Systemic Formulas: Solutions Here & Now • Research Report #15

Membrane Rejuvenation Therapy & The Intestinal Microbiome

A NEW VIEW OF GASTROINTESTINAL ENERGY/IMMUNE SYSTEM CONNECTION

By Dr. Jack Tips (Ph.D., C.C.N.)

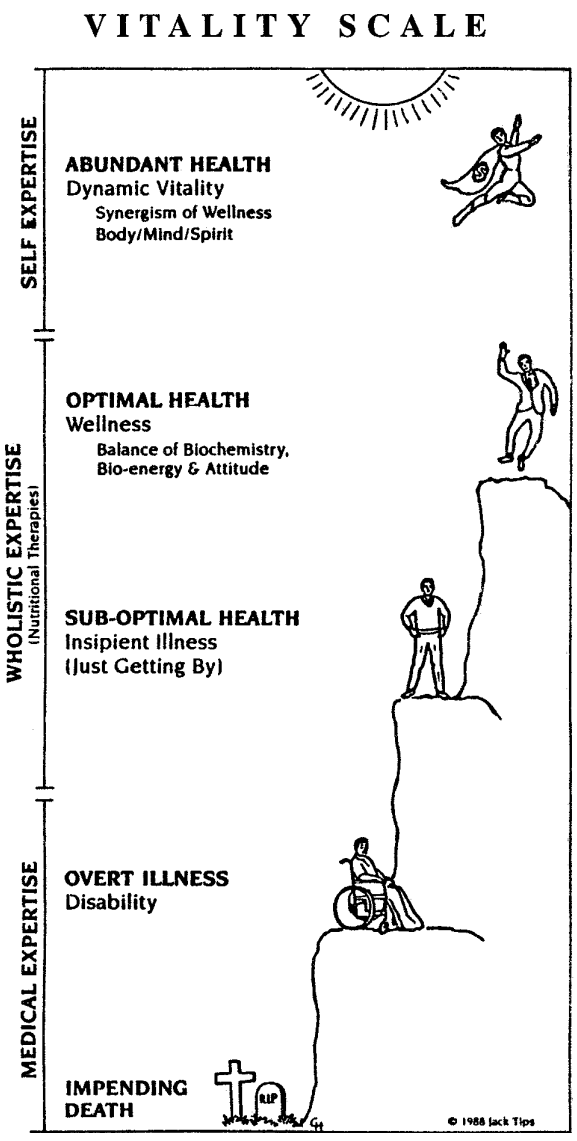
Every clinician today, if reviewing their case notes, will quickly find two all pervasive health issues affecting their patients. We can call them the Top-2 health complaints that accompany most every case. In fact, they are so pervasive, some practitioners skip over them because, "Hey, everybody's got some degree of them, and that makes them normal."

New research demands that we not skip over them, but instead, address them head on as critically important "points of leverage" upon which our clinical success depends!

These two omnipresent health issues underlie the top three diseases that afflict our society: Heart Disease, Cancer, and Iatrogenic Disease[1]. Do you know what they are? They are: 1) gastrointestinal disorders (indigestion, gas, bloating, ulcers, colitis, constipation, diarrhea, irritable bowel, Crohn's, etc.), and 2) fatigue.

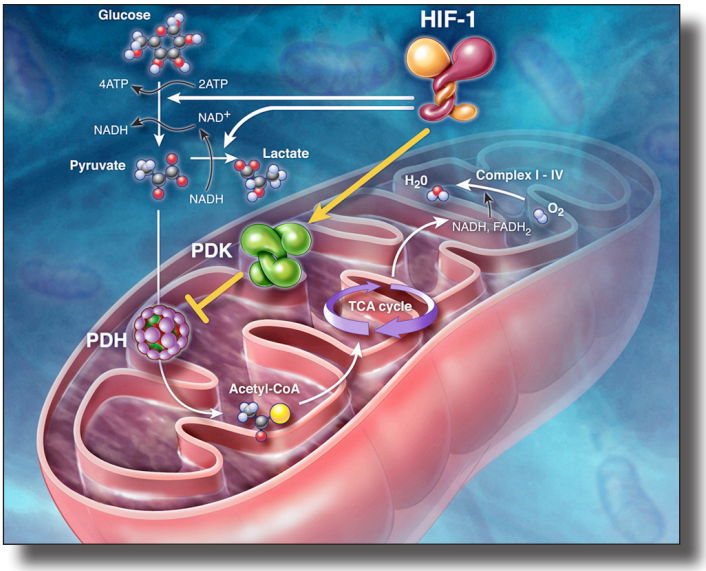
Surprisingly, the digestive system and fatigue have a common denominator – the mitochondrial membrane's ability to make ATP (Adenosine Triphosphate). Thus we are looking at a foundational energy concern that has huge ramifications, not only for the resolution of G.I. track issues, but for the entire body.

