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Gut Dysfunction and Chronic Disease: The Benefits of Applying the 4R® GI Restoration Program

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ABSTRACT: *Each day, the typical healthcare practice is challenged by several cases involving gastrointestinal (GI) complaints. Moreover, many conditions in which symptoms are not localized to the GI but may be systemic often involve an underlying GI dysfunction. For example, research has shown associations between compromised GI function and conditions as varied as rheumatoid arthritis, asthma, metabolic bone disease, and eczema. Therefore, assessment and proper support of GI function may provide benefit for patients with a variety of chronic complaints. The GI system is quite complex, and evaluation of GI function in order to design a therapeutic support program is often a difficult undertaking in a busy practice. A conceptual framework that enables the practitioner to evaluate and target therapies aimed at improving GI function has been developed. Called the 4R® GI Restoration Program, this approach uses the concepts of* Remove, Replace, Reinoculate, *and* Regenerate *to provide a focus for evaluation and treatment. The result of this approach is the ability to implement a targeted intervention program involving nutrients, digestive enzymes, and probiotics that promote normalized GI function and optimal health.*

Gastrointestinal (GI) complaints are among the leading reasons for seeking out health care and the most common reason for hospitalization. In the United States alone, more than 70 million people suffer some form of serious GI disorder, which can range from mild symptoms to those serious enough to interfere with the patient's normal life. Commonly encountered GI-related problems are diseases such as gastritis, peptic ulcer, colon cancer, diverticulosis, and inflammatory bowel disease (IBD). Even more common are the so-called "functional" disorders, which include chronic diarrhea, constipation, bloating, and flatulence—often lumped together as irritable bowel syndrome (IBS)—as well as nutrient malabsorption and esophageal reflux.[1,2] Some diseases and disorders, such as constipation and diverticulosis, are increased significantly in people over 60 years of age and, therefore, are on the rise due to the aging of our population.[3]

THE GI–CHRONIC DISEASE CONNECTION

The symptoms of these GI diseases and disorders are localized in the gastric and intestinal area, so it is easy to understand why therapeutic support for GI function should be included in the clinical strategy for patients with these complaints. What is surprising to some, however, is that GI dysfunction can underlie many apparently unrelated conditions; that is, disorders in which symptoms are not localized in the GI tract. For example, compromised GI function may result in macromolecules that would normally be excluded from the body instead passing through the intestinal barrier and entering circulation—a condition called intestinal permeability, or "leaky gut"—which can lead to many systemic inflammatory and immune-related symptoms. Leaky gut has been implicated in rheumatoid arthritis, ankylosing spondylitis, eczema, chronic urticaria, and IBD, among other conditions.[4-9] (For more information on IBD, please refer to the Applied Nutritional Science Report entitled, *Nutritional Management of Irritable Bowel Syndrome* by James Rouse, N.D.)

Small intestinal bacterial overgrowth (SIBO), a condition in which misplaced colonic flora or pathogenic growth has proliferated in the small intestine, is an example of GI dysfunction that can underlie a range of both local and systemic complaints. The presence of SIBO has been documented in patients with conditions as varied as metabolic bone disease, rheumatoid arthritis, IBS, and chronic diabetic diarrhea.[10-14] SIBO has even been associated with vitamin B_{12} deficiency in the elderly.[15] In many cases, removal of the bacteria in the small bowel has been shown to result in improved health. For example, in one clinical study with IBS patients, eradication of SIBO and reestablishment of healthy microecology was shown to eliminate symptoms in 48% of the subjects.[13]

The normal function of the GI may be compromised even in patients who do not show overt symptoms of GI dysfunction, a fact that may predispose them to other complications. For example, approximately 44% of adults self-medicate for heartburn with antacids or other medications. These drugs function by decreasing or neutralizing the level of stomach acid, and therefore may hinder the adequate digestion of proteins and key nutrients like vitamin B_{12}. Inadequate absorption of vitamin B_{12} has been associated with neurologic effects, such as senile dementia, and is estimated to affect 10%-15% of people over 60 years old.[16] Furthermore, hypochlorhydria (low stomach acid) also predisposes an individual to exacerbation of bacterial and some parasitic infections.[17,18]

Another example is the use of non-steroidal antiinflammatory drugs (NSAIDs), both by prescription and by self-medication, which can lead to damage in the gastric mucosa. As many as 8% of the global adult population take NSAIDs at any given time, mainly for management of arthritis and inflammatory conditions, and this use is a significant cause of morbidity and mortality.[19] The consumption of NSAIDs has been associated with a high incidence of upper GI complications, including gastric and duodenal ulcers, and GI mucosal lesions and hemorrhage.[20]

As can be seen by these and other examples, healthy GI function is key to overall health and its dysfunction is related to myriad diseases and conditions (Table 1).

