April 2000 Issue | Dr. William Kelly

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Welcome to *Functional Medicine Update* for April 2000. This is the last month before our Seventh International Symposium on Functional Medicine in Scottsdale, Arizona. I hope you have made plans to attend that extraordinary celebration. New information will be presented on bioenergetics and its clinical applications in functional medicine. We look forward to seeing you in Scottsdale next month.

This month in *FMU*, we will focus on two areas, one of which is functional assessment. How can we help patients who may be at risk for severe illness in the future? If we can ask the right questions, we may be able to intervene at the level of functionality, before histopathology results. Asking the right questions may involve using assessment tools that are different from those we would use to find pathophysiology. I will take you through a few concepts that differentiate pathology assessment from functional assessment and how functional assessment applies to prevention, modification, and management of the progression of age-related diseases.

The second area of focus this month is one we have been developing in *FMU* for several months, nutritional oncology and its relationship to metastatic disease. This month's Clinician of the Month, who is an expert in this area, will share some insight into the evolution of this field.

In functional assessment, evaluating endocrine function, particularly in relation to anti-aging medicine, is currently making the news. How can one noninvasively understand more about the function of the endocrine system and its interrelationship with the immune and gastrointestinal systems? There is weblike interaction among the endocrine, immune, neurological, and gastrointestinal systems. Therefore, assessing endocrine function takes us beyond single-organ examination.

The hypothalamus/pituitary/adrenal axis (HPA axis) is an organ system that provides an important interface with the external environment. It translates the environment into intercellular messages that communicate with sites at a distance. Those sites then exhibit altered functional status, which may be revealed as signs and symptoms of increasing duration, frequency, and intensity. The HPA axis is the body's stress-modulating antenna to the external world. It senses the environment in the form of psychosocial energetics, light, or heat.

In the time-urgent society in which we now live, the HPA axis is often overworked. It can show signs of exhaustion and what Dr. Hans Selye called the general adaptation syndrome (GAS), which consists of arousal, accommodation or adaptation, and exhaustion. Adverse effects on the HPA axis result in adrenal depletion. The result may be what Dr. John Tintera in the 1950s described as hypoadrenia, a worn-out feeling and the inability to cope and function against stressors that were previously well accommodated.

In his book, *Safe Uses of Cortisol*[1], Dr. William McK Jeffries discussed hypoadrenia in connection with physiological replacement doses of hydrocortisone to benefit individuals with adrenal cortex exhaustion or depletion. Published articles such as those discussed in the commentary by Jeffcoate[2], describe using low-dose hydrocortisone or dehydroepiandrosterone (DHEA) to replete adrenal function in individuals with symptoms of hypoadrenia or adrenal exhaustion. We discussed some of those in the April 1999 issue of *FMU*.

Beyond symptoms, how does one assess the presence of altered HPA function without relying on the dexamethasone suppression test or the ACTH stimulation test? This test looks at serum levels of total adrenocortical compounds, some of which are bound to steroid-binding sex globulin and some of which are free. How does one look at the physiological levels of the free form of these hormones in individuals who are experiencing hormonal ups and downs as they live their normal lives?

Measuring Salivary Hormones

One method of functional assessment of these parameters is the salivary hormone test, which measures levels of salivary hormones. Traditional endocrinologists, who are used to using plasma or serum levels of hormones for assessment, challenge this test. They question the value of salivary hormone analysis for evaluating functional status of the endocrine system, particularly the HPA axis.

A 1990 article in the journal *Clinical Chemistry* described the salivary testing. It was titled "Concentrations of Total and Free Dehydroepiandrosterone in Plasma and Dehydroepiandrosterone in Saliva of Normal and Hirsute Women under Basal Conditions and during Administration of Dexamethasone/Synthetic Corticotropin."

Contrasting Slivary and Plasma DHEA Levels

The authors of this paper contrasted salivary hormone levels of DHEA to serum or plasma levels after a dexamethasone suppression test. They conclude there is an important difference between the salivary and plasma analytes. The authors state the response of salivary hormone levels is related to free DHEA and appears to be related to the unbound form of the hormone. It contrasts to plasma levels, which are related to a combination of the bound and unbound forms. Most plasma DHEA is bound by transport proteins, which are not the physiologically active form of the hormones. Thus, the two determinations measure two different things, according to this paper.

The authors of a 1983 paper in *Clinical Chemistry*, titled "Hormones in Saliva: Mode of Entry and Consequent Implications for Clinical Interpretation," discussed the mechanism of entry of hormones, DHEAS, thyroxin and choriogonadotropin into saliva.[4] They conclude that conjugated steroids such as DHEAS, probably reflect their concentration as the unbound form rather than as total concentration, which represents the sum of the bound and unbound forms. When measuring steroid hormones in serum or plasma, one is measuring the total amount of hormone.

Bound and Unbound Hormones

We are looking at different things when we examine salivary hormone levels and plasma levels. That is why salivary levels are typically

1{56bf393340a09bbcd8c5d79756c8cbc94d8742c1127c19152f4230341a67fc36} of those in serum. A number of variables influence how much of a hormone in the plasma is bound to protein and how much is unbound. They may be modulated in different ways. Salivary hormone represents a kind of filtrate that reflects the unbound steroid, the more physiologically active form of the hormone.

The dilemma is illustrated in a 1988 paper titled, "DHEA Sulfate in Saliva," from the Department of Obstetrics and Gynecology at the Karolinska Institute.[5] The authors looked at relationships between salivary dehydroepiandrosterone sulfate (DHEAS) and total DHEAS in the serum levels. They found no uniform relationship between them. They conclude, perhaps prematurely, that salivary DHEAS "may be of little clinical value."

Determining Reference Ranges for Salivary DHEA

In the more recent literature, a 1999 paper in *Psychoneuroendocrinology*, titled "Assessing Dehydroepiandrosterone in Saliva: a Simple Radioimmunoassay for Use in Studies of Children, Adolescents and Adults," looks at the clinical implications of salivary unbound DHEA.[6] The authors found that while salivary assays for some hormones are widely used, assays for salivary DHEA have only recently become available.

Using a radioimmunoassay serum kit for salivary hormone DHEA analysis, they were able to determine normal reference ranges for children aged 8 to 11, adolescents aged 12-17, and adults aged 30-45. The authors found salivary DHEA levels reflect the developmental gender and diurnal differences and can be of clinical benefit in looking at some endocrine changes that occur with age and developmental status.

Effects of Emotions and Stress on DHEA and Cortisol Levels in Saliva

Emotion and stress impact DHEA and cortisol levels in the saliva. A paper on this topic appeared in *Integrative Physiological and Behavioral Science.* It is based on work from the Institute of HeartMath in Boulder Creek, California, U.S. Naval Postgraduate School in Monterey, and Southampton General Hospital in Southampton, UK.[7] According to the authors, salivary DHEA and salivary cortisol can be correlated with psychological measurements of stress, determined by standard psychometric questionnaires. These measurements also correlate with heart rate variability, the so-called heartmath patterns of the heart rhythm.

The results show relationships between the ability to maintain this biochemically diverse cardiac rhythm pattern under low stress and under conditions of higher cortisol output and depleted DHEA salivary levels. At those higher levels, you begin to see altered cardiac rhythm patterns, lowered stability frequencies, and increased evidence of distress. This correlative study shows how salivary cortisol and DHEA are intercorrelated with psychosocial variables that translate to activation of the HPA axis and ultimate depletion of DHEA, shunting it into cortisol with a hypercortisol state in the saliva.

School Stress and Salivary Cortisol Levels

Another study, from the Institute of Child Development at the University of Minnesota, titled "The Start of a New School Year: Individual Differences in Salivary Cortisol Response in Relation to Child Temperament,"[8] found similar results. Some children experience high anxiety and stress on the first day

of school. Others are excited about school and approach the first day with a sense of eager anticipation. The possible correlation with the activation of the children's HPA axis, as measured by salivary cortisol levels, was the focus of this paper. The results are interesting.

