The Microbiome: achieving balanced gut microbiota as a pathway to good health

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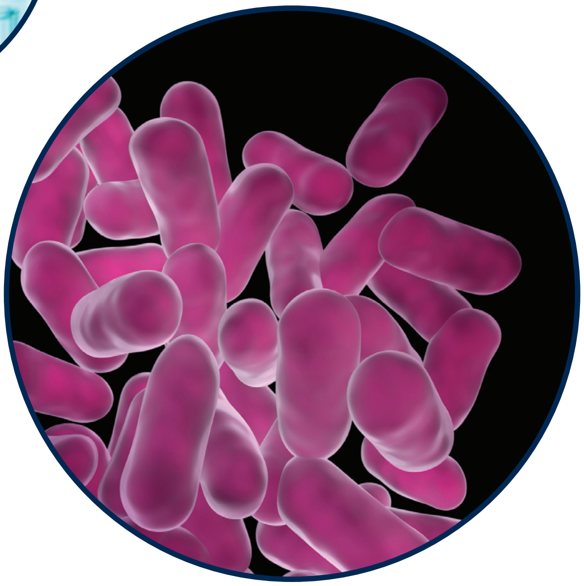

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Preface

It has been recognized for nearly a century that human beings are inhabited by a remarkably dense and diverse community of microbes, yet we are only just beginning to understand and appreciate the many roles these microbes play in human health and development. The human gut harbors about 100 trillion microorganisms—about 10-times more than the total number of cells in our body.[1] Recent research findings have shown us that gut microbes are essential to human life, collectively comprising what has been called "another organ." The microbial community in each of our bodies influences our physiology, metabolism, and immune function, playing roles in both health and disease.[2, 3] This community of bacteria helps its human host digest food, synthesize certain vitamins, and protect against pathogenic bacteria.

Recognizing the benefits of "good" microbes begs the question, what does the microbial population look like in a healthy person? And how does the population differ in a person with metabolic or digestive disease?

The high-profile Human Microbiome Project (HMP), initiated by the US National Institutes of Health, has led to an explosion of new discoveries about the resident microbes of the human gut.[4] Starting in 2008, more than 200 scientists teamed up to sequence the genetic material, i.e., the microbiome, from the gastrointestinal tract of nearly 300 healthy people. They found that each individual had an average of more than 500 microbial species. And each individual's collection of microbes was unique. Further, the researchers found genetic signatures of pathogenic bacteria lurking in most microbiomes. But instead of causing disease, these potentially "bad" bacteria lived quietly among the rest. The researchers deduced that "good" bacteria somehow control the "bad" bacteria, thereby protecting human hosts against infections.

"Good" bacteria protect us against development of harmful conditions such as metabolic syndrome, obesity, atherosclerosis, and asthma, along with certain cancers and inflammatory bowel disease. On the other hand, when the wide variety of "good" bacteria is reduced, disease risk is increased.[5, 6]

Some usual foods, dietary supplements, and medical foods contain bacteria and other microbes that can be taken orally to colonize the human gut. These are called probiotics. As our understanding of probiotics and the microbiome grows, we will increasingly use such probiotics as a way to help restore and maintain health.

In this monograph, we review how the microbiome, and the microbes it represents, influence human health and disease. It appears increasingly likely that our microbiome, or "second genome" as it is sometimes called, exerts a health influence as great as, or even greater than, the genes we inherit from our parents. While our inherited genes are more or less fixed, modern medicine in the form of probiotics makes it possible to reshape this second genome to achieve better overall health.

We now invite you to read more about how microbes can lead the way on a path to good health. It's time to harness the benefits of probiotics to support patient health and improve outcomes.

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Educational objectives

The Microbiome Monograph reviews the role of the human microbiota in achieving and maintaining health across the lifespan. This monograph is a call-to-action for all health caregivers—nurses, dietitians, nutrition specialists, family physicians, naturopathic physicians, and integrative and functional medicine professionals. After studying the four chapters of this monograph, health professionals will be able to meet the educational objectives listed below.

Gut health by the numbers

- Discuss the enormous health tolls and financial burdens of digestive discomforts and disorders in the United States today.

Roles of the gut and its microbiota

- Define key terms used to discuss the gut and its microbiota, and review key functions of each.

