June 2002 Issue | Paul Reilly, ND

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Welcome to Functional Medicine Update for June 2002. The theme of this month's issue, which I think is appropriate for our 20th anniversary, is cancer, a functional disease that requires functional medicine. That is a bold statement. In the next 90 minutes I hope to make that theme become more than an abstract concept. I believe cancer is the single most significant disease model we can look at in which functional medicine is necessary for its remediation.

We can begin the story of cancer and functional medicine with the Stockholm Karolinska study, which was published in the New England Journal of Medicine in 2000. That study discussed the environmental and heritable factors in the causation of cancer.[1] Investigators did a twin study looking at retrospective data on 44,788 pairs of twins. Since they shared the same genetic heritage, we would expect a very high concordance of cancer incidence in sets of twins. If cancer incidence was based more an environmental effect on gene susceptibilities, however, we would expect less concordance.

The results of the study were remarkable. For many of us, they confirmed what we had previously thought. There was very little concordance between twins in cancer incidence, suggesting that no more than 25 percent of breast cancer risk is hard-wired into our genes. Seventy-five percent or more is related to what we do to the genes, what washes over the genes, the experience, the function of those genes and their expression patterns

Simple things have profound influence on gene expression patterns and ultimate realization of the phenotype of disease or health and high-level function. Exercise is an example. Exercise can lower blood pressure, reduce cardiovascular disease risk, improve cognition, improve sleep, reduce stress, improve immunity, strengthen bones, improve muscle mass, provide greater states of cognitive alertness, and have profound influence on improving insulin sensitivity. If someone described a drug that could do those things, people would be incredulous. There would be a rush to invest in the company that produced it.

Although no drug can do those things, strength and conditioning exercises, both aerobic and resistance exercise, will accomplish all of those goals. Bill Evans, who was FMU Clinician of the Month in March 2001, discussed in detail the benefits of exercise.

Exercise Predicts All-Cause Mortality
In a recent paper in the New England Journal of Medicine, titled "Exercise Capacity and Mortality among Men Referred for Exercise Testing,"[2] investigators found that all-cause mortality was most strongly linked to exercise performance, as tested with an exercise EKG. This was not just cardiovascular mortality, but all-cause mortality. It is probably the best predictor of the simple, noninvasive ways of

assessing the trajectory toward health or disease.

The conclusion of the study is as follows: "Exercise capacity is a more powerful predictor of mortality among men than other established risk factors for cardiovascular disease." This would include such things as cholesterol and LDL/HDL ratios.

Simple things can have profound influence

Cancer is a disease we, as individuals and as a society, fear and dread more than any other. The general theme in traditional cancer treatment has been the complete annihilation of foreign invading cells by killing them through chemotherapeutic, radiological, or surgical methods. It is a "take no prisoners" approach to therapy. One might wonder how to design experiments to evaluate the risk/benefit tradeoff or cost-effectiveness of different approaches toward cancer treatment. How can we compare the traditional take-no-prisoners strategy to one that engages the body in immunological potentiation and functional improvement, which we might call lifestyle intervention?

The question of study design for doing cost-effectiveness analysis in clinical trials is a huge issue right now in methodological circles. A paper published last year in the Annual Review of Public Health[3] discussed design issues. According to the authors, cost-effectiveness studies require comprehensive evaluations of outcomes, other than just typical endpoints measured in clinical trials.

To evaluate cost-effectiveness fully, comprehensive endpoints should include quality-of-life measures that prove useful for interpreting endpoints other than those that may be objectively measured in the trial, and ultimately lead us into a more comprehensive decision-making process.

Challenges in Evaluating Quality of Life
How do you include quality-of-life variables such as improvement of the health span, functional ability, without simply evaluating such single parameters as negative histopathology, cytology, or blood chemical test? What was the quality of the patient's life? How is the patient doing?

Our lives are finite. We all know our lives will end at some point. The energy we have will transcend, move on, assume a different form. Energy is conserved; it is never lost. This is an inviolable physical law. The question is, what is the quality compressed within those years of living? How does it relate to the therapies we might be delivering, as a consequence of a having been diagnosed with a disease? What is the probability of recovery from that disease after undergoing the costs, emotional, physical and financial, for that treatment? These are powerful questions that have not received adequate focus in clinical decision-making.

Looking at Long-term Variables
As the authors of the paper discussed, in regard to design issues related to conducting cost-effectiveness trials, we ought to look at a broader array of variables in decision-making, rather than just the short-term variables. We should look at specific analytes and whether they are present in specific tissues before or after therapy.

Let's apply that model specifically to cancer. Let's look at the mechanisms we know lead to unregulated cell growth. One is signaling molecules that cause mitogenic cell replication—moving cells from states of

rest in their cycling to states of rapid metabolic activity—mitotic turnover, cell division, and replication. During these periods when cells are rapidly dividing, there is more opportunity for mutational events to occur in the replicative machinery, the genome of the cell. When these mutations occur in specific regions of the genome that operate and control specific critical functions in the cellular replicative process, such as the p53 tumor-suppressor gene, they can result in significant alterations in the inability to control cell division. It can dedifferentiate and become a monoclonal invasive, replicative cell, or, in other words, a cancer cell.

Compounds, molecules that enhance mitotic cellular turnover and activity, are often associated with increased oncological risk. Of those kinds of molecules, one type that has received considerable press coverage is the estrogen molecule, which we know enhances mitotic activity in certain cell types like the breast, endometrium, ovaries, and prostate. Many individuals have questioned cost-effectiveness ratios related to hormone replacement therapy (HRT) with estrogen in women.

This is a complicated question that has not been answered unequivocally. A recent paper in the Journal of the American Medical Association is titled "Hormone Replacement Therapy in Relation to Breast Cancer."[4] The authors of this paper point out that these data add to the growing body of evidence that long-term use of HRT—in this case specifically mixed conjugated equine estrogens and medroxyprogesterone acetate—is associated with an increased risk to breast cancer. According to these authors, such hormone use may be related particularly to lobular tumors in the breast. Therefore, women who engage in symptom management intervention with estrogen replacement therapy (ERT) of mixed conjugated equine estrogens do so at some degree of risk.

