Metabolic Correction: A Functional Explanation of Orthomolecular Medicine

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Abstract *Vitamins, minerals and other micronutrients take critical roles in a wide variety of highly complex and integrated cellular processes in human biochemistry. The rate and extent of the enzymatic activity that determines these processes depend on the bioavailability of these micronutrients. The healthy state where optimal (maximum) functioning, health and wellbeing is achieved; may be attained by metabolic optimization. This state is achieved when we facilitate the metabolism to reach full velocity and completion of reactions which can be considered the optimal metabolic equilibrium. A combination of genetic makeup, diet, trauma, diseases, toxins and environmental stressors among others are conditions that will often elevate the demand of nutrients in order to achieve 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 nutrients and medications can deplete 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 better health and wellbeing.*

Origin of the Problem

Maximum or optimal health requires metabolic harmony. The multiplicity of critical functions of vitamins, minerals and other nutrients at the cellular level, and especially their role as cofactors in enzyme reactions that protect genes from mutations and repair gene damage is probably unrecognized or unappreciated by most health professionals. It can be argued that the true importance of vitamins in human biochemistry is far from fully elucidated, simply due to the high complexity of cellular processes. What is commonly ignored and not fully appreciated is the essential role that various minerals play in human biochemistry. Critical enzymes require such metals as copper, zinc, manganese, selenium, etc. as an integral part of their molecular structure or mechanism of action. Enzymes play a critical role in regulating and orchestrating the rates of the multitude 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 to 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.[1] Fair nutrition is good enough to prevent the well-defined deficiencies, but not good enough to promote good health and proper development. This mediocre nutrition is unfortunately the kind which we have been taught to regard as satisfactory.[1] 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.[2]

Inadequate dietary intakes of vitamins and minerals are widespread, most likely due to excessive consumption of calorie-rich, nutrient poor, refined food. Sub-optimal intake of micronutrients often accompanies caloric excess. These inadequate intakes may result in metabolic disruptions.[3] Episodic shortages of micronutrients were common during evolution. Natural selection favours short term (emergency) survival at the expense of long term health.[3] Short term survival was achieved by allocating scarce micronutrients by triage.[3] 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 adenosine triphosphate (ATP) synthesis would be favoured over deoxyribonucleic acid (DNA) repair enzymes; as well as the 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, eventually leading to loss of healthy physiological equilibrium and the acceleration of degenerative diseases.

Metabolic Correction

The Metabolic Correction concept provides the biochemical elucidation of the utilization of nutrients for preventive and therapeutic purposes against disease. Metabolic Correction is a functional biochemical/physiological concept that explains 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 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 molecular origin of disease with the development of the concept of "Biochemical Individuality," which refers to the differing nutritional needs for optimal function among different people.[4] He also described anatomical and physiological variations among people, and how these impacted their disease susceptibility and nutritional requirements.

"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 anaemia published in 1949.[5] He defined a new perspective on the origin of disease based upon the recognition that specific gene mutations can create an altered molecular environment, which therefore modified physiological function associated with specific diseases.

In 1950, Williams also coined the term "Genetotrophic Disease" to describe diseases which resulted from genetically determined nutritional metabolic needs not being met by the individual, and which result in poor gene expression.[6] Patients with genetotrophic conditions have increased needs of one or more nutrients in order to achieve normal physiologic functioning. These conditions respond favourably when enough of the required nutrients are provided. Many chronic diseases can be conceived as subtle genetotrophic diseases, as long as nutrient supplementation fills a metabolic need to improve a 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. The need for essential nutrients, which he referred to as "nutrilites" (i.e., vitamins, essential amino acids, and essential fatty acids), differs from the (average) daily amounts recommended for the general population.

The word "Orthomolecular" was introduced by Pauling in his seminal paper, Orthomolecular Psychiatry, published in 1968.[7] 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 include other diseases and amended it to "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 term, "orthomolecular" is used to express the idea of the right molecules 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 which are causal or contributing factors of the illness.

Dr. Jeffrey S. Bland created the concept of "Functional Medicine" in 1991, which is a form of personalized medicine that deals with primary prevention and underlying causes, rather than only 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 from 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, and 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, *Genetic Nutritioneering*, in which he explains how proper nutrition and supplementation can modify genetic expression to create better health outcomes.[8]

In 2006, Dr. Bruce N. Ames presented his "Triage Theory" of optimal nutrition that states that the human body prioritizes the use of vitamins and minerals when it is getting an

insufficient amount of them to be able to keep functioning.[3] 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. While short-term deficiencies or insufficiencies are common, they are often not taken seriously by mainstream physicians. Under such 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 optimizes health and increases longevity. Dr. Ames's research shows how bodily insults accumulated over time as a result of vitamin and mineral insufficiencies and 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.[3,9-12]

"Metabolic Correction" is a functional term introduced by Drs. Michael J. Gonzalez and Jorge R. Miranda-Massari in 2011 to explain the mechanism of how nutrients are capable of correcting biochemical disruptions that promote the disease state.[13] 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.

