PARADIGM SHIFT: THE END OF "NORMAL SCIENCE" IN MEDICINE
UNDERSTANDING FUNCTION IN NUTRITION, HEALTH, AND DISEASE

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"Discovery consists of seeing what everybody has seen and thinking what nobody has thought."

—Albert Szent Gyorgyi, 1937
Nobel Laureate in Physiology and Medicine, the scientist who isolated vitamin C.

On July 4th, on a rafting trip in the Grand Canyon my wife and I experienced a different kind of fireworks. Shortly after falling asleep under the stars at the bottom of the Canyon, my wife woke abruptly with sudden severe abdominal pain. After a very rough night, a helicopter evacuated us to the Flagstaff Medical Center where she underwent surgery for a ruptured appendix.

In the recovery room, I asked the surgeon about his plan to provide adequate nutrition during her recovery from severe peritonitis and sepsis. I was aware of the studies reporting more rapid recovery from surgery and critical illness with the use of intravenous amino acids, fatty acids and other nutritional support, and that macronutrient and micronutrient needs increase dramatically in acute illness.[1] His comment reflected the pervasive view in medicine regarding nutrition: nutrients are only important in malnutrition or deficiency states. He assured me that the studies only showed benefit in moderately malnourished individuals and he would wait until day five after surgery to implement support other than dextrose with normal saline.

Those who believe that there are two categories of patients, those who are malnourished or vitamin deficient, and the rest of us, are fundamentally misguided and misinformed given the current depth of understanding about the role of nutrition in health and disease. Nutrigenomics, the study of the influence of nutrients on gene expression in acute and chronic illness, is the fulcrum for a changing medical paradigm. Kaput[2] outlines the potential for this paradigm, which he describes as "the next frontier in the post genomic era," to radically change our approach to health and disease. In fact, for the first time in medicine, we have the opportunity to not only treat disease but to create health.

Kaput explains nutrigenomics in the following way:

"The interface between the nutritional environment and cellular/genetic processes is being referred to as "nutrigenomics." Nutrigenomics seeks to provide a molecular genetic understanding for how common dietary chemicals (i.e., nutrition) affect health by altering the expression and/or structure of an individual's genetic makeup. The fundamental concepts of the field are that the progression from a healthy phenotype to a chronic disease phenotype must occur by changes in gene expression or by differences in activities of proteins and enzymes and that dietary chemicals directly or indirectly regulate the expression of genomic information. We present a conceptual basis and specific examples for this new branch of genomic research that focuses on the tenets of nutritional genomics: 1) common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure; 2) under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases; 3) some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases; 4) the degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup; and 5) dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used to prevent, mitigate, or cure chronic disease."

The study of nutrigenomics[3] is leading medicine in a radical transformation akin to the change in our conception of the universe, time and space that occurred when the deficiencies of Newtonian physics were illuminated by quantum physics. It is an era where genetic predisposition replaces Mendelian genetic determinism, where biochemical individuality replaces biochemical homogeneity, where the importance of

the biological terrain or internal milieu exceeds that of the external invader. However, acceptance of the change, seeing what is right in front of us is difficult. As RD Laing states in *The Voice of Experience*:

> *"Our most self validating premises are the most ingrained, our hardest programs are the most self validating, our way of looking is not easily disturbed by what it sees, let alone by what it cannot see."*

WHAT IS "NORMAL SCIENCE"?

> *"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."*
>
> —Max Planck

In the *Structure of Scientific Revolutions*,[5] Thomas Kuhn analyzes the process of changing paradigms in science. He describes how in each discipline of science, new advances and theories are slowly adopted, and once they are, they become "normal science," or the collective beliefs and theories of the existing scientific leaders. To overturn "normal science" often requires decades of mounting evidence that the old theories no longer hold true. Medicine is replete with examples of "normal science" becoming obsolete, and newer theories ignored because they don't fit the old paradigm. Despite the crumbling of the medical system around us, many of us hold on to the system of differential diagnosis, biochemical homogeneity and pharmaceutical therapy as the answer to most chronic lifestyle and "long-latency" nutritional deficiency diseases. There are a number of organizing principles and themes that underlie nearly all disease emerging from the medical and basic scientific literature: inflammation, oxidative stress, nutritional imbalances, mitochondrial dysfunction, hormonal imbalances, impaired detoxification, biochemical individuality and the possibility of changing gene expression through transcriptional or post translational modification of gene products. Jeffrey Bland, PhD, a student of Linus Pauling, who is featured in the Conversations section in this issue of *Alternative Therapies*, has helped to crystallize and advocate for this emerging new medical paradigm.

Medicine is now in crisis. A brief examination of the pitfalls of "normal" medicine will help illuminate the need for change. The adoption of new organizing principles and concepts that form the basis of the new medical paradigm can help us successfully navigate health and illness in the 21st century. The story of the role of vitamins in health and disease is a useful model to help us shift from a medical model based on pathology, to one based on deviations from optimal function. We have yet to accept the definition of health proposed by the World Health Organization in 1948, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity." [6]

THE SLOW ADAPTATION TO CHANGE IN "NORMAL MEDICINE": A HISTORICAL PERSPECTIVE

> *"Those who control access to funding and the channels of scientific communication tend to be believers in the established views."*[7]
>
> *"...scientists cannot see the way they see with their way of seeing."*[4]
>
> —RD Laing

There are many examples of resistance to change in the history of medicine. We are again at the edge of a major transformation. Nutrigenomics is the use of nutrients of varying and sometimes high doses to influence gene expression with the goal of not simply treating disease, but optimizing function. I believe the application of nutrigenomics is a concept poised to change medicine forever from a pathology-based science to a health-based science. A few highlights from the history of medicine will emphasize the unnecessary delays common in incorporating new discoveries into practice:

- When Edward Jenner thought of the idea of a smallpox vaccine in 1797, the Royal Society of London scolded him for risking his reputation on something "so much at variance with established knowledge, and withal so incredible."
- When the Hungarian physician Ignaz Semmelweis discovered that physicians' unwashed hands caused fatal infections among new mothers at the University of Vienna in the 1850s, he lost his own position there and died in disgrace.
- When the American writer and physician, Oliver Wendell Holmes published an article on the prevention of "childbed fever" through hand washing it only brought him bitter abuse.
- Alexander Fleming discovered penicillin in 1929. W.H. Florey and E.B. Chain, after a delay of 12 years, first used it therapeutically in 1941.
- Kilmer McCully, the boy wonder pathologist from Harvard, first proposed the role of folate deficiency and homocysteine[8] in cardiovascular disease in the late 1960s, only to be banished from Harvard to continue his work at the Veterans Administration Hospital in Rhode Island. The testing and treatment of hyperhomocysteinemia is still not accepted, nor performed by mainstream medical practitioners.

