THE FUTURE OF NUTRITIONAL PHARMACOLOGY

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As the basic science of nutrigenomics unfolds in the 21st century, a significant question remains as to how it will be applied to improve health outcomes. The field was born of the observations made by Sir Archibald Garrod at the turn of the 19th century that there are innate errors in metabolism, such as acidurias, that could be modified through dietary modifications.[1] In 1949, Roger Williams, PhD, whose group at the University of Texas was credited with the discovery of pantothenic acid, advanced the concept of genetotrophic disease, the origin of which is characterized by the inadequate intake of a specific nutrient or group of nutrients to meet the genetically determined needs of the individual.[2] Also in 1949, 2-time Nobel Laureate in chemistry and peace, Linus Pauling, PhD, coined the term *molecular disease* from his pioneering work on the discovery of the origin of the nutrient-related genetic metabolism disease phenylketonuria.[3] In 1967, Pauling extended this concept with the term *orthomolecular medicine,* which he defined as the therapeutic use of substances native to human physiological chemistry to support functional health.[4] During this time, psychiatrist and organic chemist Abram Hoffer, MD, PhD, following Pauling's concept, described the successful clinical application of therapeutic doses of specific B vitamins such as niacin and pyridoxine for the management of certain forms of schizophrenia, resulting in the birth of the field of orthomolecular psychiatry.[5]

Following on this conceptual framework for nutrient pharmacology were clinical discoveries by Butterworth concerning the therapeutic role of folic acid in the prevention of cervical dysplasia[6]; Smithells and the therapeutic use of folic acid and cobalamine for the prevention of spina bifida[7]; McCully and the therapeutic use of folic acid, cobalamine, and pyridoxine for the prevention of vascular disease associated with elevated homocysteine[8]; Shute, who advocated the use of therapeutic doses of tocopherol for the prevention of heart disease and the management of wounds and burns[9,10]; and Stone, who advocated the use of therapeutic doses of ascorbic acid for the prevention of immune dysfunctions.[11]

From this lineage the field of nutritional pharmacology has developed over the past 60 years, as described in 1981 by Spiller in the book *Nutritional Pharmacology*.[12] Over the past several decades, the field has witnessed the discovery of many potential therapeutic roles for vitamins, minerals, amino acids, fatty acids, and accessory nutrients such as coenzyme Q_{10} and L-carnitine,[13,14] as well as phytochemicals, such as the cruciferous vegetable glucosinolate derivatives.[15] One of the most compelling recent examples to support nutrient pharmacology comes from the clinically proven value of therapeutic doses of niacin to increase high-density lipoprotein (HDL) cholesterol levels.[16] This has become a standard of practice in cardiology during the past 2 decades.[17] Recently clinical outcome studies have indicated that a daily therapeutic dose of 1500 to 3000 mg of niacin results in a reduction of carotid intimal medial thickness (cIMT), an objective clinical biomarker for the reduced risk for arterial disease, as well as decreased cardiometabolic syndrome risk in insulin resistance.[18,19]

With this history in mind, there are still many health professionals who believe that the term *nutritional pharmacology* is an oxymoron. It is their belief that nutrients can have no therapeutic clinical value beyond that of preventing classical nutrient deficiency diseases such as scurvy, beriberi, rickets, various anemias, pellagra, and protein or protein-calorie deficiencies. The conceptual basis for this position is that nutrients are not drugs, and therefore to suggest that they can participate as pharmacological agents is contradictory. This position seems to be strengthened by the lack of clinical success of a number of recent placebo-controlled intervention trials that used specific nutrients to prevent disease. This list includes examples such as various antioxidant trials for the prevention of cancer and heart disease,[20,21] B vitamins for the prevention of vascular diseases in people with elevated serum homocysteine,[22] and the use of supplemental folic acid for the prevention of precancerous colonic polyps.[23]

This begs the question of whether nutritional pharmacology is more than a theoretical concept. To address this question it is important to go back to the pioneering work of Garrod, Williams, and Pauling to understand how it differs from traditional drug therapy. Each of these pioneers recognized that nutrient need was unique to the genetic background of the individual. As an example, as phenylketonuria has become more well understood, it is recognized that it exists in several forms, from mild to severe. Studies have found the mild-to-moderate forms to be treatable through orthomolecular nutrient pharmacology with the use of therapeutic doses of the cofactor for the enzyme phenylalanine hydroxylase, tetrahydrobiopterin.[24,25] The conclusion is, "the right dose for the right genotype." Not everyone has a genotype or

epigenome that requires higher doses of tetrahydrobiopterin, but for those with a specific set of antecedents a dose that is considered therapeutic is "that which is necessary" to support proper function. In this case the agent is not working as a "drug," but the therapeutic levels are necessary to meet the unique needs of the person. This concept has been described in detail by Ames, Elson-Schwab, and Silver, who demonstrated that due to the number of nutrient-sensitive polymorphisms that have now been identified and the differing binding constants of specific nutrient-derived cofactors to their substrates, the need for specific nutrients to improve health for a genetically-specific individual might be much higher than we previously acknowledged.[26] What one might consider a "drug," another might see as the appropriate intake for an individual whose needs for that nutrient are far from the mean of others in the population.

