

The ecological community of commensal, symbiotic, and pathogenic gastrointestinal microorganisms – an appraisal

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Abstract: The human gastrointestinal tract is inhabited by a vast population of bacteria, numbering ~100 trillion. These microorganisms have been shown to play a significant role in digestion, metabolism, and the immune system. The aim of this study was to review and discuss how the human body interacts with its gut microbiome and in turn the effects that the microorganisms have on its host, overall resulting in a true mutualistic relationship.

Keywords: gastrointestinal, commensal, symbiotic, pathogenic microorganisms

Introduction

The word “microbiome” was first coined by American Molecular Biologist Dr Joshua Lederberg to imply the environmental and biological community of commensal, symbiotic, and pathogenic microorganisms that share human body space and have been all but ignored as elements of health and disease.¹ The microbiome is defined as the overall collection of microbiota that resides inside humans or on their skin surface.²⁻⁵ It has been recognized for some time that the human body is colonized by at least ten times more bacteria than the figure of human cells in the body and that most of these bacteria live in the human gastrointestinal (GI) territory.⁶⁻⁸ It has been estimated that ~10–100 trillion commensal bacteria occupy the human GI tract; therefore, the figure that vastly outnumbers the number of cells of human origin.^{5,8,9} Nevertheless, “the total cell number of a human being ranges between 10^2 and 10^{16} and it is widely mentioned without a proper reference.”¹⁰ In a recent report, it was found that “the number of cells in the human microbiota is likely to be highly variable depending on nutritional input, body size, age, ethnicity, culture, and environment.”¹¹ Although worldwide most research has concentrated on microorganisms that cause disease and microbial drug resistance, due to unknown reasons, studies on the microbiome and their its benefits in the human body did has not had a similar prioritisation or urgency as those on pathogenic microorganisms in many communities and countries.^{7,12-19} There are an innumerable variety of microorganisms in nature, many of which can cause diseases in humans. However, the human body is a host to a great number and assortment of bacteria, viruses,²⁰ and fungi,²¹ which are beneficial to health and well-being. It has been reported that the normal inhabitant bacterial flora of the human body is poorly understood.²²⁻²⁵ Although they are termed commensals, bacteria comprising the gut microbiome share a much stronger relationship with the human host than the term suggests.²⁶⁻²⁹ Commensalism is a form

of symbiosis whereby one organism gains from its association with another organism, whereas the other is affected in neither a positive nor a deleterious manner. There is more of a mutualistic nature to the bond shared by human host and bacterial colonizers in that the relationship benefits both parties: the microbiome is provided with an environment to live in and a readily available source of nutrients, and the human receives metabolites from bacterial digestion which it could not have otherwise obtained.^{29–31} As the human hostages, the gut microbiome gains a level of stability that suggests a strong interrelationship between host and bacteria, which has evolved over a substantial period.^{32,33} In addition, in the process of digestion and metabolism, these bacteria play an important role in the immune system and other body functions.^{34,35} Over the last 20 years, it has been shown that it is possible to modulate the composition and metabolic activities of the gut microbiome such that the health benefits to the host are maximized while reducing the deleterious effects of pathogenic organisms.^{34,36–39} This has made the study of the microbiome a subject of great interest.

Anatomy of the gut and bacterial compositions

The GI tract starts at the mouth, connects to the esophagus and thence to the stomach and small and large intestines, and ends at the rectum. The GI tract can be visualized as a long tube that passes uninterrupted through the body from lips through to anus. The stomach, small bowel, and colon are the organs that constitute the gut. The large intestine is the most densely populated section of the GI tract. The stomach contains relatively low numbers of bacteria, primarily due to the acidic nature of gastric juice. Stomach contents are also retained for a relatively short time; therefore, the food supply for bacteria is limited. Despite this fact, microbial populations in the stomach can reach 10^3 organisms per gram of contents, rising to 10^6 /g after a meal, due to the buffering capacity of food.^{40,41} The predominating microbial species are acid-tolerant lactobacilli and streptococci, which can withstand a low-pH environment to some extent.⁴¹ Bacteria are considerably more numerous in the distal small bowel and large intestine. The transit of contents through the colon takes considerably longer time, which provides time for complex microbial communities to develop.⁴² Currently, the microbe population living in the human intestine is named “gut microbiota” (previously known as “gut flora”).⁴³ Human gut microbiota comprises tens of trillions of microorganisms, counting at least 1,000 different species of known bacteria with more than three million genes (150 times more than

human genes).^{43,44} The most abundant species belong to the phyla Bacteroidetes and Firmicutes, which account for up to 90% of all the bacteria in the distal gut.⁴⁵ Human intestine accommodates multifarious-community microbial cells that have an impact on humanoid “physiology, metabolism, nutrition and immune function while disruption to the gut microbiota has been linked with GI conditions such as inflammatory bowel disease (IBD) and obesity.”³⁷

