

January 2003 Issue | David Jones, MD, President Institute for Functional Medicine

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Welcome to *Functional Medicine Update* for January 2003. Last year was a year of change, and I expect that change will continue as we move into 2003. We are involved in a biomedical revolution that encompasses dynamic social and economic changes in the modeling of the healthcare system. The revolution will change the way clinicians provide services to individuals, as well as the services those individuals select.

As Dr. Regina Herzlinger from the Harvard School of Business suggests in her consumer-driven healthcare proposition, this will be a decade in which we will see a shift away from provider-controlled services to consumer-controlled services.¹ This shift will obviously have a bearing on the way functional medicine, as we define it, is presented and utilized. In the supply/demand curve, if there is more demand, there will be more supply, and that will lead to a paradigm shift.

We are heading toward a convergence of biomedical transitions and new discoveries based on genome and post-genome knowledge. This will connect with consumer and economic shifts in the healthcare system and growing disillusionment on the part of many healthcare providers. When all these forces converge, the age of functional medicine will emerge.

What is functional medicine? A recent article in the *New England Journal of Medicine* defines what I consider the more traditional meaning of functional medicine. The article is titled “A Program to Prevent Functional Decline in Physically Frail, Elderly Persons Who Live at Home.”² Investigators randomly assigned 188 individuals, age 75 or older, who were physically frail and living at home, and put them through a six-month, home-based intervention program that included physical therapy and focused on improving impairments in physical abilities. Individuals in the intervention who had moderate frailty showed significantly less functional decline 12 months after the start of the intervention when compared with similarly impaired control individuals.

The study discussed above demonstrates functional medicine focused on older individuals with impairments; however, functional medicine goes far beyond this concept. Certainly, physical function throughout all of one’s life is very important, but a number of other variables are also important. We talk about physiological function and cell biological function -- function that encompasses gene transcription and gene translation, as well as proteomics and the metabolome – that is, control of all metabolic function.

A recent paper in the *Journal of Clinical Endocrinology and Metabolism* illustrates another way of looking at function, in this case thyroid function.³ Investigators reported that selenium supplementation in patients with autoimmune thyroiditis resulted in normalized thyroid peroxidase antibody concentrations. These investigators administered 200 mg of selenium or a placebo in conjunction with L-T(4) orally for three months. This research, of course, does not mean thyroiditis is always a selenium-insufficiency condition. It does, however, suggest that selenium status is one variable affecting thyroid function.

A number of factors may affect a single outcome we are able to examine, such as a thyroid panel or an autoantibody against thyroid gland. In the broader definition of functionality, we examine the effect of selenium administration on physiological and physical function downstream. It may be possible to prevent the physical dysfunctions that emerge some years later from autoimmune thyroiditis by an upstream evaluation of cellular, biological, and physiological functional aspects of an individual. It is a different way of looking at the same concept, but at an earlier, preventive stage.

This study of autoimmune thyroiditis and selenium supplementation demonstrates even individuals who do not have frank selenium deficiency may be suffering from selenium insufficiency. It shows that the thyroid peroxidase enzyme and its relationship to deiodinization of T4 to T3 appear to be related to selenium status. It may be an early warning marker for selenium insufficiency, well before the appearance of reduced glutathione peroxidase levels or other more traditional selenium-deficiency pathology. The answers you find depend on where you look. If you do not look in the right place, you do not get those answers. In functional medicine we have been attempting to broaden the definition beyond physical frailty and dysfunction to a range of dysfunction

One might ask how to deduce these relationships. How do you come to conclusions? What kind of standards do you use in moving to judgment and taking action? I will cite one extraordinary paper on the topic, by Sir Richard Doll, a world-renowned epidemiologist. He was the first to bring scientific focus to the concept of smoking and lung cancer, and he was knighted for his contributions. His recent paper, published in *Perspectives in Biology and Medicine*, is titled “Proof of Causality. Deduction from Epidemiological Observation.”⁴ The paper eloquently describes how one deduces answers and ultimately arrives at an understanding of cause and effect.

Dr. Doll begins by asking what causality means if you do not fulfill Koch’s postulates directly. It is not as simple as looking at an infectious disease that fulfills the traditional early 20th-century definition. How do you determine whether something like selenium could, in fact, be related to thyroid function?

The Questions to Ask and Answer

Dr. Doll explains there are certain questions that guide a determination of causality between observed associations:

- What is the strength of that association?
 - How consistent is the association from one observation to another?
 - Does a dose/response relationship exist?
 - Is there evidence of a relationship between time of exposure to symptoms/outcome?
 - Has a plausible biological mechanism been proposed?
 - Does the observed relationship show specificity?

- What is the coherence of the evidence?
- Have different investigators expressed disparate opinions?
- Has it been experimentally evaluated?
- Can it be viewed in terms of an analogous situation with something else?

All of those questions are guides to causality. No one answer by itself determines causality, but when more and more answers begin to point in the same direction, it more and more closely approaches what we would call “proof.” If you use that series of criteria to evaluate observations to see if there is a causal relationship with a specific observation, then it may lead to deductions about things like lung carcinoma and smoking.

Smoking and Lung Cancer

In this paper, Dr. Doll explains that initially there was a lot of resistance to the concept that smoking caused lung cancer. Many people pointed out that many variables could be involved, including air pollution. In fact, air pollution was believed to be the dominant cause at the time, not smoking. This particular model of epidemiological association, according to Dr. Doll, eventually led to recognition of the causal link between smoking and lung cancer.

During this period of time, which lasted about 15 years, critics offered every possible objection to the suggested association between smoking and lung cancer. Finally, however, on the strength of the continued associations I described above, there was epidemiological strength and consistency in the data. There appeared to be a dose/response relationship based on smoking studies in animals, and a biological plausibility emerged as we began to understand more about carcinogens. The evidence appeared to be coherent, and animal experiments showing that smoking increased lung cancer incidence finally nailed down the causality.