Table 1. Diseases and Conditions Associated with GI Dysfunction

Acne rosacea	Dermatitis herpetiformis	Migraine headaches
AIDS/HIV infection	Diverticulitis	Multiple chemical sensitivities
Alcoholism	Eczema	Pancreatic insufficiency
Autism	Food allergies	Peptic ulcer disease
Celiac disease	Fibromyalgia	Pernicious anemia
Childhood ear infections	Gastritis	Peripheral neuropathies
Chronic yeast infections	Hemorrhoids	Psoriasis/Psoriatic arthritis
CFIDS	Hepatic dysfunction	Rheumatoid arthritis
Crohn's disease	Infectious enterocolitis	Spondyloarthropathies
Cystic fibrosis	Irritable bowel syndrome	Ulcerative colitis
		Urticaria

The ability of the body to maintain healthy GI function, and to heal the GI barrier when its integrity is breached, is integral not only to healthy aging but to protection from many diseases and disorders. Due to the complexity of the GI tract, this is not a simple task. A systematic approach to managing GI dysfunction and individualizing therapies for gut restoration has been developed. Referred to as the 4R GI restoration program, "*Remove, Replace, Reinoculate, Regenerate,*" this approach provides a framework in which to focus clinical assessment and intervention.

THE GI TRACT: FUNCTIONS IN HEALTH AND DISEASE

Over a lifetime, the average person ingests more than 25 tons of food that provide the nutrients each of us need to survive; however, this food may also contain damaging bacteria, viruses, and toxins. The GI mucosal layer, whose surface covers more than 320 square meters, has the unique role of providing protection to the body and allowing in only health-promoting nutrients, molecules, and other substances. In a perfect scenario, only the beneficial nutrients and phytonutrients are absorbed into the body, while non-beneficial substances are excreted without interacting with the host cells at all. Our GI tract accomplishes this feat through four main mechanisms:

(1) The unique biochemistry of digestion, by which food is digested and absorbed;

(2) The complex and extensive mucosal layer providing a barrier between the internal body and the external world;

(3) An intricate immune system, called the GALT, which can elicit both first-line and second-line immunological defense responses;

(4) A beneficial, symbiotic relationship between the GI tract and its colonic microflora.

◆ *The Unique Biochemistry of Digestion and Absorption*

Digestion and absorption of nutrients from food is an extremely complex process requiring a multitude of specialized enzymes and other processes. A lack of any of the digestive enzymes can seriously impair the health of our entire system, not only because of their effect on nutriture, but also because the digestive process provides a protective function.[22,23] Stomach acid decreases with age, a condition called hypochlorhydria, and appears to be related to the prevalence (30%) of atrophic gastritis and gastric atrophy in the over-60 population.[24] Hypochlorhydria is associated with increased levels of *Helicobacter pylori* infection, an increase in the proximal small intestinal pH, and decreased secretion of intrinsic factor, which is necessary for absorption of vitamin B_{12}.[25] In addition, studies suggest SIBO may be present in 50% to 100% of people with hypochlorhydria.[16,18] SIBO and an increased proximal small intestinal pH also can negatively influence digestion and uptake of nutrients besides vitamin B_{12}, such as amino acids, calcium, iron, zinc, folic acid, and vitamin B_6.

Other digestive dysfunctions include compromised bile acid secretion, which has been associated with the ability of *H. pylori* to infiltrate the protective mucosal layer of the upper GI,[26,27] and abnormal pancreatic secretions. Pancreatic secretions may decrease with aging, are compromised by alcohol abuse, and appear to be affected by other conditions such as pancreatitis, cystic fibrosis, diabetes, gallstones, and inflammation.[28,29] Pancreatic dysfunction necessitates oral replacement of pancreatic enzymes and the neutralizing bicarbonate provided by the pancreatic juice.

Possibly one of the most important protective functions of a healthy digestive process is the protection from foreign antigens which, given a chance, can and do transit through the intestinal mucosa into circulation in their full protein form.[30] The food we eat contains many potential antigens that can activate the immune system and cause a series of systemic complaints. When the digestion process is not adequate for destruction of these proteins into their amino acid and small peptide components, many molecules from food that would normally not be problematic can enter the system and cause undesirable symptoms.

◆ *GI Mucosal Defensive Barrier*

The GI mucosa is the protective cell layer that provides the barrier between the inside of the body and the external world, and is responsible for nutrient absorption. The GI mucosa includes the gastric epithelial layer, which covers the stomach and protects it from the damaging stomach acid. This mucosa also plays an important role in protecting the stomach from ingested toxins, drugs, alcohol, and pathogens, such as infectious bacteria or viruses. The mucus gel in the stomach includes a covering of phospholipids that render the surface layer resistant to damage by the stomach acid.[31-33]

The cells in the intestinal epithelium form tight junctions, or connections, between each other.[34] These tight junctions constitute a barrier between the molecules within the lumen of the intestinal tract and the inside of the body. Under normal, healthy conditions, this barrier does not allow flow of matter from the outside (lumen) to the inside of the body unless the matter goes through a cell. Without this barrier, molecules of all types are able to go around the cells and get into circulation, a condition known as intestinal permeability, or "leaky gut."[30,31,35,36]

