

July 2004 Issue | Mark Hyman, MD Medical Director

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Welcome to *Functional Medicine Update* for July 2004. We are still reliving the extraordinary emotional experience we had at the 11th International Symposium on Functional Medicine. It is always such a pleasure when 400 of our colleagues get together to celebrate the evolution of this model of medicine, and to observe the incipient paradigm shift as it starts to occur. It was rewarding to share our clinical experiences and to hear from top researchers and medical clinic directors about how functional medicine concepts are emerging to be fundamental tools in managing complex, chronic, age-related diseases.

There were many topics that came out of this year's symposium that will help us focus on inquiry during the 2004/2005 year. The 12th International Symposium on Functional Medicine will be held in Palm Springs, California during the third week of May 2005. You may want to add those dates to your calendars. The topic of the 2005 symposium will be decided based on the evaluations and the outcome of the survey filled out by this year's attendees. This information will help guide our Curriculum Committee toward making decisions about the content of the 2005 symposium. The evidence indicates that we may be focusing on the area of immune function/dysfunction related to infection and autoimmunity. I wanted to give you a little glimpse as to where we might be headed in the year 2005.

Let's focus on some of the clinical applications that came out of the 11th International Symposium on Functional Medicine, the first of which relates to the regulation of neuroendocrine-immune system function through fatty acid nutrition. For most of us, this is not a new topic, but it appears to be a fascinating chapter in the history of nutrition.

We are beginning to recognize that certain fats in our diet are not just calorie-rich energy sources, either processed by our energy machinery or stored in the contractile tissues called adipocytes for a rainy day that never comes. They are also important regulators of neuroendocrine-immune system function. Fatty acids can either promote increased inflammation and alter immunological function (an adverse affect), or they can act as anti-inflammatory agents that downregulate and normalize certain aspects of immune system function. This effect of fats on immunological function between the Th1 and the Th2 type cells, the cell-mediated and the antibody-secreting cells, is a fascinating chapter of discovery concerning what were considered for so long only calorigenic portions of the diet. In fact, we went through a period where it was thought that the more fat we could take out of the diet, the healthier we would be. That is, until we saw people with all sorts of immunological problems as a result of being fat-deprived because of a lack of essential fatty acids and of the omega 3 fats. Originally, we were told that the only essential fatty acid was linoleic acid, the 18-carbon omega 6 fatty acid, meaning its first double bond was six carbons in from the methyl end of the 18-carbon chain and that it had two double bonds. It was considered a C18:6 with two double bonds.

We now recognize that omega 6 is only one of the essential fatty acids. One of the others is the omega 3 fatty acid, *alpha*-linolenic acid, sometimes abbreviated ALA. ALA is also an 18-carbon atom fatty acid, but it has three double bonds, and the first double bond is three carbons in from the methyl end of the chain; hence it is called an omega 3 fatty acid. Each of these has different metabolic properties and different physiological principles. We are learning much more about the omega 3, omega 6, and omega 9 families—the monounsaturated fatty acids. Long-chain saturated fatty acids and medium-chain fatty acids have different effects than long-chain unsaturated fatty acids. As we begin to learn more about the biochemistry of fats, we also learn more about their physiology. We should not just lump them all together and call them fats.

That probably is a pretty good admonition for all of the categories of macronutrients. We probably should not talk about “just carbohydrates,” either. We need to talk about the *kinds* of carbohydrates. Are we talking about long-chain amylostarch molecules, amylopectin molecules, shorter-chain oligosaccharides, or di- and monosaccharides, the so-called sugars? Are we talking about refined bleached white flour carbohydrates or complex, fiber-rich, flavonoid-rich, unrefined carbohydrate? All of these have different effects on physiology.

It is the same with protein. Although protein is generically called “protein,” suggesting that all proteins provide four calories per gram and have equal opportunities for function in the body, we now know there is a vast difference between different kinds of proteins. Certainly, we can differentiate the effects of vegetable-based proteins from those of animal-based proteins. And, within the family of animal-based proteins, there are different physiological effects based on their amino acid composition, their digestibility, and how they deliver the amino acids to the blood. Again, the takeaway from this discussion is that we should be cautious about using generic terms—“protein,” “carbohydrate,” and “fat.” Rather, we should talk about the individual constituents or characteristics of those macronutrient families.

That is one of the dominant themes that came out of the 11th International Symposium on Functional Medicine related to the modification of insulin sensitivity, triglyceride synthesis, lipoprotein synthesis, cardiovascular risk, and endothelial function. We should not just be looking at ratios of protein, carbohydrate and fat, one to the other, but at the individual constitution of each of those families and how they signal different changes in cellular physiology. There is now an emerging view of diet that involves more than just calories and micronutrients. It is a diet that provides dietary signals that modify gene transduction and signal transduction, and how that translates into ultimate cellular physiological function. The theme that is emerging about how nutrients influence cellular physiology takes us beyond simply the concepts of the calorie.

Going back to fatty acids as a clinical theme, let’s review some of the basic concepts. Dietary fatty acids are related to hemostasis and cardiovascular disease risk. This has been a long-standing role of fats.

“The cause of many myocardial infarctions is occlusive thrombosis, or a blood clot that stops blood flow in a coronary artery. Hemostasis involves a complex system of factors, which normally form and degrade blood clots that work within a delicate balance.”^[1]

If there is anything we can say in functional medicine, it is that the balance points in physiological function are where we should be spending most of our time. When we have imbalance at those points, we begin to see certain disease states. As Lefevre^[1] points out:

“Emerging evidence suggests that some hemostatic factors, including factor VII, fibrinogen, and plasminogen activator inhibitor-1, are associated with increased risk for cardiovascular disease (CVD). Accumulating evidence suggests a relationship between dietary fatty acids and emerging hemostatic CVD risk factors, although much of this evidence is incomplete or conflicting.

Dietary supplementation with marine n-3 fatty acids prolongs bleeding time and may decrease risk for thrombosis. Factor VII coagulant activity modestly decreases with reductions in saturated fatty acid (SFA) intake and thereby may contribute to the beneficial effects of low SFA diets. Large triglyceride-rich particles formed during postprandial lipemia can support the assembly and function of coagulation complexes and seem to play a role in the activation of factor VII, and thus may partially explain increased CVD risk associated with increased postprandial triglyceridemia. As our understanding of the role of dietary fatty acids and hemostasis evolves, it is likely that we will be able to make specific dietary recommendations to further decrease CVD risk.”^[1]

It may not be just taking out fat; it may be taking out the bad fats and adding the good fats. I am saying this euphemistically because I do not think biochemicals are necessarily either “bad” or “good.” It is how we use them and to what magnitude we consume them that gives rise to the balance.