Digestion in the human gut

It was traditionally considered that the main function of the large intestine was principally the reclamation of water and salts and that it had little or no role in digestive processes, which occurred in the stomach and small intestine. However, it has been shown that a small, but significant contribution is made to digestive processes by the large gut, as modulated by the microbiome.

Carbohydrate digestion

Carbohydrate catabolism (and, to a lesser extent, protein breakdown) yields short-chain fatty acids (SCFAs), and this is done by a process called fermentation, which is conducted by anaerobic bacteria in the gut.⁴⁶ Carbohydrates that can be grouped under the term “dietary fibers” are the most common sources of SCFAs, as well as starches that are not digested in the small intestine.^{47,48} Dietary fibers are indigestible in humans; therefore, the fermenting actions of the gut microbiota generate SCFAs for human use. The three principal SCFAs found in the human body are butyrate, propionate, and acetate, in an approximate ratio of 1:1:3.⁴⁹ Approximately 95%–99% (the clear majority) of SCFAs produced in the gut are absorbed.⁵⁰ SCFAs, predominantly butyrate, are vital sources of energy for colonocytes, and up to 70% of their energy needs may be gained through fermentation.⁴¹ It has been shown in mice that a lack of a microbiome, and therefore no production of butyrate, can lead to autophagy (self-digestion of cells in response to an energy and nutrient deficit) of the colon cells.^{9,51,52} The colonocytes of these germ-free mice were also found to be energy-deficient, as well as having reduced levels of enzymes that catalyze reactions such as those in the citric acid cycle.⁵¹ This highlights the importance of a microbiome and the substantial contribution they make to energy supply. The SCFAs are useful energy sources as well as playing a role in the human immune system. A recent study detected that SCFAs also regulate the immune system and inflammatory response.⁵² They diminish the sensitivity of lamina propria macrophages to commensal bacteria, via nitric oxide, IL-6, and IL-12 independent of

free fatty acid receptor signaling, to persuade tolerance.⁵³ The SCFAs, especially propionate and butyrate, have also been shown to inhibit the expression of lipopolysaccharide-induced cytokines, IL-6 and IL-12p40, in human mature dendritic cells.⁵⁴ The SCFAs, which were used therapeutically in inflammatory diseases in a controlled experimental setup, showed improvements in IBD and acute radiation proctitis, as it plays a direct anti-inflammatory role.⁵⁵⁻⁵⁷ Propionate and acetate have been found to show an anti-inflammatory action on human monocytes by regulating cytokine and chemokine production, such as IL-10 and MCP-1.⁵⁸ MCP-1 is one of the key chemokines that regulate migration and infiltration of monocytes/macrophages.⁵⁹ Propionate and butyrate have also exhibited anticancer properties.^{60,61}

Protein digestion

The breakdown of protein by the gut microbiota also contributes to SCFA production, but not as profoundly as carbohydrate fermentation. However, this process releases a greater variety of end products such as hydrogen, carbon dioxide, ammonia, thiols, amines, indoles, and phenols. Many of these substances are considered toxic and have carcinogenic effects. Thus, protein catabolism is a less beneficial process compared with carbohydrate fermentation.⁴¹ It can be noted that many large bowel diseases occur in the distal gut (ie, the descending and sigmoid colons). As food passes along the bowel, the most easily digestible material (carbohydrates) will be used up first; therefore, protein digestion becomes more important in the distal sections. Signature products of amino acid breakdown are branched-chain fatty acids (BCFAs), and it was found by the experiments conducted with human sudden death victims that the concentrations of BCFAs were notably higher in gut contents obtained from the distal large bowel than that of the proximal colon. SCFAs, produced during protein digestion, more than doubled from 17% to 38% in the distal large gut. This evidence points to protein breakdown and the production of toxic by-products as potential causes of diseases in the distal large gut.⁴¹

Modulation of the microbiome

As it is well established that a healthy gut microbiome has many positive effects on their human hosts and has influence on diseases, thoughts have turned to how to change and enhance the microbiome to gain further health benefits.