Health insights from The Human Microbiome Project

- Compare features of microbial communities associated with good health and with specific diseases.

Probiotics help improve digestive and overall health

- Describe why and how to use probiotics for improved digestive and overall health in US populations.

Contents

1 Gut health by the numbers

Human toll of digestive disease

Digestive disorders represent a major health concern in the United States. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a part of the National Institutes of Health, digestive disorders affect between 60 and 70 million Americans annually. Digestive health complaints account for 48.3 million ambulatory care visits, 21.7 million hospitalizations, and 246,000 deaths per year in the U.S.[7]

Financial costs of digestive disease

Digestive disorders affect between 60 and 70 million Americans annually.

Not only does digestive disease take a human toll, it also has a large financial impact. Each year in the United States, more than $142 billion dollars are spent directly and indirectly on digestive disease.[8]

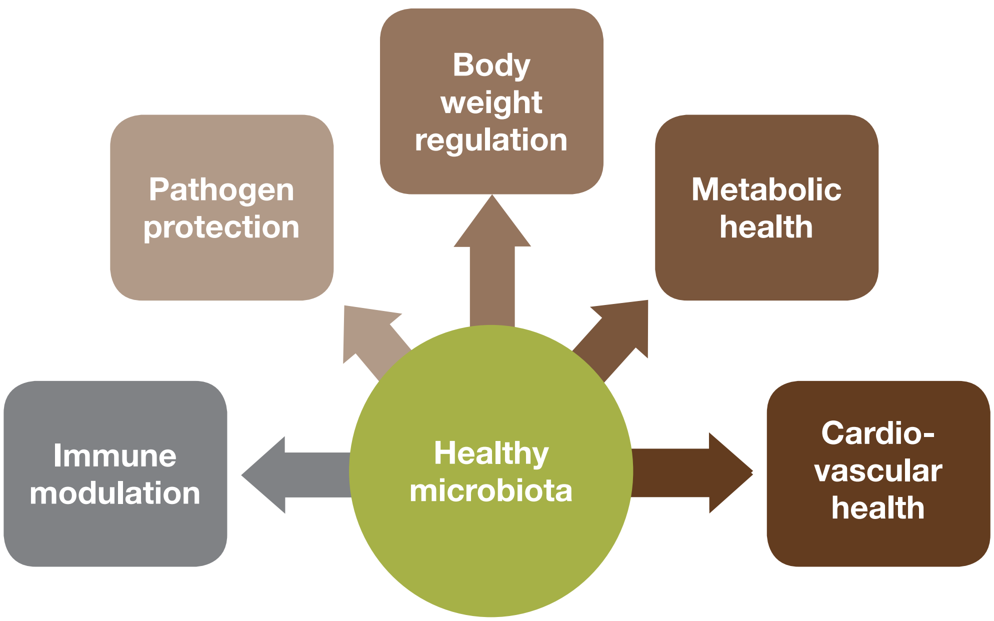
Direct costs represent $98 billion dollars of this total. Such costs include charges for hospital services, physician services, prescription drugs, over-the-counter drugs, nursing home care, home health care, hospice care, and outpatient endoscopy.

The total indirect cost of treating digestive disease is $44 billion.[9] Indirect costs comprise the implicit value of forgone earnings or production owing to (1) need for hospitalization or ambulatory care, (2) work loss associated with acute and chronic digestive diseases, and (3) premature death. Indirect costs also include the value of leisure time lost as a result of morbidity and mortality.

2 Roles of the gut and its microbiota

The gut or gastrointestinal system plays two major roles in the human body—digestion/absorption and immune surveillance. The best known role of the gut is to release enzymes that digest food for absorption of macro- and micronutrients into the bloodstream, ultimately for use by or storage in the body's cells.[10] Less well known, the gut plays a prominent role in the body's immune system. In fact, the intestine is the largest immune organ of the body. Its lining provides a protective interface against the constant challenge of food-borne antigens and microorganisms that enter from the external environment. Strikingly, more than 70% of the body's lymphoid immune cells are in the gut; collectively, these cells are called gut-associated lymphoid tissue (GALT).[11]

The microbiota of the gut likewise play important roles, including promotion of healthy immune responsiveness, protection against pathogens, and support of healthy body weight, as well as other aspects of metabolic and cardiovascular health.



