Science Brief: Probiotics – Their Benefit on Human Health

Consider the following review of scientific literature and research regarding improved digestion and immune system health with supplemental probiotics.

Transformation Enzyme Corporation (TEC) is a nutritional supplement company specializing in digestive health, offering quality probiotic and enzyme-based products to the health care professional. Through clinical and observational research, Transformation's efforts focus on teaching the importance of optimal digestion and maintaining the health of the gut as the foundation of wellness and healthy living.

A poor diet and a digestive system that fails to process food for bioavailability and absorption will undermine the body's coping ability and can create conditions favorable for disease and metabolic disorders. Based on this fact, Transformation strives to educate healthcare professionals worldwide on the benefits of a balanced diet and proper digestion. The primary benefits are:

1. **maintaining a strong digestive system**
2. **enhancing the bioavailability of nutrients to the cells**
3. **supporting a strong immune system and cellular vitality**
4. **promoting efficient, timely removal of metabolic byproducts and environmental toxins.**

This Science Brief will review the role of microbes in the human body and the most current research on supplemental probiotics and their impact on digestion and human health throughout the life cycle – infancy through adulthood.

Digestive Disorders Continue to Rise

The demand has never been greater for probiotic supplementation to assist with regular bowel function, promote gastrointestinal health, and support a healthy immune system. The beneficial bacteria normally present in the healthy gastrointestinal (GI) tract may not be properly established from birth with breast feeding and/or often become imbalanced by poor diet choices, environmental lifestyle stressors and the indiscriminant use of antibiotics. Additional issues can arise when opportunistic microorganisms feed on undigested food, creating digestive discomforts such as gas and bloating.

Digestive disorders affect one out of four Americans. According to the USDA Food and Nutrition Information Center, GERD affects 60 million Americans, constipation 6.3 million, and IBS 3 million. The most recent reports from the World Health Organization (WHO) have ranked colo-rectal cancer and stomach cancer among the top ten leading causes of death.

We are now also seeing a greater need in our younger populations. The rate of IBD among children has doubled in the last 10 years. In the October 2012 issue of *Pediatrics*, researchers report as many as 49 million antibiotic prescriptions are written for children each year. Studies show that infants treated with antibiotics before their first birthday have a risk for developing IBD five times greater than those children who never took antibiotics.

The good news is, there is also a growing body of research revealing that probiotics support the healthy balance of native bacteria, benefiting digestion, elimination, and immune function.

The Role of Microbes in the GI Tract

(adapted from 'About Probiotics' at USprobiotics.org)

The microbes present in the gastrointestinal tract have the potential to act in a positive, negative, or neutral manner. Two key roles of the beneficial bacteria are in supporting digestion and immunity, both of which have a huge impact on the health of the host. It is known that microbes in the large intestine complete the digestive process on food components that were not digested in the small intestine.

Bifidobacteria naturally present in the GI tracts of healthy breast fed infants ferment oligosaccharides and support maturation and function of the colon. Other examples of digestive support are production of lactase in lactose intolerant people and digestion of plant fibers resistant to the enzymes they encounter in the small intestine. The

probiotics accomplish this by digesting and metabolizing the food and/or by secreting enzymes such as lactase, protease, and lipase. Additionally, certain intestinal microbes are known to produce vitamins, specifically folic acid, B12, and vitamin K. Also, in studies done with special microbe-free laboratory animals, evidence is strong that, without normal microbial populations, the immune system functions poorly and resistance to pathogenic bacteria is greatly reduced.

It is apparent that there are advantages in skewing the balance of bacteria toward beneficial ones. Both lactobacilli and bifidobacteria are normal inhabitants of healthy intestines and they are considered non-pathogenic. Their presence is correlated with a healthy intestinal flora. The metabolic end products of their growth are organic acids that lower the pH of the intestinal contents, creating conditions less desirable for harmful bacteria.

The gastrointestinal tract also serves to bridge the gap between "inside the body" and "outside the body." Along this interface, microbes and foreign antigens colonizing or passing through the GI tract interact with important components of the immune system. This interaction serves to prime or stimulate the immune system for optimal functioning. Normal microbial inhabitants of the GI tract also reinforce the barrier function of the intestinal lining, decreasing passage of bacteria or antigens from the intestine into the blood stream. This function has been suggested to decrease infections and possibly allergic reactions to food antigens.

