October 2004 Issue | Joseph E. Pizzorno, Jr., ND

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Welcome to *Functional Medicine Update* for October 2004. I have the privilege of announcing the topic and dates for our 12th International Symposium on Functional Medicine, which will take place on May 24-28, 2005 at the five-star Westin Mission Hills Resort in Palm Springs, California. I have visited this facility and it is a lovely place to hold a meeting. The topic of the 2005 symposium will be, The Immune System Under Siege: New Clinical Approaches to Immunological Imbalances in the 21st Century. This topic is at the forefront of our interest because we are all concerned about infectious disease. Atherosclerosis is now being seen as an autoimmune inflammatory disease and metastatic events in cancer are related to immunological imbalances and inflammatory mediators. We are also interested in type 2 diabetes and osteoporosis and their relationship to immunological changes, and the list goes on and on.

The 2005 symposium will focus on what we know about the immune system under siege from a 21st century perspective, and how we can harness new discoveries to ameliorate, manage, and prevent specific types of disorders that cut across the spectrum of immune imbalance. The program, as designed by the Curriculum Committee, and the plenary lectures and concurrent sessions associated with this topic, will give us a whole new way of looking at immune system function. It will result in more tailored evaluation tools for designing specific therapeutic intervention programs for patients based on their immunological status. You will be hearing much more about the program soon. For those of you preparing for the symposium, we will be introducing some concepts in FMU regarding immune system balance in the months before the symposium. We will also have some clinicians and researchers who will help us to better understand these topics.

This month, I would like to focus on a discussion that sets the stage for much of what we will be speaking about in subsequent months regarding immune system function. It has to do with the methodology of developing evaluations and designing programs, so-called research methodology. How do we arrive at making decisions based upon the research? What is the type of research being done, knowing that the immune system is complex and that it interfaces with the outside and inside world? It is our internal defense mechanism, a translator system, taking outside information and converting it into physiological functional changes for defense of the organism. We need to know something about the complex orchestration of events occurring in the outside world and how that translates into internal physiological information, which is more than just one function occurring at a time. In fact, the more we study the immune system, the more we recognize that it is a little bit like studying particle physics.

Early on, we learned that there are electrons, neutrons, and protons. We also learned that energy can travel in discrete units called photons. As particle physicists became more involved in research, they

determined that there are actually subatomic particles as well, particles from which the neutrons and protons are composed. They are called bosons and fermions, the daughters and brothers of the bigger atomic particles. These are the fundamental particles that make up the nature of the universe. We have heard about these particles by other specific names, such as neutrinos and quarks, as well as other types of subatomic particles. Understanding how these particles interact helps us to better understand the physics of our universe.

Let me use some examples of how complex these interactions can be. Cholesterol gallstone disease, cholelithiasis, is a condition seen with certain epidemiological relationships. In particular, overweight women frequently have this disorder, resulting in a need for surgery. The supersaturation of bile with cholesterol results in the crystallization of cholesterol into gallstones. The bile is a mixture of three components—cholesterol and its esters, bile salts, and lecithin. The lecithin and bile salts are solubilizing agents; they are amphoteric; they have detergent-like properties because they are both water-soluble and fat-soluble to some extent. They tend to emulsify fats. When bile is made up of more of these emulsifying materials—more lecithin, more bile salts, and less cholesterol—there is a soluble matrix. If, however, the ternary phase diagram shifts and there are higher levels of cholesterol and its esters and a lower level of bile salts, even with the same amount of lecithin, a zone of crystallization may result. Cholesterol starts to crystallize out of solution and there is risk to gallstones.

What factors contribute to crystallization? Is there a single factor? Obviously, the answer is no. When the physiology of gallstone formation is examined, we find that there are literally tens of differing factors that contribute to the condition, many of which are connected to lifestyle, as well as genetics. Let us take one of those factors, the conversion of cholesterol into 7-α-hydroxycholesterol, the rate-limiting step for the formation of the bile salts chenodeoxycholic and cholic acid. There is a specific enzyme involved in that particular step, the 7-α-hydroxylase enzyme, which is genetically unique to the individual. Therefore, there is variegation and different frequency of conversion, or the facility of conversion of cholesterol into bile salts. Some people may be at higher risk to forming cholesterol stones because they cannot hydroxylate cholesterol into solubilized bile salts as effectively as others. Therefore, their ternary phase diagram of bile becomes more supersaturated with cholesterol because of a lower amount of bile salts.

However, there are substances known to promote the conversion of cholesterol to bile salts by activating the 7-α-hydroxylase enzyme. One of them is vitamin C, or ascorbic acid. Historically, there has been lore that one can lower the risk to cholelithiasis and gall bladder stones by increasing vitamin C intake. Individuals with the 7-α-hydroxylase insufficiency due to a genetic polymorphism may be more susceptible or more sensitive to vitamin C intake; therefore, not everyone can reduce gallstone risk by taking vitamin C. We are stratifying now for an individual genetic type.

In a group study of vitamin C and gallstones, there might not be a high frequency of individuals with that specific polymorphism. If 100 patients are treated with vitamin C, a statistically significant decrease in gallstone formation might not be demonstrated because most people do not have that unique sensitivity. However, the study cohort with the sensitivity may have a positive result, although it would be washed out as a consequence of not having a high enough percentage frequency to shift the average data into the positive. This has always been part of the difficulty in doing nutritional intervention trials with a poly-genomic population.

Let’s use another example. Ultimate solubility resulting from the conjugation of bile salts has to do with

conjugation of various secondary moieties, one of which is the amino acid, taurine. Taurine is a sulfated molecule that helps form a solubilized, detergent-like bile salt. Inappropriate taurine conjugation might also lower the effectiveness of bile to solubilized cholesterol and lead to cholesterol stone formation. In some individuals, risk to gallstone formation has been reduced by increasing dietary taurine supplementation, but not everyone responds in a positive manner. Who are the individuals most likely to respond? They are likely to be those who have the conjugation insufficiency, which is another cohort. What about individuals who may have decreased production of lecithin, another important solubilizing component of bile? This may comprise another subtype which might respond to choline or phosphatidylcholine supplementation to lower the risk of cholesterol deposition in bile.

The point I am trying to make is that diet as a risk factor for cholesterol gallstone disease may have many variables that are very specific to the individual genotype. Therefore, a study that only examined diet and gallstones may lose some of the discrimination in the "noise," which we call regression to the mean, or the average response. However, there are certain epidemiological associations between gallstone disease and diet that seem to stand out. For instance, the consumption of simple sugars and saturated fat is correlated with a higher risk to gallstone disease. Fiber intake and moderate consumption of alcohol are also associated with a decreased risk to gallstone disease, but high levels of alcohol intake are associated with increased risk to gallstone disease.

