August 2001 Issue | Kursheed Jeejeebhoy, MD, FRCP (C)

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Welcome to *Functional Medicine Update* for August 2001. This month's Clinician of the Month will describe the future of medicine in the 21st century and the role of nutrition in its application as we develop a functionally based medicine. Those of you who are interested in gastroenterology will be pleased to know that the focus of this month's interview is functional gastroenterology and its relationship to inflammatory conditions and immune dysfunction.

I want to begin by providing historical perspective on glucosamine sulfate in the management of osteoarthritis, degenerative joint disease. Just a few years ago, the traditional medical view of the use of glucosamine sulfate as a nutritional supplement for the modification and amelioration of osteoarthritic degenerative joint disease symptoms was that it was not based on good science. It was considered outside the bounds of conventional medicine. In August 2001, however, we find that view has changed. The change reflects the change in medicine at large, and how biologically based functional medicine is emerging from this discussion.

The goal of pharmacological treatment for degenerative joint disease, osteoarthritis, is to control symptoms of the disease, pain, and the limitation of function that occurs with the disease. Traditional treatment is with analgesic agents such as nonsteroidal antiinflammatory drugs (NSAIDs) or corticosteroid-like medications. The second goal of treatment is the remediation and possible cessation of the etiological mechanism of the disease, recovery, and healing. Drugs to treat osteoarthritis have been classified as symptom-modifying drugs and structure-modifying drugs. The more common NSAIDs, however, to not modify structure; they simply modify symptoms.

No drug among the joint structure-modifying medications actually interferes favorably with the progression of the disease. Although major advances have been made with the release of the selective cyclooxygenase-2 inhibitor (COX-2) drugs, which may reduce the risk of gastropathy, we still have no evidence that they contribute to healing the lesions that produce the degenerative changes associated with osteoarthritis. Thus, although NSAIDs may favorably affect joint damage in terms of pain and disability, they have no positive influence on the mechanism of action that creates the chronic degeneration of the joint.

COX-1 and COX-2

That leads us to a question about selective COX-2 inhibitors, which are some of the most frequently prescribed medicines of the last two years. They have enjoyed great popularity through direct-to-consumer advertising. We are told these selective inhibitors do not cause the inflammatory conditions of

the gut associated with traditional non-selective COX-2 inhibitors, such as ibuprofen or indomethacin. These traditional drugs, we are told, block both cyclooxygenase-1 and cycloxygenase-2 isoforms. The COX-1 isoform, the constitutive isoform, is very important for maintenance of mucosal integrity and immune defense of the mucosa, and prevention of its injury.

We are told, however, that the inducible COX-2 isoform can be upregulated in association with an inflammatory mediation. COX-2 can lead to systemic injury related to accentuation of the inflammatory cascade, but its downregulation will not necessarily have an adverse effect on GI integrity. The desire on the part of the drug companies was to create a drug that could selectively block the inducible form of cyclooxygenase, COX-2, without influencing the constitutive COX-1 form, the immunoprotectant isoform.

Celebrex: A Marketing Success Story

Celebrex, the first drug of this type to be approved for market, was met with significant enthusiasm, particularly following more than a year of media consumer education programs about the risks associated with traditional NSAIDs. Ironically, the release of these public education programs coincided with premarket approval of selective COX-2 inhibiting drugs. If we examine the funding for the studies published in journals like the *Annals of Medicine*, we find that the funds came from the same companies that had patents on the selective COX-2 inhibitors.

This was a good marketing approach. First you inform consumers and physicians about the dangers of the NSAID family. Then you follow with the release of supposedly selective COX-2 inhibitors. You build concern about gastropathy, the earliest warning signs of which for most patients are internal mucosal bleeding that requires an emergency room visit and hospitalization. The risk is real; the concern is real. Patients had been using these medications for many years before the public education program was undertaken, however, and that education program was coincident with the premarket approval for these medications that were supposed to protect against gastropathy

The track record in the two years since these medications reached the market has not been as positive as the early promotion promised. They have been more selective as COX-2 inhibitors, certainly, than NSAIDs like ibuprofen, indomethacin, and ketoprofen. They have not, however, necessarily prevented gastropathy. In a recent action, in fact, the U.S. Food & Drug Administration asked Pharmacia, the manufacturer and marketer of Celebrex, to send a letter to its doctor customers cautioning them about potential gastropathy Celebrex could induce in some patients. I will read a quote from the subsequent April 2001 letter Pharmacia Corporation sent its customers in response to the FDA concern about misleading information regarding the safety profile of Celebrex:

"…The FDA has objected to claims and promotional activities by or on behalf of Pharmacia that minimized the potentially serious risk of significant bleeding associated with the concomitant use of Celebrex and warfarin. Additionally, the FDA has objected to claims and promotional activities that: minimized the contraindication of Celebrex in patients who have demonstrated allergic-type reactions to sulfonamides; omitted important risk information; promoted Celebrex for unapproved uses; and made unsubstantiated comparative claims. Therefore, the FDA has requested that we correct these promotional messages accordingly.

"In post-marketing experience, bleeding events have been reported, predominately in the elderly, in association with increases in prothrombin time in patients receiving Celebrex concurrently with warfarin. Therefore, anticoagulant activity should be monitored, particularly in the first few days after initiating or changing Celebrex therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications.

Excerpts from Celebrex Letter

"Serious gastrointestinal toxicity such as bleeding, ulceration, or perforation of the stomach, small intestine, or large intestine, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs, including Celebrex.

"Celebrex is contraindicated in patients who have demonstrated allergic-type reactions to sulfonamides.

"Celebrex is contraindicated in patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.

"Celebrex is not approved for the treatment of acute pain. Celebrex is indicated for osteoarthritis and adult rheumatoid arthritis. Celebrex may be dosed 200 mg once daily for osteoarthritis and for rheumatoid arthritis 100 to 200 mg twice daily.

"The comparative safety of Celebrex and rofecoxib has not been determined. Celebrex has produced improvement in the signs and symptoms of rheumatoid arthritis comparable to the improvements produced by naproxen."

Cost of COX-2 Inhibitors

Interestingly, this class of drugs, the selective COX-2 inhibitors, in the last two years, has become one of the dominant families of drugs. The expense of these drugs, in fact, may be virtually bankrupting many of the world's disease-care delivery systems and reimbursements systems.

On a recent visit to Australia, I read a Sunday *Sun Herald* editorial in the June 10, 2001 issue, titled "The Pill That Could Break Medicare."

