December 2003 Issue | Daniel Beskind, MD, MPH, FACEP

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Welcome to *Functional Medicine Update* for December 2003. I want to remind you about the 11th International Symposium on Functional Medicine, May 11-15, 2004 at the Westin International Resort, next to Stanley Park, in Vancouver, British Columbia. Please note that the Symposium will take place before the Memorial Day Weekend this year.

We will focus on the pandemic of type 2 diabetes—its management and treatment—and new medical therapies based on mechanisms of insulin signaling and glucose transport. We will have remarkable speakers and excellent workshops to integrate the information from the plenary sessions into clinical implementation. Mark your calendars for May 11-15, 2004.

I begin this month's *FMU* from a different perspective, as a consequence of an experience I had at the Applying Functional Medicine in Clinical Practice (AFMCP) training program in Danvers, Massachusetts in October. (Incidentally, approximately 500 health practitioners have now completed the AFMCP program.)

The Danvers AFMCP group was remarkable. After they received their certificates of completion, I was inspired as I listened to them discuss what they had experienced during the course. They talked about becoming "re-enchanted" with medicine, the healing context, healing the healer, forming a community, focusing energy on solutions to a wealth of health-related problems, getting away from the bureaucracy, the importance of creative thinking, and learning of solutions they had not known about before.

Listening to their descriptions was motivational for me. It reminds all of us why we initiated the concept of functional medicine and the Institute for Functional Medicine some 12 years ago. We began IFM to foster and stimulate just that kind of response. We wanted to encourage people who dedicate their lives to the health sciences and do the hard work of dealing with people who are ill, to try to find solutions to complex health problems.

What Is Functional Medicine?
That AFMCP experience reminded me once again to examine what functional medicine is and how it differs from the medicine in which most of us were trained, the definition of our degrees, or the abbreviations after our names. First, functional medicine is patient-centered rather than disease-centered. Instead of dealing with the primacy of diagnosis, it deals with the concept of antecedents, triggers, and mediators leading to signs and symptoms of differing duration, frequency, and intensity. Identifying the complex interface of each individual with his or her environment, life experience, family history, and genes is part of the patient-centered approach of functional medicine, in contrast to a disease-centered

approach.

The second feature that characterizes functional medicine is that it deals less with disease and more with common shared mechanisms that cut across medical disciplines. Defects in the folate cycle, for example, know no specific boundaries in the sub-specialties of medicine. They are not under the exclusive rubric of cardiology, pediatrics, oncology, neurology, psychiatry, developmental psychology, obstetrics, or gynecology. The folate cycle is part of the fundamental process of human physiology. We focus on shared common mechanisms, trying to understand how they underlie disease, rather than focusing on the disease itself.

Defining Health as More than Absence of Disease
In functional medicine, we believe that health is more than the absence of disease. When we look at symptomatologies relating to later-stage acute pathologies, we realize they may be revealed initially through changes in psychological, mental, or physiological function. That can be taken down to the cellular level and even to the sub-cellular level as we look at different signaling molecules associated with altered function in the cell, tissue, organ, or organ system.

Not only is health more than the absence of disease, but each individual also possesses an internal healing process that enables him or her to resist the natural tendency of the universe toward randomization or entropy. In functional medicine we believe there is a native process within human physiology locked into our genes that resists the darkness of randomization to the universe and consistently tries to maintain order and function.

Gene/Environment Interaction
A final core concept of functional medicine is the importance of the interface between genes and the environment. We all possess genetic pluripotentiality, or a mosaic from which our genes encode for different outcomes. The interface between that unique genetic potential and the equally unique environment produces the specific phenotype of the individual.

This gene/environment interaction is a fundamental criterion for evaluating patient health. We cannot change our genes, but we can change their expression. We can change the environmental signals that cause altered gene expression, proteomic expression, and ultimately, the control of metabolism and function.

Interpretations of Functional Medicine
Those are some of the primary characteristics that identify functional medicine as a discipline. After listening to the AFMCP discussion in Boston, I let this information wash over my own genes on the flight back to Washington State. I was inspired to search the Internet to learn what is happening with the term “functional medicine.” “Functional” has been a pejorative term in medicine. It has often been used to mean psychosomatic or fictitious, as though a person with a “functional” illness has a psychological problem.

In geriatric medicine, “functional” may mean disability—as in the inability of the person to function. He or she may therefore require physical therapy to function.

In the broader context we use at the Institute for Functional Medicine, the term “functional” requires a

different level of thinking. It is a different way of approaching the patient in a healing context in the examining room. It is dealing with the context of the patient-centered mechanism in the belief that health is more than the absence of disease and with the knowledge of the gene/environment interaction.

I searched the 2003 Medline literature about functional medicine, and I encourage you to do the same on the Internet. To do so, you need to search the sub-specialties in medicine—functional neurology, functional gastroenterology, functional immunology , functional obstetrics, functional cardiology, etc. That search taught me about the different ways of thinking in this emerging paradigm of functional medicine.

"Functional Medicine" in the Current Literature
First of all, typing in the two words "functional medicine" results in 7000-8000 hits. The more recent hits, references to things that have happened in the past year, often lead back to early-warning assessment of physiological functioning. Technologies are starting to emerge as clinical tools for the assessment of function, before the onset of gross pathology. One article that describes the advances in molecular imaging appeared in the journal *Rays.* It is titled "Molecular Imaging: State of the Art."[1]

Functional Medicine and Radiology
There are many new imaging technologies. Previously, radiologists simply read X-rays. They looked at hard and soft tissue searching for pathology. But radiology has evolved into a field characterized by looking at function—SPEC scans, PET scans, MRI scans, and NMR scans. A patient is asked to exercise on a machine, or is given a contrast dye that is processed by the body and fluoresces when there is glucose metabolism in the brain. Now we are looking at metabolic function at the cellular, tissue, or organ-specific level, rather than examining static tissue for damage or pathology.

I would not have expected functional medicine to emerge out of radiology. I have always thought of radiology as being close to pathology. But radiologists today are becoming the early wave of functional medicine practitioners because of the way they are looking at the body with non-invasive imaging techniques. Our Clinician of the Month will talk about one such technology specifically relating to functional cardiology, and its implications in functional medicine.

