

February 2005 Issue | Joseph C. Maroon, MD Department of Neurological Surgery

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Welcome to *Functional Medicine Update* for February 2005. Once again, we are approaching our annual symposium on functional medicine. By now, you are probably aware of the focus of the 12th symposium-The Immune System Under Siege: New Clinical Approaches to Immunological Imbalances in the 21st Century. It will be held May 24-28, at the Westin Mission Hills Resort in Palm Springs, California. I hope we will see you there. The program is very timely, as it relates to immunological components of many chronic, age-related diseases. There is no better illustration of that than a recent series of articles that appeared in *Science* magazine discussing the origin of chronic disease. There were two interesting back-to-back articles, titled "Living with the Past: Evolution, Development, and Patterns of Disease," ¹ and "Inflammatory Exposure and Historical Changes in Human Life-Spans." ²

The authors of the first paper discuss the hypothesis that some chronic diseases in adulthood are influenced by environmental factors in the periconceptual, fetal, and infant phases of early life. I found that very interesting. We often think that chronic degenerative disease appears in mid-life as a consequence of something we did in mid-life. It may be that we should be looking at the genes and environment connection that may go all the way back to periconception, or even the preconception status of the mother and the father and how that may be reflected in the *in utero* environment. Factors such as nutrition, stress, and environmental toxins in early phases of life may combine to set in motion a trajectory in which genes expressed into function might lead to dysfunction in middle age. We may develop an epigenetic transition to degenerative disease that originated pre-conceptually. This presents an entirely different responsibility for the healthcare system, rather than just waiting until disease develops.

The second article in *Science* discusses the proposal that the reduction in lifetime exposure to infectious diseases and other sources of inflammation a cohort mechanism has also made an important contribution to the historical decline in old-age mortality. People in cultures with a high incidence of inflammation in childhood and young adulthood had historically higher levels of morbidity and premature mortality for a whole range of diseases, from vascular disorders to cancer to diabetes a constellation of inflammatory-mediated disorders that appears to reflect the mismatch between the genes in that population and their environment. When I say environment, I am including the periconceptual *in utero* and *post utero* periods.

When we begin to examine this in a broader context for evaluating the origin of disease using inflammatory biomarkers, it leads back to alterations in the immune system, or the immune system under siege. What has gone on that has created the imbalance in immunological function that increases relative risk to inflammatory dysfunction and may also be related to increased risk to opportunistic infections?

There is an almost paradoxical effect, because we would assume that if the immune system was upregulated, as it is in inflammatory conditions, that it would pay some dividends in the defense against communicable diseases. However, in any culture, it is possible to have both of those conditions or risks occurring simultaneously. One could have an increasing risk to autoimmune disease while simultaneously having an increased risk to infectious diseases. This is the concept of immunological imbalance mediated through the thymus dependent 1 (Th1), thymus dependent 2 (Th2), and the Th zero (0) innate immune system and how they are juxtaposed, balanced, or interwoven and intercalating one to the other. When there is proper balance, there is good defense against infectious disease and an appropriate response, if necessary, to injury or trauma through the inflammatory system response. However, it does not become overly activated, forgetting what is foe and what is friend, resulting in the immune system being at war with the body.

The concept of living with the past-the periconceptual/conceptual *in utero/post utero* environment, how they interface with gene expression patterns giving rise to the expression of immunological imbalance through alterations of the Th1 and Th2 systems and, ultimately, how that is expressed into the epidemiological record of disease in that culture is a fascinating, emerging view in medicine, biometrics, and epidemiology. We will be discussing that topic from a clinical perspective in much greater detail at the 12th International Symposium on Functional Medicine.

The inflammation connection to these conditions is ultimately tracked as markers of disease in a specific culture. In 21st century language, diseases with inflammatory underpinnings include coronary heart disease, cerebral vascular disease, various forms of malignancy, type 2 diabetes and its implications for vascular endothelial and kidney function, and autoimmune disease. All of these relate to the connection between environment and genes, and expression into patterns of age-related chronic diseases.

In the past, management of these conditions has principally relied on the use of agents that manage symptoms of inflammation the antiinflammatory medications. As Baby Boomers move into their 60s, the prevalence of age-related inflammatory disorders has risen because of the increasing numbers of adults in that age group. Concurrently, reliance on antiinflammatories has increased as a pharmacological mechanism for intervening in inflammatory conditions.

Recently, the FDA, in concert with behind-the-scenes conversations with Merck Pharmaceutical Company, voluntarily removed Vioxx, or rofecoxib, from the market. Not too many months previously, rofecoxib, a selective cyclooxygenase-2 (COX-2) antiinflammatory inhibitor, had been hailed as a great breakthrough in non-steroidal antiinflammatory drugs (NSAIDS), with improved efficacy and safety, along with decreased risk to gastropathy.

This particular withdrawal is without precedence in the American pharmaceutical system and, in fact, the global pharmaceutical system, because it represented a 2.5 billion-dollar-a-year product. As a consequence of the tremendous sales volume and increasing excitement about selective COX-2 inhibitors, the category, which includes celecoxib, rofecoxib, and other more recent entries into the market, constituted in excess of a 6 billion-dollar-a-year market. It was the fastest rising new category in pharmaceutical sales in the history of drugs. Removing a major player from the market as a consequence of 18-month post-market regulatory concerns about cardiovascular safety, shook the halls of the pharmaceutical industry in ways that had never been seen before. It has a greater spinoff on other areas beyond that of selective COX-2 inhibitors, and will no doubt result in changes in FDA policies. Certainly,

we are starting to see some fairly significant implications.

