January 2006 Issue | Farid Wassef, RPh, CCN Guardian Houston's Pharmacy

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Welcome to *Functional Medicine Update* for January 2006. It is the beginning of a new year. In fact, we are now at the quarter-century mark of continued service with FMU. As my colleague, Jay Johnson and I look at one another, we wonder what happened to those years. It is a pleasure, once again, to be with you at the start of our 25th year. This publication began as *Metabolic Update*, evolved to *Preventive Medicine Update*, and finally, to *Functional Medicine Update*.

13th International Symposium on Functional Medicine

I want to remind those of you who may have just joined us this year, of our upcoming 13thInternational Symposium on Functional Medicine, which will be held on April 19-22, 2006 at the Tampa Marriott Waterside Hotel & Marina in Tampa, Florida. The symposium will focus on Managing Biotransformation: The Metabolic, Genomic and Detoxification Balance Points. I am very excited about the plenary lecturers and the concurrent sessions we have put together. We are going to take a contemporary approach to this complex topic to make it clinically useful, and we will cut through a lot of misunderstanding and confusion to deliver news to use to all of the attendees. The symposium is usually held in May, but please note that it is being held earlier this year.

On April 19th, we will conduct the preconference course, which deals with the basic biochemistry and physiology of detoxification and biotransformation. We have put together a detailed session that will set the tone for the three-day conference from April 20 - 22, and we will apply the preconference information to a variety of clinical areas. I encourage you to attend the preconference course.

In preparation for the symposium, I thought it would be worthwhile to start the January 2006 issue of FMU by focusing on what we know about nutrient modulation of physiological function. What are the emerging areas of understanding that are making this topic less subject to controversy and differences of opinion, and moving it toward consensus? The topic is a moving target that is constantly open to reinterpretation. Over the last ten years, I have continually questioned what nutrients have become more accepted as participating agents in pharmacological and physiological actions that help remediate different disease processes, particularly in individuals with specific need. This goes back to arguments about specific types of nutrigenetic underpinnings requiring specific nutrigenomic interventions.

I thought we would stay focused on the question of science-based micronutrient intake and what it relates to in terms of understanding the physiology. This would go beyond deficiency and move us into the area of nutrient pharmacology. It is interesting to note that nearly 25 years ago, Dr. Gene Spiller edited what I

consider a very pioneering book, titled *Nutritional Pharmacology*[1] He went out on a limb to even coin that term, if you think about what the climate was like 20 years ago regarding nutrition in the medical and scientific community. The book would have been considered quite ambitious at that time. In his book, Dr. Spiller talked about various areas that were emerging indicating that specific nutrients could be used for pharmacological purposes. The topic has evolved quite remarkably since then.

In previous issues of FMU, we have talked about Dr. Bruce Ames' wonderful review paper that discusses genetic polymorphisms and the need for specific nutrients to push through different steps and intermediary biochemistry to activate the conversion of substrate to product, and how those nutrients serve as coenzyme activators, or how they might participate in gene expression modulators, and work through the trilogy of "omics"-the genomics, proteomics, and metabolomics that give rise to phenomics[2] We have talked about the nutritional phenotype, which is what you see in your patients. They express the complex interrelationship of their genetic predispositions with their environmental exposures since the time of conception. Those interactions give rise to who they are, how they think, act, feel, and look. Their health patterns are a complex interaction of genetic uniquenesses with environmental exposures.

Nutrition is a shared common environmental experience. The nutrients we consume in our diets are now recognized as information molecules. They participate in the regulation of receptor site activities and intracellular signaling transduction processes through what are called the kinase pathways, to give rise to alterations in DNA function, which create different physiological outcomes in cells that have received different messages from the outside environment. The genes remain the same, but their expression and how they are translated into active proteins, as well as how they are modified epigenetically, including glycation, oxidation, and phosphorylation, are controlled and modified by environmental choices. Diet selection plays a principal role in getting the most from our genes and achieving our full potential for good health. The questions are, which nutrients do we need, how much do we need, and how do we know?

Let's go back to some studies that have been done under the aegis of the Federal Government, such as the National Nutritional Health and Examination Surveys, or NHANES, as it is abbreviated. These large population surveys represent the most extensive documentation on how various nutrients are related to various health patterns. They have been done over a 20-year period, looking at nutritional status and shifts in health patterns. Certain alignment of nutrients and health outcomes can be gleaned from that data.

Folic Acid

One of the nutrients that has received a tremendous amount of attention over the last five years is folic acid. As we have talked about in previous issues of FMU, this goes back to a report that appeared in the *Lancet* in the early 1970s by Dr. John Smithels. He observed that women who give birth to sequential children with neural tube defects (NTDs), or the anencephaly seen with spina bifida cystica, had to do with the folate status of the mother, and are often the most common birth defects found in our population. He postulated that increasing folate and other B vitamins during the periconceptual period could be useful to lower the risk and incidence of NTDs. It took nearly 30 years for this concept to work its way through the body politic and ultimately be seen as not only a reasonable observation, but a justifiable physiological concern. It took a long time to identify the difference between a frank folate deficiency seen as pernicious anemia, versus a chronic folate deficiency (a long latency disorder), that results in NTDs in offspring. It is easier to identify an acute deficiency syndrome, such as vitamin C deficiency in scurvy,

than it is to identify a long-term, marginal deficiency that produces increased risk of a complex disorder like NTDs in children.

The NHANES studies demonstrated that the average intake of folate in the population may be in the gray zone for individuals who carry certain types of genetic uniqueness, particularly related to folate processing and metabolism. Aspects of folate processing are locked into genetic uniqueness through single nucleotide polymorphisms (SNPs). One very frequent SNP is the cytosine-to-thymidine 677 polymorphism of the gene that controls the production of the enzyme, methylenetetrahydrofolate reductase (MTHFR). About 5 to 10 percent of the population is homozygous for this polymorphism, and at least 15 percent of the population is heterozygous for this SNP. It is a very common polymorphism that may penetrate the population at large and result in perhaps 1 in 12 individuals, or 1 in 15 individuals, being highly susceptible to marginal folate insufficiency at a dose intake in the diet that would be adequate for other individuals.