“At this juncture, however, increasing marine n-3 fatty acids and decreasing certain SFAs are leading strategies to reduce hemostatic CVD risk factors.”^[1]

Dietary fat goes beyond becoming incorporated into serum triglycerides and into membrane phospholipids. Dietary fats of the appropriate family may also serve as gene signaling agents having to do with gene activation, and are actually messenger molecules that create different genomic, proteomic, and metabolomic outcomes. This is a large breakthrough in our understanding of the role that certain essential fats play in modifying physiology. Therefore, we cannot necessarily account for all the clinical benefits seen from the substitution of a small amount of omega 3 fatty acids for other fats, such as displacement of arachidonic acid or other long-chain fatty acids from membrane lipids. The effects are more than just the incorporation into lipids; they also have to do with the regulation of gene expression resulting from the intake of specific families of fatty acids.

Let me give you a couple of examples that are representative of many papers published over the last several years. Last year, a paper appeared in the *Journal of Nutrition*, titled “Dietary Fat Interacts with the -514C>T Polymorphism in the Hepatic Lipase Gene Promoter on Plasma Lipid Profiles in a Multiethnic Asian Population: The 1998 Singapore National Health Survey.”^[2] The investigators demonstrated that there is an interaction between a specific polymorphism in the hepatic lipase gene and dietary fat because of its ability to regulate high-density lipoprotein cholesterol metabolism. This means that HDL levels may be related to the signals that specific dietary fats have on specific genotypes that give rise to the lipoprotein cascade, ultimately regulating HDL versus TG levels. Based on different genotypes, no two people respond in the same way, but fatty acids could be regulating gene expression that helps in the development of certain lipoprotein particles, particularly the anti-atherogenic HDL, in this particular case.

That is one example of literally hundreds that have been published recently indicating that polyunsaturated fatty acids are, in fact, gene expression regulators. This is a fairly remarkable discovery that emphasizes how important the particular types of fat are in promoting health or disease. The complement DNA microarray studies published to date clearly show that omega 3 fatty acids, usually

provided as fish oil, modulate expression of a number of genes with such broad functions as DNA binding, transcriptional regulation, transport cell adhesion, cell proliferation, and membrane localization.^[3] These effects, in turn, may significantly modify cell function development and/or maturation. N-3 fatty acids influence more than one disease. They may modify functions that relate to mechanisms associated with many diseases that we will be describing here from subsequent research.

α -Linolenic Metabolism in Adult Humans

The first member of the family of omega 3 fatty acids is α -linolenic acid, or ALA. It has been studied extensively over the last 30 years. There is a wonderful review of ALA's activity that was recently published in *Current Opinion in Clinical Nutrition and Metabolic Care*.^[4] This review evaluated current knowledge of ALA metabolism in adult humans, based on findings of studies using stable isotope tracers and increased dietary ALA intake. The relative roles of ALA and of longer-chain polyunsaturated fatty acids in cell structure and function have been found to be very important in modifying the overall personalities of that cell type. Overall, ALA appears to be a limited source of longer-chain, n-3 fatty acids in man. Adequate intake of preformed n-3 polyunsaturated fatty acids, in particular docosahexaenoic acid (DHA), may be important for maintaining optimal tissue function.

ALA is not easily converted into either eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA). Therefore, people who take flax oil or flax seeds as a source of n-3 fatty acids are certainly getting reasonable quantities of ALA, but they may not be converting it very effectively into either EPA or DHA. It is the action of EPA and DHA that results in the most profound influence on gene signaling and cellular function. This is an important characteristic to keep in mind. It does not mean that there is no benefit from ALA as a substitute for saturated fats or partially hydrogenated vegetable oils. What it does indicate is that different people may not see the same clinical benefit from an ALA-supplemented diet. Flax oil contains one of the highest concentrations of ALA, over 50 percent of the fatty acid present. One may achieve a much better clinical response by giving EPA and DHA.

Dietary ALA—Decreases Risk to Fatal Coronary Heart Disease, but Increases Prostate Cancer Risk
Dietary ALA is associated with reduced risk of fatal coronary heart disease, but there is also some evidence that it is associated with increased incidence of prostate cancer risk. It appears there may be some kind of a tradeoff. A recent paper in the *Journal of Nutrition* contains a meta-analysis looking at these particular variables.^[5] The objective of the meta-analysis was to quantitatively establish the association between intake of ALA and mortality from heart disease, and the occurrence of prostate cancer in observational studies. The authors of the paper identified five prospective cohort studies that reported intake of ALA and mortality from heart disease—the Lyon Diet Heart Study being one of the most profound in this area, showing a strong inverse relationship between ALA intake and the incidence of coronary heart disease. Also reviewed were data from three clinical trials of ALA intake and heart disease. In addition, nine cohort and case-control studies were identified that reported on the association between ALA and/or blood levels of ALA, and the incidence and/or prevalence of prostate cancer. Risk estimates were combined across studies using a random effects model. It was found that high ALA intake was associated with reduced risk of fatal heart disease in prospective cohort studies, with a combined relative risk of about 0.79, or a little less than 80 percent of the risk against the control group. Three open-label trials also indicated that ALA implementation or intervention may protect against heart disease. However, epidemiologic studies also showed an increased risk of prostate cancer in men with a high intake or blood level of ALA. The meta-analysis suggests that consumption of ALA might reduce heart

disease mortality. The authors point out that the association between high intake of ALA in prostate cancer continues to be a concern and warrants further study.

As I looked at these studies, I found them quite interesting, because in some of them, blood levels of ALA were assessed and found to be elevated. In my opinion, this may indicate a block in the conversion of ALA into EPA and DHA. The association with prostate cancer may be more than just increased ALA. It may be that this is a stress marker for defects in n-3 fatty acid metabolism and the gene regulation that occurs with downstream chain elongated desaturated n-3 fatty acids, EPA and DHA. I do not necessarily jump to the conclusion that ALA produces prostate cancer. I think that if one were to do an ALA stress or challenge test, and proper elimination of ALA is not seen (conversion into EPA and DHA), it means the blood levels of ALA remain high. That may indicate there is some downstream problem with regulating cell communication, and intracellular function and signal transduction that would occur from the appropriate metabolism into DHA and EPA.

