

Focus

AllergyResearchGroup®

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The Age of Immunobiotics

New Research Proves the Power of Friendly Bacteria

- **A Novel Approach to Treating Depression**

How Probiotics Can Shift Mood by Modulating Cytokines

By Michael E. Ash, B.S.c. (Hons) D.O. N.D. F.Dip ION

A new protocol for treating atypical depression uses targeted testing and application of probiotics to re-set the gut and brain.

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- **How *Lactobacillus* GG was Discovered**

A Conversation with Barry Goldin, M.S., Ph.D., Tufts University

The scientist who discovered *Lactobacillus* GG talks about his work

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The Age of Immunobiotics

New Research Proves the Power of Friendly Bacteria for Infectious and Inflammatory Diseases

"Just one molecule can make the difference in modulating a healthy immune response. Surprisingly, it comes from bacteria." Thus begins an article in the August issue of *The Scientist*, written by microbiologist Sarkis Mazmanian of the California Institute of Technology. Summarizing his extraordinary work on a potential novel probiotic, *B. fragilis*, the biologist notes that "20 Nobel Prizes have been awarded for research on the immune response to harmful microbes. But in the grand scheme of things, bacterial infections are rare and opportunistic. Of the over 300,000 known bacterial species and possibly millions more, only about 170 are known to be pathogenic in mammals." In contrast, scientists are finally beginning to study and uncover the power of our friendly symbionts, the probiotics.

In this issue, we look at a completely novel approach to depression using probiotics. Pioneered by Dr. Michael Ash, it is the distillation of twenty years of research and work.

We also report on the two most-studied probiotics. Two stand out as immune-modulating powerhouses—both the subject of hundreds of scientific, peer-reviewed studies. These are *Lactobacillus* GG and *Saccharomyces boulardii*, and the weight of new evidence in the last few years shows both to be profound immunobiotics with an ability to promote health far beyond the digestive tract. Read further for the latest research on both.

This issue also offers guidance on administering probiotics. Probiotics work best when they are used in a staged, multi-step fashion that specifically addresses each individual's needs. (see *A Novel Approach To Treating Depression*, below).

The latest research shows that probiotics can protect against inflammation, arthritis, allergy, and infection. They shift immune response throughout the body. They are not just friendly bacteria. They are true immune modulators.

A Novel Approach to Treating Depression

How Probiotics Can Shift Mood by Modulating Cytokines

By Michael E. Ash, B.S.c. (Hons) D.O. N.D. F.Dip ION

From our early days in utero until we die, the ability of the GI tract to renew and replenish itself and maintain a stable relationship with trillions of bacteria is astounding. On a typical day the innate immune system of our gastrointestinal tract will process more immunological information than the rest of our body in its entire lifetime. It's an absolute im-

munological miracle we can consume antigenic particles of food and not drop down dead every time we do so.

In fact, the joy of modifying the gut mucosal immune system is that we can at the same time treat urinary, respiratory, inner ear and oral tissue. Gut originating immune molecules migrate out through the lymphatic

tissue and influence the vagal nerve to deliver information systemically. Mucosal immunity is the key to gut health, overall immune balance, and even brain function and mood. It's this last I am reporting on in this article, for gut immunity and neuro-immunity are intimately bound, sharing the same receptors and the

same signals. Information that initiates in the gut ends up in the brain and vice versa, providing a comprehensive cross talk between the two sets of tissues.

I have discovered that tweaking the immune system through very careful use of targeted, strain specific probiotics is a novel and effective treatment for atypical depression—the most common subtype of depression and the form most commonly seen in women today. I have arrived at this unusual approach after 26 years of practice as an osteopath, naturopath and clinical nutritionist treating over 10,000 patients. I believe many clinicians today consider probiotics in the same manner that medicine looked at antibiotics back in the 1950's: with little regard for strain specificity, timing and dose. Here I report on the very specific reasons why probiotics can treat depression, how to stage their successive application, and why timing, dosing, and

delivery mechanisms of probiotics are key to their effective use.

The Gut-Brain Dialogue

So how in the world might probiotics—friendly gut organisms—treat depression? In a few words: cytokines, inflammation and immune response. Cytokines are messenger molecules that regulate our inflammatory and immune response. They operate continuously throughout our entire body and profoundly influence neuro-endocrine functioning. Depression has

A good reliable set of bowels is worth more to a man than any quantity of brains

- Henry Wheeler Shaw, American aphorist -

been linked with altered levels of cytokines like IL-1, IL-6 and TNF α , the inflammatory cytokine. Interleukin-1B is linked to dysthymia (low grade, chronic depression).

The gut-brain link was first seriously suggested by Dr. Julius Wagner-Jauregg,

the only psychiatrist to have won a Nobel Prize back in 1927 (for medicine). He wrote; "Biological mediators primarily designed to combat pathogens may affect the course of psychiatric disorders." Way before cytokines were discovered this clinician described how innate immune cytokines influence virtually every pathophysiological domain relevant to depression including monoamine neurotransmission, tryptophan metabolism, neuroendocrine function, synaptic plasticity and regional brain metabolism.

There is a well defined correlation between the severity of depression and the levels of TNF α . Patients suffering from chronic fatigue syndrome

and sleep apnea will show excessive blood levels of TNF α (see pp 14, *NO/ONOO- A Brief Summary of the Work of Martin Pall, Ph.D.*). And when patients with cancer, multiple sclerosis, or hepatitis C are given interferons or interleukins as part of their treatment as many as 40% develop depression.

A Special Note from Stephen Levine, Ph.D. Two Fresh Approaches to Chronic Illness and Inflammation

In this special issue we present landmark work by Martin Pall, Ph.D., and by Michael Ash, B.S.c. (Hons) D.O. N.D. F.Dip ION, who offer unique approaches to chronic inflammation. Their specific interventions are distinctly different and yet very complementary.

Both researchers understand that inflammation is at the core of illness. Both are tweaking the exact same immune and cytokine molecules and mediators. Both researchers address highly inflammatory regulatory immune molecules like NFKappaB and TNF α . What Dr. Pall has done is identify the key oxidative player that triggers many common "mystery illnesses", from fibromyalgia to CFS to Gulf War Syndrome. What Dr. Ash has done is bring a profound new understanding to the role of gastrointestinal stress and offer novel approaches to treatment. These researchers have applied fundamental biological truths in unique ways to help us all.

Dr. Ash favors probiotics (with an emphasis on the two most widely researched and effective probiotics) to restore harmony and immune tolerance to the

entire gut mucosal system, and thus reduce systemic inflammation. Dr. Pall uses specially formulated antioxidant food supplements to address excess levels of nitric oxide and its damaging metabolite, peroxynitrite. Yes, their approaches appear different, but their underlying models are consistent and harmonic. Not surprisingly, clinical evidence shows that both approaches yield impressive results. I see no reason not to apply both together.