For many years, practitioners have used digestion questionnaire intake forms, and it seems that no patient escapes those questions unscathed. Everyone has something going on! But this did not used to be. Seems historically, the decline in G.I. Tract health began with the advent of antibiotics, pesticides, chronic inflammation, and the denaturing of food. Just makes sense.



1 **Iatrogenic Disease** is preventable harm resulting from medical treatment or advice to patients. Professionals who may sometimes cause harm to patients are: physicians; pharmacists; nurses; dentists, psychiatrists, psychologists, insurance companies that predispose what therapy are used, government laws that support the medical cartels, and therapists.

Also for many years, practitioners have employed questionnaires and differential evaluative questions regarding overall vitality. The body requires ATP (Adenosine Triphosphate) energy to heal. Fatigue and chronic fatigue are therefore *obstacles to cure* and must be addressed for the body to re-enter its most optimal vitality. [Please review the information in Research Report #7: ATP: The Energy of Life.]



National statistics report some 48% of all people seeking medical expertise report significant fatigue. My opinion is that another 48% simply do not know what abundant energy feels like, so they don't realize that they are moderately fatigued. The light of energy is dimmed and they've compensated with "I'm just getting old." Their constellation of symptoms quickly reveals fatigue – cold hands and feet, brain fog, poor memory, susceptibility to colds and flu, and need to drink coffee to get going in the morning, sugar cravings, etc.

New Definition of Dysbiosis. A meta analysis of the latest research clearly reveals the connection between the G.I. Tract and Fatigue. Certainly dysbiosis – best defined as, "*a loss of biodiversity of the G.I. microbiota*" meaning the ±1000 possible species of bacteria (probiotic and pathogenic) that inhabit the human intestines—is clearly linked with dysfunctional intestinal conditions.

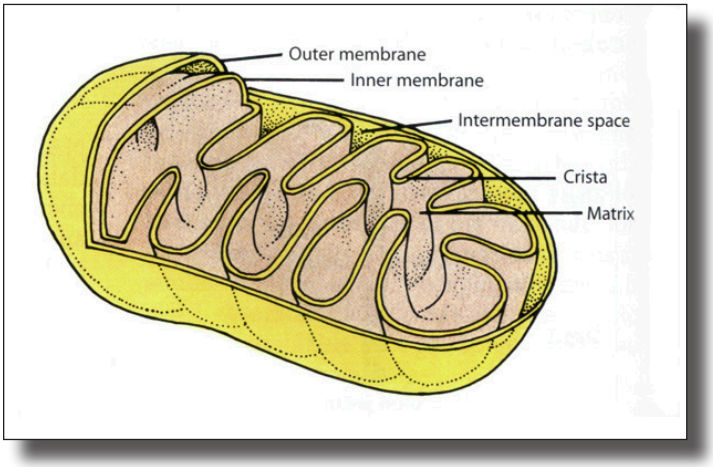
But here's the fascinating aspect, loss of bacterial biodiversity turns out to be an energy situation—specifically the impairment of the mitochondrial membranes that make ATP energy throughout the body. There is one well-established pathway of energy reduction via the dysbiotic inflammatory processes that damage the mitochondria, and there is a newly-emerging pathway of missing transcriptional proteins that epigenetically support cellular metabolic processes. The fact that dysbiosis causes fatigue introduces a whole new paradigm that supports the critically important need for Intestinal Microbiome Rejuvenation as a foundation for every natural health approach to healing.

