August 2002 Issue | Mary Louise Hardy, MD

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Welcome to Functional Medicine Update for August 2002. This issue will focus on the connection between genes and environment, with emphasis on the B vitamins.

We sometimes need to go back to the future to review things we thought we understood and have taken for granted. It is like celebrating Mother's Day or Father's Day, when we reflect on our special relationships with our parents and, at least for that day, do not take them for granted. We might call this B Vitamin Day, in the context of 2002. What role do B vitamins play in disease prevention, health promotion, and even in remediation of diagnosed conditions?

To answer that question, we first must put vitamins in context. Vitamins, or vit-amines, as Funk first called them, are life-giving amine compounds that contain an amino group nitrogen with hydrogens on it ($R\text{-}NH_2$ in chemical shorthand). These life-giving amino compounds promote specific physiological and biochemical functions by the role they play as coenzymes. Enzymes are manufactured on a cellular organelle called the ribosome, according to the genetic information in each individual's book of life. The stories in that book are the genes, and these stories are encoded and transcribed into what is called messenger RNA, or mRNA.

An Analytical View of Physiology
The mRNA leaves the nucleus of the cell, where the book of life is kept in its sealed vault by histone and non-histone proteins, locked up and protected from environmental injury. When the messenger RNA for a specific story in our life (meaning a gene) is transcribed, it goes to the ribosome, where it directs the synthesis of a specific protein . It enables the formation of peptide bonds between amino acids that have been chemically bound to another class of RNA molecule, the so-called transfer RNAs, into a polypeptide that we call a protein.

Post-Translational Modification
That protein then leaves the ribosome. It may undergo post-translational modification, like glycosylation, oxidation, phosphorylation, or some other kind of epigenetic modification, to become an active protein. It coils into its tertiary and quaternary configuration and now has the ability to carry out its function. Most of these proteins carry out functions as catalysts, which we call enzymes, that modulate specific biochemical reactions within the literally thousands of biochemical reactions that occur within cells under specialized developmental states. The net outcome varies, depending on the cell type. A liver cell, for example, carries on different biochemical functions than a neuron, a cardiocycte, or a myocyte. The activity of the cell, in combination with other cells, gives rise to the tissue and so forth in the body.

Apo Enzymes, Holo Enzymes, Coenzymes

This is a reductionist/analytic view of physiology. One thing we know is that the enzyme, or the protein that comes off the ribosome, is not always in its active state. It is what is often called an apo enzyme, meaning it is in a nascent, inactive form. It has to be converted into the holo enzyme, or the active form and the most active configuration. The agent that converts the inactive apo enzyme to a holo enzyme is frequently a coenzyme. Coenzymes are specific to unique apo enzymes, and help to insure that specificity of the enzymatic reaction.

Coenzymes are, to a great extent, nutritionally derived compounds, such as thiamin pyrophosphate, derived from vitamin B1. Others include flavin adenine dinucleotide, or FAD, derived from vitamin B2 riboflavin; nicotine adenine dinucleotide, or NAD, derived from vitamin B3, niacin; pyridoxal phosphate, derived from vitamin B6, pyridoxine; cobalamin, derived from vitamin B12; and 5-methyltetrahydrofolate, derived from folic acid or 5-formyl-tetrahydrofolate. These coenzymes play an important role in activating apo enzymes into holo enzymes so they can participate in metabolic function.

A Basic Nutrition Assumption

Within basic nutrition and nutritional biochemistry, the assumption has been that if you eat a diet of variety and moderation, your diet will provide the precursors to these coenzymes at levels more than adequate to produce saturation of enzymes. The limiting effect of enzyme function within cells, according to this view, is never nutrient insufficiency. It is, instead, a consequence of genetic aberrations in the structure of these enzymes that has to do with metabolic genetic disorders like sickle cell anemia, megaloblastic anemia, methylmalonic aciduria, Hartnup's disease, or factors related to homocysteinemia.

We consider these genetic conditions to be metabolic disorders of infancy, which are a consequence of the malformation of these enzymes because of altered protein amino acid structure from the genes. We call those point gene mutations. They have potential lethal side effects in individuals who have those genetic metabolism disorders.

Phenylketonuria

Phenylketonuria is the classic example of these disorders. It is not necessarily a coenzyme problem, but it is related to an enzyme called phenylalanine hydroxylase, which converts phenylalanine to tyrosine. When it is genetically mutated, this enzyme can result in the imperfect conversion of phenylalanine to tyrosine. The result is potential phenylalanine toxicity and/or tyrosine insufficiency, which produces retardation and may cause the death of an infant with that condition.

Over the years, however, we have learned we can influence a number of genetic metabolism disorders of infancy by selective modification of the precursors, or modification of the enzymatic coenzyme steps. With phenylketonuria, for example, the treatment of choice would be to put an infant on a phenylalanine-restricted diet to lower the load of phenylalanine. We might even supplement the baby with tyrosine to increase the level of tyrosine. This type of intervention, although the diet is not very tasty, has enabled individuals with phenylketonuric genes to reach maturity and carry on relatively normal lives. Their IQs are reasonable, and they are functional. This is accomplished by modifying the environment to work around a genetic uniqueness to improve function of an individual with point gene mutation conditions.

Single Nucleotide Polymorphisms (SNPs)

We now recognize that a wide variety of other genetic variations can produce conditions that are less

obvious than the obviously deleterious point gene mutations involved in conditions such as phenylketonuria, pernicious anemia, Hartnup's disease, and sickle cell anemia. Some of these subtle modifications in the genetic structure of these proteins are what we now refer to as single nucleotide polymorphisms (SNPs). We have found a few hundred, or at most a few thousand, genetic metabolism disorders relating to mutational defects of chromosomes that induce potentially life-threatening conditions. In contrast, there are literally millions of SNPs, a minority of which are located in areas of the genome that encode functional proteins, that do not produce an immediate risk to life but may alter function over the course of the individual's life and put him or her at higher risk later through susceptibility factors to age-related diseases.

It is sometimes possible to modify the function or genetic expression of these SNPs by certain coenzymes and cofactors that work within these processes to support proper molecular and cellular function. An individual with a specific SNP, therefore, might require a level of a certain coenzyme to promote functional activity of that enzyme that is higher than that required by another individual.

Biochemical Individuality
This is the basis of the concept of biochemical individuality, which Roger Williams talked about 50 years ago. Dr. Williams was not aware of SNPs in 1950, but he presaged their discovery by recognizing the genetic heterogeneity within animals and the wide range of nutritional needs of various animals in captivity for promotion of optimal function.