Celebrex seemed like a godsend for those with arthritis, but now it could break the Medicare bank. The author, Kathryn Shine, discusses the financial fallout from Celebrex. Patients moved from the reasonably inexpensive NSAIDs, the cost of which to the patient or the provider was less than $1 per day, to Celebrex or Vioxx, which are at least three times as expensive. Patients and doctors assumed these drugs would be safer, more effective, and more efficient for the healthcare delivery system. This article raises the question very strongly into some scrutiny.

Bankrupting the Healthcare System?

"It seemed like a win-win situation when the Federal Government agreed to subsidize the cost of the new arthritis drug Celebrex last August," Shine wrote. "The hundreds of thousands of Australians who suffer chronic arthritis pain were delighted they would save at least $40 for each script." However, since this has

occurred, the increase in cost to the healthcare system by this very expensive series of drugs, has virtually burdened the system to bankruptcy.

Consumer interest in these drugs was spurred on by direct-to-consumer advertising, which caused them to believe the drugs were safe and effective, and that they prevented the potential risk of gastropathy and serious intestinal bleeding that could occur with less expensive, over-the-counter drugs like ibuprofen. The subliminal seduction of consumers by direct-to-consumer advertising of pharmaceuticals has contributed to the rising interest in these expensive "new drugs," in the belief that they are safer and more effective. Even if Celebrex were not associated with side effects of gastropathy or nephropathy, its efficacy would still be in question. It may lower symptoms of pain and disability, but it has no effect on the disease process itself and the degeneration of connective tissue

We return, then, to the discussion of glucosamine sulfate, which the medical community has considered nonscientific and anecdotal. Glucosamine is a medication, nutritional supplement, nutraceutical, or food concentrate that may not only influence the signs and symptoms of disability of degenerative joint disease, but might also lead to healing of joint space lubricant substances, the complex sulfated mucopolysaccharides.

A recent paper published in the *Lancet* is titled "Long-Term Effects of Glucosamine Sulfate on Osteoarthritis Progression: a Randomised, Placebo-Controlled Clinical Trial." In this study, 212 patients were divided into two groups. All were patients who had osteoarthritis in the knee and degenerative changes. They were randomly assigned, half to a placebo group and half to a treatment group. The treatment group received 1500 mg of glucosamine sulfate orally daily for three years. The findings at the conclusion of this test were quite remarkable.

Results of Glucosamine Sulfate Trial

The 106 patients on placebo had progressive joint space narrowing, meaning the disease continued, with a mean joint space loss after three years of about .3 mm. In contrast, there was no significant joint space loss in the 106 patients on glucosamine sulfate. As assessed by various scoring and rating scales, symptoms worsened slightly in patients on placebo, compared with improvement observed after treatment with glucosamine sulfate. There were no differences in safety between the placebo group and the group receiving glucosamine sulfate.

The authors conclude the long-term, combined structure-modifying and symptom-modifying effects of glucosamine sulfate suggest it could be a disease-modifying agent in osteoarthritis. This conclusion is very different from what the selective COX-2 inhibitors provide. At best, these drugs improve symptoms with slightly lowered risk to gastropathy, but they do not necessarily improve the actual course of the degenerative condition in the joint.

What Is Glucosamine Sulfate?

Glucosamine sulfate is the sulfate derivative of the natural amino sugar glucosamine. Glucosamine is a normal constituent of glycosaminoglycans in cartilage matrix and synovial fluid as joint space lubricant substance. It can have various pharmacological actions in articular cartilage and joint tissue, helping to improve both connective tissue and joint space lubricant composition. Thus it leads to the healing of the

lesion, not just symptom modification of the inflammation.

More studies have been published since that clinical placebo-controlled trial. One recent paper, titled "Preferential Incorporation of Glucosamine into the Galactosamine Moieties of Chondroitin Sulfates in Articular Cartilage Explants," appeared in *Arthritis & Rheumatism*. In this study, investigators were attempting to find a mechanism by which glucosamine sulfate might have advantage in both symptom reduction and repair of damaged tissue in individuals with degenerative joint disease. The objective was to determine the metabolic fate of orally administered glucosamine in intact articular cartilage tissue. I emphasize that this is an *ex vivo*study done in animal tissues, but I think its model is applicable to understanding how glucosamine sulfate may work in human osteoarthritis, as well.

Glucosamine's Role in the Body

Glucosamine was taken up by the chondrocytes and incorporated selectively into hexosamine, but not into the hexuronic acid fractions. Galactosamine, a typical hexosamine, is a component of the glycosaminoglycan chain of articular cartilage, the so-called proteoglycans. The data also demonstrated glucosamine is the substrate of choice for the synthesis of galactosamine moieties of the chondroitin sulfates, incorporating at levels 300 percent higher than those with an equivalent amount of galactosamine. It could be described, therefore, as a preferentially taken up, conditionally essential nutrient. The results indicate that glucosamine facilitates the production of proteoglycan components that are synthesized through the hexosamine biochemical pathway and help in reconstruction of the connective tissue, as well as the joint lubricant.

In most youthful individuals, glucosamine as a matrix material may be adequately available for incorporation within chondrocyte synthesis of the proteoglycans. Thus it is already being biosynthesized by the body at adequate concentrations. It would not, therefore, be considered an essential nutrient. As a person ages, his or her body may experience trauma, and localized degenerative processes occur. The individual's body may not be able to synthesize glucosamine at needed levels. In these circumstances, therefore, glucosamine becomes what we call a conditionally essential nutrient. To functional optimally, the person may need to supply his or her body with augmented levels, beyond what the body can produce.

Functional Medicine and Degenerative Diseases

Functional medicine, functional nutrition, and functional genomics relate to a personalized preventive medical perspective, away from a rehabilitative perspective of older individuals with dysfunctional capabilities. I think, in the 21st century, we will see a definition of functional medicine emerge related to the translation of our pluripotential genetic possibilities into phenotypic function. The environment plays an important role in the expression stimulus of this genotype/phenotype conversion.

In the current example, people with degenerative joint changes, whose symptoms may make them candidates for selective COX-2 inhibitor drugs, may benefit from 1200 mg per day of glucosamine sulfate. Over the course of several months, it not only lowers the pain and disability indices, but it also seems to increase the body's synthesis of these proteoglycan materials, leading to healing of the lesions and recovery from the fundamental process in the development of the disease.

