

## LACTIC-ACID-GENERATING BACTERIA AND HEALTH

### I. INTRODUCTION

#### A. Defining Intestinal Microbiota

The gastrointestinal tract is a complex ecosystem with hundreds-to-thousands of microflora and bacteria species <sup>[1]</sup>. Some species are beneficial, such as lactobacillus or bifidobacteria.

Metabolic interactions between the ecosystem and host affect health and well being. Host cells are grossly outnumbered. A human body consists of 15-70 trillion cells <sup>[2]</sup>; for each human cell, there are 9 microflora or bacteria cells. A symbiotic relationship exists. A healthy gastrointestinal tract parallels a healthy host. In contrast, imbalances in the microbial community are implicated in diseases. For instance, bacterial compositions differ between children who develop atopic diseases and those who do not, and between children from countries with a high or low incidence of atopic disease <sup>[3]</sup>.

The gastrointestinal tract has the dual role of excluding pathogens while facilitating the absorption of nutrients. That's not an easy role because gut-associated tissue is the largest lymphoid tissue of the human body. Of particular importance is failure to exclude pathogens (leaky gut). This condition allows pathogens to access the whole body.

Food and water are common sources of pathogens, particularly in less developed countries. That's why intestinal health is considered "the first line of defense." <sup>[4]</sup>

#### B. Contributing Factors

Intestinal microbiota are considered an adaptable and rapidly renewable organ of the body. <sup>[5]</sup> Ecosystem composition can be modified.

Diet is one modifier. Species that receive their preferred nutrients will flourish. Species that don't are disadvantaged in a Darwinian competition.

Probiotic supplements are a second modifier. Lactic acid-generating bacteria are preferred components.

## C. More Than Digestion

The importance of balanced lactic acid-generating bacteria on good digestion is understood. But digestion is not the only benefit. The ecosystem within the GI tract is responsible for other essential processes including: immune system regulation, vitamin bioavailability, sleep cycle, brain health, cytokine production, and vitamin K production.

Lactic acid-generating bacteria compete against or "antagonize" an array of pathogens including *Escherichia coli* (*E. coli*, the cause of "Montezuma's Revenge"), *Staphylococcus aureus* and *Salmonella* (common causes of food poisoning), *Candida albicans* (yeast infections and syndromes), and other pathogens such as *Shigella*, *Clostridium*, *Listeria*, and *Helicobacter* species.

Claimed benefits of lactic acid-generating bacteria include improved immune health, improved mood and mental health, higher energy levels, regulation of hormone levels, reduced yeast infections, and weight control. Success is reported for treatment of diarrhea, Irritable Bowel Syndrome, Crohn's disease, gut dysbiosis, vaginal yeast infections, and urinary tract infections. Lactic acid-generating bacteria produce lactase, which helps people with lactose intolerance <sup>[6]</sup>. Advantageous effects on brain health, immune support, allergies, fertility, cytokine and chemokine production, vaccine enhancement, and Th1/Th2 status are discussed below.

Supplemental probiotics influence diabetes. Probiotics have been shown to delay the onset of glucose intolerance in animals. In a 2010 human study, *L. acidophilus* supplements had a positive effect on insulin sensitivity. People with Type 2 diabetes have gut bacteria different from those without diabetes <sup>[7]</sup>.

Brain, skin, and immune systems are physiologically intertwined and mediated by symbiotic bacteria. Links exist between intestinal bacteria, mood, and acne. Other studies have found links between intestinal bacteria and psoriasis.

## D. Understanding the Health Benefits of Lactic Acid-generating Bacteria

Positive examples of using lactic acid-generating bacteria are widespread. But the focus isn't on the pathogen or disease condition. The focus is on overall health. **The benefit is due to balanced microflora's ability to prevent pathogenic organisms from taking hold in our bodies.**

Louis Pasteur, French chemist and microbiologist, is renowned for his discoveries of the principles of vaccination, microbial fermentation, and pasteurization. On his deathbed, Pasteur reportedly <sup>[8]</sup> said: "Bernard is right. The pathogen is nothing. The terrain is everything." He was referring to the work of

Claude Bernard, the French physiologist who believed that **the focus of conquering disease should not be on pathogens but on the internal environment, which allows harmful bugs to flourish.**

**CortControl agrees with** Bernard and Pasteur.

## E. Intestinal Lining

A healthy intestinal lining has two functional properties. Both are enhanced by lactic acid-generating bacteria.

