January 2004 Issue | D. Barry Boyd, MD, MS

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Welcome to *Functional Medicine Update* for January 2004. It is always exciting to start a new year. My colleague Jay Johnson reminded me that we are starting our 22nd year of this audio magazine. A lot has happened over the course of those 22 years. Some of the visions we had when we first started this service to practitioners around the world were then in the realm of fantasy. They have evolved into new opportunities with the evolution of science resulting in improvement of health outcomes, the role of nutrition in those changes, and how lifestyle, environmental modification, and construction of a personalized program for genomic health outcome are defining the course of the new medicine.

It is an exciting time. As we reflect on where we were 22 years ago, although everything we said was not exactly correct from a 2004 perspective, certainly the direction we established appeared to be very much "on target."

11th International Symposium on Functional Medicine

We are preparing for the 11th International Symposium on Functional Medicine, to be held May 11-15, 2004 at the Westin Bayshore Resort, next to Stanley Park, in Vancouver, British Columbia. We believe this will be another step forward in the evolution of our model and the way functional medicine is seen. The focus of the 2004 symposium will be on the rising pandemic of diabetes and its cost to the healthcare system and the individual. In this particular issue of *FMU*, in preparation for that symposium, we will focus on an area that does not appear to be directly related to diabetes. I hope by the end of this issue, you conclude that insulin resistance, hyperinsulinemia, and metabolic syndrome and their relationship to diabetes are, indeed, connected to malignancy and cancer. We will move from the discussion of diabetes to broader areas. This month we will focus specifically on preparing ourselves for the insulin connection to malignancy.

The Insulin Connection to Malignancy

Many people still feel that cancer results as a consequence of being born with cancer genes, that if we have the BRCA1 and the BRCA2 genes and other inherited factors, we are going to get cancer. This is based on the deterministic model, the Mendelian concept that we are locked in and controlled by our genes, with little plasticity.

That model is rapidly changing, and we have talked a lot about how genes are expressed in different ways in different environments. There is no area in which that is more true than in cancer, where it has been recognized that the combination of heritable and environmental factors weave together to give rise to the phenotype of cancer.

That topic was discussed in a study you may be familiar with, which appeared in the July 13, 2000 issue of *The New England Journal of Medicine.* Titled "Environmental and Heritable Factors in the Causation of Cancer,"[1] this study was done in Sweden, Denmark, and Finland in collaboration with the Karolinska Institute. Investigators examined 44,788 pairs of identical twins and, as they grew up, asked what the relative concordance of cancer incidence was in the twin siblings. The assumption was that if cancer was principally genetically related, or heritable, there would be a strong concordance between twins.

Environmental Link to Cancer

The results were remarkable. With the exception of a few types of cancer where heritable factors were strong (colorectal, prostate, breast), the researchers found that no more than 10 to 15 percent of risk for sporadic cancers could be identified as being strictly hard-wired into the genes. The other 85 to 90 percent was related to what washed over the genes—the environment, the experience. The results reveal there is much room for modifiability of the cancer phenotype and preventing the genotype from becoming the cancer phenotype. This is an optimistic view.

One may wonder what happens in the case of those individuals who already have cancer. Can changing the environment have any beneficial outcome? We know that is true on some level, because therapeutic intervention—surgery, radiotherapy, or chemotherapy—is a change in the environment, in some cases a dramatic change, designed to alter the course of the expression of the cancer.

Changing the Course of Cancer

The real question is whether a more moderate, less invasive environmental change can affect the cancer process. This type of change would have to do with diet, lifestyle, and environmental factors in the adjunctive or perhaps even primary treatment of cancer. That is a much more controversial area than cancer prevention.

It would be presumptuous to say we have all the answers. By the end of this month's *FMU*tape, however, you will have some of the answers to that question. We will make some progress in laying the groundwork regarding the direction of this field and what some of the opportunities are for assisting patients down the path of recovery from cancer using adjunctive nutrition, lifestyle, and environmental interventions.

We are talking about gene/environment interaction in the etiology of cancer. What does it mean, and how can we measure it? That was the topic of a commentary that appeared in the journal *Carcinogenesis*.[2] The author of this paper reviewed data on various genotypes that may have higher susceptibility to cancer and asked if one could define, using genotypic or SNPs evaluation, those individuals who might have a higher sensitivity to their environment or their diet relative to certain incidence of cancer. Of course, the factor that is most obvious is tobacco smoking.

Doll and Peto conducted a landmark epidemiological investigation on smoking and lung cancer incidence.[3] According to these investigators, if all associations between a condition and a disease were as clear as the link between smoking and lung cancer, the field of epidemiology and its relationship to medical therapy would be much less ambiguous. The relative correlation coefficient is so strong that it almost obviates the necessity for high-powered statistics.

Smoking, Lung Cancer, and Genotype

We know, however, that certain genotypes are more likely to get lung cancer from smoking than others. Even in those cases, there is environmental modifiability. Dr. Mary Claire King, one of the discoverers of BRCA1, published an article in *Science* magazine this year discussing breast cancer and the BRCA1 and BRCA2 genes. She explained that even though 80 percent of women with the homozygous recessive BRCA1 mutations end up getting breast cancer 20 percent with the same mutation do not.[4]

What is different between the 20 to 30 percent who do not get breast cancer and the 70 to 80 percent who do? Dr. King indicates there are environmental modifiers, even for very significant hard-wired determinants for malignancy. That is the topic of the *Carcinogenesis*article. There are certain genotypes that may give rise to increasing risk to oncogenic hazard. In and of themselves, however, they do not predispose one to a certainty of getting cancer. It is when they are modified in their expression by various environmental factors that the risk increases.

Environmental Modifiers and the Course of Cancer

We will discuss those environmental modifiers in the course of this issue of *FMU.* Included among those modifiers are oxidative stress, free radical pathology, and the interactions between carcinogens and DNA. These are primary factors in environment-related carcinogenic injury. Various cell-signaling messages cause cell proliferation and increase DNA turnover and mitogenesis. Increased angiogenic signals cause blood vessel formation and a greater feeding of small islet cells or islands of malignancy. Investigations have discovered ways that diet, lifestyle, and environment influence the progression of cancer, from its initiation all the way to becoming a palpable or diagnosable tumor.

Diet has been identified as one of the major determinants for the expression of the genome into the phenome called cancer. In the 1980s, Dr. Bruce Ames discussed this topic in a *Science* magazine paper titled “Dietary Carcinogens and Anticarcinogens: Oxygen Radicals and Degenerative Diseases.”[5] Dr. Ames, then chairman of the Department of Biochemistry at the University of California/Berkeley, explained that our diets have always contained cancer-producing substances, or carcinogens. They have also been rich in anticarcinogens in their natural, unprocessed form—agents that help defend against the injurious process of carcinogenesis.

