Chronic Diseases as Inborn Errors of Metabolism: The Metabolic Correction Therapy Approach.

Michael J. Gonzalez¹, Jorge R. Miranda-Massari², Jorge Duconge³, Juan Pablo Arroyo⁴

¹Univeristy of Puerto Rico, Medical Sciences Campus, School of Public Health, Department of Human Development, Nutrition Program, School of Pharmacy, ²Department of Pharmacy Practice, ³Department of Pharmaceutical Sciences, San Juan, PR 00936, University of South Florida, ⁴Department of Applied Anthropology, Tampa, FL.

Key Words: Metabolic Correction, Chronic Disease, Inborn errors of Metabolism

Introduction:
The term inborn error of metabolism was coined by British physician, Archibald Garrod (1857-1936), in the early 20th century (1908). He is known for the "one gene, one enzyme" hypothesis, which arose from his studies on the nature and inheritance of alkaptonuria. His seminal text, Inborn Errors of Metabolism was published in 1923 (1).

Inborn errors of metabolism comprise a large number of genetic diseases which involves disorders of metabolism. The majority are due to defects of single genes that code for enzymes. Inborn errors of metabolism are inherited disorders. These disorders may be caused by the altered activity of essential enzymes, deficiencies of the substances that activate the enzymes, or faulty transport of important metabolic compounds.

Inborn errors of metabolism often require dietary changes. The particular enzyme absence or inactivity for each inborn error of metabolism dictates which components are restricted and which should be supplemented. The goals of
Discussion:

Why we should consider chronic degenerative diseases as inborn errors of metabolism?
The idea of considering chronic degenerative diseases as inborn errors of metabolism is supported by a large amount of evidence concerning the hereditary and biochemical aspects of diseases.

Some genetic disorders are inherited, while other genetic diseases are caused by acquired changes or mutations in a preexisting gene or group of genes. Mutations occur either randomly or due to some environmental exposure. Any change that affects the quantity or quality of metabolic enzymes predispose to an adverse physiological condition. Even though many conditions per se are not inherited, the predisposition to suffer or to be at risk from the condition is. This is the main reason we consider chronic degenerative diseases as inborn errors of metabolism.

Chronic diseases may be caused by genetic factors and environment (lifestyle) and their interaction (i.e. epigenetics) play an important role, and may cause genes to (or fail to manifest) in particular ways. In spite of this, if we submit two non-related individuals to the same conditions why one develops the condition and the other one does not. Clearly, genetic mutations are not the only components at work in the body, the genetic predisposition is relevant as is the biochemical individuality of each individual.

Degenerative diseases can manifest themselves in the human body when the body is out of physical and chemical balance. Degenerative diseases are not a local condition just like cancer is not just a tumor; they are chronic, systemic, metabolic dysfunctions, usually characterized by specific dietary deficiencies or insufficiencies, a host of pathological conditions and a series of chemical, physical, mental and energy imbalances.

The concept underlying an individualized, integrated metabolic program is that of biochemical individuality which addresses the patient’s deficiency and excess levels, biochemical function, energy level, and psychological factors. Certain individuals have a greater need than that supplied by the diet (even a good dietary regime). Their needs may vary from 10 to 1,000 times the physiological requirement. This could be caused by: Digestive problems, poor absorption, food sensitivities, difficulty in the metabolism of certain amino acids, fatty acids, complex carbohydrates, levels in the precursors of neurotransmitters, etc.

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. Also it 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 a cost effective measure 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.

Enzyme Control of Metabolic Reactions
Enzymes are often linked in multistep pathways, such that the product of one reaction becomes the substrate for another. In addition, the multiple steps provide additional levels of regulation, and intermediates can be shunted into other pathways to make other products. When all the enzymes in a pathway are functioning properly, intermediates rarely build up to high concentrations. This is the basis of the Metabolic Correction concept.

Metabolism and the Metabolic Correction Concept
The Metabolic Correction Concept provides the biochemical explanation of how to use nutrients for prevention 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.

Enzyme Defects Cause Metabolic Disorders
It has been documented that the main cause of enzyme defects are genetic mutations that affect the structure or regulation of the enzyme or that create problems with the transport, processing, or binding of enzymatic cofactors. In general, the consequences of an enzyme deficiency are due to perturbations of the cellular biochemistry, because of either a reduction in the amount of an essential product, the buildup or production of a toxic intermediate or side product (3) All these tribulations are probably due to a lack or limitation of necessary enzymatic cofactors and coenzymes.

