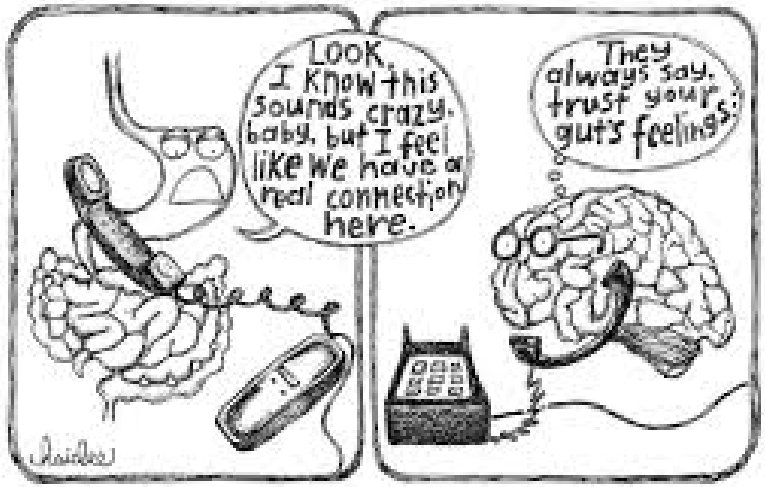
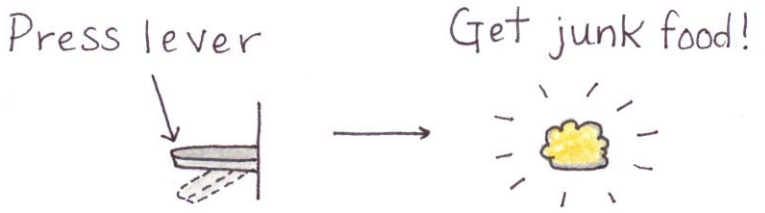
Brain-Gut-Axis



Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD

Who is really in control?



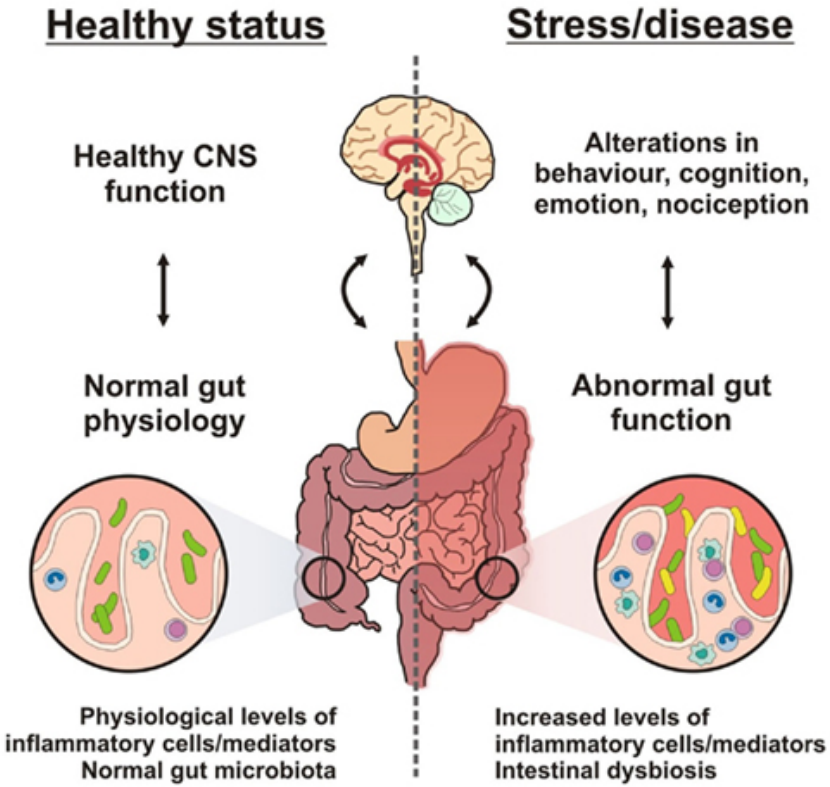
It's been a tough morning. You were late for class, missed an assignment deadline and you have a pop-quiz in class!

At lunchtime you walk straight past Jamba juice and head straight for the Sunshine store to by some junk-food.

Why does the brain 'encourage' us to seek out junk foods to comfort us? Or is it the brain at all??

Bidirectional signaling between the gastrointestinal tract and the brain is regulated at neural, hormonal, and immunological levels.