Dr. Williams originated the concept of biochemical individuality based on a presumption that we would later discover the mechanism, and we did. The discovery began with the Watson and Crick double-stranded helix delineation of the genetic informational molecule. It continued to evolve over the next 50 years through the Human Genome Project and the evolving understanding of the prevalence of SNPs

I have been focusing on specific coenzymes-thiamin pyrophosphate, flavin adenine dinucleotide, nicotine adenine dinucleotide, and pyridoxal phosphate. Another series of cofactors also participates in the regulation of enzyme function, moving from the apo enzyme to the halo enzyme form. Those cofactors are the trace minerals.

Magnesium is found in about 80 percent of enzymes as part of their active structure. Zinc plays a role. Iron plays a role with hemoglobin and other iron-containing cytochromes. Manganese and cobalt play a role with vitamin B12. Vanadium and molybdenum are active with xanthine oxidase and aldehyde oxidase. These trace mineral effects are also important as regulators of active enzyme function. Need for trace minerals can vary from person to person based on the genetic polymorphisms of the structure of the proteins, i.e. enzymes.

Functional Nutrition
This theme has been emerging over the last 50 years. We now understand that the food that produces optimal function for one person may have a vastly different effect on another. We have evolved beyond thinking that the prevention of scurvy, beri beri, pellagra, xerophthalmia, and rickets is the sine quo non for proper nutrition. We now look at functional aspects of nutrition, the effect on enzyme activity and cellular physiology.

I began this discussion by saying the conventional presumption has been that most people's diet contains

enough of the enzymes that regulate function to result in saturation relative to these coenzymes. That presumption would suggest that any additional intake of these micronutrients to influence enzyme function would be irrelevant. If the binding sites for these coenzymes and cofactors are already saturated, why add more? They would probably just wash out of the body and end up in the urine. (This is the so-called expensive urine hypothesis.) If you are already at saturation, giving a nutritional supplement only produces enriched nutrients in the sewage treatment plant.

Reaching Enzyme Saturation in SNPs

Based upon the prevalence of SNPs, we are beginning to recognize that many people with these polymorphic enzymatic structures are far from saturation with regard to specific enzymes. As a consequence, for them, enhanced levels of specific micronutrients may be beneficial for promoting enzyme or cellular physiological function. That is where the focus is right now in the current molecular nutrition revolution. The combination of genes, environment, and nutrition causes the turnover of various cellular functions and nutrient-derived or nutrient-related enzyme functions.

The current focus is on common age-related diseases. They are definitely the toughest nut to crack because we cannot identify a specific single gene associated with their origin, such as was possible with sickle cell anemia. We do not find a single "bug" or infectious organism associated with them, such as we could with pneumonia, for instance. They are complex diseases like heart disease, cancer, diabetes, psychiatric illnesses, and neurological age-related illnesses. They are complex, multi-factorial diseases that cannot be attached to mutations in a single gene or to single environmental factors. They arise from the combined action of many genes, environmental factors, and risk-conferring behaviors, many of which could be modifiable if the individual only knew what behaviors to modify based on his or her genetic uniqueness.

One of the greatest challenges facing biomedical research and the evolution of medicine is to sort out how these contributing factors interact in a way that translates into effective strategies for disease diagnosis, prevention, and ultimate therapy. This challenge has been the focus of FMU over its 20-year history. We have been trying to tease apart and understand this complex algorithm

The April 26 issue of Science magazine contained an article titled "It's Not Just the Genes."[1]That article explained that because we know genes contribute to complex disease, we are trying to understand or unravel them, but they are notoriously difficult to identify because they typically exert small effects on disease risk individually. It is only in collective activity as multigenetic factors that the magnitude of their effects is likely to be large enough to create the outcome we call disease. We can't find a single gene that produces these complex diseases.

That issue of Science magazine concentrates on the puzzle of complex diseases and focuses on three examples: maturity-onset or type 2 diabetes, neurological and schizophrenia-related disorders, and vascular disorders. No single gene mutation codes for these diseases, and we are not going to unravel these complex puzzles simply and be able to say, "Aha, I've found the gene for schizophrenia (or diabetes or heart disease)." They all have multi-gene interrelationships.

Complex Puzzles Require Integrated Approaches

Since they are so complex, we might wonder if we will ever solve the puzzle of these complex diseases. The solution appears to be possible through integrated approaches. One discipline cannot determine the

answer; we must use integrated approaches with coordinated efforts from researchers in diverse disciplines, bringing in the wisdom of clinical observation. I think the solutions to these problems will be more like an engineering problem than a basic research problem. No researcher will win a Nobel Prize by uncovering all the explanations for chronic diseases. Instead, we may combine clinical experience, observations, and anecdotes and weave them into a formalism that comes out of an understanding of mechanisms to create a model that allows us to predict the success of therapies that were previously never tried.

Medicine is now combining basic science and predictive ability, moving from a medi-science that is largely empirical. I think we will find a balance between validated clinical experience and explanations that predict outcome based on first principles. One of the series of papers in Science looks at moving along the complex path of this genotype/phenotype connection.[2]What are our genes? What is our pleuripotentiality and how is it converted into function?

I remind you once again of Linus Pauling's landmark paper, published in 1968 in Sciencemagazine. I have cited this paper on a number of occasions, but I want to applaud it once again. In that paper, titled "Orthomolecular Psychiatry," Dr. Pauling proposed that by varying the concentrations of substances normally present in the human body we might control disease.[3] This is the concept of utilizing specific nutrients that activate coenzymes to the level of need of an individual's genes to produce a phenotype of favorable outcome. It describes personalized medicine, not medicine of averages. This paper outlined an entirely new type of medicine.

Dr. Pauling's paper was not greeted enthusiastically by the medical community of 1968. I believe practitioners in the 1960s did not understand the relevance of the subtitles in that article, which covered such topics as Optimum Molecular Concentration, Evidence from Microbiological Genetics, Molecular Concentrations and Rates of Reaction, and Molecular Concentrations and Mental Disease. Medicine was not sufficiently advanced to understand the relevance of reaction rates, kinetics, thermodynamic principles, apoenzymes, Michaelis-Menten kinetics, and complementarity.

If we go back and read this article in a 2002 context, we are reminded of how prescient this paper was and how it presaged the revolution of the genome era and the current age of post-genomic medicine. Pauling cited the Hoffer/Osmond work. As you will recall, last month we had the pleasure of interviewing Dr. Abram Hoffer. For more than 50 years he has been getting us to think about mental illness and cofactor therapy with niacin, vitamin C, and pyridoxine. We are finding this whole area is becoming very supportable in light of 2002 knowledge presaged by Pauling's 1968 paper.