The investigators measured noon and evening salivary cortisol in 70 elementary school children during the first week of a new school year. Samples were obtained on the first and fifth days of school and on weekend days. They looked at changes in cortisol scores and compared them to the children's initial levels and individual personality inventories. The data indicate larger increases in cortisol occurred in the more extroverted children, who perhaps had an amplified response to school, a heightened sense of arousal of the HPA. One might have thought that shy and fearful children would have higher cortisol. This was not the case. Kids with more extroverted personalities had higher arousal levels and increased salivary cortisol output, as measured in both morning and evening cortisol saliva levels.

A similar paper dealing with older individuals dealt with activation of the HPA axis in athletic competition. This paper makes an interesting contribution to the increasing understanding of changes in HPA axis with changing events throughout the day. This 1999 paper, which appeared in *Research Quarterly for Exercise and Sport*, is titled "The Relationship between Salivary Adrenocortical Hormones Changes and Personality in Elite Female Athletes during Handball and Volleyball Competition."[9] The investigators measured salivary cortisol and DHEA in 20 elite sportswomen using radioimmunoassay five minutes before and after a handball or volleyball competition. They also used three psychometric tests—the State Trait Anxiety Inventory, the Bortner, and the Questionnaire of Personalities of Sports—to evaluate participants' personalities.

The results indicated higher concentrations of cortisol and lower concentrations of DHEA in handball players before and after competition. Salivary cortisol increased as well in the volley ball players. The results suggest adrenocortical changes, as a consequence of upregulation of the HPA axis during athletic competition, were likely to be influenced by the different energy demands required by the activities. They were also modified by individual personality characteristics and anxiety levels about winning or losing. All these factors played roles in increasing salivary cortisol and lowering salivary DHEA. The results indicate temporal effects on hormone patterns as measured sensitively as a functional assessment test using salivary cortisol and DHEA.

n a *Journal of Psychosomatic Research* paper titled "Chronic Burnout, Somatic Arousal and Elevated Salivary Cortisol Levels,"[10] investigators looked at 111 nonshift blue-collar workers free of cardiovascular disease to determine if chronic burnout was associated with somatic and physiological hyperarousal from their work and lifestyle. They used two groups of workers, 52 with no burnout symptoms and 22 with non-chronic burnout symptoms, and found very significant differences in levels of salivary cortisol. Individuals sustaining what might be called burnout had significantly elevated salivary cortisol compared to age-and gender-matched peers from the same work group with no burnout symptoms.

Support is emerging for the concept that salivary hormone patterns can provide different information from plasma hormones. Salivary hormone patterns, which are of a more functional nature, are modified by lifestyle and environmental events. They can be used for assessing aspects of chronic functional alterations in expression of these hormones that occur through arousal of the HPA axis and their ultimate effects on gonadal steroid synthesis.

A paper that appeared in *Annals of Clinical Biochemistry* shows that salivary free testosterone is also useful in assessing imbalances of hormones in women who may be shifted toward hirsutism. In this paper, the authors looked at salivary free testosterone in women with hirsutism and found a very significant shift. Levels of testosterone and DHEAS in the saliva were elevated in this group of women.[11] Salivary hormones provide a functional assessment tool, while plasma analysis may be useful in measuring endocrine pathologies. Both measures, in the right context, have clinical value in assessment.

The perspective is changing in the field of medicine and biomedical research. In the 1980s the H2 blockers, or histamine-2 receptor site blockers, became available for the management of peptic ulcer symptoms and disease. By the 1990s these drugs accounted for a significant percentage of pharmacological sales and were the number one prescribed drugs. They were very successful in controlling the symptoms of peptic ulcer disease.

Barry Marshall's work indicated that peptic ulcer disease might not be a simple stress-modulated condition. It had a bacterial etiology associated with the bacterium *Helicobacter pylori*. Proper treatment of this organism by triple therapy could lead to remediation of peptic ulcer disease at the level of cause rather than at that of symptoms.

Cimetidine and H2 Blockers

Throughout the 1990s practitioners believed that drugs like cimetidine, as H2 blockers, operated in treating symptoms of peptic ulcer disease by blocking the histamine-2 receptor site. Both *in vitro* and binding studies had demonstrated cimetidine was an H2 blocker, and H2 receptor sites are associated with acid secretion at the parietal cell of the stomach. Thus it was assumed that the efficacy of the drug and the lowering of symptoms in peptic ulcer disease were mechanistically tied to the ability *in vitro* to block H2 receptors. A number of people wondered how that was possible, given the etiology of peptic ulcers, known now to be caused by an *H. pylori* infection. It was no longer clear that peptic ulcer disease was being treated symptomatically by an H2 blocker if the condition was caused by a bacterial infection.

People have gone back to explore the mechanisms by which H2 blockers might work. Discussion in the scientific literature now indicates that H2 blockers may not work as H2 antagonism alone. This mechanism may be neither their major nor their only mode of action. Studies have found, for example, that cimetidine works as a profound immune response modifier. The ability to modify the immune response of the gastrointestinal mucosa may result in improved vigilance of the body's immune system against the stealth organism *H. pylori*. The result may be a reduction in the proliferative activity of *H. pylori* and its infectious characteristics that irritate the stomach lining and leads to the peptic ulcer condition.

Immune System Stimulatory Effect of Cimetidine

Cimetidine, certainly *in vitro*, is a selective H2 blocking receptor antagonist. Data now suggest that cimetidine has a stimulatory effect on the immune system, perhaps by interacting with receptors on subsets of T lymphocytes. Studies now indicate that cimetidine affects the relative number of CD8 cells and increases natural killer cell activity and antibody-dependent cellular cytotoxicity.[12]

Cimetidine has also been used successfully to restore immune function in patients with various malignant disorders and even AIDS-related complex.[13] Cimetidine and other H2 blockers may be working by mechanisms other than preventing acid secretion, which was the previous model. We sometimes jump to the conclusion that because a drug has a demonstrable mechanistic effect *in vitro* and a positive effect in patients, the mechanism must be tied to the effect. If we do not study the closure of that link, we do not know if the mechanism exhibited *in vitro* was relevant to the whole organism or not. This might explain why we observe adverse side effects in the clinic which were not predicted by the *in vitro*studies. Other reactions may occur that relate to its *in vivo* function.

Approaches that involve restoration of gut mucosal integrity immune defense of the gut may also be adjunctively useful in the management of peptic ulcer disease. The 4R™ program (Remove, Replace, Reinoculate, Repair) has been useful for lowering the recurrence rate of *H. pylori* infection and improving immune vigilance of the gut mucosa. Without blocking parietal cell action and acid production, this program may have a profound effect on preventing the recurrence or modulating the infection during the course of therapy.

A number of laboratory techniques can be used to evaluate the functional integrity of gastrointestinal lumen, the gut-associated lymphoid tissue (GALT), mucosal integrity, colonic bacterial floral activity, and various aspects of digestion and absorption. These functional gastrointestinal tests are designed to look not at gastrointestinal pathology, but at the functional aspects of GI activity that may precede the onset of pathology, such as inflammatory bowel disease (IBD), colitis, or Crohn's disease. A paper published in the *Lancet*in 1993 followed patients with Crohn's disease after successful treatment for a Crohn's crisis. Patients whose small bowel mucosal integrity was not restored, who still had a leaky gut when they were discharged, had very high probability (76 to 81 percent) of relapse within one year. Crohn's patients with normal gut mucosal integrity and healing of the gut on release from the hospital had a less than 5 percent probability of relapse within one year. Relapse rate depended greatly on patients' GI mucosal integrity, evaluated by lactulose/mannitol challenge, on discharge.[14]

The repair phase of the 4R program involves enhancing GI mucosal integrity. Nutrients like glutamine, pantothenic acid, a nonirritating form of zinc, and various antioxidants can help to promote proper GI mucosal restoration. A breakdown in GI mucosa integrity disturbs intercellular junctions, and large molecular weight molecules can leak across from the lumen contents. These molecules can have a direct effect on the GALT, or they can travel in the portal blood directly to the liver. In the liver they can interact with Kupffer cells (the embedded immune system of liver) or with the hepatic detoxification enzyme systems. This interaction can cause upregulation of oxidative reactions in the liver, as well as immune reactions that can create alterations in liver function, ultimately damaging the liver and possibly leading to cirrhosis.