There are certain things that pop out of the literature as gross epidemiological markers, but when it comes to individual nutritional associations, a different type of study methodology is required, a different type of stratification. I have been quoting from an interesting review paper that appeared in the *Journal of the American College of Nutrition*, titled "Diet as a Risk Factor for Cholesterol Gallstone Disease."[2]

Another important issue in research relates to whether research risks are reasonable in relationship to anticipated benefits. That is the title of a recent paper in *Nature Medicine*,[1] in which the authors raise the question about some of the clinical research using the placebo-controlled model. Even well-designed controlled trials may be marginal regarding the relative risk to which the participants are subjected. These trials often do not address the broader questions such as how we stratify uniqueness in the cohorts that might lead to differences in the way they respond, i.e., accounting for biochemical individuality. How do we recognize that there is more than one thing going on, when only one endpoint is being studied? How do we deal with the possibility, and often occurrence, of atypical adverse effects, which are probably not atypical, but reproducible in the people who have them? We call them atypical because they occur at low frequency, but the question is, when are research risks reasonable in relationship to anticipated benefits?

When we begin to examine the ethics of clinical trials, we get into how institutional review boards (IRBs) function. IRBs review various experimental protocols and determine the ethics and the risk-to-benefit of a trial proposal. An IRB might ask whether a trial puts people at undue risk. What are the ethical questions related to placebo controls, knowing that sometimes the placebo is a very powerful force in medicine and may play an important role in outcome that is not to be dismissed as trivial? IRBs play an important role in research as to how we eventually answer more complex questions—real-world questions about what a person should eat, or think, or believe, or drink, how they should exercise, what environment they should be exposed to, or what type of nutritional intervention program they should be involved in. How does the information obtained from trials relate to how a trial is performed? These are important ethical issues being brought to the foreground in the research literature, and discussions may ultimately result in a new decision-making process based on multidimensional or multifactorial questions. The placebo-controlled

clinical trial may remain as the “gold standard” if one is looking at a single molecule against a single endpoint; for example, a drug for a condition that can be directly measured, such as blood pressure. But it may not be the methodology of choice if one is trying to examine other more complex questions related to an individualized response to a complex environment.

What about multivitamin supplements? That topic is still considered fairly controversial in some quarters as to whether it is cost effective to take a nultivitamin supplement or whether it results in expensive urine. Some feel nutrients get flushed out of the body through yellow urine, indicating that supplements clearly are not useful. I think there is a flaw in that logic: If the supplements were not flushed out of the body, but were retained, then in eating diets that contain vitamins, we would eventually accumulate so many that we would turn into a crystallized vitamin. One has to get rid of supplements; we do not hold onto vitamins throughout the course of our lives. In particular, the water-soluble nutrients are always turned over. The concept that they are just spilled into the urine does not address the question as to whether they were absorbed and did something on their way through the body. Perhaps they have some positive impact on promoting proper cellular function.

Cost Effects of Daily Multivitamins for Older Adults

In January of this year, the Lewin Group, Inc. published a report on a study it was enlisted to carry out on the cost effects of daily multivitamins for older adults.[3] This was an extensive review and assessment of the cost effectiveness of multivitamins that resulted in some extraordinary conclusions. In order to evaluate whether taking a daily vitamin and/or mineral supplement has value, one cannot simply look at the course of one day. A timeframe of a month or a year would be better, as well as reviewing data over a broad range of individuals. Appropriate endpoints and markers are needed that can be carefully evaluated to determine whether there is any cost effectiveness. This particular study looked at a population group 65 years of age or older and certain high-prevalence conditions in that population to see if the incidence of several conditions was mediated or modified by multivitamin/multimineral intake. These conditions included coronary artery disease (CAD), colorectal cancer, diabetes, osteoporosis, prostate cancer, and dementia. Over the years in FMU, we have discussed many studies on nutrient intake related to those clinical areas. When this study was done, the investigators felt that the potential savings resulting from the reduction in the relative risk of CAD and improved immune function, and subsequent reduction in infection through providing older adults with a daily multivitamin supplement, is approximately 1.6 billion dollars. (The five-year estimate of gross cost of providing the Medicare beneficiary population with a daily multivitamin, if it was to be employed across the board, would be about 2.3 billion dollars, and the overall cost reduction in total for all the major age-related diseases, including CAD is 3.9 billion, making the net cost of potential savings approximately 1.6 billion dollars.)

We are looking at gross numbers in this study. We are not looking at individual lives. We are not looking at individual responses. We are not looking at functional changes that might have improved quality of life, things like range of motion, soreness, sleep patterns, prevention of colds and infection, and even things like memory, recall, and cognitive function. We all know from the studies done by Dr. Lindenbaum over 25 years ago that cognition is improved in older-age individuals who take vitamin B12 and folate-containing nutritional supplements.

The cost effectiveness study done by The Lewin Group is very interesting, again trying to address how we state whether there is value. How do we come to decision making? How do we tell a patient he will get benefit from taking a daily multivitamin/multimineral. How do we convince a patient that the return

on his investment will be greater than the cost if he just stays with the program? Again, we often have to use inferential information for decision making because we do not have the value of a prospective trial on that person over time against a placebo. That would be like observing a person's identical twin living an identical lifestyle to see what the outcome is. We have to make the best estimates based upon this type of patterned information.

Cooling Off Hot Flashes

Let's take another example, which I think is a fascinating one—hot flashes. We have seen a lot in the news recently about the use of equine estrogens and synthetic progestins for the management of menopausal symptoms. It was not long ago that this was considered the preventive medicine of its time. Conditions associated with postmenopausal health problems in women, such as bone loss, loss of cognitive function, cardiovascular disease, as well as sexual dysfunction, and a reduced sense of vitality, would all be neutralized, or would be managed by the combination of equine estrogens and synthetic progestins. Then, the Women's Health Initiative began to give us information about this association, or this hypothesis, and it was found that not only was the hypothesis somewhat overstated, but on further inspection with multiple studies, it was found to be incorrect. Some women had increased risk to conditions for which they were supposedly being protected by equine estrogens and synthetic progestins.

One of the conditions for which synthetic progestins and equine estrogens are used is hot flashes. Over the last five years, the question has been raised about where hot flashes come from. What is the physiological mechanism by which women suffer from hot flashes? Is it an estrogen deficiency, for which the use of estrogen replacement therapy (ERT) is the treatment, the simple model of estrogen deficiency/flashing, and estrogen administration/no flashing?