So there's a "gut-fatigue" connection, and right in the middle of it all is the immune system and the setpoint of inflammation that drives all the chronic degenerative, autoimmune diseases. This is huge! Science is reaching for a new understanding—that of common denominators in all disease instead of the fragmented medical perspective of "specialization" and "isolation" that is more applicable to a mechanical device than a living organism. Inevitably the facts are driving knowledge to the truth of the holistic, natural health model.

Mitochondrial Diseases. In the first decade of the 21st Century, medical and scientific research brought forth a new paradigm of health and disease. [See Research Report #2: *Mitochondrial Dysfunction and the NO/ONOO Cycle*.] They lumped virtually all the chronic-degenerative disease and autoimmune diseases into the new category, "Mitochondrial Diseases." Just imagine the repercussions! If the mitochondria distress can be corrected and optimal function restored, then that becomes a *point of leverage* over all chronic-degenerative disease, all

autoimmune disease, and all the "no known cause, no known cure diseases." Again, this insight is huge because it points to a nutritional method to help the body correct the dread diseases.

It's all about the membrane. Mitochondrial issues are really membrane issues – it's the serpentine, inner mitochondrial membrane, called the *cristae*, that is the "battery" that generates the electrical grid energy required to make ATP. Referring to Research Report #14, "*Membrane Rejuvenation Therapy—The Key to Hormone Balance, Whole Body Energy, Glucose Metabolism Balance & Disease Reversal*" we've discovered that yes, indeed, the body can repair the membranes and the wonder-molecules that do the job, while terribly absent from the SAD (Standard American Diet) are readily available supplementally.



Here's the situation in a nutshell: The mitochondrial powerhouses must have healthy membranes in order to generate ATP, via the *electron transport system* [See Research Report #7: *ATP: The Energy of Life*.] And just to keep us on track with the G.I. Tract, peristalsis – the intestinal contractions that move the chyme and waste materials through the intestines – is based on ATP, thus **constipation is a lack of cellular energy**.

Fatigue and Chronic Fatigue Syndrome is, in essence, a simple matter of mitochondrial cristae membrane permeability. The greater the cristae permeability (damage), the less the electron transport system works to initiate phosphorylation, so less ATP energy is made. Less ATP = Fatigue. Repair the membrane and energy is restored.

Damaged mitochondrial cristae membranes can initiate apoptosis—and cause cell suicide. Further, they call in the immune system to help dispose of the discombobulated cell protein components, and thus encourage the immune system to attack "self" which is the essence of autoimmune disease.

As a overview of this inner cellular membrane process, the mitochondrial cristae membrane is virtually impermeable, unlike the plasma membrane (cell wall), outer mitochondrial membrane, and nuclear membranes. It's the fatty acid, *cardiolipin*, that does not contribute to the lipid bi-layer membrane structure and keeps the cristae firm, rigid, and non-rafting. This is because the cristae are the biochemical and bioenergetic home of *oxidative phosphorylation* – the metabolic pathway that uses energy released by nutrient oxidation to produce ATP and thus is a highly efficient way of creating energy, compared to alternative, back-up process of *fermentation anaerobic glycolysis*.

So the mitochondrial cristae are generators of free radicals. That's one of their important jobs. When there is too much free radical damage to the membrane caused by reactive oxygen species (ROS), aka free radicals; and by reactive nitrogen species (RNS) [explained in Research Report #2: *Mitochondrial Dysfunction and the NO/ONOO Cycle]*, then cell-programmed death (apoptosis) occurs. When this happens on a large scale, it's called necrosis—the death of most or all of the cells in an organ or tissue due to disease, injury, or failure of the blood supply.

Looking at the gestalt of factors that can cause mitochondrial dysfunction and cell death, we find

that the natural therapies excel in helping the body correct such – botanicals and nutritional molecules are exactly what the body requires. Here are some of the mitochondrial membrane disruptors:

- **Pathogens (Virus, Fungus, Bacteria, Mycobacteria)** can be a causative agents – and there are botanical "pathogen purges" such as Systemic's G.I. Pathogen Purge Program to help the body, as well as energy-based homeopathic remedies that address *miasms*—altered epigenetic processes of susceptibility to certain disease manifestations.