That raises the question in the public health milieu as to whether we should administer folate in the diet by fortifying our grains to cover individuals that represent 5 to 10 percent of the population with this polymorphism. This is a very different discussion than that which was discussed when the Food Nutrition Board met and decided on what were originally the Recommended Dietary Allowances (RDAs), later to become the Dietary Reference Intakes (RDIs). These RDA and RDI associations were not built upon the principles of polymorphisms that evolved from the Human Genome Project. We are looking at a very new "aha" or discovery that, when reflecting back on the standards we have used to judge nutritional adequacy, make some of those assessments questionable. That is why there are many people who feel there will be no further modification of the RDIs or RDAs, because they have run their useful lifetime. We now recognize that we need to individualize nutritional recommendations based upon genetic and health status uniqueness. This is a new development in the field of nutrition, as we move into the area of genomics and start to attach nutrition and health to genomic principles.

Science-Based Micronutrient Fortification-Which Nutrients, How Much, and How to Know?
When we apply this concept to folate, it is an interesting example of how the field has evolved. I am now looking at an interesting recent editorial that appeared in the American Journal of Clinical Nutrition. The author talks about the synthesis of folic acid, which was first accomplished by scientists at Lederle Labs back in 1947, and considered one of the milestones achieved during the era when vitamins were discovered.3 This was to manage a particular medical need related almost entirely to folate deficiency, which was seen as different hematological aberrations, particularly certain types of anemia associated with an altered shape of the red blood cell. It was later found that high levels of folic acid could mask the signs of vitamin B12 deficiency and that over time this deficiency could impair the neurological system. In defining the upper limit of tolerability for folic acid, continued emphasis should be placed on establishing levels that will not mask vitamin B12 deficiency symptoms. When most people think of higher doses of folic acid, they see it as a potentially toxic nutrient because the government has so closely regulated the dosage in a single preparation at 800 mcg in a pregnancy formula, and generally about 400 mcg in a non-pregnancy formula. This suggests that doses above those ranges would be considered toxic.

This whole story is being reevaluated based upon understanding the MTHFR polymorphisms and that individuals may need higher levels of folic acid to promote certain positive physiological functions. There may be effects of folic acid on physiology that go beyond the traditional MTHFR effects of producing 5-methyltetrahydrofolate and reducing homocysteine. We also need to consider the effect that folic acid

conjugers have on the activation of biopterin synthesis. That has to do with things like nitric oxide production in the vascular endothelium, and central nervous system production of dopamine, which has to do with neurotransmitters and the prevention of depression.

S-adenosylmethionine (SAM), which is the product of folic acid metabolism, has been used for the treatment of depression. There may be people with specific defects in folate pathways that require higher doses of folate in order to increase SAM levels in the brain and lower the risk to biochemical, neurological insufficiencies seen as clinical depression. There may be people with hypertension who require higher doses of folic acid to similarly activate the formation of biopterin, the central coenzyme responsible for activating endothelial nitric oxide synthase, or eNOS, which converts arginine into nitric oxide in the vascular endothelium and produces vasorelaxation effects upon vascular smooth muscle and lowers blood pressure.

I am talking about a different view that is emerging about how a nutrient can be used and how it influences physiology based upon different genetic uniquenesses. We have just introduced the concept of individualized folate nutriture and its effects on methylenetetrahydrofolate reductase polymorphisms and tetrahydrobiopterin synthesis for optimal biochemical function.

Going back to the question of science-based micronutrients, which nutrients, how much, and how to know, we get into functional assessments that go beyond deficiency assessment. Almost all of the standard laboratory methods that have been developed to evaluate micronutrient status were established around deficiency levels. What is the level below which that nutrient is considered to be deficient? We generally measure nutrients in biological fluids-plasma, serum, or urine. These measurements are not intracellular functional analyses of how a nutrient may be influencing a specific tissue or organ system function, such as the vascular endothelium with hypertension, or the neuron as it relates to dopamine synthesis and mood and memory.

We are witnessing a remarkable transition from looking at low levels of a nutrient associated with a deficiency in the general population, to specific functional assays of a nutrient in an individual that lead to a functional outcome-in this case, folic acid. Nutrients are not just related to homocysteine and methylmalonic acid; they can also be related to hypertension and neurological function.

Using that example as a measuring stick for determining what nutrients have passed scrutiny tests for being potentially valuable in doses considered greater than the normal dietary intake for promotion of improved physiological function, there are nutrients that fall within the vitamin category, the essential trace mineral category, and what might be called the accessory nutrient category, or conditionally essential nutrients, all of which fulfill those criteria. I would like to talk about a few of those to illustrate how far we have come over the last 10 years.

Chromium

Chromium is a very interesting essential trace mineral. In 1978, I had the pleasure of being on sabbatical and I spent the year at Evergreen State College in Olympia, Washington overseeing a course in nutritional biochemistry. I had the privilege of working with the same 59 students all year. It was an unusual curriculum, and a very intensive, year-long learning program. During that time, a number of guest lecturers visited our class. One of them was Dr. Walter Mertz from the United States Department of Agriculture (USDA), who talked about chromium, the essential trace mineral responsible for what he

called the glucose tolerance factor. Dr. Mertz was one of the primary investigators involved with trace mineral research at the Beltsville, Maryland Research Laboratories under the aegis of the USDA. He was a very articulate spokesperson and a good scientist. He presented compelling data from animal studies showing how chromium deficiency related to glucose intolerance in what appeared to be conditions like diabetes. He went on to show that the chromium level in the standard American diet had gone down considerably, and that the USDA Handbook No. 8 Food Tables were not even reporting chromium levels. Chromium levels in foods had decreased as a consequence of a change in agricultural patterns and, therefore, there was significant concern about the adequacy of chromium in the standard American diet, and how it might relate to blood sugar abnormalities and diabetes.

That concept was not well received in the 1970s. It was considered antithetical to thought. I recall speaking about chromium at a number of symposia and meetings during the late 1970s and early 1980s, and unless I was addressing what you might call an "enlightened group, that concept fell on unreceptive ears. Over the last 20 years, the concept of chromium and its relationship to glucose tolerance factor has gained much more credibility and support. Dr. Kursheed Jeejeebhoy (a Clinician of the Month on FMU in August 2001), is a world expert in parenteral nutrition. He conducted a considerable number of studies examining parenteral nutritional formulas that were not replete in chromium, and their relationship to glucose tolerance. He showed that in humans, a chromium functional deficiency occurred over a certain period of time in those on intravenous feeding formulas that were low in chromium, often resulting in insulin resistance and glucose intolerance.

