 2019, 17:809-817.

[3] Su, Grace et al. Clinical Practice Guidelines. *Gastroenterology*; 2020, 159:706.

[4] Suez, J., The pros and cons and many unknowns of probiotics, *Nat. Med.,* 2019, 25: 716-729.

PREBIOTICS

(ON A WINDOWS BASED COMPUTER, LEFT CLICK THE MIDDLE OF THE IMAGE BELOW. AT THE NEXT SCREEN LEFT CLICK THE "SHARE" TAG IN THE UPPER RIGHT CORNER OF THE SCREEN. THEN LEFT CLICK THE HTTPS:// ADDRESS OF THE VIDEO TO START THE PRESENTATION.)



Prebiotics have been defined as substrates that are selectively utilized by host microorganisms conferring a health benefit. Prebiotics initially were composed of non-digestible dietary fiber consumed by the host that nourished intestinal microorganisms. In addition to dietary fiber, prebiotics now include resistant starches *(*See the section: Resistant Starches*)*, bovine milk fats, selected amino acids and human breast milk oligosaccharides. *(*See the section: Human Milk Oligosaccharides.)

Several studies[1-3] have also shown the beneficial effects for adults of feeding human breast milk oligosaccharides that have been synthesized in the laboratory.

[1] Suligoj, T. Effects of human milk oligosaccharides on the adult gut microbiota and barrier function, *Nutrients,* 12:2808 (2020).

[2] Elison, E*.* Oral supplementation of healthy adults with 2'-O-fucosyllactose and lacto-N-neotetraose is well tolerated and shifts the intestinal microbiota*. British Journal of Nutrition*, 116, 1356-1368 (2016).

[3] Palsson, O., Human Milk Oligosaccharides Support Normal Bowel Function and Improve Symptoms of Irritable Bowel Syndrome: A Multicenter, Open-Label Trial, *Clin Transl Gastroenterol.* 2020 Dec; 11(12)

A list of prebiotic containing food items can be found at the end of the monograph. (See List I)

POSTBIOTICS

(ON A WINDOWS BASED COMPUTER, LEFT CLICK THE MIDDLE OF THE IMAGE BELOW. AT THE NEXT SCREEN LEFT CLICK THE "SHARE" TAG IN THE UPPER RIGHT CORNER OF THE SCREEN. THEN LEFT CLICK THE HTTPS:// ADDRESS OF THE VIDEO TO START THE PRESENTATION.)

According to scientific consensus, a postbiotic is composed of non-living microorganisms and/or their component parts that confer a health benefit on the host.

Non-living components can include cell fragments like cell wall components or proteins contained in the membranes of the dead microbes.

There are advantages to using postbiotics instead of probiotics. Some of those advantage include the following:

- **Postbiotics have a high degree of stability with prolonged shelf-life and are easy to standardize, transport and store.**

- **Postbiotics have no risk of virulence gene transfer and do not present a threat of becoming antibiotic resistant.**

- **Postbiotics present no risk of translocation from the intestinal tract into the blood stream or to other tissues.**

- **Postbiotics do not interfere with other beneficial microbes.**

In theory, those 100 billion+ microbes that are swallowed every day from the mouth and are destroyed by gastric acid and proteolytic enzymes in the stomach become postbiotics.

Likewise, those that survive the stomach and begin to proliferate in the small intestine and subsequently are killed by the antimicrobial effect of bile acid and pancreatic enzymes also form postbiotics.

To date, the research on postbiotics created in this fashion is almost non-existent. Furthermore, there are strains of pathogenic microorganisms that may live in the mouth and stomach such as *Porphymonas gingivalis* in the gum disease periodontitis and H. pylori in the stomach. It is unknown whether the destruction of pathogenic organisms like these have a beneficial postbiotic effect, or not, after successful destruction by the intestinal immune mechanisms.

Like prebiotics, postbiotics can be found in food products, dietary supplements, and infant formula. (See the section: Human Milk Oligosaccharides--HMO's).

Comparing Natural Versus Synthetic Pre and Probiotics

A view has been proposed that synthetic prebiotic and probiotic nutrients that are made artificially in an industrial process are identical to those found in food sources. However, the production process for pre and probiotics is quite different from the way plants and animals create them. Despite having a similar chemical structure, the body may react quite differently to the synthetic products compared to natural food sources.