That leads to an interesting revelation. When one looks in the literature for information about the mechanism for hot flashes and night sweats in perimenopausal women, one expects to find a definitive answer because of the wide use of equine estrogens (at one time the number one prescribed medication in the U.S.). One would believe there must be a definitive understanding of what is going on, but that is not the case. Even today, we do not understand the mechanism that results in hot flashes and night sweats. Therefore, the treatment with equine estrogens was a symptom treatment alone, based upon empirical evidence that 70 percent of women who take an ERT product will achieve remediation of symptoms. But this was not built on any known mechanism of action.

In a paper in the *Journal of Clinical Oncology*, titled "Cooling Off Hot Flashes,"[4] the author states that vasomotor symptoms represent the most common complaint among perimenopausal women. It is estimated that up to 60 percent of postmenopausal women experience these symptoms, up to 20 percent of women find them intolerable, and a similar proportion of women suffer symptoms up to 15 years after menopause. In 2001, up to 4,000,000 women complained of severe symptoms for which they sought intervention in 2002. There are probably more today because of a greater number of women going through menopause. Women who suffer hot flashes may complain of associated symptoms such as depression, anxiety, and difficulty with sleep patterns and sexual function. Women who undergo premature menopause often suffer symptoms of longer duration.

Where do these hot flashes come from? The pathophysiology of the phenomenon is not well understood. Estrogen action in the central nervous system (CNS) is complex and it may not be just estrogen alone. It

may be estrogen metabolites like hydroxylated estrogens that are also exerting influence on the CNS, the so-called hypothalamus/pituitary signaling. Estrogen exerts its function not only through an interaction with its receptors, but also through an interaction with other receptors importanty in the regulation of sleep, mood, and cognition. We have moved beyond 17-β estradiol to looking at the other estrogen metabolites and how they influence these hypothalamic pituitary functions.

Non-Hormonal Agents and Hot Flashes

Some non-hormonal agents have shown promise for the management of hot flushes, which suggests that more than just estrogen is involved. Dr. Charles Loprinzi at the Mayo Clinic Center in Rochester, MN, has talked about the use of venlafaxine in managing symptoms of hot flushes in women who have had hysterectomies.[5] A half dose of the antidepressant (75 mg versus 150 mg) results in a 60 percent reduction in the hot flush score in women. We are beginning to see that there may be some interesting interrelationships among agents that modify hypothalamus/pituitary function and hot flashes.

Frequency of Menopausal Hot Flashes and Blood Glucose Levels

If hot flashes result from more complex hormonal signaling than just estrogen alone, what about other things that modify HPA axis function, such as stress, or blood sugar and insulin? In a recent paper in *Nursing Research*, investigators reported that frequency of hot flashes was correlated with alterations in blood sugar.[6] When women had low blood sugar followed by rapid increases in blood sugar, an increased frequency of hot flashes was observed. What is called reactive hypoglycemia and dysglycemia/dysinsulinism may also have associations with hot flashes and night sweat conditions seen in perimenopause. It appears that stress, diet variables, and hormonal imbalances play a role in this complex web, not just estrogen alone. We still do not know exactly how estrogen plays a role in modifying the frequency of hot flashes, or how the mechanism works.

The complex interactions of a program developed for a woman with menopausal symptoms would be more than just a simple intervention with mixed conjugated equine estrogens. It might include diet alterations, stress reduction, lifestyle modification, and a regular exercise program. All of these have been found to modify and ameliorate hormonal imbalances associated with the onset of menopausal symptoms.

This is much more complicated than just giving a pill against a single endpoint. Once again, we are talking about polyfunctional or multifactorial agents and their relationship to multiple symptomatologies. It is more than just hot flashes. A woman may have a lowered quality of life as a consequence of hot flashes and night sweats, but what about her other health risks, such as cardiovascular disease, cognitive decline, and bone loss? In these areas, we need to be looking at more complex intervention programs that deal with all of these variables. Dr. Allan Warshowsky talked about this topic eloquently in his interview as an FMU clinician in February of this year.

Estrogen for Treatment of Hot Flashes in Postmenopausal Women

The literature is beginning to support this concept. If you have been reading the *Journal of the American Medical Association* recently, you probably saw a series of papers published in 2004, titled "Postmenopausal Estrogen for Treatment of Hot Flashes."[7],[8] The author says that evidence supports estrogen for the reduction of hot flashes as a clinical endpoint, but that it does not appear to have any other significant benefit beyond modification of that endpoint. The other risk factors may still be present. A woman may actually be "persuaded" into thinking she is OK because her symptoms are decreasing while on estrogen therapy, yet her relative risk to cognitive decline, CVD, and bone loss may still be

increasing. These are very interesting parts of the story. Sometimes, interrupting the symptoms is like taking the smoke detector out of your children's upstairs bedroom. You do not hear it go off so you think everything is fine, but you still have the fire to worry about.

In a paper in *JAMA*,titled "Effects of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy,"[9] the authors state in the last sentence of the conclusion: "Thus, CEE (conjugated equine estrogen) should not be recommended for chronic disease prevention in postmenopausal women." That is a very different type of conclusion than we were presented with just a few years ago. In fact, in the editorial that follows these papers titled "The WHI Estrogen-Alone Trial—Do Things Look Any Better?"[10], the answer was no, they did not look any better. In moving away from CEEs to estradiol itself, there still did not appear to be a significant benefit on other health risks by estrogen intervention alone. The authors state:

"In the absence of evidence for an overall net benefit of postmenopausal treatment with estrogen alone, and with the evidence that estrogen plus progestin is harmful, neither therapy should be used for preventing disease. Although it is possible that other forms or doses of hormones could be more beneficial, this must be demonstrated in disease-end point trials before any hormone regimen can be recommended for disease prevention. Fortunately, there are other good approaches to preventing CHD and fractures for which trials have found benefits to outweigh harms."

We are talking about lifestyle multifactorial intervention trials, not single agents against single endpoints. Sometimes, one needs to question the double-blind, placebo-controlled trial as to whether it leads us down the wrong path and actually mis-affiliates a benefit against a treatment, rather than looking at the total complex situation with respect to relative risk and benefits.