The implication in this article is that as our diets have changed over the years, they have tended to increase the potential for carcinogenic insult, with reduction of the density of the anticarcinogens as we have removed fiber, vitamins, minerals, and phytochemicals, and made our diets “white.” We have taken out all the colored and textured materials and fed them to our pets in pet food supplements, a practice that has led to healthy and springy pets but resulted in tired and worn-out pet owners.

Carcinogens and Anticarcinogens in Food

By reducing the number of anticarcinogens and increasing the potential of carcinogenic exposure, Dr. Ames suggested we have tipped the balance into increased oncogenic risk. Our food is not completely benign with regard either to protection against or promotion of cancer. Deep-fat frying of fat-rich foods, for example, can result in metabolites or breakdown products—oxidation products of fatty acids that may be carcinogenic. Char broiling meat may produce pyrrolizidine alkaloid materials that are potential carcinogens from the charring activity on the meat protein.

Many things we do to our foods and many things that are already in our foods could be viewed as potential carcinogens. Removing that carcinogenic potential and getting higher density of anticarcinogens

in our diet, which means consuming a diet of color, texture, and variety, appears to be associated with the prevention of cancer.

Changing Diet, Changing Risk

An article in the *Journal of Nutrition* looked at the nutritional changes in our overall public health and public nutrition system and their association with the increased prevalence of certain diseases. By modifying the diet—increasing consumption of whole grains, fresh fruits, vegetables, fiber-rich foods, and nutrient-dense foods, and getting more phytonutrients—we might, according to this article, turn back some of the increasing incidence of specific, age-related cancers.[6]

That is easier said than done, because we are seduced by marketing to consume foods that bring high profit to the producer but low nutrient value to the consumer. These highly marketed foods are shelf-stable, sweet or salty. As a result, they now represent the mainstay of the diet of the youth of our country. We can see the resulting changes in disease prevalence. Returning to a diet that contains more fresh produce and whole foods sounds wonderful in theory, but in reality it is complicated. It will require a different social consciousness than that with which we have been living since the emergence of “Space Food Sticks” some 50 years ago.

We have packaged foods from preprocessed information and added chemicals with the assumption that if they were good enough for the astronauts, they are good enough for us. That mentality, established in the 1950s, continues to influence the way we think about our diets today. We have to overcome a cultural bias and turn back to foods associated with a lower incidence of cancer.

One of the first things we have to do to bring about this change is to alter the way nutrition science is integrated into healthcare education and the way it relates to interventions for both the prevention and treatment of cancer. Dr. John Milner addressed this topic in a recent paper in the *Journal of Nutrition.*[7] Dr. Milner is in the Nutritional Science Research Group, Division of Cancer Prevention, at the National Cancer Institute. He has been an eloquent spokesman for the need to introduce better education about nutrition for health providers.

According to Dr. Milner: “Increasing evidence points to numerous dietary components that modify cancer incidence as well as the biological behavior of tumors.” These inhibitory or stimulatory effects depend not only on the dietary component examined, but on a number of factors, including the cellular DNA profile, which leads us into the concept of nutrigenomics and how specific genotypes may be more responsive to specific nutrients than others.

Misleading Research

“Unfortunately,” Dr. Milner continues, “the diet and cancer research domain is strewn with studies that were inadequately designed to monitor biological endpoints, used invalid biomarkers, or monitored irrelevant intakes or exposures.”

In other words, a lot of misinformation is floating around today. In many cases, no cohort analysis was done; studies didn’t stratify individuals with higher sensitivities to certain things. We have made general conclusions based on averages. Eventually, you can boil all data down to the mean so you know everything about someone who does not exist. This is the statistically average person who is not representative of any real person.

Nutrigenomics
We are beginning to look in much more detail at individual diets or dietary components and they way they influence specific genotypes in terms of nutrigenomic or nutrition expression patterns. We need to integrate this genomic concept into the education of healthcare providers so they can begin to look at patients as unique individuals rather than using the rule of averages.

As Dr. Milner goes on to point out: “We must effectively communicate, within a responsible bioethical framework, the potential value of knowledge about genes and gene products.” That is still a big challenge for the educational system of healthcare providers. Practitioners who came up through the education system over the last 30 or 40 years received little or no nutrition education. This is an area in which naturopathic medical education is in a leadership position. A foundation of its education is the role of nutrients, diet, lifestyle, and the environment in modulating function through a variety of different disease states. We can learn a lot from the curriculum of the naturopathic medical education system.

With regard to the specifics of the type of diet we might transition to, I am reminded of a paper published in the *Journal of Nutrition* co-authored by our own Dr. Robert Lerman from the Institute for Functional Medicine. Another author of this paper, titled “The Macrobiotic Diet in Cancer,”was Dr. Lawrence Kushi, son of Michio Kushi.[8] In this paper they looked at the relative effects of macrobiotics as a dietary principle for modulating cancer incidence. The authors state:

“Macrobiotics is one of the most popular alternatives or complementary comprehensive lifestyle approaches to cancer. The centerpiece of macrobiotics is a predominantly vegetarian, whole-foods diet that has gained popularity because of remarkable case reports of individuals who attributed recoveries from cancers with poor prognoses to macrobiotics and the substantial evidence that the many dietary factors recommended by macrobiotics are associated with decreased cancer risk. Women consuming macrobiotic diets have modestly lower circulating estrogen levels, suggesting a lower risk of breast cancer.”

Diet and Gene Expression in Cancer
We recognize similarly altered hormone levels in men using the macrobiotic diet as their principal focus, and lowered incidence of prostate cancer. At present, this information is built principally on empirical evaluative studies. It can, however, be tied to fundamental principles of science that are now evolving to explain how specific dietary components, macro- and micronutrients as well as phytonutrients, influence gene expression and the phenotype of the individual to prevent the initiation, propagation, angiogenesis, and metastasis of cancer. It opens the door for us to understand both the prevention and possible therapeutic value of specific types of diets built around constructs like the macrobiotic diet.

One of the components of whole-food diets rich in unrefined fruits, vegetables, and whole grains is a higher content of other phytochemicals. One of those phytonutrients is the family of phytosterols, plant cholesterol-like molecules that do not have cholesterol activity. They are not precursors to hormones as is animal cholesterol. Examples of these phytosterols are β-sitosterol, campesterol, and stigmasterol, found in foods such as soybeans and many other whole-vegetable products.