It is now recognized that trivalent chromium is an essential nutrient that plays a role in a number of metabolic systems. Research indicates that chromium is implicated in insulin function, diabetes mellitus, metabolic syndrome, polycystic ovary syndrome, gestational and steroid-induced diabetes, and depression.4 In fact, the FDA has approved health claims related to chromium, which is quite remarkable, considering the 30-year controversy that has been going on about it.5

As we look at more recent work by Dr. Richard Anderson, a respected investigator in the chromium research area, we see that chromium plays an important role as one of myriad substances needed in trace quantities for improvement of physiological function. We cannot ascribe a chromium deficiency disease, but we look at its relationship to function in the range of somewhere between 400 and 1000 mcg a day. This illustrates a remarkable change in the importance of trace minerals from years ago. This is an indication of what is occurring as we move from focusing on deficiency conditions to looking at functional disorders and the role various nutrients play in conditions like glucose intolerance. By the way, chromium is stored as a glucose tolerance factor bound form in a trivalent state in the liver. It is released during an oral glucose load. It is involved with insulin sensitivity and plays a very important role in the glucose transport process. The nutritional need for chromium in physiology is now quite well recognized. Our highly processed diets are often depleted of many important trace minerals.

Vitamin E

Let me move to another example-the fat-soluble vitamins and vitamin E, which is a mixed story. We are familiar with the work of the Shute brothers from London, Ontario in the 1950s. They told us about the important role of the vegetable oil concentrate called tocopherol (from the Greek word "to give birth"), that was found to be absolutely necessary in the birthing of animals. (It has never been identified in humans to have that effect.) The vitamin E family is a series of different molecules. The alpha, beta, gamma, and delta tocopherols, plus the tocotrienols, are extracted at low levels out of oils from soy beans

and wheat germ (to name just two) that give rise to vitamin E antioxidant activity potential. The Shutes suggested that vitamin E is very important for the prevention of heart disease. The Nurses' Health Study, conducted many years later, found that individuals in the highest quintile of dietary vitamin E intake had a nearly 50 percent lower incidence of heart attack. This tended to confirm the Shutes' epidemiological association between vitamin E and cardioprotection. Many other subsequent small studies were done that implicated, or at least suggested, that vitamin E was cardioprotective.

More recently, larger clinical intervention controlled trials have been done, using a-tocopherol, both the synthetic DL-a- and the natural source RR-tocopherol as the acetate or succinate form. These studies were equivocal, and led to much negative press surrounding vitamin E's role as either cardioprotective or cancer preventive. For example, one research group published studies indicating that vitamin E, when given along with statins and/or niacin, was not beneficial and they suggested its use should be questioned. That put a stigma on the vitamin E story. Where are we right now as it relates to single nutrient intervention studies-the double-blind, placebo-controlled trials from which we try to ascribe a value or a risk? There is a good article in the Journal of the National Cancer Institute that examines that question6 The author talks about randomized trials of aspirin and vitamin E as potential agents for cancer prevention that draw support from epidemiological and observational evidence. Both aspirin and vitamin E have plausible biological mechanisms as antioxidants. It appears that natural vitamin E has the ability to protect people from cancer and that various aspirin-like derivatives (non-steroidal, anti-inflammatory drugs [NSAIDs]), as well as a proven ability to protect against heart disease and stroke. Could benefit be achieved in reducing the risk to cancer by using aspirin and vitamin E together?
A variety of papers have been published recently that examine that question. As reviewed in the Journal of the National Cancer Institute articles, the Journal of the American Medical Association published two papers in the summer of 2005 written by Buring and his colleagues that looked at the interrelationship between aspirin, vitamin E, and cancer.7,8 These were large, randomized control trials as part of the Women's Health Study protocol. Forty thousand healthy women were randomly assigned to take aspirin, vitamin E, and/or a placebo for ten years in the hope of clarifying what clinical associations might exist between aspirin, vitamin E, and cancer risk. According to the results, no association was found, and the findings raised questions about where to go with these kinds of chemoprevention trials using purified nutrients and/or pharmacological agents.

The Buring studies raised all sorts of questions. Many researchers do not think these studies are the final word. For instance, Dr. Nancy Cook of Brigham and Women's Hospital, and lead author of one of the two JAMA papers, believes that further aspirin studies may still yield positive results for specific types of cancer. Taking single nutrients out of complex dietary convention and using them in an intervention trial as if they are drugs, may be the wrong way to address the question as to whether nutrients influence disease.

Single-Agent Intervention Trials
Single-agent studies on beta carotene or vitamin E may not mimic what is going on when we consume these substances in higher doses in the diet as a complex mixture, along with the myriad of other physiologically active agents in foods and food concentrates. Is there a different mechanism of action for a drug versus a nutrient? Perhaps nutrients work in combination with one another as part of a natural selection process of how they were found in the diet and how they evolved a relationship in human physiology that is different than a drug designed specifically as a new-to-nature molecule to modulate one enzymatic step or one physiological function. As a consequence of a major action for which it was

selected, it has a reproducible effect as a single agent, whereas that single nutrient may have evolved as a complex part of the diet over many years to work in combination with other signaling-active substances in the genomic pathways. These are complex issues, but they seem to be emerging out of the data coming from these clinical trials.

How can we rationalize the strong association of nutritional epidemiological data with the lack of support we see in single-agent intervention trials? It appears that single intervention trials are not duplicating what is really going on in human physiology when we eat a single substance or agent in a complex diet, which interacts with multiple other agents. We get into more complex study designs that may not be as amenable to the double-blind, placebo-controlled, one-agent-for-one-outcome variable type of philosophy upon which drug efficacy studies were built. We have to be cautious not to get painted into a corner in this field, assuming that because data derived from a single agent against a single endpoint outcome study was not positive, and that it means nutrients do not play a role in improving physiological function-in this case, chemoprevention or heart disease prevention when used in the context of a natural selection process that evolved over time in a complex diet.

Are we using the right substances when we do these particular intervention trials? In our attempt to reduce the complexity, we take a complex mixture (in this case, vitamin E as a natural source, containing a mixture of alpha, beta, gamma, and delta forms), and we may purify it down to a single form in order to make it a simpler trial. For example, we may use an alpha-tocopherol derivative alone, rather than the mixture found in the natural source. In the case of vitamin E, that means we would eliminate g-tocopherol, which has been identified as an important part of the story. Maybe we have just taken out one of the components of the vitamin E mixture that is critically important for modifying the endpoint we are trying to evaluate.