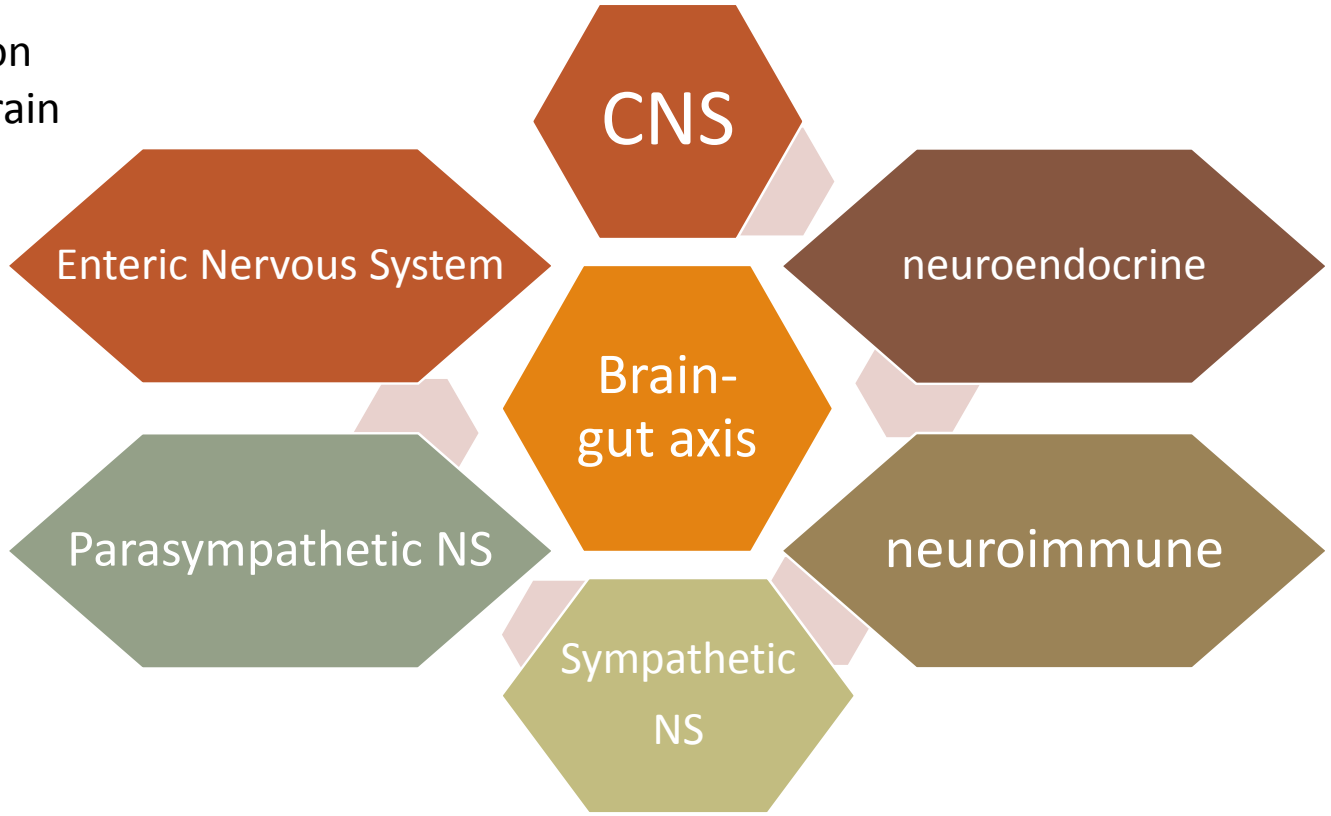
vital for homeostasis



Front. Physiol., 07 December 2011

brain–gut–enteric microbiota axis

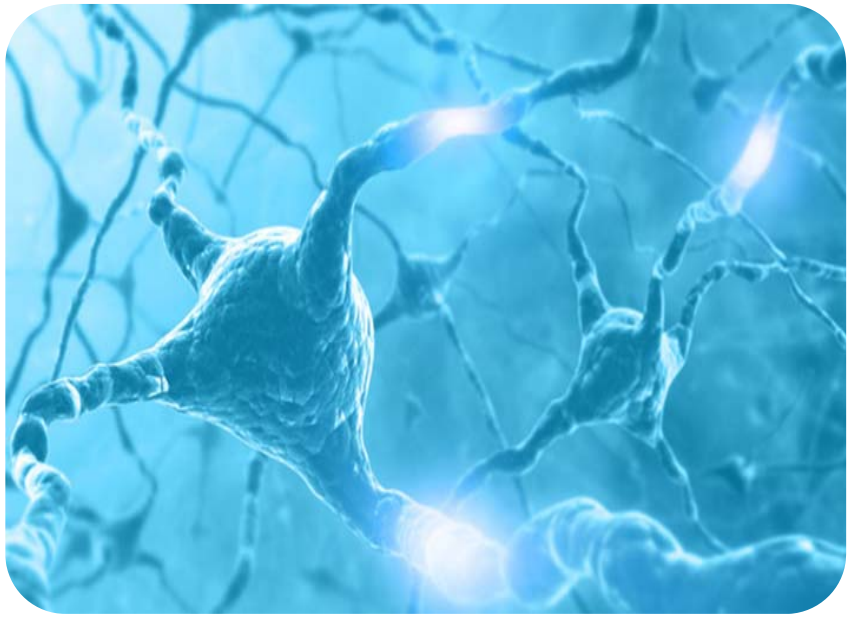
"Bidirectional communication network, signals from the brain can influence the motor, sensory, and secretory modalities of the GIT and conversely, visceral messages from the GIT can influence brain function."

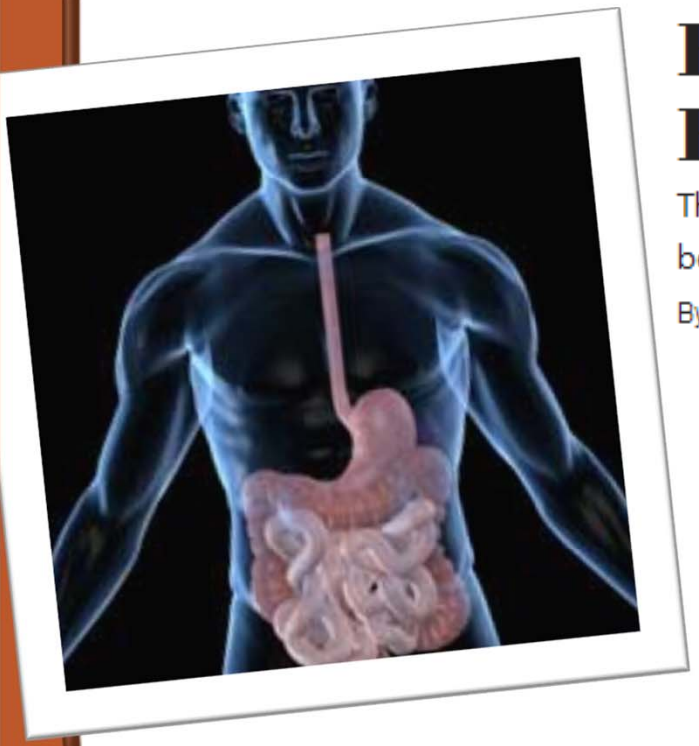


O'Mahony et al., 2011

Gut Bacteria May Manipulate Your Mind

Certain species of gut bacteria can interact with our nervous system in ways that appear to affect our stress responses – and stress response can affect the gut bacteria too!





Think Twice: How the Gut's "Second Brain" Influences Mood and Well-Being

The emerging and surprising view of how the enteric nervous system in our bellies goes far beyond just processing the food we eat

By Adam Hadhazy

Scientific American

GUT CHECK: A complex, independent nervous system lines the gastrointestinal tract that has been dubbed the "second brain".

Image: ISTOCKPHOTO/ERAXION

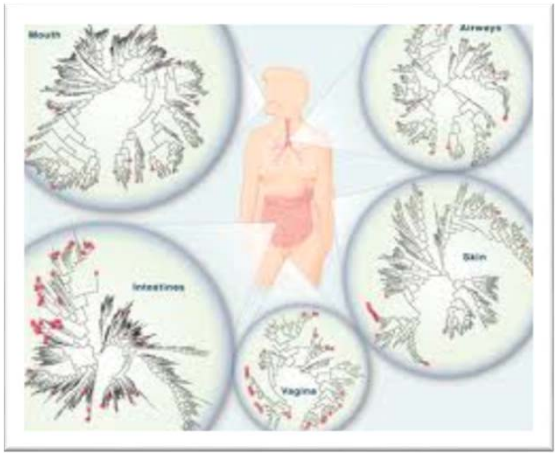
Enteric Nervous System

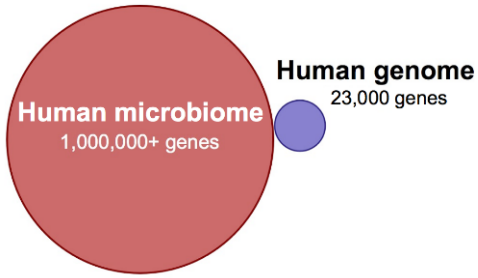
(not discovered until late 1900's is part of the autonomic nervous system.)

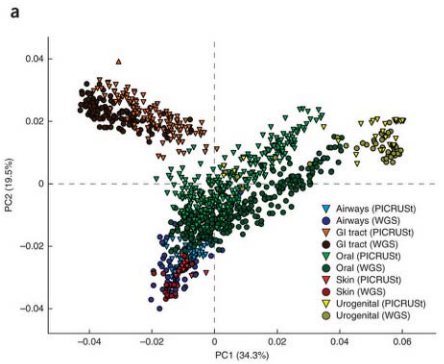
500 million neurons yet has no conscious thoughts.	With reflexes and senses can have 'on site' control of gut behavior – what else does it control?	No thought processes (religion, philosophy, or poetry) yet it can alert you to danger – & influences your response!	90% of vagus nerve information flow is *from* the gut to the brain – how much of that is conscious?

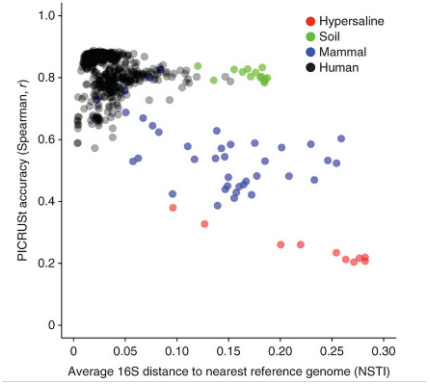
Recall, the autonomic nervous system is the network of peripheral nerves that control visceral functionality.

Numbers matter!