The medical literature has been replete with all kinds of post hoc reviews as to how the removal of Vioxx could happen, and that we knew about the lack of cardiovascular safety, yet did nothing about it. There is an editorial in the *Lancet*, titled "Vioxx: An Unequal Partnership Between Safety and Efficacy" in which the authors talk about the VIGOR trial, the Vioxx intervention trial. Apparently, there were indications of increasing cardiovascular incidence in people taking Vioxx buried in the data from that trial that were overlooked.³

In *The New England Journal of Medicine*, there were some hard-hitting editorials about the Vioxx debacle. An editorial by Eric Topol, titled "Failing the Public Health-Rofecoxib, Merck, and the FDA," was a powerful indictment of the regulatory process relative to some of the data in the VIGOR trial.⁴ There is a table in that editorial which illustrates the number of patients with myocardial infarction (MI) or stroke versus total patients exposed, showing a significant increase in relative risk. These data were not compiled from the VIGOR trial, but the so-called APPROVe study, the Adenomatous Polyp Prevention Study using rofecoxib, that also demonstrated increases in cardiovascular disease or vascular catastrophe, leading to death.

There is another good editorial about Vioxx in *The New England Journal of Medicine* by Dr. Garrett FitzGerald. Some of you are familiar with that name because we have quoted his work in previous issues of FMU. We discussed the concern he raised about the potential cardiovascular risks of rofecoxib and possibly other selective COX-2 inhibitors.⁵ Dr. FitzGerald's papers, and those of some of his colleagues, indicated that a selective COX-2 inhibitor one that is not induction-selective, but rather selective for the COX-2 enzyme itself would inhibit the activity of the enzyme COX-2 in all tissues where the molecule was accessible to the enzyme, including the vascular endothelium. In the vascular endothelium, COX-2 is a constitutive enzyme necessary for the production of prostacyclin from arachidonic acid. Prostacyclin is an important substance secreted by endothelial cells that juxtaposes and buttresses against the proinflammatory, prothrombotic agent produced by platelets called thromboxane A₂. When the vascular endothelium produces adequate levels of prostacyclin to be balanced against thromboxane, there is normal clotting. If, however, there is a reduction in the production of prostacyclin and no significant alteration in thromboxane, the balance is tipped more toward platelet adhesion, platelet clotting, and issues related to thrombosis.

That is what Dr. FitzGerald predicted would be the case, particularly when looking at the VIGOR trial data, which suggested increasing cardiovascular incidence. He reminds us that in 1999, he and his colleagues reported that a reduction of prostaglandin I₂, or prostacyclin, was seen in the healthy volunteers who had been placed on a selective COX-2 inhibitor. They predicted there might be some cardiovascular risk associated with these compounds.

Once again, this reminds us that there is some value in understanding not only the specific function of a drug in a target tissue, but how that molecule interferes, influences, or interacts with other tissues to produce an outcome that may not be initially seen in a normal clinical trial. The outcome may only be seen on post-market surveillance studies after months or years of use of that particular substance.

That is what Peter Stone was referring to in his interesting editorial in *The New England Journal of Medicine*, in which he talks about triggering MI.⁶ He discusses inflamed volatile plaque and how this

process can trigger a major coronary event by alterations in the clotting mechanism and subtle changes in the prostanoids that control and regulate thrombus formation and platelet adhesion. This process can have dramatic effects on cardiovascular health.

Traditional NSAIDs are of concern because of their gastropathy risk, selective COX-2 inhibitors are of concern relating to cardiovascular risk, and narcotic medications used for treatment of pain are of concern relating to addiction. An ever-increasing aging population is suffering from various types of inflammation. It takes us back to the origin of inflammation and how we can modulate it in ways that may not require single molecule interventions with antiinflammatories. That seems like a reasonable place to start. We will be speaking about that with our Clinician/Researcher of Month, and I want to lay some groundwork for that discussion.

What have we learned about the connection among insulin resistance, hyperinsulinemia, metabolic syndrome, and inflammation? There is an emerging body of literature suggesting that a wide variety of age-related inflammatory conditions can be connected to metabolic syndrome/hyperinsulinemia. This includes a recent paper in the *Journal of the American Medical Association*, in which findings support the hypothesis that metabolic syndrome contributes to cognitive impairment in elders, but primarily in those with a high levels of inflammation.⁷

We have also talked about work in previous issues of FMU that connects metabolic syndrome/hyperinsulinemia to endothelial dysfunction and "essential" or idiopathic hypertension. We have seen obvious connections in multiple studies between metabolic syndrome, inflammatory mediators including high-sensitivity C-reactive protein (CRP), and adhesion molecules such as secretory intracellular adhesion molecule-1 (ICAM-1) or vascular adhesion molecule-1 (VCAM-1) and that these are elevated in conditions of metabolic syndrome and hyperinsulinemia. Therefore, every one of these age-related diseases has an inflammatory connection through metabolic syndrome and hyperinsulinemia.

Where did hyperinsulinemia begin? Could its trajectory have begun *in utero* as a consequence of the way the genes were imprinted and expressed? Could epigenetic effects have occurred on the genome expression patterns that ultimately gave rise to a higher susceptibility, or higher sensitivity to insulin resistance and dietary modification of gene expression that is ultimately expressed as type 2 diabetes? It does not result because of eating three doughnuts and living on white bread. It is a complex interrelationship between gene expression patterns that occurred conceptually all the way through mid-life.

