

# **Metabolic Correction: A Functional Biochemical Therapeutic Approach**

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Keywords: Metabolic Correction, chronic diseases, genetotropic disease, biochemical individuality, nutrient insufficiency, genetic polymorphism

## **Abstract**

Human development and physiology depend on myriad biochemical processes, many of which are codependent and interrelated. The rate and extent of many reactions depend on the enzymatic activity which, at the same time, depends on the bioavailability of micronutrient cofactors such as vitamins and minerals. To achieve a healthy physiological state, the organism needs biochemical reactions to occur at a certain rate and extent. This state is possible when the metabolic reactions reach full velocity and completion, which can be considered the optimal metabolic equilibrium. A combination of genetic makeup, erroneous dietary patterns, trauma, diseases, toxins, and environmental stressors will often elevate the demand of nutrients in order to attain the optimal metabolic equilibrium.

Metabolic Correction is a functional biochemical/physiological concept that explains how improvements in cellular biochemistry help the body achieve metabolic or physiological optimization. Brilliant minds such as Roger J. Williams, Linus C. Pauling, Jeffrey Bland, and Bruce N. Ames have contributed in a fundamental way to our understanding of the importance of micronutrients to attain the healthy state. The Metabolic Correction concept becomes important since our food is decreasing in nutritional value; diseases increase the demand for certain nutrients and medications deplete many nutrients. These nutrient insufficiencies are causing enormous cost due to increased morbidity and mortality. In summary, Metabolic Correction increases enzymatic function that enhances biological functions contributing to health improvement and well-being.

## **Metabolism, Physiologic Function a Genetic Polymorphism**

To achieve the best possible state of health, a particular metabolic equilibrium is necessary. The array of critical functions of vitamins, minerals, and other nutrients at the cellular level, and especially their role as cofactors in enzyme reactions is probably unrecognized or unappreciated by most health professionals. The whole significance of micronutrients in human metabolism has not been completely elucidated, simply due to the high complexity of cellular processes. Critical enzymes require metals such as copper, zinc, manganese, selenium, and vitamins such as the B-complex as an integral part of their molecular structure or mechanism of action. Enzymes play a critical role in regulating and orchestrating the velocity of the plethora of biochemical reactions that take place in living organisms.

Metabolic nutrition is generally recognized as the study of how diet and nutrition affect the body's metabolism. Nutrition in general is a very complex science, but its importance is relatively easy to understand. Aside from starvation there are three levels of nutrition: poor, fair, and good. Poor nutrition brings severe underdevelopment of the young as well as deficiency diseases such as beriberi, scurvy, pellagra, rickets, kwashiorkor, and all the ill-defined combinations and variations of these afflictions.<sup>1</sup> Fair nutrition is good enough to prevent the well defined deficiencies but not good enough to promote good health and proper development. This second-rate nutrition is unfortunately the kind that we have been taught to regard as satisfactory.<sup>1</sup> Good nutrition is the one that provides not only the needed energy but high-quality protein, carbohydrates, and fats, in addition to the necessary vitamins and minerals. The concept of a

balanced diet was developed to prevent deficiency diseases based on the knowledge that an appropriate mixture of food items will provide the minimum requirements of the nutrients needed by the body. We should be aware that this supposedly good nutrition may not be enough for physiological optimization leading to excellent health. We should acknowledge that food alone may not provide sufficient micronutrients for preventing deficiency.<sup>2</sup>

Inadequate dietary intakes of vitamins and minerals are widespread, most likely due to excessive consumption of calorie-rich, nutrient-poor, refined food (the hidden hunger concept). Suboptimal intake of micronutrients often accompanies caloric excess. These inadequate intakes may result in metabolic disruptions.<sup>3</sup> Episodic shortages of micronutrients were common during evolution. Natural selection favors short-term (emergency) survival at the expense of long-term health. Short term survival was achieved by allocating scarce micronutrients by triage.<sup>3</sup> As micronutrients become scarce, a triage mechanism for allocating scarce micronutrients is activated. This triage means, prioritization of the use of relatively scarce nutrients to the most fundamental life preserving functions. In metabolic reactions, enzymes involved in ATP synthesis would be favored over DNA repair enzymes, as well as production of immune system components and neurological chemicals. When there is a lack of synergistic components of the metabolic network, an array of negative metabolic repercussions arise, leading eventually to loss of healthy physiological equilibrium and the acceleration of degenerative diseases.

