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This month, we will discuss applications of functional medicine to chronic illness. We will review four areas. We'll have an update on insulin resistance and also review gut dysbiosis and its relationship to inflammatory disorders. We will also discuss the relationship of defects in detoxification to chronic symptoms and disease risk as well as oxidative stress, mitochondrial dysfunction, and increased oxidative signaling and their relationship to increased cell damage, apoptotic cell death, and loss of cellular function.

Let's start off by quickly reviewing the Northwest Lipid Research Clinic results that were recently published in the *Journal of the American Medical Association* (1997;278:1509). In this study, which was the result of a long-standing, ongoing research project, investigators looked at dietary modification of lipid profiles related to cardiac risk. They studied varying types of fat restriction, with fat intake from 34 to 36 percent of calories or 22 to 27 percent of calories. They looked at the influence of these differing reductions in dietary fat on management or normalization of blood lipid profiles – lowered total cholesterol, lowered LDL cholesterol, and cholesterol/HDL ratio.

They found that after one year, moderate restriction of dietary fat intake provided meaningful and sustained reduction in the atherogenic LDL cholesterol – the more dense LDL particles – and that one did not need to go to extreme restriction of fat to get these benefits. In fact, extreme restriction of fat intake offered little further advantage in total cholesterol, high-density lipoprotein cholesterol, or lowering of low-density lipoprotein cholesterol. It appears that some kind of intervention that lowers total fat, particularly saturated fats, while increasing the carbohydrate and protein content of the diet does have meaningful benefit, but one does not need to have a very marked restriction of fat to get this desired effect.

Looking at the specific data in the results of this study, you will see quite high standard deviations of dietary response to percentage of fat calories from individual to individual. This illustrates an important tenet that underlies the principle Dr. Roger Williams described some 60 years ago as "biochemical individuality." The average effects of fat restriction were sensitive to modest restriction of fat, but some individuals needed to restrict fat very significantly to get the same kind of benefit in lowering total and LDL cholesterol. This general theme applies to most dietary therapies, because although the average might be good, it is the specific benefit for an individual patient that really is important.

Some patients have extraordinary sensitivity to total fat and dietary cholesterol. Other individuals have

modest sensitivity. Some individuals are more sensitive to the type of fat – saturated versus omega 3 highly polyunsaturated oils. The total cholesterol of these individuals will come down dramatically when they switch from saturated to unsaturated medium-chain triglycerides or long-chain, unsaturated oils like omega 6 GLA or omega 3 EPA, DHA, or ALA.

I believe we should stay away from absolute rules. You will hear about formulas – 40/30/30, 50/25/25 – and what exactly is the right disposition of calories in fat, protein, and carbohydrate to get the best insulin response. The answer, I believe, is that it varies from patient to patient. We should keep reminding ourselves about genetic polymorphism and varying dietary susceptibilities or sensitivities.

In addition to dietary fat, researchers are beginning to recognize that inflammation may play a very important role in determining heart disease risk. Inflammatory markers like C-reactive protein (CRP) or serum amyloid A protein are systemic markers of inflammation seen with chronic infections like Chlamydia, Giardia, or *Helicobacter pylori.* These chronic infections result in upregulation of the immune system and increased production of proinflammatory markers like CRP.

The authors of a recent review in *Clinical Chemistry* (1997;43:2017) point out that C-reactive protein is an undervalued and underutilized analyte in determining risk not just of coronary heart disease but of a variety of other age-related diseases, including dementia and loss of brain function. CRP in plasma and serum is simple and inexpensive to measure. It gives some prognostic sense of the inflammatory status of the patient. This status can be modified by finding the actual etiological agent or cause of the inflammation induction process. The inflammatory markers are responsive not only to such things as chronic infection, but also to toxin exposure and the immune complex formation that comes with allergic response.

The clinical takeaway from this information is that markers for inflammation are associated with cardiac risk and other age-related dysfunctions. They have not traditionally been included in a risk assessment panel. New evidence indicates they should be.

C-reactive protein elevations are also associated with chronic injuries like chronic obstructive pulmonary disease. A recent paper in *Molecular Medicine Today* (1997;3:539) discussed C-reactive protein in acute and chronic lung injury. It explained that all of these degenerative conditions associated with inflammation may be marked through CRP and serum amyloid A protein. I emphasize this because this is a test and analyte that can be called for in most laboratories. It is easily measured as an additional test within the standard serum sample and can give insight into non-cholesterol identifiable risk factors associated with inflammatory processes that we now know to be etiological agents in coronary heart disease and other age-related disorders.

The connection between inflammation and heart disease is still an area of great interest in experimental medicine. The evidence seems to indicate that when there is an altered inflammation profile, the inflammatory markers or inflammation-producing cells of the immune system secrete a class of molecules called intracellular adhesion molecules (ICAMs). (*Journal of Immunology.* 1994;153:2681) In the localized arterial wall, the ICAMs create an opportunity for macrophages and monocytes to bind to and infiltrate the arterial wall and be converted into foam cells.