We need to keep our eyes on this story as it evolves, but I would not necessarily jump to the conclusion that ALA is toxic. What I would suggest is that its metabolism and control into the longer-chain, desaturated n-3 fatty acids is quite important. The clinical takeaway from these studies is that EPA and DHA supplements may be better in terms of providing the appropriate balance that one might be trying to achieve clinically, rather than giving ALA.

Effect of CLA on Body Composition and Plasma Lipids in Humans

Similarly, ALA has been shown to lower the release of eicosanoids and nitric oxide (NO) from human aortic endothelial cells in culture, as has conjugated linoleic acid (CLA).^[6] We have heard much about that. CLA is a fatty acid derived from the omega 6 family. CLA, as well as ALA and EPA, will lower the adverse effects that occur on endothelium associated with insulin resistance. Again, we see some basic mechanisms by which these fatty acids regulate cellular function that may be associated with major disease families, such as atherogenesis. CLA, which is a derivative of the omega 6 linoleic acid, and ALA, which gets converted into EPA and DHA, both have interesting regulatory effects on gene expression.

Lessons from DHA Status Regulation, Diet and Epidemiology

The DHA and EPA story is starting to look as if each of them is essential in its own right. That question has been raised in a series of interesting papers. One is titled “Is Docosahexaenoic Acid (DHA) Essential? Lessons from DHA Status Regulation, Our Ancient Diet, Epidemiology and Randomized Controlled Trials.”^[7] This is an interesting review paper. Michael Crawford is one of the authors and he has been involved in the fatty acid research area for more than three decades. According to details in this paper, the evidence appears to indicate that consumption of EPA and DHA directly from the diet may be critically important for brain function, ocular development in the fetus, brain development in the infant, and, ultimately, for controlling neurobiochemical function in adults. It may have a lot to do with regulation of neuroendocrine-immune system function. This is a fascinating part of the emerging story about fatty acids indicating that we should not anticipate that diets supplying only the homologues of these chain-elongated fatty acids of the n-3 family are sufficient. Perhaps we need to give DHA and EPA in the diet directly. They come from fish or marine lipid-containing foods. Fish actually concentrate DHA in their bodies from marine algae. Algae are the organisms that biosynthesize long-chain, unsaturated n-3 fatty acids, and they are concentrated at high levels in specific types of fish oils. There are ways of extracting intercellular algae rich in DHA directly in some of the non-fish-derived fish oils. It seems paradoxical that one can

give a non-fish-derived fish oil, but that is because these specific fatty acids in the fish oil did not originally come from the fish; they came from algae.

Effect of EPA and DHA on Oxidative Stress and Inflammatory Markers in Type 2 Diabetic Patients
EPA and DHA are important modulators of insulin signaling and cellular function, and they have been found to lower blood pressure in type 2 diabetes patients. This is discussed in a paper in *Free Radical Biology and Medicine*, in which the authors looked at the supplementation effects of n-3 fatty acids in type 2 diabetes patients.^[8] They evaluated the effect they had on oxidative stress by measuring F2-isoprostanes, C-reactive protein, interleukin-6, and tumor necrosis factor α (TNF- α) before and after intervention with EPA/DHA supplementation. Doses used in this study were about 4 grams per day of purified EPA, DHA, or olive oil. Thirty-nine diabetic men and 12 diabetic women, averaging 61.2 years of age participated in the trial. Their baseline urinary F2-isoprostanes were positively associated with the level of hemoglobin A1c (HbA1c) and fasting glucose, meaning more glycosylation, poor glucose control, and increased oxidative stress. The elevation in fasting glucose with increased F2-isoprostanes also meant dysglycemia, increased glucotoxicity, and increased oxidative stress. You might think giving a highly oxidizable fatty acid would stimulate free radical oxidation and possibly increase isoprostane levels, but the reverse occurred. The isoprostane levels decreased significantly with the DHA and EPA. The investigators report that this is the first study demonstrating that EPA/DHA supplementation reduces *in vivo* oxidative stress in individuals with type 2 diabetes, hyperinsulinemia, and elevated fasting glucose. This is a fascinating, almost counter-intuitive study showing that regulating proper cell signaling of the molecule insulin and glucose signaling processes ultimately produces an antioxidative effect, even though we might think of these fatty acids as being prooxidants. We sometimes have to discard a previous bias and remember systems biology and how these agents work together.

EPA and DHA are also actively involved in support of immune function. A good review on the immune effects of EPA and DHA appeared in the *American Journal of Clinical Nutrition*.^[9] In a placebo-controlled, double-blind, parallel study, 42 healthy subjects were randomly allocated to receive supplementation with either placebo (olive oil), EPA (4.7 g/d), or DHA (4.9 g/d) for 4 weeks. It was found that supplementation with DHA suppressed T lymphocyte activation, as assessed by expression of CD69, whereas EPA did not appear to have that same effect. Therefore, EPA alone does not influence CD69 expression. No other marker of immune function assessed in this study was significantly affected by either EPA or DHA. There are differential effects on the immunological system of EPA versus DHA, which means we might expect different clinical outcomes with different immunologically-related disorders.

There is now emerging evidence from a variety of studies that supplementation with fish oils can have positive benefit on lowering renal inflammation, and slowing of renal function and lowering progression to renal failure. One of the papers published on this topic appeared in the *Journal of the American Dietetic Association*.^[10] Fish oil supplementation in a population undergoing chronic hemodialysis therapy may be beneficial for various challenges to the progress in this population group. Pruritus symptoms were improved in individuals who were supplemented with fish oils. As we learn more about the roles these fatty acid families play in various immunological, cardiovascular, and endocrine function, we are seeing that the regulation of intake can have positive therapeutic benefit.