Medicine is also replete with discarded therapies that were well accepted at the time, such as the removal of the colon or all the teeth to treat chronic disease, or more recently low fat diets for weight loss and the prevention of cardiovascular disease,[9] and hormone therapy for prevention of heart disease in post-menopausal women.[10]

There is much in medicine and science that we cannot see with our current vision. A new framework and new organizational concepts are needed in a science with very few true "theories." Medicine, as Lewis Thomas stated, is the youngest science. Linus Pauling explains that though "medicine is largely based on the sciences, it has not yet become a science."[11] We need a unify-

ing theory of health and disease. We are only now are on the verge of forming a clear picture of what that might look like. A theory can be defined as "a set of facts, propositions, or principles analyzed in their relation to one another and used, especially in science, to explain phenomena."[12] Medicine has come of age and we are at the edge of development on an entirely different worldview and theory of health and disease. The theory of nutrigenomics is leading that new frontier.

We can gain insight from examining the historical context of a few previous theoretical leaps in medicine:

Pellagra, beriberi, and other nutritional diseases at the turn of the century were considered the result of "foreign invaders" or some external "toxic factor." This was entirely in keeping with the infectious model of disease at the time. It required radical self-experimentation to shatter this concept. Pellagra was prevalent 100 years ago and was manifested by dermatitis, diarrhea, dementia, and death. It was thought to be the result of an infection carried by insects. However, in 1914, Joseph Goldberger, an officer in the US Public Health Service, doubted the infection theory because no doctors or nurses caught pellagra from their patients. To disprove the theory he actually ate skin scraping and excreta from people with pellagra. He subsequently was able to show that it was the absence of something in food that caused the illness. It wasn't until many years later that the Nobel Prize committee awarded a prize for vitamins. Their reluctance may have been influenced by the comments of skeptics that vitamins were only hypothetical entities postulated to explain various phenomena: "no one had ever seen one."

> *At times we shall simply have to admit that, one way or another, what we can neither explain nor understand certainly doesn't cease to exist because we cannot see how it does or why it should.*[4]

At one time, our belief that ulcers were caused by stress or psychological factors was so ingrained in medicine that despite repeated observations of bacteria at the site of ulcers, their etiologic role was ignored until a gastroenterologist and pathologist from Australia saw what everyone else could not.

A 1967 review of the causes of peptic ulcer disease blamed dominant mothers and passive fathers for ulcers.

> *"...certain patterns of relationships were more common in 'ulcer' families. Thus the mothers of ulcer patients tended to have psychogenic symptoms, and to be striving, obsessional, and dominant in the home; fathers tended to be steady, unassertive, and passive...The description of these families...emphasizes the conflict in duodenal ulcer patients between dependence engendered by a powerful mother and demands of adult roles."*[13]

This view held strong until 1982 when Barry Marshall, MD, ingested cultures of *Helicobacter pylori* and developed gastritis. After Dr. Marshall underwent endoscopy and biopsy, and the pathogen was re-isolated, suddenly a bland diet, antacids and psychotherapy were no longer the prescription to ameliorate ulcers; antibiotics provided a cure. Only after his discovery was published in the *National Enquirer* in 1990, and came to popular attention, did researchers begin to look more closely at the connection between bacteria and ulcers.

Ancel Keys, PhD, also known as "Mr. Cholesterol," proposed in the 1950s that dietary fat and its effect on cholesterol was the key culprit in cardiovascular disease. Thus was born the low-fat diet which was based on little more than epidemiological research with its inability to prove causation. Fifty years later his theory is being challenged and Walter Willett, MD, MPH, from the Harvard School of Public Health, has published extensively on the lack of correlation between dietary fat and cardiovascular disease or obesity.[14]

As early as 1964, John Yudkin, a professor and physician at Royal Free & University College Medical School, University College London, challenged the unproven assumption that fat in the diet caused fat in the arteries. In the pre-Atkins era, he warned about the dangers of high sugar consumption and the risk of cardiovascular disease.[15,16]

> *"Epidemiological studies show that coronary heart disease is more common in wealthier countries than in poorer. Such studies cannot, however, isolate which of the dietary or non-dietary characteristics of affluence help to cause the disease; they provide only clues that need to be subjected to experimental study. Experiments should be designed on the basis of their ability to produce the multiple abnormalities associated with coronary heart disease (CHD) and not only hypercholesterolemia. They should also explain the association of CHD with obesity, diabetes mellitus, cigarette smoking, and physical inactivity. These considerations suggest that the underlying abnormality that produces CHD is a disturbed* ***hormonal*** *balance. Experiments have shown that a high consumption of sucrose produces not only the wide range of abnormalities seen in CHD but also an increased blood concentration of insulin and cortisol. Since a low intake of sucrose confers many other health benefits, it is a more logical dietary recommendation than that of substituting polyunsaturated fat for saturated fat."*[17]

Remembering basic biochemistry is helpful in understanding why sugar, not fat, may be more important in regulating our cholesterol.[18] A simple fact of biochemistry is often overlooked: cholesterol is formed from sugar, or more specifically fructose. Cholesterol is synthesized within the cell from acetate. Acetate is derived from dietary fructose. Sucrose (table sugar) is broken down into glucose and fructose. High fructose corn syrup also contributes to acetate and hence cholesterol formation. So it is sugar, not fat, that is the major culprit in elevated cholesterol. It is clear that 100% of type 2 diabetic men

have atherosclerosis, and that two-thirds of all patients presenting to the emergency room with myocardial infarction were either glucose intolerant,[19] or undiagnosed diabetics when given a 2-hour glucose tolerance test.