### Metabolic Correction

The Metabolic Correction concept provides the biochemical explanation of the utilization of nutrients for preventive and therapeutic purposes against disease. Metabolic Correction is a functional biochemical/physiological concept that clarifies how improvements in cellular biochemistry help the body achieve metabolic or physiological optimization. Impaired

or incomplete cellular biochemical reactions are amended with Metabolic Correction.

### The History of Metabolic Correction

Brilliant and incredibly knowledgeable pioneers ("medical mavericks") provided the groundbreaking basis of what we call Metabolic Correction. Their innovative scientific contributions have substantially advanced our understanding of molecular nutritional biochemistry and especially how it can influence the pathological or disease state.

In 1947, Dr. Roger J Williams contributed to the evolution of the understanding of the molecular origin of disease with the development of the concept of biochemical individuality.<sup>4</sup> He described anatomical and physiological variations among people and how they related to their individual responses to the environment and their particular physiology. He coined and gained recognition for the term *biochemical individuality* and how this related to differing nutritional needs for optimal function among different people.

*Molecular medicine* was a term used by two-time Nobel laureate in chemistry and peace Dr. Linus C. Pauling, in his landmark article on the mechanism of the cause of sickle cell anemia published in 1949.<sup>5</sup> It defined a new perspective on the origin of disease based upon the recognition that specific mutations of the genes can create an altered molecular environment and therefore the modified physiological function associated with specific diseases.

In 1950, Williams also coined the term *genetotrophic disease* to describe diseases that resulted from genetically determined nutritional metabolic needs not being met by the individual and which result in poor gene expression.<sup>6</sup> Patients with genetotrophic conditions have increased needs of one or more nutrients in order to achieve normal physiologic functioning. These conditions respond dramatically when enough of the required nutrients are provided. Many chronic diseases can be conceived as subtle genetotrophic diseases, as long as a nutrient supplementation fills a metabolic need that improves the patient's condition.

With this concept, Williams opened the eyes of the research and medical communities that expression of genes and therefore phenotypic function was modifiable through altered diet and nutritional status. He pointed out that human biochemical variation in function was much greater than nutrition and medicine recognized prior to his publications. We should also mention here that Dr. Henry Turkel was probably the first to clinically show that nutrition and supplementation can modify genetic programming with his work with Down syndrome.<sup>7</sup> Turkel was probably also the first clinician to use Metabolic Correction as therapy when he got rid of harmful gene expressions in retarded children by removing accumulated metabolic byproducts with nutrition and high-dose supplements improving cognition, physical health, and appearance of these children<sup>7</sup>.

The word *orthomolecular* was introduced by Pauling in "Orthomolecular Psychiatry," his seminal 1968 article published in the journal *Science*.<sup>8</sup> Pauling defined orthomolecular psychiatry as the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the body. He later broadened this definition to other diseases to name it orthomolecular medicine, which he defined as the preservation of good health and the treatment of disease by varying the concentrations in the human body of substances that are normally present in the body and are required for health. The adjective orthomolecular is used to express the idea of the right molecule in the right concentration. The key idea in orthomolecular medicine is that genetic factors affect not only the physical characteristics of individuals, but also their biochemical milieu. Biochemical pathways of the body have significant genetic variability and diseases such as atherosclerosis, cancer, schizophrenia, or depression are associated with specific biochemical abnormalities that are causal or contributing factors in the illness. Several arguments support

# Metabolic Correction

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the thesis that the optimum molecular concentrations of substances may not be achieved solely by dietary means. The need for essential *nutrilites* (vitamins, essential amino acids, and essential fatty acids) may differ from the (average) daily amounts recommended for the general population.

Dr. Jeffrey S. Bland created the concept of functional medicine in 1991, a form of personalized medicine that deals with primary prevention and underlying causes of disease, instead of just the symptoms of serious chronic diseases. Functional medicine is anchored by an examination of core clinical imbalances that underlie various disease conditions. Those imbalances arise as environmental inputs such as diet, nutrients (including air and water), toxins, exercise, and trauma together with a unique set of genetic predispositions, attitudes, psychological stress, and beliefs. The core clinical imbalances that arise from malfunctions include hormonal and neurotransmitter, oxidation-reduction and mitochondropathy, detoxification and biotransformation, immune, inflammatory, digestive, absorptive, microbiological, and structural imbalances from cellular membrane function to the musculoskeletal system. Improving balance is the precursor to restoring health and it involves much more than treating the symptoms. Functional medicine is dedicated to improving the management of chronic disease by integrating the interventions at multiple levels to address these core clinical imbalances and to restore each patient's functionality and health. Functional medicine is not a unique and separate body of knowledge. It is grounded in scientific principles and information widely available in medicine today, combining research from various disciplines into highly detailed yet clinically relevant models of disease pathogenesis and effective clinical management. Bland published a landmark book in 1999 titled *Genetic Nutrioneering*, in which he

explains how proper nutrition and supplementation can modify genetic expression to create the best possible health outcomes.<sup>9</sup>