The Risk/Benefit Trade-off

Why is this therapy continued in the face of this advancing information? It is continued because the symptoms a woman experiences as she goes into perimenopause can be so debilitating and difficult that she seeks escape at almost any price, knowing the relative risk of breast cancer is very small. If the risk were more glaringly obvious, the therapy would be disallowed. It is somewhat similar to smoking and lung cancer. Does every smoker get lung cancer? Of course not. The tobacco industry has for decades been able to state that "there is no unequivocal evidence that smoking causes lung cancer." It is just an associative factor.

Although the evidence that smoking causes lung cancer is just associative, that evidence continues to mount, from animal studies, from in vitro studies, from cell culture studies, and from human epidemiological studies. The weight of that evidence is now so overwhelming that a decision is obvious—smoking does cause lung cancer, particularly in individuals who have specific types of susceptibility. We could apply the same argument to ERT, mixed conjugated equine estrogens, and breast cancer in women.

Evaluating Genetic Risk to Breast Cancer

Some women are more susceptible to the mitogenic changes that occur in breast tissue as a consequence of taking molecules that amplify cell cycling and alter genomic expression. That susceptibility may be related to the metabolism of those estrogen molecules and their influence on cell receptors and genomic messaging. That issue is reviewed in the New England Journal of Medicine, in an article titled "Production and Action of Estrogens."[5]According to the authors of this article, it is not just estrogens themselves (such as estrone and estradiol) but also their metabolites, the hydroxylated byproducts that

occur as a consequence of hepatic and breast hydroxylation reactions, that produce the 4-, 16-, and 2-hydroxylated estrogens. These are the substances that have differing influences on cell cycling.

When the 4-hydroxylated estrogens are methylated through the activity of the enzyme catecholmethyltransferase to produce the 2-methoxyestrogens, they are anti-estrogens, estrogen breaks, whereas the 4-methoxylated estrogens and the 4-hydroxyestrogens can have differing influences on cell regulation. In fact, the 4-hydroxyestrogens can be oxidized into the quinones, which can be apurinic and damage the DNA of the breast, endometrium, and ovaries, and increase oncogenic risk.

Metabolism of Estrogen

Therefore, it is the metabolism of estrogen that, in part, determines a woman's susceptibility to breast cancer. We are learning that estrogen metabolism is nutritionally modifiable based upon specific agents that influence the function of gene products or their expression . We are now, for the first time, beginning to understand the mechanisms by which nutrition plays a role in chemoprevention. It is not just statistical, epidemiological, the luck of the draw. We are beginning to understand which women, with what specific genotypes, may be at what risk, and what nutrients could modify that genotypic susceptibility into a non-cancer-producing phenotype.

Estrogen action becomes the theme of the story—its binding to the receptor site, its transport by sex-binding hormone globulin, its translocation to the nucleus. What are the metabolites? Is the process related to plasma concentrations hydroxyl derivatives that may ultimately be sulfated, glucuronidated, or methoxylated? What is the interrelationship between estriol to 2-methoxyestradiol, estradiol, and estrone on the mitogenic response to oncological risk? These questions now being asked, and their answers, are opening possibilities for reframing the equations of risk and benefit in light of genomic and functional medicine.

Estrogen as a Breast Cancer Risk Factor

Estrogens can be seen as a breast cancer risk factor in women who have specific susceptibilities, and who have certain nutrition and lifestyle habits. This statement applies to information we learned years ago about smoking and breast cancer in women. You may recall that the N-acetyltransferase genotype affected breast cancer risk in women. Women smokers who were slow acetylators had higher breast cancer risk. Specific genotypes and environmental susceptibilities increase phenotypic outcome possibility. This new information supports the concept that diet, lifestyle, and environmental factors play important roles in both the prevention and possible treatment of cancer.

We have some extraordinary new reviews in this area. The whole concept of receptors and breast cancer in medicine is discussed in a review by Dr. Fritz Parl, one of our previous FMUClinicians of the Month (April 2002). He talks about the way estrogen synthesis and metabolism control these mitogenic and cell-replicative cycles.

Synergistic Effect of Dietary Factors

When we eat complex diets and live in complex environments, we experience synergy, either positive or negative, between different factors. We don't take one nutrient at a time. Paul Talalay, at Johns Hopkins University, has been doing a lot of work on cruciferous vegetables and chemoprevention. He developed a mathematical model for synergy, that permits its evaluation in an objective manner. It is a multiplicative effect; the whole is greater than the sum of its parts.[6]

We are talking about true synergy. How do you demonstrate synergy at the physiological level? What are the mechanisms by which you can show this multiplicative value when you take more than one thing at a time and get interactions? The permutations and combinations of multiple substances taken simultaneously are extraordinary. Think of taking just 10 different things at a time and all the permutations and combinations you can have of those, one-at-a-time, two-at-a-time, three-at-a-time, four-at-a-time, and so forth.

Complex Studies Yield Simple Truth

The extraordinary complexity of these types of studies has become a barrier for many individuals. They refuse to accept that anything is there; if they cannot see it, it does not exist. If they cannot prove it by some reductionist method, it does not exist. Experience, however, is a strong teacher. We are beginning to see the emergence of light in the area of cancer therapy and the role of nutrition. When we piece together the information from several studies, it becomes just as clear as the smoking and lung cancer story. It is so profound and so reproducible that even in the absence of complete proof, you have to conclude that something is there.

What does the association among diet, nutrition, and cancer prevention look like? In an editorial in the Journal of Nutrition, titled "Diet, Nutrition and Cancer Prevention: Where Are We Going from Here?"[7] Dr. Go and colleagues discuss the national declaration of the war on cancer that occurred three decades ago. They point out we are only now beginning to recognize that diet, lifestyle, and environment are the principal factors we should focus on to achieve the objective of lowering the incidence of cancer. If we don’t put our energy into those areas, we will never be successful in winning the war on cancer, because the most effective way of winning it is to prevent it.