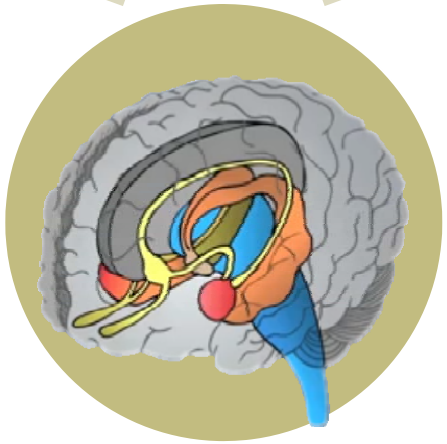


Nature Biotechnology **31**, 814–821 (2013)

Emotions

Immune and Stress response

“Help, I’ve eaten something bad…”



GI turmoil = sour mood

release is inhibited it can counteract osteoporosis

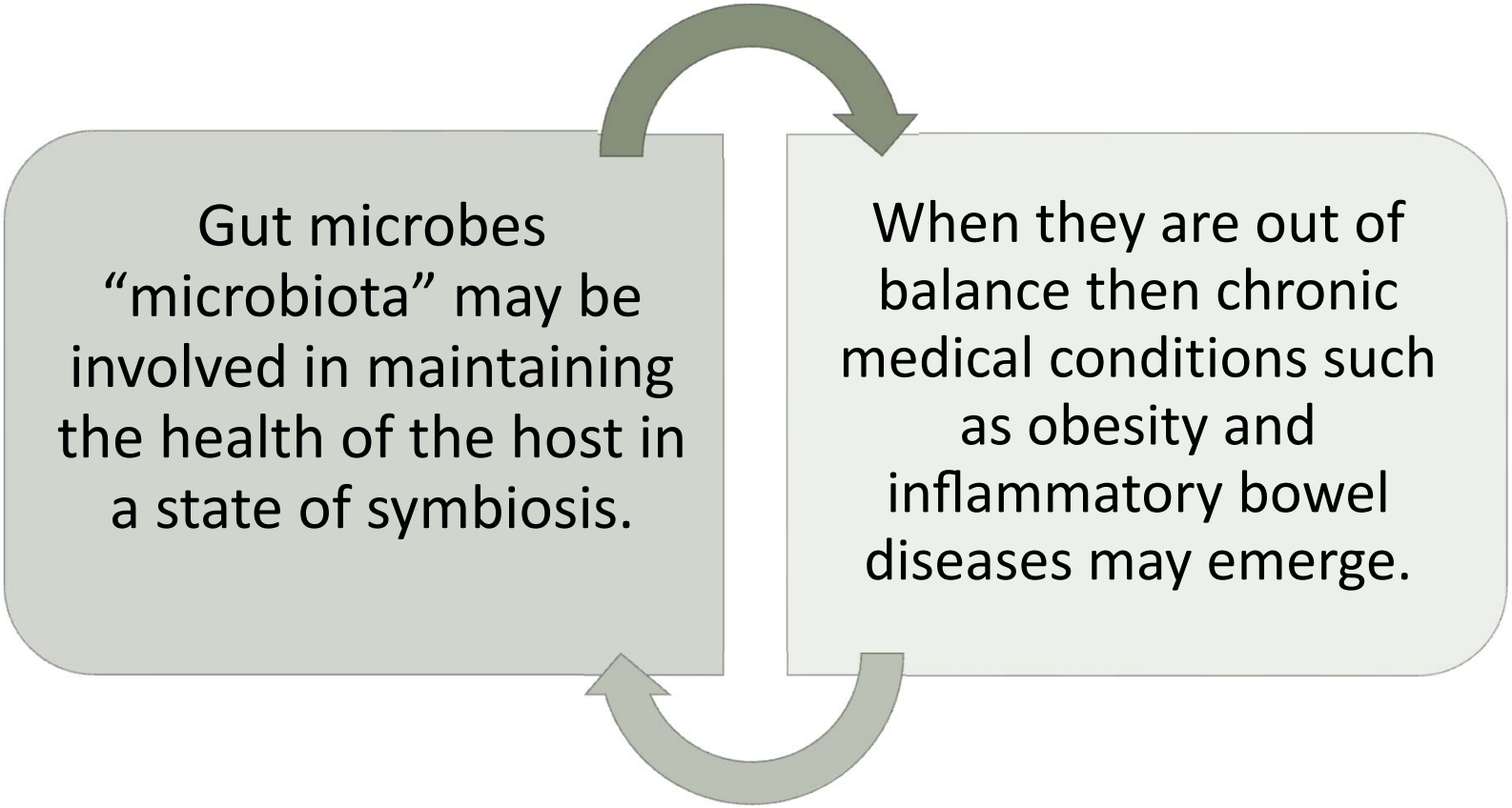
The same genes involved in synapse formation between neurons in the brain are involved in the alimentary synapse formation.

Might explain autism and GI motor abnormalities

Serotonin seeping from the gut may play a role in autism – show elevated gut-produced serotonin in blood.

Immune system uses the gut to expel foreign invaders.

Autoimmune diseases might be associated with the gut.

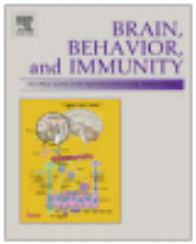

Gut microbes "microbiota" may be involved in maintaining the health of the host in a state of symbiosis.
When they are out of balance then chronic medical conditions such as obesity and inflammatory bowel diseases may emerge.

Brain, Behavior, and Immunity 24 (2010) 9–16

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi



Invited Review

Mood and gut feelings

Paul Forsythe [a,b], Nobuyuki Sudo [c], Timothy Dinan [d], Valerie H. Taylor [e], John Bienenstock [a,b,f,*]

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[e] Department of Psychiatry and Behavioral Neuroscience, McMaster University, Hamilton, Ont., Canada
[f] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ont., Canada

Forsythe, P. et al (2010) Brain, Behavior, and Immunity 24:9–16

co-morbid depression

3x risk of death within 5 years

- myocardial infarction + depression

Higher rates of

- obesity, hypertension, metabolic disorder and diabetes

Forsythe, P. et al (2010) Brain, Behavior, and Immunity 24:9–16

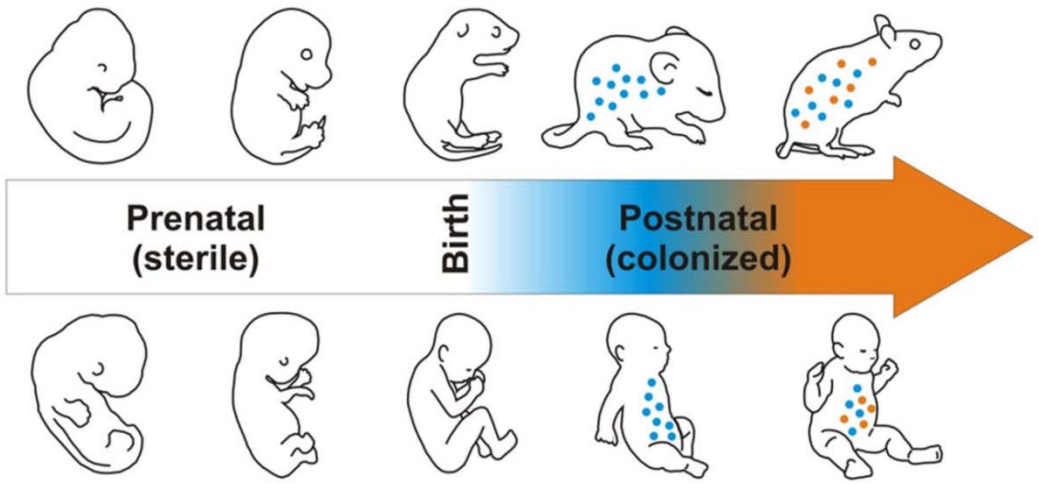
Human gut is sterile at birth.