Eosinophilia Myalgia Syndrome (EMS)

Dr. Doll uses another model, the toxic oil syndrome that produced eosinophilia myalgia syndrome (EMS). This syndrome was very similar to a problem that occurred in the United States with tainted tryptophan several years ago. The toxic oil syndrome, which occurred in Spain, involved tainted olive oil. In this case, the manufacturers had imported commercial, non-food-grade rapeseed oil that contained aniline into Spain. The oil was refined to remove the aniline; however, traces of this toxic substance were still present. This contaminated oil was mixed with olive oil and sold on the street as food-grade olive oil. Consumption of this oil with the aniline residues led to very serious EMS, including autoimmune dysfunction and some deaths.

In tracing through this syndrome, it was once again difficult to get a distinct causality from the epidemiological record, and a number of explanations were offered. Causality was determined by going through the questions in the above list and asking how many of these criteria were fulfilled in the association between EMS and the consumption of this black market olive oil.

Evidence-Based Medicine

That’s what we try to do in functional medicine. We use all types of data: epidemiological data; cell culture work; animal studies; historical (retrospective) studies; short-term trials; individual case management studies; and even, obviously, the double-blind, randomized, placebo-controlled trial. All of these types of data are combined to help define causality.

Is functional medicine evidence-based? In a recent article titled “Evidence-Based Medicine, Opinion-Based Medicine, and Real-World Medicine,” Dr. John Hampton states the following:

“The freedom of a doctor to treat an individual patient in the way he believes best has been markedly limited by the concept of evidence-based medicine. Clearly all would wish to practice according to the best available evidence, but it has become accepted that ‘evidence-based’ means that which is derived from randomized, and preferably double-blind, clinical trials. The history of clinical trial development, which can be traced to the use of oranges and lemons for the treatment of scurvy in 1747, has reflected a progressive need to establish whether smaller and smaller effects of treatment are real. It has led to difficult concepts such as ‘equivalence’ and aberrations such as ‘meta-analysis.’ An examination of evidence-based practice shows that it has usually been filtered through the opinions of experts and journal editors, and ‘opinion-based medicine’ would be a more appropriate term. In the real world of individual patients with multiple diseases who are receiving a number of different drugs, the practice of evidence-based (or even opinion-based) medicine is extremely difficult. For each patient a judgment has to be made by the clinician of the likely balance of risks and benefits of any therapy. Good practice still requires clinical freedom for doctors.”⁵

This is a powerful statement as we move from evidence-based to what Dr. Hampton calls “opinion-based medicine” to real-world medicine, seeing real patients, not experimental animals in a study, and how we come to judgment in managing their individual conditions.

When we start asking the questions presented by Dr. Doll, new data become available along with observations that take us into new areas. We as a society are consuming an increasing number and quantity of pharmaceutical compounds. A speaker at a seminar I once attended pointed out that, after those drugs are metabolized and excreted, they go into our waste effluent stream and end up in rivers, lakes, and oceans. We must, therefore, be medicating these water sources. I had not considered that concept before, so I was particularly interested in a recent editorial in the *Lancet*, titled “Environmental Stewardship and Drugs as Pollutants.”⁶ The author states:

“It is early morning—do you know where your drugs are? More than likely, some are on their way to local streams, rivers, and perhaps even farms, as sewage biosolids used as fertilizer. The public’s inseparable connection to the environment is illustrated by an emerging understanding of drugs as environmental pollutants. That any chemical introduced commercially has the potential to find its way into the environment is not surprising, but pharmaceuticals and personal-care products as environmental pollutants have captured the attention of the public and the mass media because such pollutants result not primarily from manufacturing but from widespread and continual use in human and veterinary clinical practice.

“Beginning in the 1970s, an escalation of research and monitoring, mostly by analytical chemists, has revealed the propensity for drugs and metabolites to enter the environment—usually by treated and untreated sewage. Many drugs from a wide array of therapeutic classes have been established as ever-present trace environmental pollutants in surface and ground waters, generally occurring at concentrations (eg, ng/L-mcg/L) far below human therapeutic levels.”

Medicating the Food Chain

Drugs may be bioconcentrated by various organisms, and that might lead to medicating biota and even

the food chain. These processes, in addition to oxidizing our waste with ozonization, can create secondary products of these molecules that may create an even higher toxic risk. The author points out that with the increasing use of synthetic substances -- such as estrogen compounds (eg, ethinylestradiol) used for the management of menopause -- we are seeing increasing levels of hormonal materials going directly into our waste water and effluent from the metabolism and excretion of these synthetic steroid molecules.

We should not discount any data or observations. They are all part of evaluating the web of understanding and specific aspects of functionality at the cell/tissue/organ/organ system and whole organism level.

I want to spend the rest of our time together in this issue of *FMU* reviewing some of the clinical takeaways we learned about in 2002 that will help us, as pathfinders, in 2003.

Glycemic Control and Healthcare Expenditures

Insulin resistance/hyperinsulinemia, or what Dr. Gerald Reaven termed “syndrome X,” is a condition in which there are high levels of insulin with insulin receptor refractory response, and an insufficient insulin-signaling process that occurs in the cell.

Improved glycemic control would result in considerable reduction of healthcare utilization. In 2002, a number of studies were published on this topic. One study, published in the *Journal of the American Medical Association*, concluded that a sustained reduction in hemoglobin A1C (HbA1C) levels in adults with type-2 diabetes is associated with a significant reduction in healthcare expenditures.⁷

Hemoglobin A1C (HbA1C)

When I first learned of HbA1C in the late 1970s, most people believed there was a step function; that is, HbA1c levels below a specific point indicated a non-diabetic state, whereas levels above a certain amount meant diabetes. The number at which this transition to diabetes occurred started off at around 7.5 percent of total hemoglobin as HbA1c, and went up to as high as 9 percent. Now, HbA1C levels are not considered on the basis of a step function, but rather from the standpoint of a curvilinear relationship between HbA1C levels and glycemic control. We can't necessarily say that at a particular level you are safe from diabetes and at another level you are at risk. Instead, there is a continuous, increasing relationship between the level of HbA1C and relative risk of vascular complications.

Lowering HbA1c below 5 percent would be considered desirable since many individuals who are nondiabetic actually have some relative risk to insulin difficulties and poor glycemic control.

