Understanding Chronic Digestive Illnesses through the Lens of Digestive Ecosystems

DEDICATION

The monograph is dedicated to the following individuals who helped me bring this monograph to fruition.

TO: ***Caroline, for giving me the inspiration to write this monograph and for allowing me to share her medical history . .***

TO: ***The late Dr. Douglas Archer, Professor, University of Florida Food Science and Human Nutrition, who introduced me to the importance of nutritional science. . .***

TO: ***Dr. Bobbi Langkamp-Henken, Professor, University of Florda Food Science and Human Nutrition, who provided me with suggestions for refining topics in the monograph . . .***

TO: ***My wife, Barbara, my partner in work and in life, who read and re-read the multiple versions of this monograph and recommended changes to improve its clarity, simplicity, and ability to convey an understandable message to my patients.***

The following monograph was written by . . .

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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 based on information obtained from this monograph are advised to discuss those changes first with their medical care providers.

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CAROLINE'S CASE HISTORY

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 and had previously been evaluated by several gastroenterologists, functional and integrative medicine specialists, and a nutritionist.

Caroline's 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. She grew up in a family with limited financial resources, and dental care was never considered a priority. By the time Caroline was an adolescent, many of her teeth had some degree of dental decay that required dental fillings many of which were subsequently replaced over the next 20 years 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 had recently been referred to a clinic that specializes in intestinal disorders, and after multiple visits and normal studies, she was told that her condition might best be handled by a psychiatrist.

The psychiatrist who cared for Caroline prescribed antianxiety and antidepressant medications which she took briefly but discontinued their use, indicating that they made her feel worse.

Caroline had repeatedly tried different diets in hopes that she could find one that helped her symptoms. She 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.

Caroline had been treated for small intestinal bacterial overgrowth (S.I.B.O) empirically with several rounds of antibiotics.

When first evaluated, Caroline was taking twenty-seven 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.

SECTION ONE

TREATING CAROLINE REQUIRED A DIFFERENT PARADIGM

Caroline's diagnostic evaluation by prior care providers had been exhaustive. However, traditional diagnostic methods such as endoscopy, imaging studies, stool, and blood tests, although vital, had not succeeded in defining the cause of her symptoms nor had they improved her sense of well-being.

Carolyn's symptoms, therefore, were considered using a more holistic approach, one which viewed her condition as dysfunctional digestive ecosystems.

ECOSYSTEMS DEFINED

Ecosystems are networks or communities of living organisms and non-living environmental factors interacting together as a system.[1]

The digestive tract can be conceptualized as a comprehensive ecosystem, where body cells and microorganisms interact within a defined environment. In this monograph, however, the digestive tract will be viewed as more than a single ecosystem but as a collection of distinct, interconnected microenvironments, or ecosystems, that includes the oral cavity, esophagus, stomach, small and large intestines with contributions from accessory microenvironments like the nasal

cavity, frontal sinuses, middle ear, mastoids, salivary glands, lungs, pancreas, gallbladder, liver, and appendix which all interact with each other.

Each of the individual ecosystems form a unique microenvironment where specific interactions take place. Each one is intricately structured, not just anatomically, but microbiologically and influenced by environmental factors. Disruptions in any of these interconnected ecosystems can result in chronic digestive illnesses.

To fully understand the dynamics within the digestive tract, it is important to appreciate how each part contributes to the overall function and health of the total system.

Unraveling the complex interactions between the host cells, the human microbes and the environmental exposures is fundamental to understanding how dysfunctional ecosystems play a role in chronic digestive illnesses.

Alessio Fasano, M.D., chief of Pediatric Gastroenterology and Nutrition at Massachusetts General Hospital for Children states, "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 . . ." [2]

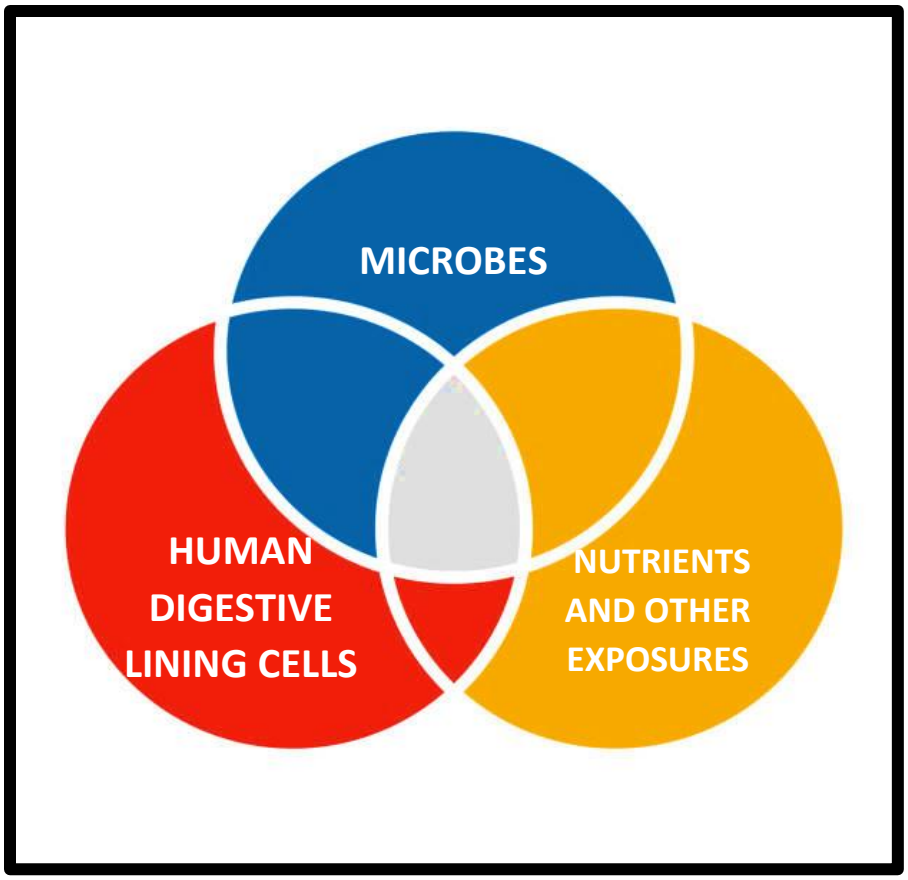
[1] **Wang, S., Microbial Collaborations and Conflicts: Unraveling Interactions in The Gut Ecosystem, *Gut Microbes,* vol 15, Issue 1, 2024.**

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

DISSECTING THE COMPOSITION OF EACH ECOSYSTEM

Each digestive tract ecosystem is a combination of three components, human cells, microorganisms, and environmental exposures. The complexity of human digestive ecosystems is akin to a well-orchestrated symphony, where every player has a critical role.

At its core, all biological reactions are fundamentally about molecular interactions, like oxygen reacting with hydrogen to form water (H2O). For a "well-orchestrated" digestive ecosystem to exist, harmonious interactions must take place between the molecules of human intestinal cells, nutrients, and microorganisms.



The Trifecta Of Intestinal Well-Being

Part 1

Human Cells That Line The Digestive Tract

The cells lining the digestive tract are key players in the ecosystem. They are not just passive barriers. They actively interact with both the microbes and the environment. They

secrete substances like mucus and enzymes, absorb nutrients, and form a barrier that acts as the body's first line of defense against pathogens. (See the section: In Defense of The Realm-Barriers That Protect the Body).

Genes within these cells influence the operation of the cells like enzyme production, immune responses, and cell turnover, shaping how effectively the digestive tract functions and interacts with other components of the ecosystem.

The totality of the body's cells and their genes are referred to collectively as the *human genome*.

PART 2
THE MICROBIOME

The second major component of digestive tract ecosystems is the microbiome. The digestive tract microbiome represents all the microbes that live in the digestive tract and their genes.

Intestinal well-being requires that the digestive tract lining cells and microbes exist mutualistically within the ecosystem—each benefiting from the interaction with the other.

Terminology: The terms *digestive tract* and *digestive system* will be predominantly used throughout the monograph as opposed to lesser inclusive terms like *gut, intestinal tract,* and *intestinal system.* The terms *digestive tract* and *digestive system* include the oral cavity, esophagus, stomach, small

intestine, large intestine and accessory digestive organs like the pancreas and liver, whereas the terms *gut,* ***intestinal tract* and ***intestinal system*** are frequently interpreted without inclusion of the oral cavity.**

PART 3
ENVIRONMENTAL EXPOSURES (THE EXPOSOME)

The exposome refers to the totality of exposures experienced over a lifetime from a variety of external and internal sources. Examples of external exposures include diet (nutrients), medications (including antibiotics), toxins and food additives. Examples of internal exposures include things like pH, temperature, oxygen availability, water availability, bile salts, and digestive enzymes.

1. **pH levels (acidity or alkalinity):**
   The pH levels within different portions of the digestive system can influence the ecosystem by establishing which microbes will thrive there. As an example, the stomach contains a highly acidic environment which inhibits most bacteria except those that are specially adapted like *Helicobacter pylori*. In the colon, however, the pH tends to be more neutral thereby supporting a separate set of microbe communities.

2. **Temperature**

   The body maintains a core temperature of approximately 98.6°F which is ideal for human cells and many microbial species that inhabit the digestive ecosystems. Deviations in body temperature due to illness or other conditions can change the ecosystem by influencing microbial growth rates and composition.

3. **Oxygen availability:**

   Different portions of the digestive tract ecosystems have varying levels of oxygen ranging from the oxygen present conditions in the stomach and small intestine to the oxygen free conditions that exist in the large intestine. This variation significantly affects the type of microorganisms that can survive in these areas.

   For example, oxygen deficient bacteria (anaerobes) predominate in the colon where they play an essential role in fermenting undigested carbohydrates.

   In the oral cavity, for example, where oxygen concentrations are diminished in tissues below the gumline, oxygen deficient microorganisms like *Porphymonas gingivalis* may cause serious deep gum inflammation and infection (periodontitis). Oxygen concentrations, therefore, dictate the type of microorganisms that exist in an ecosystem.

4. **Water activity and availability:**

   Water availability in the digestive tract can influence the survival of microbes and their growth. Areas of the digestive

tract that are less hydrated may limit microbe activity whereas those that are more hydrated can support a more diverse and active microbial population. (See the section: Hydration)

5. **Digestive enzymes and bile acids:**
   These biochemicals produced by the body can inhibit or promote the growth of specific microbes. Bile acids, for instance have antimicrobial properties that can affect the survival and colonization of bacteria in the small intestine ecosystem. (See section: The Multifaceted Features of Bile)
   A comprehensive list of factors that can alter digestive ecosystems can be found at the end of the monograph. (See Table 1).

   Any alteration of those relationships can result in digestive illnesses.

   The remainder of the monograph will emphasize the working of various ecosystems throughout the body, the effect of dysfunction of the ecosystems, and provide recommendations for rehabilitating and rejuvenating ecosystems.

THE BODY COMPARED TO THE MYTHOLOGICAL CHIMERA

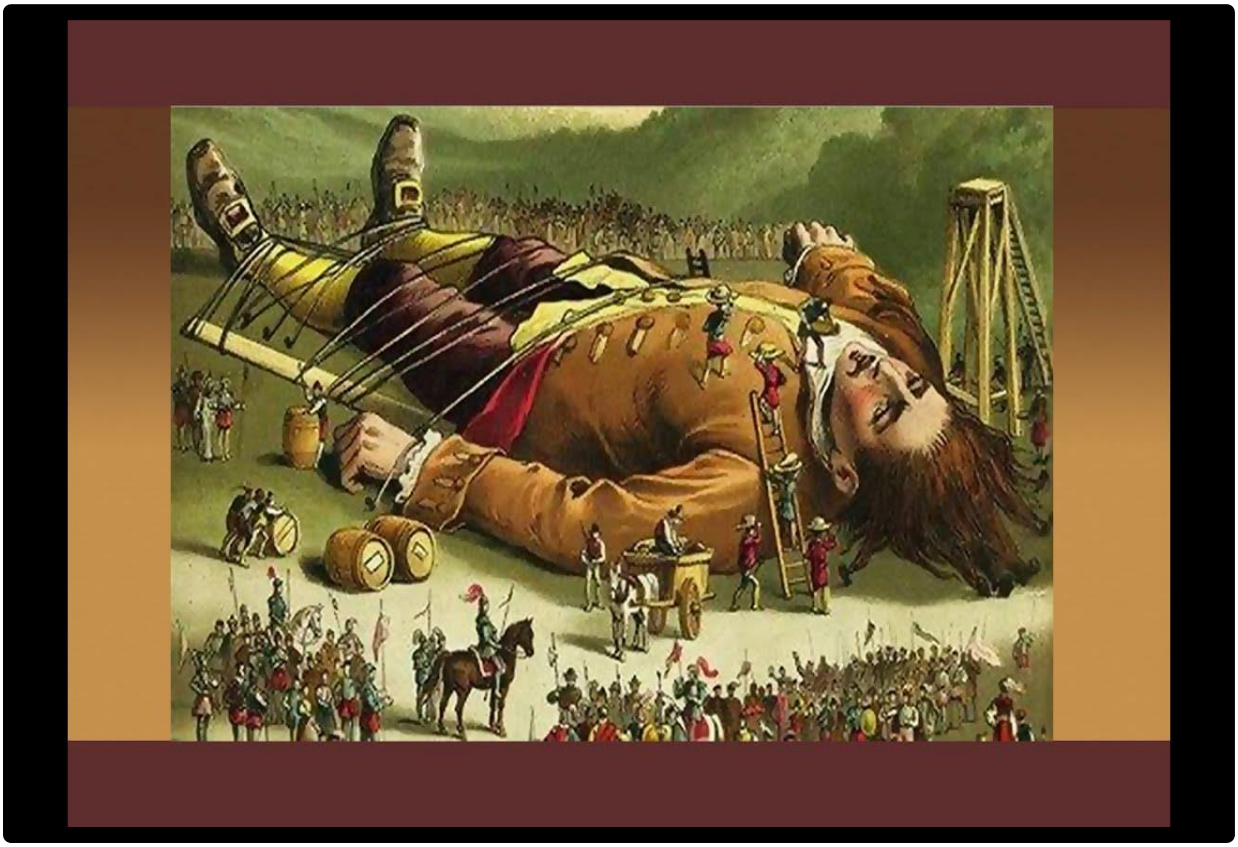
The body is much like the Greek mythological creature, the Chimera, which was composed of three different living animals, a lion, a goat, and a serpent, each with different DNA compositions living as one entity. The human body is thus chimeric with bacteria, viruses, protozoa, fungi, and archaea all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

Some of the important ways that humans benefit from their microbes include the following: (See the section: How Humans Rely on the Beneficial Microbes in Their Colon.)

- **They protect against other microorganisms that are 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 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.

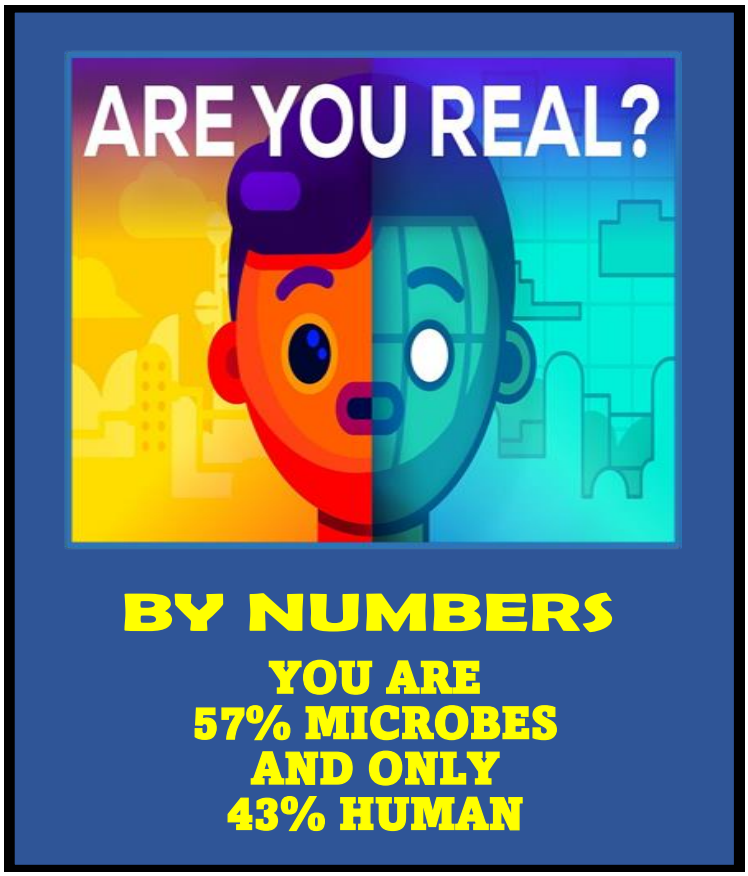
If we adopt the paradigm that we are "*Gullivers"* in a universe of varied, prolific, and powerful microorganisms, then we are faced with the choice and challenge of either coexisting peacefully for mutual benefit, as Gulliver did during his early stay with the Lilliputians, or become adversaries bent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

[1] Yong, Ed. I Contain Multitudes: The Microbes Within Us and A Grander View of Life. First US edition, Bodley Head, 2016

SECTION TWO

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

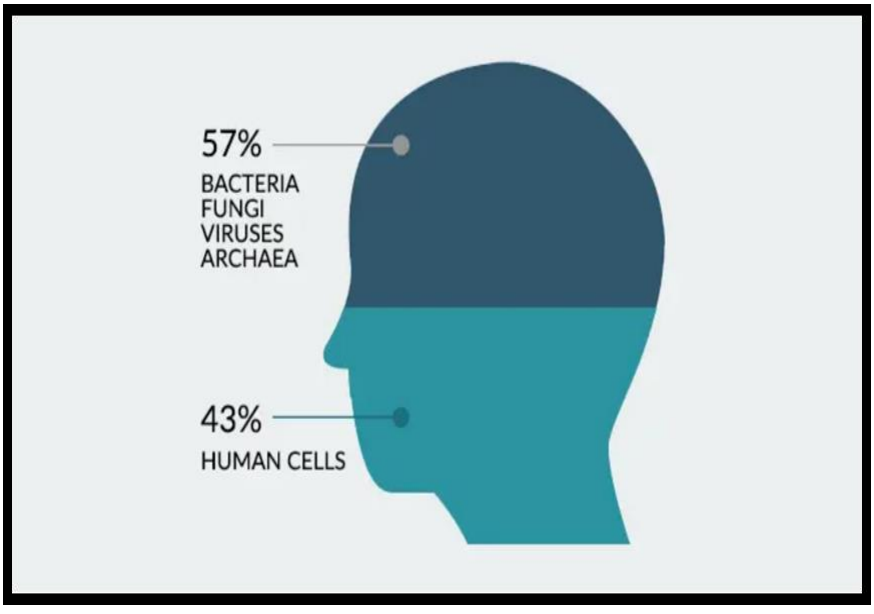
Bryson, Bill. *A Short History of Nearly Everything*. Broadway Books, 2003.

ADULT HUMANS HAVE 30 TRILLION BODY 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.[1]

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



A NEW YOU . . .

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

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 digestive tract microbiomes have a staggering amount of microbial genetic

diversity, and that at least half of the genes identified are unique to an individual.

Their research concluded that the adult human digestive tract 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.

[1] Tierney, BT, The Landscape of Genetic Content in the Digestive Tract and Human Microbiome, *Cell Host Microbe*. 2019 Aug 14;26(2):283-295.e8.doi: 10.1016/j.chom.2019.07.008

SECTION THREE

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.[1] Interruption of this remodeling process, may lead to a state of ecological imbalance with loss of the density, diversity, and functionality of intestinal microorganisms.

Microbial dysbiosis during infancy may lead to health-related consequences in the neonatal stage or later in life. Infants may experience increased risk of developing inflammatory diseases such as asthma and allergy[1], type I diabetes[2], celiac disease[3], inflammatory bowel disease[4], and obesity[5] when exposed to microbial dysbiosis early in life.

[1] Arrieta, M. C., Early Infancy Microbial and Metabolic Alterations Affect Risk of Childhood Asthma. *Sci Transl Med* (2015) 7(307): 307ra152.

[2] Kostic A.D., The Dynamics of The Human Infant Gut Microbiota In Development And In Progression Toward Type I Diabetes. *Cell Host Microbe* (2015) 17 (2): 260-73.

[3] De Palma, G., Nadal, I., Collado, M. C., Sanz, Y. (2010). Effects Of a Gluten-Free Diet On Gut Microbiota And Immune Function In Healthy Adult Human Subjects*. British Journal of Nutrition,* 103(9), 1339-1351. doi:10.1017/S0007114509993426.

[4] Lloyd-Price, J., Arze, C., Ananthakrishnan, A. N., Schirmer, M., Avila-Pacheco, J., Poon, T. W., Andrews, E., Ajami, N. J., et

al. (2019). Multi-Omics Of The Gut Microbial Ecosystem In Inflammatory Bowel Diseases*. Nature,* 569, 655–662. doi:10.1038/s41586-019-1237-9.

[5] Cho, I., & Blaser, M. J. The Human Microbiome: At The Interface of Health and Disease. *Nature Reviews Genetics*, (2012). 13(4), 260-270. doi:10.1038/nrg3182.

Studying the patterns of microbiome assembly and how disturbances to this process take place is of critical importance to understanding the origin of chronic digestive illnesses.

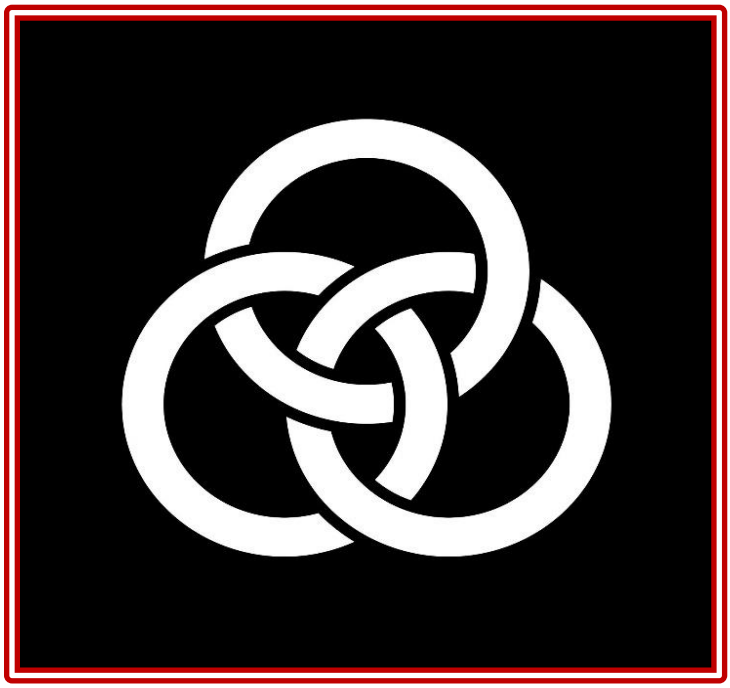
The first six months after birth has been dubbed a "window of opportunity"[2] during which contact of the gut lining with specific microbe-associated molecular patterns (MAMPs) triggers a cascade of reactions that are critical for maturation of the infant's digestive tract.

[1] Yatsunenko, T. et al., Human Digestive Tract Microbiome Viewed Across Age and Geography, *Nature* 486 222-227 (2012).

[2] Hill, C.G. Evolution of Gut Microbiota Composition From Birth To 24 weeks In The INFANTMET Cohort. *Microbiome* (2017) 5(1):4.

SECTION FOUR

HOW ECOSYSTEMS RELATE TO EACH OTHER



FIRST THREE ECOSYSTEMS: The first three ecosystems of the digestive system are the oral cavity, esophagus, and stomach.

Physical changes: **Functionally these three ecosystems work primarily as the body's food processor physically changing the size and the consistency of nutrients in preparation for absorption.**

Chemical changes: Chemical alterations 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.

Microbial changes: Billions of microorganisms 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 bacterium 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.

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.[1-2] (See the section: Staggering and Fantastical Numbers.)**

[1] Schmidt, T., Extensive Transmission of Microbes Along the Gastrointestinal Tract, *eLife.* Feb. 12, 2019; 8: e42694

[2] Loesche, W, *Dental Caries: A Treatable Infection*, Publisher, Thomas, 1982.

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-- "an arms race" between pathogenic organisms and the body's defense mechanisms.

Every dental restoration or treatment like cavity fillings, crowns, bridges, extractions, implants, root canal procedures etc., memorializes a battle that took place between the oral cavity microbes and the body. And. . . the microbes won!

Esophagus And Stomach Ecosystems

The esophageal ecosystem comprises a complex interplay of various components that work together to maintain the health

and functionality of the esophagus. The key constituents include the following:

Microbiota: The esophagus hosts a diverse community of microorganisms, including bacteria, fungi, and viruses. These microbial communities vary depending on factors like diet, health status, and overall microbial colonization of the digestive tract. The bacterial composition, for example, can include species such as *Streptococcus*, *Prevotella*, and *Veillonella*. Although some of the microbes present in the esophagus are shared with those that are present in the oral cavity, the esophagus has its own unique ecosystem with its own microbial signature. A virtual tsunami of microbes pass over the esophagus every 24 hours traveling from the oral cavity to the stomach.