Intestinal permeability is commonly seen in patients with intestinal inflammation, food allergies or intolerances, and celiac sprue. Intestinal permeability has also been documented in patients after radiation or chemotherapy treatments, probably due to the killing of proliferating cells, and is induced by stress. Poor nutrient intake or absorption, or lack of enteral nutrition as seen with parenteral nutrition, cannot support the healthy regeneration of the rapidly proliferating cells in the small intestine, and therefore can also profoundly affect the integrity of the GI and promote intestinal permeability.[37] Endogenous toxins, such as bacterial and fungal byproducts produced by resident flora, and exogenous toxins, like incompletely digested food, food additives, alcohol, over-the-counter drugs like NSAIDs, and foreign microbes, can also nega-

tively influence intestinal integrity.[37-39] Table 2 lists some major factors that have been shown to increase intestinal permeability.

Table 2. Factors Associated with Development of Intestinal Permeability

Premature birth	NSAIDs
Gastrointestinal infections	Corticosteroids
Cancer radiation therapy	Excessive stress
Alcohol	Food allergies
Nutrient insufficiencies	Fasting
Excessive simple sugar consumption	Whole food exposure prior to 4-6 months of age

◆ *The Gut-Associated Lymphoid Tissue (GALT)*

Approximately 60% of the total immune system, and more than 80% of the immunoglobulin (Ig)-producing blasts and plasma cells, are located within the mucosa of the GI tract.[21,40] The primary purpose of this gut-associated lymphoid tissue (GALT) is to provide a first line of defense against foreign invaders, such as food antigens, pathogenic bacteria, or toxins. One of the major differences between the GALT and the blood-borne, or circulatory, immune system is that the GALT can produce two layers of defense to a foreign pathogen or antigen via the immune system: localized secretory IgA (sIgA) and systemic IgE or IgG. The importance of these two systems is exemplified by the fact that more Ig are synthesized per day in the GI tract than in the rest of the body combined.[22,40]

When an invader is ingested, the GALT first uses sIgA as a defense; it can be thought of as an "antiseptic paint" covering the intestinal tract. As the predominant Ig on the surface of the gut mucosa, sIgA can effectively prevent infection, neutralize viruses, and remove antigens before they cross the mucosal barrier and reach systemic circulation, leaving them to be excreted directly through the feces.[41,42] Therefore, sIgA prevents these invaders from entering the system without activating the complement or inflammatory systems.[43] A low level of total sIgA in the GI tract is associated with altered intestinal permeability and an increased uptake of food antigens, resulting in atopic symptoms.[44]

Immunologically active materials that escape the sIgA surveillance can enter the mucosal layer. If they do, the GALT can activate a second line of defense, the circulating IgE or IgG response, which will induce a systemic immune response to the invading insult. During this systemic immune response, antibodies are generated, cytokines are produced, and the full forces of the immune system are brought to the insult. Along with activation of the systemic immune system, an inflammatory response often commences at the site in which the invading material has made its way past the mucosal barrier. This inflammation closes off invading materials and activates the inflammation cascade, which results in the production of molecules that can destroy invading pathogens. However, activation of the inflammatory cascade can also lead to damage of intact tissue.

◆ *Colonic Microflora and the GI*

The colonic mucosa houses the beneficial symbiotic colonic microflora, which has a direct impact on all the mechanisms discussed above, including digestion and the development and support of GALT function. The intestinal microflora influences digestion not only by its own nutrient needs and ability to digest large carbohydrates, such as fibers that escape hydrolysis in the stomach and small intestine, but also through a feedback effect on transit time. Much research has focused on the mechanisms used by the beneficial colonic bacteria, such as those in the *Bifidobacterium* and *Lactobacillus* genuses. For example, the production of short-chain fatty acids (SCFA) by these bacteria appears to promote intestinal growth and differentiation, which may protect the intestinal mucosa from permeability and support its absorptive function. SCFA may protect intestinal integrity by stimulating intestinal mucosal cell turnover and intestinal mucosal blood flow.[45]

A clinically important function of the beneficial symbiotic bacteria is their antagonistic activity toward pathogens. They use several mechanisms to provide an environment that is resistant to colonization by pathogens, including competitive inhibition for bacterial adhesion sites. For example, the type A1 *L. acidophilus* inhibits the adhesion of several enteric pathogens to human intestinal cells.[46] Beneficial symbiotes can also produce various antimicrobial substances, thereby inhibiting pathogens by bacteriostatic and bacteriocidal mechanisms.

GI RESTORATION: MAKING THE COMPLEX SIMPLE

GI dysfunction is associated with a myriad of diseases, symptoms, and conditions. Evaluation of GI function, with resultant support for balanced, healthy function, can benefit the majority of patients, whether they have a defined GI disease or not. Understanding how to evaluate and therapeutically support GI function, however, is a difficult undertaking in a busy practice. A conceptual framework with which to target therapies aimed at improving GI function has been developed. Called the *4R GI restoration program*, this conceptual process is designed to provide a focus for evaluation of GI function status, resulting in targeted nutritional, digestive enzyme, and probiotic support that promotes the normalization of important GI functions.