Several lines of evidence support a role for oxidative stress and inflammation in many conditions. Epidemiological studies on heart disease are very clear, and there are literally hundreds of animal and in vitro studies that suggest a correlation between antioxidants and cardioprotection. Mechanisms are starting to emerge that make a connection between reactive oxygen species and antioxidant protection, and protection against atherolsclerotic physiology.

Vitamin E is one of those antioxidants (at least in the lipid-soluble realm), that has been extensively discussed in the literature. Vitamin E exists in a series of different forms-the alpha, beta, gamma, and delta forms-and it also exists as synthetic alpha (called DL-alpha), which is a racemic mixture of eight different stereo-isomers. It can also exist as the natural source RRR vitamin E a-tocopherol, which is a single enantiomer, just one of the eight made by nature.

In some supplementation studies using a-tocopherol, the major form of vitamin E has been found to reduce biomarkers of oxidative stress. The prospective vitamin E trials almost always use a-tocopherol exclusively. Is a-tocopherol the only form of vitamin E that is useful in the prevention of vascular disease? To answer that question, we need to ask why a-tocopherol was chosen to begin with as the principal form of vitamin E sold in supplements. It is historical, because in the early research, a-tocopherol was found to have the highest potency. What was the potency built upon? It was built upon the ability of that substance to prevent rat fetal resorption, which was the bioassay, meaning the amount of vitamin E required to prevent a rat from resorbing its fetus. People do not take vitamin E to prevent fetal resorption. Does that bioassay map very well against the physiological effect in humans? Maybe using a-

tocopherol because it has the highest potency is the wrong way of assessing potency in humans.

Gamma-tocopherol is the most prevalent form of vitamin E in plant seeds. Vegetable oils such as corn, soybean, sesame, and nut oils, including oils from walnuts, pecans, and peanuts, are rich sources of g-tocopherol. They represent 70 percent of the vitamin E consumed in the typical US diet from a food form. If we look at the epidemiological studies on vitamin E intake and heart disease, we see g- tocopherol analysis, not a-tocopherol analysis. Yet, these intervention trials were done with a-tocopherol, looking at cardioprotection.

Gamma-tocopherol is a powerful antioxidant. It is somewhat less potent as an electron donator than a-tocopherol. We might say that it is slightly less powerful as an antioxidant. However, g-tocopherol's unsubstituted C5 position on the chromanol ring appears to make it better able to trap lipophilic electrophiles, such as reactive nitrogen species. In pioneering studies, Cooney et al. found that gamma-tocopherol is superior to a-tocopherol in detoxifying nitrogen dioxide.9 Gamma-tocopherol has been shown to inhibit smooth muscle cell proliferation by inhibiting protein kinase C activity, while b-tocopherol had no effect, indicating that its effect is independent of its antioxidant activity.10 We are concerned with more than antioxidant effects when we look at tocopherols and the difference between g- and a-tocopherol effects may go beyond that of its antioxidant effects.

Animal studies (rat studies in particular), have shown that there is a significant difference between the physiological effects of a-tocopherol and g-tocopherol, particularly when focused on platelet aggregation and delay of arterial thrombogenesis.11

Gamma-tocopherol supplementation results in a stronger inhibition of superoxide generation and lipid peroxidation. Therefore, we could say that possibly, the epidemiological work looking at the dietary association between vitamin E intake and lowered cardiovascular risk was a surrogate measure of g-tocopherol intake, but the clinical intervention studies used a-tocopherol, so it may have been the wrong nutrient for the outcome variable that we were looking at.

The point I am trying to make is that we are evolving a much more sophisticated understanding of how to measure, what to measure, and when to measure. We know that vitamin E increases the production of vasodilator prostanoids in human aortic endothelial cells and has an effect on lowering cyclooxygenase-2 and phospholipase A2 arachidonic acid.12 We also know that vitamin E influences the glutathione redox pathway and therefore has something to do with the maintenance of proper intercellular redox buffering-the glutathione-to-glutathione disulfide ratio. In fact, we know that mixed antioxidant-enriched diets in animals improve glutathione redox status and mitochondrial function, and lower the rate of senescence in animals predisposed to it, or increased biological aging. This is discussed in some nice work by Drs. Sohal and Packer, two well-known investigators in the molecular gerontology area at the University of Southern California School of Medicine13

We are starting to witness different associations between vitamin E and vascular function, immune function, inflammatory function, and cardiovascular and metastatic function that take us beyond the synthetic or single isomer a-tocopherol into the mixed tocopherols, which is more a food-based form that delivers different nutrigenomic messages.

An Overview of DHA from Cognitive and Behavioral Tests in Humans and Animals

What I am talking about is the evolution of a model. Sometimes, we would like clear answers and no ambiguity. Unfortunately, because of the rapid evolution of this field over the last ten years, we are still in a state of hypotheses more than facts and proof, but we are moving to knowing what we should know. For instance, we now know that docosahexaenoic acid (DHA), a long-chain, omega-3 polyunsaturated fatty acid, is very important for brain, ocular, and immune development. An association between cognitive and behavioral effects and brain DHA can be seen in animal studies, and suggests negative consequences for children who do not get adequate levels of DHA *in utero* and *post utero*.[14] This is a new "aha" that we did not know about ten or 15 years ago when it was not considered important. How many children have been fed infant formula devoid of DHA, resulting in some adverse neurological effects in their development? Who knows the answer to that question, as we move from breast feeding to infant formula to the new recognition of the role that DHA has in brain development? These are the questions that are framing a new form of functional medicine and a new form of nutrient pharmacology. This is a good time to segue into our discussion with our Clinician of the Month, who will talk about the pharmacological relationship to health patterns.

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician/Researcher of the Month. This month, we are privileged to have someone who has had a voice in functional medicine for more than a decade. Farid Wassef received his Bachelor of Science Degree from the Massachusetts College of Pharmacy. He has extensively diversified his expertise through post-graduate training at the International and American Association of Clinical Nutritionists, and now works at the Guardian Houston Pharmacy store and at Memphis Star Health Services in Stouffville, Ontario. He is a leader in the Canadian functional medicine movement, and has been a member of the Institute for Functional Medicine Advisory Board. He has a perfect record of attendance at all our international symposia. More than that, he is a leader in thought, and he understands what the future might look like as we move toward a distributive healthcare system.