Epithelial Cells: These cells line the esophagus and are critical for barrier function, protecting the underlying tissue from mechanical damage, pathogens, and chemical injury. They also play a role in immune responses and disease development.

Immune cells: Various immune cells are present in the esophagus, including lymphocytes, macrophages, and dendritic cells. These cells help monitor and respond to pathogens, allergens, or other foreign particles.

Mucus: Mucus is produced by glands in the esophagus. Mucus helps protect and lubricate the esophageal lining. It also traps and helps eliminate microbes and debris.

Enzymes and Antimicrobial Peptides: These are secreted by lining cells and glands in the esophagus. They help break down ingested materials and protect against microbial infections.

Nerve Networks: The esophagus is innervated by the enteric nervous system which controls various functions such as peristalsis and sphincter control.

Physical and Chemical Barriers: These barriers include the esophageal sphincters that regulate the flow of material between the esophagus and adjacent structures and the acidic environment at the esophagus-stomach junction, which inhibits the growth of harmful bacteria.

An understanding of the esophageal ecosystem is required for diagnosing and treating esophageal illnesses, including gastroesophageal reflux disease (GERD), esophagitis, and Barrett's esophagus.

Human cells defend against these 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, 99.9% of swallowed organisms are destroyed.

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 Diagnosis). 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**

The Small Intestine ecosystem

The small intestine of the adult human is twenty-two feet long. It is influenced by accessory digestive organs--liver, gallbladder, and pancreas. These accessory digestive organs also have unique ecosystems. The small intestine ecosystem is 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.

Physical changes: **By the time nutrients reach the small intestine 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 small intestine 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. The small intestine has only a modest repertoire of genes that are programmed to accomplish the digestive processes of breaking down sugars, fats, and proteins.

Microbial changes: **Although 99.9% of the swallowed 100 billion microorganisms may have been destroyed in the acid pool of the stomach, that still leaves millions of acid resistant microbes that will survive and pass into small intestine. Examples of surviving microbes are *Porphyromonas gingivalis,* which is one of the principal bacteria found in deep gum disease, (periodontitis).**

P. gingivalis **is the master of destruction and deception. It can survive transit through the stomach and is able to resist the body's immune system.** ***P. gingivalis*** **has been found to exist in feces and colon tissue samples from patients with colon cancer.[1] Likewise,** ***Fusobacterium nucleatum*****, another**

bacterium found in periodontitis has been found in colorectal cancer tissue.[2]

[1] Kerdreux, M., Porphymonas gingivalis in Colorectal Cancer and its Association to Patient Prognosis, *J. Cancer*, 2023; 14(9): 1479-1485.

[2] Castellarin, M., Fusobacterium nucleatum Infection is Prevalent in Human Colorectal Carcinoma, *Geneome Res* 22. 292-306 (2012).

Some microbes exist as spores and are resistant to acid and enzymes in the stomach and may pass into the small intestine as well.

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 the stomach. 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 the small intestine in large amounts

resulting in a condition known as small intestinal bacterial overgrowth (S.I.B.O.). (See the section: S.I.B.O.)

THE COLON ECOSYSTEM

COLON ECOSYSTEM: Undigested nutrients such as dietary fiber proceed into the last 5 to 6 feet of the digestive tract, the large intestine, which, along with the last few feet of the small bowel, forms the most complex ecosystem in the digestive tract—to be discussed later. (See Section 8)

Section Five

In Defense Of The Realm--
Barriers That Protect The Body

Barriers within the intestinal tract form a dynamic system to protect the body. It is becoming increasingly evident that maintaining stable intestinal barriers is crucial to preventing various potential harmful substances and pathogens from entering the body. Disruption of these barriers is colloquially referred to as “leaky gut” or “leaky gut wall syndrome” and appears to be characterized by the entry of bacterial metabolites and toxins into the circulation.

Four Major Barriers

The body has four major protective barriers that selectively allow the passage of nutrients, water, and other vital chemicals while restricting the entry of potentially harmful elements.

Three of these barriers exist in the digestive tract and one in the brain. These barriers are the enterocytes, tight junctions, entero-vascular barrier (EVB) and the blood-brain barrier. Each of these barriers plays a critical role in maintaining homeostasis and protecting the body from external threats.

ENTEROCYTES

Enterocytes are the single layer of cells that line the surface of the digestive tract from the oral cavity to the anus. These cells, with their protective mucus coating, form a formidable barrier against microbes, toxins, and food antigens attempting to pass from the digestive tract into the bloodstream.[1]

Enterocytes serve as both a physical and chemical barrier, fortified with Immunoglobulin A (IgA), a protective antibody that can neutralize potential threats.

Host immune cells, such as dendritic cells, are found amongst the enterocytes to surveil and identify foreign substances traversing the digestive tract. These cells communicate with the immune system, alerting it to the presence of potential threats.

Specialized receptor cells, including Toll-like receptors (TLRs), are equipped to identify various pathogens through the recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[1],[2] These receptors play a critical role in the body's innate immune response, capable of activating an arsenal of antibodies and cytokines ready to defend the host.

TIGHT JUNCTIONS

A second barrier exists in the form of tight junctions, which are the spaces located between the enterocytes. These junctions prevent the movement of harmful substances between cells into the bloodstream. Tight junctions are composed of a complex network of proteins that regulate paracellular permeability and maintain the integrity of the epithelial barrier.[4,5]

The integrity of tight junctions is critical for preventing the translocation of pathogens and toxins from the gut lumen into the bloodstream. Disruption of tight junctions, as seen in conditions like inflammatory bowel disease (IBD), fatty liver disease, chronic alcoholism, and celiac disease, can lead to increased intestinal permeability and subsequent systemic inflammation.

ENTERO-VASCULAR BARRIER (EVB)

The third barrier, the entero-vascular barrier (EVB), presents an additional layer of defense against substances that have breached the enterocytes and tight junctions. The EVB regulates the passage of molecules from the enterocytes and tight junctions into the bloodstream. This barrier is essential for maintaining selective permeability and preventing systemic exposure to harmful substances.

The EVB's function is critical in preventing the spread of infections and toxins throughout the body. Dysfunction of this barrier can lead to conditions such as sepsis and systemic inflammatory response syndrome (SIRS), where pathogens and

their toxins enter the bloodstream and trigger widespread inflammation.[6]

BLOOD-BRAIN BARRIER

The blood-brain barrier (BBB) is a highly selective and protective barrier that separates the circulating blood from the brain. Its primary function is to maintain the brain's stable environment.

The blood-brain barrier allows selective transport of essential nutrients and molecules into the brain. This selective function ensures that nerve cells in the brain (neurons) receive the necessary nutrients for metabolic function while protecting the brain tissue from potentially harmful substances.

[1]Turner, J. R. (2009). Intestinal Mucosal Barrier Function In Health And Disease. *Nature Reviews Immunology*, 9(11), 799-809.

[2] Kawai, T., & Akira, S. (2010). The Role Of Pattern-Recognition Receptors In Innate Immunity: Update On Toll-Like Receptors. *Nature Immunology*, 11(5), 373-384.

[3] Takeuchi, O., & Akira, S. (2010). Pattern Recognition Receptors And Inflammation. *Cell*, 140(6), 805-820.

[4] Fasano, A. (2012). Intestinal Permeability and Its Regulation By Zonulin: Diagnostic And Therapeutic Implications. *Clinical Gastroenterology and Hepatology,* 10(10), 1096-1100.

[5] Groschwitz, K. R., & Hogan, S. P. (2009). Intestinal Barrier Function: Molecular Regulation And Disease Pathogenesis. *Journal of Allergy and Clinical Immunology*, 124(1), 3-20.

[6] Opal, S. M., & van der Poll, T. (2015). Endothelial Barrier Dysfunction In Septic Shock. *J Intern Med*, 277(3), 277-293.

Conditions That Have Been Associated With Abnormal Intestinal Barrier Function

- 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 Digestive Tract Microbiota in Covid-19: An insight into Pathogenesis and Therapeutic Potential, *Front. Immunol.* 14 October 2021, volume 12.

[2] Nagpal, R. Obesity-linked Digestive Tract Microbiota Dysbiosis Associated With Derangements And Digestive Tract Permeability And Intestinal Cell Homeostasis Independent Of Diet, *J. Diabetes. Res*. 2018, Sep 3.

[3] **Kessoku, T., The Role Of Leaky Digestive Tract In Nonalcoholic Fatty Liver Disease: A Novel Therapeutic Target, *Int J. Mol Sci.,* 2021 Aug; 22(15): 8161.**

[4] **Shunying, Y, Leaky Digestive Tract In I.B.D: Intestinal Barrier—Digestive Tract Microbiota Interaction*, J. Microbiol Biotechnol*., 2022 July 28; 32 (7): 825-834.**

[5] **Zhanxiang, Z. Targeting the Digestive Tract Barrier For The Treatment Of Alcoholic Liver Disease*, Liver Res*. 2017 Dec; 1 (4): 197-207.**

[6] **Fukui, H. Digestive Tract-Liver Axis In Liver Cirrhosis: How To Manage Leaky Digestive Tract And Endotoxemia*, World J Hepatol*. Mar 27, 2015; 7 (3): 425-442.**

[7] **Pagliari, D. Digestive Tract Microbiota-Immune System Cross Talk And Pancreatic Disorders*, Mediators Inflamm*. Feb 1, 2018.**

[8] **Sadagopan, *A,* Understanding The Role Of The Digestive Tract Microbiota Men In Diabetes And Therapeutics Targeting "Leaky Digestive Tract": A Systematic Review, *Cureus* 15 (7): July 8, 2023.**

[9] **Liu, L Digestive Tract 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 Digestive Tract, 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 the above referenced conditions remains a matter of investigation and scientific debate.

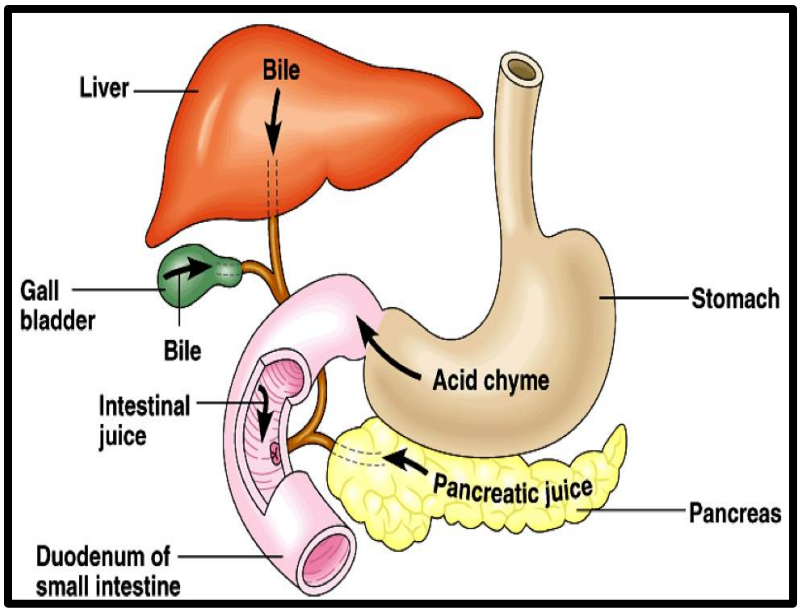
CONCLUSION

The body's protective barriers—enterocytes, tight junctions, entero-vascular barrier, and blood-brain barrier—work in concert to safeguard the internal environment from external threats. These barriers, along with the vigilant actions of the immune system, ensure that the body remains free from harm.

Understanding the mechanisms and importance of these barriers is a necessary step for developing strategies to maintain and restore their integrity to prevent disease.

SECTION SIX

BILE—A MAJOR SECRETION THAT INFLUENCES THE DIGESTIVE TRACT ECOSYSTEMS



Bile is a secretion made in the liver and stored in the gallbladder. It has traditionally been thought of as a digestive detergent facilitating fat absorption.

Over the last several decades, however, this complex fluid has been found to be pivotal in various physiologic processes, showcasing its versatility and indispensable nature in human health.

The role of bile in digestion of fats

Bile's traditional role has been to facilitate the digestion and absorption of fats in the small intestine. Bile contains bile acids which emulsify fats. This emulsification process increases the surface area of fats making them more accessible to digestive enzymes and more easily absorbed by small bowel cells.[1]

Bile as a signaling molecule

In addition to digestion, bile acids act as signaling molecules, influencing metabolism and energy production. They bind to receptors in different tissues including the liver, intestines and fatty tissues thereby modulating lipid, sugar, and energy metabolism. This signaling capability underscores the importance of bile acids in maintaining metabolic health and highlights its potential as a therapeutic agent for metabolic diseases.[1]

Bile as an agent to clear the body of bilirubin and cholesterol

Bile also plays a critical role in the excretion of waste products and toxins. Bilirubin, which is a byproduct of the breakdown of red blood cells, and excess cholesterol are both eliminated from the body through bile.

Bile serves as the primary avenue for the body to regulate and eliminate excess cholesterol. Approximately 500 mg of cholesterol is converted into bile acids daily in an adult human liver illustrating the liver's capacity for cholesterol clearance through bile acid production and underscoring bile's vital role in maintaining cholesterol homeostasis and preventing cardiovascular disease.[2]

Bile as an antimicrobial agent

Bile acids have antimicrobial properties contributing to the regulation of intestinal microbes. For example, microbes that are swallowed and are acid resistant can reach the small intestine and produce an overgrowth of organisms that compete for nutrients with the host cells—small intestinal bacterial overgrowth (S.I.B.O.). There are many other reasons that account for excess numbers of microbes populating the small intestine. Bile, along with secretions of enzymes from the pancreas, can inhibit that overgrowth. (See the section—S.I.B.O.).

The antimicrobial activity demonstrates the importance of bile in immune defense and in balancing the number of microorganisms that exist in the small intestine.

Ying and Yang: Microbes have been able to survive in the digestive tract by perfecting survival skills that counteract the antimicrobial capabilities of bile. Microbes can alter the chemical configuration of the bile molecule and thus reduce its antimicrobial effect. These alterations that microbes can perform include the chemical processes of deconjugation, dehydroxylation, dehydrogenation, epimerization, and a newly found chemical manipulation conducted by microbes, i.e., conjugation to amino acids[3].

Recently, intestinal fungi have been found capable of transforming bile acids resulting in multiple new bile compounds that have never been known to previously exist.[4]

Bile as an anti-cancer secretion

By modulating cells signaling pathways and influencing digestive tract microorganisms, bile acids have been found to reduce the risk of cancer development in the colon and rectum[5].

[1] Mohanty, I. The Changing Metabolic Landscape Of Bile Acids—Keys To Metabolism And Immune Regulation, *Nature Reviews Gastroenterology and Hepatology*, (2024).

[2] Yntema T. Emerging Roles of Gut Microbial Modulation of Bile Acid Composition in the Etiology of Cardiovascular Diseases. *Nutrients*. 2023; 15(8):1850. https://doi.org/10.3390/nu15081850

[3]Garcia, C., Production Of New Microbially Conjugated Bile Acids By Human Digestive Tract Microbiota, *Biomolecules*, 2022 May; 12(5): 687.

[4] Wei, X, Biotransformation of Chenodeoxycholic Acid by Human Intestinal Fungi and the Effect On FXR, *Phytochemistry*, vol. 224, Aug 2024, 114162.

[5] Ajouz, H. Secondary Bile Acids: An Unrecognized Cause of Colon Cancer*. World Journal of Surgical Oncology,* 12, 164. (2014).

SECTION SEVEN

A COMMON MANIFESTATION OF A DYSFUNCTIONAL ECOSYSTEM

S.I.B.O.

DEFINITION: The definition of S.I.B.O. presently lacks precision. The term is used when symptoms, clinical signs and laboratory tests are attributed to a change in the population of microorganisms 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 S.I.B.O. were conducted 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.

The term S.I.B.O. might be limited in capturing the full scope of microbial disturbances that can occur in the small intestine. The more expansive term "Small Intestinal Microbial Overgrowth (S.I.M.O.) would better reflect the possibility that other organisms, including viruses, protozoa, fungi, and archaea might also proliferate abnormally and contribute to the condition.

It is also possible that the concept of *microbial overgrowth* may not be the overriding physiologic principle causing the disturbance and that it might be a critical alteration in the diversity or functionality of the existing microorganisms that are living in the small bowel that is causing the condition.

In addition to alterations in the microbe population, other factors that lend themselves to overgrowth of microbes could exist like disturbed motility, altered anatomy, reduced acid concentrations, immune deficits, and/or bile composition

alterations, all of which are listed below and can contribute to the condition.

The condition, therefore, might be more accurately depicted using the acronym, A.G.E.D., representing Altered Gastrointestinal Ecosystem Dynamics.

TESTING LIMITATIONS

In recent years, the diagnosis of S.I.B.O. has relied upon 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.

NEW TECHNOLOGY: A recent innovation using 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.

[1] Achufusi, T., Small Intestinal Bacterial Overgrowth: Comprehensive Review Of Diagnosis, Prevention, And Treatment Methods*. Cureus* 12(6): e8860. DOI 10.7759/Cureus.8860.

[2] **Waimin JF, Smart Capsule for Non-Invasive Sampling and Studying of The Gastrointestinal Microbiome. *RSC Adv.,* Apr 2023;10(28).**

Treatment

With the limitations of current diagnostic techniques, medical care providers often initiate an empiric trial of antibiotics as a diagnostic tool in those suspected of having the condition. The strategy, however, 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.

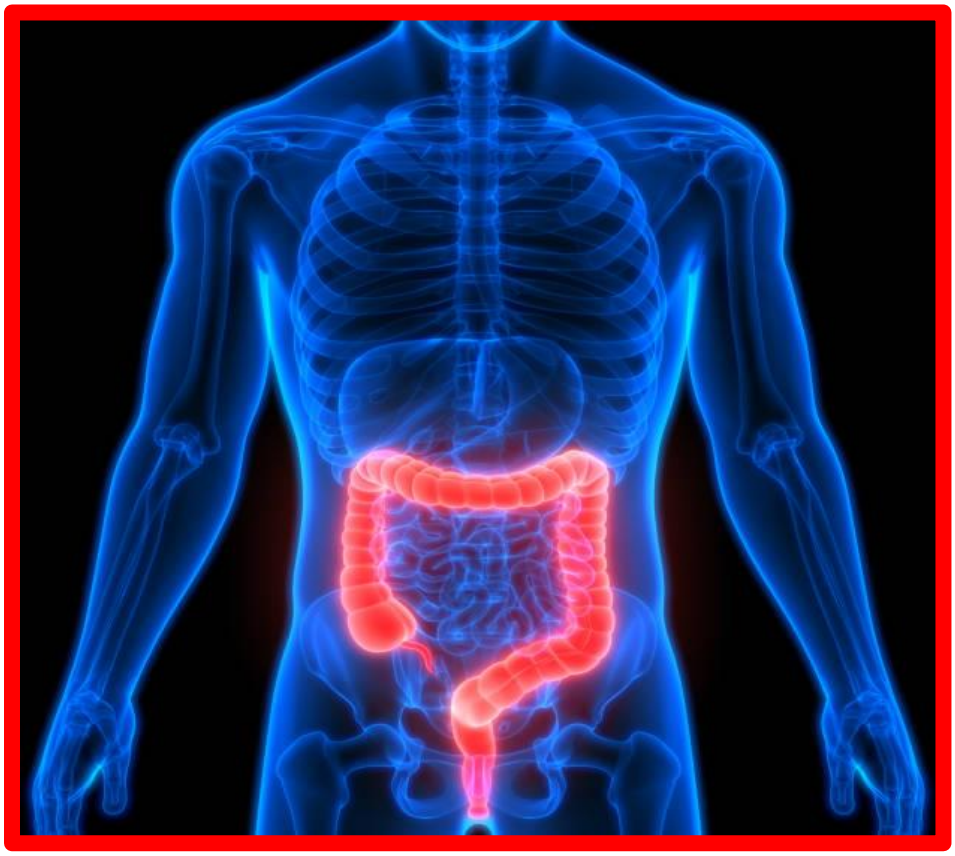
Several broad-spectrum antibiotics have been used for treatment including tetracyclines, fluoroquinolones, co-trimoxazole, and rifaximin. Rifaximin has emerged as the preferred antibiotic agent for S.I.B.O. management since it has a reduced toxicity profile and may be capable of preserving colon microorganisms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

[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.**

SECTION EIGHT

LIFE ALTERING ROLES OF THE MICROBES OF THE LARGE INTESTINE (COLON)

The most complex of all the digestive ecosystems is the large intestine. It is more than a conduit for waste products.



Motility slows in the colon. In normal adults, it may take 20-40 hours for undigested residue to traverse the colon. During that time, complex interactions occur in the colon ecosystem

between colon microorganisms, absorptive lining cells and the body's immune system. (See Section Nine).

SECTION NINE

HOW HUMANS RELY ON THE BENEFICIAL MICROBES IN THEIR COLON

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 THE FUNCTIONS OF BENEFICIAL MICROBES IN THE BODY

- **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 digestive tract lining.[6]**
- **Regulate hormones responsible for hunger and satiety.[7]**
- **Regulate hormones responsible for bone growth.[8]**
- **Reinforce the digestive tract lining defenses against toxins.[9]**
- **Reinforce the digestive tract lining defenses against harmful microbes.[9]**
- **Reinforce the digestive tract 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 digestive 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 Digestive Tract 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 Digestive Tract Microbiome and Gastrointestinal Health In Humans, *Nutrition Research*, (95), Nov 2021, 35-53.

[4] Backhed, Fredrik, The Digestive tract 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 Digestive tract 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 Digestive tract 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, Digestive Tract Microbiota—Motility Inter-Regulation: Insights In Vivo, Ex Vivo And In Silico Studies, *Digestive tract Microbes.* 2022; 14(1): 1997296.**

[12] **TianRong Ma*,* Effect Of The Digestive Tract 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 Digestive Tract-Vascular Barrier as a New Protagonist in Intestinal and Extraintestinal Diseases, *Int. J. Mol. Sci*, 2023 Jan: 24(2).**

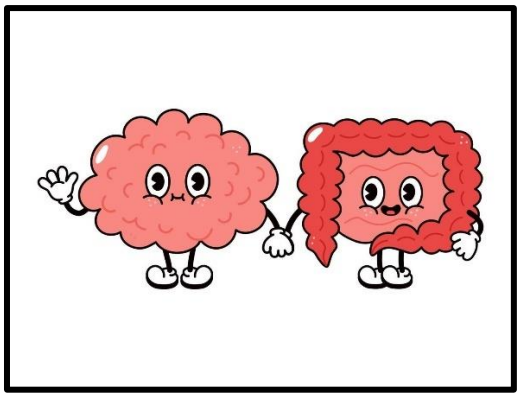
[15] **Appleton, J., Commentary: The Digestive tract-Brain Axis: Influence of Microbiota on Mood and Mental Health, Integrative Medicine, vol 17 (4), Aug. 2018.**

[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.

SECTION TEN

THE IMPORTANCE OF COMMUNICATION BETWEEN THE DIGESTIVE TRACT AND THE BRAIN



THE GUT-BRAIN AXIS

The human body is a complex and interconnected system where various organs and systems communicate with each other to maintain overall homeostasis. One of the most important connections in this network is the gut-brain axis. This bi-directional communication system between the gastrointestinal tract and the brain influences numerous physiological processes, including mood, behavior, and cognitive functions.

The gut-brain axis is facilitated through multiple pathways, including microbial metabolites, neural pathways, the endocrine and the immune systems, each playing a unique role in maintaining this intricate relationship.

Microbial Metabolites[1]

Microbial metabolites represent one method of communication between the digestive tract and the brain. These are substances produced by gut microbes that can influence brain function and mental health. For instance, butyrate, a short-chain fatty acid produced by microbe fermentation of dietary fibers, has anti-inflammatory properties and supports the integrity of the gut lining. This metabolite can cross the blood-brain barrier and has been shown to exert neuroprotective effects, reducing inflammation in the brain and potentially reducing the risk of neurodegenerative diseases like Alzheimer's dementia and Parkinson's disease.

Neurotransmitters[2]

Intestinal microbes also produce neurotransmitters such as serotonin, dopamine, and gamma-aminobutyric acid (GABA), which are essential for regulating mood, anxiety, and cognition. Approximately 90% of the body's serotonin is produced in the gut, highlighting the significant influence of gut microorganismsm on mental well-being.

Neural Pathways[3]

The neural pathways provide a rapid and direct means of communication between the gut and the brain. The vagus nerve, in particular, plays a pivotal role in this fast-paced signaling. It facilitates immediate responses to changes within the gut environment. Through the vagus nerve, the brain can quickly receive information about gut conditions, such as the

presence of pathogens or the state of digestion, and respond accordingly to maintain homeostasis.

This swift communication is crucial for immediate reflex actions, such as vomiting in response to ingested toxins, and regulation of digestive processes. The neural pathways ensure that the brain is continuously updated with the latest information from the gut, allowing for timely and appropriate responses.

Endocrine Pathway[4]

The endocrine pathway operates on a slower timescale. This route involves the release of hormones, such as cortisol, which can influence brain function over a longer period. Cortisol, known commonly as the stress hormone, is produced by the adrenal glands in response to stress and affects various aspects of brain function, including mood, memory, and learning.

Hormones like cortisol can alter the gut microbiota composition, which in turn can impact the production of neurotransmitters and other metabolites. This cyclical interaction between the endocrine system and gut microbes highlights the complex and sustained nature of their communication.