It is clear that the best lipid predictor of cardiovascular risk is not low-density lipoprotein (LDL) cholesterol, but the total cholesterol to high-density lipoprotein (HDL) ratio. Despite the absence of data in the abstract, a recent meta-analysis of the effects of dietary fatty acids and carbohydrates on the ratio of TC:HDL cholesterol[20] found the best predictor of the TC:HDL ratio was the amount of carbohydrates in the diet, not fat. In fact, its effect was nearly three-fold higher than the worst fat (butter) yet this result was not mentioned in the abstract of the paper. Despite our focus on lipid lowering, low-fat diets and statins over the last 20 years, the incidence of cardiovascular disease is on the rise. Like many studies where the results contradict the prevailing beliefs, the abstracts and conclusions do not reflect the data in the body of the paper. In an analysis of 44 articles and their abstracts published in major medical journals during a one-year time frame, the authors concluded that "data in the abstract that are inconsistent with or absent from the article's body are common, even in large-circulation general medical journals."[21] (See Figure 1.)

These examples illustrate the way medicine is rooted in beliefs, not necessarily objective reality, and how current medical practice is based on "normal science," not necessarily a newer conception of human physiology based on complex, self-regulating, higher order functioning elucidated by research in genomics, nutritional biochemistry, and molecular biology.

CHRONIC DISEASE AND THE FAILURE OF THE CURRENT MEDICAL PARADIGM

The current problems in medicine fall into two general categories. The first is the failure of access and universal coverage as a right for all citizens. This is the topic for another essay and a complex political problem. The second is the failure of the current model of medical diagnosis and treatment to successfully address the chronic disease burden in our society which affects 125 million Americans.

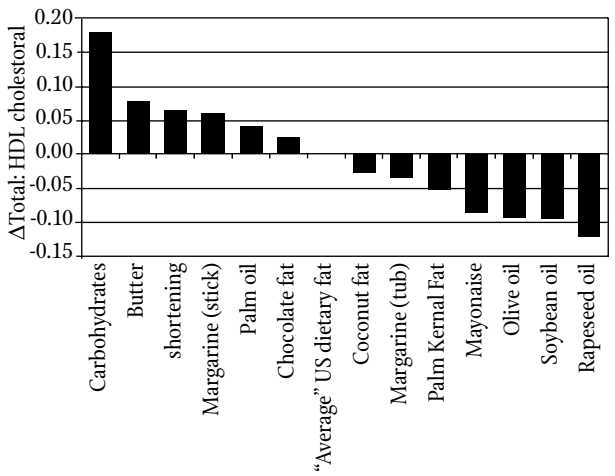

FIGURE 1 Predicted changes (delta) in the ratio of serum total to HDL cholesterol when mixed fat constituting 10% of energy in the "average" US diet is replaced isoenergetically with a particular fat or with carbohydrates.

Not only does our current approach fail to effectively diagnose and treat the underlying causes of chronic disease, found in the complex interaction of genes, lifestyle, and environment, it does great harm. As a nation we spend $1.6 trillion on healthcare each year. This represents 15% of our gross national product (GNP) or approximately $5,000 per person per year, or more than double the percentage of GNP spent by any other nation on healthcare. Despite this, we are 12th out of 13 industrialized nations in 16 major indicators of the health status of a population, such as life expectancy and infant mortality.[22] In fact we are 27th in life expectancy. Cuba is 28th. Yet that is not the worst problem. Our own healthcare system has been estimated to be anywhere from the 1st to the 3rd leading cause of death from hospitalizations,[23] hospital infections,[24,25] atypical drug reactions,[26] bedsores,[27] medical errors,[28] negligence,[29] unnecessary procedures and surgery[30] and more. The cost attributed to the harm caused by our medical system has been estimated at over $200 billion.

Other problems endemic to our medical system include: the fundamental limitations of our gold standard research tool, the randomized controlled trial (RCT) to assess lifestyle and nutritional interventions and long-latency deficiency diseases;[31] the lack of publication of negative medical trials,[32] thus providing a positive bias in medical literature; direct to consumer pharmaceutical marketing;[33] and heavy marketing of off-label uses of medications, including hormone replacement therapy.[32] Other problems are inherent to the practice of funding of research by private industry, often resulting in a financial conflict of interest[34] leading to suppression of studies or incomplete or biased conclusions. The most well known example of the latter was the comparison between generic thyroxine and Synthroid where the pharmaceutical company prevented the publication of the article, because the outcome was not favorable to the manufacturer of the trade name drug. With the exception of the National Institutes of Health and some private foundations, most of the research agenda is set by the pharmaceutical industry. Even the post-graduate education of physicians is primarily controlled and orchestrated by the pharmaceutical industry.[35,36]

Recent data point to the dangers of medical care and the fact that more care is not necessarily better. In areas where there are more physicians and a higher cost of care, there is less patient satisfaction and worse outcomes than areas with a lower cost of care.[37-39] Even when there are agreed upon standards for care and prevention, they are not met. The frequent lack of implementation of clinical science to clinical practice is inadequate and dangerous. For example, only 40% of patients receive aspirin after myocardial infarction,[40] and a recent study

of adults in 12 metropolitan areas found that only 54.9% of patients received the recommended preventive, acute or chronic care using 439 indicators in 30 acute and chronic conditions. The authors conclude,

> *"The deficits we have identified in adherence to recommended processes for basic care pose serious threats to the health of the American public. Strategies to reduce these deficits in care are warranted."*[41]

Lastly, the most important reason for the deficits in our healthcare is that we are locked into an old paradigm in medicine, "normal medicine." The model we use to diagnose and treat disease is based on "normal" science; the single invader, single disease, and single drug model of medicine. We have yet to embrace the new paradigm that for the first time allows us to personalize medicine. For the first time in medicine we have the opportunity to focus on optimizing function and enhancing health by understanding the complex high order functioning of the human being. The new paradigm allows us to remediate disease not by symptom suppression, but by assessing and treating the cause of dysfunction and illness. Van Ommen, in *The Human Genome Project and the Future of Diagnostics, Treatment and Prevention* published in the *Lancet* in 1999, foretold a new era in medicine:

> *"The combination of large-scale gene-expression analysis with pharmacological and nutritional studies will ultimately allow the stratification of individuals by their genetically determined abilities for drug and nutrient metabolism. Tailor-made treatments and lifestyle regimens will improve the effectiveness of therapies and reduce side effects. This will apply equally to monogenic disease and more complex gene-environment interaction disorders, like cardiovascular disease, cancer, hypertension, arthritis, migraine, epilepsy, Parkinson's disease, and Alzheimer's disease."*[42]