Later, Dr. Bruce N. Ames presented his triage theory of optimal nutrition in 2006, which states that the human body prioritizes the use of vitamins and minerals when it is getting an insufficient amount of them in order to keep functioning.<sup>3</sup> Triage means deciding which patients to treat when faced with limited resources. When faced with limited nutritional resources, the human physiology must decide which biological functions to prioritize in order to give the total organism, and the species, the best chance to survive and reproduce. Under such a limited scenario, the body will always direct nutrients toward short-term health and survival capability and away from regulation and repair of cellular DNA and proteins that optimize health and increase longevity. Ames's research shows how bodily insults accumulate over time as a result of vitamin and mineral insufficiencies, and how this can lead directly to age-related diseases. The triage hypothesis states that the risk of degenerative diseases (associated with aging, including cancer, cognitive decline, and immune dysfunction) can be decreased by ensuring adequate intake of micronutrients.<sup>3,10-13</sup> While short-term deficiencies or insufficiencies are common, they are often not taken seriously by mainstream physicians.

*Metabolic Correction* is a functional term introduced by Dr. Michael J. Gonzalez and Dr. Jorge R. Miranda-Massari in 2011 to explain the mechanism of how nutrients can correct biochemical disruptions that promote the disease state.<sup>14</sup> Metabolic Correction embraces all these previously described biochemical/physiological concepts to explain how improvements in cellular biochemistry may help the body achieve metabolic or physiological optimization. Metabolic Correction intervenes with impaired biochemical reactions that are associated with a lack of well being. In

other words, Metabolic Correction is a fine-tuning of the cellular physiology to improve function, therefore preserving health, preventing tissue damage, and reverting disease.

## The 3 Main Reasons to Use Metabolic Correction

### *Inferior Nutritional Value of Food and Availability of Nutrient-Dense Foods*

We must eat a wide variety of food to obtain the substances that we need. A big problem that we face is that the nutritional value of foods that people eat seems to be greatly inferior to the listed values given in food tables. A study looking into this issue showed declines in protein of 6%; calcium, 16%; phosphorus, 9%; iron, 15%; riboflavin, 38%; and vitamin C, 20%.<sup>15</sup> There is a dilution effect, in which yield-enhancing methods such as fertilization and irrigation may decrease nutrient concentrations, an environmental dilution effect. Recently, evidence has emerged that genetically based increases in yield may have the same result, a genetic dilution effect. Modern crops that grow larger and faster cannot necessarily acquire nutrients at the same, faster rate, whether by synthesis or from the soil. Today's foods are not as nutritious as those eaten in the past. US and UK governmental statistics show a decline in trace minerals of up to 76% in fruit and vegetables over the period 1940 to 1991.<sup>16</sup> The nutritional decline findings alone give reason to eat organic fruits and vegetables. In fact, for nearly all nutrients, organic fruits and vegetables remain the most nutrient-dense foods. This information makes the updated food pyramid not so much current as reflective of the need for an increase in fruits and vegetables in order to get the same nutritional benefits. Also, Americans on average do not even come close to the recommendations to limit added sugars, refined carbohydrates, and added fats and oils.