FAQ: Where Are Microbes Found in the Body?

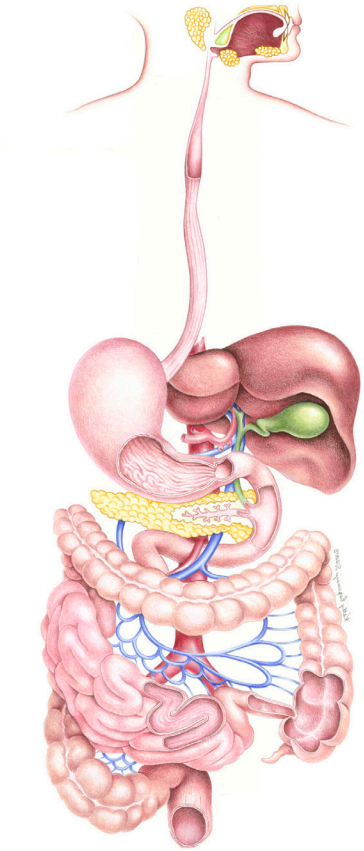
The human body, like all animals, is host to as many as 1,000 different species of bacteria that reside on our skin and in our mouth, GI tract, and the vagina in women. In fact, it is estimated that there are more microbes associated with the human body (about 10^{14}) than there are human cells in it (about 10^{13}) (CAST 2007). *Figure 1* shows the location of some of the most commonly supplemented probiotics.

Health-Supporting Benefits of Probiotic Supplementation

(adapted from 'Probiotics: Their Potential to Impact Human Health,' Council for Agricultural Science and Technology (CAST) Issue Paper Number 36)

The literature and research continues to grow exponentially in the field of supplemental probiotics. The beneficial effects of supplementing a healthy diet with probiotics likely results from several complex, interacting mechanisms that will differ for different strains and sites of action. These mechanisms may include competition for binding sites to the intestinal wall, competition for essential nutrients, production of antimicrobial substances, stimulation of mucin production, stabilization of the intestinal barrier, improvement of gut transit, metabolism of nutrients, and immunomodulation.

Contrary to what was once believed, current research is showing probiotics generally do not have a large or consistent impact on populations of intestinal microbes, but exert their effects in a more transient manner. This is likely because the native microbiota are a well-adapted, naturally stable association of microbes that effectively resist change (see review issued by the French Food Safety Agency [AFSSA 2005]). On the other hand, probiotics have been shown to impact the biochemistry of the intestinal environment, and administration of probiotics during periods of disruption of normal microbial balance (such as



Mouth	*L. acidophilus* *L. salivarius* *L. casei*
Stomach Sparsely colonized (~10^3 CFU/g of contents)	*L. reuteri*
Small intestine Microbial colonization is sparse in the duodenum, increasing until it reaches ~10^{6-7} CFU/g of contents in the distal ileum	*L. reuteri* *L. acidophilus* *B. longum* *L. salivarius* *B. bifidum* *L. casei* *B. infantis*
Large intestine (colon) Richly colonized with a great diversity of microbes reaching 10^{11} CFU/g of contents	*L. rhamnosus* *L. plantarum* *B. coagulans*
Vagina	*L. acidophilus* *L. salivarius* *B. bifidum* *B. infantis* *L. plantarum*

Figure 1. Location of beneficial bacteria in the human body

during antibiotic therapy) seems to provide opportunity for probiotics to positively affect health.

In the past decade there has been a shift of focus from probiotic-induced changes in populations of microbes to more readily measurable end points. The following section is an overview of the benefits of probiotic supplementation on human health (the full text and findings can be found at usprobiotics.org, CAST Issue Paper 37).

Regulation of the Immune System

Of paramount importance to the function of many probiotic bacteria is their ability to impact the immune system. This is perhaps the most broadly studied mechanism of probiotic impact on human health and provides a key means by which probiotics may mediate effects all through the body of the host. Different probiotics are able to stimulate, as well as regulate, several aspects of natural and acquired immune responses. This interaction has broad-reaching significance to human health and could impact infectious disease, response to vaccines, cancer, allergic disease, autoimmune disorders, and inflammatory diseases. Animal studies show that different strains of probiotics can have different effects on the immune system. Effects also are dependent on dose and on immune status of the host. Different probiotics can stimulate immune responses or down-regulate inflammatory responses.