- **Ischemia** – an inadequate blood supply to an organ or part of the body, especially the heart muscles where the mitochondria must function at peak performance to provide ATP for the next heartbeat. There are nutrient supplements with carnitine, cardiolipin, d-ribose, Coenzyme Q-10, magnesium and hawthorn to support heart health. These nutrients are consolidated in the HQ (Heart Energy Formula).

- **Glucose Metabolic Diseases** – such as insulin resistance (founded in G.I. Tract dysbiosis, inadequate nutrition, and the mitochondrial membrane energy processes). Again, nutrients (and exercise) help the body overcome these concerns. Dr. Shayne Morris has developed the Metabo-Shake to address this issue.

- **Environmental toxins** – mercury, lead, pesticides, chemicals. These increase the inflammation processes, increase free radicals, and increase cristae permeability and thus established the natural health premise that toxins cause chronic fatigue. Toxins in the extracellular matrix interfere with cellular processes via free radicals and inflammatory cytokines. This is addressed by the Systemic Detox Done Right Program. Toxins in the mitochondrial membranes can be expelled by glutathione addressed by GCEL (Intracellular GSH).

- **Impaired nerve conduction** – nerve inflammation (from pesticides), demyelination (autoimmune processes), spinal subluxations. Similar nutrients, the phospholipids, are foundational to the body's corrective processes.

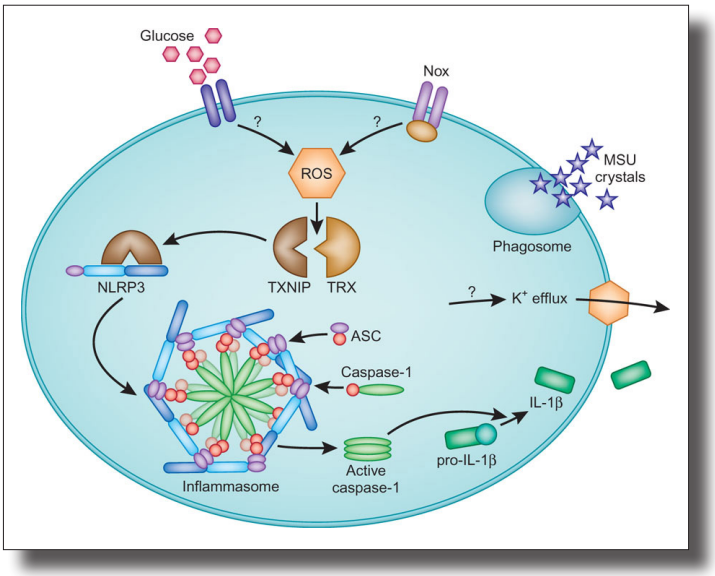
- **Nitric Oxide (NO)** – a major signaling molecule in neurons and in the immune system, either acting within the cell in which it is produced or by penetrating cell membranes to affect adjacent cells. Nitric oxide is generated from arginine by the action of nitric oxide synthases (NOS).

When the mitochondrial membrane is damaged, it releases a protease enzyme called *caspase* which causes three outcomes: 1) inflammation[2], 2) apoptosis—cell death, 3) necrosis. The inflammation connection is most germane to our discussion here because caspase molecules trigger the cell to create molecules called *inflammasomes* that excite the immune system and wreak further havoc. Inflammasomes are very active in people with diabetes, metabolic syndrome, cancer, and they disregulate the gut microbiome.

For emphasis, we've just tied our cellular biology lesson from the inner mitochondria in the inner cell structure right back to the body's influence over the gut ecology and the production of gut ATP processes[3].

2 Alnemri ES, Emad S; et al. (1996). "Human ICE/CED-3 Protease Nomenclature."

3 Franchi, Munoz-Planillo, Nunez. Sensing and reacting to microbes through the inflammasomes. Nature Immunology, 2012;13(4): 325-333.



Inflammasomes are the pivotal control vector for the body's immune defenses and participates in the "set point" of inflammation that governs immunological sensitivity and the amount of collateral damage the body allows regarding inflammatory diseases[4].