### *Adverse Side Effects of Medication and Iatrogenic Deaths*

More than 100,000 deaths are reported annually due to medication properly prescribed and taken as

## Metabolic Correction

directed.<sup>17,18</sup> The incidence of serious and fatal adverse side effects in US hospitals is extremely high; these are frequent and more so than generally recognized. Fatal adverse side effects appear to be the fourth leading cause of death in the US. If medication is necessary, providing Metabolic Correction principles may reduce medication requirements, reduce adverse side effects, and improve therapeutic outcome.<sup>14</sup>

### *Compensate for the Increased Demand of Nutrients Due to the Disease State*

Burns lead to loss of protein and essential nutrients.<sup>19</sup> Surgery increases the need for zinc, vitamin C, and other nutrients involved in cellular-tissue repair.<sup>20</sup> Broken bones need calcium, magnesium, and vitamin C for healing.<sup>21</sup> Infections challenge the immune system and place high demand on nutritional resources such as zinc, B-complex vitamins, and vitamin C.<sup>22</sup> The same nutritional demand is present when one is exposed to chemical, physical, and emotional stress. Chronic disease sufferers are at higher risk of interaction of drugs and nutrients. There are thousands of conceivable genetic defects (inborn or acquired), so it is likely that many people have higher genetic requirements for many micronutrients. We need a better understanding of the interrelationship between nutritional biochemistry and the disease-pathological state.

### **Biochemical Mechanism of Metabolic Correction: Molecular Concentrations and Rate of Reaction: Ames Km Concept**

The majority of the chemical reactions that take place in living organisms are catalyzed by enzymes. The mechanisms of enzyme-catalyzed reactions in general involve (1) the formation of a complex between the enzyme and a substrate and (2) the breakdown of this complex to form the product of the reaction. The rate determining step is usually the breakdown of the complex to form the product. Under conditions such that the concentration of the complex corresponds to equilibrium with the

enzyme and the substrate, the rate of the reaction is given by the Michaelis-Menten equation.<sup>8</sup>

The rate of an enzyme-catalyzed reaction is approximately proportional to the concentration of the reactant, until concentrations that largely saturate the enzyme are reached. The saturating concentration is larger for a defective enzyme with decreased combining power for the substrate than for the normal enzyme. For such a defective enzyme, the catalyzed reaction could be made to take place at or near its normal rate by an increase in the substrate concentration. This mechanism of action of gene mutation is only one of several that lead to disadvantageous manifestations that could be overcome by an increase in the concentration of enzymatic cofactors. These binding problems may result in metabolic inefficiency with the accumulation of metabolic byproducts. In general, this is the law of mass action: as the vitamin and mineral concentration increases, enzyme efficiency increases. These considerations obviously suggest a rationale for Metabolic Correction wherein you provide the required cofactors in the amount needed to improve function. This increased enzyme efficiency may allow a genetic defect to be overcome. This biochemical activity follows the chemical principle of Le Chatlier, which states that when stress is applied in an equilibrium situation, it will move in the direction that minimizes stress. In this case there is an unfavorable equilibrium of active enzyme that with the addition of the necessary nutrients will be moved toward a more physiologically favorable metabolic state.<sup>23</sup>

Many human genetic diseases due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding coenzyme, which can partially restore the enzymatic activity.<sup>10</sup> Several single nucleotide polymorphisms in which the variant amino acid reduces coenzyme binding and thus enzymatic activity can be remedied by raising

cellular concentrations of the cofactor through high-dose nutrient therapy.

Inadequate intakes of vitamins and minerals from food can lead to DNA damage, mitochondrial decay, and other pathologies. Ames suggests that evolutionary allocation of scarce micronutrients by enzyme triage is an explanation for why DNA damage is commonly found in micronutrient deficiency.<sup>3</sup> Motulsky has also argued that many of the common degenerative diseases are the result of imbalanced nutritional intake with genetically determined needs.<sup>24,25</sup>

As an example, folic acid and vitamin B12 have an important function in the maintenance of nuclear and mitochondrial genome integrity. Both *in vivo* and *in vitro* studies with human cells show that deficiency of these vitamins causes an array of problems in the nuclear and mitochondrial DNA that can be minimized with increased folate and cobalamin concentrations. In order to acquire the protective effect of these vitamins, they are needed in concentrations that are obtained at intake levels above the current recommended dietary intakes of folate (>400 µg/day) and vitamin B12 (>2µ/day).<sup>26</sup>

Chromosome breaks lead to mutations that precede tissue damage and disease. Many types of physiological impairments due to inadequacy of vitamins and minerals can lead to suboptimal organ-system function including poor drug metabolism, insufficient neurotransmitter production, and impaired immune defenses. Chronic vitamin-mineral undernutrition reduces immune competency and central nervous system efficiency, while increasing morbidity, which may lead to increases in degenerative diseases. This approach to optimizing health by improving enzyme efficiency and thereby metabolism and physiology is the basis of Metabolic Correction.