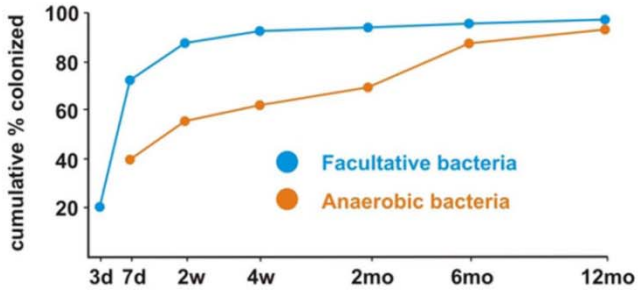
Immediately after birth, it is colonized by numerous types of microorganisms.

By 1 year of age, babies retain their unique bacterial profiles and converge toward the adult individual gastrointestinal tract characteristics.

If there are significant changes such as disease, infections, stress, and diet – the microbiome tends to revert to that which was established in infancy.

Forsythe, P. et al (2010) Brain, Behavior, and Immunity 24:9–16

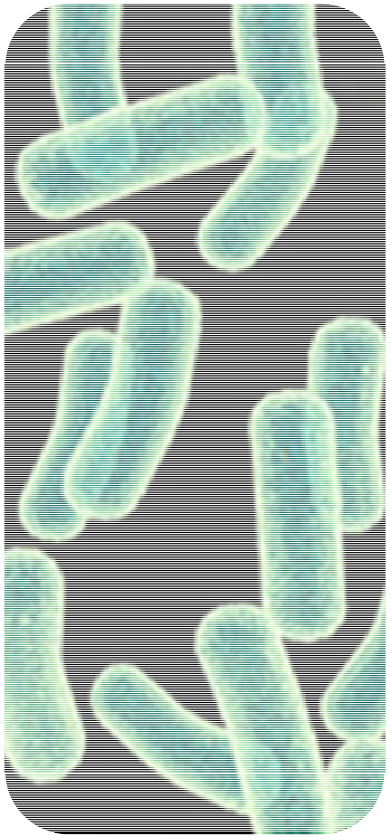




"Subsequent to the sterile uterine environment, colonization begins at birth with facultative bacteria (blue) colonizing the GIT immediately. The anaerobic bacteria colonize later (orange). By 1 year of age the microbiome has a stable adult-like signature. Rodents follow a similar colonization pattern to humans and this forms the rationale for the use of germ free animals to study the impact of the microbiota."

Grenham, S. et al (2011) Frontiers in Physiology "Brain-0ut-microbe communication in Health and Disease"

Immune system & cytokines	• Development of immune system is largely dependent upon exposure to microorganisms.
Germ Free (GF) animals (mice)	• Almost devoid of immune activity • Colonization gut microbiota was able to restore immune function of B & T cells
Antidepressant drugs	• Have effects on gut inflammation levels.



Forsythe, P. et al (2010) Brain, Behavior, and Immunity 24:9–16

Available online at www.sciencedirect.com

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Current Opinion in Pharmacology

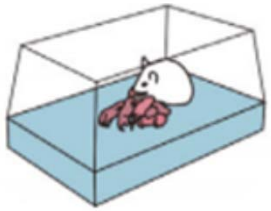
Communication between gastrointestinal bacteria and the nervous system

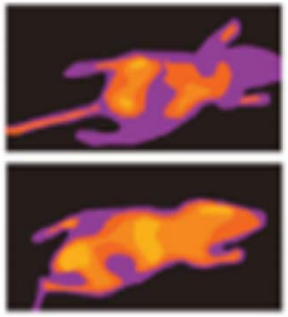
Javier A Bravo[1], Marcela Julio-Pieper[1], Paul Forsythe[2,3], Wolfgang Kunze[4], Timothy G Dinan[6,8], John Bienenstock[2,5] and John F Cryan[7,8]

In the past few years, intestinal microbiota has emerged as a novel target for the treatment of gut–brain axis alterations. These include functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), which can be comorbid with stress related psychiatric conditions. Thus, modulation of the microbiota (e.g. with the use of probiotics) could be proposed as a novel strategy not only for the treatment of IBS but also as an adjuvant for psychiatric treatment of anxiety and depression.

Bravo, J. A., et al. (2012) Current Opinion in Pharmacology, 12:667–672

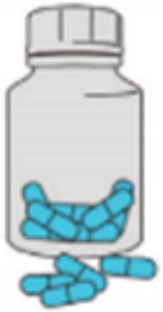
Germ-free animal studies are used to evaluate the role of microbiota on CNS development.

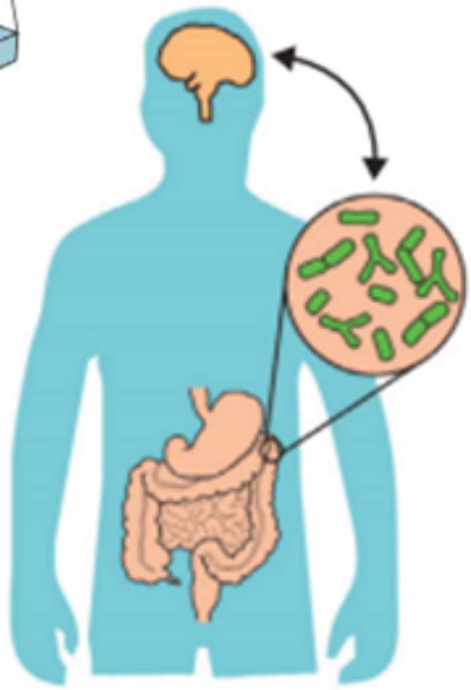




Intestinal pathogenic bacteria can induce anxiety-like behaviors

Wide-spectrum antibiotics are used to affect microbiota composition.





Probiotic treatment promotes intestinal health and improves behaviors associated with stress-related conditions.

Figure adapted from Bravo, J. A., et al. (2012) Current Opinion in Pharmacology, 12:667–672

Psychoneuroendocrinology (2012) 37, 1369–1378

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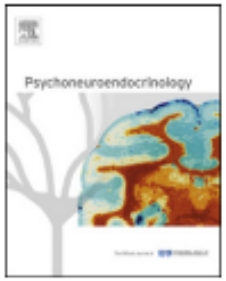


REVIEW

Regulation of the stress response by the gut microbiota: Implications for psychoneuroendocrinology