Gut digestion and absorption

Within the stomach and intestines, food is broken down into absorbable macro- and micronutrients by physical churn, acidification, and enzymatic breakdown.[10]

Macronutrients (proteins, carbohydrates, and fats)

- Proteins are broken down to amino acids, which are absorbed and used to build muscle fibers, cell structures, and enzymes that regulate cell functions.
- Carbohydrates (starches and sugars) are digested into monosaccharides, including glucose, which are absorbed from the intestinal lumen and serve as the primary and preferred energy source for the body.
- Fats are digested to glycerol and fatty acids, which are likewise absorbed to provide immediate energy, utilized in membrane formation, or stored as body fat.

Micronutrients (vitamins, minerals, and trace elements)

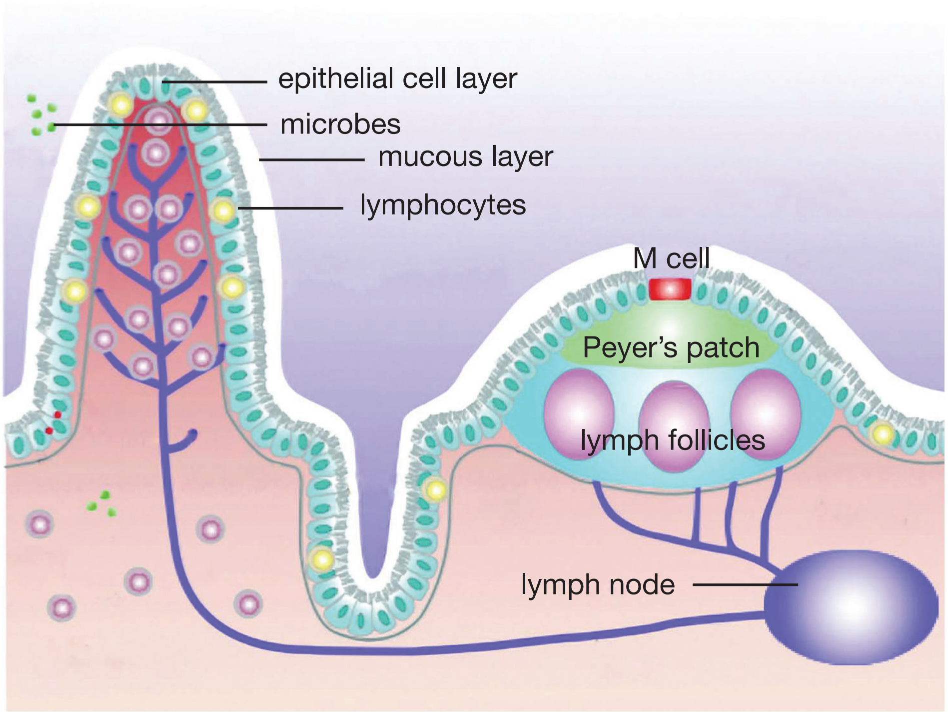
- Micronutrients—in the form of vitamins, minerals, and trace elements—are also released from digested food, then transported across the intestinal wall to the bloodstream where they are moved to cells to play specific regulatory roles.

The exocrine pancreas is the organ with the highest level of protein synthesis in the adult; each day the pancreas produces liters of fluid filled with enzymes that are capable of breaking down nearly all organic substances. For optimal health, the pancreas must produce sufficient enzymes of the right character to match the dietary intake.[12]

For instance, insufficiency of lactase is associated with lactose intolerance. Gene defects lead to this abnormality, but they can be overcome by intake of enzyme supplements.[13] The disease cystic fibrosis is associated with clogging of pancreatic ducts, so treatment often includes pancreatic exocrine replacement therapy (PERT).[14, 15]

The gut immune system

The other major function of the gut is for immune protection. The intestinal protective system is made up of a barrier of epithelial cells and the immune cells within it, a coating of mucus, and resident microbes. The lining of the intestinal lumen itself is a crucial mechanical barrier between the microbiota living in the gut and the blood. This lining consists of a single row of epithelial cells and a surface layer of mucus.