Other hormones that are driven by microbe interactions influence hunger, satiety and secretion of insulin.

Immune Pathway[5]

The immune pathway acts like alarm bells, using cytokines—small proteins released by immune cells—to signal long-distance communication between cells. Cytokines can influence brain function by crossing the blood-brain barrier and modulating neuronal activity and neuroinflammation. This pathway is particularly important in the context of immune responses to infections, inflammation, or gut dysbiosis.

When microorganisms in the digestive tract are imbalanced, they can trigger an immune response, leading to the production of pro-inflammatory cytokines. These cytokines can affect brain function, potentially leading to mood disorders, cognitive impairments, and increased vulnerability to psychiatric conditions.[6] Conversely, anti-inflammatory cytokines can promote brain health by reducing neuroinflammation and supporting neuronal survival and function.

Conclusion

The gut-brain connection is a vital aspect of human health, orchestrated through multiple pathways that allow for both rapid and sustained communication between the gastrointestinal tract and the brain. Microbial metabolites serve as chemical messengers, while neural pathways provide quick and direct signaling. The endocrine system communicates through hormones, and the immune pathway acts as an alarm system through cytokines.

Understanding these pathways not only highlights the importance of maintaining digestive health but also opens avenues for novel therapeutic approaches with the potential to treat mental health disorders and improve cognitive function.[7]

[1] De Vadder, F., et al. Gut Microbiota Regulates Maturation Of The Adult Enteric Nervous System Via Enteric Serotonin Networks. *Proceedings of the National Academy of Sciences,* vol. 116, no. 19, 2019, pp. 9755-9764.

[2] Strandwitz, P. Neurotransmitter Modulation By The Gut Microbiota. *Brain Research*, vol. 1693, 2018, pp. 128-133. Updated in 2020.

[3] Breit, S., et al. Vagus Nerve As Modulator Of The Brain-Gut Axis In Psychiatric And Inflammatory Disorders. *Frontiers in Psychiatry,* vol. 9, 2018. updated 2021.

[4] Fung, T. C., et al. The Microbiota-Immune-Brain Axis As A Link Between Gut Feelings And Mental Health. *Journal of Experimental Medicine,* vol. 216, no. 2, 2019, pp. 197-213.

[5] Cryan, J. F., et al. The Microbiota-Gut-Brain Axis. *Physiological Reviews,* vol. 99, no. 4, 2019, pp. 1877-2013.

[6] Sarkar, A., et al. The Role Of The Microbiome In The Gut-Brain Axis. Psychobiotics And The Gut-Brain Axis: *Science, Research and Practice,* edited by Owen J. Wolkowitz and Nelson B. Freimer, Academic Press, 2021, pp. 47-70.

[7] Riehl, L., et al. The Importance of the Gut Microbiome and its Signals for a Healthy Nervous System and the Multifaceted Mechanisms of Neuropsychiatric Disorders, *Front. Neurology*, DOI 10.3389/fnins.2023.1302957.

SECTION ELEVEN

MICROBE FUNCTIONALITY

A PARADIGM SHIFT

The understanding of the microbiome has evolved significantly. In the past, research focused primarily on the density (numbers) and diversity (species) of microbes present in the digestive tract. While these items are essential, it has become clear that they are not sufficient to fully understand the microbiome's role in defining intestinal well-being.

A paradigm shift is now occurring towards understanding not only the numbers and kinds of microbes present but the functionality of those microbes present.

DENSITY AND DIVERSITY

Density: This refers to the sheer number of microbes in a given environment. Knowing the population size can provide insights into the overall microbial load and potential competition for resources within the ecosystem.

Diversity: This involves identifying different species, strains, and sub-strains of microbes present within an ecosystem. High diversity has generally been thought to be associated with a healthier microbiome, as it suggested a *balanced ecosystem* capable of performing various functions and resisting pathogenic invasions.

The New Frontier: Functionality

Simply knowing the numbers and types of microbes that are present in the ecosystem is no longer adequate. The new focus is on understanding the functionality of these microbes—what roles they play and how they interact with their environment and with the human host. This shift in focus is critical for several reasons:

1. **Metabolic Activities: Different microbes can have vastly different metabolic capabilities. For instance, some bacteria can produce short-chain fatty acids (SCFAs) from dietary fibers, which benefit the host, while others might produce harmful metabolites. Understanding these metabolic activities helps in predicting the impact of the microbiome on host health.**

2. **Microbial Interactions: Microbes interact with each other through various mechanisms such as competition, cooperation, and communication. These interactions can influence the stability and functionality of the entire ecosystem. For example, some microbes produce antibiotics that inhibit the growth of competitors, while others might form biofilms that protect the community.[1]**

3. **Host Interactions: Some microbes interact with the host's immune system, influencing inflammation, immune tolerance, and susceptibility to diseases. Understanding these interactions is key to developing therapeutic strategies for conditions like inflammatory bowel disease (IBD), allergies, and autoimmune disorders.**

4. **Environmental Adaptation: Microbes adapt to changes in their environment, such as pH shifts, nutrient availability, and the presence of antibiotics or other drugs. Knowing how microbes respond and adapt to these changes can help in managing and predicting the outcomes of various interventions.**

[1] Ezeobiora, C., Uncovering The Biodiversity And Synthetic Potentials Of Rare Actinomycetes. *Future Journal of Pharmaceutical Sciences* 8, Article number: 23 (2022)

THE PARADIGM SHIFT[1-5]

The shift towards microbe functionality represents a paradigm change in microbiome research and its applications in medicine and nutrition:

Personalized Medicine: Understanding the functional capabilities of an individual's microbiome can lead to personalized therapeutic approaches. For instance, probiotics or dietary interventions can be tailored based on the specific functional deficiencies or imbalances in a person's microbiome.

- **Disease Mechanisms: Functional insights can help elucidate the mechanisms through which dysbiosis contributes to diseases. For example, identifying specific microbial enzymes or pathways involved in disease progression can lead to targeted therapies.**
- **Nutritional Science: Functional analysis can refine dietary recommendations. Instead of general advice, like "eat**

more fiber," specific types of fiber that promote beneficial microbial functions in an individual can be recommended.

- **Microbiome Engineering**: Understanding functionality allows for the potential engineering of microbiomes. This could involve introducing or enhancing beneficial functions (e.g., SCFA production) while suppressing harmful ones.

Conclusion

The shift from focusing solely on microbial density and diversity to understanding microbial functionality represents a significant advancement in microbiome research. This new approach provides a more comprehensive understanding of how the microbiome influences health and disease, paving the way for personalized and more effective interventions.

New scientific disciplines and methods contribute to a comprehensive understanding of the microbiome, its functions, and its interactions with the environment and the host.

See the Glossary at the end of the monograph assisting with interpretation of these new disciplines and methods.

[1] Liu, Xiang, Functional Metagenomics Reveals Novel Pathways Of Human Gut Microbiome Influence On Metabolism, *Nature Communications*, 2021.

Summary: This paper presents functional metagenomics as a tool to uncover novel metabolic pathways influenced by

the gut microbiome, highlighting the importance of functional understanding.

[2] Zhao, Liang, Microbial Community Functional Structures Shape Dysbiosis-Induced Obesity, *Nature Communications*, 2019.

Summary: This study shows how functional profiles of microbial communities, rather than just their composition, are crucial in understanding the link between dysbiosis and obesity.

[3] Wang, J., Functional Genomics Of Host–Microbiome Interactions In Metabolic Disease, *Nature Reviews Microbiology*, 2020.

Summary: This review emphasizes the role of functional genomics in elucidating host-microbiome interactions in metabolic diseases, marking a shift towards functional analyses.

[4] Thursby, Elizabeth, The Human Gut Microbiome In Health And Disease, *Biochemical Journal,* 2019.

Summary: This article reviews how understanding microbial functions, such as metabolite production and immune modulation, is essential for linking the microbiome to health and disease.

[5] Costea, Paul I., Advances In Functional Microbiome Analysis. *Nature Reviews Microbiology,* 2021.

Summary: This paper reviews advancements in tools and methodologies for functional microbiome analysis, emphasizing their importance in microbiome research.

SECTION TWELVE

ENDANGERED MICROBES

Over the past century, a disturbing trend has emerged. Many digestive tract microbes have gone on the endangered species list.

As each generation has systematically removed nutrients from their diets that once had nourished vital microbes, and as increasing numbers of more powerful antibiotics have been introduced, they have unwittingly compromised the chemical pathways that sustain well-being.

This depletion has set the stage for chronic digestive illnesses and a notable rise in autoimmune diseases.[1, 2]

The Impact of Modern Dietary Practices

Modern dietary practices, particularly the introduction of highly processed food substances, have contributed significantly to the loss of microbial density and diversity. The shift from unprocessed or minimally processed, fiber-rich foods to ultra processed items has starved beneficial microbes in the gut, which rely on dietary fiber as a primary food source. This starvation has led to the gradual extinction of many beneficial microbial species, weakening the overall resilience of gut ecosystems.

The Role of Antimicrobials and Chemical Additives

The widespread use of antimicrobials, both as prescriptions and in agricultural practices, has further decimated microbial populations. Antibiotics, while lifesaving, do not discriminate between harmful and beneficial bacteria, leading to collateral damage within the digestive ecosystems.

Additionally, the food supply has been adulterated with a plethora of chemicals—herbicides, pesticides, colorants, shelf-life extenders, and emulsifiers—all of which pose a threat to microbial health. These additives have disrupted the delicate balance of gut ecosystems, allowing pathogenic microbes to proliferate unchecked.

Lifestyle Choices and Microbial Health

Lifestyle choices have played a significant role in the degradation of our microbiomes. Alcohol, tobacco, and recreational drugs are known to have detrimental effects on gut health, damaging or destroying beneficial microbes. Poor hygiene practices, particularly inadequate oral-dental care, can lead to the unfettered proliferation of harmful microorganisms, further compromising gut health.

The Path to “Rewilding” Digestive Ecosystems

The concept of "rewilding" digestive ecosystems is emerging as a critical strategy for restoring digestive well-being. Reintroducing nutrients that promote the growth of beneficial microbes is one of the key measures to this process. This

involves incorporating a diverse array of fiber-rich foods, fermented products, and prebiotics into the diet.

By nurturing gut microbiomes, chemical pathways that support digestive health may be restored. This approach not only helps prevent digestive disorders but also plays a role in the broader prevention and management of autoimmune diseases.

In essence, the health of our digestive tract is intricately linked to the health of our microbes. Ensuring the survival of our beneficial microbes and allowing them to flourish is critical for our overall well-being.

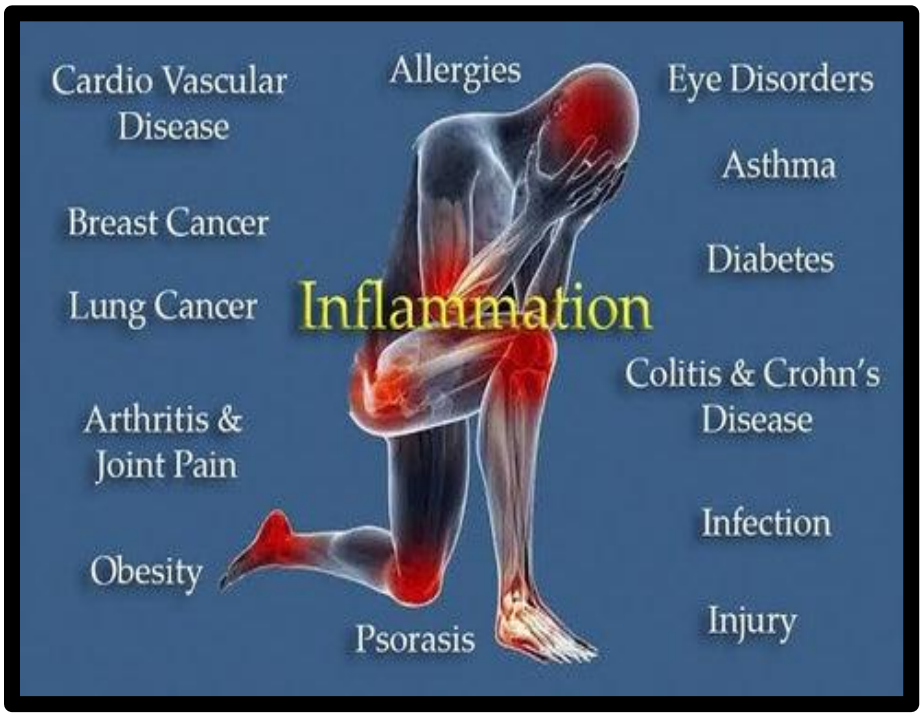
[1] Christovich, A., Gut Microbiota, Leaky Gut, And Autoimmune Diseases (Mini-Review), *Front. Immunol.*, 26 June, 2022, vol 13.

[2] Heravi, F, Gut Microbiota and Autoimmune Diseases: Mechanisms, Treatment, Challenges and Future Recommendations, *Current Clinical Microbiology Reports*, (2024) 11:18-33.

SECTION THIRTEEN

INFLAMMATION

INFLAMMATION – THE BEDROCK OF CHRONIC ILLNESSES



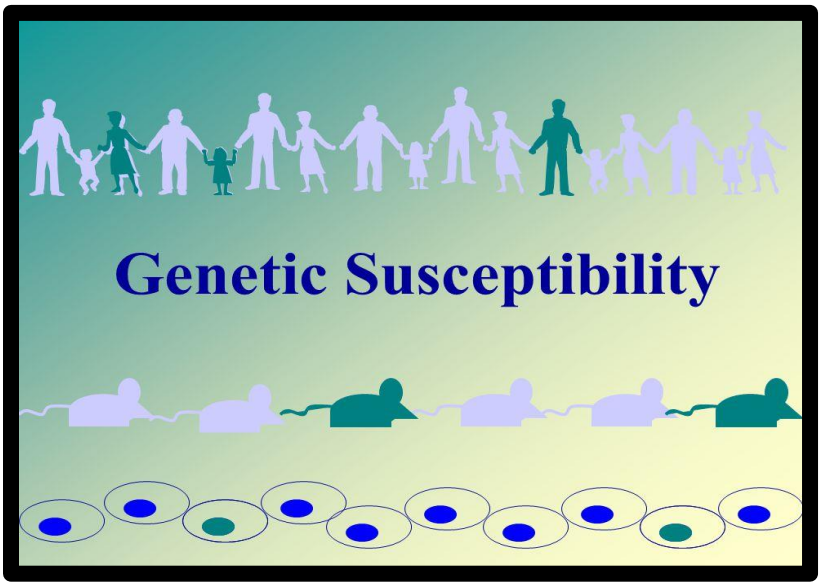
Dr. Alessio Fasano takes the position that inflammation is the underlying physiologic process causing most chronic illnesses. He describes five factors that are responsible for

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 respond to threats**
- **Microbiome—the density, diversity, location, and functionality of microorganisms that live in and on the body**

Analyzing these factors helps diagnose and treat chronic digestive illnesses.

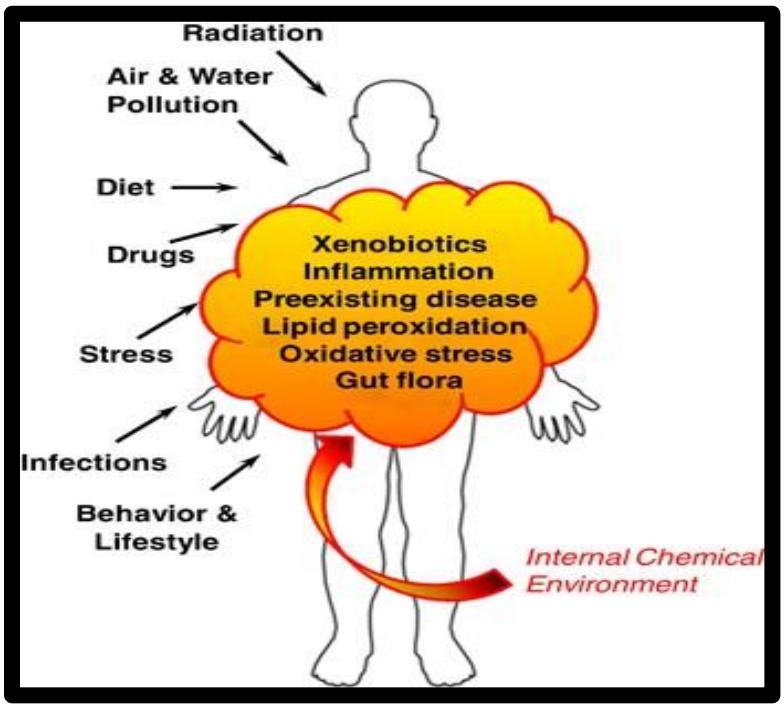
Inflammation – Genetic Susceptibility



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, including alcohol, tobacco, and recreational drugs)

- **Environmental exposures** including air, water, sunlight, radiation, gravity, temperature, gases, toxins, food additives and environmental pollutants

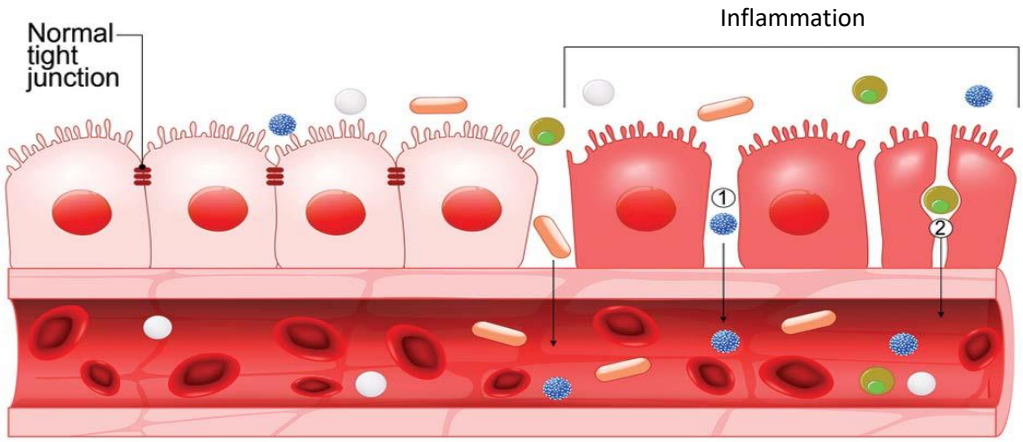
- **Microorganisms**

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



Intestinal barriers modulate permeability. As previously discussed, barriers are designed to prevent the entry into the body of microorganisms, toxins, food antigens and other foreign elements that might cause harm to the body while allowing the absorption of nutrients, electrolytes, and water.

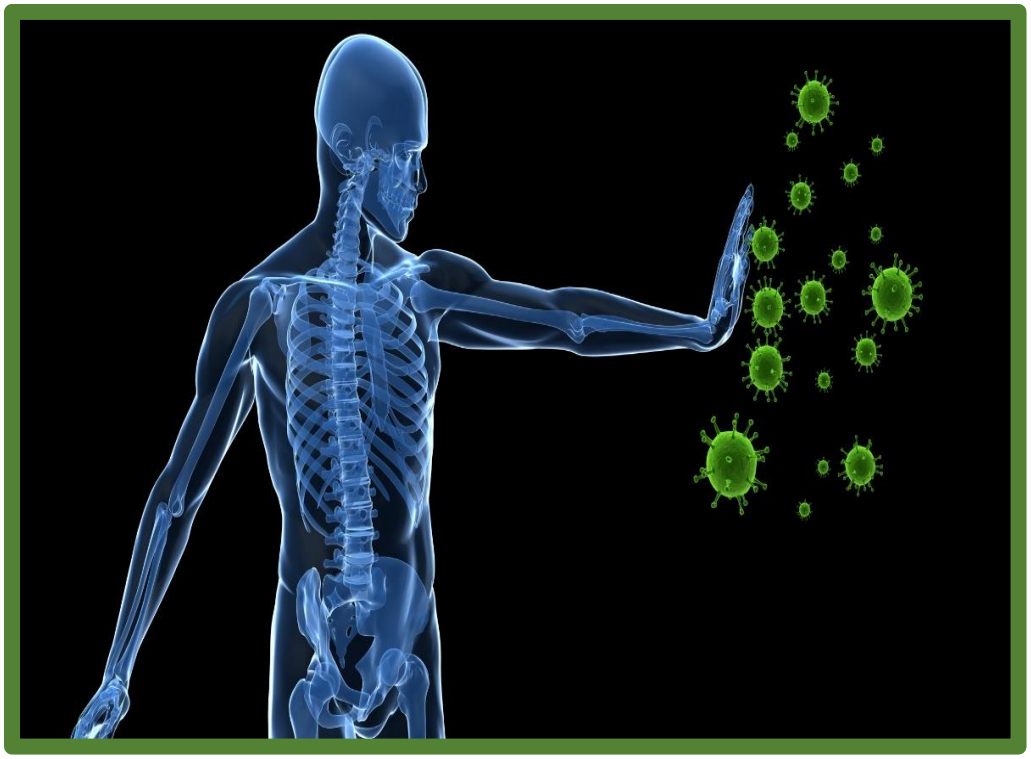
Microorganisms are the guardians of the gates. They produce chemicals, most importantly short-chain fatty acids, and specifically butyrate, that moderate permeability of the digestive tract.

Butyrate producing organisms are nourished by the presence of dietary fiber. In the absence of dietary fiber, barriers become

porous and harmful microbes and chemicals are able to reach body organs creating chronic digestive and systemic illnesses.

Disruption of the intestinal barrier is commonly referred to as "leaky digestive tract syndrome," "leaky digestive tract" or "leaky gut," however, these labels do not represent a real medical diagnosis. The abnormally increased lining permeability is more appropriately referred to as "abnormal intestinal barrier function."

Inflammation – Immunity and Immunosenescence



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.

With aging, there is increased dysfunction of the immune system that contributes to an impaired response to pathogens, and greater morbidity and mortality. The loss of immune function with age is called *immunosenescence.*

The CDC estimates that 80% of those 65 years and older have at least one chronic condition and 50% have two. These are felt to be primarily associated with deficiencies of their immune system.[1]

One of the major causes of age-related immune deficiencies is thymic involution, the shrinking of the thymus gland that begins at birth at a rate of 3% a year and continues to shrink at a rate of about 1% per year after the age of 35-45.[2]

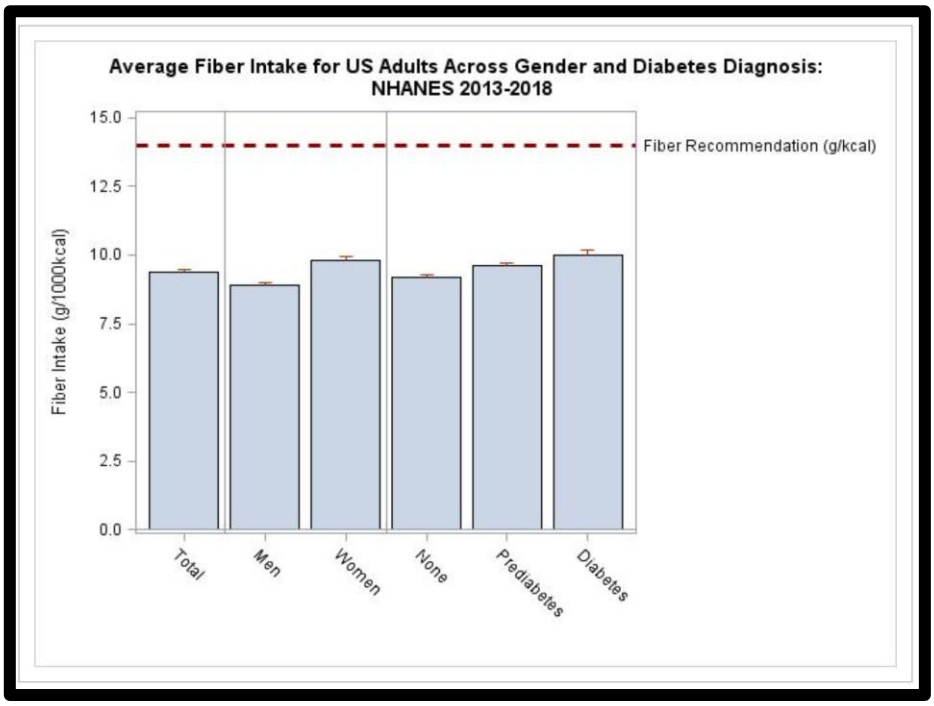
[1] CDC.gov
--Chronic Disease Prevalence in the US: Socio-Demographic And Geographic Variations By ZIP Code Tabulation Area
-- Prevalence Of Multiple Chronic Conditions Among US Adults, 2018
-- Public Health And Aging: Trends In Aging—United States And Worldwide

[2] Lee, K-A, Immunosenescence and Aging, *Front. Aging* 3:900028, doi: 10.338 9/fragi.2022.900028

SECTION FOURTEEN

THE SILENT CRISIS OF FIBER DEFICIENCY IN THE U.S. ADULT POPULATION

Despite its benefits, dietary fiber intake remains below recommended levels for a large segment of the U.S. population. Specifically, only about 5% to 9% of adults meet the recommended daily intake of dietary fiber.



The recommended fiber intake is 14 grams of fiber for every 1,000 calories consumed each day.[1] This amounts to roughly

28 grams of fiber per day for women and 35 grams of fiber per day for men.