Iron deficiency--A Common Diagnosis With Intestinal Implications

It's estimated that 3.5 billion people worldwide suffer from iron deficiency.[1] Iron deficiency is the most common cause of anemia in the United States[2].

There are multiple causes for iron deficiency. The causes fall into four general categories:

- **INCREASED IRON LOSSES**
  - **Examples:**
    - **Acute bleeding**
    - **Chronic bleeding—**
      i. **Menstruation**

ii. **Inflammation**
iii. **Cancer**
iv. **Vascular malformations**
v. **Destruction of red blood cells (hemolysis)**

- **DECREASED INTAKE OF IRON IN THE DIET**

  Examples:

  - **Vegetarian diet**
  - **Malnutrition**
  - **Dementia**
  - **Psychiatric illnesses (e.g., anorexia nervosa, bulimia)**

- **DECREASED IRON ABSORPTION**

  Examples:

  - **Use of acid reducing medications (e.g., Prilosec®, Nexium®, Prevacid®, Protonix®, Dexilant®)**
  - **Autoimmune gastritis**
  - **Pernicious anemia**
  - **Celiac disease**
  - **Intestinal surgery (bariatric gastric bypass, partial gastrectomy)**
  - **Duodenal-gastric bile reflux**
  - **Intestinal infections (e.g., Helicobacter pylori, intestinal parasites)**

- **INCREASED IRON REQUIREMENTS**

  Examples:

  - **Pregnancy**
  - **Breast-feeding**

Restoring Iron

To provide adequate supplies of iron for the production of red blood cells and to replace the losses that occur in urine, sweat, and stool, around 1 to 2 mg of "heme iron" is required daily. Heme iron is found in red meat and liver. Non-heme iron, which is found in cereals, egg yolk, and green leafy vegetables is not efficiently absorbed.

For those who prefer not to incorporate red meat and liver in their diet, medicinal iron may be necessary to prevent iron deficiency anemia.

Helpful And Harmful

Vitamin C has been shown to increase iron absorption and can be found in citrus fruits. On the other hand, black tea may inhibit iron absorption. Individuals with iron deficiency, therefore, should be encouraged to wait several hours after a meal before drinking black tea or eliminate black tea altogether from their diet. Likewise, individuals should not take iron supplements within two hours after taking an antacid.
Other medications and nutrients that may reduce iron absorption include medications that reduce acid in the stomach as noted above or those that may delay iron absorption including tetracycline antibiotic, milk, and carbonated beverages.

Evidence also shows that calcium, phosphorus and magnesium salts present in most multivitamin preparation that contain iron impair the absorption of the elemental iron.

Multivitamin preparations that contain iron, therefore, are not recommended as adequate therapy for iron deficiency anemia.

Timing Of Doses

Timing of iron doses may be important. Taking iron supplements between meals or at bedtime tends to avoid the alkalinizing effect of foods that interfere with conversion of iron to an absorbable form and takes advantage of the acid conditions in the stomach that exist overnight.

Selecting Medicinal Heme Iron

An acceptable approach for treating iron deficiency in adults consists of administering a daily dose of 150 to 200 mg of elemental iron. This can be accomplished by taking three ferrous sulfate tablets a day, each of which contain 65 mg of elemental iron.

Up to twenty percent of individuals, taking 180 mg of elemental iron per day, however, develop gastrointestinal discomfort. Side effects may include nausea and abdominal pains occurring within an hour after ingestion of the supplement. Constipation may also be a side effect and can be treated by taking a mild laxative.

For those individuals that develop gastrointestinal side effects, dose reduction may be necessary. A change in the formulation of the iron salt is sometimes beneficial. These maneuvers may

allow those who develop side effects to continue using oral therapy and avoid intravenous infusions of iron.

When changing iron supplements, it's important to realize that switching from iron sulfate to iron gluconate requires doubling the iron gluconate dose since iron gluconate only contains 36 mg of elemental iron compared to the 65 mgm in iron sulfate. Iron fumarate supplements must also be doubled when switching from iron sulfate since fumarate salts contain only 33 mg of elemental iron.

Guidelines When An Iron supplement Is Used

Only 10% of iron contained in medicinal form can be absorbed. The amount of daily elemental iron for adults and postmenopausal females should, therefore, be at least 10 mg to provide the 1 mg daily requirement. The 1 mgm requirement is just to replace daily losses and not to treat iron deficiency anemia.

