PREBIOTICS --- The Natural Way to Conquer Obesity, Allergies, High Blood Pressure, High Cholesterol and Triglycerides, Cardiovascular Disease, Diabetes, Immune-Related Disease, and Premature Aging

PREBIOTIC IMMUNOLOGICAL AND METABOLIC BENEFITS:

Prebiotics are food that passes through the small intestine and into the colon in an undigested state. It thus becomes food for the natural flora of the colon. Prebiotics are concentrated sources of undigestible carbohydrate taken as supplements for the purpose of increasing the population of beneficial bacteria in the colon. A major benefit of prebiotic supplementation is the production, through fermentation of the prebiotic by the beneficial bacteria, of increased quantities of short chain fatty acids. The most specific intent is to not only increase the overall quantity of SCFA, but to increase the proportion of butyrate, the most critical of the SCFA. In addition to SCFA, there are other end products of prebiotic fermentation that have …

FAR-REACHING IMMUNOLOGICAL AND METABOLIC EFFECTS.

The newborn infant leaves a germ-free intrauterine environment to enter a contaminated extrauterine world and must have adequate intestinal defenses to prevent the expression of clinical GI disease states. Although the intestinal mucosal immune system is fully developed after a full-term birth, the actual protective function of the gut requires the microbial stimulation of initial bacterial colonization. Breast milk contains prebiotic oligosaccharides, like inulin-type fructans, which are not digested in the small intestine but enter the colon as intact large carbohydrates that are then fermented by the resident bacteria to produce SCFA and other health-promoting end-products.

Breast-fed infants use inulin-type fructans to produce increased bifidobacteria and some lactobacilli, whereas formula-fed infants produce more enterococci and enterobacteria. The flora stimulated by prebiotic fermentation is important to the development and sustainment of intestinal barrier function. For example, normal flora stimulates the synthesis and secretion of secretory IgA, the antibody that coats and protects mucosal surfaces against harmful bacterial invasion.

In addition, appropriate colonization of the gut helps to produce a balanced T helper cell response, facilitating the natural shift from the Th2 dominance of the prenatal state toward development of Th1 and Th3/Tr1 immune defenses. (Th2 imbalance contributes to atopic disease, and Th1 imbalance contributes to Crohn's disease and H. pylori-induced gastritis.) Furthermore, a series of pattern recognition receptors, like toll-like receptors on gut lymphoid and epithelial cells that interact with bacterial toxins help modulate both intestinal innate immunity and an appropriate adaptive immune response. Inulin-type fructans, being bifidogeneic and promoting the generation of SCFA, can

stimulate a balanced and effective mucosal immune system in newborns and infants.

Before the adoption of our (debilitating) modern diet, humans consumed up to 10 times as much prebiotic fiber as modern populations, and their bodies were flooded with far more fermentation bi-products. Our fiber-poor modern diet has weakened the signals along the gut-brain axis, the gut-immune system axis, and the gut-liver axis so as to produce a state of what one researcher calls "simmering hyperactivity" --- creating overwhelming Immuno-Neuro-Endocrine stress. That researcher attributes the "plagues" of civilization to our deteriorating human microbiome resulting from prebiotic deficiency. He calls this problem "starving our microbial self." We simply are not adequately feeding our essential microbiota.

Diets high in polyunsaturated fats (PUFAs) as well as sugars deplete anti-inflammatory bacteria, thin the mucus layer of the gut, and foster systemic inflammation. Potentially dangerous opportunists bloom in the gut. In one intervention on human volunteers, it was found that switching to a high-oil, high-protein diet spurred an expansion of bile-tolerant bacteria, one of which, Bilophila wadsworthia, was linked to inflammatory bowel disease. On the other hand, preventing the skewing of microbial self is not difficult. Nothing more complicated than adding prebiotics to the diet keeps the health-enhancing microbes proliferating, the mucus layer healthy, and the gut barrier intact, all the while preventing systemic inflammation.