Prebiotics

A prebiotic is defined as a nonviable food component that confers a health benefit on the host associated with the

modulation of the microbiota.^{62,63} Although most foodstuff will change the levels of bacteria in the gut,⁶⁴ nonviable food ingredients such as inulin, fructo-oligosaccharides, and galacto-oligosaccharides have a more specific effect on the growth of beneficial bacteria, such as bifidobacteria and lactobacilli.⁶⁵ Both are gram-positive anaerobes, which are specialized in the breakdown of carbohydrates in the gut.⁶⁶ As mentioned above, carbohydrate digestion produces SCFAs, which is beneficial to the gut. A few negative effects of prebiotics have been recorded, such as a slight laxative effect and flatulence from both inulin-derived oligosaccharides and galacto-oligosaccharides; however, this is only the case when significant quantities are consumed, and therefore, overall, the benefit far outweighs any potential drawbacks. To make a prebiotic function effectively, it must be able to pass undigested through the GI tract and to reach its target bacteria in the gut, where it can be fermented. Furthermore, the target bacteria themselves must be present in the gut for there to be any modulatory effect.⁶⁷ Many common foodstuffs such as onions, garlic, and bananas naturally contain oligosaccharides with prebiotic potential.⁶⁸ However, it is believed that these polysaccharides are present in a too low concentration to significantly alter the levels of bacteria in the gut. This has led to the initiative of extracting and purifying prebiotics and then fortifying common foodstuffs such as table spreads, drinks, and cereals.⁶⁸ This has been proven to be a less expensive method of modulating the gut microbiome than using prebiotics.⁶⁴ Prebiotic compounds can be extracted from plant sources. Another technique to produce galacto-oligosaccharides is to break down lactose, an abundant by-product in the manufacture of dairy goods, using β -galactosidases.⁶⁵ This method consumes substrates that would otherwise have gone to waste as well as can produce the prebiotic.

Probiotics

Probiotics used in humans are live bacteria and yeasts, which are delivered to the gut via oral ingestion.⁶⁷ They are often ingredients in food products, which have a unique selling point, making them very popular with members of the public, but is there any truth in the usefulness of probiotics? Like prebiotics, to make probiotics effective, they must be resistant to digestion in the upper gut, such that they can reach sections of the bowel where they can seed and grow.⁶⁷ Probiotics have been shown to confer beneficial effects on the host. They compete with pathogenic microbes for nutrients and space to grow, inhibiting pathogenic growth.⁶⁹ Furthermore, some probiotics such as bifidobacteria, but mainly lactobacilli, produce peptides called bacteriocins that have antimicrobial

properties and are used to kill pathogenic bacteria.⁷⁰ Although several research reports have confirmed that the consumption of probiotics has numerous health benefits,^{71–74} nevertheless, “health authorities have only approved claims on (a) lactose intolerance and lactose digestion and (b) cholesterol reduction mostly because of biomarker deficiency.”⁷⁵ The risk of myocardial infarction is three times higher in those with a high lipid profile than in those with normal levels of blood lipids.⁷⁶ The cholesterol-reducing ability of probiotics has been extensively studied and has revealed that total plasma cholesterol and low-density lipoprotein cholesterol can be reduced by 7.84% and 9.27%, respectively.^{77,78} Existing accessible antimicrobial treatments for yeast vaginitis, candidiasis, bacterial vaginosis, and urinary tract infection can often lead to a number adverse drug reactions, such as diarrhea, superinfections, depression, and even renal failure.⁷⁵ Moreover, antimicrobial resistance inclines to decline the usefulness of this therapy over time.^{17–19} Lactobacilli have been shown to create biosurfactants and collagen-binding proteins that inhibit pathogen adhesion to the vaginal wall. This actually explains the reason why the vaginal mucosa is conquered by lactobacilli, making access to pathogens problematic.⁷⁹ Probiotics available in the marketplace for oral health include species of *Lactobacillus* and *Bifidobacterium*.⁸⁰ Several studies have demonstrated that *Lactobacillus* and *Bifidobacterium* can decrease the oral levels of the cariogenic species *Streptococcus mutans*.^{81–84} *Streptococcus salivarius* K12 has also been recognized to generate several proteins that are active against closely related strain (bacteriocins) such as *Streptococcus pyogenes* and *Streptococcus pneumonia* and avert repeated pharyngitis, otitis media, and tonsillitis.^{85,86} Microbial β -galactosidase in yogurt is resistant to gastric acid and supports lactose digestion.⁷⁵ Multiple studies detected that the symptoms of lactose malabsorption improved due to extra production of β -galactosidase by probiotic cultures.^{87,88} Furthermore, it has been observed that milk containing *Lactobacillus acidophilus* also aids lactose absorption and shows improvement in lactose-intolerant patients.⁸⁹ Probiotic supplementation can also modify the quantity of colonic microbiota and improve symptoms in lactose-intolerant subjects.⁹⁰