Farid, it's a great pleasure to have you on FMU. Let me begin by asking how you made the transition to nutritionist, focusing so much of your energy on patient counseling and therapy, as well as becoming a best-selling author with your book, Breaking the Age Barrier: (Strategies for Optimal Health, Energy and Longevity)?15 That's a big departure from the traditional role of a pharmacist. It sounds like you had an epiphany along the way.

FW: Absolutely. Thank you, Jeff, for that lovely introduction, and it's my pleasure to be with you. The greatest influence on my career came from my father. We have operated our pharmacy here in Stouffville, Ontario for the last 35 years, and this is where I got first-hand exposure to some of the shortcomings of pharmaceutical care. When I graduated from pharmacy school in the late 1980s, I was ready to make a difference in people's lives. Like many other healthcare professionals, I became discouraged and disillusioned with the system. One of the things I wanted to do was find solutions for people. I wanted to help them age better. I didn't want to just stand by, watch their medication lists grow longer, and assume the role of insuring compliance. I didn't want to just get people to take eight to ten drugs and somehow try

to manage side effects and adverse events. It was an extremely frustrating situation.

Counseling Patients

I decided that people deserve more care than just two or three minutes at a prescription counter. In 1993, as bold and unheard of as it was, I opened an office adjacent to my pharmacy and began to counsel patients about what was going on with their prescription care. Had the right medication been selected? Was the diagnosis accurate? What other factors were driving the pathology? I came across some basic principles that have served me well. One is that the nature of chronic disease is multi-factorial and that intervention needs to be multi-dimensional. In the process of reviewing all of this, I stumbled upon nutrition, and it has been a wonderful journey for me over the last 15 years learning how to improve people's diets. We now know that diet has a tremendous influence on health.

These are the things that I examined and researched as I started to write my book, Breaking the Age Barrier: (Strategies for Optimal Health, Energy, and Longevity). There are 6000 diseases with genetic components, and we are still counting. These diseases are decreasing the quality of people's lives, and result in people dying early or ending up on eight to ten medications. Many of the chronic, age-related diseases result from poor lifestyles and diets. That is what led me to learn more. I think this will be my 10th year in a row attending the functional medicine symposia, and all of them have served to build a good foundation for me. I learn all the cutting-edge information and bring it back to my practice. It helps me make sense of what I see every day.

These are the kinds of things I encourage pharmacists to do. People are interested in self care. They want more from their pharmacists, and are willing to pay for it. I encourage pharmacists to get involved with functional medicine to see how they can enhance the lives of their patients. When I started out 17 or 18 years ago, I didn't feel I was making a difference. Now, I do, and it's been very rewarding for me. I'm glad I made the change and I haven't looked back.

JB: You have said some things I would like to follow up on, because I believe they touch every one of our listeners, no matter what their backgrounds or disciplines. First, let me deal with the phrase you used-"self care." Dr. Jim Gordon, the director of the Center for Mind/Body Medicine in Washington, DC, has suggested from data accumulated from consumer surveys that the transition in health care we're undergoing right now is going to be driven by consumer interest in self care. Dr. David Eisenberg, a professor of medicine at Harvard Medical School, is the principal author of a study that examined the use of unconventional medicine in the United States and which found that it was much more broadly used than previously thought. It constitutes several billion dollars of expenditures, and it rivals out-of-pocket expenses for hospitalization. There are more patients seeing unconventional providers than those seeing family doctors. That all relates to the term, "self care." It seems that when a person wants to get diagnosed and treated for a disease, he or she goes to a doctor. When patients want to deal with something related to what is referred to as the "walking wounded," they often look at self care. It is difficult to identify good professionals who can provide quality information about self care. They don't generally get the information from their doctors who are trained in pathophysiology. As a result, patients go to the health food store or to an exercise facility to seek out someone who might have that capability. Here is where an educated pharmacist or other ancillary healthcare professional can provide a significant contribution. There may be more people looking for self care than are going to hospitals.

Self-Care Movement

FW: You're absolutely right. You mentioned two researchers, but several prognosticators in our own profession were sounding the alarm back in the mid-1990s, letting pharmacists know that the self-care movement is huge and that the over-the-counter category is growing tremendously. People are spending money out-of-pocket with very little guidance, without being matched up with a qualified healthcare practitioner, and some of them are going about it blindly. As pharmacists, we've heard about this over and over again for the last 10 years, and that this is an area where we can evolve and become experts in self care. In fact, patients are demanding it. It's much more than a trend; it's here to stay. The baby boomer generation wants health and wellness-more integrative care-and they want to understand all of it. Because of the amount of information in the media about nutrition and various fad diets, pharmacies are becoming inundated with vitamin and mineral preparations, herbal remedies, and so forth. We can no longer say that there's no data to back this up or that this is just a passing trend. We need to examine this.

Integrating Information into Pharmaceutical Care

Beyond becoming a self-care expert, it's a great opportunity to engage patients and understand how we can help them integrate the information into their pharmaceutical care. We also need to be able to critically appraise information. Pharmacists, as well as doctors and other healthcare professionals, need to understand about evidence-based medicine. We need to collaborate with one another. We need to understand patient-centered care. We need to understand about health promotion and preventive care. These are the four pillars that have been proposed by every single province in Canada and every state in the United States. These are the kinds of things we need to instill in health care that are going to solve a lot of problems and help us to move forward. That's what I've done. I've known about this forecast for a decade and a half and I've taken it upon myself to collaborate with physicians and to get involved with patients by sitting down with them for a half hour to an hour at a time. It's really not that difficult. That time spent with patients often results in some good answers as to what's going on with them. We can no longer practice assembly-line medicine where we give people two or three minutes of time and expect to solve all their complex, chronic problems. That's just not working. The self-care movement is well entrenched and people are interested in it. Pharmacists can seize this opportunity. It's something I certainly have recognized.

JB: Let's move to some of the realities you deal with every day. Clearly, most pharmacists spend their professional lives on the other side of a counter, during which they are providing a product to an individual with a little bit of information that could be encoded in less than a minute in a sound byte. There's a barrier between the customer and the pharmacist in the form of that counter. When you cross that counter and become a counselor, a therapist in part, that's establishing a whole different relationship with a customer. Now, they are more likely to be seen as real people with complex lives. How does that transition occur?