A recent report describes the important role of probiotics in improving function in patients with cirrhosis of the liver. This report, which appeared in the *American Journal of Gastroenterology*,is titled "Probiotics for the Hemodynamic Alterations of Patients With Liver Cirrhosis."[15] In first considering the relationship between the liver and the GI tract, one might not conclude that oral acidophilus or bifidobacterial supplementation would have any impact on patients with liver cirrhosis. That understanding emerges, however, when you look at the interconnection of gut floral activity, mucosal integrity, and the absorption of toxic molecules that alters oxidative demand on the liver and causes oxidative stress.

Authors of this report describe a 76-year-old patient with viral-related liver cirrhosis who was given a high-potency probiotic preparation containing about 10^{11} lactic acid bacteria per gram of lactic acid bacteria, including *Bifidobacteria* and *Lactobacillus acidophilus*. After one month's washout, the patient received a second one-month cycle of treatment. Then the authors examined both blood flow in the portal vein and the overall effects on liver function. The results indicate improvement in liver function and blood flow as a consequence of administering probiotic supplements to individuals with liver cirrhosis.

Probiotics Versus Antibiotics

Oral antibiotics are frequently administered to diminish digestive flora and reduce the production of mediators involved in the pathogenesis of hepatic encephalopathy, portal hypertension, or variceal bleeding, but no clear evidence correlates antibiotic supplementation with lowered risk of these problems. Supplementation with probiotics to restore proper gut flora, however, might have a positive impact on liver function through its downstream effects on liver metabolism. Again, the gut/liver/brain/immune system connection appears in the literature.

Hepatic oxidative stress-related disorders include gut lipopolysaccharide-induced toxicity, exposure to various xenobiotic hepatotoxins, or exposure to food-borne toxins that upregulate oxidative stress and deplete detoxification phase II enzyme profiles, creating imbalanced detoxification. Over the last six years in *FMU*, we have heard anecdotal reports about managing these patients. Subscribers have described their clinical experience with patients to whom they introduced the nutritional support program for liver injury. These patients may have elevated bilirubins or liver enzyme profiles. Supplementation had a positive impact. Supplementation included N-acetyl-cysteine, lipoic acid, selenium, and the herb silymarin (standardized milk thistle concentrate, which contains powerful, liver-specific hepatoprotective agents).

A report by Dr. Burton Berkson, a former *FMU* Clinician of the Month, appeared in *Medizinische Klinic* in 1999. In the article, titled "A Conservative Triple Antioxidant Approach to the Treatment of Hepatitis C,"[16] Dr. Berkson describes the management of hepatitis C, chronic liver infection, and oxidative hepatic injury with a combination of lipoic acid, silymarin, and selenium. This is a case report of three patients. He explains there are no remarkably effective treatments for chronic hepatitis C in general use. Interferon and antivirals have a less than 30 percent response rate, and residual viremia usually causes a newly transplanted liver to become infected again.

Dr. Berkson selected this triple antioxidant combination as a conservative treatment for hepatitis C because alpha-lipoic acid, silymarin, and selenium protect the liver from free radical damage and increase the level of fundamental antioxidants that interfere with viral proliferation. The three patients he describes followed this triple antioxidant program and recovered quickly, and their laboratory indicators remain remarkably improved. Liver transplantation was avoided, and the patients were all back at work carrying out normal activities and feeling healthy.

Liver replacement is a costly medical procedure. One year of triple antioxidant therapy, described in this paper, was less than $2000, compared to more than $300,000 for liver transplant surgery. This therapy appears to have both humanistic value to the patient and significant cost benefit. The antioxidant doses employed to achieve positive benefit are generally 600 mg of lipoic acid in two divided doses of 300 mg each, 900 mg of silymarin in three divided doses of 300 mg each, and 400 mcg of selenium as selenium

methionine daily. These are nutritionally therapeutic but not extraordinarily high doses.

These case histories, although few, reflect the feedback we have received from clinicians who have listened to *FMU* and related their own experiences with patients with have chronic virally induced liver dysfunction. Hepatitis C is an increasing problem, and this triple therapy may help manage it as an adjunct to pharmacological compounds.

In connection with modifying the expression of reactive molecules associated with upregulation of the inflammatory cascade, we have often discussed omega-3 fatty acids. A recent review paper in the *American Journal of Clinical Nutrition* describes the use of omega-3 fatty acids in inflammatory disorders.[17] This series of papers resulted from a symposium last year. "N-3 Fatty Acid Supplements in Rheumatoid Arthritis" was one paper in this series. We have frequently cited the paper's author, Dr. Joel Kremer, a rheumatologist, whose clinical control studies and placebo-control studies use fish oils in the management of rheumatoid arthritis.

In this review, Dr. Kremer explains reports of the benefit of omega-3 fatty acid supplements in reducing symptoms of inflammation, not only in rheumatoid arthritis, but also in inflammatory bowel disease and immunoglobulin A nephropathy in clinical trials. The amount required is not extraordinary. The minimum dose appears to be around 3 grams of EPA and DHA daily, as preformed, longer-chain polyunsaturated omega-3 fatty acids. You cannot get the same benefit apparently from alpha-linolenic acid from flax seed oil. You must use the longer-chain fatty acids derived from fish oil concentrates. Three grams equals about six capsules of 1 gram each of 50 percent omega-3 material, a common potency of 50 percent fish oil concentrate. That is about two capsules three times a day.

The same thing might also be applied to the use of specific omega-6 fatty acid-containing supplements. These are gamma linolenic acid (GLA) omega-6 supplements derived from borage, primrose, or black currant seed oil. In another paper in this series, Drs. Belch and Hill discuss omega-6 GLA from borage oil and primrose oil in managing rheumatological conditions.[18]

Experience in our own Functional Medicine Research Center and that of other clinicians in this area indicates that a balance between omega-3 EPA and omega-6 GLA may provide the best benefit in modifying proinflammatory eicosanoids. This is generally a 2:1 ratio of EPA to GLA. If one is giving 6 grams per day of EPA/DHA mixture, he or she should give 3 grams per day of a GLA-containing mixture, 8 to 12 percent GLA in primrose or borage oil. The balance of those two may provide the best therapeutic benefit in controlling the second signal messengers of inflammation associated with the proinflammatory eicosanoids.

In relation to inflammatory bowel disease (IBD), another paper in this series describes work at the Orsola and Civil Hospitals in Bologna, Italy using enterically coated omega-3 fatty acids for IBD treatment.[19] The doses are about the same as those we described for rheumatoid arthritis, in the range of about 3 to 3 ½ grams a day of EPA/DHA-containing materials. That would be six 50 percent omega-3 fish oil capsules daily. Using lower potency omega-3 capsules would necessitate giving more capsules each day. Higher-potency supplements and fewer capsules represent a better choice.

