

# **Microbial Connections**

*How Recent Epidemiological Studies are Reshaping Clinical Practice and  
Our Understandings of Microbiology and Immunology*

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# **Microbial Connections**

## **Part I**

### **Epidemiological Studies Usher in a New Era in Our Understanding of Microbiology and Immunology**

Recent epidemiological studies have begun to make mainstream some of the very concepts regarding microbiology and immunology that those of us in the natural health fields have long subscribed to. Doctors of Chiropractic, Natural Hygienists and Nature Curists have long warned of the dangers we have brought upon ourselves by ignoring our connections with the natural world and its microbial inhabitants. Medical science is known for its antagonism to the microbial world with its war chest of antiseptics, antibiotics and vaccines. Most of those who engage in a naturally oriented practice acknowledge the value of these medical tools under limited, special circumstances but bemoan the widespread, virtually indiscriminate use of them that has led to serious repercussions for both individuals and the public health.

Ours is a world immersed in microbes that are around us, upon us and inside of us, a fact obscured by our limited vision and their microscopic size. Within the large intestine alone are bacterial populations numbering over ten to the fourteenth power, a number far exceeding the entire human population of the planet.

The western world has gone through evolving stages of understanding regarding our relationship to the world of microbes. Louis Pasteur, who largely shaped the modern day

perspective of bacteria, viewed them as threats to our health, as entities to be controlled and vanquished in our communities, homes and bodies. Pasteur's hostile attitude towards bacteria still plays a powerful role in the medical community, but more balanced perspectives have been coming to the forefront. Voices from the past with different perspectives on microbes, bacteria in particular and their role in human health and disease are being increasingly echoed today and are supported by science and clinical experience.

Antoine Beauchamp was one of those dissenting voices. A contemporary of Pasteur's, Beauchamp viewed man's internal environment (what we would refer to today as *host resistance*), as playing a greater role than the bacterial agent in determining disease manifestation. Nineteenth century Russian Bacteriologist Eli Metchnikoff went a step further, advocating the ingestion of lactic acid bacteria for their life extending effects, an opinion now shared by a growing body of the scientific community. A balanced view of bacterial/human relationships is one which understands that humans and bacteria live in an intermingled sea of life with interactions between us that are complex and in a multitude of ways essential to our well being.

Bacteria have a critical place in human ecology, including their role in continuously reshaping the environment through their recycling of organic materials, the protection afforded through their competitive actions against microbial pathogens and their far reaching, immune modulating, effects.

Many of science's long held views regarding the place of bacteria in human affairs have been shortsighted. Newer, science based, understandings of human/microbial relationships are creating dramatic opportunities for progress against many chronic diseases in terms of their reversal and prevention. Previously held views of the bacterial world limited to simply *seek out and destroy*, have led to dangerous consequences that today pose serious public health threats to us as individuals and as a nation. Over the past decade a surge of epidemiological and microbiological research has opened the gates to documenting the problems we have created by such shortsighted attitudes. The implications of our misunderstandings of the microbial world have come to haunt us. Science is beginning to appreciate the need, in many cases, to increase our microbial exposure. The promotion of human health and the reversal of many chronic disease states may depend upon clinicians understanding new epidemiological data and being able to apply recent findings with their patients.

## The Hygiene Hypothesis

*"What doesn't kill you makes you stronger"*

Author Unknown

An important study that has led to major changes in the way science views human/bacterial relationships is the evolving theory of the *Hygiene Hypothesis*. Backed by a wealth of epidemiological data, this theory has received attention by the scientific community and by epidemiologists who study the frequency and distribution of disease in human populations.

The *Hygiene Hypothesis* contends that it is through early exposure to a variety of microbial challenges that our immune system develops efficiently, lessening the potential for immunological and infectious disease problems throughout our lives. Proponents of the *Hygiene Hypothesis* contend that there is an inverse relationship between the incidence of infectious micro-organisms encountered during the formative years and the later development of a wide variety of allergic/immune disorders. Through increased exposure to micro-organisms, the immune system, it is contended, becomes better balanced in its response to the outside world, more efficient in maintaining health and less likely to develop a myriad of serious disorders.

This is a turn around in medical thinking which has for the past century has had a compulsion to avoid dirt and germs scrupulously, encouraging the public to employ disinfectants, bactericidal sprays and veridical washes vigorously upon our environment. These behaviors may well have contributed to the growing prevalence of allergic issues, asthma, autoimmune diseases and other chronic ailments we are experiencing. The prevalence of asthma alone has doubled in the past twenty years while autoimmune disorders afflict from 14 to 22 million Americans<sup>1</sup>.

. Our ancestors, for millions of years, were continuously exposed to their microbial co-inhabitants. In living in close contact with the microbial multitudes, man became resistant to them and lived reasonably harmoniously with them as long as he was well nourished and obtained the other basic essentials for good health. Increasing public health evidence

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<sup>1</sup> U.S. Department of Health and Human Services , NIAID Press Office Release January 10, 2003

supports the Hygiene Hypothesis, i.e. that it is through exposure to a wide range of microbes at an early age that we stimulate receptors in our immune system that protect us from *over-reacting* to those same components in adulthood and the consequent development of chronic immune disorders.

Primitive man ate food directly from the soil and through this exposure alone took in millions of micro-organisms daily. Ongoing and intimate contact with bacteria from the soil and elsewhere was part and parcel of the human condition for millions of years. It is only over the past century that this connection has been severed, during which time there has been a colossal rise in human degenerative diseases related to immune system malfunction.

Epidemiologists, among whom Dr. David Strachan of the London School of Hygiene and Tropical Medicine is prominent, have increasingly substantiated the relationship between exposure to earth based micro-organisms and chronic disease problems. Dr. Strachan proposed the *Hygiene Hypothesis* in 1989 at the London School of Hygiene and Tropical Medicine. In it, he presented epidemiological evidence<sup>2 3</sup> that the younger children from large families were less likely to develop a host of disease problems including asthma, hay fever and eczema. Dr. Strachan hypothesized that exposure to the microbes in the dirt, brought into the homes by their older siblings, improved the younger children's immune function and protected them from the development of allergic and asthmatic problems. The suggestion that a more microbe rich environment might be beneficial to

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<sup>2</sup> Strachan, D.P. (1989) Hay fever, hygiene and household size. Br. Med J 299, 1259-1260

<sup>3</sup> Strachan, D.P. (1996) Socioeconomic factors and the development of allergy. Toxiol Lett 86 (2-3), 199-203.

the efficient maturation of the immune system had been previously raised by Godfrey who observed different levels of IgE between urban and rural residents of communities in Gambia.<sup>4</sup>

Paolo M. Matricardi, M.D. and his colleagues later linked seropositivity for hepatitis A virus, *Toxoplasma gondii*, and herpes simplex virus type 1 to a decreased risk of hay fever, asthma, and atopic sensitization.<sup>5</sup> In a related study by Braun-Fahrlander, the level of endotoxin found in dust samples from bedding, was inversely related to the occurrence of hay fever, atopic asthma, and atopic sensitization among children in rural areas of Germany, Austria, and Switzerland<sup>6</sup>. These studies demonstrate the value of microbial exposure in the natural environment so as to foster an immune system that responds in a *balanced fashion* to the outside world thereby reducing the risk for the development of allergic and immune disorders. Dr. Matricardi commented, “*We must learn how to safely ‘train’ our immune system, especially during infancy, in order to prevent allergy.*”

In an editorial that accompanied the Braun-Fahrlander study, Dr. Scott T. Weiss, a Professor of medicine at Harvard Medical School in Boston commented that; “*...a number of environmental factors are known to be associated with a lower incidence of allergic disease early in life...the challenge will be to determine the extent of exposure that will ensure safety and have the desired outcome – the development of a healthy child*

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<sup>4</sup> Godfrey RC. (1975) Asthma and IgE levels in rural and urban communities of the Gambia. Clin Allergy 5,201

<sup>5</sup> Matricardi PM, Rosmini F., Panetta V, et. al. Hay fever and asthma in relation to markers of infection in the U.S. J Allergy Clin. Immunol 2002; 110:381-387

<sup>6</sup> Braun- Fahrlander C., Riedler J, Herz U., et.al. Environmental exposure to endotoxin and its relation to asthma in school age children. New Engl J Med. 2002;347 : 869-877

*with a very low risk of autoimmune disease*".<sup>7</sup> Those factors include, according to [Respiratory Reviews.Com](http://www.respiratoryreviews.com)<sup>8</sup> in the article "*Hygiene Hypothesis Gains Support in the United States and Europe*" oral supplementation with specific probiotics and having a dog or other pet in the home since before birth.<sup>9</sup>

Related laboratory studies by researchers at the National Jewish Medical and Research Center, have gathered additional support for the Hygiene Hypothesis. They found that early infection with the bacterium *Mycoplasma pneumoniae* reduced a mouse's subsequent response to allergens. "*For the first time, we have shown that a bacterial infection can modify the allergic response,*" said Dr. Richard Martin, Vice Chair of the Department of Medicine at National Jewish Medical and Research Center.<sup>10</sup>

A basic understanding of the immune system makes these discoveries supporting the Hygiene Hypothesis, easy to appreciate and explain why individuals in westernized countries are becoming increasingly susceptible to a number of diseases. Sburu Kugathasan, M.D. an Associate professor of Pediatric Gastroenterology at the Medical College of Wisconsin comments:

*"Medicine has a lot of history behind it related to why certain diseases are so widespread and certain diseases are not widespread. The immune system is there for a reason. It's there to recognize the bad guys. The immune system allows your body to kill those bad guys and allows you to survive. In order to harden the immune system, the immune system requests some kind of stimulation all the time. The Hygiene Hypothesis*

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<sup>7</sup> Weiss, S.T. Eat dirt – the hygiene hypothesis and allergic diseases. *N Engl J Med.* 2002;347: 930-931.