On average, women consume about 9.9 grams of fiber per 1,000 calories, and men consume about 8.7 grams per 1,000 calories (See above graphic chart).

[1] U.S. Department of Agriculture and U.S. Department of Health and Human Services *Dietary Guidelines of Americans,* 2020-2025.

The reasons for fiber deficiency range from lack of awareness about the benefits of fiber to the prevalence of ultra-processed foods low in fiber content.

This widespread deficiency has profound implications, particularly in terms of maldigestion and malabsorption. Both of these conditions can lead to a gradual depletion of essential vitamins and minerals including the following:

- **Calcium**
- **Phosphorus**
- **Potassium**
- **Magnesium**
- **Folic acid (vitamin B9)**
- **Vitamin B12**
- **Iron**

In some instances, measuring levels of essential vitamins and minerals in the blood may be part of the diagnostic process.

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SECTION FIFTEEN

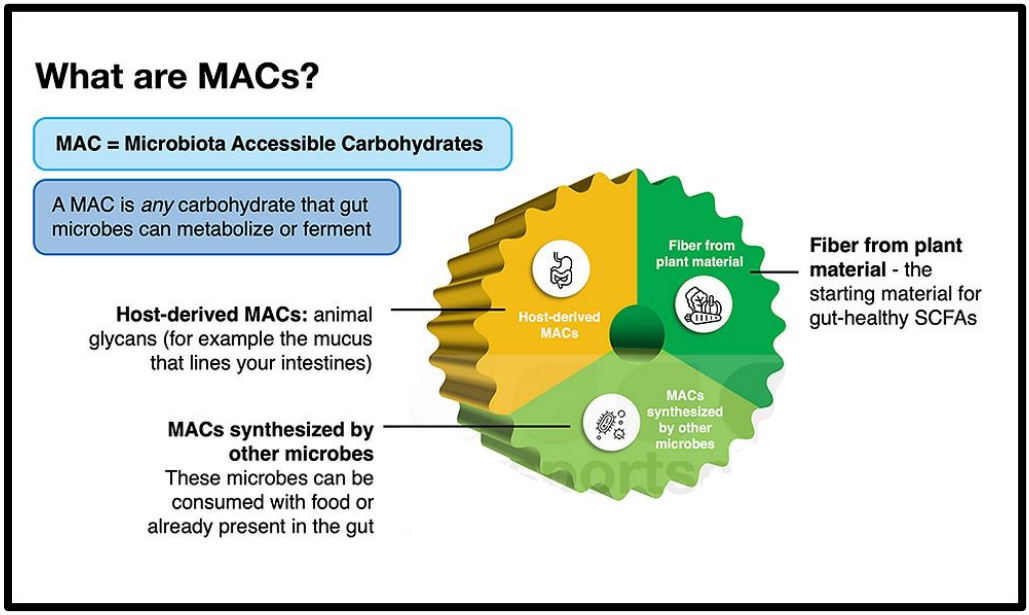
MICROBIAL ACCESSIBLE NUTRIENTS

MORE ABOUT DIETARY FIBER

HEALTH BENEFITS

Dietary fiber is often heralded as the cornerstone of healthy eating. It is felt to play a pivotal role in maintaining overall health. 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 Carbohydrates).



Researchers emphasize that "MACs" 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]

[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.

Evidence shows that dietary fibers offer a myriad of health benefits, including reducing the risk of chronic diseases such as diabetes, heart disease, and colorectal cancer. (See the section: How Humans Rely on their Microbes).

Dietary fiber is not just about improving bowel function but is crucial for systemic health and prevention of serious health conditions.

DIETARY FIBER DEFINED BY CHEMICAL CHARACTERISTICS

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 digestive tract 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.

Many studies on fiber have focused on the benefits of consuming an isolated, single fiber or fiber extract. This is not, however, how humans consume dietary fiber. Plant-predominant 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.

SECTION SIXTEEN

UNIQUE FIBER-LIKE PRODUCTS COMING-OF-AGE

Traditionally, dietary fibers have come from fruits, vegetables, nuts, seeds, whole grains, beans, and legumes. There are, however, unique forms of dietary fiber. Some of these unique fibers include resistant starch, potato starch, agricultural and food industry byproducts, seaweed, mushrooms, human milk oligosaccharides, chitin and chitosan, and lignin.

RESISTANT STARCH

Starch is a carbohydrate made up of multiple branches of sugar-glucose molecules. Plants make starch during photosynthesis and store the starch as their supply of energy. Foods that humans eat that are rich in starch serve as 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 foods that contain resistant starch, 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 starches" and are now classified as a form of dietary fiber. (See List 3)

Once resistant starches enter the large intestine, they are fermented by digestive tract microorganisms to produce active metabolites (i.e., short chain fatty acids). Since resistant starches bypass the small intestine, they do not contribute to blood glucose levels.

Studies of our human ancestors suggest that they consumed a high fiber intake due to consumption of wild plants, fruits, nuts, seeds, roots, and tubers—a large percentage of the intake being from resistant starches. Estimates suggest that their diets may have provided 75-150 g of total fiber per day[1,2].

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[2] Cordain, L., Origins And Evolution Of The Western Diet: Health Implications For The 21st Century. *Am J Nut.* 81(2) (2005).

POTENTIAL SIDE EFFECTS TO INGESTING RESISTANT STARCHES

Like all carbohydrates that are fermented in the digestive 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 starches, therefore, must be done slowly in gradual increments to avoid side effects.

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POTATO STARCH

Potato starch 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 is a type of resistant starch which is not digested in the stomach of the small intestine and reaches the colon intact. Once in the colon, potato starch is fermented by microorganisms leading to the production of short-chain fatty acids (SCFAs), in particular, butyrate.

Butyrate has been found to have beneficial effects on the digestive tract and on overall health. By increasing the levels of butyrate, potato starch has the following impacts:

Improvement of barrier function

Butyrate serves as a primary energy source for the cells lining the colon which helps in maintaining its integrity and function. Strong barrier function is crucial to preventing pathogens and toxins from entering the tissue and thereafter the bloodstream. Studies suggest that butyrate can enhance the production of tight junction proteins which are key components in maintaining the integrity of the digestive tract barrier.[1]

Exertion of anti-inflammatory effects

Butyrate has been shown to possess anti-inflammatory properties. Butyrate can decrease the production of pro-inflammatory cytokines. This modulation of the immune response helps prevent and reduce inflammatory diseases in the digestive tract, such as inflammatory bowel disease (IBD).[2]

Potential protection against cancer

The role of butyrate and cancer protection is linked to its ability to induce programmed cell death within cancer cells (apoptosis), inhibit cell proliferation, and promote differentiation in the colon. By these mechanisms, butyrate can help in preventing the development and progression of colorectal cancer. Additionally, its anti-inflammatory effects contribute to the lower risk of cancer development since chronic inflammation is known as a risk factor for cancer.[3]

CONCLUSION:

The intake of potato starch, due to its resistant starch content, can increase the production of butyrate in the colon. This short-chain fatty acid has multiple beneficial effects, including improving the intestinal barrier function, exerting anti-inflammatory effects, and potentially offering protection against colorectal cancer. However, the extent of these benefits can depend on various factors, including the amount of potato starch consumed, its method of preparation, and the individuals' digestive tract microbe composition.

AGRICULTURAL AND FOOD INDUSTRY BYPRODUCTS AS FIBER

Byproducts include skins, seeds and stems of fruits and vegetables which are typically discarded during processing. These byproducts are rich in dietary fiber and other nutrients and can be repurposed into food ingredients. An example might include apple pomace (*figure above*), the leftover material from apple juice production which is high in fiber with pectin being a significant component. Pectin makes up 15% of apple pomace's dry weight. Commercial development of apple pomace for human consumption still requires further research

focusing on standard methods of nutrient reporting and human clinical trials.[1]

[1] Skinner, R., A Comprehensive Analysis of the Composition, Health Benefits, and Safety of Apple Pomace, *Nutrition Reviews*, Vol 76, issue 12, Dec 2018, 893-909.

SEAWEED AS FIBER

Seaweed is a marine alga found in oceans around the world. It is a crucial component of the marine ecosystem but also a valuable nutritional resource for humans. Recent research has demonstrated its potential as a dietary fiber.

Unlike the fibers found in terrestrial plants, the fiber in seaweed has unique properties that contribute to its effectiveness in promoting health. For instance, alginate, a typical soluble fiber

found in seaweed such as kelp, in addition to its qualities as a source of fiber, can significantly reduce fat digestion and absorption in the human body[1]. This property alone makes seaweed an excellent food for managing weight and combating obesity.

Other benefits of seaweed include the following:

1. **Nutrition-rich:**

Seaweed is renowned for its high content of vitamins and minerals and is an excellent source of iodine which is essential for thyroid function. It also contains vitamins A, C, E and K as well as B vitamins. It is rich in antioxidants that help protect cells from damage.[2]

2. **Source of unique bioactive compounds**

Seaweed contains various bioactive compounds such as fucoxanthin and fucoidans, which have been studied for their anti-inflammatory, antioxidant, and anti-cancer properties[3].

3. **High in fiber**

Seaweed has a high dietary fiber content. Other beneficial effects include its positive effect on bowel function and its ability to lower blood sugar and cholesterol levels.[4]

4. **Heart health**

Regular consumption of seaweed has been found to contribute to cardiovascular health due to its content of omega-3 fatty acids in dietary fiber.[5]

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FUNGUS AS FIBER—MUSHROOMS

Mushrooms have long been celebrated for their unique flavors and nutritional benefits. Among the many attributes, mushrooms have been found to be a source of dietary fiber.

Mushrooms have been found to have a low-calorie content and are rich in nutrients including proteins, vitamins, minerals, and dietary fiber.[1] The fiber in mushrooms is primarily found in their cell walls.

Components of mushrooms are capable of benefitting intestinal microorganisms, i.e. acting as prebiotics. (See the section: Prebiotics). Mushrooms contain non-digestible components that can be fermented by beneficial microbes promoting their growth and activity. Some of those components include the following:

1. **Polysaccharides**:

   - **Beta-glucans: mushrooms are rich in beta-glucans, a type of polysaccharide that has prebiotic properties. Beta-glucans stimulate the growth of beneficial gut bacteria and enhance the immune response.**

   - **Chitin: Chitin is another polysaccharide found in the cell walls of mushrooms. Chitin, likewise, and its derivative chitosan have both been shown to have prebiotic effects, promoting the growth of beneficial gut microorganisms.**

2. **Fungal Polysaccharides:**
   - **Mushrooms contain various other polysaccharides that have been demonstrated to have prebiotic effects. These include mannans, xylans, and galactans which can contribute to the growth and activity of microorganisms in the intestinal tract.**

Mushrooms have been found to increase the feeling of fullness which can aid in weight management by reducing overall calorie intake.[2] Mushrooms have also been linked to a lower risk of cardiovascular disease.[3]

Additionally, mushrooms have been associated with reduced risk of type II diabetes and improvement in blood sugar control[4].

When mushrooms are selected for their fiber content, it is important to consider their variety as different types of mushrooms have different levels of fiber. For example, white button mushrooms, shiitake mushrooms, and portobello mushrooms are among those that are particularly high in dietary fiber[5].

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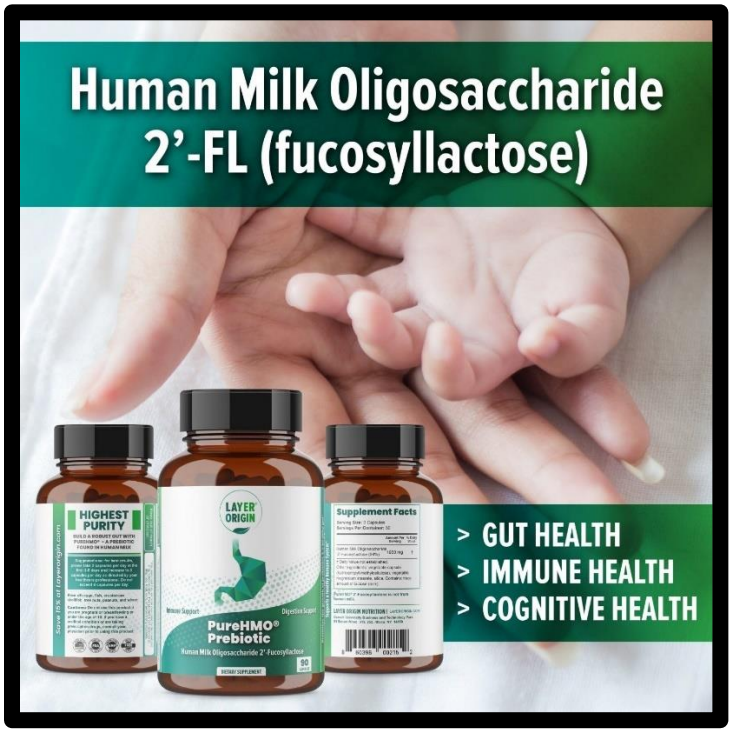
HUMAN MILK OLIGOSACCHARIDES



Human breast milk contains a variety of nutrients and bioactive components essential for infant nutrition[1]. After lactose and lipids, human milk oligosaccharides (HMOs) are the third most abundant nutrient in breast milk. HMOs have at least 150 soluble sugar-based structures - known as glycans. They are found in varying concentrations and fluctuate throughout the lactation period[2].

HMOs reach the colon of the newborn and infant undigested and serve as a nutrient source for specific bacteria, such as *Bifidobacterium*. They influence digestive tract microbe

composition and function directly or through cross-feeding interactions.

Over the years, studies have associated HMOs and their metabolic end products, such as short-chain fatty acids (SCFAs), with a broad range of benefits in infant health, influencing the infant's neural development, conferring protection against gastrointestinal diseases and regulating the infant's immune system[3]. Some of these benefits include the following:

1. DIGESTIVE TRACT HEALTH:

HMOs are known to promote the growth of beneficial digestive tract bacteria, such as *Bifidobacterium*, which can improve digestive health and enhance the overall digestive tract microbiota. This is like the role they play in infants, fostering a healthy digestive system.

2. IMMUNE FUNCTION:

Studies suggest that HMOs can help strengthen the immune system by reducing digestive tract inflammation and potentially enhancing the body's defense against pathogens[4]. This is particularly beneficial for adults looking to boost their immune resilience.

3. ANTI-INFLAMMATORY PROPERTIES:

HMOs may reduce inflammation in the body. Chronic inflammation is linked to various health issues including heart disease and diabetes. HMOs, therefore, could theoretically offer preventative benefits in these two areas.

4. POTENTIAL REDUCTION OF PATHOGEN ADHESION:

HMOs can prevent the adhesion of pathogens to the digestive tract lining which is a critical step in preventing infections. This protective mechanism is vital for maintaining intestinal health and preventing gastrointestinal infections.

5. METABOLIC HEALTH:

Emerging scientific research indicates that HMOs might help regulate cholesterol levels and improve glucose metabolism, which are important factors in managing metabolic syndrome and type II diabetes.

HMOs, however, cannot yet be included under the formal umbrella of *prebiotics* since well designed, human studies are still lacking.

USE IN ADULTS: Recent studies have opened new horizons exploring the use of HMO's in capsule form that have been manufactured containing some of same chemical compounds that are found in breast milk.[5,6,7,8,9,10,11]

HMOs have been designated generally regarded as safe (GRAS) and some pill formulations have been introduced as food supplements. When designing strategies to improve intestinal ecosystems, HMOs may become one of the prebiotics of the future.

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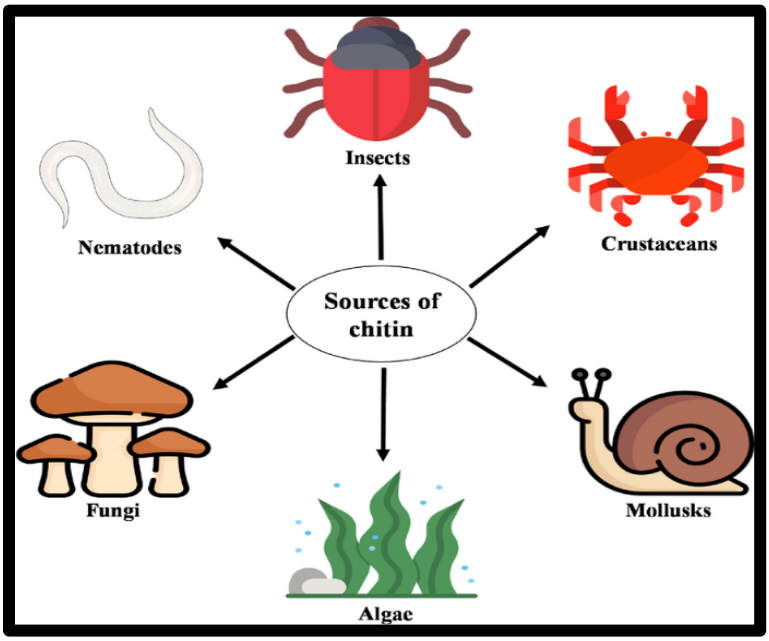
CHITIN AND CHITOSAN AS FIBER



Chitin and chitosan are unique fiber-like substances that have garnered attention for their potential health benefits when used as dietary fiber.[1-6] Despite not being as widely recognized as other types of dietary fibers, chitin and chitosan offer unique benefits due to their chemical structure and physiologic effects.

Chitin is a long chain polymer and major component of the shells of crustaceans such as crabs, shrimp and lobsters, the cell walls of fungi such as mushrooms, and the exoskeletons of insects.

Chitosan is a metabolic byproduct derived from chitin leading to a compound that is more soluble in water than chitin and has distinct biochemical properties. Due to these characteristics,

chitosan is more commonly used as a dietary supplement in food products compared to chitin.

One of the primary benefits of chitin and chitosan as dietary fibers is their ability to bind fats and cholesterol in the digestive tract, potentially reducing cholesterol levels and aiding in weight management.[7]

Additionally, chitin and chitosan have been studied for their effects on blood sugar regulation.[8] These fibers can slow down the absorption of sugar from the digestive tract, leading to a more gradual rise in blood sugar levels after meals. This could potentially benefit individuals with diabetes or those at risk of developing diabetes by helping to control blood sugar levels after meals.

The impact of chitin and chitosan on overall gastrointestinal health is another area of interest. As with other dietary fibers, chitin and chitosan can promote a healthy digestive system by supporting the growth of beneficial digestive tract microorganisms and enhancing bowel regularity. Furthermore, the fermentation of chitosan by digestive tract microbes produces short chain fatty acids which serve as energy sources for the colon cells and have an anti-inflammatory effect.

Despite these potential benefits, the inclusion of chitosan in the diet must be approached with caution, especially in those with seafood allergies as some of these compounds are derived from crustaceans. Furthermore, the quality and source of

chitosan supplements can vary, which may affect the efficacy and safety of these products.

Chitin and chitosan, therefore, represent an interesting category of unique dietary fibers with potential health benefits including blood sugar regulation, and promotion of gastrointestinal health. Further research is required to define optimal dosages and forms of consumption.

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SECTION SEVENTEEN

CONDITIONS THAT ILLUSTRATE DYFUNCTIONAL DIGESTIVE ECOSYSTEMS

I. CHRONIC CONSTIPATION

WHAT IS CONSTIPATION?

Chronic constipation is a digestive disorder characterized by infrequent bowel movements, difficulty passing stool, or both.

Medically, chronic constipation is defined as having fewer than three bowel movements per week, accompanied by hard, dry stools that are difficult to pass. The condition can be acute,

lasting a few days to weeks, or chronic, persisting for months to years.

Constipation may just be an annoyance but can also represent a serious underlying condition. When present for more than a brief period or when simple dietary or medical treatments do not completely resolve the problem, a professional medical practitioner should be consulted.

DIAGNOSTIC TESTS TO ESTABLISH CAUSE:

- **Blood Tests: To check for underlying conditions such as hypothyroidism or diabetes.**
- **Colonoscopy: To examine the colon and rectum for abnormalities.**
- **Transit studies: To track the movement of stool through the colon using x-ray markers**
- **Abdominal imaging studies: CT scans, MRIs, ultrasound exams and use of imaging capsules.**
- **Breath tests: To identify small intestinal bacterial overgrowth and/or excess methane gas production.**

CAUSES FOR CONSTIPATION

Constipation can result from various factors and is often multifactorial in nature:

- **Dietary Factors**: Low dietary fiber intake, inadequate fluid consumption

- **Lifestyle Factors**: Sedentary lifestyle, lack of physical activity, use of alcohol, tobacco, and recreational drugs

- **Medical Conditions**: Examples include hypothyroidism, diabetes, and neurological disorders such as Parkinson's disease or multiple sclerosis.

- **Medications**: Certain medications, including opioids, calcium, iron, aluminum, antihistamines, and some antidepressants are associated with chronic constipation.

- **Psychological Factors**: Stress, anxiety, and depression

- **Structural Issues**: Obstructions or abnormalities in the digestive tract, including strictures, adhesions, tumors, radiation damage or rectoceles

- **Pelvic Floor Dysfunction**: Pelvic floor dysfunction refers to issues with the coordination of the pelvic floor muscles involved in bowel movements and urination caused by traumatic injury, prior pelvic surgery (hysterectomy or prostatectomy), aging, and/or connective tissue disorders

- **Antibiotics:** Recent courses of antibiotics can alter the gut microbiota composition, potentially leading to constipation by disrupting the balance of beneficial bacteria that aid in digestion.

- **Colonoscopy or Bowel Irrigation Therapy: A vigorous laxative prep for colonoscopy and/or irrigations administered with irrigation therapies can wash or rinse away critical gut microbes that help control water balance and motility resulting in constipation. In most of these cases, the alteration of bowel motility is limited in duration.**

TREATMENT OF CONSTIPATION

Treatment strategies for constipation vary depending on the underlying cause and the severity of symptoms. Common treatments include:

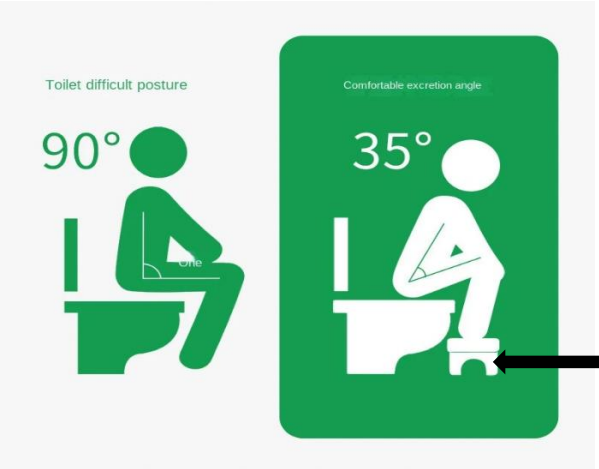
- **Dietary modifications: Modifications include increasing dietary fiber with ingestion of fruits, vegetables, nuts, seeds, beans, legumes, whole grains, and other fiber-like substances. (See LIST I at the end of the monograph for high fiber foods and the section in the text on fiber-like products)**

- **Adequate hydration: Hydration should be achieved primarily with water, drinking 60-80 ounces of fluid (primarily water) every 24 hours--or more under special circumstances like fever, illness, activity, high ambient temperature, pregnancy, and lactation. (See the section: Hydration)**

- **Lifestyle changes: Changes include regular physical activity, with establishment of a routine for bowel movements and responding promptly to the urge to defecate.**

- **<u>Biofeedback therapy</u>: A treatment directed by a specially trained physical therapist who can help the patient retrain the pelvic floor muscles in cases of pelvic floor dysfunction.**

- **<u>Changing body positioning during defecation</u>: Use a Squatty Potty®. The greater the hip flexion achieved by squatting, the straighter the rectoanal canal will be resulting in less straining to defecate.**



- **<u>Probiotics:</u> Foods containing probiotics can be added as nutrients in the diet and are also available as commercially designed and manufactured supplements. (See the section: Probiotics and the section on Fermentable Foods).**

- **<u>Prebiotics (dietary fiber)</u>: Foods containing prebiotics can be added to the diet and are available as commercially designed and manufactured supplements. (See the section: Prebiotics and the list of high fiber foods at the end of the monograph)**

- **Polyphenols**: Polyphenols can be found in green tea, fruits, vegetables, coffee, chili peppers, flax seeds, sesame seeds, and whole grains. (See the section: Polyphenols)

- **Reducing methanogens:** Methanogens are microbes found in the class of microorganisms known as archaea. Methanogens produce methane from hydrogen that accumulates in the intestinal tract. Methane has been found to reduce gut motility and may be a major cause of constipation in some individuals.

  If the concentration of methane is found to be excessive on testing, antibiotic therapy may be helpful.

Step-Wise Management

In a recent evidence-based study[1] published by the American Gastroenterology Association evaluating management of chronic idiopathic constipation, the following guidelines were recommended:

[1] L Chin, Pharmalogical Management of Chronic Idiopathic Constipation, *Am. J. Gastroenterolgy*, vol 118, 936-948 (2023)

Step 1: Begin therapy with an increase in dietary fiber. (See List 1)

Step 2: Add psyllium husk powder (Metamucil®,Benefiber®, Organic Konsyl®) to the treatment plan, if needed. Make sure that hydration is adequate when using fiber supplements.

BRAND	SERVING SIZE	DIETARY FIBER grams	SOLUBLE FIBER grams	INSOLUBLE FIBER grams
BENEFIBER®	2 tsp	3	3	0
KONSYL®	1 tsp	5	3	2
METAMUCIL®	1 tsp	3	2	1

(For exact measurements check product labels).