In reference to delivery system, is it better to use enterically coated or normal soft gelatin capsules? McCall's clinical studies with six patients with ulcerative colitis used the normal fish oil capsules and

soft gel capsules and reported a significant improvement in symptoms and histologic appearance, along with a significant decrease in leukotriene B4 neutrophil production.[20]

Others have used enterically coated capsules or tablets, which reportedly deliver EPA/DHA lower in the digestive tract for better absorption by the GI mucosa. We really cannot yet determine which form is better. Any delivery form of EPA/DHA does appear to have positive benefit, at least from clinical studies, in mediating inflammatory symptoms of IBD and rheumatoid arthritis. I am not aware of any clinical studies that indicate whether the EPA/GLA mixtures I described earlier in managing IBD enhance the effect. The logic we have developed of modulating the inflammatory cascade involves reducing the number of 2-series proinflammatory prostaglandins, increasing the 1- series prostaglandins, and blunting the activity of the 2-series. A mixture of EPA/DHA along with balance with GLA may be helpful in IBD, as it is in rheumatoid arthritis.

Wiskott-Aldrich Syndrome

I recently discussed patient management with Dr. Vincent Marinkovich, a clinical immunologist and allergist from Stanford Medical School, who was a presenter at the Sixth International Symposium on Functional Medicine. As an *FMU* Clinician of the Month in November of 1999, he spoke about allergy. He is also an esteemed member of the faculty of our Applying Functional Medicine in Clinical Practice program, in which we do onsite physician education and training in Gig Harbor.

Dr. Marinkovich was a student of chemistry under Dr. Linus Pauling at the California Institute of Technology. He then worked in immunological research at Cal Tech with some of the pioneers of modern immunology. He held a variety of research roles and then assumed a teaching research position at Stanford University School of Medicine. Dr. Marinkovich shared with me a fascinating anecdote about his experience when he joined the clinical faculty, managing children who had Wiskott-Aldrich syndrome (WAS).

An "Irreversible" Genetic Condition

WAS is a very serious genetic metabolism disorder. In the 1960s, when Dr. Marinkovich first joined the clinical faculty at Stanford, he inherited from his predecessor in the department seven patients with WAS. These children all had severe immune deficiency-related symptoms. The assumption at that time was that these children had suffered an irreversible genetic insult to their immune system, and nothing could be done for them. They had severe recurrent ear infections (serous otitis media), eczema, and thrombocytopenia. WAS patients generally died young in life.

When Dr. Marinkovich inherited these children from his predecessor, he was concerned about how to care for them. When he looked at the presenting symptoms, which included middle ear infections, and thrombocytopenia, and eczema, he thought he should examine what appeared to be an allergic component in these children.

Pasteur said, "Chance favors the prepared mind." Dr. Marinkovich was prepared to look in a new way at the treatment of Wiskott-Aldrich syndrome in these children. He observed that the thrombocytopenia, eczema, and recurring serous otitis media infections in these children so resembled allergy and clinical immunological activation that perhaps they are immune-compromised. Rather than simply considering

them as having an irreversible inborn error of metabolism about which he could do nothing, he determined to test them to see if they were allergic and if allergy was precipitating some of their problems. He was considering the antecedents, triggers, mediators, signs, and symptoms model of patient-centered assessment of functional medicine. It is a beautiful example of functional versus pathology assessment.

When he did allergy testing, Dr. Marinkovich found these children were highly allergic to many foods and environmental factors; they were hyper-reactors in many ways. He talked with their parents and told them he was not sure whether it would make a significant difference, but he would like to do something in these children to lower their allergen exposure. He modified their diets and environments to lower exposure to substances to which they were hypersensitive, probably as a consequence of a unique immunological potential.

The results are fascinating. All seven of these children, who generally would be expected to die in their teens, lived into their 20s. Although they still died young, they weren't children or teenagers. They died in their middle 20s, not as a consequence of the traditional WAS symptoms, but of cancer. Their immune systems were so compromised that when the allergens were removed and they were allowed to survive in the absence of allergens that activated the process, other immunological factors came into play. That is increasing risk to the transformational process.

Another article on WAS appeared in the *Journal of the National Cancer Institute,* titled "Wiskott-Alkott Syndrome: Molecular Pieces Slide into Place."[21] Although it was first described in the 1930s, this syndrome is now seen to be an X-linked (affecting only boys) disorder related to immunodeficiency, low blood platelet levels, and eczema. Lowering the antigenic exposure improves the prognosis in these children. We still see an underlying defect in their immunological defense system that makes them susceptible to transformational process. What Dr. Marinkovich observed has been translated into cancer research that is being done at the National Cancer Institute. This is an example of how looking at something from a different perspective produces a different result.

On side I we talked about assessment of function and intervention strategies built on functional changes. Our second topic of focus this month is oncology, metastastic disorders, and management of various forms of cancer. A letter I received recently moved me to be much more dedicated and mindful about managing cancer and reducing the pain and suffering of the cancer patient. This letter describes the kinds of things that frustrate us, make us want to do better, and exhort us to higher levels of activity. This is about a young girl, seven years old. Her mother wrote:

"Tuesday was horrible, She cried pretty much the whole day. We were all frazzled. When they examined her, they suggested trying muscle relaxers and Valium. (We wondered where ours were!) They felt the back pain was because of muscle spasms. This is typical of someone with involvement in the center of the brain: it just eventually happens. But then that night in the hospital, she spiked another fever. When the doctors heard this on Thursday, they felt that something more was going on in her brain: maybe there was new tumor growth, maybe damage of some kind. She was clearly not herself. She hardly smiled, she cried a lot, she had a lot of muscle spasms. The doctors were troubled by the various developing symptoms. They came in and had the "quality vs. quantity" of life talk with us.

This hit hard at first. It's not that we weren't prepared for this possibility. It's just that things had been

going so well until mid-December, it caught us off guard. We have had a difficult month. (She could do no eating or drinking, had a feeding tube, more chemo, low counts, unexplained fever, home for 48 hours, another fever, home for 24 hours, back to the hospital.) My husband and I took a long walk, then got together with some friends who said some prayers for us. This was very helpful. By the time we went to sleep, we were exhausted but felt better.

The next morning, they scheduled another MRI just to confirm their suspicions, as well as a spinal tap. They wanted to rule out meningitis and see just what the tumor had done. That was a long day, and the more the day wore on, the more we just wanted to go home! We hadn't seen our other two children for four days, and we wanted to be with them. Even so, it was a difficult decision. We moved on as exhausted individuals, needing a break. We got some preliminary results back, which said her tumor had not grown and that it had still shrunk. The doctor reiterated that these were preliminary results and the radiologists would study them and compare them to her previous ones. He said we should get the results early next week. Then, depending on the findings and the consultation of all our physicians, if things looked at all promising, we could start another course of chemo later in the week.

"We decided that whatever road we go down, we want to do it with joy, love and happiness, even if it is to bring our daughter home to die. The doctors told us if the tumor proves resistant to the current chemo, they probably would use a different kind, but that it wouldn't be a cure. It would just prolong her life a little longer. It would probably make her sicker and could cause more complications. All of us feel this "quantity" is not what we want for her. When we told her we were going to take her home, she perked up and grinned. We know home is where she is most comfortable and happy. And we know that if this is her time, then she will be released from all her pain and disease.

This has been a difficult year on all of us. She would at least be able to go on to love, joy and peace. We are very proud of her and all she has accomplished in her short life so far. In her words, "Whatever the outcome of the test results, we will all be okay."

That is a profound letter. It gets your attention. All of us have had those experiences, either with loved ones or patients, and the level of frustration when we cannot find the solution to those problems, is tremendous. That kind of context is what we are going to be talking about—approaches that people have opened their minds to. We are going to have our Clinician of the Month, Dr. Nicholas Gonzalez, tell us about ways that he is approaching some of these difficult cancer cases.