The same conclusion emerges from a paper by Dr. Lawrence Kushi, Joan Cunningham, James Hebert, Robert Lerman (a member of our functional medicine staff), Elisa Bandera, and Jane Teas. This paper, which discusses the macrobiotic diet and cancer, appeared in the Journal of Nutrition.[8] It is one of the most scholarly and complete articles I have seen about the role of a specific dietary intervention approach and how it may influence the cancer process. It is based on biomedical, epidemiological, biological, and animal work. The authors recognize that the macrobiotic diet, the Michio Kushi approach, is consistent with information is emerging from research labs that helps minimize the factors that alter the intercellular communication in ways that we associate with cancer—dedifferentiated, unregulated cell growth.

The Whole Foods Diet

Other diets, such as the Mediterranean Diet, have historically been associated with lower incidence of cancer.[9] Do these diets have anything in common with the macrobiotic diet? They certainly do. They contain significant amounts of natural, fresh, unrefined foods, low amounts of synthetic ingredients, and low amounts of food technology factors that make foods shelf-stable. These diets must be based on rules of reason. Clearly, we do not want to expose people to aflatoxins, mold metabolites, and toxic amines that come from poor preservation of food. On the other hand, we also want to recognize that fresh and whole foods contain substances unique to them, and organic foods may even have additional value.

Organic, as a system of agriculture, may have profound influence beyond just the removal of pesticides. It teaches us about ecology. It reminds us that food for one person is the waste of another. It reminds us we are part of a system, not separate from it.

Cancer as a Disease of Energy Flow

It may be that part of the process of the unregulated cell growth of cancer is related to the flow of energy. Cancer, which is a disease of the late 20th and early 21st century, may be a disease of energy, lack of control, energy flowing through our bodies in such a way as to create unregulated growth. By redeveloping a sense of community, interconnection, and purpose, we may quell that unregulated cell growth and induce quiescence.

It is an interesting metaphor. A number of books about cancer have suggested it is a disease of our time because of its unregulated, high-energy, uncontrolled growth. Perhaps there is something about living within a community, eating natural, organic foods, that speaks a strong message to our genes through our interconnection to our environment

What are the processes that lead to cancer? In its development, cancer goes through five separate phases. First is the initiation phase, followed by the propagation phase. During the third, angiogenesis phase, the cancer cell must feed itself with blood. In the fourth, apoptotic stage, if the body recognizes the cancer cell as a foreigner, it can be expunged by normal cell suicide mechanisms. The fifth and final phase is the metastatic phase, in which the cancer sends its cells out to distant sites for proliferation.

Research has discovered that nutrition, environment, and lifestyle play roles in modifying each step in this cancer process. They have the ability to affect initiation, propagation, angiogenesis, apoptosis, and metastatic events. We must ask ourselves, therefore, if nutrition represents prevention or treatment. If it is treatment, is it adjunctive or primary treatment for the cancer? The emerging consensus is that nutrition is both prevention and treatment. Most individuals with cancer use whatever means they have available to create their best chance for survival. They generally do not use just one thing at a time. They do not employ only nutrition or only chemotherapy. They look at everything that is available. Therefore, following a cancer diagnosis, nutrition is almost always adjunctive treatment, used along with whatever else the patient may select for his own treatment.

Dr. Folkman’s War

Judah Folkman, a major contributor to our understanding of this field, is the researcher who discovered the key role of angiogenesis in tumor growth. He has also been a valiant warrior for the last three or four decades. In the book Dr. Folkman's War, author Robert Cook discusses angiogenesis and the struggle to defeat cancer.[10] This book is not just about angiogenesis or Dr. Folkman. It is about the whole nature of this particular transition, the paradigm shift we are undergoing in recognizing where cancer comes from and how to win the war to defeat it, mobilizing the body's own capability for recovery and immunological defense and healing. It is a powerful book.

Dr. Folkman’s War also covers the transliteration of some information and how it can sometimes be prostituted and used for profit instead of healing. Cook mentions the promotion of shark cartilage and the exaggerated claims that sharks don't get cancer (although we now know sharks do get cancer). Some individuals seized and sensationalized the concept of anti-angiogenesis and began excessively promoting shark cartilage. That type of sensationalism, which leads people to false expectations and sets them up for disillusionment, is an example of events that can seriously damage this field. Practitioners are responsible for putting information into an authentic context for patients who are facing cancer. They must give patients realistic expectations and hope, but they should also explain that no one has the final answers, and there is no such thing as 80 percent recoveries that they can guarantee

A number of macronutrients influence the cancer process. Some studies indicate that specific amino acids in protein may influence cancer. Those of you who have been subscribing to FMU back to its Metabolic Update days may remember an interview with Dr. Gary Meadows from the Washington State University College of Pharmacy. He discussed the effect of phenylalanine and tyrosine restriction on melanoma. He recently wrote a paper that appeared in the Journal of Nutrition, in which he discusses the role of restriction of those amino acids in preventing the expression of genes associated with human melanoma.[11]

Some amino acids, therefore, may be more active than others in promoting cell division. Phenylalanine and tyrosine are precursors of the dopamine family, so there may be a relationship with neurotransmitters that influence cell replication. Think about stress and cancer. Could it operate through these mechanisms, in which certain hormone messengers associated with stress increase cell cycling and the processes we associate with cancer?

A paper published in the Journal and Parenteral and Enteral Nutrition compares the role of a high-protein diet enriched with arginine, fiber, and antioxidants to a control diet in improving immune function in critically ill patients.[12] This paper confirms what we have thought for years. It examines the role of a high-protein diet enriched with therapeutic doses of arginine and nitric oxide synthase, substrate, fiber, and antioxidants to improve immunological defense in critically ill patients. This diet showed marked benefit. We might use nutrients beyond normal levels to augment the function of an individual who is in a disease process

Fatty acids are also involved in this process. We used to think of fats having little benefit beyond providing 9 calories per gram as a calorie-rich source of energy. Now we know fatty acids engage in cellular communication and gene expression. Fatty acids of the omega 3 family, along with omega 6 GLA, influence gene expression patterns and can modify inflammatory mediators.