In the early 1950s, Hoffer and Osmond talked about a new approach to schizophrenia and the results of empirical research.[4] Last month in FMU we discussed many of Dr. Hoffer's more than 300 publications in this area. He and Dr. Osmond successfully used nicotinic acid and niacinamide, vitamin B3, to treat certain forms of schizophreniform disorders that were nonresponsive to other available therapies. They showed there was something unique about the ability to detoxify endogenous neurochemicals that produced hallucinogenesis, or at least a schizophrenic-like response.

These two researchers talked about adrenochrome and adrenolutin and their relationships as oxidized byproducts of adrenaline in the brain, which might induce hallucinogenic reactivities. The specific

substance-adrenochrome, adrenolutin, dopaminochrome, or another oxidized molecule in the brain-that causes the problem is probably less important than the recognition that empirically niacin works in many patients who have schizophrenic-like diagnoses. We may still be in search of the mechanism that everybody agrees on, but the clinical observations in this subset of patients are absolutely reproducible and extraordinarily valuable

John Smythies wrote a more recent paper on this particular topic, published in the Journal of the Royal Society of Medicine just six years ago. He discussed endogenous neurotoxins relevant to schizophrenia.[5] Dr. Smythies was a young investigator who collaborated with Drs. Hoffer and Osmond in the early 1950s. He has continued to follow up on this work. In his 1996 paper Dr. Smythies wrote:

> "The search for an endogenous psychotomimetic agent that might play a role in schizophrenia has failed for 40 years to show one. Previous candidates have included O-methylated derivatives of catecholamines, and N- and O-methylated derivatives of indolealklamines, which for various reasons failed the test. In 1954, Hoffer, Osmond, and Smythies reported that adrenochrome, the in vitro oxidation product of adrenaline, was psychotomimetic in humans."

Endogenous Hallucinogens
Subsequent research over the last 40 years has looked at various types of molecules similar to this called dopaminochromes, which are formed in the substantia nigra and noradrenochrome in the locus coeruleus. These particular molecules may be more likely the endogenous hallucinogens.

> "Neuromelanin has for long been regarded as an uninteresting inert cellular pigment with no clear function. However, recent interest has focused on its power to chelate heavy metals, in particular iron, and the hypothesis has been advanced that it normally plays a role in protecting the cell from heavy metal toxicity."

It may be made up, in part, of potentially toxic oxidation products of catecholamines that may have additional roles in this pathway of endogenous hallucinogenesis, oxidative stress, neuronal uncoupling, and so forth-things that are only now being uncovered.

Neurotoxic Quinones
These neurotoxic quinones are formed by auto-oxidation of catecholamines, of which a simplified account can result in the potential hydroxy derivatives like indole 5,6-dihydroxyindoles, that are capable of forming quinones. These quinones can then induce problems within neurochemistry. That can lead to disturbances in one-carbon metabolism within the folate cycle in the brain that results in neuropsychiatric disorders, not just schizophrenia but, as Dr. Smythies goes on to point out, possibly also in other areas like depressive disorders.

In a paper in Biological Psychiatry, Smythies and colleagues talk about the relationship of these products to depletion of the folate pool and the possible role of folate, B6, and B12 in the treatment of depressive disorders.[6]

We can take the concept of dietary factors and the relationship to neurochemistry to next step by looking

Richard Wurtman's work at MIT. In 1976 Dr. Wurtman wrote a paper titled "Brain Acetylcholine: Control by Dietary Choline."[7] Choline is a B vitamin. Wurtman showed that B vitamins not only helped to reduce endogenous toxins, but also that they would upregulate the formation of neurotransmitters. In this case choline activated the production of acetylcholine in specific regions of the brain.

With colleagues John Growdon and Edith Cohen at MIT, Dr. Wurtman published a paper titled "Treatment of Brain Disease with Dietary Precursors of Neurotransmitters," using choline and dietary tryptophan to enhance specific neurotransmitters, acetylcholine or serotonin, respectively.[8]

Nutrients and Brain Function

In a review paper titled "Precursor Control of Neurotransmitter Synthesis," published in Pharmacological Reviews in 1981, Dr. Wurtman again indicated how brain chemistry depends on adequate delivery of specific nutrients that are precursors to neurotransmitters. He pointed out that dietary variables and the transport across the blood/brain barrier can influence endogenous neurotransmitter synthesis. These factors are unique to the individual, so the level that is optimal for one can be significantly different from that of another.[9]

That conclusion was also illustrated in a paper talking about brain choline, its sources and effects on the synthesis and release of acetylcholine, and the relationship with Alzheimer's disease and genetic risk to Alzheimer's based on unique metabolism of choline and its production of acetylcholine. This paper appeared in Alzheimer's Disease--A Report of Progress back in 1982.

That preliminary discussion provides segues to a recently published report by Ames, et al., to which I alluded in our last issue of FMU. Dr. Ames, a biochemist at the University of California/Berkeley, known throughout the world for developing the Ames test, was the principal author of this paper. Its title is "High-Dose Vitamin Therapy Stimulates Variant Enzymes with Decreased Coenzyme Binding Affinity (Increased Km): Relevance to Genetic Disease and Polymorphisms."[11] This article talks about each of the B vitamins-B1, B2, B3, B6, B12, folic acid-and the increasing recognition of the number of existing polymorphisms that require enhanced levels of specific nutrients to promote cofactor synthesis and enzyme function to overcome "sluggish" polymorphic enzyme steps.

We cannot change the genes. We cannot (at least with the technology now available) change the structure of the enzymes, but we can change the coenzyme loading effects to push mass action, by Le Chatelier's Principle, a sluggish equilibrium to completion. Dr. Ames revisits this model, which Dr. Pauling talked about in 1968 in his article in Science magazine, in a paper in the American Journal of Clinical Nutrition.

Overcoming Enzyme Blocks

In his article, Dr. Ames discusses methylene-tetrahydrofolate reductase as a highly polymorphic enzyme that requires enhanced levels of folic acid and NAD, coming from niacin, vitamin B3, to overcome these enzyme blocks. He talks about glucose-6-phosphate dehydrogenase, or G6PD, another common genetic polymorphism found in the human population. G6PD, in fact, is the most common such polymorphism that has been described to date. It requires higher levels of the B vitamins, particularly NAD, or niacin-derived coenzymes.

The family of these B vitamins is very useful in a variety of polymorphisms that, in the absence of

adequate or optimal levels of cofactor loading, can produce untoward effects on metabolism that may be seen downstream as "diseases of unknown origin." Dr. Ames talks about a number of these disorders. To emphasize his point, he places specific emphasis on those that are well known to be genetic metabolism diseases of infancy. An example is gyrate atrophy of the choroid and retina with ornithine aminotransferase genetic polymorphisms related to pyridoxine needs. Another is cystathionine beta synthase activities and homocysteinuria, the increased levels of homocysteine related to B6 and magnesium.