So, when the immune system is on high alert, it demands a lot of energy. When the mitochondrial membranes are inflamed and damaged, they cannot produce ATP as efficiently. Fatigue is the result and a lack of ATP is a starting point for all degenerative diseases.

The next immunological step is the cytokine response to the molecular messages of the distressed mitochondria. Now another component of the immune system engages in the inflammation processes. Inflammatory cytokines directly impact the intestinal microbiome. With 70% of the human immune system in the gut, inner body inflammation impacts the gut immune processes via cytokines and altered biodiversity. This is congruent with the holistic model. Cause-effect relationships are systemic.

4 Martinon, Mayor, Tschopp. The inflammasomes: guardians of the body. Annual Review Immunology. 2009;27:229-266.

Two Way Street. With the intestinal immune system put into hyper alert, the intestinal microbiome colonies feel the threat and take defensive and offensive action. The new level of heightened mistrust and overt warfare immediately impacts what is known as "leaky gut." Zonulin molecules open tight junctions. Inflammation processes weaken the mucosal barrier. New immunological challenges contribute to inflammation, disease, and aging. Here we find the creation of a potentially insidious situation of the body's mitochondria raising the inflammation alert in the gut and the gut raising and reinforcing the inflammation in the body.

If only we could help the body stop this self-perpetuating cascade of cell death, and destruction; then we'd have the key to reducing inflammation and bring back the peace and harmony the body craves. Blessedly, Nature does provide a way. And Nature's way is through nutritional molecules becoming available to the body, and healing directives that come from natural health care professionals. The answer is in Research Report #14: *Membrane Rejuvenation Nutrition – The Key To Hormone Balance, Whole Body Energy, Glucose Metabolism Balance, and Disease Reversal*. That report cites the specific phospholipids such as cardiolipin that the cells use to repair the mitochondrial membrane and turn off the faucet of inflammation.

The simple key to maintaining the plasma membrane, the mitochondrial membranes and the nuclear membrane is to have a dietary intake of undamaged phospholipids. It's interesting how, in an age of rampant membrane inflammation, the U.S. culture shuns the very foods that are healing: raw milk (cow, goat); organic, free range egg yolk; lightly cooked

A2 Dairy is A-OK. In his groundbreaking book, *The Devil In The Milk*, researcher Dr. Thomas Cowin writes, "All proteins are long chains of amino acids. Beta casein is a chain 229 amino acids in length. Cows who produce this protein in their milk with a proline at number 67 are called A2 cows, and are the older breeds of cows (e.g. Jerseys, Asian and African cows). But some 5,000 years ago, a mutation occurred in this proline amino acid, converting it to histidine. Cows that have this mutated beta casein are called A1 cows, and include breeds like Holstein.

Proline has a strong bond to a small protein called BCM 7, which helps keep it from getting into the milk, so that essentially no BCM 7 is found in the urine, blood or GI tract of old-fashioned A2 cows. On the other hand, histidine, the mutated protein, only weakly holds on to BCM 7, so it is liberated in the GI tract of animals and humans who drink A1 cow milk.

BCM 7 has been shown to cause neurological impairment in animals and people exposed to it, especially autistic and schizophrenic changes. BCM 7 interferes with the immune response, and injecting BCM 7 in animal models has been shown to provoke Type-1 diabetes. Dr. Woodford's book presents research showing a direct correlation between a population's exposure to A1 cow's milk and incidence of autoimmune disease, heart disease, Type-1 diabetes, autism, and schizophrenia.

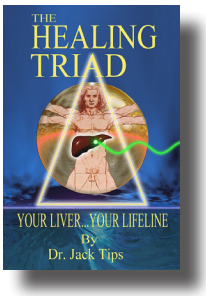
grass fed, A2 beef. Where did the U.S.A. public get the faulty information to avoid meat, eggs, and milk? It wasn't from savvy nutritionists!

So the ingestion of membrane-supportive phospholipids provides the nutrients that the membranes will gladly use to replace damaged areas, stop inflammation, and prime the ATP manufacturing process called beta oxidation. Because it's difficult to get what the membranes want from the SAD (Standard American Diet), people often turn to supplementation to provide that nutritional boost.