We could apply the concept Dr. Daniel Beskind will discuss this month to a variety of other areas of functional assessment in evaluating potential disease. Years before a person gets to a state of pathology he or she may experience declining function or loss of organ reserve, to use once again the Dr. James Fries concept we have frequently discussed.

When you key in "functional cardiology" on Pub Med or Medline, a number of interesting articles come up on topics every primary care physician should know about, using functional imaging technologies to assess cardiovascular function. Functional cardiology began with the exercise EKG, a functional assessment as contrasted to the static resting EKG. The functional EKG under exercise load, the so-called BRUCE procedure, was a functional test to examine cardiovascular reserve to see how the heart vasculature responds under an exercise load, and looking for electro-cardiac irregularities. This was the leading edge of what has developed into more sophisticated technology for evaluating cardiac and vascular function. Cardiologists now measure cardiac function in older adults with scanning technologies such as MRI imaging. These functional assessment tools evaluate patients before the onset of acute pathology.

Functional Neurology Assessment
A number of new technologies have been developed to evaluate neurological function. New Power System EEG interpretations, for example, use computerized algorithms to evaluate complex patterns of EEGs. Neurologists can use functional imaging to pick up visual pathways and examine cortical changes with noninvasive scanning technologies to differentiate multiple sclerosis from other types of neurological injury.

Looking at cognitive reserve as a functional measure for the precedent to Alzheimer's disease is a new concept. People are asked to perform serial tasks, submit to cognitive testing, or take reading comprehension tests, and then use memory under stress to see how well they can recall.

This is an example of functional assessment of neurological reserve, as contrasted to sitting in a calm place where someone asks questions. That type of questioning does not put the same demand on the reserves to see where the weakness in the system might be. Functional medicine tries to understand early changes in function before the onset of an acute pathology. Functional neurology is an emerging field.

Functional Gastroenterology
The literature contains a number of citations for functional gastroenterology. In that area, the term "functional" is used more in the pejorative sense to mean psychosomatic. It is generally applied to irritable bowel syndrome (IBS), which is in part organic and appears to be partly psychological. Because functional gastroenterological disorders cannot be identified by standard pathology, they are lumped together as functional disorders.

Functional Gastroenterological Disorders
Approximately 50 percent of the business of gastroenterologists could be classified as dealing with functional gastroenterological disorders. They represent the dominant complaints for which patients seek the services of gastroenterologists. Yet these conditions do not lend themselves to tidy pathology intervention. Doctors are not sure what to do with a person who has a functional gastroenterological problem, such as chronic, recurrent IBS.

A complex treatment program is generally recommended, since past experience has taught us that one drug probably will not be effective. The patient may require psychological counseling, along with dietary changes, and perhaps the use of the 4R Program to reinoculate the bowel with friendly bacteria. Remediating the dysfunctional gastroenterological disturbance requires ridding the system of some of the bacteria that interact adversely with the immune receptor sites of the mucosal immune-associated tissues and restoring normal function of the gut enteric immune system.

Inflammatory Bowel Disease
In contrast to IBS, inflammatory bowel disease is a more pathology-based condition in which one has bleeding and lesions that can be identified by endoscopy. There might be an acute risk of hemorrhage. That condition might require a different strategy from that of a person who is experiencing complex functional symptoms, with multiple symptoms of alternating severity, duration, and frequency.

Functional gastroenterology provides an interesting model. We have evolved from using the term "functional medicine" to refer to conditions that are not real and all in the mind to an understanding of the combination of environment, genes, enteric bacteria, and many variables that influence the outcome we

call functional disturbances.

Functional Endocrinology
A Pub Med search of functional endocrinology brings up thousands of references. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivity are all considered functional endocrinological disturbances. They all have something to do with the hypothalamus/pituitary/adrenal axis, an interface with the immune system, and some connection to the inflammatory cascade. It is a complex etiology across multiple organ systems that lends itself better to understanding the web than understanding a single organ and treating disorders one organ at a time.

In functional endocrinology, one looks at the interaction of various tissue types that comprise the neuroendocrineimmune system. I did not say the nervous system, the immune system, and the endocrine system are separate. It is as a holographic neuroendocrineimmune system. They interface with one another. Part of each may be seen in any one of them. That is emerging to be part of this functional assessment.

Functional medicine does not lead to a specific treatment. It is a way of thinking about the body—the interacting, weblike system of processes that interface the genes and the environment and give rise to the outcome of performance in the individual.

Functional Immunology
Functional immunology may be where the action really is. Keying those words into Pub Med brings up references to some of the most exciting new research of all. This research is related to diseases of aging, precocious senescence, and chronic degenerative diseases that cut across ICD9 codes, from cardiovascular problems to diabetes to neurological disorders to cancer to IBD. The immune system represents the barrier between the outside and inside world, and functional immunology encompasses the way our bodies respond.

More than any other single system, the immune system probably reveals more about how the organism responds to its environment and the translation between genes and phenotype.

There is a tremendous bonus in knowing more about immunological function as it relates to changing environments and the interface between genes and environment. Functional immunology hits on Pub Med include many references to functional genomics—specific genotypes that give rise to altered immunological function in response to specific environmental factors. Individuals who have a higher production of antigliadin antibodies when exposed to gliadin (gluten from wheat or grain proteins) in their food, represent one example. These unique immunological responses are locked into the genes in response to a specific environment. A food for one becomes a potential poison for another.

We begin to examine genetic uniqueness, and that is a large component of the functional medicine model. Roger Williams introduced the term biochemical individuality to describe how individual patients respond differently to the same environmental factors. Functional genomics, allergy, and clinical immunology are interrelated. Genetic polymorphisms relate to the severity of imbalance of either thymus-dependent helper 1 cell or thymus-dependent helper 2 cell reactivity. For instance, Th2 reactivity might result in atopic dermatitis and the atopic-related disorders. With Th1, you have conditions more closely associated with autoimmune disease and arthritis—the classic inflammatory conditions.

The Strengthening Concept of Functional Medicine
As we begin to understand more about polymorphisms, genomics, their interrelationships with environment, and how they modify function, the functional medicine concept becomes continually stronger.