The phytosterols not only help lower plasma cholesterol when they are consumed in higher quantities in the diet, but recently they have also been suggested as having a role in lowering the incidence of cancer, possibly through their effects on immune function, cholesterol synthesis, and cell growth.[9]

Phytosterol Consumption and Cancer
Intervention trials have compared diets containing several hundred milligrams of purified phytosterols against placebo in men with benign prostatic hyperplasia. These trials showed a significant reduction in BPH in the men consuming the phytosterols. This research shows, basically, a positive impact on function of the prostate in men consuming higher levels of these phytosterols.

Similarly, it appears that phytosterols may have favorable effects on reducing the risk of breast cancer. Phytosterols also appear to have a favorable effect on reducing the risk of colon cancer. We are starting to see it is not only the ratio and type of protein, carbohydrate, and fat in the diet that is important, but also the additional substances found in the unrefined diet called phytochemicals, or phytonutrients like plant sterols.

We also know the importance of the type of dietary fat consumed. This is an emerging theme. The omega 3 fatty acids appear to be “anticarcinogenic” to some extent, compared to omega 6 or the highly saturated fatty acids. This topic was discussed in a paper in *Nutrition Research*.[10] I was one of the authors of this paper, along with Dr. Ewan Cameron, who was at that time medical director for the Linus Pauling Institute of Science & Medicine, and Dr. Richard Marcuson, the biostatistician at the Pauling Institute.

In this study, we examined the effect of various oils on mammary cancer in C3H mice, which are bred to get spontaneous breast cancer. We accelerated the cancer process in this strain of animals by exposing them to dimethylbenzanthracene (DMBA), a known carcinogen. We put them on a controlled mouse-chow diet, one that was enriched in the same levels of different fatty acids, either safflower oil, corn oil, fish oil, linseed oil, or lard. We looked at saturated fat, monounsaturated fat, linoleic acid-rich oils, omega 3 α -linolenic acid, and also omega 3 eicosapentaenoic acid (EPA).

Mouse Study Results
The scope of the study was fairly large. We studied 300+ mice divided into six groups. One group did not receive carcinogens at all, and all of the animals were coded. The veterinarian at the Pauling Institute evaluated the animals throughout the 40 to 50 weeks of the study. The study was ended early when 80 percent of the animals in two groups had extensive tumors, whereas in two groups few animals showed tumors. It did not require much statistical analysis to see that something remarkable had occurred.

The assumption was initially made that one of those two groups must be the placebo group of animals that did not receive the carcinogen and was on the mouse-chow diet. When the code was broken, however, we found that assumption was false. The group showing the fewest tumors was the linseed oil group, and very close in results was the fish oil group, rich in EPA, the omega 3-enriched oils. The oil consumption seemed to have a remarkable effect on the progression of breast cancer in this animal model.

We concluded there is something about fatty acid composition of the diet, as well as fat amount that affects the potential for progression of a cancer, in this case a form of breast cancer. That study was published in 1989. Since then, many other studies have been published, and human epidemiological work has been done. It appears there is certainly some relationship between dietary fat type and incidence of breast cancer.

Oxidation of Omega 3 Fatty Acids

I want to add a caveat. Omega 3 fatty acids are highly unsaturated and thus very susceptible to oxidation. The breakdown products of oxidized omega 3 fatty acids are acids and aldehydes which, in their own right, can be potential carcinogens. When I talk about the health benefits of omega 3 fatty acids, the assumption is that they are fresh (not deep-fat fried or subjected to high-temperature or prolonged oxygen exposure.) Flax, for example, is very sweet for the first hour or so after it is ground. If it sits around for half a day, though, it gets bitter. That is a consequence of the spontaneous production of lipid peroxides present in the highly oxidizable α -linolenic acid. It can easily undergo rancidification. Omega 3 oils need to be protected against oxidation. Studies of diets rich in non-oxidized omega 3 fatty acids appear to show a dramatic ability to help modify the risk and progression of tumors.

The vitamin and mineral component of diets might also influence oncogenesis. Folate is an example. We have followed the folate story in *FMU* for nearly 15 years. We are beginning to recognize that single nucleotide polymorphisms (SNPs) are related to altered folate metabolism. We have frequently talked about the methylenetetrahydrofolate reductase, or MTHFR 677C→ T polymorphism that is seen in about 20+ percent of the population. The homozygous recessive, so-called TT subtype, is found in about 10 percent of the population.

Individuals with that polymorphism seem to have difficulty with folate metabolism and conversion to 5-methyltetrahydrofolate, the active methyl transfer form of folate that helps convert homocysteine ultimately into S-adenosylmethionine (SAM). In cases of MTHFR polymorphism, the requirements for proper management of folate chemistry are higher, and lower levels of folate intake can lead to methylation problems that can affect cancer risk.

This is an interesting, emerging story. A number of papers, extending back to the 1960s, show that folate-deprived diets in animals made them much more susceptible to carcinogens. We are beginning to recognize that one of the detoxification processes of the body is driven by methylation, and that methyl groups come through the SAM/homocysteine pathway that uses 5-methyltetrahydrofolate.

Contributors to Folate Insufficiency

The authors of a recent paper in the *Journal of Nutrition* describe the MTHFR 677C→ T polymorphism as increasing the relative risk of folate-related problems. They state that alcohol intake above one drink a day on top of an MTHFR 677C→ T polymorphism is associated with folate insufficiency.[11] When we think about stress, dietary problems, genetic polymorphisms, and carcinogen exposure, we see how diet, environment, and genes are linked in their effects on the incidence of initiation of a tumor.

The role of folate in colon cancer development has been studied extensively. One study points out that even though dietary folate intake and folate levels are inversely associated with colorectal cancer risk, caution is important because there is evidence in animal models that excessive folate(supraphysiological levels) may promote the progression of established neoplasms.[12]

Folate chemistry is interrelated with microscopic neoplastic changes in cells in the colonic mucosa and substances that are always present in the contents of the colon. Among those contents are potential carcinogens; bacteria have fermented or metabolized specific constituents and produced secondary metabolites like nitrosamines, nitrous compounds, or oxidized sterols that may be *in situ* carcinogens.

The folate story becomes important for maintenance of proper mucosal architecture and mucosal defense

systems. Again, MTHFR polymorphisms, folate insufficiency, and other factors are emerging from the folate/cancer connection.

Phytonutrients called polyphenols help lower the inflammatory response and lessen its potential role in both angiogenesis and metastatic events. A variety of substances have beneficial effects. They include isoflavones found in soy; polyphenols in various fruits and vegetables; and resveratrol (cinnamic acid polyphenol derivative that also participates in some of these processes), found in grapes and grape skins.