<sup>8</sup> "Hygiene Hypothesis Gains Support in the United States and Europe" [Respiratory Reviews.Com](http://www.respiratoryreviews.com) Vol. 8. No.1 January 2003. Go to [http://www.respiratoryreviews.com/jan03/rr\\_jan03\\_hygiene.html](http://www.respiratoryreviews.com/jan03/rr_jan03_hygiene.html)

<sup>9</sup> The assumption is that the pet is allowed to pass in and out of the house so as to carry outdoor microbes into the living space shared by the baby/child.

<sup>10</sup> "Bacterial Infections alter allergic Response" National Jewish Medical and Research Center News February 25, 2003. See [www.nationalljewish.org/news/hygiene\\_martin\\_022502.html](http://www.nationalljewish.org/news/hygiene_martin_022502.html)



*suggests that the more hygienic one becomes, the more susceptible one is to various autoimmune diseases. The autoimmune diseases, the diseases that result from all the activation of your immune system, are increasing. The hygiene hypothesis...acknowledges that the maturation of the immune system needs some kind of hardening, some kind of resistance. Put another way, your body cannot really build up good muscles without doing exercise.”<sup>11</sup>*

Dr. Strachan’s study and others that followed it have helped to solidify what many have long felt to be true...that modern lifestyles that limit microbial exposure have created biological repercussions for our species, manifested primarily by rapidly escalating immune/allergic disorders.

## **Immune System Overview**

Our immune system provides defense against invasion by pathogens and toxic materials by differentiating between what is us and what is not us, or what is “self” and what is “non-self.” In doing so the immune system permits what it perceives as safe materials to have safe passage in our bodies while suspicious agents can elicit open warfare as the immune system seeks to guard us from them.

In abnormal situations the immune system can attack our own cells if it fails to recognize them as “self”. The result of this can be an “auto-immune” disease such as rheumatoid arthritis.

Allergies to what are harmless materials to many e.g. ragweed pollen or dog dander, can provoke an allergic immune response...

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<sup>11</sup> “Hygiene Hypothesis: Are We Too “clean” for our own Good?” [Health Link](http://www.healthlink.mcw.edu/article/1031002421.html) Medical College of Wisconsin  
[www.healthlink.mcw.edu/article/1031002421.html](http://www.healthlink.mcw.edu/article/1031002421.html) Created 2004-09-24

The two major classes of lymphocytes are B cells and T cells (B cells from bone marrow and T cells which migrate to the thymus). In the bloodstream the lymphocytes patrol for antigenic materials on “seek and destroy” missions.

When a B cell encounters the antigen that it is programmed to neutralize, it clones into plasma cells which in turn manufacture identical antibody molecules to release into the blood. These antibodies combine with the antigen becoming an *antibody/antigen complex* which can then be neutralized by phagocytic cells.

T cells help regulate the immune system, making it *more* aggressive via helper or inducer T cells or *less* aggressive via suppressor T cells. T cells secrete cytokines or lymphokines which can destroy foreign cells and inhibit parasites and viruses and either increase or decrease the inflammatory response and/or the allergic response depending on the variety of cytokine/lymphokine released.

T-helper cells are further divided in terms of their patterns of cytokine secretions and are referred to as “Th1” and “Th2” cells. These are important immune regulators with the task of coordinating immune system responses. Th1 cells are thought to increase delayed type hypersensitivity skin responses to viral and bacterial antigens and lead the attack against intracellular pathogens such as viruses and fight cancer cells. Th2 cells are believed to increase protection against extra cellular pathogens such as parasites. If the Th1 pathway is overactive it is thought to contribute to the development of

autoimmune/inflammatory conditions. The Th2 pathway, if overactive, is thought to contribute to allergic type disorders and IgE related disease states. Both pathways work best when in balance, i.e. Th1 and Th2 pathways reflect one upon the other so that an increased presence of one inhibits the other. The two pathways thus complement rather than compete with each other. The Th1 pathway is characterized by a cell mediated pro-inflammatory reaction involved in autoimmune responses where antibodies are produced against body tissues. The Th2 pathway is involved in allergic type responses and the airway hyper-responsiveness seen in asthma.

T-regulatory cells are therefore intimately involved in determining the balance of the immune response. Dividing immune reactions into two pathways is a simplification since infectious agents generally promote some response from both, yet Th1 cytokines inhibit the release of Th2 cytokines and vice versa. This helps explain how an imbalance of the TH1/Th2 pathways can be responsible, in part, for the development of allergic and autoimmune disorders.

## **Gut Function, Gut Flora and the Hygiene Hypothesis**

Astute clinicians involved with clinical nutrition, know that the importance of the GI tract goes far beyond that of its digestive functions alone i.e. that part and parcel of the gastrointestinal tract is the majority of the body's immune related cells. The GI tract, sterile at birth, is colonized by bacteria shortly afterwards which stimulates the immune system to respond to pathogens and inhibit their colonization.

Proponents of the *Hygiene Hypothesis* have argued convincingly that adequate gut colonization is of utmost importance in the priming of the immune system. This occurs via adequate environmental exposures. Notably for clinicians, when a child has not been adequately exposed to environmental microbes to allow for healthy gut colonization, *the administration of beneficial strains of probiotic gut micro flora, improves gut specific immune responses.*<sup>12</sup> In children with food allergies, these gut specific immune responses appear to be defective and could be *prevented in many cases by the appropriate administration of probiotics.*<sup>13</sup>

Children raised close to the earth such as those raised on farms, have demonstrated a reduced susceptibility to allergy.<sup>14</sup> Pets, particularly if allowed to go between the indoors and outdoors, have also been shown to be associated with a lower incidence rate of allergic disorders.<sup>15</sup> *Regular bacterial exposure is essential for the development and promotion of a balanced immune system.*

Our use of antibiotics, employed in both the food supply and utilized extensively in medical therapy, has complicated matters. The flood of antibiotic agents does more than alter our bacterial flora and make us subject to opportunistic infections; *it alters immune*

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<sup>12</sup> Isolauri E., Majamaa IF, et. Al. (1993) *Lactobacillus casei strain GG reverses increased intestinal permeability induced by cow milk in suckling rats.* Gastroenterology 105, 1643-1650

<sup>13</sup> Kalliomaki M., et. al. (2001) *Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial.* Lancet 357, 1076-1079

<sup>14</sup> Riedler J, et.al. (2001) *Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey.* Lancet 358, 1129-1133

<sup>15</sup> Svanes C. et. al. (1999) *Childhood environment and adult atop: results from the European Community Respiratory Health Survey.* J. Allergy Clin Immunol 103,415-420

responses, making us subject to allergies and related immune problems<sup>16</sup>. The effects antibiotics have in increasing the risk of asthma and hay fever have been directly linked to their negative influence on bacterial colonization of the gut in the early years of life.<sup>17</sup>

## **Autoimmune Disorders and the Hygiene Hypothesis**

Autoimmunity involves chronic immune dysregulation that results in extensive body dysfunction. Reduced microbial exposure in early life appears to be a risk factor for not only allergy related problems but also for autoimmune related issues. The relationship between allergies and autoimmune problems appears connected in this regard with autoimmune disorders such as juvenile diabetes and juvenile rheumatoid arthritis both arising early in life suggesting they may have similar causes behind them.