An example of Metabolic Correction is that high-dose B vitamins can counteract a poor Km. As many as

# Metabolic Correction

► one-third of mutations in a gene result in the corresponding enzyme having an increased Km (decreased binding affinity) for a coenzyme, causing a lower rate of reaction.<sup>10,11</sup> About 50 different human genetic diseases due to a poorer binding affinity of the mutant enzyme for its coenzyme can be remedied by feeding high-dose B vitamins, which raise levels of the corresponding coenzyme; many polymorphisms also result in a lowered affinity of enzyme for its coenzyme and thus may be in part remediable.<sup>10</sup>

To summarize, Metabolic Correction has two important biological actions: (1) optimization of cellular function by improving enzymatic efficiency and (2) producing a pharmacological effect to correct abnormal cell function due to a biochemical disarray occasioned by the disease process.

An optimum intake of micronutrients and metabolites, which varies with age, environmental factors, and genetics, should tune up metabolism and markedly increase health at a modest cost, particularly for the poor, obese, and elderly.<sup>11</sup>

## Deficiency, Marginal Deficiency, Insufficiency

A nutrient deficiency is a physiological state in which a depletion of a nutrient is associated with the impairment of certain biochemical reactions and lack

of well-being. A marginal deficiency or insufficiency refers to the early stage of the deficiency or an early shortage of the needed nutrient to cover all the necessary biochemical pathways to optimize physiology to be able to reach the healthy state.

Deficiencies have five important stages: (1) Depletion stage, or preliminary deficiency stage, in which the body stores are gradually depleted of the necessary cofactors; (2) biochemical stage, or secondary deficiency stage, in which the functional enzymes are decreased and the body manifests a decline in function due to the lack of necessary cofactors; (3) physiological stage, or tertiary deficiency stage, in which enzyme activity is sufficiently impaired to affect immune and behavioral parameters. Personality changes and decrease in the resistance of disease occur. This is accompanied by a variety of nonspecific symptoms such as loss of appetite, depression, irritability, anxiety, insomnia, and somnolence, in which the person may not be sufficiently ill to seek medical attention but his general health is far from optimal; (4) clinical stage, or semifinal deficiency stage, in which classical clinical deficiency disease is manifest; (5) anatomical stage, or final deficiency stage, in which death will occur without any nutritional intervention. Suboptimal intake of

vitamins just barely above levels causing vitamin deficiency is a risk factor for chronic diseases and common in the general population, especially in the elderly.<sup>27-29</sup>

## 10 Principles That Identify the Concept of Metabolic Correction in Disease Therapy

1. Metabolic Correctors, along with proper nutrition, come first in medical treatment. Knowledge of the safe and effective use of the combination of nutrients, enzymes, hormones, and other naturally occurring molecules in their active forms is essential to assure an effective therapeutic outcome. However, some patients may need more acute treatment for their particular condition, for which pharmacological therapy is recommended.
2. Metabolic Correctors have a low risk of toxicity. Pharmacological drugs always carry a higher risk and therefore should be of second choice if there is a Metabolic Correction alternative treatment.
3. Some laboratory tests might be useful in identifying the nutritional needs of some patients but these tests may not be readily accessible to all patients or may present certain limitations. In addition, some laboratory tests do not necessarily reflect nutrient and enzyme levels within specific organs or tissues, particularly in the nervous system. For many patients therapeutic trial and dose titration is often the most practical therapy approach, especially when utilizing synergistic Metabolic Correction formulations.
4. Biochemical individuality is a central precept of Metabolic Correction. Hence, the search for optimal nutrient combination doses is a practical issue.



Dr. Michael J. Gonzalez is professor at the Nutrition Program, School of Public Health in the Medical Sciences Campus, University of Puerto Rico, and adjunct faculty at the University of Western States. Dr. Gonzalez is a Fellow of the American College of Nutrition and has authored over 200 scientific publications. He has served as a member on several scientific editorial boards. He has served as consultant for several companies where he has been responsible for designing formulations of nutritional supplements and pharmaceutical products. He has also been a consultant for the Center for the Improvement of Human Functioning (now Riordan Clinic), in Wichita, Kansas. He has obtained several research awards for his work on nutrition and cancer. He is currently codirector of RECNAC II project and research director of the InBioMed Project Initiative. Dr. Gonzalez also serves as a nutrition consultant to the Puerto Rican Basketball National Team and is part of the Medical Commission of the Puerto Rican Basketball Federation. He is part of the medical staff of the Vaqueros de Bayamon professional basketball team. He is in a part-time clinical practice with Dr. Miguel J. Berdiel in Ponce, PR. In December 2013, Dr Gonzalez was exalted as Distinguished Ponceño in Medicine. In 2015 he was selected as member to the prestigious Puerto Rican Academy of Arts and Sciences and to the Iberoamerican Academy of Culture and Sciences.