My takeaway from listening to the AFMCP graduates, reevaluating the underpinnings of the Institute for Functional Medicine, and looking at the contemporary literature, is that functional medicine is more than a name. We are seeing a concept emerge. Functional medicine is a concept of patient-centeredness, of mechanism rather than disease, of health as more than absence of disease. It is the concept of functional genomics, in which genes and environment interact individually to give rise to the outcome called the person.

A clinical case study that illustrates the above discussion might be something like the following: Patient Mrs. Smith cannot eat beef. When she does so, she has an allergic reaction. In traditional allergy testing, Mrs. Smith's plasma does not reveal a specific IgE to beef. A traditional allergist would say hers is a functional disorder, meaning psychosomatic, or not real. A recent paper published in the *Proceedings of the National Academy of Science*offers a different perspective on this type of case. The title of this paper is "Human Uptake and Incorporation of an Immunogenic Nonhuman Dietary Sialic Acid."[2]

This paper explains that beef and dairy products contain small amounts of N-glyco-lylneuraminic acid (Neu5Gc) that is rare in poultry or fish. This molecule, a phospholipid-like specific complex fatty acid (found on glycoproteins) is more prevalent in beef and beef derivations. These red meat-derived glycoproteins might, in reactive individuals, initiate production of antibodies against Neu5Gc acid, including specific IgM, and IgG. According to these investigators, this situation represents an instance in which humans absorb and metabolically incorporate a nonhuman dietary component from beef products, and these substances may act like xenoreactive or foreign substances in the body. The body's immune system reacts, producing an autoreactive response with antibodies against these molecules, with potential implications for human diseases like those associated with inflammatory processes that are triggered by immune system upregulation.

A Case for Biochemical Individuality
In this case, it is not the beef itself that is producing an allergic reaction. Components within the complex chemical structure of beef, in this case these glycoproteins, initiate a specific immunological reaction. We might ask what subtypes of individuals have this type of reaction. Is a certain blood type involved? Is a certain genotype involved? Is a certain genetic personality type more likely to produce antibodies to these glycoproteins? Not all people will have the same reaction.

In medicine, based on the law of averages, if you are not average, then you are considered unusual or abnormal. People who have atypical reactions are often told their reactions are "functional," meaning the problem is in the patient's mind and not real. In the redefinition of "functional," we say the patient has a functional immunological response; it is real. It has to do with the functioning of his or her unique immune system.

This is an interesting example of the difference between the use of the word "functional" pejoratively, to mean psychosomatic, versus "functional," meaning it is definable based on some altered physiological outcome. When we do an analysis of food to see how people might individually respond, we have only

touched the surface. There are thousands of compounds in normal foods for which individual people may have functional immunological reactions. This is a lot more than traditional allergists ever thought they might be dealing with when they were doing their scratch testing.

Another interesting example of this concept is that there may be a risk of hearing loss in treatment with a specific antibiotic. This is most frequent in long-term complications of pneumococcal meningitis treated with antibiotics like ceftriaxone. A recent animal clinical study published in the *Annals of Neurology* found that adjunctive antioxidant therapy along with the antibiotic traditionally used in the treatment of pneumococcal meningitis significantly reduced long-term risk of hearing loss 14 days after infection.[3] Hearing was assessed by auditory brainstem response audiometry.

The investigators found that, compared to placebo, administering the antibiotic along with antioxidants such as N-acetylcysteine brought about tremendous improvement in outcome, or retention of hearing. The antioxidants attenuated the morphological correlates of the meningitis-induced hearing loss, namely long-term blood-labyrinth barrier disruption, spiral ganglion neuronal loss, and fibrous obliteration of the perilymphatic spaces.

Adjuvant Antioxidant Therapy in Meningitis
According to the results of this study, adjuvant antioxidant therapy appears to be highly otoprotective in meningitis and therefore offers a promising treatment option. This work was done at the Department of Neurology, Ludwig-Maximilians University in Munich, Germany.

What we are looking at here is a functional change that relates to the progression of a neurological-related injury from pneumococcal meningitis organisms, and changing outcome at a physiological level. The patient may get over the infection without the use of antioxidants, but it may leave hearing loss that can be prevented by modifying the functional changes of the immune system with antioxidants. This is another chapter in patient therapy in the future of medicine

That leads us into some speculative discussion. A recent article in *Fortune* magazine is titled “The Secret Killer. Scientists Believe They May Have Found a Common Link in Diseases from Cancer to Alzheimer’s to Heart Disease.”[4] This research leads to a breakthrough in anti-aging. Author David Stipp discusses the story behind the search for that link.

If you are a student of functional medicine, you already know the secret killer is chronic inflammation. Inflammation is the process that leads to functional changes in the body’s signaling system that increase inflammatory mediators and cut across many ICD9 codes to inflict such disparate diseases as Alzheimer’s disease, IBD, arthritis, and secondary signs of diabetes. According to this author, inflammation explains why epidemiological evidence associates the use of specific anti-inflammatories over periods of time with lowered incidence of certain degenerative diseases in age, such as neurodegeneration or cardiac-related dysfunction. The secret to anti-aging may be the implementation of an appropriate anti-inflammation program, one that balances the inflammatory mediation system.

Inflammation and the Interacting Web of Neuro-endocrine-immune Function
To accomplish that balance, we must deal with that part of functional immunology having to do with the neuro-endocrine-immune system. The interacting web we have described forms the basis of what is taught in functional medicine. About 50 percent of the immune system is clustered around the

gastrointestinal system. We think that a locus or focus of intervention is the gut. We are concerned with gut-associated lymphoid tissue (GALT), enteric bacteria, Proteus and other kinds of parasites, the integrity of the gastrointestinal mucosa, nutrient transport and absorption, and mucosal-associated lymphoid tissue (MALT).

All of these entities are components of the signaling process to the immunological system that is seen in the GALT, and transmitted to the embedded lymphocytes called Kupffer cells in the liver. The Kupffer cells signal through chemical communication to the circulating white cells, which communicate with microglia, which are embedded cells of immune origin in the brain. A weblike interaction of cell signaling is tied to the inflammatory cascade. That is interesting theoretically, but from a practical standpoint, what happens on a daily basis that can modulate or modify this inflammatory cascade that may increase the risk of biological aging or age-related diseases in certain individuals?