A NEW PARADIGM: UNDERSTANDING AND ENHANCING FUNCTION

> *"The science of medicine is perhaps the most frequently cited case of increasing specialization seeming to follow inevitably from increasing knowledge, as new cures and better treatments for many diseases are discovered. But as medical biochemical research comes up with deeper explanations of disease processes (and healthy processes) in the body, understanding is also on the increase. More general concepts are replacing more specific ones as common, underlying molecular mechanisms are found for dissimilar diseases in different parts of the body. Once a disease can be understood as fitting into a general framework, the role of the specialist diminishes. Physicians…may be able to apply a general theory to work out the required treatment, and expect it to be effective even if it has never been used before."*
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> —David Deutch, PhD, *The Fabric of Reality*

The science of medicine today is maturing and the old concept of the single agent (bacterium) causing a single disease (infection) treated with a single molecule (antibiotic) is being replaced by understanding of the complex higher order function involved in health and disease. Finally, we are able to peer into the underlying mechanisms of disease informed by the light of genomics, proteomics, metabolomics and nutrigenomics. Medicine is nearly ready to discard the old descriptive, phenomenological approach that emerged from the exigencies of medical practice in the early 20th century, where infectious disease was primary and the Pasturean model of outside invaders ruled. The organization of medicine into sub-specialties is an artifact of descriptive medicine that bears little relevance to biological principles. The current classification of diseases (ICD-9) is now less useful in understanding mechanisms and guiding innovative therapies in health and illness. Finally, we can move toward understanding and treating disease with a dynamic, functional model based on an intricate understanding of the nature of the interaction of the genome with the environment, especially in the field of nutrigenomics.

Insights from the history of vitamins illuminate the current "paradigm shift" in medicine. The current review of vitamin D in this issue is but one example of the shift in therapy from simply treating disease to optimizing function. The old model of nutrition is based on providing the minimum amount of nutrients, vitamins and minerals to prevent index deficiency diseases. How much vitamin C is needed to prevent scurvy, how much thiamine is needed to prevent beriberi? How much niacin is needed to prevent pellagra, or how much vitamin D is needed to prevent rickets? The answer is not very much. This is based on the concept that individual nutrients have one physiologic role, to prevent the index deficiency diseases. The current dietary reference intakes (DRIs) are based on this outdated concept. The deciphering of the genome now helps us recognize the biochemical variability within the population, and our unique nutritional and biochemical needs. We have approximately 30,000 genes, not that different from an earthworm. What makes us different are the 1.5 million polymorphisms (single nucleotide polymorphisms or SNPs) that create unique biochemical needs within the population. One-third or more of these SNPs or "mutations" affect coenzyme-binding sites for vitamins or nutrients, and therefore have a role in disease and dysfunction. Bruce Ames, in his landmark review of genetic variant enzymes and vitamin therapy states that:

> *"Our analysis of metabolic disease that affects cofactor binding, particularly as a result of polymorphic mutations, may present a novel rationale for high-dose vitamin therapy, perhaps hundreds of times the normal dietary reference intakes (DRI) in some cases."*[43]

What is also absent from our current nutritional recommendations is the notion that vitamins are multifunctional substances with broad and varied roles in human biology. A single nutrient may catalyze hundreds of biochemical reactions and suboptimal levels may lead to cellular and molecular dysfunction that is not recognized as a "deficiency" disease.[44] The notion that higher doses may be needed for the optimal functioning of the total organism is not accepted, despite new evidence that suboptimal nutrient status may contribute to "long-latency" deficiency diseases that afflict us today, such as cardiovascular disease, cancer, osteoporosis, neurodegenerative disease, and immune dysfunction. The fundamental flaw in the establishment of recommended nutrient intakes is the presumption that if a nutrient intake is sufficient to prevent the index deficiency disease, then it is adequate for the functioning of the total organism. Robert Heaney, in his EV McCollum Award Lecture in 2003, *Long-latency deficiency disease: insights from calcium and vitamin D*,[31] admonishes us that this view overlooks two important facts. First, there are long term consequences of lesser degrees of deficiency that may operate through similar mechanisms as the index disease, and second there may be very different mechanisms involved in the development of long-latency deficiency diseases.

EXAMPLES OF THE NEW PARADIGM

The old paradigm of diagnosis and classification of diseases into organ systems and specialties becomes meaningless in the light of our understanding of the basic mechanisms of dysfunction in the human body. One disease may have multiple causes, and one initiating factor may cause multiple diseases. Cardiovascular disease and celiac disease may be among the clearest examples of this concept. We recognize cardiovascular disease by its pathology, atherosclerotic plaques. However, the development of those plaques may be triggered by multiple factors. These include insulin resistance,[45] folate deficiency and hyperhomocysteinemia,[8] occult infections,[46] heavy metal toxicity,[47] inherited dyslipidemias, stress, and other factors that increase inflammation.[48]

The diagnosis and treatment of each of these conditions vary, and the success of medical therapy rests on making the proper assessment of the etiologic factors (and they are often multiple) involved. Applying the classic low-fat diet (usually high in refined carbohydrates), beta-blocker and statin may actually exacerbate the underlying problem in the patient with insulin resistance, or miss the problem entirely. An example of the latter was a patient of mine with a history of two angioplasties, a coronary artery bypass graft (CABG) and a stroke, who was found to have a severe elevation of homocysteine at 22 µmol/L (normal 6–8 µmol/L), and a homozygous 677C to T polymorphism of methylenetetrahydrofolate reductase (MTFHR), a variant enzyme requiring extraordinarily high doses of folate to facilitate coenzyme binding and MTHFR enzyme activity.

On the other hand, a recent patient exemplified the problems of our current classification system for disease. At 57, he described himself in general good health and was eager to climb Kilimanjaro. However, I noted that he took 15 different medications for his colitis, asthma, alopecia areata and hypertension. He was well treated by an internist, gastroenterologist, pulmonologist, and dermatologist, all of whom made the correct "diagnosis" and provided the appropriate medications for that diagnosis. It was immediately apparent to me that all of his "diseases" were inflammatory and no physician had investigated the cause of the inflammation despite the fact that all of his diagnoses could be explained by the inflammation caused by something he was eating—gluten. Tests confirmed the diagnosis of celiac disease, which had been missed for over 40 years. Within six months, he was off most of his medications, lost 25 pounds, his blood pressure improved, he had no more asthma symptoms, had normal bowel movements and his hair was growing back. A recent review of celiac disease in the *New England Journal of Medicine*[49] catalogued the myriad diseases that can be caused by celiac disease, from anemia to osteoporosis, from autoimmune diseases to thyroid dysfunction, from schizophrenia to psoriasis. Yet each of these conditions may be triggered by multiple factors, not just eating gluten. Thus his genetics required that he not eat a particular food protein in order to maintain health, while another patient with exactly the same "disease" may need an entirely different treatment.