Do Antioxidants or Supplemental Nutrients Sabotage Cancer Therapy?

A recent article in the *Wall Street Journal* is titled "Popping Megavitamins May Sabotage Therapy to Eradicate Cancer."[22] According to the author, individuals who take various kinds of antioxidants like vitamin C and E, thinking they would provide benefit during therapy, may have uncoupled the success of the chemotherapy. This supposition is based on a recent paper Dr. Rudolph Salganik and his colleagues from the University of North Carolina at Chapel Hill presented to the American Society for Cell Biology meeting. They had found that antioxidant vitamins block a natural housecleaning process called apoptosis, in which a reactive form of oxygen triggers the mass suicide of sick or cancerous cells. The researchers fear the vitamins may deflect the punch of radiation or chemotherapy to help the cancer cells survive.

This research leads to reactionism regarding how much nutrition to give to provide support. The situation is still evolving; no consensus message has emerged in this area. Opinions differ. We are just beginning to understand the relationship of nutrition to cancer treatment.

Nutrition conservatives like Dr. Barbara Brummer, a nutritional epidemiologist at the University of Washington and a researcher affiliated with the Fred Hutchinson Cancer Research Center in Seattle, believe caution is warranted because antioxidant nutrients are chemicals. The chemical environment around a tumor cell can be different from that of a normal cell. The key question in cancer nutrition for the future, in treating individuals receiving radiation, according to Dr. Brummer, is "How can we exploit that to preserve good tissue and deliver the hit to the tumor?" That was the message in the *Wall Street Journal* article.

Another view of nutrition and cancer appeared in the July 1999 issue of the journal *Oncology*.[23] One of the authors, Dr. Dan Labriola, is a former *FMU* Clinician of the Month and director of the Northwest Natural Health Specialty Care Clinic in Seattle, Washington. His coauthor is Dr. Robert Livingston, professor of medicine, Division of Oncology, at the University of Washington Medical Center. They discuss patients who treat themselves with oral antioxidants and other alternative therapies during chemotherapy. The authors consider the possible interactions between dietary antioxidants and chemotherapy. They talk about the possible influence of these nutrients on the outcome of chemotherapy as a consequence of ameliorating its effects with nutritional intervention.

According to these authors, "Clinical warning signs of antioxidant-reactive oxygen species interactions include tolerance to conventional drug administration that is much better or worse than expected, unusual toxic effects from treatment, or unanticipated refractoriness to conventional treatment. Asking the patient about use of alternative therapies can provide clues to otherwise unexplained clinical responses and perhaps avoid unnecessary treatment failure secondary to this adverse interaction.

"Is there any actual evidence of antioxidant-chemotherapeutic drug interactions? There are many anecdotes about such interactions. Unfortunately, however, the current reporting system includes no mechanism for monitoring for these interactions. At present, treatment failures are not compared to patients' use of nonconventional treatments. One of the objectives of this article is to increase oncologists' attention to potential interactions by articulating these mechanisms."

One concludes from this discussion only that more information is needed. At present we have only conjecture and speculation. An article by Dr. David Lamson and Dr. Matthew Brignall, published in *Alternative Medicine Review*, presents another position on this topic.[24] The article is titled "Antioxidants in Cancer Therapy; Their Actions and Interactions with Oncologic Therapies."

The authors state, "There is a concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and some forms of chemotherapy, and thereby decrease the effectiveness of the therapy. The question has arisen whether concurrent administration of oral antioxidants is contraindicated during cancer therapeutics. Evidence reviewed here demonstrates exogenous antioxidants alone produce beneficial effects in various cancers, and except for a few specific cases, animal and human studies demonstrate no reduction of efficacy of chemotherapy or radiation when given with antioxidants. In fact, considerable data exist showing increased effectiveness of many cancer therapeutic agents, as well as a decrease in adverse effects, when given concurrently with antioxidants."

We are in a period of controversy about the role of therapeutic nutrients during conventional cancer therapy. Chemotherapeutic agents can be divided into several categories, including alkylating agents such as cyclophosphamide, or antibiotics that affect nucleic acids, like doxorubicin or platinum compounds like cisplatin, or mitotic inhibitors like vincristine, or antimetabolites that interrupt DNA replication, like 5-fluorouracil. A variety of agents have different effects on the cancer tissue. Therefore, a blanket statement that antioxidants or nutrients will adversely affect the mechanism of these agents seems inappropriate. We must look at the exact mechanism of action of the drug, how it influences cell physiology, and what evidence supports the nutrient in that form of cancer with that form of therapy, in possibly improving function.

Possible Routes of Action of Vitamin C and Vitamin E

Authors Lamson and Brignall discuss vitamin A and carotenoids with radiotherapy and chemotherapy, and vitamin C with radiation and chemotherapy. Vitamin C has been extensively tested in a variety of types of cancer. It appears to have a beneficial effect at high levels, and high-dose vitamin C may improve chemotherapy by producing ascorbyl radicals. Ascorbyl radicals are selective chemotherapeutic agents in their own right, compared to ascorbic acid as a nutrient.

In a variety of cell cultures and *in vitro* studies, Dr. Kedar Prasad has found Vitamin E succinate has very positive benefit during chemotherapy. In fact, Dr. Prasad, an investigator at the University of Colorado Medical School, has done both *in vitro* and in animal studies, showing that antioxidants like vitamin E can be positively beneficial during chemotherapy.[25]His experience is principally with vitamin E succinate. Together with omega-3 fatty acids, in chemotherapy and radiation-treated animals, as well as in some limited human clinical trials, vitamin E appears to increase the activity of 5-fluorouracil, doxorubicin, and cisplatin *in vivo.*There is no evidence that vitamin E reduces the effect of chemotherapy *in vivo.*

As a counterpoint to the Labriola paper, the Lamson and Brignall paper discusses the potential benefits of nutrients like vitamin C, vitamin A, vitamin E, selenium, and coenzyme Q10 during chemotherapy. Two other substances Lamson and Brignall consider are melatonin (known to increase tumor cell apoptosis and the tumor response in patients treated with tamoxifen, cisplatin) and N-acetyl-cysteine (NAC). NAC does not appear to block the therapeutic effect of radiation or the therapeutic effect of cyclophosphamide, and it appears to be associated with some benefit in outcome after chemotherapy in tumor-bearing individuals.

Although the topic requires further study, both *in vitro* studies and limited observational studies in humans seem to support the use of combination antioxidant treatment during most chemotherapeutic regimes indicate it does not produce toxic side effects. We continue to learn in this area. We will learn more from our Clinician of the Month in the following discussion.

INTERVIEW TRANSCRIPT

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JB: This month's *FMU* Clinician of the Month is Dr. Nicolas James Gonzalez, a physician from the New York City area. Dr. Gonzalez received his medical degree from Cornell Medical College and is in private practice in New York City. He uses intensive nutritional therapy in the treatment of advanced cancer and other incurable diseases. He has made extraordinary contributions to our understanding of integrative approaches for the management of malignancy and metastatic diseases.

In 1993, he presented cases to a session of the National Cancer Institute in Bethesda, Maryland. As a result of that presentation, the associate director of NCI suggested that he pursue a pilot study on his treatment with patients with pancreatic cancer. We will discuss that study with Dr. Gonzalez, as well as his later studies. Dr. Gonzalez has had clinical immunology training with Dr. Robert Good and his group at the University of South Florida. Welcome to *Functional Medicine Update*, Dr. Gonzalez. Thank you for sharing some of your time with us today.

NG: Thank you for having me here.

JB: What led you into the field that you are in today

NG: I was interested in cancer research from the time I started medical school at Cornell. In fact, I chose Cornell was because it was associated with Sloan Kettering. That was one of our teaching hospitals. Robert Good, who was president of the Sloan Kettering Institute, was a preeminent cancer researcher in the world. I wanted to work with him. When I was a second-year medical student, he adopted me into his group as a "gofer." My orientation was very orthodox. My goal in life was to be chief of medicine at Sloan Kettering. I had my life planned. I was already working under Dr. Good and I thought things couldn't be better.