A paper in Current Opinion in Clinical Nutrition and Metabolic Care discusses the role of fatty acids in regulating gene expression.[13] Short-chain fatty acids, such as butyric acid, produced in the gut by friendly bacteria, by the fermentation of non-digestible carbohydrates like fiber or oligosaccharides, inhibit invasive human colonic cancer by modulating the expression of various genes in the colonocyte. These genes then communicate an effective message of quiescence.[14]

The Role of Carbohydrates
Carbohydrates also play a role in the cell-signaling mechanism. Insulin and insulin-like growth factor are related to colonic cancer. An article in the Journal of Nutrition reviews this topic.[15] The author discusses hyperinsulinemia and increased stimulation of the cell replicative process, because insulin is both a gene response modifier and a glucose management hormone. There are rich numbers of peroxisome-proliferated activated receptors (PPARs) in the cytoplasm of colonic cells. These PPARs interrelate with insulin modulation to affect cell signaling, intercellular communication, and signal transduction. Hyperinsulinemia and glucose intolerance may also track back to increased risk of cell replication.

There is a strong relationship between insulin resistance, hyperinsulinemia, and diet. Insulin resistance increases the production of C-reactive protein (CRP), an inflammatory marker. A recent paper in the American Journal of Clinical Nutrition discusses this topic.[16] The authors examined the relationship between a diet with a high glycemic load and plasma concentrations of high-sensitivity CRP. This

relationship is an important consideration in cancer because angiogenesis is associated with high levels of inflammatory mediators. Increased inflammation, as indicated by high CRP levels, reveals increased angiogenic potential. This is another way a high glycemic diet could influence cell replication and cell progression in cancer.

Botanical Factors and Antioxidants in the Modulation of Inflammatory Mediators
Factors other than insulin and glucoregulation can also modulate inflammatory mediators. Anti-inflammatory botanicals found in vegetable-based diets influence the production of eicosanoids, lipoxygenase leukotrienes, or interleukins. These powerful adjunctive agents can be used in cancer therapy. They include the pentacyclic triterpenoids found in some plants, such as the spices curcumin, turmeric, and rosemary. These substances have anti-inflammatory activities and can be used as an adjunct in cancer therapy. In a recent paper in Integrative Cancer Therapies, Dr. Jeanne Wallace discusses the use of botanicals to modulate the angiogenic inflammatory mediators.[17]

Antioxidants play an important role as well. A review of antioxidants and cancer therapy, their actions and interactions with oncologic therapies, by Davis Lamson and Matthew Brignall, appeared in Alternative Medicine Review.[18]

The Functional Approach to Cancer Management
The field is opening up. The functional approach toward cancer management involves not just a single agent, a single molecule against a single diagnosis, but a comprehensive combination that can reduce the risk of promotion, angiogenesis, metastatic events, and increased apoptotic cell suicide. The underpinnings of this field lie in epidemiology, observational animal work, cell biological work, and gene expression work. All the tools of science are being brought to bear on the connection between nutrition and cancer management

INTERVIEW TRANSCRIPT

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JB: This month’s Clinician of the Month is an appropriate choice for our 20th anniversary issue. He is well respected in the Pacific Northwest Community, as well as nationally and internationally, for his work in nutritional oncology. He is a naturopathic physician, a licensed acupuncturist, and a member of the Seattle Cancer Treatment and Wellness Center. Dr. Paul Reilly graduated from Bastyr University in 1985.

Dr. Reilly completed his master’s degree in Acupuncture in 1995 and holds national accreditation as a licensed acupuncturist. He has risen to prominence for his work in adjunctive cancer treatment and nutritional oncology. It is a privilege to welcome you, Paul, to Functional Medicine Update and our 20th anniversary celebration. What led you to direct your career toward nutritional oncology?

PR: It was actually an unplanned transition. I began working with some patients who saw an oncologist

locally and, as he saw patients doing better with nutritional support, he began sending more patients. Over a period of several years, we became increasingly interested in integrated cancer therapy. In fact, he was instrumental in helping to open the Seattle Cancer Treatment and Wellness Center about five years ago.

The Evolution of Nutrition in Cancer Management

JB: A member of our functional medicine staff, Dr. Robert Lerman, was for more than 20 years a professor of medicine at the Boston University Medical Center. With Dr. Lawrence Kushi, Michio Kushi's son, Dr. Lerman is co-author of a recent article in JAMA. (See reference #8.) That article discusses the macrobiotic adjunctive approach toward cancer prevention and treatment. It demonstrates the increasing sophistication and scientific support toward nutritional adjunctive therapy. How have you used the literature in your nearly 20 years in this field, and how have your colleagues responded to it?

PR: There has been quite a bit of change over time as we begin looking at nutrition and cancer. At first, we were looking primarily in terms of prevention. The evidence is pretty overwhelming at this point that diet and lifestyle have a major impact on cancer.

That was the topic of an article in the New England Journal of Medicine in 2000. They looked at the common cancers and what impact genetics versus diet had. (See reference #1.) It was a twin study, so they had the same genetics in two siblings. They found that for all of the major cancers, diet and lifestyle were far more important than genetics as a risk factor. I thought it was an elegant way to confirm what all the different epidemiological studies, in vitro studies, and animal studies had shown—that diet can definitely make a difference in cancer.

We are also learning that by changing the diet, you can help not only with prevention of cancer, but also in the later stages, the promotional and the progression stages. As a clinician, it's often too late to worry about prevention when I see a patient who already has cancer. What I look for are the things we know in a diet that will promote the growth of preexisting cancer and what things we can remove without having a negative impact on the patient.

Starve the Tumor, Feed the Patient

My mantra is starve the tumor and feed the patient. That's what I try to do. I find that many diets have a common thread in the middle. They vary in their preponderance of macronutrients or micronutrients, but the common thread is that you need to get most of the garbage in the American diet out. If you put in real food, close to the way it's grown, organic if possible, ensure adequate protein, and get rid of things like sugar, alcohol, arachidonic acid, and processed trans fatty acids, people will do better.