The nature of prebiotic fermentation and the consequent pH of the intestinal contents dictate proliferation of specific resident bacteria. The pH of the colon is critical to healthful probiotic function. To illustrate: Propionibacterium freudenreichii is an important part of defense against colon cancer in that it kills colorectal adenocarcinoma cells via its metabolites, the SCFA acetate and propionate. However, it has been shown that the beneficial effects of this bacterium only occur over a colon pH range of 5.5-7.5. When the colon pH is much below 6.0, the very same bacterium that prevents colon cancer actually causes it. At that lower pH, this bacterium does not destroy colon cancer cells by apoptosis but rather kills colon cells by necrosis --- destruction of the colon epithelium. This destruction is characterized by drastic depletion in ATP of colonocytes, sudden mitochondrial depolarization, inner membrane permeabilization, radical increase in ROS accumulation associated with oxidative damage, and ultimately colonocyte death by necrosis. The key to maintaining proper colon pH and thus the healthful benefits of normal flora is the use of prebiotics to create an overall beneficial intestinal milieu.

It is important to understand that the benefits of SCFA are not just realized within the colon as the SCFA provide nutrition for colonocytes and improve the function of the gut epithelium --- also, the SCFA are absorbed into the blood stream and have wide-reaching immunomodulating effects. The increase in

caecal SCFA after prebiotic supplementation correlate well with the increase in SCFA in both the portal serum and the aortic serum. In particular, the rising concentrations of acetic, propionic, and butyric acid all correlate well with those of the portal serum, while butyric acid concentration in the caecal content is most reflected in the aortic serum.

Prebiotics ensure selective stimulation of beneficial bacterial strains, but they do not stimulate the same intestinal microbiota in humans and rodents. In humans, prebiotics specifically increase bifidobacterial populations, whereas lactobacilli populations are increased significantly in the microbiota of rodents.

Prebiotics stimulate the activity of lactic acid producing bacteria (especially bifidobacteria) much more than butyrate-producing bacteria. Butyrate is produced by the clostridium eubacterium, and ruminococcus genera, whereas other SCFAs such as acetate or propionate are produced by lactic-acid bacteria of the bifida bacterium and lactobacillus genera. So, butyrate alone cannot explain the effects of prebiotics on the gut immune system; priopionate and acetate must also play key roles in the regulation of immune system expression. To illustrate, cells cultured with acetate, proprionate and butyrate produce high levels of IL-10, whereas butyrate alone has little effect.

All studies on mice to determine the effect of prebiotics on allergy showed a preventive effect of prebiotics. An anti-allergenic effect of FOS was characterized by a reduction in mast cell levels and in the rate of edema formation in the duodenum during sensitization. In general, FOS and/or GOS decreased the Th2 response and induced activation of the Th1 pathway when mice are sensitized. In humans, infants with a parental history of atopic eczema, allergic rhinitis, or asthma showed a decrease incidence of atopic disease, wheezing, and allergic urticaria when given a GOS-inulin supplement. There was an increase in bifidobacteria in the feces and a fall in the level of IgG1, IgG2, IgG3, and cow's milk protein-specific IgE. In conclusion, a prebiotic strategy appears to be more promising than a probiotic strategy in the prevention of allergy.

The endocrine aspects of Immuno-Neuro-Endocrine health associated with normal biota are demonstrated by the fertility of Hadza women. The Hadza are tribes of wandering foragers in Tanzania who have lived for thousands of years in a sparse and difficult natural environment. Despite the limited availability of nutrition, the women are extremely fertile and produce babies of perfect health. It is found that the Hadza gut microbiome harbors incredibly high diversity of bacteria, indicating great stability and flexibility. These women consume a tremendous quantity of high-fiber foods. The resulting healthy microbiota enables them to obtain nutrition for fertility and reproductive success despite the limited nutrition resources of their environment. The mechanisms by which this fertility is supported are now coming out in the

many studies showing the direct communication between the gut and the hypothalamus.