Drs. Gonzalez and Jorge Miranda-Massari, founders of InBioMed, are leaders in the development of nontoxic chemotherapy treatments for cancer. The findings of their work with intravenous vitamin C as an anticancer agent, published in 2002, were confirmed by the NIH in 2005. They published the first phase I clinical study utilizing intravenous vitamin C for treatment of terminal cancer patients in 2005, and also published in 2005 the most comprehensive review on vitamin C and cancer as a follow-up on the work of two-time Nobel laureate Dr. Linus C. Pauling. They have brought many new concepts into the scientific field, such as the bioenergetic theory of carcinogenesis, the systemic saturation phenomenon of intravenous vitamin C, and the metabolic correction concept for disease treatment and prevention. Dr. Gonzalez was inducted into the International Hall of fame of Orthomolecular Medicine in April 2016

# Metabolic Correction

Doses of nutrients and their combinations above the recommended daily allowances are often effective. Many patients tolerate megadoses and respond well; however, dose titration is indicated in otherwise unresponsive cases.

5. The Recommended Daily Allowance (RDA) of the United States Food and Nutrition Board is intended for normal, healthy people. By definition, diseased patients are not normal or healthy and not likely to be adequately served by the RDA. Practically every person is deficient or insufficient at some level of nutrients due to our poor diet.
6. Environmental pollution of air, water, and food is common. Diagnostic search for toxic pollutants is justified.
7. Optimal health is a lifetime challenge. Biochemical needs change and our Metabolic Correction prescriptions need to change based upon follow-up, repeated testing, and therapeutic trials to permit fine-tuning of each prescription and to provide a degree of the best possible health outcome.
8. Nutrient related disorders are always treatable and deficiencies and insufficiencies are curable. To ignore their existence is malpractice.
9. Genetic and hereditary disorders are often responsive to Metabolic Correction.
10. Inspire the patient to realize that health is not merely the absence of disease but the positive attainment of optimal function and well-being. This requires an active role of the individual in his lifestyle, a commitment to continuous education and a responsible attitude with his health.

## Conclusion

To run your metabolism effectively, you need the basic macronutrients required for fuel, fat, protein, and carbohydrate. But you also need 15 or so vitamins that are coenzymes and 15 or so minerals that are required cofactors by enzymes, and then you need two essential fatty acids, omega-3 and omega-6, and also there are seven or eight essential amino acids. In addition other important nutrients, such as coenzyme Q10, acetyl-L-carnitine, lipoic acid, must be considered in our quest for physiological optimization. Virtually every metabolic pathway requires micronutrients.

What determines the optimal concentration of a nutrient is its physiological functionality. Many people do not function at 100% efficiency; nevertheless, they do not present any

detectable disease or severe symptoms but can improve their functionality if supplied with the needed substances in the optimum concentrations. Certain individuals have a greater need than that provided by the diet (even a good dietary regime). Their needs may vary from 10 to 1000 times the physiological requirement. This could be caused by digestive problems, malabsorption, food sensitivities, difficulty in the metabolism of certain amino acids, fatty acids, complex carbohydrates, low levels in the precursors of neurotransmitters, and so on.

This lack of needed cofactors has the problem that it shows no specific symptoms. Some vague symptoms such as lethargy, irritability, insomnia, and difficulty in concentrating may be present. It also affects the body's ability to resist disease and infection; its ability to recover from exercise, surgery, disease; the ability of the brain to function at a high level. Detecting and treating disease at its earliest stages of cellular biochemical abnormality, rather than waiting for clear clinical symptoms, is cost effective and of benefit to the patient. We must have very clear in our minds that nutrient deficiency diseases are the end product of a long and complex series of nutrient depletion reactions.

It should also be addressed here that vitamins also have certain influences on metabolism that are not related to coenzyme effects. Vitamins can have effects upon a specific cellular organelle, hormone, or supramolecular structure within a cell that may optimize its function.

Deficiencies in these micronutrients may not be severe enough to create immediate clinical symptoms, but the long-range implications could lead to an increased risk of diseases.