Such supplementation is already showing that Membrane Rejuvenation Therapy improves mitochondrial function, so this has powerful ramifications for people with chronic degenerative, autoimmune, and free radical pathological concerns. Also, improvements are being documented regarding heart, memory, neurological concerns as well as chronic fatigue syndrome and fibromyalgia[5].

In the USA, clinicians are using a product called VISTA1 & 2 (a rare formula containing cardiolipin and a dozen phospholipids and phospholipid precursors) with a certified organic, plant-derived multi B-vitamin and mineral product called Spectra1 & 2, in concert to lower inflammation as shown by reduction in homocysteine levels in the blood and repair damaged mitochondrial membranes as evidenced by significant improvements in energy. Such supplementation is universally needed and not contraindicated for people who are on interventive medical therapies.

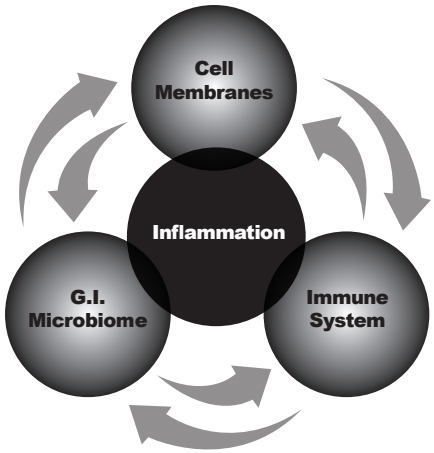
The New Healing Triad



In 1987, I authored a book entitled "*The Healing Triad – Your Liver, Your Lifeline.*[6]" It presented Dr. Alexander Stuart Wheelwright's research regarding Digestion, Elimination, and the Liver in light of botanical therapeutics and detoxification and a Chinese Medicine healing approach. While a cornerstone of 20th Century wisdom, it seems there is now a new Healing Triad for the 21st Century—the Intestinal Microbiome, the Immune System, and the Mitochondrial Membrane.

5 Agadjanyan, Vasilevko, Ghochikyan, Berns, Kesslak, Settineri, Nicholson. Nutritional supplement restores mitochondrial function and reduces moderately severe fatigue in aged subjects. Journal of Chronic Fatigue Syndrome 2003;11(3):23-26

6 The Healing Triad: Your Liver—Your Lifeline available at www.appleadaypress.com



To summarize the preceding information in light of the body's modern day struggle with escalating inflammation leading to dread diseases, we can see how an imbalance in the body's two immune systems – the innate first line defenses (Th-1), and acquired memory-based defenses (Th-2) has been altered by the increase of mitochondrial inflammatory messengers that elevate pro-cytokine activity (Interleukin 1-8 and Interleukin 1-beta[7]).

The elevated cytokines have a direct impact (either by accident or by design to use inflammation toward "adapt and survive") on the intestinal microbiome[8] biodiversity and proliferations of certain species (*firmicutes*) as well as mutations of existing species toward more confrontational engagements with the human immune system. This creates an inflammatory feedback loop that raises inflammation throughout the body.

The end result is a hypersensitive, hyper-inflammatory immune system that alters the intestinal microbiome which in turn alters the immune response. This is Nature's survival mechanism, but Nature seemingly never intended for it to operate in the absence of membrane replacement nutrients. The plight of today's people is that the switch is turned on, and few people are doing the right things to turn it off. Chronic inflammation leads directly to chronic-degenerative and autoimmune disease.

Viewing this inflammatory triad (or healing triad when nutrients are applied) in light of recent epigenetic information sets a stage that directly contradicts the medically espoused position of "There is no cure. All you can do is take suppressive drugs that cause terrible side effects." The answer is, and always has been, nutritional cooperation with Nature's prime directive to adapt and survive.

While drug antibiotics have done much to derange the intestinal microbiome and destroy biodiversity, the lack of viable phospholipids in the diet has also contributed to dysbiosis via the mitochondrial/immune system inflammatory processes. This is why there is an outcry from natural health advocates -- both trends come from the position of modern medicine with the beneficiary being Big Pharma selling overpriced drugs and making health care a system that is bankrupting the richest nation on earth. It's humbling and appalling to realize the benefits that can come from simple nutrition, or more specifically in the 21st Century, the dire need for specific phosopholipid supplementation.