Delivery of Functional Proteins: Enzymes & Cytokines

Probiotic bacteria are capable of delivering enzymes or other functional proteins. As discussed previously, perhaps the best example of this is the microbe-mediated delivery of the enzyme that turns lactose into the more readily digested glucose and galactose in people unable to digest lactose fully. Some probiotic-derived enzymes may help to digest food that enters the small and large intestines. Braat and colleagues (2006) successfully used a genetically engineered *Lactococcus* to deliver the cytokine IL-10, which can decrease the inflammatory response, to the intestinal tracts of Crohn's patients. The treatment induced remission in five of the ten patients treated in the study, and three others showed clinical signs of improvement.

Producing Antimicrobial Substances

Several probiotic bacteria have been shown to produce a range of antimicrobial substances including organic acids (lactic acid and acetic acid), hydrogen peroxide, carbon dioxide, and diacetyl, as well as bacteriocins and bacteriocin-like substances (Mishra and Lambert 1996; Ouwehand et al. 1999). Both lactic and acetic acids inhibit microbes by decreasing the pH of the intestinal contents, which retards every aspect of bacterial metabolism (Mishra and Lambert 1996). Hydrogen peroxide inhibits the growth of both Gram-positive and Gram-negative bacteria (Hollang, Knapp, and Shoesmith 1987; Mishra and Lambert 1996). Diacetyl exerts its growth-inhibitory effect by interfering with arginine utilization by reacting with arginine-binding proteins (Jay 1986).

FAQ: What exactly is intestinal flora?

In the scientific literature, flora is defined as the microorganisms that normally inhabit a bodily organ. The natural flora found in the human intestines is referred to as native microbiotica. Our microbiota is unique to the individual, diet, lifestyle, and environment. They consist of beneficial, neutral, and potentially pathogenic microorganisms. In the healthy individual, the beneficial are dominant.

FAQ: How are probiotics different than enzymes, and why do so many people get them confused?

Probiotics and enzymes are similar in that they both support healthy digestion.

- Digestive enzymes are proteins that catalyze the breakdown of food into nutrients for absorption into the blood stream.
- Probiotics are live supplemental microorganisms that support the native microbiota.

Many probiotic strains are also known for their ability to secrete enzymes and/or metabolize food in the intestines, thereby assisting the digestive process.

Bacteriocins are defined as proteins or protein complexes of high molecular weight produced by certain bacteria that kill bacteria, usually closely related to the strain producing the bacteriocin (Klaenhammer 1988). Probiotic bacteria have been shown to produce two types of antibacterial substances: low molecular weight antimicrobial substances (e.g., reuterin, produced by *L. reuteri*) and bacteriocins (Ouwehand 1998).Whether all or some of these substances are produced by these bacteria once they are inside the host is not known. Recently, however, Corr and colleagues (2007) documented that an anti-Listeria activity observed in animals fed a bacteriocin-producing strain of *Lactobacillus salivarius* was lost in mutants no longer able to produce the bacteriocin. This is the first definite proof that pathogen inhibition results directly from bacteriocin production by the probiotic.

Stimulation of Mucin Production

A gel-like mucus layer composed of complex proteins bound with sugar molecules (mucins) covers the intestinal surfaces. The mucus layer shields the gut surface

from direct contact with the contents passing through the intestine and acts as a barrier against invasion by pathogenic organisms and toxins (Sanderson and Walker 1994; Yolken et al. 1994). Mucus can protect against enteric pathogens by serving as a physical barrier, by housing antibodies that can bind potentially harmful antigens, and by releasing mucins into the intestinal tract thereby removing bound pathogens from the intestinal cells (Dai et al. 2000).