The amount of iron for women during their reproductive years should be 20 mg of elemental iron or more to replace added losses from menstruation.

Pregnant females and mothers who are breast feeding require 30 mg or more of elemental iron to achieve an absorption dose of 3 mg.[4]

TABLE 1[4]

PREPARATION	DOSE	ELEMENTAL IRON
Ferrous sulfate	325 mgm	65 mgm
Ferrous gluconate	300 mgm	36 mgm
Ferrous fumurate	100 mgm	33 mgm

A daily supplement might be one ferrous fumurate or one ferrous gluconate tablet which would deliver roughly 3.3-3.6 mgm to cover daily losses. For females during their reproductive years, pregnant females, breast feeding mothers or those with iron deficiency anemia dosing requirements may be higher and ferrous sulfate may be a better choice. A medical care provider should be consulted.

The amount of elemental iron absorbed is not constant and thus, periodic blood tests to check for anemia and for iron concentrations are recommended.

Delayed-release iron preparations and those that are enteric-coated have been promoted as better tolerated than the non-enteric-coated tablets. They are, however, substantially more expensive.

It's possible that they may be less effective since most of them contain less iron than the non-enteric-coated tablet and the iron contained therein may not be released in the upper portion of the small intestine where iron is absorbed.

Those who have used enteric-coated preparations and not responded, may improve with the administration of a non-enteric ferrous salt preparation like the ones illustrated above.

[1]*United Nations sub-committee on nutrition (ACC/SCN). Fourth report on the world nutrition situation. United Nations; 2000*

[2] *Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. MMWR Morb Mortal Wkly Rep 1998; 47 (RR3): 1 – 29*

[3]**J. Story, editor.** *Guidelines for adolescent nutrition services. 2005*

[4] **M. Alleyne, Individualized treatment for iron deficiency in adults,** *Am J. Med. 2008 November; 121(11):943-948*

REMAIN ALERT TO CHANGE . . .

Not all chronic intestinal illnesses remain chronic. Sometimes "chronic" may suddenly become "acute".

According to the American College of Emergency Physicians, the following are some intestinal related warning signs that may indicate a medical emergency:

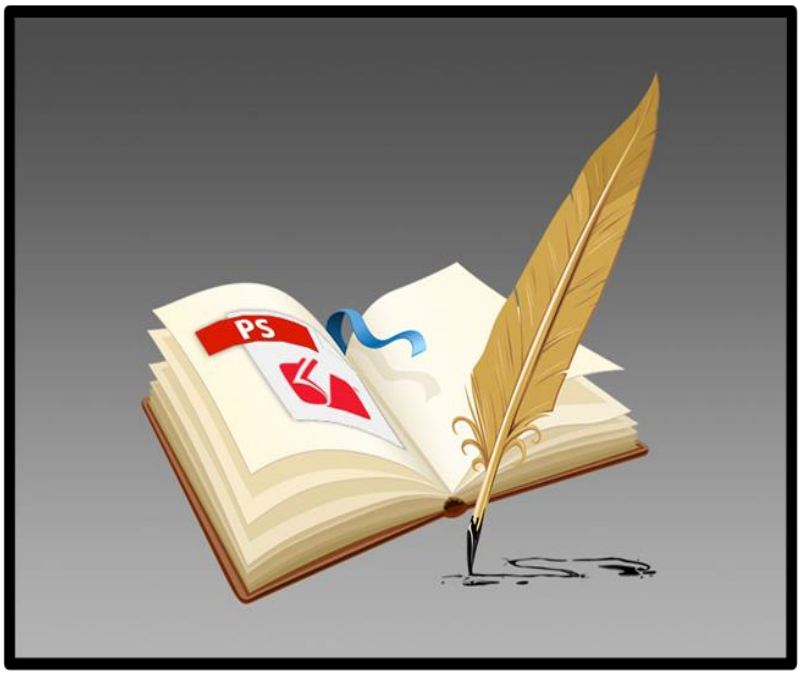
- **Recurrent or large amounts of rectal bleeding**
- **Persistent diarrhea**
- **Persistent inability to have a bowel movement or pass gas**
- **Severe or persistent vomiting**
- **Vomiting blood**
- **Sudden dizziness or weakness**
- **Fainting or loss of consciousness**
- **Sudden, severe or prolonged periods of abdominal pain or pressure**
- **Difficulty swallowing food or fluids or painful swallowing**
- **Swelling of the mouth, tongue, throat or airway**

If any of the above conditions arise, there are four reasonable options:

- **Call 911**
- **Make immediate contact with one of your medical care providers**
- **Go to an urgent care medical facility**
- **Go to a hospital emergency department**

Postscript

What Happened To Caroline?