HEALTH BENEFITS OF PSYLLIUM HUSK POWDERS IN ADDITION TO RELIEF OF CONSTIPATION

A. **Prebiotic action:** Psyllium husk powders promote the growth of beneficial microbes in the intestinal tract. The increase in these microbes reduces inflammation and enhances nutrient absorption.

B. **Blood sugar regulation**: Psyllium powders slow down the digestion and absorption of carbohydrates. This helps to stabilize blood sugar levels.

C. **Cholesterol reduction**: Psyllium husk powders can help lower cholesterol levels by binding to bile acids in the small intestine. The binding of bile reduces the substrate upon which cholesterol is made. This process stimulates the liver to use its cholesterol stores to produce additional bile acids thereby reducing cholesterol levels in the bloodstream.

Step 3: **If steps one and two are not adequate, add one or more of the following osmotic laxatives:**

- **Polyethylene glycol (Miralax®)**
- **Magnesium oxide, if the individual does not have kidney disease**
- **Lactulose. Lactulose is a chemical formulation of fructose that is not digested in the small intestine. Lactulose comes as a sweet tasting syrup. Increasing or decreasing the dose is done based on response.**

Step 4: **If steps 1-3 are not adequate, a stimulant laxative using Bisacodyl (Dulcolax®), sodium picosulfate or senna derivatives can be added. The first two laxatives are recommended for use for no more than four weeks. Senna derivatives can probably be used safely for more than four weeks.**

Step 5: If steps 1-4 are not adequate, a secretagogue laxative can be added. Secretagogue laxatives increase the secretion of chloride ions from the body into the colon lumen which results in the associated delivery of water into the lumen thus softening the fecal mass and rinsing the colon.

There are several different classes of secretagogue laxatives. They all require a prescription and are rigidly monitored by insurance carriers.

- **Lubiprostone (Amitiza®)**
- **Linaclotide (Linzess®)**
- **Prucalopride (Motegrity®)**
- **Plecanatide (Trulance®)**

MANAGEMENT OF ALL BUT SIMPLE, SELF LIMITED PERIODS OF CONSTIPATION SHOULD BE DONE UNDER THE SUPERVISION OF A MEDICAL CARE PROVIDER.

CONCLUSION

Chronic constipation can significantly affect digestive well-being. Understanding the symptoms, causes, and available treatments is essential for effective management. Through lifestyle modifications, dietary changes, and appropriate medical interventions, most individuals can achieve relief.

For persistent or severe cases, a medical care provider should be consulted.

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Fatty Liver Disease

The most common form of liver disease in the United States is Metabolic Associated Steatotic Liver Disease (MASLD), formerly known as Non-Alcoholic Fatty Liver Disease (NAFLD).[1] MASLD encompasses a range of liver conditions that affect people who drink little to no alcohol. It is characterized by an

excess of fat stored in liver cells and is closely associated with obesity, insulin resistance, increased fats in the blood *(dyslipidemia),* hypertension and type 2 diabetes.

In its earliest form, there may be no abnormalities found on blood tests and no symptoms. It is frequently first recognized on an imaging study of the abdomen done for some other reason that shows an increased content of fat in the liver.

MASLD can progress to a more severe form known as *steatohepatitis,* which involves liver inflammation and can lead to fibrosis (scarring of the liver), cirrhosis, and even liver cancer.[2,3] In patient with steatohepatitis, blood tests usually show abnormally elevated liver enzyme levels and may also show elevated cholesterol and triglycerides levels and evidence for sugar intolerance (diabetes).

It has been suggested that the prevalence of MASLD has been rising in the United States due to increasing rates of obesity and metabolic disorders.

[1] Younossi, Zobair M., Prevalence of Nonalcoholic Fatty Liver Disease in the United States: The National Health and Nutrition Examination Survey 2017-2018. *Hepatology,* 2021.

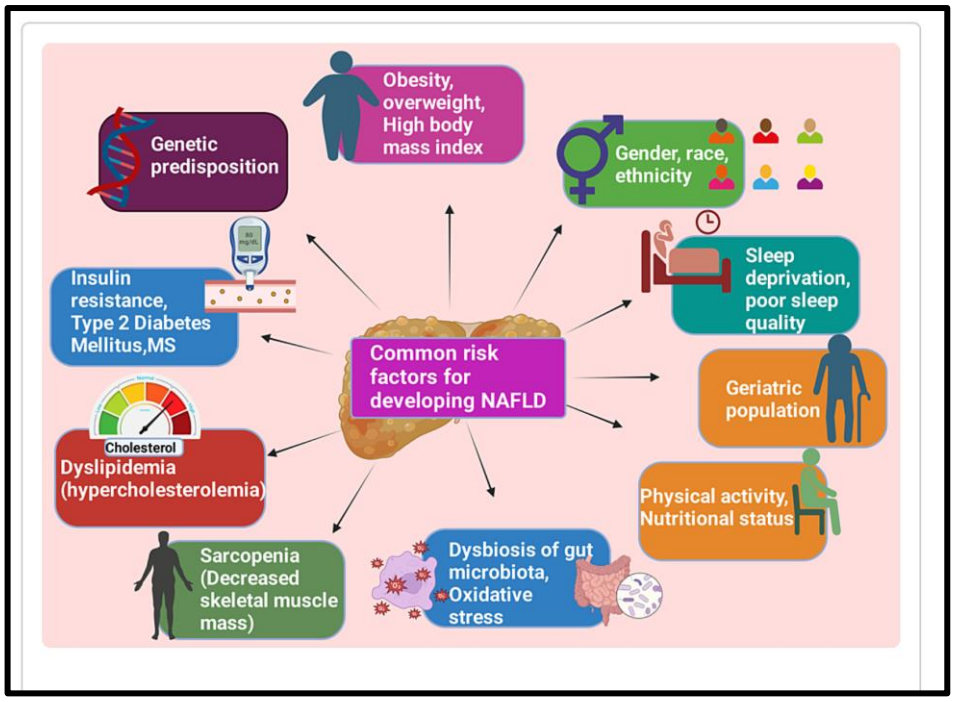
Summary: This study estimates the prevalence of NAFLD in the United States using data from the National Health and Nutrition Examination Survey (NHANES).

[2] Younossi, Zobair M., Epidemiology and Natural History of Non-Alcoholic Fatty Liver Disease, *Metabolism*, 2020.

Summary: This paper provides an overview of the epidemiology and natural history of NAFLD, including its increasing prevalence and association with metabolic syndrome.

[3] Chalasani, Naga, Nonalcoholic Fatty Liver Disease: Clinical Associations and Management, *Hepatology*, 2019.

Summary: This guideline provides evidence-based recommendations for the management of NAFLD, highlighting its clinical associations and management strategies.



The Multiple-Hit Model

Various liver insults appear to contribute to the development of MASLD, primarily through metabolic dysfunction. Here are key factors and insults that have been recognized in the development of MASLD:

Metabolic and Lifestyle Factors

1. **Obesity:** Excessive body weight, particularly visceral adiposity, is a significant risk factor. Adipose tissue releases free fatty acids (FFAs) and pro-inflammatory cytokines, contributing to liver fat accumulation.

2. **Insulin Resistance**: A hallmark of MASLD, insulin resistance leads to increased lipolysis (breakdown of fat) and FFAs in the bloodstream, promoting hepatic fat accumulation.

3. **Type 2 Diabetes Mellitus**: Associated with both insulin resistance and hyperglycemia, which exacerbate liver fat accumulation and inflammation.

4. **Dyslipidemia:** Elevated levels of triglycerides and low levels of high-density lipoprotein (HDL) cholesterol contribute to hepatic steatosis.

Dietary Factors

1. **High-Fat Diets**: Diets rich in saturated fats and trans fats can increase liver fat content.

2. **High-Fructose Diets**: Excessive fructose intake, particularly from sugary beverages, promotes hepatic lipogenesis and fat accumulation.

3. **Overnutrition**: Overall excessive caloric intake, irrespective of macronutrient composition, can contribute to MASLD.

Genetic Factors

1. **Genetic Predisposition:** Variants in genes such as PNPLA3, TM6SF2, and others are associated with increased susceptibility to MASLD.

2. **Epigenetic Modifications**: Changes in DNA methylation and histone modification can influence gene expression related to lipid metabolism and inflammation.

Inflammatory and Immune Factors

1. **Chronic Inflammation**: Systemic inflammation from obesity and metabolic syndrome contributes to liver inflammation and fibrosis.

2. **Cytokines and Adipokines**: Pro-inflammatory cytokines (e.g., TNF-α, IL-6) and adipokines (e.g., leptin, resistin) exacerbate hepatic inflammation and insulin resistance.

Oxidative Stress

1. **Reactive Oxygen Species** (ROS): Oxidative stress from ROS can cause cellular damage, lipid peroxidation, and further inflammation in the liver.

2. **Mitochondrial Dysfunction**: Impaired mitochondrial function increases oxidative stress and disrupts energy metabolism in liver cells.

Gut-Liver Axis

1. **Gut Dysbiosis**: Imbalances in the gut microbiota can influence liver metabolism through the production of metabolites and endotoxins.

2. **Intestinal Permeability**: Increased gut permeability (*leaky gut*) allows endotoxins like lipopolysaccharides (LPS) to enter the bloodstream, triggering hepatic inflammation.

Environmental Factors

1. **Toxins and Pollutants**: Exposure to environmental toxins such as pesticides, heavy metals, and industrial chemicals can contribute to liver injury and steatosis.

2. **Medications**: Certain drugs, including corticosteroids, methotrexate, and tamoxifen, can induce fatty liver.

Hormonal Factors

1. **Sex Hormones**: Differences in estrogen and testosterone levels can influence the development and progression of MASLD. Postmenopausal women may be at higher risk due to lower estrogen levels.

2. **Thyroid Hormones**: Hypothyroidism can impair lipid metabolism and increase the risk of liver fat accumulation.

Sedentary Lifestyle

1. **Physical Inactivity**: Lack of regular physical activity contributes to obesity, insulin resistance, and poor lipid metabolism, all of which are risk factors for MASLD.

Stress and Sleep Disorders

1. **Chronic Stress**: Prolonged stress can influence hormonal balance, leading to metabolic disturbances and inflammation.

2. **Sleep Apnea: Obstructive sleep apnea is associated with intermittent hypoxia and systemic inflammation, contributing to liver steatosis and fibrosis.**

In summary, MASLD is a multifactorial disease involving a complex interplay of metabolic, genetic, dietary, inflammatory, and environmental factors. Understanding these various liver insults is critical for developing targeted prevention and treatment strategies.

ACCEPTED TRIALS OF THERAPY FOR MASLD

Lifestyle Modifications

- **Diet and Exercise: Weight loss through calorie restriction and increased physical activity remains a cornerstone of MASLD management. The Mediterranean diet has been shown to improve liver histology and metabolic parameters[1].**

[1] Armstrong, M. J., et al. (2023). Dietary Modifications and Physical Activity in Managing Metabolic Associated Steatotic Liver Disease: Role in Reducing Liver Fat and Improving Insulin Sensitivity. *Journal of Hepatology*, 78(4), 1123-1134.

Summary: This study discusses the benefits of weight loss through calorie restriction and increased physical activity, particularly emphasizing the Mediterranean diet in improving liver histology and metabolic parameters.

Pharmacotherapy

Pioglitazone: A PPAR-gamma agonist that improves insulin sensitivity and reduces hepatic steatosis and inflammation. It is particularly effective in patients with NASH.[2]

[2] **Gensluckner, K., et al. (2024). Efficacy of Pioglitazone in Reducing Liver Fat and Improving Liver Enzyme Levels in Patients with Non-Alcoholic Steatohepatitis. *Hepatology Research,* 85(2), 345-356.**

Summary: Recent studies confirm the effectiveness of pioglitazone, a PPAR-gamma agonist, in improving insulin sensitivity, reducing hepatic steatosis, and inflammation, particularly in patients with NASH.

Vitamin E: An antioxidant that has shown benefits in non-diabetic adults with MASLD, improving liver histology by reducing oxidative stress and inflammation[3].

[3] **Thomas, E., et al. (2023). Role of Vitamin E in Improving Histological Features in Metabolic Associated Steatotic Liver Disease Patients Without Diabetes. *Liver International*, 43(1), 78-89.**

Summary: This comprehensive review underscores the benefits of Vitamin E, an antioxidant, in improving liver histology by reducing oxidative stress and inflammation in non-diabetic adults with NASH.

GLP-1 Receptor Agonists: Medications like liraglutide and semaglutide have shown promise in reducing liver fat content and improving liver histology in MASLD patients by enhancing insulin secretion and reducing appetite[4].

Armstrong et al. (2023) highlight the potential of GLP-1 receptor agonists in treating MASLD, with ongoing trials indicating significant improvements in liver fat reduction[4].

[4]**Armstrong, M. J., et al. (2023). Potential of GLP-1 Receptor Agonists in Treating Metabolic Associated Steatotic Liver Disease: Evidence from Ongoing Trials. *Diabetes Care*, 46(6), 987-998.**

Summary: This article highlights the promise of GLP-1 receptor agonists, such as liraglutide and semaglutide, in reducing liver fat content and improving liver histology by enhancing insulin secretion and reducing appetite.

SGLT2 Inhibitors: Drugs such as empagliflozin help reduce liver fat and fibrosis by promoting glucose excretion and improving insulin sensitivity[5].

[5] **Gensluckner, K., et al. (2024). SGLT2 Inhibitors in the Management of Hepatic Steatosis in Metabolic Associated Steatotic Liver Disease. *Journal of Clinical Endocrinology & Metabolism*, 109(3), 543-554.**

Summary: This study shows that SGLT2 inhibitors, such as empagliflozin, help reduce liver fat and fibrosis by promoting glucose excretion and improving insulin sensitivity.

FXR Agonists: Obeticholic acid, an FXR agonist, has shown potential in reducing liver fibrosis and improving histological features in MASLD.[6]

[6] **Li, Y., et al. (2023). Effectiveness of FXR Agonists in Managing Liver Fibrosis Associated with Metabolic Associated Steatotic Liver Disease. *Hepatology Communications*, 7(5), 1234-1245.**
Summary: This review discusses recent findings on obeticholic acid, an FXR agonist, showing potential in reducing liver fibrosis and improving histological features in MASLD.

Surgical Interventions

Bariatric Surgery: Effective in patients with severe obesity, bariatric surgery significantly reduces liver fat, inflammation, and fibrosis, offering a potential cure for MASLD in this population.[7]

[7] Li, Y., et al. (2023). Long-term Benefits of Bariatric Surgery in Resolving Metabolic Associated Steatotic Liver Disease and Preventing Disease Progression. *Surgery for Obesity and Related Diseases*, 19(2), 234-245.

Summary: This review highlights the effectiveness of bariatric surgery in significantly reducing liver fat, inflammation, and fibrosis in patients with severe obesity, offering a potential cure for MASLD.

SECTION EIGHTEEN

LOW FODMAP DIET

WHY THE LONG-TERM USE OF 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

conduct essential functions necessary for human survival. (See the section: How Humans Rely on Their Microbes).

Like all living substances, microorganisms require a source of energy to exist. Their preferential source of energy comes from dietary fiber ingested by the human host—often referred to as NDOs (non-digestible oligosaccharides).

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

The low FODMAP diet, however, eliminates dietary fibers from the diet. Without dietary fiber, microbes enter a state of starvation[1].

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

One of the functions of the mucus layer is to form 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 can 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.

Recent iterations of the diet suggest that if the diet is used it should be done for limited periods of time with gradual reintroduction of dietary fibers as tolerated.

[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.

SECTION NINETEEN

INTRODUCING FIBER
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 plant predominant fibers should be introduced slowly allowing the digestive tract 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 digestive tract wall resulting in abdominal bloating, distention, and pain.

The digestive tract wall may be hypersensitive to stretching when fiber is first introduced. In time, however, the digestive tract may adapt to a new and more comfortable normal. The process of adaptation, however, may take many months to

reach a state of complete comfort, particularly in those whose diets contained only small amounts of dietary fiber initially.

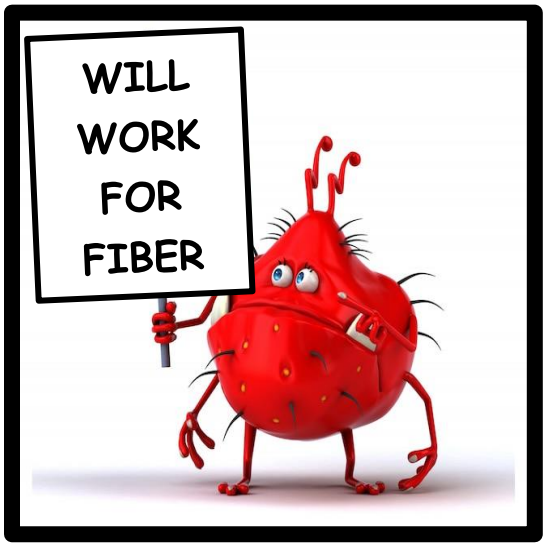
SECTION TWENTY

THE CONSEQUENCES OF NEGLECTING BENEFICIAL MICROBES

The last portion of the small intestine, the ileum, combined with the large intestine (colon) can be compared to a forest.

A thriving forest can be filled with large numbers of plants, flowers, bushes, vines, trees, grass, 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 forest* composed of thousands of different species, strains, and sub-strains of microbes.

Like all living things, for the *microbial forest* to thrive, it must be supplied with a source of energy, i.e., nutrients. The primary source of that energy comes from dietary fiber.



WHAT HAPPENS WHEN MICROBES ARE STARVED OF NUTRIENT FIBER?

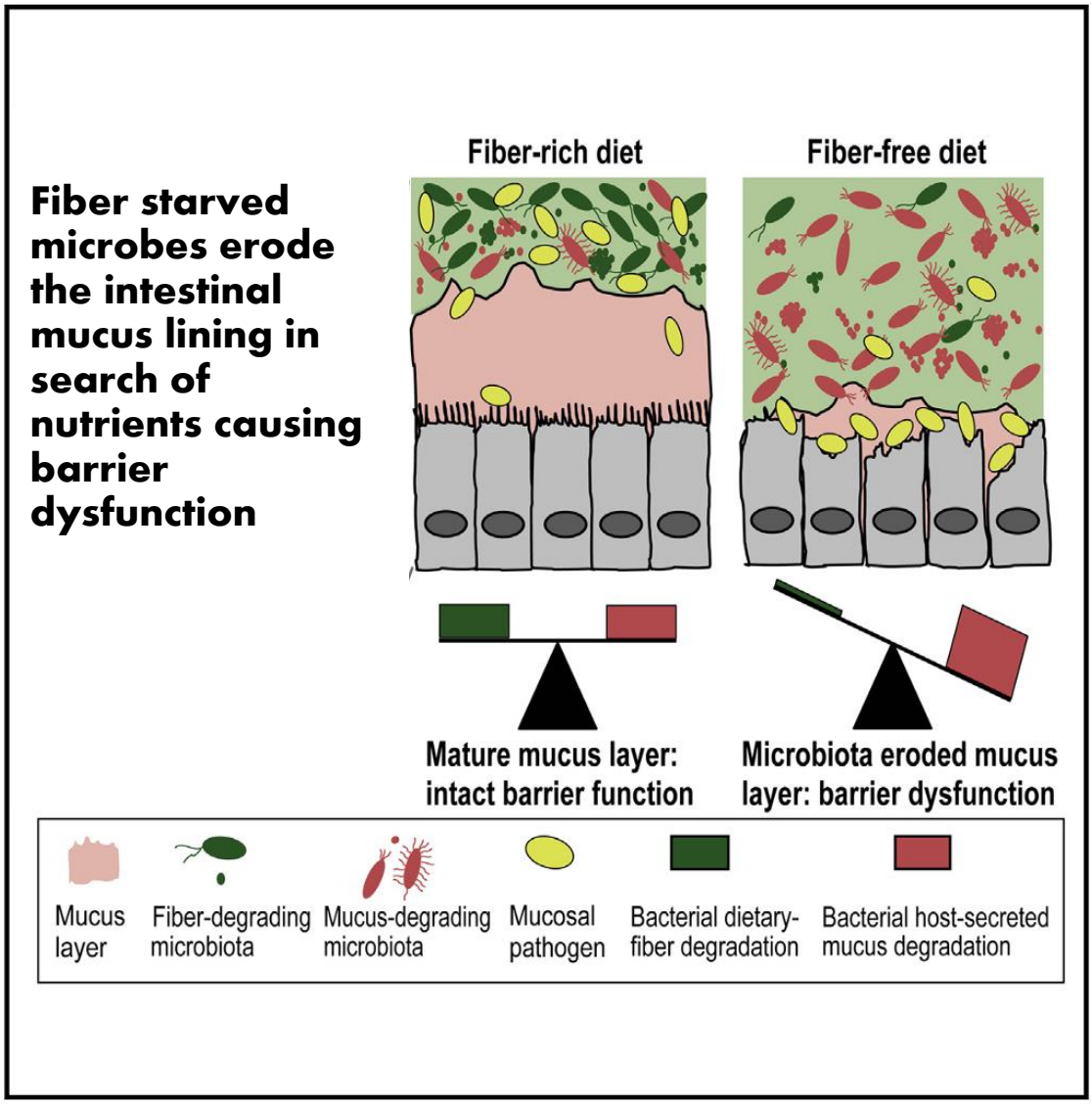
During periods of fiber deficiency, microbes in the lower intestines adapt their metabolism to derive energy from alternative sources other than dietary fiber in the following ways:

- **Fermentation of Other Sources**:
  During normal cellular turnover, there is a constant sloughing of dead cells from the surface of the intestinal lining with renewal of new cells. Sloughed cells and dead microbes that have been destroyed in the upper organs of the digestive tract by gastric acid, pepsin, bile, and pancreatic secretions can also serve as nutrients for live microbes in the last portions of the digestive tract. (See the section: Postbiotics)

- **Protein Fermentation**: **When carbohydrate sources are limited, digestive tract bacteria may increase the fermentation of proteins and amino acids. Depending on the type of protein and its amino acid content the fermentation can produce short chain fatty acids. However, fermentation of certain types of protein with specific amino acid contents can also result in the production of potentially harmful substances like ammonia, phenols, and sulfides, which can have negative effects on digestive tract health with some evidence suggesting they can increase the risk of colon cancer.**

- **Mucin Degradation:** **In the absence of dietary fiber, some bacteria can switch to utilizing mucins, which are glycoproteins that form the mucus lining of the digestive tract. By breaking down mucins, these bacteria can access sugars and other nutrients locked within the mucus layer. However, excessive degradation of mucins on the mucus layer can compromise the integrity of the digestive tract barrier, potentially leading to increased digestive tract**

permeability with penetration of toxins, invasion of pathogenic microbes and entry into the body of food antigens thereby activating the immune system and resulting in inflammation.[1]



- **Cross-feeding**: Microbial communities in the digestive tract are highly interdependent. In times of nutrient scarcity, some microbes can produce metabolites that others can use. This cross-feeding can help sustain the

microbial community when preferred nutrients like fiber are scarce.

[1] Desai, M. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility, *Cell,* doi.org/10.1016/j.cell.2016.10.043

CHANGE IN MICROBIAL COMPOSITION WITH LACK OF FIBER AND OVER EXPOSURE TO ANTIBIOTICS

Over time, if the diet lacks fiber consistently—or is repeatedly exposed to antibiotics--there can be a shift in the composition of the digestive tract microbiota. Fiber-degrading bacteria might decrease in numbers and antibiotic resistant bacteria may increase. These shifts affect the overall health and functioning of the digestive tract ecosystems.

It becomes a "perfect storm" when individuals become seriously ill, in particular, those in an intensive care unit. Antibiotics are frequently administered to fight infection, and the illness may cause a loss of appetite, nausea, or vomiting during which times the oral intake of dietary fibers drops off significantly.

Professor Dantas Gautam, professor of laboratory and genomic medicine at Washington University School of Medicine, St. Louis, Missouri, made the following comment in a BBC

interview[1] about the effects on intestinal microbes when antibiotics are administered

> **[1] "Do Antibiotics Really Wipe Out Your Digestive Tract Bacteria?" BBC, 08-28-2023.**

"We know that the more diverse our digestive tract bacteria population is, the better. But every course of antibiotics disrupts this population because antibiotics are not targeted enough to only kill the pathogenic bacteria causing the infection. Instead, they go after all bacteria in our digestive tracts, and there is collateral damage."

"Think of a forest where you are trying to get rid of one weed infection; the way we deploy antibiotics is to carpet-bomb the forest, killing the good and the bad."

"When scientists have looked retrospectively at the microbiomes of people who have had an infection followed by a course of antibiotics, they found that microbiome diversity usually recovers within a few months, however, in some people species of good bacteria never show up again."