The first is a mechanical barrier. Bacteria lining the intestines reinforce the barrier that prevents pathogens from seeping out of the GI tract and into the body.<sup>[9]</sup> This is particularly important in the large intestine, where fecal matter accumulates before being excreted. Without a strong barrier, toxins from feces can be reabsorbed, placing an additional burden on the immune system.

The second feature is a thick mucus coating that lines the intestines. *Lactobacillus* and *Bifidobacterium* are important because they produce butyric acid, which is essential to growing the thick mucus coating.

Pathogens become trapped in the mucus. Then the mucus sloughs off and carries pathogens with it, leading to faster elimination.

## II. LACTIC ACID-GENERATING BACTERIA SUPPLEMENTS AND IMMUNITY

There is a connection between the gastrointestinal tract, the overall immune system, and lactic acid bacteria presence. Disease and destruction appear when pathogens overwhelm the body's natural defenses.

Mechanisms that minimize pathogen buildup follow.

### A. pH Control

Lactic acid-generating bacteria support immune health by keeping the digestive tract at a pH less than 7.0. (Acids, by definition, have a pH less than 7.0, and lactic acid is no exception.) Undesirable species tend to thrive when the pH is greater than 7.0.

A low pH makes it difficult for undesirable bacteria to take root and grow. Examples of disadvantaged species include:

- *salmonella* (which causes food poisoning),
- *shigella* (which causes diarrhea), and
- *E. coli* (which can cause intestinal disease and chronic kidney failure).

## B. Regularity

Good gut bacteria help keep you regular by producing acetylcholine, which activates the smooth muscle of the intestines.<sup>[10]</sup> Lactic acid, in particular, plays a role in the production of the neurotransmitter acetylcholine, which facilitates the transmission of nerve impulses that cause intestinal muscle contractions.

The shorter the bowel transit time, the less opportunity there is for toxins to be reabsorbed into the blood stream. Pathogens have less opportunity to accumulate.

## C. Increasing the Desirables to Reduce the Undesirables

Micro-species exist in equilibrium. Supplementing with lactic acid-generating bacteria shifts the equilibrium toward a healthy bacteria balance. The improved equilibrium sets up a positive feedback loop as lactic acid-generating bacteria secretions further weaken the remaining pathogens.

Healthy flora supplements utilize the same strategy. They produce fatty acids and other byproducts, which make it difficult for fungus and yeast to survive.

## D. Decrease the Probability of Pathogen Penetration

Transport across a barrier is proportional to concentration.

By minimizing the concentration of undesirables within the digestive tract, the probability of penetrating the intestinal wall decreases. Fewer pathogens make it into the central immune system.

The overall immune system is not overwhelmed by intestinal pathogens, which needlessly consume immune resources. Instead, the central immune system stays fully staffed.

### III. IMMUNITY FROM INTESTINALLY PRODUCED CYTOKINES/CHEMOKINES

#### A. Lactic Acid-generating Bacteria and Immune Modulation

Cytokines and chemokines are produced inside the intestines. Intestinal epithelial cells respond to certain bacteria by producing an array of cytokines and chemokines which support host immunity. Various experiments indicate that the ability to secrete various cytokines is mediated to a large extent by cell wall components.<sup>[11]</sup>

Production of cytokines within the intestines is thoroughly discussed in the literature. For example,

1. IEC (intestinal epithelial cells) act as the first line of host defense against a pathogenic bacterial invasion or inflammatory stimuli by secreting an array of cytokines and chemokines.
2. *L. acidophilus* NCFM is able to modulate the production of inflammatory mediators, such as TNF- $\alpha$ , IL-1 $\beta$ , CCL2, and IL-6, in dendritic cells (DC) and IEC.<sup>[13]</sup>
3. Bifidobacterium lactis has been found to reduce TNF- $\alpha$  and systemic cytokines, which are important biomarkers in inflammation expression and treatment.<sup>[14]</sup> Most Bifidobacterium strains stimulate the production of high levels of IL-10 but only modest levels of IL-12 and TNF- $\alpha$ .<sup>[15]</sup>
4. Cytokines and chemokines affect the immune cells scattered in the GI tract and recruit immune cells to the GI tract.<sup>[12]</sup> They play a major role in mediating immune and intestinal inflammatory responses.<sup>[16]</sup> Recently, it has been reported that commensal bacteria, such as *L. rhamnosus*, *L. acidophilus*, and *E. coli*, could upregulate the production of many members of the cytokine and chemokine family, such as IL-1, CCL2, and CCL20.<sup>[17]</sup>
5. It is interesting that Interleukin-2 (IL-2) was also significantly reduced through the consumption of particular strains, suggesting that bacterial populations have a direct effect on systemic inflammatory cascades.<sup>[18]</sup>