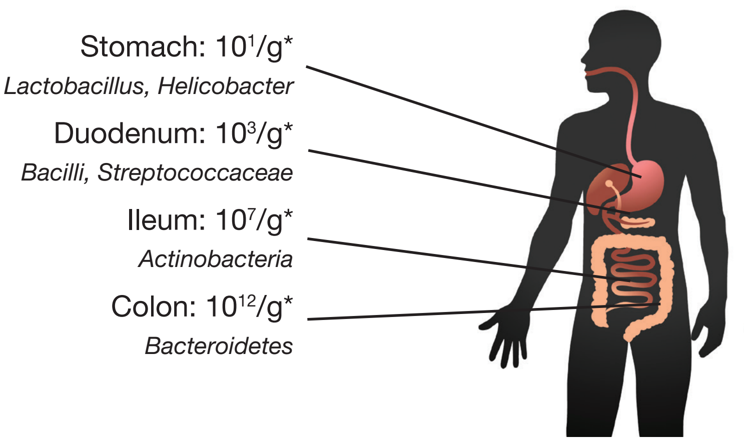
Immune surveillance is carried out at the intestinal barrier and involves gut-associated lymphoid tissue (GALT). The GALT is organized into different compartments such as lymph nodes, lymph follicles, and Peyer's patches. The GALT limits the passage of bacterial and food antigens from the GI lumen through the intestinal mucosa. It does, however, allow the passage of some antigens (minute samples of viable or dead bacteria and protein and peptide fragments of food) using specialized cells such as the M cells that cover the Peyer's patches. Within the organized lymph tissues (follicles and nodes), specialized antigen-presenting cells (APCs) process and present the antigens to lymphocytes, a type of immune cell. The APCs are thus very important in stimulating a balanced immune response, i.e., removal of harmful pathogens versus induction of tolerance to beneficial bacteria and to non-pathogenic environmental and dietary antigens.[11, 16]

The human gut microbiota

At the same time, the functional gut is host to over 100 trillion bacteria, including more than 500 species[17] that account for 10-times as many cells as there are human cells in the body.[1]

These resident organisms can be grouped as commensal, mutualistic, and pathogenic organisms. Commensals provide few or no benefits to the host but are otherwise harmless, e.g., most *Escherischia coli* living in the gut. Mutualistic bacteria provide some benefits to the host but also benefit from their host. In this category, certain *Lactobacillus species* benefit the host by helping break down food, promoting absorption, and keeping down the populations of harmful bacteria. In turn, *Lactobacillus species* derive energy from fermenting some of the host's dietary carbohydrates. An example of a pathogenic or harmful bacterium is *Clostridium perfringens*, a food contaminant that releases toxins and causes host diarrhea, sometimes quite severe.

Bacteria types	Definitions and examples
Commensal	Resident bacteria that neither effect nor benefit from their human host, e.g., most *Escherischia coli* strains
Mutualistic	Resident bacteria that can benefit from their host and provide benefit to the host, e.g., *Lactobacillus spp.*
Pathogenic	Resident bacteria that harm the host, e.g., *Clostridium perfringens*



* Number of organisms per gram of homogenized tissue or fluid

The bacterial cells present in the mammalian gut increase in both numbers and diversity from proximal to distal ends of the gut, starting with 10^{1} to 10^{3} bacteria/gram of contents in the stomach and duodenum, progressing to 10^{4} to 10^{7} bacteria/gram in the jejunum and ileum and ending in 10^{11} to 10^{12} bacteria/gram in the colon.[3]

Additionally, the microbial composition varies between these sites. The stomach harbors mostly *Lactobacillus, Veillonella,* and *Helicobacter,*[1] while the small intestine is home to *Bacilli*, *Streptococcaceae, Actinobacteria, Actinomycineae,* and *Corynebacteriaceae*. The bacteria of the large intestine are mostly anaerobic: *Lachnospiraceae* and *Bacteroidetes.*[3]

Our understanding of the microbiome and its role in human health is expanding rapidly, as will be detailed in Chapter 3. The microbial community in each of our bodies influences our physiology, metabolism, and immune function, playing roles both in health and in disease.[2, 3]

3 The Human Microbiome Project

To discuss the microorganisms of the human body, it is necessary to understand some basic terms. Taken together, all **microorganisms** living in or on the human body are called the **microbiota**. Such microbes are important residents in the gut, especially in the intestines. They also dwell on skin surfaces, in the mouth, and on nasal or vaginal membranes.