Syndrome X

Metabolic syndrome, or syndrome X, is associated with hyperinsulinemia, dense LDL particles, elevated triglycerides, low HDL, increased blood pressure, and abdominal obesity. Waist circumference, a means of determining abdominal obesity, is a big risk factor. Many individuals have asked if visceral adipose tissue (VAT) precedes diabetes or if there is a metabolic transition that actually precedes and encourages the weight gain. This is a chicken-and-egg argument. Does insulin resistance/hyperinsulinemia, coupled with other factors, encourage the accumulation of VAT, or does VAT cause insulin resistance and later-stage type 2 diabetes? There is evidence to indicate it is attributable to both factors. A review in *Nutrition Reviews* describes the push/pull association between serum lipids, body composition, and insulin/insulin

resistance.⁸

Diet Control and the Glycemic Index

How do you control the diet to lower HbA1C to regulate insulin more effectively and reduce some of the insulin signaling processes associated with metabolic syndrome? Could the glycemic index of the diet be a factor? We have heard a lot about the glycemic index of the diet in the past 10 years, which was defined by Wolever and Jenkins. A good review about the glycemic index at its 20-year anniversary appeared in the *American Journal of Clinical Nutrition*.⁹

Clearly, individuals who regularly consume a high glycemic index diet, a diet that causes great surges of blood glucose and postprandial insulin, are more at risk to cardiovascular disease, diabetes, and other chronic health-related problems.¹⁰ The glycemic index of an individual food or even a collective group of foods does not necessarily indicate the overall glycemic index of that diet, however. It is only a direction finder.

Individuals who eat more legumes, unrefined whole grains, and fresh fruits and vegetables historically have better glycemic control than those whose diet primarily features the color white. White flour, white sugar, and white fat generally have higher glycemic indices, and induce higher postprandial glucose and insulin. Over time, the practice of consuming a diet of foods with a high glycemic index appears to be associated with increased risk of insulin resistance, hyperinsulinemia, and later-stage type 2 diabetes. This is also discussed in the *American Journal of Clinical Nutrition*.

Medical Therapy for Syndrome X

What do we do for a patient who has begun to shift toward increased HbA1C, increased triglyceride/HDL ratio, increased waist circumference area, increased waist-to-hip ratio, and increased percentage of body fat? All of these things are associated with insulin resistance. Medical nutritional therapy for syndrome X was the topic of an article in *Nutrition Reviews*.¹² The authors of this article indicate that a diet containing unrefined, complex carbohydrates, high in fiber and vegetable protein, more unsaturated fats within a limited total amount of fat is desirable.

Individuals may respond differently to carbohydrates based upon their own physiological personality, and no single diet is perfect for every type of person. Therefore, the concept of a number or a zone for which everyone should strive is unrealistic based upon what we have learned about biological heterogeneity in the human population.

Micronutrients and Glucose Control

We need to construct a diet to meet the needs of the individual and also look at the micronutrient levels of specific foods known to help stabilize insulin, glucose, and glucose transport. These include nutrients like α -lipoic acid, which is used as a drug at higher levels for type 2 diabetes in Europe. These levels may be from 600 mg per day to as high as 1200 mg per day.

The amino acid arginine has been used to help normalize blood sugar, and chromium has been used as glucose tolerance factor or a chromium mineral supplement. Coenzyme Q10 is important in glucose control. Magnesium is a mineral whose importance in regulating blood sugar levels is often overlooked. The omega-3 fatty acids are also recommended, including α -linolenic acid (ALA) from flaxseed oil and

eicosapentaenoic acid (EPA) from fish oils. We need to get away from saturated fat-rich or partially hydrogenated vegetable oil-rich diets from fast foods, and into more unrefined omega-3 oil-rich diets. (We may be asked for references on some of these. For example, magnesium and CoQ10. I am not sure how direct the evidence is here.)

Selenium, which we mentioned above, is also an important nutrient for management of glucose and insulin. Vanadium, given therapeutically as vanadyl sulfate, is more part of a therapeutic rather than a prophylactic approach. One should use vanadium at high doses only for short periods of time. There is no evidence that one should be on high levels of vanadium for an extended period of time. Last, higher levels of intake of both vitamin C and vitamin E are associated with improved glycemic control.¹¹

Chromium Supplementation In Animals

Several papers appeared in the literature in 2002 on chromium supplementation in animals. Supplementation with oral chromium picolinate improved carbohydrate and lipid metabolism in obese, hyperinsulinemic animals. This study appeared in the *Journal of Nutrition*.¹³ A human dose equivalent is probably in the range of 300–600 mcg per day of chromium as chromium picolinate or glucose tolerance factor chromium.

A meta-analysis study of human trials on chromium supplementation looking at glucose and insulin responses to dietary chromium supplements appeared in the *American Journal of Clinical Nutrition*.¹⁴ When the investigators conducted a meta-analysis, chromium appeared to have no effect on glucose or insulin concentrations in non-diabetic subjects. In those who had type 2 diabetes, however, the effect seemed to vary from very positive to no effect.

My clinical experience, and that of colleagues I've spoken to over the years, indicates significant improvement of insulin regulation and glucose control may occur in individuals with hyperinsulinemia or metabolic syndrome by supplementation with chromium as chromium picolinate, chromium chelate, or the glucose tolerance factor chromium. I would not want to say chromium is of no value in the non-diabetic subject. Clinical experience may prove otherwise when individualized to the patient.

Lipoic Acid

Lipoic acid, from as little as 100 mg per day to as high as 600 mg per day, can have a dramatic effect on improving insulin regulation a

A discussion of the use of lipoic acid in the treatment of insulin resistance/hyperinsulinemia appeared in *Diabetes Care*. At fairly high doses—600 mg twice daily for four weeks—in both obese and lean individuals with type 2 diabetes, lipoic acid helped improve glucose transport and insulin stimulation.¹⁶

The role of lipoic acid in improving insulin and glucose control in GLUT-1 and GLUT-4 was discussed in an article in *Diabetes*.¹⁷ A number of publications describe the role of lipoic acid in protecting against oxidative stress, glucose transport defects, and hyperinsulinemia. These studies all describe its important role in the insulin-mediated pathway.¹⁸

The next important area of discussion for 2002 is hormone replacement therapy (HRT), focusing in particular on therapy for peri- and post-menopausal women. We saw a storm of controversy surrounding

HRT in 2002 and we have discussed this controversy in *FMU*. A recent article in the *Lancet*, titled “Evidence from Randomised Trials on the Long-Term Effects of Hormone Replacement Therapy,” highlights the issue.¹⁹ The authors of this paper stated exactly what we have all learned: substantial new data indicate that, compared to placebo, HRT does not show the purported value for protection from cardiovascular disease and it appears to be best in managing one symptom: flushing.