Symbiotics

A symbiotic is a combination of a prebiotic and a probiotic.⁹¹ There is a sound logic behind the symbiotic concept; the probiotic component will aid in metabolism and host immunity, whereas the prebiotic selectively stimulates the growth of the probiotic, and other beneficial bacteria already extant in the gut. Overall gut health is positively modulated. The effective-

ness of symbiotics has been investigated in several diseases. The symbiotic therapy involving *Bifidobacterium longum* and Synergy 1 has been shown to have benefits to both Crohn's disease (CD) and ulcerative colitis (UC) patients. *B. longum* was chosen from a selection of nineteen bifidobacterial strains. This choice was made based on testing for desired characteristics: aerotolerance, acid tolerance, bile salt resistance, adhesion to epithelial cells, and ability to use oligofructose as an energy source, as well as a capacity to withstand freeze-drying and storage. The bacterium that predominated in all categories was *B. longum*.⁹² Synergy 1 is made from inulin from the chicory plant and oligofructose.⁶⁷ Another important bacterium is *Faecalibacterium prausnitzii*, which is found in ample quantity (5% of the total bacterial population) in the human intestinal microbiota of healthy adults.⁹³ This species is a highly functionally active member of the microbiome, influencing numerous host pathways.⁹⁴ Several intestinal disorders were noticed to contain low numbers of *F. prausnitzii*, particularly in IBD patients.^{93,95} Hence, the number of intestinal *F. prausnitzii* can be recommended as an indicator of intestinal health.^{93–95} Immunologic dysregulation is the reason of numerous noninfectious human illnesses. The GI tract is the principal location of contact between the “host immune system and microorganisms, both symbiotic and pathogenic.”⁹⁶ Intestinal bacteria are considered for the development and function of the immune system. From the clinical, epidemiological, and immunological evidence, it was concluded that the absence of valuable microorganisms that sponsor appropriate immune development leads to the inflammatory responses including IBDs.⁹⁷

Diet-related dysbiosis, coeliac diseases, gluten-free diet (GFD), breast milk, western diet, and polyphenols

The impact of food on the arrangement of the microbiota has been shown during the preliminary colonization phase: breastfed newborns have advanced levels of *Bifidobacteria* spp., whereas formula-fed infants have higher levels of *Bacteroides* spp., as well as amplified *Clostridium coccoides* and *Lactobacillus* spp.⁹⁸ The microbiota was assumed to maintain a relatively steady state all the way through life after the postnatal epoch. Nevertheless, quite a recent study have revealed that dietary influences modify the microbial community, resulting in biological deviations to the host.⁹⁹ It is extensively documented that the intestinal microbiota plays a role in preventing the commencement and continuation of intestinal inflammation in an ample number of chronic intestinal diseases.¹⁰⁰ Several studies reported that Celiac disease (CeD) patients with GI indicators are also recognized

to have an altered microbiota.^{101–104} It has been observed that the numbers of *Bifidobacterium* spp. and *B. longum* were significantly reduced, and the numbers of *Bacteroides* spp. were increased in stools and duodenal biopsies of CeD patients, untreated and treated with a GFD, compared with control subjects.^{101,102} In addition, specific bacterial strains isolated from patients with active and nonactive CeD have been shown to have augmented virulence features. These outcomes recommended that microbiota modifications are of significance to the inflammatory status characteristics of the vigorous stage of the disease. These alterations could perform both a secondary role by enraging CeD pathogenesis and engendering a vicious circle and a primary role in contributing to disease onset.¹⁰⁰ Diet is the most important eco-friendly factor impelling gut microbiota multiplicity and functionality, which might be pertinent to subjects following dietary remedies. The CeD is an enteropathy caused by an atypical immune response to cereal gluten proteins, and the solitary therapy is the obedience to a GFD.¹⁰⁵ Human milk is a comprehensive source of sustenance for the newborn.¹⁰⁶ Human microbial colonization commences at birth and progresses and modifies in species profusion for ~3 years while waiting for the microbiota to grow into adult form. Toddlers go through noteworthy, evolving ups and downs of microbial colonization that encourage their health status as well as their immune system.¹⁰⁷ Exclusive breastfeeding for 6-months encourages the infant's progress towards the multiplying of a defensive intestinal microbiota. The milk glycans among the many components of milk have been identified as chauffeurs of microbiota development and overall gut health because of its inherent properties of pleiotropic functions, conferring protection against infectious diseases.¹⁰⁶ Furthermore, intestinal permeability in preterm infants characterizes a life-threatening balance between the absorption of nutritional agents and protection from dangerous pathogens. Newborns who received either exclusive or a majority of feeding as human milk revealed significantly lower intestinal permeability when compared to infants receiving minimal or no human milk in postnatal days.¹⁰⁸ Western diet, which contains highly refined haphazard foods with poor nutritional quality essentially constituting sugar and fat, causes dysbiosis that upsets both host GI tract metabolism and immune homeostasis.^{109–111} Another study highlighted typical Western diet converts the microbiota composition shifting to an overgrowth of Firmicutes including *Clostridium innocuum*, *Eubacterium dolichum*, *Catenibacterium mitsuokai*, and *Enterococcus* spp., as well as a significant reduction in several *Bacteroides* spp.; however, traditional food regimes rich in plant polysac-