For many years I've talked about chronic inflammation. Oxidative stress, which is ultimately electron imbalance leading to free radical damage; is the underpinning of much chronic inflammation. No matter the cause--environmental, physical or emotional trauma, infections, ionizing radiation, chemicals—all stress leads to chronic inflammation, and compromised immune function. This is a profound epiphany that I myself had over twenty-five years ago when I coauthored *Antioxidant Adaptation* with Parris Kidd, Ph.D..

Animal studies have supported clinical observations in humans. When animals are injected with molecules that stimulate cytokines, they become lethargic, fatigued, and anorexic. This is called “sickness behavior” and is associated with acute and some types of chronic infections.

The gut is a locus of many of these cytokines as the majority of our innate immune system is in the GI tract. The literature on the profound dialogue between the gut and the brain is surprisingly robust and at the same time, woefully under the main-stream radar.

In a fascinating 2007 study in *Brain, Behavior and Immunology*, researchers found that when the gut releases molecules signaling local infection, anxiety is enhanced—most likely through the vagus nerve. The vagus nerve provides a neural highway from the neurons of the gut right into the brain. Researchers inoculated mice with the intestinal bug *Campylobacter jejuni*, and found that vagal sensory neurons as well as the hypothalamus, amygdala and other important brain areas associated with anxiety and stress were activated. Infected animals also showed more cautious behavior. The authors conclude that treating infection and inflammation in the gut may help symptoms like anxiety and depression.

In another 2009, randomized, double-blind study in the *European Journal of Clinical Nutrition*, 39 patients suffering from chronic fatigue syndrome were given either placebo or probiotics. Two months of supplementation with probiotics was associated with a significant decrease in anxiety symptoms ($p = 0.01$, highly significant). In a 2007 study, consumption of yogurt-containing probiotics improved mood. This double blind placebo controlled trial explored 124 patients and found that mood improved in those who were initially depressed.

How Pathogens Sing the Blues

When our immune system encounters a gut pathogen, proteins on the

pathogen’s surface bind to specialized receptors. Inflammatory cytokine chemicals such as IL-1, IL-6 TNF α and the chemokine IL-8 are triggered. These in turn stimulate the inflammatory regulator, NF Kappa B. This is necessary for an aggressive immune response that will help eradicate that pathogen. The immune system when healthy has a series of checks and balances to contain the damage and return to a neutral state after eradication. But in chronic low-grade gut

The gut lining first needs to be matured through the selective use of probiotics that specifically stimulate SIgA, and must then be exposed to key strain specific probiotics.

infection, or dysbiosis, there may be persistently variably elevated cytokines. These impact mood in a waxing and waning manner.

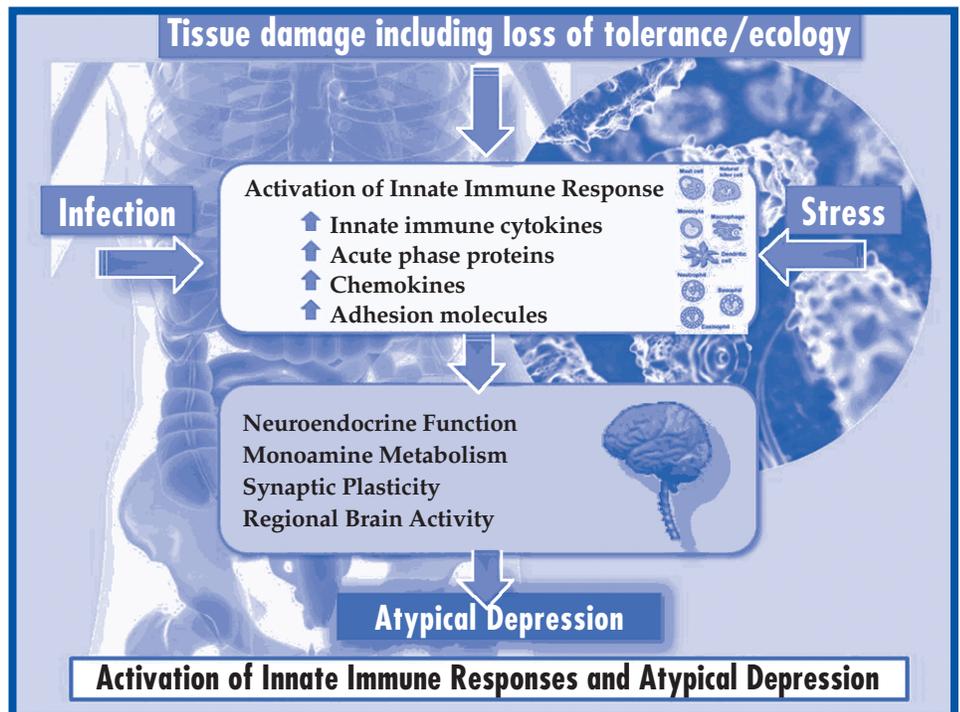
How important to our immune health are friendly gut bacteria? Immeasurably so. When rat pups were separated from their mother—causing extreme stress—and then reintroduced to their moms days later, their immune system was forever altered. They were permanently more sensitized to stress dis-

playing high levels of anxiety. However, when rat pups were separated and provided probiotics, and then returned to their mothers, their immune system was equal to that of their never-separated peers and were no more anxious than their non-separated siblings. This shows how profoundly important our gut biota is—to both immunity and mood. Our microbiota not only live with us, they carry an enormous skill set that helps us navigate life, from release of key nutrients to modulation of

our immune system. We are a giant two-legged petri dish, more efficient at keeping our bacterial companions alive than any other medium on earth. To celebrate this unique ecological niche

they provide a range of immune specific effects and help us to safely navigate a threatening world of pathogens and antigens.

In addition, serotonin levels can be impaired by chronic gut pathogens. Certain pathogens including bacteria, and viruses favor tryptophan as a primary fuel source. The body may recognize that tryptophan starvation (through the release of a specialized enzyme) is an effective strategy to help



suppress and eliminate that pathogen. However, reduced tryptophan means reduced levels of the feel-good neurotransmitter, serotonin. And prescribing an SSRI in this situation can mean that increased circulating levels of serotonin will go right into the gut. The majority of serotonin receptors in the GI tract promote peristalsis—so, like many on SSRI's, you may get diarrhea. In turn, the induction of inflammatory cytokines in response to increased levels of the pathogen will cause further mind-body disturbance by preventing the uptake of serotonin at the synapses because of inflammatory enzymatic binding.

You can see the exquisitely complex dance of pathogens and the neuroendocrine and immune system. The common thread of chronic illness is persistent, low-grade inflammation and disturbed cytokine patterns. Not surprisingly, a response to conventional antidepressant medications is associated with a decrease in inflammatory biomarkers.

A Little Help from My Friends

And so we come to probiotics—which by regulating cytokine levels in the gut, can influence infection and inflammation throughout the body, and even help balance brain function and mood. In recent years the interface between neuropsychiatry and gastroenterology has converged into a new discipline referred to as enteric neuroscience. Emerging studies have

shown that intestinal bacteria can directly communicate with the central nervous system by way of the vagal sensory nerve fibers and the peripheral immune system. If we understand how potent a neuro-immune effect probiotics can have, we can use them in a stepwise fashion to tickle and coax our immune system into a state of tolerance and ideal, balanced responsiveness. And because the immune and nervous systems are intimately entwined, our brains will respond as well.