With flushing as the principal presenting symptom, we know that HRT will, in fact, lower the symptoms. The question is, at what risk? That question has led to discussions about the relative role of HRT. What are its effects on other cellular physiological processes? What is the relation to other relative risks? Earlier this year, I cited an editorial that appeared in the *Journal of the American Medical Association*, titled “Postmenopausal Hormone Therapy and Quality of Life—No Cause for Celebration.”²⁰ This article followed up on the quality of life and depressive symptom study that appeared in the same issue. That article indicated that women whose principal menopausal symptom is flushing did get positive benefit from HRT, but for all other women the adverse effect of HRT appeared to be greater than its benefit.²¹

HRT, Breast Cancer and Cardiovascular Risk

Then we looked at HRT in relation to breast cancer risk. Information on that topic was presented in 2002 in the *Journal of the American Medical Association*.²² The data reported in that paper added to the growing evidence that long-term use of HRT is associated with increased breast cancer risk and may be particularly related to lobular tumors.

We also examined the risks and benefits of estrogen plus progestin in healthy postmenopausal women from the HERS Trial data.²³ That trial did not show the anticipated cardioprotective effects from HRT. In fact, it demonstrated that HRT might even pose a cardiovascular risk for some women. This information also appeared in the *Journal of the American Medical Association*. There are many papers on this topic, including an editorial titled “Failure of Estrogen plus Progestin Therapy for Prevention.”²⁴

We are witnessing a tremendous change with regard to HRT and an evaluation of alternatives.

That leads to a discussion of soy and soy products and the relationship to lignans from flax in the diet. Many papers are now discussing the role of isoflavones that inhibit cell proliferation and have both estrogen receptor-dependent and -independent pathways. A paper in *Nutrition and Cancer* describes how isoflavones inhibit these processes.²⁵ We tend to overreact to this type of news. We may think that if a little isoflavone is good (40-60 mg per day from a couple of portions of soy food), then 200 mg per day in a purified pharmacological dose form would be a whole lot better. The data do not appear to support that assumption. The data indicate that the traditional equivalent to what people get in their diet may be the safe and effective range.

We consider soy isoflavones in combination with lignans from plant foods, particularly flax, because flax contains some of the highest level of lignans. We now know that lignans also serve as modifiers of relative risk to hormone-related dysfunction in women. Therefore, the lignan combination of flaxseed meal with soy foods a couple of times a day may be a prudent way to approach some of these difficulties.

How do we improve the metabolism of estrogen so that the friendly estrogens are excreted without a

buildup of the mitogenic estrogens in the body? This relates to substances in the diet that stimulate the production of the 2-hydroxy and subsequent 2-methoxylated estrogens, reducing the production of the 16-hydroxy and 4-hydroxyestrogens. That leads to a discussion of the Brassica vegetables and the Crucifers. We heard a lot about these vegetables last year, and the glucosinolates present in cabbage, broccoli, Brussels sprouts, and cauliflower.

A series of papers have discussed the use of indole-3-carbinol, a glucosinolate byproduct that comes from eating cruciferous vegetables. Indole-3-carbinol appears to be efficacious as a chemopreventive agent when consumed at normal levels of intake. That topic is discussed in a paper in *Carcinogenesis*.²⁶ Another paper, which appeared in *Nutrition and Cancer*, is titled “Abrogation of Estrogen-Mediated Cellular and Biochemical Effects by Indole-3-Carbinol.”²⁷ Another paper describes the determination of urine levels of the metabolic byproducts of indole-3-carbinol in women who have consumed oligomers of indole-3-carbinol, one of which is diindolylmethane, a breakdown product polymer of I3C. Individuals who consume I3C will excrete various of these oligomeric I3C derivatives in their urine, one of which is diindolylmethane.²⁸

Indole-3-carbinol and diindolylmethane appear to induce apoptosis in cervical cancer cells in culture and preneoplastic cervical epithelium, causing reversion back to normal cell architecture.²⁹ In the acidic stomach environment, I3C is converted to a variety of its oligomers, which have varying effects on gene response and cellular physiology. When broccoli, Brussels sprouts, or cauliflower is consumed, the body converts I3C into oligomers that have a variety of effects on the body. The upstream I3C precursors serve the downstream control of these regulating phytonutrient substances. These substances may be considered secondary or even tertiary metabolites, because when the glucosinolate is consumed, it is converted into I3C by myrosinase and subsequently in an acid stomach into oligomers of I3C, which have effects on gene expression and cellular physiology. We are seeing some interesting changes in our view of the way diet can regulate estrogen metabolism and a woman’s risks in relation to her own estrogen.

Men’s Estrogen Issues

We also learned in 2002 that women are not alone in having estrogen issues. Men may also be at risk. The 16- and 4-hydroxyestrogens may induce prostatic dysfunction. Most men do not think of estrogen in the prostate, but it plays an important role, although in small amounts, in the regulation of aspects of prostate function. Estrogen metabolism is as important in men as it is in women, and diet plays a role in estrogen metabolism, cell sensitivity, transport through sex hormone-binding globulin, and its relative excretion as the biotransformed substances.

Early Detection and Functional Medicine

We have learned about the importance of diet, genes, and environment on hormone normalization. This relationship provides a fine example of the functional medical concept. We do not wait for a proliferative mass to develop before we take action. Even breast examination is a late-stage evaluation for what may be occurring at the cellular level.