In particular, I focus on trying to reduce insulin and hyperinsulinemia in patients because there have been multiple studies showing insulin is a major promoter of many tumors. Presenters at the American Society for Clinical Oncology (ASCO) two years ago described two different studies looking at insulin and survival in cancer. In the most remarkable study, a Dr. Goodwin found that hyperinsulinemic women with breast cancer had a recurrence of cancer 10 times higher than did women with normal insulin levels. There is not a chemotherapy drug out there that makes a tenfold difference in survival. Here is a simple dietary protocol that we can work on to make a dramatic impact on a woman's risk.

Nutrition and the Hallmarks of Cancer

JB: In a seminar for professionals in this area, you spoke about the hallmarks of cancer. One is growth

signals. We know the insulin molecule has a growth signaling capability. You also talk about insensitivity to anti-growth signals, the evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Do you feel there are ways to use nutrition in dealing with each of those areas of difficulty in patients with cancer?

PR: I think we are beginning to learn ways. We're finding more and more that cancer is a problem in cell regulation as much as in DNA. It's true that there are mutations that occur in cancer, but even when those mutations are present, if you change the extracellular environment, it impacts how those changes manifest. As we go along, we are finding there are nutrients that affect the growth signals. There are nutrients that promote apoptosis. Some of them, like green tea, are quite common nutrients. There are nutrients like soy that can affect angiogenesis, or vitamin E succinate that can affect anti-angiogenesis. Some of the polysaccharides or the fractionated citrus pectin can affect metastasis. No one of those nutrients alone is enough to be called a cure for cancer, but if you add up enough of those cumulative improvements, you can change the balance between the growth and the non-growth outcome in a patient and improve survival.

How to Prevent and Treat Cancer with Natural Medicine

JB: You describe that program in How to Prevent and Treat Cancer with Natural Medicine, the book you wrote recently with Drs. Murray, Birdsall and Pizzorno. You incorporated many of these elegant ideas in a very understandable format in that book. Is it available yet?

PR: It will be on the market in August of this year.

Dr. Reilly's Clinical Approach

JB: I imagine most of the patients you see have already been diagnosed with cancer and may have begun some type of traditional therapy. How do you support the patient with cancer who elects to follow traditional therapies? I have heard that if a patient is having radiation or chemotherapy you should not introduce therapeutic nutrition because it might reduce the efficacy of the traditional therapy. How do you approach that problem?

PR: It's a very common misconception, and it's based on a somewhat simplistic view of how chemotherapy or radiotherapy work, which is the idea that it damages the DNA and the cell just kind of miraculously goes away. In fact, what we now know about all of those therapies is that there is a second phase to the process, which is apoptosis. In fact, nutrients facilitate that second phase of apoptosis, thereby actually increasing tumor kill.

When I began working more and more with cancer patients, I decided to look for research that could back up whether or not we could safely use nutrients with patients. As hard as I dug, it was very difficult to find any research that could demonstrate harm. I kept finding article after article saying that with nutrients you reduce side effects without any impact on the tumoricidal activity, or, more often, you reduce side effects and, in fact, survival is a little bit better, or tumors shrink a bit more. Patients are able to complete treatment without having to discontinue due to side effects. At this point, I'm aware of about 400 articles, and better than 95 percent of them show benefit. There are a few specific combinations that I think are unresolved, and we just avoid those.

Accepting Nutrition in Cancer Treatment

JB: When we first began this audiotape series 20 years ago, in 1982, standard medicine would not have entertained the concept that nutrition could be beneficial in treatment of cancer. Do you see a softening of that resistance in the year 2002? Is traditional medicine being influenced by the weight of this evidence you're describing?

PR: I think we are beginning to see a shift in the overall approach to this. The Journal of Clinical Oncology in 1995 contained an excellent article titled "Shifting the Cancer Paradigm: Must We Kill To Cure?", which addressed that issue.19 According to the authors, the infectious disease model of killing an invader could be not only not the best approach, but might, in fact, be counterproductive. What you want to do at times is select for resistance to a more aggressive tumor.

The article talked about affecting some of those regulatory signals, and suggested that's the direction in which we want to move. That is also the direction we are finding research in pharmaceuticals is moving. Gleevec is a perfect example of a new drug that affects growth signaling in chronic myelogenous leukemia, rather than killing the leukemia cells. As we get more sophisticated in our understanding of cancer biology, we are at the same time getting more sophisticated in our understanding of nutrition's impact on a cellular and genetic level. I think there will become a merging of the approaches.

Antioxidants in Cancer Therapy

JB: In FMU a couple of years ago we had a discussion about antioxidants and cancer therapy (April 2000). Some concerns were raised about changing the redox potential of a patient who may be undergoing chemotherapy with antioxidants. Obviously, things have changed with regard to research and clinical observations in the field. What is your opinion about the use of antioxidants?

PR: I would have to have to say that's a twofold question. First, as I mentioned earlier, the vast preponderance of the evidence suggests improved outcomes, and medicine is an evidence-based science. We have to go by research, not by theory. The concern at that time, as it was voiced, was that there could be some long-term pharmacodynamic interference. But the reality is, if you have better survival, then those people will be grateful not to have to worry about long-term pharmacodynamics. When you're really looking at tumor response rates and survival, that's the ultimate determinant.

The other concern is the number of patients who do not even take part in conventional therapy because of their concerns about side effects, or who have significant impact from that therapy. For example, between 1 and 5 percent of patients who go through conventional therapy end up with a secondary cancer from the treatment itself. Then you have patients who may survive their treatment, but are in chronic heart failure or chronic renal failure from the treatment itself. You need to add up all of those factors as well in the survival. When you add them up, the benefits of using the nutrition far outweigh any theoretical concern at this point.

Outcome Studies

JB: I believe this is where the difficulty arises with outcome studies. I've learned that even in traditional oncological treatment, we don't have very good outcome studies, because each patient is individualized to his or her own cancer and treatment. Finding a statistical norm is often very difficult. How do we respond to those who say there are no outcome studies on nutritional support for the tumor-bearing patient?