#### B. Microbes Are Required to Produce Cytokines

Intestinal epithelial cells, intestinal dendritic cells, and micro-organisms work together to generate the cytokines. In laboratory experiments, cytokines are not produced in the absence of micro-organisms because microbiota are essential reactants.

Stimuli provided by colonized bacteria are essential for the development of a fully functional and balanced immune system. This includes homing of B and T cells to the lamina propria, maturation of IgA plasmocytes, IgA production, and tolerance toward innocuous food and microbial antigens.

Cytokines capable of controlling Th1 and Th2 responses do not fully mature in a shortage of microbial stimuli.<sup>[19]</sup>

## C. Intestinal Epithelial Cells (IEC) and Dendritic Cells (DC) Interact to Produce Cytokines

### 1. Intestinal Epithelial Cells (IEC)

Probiotics exert beneficial effects on the health of the host through establishing mutualistic relationships with the IEC and DC.

The human gastrointestinal (GI) tract is lined by a single monolayer of intestinal epithelial cells.<sup>[20]</sup> IEC are recognized as immunological sentinels of the GI tract and play a key regulatory role in maintaining host innate and adaptive mucosal immunity.

Intestinal epithelial cells distinguish between species in the GI tract microbiota. Because contact is continuous, it is clear that advantageous bacteria should not elicit an inflammatory response as intense as pathogenic bacteria.<sup>[21]</sup> Investigators showed that IEC remain hyporesponsive to nonpathogenic commensal bacteria. IEC sense bacteria through expression of conserved pattern recognition receptors, such as the Toll-like receptors (TLRs).<sup>[22]</sup> These receptors activate nuclear factor kappa B (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK), the immune-related transcriptional factors that induce synthesis of cytokines and chemokines.

### 2. Dendritic Cells (DC)

Dendritic Cells are the gatekeepers of an immune response and are the principal stimulators of naive Th cells.

DC are distributed in most tissues and, in particular, at sites that interface with external environment. This includes the mucosa of the gastrointestinal tract, where they reside in the Peyer's patch, lamina propria, and draining mesenteric lymph nodes.<sup>[23]</sup>

DC recognition of molecular structures on bacteria also occurs through Toll-like receptors (TLRs). Activation of these surface receptors by bacterial components regulate the immune response and

mediate between the innate and the adaptive immune function. DC populations are central to the immune-modulating effects of symbiotic bacteria.

Dendritic cells (DC) play a pivotal immuno-regulatory role in Th1, Th2, and Th3 cell balance.

## D. Cytokines and Th1, Th2, Th3

Cytokines are functionally similar to hormones, but are not associated with a specific gland. Cytokines contribute to Th1, Th2 or Th3 states. It has been widely suggested that the delicate balance between Th1 and Th2 immunity, as well as tolerance (Th3), is pivotally controlled by the stimulating DC.<sup>[24]</sup> Stimulation depends on the micro-organisms present.

Th1 immune responses critically depend on the ability of DCs to produce IL-12 and are characterized by the production of interferon IFN- $\alpha$  and IL-2, which induce cell-mediated immunity.

Th2 immune responses involve IL-4, IL-5, IL-6, and IL-13 and induce humoral immunity. IL-10 is an anti-inflammatory cytokine that suppresses IL-12 production and IFN- $\alpha$  production, thus favoring a Th2 or Th3 response.