The summer after my second year of medical school, I met William Kelly, the eccentric, controversial dentist who had developed a very aggressive nutritional program to treat advanced cancer. He had just come out of a difficult period during which he was linked to the Steve McQueen case. McQueen died in 1980, and I met Kelly in the summer of 1981. Kelly was very sincere in his wish to have his work properly evaluated. He said something that is still with me 19 years later. He said he wanted his work evaluated so that if it's valuable, it can put into the hands of the orthodox medical community and made available to anyone who wants it.

Dr. William Kelly

I had lunch with Kelly in a chiropractor's office. It was a bizarre situation; I didn't even want to meet him. I was so orthodox that I went to Dr. Good and told him I had met this fellow who was very eccentric and claimed he had been getting some good results with a nutritional approach to cancer. Good was skeptical, but he was a good teacher. He thought that even if Kelly turned out to be nothing but a charlatan, it would be great to do this kind of investigation of his work as a student project. He thought it would teach me some epidemiological work and how to evaluate cases.

As a result of that chance meeting and Dr. Good's support, I began, as a medical student, to evaluate

Kelly's work. That evolved into a major investigation of Kelly's cases when I was doing my immunology fellowship under Dr. Good after he had moved from Sloan Kettering to the University of South Florida. I went through thousands of Kelly's cases. There was no question that, as eccentric and controversial as he might be, Kelly was getting good results with cancers that nobody else was getting. I felt it was an ethical issue; this work had to be continued. When Kelly dropped out of the scene and closed his practice in l986 or1987, I finished my immunology fellowship training and came back to New York and tried to keep the therapy alive.

JB: Several colleagues and I spent three days with Dr. Kelly when he was living Twisp, Washington, in the Cascade Mountains. He told us about his methods. "Eccentric" is a very appropriate word to describe him, but something beneath that eccentricity seemed very real and interesting. You took it a lot further than we did, but we came away feeling someone needed to explore this therapy. You were the one who did so, and I applaud you for your intellectual inquiry process.

The Kelly method is one of a number of historical alternative approaches to cancer management. What made you pursue Kelly versus other methods that have also been available?

NG: I began pursuing Kelly because of my initial investigation of his records. At that point, he kept his records in his Dallas office, although he still had an office in Washington State. We found case after case of appropriately diagnosed patients with advanced or terminal cancer who were alive 5, 10, and 15 years later. It was so compelling I never thought of doing anything else. This was a commitment I made early on to Kelly. Of course, in my studies and travels through alternative medicine at that time and since, I've learned of Gerson, and Burzynski is a friend of mine. I've gotten to know a lot of the other practitioners in the field.

Kelly's work was unique among alternative approaches. He developed his own method of metabolic typing. He employed a variety of diets, ranging from pure vegetarian to pure meat. His cancer therapy was based on the use of high-dose pancreatic enzymes, which dates back to Dr. Beard's work at the turn of the century. He was unique in his use of high-dose pancreatic enzymes. It wasn't really a megavitamin therapy; it was really a high-enzyme therapy with these individualized diets.

As I've gotten into the field, I learned of Gerson's work and that of other people. With Kelly we have been able to make systematic evaluations of his work and then take it into clinical trial situations. Unfortunately, other alternative doctors have either not yet been able to do or have been prevented from doing it.

JB: Let's discuss the approach you've been employing and how it segues into clinical study. You have had some dramatic results with what might be considered inoperable or terminal pancreatic cancer. Some individuals might agree this ties closely to pancreatic enzymes, but it is more than a simple connection. Would you tell us about the approach you've employed clinically and how you see it fitting into the disease cancer?

NG: Our approach has three basic components. The first is diet. We have 10 different diets, ranging from pure vegetarian to pure meat. Every diet is individualized, so we don't have one cancer diet. We find pancreatic cancer patients, for example, tend to be more on the vegetarian side, but even their diets tend to be individualized.

The second component of the approach is large doses of supplements. We use vitamins, minerals, trace elements, and antioxidants, but we use them in a very specific way to manipulate autonomic physiology. One aspect of our program is that we are trying to get the sympathetic and parasympathetic nervous systems into balance, and we use nutrients to do that. Kelly believed that cancer, and any other disease, occurs primarily because of autonomic imbalance. People might have too strong a sympathetic nervous system and a weak parasympathetic system, or vice versa. What we try to do with nutrients specifically is to bring that nervous system into balance.

Specifically, in terms of cancer, we use high doses of the pancreatic enzymes. Vitamins and minerals are very valuable, useful, and critical to the program, but the pancreatic enzymes are the main anti-cancer elements specifically.

At the turn of the century, John Beard, the eminent Scottish embryologist, was a professor at the University of Edinburgh. He first proposed that the proteolytic pancreatic enzymes not only serve a digestive function, which has been known for 100 years, but that they also represent the main anti-cancer substance in the body. In animal studies and in some clinical experience, he developed an elaborate theory to explain how they work. Ninety-five years later, I still think the work is extremely elegant biochemically and physiologically. Our patients take 60 to 70 capsules of pancreatic enzymes through the day, and we believe that's the main anti-cancer effect.

The third component of our program is detoxification, which used to cause raised eyebrows, even among alternative doctors. That has changed somewhat now, because of your work and your emphasis on the importance of detoxification. We find that unless the patient is detoxifying the metabolic waste from the cancer breakdown, he or she is going to get really sick and won't be able to stay on the therapy. Detoxification is as critical as the supplements, the enzymes, and the diet.

We use a series of procedures, including coffee enemas, to help the liver work more efficiently. We believe coffee enemas help the liver work more effectively and are very useful in getting patients through crisis when they have a massive amount of tumor breakdown. It is wonderful to be able to break down a tumor, but then you are left with an enormous load of tumor waste circulating in the body that can really cause autoimmune and serum sickness-like response. If you get the liver to kick in and work effectively, you can detoxify these wastes. I know you are very interested yourself in detoxification. So, the three components, to sum up, are diet, supplements with large doses of pancreatic enzymes, and detoxification routines.

JB: When you deliver this therapy, are many of the patients on chemotherapeutic or radiotherapeutic regimes, or do you require them to be nontoximolecular as they enter the program?

NG: We really want them to be nontoximolecular, to use your very good phrase. First of all, our therapy is very aggressive, and if patients are getting another aggressive therapy like radiation or chemotherapy, they're going to get too sick. Second, the two therapies are basically at war with each other. We are trying to build up the body; chemotherapy is breaking it down. We take patients who have either finished chemotherapy or haven't done it or have a type of cancer for which chemotherapy or radiation is not indicated. This is generally true with pancreatic cancer. We don't encourage combining our therapy with other therapies. We think it's too tricky and we'll do things that will cancel chemo, or chemo will do things that will cancel our therapy, and you end up with less therapy. We don't combine it with other

toxic therapies.

JB: If a patient cites an oncology journal that says he or she has such-and-such percentage of positive outcome with this with chemotherapeutic drug A, and asks what results your therapy will provide in comparison, how do you help the patient make that important decision in his or her life?

NG: You have to individualize for each patient. For example, if a patient comes to me with stage I Hodgkin's disease, the literature clearly shows that from 50 to 80 percent of these patients can be cured with chemotherapy. Hodgkin's is one of those few cancers that does respond to chemotherapy. Precious few cancers do respond well to it. Medically/legally, we really can't take that patient because documented literature shows the patient has a 50 to 80 percent chance with chemotherapy. We do take advanced Hodgins patients who have failed chemo. They're always sicker and trickier to treat, but we do well with them anyway.