Think of probiotics as old friends—gentle protectors and supporters with

will slowly catch up to your natural-born peers but it may take as long as two years. But if you were fed formula, your gut biota may not be ideal. You may be more likely to suffer from allergies or immune-related issues. Add in early and frequent antibiotic treatment and a diet of pre-biotic deficient, processed foods and you may now have a gut lining that was never given the opportunity to mature properly. Your core microbiota, which you will carry through your life, is essentially established by age two but has remarkable plasticity as well, responding both positively and negatively to medications and probiotics.

When used correctly, probiotics ameliorate mucosal inflammation in the gut, liver, synovium and brain.

whom you began your life's journey. Your own personal microbiota is your own symphony, one that begins the moment you're born (actually, it may even begin before you're born, since the cord blood of caesarean born infants carries at least sixteen different species of bacteria). It is influenced by your diet, medications, your geography, and your genetics.

In ideal circumstances, you inherit healthy *lactobacilli* from your mother's vaginal canal, and breastfeeding provides you with immunoglobulins, Bifido species and antibodies that help your gut lining mature properly, learning tolerance and balance. Those first months of your life may establish a 'setpoint' for immune susceptibility that is key to health. If you were born caesarean but breastfed, you

In treating patients, the first thing to do is take a complete history—back to birth. It's very important to know that early history during those formative

months and years, as it will help guide your treatment protocol.

However, you can't just take a handful of probiotic capsules containing variable strains and expect to regain your health. The principle function of a probiotic is as an immune modulator but some strains increase pro inflammatory cytokines and others increase IL-10, the main immune inflammation controller.

I have discovered that in order for probiotics to work most effectively, the gut lining first needs to be matured through the selective use of probiotics that specifically stimulate SIgA (secretory Immunoglobulin A), and must then be exposed to key strain specific probiotics. SIgA is the great, forgotten immunoglobulin,

The Three Steps to Successful Use of Probiotics in Depression

- Establish that your patient is suffering from atypical depression (inflammation driven)
- Examine their levels of SIgA by salivary analysis and correcting if required.
- Use the most effective human derived strains of 'old friends' to suppress excess inflammatory cytokines

by induction of IL-10 and regulate immune response systemically.

Remember, you don't have to be aggressive to be pervasive. You can take a small dose of probiotics that stay in the gut yet influence the entire body systemically. You do need to be consistent and persistent as it may take some months to change long term dysbiosis.

but I've championed it for twenty years because it is so beneficial to the GI tract. SIgA determines our ability to communicate to our immune system exactly what bacteria we are harboring and what to do about it. If you don't have enough SIgA, you can consume probiotics forever and never transfer enough of their relevant information to the appropriate immune tissues in enough volume to impact health. SIgA and the T-regulatory family of cells work in a cooperative manner to maintain tolerance, yet SIgA requires bacteria in the mucosal lumen to be stimulated. The use of an anti-inflammatory, SIgA-promoting yeast species can be a valuable adjuvant to optimizing gastrointestinal immune tolerance.

The Treatment Plan

The first step is to determine if your patient is an atypical depressive. Typical features include: a tendency towards excessive sleep without feeling refreshed, cravings for carbohydrates, low energy, a feeling their limbs are heavy, poor response to SSRI's, more often female, and highly sensitized to stress and relationship breakdowns. I also do an organic acid urinary profile to look for tryptophan catabolite ratios: Quinolate/Kynurenate. These are metabolites of tryptophan that can lead to excitotoxicity and excess stimulation of NMDA receptors (see pp 14, *NO/ONOO- A Brief Summary of the Work of Martin Pall, Ph.D.*). If a patient has a reasonably good clinical workup to support a diagnosis of atypical depression, and has raised ammonia, quinolinic acid or kynurenine in the urine (all indications of dysbiosis) I consider it likely their depression is a GI-mediated immune event. You can also check their stool for pathogens, or their blood for raised levels of cytokines such as IL-6, IL-1, IL-4, and TNF α as well as the anti-inflammatory IL-10. Also consider increased gut permeability as a compounding barrier defect allowing cell particulates (LPS) to trigger inflammatory cytokines.

If so, the next step is to do testing to establish levels of SIgA, the predominant immunoglobulin in the

body, and the key anti-inflammatory, immunomodulating molecule protecting our mucosa in the mouth, nose, lungs, gut, and vaginal tissue. If you give probiotics in a cavalier manner to someone who does not have enough SIgA, you won't get a good clinical response because of diminished immune interpretation. In other words, the immune system does not process information from bacteria and pathogens as effectively as it needs to when levels of SIgA are low. I discovered nearly twenty years ago that if we can improve an individual's SIgA status, we will then see a change in how they respond to subsequent probiotics. I measure SIgA from a salivary sample, since it's systemic across mucosal tissues.

If SIgA is low, I give *Saccharomyces boulardii*, which is superb at promoting SIgA and has hundreds of peer-reviewed studies demonstrating its safety and effectiveness. I begin with as little as ¼ capsule in children and ½ capsule in adults, because this probiotic is very potent. *Saccharomyces boulardii* helps the body break down carbohydrates more effectively, reduces gut candida and neutralizes *clostridium difficile* toxins A and B, thus improving mucosal barrier effectiveness. It also lowers inflammatory IL-8.

I may also give a month or two of a nutritional product called Garum Americum®, as this has quite quick effects in the improvement of mood and sleep and really helps the patient to feel that a change is occurring. It can take a couple of months with probiotics getting the dose and timing correct to see any change in the pattern of mood and behavior.

Once SIgA levels are up, I add in *Lactobacillus GG*, another probiotic with hundreds of studies demonstrating its benefit. This probiotic is a standout because it is so well studied. No other probiotic except *Saccharomyces boulardii* comes close. LGG is a known inducer of anti-inflammatory cytokines in humans like IL-10. It also increases the production of regulatory T-cells, which help to maintain control over

inflammation. LGG is a human-derived strain and I believe using human strains (ones that have been isolated from the gut of a healthy human) is important because they are well recognized by the innate immune system receptors and are efficient at priming immunoregulation. They will, when used correctly, ameliorate mucosal inflammation in the gut, liver, synovium and brain. Both LGG and *Saccharomyces boulardii* are the best studied and probably most effective probiotics we have today.

I then also add in other human strains of *lactobacillus* and bifido species, as well as Vitamin D, proteolytic enzymes, and herbs, including, as required; artemisinin, black walnut, olive leaf, TOS-free *uña de gato*, and oregano to modify bacterial communities and help kill gut pathogens.

This approach can work phenomenally well. A recent female patient of mine suffered from classic atypical depression after her divorce. She has reduced her antidepressant medications to 1/5th of her initial dose, has started her own business and has lost twenty-one pounds on this simple protocol. I expect that in another half year she will be able to discontinue all of her medications and yet remain depression-free.