Dr. Will Bulsiewicz in his book, *Fiber Fueled,* describes the damage encountered in a fiber starved digestive tract in these terms:

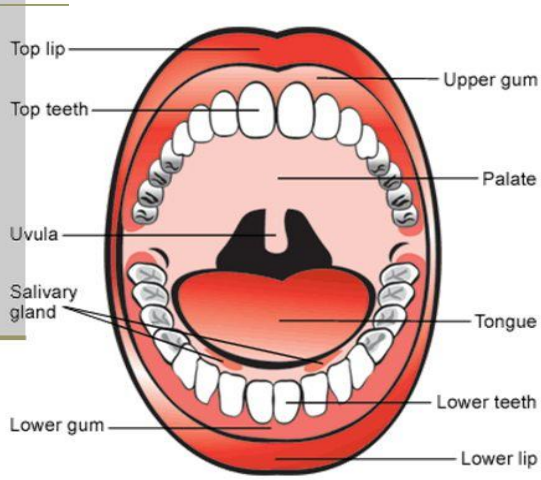
> ***Imagine your digestive tract as a dried-out, postapocalyptic wasteland, with a lone tumbleweed rolling through. The tumbleweed represents your fiber! . . . Of all the essential nutrients, this may be our greatest, most prevalent deficiency.***

SECTION TWENTY-ONE

THE GATEWAY TO THE DIGESTIVE TRACT ECOSYSTEMS

THE ORAL CAVITY

THE HUMAN DIGESTIVE TRACT BEGINS AT THE TIP OF THE TONGUE



- 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.

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

Large numbers of foreign substances, e.g., food antigens, drugs, toxins, and other xenobiotics are constantly entering the oral cavity along with huge number of microorganisms. The oral cavity is, therefore, always in a PRO-INFLAMMATORY STATE.

ORAL CAVITY

MICROBES POPULATE THE ORAL CAVITY AS PLAQUE AND TARTAR AND INVADE THE TEETH AND GUMS

SECTION TWENTY-TWO

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] adverse outcomes of pregnancy,[24] benign prostatic hyperplasia[25] and cryptogenic ischemic stroke before the age of 50.[26]

WHAT HAPPENS IN THE MOUTH MAY NOT STAY IN THE MOUTH!

CARDIOVASCULAR DISEASE

[1] Sanz, M. et al., Periodontitis And Cardiovascular Diseases: Consensus Report, *J Clin Periodontal*. 2020 Mar; 47(3): 268-288.

[2] Castillo, A., Periodontitis And Cardiovascular Disease: Consensus Report., *J. Clin Periodontol*. 2020 Mar; 47 (3).

NEUROLOGIC DISEASE

[3] Li, X., Neuroinflammation: A Distal Consequence Of Periodontitis, *J Dent Res*. 2022 Nov; 101(12): 1441-1449.

Bone Disease

[4] **Jayusman, P., Overview On Postmenopausal Osteoporosis And Periodontitis: The Therapeutic Potential Of Phytoestrogens Against Alveolar Bone Loss, *Front. Pharmacol*, 23 Feb 2023, vol 14.**

[5] **Yu, B., Osteoporosis And Periodontal diseases—an update on their association and mechanistic links*, Periodontology* 2000, vol 89 (1), 99-113.**

Liver Disease

[6] **Gao, Y, *Porphyromonas gingivalis* Exacerbates Alcoholic Liver Disease By Altering Digestive Tract Microbiota Composition And Host Immune Response In Mice, *J Clin Periodontol*. 2023, Sep.**

[7] **Costa, F.O., Periodontitis In Individuals With Liver Cirrhosis, A Case Control Study. *J. Clin. Periodontal*, 2019: 46(10) 991-8.**

[8] **Han, P., Interaction Between Periodontitis And Liver Diseases, *Biomed Rep*, 2016 Sept; 5(3): 267-276.**

Cancer

[9] **Lo, Chun-Han, Periodontal Disease, Tooth Loss And Risk Of Esophageal And Gastric Adenocarcinoma: A Prospective Study, *Digestive tract*, 2021 Mar: 70(3): 620-621.**

[10] **Nasiri, K*., Periodontitis And Progression Of Gastrointestinal Cancer: Current Knowledge And Future Perspective, *Clin. and Translational Oncology*, 25, 2801-2811, 2023.**

[11] **Janati, A., Periodontal Disease As A Risk Factor For Sporadic Colorectal Cancer: Results From COLDENT Study, *Cancer Causes Control,* 2022 Mar;33(3):463-472.**

[12] **Jingru, Y., Poor Dental Health And Risk Of Pancreatic Cancer: A Nationwide Registry-Based Cohort Study In Sweden, 2009-2026, *British Journal of Cancer* 127, 2133-2140 (2022).**

KIDNEY DISEASE

[13] **Ling, L, Periodontitis Exacerbates And Promotes The Progression Of Chronic Kidney Disease Through Oral Flora, Cytokines, And Oxidative Stress, *Front Microbiol*. 2021, Jun 11.**

[14] **Sharma, P., Association Between Periodontitis And Mortality In Stages 3-5 Chronic Kidney Disease: NHANES III And Linked Mortality Study. *Journal of Clinical Periodontology,* 43, 104-113.**

LUNG DISEASE

[15] **Bansal, M., Potential Role Of Periodontal Infection In Respiratory Disease—A Review*, J Med Life*, 2013, Sep 15; 6(3): 244-248.**

[16] **Xiong, K. Research On The Association Between Periodontitis And COPD*. Int J Chron Obstruct Pulmon Dis.* 2023; 18: 1937-1948.**

ALZHEIMER'S DEMENTIA

[17] **Na, H., et. Al., A Distinctive Subgingival Microbiome In Patients With Periodontitis And Alzheimer's Disease Compared With Cognitively Unimpaired Periodontitis Patients, *J Clin Periodontology,* 18 Oct 2023.**

[18] **Wu, D., The Link Between Periodontitis And Alzheimer's Disease—Emerging Clinical Evidence, *Dentistry Review*, 3: (1) March 2023.**

[19] **Kanagasingam, S., Porphymonas Gingivalis Is A Strong Risk Factor For Alzheimer's Disease, *Journal of Alzheimer's Disease Reports 4*, (2020) 501-511.**

RHEUMATOID ARTHRITIS

[20] **Kobayashi, T., Periodontitis And Periodontopathic Bacteria As Risk Factor For Rheumatoid Arthritis: A Review Of The Last 10 Years, *Japanese Dent Sc. Rev*., vol 59, Dec 2023, 263-272.**

SEVERITY OF COVID

[21] **Al-Maweri, S., The Impact Of Periodontal Disease On The Clinical Outcomes Of COVID-19: A Systemic Review And Meta-Analysis, *BMC Oral Health*, (2023) 23:658.**

[22] **Marouf, N*., Association Between Periodontitis And Severity Of COVID-19: A Case-Control Study, *Jour of Clin Periodontology, 2021;48:483-491.***

MACULAR DEGENERATION

[23] **Pachiappan, A. Invasion Of Human Retinal Pigment Epithelial Cells By *Porphyromonas gingivalis* Leading To Vacuolar/Cystolic Localization And Autophagia Dysfunction In Vitro, *Sci Report*. 2020; 10: 7468.**

ADVERSE PREGNANCY OUTCOMES

[24] **Nannan, M., Periodontal Disease In Pregnancy And Adverse Pregnancy Outcomes: Progress In Related Mechanisms And Management Strategies. *Front Med,* 2022:963956.**

BENIGN PROSTATIC HYPERPLASIA

[25] **Wang, S-Y, *P. gingivalis* In Oral-Prostate Axis Exacerbates Benign Prostatic Hyperplasia Via IL-6/IL-6R Pathways. *Miliary Medical Research,* (2024) 11:30.**

CRYPTOGENIC ISCHEMIC STROKE

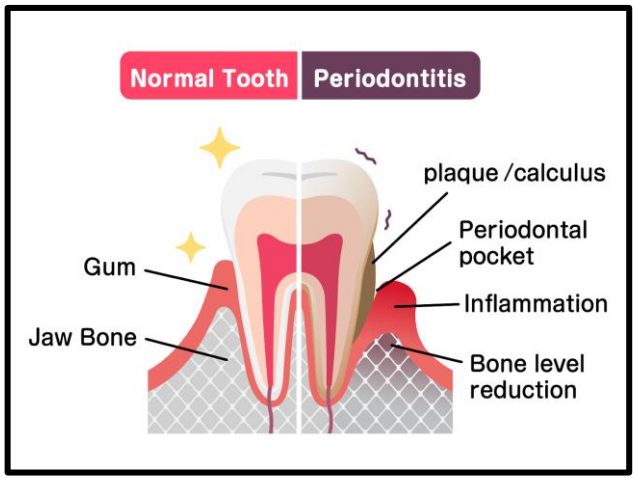
[26] **Leskela, J., Periodontitis, Dental Procedures, And Young-Onset Crytogenic Stroke, *Journal of Dental Research*, 2024, vol. 103(5) 494-501**

Associations are *not the same as causation*, and, as yet the exact relationships between inflammation in the oral cavity and physical ailments in other parts of the body is still not well defined and, in some cases, contentious. Authorities, however, agree that the available evidence is compelling and worthy of continued research.

SECTION TWENTY-THREE

PREVALENCE OF UNTREATED ORAL PATHOLOGY

PERIODONTITIS: AN ILLNESS OF EPIDEMIC PROPORTIONS



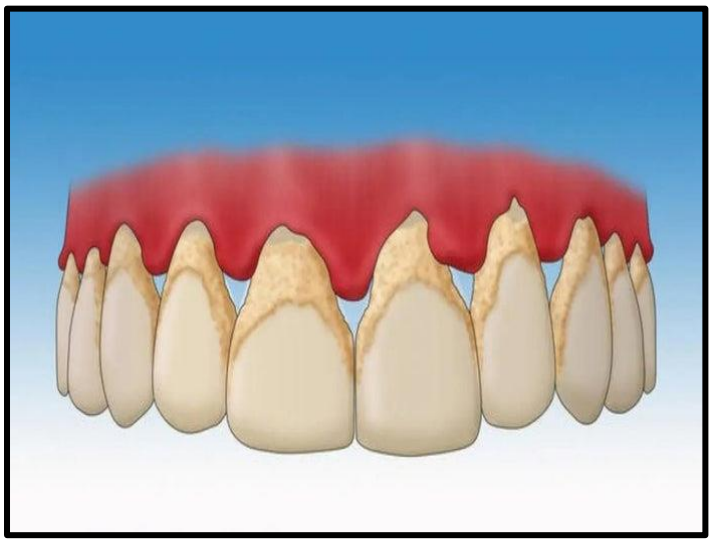
In 2015 the number of people globally with untreated oral conditions was 3.5 billion. This represented 47% of the world population. Of that, 538 million people had severe gum (periodontal) disease.

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, 70% have mild to severe deep gum disease, periodontitis[1]. These numbers have increased with population growth and aging.

[1] Eke, PI, Periodontitis in US Adults: National Health and Nutrition Examination Survey 2009-2014. *J Am Dent Assoc*. 2018 Jul;149(7): 576-588.e6.

SECTION TWENTY-FOUR

THE INFLAMMATORY PROGRESSION IN THE ORAL CAVITY FROM PLAQUE TO GINGIVITIS TO RECEDING GUMS TO PERIODONTITIS AND . . . BEYOND[1]



PLAQUE—THE NIDUS FOR ORAL INFLAMMATION

Once microorganisms enter the mouth, they must rapidly find a way to remain alive and multiply. As a survival strategy, they self-generate a clear, sticky secretion that protects them from being brushed, flossed, or rinsed away known as plaque. Within plaque, different species and strains of microbes can multiply, share nutrients, and exchange genes. If left undisturbed for more than a few days by the host's failure to exercise vigorous oral hygiene measures, plaque can calcify into tartar.

> **[1] Curtis, M., The Relationship of The Oral Cavity Microbiota to Periodontal Health and Disease, *Cell Host & Microbe*, 2011, Oct 20: (10) 4, 302-306.)**

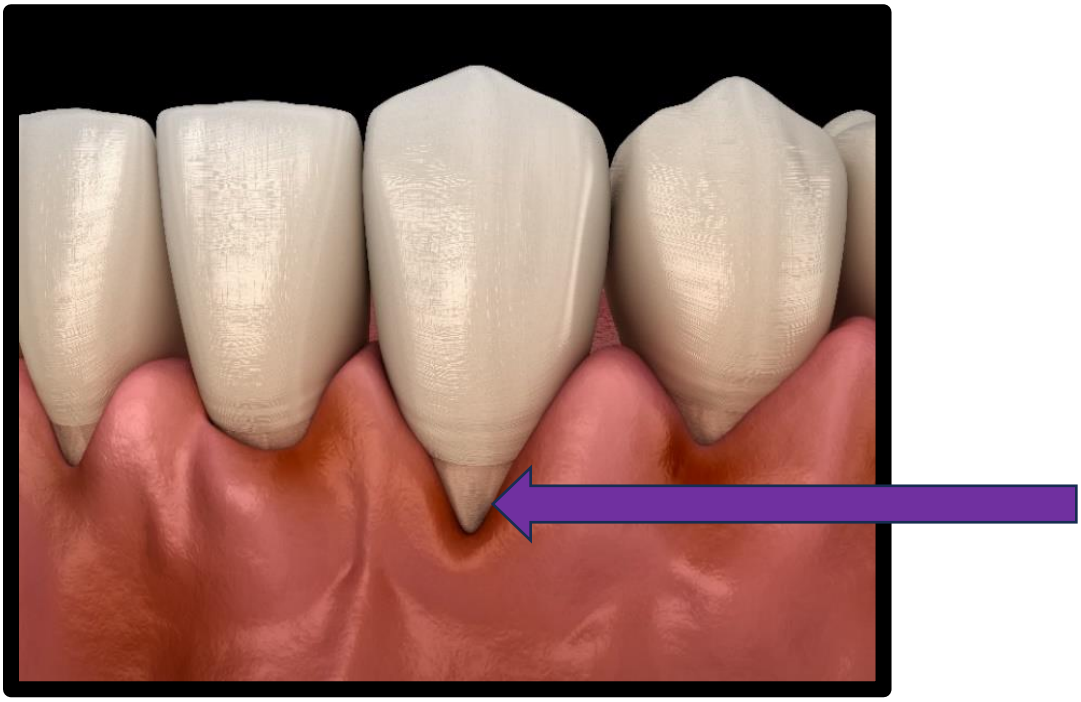
Although plaque can be removed from the teeth by vigorous home hygiene measures like flossing, brushing, water irrigations and rinses, once plaque calcifies into tartar, its removal requires the help of a dental professional who can use high pressure, ultrasonic washing devices (e.g., Cavitron®) and scraping tools.

Microorganisms in plaque metabolize food items that pass through the mouth, particularly refined sugar (sucrose). In the process of utilizing food nutrients, they produce waste products including acids and gases. These wastes are responsible for destroying dental enamel of the teeth i.e., *dental cavities*, causing bad breath, i.e., *halitosis,* initiating gum irritation, i.e., *gingivitis,* and causing gum infections below the gum line, i.e., *periodontitis.*

Maintaining good oral hygiene habits at home and visiting the dentist and dental hygienist at frequent intervals is felt to be beneficial and may contribute to overall human well-being.

RECEDING GUMS
AND
PERIODONTAL POCKETS

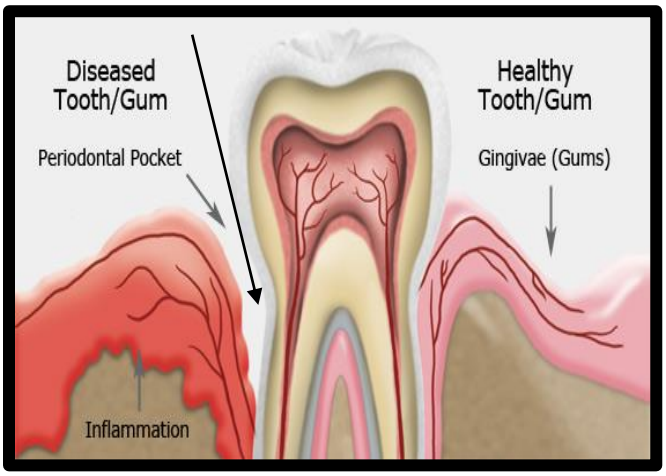
In response to inflammation, gums pull away from the tooth exposing the root. This process is known as receding gums.



As gums pull away, they form a pocket between the gum and the tooth. These 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.

GINGIVITIS

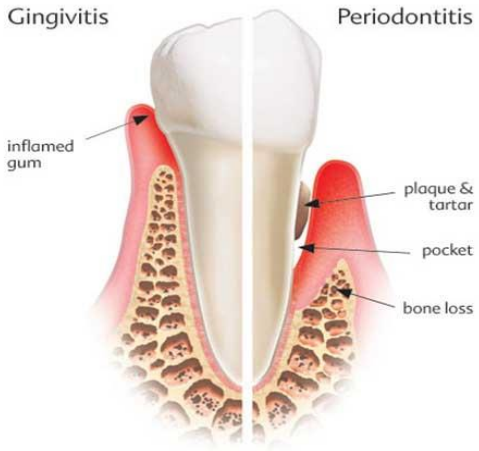
SYMPTOMS OF GINGIVITIS: **Gingivitis is characterized by reddening of the gums at the margin between the teeth and gums, swelling of the gum tissue, and bleeding with brushing and/or flossing.**

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

Dr. Iain Chapple, professor of periodontology and head of research at the Institute of Clinical Sciences of the University of Birmingham in the United Kingdom makes the following point, "It is time for a paradigm shift: we must control gingivitis and not wait until periodontitis develops. . .

There is the need to focus attention on the prevention of periodontitis and, therefore, adequately treat gingivitis, a previous stage of the disease characterized by inflammation and bleeding gums."

PERIODONTITIS

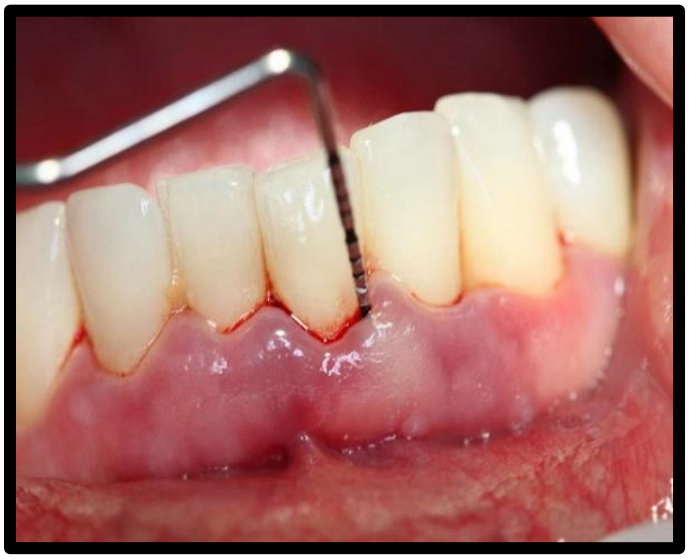


PERIODONTITIS DEFINED:

Periodontitis is a serious gum infection that damages the soft tissue and destroys the bone that supports the teeth. It is caused by the accumulation of bacteria and plaque on the teeth and gums. If left untreated, periodontitis can lead to tooth loss. Key characteristics of periodontitis include swollen, red, and bleeding gums, bad breath, receding gums, and the formation of pockets between the teeth and gums where bacteria can accumulate.

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 can resist 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 PG expresses from its surface. These chemicals are known as "gingipains"[1]. The production of gingipains is unique to PG.

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] **N. Li, Gingipains From Porphyromonas Gingivalis—Complex Domain Structures Confer Diverse Functions, *Eur J Microbiol Immunol (Bp).* 2011 Mar; 1(1): 41-58**

Gingipains have been found in multiple organs throughout the body and support the hypothesis that pathology in the oral cavity may be a factor in causing chronic illnesses.

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.

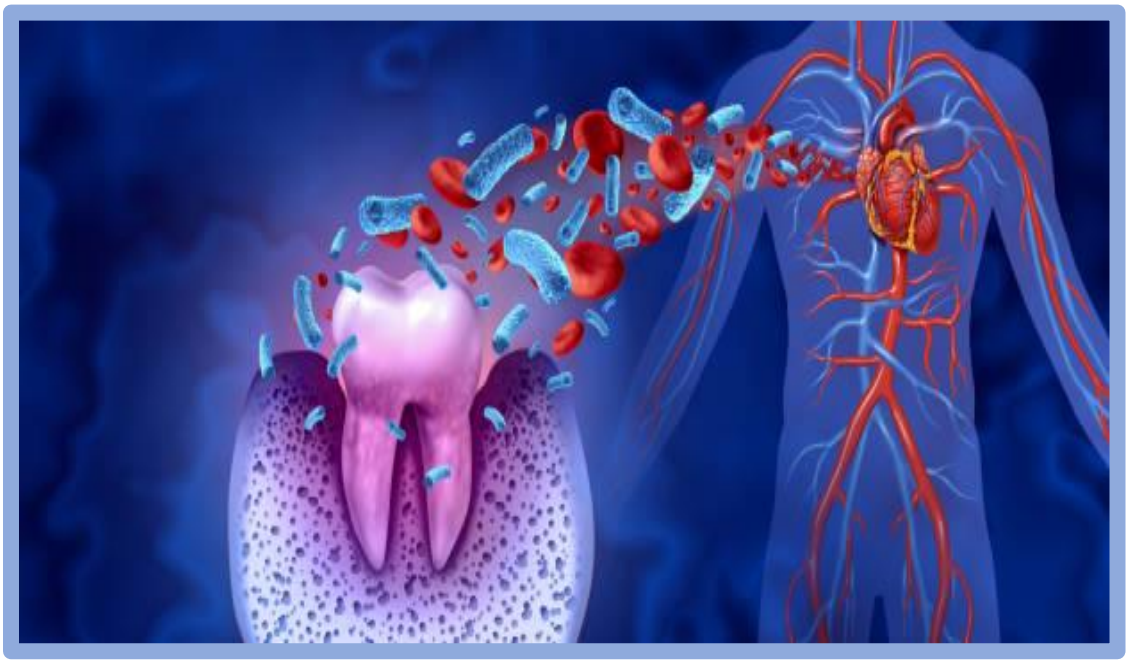
The goal of treatment is to thoroughly clean the pockets around the teeth to prevent damage to the surrounding gum tissue and bone and to remove the biofilm of plaque on the teeth and gums.

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.

Vigorous 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 and the use of mouth rinses can reduce the risk of developing teeth and gum disease.

How Oral Cavity Microbes Might 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.

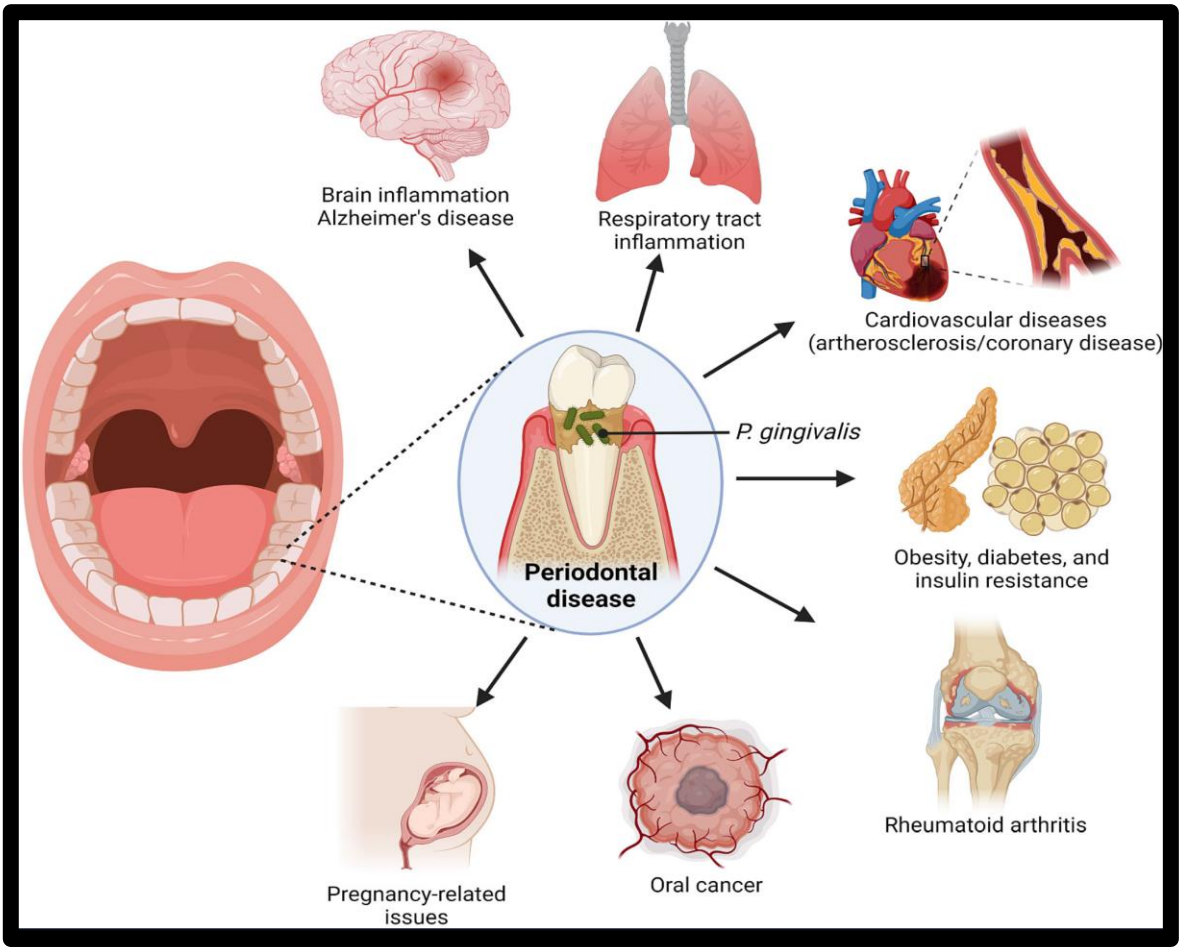
Adjacent tissues that may be affected by extensive exposure to pathogenic microorganism include Eustachian tubes that drain the middle ear, nasal cavity which drains facial sinuses, lacrimal ducts that drain tears from the eyes, salivary glands, and tonsillar tissue.