Homocysteine Elevations and Pyridoxine

We know of homocysteine elevations as a consequence of folate and B12. This is another genetic metabolism disorder related to the need for B6 to prevent homocysteine elevations. The level of pyridoxine needed to overcome this elevation is from 50 to 1000 mg per day, compared to the RDI level of pyridoxine, which is less than 2 mg per day. Many people may need 25 to 500 times the RDI each day to overcome their metabolic genetic uniqueness and prevent the buildup of this amino acid that can create endothelial injury and neurotoxic effects.

What happens if you administer these high levels of nutrients to everyone, just to cover your bases? Are there potential adverse risks associated with that nutrient administration? In the case of B6, reports years ago indicated that sensory peripheral neuropathy could result from high-dose B6 supplementation. One such paper, which appeared in journal Neurology, was titled "Sensory Neuropathy with Low-Dose Pyridoxine." The authors reported that doses of 200 mg to 5000 mg of pyridoxine a day for an extended period of time led to symptoms of peripheral neuropathies in 16 patients.[12]

Such reports have caused overreaction to sensory peripheral neuropathy and B6. Generally, it is seen in only a small number of patients[13,14], at very high doses-gram doses per day-but it is something to be aware of because, certainly, we cannot jump to the conclusion that if a little is good, a whole lot more is better. Dose/response relationships are unique to the individual. Therefore, if we look at vitamin B6, we would advise caution when reaching doses above several hundred milligrams.

Time-Release Niacin and Nutrient Safety Levels

A number of reports in the literature indicate that high levels of time-release niacin can produce hepatotoxicity with elevated liver enzymes.[15] This condition seems to be reversible with removal of the niacin supplement. Niacin in the non-time-release form appears to be safer than time-release, and niacinamide appears to be safer even than niacin.

Because of their relatively quick first-pass detoxification and elimination through the urinary tract, B-complex vitamins are generally very safe at levels far in excess of the RDI. B-vitamin-dependent polymorphisms are very common. If we compare the potential for improving functional outcome with increased levels of B-vitamins to simply preventing pellagra and beri beri, we might decide to recommend higher doses of B vitamins in many basic nutritional programs, to cover the bases, so to speak. We might use B vitamins in a range that would manage the coenzyme-related polymorphisms that depend on higher levels of coenzyme loading to convert apo enzymes into holo enzymes. That is the whole theme of Dr. Ames's paper. He discusses vitamin B1, B2, B3, and B6 and the relationship to functional outcomes in neurological, cardiovascular, and immunological influences that are occurring as a consequence of higher levels of intake in those individuals with genetic needs.

An example is statins and the risk of polyneuropathy. One side effect of the cholesterol-lowering statin drugs is the production of polyneuropathies in some individuals. This possibility was recently reported in the journal Neurology.[16] According to the authors, the frequency of neuropathies is not so high as to discourage completely the use of statins because the relative risk of vascular disease with elevated cholesterol exceeds the risk of polyneuropathies.

There may, however, be individuals who are at risk to polyneuropathies for whom coenzyme Q10 and other B vitamin-enhanced intake will reduce their risk of polyneuropathy with statin administration. This would be a way, therefore, to deal with an environmentally modifiable factor for producing improved function when an individual is on a specific pharmacological therapy. When they are given statin drugs, individuals who have these polymorphisms that make them more dependent on specific B vitamins may, therefore, be more at risk to these specific types of neuropathies.

Cohort Analysis

These relationships represent a new field of investigation-cohort analysis of higher risk groups based upon unique genetic polymorphisms. This individualized analysis is preferable to the kind of research we have seen over the last several years, which lumps everyone together and applies the law of averages to evaluate outcome. We are now seeing cohort analysis of individual risk groups.

That type of analysis might also be beneficial in looking at individuals who, on statin therapy, either experience reduction in their HDL or do not have a favorable improvement in their cholesterol/HDL ratio. A recently published report in the American Heart Journal showed that administration of 50 mg of niacin twice daily to individuals on statins resulted in a statistically significant increase in HDL levels. This study suggested there may be individuals within the cohort studied who were highly sensitive to the need for increased niacin to improve HDL.[17] If you consider that increased HDL has a strong inverse relationship to heart disease risk, this finding represents a favorable outcome in improving secondary prevention. We need to look at the individuality of the patient in the context of his or her nucleotide polymorphisms and how many of those may be B vitamin-responsive-vitamin B1 as thiamin pyrophosphate, B2 as FAD-responsive, and B3 as NAD-responsive, or P5P-responsive for vitamin B6.

Alzheimer's disease, the most common cause of dementia in the elderly, is a progressive neurodegenerative disorder that gradually robs the patient of cognitive function. The prevalence of Alzheimer's disease in the United States is estimated at 2.3 million. Incidence seems to double every five years after the age of 60. The increased prevalence among those aged 60 to 64 years suggests the United States will have between 5 and 7 million Alzheimer's patients in the next 10 years.

In 1991 the cost to the U.S. healthcare system was estimated at about $20.6 billion, going up to total cost, when we talk about all the services provided, to about $76.3 billion annually. Management of a single patient represents approximately $47,000 a year.[18] This care places a huge burden on the healthcare system.

Homocysteine and Alzheimer's Disease

Researchers are working to determine how much of Alzheimer's incidence is related to brain biochemisty, genetic polymorphisms, and undernutrition. A study in the New England Journal of Medicine showed that homocysteinemia is an independent risk factor related to Alzheimer's disease.[19]

Another paper, published in the American Journal of Clinical Nutrition, is titled "Homocysteine, B Vitamin Status, and Cognitive Function in the Elderly."[20] An editorial following that paper states that much of what we diagnose as Alzheimer's disease may be a long-stage outcome from suboptimal nutriture for B vitamins necessary for regulating that individual's homocysteine metabolism, and polymorphisms and risk tie together with ultimate outcome of a diagnosed disease. By the time the disease is diagnosed, according to this editorial, it is too late. We need to understand these particular risk factors and genetic uniquenesses early on.[21] Again, this hearkens back to Roger Williams's concept of genetotrophic diseases, proposed in the Lancet some 52 years ago.

B Vitamins and the New Medicine
Our understanding of neurodegenerative diseases, cardiovascular diseases, and diabetes is rapidly improving. We are beginning to understand the relationship of these disorders to polymorphisms and modifiable factors that may tie back to the simple B vitamins-B1, B2, B3, B6, folic acid, pantothenic acid. These vitamins may be able to optimize physiological function at doses far in excess of the level required to prevent beri beri or pellagra.

This is the new medicine we have been describing. This is personalized medicine, and it is starting to get the underpinnings in terms of fundamental basic sciences and clinical experiential outcome that will give it legs, so to speak, and a future. It is the 21st century model of medicine that does fulfill the criterion of being evidence-based.