PR: There are some. At this point, they're quite small. The problem we have run into is, as you say,

getting enough matched patients so that we can do the same thing with each patient. In using natural therapies, we individualize treatment. It makes it difficult to say, well, we're just going to add vitamin E, or we're just going to do selenium. What people are beginning to look at now is perhaps having sort of a basic protocol of certain nutrients that would be appropriate across the board. We could look at advanced cancer patients, who often have a relatively short survival time, and look at how those patients compared when half of the group gets a matched nutritional protocol and the other half gets just standard care.

There have been studies looking at chemotherapy or radiation therapy and survival. When you look at overall survival, the statistics can actually be very depressing. Fifty percent of people who are diagnosed with cancer will die of their disease. More important is the fact that even though you sometimes get a response to chemotherapy, you don't always get significant improvement in survival. The Lancet looked at the increase in survival with chemotherapy in July of 2001 and found the average gain of overall survival within 10 years of chemotherapy was only about 5.4 months for premenopausal women and about 2.9 months for postmenopausal women.20 That's a relatively small gain when you look at all of the negative side effects of chemotherapy.

The Clinical Approach

JB: Let's discuss your approach when a patient comes in. You've talked about insulin signaling and managing hyperinsulinemia and insulin sensitivity. You alluded to angiogenesis and promotion of cell recognition and cell death through apoptotic changes. What kind of tools would you use? Would you start with a detoxification approach?

PR: I think the most important thing for all of these patients, is getting them onto a good healthy diet. Take away the things in their diet that are fueling the uncontrolled growth of the cancer. I would not necessarily do a detox diet at this phase, because it's important that they get adequate protein and nutrients, but I'd clean them up onto an extremely healthy diet.

Then we add nutrients that are specific for whatever phase of treatment they will be in. Whether for surgery, radiation, or chemotherapy, there are specific nutrients that are most appropriate for each particular agent. Next, we might add herbs or vitamins that have shown benefit in their particular type of cancer. For example, melatonin in most of the hormone-responsive cancers has been shown to increase responses. Last, we'll do individual treatment for whatever else is going on. We see our patients regularly, so that as we see how they're responding to treatment or if their blood counts are dropping or they're having a complication, we can modify the protocol as they go along.

The Typical Cancer Patient

JB: Would you give us an overview of a typical patient you've seen, and describe what kind of improvements you've seen as a typical response?

PR: In general, what I see and, more important, what some of the oncology nurses at the offices of doctors who refer to us see, is that those patients have far fewer complications. Very rarely will we have patients who must be hospitalized due to complications of treatment, whereas that's a very common complication in regular therapies. Second, their quality of life is better during treatment. When you see patients in our treatment room, they're very often sitting there eating their lunch, playing cards, laughing, having a good time, because they're not having the level of side effects that often occurs. Finally, we find that, in general, patients do much better in terms of their predicted survival and their actual survival. In

some cases, the results come as close as possible to what could be a miraculous turnaround.

Communicating with Patients
JB: How do you deal with a patient's expectations and presumed outcome? Of course you want to provide hope and opportunity for a patient with cancer, but you also want to provide some sense of realism without unrealistic expectations. How do you balance that in your communication with patients?

PR: During that dialogue, I emphasize that I'm not promising a cure. Nor do I have all the answers. At the same time, however, I talk to them about the bell-shaped survival curve and how for all cancers, there is a percentage of people who are at the far end of that bell-shaped curve. Generally, what we find is that those are the people who have taken an active role in their treatment. They have changed their diet; they've reduced their stress; they've reduced factors that caused the cancer in the first place.

If they can make enough changes in their lifestyle, along with their conventional therapy, they have the maximum chance to move themselves along that curve. I essentially try to make it clear to them that we still cannot cure everybody, but we certainly can see longer survival and better quality of life. Occasionally, we hit those home runs where someone who was not expected to live is alive five years later with no evidence of their disease at all.

Integrating Nutrition into Traditional Protocols
JB: From what you've said, it seems obvious that nutritional intervention should be part of every cancer therapy, regardless of what that therapy might be. Yet, obviously, nutrition is not a part of most standard treatment. Why is that the case?

PR: As with so many other specialties, much of the research is funded and driven by pharmaceutical companies, so they are getting the majority of the publications that talk about drug interventions or new forms of radiology, and so on. Doctors don't have time to study all the research on nutrition and botanicals. Seeking out and finding these articles is a full-time job.

Part of our role at Cancer Treatment Centers of America is to lead the study of this new paradigm of treating cancer and prove its superiority so that it will become a market-driven change. Many of the changes happening in medicine now are coming from the bottom up. The patients are insisting that their doctors learn about this. As it becomes more and more clear that patients do better when they pay attention to their diet, when they pay attention to micronutrients and macronutrient levels, more and more patients will demand that type of therapy. Also, when insurance companies see they're saving money because fewer patients are hospitalized with complications, they'll begin to cover more of these interventions as well.

Problems in the Age of Specialization
JB: I have a personal experience that validates what you've just said. A friend I've known for many years is a fine oncologist who is well respected and a very humanistic person. One Saturday, he came out to the office and we were talking about the literature, just as you were describing. I made an offhand comment about the increasing body of literature suggesting that vitamin E could help prevent some of the adverse side effects of adriamycin toxicity, cardiac toxicity. He was shocked by that statement.

He asked where I got the literature. I told him there had been quite a few studies on this. It started in

animals, I think in dogs, and then moved into some open label trials with humans. He said he followed his literature carefully, but he did not recall seeing that. I invited him to go to our literature, library, microfiche, and computer searching system to see what we could find. This was probably 10 years ago. We picked up about 17 papers from our files on this topic from the animal studies to the human observations.

Problems of Communication

He read over the abstracts and looked at some of the articles I had printed out from that search. He looked up at me in surprise and said he hadn't realized one abstract was in Oncology, a journal he read every month. He called it "his" journal. He said the reason he hadn't read it was because he didn't know what alpha-tocopherol was. The title of the paper was "The Effect of Tocopherol on Adriamycin Cardiac Toxicity." We get into a vocabulary issue sometimes.

PR: That's where integrated therapy is important. I often have to remind patients that I'm not going to second-guess which agent or dose their oncologist has recommended because that's his area of specialty. He has spent 12 years learning those things. In the same way, my area of specialty is the nutrition to go along with that therapy; that's my strength. We have other people whose strength is using Oriental herbs. Let the specialists do their specialties, but recognize the importance of each and start working as a team.