Another recent article, published in *Nature Reviews*,is titled “Nutrigenomics: Goals and Strategies.”[5] In this article, nutritional modification of genetic expression is defined as nutrigenomics, a term we have heard discussed extensively recently. According to this article, food is information. When we eat, we consume information that creates different messages to our genes and alters their expression patterns. Over days, months, years, and decades of living, we eventually reshape physiological function and outcome. Functional medicine is concerned with understanding this interaction and trying to modify factors that people engage in every day, such as eating, to lead to appropriate gene expression patterns.

The authors of this article use as an example the modulation of proinflammatory mediators and metabolic stress through dietary factors, or various nutrients. They point out that in complex gene array physiological evaluation, certain nutrients in certain foods—phytonutrients like flavonoids or polyphenols, or terpenoid molecules—have specific functional effects on the expression of inflammation-related genes through complex signaling processes. Therefore, food is information that leads to the initiation of certain signals. These signals are transduced across cells. They produce messages to genes that activate specific nuclear regulatory factors, such as NF-κB or AP1.

Signaling the Genes
These nuclear regulatory factors set complex gene patterns in motion and create downstream effects through first- and second-signal messengers such as interleukins and later the proinflammatory prostanoids to produce inflammation at the local site. We see this in a gross sense with elevations of reactive proteins in the blood, such as high-sensitivity C-reactive protein (CRP) or amyloid A protein. These are the late-stage markers of what is going on at the cellular level. These processes all reflect functional changes that have occurred early on in cells, tissues, and organs as a consequence of the interaction between genetic pluripotentiality, e.g., uniqueness, and environment, e.g., the diet.

This discussion of nutrigenomics focuses attention on modification of inflammatory processes with specific dietary principles. Tie this back to my previous explanation of the glycoproteins related to Neu5Gc in beef. In certain individuals, these substances may initiate the proinflammatory cascade and could be related, as are many other factors in other unique individuals, to increasing risk for all of the inflammation-related chronic illnesses—osteoarthritis, rheumatoid arthritis, neurological illnesses, or cardiovascular disease. This opens up a large potential paradigm for both prevention and treatment that is individualized to the patient.

Gene/environment interaction and its relationship to the etiology of complex chronic disease is at the forefront of exploration. A recent editorial in the *Annals of Internal Medicine*discussed gene/diet interactions and the etiology of a common complex related to the outcome we call disease or dysfunction.[6] Before we get to dis-ease, we experience altered function.

By reading the literature and looking at the trajectory of the information, we are on the cusp of seeing a functional-based medicine begin to become a major part of the future of clinical implementation.

Another paper in the *Annals of Internal Medicine* istitled “Gene-Diet Interactions in Brain Aging and Neurodegenerative Disorders.”[7] The authors discuss specific substances in the diet that may increase or decrease inflammatory processes in the brain, and how they can either cause or prevent neurodegenerative disease. Alzheimer’s, Parkinson’s, and other dementias may not be mysteries after all. They may result as a consequence of sending signals of alarm, i.e., inflammation, over decades of living in genetically susceptible individuals. These are targets for early nutritional intervention. They relate to both genetic and epigenetic modulation and their effects on the phenotype of the individual.

A review that discusses this topic appeared in *Molecular and Cellular Biology.* It is titled “Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation.”[8] We are starting to see a virtual paradigm shift in the way we view dis-ease, where it comes from, and how it is produced.

In Memoriam—John R. Lee, MD (1929-2003)

I would be remiss in this issue of *FMU* if I did not pause for a moment to honor John Lee, a founding father of the concept of function and the modulation of function with appropriate environment. Dr. Lee was a leader in the paradigm shift. I had the good fortune to know him for many years, as both a colleague and a friend. He was also a Clinician of the Month on *FMU*.[9]

On Friday, October 17, Dr. Lee, one of the founding discoverers of the powerful role of nature-identical progesterone and the dysfunction associated with equine-mixed conjugated estrogens, passed away as a result of a heart attack. His death is a tremendous loss to the field and to humanity. Dr. Lee was an amazing man and a physician’s model at every level in his commitment to excellence, to his patients, to truth, and to finding what is right, even sometimes in spite of personal and professional peril. No one can replace Dr. Lee. He left behind a tremendous legacy of understanding. In fact, to some degree, the Women’s Health Initiative, and some of the studies we have seen published concerning the adverse effects of mixed conjugated equine estrogens and synthetic progestins, were all stimulated by the groundswell of international understanding pioneered by Dr. Lee.

It is with great sadness that we mourn the loss of Dr. Lee, but we have been impacted irreversibly in terms of taking his message forward. This goes back almost 10 years for us in *FMU*. In March 1994 we interviewed Dr. Lee as Clinician of the Month. What he has done in the subsequent 10 years to change the paradigm in the world regarding hormones has been remarkable. Dr. Lee’s work will benefit countless women and men who are now learning about estrogen issues.

Estrogen Research
This discussion ties closely with the interview with our Researcher of the Month in last month’s issue of *FMU*, Dr. Eleanor Rogan. She just received tremendous support for her concepts on estrogen

metabolism, their effects on the increasing risk of breast cancer, and the 4-hydroxyestrogens. A marvelous article appeared in the October 4, 2003 issue of *Chemical and Engineering News.* It istitled "Weighing Risks of Estrogen," and in it her work is heavily validated by many other investigators.[10]

Let's turn to side 2 for our Clinician of the Month interview.

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician of the Month interview. We will be speaking to Dr. Dan Beskind, a physician in Tucson, Arizona, who is an expert in the field of functional assessment.

Dr. Beskind received his master's degree in Public Health at the University of Arizona, and his medical degree at the University of Vermont. His recent focus has been in the application of functional medicine. He has developed the concept of understanding early warning signs and symptoms of later-stage pathology, so that one can make changes while still in control, rather than simply relying on drugs or surgery.

Noninvasive Vascular Assessment
Welcome to FMU, Dr. Beskind. You have been actively involved in noninvasive vascular assessment. Please tell us what you're doing and how you were led into this work.