The Orthomolecular Model of Medicine for the 21st Century

I would use this as a specific interesting example of how the tide is changing. We are stepping across a threshold in medicine. As these papers appear in the literature and provide a new understanding of the aging process, we discover individual needs for specific substances that go beyond the Recommended Dietary Allowance. These discoveries are opening the door for functionally based medicine. This view is compatible with the orthomolecular medicine model Linus Pauling described in his landmark paper in *Science* magazine in 1967. Most of Pauling's medical colleagues considered that article an artifact, not pertinent to clinical medicine, very theoretical in referring to mass action effects, enzyme kinetics, and about pushing sluggish reactions by increasing substrate concentrations.

The average practicing physician in the 1960s thought these concepts were far beyond the bounds of what they would ever do in managing patients with age-related disorders. Now we see orthomolecular medicine is the language of the 21st century medicine. This is how we are going to personalize medicine and make it applicable, not just to the 70 kg white, Anglo Saxon average Protestant individual, but to each individual's 23 pairs of chromosomes in the chapters in his or her book of life.

Insulin Management

The same theme can be applied to insulin management and its influence on gene expression and age-related diseases. At the Eighth International Symposium on Functional Medicine, Dr. Gerald Reaven updated us regarding what is happening with insulin resistance and hyperinsulinemia. In *FMU* Clinician of the Month interviews in the past year, both Dr. Reaven and Dr. Schwarzbein discussed dietary modification of insulin resistance. More recently, a paper appeared in the *Journal of the American Medical Association*, which speaks strongly in favor of functional testing. The title of the paper is "Relation of Impaired Fasting and Postload Glucose with Incident Type 2 Diabetes in a Dutch Population." It is remarkable to think how the context of medicine is changing with the publication of these types of studies.

The study was designed to look at individuals with impaired glucose tolerance or impaired fasting glucose. It was, in a sense, a comparison between the World Health Organization criteria for dysinsulinism and dysglycemia, and the American Diabetic Association's criteria for establishing dysglycemia.

Revised Diagnostic Criteria for Diabetes

The ADA revised its criteria for establishing a diagnosis of diabetes and impaired glucose tolerance last year. It moved away from recommending the oral glucose tolerance test in favor of new, refined titer, fasting blood sugar/fasting glucose criteria. The World Health Organization criteria, however, have used both fasting blood sugar and fasting insulin and the results from a two-hour postprandial oral glucose tolerance test.

Is there value in taking the extra step, which is costly and more demanding to the patient, of a two-hour postprandial or a glucose tolerance test, or an insulin tolerance test after a 75 gm glucose load? Some people might consider that overutilization of medical services and an unnecessary expense. This paper in *JAMA* presents data about the difference in impaired glucose tolerance after an oral glucose challenge.

Evaluating the Oral Glucose Challenge Test

This was a population-based cohort study conducted from October 1989 to February 1992 among 1342 non-diabetic white residents in the Netherlands, age 50 to 75 years. Researchers measured fasting glucose concentrations and glucose 2 hours after a 75 gm glucose tolerance test, at baseline and follow-up four to eight years later, in 1996 to 1998. They sought to determine how many of these people who had impairments in their fasting blood sugar or their postprandial blood glucose after a 75 gm glucose load ultimately developed diabetes.

The cumulative incidence of diabetes was 6.1 percent, 8.3 percent, and 9.9 percent according to the WHO-1985, ADA, and WHO-1999 criteria, respectively. You will remember that the ADA criteria do not suggest using the two-hour postprandial sugar, and the WHO criteria do. The difference was 8.3 percent compared to 9.9 percent. The cumulative incidence of diabetes (WHO-1999 criteria) for participants with both impaired fasting glucose and impaired glucose tolerance, was 64.5 percent compared to 4.5 percent for those with normal glucose levels at baseline that would have been picked up by the ADA criteria. In other words, the participants with combined impaired fasting sugar (elevated blood sugar on fasting) and impaired glucose tolerance (which requires performing the 75 gm load test) was 64 percent compared with 4.5 percent for those who had normal fasting glucose and normal glucose tolerance. The incidence of false positives is reduced about two-fold relative to the fasting glucose test.. The odds ratios for diabetes (WHO-1999 criteria), adjusted for age, sex, and followup duration, were 10.0 and 39.5 respectively for those having isolated impaired fasting glucose or impaired glucose tolerance, and when they had both fasting glucose and glucose tolerance impaired, the ratio went up to 39.5, the relative risk. The striking thing about the study is that the application of only the fasting glucose criterion would have missed nearly one third of the subjects who went on to develop diabetes.

Value of Thorough Testing

The study shows the likelihood of developing diabetes was strongly related to both fasting blood sugar impairment and impaired glucose tolerance at two hours, and the presence of both factors gave a much more sensitive marker for later-stage incidence of diabetes. I emphasize the importance of functional markers, and impaired glucose tolerance is a functional marker for stressing the system with an oral glucose load and assessing the system’s ability to accommodate that stress.

What we are saying is that the lack of organ reserve in an individual who is dysinsulinemic will be seen as an aberration in both postprandial insulin and postprandial glucose. We call this impaired management of glucose and insulin, insulin resistance, dysinsulinism, hyperinsulinemia, which is a much stronger predictor of cardiovascular disease and potential risk of diabetes and other factors than fasting blood sugar alone. We are only halfway there when we understand that functional abnormality in the patient, however. We then have to determine how to modify that relative uniqueness through the genotype/phenotype connection.

Maturity-Onset Diabetes Study

Another paper in the *New England Journal of Medicine* is titled "Prevention of Type 2 Diabetes Mellitus by Changes in Lifestyle among Subjects with Impaired Glucose Tolerance." Participants in this study were individuals with impaired glucose tolerance and normal to slightly elevated fasting blood sugars. In other words, they were primarily maturity-onset, insulin-resistant hyperinsulinemic individuals who did not demonstrate fulminating type-2 maturity-onset diabetes. Their condition would have been picked up

by a two-hour postprandial insulin and glucose evaluation, however.

In this study, 522 middle-aged, overweight subjects (172 men and 350 women; mean age, 55 years; elevated mean body-mass index). A BMI above about 26 or 27 would be considered obesity, and the mean in this group was 31, with impaired glucose tolerance that was measured by the oral glucose tolerance test. Each subject was assigned to an intervention group in which they received either the standard diet and standard information, or individualized counseling aimed at reducing weight, total fat intake, intake of saturated fat and increasing intake of fiber, as well as physical activity. An oral glucose tolerance test was performed annually; the diagnosis of diabetes was confirmed by a second test. The mean duration of follow-up was 3.2 years.