The Importance of Integrated Therapy

JB: That's a good message for this 20th anniversary of FMU. That has been the underlying theme we have tried to communicate through this 20-year period. There are people who have all sorts of wisdom in different areas of investigation. Rather than having them remain like individual pearls on the beach, we ought to string them together to make a necklace. It sometimes seems that barriers of pedigree, language, and vocabulary insulate and isolate us, preventing us from sharing the best of what we know and delivering that information to the individuals in need.

PR: I think we need to build more bridges rather than more fences. Part of it is just increasing the dialog between specialties or even among different fields, so we begin to understand the approach and the science behind what each of us is doing.

A New Era in Cancer Prevention and Treatment

JB: When I was in Scandinavia I talked with Drs. Hemminki and Lichtenstein, two of the principal authors of the New England Journal of Medicine paper you talked about on environmental and heritable factors in the causation of cancer. I asked them, based on their research at the Karolinska Institute in Sweden, if they felt this would be the start of a new era in cancer prevention and cancer treatment. I was referring to the important role that environment plays in these cell signaling mechanisms that ultimately lead into oncological events. They both felt we were at the threshold of a great paradigm shift. The view that cancer had to be killed and that this was a military action with no prisoners to be taken was ending. It was being replaced by a new model that stressed the importance of finding the right biological modifiers for intercellular communication to create an outcome of recognizing foes from friends and getting rid of foes naturally. How do you view that from your perspective as a leader in this field?

PR: I think you said it perfectly. We are slowly moving to a model in which cancer can be a chronic illness. There may be cancer cells there, but if they are not growing in an unregulated manner, they will not threaten the life of the patient. I often tell patients when they first come to see me that if they make

the changes, we can hope it will help overcome their cancer. I tell them they should be making these changes anyway, because it will also help them in terms of their risk of premature aging, heart disease, and all the degenerative illnesses that will reduce their quality of life. It becomes a win/win situation. If they make these changes they will, we hope, survive their cancer, and they will live much healthier lives for much longer on all levels at the same time.

Life Lessons from Cancer
JB: We all have lessons to learn in life, and some lessons are harder to learn than others. I infer from your statements that cancer provides an opportunity for a person to look deeply and introspectively into his or her own lifestyle and ask who's in control.

PR: Right. It's a very loud message that something is not working properly. The old definition of insanity is to keep doing the same thing and expect a different outcome. I think if you want a different outcome, you need to change the things that allowed the cancer to occur in the first place.

Conclusion
JB: Thank you for that empowering message. We wish you the best in your continued work and look forward to the publication of How to Prevent and Treat Cancer with Natural Medicine

I thank Dr. Reilly for his insightful, optimistic, and empowering comments. I want to follow up with a few of the themes he introduced. Let us talk first about soy, the use of which has been quite controversial in both cancer prevention and cancer therapy.

Dr. Mark Messina was chairman of a recent symposium on the role of soy in preventing and treating chronic disease. Following that symposium, an article titled "Gaining Insight into the Health Effects of Soy, But a Long Way Still to Go: Commentary on the Fourth International Symposium on the Role of Soy in Preventing and Treating Chronic Disease," appeared in the Journal of Nutrition.[21] In that article Dr. Messina suggests we still need to answer a lot of questions before we fully understand the role of isoflavones, lignans, and other soy components in physiological function and can come to "unequivocal conclusions." The emerging evidence, however, clearly indicates that soy plays a positive role in the prevention and possible treatment many common age-related chronic diseases, including cancer.

Soy’s Hormonal Effects
A number of researchers have investigated the hormonal effects of soy in premenopausal women and in men. Mindy Kurzer recently published a paper on the effects of soy on both men and premenopausal women.[22] There is strong evidence that 40-70 mg per day of soy isoflavones showed few effects on plasma hormones or semen quality in men, and the data do not support concerns about effects on reproductive hormones and semen quality. Therefore, the effects are more modulatory or adaptogenic than pharmacological.

The term "phytoestrogen," which has been used to describe soy isoflavones, labels and stigmatizes them as if they were similar to equine conjugated estrogens. They are not. They are modulators. They are agonist/antagonists of estrogen action that have a normalizing effect, and that is what Dr. Kurzer's work appears to suggest.

Soy and Breast Cancer

What does a critical review of the literature reveal about soy and breast cancer? In a paper published in the Journal of Nutrition, Messina and Loprinzi examine the interrelationship of soy and breast cancer.[23] Overall, the data are not impressive that the consumption of soy affects the risk of developing breast cancer, or that soy consumption affects the survival of breast cancer patients. As Dr. Messina stated, "Consequently, if breast cancer patients enjoy soy products, it seems reasonable for them to continue to use them."

Soy may be part of an overall strategy, but it is not the only strategy for modulating a hormone-dependent cancer. Individuals with serious fear about breast cancer, estrogen-positive receptors, and soy, may be reassured that soy isoflavones are agonists/antagonists and therefore can have a dual effect, depending on estrogen status and estrogen signaling.

Adaptogenic Effects

The physiological concentrations of dietary genistein are dose-dependent. At high pharmacological doses, they may activate cell replicative growth in breast cancer tissue. This was shown recently in an animal study in which mice were implanted with human breast cancer tumors and given high [I'm not so sure they were all that high as I read it they gave 1000µg/g in the diet this should be compared with something like 50 mg isoflavones in a 45g serving of UltraMeal. His point is well taken and many studies even those we cite as good news use absurdly high doses, I don't think this study supports his point.] pharmacological doses of genistein.[24] It did appear to increase cell turnover. I want to emphasize and differentiate between normal dietary intake levels of 40-70 mg of isoflavones and therapeutic pharmacological doses in the range of hundreds of milligrams per day. We often get confused when we talk about diet versus pharmacy. We should make a differentiation on the dose/response relationship.