This concept provides some insight into why the placebo-controlled nutrient intervention trials might have been unsuccessful in demonstrating that therapeutic doses of nutrients can serve as positive agents in the primary prevention of disease. A new-to-nature drug is developed through screening to have a very high activity against a biological target, such as the inhibition of a specific enzyme (eg, cyclooxygenase, angiotensin converting enzyme, HMG-CoA reductase). The activity of this molecule may be potent enough to block or inhibit all enzymes of a specific type regardless of their polymorphic state. This results in a therapeutic drug that possesses only a small degree of genotypic specificity. A nutrient, however, is a weak "drug" in comparison; hence, the nutrient's therapeutic effect may be much more dependent upon the polymorphic specificity of the biological target(s). The difference in mechanism and activity between a new-to-nature molecule that was specifically selected to have a very high affinity for substrate regardless of small differences in structure due to polymorphisms and that of a nutrient that works by weaker affinity for substrate and whose activity is much more dependent upon the specific polymorphism may help explain why intervention trials using nutrients have been disappointing. Buried within the data on nutrient intervention trials might be cohorts of people that had a very strong positive therapeutic outcome. Individuals with unique genetic or epigenetic sensitivity to the nutrient would have their contribution to the overall clinical outcome overwhelmed by the majority of the participants in the study who did not possess the "sensitive genotype." To observe this effect, the study would have to stratify the participants based on their unique genetic/epigenetic sensitivity and then power the study properly to include enough of these individuals to be of statistical significance if there were a positive clinical effect in this subgroup.[27]

This concept has significant support from traditional pharmacology. For example, it has been found that some antihypertensive medications are not effective for certain genetic polymorphisms.[28] It has been suggested that genetic polymorphism testing before administration of an antihypertensive medication would improve clinical outcomes. Methylenetetrahydrofolate reductase (MTHFR) polymorphisms have been found to represent a nutrigenomic contributor to both the risk for hypertension and cardiovascular disease.[29,30] This would imply that a folic acid intervention trial that was stratified for the polymorphisms associated with risk for folate-dependent hypertension would be more likely to determine a significant relationship between folic acid and blood pressure than a study that was done with participants with heterogeneous MTHFR polymorphisms, the majority of which were not as responsive to folic acid.

Similarly, it has been found that vitamin D status influences blood pressure, but it is most sensitive in those individuals with specific angiotensin-converting enzyme (ACE) and vitamin D receptor (VDR) polymorphisms.[31,32] Once again, this implies that the selection of study participants based on their ACE and VDR polymorphism status might significantly influence the outcome of a hypertension intervention trial with vitamin D.

It is known that the therapeutic effect of many drugs can vary by a factor of more than 100 from one person to another based on differing pharmacogenetics.[33] The dose of drug that is therapeutically successful for one person might be 100-fold higher than that required for another based upon each individual's genetic variations in specific cytochrome P450 or phase 2 conjugating enzyme activities. In clinical studies, people who are "nonresponders" due to their differing pharmacogenetics, if few in number, would not adversely affect the statistical outcome of the study, but for them the drug would fail to produce a positive clinical effect at the dose administered in the study.[34,35]

This discussion differentiates the public health issues related to nutrient intake from that of individual therapy. In the absence of the biological sensitivity of the nutrient to the "wild type" genotype being high, it would be difficult to prove through a traditional, non-genetically stratified intervention trial that there was improved clinical outcome from general supplementation with a specific nutrient. This would argue against a public health message for nutrient therapy with the substance in question. Clinical medicine, however, speaks not to the "law of averages" but rather to the need of the individual patient. In this case the specific genotype of the individual might dictate the need for specific nutrient pharmacology. These are challenging concepts to prove using a traditional randomized clinical trial format. The participation of patients who have been screened for unique genetic sensitivities related to specific biological endpoints in clinical trials is much more complicated and expensive to achieve. It is unlikely that a significant amount of data from this type of trial will be available soon. This may prevent the clarification of the nutrient pharmacology question in the near future and result in only those nutrients that are effective at high levels—such as the therapeutic effect of niacin on the elevation of HDL, which occurs at levels of intake 75 to 150 times the reference daily intake—to be recognized in medicine as "a standard of practice." As the field of nutrigenomics and nutritional epigenomics advances, however, it is likely that the concepts of Garrod, Williams, Pauling, and Hoffer will be found to be correct when nutritional pharmacology is applied to the right patient with the right dose of the right nutrient.

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