THE MICROBIOME AND THE GUT-BRAIN AXIS: INTEGRATIVE MEDICINE APPROACHES WITH IMPLICATIONS FOR INFLAMMATORY DISORDERS

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The Human Microbiota

- Refers to the microscopic organisms of a particular environment (i.e. the gut), which includes bacteria, fungi, and archaea.

- The Human Microbiome refers to their genes.

- Humans are colonized by huge numbers of microorganisms, traditionally thought to be 100 trillion in number, which would total ten times more non-human cells than human cells. More recent estimates significantly lower that 10:1 ratio (recognizing that all the numbers are estimates).
The gastrointestinal tract is a point of interaction between the body’s largest concentration of immune cells, a vast network of 500 million neurons and the gut microbiota. With an estimated mass of 1–2 kg, the approximately 100 trillion bacteria that constitute the human gut microbiota consist of at least 1,800 genera and up to 40,000 species of bacteria [2] and together possess 100 times the number of genes in the human genome [3].

Forsythe and Kunze,

"A 'reference man' (one who is 70 kilograms, 20–30 years old and 1.7 metres tall) contains on average about 30 trillion human cells and 39 trillion bacteria..."

Those numbers are approximate — another person might have half as many or twice as many bacteria, for example — but far from the 10:1 ratio commonly assumed.
“The numbers are similar enough that each defecation event may flip the ratio to favour human cells over bacteria”
Table 1. Bounds for bacteria number in different organs, derived from bacterial concentrations and volume.

<table>
<thead>
<tr>
<th>Location</th>
<th>Typical concentration of bacteria (^{(1)}) (number/mL content)</th>
<th>Volume (mL)</th>
<th>Order of magnitude bound for bacteria number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (large intestine)</td>
<td>(1 \times 10^{11})</td>
<td>400 (^{(2)})</td>
<td>(10^{14})</td>
</tr>
<tr>
<td>Dental plaque</td>
<td>(1 \times 10^{11})</td>
<td>&lt;10</td>
<td>(10^{12})</td>
</tr>
<tr>
<td>Ileum (lower small intestine)</td>
<td>(1 \times 10^{8})</td>
<td>400 (^{(5)})</td>
<td>(10^{11})</td>
</tr>
<tr>
<td>Saliva</td>
<td>(1 \times 10^{9})</td>
<td>&lt;100</td>
<td>(10^{11})</td>
</tr>
<tr>
<td>Skin</td>
<td>(&lt;1 \times 10^{11}) per m(^{2}) (^{(3)})</td>
<td>1.8 m(^{2}) (^{(4)})</td>
<td>(10^{11})</td>
</tr>
<tr>
<td>Stomach</td>
<td>(10^{3} - 10^{4})</td>
<td>250 (^{(5)}) - 900 (^{(6)})</td>
<td>(10^{7})</td>
</tr>
<tr>
<td>Duodenum and Jejunum (upper small intestine)</td>
<td>(10^{3} - 10^{4})</td>
<td>400 (^{(5)})</td>
<td>(10^{7})</td>
</tr>
</tbody>
</table>

\(^{(1)}\) Except for skin, concentrations are according to \([9]\). For the skin, we used bacterial areal density and total skin surface to reach an upper bound.

\(^{(2)}\) See derivation in section below.

\(^{(3)}\) Skin surface bacteria density is taken from \([11]\).

\(^{(4)}\) Skin area calculated as inferred from standard formula by DuBois for the body surface area \([12]\).

\(^{(5)}\) Volume of the organs of the gastrointestinal tract is derived from weights taken from \([13]\) by assuming content density of 1.04 g/mL \([6]\).

\(^{(6)}\) Higher value is given in \([14]\).