Effects of Diet and Exercise on Progression of Diabetes

The results were quite remarkable. Individuals whom the glucose tolerance test identified as having impaired glucose tolerance, and who were likely to become diabetic, could reduce the progression of this condition into diabetes by selective lifestyle intervention using diet and exercise. The investigators conclude that type-2 diabetes can be minimized by lifestyle changes in high-risk subjects. They identified those at risk, I add parenthetically, by functional testing, the fasting blood sugar in combination with the glucose tolerance test.

This is exactly what Dr. Reaven told us two months ago in his COM interview. He said it is possible to modify the very specific nature of the signals that go to the genes that control glucose transport. This modification is accomplished through lowered saturated fat intake, increased micronutrient density of the diet, lowered intake of simple carbohydrate, and regular activity. In this way, one can signal a different function through the peroxisome-proliferated activated receptors a and g , which have a regulatory effect on mitochondrial function. They participate in cross-talk with insulin and influence protein tyrosine kinase expression. They affect cells that ultimately control not only glucose transport, but also a variety of cellular personalities that lead to inflammation and possibly adipocyte hypertrophy, which causes fat accumulation and changes triglyceride storage.

Functional Evaluation of Diabetes Risk

The oral glucose tolerance test facilitates the assessment of the individual’s propensity to type II diabetes. It also should encourage the individual to modify behavior in order to change phenotype. Together with a functional medicine-oriented practitioner, he or she can determine specific diet intervention therapy to meet his or her needs and achieve a positive clinical outcome, the highest evidence-based response to this type of a diet intervention therapy.

We are witnessing an interesting transition in medicine. We have moved from diagnosis based on the average and medical taxonomy to examining the metabolic underpinnings of the condition and personalizing intervention based on a person's individual need.

Insulin Resistance as a Marker

Insulin resistance could be one of the "missing links" that tie metabolism, genetic expression, diet, and environment together with age-related diseases. Diabetes is not the only disease for which

hyperinsulinemia/insulin resistance is a risk factor. Cardiovascular disease, irritable bowel, and inflammatory bowel disease are also associated with hyperinsulinemia. Inflammatory conditions of joints and other tissues are associated with insulin resistance and hyperinsulinemia. Insulin dysregulation is a central feature in aging or age-related diseases, and a modifiable risk factor of biological aging.

Gerald Reaven is a coauthor of a paper on that topic in *Free Radical Biology & Medicine.* The authors talk about hyperinsulinemia and call it the missing link among oxidative stress and age-related diseases. The authors point to mounting evidence for Denham Harman's hypothesis that oxidative reactions are one feature of accelerated biological aging. Free radicals and their relationship to oxidative stress create cellular damage. In diabetes, it can lead to the damage of the eyes, nerves, or kidneys we associate with the secondary side effects of diabetes.

Hyperinsulinemia as a Functional Marker

Hyperinsulinemia may also have functions beyond the secondary side effects of diabetes that promote aging. These functions may be independent of the elevations of blood sugar. Elevated levels of insulin in tissues or in plasma influence gene expression in such a way as to increase the messengers of alarm. The alarm messengers are associated with cytokines or inflammatory processes that cut across processes like metastatic injuries, inflammatory problems, and coronary heart disease.

By its effects on the inflammatory process, antioxidative enzyme systems, and free radical generation, hyperinsulinemia could enhance oxidative stress and serve as a pro-aging phenomenon. It might also explain why calorie restriction, in part, lowers the risk or the rate of biological aging in animals. By lowering insulin flux by calorie restriction, one might then get increased regulation of oxidative metabolism and lowered inflammation messages to the genes. Reaven is right on the point when he asks if we see a convergence of various mechanisms of which insulin plays part of the role.

Modification of Insulin

How do we modify the signals of insulin that are producing some of these untoward phenotypic expressions? Obviously, we talk about dietary modification, exercise increasing the translocation of the GLUT-4 transporter to the cell membrane so more glucose can be transported across the cellular membrane thus improving the energy economy of the cell.

We have discussed these processes in previous issues of *FMU,* and Dr. Reaven alluded to them in his presentation, as did several other clinicians who have focused on this insulin/protein/carbohydrate metabolism connection. Dr. Schwarzbein presented metabolic data that were similar to those of Dr. Bill Evans when he talked about the biochemistry of exercise and its relationship to insulin sensitivity.

Alpha-Lipoic Acid and Protein Turnover/Glucose Transport

Lipoic acid is a nutrient we have also explored in previous *FMU* issues. Dr. Burt Berkson talked about this nutrient some time ago as a COM. He talked about it as a liver-protective nutrient for hepatotoxicity, caused hepatitis virus and toxins like *Amanita,* the death cap mushroom, and how we can protect against liver toxicity. N-acetyl-cysteine plays a role as well, but lipoic acid is a principal player.

We recognize now that lipoic acid does more than just protect against hepatotoxic injury and oxidative stress. It also plays a role in improving insulin signaling and reducing the dysfunction that occurs in hyperinsulinemia/insulin resistance. The results of an animal study published recently in *Free Radical Biology & Medicine* describe this role. Investigators evaluated the role of a -lipoic acid (ALA) on stimulating glucose transport and enhancing the process by which insulin works in skeletal muscle from insulin-resistant animals. They showed that therapeutic administration of a -lipoic acid improved glucose transport.

ALA and Diabetes Treatment

The findings suggest the cellular mode of action for ALA is restricted to signaling factors unique to the activation of glucose transport. In Europe, supplemental a -lipoic acid is administered at levels from 200 to 1000 mg per day. It is given to individuals with frank hyperinsulinemia or insulin resistance, who have elevated triglyceride and reduced HDL levels, the hallmarks of insulin resistance and metabolic syndrome X. Patients may experience a favorable outcome using this supplementation, in terms of gene expression and the regulation of glucose transport.

We have focused our discussion on a -lipoic acid in relation to its antioxidant effects. We should also think of it as an insulin-modulating substance. Doses for humans can generally be graded up from 200 to more than 1000 mg per day. You should exercise caution in using a -lipoic acid in insulin resistant/hyperinsulinemic individuals, however. If an individual has a very high level of plasma insulin and you stimulate insulin action too quickly, you can get a hypoglycemic response. I generally suggest starting at a lower dose and grading up to the dose that matches or titrates against that particular person's glucose and insulin needs.