A high formation of SCFA per se stimulates PPAR-γ, which increases GLUT-4 and insulin sensitivity. The decreased insulin resistance explains the benefits on weight loss, diabetes, and triglycerides associated with prebiotic supplementation. Do all types of dietary fiber giving rise to high amounts of SCFA have an effect on weight gain? Different fibers yield different formations of SCFA. For example, propionic acid has been shown to increase satiety, while butyric acid has anti-inflammatory effects through NF-kappa-B, which in turn may influence parameters associated with the Metabolic Syndrome.

CONTROLLING THE IMMUNO-NEURO-ENDOCRINE STRESS ASSOCIATED WITH METABOLIC SYNDROME AND ALL ITS MANIFESTATIONS (OBESITY, CARDIOVASCULAR DISEASE, CANCER) IS THE GREATEST BENEFIT OF PREBIOTIC SUPPLEMENTATION.

The presence of abnormal gut microbiota exposes the host to a vast amount of LPS (endotoxin) found on the outer membranes of Gram-negative bacteria. Systemic reactions to LPS lead to highly lethal septic shock, a very undesirable outcome of host-microbiota interactions. One way to avoid this disastrous scenario is to minimize the toxic potential of LPS, which can be done via dephosphorylation of the LPS endotoxin component through the action of alkaline phosphatases, specifically the intestinal alkaline phosphatase --- achieved via prebiotic supplementation.

Obesity and metabolic disorders (insulin resistance, hyperlipidemia) are tightly linked to a chronic low-grade state of inflammation (elevated levels of circulating inflammatory markers such as IL-6 and C-reactive protein). Both animal and human models have shown that changes within the microbial ecology or functional activities of gut microbiota can induce a metabolic shift toward this pro-inflammatory phenotype, with whole body, liver and adipose tissue weight gain, and impaired glucose metabolism. Factors of microbial origin (e.g., bacterial LPS) are hypothesized to lie at the basis of such systemic inflammatory effects.

Mounting evidence suggests that the systemic inflammation observed in obesity does not result from the accumulation of fat, but causes it. Studies show that adding inulin to the diet of obese women increased the count of F pratausnitzii, and other clostridial bacteria that reduce systemic inflammation. Weight loss in these obese women was minor at first, but later analysis of this and other similar studies reveals that the intervention works best on patients who, at the outset, already harbored clostridial clusters that are associated with a low-inflammatory status. Those without the proper intestinal flora did not benefit as much from the prebiotic until after the microbiota was fully established with long-term prebiotic supplementation.

In one study, microbes were transplanted from lean donors to patients recently diagnosed with Metabolic Syndrome. The recipients saw improvements in insulin sensitivity and the enrichment of their microbiota. However, 6 months after the bacterial transplant, the patients had relapsed, with metabolic improvements fading and the precursors to Type 2 diabetes returning. The researcher emphasized that the long-term key to success here was not transplanting microbes but fostering an ideal environment for healthy microbe development through prebiotic supplementation.

The link between the gut microbiota and the development of obesity and associated disorders such as insulin resistance, Type 2 diabetes, and fatty liver disease is a loss of or an excess of inter-organ communication. The key disrupter of inter-organ communication is metabolic endotoxemia (an increase in plasma lipopolysaccharide (LPS). LPS is one of the triggering factors leading to the development of metabolic inflammation and insulin resistance. Gut microbes contribute to the onset of low-grade inflammation via mechanisms associated with gut barrier dysfunction.

The gut lining includes enteroendocrine cells that communicate with the brain, with the liver, and with adipose tissue. This inter-organ communication can be discussed in the context of gut-to-peripheral organ axes: intestine to brain, intestine to adipose, and intestine to liver. The key to maintaining proper communication along these axes is minimizing the production of gut endotoxins with prebiotic (and to a certain extent with probiotic) supplementation.