Weight Loss/Diabetes Connection

Let's look at another interesting example of this complexity that has to do with the weight loss/diabetes connection. Most of us have heard through lectures and through the body politic and the scientific literature that excessive adipose tissue weight gain, particularly visceral adipose tissue, will, in fact, cause diabetes, and that there is a direct association between body fat and diabetes. If you have been listening to FMU for the last few years, you have probably heard me challenge that hypothesis. There is no question that there is a strong association between body fat and type 2 diabetes. The question we have raised is whether body fat necessarily causes diabetes or whether it is one of the covariables associated with a metabolic disturbance that produces type 2 diabetes, hyperinsulinemia, hypertension, CVD risk, increased inflammatory mediators, increased adhesion molecules, and increased obesity as a consequence of a change in the physiology of adipocyte cells. The real question is one of the chicken and egg, and we have always assumed that the chicken (i.e., diabetes), came from the egg (i.e., body fat). Now, it is reasonable to ask whether this is, in fact, correct.

We are not being told that trying to achieve proper or ideal body mass index (BMI) or proper body composition is ill founded. We are still talking about the importance of maintaining leanness, but the real question is, what should be the major focus in our intervention? Should it be just taking off pounds of fat, or should it be trying to build pounds of muscle that create an opportunity for altered cell signaling and a differential effect on insulin sensitivity?

I am again getting away from the single endpoint concept of body-fat produces-diabetes. The endpoint would be diabetes and the indicator would be body fat. I am looking at a multifactorial model of how diabetes develops through interactions between genes and environment, of which body fat is a component.

Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease

A paper was published recently in *The New England Journal of Medicine* that bears in part on this question, and which is quite fascinating. It is titled “Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease.”[11] This paper is probably counter-intuitive to those of you who have believed that body fatness, in and of itself, causes diabetes. In this remarkable study, the investigators evaluated the insulin sensitivity of liver, skeletal muscle, and adipose tissue with a euglycemic-hyperinsulinemic clamp procedure and isotope-tracer infusions, as well as levels of inflammatory mediators and other risk factors for CHD in 15 obese women before and 10 to 12 weeks after abdominal liposuction. Eight of the women had normal glucose tolerance, although their BMI was certainly showing obesity at 35+, and seven had type 2 diabetes with a BMI nearly 40 (39.9 on average). Liposuction was found to decrease the volume of subcutaneous abdominal adipose tissue by 44 percent. This was a gross liposuction with tremendous loss of subcutaneous body fat via the liposuction technique. It was 44 percent reduced in patients with normal glucose and 28 percent reduced in those with diabetes. The authors of this study found that there was no significant reduction or change in the concentrations of C-reactive protein, interleukin-6, TNFα, or adiponectin. There was also no significant change in blood pressure, plasma glucose, insulin, or lipid concentrations in either group. Therefore, they came to the conclusion that abdominal liposuction, although it did remove tremendous amounts of body fat, did not significantly improve obesity-associated metabolic abnormalities, and that decreasing adipose tissue mass alone will not achieve the metabolic benefits of weight loss.

This is to be contrasted to gastric bypass surgery. In that case, individuals that are type 2 diabetics do experience, at least in the short term, improved insulin sensitivity. In the long term, it appears as if they return to insulin resistance some years after recovery from the surgery. There is something much more complex going on than just the issue of body fat. That is the important takeaway from these studies. In the editorial that follows this study in *The New England Journal of Medicine*, titled "Thermodynamics, Liposuction, and Metabolism,"[12] David E. Kelley points out that we cannot draw unequivocal conclusions from this liposuction study because subcutaneous fat rather than visceral adiposity was removed. Visceral adiposity is that which delivers lots of blood fats directly into the major hepatic artery, and therefore may be a much higher risk in terms of the relative effects on insulin and diabetes. However, given the history I talked about with gastric bypass surgery, it appears as if there may be other factors going on besides the thermodynamics of calories alone in signaling for insulin resistance, and ultimately type 2 diabetes, CVD risk, and inflammatory mediators. It is something related to the physiology of the adipocyte.

When we start looking at single agents against single diseases and simple-minded studies, which have been the gold standard, we are often led to conclusions that are not accurate. They are not realistic and they lead to clinical decision making that in some patients may be good, but in many others may not be good because they did not meet specific needs.

It is the revolution occurring in medicine that is going to teach us how to get better in achieving higher

outcomes from specific tailored programs, moving away from the medicine of the average to the medicine of the individual. This has been the theme of functional medicine since its inception.

Frequent Intentional Weight Loss and Lowered Natural Killer Cell Cytotoxicity in Postmenopausal Women

For instance, in weight loss alone, if a person goes on weight cycling by repetitive weight loss/weight regain, he/she can develop immunocompetence over time. This was recently discussed in an article in the *Journal of the American Dietetic Association*.[13] By focusing on just calorie restriction alone, weight recycling may actually lower natural killer cell cytotoxicity and alter immunological vigilance over time, putting that individual at higher risk to conditions associated with lowered immune potential. The editorial that preceded this article is titled "Weight Cycling and Immunocompetence."[14]

One needs to be cautious about making simple-minded decisions from complex data sets that are cohort-variable based upon genetic diversity. It is from that kind of standard that we will be seeing the emergence of a new form of medicine built upon a different decision-making strategy that will take these multiparameter, multifactorial components into account. Then we can start looking at cohort analysis and individualizing treatment from specific characteristics of the group.

Let's move to our Clinician of the Month, who will carry this theme to a much higher level.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: It's time for our Clinician/Researcher of the Month. This month, we are fortunate to have an individual who falls under both categories of researcher and clinician. He is an institutional leader and an icon in our field. I'm speaking about Dr. Joseph Pizzorno. His name is synonymous to many of you with the worldwide development of the science of natural medicine and naturopathic medicine. Dr. Pizzorno and I have been friends and colleagues for the better part of 25 years and it's been a great privilege to watch the impact of his work on the field of health care. He is a past FMU Clinician of the Month and we are revisiting him now, some ten years later.

Let me give you a quick vignette on Dr. Pizzorno's background for those of you who are not familiar with his work. He has effectively created policy change in many, many areas. I can only scratch the surface here. It began when he worked with a group of physicians to improve and renew Washington State licensure for naturopathic doctors. In the late 1970s/ early 1980s, he was involved in the formation of Bastyr University, the first fully accredited university in the area of natural medicine and naturopathic medicine. He has been involved as a leader in education and is the author of the Textbook of Natural Medicine, which is probably the premier publication that people use in the field worldwide for gaining skill in the area of natural medicine. It is the text used in many institutions of post-graduate education. He was also appointed to the White House Commission on Complementary and Alternative Medicine (CAM) Policy, where he was a member for several years. He was active in the culmination of their final

"white paper," a mandate as to what needed to happen in health education and healthcare delivery, which incorporated some of the CAM concepts. He was recently appointed to the Medicare Coverage Advisory Committee regarding issues related to financing and brings a natural medicine perspective to that group. This is a remarkable chapter in his book and in the field. Last, but not least, he was awarded the Linus Pauling Functional Medicine Award this year, and joined an esteemed group of his colleagues that have previously won the award over the last 11 years. We at the Institute for Functional Medicine felt very privileged to have Dr. Pizzorno join the ranks of the Linus Pauling Award winners.