DB: Thanks, Jeff. It's an honor to be on FMU. I want to express my gratitude to you, because it's really your passionate energy in educating all of us on the functional medicine model that has developed into this major paradigm. We have all these wonderful practitioners coming together. I thought the 10th International Symposium on Functional Medicine in Tucson last year was fantastic.

As an example, I just finished a shift today in the emergency room. That's the most downstream form of medicine. We are great at crisis care, and we had some major fender benders today. We were able to take a 70-year-old woman with internal bleeding right off to the operating room, intubate her, and put in a chest tube. We also treated a 16-year-old with bilateral ankle fractures. Ninety percent of the people I saw today had chronic degenerative disease conditions that we couldn't do much for. We spent a lot of money on them today. That's what really pushed me into moving upstream into a proactive approach on how we can assess people more effectively.

I use the functional medicine model with all my patients—the patient-centered diagnosis, looking at the antecedents, triggers, mediators, and precipitating events, and using the complex web of incorporating nutrition, gut, liver, oxidative stress, inflammation, and the endocrine system. By addressing all these issues, we hope we can help people so they don't end up in the emergency room unless they are in a crisis situation. I'm sorry to back up, but I just wanted to say that I really like to apply this holistic

approach.

Cardiac Disease
Regarding cardiac disease, I gravitated into this particular area because it is the most prevalent problem we see today. It is the number one killer in our society. I don't have to go through all the numbers, but over a million people die from cardiovascular disease (including heart attack) in the US every year.Over 500,000 of them have no prior symptoms. Their first symptom is the acute myocardial infarction.

What is even scarier is that up to half of those people, possibly a quarter of a million people, will experience sudden death. Those are the people we can intervene with. After seeing that over the past decade, I want to try to identify the people at risk and minimize that risk.

New Technologies in Cardiovascular Assessment
JB: It's timely you should bring this up. Right before I had the privilege of welcoming you to FMU, I was eulogizing Dr. John Lee, who passed away unexpectedly from a heart attack a week ago. It's a good time to acknowledge that to preserve function is to preserve wisdom in our society. It is to keep people like Dr. Lee, who had a tremendous amount to share, at a level on which they can continue to make contributions.

A lot of people see these high-tech machines as somewhat daunting and separate from their bodies. It's scary to them. What kind of information can one get and what kind of tools are available to get that information, using the new technololgies in cardiovascular functional assessment?

DB: The key difference between what an office-based practitioner can do and what can be done using some of these tools is to go from population-based guessing to individual risk assessment. You can look at a family with two brothers and a sister whose only history is that their father died of a heart attack at age 49. We can evaluate them with electron beam tomography (EBT) CT scan, for example, and find that one of them has 90 percent more plaque than other men of similar age. In that case, we need to take a clinical approach that's more aggressive in terms of risk reduction. We'll look at labs and subclass patterns.

The other brother and the sister get a score of 0, and you can tell them they're not laying down plaque; they're not oxidizing their LDL particles; it doesn't look like they're laying down their cholesterol molecules, so maybe we can work through more conservative measures. By conservative measures, I mean aggressive nutritional intervention and a more holistic approach.

Identifying the At-Risk Person
We really can identify the at-risk person. It's more difficult trying to identify that intermediate risk group. When I see a patient, I ask myself what chance that person has of having a heart attack in the next 10 years. If it's someone at low-risk—young, no risk factors, no family history of heart disease—then an EBT is probably unnecessary because the 10-year risk for heart attack would be less than 10 percent for that person.

The same applies for high-risk people. I don't need a scan to tell me that someone with diabetes, high cholesterol, hypertension, and a family history, needs treatment to normalize the risk factors. But there's that intermediate group—men over 45 with one or two risk factors, and the same for women over 50 whose

10-year risk of a heart attack is between 10 and 20 percent. For those intermediate-risk people who comprise probably 30 to 40 percent of American adults, we are finding that the calcium score can be the most important determinant in deciding how aggressively we treat them.

Public Health Model vs. Individual Risk

JB: Obviously, you're used to talking to patients about this subject. Let me pick up a couple of pearls you dropped. First, you talked about the difference between a public health model, i.e., risk factors, and individual risk. Would you amplify that? That point may be lost on people who don't understand the difference between the public health high cholesterol issue and individual risk factors.

DB: When we look at the traditional risk factors—hypertension, smoking history, family history, diabetes, and so on—we try to make a generalized assessment. For instance, a patient may have a cholesterol of 220. Based on the NCEP guidelines, we put him on a statin medication. If that patient is one of the people who falls into that category, he may be receiving a medication that can have potential side effects and isn't necessary.

If you look at patients individually, you can treat them more specifically. If you do an endothelial function test, looking at the elasticity of their blood vessels, and an EBT CT that shows they are over the 75th percentile in their age group, then you definitely want to treat them more aggressively.

Individualizing Risk Assessment

Clearly, we know from six international studies that the statins have their place and will reduce events by about 35-40 percent in those at risk. Anybody over that 75th percentile needs to have a more in-depth look at his or her sub-class patterns. Whereas, if someone gets a 0 score and has a cholesterol of 220, maybe you identified the person who just has a high cholesterol, but that's okay.

High cholesterol alone can never predict who will develop coronary disease. It goes all the way back to the Framingham Study. This helps identify whether they're laying down plaque and whether they're developing that whole inflammatory model. I'd like to talk a bit more about that, where the macrophages turn into foam cells; the foam cells secrete proteinases that degrade the plaque, and that's probably what leads to the plaque rupture. It helps you individualize who is at risk.

Just to go on a step further, if someone is over the 75th percentile, I want to look at his or her C-reactive protein, the highly sensitive C-reactive blood protein test and identify whether there is inflammation going on in the body or not. If inflammation is going on, and the person is over the 75th percentile, I want to be aggressive in getting the risk factors modified.

Electron Beam Tomography

JB: You mentioned an abbreviation with which some of our listeners may not be familiar—EBT or electron beam tomography. Would you tell us about the specificity and precision and why that technology might have unique value in achieving the objectives you just mentioned?

DB: The EBT, known as the electron beam CT, takes very rapid pictures of the heart. The person is hooked up to a monitor that takes the pictures while the heart is at a standstill. It's 3 to 10 times faster than the mechanical CTs or multi-detector CTs, because it doesn't have to spin around you in any way. It's a beam that's shot down under you and then fans up through you.