## IV. LACTIC ACID-GENERATING BACTERIA TO MITIGATE DIGESTIVE PROBLEMS

Predictably, intestinal micro-organisms perform specific functions that improve our ability to digest, absorb, and eliminate the foods we eat. When the balance is off, discomfort arises. For example, gas can be due to an overgrowth of undesirable gas-producing bacteria. Many gas-producing bacteria are the pathogenic type that thrive in a slightly alkaline environment. An increase in lactic acid-generating bacteria can acidify the environment, disadvantage the pathogen, and reduce gas generation.

Changes in the gut microbiota composition are classically considered one of the many factors involved in inflammatory bowel problems. Examples include:

- Irritable bowel syndrome
- Inflammatory bowel disease (IBD)
- Infectious diarrhea (caused by viruses, bacteria, or parasites)
- Antibiotic-related diarrhea

## A. IBS and IL-10/IL-12

At baseline, patients with IBS demonstrated an abnormal IL-10/IL-12 ratio, indicative of a pro-inflammatory, Th-1 state.<sup>[25]</sup> IL-10 levels were lower (575 108 pg/mL vs 968 220 pg/mL), and IL-12 levels were increased (15 2 pg/mL vs 6 4 pg/mL). The ratio was improved by bifidobacteria feeding alone. The authors believe this is the first evidence for an anti-inflammatory approach in IBS.

Supplementing with beneficial bacteria serves three useful gastrointestinal tract functions: (1) absorption of otherwise indigestible nutrients, especially complex carbohydrates, (2) colonization resistance to pathogenic microorganisms, and (3) down-regulating inflammatory cytokines.

## B. Crohn's disease (CD) and ulcerative colitis (UC) inflammatory bowel disease (IBD)

Crohn's disease (CD) and ulcerative colitis (UC) are two distinct clinical forms of inflammatory bowel disease (IBD). They are characterized by chronic relapsing inflammation that is similar to autoimmune diseases. Loss of tolerance to the patient's own symbiotic micro-organisms has been implicated in the development of both diseases.

Decreased levels of bifidobacterium and lactobacillus strains<sup>[26]</sup> have been described in CD and UC fecal samples. Raised counts of Enterococcus and Bacteroides species were found in inflamed mucosa of patients with IBD.

High levels of inflammatory cytokines (TNF- $\alpha$  and IL-1 $\beta$ ) and IL-8 are produced by inflamed colonic mucosa of both UC and CD patients.

In addition, lamina propria T cells from IBD patients secrete elevated levels of IL-6. IL-6/STAT-3 signaling is upregulated.

Bifidobacterium and lactobacillus supplementation is suggested.

## C. Antibiotic-related Diarrhea

Treatment with antibiotics kills both friendly and pathogenic microbes. The antibiotic doesn't discriminate. Diarrhea is not uncommon.

Replacement with lactic acid-generating bacteria is recommended. It's better to guide the replacement of the intestinal ecosystem than leave it to chance.



## V. PROBIOTICS AND BRAIN INTERACTION

### A. Symptoms

Researchers at UCLA's Ahmanson-Lovelace Brain Mapping Center<sup>[27]</sup> have shown that intestinal bacteria affect human brain function. The connection was studied in a resting state and in response to an emotion-recognition task.

### B. Stress, Brain Scans, and Neurotransmitters

Science has long understood that the brain sends signals to the gut. Stress and other emotions contribute to gastrointestinal symptoms. The UCLA study shows what has been suspected, but proven only in animal studies: the gut affects the brain as well. Communication is a two-way street.<sup>[28]</sup> The term "gut feeling" is scientifically supported.

During a resting brain scan, women consuming probiotics showed greater connectivity between a key brainstem region known as the periaqueductal grey and cognition-associated areas of the prefrontal cortex.

One pathway is probiotic ability to produce neurotransmitters. Gamma-aminobutyric acid (GABA), serotonin, catecholamines, and acetylcholine are produced by gut bacteria. These neurotransmitters are secreted within the gut and trigger cells within the gut's lining to release signaling molecules that affect brain function and behavior.

In an example, probiotics lowered stress and anxiety/depression-related behavior. Stress is chemically marked by high cortisol levels. Two studies found that *Lactobacillus rhamnosus* increased GABA, an inhibitory neurotransmitter for cortisol. Higher GABA, in turn, lowered cortisol.

A second pathway wherein probiotics affect the brain is through anti-inflammatory actions. Chronically elevated levels of inflammation are known causes of depression, mood, and cognitive disorders. Probiotic secretions from the gut support brain health by lowering inflammation.