Waist-to-Hip Ratio as Evaluation Tool

Incidentally, waist-to-hip ratio can be a useful anthropometric tool for evaluating patients who may be at risk for insulin resistance, along with the fasting triglyceride and HDL ratio. A fasting triglyceride-to-HDL ratio greater than 5:1 is a strong indicator of the potential for insulin resistance. An increased waist-to-hip ratio also tracks back against impairments in two-hour postprandial glucose and insulin levels. That was shown in the *JAMA* paper I discussed earlier.

Circulating Antibodies and Malondialdehyde-Modified Proteins

Individuals who exhibit insulin resistance, poor oxidative phosphorylation, and more anaerobic glycolysis to produce energy because they are not getting the proper oxidative breakdown of glucose in the mitochondria, also experience more oxidative stress. They are producing more oxidants, and the resulting oxidative stress leads to damage to unsaturated lipids. These could be unsaturated lipids in the plasma, or in membranes of cells. The damage to these lipids produces a byproduct called malonaldehyde, or malondialdehyde. Malondialdehyde is a very small molecule that reacts rapidly with proteins to form Schiff bases by reaction of a carbonyl group with the E-amino group of lysyl residues in proteins in plasma.

Damaged Proteins and Autoimmune Disorders

A simple chemical reaction of involving this lipid peroxidation byproduct or rancidity product of lipids, which comes from the free radical oxidation associated with dysglycemia, results in damaged proteins. The body may perceive these damaged proteins as strangers, causing the body to become allergic to itself as a consequence of cross reacting with these malondialdehyde-modified proteins.

That topic was recently reviewed in a paper published in *Free Radical Biology & Medicine.*The authors show that circulating antibodies that recognize malondialdehyde-modified proteins are found in healthy subjects. The higher the level of oxidative stress, and the higher the dysinsulinism and dysglycemia, the more malonaldehyde produced, the more damaged proteins, the higher the titer to these proteins and the more likelihood of cross-reactivity to the immune system, producing an inflammatory cascade. This may be why we see immune-like dysfunctions in diabetics and individuals with dysinsulinism, because we start building higher titers, not only of the glycosylated proteins, but also of the malonaldehyde-length proteins.

You may not see elevated fructosamine in your patients. They may not have frank dysglycemia or elevated glycohemoglobins, so they don't have a lot of glucose reacting with hemoglobin proteins. Therefore, you may not be concerned about activation of the immune system. But are you looking at the byproducts of lipid oxidation, the malonaldehyde which comes from free radical damage? This process may be leading to an antibody against these malonaldehyde-modified proteins, the Schiff bases that create some of the immunological effects. A combination of glycated proteins, the so-called advanced glycosylation endproducts (AGEs), as well as malonaldehyde-modified proteins from oxidative stress from uncoupling of mitochondria dysinsulinism, gives rise to a double-barreled risk to immune dysfunction.

Improving insulin stimulation, insulin signaling, and glucose transport can have effects across many organ systems and many subspecialties in medicine, including cardiology, diabetes management, rheumatology, gastroenterology, oncology, and neurology. All are related to dysfunctions in the insulin-signaling and glucoregulatory pathway and are an interesting example of the emergence of functional medicine models.

Susceptibility Tied to Genotype

Given the new genetic information we have at our fingertips, we now recognize specific genotypes that are more susceptible than others to oxidative stress, vascular and neurological injury, and lipid modification of the diet. We are moving into an age of functional-based, or a functional genomic-based medicine. New genomic probes and methods of evaluating genetic uniqueness made available by the Human Genome Project are providing new assessment tools for the clinical laboratory.

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We have spoken in the past about the importance of homocysteine measurement in functional evaluation. Another marker that is correlated slightly with homocysteine is the apoE gene. The apolipoproteins function in and include the lipid transport protein apoA, apoB, and apoE genes. These apolipoproteins, which transport lipid to form lipoproteins, have different personalities and different effects on the vascular endothelium and other tissues. The apoE gene exists as three common alleles: apoE2, apoE3, and apoE4.

A recent speculative paper published in *Medical Hypothesis* is titled "Medical Utility of ApoE Allele Determination in Assessing the Need for Antioxidant Therapy." The authors point out that the apoE4 allele is associated with a variety of conditions that range from Alzheimer's disease to coronary heart

disease to stroke and postoperative cognitive dysfunction, and also head trauma. Boxers and other athletes who have experienced head trauma have a higher risk of dementia if they carry the apoE4 allele.

ApoE4 and Increased Oxidation Capacity

We now know that purified apoE *in vivo* protects cells from hydrogen peroxide cytotoxicity, and toxicity induced by b -amyloid peptides, with apoE2 and apoE3 having a much higher protective ability than apoE4. Increased levels of apoE4 actually can result in much decreased antioxidant protection against oxidant stress conditions. Increased levels of oxidative stress would be predicted to enhance b -amyloid peptide deposition, which may, therefore, be most likely to occur in those who carry the E4 alleles, according to this article. It has been observed that plasma lipoproteins from apoE-deficient mice are more susceptible to *in vivo* oxidation than lipoproteins from wild mice. In addition, mice lacking apoE are prone to atherosclerosis.

Individuals who carry the apoE4 allele, therefore, may have a significantly decreased endogenous antioxidant capacity, or increased oxidation capacity than individuals who do not carry the apoE4 allele. ApoE4 is a genotypic marker for oxidant stress, inflammation, and lipid sensitivity. An article in the *American Journal of Clinical Nutrition* indicated apoE4 is highly cholesterol sensitive and more inflammation prone, whereas apoE2 is more sucrosensitive and more susceptible to hypertriglyceridemia and insulin resistance. ApoE3, the most common allele in the American gene pool, constitutes 50 percent or more of the apoE variants. ApoE3 is not necessarily cholesterol- or sucrosensitive. Evaluation of apoE genotype would be a good addition to genotypic evaluation as practitioners begin to determine how to personalize therapy.

INTERVIEW TRANSCRIPT

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JB: This month’s Clinician of the Month is Dr. Kursheed Jeejeebhoy. For the last 20 years, through his work in parenteral nutrition, Dr. Jeejeebhoy has been a thought leader in understanding the role of trace minerals in human nutrition. Dr. Jeejeebhoy is a gastroenterologist who also has a PhD from the University of London. He is a professor of medicine in the department of medicine, department of nutritional sciences, and the department of physiology at St. Michael's Hospital in Toronto, Ontario.