Go with the Gut

The gut influences the brain, and the brain influences the gut. This bi-directional perspective provides a fertile area for surprising insights into CNS pathologies that have until now proven highly elusive to effective treatment. Ask yourself—what's better? A gut reaction or a reasoned response? Instinct or intellect? Or is the answer literally: what's the difference?

References available at:

<http://www.allergyresearchgroup.com/Sep-2009-Focus-Newsletter-Probiotics-Can-Shift-Mood-sp-97.html>

How *Lactobacillus* GG was Discovered

A conversation with Barry Goldin, M.S., Ph.D., Tufts University

Focus: Why did you go on a hunt for a special probiotic in the first place?

Goldin: Both Dr. Gorbach and I were interested in colon cancer and the factors that may influence it. We started looking at ways to alter bacterially derived carcinogens in 1974, and we began to study probiotics. We decided to try and isolate one superior strain and our conditions were: good survival in acid, since the organism has to go through the gastric barrier; resistance to bile acids since it will confront bile in the duodenum; antimicrobial ability; and the ability to stick to the gut epithelium. LGG is among the stickiest to date of strains that have been tested by us and others.

Focus: How did you determine stickiness?

Goldin: We collected buccal cells from the inside of the cheek in volunteers. Basically we used a tongue depressor and scraped their cheek, then took those cells, put them on filters, and measured stickiness. We also got cells from ileostomy patients who'd had part of their bowel removed, and tested those cells in the same way. We isolated quite a number of organisms until we found LGG, which scored the

In 1985, Dr. Barry Goldin and Dr. Melvin Gorbach, M.D. isolated *Lactobacillus* GG after nine years of research. Since then, it has become the best studied probiotic in the world. Here, Dr. Goldin discusses his discovery and its implications.

best on all our criteria. In fact, it had a morphology that was distinct from all the other organisms. It would grow a white, milky kind of colony. It had this very sticky property, which I assume was the result of polysaccharides. To this day nobody has absolutely defined the cause of LGG's stickiness.

Focus: And how did you determine antimicrobial ability?

Goldin: In the conventional way. We grew a pathogen out on an agar plate and then put the LGG (or other probiotic) in and if it was antimicrobial you'd see a clear area around the LGG colony.

Focus: When you isolated the organism, did you have any idea how beneficial it would turn out to be for human health?

Goldin: We had no idea. By pure serendipity a colleague of ours at Tufts, a virologist who had isolated the toxin produced by *C. difficile* bacteria,

decided to add LGG to the *C. difficile* culture and found out it counteracted the toxin. So then we gave it to people who had recurring *C. difficile* infection, and relapses were prevented.

Today LGG is the most widely studied probiotic in the world, one of the few for which there is good evidence for medical usefulness.

Focus: Do you use it yourself?

Goldin: My family uses it. I myself have a rock solid GI tract. But my wife and daughter use it. My daughter recently had severe tonsillitis and was miserable with a terrible earache and bad sore throat. I took her to the ENT, who prescribed her Clindamycin and LGG to prevent diarrhea. I looked over at him and said, "Hey, that's the organism I co-discovered." She took the LGG and didn't get diarrhea.

Focus: Are you continuing your work on LGG?

Goldin: We're studying the combination of prebiotics and LGG right now, to see if we can increase the counts or effectiveness of the organism. We also have a research study looking at how LGG influences the gastrointestinal immune system.

***Lactobacillus* GG: A Potent Immune Regulator Effective in Many Disorders**

New Research Reveals Probiotic's Anti-Toxin, Anti-Inflammatory, Immune Boosting Properties

Lactobacillus GG is the most prolifically researched probiotic in the world—over 400 studies have been published that document its remarkable immune-modulating properties.

This unique immunobiotic was isolated from a healthy human in 1985 by a team of two Tufts University researchers, Barry Goldin, M.S., Ph.D. and Sherwood L. Gorbach, M.D. They spent nearly a decade testing organisms until they discovered one that was a potent antimicrobial, survived stomach and bile acid, and was very, very sticky—it adhered well to the gut mucosa. Naming the organism *Lactobacillus* GG, after the first initials of their last names, Goldin reports that the organism was unique in the “white, almost milky creamy colonies it would form, probably because of a polysaccharide in the cell wall.”

LGG continues to be studied around the world—from Florida to China, Korea to Germany, Finland to Australia, Boston to Italy. In the last two years alone researchers have uncovered new benefits of this probiotic strain far beyond digestive health, as well as deciphering the mechanisms by which this hardy organism inhibits pathogens and their toxins, and helps restore and re-set immune function.

Like the Vitamin C of probiotics, *Lactobacillus* GG is both the most researched and most trusted, safe, effective immune-boosting probiotic we know of.

New Research on Preventing Diarrhea

In 1987, Goldin, Gorbach and their colleague Chang published a study in *The Lancet* entitled “Successful treatment of relapsing *Clostridium difficile*

colitis with *Lactobacillus* GG.” Chang, a virologist at Tufts who had recently isolated the infamously destructive toxin of *C. difficile*—the bacteria that causes a devastating and often recurrent diarrhea—gave the super probiotic strain to suffering patients after a course of antibiotics, and relapses were prevented.

That study was the first proof that this unique organism could benefit human health. The work on this unique immunobiotic and *E. coli* continues, and in 2008 a study of a strain of *E. coli* that triggers acute diarrhea, gut hemorrhages and hemolytic uremia, found that **the probiotic prevents *E. coli* from causing destructive changes to tissue.** The study showed that pretreatment with LGG diminished the number of lesions and reduced the permeability of the gut mucosal cells. Only the live organism worked; heat-inactivated organisms were not effective.

LGG has also proven effective in combating many other troubling gut pathogens. **This probiotic inhibits *Clostridium*, *Bacteroides*, *Pseudomonas*, *Staphylococcus*, *Streptococcus* and *Enterobacteria*—yet does not inhibit other beneficial *Lactobacilli*.**

A 2008 study of 559 children showed that this strain of *Lactobacillus* significantly lowered the frequency and duration of acute infectious diarrhea, as well as the requirement for intravenous therapy and hospital stays. A 2009 Taiwan study found that the organism inhibits the shedding of rotavirus in fecal samples from infected children.

Adults with gut infections fare well with LGG also. LGG proved effective in five meta-analyses of probiotic trials analyzed at Tufts-New England Medi-

cal Center in 2008; the largest analysis looked at 2810 subjects in 25 randomized, controlled trials. Tufts researchers found that this particular strain of *Lactobacillus*—as well as *Saccharomyces boulardii*—helped prevent antibiotic-associated diarrhea. And a 2007 study from Poland looked at eight randomized, controlled trials involving nearly 1000 individuals. LGG was associated with a significant reduction in the duration of diarrhea. In addition this probiotic reduced diarrhea associated with chemotherapy for colorectal cancer, according to a 2007 study from Helsinki University Department of Oncology.

LGG Prevents Many Infections And Autoimmune Conditions

***Lactobacillus rhamnosus* heals more than the gut in infants and young children. It helps prevent eczema.** When pregnant mothers take LGG, their newborns have less eczema. LGG can reduce atopic dermatitis in those newborns, as well as reduce the risk of allergy by half when given to expectant mothers and then to infants in their first six months of life. A 2009 study from Germany found that newborns treated with LGG had half the rate of atopic dermatitis.