Evidence indicates that limiting contact with the natural world increases the predisposition to autoimmune disorders. Epidemiological data regarding childhood diabetes and allergic problems (atopy) in children is similar and reduced exposure to the common infections of infancy has been linked to an increased risk of diabetes.<sup>18</sup> Inflammatory bowel diseases (ulcerative colitis and Crohn's) exhibit significant variation between less developed nations and those in the industrialized world. A higher percentage of these problems are found in westernized nations where hygienic standards

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<sup>16</sup> See Farooqui IS, Hopkin J.M. (1998) *Early childhood infection and atopic disorder*. Thorax 53, 927-932

<sup>17</sup> Bjorksten B, et. al (1999) The intestinal microflora in allergic Estonian and Swedish 2 year old children. Clin Exp Allergy 29, 342-346

<sup>18</sup> Gibbon C. et. al. (1997) Early infection and subsequent insulin dependent diabetes. Arch Dis Chil, 384-385

are more stringent<sup>19</sup> and a lower level are found in less developed nations where exposure to infectious agents is greater.

Gent et.al. tested the hygiene hypothesis in a matched, case control, study looking at variables involving domestic hygiene, with patients having Crohn's or ulcerative colitis. The study concluded that "*good domestic hygiene may protect from exposure to a full range of agents that program the immune system of the gut during infancy*". The study authors predicted that the improvement of domestic hygiene in developing countries could potentially lead to increases in the incidence of Crohn's disease in those populations.<sup>20</sup>

In a study conducted at the University of Iowa<sup>21</sup>, whipworms as found in pigs, (*Trichura suis*) were administered to six patients suffering from bowel disease. All six patients went from chronic illness to complete remission. It is thought this occurred because the micro-organisms from the worms had a positive affect on the body's immune response to bacteria and viruses.

Commenting on this study Dr. Kugathasan reflected:

*"Think about countries in Africa like Gambia, a country that has been studied very well. Ninety to ninety nine percent of people in Gambia have intestinal worms at some point in their lives. But the chronic immune disease like asthma, Crohn's disease or multiple sclerosis are not heard of, never even mentioned in their life. They don't know anything*

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<sup>19</sup> Langman MJS, Burnahn JR. (1983) Epidemiology of inflammatory bowel disease. In: Inflammatory bowel disease, p. 17-23. Allan RN. et.al. editors Edinburgh: Churchill Livingstone.

<sup>20</sup> Gent AE, Hellier MD, et. al. (1994) *inflammatory bowel disease and domestic hygiene in infancy*. Lancet 343, 766-767

<sup>21</sup> See "*Hygiene Hypothesis: Are We Too "clean" for our own Good?*" [HealthLink](http://www.healthlink.mcw.edu/article/1031002421.html) Medical College of Wisconsin  
[www.healthlink.mcw.edu/article/1031002421.html](http://www.healthlink.mcw.edu/article/1031002421.html) Created 2004-09-24

*about such disease in those countries. While one may argue that maybe their population is genetically not predisposed to these diseases, other factors appear to be in play.”<sup>22</sup>*

The problem with making an environment “too clean” is exemplified by modern hospitals. The massive use of antibiotics and antiseptics has led to mutant antibiotic resistant bacterial strains that have contributed to significant morbidity and mortality each year. In our attempts to destroy micro-organisms we’ve generated strains of “super bugs” which we lack resistance against.

In environments such as the operating room, “cleanliness is next to godliness” which is well and good since internal tissues were never meant to be exposed to the outside world. In everyday living, however, where keeping a reasonable connection with the microbial world is important, adhering to such strict cleanliness is having a boomerang effect.

The *Journal of the American Medical Association* reported that researchers at several institutions in Rome conducted studies indicating that “exposure to pathogens that stimulate gut-associated lymphoid tissue may be necessary in order to prevent atopy (skin disorders) and allergies.”<sup>23</sup> There are 400 or more strains of bacteria that inhabit our guts and protect us from disease by creating a healthy microbial balance. Devoid of healthy bacterial populations in the GI tract a vacuum is created that can be invaded by opportunistic pathogens resulting in digestive disturbances, asthma, allergies, autoimmune and dermatological conditions.

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<sup>22</sup> Ibid.

<sup>23</sup> *Journal of The American Medical Association* “The Hygiene Hypothesis” Vol. 283 No. 10 March 8, 2000 reported by Rebecca Voelker

I've often marveled at my two dogs who spend a good part of each day outside running around in the yard, digging in the dirt and ingesting a fair amount of "foreign" materials on a daily basis. These two wards of mine (*Challenge*, an Airedale/Lab mix and *Bella*, a Shepherd/Doberman mix) have been corroborating on a two volume book series entitled "*Places Our Noses and Tongues Have Been*"<sup>24</sup> which describes the many interesting things they have sampled from the outdoor world over the years. Despite their adventuresome lifestyles, they have remained largely free of infectious, allergic and autoimmune disorders unlike many "super clean" western humans and canines that spend their lives inside scrupulously clean western homes and don't have the advantages of being connected to the earth as my two dirt loving pups do. There may be much we can learn from them.

The importance of a balanced gut ecology has been well established by clinicians over the years. Likewise, in practice, the prudent practitioner is wise to emphasize the importance of healthy GI flora in a variety of conditions including infectious diseases, autoimmune conditions, allergies, digestive problems, dermatological conditions, a wide variety of inflammatory problems, fungal and yeast overgrowths, etc. There are a myriad of ways that probiotic bacteria foster human health, the primary one being by protecting patients through a competitive action i.e. by suppressing the growth of harmful microorganisms including pathogenic bacteria, fungi and yeast.

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<sup>24</sup> Goldberg, Challenge B. and Goldberg, Bella T.; *Places Our Noses and Tongues Have Been* unpublished, copyright pending..



Our heavily processed diet, widespread employment of antibiotics and overly clean living conditions have hindered normal bacteria from being introduced and implanted into the baby and child's gut via the food and soil and are kept hindered by the same factors in adults.

Children should be encouraged to play outdoors so as to acquire adequate microbial exposure. In the western world, many children have insufficient exposure and the outcome can be a significantly increased incidence of allergies and autoimmune conditions.

The impact of the Hygiene Hypothesis reaches into the depths of numerous health and disease issues. Studies indicating the relationship between inadequate exposure to microbes and the development of chronic health problems, (in addition to the allergic and atopic ones we've explored), have been surfacing in increasing numbers. The following represent a few of many clinical areas in which our understanding in this area is surfacing:

**Multiple Sclerosis and the Hygiene Hypothesis** Posenby et. al. found that higher infant sibling exposure in the first 6 years of life is associated with a reduced risk of multiple sclerosis, possibly by altering childhood infection patterns and related immune responses.<sup>25</sup>

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<sup>25</sup> A-L. Ponsonby et al (J. Am. Med. Assoc. 2005 293:463). Also see Hernan MA, Zhang SM, Lipworth L, Olek MJ, Ascherio A. Multiple sclerosis and age at infection with common viruses. *Epidemiology*. 2001;12:301-306

**Diabetes Type-1 and The Hygiene Hypothesis:** Worldwide, it is the tropical regions of the world having the most infectious and parasitic diseases that are least affected by immune mediated type 1 diabetes. Kukreja and Maclaren of the Department of Pediatrics of Weill Medical College of Cornell University argue that “it is the fall in incidences of infectious diseases and intestinal parasites that are likely responsible for the rise in autoimmune disease like immune mediated Diabetes in the west”.<sup>26</sup>

**The Hygiene Hypothesis and Childhood Leukemia:**

It has been suggested that the disproportionate amount of childhood leukemia in developed as opposed to developing countries is likely a consequence of a number of factors including improved hygiene and inadequate development of the immune system due to inadequate environmental exposure to common infections.<sup>27</sup>

**“Hygiene Hypothesis” linked to heart disease risk:**

Investigators have suggested that “improved hygiene in early childhood might partially explain the greatest epidemic of the 20<sup>th</sup> century...coronary heart disease”. Researchers from the University Hospital in Lund, Sweden, compared 350 patients who had unstable angina or a heart attack with 350 subjects without coronary heart disease (control subjects). Childhood contagious diseases were more frequently found in the controls. The researchers found a consistent trend between the number of childhood infections and the reduction in coronary risk, e.g. having two childhood viral infections reduced the

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<sup>26</sup>Kukreja, Anjali, PhD and Maclaren, Noel, M.D.; “NKT Cells and Type-1 Diabetes and the “Hygiene Hypothesis” to Explain the Rising Incidence Rates”. *Diabetes Technology and Therapeutics* June 2002, Vol.4, No.3: 323-333

<sup>27</sup> The University of Edinburgh Department of Communications and Public Affairs: The Hygiene Hypothesis and Childhood Leukaemia. *Bulletin 1999-2000: Bulletin 6: The Hygiene Hypothesis and childhood leukaemia*

coronary risk by 40 percent; four infections was associated with a 60-percent decreased risk; and six infections lowered the risk by 90 percent.<sup>28</sup>

### **The Hygiene Hypothesis and the Rise of Inflammatory Bowel Disease**

Inflammatory bowel disease has a significantly *lower incidence rate* in those nations where there is a *lower* level of hygiene and more environmental microbial exposure.

