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Ascorbic Acid: A Personal Reflection, A Professional Review

In the early 1980s, Dr. Bland spent two years working with Dr. Linus Pauling at the Linus Pauling Institute. Dr. Bland begins this issue with a personal story of a discussion he had with Dr. Pauling about how his interest in vitamin C evolved.

The effect of ascorbic acid on cancer has been a subject of controversy for many years. In 1979, a review published in Cancer Research by Dr. Pauling, along with colleagues Cameron and Leibovitz, presented the scientific basis to support the use of ascorbic acid (AA) as a therapeutic agent in the treatment of cancer. In the years that followed, clinicians failed to reproduce Pauling's earlier reports. New knowledge on the pharmacokinetics and pharmacodynamics of AA and new clinical data have given a more complete understanding of the critical aspects of AA's therapeutic effect on cancer. In 2005, *Integrative Cancer Therapies* published a review with the objective of providing an updated scientific for the use of intravenous AA as adjuvant treatment for cancer patients. That same year, Riordan, et al. published the results of a clinical study suggesting that intravenous vitamin C therapy for cancer is relatively safe. REF #1-2

"Mitohormesis" for Health and Vitality

The hormesis perspective on biological systems under stress has yielded explanatory models for the beneficial influences on physiology of calorie restriction, intermittent fasting, exercise, and consumption of dietary phytochemicals. Examining molecular substrates of stress resistance is a new research front and a twist has emerged from recent experimental findings: Reactive oxygen species, derived from the mitochondrial electron transport system, may be necessary triggering elements for a sequence of events that result in benefits ranging from the transiently cytoprotective to organismal-level longevity. This perspective was dubbed the "mitohormesis" theory in an article published in *Medical Hypotheses*. In applying this perspective, it may be necessary for both the research community and the practicing physician to address organelle-level physiology. REF #3

Mitochondrial Signal Transduction and Dysfunctional Bioenergetics

The rate-of-living hypothesis proposes that higher rates of oxidative metabolism cause an increased production of reactive oxygen species (ROS), leading to oxidative damage and mitochondrial dysfunction with age. However, in some mouse models the tempo of aging appears to vary in an opposite manner than predicted by the rate-of-living hypothesis, with the least active having the shortest longevity. Mitochondrial uncoupling has been proposed as a mechanism that reduces reactive oxygen species production and could account for this paradox between longevity and activity. In 2007, researchers from the University of Washington published findings from their work using innovative optical and magnetic resonance spectroscopic methods applied to noninvasive measurements of ATP synthesis and oxygen uptake in vivo in human muscle. The results reject respiration

rate as the sole factor impacting the tempo of cellular aging. Instead, they support mild uncoupling as a mechanism protecting mitochondrial function. REF #4

Mitochondrial dysfunction has been implicated as a contributing factor in acute and chronic neurological disorders. In contrast with genetic forms of epilepsy, acquired epilepsy accounts for approximately 60% of all cases and is usually preceded by injury such as an episode of prolonged seizures, childhood febrile seizures, hypoxia, or trauma. The role of mitochondrial dysfunction in epilepsies is emerging, underscored by animal studies that show that epileptic seizures result in free radical production and oxidative damage to cellular proteins, lipids, and DNA. Research has focused on the role of oxidative stress and mitochondrial dysfunction both as a consequence and as a cause of epileptic seizures. REF #5

Since neuronal development and structure as well as axonal and synaptic activity involve mitochondrial genes, it is not surprising that most mtDNA diseases are associated with brain disorders. What about mtDNA and cognition? As of 2003, only one study had suggested an association, so a group of French researchers set out to provide direct evidence of mtDNA involvement in cognitive functioning using a mouse model. Their findings, published in *Nature Genetics*, were that in interaction with nuclear DNA (nDNA), mtDNA modified learning, exploration, sensory development, and the anatomy of the brain. REF #6

Insulin resistance appears to be the best predictor of the development of diabetes in the children of patients with type 2 diabetes. Researchers from the Howard Hughes Medical Institute and Yale University set out to find the responsible mechanism. Their data, published in the *New England Journal of Medicine* several years ago, supports the hypothesis that insulin resistance in the skeletal muscle of insulin-resistant offspring in patients with type 2 diabetes is associated with dysregulation of intramyocellular fatty acid metabolism. Additional data from other sources also supports the hypothesis that an age-associated decline in mitochondrial function contributes to insulin resistance in the elderly. REF #7-8

Why is a drug like metformin effective in the treatment of hyperglycemia- or insulin-resistance-related complications? According to experimental models, metformin has different cellular effects, some of which are not completely understood yet. Although it is clear that metformin has non-mitochondrial effects, since it affects erythrocyte metabolism, the mitochondrial effects of metformin are probably crucial in explaining the various properties of this drug. REF #9

It is Dr. Bland's suggestion that therapies that improve insulin sensitivity are antioxidant by nature because they improve mitochondrial bioenergetics, and in contrast, interventions that enhance mitochondrial dysfunction are associated with increased insulin resistance. One study demonstrated that one week of a high-sucrose diet altered mitochondrial pyruvate oxidation in rats and suggests that, in the context of a high-sucrose diet, impaired mitochondrial respiration could contribute to the development of insulin resistance. REF #10