In response to food intake, the intestine senses various messages from different origins, including nutrients, hormones, and end-products of bacterial metabolism. In response, the intestine generates different types of messages (hormones and sympathetic and parasympathetic afferent nerves) that communicate with the peripheral organs such as the liver and adipose tissue as well as the brain (particularly the hypothalamus). In turn, these organs generate signals to modify energy storage versus energy expenditure, plus other key messages generated by the brain, such as efferent signals via the sympathetic and parasympathetic nerves.

LPS interferes with these communication axes systemically in 2 ways. First, the toxic bacterial products activate the immune system in the gut lining (where nearly 75% of the immune system resides). Dendritic cells, mast cells, and macrophages are inappropriately activated by LPS, thus setting off a massive pro-inflammatory chain reaction that disperses through the entire body. Pro-inflammatory cytokines are released that may result in acute symptomatic disease, but always result in low grade chronic inflammation.

The second way LPS distorts the communication axes originated in the gut is by dominating the communication line between the gut and the brain, the gut and adipose, and the gut with the liver. The inappropriate responses of these target organs to LPS are the major factor involved in the early development of inflammation and the metabolic diseases obesity, Type 2 diabetes, hypertension, and fatty liver.

Studies show a direct link between abnormal gut microbiota with excessive gut permeability and low-grade inflammation and insulin resistance. The breakdown in gut barrier function particularly results in obesity in individuals with the hepatic inflammatory phenotype associated with obesity and Type 2 diabetes. Individuals of this phenotype are those with a very strong pre-disposition to fatty liver, high triglycerides, metabolic syndrome, and eventually Type 2 diabetes. Even extraordinary calorie-restrictive diets yield mostly frustration in these individuals in terms of weight loss and lipid control. Dietary sugars and carbohydrates are very easily converted to triglycerides. Dietary polyunsaturated fatty acids also increase systemic pro-inflammatory free fatty acids and their derivatives in these patients by increasing plasma LPS. For these individuals …

A BURGER + FRIES + COLA = EXTREME INFLAMMAGING.

The most direct way to control obesity and the consequences of Metabolic Syndrome in these patients is to reduce LPS production in the gut by prebiotic supplementation. Prebiotics reinforce the gut barrier, promote gut hormones that control appetite, promote glucose homeostasis, decrease systemic inflammation and obesity, and counteract hepatic steatosis and hepatic insulin resistance.

It is interesting that while prebiotic supplementation (and certain probiotic supplementation) is the most direct and powerful way to favorably influence the communication line of the gut with the brain, the liver, adipose tissue, muscle tissue, and the pancreas, there is one particular bacterial species that actually disrupts this communication line. That species is the ever-popular Lactobacillus acidophilus. --- Yes --- the most popular of all probiotic supplements makes people fat, sick, and old. Many bacteria used as probiotics have been tested, and none except L acidophilus increase the expression of CB2, the obesity-generating messenger in the colon to adipose axis.

In studies on obese mice and on mice bred to be diabetic, certain species of bacteria are identified exclusively in obese and diabetic mice. There are also certain strains of bacteria identified exclusively in lean mice that are not found at all in obese and diabetic mice. The most significant findings of these studies is that even in mice genetically bred to be obese or diabetic, the gut microbiota can be altered with prebiotics so as to control the obesity and the diabetes by improvements in adipose tissue metabolism.

Adipocytes produce and secrete adipokines. Disruption of adipokines causes obesity and all the manifestations of Metabolic Syndrome including Type 2 diabetes. During intestinal inflammation caused by LPS, pro-inflammatory cytokines induce expression of a factor that disrupts adipokines. Inflammatory markers induced by LPS are shown to positively and significantly correlate with the level of adipokine disrupters in the adipose tissue of diabetic mice. In genetically predisposed individuals, the pro-inflammatory cytokine TNF-α induces disruption of the adipokine system in massively obese humans, indicating a direct link between LPS-induced inflammation and adipose tissue.