PIONEERS OF THE NEW PARADIGM

Vitamins: Beyond Deficiency Diseases

A few pioneers set the groundwork for the current revolution in medicine. Their work and insights nearly half a century ago are now being vindicated, and a retrospective view of their work may illuminate the next frontier in medical science.

Nutritional science has been the poor second cousin in medicine. It is seen as a secondary factor in health, and best left to the dietician. Physicians have abdicated the science and practice of nutrition. This is why we do not have clear nutritional guidelines or consensus, despite abundant evidence and why there is so much professional and public confusion around nutrition. We need to cultivate different tools of assessment and research that allow us to better answer questions about nutrition and nutraceutical therapies. Dr. Robert Heaney provides guidance about how to use observational research to better infer causality in nutrition. This is difficult because we are looking for the absence of a problem; for benefit rather than harm. He suggests that we can use the usual principles for causal inference from observational data in the nutritional context such as:

> *"biological plausibility, correct temporal sequence, dose-response relations, experiments of nature found in inborn errors of metabolism and demonstration of causal connection in animal models. These principles are all well understood in a general way, and what I suspect may have been lacking up till now was the conviction within the field of nutrition that long-latency deficiency diseases exist,*

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> *that they are nutritional problems, and that the use of such inferential and investigative stratagems may be both appropriate and necessary."*[31]

How we think about vitamins has been shaped by the deficiency diseases through which they were discovered. Vitamins are still defined by single deficiency diseases, such as pellagra, beriberi, scurvy, and rickets. That thinking is the basis for the current dietary reference intakes (DRI), which recommends the minimum amount to prevent deficiency diseases, not the varying amounts needed by a polymorphic population for optimal health, that may be hundreds of times the DRIs. Most physicians and consumers don't realize that DRIs are the minimum necessary to prevent index deficiency diseases. Medicine has failed to recognize that nutrients are multifunctional substances with multiple roles. For example, as we have seen in this issue of *Alternative Therapies in Health and Medicine*[50] and other recent reviews,[51] vitamin D not only prevents rickets, but may have a role in treating or preventing heart disease, multiple sclerosis, polycystic ovarian syndrome, depression, epilepsy, type 1 diabetes, and cancer. Folate not only prevents megaloblastic anemia, but also prevents neural tube defects, cardiovascular disease, dementia, depression, colon and breast cancer and more. Magnesium plays a role in over 300 enzyme reactions. Conventional thinking has been biased against the therapeutic use of vitamins in disease and has avoided the question of whether vitamins have a role in optimizing health. Study of nutrients over long term has been complicated by the fact that the desired outcomes are the absence of problems. This is in direct opposition to pharmaceutical agents, which are meant to alter pathology. Nutrients restore normal function, and they do so by optimizing normal biological functions, mostly by their action as coenzymes in thousands of biochemical reactions.

Imagine a drug that could cure within days or weeks a fatal disease using a very small dose, without toxicity and with a 100% success rate. Such a drug does not exist and will never exist. But that is the power and potential of nutrients. They function within the genetic and evolutionary environment of the cell to enhance and facilitate the optimal functioning of our biology. They are "vital" to our very survival. Their effectiveness in curing deficiency diseases is dramatic, but their role in the prevention and management of long-latency chronic diseases is more relevant to our time. Many patients worry about the dangers of medications and their compliance with pharmaceuticals is disturbingly low, as 20% of prescriptions go unfilled and 85% are never refilled.[52] The decision to see a doctor should not be one measured by concern for risk and danger, but by the opportunity and anticipation of enhanced health and well being. Herein lies the potential of nutrigenomics and the new medical paradigm that allows us to understand the integrative function of complex organisms, and the essential and primary role of nutrition in maintaining that function. A closer examination of the work of a few key pioneers in this field may help illuminate the next revolution in medicine, one that shifts us from disease treatment and disease prevention to health promotion.[53]

Linus Pauling

Linus Pauling, in his later years, was dismissed as a once respected Nobel Prize winning scientist who had become a quack by recommending "mega-vitamin" therapy and high dose vitamin C. However, a careful reading of history reveals a different story, a story of a thoughtful scientist who discovered the three-dimensional structure of proteins, who but for the political persecution of the McCarthy era and the lifting of his passport, would have had access to the X-ray photographs of DNA taken by Rosalind Franklin, and who might have beat Watson and Crick to the description of the double helix. He was also the father of modern molecular biology, being the first to describe the single amino acid substitution of sickle cell anemia in his article in *Science* in 1949.[54] During his later years, he applied his grounding in chemistry, physics, and mathematics to biochemistry and the study of living systems, particularly the role of enhancing enzyme reactions in treating disease and creating optimal health. He was prolific and prescient in his research and presaged a fundamental paradigm shift in medicine and nutrition, as he did in chemistry and molecular biology. In his landmark paper, *Orthomolecular Psychiatry*,[55] he proposed a theory that foretold the era of genomics, SNPs (single nucleotide polymorphisms) and personalized medicine; an era where genetic variations in enzymes based on SNPs, which may once have been adaptive, but now promote dysfunction and disease, may be remediated by providing increased concentrations of coenzymes (vitamins) to increase binding and to activate a defective enzyme. He spent the last 20 years of his life in this research, but because vitamins were considered useful only in the prevention of index deficiency diseases, and because the prevailing medical paradigm was that, except for a few inherited inborn errors of metabolism, all of our nutritional needs are the same, his research was and continues to be ignored by most. His insights came from a deep understanding of the nature of chemical reactions in living systems and he spent the last twenty years of his scientific career examining the role of nutrients in health, or in what he called "orthomolecular medicine." Before the genome was decoded, before we fully understood the role polymorphisms play in creating different nutritional needs within the population, Dr. Pauling envisioned the science to come. An excerpt from his prescient paper in *Science*[54] in 1968 illustrates the clarity of his vision of what was to come:

> *"The rate of an enzyme-catalyzed reaction is approximately proportional to the concentration of the reactant, until concentrations that largely saturate the enzyme are reached. The saturating concentration is larger for a defective enzyme with decreased combining power for the sub-*

strate than for the normal enzyme. For such a defective enzyme the catalyzed reaction could be made to take place at or near its normal rate by an increase in the substrate concentration.... Similarly, the still greater disadvantage of low reaction rate for a mutated enzyme with K only 0.01 could be overcome by a 200-fold increase in substrate concentration, to [S] 400. This mechanism of action of gene mutation is only one of several that lead to disadvantageous manifestations that could be overcome by an increase, perhaps a great increase, in the concentration of a vital substance in the body. These considerations obviously suggest a rationale for megavitamin therapy."