If there is anything we know about what n-3 fatty acids apparently do, it is that they assist in establishing

gene expression signaling that helps to maintain immune balance. This is discussed in a report titled “N-3 polyunsaturated fatty acids and allergic disease.”^[12] This is a review of evidence that ties together n-3 fatty acids and the reduction of allergic disorders. The authors state that n-3 fatty acids are now recognized as important, but that we still do not know about all the mechanisms by which they seem to effect a lowered incidence of atopic and allergic disorders, at least in population-based studies. There is a need for ongoing, further research into the role of how n-3 fatty acids participate in the reduction and incidence of allergic disease, particularly in early life before atopy is established. N-3 fatty acids appear to play an important role as cell regulators of immune function. Recall that I previously mentioned proper nourishment of mothers with regard to n-3 fatty acids during pregnancy.^[13]

Docosahexaenoic Acid and Nerve Membrane Phospholipids: Bridging the Gap between Animals and Cultured Cells

DHA is incorporated into nerve membrane phospholipids. This may help bridge the gap between some of the studies we have seen from a clinical observational perspective related to the improvement in neurological function that occurs in people who increase their n-3 fatty acids, and that which we see in cell culture studies. A good review paper on this topic appeared in the *American Journal of Clinical Nutrition* that talks about the dose-dependent responses of cells and the brain to DHA supplements that can be compared by looking at the DHA incorporation rate in neuronal phospholipids.^[14] Clearly, there is turnover in brain phospholipids, or neurological phospholipids, and there is a re-incorporation based on the availability of the n-3 fatty acids

Even conditions like cystic fibrosis may be modified in their phenotype by the role that fatty acids play in the diet. The gene locus for cystic fibrosis was first identified in 1989. There were great expectations for rapid progress in the understanding and effective treatment of the disease. It was generally believed that cystic fibrosis was a monogenic disease that would soon be treatable with gene therapy. Now, 15 years later, we have not been able to do that. What has been identified is a wide variety of mutations (1200) in the so-called cystic fibrosis transmembrane conductance regulator (CFTR) gene that have to do with the transport of substances across the GI mucosa.^[15] We now know that transport of fatty acids is altered in the cystic fibrosis patient, and that n-3 fatty acids become more important. The western diet, which has a high level of n-6 fatty acids and a fairly low level of n-3 fatty acids, may further aggravate some of the imbalances apparent in the cystic fibrosis patient with n-3 fatty acid transport difficulties. The studies tend to indicate that improved intake of n-3 fatty acids can help modify inflammatory conditions for a better outcome prognosis.

It is not just fatty acids that modulate immunological function. There are many micronutrients which do so—folate, vitamin B6, vitamin B12, selenium, magnesium, vitamin A, and vitamin E—micronutrients that modulate natural killer cell and immunological function. Add zinc, copper, and iron to that list as trace minerals important for immunological function. There is a good review of the influence of micronutrients on natural killer cell immune function in healthy living subjects, age 90 years or older, indicating that improving their micronutrient status helped to improve their NK cell activity and cell-mediated defense. This review appeared in the *American Journal of Clinical Nutrition*.^[16]

The relationship between micronutrients, n-3 fatty acids, and immune function is further complicated, or at least amplified, by the role that gut microflora play in immune function. More than 50 percent of our immune function is clustered around the gut. If we have imbalanced enteric bacteria, we may have altered

immunological function. It is interesting to look at antibiotic use, a condition that may sterilize the gut and cause alterations in enteric bacteria, in relationship to the risk of breast cancer. This is discussed in a paper that appeared in the *Journal of the American Medical Association*.^[17] The authors report that the use of antibiotics may be associated with increased risk of incident and fatal breast cancer. The specific mechanism has not been determined, but one possibility the authors postulate could be alteration in the enteric bacteria and the altered effect their metabolites have on normalizing the immune system. We might look at the intestine and the microflora as partners in the protection of the immunological condition of the host. We might even think of this as “the intelligent intestine” that has cross communication with enteric bacteria. There is a wonderful review on “The Intelligent Intestine” in the *American Journal of Clinical Nutrition*, which talks about immune system activity by interaction between the gut-associated immunological system, the lymphoid tissue in the gut, and the effects that diet has on enteric bacteria and their function.

Wheat Gliadin Promotes Interleukin-4-Induced IgE Production

As has been pointed out in many papers, food may contain dysinformation. Gluten in wheat may be sensitizing in certain people and promote upregulation of specific Th-2 cytokines, such as IL-4 that may have peripheral or non-local effects on altering the immune system. This is discussed in an article in the journal, *Cytokine*.^[19] Altered gut flora may be dysbiotic and produce adverse effects on the immunological system. There is a wonderful review on this subject in the *Journal of Clinical Nutrition*.^[20]

The point I am trying to make is that a combination of fatty acids, micronutrients, proper diet, and the regulation of enteric bacteria using prebiotics and probiotics, may frame an interesting way of approaching the imbalance associated with inflammatory and atopic disorders. This is interesting “food for thought” that we will be exploring further in future issues of FMU.

INTERVIEW TRANSCRIPT

CLINICIAN OF THE MONTH

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JB: It's time for our Clinician of the Month. We are pleased to have Dr. Mark Hyman as our guest. Many of you know him very well. For those of you who don't, you are in for a real treat. Dr. Hyman completed his BA in Asian Studies at Cornell University and his medical degree at the University of Ottawa in Canada. He completed his postgraduate training at a Family Medicine Program of the University of California at San Francisco. He is Board Certified in Family Medicine. He has a broad-based background, which includes study of the Chinese language and traditional Chinese Medicine in China. He has had a wide-range of experience in medicine, from private practice to group practice. Currently, he is Medical Director at Canyon Ranch in the Berkshires in Lenox, Massachusetts. Recently, he took over as editor of

a major journal in our field—Alternative Therapies in Medicine—and he is doing a tremendous job heading up that editorial board and setting the direction of that periodical. Dr. Hyman is also active in collaborative work with medical schools involved with integrative medical curriculum. He is a true clinician's clinician. He understands patient psychology, motivation, and the mechanisms that relate to complex, chronic disease. He uses a wide diversity of tools available to the practitioner to ameliorate medical problems.

I've asked Dr. Hyman if he would be willing to speak to us about the implementation of functional medicine in clinical practice through his own experience. Mark, it's a real pleasure to welcome you to Functional Medicine Update. My first question is, what type of patients do you see in your practice? I'd like to get a sense of the array of different problems and patient types that are part of the spectrum of your clinical intervention.

MH: Thanks, Jeff. I'm really happy to be on Functional Medicine Update. It's been an inspiration to me for many years and I'm happy to be sharing my experiences with you, which have been very broad at Canyon Ranch. Canyon Ranch is an interesting place because it's a health resort. People come here for many reasons, from just trying to de-stress and relax, to dealing with complex and difficult health problems that have been resistant to treatment. I often joke and say I'm a "resort doctor" (the doctor of last resort), particularly since my book —Ultraprevention, The Six Week Plan that Will Make You Healthy for Life—has been published. Subsequently, there has been a real influx of people who are looking for an alternative to conventional practice. They are not necessarily looking for alternative benefit, per se, but for a new approach to medicine. I think that's really what we've evolved here at Canyon Ranch—an ability to work with people in an in-depth way over long periods of time to find the route of their illnesses. And we've had remarkable success. We've put together a team of practitioners—physicians, nutritionists, behavioral therapists, exercise physiologists, and so on. They all work together to help engage the patients, and to teach them what they need to know to take care of their bodies to help navigate them through the potential for healing that lies in functional medicine.