A point/counterpoint debate about soy intake for breast cancer patients recently appeared in Integrated Cancer Therapies, looking at whether or not soy is desirable for a cancer patient, particularly a breast cancer patient.[25] My understanding from this paper is that the evidence indicates the benefits at normal dietary intake outweigh the risk. It is desirable to include soy as part of a complete diet approach, but not as a pharmacological magic bullet. This would be true unless there is strong evidence, when measuring hormone panels in women with estrogen-positive receptor breast cancer, that some untoward and unexpected influence on estrogen metabolites or estrogen levels is occurring. That occurrence would be the exception, not the rule.

Isoflavone Effects on Breast Tissue

Many groups, including the Medical Research Council Biostatistics Unit at the Institute of Public Health in Cambridge, England, have recently studied isoflavones and breast cancer. The results of those studies indicate isoflavones have no demonstrable adverse effect on breast density, estradiol, or gonadotrophins in double-blind, randomized, placebo-controlled trials when they are given at doses considered to be at the average dietary level.[26]

If anything, isoflavones favorably influence estrogen metabolism and help to increase 2-hydroxyestrogens at the expense of the 16-hydroxyestrogens. They would, therefore, be considered to have beneficial effects on estrogen metabolism and excretion.

Soy and Thyroid Function

We also have seen papers indicating that soy does not have an adverse effect on thyroid function when it is taken at normal dietary, not pharmacological, levels. This research indicates that information about the risk of producing goiter from soy intake is unfounded and reactionary. If we were to examine the role of isoflavones at normal dietary levels across the range of estrogen-producing and metabolizing effects, including premenopausal, menstruating, perimenopausal, and menopausal women, we would find that, in all cases, there is evidence of amelioration and benefit, not adverse effects. This finding applies to many papers. The March 2002 Journal of Nutrition contains a compilation of all the papers presented at the International Soy Conference. Take a good look at all those papers and draw your own conclusions about soy. My conclusion is that inclusion of modest levels of soy is desirable.

Phytonutrients also play a role in modifying detoxification function. Phytochemicals from cruciferous plants can help protect against cancer by modulating carcinogen metabolism. As I mentioned earlier, Dr. Paul Talalay at Johns Hopkins has been a leader in this field for more than a decade. He wrote a review in the Journal of Nutrition about the role of crucifers containing glucosinolates and their influence on phase I and phase II enzyme induction and detoxification.[27]

Chemicals such as indole-3-carbinol help modulate estrogen metabolism and lower the risk to the 16-hydroxyestrogens that are more proestrogenic and cell proliferative.

Indole-3-Carbinol

Some individuals have asked if there is any value in males consuming crucifers rich in indole-3-carbinol as a downstream metabolite. A paper in the journal Oncogene discusses the influence of indole-3-carbinol on inducing cell growth inhibition, G1 cell cycle arrest, and apoptosis in prostate cancer cells. The authors suggest it may be of benefit to males to prevent prostatic hypertrophy, hyperplasia, and perhaps even prostatic conversion into prostate cancer.[28] These regulatory phytochemicals have a non-gender-specific effect on detoxification and cell cycling.

The effect is based on their total intracellular accumulation of these phytochemicals from crucifers (cabbage family), allium (garlic and onion family), and apiaceous (carrot and celery family) vegetables. The phytochemicals in all of these vegetables help increase and influence the detoxification enzyme function, including and principally the phase II detoxification enzymes, the conjugation steps. They increase intracellular glutathione levels with effects on redox potential of the cell. They have a beneficial effect on establishing quiet-cell architecture, meaning the cells are not rapidly dividing. A recent review in Carcinogenesis discusses the role of phytochemicals on regulating intracellular glutathione and detoxification phase II enzymes.

The gut itself plays a role in altering immune system function. Polyamines in the gut lumen influence cell replication and can be produced by certain bacteria, compounds like spermidine, spermine, cadaverine, and putrecine, the toxiform or putrefactive bacteria in the gut. These polyamines influence neoplastic growth and disease. A series of papers in the European Journal of Gastroenterology and Hepatology discuss polyamines in the gut lumen, their bioavailability and metabolism. The papers describe the role these polyamines play in neoplastic growth and disease as a consequence of the putrefactive reactions that occur with certain gut bacteria in the colon.[30,31,32,33,34] These polyamines can, therefore, be associated with colon cancer. Inhibition of polyamine metabolism by polyamine analogs and

nonsteroidal antiinflammatory drugs, agents that lower inflammatory processes in the gut, may be useful for helping to prevent colorectal cancer.

A diet rich in antiinflammatory phytonutrients and rich in probiotics and prebiotics that facilitate friendly bacteria could be called an anti-cancer therapy. It could provide diversion of polyamines in the gut and improve gut floral integrity. We can look at the gut as a bioreactor producing substances that may have mutagenic, carcinogenic, or cell replicative risk. By modifying the environment of this bioreactor through diet, lifestyle, stress factors, and bacteria, we can send a quiescent signal to the rest of the body, a signal that the cells do not need to divide rapidly.

Dietary fiber and non-digestible carbohydrate are an important part of both chemoprevention and perhaps adjunctive nutritional therapeutic programs for individuals with cancer. We now know there are many types of fiber, including soluble and insoluble fiber, oligosaccharides, and fructans.[35] Some fiber stimulates friendly bacteria, causing the death by starvation of unfriendly bacteria capable of deconjugating bile acids and producing nitrocytic compounds and excessive quantities of biogenic amines.

How do we use diet to regulate the flora of our gut? Can acidophilus or bifidobacteria supplementation improve the immune function of our bodies? A number of papers have described the benefit of oral supplements with bifidobacteria or lactobacillus. One such study, recently published in the American Journal of Clinical Nutrition, was titled "Enhancement of Immunity in the Elderly by Dietary Supplementation with the Probiotic Bifidobacterium lactis
HN019[1-3,36]

We have an arsenal of tools in our diet, lifestyle, and environment that we can use to promote improved function at every level, reducing all the steps associated with propagation, metastasis, and angiogenesis of tumors and increasing apoptotic cell suicide.

I thank Dr. Reilly for discussing this field with us, and I want to end this 20th anniversary issue by thanking all of you for your years of supporting FMU. I look forward to being with you again in July.

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