We need to abandon outdated paradigms of nutrient intake merely to prevent deficiencies and expand them to prevent and treat chronic diseases and achieve optimal health with Metabolic Correction.

## Notes

1. Williams RJ. Supernutrition as a strategy for the control of disease. *J Orthomol Psychiatry*. 1972;1:98–103.
2. Misner B. Food alone may not provide sufficient micronutrients for preventing deficiency. *J Int Soc Sports Nutr*. 2006;3:51–55.
3. Ames BN. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. *Proc Natl Acad Sci USA*. 2006;103:17589–17594.
4. Williams RJ. Biochemical individuality and its implications. *Chem Eng News*. 1947;25(16):1112–1113.
5. Pauling L, Itano H, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science*. 1949;110: 543–548.
6. Williams R. Concept of genetotrophic disease. *Nutr Rev*. 1950;8: 257–60.
7. Turkel H. Medical amelioration of Down's Syndrome incorporating the orthomolecular approach. *J Orthomol Psychiatry*. 1975;4:102–115.
8. Pauling L. Orthomolecular psychiatry. Varying the concentrations of substances normally present in the human body may control mental disease. *Science*. 1968,160(3825):265–271.
9. Bland J. *Genetic Nutrioneering*. Los Angeles: Keats Publishing; 1998.
10. Ames BN, Elson-Schwab I, Silver EA. High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme-binding affinity (increased Km): Relevance to genetic disease and polymorphisms. *Am J Clin Nutr*. 2002;75:616–658.
11. Ames BN. The metabolic tune-up: metabolic harmony and disease prevention. *J Nutr*. 2003;133(5 Suppl 1):1544S–1548S.
12. Ames BN. A role for supplements in optimizing health: the metabolic tune-up. *Arch Biochem Biophys*. 2004;423(1):227–234.
13. Ames BN, Suh JH, Liu J. Enzymes lose binding affinity for coenzymes and substrates with age: A strategy for remediation. In: Rodriguez JKR, Kaput J, eds. *Nutrigenomics: Discovering the Path to Personalized Nutrition*. Hoboken: John Wiley & Sons Inc.; 2006:277–293.
14. Miranda-Massari JR, Gonzalez MJ, Jimenez FJ, Allende-Vigo MZ, Duconge J. Metabolic correction in the management of diabetic peripheral neuropathy: improving clinical results beyond symptom control. *Curr Clin Pharmacol*. 2011;6(4):260–273.
15. Davis DR, Epp MD, Riordan HD. Changes in USDA food composition data for 43 garden crops, 1950 to 1999. *J Am Coll Nutr*. 2004;23(6):669–682.
16. Worthington V. Nutritional quality of organic versus conventional fruits, vegetables, and grains. *J Altern Complement Med*. 2001;7(2):161–173.
17. Leape LL. Institute of Medicine medical error figures are not exaggerated. *JAMA*. 2000;284(1):95–97.
18. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279(15):1200–1205.
19. Prins A. Nutritional management of the burn patient. *S Afr J Clin Nutr*. 2009;22(1):9–15.
20. Rahm DH, Labovitz JM. Perioperative nutrition and the use of nutritional supplements. *Clin Podiatr Med Surg*. 2007;24(2):245–259.
21. Kakar S, Einhorn T. Importance of nutrition in fracture healing. In: Holick M, Dawson-Hughes B, eds. *Nutrition and Bone Health*. Totowa, NJ: Humana Press; 2004.
22. Bendich A. Antioxidant vitamins and human immune responses. *Vit Horm*. 1996;52: 35–62.
23. Bland J. The justification for vitamin supplementation. *J Holistic Med*. 1981;3:12–22.
24. Motulsky A. Human genetic variation and nutrition. *Am J Clin Nutr*. 1987;45:1108–1113.
25. Motulsky A. Nutrition and genetic susceptibility to common diseases. *Am J Clin Nutr*. 1992; 55:1244S–1245S.
26. Fenech M. Folate (vitamin B9) and vitamin B12 and their function in the maintenance of nuclear and mitochondrial genome integrity. *Mutat Res*. 2011.
27. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. *JAMA*. 2002;287(23):3127–3129.
28. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA*. 2002;287(23):3116–3126.
29. Saul A. Can vitamin supplements take the place of a bad diet? *J Orthomol Med*. 2003;18:213–216.