The **microbiome** is a term that represents the totality of genes in these microorganisms, while the **genome** refers to genes of a higher organism such as a human. Just as the study of genes in the **human genome** of individuals has provided remarkable insights into health and disease, the study of the microbiome already has revealed insights into human health and disease and is expected to provide even more insights as knowledge grows.

Taken together, the genetic information in each of our human bodies includes a genome and a microbiome. Of this total genetic material, more than 99 percent is microbial.[18]

Exploring the composition of 'healthy' and 'unhealthy' microbiota

The Human Microbiome Project (HMP) is an interdisciplinary research effort at the National Institutes of Health; HMP aims to characterize the microbial communities found at several different sites on the human body, including nasal passages, oral cavities, skin, gastrointestinal tract, and the urogenital tract, and analyze the role of these microbes in human health and disease. HMP was established with the mission of generating research resources enabling comprehensive characterization of the human microbiota and analysis of their role in human health and disease.[4, 19]

Starting in 2008, more than 200 scientists in the HMP consortium spent five years analyzing samples from nearly 300 healthy adults. The samples came from 15 different sites in men and 18 different sites in women, including their mouths, noses, guts, behind each ear and inside each elbow.[20]

There is no single healthy microbiome. Rather each person harbors a unique and varied collection of bacteria that's the result of life history as well as his or her interactions with the environment, diet, and medication use.[20]

While the composition of each person's microbiome is unique, the microbes derive energy to survive by using consistent metabolic pathways, which are described as the "functional core," or the metabolome of the microbiome. Although the metabolic pathways of this core are consistent, the particular genes that implement them vary.[20]

Changing microbiota with maturation and aging

Microorganisms are introduced to the gastrointestinal tract at birth. Several factors, including method of delivery (vaginal vs. cesarean), the environment in which the birth takes place, and the manner of feeding (breast vs. formula) influence the precise microbial community that develops.[21]

An individual's adult microbiota are established at an early age (2-3 years old) and remains fairly stable through the life span, although diet, disease, the use of medications (in particular antibiotics), pregnancy, and aging can have an influence.[22]

As we age, our microbiota display more inter-individual variation, apparently influenced by both living environment and diet. The microbial community of people in long-stay care was found to be significantly less diverse than that of community dwellers, and the loss of community-associated microbiota correlated with increased frailty.[23]

Diversity is important for a healthy microbiome

An interesting aspect of our microbial community is the importance of diversity. In fact, diversity appears to matter more than quantity. For example, studies in rugby players in Ireland found that increased diversity was associated with lower inflammation and healthier metabolic markers and that exercise increases this diversity.[24] Conversely, decreased diversity has been associated with a number of health problems including obesity,[25] inflammatory bowel disease,[26] insulin resistance,[27] frailty in the elderly,[23] and allergy in children.[28]

In addition to diversity of species, the species composition, i.e., proportion of different species in the population, also influences health status.

Benefits of a healthy gut microbiota

The number, species, and diversity of the microbial community in our gut influences our physiology, metabolism, and immune function affecting both health and disease across the lifespan.[2, 3]

Development of immune responses

Gut microbes are important in the development of immunity. Since the intestinal mucosa is the largest body surface area in contact with the antigens of the external environment, this role is not surprising.[29] The presence of a microbial population has been linked to healthy maturation of the immune system, as well as to abnormal immune responses.[3, 30]

Healthy development of the intestinal microbiota in infants is characterized by rapid colonization with microbes of increasing abundance and diversity.[31] At birth, the newborn's gastrointestinal tract—including the gut-associated lymphoid tissue (GALT)—is immature. As the naive intestinal tract is exposed to the myriad of foreign substances over time, the GALT develops to become a functionally mature immune system in older children and adults. Thus, microbial antigens, derived from the intestinal microbiota and from the environment, appear to play a crucial role in the maturation of GALT and in the development of resistance to microbial pathogens.

Studies have shown that the immune system is poorly developed in animals raised in germ-free conditions. Such animals have fewer specialized immune cells in the gut, display lower levels of immunoglobulins, and are more susceptible to disease than are conventionally-reared animals. On the other hand, the incidence of chronic immune dysfunction (allergies, autoimmune disorders, inflammatory bowel disease) appears to be increasing in developed countries. A "hygiene hypothesis" suggests that normal immune function may be impaired when exposure to microbes is limited.