That brings us to the question of whether carbohydrate is the scourge of our society. As a consequence of altering our gene expression patterns epigenetically through our altered environment, did we suddenly produce a whole generation or two of children who are now uniquely sensitive to carbohydrate? We never changed their genes, but perhaps we changed the way their genes are expressed based upon the environment in which they were conceived, born, and nurtured. That hypothesis prompts other questions, such as why do we see so much autism and autistic spectrum disorders in children? Why do we see so much attention-deficit disorders (ADHD) these days? Are these related, not to genetic changes, but rather to epigenetic changes through altered environment of development *in utero* and *post-utero* that create a different outcome of gene expression based upon differing environments?

What are things that have changed in our environment over the last 50 years that might lead to these

expression patterns? That brings to mind simple things like busier lifestyle, noise, radio frequencies, toxins, and pollution. What about violence, stress, aggression, microwaves, the music we listen to, the media we are exposed to, and the media we are exposed to? We receive so much from all these energy fields.

In addition, there have been many changes in our diets. Processed foods include the addition or removal of many components. It is a complex, multi-parameter equation that ultimately leads to the following question: without changing genes, how have we changed the environment that controls gene expression and imprints epigenetic patterns, creating a trajectory toward some of the diseases that appear to be occurring with a higher prevalence in our society?

Let me go back to the issue of carbohydrates and metabolic syndrome. Is there something going on relative to the *type* of carbohydrates and the postprandial state? How does that relate to hyperinsulinemia and alterations in liver, glucose and glycogen control, adipocyte physiology and the fat cell, and all the other regulatory hormones involved with managing blood sugar? This is what David Jenkins and David Ludwig discuss in a recent editorial in the *American Journal of Clinical Nutrition*.⁸ It is not just carbohydrates. It may be the matrix in which carbohydrates are delivered that creates the potential for either control of or lack of control of insulin and blood sugar. It has been suggested that we are spending a lot of time castigating the word "carbohydrate." Carbohydrate is broken down into a lot of sub-carbohydrate types, such as sugars, refined white starch, amylopectin carbohydrate, or unrefined carbohydrates with natural fiber. Jenkins and Ludwig suggest that perhaps we can have our cake and eat it, too, provided the cake is made from healthful fat and low-glycemic index flour.

We should also take into account that carbohydrate-rich natural foods contain a variety of phytonutrients or phytochemicals that modify and influence the metabolism of carbohydrate and other nutrients, and also play a role in stabilizing or destabilizing insulin. A white starch product has had its phytonutrients removed through processing. That will have a different effect on overall metabolism and gene expression patterns than consuming the same amount of carbohydrate in a phytochemically nutrient-dense matrix. This may explain why there is a difference in the epidemiological evidence on chronic disease between people who eat white, starch-rich diets and those who eat a diet high in fruits, vegetables, and whole grains. Many papers have shown a reduced risk to major chronic inflammatory diseases in cultures where there is a high consumption of minimally processed fruits, vegetables, and grains.

You might want to look at an interesting review in the *Journal of the National Cancer Institute* that discusses the benefits of eating minimally-processed diets, and reduction of risk to all the inflammation-related age-associated disorders-not just heart disease and cancer.

Mark McCarty is the author of a good article in *Medical Hypotheses*, titled "Proposal for a dietary 'phytochemical index.'"¹⁰ He proposes that we may need to look at nutrient density using what he calls a "phytochemical index"-not just vitamins, minerals, proteins, carbohydrates, fats, and calories, but the relative density of flavonoids, polyphenols, and the various terpenoid molecules that influence the relative phytochemical density. He points out:

"There is ample reason to believe that diets rich in phytochemicals provide protection from vascular diseases and many cancers; direct antioxidant activity as well as modulation of enzyme expression or hormone activity contribute to this effect."

If we look at a diet from a phytochemical-density perspective, we might come to a different conclusion about what is a "good diet" versus a "bad diet," for carbohydrate consumption. If we completely eliminated carbohydrates from the diet because of their current "bad" reputation, it would result in a bad diet. Where are phytochemicals found? They are found in carbohydrate-rich food. There are few phytochemicals in animal products. Phytochemicals, by definition, are plant-derived nutrients. If you ate a diet exclusively of animal products (unless you were eating certain organs like liver), you would be getting a very low level of some of these phytochemicals, far less than you would get from a plant-based diet rich in minimally processed fruits, vegetables, and grains.

Epidemiological studies tell us that there is a strong relationship between insulin sensitivity, lowered cardiovascular disease incidence, and lowered diabetes in individuals who eat minimally processed fruits, vegetables, and grains. There is also lower body weight in those cultures. Perhaps there is a connection between satiety, thermogenesis, improved gluco-regulation, and lipid regulation that occurs with consumption of these diets.

There is a good article in *Nutrition Reviews* that discusses the epidemiological finding that people in cultures that consume minimally processed fruit and vegetable diets (which are carbohydrate-rich, I might add, because they generally contain a higher level of grains) have a lowered incidence of inflammatory age-related disorders.¹¹ The group of investigators from the Centers for Disease Control and Prevention in Atlanta have done a nice job in this paper.

Individuals who consume minimally processed, phytonutrient-rich diets that are reasonably high in carbohydrates (as whole grains), also have favorable benefit from vitamin and mineral density. Plants synthesize vitamins that animals depend upon for their function. One example would be the plant density of vitamins B1, B2, and the rest of the B vitamin complex family, including folate and vitamin B6.