Oxidative Damage and Diseases of the 21st Century

Some research has produced findings of a link between erythrocyte metabolism (particularly redox metabolism) and erythrocyte shape. It has been hypothesized that there is a correlation between erythrocyte morphology and erythrocyte oxidative damage in chronic fatigue syndrome (CFS). In an Australian study involving 31 CFS patients and 41 healthy control subjects, the evidence of oxidative damage in the CFS patients was statistically significant. The CFS patients also had significantly more stomatocytes in their blood than the normal subjects. REF #10

Dr. Martin Pall, a leading researcher and former FMU clinician of the month, has published numerous papers proposing an exquisite hypersensitivity to organic solvents in people with multiple chemical sensitivity (MCS). In his hypothesis, Dr. Pall suggests a mechanism centered on the activation of N-methyl-D-aspartate (NMDA) receptors by organic solvents producing elevated nitric oxide and peroxynitrite, leading in turn to increased stimulation and subsequent hypersensitivity of NMDA receptors. REF #11-12

In 2004, Dr. Bruce Ames, a highly respected researcher and Professor Emeritus at the University of California, Berkeley, published an article titled "A Role for Supplements in Optimizing Health: The Metabolic Tune-Up." Dr. Bland reviews this article and recounts a recent conversation with Dr. Ames about genomic instability. REF #13

Treating Mitochondrial Disorders

While progress has been made in defining the specific biochemical defects and underlying molecular mechanisms of mitochondrial disorders, limited information is available about the development and evaluation of effective treatment approaches. Metabolic therapies that have been reported to produce a positive effect include Coenzyme Q10 (ubiquinone); other antioxidants such as ascorbic acid, vitamin E, and lipoic acid; riboflavin; thiamin; niacin; vitamin K; creatine; and carnitine.

Coenzyme Q10 (CoQ10) is the most widely used supplement in the treatment of mitochondrial disorders because it transfers electrons from complexes I and II to complex III, a process that is coupled to ATP synthesis. In its reduced form (ubiquinol), CoQ10 also inhibits lipid peroxidation and can protect mitochondrial inner-membrane proteins and DNA from oxidative damage. CoQ10 also helps stabilize the OXPHOS complexes within the inner mitochondrial membrane by maintaining optimal membrane fluidity. REF #14

In a mouse study designed to test the prevalent view that uptake of exogenous CoQ10 by tissues other than plasma and liver either did not occur or was minimal, researchers found that uptake of exogenous CoQ10 was higher in mitochondria of heart and skeletal muscle than those in the liver. CoQ10 administration also elevated the α-tocopherol concentration in tissue homogenates and their mitochondria. REF #15

The efficacy of L-carnitine (LC) administration on fatigue, nutritional status, and oxidative stress has also been tested. As fatigue is one of the most common side effects of

chemotherapy and radiotherapy, one study was designed to test the efficacy and safety of LC in a population of patients with advanced cancer. In this study of 12 patients, LC was administered orally at 6 g/d for 4 weeks. The results were that nutritional variables (lean body mass and appetite) increased significantly after LC supplementation. Levels of reactive oxygen species decreased and glutathione peroxidase increased but not significantly. #16

The Marshall Protocol

The Marshal Protocol is a program developed by Dr. Trevor Marshall that some clinicians have been using with chronic fatigue syndrome. Advocates of this experimental approach have reported success in the relief of symptoms. Dr. Bland does not express an opinion about the efficacy of The Marshall Protocol, but instead maintains his long-held view that there is not one specific intervention that will work for all individuals. Reference/links are provided for those wanting to investigate The Marshall Protocol further.

Clinician/Researcher of the Month

Mary Ann Lila, PhD
University of Illinois
1021 Plant Sciences Laboratory, MC-634
1201 South Dorner Drive
Urbana, IL 61801

Dr. Mary Ann Lila is a well respected researcher in the field of phytochemistry. At the University of Illinois, Urbana, she heads the College of Agriculture, Consumer, and Environmental Sciences. Her research focuses on the bioactive properties of anthocyanins, proanthocyanidins, isoflavones and associated flavonoids from food crops and from intensively-managed bioreactor-based cell cultures derived from the same plant genotypes; and bioexploration in the global arena for endemic and indigenous plant species, whose extracts can interface with human therapeutic targets to maintain health and prevent chronic diseases.

Dr. Bland and Dr. Lila discuss phytochemicals and the secondary metabolites produced by plants, from a basic overview to xenohormesis (a concept discussed in recent issues of FMU). Dr. Lila has diverse research interests. She is part a botanical center based at Purdue University that is looking into how specific metabolites in plants can affect bone health, dementia, and other age-related diseases. Dr. Lila also belongs to an international biodiversity group working in central Asia, looking at plants that have bioactive properties (plants previously hidden from western medicine until the break-up of the former Soviet Union). REF #22-28

In Closing: Additional Comments about Secondary Metabolites

Dr. Bland closes this issue with additional insights and references concerning ongoing research into the benefits of phytochemicals, including two 2007 studies related to fruit/vegetable intake and cancer. REF #29-33

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