With that short biographical sketch, I'd like to welcome you to FMU, Joe. Perhaps for those individuals who are not that familiar with naturopathic medicine, you would tell us about what characteristics differentiate naturopathy from other branches of health care.

JP: Thank you, Jeff, for your kind introduction, but more importantly, thank you for being such a teacher to me and to so many for the last 25 years. It's very clear that the advancements I've been privileged to be a part of would not have happened without your wise counsel and your brilliant education.

JB: Thank you so much. We've had an extraordinary group of people over the last 25 years that have been both our teachers and our colleagues. It's amazing how we learn from one another when the right people get together.

Naturopathic Medicine versus Other Branches of Medicine

JP: It's been a wonderful journey together. You asked about naturopathic medicine. In general, people would first think about that as a profession. I think about it more as a way of life and a way of thinking about health care. What characterizes naturopathic medicine is not what we use, which is how many people tend to think of us. They see us as people who use herbs, vitamins, and things of that nature. I prefer to view it as a fundamentally different way of thinking about health care than what has been seen in conventional medicine for most of the last century. What characterizes naturopathic medicine is a very strong philosophical basis in how we think about patients. We try not to think about them as diseases to diagnose, or as therapies to relieve symptoms, but rather as understanding why people are sick and how they can become healthy. We're far more interested in understanding what the characteristics of that person's own unique genetics are, what environment they're in regarding toxic exposure, what nutritional deficiencies they may have, and what lifestyle behaviors they may be engaging in that are setting up physiological dysfunction in their bodies that leads to disease. For example, as a naturopathic doctor, when a patient comes to see me with a condition like migraine headache, I could use a conventional drug approach like Sumatriptan, which relieves the symptoms, but it does not address the underlying causes of the disease. Or, you could take what I would call a "green drug approach," one which concerns me a lot, and one I see a lot of people who use natural therapies doing. They will use an herb like feverfew, for example, to treat the migraine. How effective that will be in relieving the symptoms does not address the underlying cause of why that patient has migraine headache.

The kind of approach I like to take, and one which I think is consistent with what you've been doing in the world of functional medicine, is to look at the underlying physiology that has led the person to the endstage symptomatology of migraine headache. When we look into it, we find a lot of reasons why that person is having migraine headache and those reasons, those physiological dysfunctions, lead not just to migraine headache, but also to many other healthcare problems they are experiencing. For example, about 40 percent of people with migraine headache have mitochondrial dysfunction. About 40 percent of those

with mitochondrial dysfunction have it because they don't have enough magnesium in their body. Forty percent of 40 percent means that 1 out of 6 people with migraine headache should be given extra magnesium, either a dietary supplement, changing the diet, or looking at what may be causing lack of proper magnesium absorption or magnesium leaving the body too quickly. One out of six people will respond to magnesium; yet, five out of six will not. The way a lot of people approach the use of natural therapy is to do a "grab-bag approach" of using a wide range of therapies they hope will work, but they don't actually understand the physiology.

I know I got a little far afield from naturopathic medicine in terms of specific detail, but the idea here is to understand why the person is sick and how to help him become healthy by correcting underlying causes of his illness.

JB: There are a number of very important concepts embedded in your thoughts that I would like to explore. In the area of differential diagnosis, when a physician looks in the book for an international diagnostic code, an ICD9, he is often led to the belief that something like migraine headache (because it may have a specific singular number), is a singular disease and that we can put a ring around it and just call it a disease. The example you just used, which is one of many, suggests that there are subtypes or subcategories of diseases, so disease may be misleading if we start thinking of it as a singular entity. Is that an implication of what you're saying?

JP: It is. As you know, I am Founding Editor of the journal, Integrative Medicine: A Clinician's Journal, and there was an editorial on this about a year ago titled, "Is Disease Real?" I meant to be provocative. If you look at a condition like juvenile onset diabetes, for example, where it's clear that the pancreas has been seriously damaged and is not producing insulin, the disease name, IDDM, actually describes the physiological dysfunction. However, if you look at adult onset diabetes, or type 2 diabetes, there are wide ranges of different physiological effects, only one of which might be low insulin. Most often, there's plenty of insulin, but the body is not responding to it. The use of the term diabetes in that condition, while it actually describes elevated blood sugar, obscures the physiological dysfunction that the patient is experiencing. It leads conventional medicine to use therapies and agents which, while they may reduce the blood sugar, don't deal with the actual problem the patient is experiencing, so you continue to get the sequelae of the disease.

JB: That begs another question. I may be misstating this, so please correct me if I'm wrong. In my years of experience of observing naturopathic medicine, it appears that there may be two separate camps. One camp is a group that would be characterized as believing that the understanding of physiology and even aspects of cellular physiology might be of value in developing a specific clinical treatment program for the patient. There appears to be another group that might say that those are just artifacts. We know more about less and less, and eventually we know everything about nothing, so it's better to deal with the natural history of the disease and to look at it in the context of the historical record and ethnography. By digging deeper, we obscure how to properly manage the patient. Is that an accurate characterization of some of the polarization that appears in the field?

JP: I think that's a good observation. The field of naturopathic medicine is quite eclectic in many ways. I think we all share the core belief of patient focus rather than disease focus, as well as a strong belief in the body to heal itself, if given a chance. Many of us approach that differently. My own background and orientation is much more biomedical and much more in the hard sciences. There are those who would

prefer to take a more constitutional, whole-body, or other kind of approach. For example, people who use homeopathy will not get into biochemistry the way I would. There are those who lean more toward the more nature cure side, and they don't really look at the biochemistry, but at fundamental changes in how the person lives, what they eat, how they rest, and how they detoxify their bodies. There are many aspects of how this profession is practiced.

JB: When I was first associated with you and your colleagues, the better part of 25 years ago, as I recall, there were only two states in which naturopathic physicians were licensed—Oregon and Washington. There has been a great extension of that now. In how many states are naturopathic physicians presently licensed?

JP: Actually, it was seven back then, and it is now 13.

JB: Does that 13 include the recent addition of California?

JP: It does.

JB: It seems like a big step forward for the profession with licensure in California.