Polyphenols that are catechin-like or ellagic acid-like serve as profound modulators of certain processes related to inflammation and to potential metastasis. A complex diet rich in color—blue, green, and orange—has some benefit. The effect is not derived from just one nutrient at a time. I am referring to an article in the *Journal of Nutrition.*[14]

As we lower the expression of inflammation by downregulating the inflammatory enzymes like cyclooxygenase, we lower the relative risk of metastasis and angiogenesis, particularly in epithelial and mucosal tissue. Epidemiological studies have associated consumption of green tea, which is high in EGCG, with lowered cancer incidence. EGCG has been demonstrated to be a down-regulator of certain types of inflammatory function in the gut.

Information is emerging to describe the mechanism of EGCG and its potential influence on the cancer process.[15]
Drinking a couple of cups of green tea per day appears to be an effective way of increasing total phytonutrient exposure and, possibly, to modulate, regulate, or affect physiological processes in an effort to prevent cancer or possibly provide adjunctive cancer treatment.

Other cancer-preventive foods are the cruciferous vegetables—broccoli, cauliflower, Brussels sprouts, and cabbage. These vegetables, which have a unique odor when cooked, contain sulfur- and nitrogen-based phytochemicals called glucosinolates. Digestive enzymes break down glucosinolates. An enzyme called myrosinase, which is present in the cells of the plants, also aids in this breakdown process when the crucifers are chewed. Myrosinase breaks down glucosinolates and liberates a secondary set of chemicals into the body, such as indole-3-carbinol (I3C) and phenylisothiocyanate, into hydroxy-3-butene and sulforaphane.

These substances affect gene expression in specific ways to upregulate the expression of various cytochrome P450s or phase II detoxification enzymes like quinone reductase or glutathione S-transferase. Certain vegetable products may have unique abilities to improve detoxification of chemicals and help regulate specific cell functions.

A recent study of MCF7 in human breast cancer cells found that I3C, one of the glucosinolate metabolites from cruciferous vegetables, could arrest the cycle of proliferation of the breast cancer cells in culture.[16] This study suggests I3C not only has a detoxification effect, but also a cell cycling effect, causing a slowdown of the rapid proliferation rate of the cells. This has also been shown in human prostate cancer cells, showing G1 cell cycle arrest and increased apoptosis of transformed prostate cells when exposed to I3C.[17]

An array of glucosinolate-rich foods may participate in regulating cell cycling and downregulating the message of oncogenesis. That also holds true for the cress family of vegetables—garden cress, winter cress, summer cress, and watercress. All of these cresses have glucosinolates that help prevent preneoplastic lesions and genotoxic effects. For example, beneficial compounds in garden cress were discussed in an article in *Carcinogenesis*.[18]

Limonene-Induced Regression of Mammary Carcinomas

Limonene, a monoterpene derived from citrus, alters prenylation and farnesylation of various substances having to do with cell cycling, cell regulation, and cell turnover. Farnesylation and prenylation are biochemical modifications of proteins and other molecules that occur in the body. These processes are part of manysignaling pathways and are a way the body uses to change how aprotein functions.

When given at higher doses to animals, limonene promotes regression of mammary carcinomas. In fact, some early investigative work in human intervention trials has been done at the National Cancer Institute using limonene in supplemental doses to see if it can have a positive effect on regressing malignancy.

One paper that discusses the limonene-induced regression of mammary carcinomas appeared in *Cancer Research.*[19] This paper explains how monoterpenes block farnesylation and isoprenylation and have an impact on cell cycling and gene expression. It discusses some of the epigenetic effects that relate to the oncogenic process and metastasis.

We are talking about the way diet and lifestyle communicate with the genes. Food is information. Our lifestyle contains information from which our genes receive a message that creates the phenotype. Cancer is not inevitable. It is modifiable through the information you send to your genes. The genes will respond in their expression patterns to the messages to which they are exposed by forming alarm or cell-proliferative messages.

Cancer may be a disease of disordered energy that appears in a society that is too time-urgent and overwhelmed with energy processing. That energy flows through our bodies, resulting in undirected, uncontrolled, non-differentiated clonal effects. Diseases reflect societal processes of uncontrollable energy. A good diet may help quiet, direct, and keep coherent the information and energy that travel through our bodies and regulate cell function and differentiation.

This is a metaphorical discussion of evolving molecular biology and molecular oncology. It goes together with the epidemiological conclusion that the best diet is one that is less processed, richer in color, and higher in specific phytochemicals, vitamins, and minerals. Cultures that have consumed such diets historically have had lower incidence of certain types of cancers, particularly those commonly seen in the Western world, which are cancers of the immune and endocrine systems. We are sending ourselves many signals of proliferation, and we need to quiet them down and get them to rest. In mid-life we should be a state of cells at rest, regenerating daughter cells to be consistent with parent cells and staying in check throughout the course of a long mid-life for 50 years or more.

That message comes through in this research. On side 2, we will see how a clinician/researcher views this picture and translates esoteric, fundamental information into clinical management programs.

INTERVIEW TRANSCRIPT

Clinician of the Month
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JB: It is time for our Clinician of the Month. This month we are privileged to have an individual with a tremendous background in the management of cancer oncogenesis. He will explain how that subject can be approached from different perspectives and where this field is headed. We are fortunate to have someone with a broad base of understanding and the ability to examine these issues from different perspectives. Dr. D. Barry Boyd has been a speaker at cancer conferences sponsored by Dr. James Gordon and is himself an esteemed oncologist.

Dr. Boyd has a master's degree in nutritional biochemistry from Columbia University, and he received his MD at Cornell University. He has been an adjunct clinical professor of medicine, working in oncology and hematology at Yale University School of Medicine in Connecticut. In his private practice he has achieved a balance between the traditional way he was taught and the integration of his skills and training into a broader-based practice. That does not often occur in today's world of medicine. Dr. Boyd, it is a privilege to welcome you to Functional Medicine Update.

BB: Thank you, Jeffrey. I appreciate your offering me the opportunity. It's wonderful work you are doing, as well.

The Transition from Traditional to Functional Medicine
JB: How did you make the intellectual transition from the way you were trained into looking at other alternatives as you moved through your career?

BB: My original training was in medical nutrition at Columbia's Institute of Nutrition. Then I went on to medical school, studied oncology, and went into the practice of medical oncology. Shortly into my practice, it was my patients who caused me to change. They didn't drag me kicking and screaming, but they got me more and more involved in appreciating the growing evidence base in nutrition and cancer. I had four years of nutrition in graduate school and one hour of nutrition in medical school. I always tell my patients that they spend about 30 percent of their waking day either thinking about, shopping for, preparing, cooking, or eating food. Yet physicians know virtually nothing about nutrition.