The program simplifies the complex interactions and systems by asking four main questions:

(1) What does this patient need to have *Removed* (e.g., pathogenic growth in the intestinal tract, allergenic foods in the diet, etc.) for healthy GI function?

(2) What does this patient need to have *Replaced* (i.e., stomach acid, digestive enzymes, etc.) to support improved GI function?

(3) What does this patient need to support and/or reestablish a healthy balance of microflora; that is, does he/she require probiotic *Reinoculation* and/or prebiotic support?

(4) What does this patient need to support the healing of the mucosal layer; that is, does he/she require targeted nutritional support for GI barrier *Regeneration*?

◆ *Remove*

Remove focuses on eliminating pathogenic bacteria, viruses, fungi, parasites, and other environmentally derived toxic substances from the GI tract. Dietary modification is important, since foods to which a patient is intolerant or allergic can exacerbate GI dysfunction and stimulate immune and inflammatory responses systemically. Table 3 lists some common symptoms and diseases that have been associated with food allergies and intolerances.

Table 3. Symptoms and Diseases Associated with Food Allergy and Intolerances

System	Symptoms/disease
Gastrointestinal	Canker sores, celiac disease, chronic diarrhea, stomach ulcers, duodenal ulcers, recurrent mouth ulcers, indigestion, nausea, vomiting, constipation, gas, gastritis, irritable bowel syndrome, malabsorption, ulcerative colitis, Crohn's disease, colic (babies)
Genitourinary	Bed wetting, chronic bladder infections, nephrotic syndrome, frequent urination
Immune	Serous otitis media
Mental/Emotional	Attention Deficit Disorder, depression, anxiety, memory loss, epileptic seizures, schizophrenia
Musculoskeletal	Joint pain, myalgias, rheumatoid arthritis
Respiratory	Asthma, chronic or allergic sinusitis, constant runny nose or congested nose, nasal polyps
Cardiovascular	Irregular heart rhythm, vasculitis, inflammation of the veins producing purpura, spontaneous bruising, urticaria, edema
Skin	Eczema, psoriasis, urticaria, red itchy eyes, itchy skin
Miscellaneous	Migraine headaches

The underlying mechanisms that elicit food intolerant or allergic responses are complex and controversial, and a variety of assessment techniques have been used to evaluate food allergies. Unfortunately, none appear to be completely adequate, and it appears that the most cost-effective and accurate avenue to determine food allergy is an oligoantigenic diet, containing only those foods known to pose little risk of an allergic or intolerant reaction. Several studies have shown that avoidance of the suspected foods leads to substantial improvement in clinical symptoms; therefore, oligoantigenic diets are typically part of *Remove*.[47-49] If a clinician or patient wants to confirm food sensitivity, the potentially offending food can be reintroduced and symptoms monitored.

Pathogens are also important to consider, since they are a source of antigenic stimuli and promote other symptoms. For example, *H. pylori* colonizes the upper GI, and has been associated with many health conditions including gastritis and peptic ulcer disease. Pathogens can take up colonization anywhere in the GI mucosa and cell wall components of bacteria, yeasts, and parasites can be absorbed, which may cause systemic symptoms that are difficult to pinpoint to the pathogen directly. Laboratory tests evaluating microbiology, parasites, and presence of serum antibodies to pathogens are often useful to verify unwanted microbial organisms in the GI and monitor response to treatment.

Removing these organisms may require knowledge of sensitivity and resistance of specific organisms to specific therapeutic agents. Catechins have been shown to inhibit proliferation of *H. pylori* and even to eradicate it.[50-52] In one study, catechins were shown to decrease *H. pylori* load in animals without inhibiting stomach acid secretions and without inducing GI hemorrhage.[53] Astaxanthin, an antioxidant and a member of the carotenoid family, is also bacteriostatic; it has been shown to reduce *H. pylori* bacterial load and gastric inflammation, both alone and working in concert with vitamin C.[54,55] Examples of botanicals that can help to eliminate pathogens are discussed in detail in the Applied Nutritional Science Reports: *Herbal Antimicrobials for Intestinal Infections* by James Rouse, M.D. and *The Role of Standardized Herbal Formulas in Contemporary Healthcare Delivery* by Margaret Parker, L.Ac., OMD.[56]

Milk Ig concentrates contain Ig derived from the whey portion of cow's milk and, similar to endogenous sIgA, they function by combining with antigens or with molecular sequences on the surfaces of potentially pathogenic organisms. Since these Ig are unable to attach to the GI mucosa, they cover the attachment sites of the antigens' potential pathogens, carrying them out of the system to excretion.[57]

Obtaining a patient's history of response to environmental stimuli, and discussing with them their daily exposure to noxious substances like perfumes and pesticides, is a means to identify environmental toxins to which they may be sensitive. Evaluation of pathogen presence and eradication of exogenous and endogenous toxins is important since, even in the normal, healthy GI, food proteins, gut bacterial breakdown products, and environmental toxins can and do reach the systemic circulation. Therefore, removal of offending substances and microorganisms becomes key to a GI restoration program.