We've had patients for five or six years who had failed chemotherapy with stage IV Hodgkin's. Each case has to be individualized. If a patient comes in with stage IV pancreatic cancer and shows me the latest chemo results, he or she will have read them and know there is no effect at all. In that case we would prefer him/her not to have had chemo. We won't take patients with Hodgkin's for medical/legal reasons until they have had chemotherapy. Once they've failed it, we can do it. It's a tricky area; you're right.

JB: Today's most informed patients search the web and get information from all sources, to make what may be the most important decision of their lives, how to proceed in therapy if they have cancer. They may see both you and a traditional oncologist. They are armed with information about your program when they see the traditional oncologist, and armed with information about the traditional oncology approach when they come to see you. I'm sure that, over the years, you have developed a very adept communication mechanism to give them their options and allow them to make the choice.

NG: That's correct. In fact, we go through a very rigorous selection process before we even let a patient get into the office. We ask about their previous experiences with doctors, what therapies they've had, and why they want to do our therapy. We interview them. There is a rigorous selection process. As our work is getting better known in the orthodox world, oncologists are increasingly willing to work with us. Many want to work with us and refer patients to us. This has been a change, particularly in the last two to three years. We can now work with oncologists for the benefit of patients.

Oncologists want their patients to get well, too. If they think there's a better therapy out there for a particular cancer or a particular patient, they want to know about it. They're on the front lines. It has been very gratifying, as you and I know, there is a lot of politics, in oncology particularly. A lot of doctors are not at all receptive, but many are really happy about the work that is proving to be positive. We have had a lot of referrals from oncologists in the last six months.

JB: One indication your work is being taken seriously is your recent ability to gain access to the world of clinical trials and the notoriety you are getting in the lay press. You have generated some healthy dialogue about where cancer treatment is going. Would you describe your current clinical study, its objectives, and how it came about?

NG: As you said in the introduction, in 1993, Michael Friedman, who was then associate director at the NCI, invited me to Bethesda to present a series of cases. These were patients with advanced cancer who either had documented tumor regression or long-term survival just on my therapy. As a result of that meeting, he suggested I do a pilot study. A pilot study is a preliminary study that is often used with a new therapy to see whether there's anything of value. The next step would be a controlled trial.

Dr. Friedman suggested I take pancreatic cancer, because it's the worst cancer there is. He said if I showed any effect at all with that, people would have to take me seriously. The Nestle Corporation was anxious to fund the study. They give out a certain number of grants to innovative research, some of them in nutrition. They funded this trial that was suggested by the NCI. The NCI reviewed the protocol.

A pilot study has no control group; it's basically a one-arm study. Dr. Freidman suggested that because pancreatic cancer is so aggressive, we didn't even need a lot of patients. He felt 10 would be adequate; we ultimately had 11. One patient dropped out, although we include all 11 in the data collection. Eight of those 11 were stage IV. These were very sick, very advanced patients. I deliberately took advanced patients, so no one could question the data. As you know, however, people will still question it, no matter what you do, and that's the way it is.

Normally, the survival for that type of cancer is about 4 to 5 months. Gemzar is the new chemotherapy approved for the treatment of pancreatic cancer. In the Eli Lily study of Gemzar with 126 patients, not a single patient lived longer than 19 months, and the median survival was about 5 ½ months. In our little study of 11, we had five patients who lived two years, and four who lived three years. We've got two who have passed four years now. This is well above and beyond what's ever been seen with pancreatic cancer, even in large studies.

Based on that, the NCI decided to fund a large-scale, randomized controlled trial where my therapy will be directly compared to chemotherapy. It's a big study. It's a 1.4 million dollar study with about 90 patients, with about 45 or 50 in each group. It is being done at Columbia University under the auspices of the head of the Department of Oncology, Karen Antman, and the head of surgical oncology, John Chabot. It is very exciting. To me, it shows that if alternative practitioners keep their nose to the grindstone and collect data, people will listen. You may run into obstacles and roadblocks, but if you collect and present good data, they will listen.

That's been my experience. It's taken me 17 or 18 years, but they are listening. We did get the grant. The study is being run in a top way; it's a very good study. I was involved in writing the protocol. There was no attempt at sabotage. Alternative practitioners often ask if I'm sure this isn't a setup. It absolutely is not. This is a sincere, honest, academic attempt to see how good my therapy really is.

JB: I applaud you. Tenacity, commitment, scholarship, and dedication can create great change. You deserve accolades for all of those characteristics. I was impressed by the directness and forthrightness with which you brought to my attention an editorial in the *Washington Post,* which was somewhat critical of the clinical study and this work From your perspective, where do you feel there was some misrepresentation?

NG: It was a sham basically. It turns out the author of the article is a physician, although she had not identified herself to me as a physician. I learned about that on my own. I will say 99 percent of the press

we've had has been very positive. CNN did a wonderful piece that ran around the world. The *Boston Globe* did a great piece. This is the only negative article we've had.

For some reason or other, the author had her nose out of joint about my work. It was just misrepresented. For example, in terms of my training, she said I had just "dropped out of my residency," as if I then wandered around America trying to find myself. I left my internship year because Robert Good, one of the most published authors in the history of medicine, asked me to join his group as a full Fellow with a fully funded research grant. It was an extraordinary opportunity. He allowed me to continue my Kelly research. It was unusual. Usually you do your fellowship after you finish your residency, but he thought I was confident and capable enough to join his group as a full Fellow right out of internship. She left that out.

There were a lot of misstatements. They tried to attack the data, but the fact of the matter is the data were reviewed by independent pathologists, contrary to what the article implied. We had the former VP of the American Cancer Society review cases. We had a second independent oncologist review the cases, just so we wouldn't be criticized. We couldn't have been more impeccable in our academic documentation, but the *Washington Post,* for whatever reason, pretended that didn't exist.

There has been such criticism of that article that the *Washington Post* asked an outside journalist to review it. He told me he has found more than 100 errors in that article just in his own research, checking. I'm not sure how that's going to fall out, but I think the *Washington Post* is a little nervous about it.

JB: How do you see the treatment you've described—the diet, supplements and pancreatic enzymes, and detoxification—applying to other forms of cancer?

NG: We treat all types of cancer, from leukemia to brain cancer. The enzymes seem to work against any type of cancer. People make the connection that you implied initially in your introduction, that pancreatic enzymes make work for pancreatic cancer, and that may be it. We chose pancreatic cancer only because it is a very bad cancer. Our experience, however, has indicated that pancreatic enzymes will work with any type of cancer, including blood cancers like leukemia, solid tumors like those in breast cancer, colon cancer, lung cancer, and brain cancer. We treat a variety of types of cancer, and they seem to respond equally well.

One good thing about the enzymes is that they don't seem to attack normal tissue. They are selective for cancer cells. We don't know why the molecular biology hasn't been worked out yet, but it seems to be a specific way of attacking cancer cells without affecting normal tissue. It does seem to work for all tumors across the board, even rare tumors, like rare sarcomas.

JB: Are there any serious side effects that, as an attending physician, you need to watch out for in these patients? You have talked about the tumor mass, as it is degraded, producing almost serum-like sickness. What is your experience with side effects?

NG: Patients can get very sick on this program. I would caution physicians not to try to start treating patients with high-dose pancreatic enzymes. The doses have to be individualized. We have people cycle on and off the supplements. We find that if you keep them on the enzymes too long, they get too sick. They get nausea, vomiting, fevers, chills, and skin rashes. They can get almost as sick as patients on

chemotherapy, not from the enzymes themselves, but from the body's reaction to the mass of dead tumor waste.