On Side II our Clinician of the Month will expand this integration concept in the new medicine of the 21st century.

INTERVIEW TRANSCRIPT

Mary Louise Hardy, MD

Director of Integrative Medicine
Cedars-Sinai Medical Center
Steven Speilberg Bldg.
8723 Alden Drive
Room 299 D
Los Angeles, CA 90048

JB: Our Clinician/Researcher of the Month this month fills both roles. Dr. Mary Louise Hardy is Director of Integrative Medicine at Cedars-Sinai Medical Center. She received her undergraduate degree in biochemistry at Vassar College and her MD at Louisiana State University School of Medicine, followed by an internship at New England Medicine Center, Tufts University, Boston. She went on to the Institute of Medical Herbalism for Certificate and Advanced Certificate training. Dr. Hardy is a balanced professional, both in her activities in traditional internal medicine and her constantly expanding expertise in botanical medicine. She combines clinical work with research and integrative and traditional medicine. She has worked with Dr. David Heber, from the University of California Los Angeles, whom we have interviewed in the past on FMU, who is involved in studies in nutritional medicine.

Origins of Interest in Botanical Medicine

Dr. Hardy, we are pleased to have you as our guest. Botanical medicine has great opportunities for providing good, but it is also fraught with misunderstanding and confusion. We are happy to have you help us separate the wheat from the chaff. How did you move from biochemistry into medicine, and then into botanical and integrative medicine, and working at the Cedars-Sinai Integrative Medicine group, which is respected round the world for its quality work?

MH: I grew up in a medical family. I'm a fifth-generation physician. This was in some ways the family business. I like to joke that growing up in the Deep South, in New Orleans, the most alternative thing I did was go into medicine at all as a woman. Everything else was kind of a snap after that. I saw a lot of different styles of medicine just in the experiences inside my own family. I made rounds with my grandfather, who was an old-style family practitioner, so I was lucky to have that kind of base upon which to build my own medical practice. I was always passionately interested in what my patients had to say and what their lives were like, because that was clearly the source from which my grandfather's practice arose.

I was lucky to be able to go to a liberal arts college, so I not only learned my science, but I also had a really well rounded background. I learned my science almost as a philosophy of science, or as a professional who was learning science. We didn't memorize things for the sake of memory. Of course we had to learn the inner pathways of intermediary metabolism. Then we were tested on what would happen if you stressed a pathway here; what would happen if you hit a rate-limiting step based on substrate or based on some characteristic of the enzyme in this reaction.

Science as an Accumulation of Expertise

We learned a lot of our material from original studies, and if you spoke the original language, you were supposed to get the study in the language in which it was originally published. That was a great grounding in realizing that science wasn't a matter of rote memorization; it was a matter of the cumulative efforts of a number of brilliant people to solve problems. Knowledge was, in some ways, accreted, each person contributing his piece over time.

Then I went to medical school, which was both a blessing and kind of a shock. It was much less of an intellectual pursuit and much more just a process of mastering a massive volume of material. But that was the grounding for the interest I had in science and the family tradition I inherited.

Communicating with Patients

I got my medical school training in New Orleans, where there's a pretty active folk tradition, especially if you're available to hear it. I started having experiences with alternative practitioners at the same time I was acquiring my conventional medical skills. That continued through the rest of my medical training, and then my residency was in Boston at Tufts New England Medical Center, which is on the edge of Chinatown. We provided primary care for a very unassimilated traditional Chinese population. An experience I had that provided an epiphany was to have flash cards made so I could speak to my patients when we didn't share a common language. I had a whole series of cards to ask them about their medical conditions. Then, on my last card, I asked: "May I examine you?"

As a well-trained, conventional physician, I would take out my stethoscope, and as an absolutely ethnocentric patient, the mostly women I was seeing would roll back their cuffs, unbutton two buttons around their naval, and stick out their tongue. I realized there was something fundamentally missing in

that transaction when we came at it from two such different perspectives. Learning to communicate was the beginning of the really professional part of my training in trying to understand what was happening with the traditional Chinese medicine patient.

Learning from Patients
My patients often led me as I went into practice. There would be conditions for which the Western medical model did not have a good solution. PMS is a classic example. I listened to my patients, and when they told me about things that made them better, I would investigate. Over the last 15 years, I've taken a lot of training and have had a personal interest in botanical medicine, which I've pursued in a number of different ways. That's the tiny capsule version of how my training happened.

Coming to California from Boston was an interesting transition because here there was a lot more overt practice of alternative methodology, even 15-20 years ago. Actually, the patients, again, were very receptive to the idea of a physician having something intelligible to say about the therapies they were interested in.

Balancing Complementary Forces in Medicine
JB: That rich background gave you a broad perspective as you moved from private practice in internal medicine to your position as associate clinical professor of medicine at the University of Southern California and Medical Director of Integrative Medicine at the Cedars-Sinai Integrative Medical Group. The transition from private practice to your current position, in which you are overseeing and educating some of your colleagues, must have been an interesting one.

MH: In my private practice, I was doing some of this, but just not as much. If I had to describe my career in a nutshell, I'd say it was a balancing of opposites, or a balancing of complementary forces. It is the academic versus the practical, conventional medicine versus alternative medicine. These two balancing back and forth would continue. I think it's a much richer perspective than trying to force oneself into one extreme or the other. You lose what you're calling richness and I call perspective. I think that, ultimately, patients suffer if they don't have the widest range of possibilities available.

Basic Information for Patient Communication in Integrated Medicine
JB: For the benefit of our practitioner listeners, who may be exploring or already practicing integrated and nutritional medicine, please explain how to find this balance How do you bring this knowledge, this wisdom, into your daily work as you communicate with patients?

MH: I speak from my personal perspective and from what I believe an integrative physician should be. Discussions of what an integrative physician should be are all over the map, from the physician transformed into the alternative provider to the physician basically just having a peripheral role. There probably will be a number of levels on which physicians will engage with this material. There should, however, be some basic, first-tier knowledge that most physicians in this country should possess.

Most of the information they're going to want to know about is safety information. Even if I don't understand the rationale behind what my patients are doing, I need to know at least enough to engage intelligently with them when they bring up an issue such as whether or not to take ginkgo. What are the pros and cons? I may not know enough to prescribe gingko de novo, but I should know enough at least that, when someone brings this up to me as a physician prescribing medication, I am aware if there is a

potential for interaction. What does a good product look like? What about this patient's particular medical condition would put him or her at risk for that therapy? Those are basic pieces of information that most physicians should know.