The Transition from Pharmacist to Counselor

FW: First, pharmacists in North America are recognized as primary healthcare practitioners. We are the first point of entry into the healthcare system in a number of instances. During a busy day dispensing medication, we need to decide when a patient approaches us if that particular situation warrants a three-to-five-minute discussion, or whether it warrants more assessment and requires more probing questions. I'm able to decipher that need very quickly and I invite people to make an appointment. Twelve or 13 years ago, I wondered who would sit down with a pharmacist and pay them for between a half hour and perhaps even two hours of their time. Much to my surprise, people are willing to do that. The public trusts us. They are tremendously loyal to us, and we have never really parlayed that into an office-based practice

where we charge for our time. We mistakenly associated ourselves primarily with pharmaceutical medicine when we really needed to align ourselves with clinical services.

In speaking to some of my colleagues here in Canada and in the US, I've discovered they are getting into things like diabetic care, asthma care, cardiovascular disease care, and looking at what is the best medicine to select in each situation. What is the best dietary approach to take? What kind of nutraceutical approaches can be integrated into a multi-dimensional approach to get the patients well? We have to rely upon many interventions. We can't just fixate on any one thing.

I think the biggest factor in making this transition is that each pharmacist needs to conduct a self-evaluation and realize that the time is ripe to begin to make sense of what they see every day. Why is cardiovascular disease so prevalent? Why has cancer moved into the number two disease spot, when it didn't even crack the top ten 50 years ago? Why is there such an epidemic of obesity? Why is diabetes now the fastest-growing illness? Asking some of these questions will lead to some very profound answers. We now know that stress has a lot to do with some of the chronic, age-related diseases. We also know how chronic inflammation links diseases. We know about oxidative stress in the body. We know about how dietary factors, such as macro- and micronutrient balance, fatty acid balance, glycemic load, dietary fiber content, and even things like the pH of the diet to sodium/potassium balance, all have a tremendous influence on a person's functional health. We have pharmacology and pathophysiology, but we need to look at functional biochemistry and functional physiology to figure out how we can influence the other end of the spectrum to improve care. It can be done. Every day, we see people getting off medication, or finding a minimum dose on which we can manage their diseases, free of side effects and adverse events with other interventions, and motivating people to make changes in their lives. I can't tell you how rewarding it is. People want this type of care.
JB: When you are counseling a customer (now a patient), do you have difficulty bridging the two worlds of pharmacology and nutrition? Are they in conflict, or is there a way to harmonize what might appear as two disparate philosophies?
Bridging the Worlds of Pharmacology and Nutrition
FW: It's a matter of perspective. For instance, we might look at someone with high cholesterol and recognize that he or she is at risk for cardiovascular disease, or heart attack and stroke, so we might put that person on statin therapy. They may come back to the pharmacy and tell us that the doctor wants to increase the dose because they haven't yet reached "target," and they still don't know why the cholesterol keeps soaring. Here is an opportunity where, instead of just filling a prescription for increased dosage of a drug, the patient may want to talk about side effects, muscle pain and fatigue, or abdominal cramping. Patients are very educated. They will challenge us. They're reluctant to take more medicine. They're reluctant to expose themselves to side effects; they're very cautious. They want to get help, but at the same time they don't want to surrender to high-dose, pharmaceutical polypharmacy approaches. It was acceptable a generation ago, but it's not acceptable now.

As a pharmacist, along with my understanding of functional medicine, I can look at dietary cholesterol. We can lower it, but that may only influence serum cholesterol by about 20 percent. We now know that the bulk of cholesterol is produced in the liver, and that excessive insulin is a potent molecule that will signal the liver to wrap up cholesterol production, for several reasons. Is the person in a state of chronic inflammation? We know cholesterol can be a reparative molecule. Or, is the person locked into a state of biochemical stress? We know that cholesterol is a precursor to cortisol and perhaps the patient needs more stress hormones. If we understand physiology and biochemistry, we can begin to peel off the layers

and look at why this is happening, and where in the web of biochemistry to push and tug. What other interventions can we suggest to go along with statins to bring the cholesterol down? It may mean a number of other interventions, and it needs to be done on an individualized basis. That's really what I do.

I look at why the medicine isn't working from a pharmacological perspective. Why is the problem getting away from us? What are the drivers of these problems? This is where functional medicine points to many of the answers. It points to multi-factorial causes and gives one the ability to come up with a systematic approach using various interventions to address the problems. The problem in pharmacology is that, while we know a lot about all the different pathways, and we know a lot about many of the players, we don't know how all the mediators are connected. We don't bother to identify the triggers, and we don't bother to take each patient's uniqueness into consideration. If 10 people visit a doctor for depression, they all walk out with a prescription for an SSRI. In some cases it helps, in some cases it hurts, and in some cases it has no effect. We can't continue to practice protocol medicine. We need to understand why pharmacological approaches fail. This is why I have benefited so much from learning about functional medicine. It helps me to make sense of the aberrant biochemistry I see and to determine what action to take. It takes some time and patience to sort it all out, but it is very fruitful when you understand how to bring the patient along.

JB: How about the dialectic with the doctor of record for that particular customer or patient? Does this establish an opportunity for a dialogue, or do you find that it ends up in a dialectic confrontation?

Developing a Relationship with Physicians in the Community
FW: Thirteen or 14 years ago, it was a tough go between physicians and myself. But in that time, I recognized what I needed to do to establish myself as a credible source of information, and practice pharmaceutical care and self care in a responsible manner. In 1996, I touched base with 150 physicians in my area who refer patients to me, and I began to send them periodic newsletters. The newsletters were based on clinical information the doctors see in their journals. I helped review the information and crystallize it for them. I gave them some clinical pearls and let them know that I was on top of the information. Little by little, this helped me to become established as a credible person in the community. It helped me to facilitate when I would phone a physician and thank them for referring Mrs. So and So. I would say that I had assessed the situation and instead of, in this case, raising the dosage of a statin, I would tell the doctor what I would recommend. Then I would ask what he or she thought about my recommendation. They would respond by saying that I made a lot of sense, and if I felt that strongly about it, they would be open to my approach because they didn't want to run the risk of side effects and just arbitrarily raising medication dosage, but that they were at their wit's end as to what to do with this patient. We need to engage physicians in this manner, but we first need to distinguish ourselves in the community. I go out into the community and give lectures. I speak to doctors and send them letters. I publish articles in various magazines and journals, and send information to the doctors. All of that goes a long way in distinguishing one's self as a primary healthcare practitioner. This is what pharmacists need to do. Surveys have told us that.