Protection from pathogens

An important role of the gut microbiota is its role to inhibit growth of pathogens. This is accomplished by competitive exclusion as a result of (1) occupation of attachment sites, and (2) consumption of nutrient sources. In addition, the gut microbes stimulate the host to produce various antimicrobial compounds, which is sometimes called "cross-talk" between the host and the microbial population.[3, 29]

Regulation of body weight

Another more recently recognized role of gut microbiota is the regulation of body weight. Several possible mechanisms by which the gut microbiota influence body weight are currently under investigation:[25]

- A healthy gut microbial community is capable of breaking down otherwise indigestible diet components, thus affecting the energy balance.
- A healthy gut appears to support mechanisms that result in increased fatty acid metabolism.
- The anti-inflammatory properties of a healthy gut microbiota may help prevent the development of adipose tissue associated with low grade inflammation.

Bacteria such as *Lactobacillus gasseri SBT 2055, Lactobacillus rhamnosus ATCC 53103*, and the combination of *Lactobacillus rhamnosus ATCC 53102* and *Bifidobacterium lactis Bb12* may be involved in achieving a healthy body weight. [32]

Benefits beyond the digestive tract

Hippocrates reportedly said "death sits in the bowels" and "bad digestion is the root of all evil" in 400 B.C., showing that the importance of the intestines in human health has been long recognized.[3]

Probiotic benefits may extend beyond the digestive tract to include metabolic health, cardiovascular health, and mood.

Metabolic health. Links between the microbes in the human gut and the development of obesity, cardiovascular disease and metabolic syndromes, such as type 2 diabetes, are recognized; however, mechanisms linking the microbiota to changes in human metabolism still remain unclear. The beneficial microbe *Faecalibacterium prausnitzii,* in particular, is less abundant in patients who are obese and diabetic, but increases after gastric bypass surgery with weight loss.[33]

Cardiovascular disease (CVD) and health. The pathogenesis of CVD is indeed an active topic of research. Interestingly, recent work has shown that the microbiota contribute to the progression of CVD by its action in converting dietary choline and L-carnitine (from red meat) into chemical agents that promote atherosclerosis. Although more research is needed, this link has medical implications for future prevention and treatment of CVD.[34]

Healthy mood and pain perception. It was recently suggested that the microbiome in the gastrointestinal tract is an important participant in determining mood; this link is generally described as the gut-brain axis, a bidirectional communication by way of the vagus nerve. It has been suggested that certain beneficial bacteria (probiotics) may be important for helping avert depression and maintaining good mood. When mice ingested *Lactobacillus rhamnosus (JB-1)*, they showed reduction in stress-induced corticosterone production and lower anxiety- and depression-related behavior.[35] Additional research is certainly needed in this exciting new area of study.[36]

The gut-brain axis has also been implicated in abnormal perception of pain and discomfort. Alterations in the interactions between the gut and the brain appear to have important roles in the pathogenesis of irritable bowel syndrome (IBS). A body of largely preclinical evidence suggests that the gut microbiota may modulate these interactions.[37]

Gut microbiota and disease states

There is a growing preponderance of evidence showing the health problems associated with an unhealthy microbiota. Not only is an altered gastrointestinal microbial community associated with problems of the gastrointestinal system (e.g., diarrhea and infection,[3] inflammatory conditions like irritable bowel syndrome and inflammatory bowel disease,[38] colorectal cancer[39]), but it also can affect the cardiovascular system (e.g., atherosclerosis),[34] body weight (obesity, malnutrition),[25] body surfaces (e.g., allergic conditions),[40, 41] metabolism (e.g., both type 1 and type 2 diabetes),[18] and even has been associated with depression.[36]

4 Probiotics and prebiotics help achieve a healthy gut

Up until now, this monograph has addressed the health and financial burdens of digestive discomforts and disorders, as well as the benefits of having a healthy gut. It will now briefly review some exciting new lessons we have recently learned about how to achieve and maintain a well-functioning gut as a way to improve our overall health.

A naturally balanced gastrointestinal system is intact and functional, replete with digestive enzymes to release nutrients from food consumed—along with "good" resident microbiota and their food sources.

The net result is a well-nourished human host with an effective immune surveillance system. Scientists today are becoming increasingly aware of the importance of having the right microbial population to support good health.