charides are linked with a Prevotella enterotype.^{52,112} It also reported that such a typical diet can cause 71% upsurge in plasma levels of endotoxins, proposing that endotoxemia may progress in folks with GI barrier dysfunction associated with dysbiosis.¹¹³ Dietary polyphenols extant in a wide-range of vegetables and fruits have been associated with positive health benefits.^{114,115} It has also been reported that variances in the dispersal of bacteria are linked with dietary habits and this in reality provokes and promotes the host to be exposed to microbial metabolites.¹¹⁵ Another group of scientist revealed that the gut microbiome of children living in remote West African countries was significantly different from that of the children of the same age from the most sophisticated European countries.¹¹⁶ Similar observation of differences in gut microbiome was found between communities, in rural and urban areas, and residents in non-industrialized and industrialized societies.^{117,118} Multiple studies reported that dietary polyphenols are entrusted to conserve the intestinal health by protecting the gut microbial equilibrium through the encouragement of the development of beneficial bacteria (ie, lactobacilli and bifidobacteria) and the inhibition of pathogenic bacteria, wielding prebiotic-like properties.^{119–125}

Fecal microbiota transplantation (FMT)

FMT (or bacteriotherapy) is the relocation of stool from a healthy giver into the GI tract with the determination of treating recurrent *Clostridium difficile* colitis.¹²⁶ *C. difficile* infection (CDI) is the leading cause of antibiotic-associated diarrhea, and the infection rates are increasing.^{127–129} CDI treatment choices are restricted and seem to lose efficacy due to resistance. Recurrent disease is particularly puzzling; extended treatment with oral vancomycin (Eli Lilly and Company, Indianapolis, IN, USA) is becoming increasingly common, but is expensive.¹²⁷ The emergence of the hyper-virulent *C. difficile* strain has been related to a rise in disease severity, with mortality reported in up to 6.9% of cases.¹³⁰ The associated economic burden is also significant.¹²⁸ Nosocomial CDI upsurges the cost of treatment by fourfold, translating to a cost reported up to \$4.8 billion/year in the USA.^{131,132} FMT embraces substantial potential as a therapy for recurrent CDI with very minimum cost, but still requires more research.^{127–129}

Microbiome and its relationship to disease

IBD

IBD is a general term used to define many conditions that cause inflammation of the GI tract, with the two main forms being UC and CD. Both are chronic illnesses that