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The Human Microbiota

- The relationship of these microorganisms with their human hosts is not merely a commensal one, but rather a mutualistic one, that provides important metabolic and biological functions
Beneficial Functions of Gut Microbiota

• Defense against pathogen colonization by nutrient competition and production of antimicrobial substances
• Fortification of intestinal epithelial barrier and induction of secretory immunoglobulin A synthesis to limit pathogenic bacteria penetration into tissues
• Facilitation of nutrient absorption by metabolizing indigestible dietary compounds
• Participation in the maturation and functionality of the host immune system by providing diverse signals for “tuning” the host immune status

Petra et al; Clin Ther. 2015 May 1; 37(5): 984–995.
Dysbiosis:

A state of imbalanced microbial ecology that contributes to disease

The overgrowth of micro-organisms of low intrinsic virulence induces dysfunction and/or disease by altering the nutritional status and/or the immune response of the host organism
Dysbiosis: Advances in Measuring GI Bacteria

- Beyond culture: Genomic technology has changed the way we measure GI bacteria
- This allows analyses of microbial composition independent of culture, which has revolutionized the study of GI bacterial flora
  - But there are issues regarding variability in assays, which can result in interlab variability
Non-Culture Ways to Characterize Gut Flora

- The Microbiome – via Genomics, based upon DNA or RNA (the recent emergence of low-cost, high-throughput gene sequencing techniques)

- The Metabolomic Microbiome – via Metabolomics, based upon metabolic end-products and by-products
The Neuroimmune Connection

1. CNS acts reciprocally with the immune system
2. CNS drives immunity
3. Immune system regulates the CNS

Immune system

Nervous systems

Immunotoxicity

Neurotoxicity

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Glia and Neurons Work Together

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Important Functions of the Blood-Brain Barrier

• Physical or anatomical barrier for protection of the brain from blood milieu

• Biochemical barrier for selective transport

• Regulatory interface for metabolism or modification of blood- or brain-borne substances
The presence of neural antigens on different cells in the nervous system, which may become targets of neuroautoimmune reaction and antibody production.
These findings suggest that host bacteria vitally regulate microglia maturation and function, whereas microglia impairment can be rectified to some extent by complex microbiota.
Host bacteria constantly control maturation and function of microglia in the CNS
Concept of Brain Effects Secondary to Pathology Elsewhere in Body

Gut-Brain Axis
Tight Junction

Paracellular Uptake

Transcellular Uptake
Gut-Associated Lymphoid Tissue (GALT)
Modulation of tight junction barrier by environmental factors, induction of mucosal immune dysregulation and production of proinflammatory cytokines, in particular IL-1β.

- Stress
- Infections
- Drugs & Xenobiotics
- Enzymes
- Defensins
- Dietary Proteins & Peptides
- Advanced Glycation End Products
- Antibodies
- Neurotransmitters
- Anti-Bacterial Peptides

IL-1β, after binding to IL-1β receptor located adjacent to the tight junction complex induces NF-κB activation, and increases myosin L-chain kinase expression and activation. Activation and synthesis of MLC kinase result in tight junction destruction and intestinal permeability.

modified from Al-Sadi et al., The Journal of Immunology, 183: 5652-5661, April, 2009

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The Role of Environmental Factors in Gut-Brain Inflammation

- Stress
- Infections
- Drugs & Xenobiotics
- Enzymes
- Defensins
- Dietary Proteins & Peptides
- Advanced Glycation End Products
- Antibodies
- Mucins
- Anti-Bacterial Peptides

Tight junction opening

IL-1β

NF-κB activation and translocation into the nucleus

Myosin L-chain kinase activation by NF-κB

Induction of inflammation

Entry of bacterial (LPS) and food antigens in circulation

COURTESY OF A. VODJANI, PhD
T-cell attachment and transmigration after blood-brain barrier breakdown

COURTESY OF A. VODJANI, PhD
Gut Microbiota

Brain

Endocrine

Immune
The resultant microbial diversity, and consequent functional redundancy within an ecosystem, supports overall ecosystem resilience and stability (31, 32). Since resilience and stability largely define the ability of an ecosystem to resist stress, diversity is key to the overall health of the gut microbiota (33).
Gut Microbiota Composition

An individual’s gut microbiota composition depends on:
• Mode of delivery at birth
• Genetic predisposition
• Age
• Nutrition
• Physical activity
• Environmental factors
• Stress
• Infections
• Other diseases
• Use of antibiotics

Microbial colonization of the gastrointestinal tract begins immediately after birth and is carried out by microbes that are derived from the mother and the environment.