In a letter to Linus Pauling, Albert Szent-Gyorgyi, the scientist who won the Nobel Prize for first separating ascorbic acid, wrote:

"As to ascorbic acid, right from the beginning I felt that the medical profession misled the public. If you don't take ascorbic acid with your food you get scurvy, so the medical profession said that if you don't get scurvy you are all right. I think that this is a very grave error. Scurvy is not the first sign of the deficiency, but a pre-mortal syndrome, and for full health you need much more, very much more."

Roger J. Williams, PhD

Dr. Roger Williams, a pioneer in nutritional biochemistry and the discoverer of pantothenic acid (B5) and folic acid, was the first to recognize that nutritional status can influence the expression of genetic characteristics. In 1956, he published a groundbreaking work, *Biochemical Individuality*, where he stated that "there is no such thing as a truly 'normal' individual" and that people have

"unique biochemical profiles based upon their own genetic structure, nutrition, and environment. ....Individuality in nutritional needs is the basis for the genotrophic approach and for the belief that nutrition applied with due concern for individual genetic variations, which may be large, offers the solution to many baffling health problems. This certainly is close to the heart of applied biochemistry."

Dr. Williams was the first to challenge the standard recommended dietary allowances as adequate for the entire population. Rather than focus on prevention of deficiency, he suggested we identify individual needs and use them to optimize function. But despite his insights fifty years ago, many Americans are still not even achieving the basic amounts needed to prevent the deficiency diseases. The United States Department of Agriculture (USDA) reported that a significant percentage of the United States population receives well under 70% of the U.S. Recommended Daily Allowance (U.S. RDA) for vitamin A, vitamin C, B-complex vitamins, and the essential minerals calcium, magnesium, and iron. A separate study found that most typical diets contained less than 80 percent of the RDA for calcium, magnesium, iron, zinc, copper, and manganese, and that the people most at risk were young children and women, adolescent to elderly.

Drs. Willett and Stampfer, renowned nutritional epidemiologists from the Harvard School of Public Health, admonished us over ten years ago of the dangers of nutritional insufficiencies in our population.

"In national surveys, a substantial portion of the US population consumes levels of several vitamins that are well below recommended intakes, and recent evidence strongly indicates that such low intakes are associated with serious health consequences."[56]

Bruce Ames, PhD

Dr. Ames is a Professor of Biochemistry and Molecular Biology, at the University of California, Berkeley and one of the most cited scientists in all fields (23rd most cited). He has taken the work of Linus Pauling and Roger Williams further. He has delved deeply into and reviewed the broad body of research highlighting the potential of individualized nutrient therapy to not only prevent and ameliorate disease, but to offer the potential of a "metabolic tune-up" and "metabolic harmony."[57] He suggests that by providing the optimum intake of micronutrients and metabolites, which vary with age and genetic constitution, metabolism can be "tuned up" and provide a significant increase in health, especially in the poor and elderly. He illustrates how targeting a number of mechanisms involved in nutritional imbalances can provide a renewed and optimally functioning metabolism.

First, we have the opportunity to address the widespread prevalence of nutrient deficiencies and their influence on chronic disease, such as DNA damage, specifically chromosome breaks due to the incorporation of millions of uracils into the DNA of each cell resulting from inadequate folate, B6 and B12. Other prevalent nutrient deficiencies include inadequate iron intake, which is found in 25% of menstruating American women and 2 billion women around the world and results in leakage of oxidants from the mitochondria, leading to damage to the mitochondria and its DNA; and, inadequate zinc intake, affecting 20% of the world's population leading to oxidation, DNA damage, and immune dysfunction.

Second, we now understand the importance of the Km (binding affinity) or Michaelis constant concept, which explains the myriad of different variations in the binding affinity of mutant or polymorphic enzymes for its coenzyme, requiring high-dose vitamin therapy.[43] Linus Pauling originally described this well before most of the SNPs were identified. These SNPs affect up to thirty percent of our genome involved in coenzyme binding. SNPs may require us to prescribe high-dose nutrient therapy to ameliorate any negative phenotypic expression, such as cardiovascular disease, which occurs when someone with the MTHFR 677C to T polymorphism does not

get the much higher doses of folate they require. Ames suggests that for each example of a genetic disease or polymorphism that involves a derangement of metabolism, there likely exists multiple forms of the disease that reflect slight increases in the Km for that enzyme, which are not commonly thought of as genetic diseases. Therefore, in these cases, higher doses of the coenzyme or nutrient can create increased health through a metabolic tune up.

And lastly, we can now address the mitochondrial oxidative decay that is characteristic of age (and many chronic diseases) by providing normal mitochondrial metabolites such as acetyl-carnitine and lipoic acid at high doses.[58] This does the following: restores the Km for acetyl carnitine transferase and the velocity of the reaction, as well as mitochondrial function; reduces levels of oxidants, neuron RNA oxidation and mutagenic aldehydes; and, increases old-rat ambulatory activity and cognition. Addressing mitochondrial dysfunction is a key component of creating optimal health and many degenerative and chronic conditions. A recent paper in the *Archives of Neurology* found that very high doses of Coenzyme Q10, a conditionally essential nutrient (that is, a nutrient that becomes essential under certain conditions such as aging or disease), resulted in a slowing of the functional decline of Parkinson's disease.[59] Other agents that have shown to be beneficial in animal models of Parkinson's disease include creatine, nicotinamide, and acetyl-L-carnitine.[60] What is remarkable about all these interventions is their low cost and low toxicity. *The substances discussed by Drs. Pauling, Williams, Ames and others are not miracle drugs, but simply the basic raw materials of all living things that, when provided in the optimal amounts for the individual, produce remarkable results.*