He has an extensive publication list in a wide range of fields and discoveries. One paper that relates in particular to today’s discussion appeared in the Journal of Parenteral and Enteral Nutrition. In this paper, titled "Nutrition Support in Clinical Practice: Review of Published Data and Recommendations for Future Research Directions," Dr. Jeejeebhoy presents a historical perspective of what we now know as "essential

nutrients." His own work with total parenteral nutrition has increased our understanding in many of these areas. Dr. Jeejeebhoy, welcome to FMU. How did you become interested in nutrition?

KJ: Thank you, Jeffrey. It's a pleasure to be on your program. My interest in nutrition was actually quite simple. When I came as a young doctor on staff, I was given the worst patients with GI problems. I came rapidly to realize that the really seriously sick individuals were not sick from their gastrointestinal disease. They were sick because their gut was unable to nourish them properly. As a way of treating them, I realized the one thing my colleagues had not done was to look into their nutritional status. That's what got me into the area of nutrition. In gastrointestinal disease, we often fail to understand that a lot of the morbidity, and perhaps some of the mortality, is related to malnutrition, and not to the bowel itself.

Gastroenterology and Nutrition

JB: Because gastroenterology, as a medical subspecialty, is so very involved in the digestion and assimilation of nutrients, one might expect it to have a great deal of interest in nutrition. I have often wondered why that is not the case and there seems to be so little interest in nutrition in the clinical practice of gastroenterology.

KJ: I think it's mainly because of training. Nutrition is often taught in endocrinology; and endocrinologists have been interested in nutrition. So are hematologists. The area of nutrition is so broad that it tends to get diffused among different subspecialties, and I suspect some of the difficulty arises because of the subspecialization. Second, the training in gastroenterology, as it has evolved, has gone either into the area of intestinal function, where most basic researchers work, or into endoscopy, which is a mechanical process.

Unfortunately, because of this polarization, the middle ground, which is so important to patients, is often forgotten. The American Gastroenterological Association now recognizes this area needs to be developed. There is, in fact, a specific section on nutrition and obesity. So they are looking at both sides of the spectrum. A very active group is promoting nutrition as an important subspecialty in gastroenterology.

Chromium

JB: Please share your chromium story. Many of our listeners may be unfamiliar with that history. It might be helpful to see how these advances in understanding are made.

KJ: As you know, patients with gastrointestinal disorders sometimes have historically had a major part of their small intestine surgically removed. Once the small intestine has been removed, the body’s ability to absorb nutrients is severely compromised. These patients had severe malabsorption, and we had to feed them intravenously. When you feed them intravenously, you have to put the many different elements that exist in food into a mixture. We calculated that 42 or 43 different nutrients are in a TPN mixture as it is given today.

When we first did that, I wasn't as familiar with a number of the trace elements as I am now. We had a patient who, after being on IV feeding with what we thought was a pretty complete mixture, started to get a loss of sensation in her lower limbs. She informed me she felt as though she was "walking on cotton wool." When we investigated, I found she was diabetic. However, the problem of diabetes was somewhat

of a puzzle to us, because she was fairly young and had no family history of diabetes. In addition, her diabetes was characterized by severe injury to the nerves in her lower limbs. This was an unusual situation and for about a year, I didn't quite understand what was happening.

Chromium Deficiency-Induced Diabetes

Just by accident, I happened to read the studies by Dr. Walter Mertz and his colleagues in Beltsville, Maryland, in the agricultural unit there. I realized that chromium was important in insulin action, and that animals that had been made chromium-deficient became metabolically diabetic. That made me look into this patient once again, and I thought she was perhaps chromium-deficient.

That is indeed what we found. Her blood levels of chromium were reduced, and we decided to give her some chromium. The pharmacist was quite confused as to how to do this intravenously, but we then put together a mixture and infused it with chromium. We were pleasantly surprised to find that, first, her diabetes disappeared, and second, over a period of months, her nerve damage improved dramatically. Not only subjectively, but also by nerve conduction studies, we showed there was marked improvement. We then realized that, in fact, she had chromium deficiency, and this was probably the first definitely published case of human chromium deficiency.

Human Chromium Deficiency

JB: From that work, how quickly did your colleagues accept the fact that chromium was a missing essential nutrient in TPN and start to realistically consider the need for it?

KJ: It was a slow process. When I made that observation from a single patient, my colleagues were skeptical, and I don't fault them for that. But then, subsequently, several other individuals noted the same thing in their patients. They became sensitized to the fact that the diabetes that was occurring in this situation might be due to chromium deficiency. So they looked at their patients afresh, and several more publications came out showing chromium deficiency. It got accepted and, in fact, the recommendation now for the trace element mixture is that it contains chromium. Once other people reproduced what we had found, this became accepted.

Individual Trace Mineral Needs

JB: Many doctors have little understanding of the role trace and ultra-trace elements play in nutrition. I guess we've assumed that because they're needed in such small amounts they must always come along with a standard diet. Do you know of any data on the biological heterogeneity of the population relative to trace mineral needs?

KJ: That is an excellent question. I think the future of nutrition is really the interaction between one's genetic makeup and his or her diet. I don't think one diet fits everybody. It's a very important point you bring out, namely that people are heterogeneous genetically and, therefore, diets and nutrient needs might be altered. The term I would like to introduce is "conditioned nutrient requirements." I'd like to change the subject slightly but remain in the area of micronutrients, to explain what I'm talking about.

If an individual eats a diet that is very rich in carbohydrates, for instance eats a lot of rice, and takes

absolutely no vitamin B, he or she will develop a severe vitamin B deficiency. On the other hand, if he or she does not eat carbohydrate and does not take vitamin B, the person will not develop the signs of vitamin B deficiency. In other words, the high carbohydrate diet conditions the individual to an increased requirement for vitamin B, particularly thiamin.

Conditioned Nutrient Requirements

In the same way, some individuals are insulin resistant. This means that when they eat a small amount of carbohydrate, or any kind of energy food, their insulin levels go up extremely high. These individuals do poorly on high-calorie diets. They do better when they're somewhat starved, and they are the individuals who become diabetic in the long run. On the other hand, other individuals are very insulin sensitive. They can take a lot of energy and not have high insulin levels, and they can pack away large amounts of calories without having any problems. The requirements for a number of nutrients, whether they are macronutrients in the form of energy, or micronutrients in the form of vitamins, are conditioned by what you eat and by your genetic structure.