◆ *Replace*

The second concept of GI restoration, *Replace*, refers to the replenishment of enzymes and other digestive factors lacking or in limited supply in an individual's GI environment. GI enzymes that may need to be replaced include proteases, lipases, and saccharidases normally secreted by cells of the GI tract or by the pancreas. Other digestive factors that may require replenishment include hydrochloric acid and intrinsic factor, normally produced by parietal cells in the stomach wall.

Hydrochloric acid is particularly important to consider, especially in individuals older than 60, since hypochlorhydria can result in a variety of symptoms, impair the absorption of nutrients, and predispose an individual to increased intestinal infections. Hydrochloric acid production depends on zinc, therefore decreased stomach acid levels may indicate a zinc deficiency.[58] If hypochlorhydria is properly diagnosed, replenishment with betaine hydrochloride, the digestive enzyme pepsin, and intrinsic factor may be helpful.

The small intestine acts as the principal site of digestion and absorption. As mentioned, intact proteins and other large molecules can cross the intestinal lining, and digestive enzyme supplementation may enhance the breakdown of these particles, helping to prevent them from crossing the barrier intact. Food allergy has been associated with inadequate digestive protease function since poorly digested protein fragments can leak across the gut wall into the systemic circulation; therefore, symptoms associated with food allergy may suggest impaired digestive function.

Experimental studies over the past 10 years have shown that the digestive enzyme lipase, critical in fat digestion, can be supplemented to relieve the problems of fat malabsorption or steatorrhea.[59,60] Similarly, many people suffer from undiagnosed lactose intolerance and supplementation with the digestive enzyme, lactase, has been used successfully.[61] *L. acidophilus* NCFM® has been shown to facilitate lactose digestion in lactose-intolerant individuals as well.[62] Laboratory tests such as gastric analyses, fat absorption tests, and stool analyses may be useful tools to verify the need to replace enzymes and other digestive factors.

In addition to digestive factors, those nutrients in which a patient is likely to be specifically deficient should be considered. For example, extensive evidence suggests a strong association between *H. pylori* infection and a severely compromised secretion of gastric vitamin C.[63,64] Since vitamin C may help eradicate *H. pylori*, this deficiency, when coupled with poor intake of vitamin C, may promote further colonization of *H. pylori* and

further damage. Vitamin C at doses of 500 mg per day has been shown to help resolve intestinal metaplasia and support healing of the gastric mucosa after *H. pylori* eradication.[65] As another example, many individuals with IBD have zinc deficiencies.[66] As a consequence, a variety of functional problems may result including interruption of protein synthesis and reduced cell-mediated immunity. This latter problem exacerbates the inflammatory condition of the gut and retards recovery.[67]

◆ *Reinoculate*

Reinoculate refers to the reintroduction of desirable bacteria, or "probiotics," into the intestine to reestablish microflora balance. Probiotics serve a variety of functions in the GI tract: they synthesize various vitamins, produce SCFAs necessary for colonic cell growth and function, degrade toxins, and prevent colonization by pathogens. Perhaps their most important function is antagonistic activity toward pathogens. A variety of supplemental sources may be considered helpful in the *Reinoculation* phase, including *L. acidophilus, Bifidobacterium bifidus, B. infantis, and B. breve. L. acidophilus* NCFM®, a type A1 strain, has been shown to survive intestinal tract transit and adhere to colonic cells. In animal models of cancer induction, consumption of *L. acidophilus* NCFM® has resulted in inhibition of aberrant crypt formation, suggesting it may decrease risk of colon cancer. When used in human clinical trials, *L. acidophilus* NCFM® has been shown to decrease incidence of pediatric diarrhea, significantly decrease levels of toxic amines in the blood of dialysis patients with small bowel overgrowth, and facilitate lactose digestion in lactose-intolerant individuals.[61] (For more information on the beneficial effects of *L. Acidophilus* and *Bifidobacterium*, please refer to the Applied Nutritional Science Report entitled, *Proven Therapeutic Benefits of High Quality Probiotics* by Robert Roundtree, M.D.)

In addition to directly reintroducing bacteria, indirectly bolstering the *Reinoculation* process with prebiotics, which selectively promote beneficial flora without simultaneously supporting pathogenic flora, may also be beneficial. Prebiotics include the fructans, inulin and fructooligosaccharides, rice fiber, some soy fibers, and arabinogalactans.[68-71] Soluble rice fiber, in particular, has been shown to improve total bile acid excretion and decrease fecal bacterial enzyme activities associated with pathogens and imbalanced flora, such as beta-glucuronidase, mucinase, and nitroreductase.[72]