The course of microbial colonization of the newborn gut is determined by a complex interaction of factors, including the mode of delivery, feeding practice, and the bacterial load in the environment. When the baby is born, the intestinal tract is sterile, and some vaginal and dermatic flora start to plant in the infant intestine, and they reach an initial balance after 1 to 2 weeks, and then the feeding patterns may become the main factors [7, 21, 25].

The intestinal microbiotas of infants are different from the adult; similarities appear around 1 year of age and converge towards a more commonly shared adult-like microbiota [25].

Around the world, a C-section rate of approximately 19 percent seems to be ideal for the health of both women and newborns. In the United States, however, about one in three births happen by C-section, a rate that has risen dramatically over the past few decades, from 5 percent in 1970 and 20 percent in 1996. By contrast, about 16 percent of births in Finland and 24 percent in the United Kingdom are from C-sections.

Molina et al, JAMA December, 2015
C-SECTION AND INFANT MICROBIOME

- The mode of delivery and environment affected the composition of infant intestinal flora.

- In caesarean children in this study, the dominant bacteria were Veillonellaceae and Enterobacteriaceae, and the abundance of Bacteroidaceae and Bifidobacteriaceae was very little, and thus their intestinal flora were different from infants delivered vaginally.

- Some previous studies have reported that the abundance of the intestinal flora of caesarean children was very low, and the colonization of the intestinal flora lagged behind full-term infants.

- It was noteworthy that the initial colonization of Bifidobacterium and Bacteroides was not normal, which would affect the intestinal flora evolution, and the influence might last a long time [5, 6, 27].

IMMUNE PRIMING

- In humans, Bifidobacterium longum is the typical “maternal probiotic”

- Its concentration decreases with age within the first months and with weaning (33).

- B. longum is critical for immune priming, PP (Peyer’s Patch) development and IgA-production (34) and accordingly should be considered as the first immune-priming probiotic.

Million et al, Human Microbiome Journal
Available online 17 February 2018
New Insights in Gut Microbiota and Mucosal Immunity of the Small Intestine
https://doi.org/10.1016/j.humic.2018.01.004
Impact of Diet in Shaping Gut Microbiota Revealed by a Comparative Study in Infants During the First Six Months of Life

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The development of the gut is controlled and modulated by different interacting mechanisms, such as genetic endowment, intrinsic biological regulatory functions, environment influences and last but no least, the diet influence. In this work, we compared the fecal microbiota of breast-fed (BF), formula-fed (FF), and mixed-fed (MF) infants from Hebei Province, China. By using high-throughput 16S rDNA sequencing analyses, we found some differences in gut microbiota in the three groups. Firmicutes and Proteobacteria were the dominant bacteria at the phylum level in the three groups, where FF infants showed a significant depletion in Bacteroidetes (p < 0.001) and Actinobacteria (p < 0.05). Enterobacteriaceae was the dominant bacteria at the family level in the three groups, but FF infants showed higher Enterobacteriaceae enrichment than BF and MF infants (p < 0.05). The abundance of the Bifidobacteriaceae was only 8.16% in the feces of BF infants, but higher than in MF and FF infants (p < 0.05). The number of genera detected (abundance >0.01%) in BF, MF, and FF infants was only 15, 16, and 13, respectively. This study could provide more accurate and scientific data for the future study of infant intestinal flora.

Keywords: Infant intestinal microbiota, breast-fed, formula-fed, mixed-fed, high-throughput sequencing
BREAST FEEDING AND THE MICROBIOME

- Although it is now apparent that the feeding pattern is not the sole determinant of the levels of bacteria in the infant gut, it is clear that feeding does have a crucial impact. Breastfeeding elevates the levels of bifidobacteria and lactobacilli in the infant gut, and the consumption of breast milk could significantly reduce the risk of necrotizing enterocolitis in infants relative to those who were formula fed [1], so breastfeeding is accepted as being highly beneficial to infants.

BREAST FEEDING AND THE MICROBIOME

- Breast milk is a nutritious food for the newborn, which contains the appropriate nutrients for the growing infant, and it can also have a significant impact on the gut microbial composition by virtue of being a source of prebiotics, which beneficially effect the infant by selectively stimulating the growth of one or a limited number of bacteria in the gut [16]. From the nutritional point of view, breastfeeding is considered the sublimate feeding pattern; its sustainable protective effect could reach to two years after the birth.