Caroline is better—not perfect, but better. Caroline has tried to remain compliant with most of the recommendations given above. Many of her presenting symptoms have abated. Her energy level has improved. She is getting more restful sleep. Her mental acuity has returned. Body aches and pains have diminished. Her burping, bloating, flatulence, and distention have all decreased. Foods that she thought she would never be able to tolerate again are now appearing on her plate after many years of avoidance without precipitating an increase in symptoms.

Caroline still, on occasion, has periods of bowel irregularity with occasional diarrhea interspersed with periods of

constipation. The episodes, however, are less frequent and are brief. She attributes these episodes mostly to times when she did not eat enough fiber or was prescribed an antibiotic.

Caroline feels she is on the right path. She pays more attention now to what she allows to go through her mouth as well as to her dental care. She says that she can now see a more hopeful and healthy future ahead of her.

Into The Future

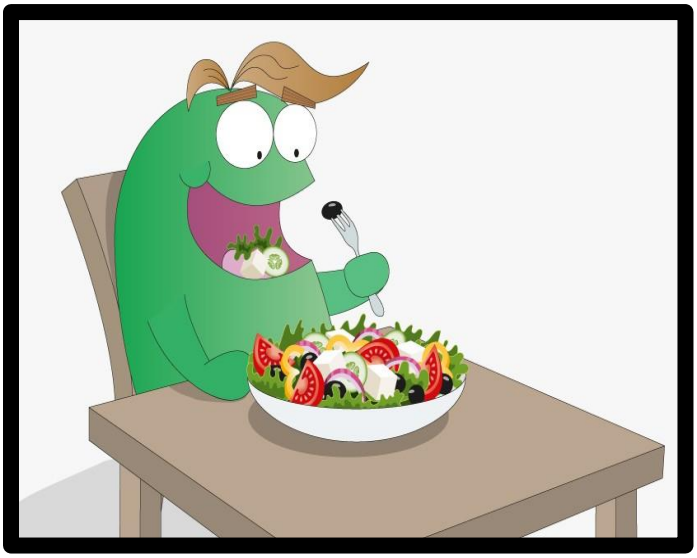
This monograph has tried to point out that an individual's well-being is influenced enormously by the density, diversity and functioning of microorganisms that live in and on the body. Since the microbe population is constantly in flux, it remains a challenge to know how to beneficially influence a specific individual's microbe population.

Seth Bordenstein, professor of biology at Pennsylvania State University makes the comment, "Arguably, the biological field is at one of its greatest inflection points since Charles Darwin introduced the theory of evolution. It's because of the new interest and appreciation of the microbial world in ways that we have never recognized before."

The question posed to doctors in almost all specialties is "What should I eat?" Professor Rachel Carmody, Harvard

Department of Human Evolutionary Biology, response to this question is. . . "it all depends what microbiome you're targeting, and at present, we don't even know how to define what a healthy microbiome is".

Basic questions and answers to how the microbiome is connected to other parts of the body remain. The mechanisms underpinning the connections continue to be active areas of scientific exploration. These areas include defining which microbes are involved, what nutrients they rely upon, and how environmental factors influence them.



You are what your microbes eat!

Once these questions are answered, the goal of creating *personalized microbiomes* will be attainable.

Many of the recommendations found in the monograph are also found in the YouTube presentation that follows, *Live To Be 100.*

IF USING A WINDOW BASED COMPUTER, PRESS CONTROL AND THEN LEFT CLICK YOUR MOUSE IN THE CENTER.

There remain many uncertainties in science and gaps in understanding how the body functions. There are dangers in promising that the latest finding will change a person's life or change the world.

The present state of the art suggests that if the density, diversity and robust functional capabilities of the human microbe population is repeatedly assaulted by excessive antibiotic exposures, lack of fiber containing diets, overuse of unregulated supplements, and lifestyle perturbations such as stress, minimal exercise, lack of attention to dental care, poor sleep patterns, and use of mind-altering drugs like alcohol, tobacco, and marijuana, then chronic human illnesses may persist.