We want to back up in our prevention toward the cellular perspective -- the functional aspect -- from the physiological perspective. This process is described in an article titled “Development of a Multi-Organ Model for Evaluating Chemopreventive Agents: Efficacy of Indole-3-Carbinol.”³⁰ While we want cellular-specific activities, we would like to get a beneficial effect, in the breast for example, without having an

adverse effect on the liver or on the kidneys when we begin to supplement with specific agents that help to normalize function.

Seeking Balance

There are no substances, including air and water, that are not toxic at some level. Therefore, we should balance levels of intake. We want to adhere to Dr. Richard Doll's concept of looking at causality and efficacy, putting all the pieces of the puzzle together. That is the logic tree we try to use in functional medicine to promote or describe specific approaches toward prevention or management of conditions.

INTERVIEW TRANSCRIPT

Clinician of the Month

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JB: Welcome to our Clinician of the Month interview. We begin the New Year with a special guest—my long-time colleague and friend David Jones, MD, president of the Institute for Functional Medicine (IFM). You have listened to Dr. Jones in previous FMU interviews, but today we will focus on his view of the future of medicine in 2003. We will discuss medical education, trends and changes that are taking place, and how the IFM maintains a leading edge in the face of such change.

David, welcome to Functional Medicine Update. In May of 2002, IFM conducted its most successful meeting—the Ninth International Symposium on Functional Medicine—in Ft. Lauderdale, Florida. After reviewing the course evaluations and being a major contributor to that meeting, what are your impressions? What we have learned?

DJ: First of all, thank you for inviting me to be Clinician of the Month. I am still a clinician. I still run a practice and have two very good associates who come from a background in nutritional medicine and are graduates of our Applying Functional Medicine in Clinical Practice course. Here in Ashland, Oregon, our clinic is very busy because of the education we have all received through the IFM.

Your specific question about what we learned and what we experienced in Ft. Lauderdale brings me to two issues that I think about all the time as president of the IFM and about its origin nine years ago. It's been quite a journey, and Ft. Lauderdale was a two-pronged experience for me.

High Quality of IFM Practitioners

The first issue is the quality of people who, over the years, have embraced the notion of functional medicine. We are looking at the scientific basis for evaluating and developing treatment plans for complex chronic illness and for primary prevention, examining the underlying biological processes that lead to chronic illnesses. The high quality of practitioners who have been drawn to our particular matrix

of biological processes is humbling to me. These practitioners are highly motivated.

Many of them are FMU listeners, so I'm speaking directly to them now in appreciation. When we took the Hippocratic Oath, or the oath specific to our particular kind of healthcare practice, we took that commitment very seriously. We wanted to work as partners with our patients and their health problems to help them see the underlying causes of those problems. That's very humbling for me. A number of very high-quality practitioners look to us to help form the intellectual matrix that organizes a huge amount of information so it can be applied in real time in a one-to-one relationship with patients.

Balancing Research Information with Clinical Application

The second issue is balancing what we know at the IFM because of the leadership you give, Jeff, in terms of organizing information, and the connection we have, through the IFM, with leading scientific institutions, universities, and organizations around the United States. We know where this is going and, at the same time, we listen very carefully to our attendees and our members as to how they want us to present that information.

The experience at Ft. Lauderdale was like being at the forefront of clinical practice, where you combine leading-edge information with clinical application. That's the constant conundrum for us. We always strive to find the point of intersection between good, reliable information and its application in clinical practice in a way that does no harm. We strive, in fact, to find ways to improve patient care as early as possible by applying leading-edge interventions, based on emerging evidence and scientifically sound thinking.

Folic Acid as Example

Fifteen years ago, for example, well before the role of folic acid supplementation in preventing spinal defects in children was accepted, you and I were talking about it in our study groups. That same information might have prevented thousands of spinal defects had it been released and placed in a matrix that could be used clinically in everyday patient encounters.

That's what humbles me. We have access to that information; we have providers who are excited about applying that information; and we have to be circumspect in finding where that edge is that makes it possible to apply it in a safe and efficacious way.

Presenting the Research

That's what happened for me in Ft. Lauderdale. And that's what's going to happen in Tucson in May of 2003. In Tucson we are bringing together world-renowned researchers who have transformed the field of cardiology, including Dr. Paul Barton Duell, the expert in using homocysteine in clinical practice, from the Oregon Health Sciences Center; Dr. Walter Willett from Harvard; Dr. Mark Houston from the Vanderbilt University Medical Center; Dr. John Cooke from Stanford University; and Dr. Serge Renaud from France, the leading researcher in the Lyon Study.

Around the topic, The Heart on Fire—Modifiable Factors beyond Cholesterol, we will have world leaders in cardiology giving us their take on inflammation as an underlying process that causes complex illness. It is involved far more extensively than in the cardiovascular system, although that will be the focus this year. We also have a host of clinicians with a functional medicine orientation for our afternoon workshops. We have never before put together the number of workshops with the variety of people we're

going to have this year. We will conduct eight workshops each afternoon.

Making Functional Medicine Practical

I am humbled and excited about where we have taken the concept of functional medicine so that it can be applied in real time on Monday morning after people leave our educational activities. At the same time, we constantly go through reevaluation of how to make it more practical; how to take it from a theoretical view right down to what happens between two people — a healthcare provider and a patient — to change patients' lives. We are finding the educational tools to make that possible.

For me, toward what I thought was going to be the end of my career, it is very exciting to begin in such a large way to execute something you said to me many years ago, Jeff. I'll never forget it and I've mentioned it a number of times to you and to audiences. You said: "David, there's nothing short of changing the world that's worth doing." There's no question in my mind that through the IFM we will change the way patients are taken care of, not only in the United States but around the world.

Applying Functional Medicine in Clinical Practice

JB: That's a wonderful answer covering a huge expanse. I want to follow up on one of the things you mentioned. The symposium in Tucson on May 21-25, 2003, will be the 10th International Symposium on Functional Medicine. A lot of things are being planned. Three AFMCP training programs will have taken place between the Ft. Lauderdale symposium and the one in Tucson, so we ought to have good momentum going into Tucson with regard to the enthusiasm you describe.