When prebiotics are included in the diet, increased levels of fecal fermentation and intraluminal concentrations of SCFAs, such as propionate, acetate, and butyrate, are produced from fermentation of the fibers by the colonic microflora. SCFAs are proposed to supply up to 70% of the energy used by colonic epithelial cells; therefore, prebiotic support improves intestinal integrity and promotes intestinal mucosal cell regeneration.[73] In particular, arabinogalactan has been reported to increase *Lactobacillus* and decrease *Clostridia* genuses; it also decreases fecal ammonia levels and supports SCFA production.[71,74] Interestingly, arabinogalactan has been reported to support immune activities, and appears to potentiate natural killer cell and reticuloendothelial system activity.[75,76]

As discussed previously, supporting *Reinoculation* also supports regeneration and healing of the total intestinal tract, since through the production of factors such as SCFAs, the microflora interact with mucosal epithelial cells and the GALT to support their function. In addition, some of the phytonutrients that promote healthy microflora also have other functions that are equally supportive to a healthy GI tract. One example is the catechins; these phytonutrients are bacteriostatic, but also have been documented at a dose of 300 mg per day to promote *Lactobacillus* and *Bifidobacteria*, while decreasing levels of *Enterobacteriaceae, Bacteriodaceae*, and eubacteria.[77]

◆ *Regenerate*

Regenerate refers to providing support for the healing and regeneration of the GI mucosa. Part of the support for healing comes from removing insults that continually re-injure or irritate the mucosa, and from promoting healthy microflora. Pre- and post-testing with inert sugar combinations, including lactulose/mannitol, can be performed to evaluate the intestinal barrier function. Once the need for nutrient support of regeneration is established, nutrients that play pivotal roles in GI mucosal integrity or epithelial cell differentiation, growth, and functioning should be considered.

The *Regenerate* phase of GI restoration benefits from all of the clinical approaches discussed so far. Still, some factors are particularly helpful for healing and regeneration of the GI tract, and these are discussed below.

Plantain Fruit—In the gastric environment, the mucus coating is particularly important in protecting the body from infestation by microbes such as *H. pylori*, and against damage from acid and other agents like alcohol and NSAIDs, which can cause gastric lesions. Many food and botanical phytonutrients support the upper GI mucus layer, including plantain fruit, which has been used therapeutically as an anti-ulcerogenic and has been shown to promote mucus secretion and stimulate mucosal cells. One reason may be its protective lectins, another may be the presence of specific flavonoids which have been shown to promote mucus thickening and protect the gastric layer from damage by exogenous agents.[78,79]

Phosphatidylcholine—The amount of phosphatidylcholine in the mucus of the GI layer has been shown to be compromised upon insults by toxins or pathogens.[32] Recent studies show that consumption of phosphatidylcholine (lecithin) with ulcerogenic substances like aspirin or bile salts protects the gastric layer from damage and accelerates healing.[32,80,81] Phosphatidylcholine, when co-administered with NSAIDs, has also been shown to protect the intestinal mucosa from injury by these GI toxic substances.[33]

L-glutamine—Glutamine is a preferred fuel for the rapidly replicating cells of the GI mucosa.[82] Glutamine may promote production of glutathione in the GI cells as well, which provides additional protection from oxidative insults during inflammation and supports healing.[83] The uptake of glutamine by the mucosal cells from both the intestinal lumen and arteriolar circulation is increased in catabolic states and during glucocorticoid therapy. Traditionally, glutamine has been thought of as playing a metabolic role; that is, supporting GI mucosa respiration, regulating acid-base balance through the production of urinary ammonia, and acting as a precursor for nucleic acids and proteins. However, recent data suggest glutamine plays a more vital role in the GI; in particular, that it can induce certain genes involved in growth and differentiation of GI mucosa cells.[84]

Clinically, dietary glutamine is known to be important for maintenance of GI mucosa during stress, injury, sepsis, and inflammation.[45] Dietary deficiency of glutamine is associated with atrophy and degenerative changes in the small intestine following intestinal injury, infection, stress, surgery, and radiation; therefore, it is considered a "conditionally essential" amino acid.[85,86] SIgA synthesis also appears to require adequate dietary intake of glutamine, and animal studies have demonstrated improvement in

gut immune function and protection of IgA-producing cells following glutamine administration.[87]

Lactoferrin and Lactoperoxidase—Lactoferrin is an important component of the endogenous defense system; it is released from GI mucosal cells when gut integrity is compromised by pathogens or inflammation, and it is found in high concentrations in most exocrine secretions, such as tears, saliva, bile, and pancreatic fluid.[88] Lactoferrin is bacteriostatic, and this property is presumed to be due to its ability to bind and sequester the iron necessary for bacterial growth. Lactoferrin is found in milk as well, and has been shown to survive transit in the GI tract; therefore, whey concentrates of lactoferrin can serve as an exogenous source for this protective molecule.[89,90]

Lactoperoxidase is another antimicrobial found in human exocrine secretions, and is one of the most prominent enzymes in whey.[91] Together with lactoferrin, lactoperoxidase may provide antimicrobial, antiviral, and antioxidant activities; stimulate the immune system; and promote healing of the GI tract.[88,92]