Fig. 4. Relative abundance of the intestinal flora at the genus level in infants (percent).
Exclusive and partial formula-feeding have been shown to alter the gut microbiome toward adult patterns, increase proinflammatory bacterial taxa, increase gut permeability, and result in lower concentrations of fecal short-chain fatty acids compared with exclusive breastfeeding. Exposure to proinflammatory bacteria and antigens during the neonatal period may profoundly influence oral tolerance and have long-term consequences on immune health.
Recent studies have confirmed this “window of opportunity” as a limited time range when microbial colonization critically impacts the early-life education of the immune system. ... Similar time sensitivity has been reported for IgE regulation (only colonization with a diverse microbiota < 4 weeks regulates IgE in GF mice), induction of tolerance by Treg cells (colonization < 2 weeks in mice), and down-regulation of TLR4 signaling in mouse intestinal epithelial cells (colonization < 2 weeks in mice). Breastfeeding is important during this window of opportunity, as suggested by the fact that it prevents inflammatory bowel disease (both Crohn’s disease and ulcerative colitis) later in life, whereas antibiotics within the first month of life are associated with an increased risk of allergy and asthma by age 6.
The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions. Recent advances in research have described the importance of gut microbiota in influencing these interactions...

In clinical practice, evidence of microbiota-GBA interactions comes from the association of dybiosis with central nervous disorders (i.e. autism, anxiety-depressive behaviors) and functional gastrointestinal disorders. In particular, irritable bowel syndrome can be considered an example of the disruption of these complex relationships, and a better understanding of these alterations might provide new targeted therapies.
### Table 1 Main principal mechanisms of the bidirectional brain-gut-microbiota axis

<table>
<thead>
<tr>
<th>From gut microbiota to brain:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production, expression and turnover of neurotransmitters (i.e. serotonin, GABA) and neurotrophic factor (BDNF)</td>
</tr>
<tr>
<td>Protection of intestinal barrier and tight junction integrity</td>
</tr>
<tr>
<td>Modulation of enteric sensory afferents</td>
</tr>
<tr>
<td>Bacterial metabolites</td>
</tr>
<tr>
<td>Mucosal immune regulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>From brain to gut microbiota:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alteration in mucus and biofilm production</td>
</tr>
<tr>
<td>Alteration in motility</td>
</tr>
<tr>
<td>Alteration of intestinal permeability</td>
</tr>
<tr>
<td>Alteration in immune function</td>
</tr>
</tbody>
</table>
Figure. Diagrammatic representation of the microbiota-gut-brain (MGB) axis highlighting the proposed bidirectional communications. Gut microbiota can release molecules that may activate the neuroenteric plexus and stimulate brain production of neuropeptides, as well as increase gut-blood barrier and blood-brain barrier (BBB) permeability. The brain releases molecules that stimulate the neuroenteric plexus and gut function. The vagus nerve sends orthodromic and antidromic. CRH = corticotropin-releasing hormone; NT = neurotensin; SP = substance P; Ach = acetylcholine; IL-6 = interleukin 6; TNF = tumor necrosis factor; VIP = vasoactive intestinal peptide; 5-HT = 5-hydroxytryptamine.
MICROBIOTA-GUT-BRAIN AXIS

The microbiota-gut-brain axis is a complex multiorgan bidirectional signaling system between the microbiota and the brain that plays a fundamental role in host physiology, homeostasis, development and metabolism.

Growing evidence shows reproducible and consistent effects of microbial states on mouse behavior, supporting a role for microbiota in modulating behavior.

Differences in anxiety-related behaviors are commonly reported in mice with altered gut microbiomes, implicating the role of gut microbiota in stress and depression.