My patients brought me back to this, and I've developed a growing expertise because of my biochemistry background in nutrition and cancer. The surprising thing is the enormous amount of information that is out there. Unfortunately, many patients don't know where to get this information. The field of nutrition is very broad, and it's difficult to sort it out. This got me interested. As a result, because nutrition is often characterized as alternative medicine, I developed more and more expertise in other areas of complementary medicine. I am now much more involved in that. I also run the Integrative Medicine Program at Greenwich Hospital.

Integrative Medicine Program at Greenwich Hospital
JB: We are obviously talking to the right person. You probably understand both the positives and

negatives, and what are reasonable and realistic expectations. Would you tell us something about the program at Greenwich Hospital? How does it work? How does a patient gain access to your program and what kinds of things can they expect?

BB: We did a series of surveys of other integrative medicine programs. We looked at common programs like the one at Beth Israel Hospital. A lot of the bigger centers run such programs. We briefly entertained the idea of joining with the Mind Body Institute at Harvard, but when we essentially became a hospital of Yale, we realized that the Harvard/Yale Mind Body Institute wouldn't work. It works in football games, but we didn't think the collaboration would work.

What we did when I outlined this program was to develop it around disciplines. Even though we are medical oncologists and nutritionists, the real approach was to look at every discipline and then form integrative approaches within each area. For instance, in medical oncology we developed a massage program on the oncology floor. We moved on to treat patients' family members with massage because of the role of stress in the caregivers. We moved massage therapy into the OB and certainly into the neonatal side.

Each time we introduced a modality into a different specialty, it was concurrent with research, so we tried to do little pilot studies that would bring physicians on board. When we started, we had a committee of two physicians and three staff members. By the time we were established, we had about 50 members of the medical attending staff, which is a large number of people who are interested but were afraid to admit it.

It's been very successful because we approached it from a discipline standpoint rather than what I call the "potpourri" approach, which is to open up a free-standing center and offer acupuncture, massage therapy, homeopathy, and naturopathy. This way, we convince the physicians that these modalities work, that they are important, and that they can be integrated. What I call integrative medicine is truly integrating it into the body of care within the hospital.

Third-Party Reimbursement
JB: That is exciting. Have your patients had success getting third-party reimbursement for some of the services?

BB: As you know, that's difficult. Oxford is a participant because we're one of the areas in which there's a significant inroad with them. They have a complementary medicine program. We have certified acupuncturists. In addition, we have a significant amount of funding to help provide care for patients who don't have the ability to remunerate.

With massage therapy, we initially had funding for a one-month study, and within two weeks, that was funded in perpetuity. We have a full-time massage therapist, and it's free to patients. We also have small funded programs in preoperative relaxation for elective surgical patients. They provide a small stipend and the nurses are trained to do this. You can use funding; there are areas where some of the managed care companies will pay. The goal of the research, though, is to provide evidence that it's good quality medicine and they should pay it.

Growing Interest in Complementary/Alternative Medicine

JB: That is very forward-looking. I had the privilege of speaking at the Dana Farber Cancer Institute last year as part of one of their Lenny Lecture Series. Dana Farber has a complementary/alternative medical unit sponsored by the Lenny Program. I was impressed by the number of doctors from the entire New England Medical Center complex who were interested. When I gave my lecture, around 150 staff physicians from different departments were in attendance. It indicates to me that interest is growing.

BB: The future is very bright because the residents in training are fascinated. Many of them are interested in this. It's very different from the skepticism among people who were trained 10, 15, 20 years ago or longer. Those earlier-trained practitioners are more ingrained and view this as quackery. We need to show them there's a huge world out there of other things that we avoid. Clearly, nutrition is the heart of this, and that's what patients want to know about.

Nutrition in Prevention and Therapy
JB: That leads me to the question that was raised when I was at Dana Farber. Do we see nutrition more in a preventive mode, or do we see it also as applying to an adjunctive therapy mode affecting the way a patient who has cancer is treated?

BB: In my early work, as I would lecture patients, I would devote a lot of time to cancer prevention and nutrition. There was a lot of work early on about macro- and micronutrients and prevention. With low-fat diets and breast cancer, an enormous body of epidemiological work up until the Nurses' Health Study suggested that relative fat intake had very little to do with breast cancer. The same thing applied to fiber, and you know about beta-carotene and the whole issue with lung cancer and how that turned out to be a pro- rather than an anti-carcinogenic intervention in heavy smokers.

The fascinating question to me is, can you bridge the gap between prevention and treatment? I explored the relationship between the insulin IGF system and cancer, which has clearly exploded in the last year with the research, particularly with the American Cancer Society study. The biology of cancer strongly suggests there is both a preventive and a therapeutic role for the relationship between insulin and IGF-1 growth factor stimulation in both the development of cancer and in its impact on prognosis and therapy. This has been the heart for me. I see this insulin connection and the IGF system as a target that has an impact both on cancer etiology and how you do when you get cancer.

Nutrition and the Stages of Cancer
JB: Do you believe nutrition plays a role in each of the stages of cancer? If we think of the stages as initiation, propagation, angiogenesis, and metastasis, do you think nutrition is related to each those steps?

BB: Clearly, it is; in some cases it has a different role and in some cases the relationship is overlapping. Let me explain. The initiation phase of malignancy, of course, is the initial mutagenic, genotoxic event that damages the DNA. Obviously, that initiation event can be a predetermined, inherited defect, or it can be something based on exposure.

From the standpoint of nutrition, one of the most interesting areas is the post-initiation event, which is really tumor promotion. That reflects anything that enhances cell proliferation. Clearly, there's a role between, for instance, red meat and colon cancer. One thing we know is that the way you cook the meat may lead to high levels of aromatic hydrocarbons that are pro-carcinogenic. That's one setting in which nutrition is important because the nature of food preparation can increase carcinogenic exposure. In

addition to that, of course, is contamination—the presence of carcinogens within foods as part of the initiation event.

Nitrosamines and Vitamin C

Nutrition plays a role in the third part of initiation. Gastric cancer was very common at the turn of the last century. First of all, there was no refrigeration so people ate smoked and pickled foods. As a result, high nitrite exposures led to increased nitrosamines in the GI tract. A concurrent thing that suppresses nitrosamine production in the stomach is the presence of high levels of vitamin C. Also, back then you didn't have fruits and vegetables. Thus you had a "double whammy" of the high levels of carcinogens in foods combined with low levels of vitamin C from fresh fruits and vegetables to suppress that, so the initiation event was much more likely for gastric cancer.