Type of Patients Who Seek Integrative Care

JB: What type of patients seek out that remarkable type of integrative care?

MH: Young women who are going through menopausal problems from PMS to menopause to bone density. Today I saw a woman who has had severe ulcerative colitis for many years. She's tried almost every alternative therapy. She's on Imuran (azathioprine) and prednisone. Her sister has rheumatoid arthritis which is resistant to treatment. I see people with chronic fatigue syndrome, fibromyalgia, chronic arthritis, migraine headaches, weight issues, those who are interested in preventing cardiovascular disease, and a lot of people with insulin resistance. We treat a tremendous number of people with insulin resistance, and diagnose them here. We see people who are trying to deal with mental health and mood issues, and people who are trying to deal with preventing Alzheimer's and maintaining optimal brain function. We deal with a whole spectrum of disorders. I see myself as a super generalist. There's almost nothing I don't take care of.

JB: You talked about a team that obviously includes individuals in the health community with divergent skills and backgrounds. How do they work together? How do you consult on patients across these different areas of expertise?

MH: We have different mechanisms for doing that. We share notes in the charts. We share phone calls and communicate with each other via phone calls. We have a health package coordinator who controls the flow of patients through the system. When people are in our package, their background data is communicated to all our practitioners, and we all know who's seeing whom. For example, if I know someone needs a particular treatment, such as an elimination diet, I'll work with them and call the nutritionist to talk to him/her about the patient. Then we follow them on the phone, and we communicate pretty vigorously together to try to figure out the best approach from a behavioral point of view, nutritional point of view, and functional medicine point of view.

JB: When you first brought it to Canyon Ranch, the concept of functional medicine was considered pretty new. Anything new always has a communication barrier. How have you integrated functional medicine into what you do and communicated it to your colleagues?

How An Integrative Health Team Works Together

MH: It's been an interesting experience. Basically, when I came across functional medicine, I told myself that if there was anything true about it, then I owe it to my patients to find out about it and try it. I began very quietly to "try it on," to experiment with the concepts, methods, and the therapies, and began to have amazing success. I am still often amazed at how people get better, just applying the principles of the matrix in functional medicine. The results spoke for themselves. I didn't really need to do a lot of convincing, other than just seeing the results that happened in people over time, and the letters that got written, the positive feedback from patients. We call it "the Jacuzzi effect"—people talking about their experiences—and it sort of filtered out through there.

At the same time, I had the job of discussing and educating my colleagues about the value of this approach to medicine. Part of it was through encouraging them to take the Applying Functional Medicine in Clinical Practice (AFMCP) course, attending the functional medicine symposia, and your seminars. All those things help to fill in the blanks and give people the tools to understand the matrix. Now, it's become second nature. It's our practice. I can't imagine doing anything else. In my view, there's no other way to practice medicine.

JB: You speak with positive affirmation, but clearly, you've had to cross some bridges and introduce some concepts that had barriers in front of them. What was the biggest barrier you experienced in introducing these concepts to your patients and your colleagues?

MH: I think the comprehensive diagnostic stool assessment (CDSA) was probably the biggest barrier. I began to break down some of those barriers by shifting over to look at these functional processes. By bringing it down to that level, people really got it. The best way I found to break the barriers was to discuss things like inflammation, detoxification, nutritional status, and to really understand the signs behind it and be able to communicate those concepts in an effective way that was scientific, literature-based, and that it was really irrefutable. Then, I suggested that we might try to apply therapeutic methods that allowed us to take advantage of these new concepts, and see what happened. Of course, we always trying to start with the principle, "First, do no harm." Obviously the tools we're using are relatively free of significant risk. Diet, nutrition, exercise, mind/body therapies, vitamins/minerals, herbs, for the most part are very safe and have a large margin of error in terms of harm you could do to somebody. By doing that, by being systematic, and by really knowing my stuff, so to speak, I was able to help convince a lot of people around here that this is a valuable model of health care.

JB: For a person who may be just starting in functional medicine, what would be your affirmation as to how they would gain a certain level of competence to make them feel comfortable with implementing functional medicine with their patients?

MH: It's such a huge field. I always say that the science of medicine is very complex. Learning about the concepts involved in functional medicine is like learning a new language. It takes time and study, and it takes experience. But the practice of functional medicine is relatively easy. You can learn some of the therapeutic principles and apply them without having a huge understanding of biochemistry or physiology. Tackling the big problems that have a high reward and a good outcome in functional medicine is probably the easiest way to get into it; for example, insulin resistance. That's a slam dunk. Helping people with irritable bowel syndrome, for the most part, is a slam dunk. Helping people with chronic migraine headaches and food allergies—another slam dunk. There are some really easy entry points for people. They don't have to do everything all at once. It can be a slow accumulation of experience and knowledge. If one starts with just one thing to focus on, let's say helping people deal with insulin resistance, and learn about the issues surrounding inflammation, mitochondrial dysfunction, oxidative stress, and nutritional imbalances, with one particular condition, like insulin resistance. Those principles really apply to everything in medicine. That's the beauty of functional medicine. It gives one a filter to understand the function of the human body and apply those same principles to multiple conditions across a wide array of problems. When you learn about one problem, you've really learned about all of them, because they all come down to the same basic core of dysfunctions in the body—metabolic dysfunction, inflammation, detoxification, oxidative stress and nutritional imbalances. These things are common themes throughout every illness, whether it's ulcerative colitis or insulin resistance. It's the same approach. The therapies might be a little different, the treatment might be a little different, but the thinking process is very much the same.

JB: In listening to you, I am reminded of what Pasteur said: “Chance favors a prepared mind to make a discovery.” Your mind was certainly prepared, it seems, for this model because of your background in Asian Studies, and your examination of eastern medical models, which are more weblike and less analytical/ reductionistic. In the absence of having that kind of background and perhaps preparing your mind to make these associations, do you feel you still could have arrived at mastery with functional medicine?