Arabinogalactans—Arabinogalactans are non-starch polysaccharides found in many vegetables and grains, and can be obtained at high levels from larch.[71] They are considered a fiber, but have many more interesting health-promoting qualities, including functioning as a prebiotic; that is, they have been shown to preferentially increase colonic *Lactobacillus* and *Bifidobacteria* over other bacterial genuses—including *Clostridia,* which has been shown to be decreased with arabinogalactans—thereby promoting a healthy GI microbial balance in humans.[74,76] Consumption of arabinogalactans has been shown to increase SCFA production while decreasing generation of fecal ammonia; stimulate human natural killer cell activity; block metastases of tumor cells in animal models; and enhance the reticuloendothelial and complement systems.[75,76,93,94]

REGENERATE WITH A HEALTHY DIET

Key to any successful regeneration strategy is providing the nutrients necessary for the mucosal epithelial cells to proliferate and differentiate, thereby producing the tight connections that constitute the intestinal barrier. Overall nutrition must be considered in an individual who has compromised gut function. For example, micronutrient deficiencies of vitamins and trace elements are strongly associated with immune response and induction of inflammation.[95] Clearly, sIgA is important in overall health, and it is affected by nutritional adequacy as well. Assessment of individual nutrient needs may include a dietary history, nutritional analysis, and any other investigative techniques that reveal the presence of nutritional insufficiencies. Micronutrients particularly important for support of GI regeneration include vitamins C and E and the carotenoids, for their antioxidant effects, and zinc and vitamin B_5 (pantothenic acid) for their roles in supporting the healing mechanisms.[96,97]

Furthermore, the intestinal barrier may be compromised by food allergens or toxins, pathological intestinal infection, localized inflammation, and IBD or other less common GI diseases. Providing an environment that supports healing is essential. One consideration is the elimination of allergens, irritants, and sources that may be causing or promoting an inflammatory reaction or disease process, as discussed previously. Common dietary sources of irritants and allergens may include alcohol, caffeine, gluten-containing grains, and cow's milk. Therefore, a diet that is high in nutritional value and has a low antigenicity profile provides a basis for regeneration of the GI tract.

THE CLINICAL APPLICATION OF GI RESTORATION TO CHRONIC DISEASE

The *Remove, Replace, Reinoculate, Regenerate* clinical approach is a conceptual program, meant to outline the points to consider when clinically evaluating and applying therapies to a patient with underlying GI dysfunction. While the overall concept defines a basic approach, its use is individualized to the needs of each person based on his or her own unique combination of GI factors. The different steps themselves can be approached together, as in one therapy, or in a step-wise fashion, depending on the nature and course of the condition.

Table 4. The 4R GI Restoration Program: The Clinical Questions

Remove refers to the elimination of any factors that may be causing or exacerbating a dysfunctional GI; these factors may include pathogenic microflora (e.g., bacteria, fungi, parasites); foods to which an individual is sensitive, intolerant, or allergic; environmental stressors such as pollutants; and stress. Clinical approaches may include:

- Oligoantigenic "elimination" diet
- Botanical antimicrobials
- Bacteriostatic/bacteriocidal phytonutrients (e.g., catechins and astaxanthin, which are bacteriostatic for *H. pylori* and other pathogens)

Replace refers to the replacement of factors that may be inadequate or lacking. Such factors may include:

- Digestive enzymes
- Hydrochloric acid
- Mucosal secretion protectants such as phosphatidylcholine, plantain polysaccharides
- Nutrients (e.g., vitamin C, zinc)
- Fiber to support transit and general GI function
- Bile acids

Reinoculate refers to the reintroduction of desirable GI microflora, also called "friendly bacteria" or "probiotics," to obtain a more desirable balance of microflora and support for these probiotics with prebiotic fibers. Probiotics and prebiotics may include:

- *Bifidobacterium*
- *Lactobacillus*
- Fructooligosaccharides
- Soluble rice fibers
- Arabinogalactans

Regenerate refers to providing nutritional support for regeneration or healing and growth of the GI mucosa. Factors key in supporting GI mucosa may include:

- Glutamine
- Adequate overall nutriture and an oligoantigenic diet
- Micronutrients shown to support GI healing (e.g., pantothenic acid, vitamin C, and the carotenoid astaxanthin)
- Mucosal lining support (e.g., phosphatidylcholine, plantain fruit, licorice)
- Support for GALT function (e.g., lactoferrin, lactoperoxidase, whey immunoglobulins)
- Antioxidants known to function in the GI (e.g., catechins)
- Nutritional anti-inflammatories (e.g., curcumin, GLA, EPA, DHA)

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GUT DYSFUNCTION AND CHRONIC DISEASE: THE BENEFITS OF APPLYING THE 4R® GI RESTORATION PROGRAM A SUMMARY

By Deann J. Liska, Ph.D. and Dan Lukaczer, ND

By supplying essential nutrients and eliminating toxic by-products, the gastrointestinal (GI) tract is vital to nearly every aspect of health, including memory and alertness, heart health, joint mobility, respiratory function, skin complexion, and more. Unfortunately, GI irregularities and dysfunction are among the more frequent complaints and causes for people to seek medical attention. Common "functional" GI complaints include chronic diarrhea or constipation, bloating, flatulence, heartburn, and esophageal reflux; while more serious GI conditions and diseases include stomach inflammation, GI ulcer, colon cancer, diverticulosis, and inflammatory bowel disease (IBD).[1,2]