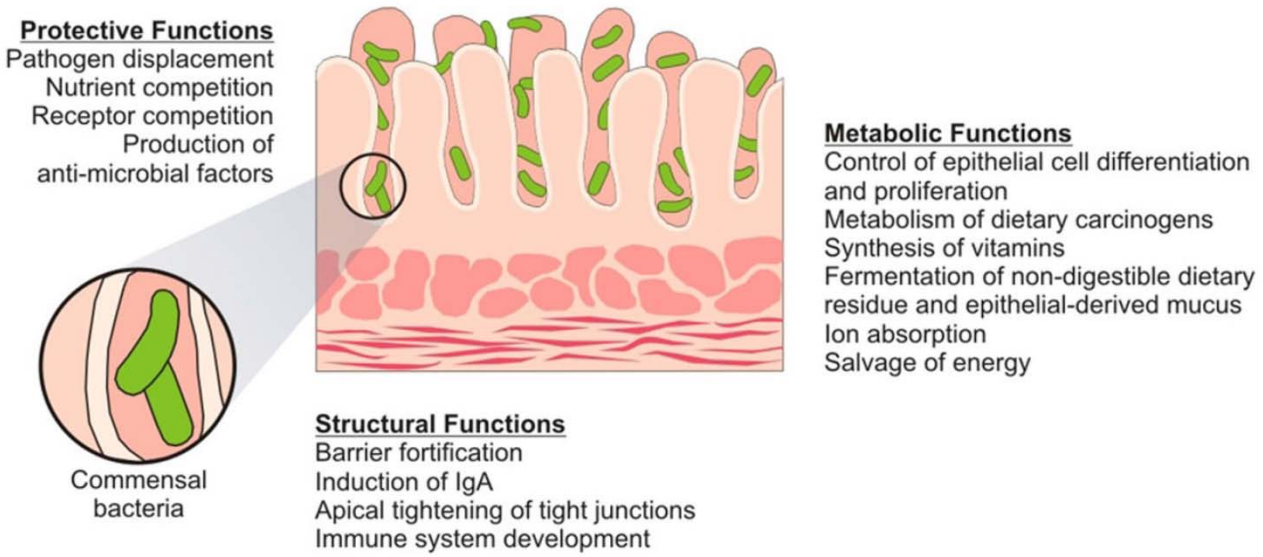
Timothy G. Dinan *, John F. Cryan

Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

Received 1 February 2012; received in revised form 7 March 2012; accepted 7 March 2012

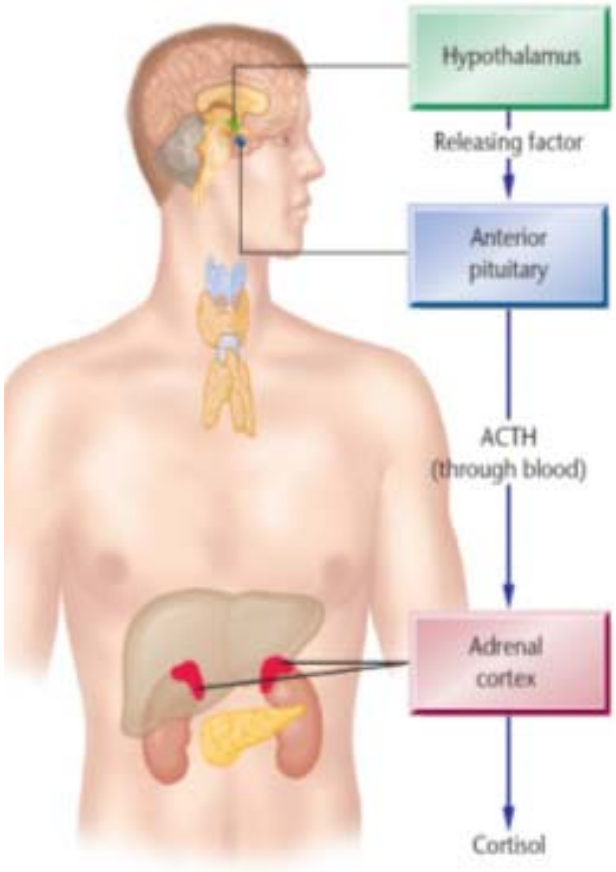
Functional relevance of the microbiota

microbiota is essential for normal GIT motility



Grenham, S. et al (2011) Frontiers in Physiology “Brain-0ut-microbe communication in Health and Disease”

The hypothalamus–pituitary–adrenal axis



Hypothalamus secretes corticotropin-releasing hormone (CRH)

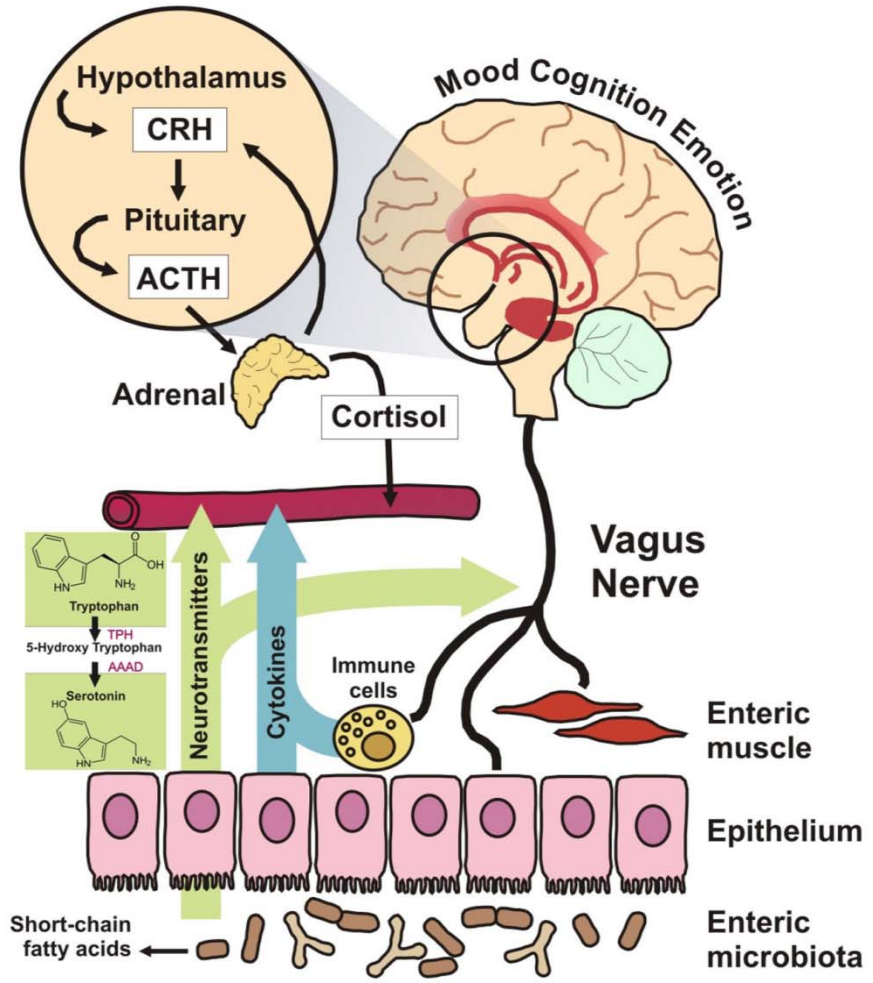
CRH stimulates the anterior pituitary to secrete adreno-corticotropin hormone (ACTH) into the peripheral circulation.

ACTH acts on the adrenal glands causing synthesis and release of cortisol.

Binding of cortisol to an intracellular glucocorticoid receptor (GR) in a wide variety of tissues that instigates signaling pathways crucial to an adaptive stress response.

Major physiological roles for the HPA axis is preventing excessive tissue damage due to inflammation.

Over time this activity diminishes and cortisol secretion stabilizes below normal levels.



Proposed mechanisms of action.

"There are a variety of proposed mechanisms, including both humoral and neural routes, through which the microbiota can modulate signaling along the brain–gut axis.

For example, recent studies suggest a role for both the vagus nerve and modulation of systemic tryptophan levels in relaying the influence of both resident and exogenous microflora along this bidirectional communication axis."