One of the key things is that it's very reproducible. Currently, the EBT is the only scanner I know of that is FDA-approved to track calcium in the coronary arteries because of the low variability in the result. The issue with the mechanical scanners is you're definitely going to get more radiation exposure—3 to 10 times more—and there's at least a 30 percent variation from scan to scan because of the speed issue.

EBT Scan Advantages

There was a nice study out of Europe saying that even improving the way they do the test with multi-slides, there was still between a 27 and 31 percent variation from score to score, which makes it very hard to track.

I'm not saying that the multi-detector or the spiral isn't useful. I'm just saying that for tracking coronary calcium, I think the EBT right now has been shown to be highly reproducible with minimal radiation exposure, and you can track it.

EBT or Stress Testing

JB: One of the things we've heard is that calcium in the arteries doesn't necessarily track back against "soft plaque" or unstable plaque. Thus you might be measuring something that doesn't track with morbidity or mortality.

DB: That is correct. You will not see soft plaque in the coronary arteries. Whenever I'm evaluating somebody, I always want to know about symptoms. The negative predictive value of the test is 96 percent. If someone has chest pain, shortness of breath, neck pain, jaw pain, or anything that might be an anginal equivalent, I can tell them with a 24-out-of-25 certainty that it is not coming from the coronary arteries if the patient gets a low score on the EBT calcium assay.

If the patient gets a high score and is experiencing those symptoms, I'll definitely want to get a stress test done. But I always listen to the patient. Again, this goes back to the model. Someone may tell me that every time he walks up a hill he becomes extremely winded and feels like there's an elephant sitting on his chest. Pain is radiating into his left arm, and it goes away as soon as he sits down, and he stops sweating profusely. That's the 1 patient out of 25 who needs a stress test. Let me give you an example I had two days ago here in the office.

Case History

I saw a 59-year-old gentleman who needed preoperative clearance for a radical prostatectomy. We did a stress test on him and he got up to 100 percent of his heart rate, a rate of 154 or so, and he had 3 millimeters of FT depression in the inferior and lateral leads on the EKG, suggesting a positive stress test. I told him that the EBT would be very useful in his case because he didn't have any symptoms. I told him that if he got a low or 0 score, I could tell him almost with certainty that this was a false positive and he didn't need to do any further testing. He said okay.

He went ahead and did the test and got a score of 1.0, which put him in the best percentile, the top 1 percent in his age group for the best score, the lowest score. I could tell him with a 96 percent certainty that this was a false positive, and we avoided having to do a nuclear stress test. Furthermore, if he was in a hospital situation, he probably would have gone on to a catheterization, a potentially invasive procedure that could have terrible side effects. I just didn't think it was necessary. That was another very useful way of using the EBT is to rule out false positive stress tests.

Calcium and Elasticity of Blood Vessels
JB: Have you found any data suggesting that the calcium score is related to elasticity of blood vessels? That would take us into a discussion of insulin signaling and factors that alter vaso-elasticity.

DB: There was a small study done on that at UCLA. They didn't use the hypertension diagnostic tool—the one we use here to measure the elasticity of the blood vessels. The study showed a strong correlation between the elasticity scores of patients and their calcium scores.

The authors felt that would be a nice, easy, noninvasive office-based way to check for endothelial function. We do it here, and I think it's outstanding. There are age-related norms and you look at both large artery and small artery vessel elasticity. You can tell whether they've got normal endothelial function if they get normal results on this test. I think it's a great way to use the two tests to look at endothelial function and whether or not you're laying down plaque. There's definitely a correlation between these factors, and I like to use both tools to individualize the patient's care.

Functional Assessment Technology
JB: When we look at the functional assessment technology, are there parts of our physiology other than the vasculature, about which we can get early-warning information by this technology?

DB: We can use the EBT in other areas. We've been doing the virtual colonography with the EBT CT to identify polyps and colon cancer. It's an excellent alternative for those people who are not going to have the more invasive procedure, the traditional colonoscopy, which is still the gold standard. Unfortunately, only about 30 percent of people are getting the tests performed and the screening done when they should.

More than 50,000 deaths occur from colon cancer each year, and I think we can identify those people noninvasively. You still have to do the prep and get cleared out. It's not quite as aggressive a preparation as the one for the traditional colonoscopy, but the nice thing is you don't have any sedation, and it's noninvasive so there's no risk of perforation.

Virtual Colonoscopy
Even though the risk of perforation is low for the traditional colonoscopy, if you're the one who gets perforated, it can result in significant complications or even death. I've found virtual colonoscopy very useful. Nine out of 10 polyps under 1 centimeter are benign. Unless you identify those polyps over 1 cm, those patients are being assessed and we also get to look at all of their other internal organs—kidneys, aorta, and spleen.

In fact, we just had a woman who had a 5 cm ovarian mass. I sent her to have an ultrasound of her ovaries with her gynecologist to make sure that it wasn't a cancerous mass that would not have been identified under the traditional method. Other testing that can be done is the noninvasive angiogram on the EBT. You can inject dye and take pictures of the coronary arteries, and it's really quite sensitive when looking for obstruction. A lot of cardiologists are using it.

Noninvasive Functional Assessment
JB: Having observed many of these patients and their data over the years, do you see a trend toward the use of noninvasive functional assessment technologies? If so, do you think that will be a determinant in changing the paradigm of medicine? Often, we don't believe anything until we can see it, and then, when

we see it, it suddenly becomes real.

DB: That's the million-dollar question. Prospective studies are now being done. There's one that just came out last May clearly showing that the EBT CT identified people at risk and predicted cardiac events better than the traditional risk factors.

As more of these prospective studies come out showing the benefit, I think the insurance companies will embrace the technology and reimburse for the test. I often give my patients a note saying why I think this test is a good one, and they submit it to their insurance company. Some of them are getting reimbursed for the CT. I do think it will be embraced, and I think we're going to be able to show it saves lives and decreases the need for other tests if it's used properly.

Early Warning Assessment

JB: Some individuals hearing you talk might think this is a very creative thing that you're doing. They always thought of this technology as separating out people who are going in for coronary artery bypass surgery. It sounds as though you're also using this technology to evaluate earlier stages of dysfunction, where lifestyle and less invasive technologies might be useful.