A paper in the *American Journal of Clinical Nutrition* discusses the interaction between adherence to a Mediterranean diet and the methylenetetrahydrofolate reductase (MTHFR) 677C→T mutation on homocysteine concentrations in healthy adults—the ATTICA Study.¹² The Mediterranean diet is not a strict vegan diet. It contains animal products that may be an important source of vitamin B12, but it also has a high level of minimally processed grains, fruits, and vegetables. This diet is associated with very low incidence of homocysteine elevation in those who carry the MTHFR 677C→T polymorphism, where there is a block between the conversion of tetrahydrofolate to 5-methyltetrahydrofolate. These individuals appear to require higher levels of folate in their diet to get an adequate level of 5-MTHFR, a substance that serves as the central methylating agent necessary in the folate cycle to lower homocysteine and to produce S-adenosylmethionine, or SAM. These people may need exogenous folate to lower their homocysteine. In individuals consuming the Mediterranean diet which is naturally rich in B vitamins, who also had an MTHFR 677C→T polymorphism, their homocysteine levels are lower, which would affect their relative risk to heart disease.

If you eat a diet rich in phytochemicals, even though it contains carbohydrate, the relative markers to all the age-related inflammatory diseases are lower. This is further confirmed in a paper in the *Journal of Nutrition*.¹³ The authors looked at plasma high-sensitivity CRP and its relationship with homocysteine concentrations. It was found that in both Hispanic and non-Hispanic older-age individuals, when consuming minimally processed diets rich in fruits, vegetables (which provides higher amounts of whole grains), their plasma CRP and homocysteine levels were lower, and their relative risk to vascular

disorders and stroke was significantly reduced. This work came out of the Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University.

This tells us how important it is not to throw the baby out with the bath water as it relates to phytochemicals and carbohydrates. If we convince people that carbohydrates are bad, we may further aggravate the situation by lowering intake of important phytonutrients in the diet.

Many phytonutrients have effects on mitochondrial function and energy production. In a recent study, animals supplemented with vitamin E and coenzyme Q10, two important parts of the electron transport chain and energy production in the mitochondria, were found to have reduced circulating markers of inflammation, suggesting that mitochondrial oxidative stress is interconnected to inflammatory conditions and poor energy production.¹⁴ Dietary supplementation with vitamin E alone reduced the baseline inflammatory status indicated by increased high-sensitivity CRP. Cosupplementation with coenzyme Q10, however, was found to significantly enhance the inflammatory effect of vitamin E, showing synergy on the relationship between those essential substances.

Coenzyme Q10 is manufactured in the body; it is not considered an essential nutrient, whereas vitamin E is considered essential because it is not synthesized in the body. We might consider coenzyme Q10 as a conditionally essential nutrient in many people who may have inflammatory stress or oxidative stress, or who are on medications or in an environment that suppresses the biosynthesis of coenzyme Q10. We all know about the relationship of statins to lowering *de novo* biosynthesis of coenzyme Q10. Here we see that vitamin E and coenzyme Q10 supplementation, taken together, can have beneficial effects on lowering inflammatory potential.

As we move the story a step further from the carbohydrate/insulin sensitizing inflammatory connection to phytochemicals, we also need to move toward looking at what might be the seat of inflammatory initiation in the body. That takes us back to where the seat of the immune system is located. We will be discussing the implications of this topic in the plenary lectures and breakout sessions at the 12th International Symposium on Functional Medicine. I am referring to the gut-associated lymphoid tissue (GALT).

The GALT is an important part of the immune system, constituting about 50 percent or more of the immune system mass of the body, and producing about 70 to 75 percent of the antibodies generated against specific epitopes or antigens. It is also an important seat for regulating the Th0, Th1, and Th2 immune function, so it is a poisoning system for the rest of the body. Breakdowns in the gut mucosal integrity leading to what has been euphemistically called "leaky gut syndrome," or impaired mucosal permeability, can expose the immune system of the gut to various kinds of unfriendly molecules that are part of the gut contents. This initiates upregulation or imbalance of the immune system, the Th1 and Th2 regulation, and triggers inflammatory conditions.

Dr. Mary Ellen Sanders eloquently discussed the use of pre- and probiotics in the December 2004 issue of FMU-gut bacteria, friends and foes, and how to alter the balance. There is a recent article by Dr. Rastall from the Food and Bioprocessing Sciences Group, School of Food Biosciences, University of Reading in England in the *Journal of Nutrition*. He discusses the use of symbiotic forms of bacteria, a probiotic together with a prebiotic targeted at the specific immune function in the host.¹⁶ This follows up on Dr. Sanders' important lesson on the significant role that pre- and probiotics play in gut immune function.

Probiotic Consumption in Postmenopausal Women with and without a History of Breast Cancer

A woman who is properly metabolizing the contents of her gut and who has proper gut flora, can convert certain types of lignans that are found in unprocessed diets to estrogen-protective substances. Lignans are another part of the phytochemical family found in carbohydrate-rich, minimally processed diets. Lignans can be converted by friendly bacteria into estrogen-protective substances (equols) which have a history of lowering the incidence or risk to breast cancer,¹⁷ although it remains unknown what components of the diet may support this conversion. A friendly gut flora produces more secondary metabolites, such as equol. Equol apparently has a favorable effect on estrogen signaling and estrogen metabolism, and can reduce relative risk to a self-proliferative disorder.

Equol Inhibits Bone Loss in Ovariectomized Mice

The gut and gut flora can play many roles in normalizing immune function, varying from the direct effect of the GALT to the indirect effect through metabolism of various nutrients, including the production of equol from lignans. Equol is a metabolite of diadzein, one of the soy isoflavones, and has been found to inhibit bone loss in ovariectomized animals and to normalize hormone metabolism and estrogen activity.¹⁸

Lactobacillus GG Bacteria Ameliorate Arthritis in Lewis Rats

Regarding the probiotics and inflammatory conditions, such as arthritis, the takeaway is that gut immune function is an important seat of control over the overall systemic immune system. Diet plays a very important role in modulating the process, even to such things as arthritis risk. You might want to look at a recent article in the *Journal of Nutrition* that discusses this, titled "*Lactobacillus GG* Bacteria Ameliorate Arthritis in Lewis Rats.