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.

ASSOCIATIONS BETWEEN PERIODONTAL DISEASE AND SYSTEMIC DISORDERS



SECTION TWENTY-FIVE

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.**

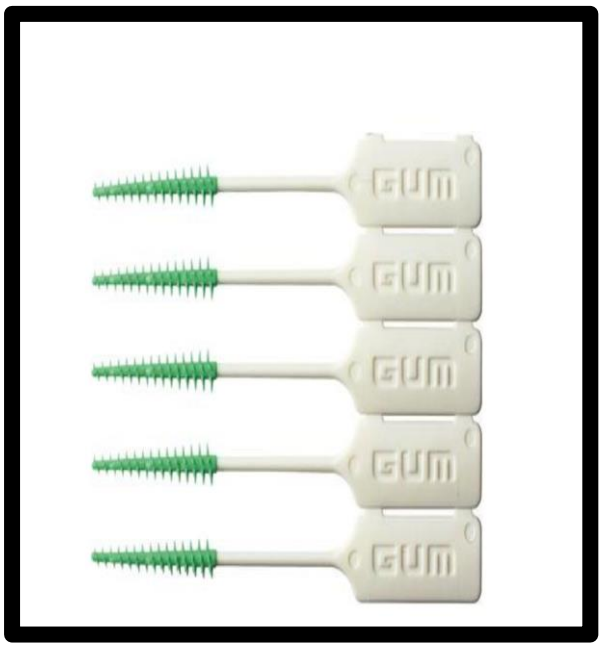
- **Change the tip of the electronic oscillating toothbrush at one-to-three-month intervals.**

- **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.**

SECTION TWENTY-SIX

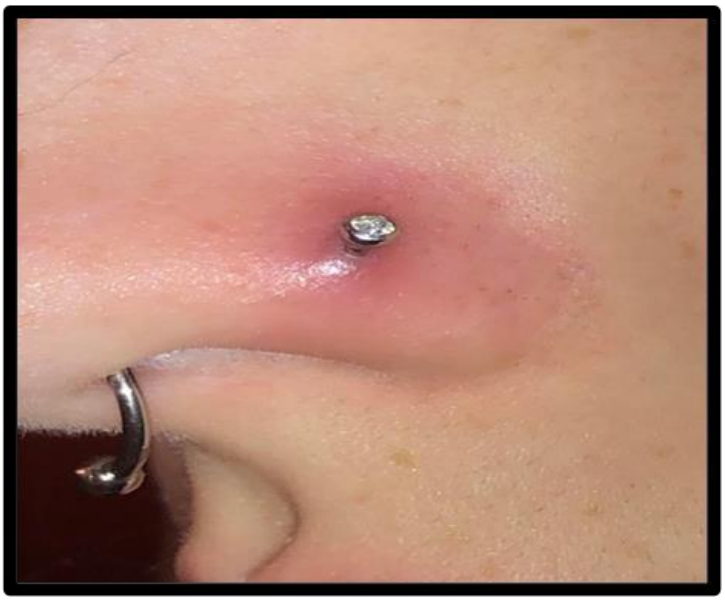
GENERAL RECOMMENDATIONS

EYES AND NOSE

- **Only use steroid containing nasal inhalers and eye drops and oral inhalers that contain corticosteroids 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.**

SECTION TWENTY-SEVEN

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] See List 4

SECTION TWENTY-EIGHT

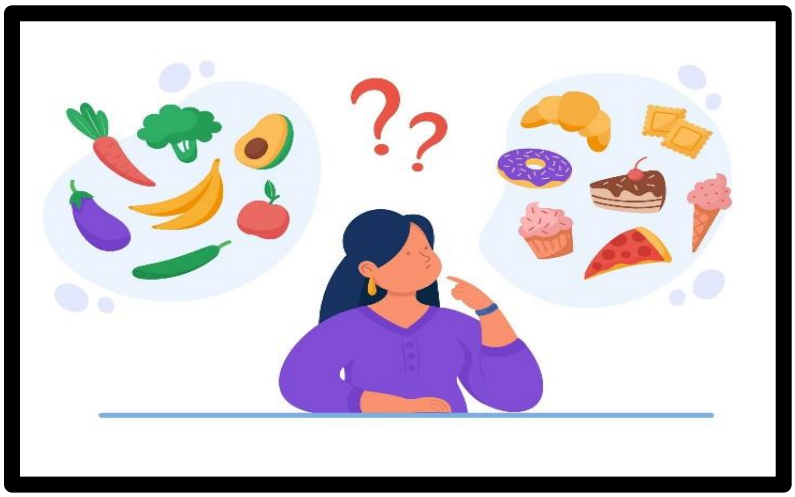
THERAPEUTIC STRATEGIES TO REHABILITATE INTESTINAL ECOSYTEMS

DIETARY MEASURES

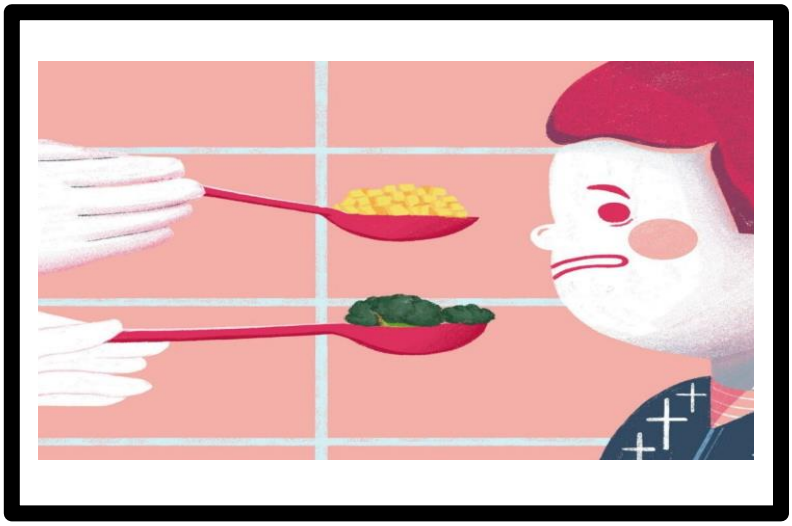
What To Eat Depends On Who You Are Feeding

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

FOCUS ON A PLANT-PREDOMINANT DIET

"An overall inspection of the literature suggests that plant-based diets with a moderate lipid content, characterized by the consumption of vegetables, fruits, whole-grain cereals, legumes or pulses, nuts, and unsaturated fats, with low-to-moderate amounts of poultry and seafood and low quantities of red meat and sugar, may offer substantial health benefits.[1]"

Vegetarian diets have been adopted for thousands of years. These diets can be defined as "any dietary pattern that excludes meat, meat-derived foods, and to varying extents, other animal products, whereas plant-based is a broader term, used to characterize dietary patterns that relies mostly on foods of nonanimal origin but does not exclude foods of animal origin.[1]"

Some of the popularized plant-based diets include the following: The Mediterranean Diet, the DASH Diet, and the Anti-Inflammatory Diet.

All of these diets focus on the intake of diverse, plant-based foods, which can lead to improved overall health, reduced risk of chronic diseases, and a balanced digestive tract microbiota.

Mediterranean Diet

The Mediterranean diet is based on the traditional dietary patterns of countries bordering the Mediterranean Sea. It is characterized by a high consumption of vegetables, fruits, whole grains, nuts, and olive oil; moderate intake of fish and poultry; and low consumption of red meat and sweets. This diet is rich in dietary fiber, antioxidants, and unsaturated fats, which are beneficial for heart health and inflammatory responses.

Research indicates that the Mediterranean diet can improve the digestive tract microbiome diversity, which is associated with better health outcomes. This diet has been linked to a reduced

risk of cardiovascular diseases, metabolic syndrome, diabetes, and certain types of cancer[2].

DASH DIET

The DASH diet is primarily aimed at reducing hypertension but has also been shown to support overall cardiovascular health[3]. Like the Mediterranean diet, it emphasizes the intake of fruits, vegetables, whole grains, and lean meat proteins, and it recommends low-fat dairy products. It also limits foods high in saturated fats and sugar.

Studies have shown that following the DASH diet can lead to improvements in blood pressure, lipid profiles, and insulin sensitivity. Furthermore, the fiber-rich foods promoted by the DASH diet support a healthy microbiome by promoting the growth of beneficial digestive tract bacteria.

Anti-Inflammatory Diet

The Anti-inflammatory diet[4] focuses on consuming foods that reduce inflammation in the body. Chronic inflammation is linked to many diseases, including heart disease, diabetes, and cancer. This diet encourages the consumption of foods rich in omega-3 fatty acids, antioxidants, and phytonutrients, which can be found in foods like fatty fish, nuts, seeds, fruits, and vegetables. By reducing the intake of processed foods, red meats, and alcohol, this diet not only helps in managing inflammation but also supports a diverse and healthy digestive tract microbiota. The anti-inflammatory properties of this diet are beneficial for reducing the symptoms of autoimmune diseases and improving overall immune function.

COMMON BENEFITS: All three diets share similarities in their food composition that contribute to their health benefits. The high fiber content from fruits, vegetables, and whole grains in these diets supports digestive tract health by promoting the growth of beneficial microbes. These microbes play a crucial role in nutrient absorption, immune function, and even the

regulation of mood through the digestive tract-brain axis. Additionally, the focus on plant-based foods and reduction in processed and high-fat foods help maintain a healthy weight, reduce inflammation, and decrease the risk of chronic diseases.

CONCLUSION: The Mediterranean diet, DASH diet, and Anti-inflammatory diets along with varying forms of vegetarian diets not only promote a healthy body by reducing the risk of chronic diseases but also support a healthy microbiome, which is vital for overall well-being. Adopting any of these diets can lead to significant health benefits and contribute to a balanced and diverse digestive tract microbiota, enhancing both physical and mental health.

[1] **Yannakoulia, M. Nutrition in Medicine—Diets, *N. Engl J Med,* 2024; 390:2098-106.**

[2] **E. Estruch, et al., Primary Prevention of Cardiovascular Disease with a Mediterranean Diet, *The New England Journal of Medicine*, vol. 368, no. 14, pp. 1279-1290, 2013.**

[3] **L.J. Appel, et al., A Clinical Trial of the Effects of Dietary Patterns on Blood Pressure, *The New England Journal of Medicine*, vol. 336, no. 16, pp. 1117-1124, 1997.**

[4] **P.C. Calder, et al., Anti-inflammatory effects of omega-3 fatty acids in relation to cardiovascular disease, *Prostaglandins, Leukotrienes and Essential Fatty Acids*, vol. 135, pp. 1-10, 2018.**

SECTION TWENTY-NINE

VARIETY IS THE SPICE OF LIFE AND THE WAY TO FEED YOUR MICROBES

The advice to eat a high-fiber diet should be expanded to include instructions that the diet must include a variety of fiber sources and that the fiber sources must be able to reach the portions of the digestive tract where beneficial microbes exist capable of fermenting the fiber to produce chemicals that benefit the body.

Key points to consider, therefore, include the following:

1. **Diversity of Fiber Sources: Consuming a variety of fiber types, such as inulin, pectin, cellulose, and hemicellulose, nourishes different microbial communities. (See Section: Commercially Available Products that Act as Prebiotics)**

   Each type of fiber is fermented by specific microbes, leading to the production of different beneficial metabolites like short-chain fatty acids (SCFAs).[1-2]

2. **Fermentable Carbohydrates: The diet should include a range of fermentable carbohydrates (prebiotics) like fructans (inulin),**

oligosaccharides (found in legumes and certain vegetables), and resistant starches (present in foods like "greenish" bananas and cooked-and-cooled potatoes) to support the growth of various beneficial microbes such as *Bifidobacteria* and *Lactobacilli*. (See the section: Commercially Available Products that Act as Prebiotics)

3. **Personalized Nutrition:** **The gut microbiome varies significantly among individuals, so a personalized approach to fiber intake is required. This involves adjusting fiber types and amounts based on individual digestive responses and gut microbiota composition.**

4. **Functional Benefits:** **Different fibers provide different health benefits. For example, inulin and fructo-oligosaccharides (FOS) are known for their ability to promote the growth of *Bifidobacteria*, which can enhance gut immune function. On the other hand, fibers like pectin and guar gum help in stimulating hormone-producing cells that control hunger, satiety and insulin secretions.**

5. **Broad Spectrum Approach: Eating a wide variety of dietary fibers can reduce the risks associated with focusing on a single fiber type or falling into a pattern of eating a select few fiber containing items repeatedly. The broad-spectrum approach improves the supply of substrates for a diverse microbiota, promoting resilience and stability within the gut ecosystem.**

Refining the advice on what it means to eat a high fiber diet aligns with recent research emphasizing the importance of dietary diversity for optimal gut metabolism.

[1] Oliphant K., Macronutrient Metabolism By The Human Gut Microbiome: Major Fermentation By-Products And Their Impact On Host Health, *Microbiome* volume 7, Article number: 91 (2019).

[2] Sidhu, S., Effect of Plant-Based Diets on Gut Microbiota: A Systematic Review of Interventional Studies, *Nutrients* 2023, *15*(6)1510; https://doi.org/10.3390/nu15061510

SECTION THIRTY

THE DO'S AND DON'TS FOR ACHIEVING INTESTINAL WELL-BEING

AVOID ULTRA-PROCESSED FOODS

Ultra-processed foods are industrially formulated food products made entirely or mostly from substances extracted from foods, derived from food constituents, or synthesized in laboratories from food substrates or other organic sources

such as flavor enhancers, colorants, and additives used to impart sensory properties. These foods typically contain little or no whole foods and are characterized by high levels of sugar, fat, salt, and chemical additives. Examples include sugary drinks, packaged snacks, reconstituted meat products, and pre-prepared frozen meals.

Ultra-processed foods are designed to be convenient, highly palatable, and shelf-stable, often at the expense of nutritional quality. Studies suggest that this group of food increases the risk of intestinal inflammation and activation of the immune system.[1]

[1] Maki, K.I., Ultraprocessed Foods: Increasing Inflammation And Immune Dysregulation? *Nat Rev Immunol* (2024). https://doi.org/10.1038/s41577-024-01049-x

AVOID TOXINS AND CONTAMINANTS IN WATER

DRINK DISTILLED WATER

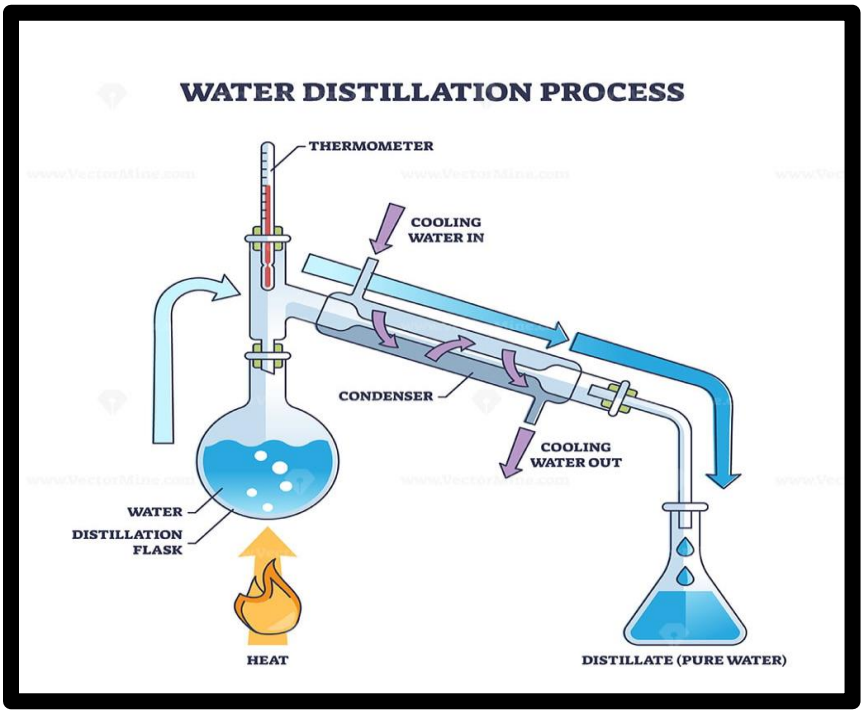
Distilled water is prepared by boiling water and condensing the steam. Any chemical element that has a boiling point of more than 212^{o} (F) does not rise in the steam. Over 90% of all elements that are known to exist have boiling points over 212^{O} (F) and, therefore, will not come to a boil and create steam at 212^{o} (F). These elements remain in the water distillation boiling chamber. The other 10% of elements that have boiling points less than 212^{o}, rise in steam. Almost all of them are

gases which are vented out before the steam is condensed to form distilled water.

Distilled water is often further treated by passing it through activated charcoal and ozone.

Activated charcoal is effective at removing volatile organic compounds (VOCs) that might not be removed by the distillation process alone.

Ozone is a powerful oxidizing agent that can effectively kill bacteria, viruses, and other pathogenic organisms that might remain after distillation. Ozone can also break down various organic and inorganic contaminants including some that activated charcoal might not remove.



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 common misconception that drinking distilled water is unhealthy and that it depletes the body of minerals. This notion lacks scientific backing.

<u>Myth Debunked:</u> The claim that distilled water depletes the body of minerals is unfounded. While it is true that distilled water lacks minerals found in other types of water, the human body does not rely on water as its primary source of minerals.

<u>Mineral Intake</u>: Dietary minerals should come predominantly from the foods that are consumed. The idea that drinking water is a significant source of minerals is misleading. For example, to achieve a daily intake of 2300 milligrams of sodium per day from water, i.e, the 2020-2025 Dietary Guideline for Americans, one would have to drink an impractical and unhealthy amount of water—dozens of glasses of water.

<u>Health and Safety</u>: Numerous health experts and organizations confirm that distilled water is safe to drink. Individuals may find that distilled water lacks taste, or tastes "flat". This absence of taste is due to the absence of minerals that individuals have become used to when consuming other forms of water.

AVOID 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 digestive tract 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 digestive tract." As shown before, increased permeability of the digestive tract lining facilitates translocation of microorganisms, toxins, and food antigens into the body. The flow of these substances from the digestive tract through a permeable digestive tract 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. All recent evidence points to the conclusion that alcohol ingestion should be totally avoided when possible. There are no defined safe limits of 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".[8] The report points out that some studies that previously showed cardiovascular benefits from drinking alcohol 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 does not 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.[8]"

[1] Day, A. Digestive Tract 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. T*oxicology 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] B White, The Impact Of Alcohol In Inflammatory Bowel Diseases, *Inflammatory Bowel Diseases*, vol 28, 3: March 2022, 466-473

[7] K. J. Biddinger et al. JAMA Netw Open. DOI:10.1001/jamanetworkopen.2022.384

[8] World Heath Federation, (2022) Policy Brief—The Impact of Alcohol Consumption on Cardiovascular Health: Myths and Measures. https://world-heart-federation.org/wp-content/uploads/WHF-Policy-Brief-Alcohol.pdf

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 the following:

- **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**

Studies confirm that exposure to nicotine-free e-cigarette aerosols causes epithelial barrier dysfunction in the human gut. They demonstrate that the dysfunction is associated with the induction of pro-inflammatory cytokines.[3]

[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.**

[3] **Sharma, A. E-cigarettes Compromise the Gut Barrier and Trigger Inflammation, IScience, January 05, 2021 DOI:https://doi.org/10.1016/j.isci.2021.102035**

AVOID RECREATIONAL DRUGS

Avoid recreational drugs. Recreational drugs are substances taken for pleasure rather than for medical reasons. They are used primarily to alter one's mood, perception, or consciousness. Recreational drugs have been found to alter the intestinal microbiome.[1-5]

[1] Cuesto, S., Digestive Tract 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 Digestive Tract Microbiota And Intestinal Mucosal Barrier Integrity In Mice With Heroin Dependence, *Front. Nutr,* (8) Nov 4, 2021.

[3] Baslam, A., Modulation Of Digestive Tract 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-Digestive Tract Axis, *Front. Med*, 2022; 9: 783121, May 10, 2022.

[5] Inserra, A., Effects Of Repeated Lysergic Acid Diethylamide On The Mouse Brain Endocannabinoidome And Digestive Tract Microbiome. *Br J Pharmacol*. 2023 Mar; 180 (6): 721-739.

MINIMIZE INHALATION OF AIR POLLUTANTS

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 digestive tract.[5]

The digestive 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 digestive 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 digestive tract microbiome.[11]

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

The digestive 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 Interstitial Uptake And Subsequent Re-Entrainment 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 Digestive Tract Microbiota At 6-Months Of Age, *Digestive tract Microbes*, 14:1, 2022**

AVOID
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 digestive tract microbes is associated with these sleep deprivation induced diseases.[2]

[1] Ali, T. Sleep Disturbances In Inflammatory Bowel Disease. *Inflamm. Bowel Dis*. 2014, 20, 1986-1995

[2] Sun, J. Sleep Deprivation and Digestive Tract Microbiota Dysbiosis: Current Understandings and Implications, *Int J Mol Sci.,* 2023 Jun; 24 (11): 9603

AVOID SELF MEDICATING WITH MULTIPLE UNREGULATED DRUGS[1]

HYPER-POLYPHARMACY

The word “hyper-polypharmacy” is a portmanteau combining “hyper” meaning excessive and “polypharmacy” which refers to the use of multiple medications, usually ten or more. The term emphasizes that extreme numbers of medications present risks including adverse drug reactions, alteration of the gut microbe populations, medication errors and greater health costs.

Many medications taken are sold as unregulated dietary supplements. The supplement industry operates under different regulatory conditions compared to prescription medications. This leads to significant challenges in ensuring the safety and efficacy of these products.

Unlike pharmaceuticals, which must undergo rigorous testing and approval processes by the U.S. Food and Drug Administration (FDA) before they can be marketed, over-the-counter supplements do not require pre-market approval from the FDA. This means that the responsibility for the safety and efficacy of dietary supplements lies primarily with the manufacturers and not with the regulatory agency.[1]

Many dietary supplements are manufactured overseas, where regulations and manufacturing standards can vary widely. In some countries, the lack of stringent regulatory oversight and quality assurance measures can result in products that are of questionable quality and may even contain harmful contaminants or not contain the advertised ingredients at all.[2]

This situation is compounded by the fact that the FDA's authority over dietary supplements is limited to post-market regulation, which means the agency can only act against a supplement if it is proven to be unsafe after it has already been sold to consumers.[3]

The minimal oversight by the FDA in this area leads to a market flooded with products with claims related to health that are not always substantiated by scientific evidence. Rarely are these

claims supported by robust scientific studies, and the results of those studies that are conducted are often not widely published or peer reviewed as those concerning prescription drugs.

This lack of transparency and accountability can put consumers at risk, who may believe they are consuming safe and effective products when this may not be the case.

Given these concerns, it is critical for consumers to remain skeptical of bold claims related to health made by dietary supplement manufacturers.

ADVERSE DRUG REACTIONS (ADRS): One of the most significant risks associated with hyperpolypharmacy is the heightened potential for adverse drug reactions (ADRs). The interaction between multiple medications (drug-drug interactions) can lead to unpredictable side effects where one drug may inhibit or enhance the metabolism of another, reducing efficacy or increasing toxicity.

A healthcare professional should be consulted before using any new dietary supplement.

OTHER RISKS OF HYPER-POLYPHARMACY

POLYPHARMACY CASCADE: The use of multiple medications (prescription and non-prescription) can trigger a polypharmacy cascade, wherein the side effects of one drug are mistakenly interpreted as symptoms of another condition, leading to

further medication prescriptions. This vicious cycle can exacerbate health issues and complicate treatment regimens.

COGNITIVE IMPAIRMENT: The cognitive burden imposed by managing numerous medications can lead to medication errors, non-adherence, and cognitive impairment. This, in turn, increases the risk of adverse outcomes such as falls, hospitalizations, and diminished quality of life.

[1] **U.S. Food and Drug Administration, "Dietary Supplement Products & Ingredients."**

[2] **T. E. Gundersen, Challenges In The Dietary Supplement Industry: A Review, *Journal of Dietary Supplements*, 2020.**

[3] **Office of Dietary Supplements - National Institutes of Health, "Regulations Governing Dietary Supplements."**

EFFECT ON THE MICROBIOME: Many medications, including antibiotics, antacids, and psychotropic medications, can disrupt the gut microbe population, reducing beneficial bacteria and allowing pathogenic bacteria to thrive.

ALTERATION OF MICROBE METABOLISM: Changes in gut microbes can affect the metabolism of medications, leading to unpredictable drug levels and potential toxicity or therapeutic failures.

AVOID DRINKING UNPASTEURIZED MILK OR INGESTING PRODUCTS MADE FROM UNPASTURIZED MILK

The following excerpt comes from the Food and Drug Administration letter to State, Local, and Tribal Health Partners . . . dated May 6, 2024.