The monograph, therefore, has suggested the following:

- **Ingestion of primarily a plant predominant diet**
- **Rigorous oral home hygiene measures**
- **Frequent visits to the dentist and dental hygienist to avoid dental decay and gum inflammation.**

- **Avoidance of recreational drugs including, but not limited to, alcohol, tobacco, cocaine, LSD, marijuana, and smoking e-liquids (vaping)**
- **Avoidance of measures that alter protective body secretions--(mucus, saliva, stomach acid, bile, and pancreatic enzymes)**
- **Improvement of ambient air quality**
- **Improvement of hydration**
- **Participation in regular exercise**
- **Socialization with friends and family, and**
- **Remaining aware that over-the-counter supplements are unregulated and should only be use with proper medical guidance**

In the not too distant future, technology will provide the ability to manipulate the human geneome and to create personalized microbiomes. At that time, every human experiment and study that has been done in the past may have to be revisited and treatments reanalyzed as the interactions between the body and its microbes are considered.

As science unravels the mysteries of the human geneome and its interactions with the human microbiome, the monograph will be updated.

Stay tuned . . .

DCK

List 1

FOODS CONTAINING FERMENTABLE FIBER

Fruits

- Apples
- Apricots
- Bananas
- Blackberries
- Blueberries
- Coconut
- Dates
- Figs
- Kiwifruit
- Nectarines
- Oranges
- Peaches
- Pears
- Plums
- Pomegranates
- Prunes
- Raisins
- Raspberries
- Strawberries

Vegetables

- Acorn squash
- Artichokes
- Arugula

- **Asparagus**
- **Avocados**
- **Beets**
- **Broccoli**
- **Brussels sprouts**
- **Cabbage**
- **Carrots**
- **Celery**
- **Collard greens**
- **Corn (sweet, boiled)**
- **Cauliflower**
- **Eggplant**
- **Green beans**
- **Green peas**
- **Edamame**
- **Kale**
- **Okra**
- **Olives**
- **Onions**
- **Parsnips**
- **Peppers**
- **Potato (baked, with skin)**
- **Pumpkin**
- **Radishes**
- **Rutabaga**
- **Shallots**
- **Snap peas**
- **Snow peas**
- **Spinach**

- Squash
- Sweet potatoes
- Tomatoes
- Turnips
- White mushrooms
- Zucchini

Nuts

- Brazil nuts
- Cashews
- Chestnuts
- Granola
- Hazelnuts
- Macadamia nuts
- Pine nuts
- Peanuts
- Pecans
- Sunflower kernels
- Walnuts

Seeds And Grains

- Chia
- Flax
- Hemp
- Pistachios
- Pumpkin
- Quinoa
- Sesame
- Sunflower

Beans And Lentils

- Wheat bran
- Baked beans
- Black beans
- Black-eyed peas
- Garbanzo beans
- Kidney beans
- Lentils
- Lima beans
- Mung beans
- Northern beans
- Navy beans
- Pinto beans
- Split peas
- Soybeans
- Soy yogurt
- Tempe
- Tofu

List 2

Types Of Food Additives And Their Uses

THE MAINSTAYS OF PROCESSED FOODS

- **Anti-caking agents—stop ingredients from becoming lumpy.**
- **Antioxidants—prevent foods from oxidizing are becoming rancid.**
- **Artificial sweeteners—increase sweetness.**
- **Bulking agents—increase the volume of food.**
- **Colorants—enhance added color.**
- **Emulsifiers— stop fats from clumping together.**
- **Food acids—maintain the right acid level.**
- **Flavor enhancers—increase the power of a flavor.**
- **Flavors—add flavor.**
- **Flour treatment—improve baking quality.**

- Foaming agents—maintain uniform aeration of gases within the food.
- Gelling agents—alter the texture of foods through gel formation.
- Glazing agents—improve appearance and protection of food.
- Humectants—keep food moist.
- Stabilizers and foaming agents—maintain even food dispersion.
- Mineral salts—enhance texture and flavor.
- Preservatives—stop microbes from multiplying and spoiling the food.
- Propellants--help propel food from a container.
- Raising agents—increase the volume of food using gases.
- Thickeners and vegetable gums—enhance texture and consistency.