Following our discussion pertaining to the modulation of inflammatory-related disorders, insulin modulation, and gut-associated immune function modulation through pre- and probiotics and maintenance of proper gut flora, let me speak to the role of essential fatty acids in this process.

There is a long-standing history indicating that (populations consuming omega-3 fatty acid-rich diets, such as those that go back to the Greenland Eskimo, have a very low incidence of what we now call inflammatory-related disorders, such as coronary artery disease and arthritis. The association that emerged between these observations was that omega 3 fatty acids modulated the arachidonic acid cascade by lowering the production of the 2- series eicosanoids, such as prostaglandin E2, which is proinflammatory, pro-platelet adhesive, and pro self-proliferative. By the 3-series prostaglandins that came through the modulation of metabolism of eicosapentaenoic acid (EPA), we would likely see reduced inflammatory mediation. That process all looked very reasonable, except one could never quite figure out why such a low level of omega 3 fats in the diet seem to have such a profound effect. When we look at the incorporation of omega 3 fats into red cell membranes or other phospholipid components, it seemed to be a small incorporation for a big clinical effect. The question has always arisen as to why there is such a remarkable effect.

What has emerged over the past few years is the recognition that omega 3 fatty acids play a role in modulating inflammatory conditions beyond that of causing production of 3-series prostaglandins. They are also involved in direct regulation of gene expression in the cassette of genes involved with the production of inflammatory mediators. This includes not only prostaglandin E2, but upstream from that, things like TNF α , IL-1 and IL-2, and the particular essential fatty acids of the omega 3 family that may act

on PPAR receptors, meaning that they may serve as natural thiazolidinedione medications. Some data suggest that they may help stimulate the nuclear orphan receptor PPAR family to properly regulate gene expression. That would have a positive benefit on insulin sensitivity and lowering inflammatory mediators through the effect on gene regulation.

This is a remarkable observation that takes us well beyond the simple model of EPA modulating 2-series prostaglandins to recognizing that it has a panoramic effect on altering reporter gene expression pertaining to inflammatory processes. There is a nice review of the concept of omega 3 fats regulating gene expression in *Nutrition Reviews*.²⁰

It may help us to understand why fish intake, rich in omega 3 oils, is associated with reduced progression of coronary artery atherosclerosis in postmenopausal women. This is discussed in a paper in the *American Journal of Clinical Nutrition*.²¹ The authors discuss how fish is a combination of unique proteins, along with unique fatty acids. Proteins in some fish can hydrolyzed into specific antiinflammatory and antihypertensive ACE inhibitor-like peptides. The combination of whole fish containing omega 3 oils with the fish protein may give rise to these remarkable epidemiological observations of lowered inflammatory disease risk.

With that information, we are ready to talk with our expert, our Clinician /Researcher of the Month, who will tell us how all of this fits into clinical practice.

INTERVIEW TRANSCRIPT

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JB: It's time for our Clinician/Researcher of the Month. This month, we are fortunate to have a clinician that stands head and shoulders above many of his peers Dr. Joseph Maroon. I met and heard him lecture recently at an American College of Nutrition meeting. I've also reviewed his publication list and his Curriculum Vitae, which represent a vast set of truly remarkable credentials and accomplishments.

As a college student, Dr. Maroon was awarded a football scholarship at a major "Big Ten" university where he became a Scholastic All-American. He went on to pursue neurosurgery, his love and specialty of many years. He is widely acclaimed in the field of neurosurgery, and was recently voted as being at the top of his game by his peers. While doing all of that, as well as advancing technologies and techniques, publishing articles, writing books, giving lectures, and dealing with complicated case histories and patient management, he has also found time to continue his commitment to physical fitness and competition. He has been involved in over 50 Olympic distance triathlons, including the Ironman Triathlon in Hawaii. Those of us who have dreamed or aspired to be part of that world can live vicariously through Dr. Maroon's accomplishments. This is a man who has done it all. He has been able to balance multiple factors of excellence simultaneously.

Dr. Maroon has recently become interested in some of the adjunctive roles nutrition can play in medicine.

That led me into my first discussion with him. Welcome to FMU, Dr. Maroon. With all the experiences you have had, it might be comfortable to simply enjoy the place you have established in your profession, without the need to grow and change. What led you into taking an additional interest in nutrition that has recently become a part of your practice?

Physical Fitness and Nutrition

JM: Thank you, Jeffrey. I guess it goes back to my athletic background and my commitment to physical fitness. Although there have been periods when it hasn't been that way, I've maintained a fairly good schedule of athletic commitments throughout my life, particularly over the last 12 years. I'm now participating in Ironman Triathlon distance races. I find that fuel for the body becomes very essential when training and performing in these events. It is clearly noticeable that what you put into the body makes a huge difference. In terms of nutritional supplements, those I've gotten into are now very well recognized, such as L-carnitine, coenzyme Q10, the vitamin B complexes, and magnesium. Whether you train at a high level or not, the inflammatory response of the body can be very beneficial, as it is designed to be. It can also create a lot of pain and problems—the rubor/dolor/tumor type of syndrome that we learned about in medical school—redness, pain, heat, and swelling. When this runs amuck, it is now well recognized, particularly by alternative treatment physicians, that many of the diseases we are afflicted with—different kinds of arthritis, cancer, heart disease, and stroke, the vascular concept of endothelial membrane breakdown and deposition of fats—are all the common etiology of inflammation.