are characterized by inflammation, which often goes into remission and then flares up throughout the sufferer's lifetime. A study conducted in Germany tested the hypothesis of a genetic link in IBD. Monozygotic twins were found to have a tenfold increased risk of developing the condition than dizygotic twins, emphasizing a strong genetic link in sufferers of IBD, especially CD.¹³³ Recent advances have provided substantial insight into genetic relation with IBD. Epidemiological data shows the prevalence among different geographical areas, ethnic groups, familial predisposition, and concordance in twins.^{134,135} IBD is a peaks-and-valleys disease categorized by diarrhea, abdominal pain, and weight loss.¹³⁵ Recently, it has been observed that IBD has a strong correlation with sleep, circadian rhythms, and melatonin.¹³⁶ Sleep disorders have become a global issue; currently, in modern society, lack of sleep, shift work, or circadian misalignment is an extremely common issue. The total sleep time has increasingly declined over the last 25 years as the change of work environment, frequent long flights, and mobility have been internationally altered and posed a challenge to human circadian homeostasis.^{137,138} Insomnia and other sleep disorders are associated with many serious adverse health miseries, economic consequences, and, furthestmost significantly, has amplified all-cause mortality.¹³⁹ It has been observed that there is a strong correlation between sleep and the immune system. Although the total issue regarding sleep and immunity is complex and poorly understood,¹³⁹ sleep strengthens immune function¹³¹ and deprivation has been shown to have damaging effects on the immune system and can lead to leukocytosis and an increase in natural killer cells, which can lead to increased inflammatory cytokine production.¹⁴⁰⁻¹⁴² Environmental factors were also considered as an indispensable gear of the pathogenesis of IBD and chiefly accountable for its mounting incidence worldwide.¹⁴³ Many environmental hazardous aspects have been identified "including smoking, appendectomy, oral contraceptives, diet, breastfeeding, infections/ vaccinations, antibiotics, and childhood hygiene."¹⁴² None of these environmental factors were isolated as the definite cause of IBDs.^{143,144} The identification of various alterations of the gut microbiota composition in IBD has enabled using very advanced next-generation sequencing technology.¹⁴⁵ Alterations in the ecological system have been reported within the gut, that is, intestinal microbes and the immune system.^{146,147} "The most consistent observation in IBD is reduced bacterial diversity, a decrease of Firmicutes, and an increase of Proteobacteria."¹⁴⁵ Although many factors such as "host, genetic, and environmental" influences have been identified as for the pathogenesis of IBD,¹⁴⁰ currently,

only smoking has been identified as the most potential and specific environmental factor for the onset of IBD.¹⁴⁸⁻¹⁵⁰

CD

CD is a patchy transmural inflammation in the GI tract, which is found anywhere from the mouth to the rectum. Typically, the most common sites of inflammation are the distal sections of the small intestine such as the ileum and the colon. The severity of the condition can range from no symptoms at all (during times of remission) to acutely life-threatening.¹⁵¹ Epidemiologically, the condition is most prevalent in the developed nations of Europe and the USA, with significantly lower incidence in the Southern Hemisphere.¹⁵² Although the pathology and physiology involved in CD are not completely understood, there appear to be many factors that predispose to the condition: bacterial activity in the gut, genetic susceptibility, and irregular immune response.^{151,152} The inflammatory response found in CD is defined by the release of type 1 helper T-cell cytokines, namely tumor necrosis factor-alpha (TNF- α), interferon gamma (IFN- γ), and IL-12.¹⁵¹ The traditional treatments for CD are steroids, anti-inflammatory drugs, and, in particularly severe cases, surgical resection of inflamed portions of the bowel, with ~70% of sufferers requiring surgical intervention during their lifetime.¹⁵¹ However, there is an increasing interest in alternative therapies involving probiotics, prebiotics, and symbiotics. Probiotics have been extensively tested, with varying results. For example, *Lactobacillus* GG was found not to reduce the rates of recurrence in the disease, and Nissle 1917, a strain of *Escherichia coli*, was found to promote quicker remission of the disease, but not to affect the rates of remission between subjects.⁶⁷ The use of prebiotics, on the other hand, has not been explored as deeply, and the few studies conducted have been little more than pilot studies. Symbiotics have shown more potential than either probiotics or prebiotics in isolation. A double-blind randomized control trial was conducted on 35 patients with CD to ascertain the effectiveness of the symbiotic therapy comprising *B. longum* and Synergy 1.¹⁵³ In the present study, appropriately selected subjects ingested either the symbiotic or a placebo every day, for the duration of 6 months. Patients were required to keep a bowel habit diary for the duration of the test. Furthermore, at the beginning, 3 months, and finally 6 months into the study, patients were required to undertake a Crohn's disease activity index (CDAI) assessment, fill out an IBD lifestyle questionnaire, and undergo flexible sigmoidoscopy or colonoscopy. Biopsies were taken for histological analysis. The study found that there were significant improvements in the CDAI and

histological scores of the symbiotic group compared with the placebos. The numbers of *B. longum* in the gut mucosa were found in higher abundance coupled with larger populations of other bifidobacteria. Another important finding was that after 3 months of therapy, the levels of TNF- α (the principal inflammatory cytokine in CD) were markedly reduced in the symbiotic group. However, the reduction in TNF- α was not as significant at the 6-month check-up. Overall, this study showed that symbiotics have the potential to be a viable treatment for CD, which may become more commonplace with time and development.