You get a very vigorous autoimmune response to the tumor waste, and people can get quite sick. It's not a simple, easy, magical therapy. It requires a lot of experience. I worked with Kelly for years before I felt capable of putting a patient on a single dose of enzymes. When you use high-dose pancreatic enzymes, you have to be experienced and guided initially. Some patients who go through my therapy experience minimal side effects. It's very idiosyncratic, but the majority of patients go through periods when they feel quite ill. You have to know what you're doing in terms of management. What symptoms are due to the disease? What symptoms are due to the tumor breakdown? That sort of thing. When you have to change the dose, lower the dose, stop the pills for a few days, all these things require a certain amount of experience.

JB: Do patients go through a period of cachexia as they might with traditional chemotherapy?

NG: Yes. In fact, I just got off the phone this morning with a patient who has lung cancer who has done very well. He said he can't eat. He'd been on enzymes for about 15 days. I think he'd had such a massive amount of tumor breakdown, he was just floating in toxic debris. I told him to stop all his pills and increase his coffee enemas. When patients get toxic on our program from tumor destruction, they characteristically lose their appetite. It's one of the first things we see. They get fatigued and washed out. Kelly's work used to describe it as a "goopy-like feeling." They feel goopy, flu-like. If they continue on the enzymes and get more toxic, they lose their appetite and start losing weight.

JB: When we talk about pancreatic enzymes, it's not just a generic term. Aren't there specific types and potencies that deliver the effective results?

NG: In 1979 you wrote a monograph about pancreatic enzymes, that was one of the best things I'd read at that time. Pancreatic enzyme biochemistry and physiology are very complex. Many issues are raised by the use of pancreatic enzymes. First, I give them orally, so how can they be absorbed? We have known for approximately 20 years that pancreatic enzymes taken orally are absorbed into the bloodstream through both passive diffusion and an active transport mechanism. The body seems determined to conserve pancreatic enzymes, and there is a very sophisticated receptor-mediated active transport mechanism for the absorption, reuse, and recycling of the proteolytic pancreatic enzymes.

The enzymes we think are most effective against cancer are the proteolytic enzymes, things like trypsin, chymotrypsin, carboxypeptidase. However, the lipases seem equally important in some respects, because they seem to attack the cancer cell membrane directly, the phospholipid layer. We find that proteolytic enzymes without the lipases don't work as well.

One hundred years ago, Beard learned from his own experiments that even amylase, which you wouldn't think would have any effect on a cell membrane, seems to be additive in its effect. Proteolytic enzymes without the lipases don't work well. Proteolytic enzymes with lipase but without amylase don't as well as all three components. The three basic types of enzymes are the amylytic enzymes, the proteolytic enzymes, and the lipases. These are the protein-digestive enzymes, the fat-digestive enzymes, and the carbohydrate-digestive enzymes. To get maximum anti-cancer effect, you need all three of them.

We have had to develop our own method for making enzymes, which has taken about 10 years. A lot of enzyme preparations available are produced through an elaborate purification process in which they are trying to get rid of unknown factors and purify the trypsin activity and the chymotrypsin activity. We find the more purified an enzyme is, the less effective it is against cancer. It may be good as a digestive aid, but it is not effective against cancer. At least 30 pancreatic enzymes have been identified at this point. Probably dozens more haven't been identified. We believe there are unidentified factors in the pancreas that probably help in the anti-cancer effect. We've gone from a very purified product to a less purified product. You have to strike a balance. It's complex. Even the manufacturing process is complex, because pancreatic enzymes are very complicated, three-dimensional proteins that are very unstable in certain circumstances.

JB: I know there's a discussion right now regarding whether vegetable-derived enzymes or animal-derived enzymes are preferable in certain nutritional therapeutics. The enzymes you've described in this discussion are animal-derived enzymes, which would have the highest proteolytic or lipolytic activity.

NG: Correct. Vegetable-derived enzymes do not attack cancer. You need the proteolytic enzymes. We're even more specific in that we use porcine, pig-based pancreatic enzymes simply because the homology between the pig pancreatic enzymes and the human is very similar.

For years, doctors used pig insulin to treat diabetes because the homology between human and pig insulin is very close. The same is true with the proteolytic and the other pancreatic enzymes. Sheep enzymes are not as good. Sheep are not carnivorous; they are herbivores. They have very low proteolytic activity in their pancreases, so sheep pancreatic enzymes are too weak. Pigs are omnivorous; they eat like humans. They eat meat and vegetables, and they have high proteolytic activity in their pancreas. How do you prepare the product without destroying proteolytic activity? People have discussed that for 50 years, going back to Ezra Levin's patent in 1950 for isolation of pancreatic enzymes. It is a tricky issue, as you suggested in your 1979 monograph.

JB: When can we expect to see some results from the RCT at Columbia?

NG: Publication of our first study aroused a great deal of interest, but everybody wanted to be randomized to my arm. Columbia has now had 200 calls from patients with pancreatic cancer. Only three people have agreed to be randomized; 197 said they would participate only if they could be guaranteed the Gonzalez arm. In a randomized trial, as you know, your name is basically taken out of a hat. You are told you are going to get chemo or Gonzalez. One hundred ninety-seven patients said they weren't going to do that, that they wanted Gonzalez.

Columbia has petitioned the NCI to make it a case-controlled study, not a randomized study. The patients who want to get chemo and would rather die than give up smoking or would rather die than drink carrot juice, get chemotherapy, which is fine. The patients who want me get me. The NCI's attitude is that when you're dealing with inoperable pancreatic cancer, everybody knows the survival is so poor, that even though a randomized trial is the gold standard, a case control would be acceptable. We are in the process of switching over to a nonrandomized study. We may end up running two studies, the non-randomized one and a randomized one, to answer any critics who say it wasn't randomized. Hopefully, then, we'll accrue the patients in each arm very fast. With pancreatic cancer, the survivals are so short that we think within a year we'll have substantial data. That would be my hope.

JB: I'd like to close by giving you a chance to talk about what you think is on the horizon in cancer treatment. There are all sorts of new biologically based approaches that involve receptor site modulation, or cell signaling modulation, changing cell differentiation, and moving to genomic types of manipulative techniques. What do you foresee on the horizon?

NG: It's a question of how you approach cancer. You can approach it through the telescope or through the microscope. Both ways are valid. We're approaching it more telescopically, although I think molecular biology is very important. What we know is that clinically, and this goes back 90 years, before the genome might have even been attempted, pancreatic enzymes seem to kill cancer cells. The molecular biology hasn't been worked out. It would absolutely fascinating to see how that falls out. As we get better known, we're starting to get research funding to do those kinds of things. I'm not sure where it's going to lead.

I think orthodox oncology is in trouble. Just this past Saturday, I opened up my *New York Times* and there was an article on the one positive study that showed some results with bone marrow transplants in breast cancer. It has now been discredited as a total fraud. The doctor basically made up the data. It has been totally discounted. I think the world of chemotherapy is getting a little bit desperate because the results, despite the billions of dollars in research funding, haven't been very good. I don't see this as a criticism because we're all working together trying to get the best therapy for our patients.

I think increasingly, it's going to go nutritional. I'm sure you've seen this in the last five years, even in the orthodox world. There has been such interest in nutritional approaches to cancer, or the effects of nutrients in cancer prevention as well as treatment. I think there's going to be a real change in emphasis away from the toximolecular model toward the nutritional, natural, physiological approach.

JB: An article that appeared in *Intouch* magazine (Aug/Sept 1999), titled "Dr. Gonzalez's Regimen," talks about your approach.[26] For anyone who wants to read a nice review, this is a good citation. Are there other places in the literature you would send people to read more about your approach?

NG: Our website contains both lay and scientific articles, which are either referenced or included in full.[27,28] Technical background regarding pancreatic enzymes and how we use them is referenced on the web site, which is www.dr-gonzalez.com.

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