JP: It is. When we look at the population of California, the licensing there doubled the percentage of the U.S. population that now has access to licensed naturopathic doctors.

JB: You have done a tremendous service to the profession by helping develop and incorporate a successful comprehensive curriculum at Bastyr University that takes students from their first year right up to graduation. Have you seen the development of that curriculum, the increased activity of the American Association of Naturopathic Professionals, and the textbook all leading to a concept that can be transferred so that you can actually teach it better and introduce it to new students?

Extent of Naturopathic Education

JP: I think that's an accurate statement. One thing I think most people don't realize is the intensity of the education that the naturopathic doctor receives. To become a licensed naturopathic doctor, a student has to complete premed and a four-year graduate school education. During the four years, they study all the conventional basic medical sciences and all the standard diagnostic procedures, but they also study the natural diagnoses and therapies. During that period, they are also engaged in clinical training in teaching clinics. At that point, there are residencies available, but they are optional in most states for licensure. One of the changes I'd like to see in the future in naturopathic medicine is a required residency for all licensed people. But unfortunately, the resources aren't there for that right now.

One of the things that's happened, in the last 10 years especially, has been bringing professional educators into the profession. These are people that have doctorates in areas in which they teach and are developing a more consistent body of knowledge. By having a more consistent body of knowledge, I think it's easier for the concepts of this medicine to be taught. Equally important, it's easier for the concepts of this medicine to be researched. One of my greatest prides in creating Bastyr University was our strong commitment to a science-based approach to natural medicine. We have quite a large research department. What I want to tell people about the research is that we do it not to prove ourselves to the world, but we do it to get better. There is a rich body of concepts and therapies in the field of natural

medicine, and yet I don't think they are applied as well as they could be because they don't have a strong research basis from which to function. I see that rapidly changing and improving at this time.

JB: That leads to an interesting question that has been debated by scholars in the field of the health sciences and that is, how do you prove a hypothesis in a complex world where people are doing all sorts of things? They're not lab rats in an experiment. In terms of naturopathy and natural medicine, many of the therapeutic interventions require complex multifactorial changes, which is different than taking a single pill for a single endpoint. As we know, the double-blind, placebo-controlled trial is very amenable to proving hypotheses related to a single agent against a single endpoint against placebo. But when getting into multifactorial types of therapies, it becomes a much more complicated issue to prove efficacy. Would you tell us a little bit about methodologies and how these complex information sets might be handled so critics will understand that there is some substance to these associations?

Multifactorial Intervention

JP: That's an excellent question, Jeff. And it's been a huge challenge because so many of our interventions are multifactorial and not single agents. I had a good experience with this. I was brought in to consult with a conventional medical university that wanted to do a study on a chronic, degenerative disease. We went through with this group of experts and we came up with monthly algorithms for treatment of the disease. In other words, we had a diagnosis, but we would not give every patient exactly the same intervention because they've all got different pathways. We came up with a very complex, pretty sophisticated, and well-referenced algorithm that basically developed about 12 different potential interventions that could be used for patients with this disease, but each would get a different group of interventions based on their own unique presentation. It was rejected by the International Review Board. They said that only one protocol could be used and to try that protocol on the patient. Of course, that's what's being utilized right now. What has happened is that they've gotten a fundamentally poor outcome because they're not actually looking at the research that we're doing. Actually, I should say that differently. They're not actually looking at how we clinically think about patients and treat them. It is a challenge, but I think it's doable. I think it's doable by being very consistent with what the selection criteria are for the differentiation of the interventions and then doing appropriate outcomes to see if indeed, the interventions, as a comprehensive approach, are effective. Looking at just single interventions or protocols that are blindly applied to all people does not utilize the understanding that this medicine has to offer.

JB: That's well said. It reminds me, from a biochemistry perspective, of the evolving story about folic acid. If you look at just the gross population with respect to homocysteine and folate, you might not be able to find high levels of significance relating to various diseases and folate status. But if you start stratifying for the MTHFR polymorphism, the slow methylator polymorphism, then the significance of your data starts to get richer and more robust because you've looked at the individuals that are most susceptible to folate insufficiency. The problem we've had in the history of our research in the past is that we have lumped everybody together, assuming that they're all similar, and sometimes you end up getting no data of significance at all. Embedded in that are tremendously interesting cohorts that either respond very well or have an adverse response to a specific therapy. But they all get washed out in the averages.

JP: Exactly. Going back to the example of magnesium and migraine headache, if you do a Pub Med search on magnesium and migraine headache, you'll see a fair number of studies and they're all over the board. Some show effects; some don't show effects. The problem is that when only one out of six people

is going to respond to your therapy, unless the study is large enough and carefully enough designed, it won't show efficacy. But for that one out of six, it is extremely efficacious.

JB: That leads to an area in which I know you've had personal interest and expertise for the better part of the 25 years I've know you, and that's how you gather information in this more complex, multifactorial world and analyze that data. In the past, this may have been one of those theoretical questions that could have engaged long discussion without resolution because we didn't have the technology available on the desktop to be able to handle large data sets. Over the last 25 years, that's changed entirely with the advent of the high-powered, super computer that we can now buy for $1000 from our local computer supply store and with which we can crunch data that previously only the super computers could have done 20 years ago. I know you've been an expert in following the transition we call biomedical informatics. Would you tell us how that may help in harnessing answers to' some of these questions?

Biomedical Informatics

JP: Thank you, Jeff, for an opportunity to speak about this. This is work I've been doing since I left Bastyr University in 2000. I've had a long-term interest in the use of artificial intelligence as a tool to assist clinicians in dealing with complex situations. The example of migraine is a very good one. My thinking was that if indeed this approach to healthcare makes sense (understanding the patient's unique physiology), how would we go about understanding that physiology and then determining what the most optimal approaches are to restore normal physiology? I came up with the idea of mapping the body into about 5000 distinct physiological functions. For example, how well the stomach secretes hydrochloric acid, or how well one of the cytochrome P450 isoforms in the liver detoxifies chemicals a person is being exposed to, and whether those chemicals are natural chemicals from the diet or drugs that are given to the patient. When you think about it, 5000 distinct physiological functions is a tremendous number. How can anybody keep all those in mind? Not only that, but how can anybody keep in mind what all the signs and symptoms of those physiological dysfunctions might be? Once you recognize what the physiological dysfunction is, then how do you know what intervention is most appropriate for an individual that would most likely restore normal function?