Gastric Cancer today

Now the whole nature of gastric cancer has changed. It's probably less likely that it's nitrosamine related and more likely that it's related to distal esophageal, obesity-related events, combined with Barrett's esophagus. We're seeing an influx or a high incidence now of this other type of gastric cancer. That's sort of a model for the initiation and the relationship with nutrition.

My area is in the role of promotion. What stimulates cell proliferation in terms of the likelihood of evolving from a preneoplastic lesion to a fully neoplastic lesion with the acquisition of additional genetic effects is something that requires ongoing enhancement in cell proliferation. A variety of cell signals are potentially modulated by nutrition.

That is also linked to prognosis. Once you have a malignant tumor, if you continue to have high levels of tumor promoters, you will concurrently evolve into having a much more aggressive and rapidly progressive cancer.

IFG-1 Insulin and Cancer Promotion

JB: That's a wonderful segue into the discussion of IGF-1 insulin and its relationship to promotion. Clearly, that's an area in which you have been a leader in creating understanding. Would you tell us more about that?

BB: There are some fascinating models about the insulin/cancer connection. One is the growing evidence that we have been very reductionistic in the way we look at diet and nutrition. As you remember, Doll and Peto did two studies. One was a multi-national study, and the other was in the United States looking at lifestyle factors and cancer.

Of course, smoking was high on the list. But in general, diet was very high, affecting between 30 and 40 percent of cancers. The range of error was fairly significant, though, as they said. That led to epidemiology. First there was the idea about fat and breast cancer, and colon cancer and the relationship with fiber. As you go back and look carefully, it turns out that those relationships fall apart to some degree.

Correlation or Cause?

What may be missing is that they're correlative rather than causative. For instance, we dissect broccoli to look for the indole-3-carbinol to see how it affects estrogen metabolism. It may not be any one

constituent; it may be the whole. One of the ways that may be explained is the relationship of diet and obesity to the growing recognition of the metabolic syndrome.

As you know, Gerald Reaven was the first to define syndrome X. What I think has culminated our interest in this was the recent American Cancer Society prospective study.[20] They looked at more than 900,000 men and women over 18 years of age and discovered that obesity was markedly related to an increased risk of mortality from almost every cancer, with the exception of lung cancer. Virtually every other cancer was related, including myeloma, Hodgkin's disease, and lymphoma.

The Role of Insulin

The intriguing thing is that insulin and insulin receptors are present on virtually every cell and often upregulated on cancer cells. The connection between obesity and cancer has been looked at in a variety of settings, such as in colon cancer, postmenopausal breast cancer, and prostate cancer. If you start to dissect it, there is evidence that insulin and IGF-1, which is often upregulated, are connected to that.

Intriguing data are being worked on in a parallel fashion on the concept of caloric restriction and aging. A significant amount of research is now targeting the idea that insulin and IGF-1, particularly insulin receptors, are linked to that effect. By limiting levels of IGF-1 and cell proliferation, calorie restriction may enhance survival and actually reduce the incidence of malignancies as a result. It’s a fascinating and growing body of work.

Insulin Signaling and PPARS Activity

JB: The concept of cellular signals that stimulate cell proliferation is a big area. You are obviously implicating insulin and some of its related stimulatory factors, like IGF-1. That also implies that nuclear regulatory factors may be influenced in how genes are expressed in some of these cellular proliferative processes. This then suggests things like peroxisome-proliferated activator receptors, or PPARs. I would presume there’s a connection between insulin signaling and PPAR activity.

BB: Yes. As you know, the data are growing that indicate it may be part of the modulator of insulin activity. There is evidence that upregulation of PPARg through dietary fashion will limit not only insulin resistance, but also may reduce obesity in animals. A variety of nutritional and dietary interventions will upregulate that.

One study recently looked at an ethanol extract of licorice as a way of inducing this.[21] One of the intriguing things in the field of nutrition and so-called integrative medicine is to look at supplements and how they may be beneficial. That's another area.

Cell Signal Factors

The other fascinating part where there’s so much overlap of cancer is with some of the cell proliferative signals that are linked to the insulin response element within the cell that is stimulated both by IGF-1 as well as insulin. In this case, they will concurrently activate a series of growth factor pathways. One is mitogen-activated kinase, and the other is phosphoinositol-3 kinase (PI3K). The intriguing thing is that both those pathways lead to an increase in proliferation and a reduction in apoptosis. If you look at high insulin levels, for instance in breast cancer, they are clearly linked to poor outcomes and poor prognosis. There’s evidence that it’s also potentially linked to a higher grade of tumor.

If you look at some of the studies, insulin and IGF-1 act through those intermediate pathways affecting cell cycling and proliferation, those same pathways are clearly similarly linked to poor prognosis. In other words, abnormalities in PI3K and mitogen-activated protein (MAP) kinase, these intermediate pathways in cell proliferation, are found to be a poor prognostic factor in breast cancer, much like high insulin is found to be a poor prognostic factor.

That may very well be the mechanism by which insulin is working in upregulating this, reducing apoptosis, and cell proliferation. More intriguing is the idea that insulin might not only do that, but may interfere with therapy because many of the pathways involved in killing cancer cells, either chemotherapy or hormonal therapy, may be interfered with if we block apoptosis by ambient high levels of insulin.

NSAIDs and Cancer

JB: This is fascinating. When you introduce things like MAP kinases, that starts to interrelate with the inflammation pathway because that's the start of the signal transduction pathway in inflammation. That raises another question. Why do some nonsteroidal antiinflammatory drugs seem to have a lower cancer potential? You've introduced insulin signaling with inflammation and antiinflammation, so it sounds like an expanding web.

BB: One area in which I am greatly interested, as you can tell, is the concept that the metabolic syndrome with hyperinsulinemia is linked and may be the modulator of obesity and cancer mortality in this relationship. Not only is hyperinsulinemia and its potential effect on IGF-1 a part of this, but, potentially independently, metabolic syndrome is classically a proinflammatory state with high levels of interleukin-6 (IL-6) and C-reactive protein (CRP).

Concurrently, in virtually every cancer, independent of stage, the presence of high levels of IL-6 and CRP is a negative prognostic factor. There seems to be this interaction with the inflammatory pathway, both with hyperinsulinemia and potentially on poor outcomes with cancer. It may be that insulin works through the insulin receptor; it may be the metabolic syndrome and the state of inflammation itself plays a role in cancer. The other thing we haven't touched on is the relationship between stress and emotions and their potential influence on the metabolic state.

Stress and the Metabolic State

JB: Would you explain for our listeners how the modulation of those hormones could influence this pathway?

BB: One thing that intrigued me was the concern about stress and its impact on cancer. Probably the best way to put it is that there are two sides to this. There are people in conventional oncology who feel there is absolutely no relationship between stress and cancer. I think they feel it places too high a burden on patients' emotional states, in the sense that they're responsible for their cancer.