DB: Oh, absolutely. That's the majority of it. I had a woman this week with a cholesterol of 290 who had a score of 0. She was on Zocor and experiencing some vague muscle cramps. I suggested that we work through other measures and take her off the medication because I wasn't seeing any evidence that she was laying down any calcific plaque.

I said we could reevaluate her in a year or two and see if anything has changed. She was just ecstatic about that. On the other hand, I had a gentleman with a total cholesterol of 180, and an HDL cholesterol of 70, which is remarkable for a male. He had none of the traditional risk factors except for a grandparent on his mother's side with coronary disease, and he got a score of 770. That put him well over the 100th percentile in his age group. He's the person we want to identify and treat more aggressively who never would have been identified prior to this, in my opinion.

Sub-Classes of Cholesterol Patterns

JB: Let's focus on that interesting case for a moment. Do you feel any additional factor, such as insulin resistance, is at play? What other things do you look at, and how do you identify the source of the issues?

DB: I look at the sub-class patterns of good and bad cholesterol. Several good labs are doing that. You can use the Atherotech VAP test; you can use the NMR Test. They're going to give you the HDL2 and HDL3, the sub-class patterns of the LDL. They can tell whether it's the larger, more buoyant type A LDL particles or the smaller, more atherogenic type B.

Then I look at homocysteine, which you've talked about many times. We look at lipoprotein a, which is included on those sub-class patterns. Finally, I look at the C-reactive protein, the high-sensitivity CRP. That would be the decision tree I look at.

Case History

I had a gentleman with an HDL of 26, and the more protective HDL was very low; it was only 3 or 4. His triglycerides were extremely high; they were 270. This is a person who is insulin resistant; he has some abdominal obesity. I put him on a nutritional program. Generally, I don't like to put people on a "diet." I

like to work with them choosing the right nutrition. Clearly, the omega 3 fatty acids have benefit. We start working through all these interventions.

This goes back to the whole functional approach—the patient-centered diagnosis, in which we look at each of the issues—the endocrine system, nutrition, oxidative stress, the gut, the liver, the GI, the immune system—and try to get them all functioning together properly.

Insulin and Cardiovascular Disease
JB: Have you seen in your work a connection of the insulin factor to some of these cardiovascular issues, as it has started to appear in the literature?

DB: Absolutely. Many studies have shown such problems not only in insulin resistant people. They don't even have to have adult-onset diabetes; they just have to have some impaired glucose tolerance. They lay down plaque about four times more aggressively. Their inflammatory markers are higher. Clearly, several CRP, IL-6, PAI-1 factors will all be elevated, and they have the small atherogenic LDL particles, the type B LDL particles. They are setting themselves up for these cardiac events.

What's nice about it is that 90 percent of it is reversible if you can just get them on the right program. I'll give you a perfect example. One of my family members had an HDL of 27 and triglycerides of 242 one year ago; he was also about 90 pounds overweight. His CRP was 2.6, so it was mildly elevated. He got a 0 score on the EBT test so I knew we could work through nutrition and other parameters. We put him on a program of exercise, got him motivated in a program he liked, and changed his nutrition so that he wasn't eating just the refined carbohydrates. He began combining whole-grain carbohydrates with healthy sources of protein and lots of the healthy oils. I put him on 4 gm of fish oil per day for a while. He just sent me his lab tests last week. His HDL cholesterol was 49. It went from 27 to 49, and his triglycerides went from 242 down to 83. He's lost six inches off his gut and has much more energy throughout the day. I think we prevented him from potentially laying down plaque and having an event. This was all because of employing the functional medicine model.

Understanding the Model
JB: I commend you and celebrate those kinds of results. That is exactly what medicine should be doing. We need more doctors like you, and patients need to understand that approach is cost-effective. Hospitalization, for a lot of reasons, is not a cost-effective way to manage function.

Do you have additional insights you would like to share with our listeners?

DB: It's a question of understanding the model. For instance, in coronary disease, we understand the direct link with inflammation, and we understand that most of these disease processes, including hypertension, coronary disease, stroke, and colitis—all the inflammatory diseases—share these common inflammatory markers, oxidative stress markers, and endocrine dysfunction.

It's usually through lifestyle modification that we can turn the ship around, improve their level of health, and keep them out of emergency rooms. It's quite easy once we understand that and once we educate our patients about how to do it. It's just a matter of being proactive. I think the major determinant for patients is to take responsibility and educate themselves or search out people who employ this functional medicine model. Then they can get everything firing properly. You have used the metaphor of a symphony with all

the instruments playing together and making beautiful music. My patients really seem to appreciate it and it's an easy message for them.

We can use some tools. I use the diagnostics not only for patients to understand where they are, but to indicate where to go from there. You can follow them and show them a year later that they're headed in the right direction. You have gotten a regression of some calcium on the coronary artery scan a year down the road, and you've improved their endothelial function with the hypertension diagnostic on the radial artery. It's pretty amazing. You can show these things to the patients, and they appreciate it. I think we can save some lives.

Following up on Research
JB: I commend you for being a pioneer in this field and for the way you are using functional diagnostics or functional assessment to frame a different application in health promotion and disease prevention. It's remarkable. If people want to follow up with you about EBT or learn more about what you are doing, is there a place they can contact you?

DB: There are a couple of different ways. The website of our offices is SWPhealth.com and people can email me through that address. They can also call the office here at 520-529-4013, and we can give them a list of where the Imatron™ electron beam CTs are available, as well as the more integrative approaches to taking care of patients. We can do it quite inexpensively if we can just embrace this model and improve the quality of health for a lot of people out there.

JB: Thank you, Dr. Beskind. What a wonderful optimistic view you have given us as we move into 2004. Keep up the great work. We will talk again.

Applying the Functional Medicine Model

Dr. Beskind included a number of interesting elements in his discussion related to how we practice medicine. He touched on the way we see the patient, what kind of presumptions we take into the exam that lead to our diagnosis and ultimately, to our decision about treatment. He explained that early-stage understanding of function can alter the progression of disease. He talked about ways we might treat the patient and what kind of adverse side effects or other outcomes we might have to deal with later.