“It is now apparent that the increase in the incidence of autoimmune and allergic diseases in Western countries is explained by the decrease in infections. The question is posed to determine whether a similar explanation can be proposed for the increased incidence of inflammatory bowel disease. Converging clinical and experimental data strongly suggest the protective nonspecific role of infections on inflammatory bowel disease independently from the triggering role of some specific bacteria. The extension to inflammatory bowel disease of the hygiene hypothesis opens new therapeutic perspectives including the revisiting of probiotics and other forms of exposure to bacteria or parasite components.”<sup>29</sup>

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<sup>28</sup> Reuters Health Information as reported by Matias A. Loewy September 23, 2005 Hygiene Hypothesis linked to heart disease risk.

<sup>29</sup> Feileet, Helene; Bach, Jean-Francois. Increased Incidence of Inflammatory Bowel Disease: The Price of the Decline of Infectious Burden? *Current Opinion in Gastroenterology* 20(6):560-564, 2004. © 2004 Lippincott Williams & Wilkins

## Addressing the Microbial Connection Dilemma

In light of the adverse consequences resulting from inadequate microbial exposure how can the problem be addressed in a safe, effective manner? Reverting to a Paleolithic life style with its close contact to the earth would be one way. Relinquishing our penchant for a high level of cleanliness on the other hand would be a tough sell to most Americans. The stakes are high with the increasing rates of cancer, heart disease, inflammatory bowel disease, rheumatoid diseases, multiple sclerosis, allergies and related immune problems that burden us. Fortunately, much can be done to address the microbial connection with modest effort and with significant, positive repercussions.

*Part two of Dr. Goldberg's article will address specific steps clinicians can take in addressing the immunological issues raised in the Microbial Connection.*

### About The Author

Dr. Paul Goldberg is a graduate of The University of Texas Graduate School of Public Health (M.P.H. Chronic Disease Control), a Chiropractic Physician, Clinical Epidemiologist and Clinical Nutritionist. He holds Diplomate Status with the American Clinical Board of Nutrition and directs **The Goldberg Clinic** in Atlanta, Georgia. He is the Senior Director of Research and Physician Education for Original Medicine, Inc. For twenty three years he served as a Professor of Clinical Nutrition and Gastroenterology at Life University. Due to his personal struggle in overcoming rheumatoid disease as a young man and his thirty years of practice, teaching, writing and research experience, Dr. Goldberg is well known for his success in working with patients with rheumatoid disorders, inflammatory bowel diseases and other autoimmune conditions. In his practice Dr. Goldberg utilizes a highly individualized “*Foundational Approach*” that focuses on the gastrointestinal and immune systems along with genetic and lifestyle factors. Contact information can be found at [www.goldbergclinic.com](http://www.goldbergclinic.com)

# Microbial Connections

## Part II

*In part one of this series Dr. Goldberg discussed the changes in attitudes that have come about regarding microbes and their role in health and disease, due to recent epidemiological studies such as those supporting the “Hygiene Hypothesis”. In part two, Dr. Goldberg offers suggestions as to how the problems brought about by the western lifestyle and western medicine can be addressed by the clinician and their patients.*

### Restoring Our Microbial Connections

To reduce the health problems resulting from our lack of microbial connections four steps should be employed, under the guidance of the practitioner, pertaining to *outdoor exposure, indoor exposure, dietary matters and probiotic employment*

#### **I. Outdoor environmental exposure**

It is important for patients to spend time in the out of doors where they can be exposed to the normal elements of nature including fresh air, sunlight, visual beauty *and* a wide array of micro-organisms. This is imperative for the good health of adults and doubly important for infants and children whose immune systems are in the developmental process. By priming the immune system of infants and children in this way, much can be accomplished in preventing allergic and autoimmune disorders as they mature into adulthood.

## **II. The Indoor Environment**

A reasonable level of cleanliness should be maintained indoors. *The frequent, routine usage of strong chemical disinfectants throughout the house, however, should be discouraged.* To do otherwise both deprives us of the necessary contact with microbes required to maintain a healthy immune system, it also fosters the development of “super bugs” that are highly resistant to our normal immune defenses and to antibiotics, as has been seen widely over the past several decades in hospitals.

## **III. Dietary Factors**

The composition of the diet has a significant impact on the quantity and quality of the intestinal flora. A Paleolithic style diet supplies the necessary nutrients, fiber, phytonutrients and other needed components to help foster the growth of normal gastrointestinal flora while discouraging the growth of pathogenic micro-organisms. Incorporating in the diet foods that have been cultured with probiotic bacteria such as high quality kefir, yogurt, sauerkraut, pickles and other cultured and fermented food products is an additional way with which to foster a healthy internal milieu. Dietary modification can play an important role in fostering healthy gut flora. The primary way in which the clinician can impact the internal environment and address the issues raised by the Hygiene Hypothesis, however, is by utilizing specific probiotic preparations. This is a critical area for the clinician to give guidance to his patients on. These three steps are

important in restoring immune balance and should be complimented by the fourth step, the implementation of probiotics.

## **Probiotics in Clinical Practice**

Probiotics have been increasingly investigated and employed by clinicians who recognize their important role in the preservation of health and the reversal of chronic disease conditions. The growing interest by professionals is reflected in the increased usage of probiotics in clinical practices and by the dramatic increase in research articles on probiotics in peer review journals.

Much of the increased interest in probiotics has been sparked by the rising frequency of chronic diseases in particular allergies, asthma, inflammatory bowel diseases, rheumatoid diseases and related autoimmune disorders. The increasing number of patients with such conditions is complicated by the fact that remedial medical measures are generally ineffective, expensive and carry with them a high risk of serious side effects.

The formulation of the *Hygiene Hypothesis*<sup>30</sup> and the *Old Friends Hypothesis*<sup>31</sup> which suggested that a lack of parasitological exposure may also result in an immune system that

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<sup>30</sup> Strachan, David. Hay Fever, Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine. *Hygiene and Household Size* *BMJ* 1989 Nov 18;299 (6710):1259-60

<sup>31</sup> Rook, GA, Adams V, Hunt J, et al. Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders. *Springer Semin Immunopathol* 2004;25:237-55

does not mature adequately, have both triggered research into the positive influences probiotics can have on chronic ailments.

The recognition that the GI micro-flora play a critical role in disease states including inflammatory bowel disease, acute gastroenteritis, food allergies, food hypersensitivities and colon cancer<sup>32</sup> has drawn attention to the significant benefits that can be obtained by utilizing probiotics as a means of “infection control” and of intestinal re-inoculation.

Research into probiotics has led to a deeper understanding of the beneficial applications of specific strains of bacteria under varying circumstances in improving clinical outcomes. The individual nature and clinical applicability of different species and sub species of bacteria for different health problems is being recognized. The age of “Designer Probiotics<sup>33</sup>” has become a reality. An ongoing surge of information has opened the door to opportunities for safe, effective, clinical applications of probiotics both in terms of general prevention and in specific, therapeutic, protocols.

## **Designer Probiotics**

### **Specific Probiotics for Specific Needs**

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<sup>32</sup> Fooks, L.J. et. al. *Probiotics as modulators of the gut flora* British Journal of Nutrition (2002), 88, Suppl. 1, S39-S49

<sup>33</sup> A term the author has coined for the utilization of specific probiotic strains for specific clinical conditions.



The positive effects of probiotics on the intestinal tract and immune system is implicit in the definition of probiotics as “*living microorganisms, which upon ingestion in certain numbers exert benefits on the host beyond inherent basic nutrition*”.<sup>34</sup> The increasing interest in Probiotics is exemplified by the *large number* of peer reviewed articles written on Probiotics i.e. 2,755 peer reviewed articles since 1954 with the majority published over the past twenty years<sup>35</sup>.

There are over 400 different species of bacterial flora found in the human gastrointestinal tract. In a healthy individual these bacterial strains keep each other in balance. Probiotic flora play an important role in inhibiting the growth of pathogenic bacteria since they promote nonspecific host resistance to microbial pathogens<sup>36</sup>. Competing for space and nutrients are yeasts, protozoa and in some cases, parasitic organisms. A balance must be maintained among these different micro-organisms to support the health of the host. A balanced situation is referred to as “eubiosis.” An imbalanced situation where pathogens may become dominant is referred to as “dysbiosis” and most often occurs when one or more pathogens, such as E-coli or yeast have achieved the upper hand and outnumber beneficial strains e.g. Lactobacilli or Bifidobacteria. When this occurs, symptoms such as diarrhea, fatigue, gas indigestion, nausea, chronic yeast problems, food allergies, food intolerances and a wide host of other GI complaints can result.