Ulcerative colitis

UC is one of the two main forms of IBD and is characterized by the formation of ulcers in the lining of the colon and rectum, with patients usually presenting with diarrhea, and with mucus and blood in their stools.¹⁵⁴ It is distinct from CD in terms of site, presentation, and histology. The condition also exhibits more of a type 2 helper T-cell-mediated response, with the production of cytokines such as TNF- α , IL-1 α , IL-1 β , IL-5, IL-8, and IFN- γ .⁹¹ These cytokines recruit neutrophils and monocytes into the mucosa via chemotaxis. As with CD, the etiology is not fully understood, but there is evidence that points to an inappropriate inflammatory response to the gut microbiome. The main classes of drugs used to treat UC are aminosalicylates, corticosteroids, and immunosuppressant, with many patients eventually requiring a colectomy.¹⁵⁴ Probiotics such as VSL#3 (a combination of eight different probiotic bacteria) were found to induce remission in 93% of subjects compared with 36% of the placebo group. Furthermore, the rates of relapse were considerably higher (73%) in the placebo group and only 21% to those on the probiotic course. These are quite convincing figures to the effectiveness of VSL#3; however, it is worth noting that this study was conducted on a cohort of children and adolescents, and the efficacy in adults may not necessarily be the same.¹⁵⁵ Multiple studies reported that still there is doubt regarding VSL#3 efficacy and thereafter more research is suggested.^{156–158} As with CD, the combination therapy of *B. longum* and Synergy 1 has been tested on UC patients. After 4 weeks of therapy, the symbiotic group was found to have improved sigmoidoscopy scores and substantially reduced levels of IL-1 α and TNF- α (which are usually elevated in UC patients). A drop in the concentrations of inducible human beta defensins (hBD) was also recorded in the symbiotic group. This is a strong indicator that the inflammation was reduced, as hBD is only produced and released by epithelial tissue when inflamed. It was also noted that the numbers of

bifidobacteria in the gut had increased by ~42 times their original number.¹⁵² Overall, there was an improvement in bowel activity and positive clinical findings that lay down a foundation for further development of symbiotic treatment.

Irritable bowel syndrome (IBS)

IBS is a chronic illness characterized by the presence of abdominal pain or discomfort, which may be associated with an increased frequency of defecation and/or accompanied by a change in bowel habit as stated in the National Institute for Health and Clinical Excellence Guidelines.¹⁵⁹ The etiology of this condition is poorly understood, with possible causes ranging from mal-fermentation of food substrates to psychosocial factors such as stress.¹⁶⁰ However, it is noted that almost half of the IBS sufferers can identify a definitive event before their symptoms began, for example, surgery, the use of antibiotic drugs, or a spell of gastritis. These are all known to disturb the gut microbiome; therefore, it is hypothesized that this disruption to the bacteria is key to the pathogenesis of IBS.¹⁶¹ Investigations have shown that the composition of the microbiome in IBS patients differs from the norm with a higher presence of facultatively anaerobic microorganisms such as *Streptococcus* spp., *E. coli*, and *Proteus* spp. Conversely, lactobacilli and bifidobacterial populations were reduced compared with nonsufferers.¹⁶¹ Due to the potential importance of the microbiome in this condition, the idea to modulate it with probiotics and prebiotics presents itself. Many studies have been conducted, but the results are yet being not conclusive, but it shows some promise.

Bacteria in the body over time Neonates

The gut microbiome, and principally the study of its ancestries in neonates, have become subtopics of great curiosity within the arena of genomics.¹⁶² The human body does not develop a microbiome until after birth; the sterile nature of the womb prevents microbial colonization until birth. It has been shown in studies conducted in Finland,¹⁶³ as well as in India,¹⁶⁴ that the method of delivery affects the composition and development of the microbiome. Colonization of mucosa in the digestive, respiratory, urogenital tracts, as well as the skin, begins at, or perhaps even before, the time of birth when a newborn is exposed to a mother's microbiota.¹⁶⁵ Beforehand it was believed that the utero environment was mostly sterile and that a fetus was not colonized with bacteria until the time of birth.¹⁶⁵ Babies born by natural means, that is, gain their bacteria from the vaginal tract and fecal matter of the mother, resulting in a more regular and