INTERVIEW TRANSCRIPT

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We are less than a month and a half away from the Fifth International Symposium on Functional Medicine, May 3-6. The focus of the program will be Functional Medicine Applications to Disorders of Gene Expression and how to modify gene expression using the functional medicine approach.

The program will feature several extraordinary presenters. Dr. Kilmer McCulley will talk about homocysteine and age-related illness. He will also review his work on methylation, homocysteine, and cancer that he feels is as important as the atherosclerosis/ homocysteine connection. Dr. Sidney Baker will discuss the effects of nutrients in clinical medicine for maximizing genetic potential. Dr. Mitchell Kaminski from the Thorek Hospital in Chicago, a recent Clinician of the Month on *Functional Medicine Update*™, will speak about modulation of the gastrointestinal hepatic function of patients with inflammatory disorders. Dr. David Heber, professor of medicine and nutrition at the University of California, Los Angeles, will talk about nutrient influence on detoxification and xenobiotic metabolism and the ongoing work at UCLA on protection against age-related toxic disorders.

JB: Welcome to *Functional Medicine Update*™, Steve. My first question is what do you see happening in this area of the treatment and secondary prevention of breast cancer with supplements that might be of value to our clinicians?

SA:

Well, I think that there is a great deal that is happening, but most of it is in transition. Many doctors of natural medicine are aware that there is some work being done, for example, with very high doses of coenzyme Q10, high meaning 390 mg per day in the treatment of node-positive breast cancer. The work that has been done so far looks quite interesting. Most of these patients are doing very well at the end of two or three years. A couple of patients with metastatic disease have actually gone into remission. The work that has been published so far is coming from only one center, and the results are somewhat nebulous. The details of the status of these patients is rather vague. It’s not written up the way it typically would be in a standard oncology journal, so it is a little hard to know how much benefit patients are receiving. Yes, a lot of us are using this high dose with breast cancer patients, but I think we need some more research to know exactly how solid the ground is under our feet. The old research that had been done by Linus Pauling, for example, using 10 or 12,000 mg of vitamin C per day for immune stimulation or perhaps hyaluronidase effects - there are a variety of theories about how it might affect cancer patients - is a topic that also needs to be explored further. Pauling claimed that metastatic cancers of various kinds were treatable, not for the sake of cure, but in terms of life extension. He reported a quadrupling of life expectancy in late-stage patients who were given high doses of vitamin C. He also reported that he had to keep patients on the vitamin C for the rest of their lives in order to see this effect. The Mayo Clinic claims that Pauling was off base, but, in fact, the Mayo Clinic never kept patients on

vitamin C for the rest of their lives. They took them off vitamin C when it was not efficacious in the sense that the tumor mass began to grow or some other change went in the wrong direction. In that discussion, what is typically not mentioned is the fact that there is a group in Japan who independently studied Pauling's protocol and independently confirmed his data - a quadrupling of life expectancy in metastatic patients. Unfortunately, both the Japanese work and Linus Pauling's work were not controlled trials, so we only have preliminary evidence – exciting evidence, harmless evidence, cheap. It doesn't take much to use a lot of vitamin C. I use it with patients. A lot of people use it with patients, but we really don't know how firm the ground is under our feet.

The new melatonin research not just with breast cancer, but also with many cancers, coming out of Italy by Lissoni is very exciting. He'll give people 20 mg of melatonin – a very high dose – in the evening, and his hope is that he is somehow "stimulating the immune system," as we used to say. Now, I think we are getting a little bit gun shy of that term so we'll say something like immunomodulation rather than immunostimulation. Lissoni is reporting that some patients are having increased disease-free survival, increased overall survival, and increased parameters of certain indices of immune function. That work is very exciting, but certainly a lot more needs to be done there before we really know how much melatonin will help a cancer patient.

I think that really takes me to one of the areas where I think there will be a great deal of change in the next few years. The evidence that the immune system and cancer are tied together in a complex, rather than simplistic way, is going to cause a lot of us to start scratching our heads. For example, there is evidence that breast cancer patients will typically have higher, not lower, levels of T-killer cell activity. There is also evidence that immunosuppressed women, for example, women who have kidney transplants and are put on immunosuppressive drugs, will have a lower risk of breast cancer. I am hoping that this will not cause the pendulum to swing from one extreme to another where people will start to try to shoot down immune function. I don't see that as necessarily appropriate, especially in light of the fact that melatonin, coenzyme Q10, and other substances may be, in some way, stimulating immunity and simultaneously helping the patient. What it suggests is that we are not looking for substances that simply "crank up" immunity. We are looking for selective modulators that will somehow straighten out the activity of the immune system so that it goes after cancer cells, rather than just simply doing more work.

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