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<sup>34</sup> Guarner, F.; Schaafsma, G.J. Int.J. Food Microbiol., 1998,39,237-8

<sup>35</sup> National Library of Medicine/National Institutes of Health.

<sup>36</sup> Salminen S, BouleyC, et. al. Functional food science and gastrointestinal physiology and function. Br J Nutr. 1998;80 (supp): S147-71

Among the health benefits reported in the literature related to the ingestion of probiotic bacteria are: 1) Decreasing toxic metabolite production from pathogenic bacteria cells 2) Antibacterial properties towards pathogens 3) Prevention of intestinal tract infections 5) Improvement of immune system balance 5) Reduction of inflammatory and/or allergic reactions 6) anti-cancer properties 7) positive effects on blood lipids and heart disease 8) Antihypertensive effects 9) Reduction in the occurrences of urogenital infections, 10) Regulation of gut motility 11) General feeling of enhanced well being.<sup>37 38 39 40</sup>

There is ample evidence of the effectiveness of high quality probiotics when used appropriately in a variety of circumstances with the guidance of a knowledgeable health care professional. These range from their use in children and newborns, where they have demonstrated effectiveness in problems ranging from minor diarrhea and atopic related problems to reducing mortality in serious problems such as necrotizing enterocolitis<sup>41</sup> to their many uses in adults in addressing allergic, inflammatory, autoimmune and infectious conditions in addition to the general usefulness in health promotion and disease prevention.

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<sup>37</sup> Naidu, A. S.; Bidlack, W.R.; Clemens R.A. Crit, Rev, Food Sci. Nutr., 1999, 39, 13-126

<sup>38</sup> Saunders, M. E.; Huis in't Veld, J. Antonie Van Leeuwenhoek, 1999, 76, 293-315

<sup>39</sup> Sanders, M. Int. Dairy J., 1998,8,341-347

<sup>40</sup> Sanders, M. In Probiotics, Prebiotics and new Foods: Rome, Italy, 2001, pp 27-30

<sup>41</sup> Hoyos, A.B. 1999. Reduced incidence of necrotizing enterocolitis associated with enteral administration of *Lactobacillus acidophilus* and *Bifidobacterium infantis* to neonates in an intensive care unit. Int. J. Infect. Dis. 3:197-202

The benefits of probiotics are not only due to their competition with pathogens. A study trial involving 132 participants over a 2 year period showed that administering *Lactobacillus* to pregnant mothers who have at least one first degree relative with atopic eczema, allergic rhinitis or asthma and after birth to the mother and baby, significantly reduced the incidence of allergic atopic dermatitis, implying a functional modulation of immunity rather than a direct anti-pathogen reaction.<sup>42</sup>

Probiotics begin by acting directly within the GI tract. They reduce plasma levels of bacterial endotoxin by inhibiting translocation of bacteria across the lumen and thereby help to decrease gut permeability. *The net effect is to modulate systemic intestinal allergy and inflammation which thereby positively influence many allergic, immune and gastrointestinal problems*<sup>43\*</sup>.

Allergy-induced intestinal inflammation mediated by tumor necrosis factor-alpha is decreased by some *Lactobacilli* strains which also can increase mucosal regeneration of the gastrointestinal tract.<sup>44</sup>

The protective action of probiotics against bacterial gastroenteritis is well documented with in vitro evidence that probiotic strains can inhibit the growth and adhesion of a number of enteropathogens.<sup>45</sup>

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<sup>42</sup> Kalliomaki, M.S. et. al. Probiotics and prevention of atopic disease: 4 year follow up of a randomized placebo-controlled trial. *Lancet* 361:1869-1871 2003.

<sup>43</sup> Vanderhoof JA, Young RJ *J Pediatr Gastro. Nutr.* 1998;27:323-33

<sup>44</sup> Vanderhoof JA Probiotics: Future directions. *Am J. Clin. Nutr.* 2001;73:1152S-1155S

<sup>45</sup> Coconnier, M.H. et. al. 1997. Antibacterial effect of the adhering human *Lactobacillus acidophilus* strain LB. *Antimicrob. Agents Chemother.* 41:1046-1052

Studies indicate that *Helicobacter pylori* infections and complications arising from it including gastric ulcer (a risk factor for gastric cancer), may respond positively to the employment of probiotics.<sup>46</sup>

In addition to helping to reducing risks from the complications of *H. Pylori* infections lactobacilli and bifidobacteria appear able to reduce the risk of cancer in other areas of the body due to their ability to decrease certain carcinogen levels.<sup>47</sup> Researchers at the University of Tokyo have reported that *Lactobacillus casei* was effective in preventing recurrence of superficial bladder cancer in two different double blind placebo controlled trials.<sup>48</sup>

In regards to women's health issues, probiotics can play an important role in terms of both prevention and treatment. Daily oral intake of specific probiotics for example leads to an overall depletion of coliforms and yeast in the vagina including in those woman affected by bacterial vaginosis.<sup>49</sup> Probiotics can play an important role in the prevention of urogenital infections.<sup>50</sup>

Probiotic supplementation is known to enhance immunological activity in both children and adults. Strains of Lactobacilli have been shown to enhance the gastrointestinal IgA

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<sup>46</sup> Canducci, F.A. et. al. 2000. A lyophilized and inactivated culture of *Lactobacillus acidophilus* increases *Helicobacter pylori* eradication rates. *Aliment Pharmacol. Ther.* 14:1625-1629

<sup>47</sup> Hosoda, M., et. al. 1996. Effect of administration of milk fermented with *Lactobacillus acidophilus* LA\_2 on fecal mutagenicity and microflora in the human intestine. *J. Dairy Sci.* 79: 745-749

<sup>48</sup> Aso Y, Akazan H. Prophylactic effect of a *Lactobacillus casei* preparation on the recurrence of superficial bladder cancer. BLP Study Group. *Urol Int* 1992;49 (3): 125-9

<sup>49</sup> Reid, G.D. et. al. 2001. Oral probiotics can resolve urogenital infections. *FEMS Immunol. Med. Microbiol.*30:49-52

<sup>50</sup> **Prevention of Urogenital Infections Marteau, P. et. al. *Nutrition*, 1997 13, 13-6**

response to rotavirus induced gastroenteritis in children.<sup>51</sup> Among the elderly, *Bifidobacterium bifidum* and *L. acidophilus* significantly reduced colonic inflammatory infiltration compared with placebos.<sup>52</sup> Inflammatory bowel diseases and pouchitis have also been addressed with positive results with probiotics.<sup>53</sup> Some other areas that probiotics have been well demonstrated to show effectiveness in include colon cancer prevention<sup>54</sup> the lowering of blood lipids<sup>55</sup>, in atopic dermatitis,<sup>56</sup> in intestinal mucosa repair<sup>57</sup> and in modulation of the immune system.<sup>58</sup>

The GI tract flora are subject to many influences. Factors that promote overall health also assist in promoting a healthful blend of intestinal microflora. In our modern society, however, a variety of stressors challenge the gut and its flora. In light of the fact that it is within the gut that most of our immune mechanisms reside, the immune system is also challenged daily by the same stressors that affect the GI tract including antibiotic residues in the food supply, chlorinated water, psychic stressors and pharmaceuticals.

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<sup>51</sup> Majamaa H. et. al. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. *J. Pediatric Gastroenterology Nutr* 1995; 20(3): 333-8

<sup>52</sup> De Simone, C et. al. Effect of *Bifidobacterium bifidum* and *Lactobacillus acidophilus* on gut mucosa and peripheral blood B lymphocytes. *Immunopharmacol Immunotoxicol* 1992; 14 (1-2):331-40

<sup>53</sup> See Ruseler-van Embden, et. al. *Gut*, 1994, 35, 658-64 and Gionchetti, P. et. al. *Gastroenterology*, 2000, 55 Suppl. 1, S2-10

<sup>54</sup> Hirayama, K.; *Microbes Infect.*, 2000, 2, 681-6

<sup>55</sup> De Smit, I.; et. al. *Br. J. Nut.*, 1998, 79, 185-94

<sup>56</sup> Kalliomaki, M; *Lancet* 2001, 357, 1076-1079

<sup>57</sup> Hanauer, S.B. et. al. *Annu. Rev. Med.* 2001, 52, 299-318

<sup>58</sup> A. Mercenier et. al. *C. Pharm Drugs* 2003, 9,175-191

## Foundational Probiotics

In light of the importance of healthy gastrointestinal and immune functioning the ingestion of a *foundational probiotic* on a regular basis should be given serious consideration by patients wishing to maintain good health. In western society there is no other category of “food supplement” with such widespread utility that has such a direct influence on nutritional, digestive and immunological function.