Responding to this dire need, Dr. Shayne Morris developed VISTA 1 & 2 (Membrane Regeneration) with the specific, mitochondrial and other organelle membrane nutrients required for the body to initiate self-healing of damaged membranes and restore cellular energy. He also designed the eNRG (Quantum ATP) formula to support both beta oxidation and citric acid cycle ATP processes.

So, this discourse is a voice to include cardiolipin and phospholipid supplementation (VISTA) plus ATP support (eNRG) in conjunction with microbiome rejuvenation therapies – probiotics, fibers, enzymes,

7 Franchi, Munoz-Planillo, Nunez. Sensing and reacting to microbes through the inflammasomes. Nature Immunology, 2012;13(4): 325-333.

8 Sokol, Pigneur, Watterlot, Lakhdari, Bermúdez-Humarán, Gratadoux, Blugeon, Bridonneau, Furet, Corthier, Grangette, Vasquez, Pochart, Trugnan, Thomas, Blottière, Doré, Marteau, Seksik, Langella. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S Av.105(43); Oct 28, 2008

and anti-inflammatory botanicals; as well as to aim for increasing the intestinal microbiome biodiversity by using a wide variety of organic, fermented products such as fermented cabbage (raw sauerkraut), kefirs, raw milk, organic yogurt, kombucha, and even raw, organic (non pasteurized) beer.

So here's a cutting edge protocol that 'sandwiches' the fundamental processes with nutrients and directives to lower inflammation (re-set the set-point), increase biodiversity of the microbiome, and the all-important mitochondrial membrane rejuvenation:

Basic Membrane Rejuvenation Therapy

Do this in conjunction with the Systemic G.I. Wellness protocols – The Pathogen Purge and G.I. Wellness (Re-seeding/Leaky Gut)

With Breakfast

1 scoop Metabo-Shake (Glycemic Support) in water
1 each VISTA1 capsules (Membrane Regeneration)
3 droppers VISTA2 (Membrane Regeneration)
1 Spectra 1(Whole Food Multi Vit)

With Lunch

2 droppers Spectra 2

2 eNRG (Quantum ATP)

With Supper

1 each VISTA1 capsules (Membrane Regeneration)
3 droppers VISTA2 (Membrane Regeneration)
1 Spectra 1(Whole Food Multi Vit)

Comprehensive Membrane Rejuvenation Therapy

Before Breakfast

1 scoop Metabo-Shake (Glycemic Support) in water
3 droppers VISTA2 (Membrane Regeneration)
2 ROX (Anti-Ox w/ Resveratrol)
2 EVENTA (Cell Enzyme Corrector)

With Breakfast, and Supper

1 each VISTA1 capsules (Membrane Regeneration)
1 eNRG (Quantum ATP)
1 EPIC (Metabolic NO/ONOO anti-oxidant)
1 Spectra1 (organic, plant multi-vitamin/mineral)

Mid Afternoon

1 scoop Metabo-Shake (Glycemic Support) in water.
3 droppers VISTA2 (Membrane Regeneration)

With Supper

3 droppers Spectra2 (Multi Vit Fatty Acids)

Summary. The mitochondrial membrane is the key to the body's energy as well as the inflammatory processes. The inner mitochondrial membrane, the cristae, is probably the sensitive membrane to oxidative damage because of its unique membrane structure (cardiolipin) that is designed for oxidative phosphorylation and free radical generation.

When the cristae membrane becomes damaged, energy is reduced (fatigue), inflammosomes release, inflammatory cytokines are activated. This alters the microbiome biodiversity and raises the set point of inflammation throughout the body, and become a self-perpetuating, chronic inflammatory process that stresses the immune system and causes much collateral damage. This is the core of chronic-degenerative and autoimmune disease.

The body can correct this insidious, health destroying process if and when it has the various phospholipids such as the phosphatidyls: choline, serine, anolamine, inositol, and glycerol; as well as phosphatidic acid; cardiolipin; and cholesterol sulfate.

Correcting the intestinal microbiome and supplying an abundance of the cell membrane fatty acids offers a new solution for people to maintain their most optimal health and energy/vitality.