> "***Based on the limited research and information available, we do not know at this time if the HPAI H5N1 virus can be transmitted to humans through consumption of raw milk and products made from raw milk from infected cows. However, exposures on affected farms are associated with three documented cases of H5N1 illness in dairy workers.***

While the introduction into interstate commerce of raw milk for human consumption is prohibited under the FDA's authority, we know that a number of states permit the intrastate sale of raw milk for human consumption, with varying structures and requirements to these state programs.

Because of our concerns related to HPAI H5N1 virus in raw milk, we are providing the following recommendations for states as we continue to work together to address this novel issue:

1. ***Distribute messaging to the public about the health risks of consuming raw milk and raw milk products. Health risks include illness, miscarriages, stillbirths, kidney failure and death. (source: Food Safety and Raw Milk/ FDA)***

2. ***Monitor dairy cattle herds for signs of illness that would indicate infection with the HPAI H5N1 virus.***

3. ***Producers should continue to discard milk, with suitable protocols, from symptomatic cows.***

4. ***Any raw milk or raw milk products from exposed cattle that are fed to calves or any other animals should be heat-treated or pasteurized."***

Based on FDA advice, the consumption of raw milk and products made from raw milk should be restricted.

All Milk And Milk Products Should Be Pasteurized!

If raw milk products undergo pasteurization after the fermentation process, the product will no longer contain live organisms.

Since probiotics are live microorganisms that confer health benefits, the heating process during pasteurization will kill beneficial probiotic bacteria.

However, milk products may have live probiotic cultures added after the pasteurization process. In those cases, the milk product will still contain live organisms and can be considered a probiotic.

The label of such a product will contain a phrase like "contains live and active cultures" or will list specific probiotic strains in the ingredients.

GET 20-30 MINUTES OF MODERATE PHYSICAL ACTIVITY AT LEAST FIVE 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 digestive tract microbiome through various mechanisms including moderation of the intestinal immune system, reduction in

intestinal transit time, alteration in blood flow through the digestive tract, alterations in intestinal permeability, and interaction with bile metabolism.

A recent study[5] using accelerometer-based physical activity suggests that benefits of physical activity may be mediated by the intestinal microbiome.

Most 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 estimates of physical activity compared to self-reporting data.

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

The findings of the study suggest that physical activity can modify the digestive tract 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 Digestive tract 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 Digestive Tract Microbial Diversity*. Digestive tract*, 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, *Digestive tract*, vol. 48 (3), 435-439, 2001**

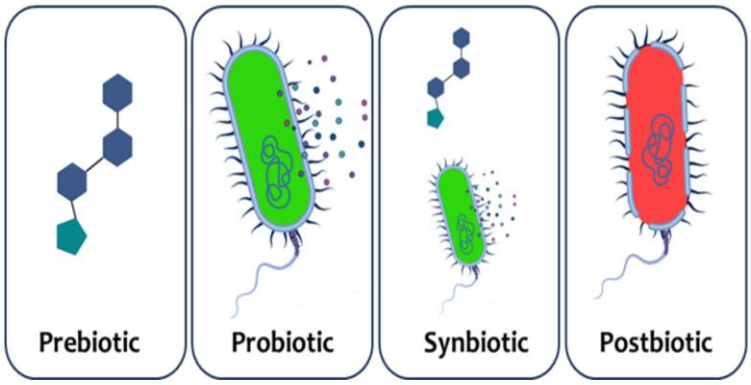
[5] **Holzhausen, E. Assessing the Relationship Between Physical Activity and The Gut Microbiome In a Large, Population-Based Sample of Wisconsin Adults, PLOS One https://doi.org/10.1371/journal.pone.0276684**

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.**

CONSIDER ADDING "BIOTICS" BUT ONLY WITH PROFESSIONAL GUIDANCE



Previous sections of the monograph have illustrated how much the human body relies upon beneficial microbes for intestinal well-being and overall health. Emphasis has been placed not only on the number and diversity of the microbes but on the functionality of the microorganisms. Also noted previously is the importance of having beneficial microorganisms in the digestive ecosystem thrive in order to benefit the human host.

Prebiotics, probiotics, synbiotics, and postbiotics have been promoted as potential products that might benefit the intestinal ecosystems. Each one is described briefly.

PROBIOTICS

Probiotics, as defined by the World Health Organization, are live microorganisms that, when ingested in adequate amounts, may confer health benefits. Probiotics are often administered to restore, replace, replenish, and "re-wild" the microbial population in intestinal ecosystems. Here are four primary ways to obtain probiotics:

I. Fermented Food Items

Fermented foods are a natural source of probiotics which contain live microorganisms. Below is a partial list of commonly available fermented food items that contain probiotics:

1. Kefir milk (pasteurized)

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 is 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 like 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. Yogurt (pasteurized)

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 is made from the milk of animals that have been grass-fed.**
- **It is organic.**
- **It is pasteurized.**

10. 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 transforms the apple cider to vinegar.

11. Kvass

Kvass is a fermented beverage that has a taste like 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.

12. Coconut kefir (pasteurized)

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

13. Yakult (pasteurized)

Yakult is a probiotic drink that originated in Japan. It contains a high concentration of a unique strain of bacteria known as *Lactobacillus casei Shirota.* The specific strain is

designed to survive passage through the stomach and reach the intestines alive. It is typically made with skim milk powder, glucose-fructose syrup, and natural flavoring. It comes in two ounce bottles and can be found in the dairy case of most grocery stores.

II. Commercially Available Sources

Probiotics are available as dietary supplements. These products do not have to meet strict regulatory standards and are considered food supplements rather than pharmaceuticals. As such, they are not required to provide direct and consistent proof of effectiveness. It is advisable to consult a medical care provider before using these products.

III. Fecal Microbial Transplant (FMT)

FMT involves obtaining fecal organisms from a healthy donor and transplanting the microbes into a recipient with an illness thought to benefit from the transplant. This method has been life-saving in cases like *Clostridium difficile* colitis when the colitis has been refractory to other therapy.

The transplant can be done by instilling a slurry of the donor's organisms into the colon of the colitis sufferer at the time of a colonoscopy or by oral ingestion of capsules that contain the donor's organisms.

IV. Autologous Transplant

An autologous transplant is a variant of FMT that involves the donor and recipient being the same individual. The person self-donates and preserves fecal material for future use if the donor becomes ill. Fecal microbe banks collect and preserve stool specimens for such procedures.

There are several existing microbe banks. They include the following:

OpenBiome: A U.S.-based fecal microbe bank providing screened and processed samples for clinical use.

Rebiotix: A company developing microbiota-based therapeutics, including FMTs.

C-IBD Fecal Microbial Transplant Bank: Located in the Netherlands, this bank provides screened donor stool for clinical applications.

Recommendations and Considerations

In 2020, the American Gastroenterology Association published recommendations regarding the use of probiotics in select conditions[1]. The evidence for the use of probiotics in most conditions was poor, highlighting the importance of consulting a knowledgeable medical care provider to determine the appropriate strain or strains of microbes to include in a probiotic if one is to be used.[2,3]

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PREBIOTICS

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, bovine milk fats, selected amino acids and human breast milk oligosaccharides. *(*See the section: Resistant Starches*)* and *(*See the section: Human Milk Oligosaccharides.)

Several studies[1-3] have also shown the beneficial effects for adults taking human breast milk oligosaccharides that have been synthesized in the laboratory. (See the section: Human Milk Oligosaccharides).

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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

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 do not interfere with other beneficial microbes.**

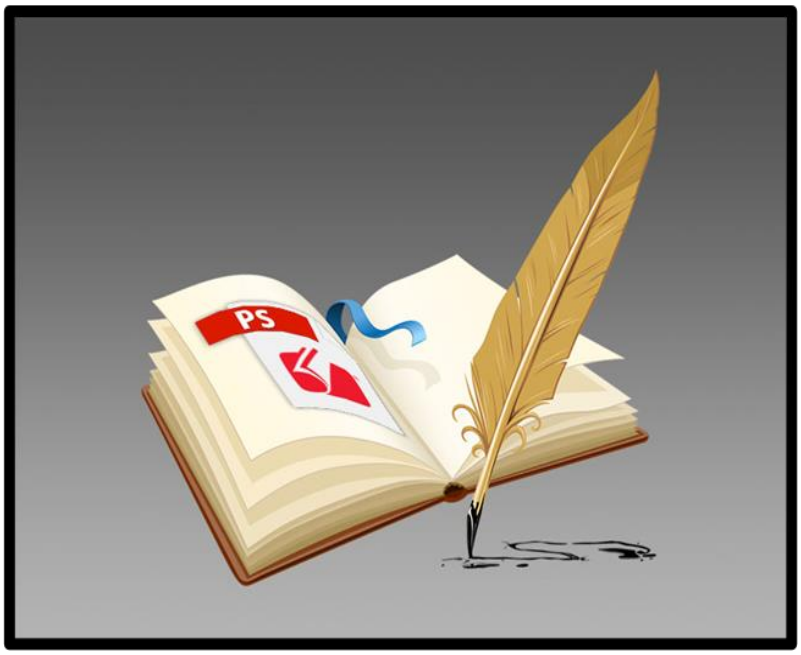
In theory, the 100 billion+ microbes that are swallowed every day from the mouth and are destroyed by gastric acid and proteolytic enzymes in the stomach become postbiotics.

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.

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.

SECTION THIRTY-ONE

A LOOK AT THE PAST
AND
A VIEW OF THE FUTURE

The Human-Microbe Pact

From the moment humans emerged as a distinct species, we forged an intimate and indispensable pact with our microbial counterparts. This symbiotic relationship was not merely a

coexistence but a deeply intertwined partnership where microbes undertook vast responsibilities of functions that humans were incapable of performing and which were essential for human survival. Some of those responsibilities were related to digestion, immunity, and protection. In return, humans provided their beneficial microorganisms with a safe habitat and a more reliable supply of nutrients.

As humans have progressed technologically and industrially, the commitment to this ancient agreement has waned, potentially charting a new path that threatens human extinction.

The Microbial Pact: Foundations of Human Health

As pointed out repeatedly in the monograph, microbes have been pivotal in performing functions that humans cannot accomplish independently. They play a critical role in breaking down complex dietary fibers into short-chain fatty acids that nourish human cells and regulate the human immune responses among other things.

The Betrayal: Modern Lifestyle and Diet

With the advent of industrialization and the subsequent changes in agricultural and food processing practices, the balance between microbes and humans has been severely disrupted. Modern diets, characterized by high sugar, refined carbohydrates, and processed foods have had a major influence on the viability of the microbe population. These foods often lack necessary fibers and are laden with substances harmful to the intestinal microbe population

including things such as antimicrobials, pesticides, herbicides, and harmful additives.

As a result, the nutrients that our beneficial microbes depend upon remain locked away or entirely absent from the human diet. The widespread use of antibiotics, though life-saving, has also indiscriminately decimated large number of beneficial bacterial populations.

These disruptions have led to a decline in microbial diversity, density and functionality, impairing their ability to perform critical functions.

Consequences of Neglect: A Health Crisis

Scientists suspect that the neglect and damage to beneficial microbes may be a contributing factor to the rising prevalence of chronic diseases. It is hypothesized that with weakened microbial populations, human bodies have become more susceptible to deficiencies and systemic dysfunctions and that the intestinal barrier, once fortified by a healthy microbiome, has become more permeable, allowing toxins and pathogens to infiltrate the bloodstream—a condition colloquially referred to as "leaky gut."

This increased permeability has been felt to contribute to chronic inflammation and suspected as a link to a host of modern ailments, including autoimmune diseases, allergies, and metabolic disorders like obesity and diabetes.

The Crossroads: Restoration or Ruin

The pivotal question facing humanity is whether we can restore this symbiotic relationship with our microbial partners.

The task appears to be daunting but not insurmountable. The monograph has proposed a number of modalities that may rejuvenate the microbiome which rely in large part on dietary shifts towards fiber-rich nutrients, avoidance of toxins and drugs that disrupt the microbe population, minimizing the ingestion of ultra-processed foods, finding clean sources of air and water, reducing the overuse of antibiotics, improving oral hygiene measures, and finding suitable probiotics and prebiotics to support microbial health.

Understanding the complex interplay between human lifestyles, environment, and microbial communities has been shown to be critical and one which has been emphasized throughout the monograph.

A Call to Action--Charting Our Future: The Human-Microbe Pact

The path we tread is fraught with the peril of continued neglect and disruption of our microbial allies. Yet, it is also illuminated by the possibility of renewal and restoration.

Recommitting to the ancient pact forged with our microbial significant others may not be merely a matter of preserving human health but ensuring the survival of our species.

LIST 1

FOODS CONTAINING FERMENTABLE FIBER THAT FUNCTION AS NATURALLY OCCURRING PREBIOTICS

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

- Almonds
- 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

Examples Of Commercially Available Compounds That Function As Prebiotics

The following oligosaccharides are widely used in the food and supplement industries for their beneficial effects on gut health and their ability to promote the growth of beneficial gut bacteria.

- **Arabinooligosaccharides (AOS)**
- **Fructooligosaccharides (FOS)**
- **Galactooligosaccharides (GOS)**
- **Isomaltooligosaccharides (IMO)**
- **Mannooligosaccharides (MOS)**
- **Pectin-Derived Oligosaccharides (POS)**
- **Raffinose Family Oligosaccharides (RFOs)**
- **Xylooligosaccharides (XOS)**
- **Inulin**
- **Lactulose**
- **Maltodextrin**
- **Soy Oligosaccharides**
- **Wheat dextrin**

- **Acacia gum (gum arabic) – Acacia gum is sourced from the sap of the Acacia tree and is rich in complex polysaccharides.**

- **Agave inulin – Agave inulin is derived from the blue agave plant (*Agave tequilana*) and other agave species, which are succulent plants native to Mexico. It is classified as a type of fructan.* Agave inulin acts as a prebiotic, promoting the growth of beneficial gut bacteria such as Bifidobacteria and Lactobacilli. This supports overall gut health and can improve digestion.**

- **A fructan is a type of sugar composed of fructose molecules linked together. Fructans are a category of polysaccharides. They include inulin and other fructose polymers. The basic structure for fructans can vary, but they generally consist of chains of fructose units that can be either linear or branched. Fructans are found in various plants including chicory, agave, onions and wheat. They are not digested by human digestive enzymes but are fermented by gut microorganisms to produce short chain fatty acids. (Sidhu, S., Effect of plant-based diets on gut microbiota: a systemic review of interventional studies, *Nutrients* 2023, 15 (6), 1510; DOI.org/10.3390/nu 15061510.)**

- **Chicory Root Inulin - A fructan commonly extracted from the chicory root plant (*Cichorium intybus*). Chicory root inulin is composed primarily of fructose units linked together, forming a long-chain polysaccharide.**

  Both chicory root inulin and agave inulin are beneficial types of soluble fiber with prebiotic properties. The primary differences lie in their sources, degrees of polymerization, and variations in functional properties.

  The degree of polymerization (DP) of agave inulin typically ranges from 2 to 60, with an average DP around 25-30. The degree of polymerization (DP) of chicory root inulin averages 10-12.

- **Arabinoxylan - A type of hemicellulose found in cereal grains like wheat, barley, rye, corn and maize. Arabinoxylans have prebiotic properties, promoting the growth of beneficial gut**

bacteria such as Bifidobacteria and Lactobacilli. It can be found in the commonly used laxative, Metamucil.®

- **Beta-glucans - Found in the cell walls of certain grains, fungi, yeasts, bacteria and algae. Beta-glucans are particularly abundant in cereal grains like oats and barley. Shiitake, maitake and reishi mushrooms are fungal souces of beta-glucans as is baker's yeast (*Saccharomyces cerevisiae*).**

- **Wheat dextrins- wheat dextrins are derived from the chemical break down of wheat starch. It is commonly used to promote regular bowel movements. A common brand of wheat dextrins is Benefiber®. Since wheat dextrins are derived from wheat, they may contain gluten. Individuals with celiac disease or severe gluten sensitivity should consult a healthcare provider before using wheat dextrins.**

- **Fructooligosaccharides (FOS) – Fructooligosaccharides are short fructose chains found in various fruits and vegetables including bananas, onions, garlic, leeks, asparagus, chickory root and Jerusalem artichokes.**

- **FOS consists of fructose molecules linked together, typically ranging from 2 to 10 fructose units. FOS stimulate the growth and activity of beneficial gut bacteria, such as Bifidobacteria and Lactobacilli. These bacteria ferment FOS, producing short-chain fatty acids (SCFAs) which are of benefit to the human host.**

- **Galactooligosaccharides** (GOS) - Composed of short chains of galactose molecules. GOS is commonly produced commercially from the sugar, lactose.

  GOS consists of short chains of galactose molecules. The degree of polymerization typically ranges from 2 to 8 sugar units. They are naturally found in human breast milk and are also present in smaller amounts in dairy products. They selectively stimulate the growth and activity of beneficial gut bacteria, such as Bifidobacteria and Lactobacilli.

- **Isomaltooligosaccharides** (IMO) – IMOs are glucose molecules linked with α-(1→6) glycosidic bonds; found in fermented foods and honey.

- **Lactulose** - Lactulose is a prebiotic and can be used for treating constipation and advanced forms of liver disease. It is not a naturally occurring substance and has to be manufactured pharmaceutically.

- **Mannan-oligosaccharides (MOS)** - Derived from the yeast cell wall. Mannooligosaccharides (MOS) are a type of oligosaccharide that consist of short chains of mannose molecules. MOS can be found in certain plants, yeasts, and fungi. They are derived from the hydrolysis of mannan, a polysaccharide found in the cell walls of these organisms. MOS act as prebiotics, substances that promote the growth of beneficial bacteria in the gut, such as Bifidobacteria and Lactobacilli.

- **Pectin – Pectin is found in the cell walls of plants. It is particularly abundant in apples, citrus fruits (oranges and lemons) and berries (strawberries, raspberries and grapes).**

- **Xylooligosaccharides (XOS) – XOS is made from xylose units, typically extracted from corncob or hardwoods. Xylooligosaccharides (XOS) are a type of oligosaccharide composed of xylose units, a simple sugar derived from the hemicellulose fraction of plant cell walls.**

List 3

Food Items That Contain Resistant Starches

Cooked and cooled poatoes[1]

- Cooked and then cooled white potatoes
- Cooked and then cooled sweet potatoes

Green bananas[2]

- Underripe or green bananas

Plantains[3]

- Green or underripe plantains

Cooked and cooled rice[4]

- Cooked and then cooled white rice
- Cooked and then cooled brown rice

Cooked and cooled legumes[5]

- **Lentils**
- **Chickpeas**
- **Black beans**
- **Kidney beans**

Cooked and cooled pasta[6]

- **Cooked and then cooled pasta**

Oats[7]

- **Rolled oats**
- **Steel-cut oats**

Barley[8]

- **Pearl barley**
- **Hulled barley**

Cornmeal[9]

- **Cornmeal**

Cooked and cooled millet[10]

- **Cooked and then cooled millet**

Cooked and cooled quinoa[11]

- **Cooked and then cooled quinoa**

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LIST 4

WATER CONTENT OF COMMON FOODS AND BEVERAGES

(Source: U.S. Department of Agriculture (USDA), FoodData Central)

1. **Cucumber: 96% water**
2. **Lettuce (Iceberg): 95% water**
3. **Celery: 95% water**
4. **Tomato: 94% water**
5. **Zucchini: 94% water**
6. **Watermelon: 92% water**
7. **Strawberries: 91% water**

8. **Cantaloupe: 90% water**
9. **Peach: 89% water**
10. **Orange: 86% water**
11. **Pineapple: 86% water**
12. **Broccoli: 90% water**
13. **Spinach: 91% water**
14. **Carrots: 88% water**
15. **Apple: 86% water**
16. **Grapefruit: 88% water**
17. **Milk (Whole): 87% water**
18. **Yogurt: 85% water**
19. **Coffee: 99% water**
20. **Tea: 99% water**
21. **Beer: 90-95% water**
22. **Soft drinks: 89% water**
23. **Soup (Chicken noodle): 90% water**

TABLE ONE

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FACTORS THAT INFLUENCE THE MICROBIOME

ACTIVITY-EXERCISE	DIET	ALCOHOL
AGE	GENDER	ETHNICITY
ANTIBIOTICS USAGE	IMMUNITY	DEPRESSION
BILE SALTS-TYPE AND AMOUNT	GRAVITY	GENES
BODY TEMPERATURE	CHEMO-RADIATION	VITAMIN DEFICIENCIES
DIAGNOSTIC RADIATION	STARVATION	STRESS
FASTING	IMMUNIZATIONS	GEOGRAPHIC LOCALE
DIGESTIVE TRACT ENZYMES	SLEEP DEPRIVATION	CIRCADIAN RHYTHMS

HORMONES	AIR POLLUTANTS	PETS
INHALED GASES	AMBIENT TEMPERATURE	SEA LEVEL ALTITUDE
MENOPAUSE	EDUCATION LEVEL	SIBLINGS
MENSTRUATION	CULTURAL/RELIGIOUS PRACTICES	MATURITY AT BIRTH-- PREMATURITY
MODE OF BIRTH NATURAL vs C-SECT	INFECTIONS	TOXINS
OCCUPATIONAL EXPOSURES	NUTRACEUTICALS	DIGESTIVE TRACT MOTILITY
PHARMACEUTICALS	BODY TRAUMA	AMBIENT RADIATION
SURGERIES	RECREATIONAL DRUGS	FOOD ADDITIVES
TOBACCO	HYDRATION	ORAL-DENTAL PATHOLOGY
WATER CONTAMINANTS	DIGESTIVE TRACT-BRAIN AXIS	BILE ACIDS

ARTIFICIAL SWEETENERS	BOTTLE vs BREAST FED INFANTS	ULTRA-PROCESSED FOOD

MICROBIOME STUDY GLOSSARY

UNRAVELING THE MYSTERIES OF MICROBIAL FUNCTION AND INTERACTION WITH THE BODY AND ENVIRONMENT

The study of the microbiome has burgeoned in recent years, driven by advances in various scientific fields such as metabolomics, genomics, and proteomics. These disciplines provide unique insights into the functioning of our microbial inhabitants and their interactions with the host and the environment. The following terms are explained to help navigate the new world of microbe exploration.

Metabolomics: **Metabolomics is the study of small molecules known as metabolites. It provides a snapshot of the metabolic state of a microbiome.**

Metabolites are the end products of cellular processes, and their analysis can reveal how microbes process nutrients, respond to environmental changes, and interact with their host. By profiling the metabolome, researchers can identify metabolic pathways that are active in microbial communities, shedding light on their functional capabilities. For instance, metabolomics has revealed how gut bacteria produce short-

chain fatty acids from dietary fibers, which are critical for colon health and energy metabolism.

Genomics: Genomics involves the study of the complete DNA sequence of organisms, including those in the microbiome. By sequencing microbial genomes, scientists can identify the genes present in a community and predict the potential functions these genes encode. This approach has uncovered the vast genetic diversity within microbial ecosystems and highlighted the presence of unique genes that enable microbes to thrive in specific environments. Genomic studies have also shown how horizontal gene transfer among microbes can spread antibiotic resistance, emphasizing the need for prudent antibiotic use.

Transcriptomics: While genomics provides a blueprint of the genetic potential of microbial communities, transcriptomics reveals which genes are actively being expressed at any given time. By analyzing RNA transcripts, researchers can determine how microbial gene expression responds to environmental stimuli, dietary changes, or disease states. This dynamic view of gene activity helps in understanding the functional roles of microbes and their adaptive strategies.

For example, transcriptomic studies have shown how gut bacteria alter their gene expression in response to different diets, influencing nutrient absorption and metabolism.

Proteomics: Proteomics is the large-scale study of proteins. This study complements genomics and transcriptomics by

identifying and quantifying the proteins produced by microbial communities.

Proteins are the workhorses of the cell, carrying out essential functions such as catalysis, transport, and signaling. By mapping the protein landscape of the microbiome, researchers can gain insights into the biochemical activities of microbes and their interactions with the host.

Proteomic analyses have identified microbial enzymes involved in metabolizing complex carbohydrates, revealing how microbes contribute to the host's digestive processes.

Metagenomics: Metagenomics bypasses the need for culturing microbes by directly sequencing DNA from environmental samples. This approach has revolutionized microbiome research by allowing the study of entire microbial communities in their natural habitats.

Metagenomic analyses provide a comprehensive view of the genetic composition and functional potential of microbial ecosystems. Metagenomic studies have highlighted the ecological roles of microbes in nutrient cycling, pollutant degradation, and symbiotic relationships.

Systems Biology Perspective: Understanding the complexity of the microbiome and its interactions with the host and the environment requires integrative approaches that combine data from multiple disciplines. Systems biology uses computational models to integrate genomic, transcriptomic, proteomic, and

metabolomic data, providing a holistic view of microbial function and interaction.

This approach helps in identifying key regulatory networks and metabolic pathways, offering insights into how microbial communities maintain stability and respond to perturbations.

Conclusion

The scientific exploration of the microbiome through metabolomics, genomics, transcriptomics, proteomics, and other disciplines has unraveled many mysteries of microbial function and interaction. These studies have highlighted the intricate relationships between microbes, the host, and the environment that make up the intestinal ecosystems, emphasizing the importance of balanced interactions to maintain intestinal well-being.

As research progresses, integrative approaches and systems biology will provide deeper insights, paving the way for personalized therapies and interventions.

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