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Conditionally Essential Nutrients: The State of the Science

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"The functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain. The optimum concentrations of these substances for a person may differ greatly from the concentrations provided by his normal diet and genetic machinery. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimum concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients. Mental symptoms of avitaminosis sometimes are observed long before any physical symptoms appear. It is likely that the brain is more sensitive to changes in concentration of vital substances than are other organs and tissues "[1].

Humans are parasites of the planet. In order to survive, there are minerals and molecules, ultraviolet waves, and other organisms on which we rely. We need some of Earth's resources to function optimally and in some cases, we need them to function at all. These nutrients on which we rely are considered essential nutrients if they are used by most humans most of the time. The mid-twentieth century was a fertile time for nutrition research, during which time a lot of feeding studies were taking place on what are now known as essential nutrients.

Today, the US Department of Agriculture (USDA) Food and Nutrition Information Center (FNIC) maintains an information database of Dietary Reference Intakes (DRI) for vitamins, minerals, and macronutrients developed by the Institute of Medicine (IOM) of the National Academy of Science (NAS). The DRI levels have largely replaced the Recommended Daily Intake or Reference Daily Intake (RDI) system still used for product labeling. The RDI is the intake considered to be sufficient to meet the needs of 97.5% (2 standard deviations below the mean) of the *healthy* population. No set of recommendations has been developed to meet the needs of the unhealthy population. Whether values are set and how they are set has tremendous implications for product labeling, allocation of public health dollars, reimbursement by health insurance companies, etc.

A nutrient is considered essential if it "serves an indispensable physiologic function, but cannot be synthesized endogenously at an adequate rate by healthy subjects."[2] *Conditionally essential nutrients* are those that can usually be synthesized in adequate amounts endogenously, but may require exogenous supplementation during some circumstances. In some cases, these increased requirements can be a result of impaired absorption (e.g. additional fat-soluble vitamins in steattorhea), increased anabolic requirements (e.g. pregnancy, and lactation), increased metabolic demand (e.g. protein in burn, trauma).

The determination of dietary essentiality had traditionally been established through classic feeding studies using purified diets with, or without, the nutrient being studied. Over time, if a nutrient is essential, a deficiency syndrome will emerge as signs and symptoms of impaired growth, function, biochemical alterations, or symptoms of illness become apparent. The quantification of the minimum required dose to prevent deficiency symptoms is determined by incremental re-feeding until the dose resulting in syndrome resolution is reached [2].

Chipponi et al. describe the stages of the deficiency syndrome that results from deprivation studies:

Stage 1 Deficiency: Physiologic function continues normally while stores are being depleted. Adipose tissue, bone, muscle, and circulating storage forms (e.g. ferritin) act to maintain serum concentrations.

Stage 2 Deficiency: The depletion of body stores results in biochemical alterations, although clinical symptoms are not yet apparent. (e.g. C-reactive protein, hemoglobin A1c, homocysteine, altered enzyme activity)

Stage 3 Deficiency: In addition to biological perturbations, clinical symptoms become apparent. (e.g. bleeding gums and easy bruising in scurvy, dementia and dermatitis in pellagra)

Most of the work done to date on nutritional essentiality was conducted at a time when laboratory methodology was more rudimentary and notably less was known about disease pathophysiology. The early work surrounding conditional essentiality was done following the introduction of central ve-

nous access for nutrient delivery in 1969,[2, 3] when uncommon nutritional deficiencies became readily apparent in those patients receiving early TPN formulas. The insufficiencies of the nutrient formula became quickly apparent, and potassium, phosphate, and essential fatty acids were soon added. Long term users were found to need additional zinc, copper, selenium, chromium, etc.[2] and recently rubidium was shown to be a conditionally essential nutrient in dialysis patients, its stage 3 deficiency syndrome manifesting as depression [4].

In the presence of polymorphisms, or under certain physiological (e.g. pregnancy, lactation, aging), or pathological conditions, humans have been shown to have unique nutritional requirements. When disease (e.g. autoimmunity to pancreatic beta cells) or circumstance (e.g. burn victims) results in a metabolic circumstance where the needs of the body cannot be endogenously supplied and the amount recommended during a state of health is insufficient, the substance becomes conditionally essential. This could be an increase in dose for an already recognized essential nutrient (e.g. thiamin in Wernicke's encephalopathy is dosed higher than the RDI), or a condition may render an accessory nutrient essential (e.g. coenzyme Q10 in congestive heart failure.)

The principle of biochemical individuality states that the optimal dose of any nutrient will normally vary between individuals. This is well supported by the science and considered in statistical considerations of biomarkers. The feeding studies that have been done have, in the nutrients studied, demonstrated what occurs in healthy, young individuals who are depleted of a single nutrient.