Wong et al; Mol Psychiatry. 2016 Jun; 21(6): 797-805
Range of Reported Microbiota-Related Effects

• Anxiety-like behavior
• Depression-like behavior
• Nociceptive responses
• Stress responsiveness
• Feeding behavior
• Taste preferences
• Metabolic consequences
ASSOCIATIONS BETWEEN GUT MICROBIAL ALTERATIONS AND CLINICAL DISORDERS

IBS
Infant colic
Inflammatory bowel disease
Hepatic encephalopathy
Parkinson’s disease
Obesity
Allergies
Autoimmune disorders
Autism
Psychiatric disorders
Craving in alcohol dependence

In summary, we demonstrated that autism is closely associated with a distinct gut microflora that can be characterized by reduced richness and diversity as well as by altered composition and structure of microbial community. Most notably, we also discovered that the genera Prevotella, Coprococcus, and unclassified Veillonellaceae were significantly reduced in autistic children. Unexpectedly, these microbial changes were more closely linked to the presence of autistic symptoms rather than to the severity of GI symptoms and specific diet/supplement regimens.
GENERAL APPROACHES TO TREAT DYSBIOSIS

● Dietary Modifications
● Probiotics/Prebiotics
● Antimicrobials as needed
  ● Medications
  ● Herbals
● Fecal Microbial Transplants
Dietary Modifications

- Organic Foods
- Avoid refined carbohydrates/trans fats/processed foods/emulsifiers
This study in *Nature* suggests that common food additives could be contributing to the development of chronic inflammatory diseases. Chassaing *et al* report that dietary emulsifiers (including carboxymethylcellulose and polysorbate-80) induce low-grade inflammation in mice by disrupting the composition of their intestinal microbiota, thereby predisposing these animals to the development of obesity/metabolic syndrome and colitis. They further suggest that the broad use of emulsifying agents might be contributing to increased societal incidence of obesity/metabolic syndrome and other chronic inflammatory diseases.
Our results suggest that diet has a dominant role over other possible variables such as ethnicity, sanitation, hygiene, geography, and climate, in shaping the gut microbiota.

We can hypothesize that the reduction in richness we observe in EU compared with BF children, could indicate how the consumption of sugar, animal fat, and calorie-dense foods in industrialized countries is rapidly limiting the adaptive potential of the microbiota...
Dietary Modifications

- Organic Foods
- Avoid refined carbohydrates/trans fats/processed foods/emulsifiers
- Avoid reactive foods
  - GF/CF
  - Food allergens/sensitivities
The gut microbiome may serve as another worthwhile area of investigation in light of recent studies showing the importance of commensal bacteria in the gut in association with healthy brain function. Animal studies of ASD have supported links between the KD and gut microbiome and mitochondrial changes. Future research will need to identify the key bacteria and cellular mechanisms that are modified by the KD and that are associated with improvements in ASD behavior in humans.

Components of the KD are possibly beneficial in improving social affect in children with ASD. Additional studies are needed to understand how the KD improves behavior. We propose a hypothesis similar to others that changes in carbohydrate and fat composition of the diet, cellular metabolism, inflammatory processes, and gut microbiome are responsible for the improved behaviors in children with ASD on the KD.

Conclusions: A modified gluten-free ketogenic diet with supplemental MCT is a potentially beneficial treatment option to improve the core features of autism spectrum disorder and warrants further investigation.
New research sheds light on how popular probiotic benefits the gut -- ScienceDaily

One of the most well-known of these is Lactobacillus rhamnosus GG (LGG). This strain of bacteria, which is part of many popular probiotic products, has a reputation as a helpful microbe. Researchers have found evidence that it can help with intestinal problems, respiratory infections and some skin disorders. Some research suggests that it may even help with weight loss.

But a key question has remained unanswered: How does LGG actually produce benefits?

Now, researchers at the University of Maryland School of Medicine (UM SOM) have come up with an explanation. It appears that LGG may act as a facilitator, modifying the activity of other gut bacteria. This is the first time this mechanism has been described; the discovery could eventually help scientists create more effective strategies to foster a healthy gut. The paper was published in the latest issue of the journal mBio.

Claire M. Fraser, PhD, professor of medicine at the UM SOM, as well as director of the Institute for Genome Sciences, studied the effect of LGG on a group of elderly subjects. "This species of bacteria has a reputation for being really useful to humans," says Prof. Fraser. "So we wanted to better understand how it might work in the human intestine."

April 16, 2015
University of Maryland Medical Center/School of Medicine

... ingesting LGG led to increases in several genes that foster several species of gut bacteria, including Bacteroides, Eubacterium, Faecalibacterium, Bifidobacterium and Streptococcus. These microbes have been shown to have a range of benefits in humans, including the promotion of a healthy immune system. (Fraser notes that LGG may also have direct effects, in addition to its ability to modify the overall ecosystem.)