Grenham, S. et al (2011) Frontiers in Physiology "Brain-0ut-microbe communication in Health and Disease"

PNAS

Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

Javier A. Bravo[a,1], Paul Forsythe[b,c,1], Marianne V. Chew[b], Emily Escaravage[b], Hélène M. Savignac[a,d], Timothy G. Dinan[a,e], John Bienenstock[b,f,2], and John F. Cryan[a,d,g,2]

[a]Laboratory of NeuroGastroenterology, Alimentary Pharmabiotic Centre, [d]School of Pharmacy, and Departments of [e]Psychiatry and [g]Anatomy, University College Cork, Cork, Ireland; [b]The McMaster Brain–Body Institute, St. Joseph's Healthcare, Hamilton, ON, Canada L8N 4A6; and Departments of [c]Medicine and [f]Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada L8S 4L8

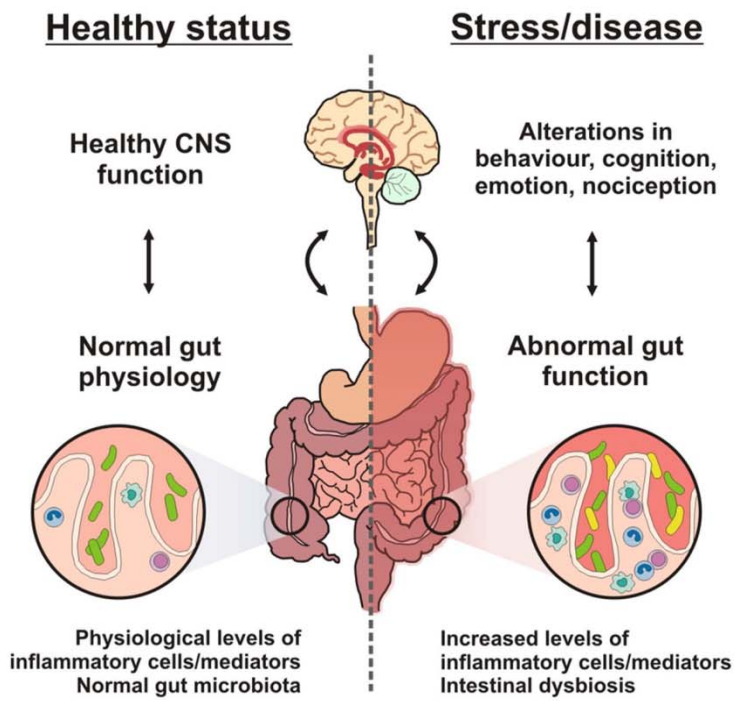
Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved July 27, 2011 (received for review February 27, 2011)

Compared behavior and gene expression in two groups of mice normal and germ free:

Germ-free

- Engaged in “high-risk” behavior
- Neurochemical changes in CNS (i.e. increase in BDNF – linked to depression and anxiety)

Stress can change the composition of the microbiota; which can increase vulnerability to inflammatory stimuli in the gastrointestinal tract.



Brain–gut–microbe communication in health and disease.

"A stable gut microbiota is essential for normal gut physiology and contributes to appropriate signaling along the brain–gut axis and to the healthy status of the individual as shown on the left hand side of the diagram. Conversely, as shown on the right hand side of the diagram, intestinal dysbiosis can adversely influence gut physiology leading to inappropriate brain–gut axis signaling and associated consequences for CNS functions and disease states. Stress at the level of the CNS can also impact on gut function and lead to perturbations of the microbiota."

Grenham, S. et al (2011) Frontiers in Physiology "Brain-0ut-microbe communication in Health and Disease"

PharmaNutrition

Available online 9 May 2013

In Press, Accepted Manuscript — Note to users

Gut Microbes as Modulators of the Neuro-immuno-endocrine System

Paul Forsythe

The McMaster Brain-Body Institute and Firestone institute for Respiratory Health Department of medicine, McMaster University, Hamilton, Ontario, Canada

http://dx.doi.org/10.1016/j.phanu.2013.05.003, How to Cite or Link Using DOI

Evolution, Medicine, and Public Health [2013] pp. 89–103
doi:10.1093/emph/eot008

REVIEW

EVOLUTION, MEDICINE, & PUBLIC HEALTH

Evolutionary biology and anthropology suggest biome reconstitution as a necessary approach toward dealing with immune disorders

William Parker*[1] and Jeff Ollerton[2]

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Parker, W and Ollertn, JEvolution, Medicine, and Public Health [2013] pp. 89–103

ABSTRACT

Industrialized society currently faces a wide range of non-infectious, immune-related pandemics. These pandemics include a variety of autoimmune, inflammatory and allergic diseases that are often associated with common environmental triggers and with genetic predisposition, but that do not occur in developing societies. In this review, we briefly present the idea that these pandemics are due to a limited number of evolutionary mismatches, the most damaging being 'biome depletion'. This particular mismatch involves the loss of species from the ecosystem of the human body, the human biome, many of which have traditionally been classified as parasites, although some may actually be commensal or even mutualistic. This view, evolved from the 'hygiene hypothesis', encompasses a broad ecological and evolutionary perspective that considers host-symbiont relations as plastic, changing through ecological space and evolutionary time. Fortunately, this perspective provides a blueprint, termed 'biome reconstitution', for disease treatment and especially for disease prevention. Biome reconstitution includes the controlled and population-wide reintroduction (i.e. domestication) of selected species that have been all but eradicated from the human biome in industrialized society and holds great promise for the elimination of pandemics of allergic, inflammatory and autoimmune diseases.

Parker, W and Ollertn, JEvolution, Medicine, and Public Health [2013] pp. 89–103

BOX 1. FACTORS POINTING AT THE IMPORTANCE OF BIOME DEPLETION IN THE PATHOGENESIS OF ALLERGIC AND AUTOIMMUNE DISEASE

- **Clinical observations:** Accidental helminth colonization halts the progression of multiple sclerosis [36].
- **Clinical trials:** Exposure to a porcine helminth, *T. suis*, effectively treats some patients with inflammatory bowel disease previously untreatable with modern pharmaceuticals [37].
- **Biomedical Research:** Helminths effectively avert or treat experimentally induced colitis, experimentally induced allergy and type 1 diabetes in rodent hosts [18, 91, 38–43].
- **Immunology:** (i) Helminth colonization enhances the production of regulatory elements [38, 44] that are known to reduce the propensity for allergic and autoimmune disease. (ii) Helminths are known to produce a wide range of molecules that tune down the immune system, thus decreasing the propensity for allergic and autoimmune disease [45]. (iii) Studies of both human [46] and rodent [47, 48, 49, 50] immune systems in individuals with a normal (not modified by modern technology and medicine) biome show an immune system with profoundly different regulation and a hyporesponsive posture compared with immune systems from biome-depleted individuals.
- **Evolutionary biology:** Mammalian coevolution with helminths and other species (e.g. protozoans) have resulted in 'adjustments' in our immune function [43] so that effective immune function is dependent on the presence of a normal biome (see text).
- **Ecology:** As with any ecosystem, profound changes in some aspects of the human biome are expected to have ramifications for many or even all other components of the biome [15].
- **Epidemiology:** The introduction of effective water treatment facilities and sewage handling systems, in combination with lingering effects of a normal biome on the immune system over decades or even generations (epigenetic effects) have created a condition in which allergic and autoimmune disease are still on the rise, but only in industrialized parts of the world.
- **Lack of alternative explanations:** Changes in breastfeeding practices, vitamin D levels and potentially psychological stress doubtless play a role in the incidence of allergic and autoimmune disease in industrialized society. However, these factors alone do not account for the widespread pandemics of allergic and autoimmune disease and, other than biome reconstitution, no other explanations are presently under consideration. Although this factor is not direct evidence for the role of biome depletion, it does underline the urgency of moving research forward at the fastest possible pace.