DJ: The other thing that has happened for the IFM is that the word is out. Graduates of the Applying Functional Medicine in Clinical Practice courses are talking to their peers and colleagues, saying this is the premier course. It is a week-long course where they rub shoulders with functional medicine experts and clinicians throughout the United States.

It is set up so that from the day they arrive to the day they leave graduates can anticipate being able to apply that information. They can get to their offices the following Monday morning knowing how to take a vast array of information and apply it in a consistent way to the clinical problems their patients bring to them. This is most exciting for me because it is the premier way of changing the organization of information. It's taking a vast amount of information and knowing there are clear underlying processes that you can organize around the patient story.

Then you know how to organize their story in such a way that you understand the antecedents that indicate how they got where they are, what triggered the problem, and what things can be done to those modifiers that continue the disorder. In March, we will have the AFMCP program in Gig Harbor, and in October we will be going back to Boston. Then in December, we will be opening up a new territory in the Los Angeles area for the doctors in the Southwest. There's a tremendous commitment on our part to get the information to a point where it can be used by providers and try to make it as comfortable for them as possible.

AFMCP in the Southwest

JB: In my travels, a number of people have asked me if we would ever have an AFMCP training program in the Southwest. I'm sure that information will come as a nice surprise. When is it scheduled to occur?

DJ: That will be the first week of December 2003 in the Los Angeles area.

AFMCP in Boston

JB: And the Boston meeting will be in the fall?

DJ: That will be around the first week in October when the trees are beautiful and the threat of snowstorms hasn't quite hit.

AFMCP in Gig Harbor

JB: And then in Gig Harbor in the spring of 2003?

DJ: Yes. That's the next course we're conducting. That will be in March of 2003. We are now accepting registrations for participants in that program. Seattle is an easy airport to get into from around the United States. There are many direct flights, and we often get very good attendance in the Seattle region. We usually get a number of participants from Asia, as well. Some folks are uncomfortable about flying since the September 11 debacle, so we are trying to respond by providing this educational activity in three areas.

Taking IFM out of the Commercial Environment

I would like to talk for just a minute about taking the IFM out of the commercial environment. When HealthComm and Metagenics merged, you and your wife Susan accepted the assets for IFM out of that environment. You immediately put them into the corporate context we now call IFM, which is now recognized by the IRS as a tax-exempt 501(c)(3) organization. We have just started our first fundraising drive. A lot of FMU listeners, as well as former AFMCP and symposium participants, will be getting our brochure. This is exciting for us because we have created a real community and there's a real sense of responsibility within that community.

Now that people know a contribution to IFM is tax-deductible, it is not unusual for us to get checks from people who spontaneously send money to make sure the Institute continues. You can't imagine what an affirmation that is for me and for our staff. As we were launched, there were certainly some financial limitations. The biggest limiting factors to our postgraduate fellowship and diplomate programs are financial, and we've put together a grant for large amounts of money from foundations. If we weren't operating in the world of the stock market crash and the 9/11 experience, we would probably have that funding at this point, because we have on the drawing board all the plans to go forward with a fellowship in functional medicine.

The Functional Medicine Community

We have great plans for IFM. The key is a sense of community. Providers all over the world look to us for reliable science-based information that is integrated from all specialties and all healthcare provider niches. They want science behind what they do. It's a huge responsibility, but at the same time, it's the most exciting thing I've ever done

I thought becoming a doctor was exciting, and it continues to be so. To be involved with the growing of this paradigm is way beyond my expectations. You said many years ago that nothing short of changing the world is worth doing. I understand now why you said that. I used to be in awe that you felt that way. I no longer am in awe because I know it's possible.

IFM Staff

JB: I want to stress the importance of the IFM staff. Although small in number, they are an incredible group. I applaud the excellence they achieve, their dedication and perseverance. They are champions. That's what it takes to create this type of change in the world—people who are warriors. We are very

fortunate at IFM to have that type of staff.

DJ: One of the foundations is going to give us a grant toward the revision of our website, a place where we feel it is important to have a sense of community. We will have a case forum content and clinical consultant so people can put their difficult case studies up and receive an organized response. That foundation is going to grant part of the resources. They believe we do have a paradigm that needs to be leveraged out into the world. Second, they've looked at our staff and what they have been able to accomplish with the resources we've had and have been astounded by the competence. They can give us money and be assured that it will be leveraged strongly toward the mission, which is making a difference in patient outcome. I second your observation that the IFM staff is absolutely remarkable.

Functional Medicine and Third-Party Reimbursement

JB: Can functional medicine be incorporated effectively into a third-party payer reimbursement system, or is it just a tool in search of codification within the business community we now see in the health sciences?

DJ: This is the biggest logistical question for our AFMCP graduates—how to configure their practices in such a way that they make a living equal to the kind of effort they put in. At the symposium in Tucson, the first pre-course will be on office management. We have chiropractors, naturopaths, MDs, and DOs who have been very successful applying this paradigm. That will be a full-day pre-course on how to make this possible.

Not only am I the president of IFM, but I have also been president of the regional Independent Physician Association (IPA) in Southern Oregon area for 10 years, so I have some experience in this area. Making a living within managed care in the conventional world is a big issue right now.

There's a question of whether internists can make a living, with Medicare just about to cut back. Internists who are dedicated to their Medicare patients are wondering if it will be financially viable to continue. The world as we know it, in terms of reimbursement, is in chaos right now.

Health Resources Account Program

The biggest issue on the floor, in my opinion, is the federal qualifying of what's called the HRA, Health Resource Account program. Together with major medical, it will put a whole different spin on patient empowerment in selecting healthcare providers. This has been very quiet on the horizon because insurance companies are not happy about this transition. Basically, health insurance will become major medical health insurance, which is what it was originally intended to be. It wasn't an entitlement for all medical care.

The marriage of that will be an employer benefit that's called a Health Resource Account that builds up over time and goes with the employee like an IRA account. That account can be used for any medical care that would qualify under IRS regulations. The valley I work in consists mainly of small employers, but contrary to some of the information the insurance companies have published, large and small employers both qualify for this new and novel approach to getting patients into the healthcare equation.