Having said that, there are a number of very essential nutrients, including zinc, selenium or antioxidants, copper and chromium. Their requirements are conditioned by one's genetics. For example, there's evidence that the Hispanic population seems to have a lot of gestational diabetes, and studies indicate that chromium supplementation seems to benefit them. This may not be true for others who do not have that kind of problem.

Changing Nutrient Needs

JB: Functional genomics is playing a major part in the evolution of nutrition and medicine. Your work has contributed to our understanding of the role of these variables, both in crisis/critical care and in ambulatory care for patients. In a review article last year in Nutrition Reviews, Walter Mertz discussed the evolution of the Recommended Dietary Allowances and how these single numbers that were stated as needs for individuals may have to be modified as we move forward, to account for these biological variabilities.

KJ: Yes, the RDAs, the Recommended Dietary Allowances, are no longer acceptable. These committees are looking into upper and lower ranges. They look at a lower figure as an index of the floor below which you get deficiency, and an upper figure that represents a level beyond which you might get some toxicity. You have to recognize that food can be both beneficial and toxic. If you eat a lot and become obese, that's not very good. Similarly for a number of vitamins, a small amount is good and very large amounts might be toxic. Vitamin D and vitamin A are examples. We have to identify the band at which the requirements have to be met. Disease modifies this band by altering absorption and by metabolism. Similarly, genetics modifies it by causing people to require more or less of some of these micro- and macronutrients.

Sarcopenia, Muscle Mass, Nutrition, and Aging

JB: Dr. Irvin Rosenberg used the term sarcopenia to describe body composition and muscle mass in individuals in relation to aging and nutritional status. You published a paper on phosphorus 31 NMR, a study in which you looked phosphocreatine recharge rates in individuals relative to their nutrition status. Would you tell us about muscle mass aging and nutritional status? Does this biomarker have value for the

average clinician in following patients?

KJ: I have been interested not only in the composition, but how well that composition works. That's really the basis of the P31 NMR studies. To explain the historical perspective, I was impressed by the fact that when we tube-fed or intravenously fed malnourished, hospitalized patients who had lost a lot of weight and were not moving around, they very quickly became extremely active and felt really well. Measurements of their muscle mass or body composition indicated it had changed little at that stage. Now that's not to say that we wouldn't like them to gain more weight and get more muscle mass. Certainly, that's more beneficial. But we were impressed with the fact that even when they were very sick, if you fed them, they had a marked improvement in their performance. That made me look into the question of muscle performance.

One of the more interesting studies we did was in individuals who were anorexic, who had tremendous weight loss and were quite wasted. When we fed them, we found very quickly that their muscle potassium content went up and their ability to contract and relax their muscles improved greatly long before they actually had a change in their body mass. We wanted to know why that happened. We used P31 NMR.

Phosphorus 31 NMR Study

Phosphorus is a component of most cells as a part of the energy-producing system, which is called ATP and phosphocreatine. Muscle contraction relaxes by receiving energy by the breakdown and resynthesis of ATP in the muscle. Using phosphorus 31 NMR, it's possible to follow the breakdown and resynthesis of this particular component without actually invading the body. In other words, we didn't have to take biopsies; we just put a coil around the leg and followed this process.

We found that malnutrition was associated with a markedly reduced rate of synthesis of ATP in muscle. I think what actually happens is that when you are malnourished the energy produced by the ATP system is reduced. The ability of the mitochondria, the organelles within the cell that generate the ATP, is actually defective. More recently, we've shown how that defect occurs. Because these organelles are not producing ATP, the muscle is not able to contract and relax effectively. Also, resynthesis of muscle, which means building up the muscle mass, depends on protein synthesis. Protein synthesis is very energy dependent. Apart from improving function, to improve the muscle mass, you have to have better function of the mitochondria.

Now coming back to your initial question, Rosenberg pointed out that elderly people have sarcopenia; they have loss of muscle mass. In addition, they also have reduced muscle function. Nutrition is very important initially in improving function. Then, on a longer-term basis, together with exercise, it actually increases the mass. The importance of both function and structural mass has to be emphasized in this context.

Mitochondrial Function

JB: We've talked, over the last three years, about mitochondrial function, the mitochondrial genome, induced damage by oxidative injury to mitochondria, and the effects it has on functional performance through oxidative phosphorylation. What did you find as it relates to the defect in mitochondria in these

individuals?

KJ: That's very interesting. We've just published a paper in the American Journal of Clinical Nutrition. It was an animal study, but we have subsequently done this in humans, and we have another paper in preparation. Essentially what we've found is that when an animal is malnourished, even very marginally, by just reducing its intake of food by about 20 percent, the mitochondrial complexes are reduced in activity. Within the cell are little organelles called mitochondria. When food is metabolized, the electrical charges of the food are passed along a number of units in the mitochondria. The charging of the membrane of the mitochondria generates energy. It's almost like a little battery. The electrical charges flow along these little complexes.

We have found that these complexes become less effective in transporting electrical charges with malnutrition, but not all the complexes. As a matter of fact, we've found this with complex 1 and complex 2 and complex 3. Complex 4 and complex 5 where ATP synthesis occurs is normal. However, even though they're normal, the electrons do not flow to the complex 4 and 5 and that's why there's a problem. We further found that protein feeding seemed to be particularly effective in restoring these complexes. Another interesting thing we found was that not only were the muscle complexes of mitochondria reduced in activity, but so were the lymphocytes, which explains why individuals who are malnourished also tend to become more susceptible to infection. In humans, we have used lymphocyte measurements to look at the effects of fasting and feeding and, in fact, restoration of mitochondrial function by feeding.

Electron Leakage with Oxidative Damage

JB: If the electrons not flowing effectively to complex 3 and 4, but ATP levels are okay, does it mean there is there some electron leakage with oxidative damage?

KJ: Yes. You're absolutely right about that. As you know, when the flow of electrons is inhibited across the complexes, these electrons leak and form so-called free radicals. The free radicals can damage the mitochondria, which in turn can reduce the function. I think basically that you're absolutely right. That's probably what goes on. Malnutrition might not only have an effect in reducing the flow of electrons, but it also might increase damage to the mitochondria, which is one of the things we do notice.

Measuring Breath Pentane

JB: In a paper you published in Free Radical Biology & Medicine 10 years ago, you talked about breath pentane as a measurement of functional oxidative stress. Do you feel this would indicate oxidative stress situation is occurring in these animals?

KJ: Yes, I think so. Not only is the complex is downregulated, but because of the block in electron flow, there would be added production of free radicals. At the moment, we are studying it at the mitochondrial level itself. In humans, however, breath pentane measurement might be used as a less invasive way of monitoring the same process.