Polymorphisms, Nutrigenomics and Genetic Nutritioneering
The enzymopathy (disturbances of enzyme function) present in these conditions are determinant in the further development of chronic degenerative diseases. Are generally characterized
by uncertain etiology, multiple risk factors, a long latency period, a prolonged course of illness, non-contagious origin, functional impairment or disability, and incurability. Nevertheless we believe that with proper metabolic correction; these polymorphic inborn errors of metabolism can be made functional through proper metabolic corrections in the patient’s physiology as a more effective manner to successfully treat or prevent disease. In order to fully understand this idea, the concept that we first have to embrace is biochemical individuality. Biochemical individuality refers to the unique nutritional needs each person has, based on their genetics, lifestyle, and environmental exposure to various stresses.

Dr. Roger Williams contributed to the understanding of the molecular origin of disease with the development of the concept of biochemical individuality (4). He described anatomical and physiological variations among people and how they related to their individual responses to the environment. He was the first to gain recognition for the term biochemical individuality and how this related to differing nutritional needs for optimal function among different people. He pointed out that even identical twins could be different in their needs for optimal function based upon the fact that they developed in different environments in utero. Although identical twins share the same genes, their differing nutrition and developmental environments can result in different expression of the genes as they grow older. The second important concept we need to understand is the recognition that nutritional status can influence the expression of genetic characteristics. It is now well recognized that our genotype gets transformed into our phenotype as a consequence of nutritional, lifestyle and environmental factors which are important in determining our eventual health patterns.

Dr. Williams 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 faulty gene expression. Motulsky explained that many the common degenerative diseases are the result of the imbalance nutritional intake with genetically determined needs for good health (5).

The principle can explain some of these discrepancies since every individual organism has a distinctive genetic background and therefore distinctive nutritional needs. Although all human beings operate on the same general physical mechanisms and the same metabolic processes, the individual physical structures and genetically determined enzyme efficiencies vary sufficiently between individuals so that the effect of all the combined reactions in one body may be completely different from that in another individual, even if of the same age, sex, and body size (4). These concepts can irreversibly change the way medicine is practiced and may result in the extension of both life expectancy and health span, or disease-free years of life.

A person’s particular genetics influences on how much of a specific nutrient they need. For example, folic acid is a B-vitamin that is relevant for cardiovascular and neurological health. One important role of folic acid is to decrease the amount of homocysteine that may accumulate as a normal part of metabolism. Homocysteine is an amino acid by product of methionine that plays a role in the development of heart disease, osteoporosis, dementia, and cancer. Folic acid is required to break down homocysteine. In order for folic acid to do this, it must be activated by the enzyme methylenetetrahydrofolate reductase (MTHFR). MTHFR is produced by the body and coded for by a specific gene. People can have different variations of this gene, which slightly changes the structure of MTHFR. This structural change can reduce its function by 30–65%, meaning that it may not be able to activate folic acid as easily. People who have the gene that decreases the MTHFR activity require higher doses of folic acid or an activated form of the vitamin to effectively push the reaction forward and decrease homocysteine. The requirement for folic acid is greater in people with this genetic variation.

G6PD (Glucose-6-phosphate dehydrogenase) human polymorphism, is a cytosolic enzyme in the pentose phosphate pathway, a metabolic pathway that supplies reducing energy to cells (such as erythrocytes) by maintaining the level of the co-enzyme nicotinamide adenine dinucleotide phosphate (NADPH). G6PD deficiency is the most common human enzyme defect. Individuals with the disease exhibit non-immune hemolytic anemia in response to a number of causes, most commonly infection or exposure to certain medications or chemicals. The NADPH in turn maintains the level of glutathione in these cells that helps protect the red blood cells against oxidative damage. Patients with this deficiency should not receive vitamin C infusions because it can cause hemolytic anemia. The regulation of gene expression gives the cell control over the versatility and adaptability of any organism and serves as a substrate for evolutionary change. This is profound since our diet has impact on our genetic code which is passed on to the next generation. The more nutritious our diet, the stronger will be the gene pool.

The Km concept
Approximately 50 different human genetic diseases are due to a poor binding affinity (Km) of the mutant enzyme for its coenzyme. This 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 the enzyme for the coenzyme (6). This should be of interest since it seems that a considerable percentage of the population is affected by polymorphisms (6).