MH: Oh, absolutely. I definitely had a “fertile field” for growing the practice of functional medicine, but I don't think it's a prerequisite. This thinking is really pervasive across society. “Systems thinking” is infiltrating all fields of social and scientific endeavor, and this is just another manifestation of that. It's the only way things operate in the universe, which is as an interconnected web of relationships. Once you begin to understand that, whether it's in social or scientific systems, the rest falls into place. It's intuitive. I think our patients understand it. I think that's why they're willing to connect with this. When I'm able to explain to them the way their body works, it's like giving them insight into the owner's manual for their bodies and they say, “Wow! This is how my body works; this is how I can take care of it. This is not some sort of a restrictive thing; this is actually learning how to live in harmony with my own biology.” You teach them, basically, how their bodies work. Then they make the choice, and they feel good. That's the immediate payoff. Yes, you can control inflammation, oxidative stress, and improve detoxification, but the bottom line is, people feel better, and that's what's motivating for them.

JB: You say that so beautifully in your book, *Ultraprevention, The Six Week Plan That Will Make You*

Healthy For Life. I think that was eloquently described in the book. You also talk in the book about how you use various tools for assisting the patient to make these observations about their health along their journey; for instance, the laboratory. Would you tell us a little bit about how you use the laboratory and what tests you might find most useful in getting people to connect to themselves perhaps in a different way.

The Role of Laboratory Tests in Functional Medicine

MH: Absolutely. I think there are two main roles for laboratory tests. One is to help the doctor, and the other is to help the patient. As I've gotten more experienced in the practice of functional medicine, I'm usually able to predict the results of the tests without ever seeing them. After doing hundreds of thousands of tests, there are certain similar patterns that emerge that you can pretty much predict. My need for testing has decreased, but from the patient's point of view, I think there's real value in showing them their biology on paper and telling them that something isn't working. For instance, when they have a sugar drink, their sugar goes up 200 points. This is a problem. Or, to get them to look at inflammation in their body and to tell them it isn't normal and that it's going to lead to significant illness later on. Or, explaining that a subtle imbalance in their hormones is making them feel bad, and advising them what they need to do about it. Or, explaining their digestive tract, what food allergies they may be reacting to; even though we all know that food allergy testing is imperfect, it still can be a motivating tool. I've found them very helpful over the years. There are a lot of tests within conventional laboratory testing that we don't use that we should be using that tell us a lot about biology without even getting into more esoteric things like metabolic analysis with amino acids, mineral levels, antioxidant status, organic acids, toxic elements, and so forth. These are obviously more complex. But even just basic stuff we're missing; I see that over and over again. We look at lipids in a careful way; at C-reactive protein; at homocysteine; at sugar metabolism, in particular; at hemoglobin A1C levels in normal patients; at a 2-hour glucose tolerance test with insulin; at a broader thyroid panel; and free T3 levels and thyroid antibodies in more people. We're going to be able to tell a lot about what's going on with their biology just by looking at some of these basic things that are overlooked in conventional testing.

JB: Let me pose a challenge to you. Let's say we just gave you three tests that you could use beyond that of the standard pathology-focused blood screen and hematological pattern. What would you choose?

MH: My favorite functional medicine test is the organic acid profile. It's also the most confusing, but once you learn it, it contains a lot of information about mitochondrial function, nutritional status, B vitamins, neurotransmitter function, oxidative stress, detoxification parameters, and digestive function. In one sweep, you can get a huge idea of what's happening. Clinically, it's been one of the most helpful tests because it seems to correlate the best with people who are sick. The worse the test, the sicker they are. As they get better, the test gets better. That's been a very useful and helpful test for me in terms of the functional medicine profile. The other thing I would say is the celiac test, something I wouldn't want to be without, although it's available in conventional labs. I think that's way under-diagnosed and very important. The third thing that I don't think I can guess at very well is toxic element analysis. That's usually accomplished with a challenge test, looking at heavy metal status. I think that's very key. With the organic acid test, the celiac profile, and the toxic element analysis, I think I can probably take care of most problems. The rest I can probably guess at.

JB: From what you've seen, do you feel that the problem of toxic element body burden is as real as has been implied in some of the more recent studies?

MH: I have a lot of experience, both personally with my own mercury toxicity, and also in patients. There's a wide array of manifestations from the asymptomatic patient with potential risks. For example, someone who has a high body burden of metals and has a risk, for example, for neurodegenerative disease because of APO E4 or family history. I worry about those patients, even though they may not feel sick. There's another subset of people who are very sick and who have significant problems. I see dramatic changes in those people. I'll give you a couple of examples. One is a patient who had severe intractable muscle cramping. She couldn't open a jar; she couldn't sleep at night. She couldn't drive her car because her foot would cramp up on the gas pedal. It was quite serious. She was about 40 years old, and had gone to many physicians. Her husband was a physician, and she had extensive workups by neurologists, nephrologists, endocrinologists, and so forth. From a functional medicine point of view, anything that cramps is magnesium deficiency and the diagnosis is usually pretty easy. I told her she was pretty magnesium-deficient. Let's give you some magnesium. That helped her symptoms a little bit. But then I told her there had to be a reason that her magnesium was so low; that it wasn't normal to be leaking that much magnesium, and that she must have a problem with her cellular ATP-dependent, calcium/magnesium pump. I told her the most common toxin I knew of that screws that up is mercury. We checked, and she had an extraordinarily high level, up to 220 after a challenge with DMPS (for chelation therapy). Over the course of nine months with DMSA orally, with saunas, with nutrient supplementation, with IV glutathione from her husband who was an anesthesiologist, we were able to dramatically reduce her mercury, and her symptoms completely disappeared. That was a fairly clear-cut case.

I had a number of other cases, one with early onset Parkinson's who was diagnosed with a benign tremor, who had an extraordinarily high level of mercury (350). She had a mouth full of amalgams. She had the amalgams out and her level came down to 50. Again, her symptoms improved. Her tremor improved, and she was much better. I think there are clinical cases where there is, in my mind, clear-cut evidence of there being benefit by reducing the mercury. In other cases, I think it's more preventive. Just the whole idea that you can have this toxic substance in your body over time and that it's a known mitochondrial toxin and immunologically active substance, is not a good thing.

JB: Those are very dramatic case histories. One of the things you have described is communicating things to the patient that he/she may never have thought of before. As you said, you're a "doctor of last resort." Often they've been seen by other physicians and had many other tests done. The question is, how do you motivate a change in the patient or communicate these new tools so that patients will accept them as something that is of value?