Five or 10 years ago (unfortunately, I can't remember the citation), 2600 physicians were surveyed and asked what they thought about pharmacists getting involved in self care, pharmaceutical care, and practicing integrative medicine. New physicians appeared to hold pharmacists in high regard and they had high expectations of them, but as they moved on in their careers, they lost confidence in pharmacists. However, when a pharmacist expanded clinical services and gave them a call, they were open and

receptive to reasonable approaches to health and wellness, and that needed to be substantiated by significant data. We back things up with data and, little by little, physicians today are much more open minded and much more experienced in working collaboratively. Today, a family physician knows he or she can't go it alone. They're busy; they're swamped, and if somebody steps up to the table, such as a pharmacist, and tells them he or she can help, they're open to it. The time is ripe for us to collaborate with physicians to do this type of care.

JB: That leads me to the last question. When you engage in a discussion with a patient, there are many ways that you can make your presentation. You can lead with the diet relationship to that condition, such as a lipid-lowering diet with statins, for instance, or you can lead with the concept of nutritional pharmacology. Or, you could take a drug/nutrient position and tell the patient the drugs he or she is taking may have adverse effects on nutrients and therefore, suggest that those nutrients be augmented. Is one of those approaches a principal route, or do you assess the patient and then make your decision about the primary route?

Multiple Effects of Medications

FW: We are getting more and more data all the time. Some of the common medications do indeed deplete nutrients to deficient and sometimes insufficient levels. I don't think you can take a simplistic approach to functional medicine. It's very linear just to look at six to eight medications a patient is on, open up a textbook and see what nutrients are likely to be depleted, and that it's just a matter of getting them on, for instance, coenzyme Q10 because they're taking a statin, or a little more zinc because they're on an ace inhibitor, and then perhaps throw in a multi-vitamin. That approach is unlikely to work. What we really need to do, and it goes back to what I said earlier, is to go beyond and really understand the multiple effects that drug is having on the individual. For instance, in the case of statins, we need to look beyond coenzyme Q10 depletion, and look at whether the statin is being properly metabolized. Is phase 1 and phase 2 detoxification working in the liver, the gut, and the kidneys? Why are they continuing to have muscle pain? I've given them coenzyme Q10 because I've looked up the research that says coenzyme Q10 is likely to be depleted, but they continue to complain of muscle pain. Here is where you have to look at the possibility that the drug isn't being properly metabolized.

This is one of the things I'm anxious to learn more about at the upcoming symposium in April. I love the topic of biotransformation because as pharmacists, that is our domain. We need to learn more about drug metabolism and detoxification and then look at the multiple effects way beyond simple drug/nutrient depletion. I go beyond that to assess how well the drug is working, how well it is being tolerated, and whether we are reaching target in this particular situation. If the answer is no in all those situations, then we need to go beyond the simple repletion of nutrients.

JB: That's very helpful. Do you feel that it's imperative for a pharmacist doing your kind of work to become a compounding pharmacist? Is that not a critical component of this focus?

The Compounding Pharmacist

FW: There is a huge need for compounding as we move toward personalized medicine, individualized care, and patient-centered care, and away from protocol medicine and a doctor-centered healthcare system. A lot of my colleagues have decided to go into compounding and have found it to be very rewarding. I chose not to do that because I'm thrilled about the counseling I'm doing. I would suggest selecting one thing that you are really excited about. What do you see in your practice? Do you have a lot

of cardiovascular disease patients in your practice, or diabetics? Do you want to help patients with smoking cessation? Do you like working with obese patients? Pick something you see in your practice that you're excited about and want to get involved with. That's the main thing. It's easy for me to say that all pharmacists should get into compounding, but if you're not interested in that, and you're not excited about it, you're not likely to be successful with it. That's the secret to growing and evolving into a primary healthcare practitioner. You need to focus on a particular area of interest.

JB: Your philosophy and mission are very motivating. It creates a sense of imperative about the quality of a distributive healthcare system that provides health information, not just disease-care information. Your book, Breaking the Age Barrier (Strategies for Optimal Health, Energy and Longevity) which can be found on amazon.com, is a very good manifesto of everything you've talked about. I certainly would recommend it for people who want to follow up on the insightful comments you've shared.

I also want to recognize you as a leader. Being a visionary in any profession carries with it an associated risk. You've been willing to step out and be counted as a member of the front-edge group of healthcare providers who are going beyond what might be considered their comfort level, to introduce your services and knowledge to your customers in a way that opens up the opportunity for discovery. That's tremendously unique. Many people feel apprehensive and wonder if they really have the stuff to open up a dialogue with customers in such a way that they'll share their private lives and collaborate with them on finding a path to better health. I think you've spoken both from an implementation perspective, and from a philosophical and humanistic perspective about a different kind of health care, one that is, as you said, more patient-centered, more humanistically oriented, and one that deals with information as the key tool for motivating people to change. Thank you so much for your advocacy, your hard work, and for sharing it with us.

FW: Thank you.

JB: We wish you the best and will check back with you at a later date. I can be assured, just on the strength of your information, you're going to set a lot of people's minds to thinking about what they can do better.

FW: We certainly hope so.

Statins and Coenzyme Q10

Mr. Wassef raised a very interesting question-what effect do statins have on CoQ10 status, and is supplementation a nutritional pharmacological antidote to the depletion caused by statins? This was the topic of an interesting mini-symposium published in *Current Topics in Nutraceutical Research* that I would like to summarize. There is a broad recognition that statins block the synthesis of the isoprenoid family of compounds. The biosynthesis of coenzyme Q10 in cells comes through the isoprenoidpolymerization pathway, the isoprenyl pyrophosphate pathway. Therefore, it is known that CoQ10 levels could be lowered by blocking prenylation and isoprene synthesis.

Dr. Chandan Prasad, associate editor of the Department of Medicine in *Current Topics in Nutraceutical Research* at the LSU Health Sciences Center in New Orleans, speaks about whether statin users should take supplemental CoQ10 as a way of balancing out the functional depletion that might occur from taking

statins.[16]

This concept is really born out of a wonderful review paper by Dr. Ronald Lieberman of the Division of Cancer Prevention, National Cancer Institute, Bethesda, Maryland, titled "Statins and coenzyme Q10 intersection of established medical therapeutics, clinical pharmacology and the emerging evidence-based science of complementary and alternative medicine for protecting cardiovascular health."[17] In this review paper, Dr. Lieberman advocates that monitoring of CoQ10 status should be considered during use of statin therapy. It may be necessary to provide for a conditionally essential nutrient that might be low due to the inhibition of its synthesis as a consequence of taking statins. He recommends more controlled research on the supplementation of CoQ10 in the range of 200 to 400 mg a day while people are on statins.