List 3
Fermented Food Items

Food sources are always the best way to obtain probiotics.

The following is a partial list of commonly available fermented food items that contain probiotics which may provide benefit to both the microbe population and the human host.

1. Kefir milk

Kefir is a fermented milk product (made from cow, goat or sheep's milk) that tastes like a drinkable yogurt.

2. Kombucha Tea

Kombucha tea is a fermented drink made of black tea and sugar (from various sources like cane sugar, fruit or honey).

3. Sauerkraut

Sauerkraut is a product made from fermented green or red cabbage.

4. Brined pickles

Fermented pickles are made with cucumbers and brine (salt plus water). It is best to look for "lactic acid fermented pickles" made by a manufacturer that uses organic products and brine, refrigerates the pickles, and states that the pickles have been fermented.

5. Miso

Miso is created by fermenting soybeans, barley, or brown rice with koji, a type of fungus. It's a traditional Japanese ingredient in recipes including miso soup.

6. Tempeh

Tempeh is a fermented product created by combining soybeans with a tempeh starter (a mix of live mold). When allowed to sit for a days it forms a dense, cake-like product. It is similar to tofu.

7. Natto

Natto consists of fermented soybeans. It has a strong smell, deep flavor and sticky texture.

8. Kimchi

Kimchi is a fermented Korean food made from vegetables, including cabbage, plus spices like ginger, garlic, pepper and other seasoning.

9. Raw aged cheeses

Raw milk cheeses are made with milk that has not been pasteurized. The label on the cheese should indicate that the cheese is raw (i.e., not pasteurized) and has been aged for six months or more. Examples of raw aged cheeses include: Gruyere, Parmigiano-Reggiano, English chedder, Camembert, Roquefort, Morbier, Raclette, Fontina, and Asiago.

10. Yogurt

Yogurt is a fermented milk product.
It is recommended when buying yogurt to look for three things:

- **It comes from goat or sheep milk if you have trouble digesting cow's milk.**
- **It's made from the milk of animals that have been grass-fed.**
- **It is organic.**

11. Apple cider vinegar with "mother"

Apple cider vinegar is a vinegar made from fermented apple juice. Apples are crushed producing juice. Bacteria and yeast are then added to begin the fermentation process producing the vinegar. The "mother" is the culture of the microbes that are added and transform the apple cider to vinegar.

12. Kvass

Kvass is a fermented beverage that has a taste similar to beer. Like kombucha tea, it goes through a fermentation process and contains probiotics.

It is made from aged, sourdough rye bread and is considered a non-alcoholic beverage because it contains only around 0.5 percent to 1 percent alcohol.

13. Coconut kefir

Coconut kefir is a probiotic-rich drink made with creamy coconut milk and kefir grains, but unlike regular kefir or yogurt, it's dairy-free and vegan-friendly.

TABLE TWO

FACTORS THAT INFLUENCE THE DENSITY AND DIVERSITY OF THE HUMAN INTESTINAL MICROBIOME

ACTIVITY-EXERCISE	DIET	ALCOHOL
AGE	GENDER	ETHNICITY
ANTIBIOTICS	IMMUNITY	DEPRESSION
BILE SALTS-TYPE AND AMOUNT	GRAVITY	GENES
BODY TEMPERATURE	CHEMO-RADIATION	VITAMIN DEFICIENCIES

DIAGNOSTIC RADIATION	STARVATION	STRESS
FASTING	IMMUNIZATIONS	GEOGRAPHIC LOCALE
GUT ENZYMES	SLEEP DEPRIVATION	CIRCADIAN RHYTHMS
HORMONES	AIR POLLUTANTS	PETS
INHALED GASES	AMBIENT TEMPERATURE	SEA LEVEL ALTITUDE
MODE OF BIRTH	INFECTIONS	TOXINS
OCCUPATION EXPOSURES	NUTRACEUTICALS	GUT MOTILITY
PHARMACEUTICALS	BODY TRAUMA	AMBIENT RADIATION
SURGERIES	RECREATIONAL DRUGS	FOOD ADDITIVES
TOBACCO	HYDRATION	ORAL-DENTAL PATHOLOGY
WATER CONTAMINANTS	GUT-BRAIN AXIS	BILE ACIDS

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