Discogenic Disease

I have a fairly large practice of patients with neck and back problems, most often, discogenic in origin. With discogenic problems, there's desiccation of the disks, subsequent narrowing of the disk space, and everything from arthropathy to spinal stenosis, lateral recess stenosis, and herniated disks. These are not just compressive phenomena, but there is a major inflammatory component. Many biochemical studies have been done on discogenic disease, biopsying and analyzing the cytokines and inflammatory molecules associated with "simple" herniated disks.

There are two components. There's the mechanical compression of the nerve root, resulting in radiculopathy. There is also a very clearcut biochemical phenomenon. The drug companies have clearly recognized this and we get into the arachidonic acid pathway and that arachidonic acid is found in high concentrations in cell membranes, as well as the substances phospholipase A and tumor necrosis factor alpha (TNF α) in the perineural area where disks are herniated. As we know, arachidonic acid is converted by cyclooxygenase (COX) to prostaglandin E₂, which is very proinflammatory. This proinflammatory substance causes the constriction of blood vessels. The pain syndromes that we experience increase clotting ability as a normal response of the body to an insult. There are also several things in the brain involving the same pathways—subdural hematomas, aneurysms, and subarachnoid hemorrhages. These are all inflammatory processes that cause disastrous consequences in the brain, as well as the heart.

COX-2 Inhibitors

In looking at this pathway, the major pharmaceutical companies realized that if they blocked COX-2 with Celebrex, Vioxx, Becktra, Advil, Aleve, and ibuprofen compounds, they would have an antiinflammatory effect. It's a major industry. Approximately 9.4 billion dollars a year is devoted to blocking COX. That's pretty phenomenal. We also know that when you block COX-1, and to some extent COX-2, there is a secondary side effect on the gastric mucosa. Vioxx, a 2.4 billion-dollar drug that preferentially blocks COX-2, was recently pulled from the market because of its cardiac and

thrombogenic effects in the body. I suspect there have been preliminary notices about Beckstra and Celebrex and that they may also come under closer scrutiny. Yes, we need to block the inflammatory response, but do we need pharmacologic agents with major side effects to do that?

The Inflammatory Process and Omega 3 Fatty Acids

In looking into this further, initially quite frankly for myself, I attended an A4M meeting a few years ago and heard Barry Sears speak. I thought, eureka! He so lucidly expounded on the inflammatory process and its deleterious effects on all of the organ systems, particularly in chronic diseases. Barry is a big proponent of omega 3 fatty acids. If you look at the omega 3 fatty acid pathway, eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA), the main active components of fish oil, work on the COX pathway, but they also enhance the formation of prostaglandin E3 (PG E3), which is primarily antiinflammatory. By competitive inhibition, fish oil acts as an antiinflammatory. I had no concept about that in my practice in the greater Pittsburgh area. I don't think most physicians recognize the antiinflammatory effect of omega 3 fatty acids. The easiest way to get them, of course, is through fish oil. With that in mind, I began looking at my own patients who come into my office with spinal stenosis, sciatica, radiculopathy from cervical disease, and I asked them what medications they were on. Invariably, they were on one of the COX inhibitors, as well as a muscle relaxant and an analgesic of some kind. When questioned, a high percentage of them complained of complications, particularly gastric complications.

I began suggesting that my patients taper off the COX inhibitors and begin taking omega 3 fatty acids, primarily through fish oil supplements and dietary manipulation. I also advised reducing the carbohydrate load. Increased insulin and deposition of fat releases inflammatory cytokines. After dietary manipulation and omega 3 fatty acids, we subsequently surveyed those patients without significant neurological deficits who did not require surgery. Sixty to 65 percent of the 200 patients who had been supplemented with omega 3 fatty acids found in fish oil were able to get completely off the COX inhibitors. This was a very exciting finding.

For the last 15 years or so, I have been the team neurosurgeon for the Pittsburgh Steelers. I have also placed the athletes I see in my practice on omega 3 fatty acids. I've done this in conjunction with my associates-Dr. Tony Yates, Dr. Richard Rydze, and Jeff Bost. We have worked with professional football players, wrestlers, and swimmers, and found that a significant percentage of them are able to markedly reduce the use of COX inhibitors. These are not double-blind, controlled, randomized studies that I've done. This is experience in my own practice dealing with highly motivated individuals and athletes who had been dependent on COX inhibitors for antiinflammatory relief. We found that we've been able to markedly reduce the use of those agents in highly motivated athletes.

Now, it could be a placebo effect. It's not the kind of study we intended to design. Regardless, I think the individuals who have been on it have generally been very satisfied with what they perceive to be significant help. Regardless of what they perceive, we know that with omega 3 fatty acids (I recommend in the 3 to 5 gram range), there are many other entities that are benefitted markedly, particularly in the cardiovascular and the cerebrovascular arenas. We know that omega 3 fatty acids inhibit coagulation, promote basal dilatation, reduce inflammation, and significantly modify plasma lipid and lipoprotein concentrations. I've had many patients on omega 3 fatty acids for joint pain tell me they think it's amazing that their cholesterol has dropped significantly. Others tell me their blood pressure has been significantly reduced.