Integrated Medical Teams

In addition, I think the physician should know enough about common alternative therapies to appropriately triage patients to care. If I see someone with back pain, the first thing I do is the Western diagnosis-make sure it's not a malignant condition. I make sure there's not an imminent surgical process that needs to happen to save function. Once I know what territory I'm in, a range of possibilities open up. They include everything from mind/body interventions to herbal interventions, topically as well as internally, manual therapies, body work, etc.

That matching function is aptly led by a physician who is part of a multidisciplinary team. That's my vision of the direction I would love to see us go, either in formally constructed teams, or informal networks of care. The physician is able to help patients decide, within a range of therapies that are appropriate for them, where they will direct their attention and effort. It engages patients in their own care and helps physicians direct the patient appropriately to get the best therapy for the least invasive work.

Medical Teamwork

JB: A number of years ago I conducted an interview with Regina Herzlinger, a professor at Harvard University in the business department, whose work was on financing and health care futures. She had written a book, Market Driven Health Care, in which she predicted we would see more and more complementary providers group together to provide services around specifically focused clinical problems, thereby bringing multiple perspectives to the solution of those problems. Is that in line with some of the things you're doing now in your present role?

MH: When we had our full active clinical practice, we had an interesting team. There were three physicians (including a fellow we were training), an osteopath, a massage therapist, and two acupuncturists. We were able also to tap into the community for additional resources as we needed them. We sent our patients to our Cedars-Sinai Pharmacy for their botanical therapies and supplements. It was exciting that we had a multidisciplinary team that worked together, got to know each other, referred to each other, and sat and thought together about patients.

We had meetings once a week at which we discussed cases. There was an opportunity for all of us to sit down together and say, okay, I'm at a tough spot with this patient. Here are the things I've done; how can you help? It was not just support for the clinician, which we know is great, because often we practice solo without the ability to bounce things off people. We also had five minds thinking about something instead of just one. Anything that's better for the patient is to be promoted.

Combining Botanical and Evidence-Based Medicine

JB: You have been able, in your practice, to balance a number of things that might appear to some people to be opposites. You have combined Western and Eastern thought, empirical and observational medicine with the reductionistic and mechanistic. Your background includes both herbalism and evidence-based, biochemically oriented botanical medicine.

You have been involved in a variety of research projects. You have provided technical support for the

National Center for Complementary and Alternative Medicine. You conducted work on breast cancer in relation to herbals like black cohosh. You studied the safety and efficacy of Ephedrine for weight loss and athletic performance. You have provided qualitative analysis of factors promoting or inhibiting integration of complementary and alternative medicine into a hospital-based program. This work spans a range of perspectives and expertise. How have you managed to make a unified whole of herbalism and the evidence-based perspective?

MH: At some point in my life someone could have said what a hodgepodge I was creating, with a little of this and a little of that. That's kind of my nature. I'm just happy that it's come together into what looks like a coherent whole to someone on the outside.

We don't have a way to train people to do this kind of work right now. That's part of our problem. Medical schools are beginning to integrate into their curricula things I acquired by individual experience or going to individual classes. I'm hoping we can start to put some of these pieces directly into medical education.

Evidence-Based Medicine

The evidence-based medicine work evolved from a project I was doing in my practice before I came to Cedars. I was participating in developing practice guidelines for inside the hospital, mostly for conventional medical diagnoses. I met a brilliant PhD nurse/statistician. I worked with her in preparing data sets, looking at the effects of intervention, individual physician practices issues in the hospital. In doing so I developed a great respect for the way to acquire data, validate it, present it, and analyze it. That project was an unexpected benefit when I came to Cedars. Not only could I do the education, the clinical piece, but I could also put some rigor into looking at our research and analyzing the work that had gone before.

Most of the work I'm doing that you're talking about, the technical support and most of the analytic pieces, are done in conjunction with the RAND Center, which is the health evidence-based medicine center at RAND. It is a rich experiential group. We are completing our fifth and sixth projects on that technical support grant, and they've spanned a great range. The first year we did Ayurvedic treatment for diabetes, as well as mind/body interventions for gastrointestinal disease. The second year we looked at SAMMY and analyzed several alternative cancer programs. This year we're looking at antioxidants in treatment and prevention of heart disease and cancer. Doing the work becomes the way to develop the skills.

Ephedrine Study

JB: I know you are currently involved in an Ephedrine study. Could you tell us about that study and its objectives?

MH: The sponsor of the study is the Office of Dietary Supplements under the auspices of the Agency for Health Care Research and Quality. The charge we have is to examine the literature on Ephedra and Ephedrine for efficacy and safety in weight loss and athletic performance enhancement. We're doing our usual exhaustive search of the literature and rigorous analysis of the material we find. Each of these projects takes about a year to do. There's a team of us who participate. We may have five or six people working for a year to produce the material.

In the SAMMY report we did, for example, we analyzed 101 studies for depression, osteoarthritis, and liver conditions. We found 101 controlled clinical trials in the literature, and 30 of them were in Italian, so we found Italian reviewers and extracted all the data, then completed the analyses out of that material. That's an example of how this material might be switched around so that at the end it is not only interesting at an academic level but also at a clinical level. You want to be able to say to a practitioner, this is the kind of patient, this is the kind of intervention, this is the treatment pattern that was most effective in terms of length or intensity of treatment. These are reasonable expectations you can set; this is the best effect we saw. When they go to treat their own patients, they have a context for that intervention.

For example, in the SAMMY study, we also did a non-rigorous kind of survey, looking at adverse events in patients represented in the studies. We can also say to the practitioner, here's a table of 100 studies; here's what was reported for adverse events.

Availability of Research Reports
JB: Are these final documents available? Can people find them and benefit from the knowledge that went into their formulation?

MH: The Agency for Health Care Research and Quality (AHRQ) funds the evidence-based practice centers. That's the aegis under which we operate. They publish their reports on their web site at http://ahcpr.gov/. Our first two reports have been published on the web. You can also request from them a bound copy that would contain our bibliography of the hundreds of other articles we've looked at as background and supportive material. As we finish this work, it is published out on the web.

http://ahcpr.gov/ for Research Reports
JB: We will make sure that web site address gets put on the summary cards for people who are going to follow up on this. Thank you for the citation.

MH: In addition, two other evidence-based practice centers have done two other reviews that will be of specific interest to your population. One is on garlic and one is on milk thistle. When you go to look for ours, look for those two, as well.

Ephedrine Controversy
JB: Thank you. Do you have any preliminary thoughts about this Ephedrine controversy right now from your experience?

MH: Unfortunately, we're right in the middle of looking at the data so I'm keeping an open mind as a matter of scientific integrity, but I think there's certainly going to be a lot of interest in what happens with this material.

Black Cohosh
JB: Tell us about black cohosh. I know you have done a definitive review. I've had a chance to read that and it's the most scholarly review I've seen.