Dr. Beskind showed once again how the functional assessment technologies may open the door for "seeing things" that we didn't previously see when we were looking for pathology, and helping us understand the cost-effectiveness of these lower-technology interventions using lifestyle, diet, and environmental modulation.

We are also reminded of the interconnectedness between the insulin signaling pathway and vascular function. We will discuss that in greater detail at our 11th International Symposium on Functional Medicine next May in Vancouver. It follows nicely from the Heart-on-Fire focus at the 10th International Symposium, to which Dr. Beskind was referring. We will carry on that discussion, focusing on insulin resistance, metabolic syndrome, hyperinsulinemia, and its relationship to hemostatic factors.

Insulin Resistance, Hemostatic Factors, and Hormone Interactions in Pre- and Postmenopausal Women

A paper just published in the *Journal of Clinical Endocrinology and Metabolism* takes the concept we are discussing, this weblike relationship between neuro-endocrine-immune system and vascular function, to another level.[11] The paper is titled “Insulin Resistance, Hemostatic Factors, and Hormone Interactions in Pre- and Perimenopausal Women: SWAN.” SWAN stands for Study of Women’s Health Across the Nation. The results of this study remind us how important it is to treat the whole person, the real person, not the hypothetical average “diseased” person.

In this study, the investigators evaluated the association of hemostatic factors with insulin resistance in relation to various reproductive hormones. Again, we are expanding the web. We have talked about cardiovascular factors, glucose transport factors, and insulin. And now we are talking about gonadal factors, reproductive factors, sex steroid hormones, looking at both the hypothalamus/pituitary-stimulating factors and the messenger hormones—estrogen/progesterone/testosterone.

Hormone Study
The investigators evaluated follicle-stimulating hormone, estradiol, testosterone, and sex hormone-binding globulin (SHBG), as well as the insulin and hemostatic factors. SHBG was used to calculate the free estradiol index and free androgen index. The study evaluated 3200 women, age 42 to 52 years, who were moving into perimenopause and menopause. This was part of the Study of Women’s Health Across the Nation.

The investigators looked at various hemostatic factors including fibrinogen, factor VIIc, tissue plasminogen activator (t-PA), and plasminogen activator inhibitor type 1(PAI-1), as well as glucose and insulin to calculate insulin resistance. This is a calculated value in which the glucose and insulin divisor is taken to come up with a number that is divided by 100. That becomes the measure of potential insulin resistance. As glucose and insulin go up, it reflects a lowered number. As glucose goes down and insulin goes up, an even lower number is reflected. But if glucose stays the same and insulin is low, a higher number is reflected, so it is possible to define the basic dynamics of insulin resistance by that denominator. Its calculated value correlates with insulin resistance.

PAI-1 Values
After adjusting for body mass index (BMI), site, and ethnicity, SHBG was correlated with PAI-1. By the way, adipocyte cells secrete PAI-1, so it is not surprising that there was a correlation between PAI-1 and adiposity, but it may be less obvious that we would see a correlation between PAI-1 and SHBG. Testosterone was associated with t-PA and PAI-1, and free androgen index was strongly correlated with t-PA and PAI-1. There were obvious sex steroid hormone androgen connections to PAI-1, and that also connected to BMI, the amount of adipocyte mass central adiposity.

The women with greater insulin resistance had lower SHBG and higher PAI-1 levels. Estrogen measures were not associated with insulin resistance in this particular study. The SHBG, which influences the amount of bioavailable hormones, significantly modified the association of PAI-1 with insulin resistance, suggesting that factors that would influence the amount of bioavailable hormone through association and dissociation with SHBG could then influence insulin resistance.

Variable Hormone Effects
This might help us understand the variable effects among insulin, estrogen, and testosterone. Studies have shown a great variability, and it may be related to the amount of SHBG and the amount of available free

hormone and how that interrelates with these messenger molecules, including PAI-1, which has a close correlation with insulin resistance and inflammation.

The point of this study is that we need to broaden the net when we evaluate patients with complex, chronic age-related diseases. We need to look at more than a single variable; we need to look at the interaction of the neuro-endocrine-immune system and use functional determinants for evaluating the trajectory of a person as he or she moves toward disease. If we wait until the patient is in the state of disease, although we still have many tools, they involve potential risk for patients. They are often not individualized to the patient's need, and they require increasing amounts of intervention expenditures.

Hypertension and Lifestyle Programs

Dr. Beskind pointed out that he has seen a number of patients with significant hypertension. In the course of less than a month, by putting them on a program designed to improve vasoarterial elasticity, improve lipid profiling, and lower inflammatory potential, their blood pressures can sometimes come down 70 mmHg systolic and 20 mmHg diastolic. This is a better result than one would get with virtually any medication associated with blood pressure control. The advantage is that you are dealing with substances and programs that do not produce adverse secondary side effects.

This is good medicine. If you believe the early-warning risk factors for stroke and heart disease can be modified by functional intervention, it leads to confidence in talking to the patient. If they will commit to these programs, they will get a positive outcome. If your attitude is that these are problematic interventions without scientific basis, that patient compliance is difficult, you will very likely justify your presumptions with negative patient outcomes.

A profound message comes from Dr. Beskind's advocacy for the use of functional cardiovascular technology to evaluate function, and for individualized programs that are built around the personalized need of the patient.

This is the framing of a new medicine. The citations with which I began this month's *FMU*, on functional neurology, functional cardiology, functional gastroenterology, functional immunology, and functional endocrinology, demonstrate there is a profound move due to these advancing technologies to understand things that previously we had to wait for pathology to confirm. We are starting to see that the early-warning signs are real, measurable, and reproducible. They will change with interventions that may be pharmaceutical or lifestyle and environmental in nature.

The nutrigenomic concept that I described is profound. Food is information. It is a regulator and modulator of signaling processes; it shifts the dynamic balance in cells toward alarm and plays a mitigating role in a variety of diseases that may have inflammation as their central component.

This is the age of a tremendous paradigm shift in medicine. It is a great way to finish the year 2003 as we move into what will be our 2004 focus on insulin resistance, metabolic syndrome, diabetes, and the relationship of inflammation to cardiovascular disease. Thanks for being with us. We look forward to the exciting unfolding of the 11th International Symposium on Functional Medicine.

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