When one looks at the literature on omega 3 fatty acids, there are many very good studies that clearly support their use, particularly in cardiovascular disease and for atherosclerotic problems. In terms of rheumatoid arthritis, there are many papers showing that omega 3s suppress the production of TNF α , as well as interleukin 1 β , and supplementation with 2 to 3 grams of DHA and EPA per day markedly reduces (up to 90 percent inhibition) of proinflammatory cytokines in rheumatoid arthritis. My office nurse has lupus arthritis, markedly affecting her hands. She was on Plaquenil for five years. She started taking 3 grams a day of omega 3 fatty acids and after about three months, she is completely off of the Plaquenil, with tremendous improvement in the use of her hands and joints.

There are now many papers on the use of omega 3 fatty acids in attention deficit hyperactivity disorders (ADHD) in children. In a recent study, they were used in place of Ritalin, with good effect.²² There are many other benefits of omega 3 fatty acids besides pain relief, in terms of their secondary, or even primary, antiinflammatory response in the body. That is an overview of how I got into these supplements, how I use them, and the results that I've seen in my patients.

JB: That's an extraordinary story. I'd like to follow up with a couple of questions. As a clinical professor in the Department of Neurological Surgery at the University of Pittsburgh Medical Center, you must have quite a bit of visibility among your peers and medical school colleagues. What kind of response have you received about using these kinds of adjunctive substances? Does this open up a new dialogue?

The Inflammatory Response and Tumor Necrosis Factor Alpha

JM: Let me put it this way. I would say generally that the more senior individuals are much less likely to accept this than the residents and younger individuals. I presented this at our resident conference and it's extremely intriguing from another viewpoint. In terms of the antiinflammatory response to fish oil, that's one thing. But another agent that I've been using, off-label, is Enbrel. Enbrel is a specific TNF α blocker (antagonist), and it's recommended and used by thousands and thousands of patients with rheumatoid arthritis. Dr. Ed Tobinick in California, as well as authors in Switzerland, have published several preliminary papers on the high concentration of TNF α in the periradicular area of herniated disks in both the neck and the low back. Tobinick has published a fairly large study on using TNF α to block pain in patients with sciatica or radiculopathy.²³

We just went through a protocol with our pharmacy committee here in Pittsburgh, and I'm now using this in very selected patients instead of surgery, if there's no neurological deficit in patients with radicular components of that nature. When it works, it's clearly, in my opinion, not a placebo effect. There is almost an immediate response. You can't get any more targeted than that drug in terms of a specific cytokine and pain relief. The concept of inflammation being a major component of radicular syndromes is clearly irrefutable. Now, we need to find agents to block that inflammatory process and hopefully avoid surgery, which I have done with these adjuncts in many of my patients.

JB: That leads to an interesting discussion about the role and mechanism of action of the essential omega 3 fatty acids. As you pointed out so eloquently, it's been felt for years that their role was to block the 2 series prostanoids the proinflammatory eicosanoids by upregulating the production of the 3 series antiinflammatory prostanoids and redirecting the arachidonic acid cascade. More recently, however, there have been indications that omega 3 fats serve as receptor agonists for nuclear orphan receptor families like peroxisome proliferated activated receptors (PPARs), and also modify the expression of the inflammatory cascade in the reporter genes that control inflammatory mediators, including TNF α and

IL-1b. It may be that what is being observed clinically is a consequence both of the 3 series prostaglandins and also the modification of gene expression of the inflammatory mediators such as TNFa.

JM: That's fantastic. This has been an incredible voyage of learning for me. Getting into the biochemistry of this has been fascinating. What you just stated is where it's at in medicine for so many of the diseases that we treat.

JB: There's one other important point you raised. I'm sure my early training was similar to yours, and medicine often focuses on the primacy of disease and that the diagnosis is tantamount to understanding the condition. Therefore, we worked hard with our professors to become skilled at the art of differential diagnosis. That made the assumption that each disease was independent of other diseases, with its own etiology, its own pathophysiology, and its own mechanism. Yet, over the last 10 to 15 years, it's been found that those distinctions can get very fuzzy. What is consistent among certain diseases, like inflammatory diseases-cerebrovascular disease, cardiovascular disease, type 2 diabetes and insulin resistance, rheumatoid arthritis, and osteoporosis-is that processes are going on, as you indicated, such as inflammation. Perhaps the connector is a process rather than a disease. That would help us to understand more about the variant roles that omega 3 fatty acids play across many different diagnostic categories and many subspecialties of medicine.

For instance, you mentioned ADHD. That's far different than neurovascular effects or something you might see in neurosurgery; something different than a rheumatologist would see; and something different than a cardiologist would see. How might these be connected? How would ADHD be connected to other processes? Obviously, it has something to do with neuronal function, and the inflammatory cascade and cellular signaling.

Panoramic Connection between Omega 3 Fatty Acids and Physiological Function

The person who first talked about the panoramic connection between fatty acids and function was Dr. David Horrobin, unfortunately recently deceased and what a loss to all of us. Dr. Horrobin, was a medical school professor in Canada for many years, and was castigated by his colleagues. He talked about these myriad effects and was criticized, because people questioned how one agent could be effective for many different clinical conditions. Obviously, that sounds like "snake oil." It could be that Dr. Horrobin was prescient in understanding that mechanisms were more important than just disease pertaining to the role of fatty acids. Does this sound like a reasonable story to you in terms of your experience?

Essential Nature of the Inflammatory Response

JM: Jeff, that was beautifully said. The way I look at this is that in one way, it's as simple as it can be, but the mechanisms are complicated, as we know. It's simple when you ask what the body's normal response is. If you take a splinter and stick it into your hand or accidentally gouge it into your arm, there's an immediate inflammatory response. Monocytes, platelets, and all sorts of biochemical and biomechanical things happen to isolate the foreigner and protect the body from disease. It's a normal response to an insult to the body. This inflammatory response is evolutionarily and biologically essential for our survival on a day-to-day basis.