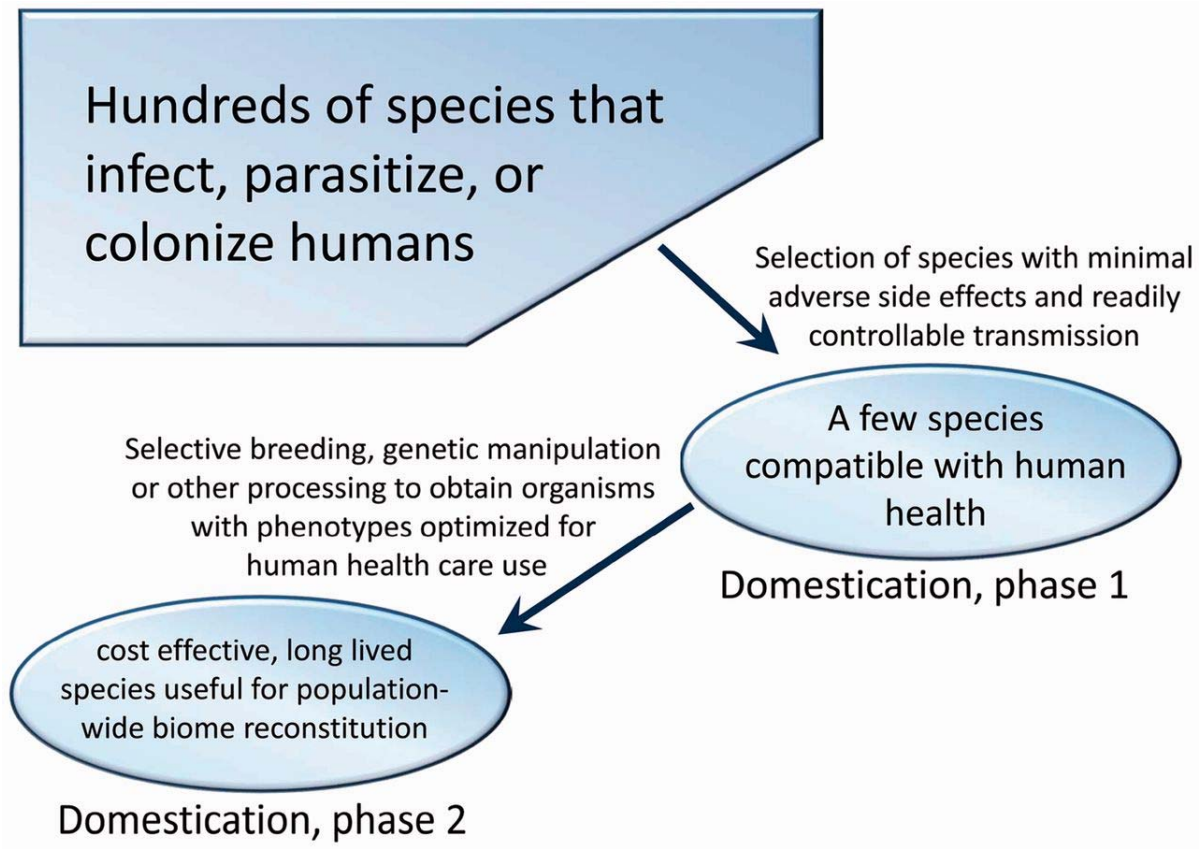
Parker, W and Ollertn, JEvolution, Medicine, and Public Health [2013] pp. 89–103

Table 1. Some diseases associated or potentially associated with biome depletion

Disease	Confirmed in humans[a]	Supported by animal models	Industrialized[b]	Role of immunity	Role of gender
Confirmed or very highly probable					
Asthma		✓	✓	✓	✓
Food allergies		✓	✓	✓	✓
Hay fever or rhinitus		✓	✓	✓	✓
Multiple sclerosis	✓	✓	✓	✓	✓
Eczema (some common types)		✓	✓	✓	✓
Lupus		✓	✓	✓	✓
Type 1 diabetes		✓	✓	✓	✓
Inflammatory bowel disease	✓	✓	✓	✓	✓

Parker, W and Ollertn, JEvolution, Medicine, and Public Health [2013] pp. 89–103

Selection and cultivation of a limited number of candidates for 'biome reconstitution' from a very broad array of organisms which colonize humans.



Parker W , and Ollerton J EMPH 2013;2013:89-103

EVOLUTION, MEDICINE, AND PUBLIC HEALTH

BOX 3. POTENTIAL HELMINTHS FOR BIOME RECONSTITUTION

- The 'rat tapeworm' (*Hymenolepis diminuta*: definitive host = *Rattus norvegicus*, with *H. sapiens* as a potential substitute; intermediate hosts = arthropods) has no adverse side effects in humans [114, 115]. The view that this helminth might help treat autoimmune disease is supported by the observation that exposure to this helminth elicits an increase in eosinophil counts [115], which is a hallmark of helminth colonization that abrogates multiple sclerosis in humans [55]. The rat tapeworm has the advantage that it can be cultivated in clean laboratory rodents and in grain beetles, components of which are already (unavoidably and harmlessly) present in the human food supply [116]. The disadvantage of the rat tapeworm is that it may require repeated exposures to have a long-term beneficial effect. Further, the rat tapeworm may not colonize immunocompetent adult humans well [115], and the lifespan of the helminth is limited to a few years. Thus, long-term treatment with a single dose of the rat tapeworm seems unlikely.
- Potentially accommodating the need for long-term colonization is the 'bovine tapeworm' (*Taenia saginata*; definitive host = *H. sapiens*, intermediate host = *Bos taurus*), which can readily survive in humans for >20 years. Although the bovine tapeworm is considered a commensal (non-detrimental) in humans [117], it produces egg sacks (proglottids) that are motile and thus present a potential psychological barrier to their use. Thus, it is expected that modification of the bovine tapeworm, either by genetic manipulation or by selection of naturally occurring variants, so that eggs or non-motile egg sacs rather than motile egg sacs are released from the host, will greatly increase the potential utility of the bovine tapeworm in humans.
- Another species already undergoing clinical trials [118, 119] is the 'human hookworm' (*Necator americanus*; host = *H. sapiens*, with incubation in soil required between hosts for completion of its life cycle). Like the rat tapeworm, this organism has a limited lifespan and thus may require repeated exposure.

Parker, W and Ollertn, JEvolution, Medicine, and Public Health [2013] pp. 89–103

Microbiota regulate intestinal absorption and metabolism of fatty acids in the zebrafish

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SUMMARY

Regulation of intestinal dietary fat absorption is critical to maintaining energy balance. While intestinal microbiota clearly impact the host's energy balance, their role in intestinal absorption and extra-intestinal metabolism of dietary fat is less clear. Using *in vivo* imaging of fluorescent fatty acid (FA) analogs delivered to gnotobiotic zebrafish hosts, we reveal that microbiota stimulate FA uptake and lipid droplet (LD) formation in the intestinal epithelium and liver. Microbiota increase epithelial LD number in a diet-dependent manner. The presence of food led to the intestinal enrichment of bacteria from the phylum Firmicutes. Diet-enriched Firmicutes and their products were sufficient to increase epithelial LD number, whereas LD size was increased by other bacterial types. Thus, different members of the intestinal microbiota promote FA absorption via distinct mechanisms. Diet-induced alterations in microbiota composition might influence fat absorption, providing mechanistic insight into how microbiota-diet interactions regulate host energy balance.