It is well documented that some members of the natural microbiota are able to degrade intestinal mucin, whereas others are able to stimulate mucus secretion (Kohler, McCormick, and Walker 2003). Mack and colleagues (1999) showed that certain probiotics are able to influence the regulation of mucin production. Growth of probiotics (*L. rhamnosus* GG and *L. plantarum* 299V) with colon cells in laboratory studies resulted in stimulation of mucin production. Furthermore, these strains were effective at inhibiting enterohemorrhagic *E. coli* attachment to mucus-producing intestinal cells, but not to non-mucus-secreting cells, thus suggesting a protective role of mucin. The ability of probiotic strains to impact mucus production is an elegant example of communication of the bacteria with the host and may provide a mechanism by which probiotics can decrease the likelihood of infection by pathogens.

Stabilization of Gut Mucosal Barrier

The native microbes colonizing human bodies play an important role in preserving the integrity and function of the barrier between the contents of the intestine and the inside of bodies. This integrity can be compromised by pathogenic bacteria, toxins, inflammation, or stress, leading to intestinal permeability and unwanted transfer of bacterial (including resident microbiota) and dietary antigens across the gut wall. This transfer leads to activation of immune responses that can result in inflammatory and autoimmune disorders. Increased gut permeability is a characteristic feature of food allergies and immunoinflammatory gut diseases.

Recent studies have shown that intake of specific probiotics is effective in preventing and repairing damage to the lining of the intestine. Some animal studies have demonstrated reduced gut permeability associated with cow's milk feeding (Isolauri et al. 1993) and inflammatory bowel disease (Madsen et al. 2001). Probiotics may mediate these effects in several ways: by inhibiting damage to intestinal cell junctions (Luyer et al. 2005; Montalto et al. 2004); improving cell growth and survival (Otte and Podolsky 2004); inducing mucin secretion (Mack et al. 2003); promoting tissue repair (Yamaguchi, Yan, and Polk 2003); decreasing bacterial adhesion (Sherman et al. 2005); and secreting repair factors and nutrients (e.g., short-chain fatty acids, polyamines, nitric acid, and stimulating production of secretory immunoglobulin A [IgA]) (Viljanen et al. 2005). The ability of probiotics to produce factors that directly strengthen intestinal barrier integrity and protect against pathogenic bacteria also has been reported (Madsen et al. 2001).

FAQ: Why isn't eating yogurt enough for probiotic repopulation?

Yogurt and fermented foods contain "live cultures" that can be beneficial, but they should not be compared to probiotics. Probiotics are specific genera, species, and strains of bacteria that have been isolated and identified with certain characteristics. The live cultures in most fermented foods have not been isolated and are not the same as probiotics. Additionally, the colony forming units (cfu) in a supplement are often much more concentrated than in food.

FAQ: With so many probiotics on the market, how can I choose a good one for my family's own situation?

I would recommend you review the research available on the specific species and strain. The manufacturer and/or your health professional should be able to provide this information to you.

FAQ: What is the difference between a prebiotic and a probiotic?

Prebiotics support and stimulate growth of beneficial and advantageous bacteria. For example, carbohydrate, fiber, or starch based prebiotics serve as food for the microbiotia and probiotics. These prebiotics supply fructo-oligosaccharides (FOS), often in the form of inulin, from foods such as Chicory Root and Jerusalem or Globe Artichoke. Bacteriophages are also classified as prebiotics since they enhance the growth of beneficial bacteria in the gastrointestinal tract by inhibiting the growth of neutral or potentially harmful bacteria. This process creates an availability of space and resources to allow the growth of beneficial organisms (see our 'Product Monograph: Transbiotic').

Clinical Applications of Probiotics

In an effort to bridge the research findings with clinical outcomes please refer to the following list from CAST giving an overview of available clinical research to date.

- Immune enhancement (Gill and Guarner 2004)
- Diarrhea (rotavirus, travelers', antibiotic-associated, *C. difficile*) (Szajewska, Ruszczynski, and Radzikow-

ski 2006; McFarland 2006; Sazawal et al. 2006)