What happens when we poison our bodies with garbage, such as trans fatty acids that are ubiquitous, and all sorts of other bad stuff we feed ourselves, leading to the body's response being one of inflammation? It's the inflammatory response in so many different humoral, cellular, and cytokine ways. The complexity

of it is understanding this response. Maybe I'm speaking dogmatically, and I shouldn't, but very few physicians that I talk to think in terms of the way you just enunciated it. The common hypothesis to most of the diseases we treat involves the inflammatory response of the body to either foreign bodies, foreign proteins, infections, and so forth. The inflammatory response is a great discovery for me, in terms of my own patients.

Subdural Hematomas and High-Dose Steroids

Let's take subdural hematomas. When you get a chronic subdural, a neomembrane forms around the blood clot in the surface of the brain. There's neovasculature of the membrane and it continues to grow. There are many papers now showing that if you put these people on Decadron, on high-dose steroids, it reduces the inflammatory response. The neomembrane doesn't form and you can obviate recurrent subdural hematomas. Well, in that one instance, the inflammatory response is what you're blocking. I think you're right on with that and it's been my observation, as well.

The other observation that is a syndrome and a disease of the medical profession, is that, generally speaking, we still don't fix the body until it's broken. There's very little maintenance. An HMO physician having to see 50 or 60 patients a day doesn't have time to talk about prevention or preventive medicine. Maybe some do, but I think, and I'm speaking generally, that we physicians are trained, as you and I were, to make the diagnosis of the pathological abnormality after it's manifested in a disease or syndrome state. We don't pay much attention until the car is broken, before we fix it. Thoughtful physicians are becoming much more aware of this, moving in that direction themselves, and hence, bringing it to their patients.

Omega 3 Fatty Acids and Cardiovascular Disease

JB: You have treated us to so many great ideas about the application and implications of not only fatty acids, but the whole thought process of prevention versus treatment. I want to ask one last technical question that I'm sure is on the minds of some of our listeners after hearing you talk about subarachnoid hemorrhage and some of the clotting-related disorders. When Bang and Dyerberg did their first work with Eskimos in Greenland, they observed that people were eating up to 70 percent of their calories as fat, yet there was a very low incidence of cardiovascular disease. But they did indicate that there seemed to be a higher incidence of stroke. Some people feel that increasing omega 3 fatty acids may run the risk of clotting-related disorders. What's been your experience with that issue, and is this of clinical concern?

JM: That's an excellent observation and explanation. My understanding is that the Inuit Eskimos primarily had hemorrhagic strokes; I don't think they were thrombotic. That has led to just the kind of apprehension or concern that you mentioned. You also have to remember that they were ingesting 12 to 15 grams a day of omega 3s. The average American diet contains perhaps one gram of essential fatty acids, or omega 3s, per day.

In my practice, I will put patients on 3 to 5 grams of omega fatty acids a day. I usually don't go over 5 grams. In most of the studies in the cardiovascular and cerebral vascular literature, researchers have not administered over 3 to 5 grams a day that I'm aware of. I have operated on many, many patients who were on omega 3 fatty acids. I have not encountered any excessive bleeding tendency or problem in my practice, but that's not to say that it can't occur. I'm just not aware of very good evidence indicating that the upper limit of normal is. I think Barry Sears would recommend 5 to 10 grams a day in certain conditions. But if you do that, should you be monitoring hematologic factors platelets and things of that nature?

Warfarin and Omega 3 Fatty Acids

JB: How about patients on Warfarin or other types of coagulation management drugs?

JM: I don't put patients on omega 3s who are on Warfarin. It could be I just don't do it because in the literature it says you shouldn't. With low doses, you probably could, but I don't do that.

JB: I think your suggestion is that if there's any doubt, one should be following protime, which we would always want to do with patients on any kind of coagulation management.

I can't tell you how much we appreciate your time. You have an extraordinarily busy schedule, and you are a person with multiple responsibilities. Taking time out to spend with us has been a special treat.

Years ago, I met and spent a little time with a gentleman who had the nickname, the "Cod Father" -Dale Alexander- who wrote the first books for consumers on fatty acids. That was back early in the 1960s, and his thing was cod liver oil. If your joints are rusted, take cod liver oil and it will oil your joints. The mechanisms weren't really known then. It's fascinating how we've evolved through observation and then through reductionistic, analytical, and mechanistic logic to eventually get to where some of these things that seemed so strange at first now seem reasonable, in light of the explanation of the mechanism. You've taken us from the elite athlete, such as the Pittsburgh Steeler football player, to the marathon endurance athlete, to the average person who comes in as a member of the walking wounded, to post-surgical and pre-surgical types of applications. That is the future of this type of medicine and medical thinking, and we like to call it functional medicine.

Cod Liver Oil

JM: Two other brief points, Jeff, if I may. In terms of cod liver oil, we know why we don't take it the way it was given years ago. It's because of the odor and the noxious taste. However, new modern manufacturing techniques with micro-distilling products have extracted the mercury, PCBs, and the dioxins, as well as new encapsulation techniques so it won't be regurgitated. It makes it much more palatable and easy to take.

Second, relative to the Pittsburgh Steelers, I want you to know that Dick Rydze, Tony Yates and I take full credit for their 11 and 1 record.

JB: I suspected you might have at least a small feeling of pride in their accomplishments. May they go all the way to the Super Bowl and that we see you there. Thanks very much for sharing all this extraordinary information with us. We appreciate it.

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