Chief among the probiotic bacteria are those in the Lactobacillus and Bifidobacteria genus. These safe bacteria are found in healthy guts of humans.<sup>59</sup> In the gut, under anaerobic conditions, lactobacilli such as *L. acidophilus* ferment carbohydrates to lactic acid fostering an environment that is hostile to many pathogens.

Other desirable probiotic strains in the Lactobacillus genus include *L. plantarum* *L. casei*, *L. rhamnosus*, *L. brevis*, *L. paracasei* and *L. salivarius*. Prominent health promoting strains within the Bifidobacteria genus include *B. bifidum*, *B. breve*, *B. lactis* and *B. longum*. Bacteria within the Lactobacilli and Bifidobacteria genus share much in common with each other, but each member has positive characteristics of its own. This makes it advantageous to utilize a foundational probiotic that contains an assortment of health promoting probiotics.

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<sup>59</sup> Borriello, S.P., Hammes, W.P. et. Al. *Safety of Probiotics That Contain Lactobacilli or Bifidobacteria*. Clinical Infectious Diseases 2003;36:775-780

*L. plantarum* has received much attention by researchers and has been shown to contribute to a good balance of intestinal flora, to promote a balanced immune system, to help in the treatment of recurrent *Clostridium difficile* associated diarrhea, to inhibit *e. coli* induced intestinal permeability, to reduce symptoms of bloating and pain in patients with irritable bowel syndrome and to create an unfavorable environment for pathogens<sup>60</sup>

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*L. casei* and *B. longum* have been noted to activate the immune system thereby assisting in the prevention of a variety of diseases including tumors in animal experiments<sup>64</sup> as well as promoting an environment that discourages the growth of pathogens.

Studies on *L.rhamnosus*, *L.acidophilus* and *B. lactis* have demonstrated their ability to enhance a number of indices of natural and acquired immunity and are thought to be beneficial for “optimizing and/or enhancing immunocompetence in healthy, immunosuppressed or immunocompromised subjects”.<sup>65</sup> *Bifidobacterium lactis* has also

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<sup>60</sup> Goossens, D. et. al. 2003. The Effect of *Lactobacillus plantarum* 299v on the bacterial composition and metabolic activity in feces of healthy volunteers: a placebo-controlled study on the onset and duration of effects. *Aliment. Pharmacol. Ther.* 18:495-505

<sup>61</sup> Wullt, M. et. al. 2003 *Lactobacillus plantarum* 299v for the treatment of recurrent of *Clostridium difficile*-associated diarrhea: a double blind, placebo-controlled trial. *Scand. J. Infect. Dis* 35:365-367.

<sup>62</sup> Mangell, PO. Et.al. 2002. *Lactobacillus plantarum* 299v inhibits *E. coli* induced intestinal permeability. *Dig. Dis. Sci.* 47:511-516

<sup>63</sup> Nobaek, S. et. al. 2000 Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am. J. Gastroenterol.* 9i5:1231-1238.

<sup>64</sup> Jung-Woo et. al. **J Immunomodulatory and antitumor effects *in vivo* by the cytoplasmic fraction of *Lactobacillus casei* and *Bifidobacterium longum***

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*1R & D Center, Korea Yakult Co., LTD., Yongin 449-901, Korea*

*2Biologics Evaluation Department, Safety Evaluation office, Korea Food & Drug Administration, Seoul 122-704, Korea*

*3Department of Veterinary Medicine, Cheju National University, Jeju 690-756, Korea*

<sup>65</sup> Gill, H. S. et. al. Enhancement of natural and acquired immunity by *Lactobacillus rhamnosus*, *Lactobacillus acidophilus* and *Bifidobacterium lactis*. *British Journal of Nutrition* (2000), 83 167-176

demonstrated anti-pathogenic and gut protective properties in animal studies.<sup>66</sup> Bifidobacteria bifidum has demonstrated pro-immunological aspects in vivo as well as helping in the digestion of lactose, helping to balance intestinal pH, producing B vitamins, inhibiting yeast growth and lowering the ability of E.coli to adhere to intestinal walls.<sup>67 68</sup>

Lactobacillus salivarius is another worthy candidate for inclusion in a foundational probiotic formulation. It has been demonstrated in animal models to modulate the immune system in a balanced fashion and strongly reduce intestinal inflammation and beneficially modulate the intestinal mucosal immune response in inflammatory situations.<sup>69</sup>

Lactobacillus paracasei has demonstrated probiotic health benefits including modulation of the immune system. A study of children found that L. paracasei given in a milk product significantly reduced the incidence of diarrhea<sup>70</sup>. L. casei strains have also been seen to reduce the release of the inflammatory cytokine TNF-alpha release as observed in normal and inflamed human colonic biopsies.

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<sup>66</sup> Wagner, R.D. et. al. Biotherapeutic effects of probiotic bacteria on candidiasis in immunodeficient mice. *Infect. Immun.* 65:4165-4172 1997.

<sup>67</sup> Schiffrin, E.J. et. al. *J. Dairy Science* 1995, 78, 491-7

<sup>68</sup> Schiffrin, E.J. et. al. *Am. J. Clin. Nutr.* 1997, 66, 515S-520S.

<sup>69</sup> Dennin, V. et. al. 2003 Screening procedure for the selection of probiotic LAB with survival and immunomodulation potential: the combination of in vitro and in vivo techniques. 2<sup>nd</sup> Probiotics and Prebiotics New Foods Conference. September, Rome Italy.

<sup>70</sup> Pedone, C.A., Arnaud, C.C. et. al 2000 Multicentric study of the effect of milk fermented by Lactobacillus casei on the incidence of diarrhea. *Int. J. Clin. Pract.* 54: 568-571



. Utilizing a combination of probiotics such as those listed on a regular basis, can be a positive step for patients to take in both the prevention of disease, the promotion of health and in helping to improve many health problems that have arisen due to the changes that have taken place in the modern world regarding our microbial connections.

## **Restorative Probiotics**

Of the many challenges presented to the microflora of 21<sup>st</sup> century guts, antibiotic ingestion tops the list. The amount of antibiotics taken in our population is reflected by the number of antibiotic prescriptions written for children e.g. 698 per 1,000 children seen in the medical office setting in 1999<sup>71</sup>. Even for those that have not taken prescription antibiotics during their lives, few escape antibiotic exposure through the food supply. Seventy percent of the antibiotics produced in the United States are administered to livestock and dairy cattle with their meat and milk residues being ingested by U.S. consumers.<sup>72</sup> Complicating this problem is that prescription antibiotics are increasingly those of the broad spectrum variety, even though there is little rationale for their widespread usage (many prescriptions are for patients with viral infections which are unaffected by antibiotic preparations). Broad spectrum antibiotics carry a significant potential of generating microbial imbalances in the gastrointestinal tract, increasing the

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<sup>71</sup> [Pediatric Infect Dis J.](#) 2002 Nov;21(11):1023-8.

<sup>72</sup> V. Witte W. Medical consequences of antibiotic use in agriculture. *Science* 1998;279: 996 -997.

risk of generating antibiotic resistant bacterial pathogens and promoting a host of potentially pathological yeast and fungal organism overgrowths.<sup>73</sup>

The effects of the imbalances created in the GI tract by the administration of antibiotics range from modest to deadly. Numerous children and adults develop antibiotic induced diarrhea each year which in some cases results in the development of a potentially fatal condition known as pseudomembranous colitis occurring when antibiotics disturb the normal bowel flora and allow pathogenic strains of *C.difficile* to overgrow. The greater proportion of intestinal lesions and diarrhea occurring in conjunction with *Clostridium difficile* infections are attributed to previous antibiotic treatments<sup>74</sup> as many clinicians have witnessed in their patients. This dilemma is frequently seen in hospitalized patients because of nosocomial contamination with *Clostridium difficile* spores. In severe cases the colonic mucosa of such patients may appear grossly abnormal and the tissues may resemble that of idiopathic ulcerative colitis.

Antibiotic associated colitis and other related complications of antibiotic administration including diarrhea type disorders and recurrent vaginal yeast infections are best prevented by avoiding the mis-use / overuse of antibiotics. If antibiotics are deemed necessary, however, the administration of appropriate probiotics, both during and after antibiotic administration, can be an important step to take to avoid the serious complications that can result from antibiotic administration.

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<sup>73</sup> Ann Intern Med. 2003 Apr 1;138(7):525-33. Changing use of antibiotics in community-based outpatient practice, 1991-1999. Steinman MA, Gonzales R, Linder JA, Landefeld CS.