This remarkable immunobiotic can also help prevent ear infections in infants. A 2008 Finnish study of infants requiring formula before the age of 2 months were given LGG and *Bidifobacterium*, or placebo, daily until they were a year old. During the first seven months, 22% of infants receiving probiotics had an ear infection compared to 50% receiving placebo. Antibiotics were prescribed for 31% of infants on probiotics and double that—60%—on placebo. The researchers conclude that

LGG and *Bifidobacterium* “offer a safe means of reducing the risk of early acute otitis media and antibiotic use... during the first year of life.”

***Lactobacillus rhamnosus* may be able to prevent strep throat.** A fascinating 2009 study from Italy found that the invasive capacity of eight strains of group A *Streptococci* (GAS)—all resistant to Erythromycin—was significantly inhibited by LGG, both live and heat-killed. The researchers studied human respiratory cells and concluded that the probiotic might be able to prevent strep throat infections. It has also cleared nasal passages in guinea pigs with allergic rhinitis.

Lactobacillus rhamnosus reduces arthritis—perhaps because allergic disorders involve perturbed skin and gut mucosa and dysregulation of the immune response, according to researchers at Finland’s University of Turku. In a 2008 report they show that elimination diets and environmental changes are not effective enough in allergy, and perhaps establishing a healthy gut microbiota is equally important.

This *Lactobacillus* strain, taken orally, along with other probiotics, actually reduces the amount of *Staphylococcus aureus* and beta-hemolytic streptococci in the nasal passages of humans. Yet the probiotics themselves do not colonize the nose. That suggests that LGG truly does have a body-wide immune-boosting effect.

***Lactobacillus rhamnosus* can help a liver damaged by alcohol.** Only 30% of alcoholics develop alcoholic liver disease, and research suggests that bacterial endotoxins may be another key factor. In a 2009 study from Rush University Medical Center, animals fed alcohol plus this particular probiotic had significantly less severe liver damage (alcoholic steatohepatitis) than those fed alcohol alone. The probiotic “reduced alcohol induced gut leakiness and significantly blunted alcohol-induced oxidative stress and inflammation in both intestines and the

liver” the researchers conclude.

Though these results are impressive, a deeper look at how this remarkable immunobiotic—with its antimicrobial and super adhesion ability—works its mucosal magic gives us profound insight into its other, body-wide health benefits. **This immunobiotic denatures toxins, decreases the inflammatory response, and produces peptides that balance the immune response while limiting the destructive potential of many pathogens.**

How Does *Lactobacillus rhamnosus* Work?

Lactobacillus rhamnosus has remarkable effects on inflammation and infection. Research shows that it **is able to significantly blunt the amounts of inflammatory cytokines that pathogenic**

***Lactobacillus GG* inhibits *Clostridium*, *Bacteroides*, *Pseudomonas*, *Staphylococcus*, *Streptococcus* and *Enterobacteria*—yet does not inhibit other beneficial *Lactobacilli*.**

bacteria seem to trigger—such as TNF-alpha, interleukins, and myeloperoxidase. Remarkably, it downregulates inflammation not only in the gut, but in the intestine, liver, lung and blood. It also seems to reduce the invasive capacity of bacteria. As a result, it can be highly beneficial in a variety of inflammatory diseases and infections.

***Lactobacillus rhamnosus* suppresses inflammatory molecules triggered by *E. coli* infections.** A 2009 study from Japan studied the mechanism by which the probiotic may work. While *E. coli* triggered inflammatory chemokines (measured by PCR), *Lactobacillus rhamnosus* “significantly suppressed” them. The researchers suggest that the probiotic does this by suppressing specific inflammatory pathways.

***Lactobacillus rhamnosus* even seems to be able to remove toxins from solution.** A 2008 study of this particular strain of *Lactobacillus* along

with other probiotics looked at the peptide toxins from cyanobacteria. LGG and *Bifido bacterium* strains were studied. This unique probiotic was able to remove between 60 and 78 percent of three specific toxins. Toxins could be removed simultaneously by the probiotic, and researchers found that a combination of probiotics enhanced their removal ability. **This fascinating study suggests that one mechanism by which *Lactobacillus rhamnosus* heals the gut and the immune system is by actually binding or denaturing bacterial toxins.**

***Lactobacillus rhamnosus* Alters The Immune Response**

Pathogens harm by invading tissue, releasing endotoxins, and stimulating a marked immune response which releases a flood of inflammatory molecules. Immunobiotics limit a pathogen’s ability to invade as well as damage our own cells, and they help reduce our inflammatory response, leading to an overall balance that is far

healthier. There is much new evidence that this probiotic is a very effective immunobiotic, one that helps regulate our own immune response.

A 2009 animal study found that this unique organism is able to lessen the damaging response of T and B cells to the pathogen *Campylobacter jejuni* in mice. Another 2008 study found that it can actually restore the liver enzyme alkaline phosphatase in cells damaged by the potent mycotoxin deoxynivalenol.

Lactobacillus rhamnosus helps limit the runaway inflammatory response in our body. NF-Kappa B is a key molecule that regulates the entire inflammatory cascade. **Amazingly, *Lactobacillus rhamnosus* seems to be able to quiet the gene that transcribes and regulates production of NF-Kappa B.** This remarkable finding is from a 2008 study from South Korea. Cells in culture were stimulated so that they would release the inflammatory

cytokine IL-8. Pretreatment of cells with this immunobiotic significantly inhibited IL-8 production. Even more importantly, the organism actually worked to quiet both the genes that help regulate IL-8 and NF-Kappa B. **This means that *Lactobacillus rhamnosus* may be working at the very deep and fundamental level of gene activity and transcription, in part by inhibiting the NF-Kappa B signaling pathway.**

Lactobacillus rhamnosus may help our gut mucosa defend itself by promoting protective responses, according to a 2008 study from Emory University. **This research found that *Lactobacillus rhamnosus* reduced cell death in vitro and when given to live animals.** The scientists used DNA microarray analysis to prove the protective effects on cells. This kind of cell death may be a precursor to a potentially deadly condition seen in premature infants, where part of the bowel dies, and sometimes the infant dies as well.

Lactobacillus rhamnosus may **augment first-line defense secretory IgA responses.** SIgA is a first line of defense for all mucosa in the body. A 2008 study on birch pollen allergy from Finland looked at the oral immune response in individuals with birch

pollen allergy. Thirty-eight individuals received either *Lactobacillus rhamnosus* or placebo for 10 weeks before birch pollen season. SIgA in saliva was measured before, during, and after the pollen season and those who took LGG had increased SIgA levels.

***Lactobacillus rhamnosus* proteins heal the gut lining.** Two proteins produced by LGG promote “epithelial

***Lactobacillus* GG denatures toxins, decreases the inflammatory response, and produces peptides that balance the immune response while limiting the destructive potential of many pathogens.**

integrity”, according to a 2008 study from the University of Tennessee. Researchers looked at two unique *Lactobacillus* proteins, p40 and p75, and found that treating cells with these proteins helped prevent oxidative damage and permeability.