MH: That's an herb that I've liked for a long time. I know you're supposed to be intellectual when looking at the stuff, but there's also a part that when you find an herb that's easy to use, is a real workhorse, and fits right into your protocols, and the science happily supports its safety, you are very pleased.

I also like the fact that it's a Native American herb. I have a great interest in the history of these things, so I find it highly ironic that the American Indians taught the eclectic physicians about this particular herb in the 19th century. They taught their European colleagues so that when we went through our Dark Ages of loss of all of our botanical practice, the use of that herb was maintained in Europe, especially by the German phytomedicine industry. That way, we were able to take it back during the renaissance of our interest in herbal medicine in the 1970s.

Black Cohosh and Menopause

Black Cohosh is an interesting herb. We use the root. It was initially thought to have estrogenic properties because the clinical effects of the beneficial outcomes on hot flashes and such in menopause were pretty well described anecdotally. The original researchers were sure it was going to be an estrogenic herb containing a flavonoid that would act on the estrogen receptor. One study did show the isolation of formononetin, but that work has not been replicated. All the currently available literature suggests, on the contrary, that the terpenoids that are the active principle, in fact, do not activate alpha or beta receptors, and in mixing studies with breast tumor cell lines, actually inhibit growth of estrogen-sensitive breast tumor cell lines.

I have patients in my practice who are entering menopause. Especially if they're at risk to breast cancer, or have already had breast cancer, this seems to be one of the safest alternatives to help them manage menopausal symptoms.

Vitex Agnus Castus

JB: That's fascinating. How would you contrast that to Vitex agnus castus that has also been used a lot in these applications?

MH: I tend to see vitex as being more useful in younger patients. It's incredibly useful in PMS; it's incredibly useful in conditions in which the second half of the menstrual cycle is a low progesterone state. Usually the corpus luteum isn't well supported. If you have your regular menses based on a failure to ovulate, or a failure to maintain the corpus luteum effectively, it's been used in infertility work with those kinds of indications.

One study from Germany suggests that Vitex agnus castus would be helpful for women with failure of the second half of the cycle and subsequent infertility. It's very useful for women who are in the perimenopausal phase. They haven't stopped their menses yet and they're starting to have a variety of symptoms including regular cycles and heavy and light cycles, or a recurrence of PMS they haven't had for years. I find vitex incredibly useful there, sometimes in combination with black cohosh. Again, the literature would support that application because most of the positive literature has been in the treatment of PMS and it's brilliant for that. The usual course length that's been show in the research to have effect is three months. You have to wait that long to see the effect to make sure you're going to see the full effect.

Valerian

JB: A lot of women in the perimenopausal stage also suffer from sleep disturbances. I know you've had some experience in writing a review on valerian. Is that an appropriate application in that area?

MH: It's a great application. I think valerian is another herb that is woefully overlooked in phytomedicine practice today from the medical point of view. Herbalists are aware of the benefits of valerian. This is a

good example where you'll know something from the scientific point of view and you'll learn something else from more the folk or the European traditional herbal tradition, if I can characterize that without diminishing it. If you look back at the eclectics, back at the European herbal tradition, valerian is described as a relaxant, not just for psychological relaxation, but also as a tissue relaxant.

If you look at the scientific literature available on valerian, you find it's an interesting herb because it's probably not a hypnotic. It doesn't "knock you out." It permits you to sleep as opposed to putting you to sleep. One really good review from Germany is probably the best study that's been done. It was done in 1996, so it's a few years old.

Normalizing Sleep Patterns with Valerian

What I learned from my review of valerian literature is an appreciation for the fact that valerian probably helps normalize abnormal sleep patterns. There's some EEG evidence available in the literature. If you read this literature carefully, you find it's not a hypnotic; it doesn't initially put people to sleep on a one- or two-dose use. But if you use it for two to four weeks, you will normalize sleep patterns. Happily for us, it works best in people with the most abnormal patterns.

Again, it's a matter of creating proper expectation for patients and telling them it isn't going to knock them out like a sleeping pill. Over time they will have more normal sleep patterns and awake more refreshed. They won't be dealing with the consequences of the benzodiazopene effect on sleep. I use that a lot for people who need restorative sleep with a chronic interruption in their sleep pattern.

Interactions of Botanical Medicines

JB: What can you say about the complex interaction of one botanical medicine with another, in which the concern is that one is antagonizing or having an adverse effect on the other, as with pharmaceutical compounds that vie for similar detox pathways?

MH: After we talk about this, we probably ought to talk about herb/drug interactions to finish off that question. Luckily, I was taught by a couple of brilliant herbalists about the combination use of herbal medicines. Amanda McQuade Crawford and Mary Bove were two of my teachers in this area. This is where I learned the most sophisticated use of the herbalist tradition.

There is a rationale for combining herbs to support, in direct and overlap therapies. There is that tradition and that's a rigorous knowledge. It is not submitted for double-blind, placebo-reviewed trials, but there is rigor in the intellectual application of experience culled over a long period time. This is one of my balancing acts. How do you balance that kind of information against the reductionistic testing model? We are not going to get trials. We might, but I think we're going to have very few of those, where we'll take an herbal formula or a set of herbal interventions, and let's say there are five things. We'll test the whole thing; we'll test all four things separately; we'll test these three together with those three, or do some kind of regression analysis to try to figure out what portion of a formula is the most active.

Validating Traditional Sources

For those kinds of interaction questions, we have to first have to look at where the most data is available. We will have to go back to traditional sources and then validate that with our biochemical knowledge. If these are the constituents, and these are their activities, and this is the pharmacology, is that a reasonable expectation? Or, does it bring up questions as we start to concentrate medications and make them less

herbal and more drug-like? Are we going to distort that traditional information and have to be prepared for new findings that we wouldn't expect from the traditional data?

Drug/Nutrient Interaction
JB: That's very interesting. Can we segue to the drug/nutrient interaction question? Is that a similar type of logic?

MH: Yes. In fact, that's one of the things I've had the most interest in for the longest time. It's like a hobby. You collect a case study here, a case report there, look at a little animal data over there. We are beginning to accumulate enough information that I think we are going to be able to start drawing some information out from that. Happily, our colleagues in pharmacology and pharmacy departments are starting to do really nice bioavailability studies and pharmacology for kinetic studies to help us understand which of a myriad of potential interactions are actually likely to be real interactions.

The last two years with St. John's Wort provide a great example of needing to have this information because you need to know that it activates hepatic detoxification enzymes, and then meticulously figuring out which substrates at that enzyme are going to be most affected. St. John's Wort also seems to affect additional cytosol receptors. With other narrow therapeutic index drugs, like Digoxin, there are real interactions.