Motivating Change in Patients

MH: I feel very fortunate, because I'm in a situation where people come to me who are ready and willing to change, or they wouldn't have even walked into my office. I'm in a little bit of an artificial situation because I know many practitioners out there are facing people who are just barely struggling to make it to life, who are economically challenged, who are not eating in a way that supports their biology, and who are not able to exercise. There are a lot of obstacles that I honestly don't face with people, because I'm lucky that I get to spend a lot of time with people and I get people who come in to see me who are ready to change. I think some people need to be coached in a way that we're not used to in medicine. Part of it is developing the skill to match the treatment to the patient. Some patients are willing to take 60 supplements a day; other patients are not willing to take anything but a multivitamin. Some people hate to exercise; some people love to exercise. Some people have certain addictions and emotional stresses that

make it difficult for them to overcome their behavior. The key is to truly listen to their story and find out what their key goal in life is that would motivate them to make changes and alter their behavior. If you can't connect with them on an emotional level to find out what their problems are—things that are not working in their life, and how they want to change them—then you're not going to be successful. You have to start there. You have to figure out what's the most important thing for them. That's always what I ask. "What do you want? What are you looking for? How can I help you?" I think those are questions we don't often ask. We tend to start out with a preset idea of OK, you've got this problem so I'm going to give you this treatment. We really need to take a step back and say, OK who is the person sitting in front of me? What is the situation in his/her life right now? What are their physical and emotional obstacles, and how can I connect with them at a place where they can get emotionally connected to the opportunity and the possibility for transformation in their health and in their life.

JB: One of the things you've said so beautifully in your book, *Ultraprevention*, and you also voiced this before your peers, I think, in your closing address at the 11th International Symposium on Functional Medicine. It appears that this kind of medicine is good medicine; whatever you call it, it's good medicine. You also exhorted the audience to become ambassadors in this change of producing a good medicine. What do you feel the barriers are to this becoming whatever it is called, and the way that patients are generally managed in this more comprehensive ultraprevention form?

MH: Part of my personality is that I'm a terminal optimist. I see change happening in a dramatic way across many sectors of society. Obviously, the consumer sector is seeking out this kind of care, as are physicians. In fact, this week, we have two residents from Brigham and Women's Hospital who are looking for something different in medicine and who found functional medicine on the web and sought us out. They have come here for a week to study functional medicine with us. If top cardiology Fellows and endocrinology Fellows from Harvard are coming and seeking this out, I think that's a very hopeful sign. When academicians at the top universities in this country are seeking us out and trying to understand this model, and are helping us to put it forward in academic centers throughout the country, I think we're moving in the right direction. I believe the obstacles at this point are less than the opportunities. The real opportunity is because the system we have now is crumbling and is so harmful to us as a society. It carries such an emotional and economic burden in terms of lives lost and economic cost, that it's going to destroy itself. We're going to be there to help create a new model.

How Functional Medicine Works—Patient Histories

JB: One of the things you do so brilliantly is to integrate this kind of vision of the future with the reality of the rich array of experiences with patients that you've had. Perhaps you would close by giving us one or two noteworthy examples from your experience about how functional medicine works. You gave us a couple having to do with heavy metal toxicity. Do you have another couple you might share with us?

MH: Absolutely. I always love to tell the story about this one gentleman because he's such a classic example of the functional medicine matrix, and how we need to think in that way in order to treat our patients successfully. He was a gentleman about 57 years old. He had multiple diseases, and he came into my office looking for sort of a wellness checkup. I asked him how he was feeling. He said he felt great. I told him I was surprised because he was taking about 15 different medications and had five or six different diseases. He said that he felt good, and that the medications seem to control everything. I noted that he had asthma, ulcerative colitis, alopecia areata (an autoimmune disease of the hair follicles), hypertension (which we now know is an inflammatory disease), and a little extra weight around the middle, which is probably an inflammatory condition called insulin resistance. I told him he was just "on

fire.” He had a pulmonologist for his lungs, a gastroenterologist for his gut, a dermatologist for his hair, an internist for his high blood pressure, and everybody was treating him as a separate disease, with separate treatments. I asked him if anybody had ever asked him why he might be so inflamed, and he said no one had ever asked him that. I suggested we look.

Basically, this is the process I go through with everybody. I ask what the major condition is and how it’s related to the matrix. In this case, inflammation was a big factor and I asked him what the triggers for inflammation are. We know they’re generally infections, toxins, or allergens, for the most part. Obviously, stress and diet play a huge role. I suggested we look for some of these things. Based on my experience, the first place I looked was for a gluten allergy. Sure enough, he had celiac disease. Six months later, he came back after getting off gluten. He was on almost no medications. His asthma was gone; he had normal bowel movements for the first time in 40 years; his hair was growing back; and he had lost 25 pounds. It was a very simple intervention, but it required asking the right questions. I think that’s really the opportunity of functional medicine. It allows us to ask the right questions.

JB: That’s an absolutely brilliant case history because it really demonstrates the power of the web, filtering things through the matrix, and the whole model you’ve described in your book, *Ultraprevention*. You’ve described the fundamental part of our curriculum in functional medicine—looking for the mechanisms more than looking for what we call the outcome of those mechanisms in diseases. Any other thing you’d like to share with your colleagues about where you see the application of functional medicine or the field going over the next year or two?

MH: I am really excited about the opportunities in this field, because more than ever before, I see these concepts emerging and popping up everywhere. It’s permeating the medical literature now. Yesterday, I pulled up the *New England Journal of Medicine* and there were two articles on homocysteine and osteoporosis. It’s all over the place. If it’s in the medical literature, and if our colleagues are reading this, and if the universities are turning out students who are interested in this, I think medicine is poised for a huge change. As practitioners of functional medicine who are curious and visionary leaders, we have to be ambassadors for this field and help bring this information to our patients and to our colleagues, and do it in a steady and deliberate fashion. I believe that within the next five to ten years, all of medicine will be radically different.

JB: I want to thank you. You’ve given us the kind of affirmation that comes out of our 11th International Symposium on Functional Medicine, which says we need to keep to task, keep our focus, and keep our vision alive. This paradigm shift that we’ve been talking about is imminent, the so-called “tipping point.” You are a leader in the field, and we look to you as a lighting rod or a barometer of where we’re going. Dr. Hyman, I want to thank you very much. Keep up the tremendous work. You’re applying the principles of functional medicine that result in making a real difference in people’s lives.

MH: Thank you, Jeff. It’s my pleasure.

I want to thank Dr. Hyman for a wonderful, and very positive, affirming discussion about the role of functional medicine and management of patients with complex, chronic problems.