***Lactobacillus rhamnosus* and other immunobiotics may activate specific T-cells (“Peyer’s patch”) according to a review by Robert Clancy of Royal Newcastle Hospital in Australia.** This may be how oral consumption of this immunobiotic helps protect against infection and inflammation as far away as the nose, ears, skin, lung or urinary

tract. Specific IgE is reduced when consuming immunobiotics, and animal studies have shown protection against bronchial infection with *H. influenza* and *Candida*. As Clancy concludes “to continue to use the term ‘probiotic’ for those bacteria which promote health... would appear outmoded and out of step with contemporary thinking and potentially confusing.”

It Actively Restores Immune Balance

Lactobacillus rhamnosus, with its antimicrobial and immune-regulating ability, along with its extremely sticky, adhesive properties, offers an entirely new therapeutic strategy for combating allergic and infectious disease. Our gut microbiota have a powerful ability to prime immune regulation. From the moment we’re born, our immune system is regulated by our flora—which in turn is influenced by everything from our mothers’ microbiota, the mode of delivery (vaginal, which colonizes the baby with *Lactobacilli*; or caesarean, which does not), whether we are breast or bottle fed, and our diet and environment. Diet directly influences the diversity of the microbiota. Host-microbe cross talk is key to maintaining immune tolerance and effectiveness.

Saccharomyces boulardii: New Research Confirms Immune-Modulating Ability

This Probiotic Yeast Increases Secretory IgA and Prevents *C. difficile* Colitis

Just as *Lactobacillus* GG is the most-studied bacterial immunobiotic in the world, *Saccharomyces boulardii* (*S. boulardii*) is the best researched probiotic yeast, with nearly 300 peer-reviewed studies. Isolated from litchi fruit in the 1920’s, *S. boulardii* colonizes the gut within three days of oral consumption

and disappears from stool within 5 days after discontinuation. New research confirms it as a first choice for preventing and treating traveler’s diarrhea, antibiotic-associated diarrhea, and *C. difficile* colitis, as well as helping improve Crohn’s disease, ulcerative colitis and irritable bowel syndrome.

Studies have shown that *S. boulardii*:

- Protects against gut pathogens
- Modulates the immune response
- Decreases inflammation in a wide range of disorders

- Inhibits bacterial toxins
- Enhances the gut's natural enzymes and nutrient transporters
- Increases the most important gut immunoglobulin, Secretory IgA

Hello Good Yeast, Goodbye Diarrhea

It's widely known that *S. boulardii* helps prevent and treat antibiotic-associated diarrhea (AAD) caused by pathogens such as *Clostridium* species, *Staphylococcus aureus*, *Klebsiella*, *Candida* and *Salmonella*. Mainstream as well as integrative medicine doctors often prescribe it along with antibiotics. "Given the broad range of protective effects in multiple gastrointestinal disorders," write researchers from Harvard Medical School in a 2006 study, "we hypothesize that *S. boulardii* modulates host signaling pathways involved in intestinal inflammatory responses." Indeed, the researchers found that *S. boulardii* blocks activation of inflammatory molecules called kinases. In another study, Harvard researchers found that the yeast blocked activation of other key inflammatory molecules like NF-Kappa B.

Other new research confirms the yeast's potency in preventing diarrhea. *S. boulardii* slashed the risk of antibiotic-associated diarrhea by nearly 2/3 in a study of 269 children with ear or upper respiratory tract infections. The children were given antibiotics plus 250 milligrams of *S. boulardii* twice daily or a placebo. Only 8% of *S. boulardii* children had diarrhea, compared to 23% taking a placebo. In another study on 151 hospitalized patients, only 1.4% of those who were given *S. boulardii* in addition to antibiotics had diarrhea, compared to 9% on placebo. In addition *C. difficile* toxin was found in 2 of the placebo patients and none of the *S. boulardii* patients.

In fact, *S. boulardii* protects against the devastating *C. difficile* colitis. When 124 patients on high dose vancomycin for

C. difficile colitis were given *S. boulardii*, rates of recurrence plummeted from 50% to 16.7%. A 2006 meta-analysis found that various probiotics help prevent antibiotic-associated diarrhea, but only *S. boulardii* prevents and treats *C. difficile* associated diarrhea.

S. boulardii is effective in preventing traveler's diarrhea as well, of which 80% is caused by *E. coli*, *Shigella* or *Salmonella* species. A study of over 1000 travelers found that rates of diarrhea dropped from nearly 40% to 29% when travelers started taking *S. boulardii* at 1000 milligrams daily, five days before and for the duration of their trip.

Diarrhea in children, in patients on enteral feeding tubes, and in AIDS patients, also responds to *S. boulardii*. Even Crohn's patients may benefit from *S.*

Saccharomyces boulardii stimulates significantly higher levels of secretory IgA than other organisms

boulardii, according to a 2008 study of 34 patients treated with either the probiotic yeast or a placebo. Those receiving *S. boulardii* experienced significant improvements in intestinal permeability. Other animal studies have shown that *S. boulardii* helps maintain the gut's epithelial integrity and ameliorate inflammatory responses in the presence of various infecting pathogens.

Secretory IgA: The Critical Mucosal Immunoglobulin

Secretory IgA (SIgA) is our first line of defense against invading microbes and is key to maintaining mucosal homeostasis and integrity. It is the main immunoglobulin found in mucus, tears, saliva, vaginal fluid, and secretions from the intestine and lining of the lungs. It resists degradation by enzymes, and provides profound protection against pathogens.

S. boulardii is uniquely able to stimulate SIgA. A June 2009 study compared *Bifidobacterium animalis*, *Escherichia coli*,

Lactobacillus casei and *Saccharomyces boulardii*. The study found that *S. boulardii* stimulated significantly higher levels of secretory IgA than the other organisms, and *S. boulardii* alone induced a higher level of the potent anti-inflammatory cytokine, Interleukin 10 (IL-10). *S. boulardii* can increase SIgA by as much as 56% in duodenal fluid, according to an animal study from the University of Louvain in Brussels. SIgA nearly doubles when mice are fed *S.b.* and then exposed to *C. difficile* toxin. In germ-free mice, inoculation with *S. boulardii* increased total IgA.

S. boulardii is anti-inflammatory: it decreases the expression of inflammatory cytokines including interleukin 8 (IL-8), IL-6, IL-1b, tumor necrosis factor alpha (TNF-a) and interferon gamma (IFN-y). It may even decrease the number of T-cells producing IFN-y. *S. boulardii* can decrease IL-8 secretion from human colon cells after stimulation with a toxin from *C. difficile*. It can also reduce inflammation by suppressing nuclear factor-kappa b (NF-kB), which is activated during infection. In one study of human colon cells, *S. boulardii* inhibited NF-kB pathways after cells were exposed to a strain of *E. coli* that causes hemorrhage. Recent research shows that *S. boulardii* actually produces a specific low-molecular weight factor that directly blocks NF-kB activation.