Going back to the example of migraine headache, my research team has now determined 21 distinct different physiological pathways that may be imbalanced in a person with migraine headache. But of course, it's different in every person. Those 21 different physiological dysfunctions have over 50 possible different interventions to normalize one or more of those physiological dysfunction pathways. As you start to look at this, it gets very complex. That's one of the wonders of the age of technology where we now have very powerful computers easily available to everybody. By utilizing an artificial intelligence system that keeps all these physiological dysfunctions in memory (it can also keep in memory all the reasons why they may become dysfunctional and what to do about them), we can develop a tool for clinicians that they can use to understand which physiological dysfunctions exist and what the causes and best potential interventions are.

JB: That obviously begs a series of other questions. If we saw that a condition we previously thought was one condition, or one disease, is broken down into more than 20 subtypes, then the question is, how do we differentiate the patient? Assessment becomes a very important part of differentiation. Beyond just labeling somebody with a disease like migraine headache, we need more exact knowledge about the differentiation of their condition into subtypes. That goes back to how we establish these diagnoses, or prognoses, or differential assessments, but you get into the signs and the symptoms, the history, the environment, and the biochemistry as different buckets of information that you need. Would you tell us a

little bit about how the clinician would make these assessments to go about making the differentiation?

JP: It takes time for the clinician. The standard right now is to spend 10 minutes or so with a patient. I don't think it's possible for a clinician to do anything other than make a disease diagnosis and suggest a drug therapy that's more symptom oriented than curative in nature. It takes time. It requires understanding the patient at a deep level, assessing the person's diet, assessing their environmental toxin exposure, looking at their lifestyle, and then carefully listening to and eliciting the signs and symptoms the patient is experiencing so you can start to develop a physiological map of the patient. I also think it will require a lot of study of biochemistry and physiology. That's one reason why I enjoy Functional Medicine Update so much, as well as the conferences you put on every year, because it gives the clinician an opportunity to delve deeply into understanding these complex physiological issues and how to recognize when they apply to a patient that the clinician is trying to help.

JB: This model sounds like what would be called a paradigm shift in thinking, because we have seen the primacy of diagnosis as the sine quo non for medical training over the last 50 or 60 years. Now, we are beginning to acknowledge that is a good place to start, but not where to stop. We need to look at precipitating factors, underlying causes, and the interconnection of those signs and symptoms to things other than the first-level diagnosis. Do you see this as a shift of that magnitude in medicine and if so, do you see some signs that we're moving toward a tipping point?

JP: Good question, Jeff. That is where I think medicine has to go, and it requires a lot more of the clinician. That's one reason we've been working so hard on this artificial intelligence system—to give people tools with which they can do this. I think it's going to take a fundamental change in thinking at the level of medical school education before we can start applying the body of knowledge that's available to assist people and give them a lot more help than we do right now. Looking at the incidence of chronic, degenerative diseases in our society, most of them have risen in every age group every decade for the last 50 years. It's clear that the current healthcare system is not working very well. And we can no longer afford it. We need to change to a system which is much more similar to the functional medical model that you've been teaching for so long and which also incorporates many of the concepts of natural medicine that so many of us have been working on for the last few decades. Until we do that, we're going to continue to have the problems we have with the healthcare system. I think it's great that we have excellent clinicians who can make a disease diagnosis. That's useful to know, but that's only the starting point in understanding the patient, not the endpoint.

JB: We could go on with this discussion for hours and, in fact, over the years we probably have. My image is that perhaps we're at a bifurcation point in the development of medical technology. We will always need medical intervention technology for people who have sustained traumatic injury or who have a crisis experience. It requires a certain set of skills and a certain set of tools to do that well—a kind of emergency room medicine to keep the patient functioning. Then we've got this other philosophy about trying to improve function that would stave off age-related dysfunctions that later become diseases of specific diagnosis that require a high-cost intervention type of medicine. Maybe you can't wrap both of them into a singular four-year medical curriculum. Maybe we're seeing a bifurcation in the system that will produce two types of doctors with different skills that live in harmony. Is that a possibility, or do you think I'm off the mark?

JP: Oh, I agree with you fully. We clearly need the almost miraculous intervention technology and

diagnostic procedures typical of conventional medicine, but that's the second choice, not the first choice for the majority of healthcare problems people are experiencing today. We shouldn't have the healthcare problems we're experiencing. I don't think it's an issue of information; I think it's an issue of getting well. You mentioned that I'm the editor of the Textbook of Natural Medicine. That textbook has over 10,000 citations, peer-reviewed scientific literature, showing that many of these natural therapies are indeed effective for a wide range of healthcare problems people experience. But that body of knowledge is not being used. A very sophisticated body of knowledge is being developed in the functional medicine arena. It's at a point now where it's usable and reproducible. The research exists to support its use, but until there's a philosophical change at the medical school level, it will not penetrate into the healthcare system and result in the necessary kinds of changes.

JB: That's a very good watchful note for all of us. I believe, as you're indicating, that philosophy often results in action rather than action resulting in philosophy. It seems as if we've pushed a model to a point of diminishing returns and it's time to start looking very seriously at the types of philosophical underpinning that naturopathic/natural medicine has to offer. I want to thank you personally, once again, for the extraordinary contributions you've made over the last two and a half decades as the rational voice of this movement. I also want to honor you as the 11th International Linus Pauling Functional Medicine Award winner. Thank you for sharing your concepts with us today.

JP: Thank you again for the honor of the Linus Pauling Award. I was surprised and deeply honored.

Dr. Pizzorno's discussion stimulates so many thoughts and followup questions. One of the many that come to mind is the concept that the therapies we often use, based upon a single-agent mentality, do not address the full complement of things necessary to get outcome from the cause rather than just treating the symptoms. I would like to go back to the insulin resistance beta cell dysfunction association that Dr. Pizzorno alluded to.

Over the last several months, we have been discussing vitamin D physiology, starting with Dr. Michael Holick from Boston University Medical School, moving to a wonderful discussion with Dr. Colleen Hayes at the University of Wisconsin Department of Biochemistry and, more recently, an exchange with Dr. Robert Heaney of Creighton University. All of these researchers have given us extraordinary new insight into the role and physiological importance of vitamin D as a prohormone being converted into its hormonal form, 1-25-dihydroxy-cholecalciferol. How does this relate to our discussion with Dr. Pizzorno regarding insulin resistance and insulin sensitivity? There is a connection. The paths are all in a web, interwoven one with the other. Let's talk about hypovitaminosis D and its association with insulin resistance and beta cell dysfunction.