The Weakest Link
Every element of your physiology must be addressed in order for your body to perform at peak efficiency. Michael Zumpano coined the term Metabolic Optimization in the early eighties to describe his systematic approach to training and nutrition. You can view the metabolic processes as links in a chain. The strength of the entire chain can be compromised by only one weak link.

A significant fraction of the American population appears to not obtain even the Recommended Daily Allowance (RDA) of some critical nutrients from their food (7,8). Levels of deficiencies that fall between the RDA and
the levels that produce recognized deficiency diseases (Subclinical Deficiencies) can have serious health consequences. Supplementation with specific nutrients has been estimated to be cost effective in preventing disease. Food alone may not provide sufficient micronutrients for preventing deficiency (9). A large proportion of older adults do not consume sufficient amounts of many nutrients. Supplements compensate to some extent, but only an estimated half of this population uses them daily.

When one component in the metabolic micronutrient network is inadequate, repercussions are experienced in a specific biochemical process or even in a large number of processes and can lead to diseases. Many of the carriers of 50 human genetic diseases that are due to defective enzymes can be remedied or ameliorated by the administration of high doses of the vitamin component of the corresponding needed coenzyme, which raises the levels of the coenzyme and at least may partially restore the needed enzymatic activity (10).

**Conclusion**

In most cases, disease results when the individual elects a lifestyle or diet that alters the expression of the genes in such a way that the weakness or uniqueness of inheritance factors result in a phenotype we call disease. That is why we can consider chronic degenerative diseases as inborn errors of metabolism. Metabolic Correction seems as a very logical approach toward attaining the healthy state.

**References:**


3. http://medicine.jrank.org/pages/2512/Metabolic-Disease-Enzyme-Defects-Cause-Metabolic-Disorders.html#ixzz2abE7pncM


International Journal of Human Nutrition and Functional Medicine is a peer-reviewed evidence-based publication produced periodically in print and/or digital formats, available as pay-per-issue, open access (free), or as a membership benefit (included or discounted), in English and/or other languages. As the title of the journal indicates, the focus of the journal is human nutrition (i.e., we publish only human-referent information, not animal studies), and functional medicine, a broad clinical and conceptual discipline that seeks to protect, restore, and optimize human health by appreciating human physiology's systems biology construct and thus the necessity of addressing the totality of factors that influence health and disease outcomes in the psyche and soma of individual patients as well as the social corpus of local and international groups of persons. The journal is dynamic and adaptive; updated information about the journal is available on-line at the website www.IntJHumNutrFunctMed.org.

Journal title: International Journal of Human Nutrition and Functional Medicine  
Abbreviation: Int J Hum Nutr Funct Med  
Website: IntJHumNutrFunctMed.org  
Facebook.com https://www.facebook.com/IJHNFM  
Editor-in-Chief Alex Vasquez DC ND DO FACN  
Review Staff—see website for updated list: Pedro Bastos MA MS (PhD candidate at Lund University, Sweden), J. William Beakey DOM LAc, Kenneth Cintron MD, Annette D’Armata NMD, Maelan Fontes MS (PhD candidate at Lund University, Sweden), Michael Gonzalez MS MHSN DSc PhD FACN, Tariq Shafi MD, Alex Vasquez DC ND DO FACN  
Notices: Footnoted  
Date of (re)printing: 7 August 2014

1 Acknowledgement here does not imply that the reviewer fully agrees with or endorses the material in this text but rather that they were willing to review specific sections of the book for clinical applicability and clarity and to make suggestions to their own level of satisfaction. Credit for improvements and refinements to this text are due in part to these reviewers; responsibility for oversights remains that of the author.

2 The intended audiences for this book are health science students and doctorate-level clinicians. This book has been written with every intention to make it as accurate as possible, and each section has undergone peer-review by an interdisciplinary group of clinicians. In view of the possibility of human error and as well as ongoing discoveries in the biomedical sciences, neither the author nor any party associated in anyway with this text warrants that this text is perfect, accurate, or complete in every way, and we disclaim responsibility for harm or loss associated with the application of the material herein. Information and treatments applicable to a specific condition may not be appropriate for or applicable to a specific patient; this is especially true for patients with multiple comorbidities and those taking pharmaceutical medications with multiple adverse effects and drug/nutrient/herb interactions. Given that this book is available on an open market, lay persons who read this material should discuss the information with a licensed healthcare provider before implementing any treatments and interventions described herein.