healthy microbiome. The species most commonly found in this community are *Acinetobacter* spp., *Bifidobacterium* spp., and *Staphylococcus* spp. On the other hand, the species of bacteria found in babies who were delivered by caesarean section (C-section) are more influenced by bacteria from the mother's skin and the general environment. There is also more chance of unwanted opportunistic invaders colonizing the newborn, to occupy niches that would normally have been inhabited by commensals. Prevailing species in C-section neonates were *Citrobacter* spp., *E. coli*, and *C. difficile*. A notable deficit in bifidobacterial species was also detected. These organisms are known to be very beneficial to the human host. It was also found that *Bacteroides* spp., which usually colonize a newborn within 3–10 days from birth,³¹ were still present in very low numbers, even 6 months into the life of the child, showing a significant delay in colonization. It has been suggested that this departure from normal gut microbiota composition and delayed colonization of beneficial commensals in babies, due to procedures such as C-sections, which need extra antiseptic measures for surgical interventions, as well as a general culture of sanitation and hygiene, has contributed to the allergy burden carried by many Western nations. Recent study pigeonholed a placental microbiome profile and found that nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla.¹⁶⁶ Thereafter, it was reported that within the first week of life, the full-term neonatal gut microbiome is largely colonized by Actinobacteria, Proteobacteria, Bacteroidetes, and, much less, Firmicutes phyla.^{165,166} Oversterilizations of our environment, a lower incidence of disease, as well as changes to diet have resulted in lowered exposure to pathogens and antigens and have led to a change in the communities of friendly bacteria that live inside humans. This has possibly led to higher incidences of atopic conditions and leads to the concept of good dirt and that commensal bacteria in early life can defend against future occurrences of allergy.¹⁶⁷ Breast milk has been found to have significant prebiotic properties to the microbiome of infants.^{168,169} Oligosaccharides constitute the third highest concentration of all nutrients that make up breast milk. Mammalian enzymes are unable to digest oligosaccharides, which led to the thinking that these carbohydrates were there to satisfy the nutritional needs of commensal bacteria, rather the child itself.^{170–172} In an experiment, it was shown that the growth of two strains of bifidobacteria, *B. longum* ATCC 15697 and *B. longum* JCM 7007, was promoted when given human milk oligosaccharides (HMOs). Conversely, when HMOs were supplied to *Clostridium perfringens*, a pathogen

that is one of the most common causes of food poisoning, an inhibitory effect was noted.¹⁷³ Finally, the maternal microbiota outlines the immune scheme of the progenies. Maternal colonization reprograms intestinal transcriptional silhouettes of the descendants, including amplified expression of genes encoding epithelial antibacterial peptides and metabolism of microbial molecules.¹⁷⁴

The elderly

The microbiome changes significantly as time passes and the age of the human host increases. There has been found to be greater differences in the gut communities of individuals aged >65 years, than that in younger adults.^{175,176} This may be attributed to a greater variation in diets of geriatrics dependent on their social situation and environment.^{110,177} An experiment was conducted – a test group of elderly subjects (mean age =78 years) was selected and classified into four groups, ranging from community-residing individuals to those in long-term residential care, two ends of a spectrum. A small number of young healthy adults (mean age =36 years) were also included in the study for comparison purposes.¹⁷⁷ Food diaries of dietary intake were kept by each individual, and an analysis of bacteria in their fecal material was conducted. It was found that community-dwelling subjects had the healthiest microbiomes, which were akin to those of the younger cohort of test subjects.¹⁷⁷ On the other hand, microbiomes of the long-term residential group were the most removed from those of a healthy adult, with a lower diversity of the species of bacteria present.¹⁷⁷ An analysis for SCFA production was also conducted, which showed that the bacteria of community subjects possessed more genes that coded for enzymes that produce SCFA than those of long-term residents.¹⁷⁷ When this data is compared with the diets of the subjects, it becomes more apparent from where this disparity stems.¹⁷⁷ Most community geriatric diets came under the category of high fiber/low fat, whereas long-term subjects fell under low fiber/high fat, with the biggest differences in food intake revolving around fruit, vegetables, and meat.^{110,177,178} This shows that diverse and healthy diet results in a similarly positive microbiome and vice versa. Another study has shown that the gut bacteria composition of centenarians differs significantly from that of young or elderly humans.¹⁷⁹

Conclusion

A multiplicity of studies involving the gut microbiome has come to a convergent conclusion that commensal bacterium in the human body plays an undeniably important role in host physiological functions. They are involved in metabolizing

foods, which allows the body to reclaim nutrients that would otherwise be lost as SCFAs such as butyrate. The microbiota has also been shown to provide protection from many chronic diseases of the gut, and they truly deserve the nickname of friendly bacteria.

Disclosure

The authors report no conflicts of interest in this work.

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