Carnitine, taurine, arginine, cysteine, glycine, choline, are all generally recognized conditionally essential nutrients. Carnitine, for example, is an FDA-approved prescription drug for carnitine-deficiency syndromes. It is also available as an over-the-counter supplement intended to support athletic performance and weight loss, by facilitating the conversion of fat to fuel. An excellent review on glycine was recently published by Want et al., in which they describe the structural (glutathione, heme, nucleic acid, uric acid synthesis) and functional (immune and metabolic regulation) roles of glycine. The authors provide support for the idea that there are inflammatory disorders (obesity, diabetes, cardiovascular disease, cancer) that require more glycine than the body is capable of synthesizing [5].

Whether 'conditionally essential' should refer only to the nutritional impact caused by a condition is debatable. For instance, the MTHFR mutation is a common SNP that has been associated with depression, miscarriage, and possibly cardiovascular disease and dementia. The SNP can be circumvented with use of the active form of folic acid, 5-MTHF. For those MTHFR homozygotes, the 5-MTHF form should be considered the required form of the nutrient. "MTHFR homozygote" is not a medical condition, although it may increase risk of disease. As discussions about conditional essentiality evolve, efforts should be made focus on prevention. E.g. "Smokers" are not a disease and yet they have unique vitamin C requirements due to the increase in oxidative damage. Similarly, "MTHFR homozygotes" should have unique folic acid recommendations.

It is important to state that conditional essentiality is distinct from the question of causality. Individuals with steatorrhea require additional vitamin A, D, E, and K, but these vitamins are not the cause of their steatorrhea. Similarly, whether a nutrient deficiency predisposes to disease, or whether a disease state induces a deficiency, is irrelevant. Regardless of cause or consequence, the question best serving public health is,

"Would the patient's health be improved if ___ were exogenously supplied?"

This question is not always so easy to answer. Vitamin B12, may cause a deficiency with a striking similarity to MS. Vitamin B12 levels have been shown to be lower in MS and vitamin B12 plays a role in immune system recognition. Since the process of remyelination is upregulated with MS activity, it stands to reason that the nutritional requirements for synthesizing myelin may also have increased requirements. A study has demonstrated that individuals with MS and B12 deficiency are more likely to have diminished neurological capacity [6]. Several trials have attempted B12 supplementation in patients with MS, but no consistent improvement has been demonstrated. This may because the outcome measure with which we are attempting to document benefit is inadequate, or that low B12 itself does not contribute to disease, but low levels may be an indicator for something else. For now, B12 deficiency remains a diagnosis of exclusion in the evaluation of demyelinating disease and B12 deficiency is more common in MS than controls, but additional supplementation does not appear to significantly, or consistently, impact disease outcomes [7].

While an increased nutritional demand in some conditions is biologically plausible, and some diseases are associated with deficiency, until fortification improves a clinically relevant outcome measure, it should not be referred to as a conditionally essential nutrient.

As a solution, one option for nutritional augmentation research efforts is to focus on a particular subset of symptoms within a disease. For instance, approximately 80% of people with PD report constipation. Cassani et al. demonstrated a probiotic supplement improved symptoms of bloat, pain, and improved stool consistency in patients with PD [8]. They did not include PD status or progression as an outcome measure for a probiotic intervention, but rather focused on gastro-intestinal health as an outcome measure.

Clinical epidemiology is evolving and we are beginning to ask the questions differently. Peterson, et al. recently compared vitamin D levels of individuals with PD to determine whether low levels were associated with increased risk of cognitive decline. After correcting for multiple comparisons, they found higher vitamin D levels to be associated with improved outcomes measures of mood, concentration, and verbal memory [9]. The `question has yet to be answered whether vitamin D supplementation can improve mood, concentration, and memory. The importance of preventing vitamin D deficiency in PD patients is only beginning to become clinically relevant, and whether higher-than-normal doses are required, or if in-

dividuals with poor mood and cognitive difficulty should be treated differently.

Another suggested research methodology is to concentrate efforts on the subpopulation of the group who have biological evidence of deficiency. There is a tremendous amount of cell line and animal research suggesting coenzyme Q10 improves mitochondrial function in PD. A pilot trial found a ~40% reduction in rate of progression in those on 1200 mg/day [10]. Beal et al. conducted a multi-center Phase III efficacy trial of 1200mg, 2400mg, or placebo which was stopped early based on calculations that it could not possibly meet clinical endpoints for efficacy. During this same time, data were published showing a statistically significant increase in frequency of deficiency in PD patients over controls. Using the SpectraCell FIA measure, ~35% of individuals with PD were shown to be deficient [11]. Perhaps a better way to ask this question is, "among individuals with PD who exhibit biochemical or clinical signs of Q10 deficiency, does supplementation result is a measurable benefit to biochemical or clinical sign or symptoms? Rather than ignoring the tremendous heterogeneity of these diseases, and trying to overpower them with large sample sizes, we should direct our research efforts toward identifying those most likely to benefit from supplementation.