Probiotics and prebiotics

One way to maintain a healthy microbial population is through the consumption of probiotics and prebiotics.[42]

Probiotics are living microorganisms that confer health benefits on their human host. Probiotic microorganisms are consumed by humans as part of food (in yogurt or other fermented food), or they can be taken in pill form as dietary supplements.

Prebiotics are food components or supplements that cannot be digested by the human host, typically dietary fibers, but the fibers confer health benefits to the host by supporting growth of probiotic "good" bacteria.[43, 44] Such microflora produce their own metabolic energy by breaking down prebiotics to metabolites such as short-chain fatty acids (SCFA). In turn, the SCFA serve as an energy source to the epithelial cells of the colon, thereby improving barrier function. Prebiotics thus support growth of "good" or beneficial bacteria; this colonization helps prevent or lessen growth of "bad" or pathogenic bacteria. Human milk oligosaccharides are recognized as important prebiotics; these soluble fibers in breast milk enhance the colonization of the infant gut by "good" microbes.[45, 46]

Synbiotics is the term used to describe an intentional combination of living probiotics administered along with the prebiotics to nourish them.[43] Such a combination has recently been reported to have potential for treating antibiotic-induced intestinal injury.[47]

Mechanisms by which probiotics exert their effects

Beneficial probiotics work to support gut health through a number of different mechanisms including:[48]

1. Competition with pathogenic organisms for dietary ingredients as growth substrates
2. Reduction of inflammation, thus altering intestinal properties for colonization and persistence
3. Production of growth substrates, e.g., vitamins and SCFA
4. Improved gut barrier function
5. Competitive exclusion for binding sites by pathogens
6. Stimulation of immune responses

The new "rules" for probiotic supplementation

What we have learned about probiotics and the gut microbiota is very new and complicated. However, evidence is rapidly building regarding the benefits of specific probiotics and about healthy microbiota.

- Not all probiotics are the same; the genus, species, and strain determine their effect.
- For probiotic therapy, use a probiotic strain specific to the indication.
- Support growth of healthy microbiota with prebiotics, and thus help limit growth of pathogens.
- More gut bacteria is not necessarily better than less. It's all about the right balance; diversity matters.

Not all probiotics are the same; the genus, species, and strain determine their effect.

Not all probiotics are the same

Reduced intestinal barrier function, i.e., increased permeability, is characteristic of several GI disorders, including inflammatory bowel disease (IBD)[49] and leaky or permeable gut.[36] Maintenance of the intestinal barrier is a key mechanism by which gut microbes and probiotic bacteria can limit translocation of foreign antigens or pathogens into the gut. However, such barrier protection is not universal among all probiotic or commensal organisms.

In fact, protection appears to be strain-specific. There is no better example of this phenomenon than *Lactobacillus salivarius*. A recent study tested 33 strains of *L. salivarius* for their ability to prevent disruption of junctions between intestinal epithelial cells. Of these, strain *UCC118* and others were protective, while 13 of the strains tested showed little or no protective capacity.[49] Based on observations like this, use of probiotics for treatment requires attention to the genus, species, and strain of the therapeutic bacterium.

Use the right probiotic for the indication

When consumed in adequate amounts, probiotics confer a health benefit on a human host. The genus *Lactobacilli* are rod-shaped bacteria that are a major part of a group of bacteria known to convert sugars to lactic acid, thus producing an acid environment that inhibits growth of several species of harmful gut bacteria.

The table below shows a short list of some probiotic species (and strains) in the *Lactobacillus* genus. These bacteria are beneficial for preventing or treating specific indications, as listed.

Probiotic genus, species, strain	**Indication**[50]
Lactobacillus salivarius UCC118[49, 52]	Protection against infection by food-borne Listeria; supports tight junctions of intestinal epithelial cells
Lactobacillus rhamnosus GG[53, 54]	Prevention and reduction of atopic dermatitis in children; reduction of episodic diarrhea in children
Lactobacillus reuteri RC-14 and Lactobacillus rhamnosus GR-1[55]	Prevention or treatment of bacterial vaginosis
Lactobacillus acidophilus NCFM and *Bifodobacterium lactis Bi-07*[56]	Reduction of cold and influenza symptoms in children
Lactobacillus plantarum HEAL9 and *L. paracasei 8700:2*[57, 58]	Reduction of common cold infections or duration of symptoms in adults
Lactobacillus acidophilus NCFM and *L. paracasei Lpc-37* and *B. lactis Bi-07 and B. lactis Bi-04*[59]	Reduction of antibiotic-associated diarrhea
Lactobacillus plantarum 299V[60, 61]	Support of gut barrier function and improvement of IBS symptoms