Why Metabolic Correction?

Inferior nutritional value of food and availability of nutrient dense foods

We need to eat a wide variety of food to obtain the substances we need. A big problem we face is that the nutritional values of foods that people eat seem to be greatly inferior to the listed values given in food tables. A study that assessed this issue showed declines in: protein (-6%), calcium (-16%), phosphorus (-9%), iron (-15%), riboflavin (-38%), and vitamin C (-20%).[14] There is a dilution effect, in which yield-enhancing methods like 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 are not necessarily able to 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. A report pointed out that US and UK Government statistics show a decline in trace minerals of up to 76% in fruit and vegetables over the period 1940 to 1991.[15] 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. Americans on average do not even come close to the recommendations to limit added sugars, refined carbohydrates, added fats and oils.

Adverse side effects of medication and iatrogenic deaths

There are more than 100,000 deaths annually due to medication properly prescribed and taken as directed.[16,17] The incidence of serious and fatal adverse side effects in US hospitals is extremely high, as they 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 requirement, reduce adverse side effects and improve outcome.[13]

Compensate for the increased demand of nutrients due to the disease state

Burns lead to loss of protein and essential nutrients.[18] Surgery increases the need for zinc, vitamin C and other nutrients involved in cellular-tissue repair.[19] Broken bones need calcium, magnesium and vitamin c for healing.[20] Infections challenge the immune system and place high demands on nutritional resources such as zinc, B-complex vitamins and vitamin C.[21] The same nutritional demand is present when exposed to chemical, physical and emotional stress. Chronic disease sufferers are at higher risk of interactions between 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

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 products of the reaction. The rate determining step is usually the breakdown of the complex to form the products. 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.[7]

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 by-products. 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 where you provide the needed 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 to the direction to minimize stress. In this case there is an unfavourable equilibrium of active enzyme that with the addition of the necessary nutrients will be moved toward a more physiologically favourable metabolic state.[22]

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.[9] 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.[3] Ames suggests that evolutionary allocation of scarce micronutrients by enzyme triage is an explanation of why DNA damage is commonly found on micronutrient deficiency.[3] Also, Motulsky has argued that many of the common degenerative diseases are the result of the imbalance nutritional intake with genetically determined needs.[23,24]

As an example, folic acid and vitamin B_{12} 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 which 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 B_{12} (>2μ/day).25

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 defences. Chronic vitamin-mineral undernutrition reduces immune competency and central nervous system efficiency; while increases morbidity which may lead to increases in degenerative diseases. This approach to optimize 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 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.[9,10] 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 coenzyme[9] and thus may be in part remediable.

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 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.[10]

Ten 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 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 should be the second choice if there is a metabolic correction alternative available.

3. Some laboratory tests might be useful in identifying the nutritional needs of some patients 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. Doses of nutrients and their combinations above the recommended daily allowances are often effective. Many patients tolerate optimal doses and respond well; however, dose titration is indicated in otherwise unresponsive cases.

5. Recommended daily allowances of nutrients are intended for normal, healthy people. By definition, diseased patients are not normal or healthy and not likely to be adequately served by obtaining recommended daily allowances. Practically every person

is deficient or insufficient at some level due to an insufficient 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 patients 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, and a commitment to continuous education along with a responsible attitude about health.

Conclusion

To encourage the most efficient metabolism, we need the basic macronutrients required for fuel, fat, protein and carbohydrate. But we also need 15 or so vitamins that are co-enzymes and 15 or so minerals that are required in enzymes, and then we 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, and 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. While most people function below 100% efficiency, they nevertheless do not present with any detectable disease or obvious (i.e., significant symptoms), yet we can improve their functionality if we supply them with the needed micronutrient substances in the optimum concentrations. Certain individuals have a greater need than that supplied by the diet (even if on a good dietary regime). This could be caused by digestive problems, malabsorption, food sensitivities, metabolic dysfunction, low levels in neurotransmitter precursors, etc. This lack of needed micronutrient cofactors manifests insidiously and is difficult to identify. Some vague symptoms, such as lethargy, irritability, insomnia and difficulty in concentrating, may be present. Also, this affects the body's ability to resist disease and infection, its ability to recover from exercise, surgery, disease, and the ability of the brain to function at an optimal 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. Nutrient deficiency diseases are the end product of a long and complex series of nutrient depletion reactions. We need to abandon outdated paradigms of nutrient intake merely to prevent deficiencies and expand them to prevent chronic diseases and achieve optimal health with metabolic correction.

Competing Interests

The authors declare that they have no competing interests.

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