Table 1: Examples of Nutrients Gaining Acceptance as Conditionally Essential in Certain Disease States

CONDITION	NUTRIENT	Phase 1 Defic	Phase 2 Defic	Phase 3 Defic
Parkinson's	Q10	Synthesized by HMG-CoA reductase (commonly inhibited by statins)	SpectaCell FIA 4-fold risk of Q10 defic [11].	TBD: Myalgia? Fatigue? Weakness? Cardiomyopathy?
Parkinson's	Glutathione	Synthesized on demand, not stored.	40% depletion of nigral GSH at diagnosis; GSH defic leads to inflammation, ROS, mitochondrial dysfunction	GSH depletion associated with aging, GSH progression
Parkinson's See also: *Epilepsy* *Mental illness* *Tics* *Addiction* *ADHD* *Migraine* *Alzheimer's* *MS, ALS, HD*	Lithium	Not stored. Typically obtained	Ecological studies from 1970s show municipal supply assoic with body level. Depletion in rainy regions, highest in desert. *To-do: Repeat in WA	Low Li associated with psychosis, depression, aggressive behavior, and suicide. Calls in the literature for more research and Li the water supply of depleted regions have been ignored. *To-do: Study Li repletion among those deficient. Reverse feeding study.
Parkinson's See also: *IBS, IBD* *Autoimmune disease* *Atopia*	Probiotics		Following probiotic supplementation, improvement in normal stools, bloat, and pain in constipated PD patients [8].	Constipation affects 80% of PD pts. Individuals who have a bowel mov. every other day are 4x as likely to develop PD as those who have 2+ bowel mov./ d. [Abbott 2001]
Parkinosn's See also: *Alzheimer's* *Epilepsy* *MS*	Vitamin D		Levels lower in PD than healthy elderly or AD [11, 7].	PD associated with osteoporosis, balance, weakness, depression- all also assoc with D. Higher vit D assoc with better mood and cognitive function in PD [9].
Metabolic syndrome	Glycine		[5]	
Coronary Heart Disease	DHA + EPA		Immune dysfunction [Calder 2010]	Cognitive decline [Calder 2010]
	Flavonoids		Inflammation	CVD, obesity, neurodegeneration, neuronal hyperexcitability: tics, seizures, ADD, etc.

In complicated, chronic, multi-system diseases like metabolic syndrome, cancer, and neurodenegeration, one cannot expect that replacing one nutrient will shift primary disease outcome measures like BMI or dementia. Physiologically speaking, if an individual had a deficiency of several nutrients,

would benefit be expected if one nutrient were replaced but not the others? Combination protocols have been very effective in HIV+ research and *H.pylori* eradication, but are rarely implemented in chronic disease research related to quality control and regulatory oversight typically being too cumbersome to work within a funding cycle [12].

In table 1, examples are given of conditions and nutrients that meet the criteria for conditional essentiality using the criteria outlines in Chipponi et al., although this concept has not been translated clinically or in federal guidelines.

There is a tremendous disconnect between metabolomics, clinical epidemiology, and public health practices for nutrient provision. Inborn errors of metabolism provide an interesting framework from which to evaluate conditional essentiality. For instance, all newborn babies are screened at birth for inborn errors of metabolism. In the case of PKU, an individual must avoid the amino acid phenylalanine in order to prevent mental retardation. Other inborn errors of metabolism require additional arginine supplementation, to overcome defects of the urea cycle. In these cases, the nutritional products are regulated by the Food and Drug Administration as foods and dietary supplements and often referred to as 'medical foods.' Insurance coverage for these medical foods is reasonably good through childhood, but inconsistently described or regulated in adults [15]. It is as though we, as a culture and a health care system, understand that metabolic differences between individuals can interfere with growth and development in infancy and childhood, but have not come to fully appreciate the degree to which unique metabolic consideration must also be given to adults. In fact, several insurance companies stop paying for specialized amino acid formulas when the individual turns 18.

Physiologists do not contend that dysfunction ensues when levels of lithium, vanadium, and flavonoids are inadequate, and yet DRIs have not been set. Are they essential? What are symptoms of deficiency? What doses are required to not experience the symptoms of deficiency? Who is responsible for educating individuals and healthcare providers? I am hopeful our evolving understanding of human metabolism, nutrigenetics, nutrigenomics, and biochemical individuality as well as improved research methodologies will lead to a revolution in nutritional medicine in the years to come.

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