Specific gut microbes are shown to correlate directly with adipose markers, suggesting that these microbes play a major role in adipose tissue metabolism. Obese and diabetic mice are characterized not only by altered microbiota, but more significantly by intestinal inflammation caused by that abnormal gut flora. The communication axes are disrupted, as shown by altered enteric glucose detection and nitric oxide release in the hypothalamus, leading to peripheral insulin resistance. Studies in humans show that low bifidobacteria correlates directly with the development of obesity and/or diabetes.

Regulation of fat storage is under the control of several mechanisms associated with composition and activity of gut microbiota. Important mechanisms involving energy-sparing, resulting in part from the fermentation of prebiotics into SCFA, have been identified. The release of those bacterial metabolites allows them to act as regulators of adiposity.

Studies show that there are at least 100 species that differ between a control diet and a prebiotic supplemented diet. This response to prebiotic supplementation is huge. Of the more than 100 species that are altered by prebiotics, 8 of the species are shown to increase more than tenfold, and 8 of the species are decreased by more than tenfold. These studies permit identification of bacteria that are promoted using a prebiotic approach, such as Akkermansia muciniphila, the abundance of which is inversely correlated with body weight. A muciniphila also correlates inversely and significantly with Type 1 diabetes in humans. Other studies show that prebiotic supplementation decreases the ratio of Firmicutes to Bacteroidetes, the ratio that is elevated in obesity.

--- Obviously, probiotic supplementation is not the answer to Metabolic Syndrome. There is no way to supplement with 100 different species of probiotic, most of which are obscure and some of which have not even yet been identified. Prebiotic supplementation is the only way to have a major impact on gut barrier function and to reduce the production of endotoxins that cause obesity, high triglycerides and cholesterol, high blood pressure, cardiovascular disease, diabetes (Type 1 and Type 2) and an elevated risk of cancer.

Paralleling the benefits of prebiotics on obesity, high triglycerides, high blood pressure, fatty liver, Type 2 diabetes, cardiovascular disease, and all of the other ramifications of Metabolic Syndrome, is the additional benefit of lowering elevated cholesterol but not lowering normal cholesterol. Three major mechanisms have been proposed to explain the cholesterol-reducing effects of prebiotics: a) Prevention of bile salt re-absorption from the small intestine, leading to an excess fecal bile salt excretion, b) Reduced glycemic response leading to lower insulin stimulation of hepatic cholesterol (and triglyceride) synthesis, c) Physiological effects of fermentation products, mainly the SCFA propionate.

A popular trend in the natural food industry is increased promotion of supplementation with polyphenolic compounds. These polyphenols are purported to have potent anti-oxidant benefits, and thus anti-inflammatory effects. But the truth about these polyphenols found in various spices, seasonings, herbs, vegetables, tea, coffee, wine, and soy is that most of them are very poorly absorbed in the gut. Thus, they reach the colon completely unassimilated and are available for fermentation by the colon microbiota.

The obvious implications of the undigestability of these polyphenols is that any beneficial effects they have result not from these chemicals as they exist in the ingested items, but from the metabolic end-products of bacterial action on these polyphenols. In some cases, the benefits of polyphenolic ingestion is due to the bacterial end-products of their fermentation that are absorbed and have immunological or metabolic effects. Some of the benefits are because these polyphenols act as prebiotics and thus alter the colonic microbiota.

The essential point to understand is that if there are benefits to be derived from these polyphenol compounds, they depend entirely upon the existence of a healthy colonic flora. That dependence explains why the studies on the purported benefits of the polyphenols are so inconsistent in their findings. Individuals with healthy flora may respond symptomatically with anti-inflammatory effects from these supplements, while those with unhealthy flora obtain little or no benefit. So, far more primary than supplementing with various herbal preparations is the development of normal intestinal flora with prebiotic supplementation.

[There can be problems with prebiotic supplementation. Many prebiotics peddled by the health-food industry support the growth of pathological bacteria as well as the beneficial. Also, some patients respond with extreme (though usually temporary) GI distress to even the highest quality prebiotic

supplementation (inulin, guar gum, glucomannan) --- with flatulence, cramping, bloating, or diarrhea.]