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Dietary fat contributes a significant caloric value to our diet. Dietary lipids supply 45-55% of the energy requirements in breastfed human infants (Boudry et al., 2010) and 40-55% of the calories in the Western diet (Meek et al., 2010). In vertebrates, dietary fats in the form of triglycerides are digested by lipases within the intestinal lumen and the released free fatty acids (FFAs) and monoglycerides are absorbed by enterocytes in the intestinal epithelium (Karasov and Hume, 1997). Fatty acid (FA) absorption at the brush border of enterocytes is enhanced by solubilization in bile salt micelles or liposomes (Kindel et al., 2010). Once absorbed by enterocytes, FAs are either oxidized to generate energy, reesterified into triglycerides and temporarily stored as cytoplasmic lipid droplets (LDs), incorporated into chylomicrons for secretion into the lymph, or released into circulation as free fatty acids (Iqbal and Hussain, 2009). These exogenously acquired FAs that enter circulation as chylomicrons or FFA are then available for oxidation or storage in extra-intestinal tissues such as liver. Many steps in the dynamic process of exogenous FA uptake into enterocytes and their subsequent assembly into LDs and chylomicrons remain unresolved. An improved understanding of factors controlling dietary FA absorption and LD formation could lead to new approaches for decreasing the efficiency of dietary energy harvest in the context of obesity and increasing efficiency in the context of malnutrition.

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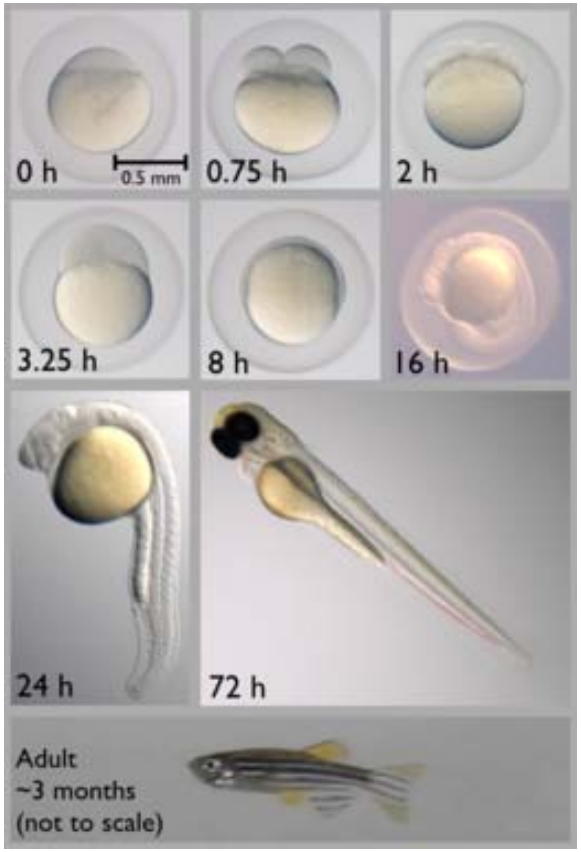


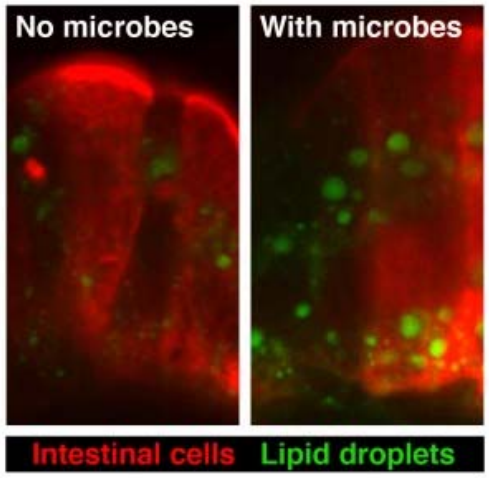
Wikipedia

Using the transparent zebrafish –
Fatty acids are visualized with fluorescent tag
Watch the absorption in the intestine in the presence or absence of microbiota

raised in germ-free environment

compare

colonized by bacteria



- Absorbed more fat from their diets
- The more the fish eat the more the Firmicute population grows.
- Larger Firmicute population increases storage of lipid droplets in the intestinal cells.
- Recall: mice/human studies high fat diet → increases Firmicute population.
- Firmicutes increase the efficiency of the intestinal cells to absorb fat.

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Gut Microbes Make for Fattier Fish

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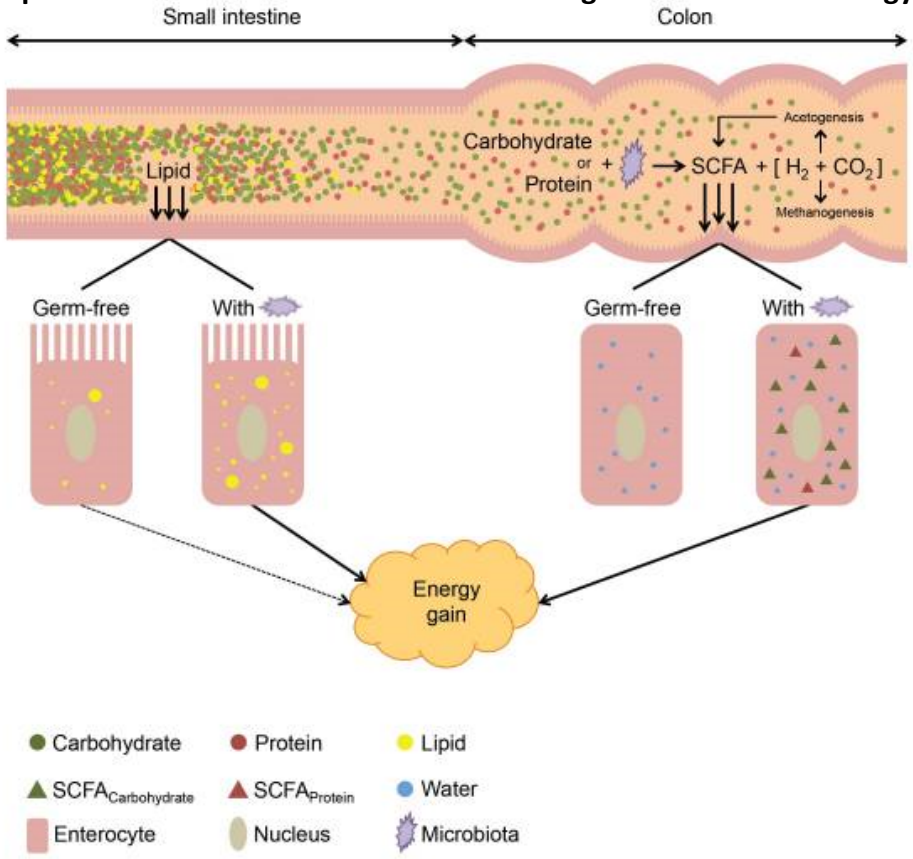
Abstract

The mammalian gut microbiota influences both sides of the energy balance equation, salvaging energy from undigested nutrients and directing the host to accumulate adipose tissue. Semova et al. (2012) use zebrafish to demonstrate that the gut microbiota also promotes dietary lipid absorption, emphasizing the many host-microbial interactions contributing to adiposity.

An expanded model for the contribution of the gut microbiota to energy harvest from dietary lipids, carbohydrates, and proteins



- Gut microbiota stimulate lipid absorption in the zebrafish proximal intestine.
- Compared with germ-free animals fed the same diet, enterocytes of animals conventionalized with a gut microbiota accumulated larger and more numerous lipid droplets.
- Increased lipid accumulation was also observed in the liver of conventionalized animals, suggesting greater uptake of lipids into systemic circulation.
- Microbial processes in the distal gut (colon) are also known to contribute to host energy gain.
- Carbohydrates and protein that resist digestion in the small intestine are fermented by the colonic microbiota, producing short-chain fatty acids (SCFA) that can be assimilated and used as energy by the host.

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