THE GI TRACT—CHRONIC DISEASE CONNECTION

Although GI dysfunction may appear to be localized in the GI tract, it can be at the root of other seemingly unrelated health conditions. The GI tract selectively chooses what should be absorbed into the body. By allowing in only health-promoting nutrients, the GI tract nourishes and protects the body. Unfortunately, as we age, it is less able to make the right choices and may allow harmful molecules into circulation—a condition known as "leaky gut."[4-9] Leaky gut is commonly seen in patients with intestinal inflammation and food allergies and intolerances.

GI infection can also contribute to various other health conditions. Small intestinal bacterial overgrowth (SIBO) has been implicated in diseases and disorders such as rheumatoid arthritis, irritable bowel syndrome (IBS), and chronic diabetic diarrhea; while *Helicobacter pylori* infection is often implicated in GI ulcer development.

Regular use of over-the-counter antacids or non-steroidal anti-inflammatory drugs (NSAIDs) can also compromise GI health. Antacids decrease stomach acid, a digestive factor necessary to properly absorb important nutrients and protect against infections, such as *H. pylori* and SIBO. Commonly used for pain management, NSAIDs can contribute to GI ulcers.[20]

THE GI TRACT: FUNCTIONS IN IMMUNITY

The GI tract comprises about 60% of the body's entire immune system, preventing infections and other ailments.[21,40] Within the GI lining are "friendly" bacteria, particularly *Lactobacillus acidophilus* and *Bifidobacterium*, which absorb nutrients and protect against harmful organisms.[46]

REVIVING GI HEALTH: THE 4R® GI RESTORATION PROGRAM

Improved GI health can be achieved through a nutritional program that incorporates the concepts of *Remove, Replace, Reinoculate*, and *Regenerate*. Recently, a core regimen of two products has been introduced that addresses each of theses four areas. This consists of:

1) A combination of *Lactobacillus acidophilus* NCFM® strain and *Bifidobacterium lactis*.

2) A formulation providing arabinogalactins, soy lecithin, green tea extract, and other GI-supportive factors.

If you require additional support, your healthcare provider may recommend targeted treatment in one of the following four areas of the program:

◆ *Remove*

If your healthcare provider has determined that you have food allergies, an accumulation of toxins, or an infection contributing to GI dysfunction, additional support for the *remove* phase may be recommended. *Remove* focuses on the elimination of food allergens, toxins, and harmful organisms that can negatively impact GI health. Eliminating common allergen-containing and frequently intolerated foods from the diet is key in improving food allergy-related symptoms.[47-49] Furthermore, supplementation with *L. acidophilus* and antibacterial phytonutrients, such as berberine and concentrated oils of thyme and oregano, may increase resistance to infections such as *H. pylori* and SIBO.[53-55]

◆ *Replace*

If your healthcare provider has determined you have low stomach acid or are lacking in other digestive factors, additional support for the *replace* phase may be recommended. *Replace* focuses on restoring healthy stomach acid levels, replenishing important enzymes, and adding "friendly" bacteria to improve digestion. While *L. acidophilus* is vital to the absorption of essential nutrients, enzymes such as lipase, protease, and lactase facilitate the digestion of fats, proteins, and lactose, respectively.[59,60] If low stomach acid has been diagnosed, betaine hydrochloride, pepsin, and intrinsic factor may help.

◆ *Reinoculate*

If your healthcare provider has determined that you need additional support in re-establishing "friendly" GI bacteria and/or are lactose intolerant, additional support from the *reinoculate* phase may be recommended. *Reinoculate* focuses on creating a healthy GI bacterial balance. *L. acidophilus* and *Bifidobacterium* provide "friendly" GI bacteria, contributing to more efficient digestion in those who are lactose-intolerant.[62] Green tea and arabinogalactans help facilitate the growth of "friendly" bacteria.[72,74-77]

◆ *Regenerate*

If your healthcare provider has determined that you have leaky gut, additional support from the *regenerate* phase may be recommended. *Regenerate* focuses on healing an irritated or injured GI tract to improve GI function. In addition to the core products, nutritional factors such as soy lecithin, L-glutamine, Chinese licorice, lactoferrin, and/or lactoperoxidase may be recommended. Soy lecithin and Chinese licorice nourish and protect the GI lining,[32,80,81] while L-glutamine facilitates new growth of intestinal cells to support the healing process.[83,84] Lactoferrin, an integral part of the immune system, can also be found in whey concentrate.[88-90] Together with lactoferrin, lactoperoxidase may provide additional protection against harmful organisms.[88,92]

In conclusion, the 4R GI Restoration Program provides a comprehensive approach to addressing GI dysfunction. While a basic core regimen addresses most aspects of GI health, additional support may be recommended based on each individual's unique combination of GI issues.