The credibility of such health claims for specific probiotic species must be established through science-based clinical studies. As probiotic properties are often strain-specific, it is important to prescribe specific organisms (by genus, species, and strain) based on evidence.[50]

Although most probiotics used today are generally regarded as safe, it is always important to consider the risk-benefit ratio before prescribing a probiotic for each individual patient.[50, 51] Use of certain probiotics for immunocompromised patients or those with a permeable gut can lead to infections, bacteremia, and sepsis.

Use prebiotics to support growth of "good" bacteria

The key to feeding bacteria in the intestine is to provide substrates for the organisms to ferment as a source of energy. This includes a diet with varying types of fiber, including resistant starch (found in bananas, oats, beans); soluble fiber (in onions and other root vegetables, nuts); and insoluble fiber (in whole grains, especially bran, and avocados).[62]

Supplemental prebiotics can be taken to enhance growth of organisms known to be beneficial, e.g., *Lactobacillus* and *Bifidobacter* species. These include carbohydrates that resist human digestion, e.g., inulin, *isomaltooligosaccharides (IMO)*, and *fructooligosaccharides (FOS)*.[44] When prebiotics promote growth of "good" or beneficial bacteria, this colonization helps prevent or lessen growth of "bad" or pathogenic bacteria.

Safety and regulations for use of probiotics

Although some probiotics have been around for a long time, new strains with potential benefits to human health are being presented to consumers at an exponential rate. Of primary importance as the new probiotics become available is the safety of these products and the ability to substantiate any health claims made about them. Regulations regarding probiotics vary from country to country; in the United States, there are no Federal Drug Administration (FDA) regulations that specifically address probiotics, so at this time they are labeled as either a usual food, dietary supplement, or medical food. No probiotic to date has been approved as a drug, a category that has a significantly higher standard of approval than does a medical food or dietary supplement.

This higher standard, while important, may also be a barrier to the development of new and valuable probiotics. In 2010, an expert panel, created as part of the Human Microbiome Project to study the ethical, legal, and social implications, was charged with looking at the current regulatory framework for probiotics and determining if it is an appropriate fit for current and future probiotics. Recommendations were based on investigation of several key issues: safety of probiotics, the need for Investigational New Drug (IND) applications in order to conduct human research, characterization of probiotics, and health claims of probiotics. The panel's recommendations included these five concepts:[63]

1. *FDA should adopt clear guidelines for when an IND is or is not required for human research on probiotics.*

2. *Regulatory oversight and burden should be proportional to risk of the probiotic.*

3. *FDA should adopt guidelines establishing an abbreviated IND process that would allow researchers, in certain situations, to bypass safety studies.*

4. *FDA should encourage the study of acceptable ways to: 1) demonstrate modulation of a condition— for example, cholesterol level—in healthy individuals without making a disease claim, and 2) measure homeostasis.*

5. *There should be a publicly available mechanism through which consumers can obtain more information on the underlying evidence supporting a particular product.*

Summary and conclusions

- Gastrointestinal problems are common and costly, and they adversely affect other body systems—in turn affecting mental, cardiovascular, skin, bone, and metabolic health.
- The Human Microbiome Project has quickly advanced our understanding of the gut's microbiota as an important determinant of gut health and overall health.
- If the gut microbiota become unbalanced, as with many digestive and metabolic diseases, healthy microbes can be restored by treatments with supplemental probiotics and prebiotics.

To the extent that we humans are bearers of genetic information, more than 99 percent of it is microbial. In fact, it appears increasingly likely that our microbiome, or "second genome" as it is called, exerts a health influence as great as, or even greater than, the genes we inherit from our parents. While our inherited genes are more or less fixed, modern medicine in the form of probiotics makes it possible to reshape our "second genome" to achieve better overall health.

Now is the time for all health caregivers—nurses, dietitians, nutrition specialists, family physicians, naturopathic physicians, and integrative and functional medicine professionals—to harness the benefits of probiotics to support patient health and improve outcomes.

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