Patient Choices

With this program, patients will be able to decide where to spend the money they have for medical care

up to that deductible. They're going to go to doctors and healthcare providers within their community who have a reputation for making changes that work. I'm very excited about this. It is exciting within the conventional medical community as well, because it puts accountability back on the shoulders of the patient/provider interaction. If that's not working, patients aren't going to take money out of their account to go see that healthcare provider. It's not going to be controlled by the insurance company. No longer will there be panels of providers, none of whom you may want to select but you have to go there because that's the only place your insurance company allows you to go.

This is a very exciting concept, but it is poorly known. Some of the big companies are moving their Human Resource Insurance Plan Benefits into this environment because they know the studies are very clear. When patients have control of the money, they are more empowered to take care of themselves. And that will open doors for functional medicine providers that have never been open before.

Functional Medicine in the HRA Environment

Patients currently feel they have to go to where their insurance has a panel, but there will be many more discretionary resources for patients to pursue for their healthcare answers. Of course, we feel that functional medicine providers will be a major force in this arena. That is why, as we revise our website, we will include a consumer side so our providers can be located. We will list AFMCP graduates and where they are located. We need to be able to integrate providers who understand the underlying functional processes of illness with patients who are looking for that kind of care.

I get chills when I see the way the world in which we are working right now is moving toward a very favorable environment compared to that which existed 10 years ago at the beginning of the IFM.

2003: An Auspicious Year

JB: It is wonderful to see all these things converging at the 10th anniversary of our international symposia. Ten years is not significant in geological time, but in the context of the changes you've described, I think 2003 is going to be a very auspicious year for the IFM and its participants.

Dr. Jones, thank you for serving so ably as president of IFM and for generating such excitement for us all as we start 2003.

DJ: This 10th symposium is going to be a party. It's going to be a celebration of where we've been and where we are. I can't think of a better celebration of what the conventional medical world is beginning to understand. I showed our program to one of the cardiologists in my IPA who has never been to a functional medicine meeting of any kind, for example, and he said he had to be there. He said he had been looking for such a conference for the last five years, because he knew cardiology was going in this direction.

What a celebration! We bring a program that bridges all healthcare providers with the very best science and speakers for our 10th-year anniversary. I can't wait!

Pharmacogenomics and Nutrition

I would like to continue by highlighting three other important areas we described in 2002 that will be further explored in 2003—aspects of nutritional pharmacology, the pharmacogenetic detoxification concept, and the TH-1/TH-2 autoimmune and hypersensitivity/inflammation connection.

I have been discussing the role of glucosinolates, derived from the cruciferous vegetables, on estrogen detoxification and metabolism. Two daily portions of cruciferous vegetables provide between 150 mg and 300 mg of I3C. This phytochemical plays a role in the expression of specific types of detoxification enzymes, the biotransformation enzymes that are part of the phase I and phase II detoxification system. These enzymes include the mixed-function cytochrome P450 enzymes in phase I detoxification and the conjugation enzymes in the phase II system.

The Many Roles of Cytochromes P450

The genetic control of metabolism and biotransformation of substances has been called “pharmacogenetics” or “pharmacogenomics.” It began as a discussion of drug metabolism, but it has been generalized to cover all substances undergoing phase I and phase II types of biotransformation processes.

The authors of a review article titled “Clinical Importance of the Cytochromes P450,” which appeared in the *Lancet*, explain that this super-family of enzymes is comprised of 57 genes.³¹ These genes code for enzymes that play a role in the metabolism of drugs and foreign chemicals. They also play a role in arachidonic acid metabolism and formation of eicosanoids, cholesterol metabolism, bile acid synthesis, steroid metabolism, vitamin D and vitamin A metabolism. A number of other functions for cytochromes P450 will no doubt be discovered in the next few years.

Cytochrome P450 was once believed to be mainly a hepatic drug detoxification system, but we now understand it includes a myriad of enzymatic reactions implicated in tissues other than the liver. In the breast, for example, cytochromes P450 can be involved in the production of hydroxylated estrogens in the absence of liver metabolism.

Inducible Forms of CYP450

There is significant clinical importance in understanding what regulates the inducible forms of CYP 450s. The expression of the inducible forms of these enzymes can be modified by environmental factors. The constitutive forms, on the other hand, are not easily modifiable by environmental factors. The overall family of enzymes numbers over 100, and they control specific functional aspects of resistance to xenobiotic chemicals or endogenous substances. Any one of the CYP 450s may compete with another one for metabolism of drugs, alcohol, environmental chemicals, or endogenous molecules. Various single nucleotide polymorphisms (SNPs) occur within these families resulting in a variety of different detoxification profiles.

Slow Metabolizers and Toxicity Risk

The genes of some individuals predetermine that they are slow metabolizers. When such individuals begin loading substrates onto that particular pathway, they might overload that step in the detoxification process and begin to develop toxicity, a drug overdose, or an environmental toxicity. In a person who is a normal detoxifier this would not be a problem, but the slow detoxifiers may be considered metabolic “yellow canaries.” They are at first risk to exposure to a given substance.

As we learn more about the CYP 450s and phase II conjugation, we learn what dietary and environmental factors regulate and modulate their function. That leads to a better understanding of the pharmacogenetics related to adverse drug reactions and adverse environmental responses. A review titled “Pharmacogenetics and Adverse Drug Reactions,” which appeared in the *Lancet*, caused us to think more

about atypical drug reactions and realize they are not atypical at all.³² These drug reactions are typical and reproducible in an individual as a consequence of that individual's unique genetics.

Various substances can modulate and improve detoxification. One that comes to mind is N-acetylcysteine (NAC). NAC, traditionally used in emergency medicine for the treatment of paracetamol or acetaminophen overdose, is now recognized as having a positive effect on many detoxification pathways.

A paper that appeared in the *Lancet* explains that NAC can help prevent hepatocellular injury and improve detoxification in individuals who may be slow sulfators or have poor glutathione conjugation ability.³³

Bifunctional Modulators

A variety of phytochemicals from various foods enhance detoxification by normalizing both phase I and phase II. These phytochemicals are called bifunctional modulators, and they may modulate the ratio of phase I to phase II activity. We do not want phase I activity to be too high while phase II is low. The result would be the production of more biotransformed intermediates, which may be more toxic than the substances we are trying to detoxify.