"This is a new idea, that some probiotics may work by affecting the overall ecosystem of the gut," said Prof. Fraser. "Previously we tended to think that LGG and other probiotics worked directly on the host. I think this finding has many exciting implications." For one, Fraser says, it lends support to the idea that we need to look at the microbes in the gut as an interconnected ecosystem rather than a series of solitary bacteria. Modifying the behavior of microbes already in the gut may be just as important as adding any single species to this population.
The resultant microbial diversity, and consequent functional redundancy within an ecosystem, supports overall ecosystem resilience and stability (31, 32). Since resilience and stability largely define the ability of an ecosystem to resist stress, diversity is key to the overall health of the gut microbiota (33).
Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors. MIA offspring display an altered serum metabolomic profile, and *B. fragilis* modulates levels of several metabolites… Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorder.
Probiotics and Behavior

Feeding certain lactobacillus and bifidobacterium strains can reduce anxiety and decrease depression-like behaviors in mice

• L. Rhamnosus
• B. Infantis
• B. longum

Bravo et al, Proc Nat Acad Sci 2011
Bercik et al Neurogastroenterol Motil 2011
Desbonnet et al, Neuroscience 2010
Psychobiotics were previously defined as live bacteria (probiotics) which, when ingested, confer mental health benefits through interactions with commensal gut bacteria. This definition can be expanded to encompass prebiotics, which enhance the growth of beneficial gut bacteria.

Psychobiotics are beneficial bacteria (probiotics) or support for such bacteria (prebiotics) that influence bacteria–brain relationships.

Psychobiotics exert anxiolytic and antidepressant effects characterised by changes in emotional, cognitive, systemic, and neural indices. Bacteria–brain communication channels through which psychobiotics exert effects include the enteric nervous system and the immune system.

Current unknowns include dose-responses and long-term effects.

The definition of psychobiotics should be expanded to any exogenous influence whose effect on the brain is bacterially-mediated.

Psychophysiological Effects Of Psychobiotics

(i) Psychological effects on emotional and cognitive processes.

(ii) Systemic effects on the HPA axis and the glucocorticoid stress response, and inflammation which is often characterised by aberrant cytokine concentrations.

Pro-inflammatory cytokines share a strong and well-studied positive association with psychiatric conditions such as depression [13]

(iii) Neural effects on neurotransmitters and proteins.

Relevant neurotransmitters include γ-aminobutyric acid (GABA) and glutamate, which control neural excitation–inhibition balance. Proteins include brain-derived neurotrophic factor (BDNF), which plays a crucial role in learning and memory processes, including spatial learning, extinction of conditioned fear, and object recognition 16, 17. BDNF is reduced in anxiety and depression, a reduction that is reversible through antidepressant action [18].

Now, promising new research from neurobiologists at Oxford University offers some preliminary evidence of a connection between gut bacteria and mental health in humans. The researchers found that supplements designed to boost healthy bacteria in the gastrointestinal tract ("prebiotics") may have an anti-anxiety effect insofar as they alter the way that people process emotional information.

"Prebiotics are dietary fibers (short chains of sugar molecules) that good bacteria break down, and use to multiply," the study's lead author, Oxford neurobiologist Dr. Philip Burnet, told The Huffington Post. "Prebiotics are 'food' for good bacteria already present in the gut. Taking prebiotics therefore increases the numbers of all species of good bacteria in the gut, which will theoretically have greater beneficial effects than [introducing] a single species."

To test the efficacy of prebiotics in reducing anxiety, the researchers asked 45 healthy adults between the ages of 18 and 45 to take either a prebiotic or a placebo every day for three weeks. After the three weeks had passed, the researchers completed several computer tests assessing how they processed emotional information, such as positive and negatively-charged words.

The results of one of the tests revealed that subjects who had taken the prebiotic paid less attention to negative information and more attention to positive information, compared to the placebo group, suggesting that the prebiotic group had less anxiety when confronted with negative stimuli. This effect is similar to that which has been observed among individuals who have taken antidepressants or anti-anxiety medication.