Ames goes on to conclude that:

> *"This is especially relevant in the dawning era of genomics, in which it will someday become routine to screen individuals for polymorphisms and thus treat persons more efficaciously by genotype, rather than just phenotype... . Nutritional interventions to improve health are likely to be a major benefit of the genomics era... . It will soon be possible to identify the complete set of genes having cofactor binding sites and the polymorphisms that fall into these regions, with an end goal of using vitamins, and possibly amino acids, hormones and minerals to effect a metabolic "tune-up."*

Robert Heaney, MD

Dr. Heaney is a Professor of Medicine at Creighton University in Omaha, Nebraska, and won the 2003 E.V. McCollum Award of the American Society for Clinical Nutrition in recognition of his contributions to nutritional science and medicine, particularly in the field of osteoporosis and calcium physiology. In his paper, adapted from his E.V. McCollum Award Lecture, *Long-latency deficiency disease: insights from calcium and vitamin D*,[31] he lays the groundwork for a new conceptualization of nutrients in health and disease. In effect, he turns nutritional science on its head by saying "prove to me that we *don't* need higher levels of nutrients for health." He laments that nutritional practice has largely been left to "nutritional quacks and charlatans," while nutritional science has been largely ignored by practicing physicians. He uses the examples of calcium, vitamin D, and folate to illuminate the multi-functional nature of nutrients in the complex, higher order functioning we call human life.

Most of the conditions associated with calcium deficiency are long-latency deficiency diseases: osteoporosis, colon cancer, nephrolithiasis, obesity, and hypertension. Mostly we associate inadequate calcium intake or balance with osteoporosis. However, low calcium intakes may be associated with colon cancer, through its influence on the biochemistry of the gut lumen. The complexing of unabsorbed fatty acids and bile acids with calcium in the gut reduces their cancer-promoting activity in the colonic mucosa. Renal stones may also be prevented by adequate calcium intake because it keeps the oxalate in solution in stone formers. Another long-term effect of calcium deficiency may involve the indirect effects of a high parathyroid hormone (PTH) which occurs in the face of low calcium intakes. The high PTH is associated with higher intracellular calcium levels through its effect on calcitrol, which opens calcium channels within cells. This elevation in intracellular calcium ions leads to increased muscle tone and hypertension, and switches adipocytes from a lipolytic mode to a liposynthetic mode, leading to obesity.

Vitamin D has been classically associated with the prevention of rickets and osteoporosis. Current vitamin D recommendations are tied to the prevention of rickets, and the presumption has been that if you don't have rickets or osteomalacia, then your vitamin D intake is adequate. Evidence from the osteoporosis literature proves otherwise, because increasing vitamin D levels in the blood to the upper levels of the reference range improves calcium absorption efficiency by two-thirds, and reduces osteoporotic fracture risk by one-third. However, as reported in this issue of *Alternative Therapies*, vitamin D has other roles. It has been known that serum 25(OH)D concentrations are inversely associated with prostate and squamous cell cancers. People with low sun exposure or increased skin pigmentation are less able to make calcitrol within tissues in an amount adequate to control cell proliferation and reduce oncogenesis. Heaney suggests that protective serum levels of 25(OH)D may be much greater than current reference values.

He describes the multiple conditions that may arise from a single nutrient deficiency, the multifunctional nature of nutrients, and the need for higher intakes for optimal health.

> *"...inadequate intake of specific nutrients may produce more than one disease, may produce them by more than one mechanism, and may require several years for the consequent mor-*

bidity and mortality to be sufficiently evident to be clinically recognizable as 'disease'."

He also suggests that the intakes of nutrients required to prevent the non-index diseases are higher than required to prevent the index disease, for example preventing osteoporosis requires 4 times the vitamin D needed to prevent rickets, or preventing neural tube defects require 4 times the intake needed to prevent anemia.

Finally he summarizes the foundational concepts of nutrigenomics, the new paradigm of medicine, in a way that should give us pause and cause us to examine our outdated beliefs.

"...because the current recommendations are based on the prevention of the index disease only, they can no longer be said to be biologically defensible. The Preagricultural human diet, insofar as it can be reconstructed, may well be a better starting point for policy... . Such a diet would have had at least some of the following features: high protein intake, low glycemic index, high calcium intake, high folic acid intake, an alkaline ash residue and high vitamin D input. It is in this nutritional context that human physiology is adapted. The burden of proof should fall on those who say that these more natural conditions are not needed and that lower intakes are safe."