- Alteration of intestinal microbiota (Agence Francaise de Sécurité Sanitaire des Aliments/ French Food Safety Agency (AFSSA) 2005)
- Harmful intestinal microbe activities (Agence Francaise de Sécurité Sanitaire des Aliments/ French Food Safety Agency (AFSSA) 2005)
- Lactose digestion (Marteau et al. 1990)
- Allergy development and symptoms (Kalliomaki et al. 2001; Viljanen et al. 2005)
- Inflammatory bowel diseases (Gionchetti et al. 2000; Kruis et al. 2004)
- Vaginal infections (Anukam et al. 2006 a, b)
- Delivery of cloned components active in gut (IL10, vaccines, anti-viral agents, toxin receptors) (Braat et al. 2006)
- *H. pylori* colonization of the stomach (Sheu et al. 2006)
- Absences from work, daycare (Tubelius, Stan, and Zachrisson 2005; Weizman, Asli, and Alsheikh 2005)
- Irritable bowel syndrome (O'Mahony et al. 2005)
- Colds (de Vrese et al. 2005)
- Growth for undernourished young children (Saran, Gopalan, and Krishna 2002)
- Colon tumors (primary evidence in animals) (Ishikawa et al. 2005)
- Dental caries (Nase et al. 2001)
- Blood pressure (Jauhiainen et al. 2005)
- Blood lipid profiles (Hlivak et al. 2005)

Probiotic Health Benefits

When looking at the research and health benefits of probiotics, it is very important to note the specific strain if available. For example, there are many different strains for *L. Acidophilus*, and each strain can provide different health benefits. While identification of the strain is important, much of the historical research has been done on the general genus and species omitting reference to the strain. As more and more research is completed there will be more strain specific studies available.

Please refer to Table 1 for the specific strains used in Transformation's probiotic formulas. For additional research on the individual strains please request copies of our technical sheets. In general, the bacteria in Transformation's probiotic formulas have been carefully selected based on the following characteristics:

- **GI Stability.** These strains are well suited for intestinal survival / gastrointestinal compatibility and have been selected due to their adherence to intestinal mucosa, GI stability, and resistance to heat, acid, pH, bile salts, pepsin, and pancreatin.
- **Intestinal Adherence.** These probiotics successfully adhere to intestinal cells of the mucosa and support native flora already present in the GI tract. Research is finding that most supplemental probiotics are transient and colonize only temporarily in support of the native flora.
- **Acid Producing / Anti-Pathogenic.** These strains produce various acids such as lactic acid, hydrogen peroxide, and acetic acid. This in turn inhibits the

FAQ: Do I need to take a probiotic for life?

Yes. Taking supplemental probiotics confers health benefits to the host by improving the environment and supporting the existing microbiota. The most current research is showing that the native microbiota is quite hardy and well established, however the probiotics are mainly transient (adhere to intestinal cells temporarily), giving rise to the need for continual supplementation.

FAQ: If I am on an antibiotic, is it pointless to take a probiotic?

No. In fact, it is very beneficial to take probiotics while on antibiotics. They support the growth and maintenance of the native microbiota, and many of the strains being studied are actually resistant to antibiotics. Several studies show the beneficial effects of probiotic supplementation, in particular its ability to reduce antibiotic diarrhea.

FAQ: Can I take too many probiotics?

The general answer is no, however the species, strains, and activity per dose should be suited to the individual's health needs.

FAQ: Should I rotate my probiotics?

If users are taking the single-strain Plantadophilus formula for an extended time, we generally suggest they switch to the higher activity and mixed strains in Probiotic so they can have balance. For example, children who have begun eating like an adult from the table can benefit from the switch to Probiotic, and also if constipation is a problem. Similarly, users of Probiotic may want to rotate to maximum strength Probiotic 42.5 when additional support is desired. Transbiotic™ is designed for eliminating *E. coli* and other pathogen transmission from food and water, making it ideal for travelers and those immune to antibiotics, so it may be beneficial to rotate to this formula if using to treat specific infection from *E. coli* for example.

growth of harmful bacteria and reduces the production of harmful nitrites and ammonia.

- **Safety.** These beneficial bacteria are proven to be non-pathogenic and have a long history of safety for human consumption.

An overview of the clinical application of Transformation's probiotic formulas is as follows:

PLANTADOPHILUS – *L. plantarum* supports the growth of other beneficial bacteria. This single-strain, gentle formula contains no FOS and is generally used when the practitioner wants to slowly introduce probiotics into the GI tract of very sensitive patients or when a single strain is needed.