A third pathway is serotonin production in the intestines. Serotonin is involved in mood control, depression, and aggression. Some antidepressants are based on raising serotonin levels. Interestingly, more serotonin is found in the *intestines* than in the brain. That partly explains why dietary changes often help depression more than antidepressants.

## C. Depression

*Lactobacillus helveticus* NS8 was compared to the SSRI, citalopram, in rats with chronic stress. The probiotic worked better than citalopram in reducing stress-induced anxiety, depression, and cognitive dysfunction. It lowered cortisol and restored serotonin and other brain neurochemical levels to normal.

## D. Communication Via the Vagus Nerve

The vagus nerve is the communication channel between intestines and brain.<sup>[29]</sup>

When researchers severed the vagus nerve, brain-gut communication ceased.

## VI. ALLERGIES

Allergy (in the form of atopic diseases such as atopic eczema, allergic rhinitis, and asthma) is a chronic disorder of increasing importance. The International Study of Asthma and Allergies in Childhood included 11,607 Finnish children aged 13-14 years; 10-20% of the children had symptoms of asthma, 15-23% allergic rhinitis, and 15-19% atopic eczema.

In a model of established allergic rhinitis, 3 days of supplementation with *L. acidophilus* L92 and *L. fermentum* CP34 were sufficient to significantly reduce allergen-specific IgE.<sup>[30]</sup>

Both probiotics (LGG or *B. animalis* ssp. *lactis* Bb-12) significantly increased the number of natural Tregs (Foxp3+ CD4+ T cells) in the lungs of asthmatic mice, with Bb-12 showing greater effectiveness.

In 2001, Kalliomäki et al. reported that LGG supplementation of pregnant women and later their infants resulted in a 50% reduction in the risk of eczema by the age of 2 years. This protective effect was maintained at the ages of 4 and 7 years.

*Lactobacillus* studies in both human infants and adults show alleviation of intestinal inflammation caused by food allergy.<sup>[31]</sup> Also, allergic children were less colonized with lactobacilli compared with non-allergic children.

## VII. FERTILITY

CortControl has a huge amount of veterinary data demonstrating that a combination of transfer factor, lactic acid-generating bacteria, and glucans increases animal fertility.<sup>[32]</sup> Lactic acid-generating bacteria is an important component.

Dr. Jean-Jacques Dugoua, a naturopathic physician from Toronto, is an expert on probiotics and human fertility. He found that supplementation with *Lactobacillus rhamnosus* GG, *Bifidobacterium bifidum*, *Lactococcus lactis*, and *Bifido breve* have been found to be beneficial. He says, "Beneficial bacteria in the female digestive and reproductive tracts have a much greater influence on fertility than most clinicians realize." He proposes that one must look at the functioning of her whole body, including probiotic supplements.

Researchers are studying fertility outcomes and lactic acid-generating bacteria from multiple angles: (1) improving IVF outcomes, (2) minimizing pregnancy complications, and (3) supporting the future health of the child and mother. Useful findings include:

Bacterial Vaginosis increases the risk of spontaneous preterm delivery of a low birth-weight infant.<sup>[33]</sup> Bacterial Vaginosis is characterized by a lack of *Lactobacilli*.

Follicular fluid surrounding a developing fetus can harbor pathogenic species of bacteria. In an Australian study, women who tested positive for follicular bacteria had only a 25% IVF success rate, as compared to the standard accepted rate of 47-50%.

Infertility correlates with increased systemic inflammation. This is seen in patients with endometriosis, preeclampsia, and preterm birth.<sup>[34]</sup> Probiotic supplementation attenuates inflammatory biomarkers.

## VIII. VACCINE ENHANCEMENT

The antibody response to vaccines is increased 3-5 times with a combination of transfer factor, lactic acid-generating bacteria, and glucans. In addition, the protection period is extended.<sup>[35]</sup>

Lactic acid-generating bacteria plays an important role. Vaccine response is not independent from the recipient's overall health. Lactic acid-generating bacteria is particularly important where clean water isn't readily available or where food-borne pathogens are not controlled.

Dealing with pathogens in the intestines is a determinant of overall health and, hence, vaccine response.

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