The clinical observation that people have had in using CoQ10 supplementation during statin therapy has been mixed. There is no definitive clinical intervention trial that has really developed a statistical analysis of the value of supplementation with CoQ10. Theoretically, or at least conceptually, it would seem like a good idea because of the potential blocking in CoQ10. In fact, a series of investigators from the East Texas Medical Center and Trinity Mother Francis Health System in Tyler, Texas, who have looked at the potential role of concomitant CoQ10 with statins for patients with hyperlipidemia, came to the conclusion, once again, that 200-400 mg per day of supplementation with CoQ10 during statin therapy was, in fact, valuable, and they support this level of supplementation to prevent CoQ10 depletion and lowering some of the adverse side effects that appear with statin therapy, including neuromuscular complaints.[18]

The other side of the coin, just to give a balanced comment, is that of Dr. Barry Bleske from the College of Pharmacy, University of Michigan, who says:

"This is a wonderful hypothesis and certainly worthy of our attention, but quite honestly, no clinical intervention trials have ever been done, and there is not even evidence that intercellular CoQ10 is actually depleted during statin therapy. This is suspected, or a hypothesized depletion in the absence of proof of hypothesis. In the absence of really having available intervention trials that would look at intercellular CoQ10 before and after statin and whether you could remediate that with oral CoQ10 therapy, that it is premature to recommend CoQ10 therapy." The time is not now to recommend CoQ10 therapy to patients receiving statin. Before this recommendation can be put forth, we must validate this hypothesis with outcome data."[19]
Again, as is the case in this emerging nutritional pharmacology area, every white has a black; every discussion has a shade of gray, and we are just emerging a fundamental platform upon which these decisions can even be made, and some of these questions are related to methodology as much as association. How do you actually study these associations? What are the ways that the studies can be properly designed to lead to outcome-based understanding and to evidence that is actually directing you to the right conclusion, rather than just misdirecting you. You have a number, but you are not sure what that number is associated with.

Again, clinically and empirically, many patients report improvement of their outcome with statin therapy when they are taking concomitant CoQ10 supplements, but I want to put in context that there is no definitive clinical intervention trial that has been done evaluating that hypothesis.

Vitamin D

What about vitamin D? That is another interesting, emerging supplement that seems to be lower than optimal in the American diet because we see low blood levels below 25 ng/mL of 25-hydroxyvitamin D very commonly in people that have a variety of immunological problems-type 2 diabetes, fibromyalgia, depression, dysphoria, and difficulties with multiple sclerosis-like symptoms. Increasing risks also of colon, some breast, and prostate cancers are also associated with low 25-hydroxy D3.

Recently, in the journal *Carcinogenesis*, the authors of an article talk about colon-specific regulation of vitamin D conversion to its active hormonal form, and this might be a very important thing for reducing the risk of colon cancer.[20] Vitamin D can be converted into the 1, 25-dihydroxy vitamin D, the active hormonal form, in the intestinal mucosa. Diets that contain higher calcium and vitamin D appear to be chemopreventive against colorectal tumor pathogenesis.

Here again is a very interesting complication of a simple question. Does vitamin D prevent colon cancer? The answer may be yes, when it is in the appropriate GI mucosal environment and has proper levels of activation of vitamin D to its 1,25-dihydroxy form, because cytochrome P450s found in the gut mucosa hydroxylate vitamin D into the active hormonal form that regulates cell cycling and the potential carcinogenesis associated with other exposures.

These things are not always easy to understand, in part because our gut is a bioreactor that can convert one substance to another by the presence of certain flora. Not everybody has the same flora. We get the proximal nutrient converted into the ultimate nutrient that influences function.

Silencing of Genes by Promoter Hypermethylation

What about the relationship of genes and cancer-the genes that control cell cycling? These are the genes that are sometimes associated with tumor promoters. A factor in keeping these genes in check, or silenced, is by methylation. Methylation is controlled, in part, by things like folate status and SAM through the methylation pathway. If you can silence tumor prompter genes by methylation, can genes that are protective also be silenced by methylation? The answer is yes, and the questions being asked now are: How is methylation of DNA controlled? Can specific non-tumor promoting areas be demethylated, while keeping the tumor promoter genes silenced? What role does folate have? What happens when we give too much folate? Would that cause a problem? Some studies show that hypermethylation of genes, or too many methyl groups stuck on the histones of genes and nucleic acids, creates its own problem associated with tumorogenesis, but how this hypermethylation is regulated is not well understood.[21]

A recent study in *Carcinogenesis* looked at the effect of differing folate levels in the development and progression of mammary tumors in animals. It was found that giving very high levels of folic acid (8mg per kg of the diet in animals, a very high dose) did not lead to any increased level of breast cancer after the exposure to a known breast carcinogen, N-methyl-N-nitrosourea.[22] The investigators came to the conclusion that you cannot over-methylate by increasing folic acid. What you want to make sure of is that you have adequate folic acid to properly methylate. That is an interesting dose/response relationship. Does the body have some kind of control mechanism upon which it will not allow excessive amounts of function to occur with excessive nutrient intake?

Benefits of Soybean Foods

hat leads us to the last question about various macronutrients that carry all sorts of phytochemicals in the diet that can regulate function. How do we study them? For instance, let's take soy. The soy controversy is really raging these days. Does soy cause harm? Does it cause or prevent dementia? Does it cause pancreas problems and digestive difficulties? Does it cause allergy? Does it cause or prevent cancer? The answers to those questions are often related to arguments based upon removing something from soy and trying to analyze it in very high doses in animals versus looking at the whole food. If you look at the whole food and the data that has been published, you find that soy as a whole food with its natural constituents, has tremendous benefit in regulating physiological function.[23] We have to look at it in the context of how and at what levels it has been consumed.

I hope I've set in context for you some of the things that are in the news related to nutrient pharmacology, where we are going, and how this relates to biotransformation and detoxification, in preparation for our April 2006 symposium. Thanks for being with us at the start of this New Year.

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