The Practitioner's Responsibility
As practitioner and physician, one should be responsible for knowing about those so one can either take them into account or suggest an alternative, more reasonable therapy for the patient. For example, if a patient's medicine is more critical to his or her general well being than the herb, then it may be possible to choose another herb. On the other hand, if the medicine is less critical to the patient's well being than this herb might be, then you might manage the medication a little bit differently.

The tricky thing about herb/drug interactions is that the majority of this data is still at the anecdotal, case report level, unvalidated. In addition, even places where we're starting to have some good pharmacologic data, like the St. John's Wort, interaction at the cytochrome P450, the substrate reactions are not consistent. For example, for things like Indinovir, which is an HIV medication, or cyclosporin, which is immunosuppressant, significant effects on tissue levels of those medications decreasing them have been consistently demonstrated.

Evaluating Available Information
On the other hand, Tegretol, which operates at the same enzyme system, shows no effect with use of St. John's Wort. It's not a black/white question. Even more than that, what's done with that information, rather than have a sophisticated, appropriate thought about St. John's Wort, might not be for this patient on this medication.

The information gets blown up in a very negative way so people assume St. John's Wort is dangerous. As with all interventions, St. John's Wort has pros and cons, and there are some things you need to know about it. I would encourage your listeners, especially physicians who prescribe medications, to attend to this area because it's one of the major places where research is actively developing.

The Feminine Perspective

JB: As I look back over the history of FMU, you are one of three eloquent clinicians and researcher I have interviewed in the area of botanical medicine. The other two were Mary Bove and Dr. Tieraona Low Dog. It is interesting that you three are all women. We have yet to encounter a male with the same vision and perspective about how these concepts are integrated within medicine. Why is this?

MH: I can't comment on the absence of men, although that's a tempting target. What I can say is that one of the reasons women feel so comfortable in this tradition is that, just as I feel I inherited the conventional medicine aptitude from my male line, I think most women feel they've inherited a naturalistic and herbal tradition through their female line. You can trace back the lineage of women's care through the ages. Throughout the Middle Ages, if you weren't in a monastery, you were usually a woman. If you were taking care of women, especially in childbirth and in issues around reproduction, you were almost certainly a woman. I think for most of us, this is a very satisfying tradition that has not just immediate applications, but historical resonances that I just really enjoy.

An Invitation
JB: I think you were very tactful in the way you phrased that. I didn't feel offended; I felt empowered. Thanks.

MH: We are looking for someone to join the party. The more, the merrier!

Encouraging Practitioner Evolution
JB: Well, we're all learning here; we're all aspiring. You have given us much news to use, as well as a philosophical underpinning. You have provided encouragement for physicians and practitioners to take the next step in their evolution. Thank you, and keep up the good work.

MH: It's been a great pleasure. Thank you for giving me this opportunity.

I will close with one last thought about the B vitamins. One of the B vitamins, niacin, and its derivative nicotinamide, has been in the news extensively recently as a consequence of the recognition that it appears to have an ability to reduce the onset of type I diabetes. A recently published meta-analysis study dealt with nicotinamide treatment in patients with recent onset of insulin-dependent diabetes mellitus. The combined analysis demonstrated a therapeutic effect of nicotinamide in preserving residual β-cell function when it was given at the early diagnosis of IDDM in addition to insulin.

The doses administered in this placebo-controlled trial were not those we would consider excessive for nicotinamide, but we would certainly consider them therapeutic and not nutritional.[22] The doses used were commonly in excess of 500-1000 mg taken twice daily. If we start examining this dosage, it might be considered nutritional pharmacological intake versus just looking at nutritional levels required to prevent pellagra.

Type I Diabetes Study Conclusions
Currently ongoing studies in the United States and in Europe are looking at early intervention under placebo-controlled blind trials, to modify type I diabetes, utilizing intervention with nicotinamide. Early reports from this research are encouraging. One such report appeared in the Journal of Pediatric Endocrinology & Metabolism. This trial seeks to demonstrate a 50 percent treatment differential potential between those that receive nicotinamide versus the control populations[23], a fairly rigorous criterion.

Research is beginning to suggest there is something about prevention of insulitis in individuals who have early-stage symptoms of juvenile onset diabetes, by the administration of nicotinamide, an interesting observation, because we know that nicotinamide inhibits the production of proinflammatory mediators like interleukin-12 and tumor necrosis factor- in peripheral whole blood in people at high risk to developing type I diabetes. This is reported in Diabetes Research and Clinical Practice[24].

B Vitamins and Oxidative Stress Inflammation
Nicotinamide appears to play a role in the reduction of oxidative stress inflammation. We can tie this back almost 50 years ago to the observations of Dr. William Kaufman, an internist in Connecticut and New York. He showed that osteoarthritis could be treated, at least symptomatically, by high doses of nicotinamide. He administered 2500 to 3000 mg a day in divided doses to patients with osteoarthritis. These patients showed improved joint mobility, range of motion, and lowered pain scores. At that time, there was no known mechanism to explain that response, this research was written off as anecdotal and unsupported.

Now we are starting to understand the bioichemical mechanisms by which high-dose niacin may influence function. They go beyond nucleotide polymorphisms to activity of an enzyme called polyadenylribososylpolymerase (PARP) and its influence on oxidative reactions and gene expression. It is a complicated topic, but insulitis reduction, osteoarthritis reduction, and also the apparent influence of nicotinamide in preserving neurological function may tie back to this similar and singular mechanism.

Safety considerations of high-dose nicotinamide were reviewed in Diabetologia[25]. The authors of this study showed that high-dose nicotinamide should be considered as a nutritional pharmacological agent. It may have potentially toxic doses in excess of 3 grams a day, but up to that level, there is no evidence that it produces hepatotoxicity. As with all pharmacological therapies, however, one might want to follow liver enzymes just to make sure the person is responding favorably. It is a very benign, reasonably safe B nutrient. It does not produce the flushing that niacin itself does, nicotinic acid, and it appears to have a role in preventing type I diabetes through reduction of insulitis and inflammatory mediators.

One might also ask about the influence of nicotinamide on type II diabetes and insulin secretion. One paper in this area, which appeared in the Archives of Diabetology, looked at a controlled trial of nicotinamide in improving insulin secretion and metabolic control in lean type 2 diabetics who had secondary failure to sulphonylurea therapy.[26] Here is another role for the B complex nutrients that cuts across neurological effects, joint space osteoarthritic effects, and β-cell function effects with diabetes and glucose tolerance.

As we study old things in new ways, we learn that some observations made decades ago were more than just curious anecdotes. They were prescient observations, and we should come back and re-explore all of these things in light of our genomic model of medicine in 2002.

Thank you. We look forward to visiting with you in September.

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