S. boulardii also helps reduce levels of nitric oxide, which is associated with inflammatory bowel disease. It neutralizes bacterial toxins and inhibits toxin-binding to intestinal receptors as well as bacterial adhesion. In this way *S. boulardii* increases the gut's integrity and helps protect it. It even increases the activity of enzymes like lactase and sucrase-isomaltase, helping aid digestion and absorption of nutrients from foods.

In a word, *Saccharomyces boulardii* restores intestinal homeostasis.

New Research Confirms Martin Pall Hypothesis

Pilot Study With Free-Radical Reducing Supplements Improves Treatment-Resistant CFS

Interview with Ingrid Franzon, N.M. M.S.c.

Introduction and Personal History:

Ingrid Franzon, M.S.c., is a nutritionist at the Integrated Functional Medicine Clinic in Falun, Sweden. Together with colleagues Bo Jonsson, M.D., Ph.D., Department of Clinical Neuroscience, Karolinska Institute, Stockholm, and Peter Wilhelmsson, N.D., IFM Clinic in Falun, she conducted a pilot study on the use of four free-radical reducing food supplements to treat chronic fatigue syndrome. The four food supplements contained combinations

of nutrients known to affect the free radical activity of nitric oxide and its metabolites. Nine patients were assessed before, during and after supplementation for eight weeks. (See *Evaluation of Quality of Life...* on page 13). In this interview, Franzon discusses her own complete recovery from severe CFS as well as the improvements several of her patients experienced taking free-radical reducing supplements.

Focus: How long have you worked in nutritional medicine?

Franzon: For twenty-five years. I started working as a nutritionist in Zimbabwe, Africa where I worked at a farm and conference center for reconciliation run by Initiatives of Change. I ran the farm clinic, and we raised money to pay for the children to get a drink of nutritious, nutrient-dense sorghum every morning before they walked several miles to school. By the following winter all the stomach flus and colds I'd seen were a thing of the past. That was my life's biggest a-ha experience and it set my course in nutritional medicine. The years in Africa probably contributed to my collapse with CFS as I did extensive dental work, and got complicated parasitic, fungal and viral infections while I was there. And it was through experiencing CFS that I learned even more about nutritional medicine.

Focus: How sick were you with CFS?

Franzon: For over a year I was so weak I could hardly walk fifty meters. I could only eat nine foods. At one

point I would go weeks hardly eating at all, just drinking water. I was given medicine for parasites and lost twenty kilos. I was afraid that I'd be disabled for good, and because my mom has been sick a lot of her life I was afraid the same thing would happen to me. In fact, four generations of our family have had similar symptoms and my little granddaughter had severe chemical sensitivities at the mere age of two. I've had genetic testing done and I have polymorphisms that lead to poor detoxification and immune compromise. Therefore I have this incredible interest in healing CFS. There has to be a cure for CFS/MCS. I got well and I believe every single person who comes to see me in the clinic can get well. Several are well on the way to recovery. The key is reducing free radical levels in the body.

Focus: How did you get well?

Franzon: I went to many different practitioners. I was too sick to take supplements at that point. For six months I only tolerated physical therapies like acupressure and craniosacral therapy. One major breakthrough was discover-

ing digestive enzymes. After the first six months I was able to eat more foods and take supplements.

Focus: So you are totally well today?

Franzon: I am healthy and live a normal and very active life. But if I get an infection, or have been flying on planes or stressed, I have to do something about it very quickly. I have had two relapses—once after caring for my father who died of a virus, and another time when I got a virus but had to complete a job and couldn't rest and recover. After that relapse I got well pretty quickly taking free-radical reducing food supplements. Because they helped me so much I decided to conduct a small study on their effect in my patients.

Focus: How did they work?

Franzon: These food supplements reduced free radical levels. One of the most exciting cases was a woman who has tried everything to help her CFS for decades. She got sick in 1986 after an infection and has been ill for twenty years. She is constantly exhausted and has cognitive problems. When she is

about to get very ill she says it feels as if a nightcap has come over her head and killed off everything in her brain. After only three days on these supplements she reported that she was sleeping better. At the end of two months she wrote me this on email:

"They have been a miracle cure for me. After 3 days supplementation I slept deeply through the night, felt better, and had more energy during the day than I've had for many years. My head and my thoughts cleared. I was so used to being "fuzzy" in my

brain that I hadn't even realized how confused I was. I was suddenly able to think things through and my ability to organize and take action returned, reminding me of what my life was like before. Even if I feel I still have a way to go before I can call myself well I now have a life – I only existed before. Only those who have been as limited and sick as I have been can understand how much these months when I took what I call my "energy pills" have meant to me. Thank you for letting me try, it has been a miracle!"

Another patient who has always told me she had a gut feeling she would never get well took part in the study and said she can now ride her horses again. She noticed a huge difference when riding a bike as well; before she was in too much pain. She wrote that, "I particularly notice how I no longer need to stop when I come to the little hill that previously made my legs painful and more or less paralyzed." She said the pain has a totally different quality and now only comes with extreme exertion.

Evaluation of Quality of Life in Persons with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Before and After Administration of Food Supplements Designed to Reduce Free Radical Activity:

By Ingrid Franzon, MSc, Bo Jonsson M.D., Ph.D., and Peter Wilhelmsson, N.D.

Many researchers have investigated effective treatments for chronic fatigue syndrome (CFS) and multiple chemical sensitivity (MCS), but Martin Pall, Ph.D., Professor Emeritus of Biochemistry and Basic Medical Sciences at Washington State University, and author of *Explaining "Unexplained Illnesses"*, is the first to suggest a plausible underlying cause and therapeutic method of treatment. Pall, who came down with a severe case of CFS in 1997 and fully recovered in 18 months, has dedicated the rest of his career to understanding and treating these illnesses.

Pall has discovered that abnormal levels of nitric oxide (NO), high levels of peroxynitrite (ONOO⁻) and superoxide activate the disabling and widely varying symptoms that characterize this entire group of unexplained illness. The fundamental approach: reducing NO-related free radical activity.

According to Pall's theory, a known stressor initiates high levels of NO and ONOO⁻—most often a pathogen like a virus or bacteria, physical trauma, exposure to pesticides (including organophosphates and carbamates), solvents, or severe psychological stress. Other stressors can include exposure to biocides and organochlorine, parasitic infections like *toxoplasmosis*, poisoning from *ciguatoxin*, carbon monoxide or thimerosal. After the acute stressor, the body is unable to recover and continues to exist in a chronic state of elevated free-radicals.

This study evaluated nine patients with treatment-resistant CFS over a period of eight weeks. The Medical Outcomes Survey Short Form-36 (SF-36) was used. This is a well-validated psychometric instrument, and is one of the tools recommended in the measurement of the entire syndrome of Chronic

Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) as it addresses physical and social activity, vitality, bodily pain, physical and mental states, and perception of general health. The multi-item scales are weighted, summed up, standardized and transformed to allow score indices: the Physical Component Score (PCS) and the Mental Component Score (MCS).