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References

1. Daren K. Heyland, Should Immunonutrition Become Routine in Critically Ill Patients? A Systematic Review of the Evidence. *JAMA*. 2001;286:944-953.
2. Kaput, Jim, Nutritional genomics: the next frontier in the post genomic era. *Physiol Genomics*. 16: 166–177, 2004;10.1152
3. Michael Mulle. *Nutrigenomics: goals and strategies, Nature Reviews, Genetics*. 2003; 4: 315-322.
4. RD Laing. *The Voice of Experience*. Pantheon, 1982.
5. Kuhn, T. The Structure of Scientific Revolutions (1962) publ. University of Chicago Press, 1962.
6. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
7. Ewald, Paul. *Plague Time: How Stealth Infections Cause Cancer, Heart Disease, and Other Deadly Ailments.* The Free Press.
8. McCully, K, Homocysteine, folate, vitamin B6 and cardiovascular disease. *JAMA*. 1998: 279 (5); 392-3.
9. Taubes, G. The Soft Science of Dietary Fat. *Science*. 2001; 291: 2536-2545.
10. Fletcher SW, Colditz GA. Failure of estrogen plus progestin therapy for prevention. *JAMA*. 2002;288(3):366-8.
11. Pauling, Linus. How to live longer and feel better, Avon Books, 1986.
12. *Encarta World English Dictionary*. 1999 Microsoft Corporation. All rights reserved. Developed for Microsoft by Bloomsbury Publishing Plc.
13. Susser, M. *Causes of Peptic Ulcer: a Selective Epidemiological Review Journal of Chronic Diseases.* 1967; 20: 435-456.
14. Willett W. Dietary Fat Is Not a Major Determinant of Body Fat MD, DrPH. *Am J Med*. 2002;113(9B):47S–59S.
15. Yudkin J. *Sugar: Chemical, Biological and Nutritional aspects of Sucrose*. 1971
16. Yudkin J. Sugar consumption and myocardial infarction. *Lancet*. 1971; 6;1(7693):296-7.
17. Yudkin J. Dietary factors in arteriosclerosis: sucrose. *Lipids*. 1978;13(5):370-2.
18. Winitz, M, Effect of dietary carbohydrate on serum cholesterol levels. *Arch Biochem Biophys*. 1964 Dec;108:576-9.
19. Anna Norhammar, Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet.* 2002; 359: 2140-44
20. Mensink R P, Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr*. 2003;77:1146–55.
21. Pitkin R. Accuracy of Data in Abstracts of Published Research Articles. *JAMA*. 1999;281:1110-1111.
22. Starfield B. Is US health really the best in the world? *JAMA*. 2000 Jul 26;284(4):483-5. Starfield B. Deficiencies in US medical care. *JAMA*. 2000 Nov 1;284(17):2184-5.
23. Zhan C, Miller M. Excess Length of Stay, Charges, and Mortality Attributable to Medical Injuries During Hospitalization. *JAMA*. 2003;290:1868-1874.
24. Forth Decennial International Conference on Nosocomial and Healthcare Associated Infections, Morbidity and Mortality Weekly Report (MMWR). 2000; 49 (7):138.
25. Weinstein RA. Nosocomial Infection Update. Special Issue. *Emerging Infectious Diseases*. 1998; 4 (3):1998.
26. Lazarou J, Pomeranz B, Corey P. Incidence of adverse drug reactions in hospitalized patients. *JAMA*. 1998;279:1200-1205.
27. Barczak CA, Barnett RI, Childs EJ, Bosley LM. Fourth National Pressure Ulcer Prevalence Survey. *Advances in Wound Care*.1997; 10-4.
28. Leape LL. Error in medicine. *JAMA*. 1994 Dec 21;272(23):1851-7.
29. Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. *N Engl J Med*. 1991; 324: 370-376.)
30. US Congressional House Subcommittee Oversight Investigation. Cost and Quality of Health Care: Unnecessary Surgery. Washington, DC: Government Printing Office, 1976.
31. Heaney, R. Long-latency deficiency disease: insights from calcium and vitamin D. *Am J Clin Nutr.* 2003;78:912-9
32. Fonda, D. Curbing the drug marketers. *Time*. 2004; 40-42
33. Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. *N Engl J Med*. 2002 Feb 14;346(7):498-505. 45.
34. Wolfe SM. Direct-to-consumer advertising—education or emotion promotion? *N Engl J Med*. 2002;346(7):524-6.
35. Kassirer JP. Financial Conflicts of Interest in Biomedical Research, *N Engl J Med*. 1993; 329:570-571.
36. Holmer A. Industry Strongly Supports Continuing Medical Education. *JAMA*. 2001; 285: 2012 - 2014.
37. Relman A. Separating Continuing Medical Education From Pharmaceutical Marketing. *JAMA*. 2001; 285: 2009 - 2012.
38. Fisher ES. The Implications of Regional Variations in Medicare Spending. Part 2: Health Outcomes and Satisfaction with Care. *Annals of Internal Medicine*. 2003;138; 288-298.
39. Fisher, ES. Medical Care—Is More Always Better? *N Engl J Med*. 349;17, 2003
40. Lenfant C. Shattuck Lecture: Clinical Research to Clinical Practice — Lost in Translation? *N Engl J Med*. 2003; 349:868-874, Aug 28, 2003
41. McGlynn EA. The Quality of Health Care Delivered to Adults in the United States, *N Engl J Med*. 2003; 348:2635-2645, Jun 26, 2003.
42. GJB van Ommen. The Human Genome Project and the Future of Diagnostics, Treatment and Prevention. *Lancet.* 1999; 354:5-10
43. Ames, B. High dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): relevance to genetic disease and polymorphisms. *Am J Clin Nutr*. 2002;75:616-58
44. Fairfield K. Vitamins for Chronic Disease Prevention in Adults. Scientific Review. *JAMA*. 2002;287:3116-3126.
45. Norhammar A. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet*. 2002; 359: 2140-44.
46. Murat V. Chlamydia pneumoniae as an Emerging Risk Factor in Cardiovascular Disease. *JAMA*. Dec 2002; 288: 2724 - 2731.
47. Gullar L. Mercury, fish oils and the risk of myocardial infarction, *N Engl J Med*. 2002;347:1747-54.
48. Ridker P. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347:1557-65.
49. Farrell RJ. Current Concepts: Celiac Sprue, *N Engl J Med*. 2002; 346:180-188, Jan 17, 2002.
50. Vasquez A. The Clinical Importance of vitamin D (cholecalciferol): A Paradigm Shift with Implications for All Healthcare Providers. *Altern Ther Health Med*. 2004. 10(5): 28-37.

51. Holick, M. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease and osteoporosis. *Am J Clin Nutr*. 2004;79:362-71.
52. Pharmaceutical Patient Compliance and Disease Management. Available at: http://www.PharmaDiseaseManagement.com. Accessed August 2004.
53. Breslow L. From disease prevention to health promotion. *JAMA*. 1999; 281: 1030-1033.
54. Pauling, L. Sickle Cell Anemia, a Molecular Disease. *Science New Series*. 1949. 110 (2865): 543-548.
55. Pauling, L. Orthomolecular Psychiatry. *Science New Series*. 1968. 160(3825): 265-71.
56. J. Stampfer and W. C. Willett, Homocysteine and marginal vitamin deficiency. The importance of adequate vitamin intake. *JAMA*. 1993; 270: 2726 - 2727.
57. Ames, B. The Metabolic Tune-Up: Metabolic Harmony and Disease Prevention, *J Nutr*. 133: 1544S–1548S, 2003.
58. Hagen T. Ames B. Feeding acetyl-l-carnitine and lipoic acid to old rats significantly improves metabolic function while decreasing oxidative stress. *Proc Natl Acad Sci U S A*. 2002 Feb 19;99(4):1870-5.
59. Shults CW. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Ann Neurol*. 2002;59(10):1541-50.
60. Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. *Ann Neurol*. 2003;53 Suppl 3:S39-47; discussion S47-8.