163 Schreiner A *Antibiotic induced diarrhea and pseudomembranous colitis* Nord Med., 1993;108(11):283-5

*Saccharomyces boulardii* has been shown to help prevent and/or address antibiotic complications. *Saccharomyces boulardii* is a non-pathogenic yeast which supports gut flora balance and general homeostasis<sup>75</sup> and can be employed in helping to deal with a number of antibiotic related problems.

Related to brewers yeast, *Saccharomyces boulardii* has been widely used, particularly in Europe, to prevent antibiotic induced diarrhea. In double blind trials, *Saccharomyces boulardii* has prevented antibiotic induced as well as other forms of infectious diarrhea.<sup>76</sup> Some patients with Crohn's disease have also been reported to have had a positive response to the administration of *Saccharomyces boulardii*.<sup>77</sup> Antibiotic induced diarrhea is also a common occurrence among elderly patients and *Saccharomyces boulardii* has been cited here also as often proving helpful.<sup>78</sup>

*Saccharomyces boulardii* has shown to be of help in reducing the incidence of antibiotic associated diarrhea in hospitalized patients<sup>79</sup>, in reducing the bacterial count in patients

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<sup>75</sup> McCullough, M. J., Clemons, K. V., McCusker, J. H., and Stevens, D. A. Species identification and virulence attributes of *Saccharomyces boulardii* (nom. inval.) **J Clin Microbiol**, 36[9], 2613-7. 1998.

<sup>76</sup> Bleichner G, Blehaut H, Mentec H, Moysé D. *Saccharomyces boulardii* prevents diarrhea in critically ill tube-fed patients. A multicenter, randomized, double-blind placebo-controlled trial. *Intensive Care Med* 1997;23:517-23.

<sup>77</sup> Plein K, Hotz J. Therapeutic effects of *Saccharomyces* on mild residual symptoms in a stable phase of Crohn's disease with special respect to chronic diarrhea—a pilot study. *Z Gastroenterol* 1993;31:129-34.

<sup>78</sup> Lewis SJ, Potts LF, Barry RE. The lack of therapeutic effect of *Saccharomyces boulardii* in the prevention of antibiotic-related diarrhoea in elderly patients. *J Infect* 1998;36:171-4.

<sup>79</sup> Surawicz, C. M., Elmer, G. W., Speelman, P., McFarland, L. V., Chinn, J., and van Belle, G. Prevention of antibiotic-associated diarrhea by *Saccharomyces boulardii*: a prospective study *Gastroenterology*, 96[4], 981-8. 1989.

with intestinal bacterial overgrowth<sup>80</sup>, been cited as an effective symptomatic treatment for AIDS related diarrhea<sup>81</sup>, been employed in preventing traveler's diarrhea<sup>82</sup>, and has shown benefit in treating flare ups of ulcerative colitis<sup>83</sup> which also may be the consequence in some cases of antibiotic administration.

A number of the probiotics previously recommended as part of a foundational probiotic formulation have also proven helpful in the prevention of problems associated with antibiotic administration, including *L. plantarum*, *L. acidophilus*, *L. rhamnosus*, and *L. paracasei*. Research has shown that these can be employed to advantage in preventing antibiotic associated diarrhea as well.<sup>84 85 86 87 88</sup>

An adverse consequence of taking antibiotics, particularly for women, is the frequent development of an overgrowth of *Candida albicans* and other pathogenic yeast strains. *Saccharomyces boulardii* has been shown to reduce the occurrence of candidiasis in

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<sup>80</sup> Bornet, M and Bergogne-Berezin, E Bacterial growth in enteral eliminations value of the addition of *Saccharomyces boulardii*. **Science des Aliments**, 6[VI], 63-73. 1986.

<sup>81</sup> Saint-Marc, T., Rossello-Prats, L., and Touraine, J. L. [Efficacy of *Saccharomyces boulardii* in the treatment of diarrhea in AIDS] **Ann Med Interne (Paris)**, 142[1], 64-65. 1991.

<sup>82</sup> Kollaritsch, HH, Kremsner, P, Scheiner O., and Wiedermann, G. Prevention of Traveler's diarrhea: A comparison of different non-antibiotic preparations. **Travel Medicine International**, 9-17. 1989.

<sup>83</sup> Guslandi, M., Giollo, P., and Testoni, P. A. A pilot trial of *Saccharomyces boulardii* in ulcerative colitis **European Journal of Gastroenterology & Hepatology**, 15[6], 697-698. 2003.

<sup>84</sup> Gorbach, SL, Chang T., Goldin B Successful treatment of relapsing colstridium difficile with lactobacillus GG Lancet 1987 p 1519

<sup>85</sup> Biller J.A., et. al. Treatment of recurrent clostridium difficile colitis with lactobacillus GG J Pedeatric Gastroenterol Nutr 1995;21:224-6

<sup>86</sup> SiitonenS, Vapaatalo H, Salminen S, et al. Effect of lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea. Ann Med 1990; 22:57-9

<sup>87</sup> Arvola T., et al. (1999) Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. Pediatrics 104:L e64

<sup>88</sup> Gotz V., et al. (1979) Prophylaxis against ampicillin-associated diarrhea with a lactobacillus preparation. Am. J. Hosp. Pharm. 36: 754-757

patients after taking antibiotics<sup>89</sup>. It has been shown effective against *Candida albicans*, *C. Krusei*, and *C. pseudotropicalis* in mice, although ineffective against *C. tropicalis*.<sup>90</sup>

The development of a *Clostridium difficile* infection remains one of the greatest dangers in taking antibiotics. *Saccharomyces boulardii* produces a protease that helps to prevent *Clostridium difficile* toxin A from binding to specific intestinal receptors<sup>91</sup> and has shown effectiveness in the treatment of recurrent *C. difficile* diarrhea and colitis when combined with vancomycin.<sup>92</sup>

The rational usage of *Sacchromyces boulardii*, particularly when used in addition to a foundational probiotic formulation, has shown significant evidence of being of value to individuals undergoing antibiotic administration as well as to those who have taken antibiotics and are suffering from adverse consequences as a result. Practitioners would be prudent to consider the administration of *Sacchromyces boulardii* to patients during and after antibiotic therapy. Taking this step can help maintain homeostasis in the GI tract when its terrain is under assault and prevent the emergence of serious antibiotic related complications.

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<sup>89</sup> Adam, M Controlled double-blind clinical trials of *Saccharomyces boulardii* Multicentre *Medecine Chirurgie Digestives*, 5[6], 401-6. 1976.

<sup>90</sup> Ducluzeau, R. and Bensaada, M. [Comparative effect of a single or continuous administration of "*Saccharomyces boulardii*" on the establishment of various strains of "candida" in the digestive tract of gnotobiotic mice] *Ann Microbiol (Paris)*, 133[3], 491-501. 1982.

<sup>91</sup> Pothoulakis, C., Kelly, C. P., Joshi, M. A., Gao, N., O'Keane, C. J., Castagliuolo, I., and Lamont, J. T. *Saccharomyces boulardii* inhibits *Clostridium difficile* toxin A binding and enterotoxicity in rat ileum *Gastroenterology*, 104[4], 1108-15. 1993.

<sup>92</sup> Surawicz, C. M., McFarland, L. V., Elmer, G., and Chinn, J. Treatment of recurrent *Clostridium difficile* colitis with vancomycin and *Saccharomyces boulardii* *Am J Gastroenterol*, 84[10], 1285-1287. 1989.

# Immune Directed Probiotics

Significant immunological differences exist among patients stemming from their genetics and the environmental factors they've been exposed to. Subsequent to these differences, the internal environment of each person's gut also differs. It is important therefore to address the specific needs of a patient's clinical condition when utilizing probiotics, i.e. to have specific probiotics to support the immune requirements of the individual. These might be referred to as "*Immune Directed Probiotics.*"

When tissues have been damaged, inflammation is a primary means by which repair occurs. The inflammatory process also defends the body against challenges by bacteria, viruses and allergens by increasing blood flow and white blood cells to the area. Cytokines, secreted by immune cells, help regulate the inflammatory response. Interleukins, a type of cytokine, can induce or suppress inflammation. A balancing act of pro and anti-inflammatory cytokine activity is the norm. Outside stimuli can suppress or induce inflammatory cytokines/interleukins, contributing to the development of allergies, colds or the promotion of chronic inflammatory conditions including autoimmune conditions.