PROBIOTIC – This six-strain formula is excellent for maintaining a healthy balance of flora in support of a healthy diet and lifestyle.

PROBIOTIC 42.5 – This ten-strain formula has the highest cfu per serving and is suggested during times of antibiotic use or chronic and severe health challenges.

TRANSBIOTIC™ – This probiotic formula with an innovative prebiotic Includes the spore probiotic *bacillus subtilis* and PreforPro® prebiotic to support the growth of healthy bacteria in the gut through a method that is neither fiber nor starch-based.

Glossary

Native Microbiota are the many and diverse bacteria residing naturally on and within the human body. There are general similarities, however the specific types and numbers of these bacteria are unique to the individual, their diet, and their environment.

FAQ: What are the advantages of human and plant origins of probiotics?

We have not seen anything in the scientific literature indicating a preference for one over the other. Once it has been isolated, the original source is a moot point. TEC's formulas include species from human and plant as well as dairy and unknown origin.

Probiotics, as defined by the Food and Agricultural Organization of the United Nations (FAO), are "live microorganisms administered in adequate amounts which confer a beneficial health effect on the host." The probiotics have been isolated and identified by the ATCC according to genus, species, and strain using appropriate molecular and physiological technologies.

The American Type Culture Collection (ATCC) is a private, nonprofit biological resource center (BRC) and research organization whose mission focuses on the acquisition, authentication, production, preservation, development, and distribution of standard reference microorganisms, cell lines, and other materials for research in the life sciences.

Live cultures obtained from fermented foods can also be beneficial to GI health, however, they are not technically called probiotics because they have not been isolated and identified by the ATCC.

Prebiotics support and stimulate growth of beneficial and advantageous bacteria.

Colony forming unit (cfu) is the unit of measure used to designate the activity or viability of the probiotics.

Table 1. TEC's specific probiotic strains

GENUS	SPECIES	STRAIN	ORIGIN	COMBINED CLINICAL BENEFITS
Bacillus	*coagulans**	GBI-30	green malt	Gut Health · Strengthened intestinal barrier / permeability · Improved mucosa integrity (competition for biding sites) · Reduced antibiotic induced diarrhea · Reduced constipation Digestive Support · Production of enzymes · Metabolization of various CHO · Production of various nutrients · Reduced symptoms of lactose intolerance, IBS, IBD, colitis, Crohn's Immune Support · Production of acids / inhibits pathogens · Production of anti-microbial substances · Management of pro- and anti-inflammatory cytokines / reduced inflammation · Reduced respiratory, urinary, and GI tract infections
	subtilis	DE111	soil	
Bifidobacterium	*bifidum*	Bb-02	human isolate	
	infantis	n/a	unknown	
	longum	Bl-05	unknown	
Lactobacillus	*acidophilus*	La-14	human isolate	
	bulgaricus	Lb-64	dairy	
	casei	Lc-11	dairy	
	plantarum	Lp-115	plant	
	rhamnosus	Lr-32	dairy	
	salivarius	Ls-33	unknown	

*aka *Lactobacillus sporogenes*

Conclusion

It is not surprising that the native microbiota have been found to play an important role in human health. Most of these bacteria are not harmful, and in fact contribute positively to human health, growth, and development.

Due to diet, lifestyle, environment, and certain medications the balance of good and bad can be altered creating a potentially

harmful situation. It is important that the balance of microbes be maintained to favor the beneficial bacteria over the pathogenic ones. Based on over thirty years of clinical experience and the current research findings, one of the most effective ways to support GI health is through regular probiotic supplementation.

FAQ: Can probiotics be used topically?

Yes. Native microbiota are also located on the skin of the host. For skin irritations that are fungal or bacterial in nature, probiotics may be applied to help balance the beneficial bacteria. Our clinical experience has shown good results in many cases. Open the capsule and moisten the powder making a paste and apply to the affected area on the skin. This can also be done in the mouth or as a rinse (gargle) for the throat.

FAQ: When is the best time to take a probiotic?

For general use or maintenance purposes we suggest taking probiotics at bedtime. The gut is most at rest throughout the night and should allow for unhindered transit to the large intestines. However, if the gut is severely imbalanced we may suggest they also be taken first thing in the morning and/or with meals.

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