Hypovitaminosis D, Insulin Resistance, and β Cell Dysfunction

Although the role of vitamin D in type 2 diabetes is well recognized, its relationship to glucose metabolism has not been well studied until recently. A paper appeared on this topic in the*American Journal of Clinical Nutrition*.[15] These investigators were from the Division of Clinical Endocrinology and Preventive Medicine and the Center for Clinical Nutrition at the Department of Medicine, University of California, Los Angeles. Their work demonstrates that we need to look at second- and third-level

questions when we start to develop individualized patient treatment programs for complex, chronic diseases. There is not one cause for these diseases—for instance, type 2 diabetes.

In this study, the researchers investigated the relationship of 25-hydroxyvitamin D (which you have all heard about in previous interviews), to insulin sensitivity in β cell function. This study included 126 healthy glucose- tolerant subjects living in California. Insulin sensitivity index and first- and second-phase insulin responses were assessed by using a hyperglycemic clamp methodology. Regression analysis showed that 25-hydroxyvitamin D concentrations were positively correlated with the insulin sensitivity index and negatively correlated with insulin resistance, both the first- and second-phase insulin responses, which means higher 25-hydroxy vitamin D, higher insulin sensitivity, or lower insulin resistance.

How could this be? Once again, it shows a strong potential endocrinological effect on β cell function, insulin sensitivity, and insulin reactions and glucose transport in type 2 diabetics, undoubtedly as a consequence of the pleiotropic effects of the hormonal form of vitamin D, the 1-25 dihydroxyvitamin D3. We are starting to look at a molecule that we thought of as only being involved with the prevention of bone loss. This was included in Dr. Heaney's eloquent discussion in last month's interview. We are now looking at its pleiotrophic effects as a hormonal initiator across cell signaling in many different cell types.

The authors of this study state that although only glucose tolerant subjects were enrolled in this study, they are not sure whether this could be used to treat type 2 diabetes. It certainly appears to illustrate the importance of vitamin D in improving insulin sensitivity, and perhaps in helping to prevent type 2 diabetes. The observations suggest that hypovitaminosis D is associated with increased risk of metabolic syndrome.

Vitamin D and Metabolic Syndrome

Why would this be? What could be the role of the hormonal form of vitamin D in the prevention of metabolic syndrome? The role of vitamin D in metabolic syndrome was suggested by a recent report from the Coronary Artery Risk Development in Young Adults Study, a population-based prospective study in 3157 black and white adults, age 18 to 30 years of age, from four U.S. metropolitan areas.[16] It was observed that dairy consumption was inversely associated with the incidence of insulin resistance syndrome among overweight adults. Therefore, dairy consumption may reduce the risk of type 2 diabetes and CVD. Overweight subjects with the highest dairy consumption had a 72 percent lower incidence of the metabolic syndrome than did those with the lowest dairy intake. We could hypothesize that this may relate to vitamin D since individuals who drink vitamin D fortified milk likely ingest larger amounts.

Therefore, it now appears that some studies are suggesting a relationship between vitamin D and insulin sensitivity. These studies do not yet prove that type 2 diabetes or insulin resistance will be ameliorated by intervention with vitamin D, but they broaden the web of understanding of the role that vitamin D plays as an immunological modifier and antiinflammatory in various cell types. We have already heard from Dr. Colleen Hayes that it helps to set the balance between the thymus dependent-1 (Th1) and thymus dependent-2 (Th2) lymphocytes, the part of the immune system that has to do with proinflammatory and antiinflammatory balance.

Aging, Th1 and Th2 Balance, and Immunological Function

One of the things we will be discussing at length at the 12th International Symposium on Functional Medicine is Th1 and Th2 balance and how it regulates immunological function. A recent interesting paper appeared in *Clinical and Experimental Immunology*, titled "Is ageing associated with a shift in the balance between Type 1 and Type 2 cytokines in humans?"[17] In this paper, the authors talk about the increasing incidence of infectious diseases in older-age people, which they suggest may relate to a shift toward Th2 cytokine expression profile. As Dr. Hayes told us, vitamin D and its metabolite, 1-25-dihydroxyvitamin D, play a role in setting the balance of the Th1 and Th2 system. Connecting these ideas leads us logically to wonder whether this is part of the explanation as to how vitamin D could play a role in the reduction of incidence of type 2 diabetes, metabolic syndrome, insulin resistance, and CVD relative risk.

We begin to look at the balance between TH1 and TH2 as an important factor in the outcome of several immune-related disorders. In elderly humans, it shows increased morbidity and mortality from infectious diseases, and we begin to see a shift toward Th2 dominance with a lowered level of Th1. In inflammatory conditions in individuals with CHD or arthritis, we often see the shift the other way, moving toward dominance of the Th1 type. By understanding some of these differentiations in immunological function and balance, and what agents help set the balance, we might be able to develop programs that would modulate not just the disease, but the underlying cause of the disease that relates to the immunological functional disturbance.

Hypovitaminosis D in Burn Patients

Patients with injuries, wounds, and burns have been shown to have low levels of vitamin D. It is proposed that the damage to the epithelial cells decreases their ability to produce active vitamin D. In an interesting paper published in *the Journal of the American Dietetic Association,*[18] a very high incidence of low serum 25-hydroxyvitamin D was demonstrated in individuals who (in this case, children), had burn trauma. The authors state that it is unclear why there is a deficiency of 25-hydroxyvitamin D; however, it appears that the reasons are related to a metabolic etiology. This has an implication on immunological function and the turnover of these active, signaling molecules.

We are witnessing an extension and expansion of our vision. The simple mindedness that there is one agent that controls one endpoint is starting to wane. The primacy of the differential diagnosis is starting to be replaced by the concept of understanding the function of the system. A model of what people call personalized medicine is emerging built around the principles of multifactorial interrelationships between genes and environment to give rise to the outcome called function.

One of the important takeaways in this discussion, and Dr. Pizzorno said it very eloquently, is that as we start to understand how to harness this information, we need to keep it at a level that can be delivered in clinical practice. Unfortunately, we will probably never have all the time we would like with each patient, which would mean hours of information-gathering and discussion. It has to be codified into a procedure and a system that will allow for cost-effective application and be non-discriminatory for those who may be less advantaged. We do not want to end up with a medicine for the elite. We find that some of the people who need these kinds of interventions are those who are the least capable of being able to afford the necessary high technology.

The challenge for us is to find simpler ways of analyzing complex information sets and delivering more

prudent information to the patient related to the management of the cause (not just the signs and symptoms) of the disease, based upon increasing understanding of function.

That wraps up this issue of FMU and sets the stage for November, with increasing interest in immunological disorders associated with chronic diseases of aging.

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