Second, they don't understand that there could be a biologically plausible explanation for the effects of stress on cancer. One of the intriguing and long-standing paradigms in the field of integrative medicine is the concept that chronic stress leads to impaired immunity and cancer causation or progression, which has many flaws. The other problem is that people draw away from conventional medicine because they're afraid it will impair their immune system, and therefore the cancer will grow.

Cancer and HIV

The first thing I do, and I've written a paper on this[22], is to dissect the concept that immune surveillance and your own immune function play a huge role in cancer. Most epithelial cancers are not well regulated by your own immune system. They are essentially hidden, if you will, because of immune tolerance.

A good example is the HIV population. Most AIDS patients, despite the fact that they're profoundly T-cell immune-deficient, get only malignancies that are linked to viral oncogenesis, whether it's the Papilloma virus or herpes virus related to Kaposi's sarcoma. Intriguingly, in a large epidemiological study, people with AIDS on an age-adjusted basis, did not get high levels of epithelial cancers. In fact, they were slightly lower than anticipated based on their age. T- cell immunity, despite all of our assumptions, had very little impact on epithelial cancers. I think when you look at a variety of other models for this, you see the same thing where there's transplantation and immune suppression. They're mostly linked to Epstein-Barr lymphomas, to Papilloma virus, etc.

Chronic Stress and Metabolic Syndrome

The intriguing thing to me is that stress may not be working at all through this pathway. An alternative is the fact that chronic stress has been well demonstrated now. There's a fascinating body of literature on both the hypothalamic/pituitary/adrenal axis effects and sympathetic and parasympathetic enervation of the adipose tissue.

There's now an enormous connection between chronic stress and the development of the metabolic syndrome. Chronic stress can actually lead to that state and its consequent effects on both insulin and inflammatory mediators. It's a fascinating way that may actually be a better explanation. It is also a way of explaining why stress reduction really does matter.

Clinical Applications

JB: That is an eloquent description of a very complex pathway. It opens up all sorts of opportunities for clinical application. In the remaining minutes we have, I'd like you to touch on how you take this information that, for the average patient, is probably a little bit more about mechanisms than they want to know, and get it worked into a program that they can actually apply.

BB: I do two things. One is, we're involved in research. One of the fascinating areas, very quickly, is whether chemotherapy actually induces a metabolic syndrome. We know that breast cancer patients gain weight after adjunctive chemotherapy. We know that weight gain after adjunctive therapy may have a negative prognostic effect.

I believe that chemotherapy actually enhances the risk of the metabolic syndrome so I target weight gain. I have two nutritionists who work with me, along with several people working in stress reduction, and I have a traditional Chinese medicine program in my own practice. We all target this together. We look at initial anthropomorphic measures. We look at waist-to-hip ratio, which is a good measure of the typical metabolic syndrome associated to adiposity. Mid-abdominal weight gain is more closely linked to the metabolic syndrome.

We then follow patients on treatment. We monitor their nutritional status. We obviously target them with a modification of what I call the Mediterranean Diet, which looks at a combination of the Atkins (not

high fat), limited carbohydrate, moderate fat, moderate protein, with a greater emphasis on the Mediterranean approach.

The Mediterranean Diet

We know from the Lyon Heart Study that using the Mediterranean Diet lowered cancer incidence. There are epidemiological and clinical studies indicating a benefit with that, and it causes weight loss. It's a fascinating way to deal with that. We also measure all the standard things—triglycerides, HDL, fasting insulin levels at the beginning, and then we monitor those.

I've had several very interesting case reports; one is a patient with pancreatic cancer who is insulin resistant. We treated his insulin resistance with vigorous diet and exercise. We also gave him a variety of supplements, including N3 fatty acids, a -lipoic acid and a couple of other measures to reduce his insulin resistance. We got his insulin levels down and he went into complete remission with chemotherapy with his pancreatic cancer. He went out of remission when his insulin levels went up. We readdressed that and he's back in remission again. It's a single case report. We have several other patients like that now who seem to be responding the same way. It suggests the idea that in addition to giving chemo, you need to treat the metabolic state of patients. It may impact how they respond to treatment.

Educating Physicians

JB: This is extraordinary. I know you're going to have a greater opportunity at our 11th International Symposium on Functional Medicine coming up in May to talk about this. I believe you'll also be doing a workshop. It sounds like we'll need more time with you to fully develop this concept, but it's certainly very exciting. And it makes sense from the emerging endocrine and cell signaling components of cancer.

BB: Exactly. That's the beauty of it. And what I'm interested in doing is, as you are doing—educating physicians about the fact that there's a science behind this. If they appreciate the science, then they understand that it's not just medication and radiation. There's much more to treating cancer patients.

Nutrition Therapy

JB: That's a very optimistic view, and it certainly answered my initial question about prevention versus adjunctive therapy. It sounds to me as though this may emerge as a primary therapy in those patients whose promotion is driven by cell signals related to insulin.

BB: Right. The other beautiful thing about it is that I always tell my breast cancer patients who are on adjuvant therapy that they have to remember that many women with adjuvant therapy don't die of breast cancer. They get a heart attack four, five, ten, or twenty years later. This essentially targets the chronic diseases of the 21st century. Not only may it reduce the risk of second cancers, but it is also clearly beneficial from a vascular disease standpoint. It's much more holistic, if you will, than just cancer.

Obesity and Insulin

JB: I don't want to put you on the spot, but I'd like to get your opinion on one interesting sidebar that you raised for me. If I heard you correctly when you were talking about obesity and insulin, obesity or the visceral adipose deposition (apple body shape/waist-to-hip ratio increases) is an effect of a metabolic transition that occurs having to do with the arrangement of insulin and other signaling molecules. Rather than obesity causing this effect, it's a covariable that comes as a consequence. Did I hear that correctly, or did I overstate what you said?

BB: It's the chicken-or-egg issue. Is visceral obesity a result or a cause? I think for many people who are doing work in this field, visceral deposition is certainly a marker and a predictor of that. Some people feel that increasing visceral obesity, which is clearly linked to central obesity, causes insulin resistance, partly because those adipose stores may be more rapidly mobilized. There's a higher level of free fatty acid flux that increases the insulin-resistant state at the cellular level. I think it may be causative, but it's not 100 percent clear.

Diet and Hormone Modulation in Cancer Management
JB: Thank you. I guess the bottom line is that if we put a person on a good weight management program and we can modulate these hormones, whether it's a chicken or an egg, it will improve the patient's condition.