The Role of Antioxidants

JB: You have done quite a bit of work in the area of vitamin E and other antioxidants. Do you think

there's a role to be played here as well?

KJ: I think there are two aspects to this. Antioxidants definitely are protective, but what may be even more effective in terms of oxidative stress, is that they promote the flow of electrons so you don't get this leak. The concept I'm coming down to is that we need to attack this process in two ways. One way is to protect the cell with antioxidants, particularly selenium, glutathione peroxidase, glutathione itself, and vitamin E. On the other side, there might be a benefit in actually promoting electron flow, which means improving ways by which the mitochondria function. This area has not been explored, and I suspect it's probably going to be the new frontier in treating oxidative stress.

Oxidative Stress, Nutrition, and Inflammatory Conditions

JB: As you have shown us over the years, particularly in the GI area, inflammatory conditions are associated with oxidative stress. What role do inflammatory mediators and oxidative stress play in inflammatory conditions like Crohn's disease or inflammatory bowel disease? And what role does nutrition play there?

KJ: Inflammation ultimately acts through the process of oxidative stress. Most of the cells we have that engulf bacteria and kill them do so by the process of oxidative stress. They produce free radicals, which kill these bacteria. Similarly, when T cells kill tumor cells, they do so by the same process, so oxidative stress in that sense is a positive thing.

On the other hand, in some situations, this process gets out of hand, as in critically sick individuals where initially there is increased oxidative stress to try and control the inflammation. If the bacteria are killed but the process continues unabated, then, of course, oxidative stress starts damaging the tissues locally. You get the surge syndrome, in which oxidative stress and inflammation continue, become injurious, and result in morbidity to the person.

Nutrition and Inflammatory Reactions in the Gut

In the same way, in the gut, with inflammatory bowel disease, you could say a futile and excessive inflammatory reaction is associated with increased oxidative stress. For example, a colleague of mine who is working in this area has found that if you give iron by mouth to animals that have inflammatory bowel disease, oxidative stress in the gut increases and, in turn, actually increases injury to the bowel. In a situation in which people have gotten bowel inflammation, nutrition might be great, but we might have to modify it so that the iron might have to go by a different route rather than by mouth.

There are a number of these very interesting interactions between nutrition and the gut. Also, the omega 3 fatty acids have an anti-inflammatory effect, and increased intake of these omega 3 fatty acids might also be protective. In fact, they have been shown to be protective in other inflammatory reactions, such as rheumatoid arthritis, for example. There is some evidence they also work well in colitis and Crohn's disease. There are ways of delivering antioxidants to the inflamed area, and by modifying the diet, it might be possible to modulate a number of inflammatory conditions.

The Gut as a Signaling Organ for Inflammatory Processes

JB: Considerable literature has recently been published regarding the reticular endothelial system of the gut, including the gut-associated lymphoid tissue (GALT) and the mucosal-associated lymphoid tissue (MALT). This seems to be an action point for many of these inflammatory processes that can increase the concentration of systemic inflammatory mediators. Do you feel the gut is a principal organ, kind of a signaling organ for the body related to these inflammatory mediated-related processes?

KJ: The gut is extraordinarily complex. Bacteria there live in harmony with an immune system that is extremely active but in some ways downregulated. The immune cells in the gut are actually not just static; they move through the thymus and come back to the gut. The gut itself is a huge immune organ. Not only is it an immune organ, but it is also exposed to a lot of stimuli in the form of bacteria. In addition, when we eat food, we introduce into the bowel a whole lot of other things that stimulate the immune system.

So there is no question that the gut is a very important area of not only local immunity, but also influencing immunity across the body. There is also the whole area of translocation of bacteria to the gut, which in itself might result in injury to areas like the liver, the heart, and systemically in general. Translocation might be responsible for some of the more serious consequences of patients in ICUs. The gut is very important in that regard, and nutrients that might protect or alter the lining of the gut might be very important in preventing disease in the rest of the body.

Association between Gut and Heart

JB: One thing you are doing in your laboratory and in your clinical work is collaborative work with Dr. Sole on the effects of antioxidants on cardiac function. Knowing there is a connection between the gut endotoxemia and cardiac dysfunction, do you see a connection between the gut and the heart in some of these processes?

KJ: Some years ago we were very interested in looking at the effect of cytokines, particularly tumor necrosis factor, which is now known to be one of the mediators of systemic inflammation and nutrition. We noted that when this cytokine becomes active, animals don't eat and they lose weight. It's exactly what happens to people who get inflammation, and we thought a good way of dealing with this would be to feed them so that their intake of food would not be reduced.

When we did that, we found the inflammation actually became somewhat worse. But we did find there's a difference in the type of nutrients we were giving them. If we gave a lot of carbohydrates or fats, we found the action of TNF was increased. But if we gave protein, it wasn't. It appears, in the face of this kind of inflammatory reaction, that modification of the diet to emphasize certain nutrients, and not others, might be very important.

Cardiac Failure Studies

In my work with Dr. Sole, we have been looking at cardiac failure. In that context, we did a controlled trial using vitamin E, which was published in the American Journal of Clinical Nutrition. We found that vitamin E actually failed to reduce oxidative stress in the heart, but giving individuals components such as coenzyme Q, carnitine, and taurine, which promote electron flow through the mitochondria, had a beneficial effect. It increased the levels in the myocardium and actually improved cardiac function.

This has just appeared in the Canadian Journal of Cardiology. We took animals with specific cardiomyopathies and showed that by giving this combination, we were able to reduce oxidative stress as well as improve reticular function.

Conditioned Nutritional Requirements

JB: As you look ahead, what do you see regarding the future of clinical nutrition and its relationship to medicine?

KJ: I think the area on the horizon should be conditioned nutritional requirements. Genetics, disease, and environmental circumstances alter nutrition. Unfortunately, what's happened with our nutritional research is that people are trying to find one cap that fits everybody. Well, that's not going to happen. I think our future research is going to be understanding the interaction of nutrition regimes on the one hand, with disease, infection, cancer, and so forth on the other hand, and environmental factors on a third side. When we start to do that kind of research we will see some spectacular results.

Optimism about the Role of Nutrition in the Future of Medicine

JB: Dr. Jeejeebhoy, you have provided us with optimism for the future and the increasing role of nutrition in the way we manage patients. Thank you for your contributions over the years. I wish you great success as you move forward in your work..

KJ: Thank you. I've enjoyed being on the program

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