Clinical Applications of Fish Oil

Going back to some of the things I discussed on Side 1 on the regulation of immune function with fatty acids and micronutrients, I would like to talk again about fish oils. What amount are talking about? Often, patients think of fish oil as cod liver oil, a ghastly substance that is hard to swallow. Actually, the therapeutic amount of oil is remarkably small for most applications. We are talking about somewhere on the order of 3 to 6 grams of n-3 fatty acids for general modulation of function in the immune, endocrine, and neurological systems. There may be cases where one might need to go to higher levels for autoimmune disorders like rheumatoid arthritis, but for general applications, 3 to 6 grams should suffice.

I want to emphasize to clinicians that I am talking about 3 to 6 grams of a combination of EPA and DHA. Depending on the fish oil formulation, there may be different percentages of EPA/DHA. One needs to look at the labeling to see if it is a high percentage EPA/DHA. It could be as much as 50 to 70 percent of the oil and even higher in some cases. Or, it may be fairly low—30 percent EPA/DHA in some lower-potency formulations. The algae-derived product, such as DHA from algae, can be 90 percent plus DHA therapeutically. A smaller number of capsules would be required to deliver a higher level of DHA or EPA. Make sure you examine the relative formulation. When I say 3 to 6 grams, I am speaking of a high-content oil with more than

60{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} EPA/DHA specifically. It may require total grams to be greater, depending on the potency of the oil.

Second, I talked about the differential effects between EPA and DHA. There may be some cases where one would want to use DHA by itself at the level of 1 to 3 grams. There may be other, probably more common cases, where one would want to use an EPA-dominant formula with a smaller amount of DHA. This would be for endothelial modification, insulin resistance, and poor cardiovascular modification. In these cases, probably a balanced EPA/DHA—perhaps 50/50—would be considered good, or even a higher EPA-containing formula. Based on the clinical outcome one is looking for, gram levels in the 3 to 6 range can be used, and the ratio of EPA/DHA can be varied for different outcomes you are trying to support in a patient.

Let me go back to the discussion about enteric bacteria and its relationship to immunological function. I spoke about feeding the friendly bacteria, which we consider the symbiotic bacteria. This has to do with what is often called “prebiotics.” Prebiotics are specific types of carbohydrates that are non-digestible but fermentable by the symbiotic bacteria that selectively feed them without feeding the unfriendly bacteria. Hopefully, they lead to selective starvation of the parasitic bacteria. Inulin, for instance, is one of the oligofructose-containing substances that serves as a prebiotic. This comes from Jerusalem artichoke or chicory. There are a variety of substances containing arabinogalactans, another form of prebiotic that stimulates growth of the friendly bacteria, such as *Lactobacillus acidophillus* or species of *Bifidobacteria*.

Prebiotics versus Probiotics

There is an interesting paper that was recently published in the *Journal of Nutrition* (an animal study) that talks about enriching the diet with a combination of oligofructose and probiotics and looking at effects on immune system markers. ^[21]

Prebiotics have very marked effects on lowering the inflammatory response of the gut. They may have positive benefit in conditions like inflammatory bowel disease (IBD), and even systemic disorders associated with increased inflammatory potential and imbalances between Th-1 and Th-2 lymphocytes.

There is a paper on this topic that appeared in *Current Opinion in Clinical Nutrition and Metabolic Care*, that discusses the effects of prebiotics in lowering inflammatory potential and other colonic inflammatory disorders.^[22]

Beyond prebiotics and probiotics, the friendly bacteria that ferment the non-digestible carbohydrates into secondary byproducts helpful in modulating immune function of the gut and which have positive effects on immune function of the whole organism, there are other things in the diet that can serve as signals for immune function. This is where the story becomes quite interesting. Often, we fail to recognize the important role that specific food proteins might have when partially digested. Oligopeptides liberated from partial digestion may have specific effects on cell signaling and modulating function of the neuroendocrine-immune system. This is quite a remarkable chapter, because it is not just the story of the food itself, but of the breakdown products of the food through partial digestion, and then the fermentation products of the food that result as a consequence of the fermentation of specific bacteria. For instance, the fermentation of lignans by specific bacteria gives rise to compounds like equol that modulate hormone action. This is a very exciting chapter in the story that explains that our diet is much more than what we put in our mouths; it is also how foods are converted by digestion and microbiological effects in the gut that may have effects on cell signaling.

Effects of Milk-Derived Bioactives

Let's look at milk-derived protein as an interesting example. In the *British Journal of Nutrition*, there is a paper that talks about effects of milk-derived bioactives on rat jejunum.^[23] These are peptide fragments from specific protein found in milk, members of the lactoglobulin family which go on to be partially hydrolyzed into bioactive substances, α - and β -lactorphins and another compound called albutensin, that go on to influence cellular function in remarkable ways. It is not just the stuff we put in our diet, but how it is broken down and the influence it has on cell receptor systems.

These milk bioactive peptides induce mucus release and immunological function in the gut, modulating immune function. This was discussed in the *Journal of Nutrition*.^[24] The influence of these bioactive peptides and certain dairy proteins may have remarkable influence on things as far ranging as blood pressure. For instance, there is angiotensin-I-converting enzyme inhibitory activity found in the gastric and pancreatic proteinase digests of whey proteins that may lower blood pressure. It has been shown to do so in animals, and there is some recent clinical evidence in humans that these bioactive peptides lower blood pressure. I cite from an article in the *International Dairy Journal* as just one of several papers in this area.^[25]

There is even now testing of peptides that may help inhibit β -amyloid aggregation.^[26] This is a pretty remarkable chapter that deserves considerably more research. β -amyloid aggregation is associated with conditions such as Alzheimer's disease. There are now a variety of targeted pharmacological interventions attempting to deplete serum amyloid β components for the treatment of human amyloidosis and Alzheimer's disease, by blocking the formation of amyloid aggregates.^[27] It appears that certain peptide inhibitors may, at least *in vitro*, prohibit amyloid aggregation. I am speculating but, could it be that specific dietary proteins, when digested in specific ways, serve as anti-amyloid agents? The accumulation of amyloid protein in cells is associated with all sorts of aspects of biological aging. In closing, I hope I have given you some sense that functional medicine intervention is more than just a simple story, because it is complex. But, as Dr. Hyman so brilliantly pointed out, the complexity of the

story does not mean that the application is complex. The application is simple; the mechanism is complex. I hope you will stay tuned, because we will be talking about many more strategies to put into our tool kit for evaluating and ultimately managing complex chronic disease based on functional medicine principles, sometimes using the neuroendocrine-immune system as signaling tools for complex diseases.

Thanks so much. We look forward to being with you in August.

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