The researchers also found that the subjects who took the prebiotics had lower levels of cortisol -- a stress hormone which has been linked with anxiety and depression -- in their saliva when they woke up in the morning./
Conclusion

The suppression of the neuroendocrine stress response and the increase in the processing of positive versus negative attentional vigilance in subjects supplemented with B-GOS are consistent with previous findings of endocrine and anxiolytic effects of microbiota proliferation. Further studies are therefore needed to test the utility of B-GOS supplementation in the treatment of stress-related disorders.
Patients with stubborn, debilitating bacterial infection may soon be treated with pills full of microbes derived from human feces.

Clostridium difficile is a bacterial infection that causes diarrhea and fever in around half a million people in the United States each year. It is linked to the death of some 14,000 US citizens annually. Some physicians now treat recurrent C. difficile infections with fecal transplants, delivering donor feces filled with healthy microbes via enemas, colonoscopies or nasal tubes that run directly to the gut.

But capsules containing the same donor bacteria are also effective at giving these 'gut microbiome transplants', according to results presented on 3 October at a meeting in San Francisco, California.

Thomas Louie, an infectious-disease specialist at the University of Calgary in Alberta, Canada, treated 31 patients with the bacterial infection, and 90% had no recurrence in the year following treatment. His patients had "very severe disease, they could not do anything," says Louie. "They could not eat. They could not tolerate an enteral diet from the nose to the small intestine." Louie has mainly treated the capsules when treating such a patient.

C. difficile often follows antibiotic use, which has disrupted a person's normal balance of gut bacteria. A gut microbiome transplant using bacteria from the feces of a healthy donor restores that balance, and can be highly effective against C. difficile, which is notoriously difficult to treat with antibiotics.

Gut reaction
The patients in Louie's study each swallowed 24–34 freshly assembled capsules of bacteria, which were coated with gelatin to survive the stomach and reach the intestines. The team followed the patients' progress for up to one year afterwards by sequencing the gut microbiome. They found that C. difficile had disappeared and bacteria associated with a healthy gut microbiome, such as Bacteroides, Clostridium coccoide, Clostridium leptum, Prevotella, Bifidobacteria and Desulfovibrio, increased in numbers.

"This pill idea really is a big advance," says Colleen Kelly, a gastroenterologist at Brown University's Alpert Medical School in Providence, Rhode Island, who performs fecal microbiome transplants using colonoscopy.

A pill made of bacteria grown in a laboratory rather than those extracted from donor feces is a future possibility, and Louie says that he has been contacted by parties interested in commercializing his pill. He adds that his team is currently...
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Here, a small open-label clinical trial evaluated the impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and GI and ASD symptoms of 18 ASD-diagnosed children.

MTT involved a 2-week antibiotic treatment, a bowel cleanse, and then an extended fecal microbiota transplant (FMT) using a high initial dose followed by daily and lower maintenance doses for 7–8 weeks. The Gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. Improvements persisted 8 weeks after treatment.
Similarly, clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended. Bacterial and phagedeep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment. Specifically, overall bacterial diversity and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* among other taxa increased following MTT, and these changes persisted after treatment stopped (followed for 8 weeks).

**Conclusions**

This exploratory, extended-duration treatment protocol thus appears to be a promising approach to alter the gut microbiome and virome and improve GI and behavioral symptoms of ASD. Improvements in GI symptoms, ASD symptoms, and the microbiome all persisted for at least 8 weeks after treatment ended, suggesting a long-term impact.
Challenges to the classical biological explanations of the individual self

Are we humans really the individual, bounded selves we take ourselves to be? Until recently, little seemed more obvious to both the natural and the human sciences.
There is now overwhelming evidence that normal development as well as the maintenance of the organism depend on the microorganisms (collectively the microbiome [5]) that we harbor.

The human is not a unitary entity but a dynamic and interactive community of human cells and microbial cells.

The microbiome is not “influencing” the genome; it is coconstituting the metaorganisms we humans are.

THE MICROBIOME AND THE GUT-BRAIN AXIS: INTEGRATIVE MEDICINE APPROACHES WITH IMPLICATIONS FOR INFLAMMATORY DISORDERS

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