T lymphocytes referred to as *T helper cells Type I* (Th1) and *T helper cells Type II* (Th2), are important in modulating allergic responses.<sup>93</sup> This ties in with the *Hygiene Hypothesis* which proposes that various atopic (allergic) conditions, including

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<sup>93</sup> Bellou Abdelouahab; Schaub, Bianca et al. *Toll Receptor Modulate Allergic Responses: Interaction With Dendritic Cells, T Cells and mast Cells.* *Curr Opin Allergy Clin Immunol* 3(6): 487-494, 2003

asthma, are on the rise because of an imbalance between Th1-type and Th2-type immune responses caused by our modern lifestyle. T helper cells play a key role in the execution of the immune inflammatory response. Depending on the prevailing distribution of T helper cells there are two main types of inflammatory responses carried out by the immune system that are inversely proportionate; Th1 and Th2 responses.

In general, *Th1 responses are antimicrobial and pro-inflammatory, whereas Th2 responses promote allergic reactivity.* These immune responses ideally balance one another as Th2 mediators suppress Th1 responses and Th1 mediators similarly inhibit Th2 responses<sup>94</sup>. The implications for this extend to autoimmune conditions which are thought to be mediated via imbalanced (excessive) Th1 responses and allergic conditions with excessive Th2 responses. Cell mediated/Th1 type responses in general afford protection against viral and bacterial infections and cancers while Humoral immunity/Th2 responses enable allergic responses.

Probiotic administration can be employed in ways that favorably influence the balance of Th1 and Th2 in the body.<sup>95</sup> Offspring from atopic mothers, for example, who ingest probiotics possessing anti-inflammatory properties (i.e. suppress Th1),

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<sup>94</sup> Kline, Joel N. M.D. *A New Model for Understanding and Treating Asthma*. October 2003. University of Iowa Department of Internal Medicine. Virtual Hospital [www.vh.org/adult/provider/internal\\_medicine/treating\\_asthma\\_9/19/2005](http://www.vh.org/adult/provider/internal_medicine/treating_asthma_9/19/2005)

<sup>95</sup> Marteau P, et. al *Probiotics and health: new facts and ideas*. *Curr Opin Biotechnol* 2002; 13:486-489.

have been reported to have a decreased risk of developing atopic eczema in the first 2 years of life.<sup>96 97</sup>

Probiotic bacteria differ widely in their abilities to enhance or suppress Th1 or Th2 and can therefore be selected for usage based on the type of clinical condition the patient presents with.

The ideal is an immune system that is in balance with neither a Th1 nor Th2 response dominating for an extended period of time. If dominance of either does occur, symptoms of immune balance are likely to accompany it. Chronic inflammation of tissues can be a sign of a dominant Th1- type response while allergic type responses are likely to be a Th2 related response.

In observing those with chronic health problems stemming from disturbances in the GI tract and the immune system, a significant variable is evident. Many chronic health problems such as allergies are accompanied by an immune system that is *overly aggressive* while in other conditions such as AIDS, the immune system *is not aggressive enough*. The clinician's goal therefore is to improve and balance immune function by the utilization of materials that nourish, support and balance the immune system, encouraging immune function to move in the proper direction to achieve balance. In light of the fact that different probiotic bacteria influence the immune

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<sup>96</sup> Kalliomaki M et. al. Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. *Lancet* 2001; 357:1076-1079.

<sup>97</sup> Rautava S, et. al. Probiotics during pregnancy and breast feeding might confer immunomodulatory protection against atopic disease in the infant. *J Allergy Clin Immunol* 2002; 109:119-121



system in varied ways, specific probiotics can be utilized to support the patient's well being in regards to their particular circumstances.

### **Promoting T helper Cell Immuno-Regulation Employing Pro-biotics**

The dramatic increase in inflammatory bowel disease and other autoimmune conditions (Th1 mediated) and allergies (Th2 mediated) is believed to be due to diminished immunoregulation leading to inappropriate immune responses<sup>98</sup>. The origins of some inflammatory bowel disease cases are associated with “an imbalance in the intestinal microflora with relative predominance of aggressive bacteria and relative paucity of protective organisms. Therefore, altering the composition of the flora by probiotics, prebiotics, or a combination of both may represent a highly physiological, nontoxic way to prevent or treat IBD.”<sup>99</sup>

Evidence has accumulated that some probiotics can induce T cell regulation<sup>100 101</sup>. Specific probiotics or probiotic combinations have been suggested for employment for patients with conditions that point to either imbalance of the Th1 or Th2 responses.

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<sup>98</sup> Rook, GAW, Brunet, LR. *Microbes, immunoregulation and the gut* [www.gutjnl.com](http://www.gutjnl.com) 9/2004

<sup>99</sup> Mitsuyama K. et. al. Intestinal microflora as a therapeutic target in inflammatory bowel disease

<sup>100</sup> Chapat L, et. al. Lactobacillus casei reduces CD8 (+) T cell mediated skin inflammation. *Eur J Immunol* 2004;34: 2520-8

<sup>101</sup> Christensen HR et. al. *Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells.* *J. Immunol* 2002;168:171-8

Specific strains of *L. salivarius* and *B. lactis* for example, have been demonstrated to suppress Th1 in vitro thus having an anti-inflammatory effect. Conditions that might benefit from such probiotics include many of the autoimmune/inflammatory related disorders e.g. ulcerative colitis, crohns disease, rheumatoid arthritis, lupus, etc.

Other strains of probiotics e.g. *L. plantarum*, *L. acidophilus* and *L. paracasei* have been demonstrated to suppress Th2 in vitro, leading to a potential reduction in allergy and asthma related syndromes. “Presuming that exuberant Th2 responses are critical for the pathogenesis of allergic diseases, the manipulation of the Th1/Th2 balance is a promising approach for modulating allergic disease.”<sup>102</sup> This can be undertaken by utilizing probiotics which suppress Th2 responses. These same probiotics (those suppressing Th2 responses) also have the potential for reducing the impact from viral infections such as colds, flu and HIV.

In light of the above, the clinician has probiotic options that can be selected to fit the needs of his or her patients. Are the patient’s problems primarily allergic in nature? Are the problems primarily inflammatory in nature? Are the problems primarily due to a lack of immune response to infectious agents? In each case the clinician can choose the best probiotic formulation suited to the patient’s needs. For those patients where there is considerable overlap in the nature of the problems, which can occur, a foundational (multiple) probiotic might serve best or the alteration of a Th1 or Th2 suppressant dominant probiotic with a foundational (multiple) probiotic. Due to the wide variety of

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<sup>102</sup> Bellou, A. et. al. *Toll Receptors Modulate Allergic Responses: Interaction With Dendritic Cells, T Cells and Mast Cells* Curr Opin Allergy Clin Immunol 3(6): 487-494, 2003

patients and circumstances encountered in practice, the experience and discretion of the practitioner is always critical.

There remain numerous questions to explore and many potential uses of probiotics left to research. Our current knowledge of probiotics in clinical practice has come a long way, however, and offers broad applications for the practitioner to utilize in meeting the general and specific needs of his or her 21<sup>st</sup> century patients in promoting good health and in reversing chronic illness. Research and clinical evidence have supported the employment of probiotics to retain our microbial connections and our health, using different formulations under varying clinical circumstances.

## **Conclusion**

Recent epidemiological studies have confirmed what natural practitioners have long known; that good health requires that we respect the microbial world we are immersed in. We have observed that medical science's predilection for assaulting the balance of microbes in the human body has often left in its wake, a dangerous ripple effect that has often led to adverse health outcomes.

With the new epidemiological, immunological and microbiology data that we now possess, natural practitioners can make an even more compelling case for lifestyle changes including increasing our contacts with the natural world, utilizing a natural diet and the clinical application of specific quality probiotics targeted for both the general and specific needs that patients have.

## About the Author

Dr. Paul Goldberg is a graduate of The University of Texas Graduate School of Public Health (M.P.H. Chronic Disease Control), a Chiropractic Physician, Clinical Epidemiologist and Clinical Nutritionist. He holds Diplomate Status with the American Clinical Board of Nutrition and directs **The Goldberg Clinic** in Atlanta, Georgia. He was the Senior Director of Research and Physician Education for Original Medicine, Inc from 2003 to 2007. For twenty three years he served as a Professor of Clinical Nutrition and Gastroenterology at Life University and is currently a visiting Professor at the University lecturing in Clinical Nutrition. Due to his personal struggle in overcoming rheumatoid disease as a young man and his thirty years of practice, teaching, writing and research experience, Dr. Goldberg is well known for his success in working with patients with rheumatoid disorders, inflammatory bowel diseases and other autoimmune conditions. In his practice Dr. Goldberg utilizes a highly individualized “*Foundational Approach*” that focuses on the gastrointestinal and immune systems along with genetic and lifestyle factors. Contact information can be found at [www.goldbergclinic.com](http://www.goldbergclinic.com)