We are seeking regulation and balance between phase I and phase II, which occurs through these bifunctional modulators. Constituents in curcumin have been shown to be bifunctional modulators, as have substances in the glucosinolate family of Brassica vegetables, including the watercress family.³⁴ Watercress contains glucosinolates that serve as bifunctional modulators. For example, a paper in *Cancer Epidemiology* titled "Effects of Watercress Consumption on Metabolism of a Tobacco-specific Lung Carcinogen in Smokers" reported watercress consumption helped improve metabolism of potential procarcinogens in smokers.³⁵

Certain molecules found in specific types of food help normalize phase I and phase II activity at intake levels that are equivalent to what people would consume in a traditional diet. Two portions a day of cruciferous vegetables, for example, would provide approximately 300 mg of I3C. We talked about doses of NAC or glutathione in the range of 200 mg to 400 mg per day. There is the relationship of curcuminoids in fairly small doses, perhaps 50 mg to 100 mg. All of these molecules have been found to have positive impact on normalizing phase I and phase II detoxification pathways.

S-adenosylmethionine

Another molecule in the news in 2002 is a therapeutic molecule derived out of the folate cycle, the N-methyltetrahydrofolate-mediated conversion of homocysteine into S-adenosylmethionine (SAM). SAM is a universal methylator.³⁶ It is involved in hormone detoxification, phospholipid formation, and metabolism of neurotransmitters. It affects DNA integrity and nucleoside base formation. It also plays an important clinical role in the management of depression.³⁷ It has been used for the management of inflammatory disorders and joint arthritides as well.

SAM has been shown to produce similar changes to that of a classic antidepressant on electroencephalograms.³⁸ It may play a role in the management of liver disorders and disease.^{39,40}

SAM's Role as a Conditionally Essential Nutrient

SAM might be considered a conditionally essential nutrient, meaning it is a therapeutic or pharmacological agent that may be used in certain individuals at doses beyond that which their body can synthesize. It is not an essential nutrient for all individuals because our bodies do make it. In individuals who have defects in the folate cycle, however, or who have increased need beyond what their folate cycle can produce, SAM may be a conditionally essential therapeutic substance.

Charles Lieber and Lester Packer wrote a review that appeared in the *American Journal of Clinical Nutrition*, on the role of SAM in the prevention of liver toxicity and also as a therapeutic agent for brain function.⁴¹ It is a pleiotropic molecule, having potential effects on depression, dementia, vascular myopathy, liver disorders, and osteoarthritis.

The doses we are talking about are not extraordinary. When taken with vitamin B12 and folic acid or 5-methyltetrahydrofolate, oral doses in the hundreds of milligrams can be efficacious. More than 2000 publications have been written on SAM. Many of them describe double-blind, placebo-controlled trials. SAM plays a powerful role as a methylating substance in the folate cycle. It is another example of a functional approach toward medicine, rather than just waiting for the pathology to exist.

Th-1/Th-2 Balance and Atopic Disorders

We will be hearing more about the Th-1/Th2 relationships to inflammation and immune function. This balance is important in the management of various conditions, including atopic disorders in children, allergic rhinitis, allergy, and inflammatory bowel disease, as contrasted to rheumatoid arthritis and other traditional joint space inflammatory conditions.

The balance between thymus-dependent-1 (Th-1) and thymus-dependent-2 (Th-2) cytokines plays a role in determining the clinical outcome of our immune defense system. Individuals who are Th-2 predominant have allergic-like symptoms with IgE-mediated function and increased mucosal immunity producing more inflammatory response. A review on Th-1 and Th-2 appeared in *Nature Medicine*.⁴²

Perilla Seed Extract

We look at nutritional agents that can modulate the balance of Th1 and Th2 in the individuals who have excessive expression of Th-2. One that has emerged from Japanese pharmacological literature is the extract and concentrated derivatives of perilla seed, *Perilla frutescens*. Concentrates of this plant food are rich in a variety of substances, particularly flavonoid and phenolic substances. These substances may modify the Th-2 hypersensitivity and can lower the IgE-mediated response. They include powerful superoxide scavenging substances, as well. This information was published in the *Journal of Agriculture and Food Chemistry*.⁴³

Studies of the IgE-mediated response indicate perilla seed extract also may exert an influence on allergic disorders. The perilla seed concentrates, extracts that are standardized to specific flavonoids, have proven to be powerful functional nutrition agents in allergic and atopic disorders, Th-2-predominant disorders. The doses reported in the Japanese pharmacological literature are in the range of 100 mg to 200 mg of the standardized perilla seed concentrates per day.⁴⁴

We are learning a great deal about the complex array of substances found in our foods, literally tens of

thousands of different chemical compounds. When taken together as combinations, these substances have remarkable effects in modulating gene expression, proteomic outcome, and metabolic influences that occur at the functional level before you get into physical dysfunction and more serious pathologies.

The same theme holds true with regard to the 2002 literature on Alzheimer's disease and its relationship to antioxidant intake. A paper and an editorial in the *Journal of the American Medical Association* looked at dietary intake of antioxidants and the relative risk of Alzheimer's disease. These papers showed that higher intake of vitamins C and E and flavonoids can have important implications in lowering risk to Alzheimer's disease, which leads to questions about the mechanism(s) involved. [45,46,47](#)

Folate, B12, B6 and Cognitive Function

Individuals who have impaired vitamin B12 intake may have impaired cognitive function, and we should consider folate, B12, vitamins C and E, and the flavonoids for improvement of function. [48,49](#)

A short-term memory performance study examined women on folate, B12, and B6. It showed that intellectual performance, memory and cognitive function can be improved by supplementation with folate, B12, and B6. [50](#) This is a new view of functional nutrition, functional medicine, and nutritional pharmacology. Looking back, 2002 was a year of great excitement in this area, That excitement will continue in 2003 in subsequent issues of *FMU*.

Thanks for being with us. We look forward to seeing you in February.

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