Four supplements containing multiple nutritional ingredients that have individually been shown to affect NO/ONOO⁻ and superoxide activity were administered to a group of nine patients with CFS/ME for 8 weeks. The SF-36 was administered at the outset, after a month of supplementation and at the end of the supplementation period. When presented with the raw data on both physical and mental fatigue, Dr. Martin Pall did an inferential statistical analysis for significance, using a paired t-test where each patient's results were analyzed at zero, four and eight weeks. The smaller a study, the more you want marked significance. Here, the results for physical symptoms were highly significant: the p value for the time period of 0-4 weeks was .006, nearly ten times stronger than p=.05, which is the minimum required for statistical significance. For 0-8 weeks the p value was .0149, and 0.482 for 4-8 weeks. Although these are also significant, the greatest improvement occurred in the first four weeks of the program, and though improvement continued to be statistically significant, it was not as dramatic. There were no significant results on mental symptom tests; perhaps the tests used for mental symptoms were not particularly revealing. These strong findings on this small study present compelling evidence that Dr. Pall's hypothesis and suggested nutrients designed to reduce NO/ONOO⁻ and superoxide activity are very useful in CFS/ME.

NO/ONOO-

A Brief Summary of the Work of Martin Pall, Ph.D.

Editor's note: Martin Pall Ph.D. has 23 publications out or in the press on what is now called the "NO/ONOO⁻ cycle mechanism".

No...oh no!

It sounds like a cry of protest and pain, and indeed it is, certainly by those who suffer from chronic fatigue syndrome, fibromyalgia, Gulf War syndrome, post-traumatic stress and multiple chemical sensitivity.

But that succinct phrase is also the essence of biochemist Martin Pall's therapeutic approach to five mystery illnesses. Pall has assembled an impressive body of data to demonstrate that elevated levels of nitric oxide (NO) and its highly damaging metabolite, peroxynitrite (ONOO⁻), are at the crux of a runaway cycle of free-radical damage in which inflammatory molecules are chronically elevated, damaging the immune and nervous systems. Peroxynitrite initiates a complex biochemical vicious cycle, known as the NO/ONOO⁻ cycle, which is responsible for multiple chemical sensitivity, chronic fatigue syndrome, fibromyalgia, Gulf War syndrome and post-traumatic stress disorder. The basic concept here is actually quite simple. Stressors act mainly through peroxynitrite-derived free radicals to initiate the cycle and once the cycle is initiated it is the cause of continuing illness.

By correcting the high levels of NO and ONOO⁻ with a range of natural antioxidants, a puzzling array of symptoms can be ameliorated and sometimes the illness itself can be completely reversed. (See *Allergy Research Group® Newsletter Focus*, July 2007.)

Pall suffered from severe chronic fatigue syndrome (CFS) and multiple chemical sensitivity (MCS) for 18 months, and

cured himself, then set about dedicating his career to investigating the cause of these disabling conditions. Now his approach has started to garner widespread attention, with publication of an entire chapter by Pall in the upcoming *General and Applied Toxicology*, 3rd edition by (editors TK), published by John Wiley, Inc. In addition, a new pilot study from The Institute for Functional Medicine Clinic in Falun, Sweden demonstrates the effectiveness of this approach. Pall also has a forthcoming article on CFS in *Current Opinion in Psychiatry*.

As Pall points out, the acute stressor(s) that lead to CFS and MCS and the other mystery illnesses range from infections to toxic exposures to physical or mental trauma. But no matter what the initiating cause, the downstream effect is free radical damage mediated by raised levels of NO and ONOO⁻.

Very specifically:

The immune system: is impacted by inflammatory cytokines and NO itself. The immune system cells are particularly sensitive to oxidative stress.

Learning and memory dysfunction: NO has several functions related to learning and memory.

Orthostatic intolerance: NO can produce vasodilation locally in the vasculature and systemically through its effects on the sympathetic nervous system.

Pain: All the elements of the NO/ONOO⁻ cycle have a role in the excessive pain of these conditions.

Depression: The NO/ONOO⁻ cycle produces inflammatory cytokines, which are implicated in depression.

According to Pall, the largest single challenge in understanding MCS is how so many diverse chemicals can trig-

ger sensitivity symptoms and produce a common response in the body. Toxic chemicals, such as organic solvents or pesticides, increase the activity of NMDA ((N-methyl D-aspartate) receptors. These are a specific type of glutamate receptor. Increased NMDA activity is known to produce increased calcium influx into cells, leading to increased activity of two calcium-dependent nitric oxide synthases, nNOS and eNOS, which produce, in turn increased nitric oxide. Nitric oxide reacts with superoxide to form peroxynitrite. So, ultimately, it is the final act, NO and ONOO⁻ that cause the damaging response.

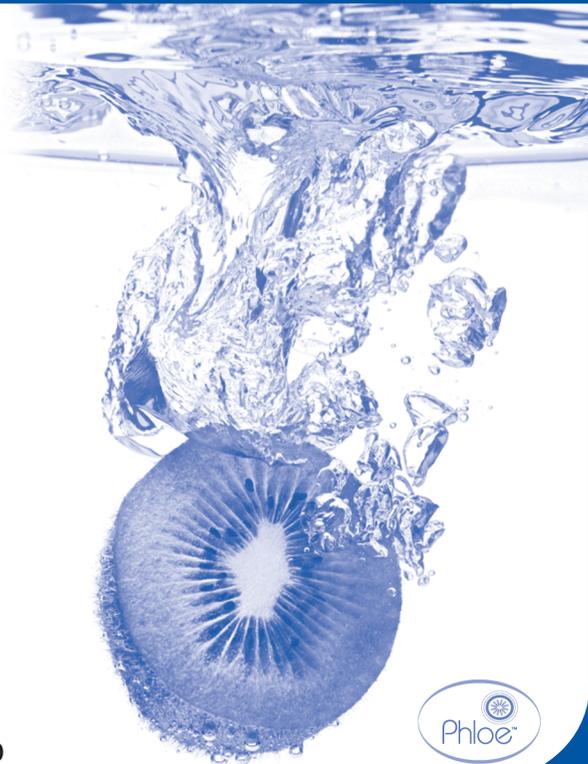
In CFS, peroxynitrite attacks important mitochondrial proteins, initiating a complex of reactions, each of which lowers oxygen utilization in the tissues. Peroxynitrite also oxidizes a compound known as tetrahydrobiopterin (BH4), which has a role in the production of important mood elevators such as catecholamines and serotonin.

Pall suggests treating with specific nutrients that lower NO and ONOO⁻. Previous clinical studies of sixteen nutrients have demonstrated improvement, and the new Swedish study of nine patients supports their usefulness. These nutrients include:

- Trimethylglycine (betaine)
- Coenzyme Q10
- Folic acid (folate)
- Hydroxycobalamin (B12)
- Ecklonia cava* extract
- Acetyl-L-carnitine
- Flavonoids
- Fish oil
- Magnesium
- Vitamin C
- Tocotrienols and Carotenoids
- Multivitamins and minerals



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