BB: Yes, I think that's the bottom line. Interestingly, one last mention is that Pi-Sunyer at St. Luke's at Columbia in New York, who has done a lot of work on this, has described the non-obese insulin-resistant patient who has occult visceral obesity.

That's an area that particularly interests me. We have to be careful not to assume that if you're not classically overweight with a high body mass index, you're free and clear. People need to be assessed for that rather than assume that's okay. And you don't have to lose 100 percent of your overweight. The Diabetes Prevention Program has demonstrated a reduction of diabetes incidence by a modest weight reduction, along with exercise. But the key is to get started, to get those things done, and that will improve your metabolic state and, hopefully, also impact on your cancer.

Thin/Fat Patients
JB: I really appreciate your mentioning that. Dr. David Heber at UCLA discussed that topic in regard to women who did not have significantly elevated BMI; I think their BMI was in the 25-26 range. Body composition analysis using bioimpedance, however, revealed they had increased percent body fat, less body muscle, and metabolic syndrome-related problems. This could be what Covert Bailey called the thin/fat person who may be at risk.

This has been a fascinating discussion. We look forward to hearing more at the 11th symposium coming up in May in Vancouver, BC.

Dr. Boyd left shared a large amount of dense information with us. I am sure you were stimulated by his comments related to signaling, cell proliferation, insulin, insulin-like growth factor-1 (IGF1), and the way they interrelate with metabolic syndrome and abdominal obesity. His comments may open up many doors to information not previously fully understood regarding ways to apply these concepts in the macrobiotic diet and other fundamental diets used for cancer prevention and remediation.

Licorice Extract in Ameliorating Diabetes, Abdominal Obesity, and Preventing Hypertension

Dr. Boyd mentioned a paper that appeared in the *Journal of Nutrition*, titled "A Licorice Ethanolic Extract with Peroxisome Proliferator-Activated Receptor-γ Ligand-Binding Activity Affects Diabetes in KK-Ay Mice, Abdominal Obesity in Diet-Induced Obese C57BL Mice and Hypertension in Spontaneously Hypertensive Rats." [21] This animal study ties together everything Dr. Boyd was talking about. I want to quickly review it.

Insulin resistance, abdominal obesity, hypertension, and dyslipidemia are closely linked in what we call the metabolic syndrome. They represent the “deadly quartet” of syndrome X. The clustering of these risk factors in what we call the metabolic syndrome not only relates to increasing risk of diabetes, but also to increasing risk of heart disease. As Dr. Boyd has pointed out, these factors are also related to increased incidence and risk of certain types of cancer, such as colonic, breast, and prostate cancer.

Nuclear Receptors

There is something about adipocyte differentiation and physiology and its interrelationship with insulin and insulin signaling, and the connection to metabolic syndrome that correlates with self-proliferative disorders that are of oncogenic concern. That is an interesting emerging story. Part of it may be related to the gene expression modifiers, the nuclear regulatory factors, those of the so-called the orphan nuclear receptor family, peroxisome-proliferated activated receptors (PPARs).

There are the α ,γ , and δ forms of PPARs, each one of which has a slightly different influence on physiology. PPARγ is a predominant molecular target for insulin-sensitizing agents. It was first discovered when the family of thiazolidinedione drugs came on the scene and seemed to be insulin-sensitizing. Now we have found that many nutritional and other agonists are natural substances that modify PPARγ activity. It is not just the thiazolidinedione drugs like troglitazone, pioglitazone, or rosiglitazone; it is also natural substances like omega 3 fatty acids, conjugated linoleic acid, DHEA, and other things that have been found to influence the signaling of these orphan nuclear receptors, the PPARs.

PPARγ may therefore be an important part of the regulation of the whole signaling process we see manifested as metabolic syndrome, abdominal obesity, insulin resistance, hyperinsulinemia, and ultimately influencing cell signaling. Insulin is not just a glucoregulatory hormone; it also influences the expression of protein tyrosine kinases, which then influence cell signaling, cell proliferation, and the oncogenic process, as Dr. Boyd described.

Animal Study of Licorice Phytochemicals and Insulin Sensitivity

In this particular study, the investigators wanted to look at animals that were already genetically predisposed toward obesity or hypertension. They measured their PPARγactivities and gave them an ethanolic extract of a family of licorice phytochemicals that purportedly modulated insulin sensitivity.

The results are quite interesting. The investigators were able to demonstrate that both the spontaneously hypertensive rat and the diet-induced obese mouse, when administered this particular licorice extract, had improvement in their glucose regulation, meaning higher insulin sensitivity. They had altered blood lipid profiles, with less prevalence of dense LDL, meaning purportedly lowered risk to cardiovascular disease, and they had lowered intra-abdominal adipose tissue.

The Role of Calorie Restriction

This occurred without changing the number of calories in the diet; I want to emphasize that. We seem to think that calories are the *prima facie* requirement for increasing body fat deposition, but it may be metabolic effects that occur relative to how the calories are processed and where they are disposed of, that also leads to changes in body composition. Things like insulin resistance or PPARγ inactivity may, according to this work, also be associated with how these calories travel to the body and where they end up as storage forms in lipid storage adipocytes associated with visceral adipose tissue accumulation.

Licorice Extracts in Disease Prevention and Management

The investigators suggest these findings indicate that the licorice ethanolic extract is effective in preventing and ameliorating diabetes, ameliorating abdominal obesity, and preventing hypertension in the spontaneously hypertensive animal. They suggest this licorice complex of phytochemicals would be effective in preventing and/or ameliorating metabolic syndrome and its potential effects on oncogenic events, such as Dr. Boyd described earlier.

I hope you can see that this is a web as we continue to emerge and amplify this topic. You cannot look at a variable in physiology as a single endpoint. You have to look at its interconnectedness to other functions.

The Web of Disease

Obesity connected to lipid metabolism connected to insulin signaling connected to cell/gene expression patterns connected to cell proliferation and mitogenic index. These are all part of an emerging view of the way chronic degenerative age-related diseases may be connected together and just differ in their expression based on genetic uniqueness. The signals we send to our genes in our modified environment of the 21st century may be increasing the expression patterns into the phenotype of specific diseases that just happen to be those that we most confront in our medical centers. Those diseases are coronary heart disease, cerebrovascular disease, malignancies, and diabetes, which is now a pandemic.

I hope this helps you see why we feel that the 11th International Symposium on Functional Medicine focused on the rising pandemic of diabetes, is a justifiable topic to spend time on with leaders in the field. It is not just diabetes alone; it is also heart disease, dementia, inflammatory conditions, coronary heart disease, and malignancy. We will be exploring those in greater detail as we move forward. Dr. Boyd left us with some interesting insights. You can see how environment plays a role in the modification of disease. We will talk again in February.

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